Summer 7-15-2013

Design and Synthesis of HIF-1 Inhibitors as Anti-cancer Therapeutics

Sarah Burroughs
Georgia State University

DESIGN AND SYNTHESIS OF HIF-1 INHIBITORS AS ANTI-CANCER THERAPEUTICS

by

SARAH KATHRYN BURROUGHS

Under the Direction of Dr. Binghe Wang

ABSTRACT

Cancer is responsible for one fourth of the total deaths and is the second leading cause of death, behind heart disease, in the United States. However, there are as many approaches to curing cancer as there are types of cancer. One important issue in solid tumors is hypoxia, a lack of oxygen, which promotes angiogenesis and anaerobic metabolism, which can increase cancer progression and metastasis. The HIF transcription factor is responsible for the mediation of many processes involved during hypoxia and is linked to poor patient prognosis, increased cancer progression, and invasiveness of tumors. With this in mind, the HIF pathway has become an attractive target for small molecule inhibition. Herein, we describe the design and synthesis of small molecules that inhibit the HIF pathway. These compounds are based off an initial "hit" compound, KCN-1, from screening of a 10,000 compound library. KCN1 is both highly effective and has a low toxicity profile. Over 200 compounds have been synthesized by the Wang lab,

with the best compound IVSR64b having an IC_{50} of 0.28 μM. Of special interest is that these compounds do not appear to have any inherent toxicity toward healthy tissues, but only affect cancer cells. Moreover, x-ray crystal structures for both KCN-1 and IVSR64b were obtained and used as the basis for computational modeling, which is still in progress.

INDEX WORDS: Small-molecule inhibitors, HIF, Hypoxia, Anti-cancer therapeutics, Medicinal chemistry

DESIGN AND SYNTHESIS OF HIF-1 INHIBITORS AS ANTI-CANCER THERAPEUTICS

by

SARAH KATHRYN BURROUGHS

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

2013

DESIGN AND SYNTHESIS OF HIF-1 INHIBITORS AS ANTI-CANCER THERAPEUTICS

by

SARAH KATHRYN BURROUGHS

Committee Chair: Dr. Binghe Wang

Committee: Dr. Alfons Baumstark

Dr. Giovanni Gadda

Electronic Version Approved:

Office of Graduate Studies

College of Arts and Sciences

Georgia State University

August 2013

DEDICATION

I would like to dedicate this work to my friends, family, and coworkers who all supported me throughout my time in graduate school. I would especially like to thank my parents, Rebecca and Spencer Johnson for their years of support and for instilling upon me the importance of education. I would also like to especially thank my fiancée Anthony Zingales for his patience, love, and encouragement during this process. Most of all, I would like to dedicate this dissertation to the previous generation of my family who are no longer here, but would be proud of this accomplishment, specifically my grandfather Mitchell R. Sharpe and my grandmother Virginia “Boom-Boom” Sharpe.

.

ACKNOWLEDGEMENTS

First and foremost, I would like to acknowledge and thank my advisor, Dr. Binghe Wang. Without his knowledge, guidance, encouragement, and support, I would not have even been in the program, let alone able to finish my degree. People say that group members pick up the personality of the advisor, and I sincerely hope that is the case. In addition, I would also like to thank those faculty members who mentored me throughout my career at GSU: Dr. Al Baumstark, who always made sure to give me a hard time in order to make sure I was prepared; Dr. Keith Pascoe, who taught me many tricks of the trade in teaching; Dr. Giovanni Gadda, who helped me navigate the intricacies of committees and service to the department; Dr. Jeremiah Harden, who encouraged me to hang in there and persevere; and Dr. Dabney Dixon, who is a role model for women in the sciences and encouraged me to network and advocate.

I would also like to thank all of my group members, past and present (Dr. Chaofeng Dai, Dr. Lifang Wang, Dr. Krishna Damera, Dr. Bowen Ke, Dr. Nanting Ni, Dr. Xiaochuan Yang, Dr. Jianmei Cui, Dr. Suazette Mooring, Dr. Jerry Cheng, Dr. Weixuan Chen, Dr. Hanjing Peng, Arpana Chaudary, Danzhu Wang, Alex Draganov, Ke Wang, Yueqin Zheng, Kai Xu, Jalisa Holmes, Hieu Dinh, Sarah Laughlin, and Zeus de los Santos). I would not have made it without you guys! I especially want to thank Dr. Suazette Mooring, who began this project, and without whose lab notebooks, papers, and assistance I would not have been able to continue this work. I also want to thank Hieu Dinh, Jalisa Holmes, and Zeus de los Santos. These 3 students who worked with me made significant contributions to this work in many ways, as well as kept me sane in the lab and I am glad to call them friends.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION

When people as what I do for a living, and I say that I am researching anti-cancer drugs; they always ask if I think we will find a cure for cancer. I have to explain that there are as many different approaches to curing cancer as there are types of cancer. One of the major disadvantages to most cancer treatments is the toxicity to healthy cells and thus the unwanted side effects such as hair loss, nausea, fatigue, loss of appetite, and bone marrow suppression. In order to combat these undesired side effects, many researchers focus on trying to find new ways to target cancer itself and not healthy tissue. Our research is focused on one specific aspect of cancer, hypoxia (a lack of oxygen), which occurs in solid tumors. The major advantage to targeting hypoxia is that it is not typically found in healthy tissues and by only affecting hypoxia areas, we can selectively treat the cancer without damaging the healthy tissue. Detailed information on hypoxia and the HIF pathway is included in the first chapter of this dissertation.

This dissertation is broken up into 4 chapters: the first is a review paper on anti-cancer HIF therapeutics which has been published as an invited review in *Future Medicinal Chemistry*; the other 3 are manuscripts of papers in preparation for publication. For each chapter, I wrote the manuscript, designed and synthesized many of the compounds, and helped conceive the concept as a whole. The biological testing was carried out by the Dr. Erwin G. Van Meir laboratory at Emory University. Other group members, including Dr. Krishna Damera, Dr. Bowen Ke, Dr. Suazette Mooring, Jalisa Holmes, and Zeus de los Santos synthesized compounds that are included with their permission, as noted.

2 HYPOXIA INDUCIBLE FACTOR PATHWAY INHIBITORS AS ANTI-CANCER THERAPEUTICS

This work is reproduced with permission from the review paper: "Hypoxia inducible factor pathway inhibitors as anti-cancer therapeutics." Sarah Kathryn Burroughs, Stefan Kaluz, Danzhu Wang, Ke Wang, Erwin G. Van Meir, and Binghe Wang. *Future Medicinal Chemistry* (2013) 5 (5) 553-572.

2.1 Abstract

Hypoxia is a significant feature of solid tumor cancers. Hypoxia leads to a more malignant phenotype that is resistant to chemotherapy and radiation, is more invasive and has greater metastatic potential. Hypoxia activates the hypoxia inducible factor (HIF) pathway, which mediates the biological effects of hypoxia in tissues. The HIF complex acts as a transcription factor for many genes that increase tumor survival and proliferation. To date, many HIF pathway inhibitors indirectly affect HIF but there have been no clinically approved direct HIF inhibitors. This can be attributed to the complexity of the HIF pathway, as well as to the challenges of inhibiting protein–protein interactions.

2.2 Hypoxia in cancer

Cancer is the second most common cause of death in the USA, with practically one in every four deaths due to cancer [301]. Moreover, the most recent data report that in 2008 there were over 12.5 million new cases of cancer diagnosed worldwide and that by 2030 this number is anticipated to swell to over 20 million [302]. Many cancers involve solid tumor formation, and during periods of rapid growth, tumors outgrow existing blood supply, leading to the development of hypoxic (partial oxygen pressure of less than 5 Torr) and anoxic regions [1].

Tumors remedy this by producing angiogenic factors that lead to the formation of tumor vasculature, although, with structural and functional anomalies. These include arteriovenous shunts, blind ends, occlusions, high angle branching patterns, and broken, leaky vessels [2]. Abnormalities in the tumor vasculature limit oxygen delivery, leading to acute hypoxia [3].

Hypoxic tumors are more resistant to radiation and chemotherapy, are more invasive, are genetically unstable, resist apoptosis and have greater metastatic potential; all of which leads to poorer prognosis overall for patients [4,5]. It has been demonstrated that tumor irradiation is three-times more effective when carried out under oxygen-rich versus anoxic conditions. Moreover, the effectiveness of anticancer therapeutics that target rapidly dividing cells is reduced against hypoxic cells due to the decreased rate of cell proliferation that increases with distance from vasculature [6]. Another factor in treatment resistance is due to the cancer stem-like cells (CSCs), which are a relatively rare subpopulation of tumor cells with self- renewal capacity. CSCs reside in hypoxic niches of tumors and are more resistant to radio- and chemo-therapy-induced DNA damage, allowing them to survive the treatment and repopulate the tumor with their progeny. Typically, prolonged hypoxia triggers cell apoptosis, but in tumors, it can lead to the selection of tumor cells with mutant p53, which are resistant to apoptosis and confer a more malignant phenotype [7]. Clinical studies have shown that many cancers with hypoxic tumors are more likely to be metastatic, including soft tissue sarcomas, squamous cell head and neck carcinomas, cervical carcinomas and malignant melanomas [8]. Therefore, hypoxia can either lead to cell death through apoptotic or necrotic pathways, or to cell proliferation through activation of various other pathways [3].

2.3 The HIF pathway

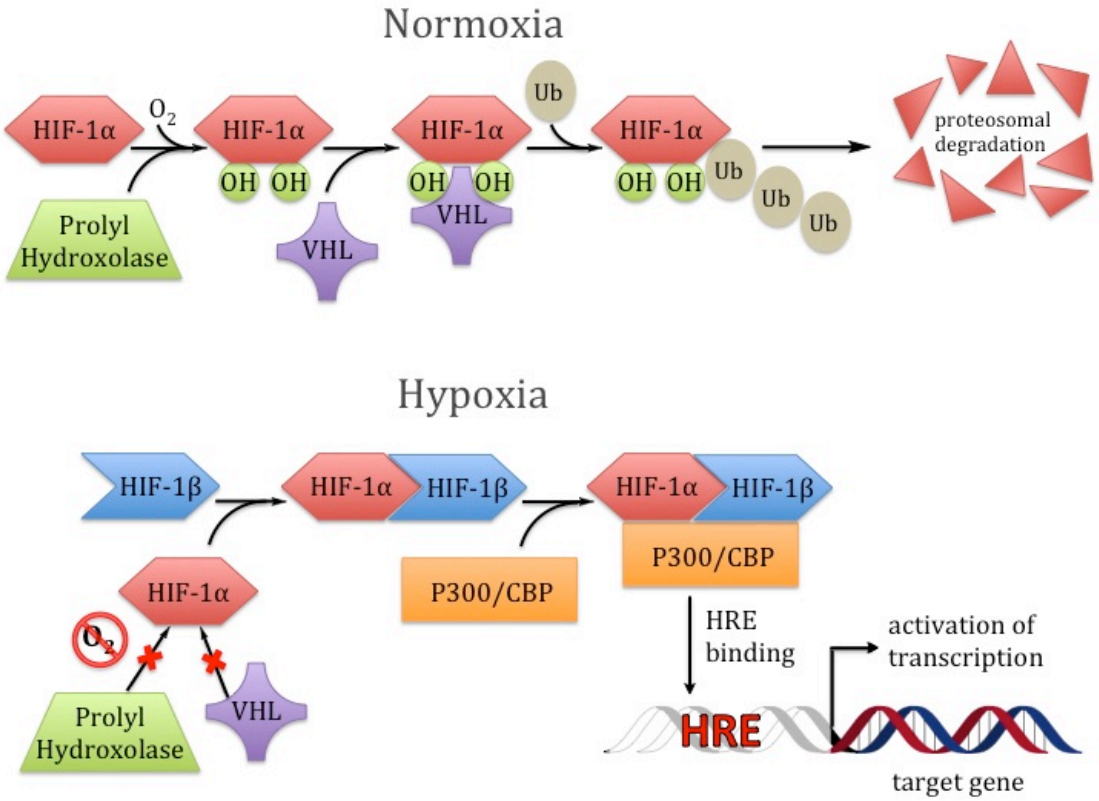


Figure 2.1 The HIF-1 Pathway

Under normoxic conditions, HIF-1a is rapidly hydroxylated by prolyl hydroxylases, which mediates binding by the VHL ubiquitin ligase complex, addition of poly-Ub which tags it for proteosomal degradation. Under hypoxic conditions, prolyl hydroxylases cannot hydroxylate HIF-1a, preventing VHL binding which leads to HIF-1α stabilization. HIF-1 α then heterodimerizes with HIF-1β, recruits the p3oo/CBP co-factors and forms an active HIF transcription complex in the nucleus that binds to HREs on target genes and activates their transcription. HIF: Hypoxia inducible factor; HRE: Hypoxia response element; Ub: Ubiquitin chains; VHL: von Hippel-Lindau tumor suppressor protein.

The hypoxia inducible factor (HIF) pathway is a major mediator of the biological effects of hypoxia in tissues (Figure 2.1) [9]. HIFs are basic-loop-helix-loop motif heterodimeric transcription factors composed of two subunits: an oxygen-regulated a subunit (HIF-1α, -2α, or -3α) and the constitutively expressed HIF-1β (also called aryl hydrocarbon receptor nuclear translocator) [10]. Under normoxic conditions, HIF-α subunits are hydroxylated by Fe^{2+}-dependent HIF prolyl hydroxylases (PHD), mostly PHD2, at two proline residues (402 and 564 in human HIF-1α) located in the oxygen- dependent degradation domain [11,12]. This dihydroxylated form of HIF-α is bound by VHL, which is an E3 ubiquitin ligase that leads to the ubiquitination of HIF-α and subsequent proteasomal degradation [13,14]. This interaction between VHL and HIF-1α has been shown in some instances to be promoted by acetylation of HIF by the ARD1 acetyltransferase at lysine 532, increasing ubiquitination and degradation [15]. However, the role of acetylation of HIF is still somewhat controversial and needs further exploration.

Conversely, under hypoxic conditions, PHDs lose activity and HIF-α units are no longer degraded. As HIF-1α or HIF-2α accumulate, they bind to HIF1-β and form the HIF heterodimers, which translocate to the nucleus and, along with co-activators (p300 and CBP), form the transcriptional complexes that bind to hypoxic response elements (HREs) in the regulatory regions of many genes [16]. HREs are composite *cis*-acting elements, comprising the necessary but not sufficient HIF-βinding site with the consensus sequence RCGTG (where R = purine A or G) and a HIF-αncillary sequence [17]. The transactivation potential of the HIF-α/p300 complexes is regulated via deacetylation of p300 by histone deacetylase [18].

HIF activity is also regulated in an oxygen- dependent manner by an asparaginyl hydroxylase, Factor Inhibiting HIF-1 (FIH1), which hydroxylates an asparagine in the C-

terminal activation domain (CAD) of the a subunit (N-803 in human HIF-1α) under normoxia and mild hypoxia. Hydroxylation of N-803 blocks interactions between HIF-1α and p300/ CBP coactivators preventing HIF activation [19]. Because FIH1 is less sensitive to oxygen drop than PHDs, it remains active under moderate hypoxia and maintains the inactivity of the HIF-α molecules that avoid the PHD-mediated degradation that occurs in mild hypoxia [20].

PHDs and FIH1 are dioxygenases that, in addition to molecular oxygen, require Fe^{2+} and 2-oxoglutarate (2-OG) co-factors for activity [20]. This provides an opportunity for regulation of their activity and in turn HIF-1α levels/ HIF activity. Iron chelation is frequently used for activation of HIF-1 in cell culture [20]. There has also been some evidence of mitochondrial involvement in HIF regulation in that, under moderately hypoxic conditions, mitochondria will produce reactive oxygen species (ROS) from complex III of the electron-transport chain, which inhibit the activity of PHDs by oxidizing Fe^{2+} to Fe^{3+}, thus accelerating the stabilization of HIF [21,22]. 2-OG is an intermediate in the tricarboxylic acid (TCA) cycle and structurally related compounds (e.g., dimethyloxalylglycine or other TCA cycle intermediates, fumarate and succinate) can inhibit activity of PHDs directly by reversibly competing for the active site with 2-OG or indirectly via increasing cellular levels of ROS [23]. Recently, heterozygous mutations in *IDH1* or *IDH2* genes were described in glioma and acute myeloid leukemia. Mutant proteins, acting in a dominant-negative fashion, are defective in their ability to oxidize isocitrate to 2-OG [24]. This initial report suggested that in cells with mutant IDH HIF-1α is indirectly stabilized because reduced synthesis of 2-OG lessens PHD function [24]. However, further studies found comparable levels of 2-OG in both wild-type and mutant cells; instead, the mutant IDHs acquire a neomorphic activity, which reduces 2-OG to 2-hydroxyglutarate (2-HG) [25]. Moreover, it was reported that (*R*)-2-HG, the product of mutant IDH, can be utilized in place of 2-OG in the active

center of PHDs. Here, (*R*)-2-HG (but not (*S*)-2-HG which acts as an inhibitor of PHDs) is oxidized into 2-OG, resulting in increased PHD activity and correspondingly decreased HIF-α levels and HIF activity [26]. More work will be required to finalize the functional consequences of IDH mutations on activity of the HIF pathway and tumor growth.

Finally, HIF-α is situated at the convergence of multiple oncogenic and tumor suppressor pathways, including the PI3K/AKT and MAPK/ ERK pathways, which regulate HIF nonspecifically in an oxygen-independent manner. Activation of the PI3K/AKT pathway has been demonstrated to increase translation of HIF-1α mRNA and HIF-1a production [27,28]. Tumor suppressors (p53, GSK3b, and so forth) interfere with HIF function by decreasing HIF-1α stability or transcriptional activity [23]. One important type of regulation is that of HIF-1α phosphorylation, which can affect both HIF-1α stability and its transactivation potential. HIF-1α can be phosphorylated by GSK3 at three serine residues (551, 555 and 589) within the human HIF-1α N-terminal transactivation domain [29,30]. This recruits Fbw7 and USP28, which then mediates HIF-1α ubiquitination and subsequent VHL- independent proteasomal degradation [31]. PLK3 also destabilizes HIF-1α by phosphorylation at two serine resides (576 and 657) [32]. Conversely, phosphorylation of HIF-1α can have a stabilization effect. It has been demonstrated that ATM can phosphorylate HIF-1α at Ser-696, which increases its stability [33]. HIF-1α is also phosphorylated in its CAD by ERK1, which increases its transcriptional activity, but not its stability [34]. Thr-796 in HIF-1α is phosphorylated by CK2 and this phosphorylation is also important for its transactivation potential and not stability [35,36]. The p42 and p44 MAPK pathways regulate HIF-1α post-translationally by phosphorylating two serine residues (641 and 643). This phosphorylation promotes nuclear accumulation of HIF-1α, which leads to an increase of HIF-1-activated transcription [37,38]. In addition, HIF-1α Ser 247 phosphorylation

coregulates the dimerization of HIF-1α/HIF-1β complex. HIF-1α can be phosphorylated on Ser-247 in the PAS-B domain by CK1, which destabilizes the HIF-1α/-1β complex, and thus diminishes its transcriptional activity [39]. HIF-1α/-1β dimerization is also regulated by means other than HIF-1α phosphorylation. For example, COMMD1 binds to the N-terminal domain of HIF-1α, competing with HIF-1β binding, and subsequently decreases the DNA binding and transcriptional activation of the complex [40]. Finally, the HIF-1α/p300 interaction is also post-translationally regulated. Both hydroxylation of asparagine 803 and S-nitrosylation of cysteine 800 in the C-TAD of HIF-1α decrease p300 binding, while phosphorylation of Thr-796 in the C-TAD does not affect p300 binding [41].

2.3.1 Distinct roles of HIF-α subunits

Among the three members of the HIF-α family, HIF-1α and HIF-2α (also called EPAS1, MOP2 or HLF) have been extensively studied, whereas significantly less is known about the third member, HIF-3α. HIF-α proteins exhibit high conservation in overall amino acid sequence, as well as similar domain structure, mechanisms of activation, heterodimerization with HIF-1β, and binding to the same HIF-binding site [20]. HIF- 1α and HIF-2α each contain an N-terminal activation domain and CAD, and both act as positive transcriptional regulators. In contrast, the truncated HIF-3α lacks a CAD and acts as a dominant negative regulator of transcription and its expression is suppressed in renal cell carcinoma [23].

Despite the above-mentioned similarities, there is mounting evidence that HIF-1α and HIF-2α subunits are functionally distinct. The fact that neither HIF-1α$^{-/-}$ nor HIF-2α$^{-/-}$ embryos can survive suggests a lack of functional complementation between the two isoforms [42]. The ubiquitous expression of HIF-1α, as opposed to the more cell type-specific expression of HIF-2α, also suggests different physiological roles. Knockdown of HIF-1α or HIF-2α by siRNA elicits

remarkably different cell-specific effects: in endothelial and breast cancer cells hypoxia-inducible gene expression has been demonstrated to be critically dependent on HIF-1α but not HIF-2α [43]; whereas in renal carcinoma cells, expression was critically dependent on HIF-2α [44]. HIF-α isoforms display unexpected reciprocal suppressive interactions in renal cell carcinoma: enhanced expression of HIF-2α suppresses HIF-1α and vice versa [44].

In certain cancers, HIF-1α and HIF-2α have been shown to play contrasting roles in tumorigenesis. Contrary to earlier conclusions, HIF- 1α expression was found to correlate with lower disease stages in clear cell renal cell carcinoma (ccRCC), non-small-cell lung cancer, head and neck squamous cell carcinoma and neuroblastoma; whereas HIF-2α expression was found to correlate with more advanced stages and was consistently scored as a negative prognostic factor [45]. The most compelling evidence about the distinct roles of HIF-1α and HIF-2α has been accumulated in the VHL-deficient ccRCC: while ccRCC always overexpress HIF-2α and sometimes overexpress HIF-1α, only HIF-2α is required for their growth [46]. In addition, both HIF-1α and HIF-2α, stabilized upon VHL inactivation, can transcriptionally down-regulate transcription of *HIF-1α* in ccRCC through a mechanism that involves binding of either sub- unit to a reverse HRE in the *HIF-1α* proximal promoter followed by a series of repressive his- tone modifications [47]. This observation is in agreement with previous reports suggesting that in the early stages of ccRCC HIF-1α provides a metabolic advantage due to activating glycolytic enzymes, but hinders progression by inducing cell-cycle arrest or apoptosis. Inactivation of HIF-1α and its replacement with HIF-2α discontinues this inhibitory effect and ccRCC rapidly progresses [45,48,49]. Together, these data support the notion that HIF-2α has a greater oncogenic potential than HIF-1α in ccRCC [50].

2.3.2 Distinct functions of HIF-1α and HIF-2α in certain types of cancer can be explained by differential direct and indirect transcriptional effects

HIF-1α and HIF-2α activate different sets of transcriptional targets (direct transcriptional effect). Several studies have shown that HIF-1α and HIF-2α differ in their capability to transactivate hypoxia-inducible genes. Some genes were transactivated exclusively by HIF-1α (notably glycolytic and proapoptotic genes) whereas others were transactivated by both isoforms [43,51]. HIF-2α, on the other hand, is a more efficient activator of genes encoding stem cell markers (see below). In a report that used siRNA methodology, HIF-2α preferentially regulated a small group of genes that had in common binding sites for the ETS family of transcription factors in their promoter regions. Knockdown of *ELK-1*, the most prominent member of the ETS family, significantly reduced hypoxic induction of the HIF-2α-dependent genes [52]. A number of regulatory elements (e.g., ATF-1, CREB-1, AP-1 and Sp1)have been described to cooperate with HREs, [16]; however data on whether their cognate factors preferentially engage in cooperation with HIF-1α or HIF-2α are scarce. Together, these studies suggest that, of the two isoforms, HIF-1α is a more universal activator [51], whereas HIF-2α is the more selective activator of transcription and the observed significant quantitative differences/specificity of activation could be accounted for by preferential cooperation of one isoform with transcription factors binding to the regulatory elements juxtaposed to HREs [23]. Sirtuins, a family of stress-responsive nicotinamide adenine dinucleotide-dependent histone deacetylases that serve as sensors of the cellular redox state, also control transcriptional activity of HIF-1α and HIF-2α [23]. Sirt1 was reported to deacetylate both HIF-1α and HIF-2α with different functional outcomes: deacetylation of HIF-1α decreases its transcriptional activity [53], whereas

deacetylation of HIF-2α resulted in enhanced transcriptional activity [54]. Thus, conditions of cellular redox/metabolic stress fine-tune activity of HIF-1α and HIF-2α.

HIF-1α and HIF-2α differentially modulate the activity of other transcription factors (indirect transcriptional effects). HIF-1α and HIF-2α have been reported to modulate (through direct or indirect interactions) the transcriptional activity of certain critical oncogenes/tumor suppressors with opposite outcomes. Notable in this respect is MYC, the function of which is antagonized by HIF-1α but enhanced by HIF-2α [46,55]. Differential regulation of the tumor suppressor protein p53 by HIF-1α and HIF-2α was also reported. On the one side, HIF-1α directly binds p53, inducing its stabilization, and eventually causing cell death [56,57]. Conversely, inhibition of HIF-2α has been shown to promote p53 activity and higher levels of HIF-2α contribute to increased radio- and chemo- resistance [58]. In this way, HIF-1α and HIF-2α can achieve opposing effects on tumor behavior through indirect transcriptional effects.

HIF-1α and HIF-2α also have different effects on CSCs, also known as tumor-initiating or tumor-propagating cells, which are undifferentiated cells with the capacity to self-renew and reconstitute tumors *in vivo* that are phenotypically similar to the parental tumor [59]. An important feature of CSCs is their enhanced resistance to radio- and chemo-therapy that limits DNA damage, allowing them to survive the treatment and repopulate the tumor with their progeny. CSCs thus represent an important therapeutic target and their complete elimination is expected to greatly enhance the treatment efficacy [59,60]. There are numerous reports implicating hypoxia and HIFs in CSC biology. For example, populations of cells enriched for CSCs can be isolated from glioblastoma tumors using the cell surface marker CD133 and hypoxia may promote the expansion of the CD133-positive cells through activation of HIF-1 [61]. Other reports highlight the prominent role of HIF-2α in CSCs: this isoform is selectively

expressed in CSCs, whereas HIF- 1α was expressed at comparable levels in both CSC and non-CSC (CD133-negative) populations [62]. In the same study, only targeting HIF- 2α by shRNA decreased the growth of CSC populations *in vitro*, inhibited CSC-mediated angiogenesis and significantly prolonged the survival of mice intracranially implanted with CSCs. In a separate study, HIF-2α colocalized with neural crest markers in a subset of immature cells in neuroblastoma tumors and HIF- 2α knockdown induced differentiation of these cells [63]. HIFs thus help maintain an undifferentiated state in some populations of CSCs as well as other stem and progenitor cells [60]. HIFs apparently control self-renewal and differentiation processes in these cells by means of trans- activating critical genes and the key transcription factors involved in these processes. In this category, interaction of HIF-1α with Notch1 helps maintain the undifferentiated cell state [64], whereas HIF-2α induces expression and transcriptional activity of the marker of the undifferentiated state – Oct4 [65]. HIF-2α also regulates the transcription factor Sox2 [66], which, in turn, controls pluripotency by direct regulation of Oct4 levels [67]. Recently, reprogramming of somatic cells into induced pluripotent cells was achieved through transduction of four defined transcription factors (c-MYC, KLF4, SOX2 and Oct4) all of which are transactivated by HIF [55,65,66]. Together, these reports provide evidence that HIFs directly control markers of the undifferentiated state (stemness) and are necessary for maintaining CSCs. Due to its critical role and selective activation, HIF-2α could be an important therapeutic target in CSCs.

2.3.3 Genes activated by HIF

Along with its co-activators, the HIF complex acts as a transcription factor for hundreds of genes, including *VEGF*, *NOS*, *GLUT1*, *LDH*, *CA9* and *MDR1* (Table 2.1) [69–107]. Many of these genes affect cancer progression through angiogenesis, erythropoiesis, increased glucose

metabolism, immune evasion, immortalization, genetic instability, increased invasion and metastasis, pH regulation, drug resistance, CSC maintenance and proliferation.

Table 2.1. Selected HIF target genes and their effects on cancer progression

Effect on cancer progression	Genes activated by hypoxia inducible factor-1	Ref.
Angiogenesis	*ANGPT2, C-MET, ID2, LEP, NOS, PDGF, SCF, SDF-1, VEGF*	[74–82]
Drug resistance	*MDR1*	[83]
Erythropoiesis	*EPO*	[84]
Genetic instability	*DEC1, DEC2, MSH2, MSH6*	[85–86]
Glucose metabolism	*GLUT1, GPI, HK1, HK2, LDH, MCT1, PGK1, PKM2*	[87–92]
Immortalization	*TERT*	[93]
Immune evasion	*NT5E*	[94]
Invasion	*C-MET, EDN-1, FN-1, MMP-2, MMP-14, SDF-1*	[75,81,95–98]
Metastasis	*C-MET, CXCR4, LOX, TWIST1, ZEB1*	[75,85,99–101]
pH regulation	*CA-9, CA-12*	[102]
Proliferation	*C-MYC, ID2, IGF-2, NOS,*	[76,78,103,104]
Stem cell maintenance	*ABCG2, JARID1B, OCT4, NANOG, Sox2, KLF4, c-myc, miR302*	[55,65–67,105–107]

Two of the most essential functions of cancer biology that HIF-1 activates are angiogenesis and glucose metabolism [108];the former controls oxy- gen and nutrient delivery and the latter generates energy and synthetic intermediates for growth and survival. VEGF is an important growth factor in angiogenesis and vascularization and plays a significant role in hypoxic conditions and has been demonstrated to increase *in vivo* tumor size and vascularization [109]. VEGF also plays a critical role in embryonic development – deletion of a single allele of the gene in *VEGF*-knockout mice is lethal within two weeks of development. HIF-1 activates *VEGF* transcription by binding to its HRE and VEGF synthesis increases angiogenesis [110]. NOS produces nitric oxide, which promotes angiogenesis and cell proliferation, and increases cell survival by inhibiting apoptosis. HIF-1 binds to the *NOS* HRE and thus upregulates NOS

expression and increases cancer progression [111]. Histological studies have associated increased malignancy and aggressiveness in cancers with increased HIF-1 and VEGF expression, and NOS expression has been confirmed in many cancers, including breast, head and neck, prostate and colorectal [111,112].

HIF-1 is a transcription factor for many genes involved in the glycolytic cascade, including *GLUT1* and *LDH*, which allow tumors to grow under hypoxic conditions by metabolizing glucose to lactate through anaerobic glycolysis [92,113]. One result of anaerobic glycolysis is decreased production of ROS generated by oxidative phosphorylation, which can prevent cellular senescence, and thus remove a constraint on tumor growth [114]. Another consequence of glycolysis and lactate buildup is hypoxic acidosis, which, if not prevented, would lead to a decrease in intra- cellular pH, cell damage and death. However, HIF-1 activates the synthesis of monocarboxylate transporters (e.g., MCT) that extrude lactate into the extracellular space [115] and CA-9 and CA-12, which use CO to generate HCO^- to dampen the effects of acidosis and increase cell survival. Not surprisingly, higher GLUT1 levels are correlated with poor survival in many cancers – including breast, head and neck, esophageal, stomach, bladder, ovarian, colorectal, and non-small-cell lung carcinomas – and CA-9 is used as a marker for cancer progression [1,116].

In addition to activating gene expression for cancer progression, HIF-1 decreases the effectiveness of anticancer therapies such as radiation and chemotherapy. HIF-1 itself is stabilized by radiation, even doubling its activity in the two days following therapy, due to the re-oxygenation and release of ROS that follows radiation treatment [117,118]. The radiation-induced production of ROS increases HIF-1α accumulation by reducing its degradation through an AMP- activated protein kinase (AMPK)-dependent pathway, where ROS-activated AMPK

inhibits the interaction between HIF-1α and VHL, thus preventing ubiquitination and subsequent degradation [119,120]. Increased HIF-1α levels have also been shown to decrease the effectiveness of chemo- therapy in various types of cancer [121–124], due to factors such as HIF-mediated regulation of drug efflux, cell proliferation and survival, metabolic reprogramming and inhibition of DNA damage [125]. One specific mechanism by which HIF-1 can decrease effectiveness of therapy is by activation of *MDR1* and the expression of the multiple drug resistance phenotype, which is present in the most aggressive cancers and correlates with the metastatic ability of multiple solid tumor cancers [126]. In addition, many anticancer therapeutics, such as doxorubicin, rely on the generation of ROS for cytotoxicity, but ROS stabilize HIF-1α [127]. Moreover, many therapeutics contain weakly basic moieties that can react with the acidic tumor microenvironment and lose efficacy [128].

2.4 Molecular targets of HIF-1 inhibitors

There are many different strategies for inhibiting the HIF-1 pathway. Small molecules have been shown to inhibit HIF activity through a variety of mechanisms including HIF-1α protein synthesis, HIF-1α protein stabilization, HIF-1α–HIF-1β dimerization, HIF-1 dimer DNA binding, and interactions with other proteins. There were two comprehensive reviews in 2012 by Semenza [129] and Xia *et al.* [130] that cover these mechanisms in detail and give fairly exhaustive lists of the small- molecules that inhibit at each level.

Many HIF-1 inhibitors affect the HIF-1 pathway upstream of HIF-1α synthesis (Figure 2.2). Cancer metabolism and regulation is a very complex system and it can be difficult to separate the desired effects on one pathway from another. This complexity can work for medicinal chemists in a synergistic manner by up- or down-regulating multiple pathways/targets by producing similar net results in the design and implementation of therapeutics. Conversely,

the inhibitors may have unexpected counter-productive effects which may contribute to the high late-stage clinical failures for anticancer drugs, which is around 70% for Phase II trials and 60% for Phase III trials [131]. These high attrition rates can, moreover, be attributed to several factors, including the hypoxic and acidic tumor microenvironment; veracity and fidelity of *in vitro* preclinical models; drug absorption, distribution, metabolism, excretion, and toxicity; drug delivery *in vivo*; and translation to the clinic [132].

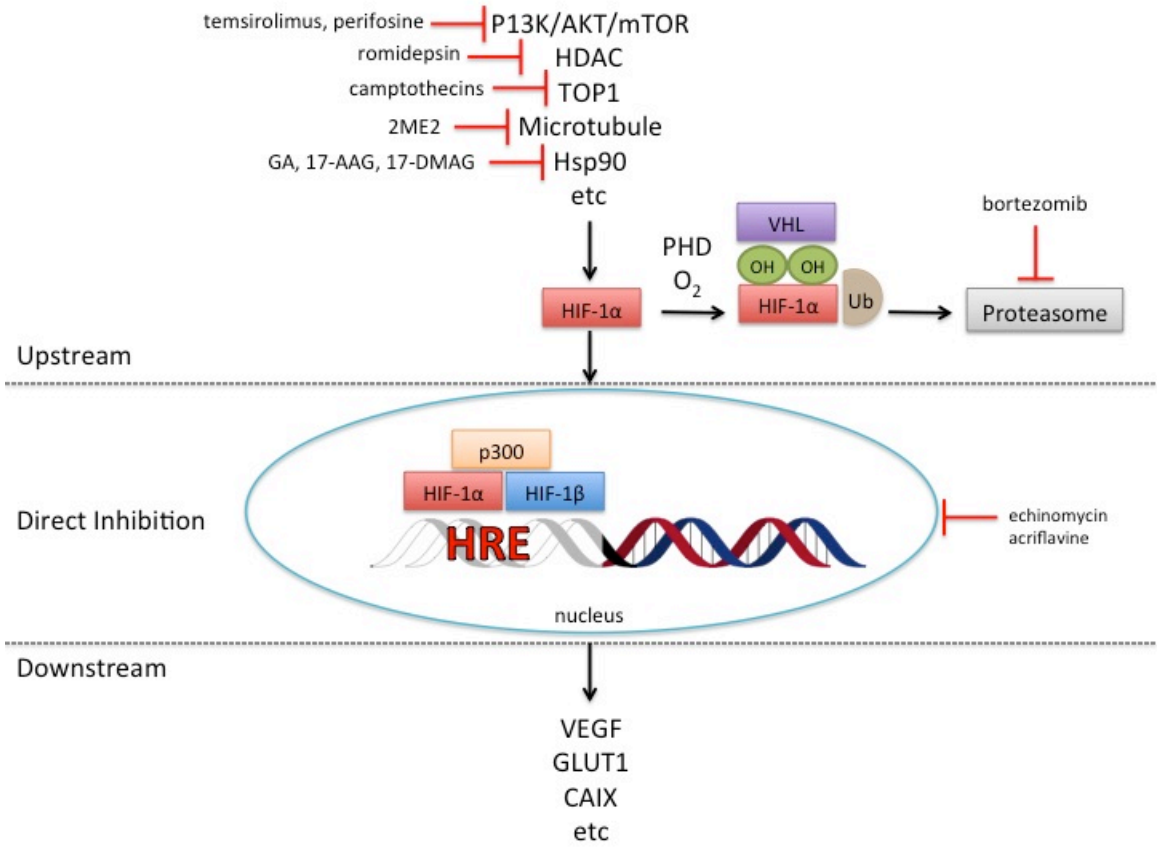


Figure 2.2. Mechanisms of HIF inhibition

HIF: Hypoxia inducible factor; HRE: Hypoxia response element; PHD: Prolyl hydroxylases; Ub: Ubiquitin chains; VHL: von Hippel-Lindau tumor suppressor protein.

In the field of HIF-1 inhibitors, the role of hypoxia is key. Tumor hypoxia has been touted as “the best validated target that has yet to be exploited in oncology” [5]. The definition of hypoxia has been well established at 0–5% oxygen, but there is a variance in the levels of oxygen defining normoxia. Atmospheric oxygen levels are approximately 20%, whereas tissues in the body have normal oxygen levels that range from 0 (bone marrow) to 14% (lung, liver, kidney and heart), with levels of approximately 10–12% in circulation [133]. Thus, *in vitro* assays that are carried out under ‘normoxic’ conditions, but are simply left open to the atmosphere ought to be considered ‘hyperoxic’ when compared to *in vivo* oxygen levels [134]. This difference in oxygen levels can contribute negatively to many preclinical studies and should be considered as a contributing factor to drug attrition.

Another factor in tumor hypoxia is the acidic extracellular environment due to the increased expression of the glycolytic phenotype. This creates a unique pH gradient for tumors that is the opposite of that of normal tissue [135]. It has been demonstrated that weakly basic anti- cancer therapeutics, such as doxorubicin, are excluded from acidic tumors [136]. This acidic microenvironment can also contribute negatively to *in vivo* studies and should be considered as another factor contributing to drug failure.

2.5 HIF-1 inhibitors in the clinic: hits and misses

Transcription factors have, for a long time, been considered undruggable targets, and to date, no specific inhibitor of HIF has been brought to market. Multiple levels of regulation and the fact that multiple signaling pathways converge on HIF-α explain the diversity of compounds that, among other targets, inhibit HIF. Although there are many challenges to targeting HIF, there have been a number of compounds that have made it to clinical trials as anticancer therapeutics, which have also been shown to inhibit HIF activity. Some of these have failed their

trials, while others have been US FDA approved for patient treatment. The following illustrates a few of these examples (Table 2.2) and what their outcomes say for the field as a whole.

2.5.1 Camptothecins: camptothecin, topotecan, irinotecan

In the 1960s, camptothecin was first isolated from the bark of a native Chinese tree, *Camptotheca acuminata*, by Wall and Wani. By the mid 1970s, camptothecin was in clinical trials due to its anticancer activity, but it was terminated because of its serious side effects [137]. Research on camptothecin was not resumed until the discovery of DNA topoisomerase 1 (TOP1) as its primary target and the successful development of water-soluble derivatives of camptothecin: topotecan (Hycamtin®) and irinotecan (Camptosar, CPT-11) [138]. The camptothecins have a unique mechanism of action that targets TOP1, an essential human enzyme that relaxes DNA supercoiling by forming single strand breaks, unwinding, then religating the strands back together. The camptothecins act as irreversible inhibitors to the TOP1–DNA complex by intercalating into DNA at the protein–DNA interface, which then prevents the religation of the DNA strands [139]. Both irinotecan and topotecan have similar mechanisms of action as camptothecin. TOP1 is an upstream regulator of the HIF-1 pathway. TOP1 inhibition leads to HIF- 1α down-regulation due to decreased protein accumulation and translation that is independent of oxygen or proteasomal degradation [140]. It has been suggested that this mechanism could be due to the activation of a novel antisense transcript from the 5′ end of *HIF-1α* and the removal of Pol II from the promoter-proximal pause site of the *HIF-1α* gene [141]. The mechanism of inhibition of HIF-1α translation by camptothecin and its derivatives is TOP1-dependent but DNA- damage independent. Irinotecan was approved for treatment of colorectal cancer in 1996 [142] and topotecan was approved for the treatment of Stage IVB recurrent carcinoma of the cervix in 2006 [303]. In 2007, the FDA approved Hycamtin for treatment of

relapsed small cell lung cancer [304]. The successful development of these camptothecin derivatives would not have been possible without further elucidation of their mechanism of action. This case illustrates how drugs (and classes of drugs) that have unknown mechanisms of action and have previously failed clinical trials can be repurposed and brought to market once the mode of action is elucidated and the pharmacokinetics optimized.

2.5.2 Bortezomib

Bortezomib (Velcade®, PS-341) is a dipep- tide boronic acid-containing compound that reversibly inhibits the chymotryptic activity of the 20S subunit of the 26S proteasome due to the high binding affinity and specificity between the boron atom and the 20S subunit [143]. The proteasome regulates protein expression and function by degradation of ubiquitinated proteins, and cleanses the cell of unfolded or misfolded proteins. Bortezomib has been shown to directly inhibit proliferation and induce apoptosis in multiple myeloma cell lines and patient tumor cells resistant to conventional therapies [144]. Proteasome inhibition by bortezomib leads to disruption of intracellular protein metabolism. The downstream biological effects of proteasome inhibition are numerous, with direct effects on both multiple myeloma cells and their microenvironment, including inhibition of cytokine secretion, suppression of adhesion molecule expression and inhibition of angiogenesis [145]. Because bortezomib's primary target is the proteasome, it prevents the degradation of ubiquitinated HIFα and leads to the accumulation of HIF-1α under normoxia. However, the stabilized HIF-1(-2) is inactive due to upregulation of FIH activity, which inhibits recruitment of p300 [146]. There has been other evidence that bortezomib does not directly affect the formation of the HIF-1-p300 complex, but interferes with the C-terminal domain of HIF-1α [147]. More recently, bortezomib was shown to inhibit the PI3K/AKT/mTOR pathway upstream of the HIF pathway in prostate cancer cells [148]. Due to

bortezomib's remarkable clinical activity against multiple myeloma, it was rapidly approved by the FDA in 2003 to treat relapsed and refractory multiple myeloma [149]. It is unknown whether HIF inhibition is critical to the clinical activity of bortezomib. Bortezomib is an excellent example of an FDA-approved anticancer therapeutic that indirectly inhibits HIF expression and function and that has differing modes of action in different cancer models, which illustrates the complexity of the field.

2.5.3 Romidepsin

Romidepsin (Istodax®, FK228, FR901228) is an anticancer agent isolated from the bacterium *Chromobacterium violaceum* that was first reported by Fujisawa Pharmaceutical Company (now Astellas Pharma) in 1994 [65]. Its mechanism of action was demonstrated in 1998 [150,151]. As a prodrug with a disulfide bond, romidepsin under- goes reduction to release a zinc-binding thiol [152]. This thiol reversibly interacts with a zinc atom in the binding pocket of Zn-dependent histone deacetylases (HDACs) to block their activity, classifying romidepsin as a HDAC inhibitor (HDACI). HDACs affect gene expression by removal of acetyl groups from acetylated lysine residues in histones. HDACs also deacetylate nonhistone proteins, such as transcription factors. *In vitro*, romidepsin causes the accumulation of acetylated histones, thus inducing cell cycle arrest and apoptosis of some cancer cell lines with IC_{50} values in the nanomolar range [153]. HDAC activity is crucial for the transactivation potential of HIF-1α and most HDACIs regulate acetylation of the HIF-1α/p300 complex [154]. It has also been suggested that the class II isozyme HDACs are involved in direct acetylation and ubiquitination of HIF-1α [155]. Romidepsin was approved as a treatment for cutaneous T-cell lymphoma in 2009 [305]. Other HDACIs are also in preclinical and clinical development, but many in the field have

moved to target other mechanisms of action due to high adverse effects associated with the HDACIs.

2.5.4 Temsirolimus

Temsirolimus (Torisel®, CCI-779), the ester version of rapamycin, is the first FDA approved inhibitor of mammalian target of rapamycin (mTOR/TORC1), which is a serine/threonine- specific kinase in the phosphatidylinositol 3–kinase (PI3K) related protein family [156]. In RCC, temsirolimus was shown to inhibit tumor growth and HIF expression by inhibition of the mTOR-dependent kinase cascade needed for *HIF* mRNA translation [157]. Inhibition of PI3K and its downstream target mTOR was demonstrated in prostate cancer (PC-3) cells to decrease HIF-1-dependent gene expression and temsirolimus was shown to suppress HIF-1 activation by increasing HIF-1α degradation rate in hypoxic PC-3 cells [158]. The FDA approved Torisel (temsirolimus) for the treatment of RCC in 2007 [306]. However, not all inhibitors of the P13K/AKT/mTOR pathway have had such success.

2.5.5 Perifosine

Perifosine is an alkylphospholipid analogue, which has demonstrated significant anti-proliferative activity in several human tumor model systems both *in vitro* and *in vivo*. It has a similar structure to miltefosine, a drug that has been approved in Europe for the treatment of cutaneous lymphomas and metastasis from breast cancer. Perifosine's activity is also due to its effect on the PI3K/AKT/mTOR pathway, an upstream regulator of the HIF pathway. Many growth factors that upregulate HIF activate the PI3K–AKT–mTOR pathway, which leads to increased HIF-1α protein translation and stability [159]. Perifosine, which inhibits AKT in a dose-dependent manner, entered Phase I clinical trials in 2003 [160] and, in 2010, reached Phase II trial due to significant growth inhibition *in vitro* and *in vivo* in the Waldenstrom

macroglobulinemia model [161]. In 2012, how- ever, perifosine failed a late-stage Phase III study on colorectal cancer due to lack of efficacy but will continue in another Phase III study as part of combination therapy with bortezomib against multiple myeloma [307]. Perifosine is one of many compounds indirectly affecting HIF expression that showed great promise in preclinical models, but has failed to exhibit efficacy in human trials.

2.5.6 2-Methoxyestradiol

2-methoxyestradiol (2ME2) is a natural metabo- lite of estradiol and is a potent antitumor agent, due to its antiproliferative, antimetastatic and antiangiogenic activity. These antitumor activities result from its pro-apoptotic activity, micro- tubule activity and production of superoxides [162]. Its main potency appears to be derived from disruption of cellular microtubules that are necessary for HIF-1α translocation to the nucleus. 2ME2 thus retards HIF-1 nuclear accumulation and activity in a manner that is both oxygen- and proteasome-independent [163]. It was subsequently found that microtubule inhibitors such as 2ME2 and taxol also inhibit HIF-1α mRNA translation [164]. A Phase I clinical trial of 2ME2 was successfully concluded in 2006 [165]. In 2011, 2ME2 nanocrystal dispersion failed to show a significant effect in a Phase II study against castration-resistant prostate cancer [166] and in 2012, in a second Phase II study against metastatic renal cell carcinoma due to both lack of objective effects and high toxicity. The cli- nicians recommended halting trials of 2ME2 in favor of a new 2ME2 analog in development [167]. Hopefully, this new analog, ENMD-1198, will have more favorable results.

2.5.7 Echinomycin

Echinomycin (quinomycin A, NSC 526417) is a cyclic peptide antibiotic agent of quinoxaline that was originally isolated from *Streptomyces echinatus* [168]. Echinomycin is

known to bind DNA in a sequence-specific manner. Binding sites for echinomycin contain the central sequence 5′-CG-3′ and the key recognition elements are contained in the sequences 5′-ACGT-3′ and 5′-TCGT-3′, which are part of the DNA recognition motifs for several transcription factors [169]. Inhibition of HIF-1 binding to the HRE (RCGTG; where R = purine A or G), a step required for induction of transcription, is a potential mechanism by which echinomycin may inhibit HIF-1 activity [170]. Echinomycin was shown in chromatin immunoprecipitation experiments to selectively inhibit binding of HIF-1 to DNA [171]. Despite echinomycin's *in vitro* apoptosis-inducing activity and the initial report of its *in vivo* antitumor effect in mice, echinomycin's clinical development was halted in the late 1980s following extensive testing as a cytotoxic agent in Phase I–II trials, which failed to show significant activity [172].

2.5.8 Ansamycins: Geldanamycin, 17-AAG, 17-DMAG

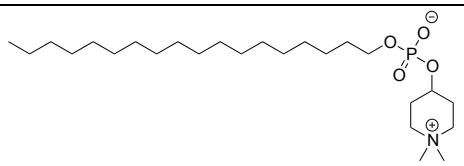
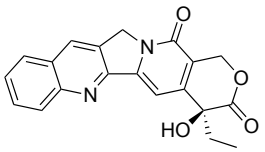
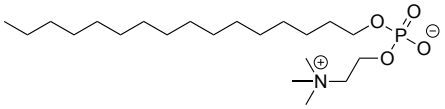
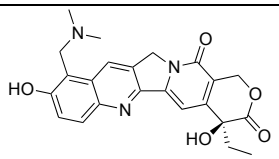
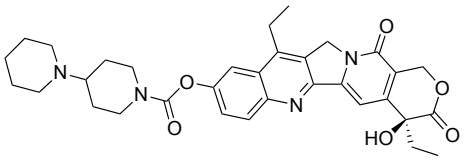
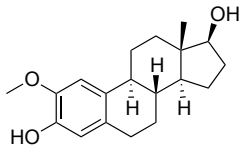
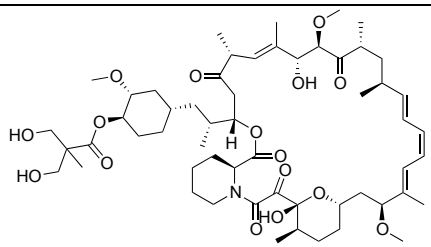
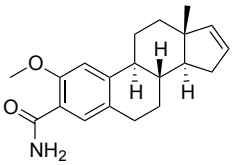
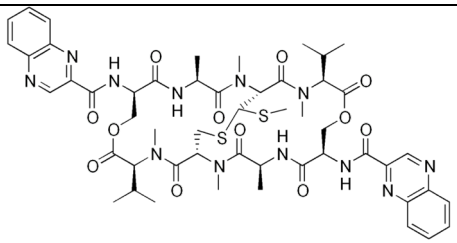
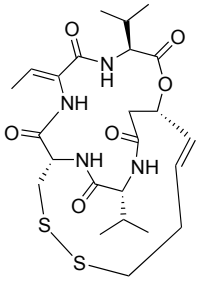
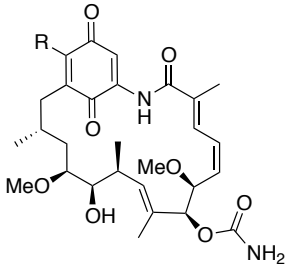
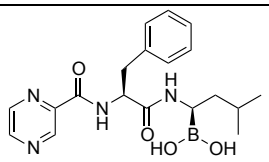
Geldanamycin (GA) is a macrocyclicpolyketide antibiotic containing a benzoquinone moiety and was originally isolated from *Streptomyces hygroscopicus* [173]. GA is a Hsp90 inhibitor, that acts by binding the N-terminal ATP-binding domain of Hsp90, leading to the destabilization and eventual degradation of Hsp90 client proteins [174–176]. Hsp90, one of the most abundant cellular proteins, assists in protein folding and degradation and is upregulated during cellular stress [177,178]. HIF is a client protein of Hsp90 and the inhibition of Hsp90 has been shown to destabilize HIF, leading to HIF degradation and decrease in transcriptional activity [179,180]. GA and its derivatives 17-AAG (tanespimycin) and 17-DMAG (alvespimycin) have demonstrated anti-tumorigenic and -angiogenic properties both *in vitro* and *in vivo*. However, GA was never brought to the clinic due to its poor pharmacological properties and hepatoxicity in animal models [181,182]. 17-AAG was the first- in-class Hsp90 inhibitor to

enter Phase I trials, where it showed promise; however, it showed poor results in Phase II trials, most likely due to its poor bioavailability and solubility [183–186]. 17-DMAG, an orally available agent, has shown promise in the clinic, with success in Phase I trials, but needs further evaluation [187,188].

2.6 Conclusions

Hypoxic conditions in the cancer micro- environment lead to increased resistance to both chemotherapy and radiotherapy. In most cases, the HIF pathway is the primary pathway responsible for this more malignant phenotype and its activation leads to increased cancer metastasis and poor patient prognosis. There has been much effort in this area to develop small-molecule inhibitors of the HIF pathway (mostly focused on HIF-1) as well as upstream and downstream effects. There have been no approved drugs that directly inhibit the HIF pathway, but there have been a few that indirectly affect the HIF path- way, as well as many more that have failed to demonstrate therapeutic efficacy in clinical trials for cancer patients. Some of these failures can be accredited to a lack of specificity and/or redundancy in the complexity of tumor signaling/ metabolism that can overcome the inhibition effects. Another contributing factor to the failure of these compounds can be attributed to the lack of patient selection in clinical trials. Although many clinical trials evaluate the efficacy of anti- cancer therapeutics and examine their effects on HIF levels, patients are not selected based on their HIF-expression levels. If patients do not have elevated levels of HIF, therapeutics that tar- get the HIF pathway may be less effective. More work needs to be done to identify novel, potent and more specific inhibitors targeting clearly defined points in the HIF pathway. Such new agents should be used in combination therapy and will hopefully overcome resistance that may develop during the initial treatment.

Table 2.2. Small anti-cancer molecules with HIF-1 inhibitory activity

 Perifosine	 Camptothecin
 Miltefosine	 Topotecan
 Irinotecan	 2-methoxylestradiol
 Temsirolimus	 ENMD-1198
 Echinomycin	 Romidepsin
 R = OMe, Geldanamycin R = N-aminoallyl, 17-AAG R = Dimethylaminoethylamino, 17-DMAG	 Bortezomib

2.7 Future Perspective

Recently, the HIF pathway was touted as "technically undruggable or at the very least as extremely challenging to target by medicinal chemists using small molecules" [189]. This attitude can be attributed not only to the difficulty of targeting such a complex pathway, but also to the challenges of targeting protein–protein interactions [190]. Small molecules typically inhibit protein function by binding with high affinity and specificity to hydrophobic pockets on or near the protein's surface. When trying to disrupt interactions between proteins, these binding sites may no longer be accessible and the interactions between proteins are so multifarious that one small molecule may not be able to interrupt the key interactions. There have been advances in this field of targeting protein–protein interaction, such as stapled peptide inhibitors of transcription factors [191] and small-molecule inhibitors of the MDM2- p53 interaction as anticancer therapeutics [192]. Some interesting features of the small molecules identified are that they tend to be large, lipophilic, and rigid structures with complex 3D shape that form few hydrogen bonds [193,194]. These structural differences vary from the typical Lipinksi rule of five for drug-like properties [195] and could portend a new paradigm for drug-like qualities for small molecules that inhibit protein-protein interactions.

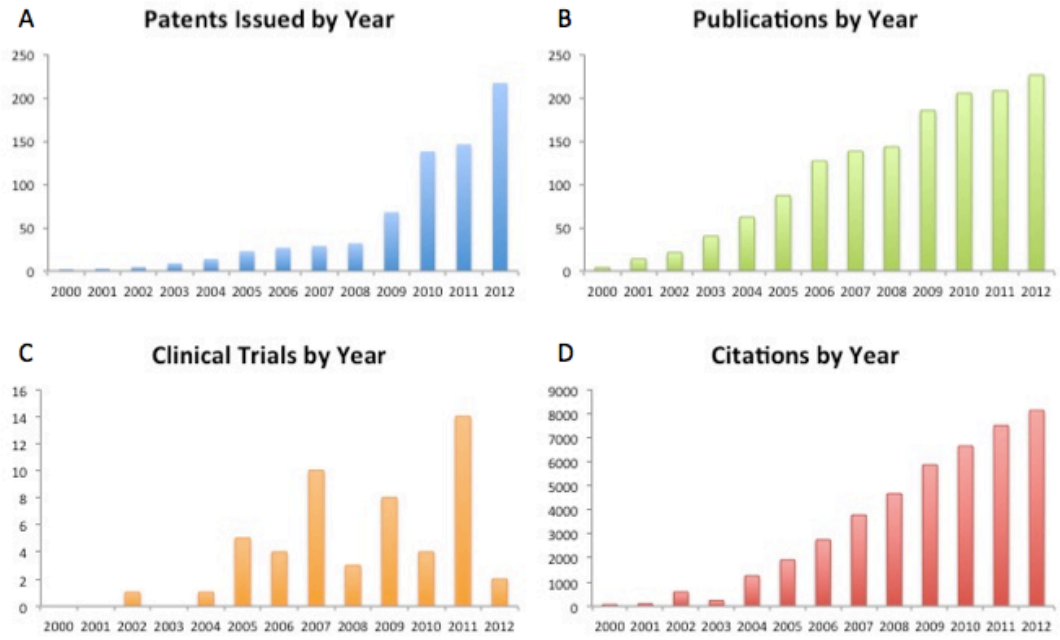


Figure 2.3. Trends of HIF inhibitors from 2000-2012

A) Number of patents issued by year. B) Number of publications by year. C) Number of clinical trials by year. D) Number of citations by year.

Interest in small-molecule inhibitors of the HIF pathway has steadily increased over the past 15 years. The number of patent applications, publications, citations and clinical trials has risen since the late 1990s and early 2000s (Figure 2.3). Although there have been few drugs that have made it all the way through clinical trials, the field is ripe and interest is increasing. It still remains to be seen whether inhibitors capable of distinguishing HIF-1 and HIF-2 complexes can be developed. In addition, new therapeutics are being developed against downstream HIF targets, such as MCT [91] and CA-IX [196]. Inhibitors of post-translational modifications of HIF-1α have also shown some promise. Kaempferol was recently shown to inactivate the p44/42 MAPK phosphorylation of HIF-1α, causing its mislocalization into the cytoplasm in hepatocellular carcinoma [197]. Results from high-throughput screenings and natural product discovery [198]

have also yielded new hits and lead compounds, but even more new methods need to be identified. Recently, novel HIF inhibitors from frankincense were identified through a new method using a molecularly imprinted polymer [199]. Acriflavine was identified as a HIF-dimerization inhibitor from a screening of drugs that had previously made it to Phase II clinical trials [200]. In addition, targeting the HIF-2α/-1β dimerization has been suggested as a valid target for anticancer therapeutics [201]. The well-known HIF/p300 interaction inhibitor chetomin [202] and its family, the epidithiodiketopiperazines, act via a mechanism of action involving disruption of the zinc-binding sites in the CH1 domain of p300 [203]. In addition, artificial a-helices have been demonstrated to interfere with the HIF/ p300 interaction [204]. Oncolytic viruses dependent upon HIF expression for their replication have also been developed and showed strong antitumor effects [205–207]. Recently, a group of collaborators, including the authors, reported a new class of HIF-1 inhibitors, that appears to target the interaction between HIF-1 and p300 and, therefore, HIF-mediated transcription [208–214]. The lead arylsulfonamide compound (KCN1) showed potent anticancer activity in several cancer models [215,216]. Moreover, these inhibitors do not show intrinsic cytotoxicity and thus are promising compounds for further clinical development.

2.8 References

1. Vaupel P, Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. *Cancer Metastasis Rev.* 26(2), 225–239 (2007).
2. Cairns RA, Kalliomaki T, Hill RP. Acute (cyclic) hypoxia enhances spontaneous metastasis of KHT murine tumors. *Cancer Res.* 61(24), 8903–8908 (2001).
3. Matsumoto S. Imaging cycling tumor hypoxia. *Cancer Res.* 70(24), 10019–10023 (2010).

4. Belozerov VE, Van Meir EG. Inhibition of hypoxia-inducible factor-1 signaling. *Curr. Opin. Investig. Drugs* 7(12), 1067–1076 (2006).
5. Wilson W, Hay M. Targeting hypoxia in cancer therapy. *Nat. Rev. Cancer* 11(6), 393–410 (2011).
6. Brown JM, Wilson WR. Exploiting tumor hypoxia in cancer treatment. *Nat. Rev. Cancer* 4, 437–447 (2004).
7. Graeber TG, Osmanian C, Jacks T *et al.* Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumors. *Nature* 379(6560), 88–91 (1996).
8. Subarsky P, Hill RP. The hypoxic tumor microenvironment and metastatic progression. *Clin. Exp. Metastasis* 20(3), 237–250 (2003).
9. Wang GL, Semenza GL. Purification and characterization of hypoxia-inducible factor 1. *J. Biol. Chem.* 270(3), 1230–1237 (1995).
10. Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O_2 tension. *Proc. Natl Acad. Sci. USA* 92(12), 5510–5514 (1995).
11. Berra E, Benizri E, Ginouves A, Volmat V, Roux D, Pouyssegur J. HIF prolyl- hydroxylase 2 is the key oxygen sensor setting low steady-state levels of HIF-1αlpha in normoxia. *EMBO J.* 22(16), 4082–4090 (2003).
12. Hirsila M, Koivunen P, Gunzler V, Kivirikko KI, Myllyharju J. Characterization of the human prolyl 4-hydroxylases that modify the hypoxia-inducible factor. *J. Biol. Chem.* 278(33), 30772–30780 (2003).

13. Maxwell PH, Wiesener MS, Chang GW *et al.* The tumor suppressor protein VHL targets hypoxia-inducible factors for oxygen- dependent proteolysis. *Nature* 399(6733), 271–275 (1999).

14. Ivan M, Kondo K, Yang HF *et al.* HIF alpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. *Science* 292(5516), 464–468 (2001).

15. Jeong JW, Bae MK, Ahn MY *et al.* Regulation and destabilization of HIF-1α by ARD1-mediated acetylation. *Cell* 111(5), 709–720 (2002).

16. Wenger RH, Stiehl DP, Camenisch G. Integration of oxygen signaling at the consensus HRE. *Sci. STKE* 2005(306), re12 (2005).

17. Kimura H, Weisz A, Ogura T *et al.* Identification of hypoxia-inducible factor 1 ancillary sequence and its function in vascular endothelial growth factor gene induction by hypoxia and nitric oxide. *J. Biol. Chem.* 276(3), 2292–2298 (2001).

18. Fath DM, Kong X, Liang D *et al.* Histone deacetylase inhibitors repress the transactivation potential of hypoxia-inducible factors independently of direct acetylation of HIF-α. *J. Biol. Chem.* 281(19), 13612–13619 (2006).

19. Dayan F, Roux D, Brahimi-Horn MC, Pouyssegur J, Mazure NM. The oxygen sensor factor-inhibiting hypoxia-inducible factor-1 controls expression of distinct genes through the bifunctional transcriptional character of hypoxia-inducible factor-1α. *Cancer Res.* 66(7), 3688–3698 (2006).

20. Kaelin WG Jr, Ratcliffe PJ. Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Mol. Cell* 30(4), 393–402 (2008).

21. Kaelin Jr WG. ROS: really involved in oxygen sensing. *Cell Metab.* 1(6), 357–358 (2005).

22. 22 Czibik G. Complex role of the HIF system in cardiovascular biology. *J. Mol. Med.* 88(11), 1101–1111 (2010).

23. Majmundar AJ, Wong WJ, Simon MC. Hypoxia-inducible factors and the response to hypoxic stress. *Mol. Cell* 40(2), 294–309 (2010).

24. Zhao S, Lin Y, Xu W *et al.* Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1 alpha. *Science* 324(5924), 261–265 (2009).

25. Dang L, White DW, Gross S *et al.* Cancer- associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* 462(7274), U739–U752 (2009).

26. Koivunen P, Lee S, Duncan CG *et al.* Transformation by the (R)-enantiomer of 2-hydroxyglutarate linked to EGLN activation. *Nature* 483(7390), U485–U144 (2012).

27. Bardos J, Ashcroft M. Negative and positive regulation of HIF-1: a complex network. *Biochim. Biophys. Acta* 25(2), 107–120 (2005).

28. Déry M-A, Michaud MD, Richard DE. Hypoxia-inducible factor 1: regulation by hypoxic and non-hypoxic activators. *Int. J. Biochem. Cell. Biol.* 37(3), 535–540 (2005).

29. Flügel D, Görlach A, Michiels C, Kietzmann T. Glycogen synthase kinase 3 phosphorylates hypoxia-inducible factor 1α and mediates its destabilization in a VHL- independent manner. *Mol. Cell. Biochem.* 27(9), 3253–3265 (2007).

30. Mottet D, Dumont V, Deccache Y *et al.* Regulation of hypoxia-inducible factor-1α protein level during hypoxic conditions by the phosphatidylinositol 3-kinase/Akt/glycogen synthase kinase 3b pathway in HepG2 cells. *J. Biol. Chem.* 278(33), 31277–31285 (2003).

31. Flügel D, Görlach A, Kietzmann T. GSK-3b regulates cell growth, migration, and angiogenesis via Fbw7 and USP28-dependent degradation of HIF-1α. *Blood* 119(5), 1292–1301 (2012).

32. Xu D, Yao Y, Lu L, Costa M, Dai W. Plk3 functions as an essential component of the hypoxia regulatory pathway by direct phosphorylation of HIF-1α. *J. Biol. Chem.* 285(50), 38944–38950 (2010).

33. Cam H, Easton JB, High A, Houghton PJ. mTORC1 signaling under hypoxic conditions is controlled by ATM-dependent phosphorylation of HIF-1α. *Mol. Cell* 40(4), 509–520 (2010).

34. Minet E, Arnould T, Michel G *et al.* ERK activation upon hypoxia: involvement in HIF-1 activation. *FEBS Lett.* 468(1), 53–58 (2000).

35. Gradin K, Takasaki C, Fujii-Kuriyama Y, Sogawa K. The transcriptional activation function of the HIF-like factor requires phosphorylation at a conserved threonine. *J. Biol. Chem.* 277(26), 23508–23514 (2002).

36. Mottet D, Ruys SPD, Demazy C, Raes M, Michiels C. Role for casein kinase 2 in the regulation of HIF-1 activity. *Int J. Cancer* 117(5), 764–774 (2005).

37. 37 Richard DE, Berra E, Gothié E, Roux D, Pouysségur J. p42/p44 mitogen-activated protein kinases phosphorylate hypoxia- inducible factor 1α (HIF-1α) and enhance the transcriptional activity of HIF-1. *J. Biol. Chem.* 274(46), 32631–32637 (1999).

38. Mylonis I, Chachami G, Samiotaki M *et al.* Identification of MAPK phosphorylation sites and their role in the localization and activity of hypoxia-inducible factor-1α. *J. Biol. Chem.* 281(44), 33095–33106 (2006).

39. Kalousi A, Mylonis I, Politou AS, Chachami G, Paraskeva E, Simos G. Casein kinase 1 regulates human hypoxia-inducible factor HIF- 1. *J. Cell Sci.* 123(17), 2976–2986 (2010).

40. VanDeSluisB,MaoX,ZhaiY*etal.* COMMD1 disrupts HIF-1alpha/beta dimerization and inhibits human tumor cell invasion. *J. Clin. Invest.* 120(6), 2119–2130 (2010).

41. Cho H, Ahn D-R, Park H, Yang EG. Modulation of p300 binding by posttranslational modifications of the C-terminal activation domain of hypoxia- inducible factor-1α. *FEBS Lett.* 581(8), 1542–1548 (2007).

42. Huang LE, Bunn HF. Hypoxia-inducible factor and its biomedical relevance. *J. Biol. Chem.* 278(22), 19575–19578 (2003).

43. Hu CJ, Wang LY, Chodosh LA, Keith B, Simon MC. Differential roles of hypoxia- inducible factor 1alpha (HIF-1alpha) and HIF- 2alpha in hypoxic gene regulation. *Mol. Cell. Biochem.* 23(24), 9361–9374 (2003).

44. Raval RR, Lau KW, Tran MGB *et al.* Contrasting properties of HIF-1 and HIF-2 in Von Hippel-Lindau-associated renal cell carcinoma. *Mol. Cell. Biol.* 25(13), 5675–5686 (2005).

45. Bertout JA, Patel SA, Simon MC. The impact of O_2 availability on human cancer. *Nat. Rev. Cancer* 8(12), 967–975 (2008).

46. Gordan JD, Lal P, Dondeti VR *et al.* HIF- alpha effects on c-Myc distinguish two subtypes of sporadic VHL-deficient clear cell renal carcinoma. *Cancer Cell* 14(6), 435–446 (2008).

47. Xu J, Wang B, Xu Y *et al.* Epigenetic regulation of HIF-1 alpha in renal cancer cells involves HIF-1 alpha/2 alpha binding to a reverse hypoxia-response element. *Oncogene* 31(8), 1065–1072 (2012).

48. Giatromanolaki A, Koukourakis MI, Sivridis E *et al.* Relation of hypoxia inducible factor 1 alpha and 2 alpha in operable non- small cell lung cancer to angiogenic/ molecular profile of tumors and survival. *Br. J. Cancer* 85(6), 881–890 (2001).

49. Franovic A, Holterman CE, Payette J, Lee S. Human cancers converge at the HIF-2α oncogenic axis. *Proc. Natl Acad. Sci. USA* 106(50), 21306–21311 (2009).

50. Biswas S, Troy H, Leek R et al. Effects of HIF-1alpha and HIF-2alpha on growth and metabolism of clear-cell renal cancer 786-0 xenografts. *J. Oncol.* 2010, 757908 (2010).

51. Sowter HM, Raval RR, Moore JW, Ratcliffe PJ, Harris AL. Predominant role of hypoxia-inducible transcription factor (HIF)-1alpha versus HIF-2alpha in regulation of the transcriptional response to hypoxia. *Cancer Res.* 63(19), 6130–6134 (2003).

52. Aprelikova O, Wood M, Tackett S, Chandramouli GV, Barrett JC. Role of ETS transcription factors in the hypoxia-inducible factor-2 target gene selection. *Cancer Res.* 66(11), 5641–5647 (2006).

53. Lim JH, Lee YM, Chun YS, Chen J, Kim JE, Park JW. Sirtuin 1 modulates cellular responses to hypoxia by deacetylating hypoxia-inducible factor 1 alpha. *Mol. Cell* 38(6), 864–878 (2010).

54. Dioum EM, Chen R, Alexander MS *et al.* Regulation of hypoxia-inducible factor 2 alpha signaling by the stress-responsive deacetylase sirtuin 1. *Science* 324(5932), 1289–1293 (2009).

55. Gordan JD, Bertout JA, Hu CJ, Diehl JA, Simon MC. HIF-2 alpha promotes hypoxic cell proliferation by enhancing c-Myc transcriptional activity. *Cancer Cell* 11(4), 335–347 (2007).

56. Moeller BJ, Dreher MR, Rabbani ZN *et al.* Pleiotropic effects of HIF-1 blockade on tumor radiosensitivity. *Cancer Cell* 8(2), 99–110 (2005).

57. An WG, Kanekal M, Simon MC, Maltepe E, Blagosklonny MV, Neckers LM. Stabilization of wild-type p53 by hypoxia- inducible factor 1 alpha. *Nature* 392(6674), 405–408 (1998).

58. Bertout JA, Majmundar AJ, Gordan JD *et al.* HIF2 alpha inhibition promotes p53 pathway activity, tumor cell death, and radiation responses. *Proc. Natl Acad. Sci. USA* 106(34), 14391–14396 (2009).

59. Hadjipanayis CG, Van Meir EG. Tumor initiating cells in malignant gliomas: biology and implications for therapy. *J. Mol. Med.* 87(4), 363–374 (2009).

60. Heddleston JM, Li Z, Lathia JD, Bao S, Hjelmeland AB, Rich JN. Hypoxia inducible factors in cancer stem cells. *Br. J. Cancer* 102(5), 789–795 (2010).

61. Soeda A, Park M, Lee D *et al.* Hypoxia promotes expansion of the CD133-positive glioma stem cells through activation of HIF-1 alpha. *Oncogene* 28(45), 3949–3959 (2009).

62. Li Z, Bao S, Wu Q *et al.* Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. *Cancer Cell* 15(6), 501–513 (2009).

63. Pietras A, Hansford LM, Johnsson AS *et al.* HIF-2 alpha maintains an undifferentiated state in neural crest-like human neuroblastoma tumor-initiating cells. *Proc. Natl Acad. Sci. USA* 106(39), 16805–16810 (2009).

64. Gustafsson MV, Zheng XW, Pereira T *et al.* Hypoxia requires notch signaling to maintain the undifferentiated cell state. *Dev. Cell* 9(5), 617–628 (2005).

65. Covello KL, Kehler J, Yu HW *et al.* HIF-2 alpha regulates Oct-4: effects of hypoxia on stem cell function, embryonic development, and tumor growth. *Genes Dev.* 20(5), 557–570 (2006).

66. Moreno-Manzano V, Rodriguez-Jimenez FJ, Acena-Bonilla JL *et al.* FM19G11, a new hypoxia-inducible factor (HIF) modulator, affects stem cell differentiation status. *J. Biol Chem.* 285(2), 1333–1342 (2010).

67. Avilion AA, Nicolis SK, Pevny LH, Perez L, Vivian N, Lovell-Badge R. Multipotent cell lineages in early mouse development depend on SOX2 function. *Genes Dev.* 17(1), 126–140 (2003).

68. Takahashi K, Tanabe K, Ohnuki M *et al.* Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 131(5), 861–872 (2007).

69. Ortiz-Barahona A, Villar D, Pescador N, Amigo J, del Peso L. Genome-wide identification of hypoxia-inducible factor binding sites and target genes by a probabilistic model integrating transcription-profiling data and *in silico* binding site prediction. *Nucleic Acids Res.* 38(7), 2332–2345 (2010).

70. Benita Y, Kikuchi H, Smith AD, Zhang MQ, Chung DC, Xavier RJ. An integrative genomics approach identifies hypoxia inducible factor-1 (HIF-1)-target genes that form the core response to hypoxia. *Nucleic Acids Res.* 37(14), 4587–4602 (2009).

71. Tanimoto K, Tsuchihara K, Kanai A *et al.* Genome-wide identification and annotation of HIF-1α binding sites in two cell lines using massively parallel sequencing. *HUGO J.* 4(1–4), 35–48 (2010).

72. Schödel J, Oikonomopoulos S, Ragoussis J, Pugh CW, Ratcliffe PJ, Mole DR. High-resolution genome-wide mapping of HIF- binding sites by ChIP-seq. *Blood* 117(23), e207–e217 (2011).

73. Mole DR, Blancher C, Copley RR *et al.* Genome-wide association of hypoxia- inducible factor (HIF)-1α and HIF-2α DNA binding with expression profiling of hypoxia- inducible transcripts. *J. Biol. Chem*. 284(25), 16767–16775 (2009).

74. Simon MP, Tournaire R, Pouyssegur J. The angiopoietin-2 gene of endothelial cells is up-regulated in hypoxia by a HIF binding site located in its first intron and by the central factors GATA-2 and Ets-1. *J. Cell Physiol.* 217(3), 809–818 (2008).

75. Pennacchietti S, Michieli P, Galluzzo M, Mazzone M, Giordano S, Comoglio PM. Hypoxia promotes invasive growth by transcriptional activation of the met protooncogene. *Cancer Cell* 3(4), 347–361 (2003).

76. Lofstedt T, Jogi A, Sigvardsson M *et al.* Induction of ID2 expression by hypoxia- inducible factor-1: a role in dedifferentiation of hypoxic neuroblastoma cells. *J. Biol. Chem.* 279(38), 39223–39231 (2004).

77. Grosfeld A, André J, Hauguel-De Mouzon S, Berra E, Pouysségur J, Guerre-Millo M. Hypoxia-inducible factor 1 transactivates the human leptin gene promoter. *J. Biol. Chem.* 277(45), 42953–42957 (2002).

78. Melillo G, Musso T, Sica A, Taylor LS, Cox GW, Varesio L. A hypoxia-responsive element mediates a novel pathway of activation of the inducible nitric oxide synthase promoter.*J. Exp. Med.* 182(6), 1683–1693 (1995).

79. Huang Y, Hickey RP, Yeh JL *et al.* Cardiac myocyte-specific HIF-1α deletion alters vascularization, energy availability, calcium flux, and contractility in the normoxic heart. *FASEB J.* 18(10), 1138–1140 (2004).

80. Han Z-B, Ren H, Zhao H *et al.* Hypoxia- inducible factor (HIF)-1α directly enhances the transcriptional activity of stem cell factor (SCF) in response to hypoxia and epidermal growth factor (EGF). *Carcinogenesis* 29(10), 1853–1861 (2008).

81. Ceradini DJ, Kulkarni AR, Tepper OM *et al.* Progenitor cell trafficking is regulated byhypoxic gradients through HIF-1 induction of SDF-1. *Nat. Med.* 10(8), 858–864 (2004).

82. Levy AP, Levy NS, Wegner S, Goldberg MA. Transcriptional regulation of the rat vascular endothelial growth factor gene by hypoxia. *J. Biol. Chem.* 270(22), 13333–13340 (1995).

83. Comerford KM, Wallace TJ, Karhausen J, Louis NA, Montalto MC, Colgan SP. Hypoxia-inducible factor-1-dependent regulation of the multidrug resistance (MDR1) gene. *Cancer Res.* 62(12), 3387–3394 (2002).

84. Semenza GL, Nejfelt MK, Chi SM, Antonarakis SE. Hypoxia-inducible nuclear factors bind to an enhancer element located 3′ to the human erythropoietin gene. *Proc. Natl Acad. Sci. USA* 88(13), 5680–5684 (1991).

85. Miyazaki K, Kawamoto T, Tanimoto K, Nishiyama M, Honda H, Kato Y. Identification of functional hypoxia response elements in the promoter region of the DEC1 and DEC2 genes. *J. Biol. Chem.* 277(49), 47014–47021 (2002).

86. Koshiji M, To KKW, Hammer S *et al.* HIF- 1α induces genetic instability by transcriptionally downregulating MutSa expression. *Mol. Cell* 17(6), 793–803 (2005).

87. Chen C, Pore N, Behrooz A, Ismail-Beigi F, Maity A. Regulation of glut1 mRNA by hypoxia-inducible factor-1: interaction between H-ras and hypoxia. *J. Biol. Chem.* 276(12), 9519–9525 (2001).

88. Yoon DY, Buchler P, Saarikoski ST, Hines OJ, Reber HA, Hankinson O. Identification of genes differentially induced by hypoxia in pancreatic cancer cells. *Biochem. Biophys. Res. Commun.* 288(4), 882–886 (2001).

89. Mathupala SP, Rempel A, Pedersen PL. Glucose catabolism in cancer cells: identification and characterization of a marked activation response of the type II hexokinase gene to hypoxic conditions. *J. Biol. Chem.* 276(46), 43407–43412 (2001).

90. Semenza GL, Jiang B-H, Leung SW *et al.* Hypoxia response elements in the aldolase A, enolase 1, and lactate dehydrogenase A gene promoters contain essential binding sites for hypoxia-inducible factor 1. *J. Biol. Chem.* 271(51), 32529–32537 (1996).

91. Sonveaux P, Copetti T, De Saedeleer CJ *et al.* Targeting the lactate transporter MCT1 in endothelial cells inhibits lactate-induced HIF- 1 activation and tumor angiogenesis. *PLoS ONE* 7(3), e33418 (2012).

92. Semenza GL, Roth PH, Fang HM, Wang GL. Transcriptional regulation of genes encoding glycolytic enzymes by hypoxia-inducible factor 1. *J. Biol. Chem.* 269(38), 23757–23763 (1994).

93. Nishi H, Nakada T, Kyo S, Inoue M, Shay JW, Isaka K. Hypoxia-inducible factor 1 mediates upregulation of telomerase (hTERT). *Mol. Cell. Biol.* 24(13), 6076–6083 (2004).

94. Synnestvedt K, Furuta GT, Comerford KM *et al.* Ecto-5′-nucleotidase (CD73) regulation by hypoxia-inducible factor-1 mediates permeability changes in intestinal epithelia. *J. Clin. Invest.* 110(7), 993–1002 (2002).

95. Huang Y, Hickey RP, Yeh JL *et al.* Cardiac myocyte-specific HIF-1alpha deletion alters vascularization, energy availability, calcium flux, and contractility in the normoxic heart. *FASEB J.* 18(10), 1138–1140 (2004).

96. Krishnamachary B, Berg-Dixon S, Kelly B *et al.* Regulation of colon carcinoma cell invasion by hypoxia-inducible factor 1. *Cancer Res.* 63(5), 1138–1143 (2003).

97. Ben-Yosef Y, Lahat N, Shapiro S, Bitterman H, Miller A. Regulation of endothelial matrix metalloproteinase-2 by hypoxia/ reoxygenation. *Circ. Res.* 90(7), 784–791 (2002).

98. Petrella BL, Lohi J, Brinckerhoff CE. Identification of membrane type-1 matrix metalloproteinase as a target of hypoxia- inducible factor-2 alpha in von Hippel-Lindau renal cell carcinoma. *Oncogene* 24(6), 1043–1052 (2005).

99. Staller P, Sulitkova J, Lisztwan J, Moch H, Oakeley EJ, Krek W. Chemokine receptor CXCR4 downregulated by von Hippel- Lindau tumor suppressor pVHL. *Nature* 425, 307–311 (2003).

100. Erler JT, Bennewith KL, Nicolau M et al. Lysyl oxidase is essential for hypoxia-induced metastasis. Nature 440(7088), 1222–1226 (2006).

101. Yang MH, Wu KJ. TWIST activation by hypoxia inducible factor-1 (HIF-1): implications in metastasis and development. Cell Cycle 7(14), 2090–2096 (2008).

102. Wykoff CC, Beasley NJP, Watson PH *et al.* Hypoxia-inducible expression of tumor-associated carbonic anhydrases. *Cancer Res.* 60(24), 7075–7083 (2000).

103. Koshiji M, Kageyama Y, Pete EA, Horikawa I, Barrett JC, Huang LE. HIF-1[alpha] induces cell cycle arrest by functionally counteracting Myc. *EMBO J.* 23(9), 1949–1956 (2004).

104. Feldser D, Agani F, Iyer NV, Pak B, Ferreira G, Semenza GL. Reciprocal positive regulation of hypoxia-inducible factor 1α and insulin-like growth factor 2. *Cancer Res.* 59(16), 3915–3918 (1999).

105. Krishnamurthy P, Ross DD, Nakanishi T *et al.* The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. *J. Biol. Chem.* 279(23), 24218–24225 (2004).

106. Beyer S, Kristensen MM, Jensen KS, Johansen JV, Staller P. The histone demethylases JMJD1A and JMJD2B are transcriptional targets of hypoxia-inducible factor HIF. *J. Biol. Chem.* 283(52), 36542–36552 (2008).

107. Mathieu J, Zhang Z, Zhou W *et al*. HIF induces human embryonic stem cell markers in cancer cells. *Cancer Res.* 71(13), 4640–4652 (2011).

108. Semenza GL. Defining the role of hypoxia- inducible factor 1 in cancer biology and therapeutics. *Oncogene* 29, 625–634 (2009).

109. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J. Clin. Oncol.* 23(5), 1011–1027 (2005).

110. Coultas L, Chawengsaksophak K, Rossant J. Endothelial cells and VEGF in vascular development. *Nature* 438(7070), 937–945 (2005).

111. Liao D, Johnson R. Hypoxia. A key regulator of angiogenesis in cancer. *Cancer Metastasis Rev.* 26(2), 281–290 (2007).

112. Jensen R, Ragel B, Whang K, Gillespie D. Inhibition of hypoxia inducible factor-1α (HIF-1α) decreases vascular endothelial growth factor (VEGF) secretion and tumor growth in malignant gliomas. *J. Neurooncol*. 78(3), 233–247 (2006).

113. Kim J-W, Gao P, Dang C. Effects of hypoxia on tumor metabolism. *Cancer Metastasis Rev.* 26(2), 291–298 (2007).

114. Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. *Cell* 120(4), 483–495 (2005).

115. Chiche J, Brahimi-Horn MC, Pouyssegur J. Tumor hypoxia induces a metabolic shift causing acidosis: a common feature in cancer. *J. Cell. Mol. Med.* 14(4), 771–794 (2010).

116. Potter C, Harris AL. Hypoxia inducible carbonic anhydrase IX, marker of tumor hypoxia, survival pathway and therapy target. *Cell Cycle* 3(3), 159–162 (2004).

117. Moeller BJ, Cao Y, Li CY, Dewhirst MW. Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors: role of reoxygenation, free radicals, and stress granules. *Cancer Cell* 5(5), 429–441 (2004).

118. Moeller B, Richardson R, Dewhirst M. Hypoxia and radiotherapy: opportunities for improved outcomes in cancer treatment. *Cancer Metastasis Rev.* 26(2), 241–248 (2007).

119. Chandel NS, Mcclintock DS, Feliciano CE *et al.* Reactive oxygen species generated at mitochondrial complex III stabilize hypoxia-inducible factor-1α during hypoxia. *J. Biol. Chem.* 275(33), 25130–25138 (2000).

120. Jung SN, Yang WK, Kim J *et al.* Reactive oxygen species stabilize hypoxia-inducible factor-1 alpha protein and stimulate transcriptional activity via AMP-activated protein kinase in DU145 human prostate cancer cells. *Carcinogenesis* 29(4), 713–721 (2008).

121. Brown LM, Cowen RL, Debray C *et al.* Reversing hypoxic cell chemoresistance *in vitro* using genetic and small molecule approaches targeting hypoxia inducible factor-1. *Mol. Pharmacol.* 69(2), 411–418 (2006).

122. Yang DI, Chen SD, Yang YT, Ju TC, Xu JM, Hsu CY. Carbamoylating chemoresistance induced by cobalt pretreatment in C6 glioma cells: putative roles of hypoxia-inducible factor-1. *Br. J. Pharmacol*. 141(6), 988–996 (2004).

123. Liu L, Ning X, Sun L *et al.* Hypoxia-inducible factor-1α contributes to hypoxia-induced chemoresistance in gastric cancer. *Cancer Sci.* 99(1), 121–128 (2008).

124. Sasabe E, Zhou X, Li D, Oku N, Yamamoto T, Osaki T. The involvement of hypoxia-inducible factor-1α in the susceptibility to g-rays and chemotherapeutic drugs of oral squamous cell carcinoma cells. *Int. J. Cancer* 120(2), 268–277 (2007).

125. Rohwer N, Cramer T. Hypoxia-mediated drug resistance: novel insights on the functional interaction of HIFs and cell death pathways. *Drug Resist. Updat.* 14(3), 191–201 (2011).

126. Comerford KM, Wallace TJ, Karhausen JR, Louis NA, Montalto MC, Colgan SP. Hypoxia-inducible factor-1-dependent regulation of the multidrug resistance (MDR1) gene. *Cancer Res.* 62(12), 3387–3394 (2002).

127. Seagroves TN. The complexity of the HIF-1- dependent hypoxic response in breast cancer presents multiple avenues for therapeutic intervention. In: *Pharmaceutical Perspectives of Cancer Therapeutics.* Springer Science and Business Media, LLC, NY, USA, 540 (2009).

128. Tan Z, Wu Y, Zhang H, Xiao X. $CoCl_2$- induced chemotherapy resistance in SW480 cells and its mechanism. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 31(3), 345–349 (2006).

129. Semenza GL. Hypoxia-inducible factors: mediators of cancer progression and targets for cancer therapy. *Trends Pharmacol. Sci.* 33(4), 207–214 (2012).

130. Xia Y, Choi H-K, Lee K. Recent advances in hypoxia-inducible factor (HIF)-1 inhibitors. *Eur. J. Med. Chem.* 49, 24–40 (2012).

131. Kola L, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug. Discov.* 3(8), 1474–1776 (2004).

132. Adams DJ. The valley of death in anticancer drug development: a reassessment. *Trends Pharmacol. Sci.* 33(4), 173–180 (2012).

133. Atkuri KR, Herzenberg LA, Herzenberg LA. Culturing at atmospheric oxygen levels impacts lymphocyte function. *Proc. Natl Acad. Sci. USA* 102(10), 3756–3759 (2005).

134. Ivanovic Z. Hypoxia or *in situ* normoxia: the stem cell paradigm. *J. Cell. Physiol.* 219(2), 271–275 (2009).

135. Gerweck LE, Seetharaman K. Cellular pH gradient in tumor versus normal tissue: potential exploitation for the treatment of cancer. *Cancer Res.* 56(6), 1194–1198 (1996).

136. Gerweck LE, Kozin SV, Stocks SJ. The pH partition theory predicts the accumulation and toxicity of doxorubicin in normal and low-pH-adapted cells. *Br. J. Cancer* 79(5–6), 838–842 (1999).

137. Wall ME, Wani MC. Camptothecin and taxol: discovery to clinic-thirteenth Bruce F. Cain memorial award lecture. *Cancer Res.* 55(4), 753–760 (1995).

138. Hsiang YH, Hertzberg R, Hecht S, Liu LF. Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. *J. Biol. Chem.* 260(27), 14873–14878 (1985).

139. Staker BL, Hjerrild K, Feese MD, Behnke CA, Burgin AB, Stewart L. The mechanism of topoisomerase I poisoning by a camptothecin analog. *Proc. Natl Acad. Sci. USA* 99(24), 15387–15392 (2002).

140. Rapisarda A, Uranchimeg B, Sordet O, Pommier Y, Shoemaker RH, Melillo G. Topoisomerase I-mediated inhibition of hypoxia-inducible factor 1. *Cancer Res.* 64(4), 1475–1482 (2004).

141. Baranello L, Bertozzi D, Fogli MV, Pommier Y, Capranico G. DNA topoisomerase I inhibition by camptothecin induces escape of RNA polymerase II from promoter-proximal pause site, antisense transcription and histone acetylation at the human HIF-1α gene locus. *Nucleic Acids Res.* 38(1), 159–171 (2010).

142. Rothenberg ML. Irinotecan (CPT-11): recent developments and future directions – colorectal cancer and beyond. *Oncologist* 6(1), 66–80 (2001).

143. Leblanc R, Catley LP, Hideshima T *et al.* Proteasome inhibitor PS-341 inhibits human myeloma cell growth *in vivo* and prolongs survival in a murine model. *Cancer Res.* 62(17), 4996–5000 (2002).

144. Hideshima T, Richardson P, Chauhan D *et al.* The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res.* 61(7), 3071–3076 (2001).

145. Hideshima T, Richardson PG, Anderson KC. Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma. *Mol. Cancer Ther.* 10(11), 2034–2042 (2011).

146. Shin DH, Chun Y-S, Lee DS, Huang LE, Park JW. Bortezomib inhibits tumor adaptation to hypoxia by stimulating the FIH-mediated repression of hypoxia-inducible factor-1. *Blood* 111(6), 3131–3136 (2008).

147. Kaluz S, Kaluzova M, Stanbridge EJ. Proteasomal inhibition attenuates transcriptional activity of hypoxia-inducible factor 1 (HIF-1) via specific effect on the HIF-1α C-terminal activation domain. *Mol. Cell. Biol.* 26(15), 5895–5907 (2006).

148. Befani C, Vlachostergios P, Hatzidaki E *et al.* Bortezomib represses HIF-1α protein expression and nuclear accumulation by inhibiting both PI3K/Akt/TOR and MAPK pathways in prostate cancer cells. *J. Mol. Med.* 90(1), 45–54 (2012).

149. Bross PF, Kane R, Farrell AT *et al.* Approval summary for Bortezomib for injection in the treatment of multiple myeloma. *Clin. Cancer Res.* 10(12), 3954–3964 (2004).

150. Ueda H, Nakajima H, Hori Y *et al.* FR901228, a novel antitumor bicyclic depsipeptide produced by *Chromobacterium violaceum* No. 968. I. Taxonomy, fermentation, isolation, physico- chemical and biological properties, and antitumor activity. *J. Antibiot.* 47(3), 301–310 (1994).

151. Nakajima H, Kim YB, Terano H, Yoshida M, Horinouchi S. FR901228, a potent antitumor antibiotic, is a novel histone deacetylase inhibitor. *Exp. Cell Res.* 241(1), 126–133 (1998).

152. Shigematsu N, Ueda H, Takase S, Tanaka H, Yamamoto K, Tada T. FR901228, a novel antitumor bicyclic depsipeptide produced by *Chromobacterium violaceum* No. 968. II. Structure determination. *J. Antibiot.* 47(3), 311–314 (1994).

153. H, Manda T, Matsumoto S *et al.* FR901228, a novel antitumor bicyclic depsipeptide produced by *Chromobacterium violaceum* No. 968. III. Antitumor activities on experimental tumors in mice. *J. Antibiot.* 47(3), 315–323 (1994).

154. Fath DM, Kong X, Liang D *et al.* Histone deacetylase inhibitors repress the transactivation potential of hypoxia-inducible factors independently of direct acetylation of HIF-1α. *J. Biol. Chem.* 281(19), 13612–13619 (2006).

155. Qian DZ, Kachhap SK, Collis SJ *et al.* Class 167 II histone deacetylases are associated with VHL-independent regulation of hypoxia- inducible factor 1α. *Cancer Res.* 66(17), 8814–8821 (2006).

156. Rini BI. Temsirolimus, an inhibitor of mammalian target of rapamycin. *Clin. Cancer Res.* 14(5), 1286–1290 (2008).

157. Thomas GV, Tran C, Mellinghoff IK *et al.* Hypoxia-inducible factor determines sensitivity to inhibitors of mTOR in kidney cancer. *Nat. Med.* 12(1), 122–127 (2006).

158. Hudson CC, Liu M, Chiang GG *et al.* Regulation of hypoxia-inducible factor 1α expression and function by the mammalian 170 target of rapamycin. *Mol. Cell. Biol.* 22(20), 7004–7014 (2002).

159. Zhong H, Chiles K, Feldser D *et al.* Modulation of hypoxia-inducible factor 1α 171 expression by the epidermal growth factor/ phosphatidylinositol 3-kinase/PTEN/AKT/ FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. *Cancer Res.* 60(6), 1541–1545 (2000).

160. Kondapaka SB, Singh SS, Dasmahapatra GP, Sausville EA, Roy KK. Perifosine, a novel alkylphospholipid, inhibits protein kinase B activation. *Mol. Cancer Ther.* 2(11), 1093–1103 (2003).

161. Ghobrial IM, Leleu X, Rubin N *et al.* Phase II trial of the novel oral Akt inhibitor perifosine in relapsed and/or refractory Waldenstrom macroglobulinemia (WM). *J. Clin. Oncol.* 26(Suppl. 15), 8546 (2008).

162. Lakhani NJ, Sarkar MA, Venitz J, Figg WD. 2-Methoxyestradiol, a promising anticancer agent. *Pharmacotherapy* 23(2), 165–172 (2003).

163. Mabjeesh NJ, Escuin D, Lavallee TM *et al.* 2ME2 inhibits tumor growth and angiogenesis by disrupting microtubules and dysregulating HIF. *Cancer Cell* 3(4), 363–375 (2003)

164. Carbonaro M, O'Brate A, Giannakakou P. Microtubule disruption targets HIF-1α mRNA to cytoplasmic P-bodies for translational repression. *J. Cell Biol.* 192(1), 83–99 (2011).

165. Dahut WL, Lakhani NJ, Gulley JL *et al.* Phase I clinical trial of oral 2-methoxyestradiol, an antiangiogenic and apoptotic agent, in patients with solid tumors. *Cancer Biol. Ther.* 5(1), 22–27 (2006).

166. Harrison MR, Hahn N, Pili R *et al.* Phase II study of 2-methoxyestradiol (2ME2) NanoCrystal Dispersion (NCD) in patients with taxane-refractory, metastatic hormone-refractory prostate cancer (HRPC). *J. Clin. Oncol.* 26(Suppl. 15), 5173 (2008).

167. Bruce J, Eickhoff J, Pili R *et al.* A Phase II study of 2-methoxyestradiol nanocrystal colloidal dispersion alone and in combination with sunitinib malate in patients with metastatic renal cell carcinoma progressing on sunitinib malate. *Invest. New Drugs* 30(2), 794–802 (2012).

168. Formica JV, Waring MJ. Effect of phosphate and amino acids on echinomycin biosynthesis by *Streptomyces echinatus*. *Antimicrob. Agents Chemother.* 24(5), 735–741 (1983).

169. Van Dyke M, Dervan P. Echinomycin binding sites on DNA. *Science* 225(4667), 1122–1127 (1984).

170. Nickols NG, Jacobs CS, Farkas ME *et al*. Modulating hypoxia-inducible transcription by disrupting the HIF-1-DNA interface. *ACS Chem. Biol.* 2(8), 561–571 (2007).

171. Kong D, Park EJ, Stephen AG *et al.* Echinomycin, a small-molecule inhibitor of hypoxia-inducible factor-1 DNA-binding activity. *Cancer Res.* 65(19), 9047–9055 (2005).

172. Onnis B, Rapisarda A, Melillo G. Development of HIF-1 inhibitors for cancer therapy. *J. Cell. Mol. Med.* 13(9a), 2780–2786 (2009).

173. Deboer C, Meulman PA, Wnuk RJ, Peterson DH. Geldanamycin, a new antibiotic. *J. Antibiot.* 23(9), 442–447 (1970).

174. Sato S, Fujita N, Tsuruo T. Modulation of Akt kinase activity by binding to Hsp90. *Proc. Natl Acad. Sci. USA* 97(20), 10832–10837 (2000).

175. Whitesell L, Mimnaugh EG, De Costa B, Myers CE, Neckers LM. Inhibition of heat shock protein HSP90-pp60v-src heteroprotein complex formation by benzoquinone ansamycins: essential role for stress proteins in oncogenic transformation. *Proc. Natl Acad. Sci. USA* 91(18), 8324–8328 (1994).

176. Dehner A, Furrer J, Richter K, Schuster I, Buchner J, Kessler H. NMR chemical shift perturbation study of the N-terminal domain of Hsp90 upon binding of ADP, AMP-PNP, geldanamycin, and radicicol. *ChemBioChem* 4(9), 870–877 (2003).

177. Taipale M, Jarosz DF, Lindquist S. HSP90 at the hub of protein homeostasis: emerging mechanistic insights. *Nat. Rev. Mol. Cell Biol.* 11(7), 515–528 (2010).

178. Bagatell R, Whitesell L. Altered Hsp90 function in cancer: a unique therapeutic opportunity. *Mol. Cancer Ther.* 3(8), 1021–1030 (2004).

179. Minet E, Mottet D, Michel G *et al.* Hypoxia- induced activation of HIF-1: role of HIF-1αlpha-Hsp90 interaction. *FEBS Lett.* 460(2), 251–256 (1999).

180. Mabjeesh NJ, Post DE, Willard MT, Kaur B *et al.* Geldanamycin induces degradation of hypoxia-inducible factor 1αlpha protein via the proteosome pathway in prostate cancer cells. *Cancer Res.* 62(9), 2478–2482 (2002).

181. Supko JG, Hickman RL, Grever MR, Malspeis L. Preclinical pharmacologic evaluation of geldanamycin as an antitumor agent. *Cancer Chemother. Pharmacol.* 36(4), 305–315 (1995).

182. Neckers LM. Chaperoning oncogenes: Hsp90 as a target of geldanamycin. *Handb. Exp. Pharmacol.* 172, 259–277 (2006).

183. Richardson PG, Chanan-Khan AA, Alsina M *et al.* Tanespimycin monotherapy in relapsed multiple myeloma: results of a Phase I dose- escalation study. *Br. J. Haematol.* 150(4), 438–445 (2010).

184. Solit DB, Osman I, Polsky D *et al.* Phase II trial of 17-allylamino-17-demethoxygeldanamycin in patients with metastatic melanoma. *Clin. Cancer Res.* 14(24), 8302–8307 (2008).

185. Ronnen EA, Kondagunta GV, Ishill N *et al.* A Phase II trial of 17-(allylamino)-17-demethoxygeldanamycin in patients with papillary and clear cell renal cell carcinoma. *Invest. New Drugs* 24(6), 543–546 (2006).

186. Heath EI, Hillman DW, Vaishampayan U *et al.* A Phase II trial of 17-allylamino-17-demethoxygeldanamycin in patients with hormone-refractory metastatic prostate cancer. *Clin. Cancer Res.* 14(23), 7940–7946 (2008).

187. Pacey S, Wilson RH, Walton M *et al.* A Phase I study of the heat shock protein 90 inhibitor alvespimycin (17-DMAG) given intravenously to patients with advanced solid tumors. *Clin. Cancer Res.* 17(6), 1561–1570 (2011).

188. Kaufmann SH, Karp JE, Litzow MR *et al.* Phase I and pharmacological study of cytarabine and tanespimycin in relapsed and refractory acute leukemia. *Haematologica* 96(11), 1619–1626 (2011).

189. Hoelder S, Clarke PA, Workman P. Discovery of small molecule cancer drugs: successes, challenges and opportunities. *Mol. Oncol.* 6(2), 155–176 (2012).

190. Valkov E, Sharpe T, Marsh M, Greive S, Hyvönen M. Targeting protein–protein interactions and fragment-based drug discovery. In: *Fragment-Based Drug Discovery and X-*

Ray Crystallography. Davies TG, Hyvönen M (Eds). Springer Berlin/ Heidelberg, Germany, 145–179 (2012).

191. Verdine GL, Hilinski GJ. All-hydrocarbon stapled peptides as synthetic cell-accessible mini-proteins. *Drug Discov. Today Technol.* 9(1), e41–e47 (2012).

192. Shangary S, Wang S. Targeting the 204 MDM2-p53 interaction for cancer therapy. *Clin. Cancer Res.* 14(17), 5318–5324 (2008).

193. Higueruelo AP, Schreyer A, Bickerton GRJ, Pitt WR, Groom CR, Blundell TL. Atomic interactions and profile of small molecules disrupting protein–protein interfaces: the 205 TIMBAL database. *Chem. Biol. Drug Des.* 74(5), 457–467 (2009).

194. Fry DC. Drug-like inhibitors of protein- protein interactions: a structural examination 206 of effective protein mimicry. *Curr. Protein Pept. Sci.* 9(3), 240–247 (2008).

195. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and 207 permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 46(1–3), 3–26 (2001).

196. M. Monti S, T. Supuran C, De Simone G. Carbonic anhydrase IX as a target for 208 designing novel anticancer drugs. *Curr. Med. Chem.* 19(6), 821–830 (2012).

197. Mylonis I, Lakka A, Tsakalof A, Simos G. The dietary flavonoid kaempferol effectively 209 inhibits HIF-1 activity and hepatoma cancer cell viability under hypoxic conditions. *Biochem. Biophys. Res. Commun.* 398(1), 74–78 (2010). 210

198. Nagle D-G, Zhou Y-D. Natural product- based inhibitors of hypoxia-inducible factor-1 (HIF-1). *Curr. Drug Targets* 7(3), 355–369 (2006). 211

199. Lakka A, Mylonis I, Bonanou S, Simos G, Tsakalof A. Isolation of hypoxia-inducible factor 1 (HIF-1) inhibitors from frankincense using a molecularly imprinted polymer. *Invest. New Drugs* 29(5), 1081–1089 (2011). 212

200. Lee K, Zhang H, Qian DZ, Rey S, Liu JO, Semenza GL. Acriflavine inhibits HIF-1 dimerization, tumor growth, and vascularization. *Proc. Natl Acad. Sci. USA* 106(42), 17910–17915 (2009).

201. Scheuermann TH, Tomchick DR, Machius M, Guo Y, Bruick RK, Gardner KH. Artificial ligand binding within the HIF2α PAS-B domain of the HIF2 transcription factor. *Proc. Natl Acad. Sci. USA* 106(2), 450–455 (2009). 213

202. Kung AL, Zabludoff SD, France DS *et al.* Small molecule blockade of transcriptional coactivation of the hypoxia-inducible factor pathway. *Cancer Cell* 6(1), 33–43 (2004).

203. Cook KM, Hilton ST, Mecinović J, Motherwell WB, Figg WD, Schofield CJ. Epidithiodiketopiperazines block the interaction between hypoxia-inducible factor- 1α (HIF-1α) and p300 by a zinc ejection mechanism. *J. Biol. Chem.* 284(39), 26831–26838 (2009).

204. Henchey LK, Kushal S, Dubey R, Chapman RN, Olenyuk BZ, Arora PS. Inhibition of hypoxia inducible factor 1-transcription coactivator interaction by a hydrogen bond surrogate a-helix. *J. Am. Chem. Soc.* 132(3), 941–943 (2009).

205. Post DE, Van Meir EG. A novel hypoxia- inducible factor (HIF) activated oncolytic adenovirus for cancer therapy. *Oncogene* 22(14), 2065–2072 (2003).

206. Post DE, Devi NS, Li ZC *et al*. Cancer therapy with a replicating oncolytic adenovirus targeting the hypoxic microenvironment of tumors. *Clin. Cancer Res.* 10(24), 8603–8612 (2004).

207. Post DE, Sandberg EM, Kyle MM *et al*. Targeted cancer gene therapy using a hypoxia inducible factor-dependent oncolytic adenovirus armed with interleukin-4. *Cancer Res.* 67(14), 6872–6881 (2007).

208. Tan C, de Noronha RG, Roecker AJ *et al.* Identification of a novel small-molecule inhibitor of the hypoxia-inducible factor 1 pathway. *Cancer Res.* 65(2), 605–612 (2005).

209. Narita T, Yin S, Gelin CF *et al*. Identification of a Novel Small Molecule HIF-1 alpha Translation Inhibitor. *Clin. Cancer Res*. 15(19), 6128–6136 (2009).

210. Tan C, de Noronha RG, Devi NS *et al.* Sulfonamides as a new scaffold for hypoxia inducible factor pathway inhibitors. *Bioorg. Med. Chem. Lett.* 21(18), 5528–5532 (2011).

211. Mooring SR, Jin H, Devi NS *et al.* Design and synthesis of novel small-molecule inhibitors of the hypoxia inducible factor pathway. *J. Med. Chem.* 54(24), 8471–8489 (2011).

212. Mun J, Jabbar AA, Devi NS, Liu Y, Van Meir EG, Goodman MM. Structure–activity relationship of 2,2-dimethyl-2H-chromene based arylsulfonamide analogs of 3,4-dimethoxy-*N*-[(2,2-dimethyl-2H- chromen-6-yl)methyl]-*N*- phenylbenzenesulfonamide, a novel small molecule hypoxia inducible factor-1 (HIF-1) pathway inhibitor and anti-cancer agent. *Bioorg. Med. Chem.* 20(14), 4590–4597 (2012).

213. Mun J, Jabbar AA, Devi NS *et al.* Design and *in vitro* activities of *N*-alkyl-*N*-[(8-R-2,2-dimethyl-2H-chromen-6-yl)methyl] heteroarylsulfonamides, novel, small-molecule hypoxia inducible factor-1 pathway inhibitors and anticancer agents. *J. Med. Chem.* 55(15), 6738–6750 (2012).

214. Shi Q, Yin S, Kaluz S *et al.* Binding model for the interaction of anticancer arylsulfonamides with the p300 transcription cofactor. *ACS Med. Chem. Lett.* 3(8), 620–625 (2012).

215. Yin S, Kaluz S, Devi NS *et al.* Arylsulfonamide KCN1 inhibits *in vivo* glioma growth and interferes with HIF signaling by disrupting HIF-1 alpha interaction with cofactors p300/CBP. *Clin. Cancer Res.* 18(24), 6623–6633 (2012).

216. Wang W, Ao L, Rayburn ER *et al*. KCN1, a novel synthetic sulfonamide anticancer agent: *in vitro* and *in vivo* anti-pancreatic cancer activities and preclinical pharmacology. *PLoS ONE* 7(9), e44883 (2012).

Websites:

300. American Cancer Society. Cancer facts and figures 2011.

301. www.cancer.org/Research/ CancerFactsFigures/CancerFactsFigures/ cancer-facts-figures-2011 (Accessed 11 April 2012)

302. World Cancer Research Fund International. General world cancer statistics: GLOBOCAN 2008 database. www.wcrf.org/cancer_statistics/world_ cancer_statistics.php (Accessed 1 April 2012)

303. US FDA approves topotecan hydrochloride (hycamtin) in combination with cisplatin for the treatment of Stage IVB recurrent or persistent carcinoma of the cervix. www.fda.gov/AboutFDA/CentersOffices/ OfficeofMedicalProductsandTobacco/ CDER/ucm095638.htm (Accessed 30 April 2012)

304. GlaxoSmith Kline receives approval for hycamtin (topotecan) capsules for the treatment of relapsed small cell lung cancer. www.drugs.com/newdrugs/gsk-receives- approval-hycamtin-topotecan-capsules- relapsed-small-cell-lung-cancer-671.html (Accessed 4 May 2012)

305. National Cancer Institute. Romidepsin. www.cancer.gov/cancertopics/druginfo/ romidepsin (Accessed 1 June 2011)

306. US FDA approves new drug for advanced kidney cancer. www.fda.gov/NewsEvents/Newsroom/ PressAnnouncements/2007/ucm108924.htm (Accessed 4 May 2012)

307. Genetic Engineering & Biotechnology News. Aeterna Zentaris regains North American rights to Akt inhibitor from Keryx. www.genengnews.com/gen-news-highlights/ aeterna-zentaris-regains-north-american- rights-to-akt-inhibitor-from-keryx/81246731/ (Accessed 11 May 2012)

308. Patent Database Search Results: ISD 1/1/2000->12/31/2012 AND HIF AND cancer AND inhibitor in US Patent Collection. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&u=%2Fnetaht ml%2FPTO%2Fsearch-adv.htm&r=0&f=S&l=50&d=PTXT&RS=%28%28%28ISD% 2F20120101-%3E20121231+AND+HIF%29+AND+Cancer%29+AND+inhibitor%29& Refine=Refine+Search&Refine=Refine+Search&Query=ISD%2F1%2F1%2F2000-%3E1 2%2F31%2F2012+AND+HIF+AND+Cancer+AND+inhibitor (Accessed 26 February 2013)

309. Web of Knowledge – All Database Results: Topic=(HIF AND CANCER AND INHIBITOR) Timespan=2000-2012. http://apps.webofknowledge.com/summary.do?SID=1F83DLk7akON2aaKN9E&produc t=UA&qid=18&search_ mode=GeneralSearch (Accessed 26 February 2013)

310. Search of: HIF and cancer – List Results – ClinicalTrials.gov. www.clinicaltrials.gov/ct2/results?term=hif+a nd+cancer+&Search=Search(Accessed 26 February 2013)

3 DESIGN AND SYNTHESIS OF WATER SOLUBLE HIF-1 INHIBITORS AS ANTI-CANCER THERAPEUTICS

The work presented in this chapter is based on a manuscript in preparation for submission to ACS Medicinal Chemistry Letters. This chapter includes compounds synthesized by Jalisa Holmes and Zeus de los Santos.

3.1 Abstract

Cancer is a leading cause of death and while progress has been made in this field, we need more effective drugs to target cancer only and not healthy cells. Thus, our goal is to target hypoxic tumors and specifically the HIF pathway. Another important factor besides potency is drug-like properties. The compounds described herein have been designed for both of these purposes and evaluated.

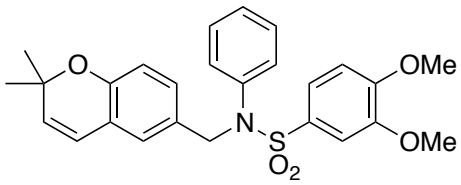
3.2 Introduction

Cancer is one of the leading causes of death, second only to heart disease.[1] One of the hallmarks of cancer is the formation of hypoxic, low oxygen, areas inside of solid tumors.[2] This hypoxic tumor microenvironment leads to many changes such as the upregulation of pro-angiogenic and pro-glycolytic pathways, as well as increased cell proliferation, genetic instability, and metastatic potential.[3] A major mediator of the hypoxic response is the Hypoxia Inducible Factor (HIF) pathway.[4] HIF consists of two parts, HIF-α, which is regulated by oxygen, and HIF-β, which is constitutively expressed.[5] There are 3 known isoforms of HIF-α: HIF-1α, HIF-2α, and HIF-3α, with HIF-1α being the most common and of which there has been the most study. Under normoxic conditions, HIF-α is hydroxylated by prolyl hydroxylase (PHD) using molecular oxygen and then degraded via a VHL-dependent ubiquitination pathway.[6] Under

hypoxic conditions, however, HIF-α and HIF-β form a heterodimer, which, along with co-activators such as p300 and CBP, forms the active transcription complex, which binds to 5'-HRE (hypoxic response element) promoter regions that are found in hundreds of genes.[7] Increased levels of HIF-α have been linked to cancer progression and poor patient outcome. HIF is becoming an attractive target for anti-cancer therapeutics.[8]

3.3 Design

A library of 10,000 products containing the 2,2-dimethyl-2*H*-chromene moiety[9] was screened for HIF pathway inhibition, with the identification of one compound designated KCN-1 (Figure 3.1, **1**, *N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide) showing potent inhibition activity (IC_{50} of 0.59 μM).[10]



1

Figure 3.1. Lead Compound KCN-1

1 was then taken on to further *in vivo* studies and demonstrated anticancer activity against brain, eye, and pancreatic cancers.[11] In addition, mice treated with **1** did not show any negative side effects. However, due to its poor solubility in water (0.009 μM), **1** was used in a 1:1 Cremophor:ethanol formulation. This type of formulation is non-ideal and can cause problems with anti-cancer therapeutics.[12] Thus, we are interested in designing more water-soluble KCN-1 analogs.

3.4 Results and Discussion

Based off of our previous studies, we decided to modify the structure of the lead compound **1** by incorporating the very water-soluble morpholine moiety into the structure. In order to accomplish this, we devised 4 classes of compounds (Figure 3.2): Class A, which incorporates a morpholinomethylphenyl or morpholinophenyl moiety instead of the 2,2-dimethyl-2*H*-chromene moiety and maintains the *N*-phenyl group; Class B, which incorporates either a morpholinomethylphenyl or morpholinophenyl moiety instead of the 2,2-dimethyl-2*H*-chromene moiety and substitutes the *N*-phenyl group for an *N*-cyclobutyl group; Class C, which has either a 2,2-dimethyl-2*H*-chromene or *N*-(2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl) moiety and either an *N*-ethylmorpholino or N-propylmorpholino group instead of the N-phenyl, and Class D, which has the 2,2-dimethyl-2*H*-chromene moiety with a *N*-phenyl-morpholine-4-sulfonamide.

Synthesis of Class A compounds (Figure 3.3) was afforded in 4 steps from 2, 3, or 4-bromomethylbenzylbromide **6a-c** or in 2 steps from 4-morpholinobenzaldehyde **8d**. **6a-c** were substituted with morpholine to yield morpholinomethylbenzylbromides **7a-c** in quantitative yield. Next, the phenyl bromides **7a-c** were converted to benzaldehydes **8a-c** via lithium-halogen exchange followed by treatment with DMF as the electrophile. The aldehydes **8a-d** underwent reductive amination with aniline to afford the secondary amines **9a-d**. Finally, **9a-d** were reacted with 3,4-dimethoxybenzenesulfonyl chloride to afford sulfonamides **2a-d**. Class B compounds (Figure 3.3) were synthesized in almost the same fashion as Class A, except that reductive amination of **8a-d** was with cyclobutylamine and was not catalyzed by any Lewis acid.

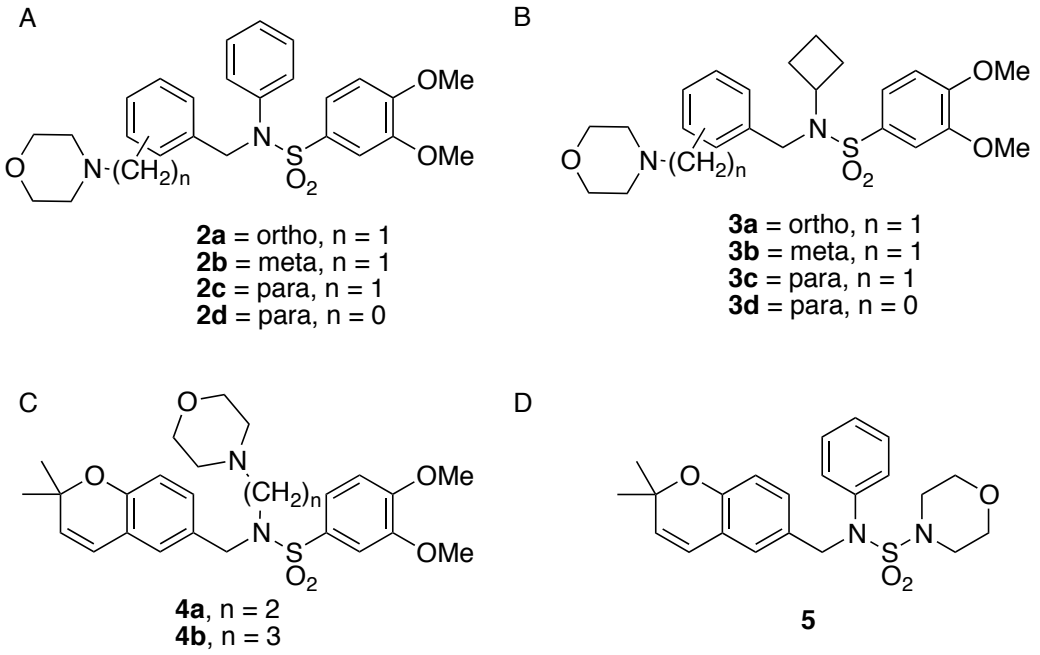


Figure 3.2. Classes of analogs.

A) Class A, morpholinomethylphenyl in ortho, meta, or para positions, or morpholinophenyl in para position; B) Class B, morpholinomethylphenyl in ortho, meta, or para positions, or morpholinophenyl in para position; C) Class C, n = 2 or 3; D) Class D.

Class C compounds were synthesized (Figure 3.4) from 2,2-dimethyl-2*H*-chromene-6-carbaldehyde **11**, which was readily synthesized from published procedures.[13] The aldehyde **11** underwent reductive amination with either ethylaminomorpholine or propylaminomorpholine to give secondary amines **12a-b**, which were then reacted with 3,4-dimethoxybenzenesulfonyl chloride to afford sulfonamides **4a-b.**

Class D compounds were synthesized (Figure 3.5) from **11** in 2 steps. First, **11** was underwent reductive amination with either aniline or cyclobutylamine to give secondary amines **13a-b**. Next, the amines **13a-b** were reacted with 4-morpholinosulfonyl chloride to afford sulfonamides **5a-b.**

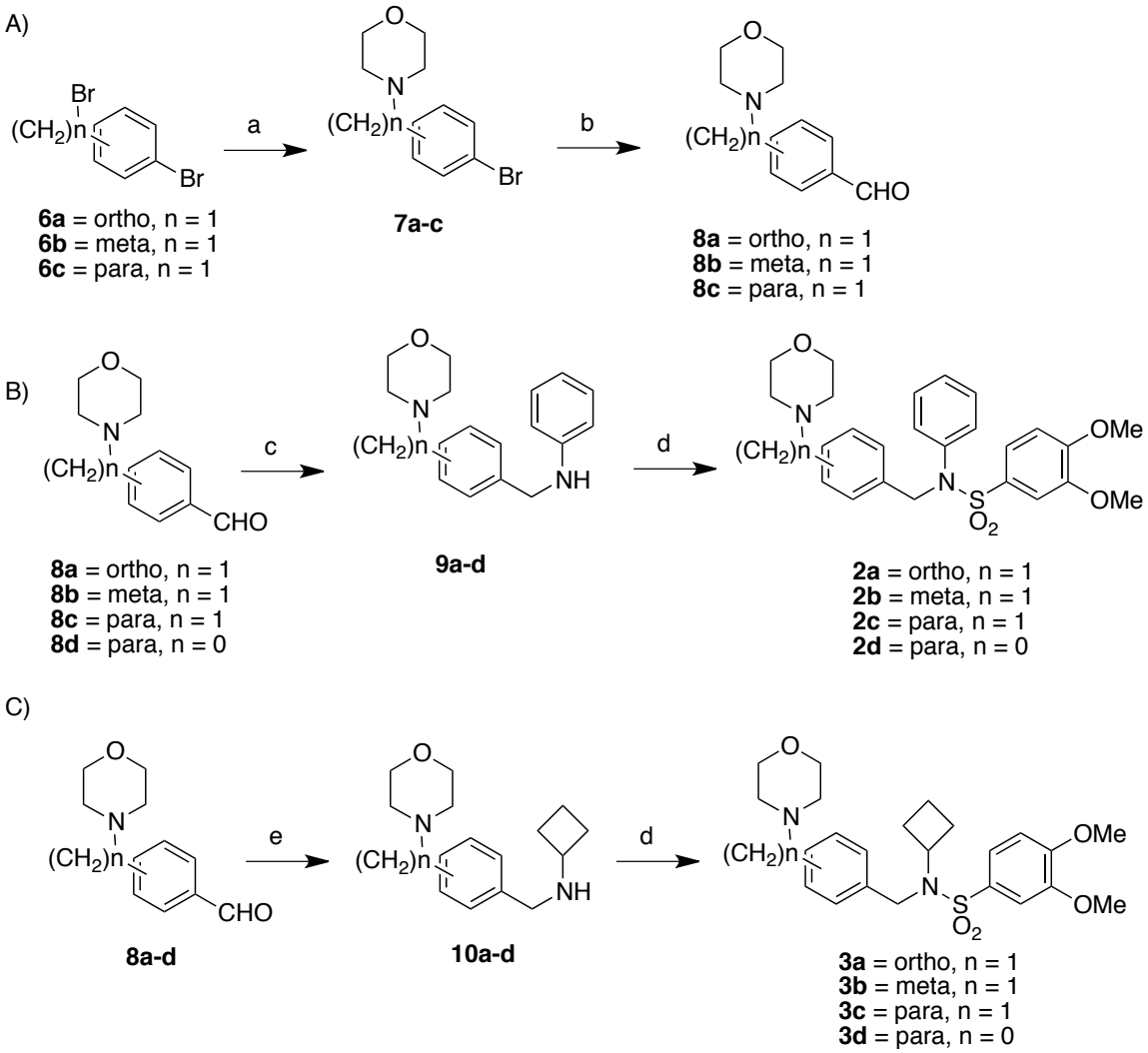
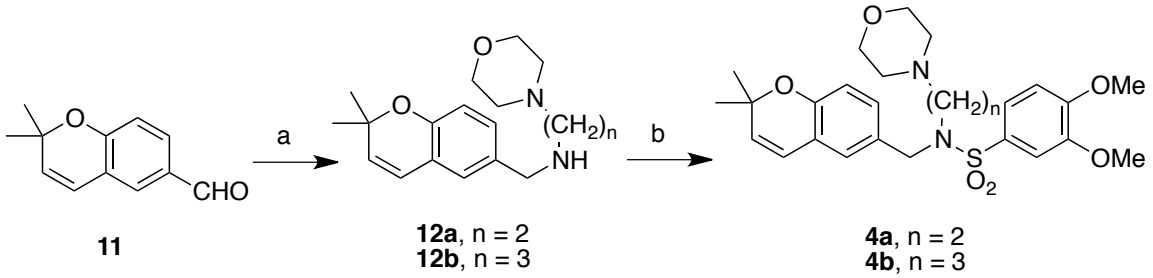


Figure 3.3 Synthesis of Class A & B Compounds

A) Synthesis of precursors; B) Synthesis of Class A. C) Synthesis of Class B; Reagents and conditions: (a) morpholine, K_2CO_3, ACN, room temperature, overnight. (b) BuLi, DMF, THF, -78^oC, 1 hr. (c) aniline, $InCl_3$, $NaBH_4$, ACN, 20 min. (d) 3,4-dimethoxysulfonyl chloride, K_2CO_3, DCM, overnight. (e) cyclobutylamine, $NaBH_4$, MeOH, overnight.

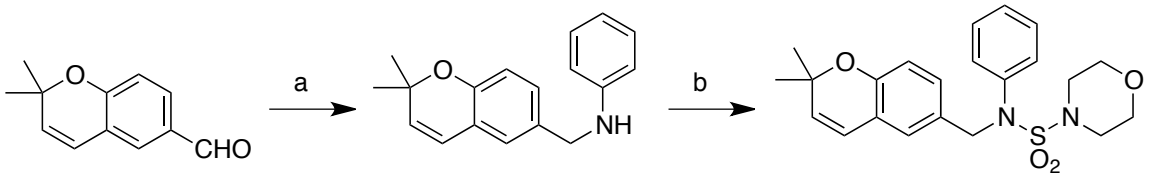


11 **12a**, n = 2 **12b**, n = 3 **4a**, n = 2 **4b**, n = 3

Figure 3.4. Synthesis of Class C compounds

Reagents and conditions: (a) amine, $NaBH_4$, MeOH, overnight. (b) 3,4-dimethoxysulfonyl chloride, K_2CO_3, DCM, overnight.

These 11 analogs were tested for their anti-HIF activity in a LN229-HRE-LUC assay.[14] Their activities are detailed in Table 3.1. The *in silico* logP and logS value of these compounds were also investigated with ALOGPS 2.1 (Virtual Computational Chemistry Laboratory, http://www.vcclab.org), with results in Table 3.1.



11 **13** **5**

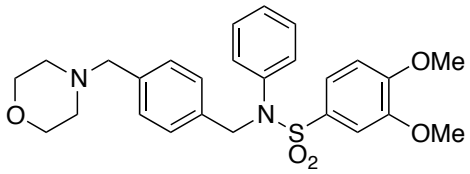
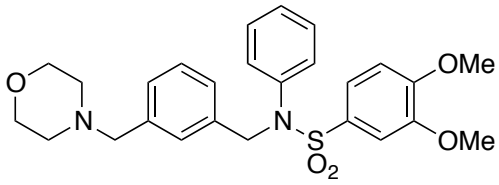
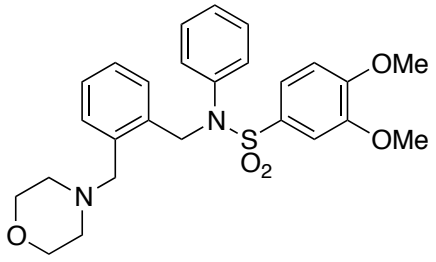
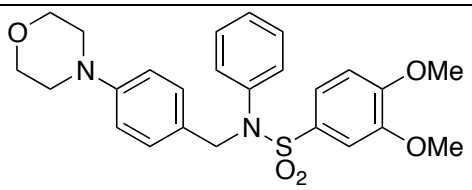
Figure 3.5. Synthesis of Class D compounds

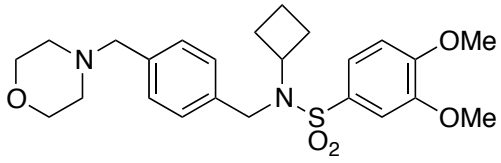
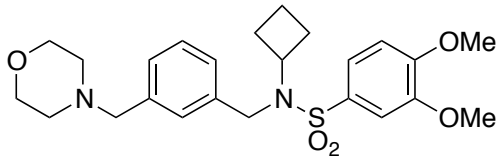
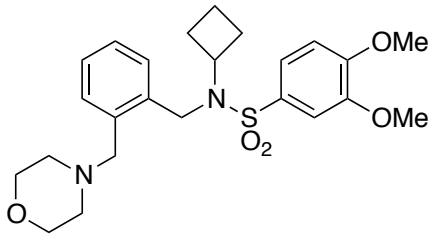
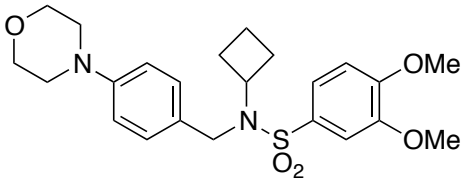
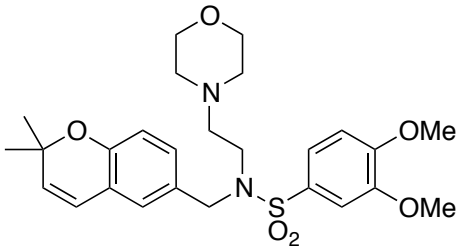
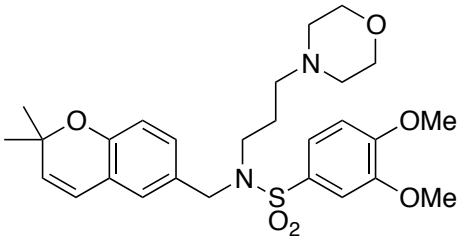
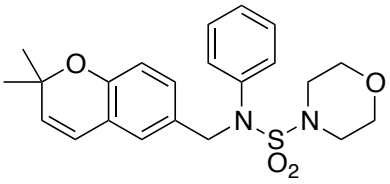
Reagents and conditions: (a) aniline, $InCl_3$, $NaBH_4$, ACN, 20 min; (b) 4-morpholinosulfonyl chloride, pyridine, DCE, reflux 2 days.

3.5 Conclusions

Based off of these findings, it can be seen that solubility is an important factor in the activity of these compounds. Even compounds without the seemingly crucial 2,2-dimethyl-2*H*-chromene moiety had moderate activity. This is most likely due to the increased logP and logS, which allow the therapeutics to be more biologically available. All of the analogs synthesized had more favorable logP and log S values compared to **1**, which has 4.07 and -6.05, respectively. In the future, we plan to incorporate more soluble moieties and further probe the SAR (structure-activity relationship) for locations to add in these soluble moieties.

Table 3.1. Analogs and data

Compound	Structure	IC_{50} (μM)	logP	LogS
2a		0.9	3.54	-4.51
2b		TBD	3.53	-4.50
2c		TBD	3.52	-4.46
2d		3.8	3.75	-4.64

3a		1.0	2.81	-3.51
3b		>5	2.80	-3.50
3c		>5	2.79	-3.47
3d		TBD	3.05	-3.64
4a		TBD	3.02	-3.71
4b		TBD	3.34	-3.97
5		>5	3.52	-4.51

3.6 Experimental

General methods and materials: All commercial chemicals were reagent grade, obtained from VWR, Aldrich, and Oakwood Chemicals and were used without further purification unless otherwise indicated. ^{1}H and ^{13}C spectra were obtained on a Bruker 400 NMR spectrometer at 400 and 100 MHz, respectively, in deuterated solvent with TMS as internal reference (δ = 0.00 ppm). For all reactions, analytical grade solvent was used. Anhydrous solvents were used for all moisture-sensitive reactions. High-resolution mass spectra were obtained by the Mass Spectrometry Facilities at Georgia State University on a Waters Micromass Q-Tof (ESI).

Typical procedure for morpholine substitution: 1 equivalent of benzyl bromide was dissolved in acetonitrile. 1.1 equivalents of morpholine and 2 equivalents of K_2CO_3 were added and the reaction stirred overnight at room temperature. The reaction was filtered through celite and concentrated to give the product.

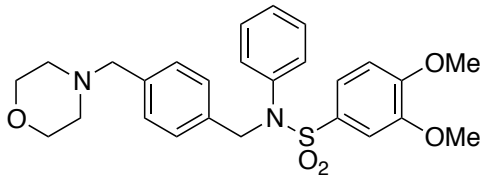
Typical procedure for reductive amination with aniline: 1 equivalent of aldehyde, 1.5 equivalents of $NaBH_4$, and 0.15 equivalents of $InCl_3$ were dissolved in anhydrous ACN under N_2. 1.5 equivalents of aniline were added and the reaction stirred until completion as monitored by TLC (typically ~20 minutes). The reaction was quenched with saturated NH_4Cl, taken up in ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated. Purified by column chromatography.

Typical procedure for reductive amination with cyclobutyl and alkylmorpholino amines: 1 equivalent each of aldehyde and amine was dissolved in anhydrous MeOH under N_2 and the reaction stirred overnight at room temperature. 1.6 equivalents of $NaBH_4$ were added and the reaction stirred for 1 hour. The reaction was quenched with 1N NaOH, stirred for an hour, then

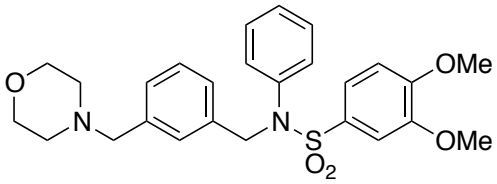
taken up in ethyl acetate, washed with brine, dried over $MgSO_4$, concentrated, and taken directly to the next step without further purification.

Typical procedure for sulfonylation with 3,4-dimethoxysulfonyl chloride: 1 equivalent of amine was dissolved in DCM. 2 equivalents of K_2CO_3 were added. 2 equivalents of 3,4-dimethoxysulfonyl chloride were added. The reaction was stirred overnight at room temperature, then washed with brine, dried over $MgSO_4$, and concentrated. Purified by column chromatography.

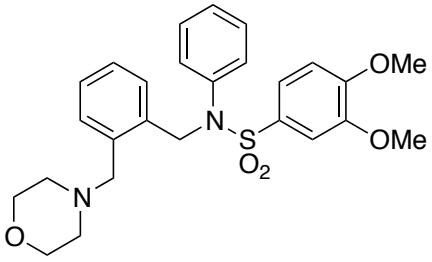
Typical procedure for sulfonylation with 4-morpholinosulfonyl chloride: 1 equivalent of amine was dissolved in DCE. 3 equivalents of pyridine and 1.3 equivalents of 4-morpholinosulfonyl chloride were added. The reaction was refluxed for 2 days, then concentrated, taken up in ethyl acetate, washed with saturated NH_4Cl and brine, then dried over $MgSO_4$, and concentrated. Purified by column chromatography.



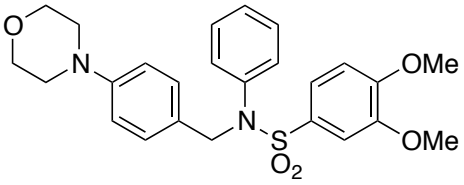
3,4-Dimethoxy-*N*-(4-(morpholinomethyl)benzyl)-*N*-phenylbenzenesulfonamide (2a) Yield: 11%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.35 (d, J = 8Hz, 1H), 7.35 (s, 1H), 7.22-7.20 (m, 6H), 7.04-7.02 (m, 2H), 6.97-6.94 (m, 2H), 4.72 (s, 1H), 3.98 (s, 3H), 3.77 (s, 3H), 3.70-3.69 (m, 4H), 3.44 (s, 2H), 2.40 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 148.7, 139.2, 135.0, 130.2, 129.2, 129.0, 128.8, 128.4, 127.8, 127.5, 121.4, 110.4, 110.4, 66.9, 63.0, 56.2, 56.01, 54.4, 53.5 ppm. HRMS (ESI) *m/z* calculated for $C_{26}H_{31}N_2O_5S$ $[(M + H)^+]$ 483.1954, found 483.1956.



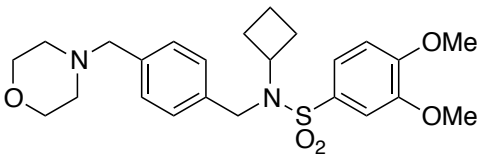
3,4-Dimethoxy-*N*-(3-(mor*p*holinomethyl)benzyl)-N-phenylbenzenesulfonamide (2b) ^{1}H NMR (400 MHz, $CDCl_3$): δ



3,4-Dimethoxy-*N*-(2-(morpholinomethyl)benzyl)-*N*-phenylbenzenesulfonamide (2c)

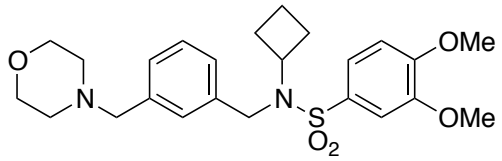


3,4-Dimethoxy-*N*-(4-morp*h*olinobenzyl)-N-phenylbenzenesulfonamide (2d) Yield: 40%.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (d, *J* = 8 Hz, 1H), 7.21 (m, 3H), 7.13-7.11 (d, *J* = 8 Hz, 2H), 7.01-6.93 (m, 4H), 6.77-6.75 (d, *J* = 8 Hz, 2H), 4.65 (s, 2H), 3.973 (s, 3H), 3.84-3.83 (m, 4H), 3.77 (s, 3H), 3.11-3.10 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 150.5, 148.7, 139.2, 130.3, 129.6, 129.1, 128.7, 127.7, 127.1, 121.4, 115.3, 110.4, 66.8, 56.2, 56.1, 54.1, 49.1 ppm. HRMS (ESI) *m/z* calculated for $C_{25}H_{29}N_2O_5S$ [$(M + H)^+$] 469.1797, found 469.1796.



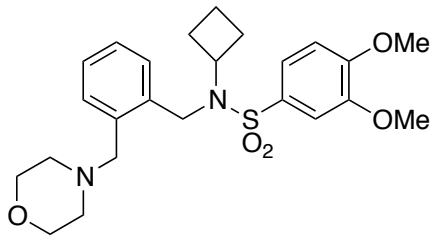
***N*-cyclobutyl-3,4-dimethoxy-*N*-(4-(morpholinomethyl)benzyl)benzenesulfonamide (3a)** Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.42 (dd, *J* = 8.4, 2 Hz, 1H), 7.34-7.25 (m, 5H),

6.95-6.93 (d, J = 8 Hz, 1H), 4.39 (s, 2H), 4.32-4.23 (quintet, J = 8 Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.74-3.72 (t, J = 4 Hz, 4H), 3.51 (s, 2H), 2.46 (s, 4H), 1.99-1.94 (m, 4H), 1.57-1.52 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 149.0, 137.8, 132.0, 129.4, 127.1, 120.91, 110.6, 109.8, 66.9, 63.0, 56.2, 56.2, 53.5, 52.9, 48.1, 29.2, 15.0 ppm. HRMS (ESI) *m/z* calculated for $C_{24}H_{33}N_2O_5S$ [$(M + H)^+$] 461.2110, found 461.2102.



***N*-Cyclobutyl-3,4-dimethoxy-*N*-(3-(morpholinomethyl)benzyl)benzenesulfonamide (3b)**

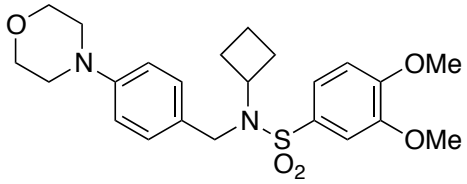
Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.41 (dd, J = 8.4, 2 Hz, 1H), 7.30-7.21 (m, 5H), 6.95-6.93 (d, J = 8 Hz, 1H), 4.39 (s, 2H), 4.33-4.24 (quintet, J = 8 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.72-3.69 (t, J = 4 Hz, 4H), 3.49 (s, 2H), 2.43 (s, 4H), 1.99-1.92 (m, 4H), 1.55-1.48 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 149.0, 138.7, 137.9, 131.9, 128.4, 128.1, 127.8, 126.0, 120.9, 110.5, 109.7, 67.0, 63.3, 56.2, 56.2, 53.6, 52.9, 48.3, 29.2, 15.1 ppm. HRMS (ESI) *m/z* calculated for $C_{24}H_{33}N_2O_5S$ [$(M + H)^+$] 461.2110, found 461.2112.



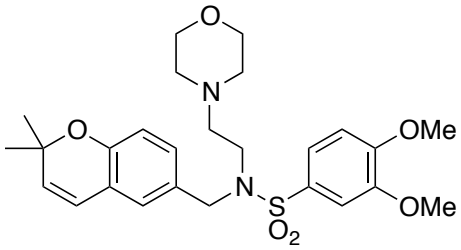
***N*-Cyclobutyl-3,4-dimethoxy-*N*-(2-(morpholinomethyl)benzyl)benzenesulfonamide (3c)**

Yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.55 (d, J = 8 Hz, 1H), 7.48-7.46 (dd, J = 8.4, 2 Hz, 1H), 7.31-7.27 (m, 2H), 7.18-7.16 (d, J = 8 Hz, 1H), 6.96-6.94 (d, J = 8 Hz, 1H), 4.68 (s, 2H), 4.51-4.40 (quintet, J = 8 Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.65 (m, 4H), 3.50 (s, 2H), 2.42 (s, 4H), 1.93-1.90 (m, 4H), 1.56-1.50 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4,

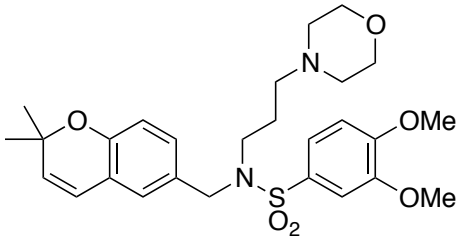
149.0, 138.4, 133.4, 132.1, 130.6, 128.0, 127.4, 126.5, 121.0, 110.5, 109.7, 67.1, 61.7, 56.3, 56.2, 53.5, 52.7, 44.5, 28.9, 15.1 ppm. HRMS (ESI) *m/z* calculated for $C_{24}H_{33}N_2O_5S$ $[(M + H)^+]$ 461.2110, found 461.2905.



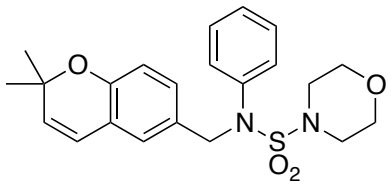
_N_-Cyclobutyl-3,4-dimethoxy-_N_-(4-morpholinobenzyl)benzenesulfonamide (3d)



_N_-((2,2-Dimethyl-2_H_-chromen-6-yl)methyl)-3,4-dimethoxy-_N_-(2-morpholinoethyl)benzenesulfonamide (4a)

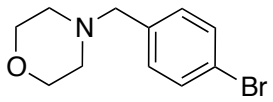


_N_-((2,2-Dimethyl-2_H_-chromen-6-yl)methyl)-3,4-dimethoxy-_N_-(3-morpholinopropyl)benzenesulfonamide (4b)

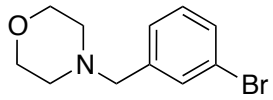


_N_-((2,2-Dimethyl-2_H_-chromen-6-yl)methyl)-_N_-phenylmorpholine-4-sulfonamide (5a) Yield: 17%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 5H), 6.92-6.90 (d, J = 8 Hz, 1H), 6.83 (s,

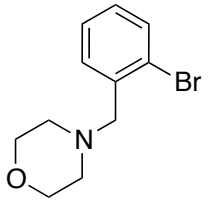
1H), 6.66-6.64 (d, *J* =8 Hz, 1H), 6.26-6.24 (d, *J* = 8 Hz, 1H), 5.61-5.59 (d, *J* = 8 Hz, 1H), 4.702 (s, 2H), 3.626 (m, 4H), 3.165 (m, 4H), 1.41 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.0, 129.6, 129.2, 129.1, 127.9, 126.9, 122.1, 116.2, 66.3, 56.3, 46.5, 28.0 ppm. HRMS (ESI) *m/z* calculated for $C_{22}H_{27}N_2O_4S$ [$(M + H)^+$] 415.1695, found 415.1692.



4-(4-Bromobenzyl)morpholine (7a) Yield: quantitative. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.40 (d, *J* = 8 Hz, 2H), 7.120-7.18 (d, *J* = 8 Hz, 2H), 3.68-3.66 (t, *J* = 4 Hz, 4H), 3.40 (s, 2H), 2.40 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 131.4, 130.8, 120.9, 66.9, 62.6, 53.6 ppm. HRMS (ESI) *m/z* calculated for $C_{11}H_{15}NOBr$ [$(M + H)^+$] 256.0337, found 256.0346.

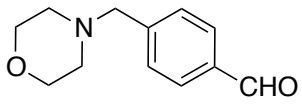


4-(3-Bromobenzyl)morpholine (7b) Yield: quantitative. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.35-7.34 (d, *J* = 8 Hz, 1H), 7.22-7.20 (d, *J* = 8 Hz, 1H), 7.15-7.11 (t, *J* = 4 Hz, 1H), 3.66-3.64 (d, J = 8 Hz, 4H), 3.40 (s, 2H), 2.38 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 131.9, 130.2, 129.8, 127.6, 122.5, 65.9, 62.7, 53.6 ppm. HRMS (ESI) *m/z* calculated for $C_{11}H_{15}NOBr$ [$(M + H)^+$] 256.0337, found 256.0347.

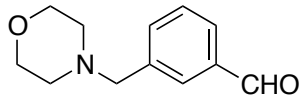


4-(2-Bromobenzyl)morpholine (7c) Yield: quantitative. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.51 (d, *J* = 8Hz, 1H), 7.47-7.45 (d, *J* = 8 Hz, 1H), 7.27-7.23 (t, *J* = 4 Hz, 1H), 7.09-7.06 (t, *J* = 8 Hz, 1H), 3.69 (s Hz, 4H), 3.57 (s, 2H), 2.49 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2,

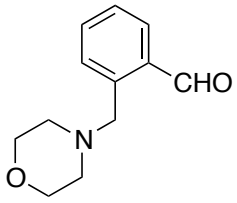
132.8, 130.8, 128.5, 127.2, 124.7, 67.6, 66.8, 62.2, 53.6 ppm. HRMS (ESI) *m/z* calculated for $C_{11}H_{15}NOBr$ [$(M + H)^+$] 256.0337, found 256.0348.



4-(Morpholinomethyl)benzaldehyde (8a) Yield: 74%.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.82-7.80 (d, *J* = 8 Hz, 2H), 7.50-7.48 (d, *J* = 8 Hz, 2H), 3.68-3.67 (m, 4H), 3.54 (s, 2H), 2.43 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 145.2, 135.5, 129.8, 129.5, 129.2, 66.9, 63.0, 53.6 ppm. HRMS (ESI) *m/z* calculated for $C_{12}H_{16}NO_2$ [$(M + H)^+$] 206.1181, found 206.1182.

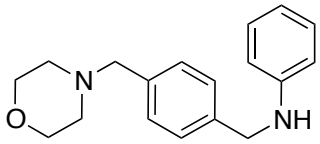


3-(Morpholinomethyl)benzaldehyde (8b) Yield: 88%.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1H), 7.77 (s, 1H), 7.70-7.68 (d, *J* = 8 Hz, 1H), 7.55-7.53 (d, *J* = 8 Hz, 2H), 7.43-7.39 (t, *J* = 7.6 Hz, 1H), 3.63 (m, 4H), 3.5 (s, 2H), 2.39 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.3, 138.8, 136.5, 135.2, 130.2, 129.0, 128.7, 66.7, 62.6, 53.42, 53.3 ppm. HRMS (ESI) *m/z* calculated for $C_{12}H_{16}NO_2$ [$(M + H)^+$] 206.1181, found 206.1183.

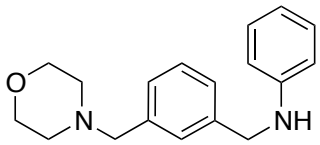


2-(Morpholinomethyl)benzaldehyde (8c) Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.37, (s, 1H), 7.82-7.80 (d, *J* = 8 Hz, 1H), 7.45-7.43 (d, *J* = 8 Hz, 1H), 7.37-7.33 (m, 2H), 3.76 (s, 2H), 3.58-3.57 (m, 4H), 2.40-2.39 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):δ 192.0, 140.4, 135.0,

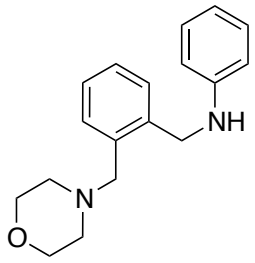
133.2, 130.6, 129.4, 127.9, 67.0, 66.9, 60.1, 55.5, 53.3 ppm. HRMS (ESI) *m/z* calculated for $C_{12}H_{16}NO_2Na$ [$(M + Na)^+$] 206.1181, found 206.1186.



***N*-(4-(Morpholinomethyl)benzyl)aniline (9a)** Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.17 (m, 4H), 6.79-6.66 (m, 5H), 4.34 (s, 2H), 3.74 (m, 4H), 3.53 (s, 2H), 2.74 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 138.4, 136.8, 129.5, 129.3, 127.5, 118.6, 117.6, 115.1, 112.9, 67.0, 63.2, 53.6, 48.1 ppm. HRMS *m/z* (ESI) calculated for $C_{16}H_{22}NO_2$ [$(M + H)^+$] 260.1651, found 260.1657.

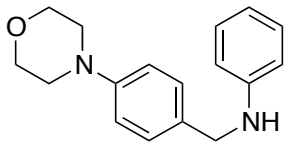


***N*-(3-(Morpholinomethyl)benzyl)aniline (9b)** Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.3607.17 (m, 6H), 6.76-6.65 (m, 3H), 4.35 (s, 2H), 3.73-3.72 (m, 4H), 3.52 (s, 2H), 2.45 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 148.1, 139.5, 138.1, 129.3, 128.6, 128.3, 128.1, 126.5, 117.6, 112.9, 67.0, 63.4, 53.6, 48.3 ppm. HRMS (ESI) *m/z* calculated for $C_{18}H_{23}N_2O$ [$(M + H)^+$] 283.1810, found 283.1809.

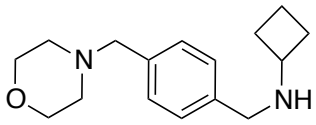


***N*-(2-(Morpholinomethyl)benzyl)aniline (9c)** Yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.44 (d, *J* = 8 Hz, 1H), 7.32-7.22 (m, 5H), 6.76-6.74 (d, *J* = 8 Hz, 3H), 5.37 (bs, 1H), 4.39

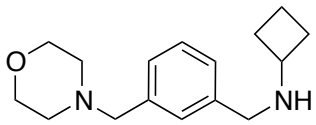
(s, 2H), 3.75 (m, 4H), 3.57 (s, 2H), 2.51 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):148.6, 138.9, 135.8, 131.5, 130.0, 129.3, 128.2, 127.2, 113.1, 67.1, 61.7, 53.5, 46.9 ppm. HRMS (ESI) *m/z* calculated for $C_{18}H_{23}N_2O$ [$(M + H)^+$] 283.1810, found 283.1805.



***N*-(4-Morpholinobenzyl)aniline (9d)** Yield: 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.32 (d, *J* = 8 Hz, 2H), 7.23-7.21 (d, *J* = 8 Hz, 2H), 6.95-6.93 (d, *J* = 8 Hz, 2H), 6.78-6.75 (t, *J* = 8 Hz, 1H), 6.69-6.69 (d, *J* = 8 Hz, 2H), 4.28 (s, 2H), 4.00 (bs, 1H), 3.91-3.90 (m, 4H), 3.19-3.18 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 148.3, 130.76, 129.3, 128.7, 117.5, 115.9, 112.9, 67.0, 49.5, 47.8 ppm. HRMS (ESI) *m/z* calculated for $C_{17}H_{20}N_2O$ [$(M + H)^+$] 269.1648, found 269.1659.

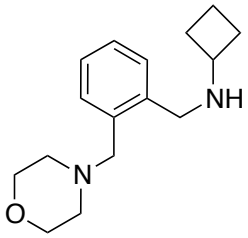


***N*-(4-(Morpholinomethyl)benzyl)cyclobutanamine (10a)** Yield: 89% unpurified. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.315-7.261 (m, 4H), 3.694-3.678 (m, 4H), 3.472 (s, 2H), 3.308-3.275 (m, 1H), 2.425 (m, 4H), 2.221-2.207 (m, 2H), 1.633-1.618 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.35, 136.31, 129.44, 128.13, 66.99, 63.17, 53.58, 50.75, 31.10, 14.79 ppm. HRMS (ESI) *m/z* calculated for $C_{16}H_{25}NO_2$ [$(M + H)^+$] 261.1967, found 261.1961.

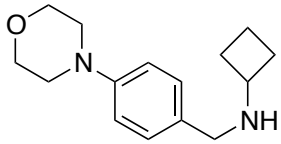


***N*-(3-(Morpholinomethyl)benzyl)cyclobutanamine (10b)** Yield: 88% unpurified. ^{1}H NMR (400 MHz, $CDCl_3$): 7.32-7.19 (m, 4H), 3.69 (m, 6H), 3.49-3.48 (m, 2H), 3.31-3.28 (quintet, *J* =

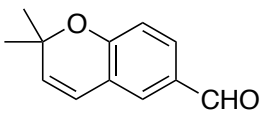
7.6 Hz, 1H), 2.43 (m, 4H), 2.24-2.20 (m, 2H), 1.74-1.63 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 140.3, 137.9, 129.0, 128.6, 127.8, 127.1, 66.9, 63.1, 53.7, 53.6 51.0, 31.1, 14.8 ppm. HRMS (ESI) *m/z* calculated for $C_{16}H_{25}NO_2$ [$(M + H)^+$] 261.1967, found 261.1963.



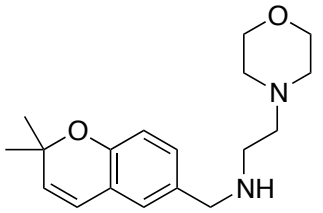
***N*-(2-(Morpholinomethyl)benzyl)cyclobutanamine (10c)** 94% unpurified. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 4H), 3.75 (s, 2H), 3.67 (s, 4H), 3.53 (s, 2H), 3.33-3.30 (quintet, J = 7.6 Hz, 1H), 2.53 (s, 1H), 2.46 (s, 4H), 2.21-2.18 (m, 2H), 1.74-1.63 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 135.7, 131.2, 130.5, 127.9, 126.7, 67.0, 61.6, 53.6, 53.5, 49.5, 30.9, 15.1 ppm. HRMS (ESI) *m/z* calculated for $C_{16}H_{25}N_2O$ [$(M + H)^+$] 261.1967, found 261.1968.



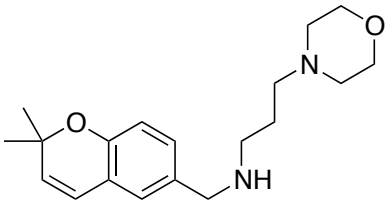
***N*-(4-Morpholinobenzyl)cyclobutanamine (10d)** Yield: 90% unpurified. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.21 (d, *J* = 8 Hz, 2H), 6.88-6.86 (d, *J* = 8 Hz, 2H), 3.86-3.84 (m, 4H), 3.62 (s, 2H), 3.30-3.25 (quintet, *J* =6.8 Hz, 1H), 3.14-3.11 (m, 4H), 2.22-2.19 (m, 2H), 1.70-1.62 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 131.9, 129.1, 115.7, 66.9, 53.5, 50.4, 49.5, 31.1, 14.8 ppm. HRMS (ESI) *m/z* calculated for $C_{15}H_{23}N_2O$ [$(M + H)^+$] 247.1810, found 247.1819.



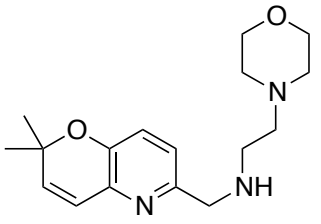
2,2-Dimethyl-2*H*-chromene-6-carbaldehyde (11) Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 7.65-7.63 (d, *J* = 8 Hz, 1H), 7.52 (s, 1H), 6.88-6.86 (d, *J* = 8 Hz, 1H), 6.38-6.36 (d, *J* = 8 Hz, 1H), 5.70-5.68 (d, *J* = 8Hz, 1H), 1.47 (s, 6H).



***N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-2-morpholinoethanamine (12a)** Unpurified. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.12 (m, 1H), 7.01-6.99 (d, *J* = 8 Hz, 1H), 6.91 (s, 1H), 6.70-6.68 (d, *J* = 8 Hz, 1H), 6.28-6.26 (d, *J* = 10 Hz, 1H), 5.59-5.56 (d, *J* = 10 Hz, 1H), 3.72 (s, 2H), 3.66-3.64 (m, 4H), 3.09 (s, 1H), 2.66-2.64 (m, 2H), 2.47-2.44 (m, 2H), 2.35 (m, 4H), 1.39 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 132.2, 130.9, 128.9, 126.2, 125.3, 122.4, 121.5, 116.1, 73.9, 66.9, 53.6, 53.2, 44.9, 27.9 ppm. HRMS (ESI) *m/z* calculated for $C_{18}H_{27}N_2O_2$ $[(M + H)^+]$ 303.2073, found 303.2063.

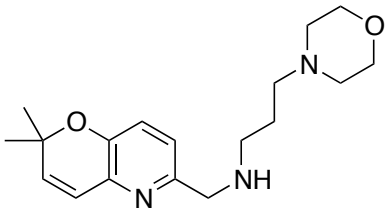


***N*-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-3-morpholinopropan-1-amine (12b)** Unpurified. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.10 (m, 1H), 6.99-6.97 (d, *J* = 8 Hz, 1H), 6.89 (s, 1H), 6.68-6.66 (d, *J* = 8 Hz, 1H), 6.26-6.23 (d, *J* = 10 Hz, 1H), 5.56-5.54 (d, *J* = 10 Hz, 1H), 3.69 (s, 2H), 3.63 (m, 4H), 2.63 (m, 2H), 2.37-2.35 (m, 4H), 1.67-1.58 (m, 2H), 1.58 (m, 2H), 1.37 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 132.3, 130.9, 128.8, 126.1, 122.3, 121.5, 116.1, 73.9, 66.9, 57.3, 53.7, 47.9, 27.6, 27.9, 26.4 ppm. HRMS (ESI) *m/z* calculated for $C_{19}H_{29}N_2O_2$ $[(M + H)^+]$ 317.2229, found 317.2237.

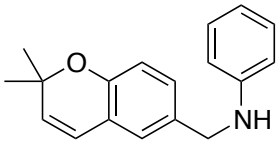


***N*-((2,2-Dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-2-morpholinoethanamine (12c)**

Yield: 76% unpurified. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.005-6.944 (m, 2H), 6.462-6.437 (d, J = 10 Hz, 1H), 5.851-5.825 (d, J =10.4 Hz, 1H), 3.763 (s, 2H), 3.675-3.653 (m, 4H), 2.706-2.676 (m, 2H), 2.493-2.462 (m, 2H), 2.380 (m, 4H), 1.420 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.31, 148.38, 140.71, 135.26, 123.86, 123.30, 122.30, 76.78, 66.93, 58.24, 54.54, 53.63, 45.35, 28.23 ppm. HRMS (ESI) *m/z* calculated for $C_{17}H_{26}N_3O_2$ [(M + H)$^+$] 304.2025, found 304.2031.



***N*-((2,2-Dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-3-morpholinopropan-1-amine (12d)** Yield: 73% unpurified. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.988-6.928 (m, 2H), 6.450-6.425 (d, J = 10 Hz, 1H), 5.834-5.809 (d, J = 10 Hz, 1H), 3.730 (s, 2H), 3.650-3.641 (m, 4H), 2.676-2.643 (m, 2H), 2.381-2.344 (m, 6H), 1.694-1.659 (m, 2H), 1.407 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.18, 148.36, 140.70, 135.20, 123.89, 123.29, 122.24, 76.81, 57.29, 54.70, 53.71, 48.12, 28.10, 26.61. HRMS (ESI) *m/z* calculated for $C_{18}H_{28}N_3O_2$ [(M + H)$^+$] 318.2182, found 318.2185.



***N*-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)aniline (13a)** Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.21 (m, 3H), 6.98-6.96 (d, *J* = 8 Hz, 1H), 6.88-6.86 (m, 1H), 6.79-6.72 (m, 3H), 6.40-6.38 (d, *J* = 8 Hz, 1H), 5.69-5.67 (d, *J* = 8 Hz, 1H), 4.37 (s, 2H), 4.06 (s, 1H) 1.51 (s, 6H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 148.5, 130.6, 129.2, 128.9, 126.5, 125.5, 122.5, 121.1, 120.5, 117.4, 113.2, 76.44, 43.11, 28.18 ppm. HRMS (ESI) *m/z* calculated for $C_{18}H_{20}NO$ $[(M + H)^+]$ 266.1545, found 266.1548.

3.7 References

1. Cancer Facts & Figures 2012. American Cancer Society: Atlanta, 2012.

2. Ruan, K.; Song, G.; Ouyang, G., Role of hypoxia in the hallmarks of human cancer. *Journal of Cellular Biochemistry* **2009,** *107* (6), 1053-1062.

3. (a) Vaupel, P.; Mayer, A., Hypoxia in cancer: significance and impact on clinical outcome. *Cancer and Metastasis Reviews* **2007,** *26* (2), 225-239; (b) Melillo, G., Inhibiting Hypoxia-Inducible Factor 1 for Cancer Therapy. *Molecular Cancer Research* **2006,** *4* (9), 601-605; (c) Wilson, W. R.; Hay, M. P., Targeting hypoxia in cancer therapy. **2011**.

4. Wang, G. L.; Semenza, G. L., Purification and Characterization of Hypoxia-inducible Factor 1. *Journal of Biological Chemistry* **1995,** *270* (3), 1230-1237.

5. Wang, G. L.; Jiang, B. H.; Rue, E. A.; Semenza, G. L., Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. *Proceedings of the National Academy of Sciences* **1995,** *92* (12), 5510-5514.

6. Maxwell, P. H.; Wiesener, M. S.; Chang, G.-W.; Clifford, S. C.; Vaux, E. C.; Cockman, M. E.; Wykoff, C. C.; Pugh, C. W.; Maher, E. R.; Ratcliffe, P. J., The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* **1999,** *399* (6733), 271-275.

7. Wenger, R. H.; Stiehl, D. P.; Camenisch, G., Integration of oxygen signaling at the consensus HRE. *Sci STKE* **2005,** *2005* (306), re12.

8. Semenza, G. L., Targeting HIF-1 for cancer therapy. *Nat Rev Cancer* **2003,** *3* (10), 721-732.

9. Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E., Natural Product-like Combinatorial Libraries Based on Privileged Structures. 2. Construction of a 10,000-Membered Benzopyran Library by Directed Split-and-Pool Chemistry Using NanoKans and Optical Encoding. *Journal of the American Chemical Society* **2000,** *122* (41), 9954-9967.

10. (a) Tan, C.; de Noronha, R. G.; Devi, N. S.; Jabbar, A. A.; Kaluz, S.; Liu, Y.; Mooring, S. R.; Nicolaou, K. C.; Wang, B.; Van Meir, E. G., Sulfonamides as a new scaffold for hypoxia inducible factor pathway inhibitors. *Bioorg. Med. Chem. Lett.* **2011,** *21* (18), 5528-5532; (b) Narita, T.; Yin, S.; Gelin, C. F.; Moreno, C. S.; Yepes, M.; Nicolaou, K. C.; Van Meir, E. G., Identification of a Novel Small Molecule HIF-1α Translation Inhibitor. *Clin. Cancer Res.* **2009,** *15* (19), 6128-6136.

11. (a) Wang, W.; Ao, L.; Rayburn, E. R.; Xu, H.; Zhang, X.; Zhang, X.; Nag, S. A.; Wu, X.; Wang, M.-H.; Wang, H.; Van Meir, E. G.; Zhang, R., KCN1, a Novel Synthetic Sulfonamide Anticancer Agent: *In Vitro* and *In Vivo* Anti-Pancreatic Cancer Activities and Preclinical Pharmacology. *PLoS ONE* **2012,** *7* (9), e44883; (b) Zhang, Q.; Kaluz, S.; Yang, H.; Van Meir, E. G.; Grossniklaus, H. E., Efficacy of the novel small molecule HIF pathway inhibitor KCN1 in the control of micrometastases in experimental ocular melanoma. *Unpublished results*; (c) Yin, S.; Kaluz, S.; Devi, N. S.; Jabbar, A. A.; de Noronha, R. G.; Mun, J.; Zhang, Z.; Boreddy, P. R.; Wang, W.; Wang, Z.; Abbruscato, T.; Chen, Z.; Olson, J. J.;

Zhang, R.; Goodman, M. M.; Nicolaou, K. C.; Van Meir, E. G., Arylsulfonamide KCN1 Inhibits In Vivo Glioma Growth and Interferes with HIF Signaling by Disrupting HIF-1α Interaction with Cofactors p300/CBP. *Clinical Cancer Research* **2012,** *18* (24), 6623-6633.

4 DESIGN AND SYNTHESIS OF NOVEL BI-ARYL METHANOLIC HIF-1 INHIBITORS AS ANTI-CANCER THERAPEUTICS

The work presented in this chapter is based on a manuscript in preparation for submission to the Journal of Medicinal Chemistry. This chapter includes compounds synthesized by Jalisa Holmes,[§] and Krishna Damera.[≠]

4.1 Abstract

Although there has been much progress in the battle against cancer, there is still a need for anti-cancer therapeutics that are not cytotoxic. To this end, we are interested in targeting the HIF pathway. Based off of initial screening, the compounds described herein have been designed to specifically inhibit the HIF pathway and have desirable pharmacological properties.

4.2 Introduction

Cancer is the second most prevalent cause of death in the United States, behind heart disease.[1] Many cancers are associated with hypoxia, a lack of oxygen. Hypoxic conditions in otherwise healthy cells can lead to cell necrosis and reoxygenation injuries. Cancer cells, however, survive and even thrive under hypoxic conditions due to their ability to turn on gene expression via multiple pathways that can change metabolism into the anaerobic, glycolytic

pathway; promote angiogenesis; turn on immortalization, increase metastatic potential, resist apoptosis, and increase resistance to radiation and chemotherapies.[2]

One such pathway is the hypoxia-inducible transcription factor 1 (HIF-1) pathway.[3] HIF is a basic-loop-helix-loop motif heterodimeric transcription factor composed of two subunits: HIF-1α and HIF-1β. HIF-1β is constitutively expressed, but HIF-1α is regulated by oxygen levels.[4] Under normoxic conditions, when there is enough oxygen present in the system, HIF1-α is dihydroxylated by HIF prolyl hydroxylases, which use molecular oxygen as the source of the hydroxyls, at prolines 402 and 564.[5] The dihydroxylated form of HIF1-α binds to von Hippel-Lindau tumor suppressor protein (VHL), which leads to the ubiquitination of the complex and subsequent proteosomal degradation.[6] Under hypoxic conditions, however, HIF-1a hydroxylation does not occur and HIF-1α is no longer degraded. As HIF-1α accumulates, it binds to HIF1-β and forms the heterodimeric complex, which, along with the co-activator p300, forms the HIF complex that acts as transcription factor for a multitude of genes. The HIF transcription complex binds to hypoxic response elements (HRE) in the regulatory regions of many genes, such as *VEGF* (vascular endothelial growth factor), *EPO* (eythropoietin), *GLUT1* (glucose transporter 1), *LDH* (lactate dehydrogenase), and *NOS* (nitric oxide synthase).[7]

Overexpression of HIF-1α occurs in many cancers, such as cervical, ovarian, lung, oesophagel, colon, breast, pancreatic, prostate, renal, head and neck, and brain carcinomas. In many cases, increased HIF-1α has been associated with increased mortality, cancer progression, and resistance to traditional chemotherapy, radiation, or photo-dynamic therapy.[8] This can be attributed mostly to the hypoxic environment created in solid tumors. As tumors grow, they need increased vasculature in order to receive oxygen and nutrients. Hypoxic conditions in the tumor can signal expression of pro-angiogenic genes such as VEGF. Although new vasculature

is established, it is often leaky and inadequate.[9] This leads to resistance to therapy because the tumor is not accessible to the chemotherapy or radiation. Given the role of the HIF pathway in hypoxia and cancer progression, it is an attractive target for cancer chemotherapy.

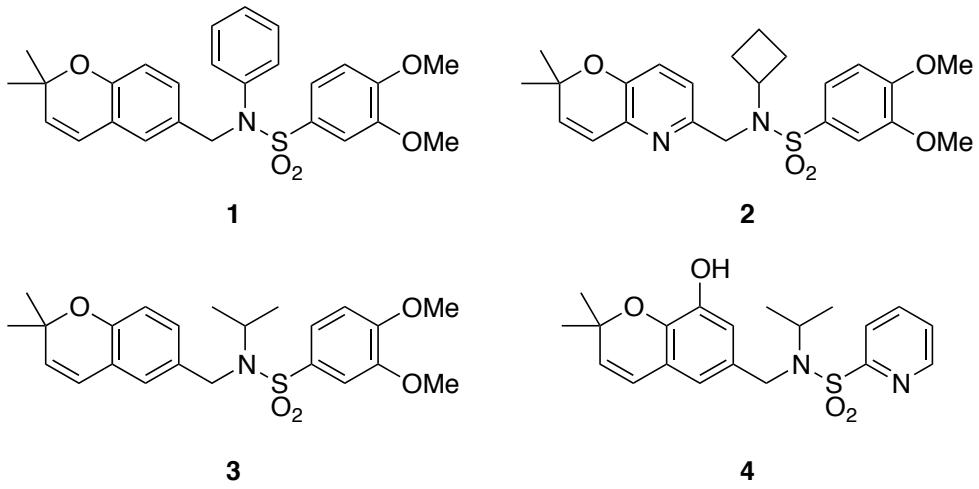


Figure 4.1. 4 lead compounds identified in the aryl sulfonamide class of HIF inhibitors.

As an initial step in the development of novel small molecule inhibitors of the HIF pathway, we initially screened a library of 10,000 compounds from a 2,2-dimethylbenzopyran combinatorial library using an LN229-HRE-alkaline phosphatase assay.[10] This initial screening yielded a few promising hits, with the lead compound identified as KCN-1 (**1**, Figure 4.1) having an IC_{50} of 0.59 μM.[11] Since then, our collaborative team has identified additional small molecules such as *N*-cyclobutyl-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (**2**, Figure 4.1**)**, *N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-*N*-isopropyl-3,4-dimethoxybenzenesulfonamide (**3**, Figure 4.1), *N*-((8-hydroxy-2,2-dimethyl-2*H*-chromen-6-yl)methyl)-*N*-isopropylpyridine-2-sulfonamide (**4**, Figure 4.1).[12] Moreover, computational studies have suggested a dual binding mode for these compounds to p300 and initial *in vitro* and *in vivo* results of **1** have shown very promising results, especially that these

classes of compounds do not have any inherent toxicity.[13] Due to poor solubility, however, **1** must be formulated in cremphor/ethanol, which has been shown to have toxicity problems in other anti-cancer therapeutics.[14] With all of this in mind, we began to search for novel structural features to broaden our SAR and perhaps discover a new lead compound in this series.

4.3 Results and Discussion

4.3.1 Design

Based off of our previous results, the SAR for the aryl sulfonamide HIF inhibitors has become somewhat flat, with many compounds exhibiting and IC_{50} values in the 250-1000 nM range. We initially chose to keep the 2,2-dimethyl-2H-chromene moiety and the 3',4'-dimethoxyphenyl moiety from **1** and link them together via a methanolic linker, which was seen in some of the less potent hits of the initial screening. We also wanted to diversify the pool of analogs by making modifications in 3 places (Figure 4.2): Class 1 compounds vary in the left hand aryl system, Ar_1; Class 2 compounds vary in the right hand aryl system, Ar_2; and Class 3 compounds vary in the linker between the two aryl groups. Since these compounds were designed to be both more potent and more soluble, the *in silico* logP and logS values were calculated with the online software ALOGPS 2.1 (Virtual Computational Chemistry Laboratory, http://www.vcclab.org).[15]

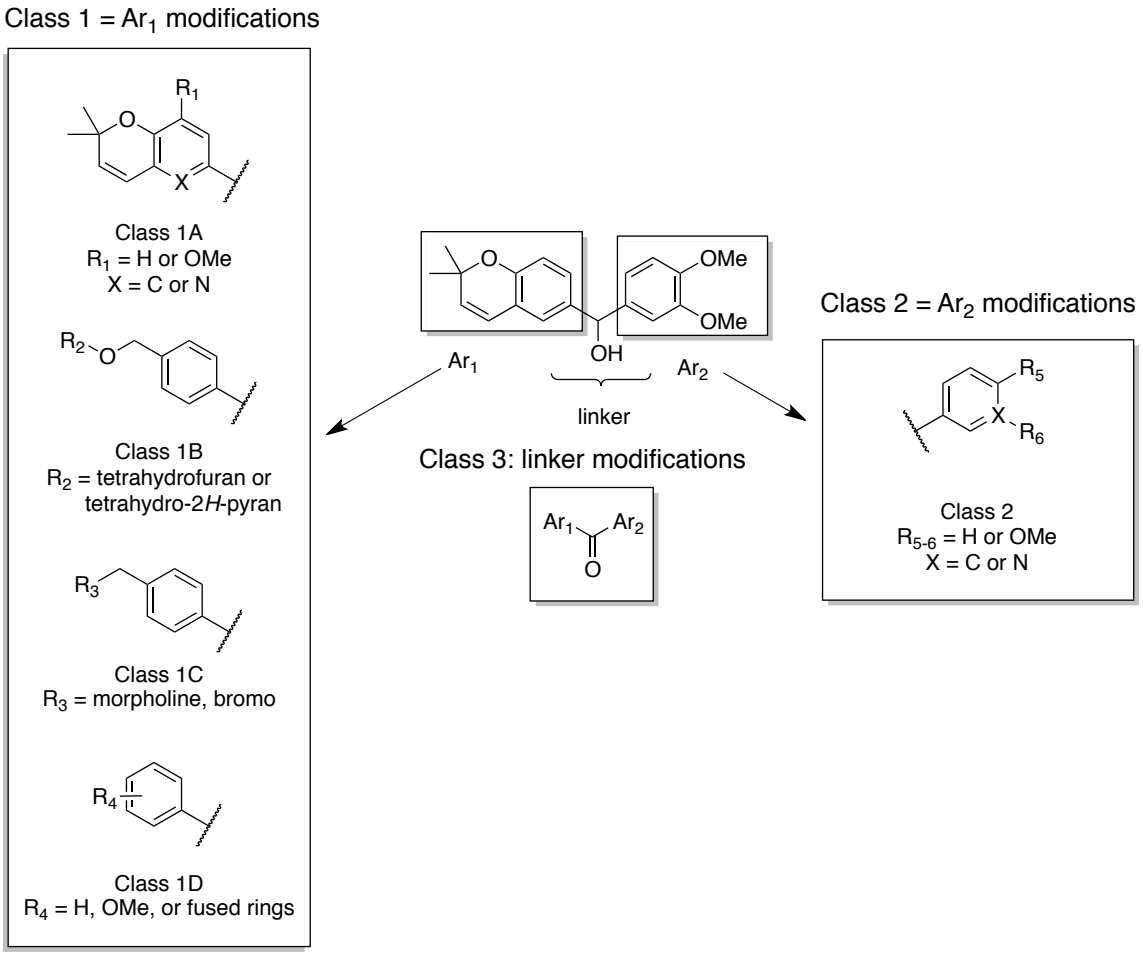


Figure 4.2. Three classes of analogs

4.3.2 Chemistry

4.3.2.1 Class I: Ar_1 modifications.

Class 1A compounds were synthesized in 1 or 2 steps from readily synthesized aldehydes **5a-c** (Figure 4.3).[12a, 16] First, aldehydes **5a-c** were coupled with 4-bromo-1,2-dimethoxybenzene through lithiation and then addition reaction to yield alcohols **6a-c**. Next, the double bond was hydrogenated to a single bond to yield compound **7c**.

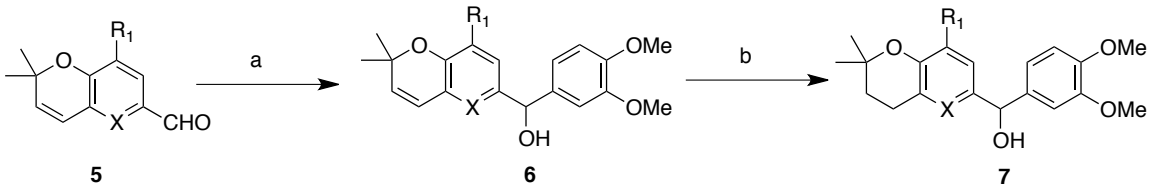


Figure 4.3. Synthesis of Class 1A compounds

R_1 = H, X = C, **5-7a**; R_1 = OMe, X = C, **5-7b**; R_1 = H, X = N, **5-7c**; Reagents and conditions: (a) 4-bromo-1,2-dimethoxybenzene, buLi, -78^{o}C, 49-63%; (b) H_2, Pd/C, MeOH, overnight.

Class 1B compounds were synthesized in 2 steps from commercially available 1-bromo-4-(bromomethyl)benzene **8** (Figure 4.4). First, **8** underwent SN2 displacement with either tetrahydrofuran-3-ol or tetrahydro-2*H*-pyran-4-ol to yield ethers **9a-c**. Next, after lithiation, **9a-c** were reacted with 3,4-dimethoxybenzaldehyde to yield alcohol compounds **10a-c**.

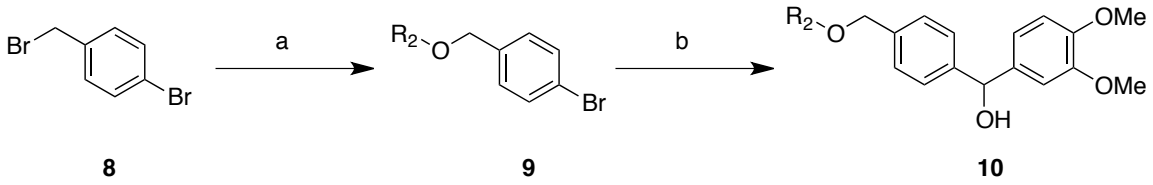


Figure 4.4. Synthesis of Class 1B compounds

R_2 = (S)-tetrahydrofuran-3-ol, **10a**; R_2 = (R)-tetrahydrofuran-3-ol, **10**; R_3 = tetrahydro-2*H*-pyran-4-ol, **10c**. Reagents and conditions: (a) NaH, alcohol, 0^{o}C to room temperature, overnight, 48-85% (b) 3,4-dimethoxybenzaldehyde, buLi, -78^{o}C, 58-94%.

Class 1C compounds were synthesized in 2 steps from commercially available 1-bromo-4-(bromomethyl)benzene **8** (Figure 4.5). First, **8** underwent SN2 displacement with morpholine, or N-methylpipirizine to yield compounds **11a-b**. Next, **11a-** were reacted with butyl lithium and then 3,4-dimethoxybenzaldehyde to yield alcohols **12a-c**.

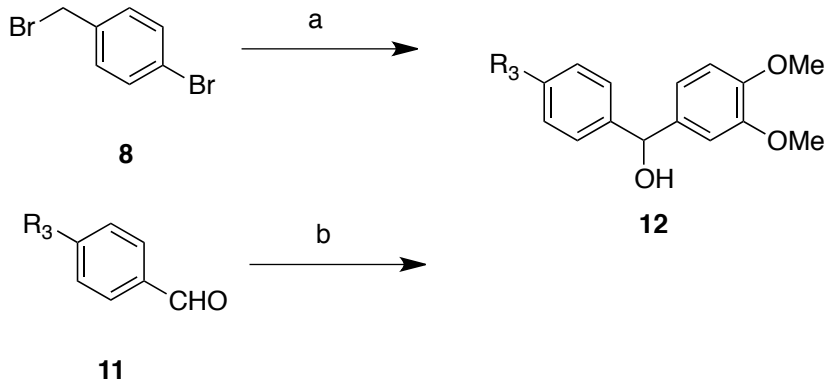


Figure 4.5. Synthesis of Class 1C compounds

R_3 = morpholine, **11-12a**; R_3 = methylbromo, **12b**; R_3 = 4-methylpiperazin-1-yl, **11-12c** . Reagents and conditions: (a) 3,4-dimethoxybenzaldehyde, BuLi, -78 ^{o}C, 85%. (b) 3,4-dimethoxybromobenzenee, BuLi, -78 ^{o}C, 89%.

Class 1D compounds were synthesized in 1 step from commercially available starting materials **13** and **14**, which consist of an aryl bromide and an aryl aldehyde, which were coupled together to yield alcohols **15a-d** (Figure 4.6).

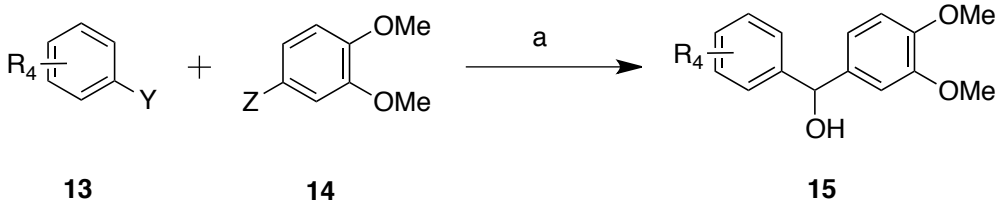


Figure 4.6. Synthesis of Class 1C compounds

R_4 = H, Y = Br, Z = CHO, **15a**; R_4 = 3,4-dimethoxy, Y= Br, Z = CHO, **15b**; R_3 =2,4-dimethoxy, Y = Br, Z = CHO, **15c**; R_4 = 4-methylbromide, Y = Br, Z = CHO, **15d**; R_4 = benzofuran, Y = CHO, Z = Br, **15e**. Reagents and conditions: (a) buLi, -78^{o}C, 46-65%.

4.3.2.2 Class 2: Ar_2 modifications.

Class 2 compounds were synthesized in 1 facile step from commercially available starting materials **16** and **17**, which consist of an aryl bromide and an aryl aldehyde, which were coupled to yield alcohols **18a-d** (Figure 4.7).

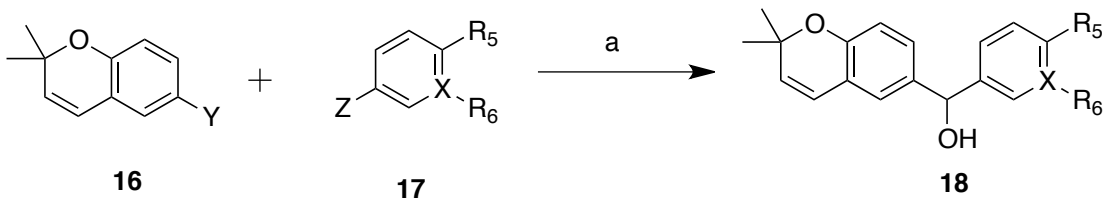


Figure 4.7. Synthesis of Class 2A compounds

R_5 = H, R_6 = H, X = C, Y = CHO, Z = Br, **18a**; R_5 = OMe, R_6 = H, X = C, Y = CHO, Z = Br, **18b**; R_5 = H, R_6 = OMe, X = C, Y = Br, Z = CHO, **18c**, R_5 = H, R_6 = H, X = N, Y = CHO, Z = Br, **18d**. Reagents and conditions: (a) BuLi, -78 ^{o}C.

4.3.2.3 Class 3: Linker modifications.

Class 3 compounds were synthesized in 1 step from alcohol compounds **6a, 10a,** and **12b**. Each alcohol was oxidized to its corresponding ketone **19a-c** (Figure 4.8).

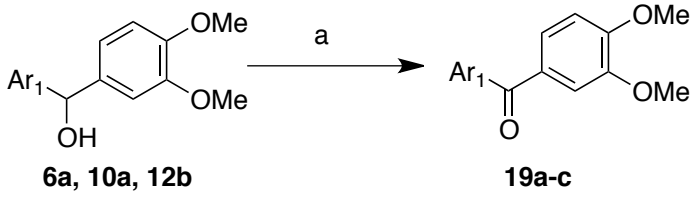


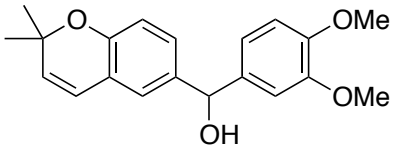
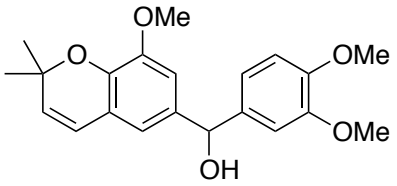
Figure 4.8. Synthesis of Class 3 compounds

Ar_1 = 6-(2,2-dimethyl-2*H*-chromenyl), **6a,** 19a; Ar_1 = 1-(4-((((*S*)-tetrahydrofuran-3-yl)oxy)methyl)phenyl, **10a, 19b**; Ar_1 = 1-(4-bromomethyl)phenyl, **12b, 19c.** Reagents and conditions: (a) DDQ, 10:1 DCM/AcOH, rt, overnight, 46-99%

4.3.3 Biology

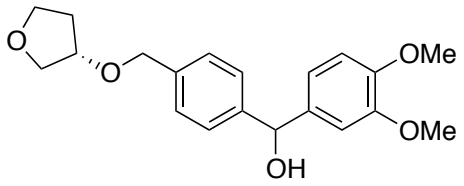
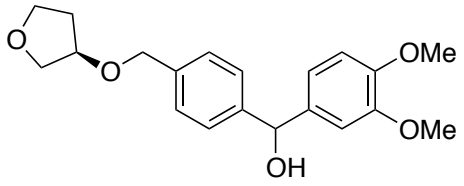
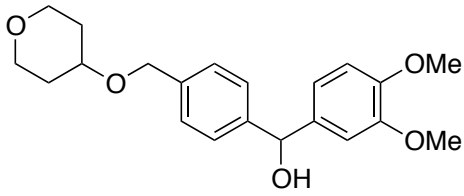
For Class 1A compounds (Table 4.1), the best compound was the original compound **6a**, with the 2,2-dimethyl-2H-chromene, with an IC_{50} of 0.6 μM. The addition of the methoxy group resulted in a 5.2-fold decrease from **6a**.

Table 4.1. Class 1A compounds and IC_{50}

	Structure	IC_{50} (μM)	logP	logS
6a		0.6	3.68	-4.43
6b[§]		3.1	3.52	-4.42

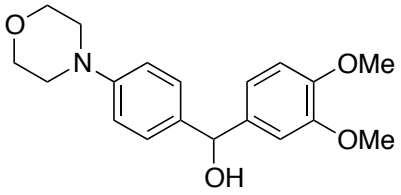
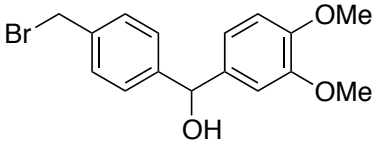
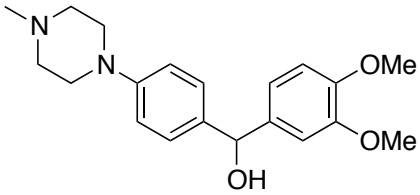
Our overall best compound was **10a** of Class 1B (Table 4.2), with an IC_{50} value of 0.32 μM. It is interesting to note that the diasteromer of **10a**, **10b,** was not as active, and, in fact, suffered a 10-fold loss of activity with the change of the stereocenter in the tetrahydrofuran moiety. In addition, exchanging the *(S)*-tetrahydrofuran for the larger tetrahydropyran moiety, compound **10c,** also resulted in a 10-fold decrease in activity. This demonstrates that this position is very important to the activity of the compound and small changes in this position are not well-tolerated.

Table 4.2. Class 1B compounds and IC_{50}

	Structure	IC_{50} (μM)	logP	logS
10a		0.32	2.29	-3.85
10b		3.2	2.29	-3.85
10c		3.2	2.62	-4.14

Unfortunately, only one of the compounds in Class 1C showed any activity (Table 4.3). **12b** had a moderate activity of 1.0 μM. It seems that the bulky bromo substituent and morpholine moiety are not well-tolerated in that position. This is unusual because the addition of morpholine moieties in various position in the aryl sulfonamide series was tolerated. It is possible that the increased activity seen in morpholine-substituted aryl sulfonamides comes from an increase in solubility, but the methanolic compounds are already quite soluble, so the same increase is not observed.

Table 4.3. Class 1C compounds and IC_{50}

	Structure	IC_{50} (μM)	logP	logS
12a		>5	2.29	-3.04
12b		1.0	3.29	-4.39
12c		>5	2.41	-2.56

In addition, only one of the compounds in Class 1D showed any activity (Table 4.4). **15a** demonstrated low activity of 2.1 μM. Methoxy groups and a fused benzopyran system were not tolerated. Unfortunately, the Class 2 compounds have not yet been evaluated for biological activity, so cannot be analyzed at this time. In addition, none of the compounds in Class 3 demonstrated any activity. This decrease in activity can be ascribed to either loss of solubility (as demonstrated by increased logP and logS values when compared to the reduced compounds) or lower affinity for the target protein, p300.

Table 4.4. Class 1D compounds and IC_{50}

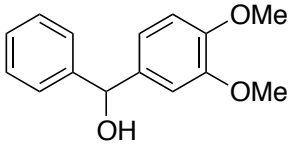
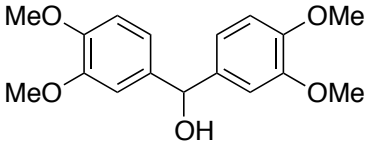
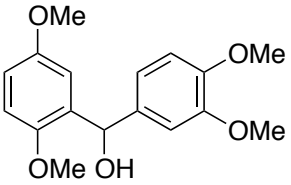
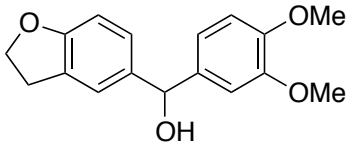
	Structure	IC_{50} (μM)	logP	logS
15a		2.1	2.55	-3.01
15b		>5	2.32	-3.41
15c		>5	2.46	-3.39
15d		>5	2.61	-3.65

Table 4.5. Class 2 compounds and IC_{50}

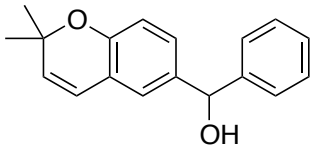
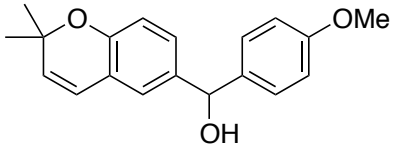
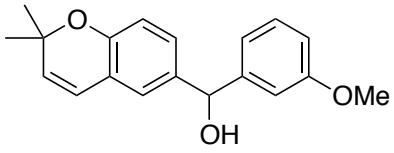
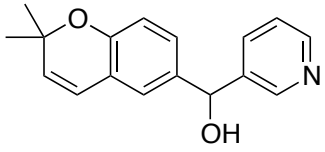
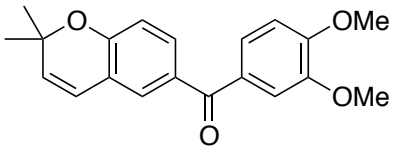
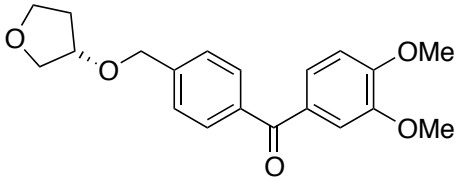
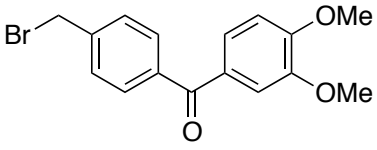
18a		TBD	3.93	-4.10
18b		TBD	3.83	-4.30
18c		TBD	3.83	-4.29
18d		TBD	2.71	-3.11

Table 4.6. Class 3 compounds and IC_{50}

	Structure	IC_{50} (μM)	logP	logS
19a		>5	4.03	-5.08
19b		>5	2.75	-4.49
19c		>5	3.78	-5.14

4.4 Conclusion

In conclusion, 21 novel bi-aryl methanolic compounds were synthesized. However, only 2/3 of these compounds have been evaluated to date for biological activity. Of those 16 that have been evaluated, 9 showed activity, with the best compound **10a** demonstrating an activity of 0.32 μM, which is a 1.8-fold increase in activity from the original compound **1**. In addition, all of the compounds have better logP and logS values than those of **1**, 4.97 and -6.05, respectively. The best compound **10a** has the second lowest logP value, 2.29, which is 2.17-fold lower than **1**. In fact, **10a** has the lowest logP value of all compounds except for **12a**, which has the same logP.

4.5 Experimental

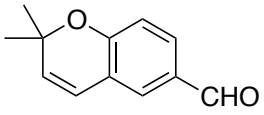
General methods and materials

All commercial chemicals were reagent grade, obtained from VWR, Aldrich, and Oakwood Chemicals and were used without further purification unless otherwise indicated. ^{1}H and ^{13}C spectra were obtained on a Bruker 400 NMR spectrometer at 400 and 100 MHz, respectively, in deuterated solvent with TMS as internal reference (δ = 0.00 ppm). For all reactions, analytical grade solvent was used. Anhydrous solvents were used for all moisture-sensitive reactions. High-resolution mass spectra were obtained by the Mass Spectrometry Facilities at Georgia State University on a Waters Micromass Q-Tof (ESI).

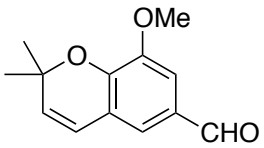
General procedure for coupling between aryl bromide and aryl aldehyde to form alcohols: 1.0 equivalents of aryl bromide was dissolved in anhydrous THF under argon and cooled in a dry ice/acetone bath. After 20 min, 1.4 equivalents of BuLi was added. After 20 min, 1.4 equivalents of aryl aldehyde was added. The reaction was stirred in the dry ice/acetone bath for 40 min before the reaction temperature was brought to room temperature and then quenched with

saturated NH_4Cl. The reaction mixture was taken up in ethyl acetate, washed with brine, dried over $MgSO_4$, and purified by flash column chromatography.

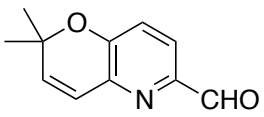
General procedure for *SN*2 displacement of bromide by alcohols: 1.0 equivalents of 1-bromo-4-(bromomethyl)benzene was dissolved in anhydrous THF and cooled in an ice bath. 1.0 equivalents of alcohol reagent and 1.5 equivalents of NaH were added and the reaction stirred overnight and the ice bath was allowed to warm to room temperature. The reaction was quenched with saturated NH_4Cl, taken up in ethyl acetate, washed with brined, dried over $MgSO_4$, and purified by flash column chromatography.



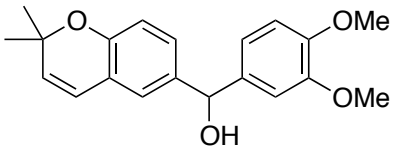
2,2-Dimethyl-2*H*-chromene-6-carbaldehyde (5a). Synthesized in 2 steps from 4-hydroxybenzaldehyde, 23%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 7.65-7.63 (d, *J* = 8 Hz, 1H), 7.52 (s, 1H), 6.88-6.86 (d, *J* = 8 Hz, 1H), 5.70-5.68 (d, *J* = 8 Hz, 1H), 1.47 (s, 6H) ppm.



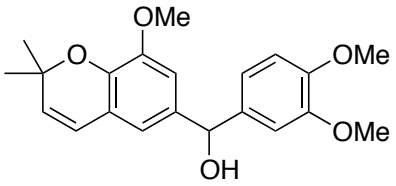
8-Methoxy-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (5b).[§] Synthesized in 2 steps from vanillin, 26%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.30 (s, 1H), 7.15 (s, 1H), 6.36-6.34 (d, *J* = 8 Hz, 1H), 5.69-5.67 (d, *J* = 8 Hz, 1H), 3.90 (s, 3H), 1.51 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 148.9, 147.9, 131.2, 129.4, 123.3, 121.4, 121.3, 110.6, 78.2, 56.2, 28.3 ppm.



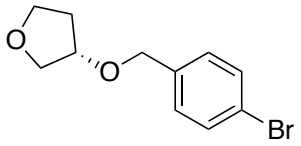
2,2-Dimethyl-2*H*-pyrano[3,2-*b*]pyridine-6-carbaldehyde (5c). Synthesized in 3 steps from 2-bromo-5-hydroxylpyridine, 23% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 s, 1H), 7.75-7.73 (d, *J* = 8 Hz, 1H), 7.12-7.10 (d, *J* = 8 Hz, 1H), 6.58-6.56 (d, *J* = 8 Hz, 1H), 6.00-5.98 (d, *J* =8 Hz, 1H), 1.51 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 153.7, 145.8, 141.3, 136.3, 123.4, 123.2, 123.0, 78.67, 28.7 ppm.



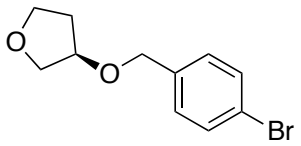
(3,4-Dimethoxyphenyl)(2,2-dimethyl-2*H*-chromen-6-yl)methanol (6a). Yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.08 (d, *J* = 8 Hz, 1H), 6.98 (s, 1H), 6.94 (s, 1H), 6.91-6.89 (d, *J* = 8 Hz, 1H), 6.85-6.83 (d, *J* = 8 Hz, 1H), 6.76-6.74 (d, *J* = 8 Hz, 1H), 6.31-6.28 (d, J = 9.6 Hz, 1H), 5.72 (s, IH), 5.63-5.60 (s, *J* = 9.6 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.20 (s, 1H), 1.43 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 149.0 148.4, 136.7, 136.3, 130.9, 127.4, 124.6, 122.3, 121.1, 118.8, 116.2, 110.9, 109.7, 76.3, 75.5, 55.9, 55.9, 28.0, 28.0 ppm. HRMS (ESI) *m/z* calculated for $C_{20}H_{22}O_4Na$ $[(M + Na)^+]$ 349.1416, found 349.1419.



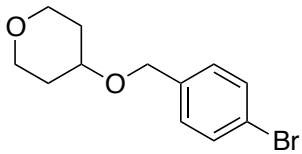
(3,4-Dimethoxyphenyl)(8-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)methanol (6b).[§] Yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94-6.82 (m, 4H), 6.61 (s, 1H), 6.298-6.26 (d, *J* = 8Hz, 1H), 5.71 (s, 1H), 5.63-5.61 (d, *J* = 8Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 1.48 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 149.0, 148.4, 148.2, 141.4, 136.5, 136.0, 131.0, 122.4, 121.7, 118.9, 117.0, 110.9, 110.8, 109.8, 75.7, 60.4, 56.3, 55.9, 55.9, 27.9 ppm. HRMS (ESI) *m/z* calculated for $C_{21}H_{23}O_5$ $[(M + H)^+]$ 355.1545, found 355.1543.



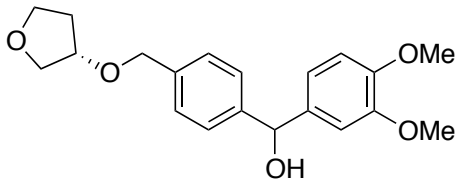
(*S*)-3-((4-Bromobenzyl)oxy)tetrahydrofuran (9a). Yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (d, *J* = 8 Hz, 2H), 7.11-7.09 (d, *J* = 8 Hz, 2H), 4.31 (s, 2H), 4.06 (s, 1H), 3.85-3.69 (m, 4H), 1.90-1.88 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 131.4, 129.2, 121.4, 79.3, 72.8, 70.2, 67.0, 32.6 ppm.



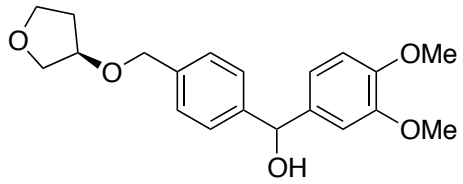
(*R*)-3-((4-Bromobenzyl)oxy)tetrahydrofuran (9b). Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.42 (d, *J* = 7.6 Hz, 2H), 7.19-7.17 (d, *J* = 7.6 Hz, 2H), 4.42 (s, 2H), 4.16 (s, 1H), 3.93-3.74 (m, 4H), 2.03-1.94 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 131.5, 129.2, 121.4, 79.3, 72.7, 70.2, 67.0, 32.6 ppm. GCMS (EI) *m/z* 256 $(M)^{\cdot+}$.



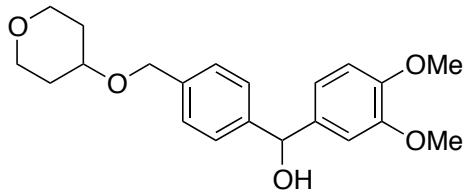
4-((4-Bromobenzyl)oxy)tetrahydro-2*H*-pyran (9c). Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.43 (d, *J* = 7.6 Hz, 2H), 7.22-7.20 (d, *J* = 7.6 Hz, 2H), 4.48 (s, 2H), 3.95-3.91 (m, 2H), 3.58-3.53 (m, 1H), 3.44-3.39 (t, *J* = 10.0 Hz, 2H), 1.92-1.89 (m, 2H), 1.67-1.58 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 131.4, 129.1, 121.3, 73.6, 68.8, 65.6, 32.4 ppm. GCMS (EI) *m/z* 270 $(M)^{\cdot+}$.



(3,4-Dimethoxyphenyl)(4-((((*S*)-tetrahydrofuran-3-yl)oxy)methyl)phenyl)methanol (10a). Yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.24 (d, *J* = 7.6 Hz, 2H), 7.19-7.17 (d, *J* = 7.6 Hz, 2H), 6.83 (s, 1H), 6.76-6.74 (d, *J* = 8.5 Hz, 1H), 6.69-6.67 (d, *J* = 8.4 Hz, 1H), 5.58 (s, 1H), 4.35 (s, 2H), 4.06 (s, 1H), 3.73-3.60 (m, 10H), 1.91-1.81 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 148.2, 143.9, 137.1, 136.9, 127.6 126.5, 118.9, 110.9, 109.8, 78.9, 75.3, 72.6, 70.7, 66.9, 55.8, 55.7, 32.4 ppm. HRMS (ESI) *m/z* calculated for $C_{20}H_{23}O_5$ [(M - H)$^-$] 343.1545, found 343.1532.

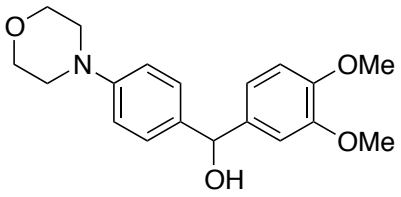


(3,4-Dimethoxyphenyl)(4-((((*R*)-tetrahydrofuran-3-yl)oxy)methyl)phenyl)methanol (10b). Yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.30 (d, *J* = 8.0 Hz, 2H), 7.26-7.24 (d, *J* = 7.2 Hz, 2H), 6.88 (s, 1H), 6.83-6.81 (d, *J* = 8.0 Hz, 1H), 6.77-6.75 (d, *J* = 8.0 Hz, 1H), 5.68 (s, 1H), 4.43 (s, 2H), 4.14 (s, 1H), 3.86-3.73 (m, 10 H), 3.39 (bs, 1H), 1.99-1.94 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 148.3, 143.8, 137.7, 136.9, 127.7, 126.5, 118.9, 110.9, 109.8, 78.9, 75.5, 72.7, 70.8, 67.0, 55.9, 55.8, 32.5 ppm. HRMS (ESI) *m/z* calculated for $C_{20}H_{23}O_5$ [(M - H)$^-$] 343.1545, found 343.1553.

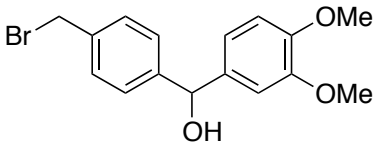


(3,4-Dimethoxyphenyl)(4-(((tetrahydro-2*H*-pyran-4-yl)oxy)methyl)phenyl)methanol (10c). Yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.28 (d, *J* = 7.6 Hz, 2H), 7.25-7.24 (d, *J* = 6.8 Hz, 2H), 6.87 (s, 1H), 6.81-6.79 (d, *J* = 8.0 Hz, 1H), 6.74-6.72 (d, *J* = 7.6 Hz, 1H), 5.63 (s, 1H),

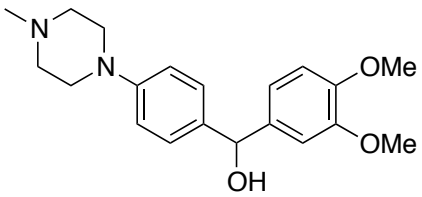
4.46 (s, 2H), 3.85-3.79 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.51 (m, 1H), 3.35-3.30 (t, J = 9.6 Hz, 2H), 1.85-1.82 (m, 2H), 1.57-1.55 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 148.3, 143.7, 137.6, 137.0, 127.5, 126.5, 118.9, 110.9, 109.8, 75.4, 73.2, 69.2, 65.6, 55.9, 55.8, 32.3 ppm. HRMS (ESI) *m/z* calculated for $C_{21}H_{25}O_5$ [(M - H)$^-$] 357.1702, found 357.1692.



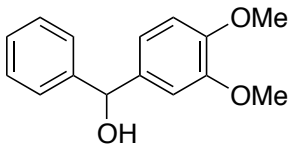
(3,4-dimethoxyphenyl)(4-morpholinophenyl)methanol (12a). Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-6.24 (d, J = 8 Hz, 2H), 6.92 (s, 1H), 6.87-6.80 (m, 4H), 5.70 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.82 (m, 4H), 3.12-3.10 (m, 4H), 2.80 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 148.9, 148.2, 136.9, 135.7, 127.5, 118.8, 115.6, 110.8, 109.7, 75.4, 66.8, 66.5, 55.9, 55.87, 49.3 ppm. HRMS (ESI) *m/z* calculated for $C_{19}H_{24}NO_4$ [(M + H)$^+$] 330.1705, found 330.1710.



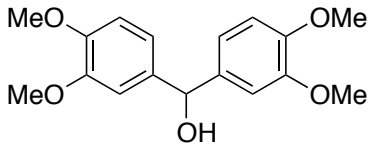
(4-(Bromomethyl)phenyl)(3,4-dimethoxyphenyl)methanol (12b). Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.43 (d, J = 7.6 Hz, 2H), 7.31-7.29 (d, J = 7.6 Hz, 2H), 7.13 (s, 1H), 7.05-7.03 (d, J = 8 Hz, 2H), 6.99-6.97 (d, J = 8 Hz, 2H), 5.92 (s, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 3.04 (s, 2H), 2.57 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 148.4, 142.3, 140.9, 137.5, 128.5, 126.7, 119.1, 111.1, 110.1, 75.6, 56.0, 55.9, 37.7 ppm.



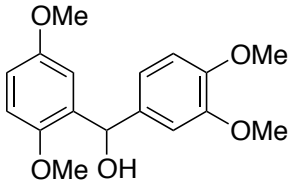
(3,4-dimethoxyphenyl)(4-(4-methylpiperazin-1-yl)phenyl)methanol (12c) Yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.24 (d, *J* = 8 Hz, 2H), 6.94 (s, 1H), 6.88-6.80 (m, 4H), 5.72 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.32 (s, 1H), 3.17-3.15 (m, 4H), 2.60-2.57 (m, 4H), 2.34 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 148.9, 148.2, 137.0, 135.6, 127.5, 118.7, 116.0, 110.8, 109.6, 75.4, 55.9, 55.8, 54.9, 48.7, 45.9 ppm.



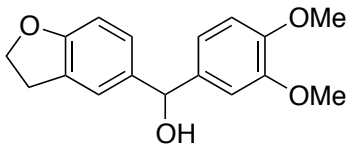
(3,4-Dimethoxyphenyl)(phenyl)methanol (15a). Yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.271 (m, 5H), 6.941 (s, 1H), 6.91-6.89 (d, *J* = 8 Hz, 1H), 6.85-6.83 (d, *J* = 8 Hz, 1H), 5.81 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.35 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 148.5, 143.9, 136.6, 128.5, 127.5, 126.4, 119.0, 111.0, 109.8, 76.0, 55.2, 55.9 ppm. HRMS (ESI) *m/z* calculated for $C_{15}H_{16}O_3Na$ [$(M + Na)^+$] 267.0997, found 267.0993.



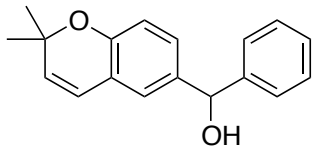
(3,4-Dimethoxyphenyl)(3,4-dimethoxyphenyl)methanol (15b). Yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (s, 1H), 6.91-6.89 (d, *J* = 8 Hz, 2H), 6.86-6.84 (d, *J* = 8 Hz, 2H), 5.78 (s, 2H), 3.89 (s, 6H), 3.87 (s, 6H), 2.19 (bs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 148.5, 136.6, 118.9, 110.9, 109.7, 75.8, 55.93, 55.87 ppm. HRMS (ESI) *m/z* calculated for $C_{17}H_{19}O_5$ [$(M - H)^-$] 303.1232, found 303.1224.



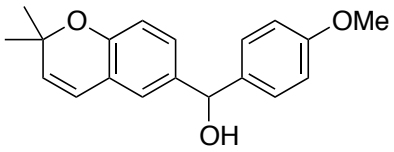
(2,5-Dimethoxyphenyl)(3,4-dimethoxyphenyl)methanol (15c). Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H), 6.89-6.78 (m, 5H), 5.99 (s, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.08 (s, 1H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 151.0, 148.8, 148.2, 135.7, 133.3, 118.8, 114.1, 112.7, 111.8, 110.8, 110.0, 72.0, 56.0, 55.9, 55.8, 55.7 ppm. HRMS (ESI) *m/z* calculated for $C_{17}H_{20}O_5Na$ [$(M + Na)^+$] 327.1208, found 327.1200.



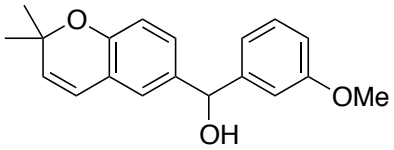
(2,3-Dihydrobenzofuran-5-yl)(3,4-dimethoxyphenyl)methanol (15d). Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (s, 1H), 7.10-7.08 (d, *J* = 8.4 Hz, 1H), 6.92 (s, 1H), 6.88-6.86 (d, *J* = 8.4 Hz, 1H), 6.82-6.80 (d, *J* = 8.4 Hz, 1H), 6.73-6.71 (d, *J* = 8.0 Hz, 1H), 5.69 (s, 1H), 4.55-4.51 (t, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.16-3.12 (t, *J* = 8.8 Hz, 2H), 2.66 (bs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 148.9, 148.2, 137.0, 136.4, 127.3, 126.6, 123.3, 118.6, 110.8, 109.5, 108.9, 75.7, 71.4, 55.9, 55.8, 29.7 ppm. HRMS (ESI) *m/z* calculated for $C_{17}H_{18}O_4Na$ [$(M + Na)^+$] 309.1103, found 309.1107.



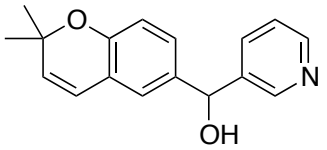
(2,2-Dimethyl-2*H*-chromen-6-yl)(phenyl)methanol (18a). Yield: 66%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.299-7.28 (m, 5H), 7.11, 7.09 (d, *J* = 8 Hz, 1H), 7.00 (s, 1H), 6.76-6.74 (d, *J* = 8 Hz, 1H), 6.31-6.29 (d, *J* = 8 Hz, 1H), 5.75 (s, 1H), 5.63-5.61 (d, *J* = 8 Hz, 1H), 2.40 (s, 1H), 1.45 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 152.4, 143.9, 136.2, 131.0, 128.4, 127.5, 127.4, 126.6, 126.5, 124.7, 122.3, 121.2, 116.2, 75.8, 73.9, 28.1 ppm.



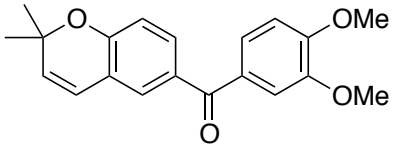
(2,2-Dimethyl-2*H*-chromen-6-yl)(4-methoxyphenyl)methanol (18b). HRMS (ESI) *m/z* calculated for $C_{19}H_{19}O_3$ $[(M + H)^+]$ 295.1334, found 295.1327.



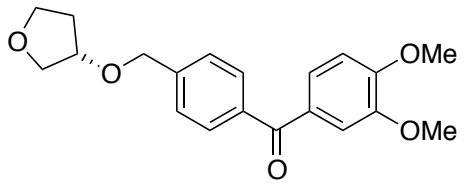
(2,2-Dimethyl-2*H*-chromen-6-yl)(3-methoxyphenyl)methanol (18c). HRMS (ESI) *m/z* calculated for $C_{19}H_{19}O_3$ $[(M + H)^+]$ 295.1334, found 295.1334.



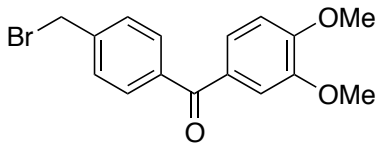
(2,2-Dimethyl-2*H*-chromen-6-yl)(pyridin-3-yl)methanol (18d).



(3,4-dimethoxyphenyl)(2,2-dimethyl-2*H*-chromen-6-yl)methanone (19a) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.69 (dd, *J* = 8, 2 Hz, 1H), 7.52-7.51 (d, *J* = 2 Hz, 1H), 7.47- 7.45 (d, *J* = 8 Hz, 1H), 7.40-7.38 (dd, *J* = 8, 2 Hz, 1H), 7.32-7.30 (d, *J* = 8 Hz, 1H), 6.93-6.91 (d, *J* = 8 Hz, 1H), 6.84-6.82 (d, *J* = 8 Hz, 1H), 6.39-6.36 (d, *J* = 8 Hz, 2H), 5.71-5.68 (d, *J* = 8 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 1.50 (s, 6H) ppm. HRMS (ESI) *m/z* calculated for $C_{20}H_{21}O_4$ $[(M + H)^+]$ 325.1440, found 325.1449.



(*S*)-(3,4-dimethoxyphenyl)(4-(((tetrahydrofuran-3-yl)oxy)methyl)phenyl)methanone (19b) Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.73 (d, *J* = 8 Hz, 2H), 7.47-7.43 (m, 3H), 7.38-7.36 (d, *J* = 8 Hz, 2H), 6.90-6.88 (d, *J* = 8 Hz, 2H), 4.59 (m, 2H), 4.26 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.90 (m, 2H), 3.87-3.83 (m, 2H), 2.08-2.05 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 195.3, 153.0, 149.0, 142.4, 137.5, 130.2, 130.0, 127.1, 125.5, 112.1, 109.7, 79.5, 72.8, 70.5, 67.1, 56.1, 56.1, 32.6 ppm. HRMS (ESI) *m/z* calculated for $C_{20}H_{23}O_5$ [$(M + H)^+$] 343.1545, found 343.1555.



(4-(bromomethyl)phenyl)(3,4-dimethoxyphenyl)methanone (19c) Yield: 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.72 (d, *J* = 8 Hz, 2H), 7.50 (s, 1H), 7.40-7.68 (d, *J* = 8 Hz, 1H), 7.31-7.28 (m, 2H), 6.93-6.91 (d, *J* = 8 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.08 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 152.9, 145.7, 130.1, 128.3, 125.4, 116.0, 112.1, 109.7, 56.1, 37.4 ppm. MS (ESI) *m/z* calculated for $C_{16}H_{16}O_3Br$ [$(M + H)^+$] 336.19, found 336.00.

4.6 References

1. FASTSTATS - Deaths and Mortality. http://www.cdc.gov/nchs/fastats/deaths.htm.

2. (a) Harris, A. L., Hypoxia--a key regulatory factor in tumour growth. *Nature Reviews. Cancer* **2002,** *2* (1), 38-47; (b) Melillo, G., Inhibiting Hypoxia-Inducible Factor 1 for Cancer Therapy. *Molecular Cancer Research* **2006,** *4* (9), 601-605; (c) Wilson, W. R.; Hay, M. P.,

Targeting hypoxia in cancer therapy. **2011**; (d) Matsumoto, S., Imaging Cycling Tumor Hypoxia. *Cancer Research* **2010,** *70* (24), 10019.

3. Wang, G. L.; Semenza, G. L., Purification and Characterization of Hypoxia-inducible Factor 1. *Journal of Biological Chemistry* **1995,** *270* (3), 1230-1237.

4. Wang, G. L.; Jiang, B. H.; Rue, E. A.; Semenza, G. L., Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. *Proceedings of the National Academy of Sciences* **1995,** *92* (12), 5510-5514.

5. (a) Semenza, G. L., Targeting HIF-1 for cancer therapy. *Nat Rev Cancer* **2003,** *3* (10), 721-732; (b) Bruick, R. K.; McKnight, S. L., A Conserved Family of Prolyl-4-Hydroxylases That Modify HIF. *Science* **2001,** *294* (5545), 1337-1340; (c) Berra, E.; Benizri, E.; Ginouves, A.; Volmat, V.; Roux, D.; Pouyssegur, J., HIF prolyl-hydroxylase 2 is the key oxygen sensor setting low steady-state levels of HIF-1alpha in normoxia. *Embo J* **2003,** *22* (16), 4082-90; (d) Hirsila, M.; Koivunen, P.; Gunzler, V.; Kivirikko, K. I.; Myllyharju, J., Characterization of the human prolyl 4-hydroxylases that modify the hypoxia-inducible factor. *J Biol Chem* **2003,** *278* (33), 30772-80.

6. Maxwell, P. H.; Wiesener, M. S.; Chang, G.-W.; Clifford, S. C.; Vaux, E. C.; Cockman, M. E.; Wykoff, C. C.; Pugh, C. W.; Maher, E. R.; Ratcliffe, P. J., The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* **1999,** *399* (6733), 271-275.

7. (a) Levy, A. P.; Levy, N. S.; Wegner, S.; Goldberg, M. A., Transcriptional Regulation of the Rat Vascular Endothelial Growth Factor Gene by Hypoxia. *Journal of Biological Chemistry* **1995,** *270* (22), 13333-13340; (b) Semenza, G. L.; Nejfelt, M. K.; Chi, S. M.; Antonarakis, S. E.,

Hypoxia-inducible nuclear factors bind to an enhancer element located 3' to the human erythropoietin gene. *Proceedings of the National Academy of Sciences* **1991,** *88* (13), 5680-5684; (c) Chen, C.; Pore, N.; Behrooz, A.; Ismail-Beigi, F.; Maity, A., Regulation of glut1 mRNA by Hypoxia-inducible Factor-1: INTERACTION BETWEEN H-ras AND HYPOXIA. *Journal of Biological Chemistry* **2001,** *276* (12), 9519-9525; (d) Semenza, G. L.; Jiang, B.-H.; Leung, S. W.; Passantino, R.; Concordet, J.-P.; Maire, P.; Giallongo, A., Hypoxia Response Elements in the Aldolase A, Enolase 1, and Lactate Dehydrogenase A Gene Promoters Contain Essential Binding Sites for Hypoxia-inducible Factor 1. *Journal of Biological Chemistry* **1996,** *271* (51), 32529-32537; (e) Melillo, G.; Musso, T.; Sica, A.; Taylor, L. S.; Cox, G. W.; Varesio, L., A hypoxia-responsive element mediates a novel pathway of activation of the inducible nitric oxide synthase promoter. *The Journal of Experimental Medicine* **1995,** *182* (6), 1683-1693; (f) Wenger, R. H.; Stiehl, D. P.; Camenisch, G., Integration of oxygen signaling at the consensus HRE. *Sci STKE* **2005,** *2005* (306), re12.

8. Zhong, H.; De Marzo, A. M.; Laughner, E.; Lim, M.; Hilton, D. A.; Zagzag, D.; Buechler, P.; Isaacs, W. B.; Semenza, G. L.; Simons, J. W., Overexpression of Hypoxia-inducible Factor 1 alpha in Common Human Cancers and Their Metastases. *Cancer Research* **1999,** *59* (22), 5830-5835.

9. Brown, J. M.; Giaccia, A. J., The Unique Physiology of Solid Tumors: Opportunities (and Problems) for Cancer Therapy. *Cancer Research* **1998,** *58* (7), 1408-1416.

10. (a) Post, D. E.; Van-Meir, E. G., Generation of bidirectional hypoxia/HIF-responsive expression vectors to target gene expression to hypoxic cells. *Gene Ther* **2001,** *8*, 1801-7; (b) Post, D. E.; Devi, N. S.; Li, Z.; Brat, D. J.; Kaur, B.; Nicholson, A.; Olson, J. J.; Zhang, Z.; Van-

Meir, E. G., Cancer therapy with a replicating oncolytic adenovirus targeting the hypoxic microenvironment of tumors. *Clin Cancer Res* **2004,** *10*, 8603-12; (c) Post, D. E.; Van-Meir, E. G., A novel hypoxia-inducible factor (HIF) activated oncolytic adenovirus for cancer therapy. . *Oncogene* **2003,** *22*, 2065-72; (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E., Natural Product-like Combinatorial Libraries Based on Privileged Structures. 2. Construction of a 10,Äâ000-Membered Benzopyran Library by Directed Split-and-Pool Chemistry Using NanoKans and Optical Encoding. *Journal of the American Chemical Society* **2000,** *122* (41), 9954-9967; (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E., Natural Product-like Combinatorial Libraries Based on Privileged Structures. 2. Construction of a 10,000-Membered Benzopyran Library by Directed Split-and-Pool Chemistry Using NanoKans and Optical Encoding. *Journal of the American Chemical Society* **2000,** *122* (41), 9954-9967; (f) Tan, C.; de Noronha, R. G.; Roecker, A. J.; Pyrzynska, B.; Khwaja, F.; Zhang, Z.; Zhang, H.; Teng, Q.; Nicholson, A. C.; Giannakakou, P.; Zhou, W.; Olson, J. J.; Pereira, M. M.; Nicolaou, K. C.; Van Meir, E. G., Identification of a Novel Small-Molecule Inhibitor of the Hypoxia-Inducible Factor 1 Pathway. *Cancer Research* **2005,** *65* (2), 605-612.

11. Tan, C.; de Noronha, R. G.; Devi, N. S.; Jabbar, A. A.; Kaluz, S.; Liu, Y.; Mooring, S. R.; Nicolaou, K. C.; Wang, B.; Van Meir, E. G., Sulfonamides as a new scaffold for hypoxia inducible factor pathway inhibitors. *Bioorganic & Medicinal Chemistry Letters* **2011,** *21* (18), 5528-5532.

12. (a) Mooring, S. R.; Jin, H.; Devi, N. S.; Jabbar, A. A.; Kaluz, S.; Liu, Y.; Van Meir, E. G.; Wang, B., Design and Synthesis of Novel Small-Molecule Inhibitors of the Hypoxia Inducible Factor Pathway. *Journal of Medicinal Chemistry* **2011,** *54* (24), 8471-8489; (b) Mun,

J.; Jabbar, A. A.; Devi, N. S.; Liu, Y.; Van Meir, E. G.; Goodman, M. M., Structure–activity relationship of 2,2-dimethyl-2H-chromene based arylsulfonamide analogs of 3,4-dimethoxy-N-[(2,2-dimethyl-2H-chromen-6-yl)methyl]-N-phenylbenzenesulfonamide, a novel small molecule hypoxia inducible factor-1 (HIF-1) pathway inhibitor and anti-cancer agent. *Bioorganic & Medicinal Chemistry* **2012,** *20* (14), 4590-4597; (c) Mun, J.; Jabbar, A. A.; Devi, N. S.; Yin, S.; Wang, Y.; Tan, C.; Culver, D.; Snyder, J. P.; Van Meir, E. G.; Goodman, M. M., Design and in Vitro Activities of N-Alkyl-N-[(8-R-2,2-dimethyl-2H-chromen-6-yl)methyl]heteroarylsulfonamides, Novel, Small-Molecule Hypoxia Inducible Factor-1 Pathway Inhibitors and Anticancer Agents. *Journal of Medicinal Chemistry* **2012,** *55* (15), 6738-6750.

13. (a) Shi, Q.; Yin, S.; Kaluz, S.; Ni, N.; Devi, N. S.; Mun, J.; Wang, D.; Damera, K.; Chen, W.; Burroughs, S.; Mooring, S. R.; Goodman, M. M.; Van Meir, E. G.; Wang, B.; Snyder, J. P., Binding Model for the Interaction of Anticancer Arylsulfonamides with the p300 Transcription Cofactor. *ACS Medicinal Chemistry Letters* **2012,** *3* (8), 620-625; (b) Yin, S.; Kaluz, S.; Devi, N. S.; Jabbar, A. A.; de Noronha, R. G.; Mun, J.; Zhang, Z.; Boreddy, P. R.; Wang, W.; Wang, Z.; Abbruscato, T.; Chen, Z.; Olson, J. J.; Zhang, R.; Goodman, M. M.; Nicolaou, K. C.; Van Meir, E. G., Arylsulfonamide KCN1 Inhibits In Vivo Glioma Growth and Interferes with HIF Signaling by Disrupting HIF-1α Interaction with Cofactors p300/CBP. *Clinical Cancer Research* **2012,** *18* (24), 6623-6633; (c) Wang, W.; Ao, L.; Rayburn, E. R.; Xu, H.; Zhang, X.; Zhang, X.; Nag, S. A.; Wu, X.; Wang, M.-H.; Wang, H.; Van Meir, E. G.; Zhang, R., KCN1, a Novel Synthetic Sulfonamide Anticancer Agent: *In Vitro* and *In Vivo* Anti-Pancreatic Cancer Activities and Preclinical Pharmacology. *PLoS ONE* **2012,** *7* (9), e44883.

14. Liebmann, J.; Cook, J.; Mitchell, J., Cremophor EL, solvent for paclitaxel, and toxicity. *The Lancet* **1993,** *342* (8884), 1428.

15. VCCLAB Virtual computational chemistry laboratory. http://www.vcclab.org (accessed 01/02/2013).

16. Prado, S.; Janin, Y. L.; Saint-Joanis, B.; Brodin, P.; Michel, S.; Koch, M.; Cole, S. T.; Tillequin, F.; Bost, P.-E., Synthesis and antimycobacterial evaluation of benzofurobenzopyran analogues. *Bioorganic & Medicinal Chemistry* **2007,** *15* (5), 2177-2186.

5 DESIGN AND SYNTHESIS OF NOVEL KCN1 ANALOGS AS ANTI-CANCER THERAPEUTICS

The work presented in this chapter is based on a manuscript in preparation for submission to ChemMedChem. This chapter includes compounds synthesized by Jalisa Holmes,[§] Zeus de los Santos,[δ] Bowen Ke,[γ] Suazette Mooring,[ϒ] and Krishna Damera.[≠]

5.1 Abstract

In the field of cancer therapeutics, a change needs to be made from cytotoxic agents to direct, targeted therapy. Herein, we describe the design and synthesis of such agents that selectively target the HIF pathway.

5.2 Introduction

One of the environments in which cancerous cells thrive is hypoxia, a condition in which the presence of oxygen is very low or nonexistent. This condition is present in many types of cancers, as the cells in solid tumor masses will have low oxygen pressure due to minimized vasculature[1]. Under these hypoxic conditions, the Hypoxia Inducible Factor (HIF) pathway activates a number of genes that eventually lead to the upregulation of many other biological

pathways including cell growth, glycolysis and angiogenesis[2]. The basic-loop-helix-loop motif heterodimeric transcription factor HIF-1 complex is comprised of two subunits: HIF-1α and HIF-1β. Normally, in cells where oxygen is present, HIF-1α is oxidized by the enzyme prolyl hydroxylase (PHD). The dihydroxylated form of HIF-1 α is then bound by the von Hippel-Lindau tumor suppressor protein (VHL), which leads to ubiquitination of HIF-1α and its subsequent proteosomal degradation.[3] In contrast, under hypoxic conditions the dihydroxylated form of HIF-1 is not formed. Instead, HIF-1α binds with HIF-1β to form a heterodimer, which binds to coactivator p300. At this point, the entire complex acts as a transcription factor of many genes, such as *VEGF* (vascular endothelial growth factor), *EPO* (eythropoietin), *GLUT1* (glucose transporter 1), *LDH-A* (lactate dehydrogenase), and *NOS* (nitric oxide synthase) by binding to 5'-HRE (hypoxic response element) promoter regions.[4] The expression of this HIF-1 pathway is associated with several types of cancer and is also related to low success rates of various treatment methods[5].

Toward the goal of finding small-molecule inhibitors of the HIF pathway, our collaborators at Emory University, the Erwin van Meir laboratory, developed an HRE-alkaline phosphatase assay to screen a library of 10,000 compounds from a 2,2-dimethylbenzopyran combinatorial library.[6] The HRE-alkaline phosphatase assay uses LN229 glioblastoma cells transfected with the alkaline phosphatase reporter and 6 copies of the HRE (hypoxia response element) for the VEGF gene.[7] This initial screening yielded a few promising hits, with the lead compound identified as KCN-1 **1** (Figure 5.1a) having an IC_{50} of 0.59 μM.[8] KCN-1 was then taken to preliminary *in vivo* studies, where nude mice were implanted with LN229 glioblastoma cells on their hind flanks. After 1 week, the mice were either injected with KCN-1 (60mg/kg; 5 days/week) or vehicle (DMSO) only. The KCN-1 mice had tumors that were 6-fold decreased in

size compared to the vehicle only mice and some of the tumors had disappeared completely. The KCN-1 mice did not appear to suffer negative side effects from the KCN-1 treatment.[9] It is important to note that these compounds do not decrease levels of HIF-1 and are not cytotoxic, in contrast to most anti-cancer therapeutics. With KCN-1 as the original lead compound, our laboratory began synthesis of a library of analogs. Over 100 compounds were synthesized. This initial library of analogs was screened against a human glioblastoma cell line LN229-HRE-Luc, with luciferase replacing alkaline phosphatase. From this initial study, *N*-cyclobutyl-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide **2** (Figure 5.1b), with IC_{50} 0.28 μM was chosen as the optimized lead for further study.[10] With such promising results from theses initial studies, we pursued further lead optimization and broadening of the library for hope of in more potent compounds and to further develop our SAR (structure-activity relationship).

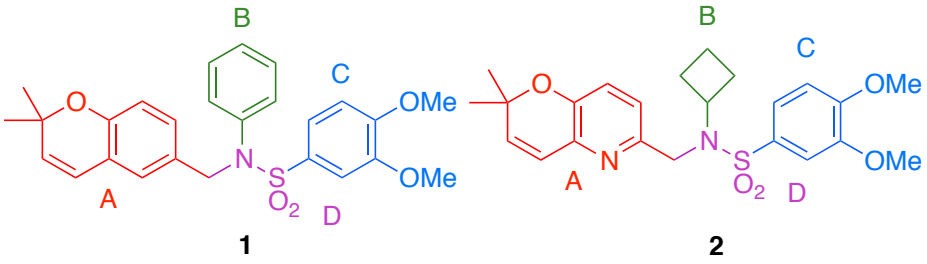


Figure 5.1. Lead compounds.

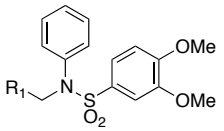
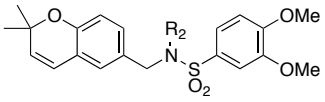
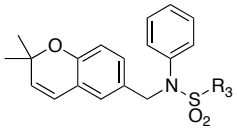
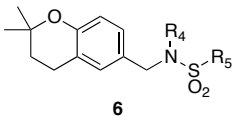
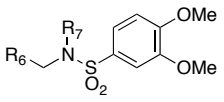
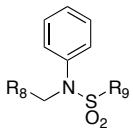
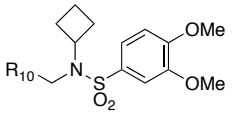
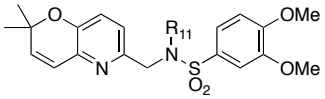
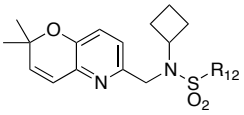
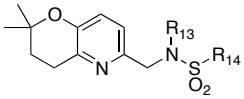
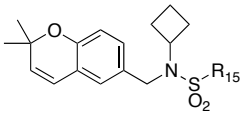
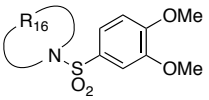
a) Lead compound **1**, b) Lead compound **2**

5.3 Results and Discussion

5.3.1 Design

Lead compounds **1** and **2** were divided into 4 parts (Figure 5.1): the left-hand core (A, red), the N-substituent (B, green), the right-hand ring (C, blue), and the linker (D, violet).

Table 5.1. Classes of analogs

Class 1A	Class 1B	Class 1C
 **3**	 **4**	 **5**
Class 1D	Class 1E	Class 1F
 **6**	 **7**	 **8**
Class 2A	Class 2B	Class 2C
 **9**	 **10**	 **11**
Class 2D	Class 3	Class 4
 **12**	 **13**	 **14**

Analogs were designed and synthesized based off of modifications of these 4 parts. In total, 11 classes of analogs, for a total of 50 compounds, were devised as described in Table 5.1. Class 1A-1F are KCN analogs: Class 1A has the A ring modified; Class 1B has the B ring modified; Class 1C has the C ring modified; Class 1D has a hydrogenated 2,2-dimethylpyranobenzene A ring, and modifications to both the B and C rings; Class 1E has both the A and B rings modified; and Class 1F has both the A and C rings modified. Class 2A-2D are 64b analogs: Class 2A has A ring modifications; Class 2B has B ring modifications; Class 2C has C ring modifications; and

Class 2D has a hydrogenated 2,2-dimethylpyranopyridine A ring. Class 3 compounds are hybrid **1**/**2** analogs with the A ring from **1**, the B ring from **2**, and modifications to the **C** ring. Class 4 is a new class of aryl sulfonamides with the A and B rings fused together and constrained in a ring.

5.3.2 Chemistry

5.3.2.1 Class 1A analogs

Class 1A analogs were synthesized in two steps (Figure 5.2) from either commercially available aldehydes or aldehydes readily synthesized from literature procedures (see supporting information S1).[11] These aldehydes **15** underwent reductive amination with aniline. The subsequent secondary amines **16** were next reacted with 3,4-dimethoxysulfonyl chloride to yield the sulfonamide final products **3a**-**3m**.

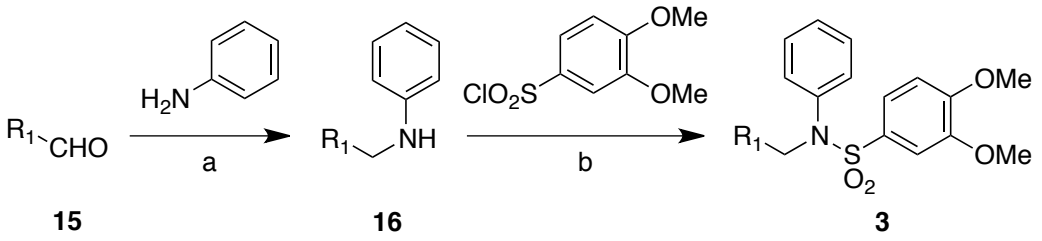


Figure 5.2. Synthesis of Class 1A analogs

R_1 = 6-(2,2-dimethylchroman-yl) (**3a**)*, 3-(7-((tetrahydro-2*H*-pyran-2-yl)oxy)-2*H*-chromen-yl) (**3b**), 6-(7-bromo-2,2-dimethyl-2*H*-chromen-yl) (**3c**), 6-(2,2,8-trimethyl-2*H*-chromen-yl) (**3d**), 6-(trimethyl-2*H*-chromene-yl) (**3e**), 6-(2,2-dimethyl-2,7b-dihydro-1a*H*-oxireno[2,3-*c*]chromen-yl) (**3f**)*, 4-(benzo[*d*][1,3]dioxol-yl), 5-(benzo[*c*][1,2,5]oxadiazol-yl) (**3h**), 4-(morpholinomethyl)phenyl (**3i**), 5-(2,3-dihydrobenzofuranyl) (**3j**), 2-bromophenyl (**3k**), 6-(5,7-difluoro-2,2-dimethyl-2*H*-chromen-yl) (**3l**), 6-(5-fluoro-2,2-dimethyl-2*H*-chromen-yl) with 6-(7-fluoro-2,2-dimethyl-2*H*-chromen-yl) (**3m**). Reagents and conditions: (a) $InCl_3$, $NaBH_4$, MeOH,

room temperature, 20 minutes, 23-91%; (b) K_2CO_3, DCM, room temperature, overnight, 11-84%.***3a** and **3f** were synthesized from **1**, see Schemes 4 and supporting information

5.3.2.2 Class 1B analogs

Class 1B analogs were synthesized in two steps (Figure 5.3) from 2,2-dimethyl-2*H*-chromene-6-carbaldehyde **17**, which was synthesized from literature procedure (see supporting information S2).[11] **17** underwent reductive amination with various amines to form secondary amines **18**, which were next reacted with 3,4-dimethoxysulfonyl chloride to yield the final products sulfonamides **4a**.

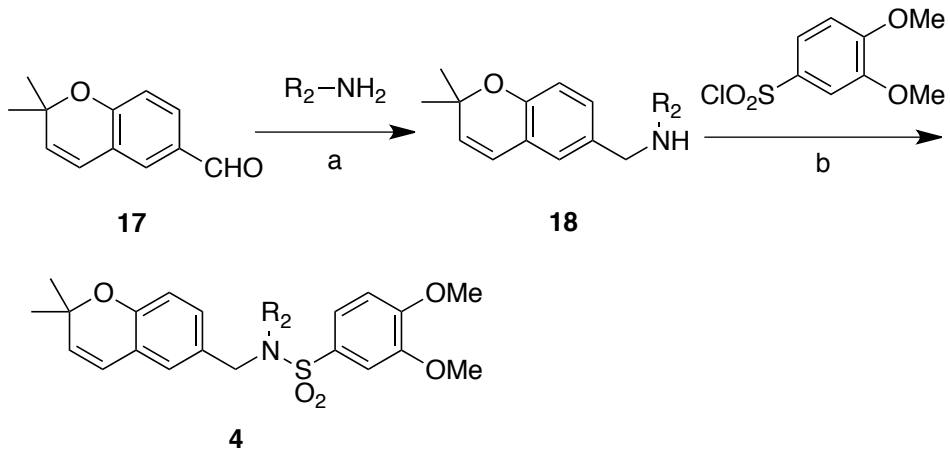


Figure 5.3. Synthesis of Class 1B analogs

R_2 = oxetan-3-ylmethyl (**4a**). Reagents and conditions: (a) $InCl_3$, $NaBH_4$, MeOH, room temperature, 20 minutes, 92%; (b) K_2CO_3, DCM, room temperature, overnight, 69%

5.3.2.3 Class 1C analogs

Class 1C analogs were synthesized in two steps (Figure 5.4) from 2,2-dimethyl-2*H*-chromene-6-carbaldehyde **17**, which underwent reductive amination with aniline to yield *N*-

((2,2-dimethyl-2*H*-chromen-6-yl)methyl)aniline **19**. **19** was next reacted with various sulfonyl chlorides to yield the final products sulfonamides **5a**-**5d**.

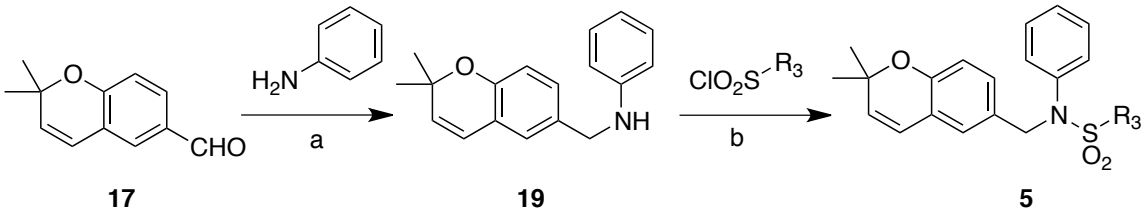


Figure 5.4. Synthesis of Class 1C analogs

R_3 = 3-methoxyphenyl (**5a**), 4-(trifluoromethoxy)phenyl (**5b**), 4-(carboxymethyl)phenyl (**5c**), 3,4-difluorophenyl (**5d**), 4-methoxyphenyl (**5e**),. Reagents and conditions: (a) $InCl_3$, $NaBH_4$, MeOH, room temperature, 20 minutes, 80%; (b) K_2CO_3, DCM, room temperature, overnight, 6-69%

5.3.2.4 Class 1D analogs

Class 1D analogs were synthesized in three steps (Figure 5.5) from 2,2-dimethyl-2*H*-chromene-6-carbaldehyde **17,** which underwent reductive amination with various amines to yield secondary amines **20**. **20** were next reacted with various sulfonyl chlorides to yield sulfonamides **21**, which were then hydrogenated to yield final products **6a**-**6c**.

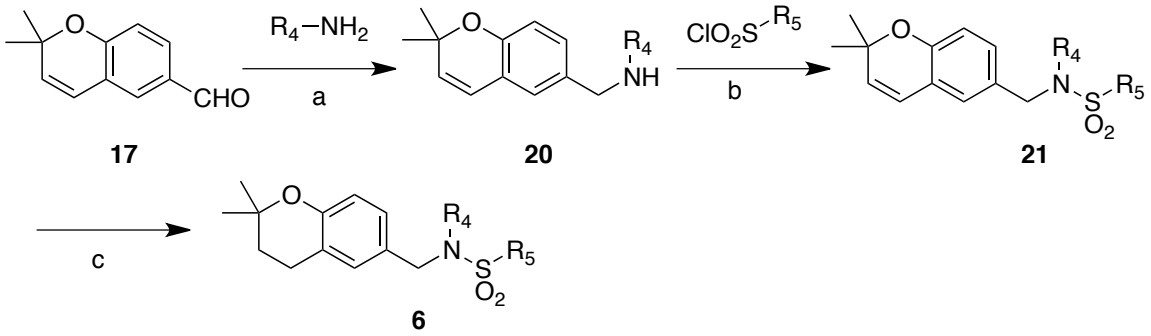


Figure 5.5. Synthesis of Class 1D analogs

R_4 = phenyl, R_5 = 4-methoxyphenyl (**6a**), R_4 = oxetan-3-ylmethyl, R_5 = 3,4-dimethoxyphenyl (**6b**), R_4 = cyclobutyl, R_5 = 3,4-dimethoxyphenyl (**6c**). Reagents and conditions: (a) $InCl_3$, $NaBH_4$, MeOH, room temperature, 20 minutes, 80%; (b) K_2CO_3, DCM, room temperature, overnight, 69-75%; (c) H_2, MeOH, overnight, 70-99%

5.3.2.5 Class 1E analogs

Class 1E analogs were synthesized in two steps (Figure 5.6) from commercially available aldehyde **22. 22** underwent reductive amination with various amines to yield secondary amines **23**, which were next reacted with 3,4-dimethoxyl sulfonyl chloride to yield the final product sulfonamide **7a**.

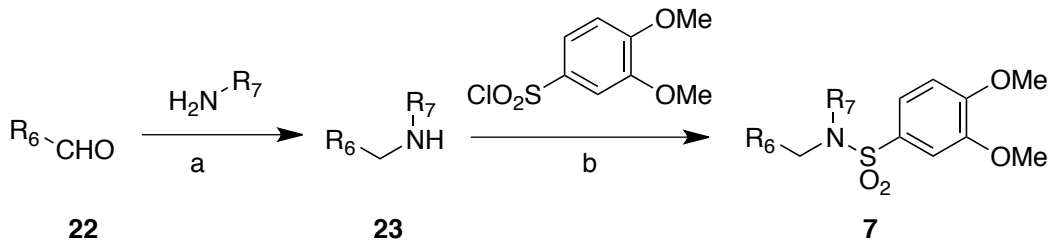


Figure 5.6. Synthesis of Class 1E analogs

R_6 = R_7 = 4-(3',4'-dimethoxybenzenesulfonyl)phenyl (**7a**). Reagents and conditions: (a) $InCl_3$, $NaBH_4$, MeOH, room temperature, 20 minutes, 86%; (b) K_2CO_3, DCM, room temperature, overnight, 73%.

5.3.2.6 Class 1F analogs

Class 1F analogs were synthesized in two steps (Figure 5.7) from commercially available aldehydes **24.** **24** underwent reductive amination with aniline to yield secondary amines **25**, which were next reacted with various sulfonyl chlorides to yield the final product sulfonamide **8a**.

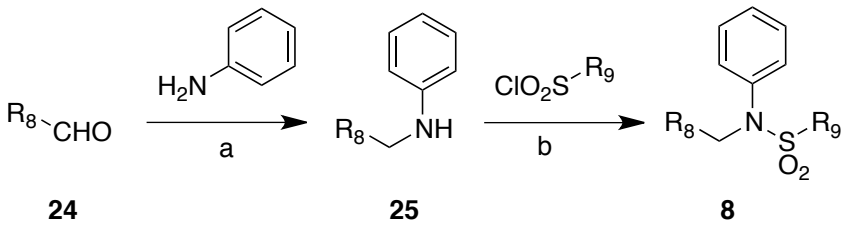


Figure 5.7. Synthesis of Class 1F analogs

R_8 = 5-(2,3-dihydrobenzofuran-yl), R_9 = 2,4-dihydroxyphenyl (**8a**), R_8 = phenyl, R_9 = 4-2'-bromoacetylphenyl (**8b**). Reagents and conditions: (a) $InCl_3$, $NaBH_4$, MeOH, room temperature, 20 minutes, 87-97%; (b) K_2CO_3, DCM, room temperature, overnight, 15-58%.

5.3.2.7 Class 2A analogs

Class 2A analogs were synthesized in two steps (Figure 5.8) from commercially available or previously synthesized aldehydes **26.** **26** underwent reductive amination with cyclobutylamine to yield secondary amines **27**, which were next reacted with 3,4-dimethoxy sulfonyl chloride to yield the final products sulfonamides **9a-n**.

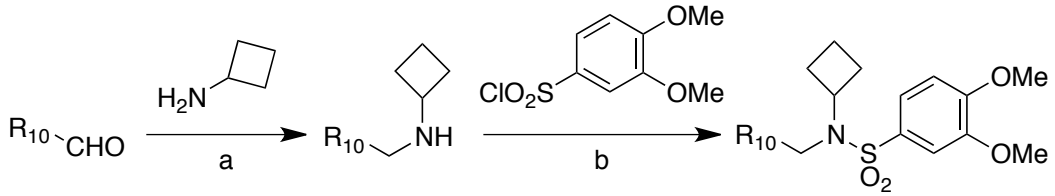


Figure 5.8. Synthesis of Class 2A analogs

R_{10} = 4-methoxyphenyl (**9a**), phenyl (**9b**), 2-nitrophenyl (**9c**), 2,4-dimethoxyphenyl (**9d**), 1*H*-pyrrol-2-yl (**9e**), 4-nitrophenyl (**9f**), 6-(5,7-difluoro-2,2-dimethyl-2*H*-chromenyl) (**9g**), 4-(morpholinomethyl)phenyl (**9h**), 5-benzo[*d*][1,3]dioxol-yl (**9i**), 5-(2,3-dihydrobenzofuranyl), (**9j**) 6-(2,2,8-trimethyl-2*H*-chromen-yl) (**9k**), 3-(7-((tetrahydro-2*H*-pyran-2-yl)oxy)-2*H*-chromen-yl) (**9l**), 6-(5,7-difluoro-2,2-dimethyl-2*H*-chromen-yl) (**9m**), 6-(5-fluoro-2,2-dimethyl-2*H*-chromen-yl) with 6-(7-fluoro-2,2-dimethyl-2*H*-chromen-yl) (**9n**) . Reagents and conditions: (a) $NaBH_4$, MeOH, room temperature, overnight, 26-90%; (b) K_2CO_3, DCM, room temperature, overnight, 11-72%.

5.3.2.8 Class 2B analogs

Class 2B analogs were synthesized in two steps (Figure 5.9) from 2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridine-6-carbaldehyde **28**, which was synthesized from literature procedure (see supporting information S2). **28** underwent reductive amination with various amines and the

subsequent secondary amines **29** were next reacted with 3,4-dimethoxysulfonyl chloride to yield the final products sulfonamide **10a-b**.

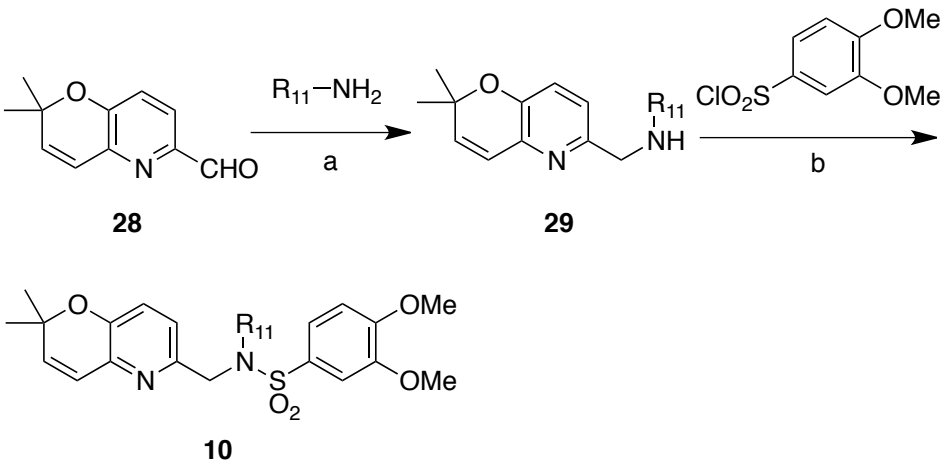


Figure 5.9. Synthesis of Class 2B analogs

R_{11} = 2-(3,4-dimethoxyphenyl)ethyl (**10a**), 2-morpholinoethyl (**10b**).Reagents and conditions: (a) $NaBH_4$, MeOH, room temperature, overnight, 38%; (b) K_2CO_3, DCM, room temperature, overnight, 29-35%.

5.3.2.9 Class 2C analogs

Class 2C analogs were synthesized in two steps (Figure 5.10) from 2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridine-6-carbaldehyde **28**. **28** underwent reductive amination with cyclobutylamine to yield *N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)cyclobutanamine **30,** what was next reacted with various sulfonyl chlorides to yield the final products sulfonamides **11a-c**.

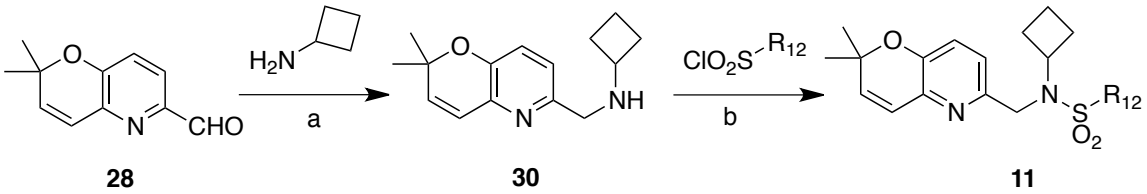


Figure 5.10. Synthesis of Class 2C analogs

R_{12} = 4-methoxyphenyl (**11a**), 4-(bromomethyl)phenyl (**11b**), 4-trifluoromethoxyphenyl (**11c**), 2-methoxyphenyl (**11d**). Reagents and conditions: (a) $NaBH_4$, MeOH, room temperature, overnight; (b) K_2CO_3, DCM, room temperature, overnight, 53-78%

5.3.2.10 Class 2D analogs

Class 2D analogs were synthesized in three steps (Figure 5.11) from 2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridine-6-carbaldehyde **28.** **28** underwent reductive amination with various amines to yield secondary amines **31**, which were next sulfonylated with various sulfonyl chlorides to yield sulfonamides **32**. The sulfonamides were then hydrogenated to yield final products **12a-b**.

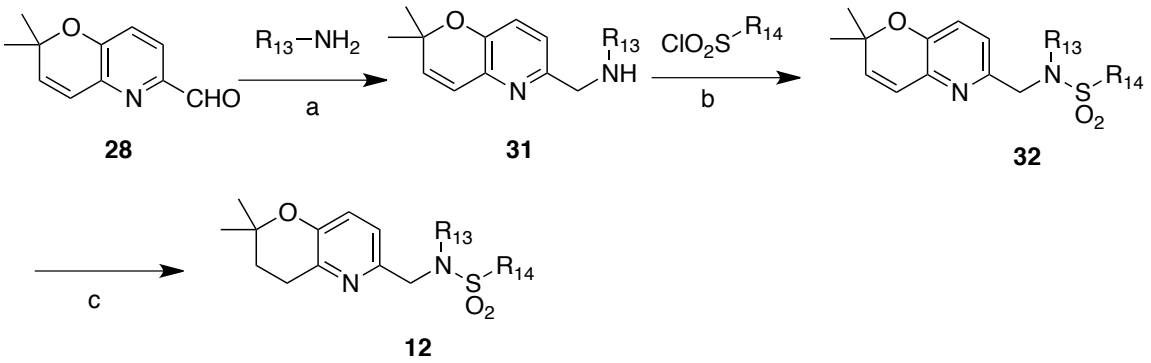


Figure 5.11. Synthesis of Class 2D analogs

R_{13} = cyclobutyl, R_{14} = 3,4-dimethoxylphenyl (**12a**); R_{13} = cyclobutyl, R_{14} = 4-methoxylphenyl (**12b**). Reagents and conditions: (a) $NaBH_4$, MeOH, room temperature, overnight; (b) K_2CO_3, DCM, room temperature, overnight, 73-78%; (c) H_2, MeOH, overnight, 89-98%

5.3.2.11 Class 3 analogs

Class 3 analogs were synthesized in two steps (Figure 5.12) from 2,2-dimethyl-2*H*-chromene-6-carbaldehyde **18**. **18** underwent reductive amination with cyclobutylamine to yield *N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine **33,** which was next reacted with various sulfonyl chlorides to yield the final products sulfonamides **13a-e**.

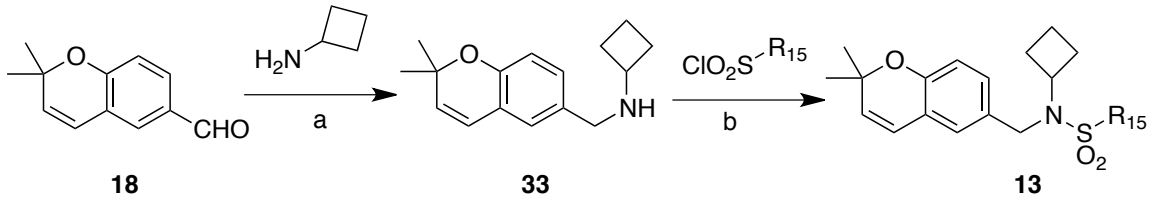


Figure 5.12. Synthesis of Class 3A analogs

R_{15} = 3,4-dimethoxyphenyl (**13a**), 4-bromophenyl (**13b**), 4-trifluoromethylphenyl (**13c**), 4-(3,5-dimethylisoxazol-yl) (**13d**), 3,4-difluorophenyl (**13e**) 2-methoxyphenyl (**13f**). Reagents and conditions: (a) $NaBH_4$, MeOH, room temperature, overnight, 90%, (b) K_2CO_3, DCM, room temperature, overnight, 56-77%

5.3.2.12 Class 4 analogs

Class 4 analogs were synthesized in 1 step (Figure 5.13) from commercially available secondary amines **34**, which were reacted with 3,4-dimethoxysulfonyl chloride to yield the final products sulfonamide **14a**.

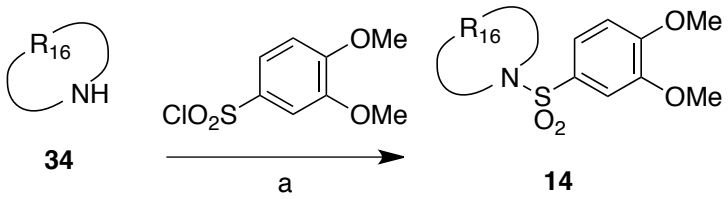


Figure 5.13. Synthesis of Class 4 analogs

R_{16} = 4-benzyl-pipirazinyl- (**14a**). Reagents and conditions: (a) K_2CO_3, DCM, room temperature, overnight,

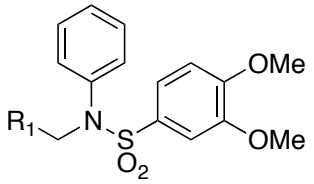
5.3.3 Biology

38 of the analogs were evaluated for their inhibitory effects on HIF-1-mediated transcription under hypoxic conditions on human glioma cells LN229-HRE-Lux. Each compound was tested against **2** as positive controls and IC_{50} values were determined as listed in tables 2-10.

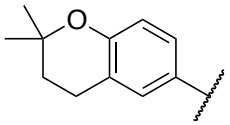
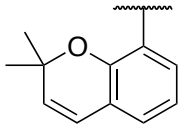
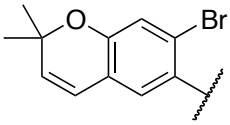
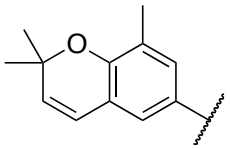
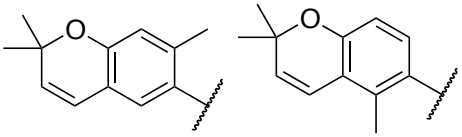
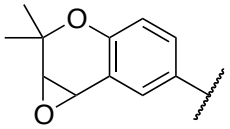
5.3.3.1 Class 1A

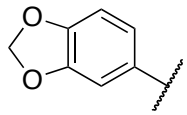
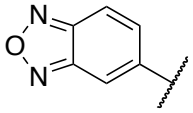
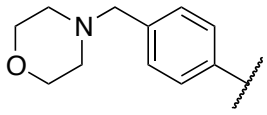
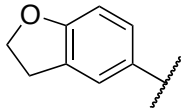
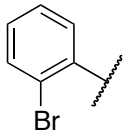
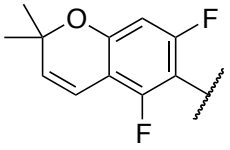
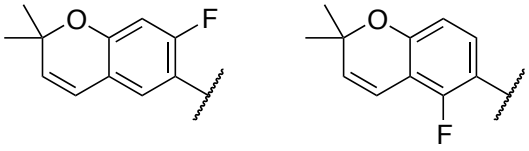
Class 1A analogs were designed to probe the importance of the features of the phenyl A ring to the activity of **1**. The first part of the A ring examined was the double bond in the pyran ring. In many cases, double bonds are not preferred in therapeutics because of the possibility of activation and/or metabolism by CYP proteins in the liver, which can lead to hepatoxicity *in vivo*. In our case, removal of the double bond, **3a**, results in only a small decrease (1.5-fold) in activity whereas the epoxidation product, **3f**, has dramatically (>13-fold) less activity. These observations let us know that our compounds do not likely require epoxidation by the liver for activity, and that, in fact, the double bond can be removed from the compound to decrease any hepatotoxicity that may arise in the future. Next, the point of attachment of the chromene ring was examined by changing it from carbon 6 to carbon 8, **3f**, which resulted in a 3-fold decrease in activity, confirming attachment at carbon 6 to be important. Next, substituents were introduced on the phenyl ring, **3c-3e**, which decreased the activity by 5-fold, which suggests a somewhat size constrained binding pocket. Finally, various other fused and open ring systems were synthesized, **3g-3i**, of which, only **3i** displayed any activity, which is most likely due to the solubility effects of the morpholine moiety.

Table 5.2. Class 1A analogs and IC_{50} data



3

	R_1	IC_{50} (μM)
3a		0.98 (n = 9)
3b		1.8
3c		3.1
3d		3.2
3e		3.3
3f		7.8

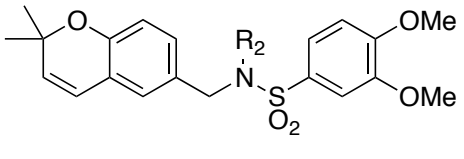
3g		>5
3h		>5
3i		1
3j		Not tested
3k		Not tested
3l		Not tested
3m		Not tested

5.3.3.2 Class 1B

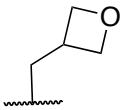
Class 1B analogs were designed to further probe the activity of the B ring and to try to introduce more polar groups and lower the logP to below 5. Although the analog **4a** had a

milogP 3.7 it was not very active, with an IC_{50} value of 4 μM. This suggests that the B ring could be pointing into a hydrophobic pocket and adding polar moieties in this position is thus unfavorable.

Table 5.3. Class 1B analogs and IC_{50} data



4

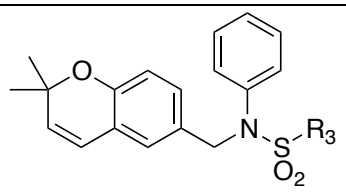
	R_2	IC_{50} (μM)
4a		4

5.3.3.3 Class 1C

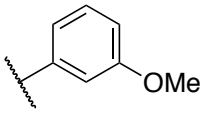
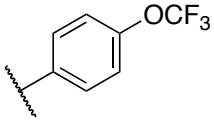
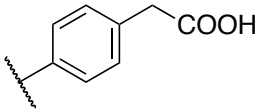
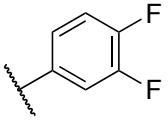
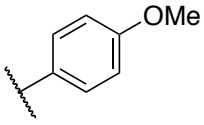
Class 1C analogs were designed to probe the activity of the moieties on the C ring. We probed the activities of this site by removing the 4'-methoxy to give **5a**, which resulted in a small 1.7-fold decrease in activity. We also removed the 3'-methoxy to give **5e**, (which was previously tested and described in our earlier work)[10] which resulted in a very small 1.1-fold decrease in activity. We next substituted the 4'-monomethoxy for a 4'-trifluoromethoxy moiety, **5b**, which resulted in a loss of activity. Thus, the 4'-methoxy moiety seems to be important for the biological activity and could possibly play a role in hydrogen bonding. We also made the 4'-methylcarboxylic acid derivative **5c** and the 3',4'-difluorophenyl derivative **5d**, but both had IC_{50}

values greater than 5 μM, respectively. Thus, the methoxy substituent in the 4' position seems to be needed for best activity while the 3'-methoxy is not as important.

Table 5.4. Class 1C analogs and IC_{50} data



5

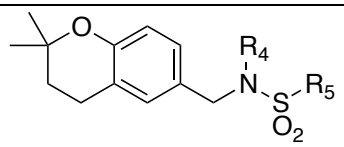
	R_3	IC_{50} (μM)
5a		1
5b		>5
5c		>5
5d		>5
5e		0.64

5.3.3.4 Class 1D

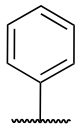
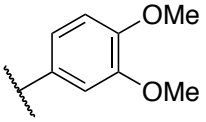
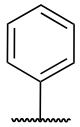
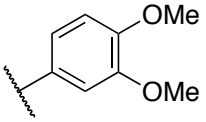
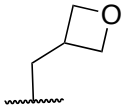
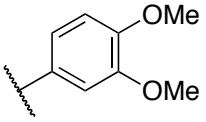
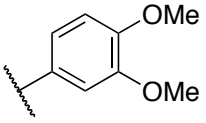
Class 1D analogs were designed to further probe the requirement of the double bond in the A ring. All class 1D analogs contain the hydrogenated chromene in the A ring position that

was originally reported in compound **3a**. Compounds **3a, 6a, 6b** all demonstrated decreased activity in comparison to their non-hydrogenated counterparts. However, hybrid **6c**, was more potent than its non-hydrogenated counterpart **16a** (discussed below).

Table 5.5. Class 1D analogs and IC_{50} data



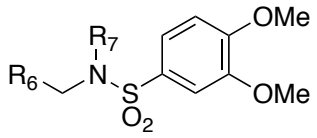
6

	R_4	R_5	IC_{50} (μM)
3a			0.98
6a			3.2
6b			>5
6c			0.39

5.3.3.5 Class 1E & 1F

Class 1E and 1F analogs did not display any activity. It seems that too many changes to the structure at once are deleterious and should be avoided.

Table 5.6. Class 1E analogs and IC_{50} data



7

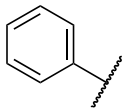
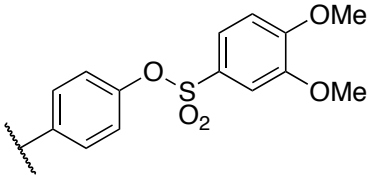
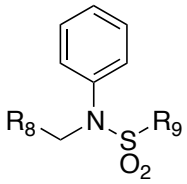
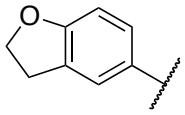
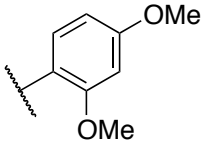
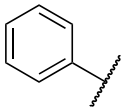
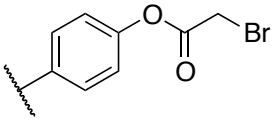
	R_6	R_7	IC_{50} (μM)
7a			>5

Table 5.7. Class 1F analogs and IC_{50} data



8

	R_8	R_9	IC_{50} (μM)
8a			>5
8b			Not tested

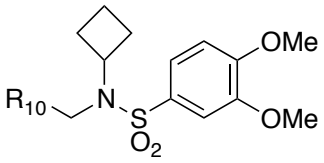
5.3.3.6 Class 2A

Class 2A analogs were designed to probe the importance of the features of the phenyl A ring to the activity of **2**. The first strategy was to remove the fused ring feature altogether and see whether a simple phenyl ring with various substituents would have activity. Unfortunately, only one such compound, **9a**, with a 4-methoxyphenyl A ring had any activity, and this activity was diminished by almost 14-fold from **2**. **9b-g** all had activities greater than 5 μM. This demonstrates the importance of the fused ring system to the activity. Next, a phenyl rings with a cyclic morpholine moiety in the 4-position was synthesized, **9h**, with the design of the substituent filling the space occupied by the fused ring. **9h** did show moderate activity, 1 μa. This compound contains a morpholine ring, which can increase the solubility of the compound. It is highly possible that increased solubility is responsible for the activity of this compound. Next, other fused ring systems were tried, **9i-j**. Both of these compounds showed moderate activity, but decreased by 2.5-fold to 6.0-fold with respect to **2**.

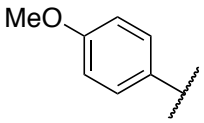
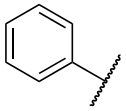
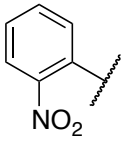
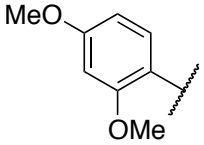
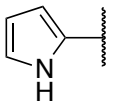
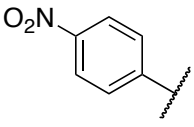
5.3.3.7 Class 2B

Class 2B analogs were designed to further probe the importance of the B ring to the activity of **2**. Many such compounds had been made in our previous work, but the new compound **10a** demonstrated no activity.

Table 5.8. Class 2A analogs and IC_{50} data



9

	R_{10}	IC_{50} (μM)
9a		3.9
9b		>5
9c		>5
9d		>5
9e		>5
9f		>5

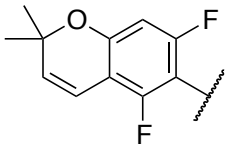
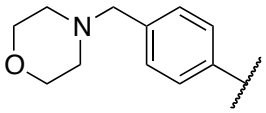
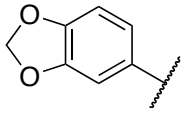
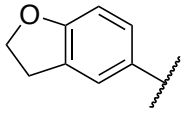
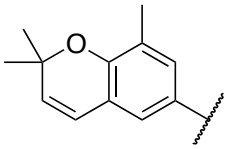
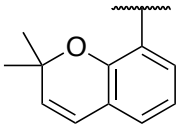
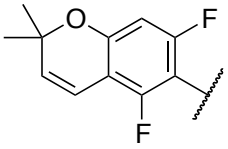
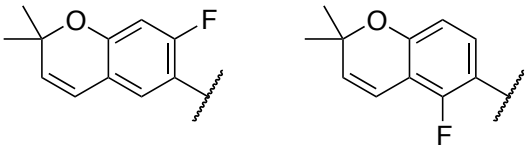
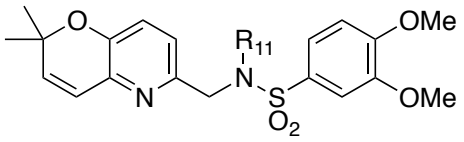
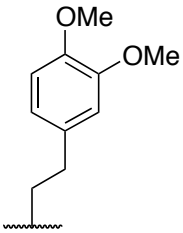
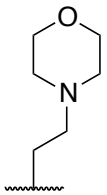
9g		2.3
9h		1
9i		1.25
9j		3.5
9k		Not tested
9l		Not tested
9m		2.3
9l		Not tested

Table 5.9. Class 2B analogs and IC_{50} data



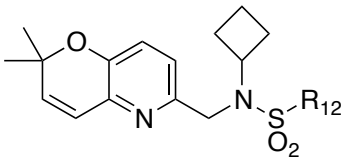
10

	R_{11}	IC_{50} (μM)
10a		>5
10b		Not tested

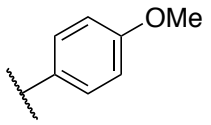
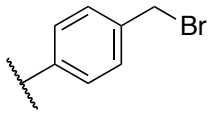
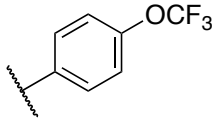
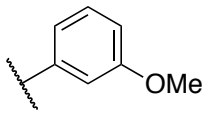
5.3.3.8 Class 2C

Class 2C analogs were designed to further probe the importance of the C ring to the activity of **2**. None of the compounds **11a-c** showed improved activity over **2**, with the best compound **11a** having activity of 1.8 μc. It is interesting to note, moreover, that **13a**, with the 3'-methoxy removed lost potency by 6.4-fold, whereas the similar analog to **1** did not lose activity. This suggests that **1** and **2** may bind to different sites or in different poses.

Table 5.10. Class 2C analogs and IC_{50} data



11

	R_{12}	IC_{50} (μM)
11a		1.8
11b		2.5
11c		4
11d		Not tested

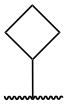
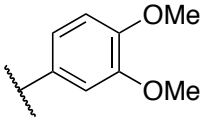
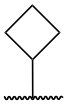
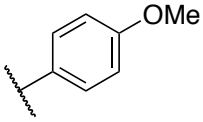
5.3.3.9 Class 2D

Class 2D analogs were designed to further probe the requirement of the double bond in the A ring. All class 2D analogs contain the hydrogenated chromene in the A ring position. It is interesting that **12a**, the hydrogenated form of **2**, demonstrated slightly better activity at 0.25 μM compared to 0.29 μM, which is a 1.1-fold increase in potency, as well as **12b**, which demonstrated slightly better activity at 1.2 μ than its non-hydrogenated counterpart **11a**, at 1.8

μM, which is a 1.5-fold increase in activity and makes **11a** the most potent compound described in this paper. Both of these compounds demonstrate that the double bond in the A ring is not required for potency, and may be eliminated with no loss of activity for **2** analogs.

Table 5.11. Class 2D analogs and IC_{50} data

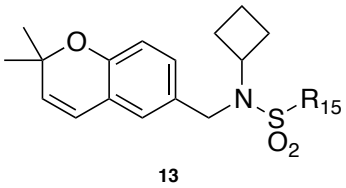
12

	R_{13}	R_{14}	IC_{50} (μM)
12a			0.25
12b			1.2

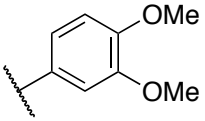
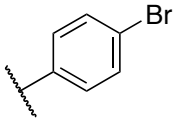
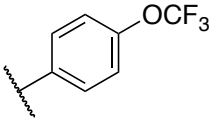
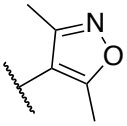
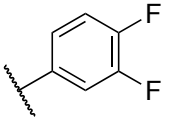
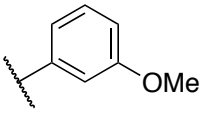
5.3.3.10 Class 3

Class 3 analogs are hybrid **1/2** compounds, with the A ring from **1** and the B ring from **2**. This combination seems to be acceptable, with **13a, 13b,** and **13e** demonstrating activity, with **16a** being the best at 0.75 μM. However, the hydrogenated counterpart to **16a**, **6c**, demonstrated activity at 0.39 μM, which is almost a 2-fold increase. This makes compound **6c** the second best overall compound synthesized herein.

Table 5.12. Class 3A analogs and IC_{50} data



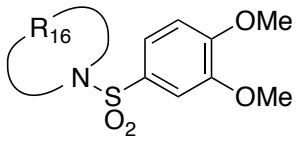
13

	R_{15}	IC_{50} (μM)
13a		0.75
13b		8
13c		>5
13d		>5
13e		4.6
13f		Not tested

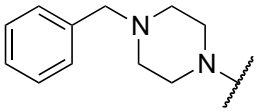
5.3.3.11 Class 4

Class 4 analogs are a new class of aryl sulfonamides with the A and B rings constrained together into various ring structures. The design was to add more heteroatoms and possible have a new backbone that could easily begin a new class of compounds. Unfortunately, this type of compound was not active and no further synthesis was pursued.

Table 5.13. Class 4 analogs and IC_{50} data



14

	R_{16}	IC_{50} (μM)
18f		>5

5.4 Conclusion

In conclusion, 50 analogs were synthesized, bringing the total number of analogs synthesized by this lab to over 200. As illustrated in Figure 5.14, a structure-activity relationship (SAR) was developed. For the A ring, the 2,2-dimethyl chromene with either a N or C in the 5 position is important to the activity. Open ring structures are not well tolerated, with the exception of some 4-position moderately polar substituents. The double bond is not crucial for activity of compounds and can be eliminated with the result of better or only slightly decreased activity. For the B ring, only hydrophobic groups, such as aromatics or small aliphatic rings or chains are acceptable. Introduction of polar moieties in this position dramatically decreases the

activity. For the C ring, 3',4'-dimethoxy is still the best, with the 4'-methoxy more crucial to activity than the 3'-methoxy. As for the D linker, aryl sulfonamides are still the best and combining the A and B rings was not successful.

The overall best compound was **12a**, with activity of 0.25 μM. This is slightly better than the previous best compound **2**, which had activity of 0.28 μM. After comparison of over 200 compounds, it appears that small structural modifications are not yielding orders of magnitude increased potency. In the future, other avenues will be pursued, such as dramatically changing the aryl sulfonamide backbone or adding water-soluble moieties to increase desired pharmacokinetic properties.

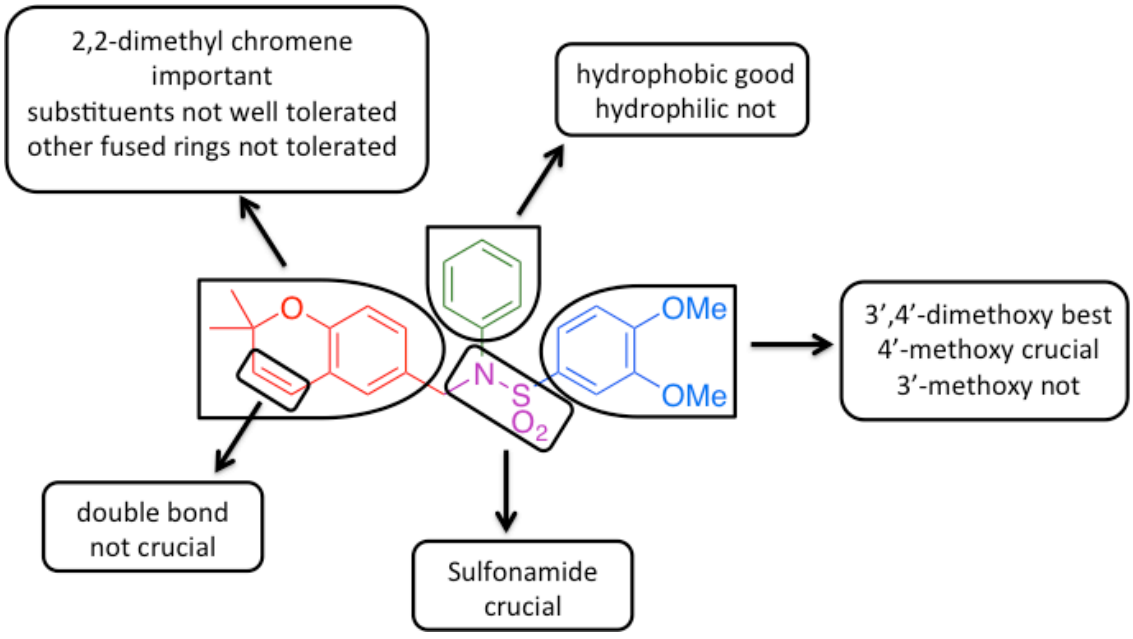


Figure 5.14. SAR of analogs

5.5 Experimental

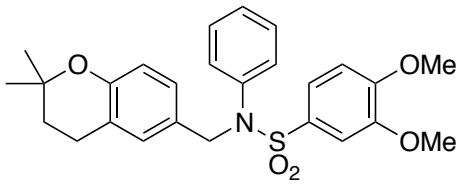
Typical procedure for reductive amination with cyclobutyl amine: 1 equivalent of aldehyde was dissolved in anhydrous MeOH under N_2. 1.05 equivalents of cyclobutyl amine were added and the reaction stirred overnight at room temperature. 1.6 equivalents of $NaBH_4$ were added and the

reaction stirred for 1 hour. The reaction was quenched with saturated NH_4Cl, taken up in ethyl acetate, washed with brine, dried over $MgSO_4$, concentrated, and taken directly to the next step without further purification.

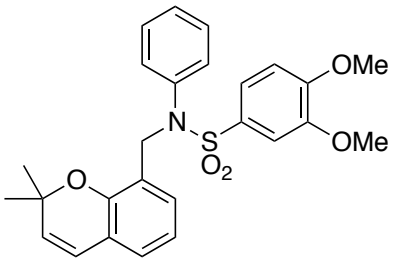
Typical procedure for reductive amination with aniline**:** 1 equivalent of aldehyde, 1.5 equivalents of $NaBH_4$, and 0.15 equivalents of $InCl_3$ were dissolved in anhydrous ACN under N_2. 1.5 equivalents of aniline were added and the reaction stirred until completion by TLC (typically ~20 minutes). The reaction was quenched with saturated NH_4Cl, taken up in ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated. Purified by column chromatography.

Typical procedure for sulfonylation**:** 1 equivalent of amine was dissolved in DCM. 2 equivalents of K2CO3 were added. 2 equivalents of sulfonylchloride were added. The reaction was stirred overnight at room temperature, then washed with brine, dried over $MgSO_4$, and concentrated. Purified by column chromatography.

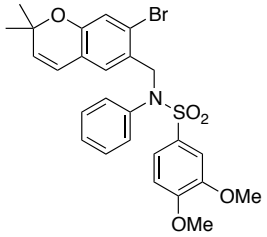
Typical procedure for hydrogenation: 1 equivalent of alkene, 10 mol% Pd/C was dissolved in anhydrous MeOH. The reaction vessel was flushed 3 x H_2 and then stirred overnight at room temperature. The reaction mixture was filtered through celite, concentrated, and purified by column chromatography.



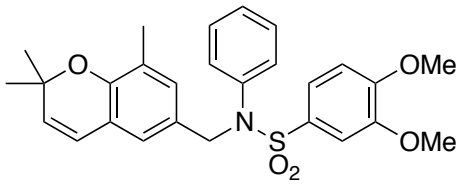
***N*-((2,2-Dimethylchroman-6-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3a)** Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (d, *J* = 8 Hz, 1H), 7.23 (m, 3H), 7.02-6.93 (m, 5H), 6.89-6.87 (d, *J* = 8 Hz, 1H), 6.62-6.60 (d, *J* = 8 Hz, 1H), 4.63 (s, 2H), 3.97 (s, 3H), 3.77 (s, 3H), 2.70-2.67 (t, *J* = 6 Hz, 2H), 1.77-1.74 (t, *J* = 6 Hz, 1H), 1.30 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 152.5, 148.7, 129.8, 129.3, 129.2, 128.8, 127.7, 127.6, 126.9, 122.2, 121.4, 120.8, 117.0, 110.4, 110.4, 74.22, 56.2, 56.1, 54.3, 32.7, 26.8, 22.3 ppm. HRMS (ESI) calculated for $C_{26}H_{29}NO_5SNa$ [$(M + Na)^+$] 490.1664, found 490.1666. HPLC ret time 17.550 min, 100%.



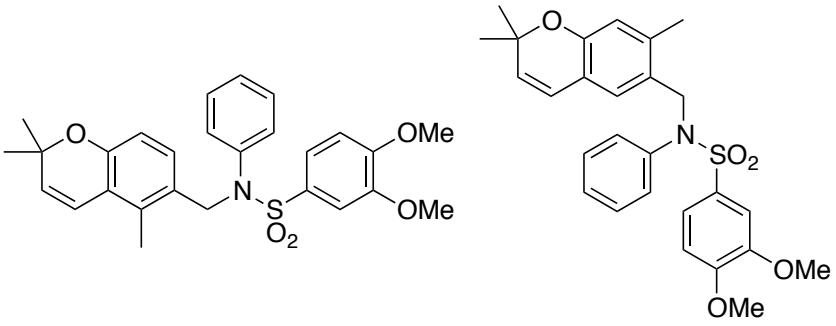
***N*-((2,2-Dimethyl-2*H*-chromen-8-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3b)** Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.34 (dd, *J* = 8, 2Hz, 1H), 7.26-7.20 (m, 4H), 7.08-7.06 (d, *J* = 8 Hz, 1H), 6.98-6.98 (d, *J* = 2 Hz, 1H), 6.95-6.93 (d, *J* = 8 Hz, 1H), 6.82-6.80 (m, 1H), 6.76-6.24 (m, 1H), 6.24-6.22 (d, *J* = 10 Hz, 1H), 5.54-5.51 (d, *J* = 10 Hz, 1H), 3.99 (s. 3H), 3.76 (s, 3H), 1.25 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 150.6, 148.7, 139.6, 130.5, 130.5, 129.9, 128.9, 128.6, 127.6, 125.7, 123.2, 122.2, 121.4, 120.9, 120.2, 110.4, 110.4, 76.3, 56.2, 56.1, 47.9, 27.8 ppm. HRMS *m/z* (ESI) calculated for $C_{22}H_{29}N_2O_4S$ [$(M + H)^+$] 417.1848, found 417.1848



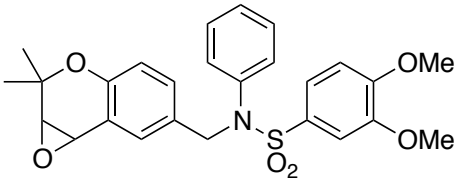
***N*-((7-Bromo-2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3c)** Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.32 (dd, *J* = 8 Hz, 2 Hz, 1H), 7.32-7.24 (m, 3H), 7.14 (s, 1H), 7.01-6.93 (m, 4H), 6.84 (s, 1H), 6.21-6.19 (d, *J* = 8 Hz, 1H), 5.63-5.61 (d, *J* = 8 Hz, 1H), 4.58 (s, 2H), 3.97 (s, 3H), 3.77 (s, 3H), 1.44 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 149.2, 148.8, 139.0, 132.3, 131.7, 130.2, 129.3, 129.0, 128.9, 128.0, 125.5, 122.5, 121.8, 121.4, 110.4, 110.4, 110.1, 76.7, 56.2, 53.7, 28.0 ppm. HRMS *m/z* (ESI) calculated for $C_{26}H_{27}BrNO_5S$ [$(M + H)^+$] 544.0793, found 544.0790. HPLC ret time 25.347 min, 97%.



3,4-Dimethoxy-*N*-phenyl-*N*-((2,2,8-trimethyl-2*H*-chromen-6-yl)methyl)benzenesulfonamide (3d) Yield: 18% over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.33 (dd, *J* = 8, 2 Hz, 1H), 7.23-7.22 (m, 2H), 7.02-6.97 (m, 4H), 6.94-6.92 (d, *J* = 8 Hz, 1H), 6.81 (s, 1H), 6.68 (s, 1H), 6.21-6.19 (d, *J* = 8 Hz, 1H), 5.56-5.54 (d, *J* = 8 Hz, 1H), 4.59 (s, 2H), 3.97 (s, 3H), 3.77 (s, 3H), 2.08 (s, 3H), 1.38 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 150.4, 148.7, 139.2, 130.7, 130.5, 129.2, 128.8, 127.7, 127.3, 125.4, 124.2, 122.5, 121.4, 120.5, 118.5, 110.4, 110.3, 76.0, 56.2, 56.1, 54.3, 28.0, 15.4 ppm. HRMS *m/z* (ESI) calculated for $C_{27}H_{29}NO_5SNa$ [$(M + Na)^+$] 502.1664, found 502.1657.

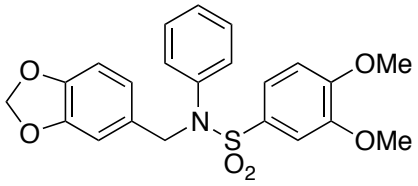


3,4-Dimethoxy-*N*-phenyl-*N*-((2,2,5-trimethyl-2*H*-chromen-6-yl)methyl)benzenesulfonamide and 3,4-Dimethoxy-*N*-phenyl-*N*-((2,2,7-trimethyl-2*H*-chromen-6-yl)methyl)benzenesulfonamide (2:1) (3e) Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.34 (dd, *J* = 8, 2 Hz, 3H), 7.20-7.18 (m, 9H), 6.98-6.91 (m, 12 H), 6.69 (s, 1H), 6.66 (s, 2H), 6.56-6.54 (d, *J* = 8 Hz, 2H), 6.49 (s, 1H), 6.40-6.38 (d, *J* = 8 Hz, 2H), 6.15-6.13 (d, *J* = 8 Hz, 1H), 5.65-5.63 (d, *J* = 8 Hz, 2H), 5.50-5.47 (d, *J* = 10 Hz, 1H), 4.67 (s, 4H), 4.64 (s, 2H), 3.98 (s, 9H), 3.78 (s, 9H), 2.35 (s, 6H), 2.24 (s, 3H), 1.36 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7,152.5, 148.7, 138.9, 138.7, 138.5, 133.6, 131.4, 130.7, 130.0, 129.8, 129.2, 129.1, 128.7, 128.6, 127.8, 125.5, 121.9, 121.6, 121.5, 120.2, 119.5, 118.7, 118.0, 113.7, 110.6, 110.6, 110.4, 75.0, 56.2, 56.1, 52.9, 52.0, 28.0, 27.6, 19.2, 14.1 ppm. HRMS *m/z* (ESI) calculated for $C_{27}H_{29}NO_5SNa$ [$(M + Na)^+$] 502.1664, found 502.1657. HPLC ret time 20.921 min, 100%.

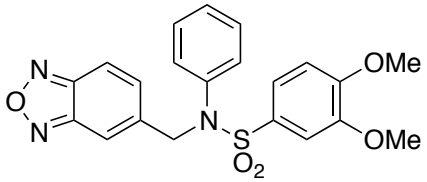


***N*-((2,2-Dimethyl-2,7b-dihydro-1a*H*-oxireno[2,3-*c*]chromen-6-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3f)** 86.5 mg KCN-1 was dissolved in 2 mL DCM and cooled to 0^{o}C. 60 mg MCPBA was added. Reaction stirred 21 hours at room temperature. Washed 2 x 1

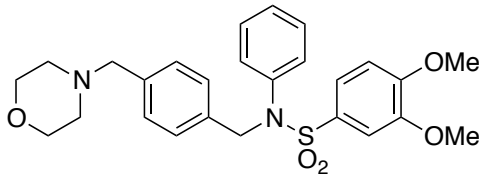
M NaOH. Concentrated. Purified by column chromatography, 40:1 DCM/methanol, to yield 119 mg of off-white semi-solid.



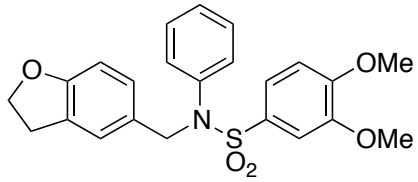
***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3g)** Yield: 55%. ^{1}H NMR ($CDCl_3$): δ 7.36-7.34 (dd, *J* = 8, 2 Hz, 1H), 7.27-7.24 (m, 3H), 7.03-6.93 (m, 4H), 6.81 (s, 1H), 6.63-6.60 (m, 2H), 5.91 (s, 2H), 4.63 (s, 2H), 3.98 (s, 3H), 3.78 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 148.9, 147.1, 139.1, 130.3, 129.8, 129.6, 129.1, 128.8, 127.9, 122.0, 121.5, 110.4, 109.0, 107.9, 101.0, 56.2, 56.1, 54.5 ppm. HRMS *m/z* (ESI) calculated for $C_{22}H_{21}NO_6SNa$ [$(M + Na)^+$] 450.0987, found 450.0991. HPLC ret time 8.047 min, 98%.



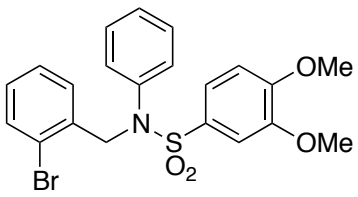
***N*-(Benzo[*c*][1,2,5]oxadiazol-5-ylmethyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3h)** Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.80 (d, *J* = 8 Hz, 1H), 7.62-7.60 (d, *J* = 8 Hz, 1H), 7.51 (s, 1H), 7.39-7.36 (dd, *J* = 8, 2 Hz, 1H), 7.26-7.26 (d, *J* = 2 Hz, 2H), 7.07-7.05 (m, 2H), 6.99-6.96 (m, 2H), 4.80 (s, 2H), 4.00 (s, 3H), 3.77 (s, 3H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ 153.0, 149.0, 148.7, 140.3, 138.6, 132.3, 129.6, 129.2, 128.7, 128.3, 121.5, 116.8, 114.9, 110.6, 110.5, 56.2, 56.1, 54.5 ppm. HRMS *m/z* (ESI) calculated for $C_{21}H_{20}N_3O_5S$ [$(M + H)^+$] 426.1124, found 426.1104. HPLC ret time 27.317 min, 100%.



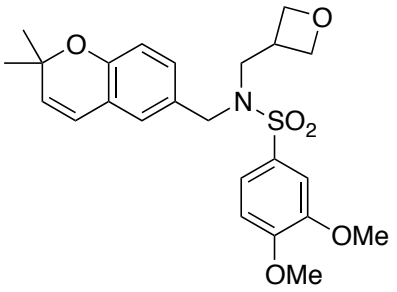
3,4-Dimethoxy-*N*-(4-(morpholinomethyl)benzyl)-*N*-phenylbenzenesulfonamide (3i) Yield: 11%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.35 (d, *J* = 8Hz, 1H), 7.35 (s, 1H), 7.22-7.20 (m, 6H), 7.04-7.02 (m, 2H), 6.97-6.94 (m, 2H), 4.72 (s, 1H), 3.98 (s, 3H), 3.77 (s, 3H), 3.70-3.69 (m, 4H), 3.44 (s, 2H), 2.40 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 148.7, 139.2, 135.0, 130.2, 129.2, 129.0, 128.8, 128.4, 127.8, 127.5, 121.4, 110.4, 110.4, 66.9, 63.0, 56.2, 56.01, 54.4, 53.5. HRMS (ESI) *m/z* calculated for $C_{26}H_{31}N_2O_5S$ [$(M + H)^+$] 483.1954, found 483.1956.



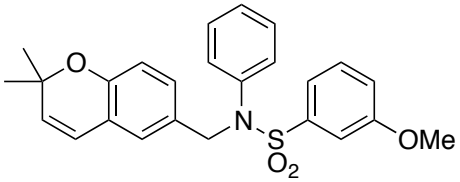
***N*-((2,3-dihydrobenzofuran-5-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3j)** Yield: 27%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (dd, *J* = 8, 2 Hz, 1H), 7.25-7.23 (m, 3H), 7.15 (s, 1H), 7.02-6.94 (m, 4H), 6.88-6.86 (dd, *J* = 8, 2 Hz, 1H), 6.61-6.59 (d, *J* = 8 Hz, 1H), 4.65 (s, 2H), 4.55-4.53 (t, *J* = 4 Hz, 2H), 3.98 (s, 3H), 3.78 (s, 3H), 3.17-3.12 (t, *J* = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 152.5, 148.8 139.2, 130.6, 129.2, 128.8 128.6, 128.0, 127.8, 127.2, 125.4, 121.4, 110.5, 110.4, 108.8, 71.3, 56.2, 56.1, 54.5, 29.6 ppm. HRMS *m/z* (ESI) calculated for $C_{23}H_{23}NO_5SNa$ [$(M + Na)^+$] 448.1195, found 448.1198.



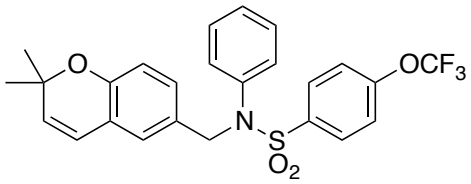
***N*-(2-bromobenzyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3k)** Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.61 (d, *J* = 8 Hz, 1H), 7.44-7.42 (d, *J* = 8 Hz, 1H), 7.37-7.35 (d, *J* = 8 Hz, 1H), 7.28-7.24 (m, 3H), 7.13-7.11 (d, *J* = 8 Hz, 2H), 7.09-6.98 (m, 2H), 6.97-6.95 (d, *J* = 8 Hz, 2H), 4.88 (s, 2H), 3.98 (s, 3H), 3.77 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ152.7, 148.8, 139.4, 135.4, 132.6, 130.3, 129.7, 129.0, 128.9, 128.8, 127.9, 127.5, 123.1, 121.6, 110.4, 56.2, 56.1, 54.1 ppm.



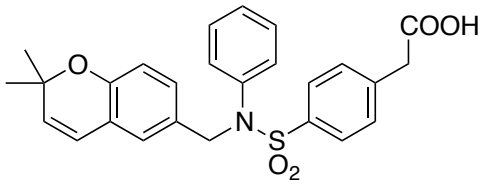
***N*-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-3,4-dimethoxy-*N*-(oxetan-3-ylmethyl)benzenesulfonamide (4a)** Yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.68 (d, *J* = 8 Hz, 1H), 7.51 (s, 1H), 7.41 (s, 1H), 7.22-7.17 (m, 1H), 7.08 (s, 1H), 6.96-6.94 (d, *J* = 8 Hz, 1H), 6.51-6.48 (d, *J* = 8 Hz, 1H), 5.88-5.86 (d, *J* = 8 Hz, 1H), 4.72-4.67 (m, 2H), 4.44-4.35 (m, 2H), 4.38 (s, 2H), 4.20 (s, 3H), 4.17 (s, 3H), 3.63-3.61 (d, *J* = 8 Hz, 2H), 3.32-3.22 (quintet, *J* = 7.2 Hz, 1H), 1.66 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 152.9, 149.5, 131.7, 131.2, 128.9, 128.6, 126.2, 122.1, 121.8, 121.8, 121.3, 116.7, 111.0, 110.0, 76.7, 75.3, 75.3, 56.5, 56.5, 53.0, 51.8, 34.8, 28.2 ppm. HRMS *m/z* (ESI) calculated for $C_{24}H_{30}NO_6S$ $[(M + H)^+]$ 460.1794, found 460.1801.



***N*-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-3-methoxy-*N*-phenylbenzenesulfonamide (5a)** Yield: 13%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.39 (m, 2H), 7.35-7.24 (m, 3H), 7.23-7.23 (m, 2H), 7.14-7.11 (m, 2H), 7.00-6.98 (m, 2H), 6.91-6.88 (d, *J* = 8 Hz, 2H), 6.62-6.60 (d, *J* = 8 Hz, 1H), 6.25-6.23 (d, *J* = 8 Hz, 1H), 5.59-5.57 (d, *J* = 8 Hz, 1H), 4.64 (s, 2H), 3.77 (s, 3H), 1.42 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 139.9, 138.9, 132.3, 130.9, 129.9, 129.4, 129.1, 128.8, 128.0, 127.9, 126.7, 122.1, 121.1, 119.8, 119.4, 116.1, 112.1, 76.3, 55.6, 54.5, 28.0 ppm. HRMS *m/z* (ESI) calculated for $C_{25}H_{25}NO_4SNa$ [$(M + Na)^+$] 458.1402, found 458.1409.

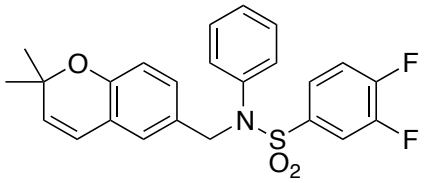


***N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-*N*-phenyl-4-(trifluoromethoxy)benzenesulfonamide (5b)** Yield: 19%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.12 (d, *J* = 8 Hz, 1H), 7.72-7.70 (d, *J* = 8 Hz, 2H), 7.47-7.45 (d, *J* = 8 Hz, 1H), 7.33-7.24 (m, 5H), 6.98-6.97 (d, *J* = 4 Hz, 2H), 6.90-6.87 (m, 2H), 6.62-6.61(d, *J* = 8 Hz, 1H), 6.24-6.22 (d, *J* = 8 Hz, 1H), 5.60-5.58 (d, *J* = 8 Hz, 1H), 4.62 (s, 2H), 1.40 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 151.0, 138.6, 137.3, 131.0, 129.8, 129.5, 129.4, 129.1, 129.0, 128.1, 127.7, 126.7, 122.0, 121.2, 121.1, 120.6, 116.1, 76.32, 54.6, 28.0 ppm. HRMS *m/z* (ESI) calculated for $C_{25}H_{22}NO_4SF_3Na$ [$(M + Na)^+$] 512.1119, found 512.1106.



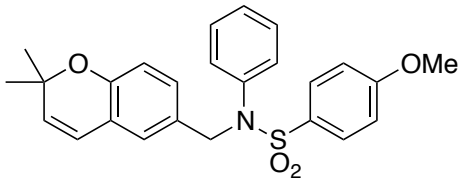
2-(4-(*N*-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-*N*-phenylsulfamoyl)phenyl)acetic acid (5c) Yield: 6%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (m, 2H), 7.18 (m, 3H), 6.91-6.76 (m, 7H),

6.36-6.33 (d, *J* = 10 Hz, 1H), 5.74-5.72 (d, *J* = 10 Hz, 1H), 4.78 (s, 2H), 3.28 (s, 2H), 1.34 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 181.2, 171.2, 148.6, 147.8, 141.6, 141.6, 140.5, 137.3, 135.5, 129.6, 129.1, 128.5, 126.5, 123.5, 123.5, 123.4, 77.4, 54.2, 40.6, 29.6 ppm. MS *m/z* found for $C_{26}H_{25}NO_5S$ [$(M+H)^+$] 465.2.



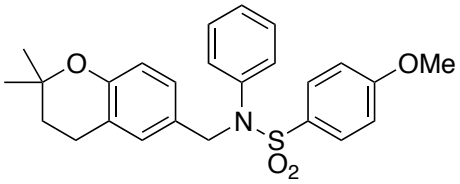
***N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-difluoro-*N*-phenylbenzenesulfonamide (5d)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.26 (m, 4H), 6.98-6.96 (dd, *J* = 8, 2 Hz, 1H), 6.90-6.87 (d, *J* = 8 Hz, 2H), 6.63-6.61 (d, *J* = 8 Hz, 1H), 6.25-6.23 (d, *J* = 10 Hz, 1H), 5.61-5.58 (d, *J* = 10 Hz, 1H), 4.65 (s, 2H), 1.41 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 138.4, 131.0, 129.4, 129.1, 129.1, 128.3, 127.5, 126.7, 122.0, 121.2, 118.0, 117.8, 116.2, 76.4, 54.7, 28.0 ppm. HRMS *m/z* (ESI) calculated for $C_{24}H_{21}NO_3SF_2Na$ [$(M + Na)^+$] 464.1108, found 464.1097.

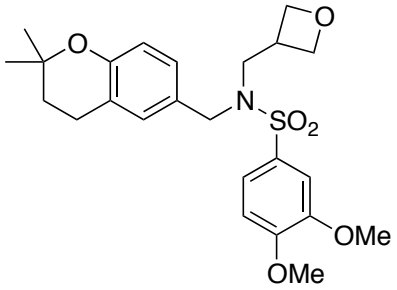


***N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-4-methoxy-*N*-phenylbenzenesulfonamide (5e)**

Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.74 (d, *J* = 8 Hz, 2H), 7.59-7.57 (d, *J* = 8 Hz, 2H), 7.20 (m, 3H), 6.98-6.87 (m, 3H), 6.60-6.58 (d, *J* = 8 Hz, 1H), 6.24-6.21 (d, *J* = 10 Hz, 1H), 5.58-5.56 (d, *J* = 10 Hz, 1H), 14.61 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.23 (s, 3H), 1.38 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 152.4, 139.1, 130.5, 129.8, 129.1, 128.8, 128.1, 127.8, 126.6, 122.1, 121.1, 116.0, 114.1, 114.0, 76.24, 55.6, 55.6, 54.3, 42.0, 28.0, ppm.

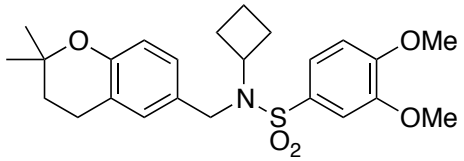


***N*-((2,2-dimethylchroman-6-yl)methyl)-4-methoxy-*N*-phenylbenzenesulfonamide (6a)** Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58 (d, *J* = 8 Hz, 2H), 7.26-7.26 (m, 3H), 7.01-6.94 (m, 4H), 6.87-6.85 (d, *J* = 8 Hz, 1H), 6.61-6.59 (d, *J* = 8 Hz, 1H), 4.63 (s, 2H), 3.90 (s, 3H), 2.71-2.67 (t, *J* = 8 Hz, 2H), 1.77-1.74 (t, *J* = 8 Hz), 1.30 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 162.6, 153.5, 139.3, 130.6, 129.8, 129.1, 129.1, 128.8, 127.7, 127.6, 126.9, 120.7, 116.9, 114.1, 113.9, 74.2, 55.6, 55.6, 54.4, 41.9, 32.7, 26.8 ppm. HRMS *m/z* (ESI) calculated for $C_{25}H_{27}NO_4SNa$ [$(M + Na)^+$] 460.1559, found 460.1537. HPLC ret time 24.296 min, 96%.



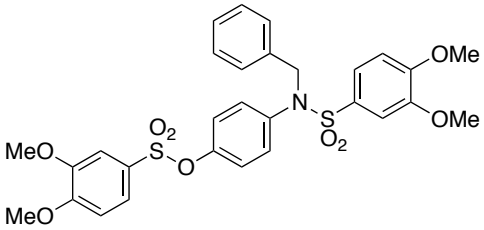
***N*-((2,2-dimethylchroman-6-yl)methyl)-3,4-dimethoxy-*N*-(oxetan-3-ylmethyl)benzenesulfonamide (6b)** Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.45 (d, *J* = 8 Hz, 1H), 7.17-7.15 (d, *J* = 8 Hz, 1H), 6.99-6.97 (d, *J* = 8 Hz, 1H), 6.93-6.92 (m, 2H), 6.74-6.72 (d, *J* = 8 Hz, 1H), 4.50-4.42 (m, 1H), 4.21-4.14 (m, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.41-3.98 (d, *J* = 8 Hz, 1H), 3.09-3.05 (m, 1H), 2.75-2.72 (t, *J* = 8 Hz, 1H), 1.83-1.79 (m, 2H), 1,34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 152.6, 149.2, 131.1, 129.2, 127.1, 121.3, 121.1,

119.4, 117.4, 110.7, 109.8, 75.2, 74.4, 56.2, 52.8, 51.4, 34.6, 32.6, 26.8, 22.4 ppm. HRMS *m/z* (ESI) calculated for $C_{24}H_{32}NO_6S$ $[(M + H)^+]$ 462.1950, found 462.1959.

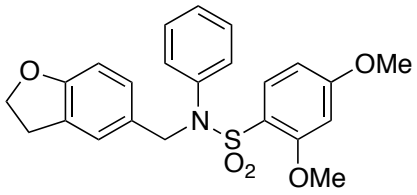


***N*-Cyclobutyl-*N*-((2,2-dimethylchroman-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide**

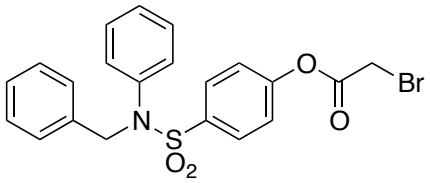
(6c) Yield: 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.41 (d, *J* = 8 Hz, 1H), 7.23 (s, 1H), 7.06 (s, 1H), 7.05-7.02 (d, *J* = 8 Hz, 1H), 6.94-6.92 (d, *J* = 8 Hz, 1H), 6.73-6.71 (d, *J* = 8 Hz, 1H), 4.31 (s, 2H), 4.27-4.19 (quintet, *J* = 7.2 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 2.70-2.74 (t, *J* = 8 Hz, 2H), 2.06-1.96 (m, 4H), 1.82-1.78 (t, *J* = 8 Hz, 2H), 1.55-1.50 (m, 2H), 1.34 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 148.9, 132.3, 129.3, 128.4, 126.3, 120.9, 117.0, 110.5, 109.8, 74.2, 56.2, 56.1, 52.9, 48.1, 32.8, 29.3, 26.9, 22.5, 15.1 ppm. HRMS *m/z* (ESI) calculated for $C_{24}H_{31}NO_5SNa$ $[(M + Na)^+]$ 468.1821, found 468.1810.



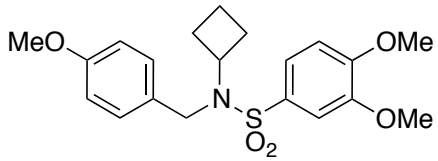
4-(*N*-Benzyl-3,4-dimethoxyphenylsulfonamido)phenyl 3,4-dimethoxybenzenesulfonate (7a) Yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 2H), 7.24-7.17 (m, 6H), 6.97-6.93 (m, 4H), 6.87-6.85 (m, 3H), 4.68 (s, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H) ppm.^{13}C NMR ($CDCl_3$): δ 153.9, 152.8, 149.1, 148.9, 148.7, 137.9, 135.5, 130.1, 129.7, 128.5, 128.4, 127.7, 126.3, 122.8, 121.5, 110.5, 110.4, 110.4, 110.3, 56.3, 56.2, 56.2, 54.6 ppm. HRMS *m/z* (ESI) calculated for $C_{29}H_{30}NO_9S_2$ $[(M + H)^+]$ 600.1362, found 600.1365.



***N*-((2,3-Dihydrobenzofuran-5-yl)methyl)-2,4-dimethoxy-*N*-phenylbenzenesulfonamide (8a)** Yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (d, *J* = 8 Hz, 1H), 7.21-7.14 (m, 4H), 7.04-7.02 (d, *J* = 8 Hz, 2H), 6.88-6.86 (d, *J* = 8 Hz, 1H), 6.62-6.60 (d, *J* = 8 Hz, 1H), 6.43 (s, 1H), 6.43-6.41 (dd, *J* = 8, 2 Hz, 1H), 4.88 (s, 2H), 4.56-4.52 (t, *J* = 8 Hz, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 3.18-3.14 (t, *J* = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 159.5, 158.2, 139.3, 133.6, 129.4, 128.9, 128.7, 128.4, 127.3, 127.2, 125.3, 120.1, 108.6, 99.3, 71.3, 56.0, 55.7, 55.7, 29.6 ppm. HRMS *m/z* (ESI) calculated for $C_{23}H_{23}NO_5SNa$ [$(M + Na)^+$] 448.1195, found 448.1180.

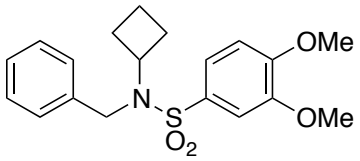


4-(*N*-benzyl-*N*-phenylsulfamoyl)phenyl 2-bromoacetate (8b) Yield: 14%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.07 (m, 14H), 4.92 (s, 2H), 3.70 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 136.5, 129.8, 128.9, 128.8, 128.5, 128.2, 127.7, 53.8, 27.2 ppm. MS *m/z* (ESI) calculated for $C_{21}H_{18}NO_4SBr$ [$(M + H)^+$] 459.0, found 460.0.

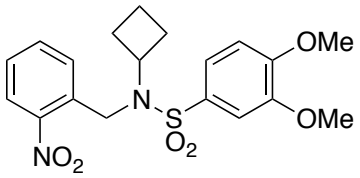


***N*-Cyclobutyl-3,4-dimethoxy-*N*-(4-methoxybenzyl)benzenesulfonamide (9a)** Yield: 47% over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.42 (d, *J* = 4Hz, 1H), 7.41-7.40 (d, *J* = 4 Hz, 2H), 7.28 (s, 1H), 6.94-6.92 (d, *J* = 8 Hz, 1H), 6.87-6.85 (d, *J* = 8 Hz, 2H), 4.34 (s, 2H), 4.27-

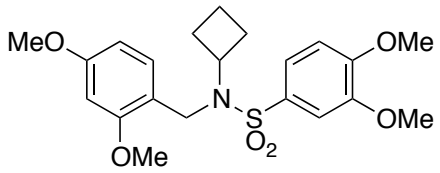
4.18 (quintet, *J* = 7.2 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.81 (s, 3H), 2.00-1.95 (m, 4H), 1.56-1.49 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 152.3, 149.0, 132.1, 130.6, 128.5, 120.9, 113.8, 110.5, 109.7, 56.2, 56.2, 55.3, 48.0, 29.3, 15.1 ppm. HRMS *m/z* (ESI) calculated for $C_{20}H_{25}NO_5SNa$ [$(M + Na)^+$] 414.1351, found 414.1355. HPLC ret time 9.539 min, 96%.



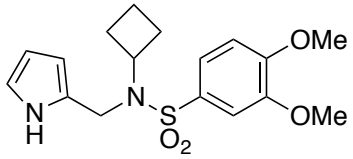
***N*-Benzyl-*N*-cyclobutyl-3,4-dimethoxybenzenesulfonamide (9b)** Yield: 17% over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-6.96 (m, 7H), 6.96-6.94 (d, *J* = 8 Hz, 1H), 4.42 (s, 2H), 4.28-4.26 (quintet, *J* = 7.2 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 2.00-1.96 (m, 4H), 1.54-1.53 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 149.0, 138.7, 132.1, 128.5, 127.2, 127.1, 120.9, 110.6, 109.7, 56.2, 56.2, 52.9, 48.4, 29.3, 15.1 ppm. HRMS *m/z* (ESI) calculated for $C_{19}H_{24}NO_4S$ [$(M + H)^+$] 362.1426, found 362.1426. HPLC ret time 8.673 min, 100%.



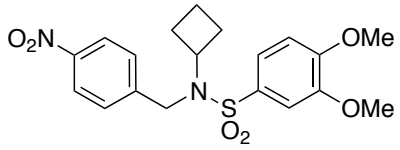
***N*-Cyclobutyl-3,4-dimethoxy-*N*-(2-nitrobenzyl)benzenesulfonamide (9c)** Yield: 42% over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.10 (d, *J* = 8 Hz, 1H), 7.97-7.95 (d, *J* = 8 Hz, 1H), 7.73-7.69 (t, *J* = 8 Hz, 1H), 7.48-7.45 (dd, *J* = 8, 2 Hz, 2H) 7.30-7.30 (d, *J* = 2 Hz, 1H), 6.99-6.97 (d, *J* = 8 Hz, 1H), 4.79 (s, 2H), 4.52-4.44 (quintet, *J* = 7.2 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 1.99-1.98 (m, 2H), 1.89-1.84 (m, 2H), 1.56 ppm (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 149.2, 147.2, 135.5, 134.0, 131.1, 129.6, 128.0, 124.9, 121.0, 110.8, 109.6, 56.3, 56.2, 52.6, 45.4, 28.9, 14.9ppm. HRMS *m/z* (ESI) calculated for $C_{19}H_{23}N_2O_6S$ [$(M + H)^+$] 407.1277, found 407.1269. HPLC ret time 9.048 min, 98%.



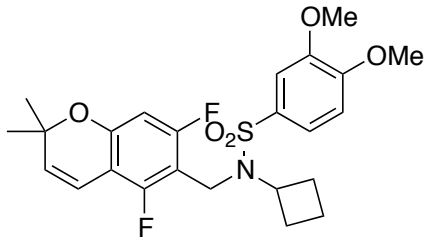
***N*-Cyclobutyl-*N*-(2,4-dimethoxybenzyl)-3,4-dimethoxybenzenesulfonamide (9d)** Yield: 11% over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.7.42 (dd, *J* = 8, 2 Hz, 2H), 7.42-7.40 (d, *J* = 8 Hz, 1H), 7.29-7.27 (d, *J* = 8 Hz, 1H), 6.95-6.93 (d, *J* = 8 Hz, 1H), 6.52-6.49 (dd, *J* = 8, 2 Hz, 1H), 6.42-6.42 (d, *J* = 2 Hz, 1H), 4.40-4.36 (quintet, *J* = 7.2 Hz, 1H), 4.34 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 2.02-1.95 (m, 4H), 1.56-1.50 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 157.0, 152.2, 148.9, 132.3, 129.1, 120.9, 119.2, 110.5, 109.8, 104.1, 98.0, 56.2, 56.1, 55.4, 55.2, 52.7, 42.2, 29.0, 14.9 ppm. HRMS *m/z* (ESI) calculated for $C_{21}H_{27}NO_6SNa$ [$(M + Na)^+$] 444.1457, found 444.1451. HPLC, ret time 11.057 min, 97%.



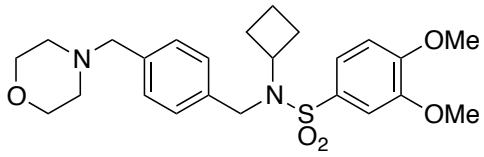
***N*-((1*H*-Pyrrol-2-yl)methyl)-*N*-cyclobutyl-3,4-dimethoxybenzenesulfonamide (9e)** Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 1H), 7.41-7.39 (dd, *J* = 8, 2 Hz, 1H), 7.20-7.19 (d, *J* = 2 Hz, 1H), 6.94-6.92 (d, *J* = 8 Hz, 1H), 6.79-6.79 (d, *J* = 2 Hz, 1H), 6.12-6.10 (dd, *J* = 8, 2 Hz, 1H), 6.05 (s, 1H), 4.28 (s, 2H), 4.25-4.19 (quintet, *J* = 7.2 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 2.13-2.02 (m, 4H), 1.65-1.54 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 149.1, 131.7, 128.0, 120.9, 118.5, 110.6, 109.5, 107.8, 107.1, 56.2, 56.2, 52.6, 41.2, 28.9, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{17}H_{22}N_2O_4SNa$ [$(M + Na)^+$] 373.1198, found 373.1184. HPLC ret time 6.325, 100%.



***N*-cyclobutyl-3,4-dimethoxy-*N*-(4-nitrobenzyl)benzenesulfonamide (9f)** Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 1H), 7.41-7.39 (dd, *J* = 8, 2 Hz, 1H), 7.20-7.19 (d, *J* = 2 Hz, 1H), 6.94-6.92 (d, *J* = 8 Hz, 1 H), 6.79-6.79 (d, *J* = 1.2 Hz, 1H), 6.12-6.10 (s, 1H), 6.05 (s, 1H), 4.28 (s, 2H), 4.25-4.19 (quintet, *J* = 7.2, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 2.13-2.02 (m, 4H), 1.65-1.54 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 149.1, 131.7, 128.0, 120.9, 118.5, 110.6, 109.5, 107.8, 107.1, 56.2, 56.2, 52.6, 41.2, 28.9, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{19}H_{23}N_2O_6S$ [$(M + H)^+$] 407.1277, found 407.1258. HPLC ret time 8.366 min, 99%.

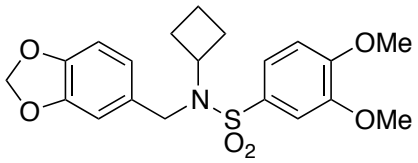


***N*-cyclobutyl-*N*-((5,7-difluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (9g)**

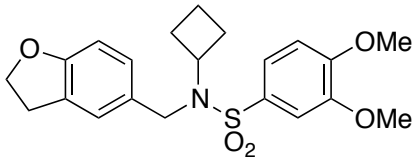


***N*-cyclobutyl-3,4-dimethoxy-*N*-(4-(morpholinomethyl)benzyl)benzenesulfonamide (9h)** Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.42 (dd, *J* = 8.4, 2 Hz, 1H), 7.34-7.25 (m, 5H), 6.95-6.93 (d, *J* = 8 Hz, 1H), 4.39 (s, 2H), 4.32-4.23 (quintet, *J* = 8 Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.74-3.72 (t, *J* = 4 Hz, 4H), 3.51 (s, 2H), 2.46 (s, 4H), 1.99-1.94 (m, 4H), 1.57-1.52 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 149.0, 137.8, 132.0, 129.4, 127.1, 120.91, 110.6,

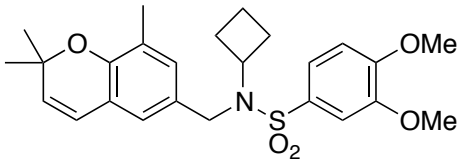
109.8, 66.9, 63.0, 56.2, 56.2, 53.5, 52.9, 48.1, 29.2, 15.0. HRMS (ESI) *m/z* calculated for $C_{24}H_{33}N_2O_5S$ [$(M + H)^+$] 461.2110, found 461.2102.



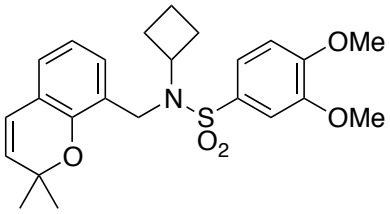
***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-cyclobutyl-3,4-dimethoxybenzenesulfonamide (9i)** Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.40 (dd, *J* = 8, 2 Hz, 1H), 7.24-7.23 (d, *J* = 2 Hz, 1H), 6.92-6.91 (d, *J* = 2 Hz, 1H), 6.81-6.74 (m, 2H), 5.96 (s, 2H), 4.30 (s, 2H), 4.26-4.21 (quintet, *J* = 7.2 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.05-1.96 (m, 4H), 1.57-1.50 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 149.0, 147.9, 146.8, 132.5, 132.1, 120.9, 120.3, 110.6, 109.8, 108.1, 101.0, 56.2, 56.2, 52.9, 48.3, 29.3, 15.1 ppm. HRMS *m/z* (ESI) calculated for $C_{20}H_{24}NO_6S$ [$(M + H)^+$] 406.1324, found 406.1315. HPLC ret time 8.912 min, 97%.



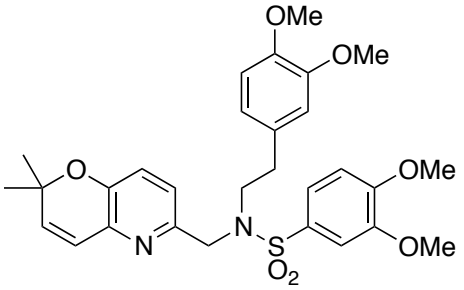
***N*-Cyclobutyl-*N*-((2,3-dihydrobenzofuran-5-yl)methyl)-3,4-dimethoxybenzenesulfonamide (9j)** Yield: 53%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.40 (dd, *J* = 8, 2 Hz, 1H), 7.26 (s, 1H), 7.23-7.22 (d, *J* = 2 Hz, 1H), 7.05-7.03 (d, *J* = 8 Hz, 1H), 6.94-6.92 (d, *J* = 8 Hz, 1H), 6.72-6.670 (d, *J* = 8 Hz, 1H), 4.58-4.54 (t, *J* = 8 Hz, 2H), 4.31 (s, 2H), 4.22-4.18 (quintet, *J* = 7.2 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.21-3.17 (t, *J* = 7.2 Hz, 2H), 2.04-1.94 (m, 4H), 1.56-1.51 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 152.3, 149.0, 132.2, 130.5, 127.4, 127.0, 124.2, 120.9, 110.5, 109.7, 108.8, 71.3, 56.2, 56.2, 52.9, 48.3, 41.9, 29.7, 29.3, 15.1 ppm. HRMS *m/z* (ESI) calculated for $C_{21}H_{26}NO_5S$ [$(M + H)^+$] 404.1532, found 404.1547. HPLC ret time 9.124 min, 97%.



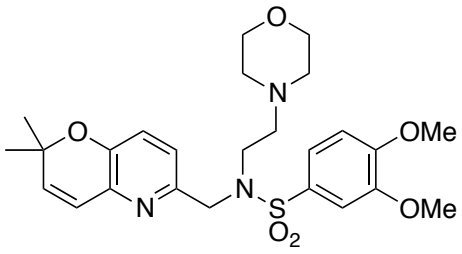
***N*-cyclobutyl-3,4-dimethoxy-*N*-((2,2,8-trimethyl-2*H*-chromen-6-yl)methyl)benzenesulfonamide (9k)** Yield: 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.40 (dd, *J* = 8, 2 Hz, 1H), 7.23-7.23 (d, *J* = 2 Hz, 1H), 6.94-7.92 (d, *J* = 8 Hz, 2H), 6.81 (s, 1H), 6.30-6.28 (d, *J* = 8 Hz, 1H), 5.62-5.60 (d, *J* = 8 Hz, 1H), 4.27 (s, 2H), 4.27-4.25 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.16 (s, 3H), 2.04-1.95 (m, 4H), 1.60-1.54 (m, 2H), 1.43 (s, 6H) ppm. MS *m/z* (ESI) calculated for $C_{25}H_{31}NO_5Na$ [$(M + Na)^+$] 480.2, found 480.2.



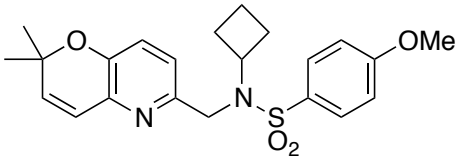
***N*-cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-8-yl)methyl)-3,4-dimethoxybenzenesulfonamide (9l)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.45 (dd, *J* =8, 2 Hz, 2H), 7.35-7.33 (d, *J* =8 Hz, 1H), 6.96-6.94 (d, *J* =8 Hz, 1H), 6.89-8.85 (m, 2H), 6.34-6.32 (d, *J* =8 Hz, 1H), 5.62-5.60 (d, *J* =8 Hz, 1H), 4.38 (s, 2H), 4.36 (m, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 2.03-1.96 (m, 4H), 1.55-1.44 (m, 2H), 1.39 (s, 6H) ppm. HRMS *m/z* (ESI) calculated for $C_{16}H_2NO$ [$(M + H)^+$] 244.1701, found 244.1707.



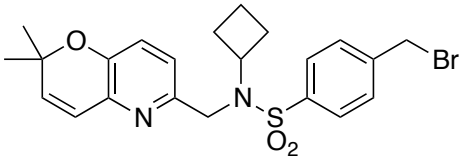
***N*-(3,4-dimethoxyphenethyl)-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (10a)** Yield: 29%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.42 (dd, *J* = 8, 2 Hz, 1H), 7.27-7.26 (d, *J* = 2 Hz, 1H), 7.21-7.18 (d, *J* =8 Hz, 1H), 7.02-7.00 (d, *J* =8 Hz, 1H), 6.93-9.91 (d, *J* =8 Hz, 1H), 6.74-6.72 (d, *J* =8 Hz, 1H), 6.60-6.57 (m, 3H), 6.43-6.41 (d, *J* =10 Hz, 1H), 5.90-5.87 (d, *J* =10 Hz, 1H)4.41 (s, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.41-3.37 (m, 2H), 2.69-2.65 (t, *J* = 8 Hz, 2H), 1.66 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ152.5, 149.1, 149.0, 148.8, 148.2, 147.6, 140.3, 135.5, 131.5, 131.0, 123.8, 123.6, 123.1, 121.1, 120.7, 112.0, 111.2, 110.6, 109.8, 77.3, 60.4, 56.2, 56.2, 55.9, 55.8, 53.5, 50.4, 34.8, 28.2, 21.1, 14.2 ppm. HRMS *m/z* (ESI) calculated for $C_{29}H_{35}N_2O_7S$ [$(M + H)^+$] 555.2165, found 555.2151.



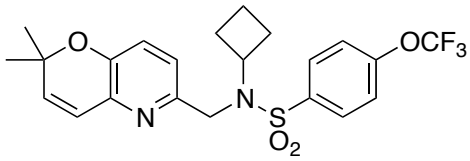
N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxy-N-(2-morpholinoethyl)benzenesulfonamide (10b) Yield: 35%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.46 (d, *J* = 8 Hz, 1H), 7.28 (s, 1H), 7.25 (s, 1H), 7.05-7.03 (d, *J* = 8 Hz, 1H), 6.95-6.93 (d, *J* = 8 Hz, 1H), 6.39-6.36 (d, *J* = 10 Hz, 1H), 5.89-5.86 (d, *J* = 10 Hz, 1H), 4.42 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 3.61-3.60 (m, 4H), 3.34-3.31 (t, *J* = 6 Hz, 2H), 2.40-2.37 (t, *J* = 6 Hz, 2H), 2.31 (m, 4H), 1.47 (s, 6H) ppm.



***N*-Cyclobutyl-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-4-methoxybenzenesulfonamide (11a)** Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.69 (d, *J* = 8 Hz, 2H), 7.31-7.29 (d, *J* = 8 Hz, 2H), 7.01-6.99 (d, *J* = 8 Hz, 2H), 6.92-6.90 (d, *J* = 8 Hz, 2H), 6.40-6.37 (d, *J* = 10 Hz, 2H), 5.84-5.82 (d, *J* = 10 Hz, 2H), 4.35 (s, 2H), 4.30-4.26 (quintet, *J* = 7.2 Hz, 1H), 3.81 (s, 1H), 1.90-1.85 (m, 4H), 1.47-1.45 (m, 2H), 1.41 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 150.3, 148.5, 140.1, 135.4, 131.5, 129.1, 129.0, 123.7, 123.6, 121.8, 114.2, 76.8, 55.6, 52.7, 49.3, 41.9, 28.8, 29.2, 27.9, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{22}H_{27}N_2O_4S$ [$(M + H)^+$] 415.1692, found 415.1682. HPLC ret time 15.143 min, 95%.

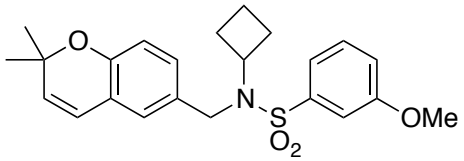


4-(Bromomethyl)-*N*-cyclobutyl-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)benzenesulfonamide (11b) Yield: 53%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.79 (d, *J* = 8 Hz, 2H), 7.55-7.53 (d, *J* = 8 Hz, 2H), 7.46-7.44 (d, *J* = 8 Hz, 1H), 7.23 (s, 1H), 6.69-6.67 (d, *J* = 8 Hz, 1H), 6.00-5.98 (d, *J* = 8 Hz, 1H), 4.56 (s, 2H), 4.51 (s, 2H), 4.36-4.32 (quintet, *J* = 7.2 Hz, 1H), 1.94 (m, 4H), 1.51 (m, 2H), 1.51 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 148.7, 142.7, 139.3, 129.8, 129.2, 129.0 127.7, 127.6, 126.5, 122.73, 78.0, 52.8, 47.9, 32.7, 29.0, 28.3, 14.9 ppm. HRMS *m/z* (ESI) calculated for $C_{22}H_{26}N_2O_3SBr$ [$(M + H)^+$] 477.0848, found 477.0852.

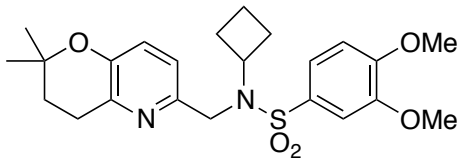


***N*-Cyclobutyl-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-4-(trifluoromethoxy)benzenesulfonamide (11c)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.86 (d, *J* =

8 Hz, 2H), 7.36-7.32 (m, 3H), 7.14-7.12 (d, *J* = 8 Hz, 1H), 6.54.-6.51 (d, *J* =10 Hz, 1H), 6.96-6.93 (d, *J* = 10 Hz, 1H), 4.50 (2, 2H), 4.34-4.33 (quintet, *J* = 7.2 Hz, 1H), 1.98-1.94 (m, 4H), 1.57-1.50 (m, 2H), 1.49 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 148.9, 139.5, 138.2, 136.5, 129.3, 127.9, 124.9, 122.3, 120.9, 120.5, 76.7, 52.7, 48.6, 29.0, 28.2, 14.9 ppm. HRMS *m/z* (ESI) calculated for $C_{22}H_{24}N_2O_4SF_3$ [$(M + H)^+$] 467.1409, found 469.1409.

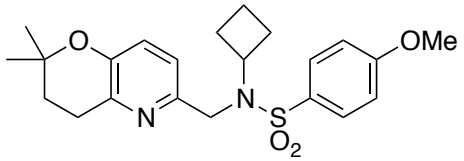


***N*-Cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3-methoxybenzenesulfonamide (11d)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.27 (m, 5H), 7.10-7.07 (m, 2H), 6.48-6.45 (d, *J* = 10 Hz, 1H), 5.91-5.89 (d, *J* = 10 Hz, 1H), 4.45 (s, 2H), 4.40-4.36 (quintet, *J* = 7.2 Hz, 1H), 3.88 (s, 3H), 1.97-1.92 (m, 4H), 1.56-1.54 (m, 2H), 1.49 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 150.0, 148.6, 141.1, 135.6, 130.1, 121.9, 119.3, 119.1, 1198.9, 111.9, 111.2, 55.9, 55.6, 52.8, 49.3, 29.7, 28.9, 28.2, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{22}H_{27}N_2O_4S$ [$(M + H)^+$] 415.1692, found 415.1688.

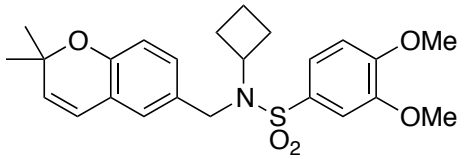


***N*-Cyclobutyl-*N*-((2,2-dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (12a)** Yield: 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.43 (dd, *J* = 8, 2 Hz, 1H), 7.38-7.26 (dd, *J* = 8, 2 Hz, 1H), 7.26 (s, 1H), 7.10-7.08 (d, *J* = 8 Hz, 1H), 6.94-6.92 (d, *J* = 8 Hz, 1H), 4.44 (s, 1H), 4.40-4.43 (quintet, *J* = 7.2 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 2.91-2.87 (t, *J* = 10 Hz, 2H), 1.96-1.91 (m, 6H), 1.57-1.50 (m, 2H), 1.33 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 149.5, 149.2, 149.0, 141.3, 131.8, 125.3, 121.0, 120.7,

110.5, 109.6, 74.8, 56.2, 52.7, 49.4, 32.8, 28.9, 26.7, 25.6, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{23}H_{31}N_2O_5S$ [$(M + H)^+$] 447.1954, found 447.1958.

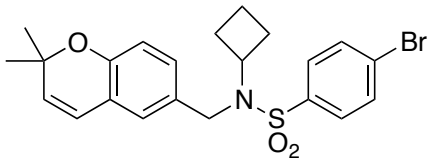


***N*-Cyclobutyl-*N*-((2,2-dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-4-methoxybenzenesulfonamide (12b)** Yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.73 (d, *J* = 8 Hz, 2H), 7.37-7.35 (d, *J* = 8 Hz, 1H), 7.09-7.07 (d, *J* = 8 Hz, 1H), 6.96-6.94 (d, *J* = 8 Hz, 2H), 4.41 (s, 2H), 4.35-4.29 (quintet, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 2.90-2.87 (t, *J* = 6 Hz, 2H), 1.96-1.89 (m, 6H), 1.52-1.48 (m, 2H), 1.36 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 149.6, 149.2, 141.2, 131.7, 129.2, 125.2, 120.7, 114.1, 74.8, 55.6, 52.7, 49.4, 32.8, 28.9, 26.7, 25.6, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{22}H_{29}N_2O_4S$ [$(M + H)^+$] 417.1848, found 417.1848. HPLC ret time 15.036 min, 95%.

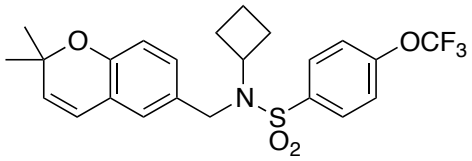


***N*-Cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (13a)** Yield: 56%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.42 (d, *J* = 2 Hz, 1H), 7.41-7.40 (d, *J* = 2 Hz, 1H), 7.24-7.23 (d, *J* = 2 Hz, 1H), 7.07-7.05 (d, *J* = 8 Hz, 1H), 6.99 (s, 1H), 6.94-6.92 (d, *J* = 8 Hz, 1H), 6.73-6.31 (d, *J* = 8 Hz, 1H), 6.32-6.30 (d, *J* = 8 Hz, 1H), 5.63-5.61 (d, *J* = 8 Hz, 1H), 4.30 (s, 2H), 4.27-4.20 (m, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.05-1.95 (m, 4H), 1.62-1.49 (m, 2H), 1.47 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 152.2, 149.0, 132.2, 131.0, 130.6, 127.9, 125.3, 122.3, 121.2, 120.9, 116.1, 111.0, 109.7, 76.2,

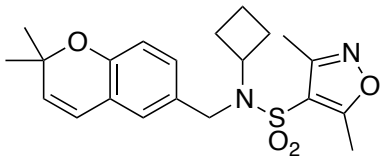
56.2, 56.2, 52.9, 48.0, 29.3, 28.0, 15.1 ppm. HRMS *m/z* (ESI) calculated for $C_{24}H_{29}NO_5SNa$ [(M + Na)$^+$] 466.1664, found 466.1678.



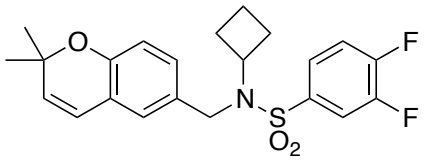
4-Bromo-*N*-cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)benzenesulfonamide (13b) Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (m, 4H), 7.05-7.03 (dd, *J* = 8, 2 Hz, 1H), 6.96-6.96 (d, *J* = 2 Hz, 1H), 6.74-6.72 (d, *J* = 8 Hz, 1H), 6.32-6.30 (d, *J* = 8 Hz, 1H), 5.95-5.63 (d, *J* = 8 Hz, 1H), 4.31 (s, 2H), 4.30-4.28 (m ,1H), 2.02-1.96 (m, 4H), 1.55-1.53 (m, 2H), 1.45 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.2, 131.1, 130.0, 125.6, 127.9, 125.3, 122.2, 121.3, 116.2, 76.3, 52.9, 48.2, 29.7, 29.3, 28.0, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{22}H_{24}BrNO_3SNa$ [(M + Na)$^+$] 484.0558, found 484.0561. HPLC ret time 26.138 min, 96%.



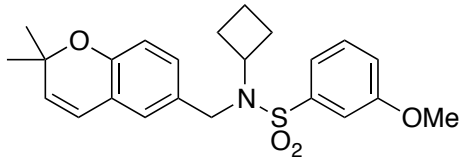
***N*-Cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-4-(trifluoromethoxy)benzenesulfonamide (13c)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.81 (d, *J* = 8 Hz, 2H), 7.33-7.31 (d, *J* = 8 Hz, 2H), 7.04-7.02 (d, *J* = 8 Hz, 1H), 6.96 (s, 1H), 6.73-6.72 (d, *J* = 8 Hz, 1H), 6.31-6.29 (d, *J* = 8 Hz, 1H), 5.64-5.62 (d, *J* = 8 Hz, 1H), 4.33 (s, 2H), 4.26-4.18 (quintet, *J* = 7.2 Hz, 1H), 2.03-1.99 (m, 4H), 1.58 (m, 2H), 1.44 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 151.9, 139.0, 131.1, 129.9, 129.1, 127.9, 125.3, 122.2, 121.3, 120.8, 116.2, 76.3, 52.9, 48.2, 29.3, 28.0, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{23}H_{24}NO_4SF_3Na$ [(M + Na)$^+$] 490.1276, found 490.1278.



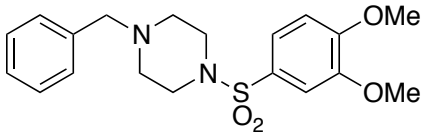
***N*-Cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,5-dimethylisoxazole-4-sulfonamide (13d)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03-7.01 (d, *J* = 8 Hz, 1H), 6.91 (s, 1H), 6.73-6.71 (d, *J* = 8 Hz, 1H), 6.31-6.28 (d, *J* = 8 Hz, 1H), 5.64-5.62 (d, *J* = 8 Hz, 1H), 4.41 (s, 2H), 4.28-4.20 (quintet, *J* = 7.2 Hz, 1H), 2.58 (s, 3H), 2.39 (s, 3H), 2.09-2.01 (m, 4H), 1.62-1.52 (m, 2H), 1.43 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 157.3, 152.4, 131.2, 129.5, 127.8, 125.2, 122.1, 121.4, 117.5, 116.3, 76.3, 52.2, 47.8, 29.3, 27.9, 15.0, 12.8, 11.1 ppm. HRMS *m/z* (ESI) calculated for $C_{21}H_{26}N_2O_4SNa$ [$(M + Na)^+$] 425.1511, found 425.1529.



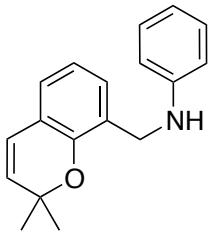
***N*-Cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-difluorobenzenesulfonamide (13e)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.54 (m, 2H), 7.29-7.28 (m, 2H), 7.04-7.02 (d, *J* = 8 Hz, 1H), 6.96 (s, 1H), 6.73-6.71 (d, *J* = 8 Hz, 1H), 6.32-6.29 (d, *J* = 10 Hz, 1H), 5.65-5.63 (d, *J* = 10 Hz, 1H), 4.32 (s, 2H), 4.23-4.19 (quintet, *J* = 7.2 Hz, 1H), 2.06-1.99 (m, 4H), 1.58-1.52 (m, 2H), 1.44 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 148.9, 137.4, 131.1, 129.7, 128.0, 125.3, 124.0, 122.1, 121.3, 118.1, 117.9, 117.0, 116.8, 116.3, 76.33, 52.8, 48.2, 29.3, 28.0, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{22}H_{23}NO_3SF_2Na$ [$(M + Na)^+$] 442.1264, found 442.1255.



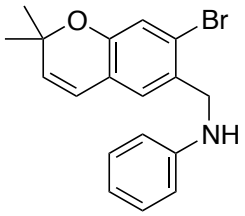
***N*-Cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3-methoxybenzenesulfonamide (13f)** Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.43 (d, *J* = 8 Hz, 1H), 7.24 (s, 1H), 7.07-7.05 (d, *J* = 8 Hz, 1H), 7.00 (s, 1H), 6.94-6.92 (d, *J* = 8 Hz, 1H), 6.73-6.71 (d, *J* = 8 Hz, 1H), 6.32-6.30 (d, *J* = 8 Hz, 1H), 5.63-5.61 (d, *J* = 8 Hz, 1H), 4.30 (s, 2H), 4.24-4.20 (quintet, *J* = 7.2 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.00-1.97 (m, 4H), 1.59 (m, 2H), 1.43 (s, 6H) ppm. HRMS *m/z* (ESI) calculated for $C_{23}H_{27}NO_4SNa$ [$(M + Na)^+$] 436.1559, found 436.1573.



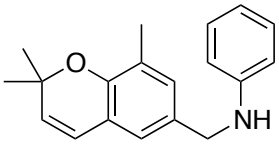
1-Benzyl-4-((3,4-dimethoxyphenyl)sulfonyl)piperazine (14a) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (d, *J* = 8 Hz, 1H), 7.32-7.25 (m, 5H), 7.21 (s, 1H), 6.98-6.96 (d, *J* = 8 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H), 3.05 (s, 4H), 2.55 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 149.1, 137.5, 129.1, 128.3, 127.3, 127.3, 121.8, 110.6, 110.4, 62.6, 56.3, 56.2, 52.1, 46.1. 53.3 ppm. HRMS *m/z* (ESI) calculated for $C_{19}H_{25}N_2O_4S$ [$(M + H)^+$] 377.1535, found 377.1531.



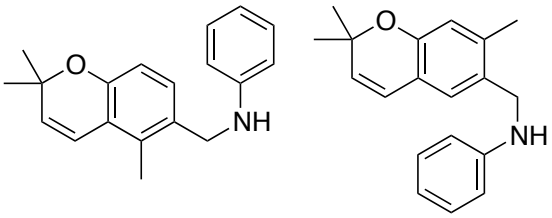
***N*-((2,2-Dimethyl-2*H*-chromen-8-yl)methyl)aniline (16b)** Yield: 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.21 (m, 3H), 6.98-6.96 (d, *J* = 8 Hz, 1H), 6.88-6.86 (t, *J* = 4 Hz, 1H), 6.79-6.72 (m, 3H), 6.40-6.38 (d, *J* = 8 Hz, 1H), 5.69-5.67 (d, *J* = 8 Hz, 1H), 4.40 (s, 2H), 4.06 (s, 1H), 1.52 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 148.5, 130.6, 129.2, 128.8, 126.5, 125.5, 122.5, 121.1, 120.5, 117.4, 113.2, 76.4, 43.1, 28.2 ppm.



***N*-((7-Bromo-2,2-dimethyl-2*H*-chromen-6-yl)methyl)aniline (16c)** Yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.19-7.18 (m, 1H), 6.94 (s, 1H), 6.76-6.73 (t, *J* = 8 Hz, 1H), 6.65-6.63 (d, *J* = 8 Hz, 1H), 6.29-6.26 (d, *J* = 8 Hz, 1H), 5.68-5.65 (d, *J* = 8 Hz, 1H), 4.20 (s, 2H), 3.98 (s, 1H), 1.49 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 148.0, 132.8, 131.8, 131.3, 129.3, 124.5, 122.7, 122.0, 117.7, 112.9, 110.5, 76.7, 47.4, 28.0 ppm.

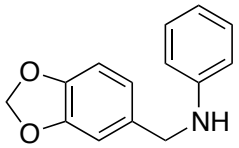


***N*-((2,2,8-Trimethyl-2*H*-chromen-6-yl)methyl)aniline (16d)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.21 (m, 2H), 7.04 (s, 1H), 6.89-6.88 (d, *J* = 2 Hz, 1H), 6.79-6.77 (d, *J* = 8 Hz, 1H), 6.70-6.68 (dd, *J* = 8, 2 Hz, 1H), 6.35-6.33 (d, *J* = 8 Hz, 1H), 5.67-5.64 (d, *J* = 8 Hz, 1H), 4.20 (s, 2H), 2.23 (s, 3H), 1.48 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 148.4, 130.8, 10.7, 129.9, 129.3, 125.7, 123.3, 122.6, 120.8, 117.5, 112.9, 76.08, 48.1, 28.1, 15.6 ppm.

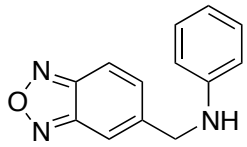


***N*-((2,2,5-Trimethyl-2*H*-chromen-6-yl)methyl)aniline with *N*-((2,2,7-Trimethyl-2*H*-chromen-6-yl)methyl)aniline (2:1) (16e)** Yield: 23%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.20 (m, 6H), 7.11-7.09 (d, *J* = 8 Hz, 2H), 6.96 (s, 1H), 6.77-6.73 (m, 3H), 6.67-6.61 (m, 11H), 6.30-

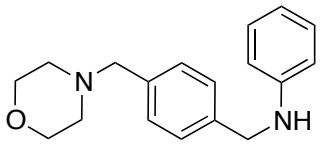
6.28 (d, *J* = 8 Hz, 1H), 5.72-5.70 (d, *J* = 8 Hz, 2H), 5.58-5.56 (d, *J* = 8 Hz, 1H), 4.19 (s, 4H), 4.17 (s, 2H), 3.71 (s, 3H), 2.32 (s, 9H), 1.45 (s, 12H), 1.44 (s, 6H) ppm.



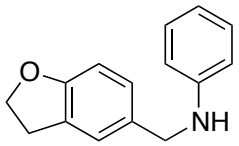
***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)aniline (16g)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.23 (m, 2H), 6.93-6.78 (m, 4H), 6.70-6.68 (d, *J* = 8 Hz, 2H), 5.99 (s, 2H), 4.29, (s, 2H), 4.05 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 148.0, 146.8, 133.5, 129.3, 120.9, 120.7, 117.7, 112.9, 108.4, 108.1, 48.2 ppm. HRMS *m/z* (ESI) calculated for $C_{14}H_{14}NO_2$ [$(M + H)^+$] 228.1025, found 228.1023.



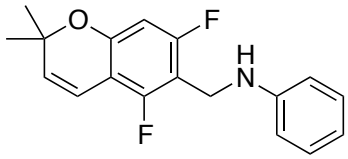
***N*-(Benzo[*c*][1,2,5]oxadiazol-5-ylmethyl)aniline (16h)** Yield: 32%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.80 (m, 2H), 7.44-7.42 (d, *J* = 8 Hz, 1H), 7.23-7.21 (t, *J* = 4 Hz, 2H), 6.80-6.77 (m, 1H), 6.66-6.64 (d, *J* = 8 Hz, 2H), 4.48 (s, 2H), 4.28-4.24 (quintet, *J* = 7.2 Hz, 1H) ppm.



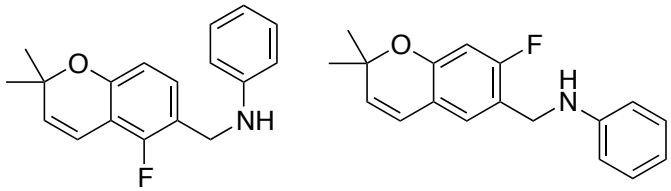
***N*-(4-(Morpholinomethyl)benzyl)aniline (16i)** Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.17 (m, 4H), 6.79-6.66 (m, 5H), 4.34 (s, 2H), 3.74 (m, 4H), 3.53 (s, 2H), 2.74 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 138.4, 136.8, 129.5, 129.3, 127.5, 118.6, 117.6, 115.1, 112.9, 67.0, 63.2, 53.6, 48.1 ppm. HRMS *m/z* (ESI) calculated for $C_{16}H_{22}NO_2$ [$(M + H)^+$] 260.1651, found 260.1657.



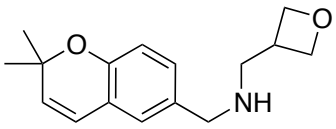
***N*-((2,3-Dihydrobenzofuran-5-yl)methyl)aniline (16j)** Yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.13 (m, 4H), 6.83-6.69 (m, 4H), 4.63-4.59 (m, 2H), 4.28 (s, 2H), 4.00 (s, 1H), 3.25-3.21 (t, *J* = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 148.3, 131.5, 129.3, 127.5, 127.5, 124.5, 117.5, 112.9, 109.2, 71.4, 65.4, 48.2, 29.8, 29.7 ppm. HRMS *m/z* (ESI) calculated for $C_{15}H_{16}NO$ [$(M + H)^+$] 226.1232, found 226.1230.



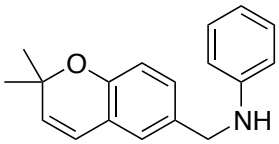
***N*-((5,7-Difluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)aniline (16l)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.17 (m, 2H), 7.03-6.99 (m, 1H), 6.77-6.63 (m, 5H), 6.38-6.36 (d, *J* = 8 Hz, 1H), 5.64-5.62 (d, *J* = 8Hz, 1H), 4.34 (s, 3H), 1.47 (s, 6H) ppm.



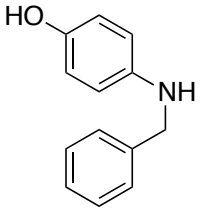
***N*-((5-Fluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)aniline with *N*-((7-fluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)aniline (1:1) (16m)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.18 (m, 4H), 7.12-7.08 (m, 1H), 6.99-6.97 (d, *J* = 8 Hz, 1H), 6.74-6.52 (m, 9H), 6.27-6.25 (d, *J* =8 Hz, 1H), 5.70-5.67 (d, *J* =10 Hz, 1H), 5.57-5.55 (d, *J* =10 Hz, 1H), 4.30 (s, 2H), 4.29 (s, 2H), 3.94 (s, 2H), 1.44 (s, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 148.0, 148.0, 131.0, 129.7, 129.7, 129.3, 129.2, 128.9, 126.9, 126.9, 121.5, 117.7, 117.7, 117.1, 115.1, 115.1, 113.0, 112.7, 112.5, 112.0, 111.9, 104.2, 103.9, 44.0, 41.8, 41.8, 41.6, 41.5, 29.7, 29.4, 29.3, 28.0, 27.9 ppm.



1-(2,2-Dimethyl-2*H*-chromen-6-yl)-*N*-(oxetan-3-ylmethyl)methanamine (18a) Yield: 92%. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.04-7.02 (d, *J* = 8 Hz, 1H), 6.93 (s, 1H), 6.74-6.72 (d, *J* = 8 Hz, 1H), 6.32-6.30 (d, *J* = 8 Hz, 1H), 5.62-5.60 (d, *J* = 8 Hz, 1H), 4.81-4.78 (m, 2H), 4.42-4.39 (m, 2H), 3.68 (s, 2H), 3.13-3.09 (quintet, *J* = 7.2 Hz, 1H), 2.96 (s, 2H), 1.68-1.45 (m, 1H), 1.45 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 132.2, 131.0, 128.8, 128.6, 126.1, 122.2, 121.5, 121.2, 116.2, 76.2, 76.0, 53.5, 52.4, 35.3, 29.6, 28.0 ppm. HRMS *m/z* (ESI) calculated for $C_{16}H_{22}NO_2$ [$(M + H)^+$] 260.1651, found 260.1657.

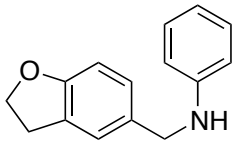


***N*-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)aniline (19)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.21 (m, 3H), 6.98-6.96 (d, *J* = 8 Hz, 1H), 6.88-6.86 (m, 1H), 6.79-6.72 (m, 3H), 6.40-6.38 (d, *J* = 8 Hz, 1H), 5.69-5.67 (d, *J* = 8 Hz, 1H), 4.37 (s, 2H), 4.06 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 148.5, 130.6, 129.2, 128.9, 126.5, 125.5, 122.5, 121.1, 120.5, 117.4, 113.2, 76.44, 43.11, 28.18. HRMS (ESI) *m/z* calculated for $C_{18}H_{20}NO$ [$(M + H)^+$] 266.1545, found 266.1548.

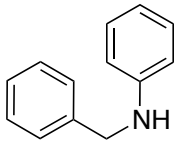


4-(Benzylamino)phenol (23a) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.32 (m, 5H), 6.71-6.69 (d, *J* = 8 Hz, 2H), 6.60-6.58 (d, *J* = 8 Hz, 2H), 4.41 (s, 1H), 4.29 (s, 2H) ppm. ^{13}C NMR (100 MHz,

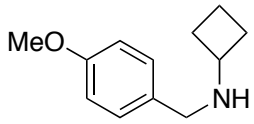
$CDCl_3$): δ 148.1, 142.1, 139.5, 128.7, 127.7, 127.3, 127.2, 116.4, 114.8, 49.6 ppm. HRMS *m/z* (ESI) calculated for $C_{13}H_{14}NO$ [$(M + H)^+$] 200.1075, found 200.1079.



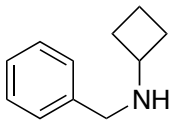
***N*-((2,3-Dihydrobenzofuran-5-yl)methyl)aniline (25a)** ^1H NMR (400 MHz, $CDCl_3$): δ 7.27-7.23 (m, 3H), 7.17-7.13 (m, 1H), 6.83-6.77 (m, 2H), 6.71-6.69 (d, *J* = 8 Hz, 2H), 4.63-4.59 (m, 2H), 4.28 (s, 2H), 4.00 (s, 1H), 3.25-3.21 (t, *J* = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 148.3, 131.5, 129.3, 127.5, 127.5, 124.5, 117.5, 112.9, 109.2, 71.4, 65.4, 48.2, 29.7 ppm. HRMS *m/z* (ESI) calculated for $C_{15}H_{16}NO$ [$(M + H)^+$] 226.1232, found 226.1230.



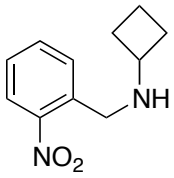
***N*-Benzylaniline (25b)** Yield: 97% ^1H NMR (400 MHz, $CDCl_3$): δ 7.61-7.53 (m, 5H), 7.44-7.42 (d, *J* = 8 Hz, 2H), 7.02-6.982(m, 1H), 6.87-6.85 (d, *J* = 8 Hz, 2H), 4.52 (s, 2H), 4.14 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 139.8, 129.6, 128.9, 127.8, 127.5, 117.8, 113.2, 48.5 ppm.



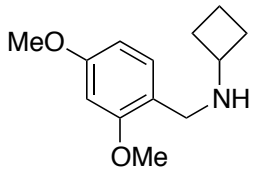
***N*-(4-Methoxybenzyl)cyclobutanamine (27a)** Not isolated. Crude product taken directly to next step.



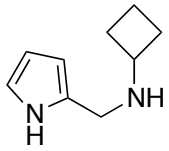
***N*-Benzylcyclobutanamine (27b)** Not isolated. Crude product taken directly to next step.



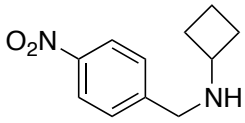
***N*-(2-Nitrobenzyl)cyclobutanamine (27c)** Not isolated. Crude product taken directly to next step. MS *m/z* (ESI) calculated for $C_{11}H_{15}N_2O_2$ [$(M + H)^+$] 207.1, found 207.1.



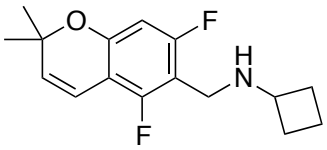
***N*-(2,4-Dimethoxybenzyl)cyclobutanamine (27d)** Not isolated. Crude product taken directly to next step.



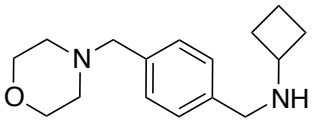
***N*-((1*H*-Pyrrol-2-yl)methyl)cyclobutanamine (27e)** Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (s, 1H), 6.88-6.88 (d, *J* = 2 Hz, 1H), 6.26 (s, 1H), 6.15-6.15 (d, *J* = 2 Hz, 1H), 4.11 (s, 2H), 3.58-3.50 (m, 1H), 2.36-2.21 (m, 4H), 2.00-1.97 (m, 1H), 1.86-1.79 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.1, 118.9, 112.3, 108.8, 50.6, 42.2, 26.6, 15.4 ppm. MS *m/z* (ESI) calculated for $C_9H_{15}N_2$ [$(M + H)^+$] 151.1, found 151.1.



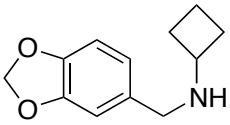
***N*-(4-Nitrobenzyl)cyclobutanamine (27f)** Yield: 26%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20-8.18 (d, *J* = 8 Hz, 2H), 7.54-7.52 (d, *J* = 8 Hz, 2H), 3.85 (s, 2H), 3.33-3.28 (quintet, *J* = 7.2 Hz, 1H), 2.36 (s, 1H), 2.27-2.21 (m, 2H), 1.81-1.65 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.1, 118.9, 112.2, 108.8, 50.6, 42.2, 26.6, 15.4 ppm.



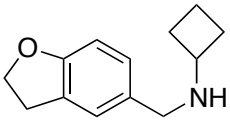
***N*-((5,7-Difluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine (27g)** Not isolated. Crude product taken directly to next step.



***N*-(4-(Morpholinomethyl)benzyl)cyclobutanamine (27h)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.26 (m, 4H), 3.69-3.68 (m, 4H), 3.47 (s, 2H), 3.31-3.28 (m, 1H), 2.43 (m, 4H), 2.22-2.21 (m, 2H), 1.63-1.62 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4, 136.3, 129.4, 128.1, 67.0, 63.2, 53.6, 50.8, 31.1, 14.8 ppm. HRMS *m/z* (ESI) calculated for $C_{16}H_{25}NO_2$ [$(M + H)^+$] 261.1967, found 261.1961.

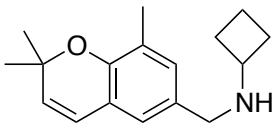


***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)cyclobutanamine (27i)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 1H), 6.75 (s, 2H), 5.93 (s, 2H), 3.61 (s, 2H), 3.30-3.26 (quintet, *J* = 7.2 Hz, 1H), 2.23-2.18 (m, 2H), 1.83 (s, 1H), 1.72-1.62 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 146.5, 134.3, 121.3, 108.8, 108.0, 100.9, 53.4, 50.8, 44.7, 31.3, 31.0, 15.0, 14.8 ppm. HRMS *m/z* (ESI) calculated for $C_{12}H_{16}NO_2$ [$(M + H)^+$] 206.1181, found 206.1181.

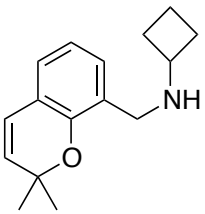


***N*-((2,3-Dihydrobenzofuran-5-yl)methyl)cyclobutanamine (27j)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (s, 1H), 7.01-6.99 (d, *J* = 8 Hz, 1H), 6.70-6.68 (d, *J* = 8 Hz, 1H), 4.53-4.49 (t, *J* = 8 Hz,

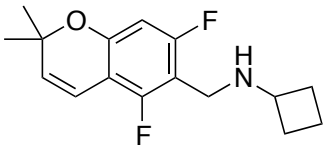
2H), 3.59 (s, 2H), 3.29-3.25 (m, 1H), 3.16-3.12 (t, *J* = 8 Hz, 2H), 2.21-2.20 (m, 2H), 1.68-1.61 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 132.4, 127.9, 127.1, 125.0, 108.8, 71.2, 53.4, 50.7, 31.1, 29.7, 14.8 ppm. HRMS *m/z* (ESI) calculated for $C_{13}H_{18}NO$ $[(M + H)^+]$ 204.1388, found 204.1392.



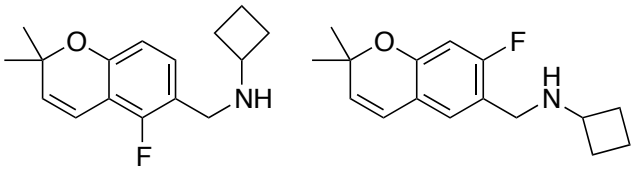
***N*-((2,2,8-trimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine (27k)** Not isolated. Taken on to next step crude.



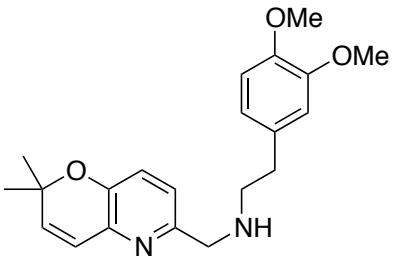
***N*-((2,2-Dimethyl-2*H*-chromen-8-yl)methyl)cyclobutanamine (27l)** Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.07 (d, *J* = 8 Hz, 1H), 6.91-6.89 (d, *J* = 8 Hz, 1H), 6.82-6.78 (t, *J* = 8 Hz, 1H), 6.34-6.32 (d, *J* = 8 Hz, 1H), 5.63-5.61 (d, *J* = 8 Hz, 1H), 3.68 (s, 2H), 3.32-3.28 (quintet, *J* = 7.2 Hz, 1H), 2.19-2.18 (m, 4H), 1.73-1.67 (m, 2H), 1.43 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 130.3, 129.7, 125.3, 122.5, 120.9, 120.3, 76.2, 53.7, 46.2, 31.1, 28.1, 15.0 ppm. HRMS *m/z* (ESI) calculated for $C_{16}H_{22}NO$ $[(M + H)^+]$ 244.1701, found 244.1707.



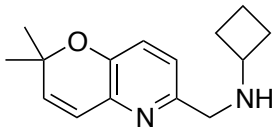
***N*-((5,7-difluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine (27m)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51-6.48 (d, *J* = 10 Hz, 1H), 6.36-6.35 (d, *J* = 8 Hz, 1H), 5.62-5.60 (d, *J* = 8 Hz, 1H), 3.73 (d, 2H), 3.30-3.29 (m, 1H), 2.18 (m, 2H), 1.71-1.70 (m, 4H), 1.46 (s, 6H) ppm.



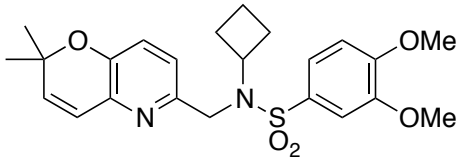
***N*-((5-Fluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine with *N*-((7-Fluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine (1:1) (27n)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.21 (d, *J* = 8 Hz, 1H), 7.12-7.08 (t, *J* = 8 Hz, 1H), 7.00-6.98 (d, *J* = 8 Hz, 1H), 6.53-6.50 (m, 1H), 6.31-6.29 (d, *J* = 8 Hz, 1H), 5.68-5.66 (d, *J* = 8 Hz, 1H), 5.59-5.56 (d, *J* = 10 Hz, 1H), 4.42 (s, 4H), 1.45-1.44 (m, 8H), 1.27-1.25 (m, 4H), 1.28 (s, 12H) ppm.



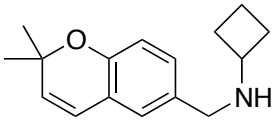
2-(3,4-Dimethoxyphenyl)-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)ethanamine (29a) Yield: 38%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02-6.97 (m, 2H), 6.81-6.75 (m, 3H), 6.45-6.43 (d, *J* = 10 Hz, 1H), 5.88-5.86 (d, *J* = 10 Hz, 1H), 3.86 (s, 6H), 3.84 (s, 2H), 2.95-2.92 (t, *J* = 6.8 Hz, 2H), 2.85-2.81 (t, *J* = 6.8 Hz, 2H), 1.46 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 148.9, 136.0, 135.3, 132.2, 123.8, 123.4, 122.4, 120.7, 120.7, 112.1, 111.4, 111.4, 76.7, 55.9, 55.8, 54.1, 50.7, 35.6, 28.2 ppm. HRMS *m/z* (ESI) calculated for $C_{21}H_{27}N_2O_3$ [$(M + H)^+$] 355.2022, found 355.2025.



***N*-((2,2-Dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)cyclobutanamine (31)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97-6.95 (d, *J* = 8 Hz, 1H), 6.92-6.90 (d, *J* = 8 Hz, 1H), 6.45-6.43 (d, *J* = 8 Hz, 1H), 5.80-5.78 (d, *J* = 8 Hz, 1H), 3.64 (s, 2H), 3.27-3.23 (quintet, *J* = 7.2 Hz, 1H), 2.41 (s, 1H), 2.15-2.11 (m, 2H), 1.69-1.52 (m, 4H), 1.38 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 148.3, 140.6, 135.1, 123.9, 123.3, 122.3, 76.8, 53.9, 51.9, 31.1, 30.9, 28.1, 27.8, 14.8 ppm. HRMS *m/z* (ESI) calculated for $C_{15}H_{21}N_2O$ [$(M + H)^+$] 245.1654, found 245.1651.



N-Cyclobutyl-N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (2), (32a) Yield = 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.42 (d, *J* = 8 Hz, 1H), 7.36-7.34 (d, *J* = 8 Hz, 1H), 7.26 (s, 1H), 7.07-7.05 (d, *J* = 8 Hz, 1H), 6.94-6.92 (d, *J* = 8 Hz, 1H), 6.45-6.43 (d, *J* = 10 Hz, 1H), 5.90-5.87 (d, *J* = 10 Hz, 1H), 4.42 (s, 2H), 7.37-7.35 (m, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 1.99-1.92 (m, 4H), 1.56-1.52 (m, 2H), 1.48 (s, 6H) ppm.



***N*-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine (32)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04-7.02 (d, *J* = 8 Hz, 1H), 6.95 (s, 1H), 6.73-6.71 (d, *J* = 8 Hz, 1H), 6.32-6.30 (d, *J* = 8 Hz, 1H), 5.61-5.59 (d, *J* = 8 Hz, 1H), 3.60 (s, 2H), 3.32-3.26 (quintet, *J* = 7.2 Hz, 1H), 2.22 (m, 2H), 1.72-1.69 (m, 4H), 1.43 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 132.5, 130.8,

128.9, 126.2, 122.3, 121.2, 116.1, 76.1, 53.5, 50.5, 31.1, 27.9, 14.8 ppm. HRMS *m/z* (ESI) calculated for $C_{16}H_2NO$ $[(M + H)^+]$ 244.1701, found 244.1697.

5.6 References

1. Kaur, B. K., F.W.; Severson, E. A.; Matheny, S.L.; Brat, D.J.; Van Meir, E. G. , *Neuro-Oncol.* **2005,** *7*, 134.

2. Tan, C. e. a., Sulfonamides as a new scaffold for hypoxia inducible factor pathway inhibitors. *Bioorganic & Medicinal Chemistry Letters* **2011,** *21*, 5528-5532.

3. Maxwell, P. H.; Wiesener, M. S.; Chang, G.-W.; Clifford, S. C.; Vaux, E. C.; Cockman, M. E.; Wykoff, C. C.; Pugh, C. W.; Maher, E. R.; Ratcliffe, P. J., The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* **1999,** *399* (6733), 271-275.

4. (a) Wenger, R. H.; Stiehl, D. P.; Camenisch, G., Integration of oxygen signaling at the consensus HRE. *Sci STKE* **2005,** *2005* (306), re12; (b) Harris, A. L., Hypoxia--a key regulatory factor in tumour growth. *Nature Reviews Cancer* **2002,** *2* (1), 38-47.

5. Bos, R. v. d. G., P.; Greijer, A.E.; Shvarts, A.; Meijer, S.; Pinedo, H.M.; Semenza, G.L.; van Diest, P.J.; van der Wall, E., Cancer. *Levels of hypoxia-inducible factor-1alpha independently predict prognosis in patients with lymph node negative breast carcinoma.* **2003,** *97* (6), 1573-1581.

6. Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E., Natural Product-like Combinatorial Libraries Based on Privileged Structures. 2. Construction of a 10,000-Membered Benzopyran Library by Directed Split-and-Pool Chemistry Using NanoKans and Optical Encoding. *Journal of the American Chemical Society* **2000,** *122* (41), 9954-9967.

7. Tan, C.; de Noronha, R. G.; Roecker, A. J.; Pyrzynska, B.; Khwaja, F.; Zhang, Z.; Zhang, H.; Teng, Q.; Nicholson, A. C.; Giannakakou, P.; Zhou, W.; Olson, J. J.; Pereira, M. M.; Nicolaou, K. C.; Van Meir, E. G., Identification of a Novel Small-Molecule Inhibitor of the Hypoxia-Inducible Factor 1 Pathway. *Cancer Research* **2005,** *65* (2), 605-612.

8. Tan, C.; de Noronha, R. G.; Devi, N. S.; Jabbar, A. A.; Kaluz, S.; Liu, Y.; Mooring, S. R.; Nicolaou, K. C.; Wang, B.; Van Meir, E. G., Sulfonamides as a new scaffold for hypoxia inducible factor pathway inhibitors. *Bioorganic & Medicinal Chemistry Letters* **2011,** *21* (18), 5528-5532.

9. Yin, S.; Kaluz, S.; Devi, N. S.; Jabbar, A. A.; de Noronha, R. G.; Mun, J.; Zhang, Z.; Boreddy, P. R.; Wang, W.; Wang, Z.; Abbruscato, T.; Chen, Z.; Olson, J. J.; Zhang, R.; Goodman, M. M.; Nicolaou, K. C.; Van Meir, E. G., Arylsulfonamide KCN1 Inhibits In Vivo Glioma Growth and Interferes with HIF Signaling by Disrupting HIF-1α Interaction with Cofactors p300/CBP. *Clinical Cancer Research* **2012,** *18* (24), 6623-6633.

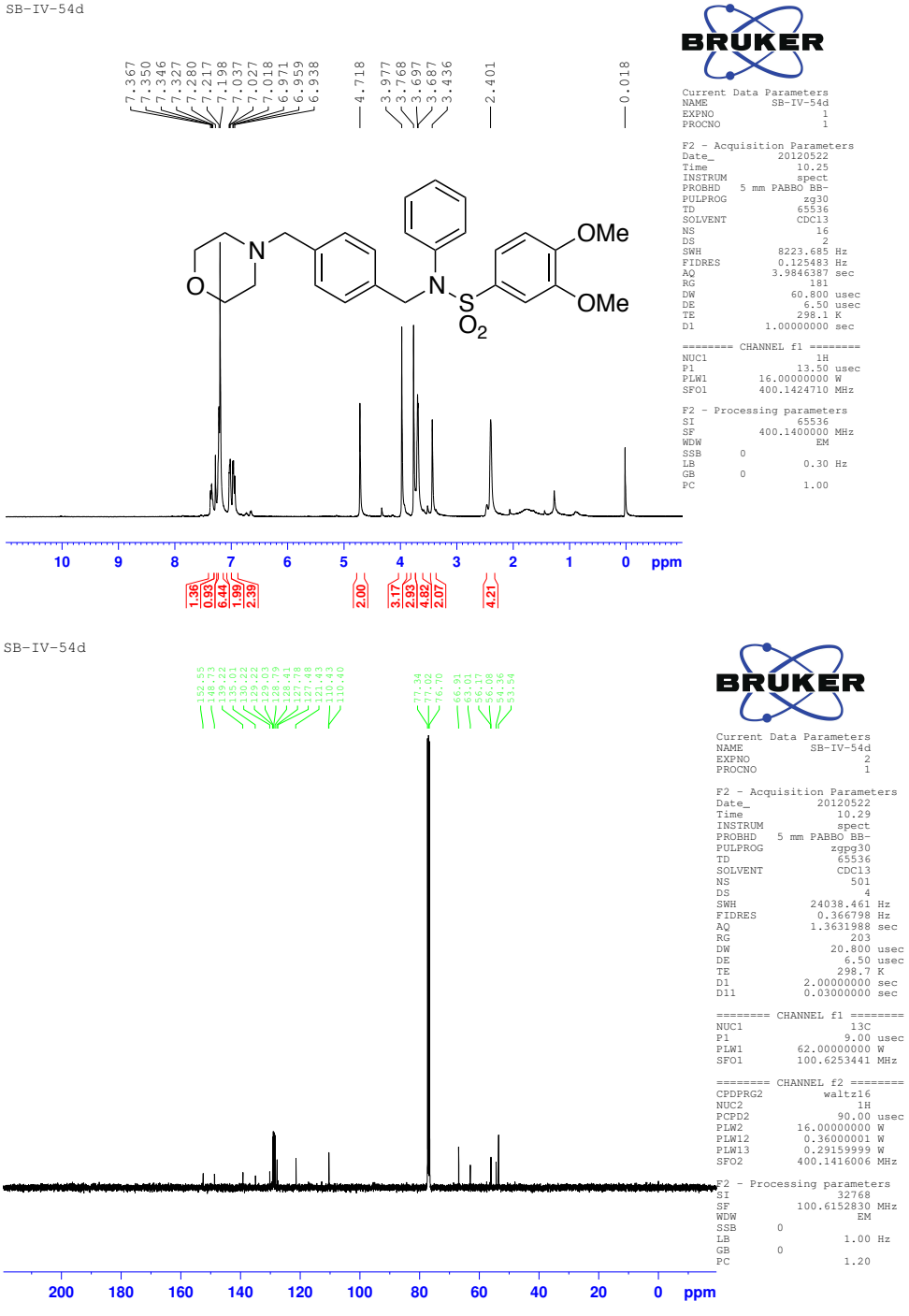
10. Mooring, S. R.; Jin, H.; Devi, N. S.; Jabbar, A. A.; Kaluz, S.; Liu, Y.; Van Meir, E. G.; Wang, B., Design and Synthesis of Novel Small-Molecule Inhibitors of the Hypoxia Inducible Factor Pathway. *Journal of Medicinal Chemistry* **2011,** *54* (24), 8471-8489.

11. Prado, S.; Janin, Y. L.; Saint-Joanis, B.; Brodin, P.; Michel, S.; Koch, M.; Cole, S. T.; Tillequin, F.; Bost, P.-E., Synthesis and antimycobacterial evaluation of benzofurobenzopyran analogues. *Bioorganic & Medicinal Chemistry* **2007,** *15* (5), 2177-2186.

APPENDICES: STRUCTURAL CHARACTERIZATION OF COMPOUNDS

Appendix A: Structural Characterization of Compounds from Chapter 3

3,4-Dimethoxy-*N*-(4-(morpholinomethyl)benzyl)-*N*-phenylbenzenesulfonamide (2a)

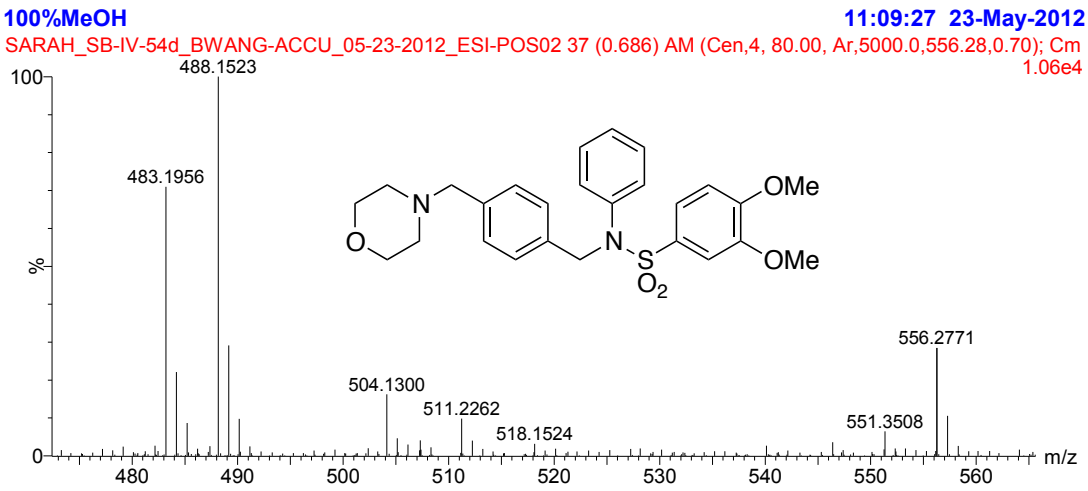


BRUKER

```
Current Data Parameters
NAME                  SB-IV-54d
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20120522
Time                      10.25
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   8223.685 Hz
FIDRES               0.125483 Hz
AQ                    3.9846387 sec
RG                         181
DW                      60.800 usec
DE                       6.50 usec
TE                      298.1 K
D1                    1.00000000 sec

======== CHANNEL f1 ========
NUC1                        1H
P1                      13.50 usec
PLW1                16.00000000 W
SFO1                400.1424710 MHz

F2 - Processing parameters
SI                       65536
SF                  400.1400000 MHz
WDW                         EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
```

BRUKER

```
Current Data Parameters
NAME                  SB-IV-54d
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20120522
Time                      10.29
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                         501
DS                           4
SWH                  24038.461 Hz
FIDRES               0.366798 Hz
AQ                    1.3631988 sec
RG                         203
DW                      20.800 usec
DE                       6.50 usec
TE                      298.7 K
D1                    2.00000000 sec
D11                   0.03000000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                       9.00 usec
PLW1                62.00000000 W
SFO1                100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                   90.00 usec
PLW2                16.00000000 W
PLW12                0.36000001 W
PLW13                0.29159999 W
SFO2                400.1416006 MHz

F2 - Processing parameters
SI                       32768
SF                  100.6152830 MHz
WDW                         EM
SSB          0
LB                       1.00 Hz
GB           0
PC                       1.20
```



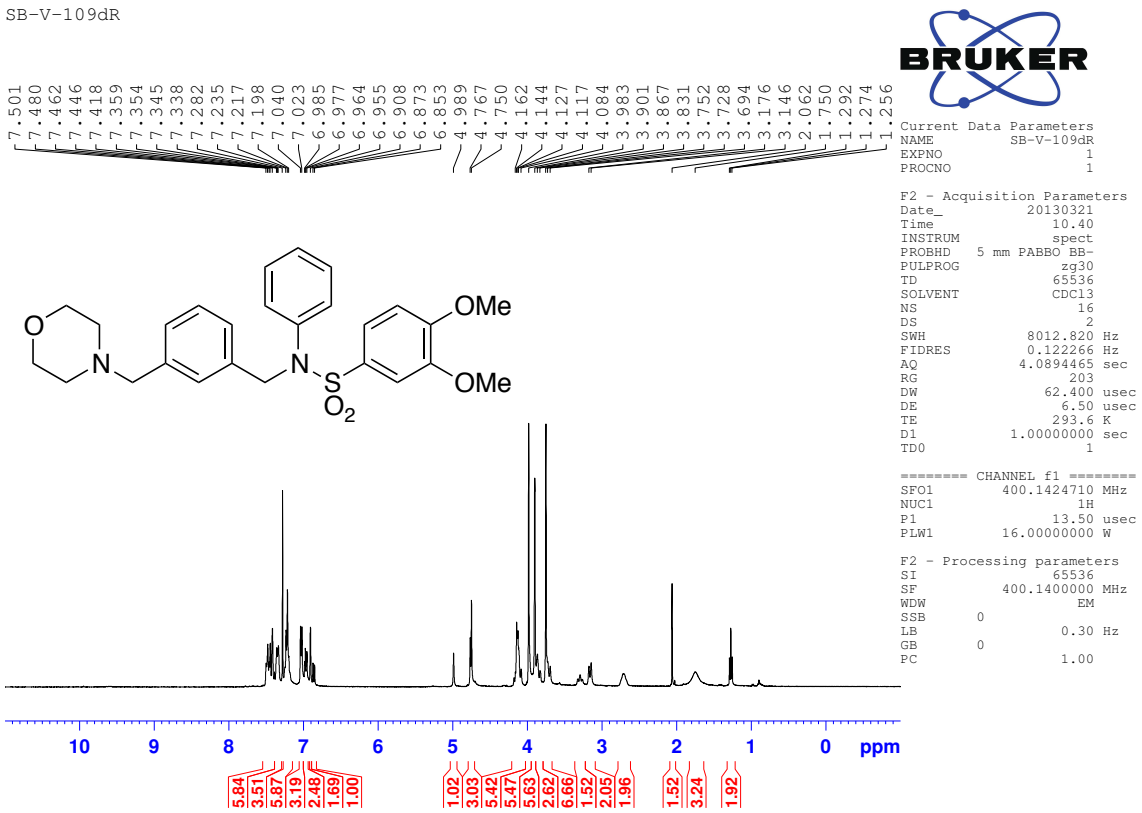
Elemental Composition Report

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
6053 formula(e) evaluated with 64 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 0-50

Minimum:				-1.5		
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
483.1956	483.1954	0.2	0.4	12.5	12.4		C26 H31 N2 O5 S

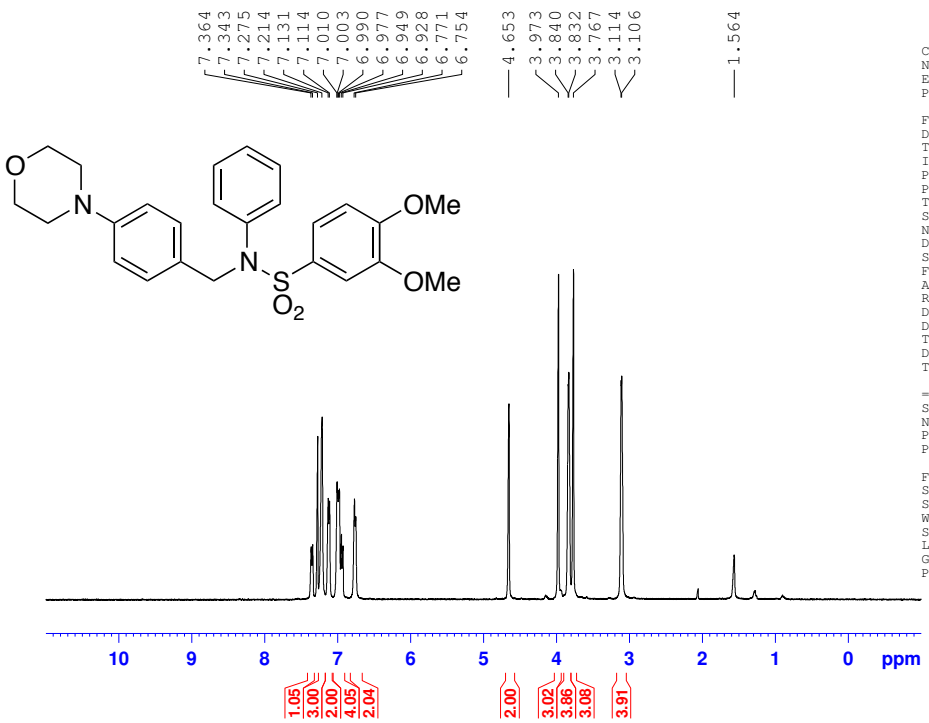
3,4-Dimethoxy-*N*-(3-(mor*p*holinomethyl)benzyl)-N-phenylbenzenesulfonamide (2b)




```
Current Data Parameters
NAME                  SB-V-109dR
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20130321
Time                       10.40
INSTRUM                    spect
PROBHD    5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8012.820 Hz
FIDRES                 0.122266 Hz
AQ                     4.0894465 sec
RG                          203
DW                       62.400 usec
DE                        6.50 usec
TE                       293.6 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1                400.1424710 MHz
NUC1                        1H
P1                       13.50 usec
PLW1                16.00000000 W

F2 - Processing parameters
SI                        65536
SF                  400.1400000 MHz
WDW                          EM
SSB                0
LB                        0.30 Hz
GB                 0
PC                        1.00
```

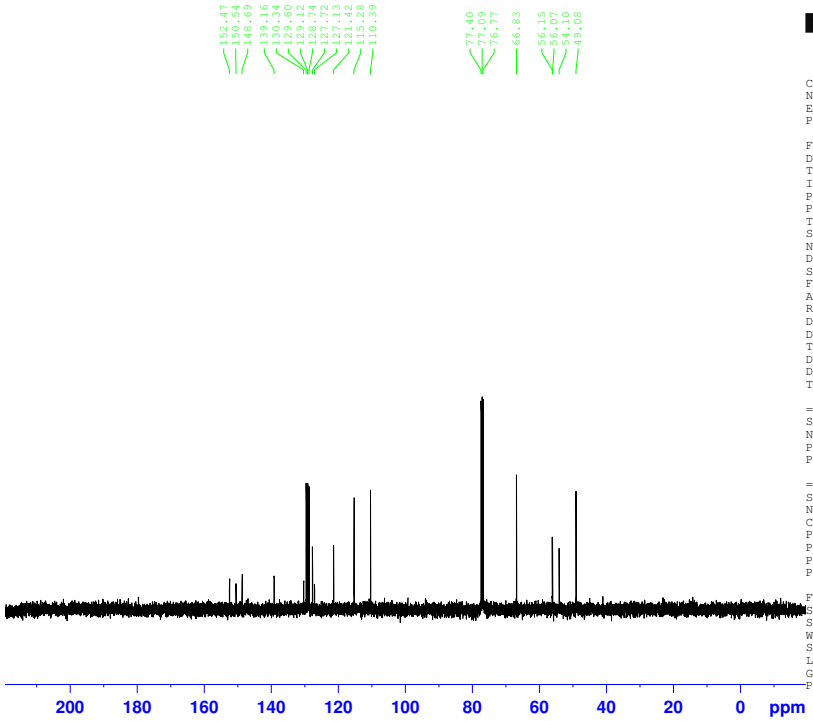
3,4-Dimethoxy-*N*-(4-morpholinobenzyl)-*N*-phenylbenzenesulfonamide (2d)

SB-V-88r1

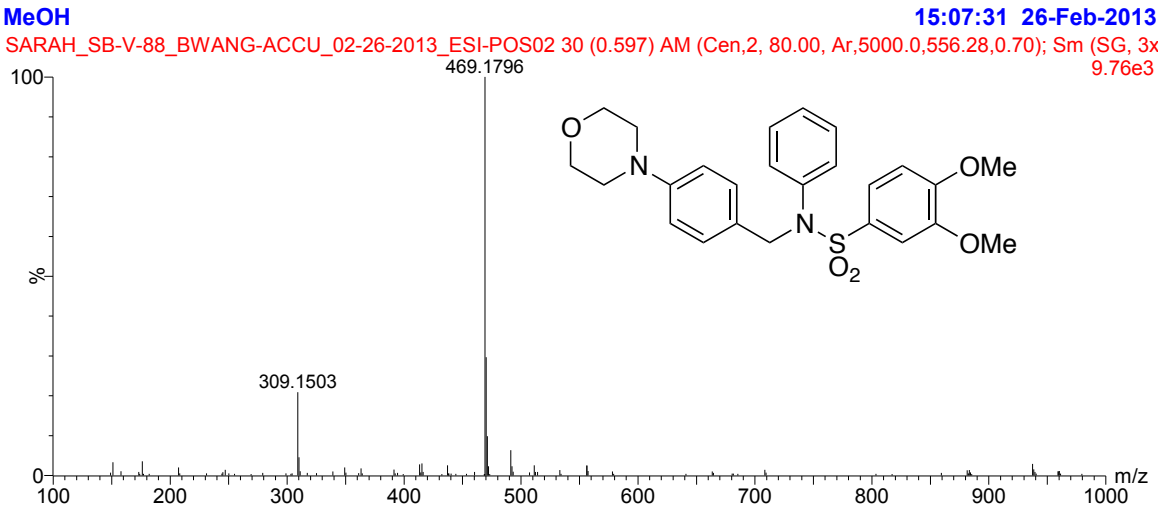



```
Current Data Parameters
NAME           SB-V-88r1
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130220
Time               13.43
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    12
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                   203
DW                62.400 usec
DE                 6.50 usec
TE                298.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                 65536
SF            400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-V-88c




```
Current Data Parameters
NAME           SB-V-88c
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130219
Time               18.19
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    30
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.2 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF           100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



Elemental Composition Report

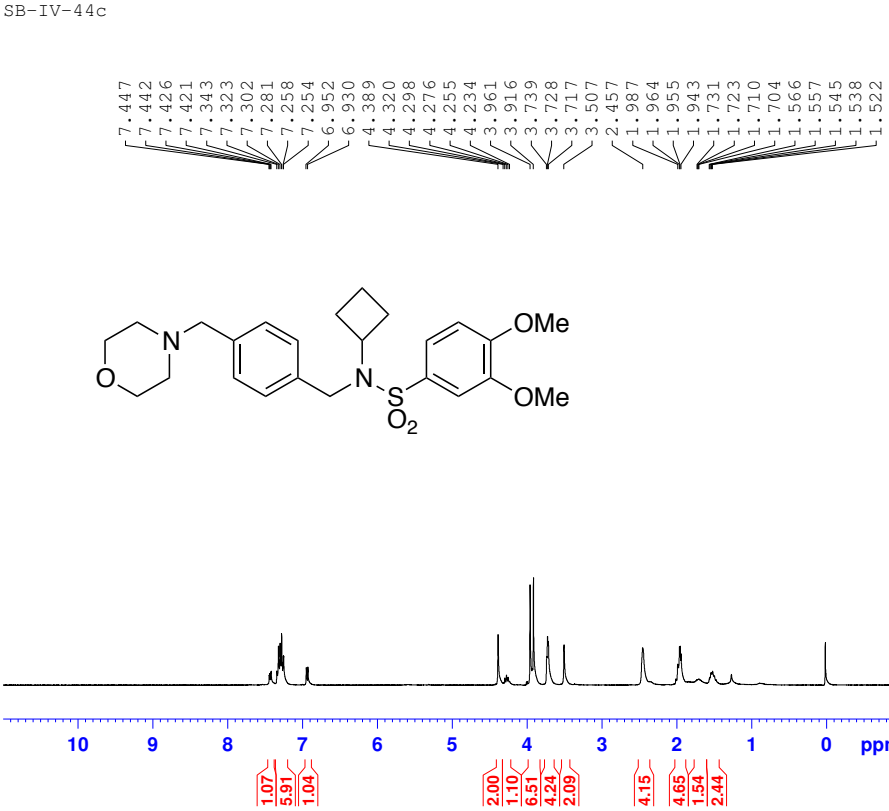
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2331 formula(e) evaluated with 5 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-6 O: 1-30 S: 1-10

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
469.1796	469.1797	-0.1	-0.2	12.5	0.3	C25 H29 N2 O5 S

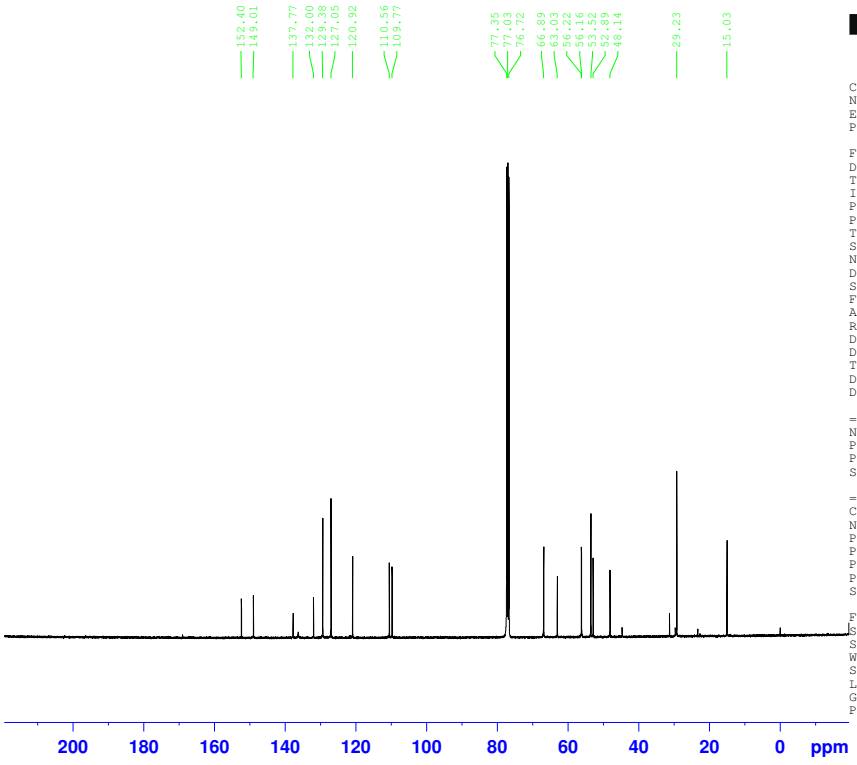
N-Cyclobutyl-3,4-dimethoxy-*N*-(4-(morpholinomethyl)benzyl)benzenesulfonamide (3a)

SB-IV-44c

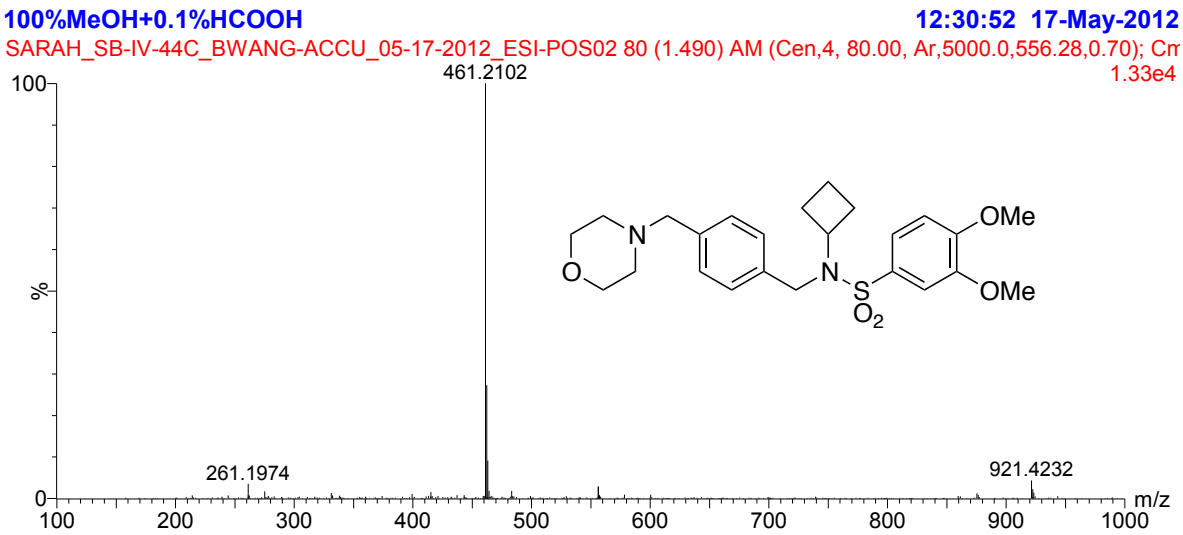



```
Current Data Parameters
NAME            SB-IV-44c
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20120430
Time               15.43
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                   203
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-IV-44c




```
Current Data Parameters
NAME            SB-IV-44c
EXPNO                   3
PROCNO                  1

F2 - Acquisition Parameters
Date_           20120515
Time               23.52
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                 10240
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                300.0 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



Elemental Composition Report

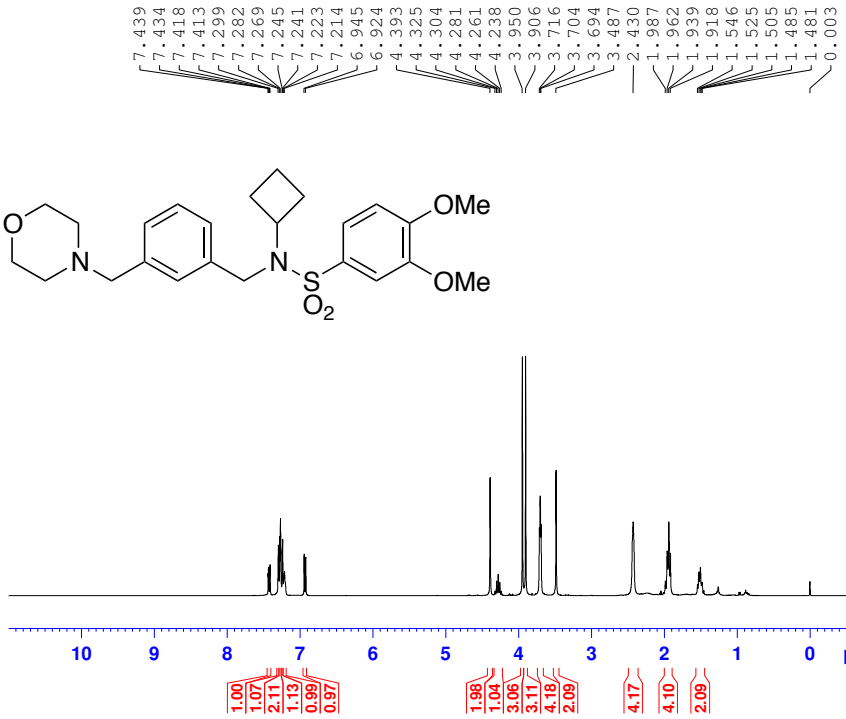
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4674 formula(e) evaluated with 14 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100 S: 0-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
461.2102	461.2110	-0.8	-1.7	9.5	5.9	C24 H33 N2 O5 S

N-Cyclobutyl-3,4-dimethoxy-*N*-(3-(morpholinomethyl)benzyl)benzenesulfonamide (3b)

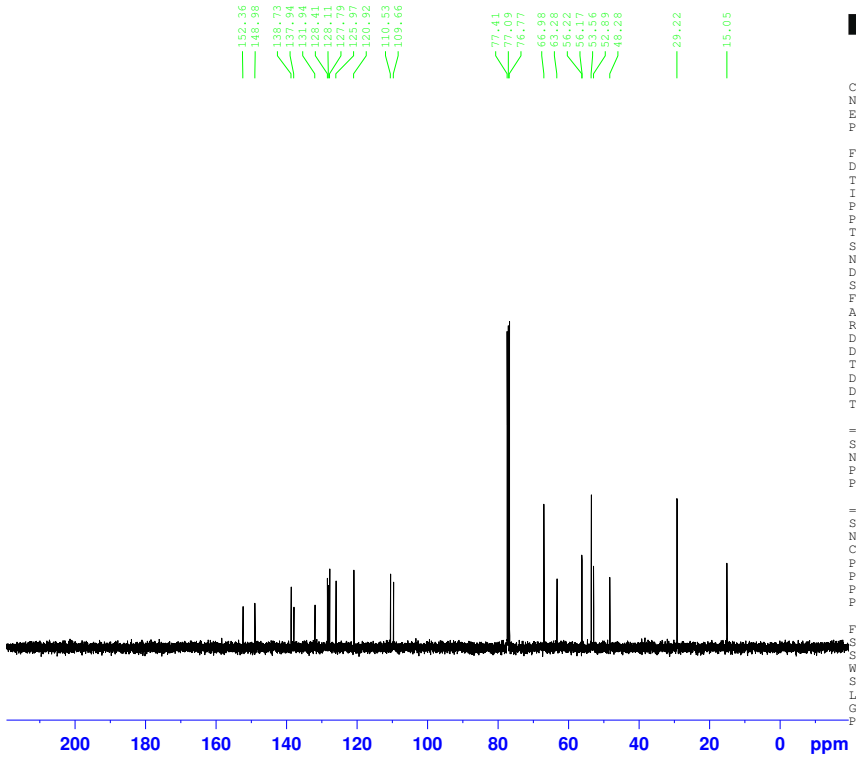
SB-V-92f



BRUKER

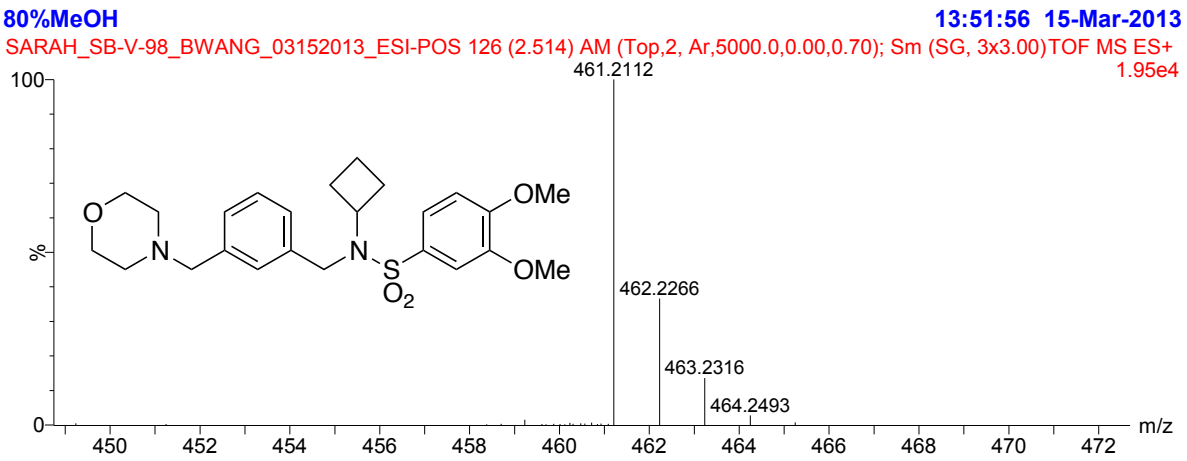
```
Current Data Parameters
NAME                  SB-V-92f
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20130312
Time                 20.47
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8012.820 Hz
FIDRES               0.122266 Hz
AQ                4.0894465 sec
RG                      57
DW                   62.400 usec
DE                    6.50 usec
TE                   293.7 K
D1                1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            400.1424710 MHz
NUC1                    1H
P1                   13.50 usec
PLW1            16.00000000 W

F2 - Processing parameters
SI                    65536
SF               400.1400000 MHz
WDW                     EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

SB-V-92f



BRUKER

```
Current Data Parameters
NAME                 SB-V-92f
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20130312
Time                 20.51
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG            zgpg30
TD                  65536
SOLVENT              CDCl3
NS                      30
DS                       4
SWH              24038.461 Hz
FIDRES               0.366798 Hz
AQ                1.3631488 sec
RG                     203
DW                   20.800 usec
DE                    6.50 usec
TE                   294.4 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            100.6253441 MHz
NUC1                    13C
P1                    9.00 usec
PLW1            62.00000000 W

======== CHANNEL f2 ========
SFO2            400.1416006 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2                90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W

F2 - Processing parameters
SI                    32768
SF               100.6152830 MHz
WDW                     EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```



Elemental Composition Report

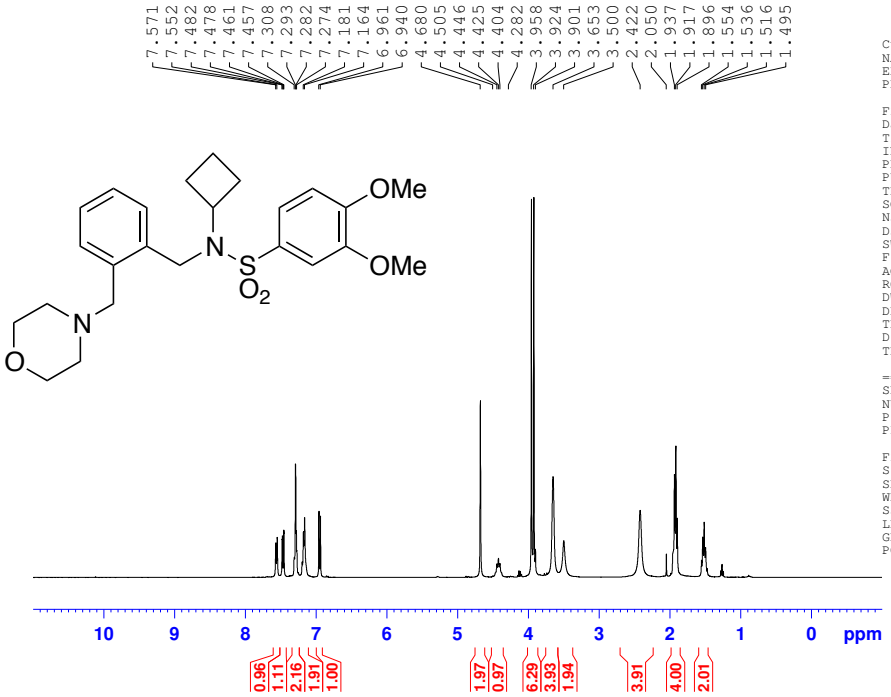
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4668 formula(e) evaluated with 10 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-30 O: 1-60 S: 1-10

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
461.2112	461.2110	0.2	0.4	9.5	243.0	C24 H33 N2 O5 S

N-Cyclobutyl-3,4-dimethoxy-*N*-(2-(morpholinomethyl)benzyl)benzenesulfonamide (3c)

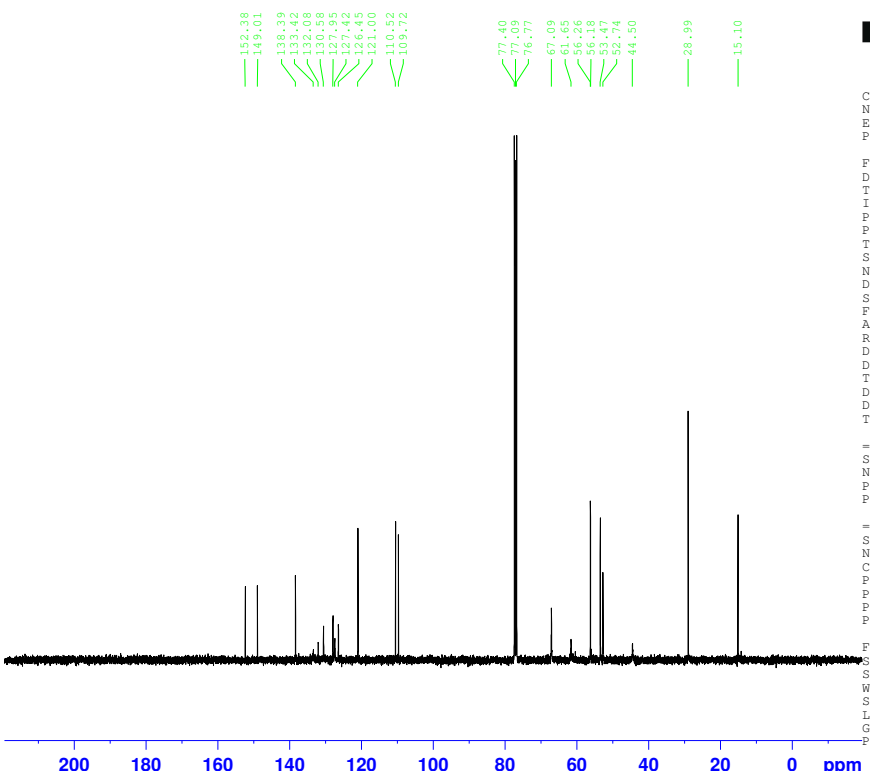
SB-V-91cR



BRUKER

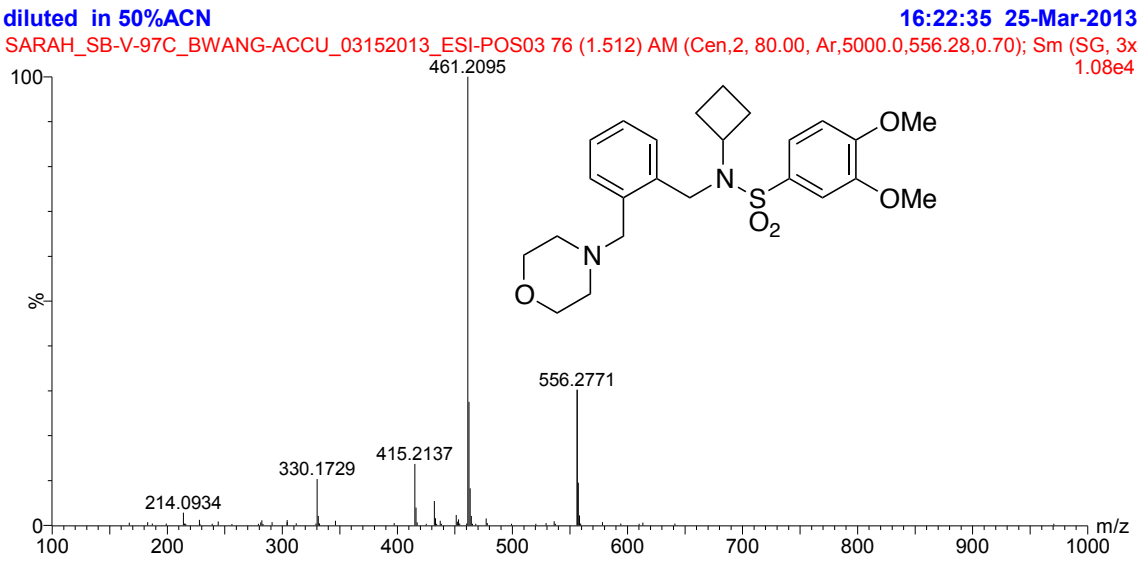
```
Current Data Parameters
NAME                  SB-V-91cR
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_              20130311
Time                 21.14
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8012.820 Hz
FIDRES               0.122266 Hz
AQ                4.0894465 sec
RG                      57
DW                   62.400 usec
DE                    6.50 usec
TE                   293.9 K
D1                1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            400.1424710 MHz
NUC1                    1H
P1                   13.50 usec
PLW1            16.00000000 W

F2 - Processing parameters
SI                   65536
SF              400.1400000 MHz
WDW                     EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

SB-V-91cR



BRUKER

```
Current Data Parameters
NAME                  SB-V-91cR
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_              20130311
Time                 21.18
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     191
DS                       4
SWH              24038.461 Hz
FIDRES               0.366798 Hz
AQ                1.3631488 sec
RG                     203
DW                   20.800 usec
DE                    6.50 usec
TE                   294.5 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            100.6253441 MHz
NUC1                    13C
P1                    9.00 usec
PLW1            62.00000000 W

======== CHANNEL f2 ========
SFO2            400.1416006 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2                 90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W

F2 - Processing parameters
SI                   32768
SF              100.6152830 MHz
WDW                     EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```



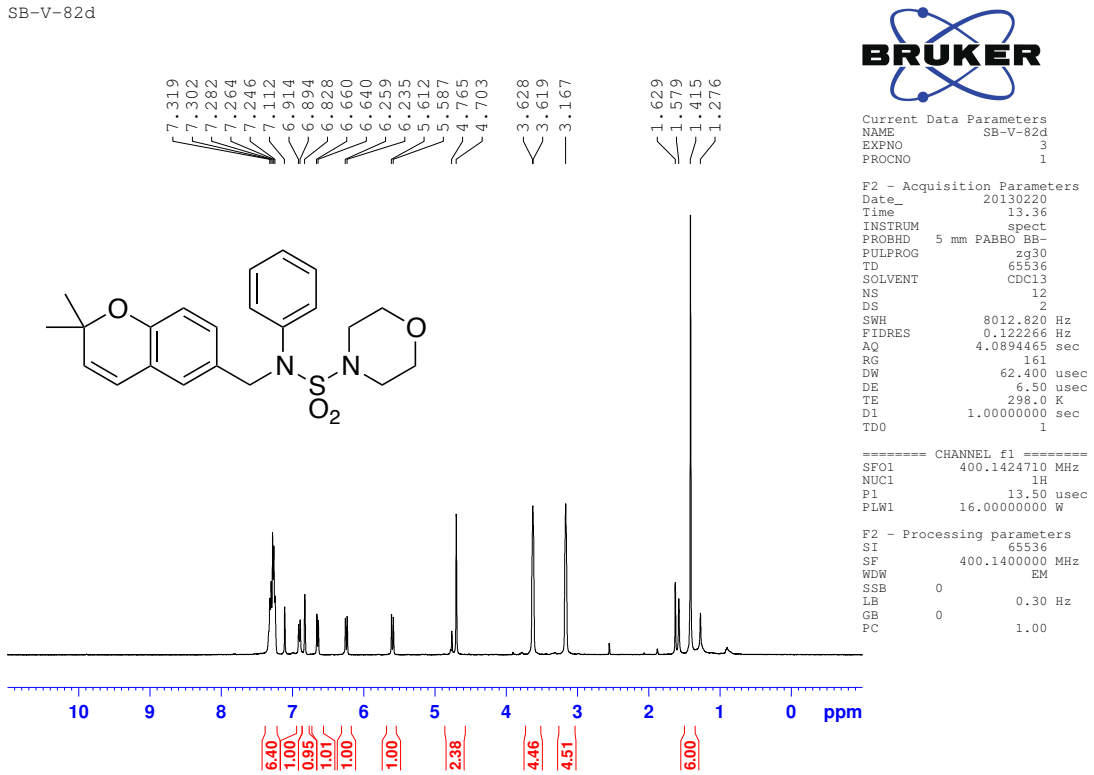
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
4668 formula(e) evaluated with 21 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-30 O: 1-60 S: 1-10

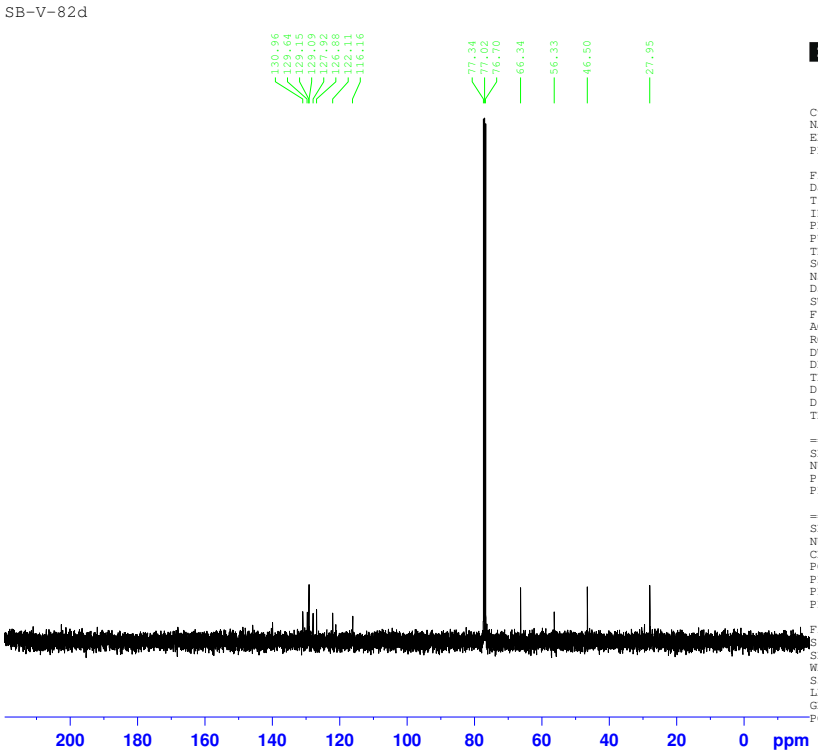
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
461.2095	461.2110	-1.5	-3.3	9.5	11.1	C24 H33 N2 O5 S

N-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-*N*-phenylmorpholine-4-sulfonamide (5a)



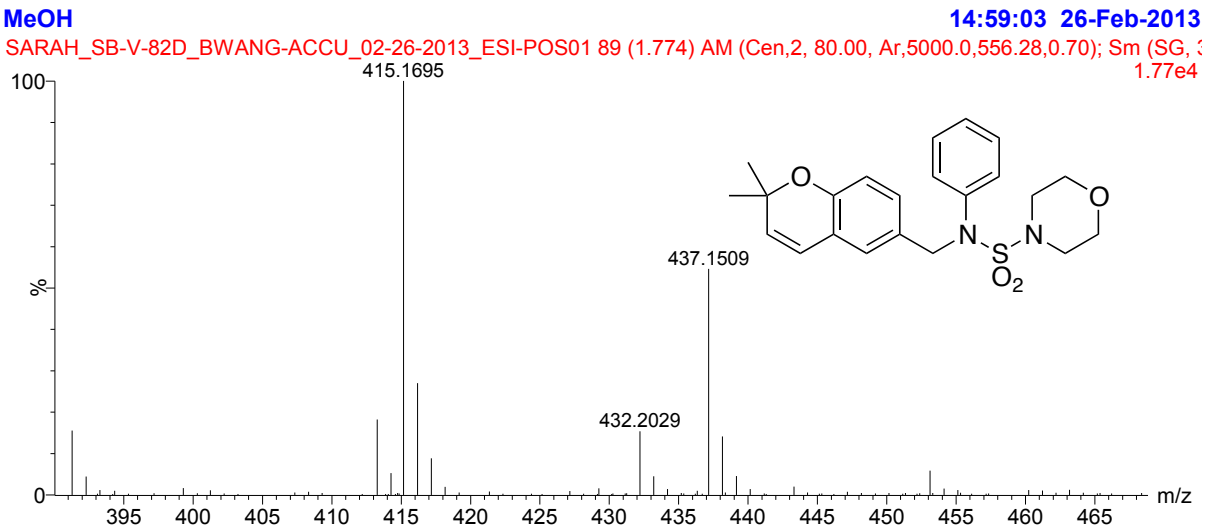
BRUKER

```
Current Data Parameters
NAME            SB-V-82d
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130220
Time               13.36
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDC13
NS                    12
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                   161
DW                62.400 usec
DE                 6.50 usec
TE                298.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                 1H
P1                13.50 usec
PLW1        16.00000000 W

F2 - Processing parameters
SI                 65536
SF           400.1400000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```



BRUKER

```
Current Data Parameters
NAME            SB-V-82d
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130219
Time               18.26
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDC13
NS                    46
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.3 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                 13C
P1                 9.00 usec
PLW1        62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W

F2 - Processing parameters
SI                 32768
SF           100.6152830 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



Elemental Composition Report

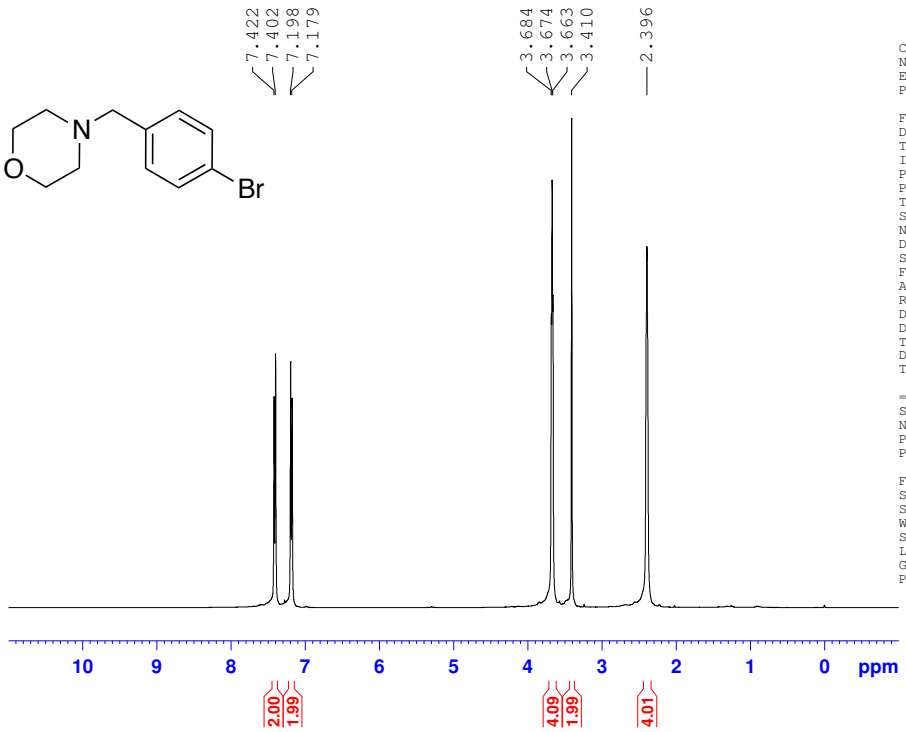
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
1658 formula(e) evaluated with 7 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-6 O: 1-30 S: 1-10

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
415.1695	415.1692	0.3	0.7	10.5	1.3		C22 H27 N2 O4 S

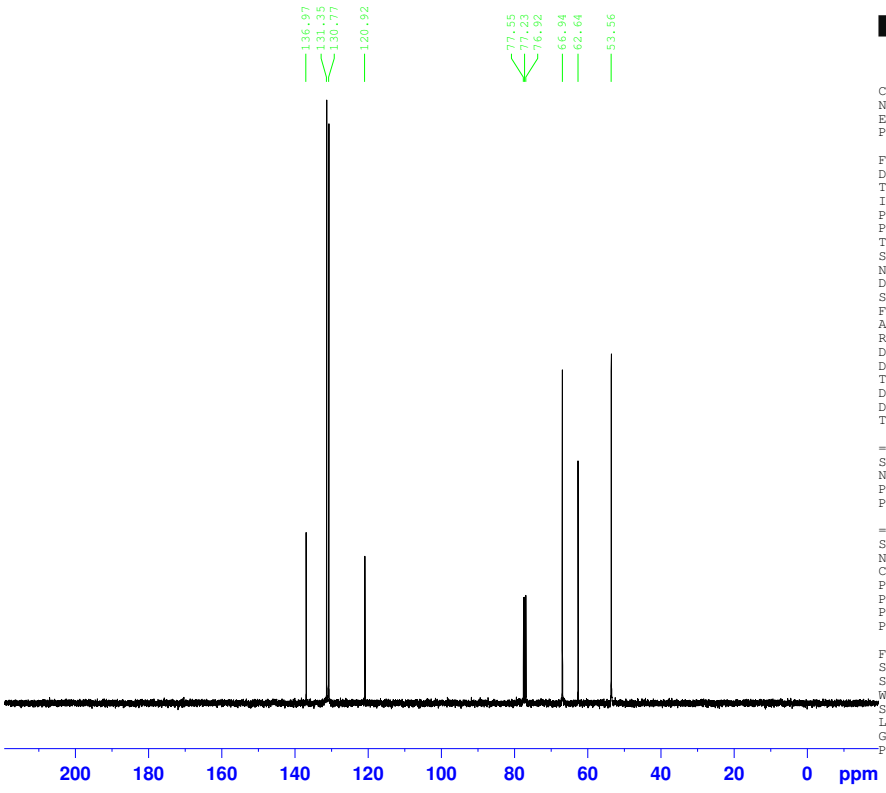
4-(4-Bromobenzyl)morpholine (7a)

SB-IV-110

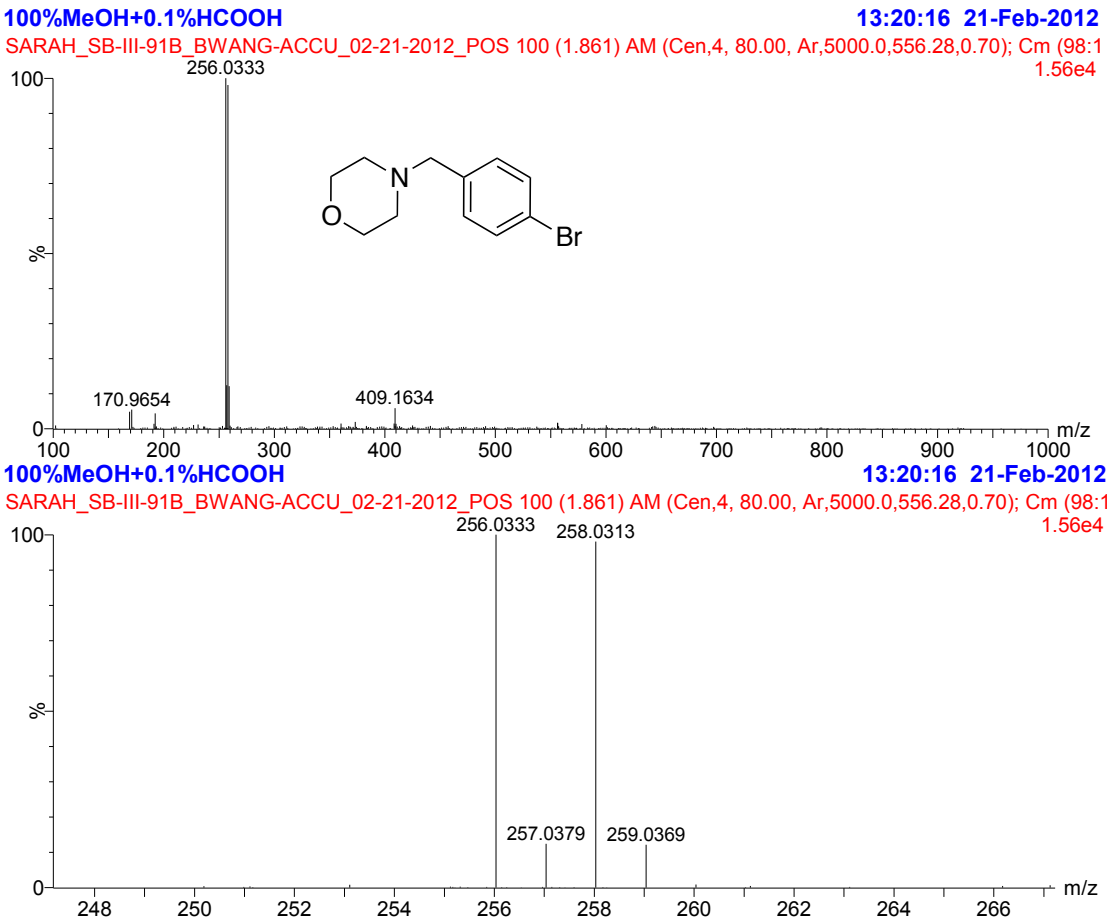



```
Current Data Parameters
NAME            SB-IV-110
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20120726
Time               13.24
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     6
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                  50.8
DW                62.400 usec
DE                 6.50 usec
TE                299.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-IV-110




```
Current Data Parameters
NAME            SB-IV-110
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20120726
Time               13.26
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    27
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                299.4 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                   13C
P1                 9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

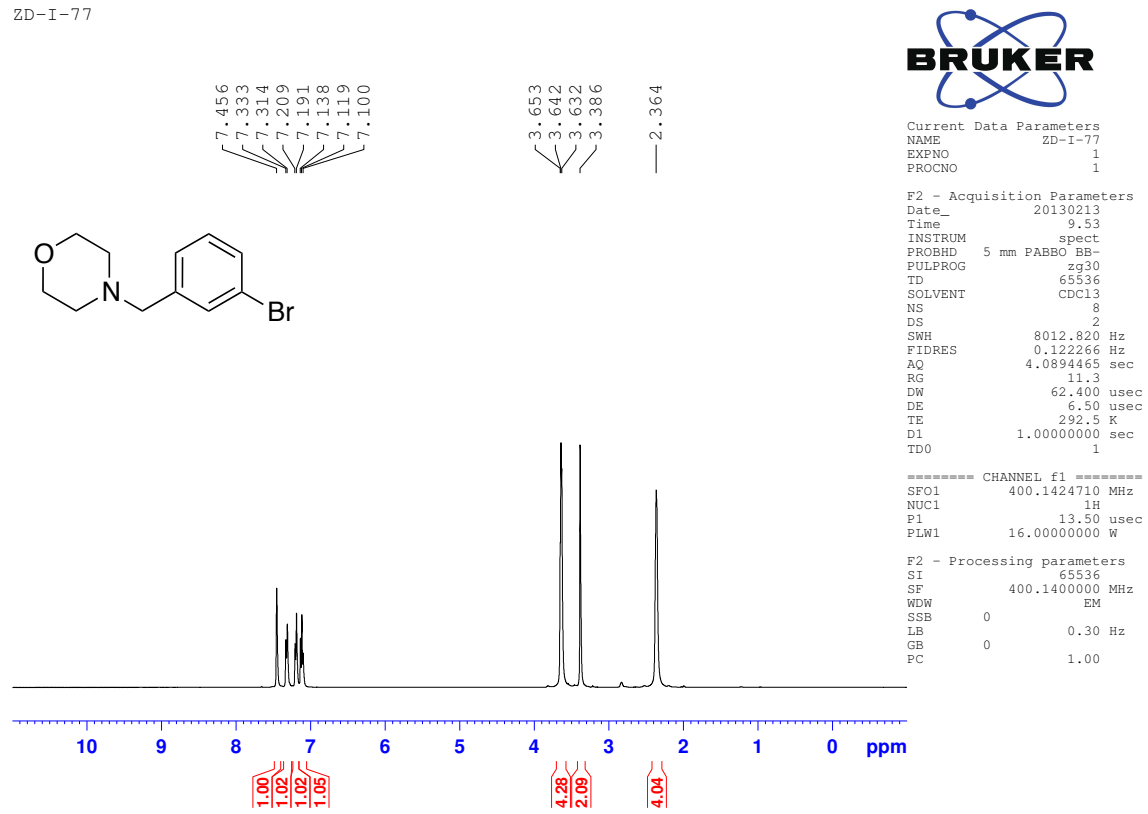


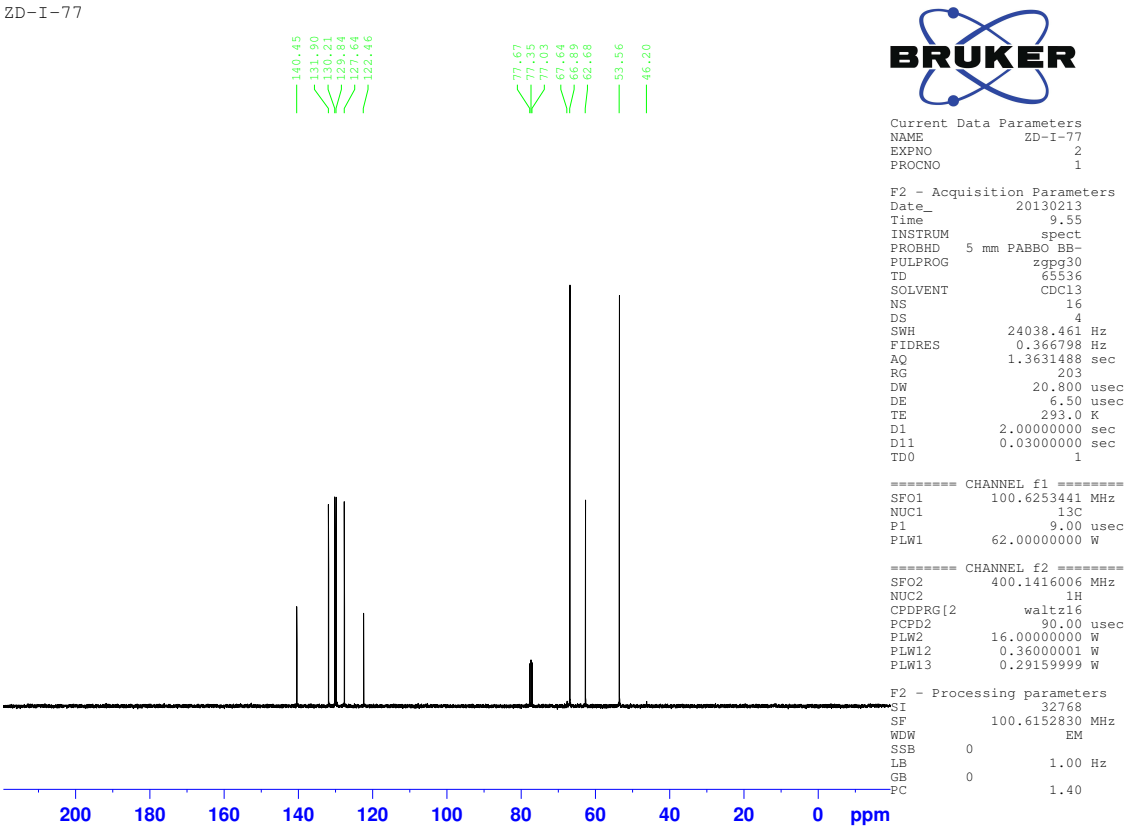
Elemental Composition Report

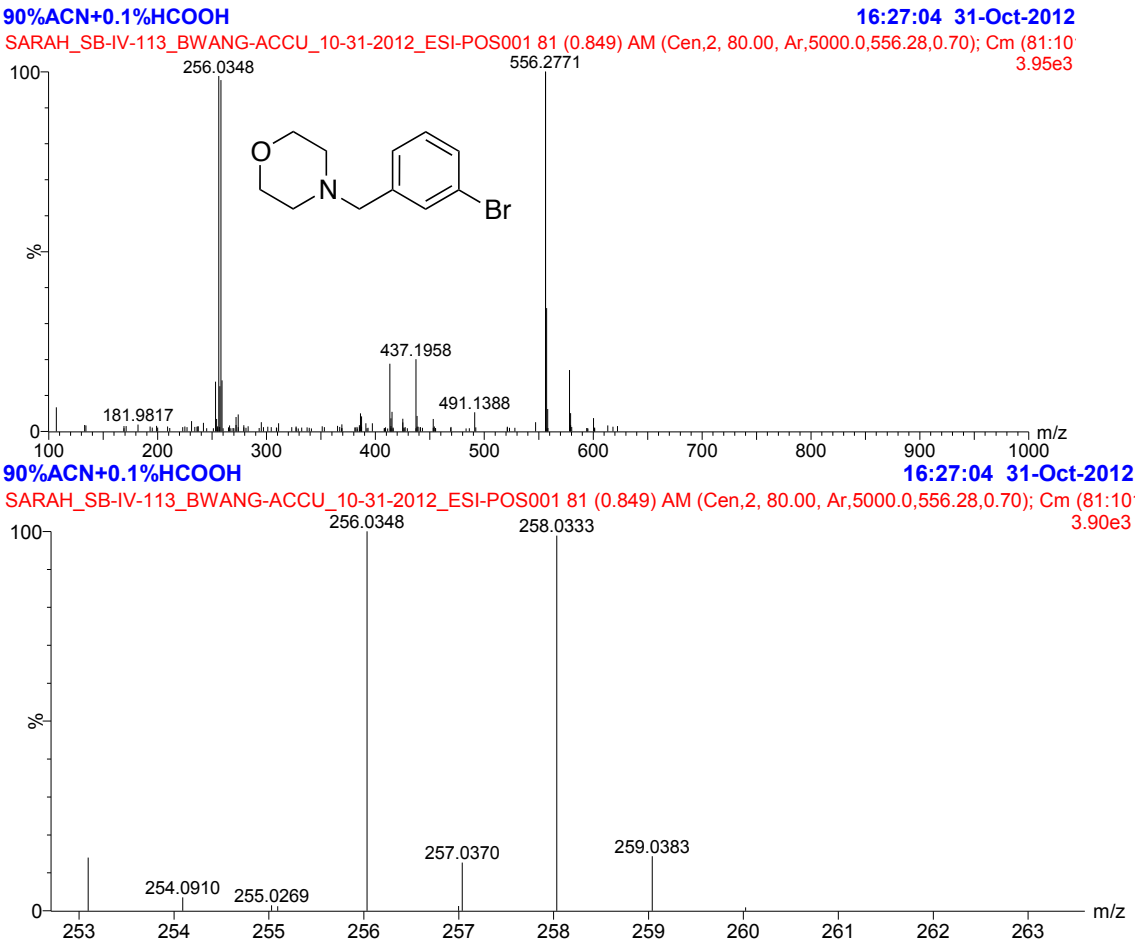
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
106 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20 Br: 1-5

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
256.0333	256.0337	-0.4	-1.6	4.5	1.6		C11 H15 N O Br

3-(2-Bromobenzyl)morpholine (7b)







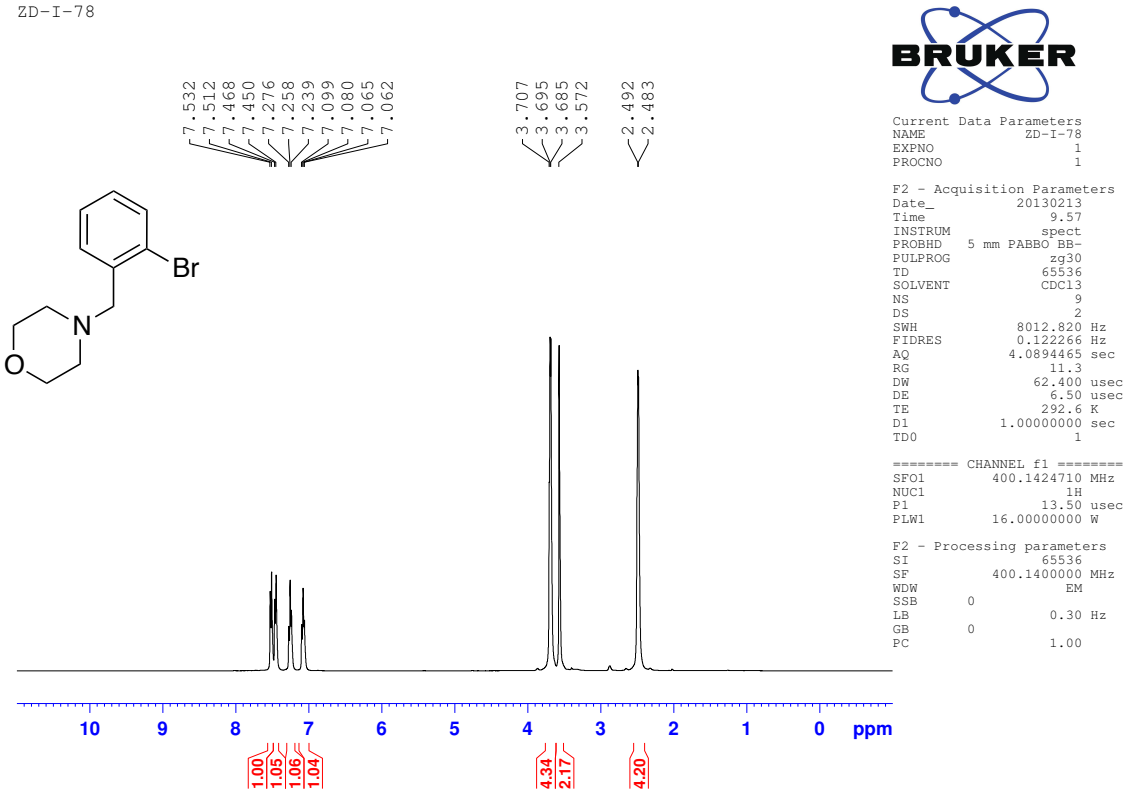
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

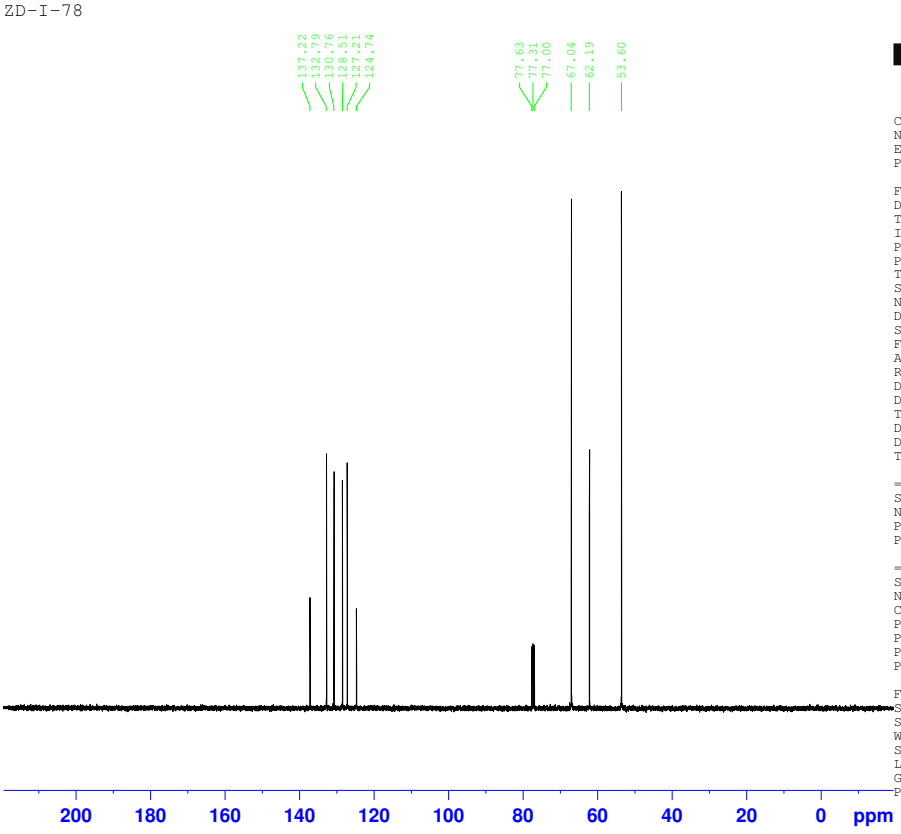
Monoisotopic Mass, Odd and Even Electron Ions
106 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-20 O: 1-30 Br: 1-5

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
256.0348	256.0337	1.1	4.3	4.5	0.7		C11 H15 N O Br

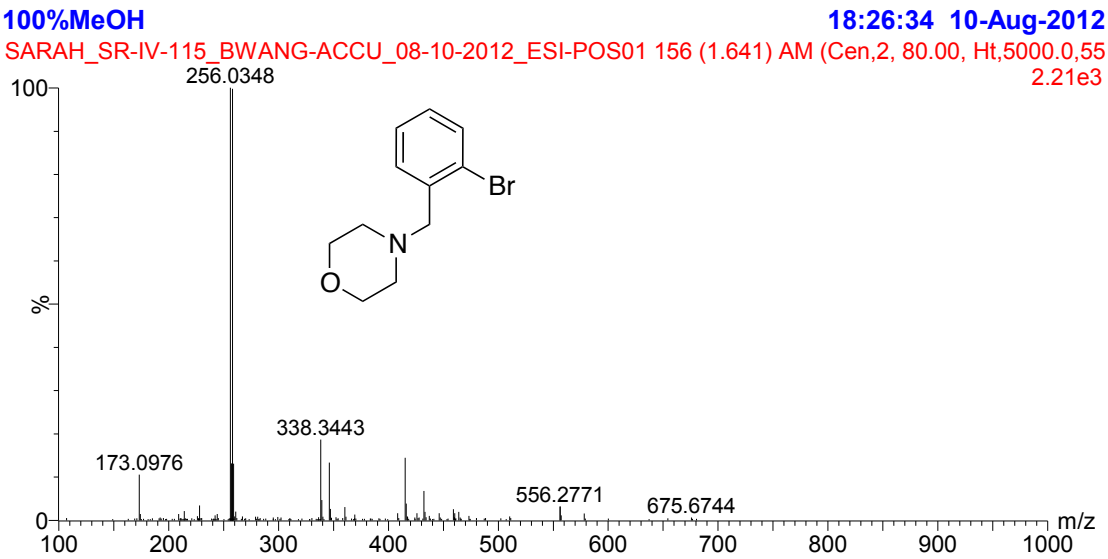
4-(2-Bromobenzyl)morpholine (7c)




```
Current Data Parameters
NAME                  ZD-I-78
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20130213
Time                   9.57
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        9
DS                        2
SWH                8012.820 Hz
FIDRES                0.122266 Hz
AQ                 4.0894465 sec
RG                     11.3
DW                    62.400 usec
DE                     6.50 usec
TE                    292.6 K
D1                 1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1             400.1424710 MHz
NUC1                     1H
P1                    13.50 usec
PLW1            16.00000000 W

F2 - Processing parameters
SI                        65536
SF               400.1400000 MHz
WDW                        EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```




```
Current Data Parameters
NAME                  ZD-I-78
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20130213
Time                   9.58
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        4
SWH               24038.461 Hz
FIDRES                0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                    20.800 usec
DE                     6.50 usec
TE                    293.1 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1             100.6253441 MHz
NUC1                     13C
P1                     9.00 usec
PLW1            62.00000000 W

======== CHANNEL f2 ========
SFO2             400.1416006 MHz
NUC2                     1H
CPDPRG[2          waltz16
PCPD2                 90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W

F2 - Processing parameters
SI                        32768
SF               100.6152830 MHz
WDW                        EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```



Elemental Composition Report

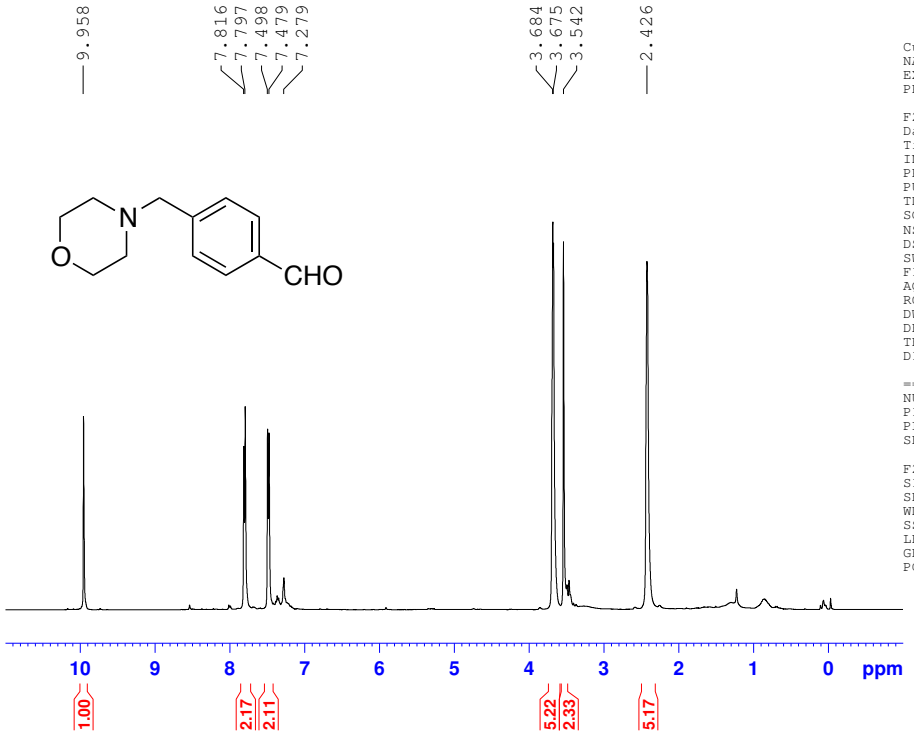
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
106 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 Br: 1-5

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
256.0348	256.0337	1.1	4.3	4.5	0.5		C11 H15 N O Br

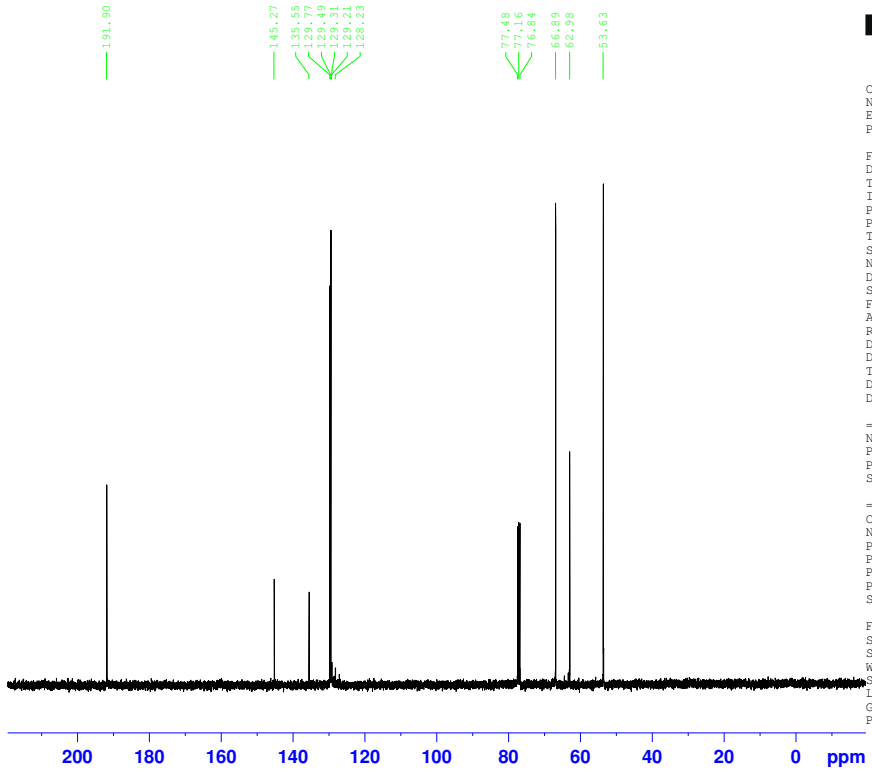
4-(Morpholinomethyl)benzaldehyde (8a)

SB-IV-30

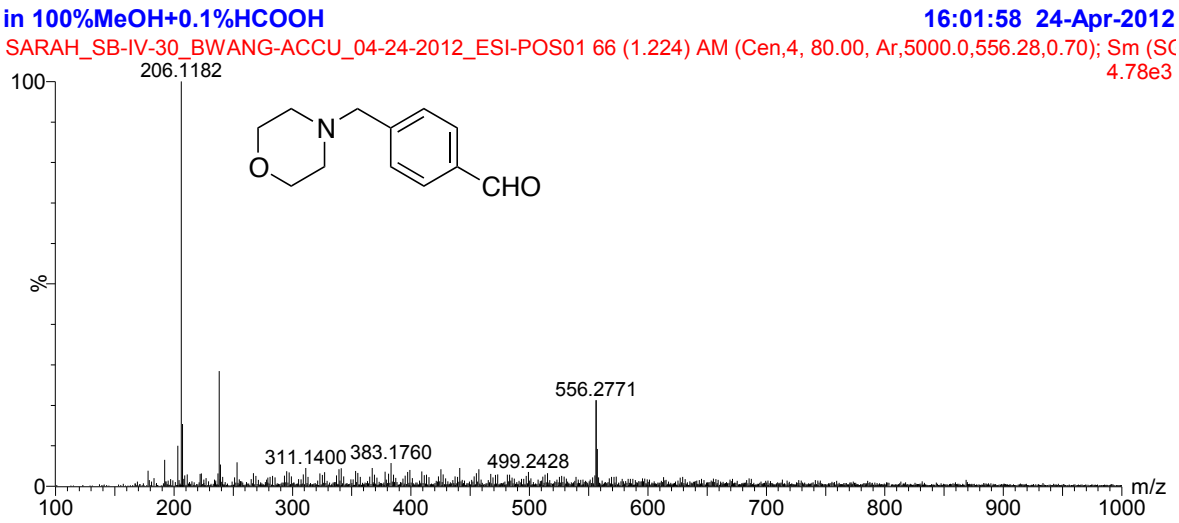



```
Current Data Parameters
NAME              SB-IV-30
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_            20120420
Time                15.49
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ               3.9846387 sec
RG                   20.2
DW                 60.800 usec
DE                  6.50 usec
TE                 298.2 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PLW1          16.00000000 W
SFO1          400.1424710 MHz

F2 - Processing parameters
SI                  65536
SF            400.1400000 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

SB-IV-30




```
Current Data Parameters
NAME              SB-IV-30
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_            20120420
Time                15.51
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG           zgpg30
TD                  65536
SOLVENT             CDCl3
NS                     29
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631988 sec
RG                    203
DW                 20.800 usec
DE                  6.50 usec
TE                 298.4 K
D1              2.00000000 sec
D11             0.03000000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.00 usec
PLW1          62.00000000 W
SFO1          100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2               90.00 usec
PLW2          16.00000000 W
PLW12          0.36000001 W
PLW13          0.29159999 W
SFO2          400.1416006 MHz

F2 - Processing parameters
SI                  32768
SF            100.6152830 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

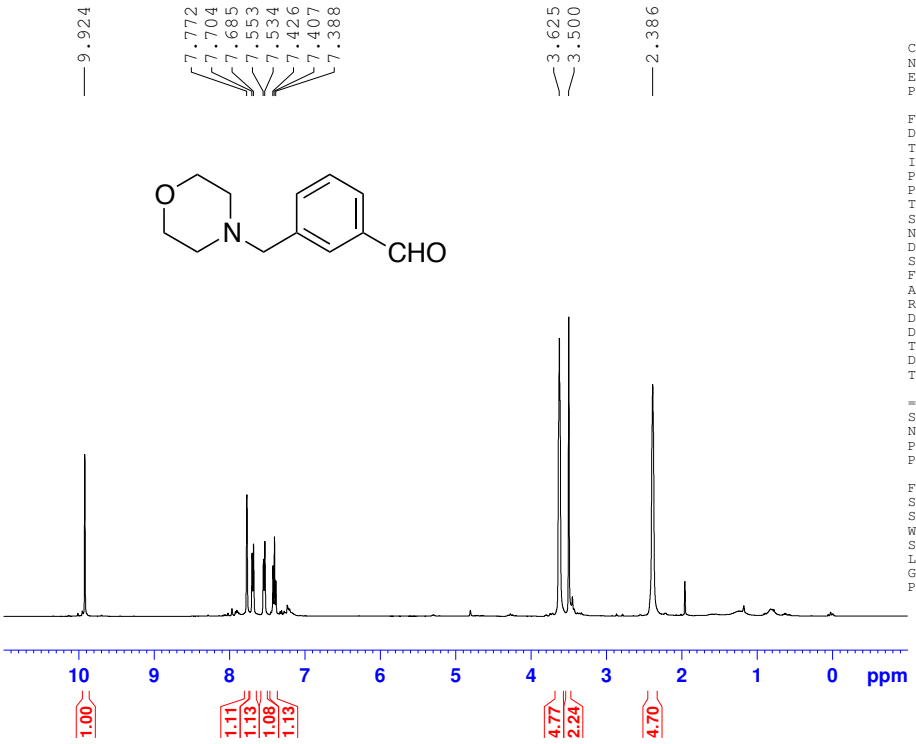


Elemental Composition Report
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
181 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-35 80Se: 0-1

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
206.1182	206.1181	0.1	0.5	5.5	5.0	C12 H16 N O2

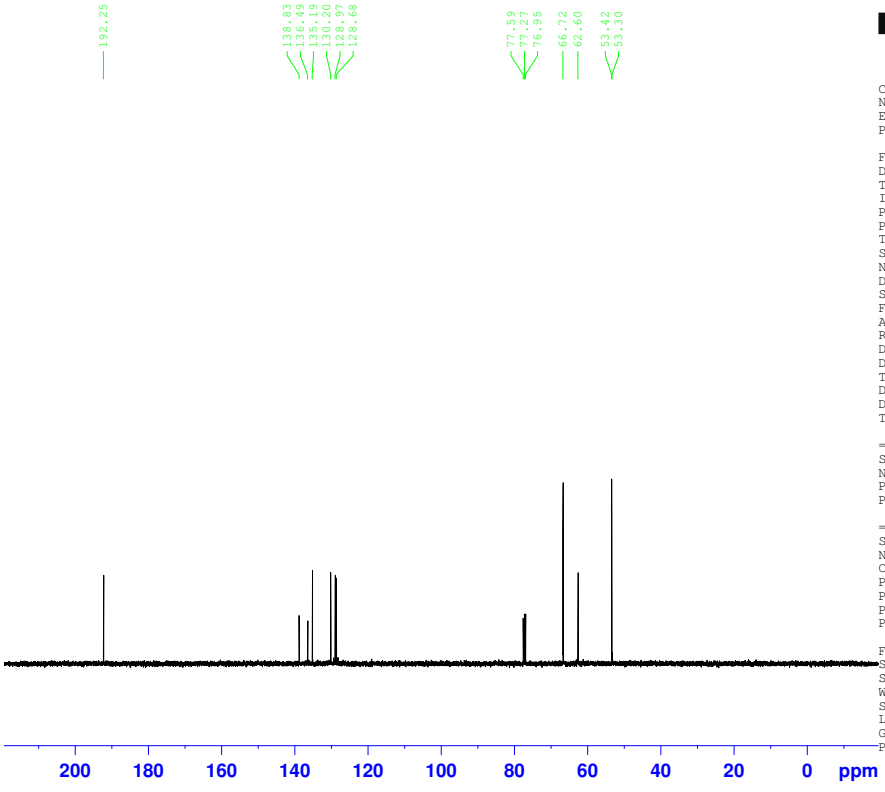
3-(Morpholinomethyl)benzaldehyde (8b)

SB-V-80b

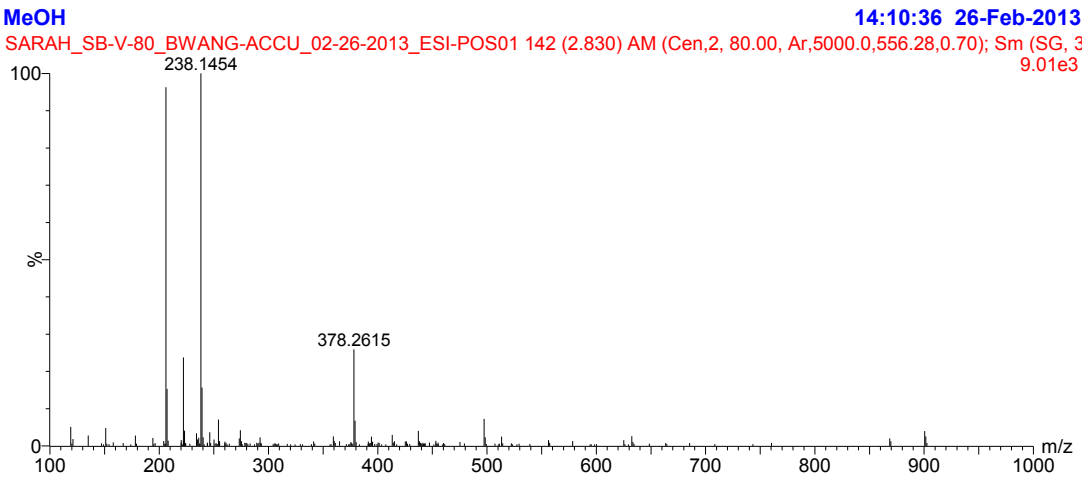


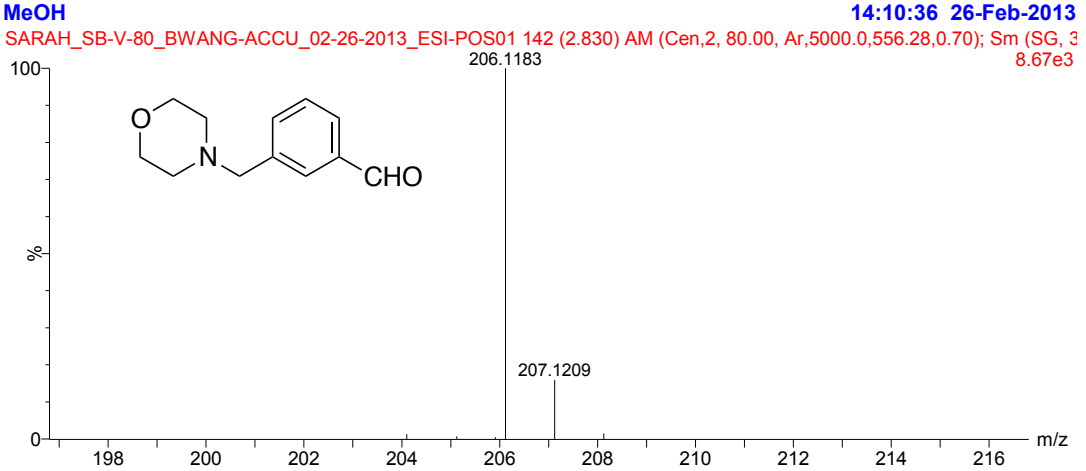

```
Current Data Parameters
NAME                 SB-V-80b
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_               20130216
Time                   18.32
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       12
DS                        2
SWH                8012.820 Hz
FIDRES                0.122266 Hz
AQ                 4.0894465 sec
RG                       18
DW                    62.400 usec
DE                     6.50 usec
TE                   298.0 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1               400.1424710 MHz
NUC1                       1H
P1                      13.50 usec
PLW1               16.00000000 W

F2 - Processing parameters
SI                        65536
SF                 400.1400000 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

SB-V-80b




```
Current Data Parameters
NAME                 SB-V-80b
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_               20130216
Time                   18.34
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                        5
DS                        4
SWH               24038.461 Hz
FIDRES                0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                    20.800 usec
DE                     6.50 usec
TE                   298.3 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1               100.6253441 MHz
NUC1                       13C
P1                      9.00 usec
PLW1               62.00000000 W

======== CHANNEL f2 ========
SFO2               400.1416006 MHz
NUC2                       1H
CPDPRG[2             waltz16
PCPD2                  90.00 usec
PLW2               16.00000000 W
PLW12               0.36000001 W
PLW13               0.29159999 W

F2 - Processing parameters
SI                        32768
SF                 100.6152830 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```





Elemental Composition Report

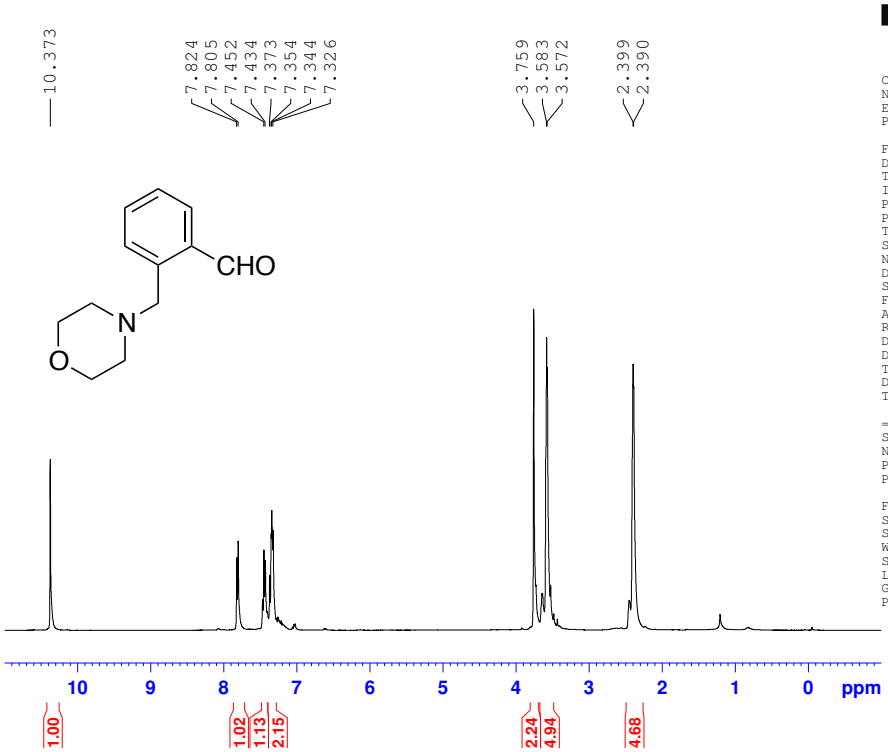
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
105 formula(e) evaluated with 1 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-6 O: 1-30

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
206.1183	206.1181	0.2	1.0	5.5	8.5	C12 H16 N O2

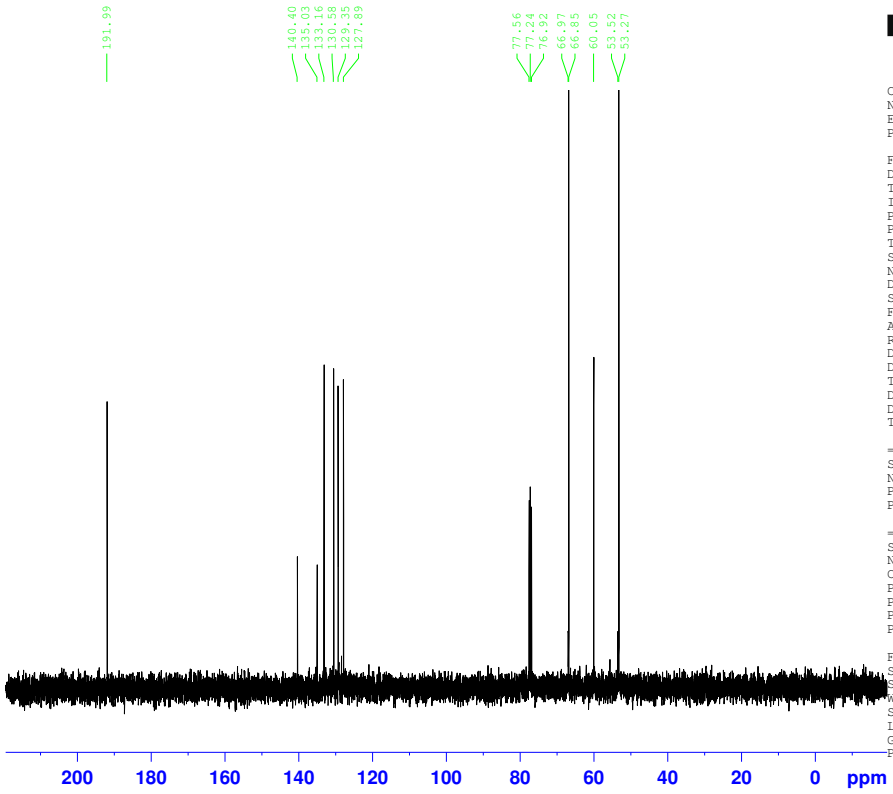
2-(Morpholinomethyl)benzaldehyde (8c)

SB-V-17c1

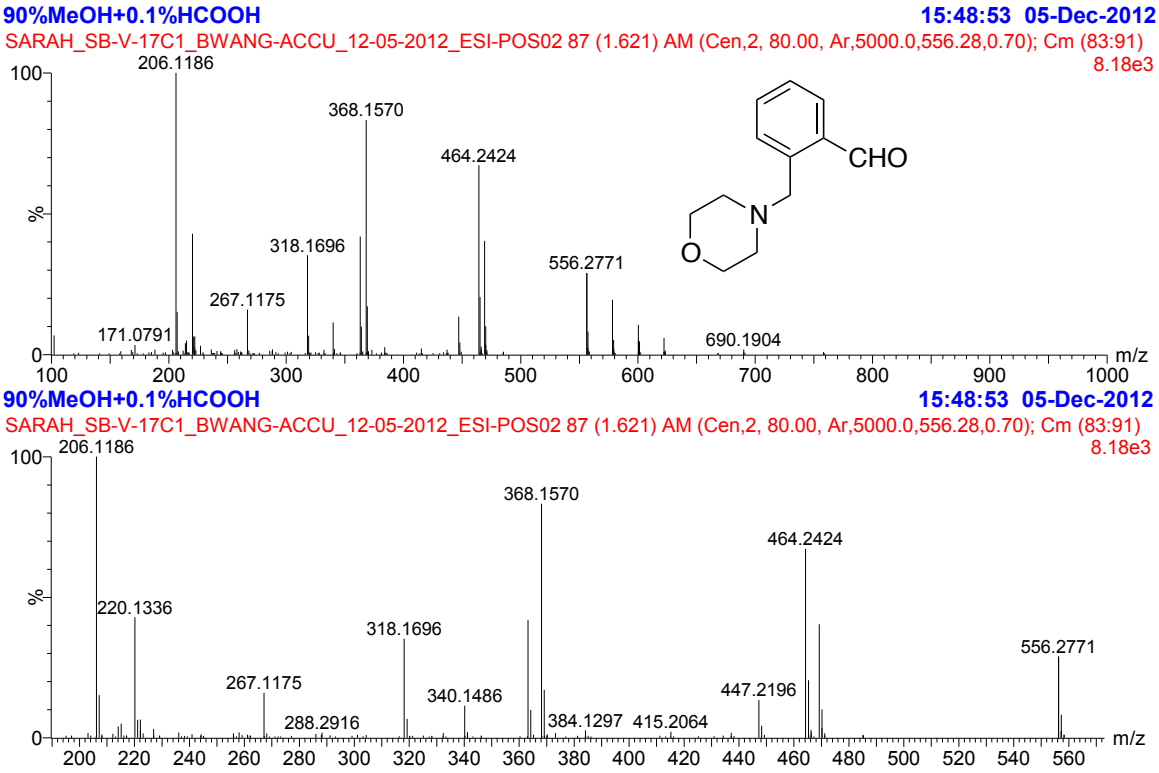



```
Current Data Parameters
NAME                 SB-V-17c1
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20121120
Time                   11.38
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8012.820 Hz
FIDRES             0.122266 Hz
AQ                 4.0894465 sec
RG                       36
DW                    62.400 usec
DE                     6.50 usec
TE                   298.0 K
D1                 1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1             400.1424710 MHz
NUC1                       1H
P1                     13.50 usec
PLW1            16.00000000 W

F2 - Processing parameters
SI                       65536
SF               400.1400000 MHz
WDW                         EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

SB-V-17c1




```
Current Data Parameters
NAME                 SB-V-17c1
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_               20121120
Time                   11.42
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       11
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                   20.800 usec
DE                     6.50 usec
TE                   298.1 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1             100.6253441 MHz
NUC1                      13C
P1                      9.00 usec
PLW1            62.00000000 W

======== CHANNEL f2 ========
SFO2             400.1416006 MHz
NUC2                       1H
CPDPRG[2             waltz16
PCPD2                  90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W

F2 - Processing parameters
SI                       32768
SF               100.6152830 MHz
WDW                         EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



Elemental Composition Report

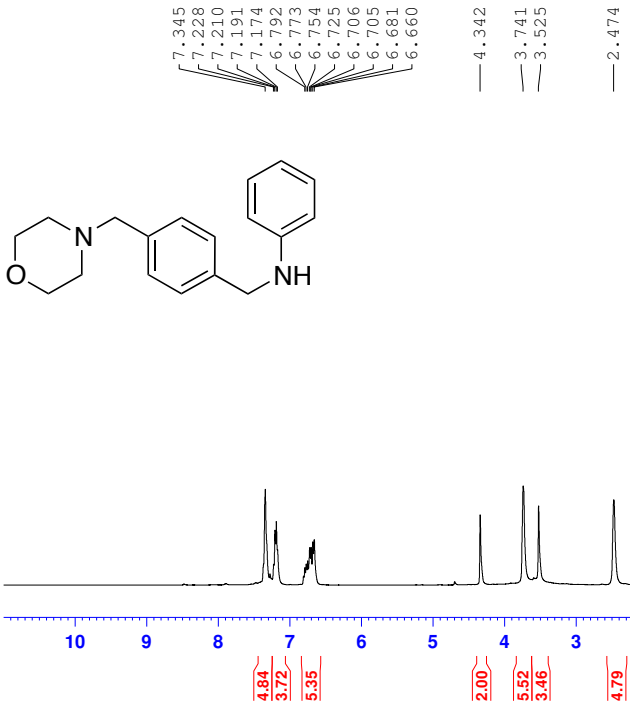
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
145 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-20 O: 1-30

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
206.1186	206.1181	0.5	2.4	5.5	5.5	C12 H16 N O2

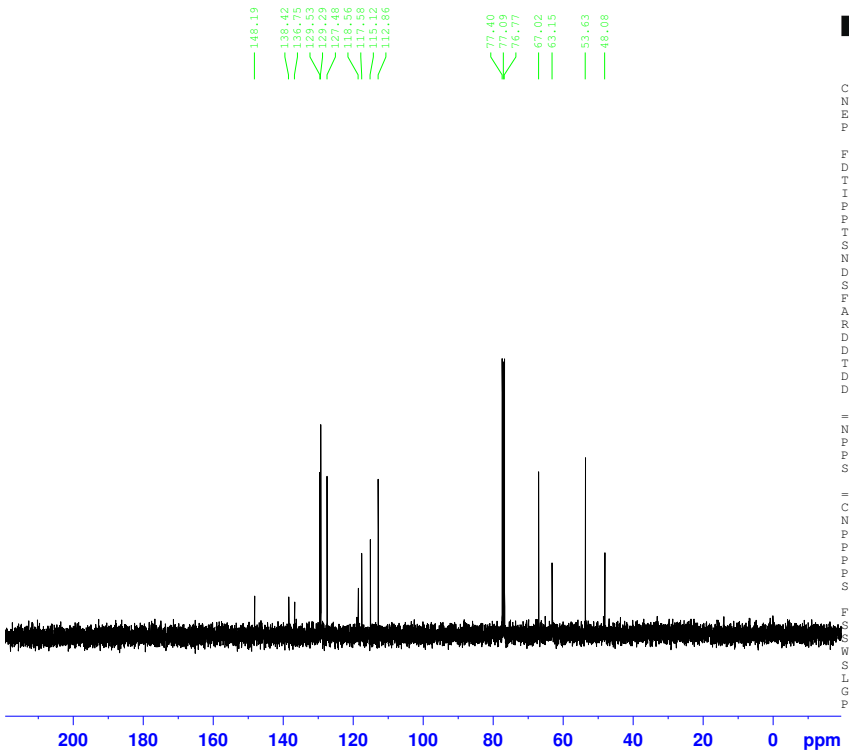
N-(4-(morpholinomethyl)benzyl)aniline (9a)

SB-IV-37a




```
Current Data Parameters
NAME                 SB-IV-37a
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20120426
Time                    11.04
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                           7
DS                           2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                        40.3
DW                    60.800 usec
DE                     6.50 usec
TE                     298.2 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PLW1             16.00000000 W
SFO1            400.1424710 MHz

F2 - Processing parameters
SI                         65536
SF                400.1400000 MHz
WDW                           EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

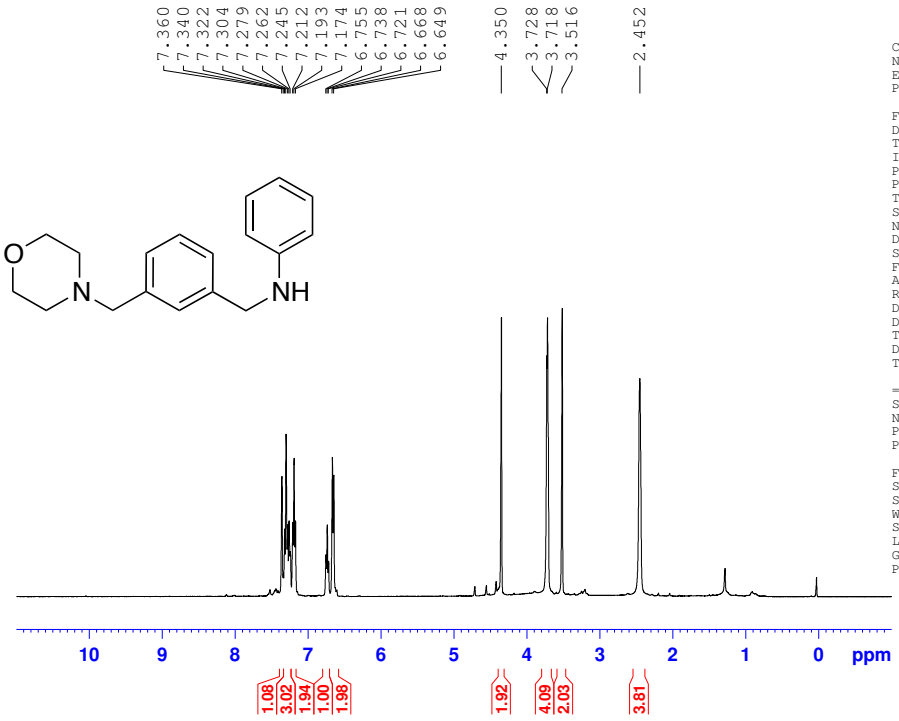
SB-IV-37a




```
Current Data Parameters
NAME                 SB-IV-37a
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20120426
Time                    11.06
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                     65536
SOLVENT                CDCl3
NS                          22
DS                           4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                         203
DW                    20.800 usec
DE                     6.50 usec
TE                     298.3 K
D1                2.00000000 sec
D11               0.03000000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                      9.00 usec
PLW1             62.00000000 W
SFO1            100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  90.00 usec
PLW2             16.00000000 W
PLW12             0.36000001 W
PLW13             0.29159999 W
SFO2            400.1416006 MHz

F2 - Processing parameters
SI                         32768
SF                100.6152830 MHz
WDW                           EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```

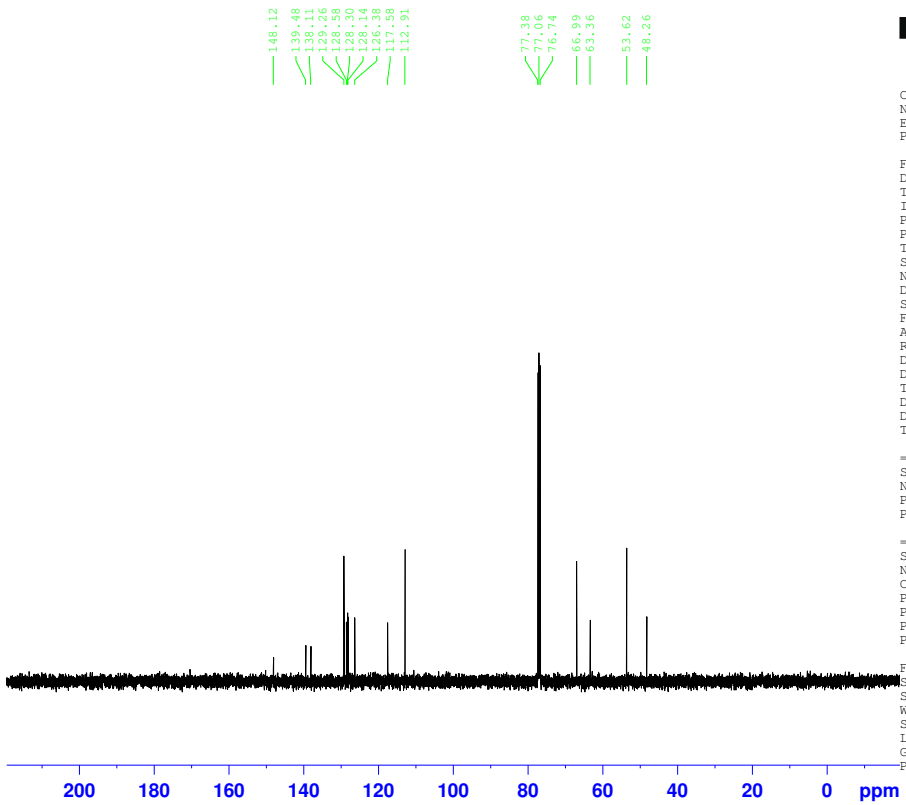
N-(3-(Morpholinomethyl)benzyl)aniline (9b)

SB-V-107d

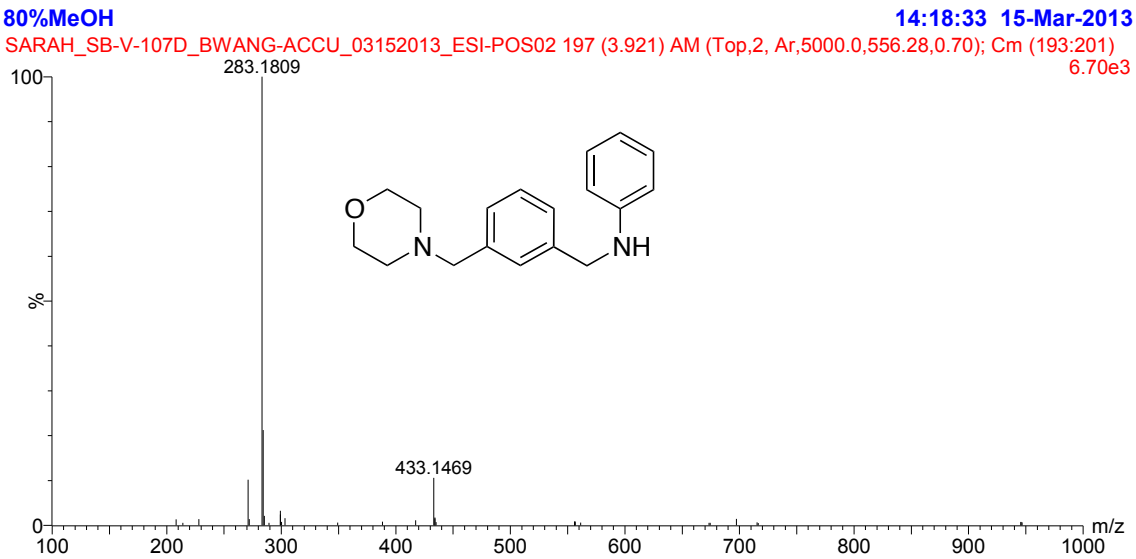



```
Current Data Parameters
NAME           SB-V-107d
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130319
Time               13.06
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     6
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                   101
DW                62.400 usec
DE                 6.50 usec
TE                294.2 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          400.1424710 MHz
NUC1                  1H
P1                 13.50 usec
PLW1          16.00000000 W

F2 - Processing parameters
SI                 65536
SF            400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-V-107d




```
Current Data Parameters
NAME           SB-V-107d
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130319
Time               13.08
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    30
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                294.8 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1          62.00000000 W

======== CHANNEL f2 ========
SFO2          400.1416006 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2          16.00000000 W
PLW12          0.36000001 W
PLW13          0.29159999 W

F2 - Processing parameters
SI                 32768
SF            100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



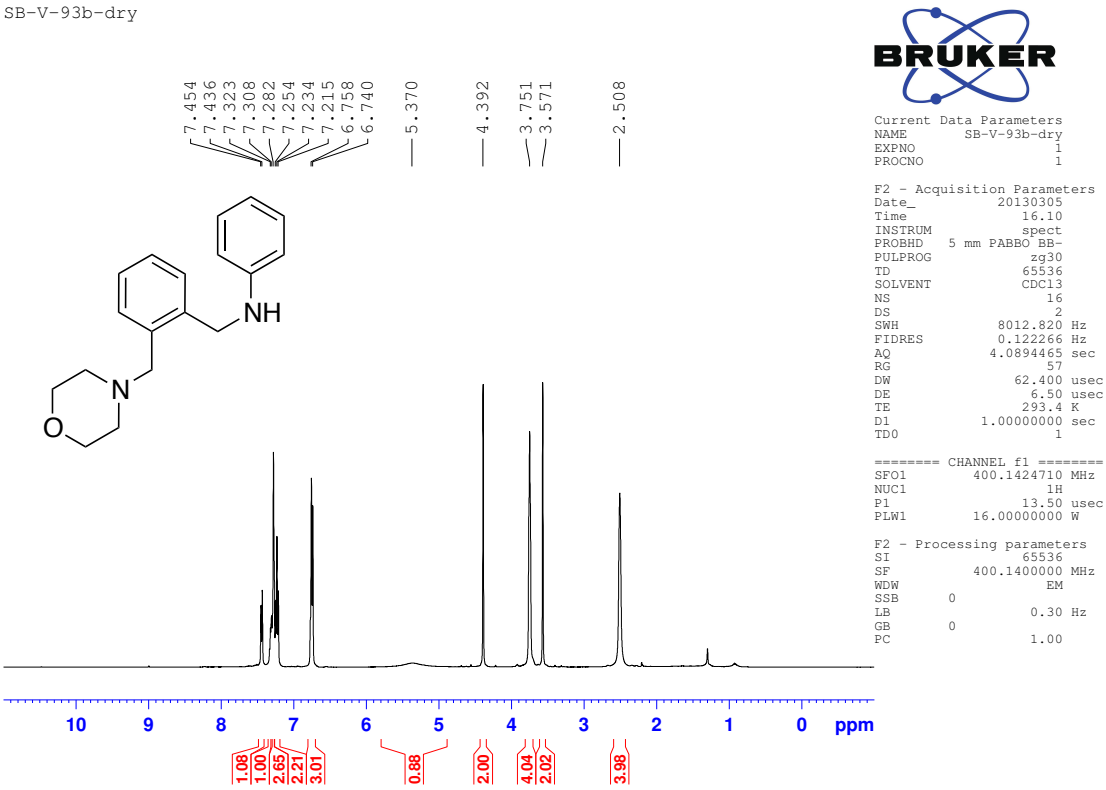
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

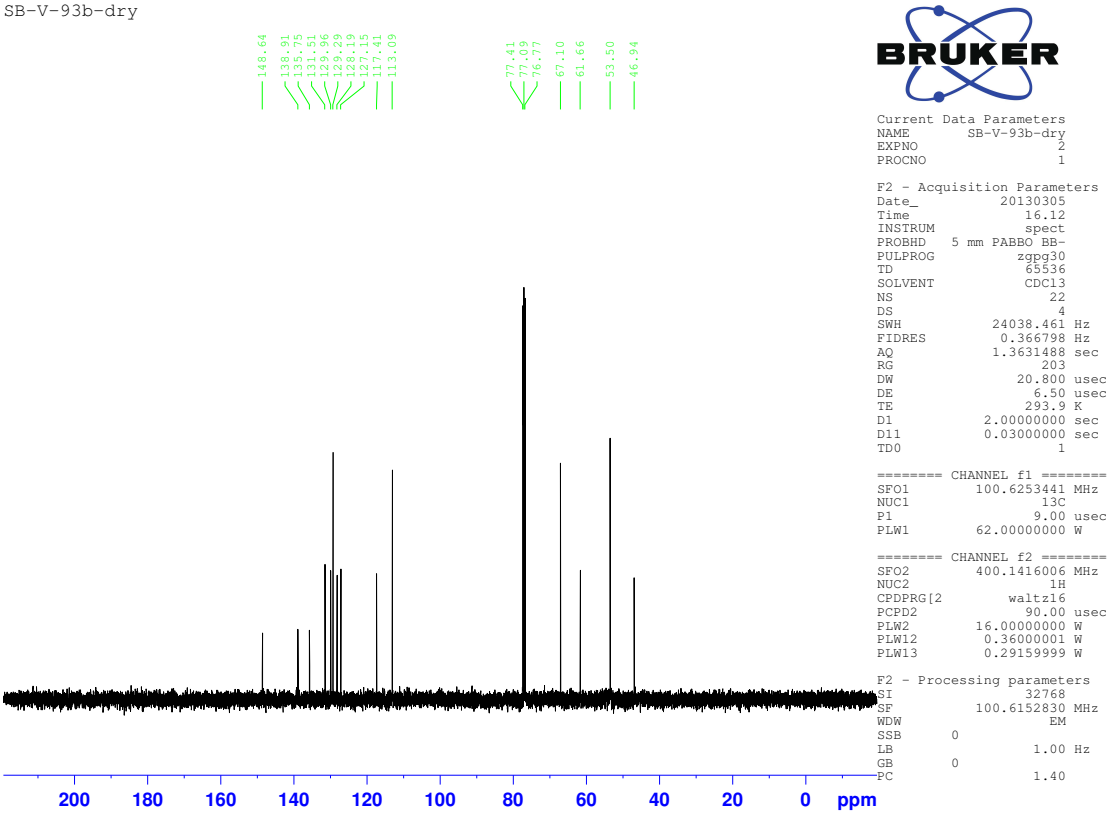
Monoisotopic Mass, Odd and Even Electron Ions
363 formula(e) evaluated with 3 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-30 O: 1-60

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
283.1809	283.1810	-0.1	-0.4	8.5	1.7		C18 H23 N2 O

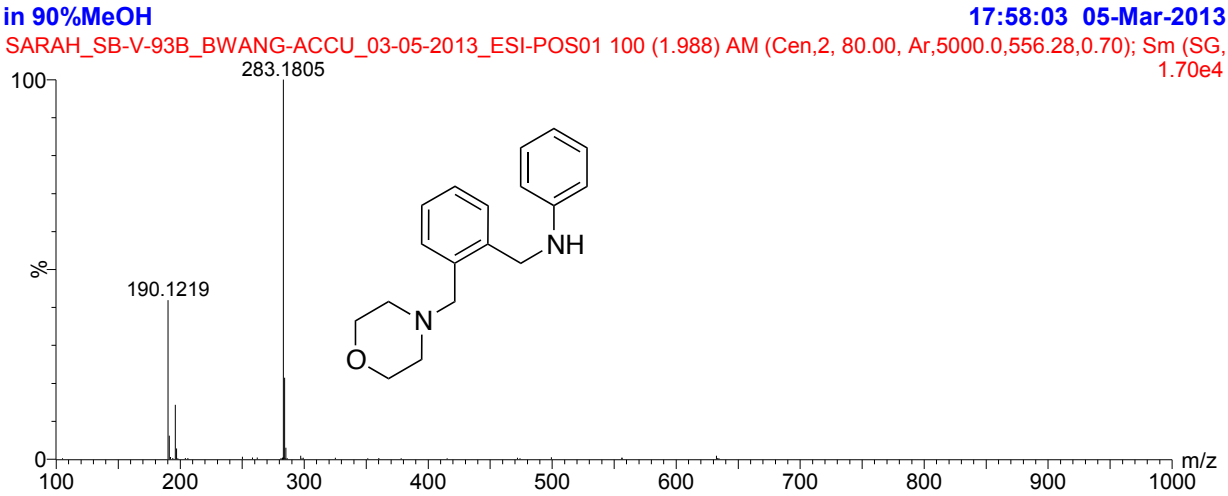
N-(2-(Morpholinomethyl)benzyl)aniline (9c)




```
Current Data Parameters
NAME        SB-V-93b-dry
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130305
Time               16.10
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDC13
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                    57
DW                62.400 usec
DE                 6.50 usec
TE                293.4 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```




```
Current Data Parameters
NAME        SB-V-93b-dry
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130305
Time               16.12
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDC13
NS                    22
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                293.9 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                   13C
P1                 9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2           waltz16
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



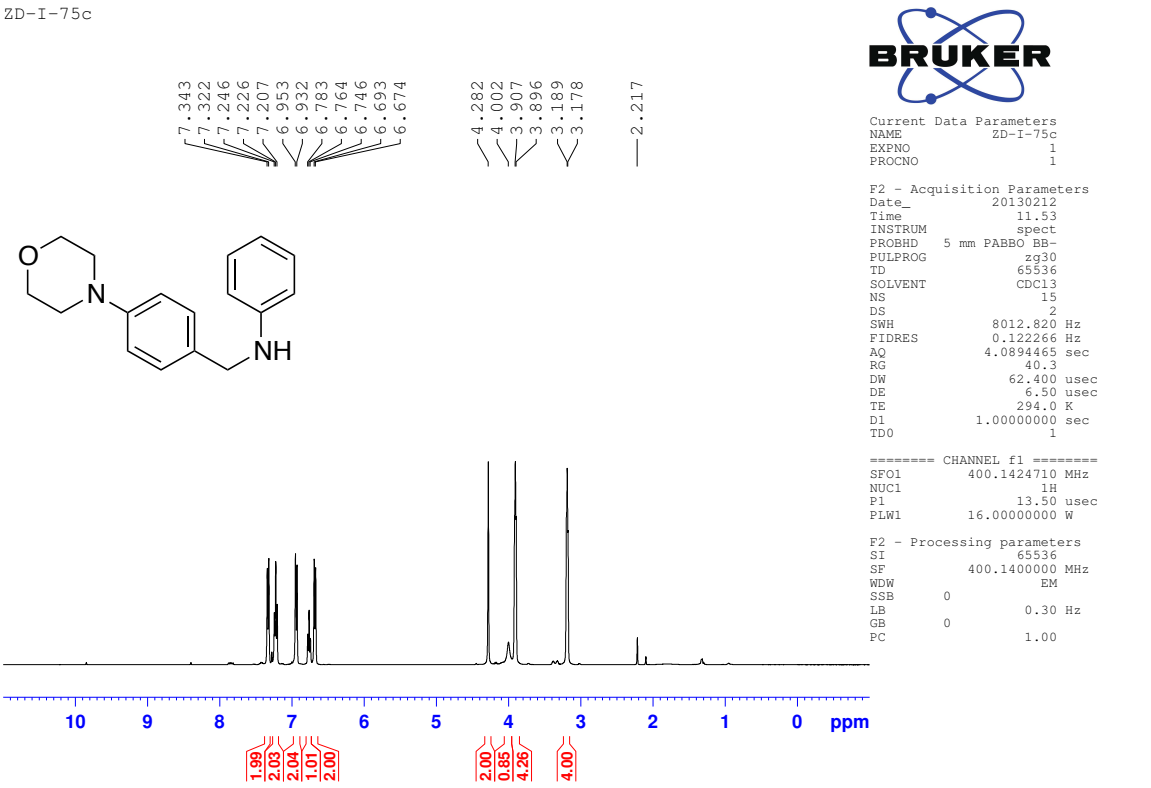
Elemental Composition Report

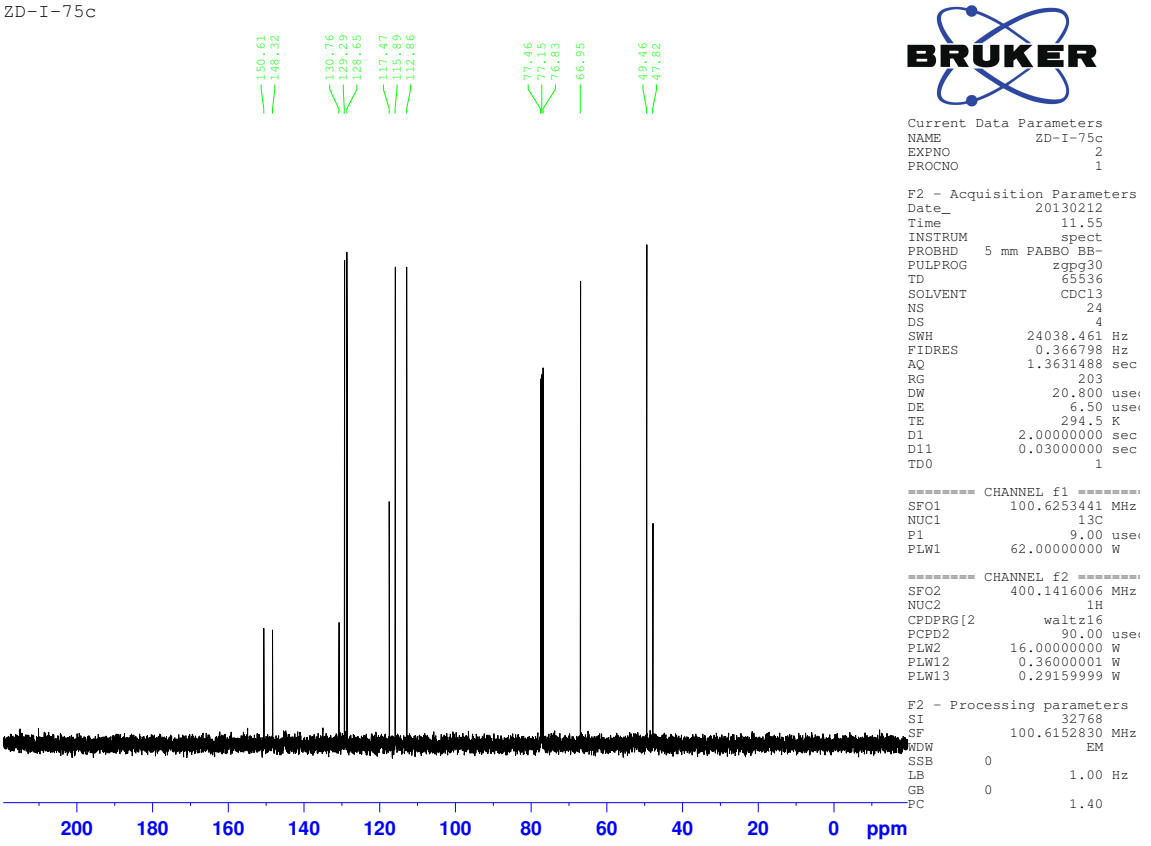
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

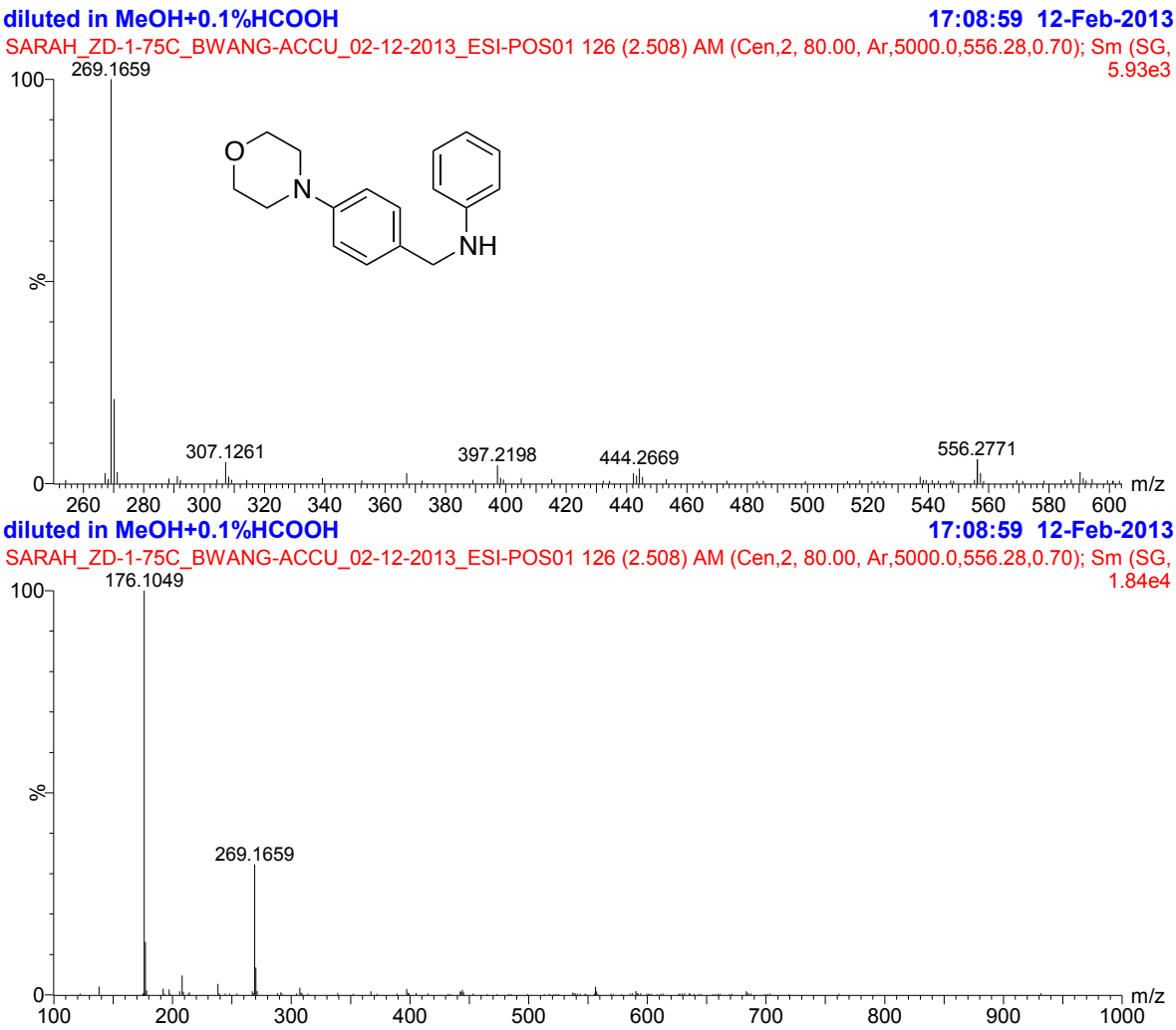
Monoisotopic Mass, Even Electron Ions
363 formula(e) evaluated with 2 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-30 O: 1-60

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
283.1805	283.1810	-0.5	-1.8	8.5	12.4		C18 H23 N2 O

N-(4-Morpholinobenzyl)aniline (9d)







Elemental Composition Report

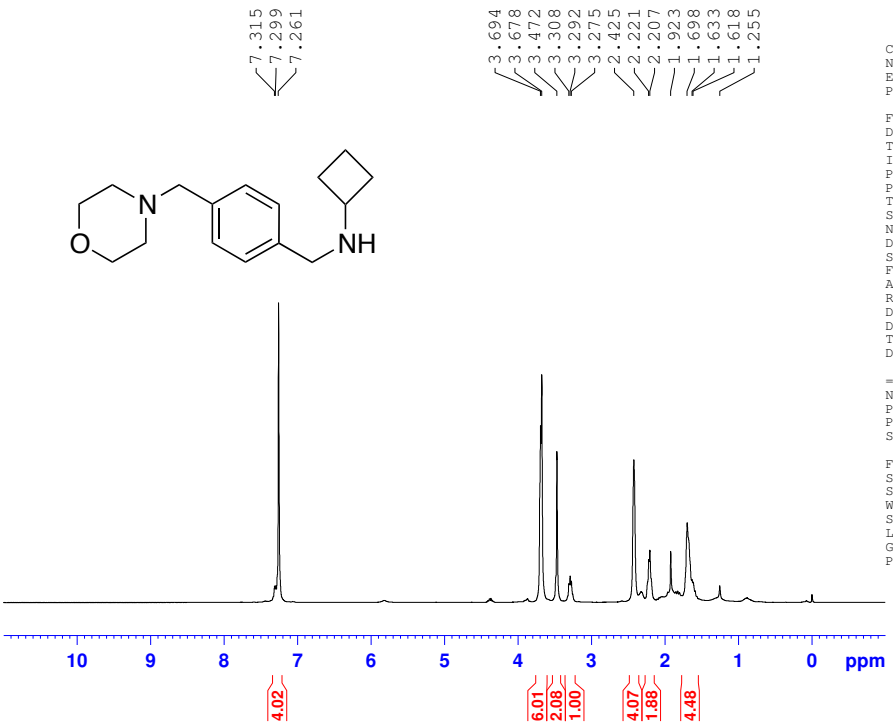
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
313 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-30 O: 1-30

Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa		PPM		DBE	i-FIT	Formula
269.1659	269.1654	0.5	1.9	8.5	n/a			C17H21N2O

_N_-(4-(Morpholinomethyl)benzyl)cyclobutanamine (10a)

SB-IV-39a



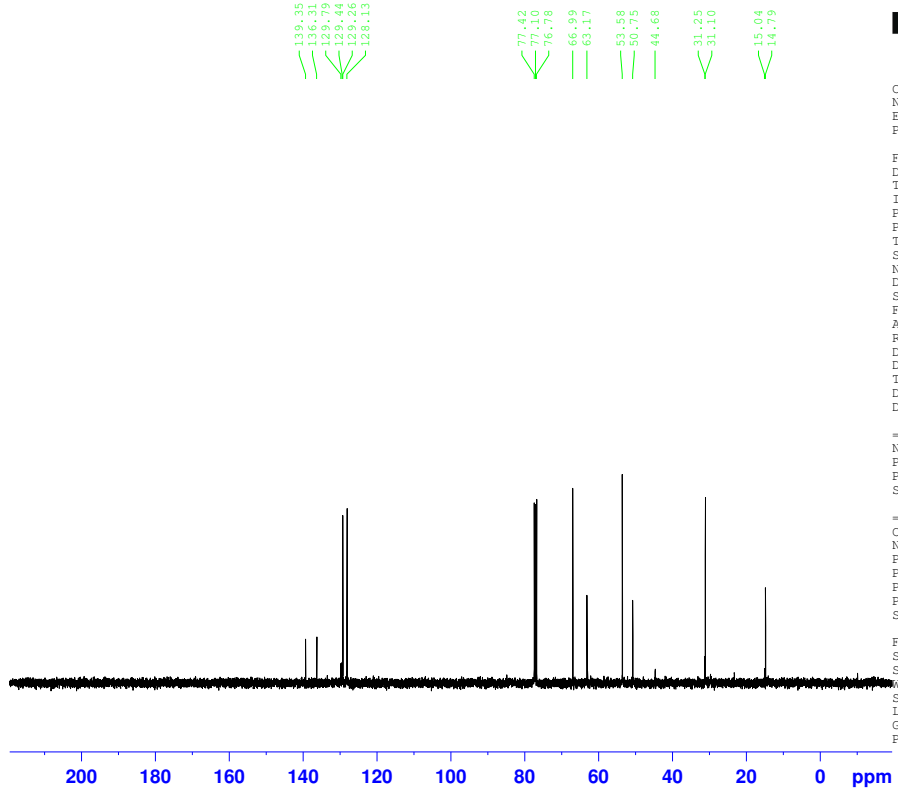
Current Data Parameters
NAME SB-IV-39a
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120425
Time 16.37
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 25.4
DW 60.800 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PLW1 16.00000000 W
SFO1 400.1424710 MHz

F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

SB-IV-39a



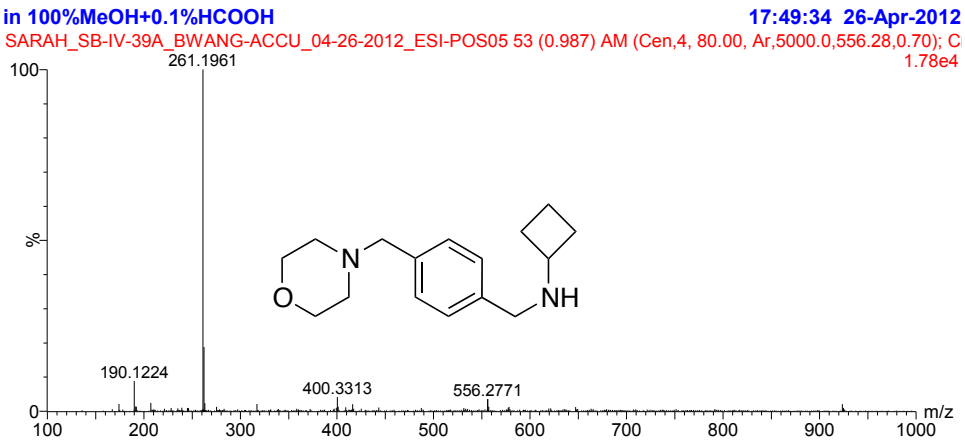
Current Data Parameters
NAME SB-IV-39a
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120425
Time 16.40
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 26
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 298.2 K
D1 2.00000000 sec
D11 0.03000000 sec

======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PLW1 62.00000000 W
SFO1 100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 16.00000000 W
PLW12 0.36000001 W
PLW13 0.29159999 W
SFO2 400.1416006 MHz

F2 - Processing parameters
SI 32768
SF 100.6152830 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Elemental Composition Report

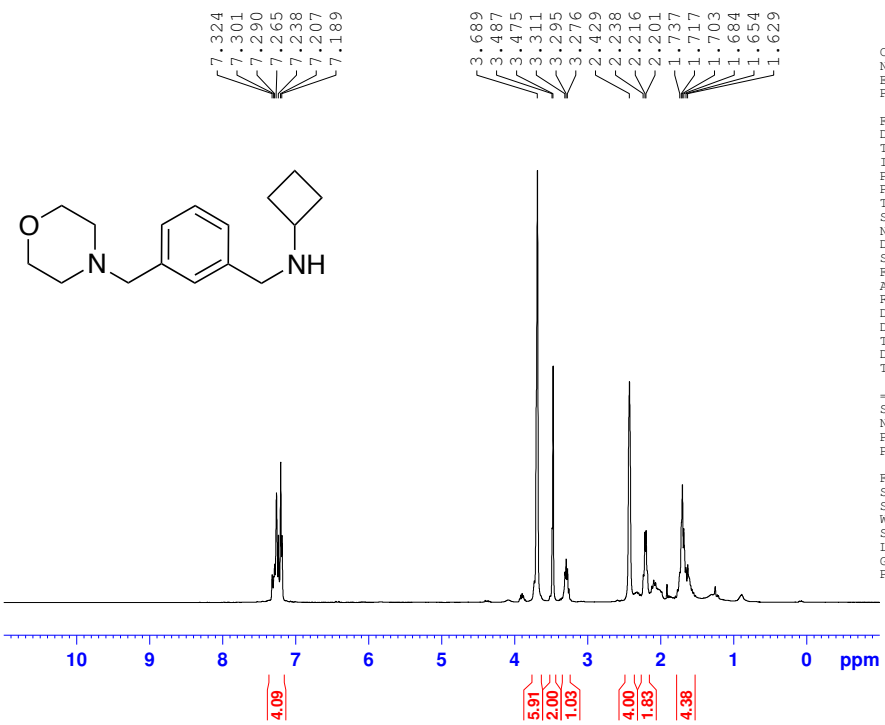
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
284 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
261.1961	261.1967	-0.6	-2.3	5.5	7.3		C16 H25 N2 O

N-(3-(Morpholinomethyl)benzyl)cyclobutanamine (10b)

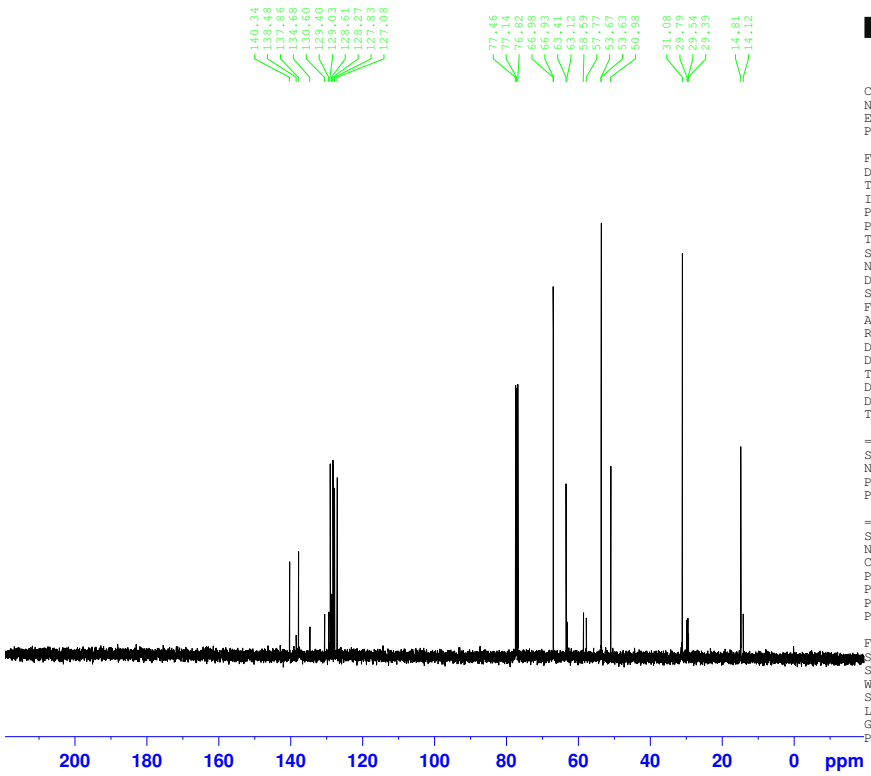
SB-V-90



BRUKER

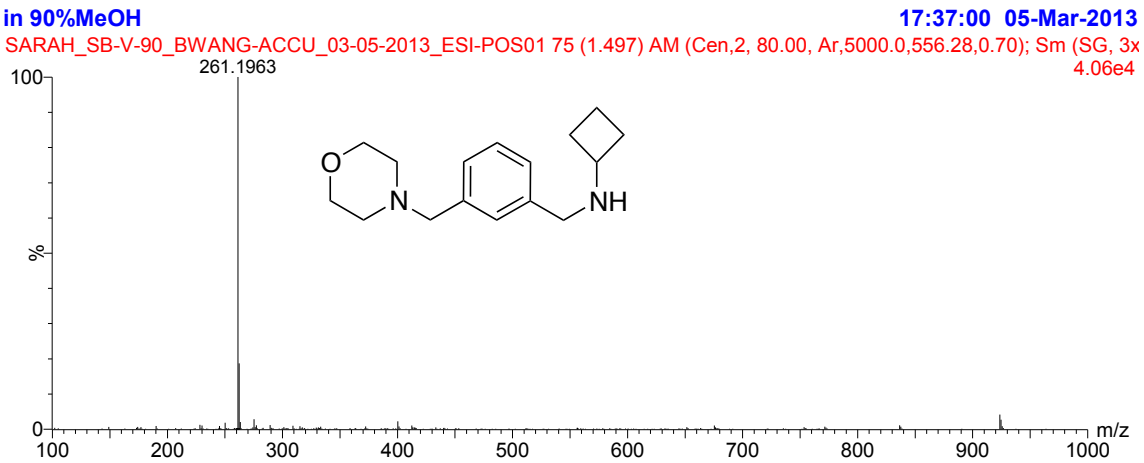
```
Current Data Parameters
NAME                  SB-V-90
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20130221
Time                  16.24
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8012.820 Hz
FIDRES            0.122266 Hz
AQ                4.0894465 sec
RG                      28.5
DW                   62.400 usec
DE                    6.50 usec
TE                   298.1 K
D1              1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1           400.1424710 MHz
NUC1                     1H
P1                    13.50 usec
PLW1           16.00000000 W

F2 - Processing parameters
SI                    65536
SF              400.1400000 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

SB-V-90



BRUKER

```
Current Data Parameters
NAME                  SB-V-90
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20130221
Time                  16.27
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       25
DS                        4
SWH               24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                      203
DW                   20.800 usec
DE                    6.50 usec
TE                   298.3 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1           100.6253441 MHz
NUC1                     13C
P1                    9.00 usec
PLW1           62.00000000 W

======== CHANNEL f2 ========
SFO2           400.1416006 MHz
NUC2                     1H
CPDPRG[2          waltz16
PCPD2                90.00 usec
PLW2           16.00000000 W
PLW12           0.36000001 W
PLW13           0.29159999 W

F2 - Processing parameters
SI                    32768
SF              100.6152830 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```



Elemental Composition Report

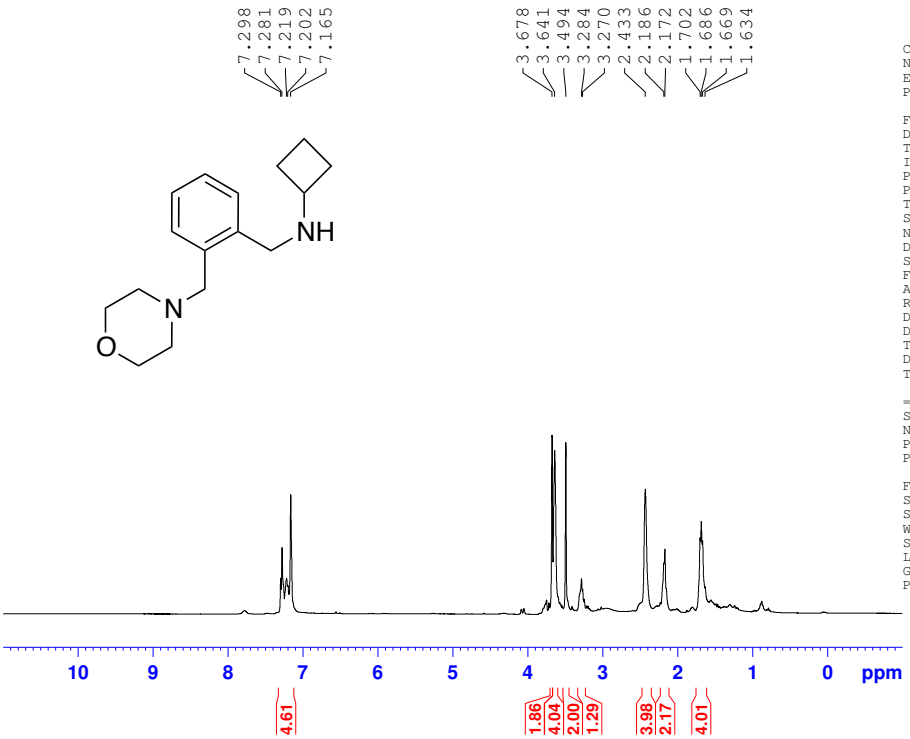
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
286 formula(e) evaluated with 2 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-30 O: 1-60

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
261.1963	261.1967	-0.4	-1.5	5.5	2.5		C16 H25 N2 O

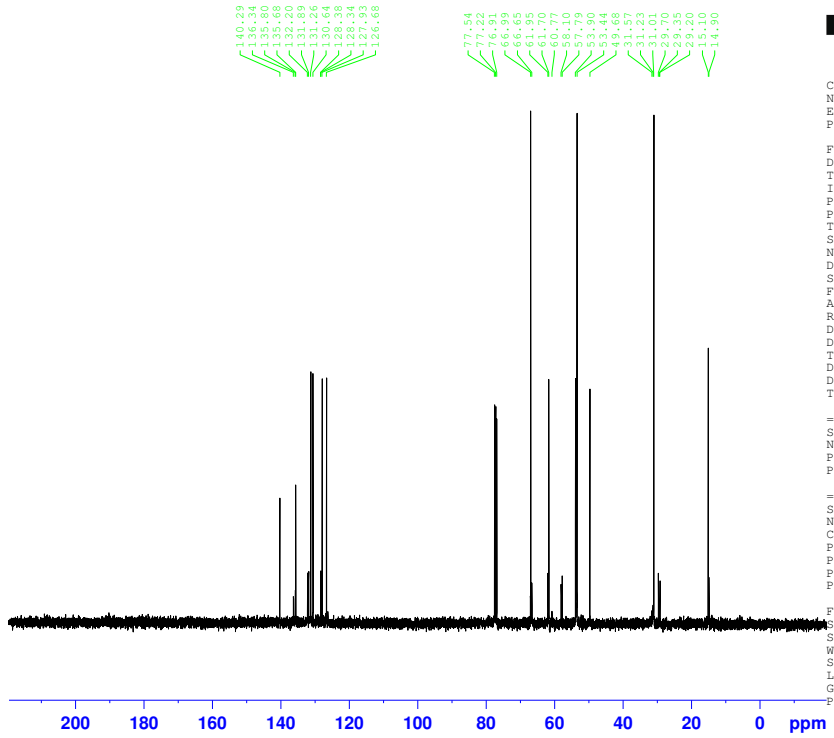
N-(2-(Morpholinomethyl)benzyl)cyclobutanamine (10c)

SB-V-91

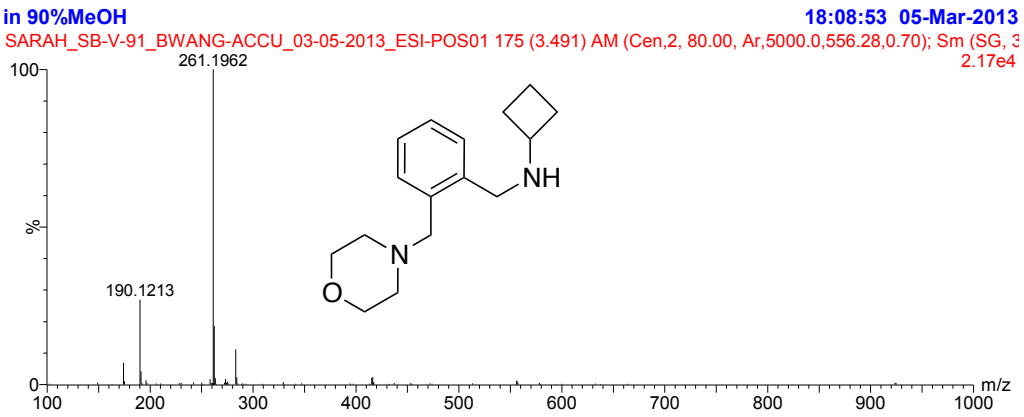



```
Current Data Parameters
NAME                 SB-V-91
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_               20130221
Time                   16.29
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDC13
NS                        9
DS                        2
SWH                8012.820 Hz
FIDRES             0.122266 Hz
AQ                 4.0894465 sec
RG                       16
DW                   62.400 usec
DE                    6.50 usec
TE                   297.9 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1            400.1424710 MHz
NUC1                      1H
P1                     13.50 usec
PLW1            16.00000000 W

F2 - Processing parameters
SI                        65536
SF              400.1400000 MHz
WDW                         EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

SB-V-91




```
Current Data Parameters
NAME                 SB-V-91
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_               20130221
Time                   16.31
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDC13
NS                       21
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                   20.800 usec
DE                    6.50 usec
TE                   298.4 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1            100.6253441 MHz
NUC1                     13C
P1                     9.00 usec
PLW1            62.00000000 W

======== CHANNEL f2 ========
SFO2            400.1416006 MHz
NUC2                      1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W

F2 - Processing parameters
SI                        32768
SF              100.6152830 MHz
WDW                         EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```



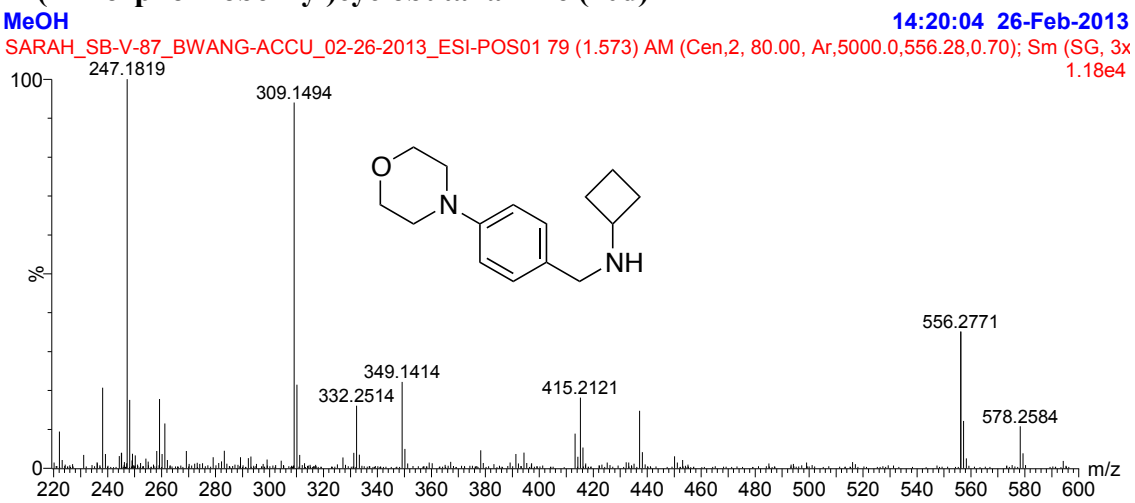
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
286 formula(e) evaluated with 2 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-30 O: 1-60

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
261.1962	261.1967	-0.5	-1.9	5.5	1.6		C16 H25 N2 O

_N_-(4-Morpholinobenzyl)cyclobutanamine (10d)



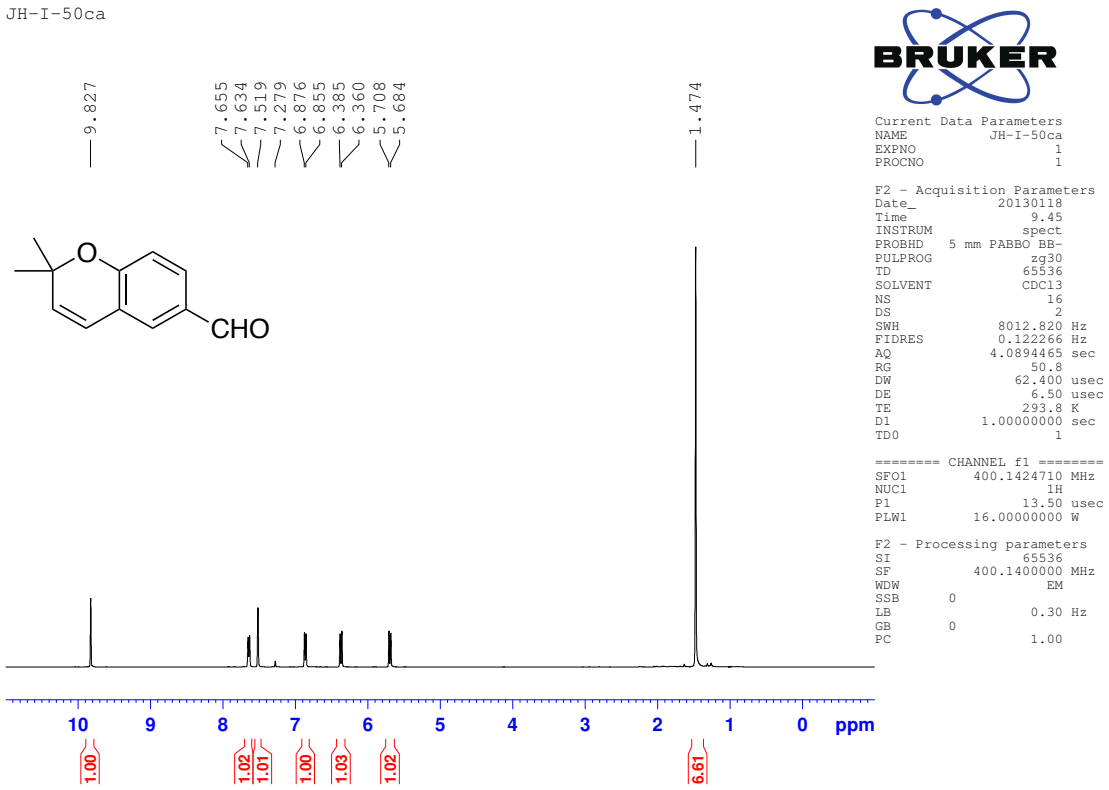
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
153 formula(e) evaluated with 1 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-6 O: 1-30

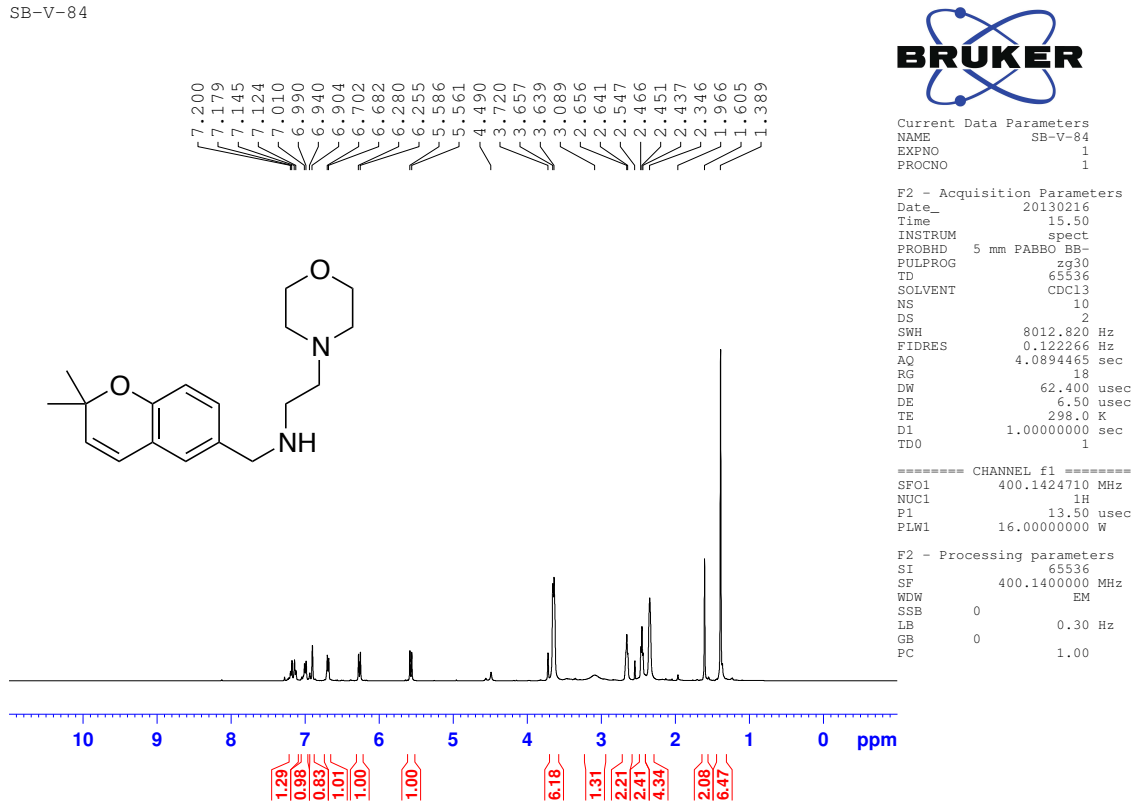
Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
247.1819	247.1810	0.9	3.6	5.5	70.6		C15 H23 N2 O

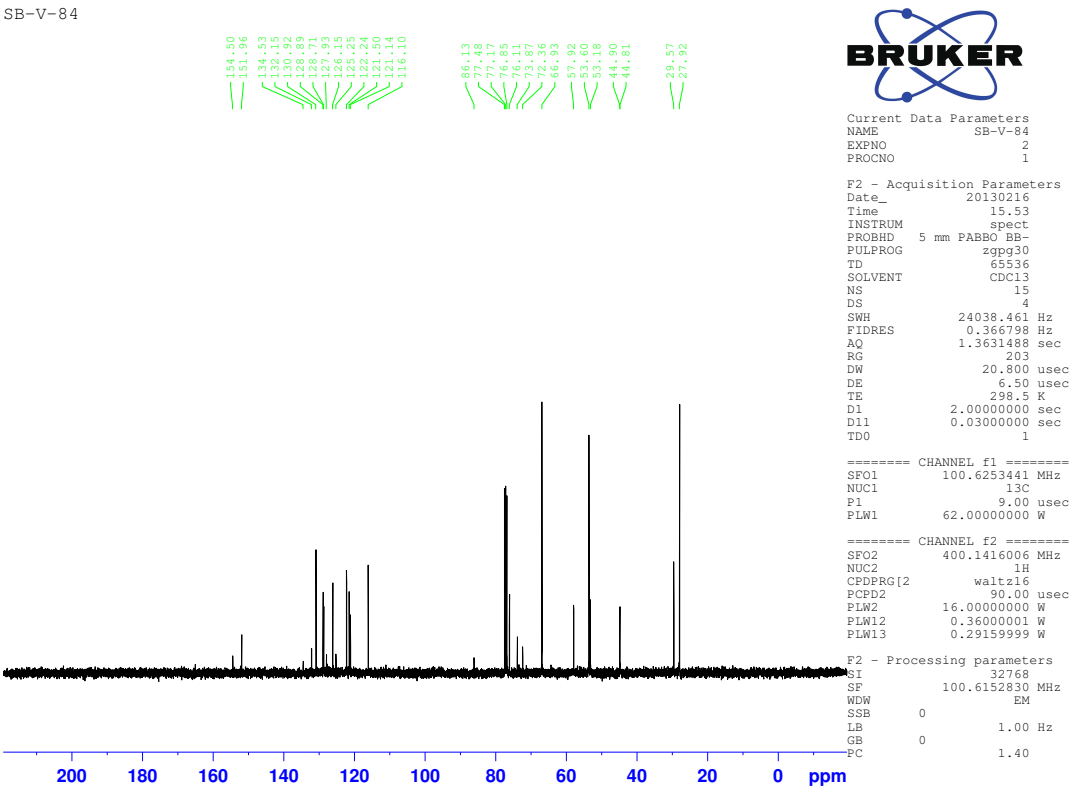
2,2-Dimethyl-2*H*-chromene-6-carbaldehyde (11)

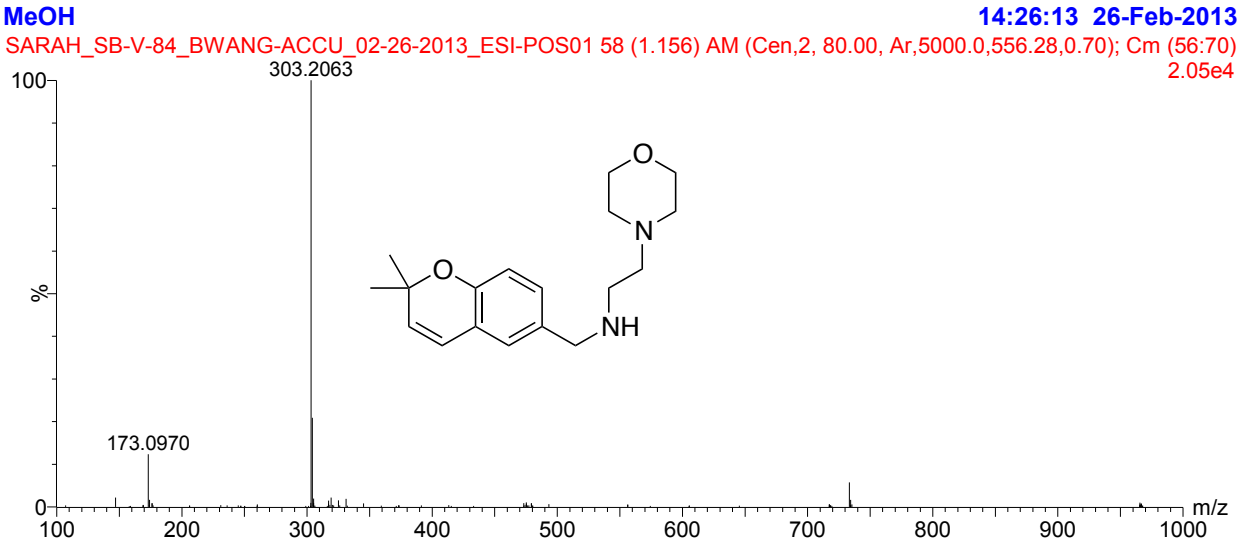


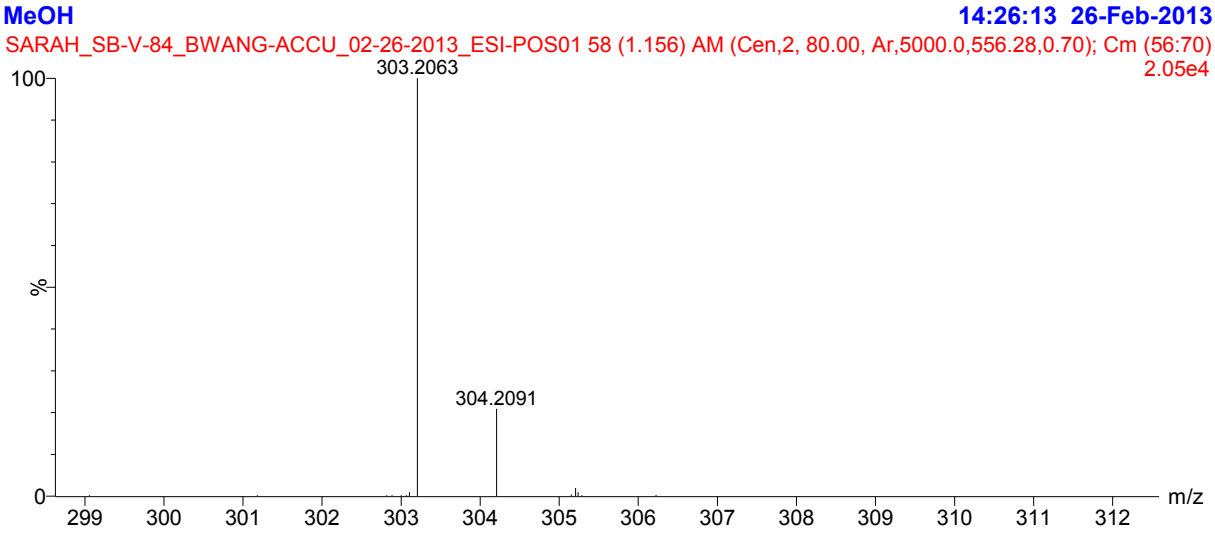

```
Current Data Parameters
NAME                  JH-I-50ca
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20130118
Time                      9.45
INSTRUM                  spect
PROBHD     5 mm PABBO BB-
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   8012.820 Hz
FIDRES                0.122266 Hz
AQ                    4.0894465 sec
RG                         50.8
DW                       62.400 usec
DE                        6.50 usec
TE                       293.8 K
D1                    1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1                400.1424710 MHz
NUC1                        1H
P1                       13.50 usec
PLW1               16.00000000 W

F2 - Processing parameters
SI                       65536
SF                  400.1400000 MHz
WDW                         EM
SSB                0
LB                        0.30 Hz
GB                 0
PC                        1.00
```

N-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-2-morpholinoethanamine (12a)









Elemental Composition Report

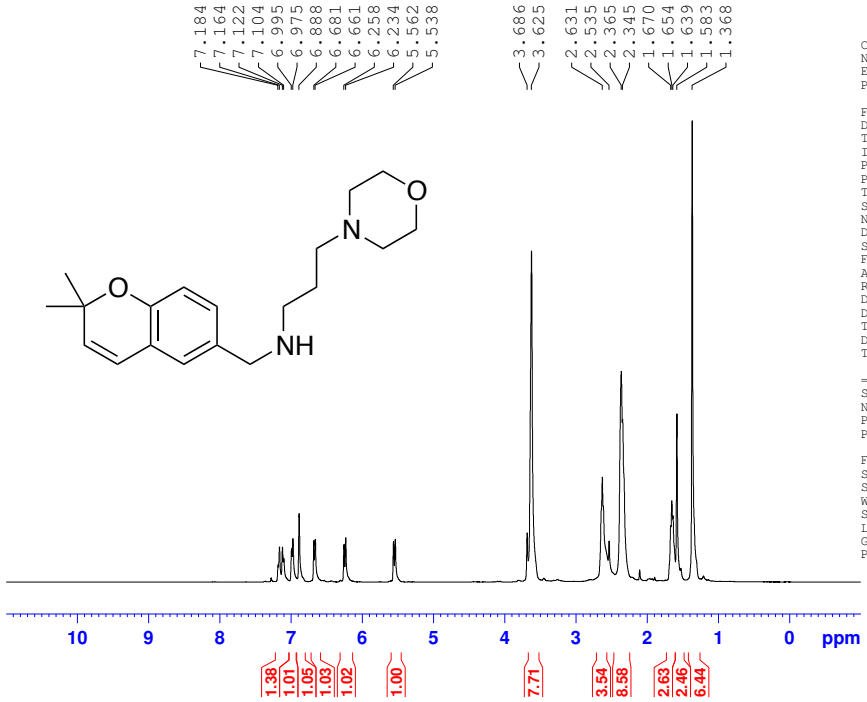
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
234 formula(e) evaluated with 1 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-6 O: 1-30

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
303.2063	303.2073	-1.0	-3.3	6.5	22.6	C18 H27 N2 O2

N-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-3-morpholinopropan-1-amine (12b)

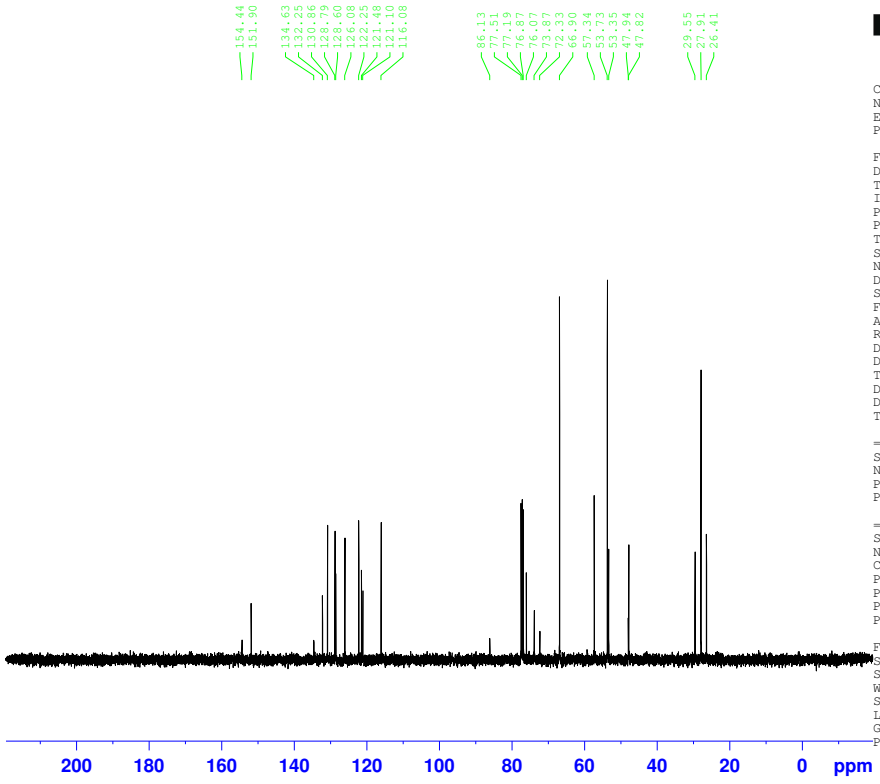
SB-V-85



BRUKER

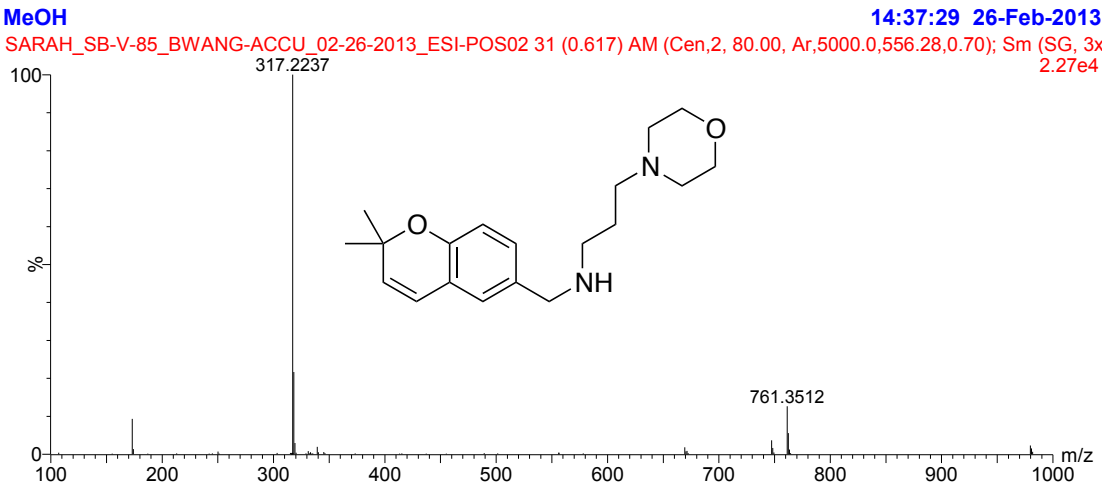
```
Current Data Parameters
NAME                  SB-V-85
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20130216
Time                  15.55
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDC13
NS                       12
DS                        2
SWH                8012.820 Hz
FIDRES                0.122266 Hz
AQ                 4.0894465 sec
RG                       18
DW                    62.400 usec
DE                     6.50 usec
TE                    297.7 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1             400.1424710 MHz
NUC1                       1H
P1                      13.50 usec
PLW1            16.00000000 W

F2 - Processing parameters
SI                        65536
SF               400.1400000 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

SB-V-85



BRUKER

```
Current Data Parameters
NAME                  SB-V-85
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20130216
Time                  15.57
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDC13
NS                       19
DS                        4
SWH               24038.461 Hz
FIDRES                0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                    20.800 usec
DE                     6.50 usec
TE                    298.6 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1             100.6253441 MHz
NUC1                       13C
P1                      9.00 usec
PLW1            62.00000000 W

======== CHANNEL f2 ========
SFO2             400.1416006 MHz
NUC2                       1H
CPDPRG[2              waltz16
PCPD2                  90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W

F2 - Processing parameters
SI                        32768
SF               100.6152830 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



Elemental Composition Report

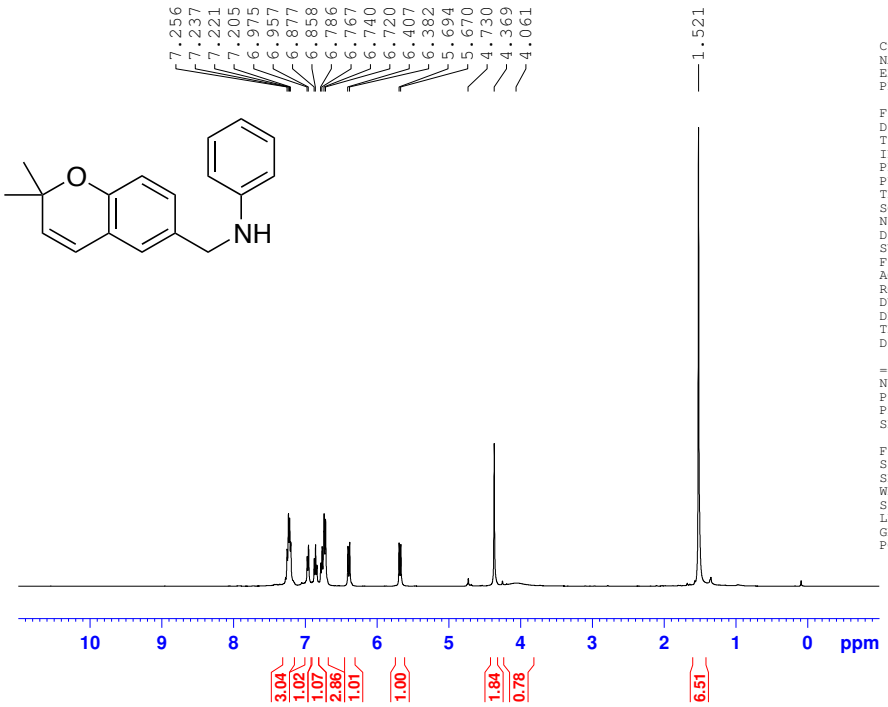
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
255 formula(e) evaluated with 1 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-6 O: 1-30

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
317.2237	317.2229	0.8	2.5	6.5	3.5	C19 H29 N2 O2

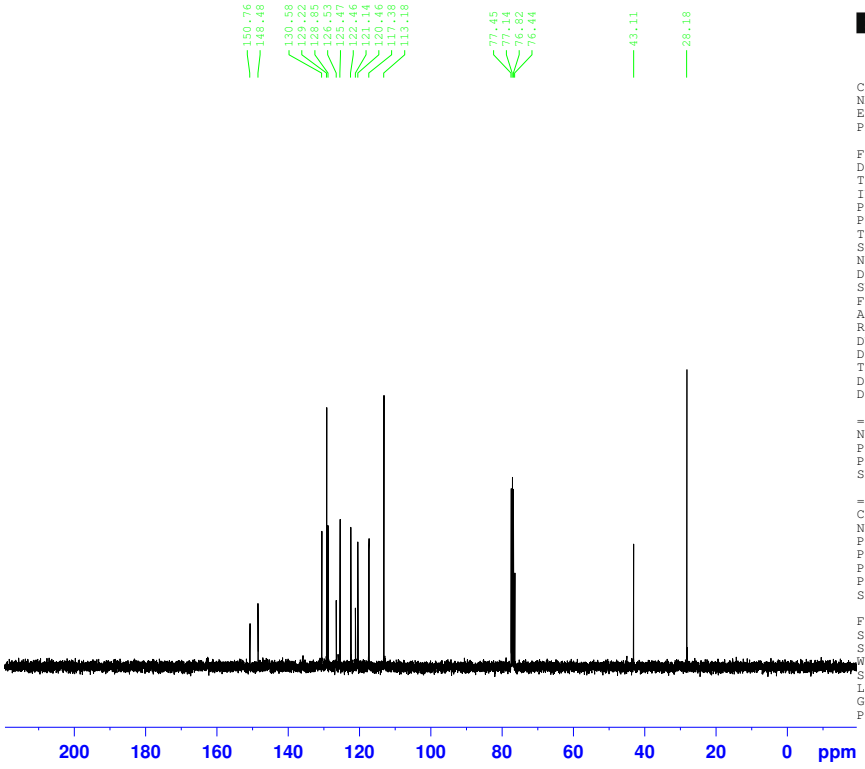
N-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)aniline (13a)

SB-IV-53

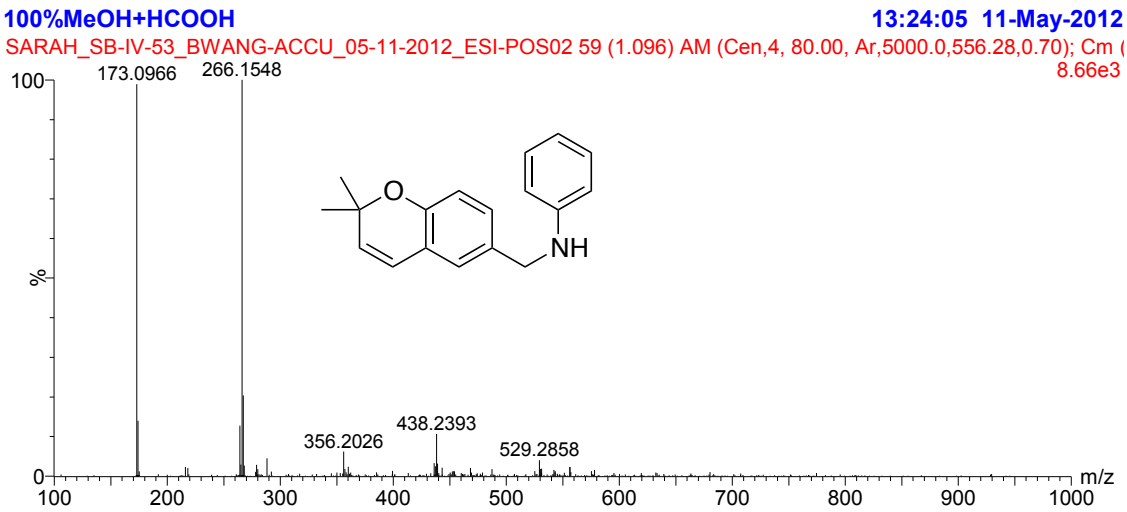



```
Current Data Parameters
NAME                  SB-IV-53
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20120509
Time                   12.26
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDC13
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      28.5
DW                    60.800 usec
DE                     6.50 usec
TE                     298.2 K
D1                  1.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PLW1               16.00000000 W
SFO1              400.1424710 MHz

F2 - Processing parameters
SI                         65536
SF                400.1400000 MHz
WDW                           EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

SB-IV-53




```
Current Data Parameters
NAME                  SB-IV-53
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20120509
Time                   12.28
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                     65536
SOLVENT                CDC13
NS                        20
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                       203
DW                    20.800 usec
DE                     6.50 usec
TE                     298.3 K
D1                  2.00000000 sec
D11                 0.03000000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                      9.00 usec
PLW1               62.00000000 W
SFO1              100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  90.00 usec
PLW2               16.00000000 W
PLW12               0.36000001 W
PLW13               0.29159999 W
SFO2              400.1416006 MHz

F2 - Processing parameters
SI                         32768
SF                100.6152830 MHz
WDW                           EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



Elemental Composition Report

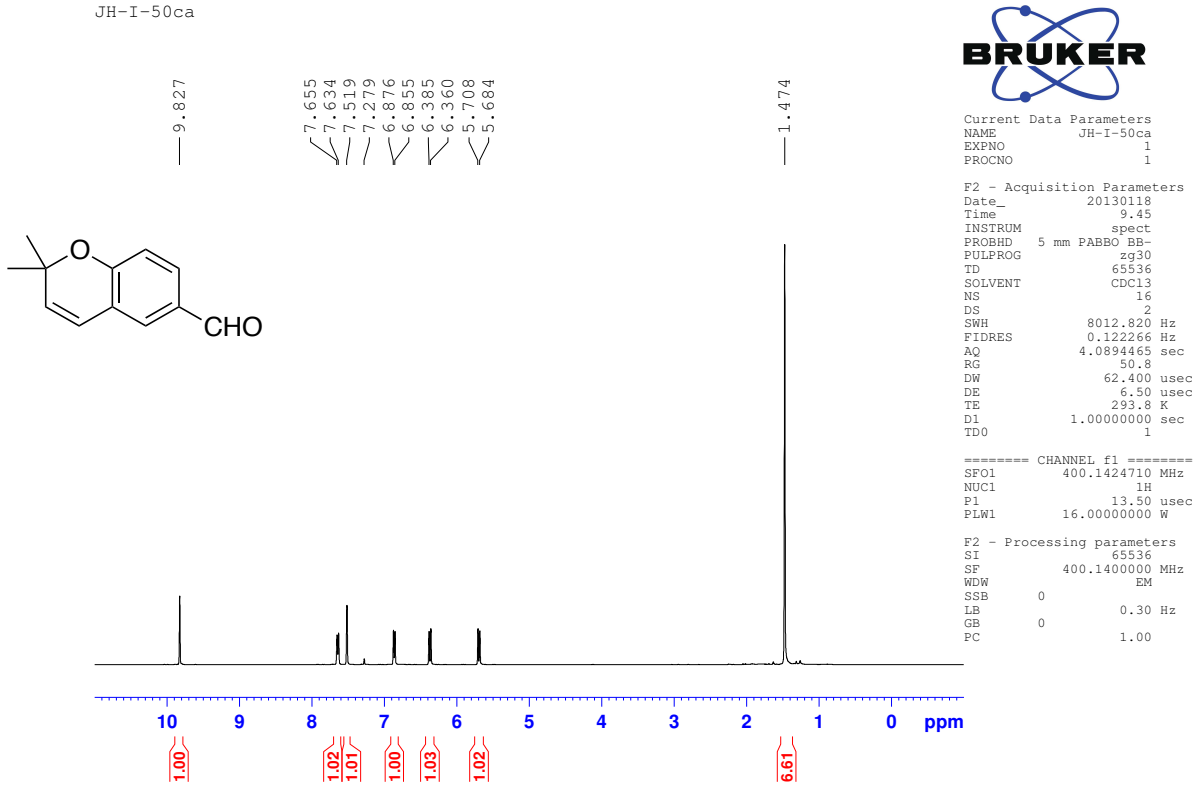
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
293 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100

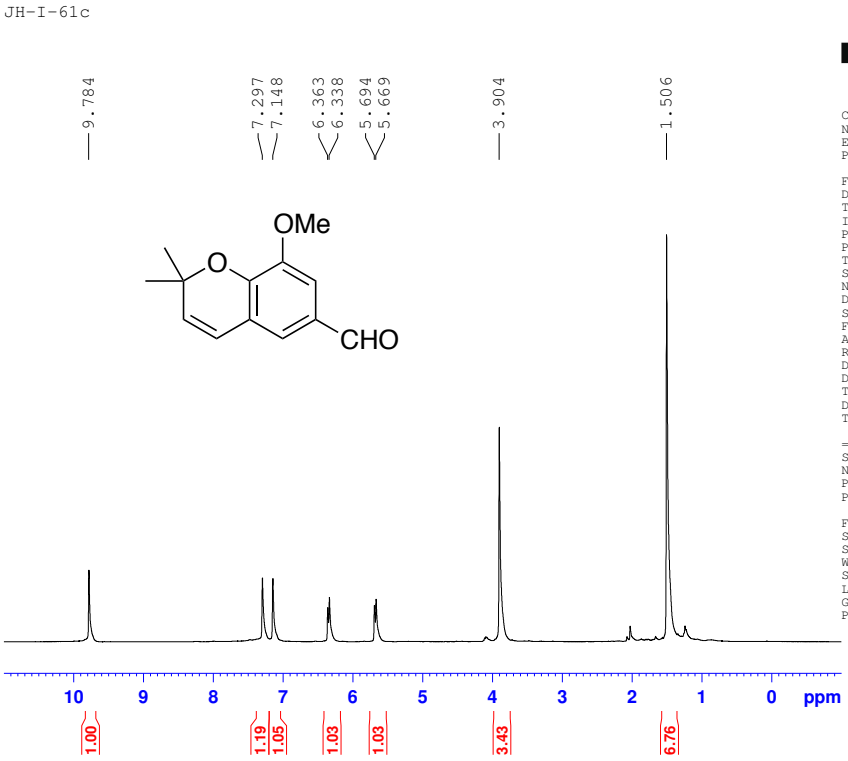
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
266.1548	266.1545	0.3	1.1	9.5	3.1	C18 H20 N O

Appendix B: Structural Characterization of Compounds from Chapter 4

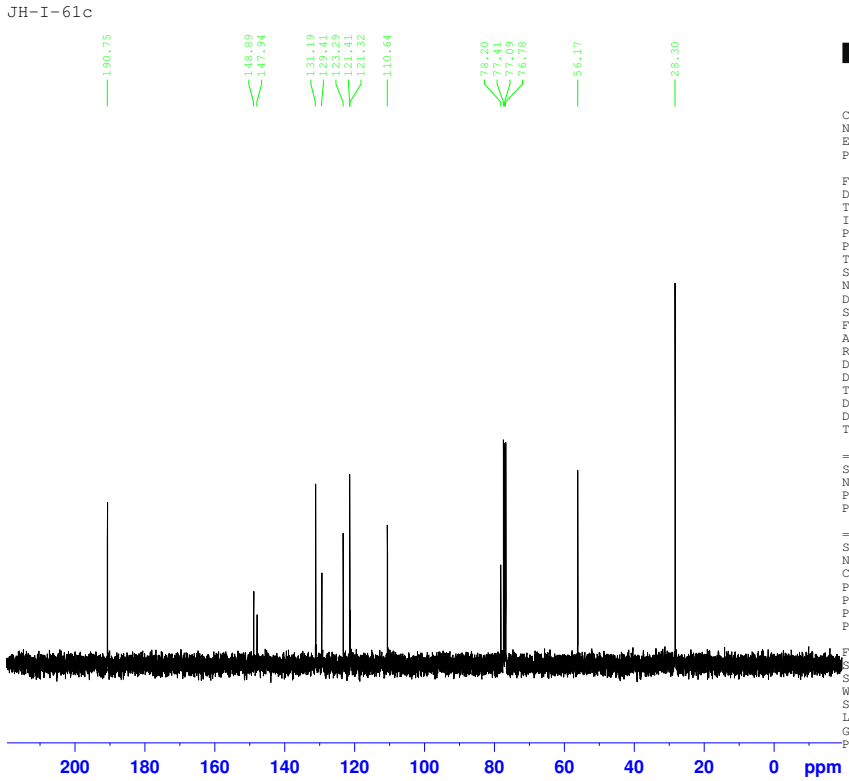
2,2-Dimethyl-2*H*-chromene-6-carbaldehyde (5a)



8-Methoxy-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (5b)

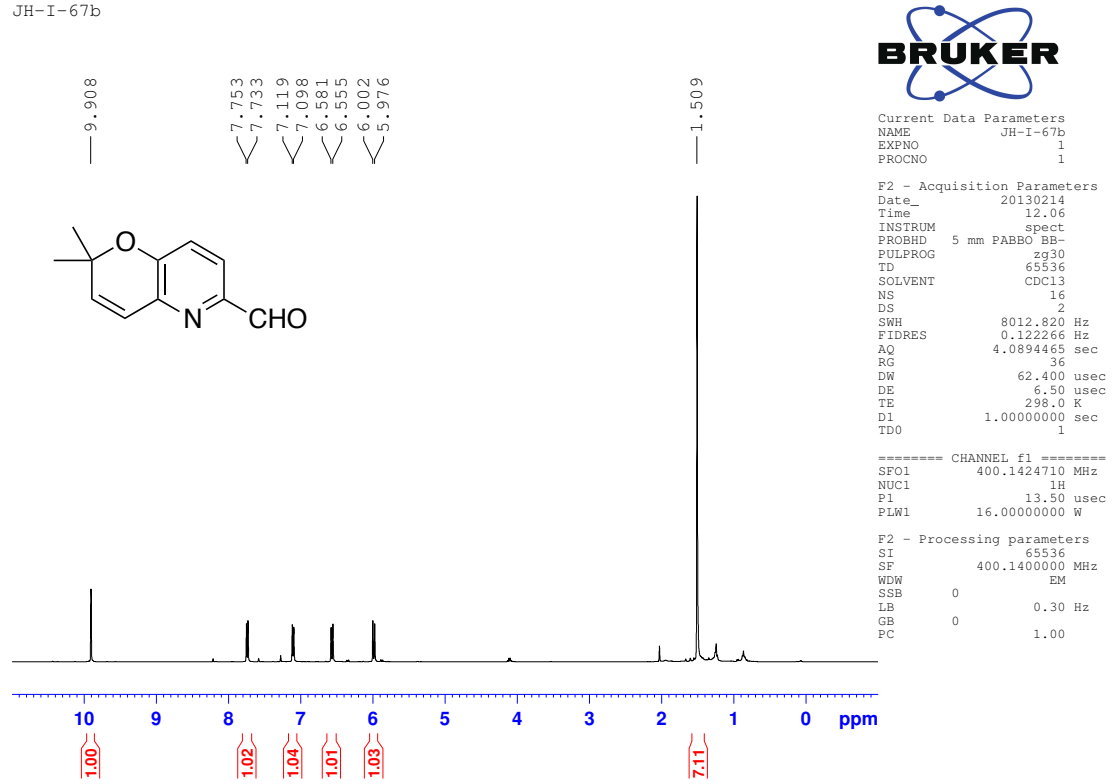


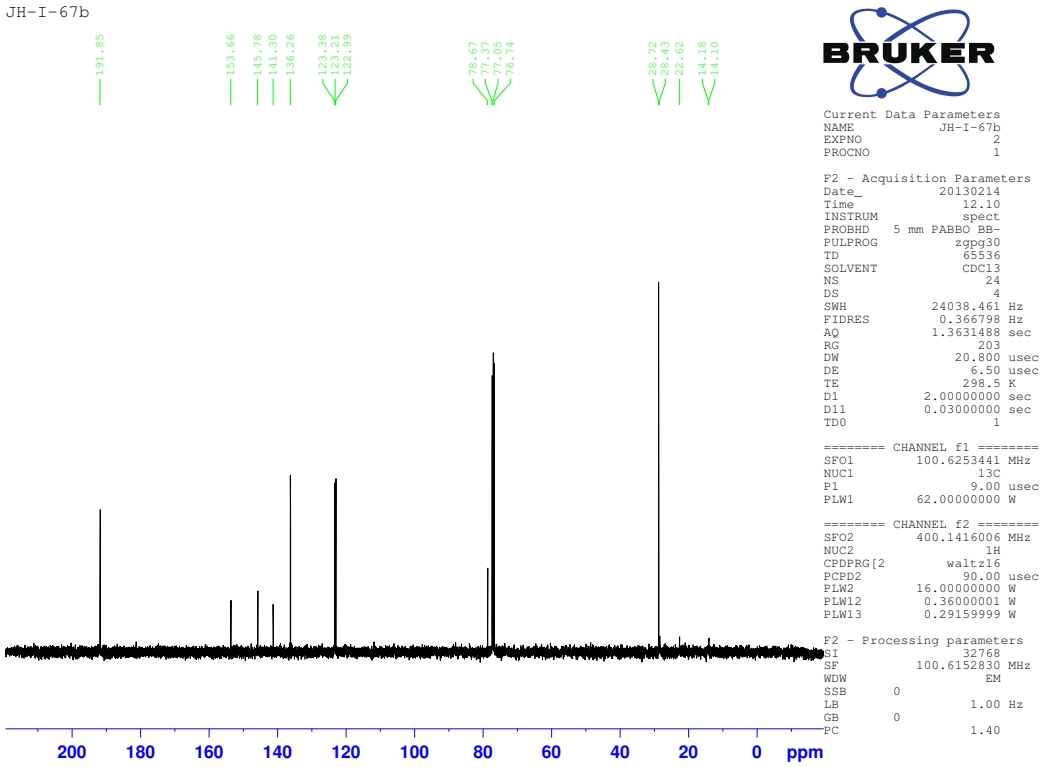

```
Current Data Parameters
NAME                  JH-I-61c
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20130207
Time                     14.11
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                           7
DS                           2
SWH                 8012.820 Hz
FIDRES              0.122266 Hz
AQ                  4.0894465 sec
RG                          36
DW                     62.400 usec
DE                      6.50 usec
TE                     297.9 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1             400.1424710 MHz
NUC1                       1H
P1                      13.50 usec
PLW1            16.00000000 W

F2 - Processing parameters
SI                      65536
SF               400.1400000 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```




```
Current Data Parameters
NAME                  JH-I-61c
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20130207
Time                     14.12
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                 CDCl3
NS                          15
DS                           4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                         203
DW                     20.800 usec
DE                      6.50 usec
TE                     298.6 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1             100.6253441 MHz
NUC1                       13C
P1                      9.00 usec
PLW1            62.00000000 W

======== CHANNEL f2 ========
SFO2             400.1416006 MHz
NUC2                       1H
CPDPRG[2             waltz16
PCPD2                  90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W

F2 - Processing parameters
SI                      32768
SF               100.6152830 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```

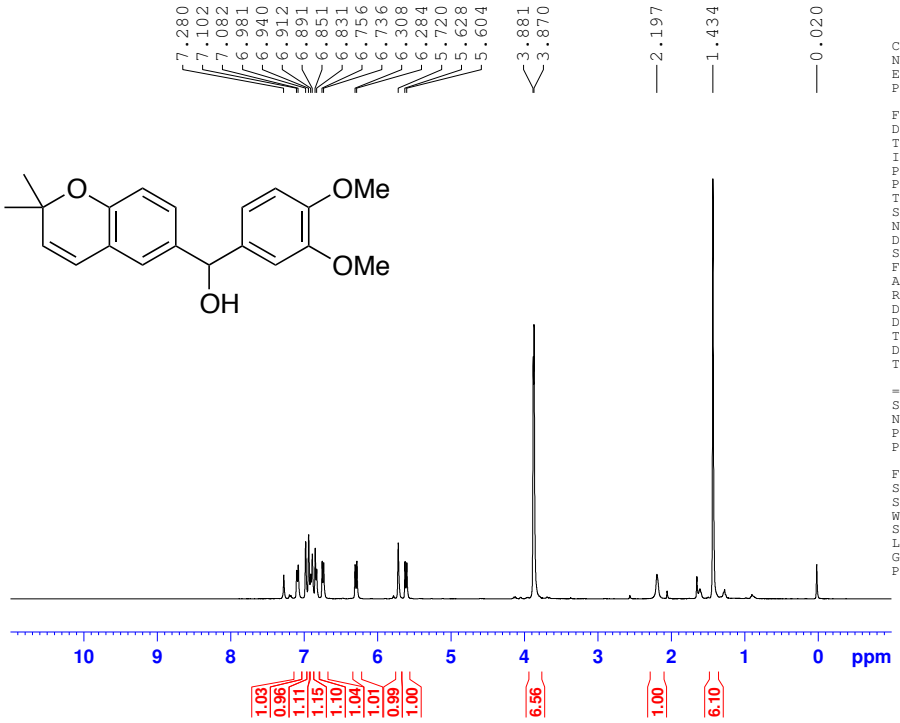
2,2-Dimethyl-2*H*-pyrano[3,2-*b*]pyridine-6-carbaldehyde (5c)





(3,4-Dimethoxyphenyl)(2,2-dimethyl-2*H*-chromen-6-yl)methanol (6a)

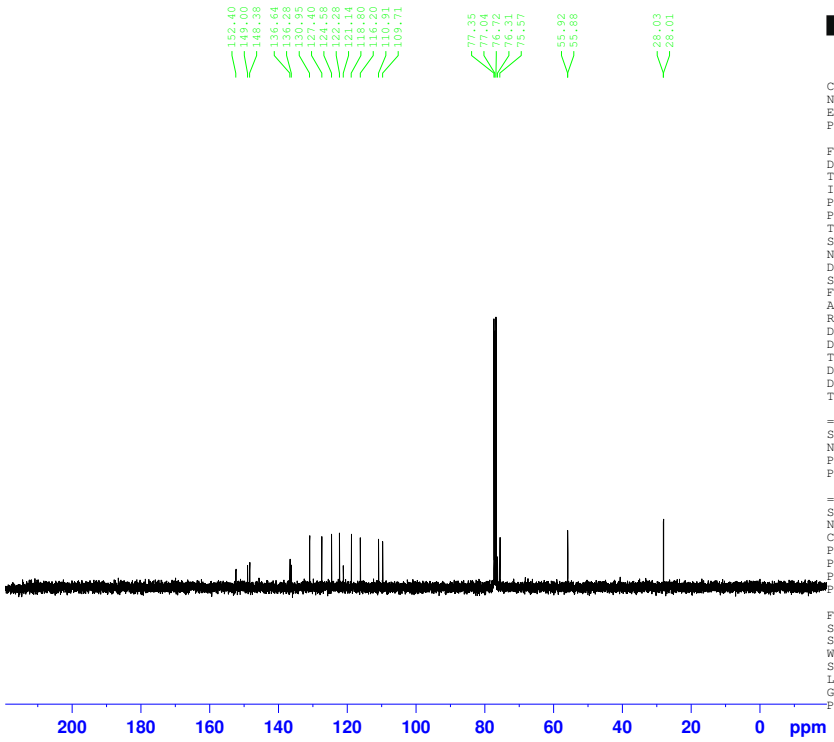
SB-V-36d



BRUKER

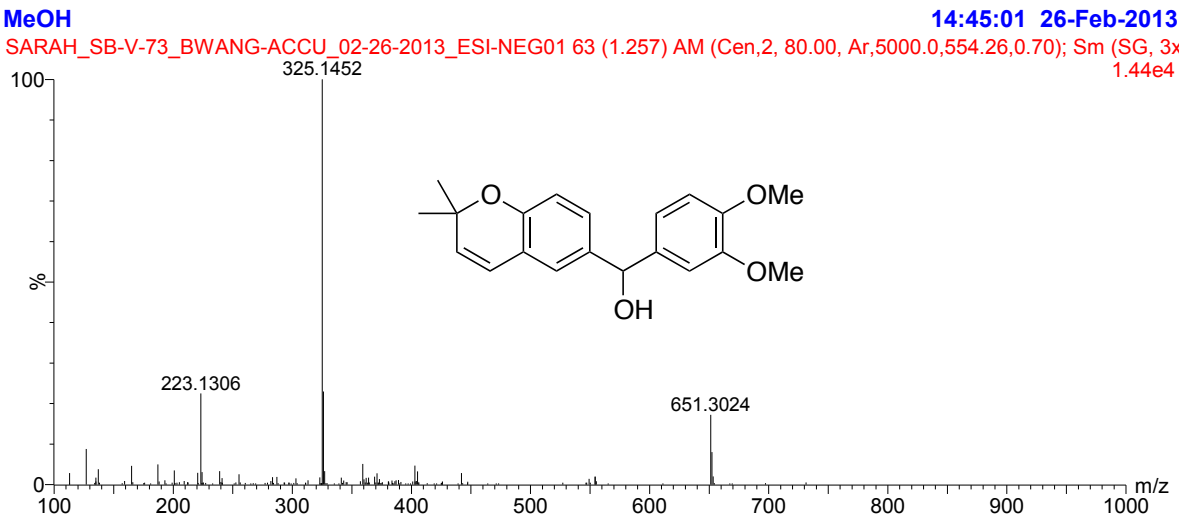
```
Current Data Parameters
NAME                  SB-V-36d
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20121207
Time                   10.29
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8012.820 Hz
FIDRES              0.122266 Hz
AQ                  4.0894465 sec
RG                       114
DW                    62.400 usec
DE                     6.50 usec
TE                    298.0 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1               400.1424710 MHz
NUC1                       1H
P1                      13.50 usec
PLW1               16.00000000 W

F2 - Processing parameters
SI                         65536
SF                 400.1400000 MHz
WDW                           EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

SB-V-36d



BRUKER

```
Current Data Parameters
NAME                  SB-V-36d
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20121207
Time                   10.33
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                     65536
SOLVENT                CDCl3
NS                        41
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                       203
DW                    20.800 usec
DE                     6.50 usec
TE                    298.4 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1               100.6253441 MHz
NUC1                       13C
P1                      9.00 usec
PLW1               62.00000000 W

======== CHANNEL f2 ========
SFO2               400.1416006 MHz
NUC2                       1H
CPDPRG[2                waltz16
PCPD2                   90.00 usec
PLW2               16.00000000 W
PLW12               0.36000001 W
PLW13               0.29159999 W

F2 - Processing parameters
SI                         32768
SF                 100.6152830 MHz
WDW                           EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



Elemental Composition Report

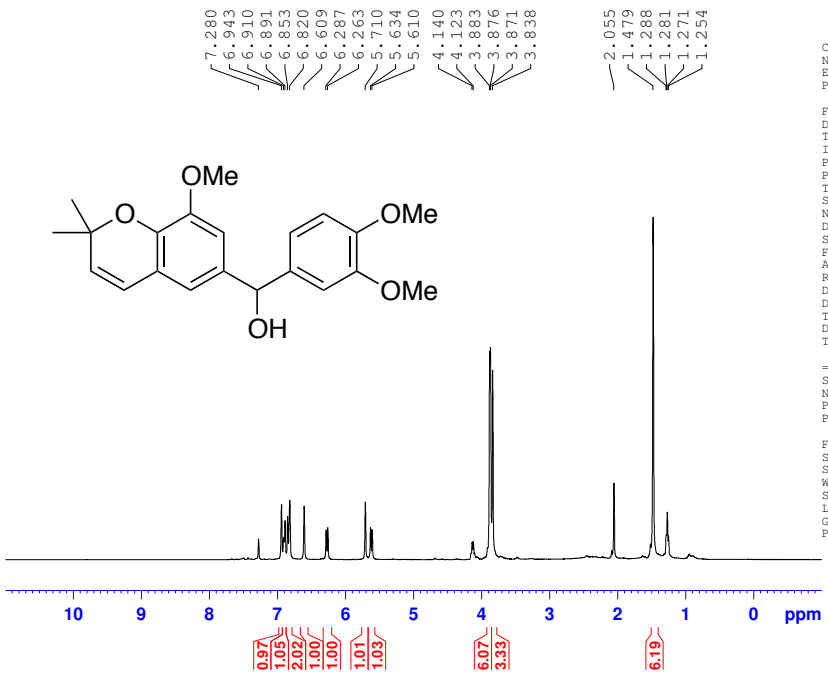
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
56 formula(e) evaluated with 1 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 O: 1-30

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
325.1452	325.1440	1.2	3.7	10.5	1.1		C20 H21 O4

(3,4-Dimethoxyphenyl)(8-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)methanol (6b)

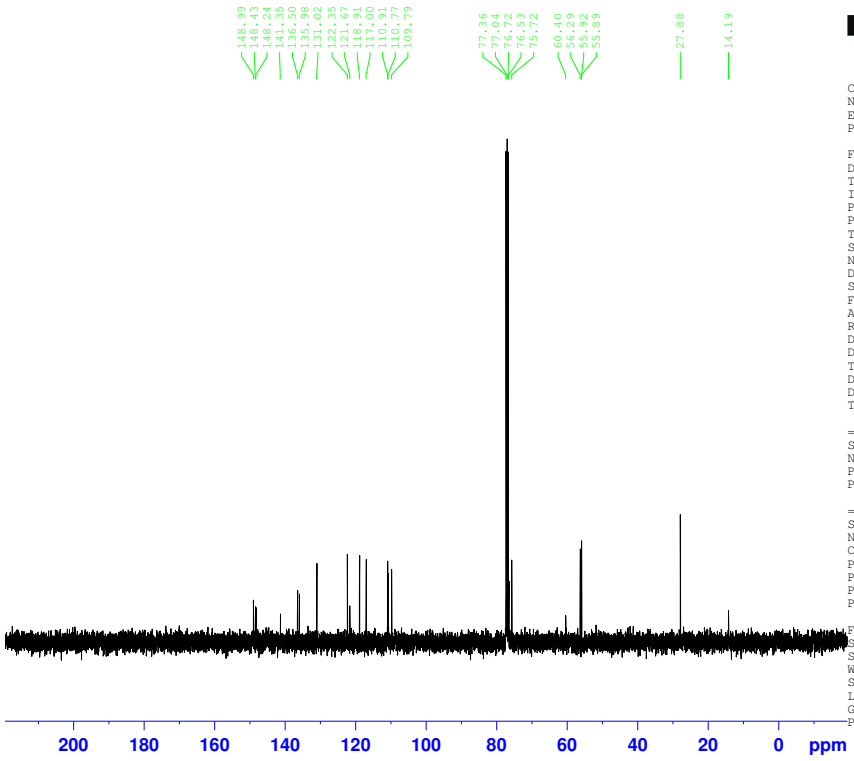
JH-I-66b



BRUKER

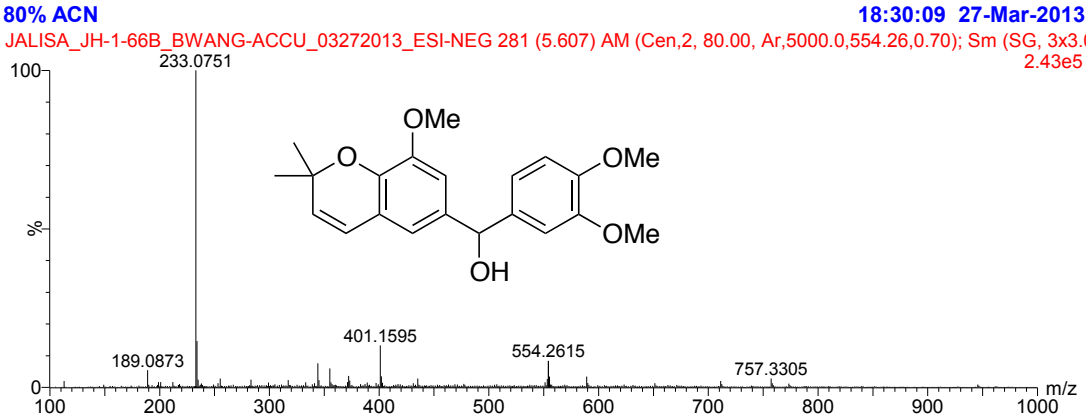
```
Current Data Parameters
NAME              JH-I-66b
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20130214
Time               12.14
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                  90.5
DW                62.400 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          400.1424710 MHz
NUC1                  1H
P1                 13.50 usec
PLW1          16.00000000 W

F2 - Processing parameters
SI                 65536
SF            400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

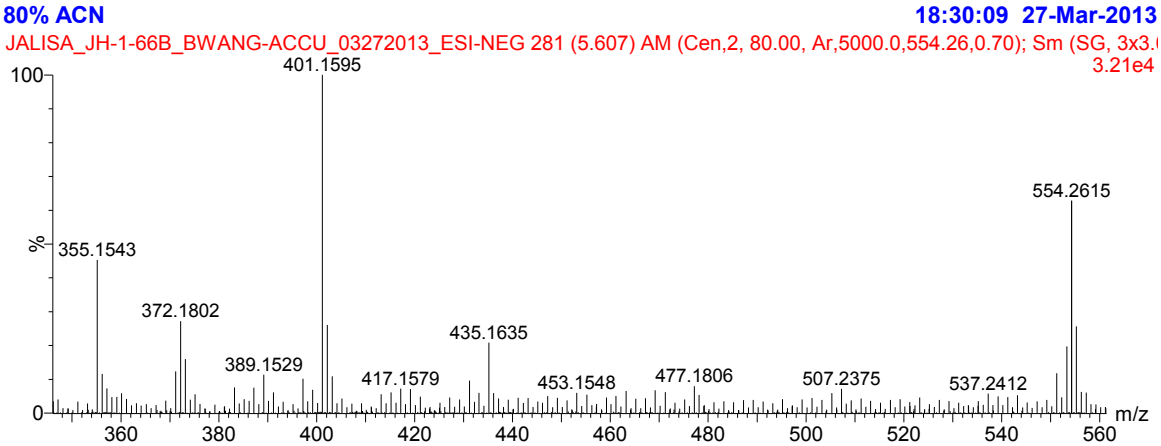
JH-I-66b



BRUKER

```
Current Data Parameters
NAME              JH-I-66b
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_           20130214
Time               12.17
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    40
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.5 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1          62.00000000 W

======== CHANNEL f2 ========
SFO2          400.1416006 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2          16.00000000 W
PLW12          0.36000001 W
PLW13          0.29159999 W

F2 - Processing parameters
SI                 32768
SF            100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



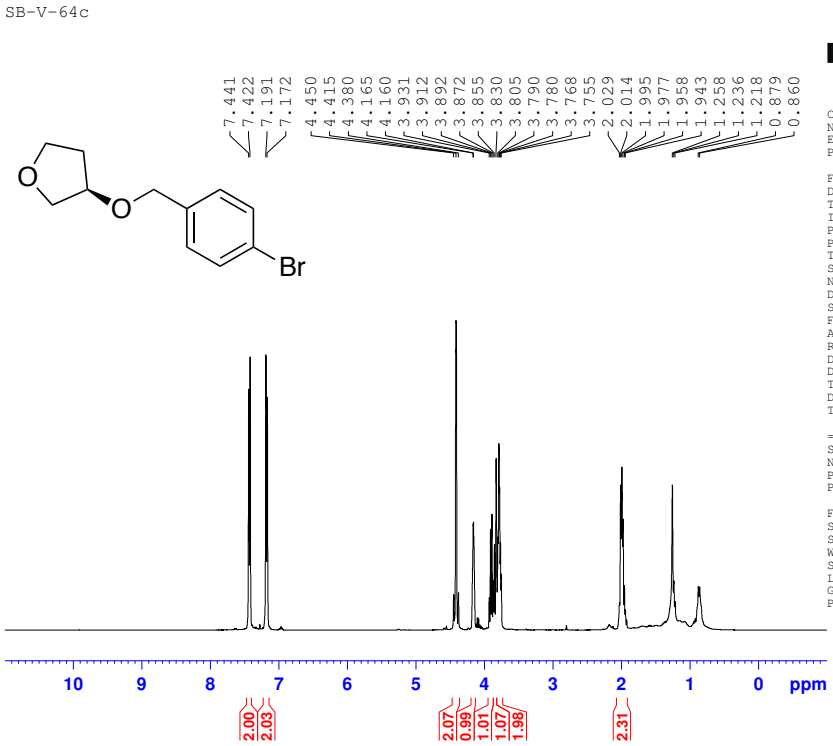


Elemental Composition Report
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

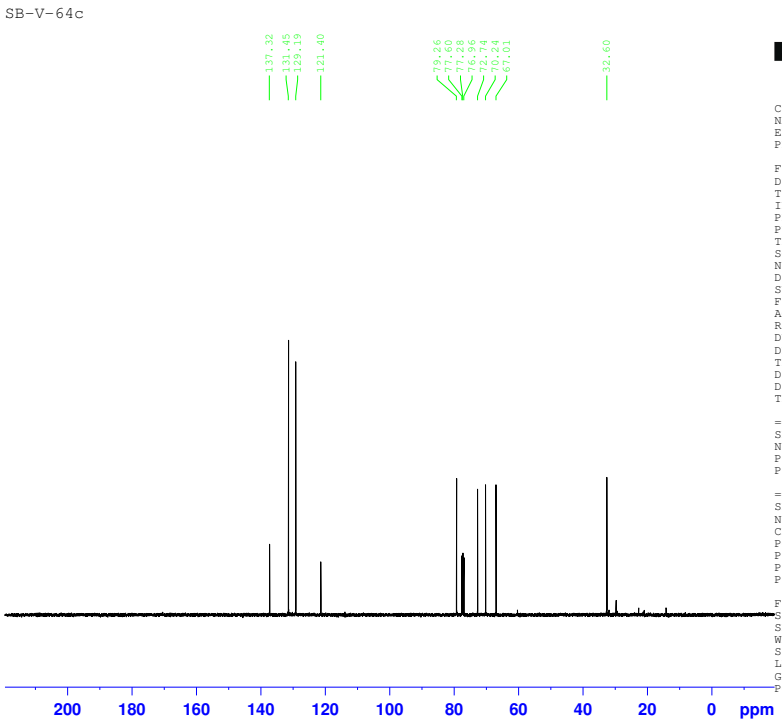
Monoisotopic Mass, Odd and Even Electron Ions
62 formula(e) evaluated with 1 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 O: 1-60

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
355.1543	355.1545	-0.2	-0.6	10.5	695.3		C21 H23 O5

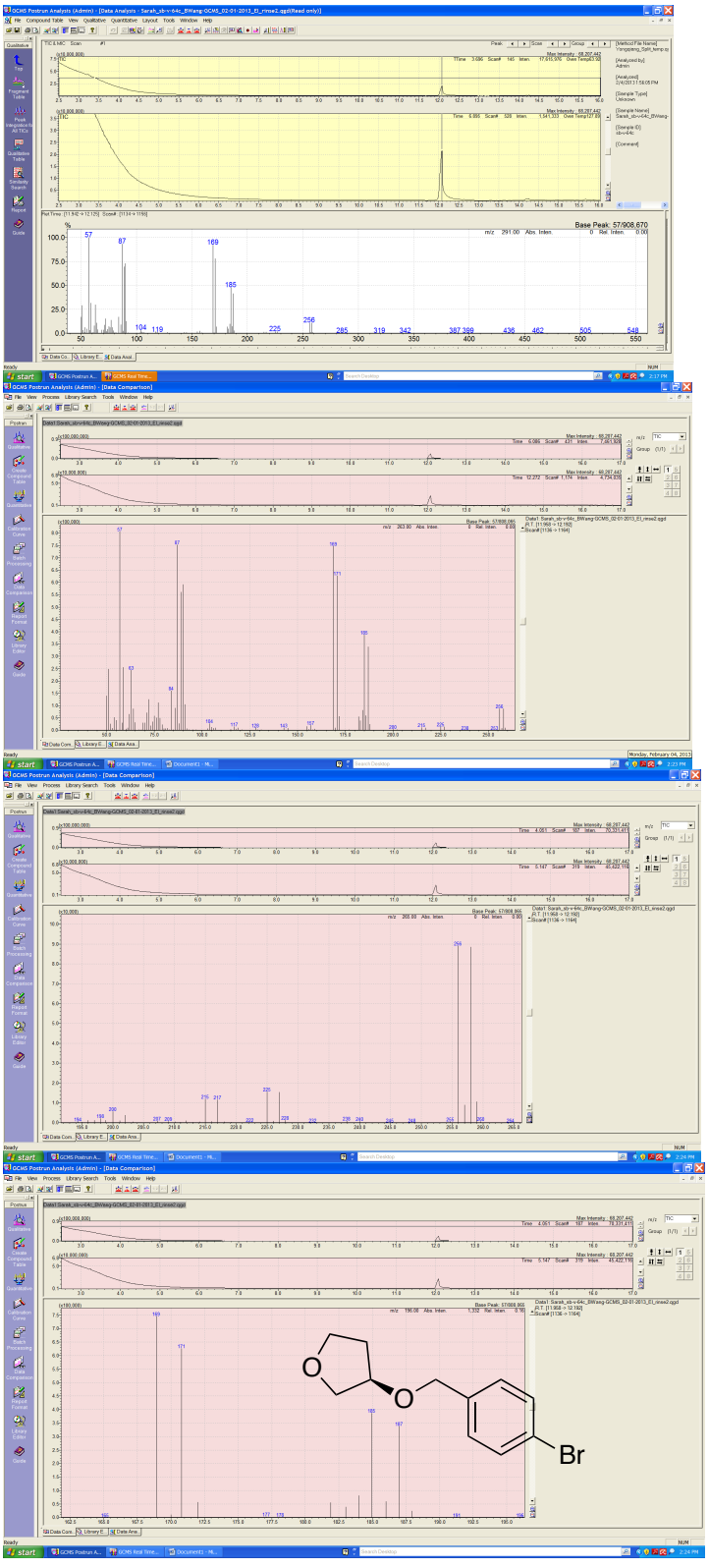
(R)-3-((4-Bromobenzyl)oxy)tetrahydrofuran (9b)



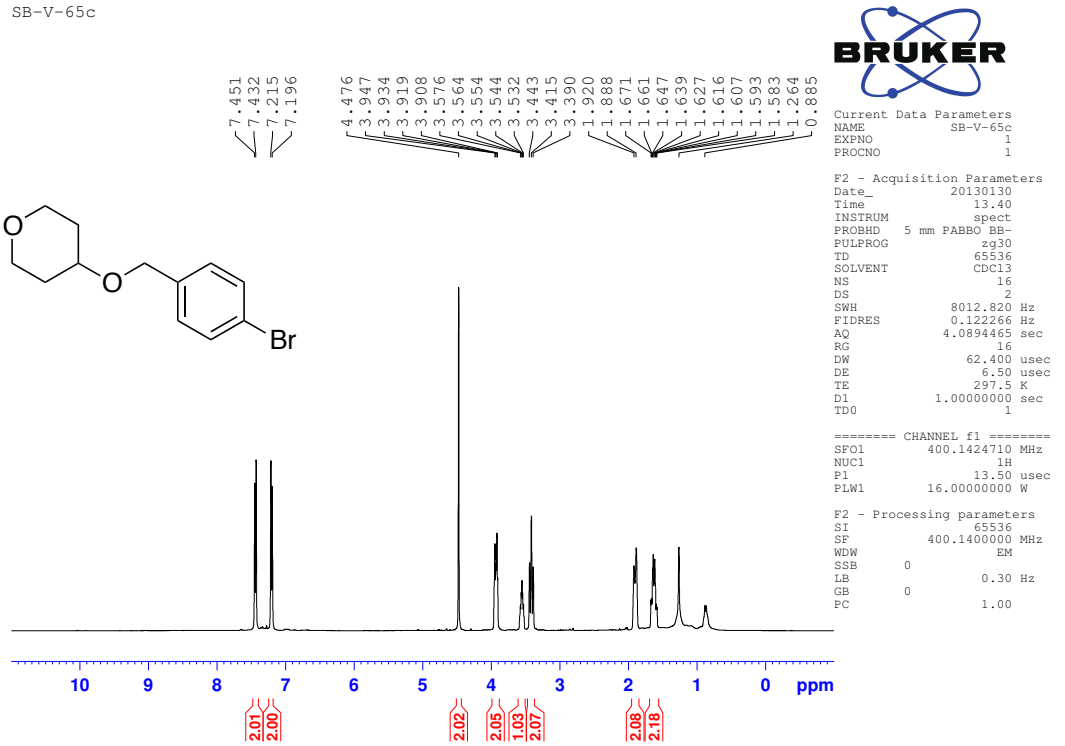

```
Current Data Parameters
NAME                  SB-V-64c
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20130130
Time                     13.34
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                         16
DS                          2
SWH                  8012.820 Hz
FIDRES               0.122266 Hz
AQ                   4.0894465 sec
RG                         16
DW                      62.400 usec
DE                       6.50 usec
TE                      298.0 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1                400.1424710 MHz
NUC1                        1H
P1                       13.50 usec
PLW1                16.00000000 W

F2 - Processing parameters
SI                          65536
SF                  400.1400000 MHz
WDW                            EM
SSB                 0
LB                       0.30 Hz
GB                  0
PC                       1.00
```

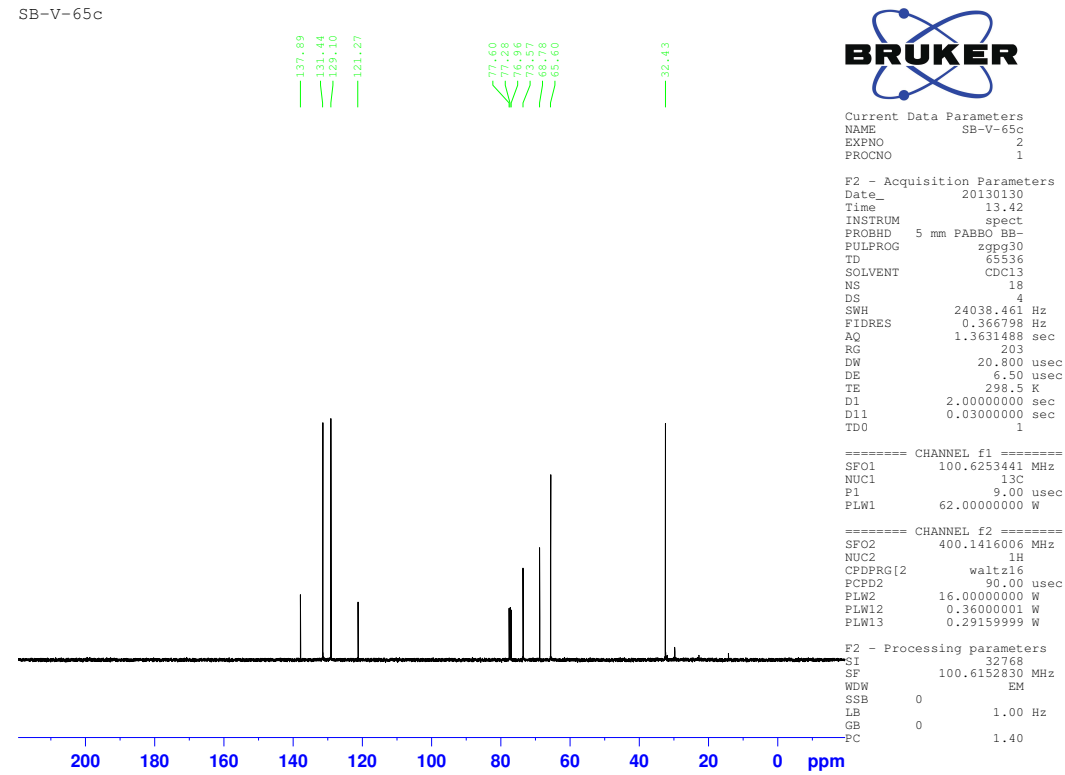


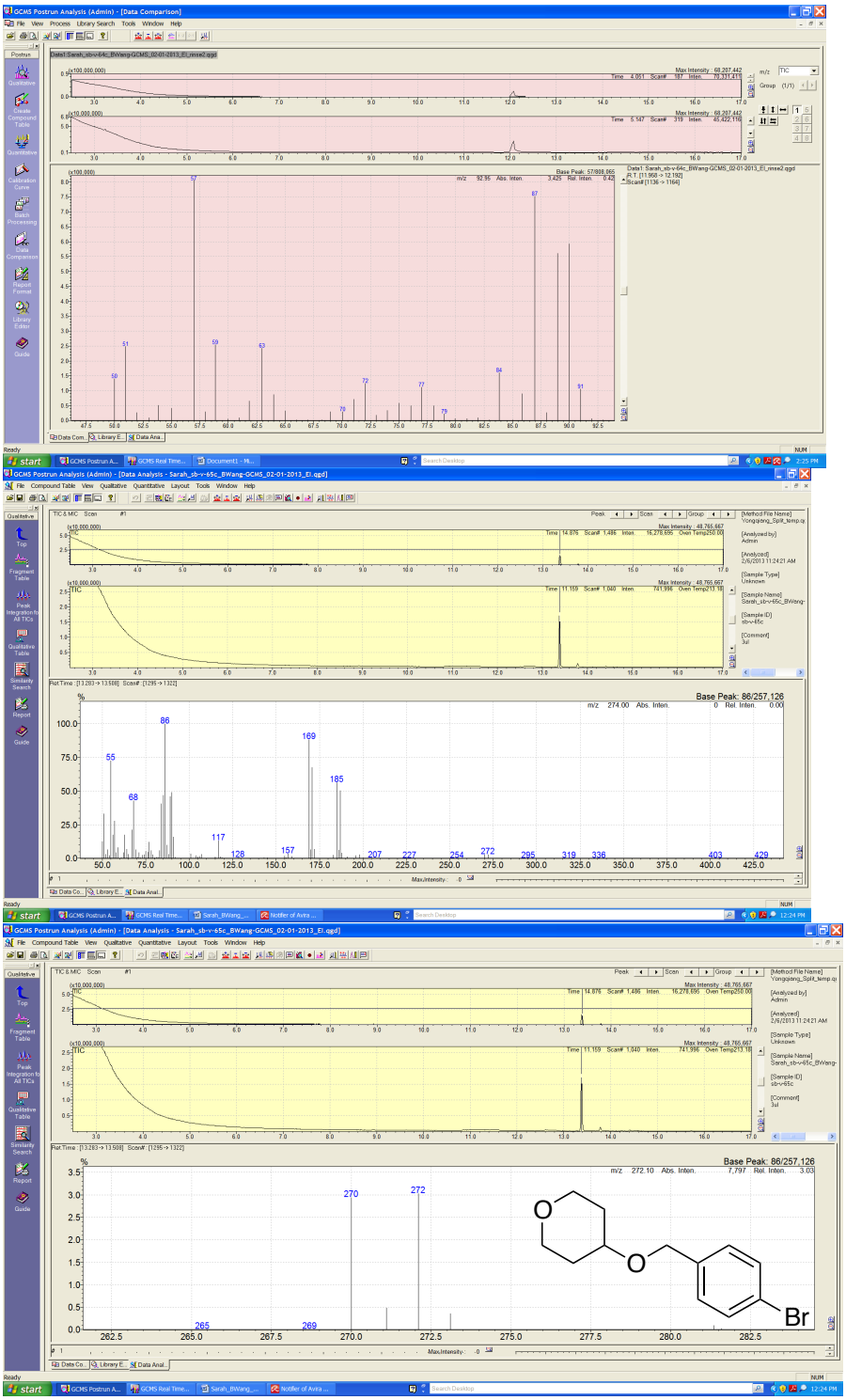

```
Current Data Parameters
NAME                  SB-V-64c
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20130130
Time                     13.37
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                 CDCl3
NS                         24
DS                          4
SWH                 24038.461 Hz
FIDRES               0.366798 Hz
AQ                   1.3631488 sec
RG                         203
DW                      20.800 usec
DE                       6.50 usec
TE                      298.3 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1                100.6253441 MHz
NUC1                        13C
P1                       9.00 usec
PLW1                62.00000000 W

======== CHANNEL f2 ========
SFO2                400.1416006 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                    90.00 usec
PLW2                16.00000000 W
PLW12                0.36000001 W
PLW13                0.29159999 W

F2 - Processing parameters
SI                          32768
SF                  100.6152830 MHz
WDW                            EM
SSB                 0
LB                       1.00 Hz
GB                  0
PC                       1.40
```


Base Peak: 57/908,670
O
O
Br

4-((4-Bromobenzyl)oxy)tetrahydro-2*H*-pyran (9c)

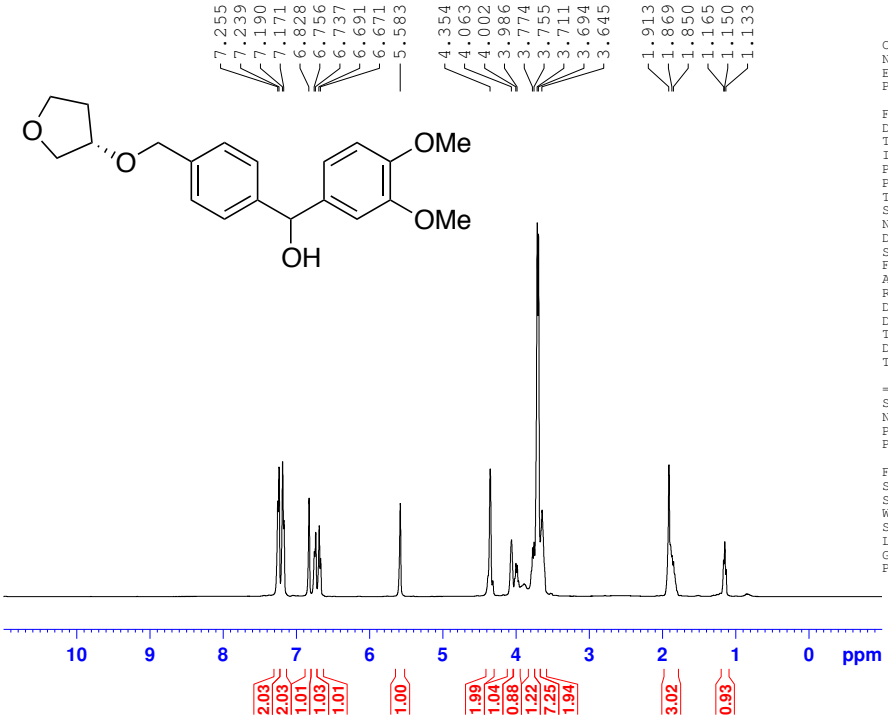





GCMS Postrun Analysis (Admin) - [Data Comparison]
GCMS Postrun Analysis (Admin) - [Data Analysis - Sarah_sb-v-65c_BWang-GCMS_02-01-2013_EI.qgd]
Base Peak: 86/257,126
Base Peak: 86/257,126
Br
O
O

(3,4-Dimethoxyphenyl)(4-((((*S*)-tetrahydrofuran-3-yl)oxy)methyl)phenyl)methanol (10a)

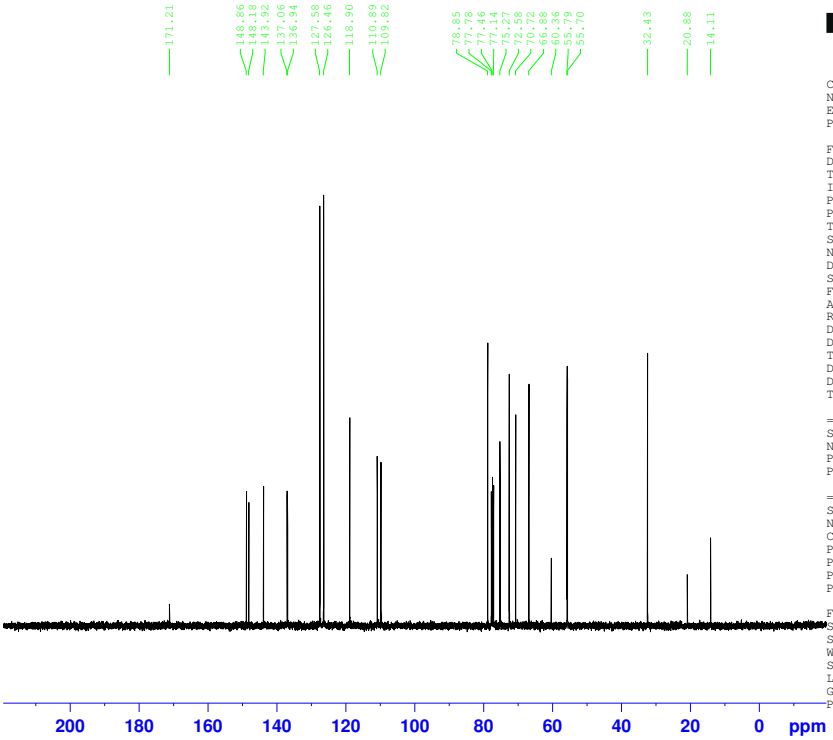
JH-I-64b



BRUKER

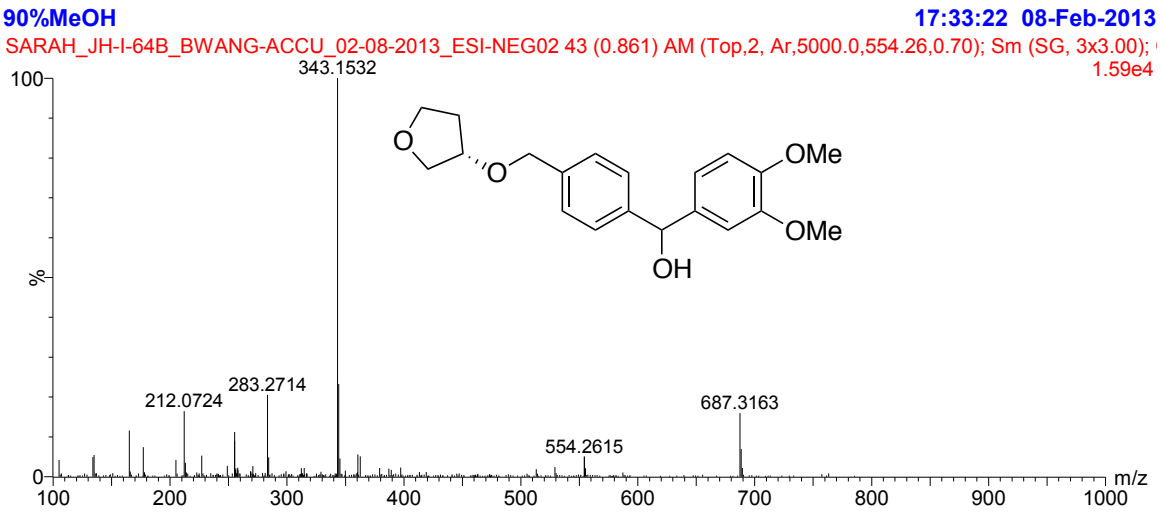
```
Current Data Parameters
NAME            JH-I-64b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130206
Time              11.41
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8012.820 Hz
FIDRES         0.122266 Hz
AQ             4.0894465 sec
RG                 11.3
DW               62.400 usec
DE                6.50 usec
TE               297.5 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

JH-I-64b



BRUKER

```
Current Data Parameters
NAME            JH-I-64b
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130206
Time              11.43
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                   25
DS                    4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631488 sec
RG                  203
DW               20.800 usec
DE                6.50 usec
TE               298.5 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                   13C
P1                 9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



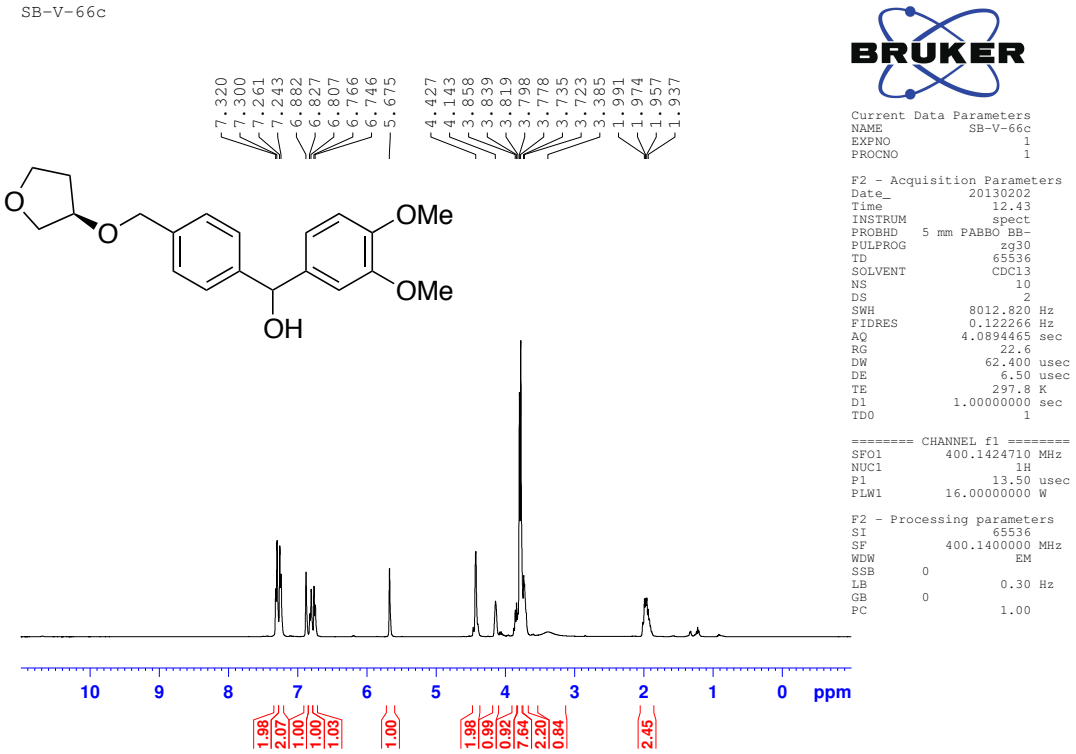
Elemental Composition Report

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

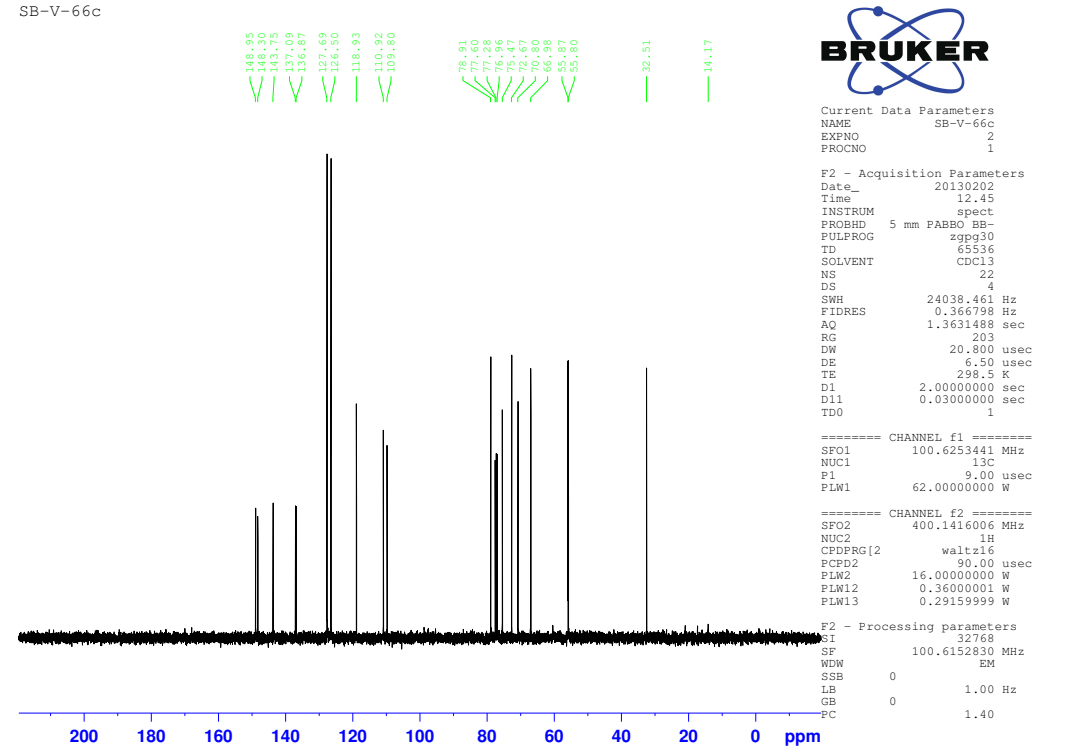
Monoisotopic Mass, Odd and Even Electron Ions
107 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-150 H: 1-150 O: 1-30 Na: 0-1

Minimum:				-1.5				
Maximum:		5.0	20.0		50.0			
Mass	Calc. Mass	mDa		PPM		DBE	i-FIT	Formula
343.1532	343.1545	-1.3	-3.8	9.5	19.1			C20 H23 O5

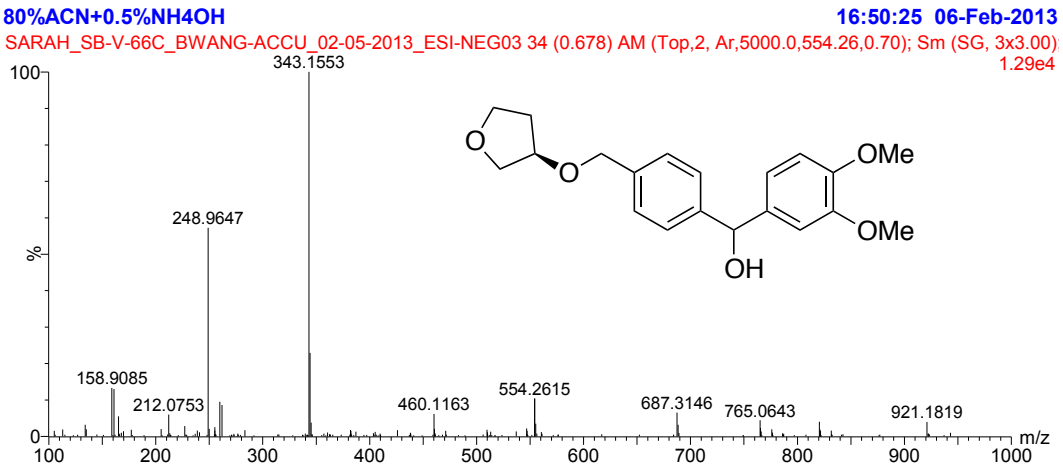
(3,4-Dimethoxyphenyl)(4-((((*R*)-tetrahydrofuran-3-yl)oxy)methyl)phenyl)methanol (10b)




```
Current Data Parameters
NAME                  SB-V-66c
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20130202
Time                   12.43
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       10
DS                        2
SWH                8012.820 Hz
FIDRES                0.122266 Hz
AQ                 4.0894465 sec
RG                      22.6
DW                    62.400 usec
DE                     6.50 usec
TE                    297.8 K
D1                 1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1             400.1424710 MHz
NUC1                       1H
P1                      13.50 usec
PLW1            16.00000000 W

F2 - Processing parameters
SI                    65536
SF               400.1400000 MHz
WDW                       EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```




```
Current Data Parameters
NAME                  SB-V-66c
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20130202
Time                   12.45
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       22
DS                        4
SWH               24038.461 Hz
FIDRES                0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                    20.800 usec
DE                     6.50 usec
TE                    298.5 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1            100.6253441 MHz
NUC1                      13C
P1                      9.00 usec
PLW1            62.00000000 W

======== CHANNEL f2 ========
SFO2             400.1416006 MHz
NUC2                       1H
CPDPRG[2              waltz16
PCPD2                  90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W

F2 - Processing parameters
SI                    32768
SF               100.6152830 MHz
WDW                       EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```



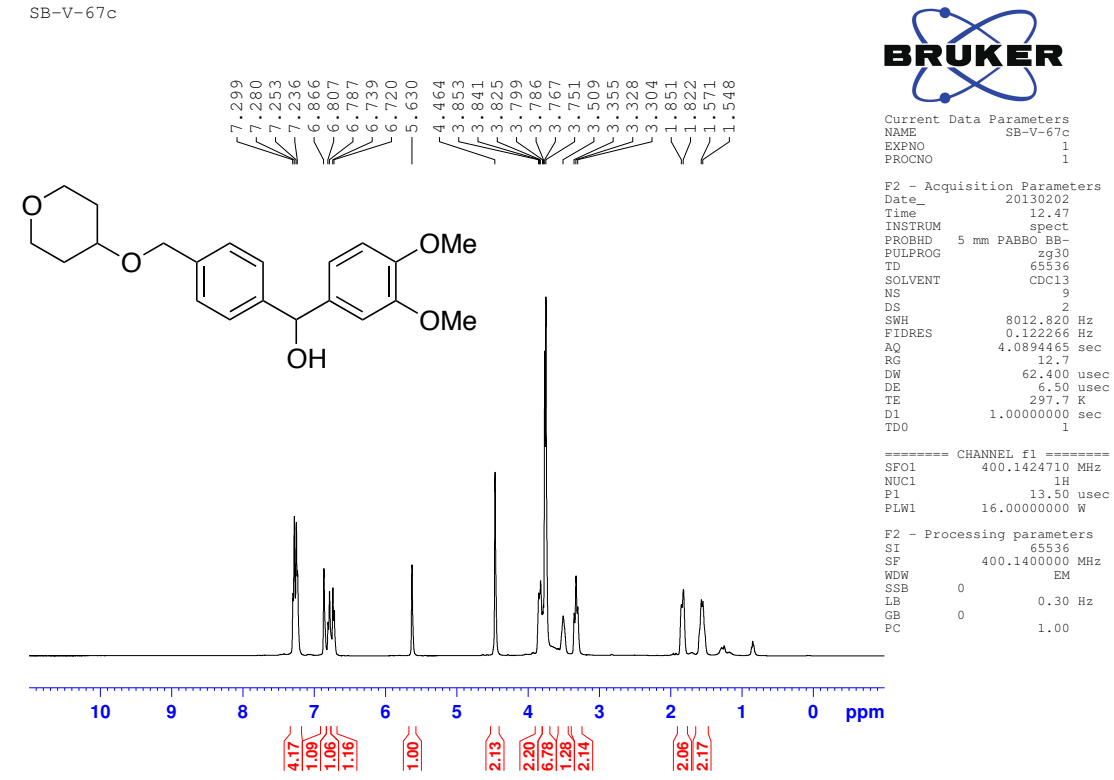
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
57 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 O: 1-30

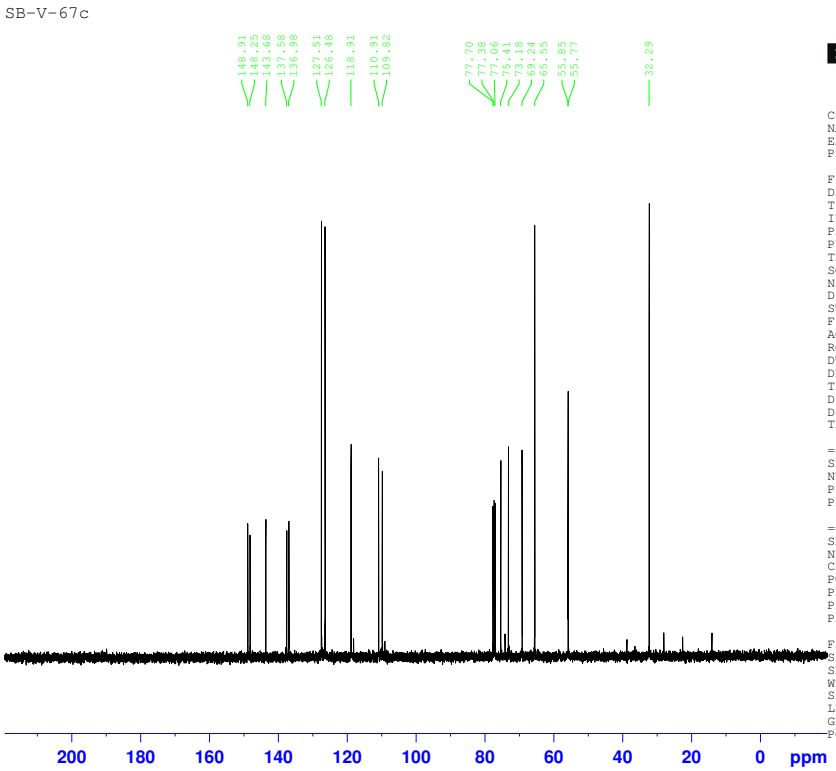
Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
343.1553	343.1545	0.8	2.3	9.5	2.3		C20 H23 O5

(3,4-Dimethoxyphenyl)(4-(((tetrahydro-2*H*-pyran-4-yl)oxy)methyl)phenyl)methanol (10c).



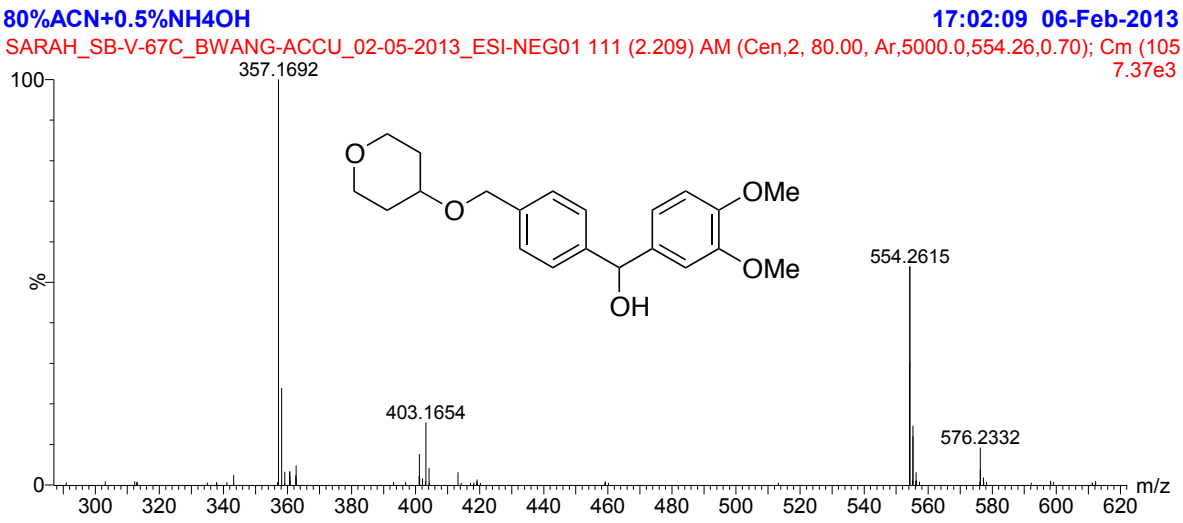
BRUKER

```
Current Data Parameters
NAME              SB-V-67c
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20130202
Time              12.47
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               65536
SOLVENT           CDCl3
NS                   9
DS                   2
SWH            8012.820 Hz
FIDRES         0.122266 Hz
AQ             4.0894465 sec
RG                12.7
DW              62.400 usec
DE               6.50 usec
TE              297.7 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1               1H
P1               13.50 usec
PLW1        16.00000000 W

F2 - Processing parameters
SI               65536
SF          400.1400000 MHz
WDW                EM
SSB       0
LB               0.30 Hz
GB        0
PC               1.00
```



BRUKER

```
Current Data Parameters
NAME              SB-V-67c
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_           20130202
Time              12.50
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT           CDCl3
NS                  17
DS                   4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631488 sec
RG                 203
DW              20.800 usec
DE               6.50 usec
TE              298.5 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1               13C
P1                9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2               1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI               32768
SF          100.6152830 MHz
WDW                EM
SSB       0
LB               1.00 Hz
GB        0
PC               1.40
```



Elemental Composition Report

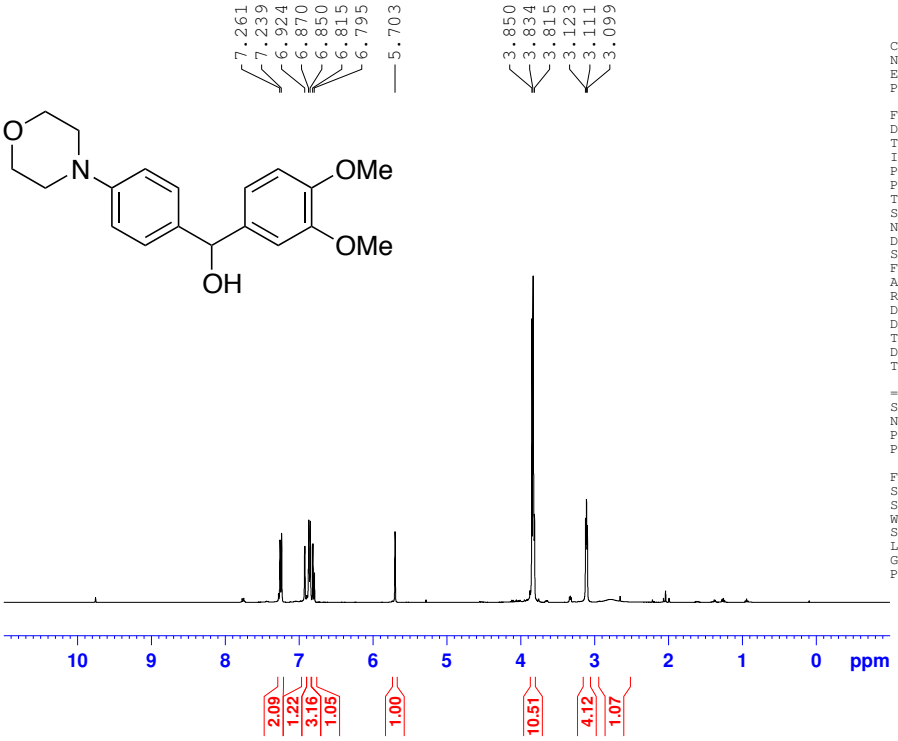
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
66 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 O: 1-30

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
357.1692	357.1702	-1.0	-2.8	9.5	4.0	C21 H25 O5

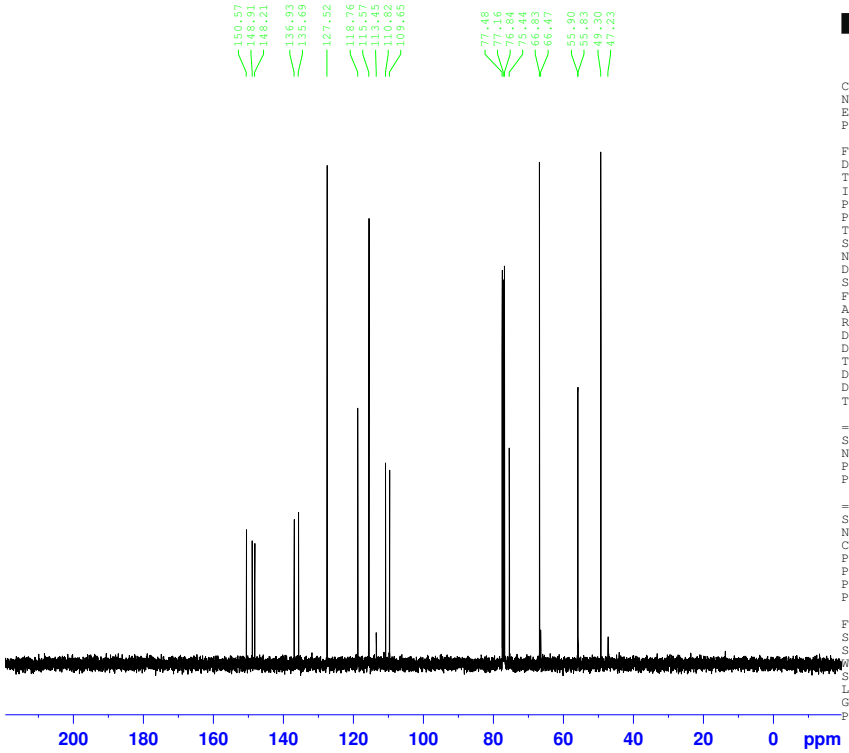
(3,4-dimethoxyphenyl)(4-morpholinophenyl)methanol (12a).

SB-V-102d

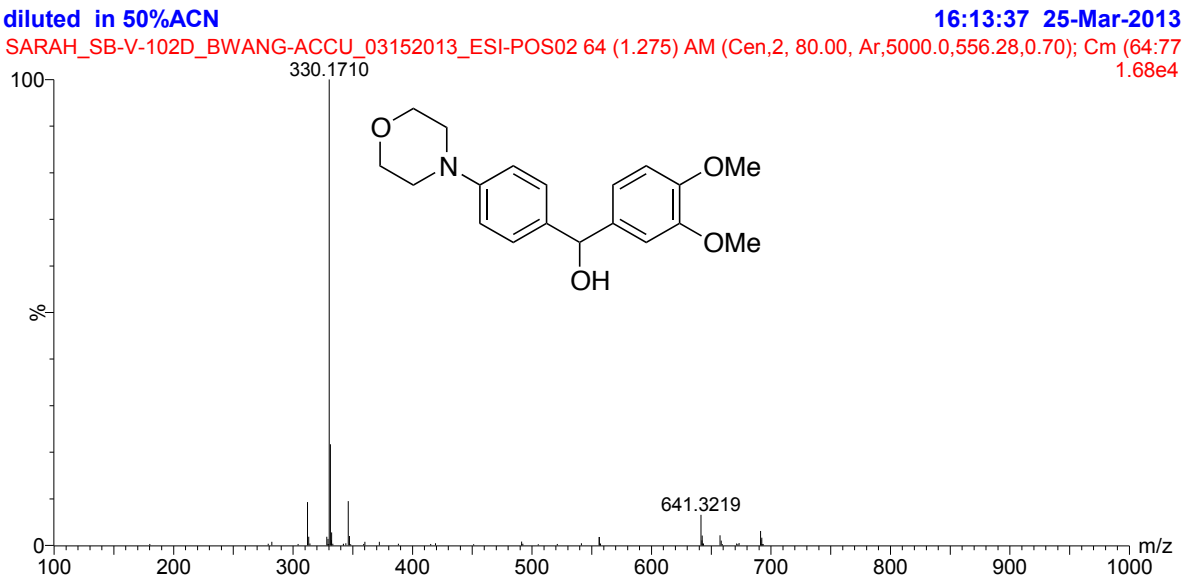



```
Current Data Parameters
NAME                  SB-V-102d
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20130311
Time                     22.29
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                         13
DS                          2
SWH                  8012.820 Hz
FIDRES               0.122266 Hz
AQ                   4.0894465 sec
RG                        28.5
DW                      62.400 usec
DE                       6.50 usec
TE                      294.0 K
D1                   1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1                400.1424710 MHz
NUC1                        1H
P1                       13.50 usec
PLW1                16.00000000 W

F2 - Processing parameters
SI                          65536
SF                  400.1400000 MHz
WDW                            EM
SSB                 0
LB                       0.30 Hz
GB                  0
PC                       1.00
```

SB-V-102d




```
Current Data Parameters
NAME                  SB-V-102d
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20130311
Time                     22.34
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                 CDCl3
NS                         29
DS                          4
SWH                 24038.461 Hz
FIDRES               0.366798 Hz
AQ                   1.3631488 sec
RG                        203
DW                      20.800 usec
DE                       6.50 usec
TE                      294.6 K
D1                   2.00000000 sec
D11                  0.03000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1                100.6253441 MHz
NUC1                        13C
P1                       9.00 usec
PLW1                62.00000000 W

======== CHANNEL f2 ========
SFO2                400.1416006 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                   90.00 usec
PLW2                16.00000000 W
PLW12                0.36000001 W
PLW13                0.29159999 W

F2 - Processing parameters
SI                          32768
SF                  100.6152830 MHz
WDW                            EM
SSB                 0
LB                       1.00 Hz
GB                  0
PC                       1.40
```



Elemental Composition Report

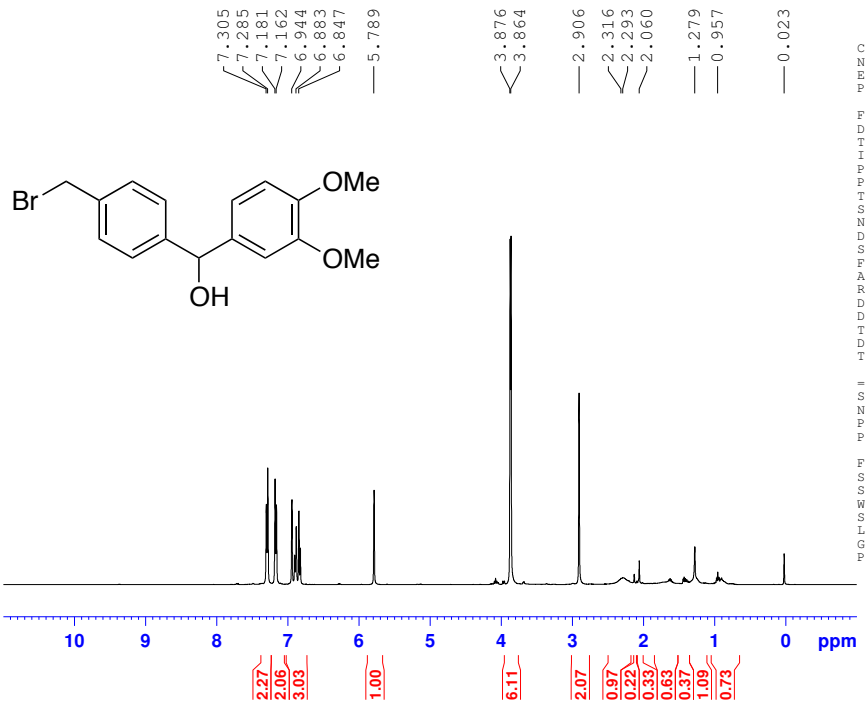
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
540 formula(e) evaluated with 5 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 N: 1-30 O: 1-60

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
330.1710	330.1705	0.5	1.5	8.5	5.0		C19 H24 N O4

(4-(Bromomethyl)phenyl)(3,4-dimethoxyphenyl)methanol (12b)

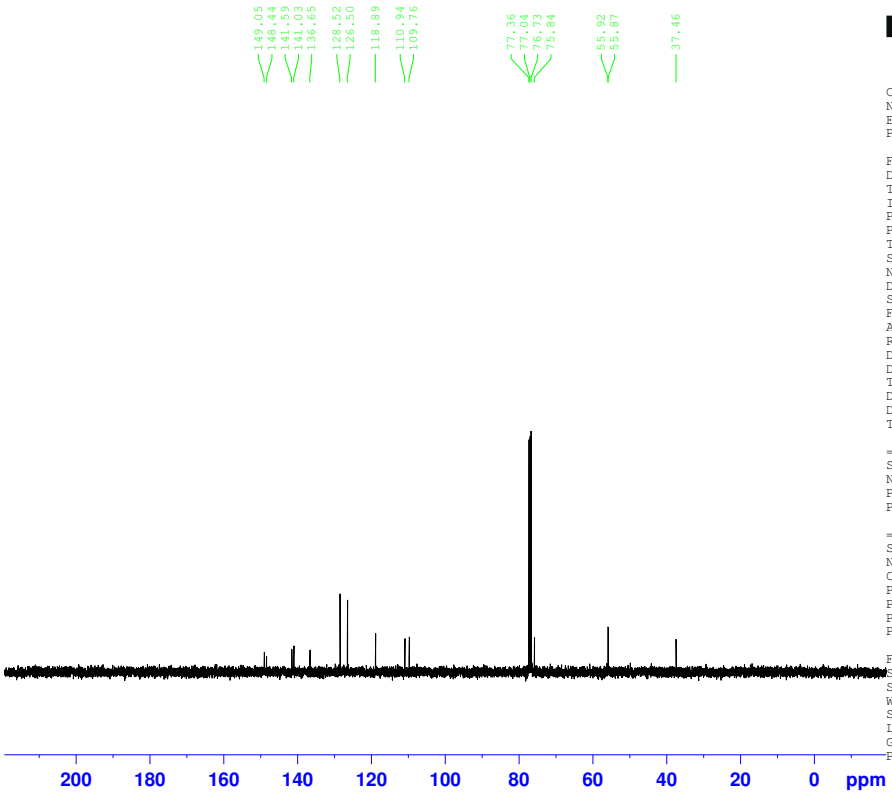
SB-V-52



BRUKER

```
Current Data Parameters
NAME                  SB-V-52
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20121212
Time                  16.10
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8012.820 Hz
FIDRES                0.122266 Hz
AQ                 4.0894465 sec
RG                      101
DW                    62.400 usec
DE                     6.50 usec
TE                    298.0 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1             400.1424710 MHz
NUC1                       1H
P1                      13.50 usec
PLW1              16.00000000 W

F2 - Processing parameters
SI                        65536
SF               400.1400000 MHz
WDW                         EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

SB-V-52

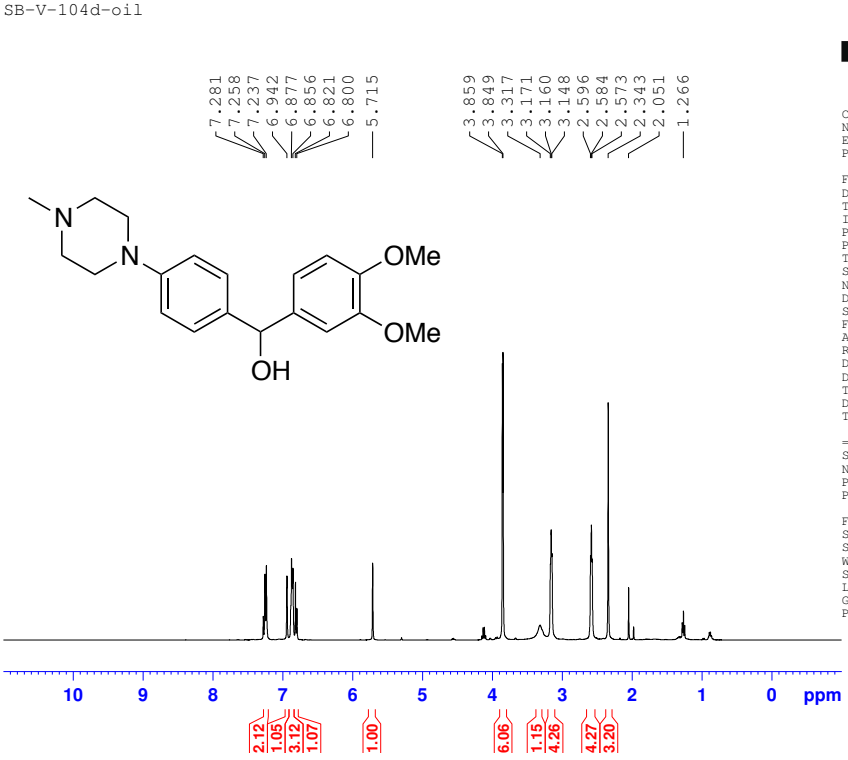


BRUKER

```
Current Data Parameters
NAME                  SB-V-52
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20121212
Time                  16.13
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       18
DS                        4
SWH               24038.461 Hz
FIDRES                0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                    20.800 usec
DE                     6.50 usec
TE                    298.5 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1             100.6253441 MHz
NUC1                       13C
P1                      9.00 usec
PLW1              62.00000000 W

======== CHANNEL f2 ========
SFO2             400.1416006 MHz
NUC2                       1H
CPDPRG[2             waltz16
PCPD2                  90.00 usec
PLW2              16.00000000 W
PLW12              0.36000001 W
PLW13              0.29159999 W

F2 - Processing parameters
SI                        32768
SF               100.6152830 MHz
WDW                         EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```

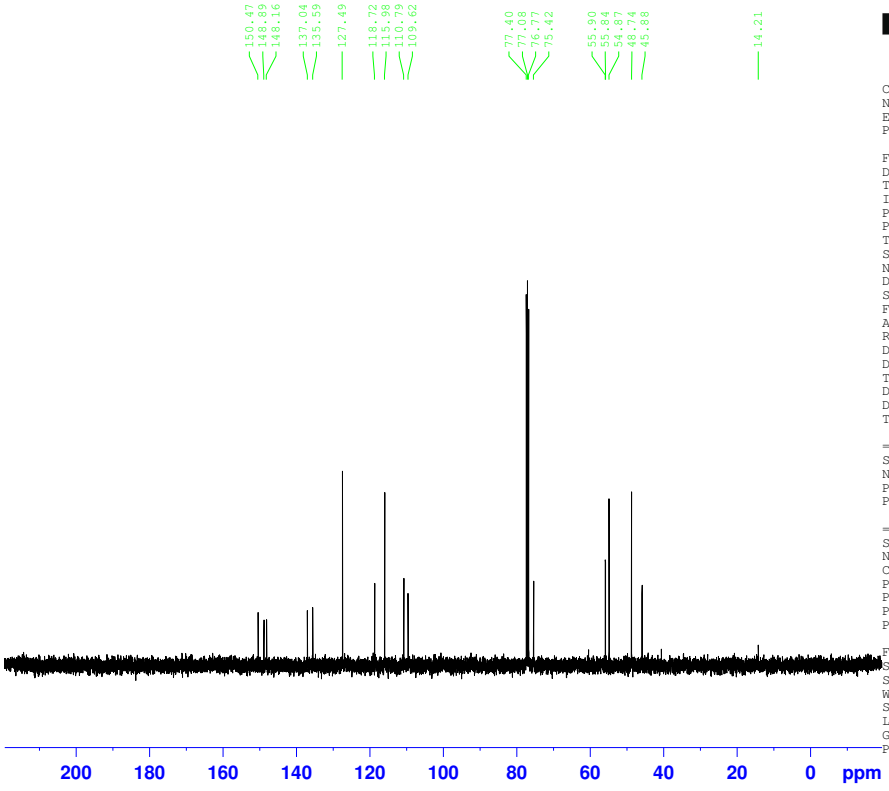
(3,4-dimethoxyphenyl)(4-(4-methylpiperazin-1-yl)phenyl)methanol (12c)

SB-V-104d-oil




```
Current Data Parameters
NAME       SB-V-104d-oil
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130322
Time              13.22
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH            8012.820 Hz
FIDRES         0.122266 Hz
AQ             4.0894465 sec
RG                 50.8
DW               62.400 usec
DE                6.50 usec
TE                293.8 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                 1H
P1                13.50 usec
PLW1        16.00000000 W

F2 - Processing parameters
SI                65536
SF           400.1400000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

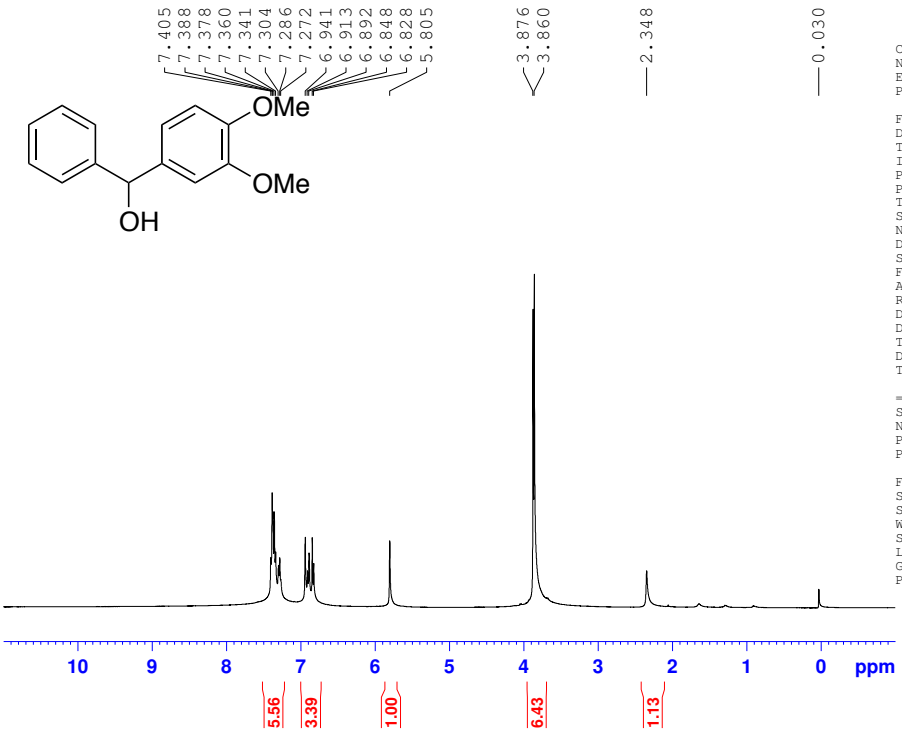
SB-V-104d-oil




```
Current Data Parameters
NAME       SB-V-104d-oil
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130322
Time              13.24
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                   25
DS                    4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631488 sec
RG                  203
DW               20.800 usec
DE                6.50 usec
TE                294.5 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                 13C
P1                9.00 usec
PLW1        62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W

F2 - Processing parameters
SI                32768
SF           100.6152830 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

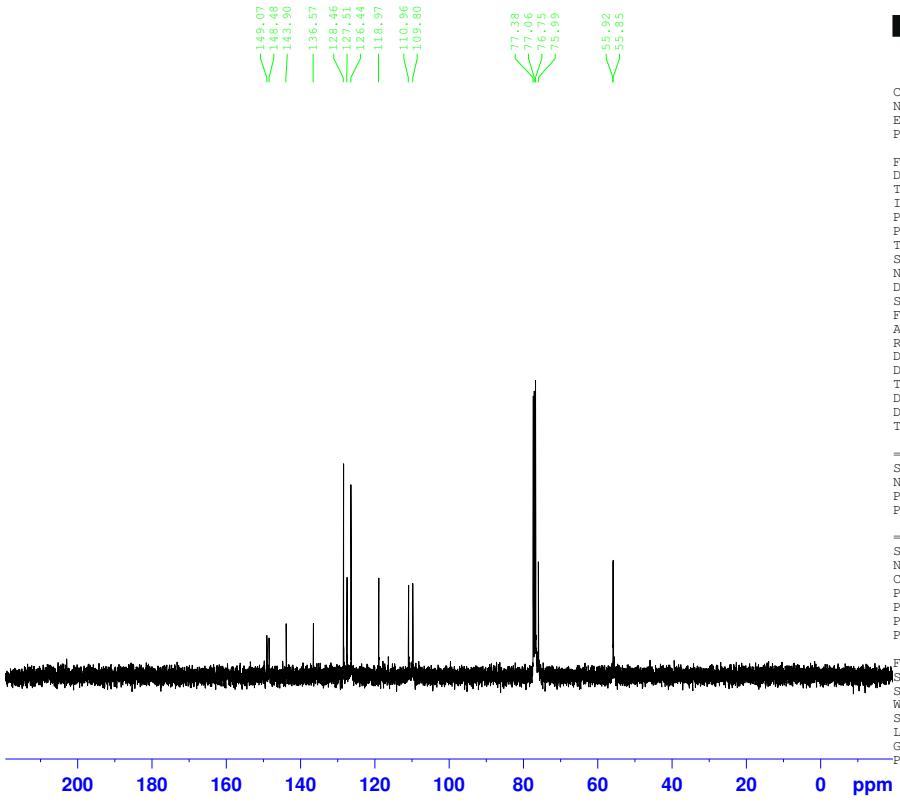
(3,4-Dimethoxyphenyl)(phenyl)methanol (15a)

SB-V-46c

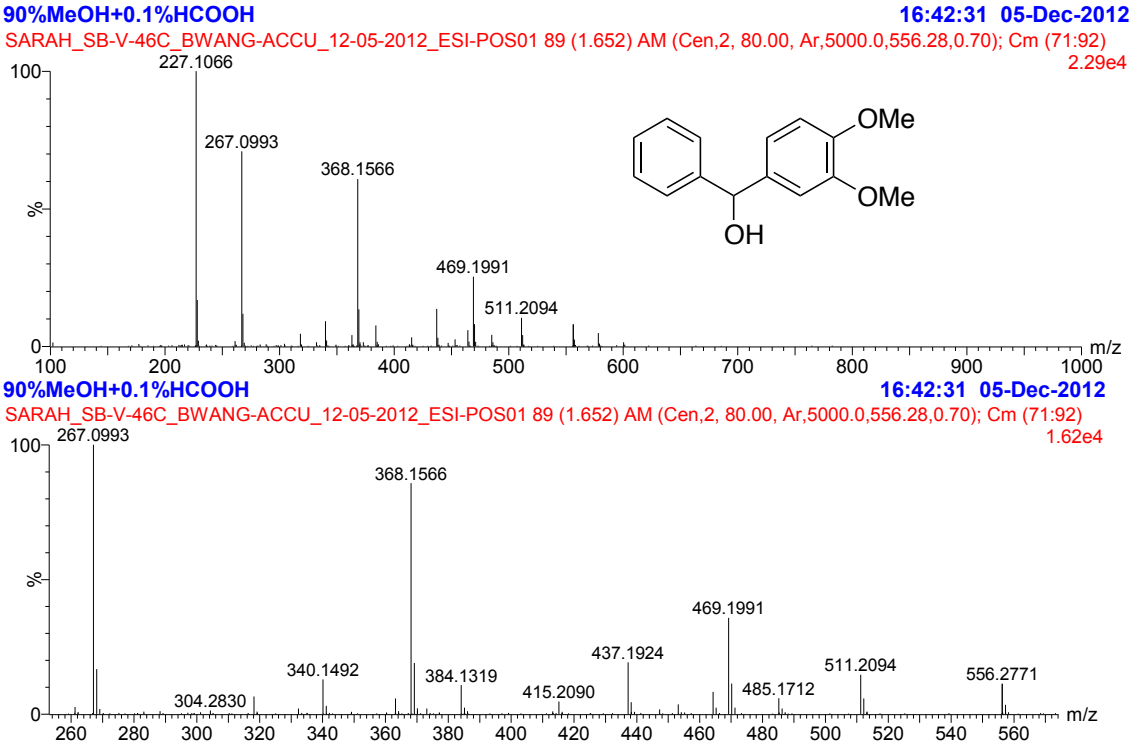



```
Current Data Parameters
NAME            SB-V-46c
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121205
Time               14.12
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                 90.5
DW                62.400 usec
DE                 6.50 usec
TE                298.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1        16.00000000 W

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-V-46c




```
Current Data Parameters
NAME            SB-V-46c
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121205
Time               14.15
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                   63
DS                    4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.4 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                   13C
P1                 9.00 usec
PLW1        62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



Elemental Composition Report

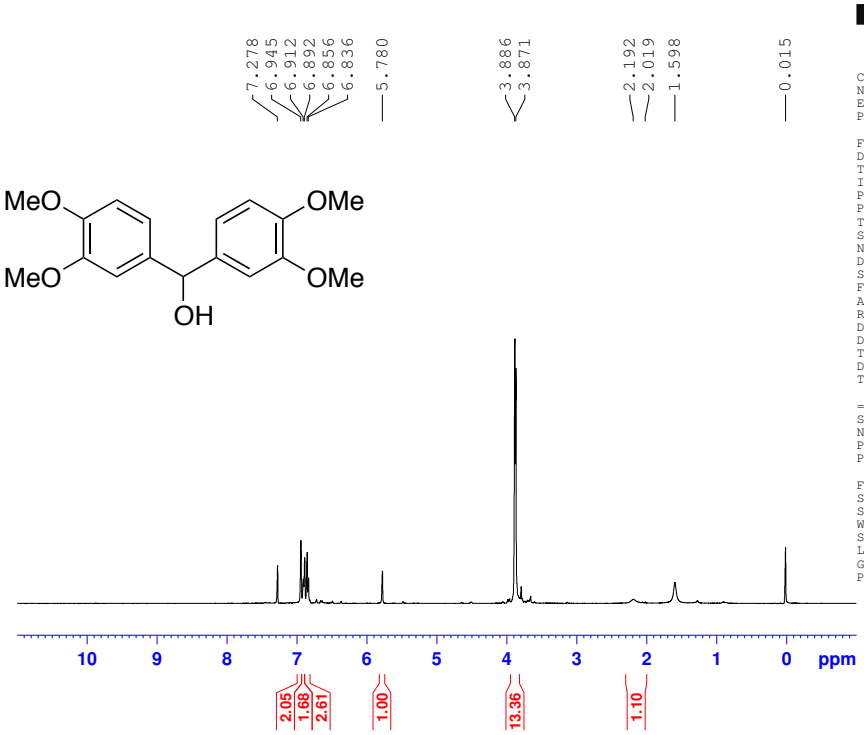
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
58 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 O: 1-30 Na: 1-2

Minimum:			-1.5			
Maximum:		5.0	5.0		50.0	
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
267.0993	267.0997	-0.4	-1.5	7.5	1.2	C15 H16 O3 Na

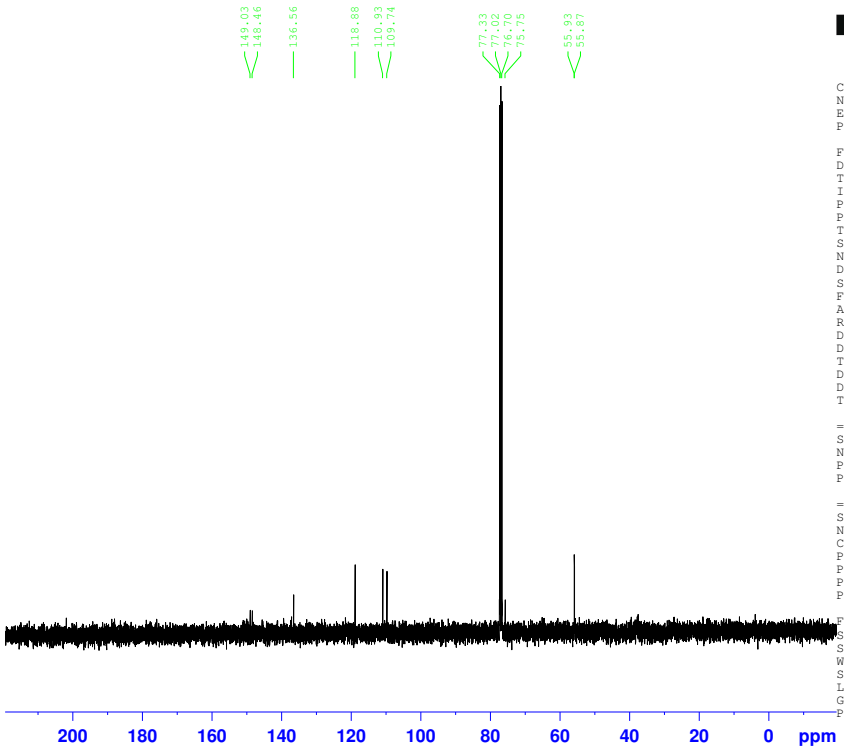
(3,4-Dimethoxyphenyl)(3,4-dimethoxyphenyl)methanol (15b)

SB-V-47c

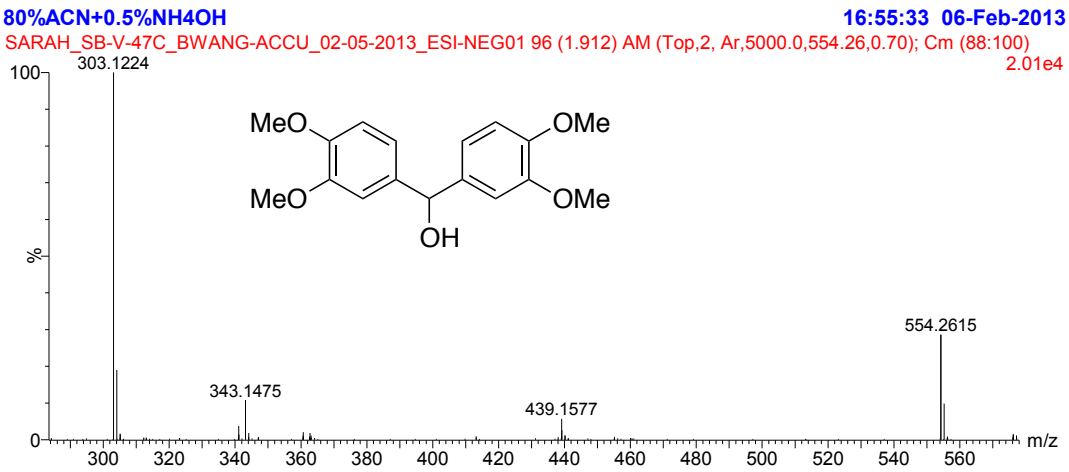



```
Current Data Parameters
NAME                  SB-V-47c
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20121212
Time                   16.26
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        10
DS                         2
SWH                 8012.820 Hz
FIDRES              0.122266 Hz
AQ                  4.0894465 sec
RG                       203
DW                    62.400 usec
DE                     6.50 usec
TE                    298.0 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1              400.1424710 MHz
NUC1                        1H
P1                       13.50 usec
PLW1              16.00000000 W

F2 - Processing parameters
SI                         65536
SF                400.1400000 MHz
WDW                           EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
```

SB-V-47c




```
Current Data Parameters
NAME                  SB-V-47c
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20121212
Time                   17.02
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                     65536
SOLVENT                CDCl3
NS                        69
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                       203
DW                    20.800 usec
DE                     6.50 usec
TE                    298.5 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1              100.6253441 MHz
NUC1                       13C
P1                        9.00 usec
PLW1              62.00000000 W

======== CHANNEL f2 ========
SFO2              400.1416006 MHz
NUC2                        1H
CPDPRG[2              waltz16
PCPD2                    90.00 usec
PLW2              16.00000000 W
PLW12              0.36000001 W
PLW13              0.29159999 W

F2 - Processing parameters
SI                         32768
SF                100.6152830 MHz
WDW                           EM
SSB          0
LB                        1.00 Hz
GB           0
PC                        1.40
```



Elemental Composition Report

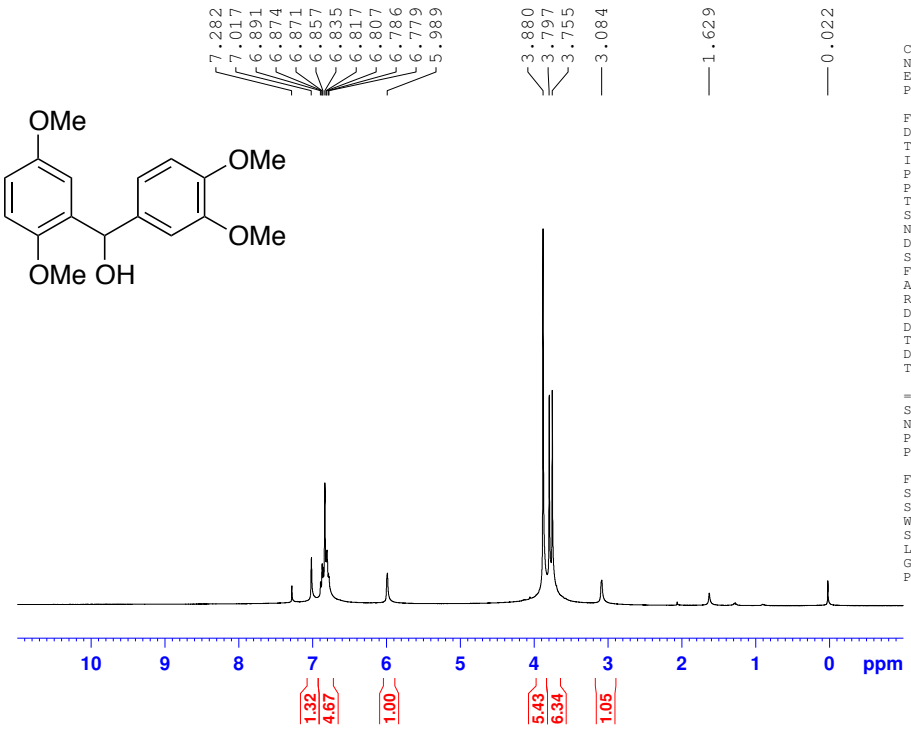
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
46 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 O: 1-30

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
303.1224	303.1232	-0.8	-2.6	8.5	131.7	C17 H19 O5

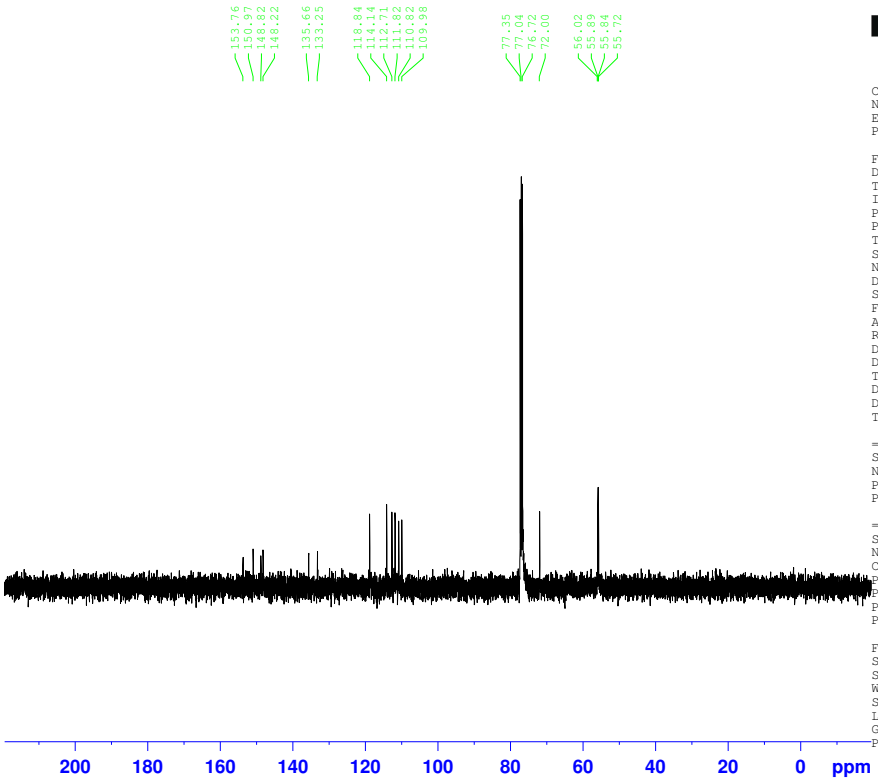
(2,5-Dimethoxyphenyl)(3,4-dimethoxyphenyl)methanol (15c)

SB-V-48d

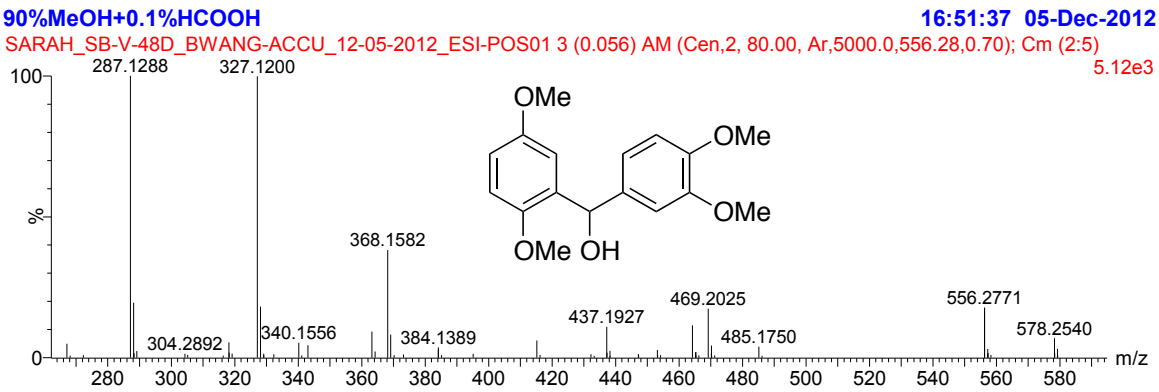



```
Current Data Parameters
NAME              SB-V-48d
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_            20121205
Time                14.22
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDC13
NS                     16
DS                      2
SWH              8012.820 Hz
FIDRES           0.122266 Hz
AQ               4.0894465 sec
RG                   90.5
DW                 62.400 usec
DE                  6.50 usec
TE                 297.8 K
D1              1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                    1H
P1                  13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                  65536
SF           400.1400000 MHz
WDW                    EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

SB-V-48d




```
Current Data Parameters
NAME              SB-V-48d
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_            20121205
Time                14.24
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                  65536
SOLVENT             CDC13
NS                     71
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631488 sec
RG                    203
DW                 20.800 usec
DE                  6.50 usec
TE                 298.5 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                   13C
P1                  9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                  32768
SF           100.6152830 MHz
WDW                    EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



Elemental Composition Report

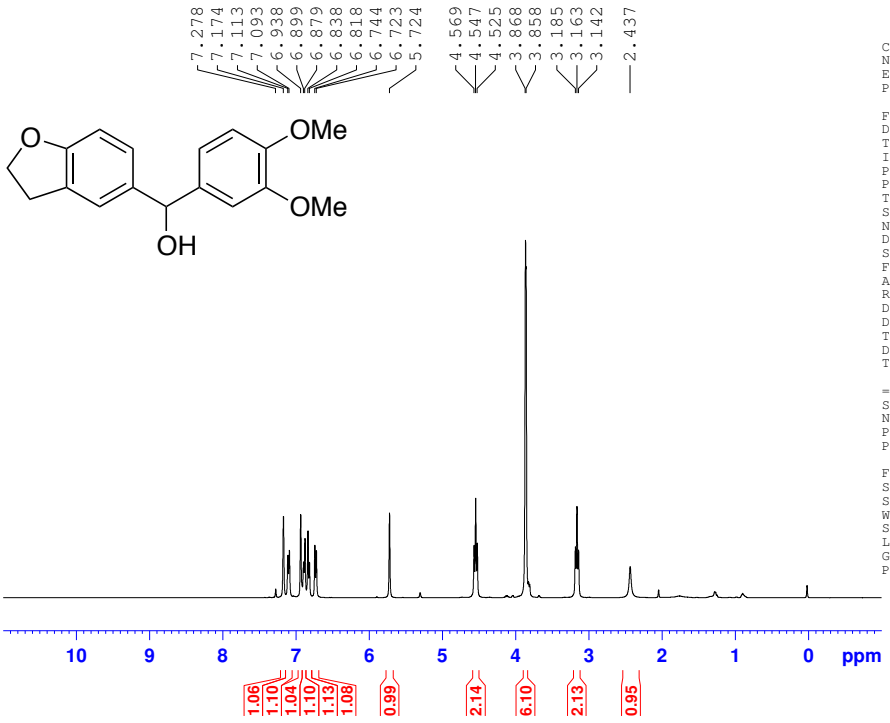
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
85 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 O: 1-30 Na: 1-2

Minimum:			-1.5			
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
327.1200	327.1208	-0.8	-2.4	7.5	42.4	C17 H20 O5 Na

(2,3-Dihydrobenzofuran-5-yl)(3,4-dimethoxyphenyl)methanol (15d)

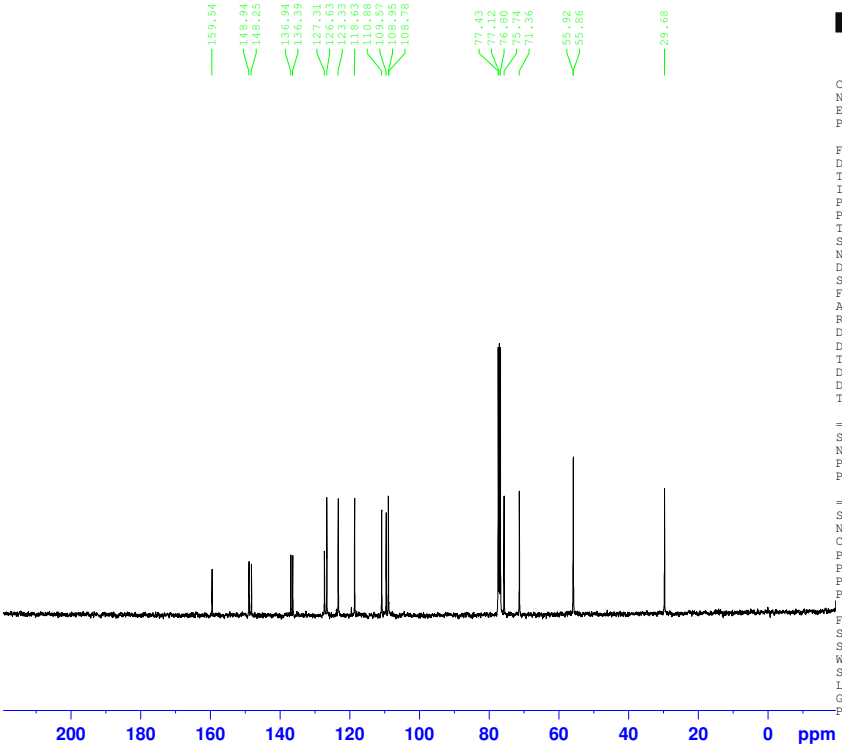
SB-V-34cR



BRUKER

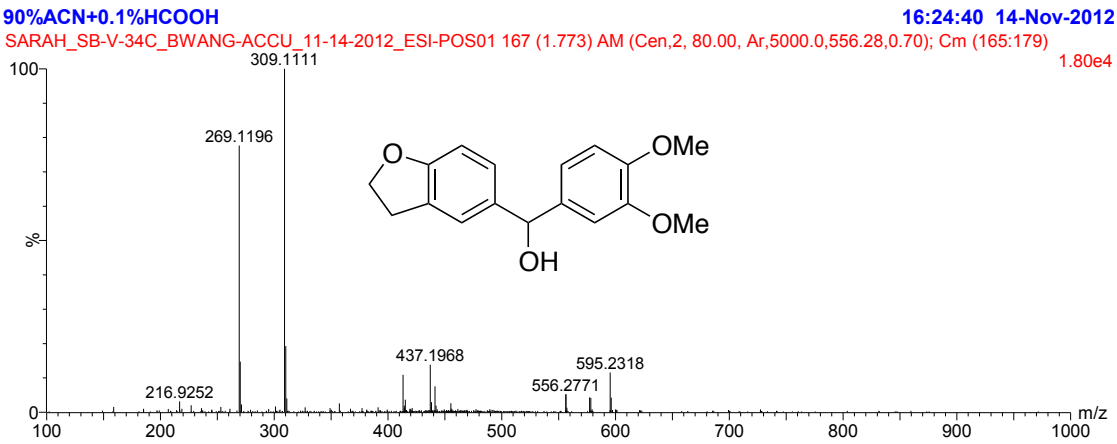
```
Current Data Parameters
NAME          SB-V-34cR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20121113
Time              15.08
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8012.820 Hz
FIDRES         0.122266 Hz
AQ             4.0894465 sec
RG                   64
DW               62.400 usec
DE                6.50 usec
TE                293.5 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                65536
SF           400.1400000 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.00
```

SB-V-34cR



BRUKER

```
Current Data Parameters
NAME          SB-V-34cR
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121113
Time              15.19
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  147
DS                    4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631488 sec
RG                  203
DW               20.800 usec
DE                6.50 usec
TE                294.8 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                32768
SF           100.6152830 MHz
WDW                  EM
SSB       0
LB                5.00 Hz
GB        0
PC                1.40
```



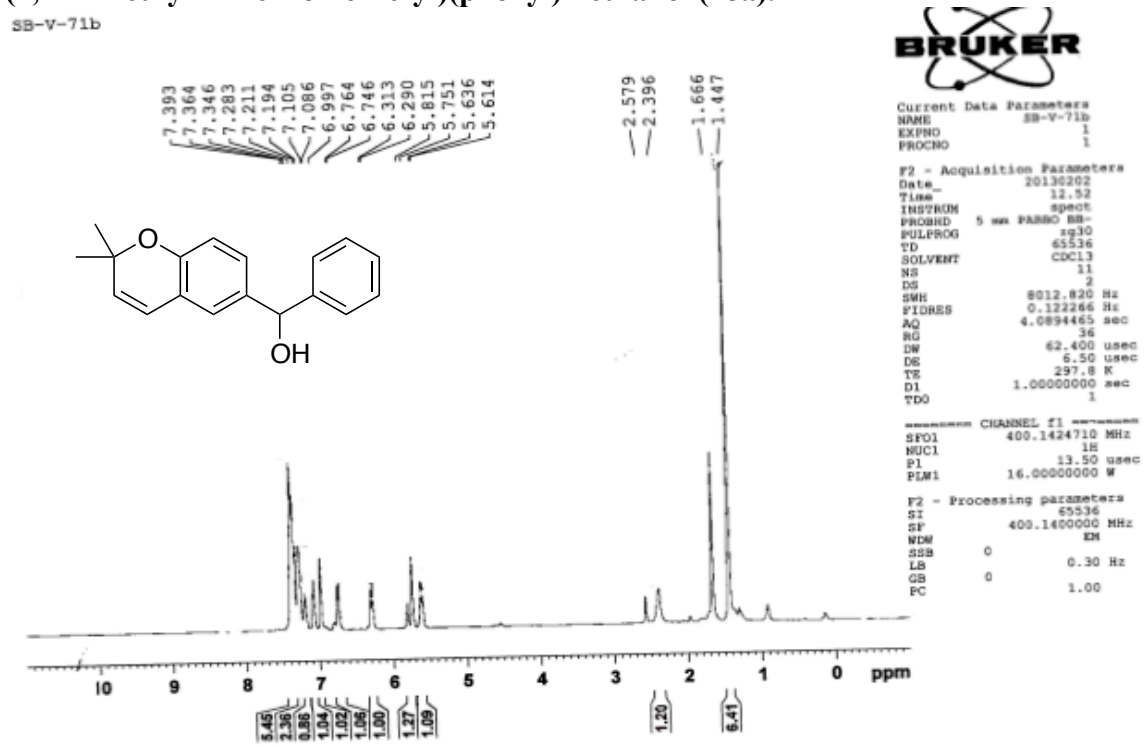
Elemental Composition Report

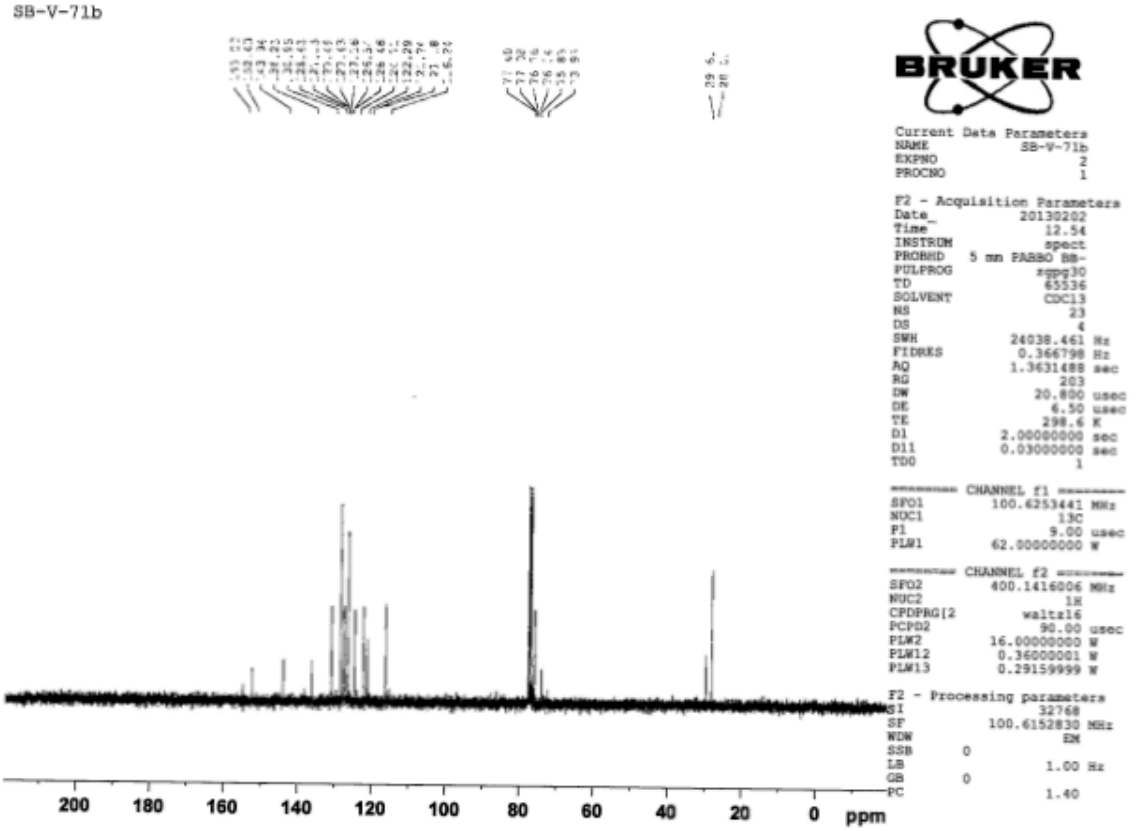
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
76 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 O: 1-30 Na: 1-2

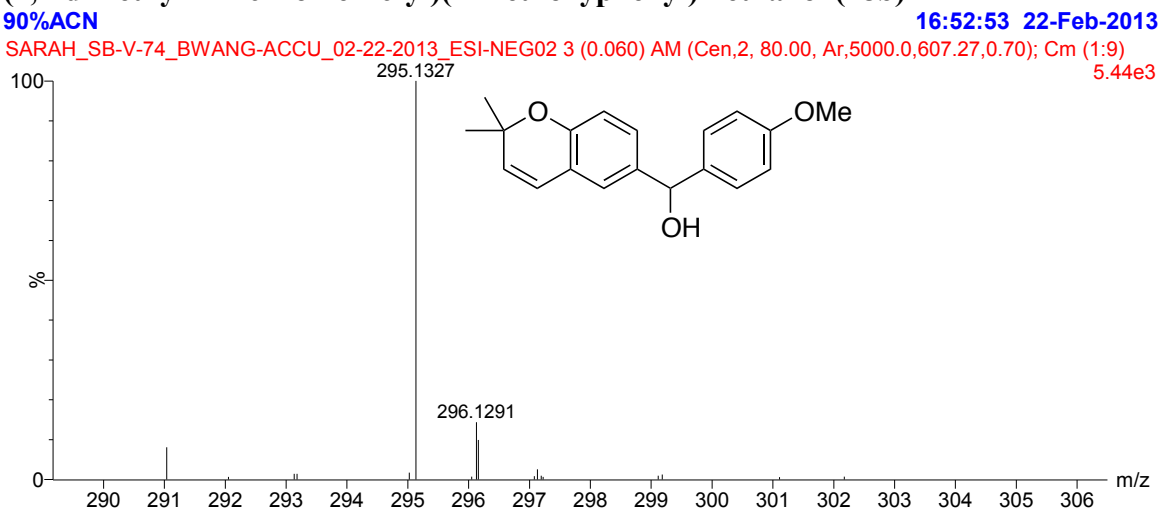
Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
309.1111	309.1103	0.8	2.6	8.5	46.0		C17 H18 O4 Na

(2,2-Dimethyl-2*H*-chromen-6-yl)(phenyl)methanol (18a).





(2,2-dimethyl-2*H*-chromen-6-yl)(4-methoxyphenyl)methanol (18b)



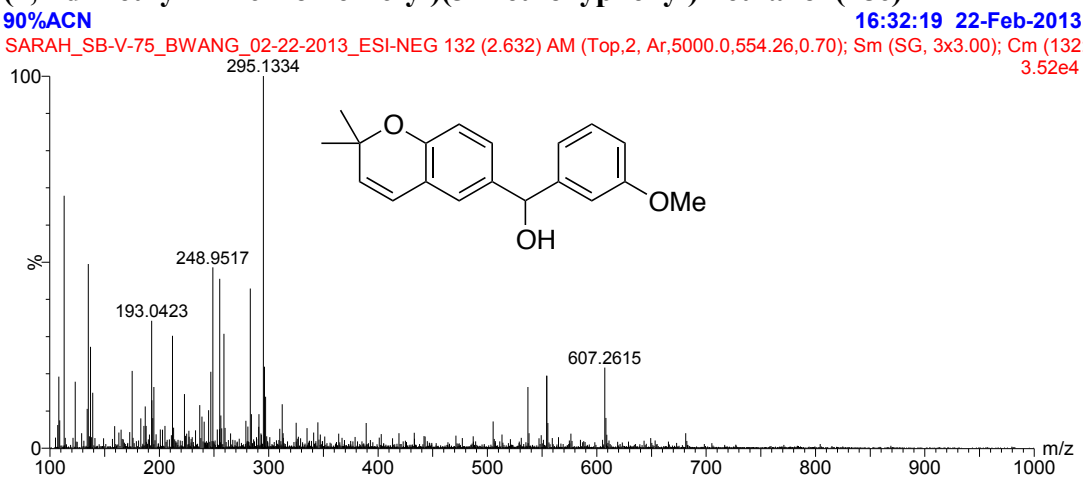
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
44 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-150 H: 1-150 O: 1-30

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT Formula
295.1327	295.1334	-0.7	-2.4	10.5	76.3	C19 H19 O3

(2,2-dimethyl-2*H*-chromen-6-yl)(3-methoxyphenyl)methanol (18c)



Elemental Composition Report

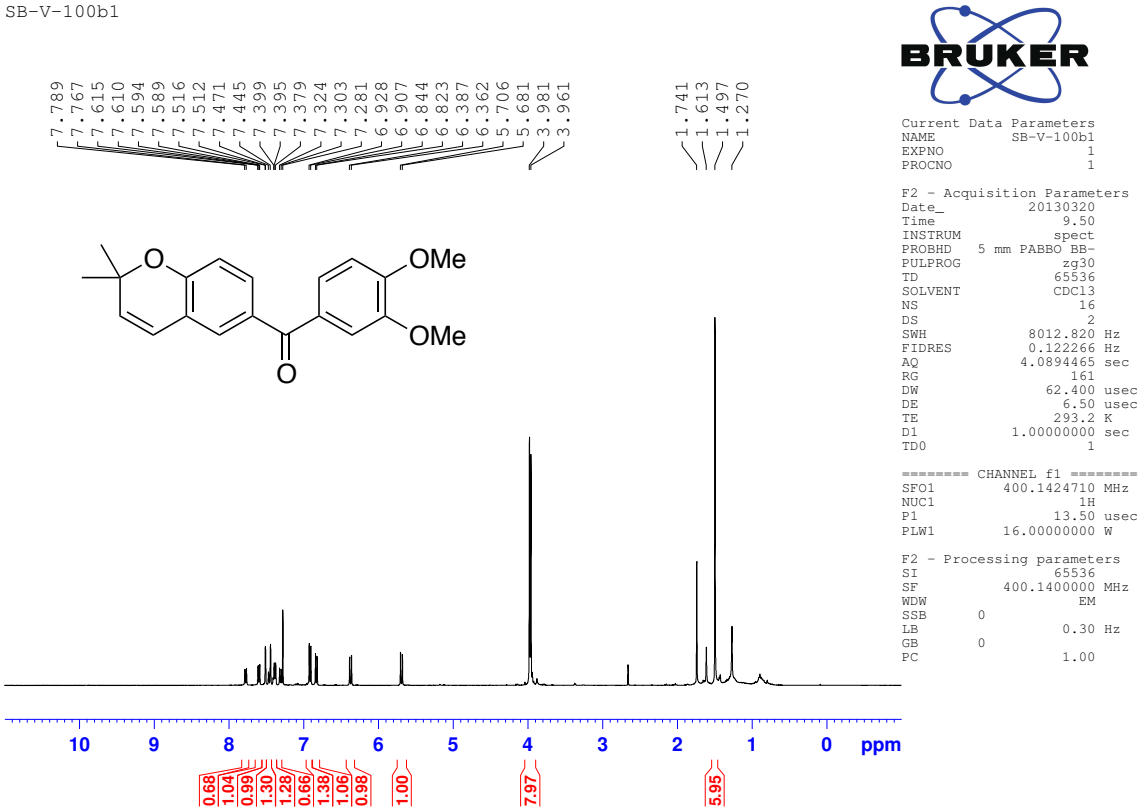
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
44 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-150 H: 1-150 O: 1-30

Minimum:			-1.5			
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
295.1334	295.1334	0.0	0.0	10.5		C19 H19 O3

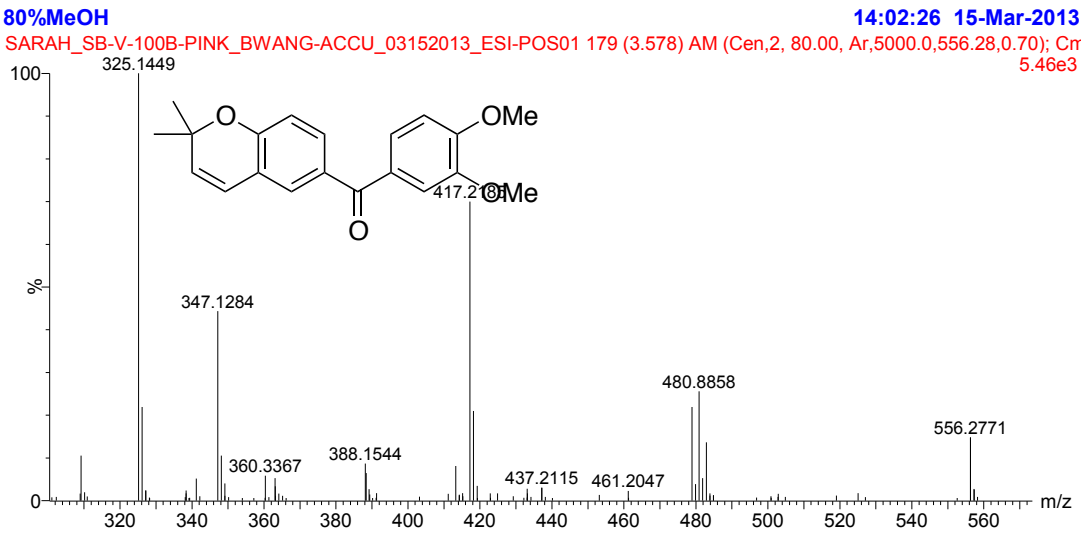
(3,4-dimethoxyphenyl)(2,2-dimethyl-2*H*-chromen-6-yl)methanone (19a)

SB-V-100b1



BRUKER

```
Current Data Parameters
NAME          SB-V-100b1
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130320
Time                9.50
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                   161
DW                62.400 usec
DE                 6.50 usec
TE                293.2 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1        400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1        16.00000000 W

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```



Elemental Composition Report

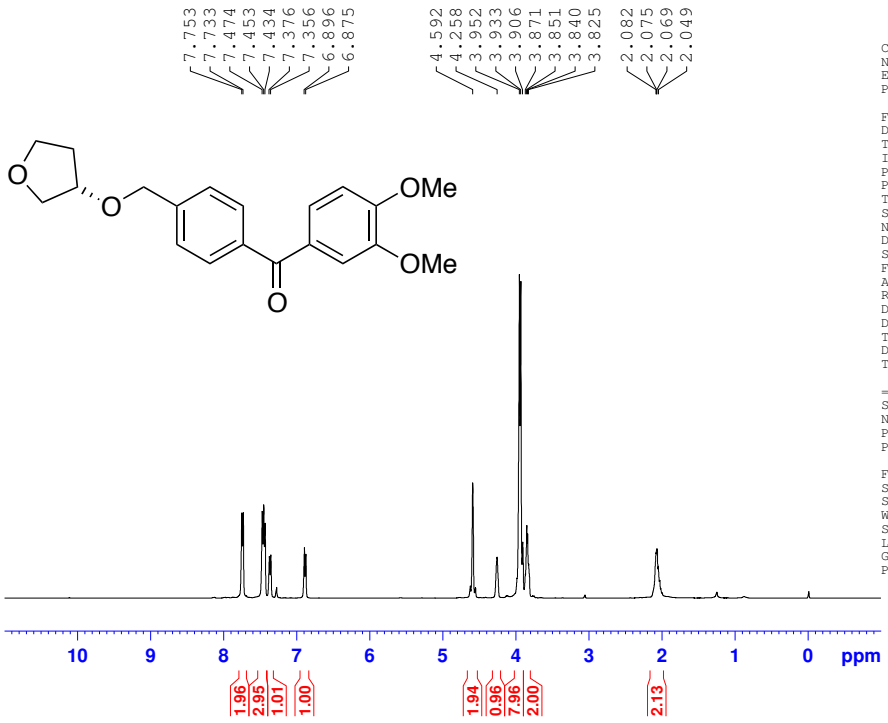
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
56 formula(e) evaluated with 1 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 O: 1-60

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT Formula
325.1449	325.1440	0.9	2.8	10.5	10.3	C20 H21 O4

(*S*)-(3,4-dimethoxyphenyl)(4-(((tetrahydrofuran-3-yl)oxy)methyl)phenyl)methanone (19b)

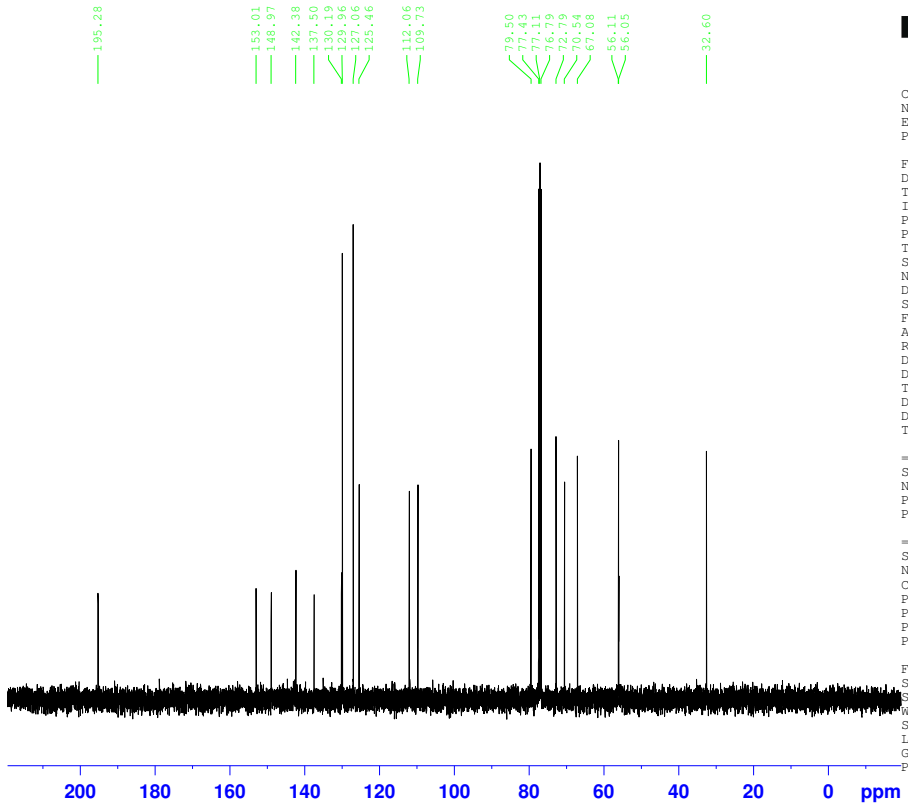
SB-V-101c



BRUKER

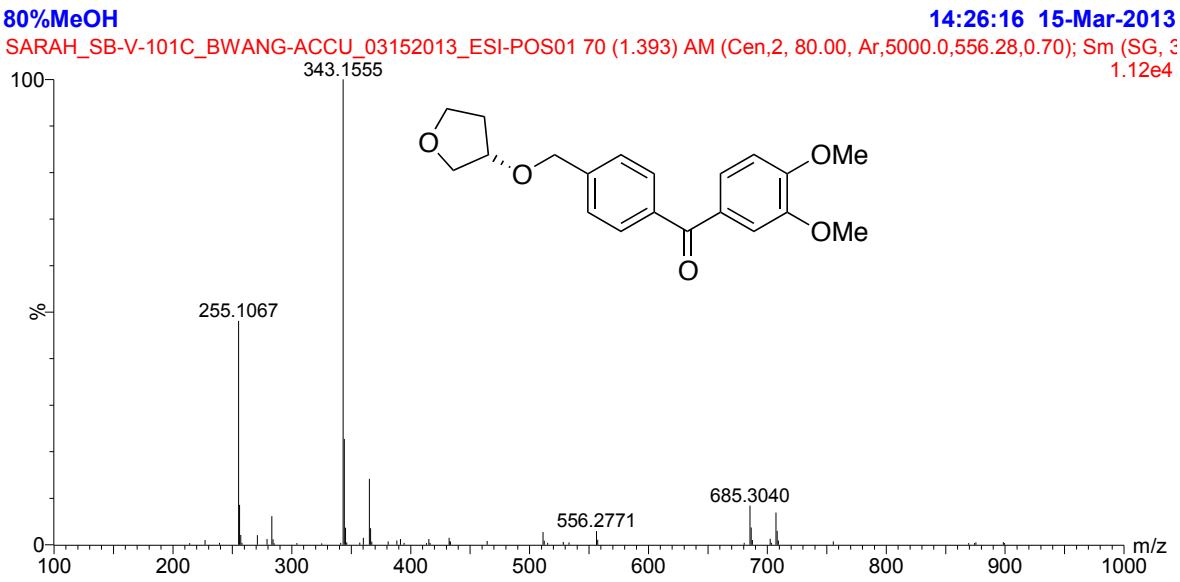
```
Current Data Parameters
NAME          SB-V-101c
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20130312
Time              21.15
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8012.820 Hz
FIDRES         0.122266 Hz
AQ             4.0894465 sec
RG                   57
DW               62.400 usec
DE                6.50 usec
TE                293.7 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                 1H
P1                13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                65536
SF           400.1400000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

SB-V-101c



BRUKER

```
Current Data Parameters
NAME          SB-V-101c
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20130312
Time              21.17
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                   21
DS                    4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631488 sec
RG                  203
DW               20.800 usec
DE                6.50 usec
TE                294.3 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                 13C
P1                9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                32768
SF           100.6152830 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



Elemental Composition Report

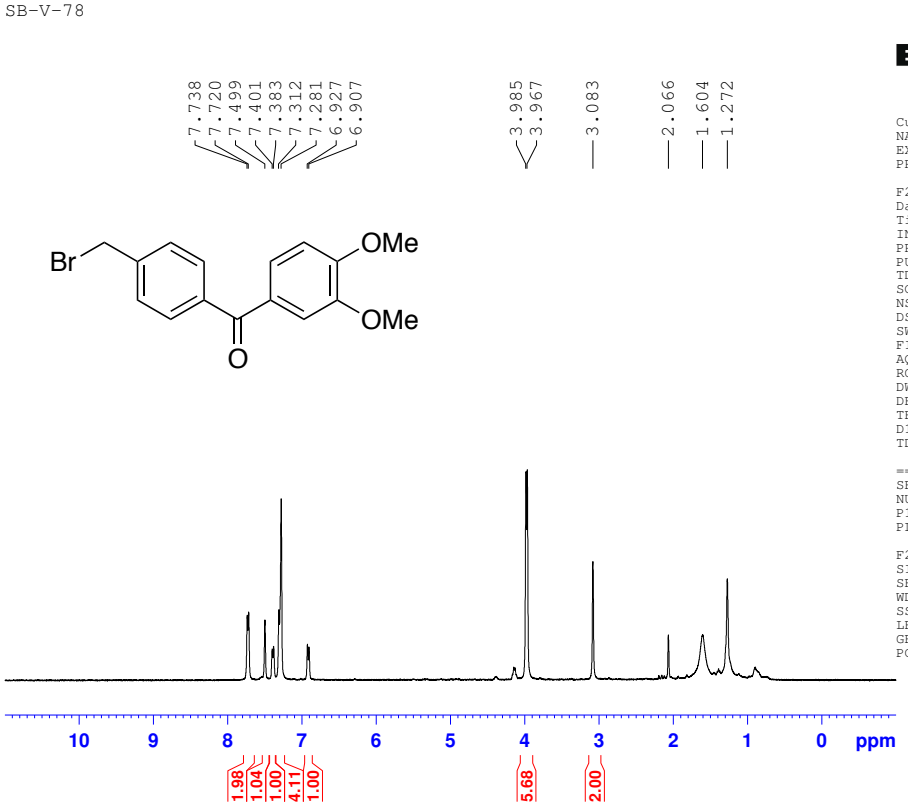
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
57 formula(e) evaluated with 1 results within limits (up to 100 closest results for each mass)
Elements Used:
C: 1-150 H: 1-150 O: 1-60

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
343.1555	343.1545	1.0	2.9	9.5	1.3	C20 H23 O5

(4-(bromomethyl)phenyl)(3,4-dimethoxyphenyl)methanone (19c)

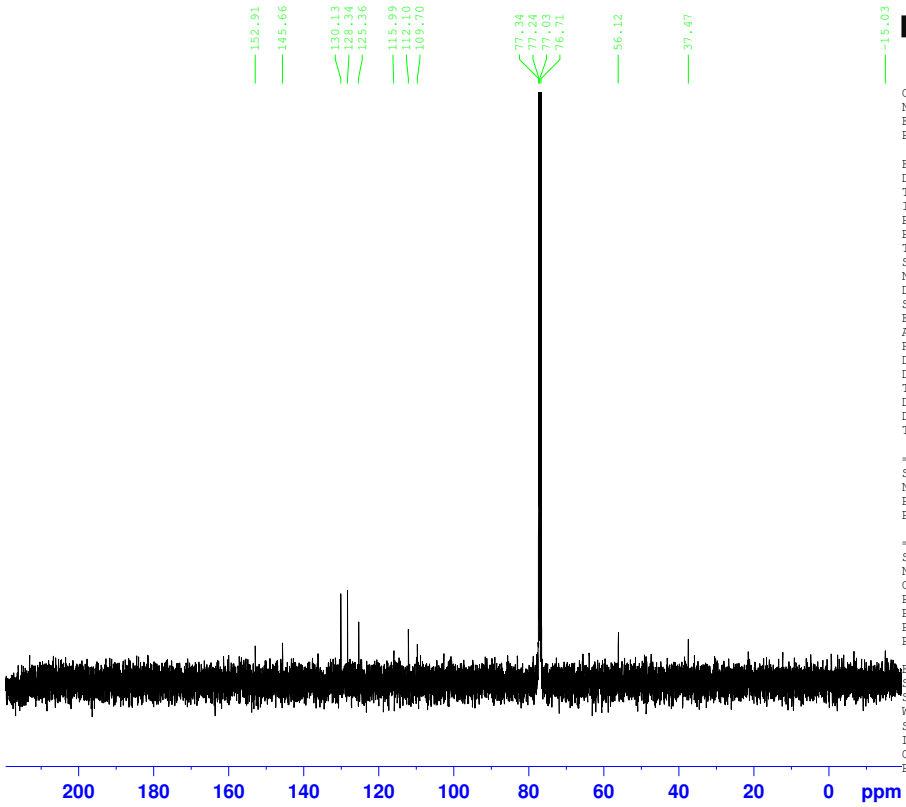
SB-V-78



BRUKER

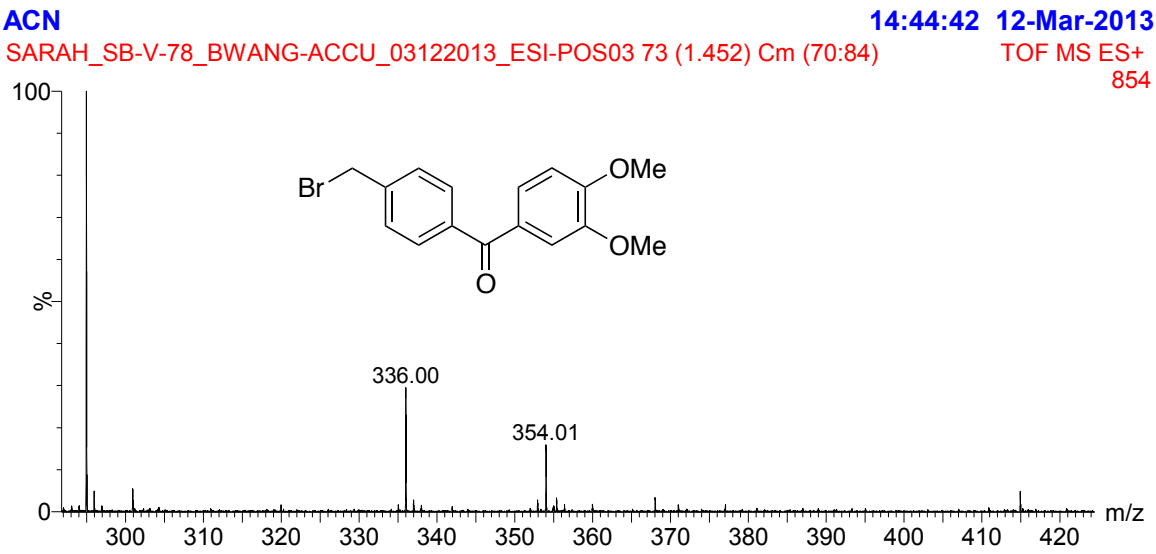
```
Current Data Parameters
NAME                 SB-V-78
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_               20130305
Time                   16.20
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8012.820 Hz
FIDRES            0.122266 Hz
AQ                4.0894465 sec
RG                      203
DW                   62.400 usec
DE                    6.50 usec
TE                   293.4 K
D1              1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1           400.1424710 MHz
NUC1                     1H
P1                    13.50 usec
PLW1           16.00000000 W

F2 - Processing parameters
SI                    65536
SF               400.1400000 MHz
WDW                      EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.00
```

SB-V-78



BRUKER

```
Current Data Parameters
NAME                 SB-V-78
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_               20130305
Time                   16.24
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      200
DS                        4
SWH               24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                      203
DW                   20.800 usec
DE                    6.50 usec
TE                   294.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1           100.6253441 MHz
NUC1                     13C
P1                    9.00 usec
PLW1           62.00000000 W

======== CHANNEL f2 ========
SFO2           400.1416006 MHz
NUC2                     1H
CPDPRG[2          waltz16
PCPD2                90.00 usec
PLW2           16.00000000 W
PLW12           0.36000001 W
PLW13           0.29159999 W

F2 - Processing parameters
SI                    32768
SF               100.6152830 MHz
WDW                      EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.00
```


ACN
14:44:42 12-Mar-2013
SARAH_SB-V-78_BWANG-ACCU_03122013_ESI-POS03 73 (1.452) Cm (70:84)
TOF MS ES+
854
100
%
0
Br
OMe
OMe
O
336.00
354.01
300
310
320
330
340
350
360
370
380
390
400
410
420
m/z

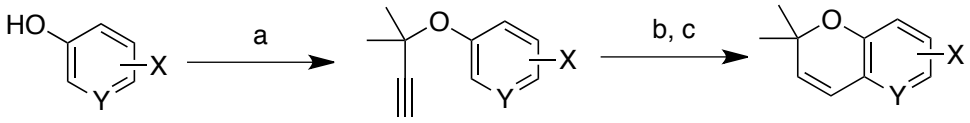
Appendix C: Structural Characterization of Compounds from Chapter 5

General methods and materials

All commercial chemicals were reagent grade, obtained from VWR, Aldrich, and Oakwood Chemicals and were used without further purification unless otherwise indicated. ^{1}H and ^{13}C spectra were obtained on a Bruker 400 NMR spectrometer at 400 and 100 MHz, respectively, in deuterated solvent with TMS as internal reference (δ = 0.00 ppm). For all reactions, analytical grade solvent was used. Anhydrous solvents were used for all moisture-sensitive reactions. High-resolution mass spectra were obtained by the Mass Spectrometry Facilities at Georgia State University on a Waters Micromass Q-Tof (ESI).

Synthesis of aldehyde compounds: Aldehydes were synthesized from either commercially available bromides or aldehydes in 1 to 3 steps (Scheme S1). First, the phenol was alkylated with 3-chloro-3-methylbut-1-yne, then the compound was cyclized at high temperature to give the chromene moiety. The bromide was converted to aldehyde via lithium halogen exchange, followed by formylation with DMF.

Scheme S1. Synthesis of aldehyde compounds[a]



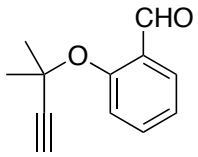
S1 **S2** **S3**
15, 17, 22, 24, 26, 28

X = bromo or aldehyde; Y = C or N. Reagents and conditions: (a); 3-chloro-3-methylbut-1-yne, DBU, ACN, overnight, 0^{o}C to room temperature; (b) reflux in N,N-dimethylaniline, 3 hours; (c) BuLi, DMF, THF -78^{o}C.

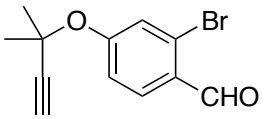
Typical procedure for o-alkylation**:** 1 equivalent of phenol was dissolved in ACN and cooled to 0^{o}C. 2 equivalents of DBU were added, then 2 equivalents of 3-chloro-3-methylbut-1-yne. The reaction was stirred overnight from 0^{o}C to room temperature. The reaction mixture was concentrated, then taken up in ethyl acetate, washed 3 x 1N HCl, 1 x saturated $NaHCO_3$, 1 x brine, dried over $MgSO_4$, and concentrated. Purified by column chromatography.

Typical procedure for pyran ring-closing: The alkyne was refluxed 3 hours in N,N-dimethylaniline. The reaction was taken up in EA, washed 5 x 1 N HCl, 1 x saturated $NaHCO_3$, 1 x brine, dried over $MgSO_4$, and concentrated. Purified by column chromatography.

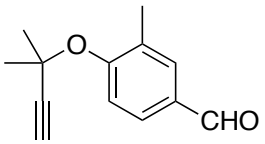
Typical procedure for formylation: 1 equivalent of aryl bromide was dissolved in anhydrous THF under N_2 and cooled to -78^{o}C. 1.4 equivalents of butyl lithium were added. After 30 minutes, 1.4 equivalents of DMF were added and then the reaction stirred for 1 hour. The reaction was then quenched with saturated NH_4Cl, taken up in ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated. Purified by column chromatography.



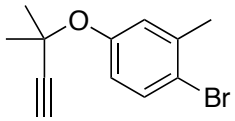
2-((2-Methylbut-3-yn-2-yl)oxy)benzaldehyde (S2b) ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (s, 1H), 8.00-7.98 (d, *J* = 8 Hz, 1H), 7.67-7.66 (m, 2H), 7.28-7.25 (m, 1H), 2.76 (s, 1H), 1.87 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 158.5, 135.0, 128.9, 128.2, 122.9, 120.9, 85.1, 75.6, 74.0, 29.7 ppm. HRMS *m/z* (ESI) calculated for $C_{12}H_{12}O_2Na$ [$(M + Na)^+$] 211.0735, found 211.0734.



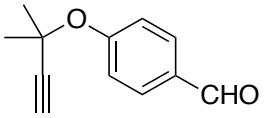
2-Bromo-4-((2-methylbut-3-yn-2-yl)oxy)benzaldehyde (S2c) Yield: 12%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.88-7.88 (d, *J* = 2 Hz, 1H), 7.46-7.46 (d, *J* = 2 Hz, 1H), 6.37-6.34 (d, *J* = 8 Hz, 1H), 5.75-5.73 (d, *J* = 8 Hz, 1H), 1.53 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 155.2, 134.8, 132.1, 130.5, 126.4, 122.3, 121.1, 111.2, 69.5, 28.5 ppm.



3-Methyl-4-((2-methylbut-3-yn-2-yl)oxy)benzaldehyde (S2d) Yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.67-7.63 (m, 3H), 2.67 (s, 1H), 2.22 (s, 3H), 1.72 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 159.6, 131.8, 130.0, 130.0, 129.3, 128.9, 116.5, 85.1, 74.7, 72.3, 29.6, 16.6 ppm.

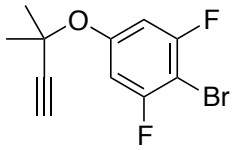


1-Bromo-2-methyl-4-((2-methylbut-3-yn-2-yl)oxy)benzene (S2e) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.45 (m, 1H), 7.15 (s, 1H), 7.05-7.02 (m, 1H), 2.65 (s, 1H), 3.21 (s, 3H), 1.70 (s, 6H) ppm.

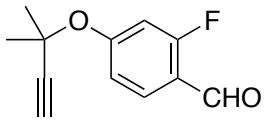


4-((2-Methylbut-3-yn-2-yl)oxy)benzaldehyde (S2j) Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.77-7.75 (d, *J* = 8 Hz, 2H), 7.30-7.27 (d, *J* = 8 Hz, 2H), 2.67 (s, 1H), 1.66 (s, 6H)

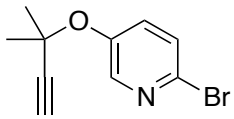
ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 161.1, 131.2, 130.6, 119.4, 84.9, 75.2, 72.4, 29.5 ppm.



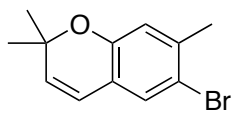
2-Bromo-1,3-difluoro-5-((2-methylbut-3-yn-2-yl)oxy)benzene (S2l) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91-6.82 (m, 2H), 2.68 (s, 1H), 1.58 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 160.9, 158.5, 158.5, 156.4, 156.3, 156.1, 104.8, 104.8, 104.6, 104.5, 90.8, 90.6, 90.3, 84.7, 75.3, 75.2, 73.3, 29.3, 29.3 ppm.

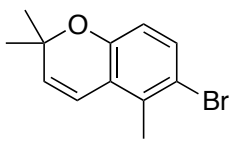


2-fluoro-4-((2-methylbut-3-yn-2-yl)oxy)benzaldehyde (S2m) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.40 (t, J = 8 Hz, 1H), 7.10-7.06 (dd, J = 8, 2 Hz, 1H), 6.93-6.90 (m, 1H), 2.63 (s, 1H), 1.66 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 157.7, 156.2, 156.1, 132.8, 132.8, 118.1, 118.1, 109.1, 109.1, 101.9, 101.7, 85.2, 74.8, 73.0, 29.7, 29.4 ppm.

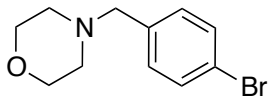


2-Bromo-5-((2-methylbut-3-yn-2-yl)oxy)pyridine (S2n) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.24 (d, J = 2 Hz, 1H), 7.45-7.42 (dd, J = 8, 2 Hz, 1H), 7.37-7.35 (d, J = 8 Hz, 1H), 2.62 (s, 1H), 1.64 (s, 6H) ppm.

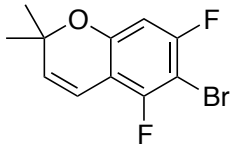




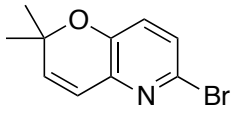
6-bromo-2,2,5-trimethyl-2*H*-chromene with 6-bromo-2,2,7-trimethyl-2*H*-chromene (1:2) (S3e) Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.28 (dd, *J* = 8, 2 Hz, 2H), 7.14 (s, 1H), 6.71 (s, 1H), 6.60-6.55 (dd, *J* = 8, 2 Hz, 2H), 6.27-6.25 (d, *J* = 10 Hz, 1H), 5.72-5.69 (m, 2H), 5.62-5.60 (d, *J* = 10 Hz, 1H), 2.41 (s, 6H), 2.34 (s, 3H), 1.44 (s, 20H) ppm.



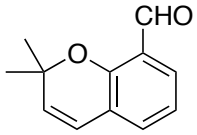
4-(4-bromobenzyl)morpholine (S3i) 500 mg 1-bromo-4-(bromomethyl)benzene (2.0 mmol), 191 mg morpholine (2.2 mmol), and 455 mg K_2CO_3 (3.3 mmol) were dissolved in ACN and stirred overnight at room temperature. The reaction mixture was filtered through celite to give a quantitative yield of a solid (512 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.40 (d, *J* = 8 Hz, 2H), 7.20-7.18 (d, *J* = 8 Hz, 2H), 3.68-3.66 (m, 4H), 3.41 (s, 2H), 2.40 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 131.4, 130.8, 120.9, 66.9, 62.6, 53.6 ppm. HRMS *m/z* (ESI) calculated for $C_{11}H_{15}NOBr$ [$(M + H)^+$] 256.0337, found 256.0346.



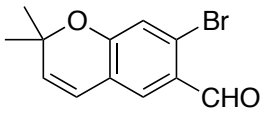
6-bromo-5,7-difluoro-2,2-dimethyl-2*H*-chromene (S3l) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91-6.89 (d, *J* = 8 Hz, 1H), 6.88 (s, 1H) 5.66-5.63 (d, *J* = 10 Hz, 1H), 1.44 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 160.5, 158.1, 158.0, 156.5, 156.5, 154.1, 154.0, 153.7, 153.6, 153.6, 153.5, 130.4, 130.4, 130.4, 114.2, 114.2, 114,2 114.2, 101.2, 101.2, 100.9, 100.9, 88.5, 88.2, 88.0, 76.7, 27.8 ppm.



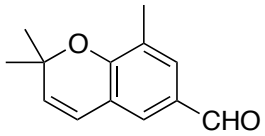
6-bromo-2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridine (S3n) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.14 (d, *J* = 8 Hz, 1H), 692-6.90 (d, *J* = 8 Hz, 1H), 6.47-6.44 (d, *J* = 10 Hz, 1H), 5.89-5.86 (d, *J* = 10 Hz, 1H), 1.46 (s, 6H) ppm.



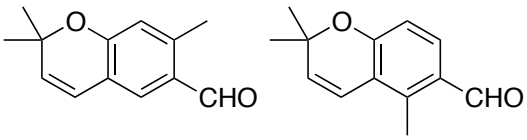
2,2-Dimethyl-2*H*-chromene-8-carbaldehyde (15b) ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (s, 1H), 7.67-7.65 (d, *J* = 8 Hz, 1H), 7.20-7.18 (d, *J* = 8 Hz, 1H), 6.93-6.89 (t, *J* = 7.6 Hz, 1H), 6.38-6.36 (d, *J* = 8 Hz, 1H), 5.73-5.71 (d, *J* = 8 Hz, 1H), 1.52 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.4, 156.2, 132.1, 131.3, 127.1, 124.2, 122.3, 121.5, 120.5, 77.6, 28.2 ppm. HRMS *m/z* (ESI) calculated for $C_{12}H_{13}O_2$ [$(M + H)^+$] 189.0916, found 189.0912.



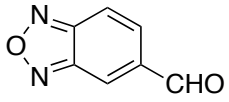
5-Bromo-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (15c) Yield = 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.90-7.89 (d, *J* = 2 Hz, 1H), 4.48-4.47 (d, *J* = 2 Hz, 1H), 6.38-6.36 (d, *J* = 10 Hz, 1H), 5.77-5.75 (d, *J* = 10 Hz, 1H), 1.55 (s, 6H) ppm.



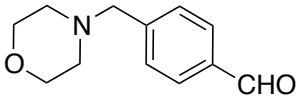
2,2,8-Trimethyl-2*H*-chromene-6-carbaldehyde (15d) Yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 7.48-7.48 (d, *J* = 2 Hz, 1H), 7.33-7.32 (d, *J* = 2 Hz, 1H), 6.33-6.30 (d, *J* = 10 Hz, 1H), 5.65-5.63 (d, *J* = 10 Hz, 1H), 2.18 (s, 3H), 1.43 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 156.7, 132.5, 131.0, 129.2, 126.4, 126.2, 121.7, 120.5, 77.7, 28.5, 15.4 ppm.



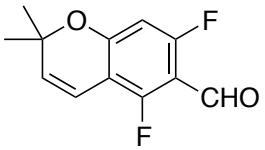
2,2,5-Trimethyl-2*H*-chromene-6-carbaldehyde with 2,2,7-Trimethyl-2*H*-chromene-6-carbaldehyde (1:2) (15e) Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.11 (s, 2H), 10.08 (s, 1H), 7.62-7.60 (d, *J* = 8 Hz, 2H), 7.44 (s, 1H), 6.77-6.75 (d, *J* = 8 Hz, 2H), 6.64-6.61 (m, 3H), 6.36-6.33 (d, *J* = 8 Hz, 1H), 5.75-5.73 (d, *J* = 8 Hz, 2H), 5.65-5.62 (d, *J* = 8 Hz, 1H), 2.62 (s, 6H), 2.59 (s, 3H), 1.45 (s, 18) ppm.



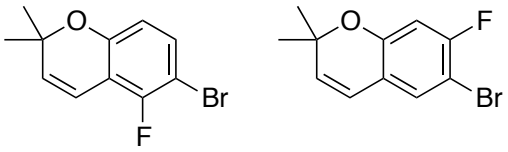
Benzo[*c*][1,2,5]oxadiazole-5-carbaldehyde (15h) Yield: 19%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.44 (s, 1H), 8.00-7.98 (d, *J* = 8 Hz, 1H), 7.96-7.94 (d, *J* = 8 Hz, 1H) ppm.



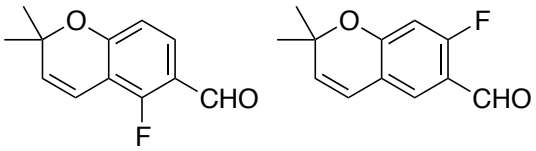
4-(Morpholinomethyl)benzaldehyde (15i) ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.82-7.80 (d, *J* = 7.6 Hz, 2H), 7.50-7.48 (d, *J* = 7.6 Hz, 2H), 3.68-3.67 (m, 4H), 3.54 (s, 2H), 2.43 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 145.3, 135.6, 129.8, 129.5, 129.2, 66.9, 63.0, 53.6 ppm. HRMS *m/z* (ESI) calculated for $C_{12}H_{16}NO_2$ [$(M + H)^+$] 206.1181, found 206.1182.



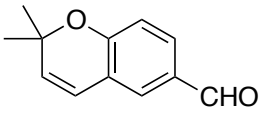
5,7-Difluoro-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (15l) ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.14 (s, 1H), 6.50-6.48 (d, *J* = 8 Hz, 1H), 6.37-6.34 (d, *J* = 10 Hz, 1H), 5.68-5.66 (d, *J* = 8 Hz, 1H), 5.60-5.78 (d, *J* = 8 Hz, 1H), 1.45 (s, 6H) ppm.



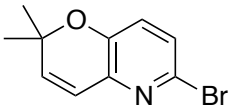
6-Bromo-5-fluoro-2,2-dimethyl-2*H*-chromene with 6-Bromo-7-fluoro-2,2-dimethyl-2*H*-chromene (1:1) (S3m) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.21 (m, 1H), 7.14-7.12 (d, *J* = 8 Hz, 1H), 6.61-6.51 (m, 3H), 6.25-6.23 (d, *J* = 8 Hz, 1H), 5.72-5.70 (d, *J* = 8 Hz, 1H), 5.62-5.60 (d, *J* = 8 Hz, 1H), 1.45 (s, 6H), 1.44 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 157.7, 155.8, 153.6, 153.5, 153.3, 153.2, 131.8, 131.8, 131.7, 131.6, 130.7, 129.8, 120.6, 119.2, 119.1, 114.9, 114.8, 113.5, 113.4, 111.4, 111.2, 105.4, 105.2, 99.3, 99.0, 98.9, 76.6, 28.0, 27.8 ppm.



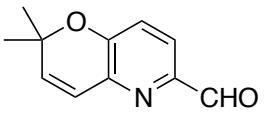
5-Fluoro-2,2-dimethyl-2*H*-chromene-6-carbaldehyde with 7-Fluoro-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (1:1) (15m)



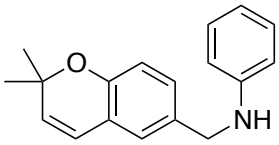
2,2-Dimethyl-2*H*-chromene-6-carbaldehyde (17) Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 7.65-7.63 (d, *J* = 8 Hz, 1H), 7.52 (s, 1H), 6.88-6.86 (d, *J* = 8 Hz, 1H), 6.38-6.36 (d, *J* = 8 Hz, 1H), 5.70-5.68 (d, *J* = 8Hz, 1H), 1.47 (s, 6H) ppm.



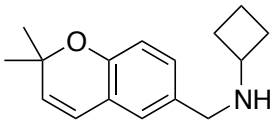
6-Bromo-2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridine (S3n) Yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.13 (d, *J* = 8 Hz, 1H), 6.91-6.89 (dd, *J* = 8, 2 Hz, 1H), 6.46-6.43 (dd, *J* = 8, 2 Hz, 1H), 5.88-5.85 (d, *J* = 8 Hz, 1H), 1.45 (s, 6H) ppm.



2,2-Dimethyl-2*H*-pyrano[3,2-*b*]pyridine-6-carbaldehyde (28) Yield: 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.72-7.70 (d, *J* = 8 Hz, 1H), 7.09-7.07 (d, *J* = 8 Hz, 1H), 6.55-6.53 (d, *J* = 10 Hz, 1H), 5.98-5.95 (d, *J* = 10 Hz, 1H), 1.48 (s, 6H) ppm.

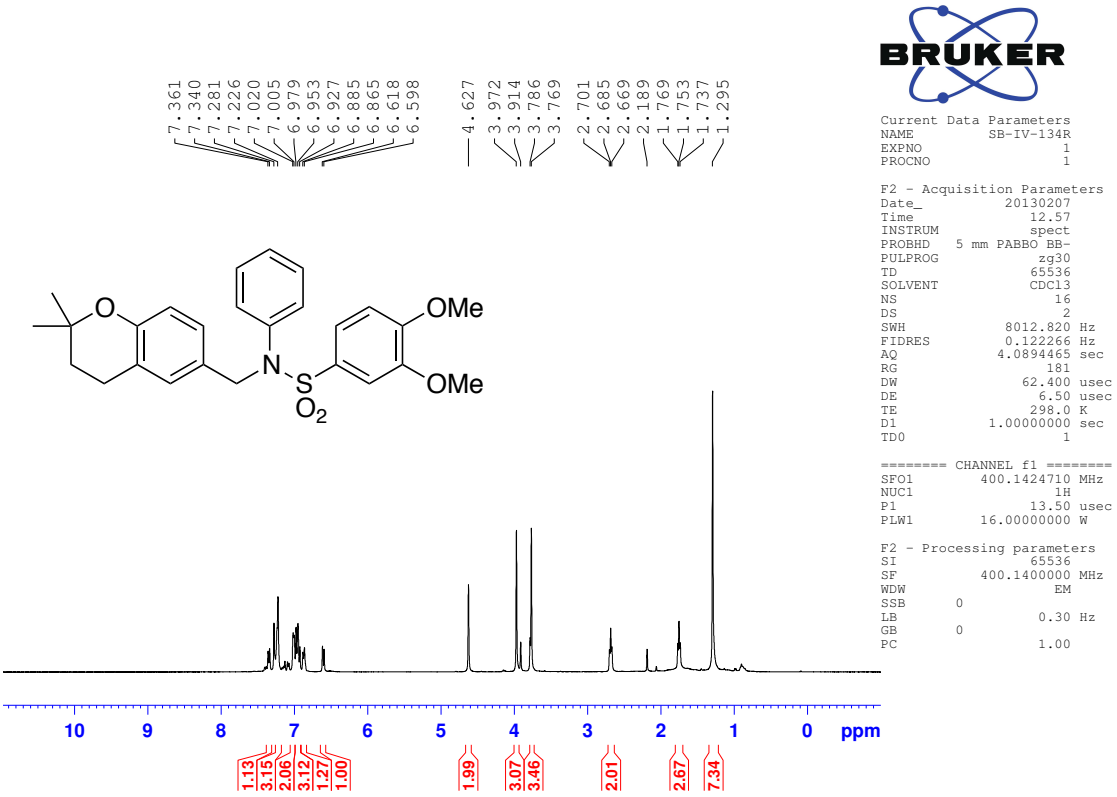


***N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)aniline (19)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.21 (m, 3H), 6.98-6.96 (d, *J* = 8 Hz, 1H), 6.88-6.86 (m, 1H), 6.79-6.72 (m, 3H), 6.40-6.38 (d, *J* = 8 Hz, 1H), 5.69-5.67 (d, *J* = 8 Hz, 1H), 4.37 (s, 2H), 4.06 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 148.5, 130.6, 129.2, 128.9, 126.5, 125.5, 122.5, 121.1, 120.5, 117.4, 113.2, 76.44, 43.11, 28.18. HRMS (ESI) *m/z* calculated for $C_{18}H_{20}NO$ [$(M + H)^+$] 266.1545, found 266.1548.



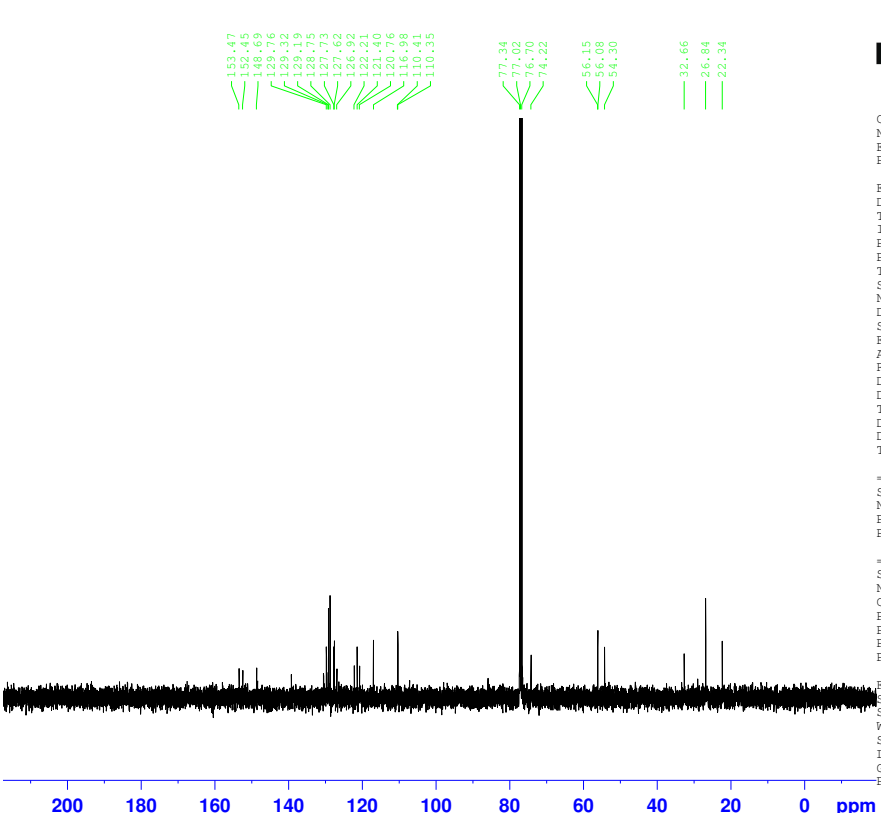
***N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine (32)** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04-7.02 (d, *J* = 8 Hz, 1H), 6.95 (s, 1H), 6.73-6.71 (d, *J* = 8 Hz, 1H), 6.32-6.30 (d, *J* = 8 Hz, 1H), 5.61-5.59 (d, *J* = 8 Hz, 1H), 3.60 (s, 2H), 3.32-3.26 (quintet, *J* = 8 Hz, 1H), 2.21 (m, 2H), 1.72-1.69 (m, 4H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 132.5, 130.8, 128.9, 126.2, 122.3, 121.2, 116.1, 76.1, 53.5, 50.1, 31.1, 27.9, 14.8. HRMS (ESI) *m/z* calculated for $C_{16}H_{22}NO$ [$(M + H)^+$] 244.1701, found 244.1697.

_N_-((2,2-Dimethylchroman-6-yl)methyl)-3,4-dimethoxy-_N_-phenylbenzenesulfonamide (3a)



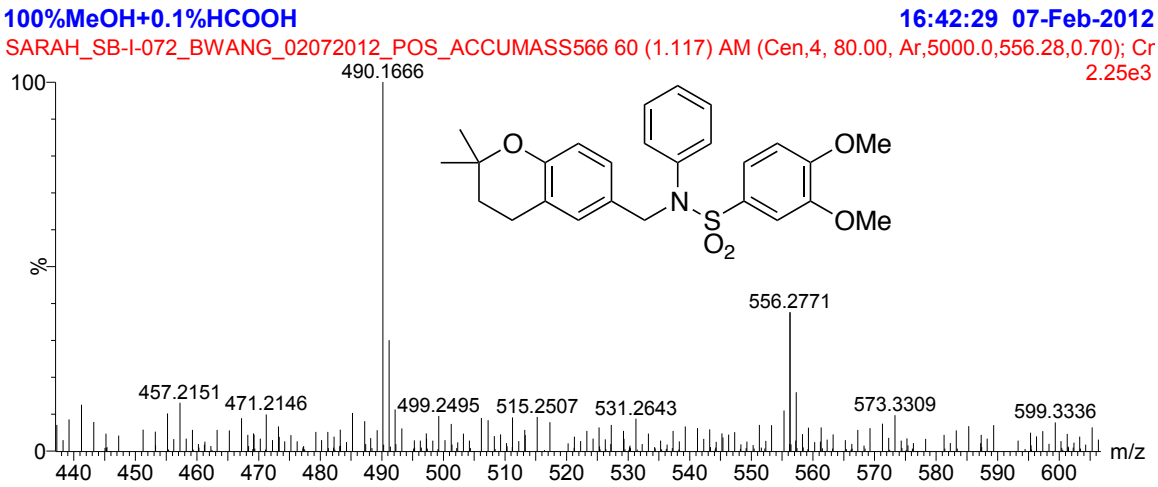
BRUKER

```
Current Data Parameters
NAME          SB-IV-134R
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130207
Time               12.57
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES             0.122266 Hz
AQ              4.0894465 sec
RG                   181
DW                62.400 usec
DE                 6.50 usec
TE                298.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          400.1424710 MHz
NUC1                  1H
P1                 13.50 usec
PLW1          16.00000000 W

F2 - Processing parameters
SI                 65536
SF            400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```



BRUKER

```
Current Data Parameters
NAME          SB-IV-134R
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130207
Time               13.04
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    67
DS                     4
SWH            24038.461 Hz
FIDRES             0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.4 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1          62.00000000 W

======== CHANNEL f2 ========
SFO2          400.1416006 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2          16.00000000 W
PLW12          0.36000001 W
PLW13          0.29159999 W

F2 - Processing parameters
SI                 32768
SF            100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



Elemental Composition Report

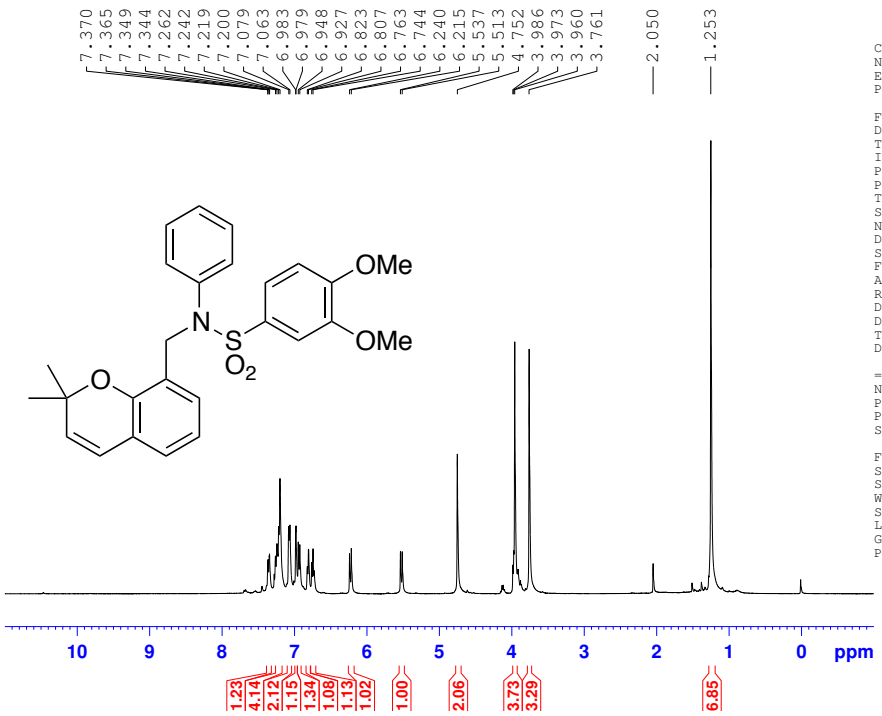
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
13307 formula(e) evaluated with 42 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
490.1666	490.1664	0.2	0.4	12.5	1.7	C26 H29 N O5 Na S

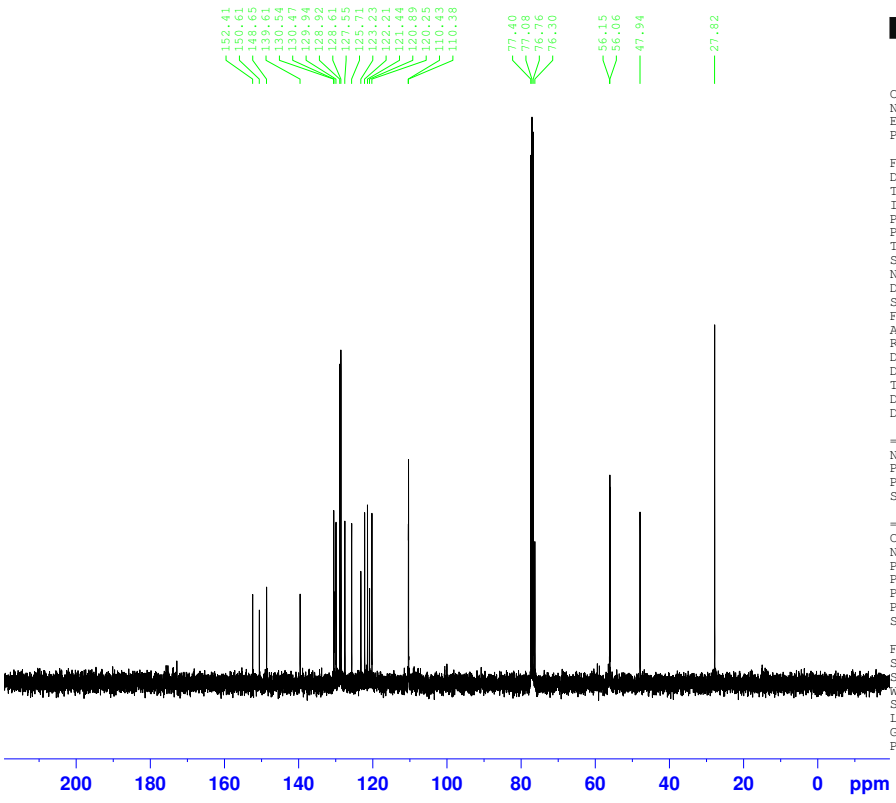
_N_-((2,2-Dimethyl-2_H_-chromen-8-yl)methyl)-3,4-dimethoxy-_N_-phenylbenzenesulfonamide (3b)

SB-IV-58d

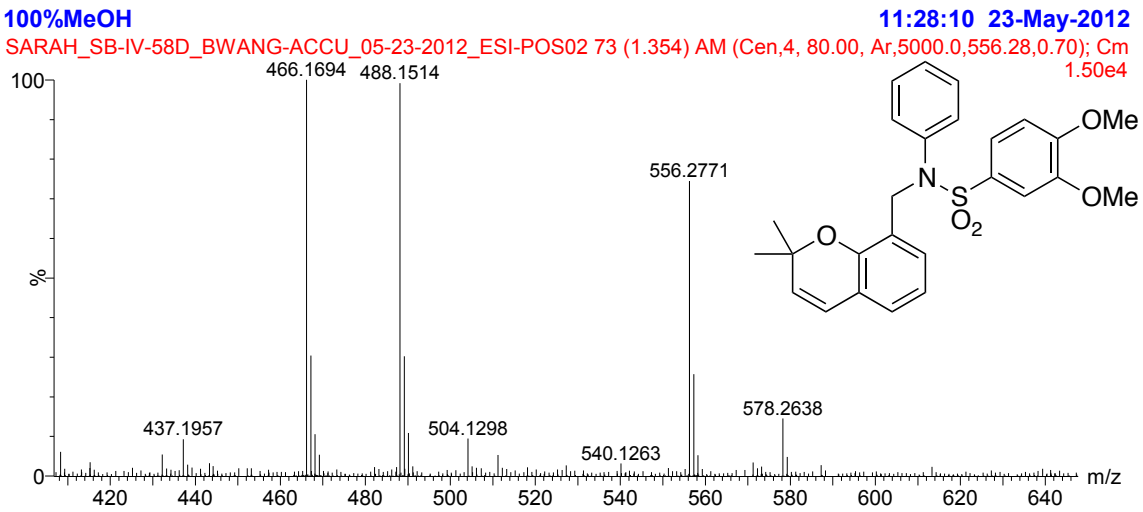



```
Current Data Parameters
NAME            SB-IV-58d
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20120522
Time               10.08
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                    36
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-IV-58d




```
Current Data Parameters
NAME            SB-IV-58d
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20120522
Time               10.11
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    64
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.7 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PLW1         62.00000000 W
SFO1        100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2        400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



Elemental Composition Report

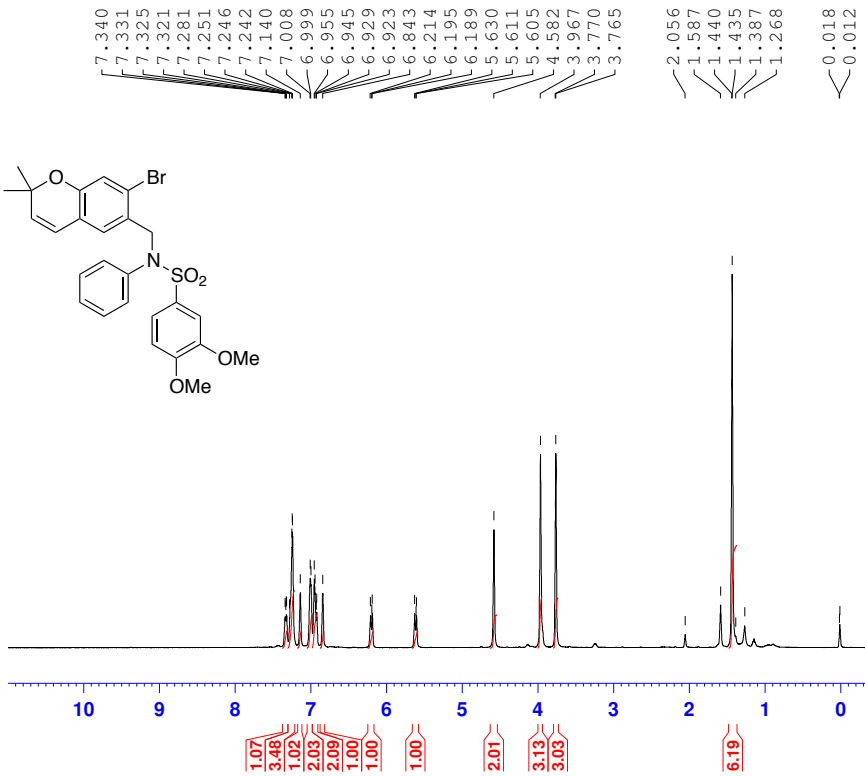
Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
5227 formula(e) evaluated with 71 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 0-50

Minimum:				-1.5			
Maximum:		5.0		20.0	50.0		
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
466.1694	466.1688	0.6		1.3	13.5	2.4	C26 H28 N O5 S

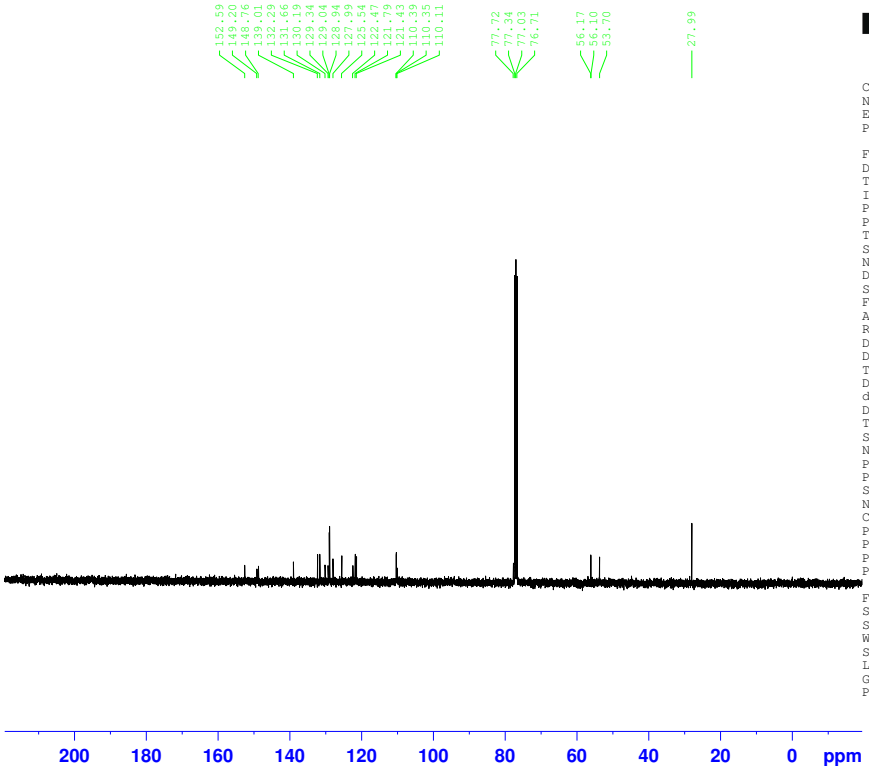
N-((7-Bromo-2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3c)

SB-III-51c

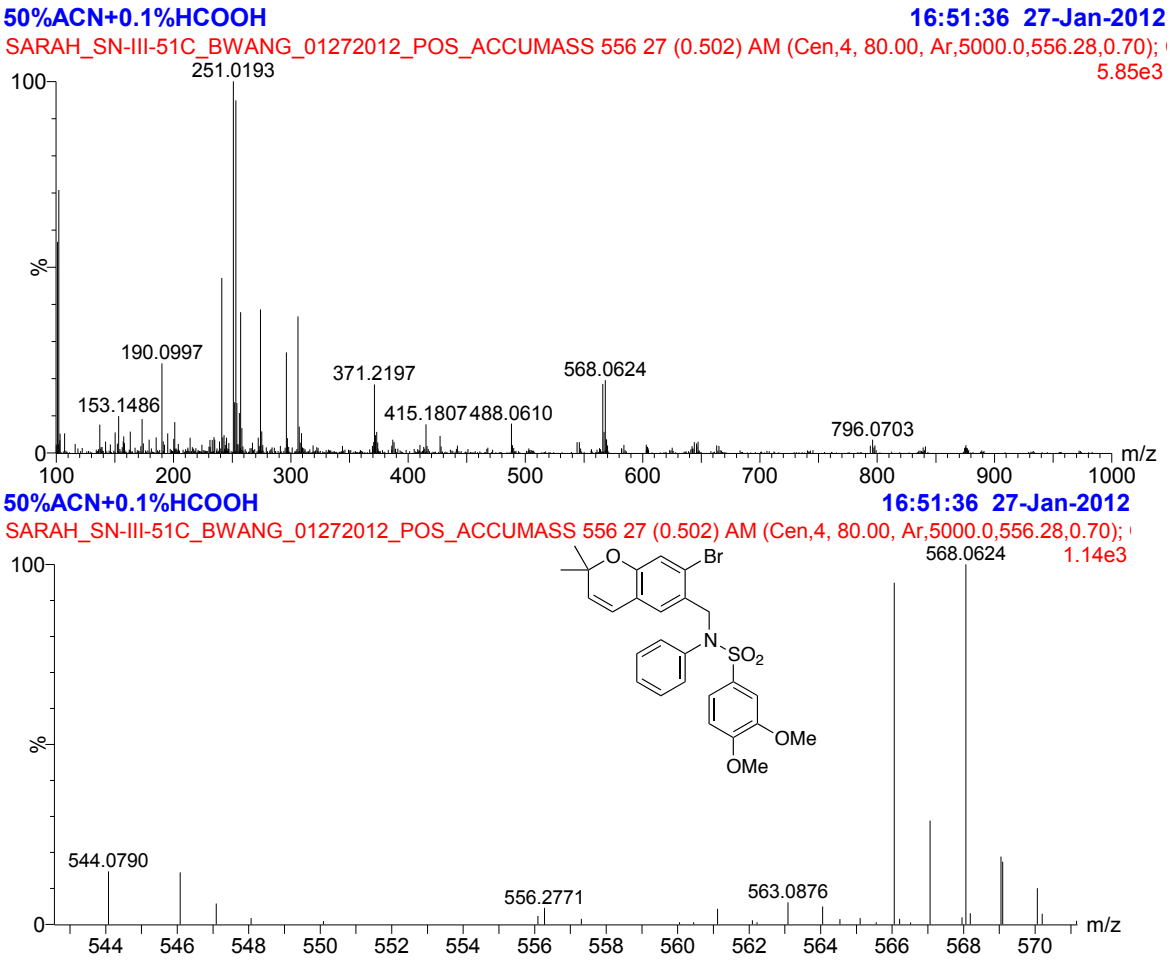



```
Current Data Parameters
NAME          SB-III-51c
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120126
Time               9.57
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8223.685 Hz
FIDRES         0.125483 Hz
AQ             3.9846387 sec
RG                  144
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                13.50 usec
PLW1        16.00000000 W
SFO1       400.1424710 MHz

F2 - Processing parameters
SI                65536
SF           400.1400000 MHz
WDW                  EM
SSB       0
LB              0.30 Hz
GB        0
PC                1.00
```

SB-III-51c




```
Current Data Parameters
NAME          SB-III-51c
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120126
Time              10.01
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                   72
DS                    4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631488 sec
RG                  114
DW                20.800 usec
DE                 6.50 usec
TE                298.1 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
TD0                   1
SFO1        100.6253441 MHz
NUC1                 13C
P1                9.00 usec
PLW1        62.00000000 W
SFO2        400.1416006 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W

F2 - Processing parameters
SI                32768
SF          100.6152830 MHz
WDW                  EM
SSB       0
LB              1.00 Hz
GB        0
PC                1.40
```



Elemental Composition Report

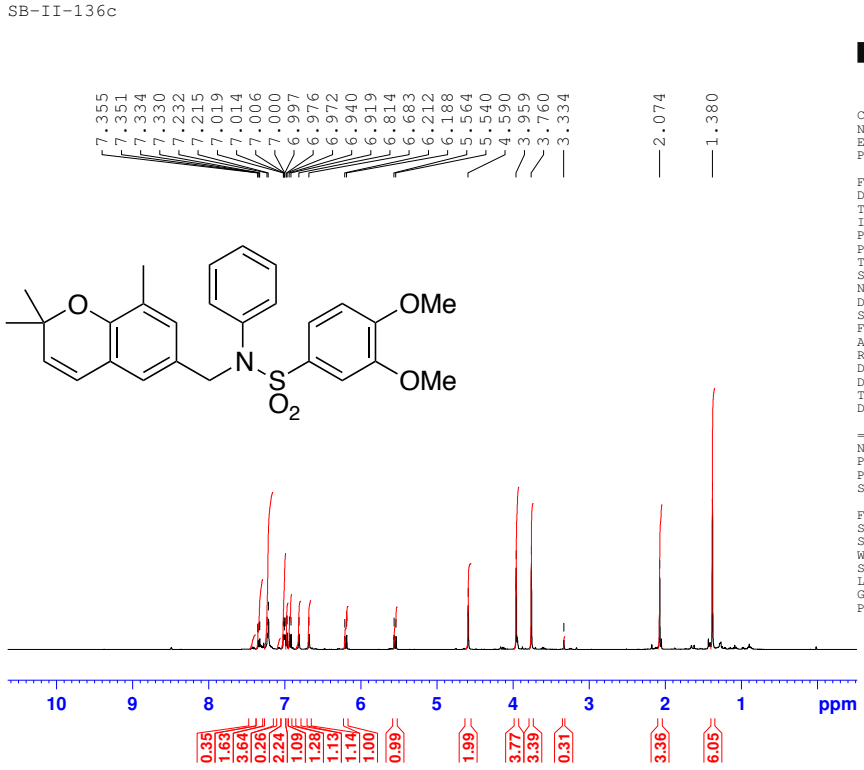
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
6479 formula(e) evaluated with 30 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-100 N: 1-15 O: 1-30 S: 1-6 Br: 1-5

Minimum:			-1.5				
Maximum:		5.0		5.0	50.0		
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
544.0790	544.0793	-0.3		-0.6	13.5	n/a	C26 H27 N O5 S Br

3,4-Dimethoxy-*N*-phenyl-*N*-((2,2,8-trimethyl-2*H*-chromen-6-yl)methyl)benzenesulfonamide (3d)

SB-II-136c



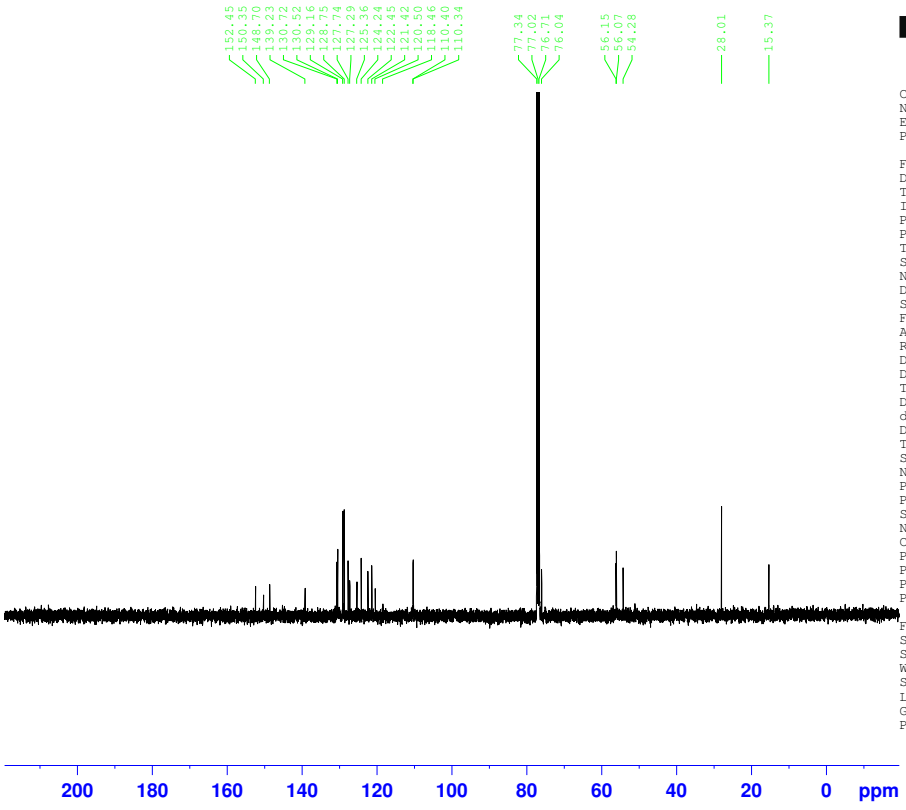
Current Data Parameters
NAME SB-II-136c
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20111019
Time 16.48
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 203
DW 60.800 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PLW1 16.00000000 W
SFO1 400.1424710 MHz

F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

SB-II-136R



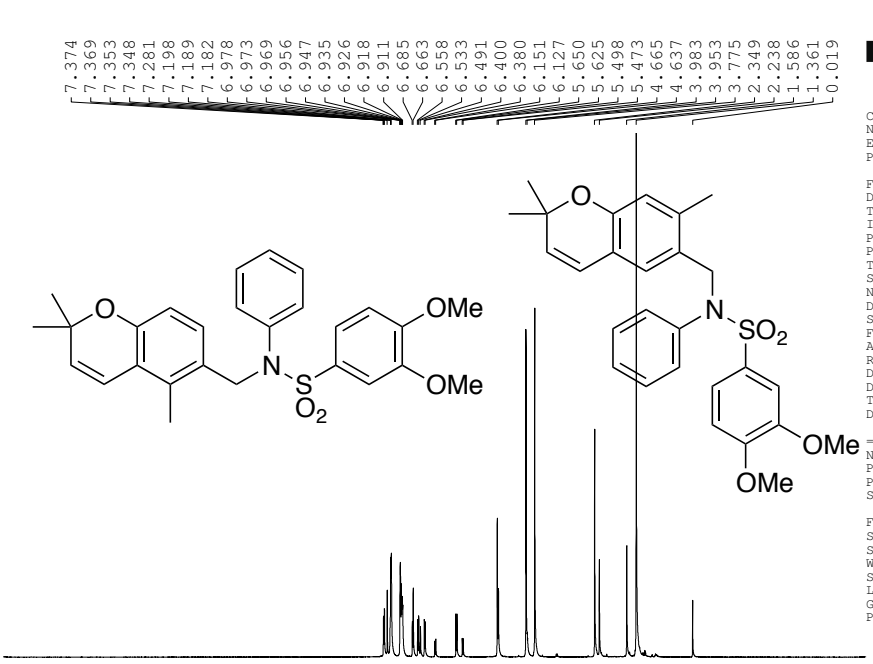
Current Data Parameters
NAME SB-II-136R
EXPNO 2
PROCNO 1

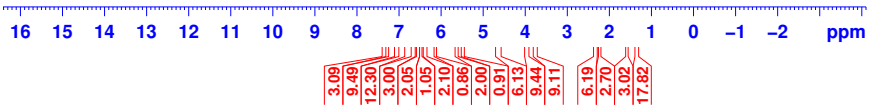
F2 - Acquisition Parameters
Date_ 20111026
Time 17.36
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 318
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 298.4 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
SFO1 100.6253441 MHz
NUC1 13C
P1 9.00 usec
PLW1 62.00000000 W
SFO2 400.1416006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 16.00000000 W
PLW12 0.36000001 W
PLW13 0.29159999 W

F2 - Processing parameters
SI 32768
SF 100.6152830 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

3,4-Dimethoxy-*N*-phenyl-*N*-((2,2,5-trimethyl-2*H*-chromen-6-yl)methyl)benzenesulfonamide and 3,4-Dimethoxy-*N*-phenyl-*N*-((2,2,7-trimethyl-2*H*-chromen-6-yl)methyl)benzenesulfonamide (2:1) (3e)

SB-III-154R

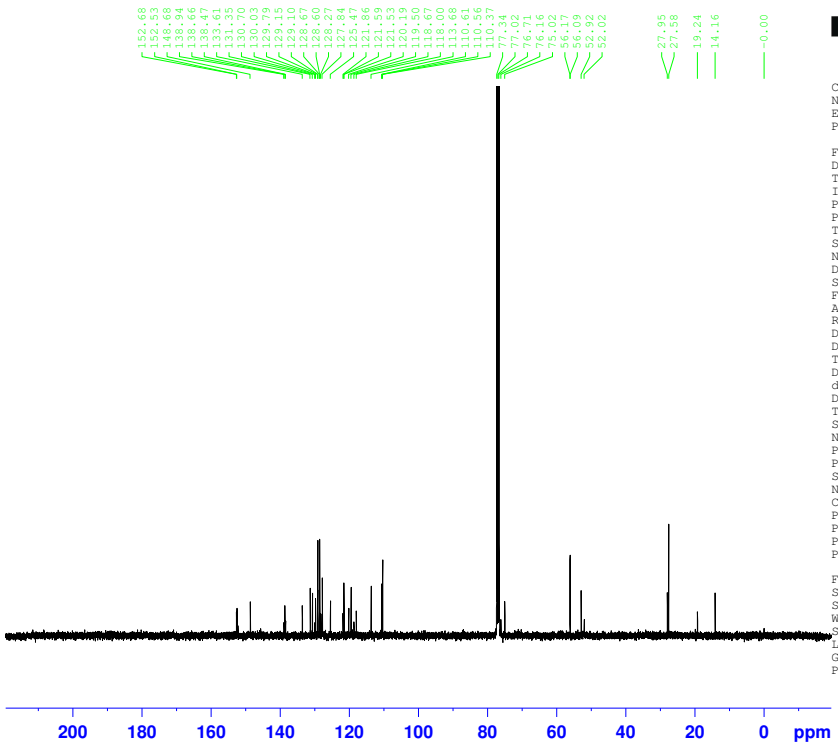




BRUKER

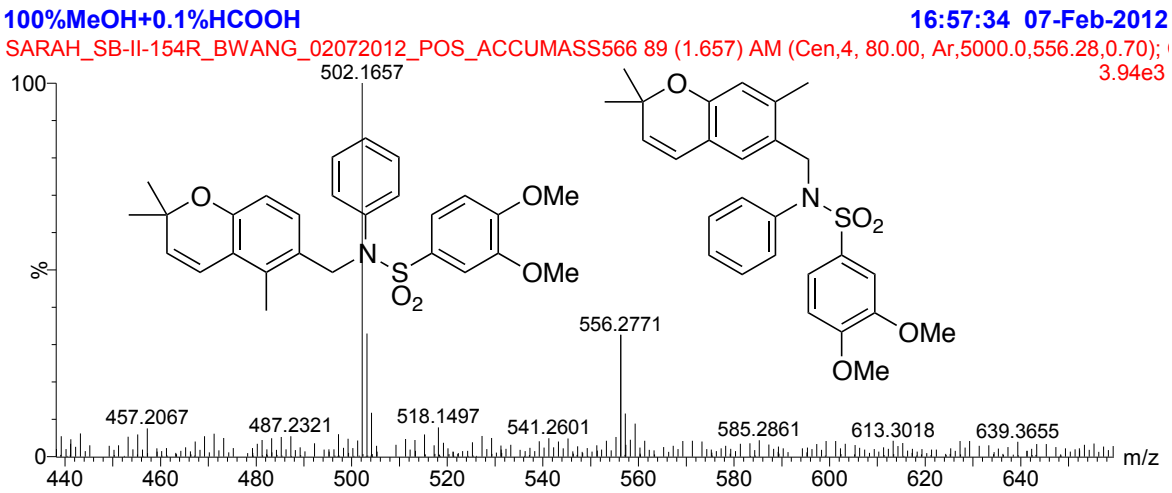
```
Current Data Parameters
NAME          SB-II-154R
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_          20111113
Time              15.15
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   15
DS                    2
SWH            8223.685 Hz
FIDRES         0.125483 Hz
AQ             3.9845889 sec
RG                  144
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1                13.50 usec
PLW1         16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI                65536
SF         400.1400000 MHz
WDW                  EM
SSB       0
LB               0.30 Hz
GB        0
PC               1.00
```

SB-II-154R



BRUKER

```
Current Data Parameters
NAME          SB-II-154R
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_          20111113
Time              15.19
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  858
DS                    4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631488 sec
RG                  161
DW                20.800 usec
DE                 6.50 usec
TE                298.1 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                   1
SFO1         100.6253441 MHz
NUC1                13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO2         400.1416006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                32768
SF         100.6152830 MHz
WDW                  EM
SSB       0
LB               1.00 Hz
GB        0
PC               1.40
```



Elemental Composition Report

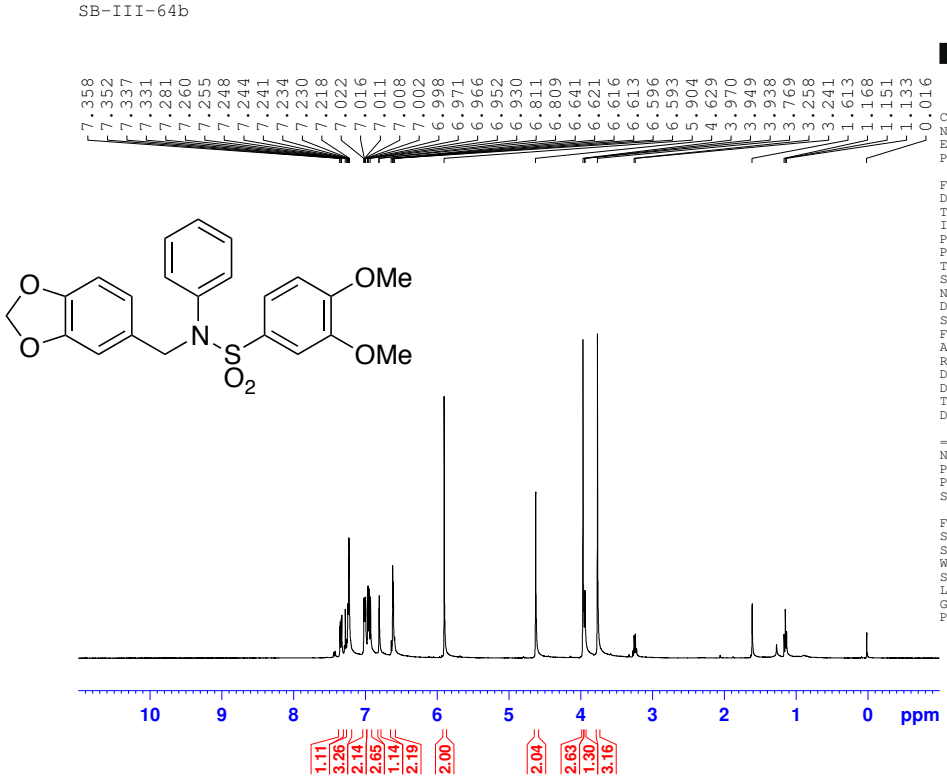
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
14388 formula(e) evaluated with 47 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

Minimum:				-1.5			
Maximum:		5.0		5.0	50.0		
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
502.1657	502.1664	-0.7		-1.4	13.5	3.1	C27 H29 N O5 Na S

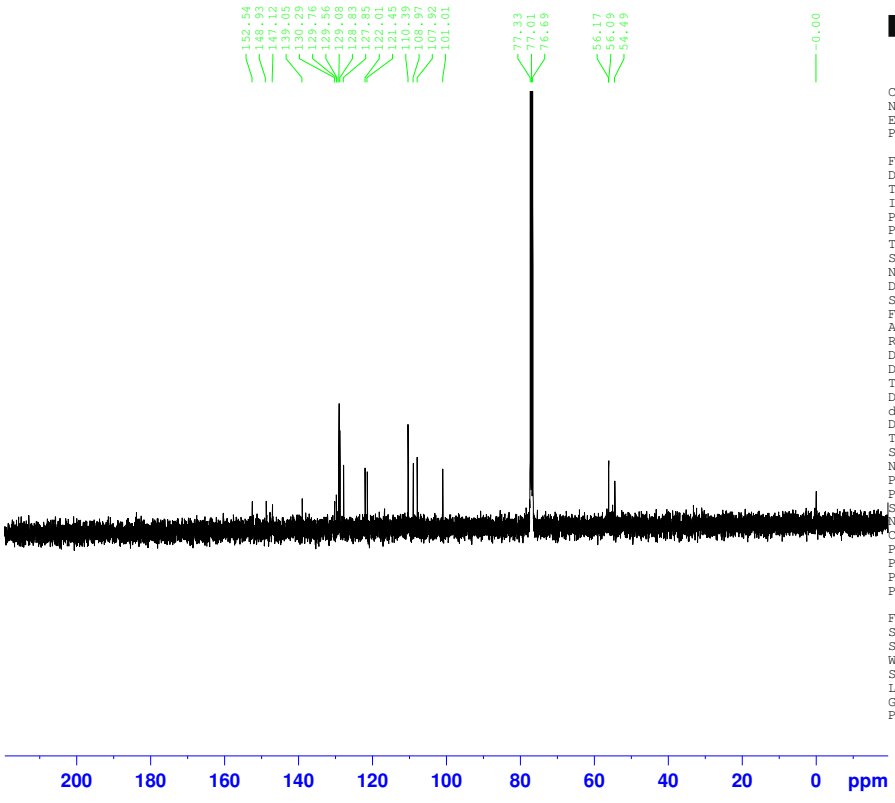
N-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3g)

SB-III-64b

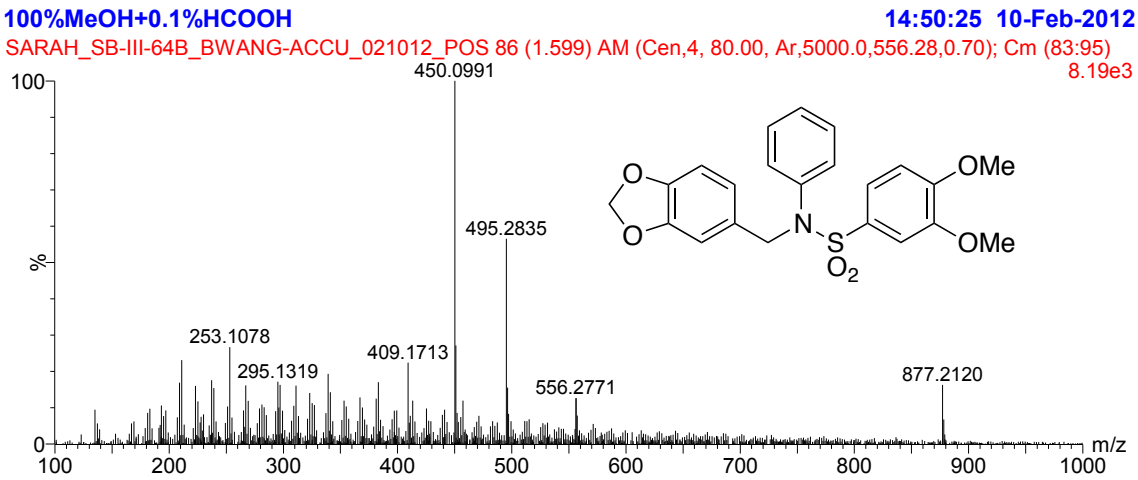



```
Current Data Parameters
NAME          SB-III-64b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120204
Time               12.29
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     7
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9845889 sec
RG                  71.8
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-III-64b




```
Current Data Parameters
NAME          SB-III-64b
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120209
Time               21.52
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   838
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   181
DW                20.800 usec
DE                 6.50 usec
TE                298.3 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                    1
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2           waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.00
```



Elemental Composition Report

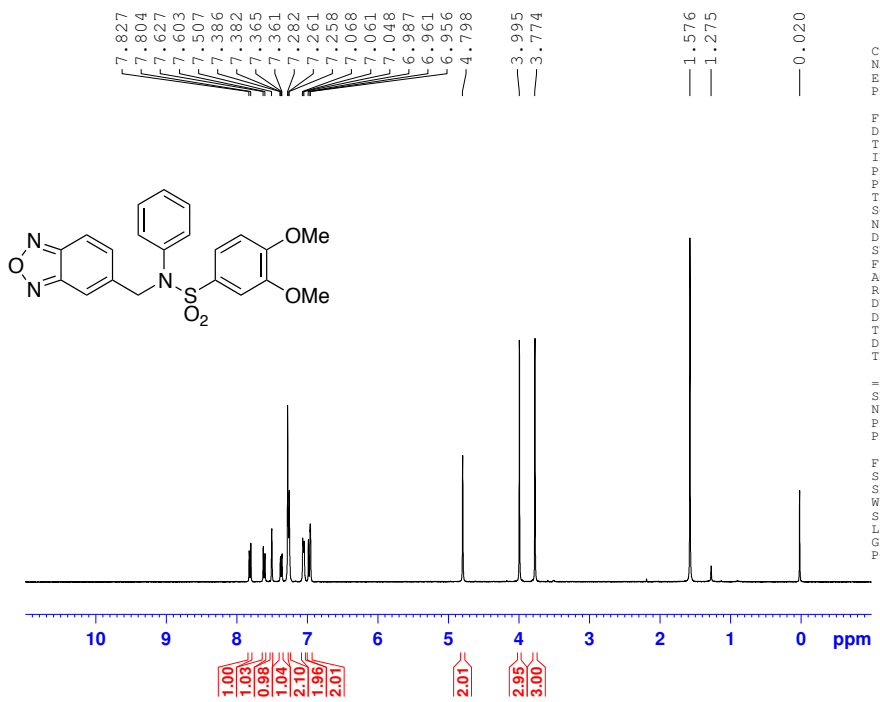
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
10028 formula(e) evaluated with 46 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 S: 1-6 Na: 0-3

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
450.0991	450.0987	0.4	0.9	12.5	2.1	C22 H21 N O6 S Na

N-(Benzo[*c*][1,2,5]oxadiazol-5-ylmethyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3h)

SB-II-155-HPLC



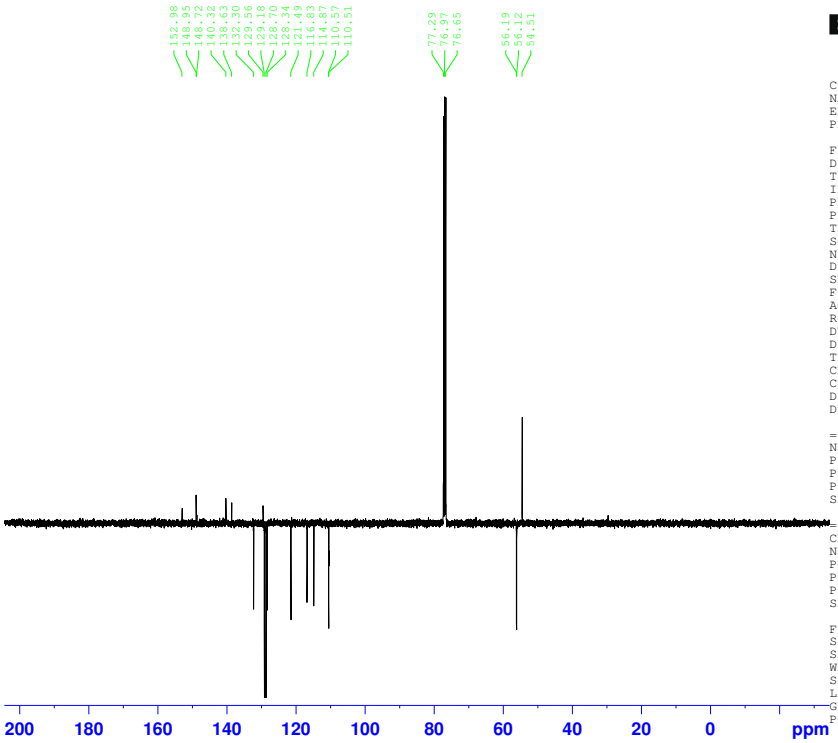
Current Data Parameters
NAME SB-II-155-HPLC
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120614
Time 10.35
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 203
DW 60.800 usec
DE 6.50 usec
TE 299.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 400.1424710 MHz
NUC1 1H
P1 13.50 usec
PLW1 16.00000000 W

F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

SB-II-155-HPLC



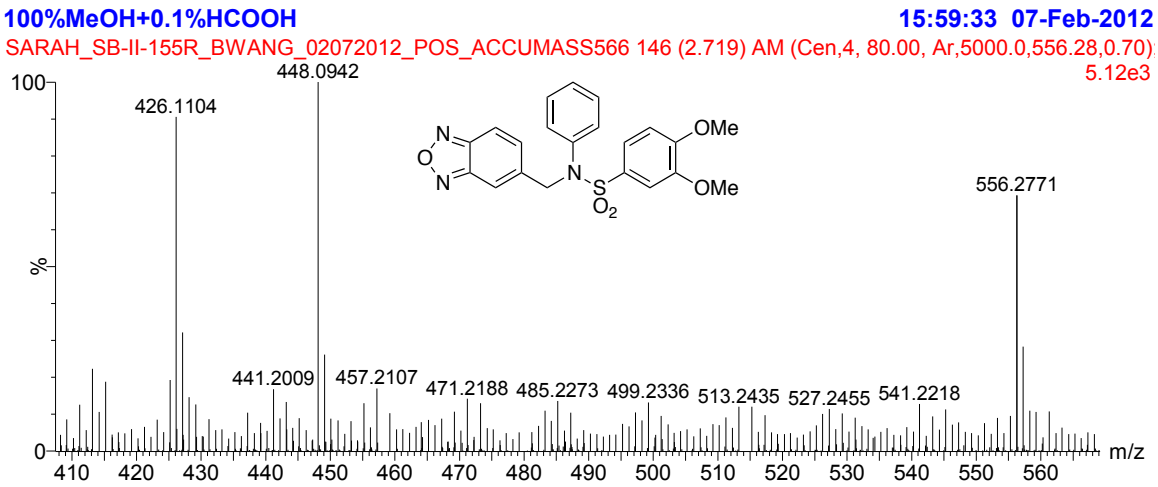
Current Data Parameters
NAME SB-II-155-HPLC
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120616
Time 9.20
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG jmod
TD 65536
SOLVENT CDC13
NS 10404
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 300.7 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
D20 0.00689655 sec

======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
P2 18.00 usec
PLW1 62.00000000 W
SFO1 100.6238353 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 16.00000000 W
PLW12 0.36000001 W
SFO2 400.1416006 MHz

F2 - Processing parameters
SI 32768
SF 100.6152830 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Elemental Composition Report

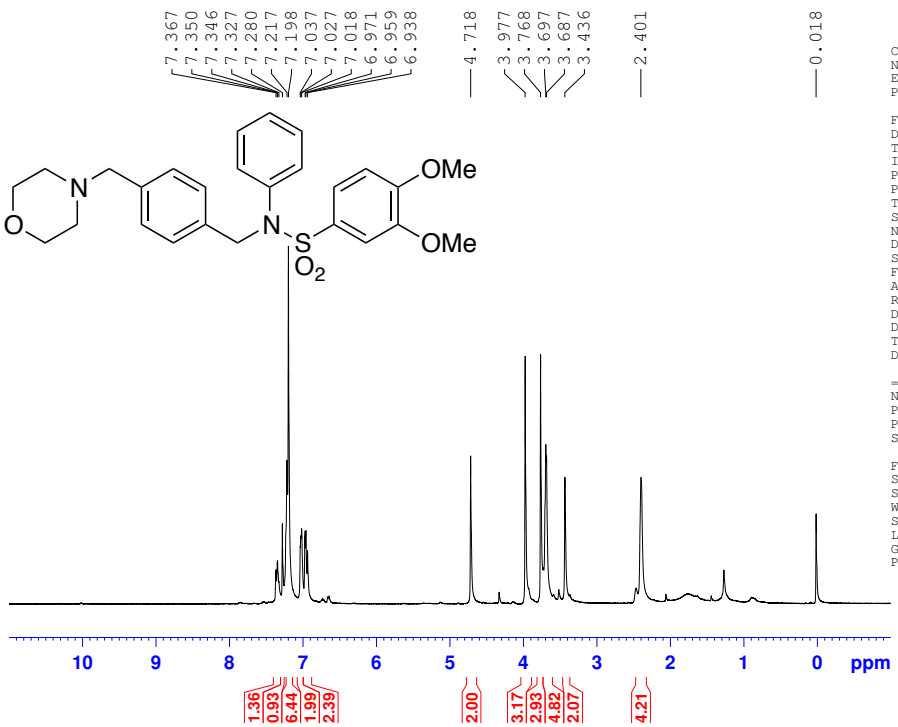
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
8255 formula(e) evaluated with 34 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
426.1104	426.1124	-2.0	-4.7	13.5	122.1	C21 H20 N3 O5 S

3,4-Dimethoxy-*N*-(4-(morpholinomethyl)benzyl)-*N*-phenylbenzenesulfonamide (3i)

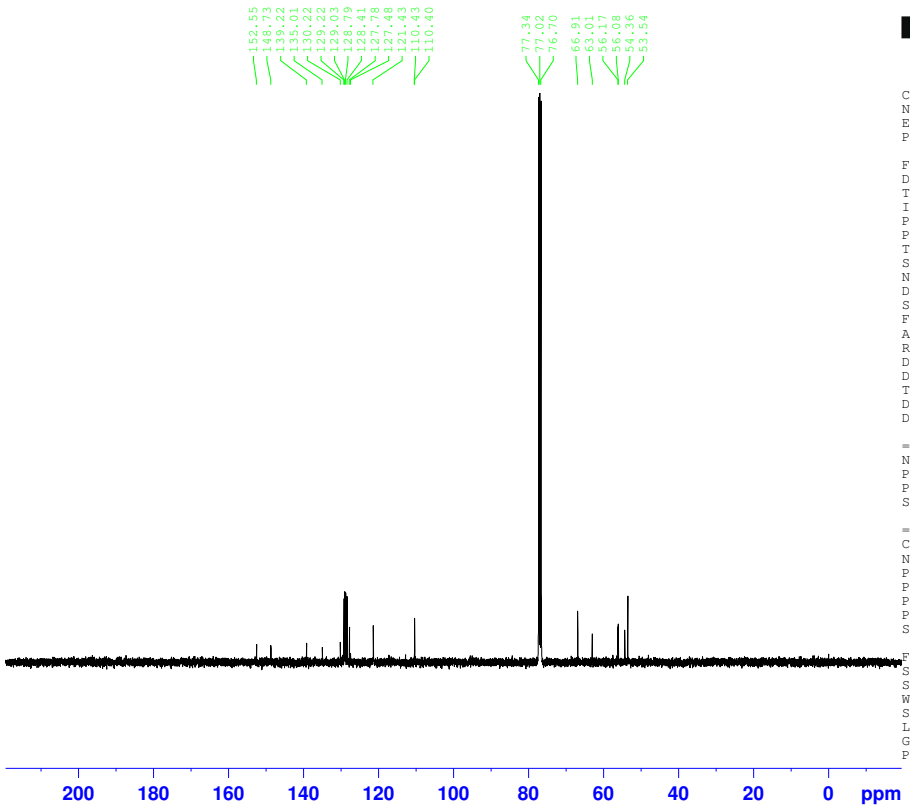
SB-IV-54d



BRUKER

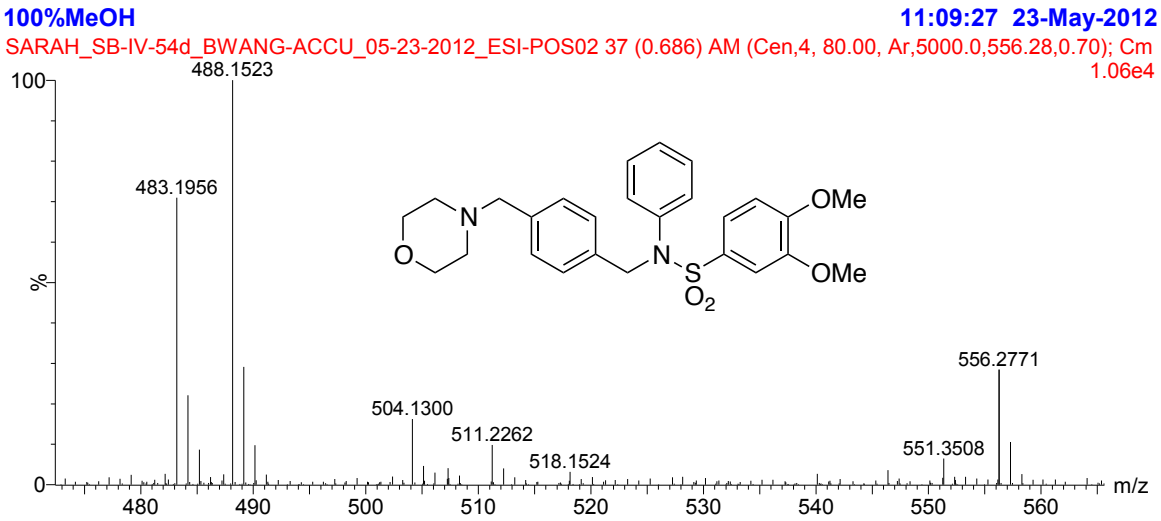
```
Current Data Parameters
NAME                  SB-IV-54d
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20120522
Time                      10.25
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   8223.685 Hz
FIDRES                0.125483 Hz
AQ                    3.9846387 sec
RG                         181
DW                      60.800 usec
DE                       6.50 usec
TE                      298.1 K
D1                  1.00000000 sec

======== CHANNEL f1 ========
NUC1                        1H
P1                       13.50 usec
PLW1                16.00000000 W
SFO1                400.1424710 MHz

F2 - Processing parameters
SI                       65536
SF                  400.1400000 MHz
WDW                         EM
SSB                0
LB                       0.30 Hz
GB                 0
PC                       1.00
```

SB-IV-54d



BRUKER

```
Current Data Parameters
NAME                  SB-IV-54d
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20120522
Time                      10.29
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                         501
DS                           4
SWH                  24038.461 Hz
FIDRES                0.366798 Hz
AQ                    1.3631988 sec
RG                         203
DW                      20.800 usec
DE                       6.50 usec
TE                      298.7 K
D1                  2.00000000 sec
D11                 0.03000000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                       9.00 usec
PLW1                62.00000000 W
SFO1                100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                   90.00 usec
PLW2                16.00000000 W
PLW12                0.36000001 W
PLW13                0.29159999 W
SFO2                400.1416006 MHz

F2 - Processing parameters
SI                       32768
SF                  100.6152830 MHz
WDW                         EM
SSB                0
LB                       1.00 Hz
GB                 0
PC                       1.20
```



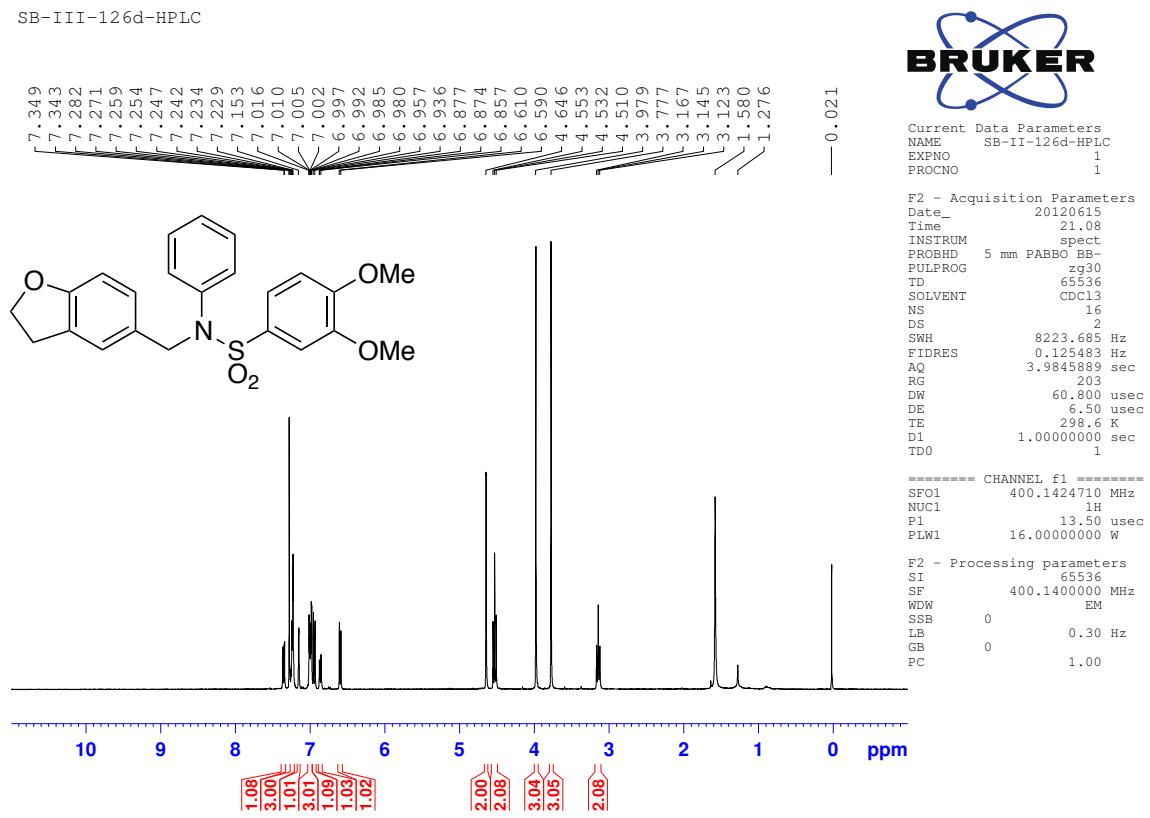
Elemental Composition Report

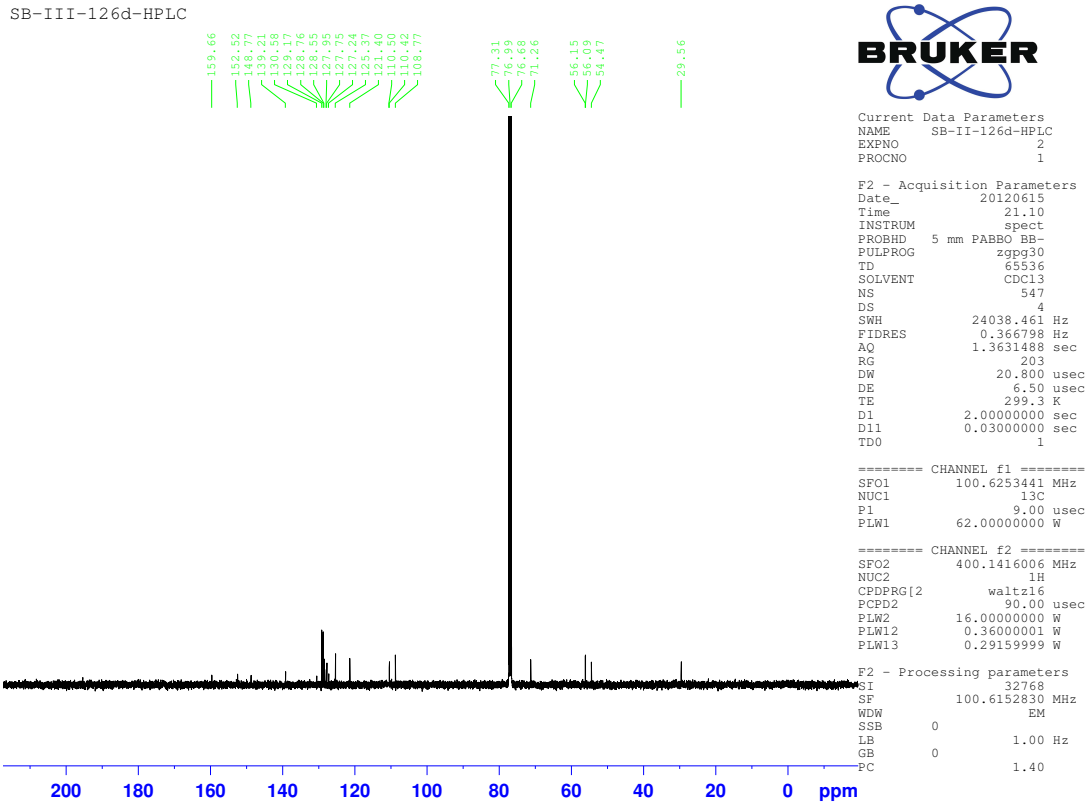
Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

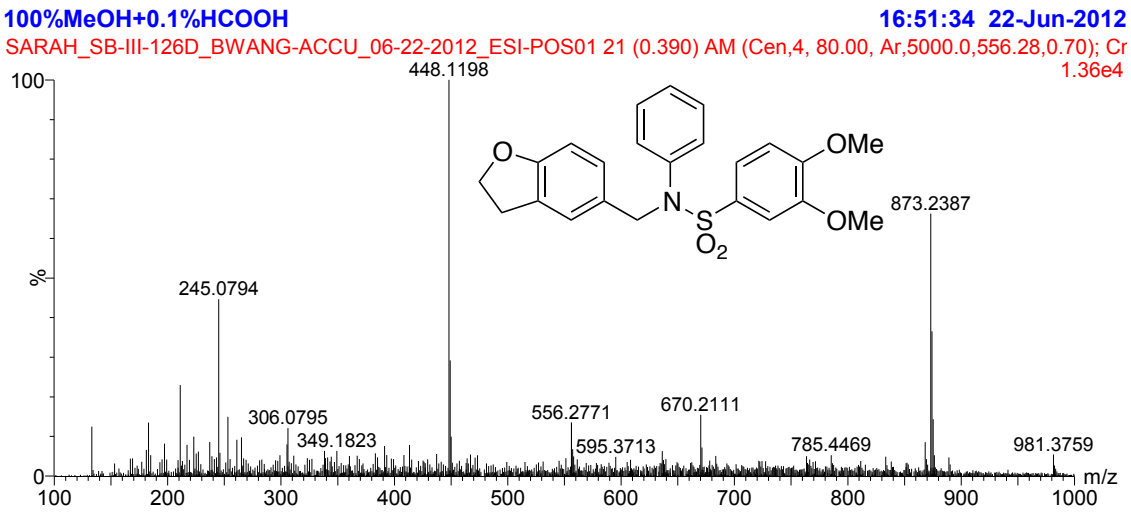
Monoisotopic Mass, Even Electron Ions
6053 formula(e) evaluated with 64 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 0-50

Minimum:				-1.5		
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
483.1956	483.1954	0.2	0.4	12.5	12.4	C26 H31 N2 O5 S

N-((2,3-dihydrobenzofuran-5-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3j)







Elemental Composition Report

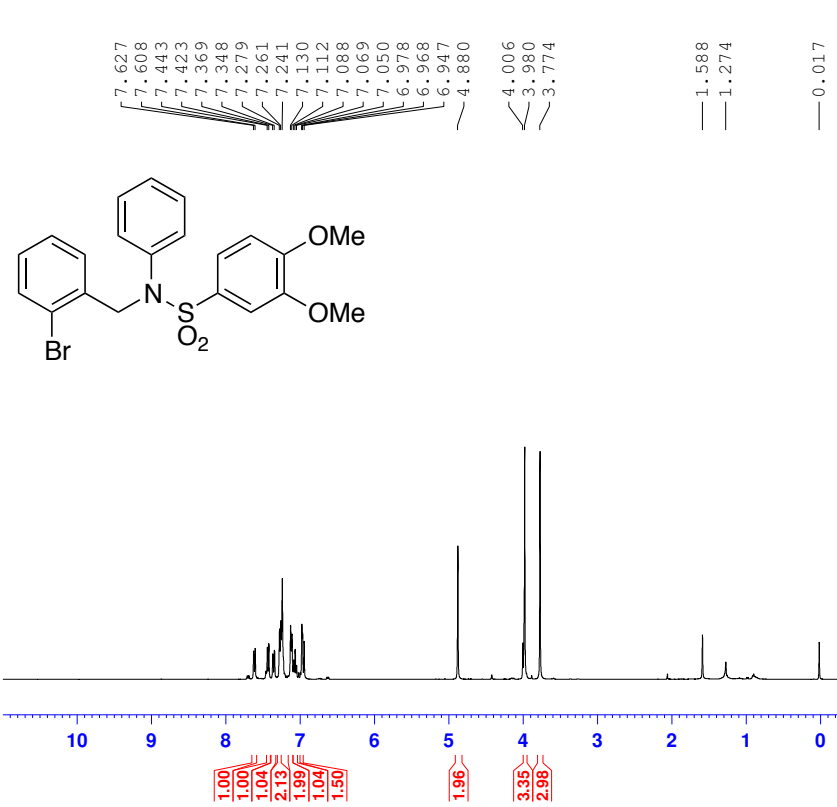
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
3015 formula(e) evaluated with 10 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 Na: 1-1 S: 1-50

Minimum:			-1.5			
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
448.1198	448.1195	0.3	0.7	12.5	10.2	C23 H23 N O5 Na S

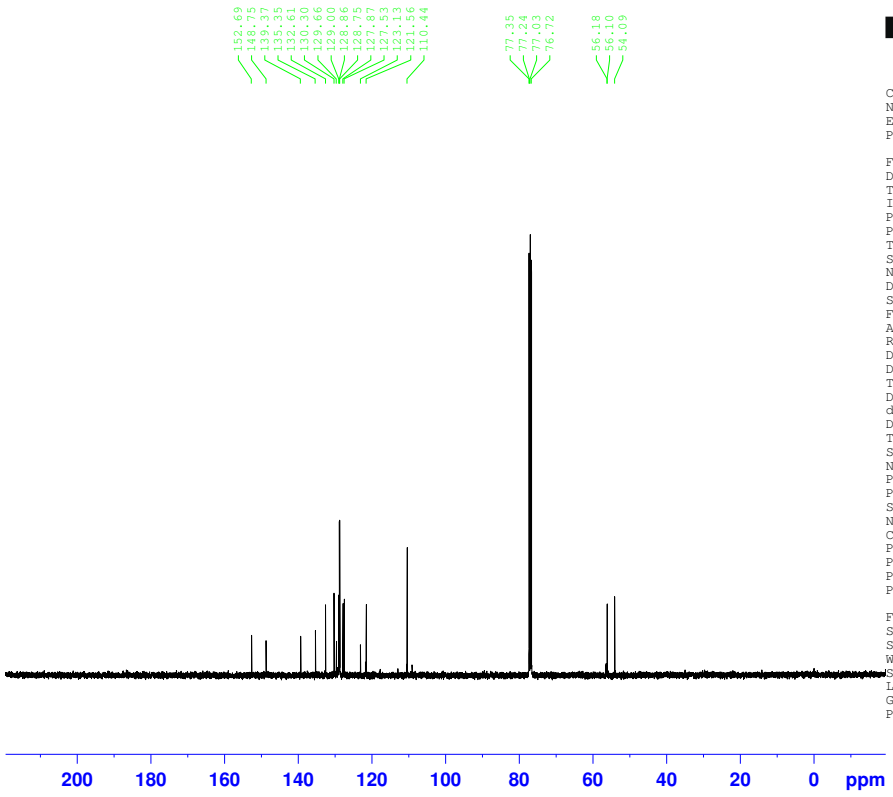
N-(2-bromobenzyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (3k)

SB-III-148d

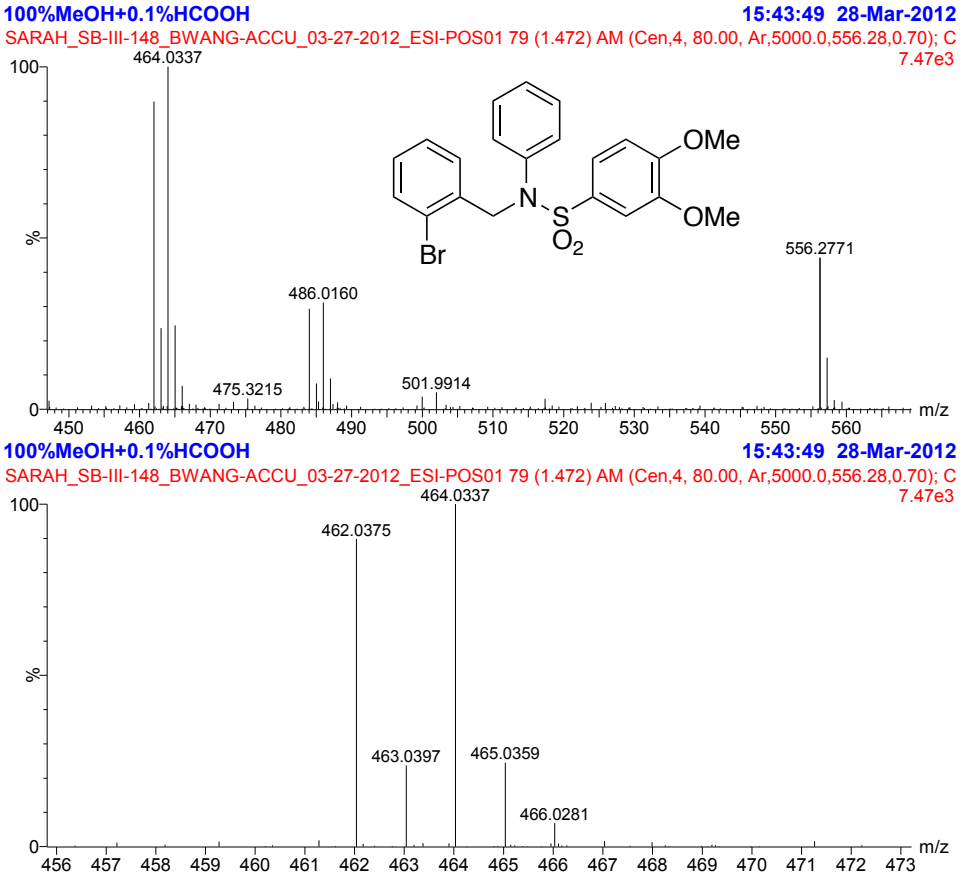



```
Current Data Parameters
NAME                  148d
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_            20120327
Time                10.41
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ               3.9846387 sec
RG                     64
DW                60.800 usec
DE                 6.50 usec
TE                298.2 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PLW1         16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI                  65536
SF           400.1400000 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

SB-III-148d




```
Current Data Parameters
NAME                  148d
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_            20120327
Time                18.10
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG           zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    438
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631488 sec
RG                    161
DW                20.800 usec
DE                 6.50 usec
TE                298.3 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                     1
SFO1        100.6253441 MHz
NUC1                  13C
P1                  9.00 usec
PLW1         62.00000000 W
SFO2        400.1416006 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                  32768
SF           100.6152830 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```



Elemental Composition Report

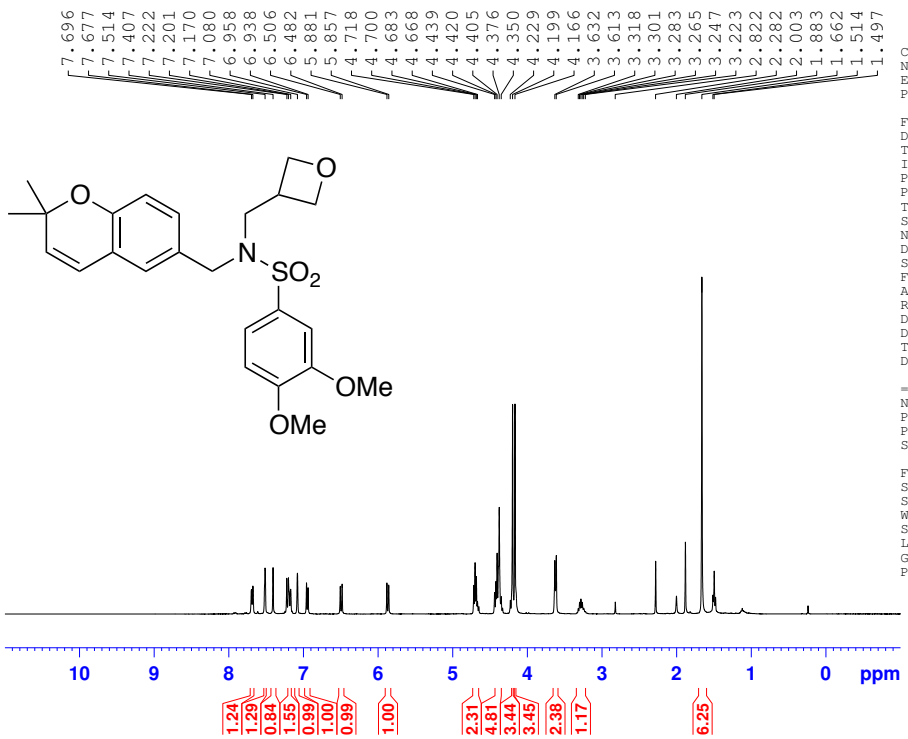
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2971 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20 S: 1-6 Br: 1-5

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
462.0375	462.0375	0.0	0.0	11.5	6.1	C21 H21 N O4 S Br

N-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-3,4-dimethoxy-*N*-(oxetan-3-ylmethyl)benzenesulfonamide (4a)

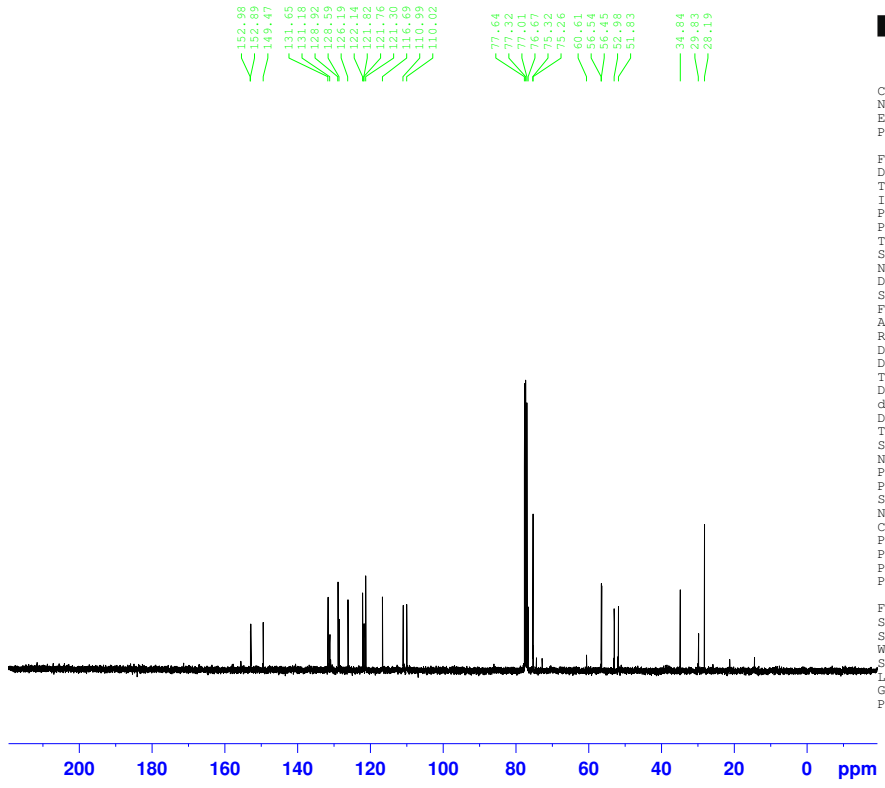
SB-IV-70c



BRUKER

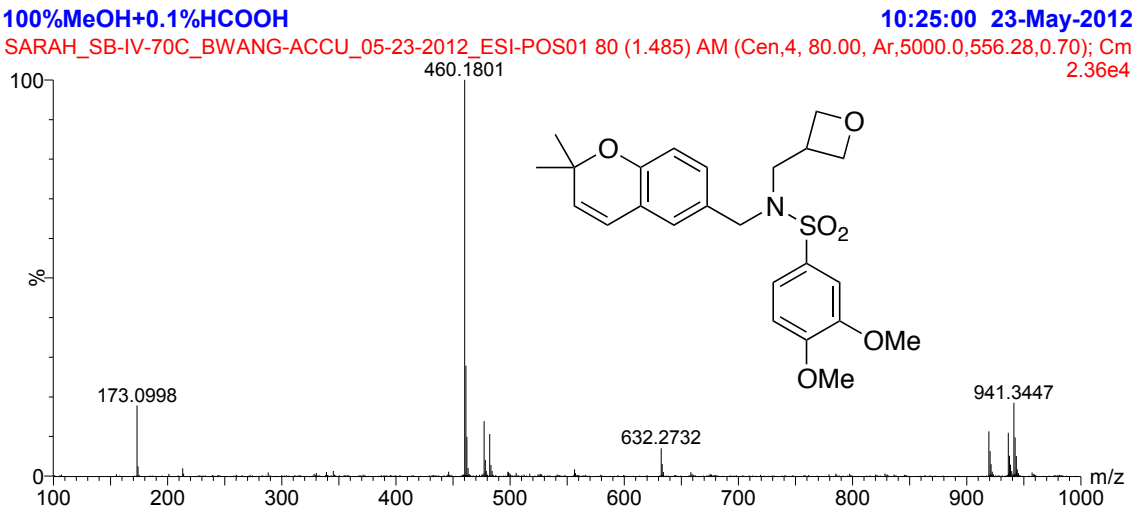
```
Current Data Parameters
NAME            SB-IV-70c
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20120521
Time               14.23
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                  40.3
DW                60.800 usec
DE                 6.50 usec
TE                298.2 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-IV-70c



BRUKER

```
Current Data Parameters
NAME            SB-IV-70c
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20120521
Time               14.30
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   102
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.9 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                    1
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF           100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 2.00
```



Elemental Composition Report

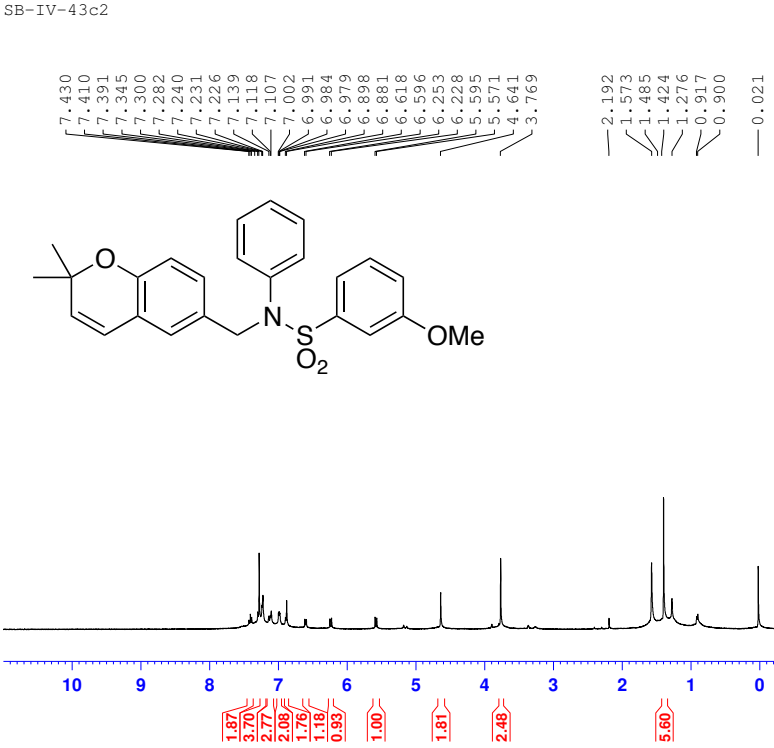
Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
5060 formula(e) evaluated with 66 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 0-50

Minimum:			-1.5			
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
460.1801	460.1794	0.7	1.5	10.5	4.4	C24 H30 N O6 S

N-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-3-methoxy-*N*-phenylbenzenesulfonamide (5a)

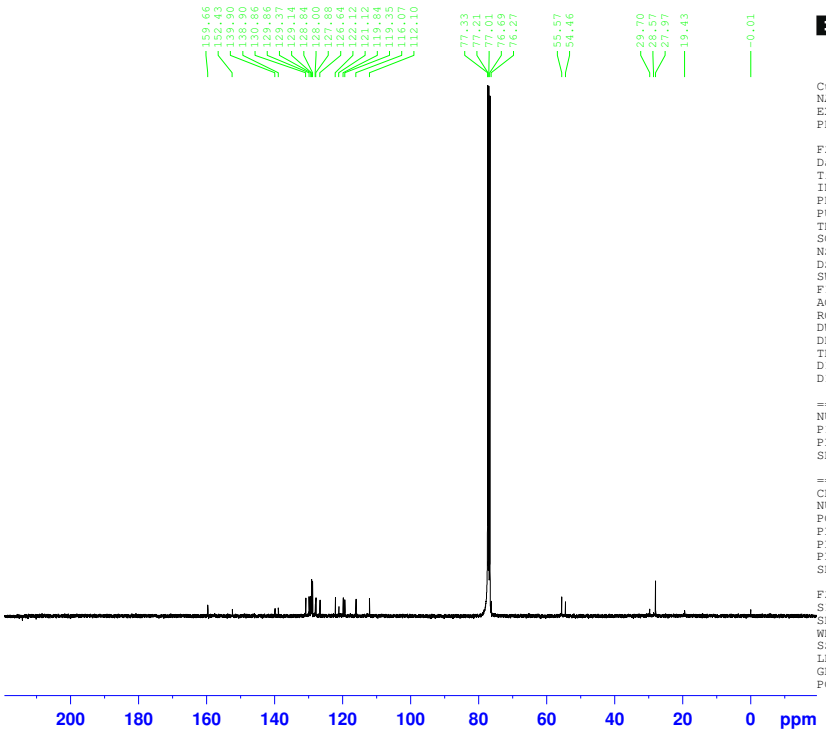
SB-IV-43c2



BRUKER

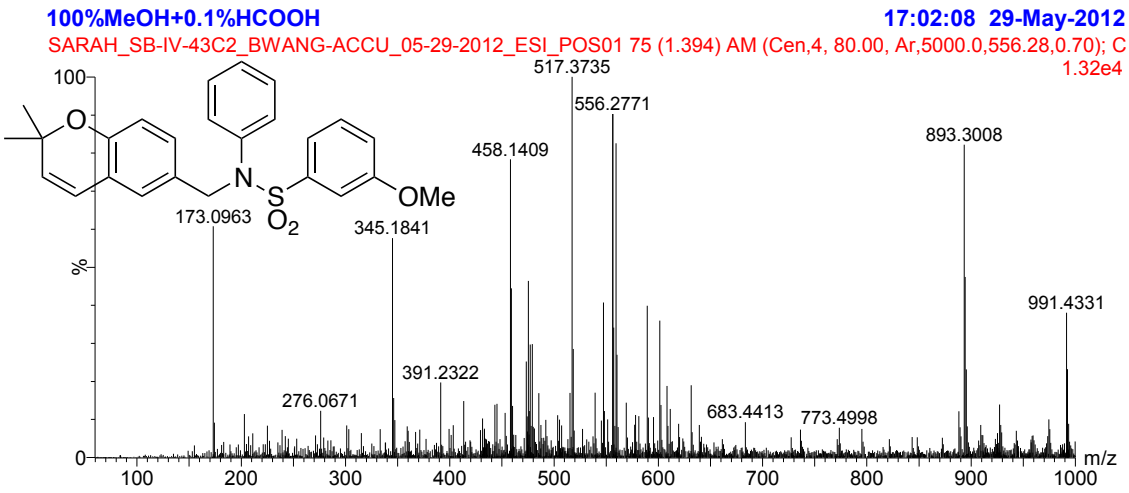
```
Current Data Parameters
NAME          SB-IV-43c2
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120517
Time               14.45
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDC13
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                   203
DW                60.800 usec
DE                 6.50 usec
TE                299.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

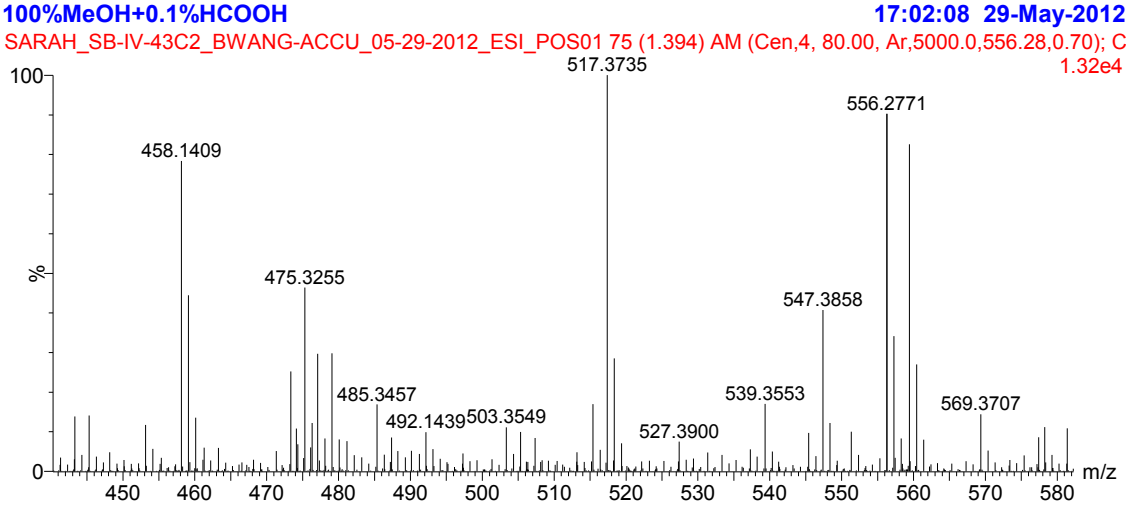
SB-IV-43c2



BRUKER

```
Current Data Parameters
NAME          SB-IV-43c2
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120522
Time               23.04
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDC13
NS                  8975
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.8 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.20
```





Elemental Composition Report

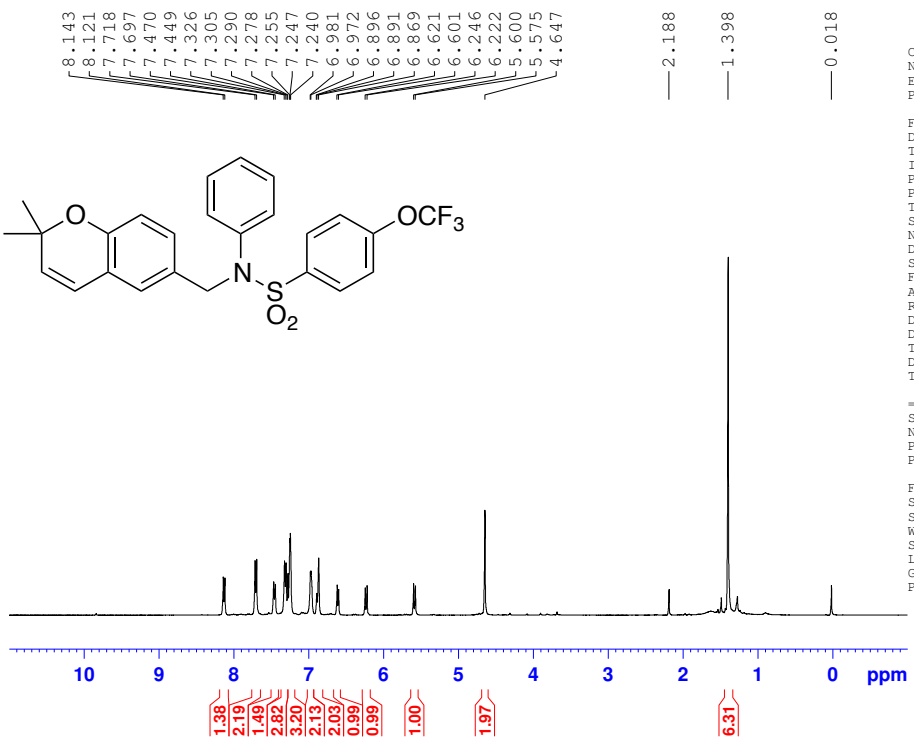
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
9185 formula(e) evaluated with 36 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 Na: 0-1 S: 0-50

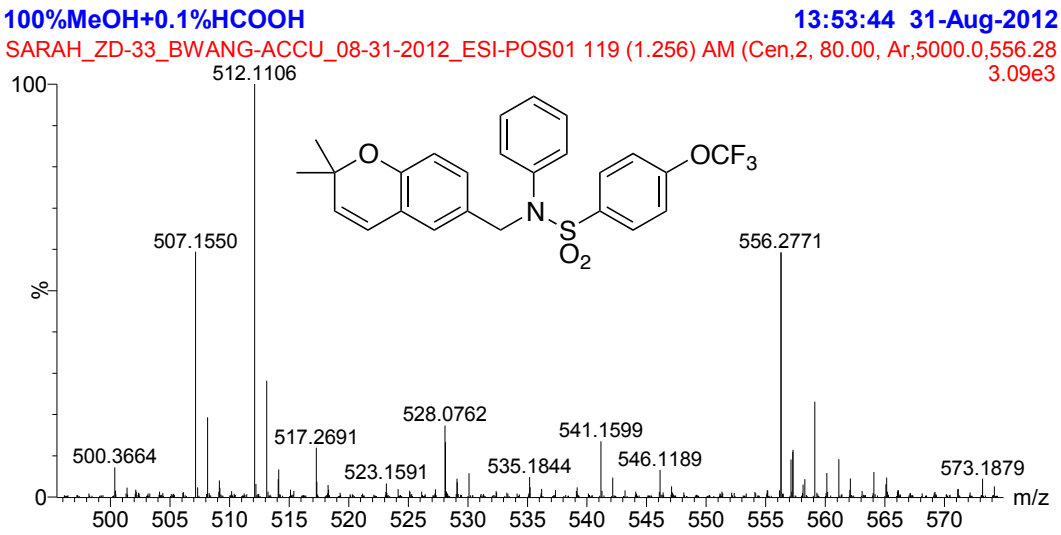
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
458.1409	458.1402	0.7	1.5	13.5	876.2	C25 H25 N O4 Na S

N-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-*N*-phenyl-4-(trifluoromethoxy)benzenesulfonamide (5b)

ZD-I-33




```
Current Data Parameters
NAME                  ZD-I-33
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120719
Time                 10.17
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8012.820 Hz
FIDRES               0.122266 Hz
AQ                4.0894465 sec
RG                      32
DW                   62.400 usec
DE                    6.50 usec
TE                   297.8 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1            400.1424710 MHz
NUC1                      1H
P1                     13.50 usec
PLW1           16.00000000 W

F2 - Processing parameters
SI                       65536
SF              400.1400000 MHz
WDW                        EM
SSB         0
LB                      0.30 Hz
GB          0
PC                      1.00
```



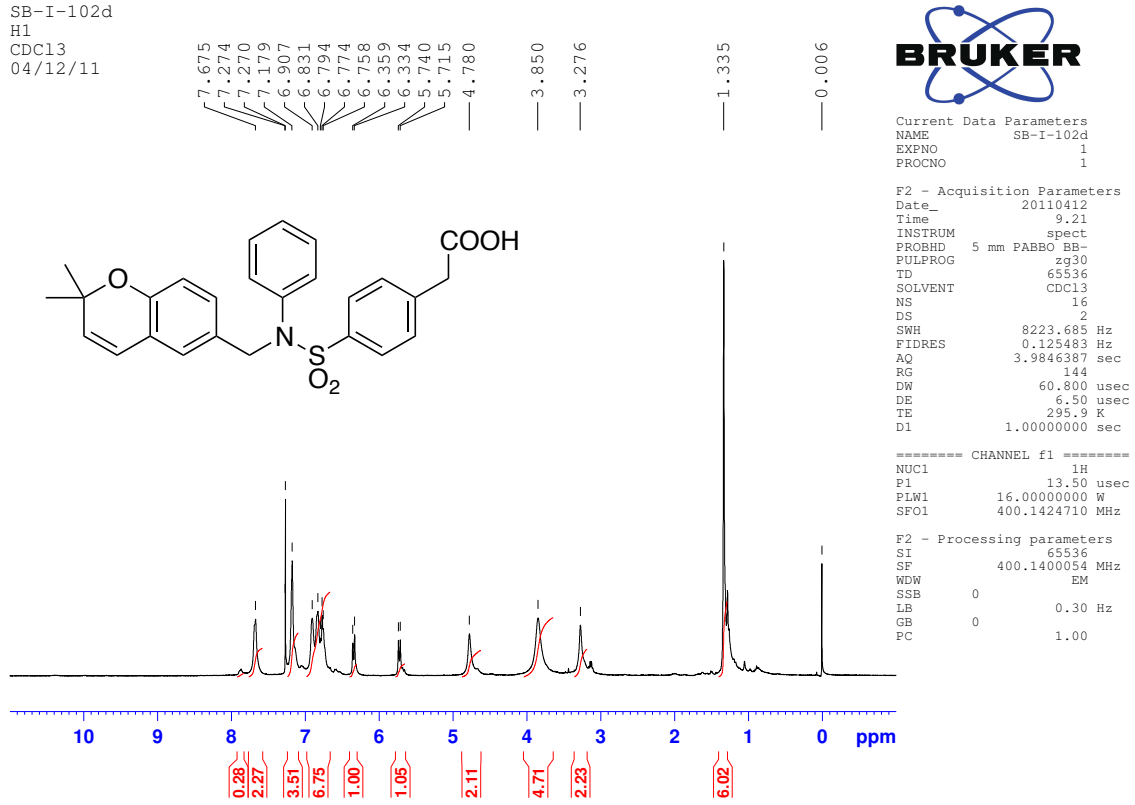
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
29508 formula(e) evaluated with 118 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 F: 1-6 S: 1-50 Na: 1-2

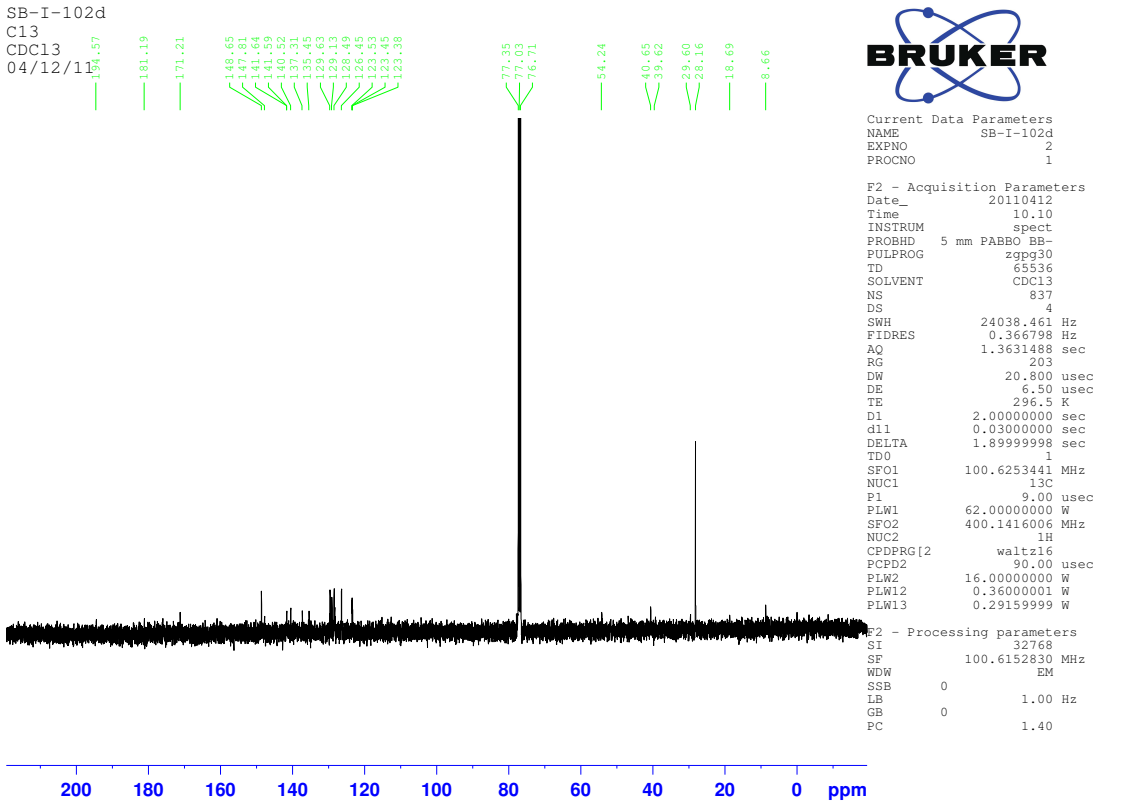
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
512.1106	512.1119	-1.3	-2.5	13.5	16.4	C25 H22 N O4 F3 S Na

2-(4-(*N*-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)-*N*-phenylsulfamoyl)phenyl)acetic acid (5c)



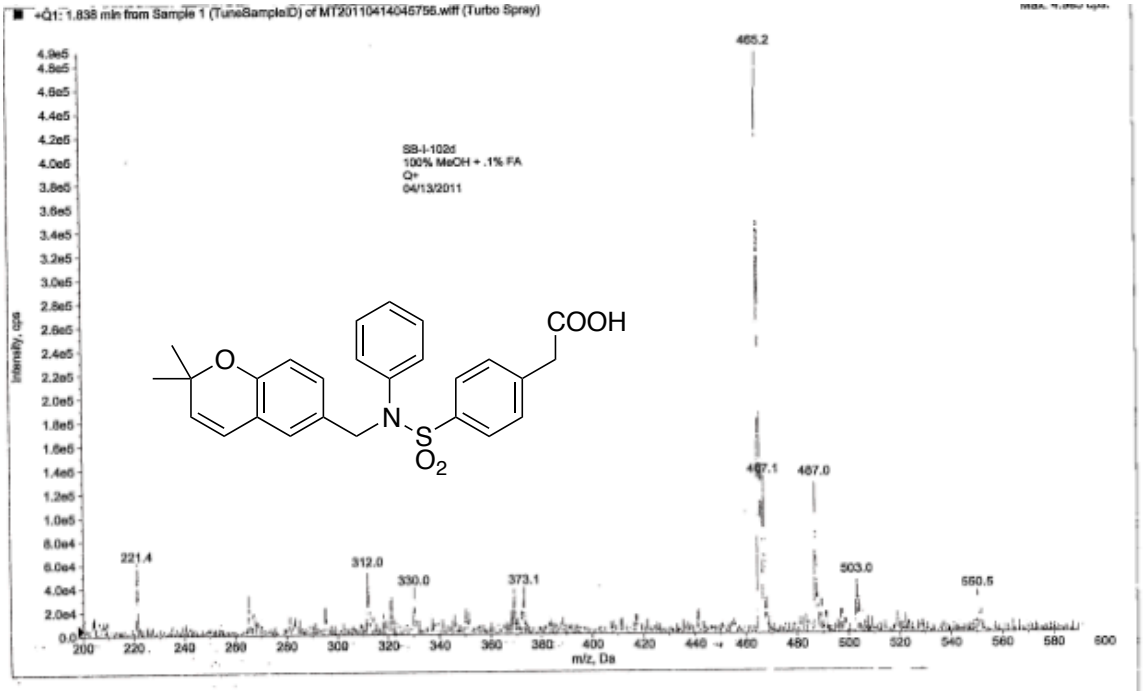
BRUKER

```
Current Data Parameters
NAME          SB-I-102d
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20110412
Time               9.21
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8223.685 Hz
FIDRES         0.125483 Hz
AQ             3.9846387 sec
RG                  144
DW                60.800 usec
DE                 6.50 usec
TE                295.9 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1                13.50 usec
PLW1        16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

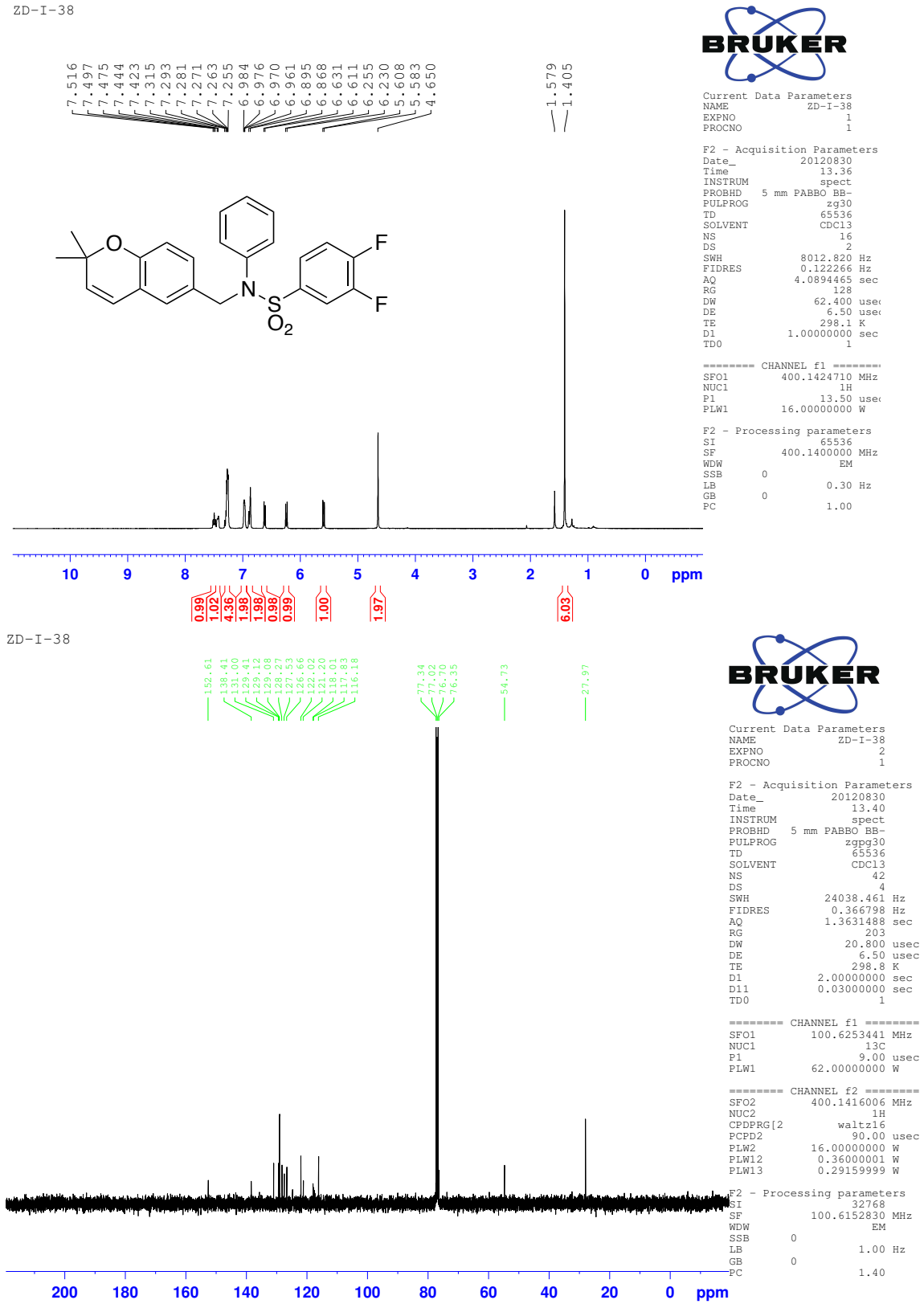


BRUKER

```
Current Data Parameters
NAME          SB-I-102d
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20110412
Time              10.10
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  837
DS                    4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631488 sec
RG                  203
DW                20.800 usec
DE                 6.50 usec
TE                296.5 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                   1
SFO1        100.6253441 MHz
NUC1                13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO2        400.1416006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

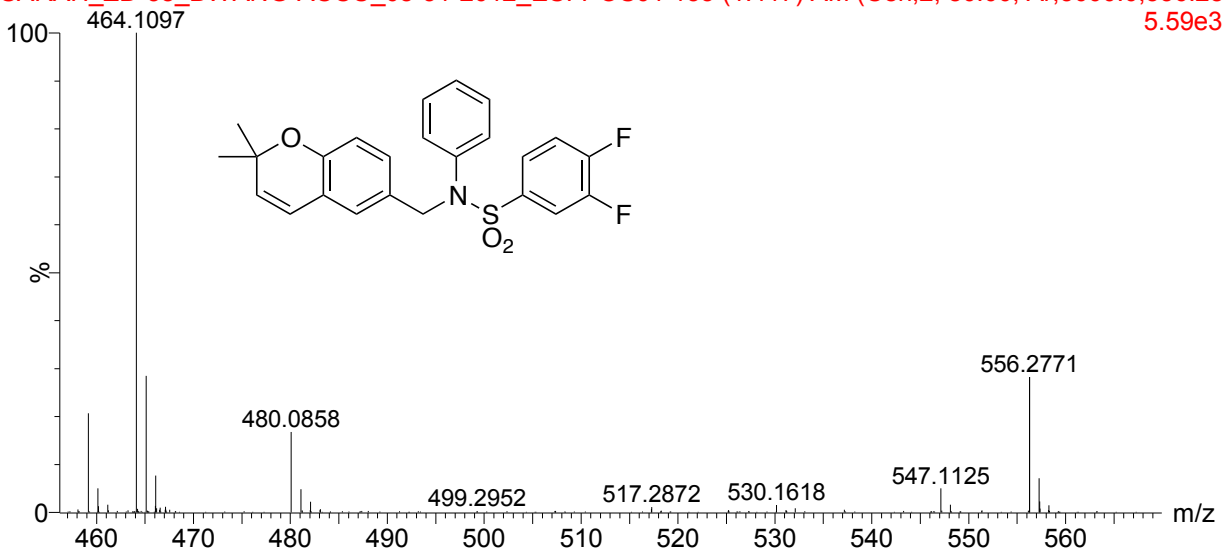

+Q1: 1.838 min from Sample 1 (TuneSampleID) of MT20110414045756.wiff (Turbo Spray)
SB-I-102d
100% MeOH + .1% FA
Q+
04/13/2011
COOH
O
N
S
O2
Intensity, cps
m/z, Da
465.2
487.1
487.0
503.0
221.4
312.0
330.0
373.1
550.5

N-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-difluoro-*N*-phenylbenzenesulfonamide (5d)



100%MeOH+0.1%HCOOH **13:45:26 31-Aug-2012**

SARAH_ZD-38_BWANG-ACCU_08-31-2012_ESI-POS01 135 (1.417) AM (Cen,2, 80.00, Ar,5000.0,556.28, 5.59e3



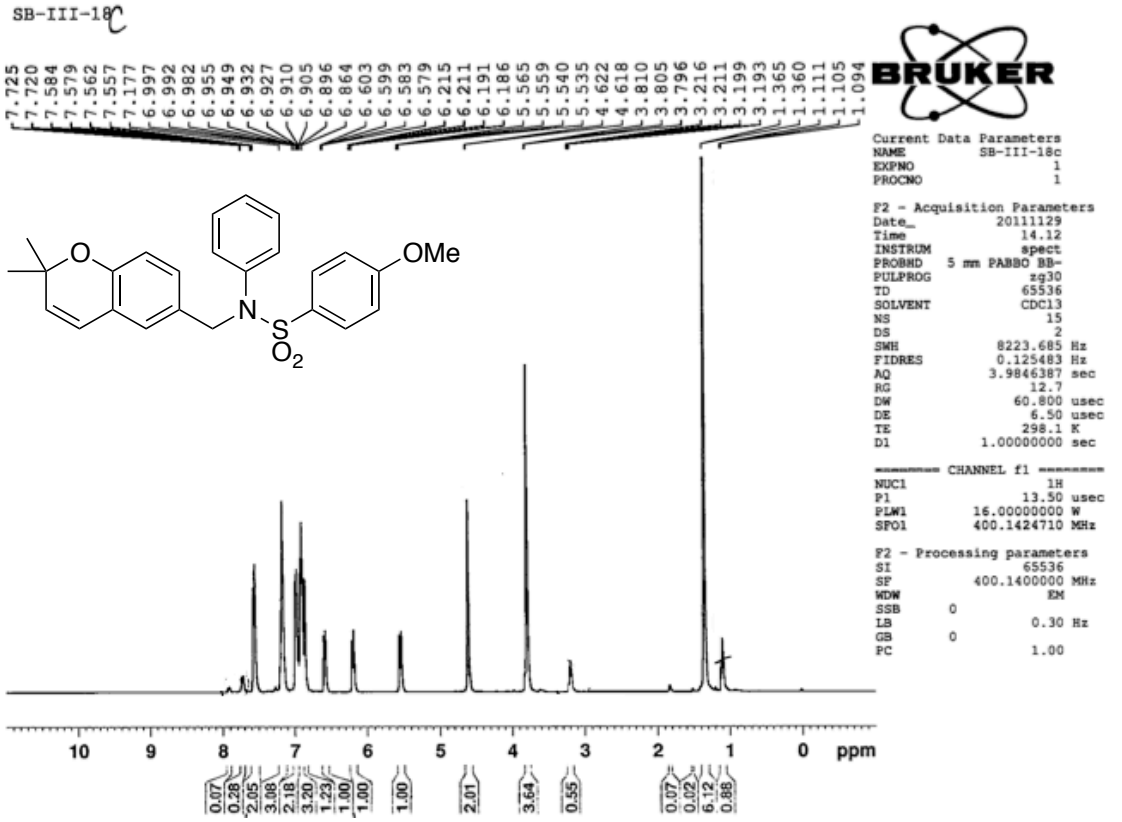
Elemental Composition Report

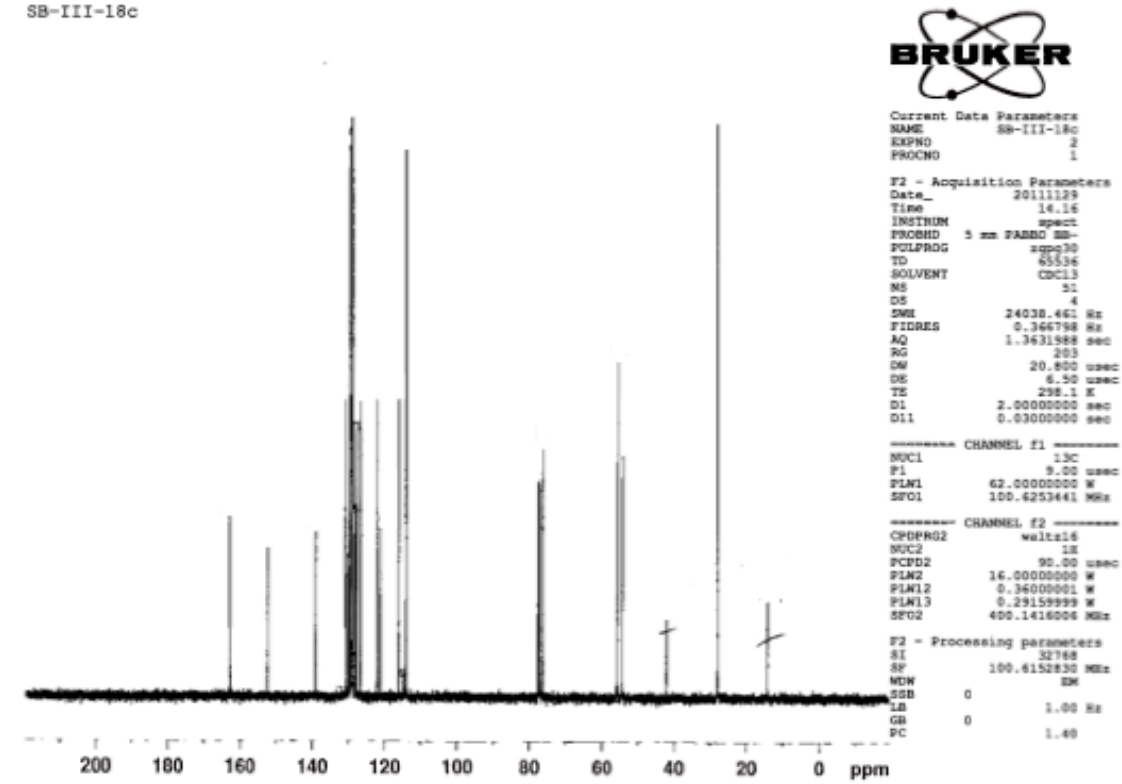
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
18747 formula(e) evaluated with 66 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 F: 1-6 S: 1-50 Na: 1-2

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
464.1097	464.1108	-1.1	-2.4	13.5	5.7	C24 H21 N O3 F2 S Na

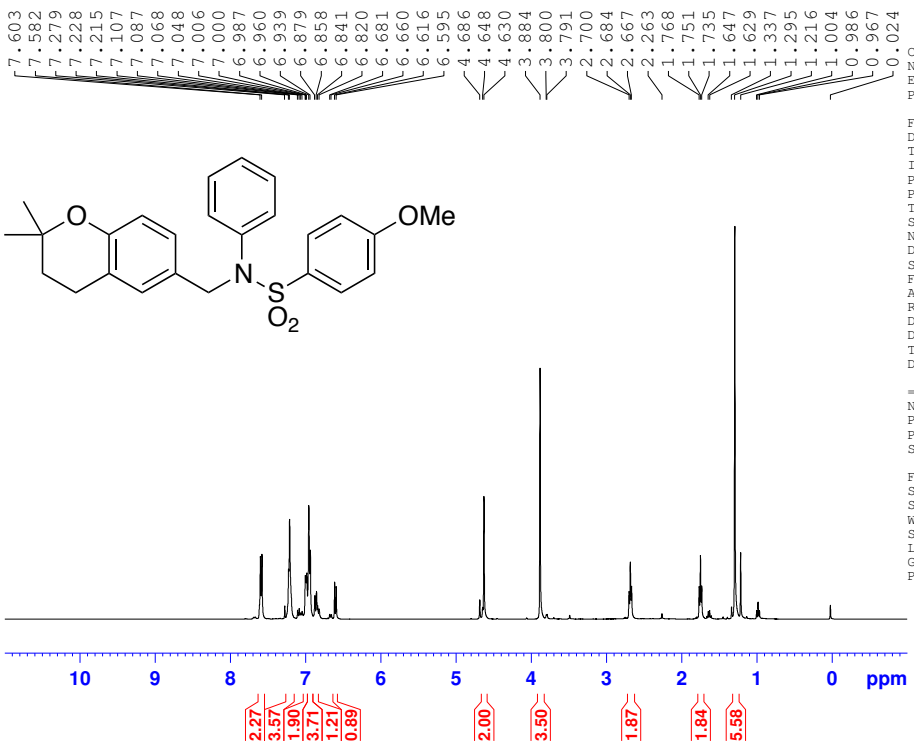
_N_-((2,2-dimethyl-2_H_-chromen-6-yl)methyl)-4-methoxy-_N_-phenylbenzenesulfonamide (5e)





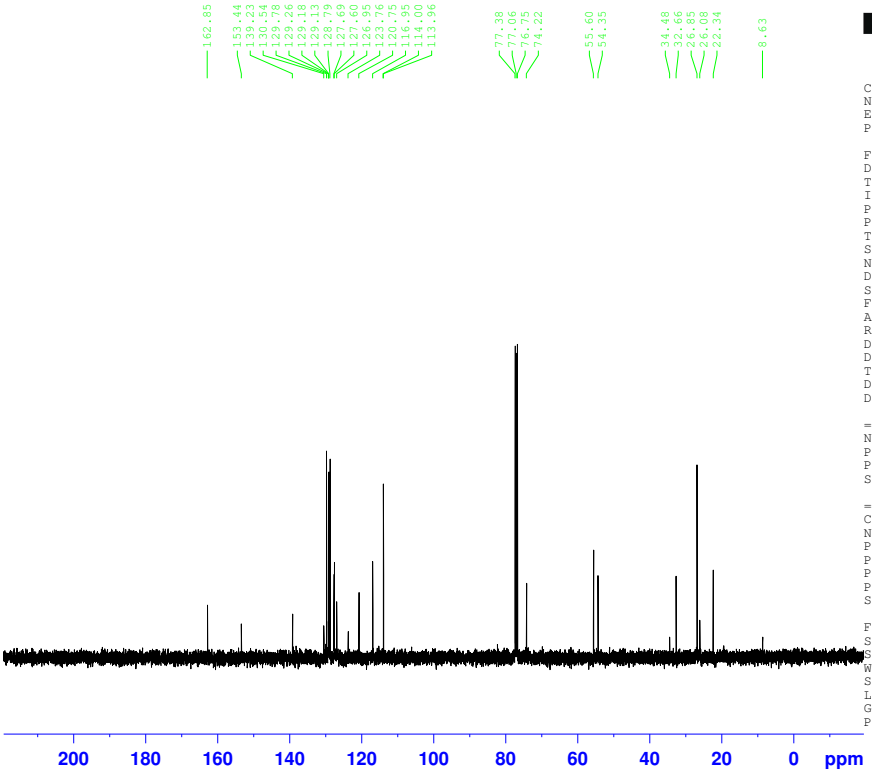
N-((2,2-dimethylchroman-6-yl)methyl)-4-methoxy-*N*-phenylbenzenesulfonamide (6a)

SB-IV-84a

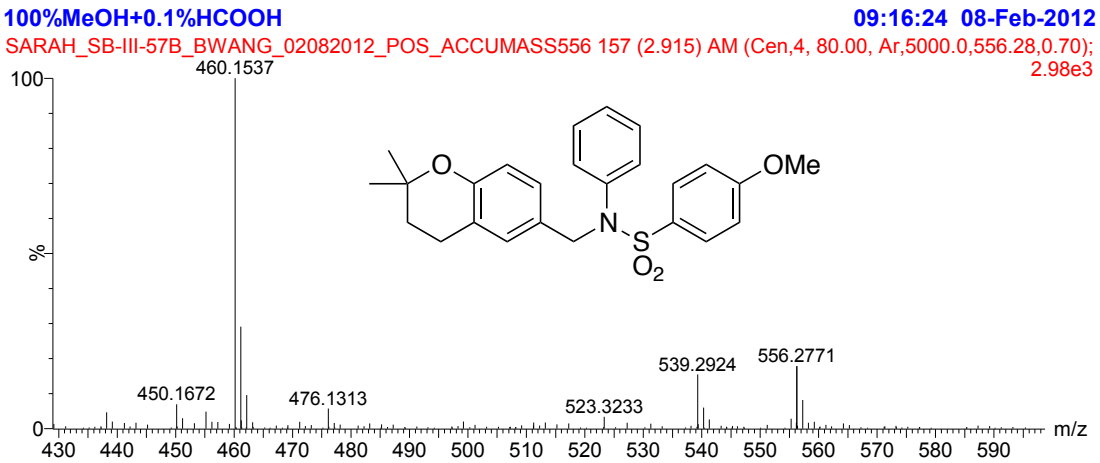



```
Current Data Parameters
NAME                 SB-IV-84a
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20120605
Time                   10.03
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      71.8
DW                    60.800 usec
DE                     6.50 usec
TE                    297.2 K
D1                  1.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PLW1               16.00000000 W
SFO1              400.1424710 MHz

F2 - Processing parameters
SI                         65536
SF                400.1400000 MHz
WDW                           EM
SSB            0
LB                      0.30 Hz
GB             0
PC                      1.00
```

SB-IV-84a




```
Current Data Parameters
NAME                 SB-IV-84a
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20120605
Time                   10.06
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                zgpg30
TD                     65536
SOLVENT                CDCl3
NS                        30
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                       203
DW                    20.800 usec
DE                     6.50 usec
TE                    297.5 K
D1                  2.00000000 sec
D11                 0.03000000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                      9.00 usec
PLW1               62.00000000 W
SFO1              100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  90.00 usec
PLW2               16.00000000 W
PLW12               0.36000001 W
PLW13               0.29159999 W
SFO2              400.1416006 MHz

F2 - Processing parameters
SI                         32768
SF                100.6152830 MHz
WDW                           EM
SSB            0
LB                      1.00 Hz
GB             0
PC                      1.40
```



Elemental Composition Report

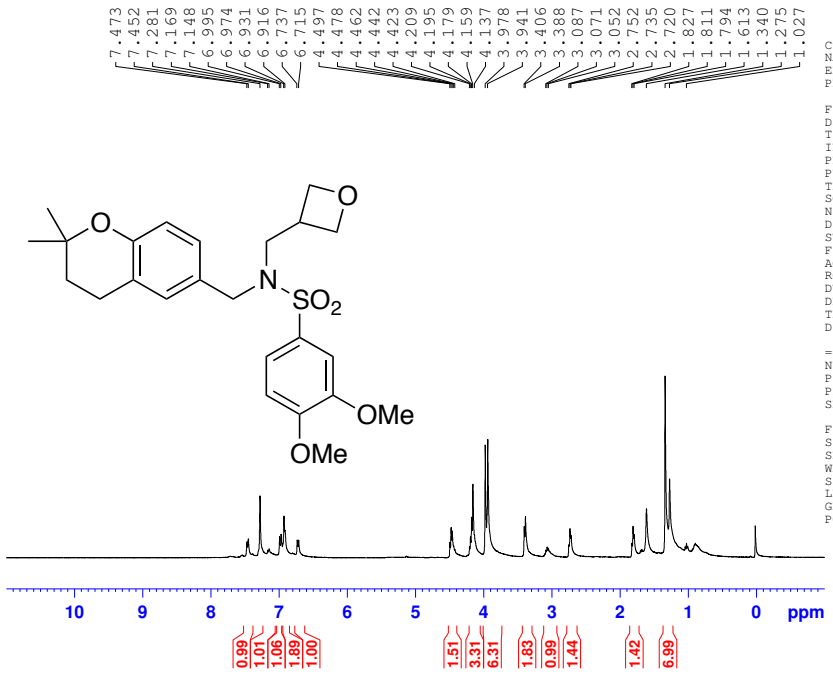
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Even Electron Ions
10789 formula(e) evaluated with 35 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

Minimum:				-1.5	
Maximum:		5.0	5.0	50.0	
Mass	Calc. Mass	mDa		PPM	DBE Formula
460.1537	460.1559	-2.2	-4.8	12.5	C25 H27 N O4 Na S

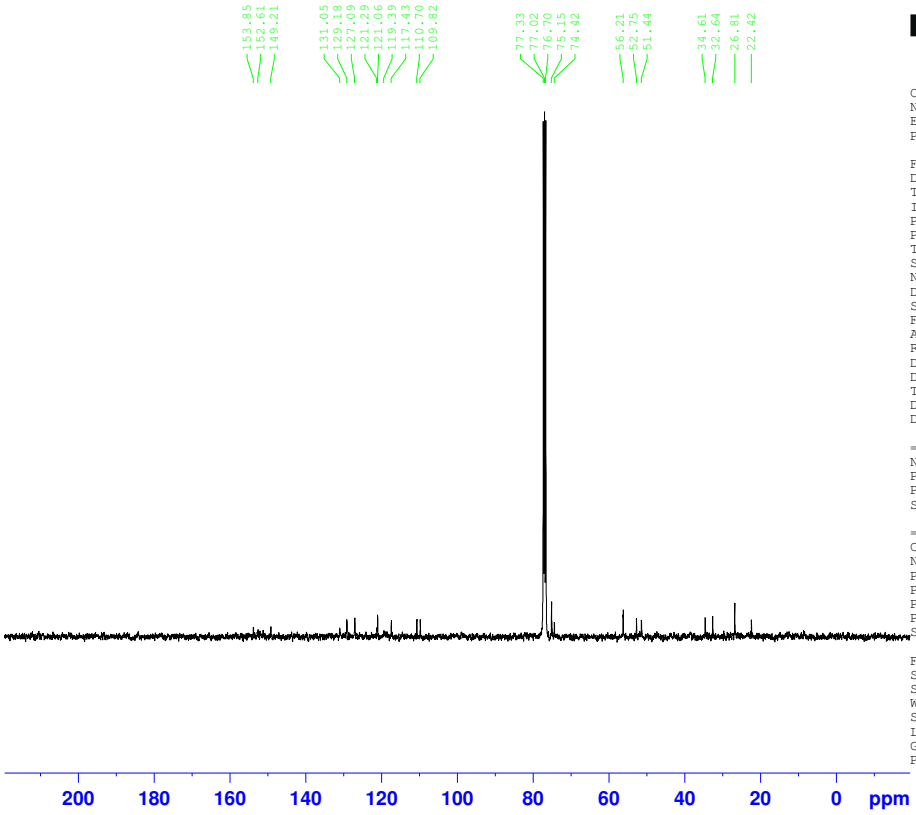
N-((2,2-dimethylchroman-6-yl)methyl)-3,4-dimethoxy-*N*-(oxetan-3-ylmethyl)benzenesulfonamide (6b)

SB-IV-76b

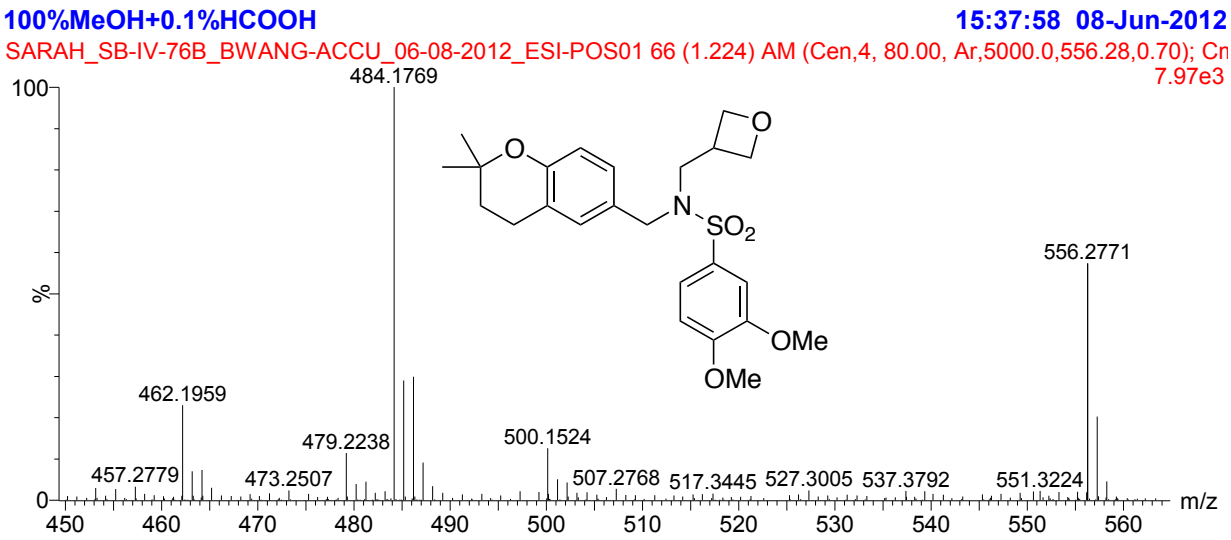



```
Current Data Parameters
NAME           SB-IV-76b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120531
Time               15.38
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                   101
DW                60.800 usec
DE                 6.50 usec
TE                298.2 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-IV-76b




```
Current Data Parameters
NAME           SB-IV-76b
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120601
Time               14.19
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   440
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   114
DW                20.800 usec
DE                 6.50 usec
TE                298.2 K
D1           2.00000000 sec
D11          0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.00 usec
PLW1        62.00000000 W
SFO1        100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W
SFO2        400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 5.00 Hz
GB        0
PC                 1.00
```



Elemental Composition Report

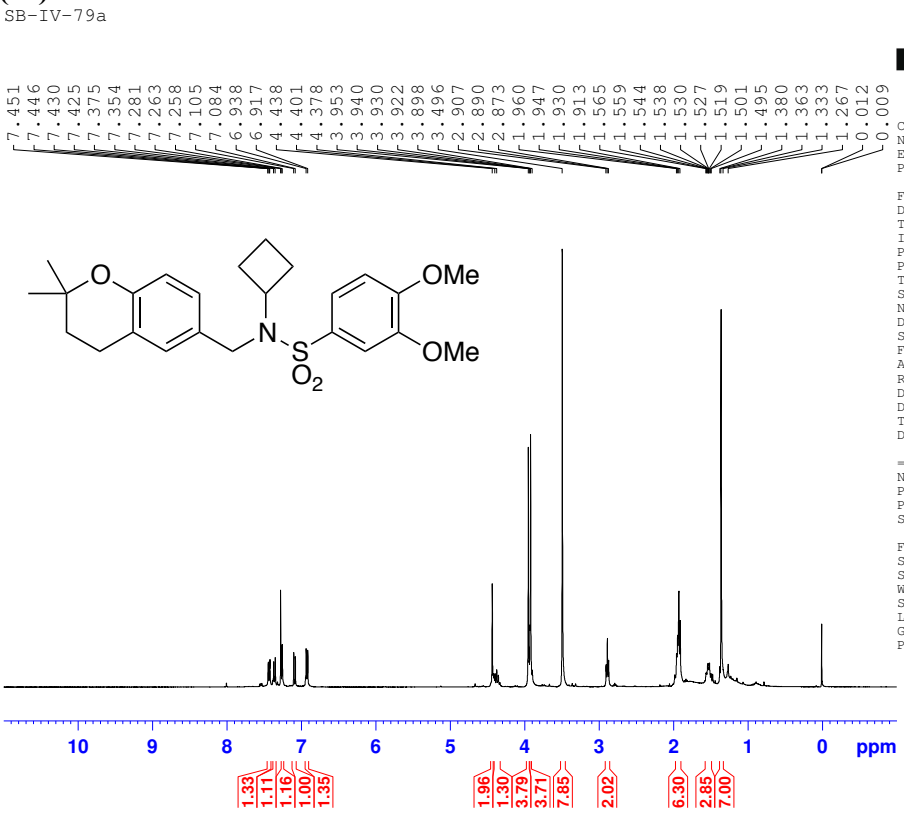
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4033 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 1-50

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
462.1959	462.1950	0.9	1.9	9.5	137.9	C24 H32 N O6 S

_N_-Cyclobutyl-_N_-((2,2-dimethylchroman-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (6c)

SB-IV-79a



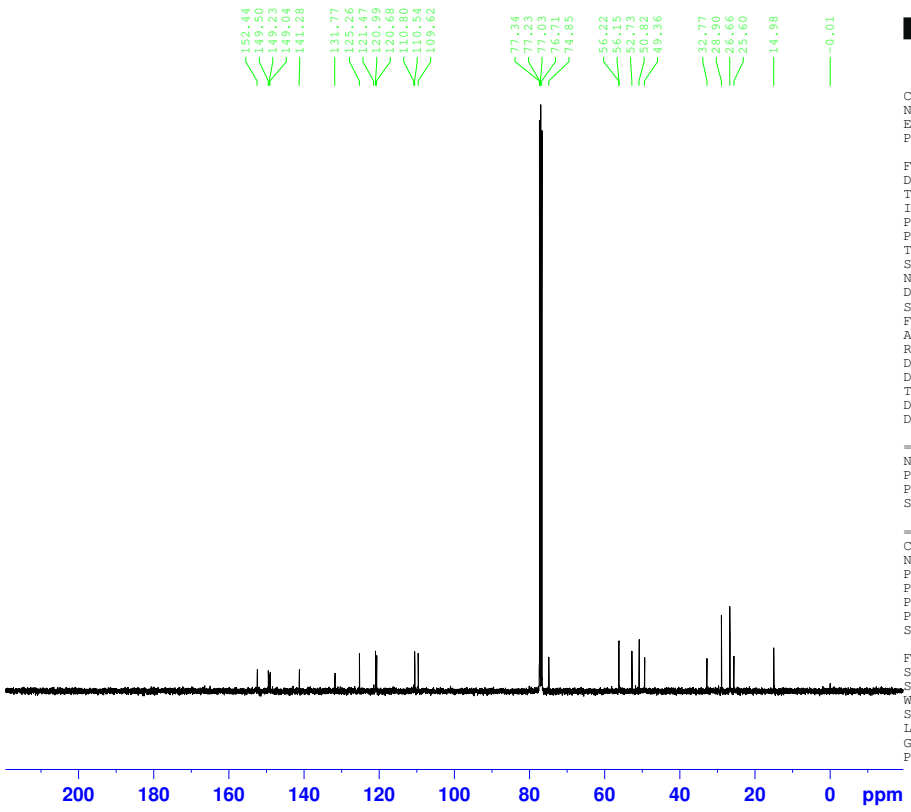
Current Data Parameters
NAME SB-IV-79a
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120601
Time 10.36
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 128
DW 60.800 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PLW1 16.00000000 W
SFO1 400.1424710 MHz

F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

SB-IV-79a



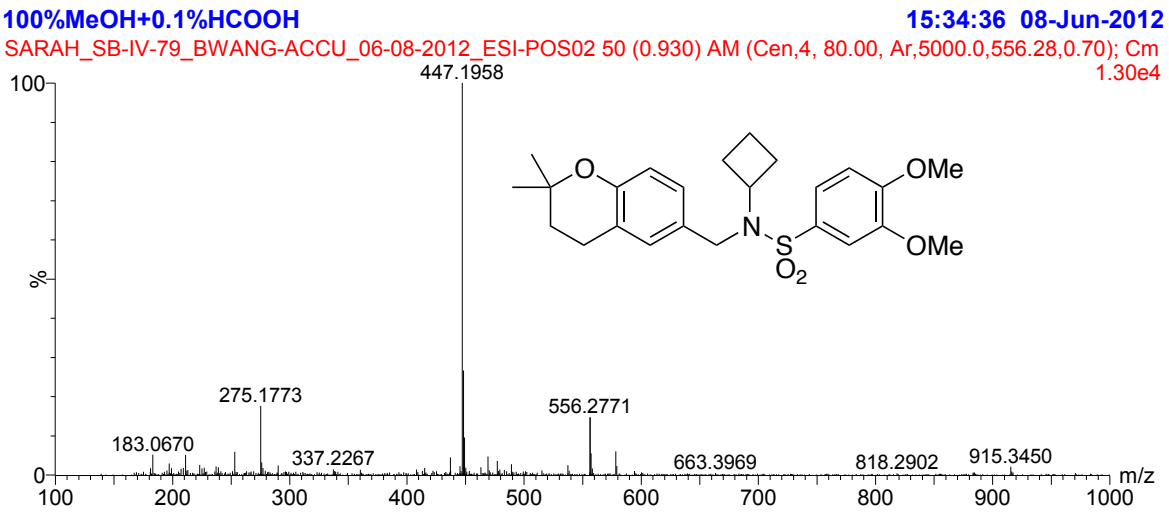
Current Data Parameters
NAME SB-IV-79a
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120601
Time 10.53
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 711
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 298.4 K
D1 2.00000000 sec
D11 0.03000000 sec

======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PLW1 62.00000000 W
SFO1 100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 16.00000000 W
PLW12 0.36000001 W
PLW13 0.29159999 W
SFO2 400.1416006 MHz

F2 - Processing parameters
SI 32768
SF 100.6152830 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.20



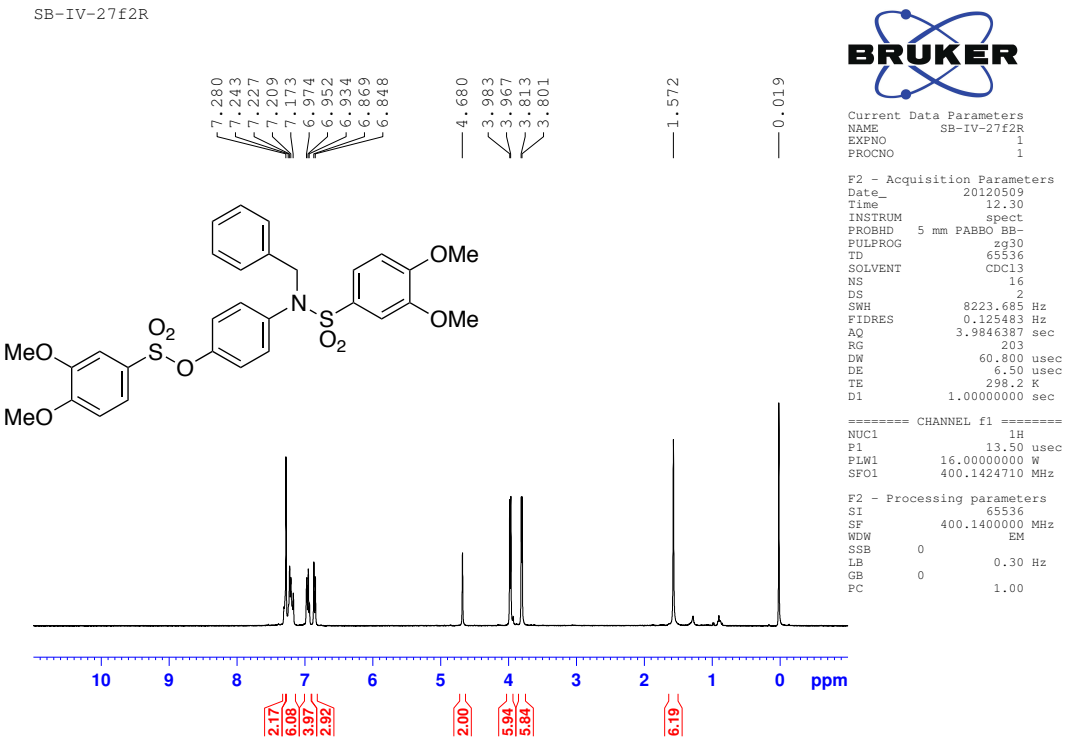
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
3713 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 1-50

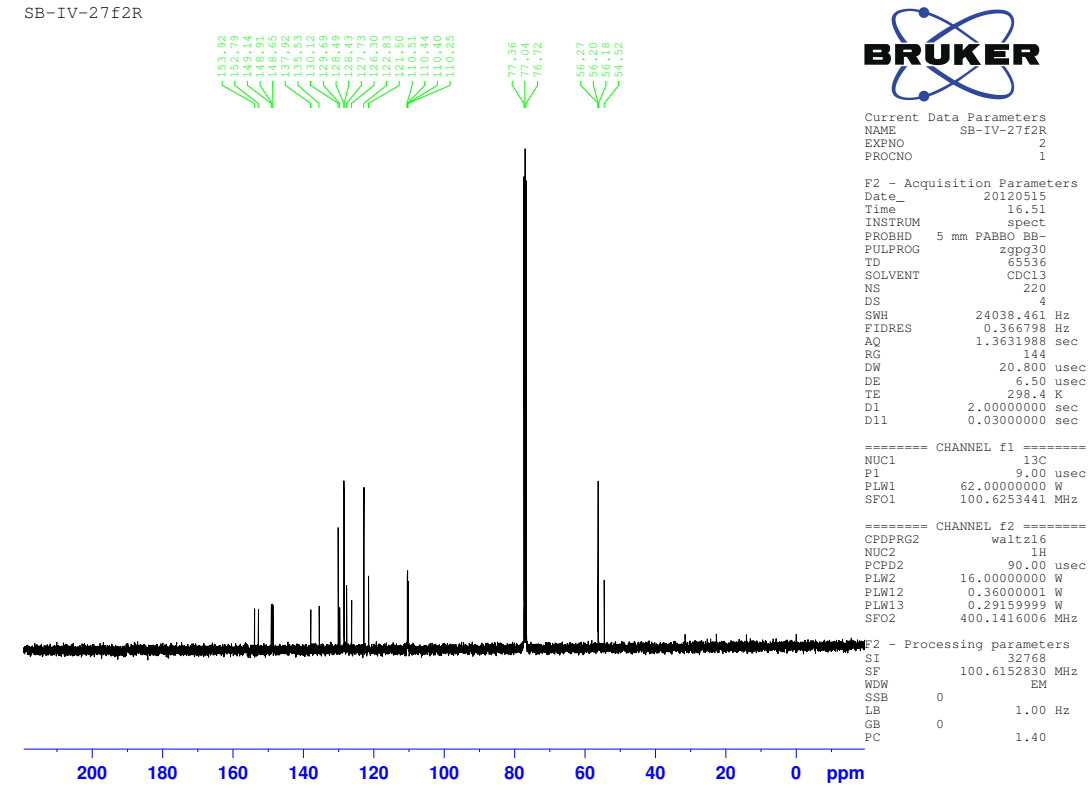
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
447.1958	447.1954	0.4	0.9	9.5	5.4	C23 H31 N2 O5 S

4-(*N*-Benzyl-3,4-dimethoxyphenylsulfonamido)phenyl 3,4-dimethoxybenzenesulfonate (7a)



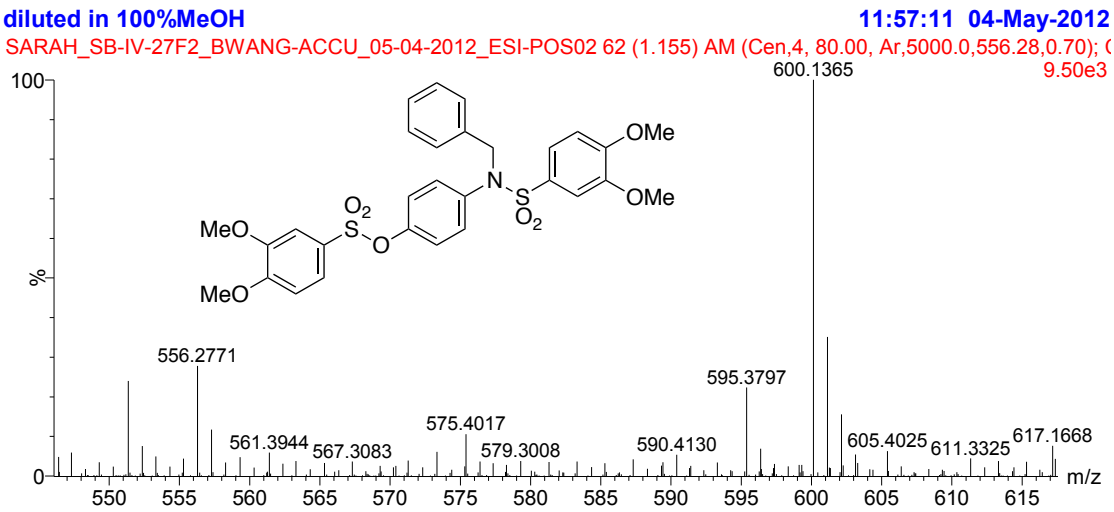
BRUKER

```
Current Data Parameters
NAME         SB-IV-27f2R
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120509
Time               12.30
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                   203
DW                60.800 usec
DE                 6.50 usec
TE                298.2 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                13.50 usec
PLW1        16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB               0.30 Hz
GB        0
PC               1.00
```



BRUKER

```
Current Data Parameters
NAME         SB-IV-27f2R
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120515
Time               16.51
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   220
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   144
DW                20.800 usec
DE                 6.50 usec
TE                298.4 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.00 usec
PLW1        62.00000000 W
SFO1        100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W
SFO2        400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB               1.00 Hz
GB        0
PC               1.40
```



Elemental Composition Report

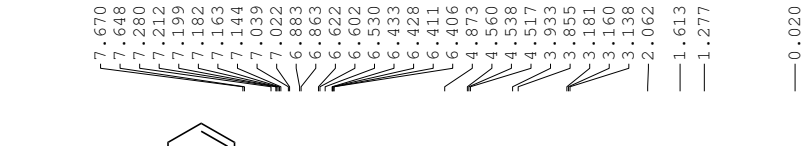
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off

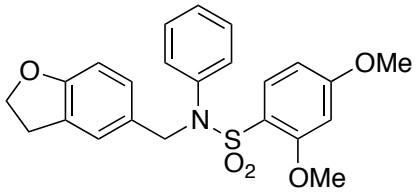
Monoisotopic Mass, Even Electron Ions
9247 formula(e) evaluated with 53 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100 S: 0-6

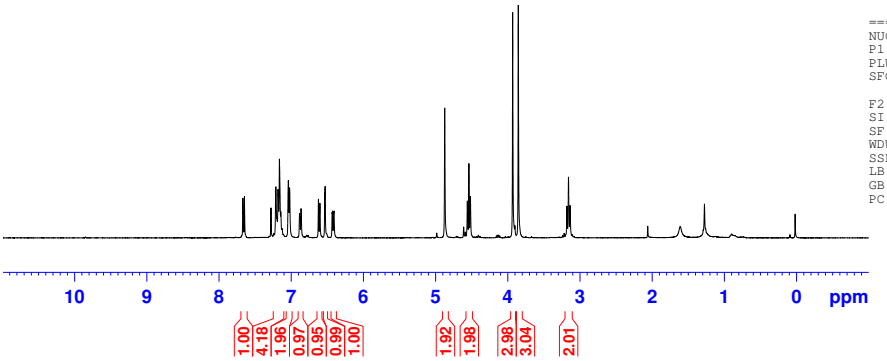
Minimum:				-1.5	
Maximum:		5.0	5.0	50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
600.1365	600.1362	0.3	0.5	15.5	C29 H30 N O9 S2

N-((2,3-Dihydrobenzofuran-5-yl)methyl)-2,4-dimethoxy-*N*-phenylbenzenesulfonamide (8a)

SB-III-128d

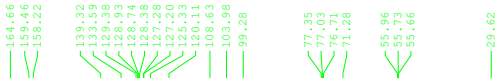


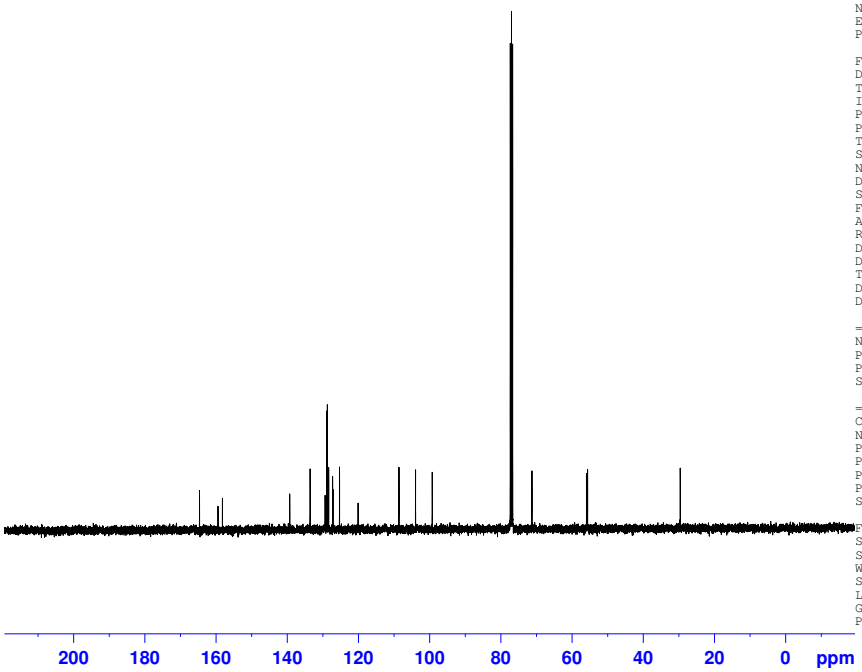




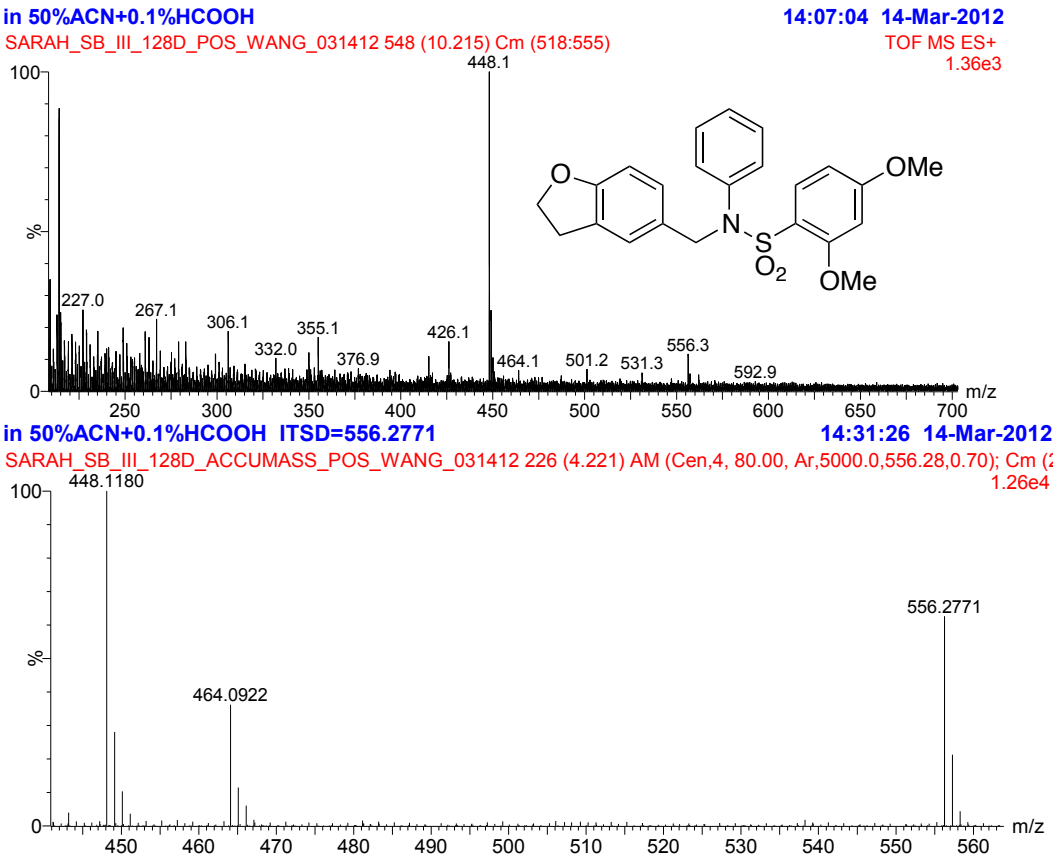
```
Current Data Parameters
NAME         SB-III-128d
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120309
Time               13.41
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                   144
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-III-128d





```
Current Data Parameters
NAME         SB-III-128d
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120309
Time               13.44
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   146
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.1 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



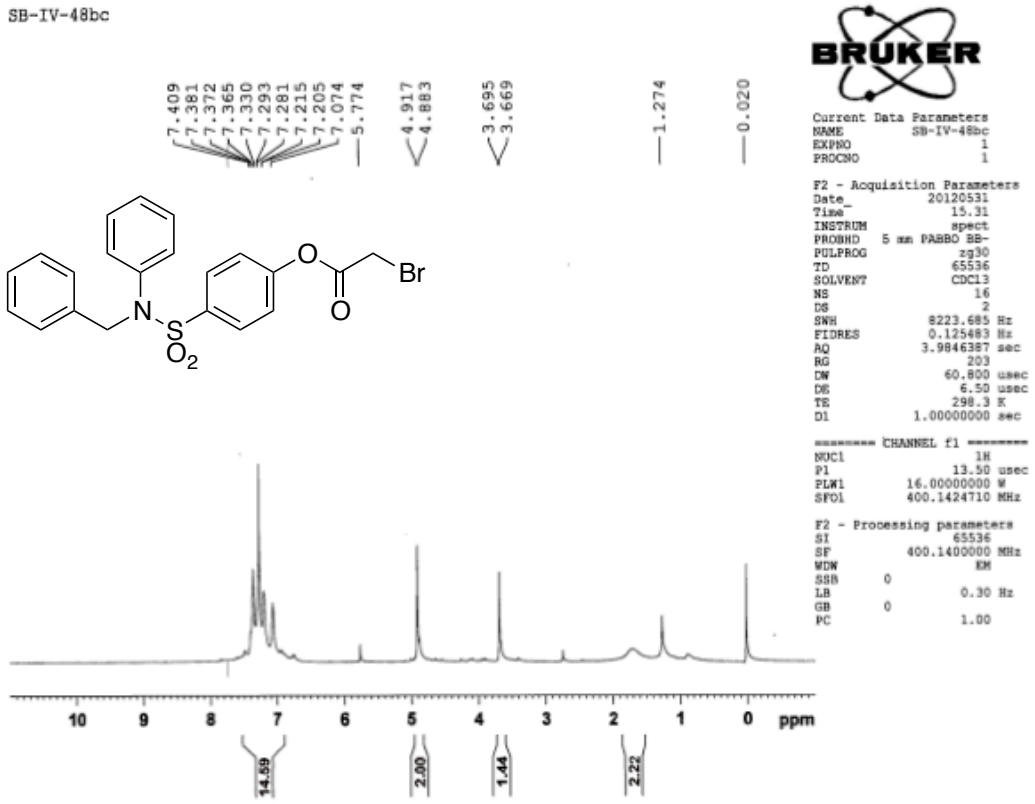
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

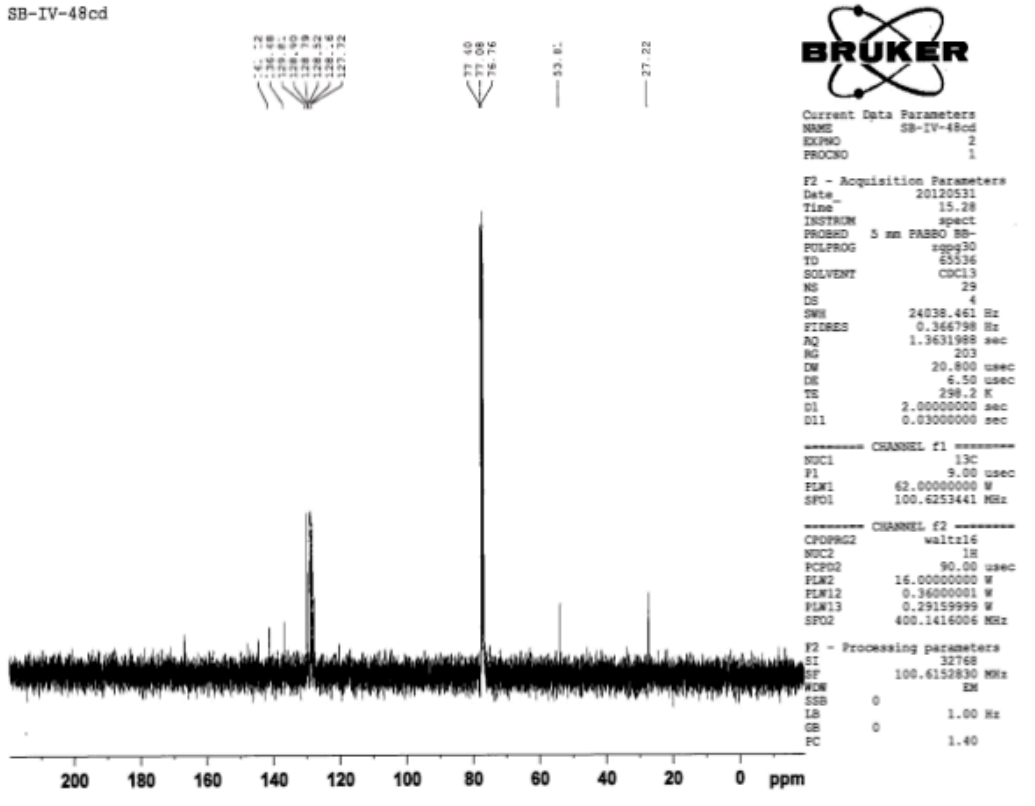
Monoisotopic Mass, Even Electron Ions
5917 formula(e) evaluated with 27 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20 S: 1-6 23Na: 0-1

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
448.1180	448.1195	-1.5	-3.3	12.5	9.5	C23 H23 N O5 S Na

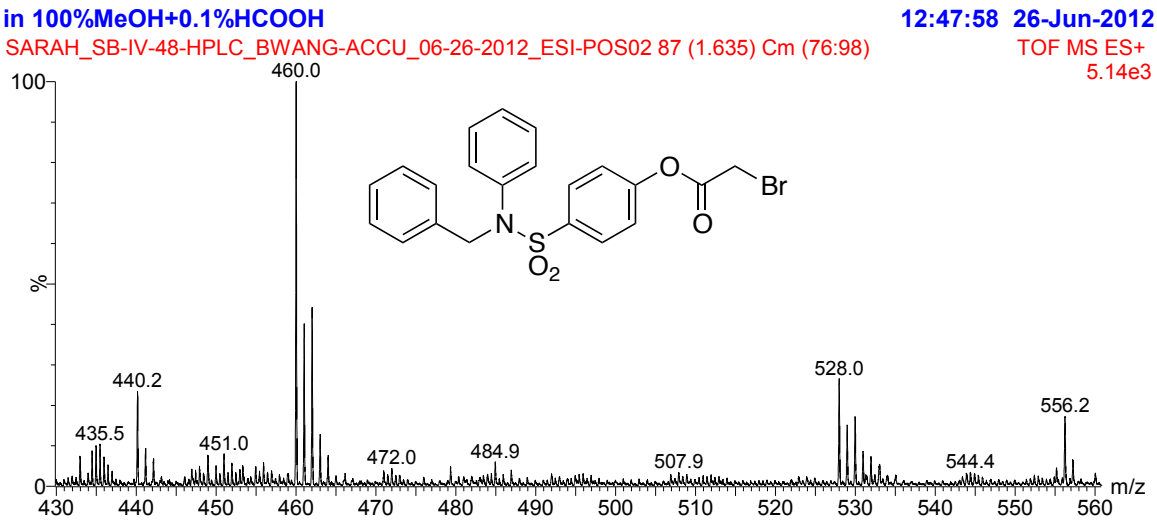
4-(*N*-benzyl-*N*-phenylsulfamoyl)phenyl 2-bromoacetate (8b)




```
Current Data Parameters
NAME                  SB-IV-48bc
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120531
Time                       15.31
INSTRUM                    spect
PROBHD   5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8223.685 Hz
FIDRES                 0.125483 Hz
AQ                     3.9846387 sec
RG                          203
DW                       60.800 usec
DE                        6.50 usec
TE                       298.3 K
D1                    1.00000000 sec

======== CHANNEL f1 ========
NUC1                         1H
P1                        13.50 usec
PLW1                16.00000000 W
SFO1                400.1424710 MHz

F2 - Processing parameters
SI                        65536
SF                  400.1400000 MHz
WDW                          EM
SSB                   0
LB                        0.30 Hz
GB                    0
PC                        1.00
```

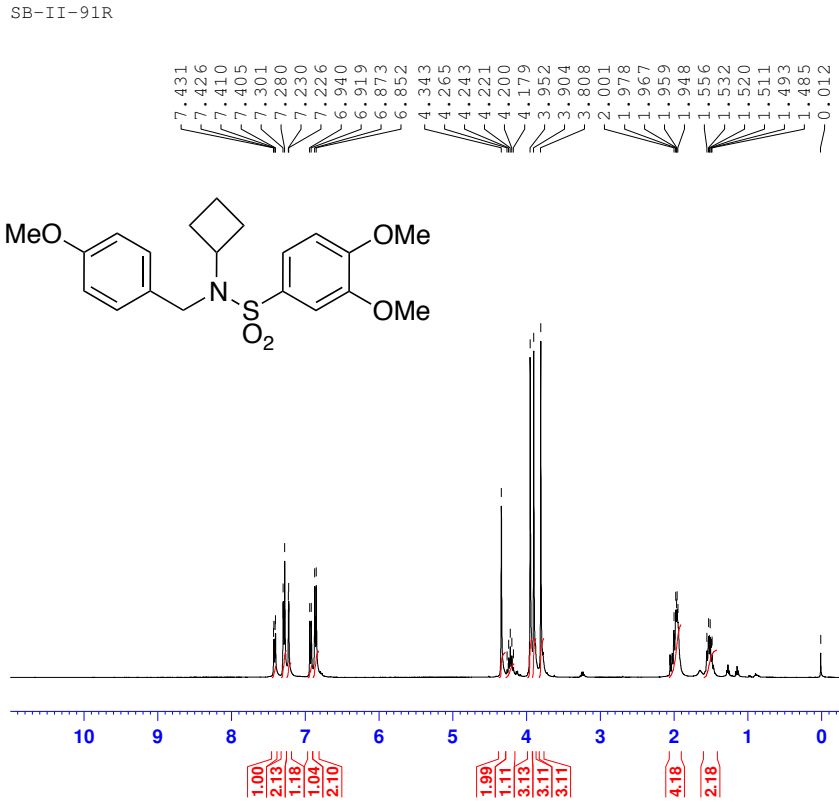



```
Current Data Parameters
NAME                  SB-IV-48cd
EXPNO                          2
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120531
Time                       15.28
INSTRUM                    spect
PROBHD   5 mm PABBO BB-
PULPROG                 zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                           29
DS                            4
SWH                   24038.461 Hz
FIDRES                 0.366798 Hz
AQ                     1.3631988 sec
RG                          203
DW                       20.800 usec
DE                        6.50 usec
TE                       298.2 K
D1                    2.00000000 sec
D11                   0.03000000 sec

======== CHANNEL f1 ========
NUC1                        13C
P1                         9.00 usec
PLW1                62.00000000 W
SFO1               100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                     90.00 usec
PLW2                16.00000000 W
PLW12                0.36000001 W
PLW13                0.29159999 W
SFO2               400.1416006 MHz

F2 - Processing parameters
SI                        32768
SF                 100.6152830 MHz
WDW                          EM
SSB                   0
LB                        1.00 Hz
GB                    0
PC                        1.40
```


in 100%MeOH+0.1%HCOOH
12:47:58 26-Jun-2012
SARAH_SB-IV-48-HPLC_BWANG-ACCU_06-26-2012_ESI-POS02 87 (1.635) Cm (76:98)
TOF MS ES+
5.14e3
100
%
0
460.0
440.2
435.5
451.0
472.0
484.9
507.9
528.0
544.4
556.2
m/z
430
440
450
460
470
480
490
500
510
520
530
540
550
560
N
S
O2
O
O
Br

N-Cyclobutyl-3,4-dimethoxy-*N*-(4-methoxybenzyl)benzenesulfonamide (9a)

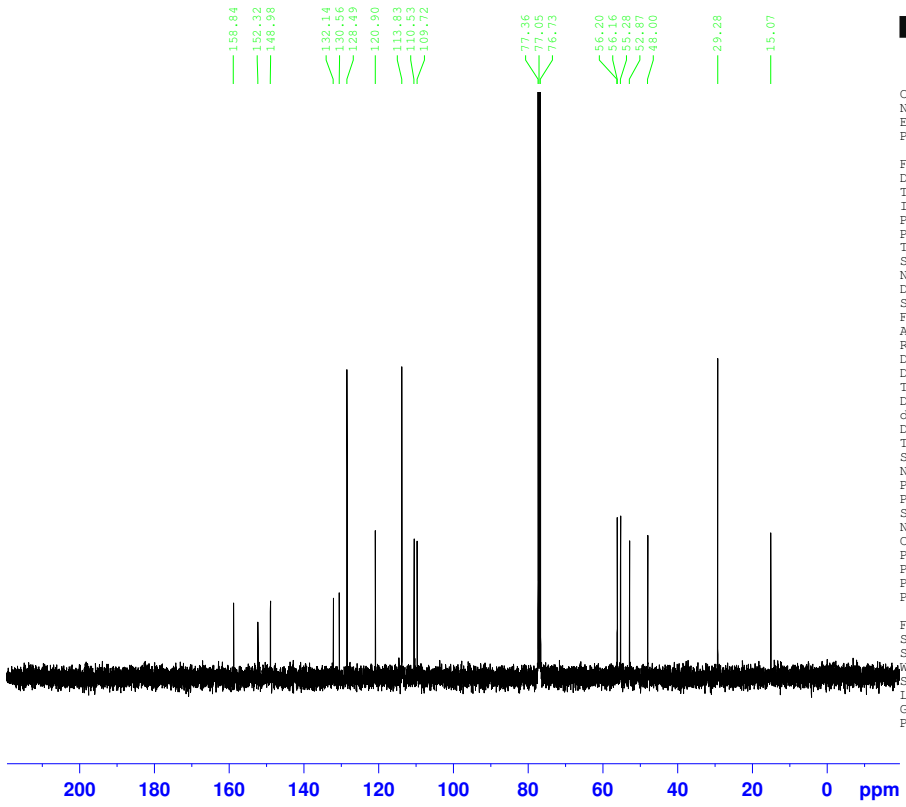
SB-II-91R



BRUKER

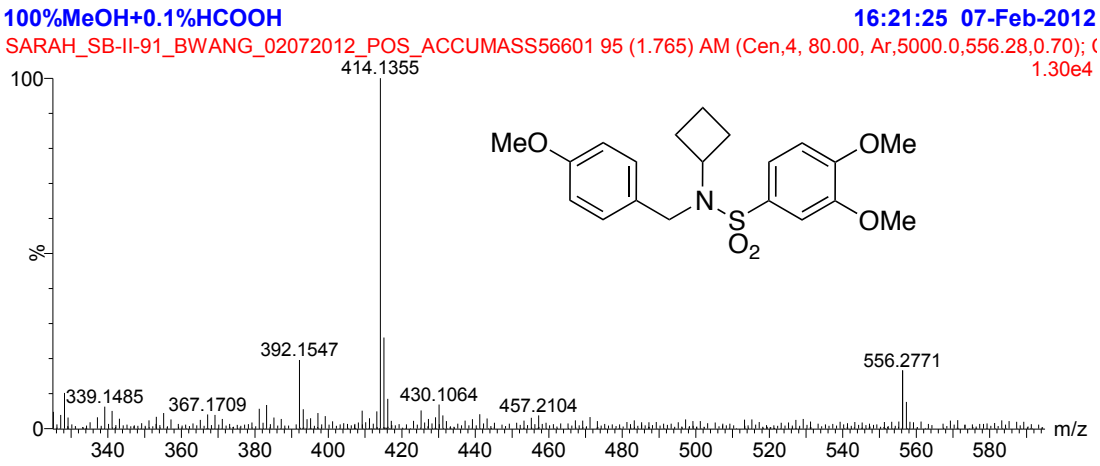
```
Current Data Parameters
NAME                 SB-II-91R
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20111101
Time                   16.47
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                       203
DW                  60.800 usec
DE                   6.50 usec
TE                   298.1 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PLW1             16.00000000 W
SFO1             400.1424710 MHz

F2 - Processing parameters
SI                        65536
SF               400.1400000 MHz
WDW                          EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

SB-II-91R



BRUKER

```
Current Data Parameters
NAME                 SB-II-91R
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_               20111101
Time                   16.53
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       56
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                       203
DW                  20.800 usec
DE                   6.50 usec
TE                   298.2 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
TD0                          1
SFO1             100.6253441 MHz
NUC1                      13C
P1                     9.00 usec
PLW1             62.00000000 W
SFO2             400.1416006 MHz
NUC2                      1H
CPDPRG[2              waltz16
PCPD2                 90.00 usec
PLW2             16.00000000 W
PLW12             0.36000001 W
PLW13             0.29159999 W

F2 - Processing parameters
SI                        32768
SF               100.6152830 MHz
WDW                          EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```



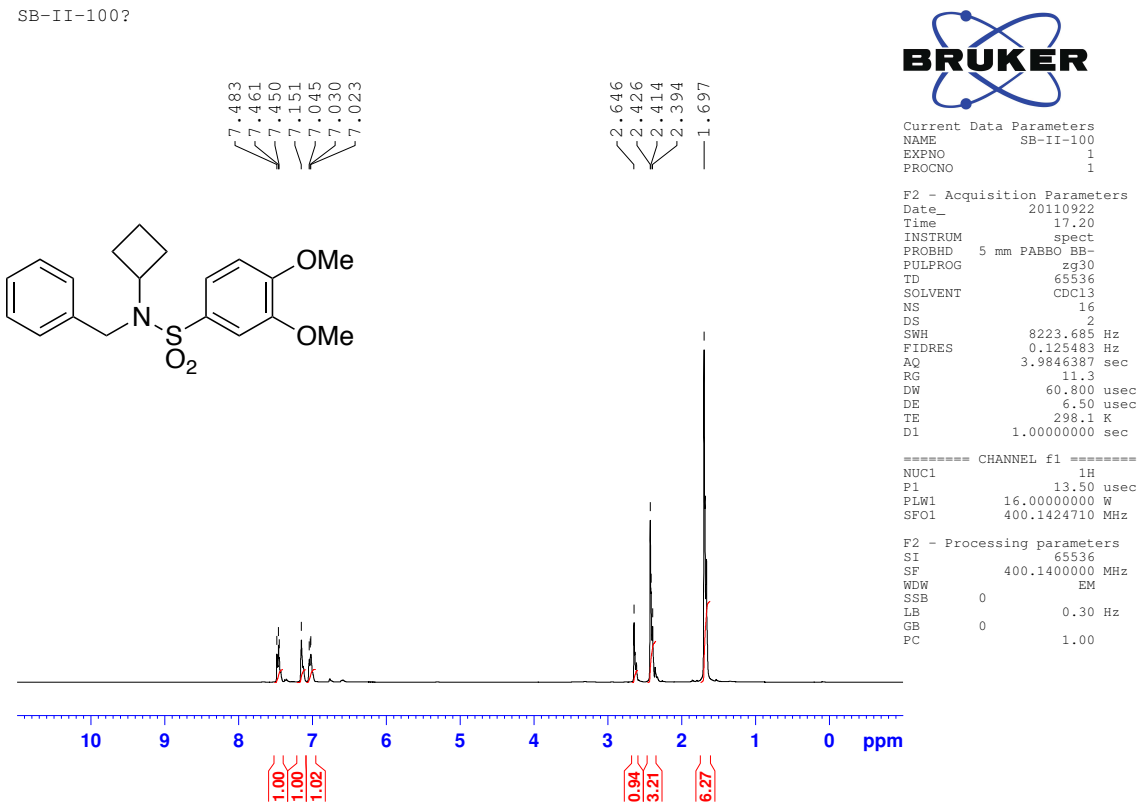
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
7428 formula(e) evaluated with 25 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

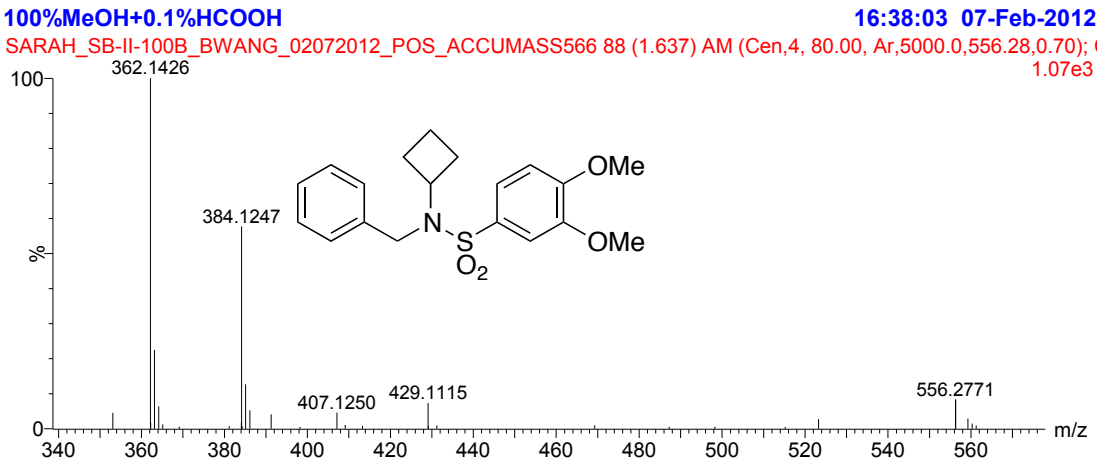
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
414.1355	414.1351	0.4	1.0	8.5	9.3	C20 H25 N O5 Na S

N-Benzyl-*N*-cyclobutyl-3,4-dimethoxybenzenesulfonamide (9b)



BRUKER

```
Current Data Parameters
NAME            SB-II-100
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20110922
Time                17.20
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ               3.9846387 sec
RG                   11.3
DW                 60.800 usec
DE                  6.50 usec
TE                  298.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                  65536
SF           400.1400000 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```



Elemental Composition Report

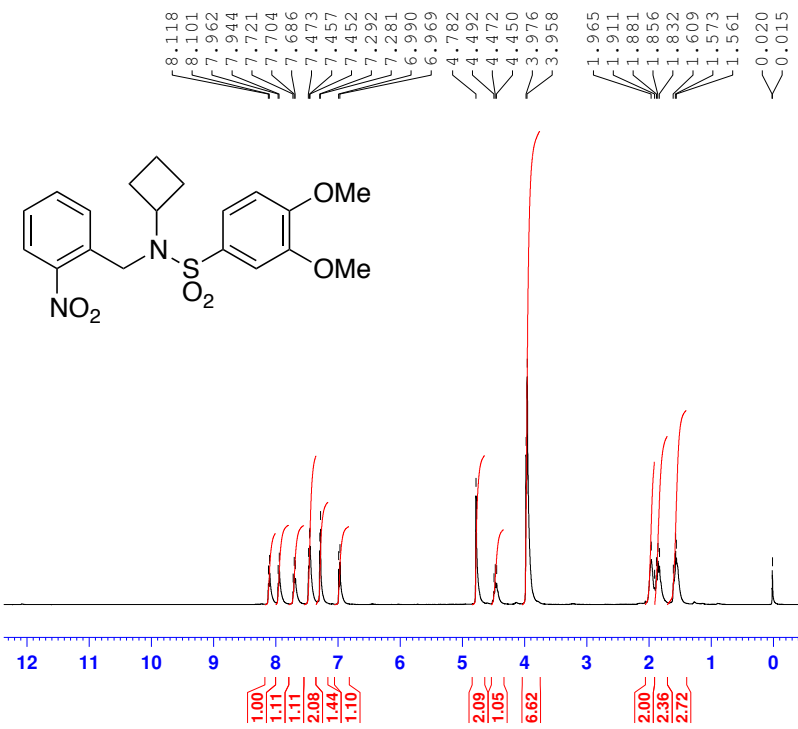
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4422 formula(e) evaluated with 9 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
362.1426	362.1426	0.0	0.0	8.5	1.7	C19 H24 N O4 S

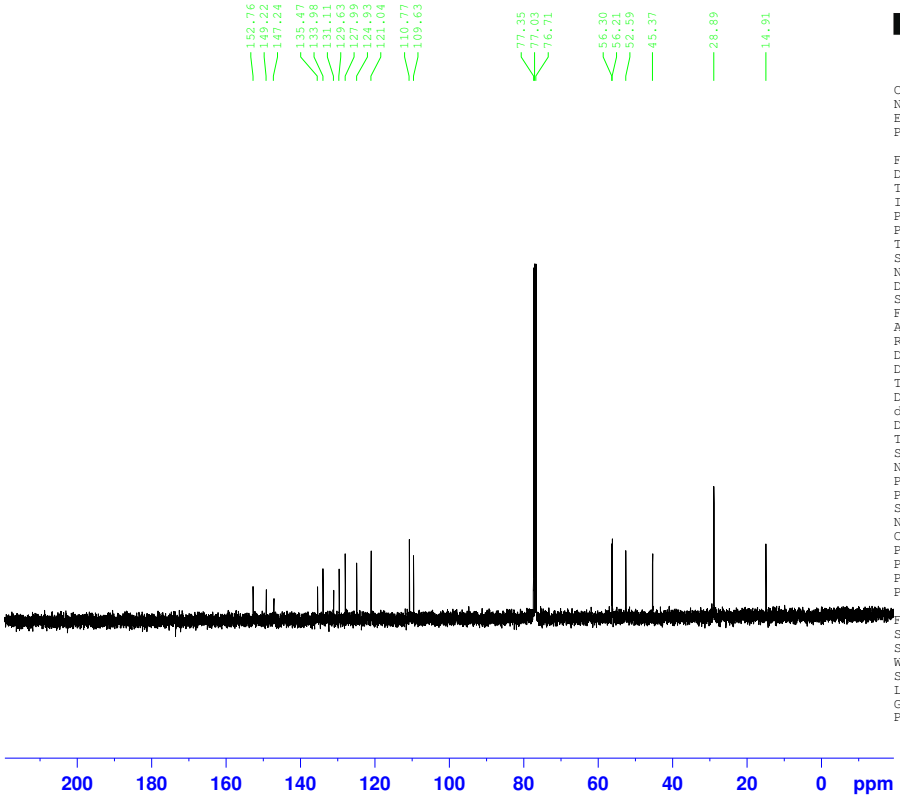
N-Cyclobutyl-3,4-dimethoxy-*N*-(2-nitrobenzyl)benzenesulfonamide (9c)

SB-II-114R

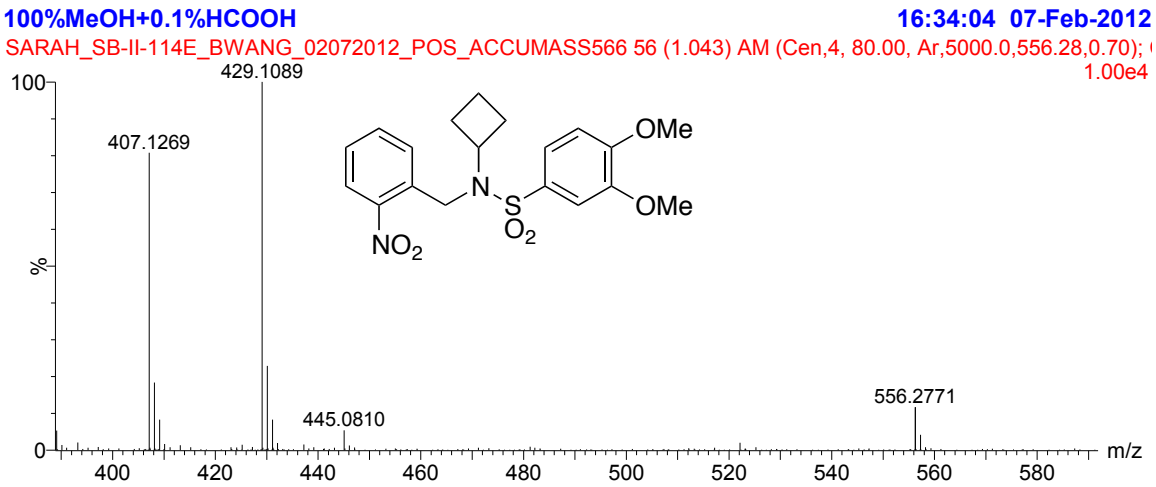


```
Current Data Parameters
NAME          SB-II-114R
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20111027
Time               16.58
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9845889 sec
RG                   203
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-II-114R



```
Current Data Parameters
NAME          SB-II-114R
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20111027
Time               16.49
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   102
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.4 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
TD0                    1
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO2         400.1416006 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



Elemental Composition Report

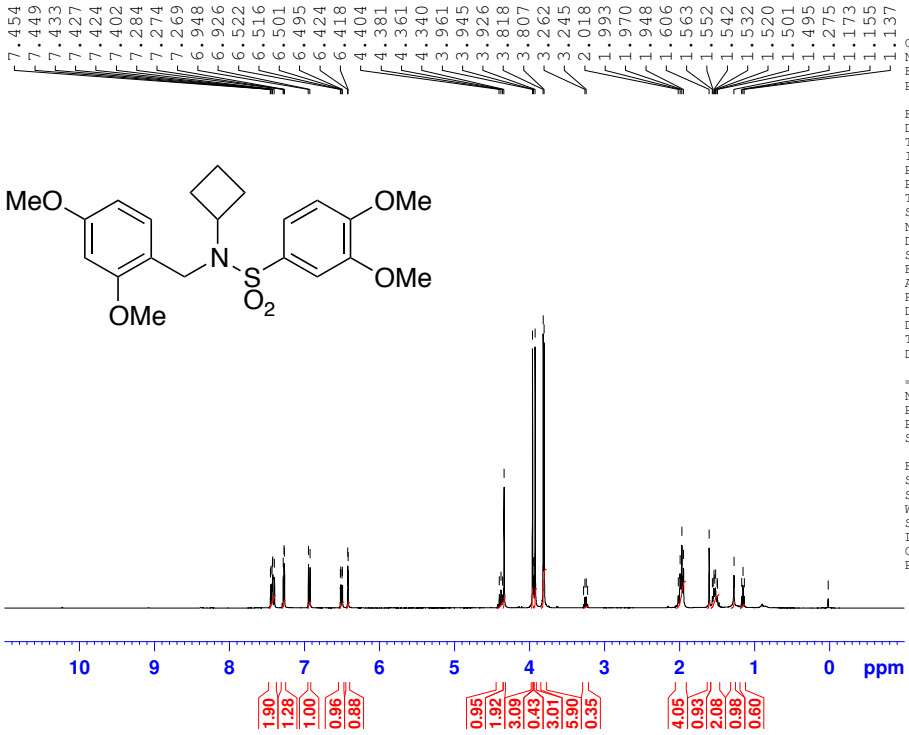
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
6985 formula(e) evaluated with 22 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
407.1269	407.1277	-0.8	-2.0	9.5	15.9	C19 H23 N2 O6 S

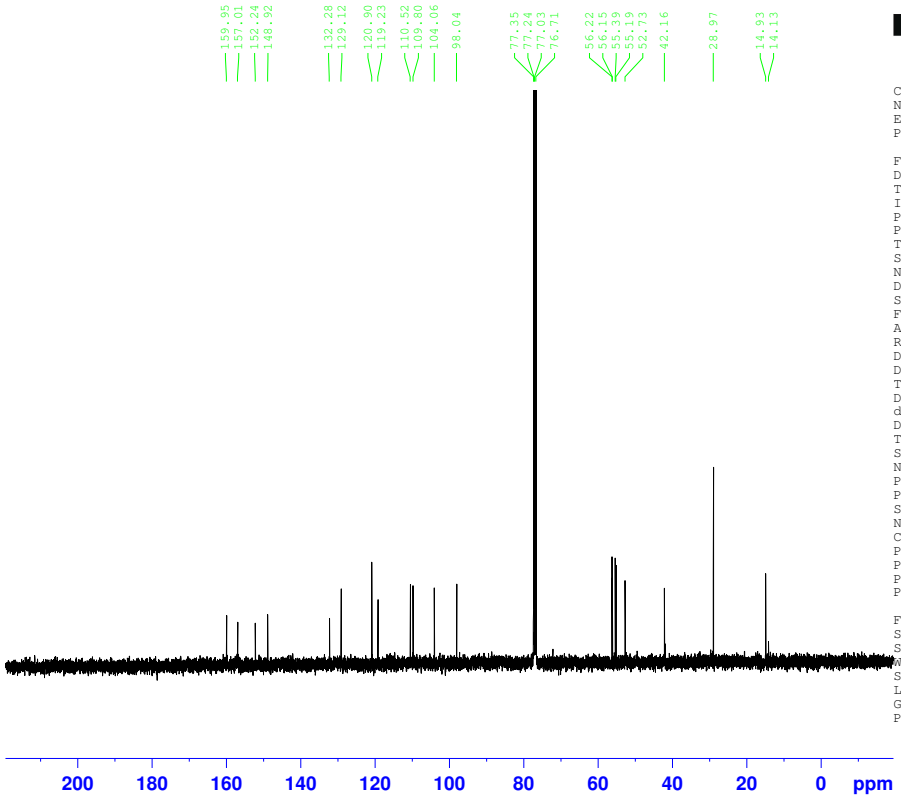
N-Cyclobutyl-*N*-(2,4-dimethoxybenzyl)-3,4-dimethoxybenzenesulfonamide (9d)

SB-II-79b

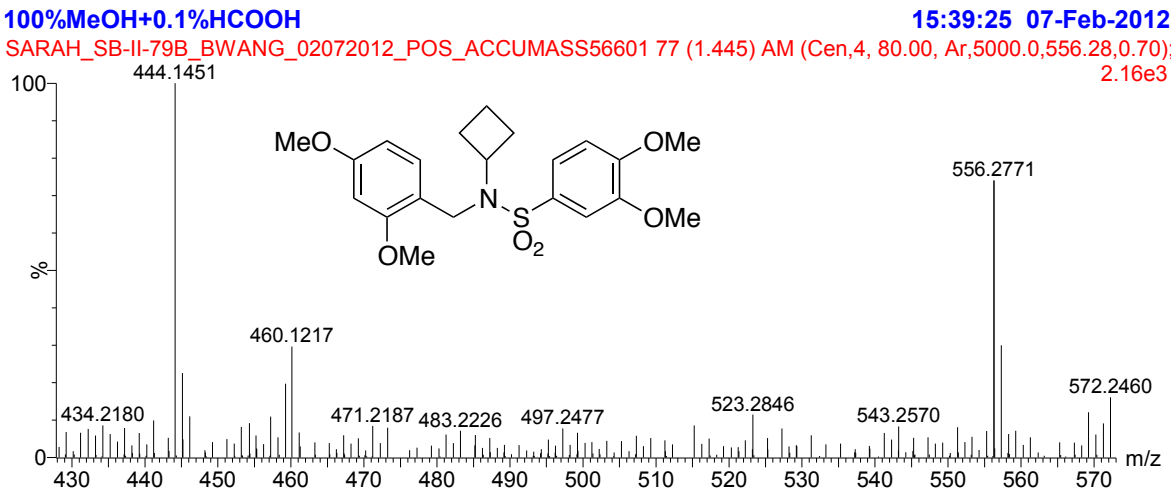



```
Current Data Parameters
NAME                  SB-II-79b
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_               20110726
Time                   10.36
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                   zg
TD                     32768
SOLVENT                CDC13
NS                        16
DS                         2
SWH                 5197.505 Hz
FIDRES              0.158615 Hz
AQ                  3.1523316 sec
RG                      71.8
DW                     96.200 usec
DE                      6.50 usec
TE            0 K
D1                 2.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PLW1              16.00000000 W
SFO1             400.1420007 MHz

F2 - Processing parameters
SI                         32768
SF                400.1400000 MHz
WDW                           EM
SSB           0
LB                      0.30 Hz
GB            0
PC                      1.00
```

SB-II-79b




```
Current Data Parameters
NAME                  SB-II-79b
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_               20110726
Time                   10.53
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                     65536
SOLVENT                CDC13
NS                       292
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                       203
DW                     20.800 usec
DE                      6.50 usec
TE            0 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
TD0                           1
SFO1             100.6253441 MHz
NUC1                       13C
P1                      9.00 usec
PLW1              62.00000000 W
SFO2             400.1416006 MHz
NUC2                       1H
CPDPRG[2               waltz16
PCPD2                  90.00 usec
PLW2              16.00000000 W
PLW12              0.36000001 W
PLW13              0.29159999 W

F2 - Processing parameters
SI                         32768
SF                100.6152830 MHz
WDW                           EM
SSB           0
LB                      1.00 Hz
GB            0
PC                      1.40
```



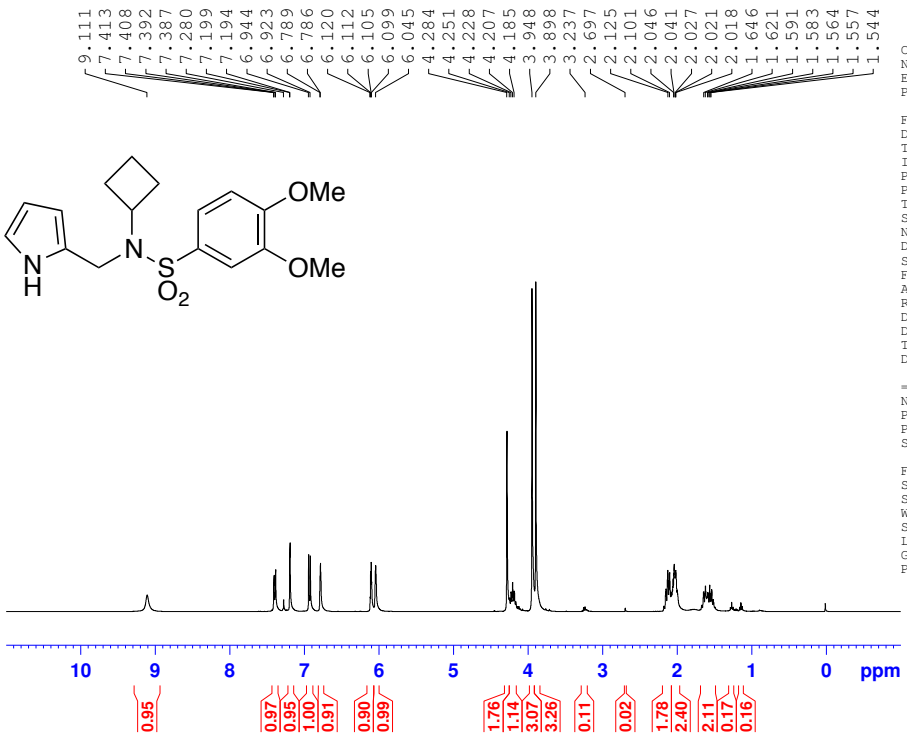
Elemental Composition Report
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
9546 formula(e) evaluated with 32 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE		i-FIT	Formula
444.1451	444.1457	-0.6	-1.4	8.5	8.7		C21 H27 N O6 Na S

N-((1*H*-Pyrrol-2-yl)methyl)-*N*-cyclobutyl-3,4-dimethoxybenzenesulfonamide (9e)

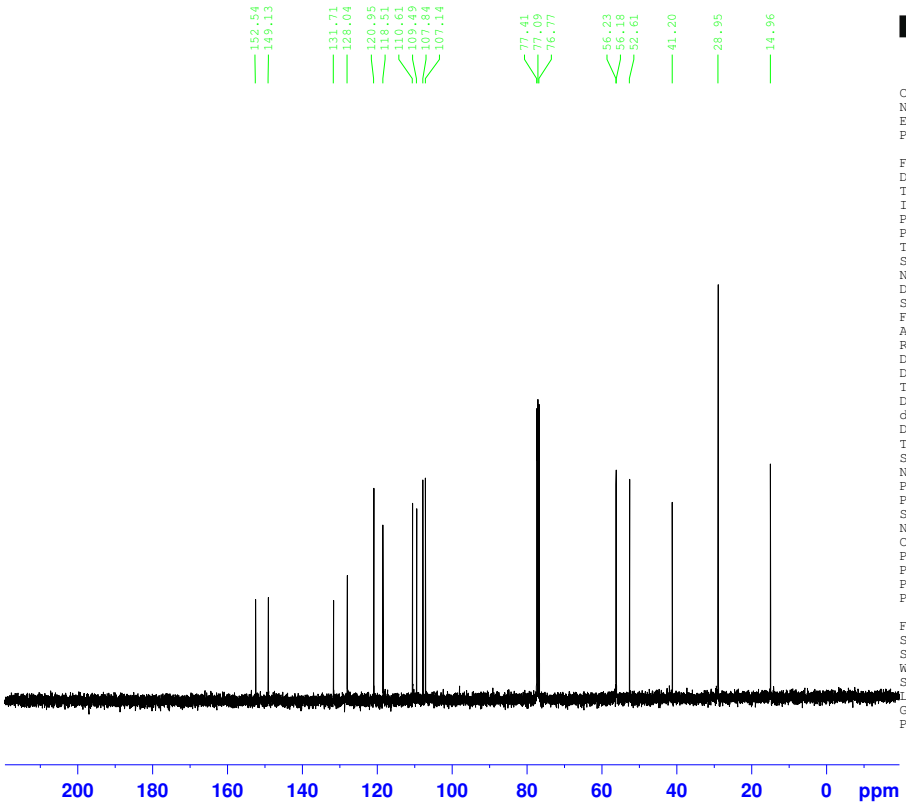
SB-III-7c



BRUKER

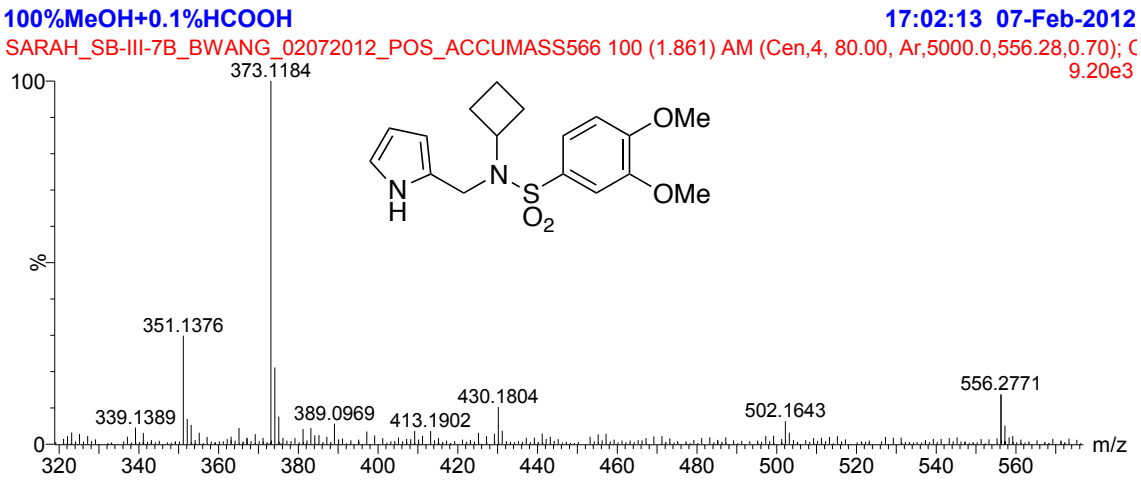
```
Current Data Parameters
NAME           SB-III-7b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20111113
Time               15.04
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDC13
NS                    22
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9845889 sec
RG                  50.8
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-III-7b



BRUKER

```
Current Data Parameters
NAME           SB-III-7b
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20111113
Time               15.10
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    86
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   161
DW                20.800 usec
DE                 6.50 usec
TE                298.1 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                    1
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1          62.00000000 W
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2          16.00000000 W
PLW12          0.36000001 W
PLW13          0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



Elemental Composition Report

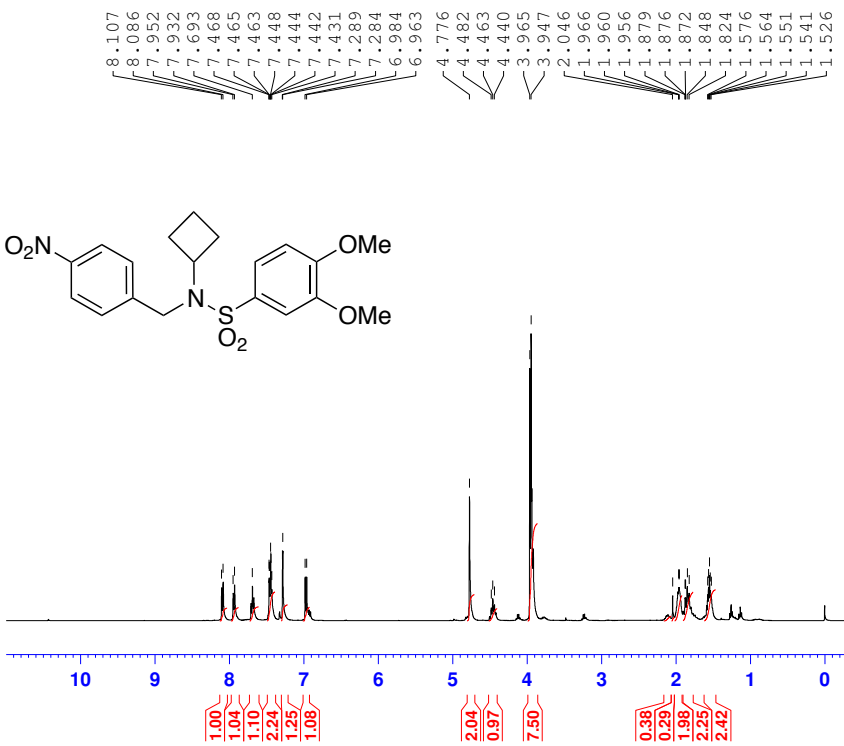
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4999 formula(e) evaluated with 11 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
373.1184	373.1198	-1.4	-3.8	7.5	1.4	C17 H22 N2 O4 Na S

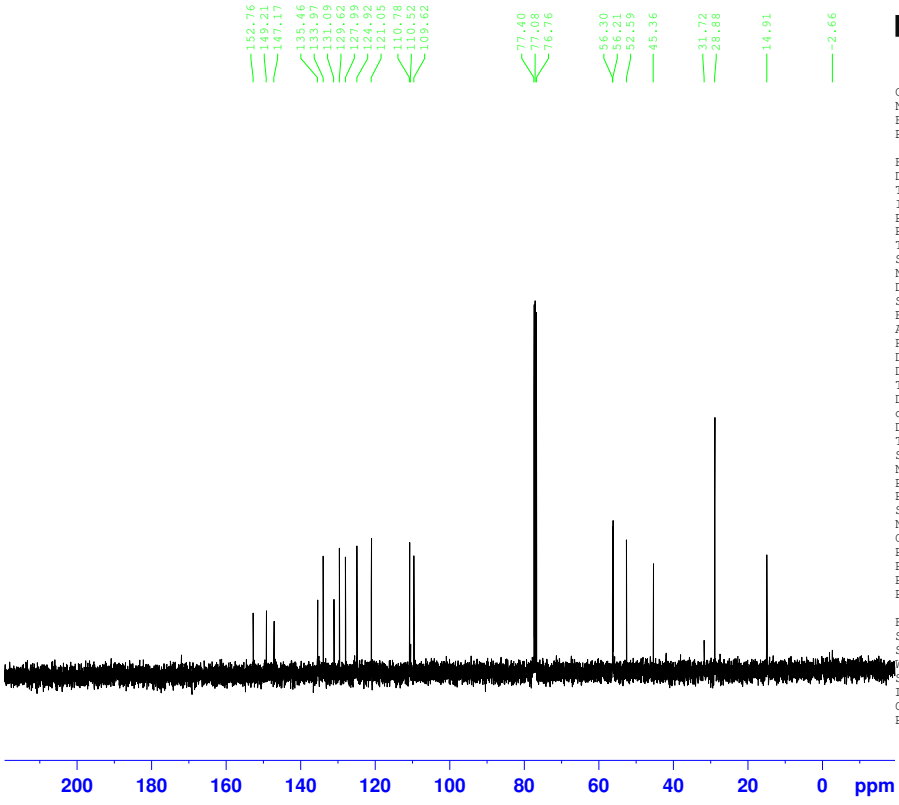
N-cyclobutyl-3,4-dimethoxy-*N*-(4-nitrobenzyl)benzenesulfonamide (9f)

SB-II-113d

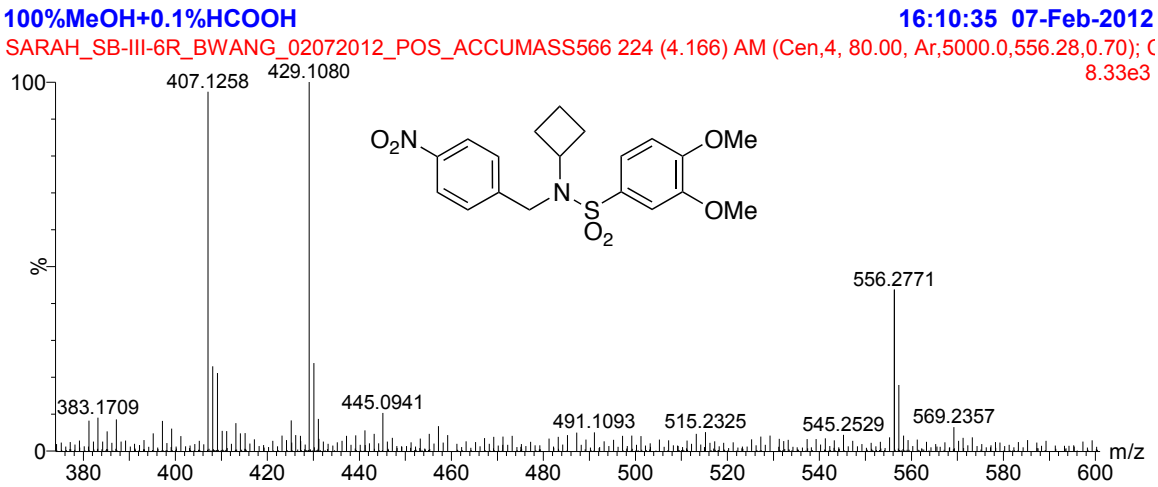



```
Current Data Parameters
NAME          SB-II-113d
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20110921
Time               17.53
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                    64
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-II-113d




```
Current Data Parameters
NAME          SB-II-113d
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20110921
Time               17.59
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    25
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO2         400.1416006 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF           100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

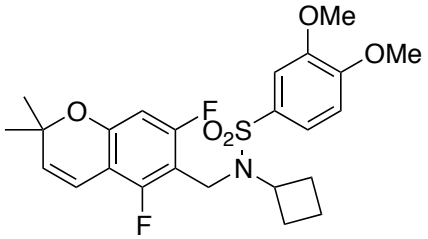


Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
6985 formula(e) evaluated with 19 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6

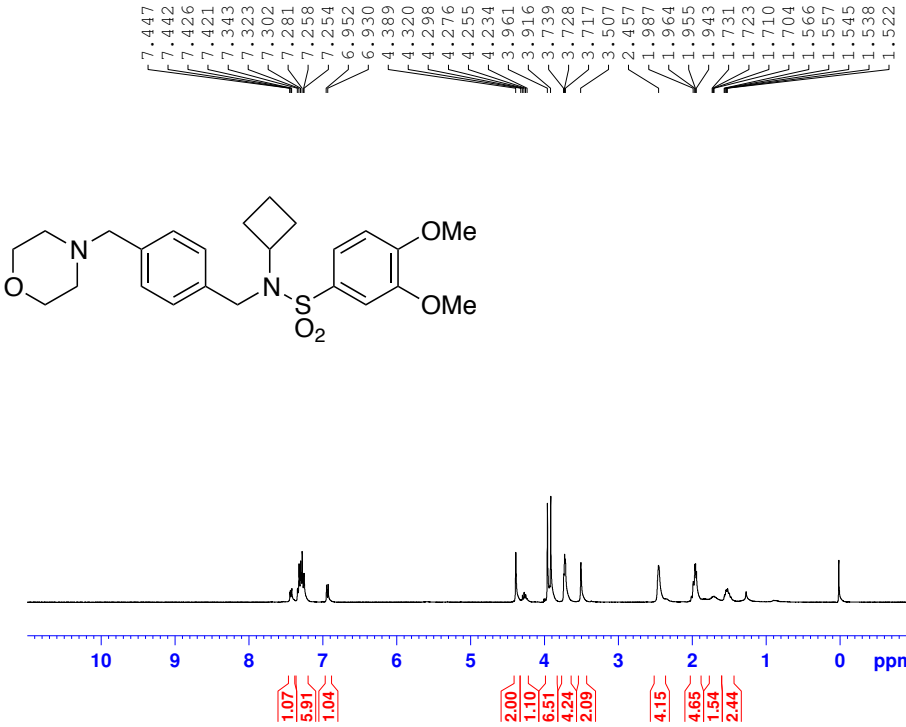
Minimum:			-1.5			
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
407.1258	407.1277	-1.9	-4.7	9.5	343.6	C19 H23 N2 O6 S



***N*-cyclobutyl-*N*-((5,7-difluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (9g)**

N-cyclobutyl-3,4-dimethoxy-*N*-(4-(morpholinomethyl)benzyl)benzenesulfonamide (9h)

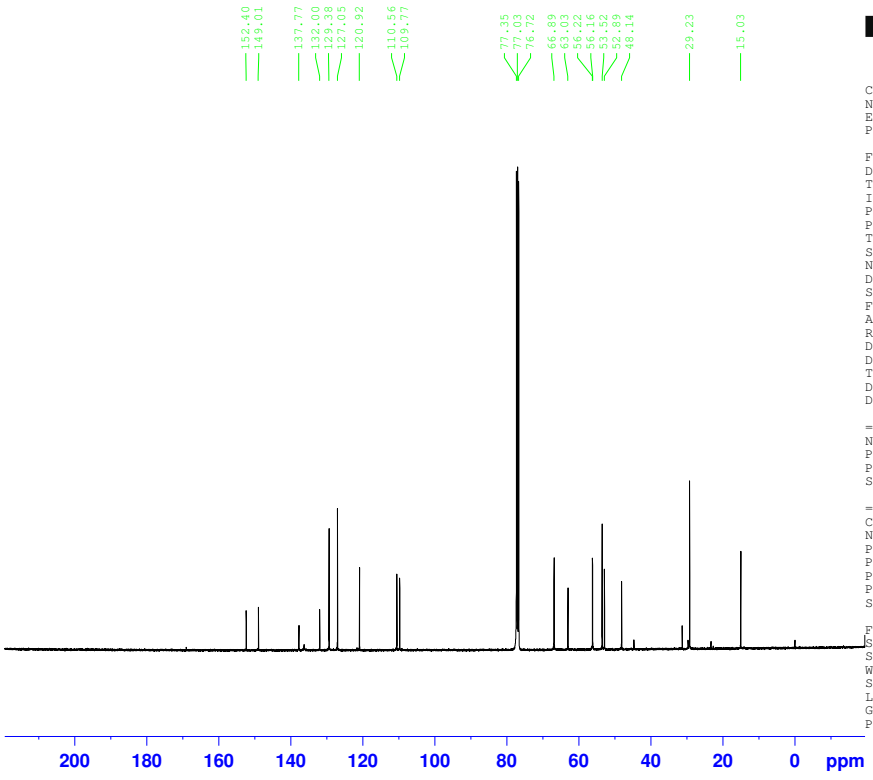
SB-IV-44c



BRUKER

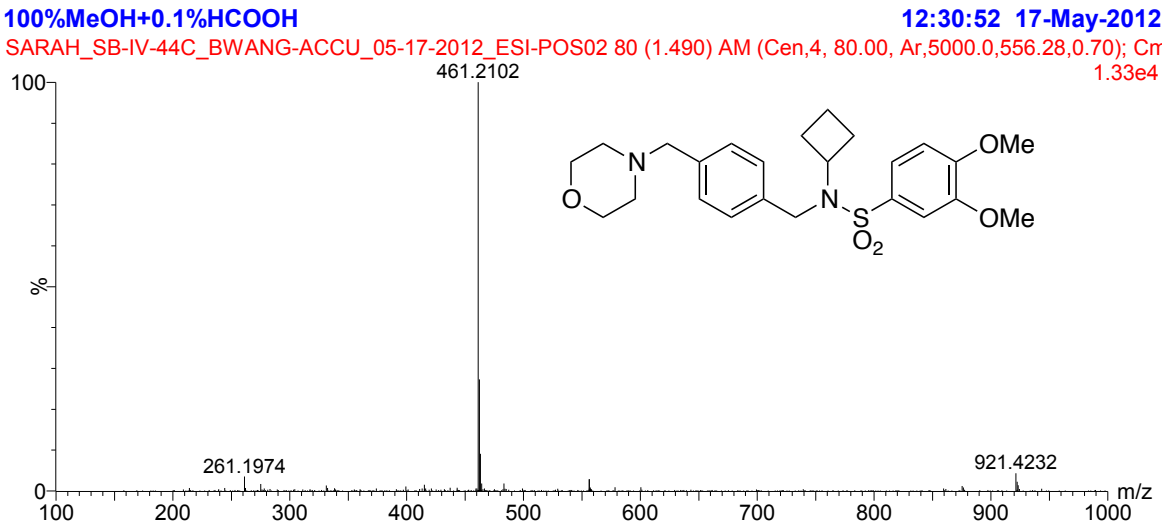
```
Current Data Parameters
NAME                  SB-IV-44c
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20120430
Time                      15.43
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8223.685 Hz
FIDRES                 0.125483 Hz
AQ                     3.9846387 sec
RG                          203
DW                        60.800 usec
DE                         6.50 usec
TE                        298.1 K
D1                  1.00000000 sec

======== CHANNEL f1 ========
NUC1                         1H
P1                        13.50 usec
PLW1                16.00000000 W
SFO1                400.1424710 MHz

F2 - Processing parameters
SI                        65536
SF                  400.1400000 MHz
WDW                          EM
SSB                0
LB                        0.30 Hz
GB                 0
PC                        1.00
```

SB-IV-44c



BRUKER

```
Current Data Parameters
NAME                  SB-IV-44c
EXPNO                         3
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20120515
Time                      23.52
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                        10240
DS                            4
SWH                24038.461 Hz
FIDRES                 0.366798 Hz
AQ                     1.3631988 sec
RG                          203
DW                        20.800 usec
DE                         6.50 usec
TE                        300.0 K
D1                  2.00000000 sec
D11                 0.03000000 sec

======== CHANNEL f1 ========
NUC1                        13C
P1                         9.00 usec
PLW1                62.00000000 W
SFO1                100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                     90.00 usec
PLW2                16.00000000 W
PLW12                0.36000001 W
PLW13                0.29159999 W
SFO2                400.1416006 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6152830 MHz
WDW                          EM
SSB                0
LB                        1.00 Hz
GB                 0
PC                        1.40
```



Elemental Composition Report

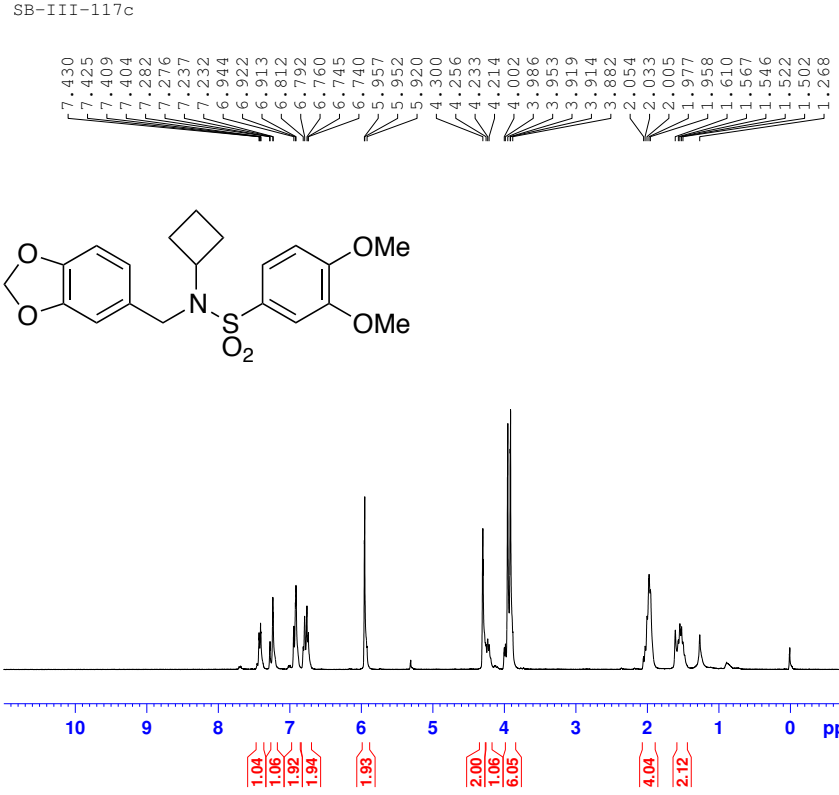
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4674 formula(e) evaluated with 14 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100 S: 0-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
461.2102	461.2110	-0.8	-1.7	9.5	5.9	C24 H33 N2 O5 S

N-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-cyclobutyl-3,4-dimethoxybenzenesulfonamide (9i)

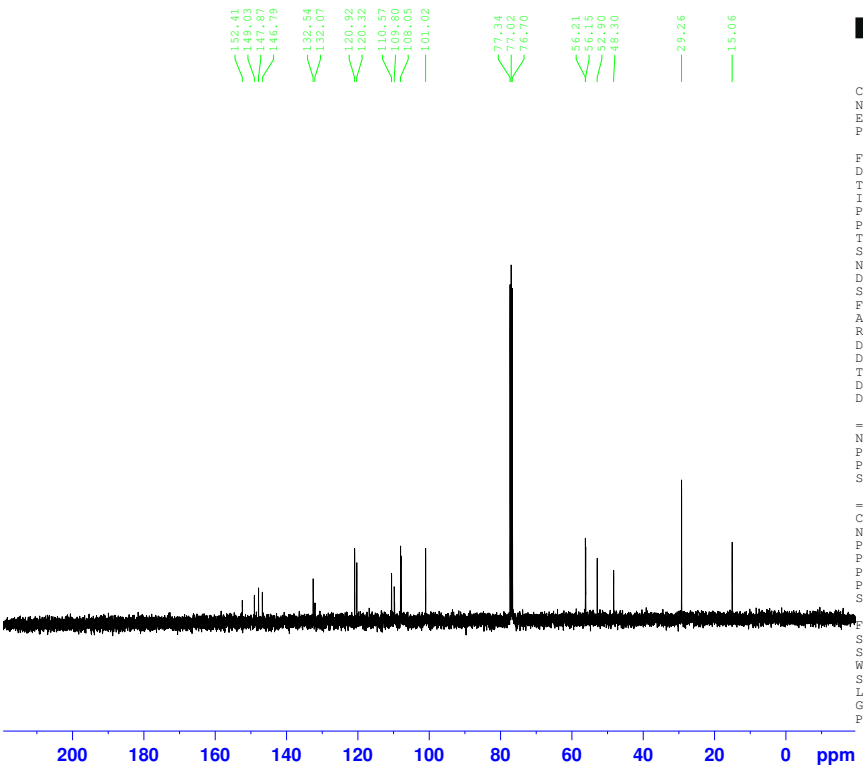
SB-III-117c



BRUKER

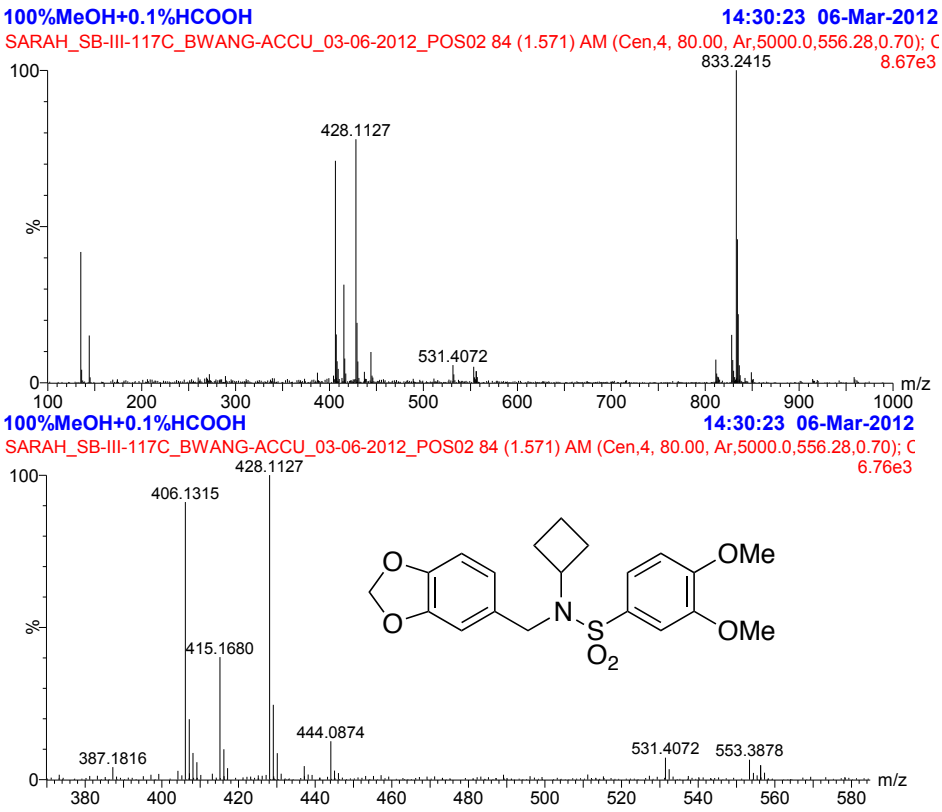
```
Current Data Parameters
NAME         SB-III-117c
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120302
Time              16.12
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    7
DS                    2
SWH            8223.685 Hz
FIDRES         0.125483 Hz
AQ             3.9846387 sec
RG                  128
DW               60.800 usec
DE                6.50 usec
TE                298.2 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                13.50 usec
PLW1        16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI                65536
SF          400.1400000 MHz
WDW                  EM
SSB       0
LB              0.30 Hz
GB        0
PC                1.00
```

SB-III-117c



BRUKER

```
Current Data Parameters
NAME         SB-III-117c
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120302
Time              16.13
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  118
DS                    4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631988 sec
RG                  203
DW               20.800 usec
DE                6.50 usec
TE                298.2 K
D1           2.00000000 sec
D11          0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                9.00 usec
PLW1        62.00000000 W
SFO1        100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2            90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W
SFO2        400.1416006 MHz

F2 - Processing parameters
SI                32768
SF          100.6152830 MHz
WDW                  EM
SSB       0
LB              1.00 Hz
GB        0
PC                1.00
```



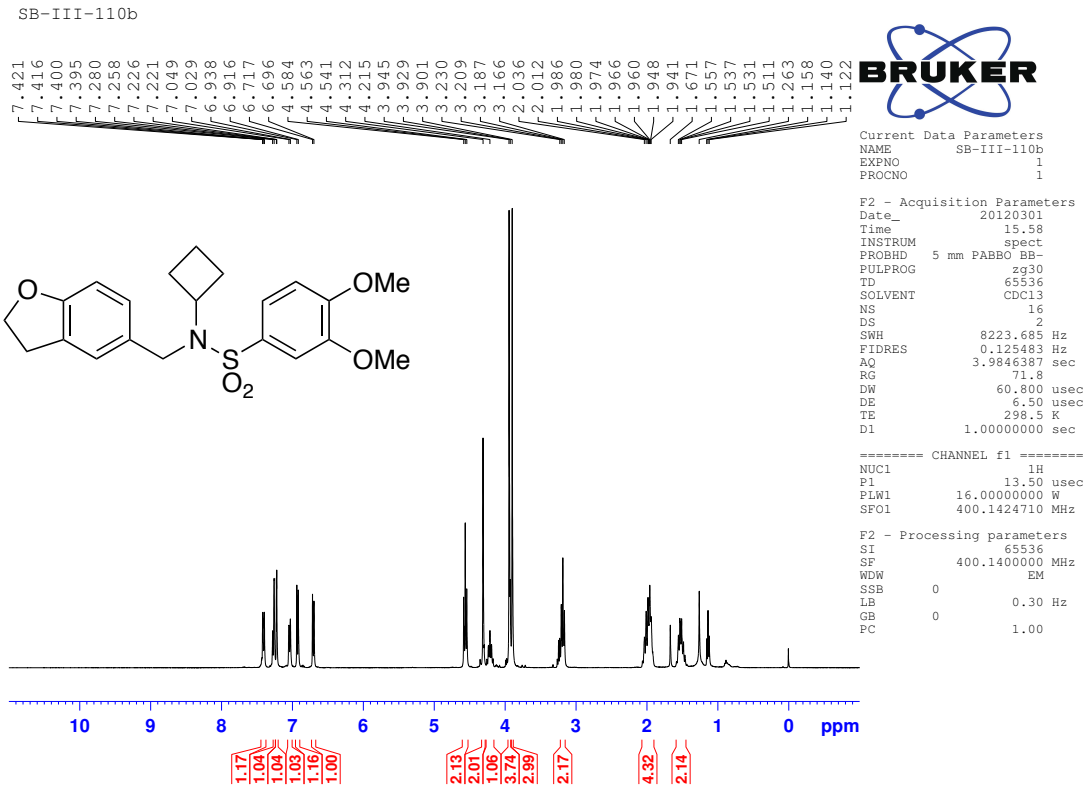
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

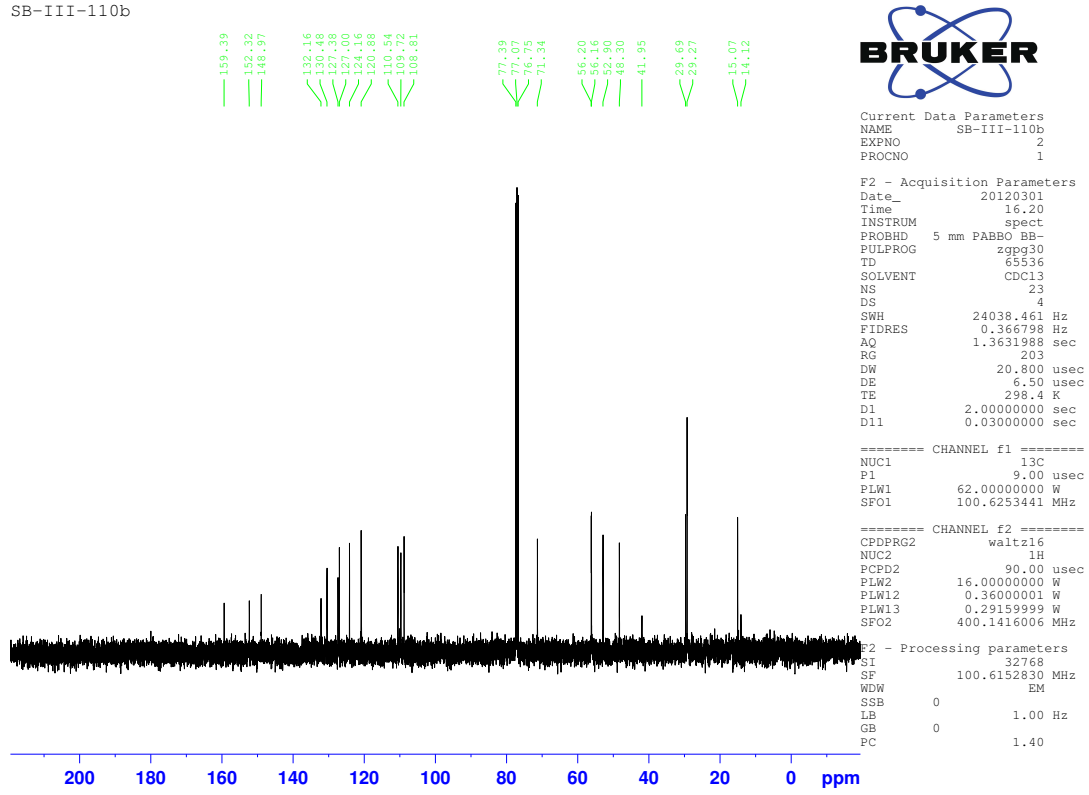
Monoisotopic Mass, Even Electron Ions
2340 formula(e) evaluated with 10 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20 S: 1-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
406.1315	406.1324	-0.9	2.2	9.5	11.6	C20 H24 N O6 S

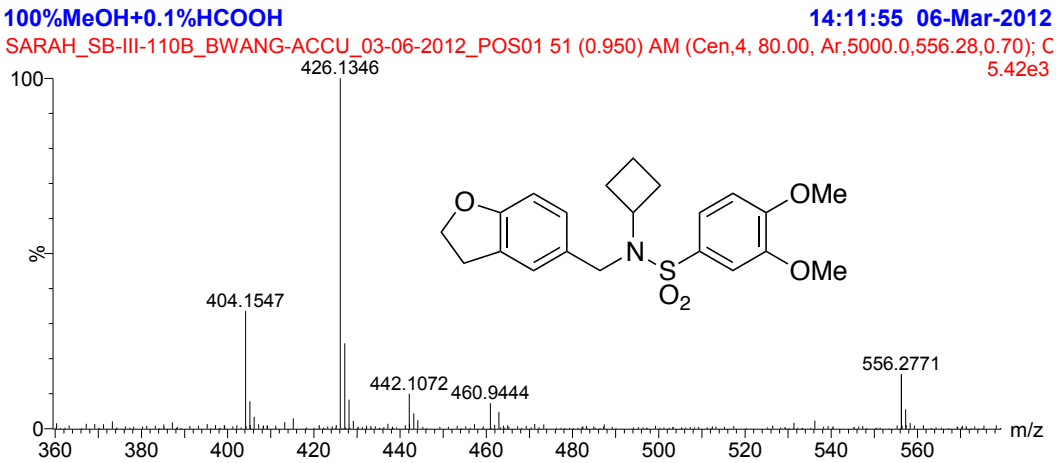
_N_-Cyclobutyl-_N_-((2,3-dihydrobenzofuran-5-yl)methyl)-3,4-dimethoxybenzenesulfonamide (9j)




```
Current Data Parameters
NAME         SB-III-110b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               15.58
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                  71.8
DW                60.800 usec
DE                 6.50 usec
TE                298.5 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```




```
Current Data Parameters
NAME         SB-III-110b
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               16.20
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    23
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.4 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



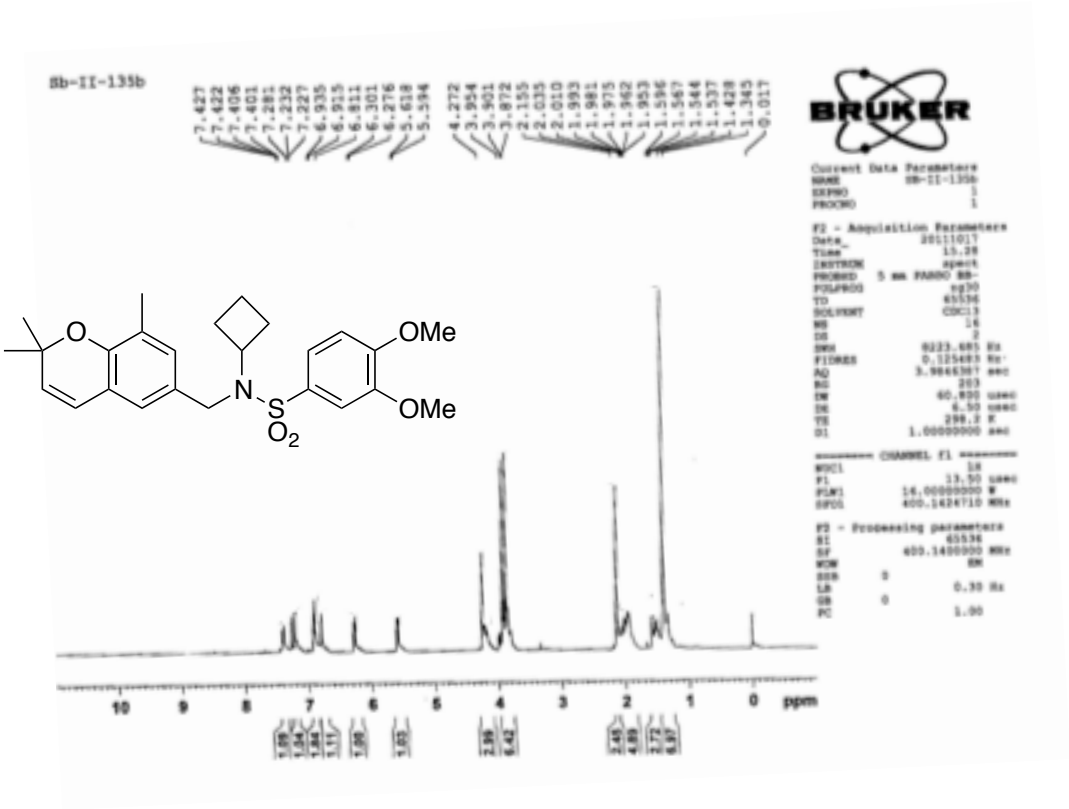
Elemental Composition Report

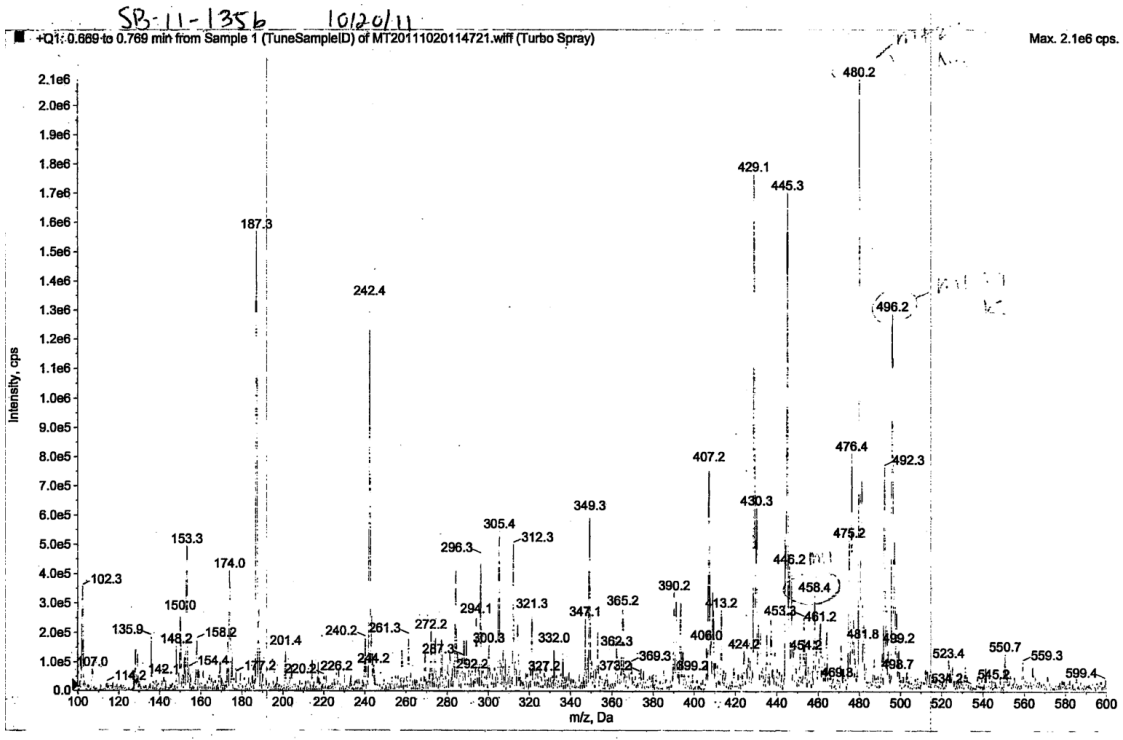
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2301 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20 S: 1-6

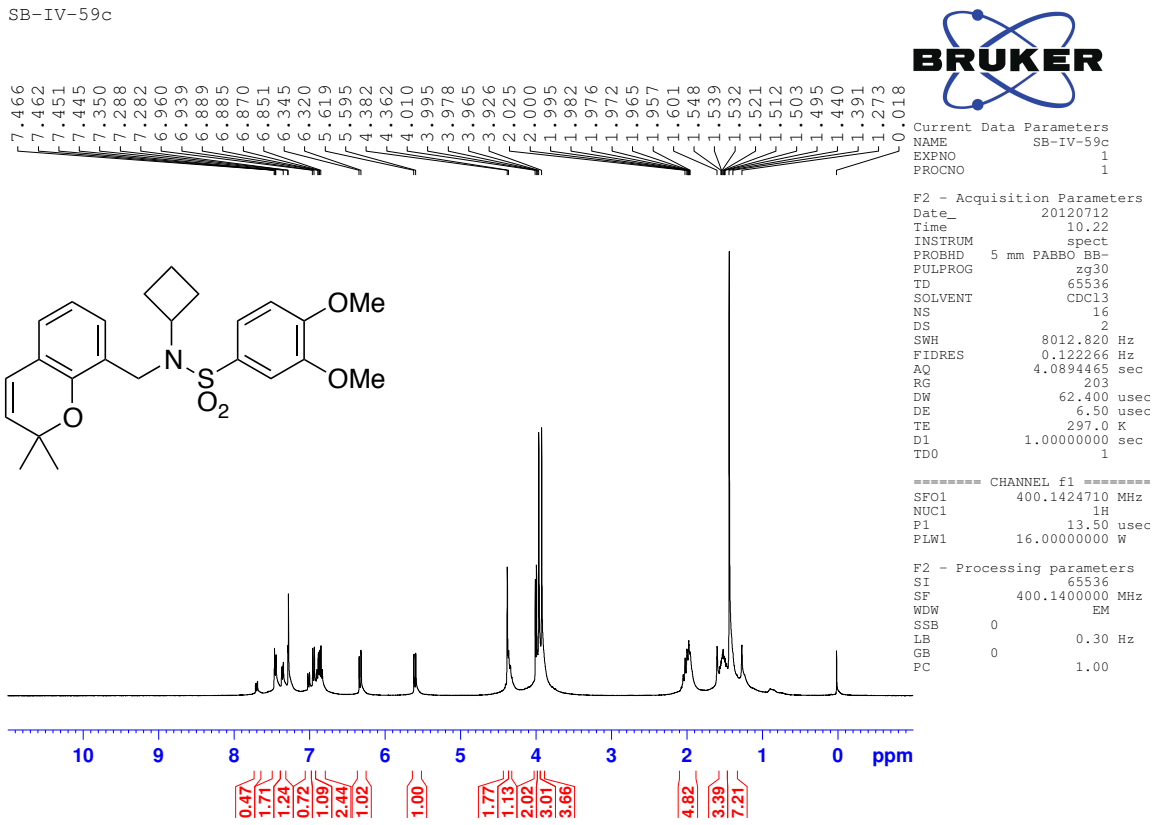
Minimum:			-1.5			
Maximum:	5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
404.1547	404.1532	1.5	3.7	9.5	3.4	C21 H26 N O5 S

_N_-cyclobutyl-3,4-dimethoxy-_N_-((2,2,8-trimethyl-2_H_-chromen-6-yl)methyl)benzenesulfonamide **(9k)**

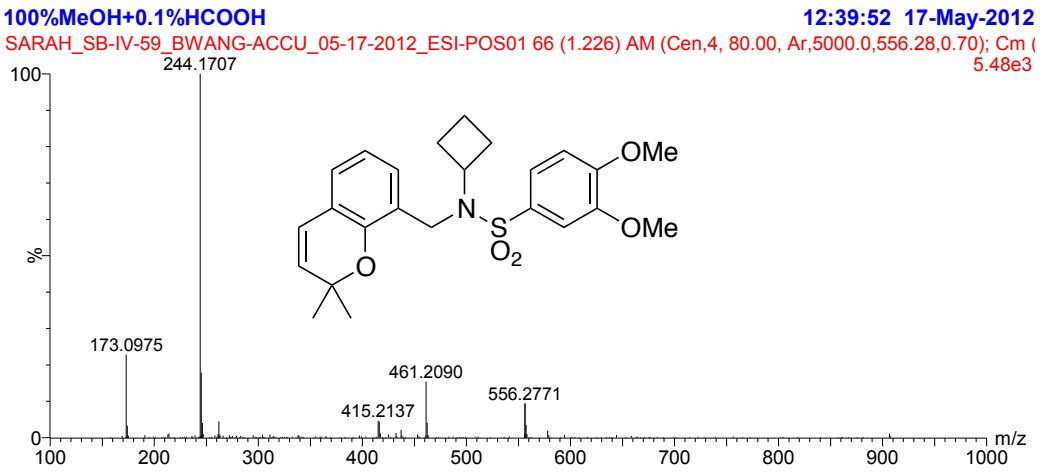




_N_-cyclobutyl-_N_-((2,2-dimethyl-2_H_-chromen-8-yl)methyl)-3,4-dimethoxybenzenesulfonamide (9l)




```
Current Data Parameters
NAME                  SB-IV-59c
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20120712
Time                      10.22
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   8012.820 Hz
FIDRES                0.122266 Hz
AQ                    4.0894465 sec
RG                          203
DW                       62.400 usec
DE                        6.50 usec
TE                       297.0 K
D1                  1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1                400.1424710 MHz
NUC1                        1H
P1                       13.50 usec
PLW1                16.00000000 W

F2 - Processing parameters
SI                       65536
SF                  400.1400000 MHz
WDW                         EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
```



Elemental Composition Report

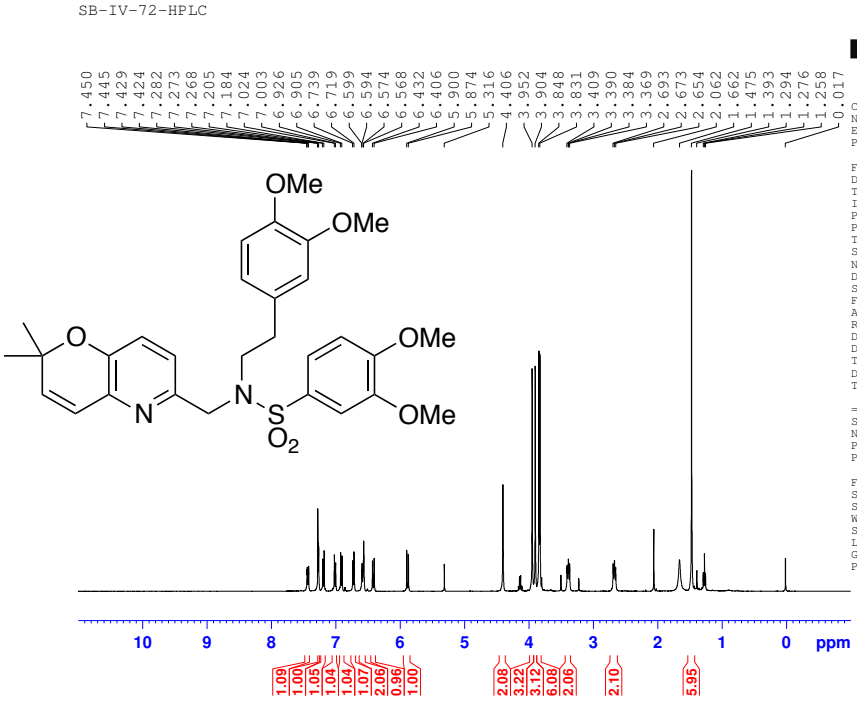
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
556 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100 S: 0-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
244.1707	244.1701	0.6	2.5	6.5	33.5	C16 H22 N O

_N_-(3,4-dimethoxyphenethyl)-_N_-((2,2-dimethyl-2_H_-pyrano[3,2-_b_]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (10a)

SB-IV-72-HPLC



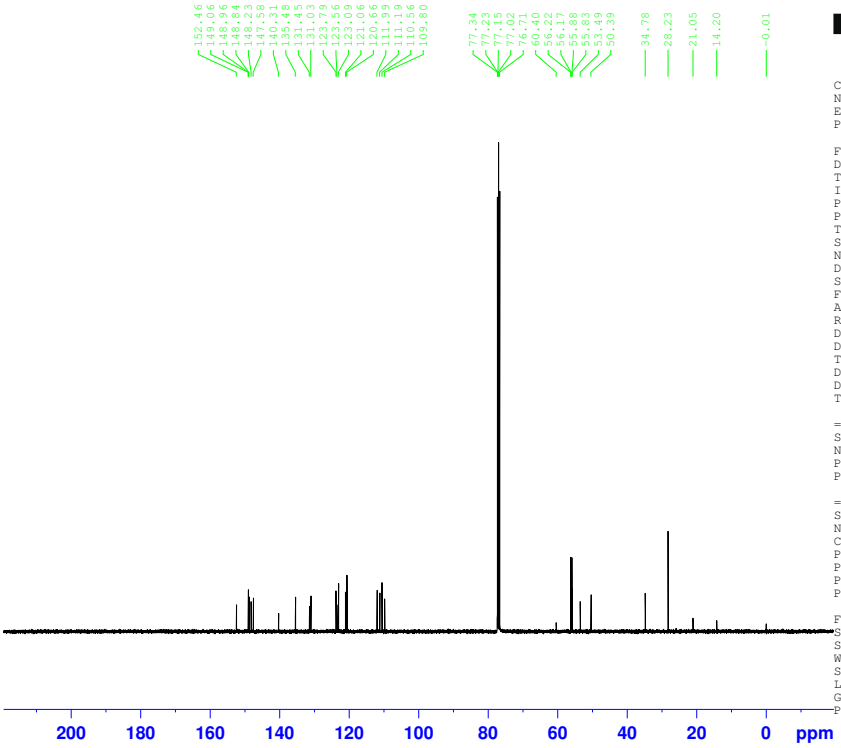
Current Data Parameters
NAME SB-IV-72-HPLC
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120619
Time 22.30
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 17
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 181
DW 60.800 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 400.1424710 MHz
NUC1 1H
P1 13.50 usec
PLW1 16.00000000 W

F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

SB-IV-72-HPLC



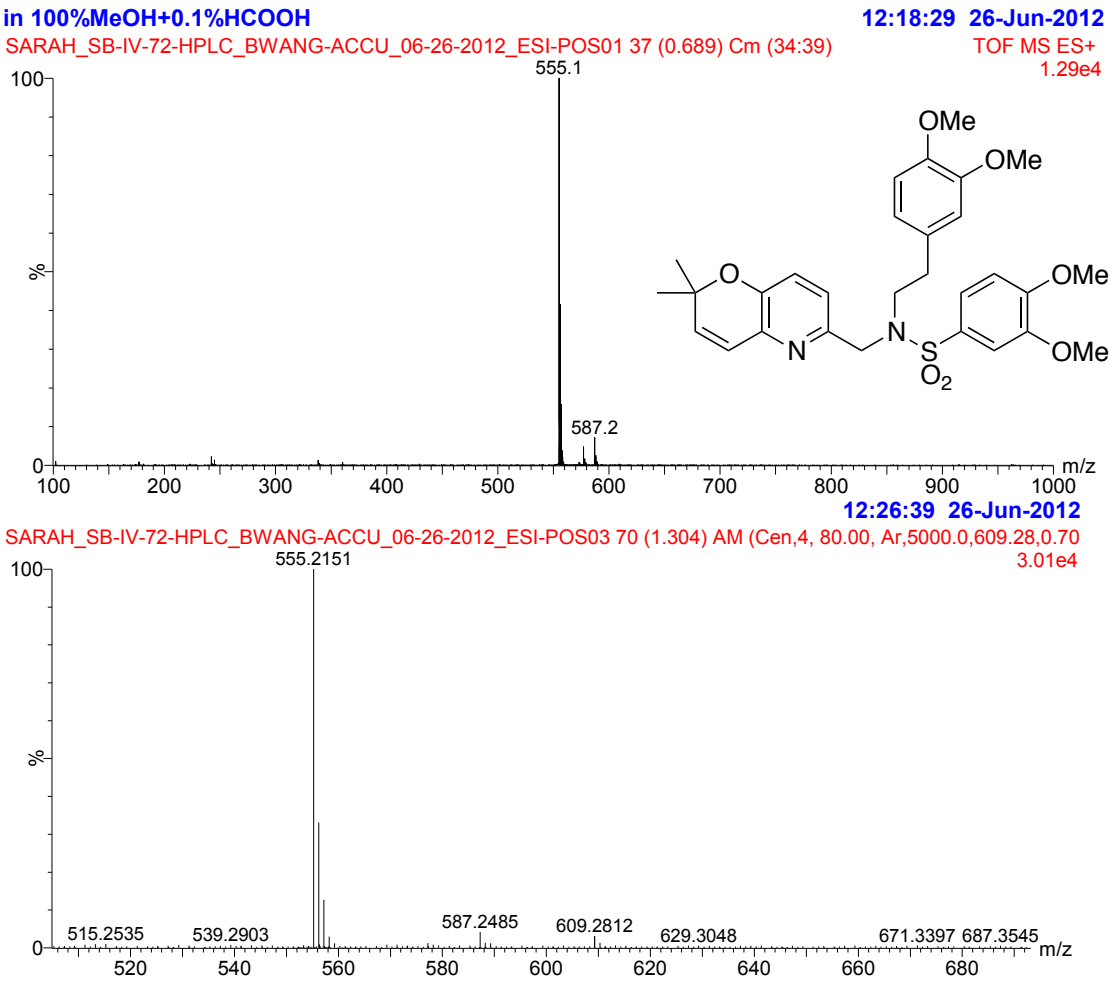
Current Data Parameters
NAME SB-IV-72-HPLC
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120620
Time 8.05
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 10000
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 298.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 100.6253441 MHz
NUC1 13C
P1 9.00 usec
PLW1 62.00000000 W

======== CHANNEL f2 ========
SFO2 400.1416006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 16.00000000 W
PLW12 0.36000001 W
PLW13 0.29159999 W

F2 - Processing parameters
SI 32768
SF 100.6152830 MHz
WDW no
SSB 0
LB 0 Hz
GB 0
PC 1.40



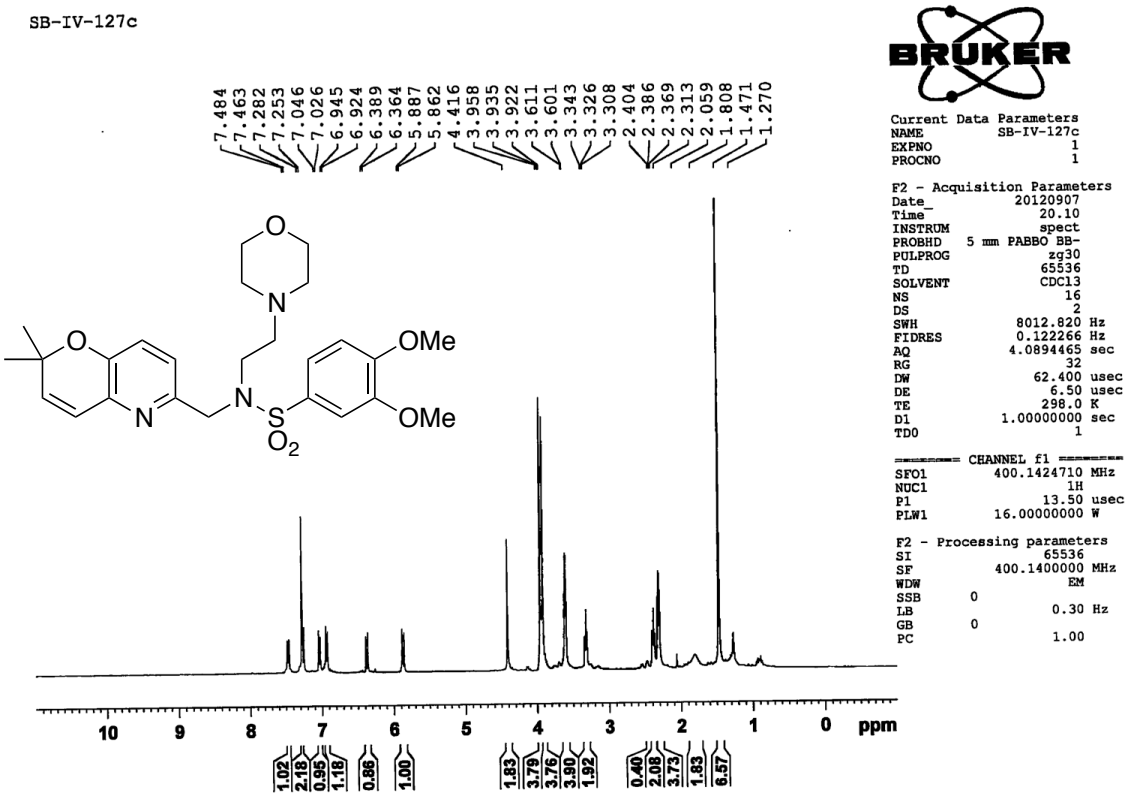
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
7830 formula(e) evaluated with 21 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 1-50

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
555.2151	555.2165	-1.4	-2.5	13.5	23.6	C29 H35 N2 O7 S

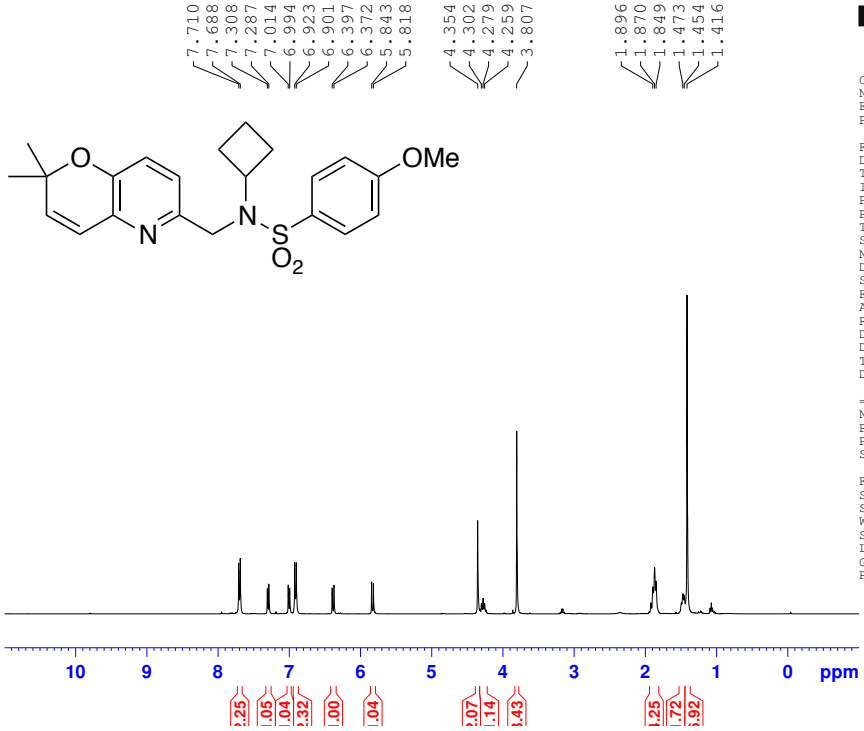
N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxy-N-(2-morpholinoethyl)benzenesulfonamide (10b)




```
Current Data Parameters
NAME                  SB-IV-127c
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120907
Time                       20.10
INSTRUM                    spect
PROBHD    5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8012.820 Hz
FIDRES                 0.122266 Hz
AQ                     4.0894465 sec
RG                           32
DW                        62.400 usec
DE                         6.50 usec
TE                        298.0 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1                 400.1424710 MHz
NUC1                         1H
P1                        13.50 usec
PLW1                16.00000000 W

F2 - Processing parameters
SI                        65536
SF                   400.1400000 MHz
WDW                          EM
SSB                   0
LB                            0.30 Hz
GB                    0
PC                            1.00
```

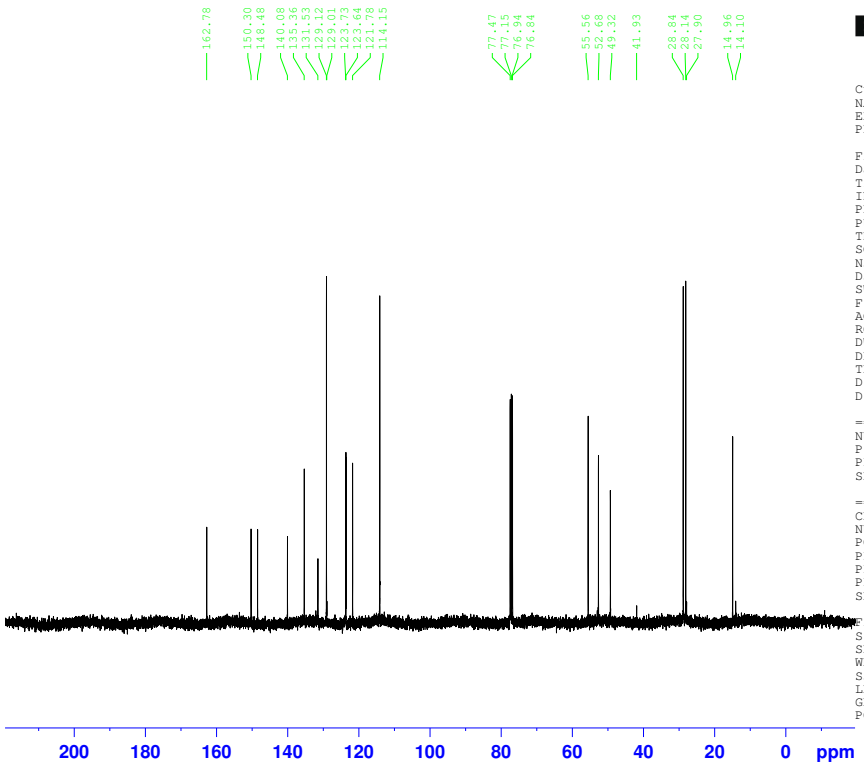
N-Cyclobutyl-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)-4-methoxybenzenesulfonamide (11a)

SB-III-109




```
Current Data Parameters
NAME          SB-III-109
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               15.52
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                    18
DW                60.800 usec
DE                 6.50 usec
TE                298.3 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-III-109

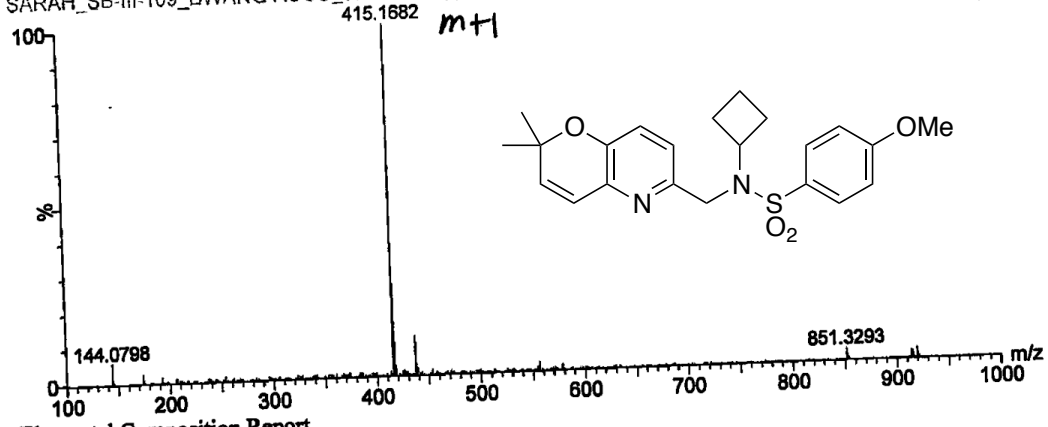



```
Current Data Parameters
NAME          SB-III-109
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               15.56
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    14
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.6 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF           100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

14:24:39 06-Mar-2012

100%MeOH+0.1%HCOOH

SARAH_SB-III-109_BWANG-ACCU_03-06-2012_POS03 91 (1.691) AM (Cen,4, 80.00, Ar,5000.0,556.28,0.70); Cn 7.84e3



Elemental Composition Report

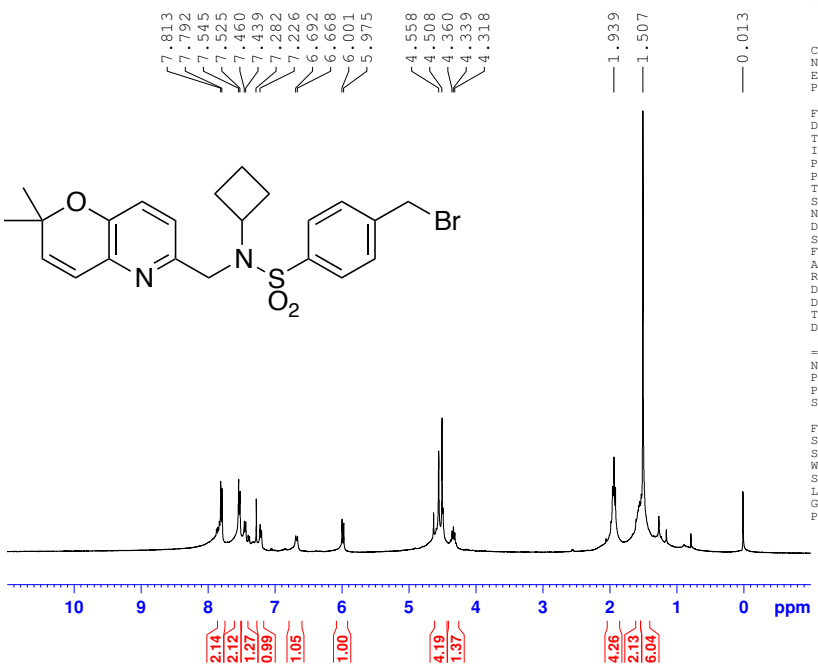
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2593 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20 S: 1-6

		5.0	5.0	-1.5 50.0		
Minimum: Maximum: Mass	Calc. Mass		mDa	PPM	DBE	i-FIT	Formula
415.1682	415.1685	-0.3	-0.7	1.5	92.9		C14 H31 N4 O6 S2
	415.1698	-1.6	-3.9	6.5	47.9		C15 H27 N8 O2 S2
	415.1694	-1.2	-2.9	0.5	417.5		C15 H35 N4 O S4
	415.1665	1.7	4.1	11.5	17.2		C18 H23 N8 O2 S
	415.1692	-1.0	-2.4	10.5	3.4		C22 H27 N2 O4 S
	415.1683	-0.1	-0.2	-1.5	307.4		C6 H27 N10 O9 S
	415.1697	-1.5	-3.6	3.5	225.3		C7 H23 N14 O5 S

4-(bromomethyl)-*N*-cyclobutyl-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)benzenesulfonamide (11b)

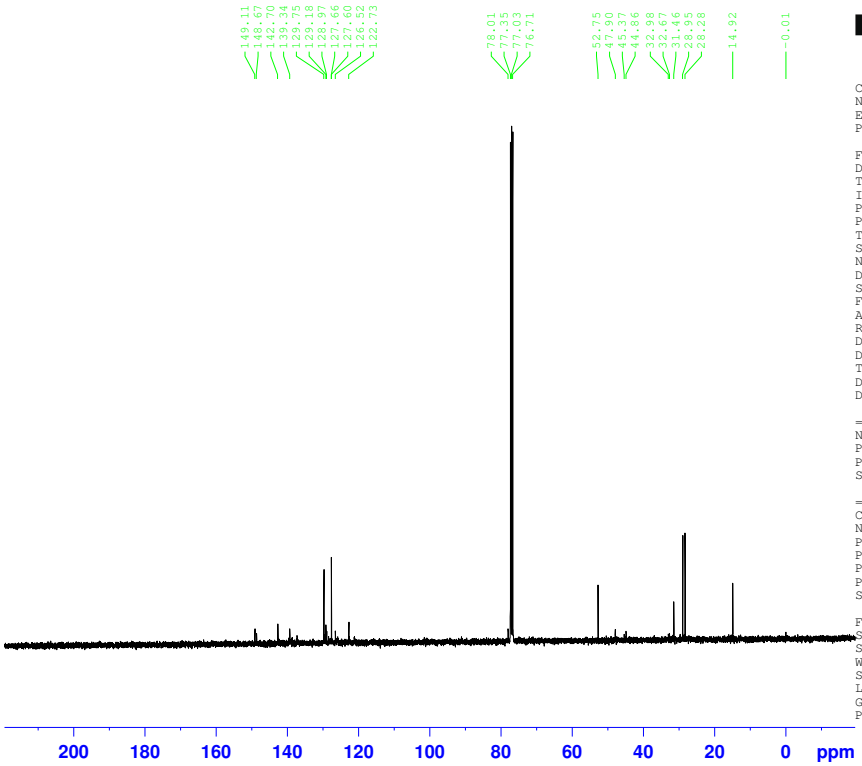
SB-IV-51c



BRUKER

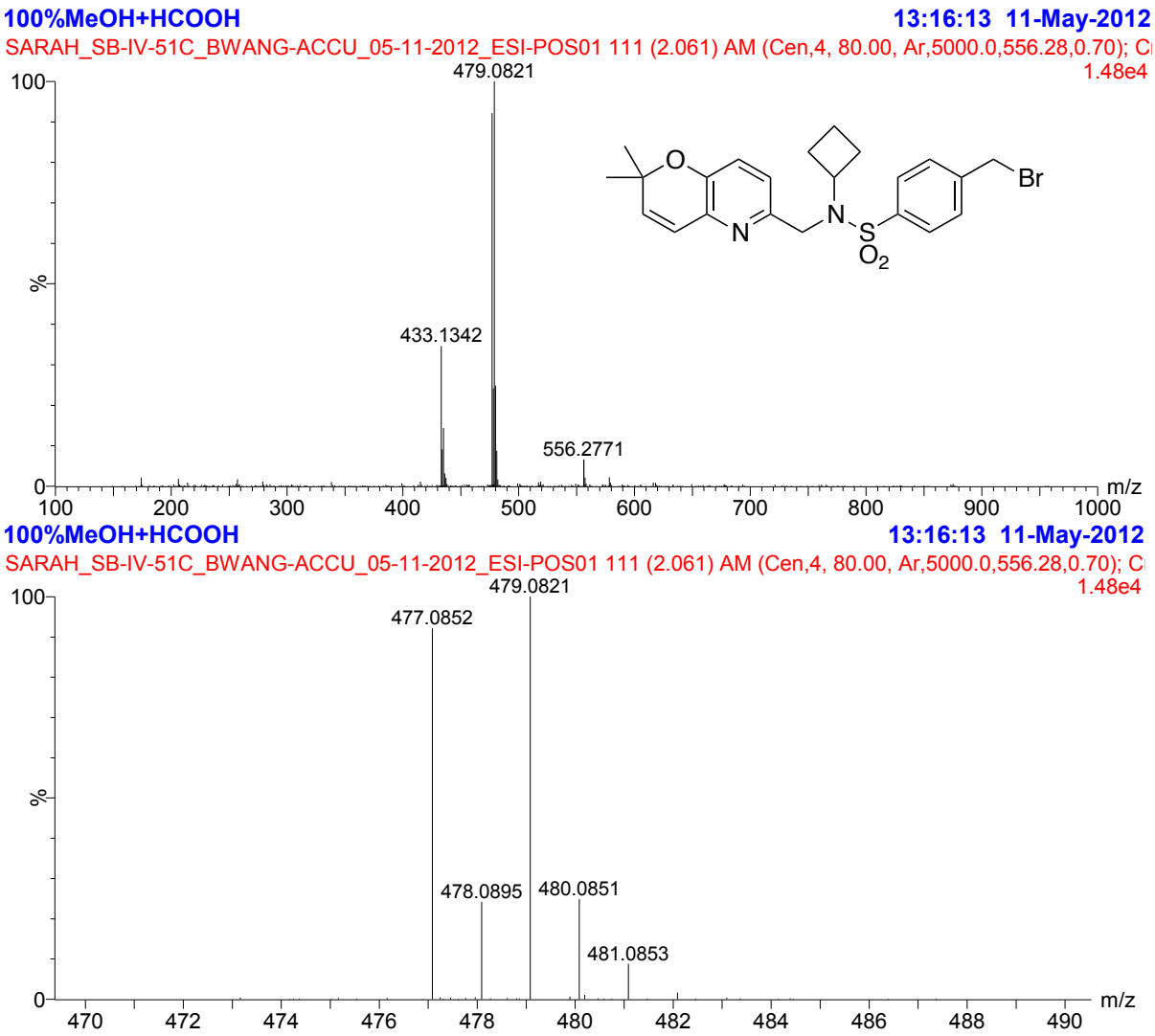
```
Current Data Parameters
NAME                  SB-IV-51c
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_               20120517
Time                  14.10
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDC13
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9846387 sec
RG                      144
DW                   60.800 usec
DE                    6.50 usec
TE                   298.9 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PLW1            16.00000000 W
SFO1           400.1424710 MHz

F2 - Processing parameters
SI                    65536
SF               400.1400000 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

SB-IV-51c



BRUKER

```
Current Data Parameters
NAME                  SB-IV-51c
EXPNO                         6
PROCNO                        1

F2 - Acquisition Parameters
Date_               20120519
Time                  13.38
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT               CDC13
NS                      408
DS                        4
SWH               24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631988 sec
RG                      128
DW                   20.800 usec
DE                    6.50 usec
TE                   300.0 K
D1                2.00000000 sec
D11               0.03000000 sec

======== CHANNEL f1 ========
NUC1                     13C
P1                     9.00 usec
PLW1            62.00000000 W
SFO1           100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                      1H
PCPD2                 90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W
SFO2           400.1416006 MHz

F2 - Processing parameters
SI                    32768
SF               100.6152830 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```



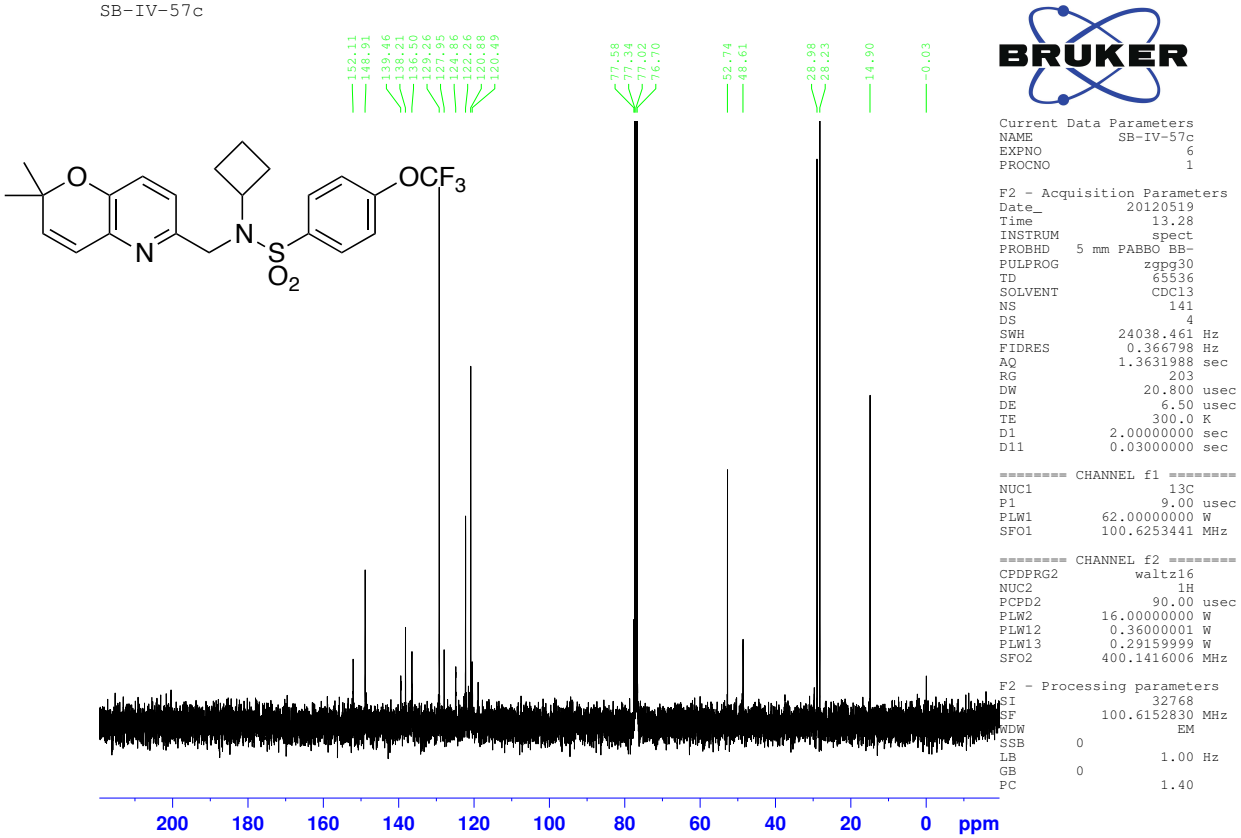
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4890 formula(e) evaluated with 10 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100 S: 0-6 Br: 1-5

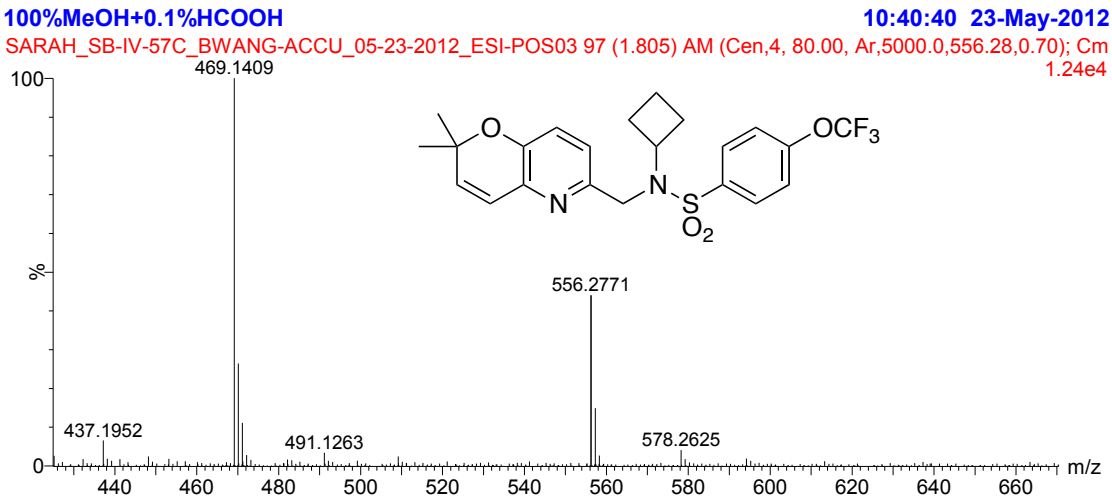
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
477.0852	477.0848	0.4	0.8	10.5	3.8	C22 H26 N2 O3 S Br

_N_-Cyclobutyl-_N_-((2,2-dimethyl-2_H_-pyrano[3,2-_b_]pyridin-6-yl)methyl)-4-(trifluoromethoxy)benzenesulfonamide (11c)



BRUKER

```
Current Data Parameters
NAME            SB-IV-57c
EXPNO                   6
PROCNO                  1

F2 - Acquisition Parameters
Date_            20120519
Time                13.28
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   141
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ             1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                300.0 K
D1            2.00000000 sec
D11           0.03000000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                9.00 usec
PLW1         62.00000000 W
SFO1        100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2            90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2        400.1416006 MHz

F2 - Processing parameters
SI                  32768
SF           100.6152830 MHz
WDW                    EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



Elemental Composition Report

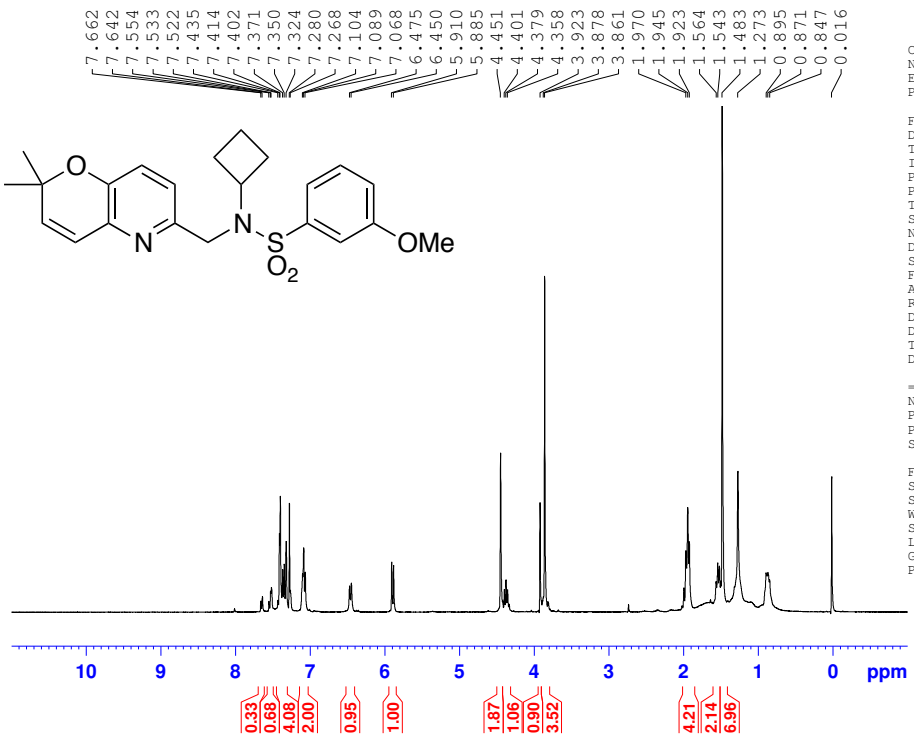
Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
18673 formula(e) evaluated with 254 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 0-50 F: 1-6

Minimum:			-1.5			
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
469.1409	469.1409	0.0	0.0	10.5	33.3	C22 H24 N2 O4 S F3

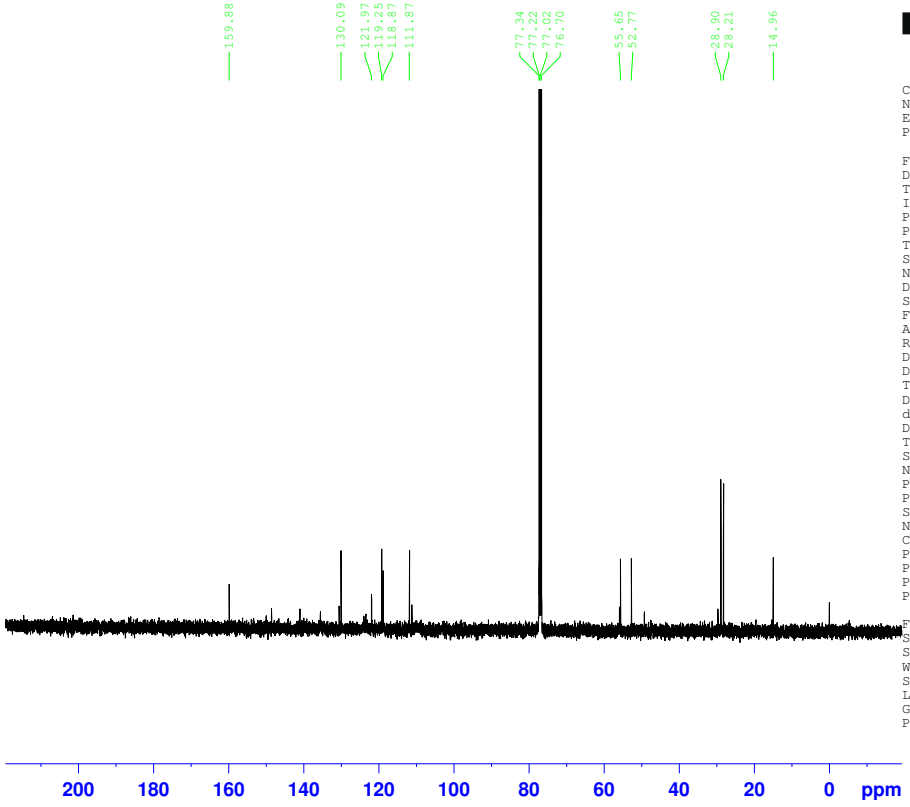
N-cyclobutyl-N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3-methoxybenzenesulfonamide (11d)

SB-IV-47c



```
Current Data Parameters
NAME          SB-IV-47c
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20120509
Time              12.40
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9846387 sec
RG                 144
DW              60.800 usec
DE               6.50 usec
TE              300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1               13.50 usec
PLW1        16.00000000 W
SFO1       400.1424710 MHz

F2 - Processing parameters
SI               65536
SF          400.1400000 MHz
WDW                 EM
SSB      0
LB               0.30 Hz
GB       0
PC               1.00
```

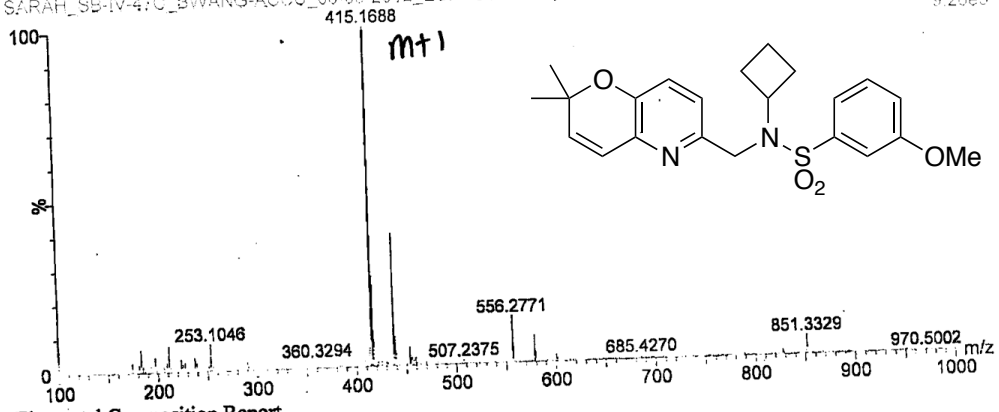
SB-IV-47c



```
Current Data Parameters
NAME          SB-IV-47c
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20120509
Time              12.43
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 403
DS                   4
SWH          24038.461 Hz
FIDRES        0.366798 Hz
AQ            1.3631488 sec
RG                 203
DW              20.800 usec
DE               6.50 usec
TE              298.3 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
TD0                  1
SFO1       100.6253441 MHz
NUC1                13C
P1                9.00 usec
PLW1        62.00000000 W
SFO2       400.1416006 MHz
NUC2                1H
CPDPRG[2        waltz16
PCPD2            90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W

F2 - Processing parameters
SI                32768
SF         100.6152830 MHz
WDW                 EM
SSB      0
LB               1.00 Hz
GB       0
PC       0
```

100%MeOH+0.1%HCOOH 11:31:47 05-Jun-2012

SARAH_SB-IV-47C_BWANG-ACCU_06-05-2012_ESI-POS03 42 (0.782) AM (Cen,4, 80.00, Ar,5000.0,556.28,0.70), Cr 9.26e3



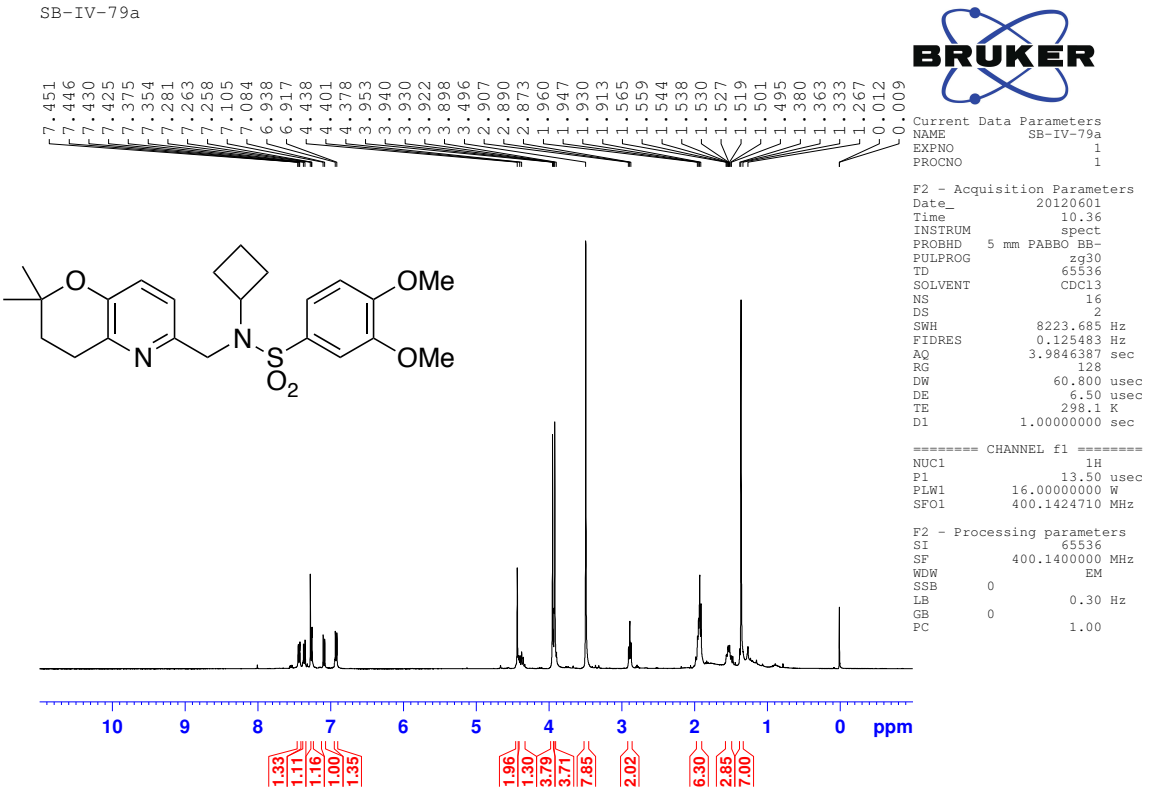
Elemental Composition Report

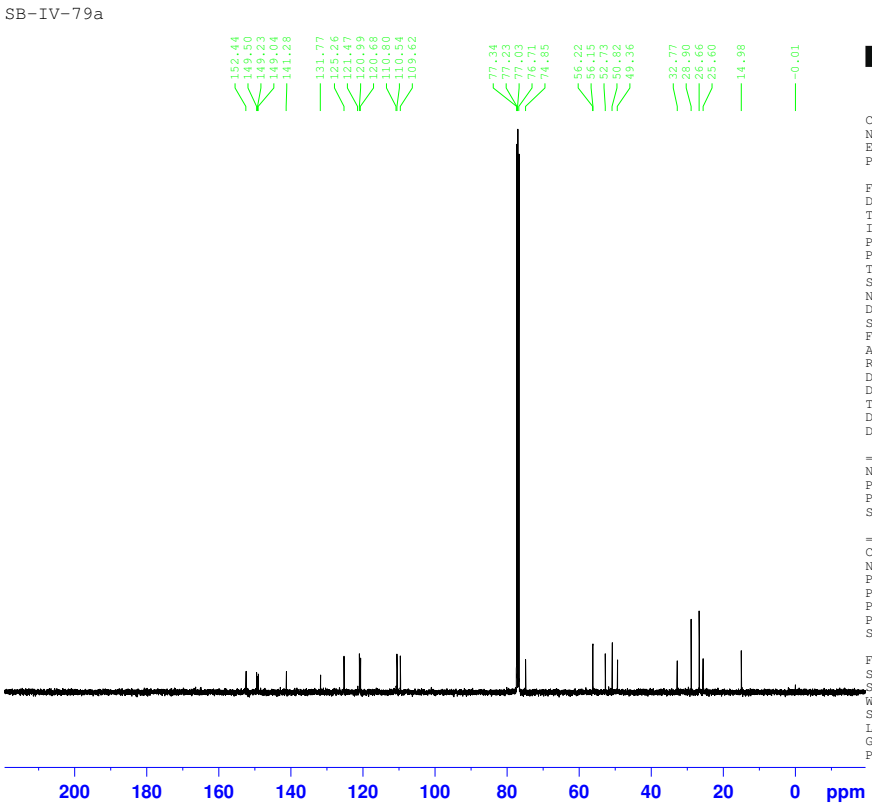
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

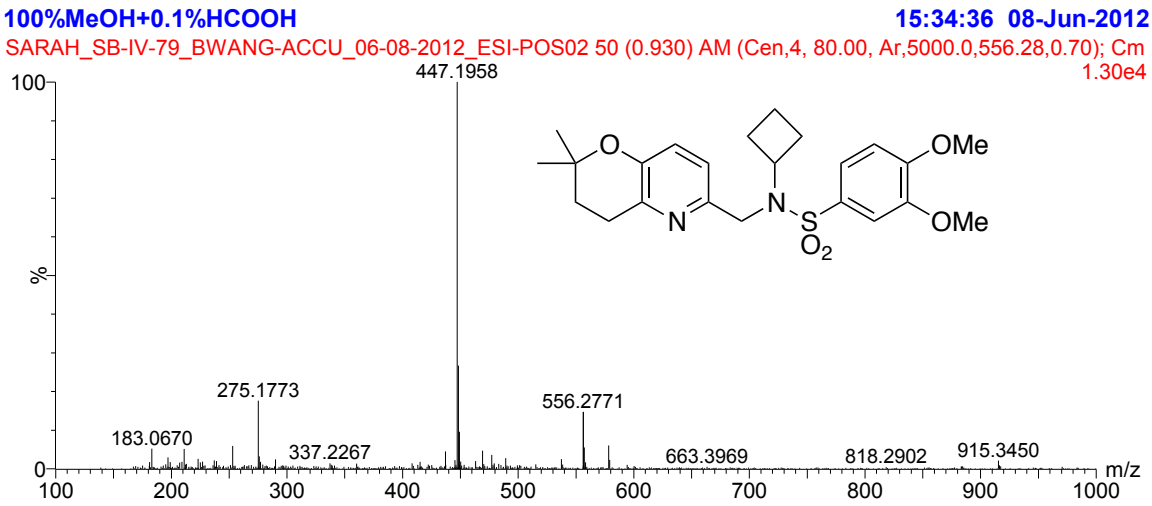
Monoisotopic Mass, Even Electron Ions
5019 formula(e) evaluated with 12 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 Na: 0-1 S: 1-50

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
415.1688	415.1685	0.3	0.7	1.5	135.5	C14 H31 N4 O6 S2
	415.1692	-0.4	-1.0	10.5	0.4	C22 H27 N2 O4 S
	415.1683	0.5	1.2	-1.5	360.8	C6 H27 N10 O9 S
	415.1694	-0.6	-1.4	0.5	578.0	C15 H35 N4 O S4
	415.1697	-0.9	-2.2	3.5	259.7	C7 H23 N14 O5 S
	415.1698	-1.0	-2.4	6.5	77.2	C15 H27 N8 O2 S2
	415.1699	-1.1	-2.6	-0.5	244.4	C9 H28 N8 O7 Na S
	415.1701	-1.3	-3.1	2.5	87.4	C17 H32 N2 O4 Na S2
	415.1674	1.4	3.4	3.5	109.9	C13 H28 N8 O2 Na S2
	415.1673	1.5	3.6	0.5	369.8	C5 H24 N14 O5 Na S
	415.1708	-2.0	-4.8	-1.5	353.4	C10 H32 N8 O2 Na S3
	415.1667	2.1	5.1	7.5	9.3	C20 H28 N2 O4 Na S

_N_-Cyclobutyl-_N_-((2,2-dimethyl-3,4-dihydro-2_H_-pyrano[3,2-_b_]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (12a)







Elemental Composition Report

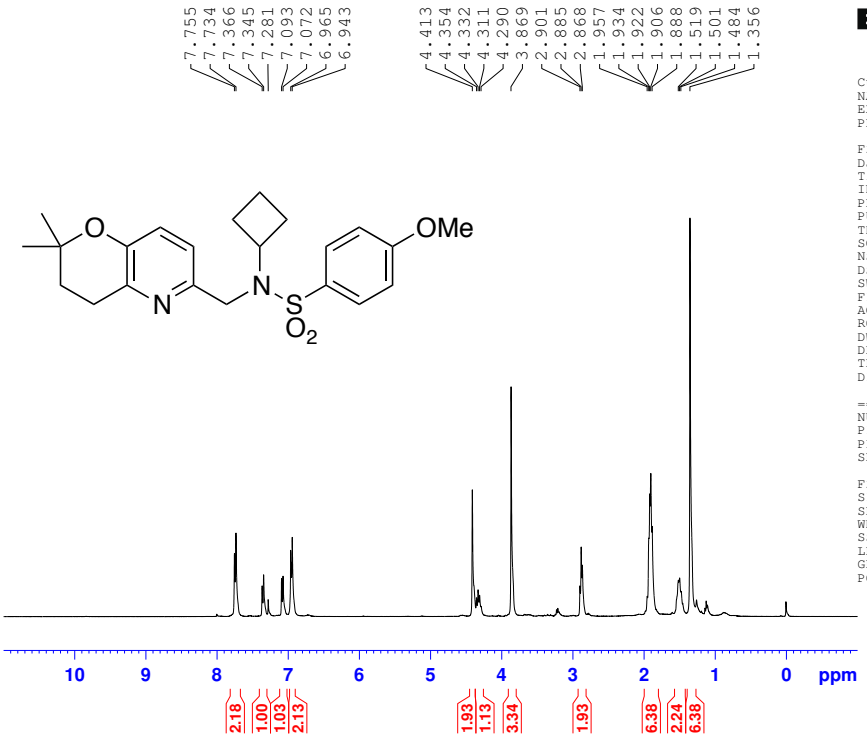
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

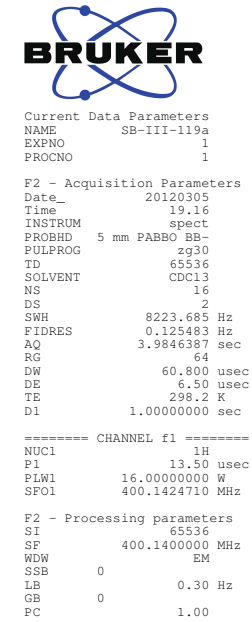
Monoisotopic Mass, Even Electron Ions
3713 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 1-50

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
447.1958	447.1954	0.4	0.9	9.5	5.4	C23 H31 N2 O5 S

_N_-Cyclobutyl-_N_-((2,2-dimethyl-3,4-dihydro-2_H_-pyrano[3,2-_b_]pyridin-6-yl)methyl)-4-methoxybenzenesulfonamide (12b)

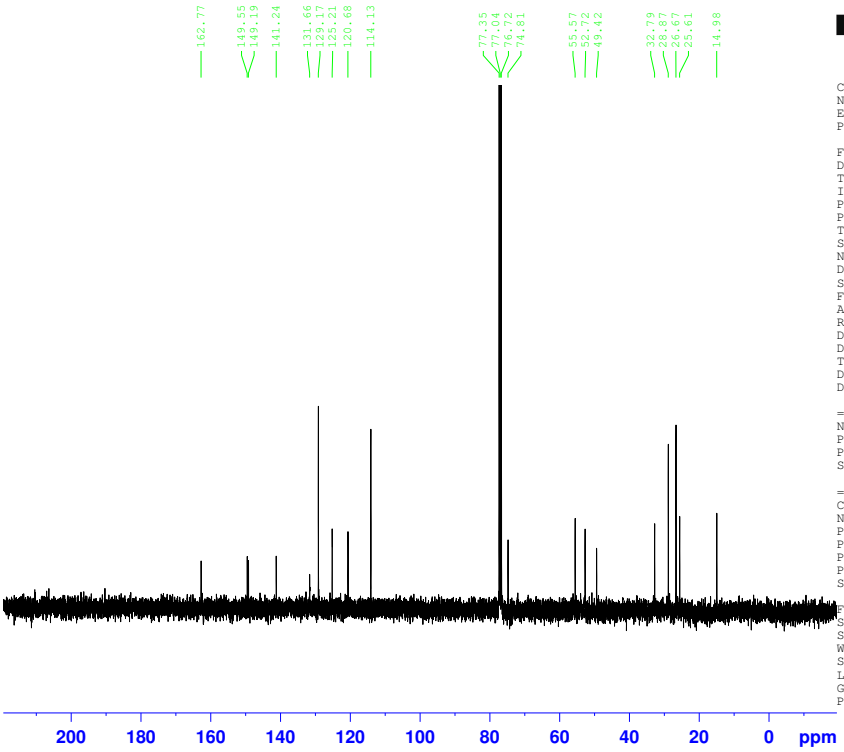
SB-III-119a



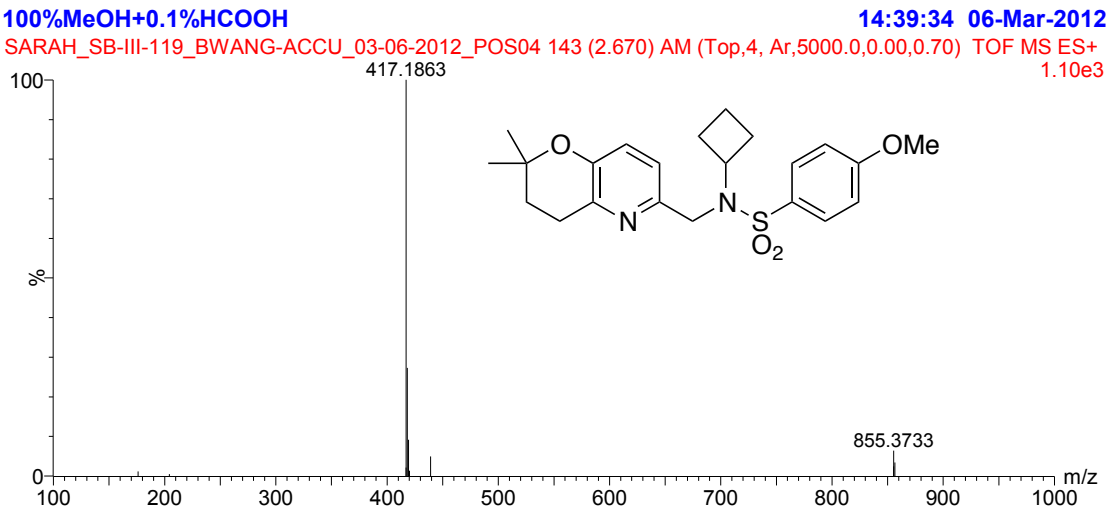



```
Current Data Parameters
NAME         SB-III-119a
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120305
Time               19.16
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                    64
DW                60.800 usec
DE                 6.50 usec
TE                298.2 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-III-119a




```
Current Data Parameters
NAME         SB-III-119a
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120305
Time               19.20
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    48
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                299.1 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



Elemental Composition Report

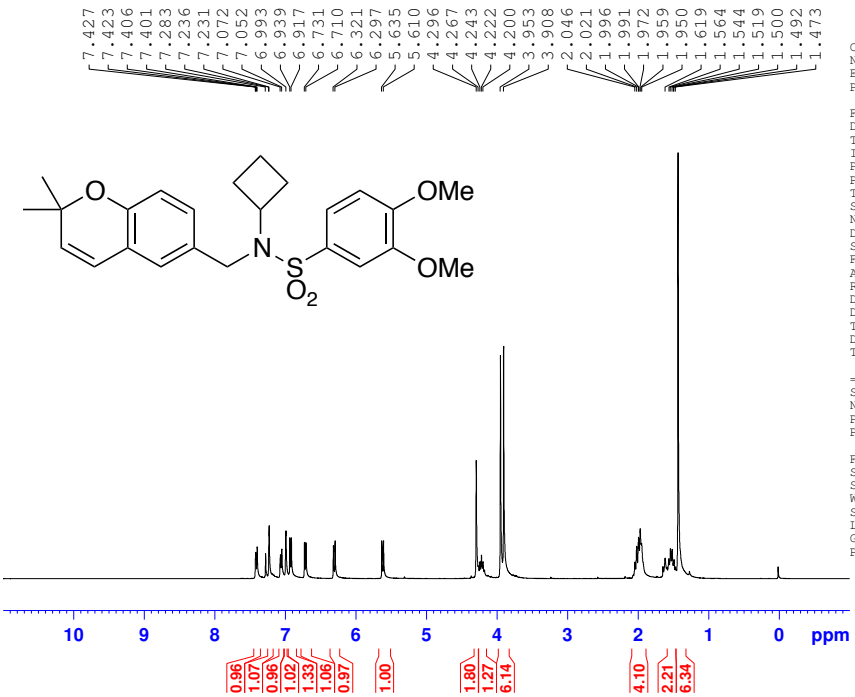
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
2613 formula(e) evaluated with 13 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20 S: 1-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
4.1848	417.1848	0.0	0.0	9.5	0.5	C22 H29 N2 O4 S

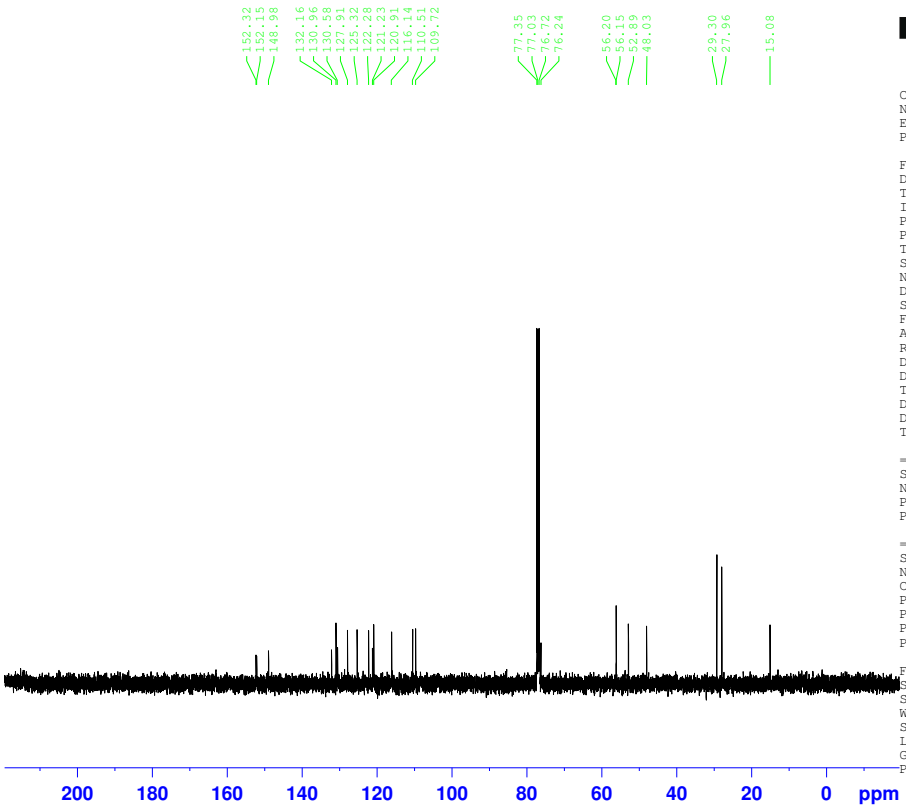
N-cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (13a)

SB-IV-63b-HPLC-B

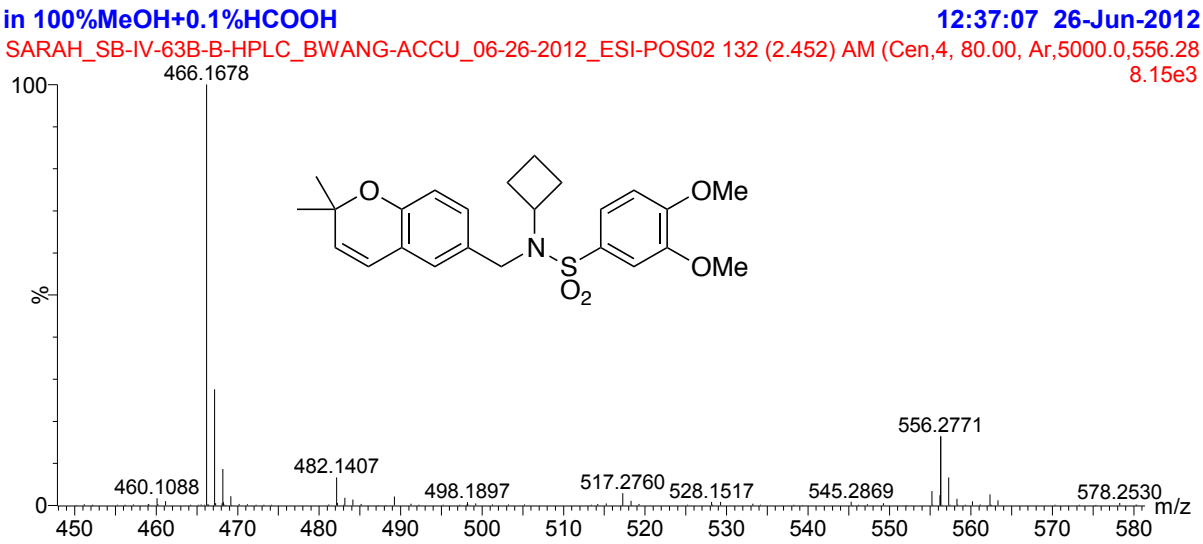



```
Current Data Parameters
NAME      SB-IV-63b-HPLC-B
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20120622
Time               15.00
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDC13
NS                     9
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9845889 sec
RG                   128
DW                60.800 usec
DE                 6.50 usec
TE                298.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

SB-IV-63b-HPLC-B




```
Current Data Parameters
NAME      SB-IV-63b-HPLC-B
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_           20120622
Time               15.03
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDC13
NS                    42
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.6 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                   13C
P1                 9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2         waltz16
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



Elemental Composition Report

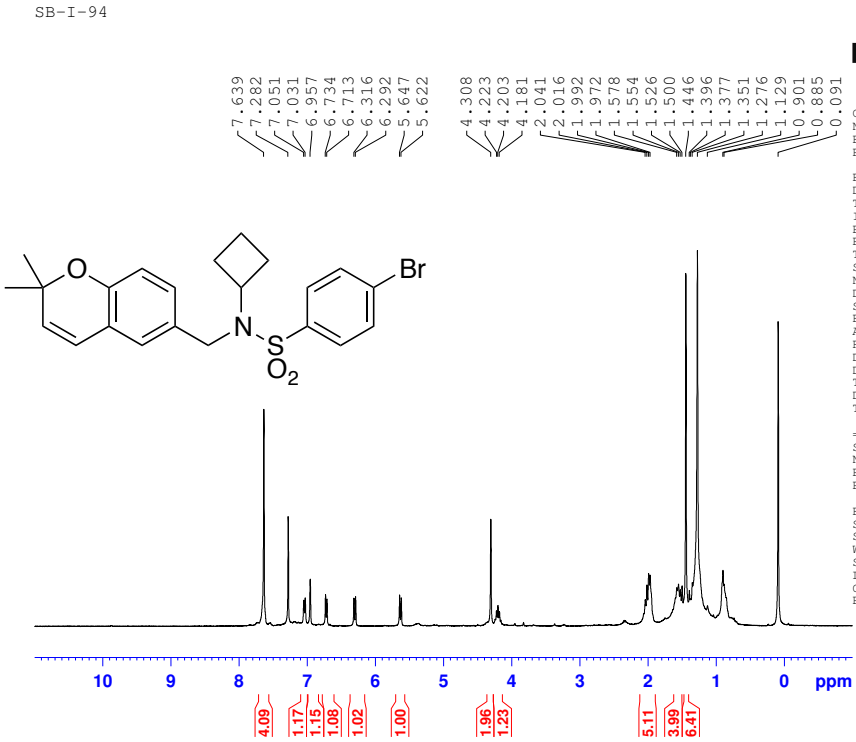
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
3521 formula(e) evaluated with 16 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 Na: 1-1 S: 1-50

Minimum:			-1.5			
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
466.1678	466.1664	1.4	3.0	10.5	3.2	C24 H29 N O5 Na S

4-bromo-*N*-cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)benzenesulfonamide (13b)

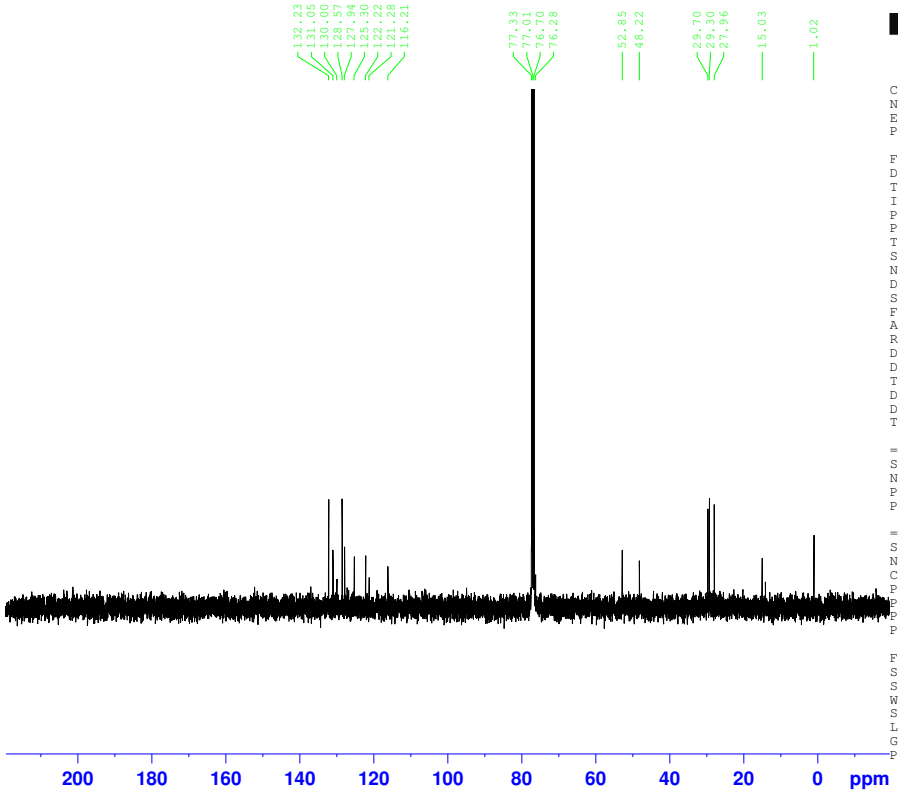
SB-I-94



BRUKER

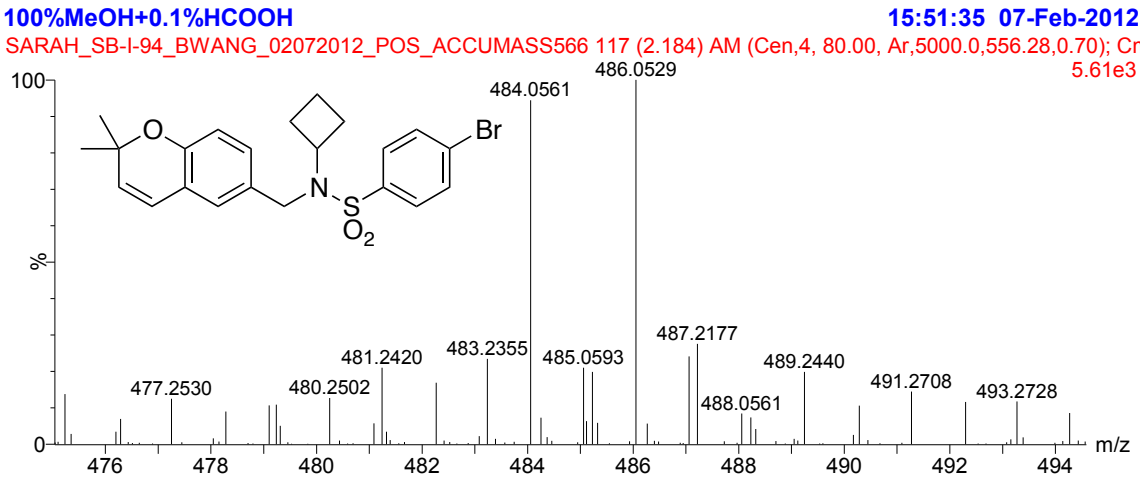
```
Current Data Parameters
NAME                  SB-I-94
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_               20130404
Time                   14.10
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                8012.820 Hz
FIDRES                0.122266 Hz
AQ                 4.0894465 sec
RG                       203
DW                    62.400 usec
DE                     6.50 usec
TE                    298.0 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1               400.1424710 MHz
NUC1                       1H
P1                      13.50 usec
PLW1               16.00000000 W

F2 - Processing parameters
SI                         65536
SF                 400.1400000 MHz
WDW                        EM
SSB           0
LB                      0.30 Hz
GB            0
PC                      1.00
```

SB-I-94



BRUKER

```
Current Data Parameters
NAME                  SB-I-94
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_               20130404
Time                   14.16
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                     65536
SOLVENT                CDCl3
NS                       212
DS                         4
SWH               24038.461 Hz
FIDRES                0.366798 Hz
AQ                 1.3631488 sec
RG                       203
DW                    20.800 usec
DE                     6.50 usec
TE                    298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1               100.6253441 MHz
NUC1                       13C
P1                      9.00 usec
PLW1               62.00000000 W

======== CHANNEL f2 ========
SFO2               400.1416006 MHz
NUC2                       1H
CPDPRG[2                waltz16
PCPD2                   90.00 usec
PLW2               16.00000000 W
PLW12               0.36000001 W
PLW13               0.29159999 W

F2 - Processing parameters
SI                         32768
SF                 100.6152830 MHz
WDW                        EM
SSB           0
LB                      1.00 Hz
GB            0
PC                      1.40
```



Elemental Composition Report

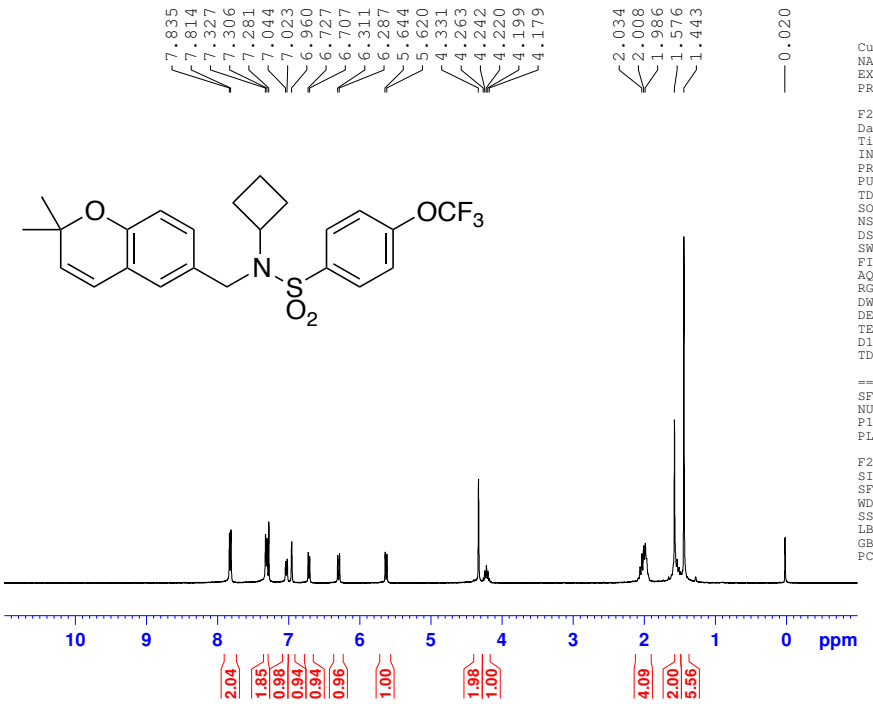
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
10169 formula(e) evaluated with 25 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3 S: 1-6 Br: 1-5

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
484.0561	484.0558	0.3	0.6	10.5	16.2	C22 H24 N O3 Na S Br

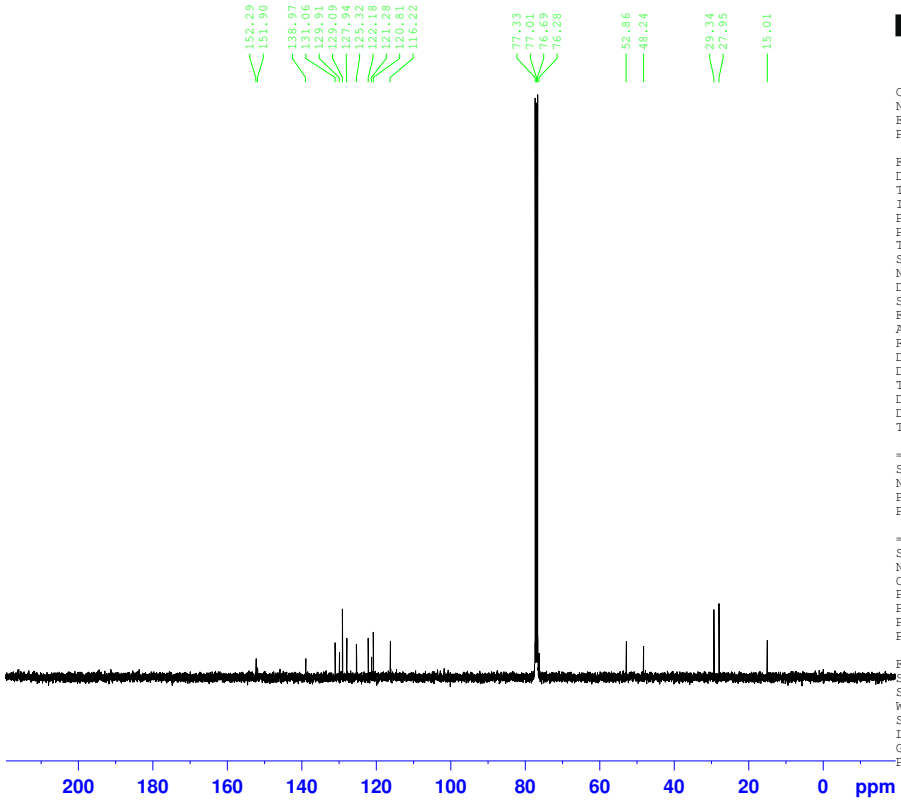
N-cyclobutyl-*N*-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)-4-(trifluoromethoxy)benzenesulfonamide (13c)

ZD1-34C

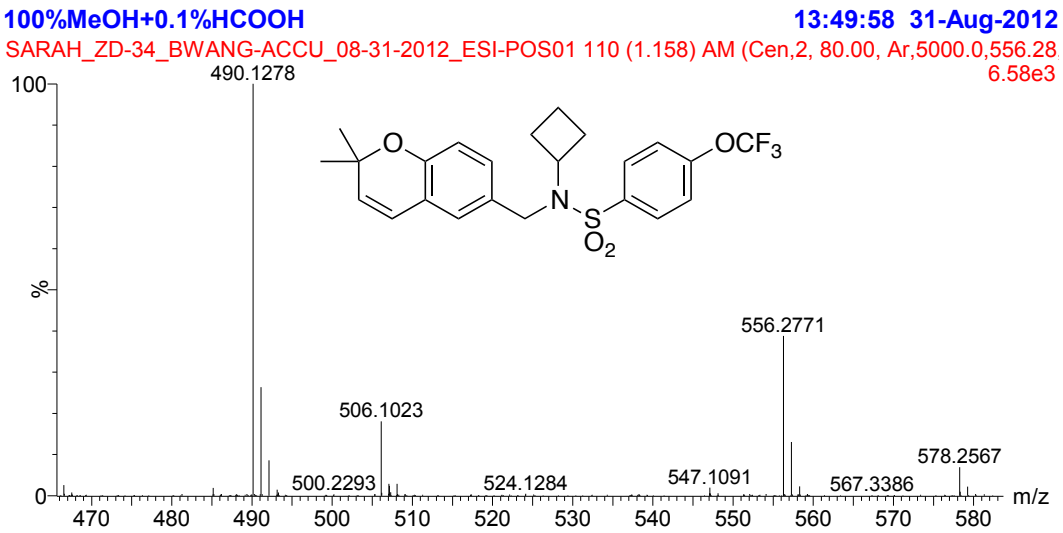



```
Current Data Parameters
NAME                  ZD1-34C
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120727
Time                   11.30
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       32
DS                        2
SWH                8012.820 Hz
FIDRES             0.122266 Hz
AQ                 4.0894465 sec
RG                      203
DW                    62.400 usec
DE                     6.50 usec
TE                    299.5 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1             400.1424710 MHz
NUC1                       1H
P1                      13.50 usec
PLW1             16.00000000 W

F2 - Processing parameters
SI                        65536
SF               400.1400000 MHz
WDW                         EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

ZD1-34C




```
Current Data Parameters
NAME                  ZD1-34C
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120727
Time                   14.25
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      366
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                    20.800 usec
DE                     6.50 usec
TE                    299.9 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1             100.6253441 MHz
NUC1                       13C
P1                      9.00 usec
PLW1             62.00000000 W

======== CHANNEL f2 ========
SFO2             400.1416006 MHz
NUC2                       1H
CPDPRG[2             waltz16
PCPD2                  90.00 usec
PLW2             16.00000000 W
PLW12             0.36000001 W
PLW13             0.29159999 W

F2 - Processing parameters
SI                        32768
SF               100.6152830 MHz
WDW                         EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.20
```



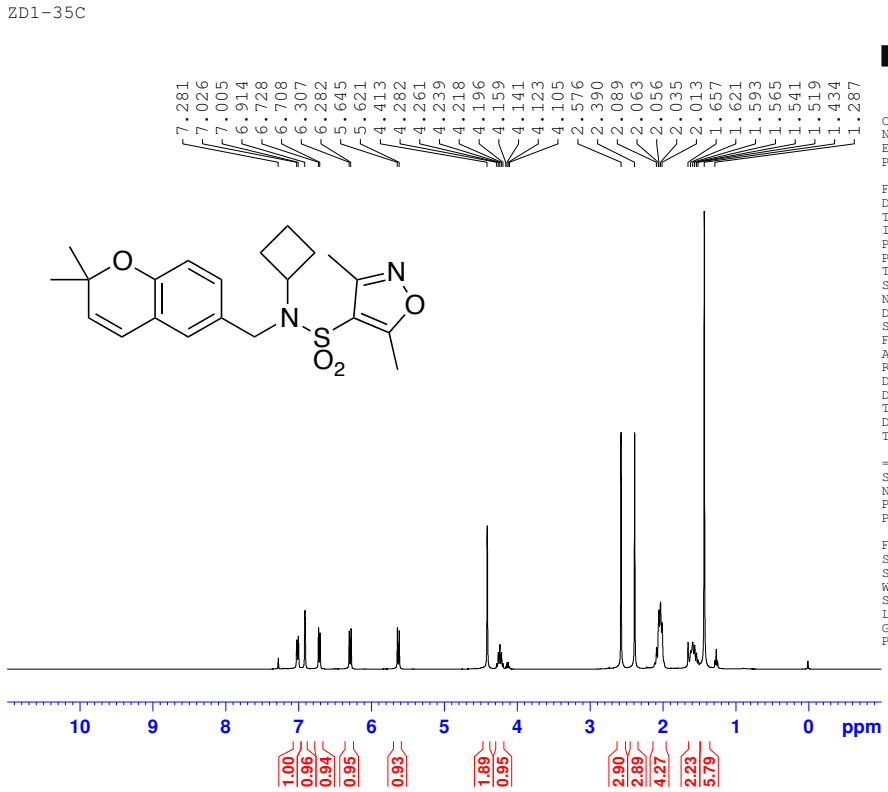
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
24118 formula(e) evaluated with 80 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 F: 1-6 S: 1-50 Na: 1-2

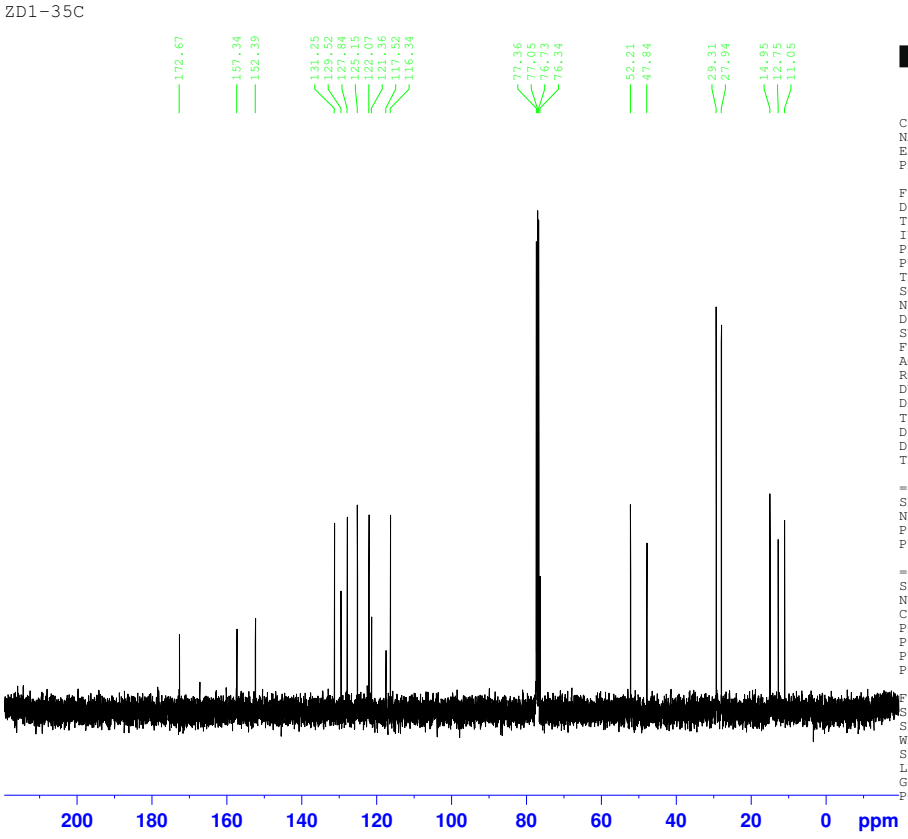
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
490.1278	490.1276	0.2	0.4	10.5	1.0	C23 H24 N O4 F3 S Na

_N_-cyclobutyl-_N_-((2,2-dimethyl-2_H_-chromen-6-yl)methyl)-3,5-dimethylisoxazole-4-sulfonamide (13d)



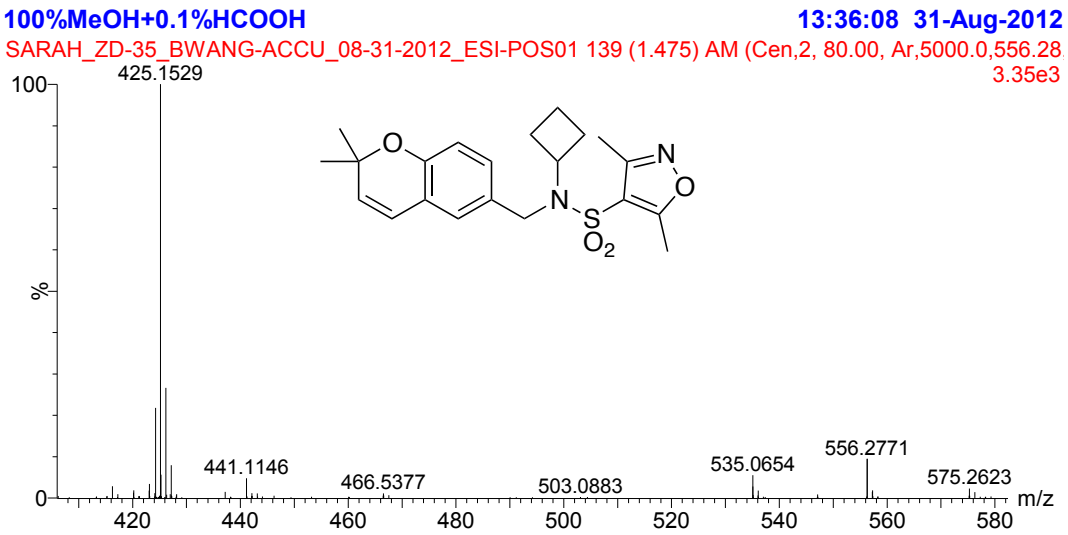
BRUKER

```
Current Data Parameters
NAME                  ZD1-35C
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120727
Time                  11.42
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      35
DS                       2
SWH                8012.820 Hz
FIDRES            0.122266 Hz
AQ                4.0894465 sec
RG                      64
DW                   62.400 usec
DE                    6.50 usec
TE                   299.4 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1             400.1424710 MHz
NUC1                      1H
P1                     13.50 usec
PLW1             16.00000000 W

F2 - Processing parameters
SI                       65536
SF               400.1400000 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```



BRUKER

```
Current Data Parameters
NAME                  ZD1-35C
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120727
Time                  14.48
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                      36
DS                       4
SWH               24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                     203
DW                   20.800 usec
DE                    6.50 usec
TE                   300.0 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1             100.6253441 MHz
NUC1                     13C
P1                     9.00 usec
PLW1              62.00000000 W

======== CHANNEL f2 ========
SFO2             400.1416006 MHz
NUC2                      1H
CPDPRG[2           waltz16
PCPD2                 90.00 usec
PLW2             16.00000000 W
PLW12             0.36000001 W
PLW13             0.29159999 W

F2 - Processing parameters
SI                       32768
SF               100.6152830 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



Elemental Composition Report

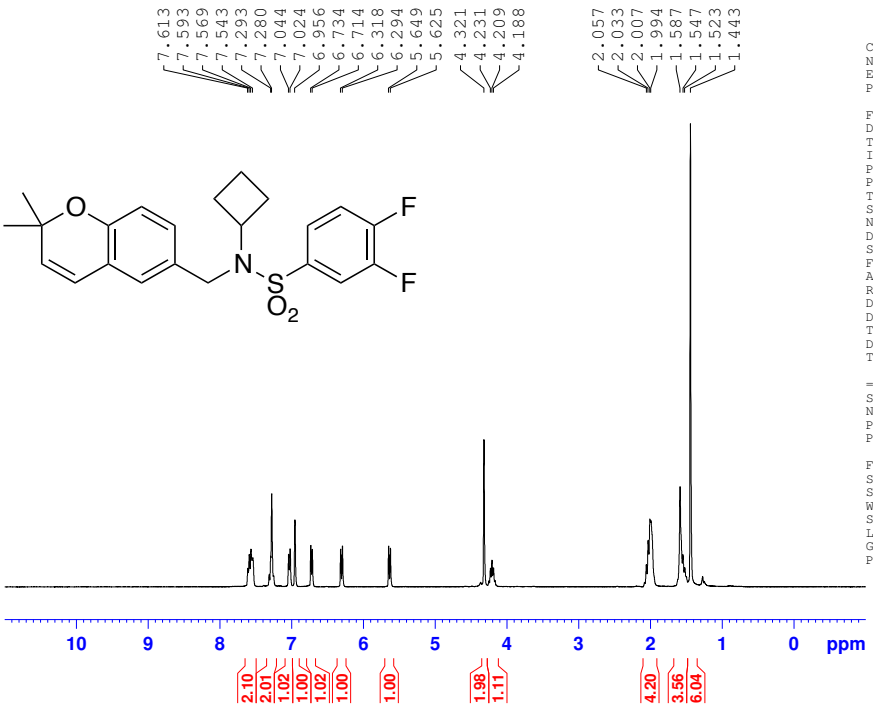
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
4305 formula(e) evaluated with 20 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 1-50 Na: 1-2

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
425.1529	425.1511	1.8	4.2	9.5	1.4	C21 H26 N2 O4 S Na

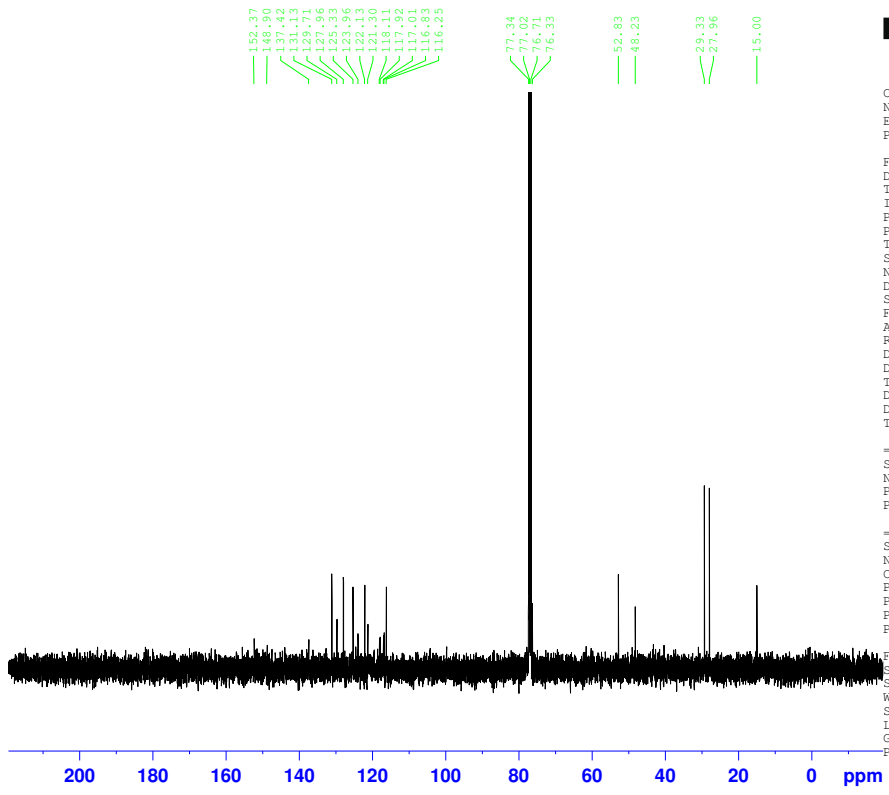
_N_-cyclobutyl-_N_-((2,2-dimethyl-2_H_-chromen-6-yl)methyl)-3,4-difluorobenzenesulfonamide (13e)

ZD-I-39

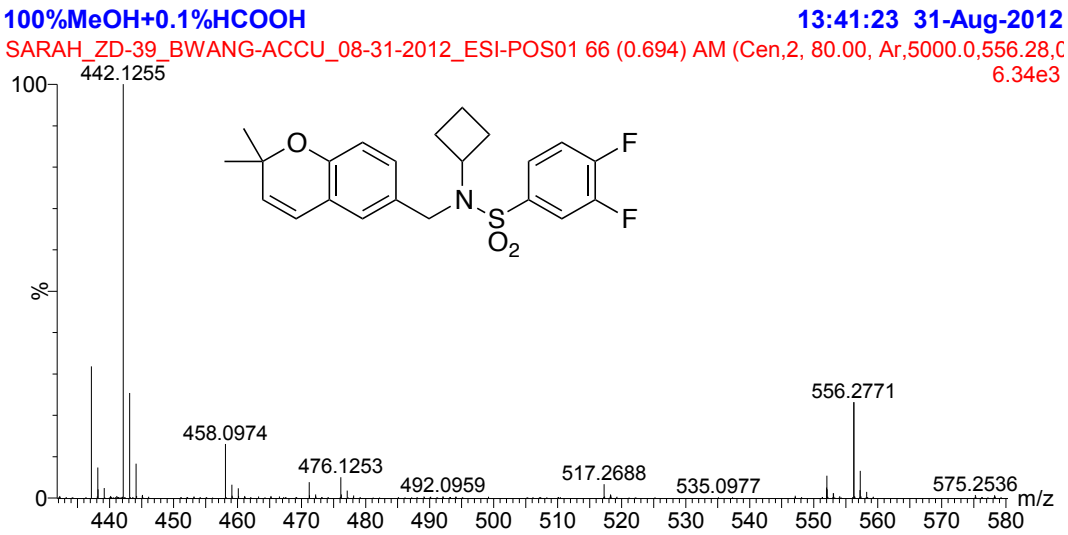



```
Current Data Parameters
NAME              ZD-I-39
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20130118
Time               10.02
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                   203
DW                62.400 usec
DE                 6.50 usec
TE                294.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1        16.00000000 W

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

ZD-I-39




```
Current Data Parameters
NAME              ZD-I-39
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20130118
Time               10.05
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   113
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                294.7 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                   13C
P1                 9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

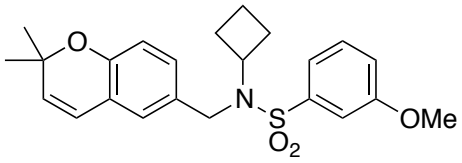


Elemental Composition Report

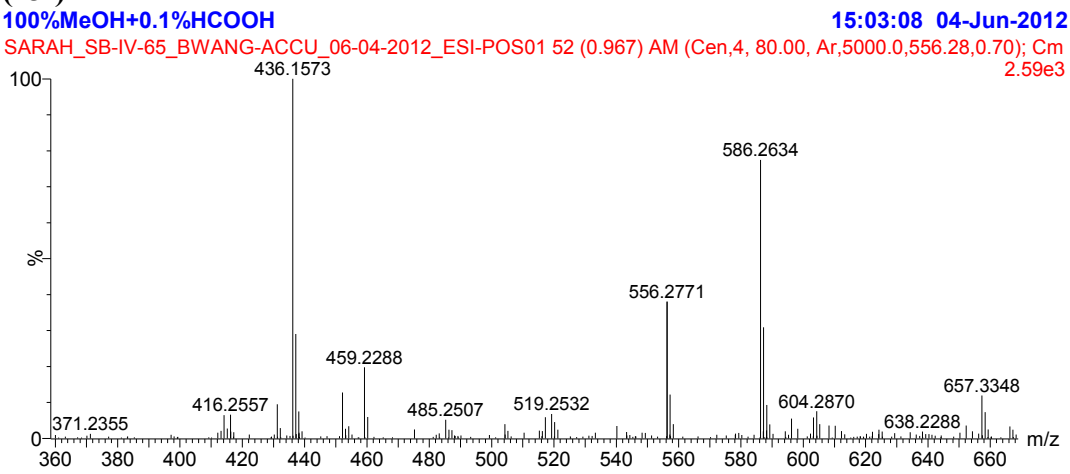
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
14806 formula(e) evaluated with 47 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 F: 1-6 S: 1-50 Na: 1-2

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
442.1255	442.1264	-0.9	-2.0	10.5	0.7	C22 H23 N O3 F2 S Na



_N_-cyclobutyl-_N_-((2,2-dimethyl-2_H_-chromen-6-yl)methyl)-3-methoxybenzenesulfonamide (13f)



Elemental Composition Report

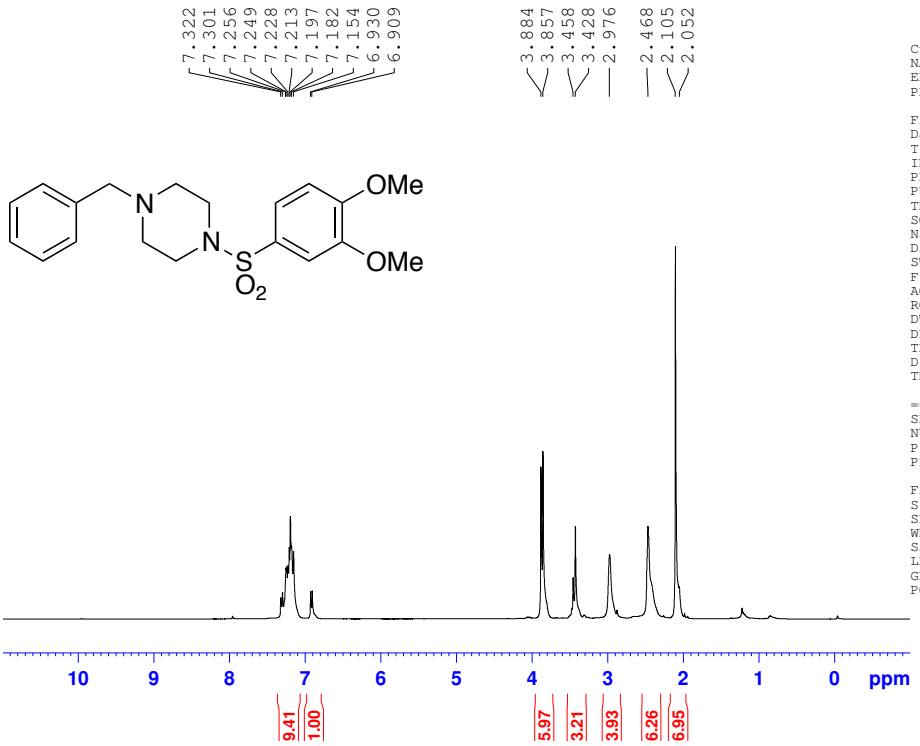
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
7783 formula(e) evaluated with 25 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 0-50 Na: 0-1

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
436.1573	436.1559	1.4	3.2	10.5	4.6	C23 H27 N O4 S Na

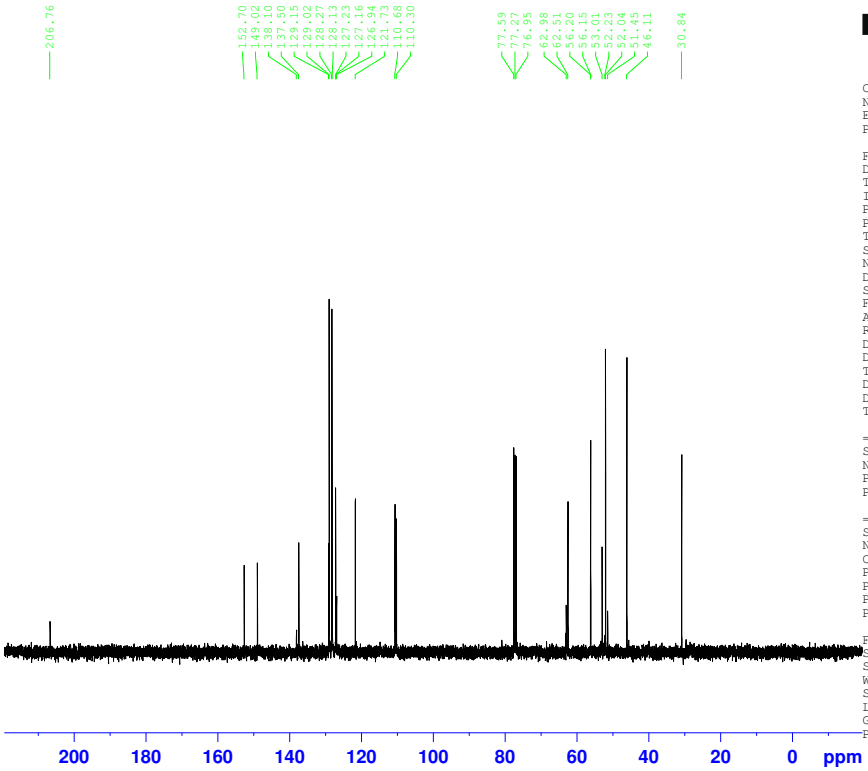
1-Benzyl-4-((3,4-dimethoxyphenyl)sulfonyl)piperazine (14a)

SB-IV-154b

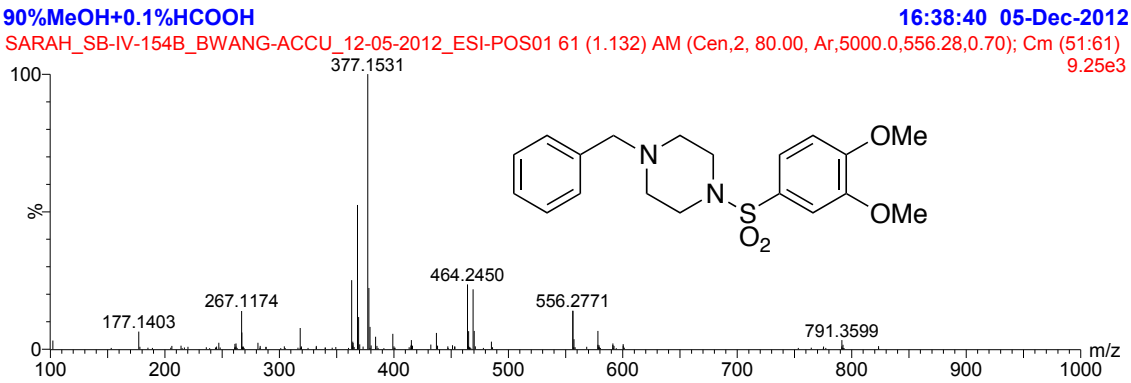



```
Current Data Parameters
NAME          SB-IV-154b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121004
Time               18.51
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                    18
DW                62.400 usec
DE                 6.50 usec
TE                298.8 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                  1H
P1                13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                 65536
SF           400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-IV-154b




```
Current Data Parameters
NAME          SB-IV-154b
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121004
Time               18.54
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    26
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                299.4 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF           100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



Elemental Composition Report

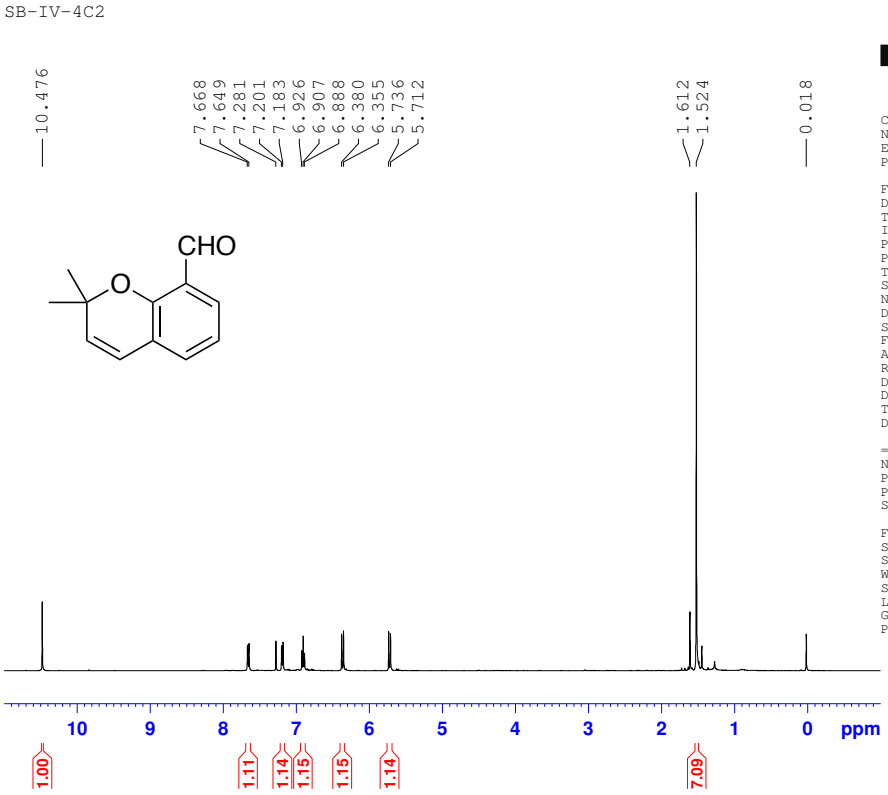
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
2076 formula(e) evaluated with 11 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-20 O: 1-30 S: 1-10

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
377.1531	377.1535	-0.4	-1.1	8.5	2.2	C19 H25 N2 O4 S

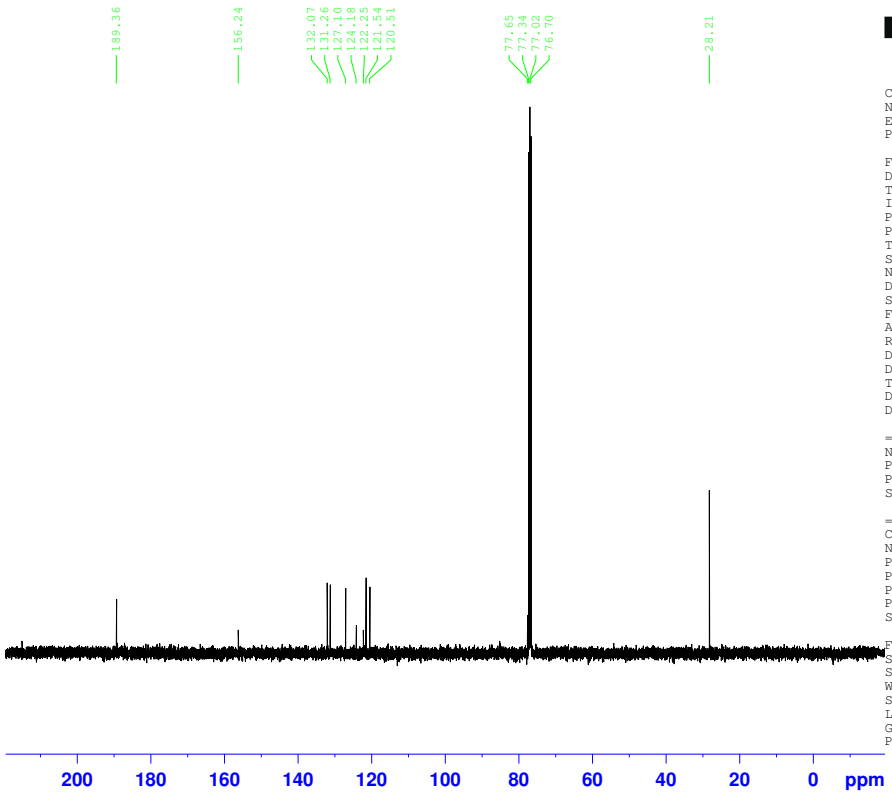
2,2-Dimethyl-2*H*-chromene-8-carbaldehyde (15b)

SB-IV-4C2

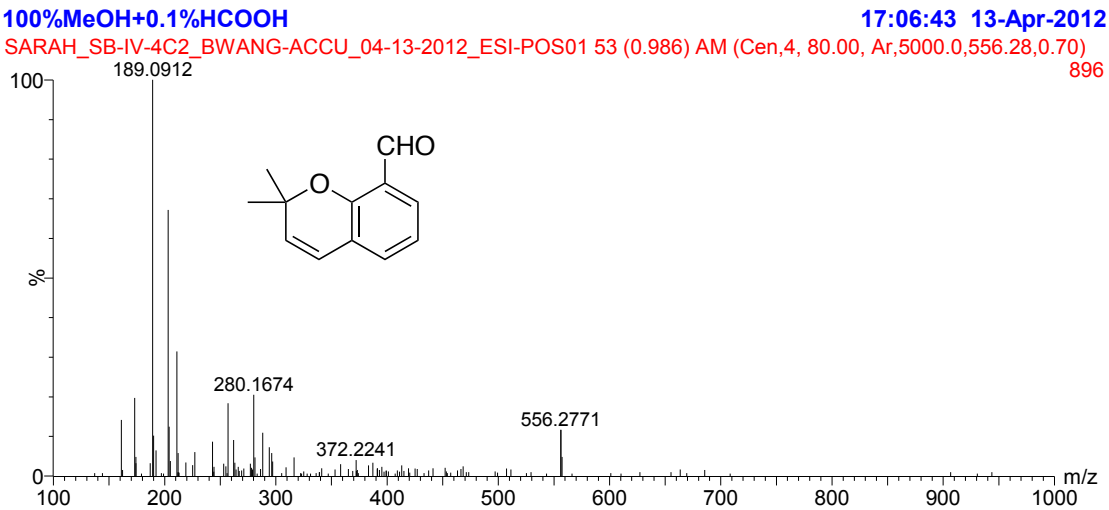



```
Current Data Parameters
NAME            SB-IV-4C2
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20120406
Time                15.05
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ               3.9846387 sec
RG                    101
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                  65536
SF           400.1400000 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

SB-IV-4C2




```
Current Data Parameters
NAME            SB-IV-4C2
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20120406
Time                15.08
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                     75
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631988 sec
RG                    203
DW                20.800 usec
DE                 6.50 usec
TE                298.7 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.00 usec
PLW1         62.00000000 W
SFO1        100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2        400.1416006 MHz

F2 - Processing parameters
SI                  32768
SF          100.6152830 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

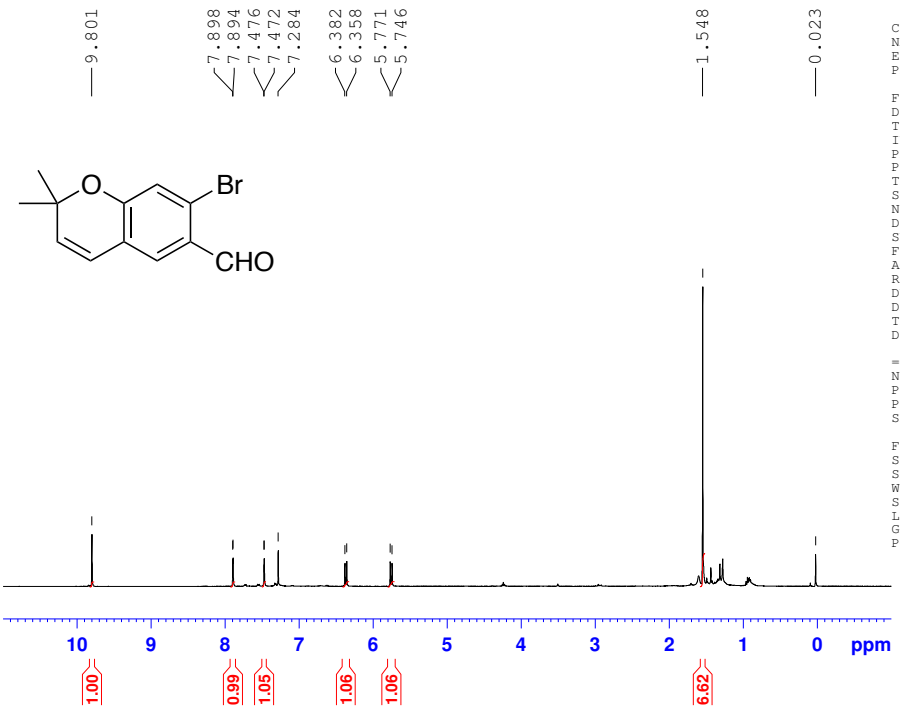


Elemental Composition Report
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 O: 1-20

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
189.0912	189.0916	-0.4	-2.1	6.5	n/a	C12 H13 O2

5-Bromo-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (15c)

SB-II-101b

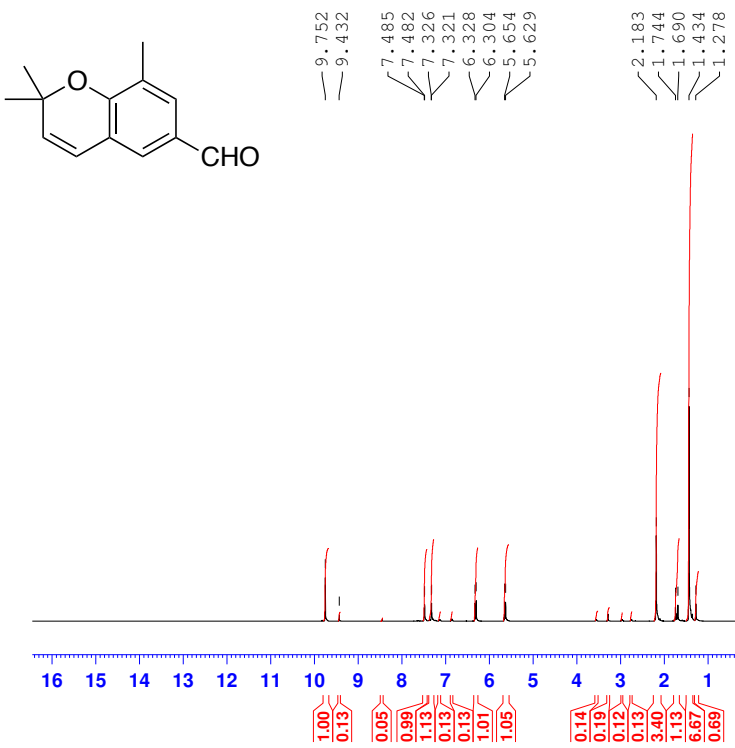


BRUKER

```
Current Data Parameters
NAME          SB-II-101b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20110816
Time               18.54
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     6
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                   203
DW                60.800 usec
DE                 6.50 usec
TE                298.8 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

2,2,8-Trimethyl-2*H*-chromene-6-carbaldehyde (15d)

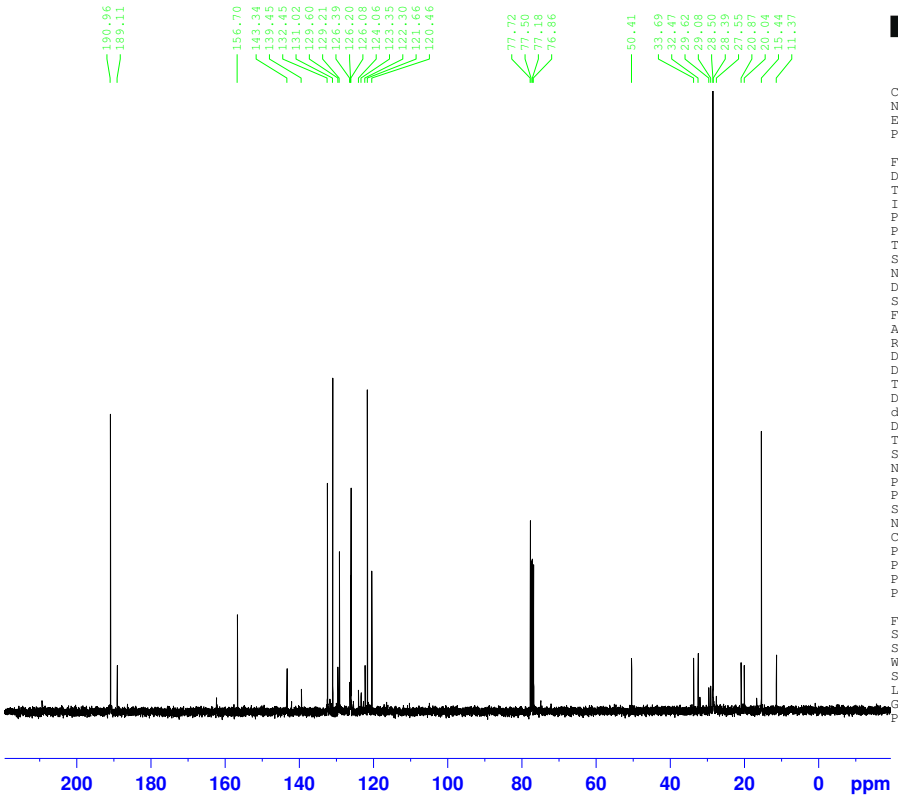
SB-II-120a



BRUKER

```
Current Data Parameters
NAME          SB-II-120a
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20110921
Time               17.39
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9845889 sec
RG                    16
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

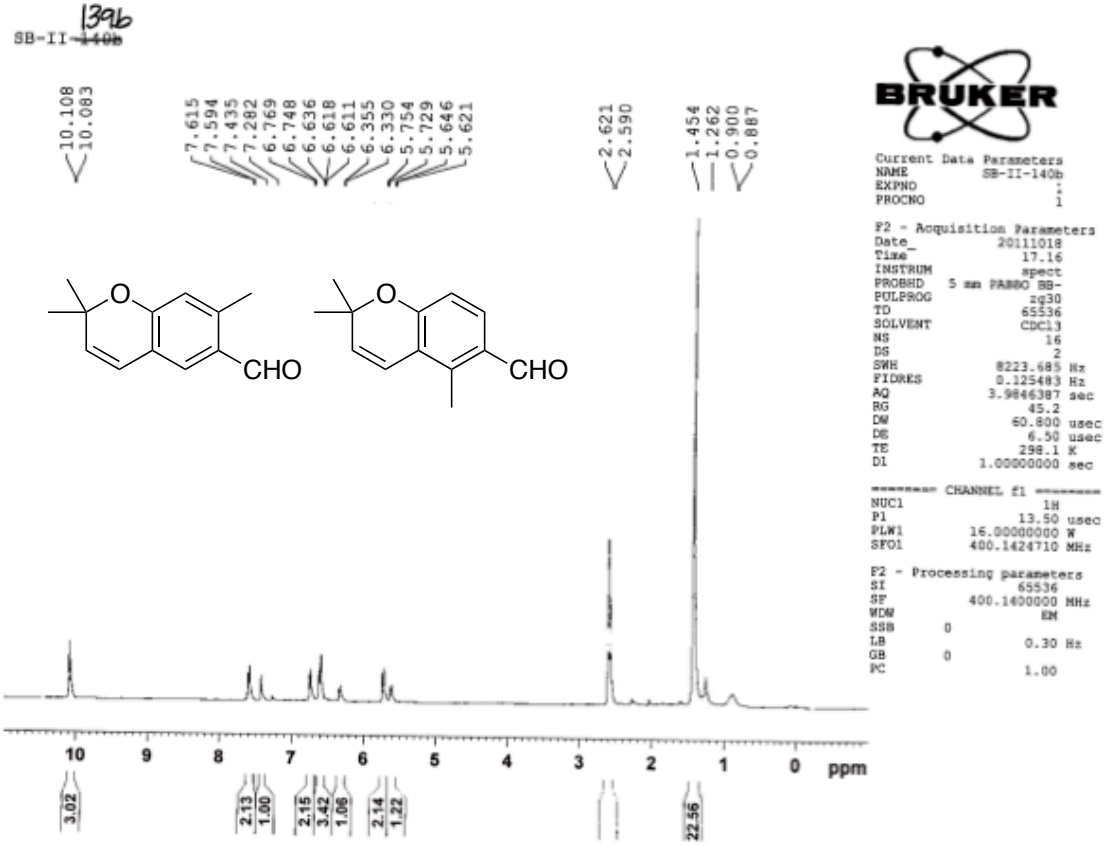
SB-II-120a



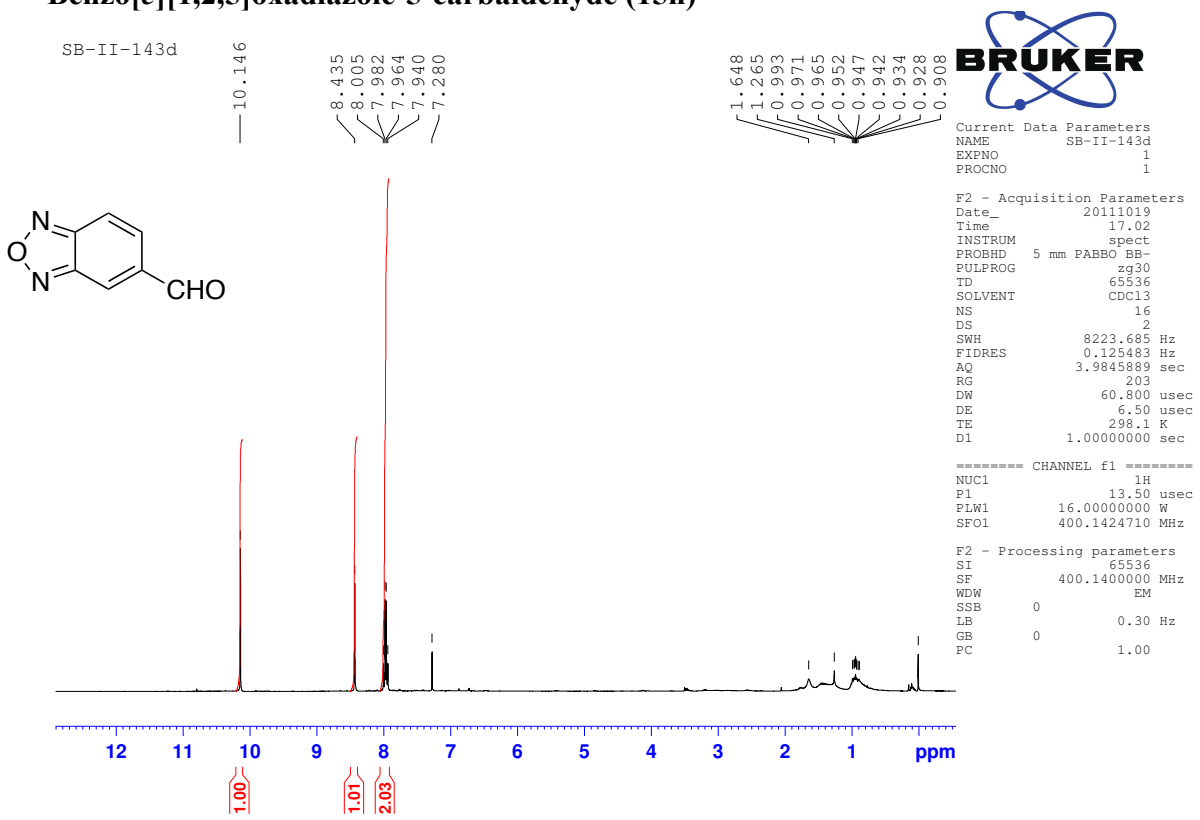
BRUKER

```
Current Data Parameters
NAME          SB-II-120a
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20110921
Time               17.45
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    32
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.1 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                    1
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO2         400.1416006 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

2,2,5-Trimethyl-2*H*-chromene-6-carbaldehyde with 2,2,7-Trimethyl-2*H*-chromene-6-carbaldehyde (1:2) (15e)

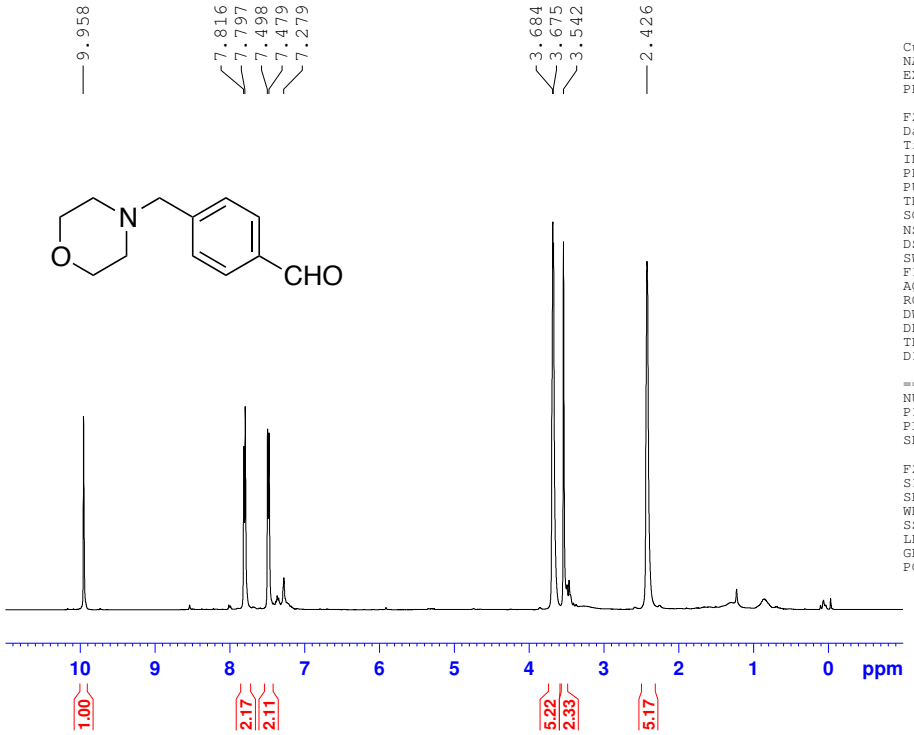


Benzo[*c*][1,2,5]oxadiazole-5-carbaldehyde (15h)



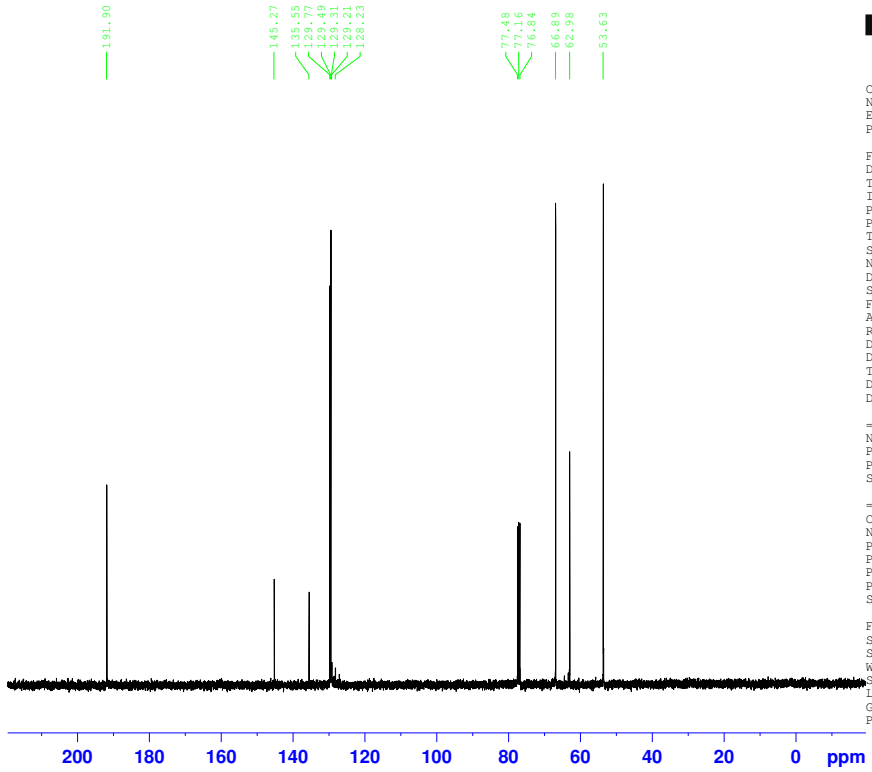
4-(Morpholinomethyl)benzaldehyde (15i)

SB-IV-30

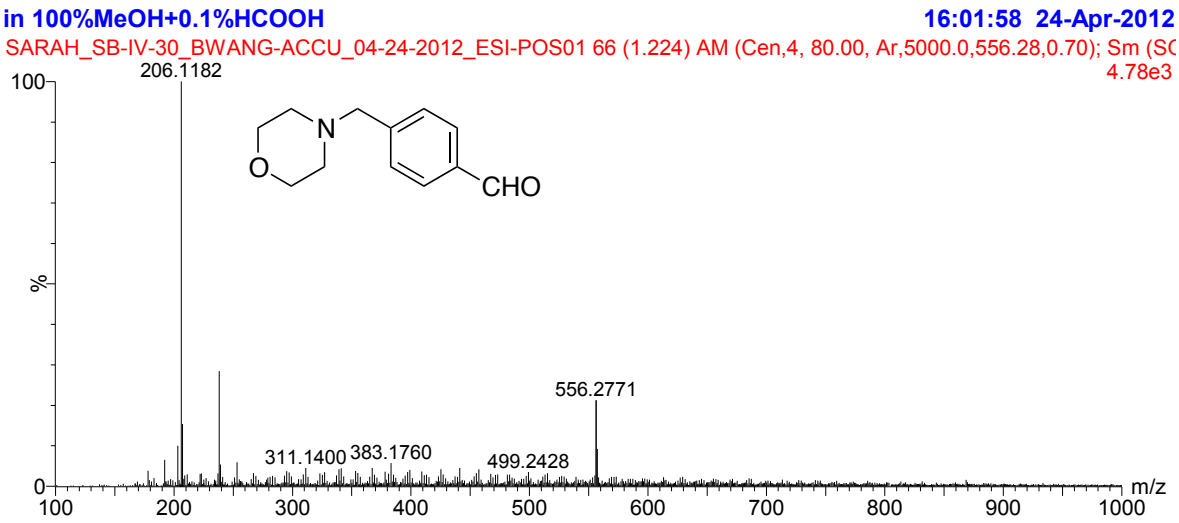



```
Current Data Parameters
NAME              SB-IV-30
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_            20120420
Time                15.49
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ               3.9846387 sec
RG                   20.2
DW                 60.800 usec
DE                  6.50 usec
TE                 298.2 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PLW1          16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                  65536
SF           400.1400000 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

SB-IV-30



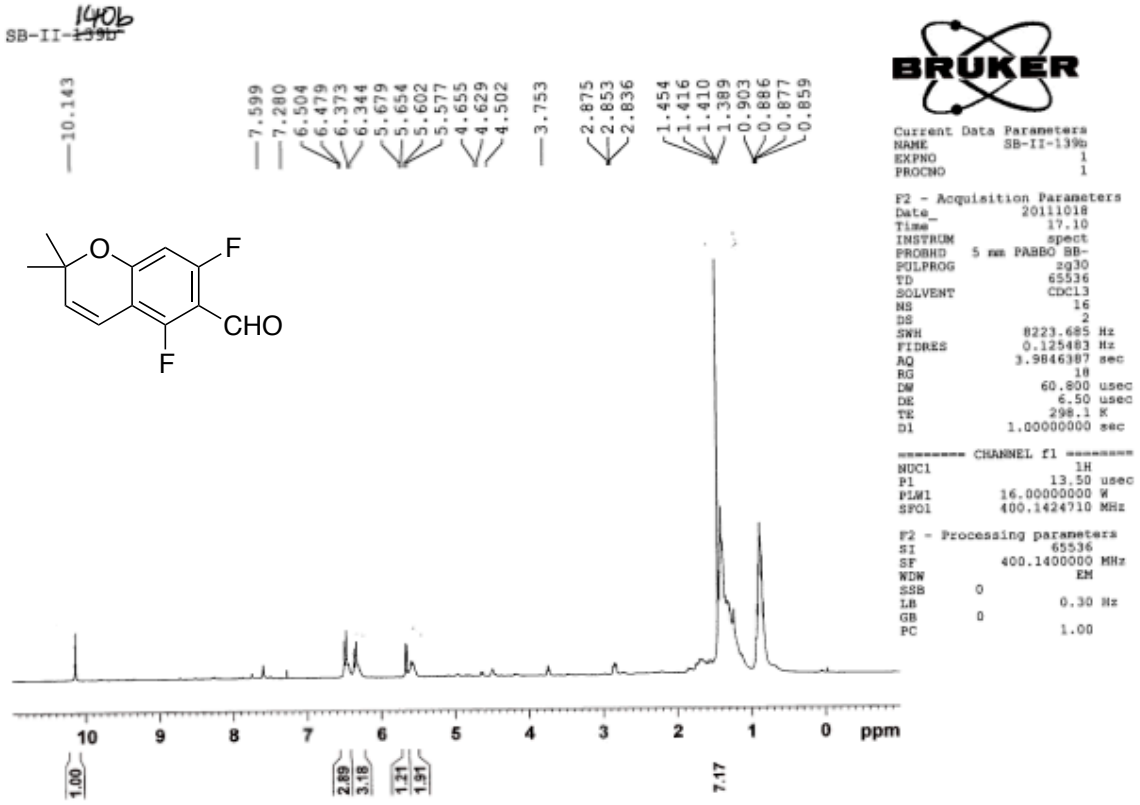

```
Current Data Parameters
NAME              SB-IV-30
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_            20120420
Time                15.51
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG           zgpg30
TD                  65536
SOLVENT             CDCl3
NS                     29
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631988 sec
RG                    203
DW                 20.800 usec
DE                  6.50 usec
TE                 298.4 K
D1              2.00000000 sec
D11             0.03000000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.00 usec
PLW1          62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2               90.00 usec
PLW2          16.00000000 W
PLW12          0.36000001 W
PLW13          0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                  32768
SF           100.6152830 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```



Elemental Composition Report
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
181 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-35 80Se: 0-1

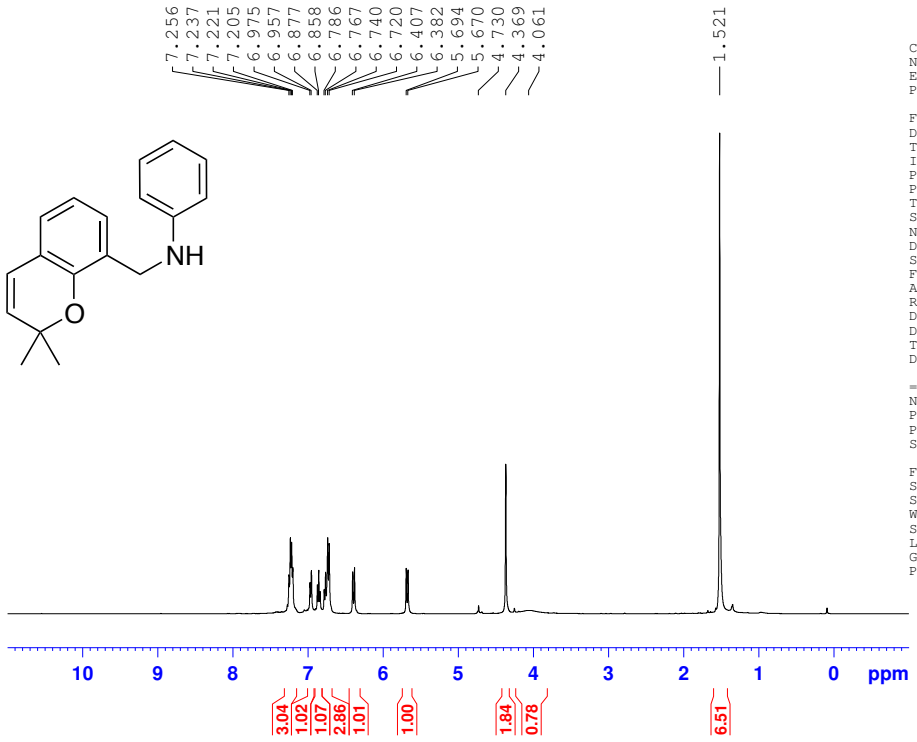
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
206.1182	206.1181	0.1	0.5	5.5	5.0	C12 H16 N O2

5,7-difluoro-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (15l)



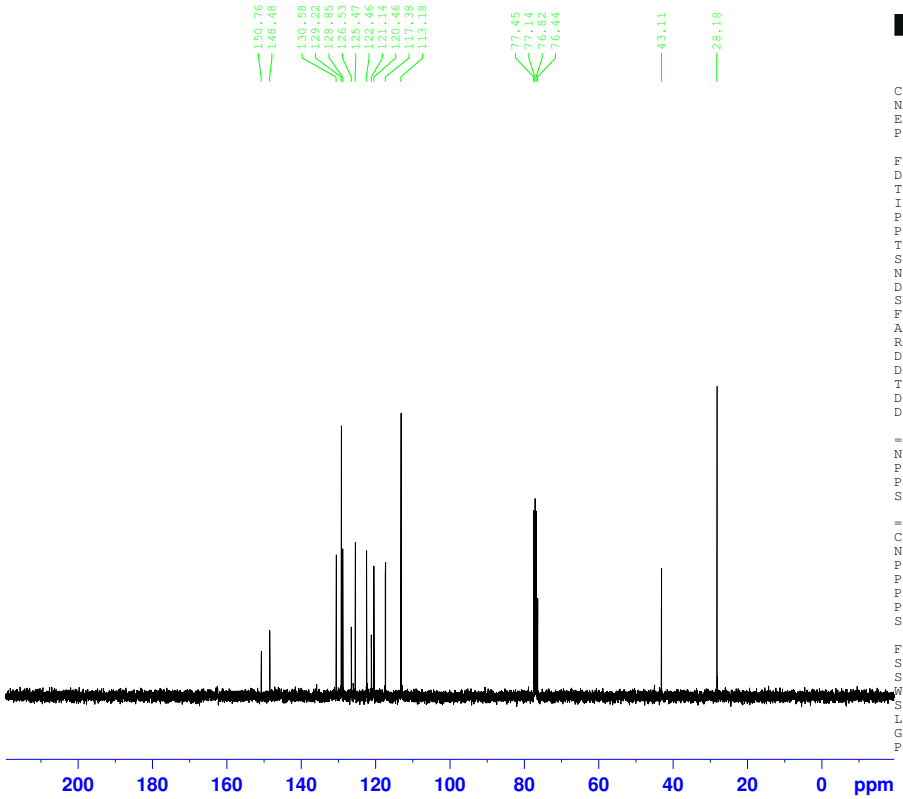
N-((2,2-Dimethyl-2*H*-chromen-8-yl)methyl)aniline (16b)

SB-IV-53

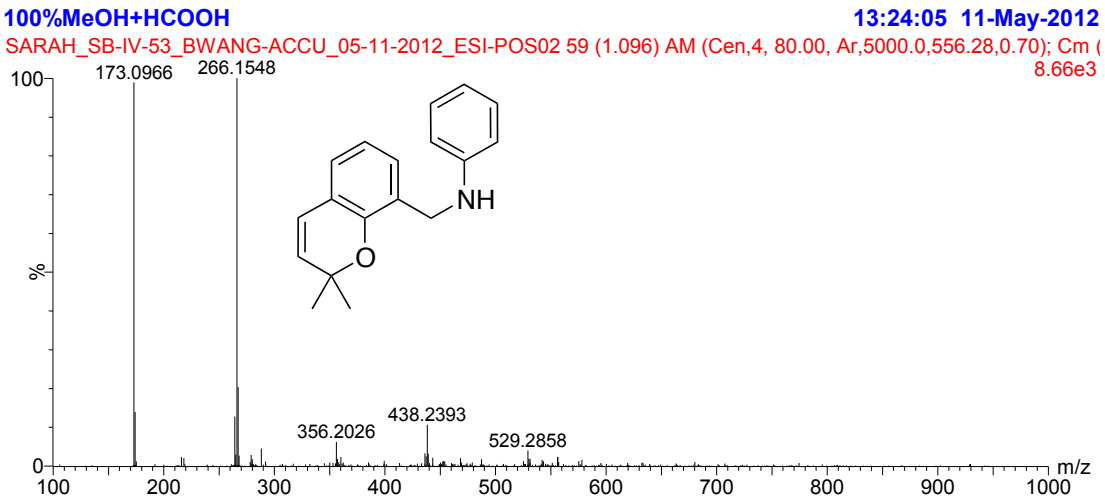



```
Current Data Parameters
NAME            SB-IV-53
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120509
Time               12.26
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                  28.5
DW                60.800 usec
DE                 6.50 usec
TE                298.2 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1                13.50 usec
PLW1        16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-IV-53




```
Current Data Parameters
NAME            SB-IV-53
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120509
Time               12.28
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    20
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.3 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                 9.00 usec
PLW1        62.00000000 W
SFO1        100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W
SFO2        400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



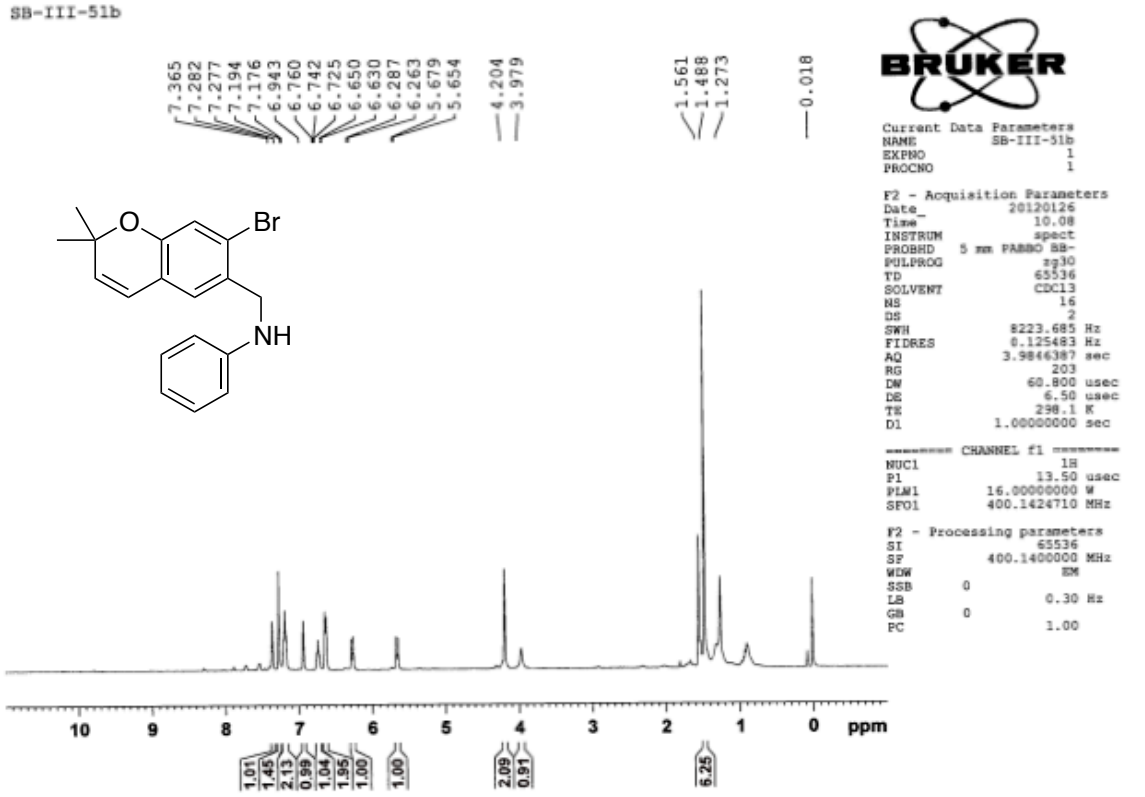
Elemental Composition Report

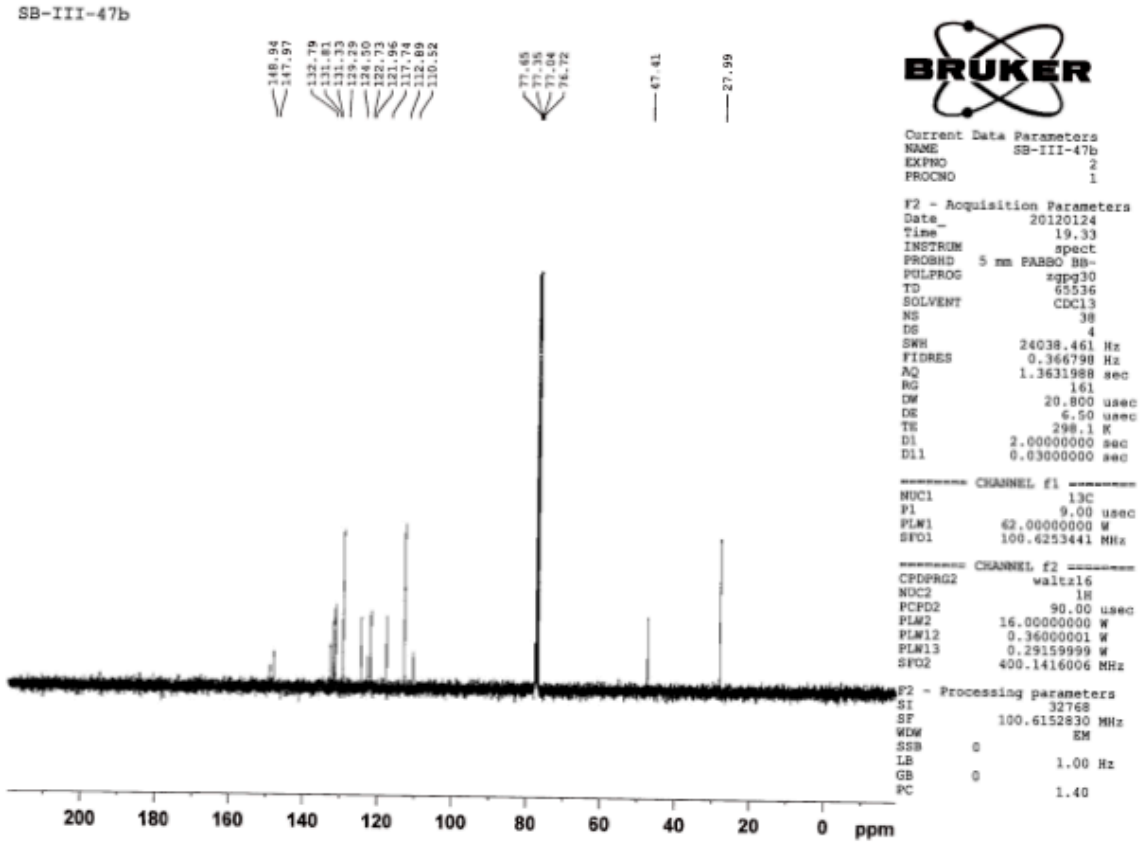
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
293 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
266.1548	266.1545	0.3	1.1	9.5	3.1	C18 H20 N O

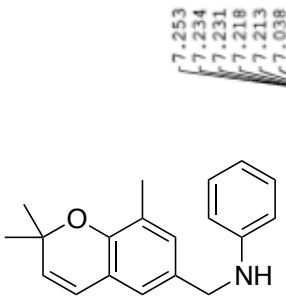
_N_-((7-Bromo-2,2-dimethyl-2_H_-chromen-6-yl)methyl)aniline (16c)





_N_-((2,2,8-Trimethyl-2_H_-chromen-6-yl)methyl)aniline (16d)

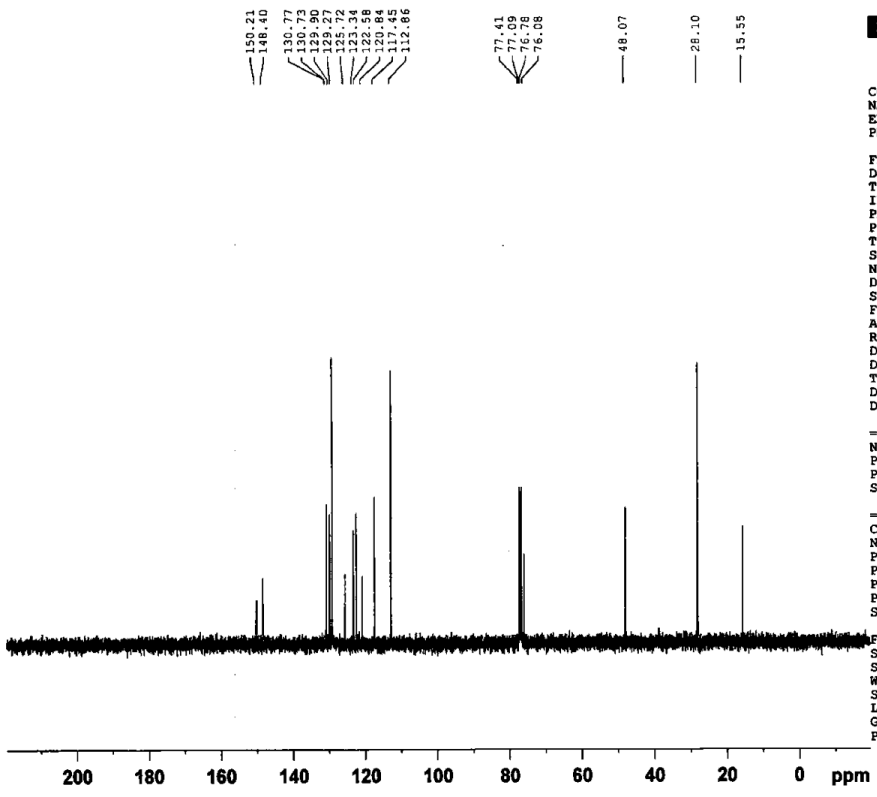
KC14b



BRUKER

```
Current Data Parameters
NAME                  KC14b
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20120203
Time                  12.21
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        7
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       32
DW                   60.800 usec
DE                    6.50 usec
TE                   298.1 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                    13.50 usec
PLW1           16.00000000 W
SFO1           400.1424710 MHz

F2 - Processing parameters
SI                    65536
SF             400.1400000 MHz
WDW                      EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

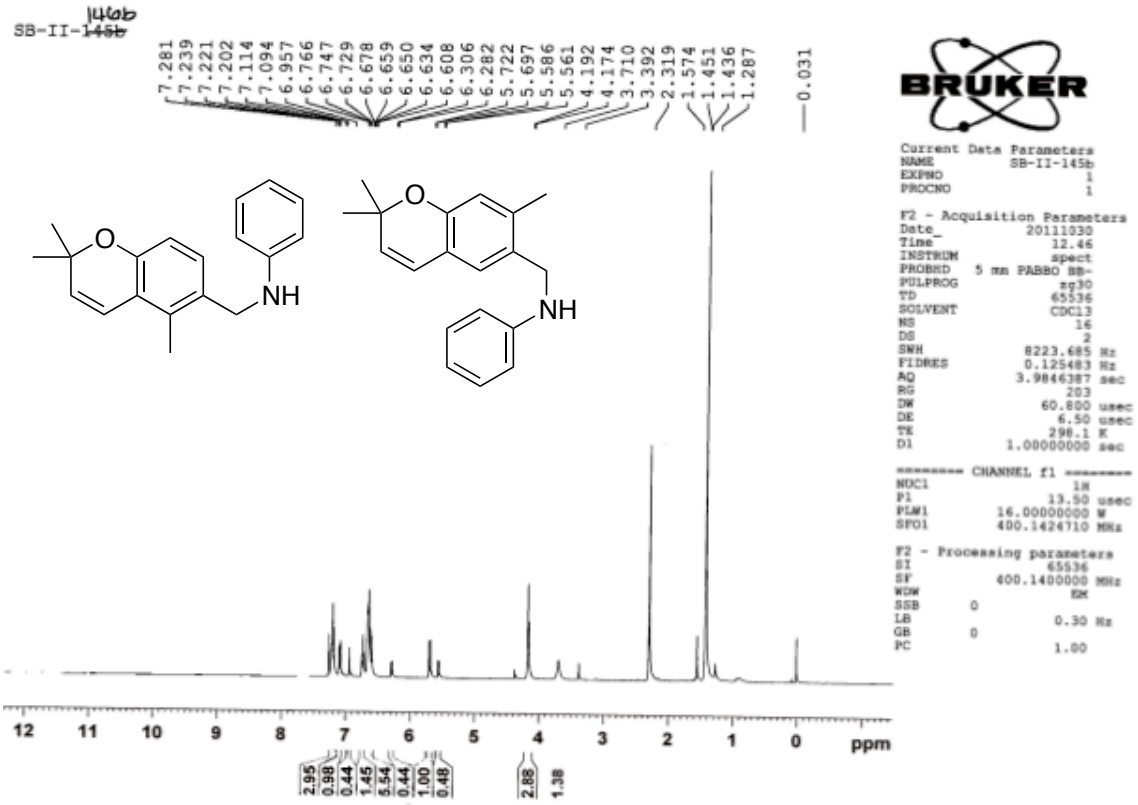
KC14b



BRUKER

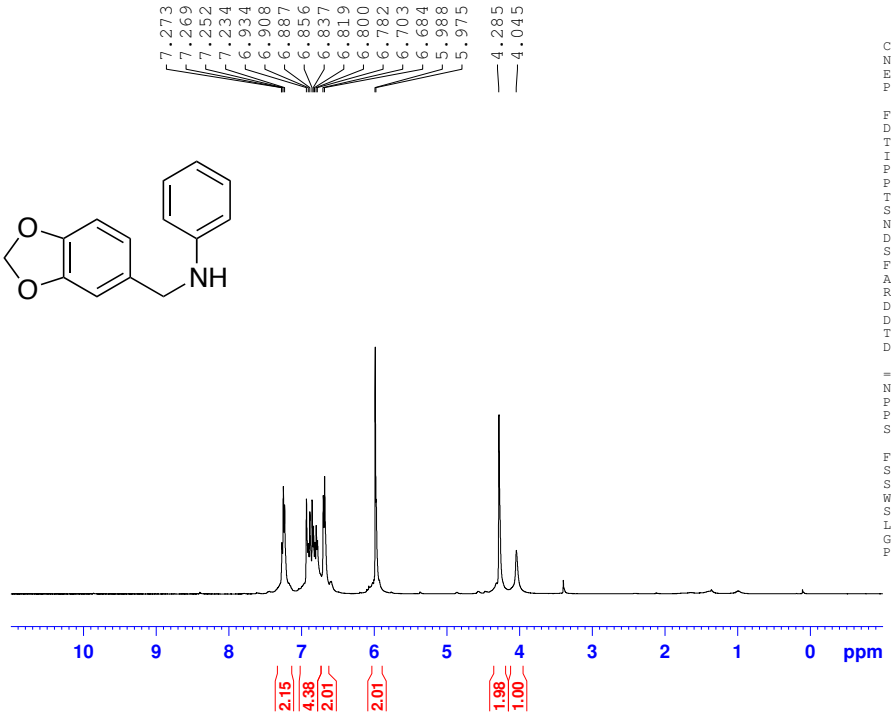
```
Current Data Parameters
NAME                  KC14b
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20120203
Time                  12.24
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       15
DS                        4
SWH            24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      161
DW                   20.800 usec
DE                    6.50 usec
TE                   298.2 K
D1                2.00000000 sec
D11               0.03000000 sec

======== CHANNEL f1 ========
NUC1                     13C
P1                     9.00 usec
PLW1           62.00000000 W
SFO1           100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 90.00 usec
PLW2           16.00000000 W
PLW12           0.36000001 W
PLW13           0.29159999 W
SFO2           400.1416006 MHz

F2 - Processing parameters
SI                    32768
SF             100.6152830 MHz
WDW                      EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

_N_-((2,2,5-Trimethyl-2_H_-chromen-6-yl)methyl)aniline with _N_-((2,2,7-trimethyl-2_H_-chromen-6-yl)methyl)aniline (2:1) (16e)



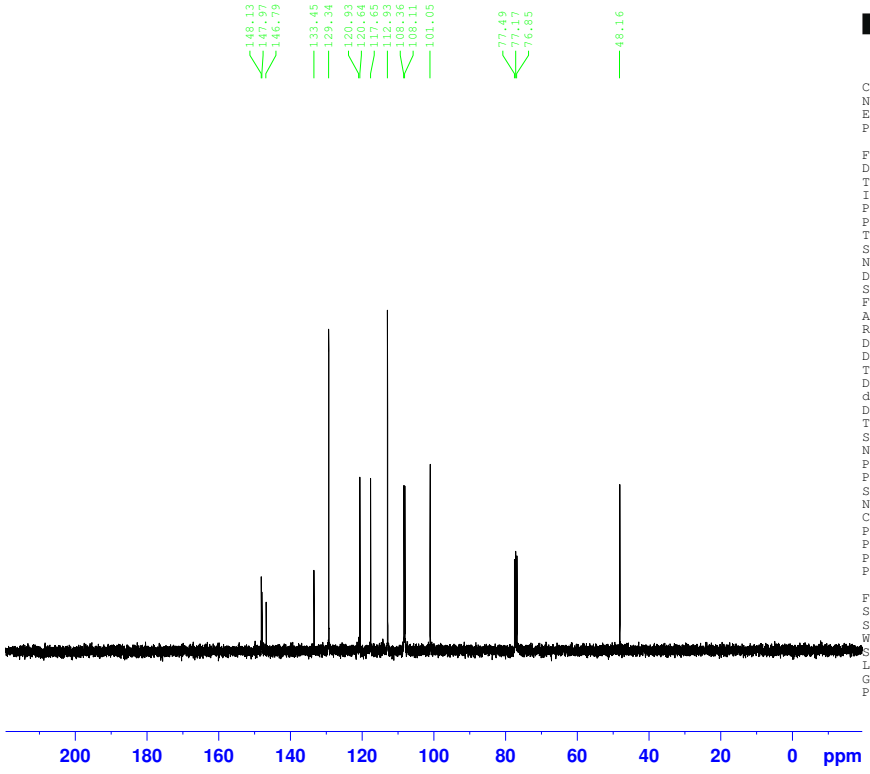
N-(benzo[*d*][1,3]dioxol-5-ylmethyl)aniline (16g)

KC13

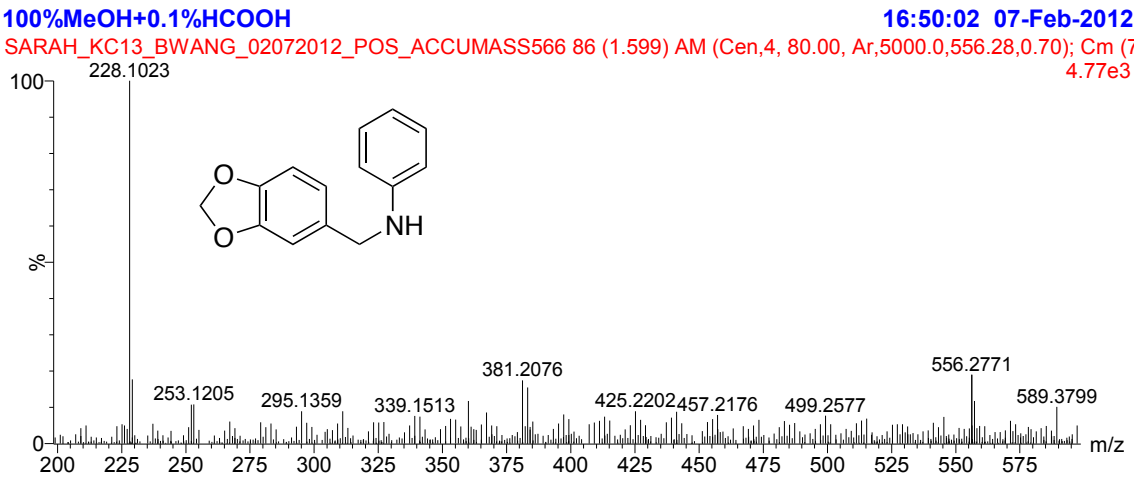



```
Current Data Parameters
NAME                  KC13
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20120130
Time                  9.17
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                       2
DS                       2
SWH               8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9846387 sec
RG                     128
DW                  60.800 usec
DE                   6.50 usec
TE                  298.2 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PLW1           16.00000000 W
SFO1           400.1424710 MHz

F2 - Processing parameters
SI                   65536
SF              400.1400000 MHz
WDW                    EM
SSB         0
LB                   0.30 Hz
GB          0
PC                   1.00
```

KC13




```
Current Data Parameters
NAME                  KC13
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20120130
Time                 14.30
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                      22
DS                       4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                     203
DW                  20.800 usec
DE                   6.50 usec
TE                  298.2 K
D1              2.00000000 sec
d11             0.03000000 sec
DELTA           1.89999998 sec
TD0                      1
SFO1           100.6253441 MHz
NUC1                   13C
P1                   9.00 usec
PLW1           62.00000000 W
SFO2           400.1416006 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2               90.00 usec
PLW2           16.00000000 W
PLW12           0.36000001 W
PLW13           0.29159999 W

F2 - Processing parameters
SI                   32768
SF             100.6152830 MHz
WDW                    EM
SSB         0
LB                   1.00 Hz
GB          0
PC                   1.40
```

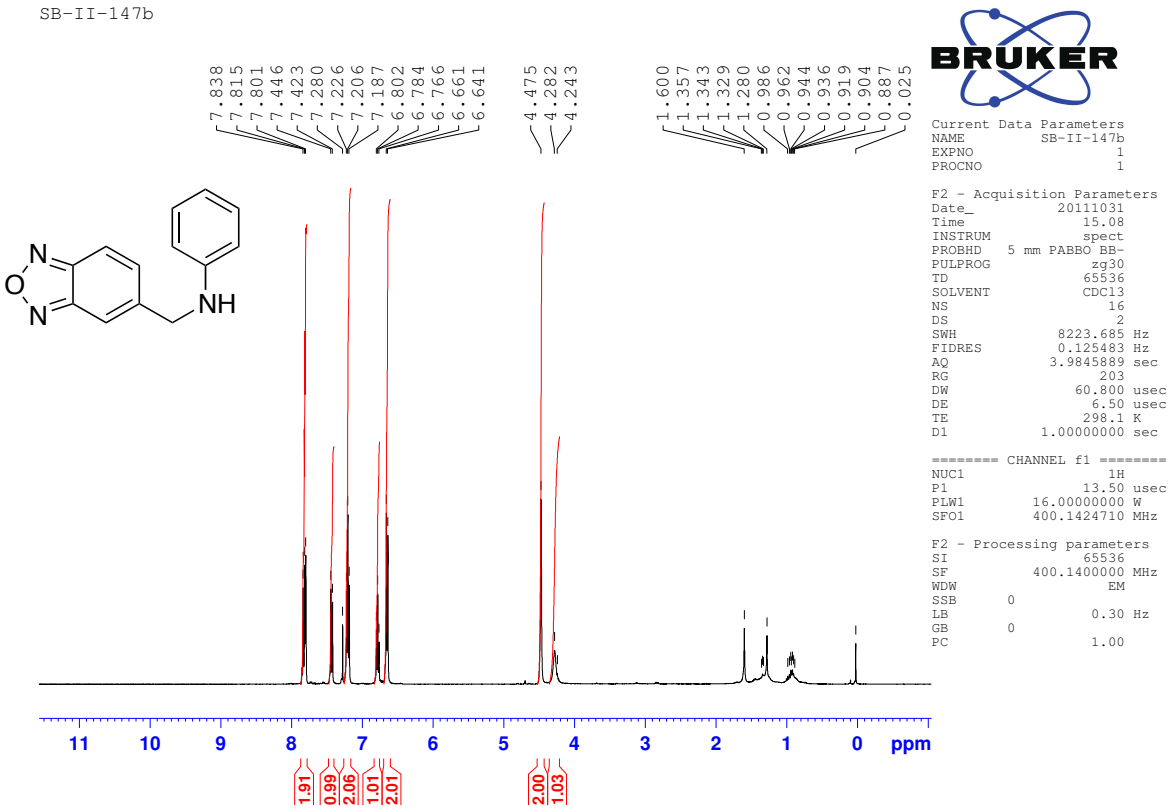


Elemental Composition Report
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
485 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-30 Na: 0-3

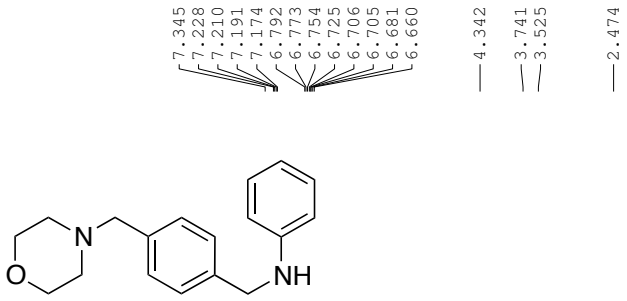
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
228.1023	228.1025	-0.2	-0.9	8.5	6.2	C14 H14 N O2

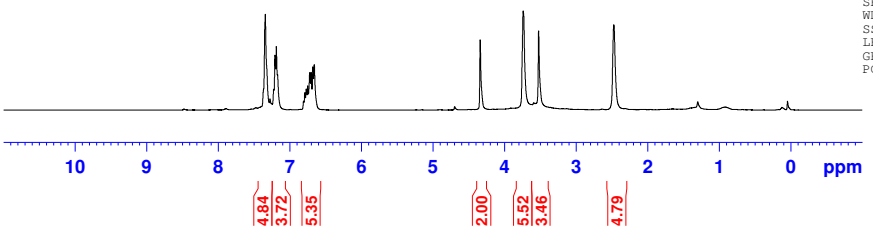
N-(Benzo[*c*][1,2,5]oxadiazol-5-ylmethyl)aniline (16h)



N-(4-(morpholinomethyl)benzyl)aniline (16i)

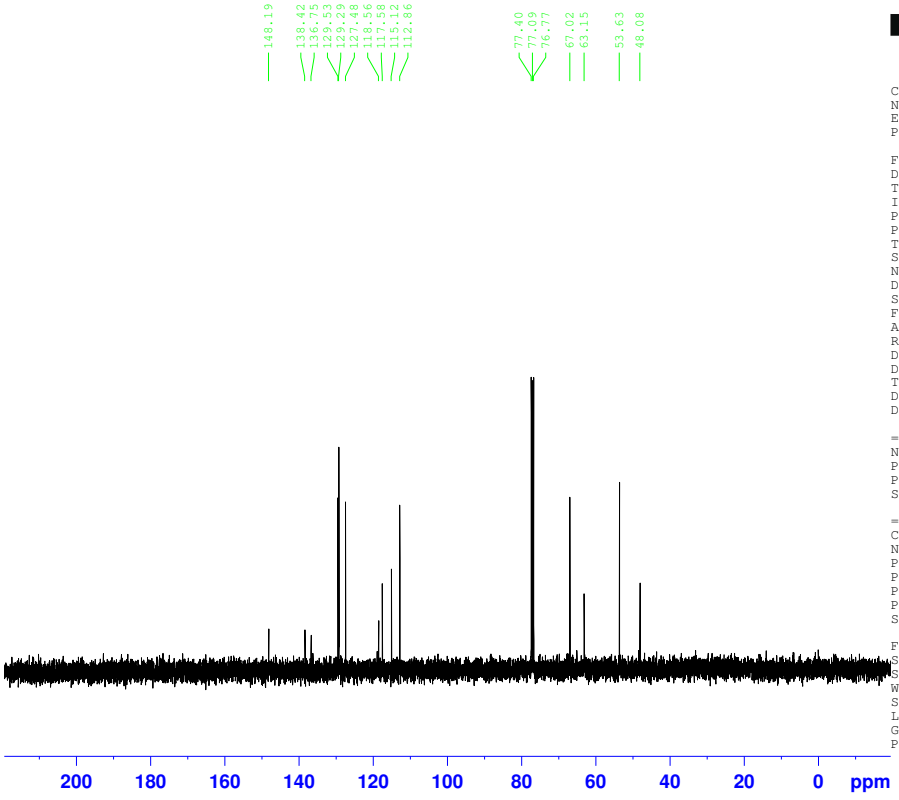
SB-IV-37a






```
Current Data Parameters
NAME          SB-IV-37a
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20120426
Time              11.04
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                   7
DS                   2
SWH           8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9846387 sec
RG                40.3
DW              60.800 usec
DE               6.50 usec
TE              298.2 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                13.50 usec
PLW1        16.00000000 W
SFO1       400.1424710 MHz

F2 - Processing parameters
SI                65536
SF           400.1400000 MHz
WDW                  EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```

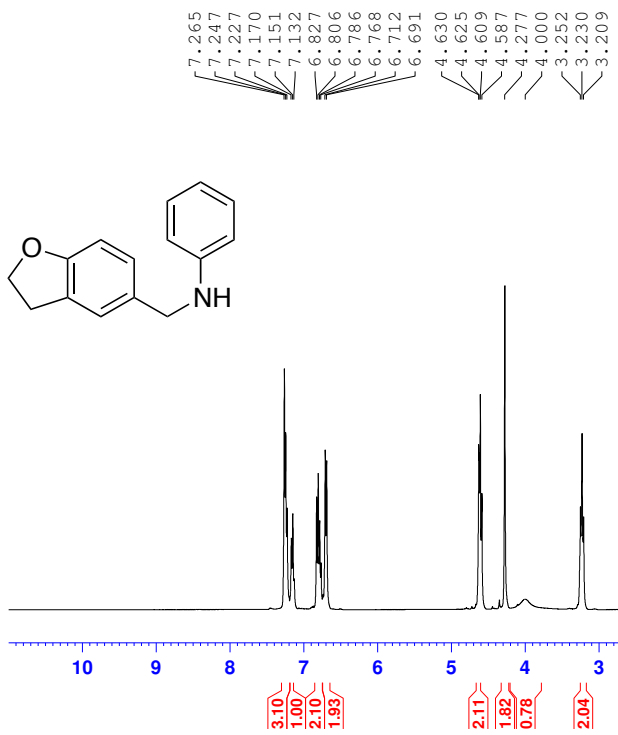
SB-IV-37a




```
Current Data Parameters
NAME          SB-IV-37a
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20120426
Time              11.06
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                  22
DS                   4
SWH          24038.461 Hz
FIDRES        0.366798 Hz
AQ            1.3631988 sec
RG                 203
DW              20.800 usec
DE               6.50 usec
TE              298.3 K
D1           2.00000000 sec
D11          0.03000000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                9.00 usec
PLW1        62.00000000 W
SFO1       100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2           90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W
SFO2       400.1416006 MHz

F2 - Processing parameters
SI                32768
SF           100.6152830 MHz
WDW                  EM
SSB       0
LB              1.00 Hz
GB        0
PC              1.40
```

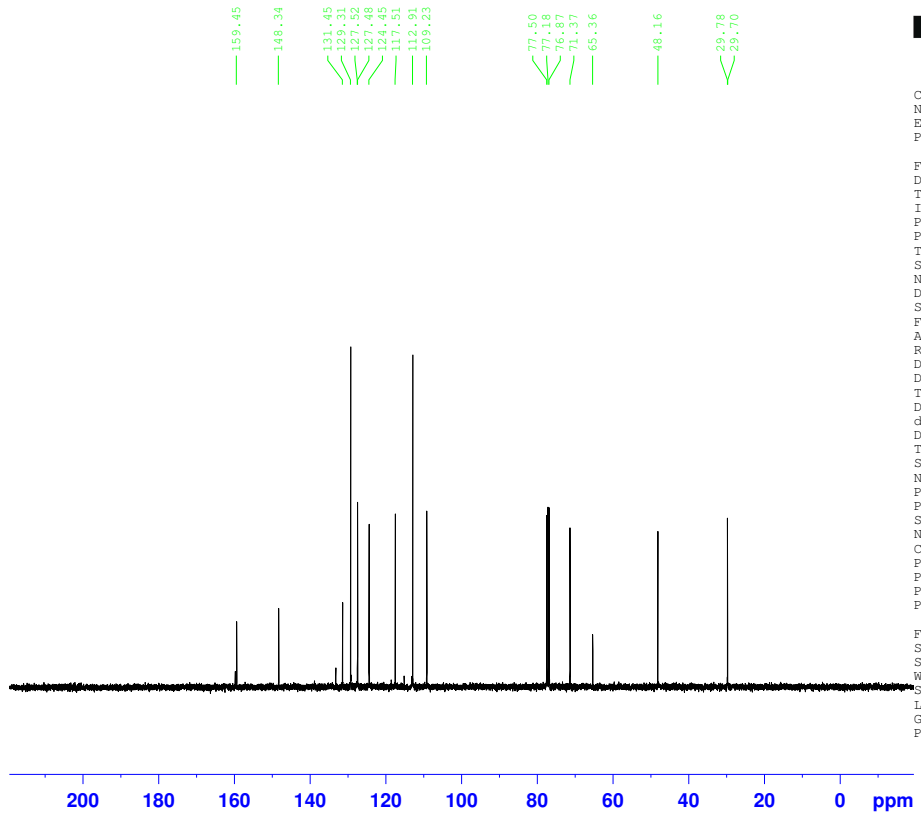
N-((2,3-dihydrobenzofuran-5-yl)methyl)aniline (16j)

SB-III-111b

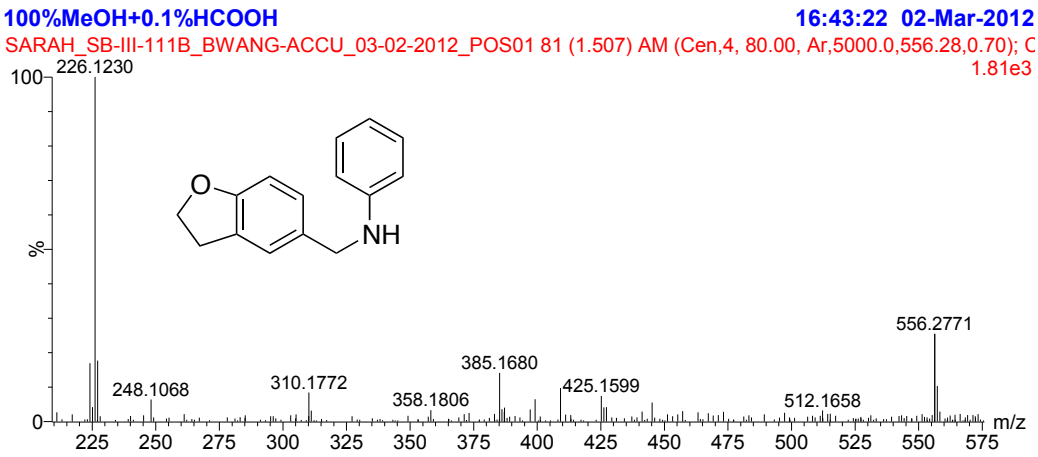



```
Current Data Parameters
NAME         SB-III-111b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               20.35
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                  25.4
DW                60.800 usec
DE                 6.50 usec
TE                298.4 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

SB-III-111b




```
Current Data Parameters
NAME         SB-III-111b
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               20.40
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    38
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.4 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                    1
SFO1         100.6253441 MHz
NUC1                  13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

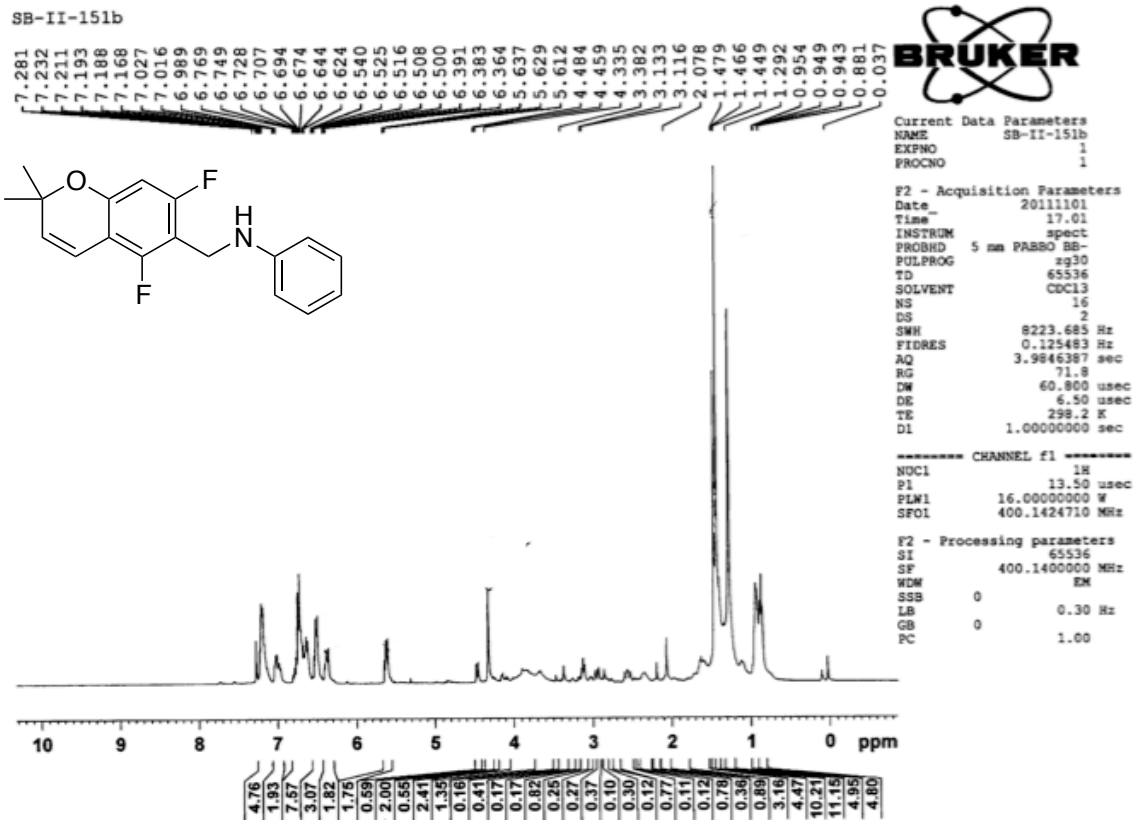


Elemental Composition Report

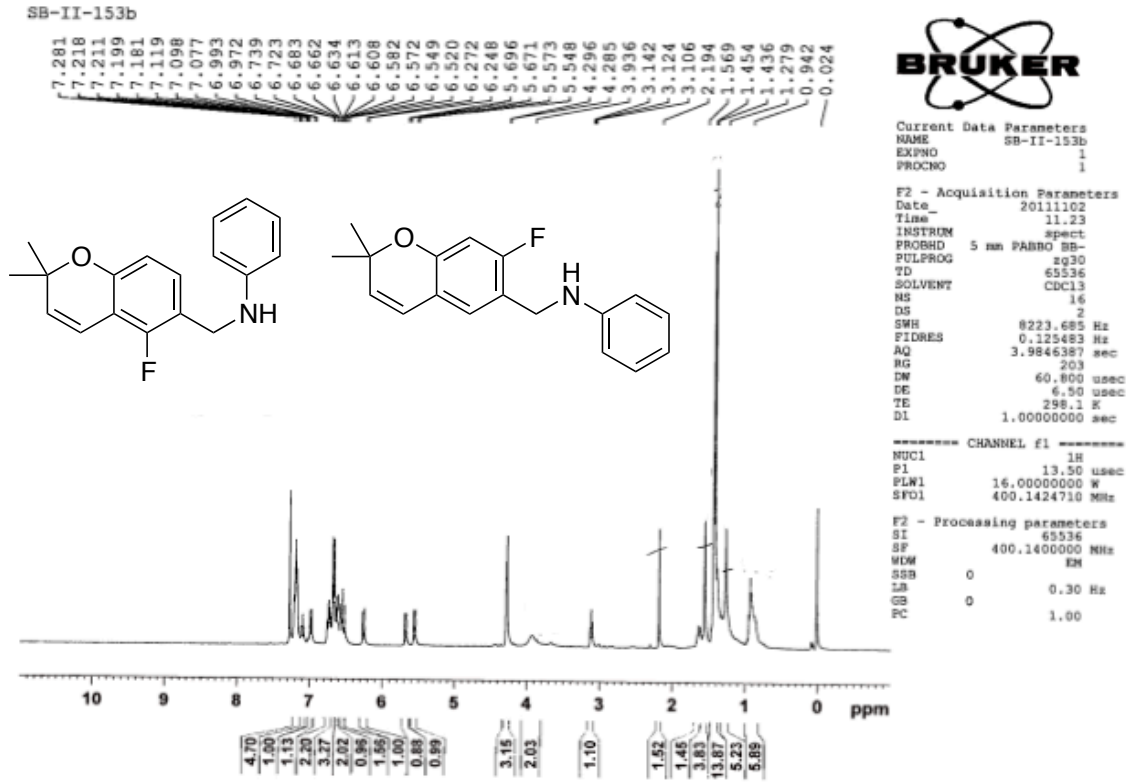
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
181 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
226.1230	226.1232	-0.2	-0.9	8.5	0.3	C15 H16 N O

***N*-((5,7-difluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)aniline (16l)**



_N_-((5-fluoro-2,2-dimethyl-2_H_-chromen-6-yl)methyl)aniline with _N_-((7-fluoro-2,2-dimethyl-2_H_-chromen-6-yl)methyl)aniline (1:1) (16m)



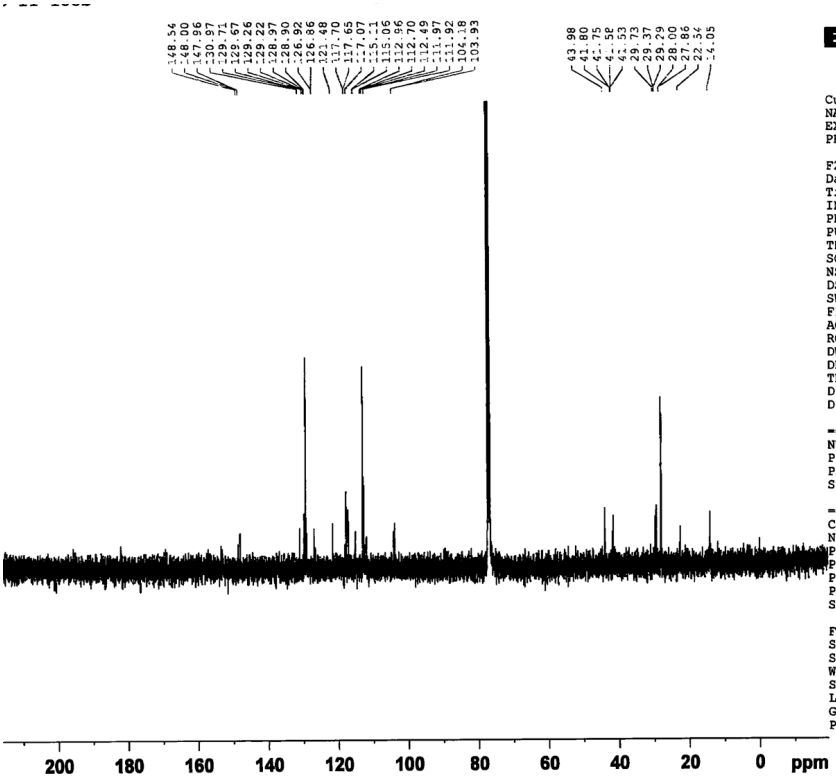
BRUKER

Current Data Parameters
NAME SB-II-153b
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20111102
Time 11.23
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 203
DW 60.800 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PLW1 16.00000000 W
SFO1 400.1424710 MHz

F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



BRUKER

Current Data Parameters
NAME SB-II-153b
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20111102
Time 11.29
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec

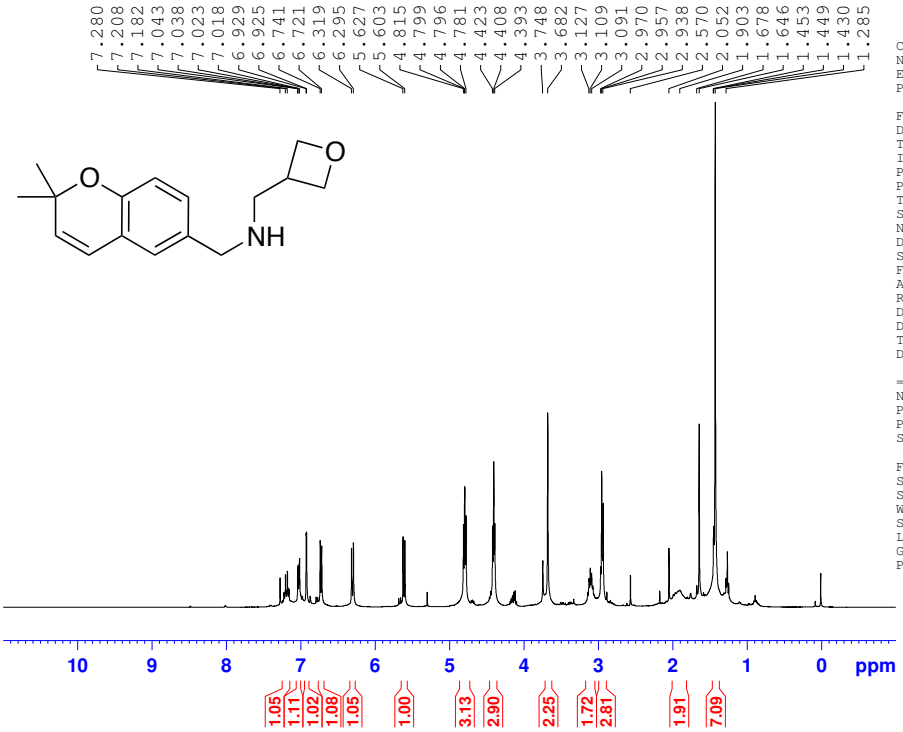
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PLW1 62.00000000 W
SFO1 100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 16.00000000 W
PLW12 0.36000001 W
PLW13 0.29159999 W
SFO2 400.1416006 MHz

F2 - Processing parameters
SI 32768
SF 100.6152830 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1-(2,2-Dimethyl-2*H*-chromen-6-yl)-*N*-(oxetan-3-ylmethyl)methanamine (18a)

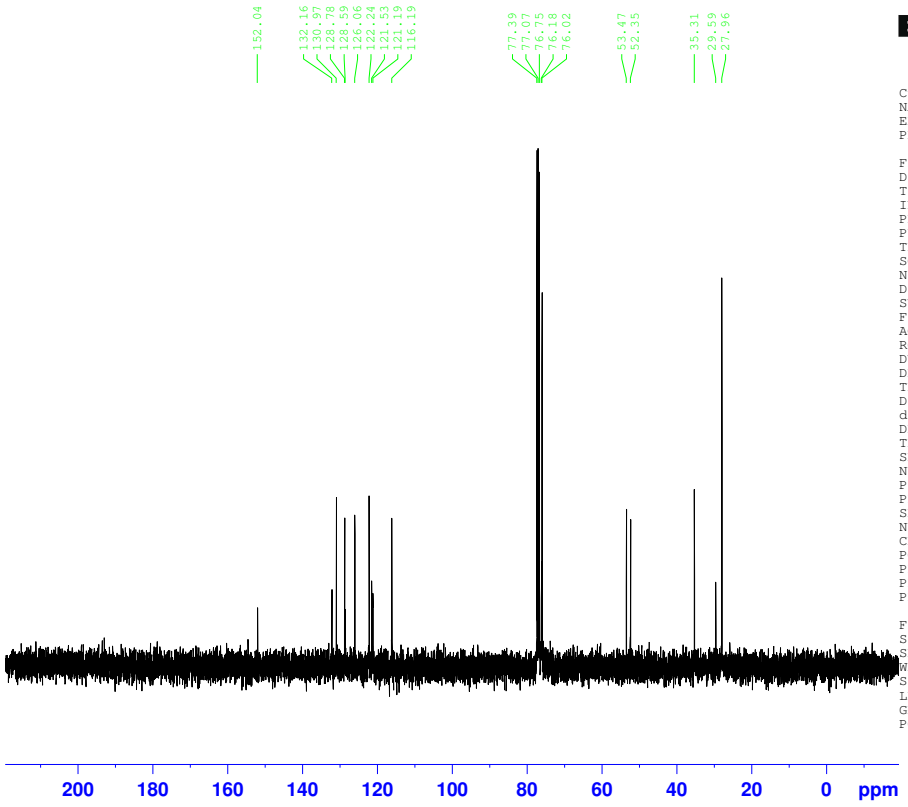
SB-IV-68



BRUKER

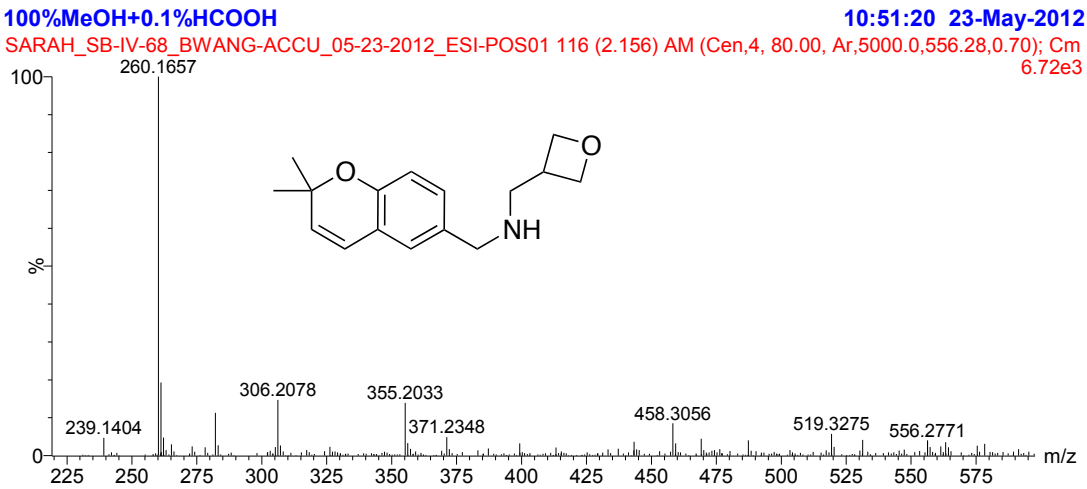
```
Current Data Parameters
NAME                  SB-IV-68
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20120517
Time                   17.54
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      40.3
DW                    60.800 usec
DE                     6.50 usec
TE                    298.3 K
D1                 1.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PLW1              16.00000000 W
SFO1             400.1424710 MHz

F2 - Processing parameters
SI                        65536
SF                400.1400000 MHz
WDW                          EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

SB-IV-68



BRUKER

```
Current Data Parameters
NAME                  SB-IV-68
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20120517
Time                   17.56
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       35
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                    20.800 usec
DE                     6.50 usec
TE                    298.9 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
TD0                          1
SFO1             100.6253441 MHz
NUC1                     13C
P1                     9.00 usec
PLW1              62.00000000 W
SFO2             400.1416006 MHz
NUC2                      1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2              16.00000000 W
PLW12              0.36000001 W
PLW13              0.29159999 W

F2 - Processing parameters
SI                        32768
SF                100.6152830 MHz
WDW                          EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```



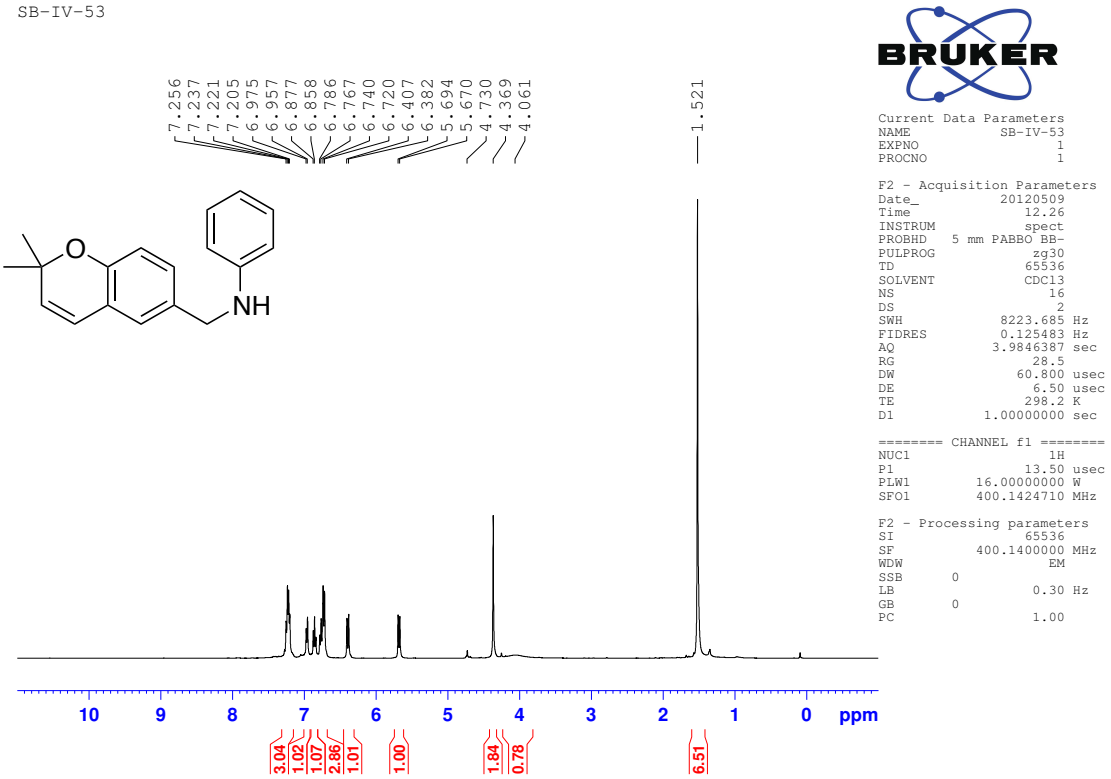
Elemental Composition Report

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

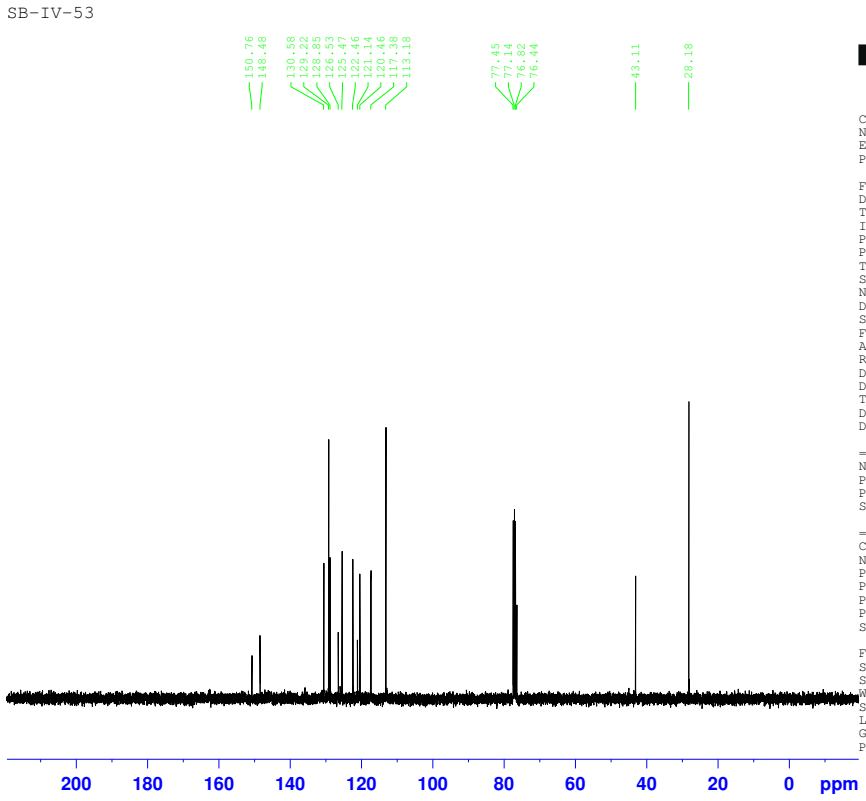
Monoisotopic Mass, Even Electron Ions
271 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100

Minimum:				-1.5		
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
260.1657	260.1651	0.6	2.3	6.5	52.6	C16 H22 N O2

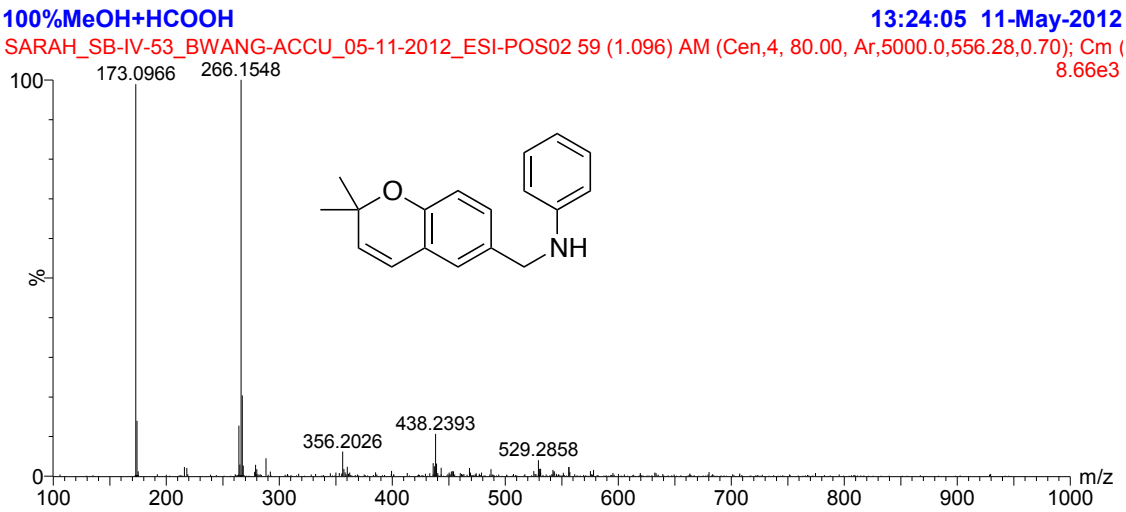
N-((2,2-dimethyl-2*H*-chromen-6-yl)methyl)aniline (19)




```
Current Data Parameters
NAME                  SB-IV-53
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20120509
Time                  12.26
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDC13
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      28.5
DW                    60.800 usec
DE                     6.50 usec
TE                    298.2 K
D1                 1.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PLW1            16.00000000 W
SFO1           400.1424710 MHz

F2 - Processing parameters
SI                        65536
SF               400.1400000 MHz
WDW                         EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```




```
Current Data Parameters
NAME                  SB-IV-53
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20120509
Time                  12.28
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT               CDC13
NS                       20
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      203
DW                    20.800 usec
DE                     6.50 usec
TE                    298.3 K
D1                 2.00000000 sec
D11                0.03000000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                      9.00 usec
PLW1            62.00000000 W
SFO1           100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                 90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W
SFO2           400.1416006 MHz

F2 - Processing parameters
SI                        32768
SF               100.6152830 MHz
WDW                         EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```



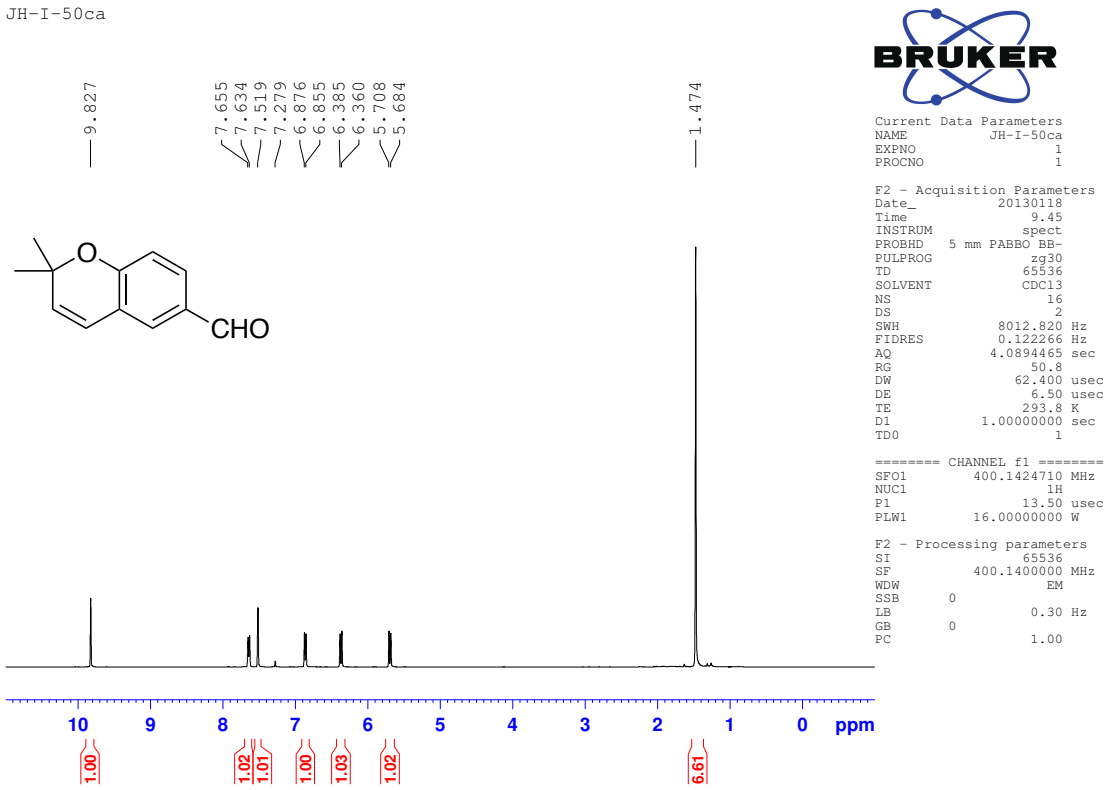
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
293 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
266.1548	266.1545	0.3	1.1	9.5	3.1	C18 H20 N O

2,2-dimethyl-2*H*-chromene-6-carbaldehyde (21)

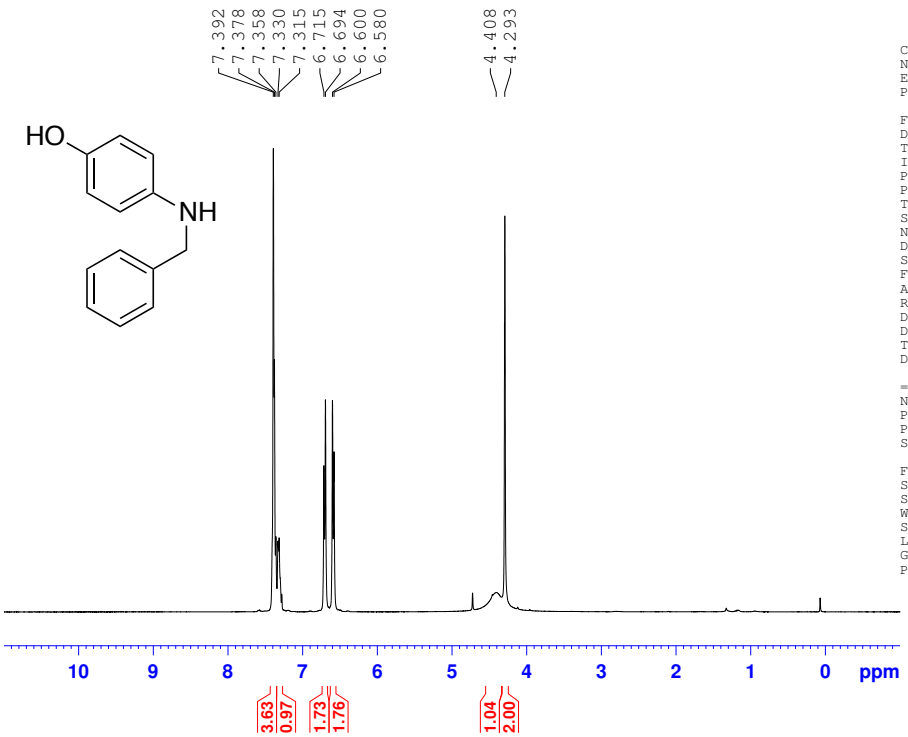


BRUKER

```
Current Data Parameters
NAME          JH-I-50ca
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20130118
Time               9.45
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8012.820 Hz
FIDRES        0.122266 Hz
AQ            4.0894465 sec
RG                 50.8
DW                62.400 usec
DE                 6.50 usec
TE                293.8 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                 1H
P1                13.50 usec
PLW1        16.00000000 W

F2 - Processing parameters
SI                65536
SF           400.1400000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

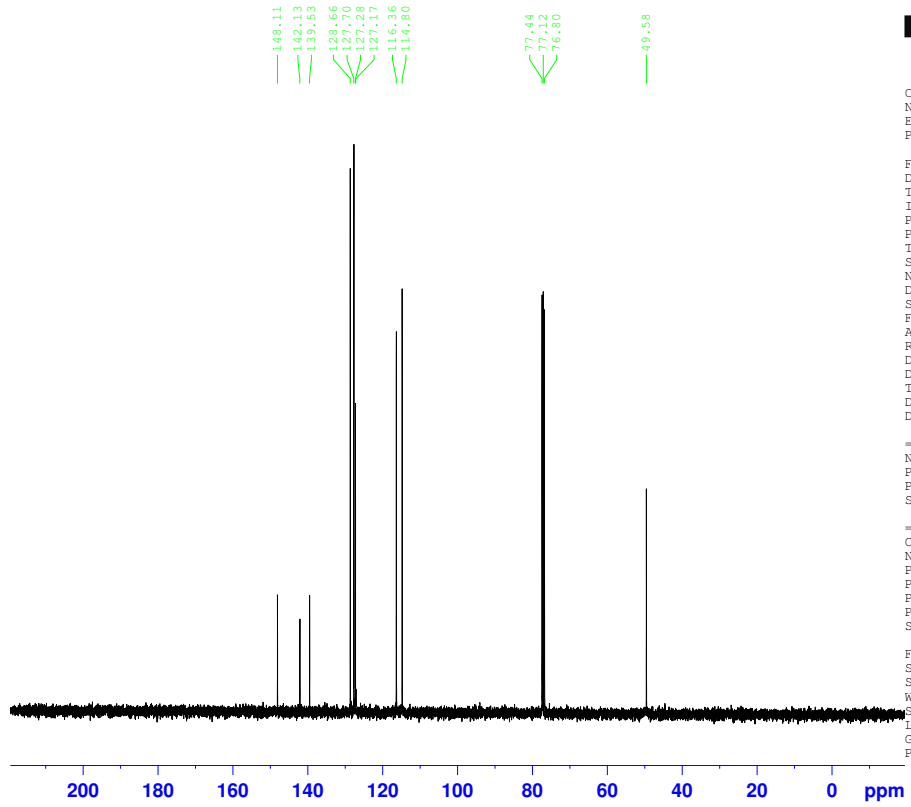
4-(Benzylamino)phenol (23a)

SB-IV-1c

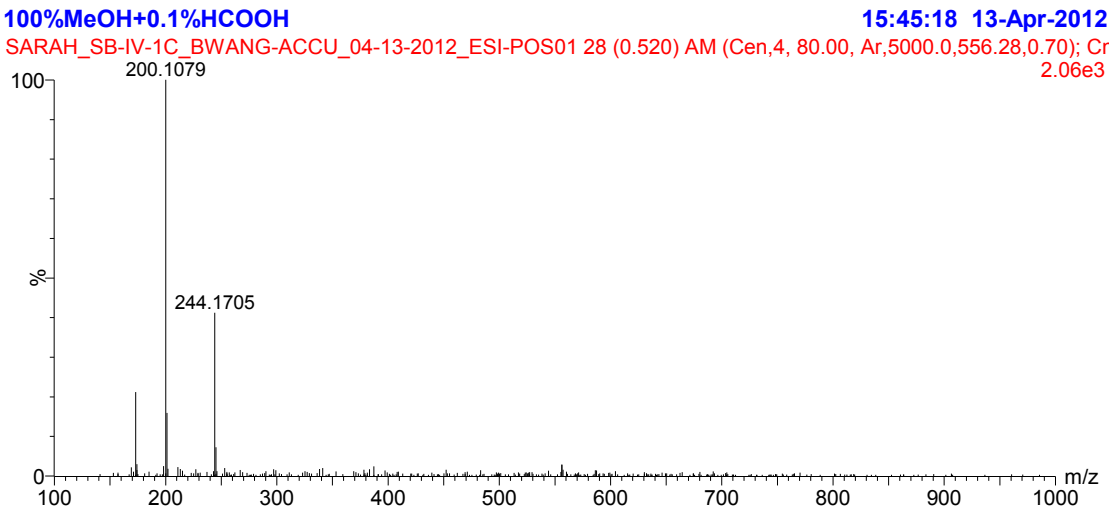


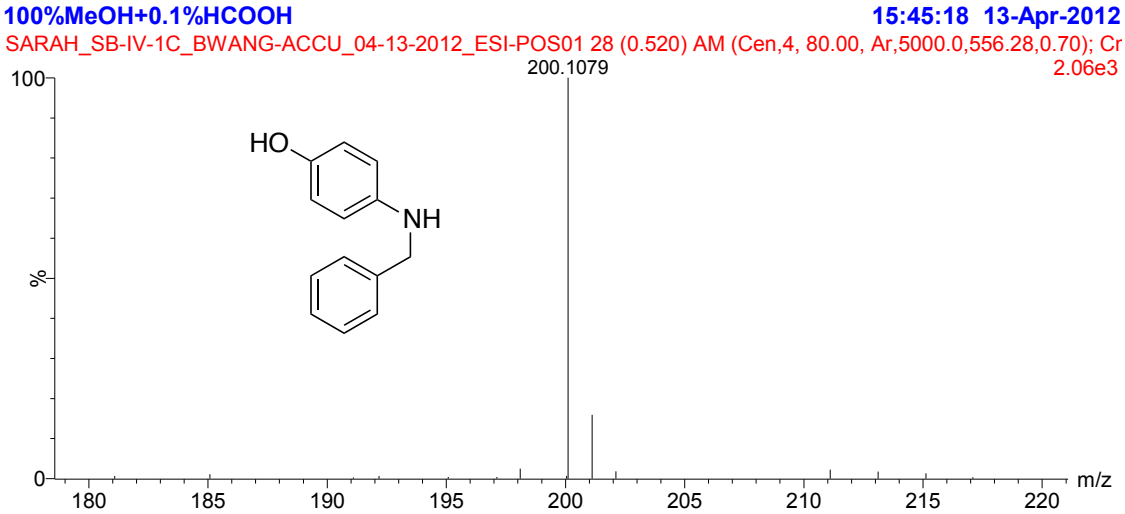

```
Current Data Parameters
NAME            SB-IV-1c
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120403
Time               15.13
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                    57
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-IV-1c



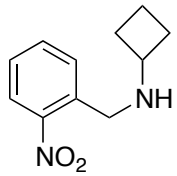

```
Current Data Parameters
NAME            SB-IV-1c
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120403
Time               15.17
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    48
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.3 K
D1           2.00000000 sec
D11          0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF           100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



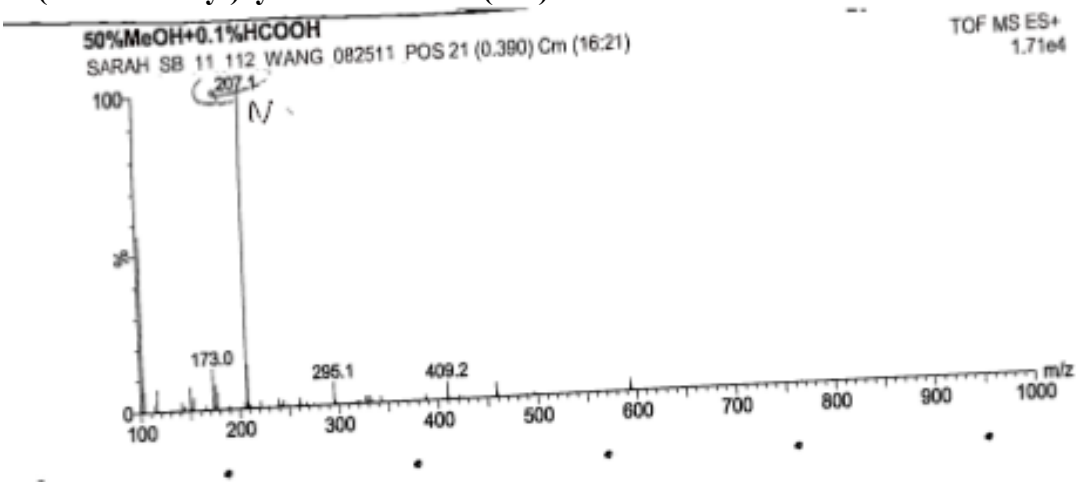


Elemental Composition Report
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
131 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20

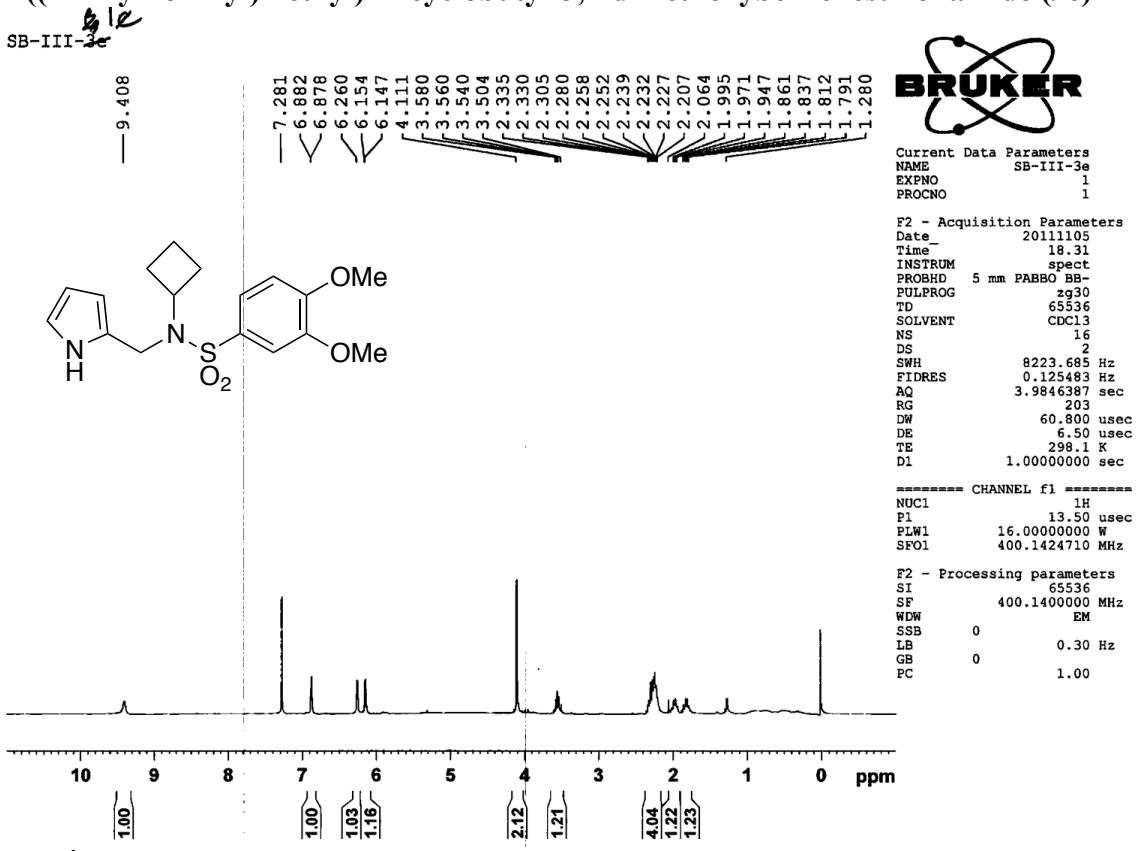
Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
200.1079	200.1075	0.4		2.0	7.5	2.0 C13 H14 N O



***N*-(2-nitrobenzyl)cyclobutanamine (27c)**

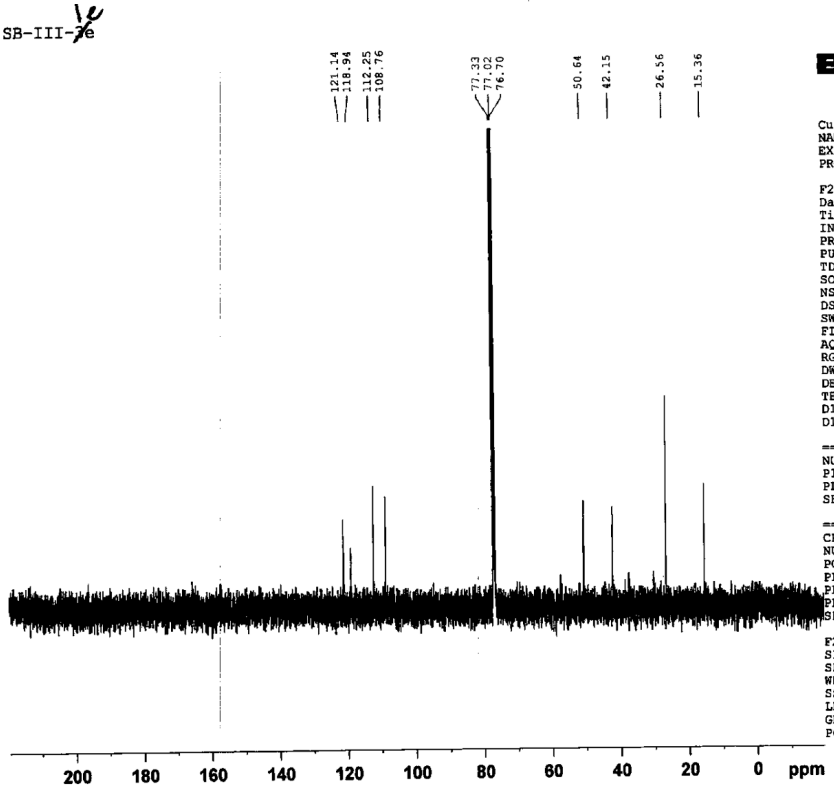


***N*-((1*H*-Pyrrol-2-yl)methyl)-*N*-cyclobutyl-3,4-dimethoxybenzenesulfonamide (9e)**



BRUKER

```
Current Data Parameters
NAME            SB-III-3e
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20111105
Time                18.31
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ             3.9846387 sec
RG                   203
DW                60.800 usec
DE                 6.50 usec
TE                298.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

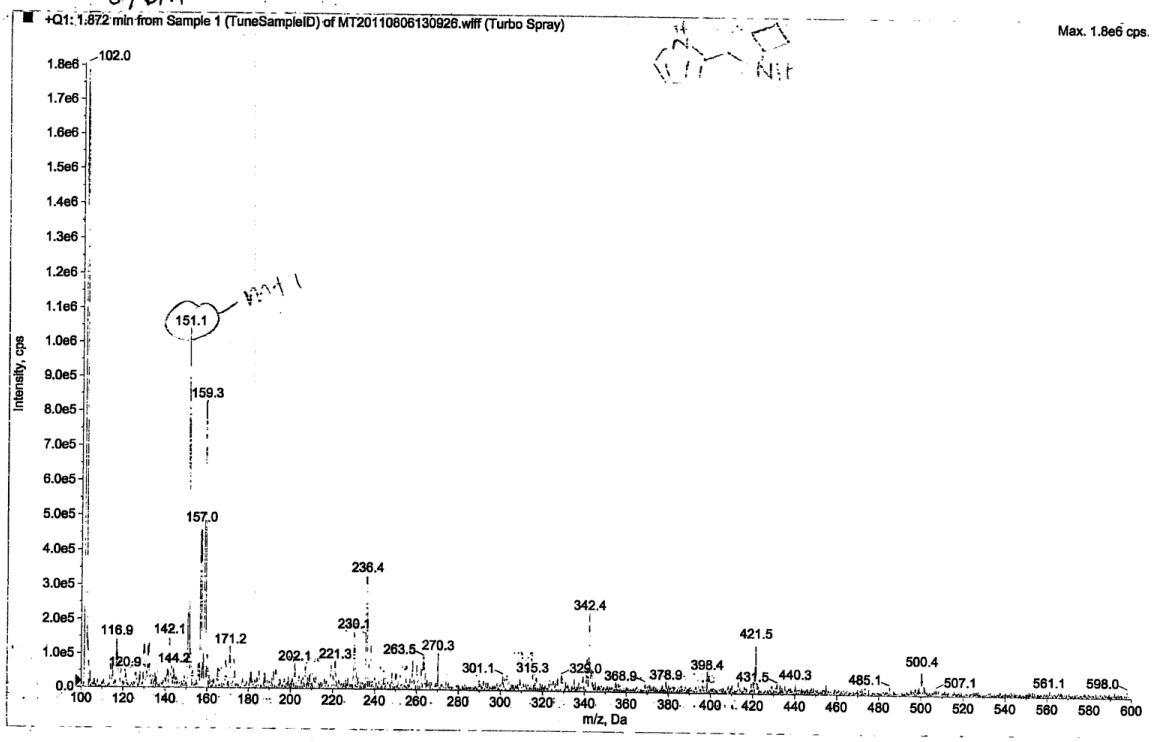


BRUKER

```
Current Data Parameters
NAME            SB-III-3e
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20111105
Time                18.58
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   408
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ             1.3631988 sec
RG                   161
DW                20.800 usec
DE                 6.50 usec
TE                298.1 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO1        100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2        400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

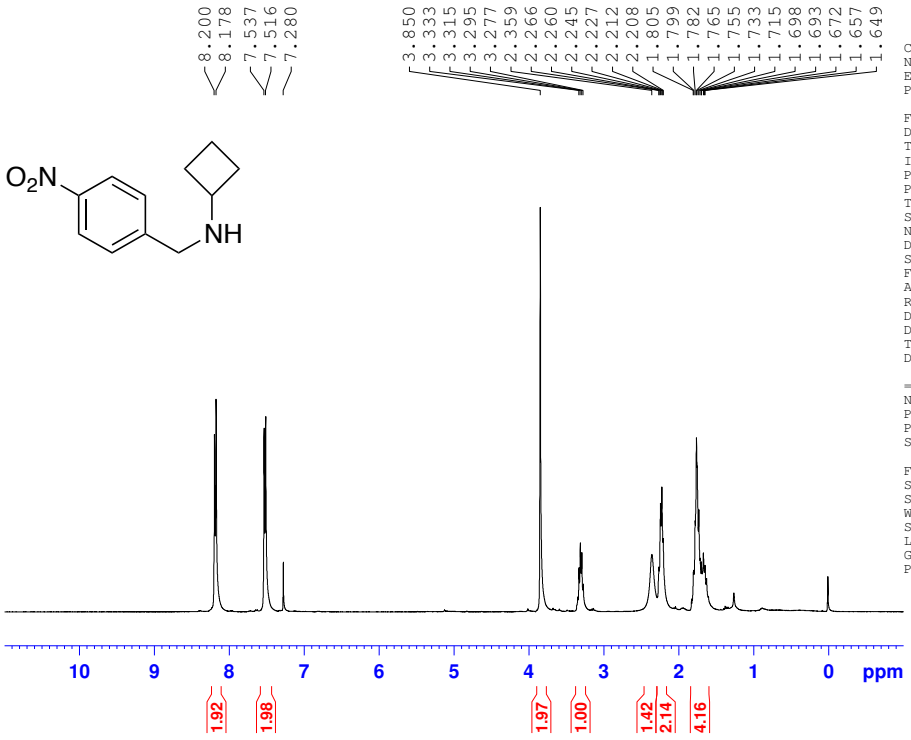
SB-11-89a
8/6/11

tm 150



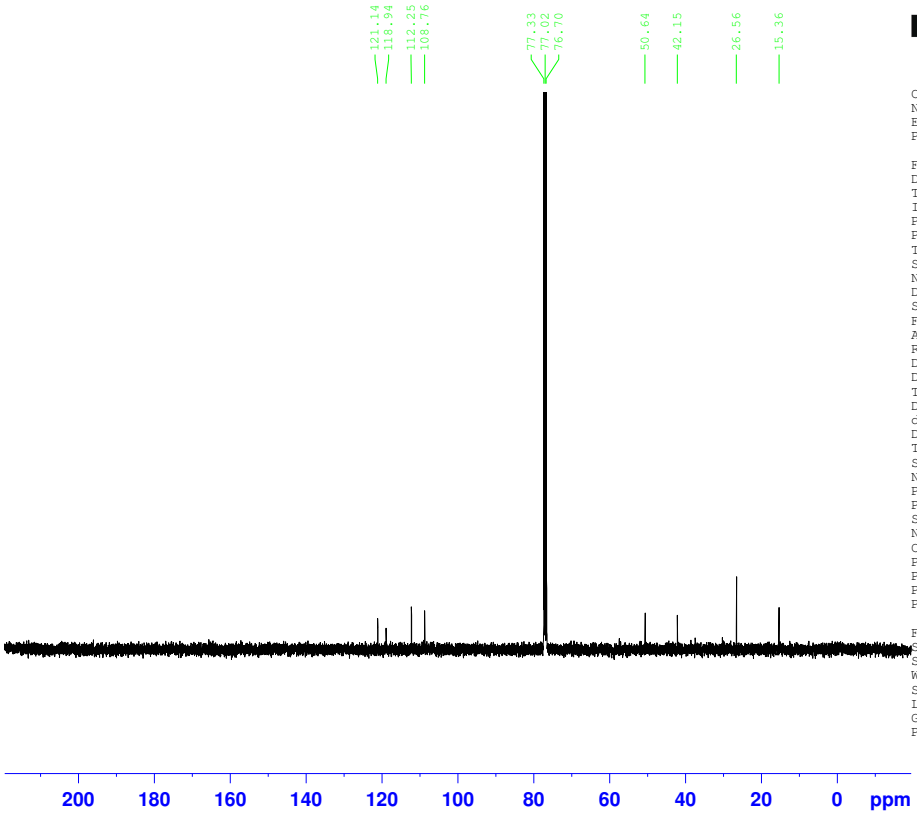
N-(4-nitrobenzyl)cyclobutanamine (27f)

SB-III-3b/c




```
Current Data Parameters
NAME          SB-III-3f
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20111104
Time              15.35
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9845889 sec
RG                 114
DW              60.800 usec
DE               6.50 usec
TE              298.1 K
D1          1.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1               13.50 usec
PLW1        16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI               65536
SF          400.1400000 MHz
WDW                 EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```

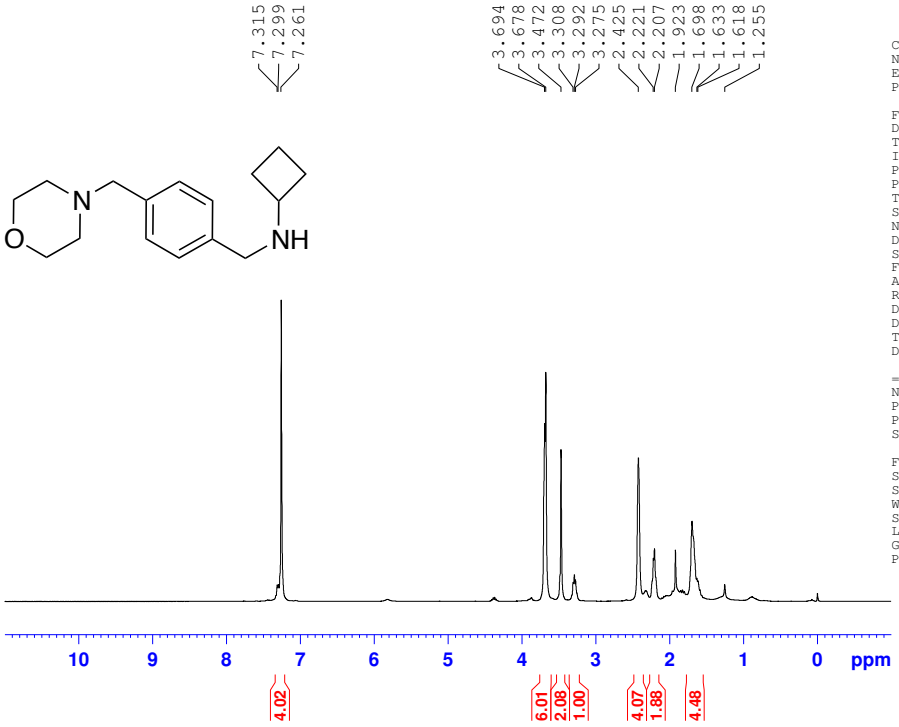
SB-III-3e




```
Current Data Parameters
NAME          SB-III-3e
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20111105
Time              18.58
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 408
DS                   4
SWH          24038.461 Hz
FIDRES        0.366798 Hz
AQ            1.3631488 sec
RG                 161
DW              20.800 usec
DE               6.50 usec
TE              298.1 K
D1          2.00000000 sec
d11         0.03000000 sec
DELTA       1.89999998 sec
TD0                  1
SFO1        100.6253441 MHz
NUC1                13C
P1               9.00 usec
PLW1        62.00000000 W
SFO2        400.1416006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2           90.00 usec
PLW2        16.00000000 W
PLW12        0.36000001 W
PLW13        0.29159999 W

F2 - Processing parameters
SI               32768
SF          100.6152830 MHz
WDW                 EM
SSB       0
LB              1.00 Hz
GB        0
PC              1.40
```

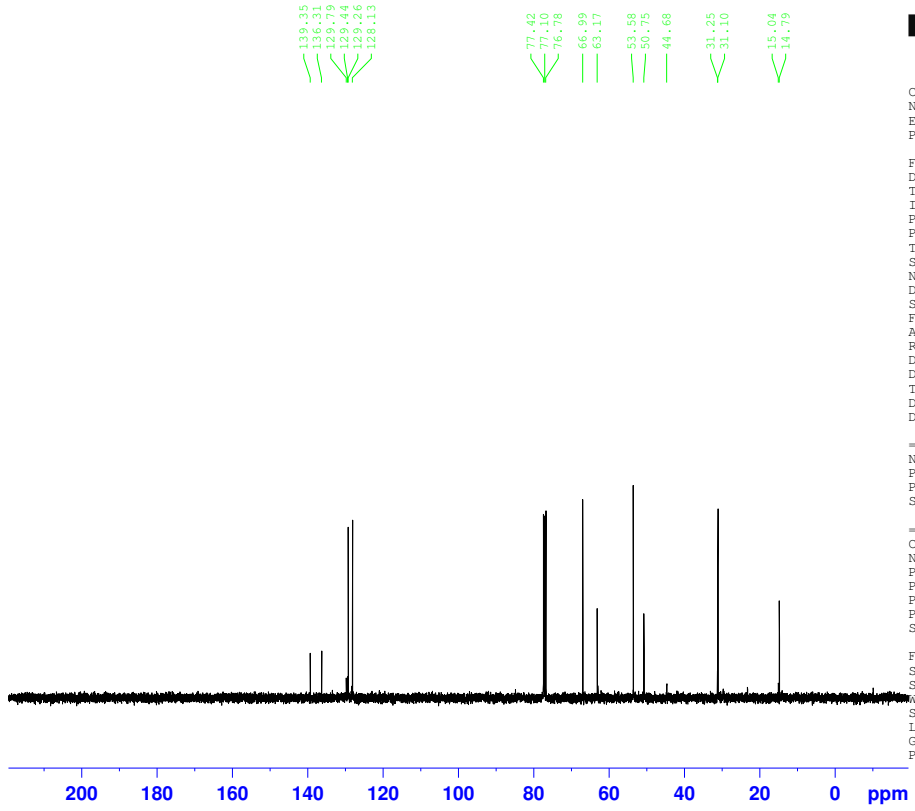
N-(4-(Morpholinomethyl)benzyl)cyclobutanamine (27h)

SB-IV-39a




```
Current Data Parameters
NAME            SB-IV-39a
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20120425
Time                16.37
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ               3.9846387 sec
RG                   25.4
DW                 60.800 usec
DE                  6.50 usec
TE                 298.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                  65536
SF           400.1400000 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

SB-IV-39a

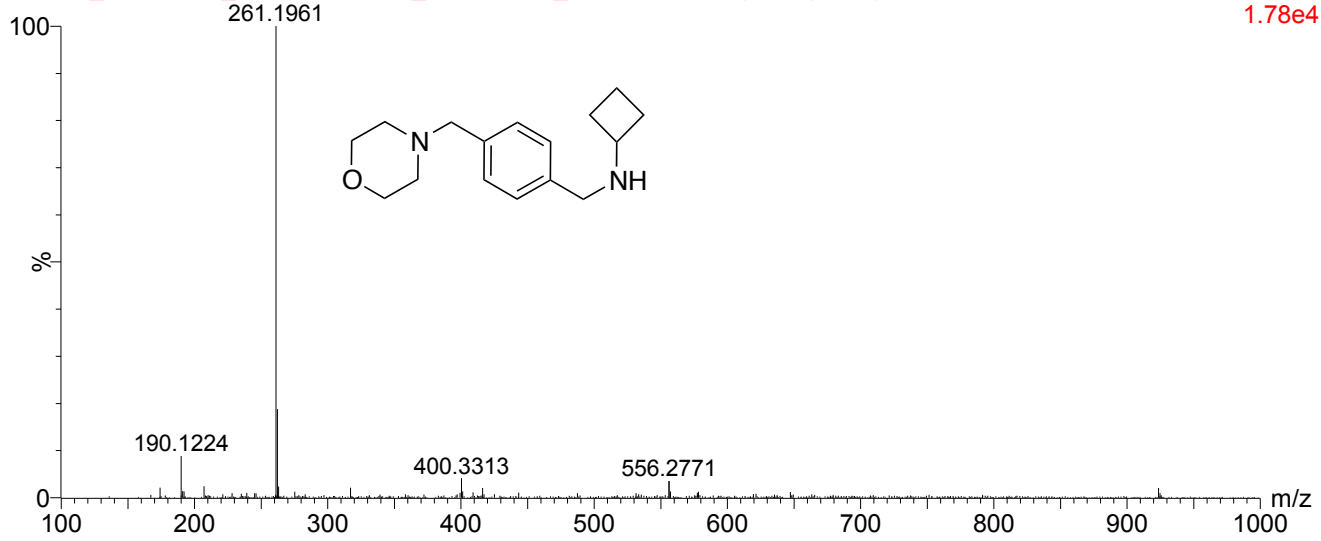



```
Current Data Parameters
NAME            SB-IV-39a
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20120425
Time                16.40
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                     26
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631988 sec
RG                    203
DW                 20.800 usec
DE                  6.50 usec
TE                 298.2 K
D1            2.00000000 sec
D11           0.03000000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                  9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                  32768
SF           100.6152830 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

in 100%MeOH+0.1%HCOOH 17:49:34 26-Apr-2012

SARAH_SB-IV-39A_BWANG-ACCU_04-26-2012_ESI-POS05 53 (0.987) AM (Cen,4, 80.00, Ar,5000.0,556.28,0.70); C

1.78e4



Elemental Composition Report

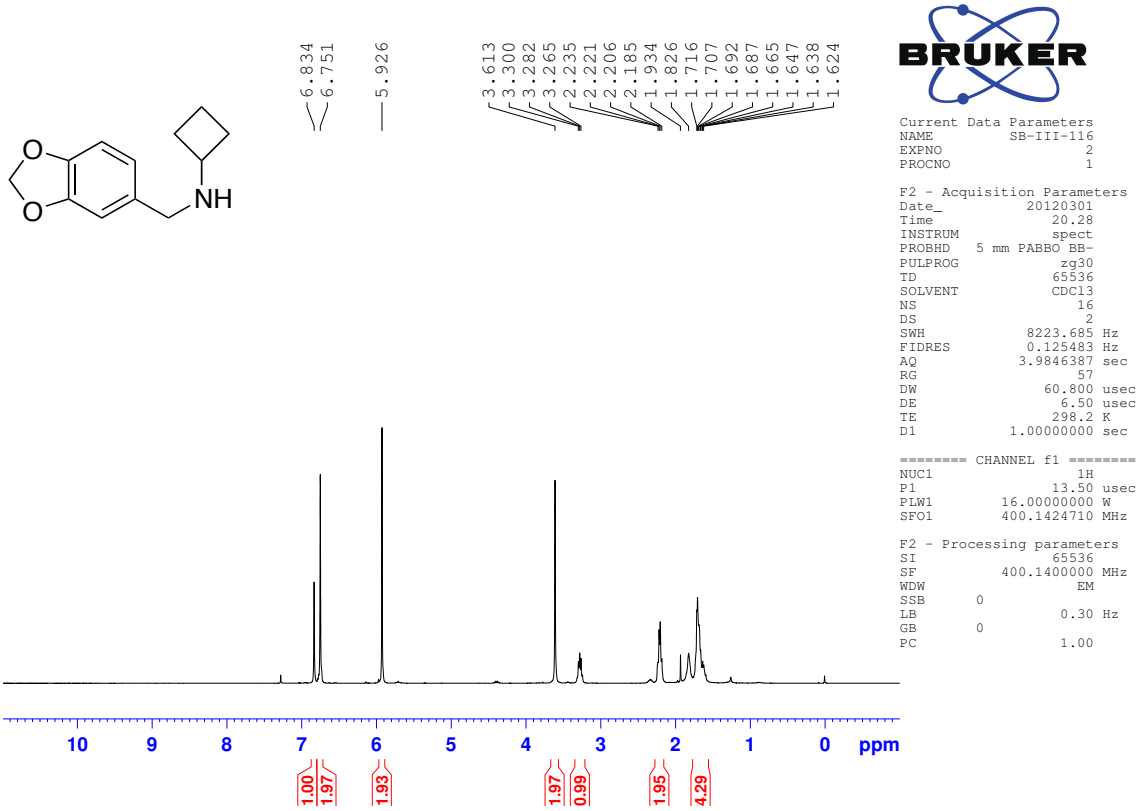
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
284 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
261.1961	261.1967	-0.6	-2.3	5.5	7.3	C16 H25 N2 O

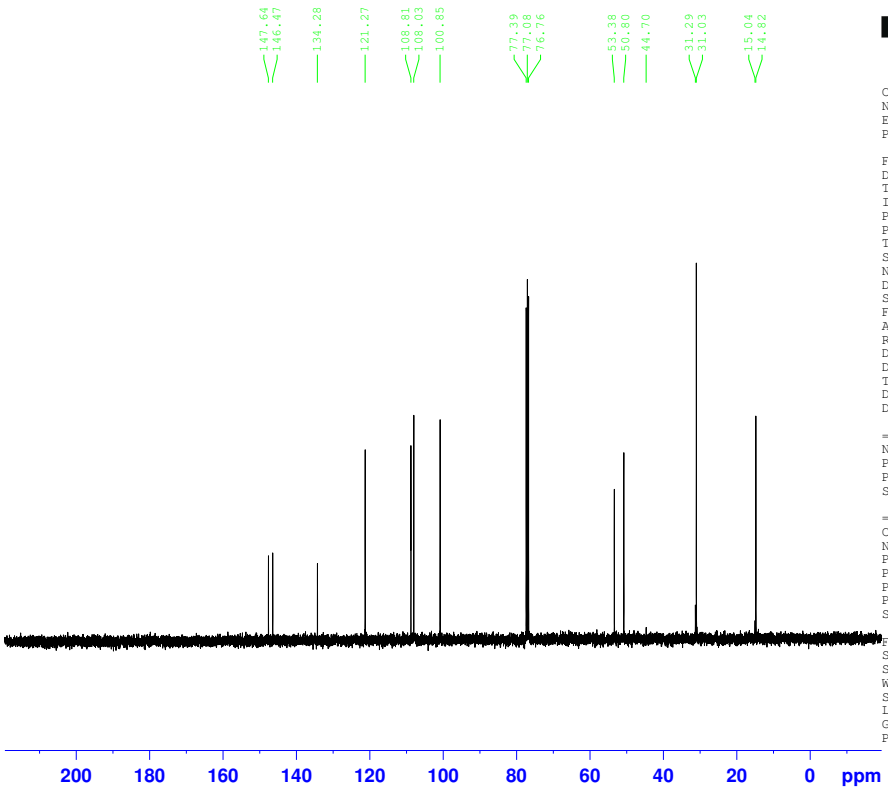
N-(Benzo[*d*][1,3]dioxol-5-ylmethyl)cyclobutanamine (27i)

SB-III-116

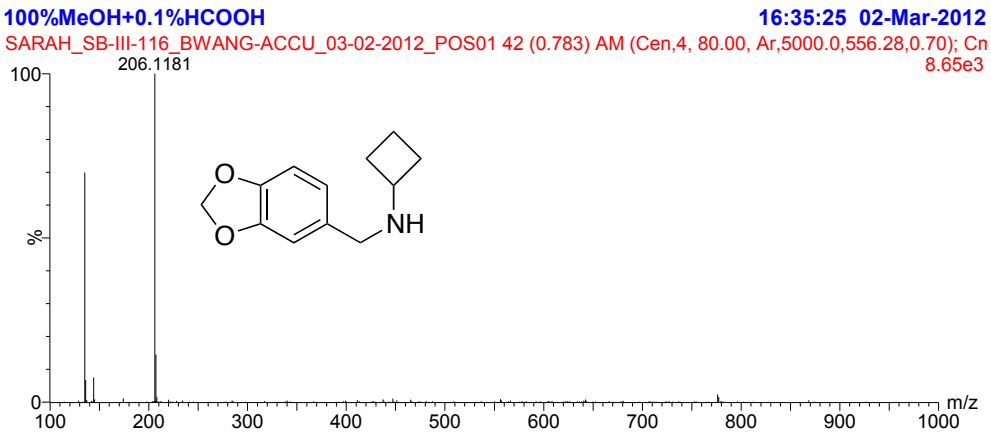



```
Current Data Parameters
NAME          SB-III-116
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               20.28
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                    57
DW                60.800 usec
DE                 6.50 usec
TE                298.2 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-III-116




```
Current Data Parameters
NAME          SB-III-116
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               20.31
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    33
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.3 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



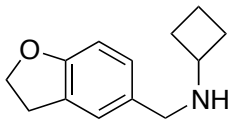
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
145 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
206.1181	206.1181	0.0	0.0	5.5	1.9	C12 H16 N O2

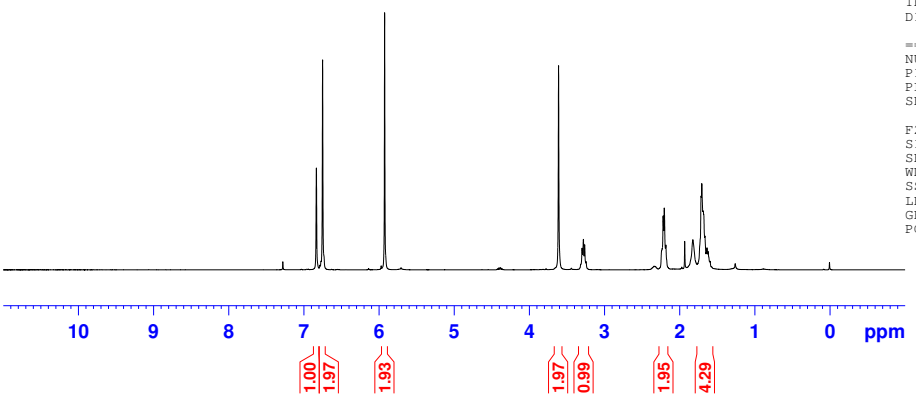
N-((2,3-Dihydrobenzofuran-5-yl)methyl)cyclobutanamine (27j)

SB-III-116



6.834 6.751 5.926

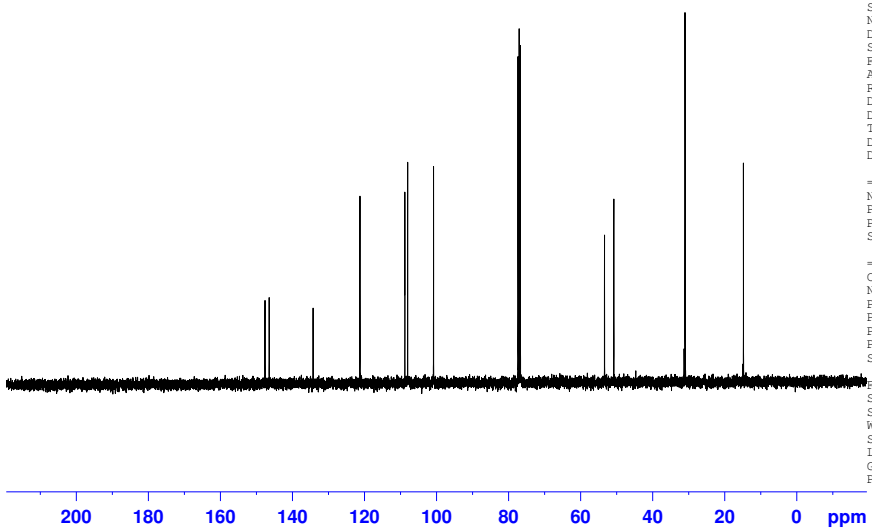
3.613 3.300 3.282 3.265 2.235 2.221 2.206 2.185 1.934 1.826 1.716 1.707 1.692 1.687 1.665 1.647 1.638 1.624



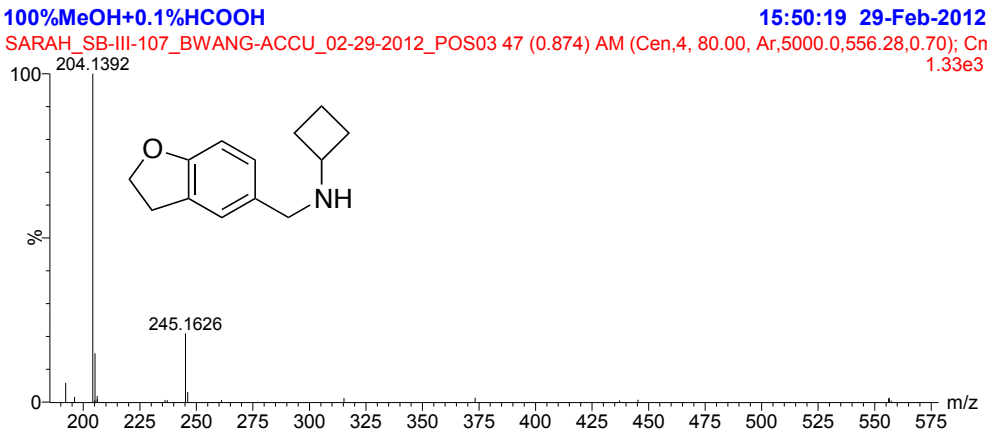

```
Current Data Parameters
NAME          SB-III-116
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               20.28
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ             3.9846387 sec
RG                    57
DW                60.800 usec
DE                 6.50 usec
TE                298.2 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1         16.00000000 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-III-116

147.64 146.47 134.28 121.27 108.81 108.03 100.85 77.39 77.08 76.76 53.38 50.80 44.70 31.29 31.03 15.04 14.82




```
Current Data Parameters
NAME          SB-III-116
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120301
Time               20.31
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    33
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ             1.3631988 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                298.3 K
D1             2.00000000 sec
D11            0.03000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.00 usec
PLW1         62.00000000 W
SFO1         100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W
SFO2         400.1416006 MHz

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

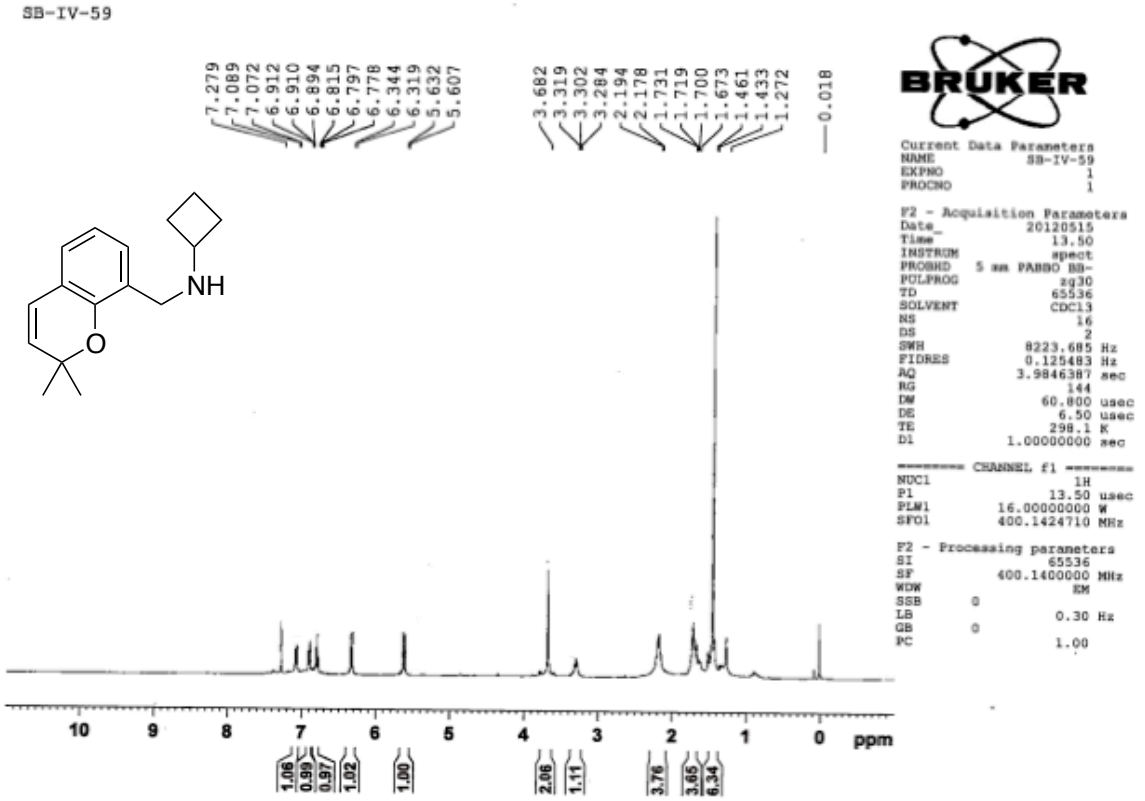


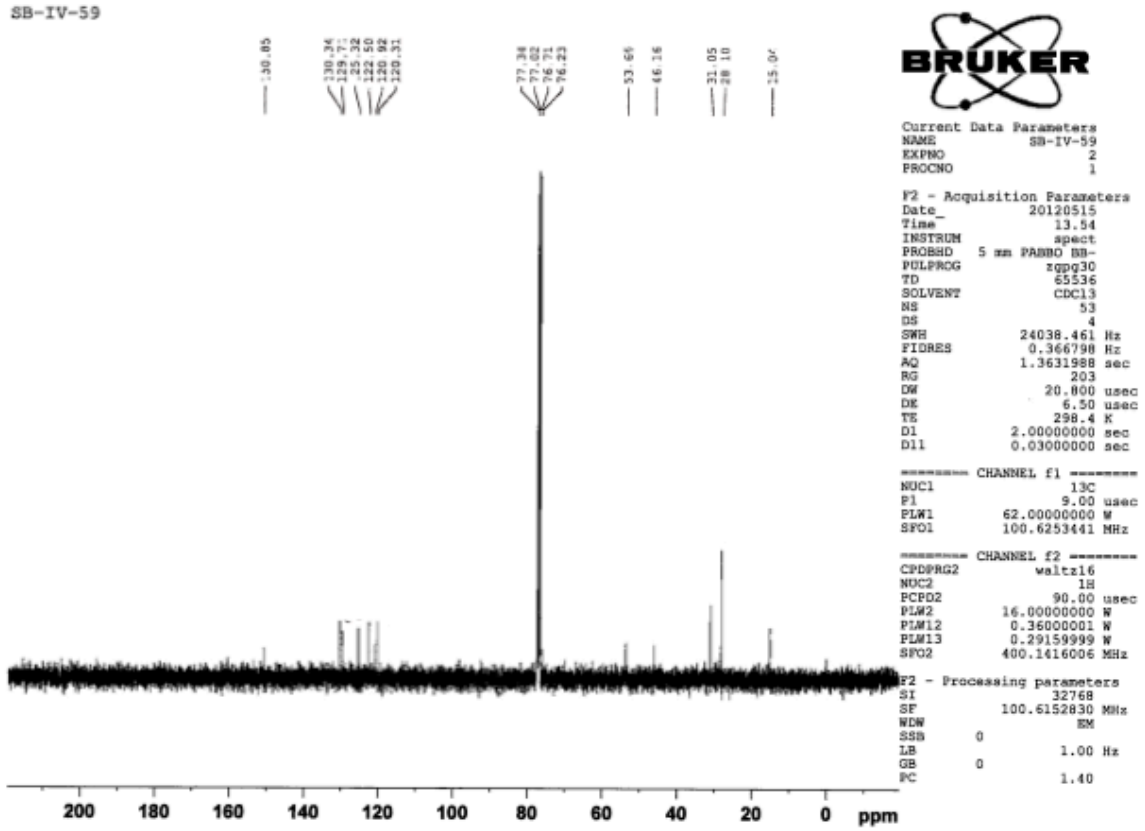
Elemental Composition Report

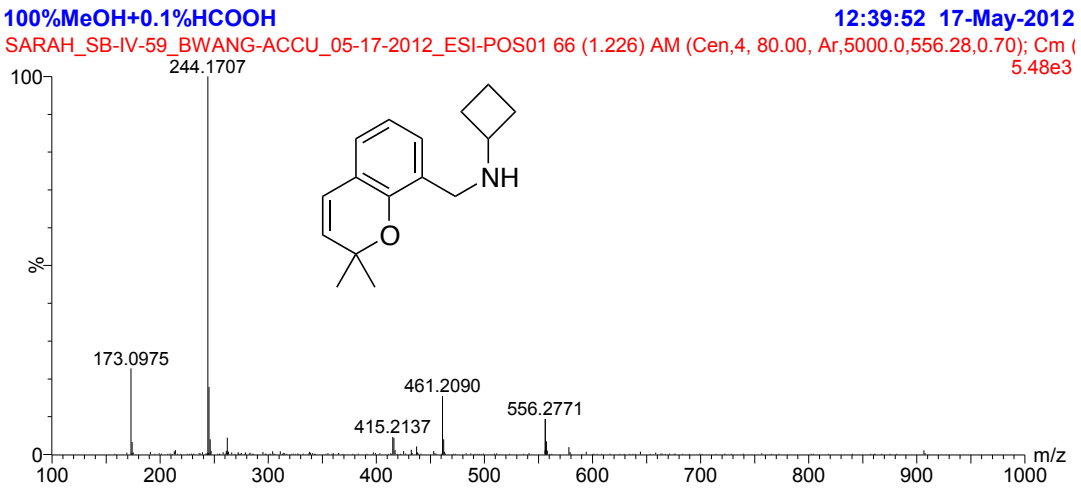
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
143 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
204.1392	204.1388	0.4	2.0	5.5	1.5	C13 H18 N O

_N_-((2,2-dimethyl-2_H_-chromen-8-yl)methyl)cyclobutanamine (27l)







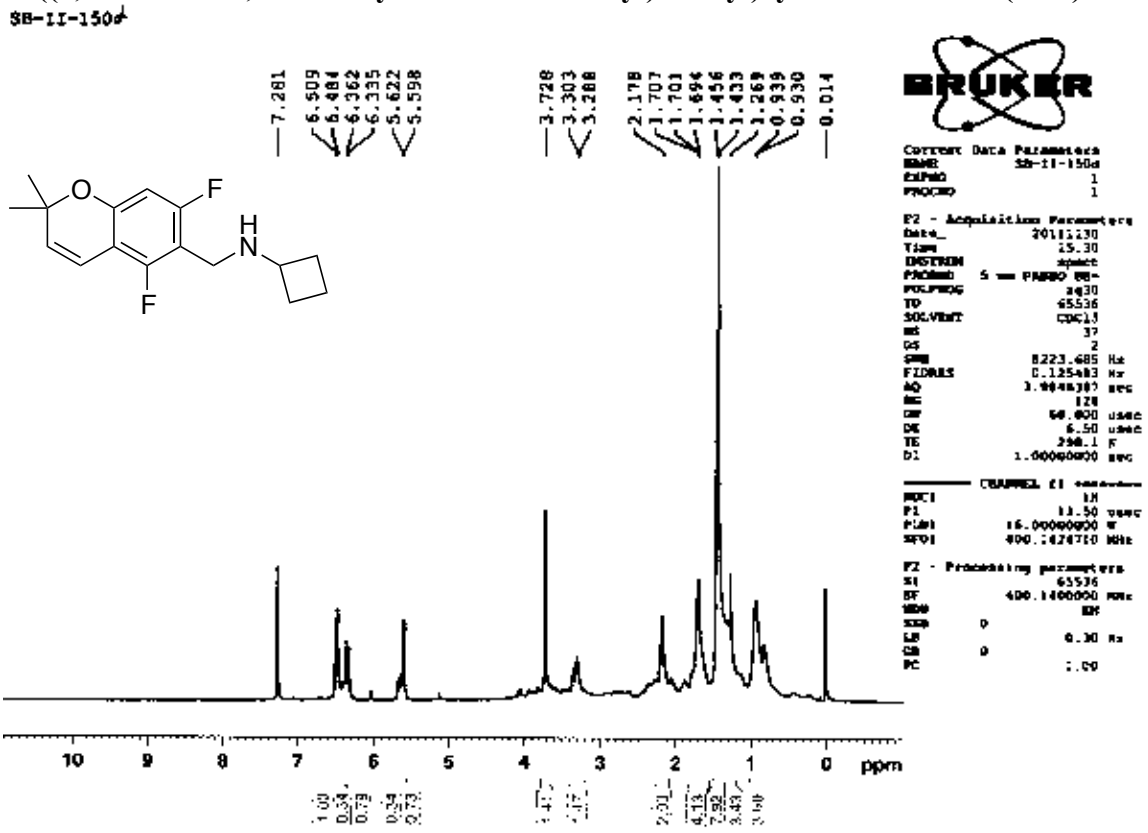
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

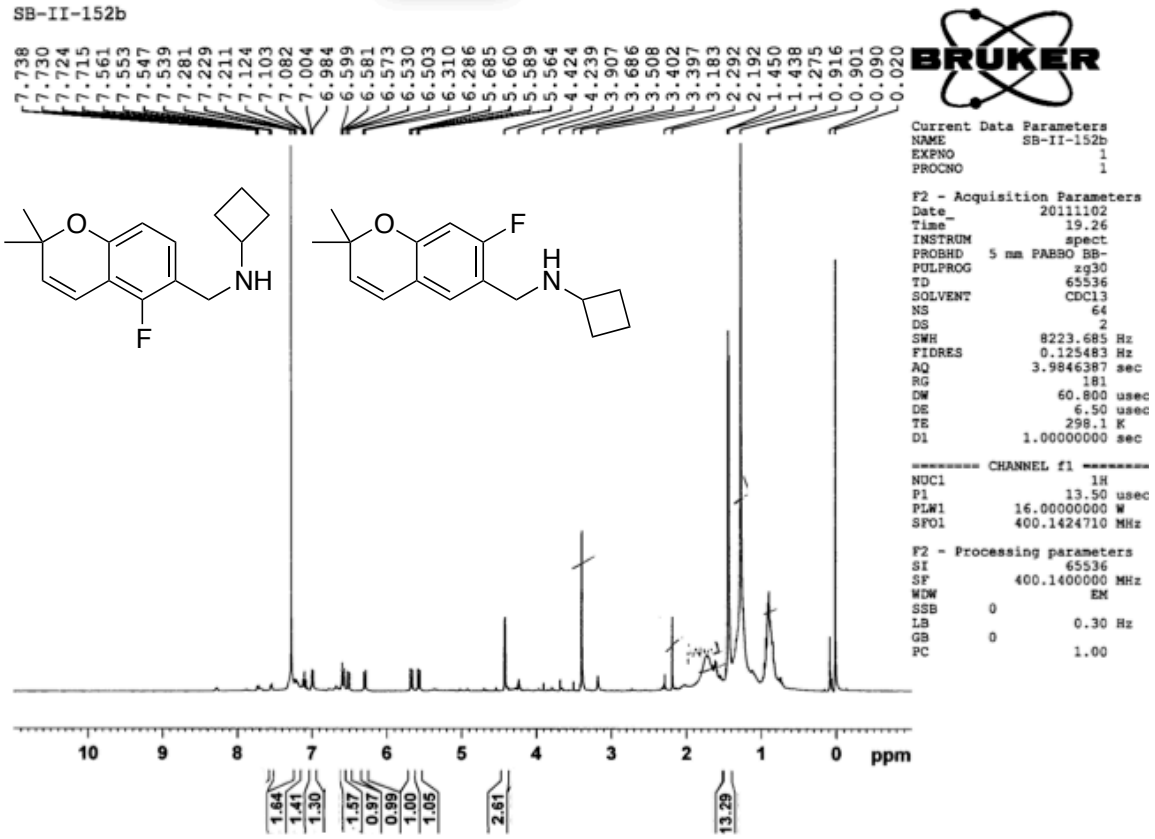
Monoisotopic Mass, Even Electron Ions
556 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-100 S: 0-6

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
244.1707	244.1701	0.6	2.5	6.5	33.5	C16 H22 N O

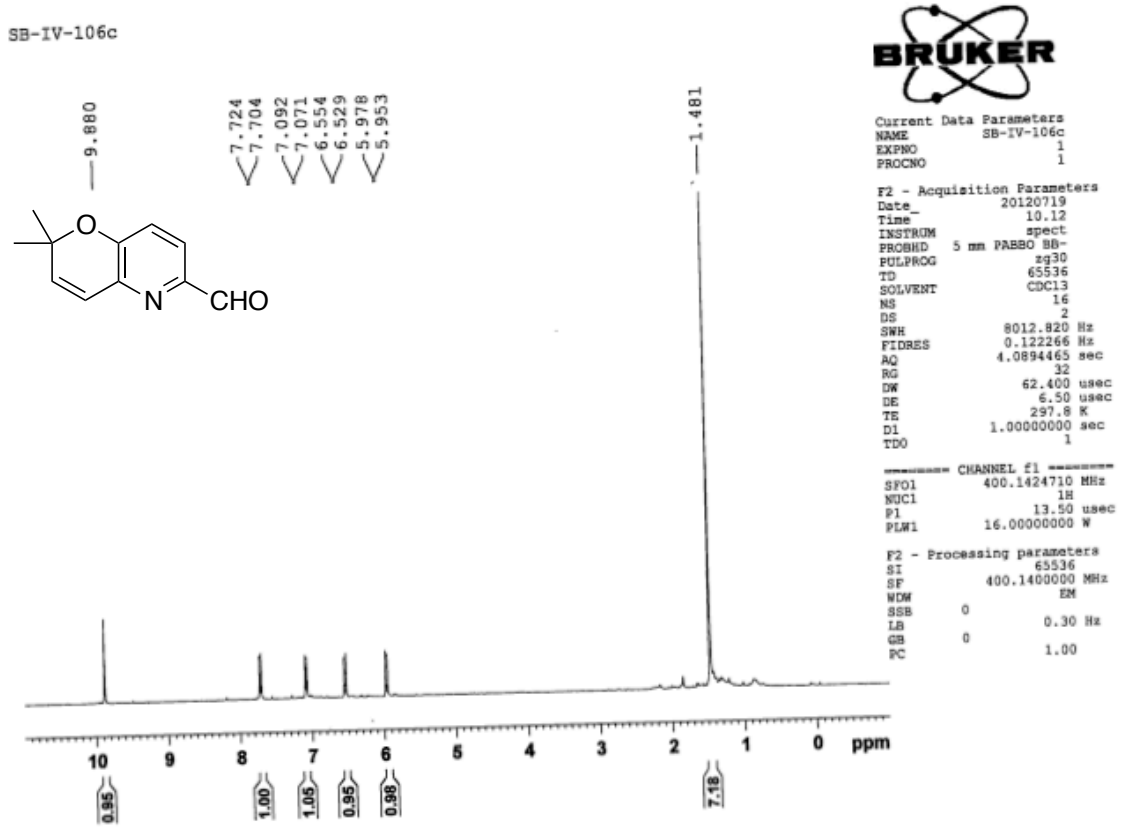
_N_-((5,7-difluoro-2,2-dimethyl-2_H_-chromen-6-yl)methyl)cyclobutanamine (27m)



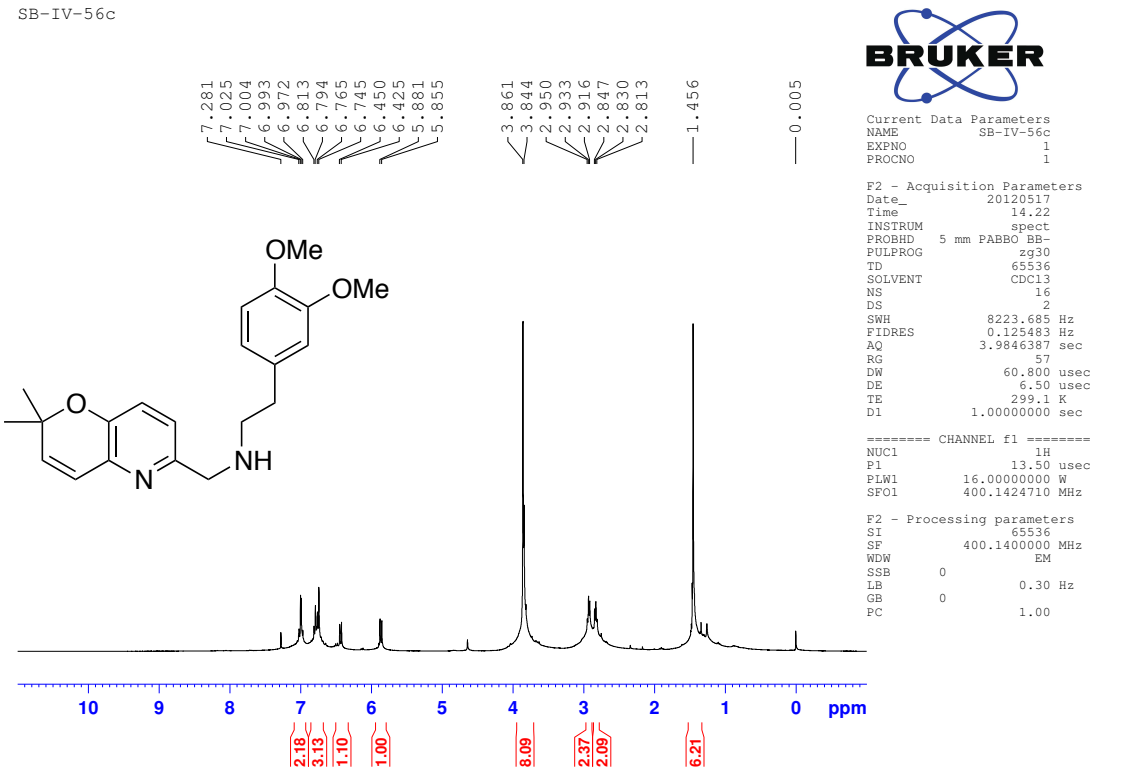
***N*-((5-Fluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine with *N*-((7-Fluoro-2,2-dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine (1:1) (27n)**

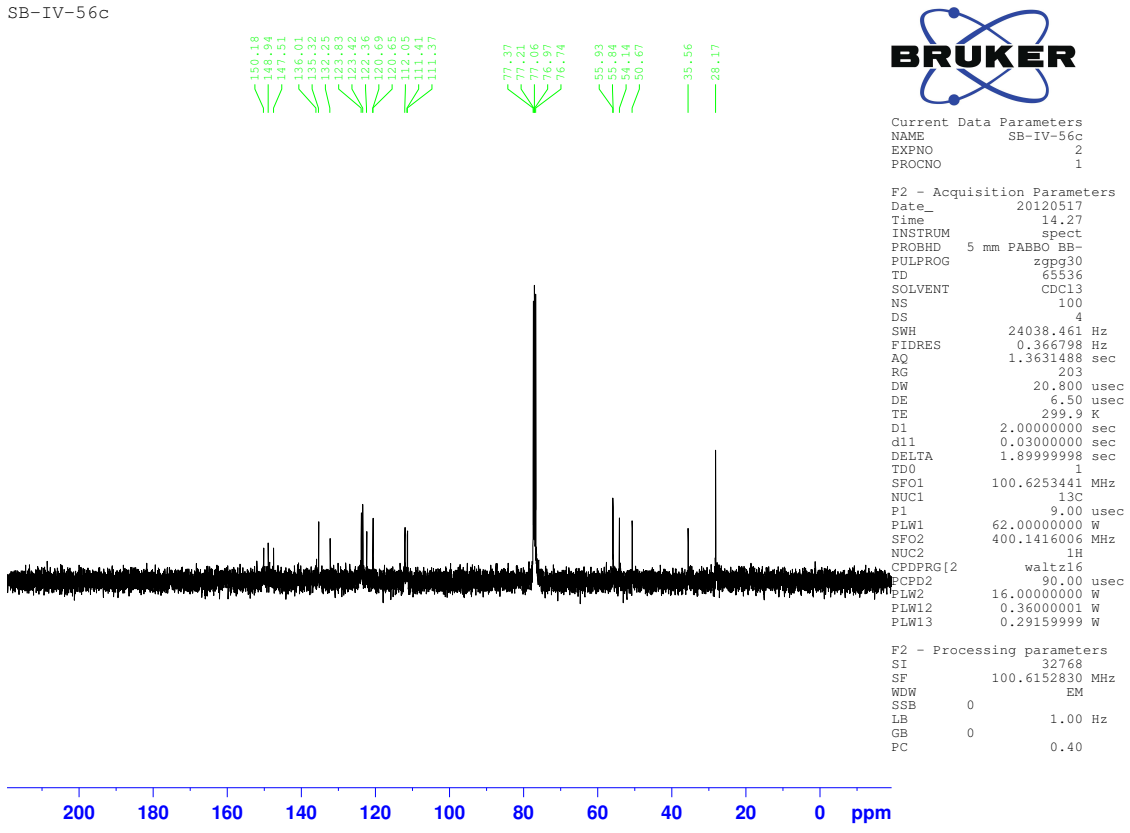


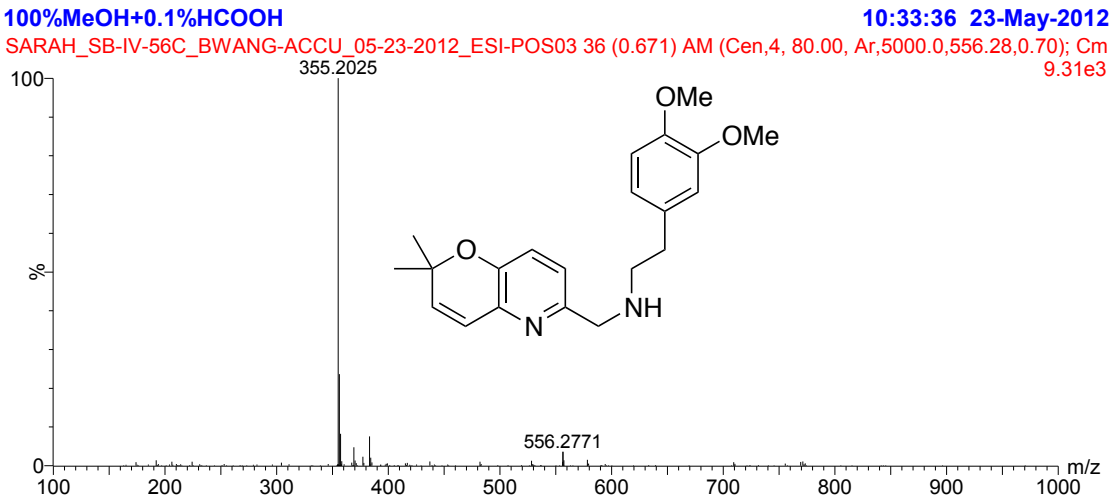
2,2-Dimethyl-2*H*-pyrano[3,2-*b*]pyridine-6-carbaldehyde (28)



2-(3,4-dimethoxyphenyl)-*N*-((2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridin-6-yl)methyl)ethanamine (29a)







Elemental Composition Report

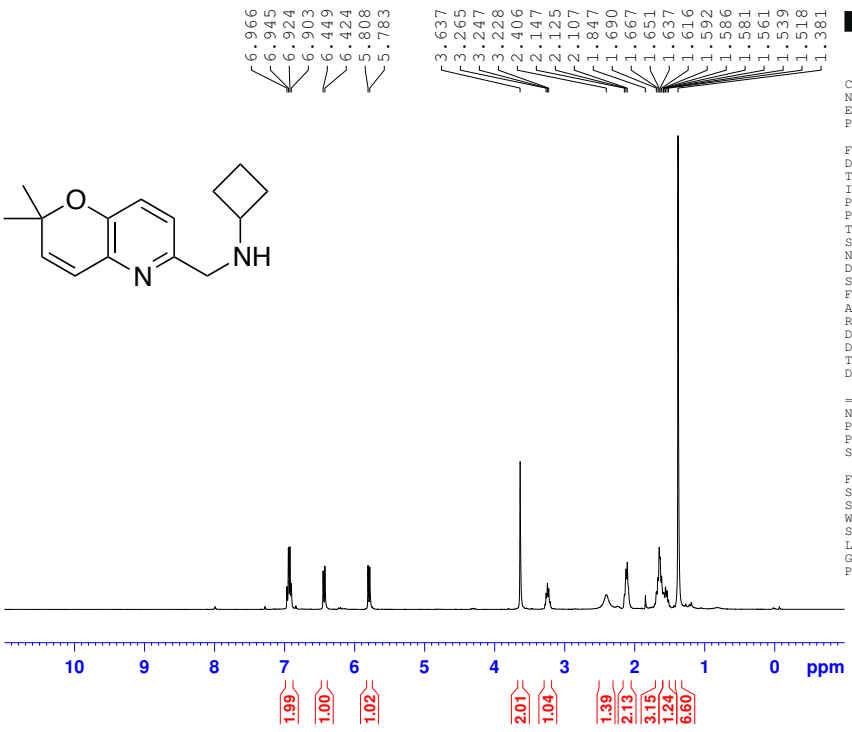
Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2194 formula(e) evaluated with 15 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-200 H: 1-200 N: 1-15 O: 1-100 S: 0-50

Minimum:				-1.5		
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
355.2025	355.2022	0.3	0.8	9.5	126.5	C21 H27 N2 O3

N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)cyclobutanamine (30)

SB-III-106



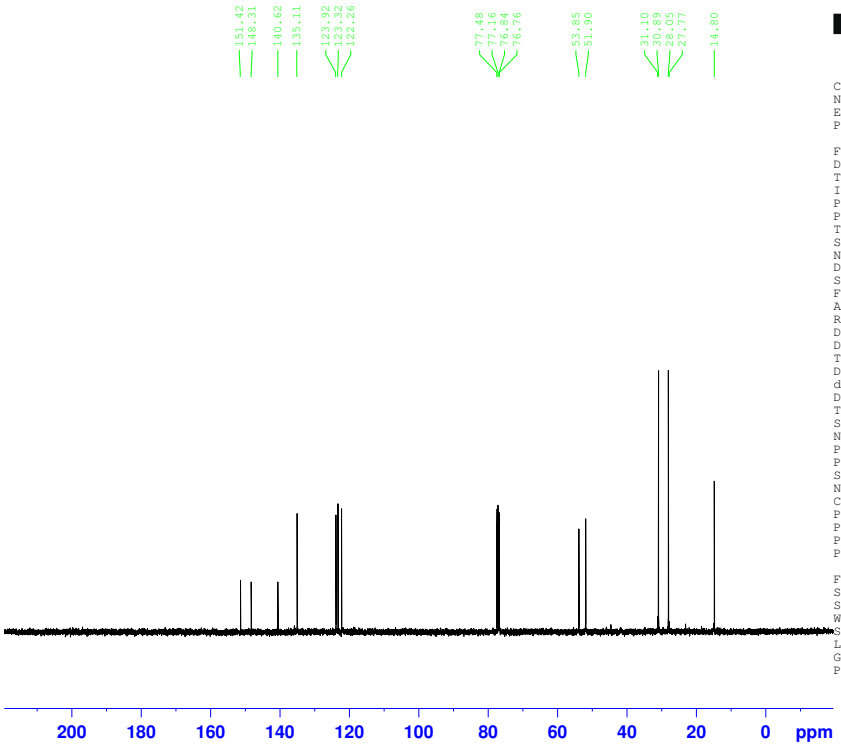
Current Data Parameters
NAME SB-III-106
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120228
Time 15.44
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 22.6
DW 60.800 usec
DE 6.50 usec
TE 295.2 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PLW1 16.00000000 W
SFO1 400.1424710 MHz

F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

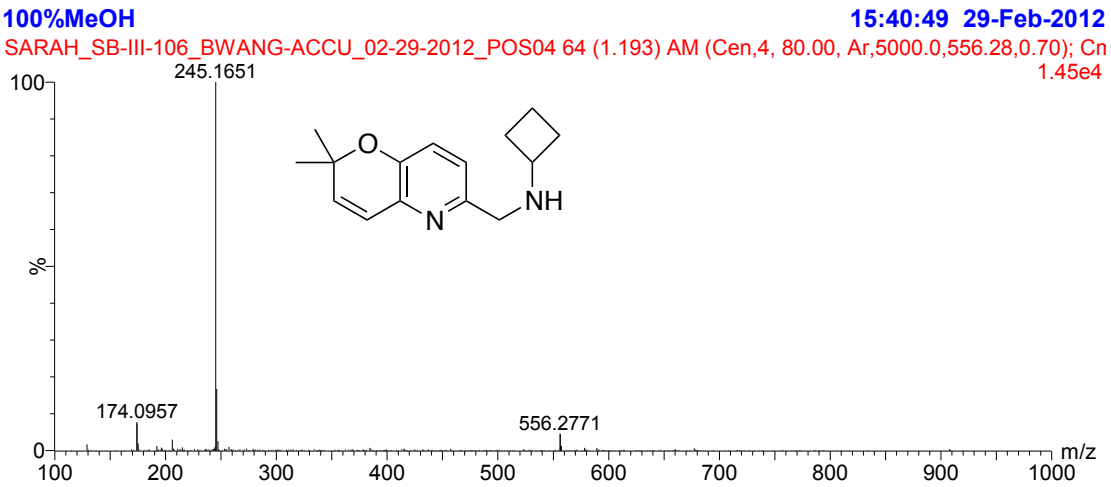
SB-III-106



Current Data Parameters
NAME SB-III-106
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120228
Time 15.47
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 114
DW 20.800 usec
DE 6.50 usec
TE 295.6 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
SFO1 100.6253441 MHz
NUC1 13C
P1 9.00 usec
PLW1 62.00000000 W
SFO2 400.1416006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 16.00000000 W
PLW12 0.36000001 W
PLW13 0.29159999 W

F2 - Processing parameters
SI 32768
SF 100.6152830 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Elemental Composition Report

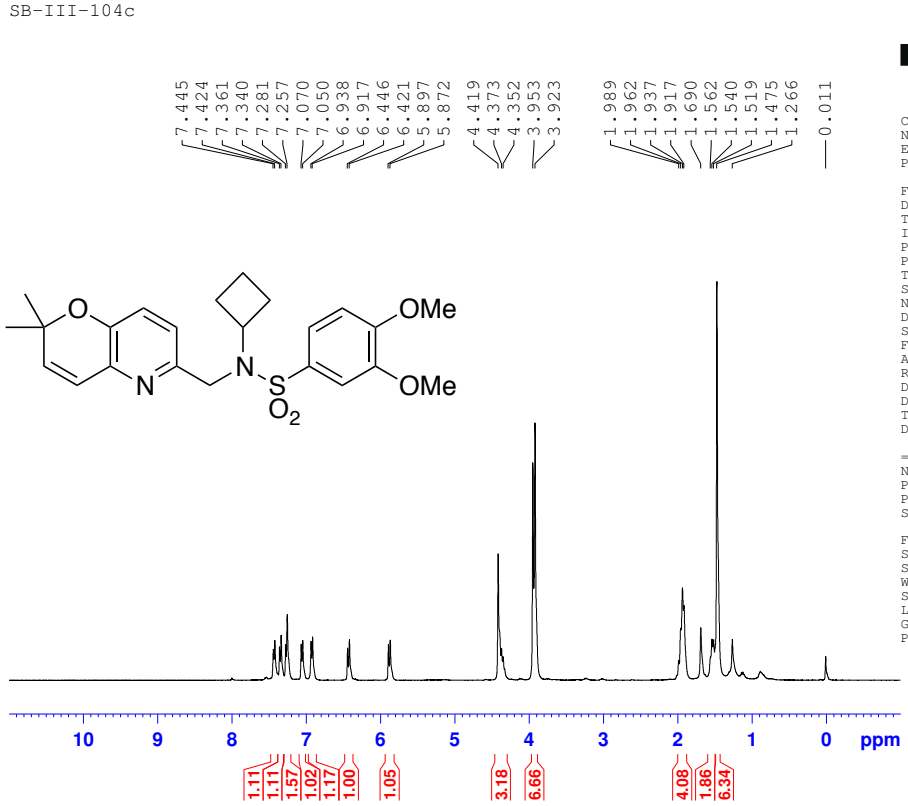
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
238 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20

Minimum:			-1.5			
Maximum:	5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
245.1651	245.1654	-0.3	-1.2	6.5	24.4	C15 H21 N2 O

N-cyclobutyl-N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (2), (32a)

SB-III-104c

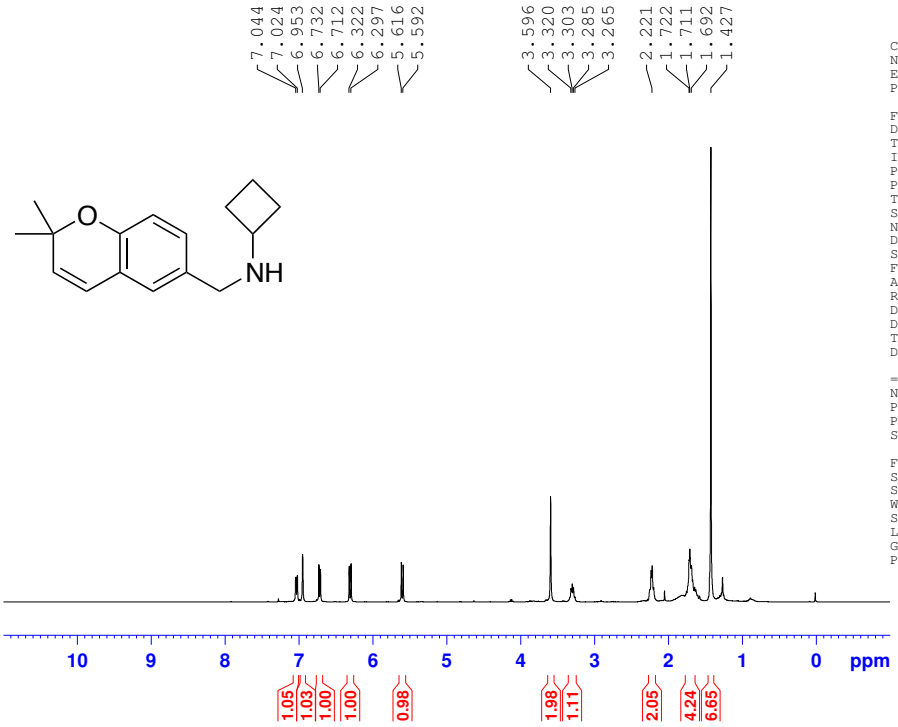


BRUKER

```
Current Data Parameters
NAME         SB-III-104c
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120228
Time               19.28
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9845889 sec
RG                   144
DW                60.800 usec
DE                 6.50 usec
TE                297.7 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.50 usec
PLW1        16.00000000 W
SFO1        400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

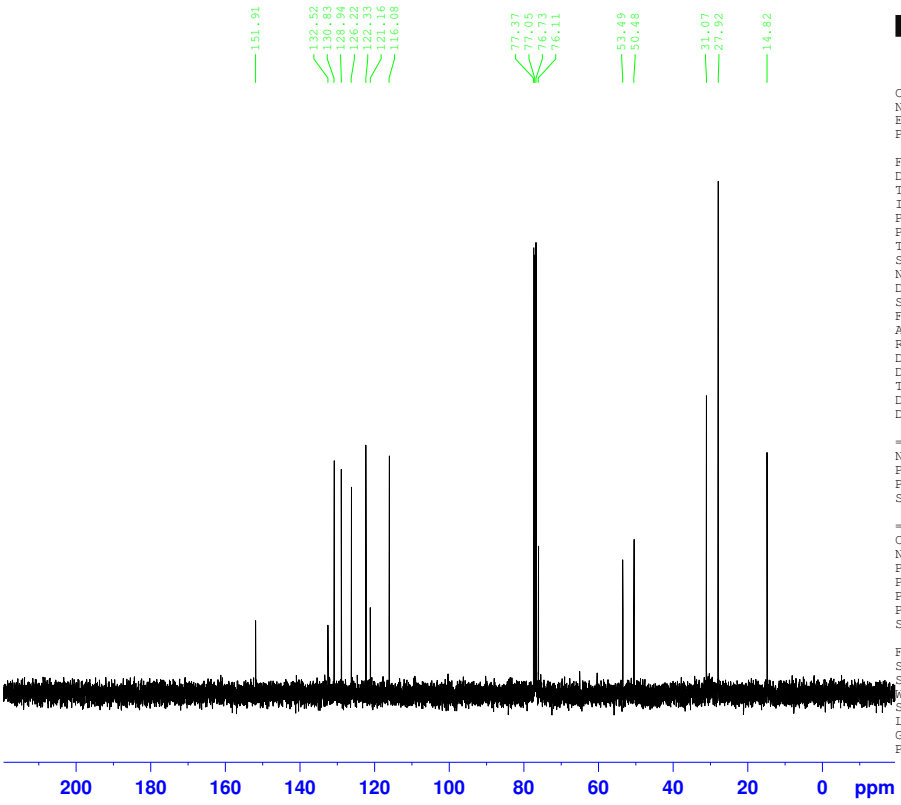
N-((2,2-Dimethyl-2*H*-chromen-6-yl)methyl)cyclobutanamine (33)

SB-IV-9a

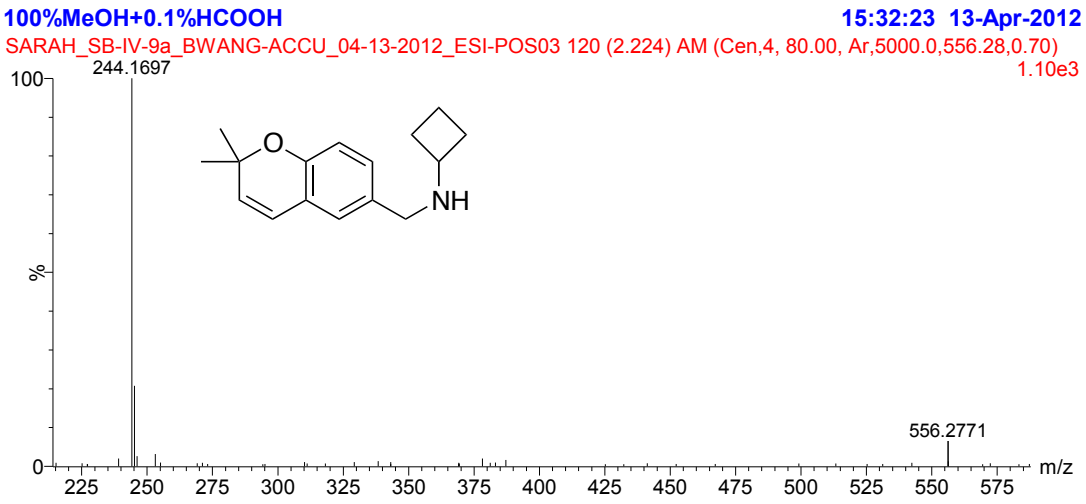



```
Current Data Parameters
NAME                  SB-IV-9a
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20120405
Time                   16.15
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       32
DW                   60.800 usec
DE                    6.50 usec
TE                   298.1 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                    13.50 usec
PLW1            16.00000000 W
SFO1           400.1424710 MHz

F2 - Processing parameters
SI                    65536
SF               400.1400000 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

SB-IV-9a




```
Current Data Parameters
NAME                  SB-IV-9a
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20120405
Time                   16.18
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       21
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      203
DW                   20.800 usec
DE                    6.50 usec
TE                   298.6 K
D1                2.00000000 sec
D11               0.03000000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                    9.00 usec
PLW1            62.00000000 W
SFO1           100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                90.00 usec
PLW2            16.00000000 W
PLW12            0.36000001 W
PLW13            0.29159999 W
SFO2           400.1416006 MHz

F2 - Processing parameters
SI                    32768
SF               100.6152830 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```



Elemental Composition Report

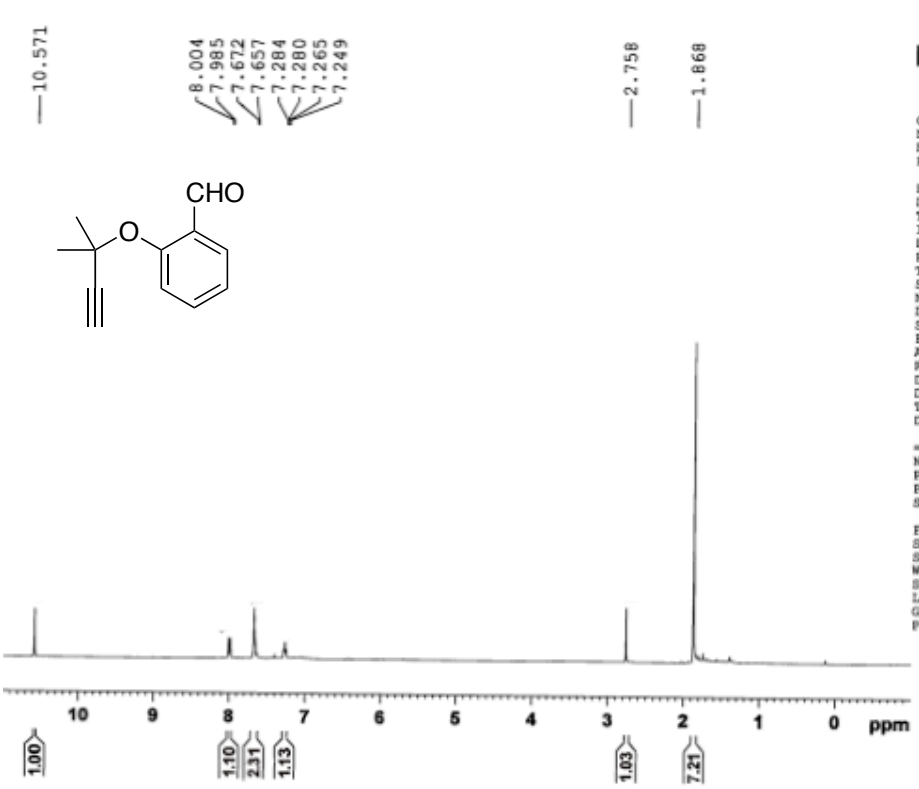
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
227 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20

Minimum:			-1.5			
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
244.1697	244.1701	-0.4	-1.6	6.5	2.7	C16 H22 N O

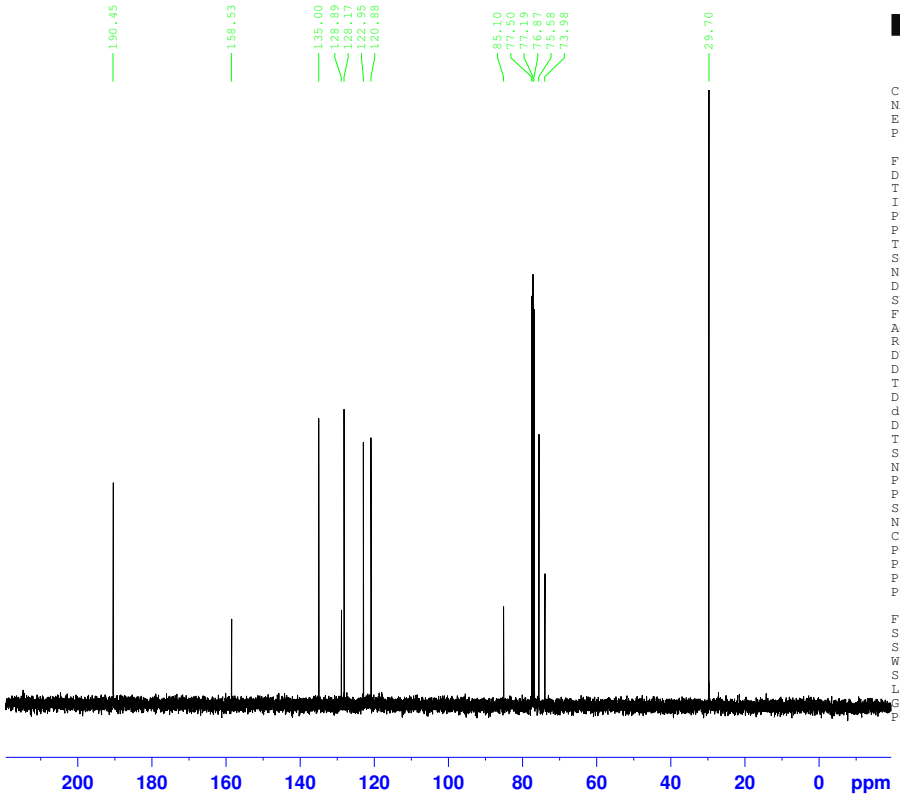
2-((2-Methylbut-3-yn-2-yl)oxy)benzaldehyde (S2b)

SB-III-156c




```
Current Data Parameters
NAME                 SB-III-156c
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_               20120403
Time                   15.21
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       57
DW                   60.800 usec
DE                    6.50 usec
TE                   298.1 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.50 usec
PLW1             16.00000000 W
SFO1            400.1424710 MHz

F2 - Processing parameters
SI                    65536
SF               400.1400000 MHz
WDW                      EM
SSB                   0
LB                    0.30 Hz
GB                    0
PC                    1.00
```

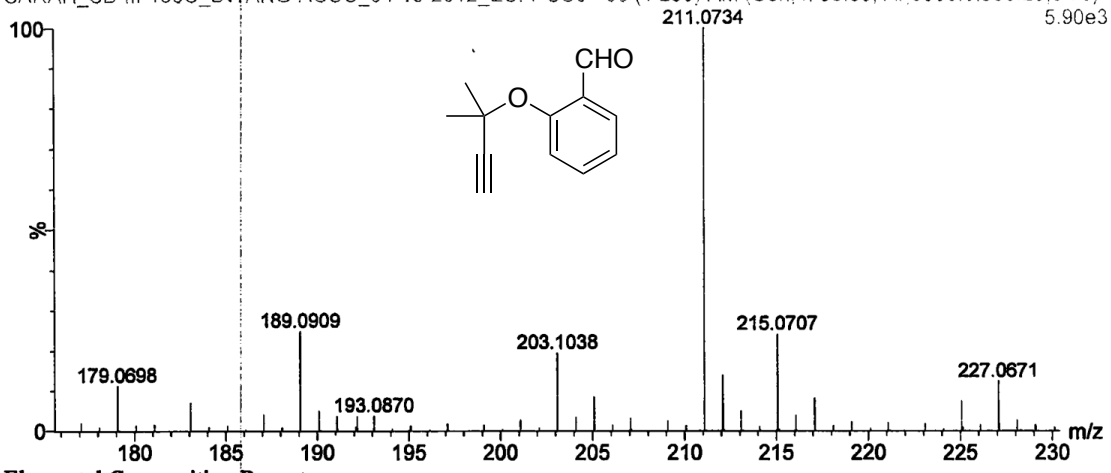
SB-III-156c




```
Current Data Parameters
NAME                 SB-III-156c
EXPNO                          2
PROCNO                         1

F2 - Acquisition Parameters
Date_               20120403
Time                   15.24
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       38
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                      203
DW                   20.800 usec
DE                    6.50 usec
TE                   298.5 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
TD0                       1
SFO1            100.6253441 MHz
NUC1                     13C
P1                    9.00 usec
PLW1             62.00000000 W
SFO2            400.1416006 MHz
NUC2                      1H
CPDPRG[2             waltz16
PCPD2                90.00 usec
PLW2             16.00000000 W
PLW12             0.36000001 W
PLW13             0.29159999 W

F2 - Processing parameters
SI                    32768
SF              100.6152830 MHz
WDW                      EM
SSB                   0
LB                    1.00 Hz
GB                    0
PC                    1.40
```

100%MeOH+0.1%HCOOH **17:01:50 13-Apr-2012**

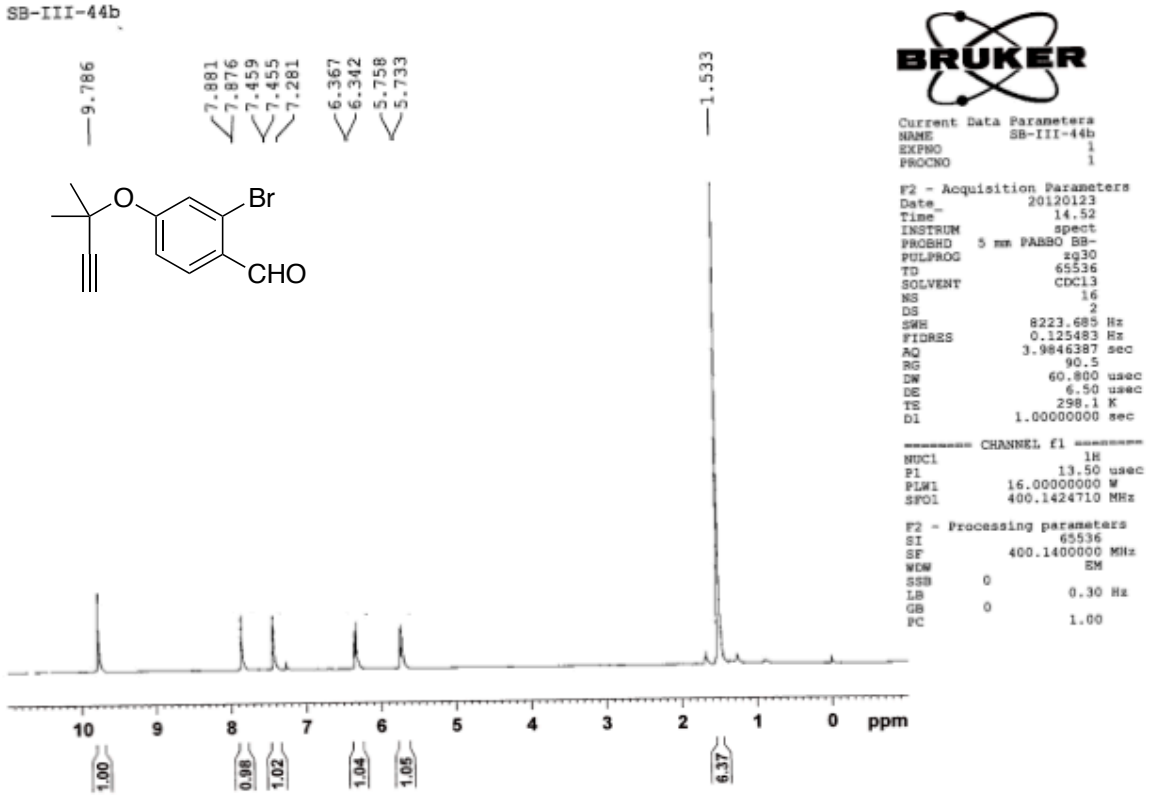
SARAH_SB-III-156C_BWANG-ACCU_04-13-2012_ESI-POS01 66 (1.230) AM (Cen,4, 80.00, Ar,5000.0,556.28,0.70)

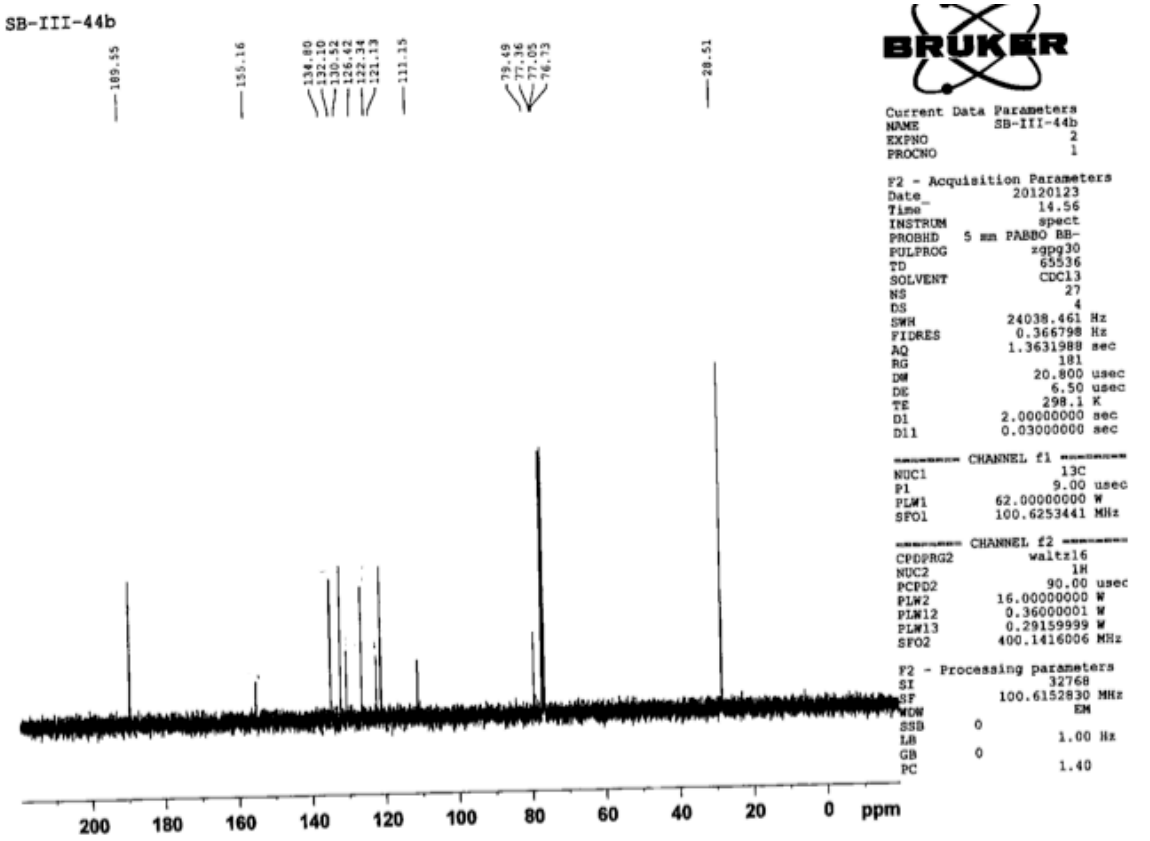


Elemental Composition Report
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
18 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 O: 1-20 Na: 1-1

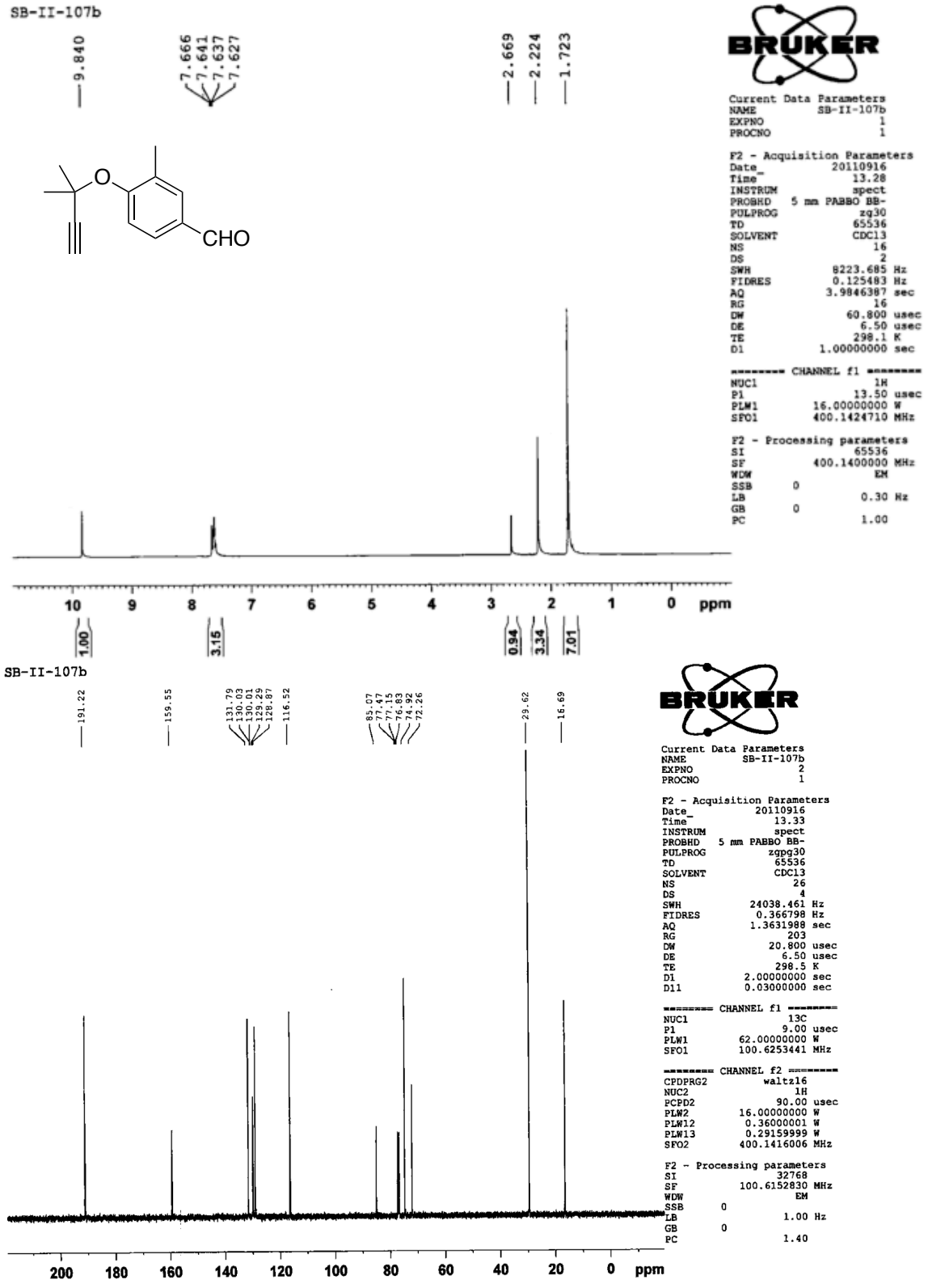
Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa		PPM	DBE	i-FIT	Formula
211.0734	211.0735	-0.1	-0.5	6.5	82.6		C12 H12 O2 Na

2-Bromo-4-((2-methylbut-3-yn-2-yl)oxy)benzaldehyde (S2c)





3-Methyl-4-((2-methylbut-3-yn-2-yl)oxy)benzaldehyde (S2d)



BRUKER

Current Data Parameters
NAME SB-II-107b
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110916
Time 13.28
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 16
DW 60.800 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PLW1 16.00000000 W
SFO1 400.1424710 MHz

F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

BRUKER

Current Data Parameters
NAME SB-II-107b
EXPNO 2
PROCNO 1

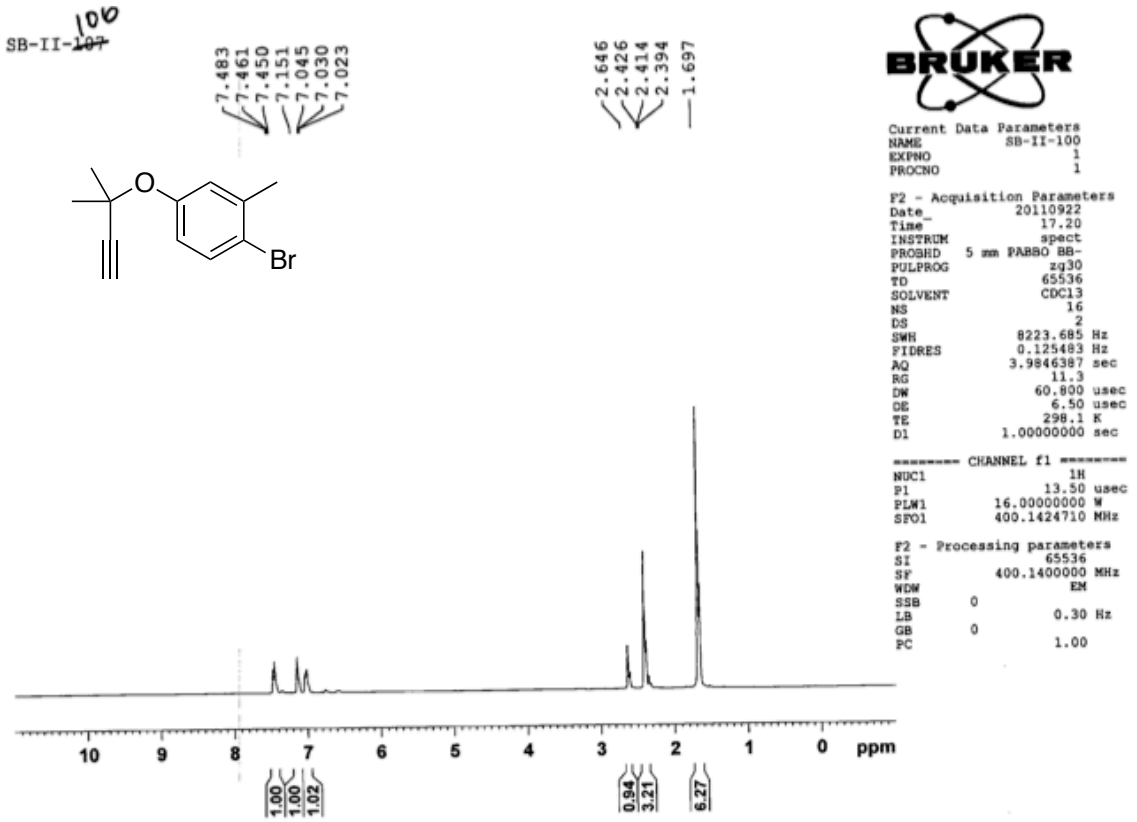
F2 - Acquisition Parameters
Date_ 20110916
Time 13.33
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 26
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 298.5 K
D1 2.00000000 sec
D11 0.03000000 sec

======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PLW1 62.00000000 W
SFO1 100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 16.00000000 W
PLW12 0.36000001 W
PLW13 0.29159999 W
SFO2 400.1416006 MHz

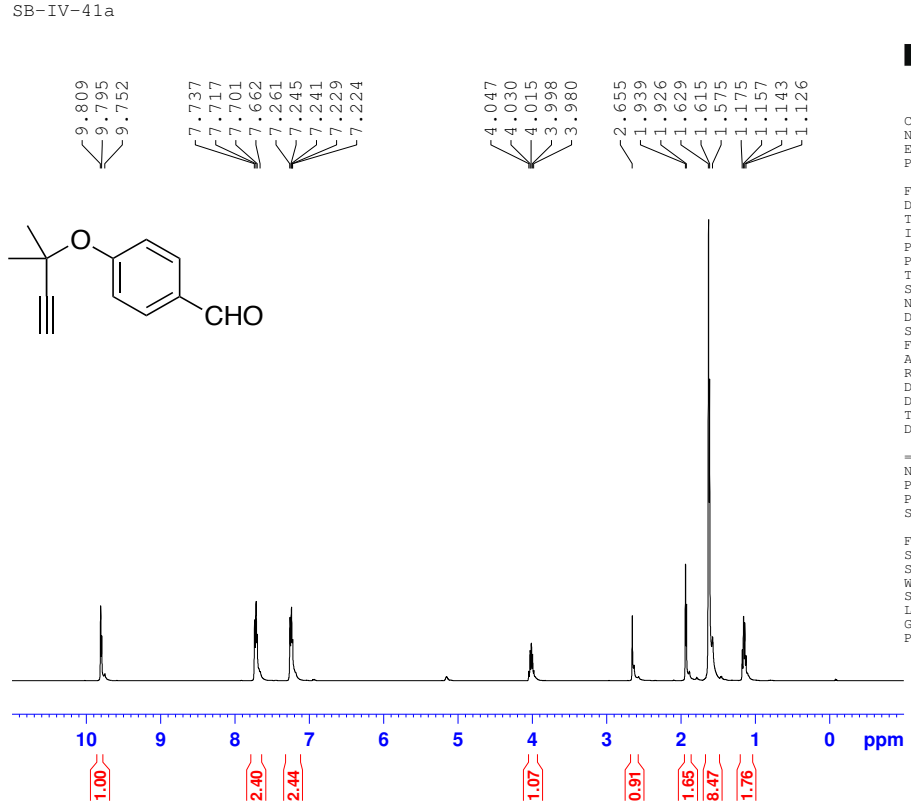
F2 - Processing parameters
SI 32768
SF 100.6152830 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1-bromo-2-methyl-4-((2-methylbut-3-yn-2-yl)oxy)benzene (S2e)



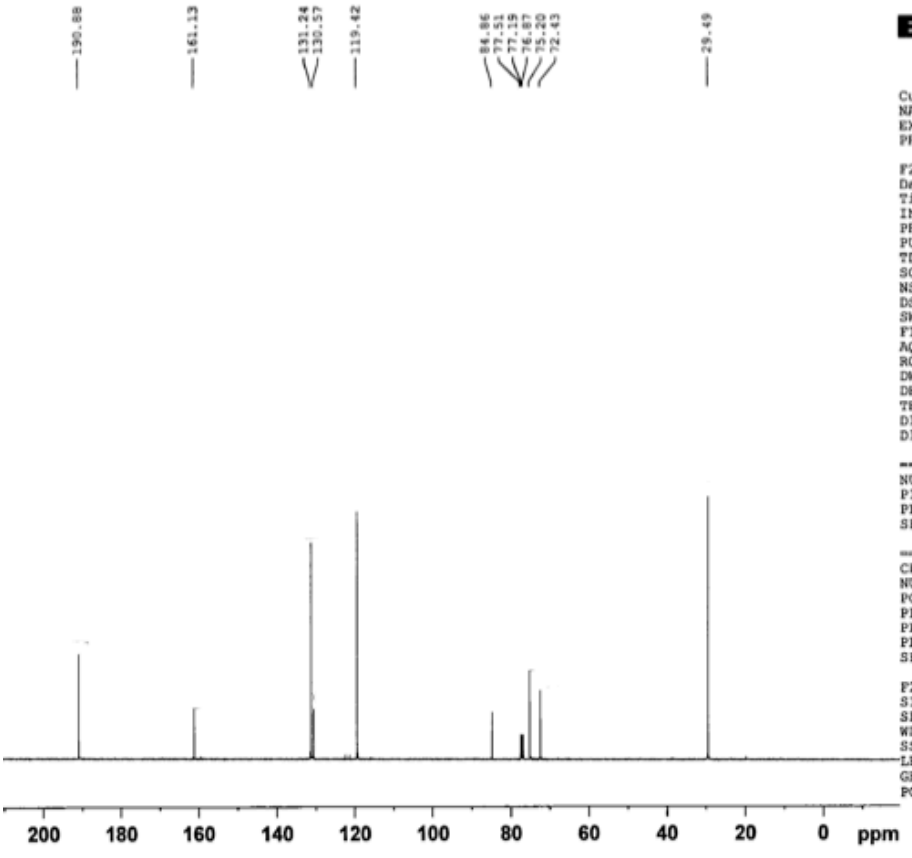
4-((2-Methylbut-3-yn-2-yl)oxy)benzaldehyde (S2j)

SB-IV-41a



BRUKER

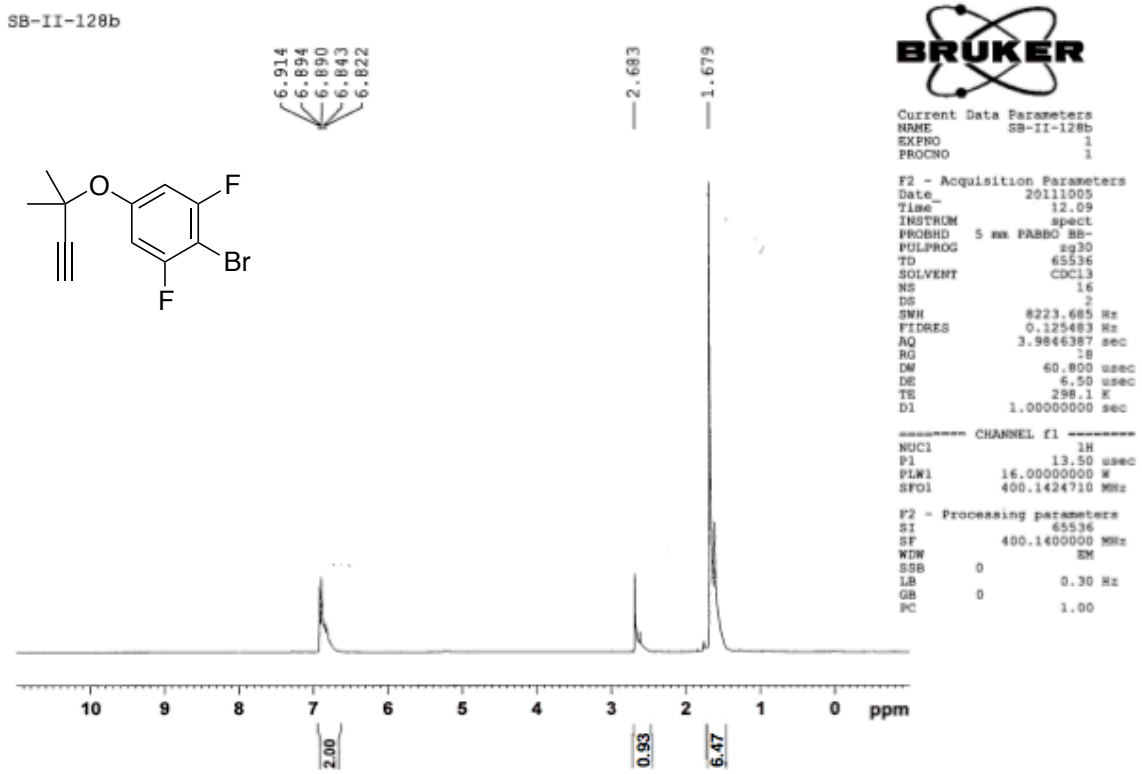
```
Current Data Parameters
NAME                  SB-IV-41a
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20120425
Time                      16.51
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8223.685 Hz
FIDRES                 0.125483 Hz
AQ                     3.9846387 sec
RG                           16
DW                        60.800 usec
DE                         6.50 usec
TE                        298.1 K
D1                    1.00000000 sec

======== CHANNEL f1 ========
NUC1                         1H
P1                        13.50 usec
PLW1                16.00000000 W
SFO1                400.1424710 MHz

F2 - Processing parameters
SI                        65536
SF                  400.1400000 MHz
WDW                          EM
SSB                   0
LB                        0.30 Hz
GB                    0
PC                        1.00
```

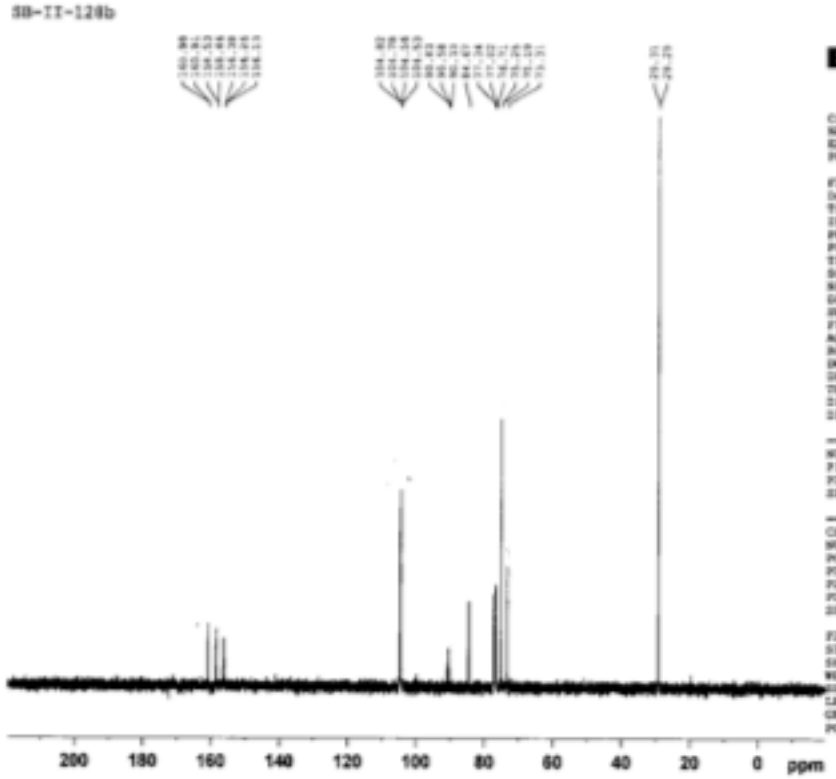


BRUKER

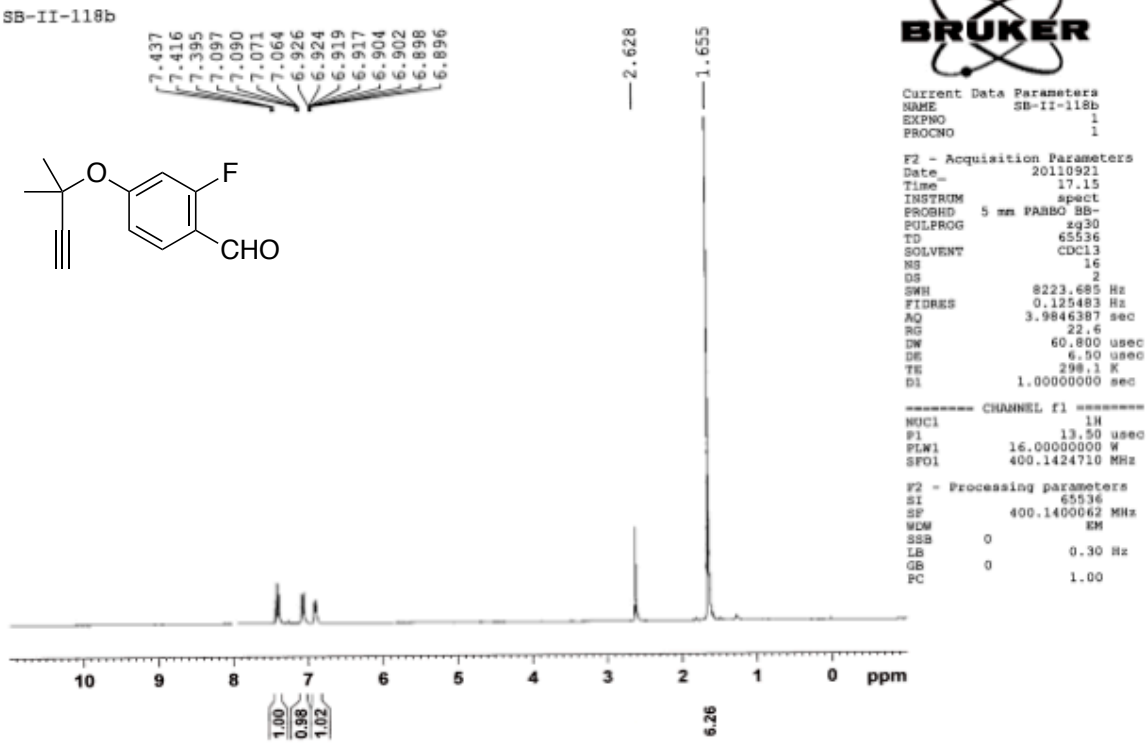
```
Current Data Parameters
NAME                      KC10
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                  20111105
Time                      18.18
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                           66
DS                            4
SWH                   24038.461 Hz
FIDRES                 0.366798 Hz
AQ                     1.3631988 sec
RG                          161
DW                        20.800 usec
DE                         6.50 usec
TE                        299.9 K
D1                    2.00000000 sec
D11                   0.03000000 sec

======== CHANNEL f1 ========
NUC1                        13C
P1                         9.00 usec
PLW1                62.00000000 W
SFO1                100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                     90.00 usec
PLW2                16.00000000 W
PLW12                0.36000001 W
PLW13                0.29159999 W
SFO2                400.1416006 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6152830 MHz
WDW                          EM
SSB                   0
LB                        1.00 Hz
GB                    0
PC                        1.40
```

2-bromo-1,3-difluoro-5-((2-methylbut-3-yn-2-yl)oxy)benzene (S2l)

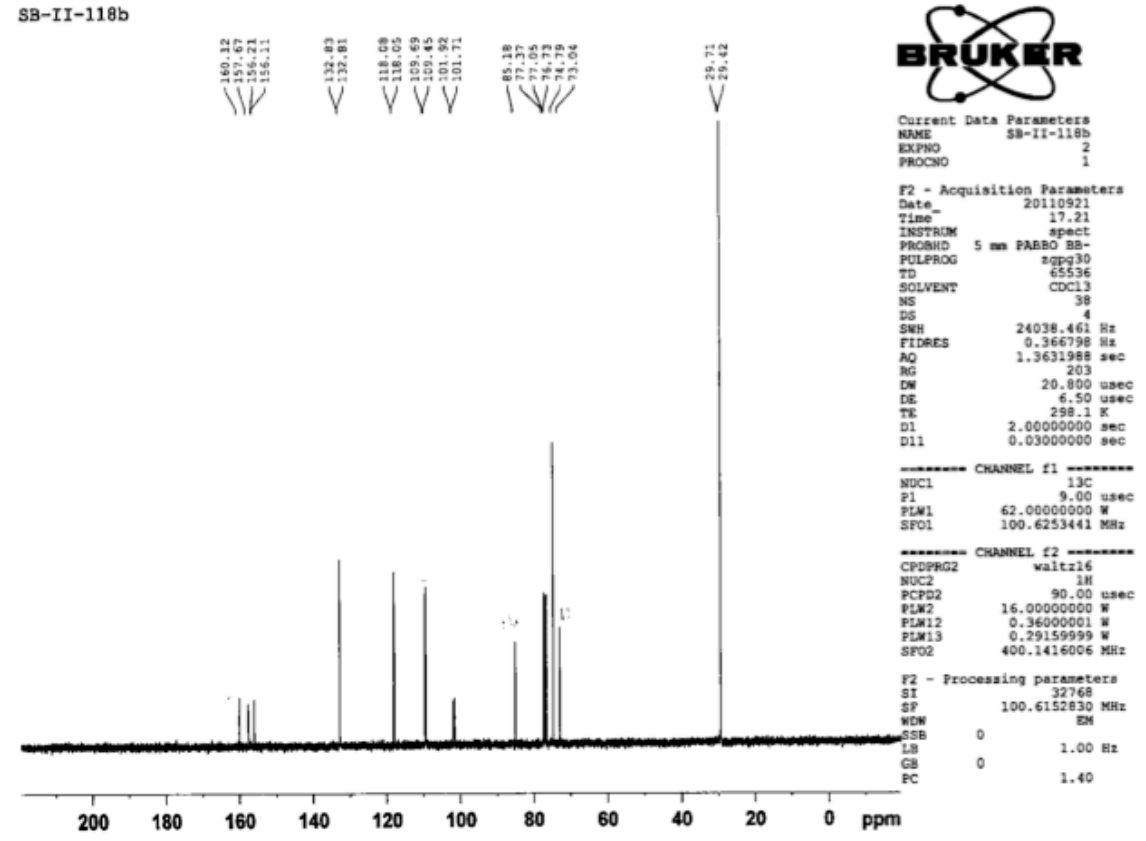




2-fluoro-4-((2-methylbut-3-yn-2-yl)oxy)benzaldehyde (S2m)

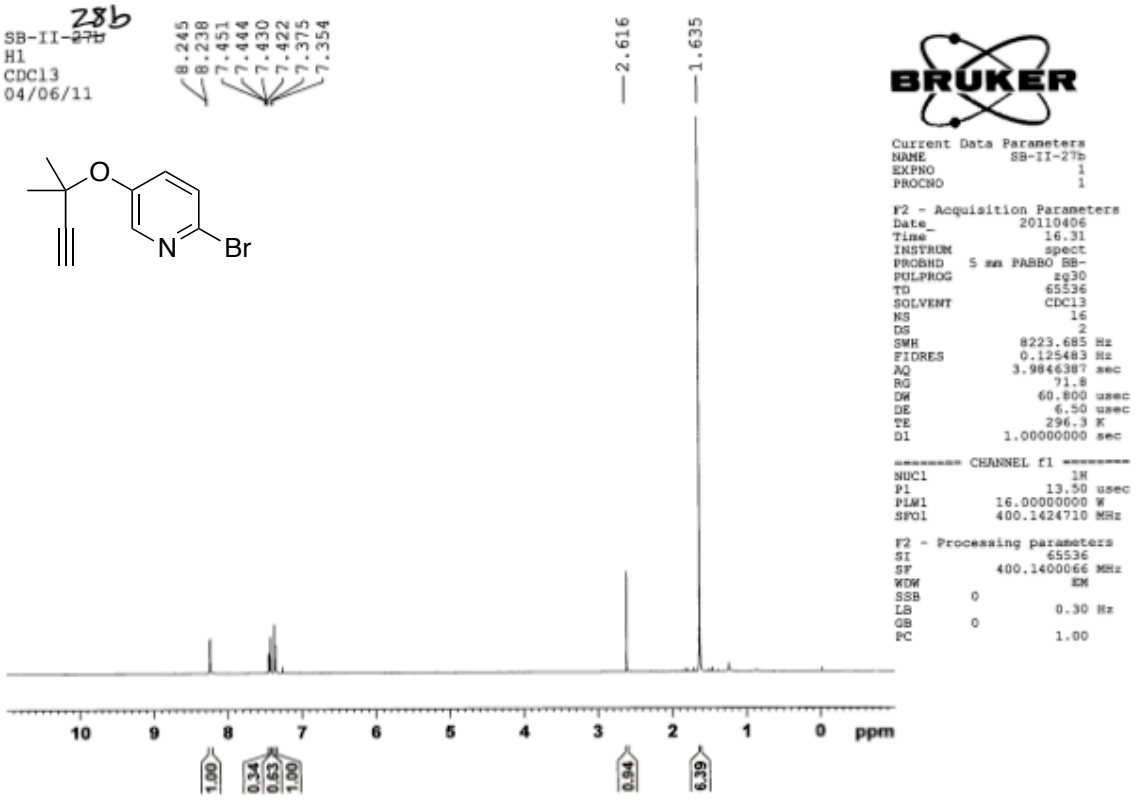



```
Current Data Parameters
NAME                  SB-II-118b
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110921
Time                       17.15
INSTRUM                    spect
PROBHD    5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                            16
DS                             2
SWH                     8223.685 Hz
FIDRES                  0.125483 Hz
AQ                      3.9846387 sec
RG                           22.6
DW                         60.800 usec
DE                          6.50 usec
TE                         298.1 K
D1                     1.00000000 sec

======== CHANNEL f1 ========
NUC1                          1H
P1                         13.50 usec
PLW1                   16.00000000 W
SFO1                  400.1424710 MHz

F2 - Processing parameters
SI                            65536
SF                     400.1400062 MHz
WDW                              EM
SSB                   0
LB                             0.30 Hz
GB                    0
PC                             1.00
```

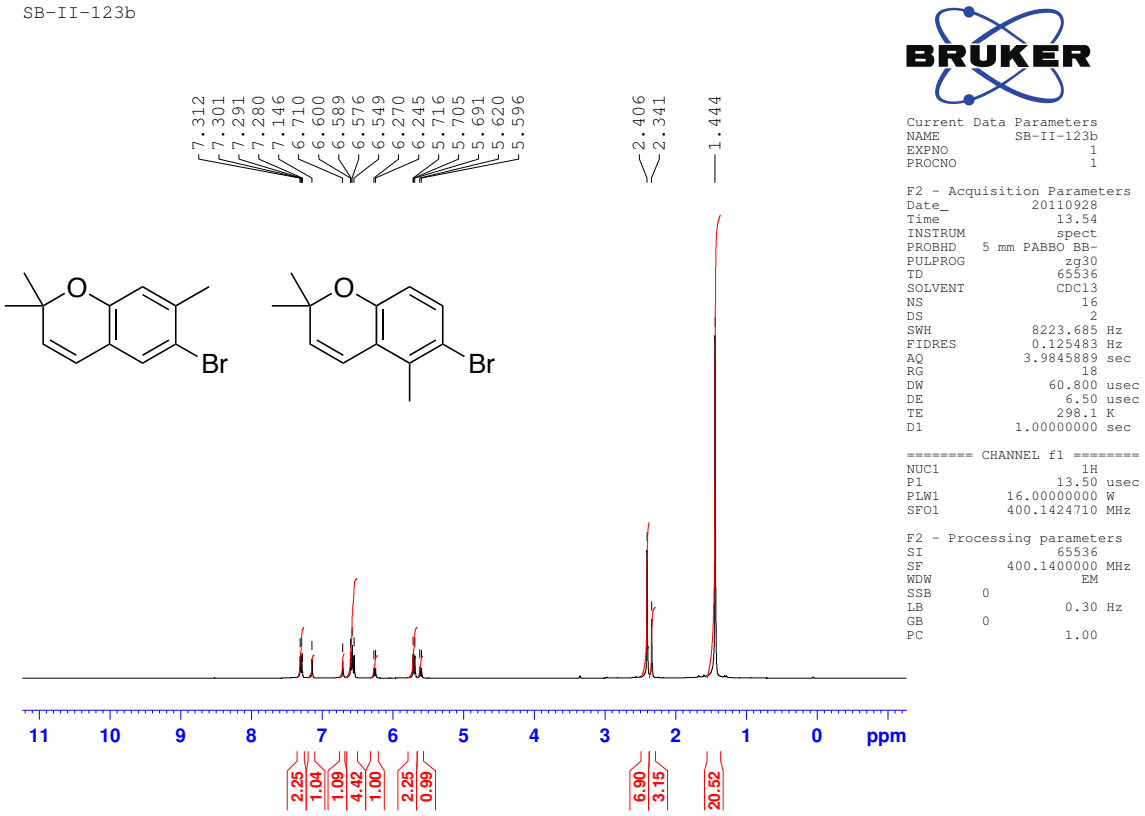



```
Current Data Parameters
NAME                  SB-II-118b
EXPNO                          2
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110921
Time                       17.21
INSTRUM                    spect
PROBHD    5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                            38
DS                             4
SWH                    24038.461 Hz
FIDRES                  0.366798 Hz
AQ                      1.3631988 sec
RG                           203
DW                         20.800 usec
DE                          6.50 usec
TE                         298.1 K
D1                     2.00000000 sec
D11                    0.03000000 sec

======== CHANNEL f1 ========
NUC1                          13C
P1                          9.00 usec
PLW1                  62.00000000 W
SFO1                  100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                          1H
PCPD2                      90.00 usec
PLW2                  16.00000000 W
PLW12                  0.36000001 W
PLW13                  0.29159999 W
SFO2                  400.1416006 MHz

F2 - Processing parameters
SI                            32768
SF                     100.6152830 MHz
WDW                              EM
SSB                   0
LB                             1.00 Hz
GB                    0
PC                             1.40
```

2-Bromo-5-((2-methylbut-3-yn-2-yl)oxy)pyridine (S2n)

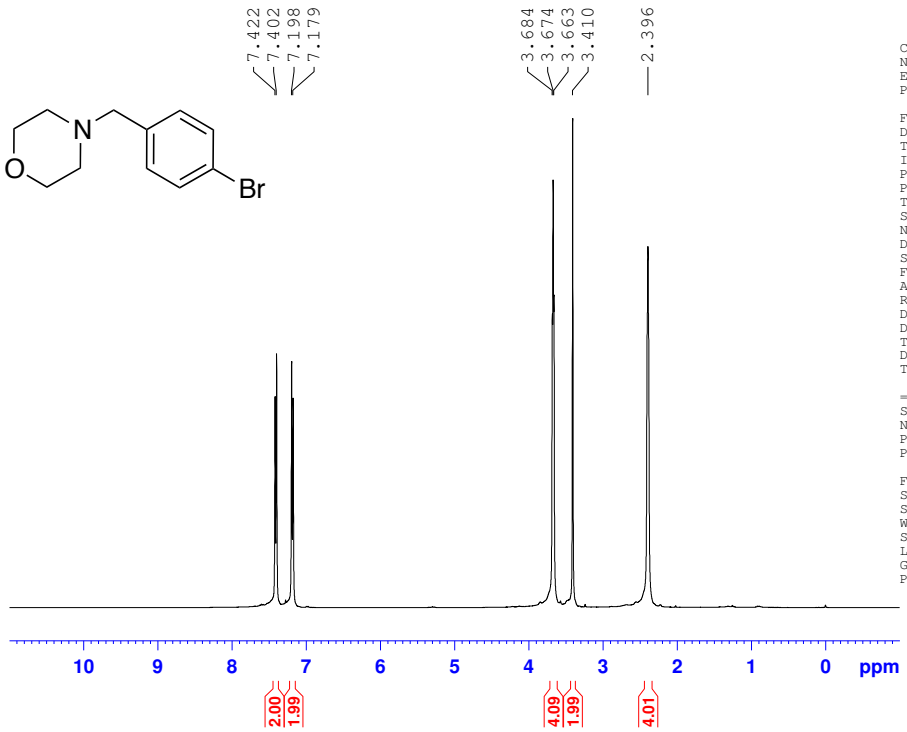


6-bromo-2,2,5-trimethyl-2*H*-chromene with 6-bromo-2,2,7-trimethyl-2*H*-chromene (1:1) (S3e)



4-(4-Bromobenzyl)morpholine (S3i)

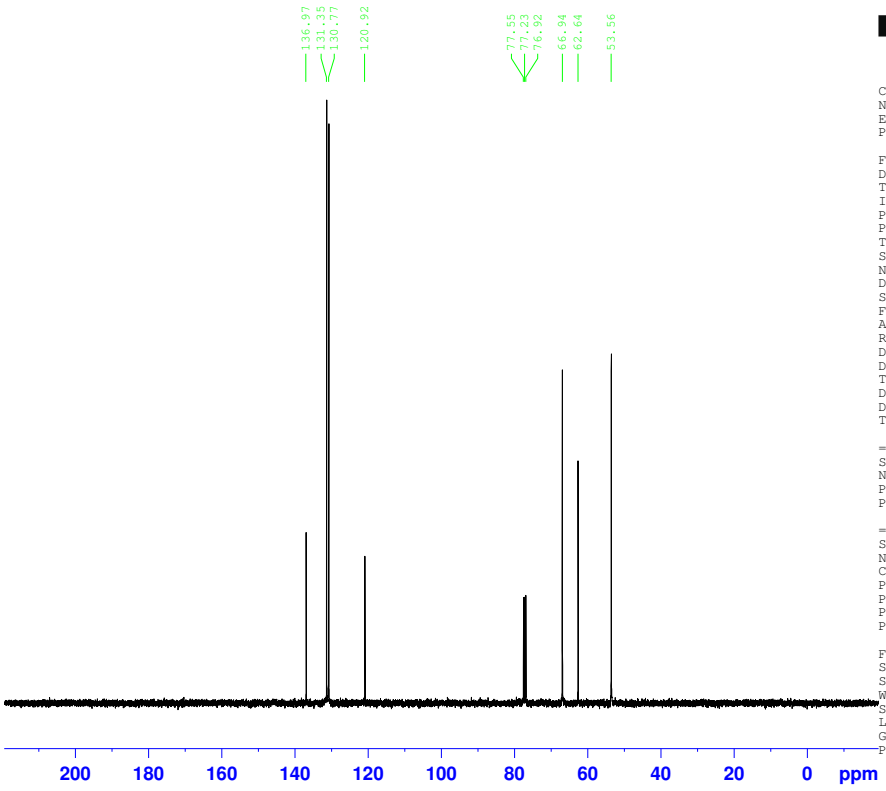
SB-IV-110



BRUKER

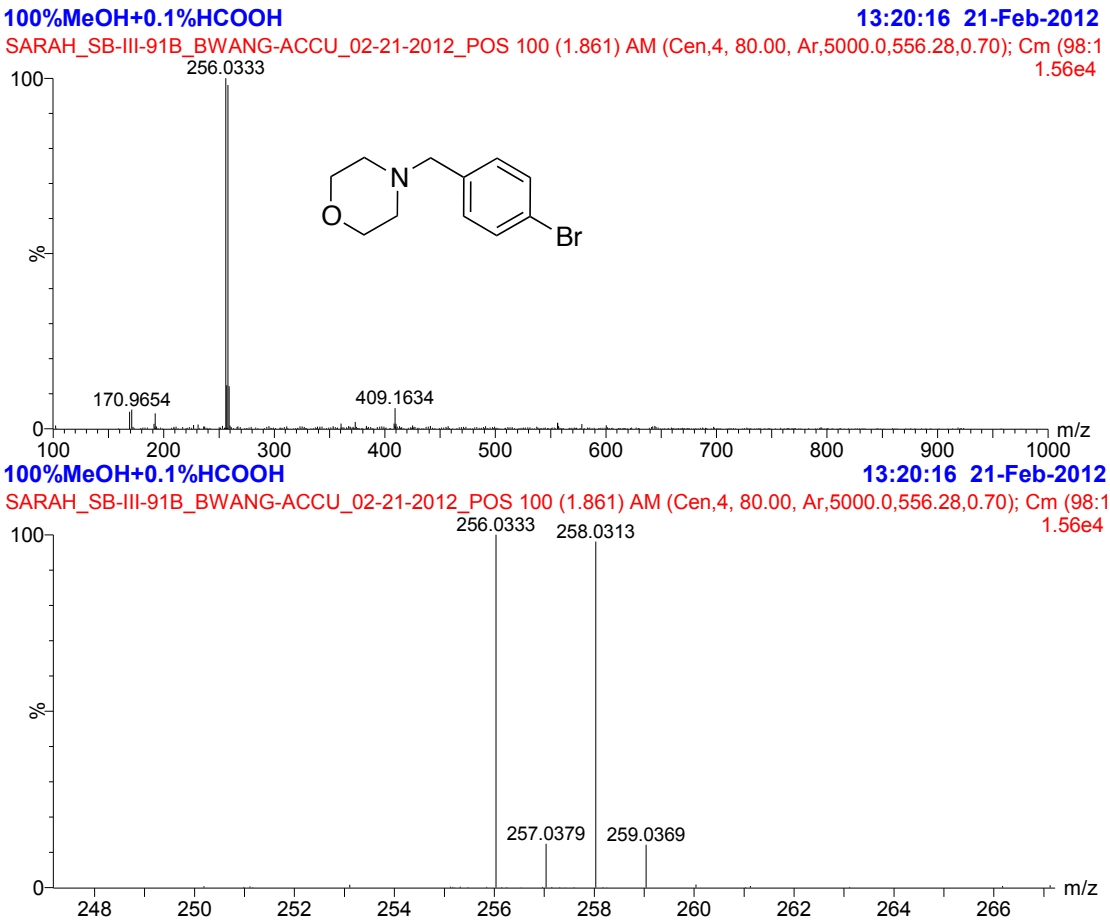
```
Current Data Parameters
NAME            SB-IV-110
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20120726
Time               13.24
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     6
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                  50.8
DW                62.400 usec
DE                 6.50 usec
TE                299.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                 13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                 65536
SF          400.1400000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

SB-IV-110



BRUKER

```
Current Data Parameters
NAME            SB-IV-110
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20120726
Time               13.26
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    27
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631488 sec
RG                   203
DW                20.800 usec
DE                 6.50 usec
TE                299.4 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6253441 MHz
NUC1                   13C
P1                 9.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W
PLW13         0.29159999 W

F2 - Processing parameters
SI                 32768
SF          100.6152830 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

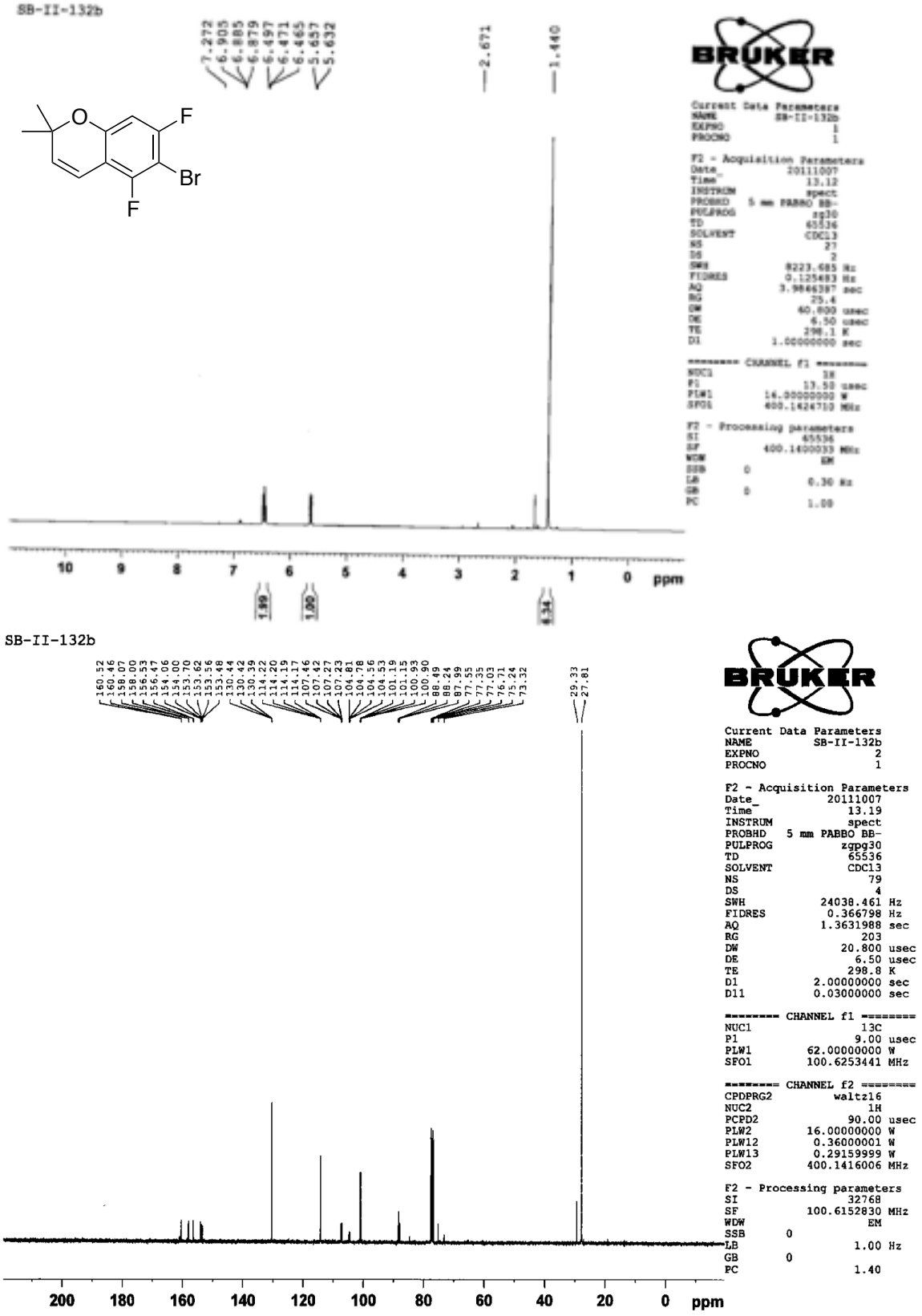


Elemental Composition Report

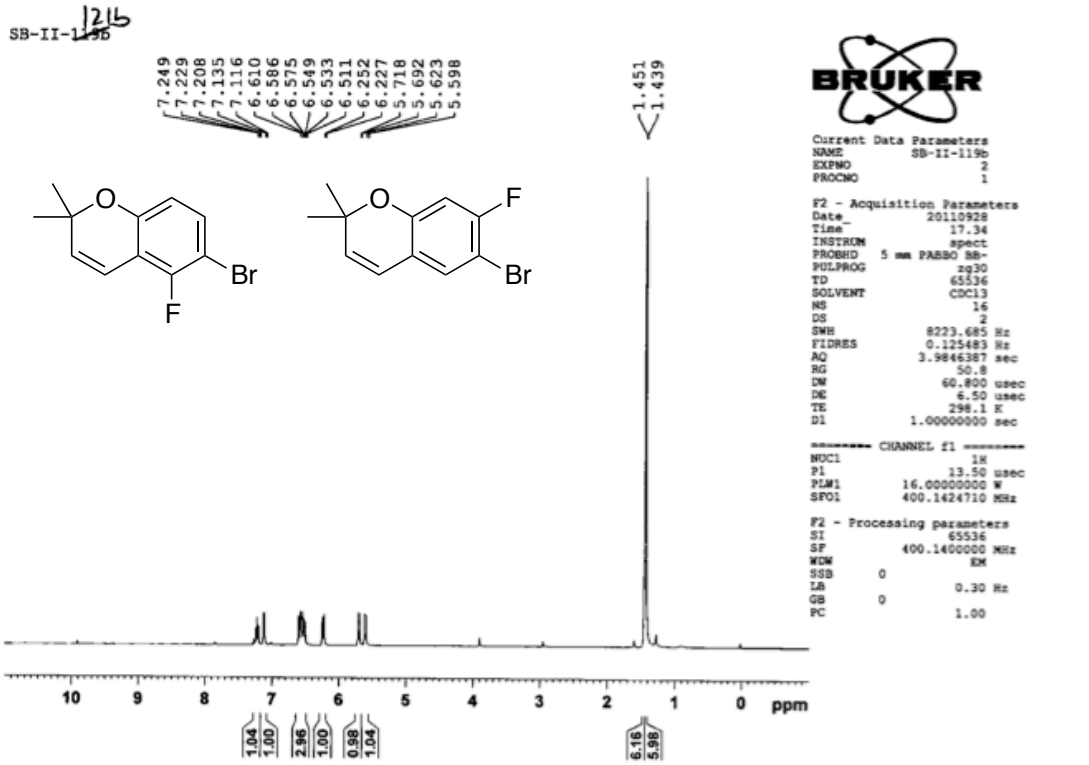
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
106 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-100 N: 1-15 O: 1-20 Br: 1-5

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
256.0333	256.0337	-0.4	-1.6	4.5	1.6	C11 H15 N O Br

6-bromo-5,7-difluoro-2,2-dimethyl-2*H*-chromene (S3l)

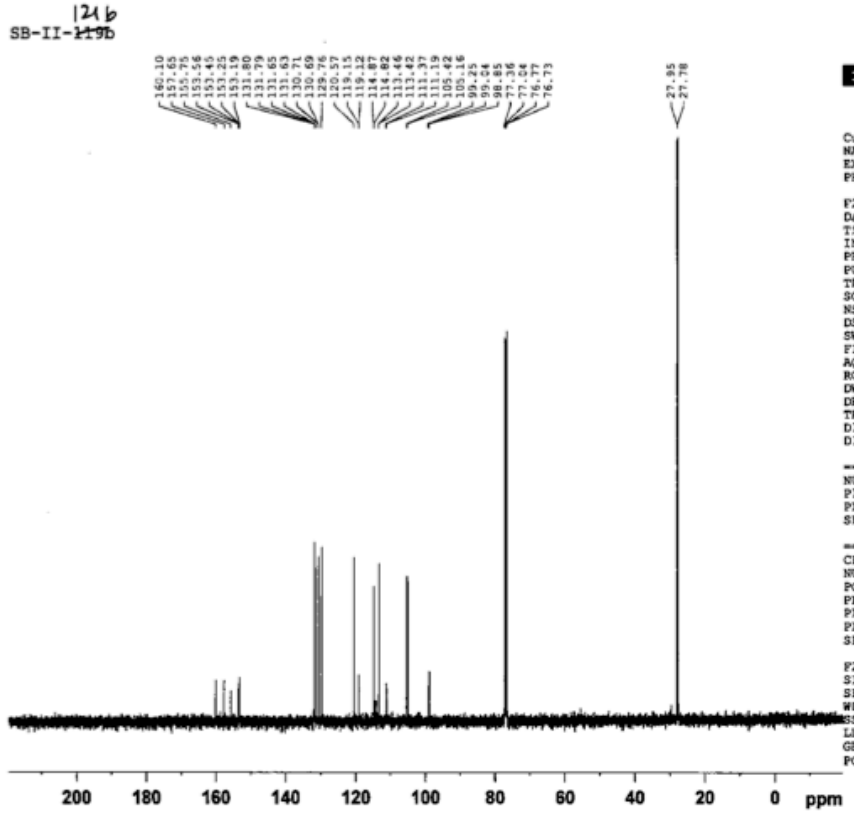


6-Bromo-5-fluoro-2,2-dimethyl-2*H*-chromene with 6-Bromo-7-fluoro-2,2-dimethyl-2*H*-chromene (1:1) (S3m)



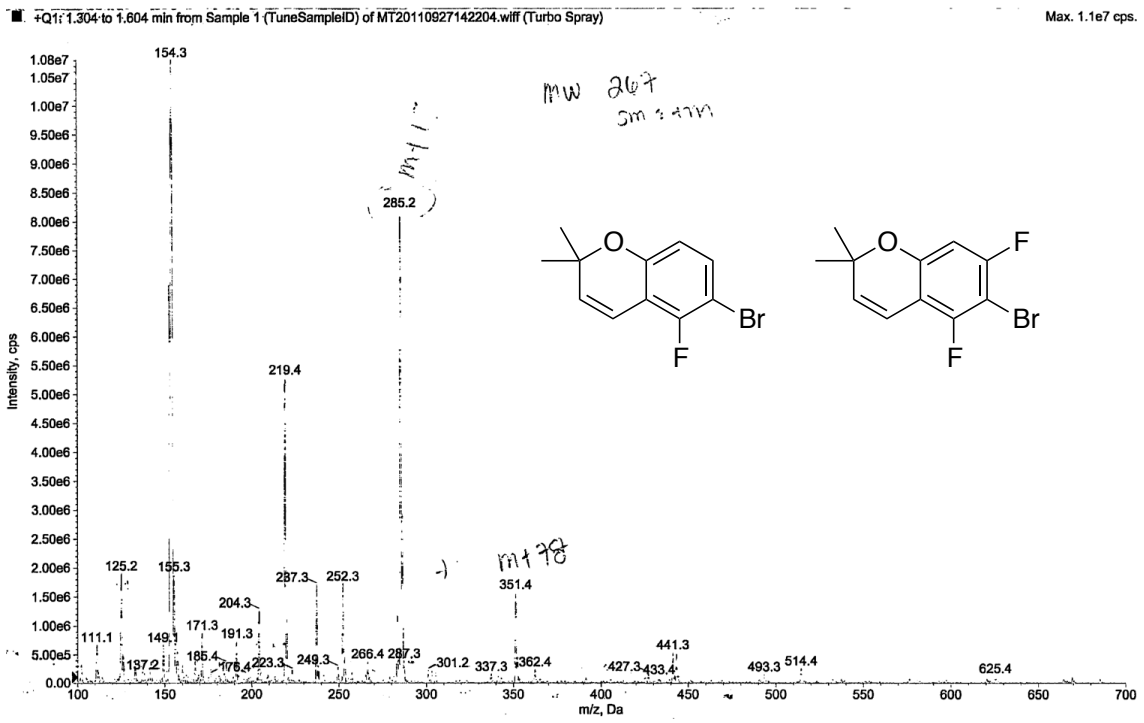
BRUKER

```
Current Data Parameters
NAME                  SB-II-119b
EXPNO                          2
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110928
Time                       17.34
INSTRUM                    spect
PROBHD    5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                     8223.685 Hz
FIDRES                  0.125483 Hz
AQ                      3.9846387 sec
RG                           50.8
DW                         60.800 usec
DE                          6.50 usec
TE                         298.1 K
D1                      1.00000000 sec

======== CHANNEL f1 ========
NUC1                          1H
P1                         13.50 usec
PLW1                   16.00000000 W
SFO1                  400.1424710 MHz

F2 - Processing parameters
SI                            65536
SF                     400.1400000 MHz
WDW                             EM
SSB                  0
LB                           0.30 Hz
GB                   0
PC                            1.00
```

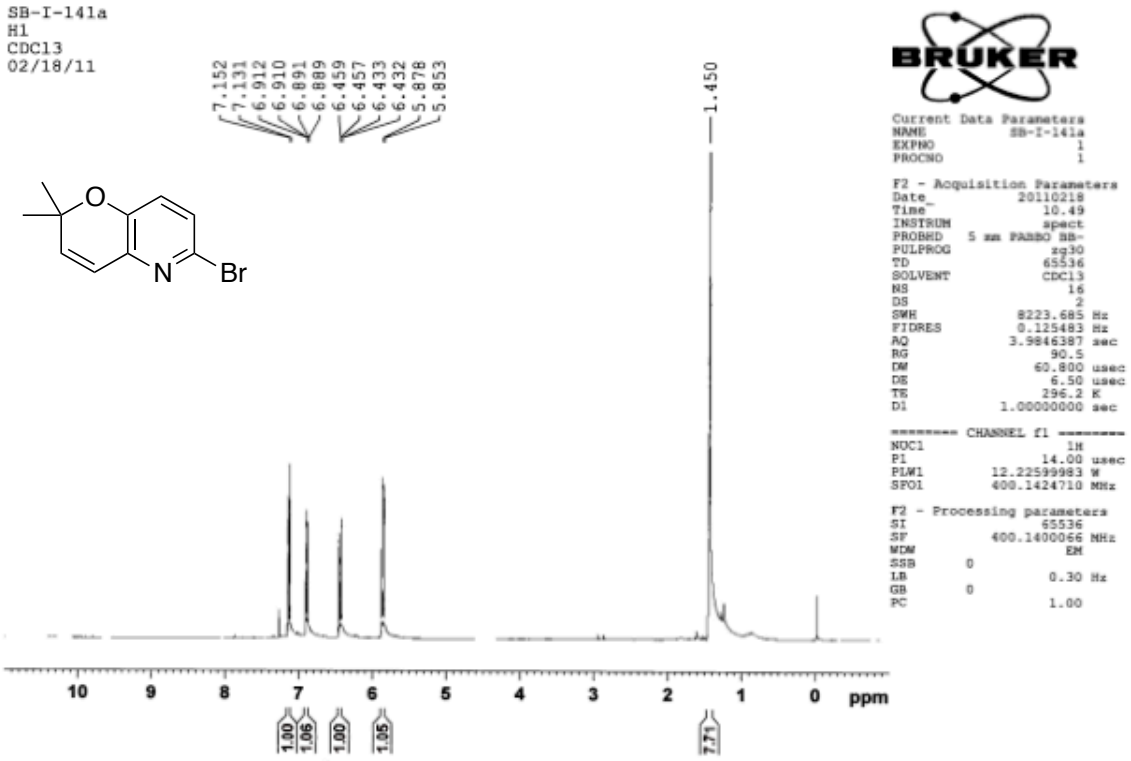


BRUKER

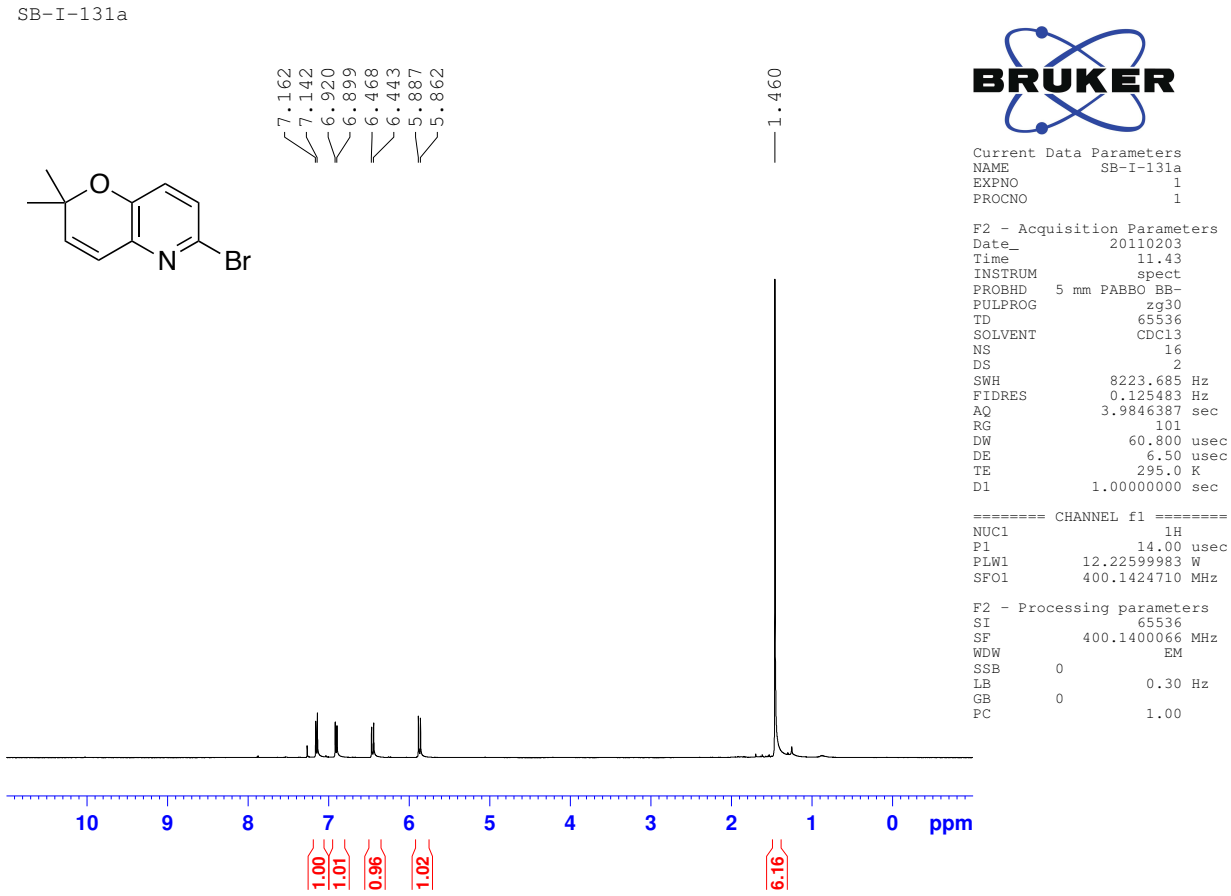
```
Current Data Parameters
NAME                  SB-II-119b
EXPNO                          3
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110928
Time                       17.42
INSTRUM                    spect
PROBHD    5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                           74
DS                            4
SWH                    24038.461 Hz
FIDRES                  0.366798 Hz
AQ                      1.3631988 sec
RG                           203
DW                         20.800 usec
DE                          6.50 usec
TE                         299.0 K
D1                      2.00000000 sec
D11                     0.03000000 sec

======== CHANNEL f1 ========
NUC1                          13C
P1                          9.00 usec
PLW1                   62.00000000 W
SFO1                  100.6253441 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                          1H
PCPD2                      90.00 usec
PLW2                   16.00000000 W
PLW12                   0.36000001 W
PLW13                   0.29159999 W
SFO2                  400.1416006 MHz

F2 - Processing parameters
SI                            32768
SF                     100.6152830 MHz
WDW                             EM
SSB                  0
LB                           1.00 Hz
GB                   0
PC                            1.40
```


+Q1: 1.304 to 1.604 min from Sample 1 (TuneSampleID) of MT20110927142204.wiff (Turbo Spray)
Max. 1.1e7 cps.
Intensity, cps
m/z, Da
154.3
285.2
219.4
125.2
155.3
287.3
252.3
204.3
351.4
171.3
191.3
111.1
149.1
137.2
185.4
176.4
223.3
249.3
266.4
287.3
301.2
337.3
362.4
427.3
433.4
441.3
493.3
514.4
625.4
MW 267
Br
F
O

6-Bromo-2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridine (S3n)



6-bromo-2,2-dimethyl-2*H*-pyrano[3,2-*b*]pyridine (S3n)




```
Current Data Parameters
NAME            SB-I-131a
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20110203
Time                11.43
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                   101
DW                60.800 usec
DE                 6.50 usec
TE                295.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 14.00 usec
PLW1         12.22599983 W
SFO1         400.1424710 MHz

F2 - Processing parameters
SI                 65536
SF          400.1400066 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```