Synthesis of Novel Sultam Scaffolds:

Method and Library Development

By

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Submitted to the graduate degree program in the Department of Chemistry and

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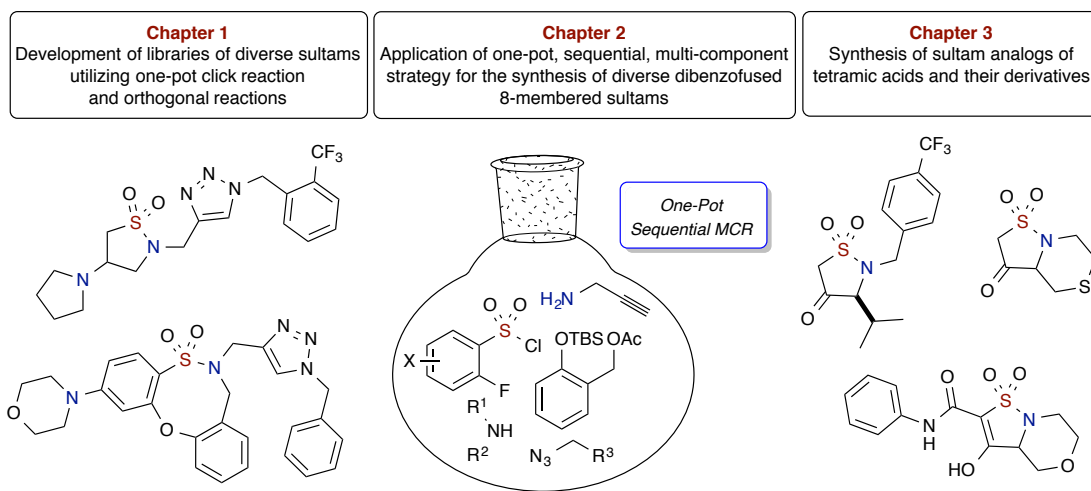

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Abstract

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University of Kansas, June 12th, 2015

The development of methods to produce diverse set of small molecules to be utilized as chemical probes in chemical biology is a continuing emerging area critical in the pursuit of broadening the understanding of biological pathways and search for new therapeutics and biological probes to improve human health. In particular, sultams as non-natural lactam surrogates have recently gained attention as a novel class of compounds with extensive chemical and biological profiles that will be further discussed in introduction to Chapter 1. The virtues of diversity-oriented synthesis (DOS) paired with "Click, Click, Cyclize" paradigm in designing methods and libraries for the production of novel and unique sultam compounds provide a facile and efficient pathway in achieving this goal. Despite these attributes, methodologies for the synthesis of sultams and their corresponding libraries are limited in literature relative to lactam surrogates. A more in detail analysis of this gap will be introduced in the introduction of each chapter. It is the purpose of this dissertation to develop novel methods and production of libraries based on scaffolds generated from these methods. Through these methods and libraries, we aim to produce various sultam compounds that present opportunities in accessing underexplored and underrepresented regions of chemical space with potentials for serving as chemical probes in search for unknown biological activities.

Figure A.1. *Outline of method development and library production presented through Chapter 1–3.*

Chapter 1	Chapter 2	Chapter 3
Development of libraries of diverse sultams utilizing one-pot click reaction and orthogonal reactions	Application of one-pot, sequential, multi-component strategy for the synthesis of diverse dibenzofused 8-membered sultams	Synthesis of sultam analogs of tetramic acids and their derivatives

An outline of the following chapters of this thesis is shown in Figure A.1. The goal of Chapter 1 is to introduce methods and library development previously reported from the Hanson group. The introduction reviews the libraries that utilize Click "3+2" Huisgen cycloaddition reaction and/or intermolecular nucleophilic aromatic substitution (S_NAr) for peripheral diversification. Then efforts on production of two novel sultam libraries based on one-pot Click-aza-Michael of RCM-derived sultam scaffolds and one-pot Click-S_NAr of "4+4" derived scaffolds.

Chapter 2 introduces a review of recent advances in synthesis of molecules containing triazole motifs via one-pot multicomponent Click reactions (MCR). This review is categorized into three sections, including 2-, 3-component MCR, 4-, 5-, 6-component MCR, and development of novel catalysts for Cu-catalyzed azide–alkyne coupling (CuAAC) reactions. This review will be then followed by studies towards application of one-pot, sequential, multicomponent reaction strategy for the facilitated

synthesis of "4+4" dibenzofused 8-membered sultam scaffolds and their analogs produced from 3-, 4-, 5-component reactions.

Lastly, Chapter 3 discusses recent advances in the synthesis of various biologically active tetramic acids and their analogs. The review is divided into three sections: synthesis of tetramic acids via Dieckmann reaction, via methods other than Dieckmann condensation, and modification of existing tetramic acids for diversification and studies towards reactivity profile of tetramic acids. Subsequent section of this chapter includes our recent work on synthesis of sultam analogs of tetramic acids via intramolecular sulfa-Dieckmann cyclization. Further diversifications utilizing condensation with isocyanates to produce 3-carboxamide substituted sultam analogs of tetramic acids are reported.

To my dearest family, Dad, Mom, and little brother
for their continuous love, help and support

and exciting. Paul has taught me not only what it is like to be a chemist but also how to deal with people, how to manage the group, and of course how to appreciate what a dollar is worth. I must say my time in Paul's group has been crazy, exciting, stressful, but yet fun and enjoyable at the same time. The incredibly diverse group also provided a chance for me to understand and interact with people from different backgrounds. Paul, I am very grateful for what you have done for me and also I am glad that I chose you as my supervisor.

I would like to thank Susanthi, Soma, Joanna, Jung Ho, and Naeem for the help, support and guidance during my Ph.D. and also former post docs including Alan, Thiwanka, Qin and Rambabu for their advice as well. In particular, I would like to thank Alan and Thiwanka for the great time I spent with them as my mentors. My undergraduate students John, Junsik, and Taylor, it was my privilege working with you guys. I appreciate and really am grateful to all Hanson Group members – past and present – I will never forget the time I spent with them going through this journey.

I would also like to acknowledge my thesis committee members: Professors Altman, Benson, Mure and Rubin for their help and guidance during my Ph.D. Thank you for your patience. In addition, special thanks to other research groups in Malott Hall, including all of the Tunge, Rubin, Malinakova, Clift and Prisinzano group members.

Lastly, I am very thankful to Dr. Gerald Lushington, Patrick Porubsky and Ben Neuenswander for providing enormous help with both purification and *in-silico*

Synthesis of Novel Sultam Scaffolds:

Method and Library Development

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
ABPP	activity-based protein profiling
ATP	Adenosine triphosphate
MeCN	acetonitrile
aq	aqueous
BEAD	benzylethyl azodicarboxylate
Bn	benzyl
BnBr	benzyl bromide
BCP	build-couple-pair
Boc	*tert*-butyloxycarbonyl
t-BuOH	*t*-Butanol
$CHCl_3$	chloroform
CuI	copper iodide
CAP	complementary ambiphilic pairing
cat.	catalytic
COSY	correlation spectroscopy
C	carbon
Cs_2CO_3	cesium carbonate
CsF	cesium fluoride
Cl	chlorine
CA	chloroacetamides
CAP	complementary ambiphile pairing
CP	complementary pairing
CMLD	Center of methodology and library development
CuBr	copper bromide
CDK2	Cyclin-dependent kinase 2
DABCO	1,4-Diazabicyclo[2.2.2]octane

DBU	1,8-diazabicycloundec-7-ene
DCM (CH$_2$Cl$_2$)	dichloromethane
Et$_2$O	diethyl ether
DIAD	diisopropyl azodicarboxylate
DIC	*N,N'*-Diisopropylcarbodiimide
DIPEA/Hünig's base	*N,N'*-Diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Boc$_2$O	Di-tert-butyl dicarbonate
DOS	diversity oriented synthesis
DMAP	4-(dimethylamino)pyridine
DTT	Dithiothreitol
Da	daltons
E$_+$	electrophile
Eq.	equivalent
Et	ethyl
EtOAc	ethyl acetate
EDC (EDCI)	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
FG	functional group
FP	fluorophosphonate
FDA	Food and Drug Administration
FCMA	formimidate carboxylate mixed anhydride
GC	gas chromatography
GSTO1	glutathione S-transferase omega 1
HFIP	hexa-fluoroisopropyl
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
ABHD6	α-β hydrolase-6

NHS	hydroxysuccinimidyl
h	hours
Hsp90	heat shock protein 90
Hz	hertz
HCV	hepatitis C virus
HTS	high throughput screening
HIV	human immunodeficiency virus
HSA	human serum albumin
HOBt	1-hydroxybenzotriazole
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
IA	iodoacetamides
IR	infrared radiation
IC_{50}	inhibitory concentration at 50%
IMDA	Intermolecular Diels-Alder
^{i}Bu	isobutyl
^{i}Pr	isopropyl
Leu	Leucine
LiOH	Lithium hydroxide
LCMS	Liquid chromatography–mass spectrometry
LG	leaving group
M	molarity
mW	microwave
MeOH	Methanol
MeI	methyl iodide
MW	molecular weight
MLPCN	Molecular Libraries Probe Production Centers Network
MAGL	monoacylglycerol lipase
Mmol	millimole(s)

MsCl	methanesulfonyl chloride
7-mmc	7-mercapto-4-methyl-coumarin
MCR	multi-component reactions
MFS	multifusion similarity
NSAIDs	Non-steroidal anti-inflammatory drugs
NMR	nuclear magnetic resonance
NIH	National Institute of Health
NEP	neutral endopeptidase 24.11
Nuc/Nu	nucleophile
^{n}Bu	n-Butyl
OMe	methoxy
PMB	*para*-methoxybenzyl
ppm	parts per million
PBPs	penicillin binding proteins
Ph	phenyl
PTSA	*p*-toluenesulfonic Acid
XLogP	partition coefficient
PI3K	phosphoinositide 3'OH kinase
K_2CO_3	potassium carbonate
PCA	principal component analysis
PMI	principal moments of inertia
PEM	protein epitope mimics
PKC	protein kinase C
RCM	ring closing metathesis
rt	room temperature
S	sulfur
Sat'd	saturated
SAR	structure activity relationship
SHs	serine hydrolases

Si	silicon
NaN$_3$	sodium azide
NaO^{t}Bu	sodium *tert*-Butoxide
NaHMDS	sodium hexamethyldisilazide
SL-PTC	solid-liquid phase transfer catalysis
SPE	solid phase extraction
SM	starting material
SAR	structure-activity-relationship
TACE	TNF-α converting enzyme
TBAF	Tetrabutyl ammonium fluoride
^{n}Bu$_4$NBr	tetra-n-butylammonium bromide
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
K$_3$PO	tripotassium phosphate
PPh$_3$	triphenylphosphine
TLC	thin layer chromatography
^{t}Bu	*tert*-butyl
Et$_3$N	triethylamine
TEBA	triethylbenzylammonium chloride
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TLC	thin layer chromatography
TLR4	Toll-like receptor 4
TopoPSA	topological polar surface area
TPP	triphenylphosphine
TOS	target oriented synthesis
Val	valine
VEGF-R2	vascular endothelial growth factor receptor-2
H$_2$O	water

Chapter 1

Development of Libraries of Diverse Sultams

Utilizing One-Pot Click Reaction

and Orthogonal Reactions

Chapter 1: Development of Libraries of Diverse Sultams Utilizing One-Pot Click Reaction and Orthogonal Reactions

> **1.1** Introduction – Sultam Libraries Generated by Peripheral Diversification Involving Intermolecular S_NAr or Triazole Formation
>
> **1.2** Library Production of RCM-Derived Scaffold via One-Pot Click-aza-Michael
>
> **1.3** Library Generation of "4+4" Scaffold involving One-Pot Click-S_NAr
>
> **1.4** Conclusion

1.1 Introduction

The need for discovery of new pharmaceutical leads and small molecule probes has led to efforts focusing on the production of small molecule libraries to be utilized in high-throughput screening (HTS). High-throughput screening of libraries of small molecules has recently emerged as a viable means of detecting less well-characterized targets, either individually or as a group of targets.[1] In this regard, diversity-oriented synthesis (DOS) presents an attractive pathway in accessing underexplored and underrepresented regions of chemical space in search for novel chemical probes that could aid in the detection of both known and unknown targets.[2] Efforts in DOS have been driven by the development and emergence of new methods, protocols and technologies to access diverse collections of small molecules in a rapid and facilitated manner.[3]

Sultams (cyclic sulfonamide analogues) represent a class of non-natural lactam surrogates that have surfaced in recent years as important targets in drug discovery due to their extensive chemical and biological profiles (Figure 1.1).[4] Biological activities include anti-inflammatory, anti-HIV, and inhibition of HIV to name a few. However, a literature

search in 2015 revealed that sultams are highly underrepresented relative to lactams.[5] To date, there are only two previous reports on synthesis of chemical libraries of sultams (Figure 1.2).[6] This presents opportunities in further producing varieties of sultam compounds that can reside in a relatively unoccupied chemical space and advance studies towards probing novel biological targets and activities.

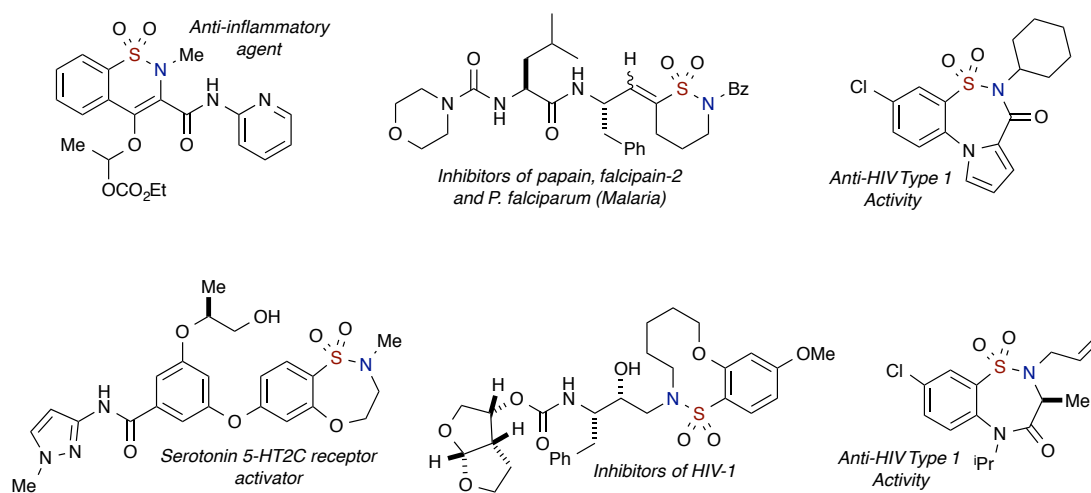**Figure 1.1.** *Representative examples of bioactive sultams.*

Figure 1.2. *Two previous reports of sultam libraries.*
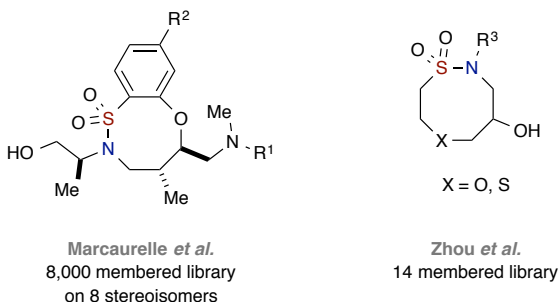
In this regard, efforts have focused on the development of methods involving rapid and facilitated protocols for the synthesis of diverse sultam scaffolds provides means for accessing novel structures to probe relatively unoccupied chemical space (Figure 1.3).[7]

Figure 1.3. *Representative sultams prior to 2010 from the Hanson group..*
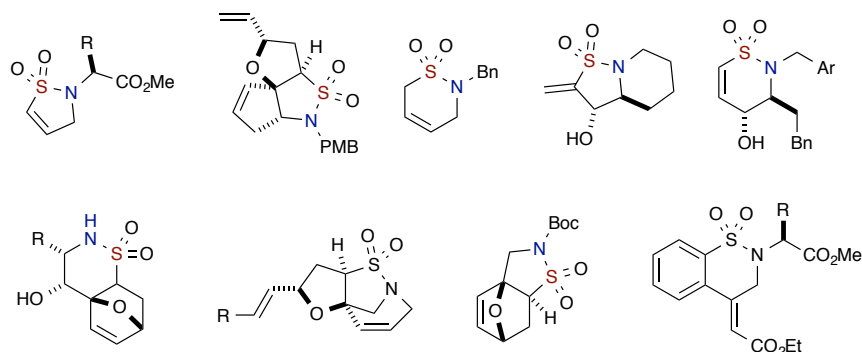
To date, the Hanson group has focused their attention on methods development to novel S- and P-heterocycles (Figures 1.4 and 1.5, P-heterocycles not shown)[8] with biological and synthetic utility, as well as the corresponding library synthesis to access varied sultams. This thesis is centered on two scaffolds, namely dibenzo-oxathiazocine dioxide and isothiazolidin-4-one 1,1-dioxide (Figure 1.6), as well as subsequent library production to generate analogs. Previous method work had developed a facile route to formal name (then parenthetically 4+4 scaffold). In the context of this thesis, we evaluated the uniqueness, vide infra (see Chp 2, page 59), as well as diversity (PMI analysis Chp 1, page 25) for this scaffold, which in turn inspired the design of libraries around it. Before detailing our library work regarding the "4+4" scaffold, this chapter will review libraries reported by the Hanson group utilizing Click reactions and/or intermolecular S_NAr reactions is introduced. Subsequently, the design and production of two libraries involving one-pot Click-aza-Michael of RCM-derived scaffolds and one-pot Click-S_NAr of "4+4" derived scaffolds are

presented in Sections 1.2 and 1.3 (Figure 1.7). These two scaffolds contain electrophilic positions that may be readily utilized for further diversification. Sultam **1.7.A** contains α,β-unsaturated sulfonamide, which is a Michael acceptor that possesses potentials in adding various heteroatom nucleophiles, and also a terminal alkyne that is utilized in "3+2" Huisgen cycloaddition to attach various triazoles. Sultam **1.7.B** contain aryl fluoride moiety that can be functionalized via Cu-catalyzed *N*-arylation, and also a terminal alkyne as well.

Figure 1.4 *Summary of benzofused sultams developed by the Hanson group.*
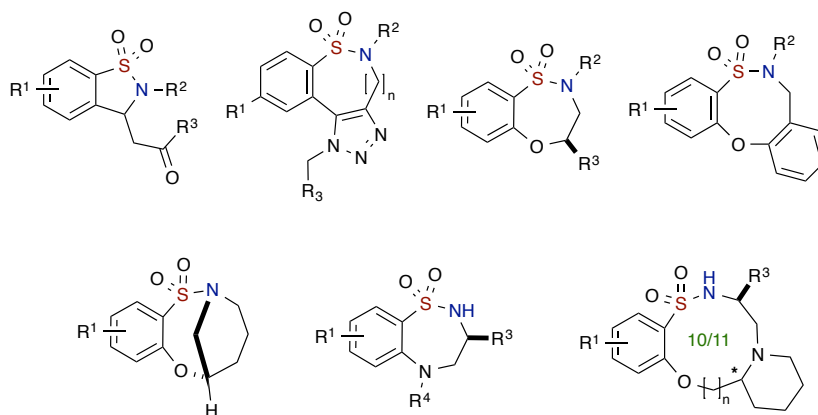
Figure 1.5. *Summary of library compounds from the Hanson group.*

S_NAr	Click/Suzuki-Miyaura	Alkylation/S_NAr	S_NAr
J. Comb. Chem. **2011**, 850	ACS Comb. Sci. **2011**, 244	ACS Comb. Sci. **2011**, 653	J. Flow Chem. **2011**, 32

OTP	Click	S_NAr
ACS Comb. Sci. **2012**, 268	ACS Comb. Sci. **2012**, 456	BJOC **2012**, 1293
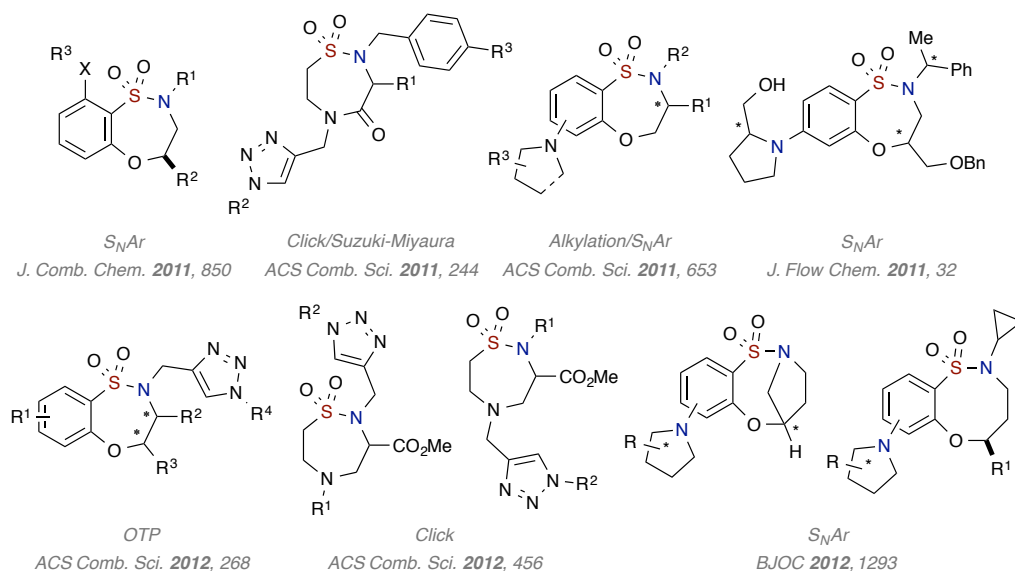
Figure 1.6. *Two main scaffolds to be discussed in this thesis.*

dibenzo-oxathiazocine dioxide

isothiazolidin-4-one 1,1-dioxide
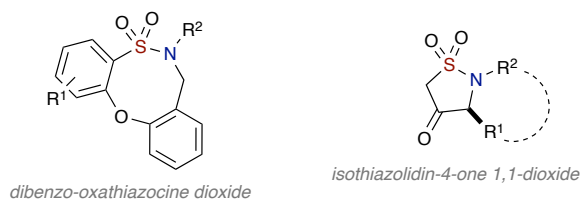
Figure 1.7. *Overview of two library scaffolds and their diversification plan.*

Electrophilic center

1.7.A "3+2" partner

"3+2" partner

Electrophilic center

1.7.B
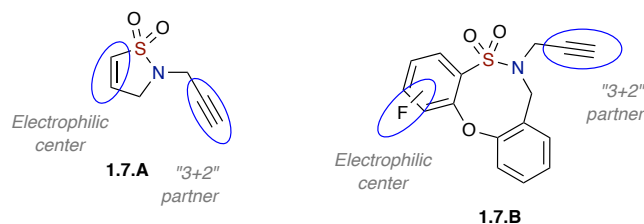
The following libraries will be discussed in the subsequent section:

-   S_NAr diversification of scaffolds derived from epoxide ring opening-S_NAr cascade sequence.

-   Pd-catalyzed Suzuki-Miyaura coupling and [3+2] Huisgen cycloaddition of thiadiazepan-1,1-dioxide-4-ones

-   Alkylation/S_NAr diversification of amino-benzothiaoxazepine-1,1-dioxide scaffolds

-   S_NAr diversification for the production of chiral benzothiaoxazepine-1, 1-dioxides

-   Application of OTP reagent for synthesis of chiral sultams with triazole moieties

-   Library of triazolated 1,2,5-thiadiazepane-1,1-dioxides via Click diversification

-   Intermolecular S_NAr for generation of unique chiral benzoxathiazocine 1,1-dioxides

In 2010, Hanson, Rolfe and coworkers reported the preparation of library compounds based on scaffolds derived from an epoxide ring opening-S_NAr cascade sequence.[9] By having a fluoro-substituent on the 6-position of benezenesulfonyl chloride, the group envisioned that it is possible to diversify the 6-position via S_NAr with various *N-*, *O*-nucleophiles.   The S_NAr reaction of sultam **1.1.1** with *N*-nucleophiles proceeded successfully in the presence of Cs_2CO_3 and DMSO in microwave heating for 30 minutes at 150 °C, whereby purification of excess amines was done by simple silica SPE after reaction (Scheme 1.1).   However, S_NAr with phenol nucleophiles required 3 equiv. of the nucleophile and purification via silica SPE was not possible, making it difficult to be applied to a parallel library synthesis platform due to requirement of aqueous workup. Application of previously reported high-load, soluble scavenger oligomeric dichlorotriazine ($ODCT_{50}$) derived from ring-opening metathesis polymerization (ROMP) was envisioned to remove unreacted excess phenols from the crude reaction mixture.[10] Original scavenging conditions required 10 hours and thus were not ideal for parallel format. These conditions were modified so that $ODCT_{50}$ could be used in microwave conditions and thus the reaction time was reduced to 30 minutes at 50 °C, which yielded final crude purity over 95 %. With these results in hand, the authors reported the synthesis of a 78-member library. Overall, 59 of 78 members provided the desired products in 12-82 % yield with 47 compounds in 90 % or higher purities.

Scheme 1.1. *S_NAr with various N-, O-nucleophiles and sequestration of excess reagents with ODCT.*
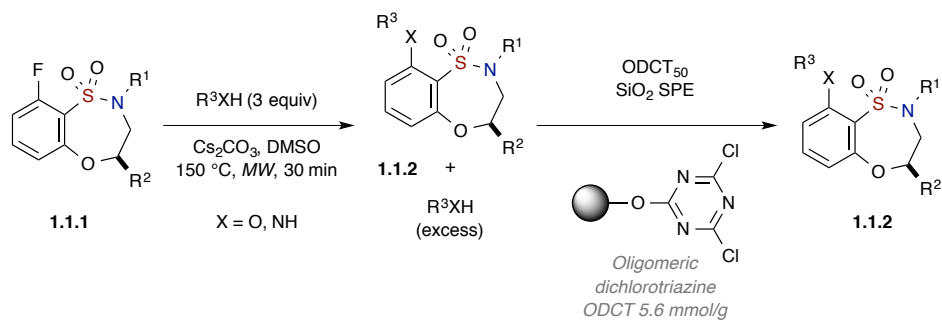
In 2011, Hanson, Fenster, Long and coworkers reported an automated synthesis of 184-member library of thiadiazepan-1,1-dioxide-4-ones.[11] Sultam scaffolds **1.2.1** were generated based on a strategy that was previously reported, where a sequence termed "Click, Click, Cyclize" was employed en route.[12] By applying 4-bromobenzyl bromide as the alkylation reagent and propargylamine as the aza-Michael partner, two handles for peripheral diversification were generated for their use in Pd-catalyzed Suzuki-Miyaura coupling and [3+2] Huisgen cycloaddition, respectively (Scheme 1.2). Initial studies revealed that the two reactions could be performed in a sequential fashion, whereby usage of immobilized copper catalyst on Amberlyst (A-21•CuI) for [3+2] Huisgen cycloaddition allowed for facile removal of copper catalyst by simple filtration.[13] Subsequent removal of solvent through concentration *in vacuo*, followed by addition of palladium catalyst in a mixture of DME/H$_2$O and cesium carbonate, and the addition of boronic acids resulted in formation of desired peripherally diversified sultams **1.2.2**. This sequential two-step reaction was applied to automated Chemspeed Accelerator SLT-100 synthesizer for the production of 225 compounds,[14] whereby 184 compounds passed through preparative/mass-directed HPLC purification. The authors noted that there was not a definitive trend between

yields and substrates, although it was evident that reactions involving thiopene boronic acid resulted in very little or no presence of products.

Scheme 1.2. *Click diversification utilizing immobilized Cu catalyst and Suzuki-Miyaura coupling.*

R^1 = Me, *i*-Pr, *i*-Bu
R^2 = MOM-OCH$_2$CH$_2$, furfuryl,
      1,3-dioxane-CH$_2$CH$_2$, Cy-CH$_2$
R^3 = Ph, 4-F-Ph, 4-Pyr, 4-Cl-Ph, 2-Thiophene,
      4-MeO-PH, 4-Me-Ph, 3,4-diMeO-Ph,
      3-(NMe$_2$)-Ph, 3,4-diCl-Ph,
      CH$_3$CH$_2$CH$_2$CHCH, 4-MeO-3-Pyr,
      4-F-3-Pyr, 3-(CH$_2$OH)-Ph, 4-Cl-3-Pyr
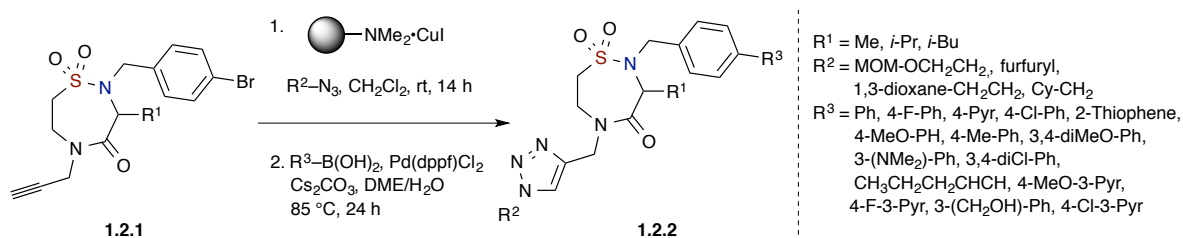
In 2011, Hanson, Rolfe and coworkers reported a library synthesis based on scale out of amino-benzothiaoxazepine-1,1-dioxide scaffolds utilizing a microwave-assisted S$_N$Ar protocol that was followed by peripheral diversification using S$_N$Ar with various cyclic amine nucleophiles. [15] Generation of the core amino-benzothiaoxazepine-1,1-dioxide scaffolds was enabled by facilitated process involving microwave-assisted, continuous-flow organic synthesis (MACOS) protocol.[16] With this technology in hand, scale out of the desired scaffolds **1.3.2** was achieved via intramolecular S$_N$Ar in the presence of ^{t}BuOK as base in DMSO, under microwave irradiation at 80 °C, 40 W power, and flow rate of 100 μLmin^{-1} (Scheme 1.3). Subsequent alkyation of sulfonamide nitrogen of **1.3.2** with Cs$_2$CO$_3$ as base in DMF at 50 °C, followed by S$_N$Ar of the resulting alkylated scaffold with various cyclic amine nucleophiles **1.3.3** in DMSO under microwave conditions at 180 °C for 50 min furnished library compounds **1.3.4** in good overall yields.

Scheme 1.3. *Scale out of scaffold **1.3.2** and diversification using alkylation and S$_N$Ar*.
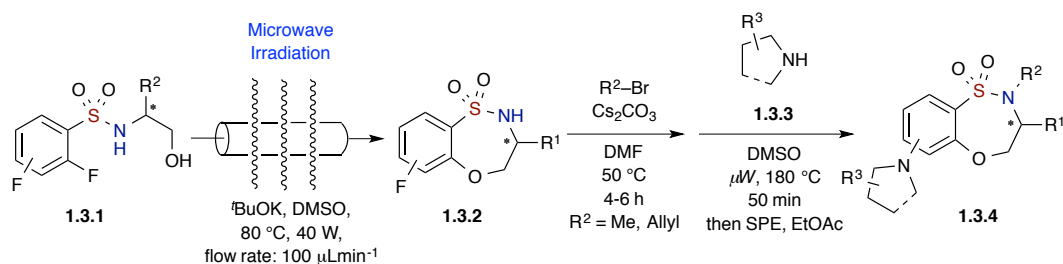
In 2011, Organ, Hanson and coworkers reported scale out of stereochemically rich sultams via MACOS and their corresponding library compounds involving intermolecular S_NAr.[17] The authors designed a collection of stereochemically rich benzofused sultams that can be rapidly generated by commercially available chiral starting materials. A two-step procedure was designed whereby a combination of chiral 2° sulfonamides, epoxides, and amino alcohols are utilized for the synthesis of core benzothiaoxazepine-1,1-dioxides via an epoxide opening/S_NAr cyclization sequence from a previously reported method (Scheme 1.4a).[18] Sequential intermolecular S_NAr diversification then would allow for a generation of a stereochemically-rich sultam library (Scheme 1.4b). Applying the optimized conditions from the previous report,[18] reaction conditions for application to MACOS setting was investigated. Epoxide ring opening/S_NAr sequence of sulfonamide **1.4.1** and epoxide **1.4.2** in the presence of DBU as base at 180 °C with a flow rate of 100-200 µLmin⁻¹ furnished scaffold **1.4.3** in gram quantities. Chiral, non-racemic sultam **1.4.4** was then reacted with various chiral cyclic amines in DMSO under Anton Parr Synthos 3000® microwave platform[19] at 180 °C for 50 min, followed by dilution, filtration, and purification via column chromatography to afford a collection of chiral benzothiaoxazepine-1, 1-dioxides compounds in good yields (Scheme 1.4.b).

Scheme 1.4. *Scale out synthesis of scaffold **1.4.3** via MACOS and library production utilizing intermolecular S_NAr.*

(a) **1.4.1** + **1.4.2** → **1.4.3**

DBU, DMSO, 180 °C, 200 W, Flow rate 100 - 200 μL/min

(b) **1.4.4** → **1.4.5**

1. DMSO, μW, 180 °C, 50 min
2. SPE, EtOAc

All 8 Stereoisomers
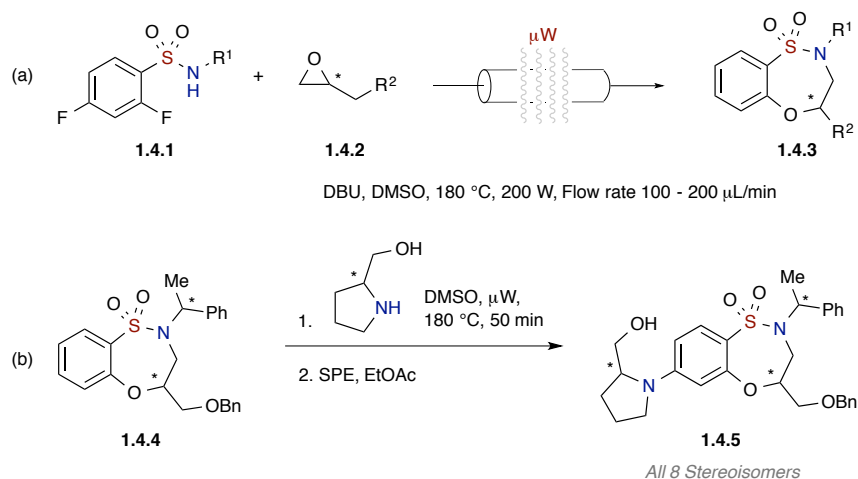
In 2012, Hanson, Faisal and coworkers demonstrated a combination of MACOS technology with ring opening metathesis polymerization (ROMP)-derived oligomeric triazole phosphates (OTP$_n$) for the synthesis of a library of chiral sultams with triazole moieties.[20] As shown in examples above, much attention has been focused on the development of facilitated methods for rapid access to a variety of core sultam scaffolds for HTS. ROMP-derived reagents have been reported in variety of synthetic applications due to the numerous beneficial attributes such as being bench stable, free-flowing solids, and readily soluble in variety of solvents.[21] Building upon these efforts, the authors demonstrated the application of ROMP-derived OTP reagents for facilitated installation of triazole moieties on scaffolds readily prepared via MACOS technology (Scheme 1.5). Scaffold **1.5.1**, which was produced in large quantities through MACOS platform, was reacted with OTP reagent **1.5.2** in the presence of Cs_2CO_3 and NaI in DMF at 90 °C to produce (triazolyl)methylated sultam **1.5.3** in good yields. Upon completion, the work up procedure was facilitated by evaporation of DMF, dilution in EtOAc, and filtration via SiO_2

SPE and sequential evaporation afforded clean products without the need for purification via column chromatography.

Scheme 1.5. *Application of MACOS and OTP reagents for the library production of chiral sultams via purification-free method.*
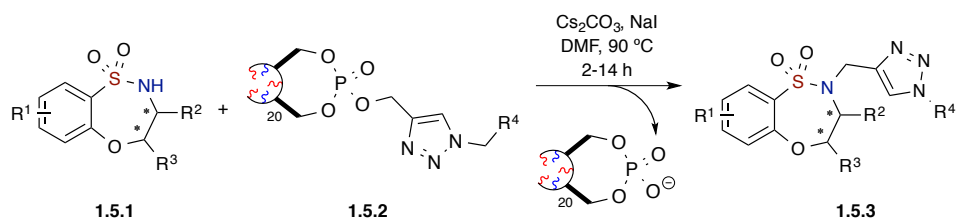
This method was next further extended to generation of library based on scaffolds synthesized from the double aza-Michael sequence in 2012. Hanson, Zang and coworkers reported production of a library of triazolated 1,2,5-thiadiazepane-1,1-dioxides utilizing scaffolds generated by the double aza-Michael pathway.[22] Building upon the previous report,[23] using two routes based on usage of propargylamine or propargyl bromide afforded two types of triazolated 7-membered sultams with the triazole moieties in different positions (Scheme 1.6). The first route employed propargyl bromide as the alkylating reagent on the sulfonamide nitrogen **1.6.1** to afford propargylated sulfonamide **1.6.2**. Subsequent elimination/double-aza-Michael sequence, followed by Cu-catalyzed [3+2] Huisgen cycloaddition furnished *N*-triazolated sultam scaffold **1.6.3**. The alternate route then involves alkylation of the secondary sulfonamide **1.6.1** to furnish **1.6.4**, followed by addition of propargylamine as the double aza-Michael partner to attach a propargyl moiety in a different position. Subsequent [3+2] Huisgen cycloaddition afforded triazolated 7-membered sultam **1.6.5** bearing the triazole functionality in an alternate location. The elimination/double-aza-Michael sequence was then applied to Chemspeed Accelerator

(SLT-100)[14] to produce a 96-member library, where 94 compounds passed with an average of 58 mg and average purity of 94 %.

Figure 1.6. *Click diversification on DaM-derived scaffolds.*
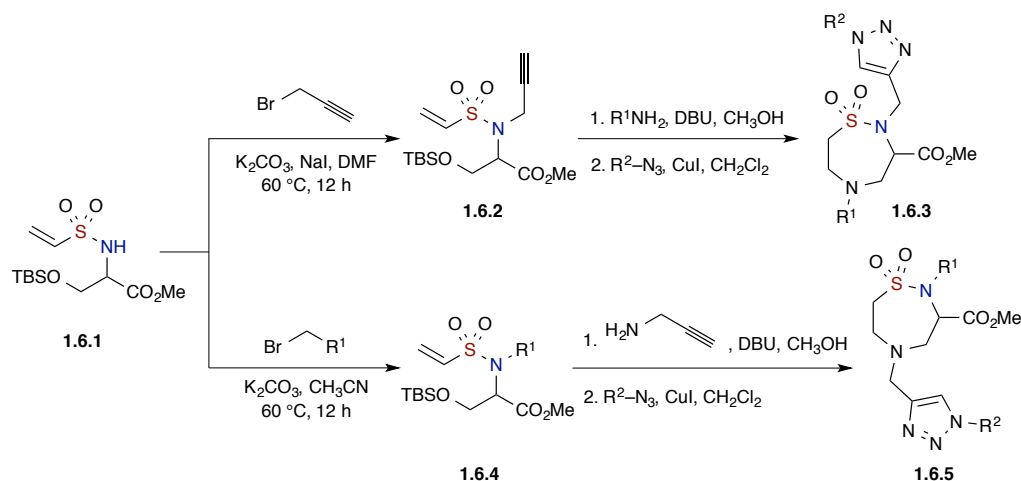
In 2012, Hanson, Loh and coworkers reported synthesis of 80-member library of unique chiral benzoxathiazocine 1,1-dioxides by a microwave-assisted, intermolecular S_NAr diversification pathway.[24] Gram quantity synthesis of eight proposed scaffolds were achieved through the use of sulfonylation, Mitsunobu alkylation, and S_NAr to generate all stereoisomers of each core following previous reports (Scheme 1.7). Each scaffold was prepared in 2.5 g scale. A variety of chiral amine/amino alcohol nucleophiles were utilized for peripheral diversification via intermolecular S_NAr with benzoxathiazocine 1,1-dioxides **1.7.1** and **1.7.2** to produce a library of chiral sultams in good yields. Optimized reaction condition was obtained in absence of base, with 5 equiv. of amine **1.7.A-J**, at a concentration of 0.5 M in DMSO under microwave irradiation at 180 °C for 50 min.

Scheme 1.7. *Synthesis of 80-member library of chiral sultams via S_NAr diversification.*

8 scaffolds of each isomers

1. R⟨pyrrolidine⟩NH

DMSO, μW
180 °C, 50 min

2. SPE, 10% MeOH
in CH₂Cl₂

F = 4-, 6-
R¹ = H, Me

1.7.1 **1.7.2** **1.7.3** **1.7.4**

Amine nucleophiles

1.7.A **1.7.B** **1.7.C** **1.7.D** **1.7.E** **1.7.F** **1.7.G** **1.7.H** **1.7.I** **1.7.J**
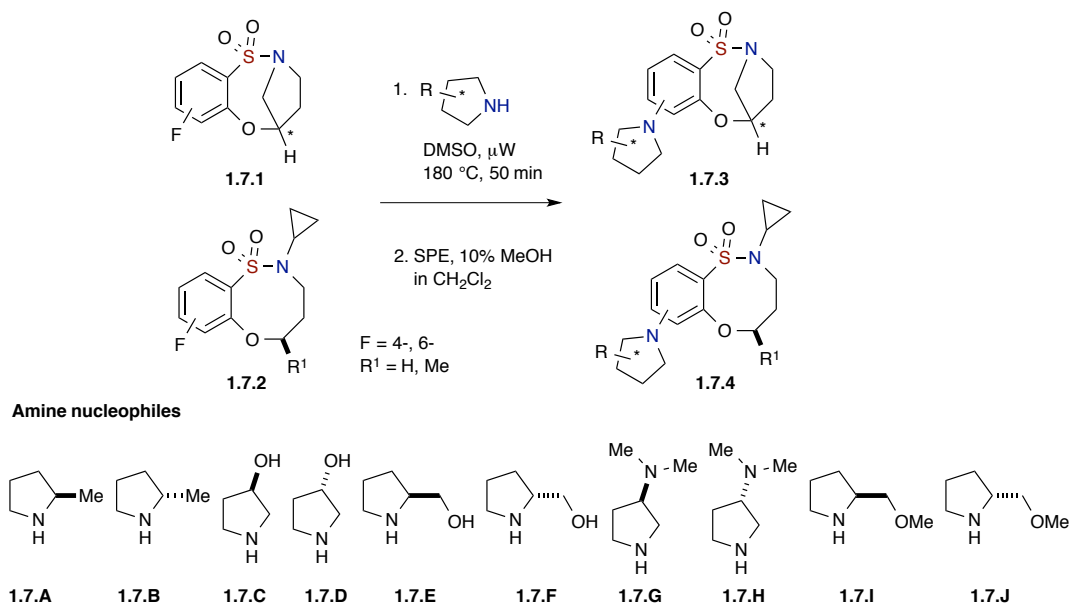
In summary, Hanson and workers have demonstrated the development of novel methods for the production of library compounds based on sultam scaffolds. Building upon these accounts, the following sections details our efforts in this regard by utilizing the Click reaction and its corresponding orthogonal reactions.

1.2 Library Production of RCM-Derived Scaffold via Click-aza-Michael

Amongst numerous bioactive sultam compounds, β-amino sultams and their corresponding sulfonate analogues are a relatively new chemotype that has shown interesting biological properties. Such reports include the inhibition of HIV-1 replication and antibacterial activity (Figure 1.2).[25] However, reports of methods to generate these cores are rather limited in the literature. In this regard, the production of library of compounds bearing β-sultam cores would allow to access a more diverse array of this class of scaffolds for further biological studies. In this section, efforts towards the generation of

diverse β-sultam, isothiazolidine 1,1-dioxide, bearing triazole moieties and tertiary amines are introduced.[26]

Figure 1.2. *Representative examples of bioactive β-sultams and sulfonates.*

1.2.A

HIV-1(IIB)-specfic reverse
transcriptase inhibitors

1.2.B

1.2.C

Bacterial serine protease inhibitors
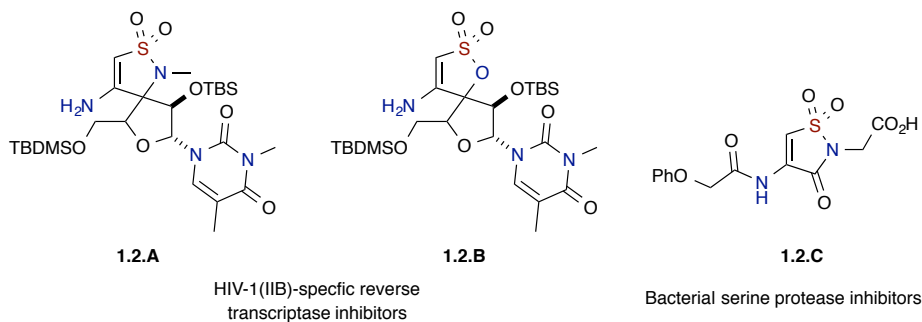
The synthesis of β-sultam libraries was envisioned by the diversification of core dihydroisothiazole 1,1- dioxide scaffold **1.8.4** via a one-pot, multicomponent protocol pairing an aza-Michael diversification reaction with other orthogonal reaction pathways (Scheme 1.8b). The corresponding core scaffold 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **1.8.4** was rapidly generated on multigram scale via a previously reported 3-step sulfonylation, RCM, propargylation protocol starting from 2-chloroethane sulfonyl chloride **1.8.1** (Scheme 1.8a).[27] Notably, the addition of metathesis catalyst [(IMesH$_2$)(PCy$_3$)(Cl)$_2$Ru=CHPh; **G-II**],[28] in 5 equal portions of 0.5 mol % (total 2.5 mol %) every 30 min was essential for maintaining the observed high conversion of the RCM cyclization.

Scheme 1.8. *Gram synthesis of core scaffold **1.8.4** via RCM and proposed Click/aza-Michael (ClaM) strategy.*
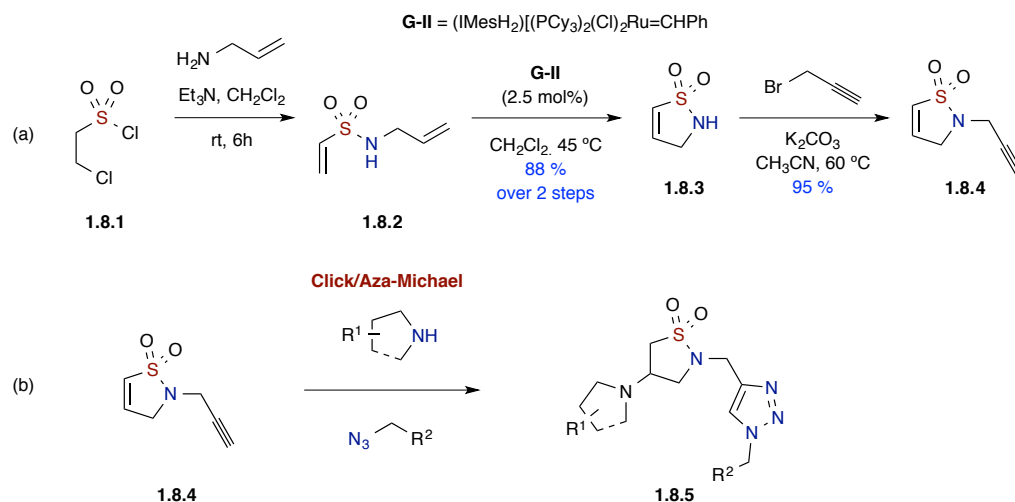
With the desired core sultam **1.8.4** in hand, initial efforts focused on the diversification of the core via an aza-Michael or Click reaction separately. After successful diversification of **1.8.4** utilizing either reaction in high yields, the combination of both reactions in a one-pot protocol was investigated. In this regard, preliminary studies for one-pot Click/aza-Michael protocol with azide **G** and pyrrolidine **6** was investigated (Table 1.1). An initial attempt combined both reaction conditions into the same pot (Table 1.1, entry 1) that yielded the desired product in 62 % yield. This yield was improved to 96 % after increasing the CuI catalyst load to 30 mol % (Table 1.1, entry 2), while additional optimization led to the use of lower equivalents of amine and base without affecting the yield (Table 1.1, entry 6).

Table 1.1. *Optimization of one-pot click/aza-Michael reaction conditions*.
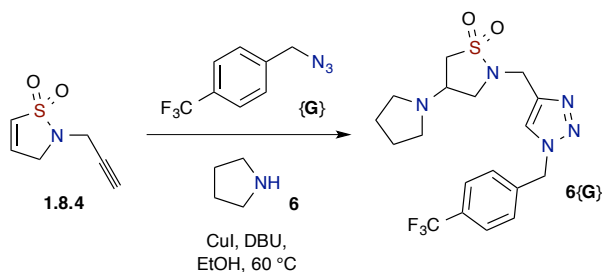
entry[a]	azide {**G**} (equiv.)	amine **6** (equiv.)	CuI (mol %)	DBU (mol%)	yield (%)
1	2	2	10 mol%	10 mol%	62 %
2	2	2	30 mol%	10 mol%	96 %
3	1	1	30 mol%	10 mol%	78 %
4	2	1.2	30 mol %	50 mol%	95 %
5	**2**	**1.2**	**30 mol%**	**10 mol%**	**96 %**

[a]Reactions carried out utilizing **1.8.4** (50 mg, 0.318 mmol, 1 equiv.) in 0.5M EtOH at 60 ºC for 12 hrs.

With these optimized conditions in hand, a validation library was investigated for the diversification of dihydroisothiazole 1,1-dioxide **1.8.4** with a variety of 2º amine nucleophiles (Scheme 1.9). Reactions were performed in 1-dram vials using reaction blocks, and resulting crude reaction mixtures were diluted in EtOAc, filtered through silica SPE and QC/purified by automated mass-directed LCMS.

Scheme 1.9. *Prototype library synthesis utilizing core scaffold **1.8.4**.*

"two-step"   "one-pot"

1.9.1   **1.9.2**
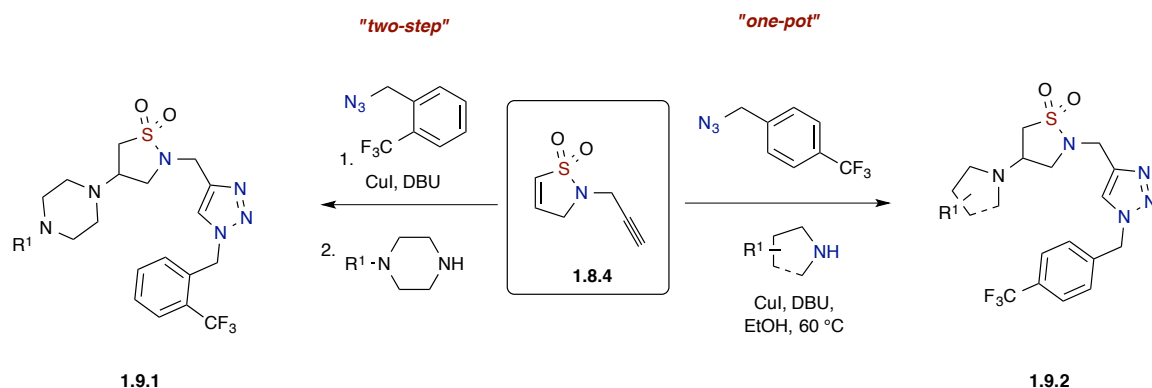
entry[a]	yield	final purity[c]	Mass	entry[b]	yield	final purity[c]	mass
2{G}	52 %	99 %	89.3 mg	**2**{O}	43 %	100 %	22.9 mg
4{G}	45 %	99 %	75.4 mg	**12**{O}	41 %	98 %	22.3 mg
5{G}	42 %	92 %	56.2 mg	**13**{O}	40 %	97 %	19.4 mg
6{G}	47 %	99 %	63.9 mg	**15**{O}	43 %	98 %	22.3 mg

[a] Reaction conditions: Dihydroisothiazole 1,1-dioxide **1.8.4** (50 mg, 1 equiv.), azide (2 equiv.), amine (1.2 equiv.), CuI (30 mol%), DBU (10 mol%), dry EtOH (0.5 M), 60 ºC, 12 hrs. [b]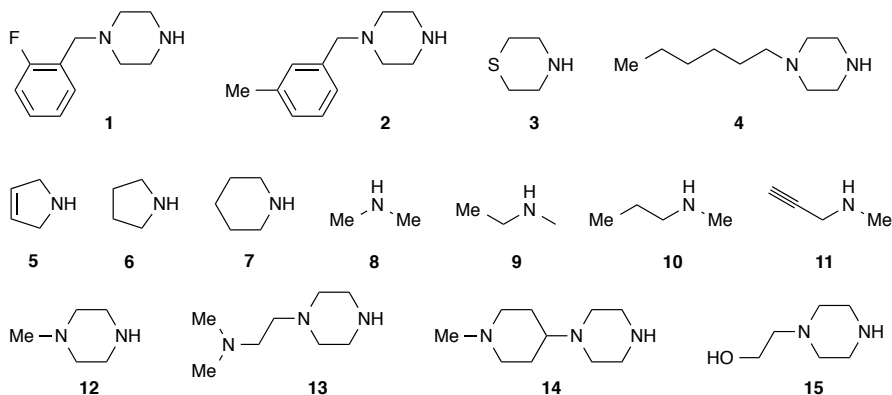Reaction conditions: Dihydroisothiazole 1,1-dioxide **1.8.4** (20 mg, 1 equiv.), azide (2 equiv.), amine (1.2 equiv.), CuI (30 mol%), DBU (10 mol%), dry EtOH (0.5 M), 60 ºC, 12 hrs. [c]Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). Purity was determined by HPLC with peak area (UV) at 214 nm and % rounded up to nearest 1%.

With the successful synthesis of the 8-member validation library, two libraries, **A** and **B**, were proposed for the synthesis of 180-triazole-containing isothiazole 1,1-dioxides derivatives via the diversification of dihydroisothiazole 1,1-dioxide **2**. For both libraries **A** and **B**, a full matrix library was designed using in-silico analysis, literature precedence, and observed synthetic results.[28] A virtual library incorporating all possible building block combinations of azides and 2° amines was constructed for scaffold **1.8.4**. Physico-chemical

property filters were applied, guiding the elimination of undesirable building blocks that led

to products with undesirable in-silico properties (Full in-silico data and detailed calculation

information is available in Ch. 4). These metric filters included standard Lipinski Rule of 5

parameters (molecular weight <500, ClogP <5.0, number of H-acceptors <10, and number

**Figure 1.3.** *Amine (1–15) and azide (A–N) building blocks.*
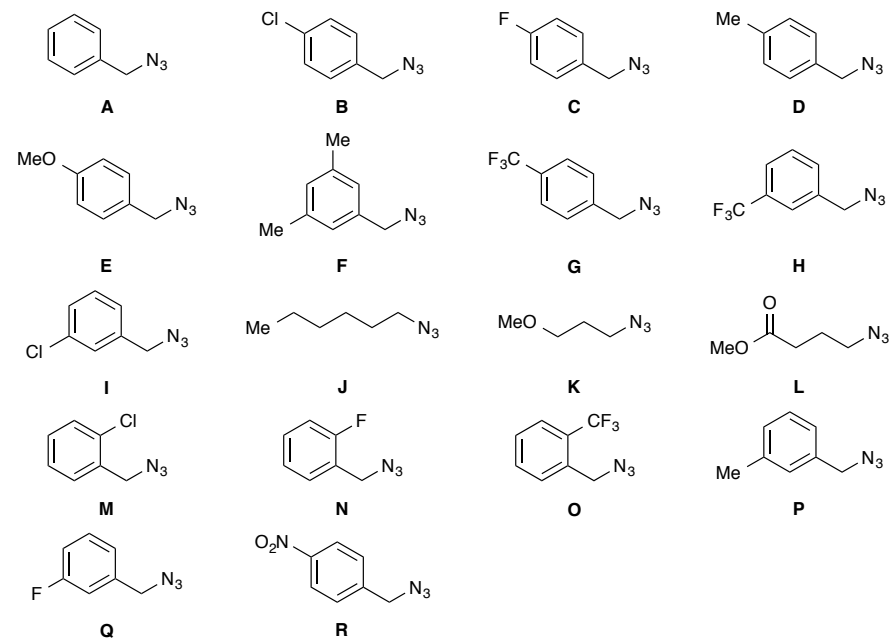
of H-donors <5), in addition to consideration of the number of rotatable bonds (<5) and polar surface area. Absorption, distribution, metabolism, and excretion (ADME) properties were calculated along with diversity analysis using standard H-aware 3D BCUT descriptors comparing against the MLSMR screening set (ca. 7/2010; ~330,000 unique chemical structures). Guided by this library design analysis, the corresponding amines **1-15** and azides {**A-R**} (Figure 1.3) were chosen for sultam libraries **A** and **B**.

Utilizing the optimized conditions, library **A** (132-member) was generated utilizing azides **A–L** with amines **1**–**11** via a one-pot click/aza-Michael transformation. Library **B** (48-member) was also generated utilizing azides **A–L** with piperazines **12**–**15** via a sequential 2-step click/aza-Michael protocol, instead of the previously used one-pot method. This 2-step sequence was necessary to efficiently remove the Cu catalyst from the crude material without the need of an aqueous work-up due to increased affinity to the SiO_2 SPE of the corresponding final compounds bearing both a triazole and piperazine moiety. Overall, all 180-triazol-isothiazole 1,1-dioxide members of library **A** and **B** were successfully generated, with 167 out of the 180 compounds possessing >90% final purity after purification by automated mass-directed LCMS.

Within the 132-member library **A** is a unique set of 12 *bis*-triazole-containing isothiazole 1,1-dioxides **A–L**{**11**} which were generated through a *bis*-click/aza-Michael due to the use of *N*-methyl propargyl amine {**11**} in the presence of 2 equiv. of the corresponding azide (Scheme 1.10).

Scheme 1.10. *One-Pot bis-click/aza-Michael to produce compounds A–L{11}.*
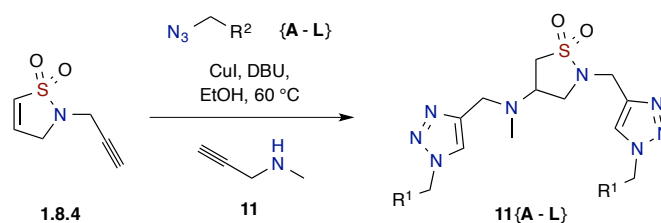

1.3 Library Generation of "4+4" Scaffold involving Click-S$_N$Ar

Building upon the importance of generating diverse sultams as drug-like molecules and a variety of biological activities shown in the previous section, we selected novel dibenzofused sultam scaffolds as a new target for library production. Sultam **1.11.4** is a unique compound that displays interesting physiochemical properties with skeletal and stereochemical diversity (Scheme 1.11a).[29] More in depth analysis of its chemical properties and known biological activities will be introduced in Chapter 2. We initially designed a set of library compounds by incorporating Cu-catalyzed *N*-arylation of the aryl-*Br* moiety and Cu-catalyzed Click reaction of terminal alkyne derived from sulfonylation of propargyl amine (Scheme 1.11b).

The desired core scaffold **1.11.4** was produced in 4.5 g quantities following a previously reported method.[29] Sulfonylation of propargyl amine using substituted *ortho*-fluorobenzene sulfonyl chloride afforded secondary sulfonamide **1.11.2** in excellent yields (Scheme 1.11a). Subsequent "4+4" cyclization of **1.11.2** via sequential aza-Michael/S$_N$Ar with *ortho*-quinone methide precursor **1.11.3** produced 8-membered dibenzofused sultam **1.11.4** in high yields.

Scheme 1.11. *Gram synthesis of core scaffold **1.11.4** and design of one-pot, multicomponent synthesis of triazole-containing sultam library.*
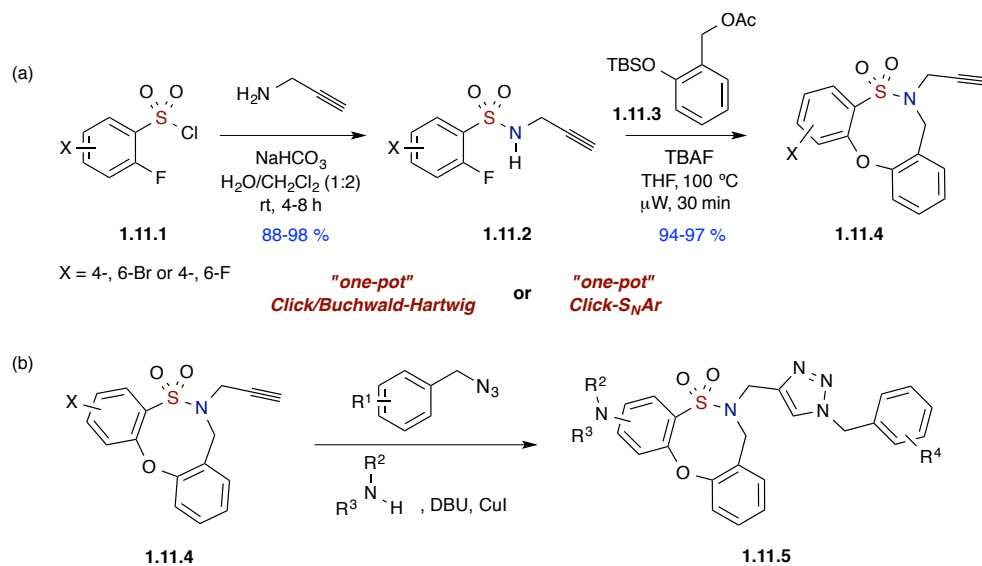
With these scaffolds in hand, we initially focused our attention on finding optimal conditions for Cu-catalyzed *N*-arylation using 4-Br scaffold **1.12.1** and *o*-anisidine **1.12.2** (Scheme 1.12a). Reaction of sultam **1.12.1** with *o*-anisidine **1.12.2** in the presence of K_2CO_3, 1,10-phenanthroline, and CuI as catalyst in EtOH as solvent at 60 °C produced aminated sultam **1.12.3** in 29 % yield. No reaction occurred when azide **1.12.4** was included into the same reaction conditions (Scheme 1.12b). When this reaction was applied to microwave conditions, decomposition of starting material was observed. These low yields and/or decomposition led us to search a different pathway for peripheral diversification by utilizing 4- and 6-F substituted sultams via $S_N Ar$ in place of Cu-catalyzed *N*-arylation

Scheme 1.12. *Initial studies for Cu-catalyzed N-*arylation *and one-pot Click/N-arylation reaction.*

(a)

1.12.1   1.12.2

CuI, K₂CO₃
1,10-phenanthroline

EtOH, 60 °C, overnight, *29 %*
or
μW @100 °C, EtOH
30 min, *decomposition*

1.12.3

(b)

1.12.1   1.12.2   1.12.4

DBU, CuI, K₂CO₃
1,10-phenanthroline

EtOH, 60 °C, overnight

1.12.5
no reaction
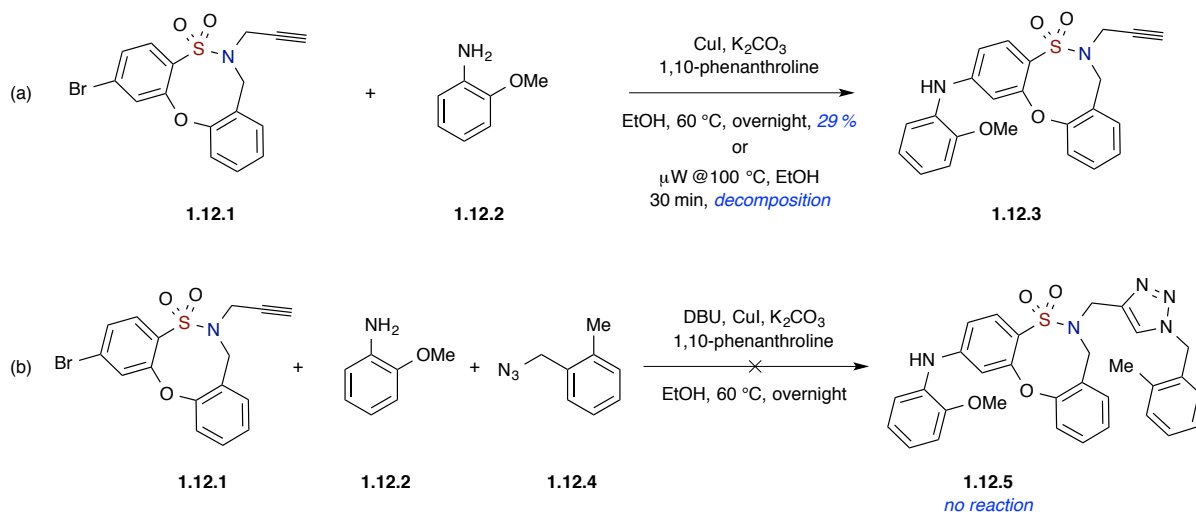
Initial investigation for application of S_NAr diversification started with 4-F substituted sultam **1.13.1** (Scheme 1.13a). Adopting the conditions shown in previous examples from the Hanson group in the introduction section, sultam **1.13.1** and pyrrolidine **1.13.2** were reacted in DMSO in the presence of DBU as base under microwave irradiation at 180 °C for 50 min. To our delight, 4-pyrrolidine-substituted sultam **1.13.3** was produced in 95 % yield. Encouraged from this result, application of one-pot three-component S_NAr/Click sequence was probed (Scheme 1.13b). Sultam **1.13.1** was reacted in one-pot with pyrrolidine **1.13.2** and azide **1.13.4** in the presence of DBU as base and CuI catalyst in DMSO under microwave irradiation at 180 °C for 50 min. Gratifyingly, three-component MCR sultam product **1.13.5** was isolated in good yields.

Scheme 1.13. *Utilization of S$_N$Ar for diversification and application to one-pot Click-S$_N$Ar.*
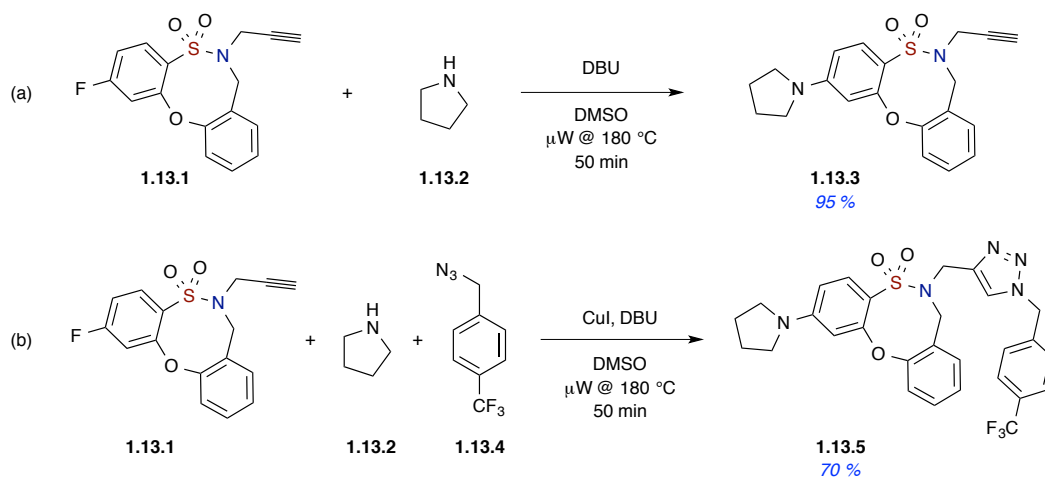
With these optimized conditions in hand, a 60-member library was designed based on two core scaffolds **1.4.A** and **1.4.B**, commercially available amines **1.4.C-J**, and benzyl

Figure 1.4. *Core scaffolds, amine, and azide building blocks.*
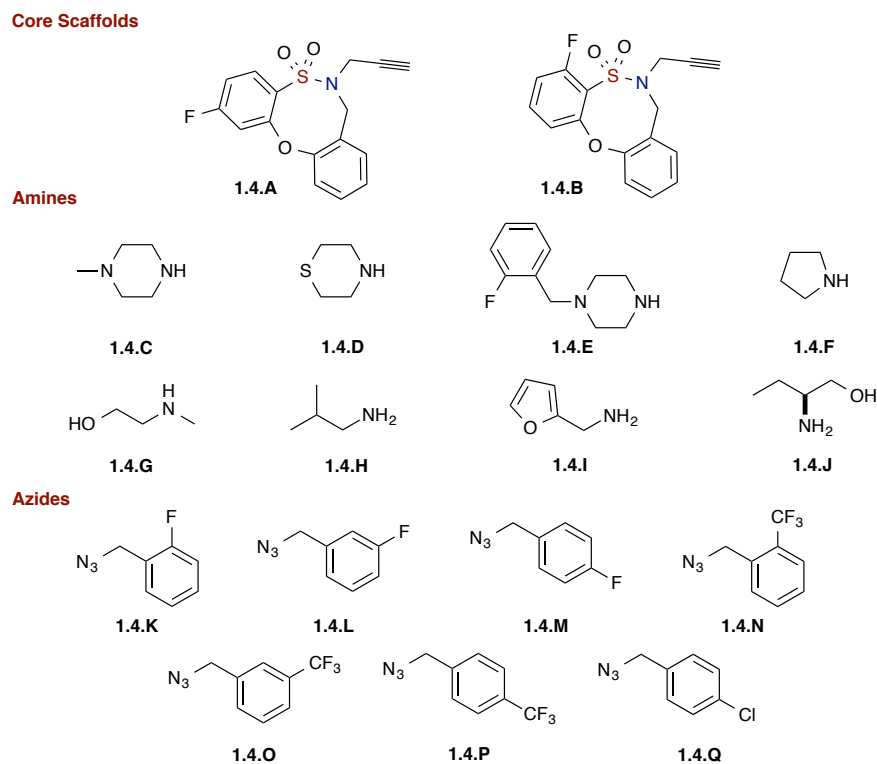
azides **1.4.K-Q** (Figure 1.4). Using the aforementioned one-pot, three-component reaction conditions, the reactions were carried out in parallel synthesis format using Anton Parr® Synthos 3000 microwave system.[19] Resulting reaction mixtures were diluted in EtOAc, filtered through SiO_2 SPE, concentrated *in vacuo*, and were purified by automated mass-directed LCMS. Overall, 54 out of 60 compounds were synthesized possessing >90% final purity, with average yield of 60 %.

Table 1.2. *Select one-pot Click/S_NAr Library representative results.*

entry[a]	yield	final purity[c]	mass (mg)	entry[b]	yield	final purity[c]	mass (mg)
1.4.A.FN	75 %	99 %	134.5	**1.4.B.HO**	57 %	92 %	51.1
1.4.A.HN	67 %	99 %	120.5	**1.4.B.HP**	38 %	93 %	34.2
1.4.A.DQ	61 %	98 %	54.7	**1.4.B.JN**	59 %	99 %	108.9
1.4.A.EQ	95 %	99 %	36.1	**1.4.B.IL**	62 %	99 %	53.2

Principle moments of inertia (PMI) analysis was conducted for the produced library compounds for assessment of molecular diversity.[30] PMI analysis is based on analyzing shape-based descriptors: the minimum energy conformation of each compound is resolved, the corresponding PMI ratios are calculated and normalized, and the resulting data is represented by a triangular plot depicting the molecular shape diversity (Figure 1.5). The results were plotted against a set of FDA approved drug molecules shown in black dots. The results show that the 60-member library compounds occupy a region that is closer to being rod-like and disc-like 3-D shape. This region is in accordance to the region that the FDA

approved drug molecules occupy, thus providing a rudimentary insight that these library compounds may have beneficial biological activities.

Figure 1.5. *PMI analysis diagram of the three scaffolds plotted against FDA approved drugs.*
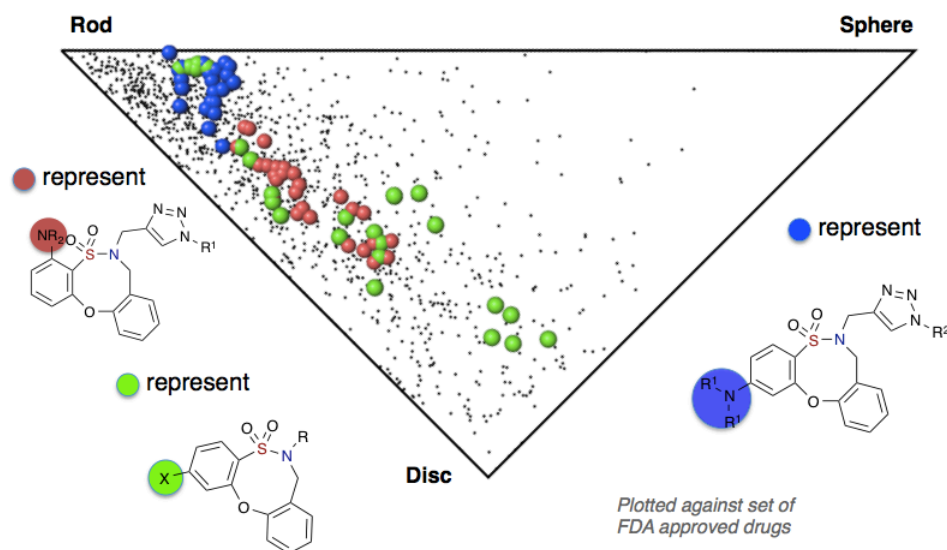
1.4 Conclusion

In conclusion, two libraries of triazole-containing isothiazolidine 1,1-dioxides were prepared utilizing a one-pot Click/aza-Michael protocol for utilization in HTS screening collections. Core dihydroisothiazole 1,1-dioxide scaffold was prepared rapidly on multi-gram scale via RCM and rapidly diversified via a one-pot multi-component click/aza-Michael protocol to generate a 180-triazole-containing isothiazole 1,1-dioxide library (**A** and **B**). All 180 compounds were successfully generated, with 167 possessing >90% final purity after purification by automated mass-directed LCMS.

Another set of 60-member library of triazole-containing dibenzofused sultams was prepared utilizing a one-pot Click/S_NAr protocol. The core

dibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide scaffolds were prepared in gram quantities via coupling of 2° sulfonamides with *ortho*-quinone methides, then rapidly diversified via one-pot three-component Click/S_NAr sequence to furnish a library of structurally unique sultams. Overall, 54 out of 60 compounds were synthesized with average yield of 60 % possessing >90% final purity after purification by automated mass-directed LCMS.

This screening set of sultams represent a diverse motif not currently reported in the literature and has been submitted for evaluation of their biological activity in high-throughput screening.

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Chapter 2

Application of One-pot, Sequential, Multi-component Strategy

for the Synthesis of Diverse Dibenzofused 8-Membered

Sultams

Chapter 2: Application of One-pot, Sequential, Multi-component Strategy for the Synthesis of Diverse Dibenzofused 8-Membered Sultams

2.1:   Introduction – Recent Advances in One-pot Multicomponent Click Reactions (MCR)

2.1 Introduction

Triazoles and their derivatives have been increasingly found in literature due to their interesting biological profiles and physiochemical properties. A number of triazole-containing molecules are known to exhibit various biological activities, such as anti-HIV,[1] antibacterial,[2] anticancer,[3] and antifungal[4] activities (Figure 2.1). The abundance of triazole derivatives in combinatorial drug discovery[5] is related to the inherent stabilizing structural features leading to bioorthogonality, thus serving as excellent peptidomimetics[6] and protein foldamers.[7] Moreover, the stability of triazoles extends to its resistance towards enzyme degradation in living systems.[8] In spite of these attributes, sultams containing triazole moieties are relatively limited in literature. Building upon the sultam-triazole libraries we generated in Chp 1 (Figure 2.2), we have designed one-pot sequential multicomponent

reactions to produce new sultam compounds with triazole moieties in a facile manner to provide scaffolds joining the two motifs together in order to screen for novel biological activities. In this regard, we herein report one-pot, sequential, 3-, 4-, and 5-component reactions to furnish dibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxides and their corresponding analogs with triazole motifs (Figure 2.2).

Figure 2.1. *Representative examples of bioactive triazoles and drug candidates.*
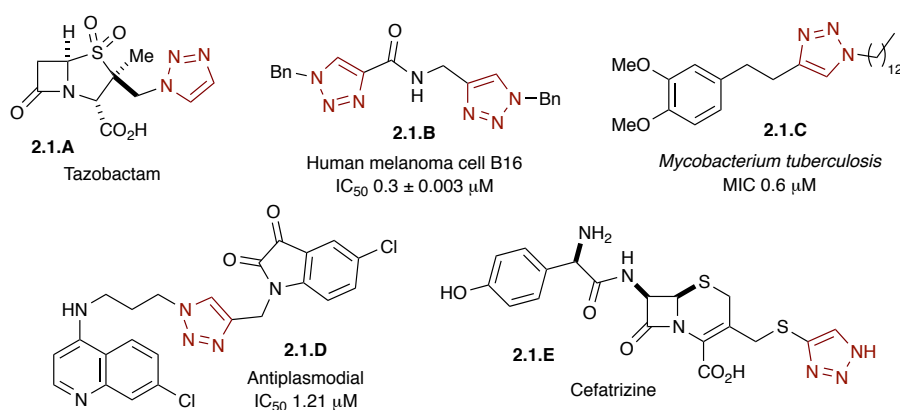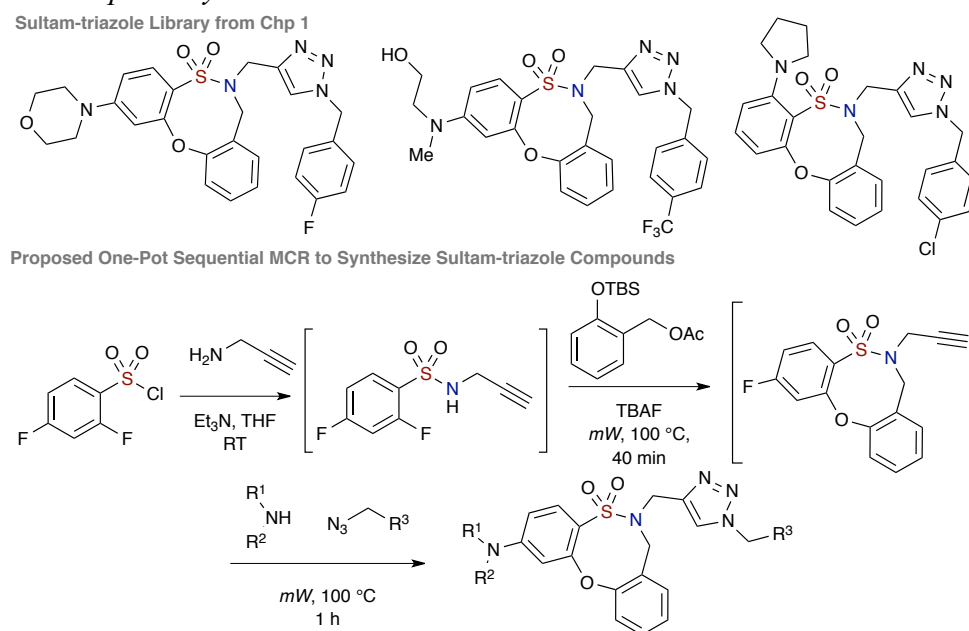

Figure 2.2. *Summary of sultam-triazole scaffolds from Chp 1 and proposed one-pot, sequential MCR pathway.*

The introduction in this chapter will focus on reviewing recent advances in synthetic method developments of one-pot, multicomponent copper-catalyzed azide alkyne coupling (CuAAC) reactions for the synthesis of triazole derivatives. In part, this review section is categorized into three subsections: (i) one-pot, 2-, 3-component MCRs, (ii) one-pot, 4-, 5-, 6-component MCRs, and (iii) development of novel catalysts for one-pot CuAAC.

### 2.1a   One-pot, 2-, 3-Component MCR

In 2014, Sun and coworkers reported the synthesis of triazoloquinazolinones by employing a one-pot, two-component tandem Click and intramolecular C–H amidation strategy.[9] Triazoloquinazolinones are a class of nitrogen-containing heterocycles with several known to have biological activities such as anticancer and antihypertensive properties.[10] Despite these attributes, direct synthetic methods to produce this motif are limited in literature. By pairing triazole synthesis with intramolecular C–N bond formation through C–H amidation, the synthesis of biologically relevant triazoloquinazolinones **2.1.3** was achieved (Scheme 2.1). Reaction of *N*-methoxybenzamide **2.1.1** with phenyl acetylene **2.1.2** in the presence of catalytic CuI and DIPEA in THF under aerobic conditions at room temperature yielded the desired triazoloquinazolinones **2.1.3** in 80% yield. The copper catalyst-enabled Click reaction enabled formation of triazole intermediate **2.1.4**, and subsequently catalyzed the intramolecular C–H amidation to afford the desired triazole **2.1.3**.

Scheme 2.1. *One-pot two-component synthesis of triazoloquinazolinone derivatives.*
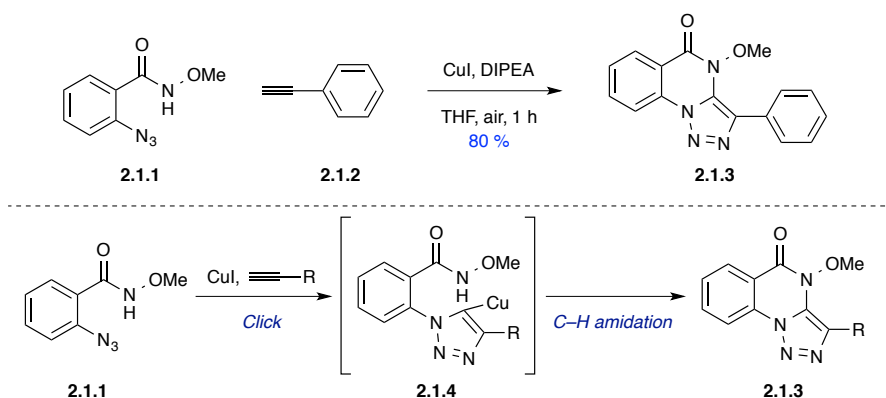
In 2011, the Müller group reported formation of triazolyl-substituted *N*-Boc protected heterocycles via three-component Sonogashira coupling–TMS-deprotection–Click sequence.[11] This sequence enables facile assembly of diverse nitrogen-containing heterocycles such as indole, indazole, 4-, 5-, 6-, and 7-azaindoles, 4,7-diazaindole, 7-deazapurine, pyrrole, pyrazole, and imidazole. Starting from iodo-*N*-Boc N-heterocycles **2.2.1**,[12] sequential addition of trimethylsilylacetylene (TMSA) in the presence of palladium and copper catalysts (Sonogashira coupling), followed by deprotection of the acetylene moiety using TBAF, and addition of benzyl or aryl azide (Click reaction), afforded the desired triazolyl substituted *N*-Boc protected heterocycles **2.2.2** (Scheme 2.2).

Scheme 2.2. *One-pot three-component Sonogashira coupling–TMS-deprotection–Click sequence towards various N-heterocycles.*
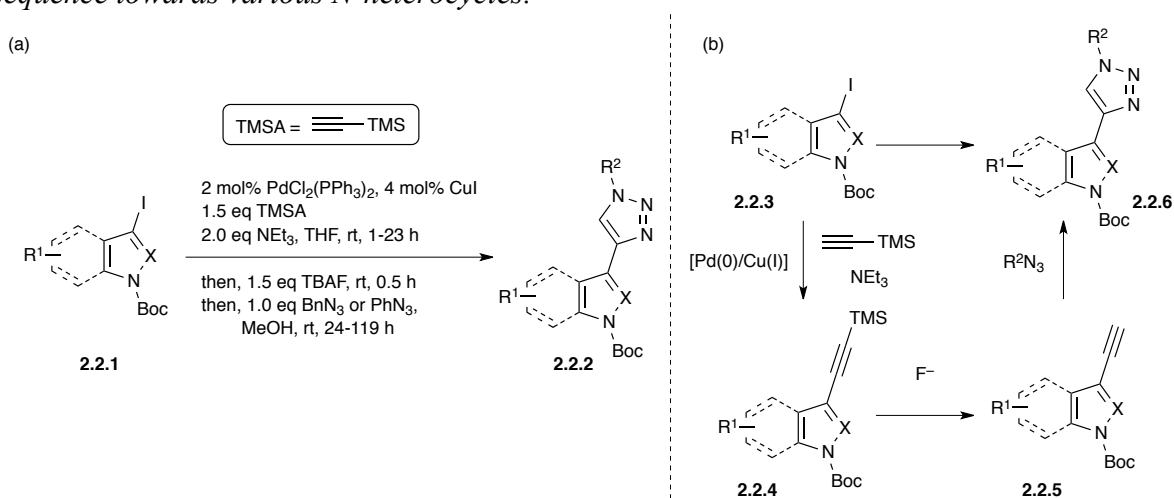

In 2012, Schoch and coworkers reported a three-component MCR strategy involving CuAAC and inverse electron-demand Diels-Alder reaction (DAinv) for site-specific dual labeling of DNA.[13] CuAAC has recently merged as an important tool in the field of bioorthogonal tagging/labeling.[14] Another method that has recently gained attention is DAinv,[15] which is known to be rapid, does not require transition metals, and allows for efficient functionalization of oligonucleotides at ambient temperature. Concurrent bioorthogonal site-specific double-modification of oligonucleotides without protection or intervening protection had not been reported yet. This report demonstrated the first successful attempt at combining CuAAC and DAinv for one-pot labeling of DNA oligonucleotides. Doubly-modified oligonucleotides **2.3.1** containing both a terminal alkyne and a dienophile were reacted with tagged dansyl tetrazines **2.3.2** and tagged azides **2.3.3** in the presence of Cu_2SO_4, tris(3-hydroxypropyltriazolylmethyl)amine (THPTA), and sodium ascorbate in one-pot to afford doubly-tagged oligonucleotides **2.3.4** (Scheme 2.3).

Scheme 2.3. *One-pot three-component CuAAC and DAinv for DNA oligonucleotides labeling.*
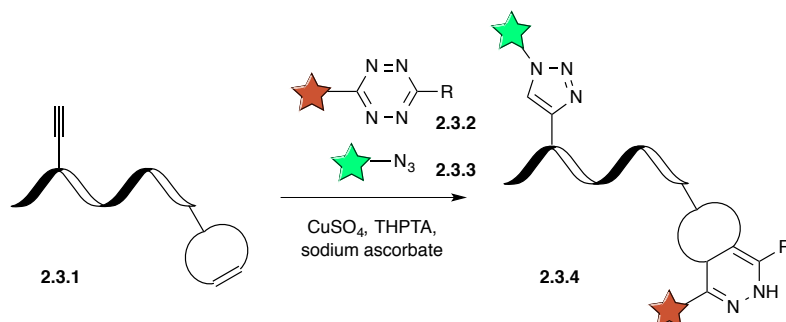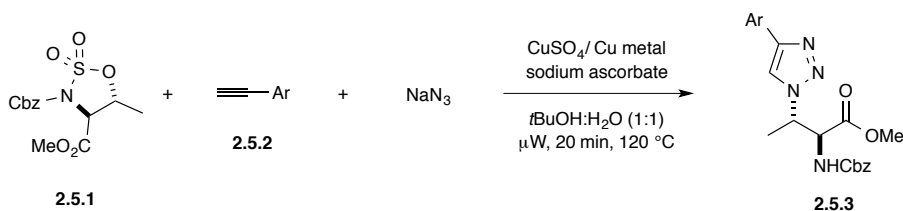

In 2013, Fang and coworkers demonstrated the use of one-pot three-component CuAAC for the production of novel triazolyl substituted tetrahydrobenzofuran derivatives to study their inhibitory activies of H^+/K^+-ATPase.[16] Development of H^+/K^+-ATPase inhibitors, also known as gastric proton pump inhibitors (PPIs), provides clinical benefits coping against gastroesophageal reflux disease (GERD), peptic ulcer, and other acid-related disorders.[17] However, currently existing PPIs possess limitations such as insufficient efficacy and hepatic toxicity.[18] A concise and efficient method for the synthesis of triazolyl substituted tetrahydrobenzofurans **2.4.4** was developed in search for novel PPIs (Scheme 2.4). Preparation of 4-azido substituted tetrahydrobenzofuran intermediate **2.4.3** was achieved by reduction of ketone **2.4.1** followed by azide substitution following the method of Haynes.[19] Intermediate azide **2.4.3** next underwent one-pot, three-component CuAAC with propargyl bromide and primary amine in water without other co-solvents at room temperature to furnish the desired triazolyl substituted tetrahydrobenzofuran **2.4.4**.

Scheme 2.4. *One-pot three-component CuAAC for the synthesis of novel triazolyl substituted tetrahydrobenzofuran derivatives **2.4.4**.*
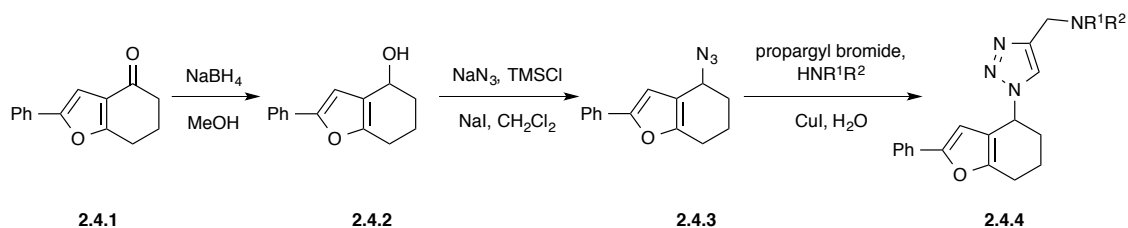
In 2013, the Varma group reported the synthesis of 1,2,3-triazole substituted unnatural amino acids via microwave-assisted using a one-pot three-component method.[20] Known methods to produce triazole-based unnatural amino acids follow the same strategy.[21] Previously reported procedures utilize the Mitsunobu reaction, which involves usage of highly toxic and explosive dry hydrogen azide for the generation of the azide intermediate. In order to circumvent this problem, one-pot three-component CuAAC with sulfamidate **2.5.1**, terminal alkyne **2.5.2**, and sodium azide was developed (Scheme 2.5). The reaction was performed in 1:1 mixture of ^{t}BuOH and water under 120 °C microwave irradiation for 20 minutes, which furnished the desired triazole-substituted unnatural amino acid **2.5.3**.
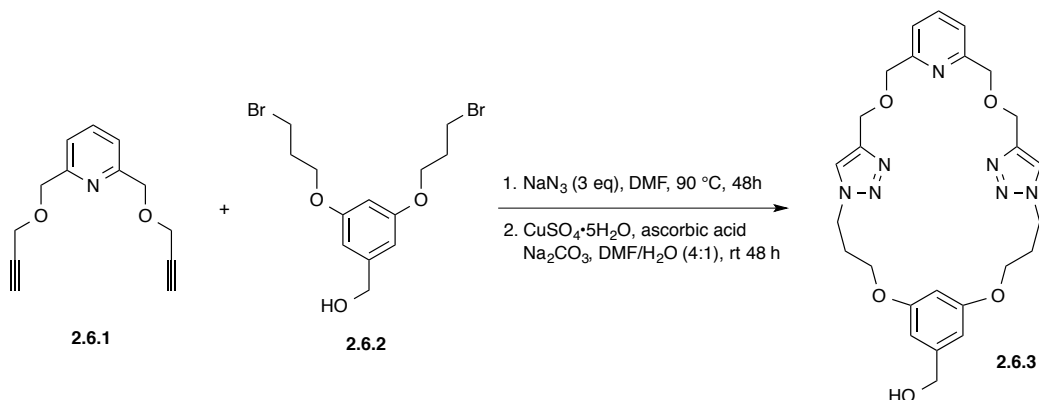
Scheme 2.5. *One-pot three-component CuAAC for synthesis of triazole-substituted unnatural amino acids.*

In 2012, Crowley and coworkers demonstrated the application of one-pot three-component CuAAC for the preparation of *exo*-functionalized pyridiyl-1,2,3-triazole macrocycles for utilization as both passive and active metal templates en route to rotaxanes.[22]

Mild and functional group tolerant triazoles have become a viable alternative to pyridine-containing macrocycles that are used for synthesis of mechanically interlocked architectures (MIA).[23] In this regard, the authors report employment of one-pot multi-component CuAAC for the facile production of triazole-containing macrocycles. Dialkyne **2.6.1** poses a threat in the sense that the resulting diazide may be explosive (Scheme 2.6). However, the *in situ* generated diazide moiety is readily captured by copper catalyst to yield the desired Click macrocycle **2.6.3** in good yields. The resulting macrocycle proved to be unsuccessful in attempts to utilize it in both passive and active metal template syntheses of rataxanes due to the coordinating ability of the 1,2,3-triazole units within the macrocycle.

Scheme 2.6. *One-pot three-component CuAAC for the preparation of exo functionalized pyridiyl-1,2,3-triazole macrocycles.*

In 2013, Naeimi and coworkers reported utilization of sonochemical synthesis for the production of 1,4-disubstituted 1,2,3-triazole derivatives via one-pot three-component CuAAC in 1:1 mixture of water and ethanol.[24] Recently, ultrasound has been gaining interest as an efficient green and sustainable tool for synthetic processes.[25] Building upon a previous report by Priebe in 1984 on the synthesis of organic azides from the corresponding activated primary halides and aqueous sodium azide under ultrasonic irradiation,[26] the authors

envisioned applying this method towards the synthesis of 1,2,3-triazoles in a one-pot fashion. At room temperature, aliphatic/benzyl halide **2.7.1**, terminal alkyne **2.7.2**, and sodium azide were reacted in the presence of 3 mol% CuI under ultrasonic irradiation power of 70 W for 5 min to furnish the desired 1,4-disubstituted 1,2,3-triazole **2.7.3** in excellent yields (Scheme 2.7). The authors hypothesized that the observed effects of ultrasonic irradiation is due to formation of cavities, which are known to act as microreactors for volatile molecules by high temperature and pressure produced during cavitation break.[25]

Scheme 2.7. *Sonochemical one-pot three-component CuAAC process for the production of 1,4-disubstituted 1,2,3-triazole derivatives.*
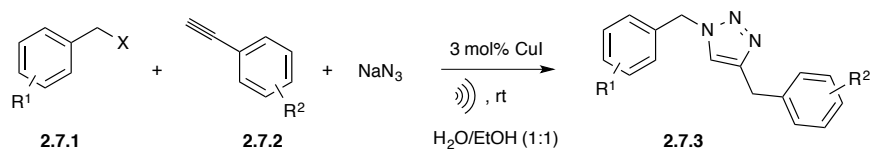
In 2013, Li and coworkers reported preparation of 5-halo-1,2,3-triazoles via one-pot three-component tandem oxidative halogenation and CuAAC.[27] Generation of more diverse and highly substituted 1,2,3-triazoles has been a desirable target due to its known benefits in various areas. In this regard, development of 5-halo-1,2,3-triazoles, which are known precursors to other functional groups[28] and also are widely used analogs for SAR studies,[29] provide a center for further diversification. However, direct halogenation is unsuccessful due to the deficient electron density of the 1,2,3-triazole system. The authors demonstrated the first effective one-pot tandem aerobic oxidative halogenation and CuAAC involving azide **2.8.1**, alkyne **2.8.2**, and CuX (X = I, Br) under O_2 atmosphere at room temperature in the presence of TBSCl to directly furnish the desired 5-halo-1,2,3-triazoles **2.8.3** (Scheme 2.8).

It was found that TBSCl activates aerobic oxidation of CuX to produce X_2 and Cu^+, which in turn undergoes aerobic oxidative halogenation and catalyze the Click reaction, respectively.

Scheme 2.8. *Preparation of 5-halo-1,2,3-triazoles via one-pot three-component tandem oxidative halogenation/CuAAC.*

In 2014, Jiang and coworkers demonstrated the development of a simple, efficient thermally-promoted protocol for one-pot three-component CuAAC catalyzed by $CuSO_4 \cdot 5H_2O$ in water.[30] Until this work, reports of utilizing Cu(II) salts as catalysts for CuAAC reactions require additional reducing agent such as sodium ascorbate, metallic copper, hydrazine monohydrate, among others.[31] Moreover, the reactions require longer times for completion. In this regard, this report focuses on development of conditions using Cu(II) salts as catalysts for CuAAC without the need of reducing agent and expedited reaction times. Optimization studies revealed 1 mol% $CuSO_4 \cdot 5H_2O$ as catalyst at 100 °C in water as optimal conditions, and showed that the reaction was greatly accelerated to be

Scheme 2.9. *Thermally promoted protocol for one-pot three-component CuAAC catalyzed by $CuSO_4 \cdot 5H_2O$ in water.*

complete in 30 min when using alkyne **2.9.1** and organic azide **2.9.2** (Scheme 2.9a). When

this method was applied to one-pot, three-component synthesis of triazoles using alkyl

bromide **2.9.4**, NaN$_3$, and terminal alkyne **2.9.5**, the reactions were complete in 50–70 min to

afford triazoles **2.9.6** in excellent yields (Scheme 2.9b).

## 2.1b One-pot, 4-, 5-, 6-Component MCR

In 2011, Qian and coworkers reported one-pot four-component synthesis of triazolyl-

pyridazone libraries via a "Click and Activate" strategy.[32] This strategy entails usage of

CuAAC step in mid-stage of one-pot reaction sequence, which is considered to be a rather

unexplored sector of one-pot Click reaction processes. Regioselective azide substitution at

the 5- over 4-position of 2-substituted-4,5-dichloropyridazinone **2.10.1** allows for preparation

of CuAAC partner **2.10.2** (Scheme 2.10). Subsequent CuAAC reaction with terminal

alkynes **2.10.3** attaches substituted triazole at the 5-position to afford **2.10.4**. By attaching

the triazole, the starting material that is rather neutral or deactivated for nucleophilic attack

has been "activated" electronically by the presence of triazole at the 5-position. At the last

stage, various amine and carbon nucleophiles were used for substrate scope studies to

achieve diverse 2,4,5-trisubstituted-3(2H)-pyridazinones **2.10.5**.

Scheme 2.10. *One-pot four-component synthesis of triazolyl-pyridazone libraries via "Click and Activate" strategy.*
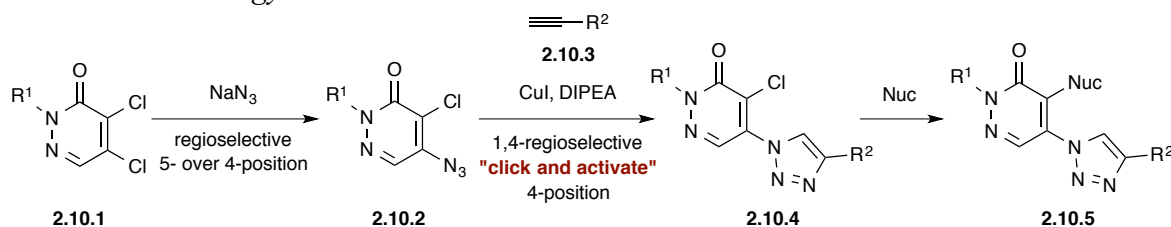
In 2012, Niu and coworkers demonstrated application of grouping copper-free three-component cycloaddition with CuAAC in a one-pot four-component fashion for the synthesis of unsymmetrical bis(1,2,3-triazole) derivatives and their corresponding peptidomimetics.[33] Conventional methods to generate unsymmetrical bis(1,2,3-triazoles) utilize double-Click strategy.[34] However, the necessity for protection-deprotection sequence renders this strategy to be cumbersome. By utilizing a previously reported method for the synthesis of triazoles in the absence of copper catalyst,[35] the authors envisioned three-component reaction of azide **2.11.1**, diketene **2.11.2**, and alkyne-containing amine **2.11.3** as linker to generate triazole **2.11.4** (Scheme 2.11). Optimization studies revealed DBU as catalyst and MeOH as solvent to be optimal in generating the desired product. After completion of the initial formation of triazole **2.11.4**, sequential addition of copper catalyst with the second azide furnished the desired unsymmetrical bis(1,2,3-triazole) **2.11.5** in excellent yields.

Scheme 2.11. *One-pot four-component CuAAC for preparation of unsymmetrical bis(1,2,3-triazole) derivatives and their corresponding peptidomimetics.*
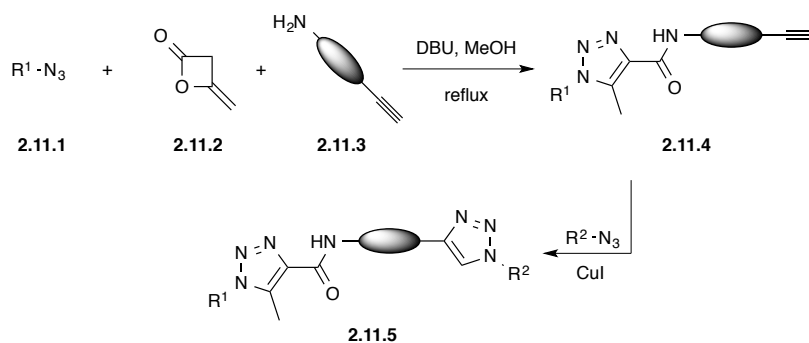
In 2012, Salehi and coworkers reported one-pot, four-component condensation of phthalhydrazide **2.12.1**, aromatic propargyloxy aldehydes **2.12.2**, active methylenes **2.12.4** (dimedone/1,3-cyclohexanedione), and azides **2.12.3** in the presence of copper catalyst for the synthesis of [(1,2,3-triazol-4-yl)methoxy-phenyl]-2*H*-indaz-olo[2,1-*b*]phthalazine-trione

derivatives **2.12.5** (Scheme 2.12).[36] Phthalazine derivatives have gained attention from the synthetic community due to their biological properties including anticonvulsant,[37] vasorelaxant,[38] and cardiotonic properties.[39] The four components, in the presence of Cu(OAc)$_2$•H$_2$O, PTSA, and sodium ascorbate as catalysts in EtOH as solvent at 80 °C afforded the desired triazole-attached phthalazine-trione product **2.12.5** in good yields. Through scope studies, both electron-rich and electron-deficient aromatic propargyloxy aldehydes afforded high-to-excellent yields.

Scheme 2.12. *One-pot four-component condensation/CuAAC for the synthesis of [(1,2,3-triazol-4-yl)methoxy-phenyl]-2H-indaz-olo[2,1-b]phthalazine-trione derivatives.*
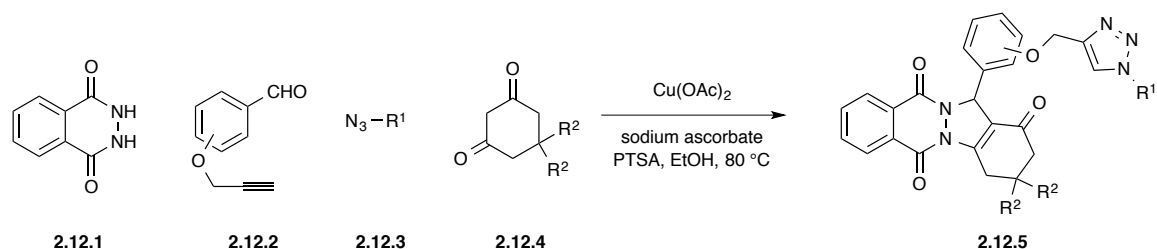
In continuation of the previous work,[36] in 2012 Dabiri and coworkers reported one-pot pseudo-five-component synthesis of triazolyl methoxyphenyl 1,8-dioxo-decahydroacridines.[40] Acridine derivatives are known to possess a wide variety of biological activities, including antimalarial,[41] antitumor,[42] antiprion,[43] anti-Alzheimer,[44] antileishmanial, and antitrypanosomal activities,[45] and thus various routes to their syntheses have been developed by the synthetic community.[46] In this report, the authors focus on the development of a facile and expedient method for the production of these acridine derivatives bearing triazole moieties. Propargylated aldehyde **2.13.1**, organic azide **2.13.2**, primary amine **2.13.3**, and two equivalents of dimedone **2.13.4** in the presence of catalytic amount of Cu(OAc)$_2$ and sodium ascorbate, and [Hmim]TFA as acidic catalyst, in a mixture of

H$_2$O/EtOH (1:1 by volume) at 100 °C for 6 h provided acridine product **2.13.5** in good yields (Scheme 2.13). This one-pot sequential Click-Knoevenagel condensation-Michael addition-cyclocondensation method achieved simple and efficient syntheses of desired acridine derivatives.

Scheme 2.13. *One-pot pseudo-five-component synthesis of triazolyl methoxyphenyl 1,8-dioxo-decahydroacridines.*
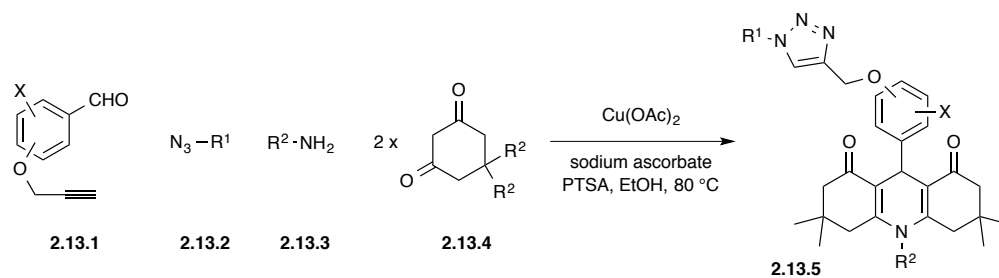
In 2012, the Wang group demonstrated a concise synthesis of chiral 2(*5H*)-furanone derivatives possessing 1,2,3-triazole moieties via one-pot four-component strategy.[47] Compounds with 2(*5H*)-furanone moieties, a type of α,β-unsaturated lactone substructure that is often found in various natural products, have received attention due to their variety of biological activities.[48] However, combining 1,2,3-triazole moiety into 2(*5H*)-furanones with various amino acids as linkers have not been previously reported. In this work, a one-pot four-component strategy involving asymmetric Michael addition-elimination, substitution, and cycloaddition starting from (*5S*)-5-menthoxy-3,4-dibromo-2(*5H*)-furanone **2.14.1** (where R^1 = menthyl) afforded the desired chiral 2(*5H*)-furanone derivative **2.14.7** bearing 1,2,3-triazole moiety (Scheme 2.14). Initial attempts showed that usage of EtOH is necessary for the first Michael addition-elimination. Therefore, modifying the conditions so that the

solvent system utilized a mixture of EtOH and CH$_3$CN in 1:8 ratios, one-pot four-component

reaction was achieved in a sequential manner.

Scheme 2.14. *One-pot four-component strategy towards synthesis of chiral 2(5H)-furanone derivatives possessing 1,2,3-triazole moieties.*
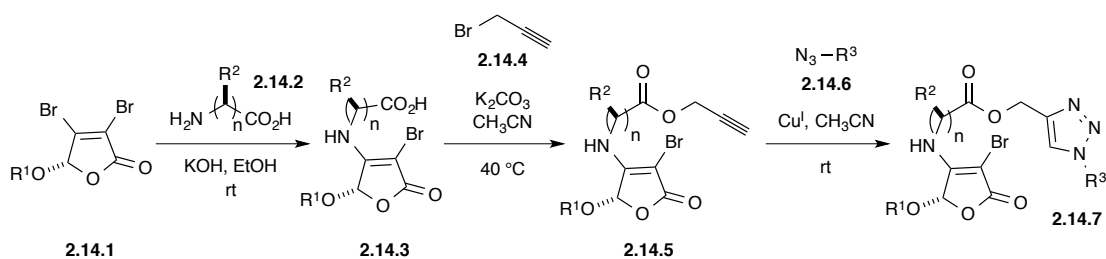
In 2013, Quan and coworkers applied one-pot four-component CuAAC for the

synthesis of functionalized 1,2,3-triazoles with 3,4-dihydropyrimidinone or amide group.[49]

Recently, 3,4-dihydropyrimidinones (DHPMs) have emerged as attractive targets for

synthesis due to their interesting pharmacological properties, where the *N*3-substituted

analogs bear the most attraction as active forms.[50] In this regard, one-pot MCR involving

CuAAC for the generation of *N*3-substituted DHPM analogs bearing 1,2,3-triazole moiety

was achieved. In continuation of previous work on synthesis of *N*3-substituted DHPM

analogs by reacting with paraformaldehyde in presence of TMSCl,[51] reaction conditions were

modified to be applied to one-pot MCR strategy. Sequential addition of paraformaldehyde in

Scheme 2.15. *Synthesis of functionalized 1,2,3-triazoles with 3,4-dihydropyrimidinone or amide group via one-pot four-component CuAAC.*

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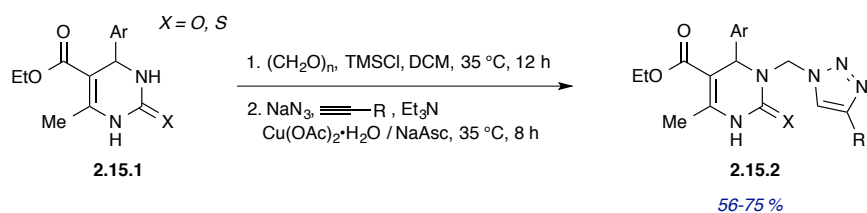
CH$_2$Cl$_2$ in the presence of TMSCl to DHPM **2.15.1**, followed by addition of NaN$_3$, terminal alkyne, and Et$_3$N in the presence of Cu(OAc)$_2$·H$_2$O/NaAsc furnished the desired product **2.15.2** in excellent yields (Scheme 2.15).

In 2014, the Santillán group demonstrated one-pot pseudo-four-component synthesis of mono- and di-benzylated 1,2,3-triazoles derived from anilines. [52] In regards to investigation of usage of 1,2,3-triazoles as steel corrosion inhibitors and/or transition metal ligands, synthesis of triazole derivatives containing aniline moiety was achieved. In the initial stages, CuAAC reaction with propargylated benzyl amine **2.16.1**, benzyl bromide **2.16.2**, and NaN$_3$ in the presence of 5 mol% Cu(OAc)$_2$•H$_2$O, 5 mol% 1,10-phenanthroline, and sodium ascorbate at room temperature resulted in mixture of mono- and di-benzylated triazole derivatives **2.16.3** and **2.16.4** (Scheme 2.16). By increasing the amount of benzyl bromide to 2 eq, the reaction solely furnished di-benzylated triazole **2.16.4**.

Scheme 2.16. *One-pot pseudo-four-component synthesis of mono- and di-benzylated 1,2,3-triazoles **2.16.3** and **2.16.4**.*
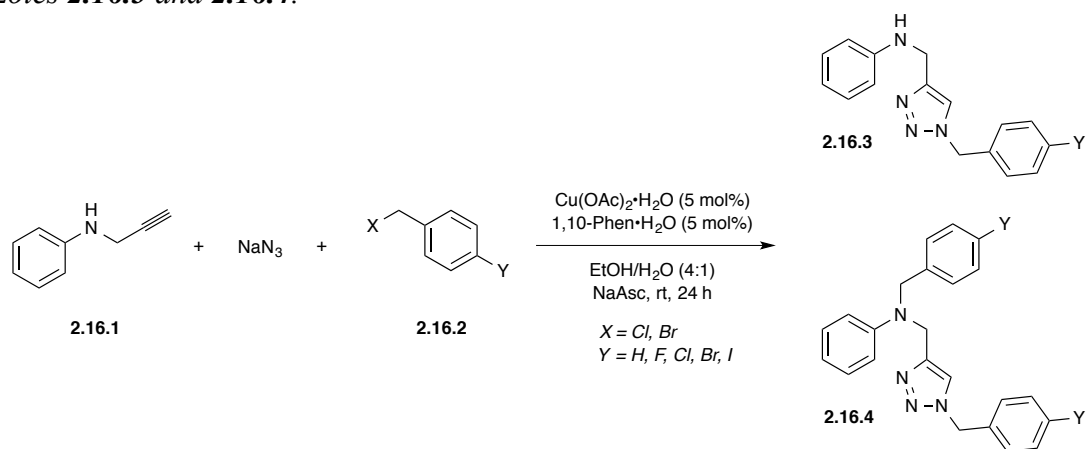
In 2014, Dabiri and coworkers reported the synthesis of (1,2,3-triazol-4-yl)methyl-3-amino-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carboxylate derivatives via one-pot four-component CuAAC reaction.[53] As introduced earlier, phthalazine derivatives

exhibit diverse biological activities.[36] Building upon previous work, preparation of novel phthalazine derivatives bearing an enamine moiety was demonstrated (Scheme 2.17). One-pot four-component condensation/CuAAC reaction involving benzaldehyde **2.17.2**, active methylene compound **2.17.3** (prop-2-ynyl-2-cyanoacetate), azide **2.17.4**, and phthalhydrazide **2.17.1** in the presence of $Cu(OAc)_2$ and sodium ascorbate as catalysts and 1-methyl-1*H*-imidazolium trifluoroacetate ([Hmim]TFA) as an ionic liquid medium provided the desired phthalazine derivatives **2.17.5** in excellent yields.

Scheme 2.17. *Synthesis of (1,2,3-triazol-4-yl)methyl-3-amino-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate derivatives via one-pot four-component CuAAC.*
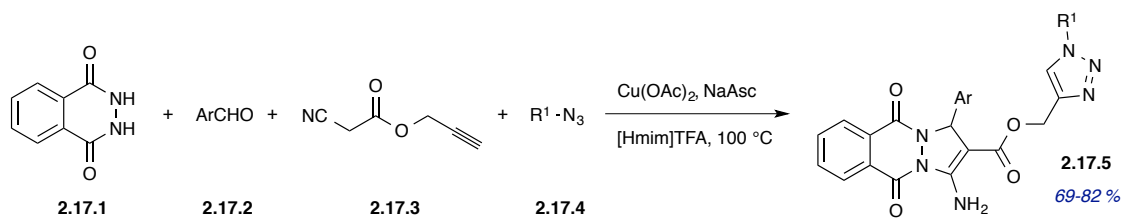
In 2015, the Kaushik group reported development of a facile one-pot five-component synthesis of glycoside annulated DHPM derivatives with 1,2,3-triazole linkage via transesterification/Biginelli/CuAAC reactions in aqueous medium.[54] As noted earlier, dihydropyrimidinones (DHPMs) have gained much attention from the synthetic community due to their potential pharmacological and biological activities.[50] By combining DHPMs with glycosides, which are the most abundant molecules in nature and play a major role in cellular metabolism, physiology, and signal transduction,[55] it will enable search for novel bioactivities by incorporating both advantages. One-pot five-component reaction of *tert*-butyl β-ketoester **2.18.2**, arylaldehyde **2.18.4**, urea **2.18.1**, propargyl alcohol **2.18.3**, and glycosyl azide **2.18.5** via transesterification, Biginelli reaction, and CuAAC in the presence

of 10 mol% CuI (relative to aldehyde) in water provided the optimal condition (Scheme 2.18). It is noteworthy that choice of solvent was crucial in performing this sequence, as shown by the results in Scheme 2.18.

Scheme 2.18. *One-pot five-component synthesis of glycoside annulated DHPM derivatives with 1,2,3-triazole linkage via transesterification/Biginelli/CuAAC.*
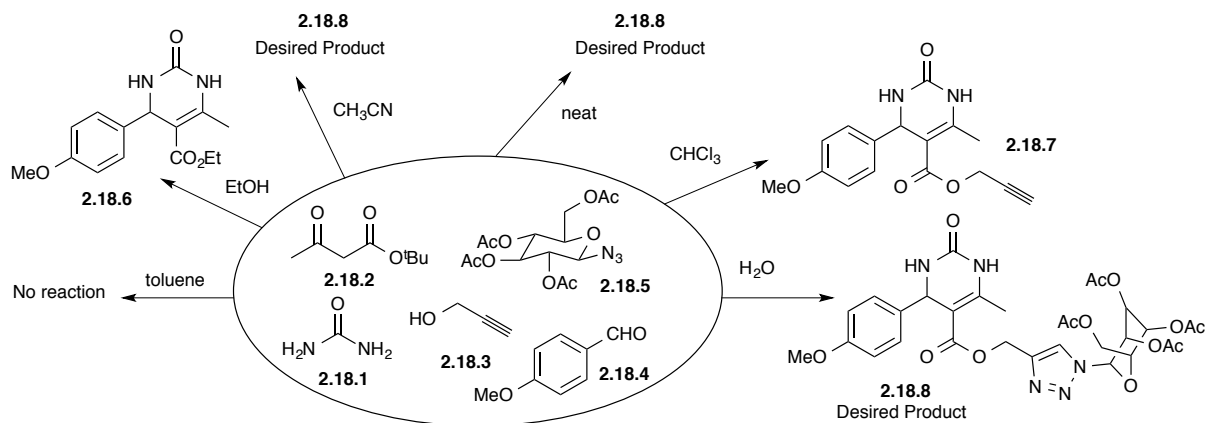
In 2014, Shaabani and coworkers reported application of CuAAC in one-pot six-component reaction to produce triazole-containing coumarin-3-carboxamides.[56] Recently, several works have revealed that compounds with coumarin backbones in junction to some nitrogen-containing heterocycles, such as azetidine, thiazolidine, and thiazoles, display significantly enhanced antimicrobial efficiency and broadened antimicrobial spectrum.[57] In attempts to combine the beneficial biological activities of coumarins and triazoles, one-pot six-component diversity oriented synthesis of coumarin-3-carboxamides with triazole ring was achieved via tandem Knoevenagel/Ugi/CuAAC (Scheme 2.19). Reaction of salicylaldehyde **2.19.2**, aromatic propargyloxy aldehyde **2.19.4**, aniline **2.19.5**, isocyanide **2.19.6**, and azide **2.19.3** in the presence of Cu(OAc)$_2$ and sodium ascorbate as catalysts

furnished the desired product **2.19.7** in excellent yields.   Various derivatives were

synthesized to produce a library of compounds with motifs that may exhibit interesting

biological activities.

Scheme 2.19. *One-pot six-component CuAAC reaction to produce triazole-containing coumarin-3-carboxamides.*
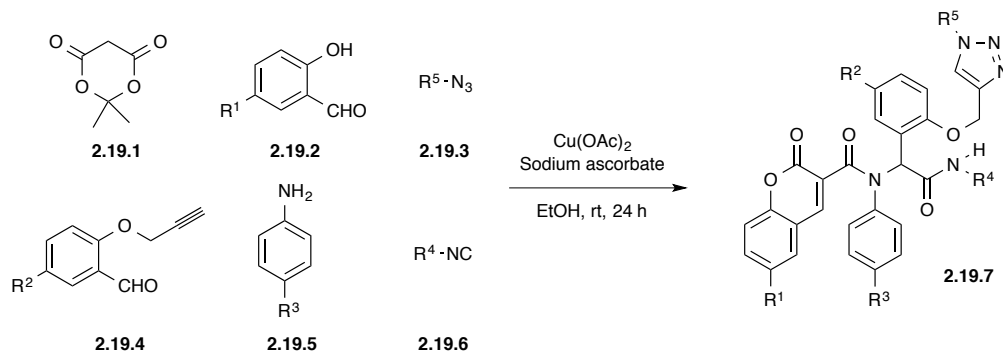

2.1c   Development of Novel Catalyst for CuAAC

In 2012, the Reddy group reported development of novel Cu^{II}-hydrotalcite (Cu^{II}-HT)

catalyst for its usage in one-pot MCR to generate β-hydroxy triazoles via regioselective

epoxide opening followed by Click cyclization in water at room temperature.[58] The

significance of this work, is that there are not many reports of studies on catalysts for the

preparation of β-hydroxy triazoles, and the majority of previously reported syntheses utilize

conditions with a wide array of drawbacks: low reactivity, use of organic solvents, use of

additives, elevated reaction temperatures, low yields, and formation of by-products.[59] The

authors focused their attention on hydrotalcites as potential novel catalyst to be utilized in the

desired reaction sequence due to the known beneficial properties in catalysis.[60] Optimization

for application to MCR with epoxides **2.20.1**, sodium azide, and terminal alkynes **2.20.3** to

produce of β-hydroxy triazoles **2.20.4** revealed catalyst mole ratio (Cu:Al) of 3:1 to be optimal in the presence of water as solvent at room temperature (Scheme 2.20). The Cu^{II}-HT catalyst was found to be easily recoverable via simple filtration, and displayed no significant loss of activity up to five runs, thus presenting potential for recyclability and use in large-scale applications.

Scheme 2.20. *Novel Cu^{II}-hydrotalcite catalyst for the usage in one-pot MCR to generate β-hydroxy triazoles.*
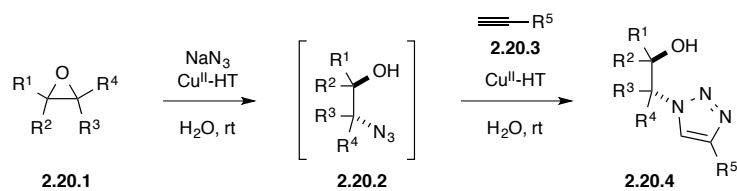

In 2012, García-Álvarez and coworkers reported utilization of (iminophosphorane)copper(I) complexes as novel catalysts for one-pot MCR involving *in situ* generated azides and alkynes in water.[61] Although there are known examples of one-pot MCR in water as solvent, there is only one previously reported catalytic system that utilizes 1-iodoalkynes in a chemo- and regioselective fashion.[62] The authors report synthesis and application of a novel copper(I) complex that is applied to one-pot three-component synthesis of triazoles **2.21.3** involving alkyne **2.21.1**, alkyl bromide **2.21.2**, and NaN$_3$ (Scheme 2.21). The novel complex displayed stability in water and air, and provided chemo- and regioselectivity. Also, it is the first example of isolated Cu(I) catalyst system that is also active with internal alkyne, 1-iodoalkyne. The presence of iodo moiety in the resulting triazole showcases how this methodology may be applicable to further functionalizations for synthetic use.

Scheme 2.21. *(Iminophosphorane)copper(I) complexes as novel catalysts for one-pot CuAAC MCR.*
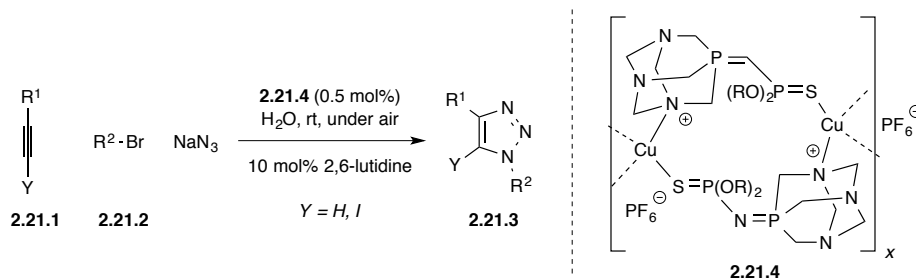

In 2012, Megia-Fernandez and coworkers reported a one-pot, three-component CuAAC method under microwave irradiation and heterogeneous catalysis for the synthesis of (alkyl sulfate)- and (alkyl sulfamidate)-1H-1,2,3-triazoles.[63] The authors envisioned three-component reaction of cyclic sulfates/sulfamidates **2.22.1** in the presence of sodium azide and terminal alkynes **2.22.2** would produce the desired products **2.22.3** in a facile manner. Aiming to simplify the isolation procedure, previously reported robust and efficient heterogeneous Click catalyst, Si-BPA•Cu^{+} or Si-BPMA•Cu^{+}, was employed (Scheme 2.22).[64] Adding all the components and the heterogeneous catalyst in a mixture of *t*-BuOH and water and reacting under microwave irradiation for 15 min at 60 °C provided the targets in excellent yields over 85%. The workup procedure involved only simple filtration of the catalyst and evaporation of the solvent mixture. The scope of this protocol was studied using various cyclic sulfates derived from glycerol and α-D-glucofuranose, highlighting the compatibility of this cascade process with wide variety of functionalities.

Scheme 2.22. *One-pot three-component (alkyl sulfate)- and (alkyl sulfamidate)-1H-1,2,3-triazoles using novel heterogeneous catalysts.*
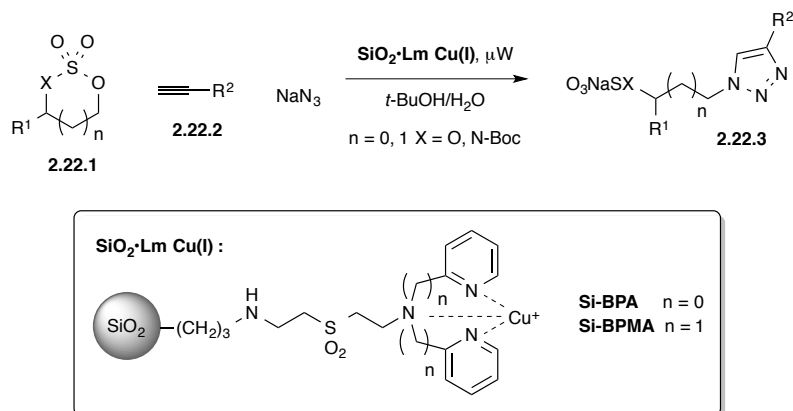
In 2013, the Ranu group reported a solvent-free one-pot three-component CuAAC catalyzed by Cu/Al$_2$O$_3$ surface under ball-milling conditions for the synthesis of 1,2,3-triazole derivatives.[65] Ball-milling (intense mechanical grinding) has recently emerged as an efficient and green method to perform chemical reactions.[66] In efforts to further enhance the eco-friendliness of CuAAC, a solvent-free one-pot three-component CuAAC was achieved with alkyl/benzyl halides **2.23.1** or aryl boronic acids **2.23.2**, sodium azide, and terminal alkynes **2.23.3** over Cu/Al$_2$O$_3$ surface under ball-milling conditions to afford triazole derivatives **2.23.4** (Scheme 2.23). The group observed that aryl halides do not undergo CuAAC in these conditions, so aryl boronic acids were utilized in place of aryl halides successfully. The three components were inserted into a ball-milling device, and optimal

Scheme 2.23. *Solvent-free one-pot three-component CuAAC catalyzed by Cu/Al$_2$O$_3$ surface under ball-milling conditions for the synthesis of 1,2,3-triazole derivatives **2.23.4**.*
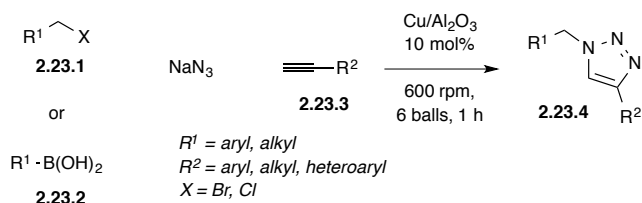
conditions were found to be 10 mol% of Cu/Al$_2$O$_3$ catalyst, ball-milling device running at 600 rpm in the presence of 6 balls for 1 h. The resulting reaction mixture was extracted with ethanol, and no chromatographic purification was required.

In 2013, Mittapelly and coworkers reported a one-pot three-component synthesis of 1,4-disubstituted 1,2,3-triazoles involving coupling of alcohol, azide, and alkynes using CuO nanoparticles.[67] In attempt to broaden the scope of one-pot MCR in combination with Click chemistry, the group utilized benzylic and allylic alcohols **2.24.1** and **2.24.2** as starting materials for the synthesis of 1,2,3-triazoles **2.24.4** and **2.24.5** (Scheme 2.24). In the presence of CuO nanoparticles, nucleophilic substitution with TMS azide of the alocohol moiety, followed by sequential capture of the resulting organic azide with terminal alkynes **2.24.3**, furnished the desired 1,4-disubstituted 1,2,3-triazoles **2.24.4** and **2.24.5** in good to excellent yields. Notably, this report enabled the use of unactivated alcohols, which generally requires preactivation of alcohol groups in order to substitute to azides.[68] Also, by capturing the reactive organic azide *in situ*, potentially unstable low molecular weight organic azides were handled safely.[69]

Scheme 2.24. *One-pot three-component synthesis of 1,4-disubstituted 1,2,3-triazoles **2.24.4** and **2.24.5** using CuO nanoparticles.*

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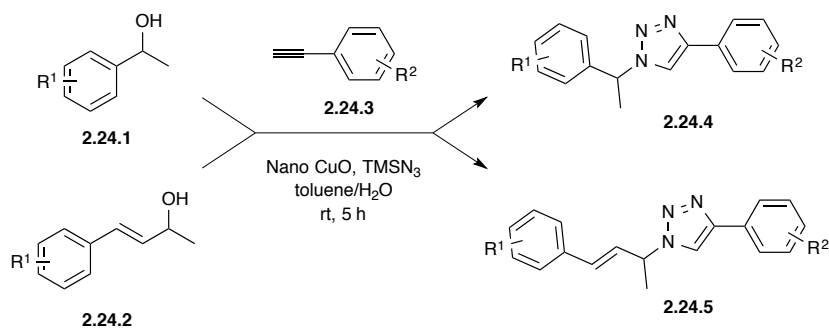
In 2013, Zhang and coworkers demonstrated the application of porous copper catalyst one-pot three-component CuAAC in water.[70] As shown in this section, major advances have been made in methodology development for production of triazoles. However, the development of heterogeneous immobilized copper catalysts that are inexpensive, readily available, easy to use, have high efficiency, and recyclable still remains a major challenge. In this regard, porous metals containing a large surface-to-volume ratio and are lightweight have recently attracted significant attention and have found wide range of applications in chemistry, mechanics, and nanotechnology.[71] Utilizing commercially available sintered copper porous material, one-pot three-component synthesis of triazoles **2.25.3** involving aliphatic/benzyl halide **2.25.1**, terminal alkyne **2.25.2**, and sodium azide was demonstrated (Scheme 2.25). The optimized conditions were 5 mol% catalyst loading in water at 55 °C. The catalyst was recyclable up to five times without loss of significant catalytic activity.

Scheme 2.25. *Application of porous copper catalyst to one-pot three-component CuAAC in water.*
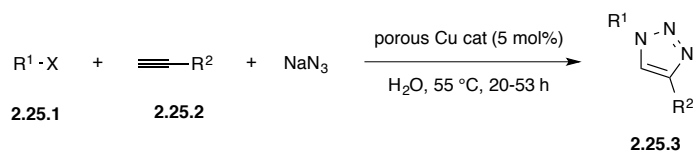
In 2014, the Astruc group reported utilization of novel, highly active, and magnetically recoverable tris(triazolyl)–Cu^I catalyst for CuAAC synthesis of triazoles.[72] The catalyst was supported on iron oxide nanoparticles and displayed excellent monodispersity, recoverability, and reusability. This nanoparticle-supported catalyst **2.26.4** was then applied towards one-pot three-component CuAAC reactions involving benzyl bromides **2.26.2**, alkynes **2.26.1**, and sodium azide to furnish triazole **2.26.3** (Scheme 2.26). This process was

performed at room temperature in water for 24 h, with 0.5 mol% catalyst loading. The catalyst was next easily recovered by using an external magnet, and reusability was observed up to five times with no significant loss of catalytic activity. ICP analysis revealed that amount of copper leached to reaction mixture is negligible around 1.5 ppm.

Scheme 2.26. *Magnetically recoverable tris(triazolyl)–Cu[I] catalyst for one-pot CuAAC synthesis of triazoles.*
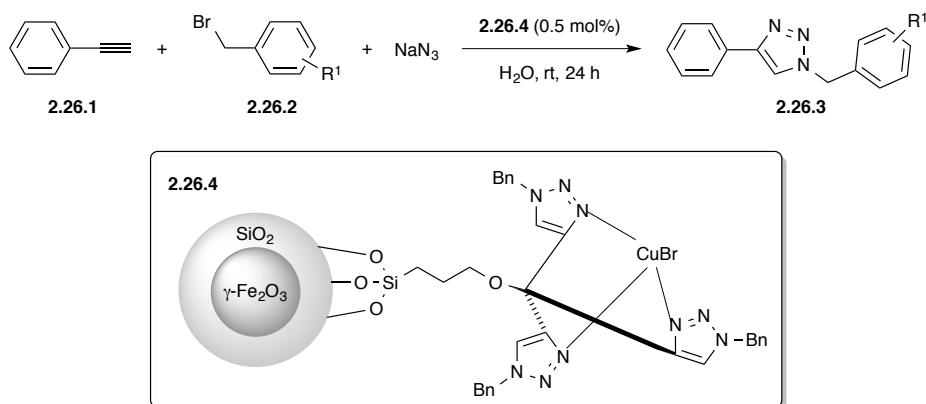
In 2014, Nasr-Esfahani and coworkers reported development of copper immobilized on nanosilica triazine dendrimer (Cu(II)-TD@nSiO$_2$)-catalyzed regioselective synthesis of various triazole derivatives via one-pot three-component CuAAC reaction.[73] Building upon previous work on preparation of Cu(II)-TD@nSiO$_2$,[74] the catalyst system was applied to production of wide range of 1,4-disubstituted 1,2,3-triazoles **2.27.6-9** (Scheme 2.27). Optimization studies revealed mixture of H$_2$O/EtOH (2:1), 0.3 mol% catalyst loading, and 5 mol% sodium ascorbate at room temperature for 20 min to be optimal. After the reactions were complete, the reaction mixture was diluted with H$_2$O and EtOAc, and the catalyst was separated by simple filtration. Upon drying, reusability of the catalyst was tested and showed no significant loss of activity up to five times. Leaching of copper from the catalyst system was found to be minimal around less than 0.1 ppm by ICP analysis.

Scheme 2.27. *Cu(II)-TD@nSiO$_2$-catalyzed regioselective synthesis of various triazole derivatives via one-pot three-component CuAAC reaction.*
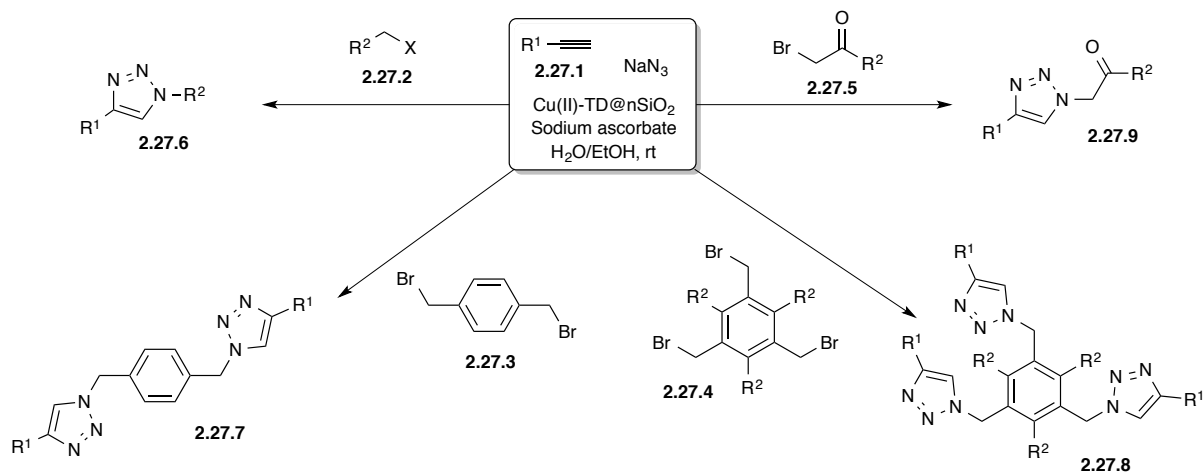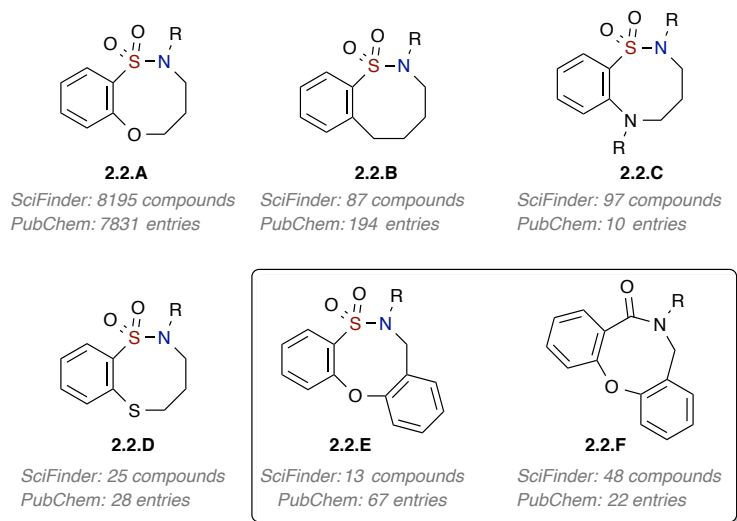

2.2 Application of one-pot, three-component strategy for the synthesis of dibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxides

The employment of various facilitation approaches, such as Build-Couple-Pair[75] and function group pairing (FGP)[76] paradigms, for the development of single-pot, multistep reaction processes in sequential fashion for the generation of functionalized heterocyclic scaffolds represents a method of high value for enabling DOS platforms and high-throughput screening (HTS). The ability of one-pot multistep reaction processes to generate core scaffolds in a quick and facile manner allows for producing scaffolds and its analogs, making use of step,[77] atom,[78] and pot economy.[79] The key feature of one-pot, sequential multistep protocol is moving through multi-reaction transformations without the need for workup or purification in between, both facilitating the process and saving resources.

Sultams (cyclic sulfonamides) are a non-natural class of heterocycles that have demonstrated a broad spectrum of biological activity.[80] Despite these attributes, reports of

eight membered benzofused sultams bearing oxygen in the core skeleton are limited to four reports to the best of our knowledge.[81,82] More detailed SciFinder and PubChem substructure searches show that these motifs containing hydrocarbon **2.2.B** or other heteroatoms such as nitrogen **2.2.C** or sulfur **2.2.D** are in fact relatively scarce (Figure 2.2). Dibenzofused sultams **2.2.E** and their corresponding lactam analogs **2.2.F** are even less abundant. In this regard, development of facile methods towards production of these structurally unique scaffolds may provide benefits to further study various biological activities involved with sultams.

**Figure 2.2.** *SciFinder and PubChem substructure searches as of 04-06-2015.*

2.2.A
SciFinder: 8195 compounds
PubChem: 7831 entries

2.2.B
SciFinder: 87 compounds
PubChem: 194 entries

2.2.C
SciFinder: 97 compounds
PubChem: 10 entries

2.2.D
SciFinder: 25 compounds
PubChem: 28 entries

2.2.E
SciFinder: 13 compounds
PubChem: 67 entries

2.2.F
SciFinder: 48 compounds
PubChem: 22 entries

The development of formal "4+4" CAP heterocyclization strategy to generate dibenzofused sultams was recently reported.[82] In the previous chapter, we described library synthesis of sultam compounds utilizing one-pot three-component Click/S$_N$Ar protocol. Building on these efforts, we herein report the development of one-pot, sequential, multistep/multicomponent strategies for the production of eight-membered dibenzofused

sultams employing *in situ* generated ortho-quinone methides (*o*-QM) in a formal "4+4" heterocyclization reaction.

Initial studies focused on optimizing the conditions for sulfonylation of primary amine **2.28.2** using ortho-fluorobenzenesulfonyl chloride **2.28.1** to generate secondary sulfonamide **2.28.3** as a precursor for the sequential "4+4" cyclization (Scheme 2.28). Originally, the reported conditions for sulfonylation required usage of K_2CO_3 as base in a biphasic 1:1 mixture of water/CH_2Cl_2 for overnight reaction at room temperature. However, we envisioned that if the sulfonylation were to proceed in THF, the reaction conditions might then be compatible with the following step. Reaction in THF and Et_3N as base at room temperature gratifyingly provided quantitative yield of the desired secondary sulfonamide **2.28.3** at a much faster rate of around 1 h, after purification through column chromatography. In efforts to streamline this process, monitoring of this process was carried out with TLC. After the disappearance of the starting materials, *o*-QM precursor **2.28.4** was next added, along with 3 equivalents of TBAF and exposed the reaction vessel to microwave irradiation at 100 °C for 40 min to afford 8-membered dibenzofused sultams **2.28.5**. The final crude reaction mixture was washed with H_2O and extracted with EtOAc, and after concentration *in vacuo*, the mixture was purified by column chromatography. To our delight, the desired cyclized products **2.28.6-13** were achieved in yields from 77–99 %, completing the one-pot three-component reaction, which involve benzenesulfonyl chloride, primary amine, and *o*-QM precursors.

Scheme 2.28. *One-pot sequential three-component method for synthesis of dibenzo[b,g][1,4,5]oxathiazocine 5,5-dioxides **2.28.6-13**.*
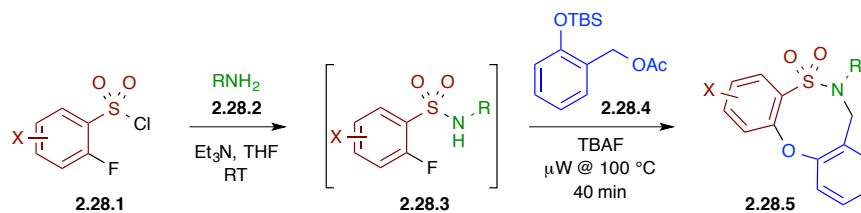
Compound	X	R	Yield (%)[a]
2.28.6	4-F	propargyl	99
2.28.7	4-F	*n*-butyl	80
2.28.8	4-F	benzyl	47
2.28.9	4-F	2-ethanol	15
2.28.10	4-F	cyclopropyl	80
2.28.11	4-F	Gly•OEt	9
2.28.12	6-F	2-ethanol	11
2.28.13	4-Br	propargyl	99

[a] Final isolated yield after flash chromatography.

It is important to note that the aqueous workup was necessary at the final stage to facilitate purification of the reaction mixture. This step is deemed necessary due to the existence of various by-products such as both organic and inorganic salts that are present in the reaction mixture. When the crude reaction mixture was put through column chromatography after concentration *in vacuo* without the aqueous workup, the process failed to yield pure product when the same solvent gradient was applied for column chromatography.

2.3 Extension of one-pot strategy via S$_N$Ar for four-component synthesis

From the conditions we developed for the library production of dibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxides, we investigated the potential of further extending the utility of one-pot sequential MCR pathway. As mentioned earlier, nucleophilic aromatic substitution (S$_N$Ar) is commonly used to further functionalize a halogen containing aromatic system. As introduced at the beginning of Chapter 1, previous reports from our group demonstrate how S$_N$Ar reactions may add peripheral diversity to existing scaffolds.[83] The reported conditions employ primary or secondary amines with either Cs$_2$CO$_3$ or 1,8-diazabicycloundec-7-ene (DBU) in DMSO in microwave conditions at 150-180 °C for 50 min.

In order to apply this useful reaction for the development of one-pot sequential pathway, a different condition was utilized. Following the one-pot, sequential, three-component strategy, benzenesulfonyl chloride **2.28.1** was reacted with primary amine **2.29.1** to produce secondary sulfonamide **2.29.2**, which was then reacted with *o*-QM precursor **2.28.4** to afford sultam **2.29.3** (Scheme 2.29). At this stage, without workup or change of solvent from previous reactions (THF), an excess of primary or secondary amine **2.29.4** and 0.1 equivalents of DBU were added to the reaction mixture. The vessel was then exposed to μW conditions at 100 °C for 1 h. After an aqueous workup and silica SPE to remove excess amines, the reaction mixture was then purified via column chromatography. The corresponding S$_N$Ar adducts **2.29.5** were isolated in excellent yields. Relative to previous harsh conditions at high temperatures in DMSO, the workup is cleaner since decomposed

DMSO can be avoided. The results demonstrate the scope of various primary and secondary/cyclic amines that may be incorporated to these reaction conditions.

Scheme 2.29. *One-pot sequential four-component method including S$_N$Ar for peripheral diversity.*
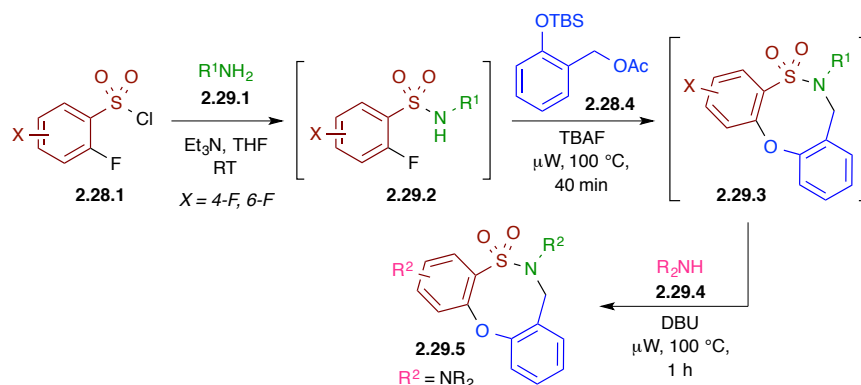
Compound	R^1	R^2 position	R^2	yield %^{a}
2.29.6	propargyl	4-	pyrrolidine	86
2.29.7	propargyl	4-	morpholine	96
2.29.8	propargyl	4-	*N*-methyl-2-ethanol amine	28
2.29.9	*n*-butyl	4-	morpholine	64
2.29.10	*n*-butyl	4-	pyrrolidine	68
2.29.11	propargyl	6-	isobutyl amine	39
2.29.12	propargyl	6-	*N*-methyl-2-ethanol amine	27

^{a} Final isolated yield after flash chromatography.

2.4 Extension of one-pot strategy via CuAAC for five-component synthesis

With these encouraging results in hand, we envisioned incorporating one more step in this sequence of reactions. An emerging functional handle that is commonly utilized in adding diversity to a scaffold is the triazole moiety, as seen earlier in this chapter. Moreover, it was demonstrated in Chapter 1 that S$_N$Ar and Click reactions are orthogonal to each other, albeit being in different reaction conditions. In order to add diversity via triazole formation,

propargyl amine was selected as the amine for the initial sulfonylation reaction. This propargyl moiety will be then available for a late stage-[3+2]-Huisgen cyclization reaction, commonly referred to as Click reaction.

Initially, we started our methodology studies by adding benzyl azide **2.30.4** with a copper source to perform Click reaction after the fourth (S_NAr) reaction is complete, in a sequential manner (Scheme 2.30). However, after considering the orthogonality of S_NAr and Click reaction, we investigated the possibility of executing the two reactions in a

Scheme 2.30. *One-pot sequential five-component reaction incorporating S_NAr/Click reaction pathway.*
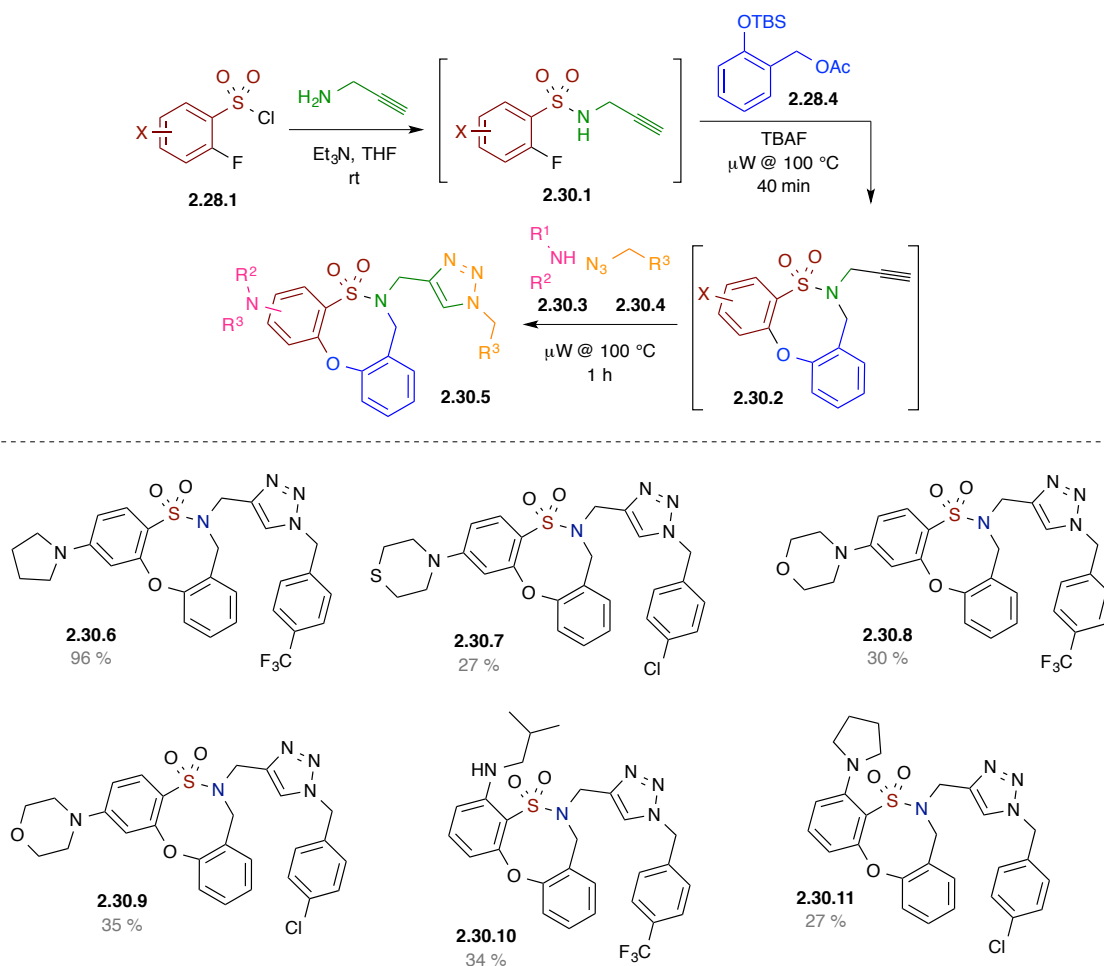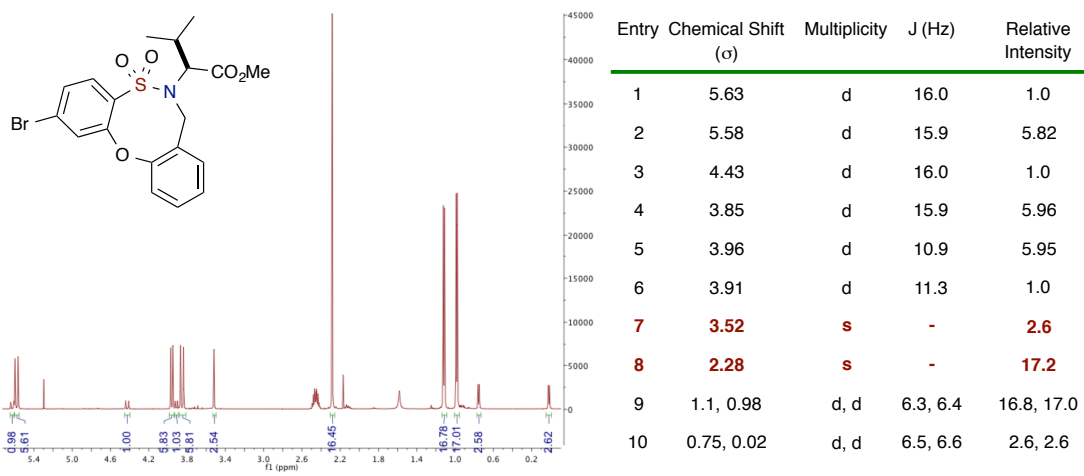
multicomponent reaction fashion. Without any purification or solvent change, after completion of the three-component reaction, 2 equivalents of benzyl azide **2.30.4**, 5 equivalents of amine **2.30.3**, 0.3 equivalents of DBU, and 0.1 mol% of CuI were added to the reaction mixture. Then, the mixture was exposed to µW conditions at 100 °C for 1 h. After an aqueous workup and silica SPE, purification was done via column chromatography. To our delight, we were able to achieve one-pot, sequential, 5-component multi-step/multi-component reaction products **2.30.5** in excellent overall yields (Scheme 2.30).

2.5 High-temperature NMR studies

Previous stepwise synthesis of the desired 8-membered dibenzofused sultams revealed that there are a set of rotamers seen in the ^{1}H NMR spectra as evident by the appearance of the two split peaks for the –OMe residing at the periphery on amino ester-derived scaffolds (Figure 2.3).[82] Initially, this phenomenon was viewed as a minor by-product (two –OMe peaks at 2.28 ppm and 3.52 ppm). The relative intensities suggested

Figure 2.3. *NMR analysis suggesting existence of possible rotamers.*

Entry	Chemical Shift (σ)	Multiplicity	J (Hz)	Relative Intensity
1	5.63	d	16.0	1.0
2	5.58	d	15.9	5.82
3	4.43	d	16.0	1.0
4	3.85	d	15.9	5.96
5	3.96	d	10.9	5.95
6	3.91	d	11.3	1.0
7	3.52	s	-	2.6
8	2.28	s	-	17.2
9	1.1, 0.98	d, d	6.3, 6.4	16.8, 17.0
10	0.75, 0.02	d, d	6.5, 6.6	2.6, 2.6

that there is an approximately 7:1 ratio of the two conformers in the case of valine•OMe-derived scaffold shown in Figure 2.3. X-ray crystallographic analysis of a single crystal confirmed the non-flat and cup-like architecture of this unique sultam,[84] but solution ^{1}H-NMR data also revealed that we have two conformers, plausibly rotamers about the N–Cα bond or two ring conformers (oxygen up as in X-ray or down in ring-flipped structure) (Figure 2.4).

Figure 2.4. *X-ray crystal structure of Val•OMe-derived sultam.*
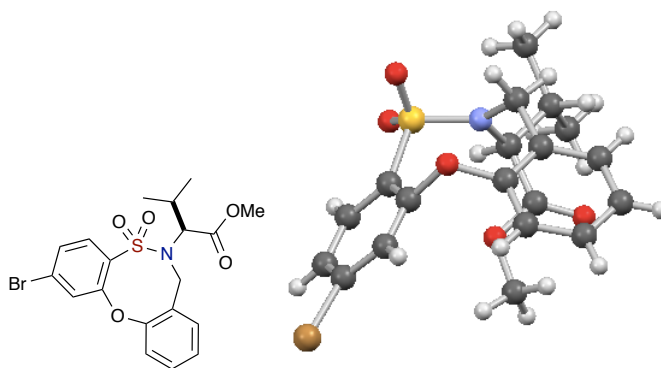
In considering rotamer vs ring conformer mentioned in the previous paragraph, consideration of innate properties of sulfonamides should be in order. In this regard, discussion among colleagues, as well as recent analysis detailed in Dr. Joanna Loh's thesis and Dr. Kyu Ok Jeon's thesis,[85] have shed light on the unique conformational control imparted by the preferred conformation of sulfonamides, which places the nitrogen lone pair anti-periplanar to the S–Ar bond to maximize the σ^* orbital delocalization. This conformation effectively allows the orientation of the lone pair to bisect the O=S=O internuclear angle.[86] In amino ester derived sultams, such as valine•OMe derived sultam shown in Figure 2.4, an additional favorable low energy Cα–H/S=O syn pentane interaction

provides additional stabilization to plausibly partition two potential rotameric structures. These features could potentially influence both aforementioned rotamers and ring-flipped structures.

In order to shed additional light on this matter, variable temperature NMR experiments were carried out to establish the barrier to rotation about the N–C bond. This phenomenon was explained by the hindered rotation around the bond between sulfonamide nitrogen and carbon substituent. Two scaffolds, alanine methyl ester-derived and valine methyl ester-derived scaffolds were selected based on the steric bulk attached to the sulfonamide nitrogen. The A-values of methyl and isopropyl substituents are 1.70 and 2.15 kcal/mol, respectively. We hypothesized that by heating the compound to higher temperatures, the two split –OMe peaks will slowly coalesce by overcoming the rotational barrier between the existing rotamers. At the same time, we hypothesized that the magnitude of steric bulk will have a linear relationship with barrier of rotation between the two rotamers.

High-temperature NMR studies were performed with the two scaffolds. The two compounds were dissolved in d[6]-DMSO, and the peaks representing the –OMe of the methyl esters at the periphery were measured (Figure 2.5, 2.6). By heating from room temperature up to 110 °C, the two rotamer peaks were measured at each temperatures. As expected, we observed the slow coalescence of the two –OMe peaks as the temperatures increased. Based on the measured peaks, the barriers of the two conformers were calculated.[87] Alanine•OMe-derived scaffold's barrier was 16.2 kcal/mol, and that of valine•OMe-derived scaffold was 21.0 kcal/mol. The significance of these values led us to tentatively assume that this is most

likely a ring-flip phenomenon and not a rotational barrier issue, which is more likely to be around 10 kcal/mol.[85]

Figure 2.5. *High-temperature NMR study of alanine•OMe-derived scaffold.*
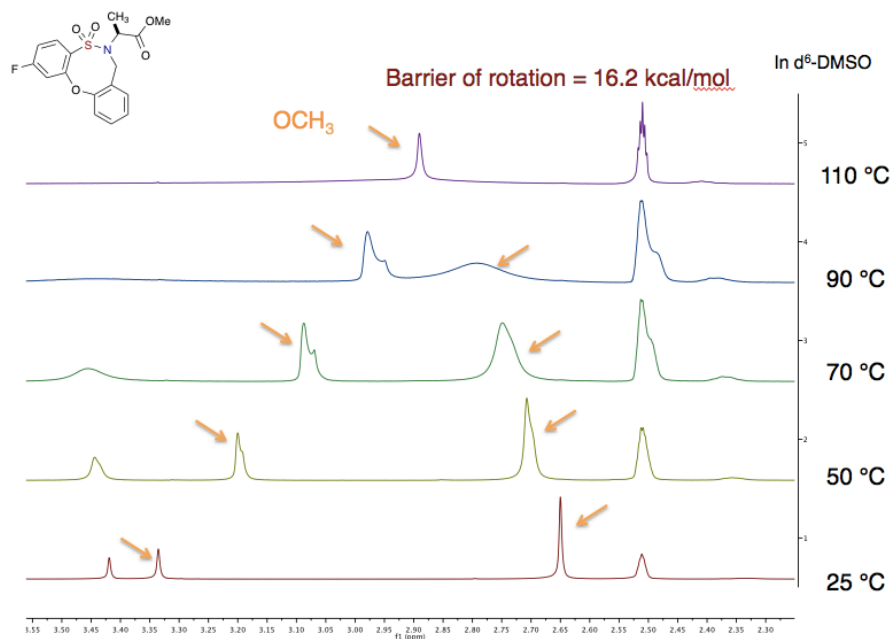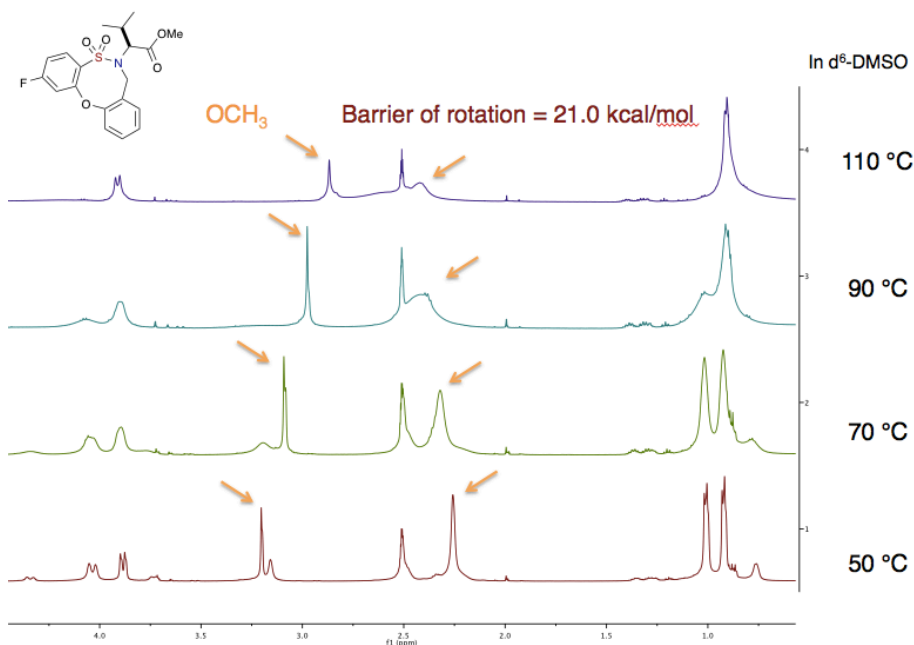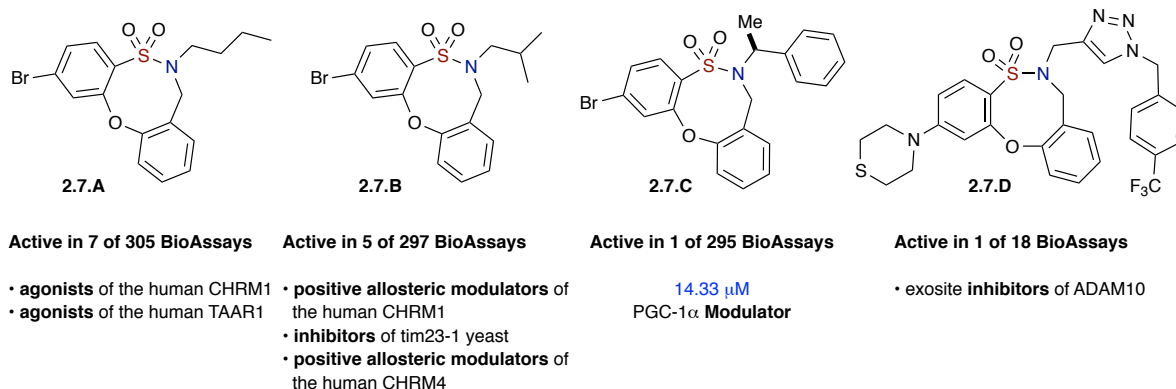

Figure 2.6. *High-temperature NMR study of valine•OMe-derived scaffold.*

2.6 Biological activity data

After submission of produced compounds to NIH Molecular Libraries Probe Production Centers Network (MLPCN) depository to be sent to Molecular Libraries Screening Centers Network (MLSCN), we were able to access the screening results in PubChem database. Gratifyingly, four compounds displayed various biological activities when screened against diverse biological assays (Figure 2.7). Sultam **2.7.A** exhibited agonist activity against both human cholinergic receptor, muscarinic 1 (CHRM1) and trace amine-associated receptor 1 (TAAR1). Sultam **2.7.B** was found to be positive allosteric modulators of both human CHRM1 and CHRM4, and also inhibitors of tim23-1 yeast. Sultam **2.7.C** displayed modulating activity against peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) at IC$_{50}$ of 14.33 μM. Notably, sultam **2.7.D**, which was generated from one-pot, sequential, five-component reaction protocol, was identified as exosite inhibitors of a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10).

Figure 2.7. *Biological assay data from PubChem database.*

2.7.A	**2.7.B**	**2.7.C**	**2.7.D**
Active in 7 of 305 BioAssays	**Active in 5 of 297 BioAssays**	**Active in 1 of 295 BioAssays**	**Active in 1 of 18 BioAssays**
· **agonists** of the human CHRM1 · **agonists** of the human TAAR1	· **positive allosteric modulators** of the human CHRM1 · **inhibitors** of tim23-1 yeast · **positive allosteric modulators** of the human CHRM4	14.33 μM PGC-1α **Modulator**	· exosite **inhibitors** of ADAM10

2.7 Conclusion

In conclusion, development of one-pot sequential three-, four-, and five-component reactions for the synthesis of diverse dibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide derivatives inspired from the method developed in Chapter 1 have been achieved. From the resulting scaffolds derived from alanine and valine methyl esters, rotational barriers between the two existing rotamers were studied through high-temperature NMR analysis. Biological data was also obtained from PubChem and has shown promising activities. The developed one-pot sequential methodology is highly efficient and yielding, and will enable further production of analogs in a highly facilitated manner for ultimate screening in a broad range of assays.

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[87] $k = \dfrac{\pi \Delta \nu}{\sqrt{2}}$ or $k = \dfrac{\pi}{\sqrt{2}}(\Delta \nu_{1/2} - \Delta \nu_{1/2}{}^{ref})$, $\Delta G = 2.303 RT[10.32 + log\dfrac{T}{k}]$

Chapter 3

Synthesis of Sultam Analogs of

Tetramic Acids

and Their Derivatives

Chpater 3: Synthesis of Sultam Analogs of Tetramic Acids and Their Derivatives

3.1 Introduction – Review of Synthesis and Modification of Tetramic Acids

Tetramic acids are well known in the literature for their existence in numerous natural products and biologically active compounds. Bioactivities include, but are not limited to, antibiotic, antiviral, cytotoxicity, and cell cycle inhibition (Figure 3.1).[1] The broad bioactivity of tetramic acids has attracted much attention from the synthetic community, spawning various types of library syntheses and their corresponding structure-activity relationships (SARs).

In contrast, the corresponding sultam (cyclic sulfonamide) derivatives of tetramic acids are relatively limited in the literature. As shown in Figure 3.2, the number of sultam analogs **3.2.C** and tautomer compounds **3.2.D** listed in SciFinder and entries in PubChem database are drastically scarce relative to tetramic acid cores **3.2.A** and their tautomers **3.2.B**. In this regard, the development of methods to produce sultam analogs of tetramic acids will

Figure 3.1. *Select examples of natural products containing tetramic acid core.*

Integramycin
HIV-1 integrase inihibitor, IC$_{50}$ = 4 μM

Equisetin
antibiotic, HIV, mammalian DNA binding

Discodermide
Antifungal against *Candida albicans*

Tenuazonic acid
Secondary metabolite toxin

Melophlins
Cytotoxic against HeLa cells
antibacterial activity

Reutericyclin
Antibiotic activity
against a variety of
gram-positive bacteria

Janolusimide
Lipophilic tripeptide neurotoxin

be beneficial to occupy underdeveloped chemical space in search for novel compounds with potential biological activities. We herein report the synthesis of monocyclic and bicyclic sultam analogs of tetramic acids, and further derivatization to generate analogues of known biologically active compounds via "Click, Click, Cyclize" methodology.[2] Further discussion of "Click, Click, Cyclize" methodology will be introduced in Section 3.2.

Figure 3.2. *SciFinder and PubChem database substructure search result as of 04-07-2015.*

3.2.A

3.2.B

3.2.C

3.2.D

SciFinder: 82439 compounds
PubChem: 8684 entries

SciFinder: 250515 compounds
PubChem: 8522 entries

SciFinder: **159 compounds**
PubChem: **110 entries**

SciFinder: **166 compounds**
PubChem: **95 entries**
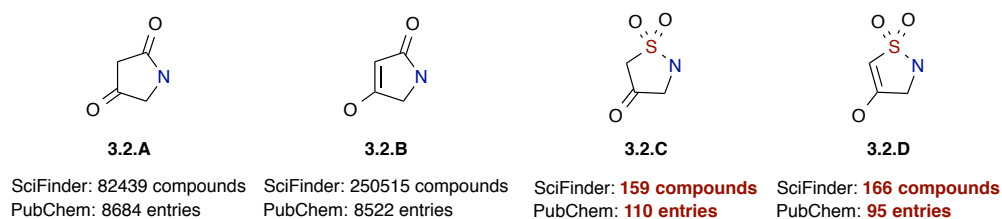
This introduction in this chapter will focus solely on review of recently developed synthetic methodods towards the production of tetramic acids and their modifications for the synthesis of derivatives, from 2010 to-date. For methods developed prior to 2010, the reader is referred to two review articles published in 2008[3] and 2010.[4] Moreover, recent efforts towards the total synthesis of natural products containing tetramic acid moieties are described in the following references.[5]

In large, this review section is categorized into three subsections: (i) synthesis of tetramic acids via Dieckmann-related chemistry, (ii) synthesis of tetramic acids via non-Dieckmann-type chemistry, and (iii) modification of tetramic acids for peripheral diversity.

3.1a Dieckmann-derived Tetramic Acid Synthesis

In 2010, Deng and coworkers[6] reported synthesis of tetramic acid analog, which has a photosensitive moiety that was used for binding studies to undecaprenyl pyrophosphate synthase (UPPS). UPPS is a bacterial enzyme that catalyzes the condensation of eight molecules of isopentenyl pyrophosphate (IPP) with farnesyl pyrophosphate (FPP) to produce C_{55} undecaprenyl pyrophosphate (UPP). UPP then functions as a lipid carrier for peptidoglycan synthesis that is involved in bacterial cell wall construction. Starting from commercially available 4-aminobenzophenone **3.1.1**, acylation with methyl malonyl chloride **3.1.2** afforded **3.1.3** (Scheme 3.1). Hydrolysis of the ester moiety with NaOH, followed by EDCI coupling with ethyl-2-homophenylalanine yielded compound **3.1.5**, which is ready for intramolecular Dieckmann condensation. Dieckmann condensation of **3.1.5** in the presence of 21% NaOEt in EtOH produced tetramic acid **3.1.6**. The synthesized tetramic acid was

employed as a photoprobe in studying the binding mode of tetramic acids in the FPP binding site.

Scheme 3.1. *Synthesis of tetramic acid derivative bearing photosensitive moiety.*
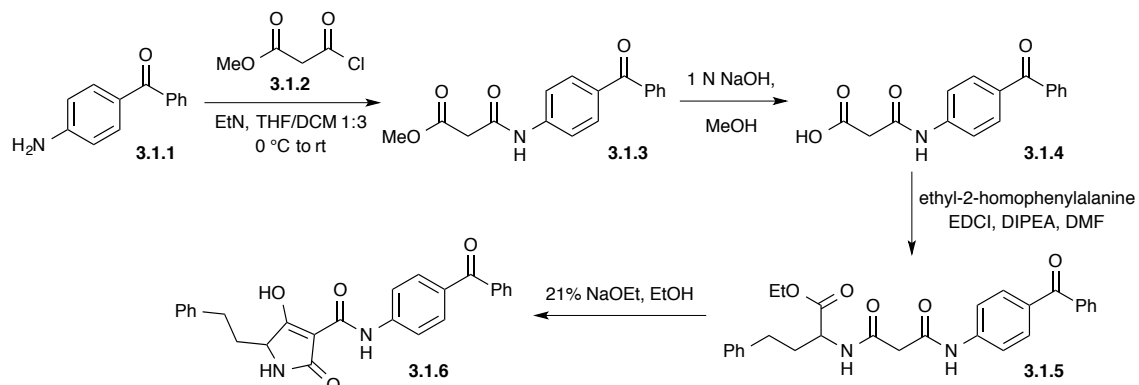
In 2010, Yang and coworkers [7] reported synthesis of novel (*E*)-3-(1-(alkyloxyamino)ethylidene)-1-alkylpyrrolidine-2,4-dione derivatives (Scheme 3.2). In building the Dieckmann cyclization precursor **3.2.5**, ethyl bromoacetate **3.2.1** was reacted with primary amine **3.2.2** to afford 2-(alkylamino)acetate **3.2.3**. Subsequent reaction with diketene **3.2.4** installed the dicarboxyl moiety to generate **3.2.5** that participates in the cyclization to form the tetramic acid core. Dieckmann cyclization of **3.2.5** with sodium methoxide furnished 3-acyl tetramic acid **3.2.6**. Formation of oxime ether moiety at the 3-position was achieved by exposing the 3-acyl tetramic acid **3.2.6** to *O*-alkyl hydroxylamine **3.2.7** in presence of NaOH to afford 3-oxime-ether-substituted tetramic acid **3.2.8**.

Scheme 3.2. *Synthesis of novel (E)-3-(1-(alkyloxyamino)ethylidene)-1-alkylpyrrolidine-2,4-dione derivatives.*

94
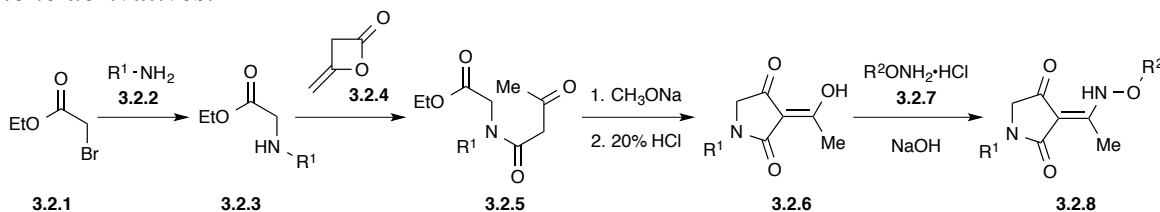
In 2010, Schobert and coworkers[8] reported the synthesis of precursors and analogs of aburatubolactam A and macrocidin A. Starting material aburatubolactam fragment **3.3.1** was prepared in six steps following literature precedent (Scheme 3.3a). Compound **3.3.1** was then acylated with 2,2-dimethyl-6-[(1*E*,3*E*)-penta-1,3-dienyl]-4*H*-[1,3]-dioxin-4-one **3.3.2** to afford amide **3.3.3**. Subsequent Dieckmann cyclization with NaOMe furnished aburatubolactam precursor **3.3.5**. A different route was employed in making analogs of macrocidin A (Scheme 3.3b). Starting from a simple tetramic acid **3.3.5**, Yoshii acylation with carboxylic acid to install the side chains at the 3-position yielded 3-acyl tetramic acid **3.3.6**. Deprotection of *N*-Boc moiety and subsequent removal of allyl group at the phenol position produced macrocidin A precursor **3.3.7**.

Scheme 3.3. *Synthesis of precursors of aburatubolactam A and macrocidin A.*
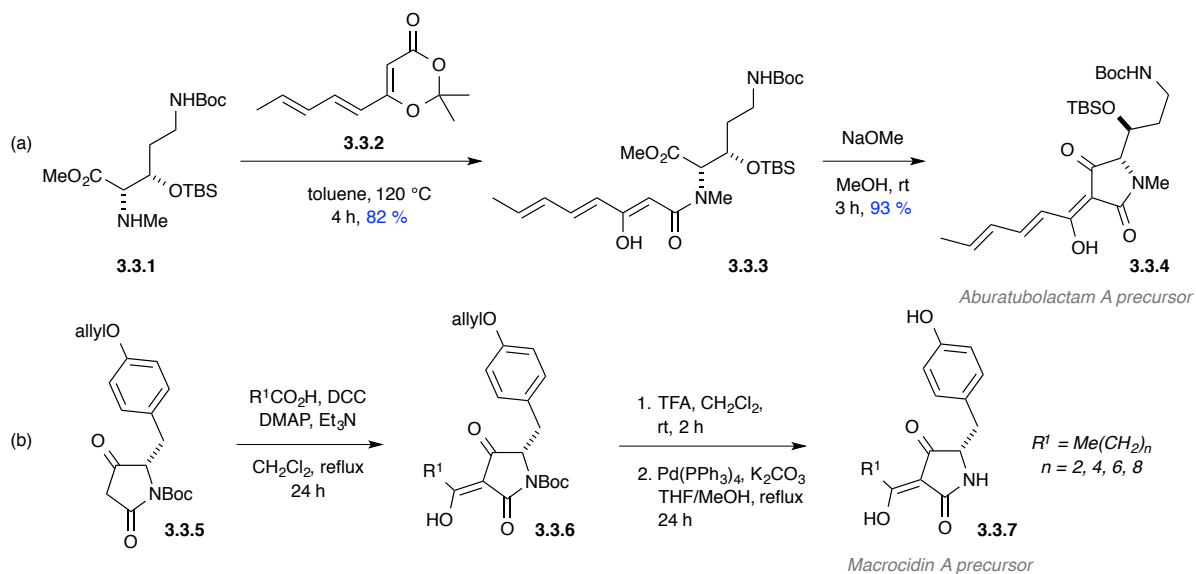
In 2011, Moloney and coworkers built upon previous work,[9] and reported the synthesis of a stereochemical library bearing tetramic acid cores. Starting from simple commercially available serine methyl ester **3.4.1**, reaction with pivaldehyde **3.4.2** afforded

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the oxazolidine motif **3.4.3** (Scheme 3.4). Subsequent acylation with carboxylic acid **3.4.4** followed by Dieckmann ring closure yielded the desired tetramic acid core **3.4.6**. This core then was further diversified through peripheral modification. The highlight of this strategy was the ability of generating a stereochemically diverse set of compounds starting from a simple starting material. The authors reported that the chiral heterocyclic libraries generated from tetramic acid cores exhibited antibacterial activity.

Scheme 3.4. *Synthesis of stereochemical library bearing tetramic acid cores.*
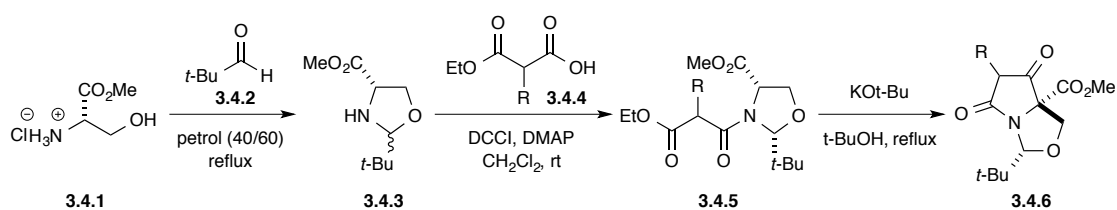
In 2011, Moody and coworkers[10] utilized a Diels-Alder approach in synthesizing spirotetramate cores of naturally occurring antibiotics. The synthesis of exocyclic methylene unit **3.5.8** that participates in Diels-Alder reaction as the dienophile is generated from a sequence of reactions starting from *S*-methylcysteine **3.5.1** (Scheme 3.5). 2,4-

Scheme 3.5. *Utilization of Diels-Alder approach in synthesizing spirotetramate core of naturally occurring antibiotics.*

96
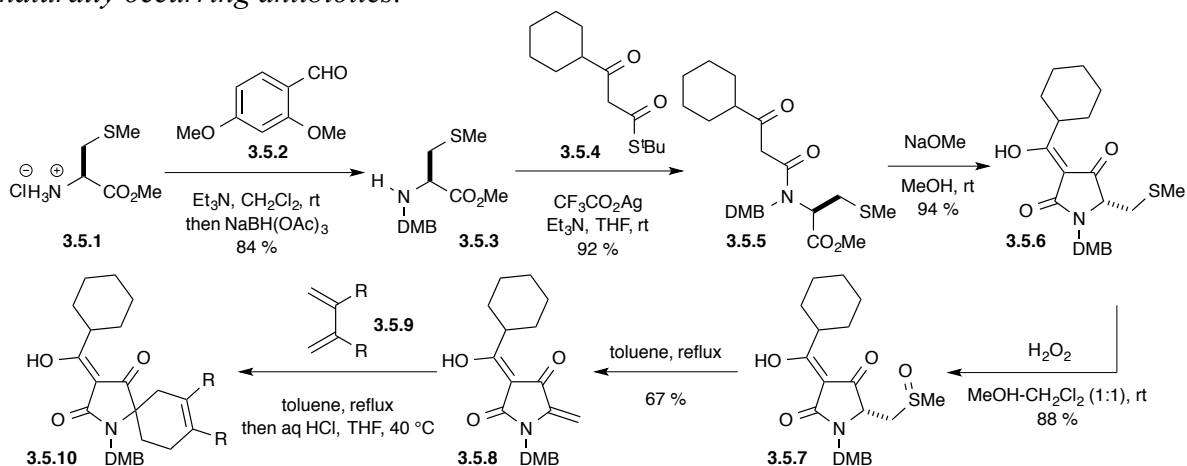
dimethoxybenzyl (DMB) protection of *S*-methylcysteine **3.5.1** with the corresponding aldehyde **3.5.2** and acylation with thioester **3.5.4** afforded Lacey-Dieckmann precursor **3.5.5**. The precursor **3.5.5** was then subjected to Lacey-Dieckmann conditions to yield tetramc acid **3.5.6**. Oxidation of the thioether of tetramic acid **3.5.6** with hydrogen peroxide, followed by thermal elimination produced the dienophile **3.5.8**. Diels-Alder reaction with various dienes **3.5.9** furnished spirotetramate **3.5.10**.

In 2013, Moloney and coworkers [9] reported synthesis of chiral bicyclic tetramic acid derivatives via chemoselective Dieckmann cyclization.[11] Starting from L-cysteine **3.6.1**, reaction with various aldehydes **3.6.2** afforded the corresponding thiazolidines **3.6.3** (Scheme 3.6). Subsequent coupling with monoethyl malonate **3.6.4** afforded the Dieckmann precursor **3.6.5**, predominantly the *cis*-isomer. Chemoselective Dieckmann cyclization with KOt-Bu successfully produced bicyclic tetramates **3.6.6**. This method was then extended to utilizing α-methyl serine **3.6.7**. Interestingly, only the *trans*-isomer

Scheme 3.6. *Synthesis of chiral bicyclic tetramic acid derivatives via chemoselective Dieckmann cyclization.*
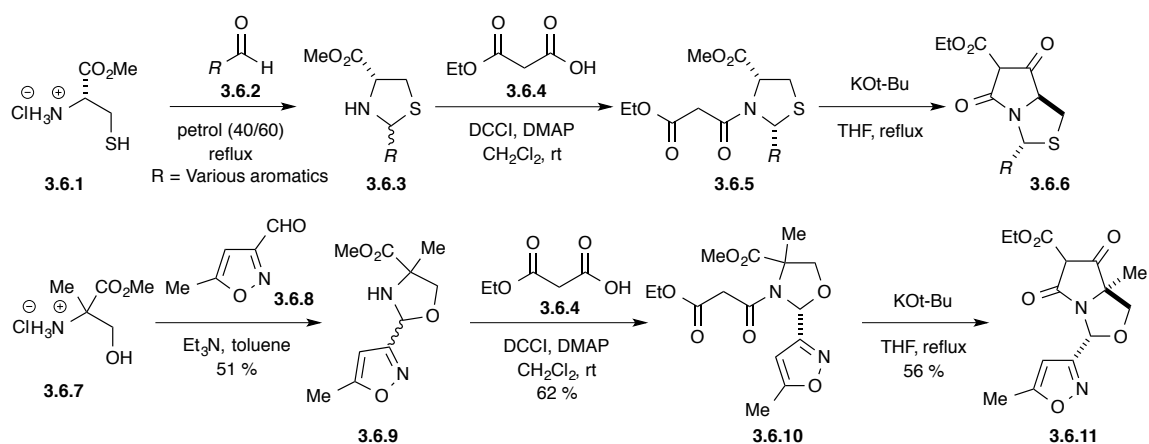
underwent Dieckmann cyclization to afford chiral α-methyl substituted bicyclic tetramates **3.6.11**.

In 2014, Liu and coworkers[12] reported the synthesis of 4-amino derivatives of tetramic acids. Diethyl malonate **3.7.1** was modified to yield monoethyl malonate **3.7.2**, which then was coupled with various commercially available amino esters **3.7.3** (Scheme 3.7a). Next, treatment with NaOMe in refluxing toluene afforded the Dieckmann cycloadduct 3-acyl tetramic acid **3.7.5**. The subsequent decarboxylation was performed by refluxing the reaction in a mixture of acetonitrile and water to afford tetramic acid **3.7.6**. With tetramic acid **3.7.6** in hand, the authors then reported the transformation of the hydroxyl group to an amine by reacting with various primary amines **3.7.7** (Scheme 3.7b). In addition, tetramic acid **3.7.9** reacted with benzaldehyde to form an exocyclic olefin-containing tetramic acid **3.7.10**. However, they observed a mixture of the desired target and

Scheme 3.7. *Synthesis of 4-amino derivatives of tetramic acids.*

98
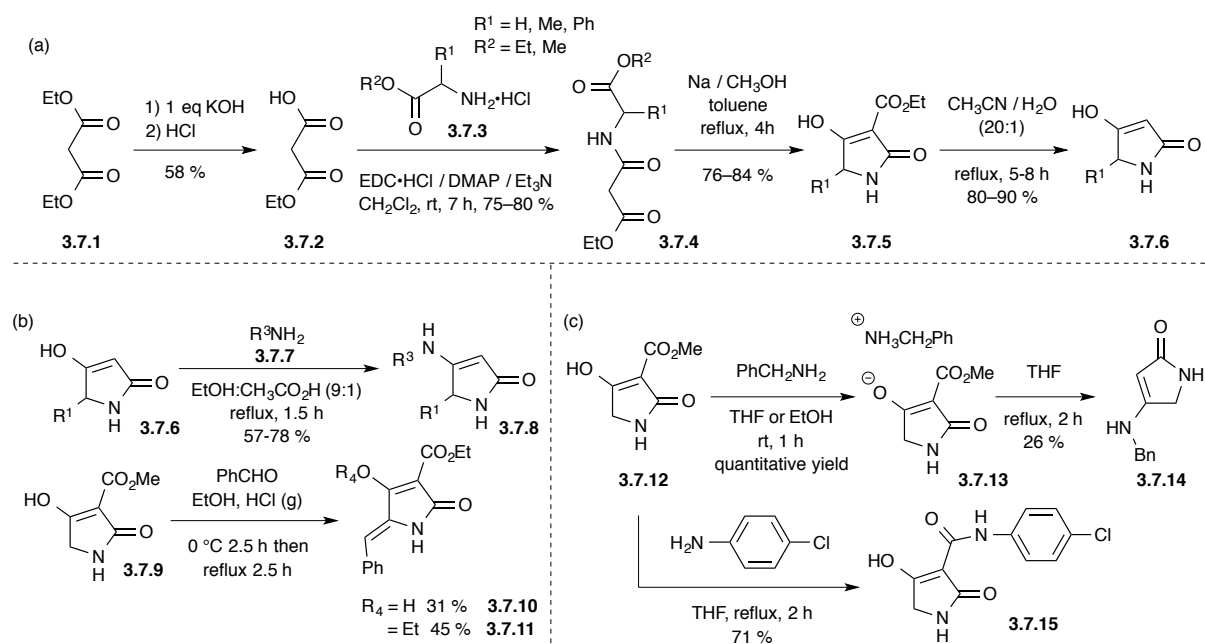
a 4-ethoxy tetramic acid **3.7.11**. In an alternate attempt to form 4-amino tetramic acids, the authors utilized 3-acyl tetramic acid **3.7.12** and reacted with benzyl amine in THF or EtOH at room temperature (Scheme 3.7c). Instead of proceeding to the desired 4-amino substrate **3.7.14**, they observed that the reaction stops at the salt formation at the 3-hydroxy position to yield **3.7.13**. However, when the mixture was refluxed in THF the desired amination product **3.7.14** was formed. When the amine partner is switched to aryl amines, they observed formation of 3-carboxamide tetramic acid **3.7.15**.

In 2014, Moloney and workers reported further modification to generate 3-acyl tetramic acids.[13] 3-Acyl side chains have been identified on numerous bioactive natural products containing tetramic acid cores, and thus became a target for further studies. By utilizing previously synthesized bicyclic tetramic acids, the authors utilized *O*-acylation/rearrangement procedure to attach 3-acyl moieties. Treatment of tetramic acid **3.8.1** with acetic acid in the presence of DCC-DMAP furnished 3-acyl tetramic acid **3.8.2** (Scheme 3.8). The resulting 3-acyl tetramic acid **3.8.2** was then subjected to aromatic

Scheme 3.8. *Development of route towards 3-acyl tetramic acid derivatives.*
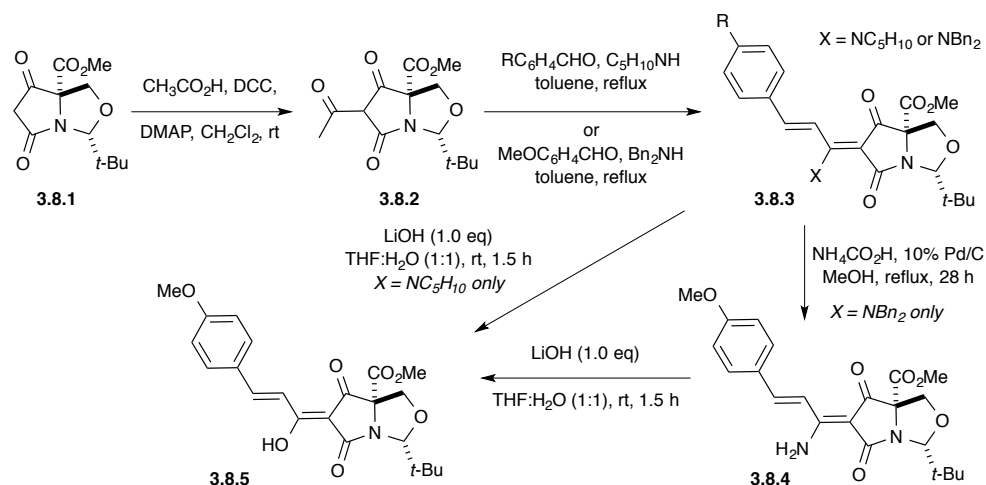
aldehydes using secondary amines (piperidine or dibenzyl amine) as base to produce enamine **3.8.3**. Depending on which secondary amine was used, the enamine was directly hydrolyzed under alkaline conditions or deprotected to form **3.8.4** and then hydrolized to afford 3-acyl substituted tetramic acid **3.8.5**.

3.1.b Non-Dieckmann/Non-traditional Dieckmann Section

In 2010, Alcaide and coworkers reported utilization of 2-azetidinone-tethered allenols in the synthesis of tetramic acids and spirocyclic seleno-β-lactams.[14] Screening of various halogenating reagents resulted in *N*-bromosuccinimide (NBS) as the optimal source of brominating the external allene **3.9.1**, which subsequently underwent selective 1,2 C–C bond migration to afford the desired tetramic acid **3.9.3** (Scheme 3.9). On the other hand, employing *N*-phenylselenophthalimide went through a different transition state **3.9.4**, which then led to oxycyclization with the loss of a proton to yield spirocyclic seleno-β-lactam **3.9.5**.

Scheme 3.9. *Synthesis of chiral tetramic acids and spirocyclic seleno-β-lactams.*
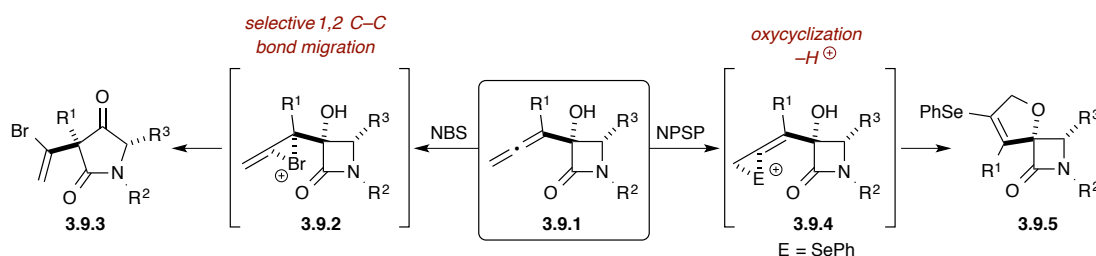
In 2010, the Dittmer group reported the usage of telluride-triggered Dieckmann cyclization for the synthesis of tetramic acids.[15] Telluride-triggered Dieckmann precursor α-bromoacyl amide ester **3.10.3** was prepared by acylating amino ester **3.10.1** with α-bromoacyl bromide **3.10.2** (Scheme 3.10). The precursor **3.10.3** was then treated with slurry

of lithium or sodium telluride in THF at room temperature, affording lithium enolate **3.10.4**, which then underwent Dieckmann cyclization to yield tetramic acid **3.10.5**. The authors noted that several of tetramic acid derivatives were unstable, and thus required conversion to the corresponding silyl enol form **3.10.6**.

Scheme 3.10. *Application of telluride-triggered Dieckmann cyclization for the synthesis of tetramic acids.*
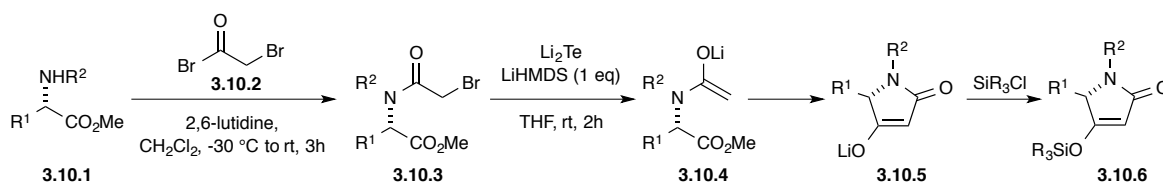
In 2010, Prousis and coworkers reported synthesis of chiral 5-carboxymethyl tetramic acids via intramolecular cyclization of (S)-*N*-Ac-L-aspartic anhydrides.[16] Regioselective addition of β-ketoester carbon nucleophile **3.11.2** into the more hindered, more electron-deficient carbonyl at the C-2 position of anhydride **3.11.1** resulted in the ring-opened product **3.11.3** (Scheme 3.11). After aqueous workup and acidification, the reaction mixture was next exposed to NaOEt in EtOH to afford the desired 3-acyl-5-carboxymethyl tetramic acid **3.11.4**.

Scheme 3.11. *Synthesis of chiral 5-carboxymethyl tetramic acids.*
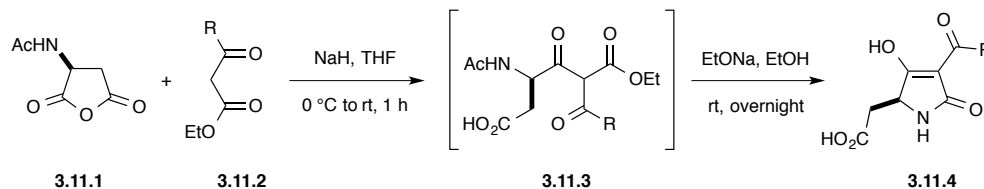
In 2010, the Avendaño group demonstrated use of pyrazino[1,2-*b*]isoquinoline-1,4-diones in the synthesis of tetramic acid derivatives.[17] Previous reports have shown that *N*-EWG-substituted diketopiperazine (DKP) moieties **3.12.1** display a novel reactivity pattern

that promoted base-mediated ring contraction reaction to generate various tetramic acids **3.12.2** and **3.12.3** (Scheme 3.12a).[18] Building upon this reactivity, Avendaño and coworkers expanded this methodology to utilizing pyrazino[1,2-*b*]isoquinoline-1,4-diones **3.12.4** to afford tetramic acids **3.12.5** containing benzo[*f*]indolizine skeleton (Scheme 3.12b).

Scheme 3.12. *Pyrazino[1,2-b]isoquinoline-1,4-diones in the synthesis of tetramic acid derivatives.*
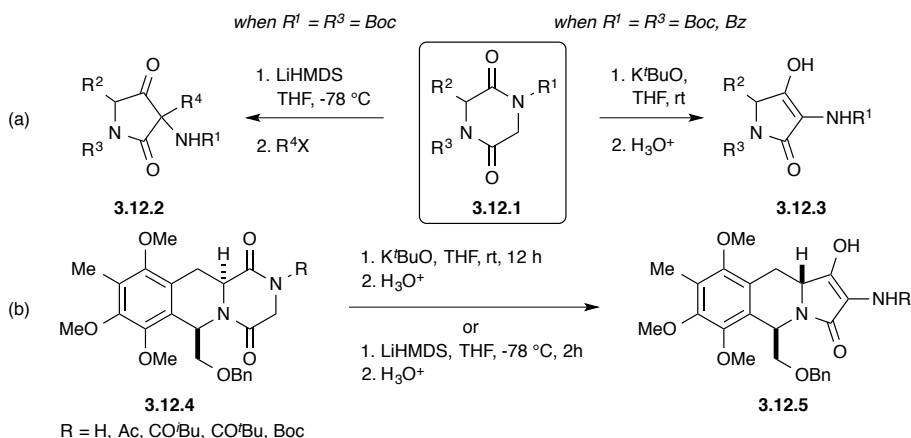
Markopoulos and Igglessi-Markopoulou group reported the synthesis of exocyclic olefin-containing tetramic acids for the utilization in ruthenium-catalyzed selective hydrogenation processes.[19] Through a one-pot C-acylation reaction with *N*-acetylglycine **3.13.1** and dimethyl or diethyl malonate **3.13.2** in the presence of N-hydroxysuccinimide (NHS) and N,N'-dicyclohexylcarbodiimide (DCC) followed by cyclization afforded 3-acyl substituted tetramic acid **3.13.3** (Scheme 3.13). The resulting tetramic acid **3.13.3** was then reacted with 4-substituted benzaldehydes to produce mono- and bis-arylidene tetramic acids **3.13.4** and **3.13.6**, which were utilized for Ru-catalyzed selective hydrogenation studies.

Scheme 3.13. *Synthesis of exocyclic olefin-containing tetramic acids.*
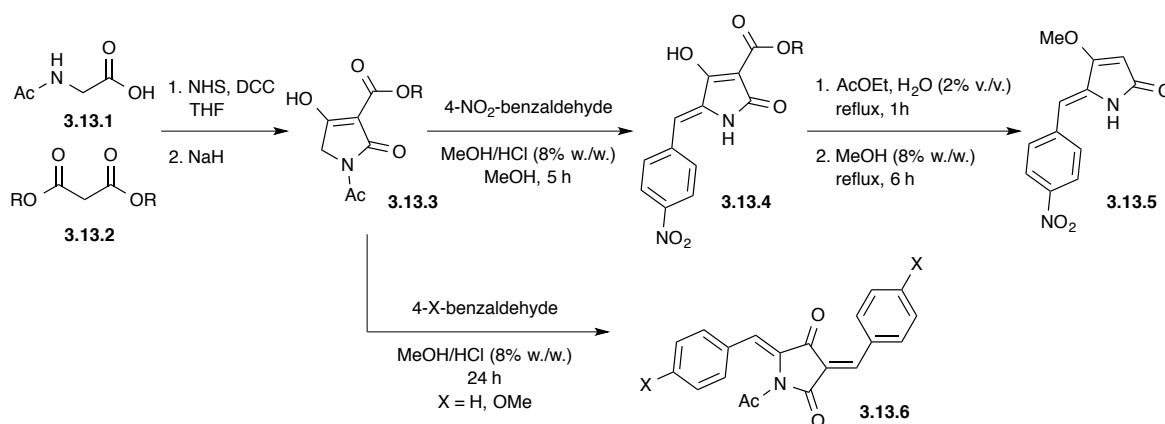
In 2011, Ďuriš and coworkers showcased a novel approach in producing constrained tetramic acids via a sequence of amidation followed by intramolecular Wittig olefination.[20] Aminobutanolide **3.14.1** was reacted with phosphorous ylide **3.14.2**, which undergoes a sequential amidation of the exocyclic secondary amine with the ester followed by Wittig cyclization of the phosphorous ylide with lactone ester furnishing bicyclic tetramic acid **3.14.3** (Scheme 3.14). Hydrogenation of **3.14.3** with Pd/C and H$_2$ in EtOAc produced tetramic acid **3.14.4**. Subsequent reduction with excess amount of sodium in a mixture of liquid ammonia and THF afforded N- and O-debenzylated product **3.14.6**. Interestingly, the

Scheme 3.14. *Tetramic acid synthesis via sequential amidation/intramolecular Wittig.*
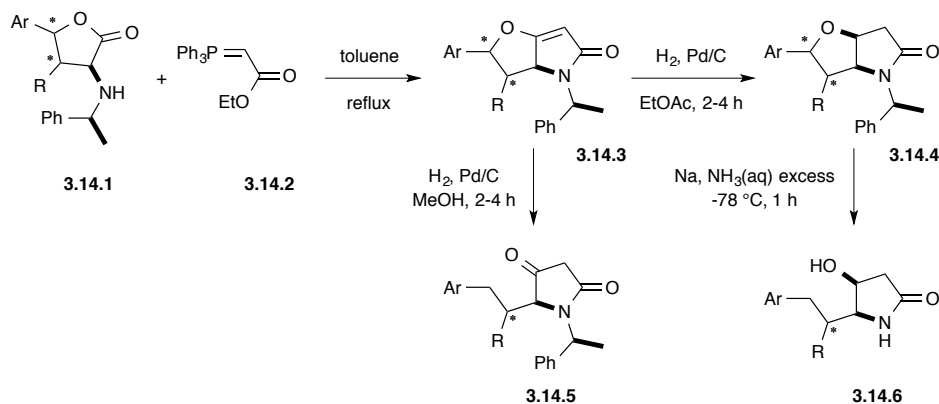
authors noted that by switching the solvent to protic solvent, MeOH, during the Pd/C and H_2 reduction step, they were able to isolate the ring-opened product **3.14.5** in one step.

In 2010 and 2012, Liu and coworkers reported the synthesis of tetramic acids via intramolecular aza-*anti*-Michael addition.[21] En route to studying routes to utilize cinnamoyl ketene dithioacetal **3.15.1**, exposure to sodium hydride in open-air conditions unexpectedly afforded a mixture of intramolecular aza-*anti*-Michael adduct **3.15.2** and **3.15.3**, an oxidative rearrangement product (Scheme 3.15). In order to drive the reaction towards the synthesis of the unexpected succinimide derivatives, further studies and optimizations revealed a sequence of intramolecular aza-*anti*-Michael, oxidation/1,2-benzyl migration to furnish the rearranged product **3.15.4** in 70% yield.

Scheme 3.15. *Synthesis of tetramic acids via intramolecular aza-anti-Michael addition.*
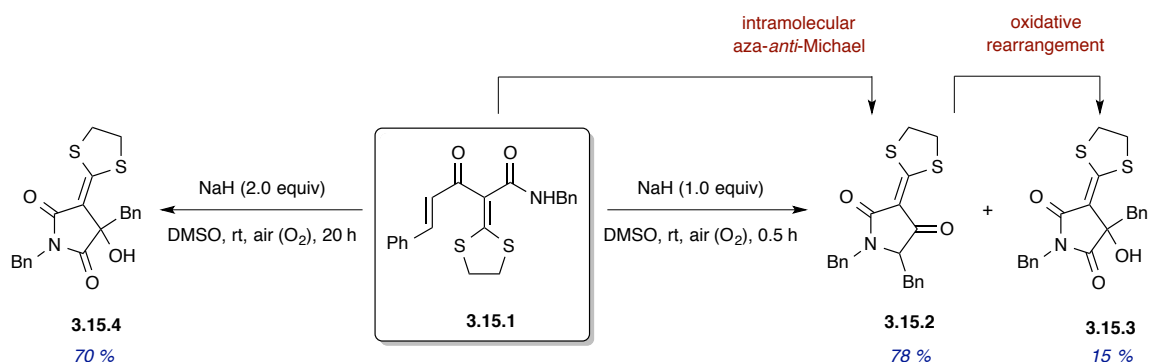
Building upon a previous report, the Burgess group reported the synthesis of omegatides, analogs from contiguous tetramic acids in 2012.[22] Starting with N-Boc-alanine **3.16.1**, coupling with Meldrum's acid via a *C*-acylation pathway, followed by decarboxylation, afforded the N-Boc protected tetramic acid **3.16.2** (Scheme 3.16). Subsequent deprotection with TFA furnished tetramic acid **3.16.3**. Through a similar sequence utilized in the previous report,[23] synthesis of omegatides was achieved.

Scheme 3.16. *Synthesis of omegatides bearing contiguous tetramic acids.*
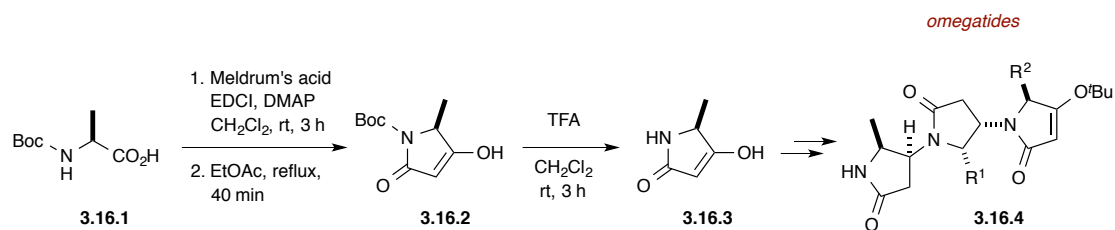
In 2012, Xu and coworkers demonstrated a strategy towards the synthesis of tetramic acids employing SmI_2-mediated coupling of nitrones and *tert*-butanesulfinyl imines with allenoates.[24] Initial work on coupling nitrones **3.17.1** with allenoates **3.17.3** afforded β-methylenyl-substituted γ-amino esters **3.17.4** (Scheme 3.17). Subsequent zinc reduction of *N*-hydroxy amines furnished *exo*-β,γ-unsaturated lactam **3.17.5**, which was stable under both neutral and acidic conditions towards double bond migration. With this result an asymmetric version was investigated, and by using chiral sulfinyl imines **3.17.2**, optically active lactams **3.17.7** were synthesized by acid hydrolysis of the resulting ester **3.17.6**. The exocyclic olefin was then cleaved by ozonolysis to yield tetramic acid **3.17.8**.

Scheme 3.17. *Synthesis of tetramic acids employing SmI_2-mediated coupling strategy.*
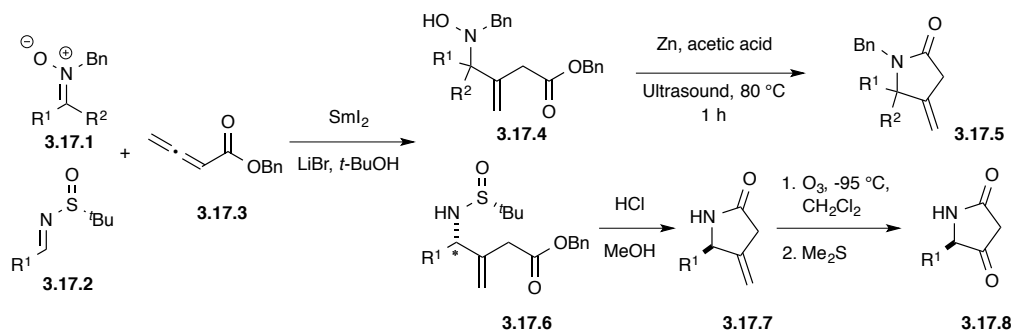
In 2013, Mao and coworkers reported the first synthesis tetramic acids using intramolecular sp^3 C–H amination mediated by hypervalent iodine (III) reagents in the

presence of Brønsted acids.[25] Various 1-acetyl *N*-aryl carboxamide derivatives **3.18.1** containing cyclopropane or cyclopentane were utilized in intramolecular sp^3 C–H amination (Scheme 3.18). Optimization studies revealed that $PhI(OPiv)_2$ has shown the best reactivity, and the presence of propanoic acid was crucial in obtaining higher yields of tetramic acid **3.18.2**. Due to the nature of this mechanism that involves a *N*-iodane species, the authors noted that annulation of alkyl amines failed due to instability.

Scheme 3.18. *Synthesis tetramic acids using intramolecular sp^3 C–H amination mediated by hypervalent iodine (III) reagents.*
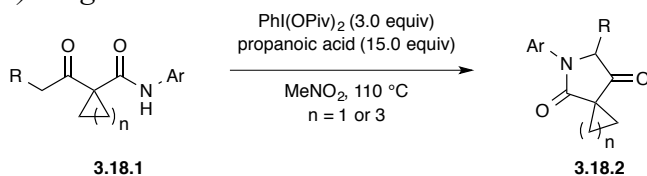
In 2014, the Yamada group reported the usage of silver-catalyzed carbon dioxide incorporation into propargyl amine and intramolecular rearrangement for the synthesis of tetramic acid derivatives.[26] Selection of base was critical for this reaction sequence, and DBU was identified as the appropriate base from screening studies. In the presence of 10 mol% AgOAc in acetonitrile under 0.1 MPa CO_2 pressure, the silver catalyst activated the alkyne **3.19.1** to incorporate a CO_2 moiety to form an oxazolidinone intermediate **3.19.2** (Scheme 3.19). Intermediate **3.19.2** readily underwent intramolecular rearrangement initiated by removal of N–H proton by DBU to generate an isocyanate intermediate **3.19.3**, followed by cyclization to furnish tetramic acid **3.19.4**. This sequence was performed in a one-pot fashion, which involved a degassing step by freeze-deaeration to remove dissolved CO_2.

Scheme 3.19. *Synthesis of tetramic acids via Ag-catalyzed CO_2 incorporation into propargyl amines and intramolecular rearrangement.*
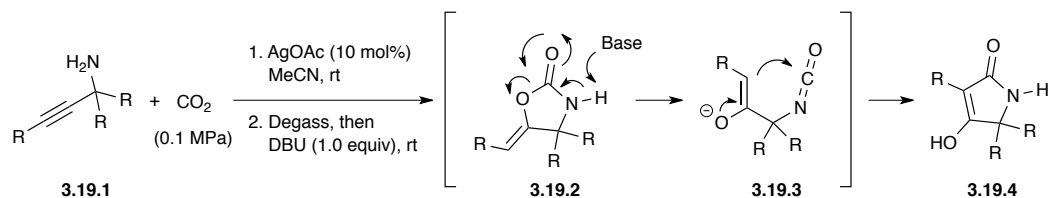
Cherian and coworkers reported syntheses of N-acyl, 3-acyltetramic acids as analogs of reutericyclin.[27] The objective of this study was to establish structure-activity relationship (SAR) reutericyclin, an antibiotic from membrane-active *Lactobacillus reuteri*. Modification of the tetramic acid core of reutericyclin was streamlined (Scheme 3.20). Amino acid benzyl esters **3.20.1** were reacted with the Bestman ylide and hydrogenated to yield tetramic acid core **3.20.2**. A further sequence involving acylation to generate intermediate **3.20.3** followed by acyl migration by addition of acetone cyanohydrin **3.20.4** to the reaction mixture produced the 3-acyl motif **3.20.5**. Subsequent N-acylation with NaHMDS and acid chloride **3.20.6** furnished the desired N-acyl, 3-acyltetramic acid **3.20.7**.

Scheme 3.20. *Synthesis of N-acyl, 3-acyltetramic acids as analogs of reutericyclin.*
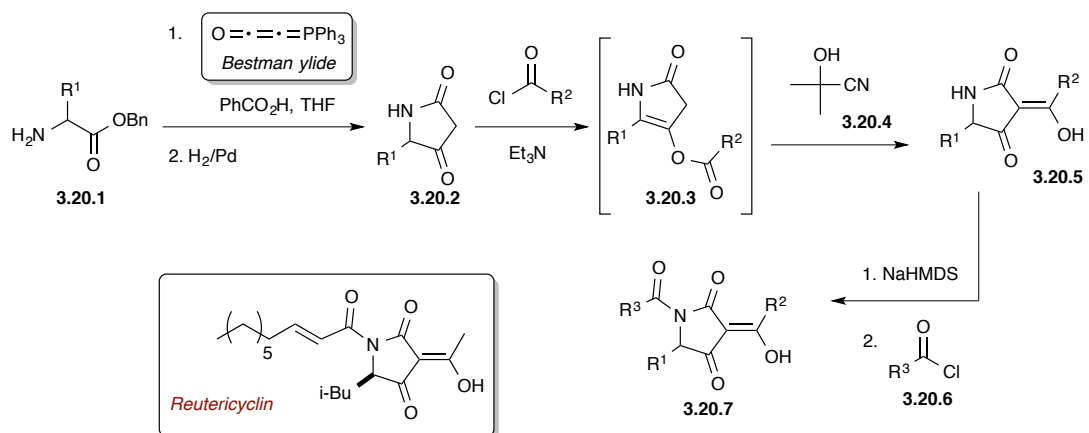
In 2014, the González-Muñiz group demonstrated the utilization of copper-catalyzed coupling of iodiphenyl-2-trifluoroacetylamine with β-ketoesters derived from amino acids en route to tetramic acid synthesis.[28] Under milder coupling conditions at room temperature in DMSO, the coupling of β-ketoester **3.21.1** with aryl iodide **3.21.2** in the presence of CuI and Cs_2CO_3 yielded coupled product **3.21.3** (Scheme 3.21). Further heating in $MeOH/H_2O$ and addition of Cs_2CO_3 at 80 °C afforded the cyclized tetramic acid **3.21.4**. With this result in hand, the authors carried out the Cu-catalyzed coupling reaction at elevated temperature and 4 equivalents of Cs_2CO_3 and achieved the synthesis of tetramic acid **3.21.4** in one pot without isolating intermediate **3.21.3**.

Scheme 3.21. *Utilization of copper-catalyzed coupling of iodiphenyl-2-trifluoroacetylamine with b-ketoesters en towards synthesis of tetramic acids.*
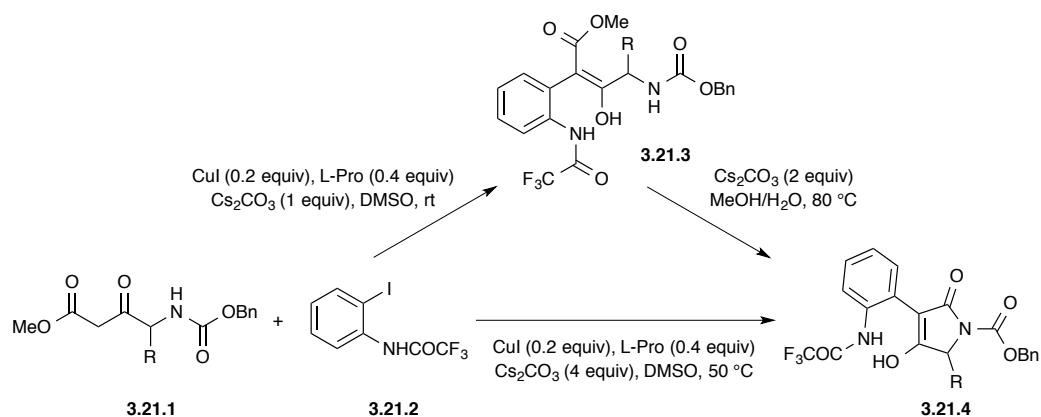
3.1.c Derivatization of TA Section

In 2010, the Kozmin group reported a library synthesis of various 7-membered heterocycles containing tetramic acid cores to be screened against proliferation of A549 cell lines and cell-cycle analysis on HL-60 cells.[29] Vinylogous urea **3.22.3** was synthesized by

condensing *o*-phenylenediamine **3.22.2** and tetramic acid **3.22.1** in benzene in the presence of catalytic amount of PTSA (Scheme 3.22). Then a one-pot transformation of urea **3.22.3** via Mannich reaction with aldehyde **3.22.4** followed by acylation with acid chloride **3.22.5** sequence was developed to furnish the desired tetramic acid-fused 7-membered heterocycle **3.22.6**.

Scheme 3.22. *Library synthesis of various 7-membered heterocycles containing tetramic acid cores.*
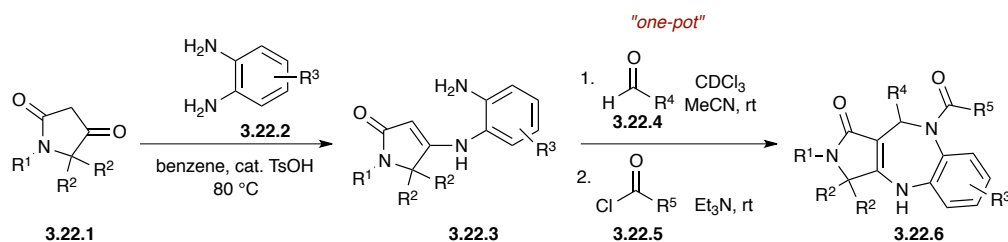
In 2010, McNab and coworkers reported the modification of pyrrolizine-1,3-dione to afford diverse heterocyclic compounds (Scheme 3.23).[30] Pyrrolizine-1,3-dione **3.23.1**, a pyrrole-fused tetramic acid, was conveniently synthesized from previously reported method.[31] Hydrogenation of tetramic acid **3.23.1** under hydrogen atmosphere with Pd/C afforded **3.23.2**. Dimethylaminomethylene product **3.23.6** was conveniently produced by reacting the starting material in solution of chloroform with DMF dimethyl acetal **3.23.5** at room temperature. Reaction of tetramic acid **3.23.1** with methoxymethylene Meldrum's acid **3.23.3** in the presence of trace amounts of Hünig's base, furnished product **3.23.4**. Finally, hydrazone **3.23.7** was synthesized by reacting with benezenediazonium tetrafluoroborate in CH$_2$Cl$_2$.

Scheme 3.23. *Modification of pyrrolizine-1,3-dione to afford diverse heterocyclic compounds.*
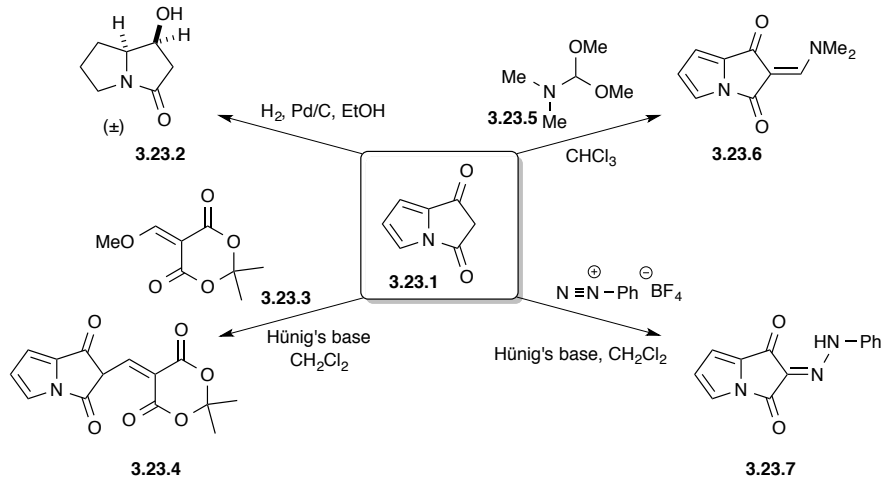
Building upon their previously reported method,[14] the Alcaide group reported the Suzuki-Miyaura reaction of bromoalkene substituted tetramic acids.[32] In investigating different reactivities of scaffolds generated from previously reported methods for the production of potentially bioactive heterocycles, the authors envisioned application of Suzuki-Miyaura reaction for further diversification. The exocyclic bromoalkene moiety of tetramic acid **3.24.1** was subject to Suzuki-Miyaura conditions in refluxing mixture of toluene/ethanol/water (18:1:1) in the presence of Pd catalyst and aryl boronic acids **3.24.2** to afford aryl substituted tetramic acid **3.24.3**.

Scheme 3.24. *Suzuki-Miyaura reaction of bromoalkene substituted tetramic acids.*
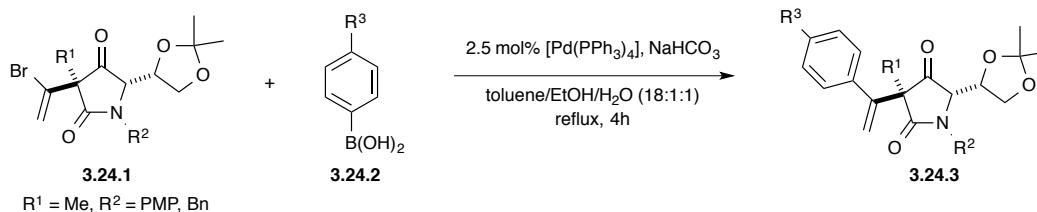
Building upon previous work, the Moloney group published studies on the development of conditions for modifying tetramic acids to their corresponding *O*-acyl and 3-acyl tetramic acids.[33]   *O*-Acylation conditions were initially studied, and optimization process identified two sets of conditions (Scheme 3.25).   Condition A, which uses the corresponding carboxylic acids in the presence of DCC and catalytic amount of DMAP, furnished *O*-acyl tetramic acids **3.25.2** in excellent yields. An alternate condition, B, utilized the corresponding acid chlorides with Et₃N to give the *O*-acylated products **3.25.2** as well. With the *O*-acyl tetramic acids synthesized, conditions to transform them into 3-acyl tetramic acids **3.25.3** were reported.   They envisioned a Fries-type acyl migration using catalytic amount of acetone cyanohydrin in the presence of Et₃N to produce 3-acyl tetramic acid **3.25.3**. In case where R^2 was decanoyl, simple treatment with DMAP in CH_2Cl_2 afforded acyl-migrated product **3.25.3** (Condition D), where as the condition only showed

Scheme 3.25. *Development of conditions for modifying tetramic acids to their corresponding O-acyl and 3-acyl tetramic acids.*
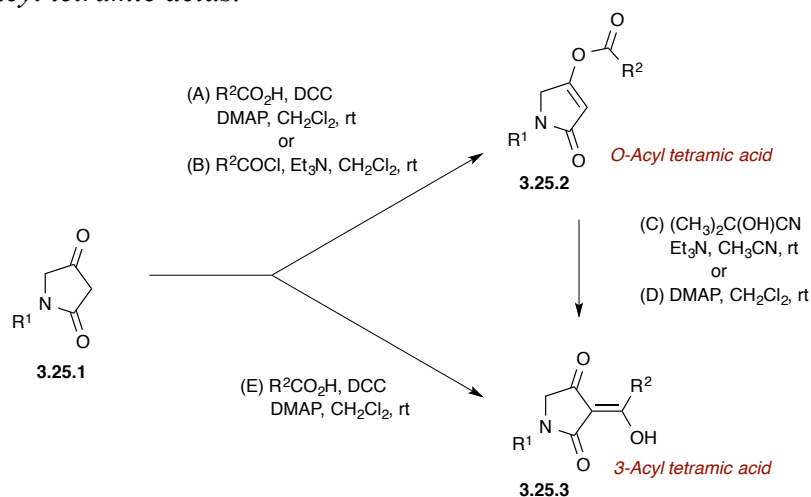
decomposition when R^2 is phenyl. In case of using linear carboxylic acids, increase in amount of DMAP to 1.3 equivalents directly produced 3-acyl tetramic acids **3.25.3** in good yields (Condition E).

In 2012, Castellucci and coworkers reported a one-pot synthesis of tetramic acids for the preparation of putative turn mimics.[34] The group focused on the skeleton of 1-acyl 3-carboxy tetramic acids being analogous to constrained β-amino acids. Benchmarking the method developed by the Igglessi-Markopoulou group,[19a] synthesis of poly-substituted tetramic acids and their 6-membered analogs **3.26.3** were demonstrated in a one-pot method, starting from benzyl malonate and *N*-hydroxysuccinimide esters of Boc-protected amino acid **3.26.1** (Scheme 3.26a). The resulting γ-amino β-oxo benzyl ester **3.26.2** then cyclized in situ, leading to polysubstituted tetramic acid and its 6-membered analog **3.26.3**. The authors then demonstrate modification of 6-membered tetramic acid analog **3.26.4** (Scheme 3.26b). Methylation of 4-enol followed by debenzylation afforded free carboxylic acid **3.26.6**, which was then coupled with alanine methyl ester to produce polysubstituted tetramic acid **3.26.7**.

Scheme 3.26. *One-pot synthesis of tetramic acids for the preparation of putative turn mimics.*
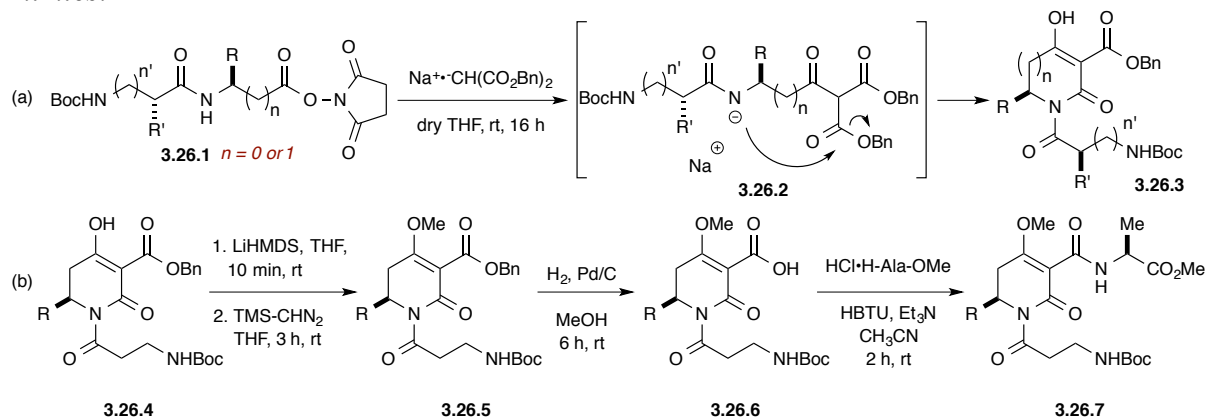
In 2014, the Pettus group demonstrated various modifications of tetramic acids prepared from the Jones' protocol.[35] Aldol adducts at the 5-position of tetramic acids are found in various natural products, including tetrapetalone B,[36] cylindramide A,[37] militarinone B,[38] paecilosetin,[39] and cryptocin.[40] By utilizing three different one-pot protocols for silylation to generate the intermediate silylated pyrrole **3.27.2** followed by addition of aldehyde in the presence of Lewis acid additive, they achieved diastereoselective vinylogous aldol reaction at the 5-position to afford substituted tetramic acid **3.27.3** (Scheme 3.27). Through optimization studies they identified SnCl$_4$ to be the optimal catalytic Lewis acid "additive." Exposure to IBX followed by DIBAL-H resulted in enhanced diastereoselectivity when linear aldehydes were used to produce **3.27.4**. Various transformations were performed, including exposure of 5-substituted tetramic acid **3.27.3** to argentic oxide with 6N

Scheme 3.27. *Modifications of tetramic acids prepared from the Jones' protocol.*
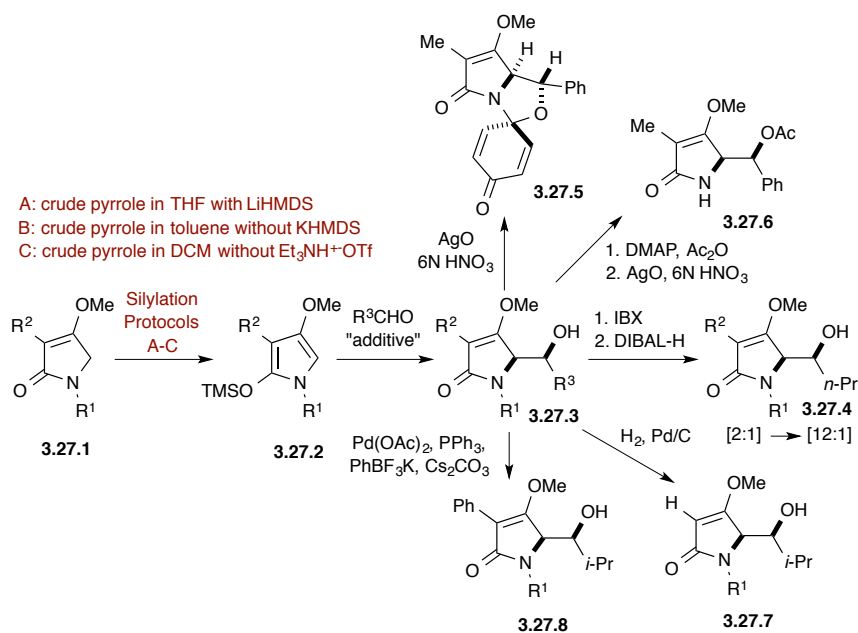
HNO$_3$, which resulted in aminal **3.27.5**. Acylation of alcohol moiety adjacent to the 5-position followed by treatment with the aforementioned condition produced deprotected tetramic acid **3.27.6**. For the case of R$_2$ = Br, coupling under Molander's conditions afforded 3-substituted tetramic acid **3.27.8**. The same 3-bromo-tetramic acid was also converted to its corresponding aldolate **3.27.7** by hydrogenolysis.

Recently in 2014, the Yoda group published their studies on using chiral, non-racemic L-phenylalanine-derived tetramic acids for the synthesis of chiral C$_2$- and pseudo C$_2$-symmetric diols that may be utilized as novel asymmetric ligands (Scheme 3.28).[41] They envisioned that tandem Knoevenagel condensation of tetramic acid **3.28.1** with aldehydes **3.28.2** followed by Michael addition with second equiv of tetramic acid **3.28.1** would produce the desired chiral tetramic acid dimers **3.28.4**. Optimization studies revealed L-proline to be the optimal catalyst for the initial Knoevenagel condensation performed in ethanol at room temperature for 1 h. Michael addition of the second equivalent of starting tetramic acid **3.28.1** furnished the desired chiral diol. This method enables readily availability of custom designed chiral diols in gram quantities that may be further utilized as versatile chiral ligands.

Scheme 3.28. *Application of chiral L-phenylalanine-derived tetramic acids for the synthesis of chiral C$_2$- and pseudo C$_2$-symmetric diols.*

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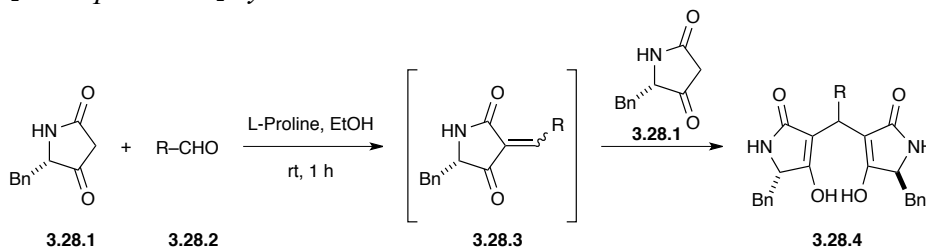
3.2 Synthesis of Sultam Analogs of Tetramic Acids via Intramolecular Sulfa-Dieckmann Cyclization

Our group has previously utilized vinyl and *ortho*-halobenzene sulfonamides as the initial linchpin that is readily available from the corresponding sulfonyl chlorides (Figure 3.3). The linchpins contain orthogonal functional groups that serve as handles for both facile cyclization and peripheral diversification reactions. Through this process, sultams are synthesized in a quick and facile manner through a "Click, Click, Cyclize" strategy.[2] Some features of "Click" chemistry include high yields, simple reaction conditions, and formation of benign byproducts.[42] By streamlining a series of "Click" reactions and performing cyclization of the resulting linchpin with orthogonal functional groups, generation of diverse scaffolds with multiple functional groups as handles can be greatly facilitated. In this report, we introduce a novel mesyl amino ester linchpin that undergoes intramolecular sulfa-Dieckmann condensation to form a novel 5-membered β-keto-sultam.

Figure 3.3. *Summary of "Click, Click, Cyclize" for synthesis of various sultams with orthogonal functionalities.*
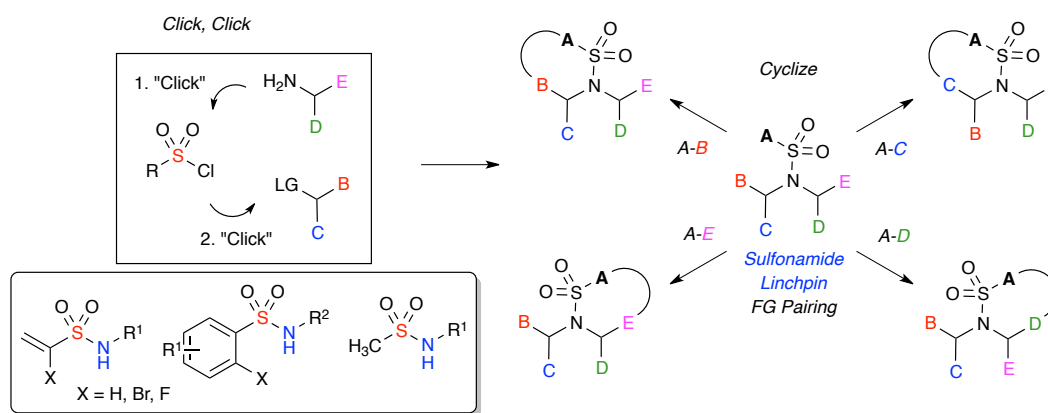
The utilization of carbanions adjacent to sulfur for cyclization was first reported by the de las Heras group in 1988, where mesylated alcohols and amines **3.29.1** were utilized to

form the corresponding sultones and sultams **3.29.3** via carbanion-mediated sulfonate/sulfonamide intramolecular cyclization reaction (CSIC reaction).[43] The CSIC reaction entails the usage of nitriles as the functional group that participates in the cyclization with carbanion **3.29.2** generated from the methyl group on the mesylated alcohol or amine to form a five-membered sultone or sultam (Scheme 3.29).

Scheme 3.29. *Carbanion-mediated sulfonate/sulfonamide intramolecular cyclization reaction.*
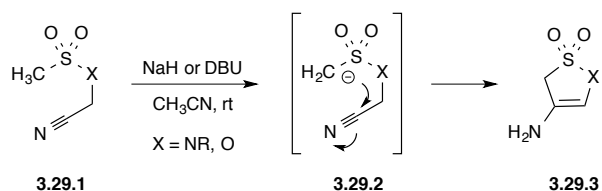
A similar strategy was also introduced in 1984, where an alkyl sulfonamide was utilized in synthesizing five-membered β-γ-diketo sultams **3.30.3/3.30.4** (Scheme 3.30).[44] Condensation of diethyl oxalate **3.30.2** with primary sulfonamide **3.30.1** followed by base-catalyzed intramolecular cyclization yielded both tautomers of β-γ-diketo sultams **3.30.3/3.30.4**, depending on the R^1 substituent.

Scheme 3.30. *Utilization of alkyl sulfonamide in synthesizing five-membered β-γ-diketo sultams.*
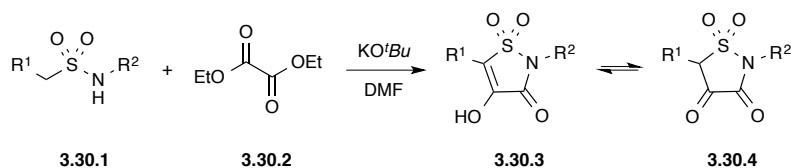
In efforts to devise a synthetic route towards synthesis of sultam analogs of tetramic acids, we developed a novel route involving "Click, Click, Cyclize" strategy. The first click reaction involves mesylation of commercially available chiral amino esters **3.31.2** in the presence of Et$_3$N as base and CH$_2$Cl$_2$ as solvent at room temperature, which readily generates
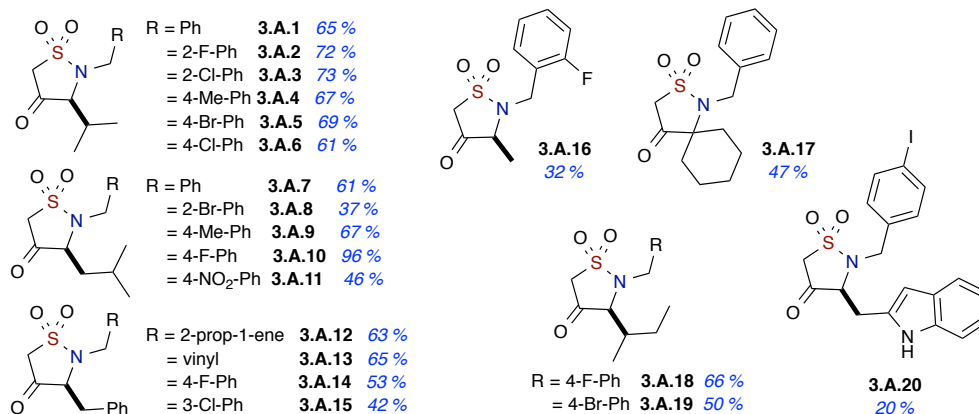
mesylated amino ester **3.31.3** in good yields (Scheme 3.31). The second click reaction

involves benzylation of **3.31.3** with K$_2$CO$_3$ as base in CH$_3$CN as solvent at 70 °C to afford

benzylated tertiary sulfonamide **3.31.4**. Subsequent sulfa-Dieckmann condensation with

LiHMDS as base furnished the desired tetramic acid analogs **3.31.6** in good to excellent

yields. This reaction involves the generation of carbanion that is adjacent to the sulfonamide

sulfur, which subsequently undergoes intramolecular cyclization by attacking the ester

moiety resulting in the desired product and methanol.

Scheme 3.31. *Development of route towards synthesis of sultam analogs of tetramic acids.*
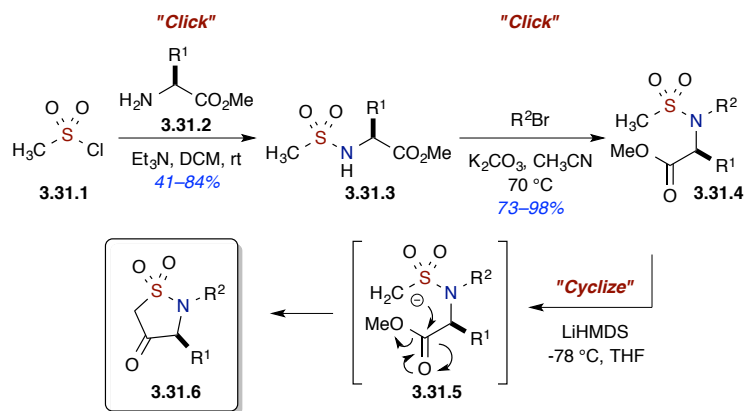
Substrate scope studies were next investigated in order to survey a variety of starting

materials that could be utilized in this reaction sequence. Amino esters derived from natural

amino acids bearing alkyl side chains (alanine, valine, leucine, isoleucine), aromatic side

chains (phenylalanine, tryptophan), and cyclic side chain (cyclohexyl) were utilized and

produced good yields, as summarized below (Table 3.1).

Table 3.1. *Intramolecular sulfa-Dieckmann condensation to produce sultam tetramic acid analogs.*

R = Ph	**3.A.1**	*65 %*	
= 2-F-Ph	**3.A.2**	*72 %*	
= 2-Cl-Ph	**3.A.3**	*73 %*	
= 4-Me-Ph	**3.A.4**	*67 %*	
= 4-Br-Ph	**3.A.5**	*69 %*	
= 4-Cl-Ph	**3.A.6**	*61 %*	

3.A.16 *32 %* **3.A.17** *47 %*

R = Ph	**3.A.7**	*61 %*
= 2-Br-Ph	**3.A.8**	*37 %*
= 4-Me-Ph	**3.A.9**	*67 %*
= 4-F-Ph	**3.A.10**	*96 %*
= 4-NO$_2$-Ph	**3.A.11**	*46 %*

R = 2-prop-1-ene	**3.A.12**	*63 %*
= vinyl	**3.A.13**	*65 %*
= 4-F-Ph	**3.A.14**	*53 %*
= 3-Cl-Ph	**3.A.15**	*42 %*

R = 4-F-Ph **3.A.18** *66 %*
= 4-Br-Ph **3.A.19** *50 %*

3.A.20 *20 %*

3.3 Utilization of Cyclic Amino esters For Synthesis of Bicyclic Tetramic Acid Analogs

The method was further extended to incorporate cyclic amino esters for the synthesis of bicyclic tetramic acid analogs. We envisioned that although this excludes one functional handle, namely the sulfonamide N–H, the resulting bicyclic core of tetramic acid analogs could occupy a unique chemical space. The modified reaction sequence involved

Scheme 3.32. *Application of cyclic amino esters for production of bicyclic tetramic acid analogs.*
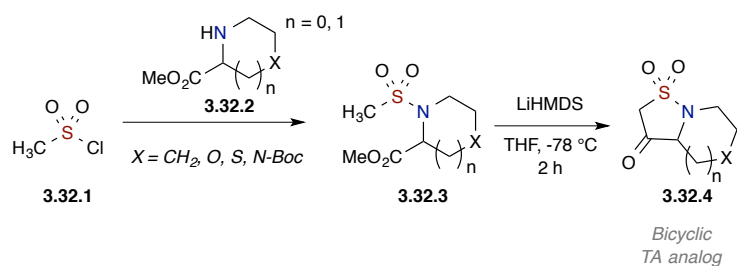
mesylation of cyclic amino ester **3.32.2**, which then underwent intramolecular sulfa-Dieckman condensation to furnish bicyclic tetramic acid analog **3.32.4** (Scheme 3.32).

Several commercially available cyclic amino esters were selected for validation (Figure 3.4). Both *R*- and *S*-proline-2-carboxylic acid methyl esters **3.4.A** and **3.4.B**, and TBS-protected 4-hydroxyproline methyl ester **3.4.C** were chosen for production of 5,5-fused bicyclic tetramic acid analogs. Piperidine methyl ester **3.4.D** and several other heterocylic derivatives, such as *N*-Boc-piperiazine methyl ester **3.4.E**, were selected for synthesis of 5,6-fused tetramic acid analogs.

Figure 3.4. *Select examples of commercially available cyclic amino esters.*
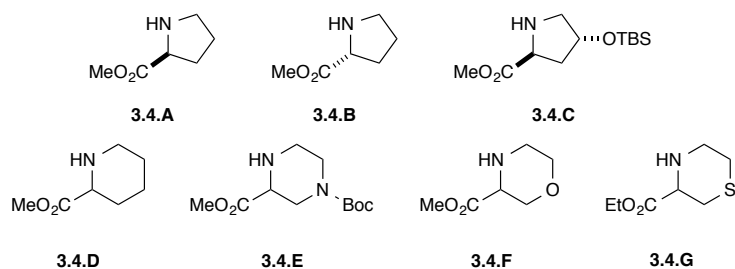
Initial optimization started by searching for an appropriate base for the generation of the carbanion of the methyl group from the mesyl moiety. Several bases were surveyed such as LDA, KHMDS, and LiHMDS. Gratifyingly, it was found that 2 equivalents of LiHMDS at -78 °C provided the best yield without racemization at the amino ester stereogenic center. However, it is noteworthy that initial attempts at intramolecular sulfa-Dieckmann condensation resulted in low yields. It was hypothesized that the low yield resulted from the solubility of sultam **3.33.2** in the aqueous layer during work up. An initial workup procedure was performed by quenching the reaction with NaHCO$_3$ and extracting with EtOAc. In order to improve the yields of this reaction, we modified the workup procedure by using 10 % HCl in place of NaHCO$_3$. This modified workup increased the yield from 43% to 87% in the case

of **3.33.5** (Scheme 3.33). Unfortunately, neither the original, nor the modified procedures, were successful in synthesizing thiomorpholine derivative **3.33.8**.

Scheme 3.33. *Sulfa-Dieckmann condensation involving cyclic amino esters.*
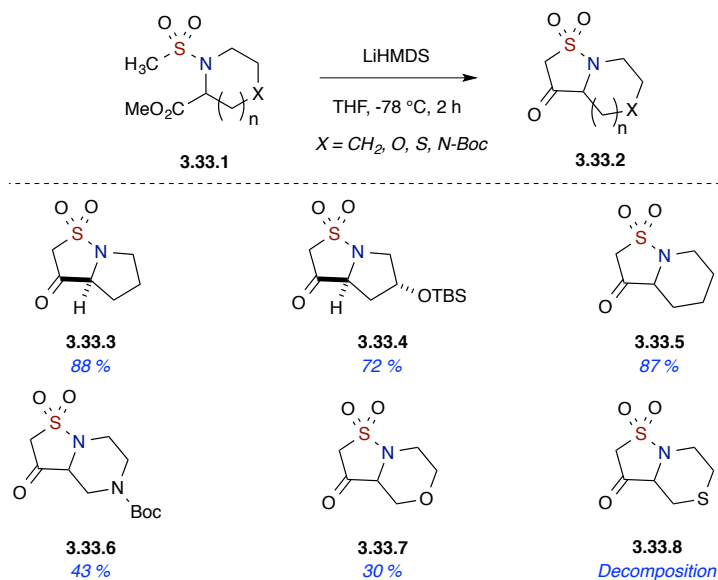
**3.4 Isocyanate Addition for 3-Carboxamide Substituted Tetramic Acid Analogs**

There has been an increasing interest in making 3-carboxamide tetramic acids in the recent years. These structures have been identified as suitable templates for new small molecule inhibitors to overcome undesirable physiochemical properties of known active compounds (Figure 3.5).[45] Moreover, high-throughput screening and docking studies have shown 3-carboxamide tetramic acids to be fruitful targets in chemical biology.[46] Unlike other known tetramic acids, the exocyclic NH is forming an intramolecular H-bond to stabilize the conformation of the molecule. In this regard, a brief summary of recent syntheses of 3-carboxamide tetramic acids is provided below.

Figure 3.5. *Known bioactive 3-carboxamide substituted tetramic acids.*

3.4.A	3.4.B	3.4.C	3.4.D
UPPS inhibitor	UPPS inhibitor	PAI-1 inhibitor	Antibiotic against various Gram-positive
IC$_{50}$ = 0.68 μM	*IC$_{50}$ = 0.12 μM*	*IC$_{50}$ = 0.69 μM*	and Gram-negative bacteria
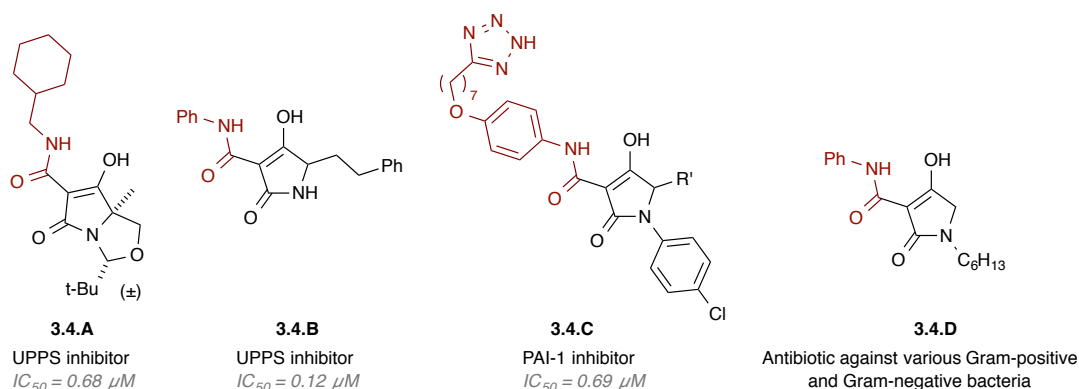
In 2002, Folkes and coworkers reported the synthesis of amido-substituted tetramic acid derivatives.[45] By reacting the substituted amino ester **3.34.1** with methyl malonyl chloride **3.34.2**, the precursor **3.34.3** to Dieckmann cyclization was afforded (Scheme 3.34). The precursor **3.34.3** was then exposed to NaOMe in MeOH for Dieckmann cyclization to yield 3-methoxycarbonyl tetramic acids **3.34.4**. Reaction with amines in refluxing xylene yielded the corresponding 3-carboxamide tetramic acids **3.34.5**.

Scheme 3.34. *Synthesis of amido-substituted tetramic acid derivatives.*
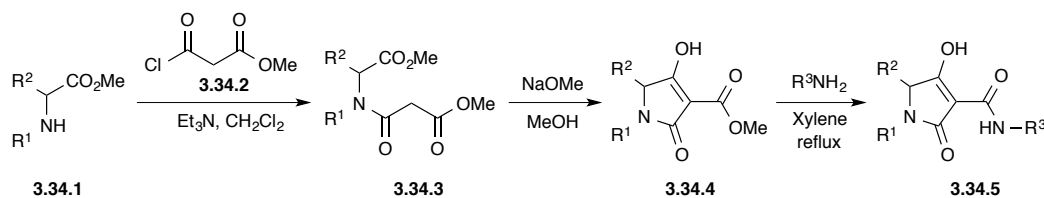
Moloney and coworkers reported a slightly different route towards 3-carboxamide tetramic acids in 2013.[47] Starting from *N*-alkyl-glycine methyl ester **3.35.1**, monoethyl malonate **3.35.2** was attached using DCC coupling reaction (Fig 3.35a). The resulting *N*-alkyl-*N*-malonyl glycine methyl ester **3.35.3** was subject to Dieckmann cyclization using NaOMe in refluxing benzene/EtOH to yield 3-ethoxycarbonyl tetramic acids **3.35.4**. Similar

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to the previous work, the ethyl ester **3.35.4** was then substituted with amines in refluxing

toluene to afford the desired 3-carboxamide tetramic acids **3.35.5**. Another route involved

the attachment of the ester portion post cyclization with butyl chloroformate **3.35.7** to

tetramic acid **3.35.6** (Fig 3.35b). Then, the resulting ester **3.35.8** was transformed to its

corresponding amide **3.35.9** by refluxing amine in toluene. Alternatively, a direct attachment

of the amide moiety was achieved by reaction of the tetramic acid **3.35.6** derivative with

phenyl isocyanate in the presence of DMAP to yield 3-carboxamide tetramic acid **3.35.10**.

This opened up an area where the amide moiety could be inserted at a late-stage modification

allowing for more diverse peripheral diversity. This method was extended to produce a

library of natural product inspired polysubstituted tetramic acids.[48]

Scheme 3.35. *New synthetic route towards 3-carboxamide substituted tetramic acids.*
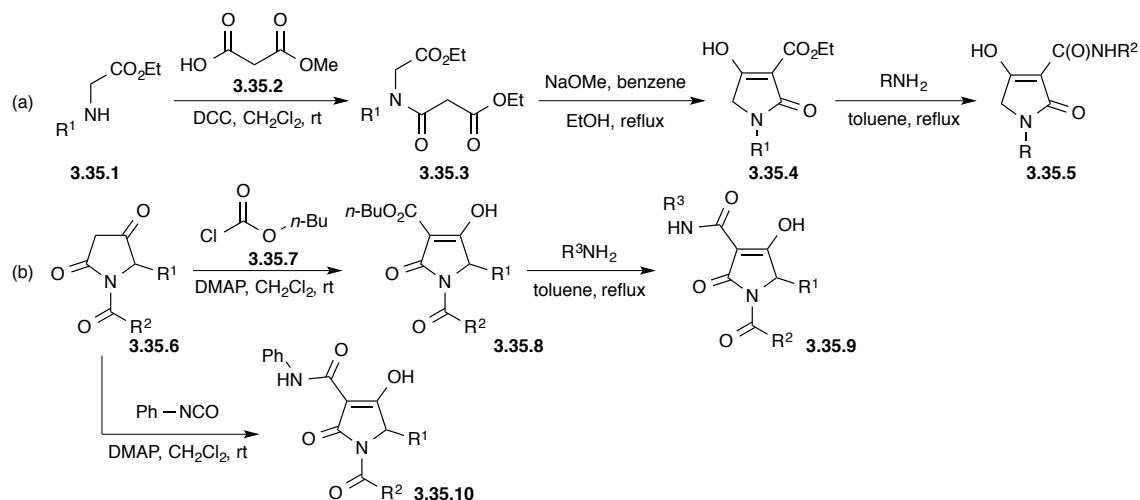
However, there are very limited reports regarding sultam analogs of tetramic acids.

To the best of our knowledge, sultam analogs of 3-carboxamide tetramic acids have not been

described in literature. We herein report the synthesis of 3-carboxamide β-keto-sultams.

Towards the aforementioned goal of accessing sultam analogs of 3-carboxamide tetramic acids, the synthesis plan involves generation of carbanion by deprotonating the most enolizable proton that is in the alpha position of both sulfonamide and ketone moieties (Scheme 3.36). Subsequent addition of phenyl-substituted isocyanates results in formation of the desired carboxamide functionality at the 3-position of sultam **3.36.2**. This method was then applied to a variety of sultams generated from the previous section, including the bicyclic sultams **3.36.3**. The results are summarized in Scheme 3.36 below.

Scheme 3.36. *Isocyanate addition to form 3-carboxamide variants.*
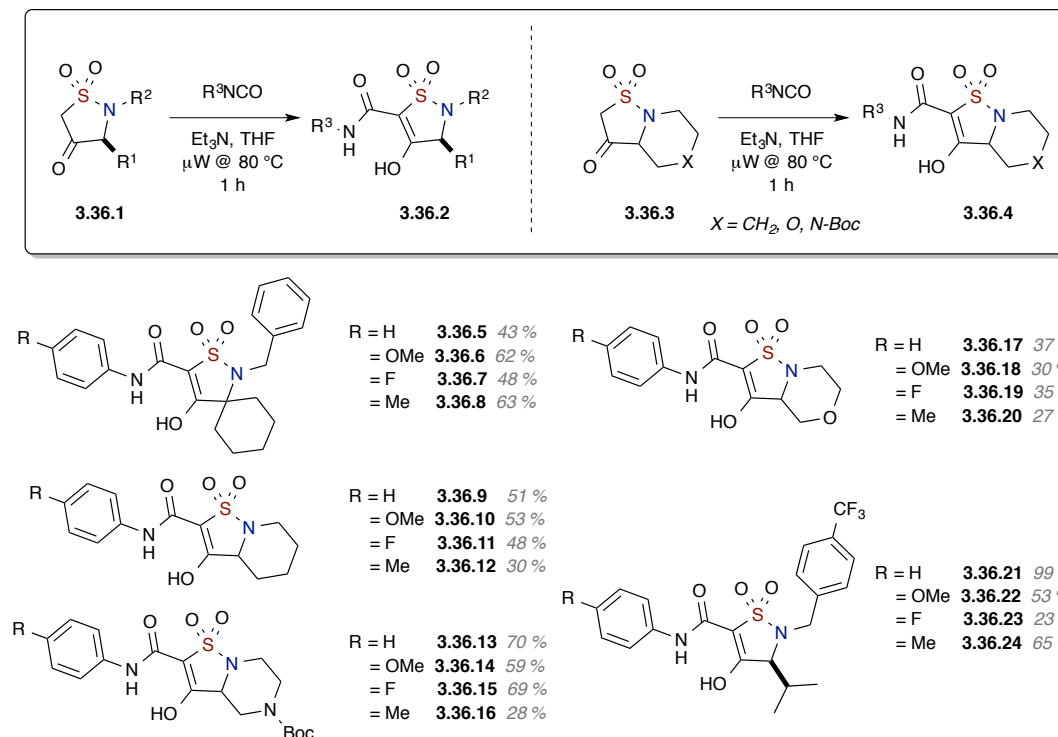
One notable aspect of the resulting 3-carboxamide substituted tetramic acid analogs is that the compounds are partially water-soluble. Due to this solubility, it was not feasible to perform aqueous work up to remove excess Et_3N and the resulting salt byproducts generated from the reaction. The reaction mixtures were concentrated *in vacuo* and submitted to

preparative/mass-directed HPLC purification in order to utilize reverse phase chromatography conditions.

3.5 Structural features and X-ray Crystallography Results

X-ray crystallographic analysis of 3-carboxamide substituted sultam **3.36.18** substantiated its formation (Figure 3.6). To our surprise, the crystal structure revealed that the compound existed in a salt form with triethylammonium ion, after going through preparative/mass-directed LCMS purification. Notably, unusually short hydrogen bonding interactions between the –OH functionalities between two molecules was observed at bond lengths of 2.414 and 2.424 Å. Common hydrogen bonding lengths between O–O are reported at around 2.8 Å, and when the distance decreased to roughly 2.5 Å it is considered a low-barrier hydrogen bond (LBHB), albeit being a controversial concept.[49,50] Potentially, this existence of LBHB may play a role in the partial solubility in water.

Figure 3.6. *X-ray crystal structure of **3.36.18** suggesting presence of LBHB.*
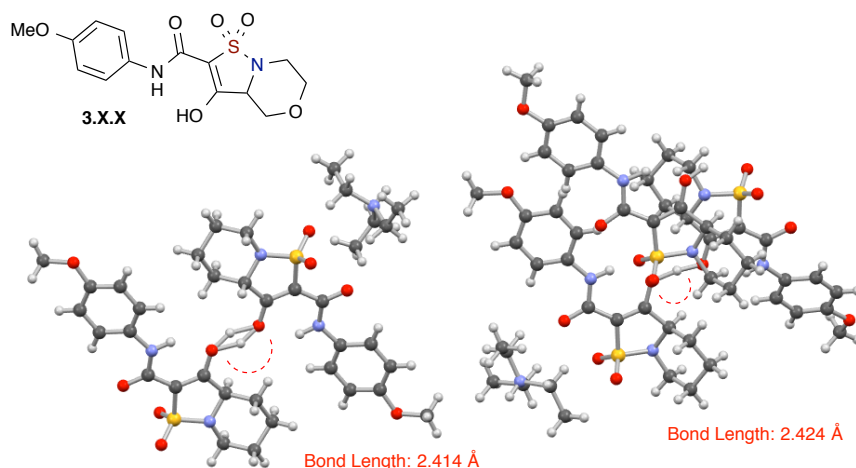
Principle moments of inertia (PMI) analysis was conducted for the compounds generated from this project for assessment of molecular diversity, as shown in Chapter 1.[51]

As mentioned earlier, PMI analysis is based on analyzing shape-based descriptors: the minimum energy conformation of each compound is resolved, the corresponding PMI ratios are calculated and normalized, and the resulting data is represented by a triangular plot depicting the molecular shape diversity (Figure 3.7). The results were plotted against a set of FDA approved drug molecules shown in black dots, and also set of NCI's NeXT screening collection shown in purple dots. Monocyclic and bicyclic tetramic acid analogs are represented in blue spheres, and 3-carboxamide tetramic acid analogs are in red spheres. The results show that the core monocyclic and bicyclic scaffolds (blue spheres) occupy the region that is slightly closer to the sphere-like area. As expected, the scaffolds containing carboxamide substituents at the 3-position (red spheres) result in the area that is relatively close to rod-like shape region. Interestingly, the region that 3-carboxamide substituted scaffolds occupy overlaps more with the reported bioactive compounds.

Figure 3.7.
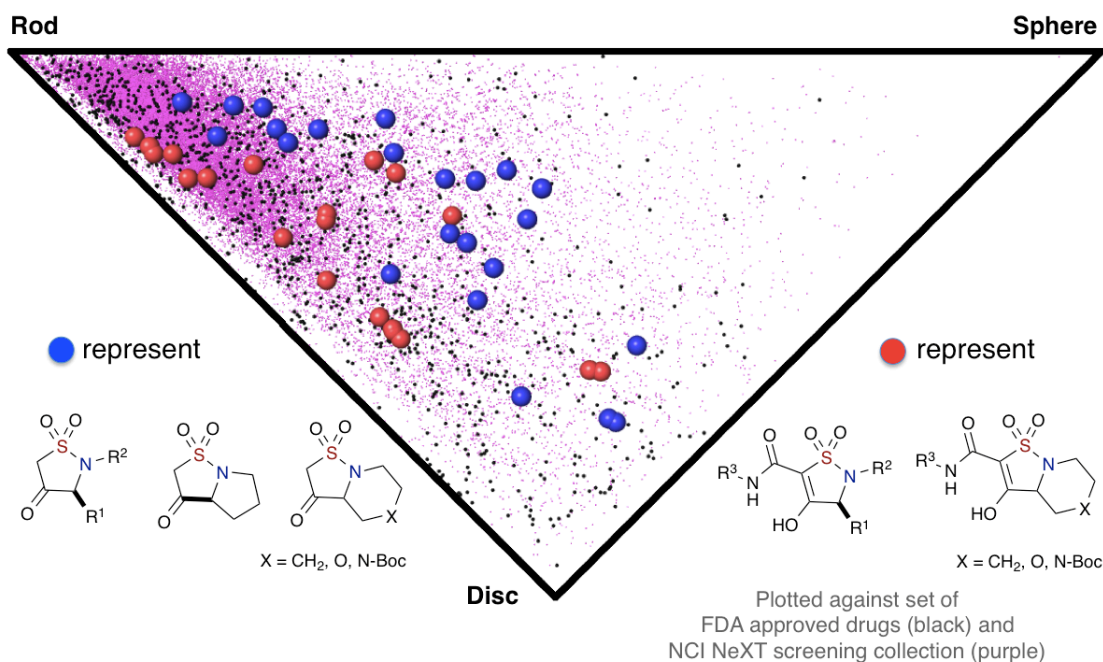
3.6 Conclusion

In conclusion, we have successfully developed a route towards the synthesis of sultam analogs of tetramic acids. This method was further extended for the production of bicyclic scaffolds, allowing for occupation of novel chemical space and search for novel biological activities. Scaffolds generated from this methodology were then further functionalized by addition of isocyanates to generate 3-carboxamide substituted tetramic acid analogs, which are novel compounds that have been gaining attention due to their unique and attenuated biological activities. Compounds generated through these efforts will provide opportunities in searching for novel biological activities, and future efforts will focus on studying chemical reactivity profiles of these entities and submission to biological screening.

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Chapter 4:

Supporting Information

Experimental for Chapters 1-3

4.1: Experimental for Chapter 1

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, cannulae, and septa. Stirring was achieved with oven-dried, magnetic stir bars. The solvents Et_2O, THF and CH_2Cl_2 were purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520). Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2 from Sorbent Technology (30930M-25, Silica Gel 60A, 40-63 um). Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance operating at 500 MHz and 126 MHz respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained in one of two manners: (i) on a VG Instrument ZAB double-focusing mass spectrometer and (ii) on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). All library syntheses were carried out in 1 dram vials utilizing Anton Parr ® Synthon 3000 microwave platform with parallel evaporations were performed using a GeneVac EZ-2 plus evaporator. Automated preparative reverse-phase HPLC purification was performed using an Waters Mass-Directed Fractionation system (Prep Pump 2525, Make-up pump 515, Sample Manager 2767, UV-DAD detection 2996, Micromass ZD quadrapole spectrometer) and a Waters X-Bridge C18 column (19 x 150mm, 5um, w/ 19 x 10mm guard column). Samples were diluted in DMSO and purified utilized an elution of water (modified to pH 9.8 through

addition of NH_4OH) and CH_3CN, with a gradient increasing to 20% in CH_3CN over 4 minutes at a flow rate of 20ml/min. The preparative gradient, triggering thresholds, and UV wavelength were selected based on the HPLC analysis of each crude sample. Analytical analysis of each sample after purification employed a Waters Acquity system with UV and mass detection (Waters LCT Premier). The analytical method utilized a Waters Aquity BEH C18 column (2.1 x 50mm, 1.7um) eluting with a linear gradient of 5% water (modified to pH 9.8 through addition of NH_4OH) to 100% CH_3CN at 0.6 mL/min flow rate were purity was determined using UV peak area at 214 nm.

4.1.1 Library Production of RCM-Derived Scaffold via Click-aza-Michael

2,3-Dihydroisothiazole 1,1-dioxide (1.8.3).

Into a r.b flask was added allyl amine (6.57 mL, 87.6 mmol, 1.1 equiv.), dry DCM (160 mL, 0.5 M), and Et$_3$N (36.6 mL, 262.2 mmol, 3 equiv.). The stirring solution was cooled to 0 ºC to which was added dropwise 2-chloroethanesulfonyl chloride (8.32 ml, 79.6 mmol, 1 equiv.). After addition, the reaction was warmed to rt and stirred for an additional 4 hrs. Upon completion, the reaction was quenched with 10% HCl aq. (60 ml), the organic layer extracted and washed with 10% HCl aq. (60 ml), H$_2$O (60 ml) and brine (60 ml). The combined organic was dried over MgSO$_4$, filtered and concentrated.

To the crude material, *N*-allylethenesulfonamide (11.5 g, yellow oil) in a r.b flask was added Ar degassed dry DCM (0.07M, 111 ml), and the reaction was heated at 45 ºC. Over the required 3 hr reaction period at 45 ºC, **G-II** [(IMesH$_2$)(PCy$_3$)(Cl)$_2$Ru]CHPh] (2.5 mol%) was added in 5 equal portions every 30 mins, essential for complete conversion of the starting material to product. After such time, the reaction was concentrated and purified by flash chromatography to yield the desired product as a brown oil (8.35 g, 70 mmol, 88% over 2 steps).

FTIR (neat): 3552, 3274, 1386, 1274, 1151, 1103 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.89 (dt, *J* = 6.5, 2.3 Hz, 1H), 6.71 (dt, *J* = 6.5, 2.3 Hz, 1H), 5.23 (br s, 1H), 4.10 (dt, *J* = 4.4, 2.3 Hz, 2H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 138.3, 127.2, 47.8;

HRMS calculated for $C_3H_6NO_2S$ (M+H)$^+$ 120.0119; found 120.0121 (TOF MS ES+).

2-(Prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide (1.8.4).
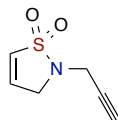
Into a 500 ml rb flask under Ar, was added 2,3-dihydroisothiazole 1,1-dioxide **1.8.3** (4.05g, 33.9 mmol, 1 equiv), dry CH_3CN (170 mL, 0.2 M) and K_2CO_3 (9.36 g, 67.8 mmol, 2 equiv). To the stirring slurry was added propargyl bromide ([80% in tol.], 7.58g, 50.9 mmol, 1.5 equiv), after which the reaction was heated at 60 ºC for 5 hrs [TLC monitoring (7:3 EtOAc:hexane, R_f **1.8.4** = 0.5, R_f **1.8.3** = 0.3]. After such time the reaction was cooled to rt, filtered through a SiO_2 SPE, washed with EtOAC (200 ml) and concentrated. The resulting crude liquid was diluted in toluene (200 ml), concentrated and dried under vacuum to yield the desired product **1.8.4** (5.06 g, 32.2 mmol, 95%) as yellow oil.

FTIR (neat): 3274, 1386, 1274, 1141, 1103 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.91 (dt, J = 7.0, 2.4 Hz, 1H), 6.72–6.65 (m, 1H), 4.15–4.10 (m, 2H), 3.99 (d, J = 2.2 Hz, 2H), 2.35 (t, J = 2.5 Hz, 1H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 135.6, 127.1, 74.1, 51.4, 33.8;

HRMS calculated for $C_6H_8NO_2S$ (M+H)$^+$ 158.0276; found 158.0279 (TOF MS ES+).

General procedure A for the synthesis of Library A via a one-pot Click/aza-Michael protocol.

To a 1-dram vial containing 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **1.8.4** (50 mg, 0.318 mmol, 1 equiv.) was added CuI (18.2 mg, 30 mol%), DBU (5 μL, 10 mol%), dry EtOH (0.64 ml, 0.5 M), amine (0.38 mmol, 1.2 equiv.) and azide (0.636 mmol, 2 equiv.). The reaction was heated at 60 ºC on a reaction block for for 12 hrs, after which time the reactions were cooled, filtered through SiO$_2$ SPE into pre-weighed barcoded vials, washed with eluent (2 ml, EtOAc:MeOH 95:5) and concentrated. The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

General procedure B for the synthesis of Library B via two-step Click, aza-Michael with amines 12 – 15 and azides A – L.

To a 1-dram vial containing 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **1.8.4** (50 mg, 0.318 mmol, 1 equiv) was added CuI (18.2 mg, 30 mol%), DBU (5 μL, 10 mol%), dry EtOH (0.64 ml, 0.5 M), and azide (0.636 mmol, 2 equiv). The reaction was heated at 60 ºC on a reaction block for for 4 hrs, after which time the reactions were cooled, filtered through SiO$_2$, washed with eluent (2 mL, EtOAc) and concentrated. The crude was transferred to a 1-dram vial, where DBU (5 μL, 10 mol%), dry EtOH (0.64 ml, 0.5M), amine (0.38 mmol, 1.2 equiv.) was added. The reaction was subsequently heated at at 60 ºC on a reaction block for for 10 hrs, after which time the reactions were cooled, filtered through SiO$_2$ SPE and concentrated into pre-weighed barcoded vials, washed with eluent (2 ml, EtOAc:MeOH

95:5) and concentrated.   The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

2-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-(2-fluorobenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide 1{M}.
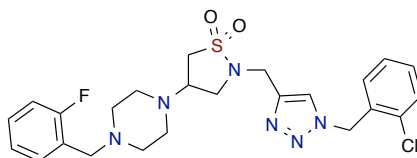
FTIR (neat): 2944, 1492, 1305, 1138 cm^{-1};

^{1}H NMR (DMSO-d$_6$, 500 MHz) δ 8.15 (s, 1H), 7.42 (m, 2H), 7.37 (dt, J = 7.5, 1.5 Hz, 1H), 7.30 (m, 3H), 7.17 (m, 2H), 5.60 (s, 2H), 4.19 (d, J = 15.0 Hz, 1H), 4.15 (d, J = 15.0 Hz, 1H), 3.49 (s, 2H), 3.43 (m, 2H), 3.30 (m, 1H), 3.17 (m, 1H), 2.98 (m, 1H), 2.37 (br s, 8H);

^{13}C NMR (DMSO-d$_6$, 125 MHz) δ 160.8 (d, J_{CF} = 242.5 Hz), 142.1, 135.1, 132.8, 131.6 (d, J_{CF} = 5.0 Hz), 129.1 (d, J_{CF} = 8.8 Hz), 128.8, 124.4, 124.3, 124.1 (d, J_{CF} = 3.8 Hz), 115.2 (d, J_{CF} = 22.5 Hz), 56.4, 54.4, 52.2, 52.0, 49.3, 49.0, 47.8, 38.7;

HRMS calculated for C$_{24}$H$_{29}$ClFN$_6$O$_2$S (M+H)$^+$ 519.1746; found 519.1739 (TOF MS ES+).

2-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-(4-(3-methylbenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide 2{A}.
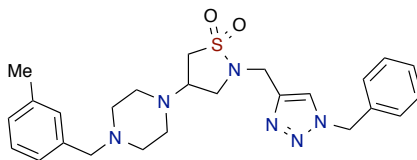
FTIR (neat): 2925, 2809, 1305, 1151, 1138 cm^{-1};

¹H NMR (DMSO-d₆, 500 MHz) δ 8.14 (s, 1H), 7.37–7.27 (m, 5H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 7.05 (d, *J* = 7.5 Hz, 2H), 5.59 (s, 2H), 4.17 (s, 2H), 3.44 (m, 2H), 3.38 (s, 2H), 3.31 (m, 1H), 3.17 (m, 1H), 2.99 (m, 1H), 2.36–2.30 (m, 8 H), 2.28 (s, 3H);

¹³C NMR (DMSO-d₆, 125 MHz) δ 142.0, 138.0, 137.2, 136.1, 129.4, 128.7, 128.1, 128.0, 127.8, 127.6, 125.9, 124.3, 62.0, 56.4, 52.8, 52.4, 49.3, 49.0, 47.7, 38.7;

HRMS calculated for $C_{25}H_{33}N_6O_2S$ (M+H)⁺ 481.2386; found 481.2389 (TOF MS ES+).

2-((1-(3-Methoxypropyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-(3-methylbenzyl)piperazin-1-yl)

isothiazolidine 1,1-dioxide 2{K}.
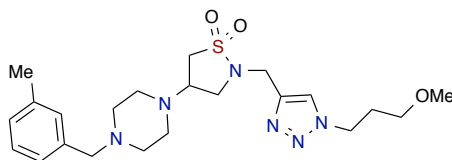
FTIR (neat): 2955, 2826, 1299, 1141 cm⁻¹;

¹H NMR (DMSO-d₆, 500 MHz) δ 8.07 (s, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.07 (s, 1H), 7.04 (d, *J* = 7.5 Hz, 2H), 4.38 (t, *J* = 6.5 Hz, 2H), 4.18 (d, *J* = 15.0 Hz, 1H), 4.14 (d, *J* = 15.0 Hz, 1H), 3.45 (m, 2H), 3.38 (s, 2H), 3.32 (m, 1H), 3.27 (t, *J* = 6.5 Hz, 2H), 3.21 (s, 3H), 3.16 (m, 1H), 2.98 (m, 1H), 2.38–2.30 (m, 8H), 2.28 (s, 3H), 2.02 (p, *J* = 6.5 Hz, 2H);

¹³C NMR (DMSO-d₆, 125 MHz) δ 141.6, 138.0, 137.2, 129.4, 128.0, 127.6, 125.9, 124.2, 68.4, 62.0, 58.0, 56.5, 52.4, 49.3, 49.1, 47.8, 46.7, 38.7, 29.8, 21.0;

HRMS calculated for $C_{22}H_{35}N_6O_3S$ (M+H)⁺ 463.2492; found 463.2486 (TOF MS ES+).

Methyl 4-(4-((4-(4-(3-methylbenzyl)piperazin-1-yl)-1,1-dioxidoisothiazolidin-2-yl)methyl)-1H-1, 2, 3-triazol-1-yl)butanoate 2{L}.
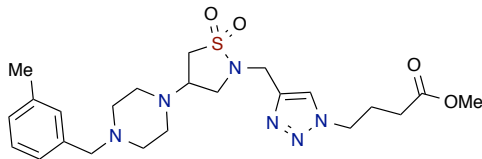
FTIR (neat): 2953, 1729, 1299, 1140 cm^{-1};

^{1}H NMR (DMSO-d$_6$, 500 MHz) δ 8.09 (s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.08 (s, 1H), 7.04 (d, J = 7.5 Hz, 2H), 4.37 (t, J = 7.0 Hz, 2H), 4.18 (d, J = 14.5 Hz, 1H), 4.14 (d, J = 14.5 Hz, 1H), 3.57 (s, 3H), 3.45 (m, 2H), 3.38 (s, 2H), 3.31 (m, 1H), 3.18 (m, 1H), 2.98 (m, 1H), 2.39–2.29 (m, 10 H), 2.27 (s, 3H), 2.05 (p, J = 7.0 Hz, 2H);

^{13}C NMR (DMSO-d$_6$, 125 MHz) δ 172.5, 141.7, 138.0, 137.2, 129.4, 127.6, 125.9, 124.2, 62.0, 56.5, 52.4, 51.4, 49.3, 49.1, 48.6, 47.8, 38.7, 30.8, 25.1, 21.0;

HRMS calculated for C$_{23}$H$_{35}$N$_6$O$_4$S (M+H)$^{+}$ 491.2441; found 491.2389 (TOF MS ES+).

2-((1-(3,5-Dimethylbenzyl)-1H-1, 2, 3-triazol-4-yl)methyl)-4-thiomorpholinoisothiazolidine 1,1-dioxide 3{F}.
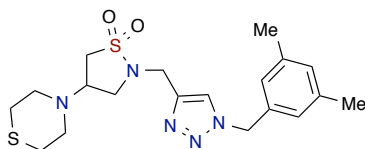
FTIR (neat): 2913, 1302, 1138, 1045 cm^{-1};

^{1}H NMR (DMSO-d$_6$, 500 MHz) 8.11 (s, 1H), 6.96 (s, 1H), 6.90 (s, 2H), 5.49 (s, 2H), 4.18 (s, 2H), 3.57 (p, J = 9.0 Hz, 1H), 3.43 (dd, J = 13.5, 9.0 Hz, 1H), 3.30 (dd, J = 13.5, 7.5 Hz,

1H), 3.21 (dd, J = 13.5, 7.5 Hz, 1H), 3.02 (dd, J = 10.0, 7.5 Hz, 1H), 2.65 (m, 4H), 2.55 (m, 4H), 2.24 (s, 6H);

^{13}C NMR (DMSO-d$_6$, 125 MHz) δ 141.9, 137.8, 135.8, 129.5, 125.3, 124.2, 57.2, 52.8, 51.1, 48.6, 46.7, 38.5, 27.1, 20.8;

HRMS calculated for C$_{19}$H$_{28}$N$_5$O$_2$S$_2$ (M+H)$^+$ 422.1685; found 422.1705 (TOF MS ES+).

2-((1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-thiomorpholinoisothiazolidine 1,1-dioxide 3{I}.
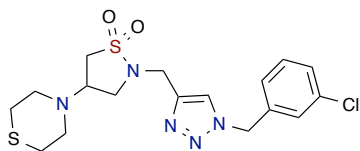
FTIR (neat): 2912, 2821, 1434, 1301, 1044 cm^{-1};

^{1}H NMR (DMSO-d$_6$, 500 MHz) 8.19 (s, 1H), 7.40 (m, 3H), 7.25 (m, 1H), 5.62 (s, 2H), 4.17 (s, 2H), 3.59 (p, J = 7.5 Hz, 1H), 3.44 (dd, J = 13.0, 8.0 Hz, 1H), 3.30 (dd, 10.0, 7.5 Hz, 1H), 3.22 (dd, J = 13.0, 8.0 Hz, 1H), 3.02 (dd, J = 10.0, 7.5 Hz, 1H), 2.65 (m, 4H), 2.54 (m, 4H);

^{13}C NMR (DMSO-d$_6$, 125 MHz) δ 142.1, 138.4, 133.3, 130.7, 128.1, 127.8, 126.6, 124.5, 57.2, 52.0, 51.1, 48.7, 46.7, 38.5, 27.2;

HRMS calculated for C$_{17}$H$_{23}$ClN$_5$O$_2$S$_2$ (M+H)$^+$ 428.0982; found 428.0991 (TOF MS ES+).

2-((1-Hexyl-1H-1,2,3-triazol-4-yl)methyl)-4-thiomorpholinoisothiazolidine 1,1-dioxide 3{J}
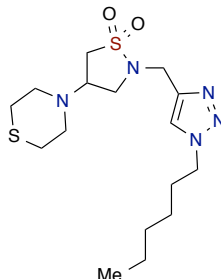
FTIR (neat): 2928, 1456, 1303, 1140, 1048 cm^{-1};

^{1}H NMR (DMSO-d$_{6}$, 500 MHz) δ 8.09 (s, 1H), 4.33 (t, J = 7.0 Hz, 2H), 4.15 (s, 2H), 3.60 (pent., J = 7.5 Hz, 1H), 3.45 (dd, J =13.0, 8.5 Hz, 1H), 3.28 (dd, J = 10.0, 8.5 Hz, 1H), 3.22 (dd, J =13.0, 7.0 Hz, 1H), 3.01 (dd, J =10.0, 7.0 Hz, 1H), 2.66 (m, 4H), 2.56 (m, 4H), 1.79 (pent., J = 7.0 Hz, 2H), 1.27–1.17 (m, 6H), 0.83 (m, 3H);

^{13}C NMR (DMSO-d$_{6}$, 125 MHz) δ 141.5, 124.0, 57.2, 51.1, 49.4, 48.7, 46.8, 38.6, 30.6, 29.6, 27.2, 25.5, 21.9, 13.9;

HRMS calculated for C$_{16}$H$_{30}$N$_{5}$O$_{2}$S$_{2}$ (M+H)$^{+}$ 388.1841; found 388.1851 (TOF MS ES+).

2-((1-(3-Methoxypropyl)-1H-1,2,3-triazol-4-yl)methyl)-4-thiomorpholinoisothiazolidine 1,1-dioxide 3{K}
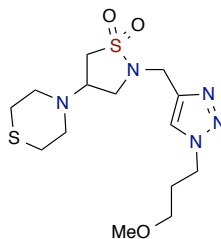
FTIR (neat): 2928, 1454, 1301, 1139, 1115, 1046 cm^{-1};

¹H NMR (DMSO-d₆, 500 MHz) δ 8.08 (s, 1H), 4.39 (t, J = 7.0 Hz, 2H), 4.15 (s, 2H), 3.60 (pent., J = 7.0 Hz, 1H), 3.45 (dd, J =13.0, 8.0 Hz, 1H), 3.31–3.27 (m, 3H), 3.23 (dd, J =13.0, 8.0 Hz, 1H), 3.22 (s, 3H), 3.02 (dd, J =10.0, 7.0 Hz, 1H), 2.67 (m, 4H), 2.56 (m, 4H), 2.03 (pent., J = 7.0 Hz, 2H);

¹³C NMR (DMSO-d₆, 125 MHz) δ 141.5, 124.2, 68.5, 58.0, 57.2, 51.1, 48.7, 46.8, 46.7, 38.6, 29.8, 27.2;

HRMS calculated for $C_{14}H_{26}N_5O_3S_2$ (M+H)⁺ 376.1477; found 376.1493 (TOF MS ES+).

2-((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 6{B}.
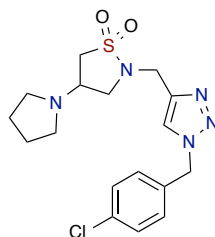
FTIR (neat): 2914, 1305, 1132, 1045 cm⁻¹;

¹H NMR (500 MHz, MeOD) δ 8.00 (s, 1H), 7.39–7.34 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.58 (s, 2H), 4.29 (q, J = 15.2 Hz, 2H), 3.50 (dd, J = 12.8, 7.9 Hz, 1H), 3.44 (dd, J = 9.2, 7.1 Hz, 1H), 3.41–3.33 (m, 1H), 3.14 (dd, J = 12.8, 7.8 Hz, 1H), 3.08 (dd, J = 9.2, 7.4 Hz, 1H), 2.50 (dd, J = 11.8, 5.2 Hz, 4H), 1.82–1.72 (m, 4H);

¹³C NMR (126 MHz, MeOD) δ 135.6, 135.5, 130.8, 130.1, 125.7, 57.6, 54.1, 52.4, 52.3, 51.8, 39.9, 24.1;

HRMS calculated for $C_{17}H_{23}ClN_5O_2S$ (M+H)⁺ 396.1260; found 396.1288 (TOF MS ES+).

2-((1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 6{D}.
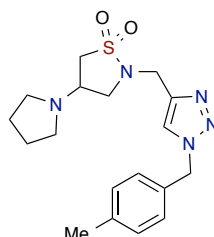
FTIR (neat): 2910, 1300, 1136, 1047 cm^{-1};

^{1}H NMR (500 MHz, MeOD) δ 7.94 (s, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 5.52 (s, 2H), 4.28 (q, J = 15.1, 2H), 3.49 (dd, J = 12.8, 7.9 Hz 1H), 3.42 (dd, J = 9.2, 7.0 Hz, 1H), 3.40–3.33 (m, 1H), 3.13 (dd, J = 12.8, 7.8 Hz, 1H), 3.07 (dd, J = 9.3, 7.3 Hz, 1H), 2.51 (td, J = 9.1, 2.5 Hz, 4H), 2.31 (s, 3H), 1.83–1.71 (m, 4H);

^{13}C NMR (126 MHz, MeOD) δ 139.3, 133.4, 130.3, 128.8, 125.1, 57.2, 54.4, 51.9, 51.9, 51.4, 39.6, 23.7, 20.8;

**HRMS** calculated for C$_{18}$H$_{26}$N$_5$O$_2$S (M+H)$^{+}$ 376.1807; found 376.1825 (TOF MS ES+).

2-((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(piperidin-1-yl)isothiazolidine 1,1-dioxide 7{B}.
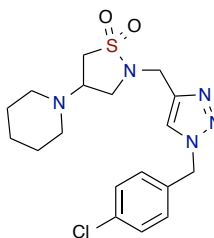
FTIR (neat): 2918, 1308, 1131, 1045 cm^{-1};

¹H NMR (500 MHz, MeOD) δ 8.03 (s, 1H), 7.42–7.36 (m, 2H), 7.36–7.27 (m, 2H), 5.61 (d, J = 15.4 Hz, 2H), 4.34–4.26 (m, 2H), 3.51–3.36 (m, 3H), 3.23–3.15 (m, 1H), 3.09 (dd, J = 9.5, 6.7 Hz, 1H), 2.40 (s, 4H), 1.60–1.51 (m, 4H), 1.45 (dd, J = 11.2, 5.6 Hz, 2H);

¹³C NMR (126 MHz, MeOD) δ δ 135.6, 135.5, 130.8, 130.1, 58.8, 54.2, 52.0, 50.7, 39.7, 26.6, 25.1;

HRMS calculated for $C_{18}H_{25}ClN_5O_2S$ (M+H)$^+$ 410.1418; found 410.1438 (TOF MS ES+).

2,3-Dihydroisothiazole 1,1-dioxide (1.8.3)
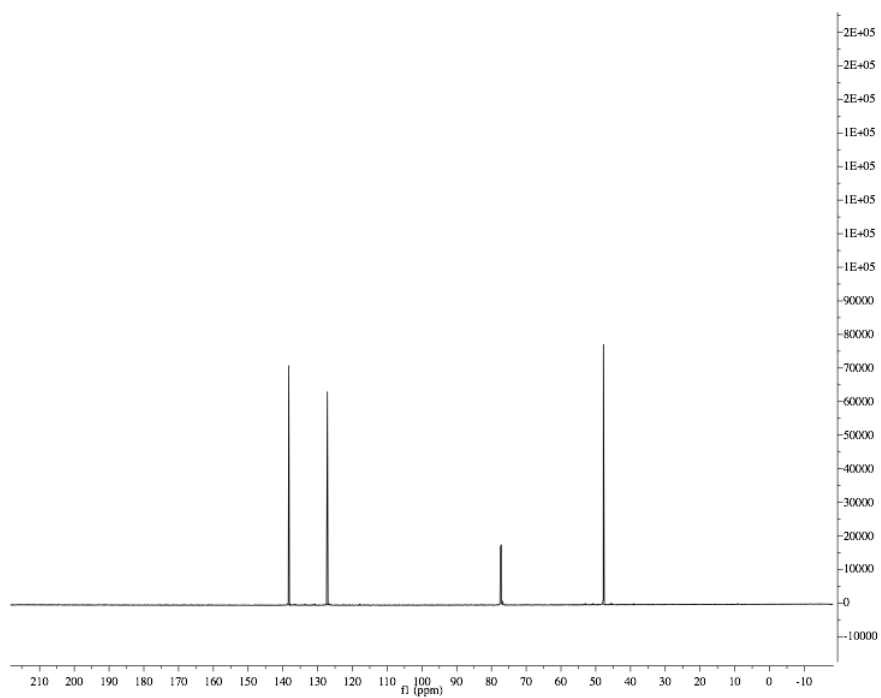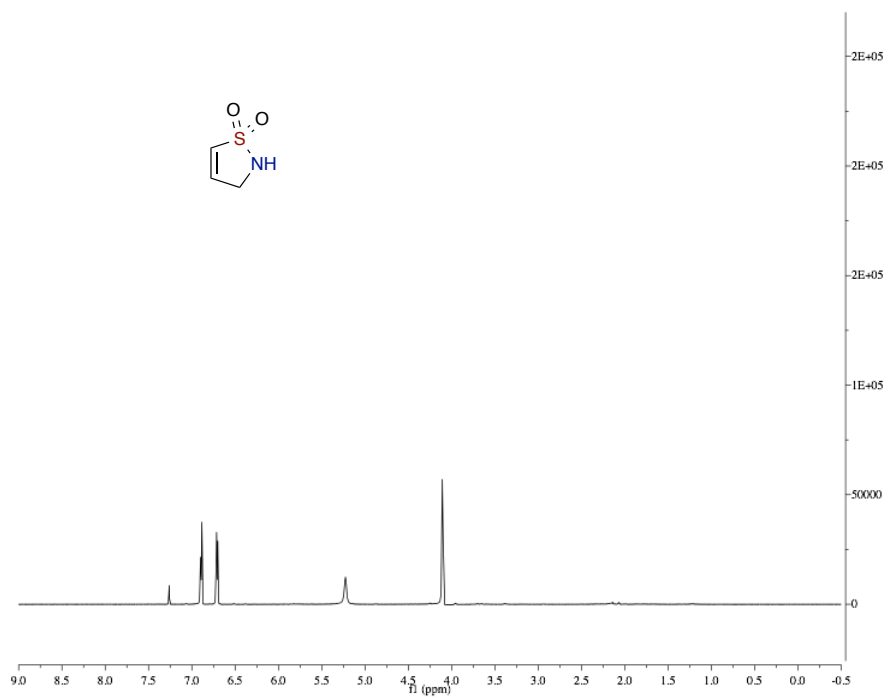
2-(Prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide (1.8.4)
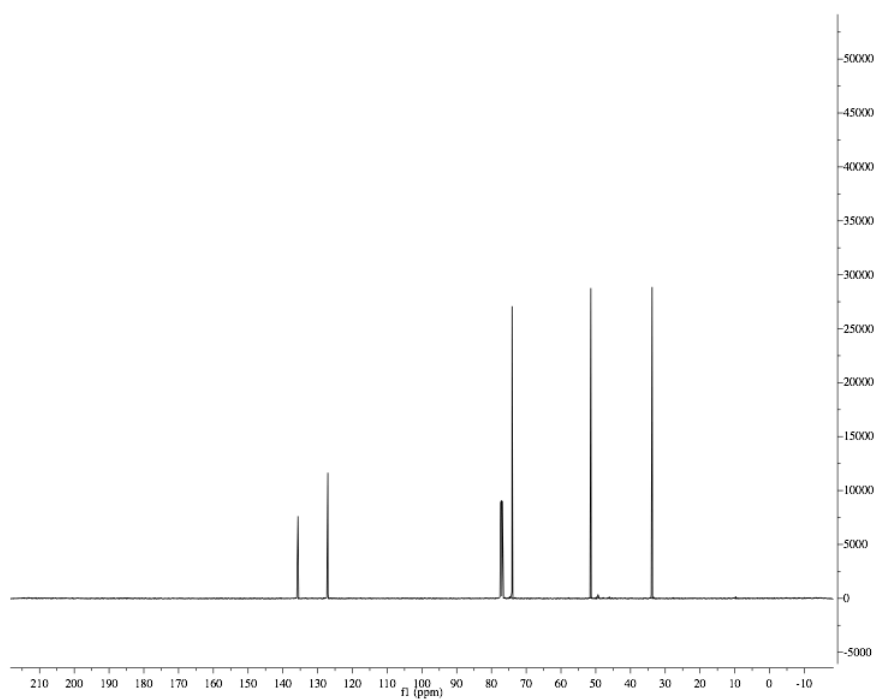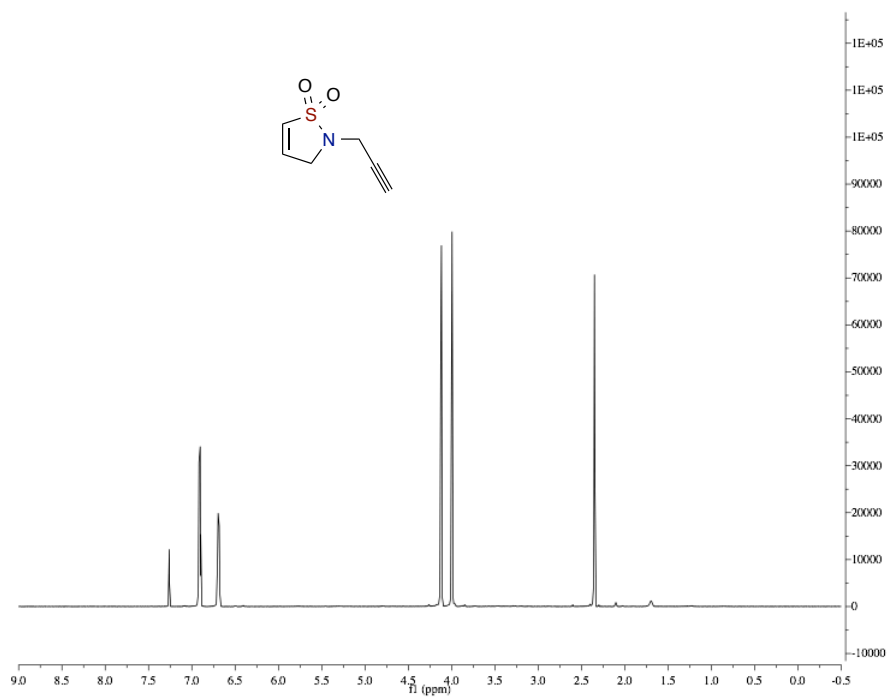
2-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-(2-fluorobenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide (1{M})
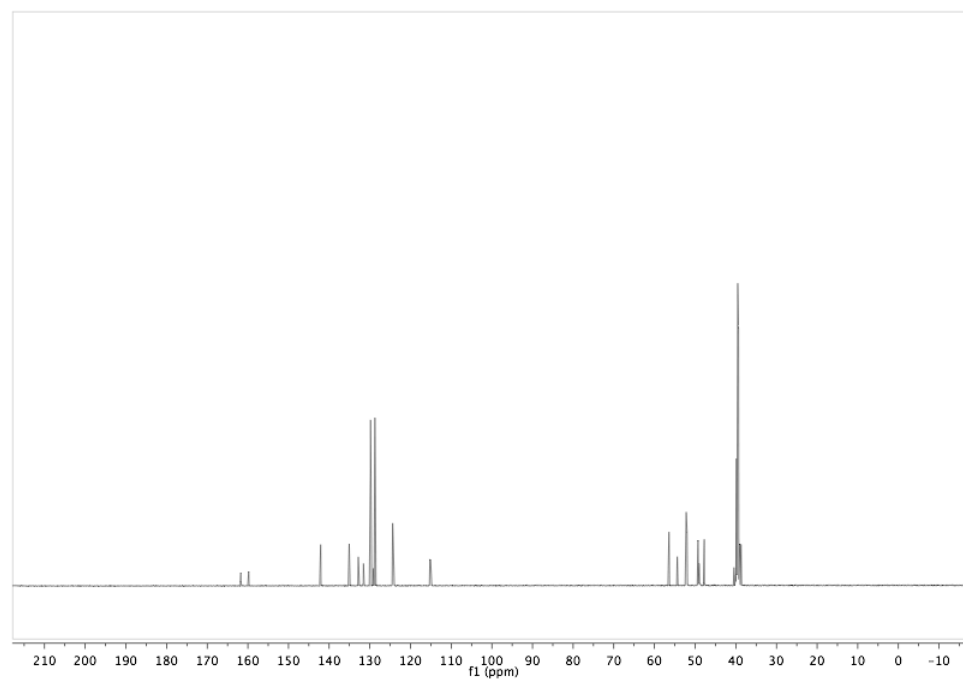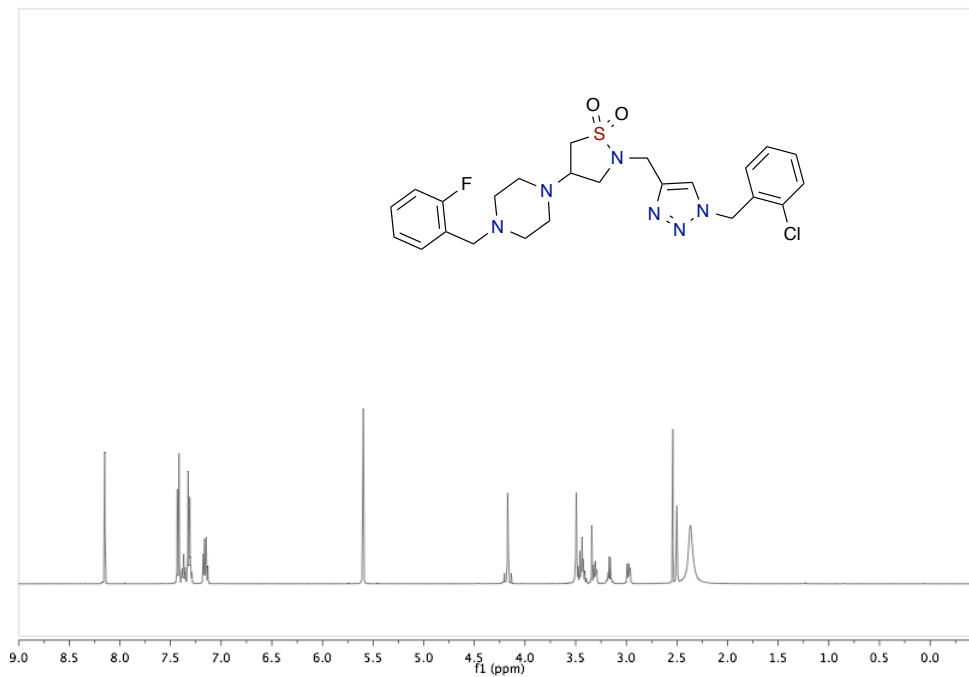
2-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-(4-(3-methylbenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide (2{A})
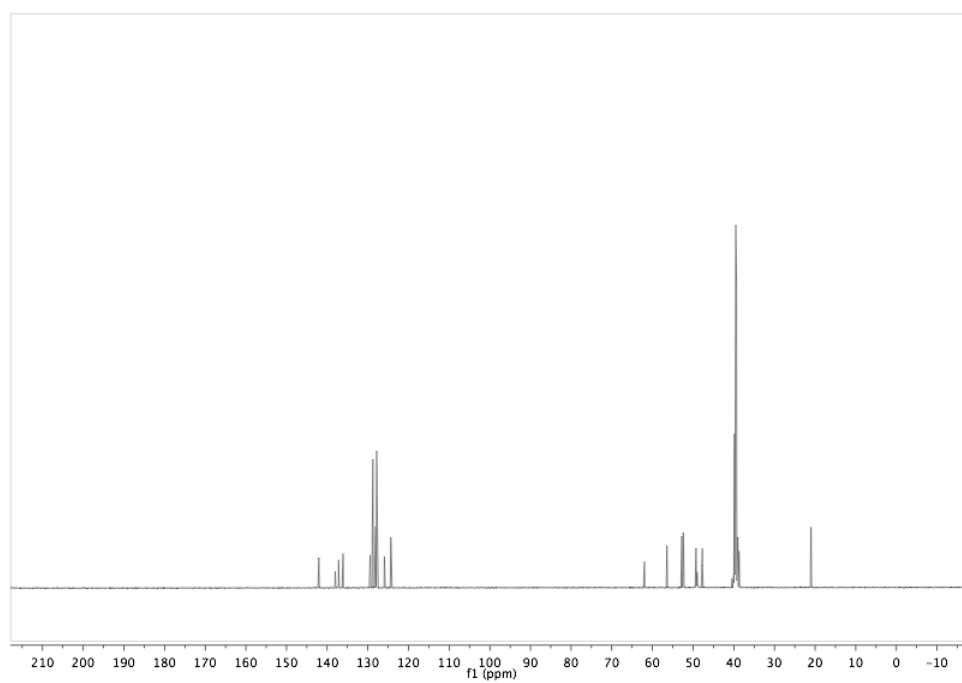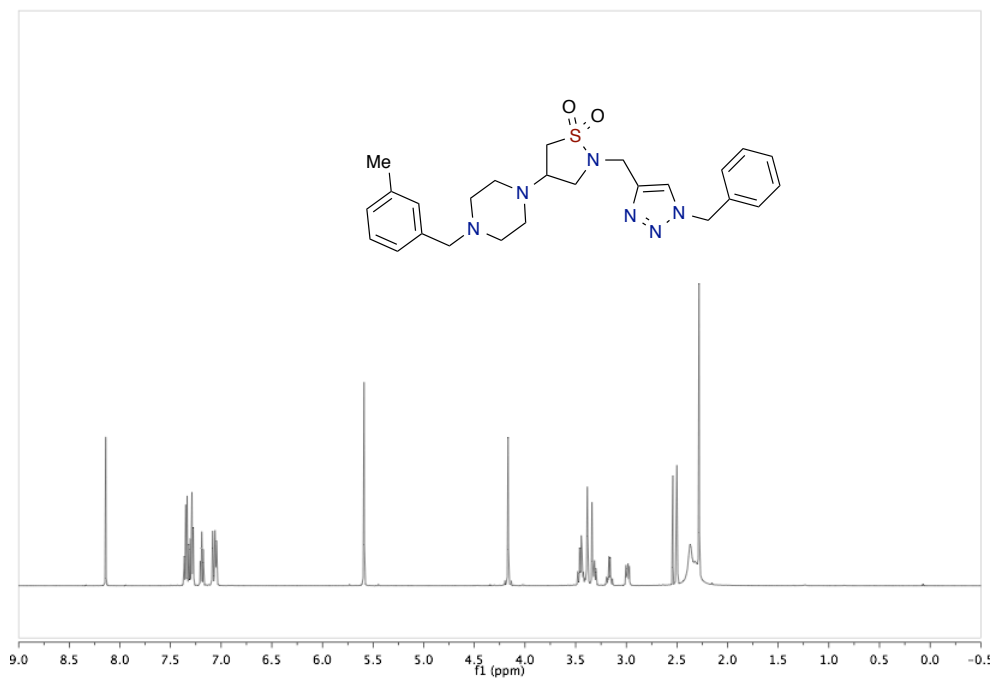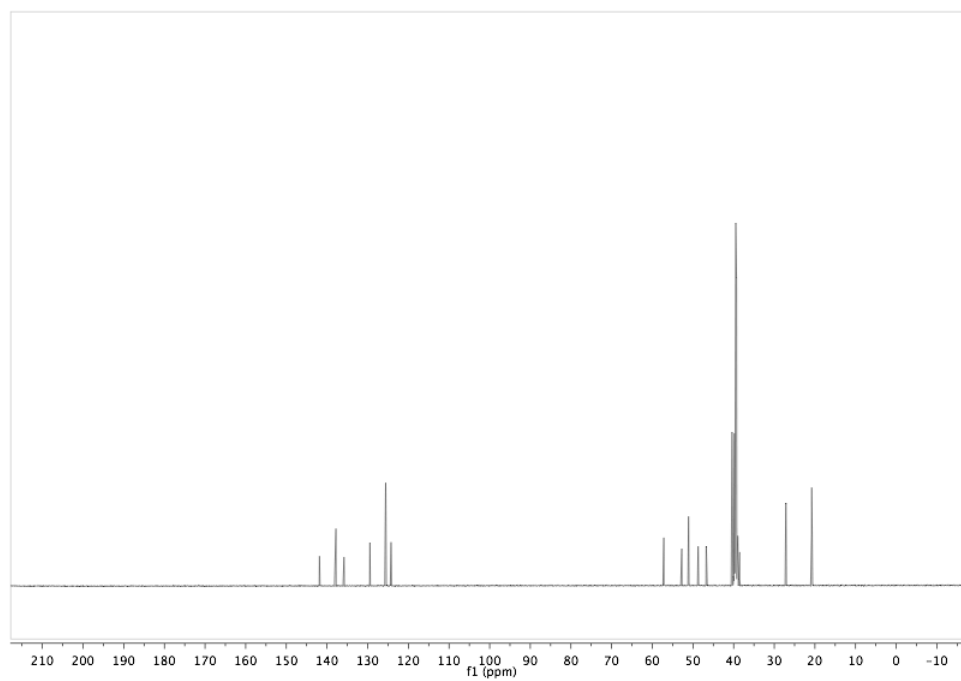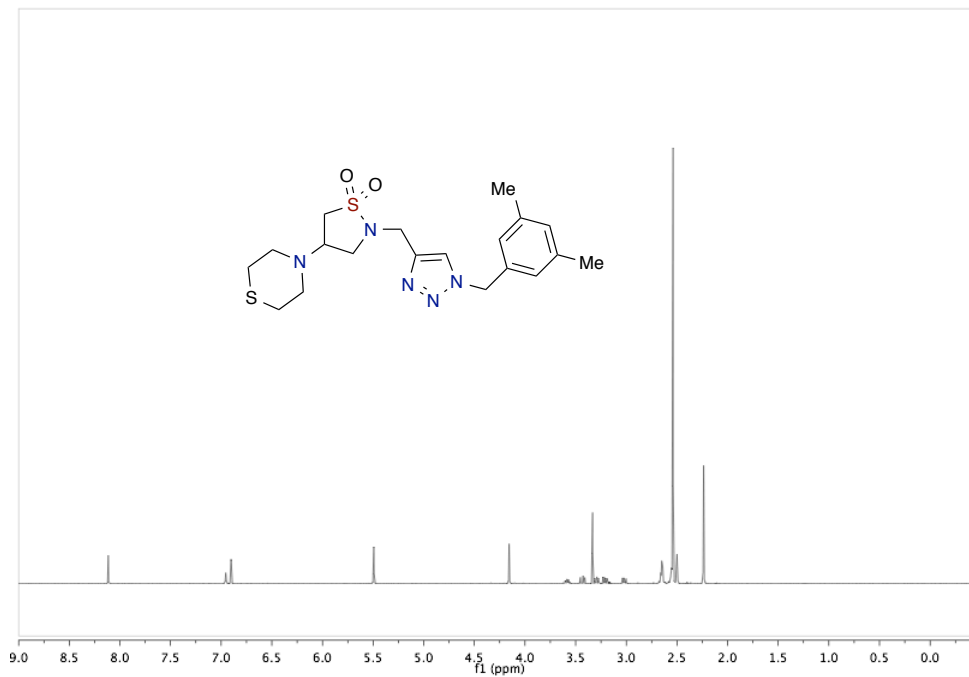
2-((1-(3-Methoxypropyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-(3-methylbenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide (2{K})
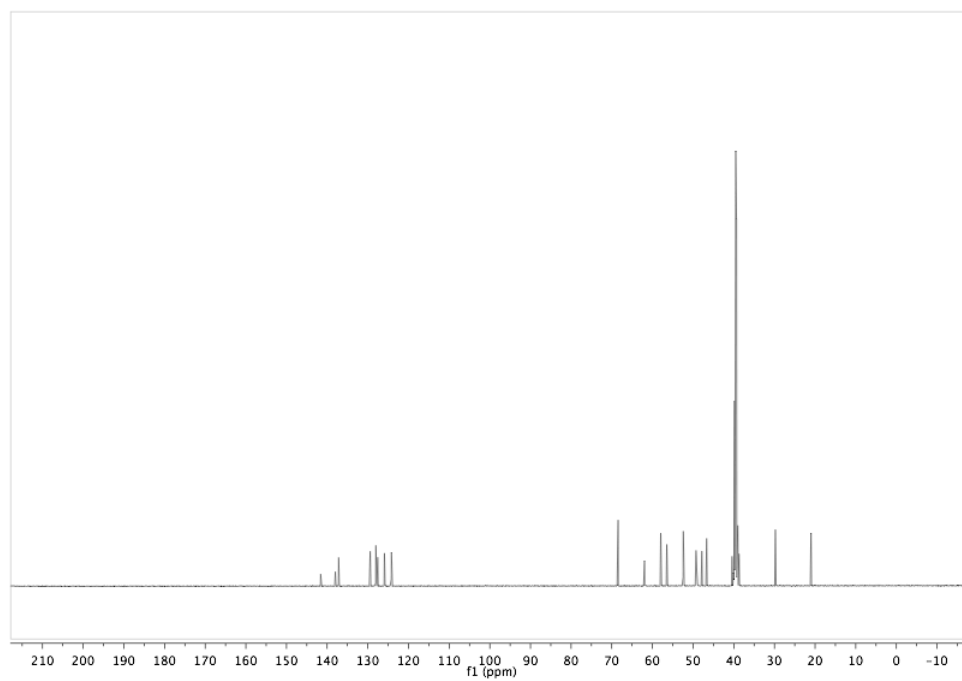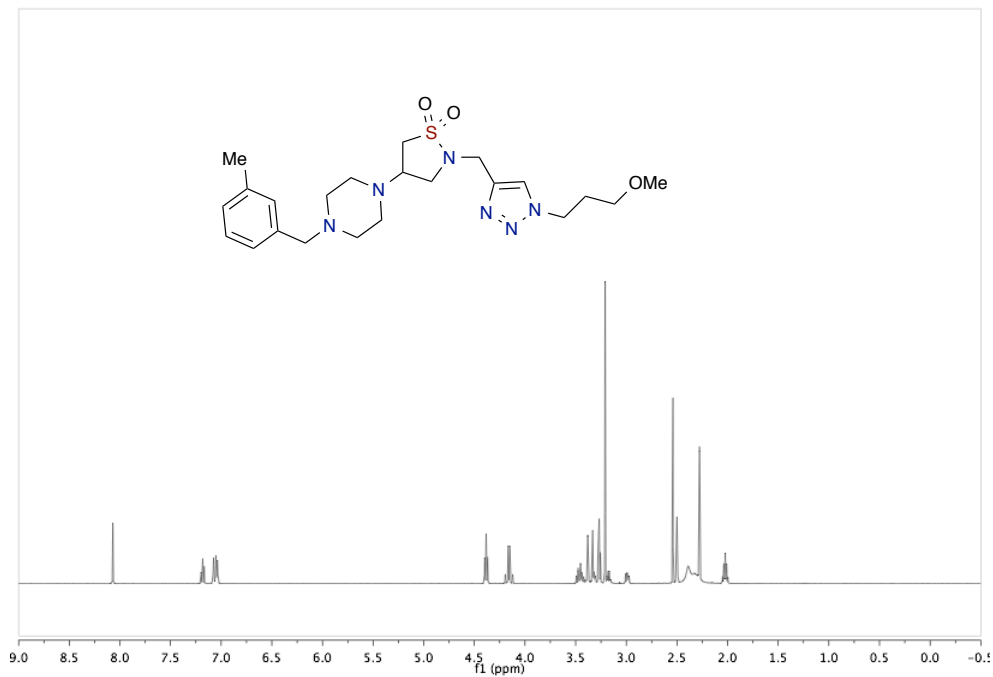
Methyl 4-(4-((4-(4-(3-methylbenzyl)piperazin-1-yl)-1,1-dioxidoisothiazolidin-2-yl)methyl)-1H-1, 2, 3-triazol-1-yl)butanoate (2{L})
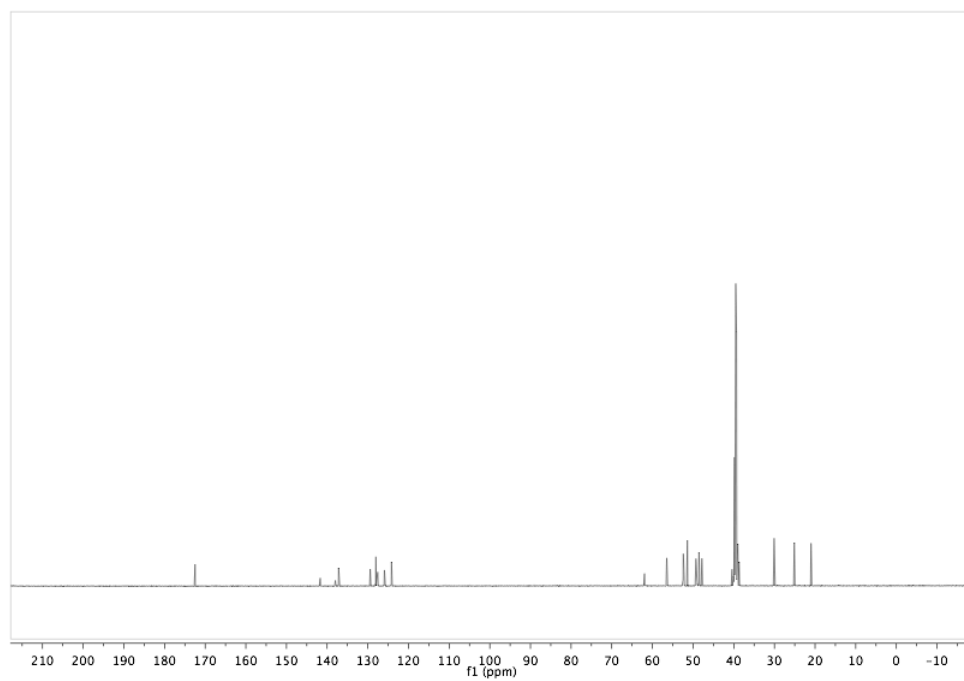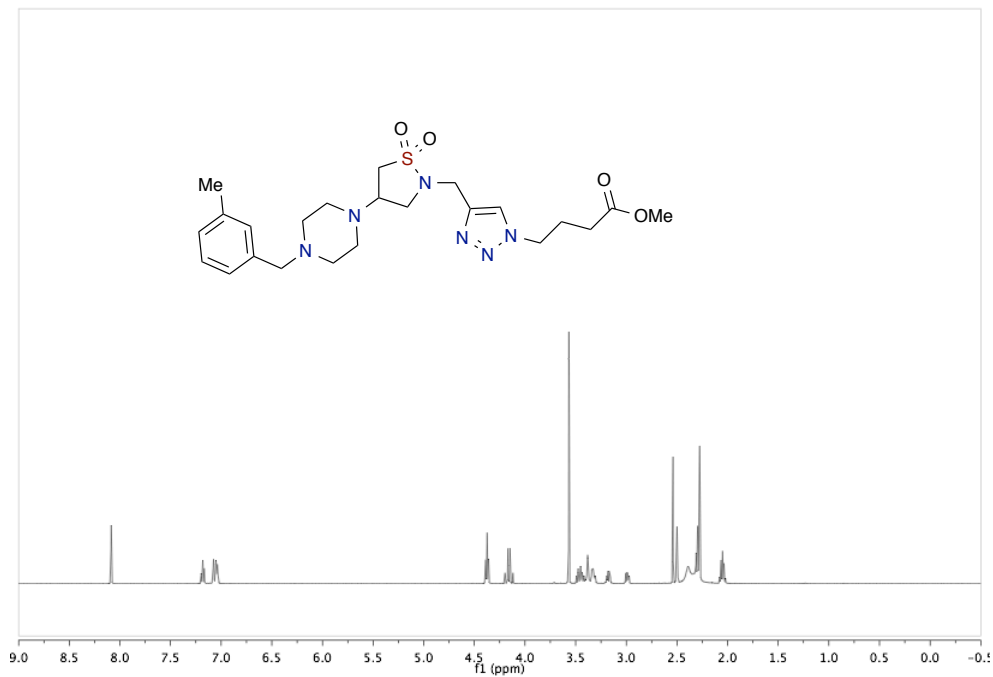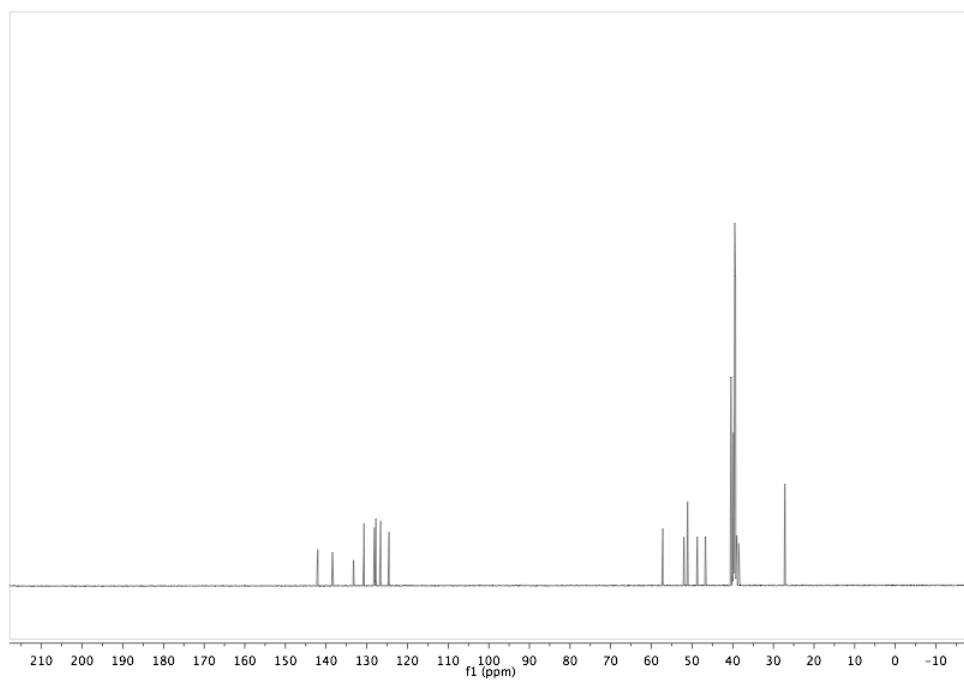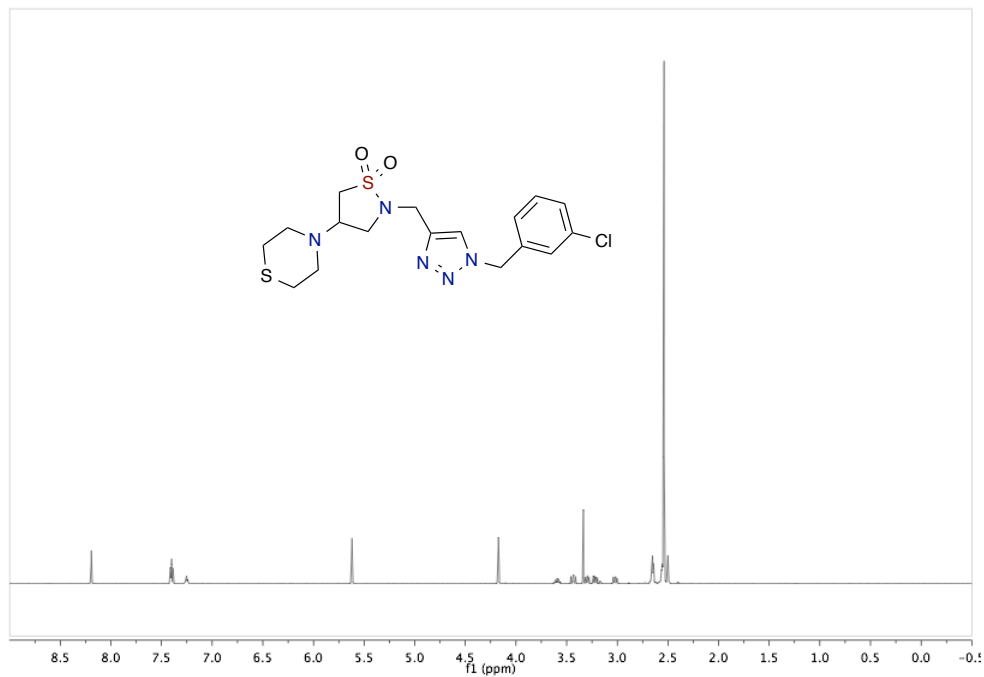
2-((1-(3,5-Dimethylbenzyl)-1H-1, 2, 3-triazol-4-yl)methyl)-4-thiomorpholinoisothiazolidine 1,1-dioxide (3{F})
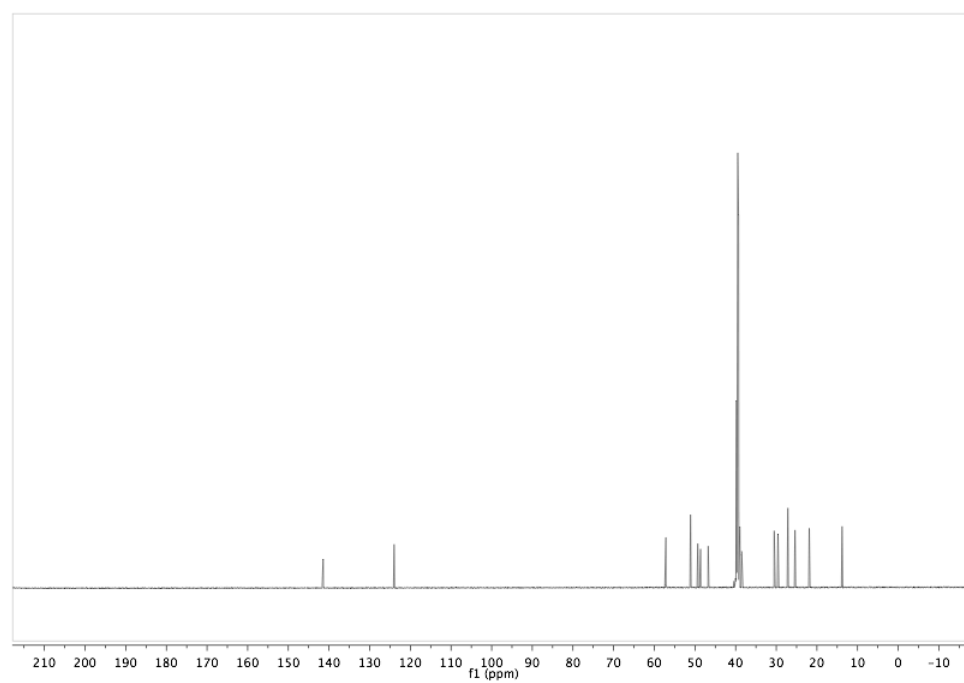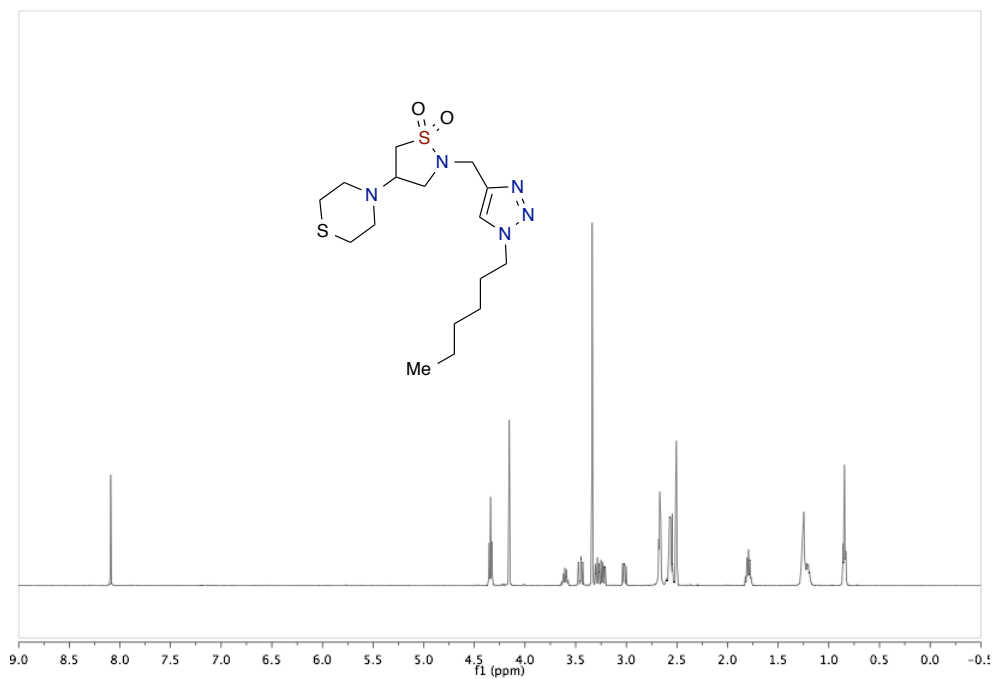
2-((1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-thiomorpholinoisothiazolidine 1,1-dioxide (3{I})
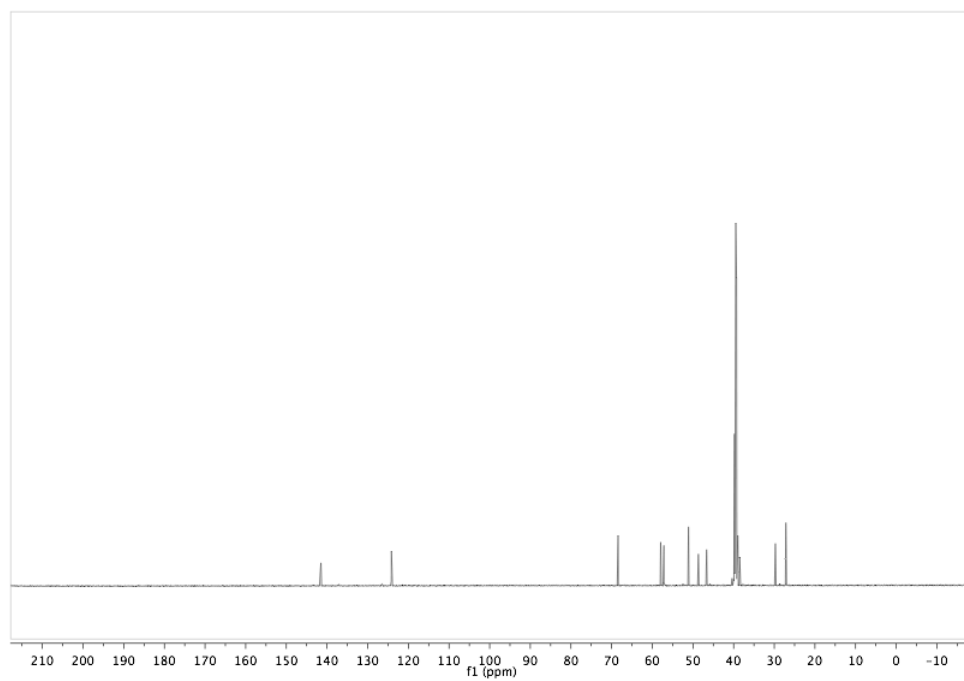
2-((1-Hexyl-1H-1,2,3-triazol-4-yl)methyl)-4-thiomorpholinoisothiazolidine   1,1-dioxide (3{J})

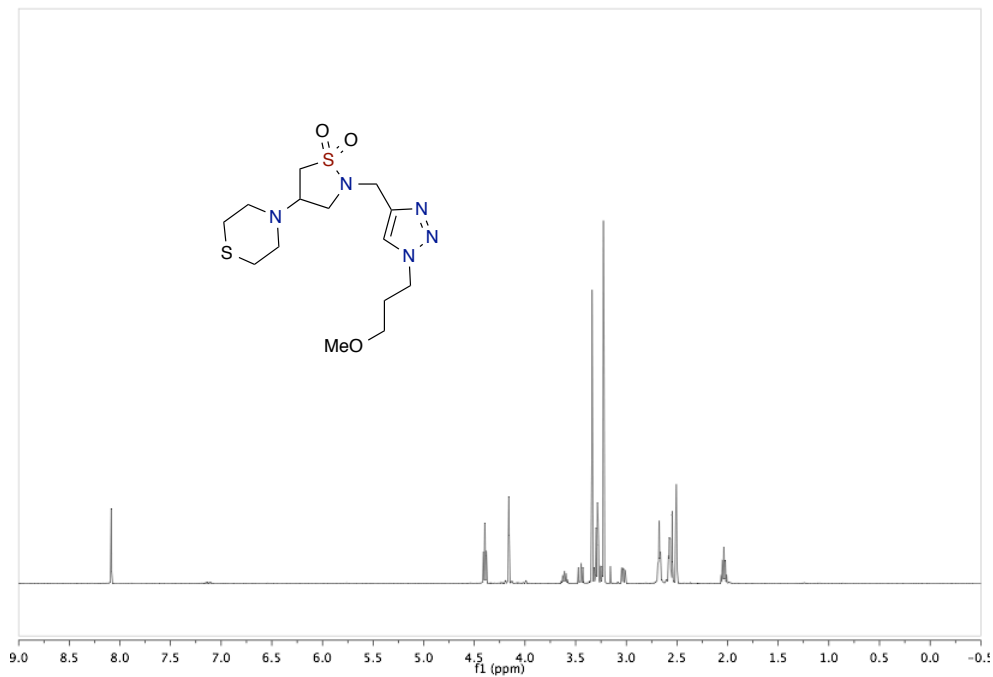**2-((1-(3-Methoxypropyl)-1H-1,2,3-triazol-4-yl)methyl)-4-thiomorpholinoisothiazolidine 1,1-dioxide (3{K})**

2-((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (6{B})
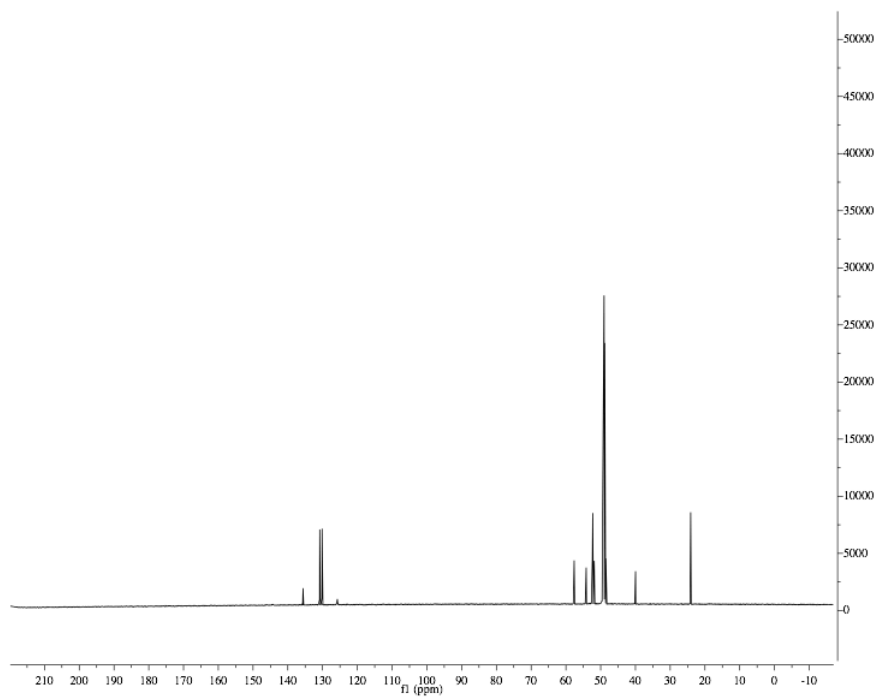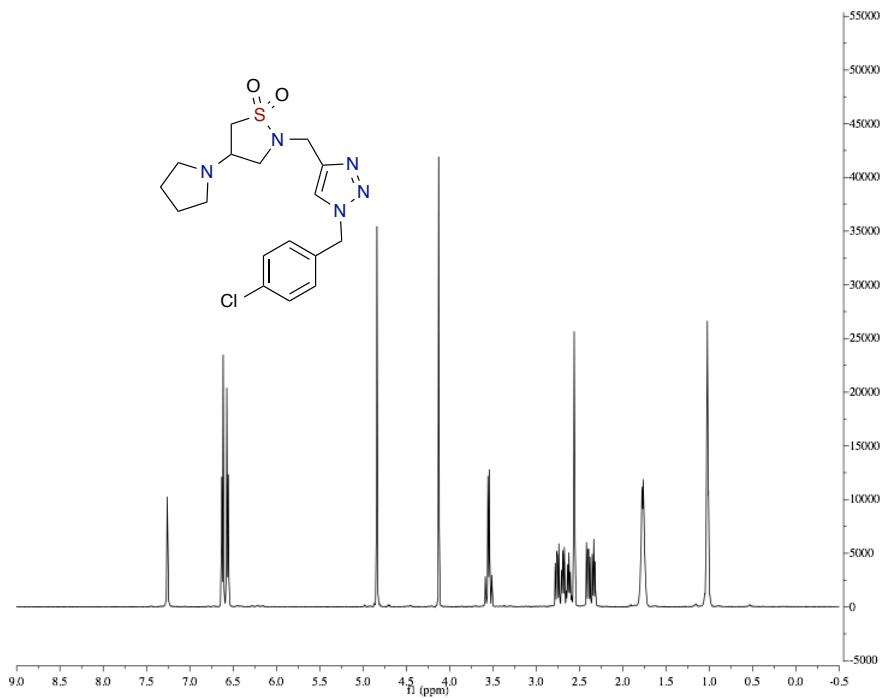
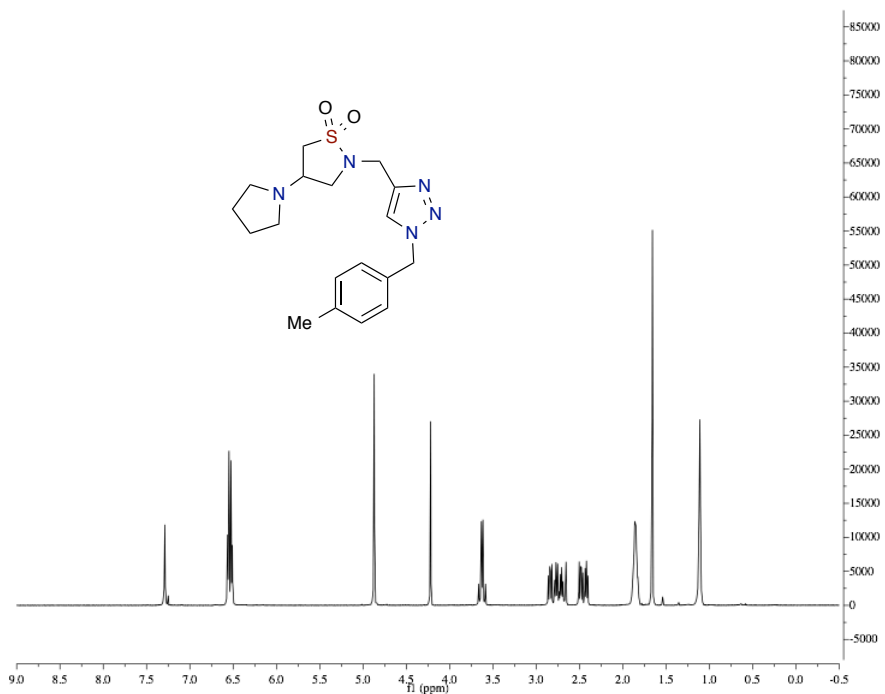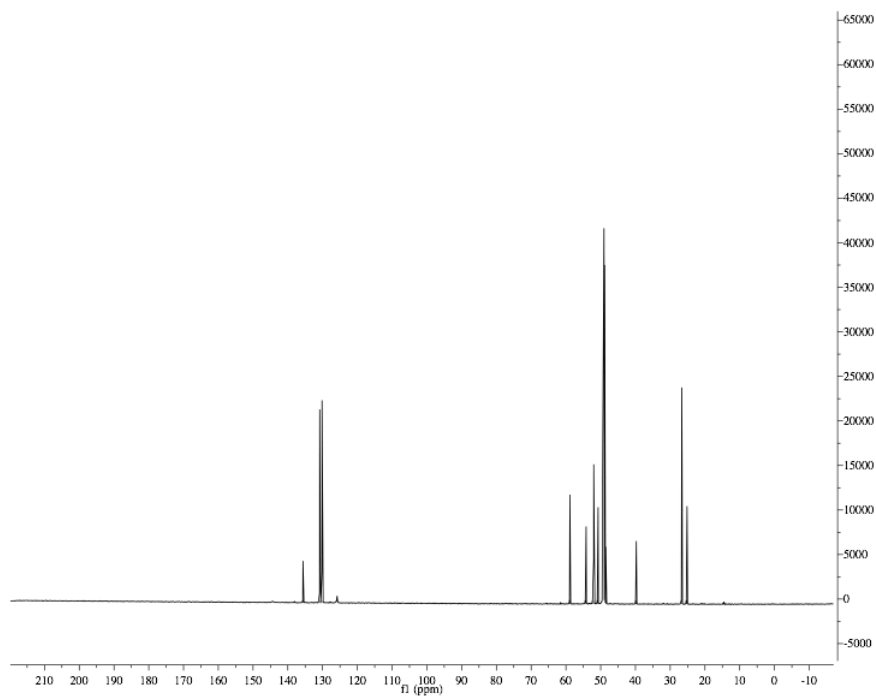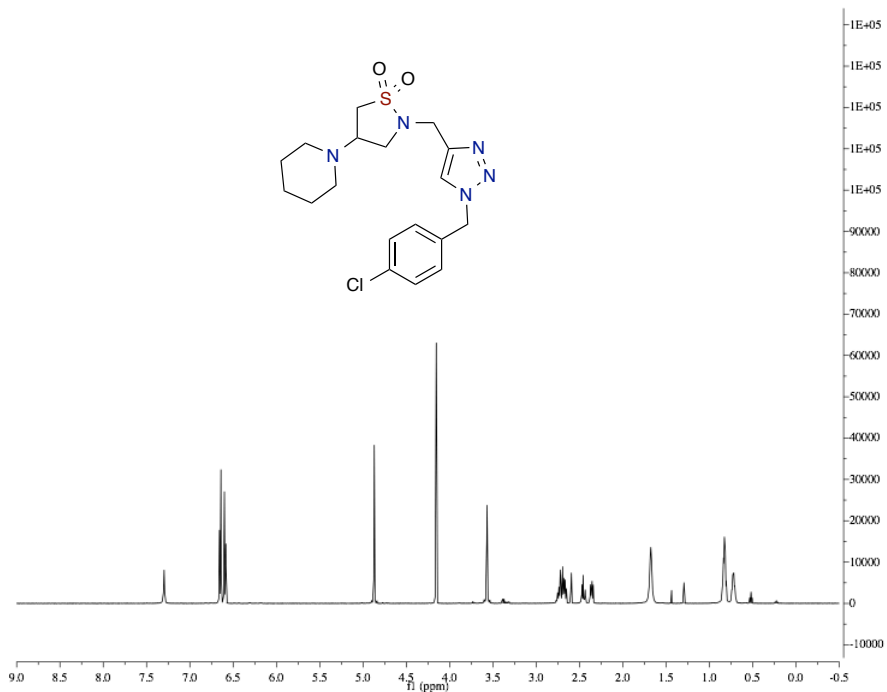**2-((1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (6{D})**
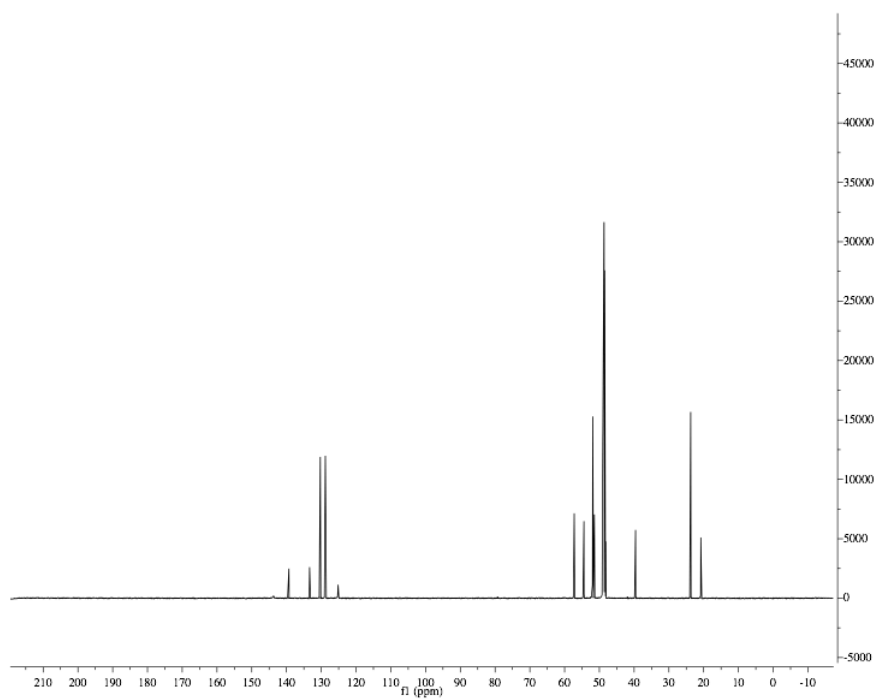
2-((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(piperidin-1-yl)isothiazolidine 1,1-dioxide (7{B})

Comp.	HRMS Expected M/z (M)$^+$	HRMS Found M/z (M+H)$^+$	Mass (mg)	Purity (%)
1{A}	484.2056	485.2153	48.1 mg	97.1 %
1{B}	518.1667	519.1739	44.2 mg	99.8 %
1{C}	502.1962	503.2058	42.8 mg	97.5 %
1{D}	498.2213	499.2291	38.3 mg	99.3 %
1{E}	514.2162	515.2245	58.6 mg	95.2 %
1{F}	512.2369	513.2458	29.3 mg	98.3 %
1{G}	552.1930	553.2005	38.3 mg	97.4 %
1{H}	552.1930	553.2022	41.3 mg	99.1 %
1{I}	518.1667	519.1757	31.8 mg	99.2 %
1{J}	478.2526	479.2626	29.1 mg	98.9 %
1{K}	466.2162	467.2246	32.6 mg	99.6 %
1{L}	494.2111	495.2186	28.5 mg	99.1 %
2{A}	480.2307	481.2389	29.3 mg	99.7 %
2{B}	514.1917	515.1992	35.8 mg	98.6 %
2{C}	498.2213	499.2295	44.8 mg	99.1 %
2{D}	494.2463	495.2545	44.7 mg	98.5 %
2{E}	510.2413	511.2496	17.7 mg	60.6 %
2{F}	508.2620	509.2706	43.0 mg	98.9 %
2{G}	548.2181	549.2261	32.2 mg	98.5 %
2{H}	548.2181	549.2242	37.3 mg	98.0 %
2{I}	514.1917	515.2001	25.4 mg	99.8 %
2{J}	474.2776	475.2872	30.7 mg	99.3 %
2{K}	462.2413	463.2486	25.7 mg	100.0 %
2{L}	490.2362	491.2389	29.3 mg	99.7 %
3{A}	393.1293	394.1394	12.9 mg	89.8 %
3{B}	427.0903	428.0991	16.8 mg	98.0 %
3{C}	411.1198	412.1292	16.2 mg	89.9 %
3{D}	407.1449	408.1539	16.5 mg	98.0 %
3{E}	423.1398	424.1484	14.0 mg	93.1 %
3{F}	421.1606	422.1705	20.9 mg	96.0 %
3{G}	461.1167	462.1259	24.1 mg	98.5 %
3{H}	461.1167	462.1251	22.0 mg	96.8 %
3{I}	427.0903	428.0991	25.8 mg	98.8 %
3{J}	387.1762	388.1851	15.0 mg	97.1 %
3{K}	375.1398	376.1493	16.2 mg	97.5 %
3{L}	403.1347	404.1437	8.1 mg	84.5 %
4{A}	460.2620	461.2720	10.6 mg	94.4 %
4{B}	494.2230	495.2325	10.8 mg	98.9 %
4{C}	478.2526	479.2604	9.2 mg	94.8 %
4{D}	474.2776	475.2846	20.5 mg	98.2 %

4{E}	490.2726	491.2820	12.8 mg	81.7 %
4{F}	488.2933	489.3016	15.1 mg	92.6 %
4{G}	528.2494	529.2567	16.1 mg	88.9 %
4{H}	528.2494	529.2580	14.3 mg	90.1 %
4{I}	494.2230	495.2308	10.6 mg	97.4 %
4{J}	454.3089	455.3181	9.9 mg	97.2 %
4{K}	442.2726	443.2823	9.0 mg	87.5 %
4{L}	470.2675	471.2753	6.0 mg	92.3 %
5{A}	359.1415	360.1506	40.0mg	92.7 %
5{B}	393.1026	394.1125	39.5mg	93.1 %
5{C}	377.1321	378.1426	21.9mg	90.6 %
5{D}	373.1572	374.1666	36.6mg	89.6 %
5{E}	389.1521	390.1592	35.9mg	95.4 %
5{F}	387.1728	388.1819	19.9mg	85.6 %
5{G}	427.1289	428.1374	34.9mg	86.0 %
5{H}	427.1289	428.1368	42.1mg	95.5 %
5{I}	393.1026	394.1121	38.4mg	94.1 %
5{J}	353.1885	354.1969	22.8mg	87.7 %
5{K}	341.1521	342.1595	23.7mg	87.1 %
5{L}	369.1470	370.1554	35.2mg	92.8 %
6{A}	361.1572	362.1671	57.3 mg	97.7 %
6{B}	395.1182	396.1288	69.3 mg	98.3 %
6{C}	379.1478	380.1569	51.0 mg	97.9 %
6{D}	375.1728	376.1825	48.7 mg	98.4 %
6{E}	391.1678	392.1744	60.5 mg	98.2 %
6{F}	389.1885	390.1976	77.1 mg	98.0 %
6{G}	429.1446	430.1522	69.2 mg	98.4%
6{H}	429.1446	430.1544	67.9 mg	97.9 %
6{I}	395.1182	396.1271	60.8 mg	98.0 %
6{J}	355.2041	356.2140	52.4 mg	96.9 %
6{K}	343.1678	344.1757	59.2 mg	98.4 %
6{L}	371.1627	372.1714	53.4 mg	96.8 %
7{A}	375.1728	376.1805	57.7 mg	98.4 %
7{B}	409.1339	410.1438	61.8 mg	98.0 %
7{C}	393.1634	394.1719	61.2 mg	97.9 %
7{D}	389.1885	390.1964	46.9 mg	99.1 %
7{E}	405.1834	406.1928	51.2 mg	98.1 %
7{F}	403.2041	404.2126	55.1 mg	96.6 %
7{G}	443.1602	444.1696	66.9 mg	96.9 %
7{H}	443.1602	444.1691	67.0 mg	98.4 %
7{I}	409.1339	410.1407	59.7 mg	98.3 %
7{J}	369.2198	370.2278	33.6 mg	97.0 %

7{K}	357.1834	358.1918	49.1 mg	97.1 %
7{L}	385.1783	386.1882	39.4 mg	97.1 %
8{A}	335.1415	336.1514	34.9 mg	99.6 %
8{B}	369.1026	370.1110	41.9 mg	100.0 %
8{C}	353.1321	354.1402	35.9 mg	99.7 %
8{D}	349.1572	350.1653	30.9 mg	100.0 %
8{E}	365.1521	366.1608	38.0 mg	100.0 %
8{F}	363.1728	364.1826	49.3 mg	99.8 %
8{G}	403.1289	404.1367	45.7 mg	100.0 %
8{H}	403.1289	404.1371	55.7 mg	100.0 %
8{I}	369.1026	370.1119	43.9 mg	100.0 %
8{J}	329.1885	330.1975	46.9 mg	99.5 %
8{K}	317.1521	318.1617	13.0 mg	91.6 %
8{L}	345.1470	346.1571	26.5 mg	98.9 %
9{A}	349.1572	350.1661	31.4 mg	99.8 %
9{B}	383.1182	384.1274	28.8 mg	100.0 %
9{C}	367.1478	368.1559	32.5 mg	100.0 %
9{D}	363.1728	364.1822	36.4 mg	100.0 %
9{E}	379.1678	380.1761	27.8 mg	100.0 %
9{F}	377.1885	378.1973	33.9 mg	98.9 %
9{G}	417.1446	418.1529	34.0 mg	99.2 %
9{H}	417.1446	418.1536	37.8 mg	99.4 %
9{I}	383.1182	384.1261	38.3 mg	99.8 %
9{J}	343.2041	344.2115	30.9 mg	98.2 %
9{K}	331.1678	332.1770	28.3 mg	97.8 %
9{L}	359.1627	360.1713	22.8 mg	98.3 %
10{A}	363.1728	364.1814	30.8 mg	99.8 %
10{B}	397.1339	398.1418	30.5 mg	99.7 %
10{C}	381.1634	382.1718	30.9 mg	100.0 %
10{D}	377.1885	378.1976	31.8 mg	96.9 %
10{E}	393.1834	394.1907	30.6 mg	100.0 %
10{F}	391.2041	392.2122	29.8 mg	99.2 %
10{G}	431.1602	432.1678	28.0 mg	100.0 %
10{H}	431.1602	432.1700	38.1 mg	100.0 %
10{I}	397.1339	398.1406	31.4 mg	98.4 %
10{J}	357.2198	358.2291	22.5 mg	99.3 %
10{K}	345.1834	346.1910	27.3 mg	100.0 %
10{L}	373.1783	374.1858	15.4 mg	99.0 %
11{A}	492.2055	493.2166	23.5 mg	99.6 %
11{B}	560.1276	561.1351	30.1 mg	98.5 %
11{C}	528.1867	529.1973	29.1 mg	98.3 %
11{D}	520.2368	521.2452	26.9 mg	97.0 %

11{E}	552.2267	553.2336	24.8 mg	99.0 %
11{F}	548.2681	549.2745	20.7 mg	88.0 %
11{G}	628.1803	629.1876	29.5 mg	96.4 %
11{H}	628.1803	629.1880	32.0 mg	94.9 %
11{I}	560.1276	561.1326	20.7 mg	94.5 %
11{J}	480.2994	481.3079	18.3 mg	94.5 %
11{K}	456.2267	457.2344	15.3 mg	99.1 %
11{L}	512.2165	513.2237	19.4 mg	97.5 %
12{A}	390.1837	391.1910	17.8 mg	99.3 %
12{B}	424.1448	425.1529	12.4 mg	97.5 %
12{C}	408.1743	409.1832	22.5 mg	99.0 %
12{D}	404.1994	405.2089	37.4 mg	98.9 %
12{E}	420.1943	421.2021	30.6 mg	99.8 %
12{F}	418.2150	419.2209	12.9 mg	93.4 %
12{G}	458.1711	459.1787	63.2 mg	99.6 %
12{H}	458.1711	459.1795	30.2 mg	97.6 %
12{I}	424.1448	425.1544	18.1 mg	97.7 %
12{J}	384.2307	385.2394	52.9 mg	97.6 %
12{K}	372.1943	373.2020	49.9 mg	97.3 %
12{L}	400.1892	401.1975	20.9 mg	97.0 %
13{A}	447.2416	448.2503	15.0 mg	94.8 %
13{B}	481.2026	482.2089	12.6 mg	95.6 %
13{C}	465.2322	466.2395	45.1 mg	98.0 %
13{D}	461.2572	462.2646	17.2 mg	98.0 %
13{E}	477.2522	478.2593	35.9 mg	96.3 %
13{F}	475.2729	476.2809	13.4 mg	91.2 %
13{G}	515.2290	516.2383	62.2 mg	98.7 %
13{H}	515.2290	516.2368	31.0 mg	94.4 %
13{I}	481.2026	482.2080	21.8 mg	96.4 %
13{J}	441.2885	442.2977	28.9 mg	94.2 %
13{K}	429.2522	430.2625	21.8 mg	95.5 %
13{L}	457.2471	458.2586	28.7 mg	92.4 %
14{A}	473.2572	NA	NA	NA
14{B}	507.2183	508.2254	6.6 mg	95.9 %
14{C}	491.2478	492.2542	17.7 mg	99.4 %
14{D}	487.2729	488.2804	19.9 mg	98.6 %
14{E}	503.2678	504.2772	17.0 mg	97.0 %
14{F}	501.2885	502.2981	1.7 mg	92.0 %
14{G}	541.2446	542.2553	83.6 mg	98.7 %
14{H}	541.2446	542.2510	18.3 mg	98.7 %
14{I}	507.2183	508.2267	24.0 mg	94.7 %
14{J}	467.3042	468.3139	79.2 mg	97.9 %

14{K}	455.2678	456.2773	30.0 mg	92.3 %
14{L}	483.2627	484.2695	17.1 mg	98.4 %
15{A}	420.1943	421.2033	17.5 mg	95.4 %
15{B}	454.1553	455.1652	13.5 mg	96.5 %
15{C}	438.1849	439.1934	30.7 mg	99.4 %
15{D}	434.2100	435.2179	14.3 mg	100.0 %
15{E}	450.2049	451.2133	19.6 mg	98.9 %
15{F}	448.2256	449.2339	13.2 mg	97.6 %
15{G}	488.1817	489.1891	62.1 mg	95.8 %
15{H}	488.1817	489.1899	42.1 mg	98.4 %
15{I}	454.1553	455.1622	16.4 mg	97.6 %
15{J}	414.2413	415.2501	44.1 mg	100.0 %
15{K}	402.2049	403.2145	43.4 mg	99.2 %
15{L}	430.1998	431.2083	23.3 mg	100.0 %

1{B}

ID PSL14-1220-1B File AR101008WT049 Date 09-Nov-2010 Time 18:38:41 Description MDF024266

3: UV Detector: 214   1.279
                                                                    Range: 1.279

```
        (4)
        100%
AU    518.2(51%)
1.0-      1.92
      24025.0508
5.0e-1-

0.0-
      0.50    1.00    1.50    2.00    2.50    3.00    3.50    Time
```

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.73	31	0.13	2221	
2	1.58	30	0.13	1669	
4	1.92	24025	99.75	1274541	518.17
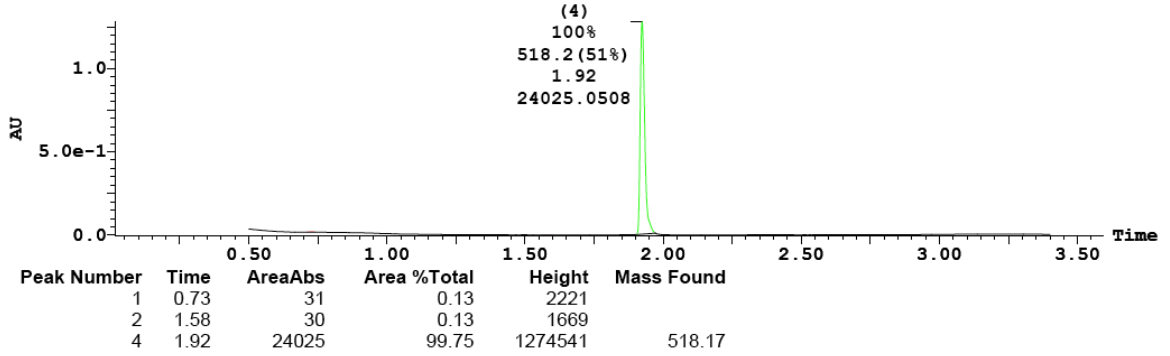
1{D}

3: UV Detector: 214   4.879e-1
                                                                  Range: 4.879e-1

```
                 (5)
                 99%
AU            498.2(47%)
4.0e-1-          1.89
              8260.1104
2.0e-1-
        (1)
        0%
        0.68
        24.7800
0.0-
      0.50    1.00    1.50    2.00    2.50    3.00    3.50    Time
```

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.68	25	0.30	1505	
2	0.72	22	0.26	1582	
4	1.86	13	0.16	988	498.22
5	1.89	8260	99.29	485221	498.22
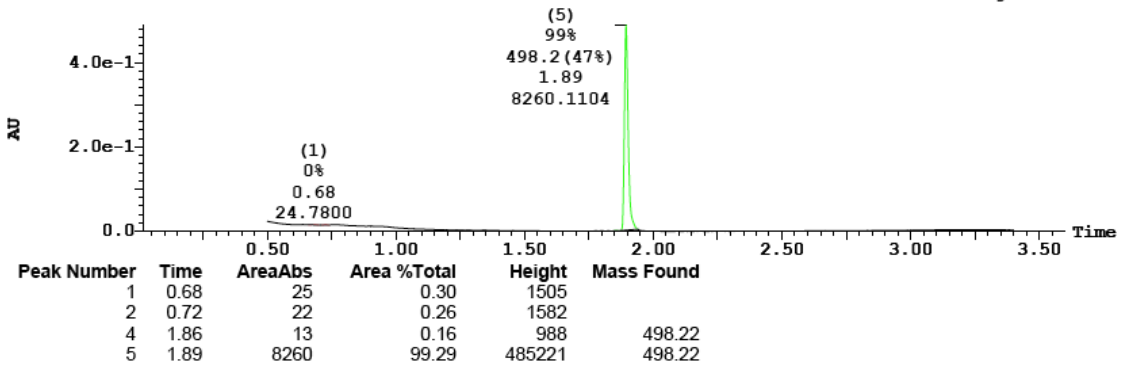
1{F}

3: UV Detector: 214   5.71e-1
                                                                   Range: 5.71e-1

```
                 (4)
                 98%
AU            512.2(58%)
                 2.02
4.0e-1-       9857.4697

2.0e-1-

0.0-
      0.50    1.00    1.50    2.00    2.50    3.00    3.50    Time
```

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.84	31	0.31	2129	512.24
2	1.90	18	0.18	1373	512.24
3	1.94	18	0.18	1239	512.24
4	2.00	99	0.99	11892	512.24
4	2.02	9857	98.33	568284	512.24
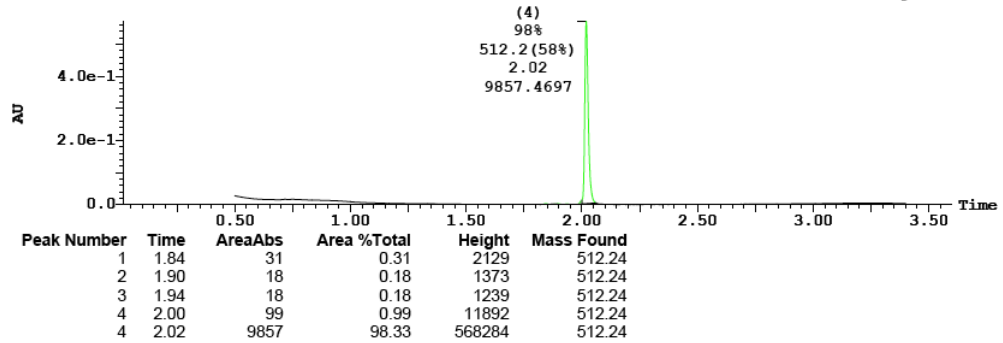
1{H}

ID PSL14-1220-1H File AR101008WT055 Date 09-Nov-2010 Time 15:26:49 Description MDF024337

3: UV Detector: 214

5.744e-1
Range: 5.744e-1

(4)
99%
552.2(61%)
1.98
9689.0596

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.02	14	0.14	987	
2	1.87	26	0.26	1878	552.19
3	1.94	54	0.55	3814	552.19
4	1.98	9689	99.05	570513	552.19
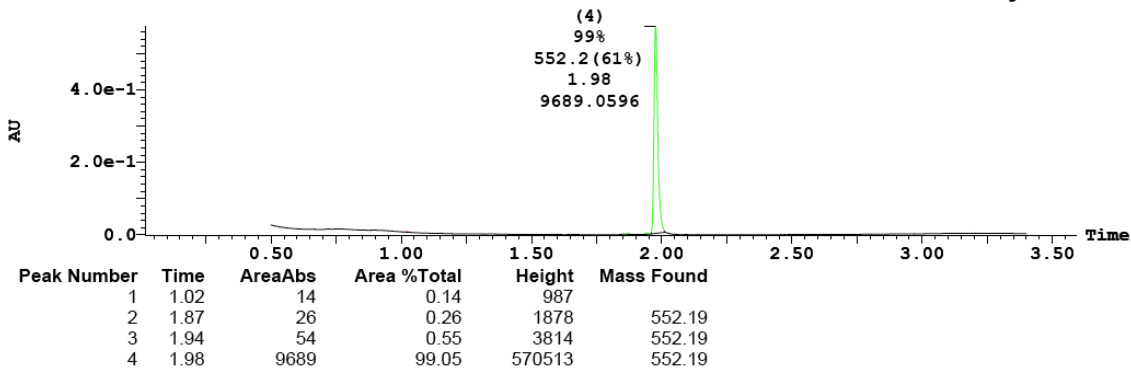
1{J}

3: UV Detector: 214

3.197e-1
Range: 3.197e-1

(4)
99%
478.3(65%)
2.01
5322.4302

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.87	14	0.26	877	478.25
3	1.98	25	0.46	1946	478.25
4	2.01	5322	98.85	317834	478.25
5	2.09	23	0.42	1357	478.25
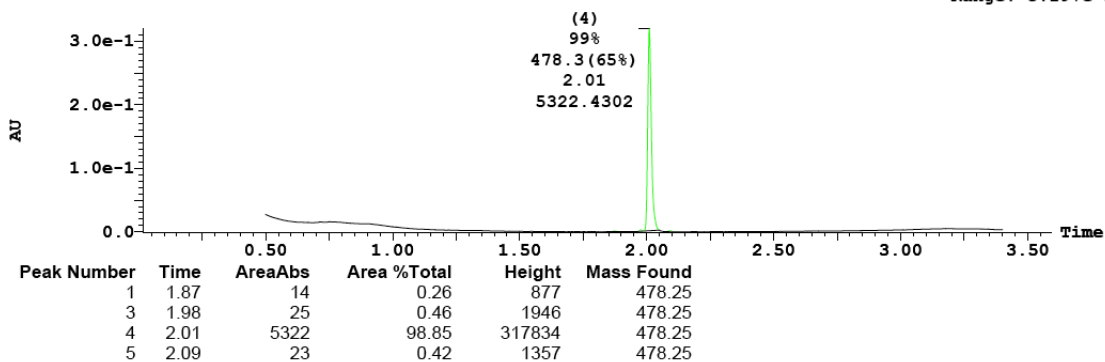
1{L}

3: UV Detector: 214

3.126e-1
Range: 3.125e-1
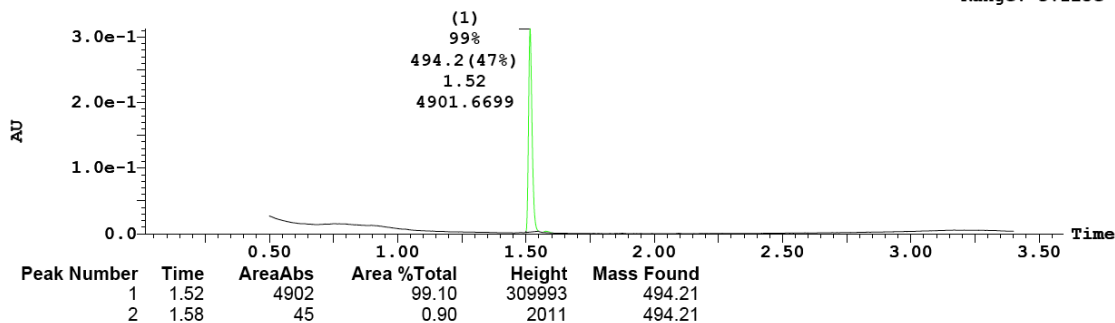
(1)
99%
494.2(47%)
1.52
4901.6699

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.52	4902	99.10	309993	494.21
2	1.58	45	0.90	2011	494.21

167

2{A}

4.448e-1
Range: 4.448e-1

(2)
100%
480.2(67%)
1.89
7395.9800
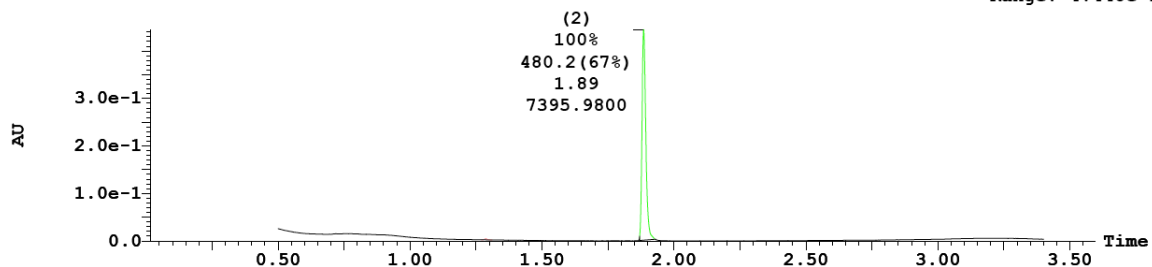
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.29	22	0.30	1457	
2	1.89	7396	99.70	443103	480.23

2{C}

3: UV Detector: 214

3.889e-1
Range: 3.889e-1

(5)
99%
498.2(62%)
1.91
6426.0801

(1)
0%
0.68
27.2800
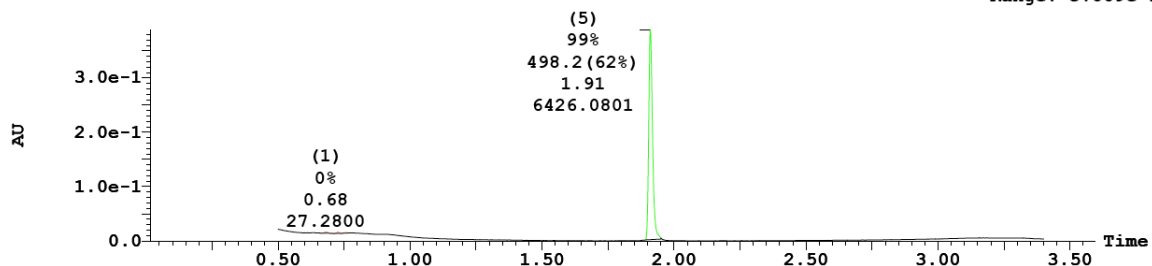
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.68	27	0.42	1581	
2	0.73	24	0.36	1744	
3	0.76	10	0.16	833	
5	1.91	6426	99.06	386602	498.22

2{F}

3: UV Detector: 214

1.166
Range: 1.166

(3)
99%
508.3(66%)
2.13
21578.6797
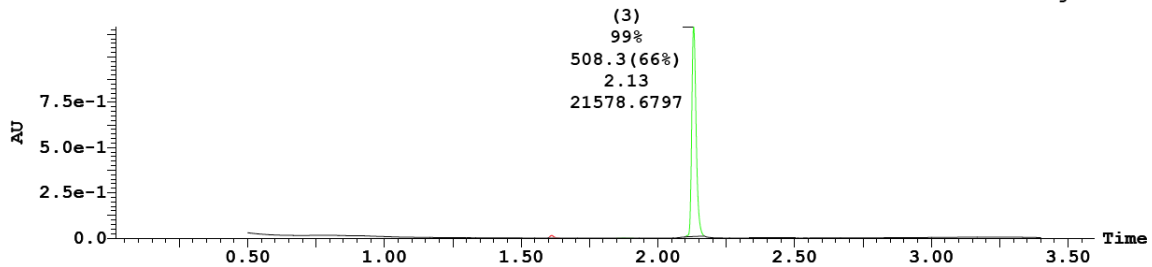
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.61	221	1.01	13834	
2	1.87	27	0.12	1247	508.26
3	2.13	21579	98.87	1156672	508.26

3{A}

2.689e-1
Range: 2.689e-1

(1)
90%
393.1(49%)
1.53
4407.3398

(2)
10%
393.1(49%)
1.57
502.6000

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.53	4407	89.76	267474	393.13
2	1.57	503	10.24	28212	393.13

3{C}
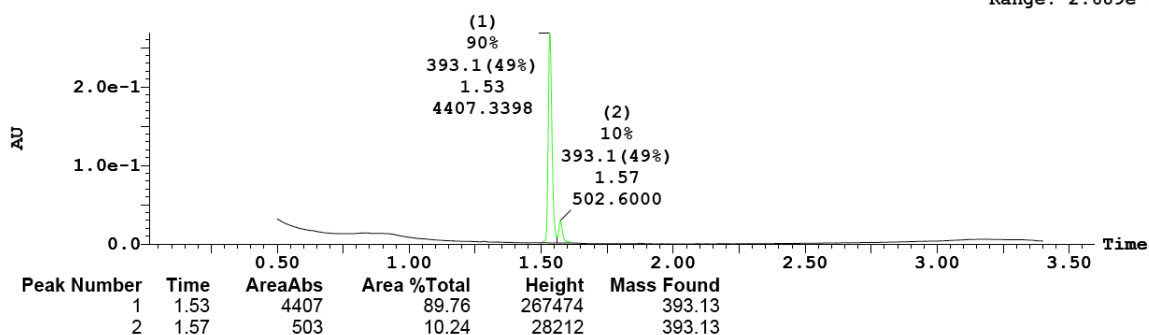
3: UV Detector: 214

2.858e-1
Range: 2.858e-1

(2)
90%
411.1(21%)
1.57
4640.5698

(3)
9%
411.1(21%)
1.64
482.4900

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.33	38	0.73	2172	411.12
2	1.57	4641	89.92	283297	411.12
3	1.64	482	9.35	30682	411.12

3{E}
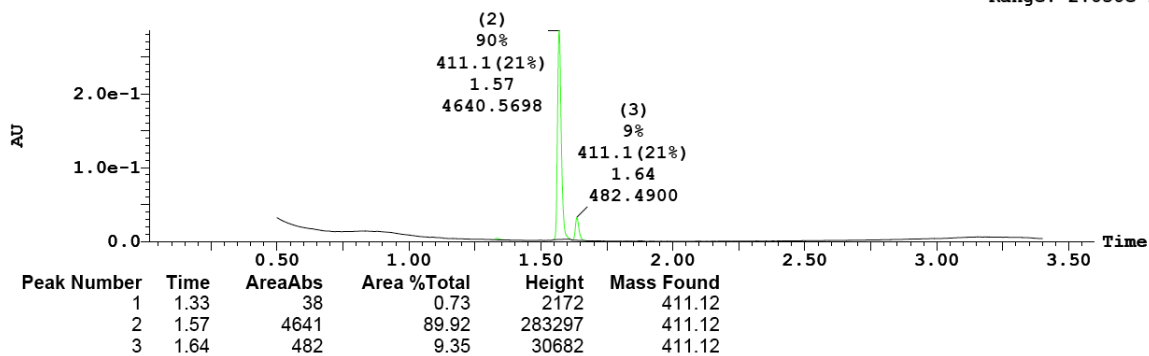
3: UV Detector: 214

2.676e-1
Range: 2.676e-1

(3)
93%
423.1(30%)
1.54
4321.0000

(4)
6%
423.1(31%)
1.60
271.1400

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.31	34	0.73	2185	423.14
2	1.50	14	0.30	1064	423.14
3	1.54	4321	93.13	264843	423.14
4	1.60	271	5.84	17076	423.14

4{A}

1.805e-1
Range: 1.805e-1

(3)
94%
460.3(59%)
1.98
3049.9299

(4)
3%
460.3(59%)
2.09
106.6900

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.28	26	0.82	1491	
2	1.87	48	1.50	2821	460.26
3	1.98	3050	94.38	179677	460.26
4	2.09	107	3.30	6264	460.26

4{C}
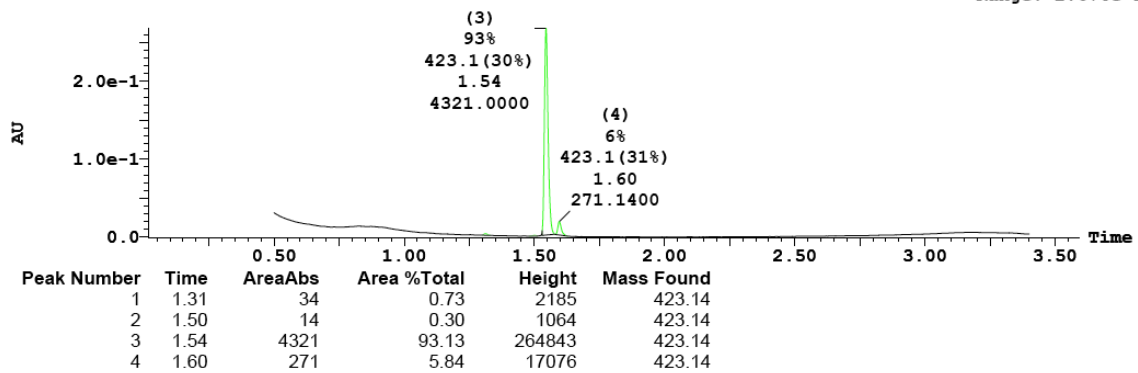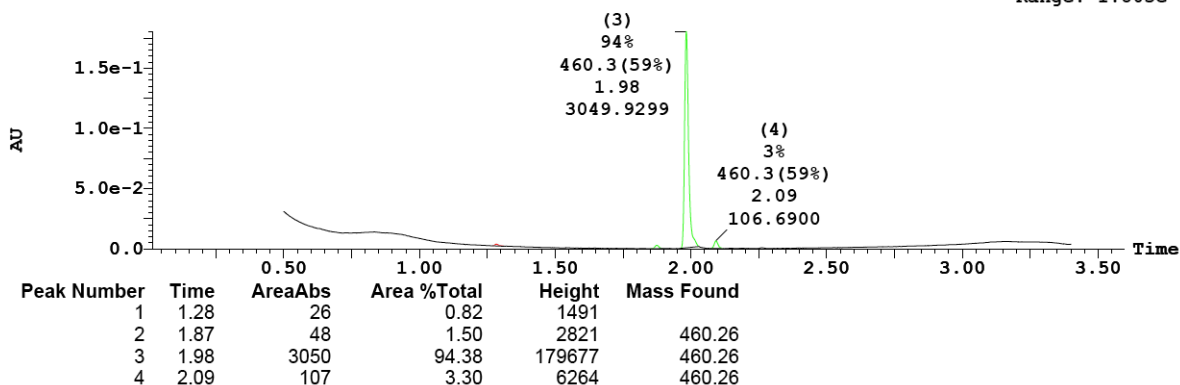
3: UV Detector: 214

1.4e-1
Range: 1.4e-1

(3)
95%
478.3(62%)
2.00
2322.0300

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.34	30	1.20	1822	
2	1.88	34	1.40	2104	478.25
3	2.00	2322	94.77	139125	478.25
4	2.09	64	2.63	4081	478.25

4{E}
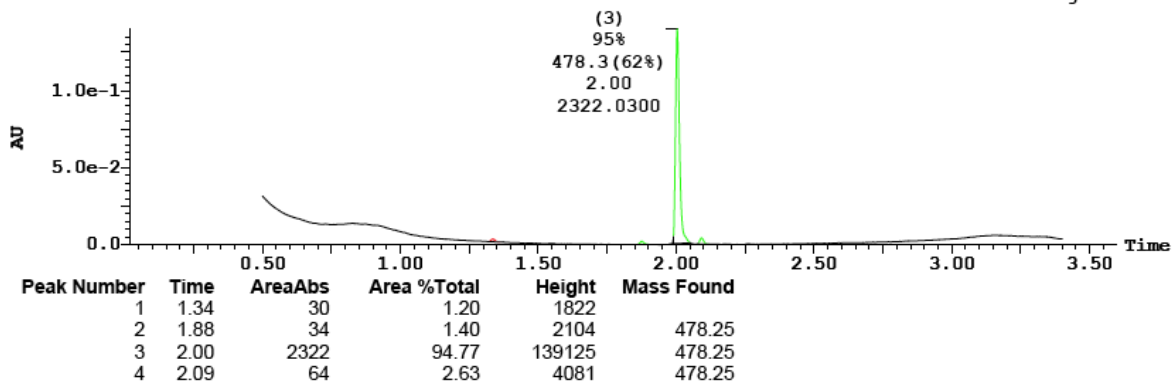
3: UV Detector: 214

2.068e-1
Range: 2.068e-1
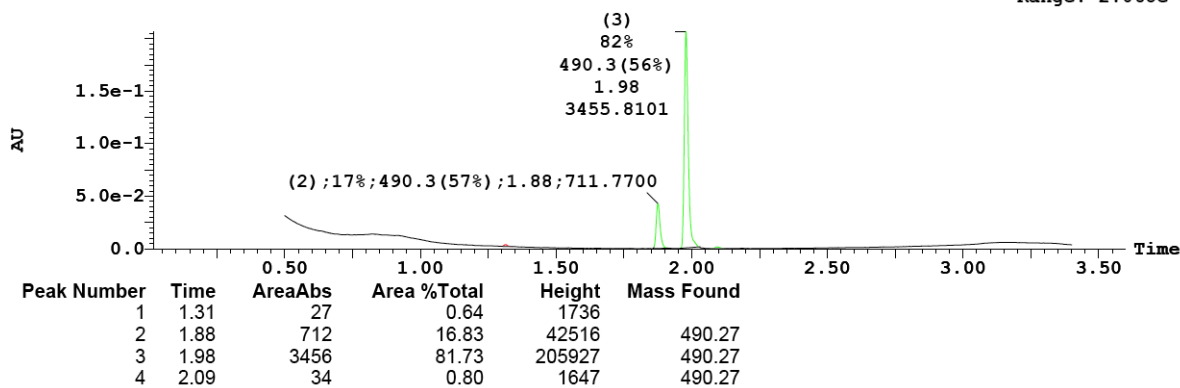
(3)
82%
490.3(56%)
1.98
3455.8101

(2);17%;490.3(57%);1.88;711.7700

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.31	27	0.64	1736	
2	1.88	712	16.83	42516	490.27
3	1.98	3456	81.73	205927	490.27
4	2.09	34	0.80	1647	490.27

5{A}

6.13e
Range: 6.13e

(8)
93%
359.1(75%)
1.40
8105.5801

(10)
3%
359.1(9%)
1.67
288.2200
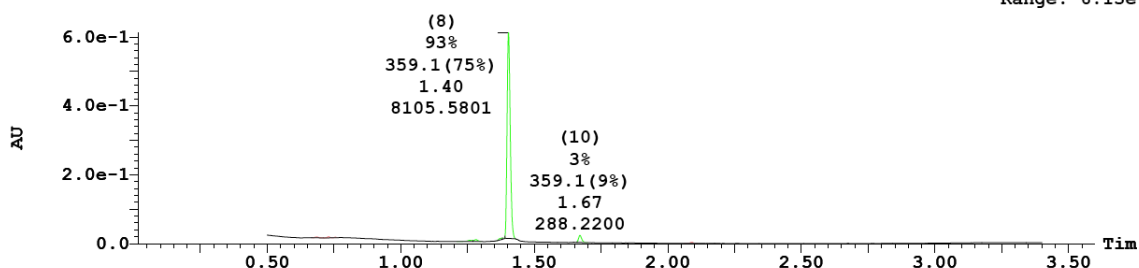
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.68	31	0.36	1715	
2	0.73	30	0.35	2228	
3	0.76	13	0.14	1076	
4	1.26	94	1.08	4197	359.14
5	1.28	95	1.09	5807	359.14
6	1.38	32	0.36	2751	359.14
7	1.38	20	0.23	1910	359.14
8	1.40	8106	92.69	598122	359.14
10	1.67	288	3.30	20729	359.14
11	2.09	36	0.41	2172	

5{C}

3: UV Detector: 214

4.567e-1
Range: 4.567e-1

(3)
91%
377.1(21%)
1.45
6247.5098

(5)
4%
377.1(1%)
1.70
308.1200
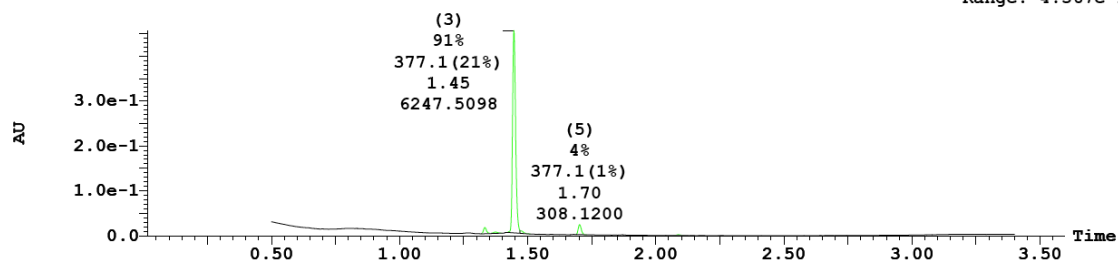
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.33	186	2.69	13587	377.13
2	1.37	63	0.92	3000	377.13
3	1.45	6248	90.56	450323	377.13
3	1.47	64	0.93	5250	377.13
5	1.70	308	4.47	22191	377.13
6	2.09	30	0.44	1866	377.13

5{E}

3: UV Detector: 214

5.918e-
Range: 5.917e-

(4)
95%
389.2(63%)
1.42
7855.7402
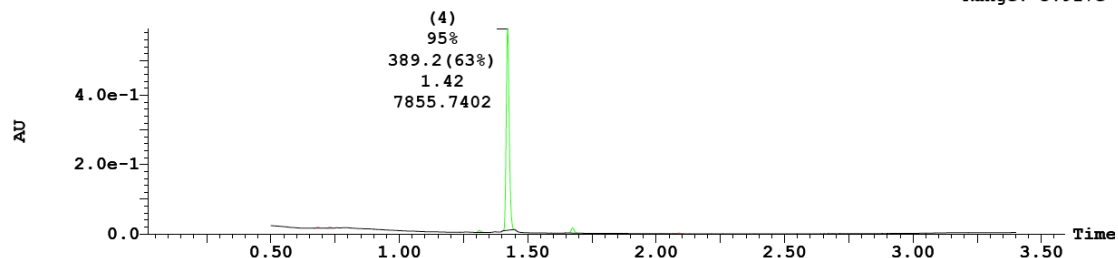
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.68	47	0.57	2115	
2	0.73	33	0.40	2385	
3	1.31	75	0.91	5764	389.15
4	1.42	7856	95.40	581431	389.15
6	1.67	201	2.45	14729	389.15
7	2.09	22	0.27	1449	

6{A}

5.442e-1
Range: 5.442e-1

(6)
98%
361.2(78%)
1.44
7335.1001

AU
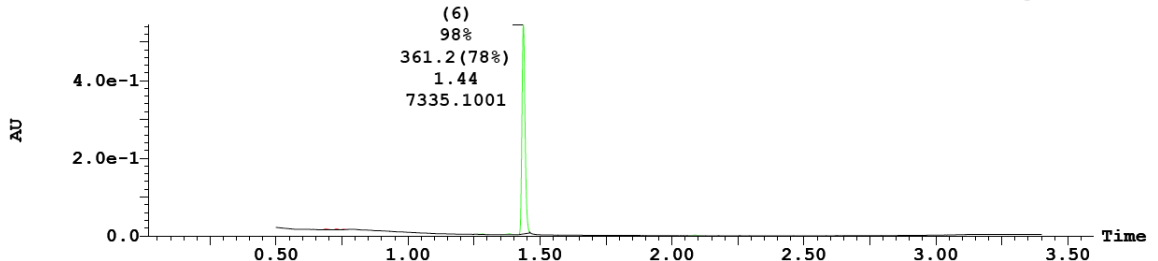
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.69	42	0.56	2150	
2	0.73	32	0.42	2475	
3	0.75	11	0.15	1099	
4	1.28	16	0.21	1075	361.16
5	1.38	45	0.60	2315	361.16
6	1.44	7335	97.70	539404	361.16
7	2.09	27	0.37	1598	361.16

6{C}

3: UV Detector: 214

4.526e-1
Range: 4.526e-1

(6)
98%
379.1(69%)
1.48
6142.7100

(2)
0%
0.73
30.9000

AU
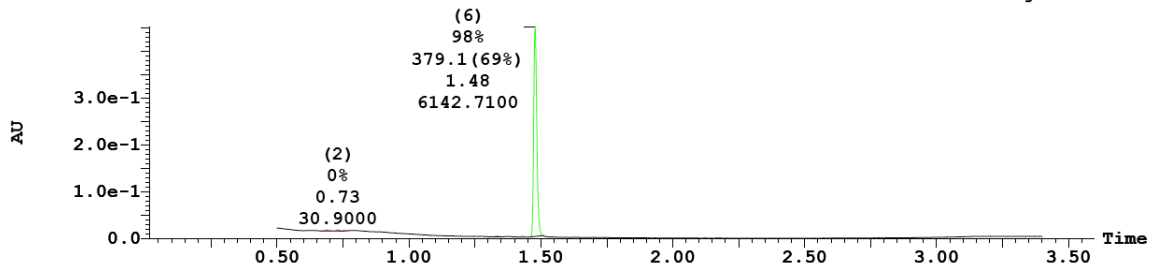
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.69	30	0.47	1854	
2	0.73	31	0.49	2444	
3	0.76	12	0.19	1090	
4	1.33	26	0.41	1796	379.15
5	1.43	31	0.49	1884	379.15
6	1.48	6143	97.94	448670	379.15

6{E}

3: UV Detector: 214

5.301e-1
Range: 5.3e-1

(7)
98%
391.2(61%)
1.45
7190.9199

AU
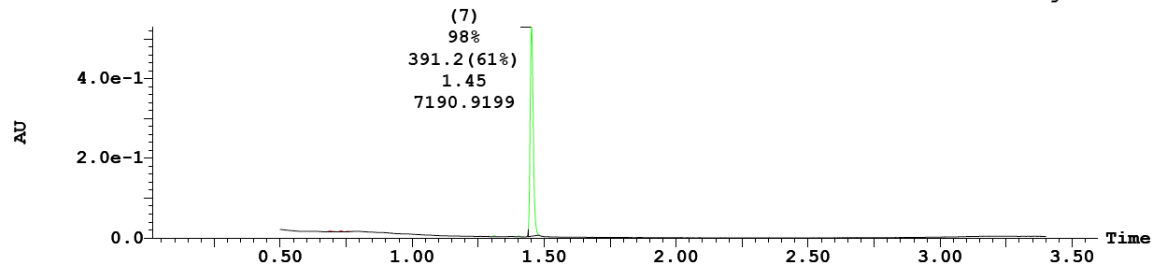
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.69	40	0.55	2104	
2	0.73	31	0.42	2443	
3	0.76	10	0.13	894	
4	1.31	25	0.35	2186	391.17
6	1.41	25	0.34	1888	391.17
7	1.45	7191	98.21	525534	391.17

7{A}

3: UV Detector: 214

5.198e-1
Range: 5.198e-1

```
         (6)
         98%
    4.0e-1        375.2(76%)
                    1.58
                  7204.4902

AU

    2.0e-1

    0.0
         0.50    1.00    1.50    2.00    2.50    3.00    3.50    Time
```
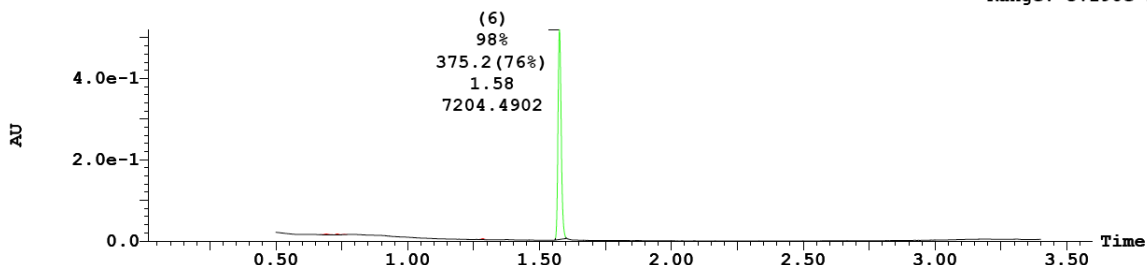
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.69	40	0.54	2050	
2	0.73	30	0.41	2479	
3	0.76	13	0.18	1190	
4	1.28	32	0.43	2395	
6	1.58	7204	98.44	515916	375.17

7{C}

3: UV Detector: 214

4.317e-1
Range: 4.317e-1

```
                    (6)
                    98%
    3.0e-1        393.2(66%)
                    1.61
    2.0e-1        6003.0298

AU         (2)
    1.0e-1  1%
            0.73
    0.0     34.1900
         0.50    1.00    1.50    2.00    2.50    3.00    3.50    Time
```
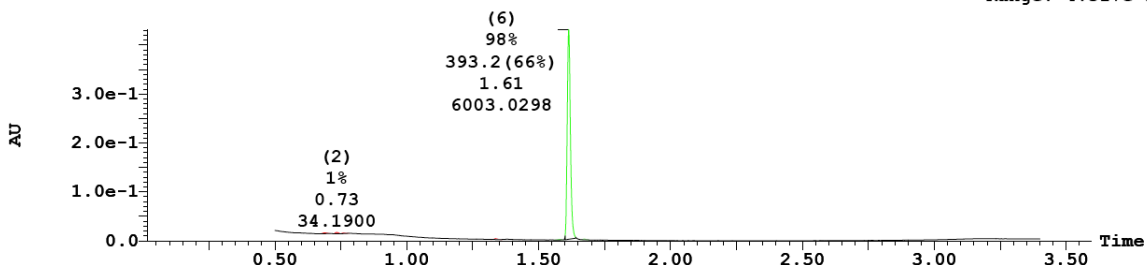
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.69	32	0.51	1826	
2	0.73	34	0.56	2622	
3	0.76	17	0.27	1334	
4	1.34	20	0.33	1439	
5	1.58	15	0.24	1122	393.16
6	1.61	6003	97.86	428423	393.16
7	1.67	14	0.23	1236	393.16

7{E}

3: UV Detector: 214

5.034e-1
Range: 5.033e-1

```
                    (6)
                    98%
    4.0e-1        405.2(63%)
                    1.58
                  6887.9199

AU
          (2)
    2.0e-1  0%
            0.74
    0.0     31.7400
         0.50    1.00    1.50    2.00    2.50    3.00    3.50    Time
```
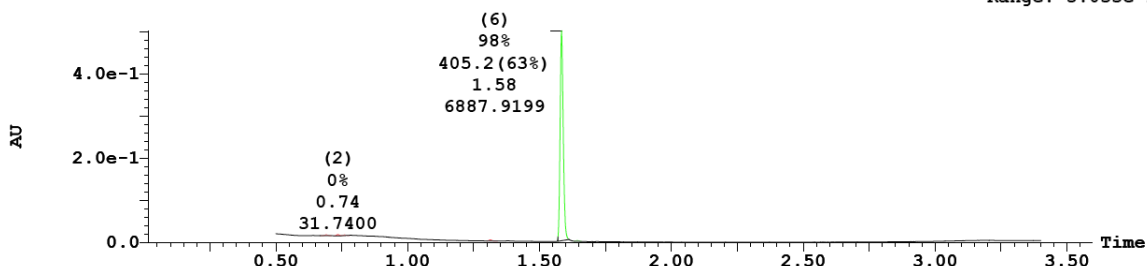
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.69	31	0.45	1838	
2	0.73	32	0.45	2575	
3	0.76	17	0.24	1357	
4	1.31	33	0.47	2366	
6	1.58	6888	98.08	499424	405.18
7	1.64	22	0.31	1637	405.18

173

8{A}

4.654e-1
Range: 4.654e-1

(2)
100%
335.1(72%)
1.30
8114.1201

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.23	33	0.41	1962	335.14
2	1.30	8114	99.59	453684	335.14

8{C}

3.801e-1
Range: 3.801e-1

(3)
100%
353.1(73%)
1.35
6548.6401

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
2	1.29	22	0.34	1209	353.13
3	1.35	6549	99.66	369657	353.13

8{E}

4.223e-1
Range: 4.223e-1

(1)
100%
365.2(66%)
1.32
7292.4600

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.32	7292	100.00	411491	365.15

174
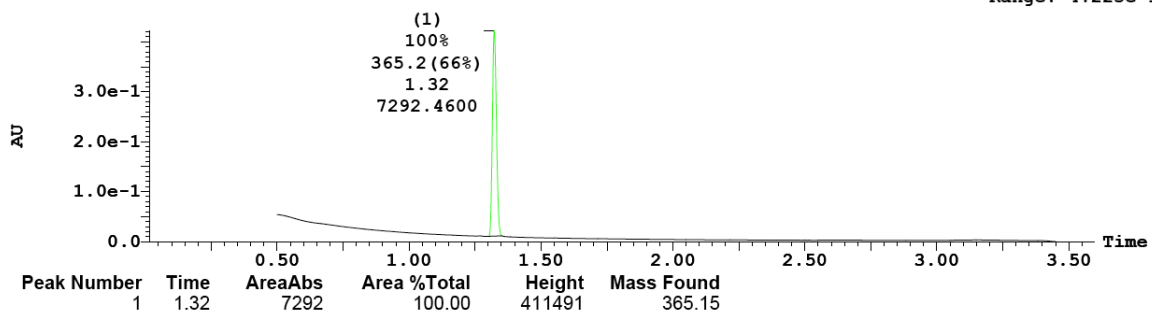
9{A}

3: UV Detector: 214

4.217e-1
Range: 4.217e-1

(2)
100%
349.2(71%)
1.41
7465.4199

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.29	17	0.23	989	349.16
2	1.41	7465	99.77	412124	349.16
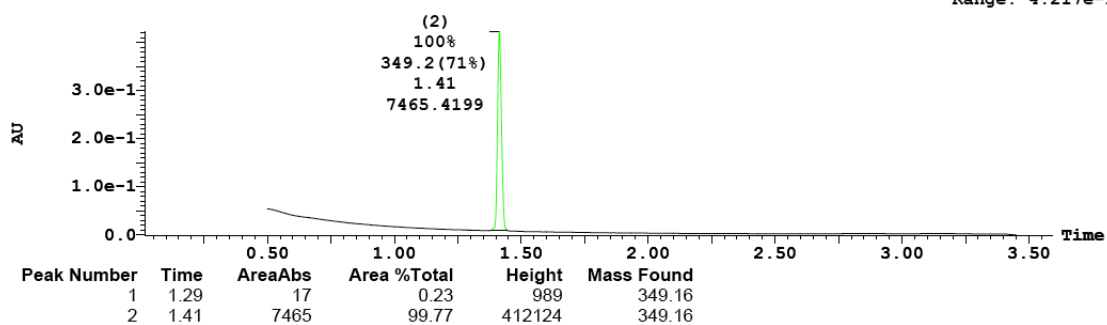
9{C}

3: UV Detector: 214

3.745e-1
Range: 3.745e-1

(1)
100%
367.1(70%)
1.46
6647.6802

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.46	6648	100.00	365710	367.15
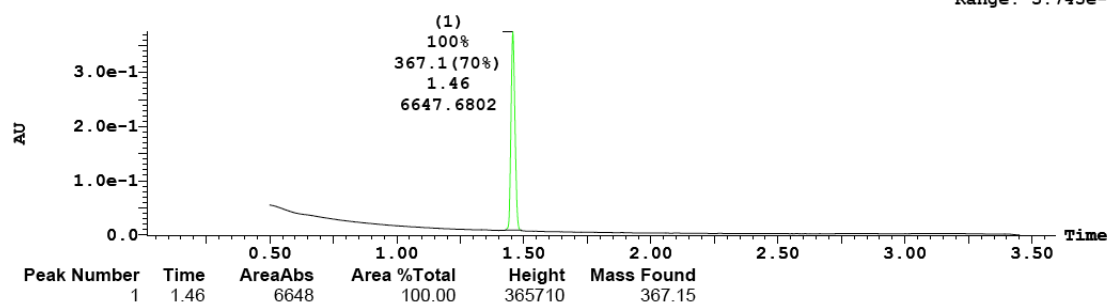
9{E}

3: UV Detector: 214

4.422e-1
Range: 4.422e-1
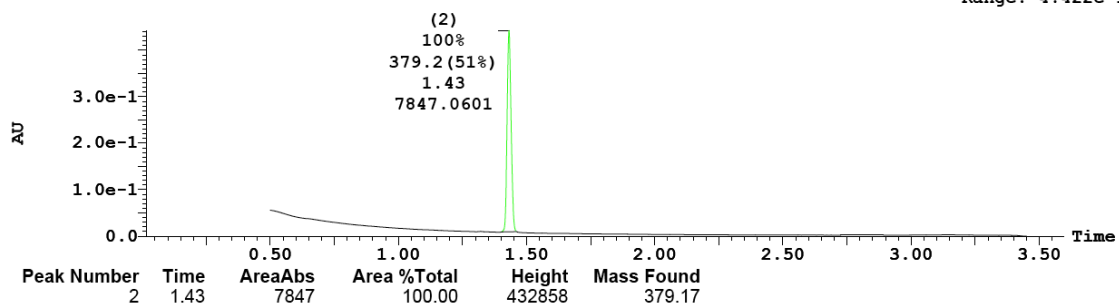
(2)
100%
379.2(51%)
1.43
7847.0601

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
2	1.43	7847	100.00	432858	379.17

10{A}

4.432e-1
Range: 4.432e-1

(2)
100%
363.2(69%)
1.61
8168.8999
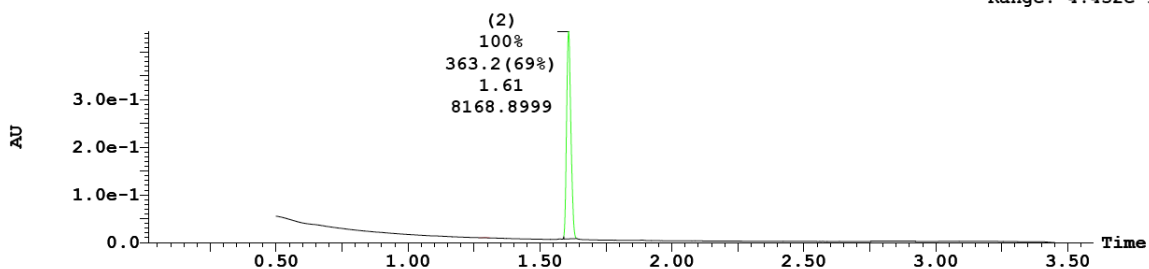
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.29	15	0.18	896	
2	1.61	8169	99.82	435541	363.17

10{C}

3: UV Detector: 214

3.201e-1
Range: 3.201e-1

(1)
100%
381.2(72%)
1.64
5845.5601
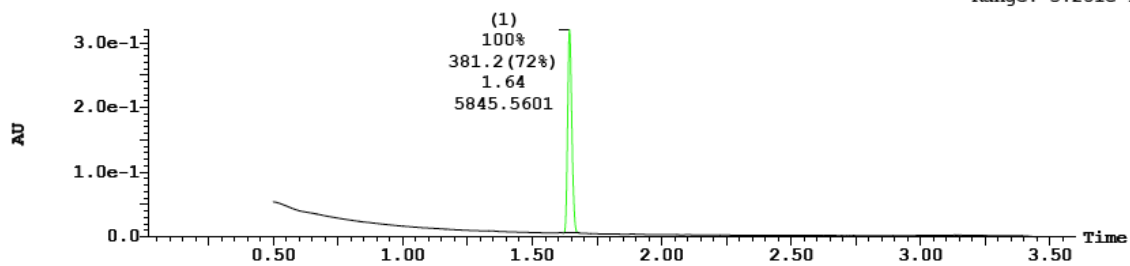
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.64	5846	100.00	313668	381.16

10{E}

3: UV Detector: 214

3.796e-1
Range: 3.796e-1

(1)
100%
393.2(68%)
1.61
6987.4199
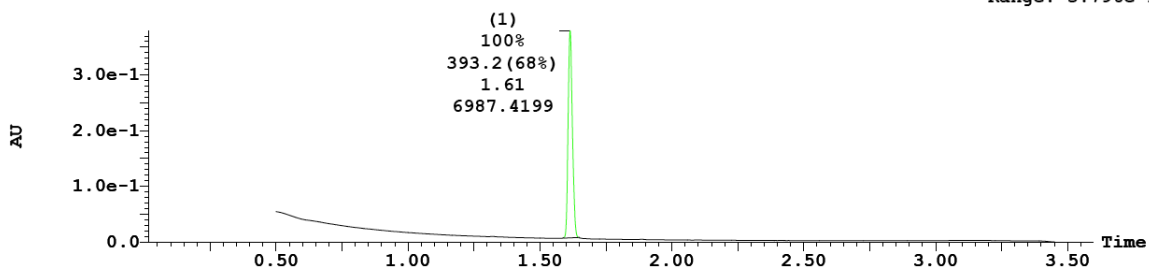
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.61	6987	100.00	372286	393.18

176

11{A}
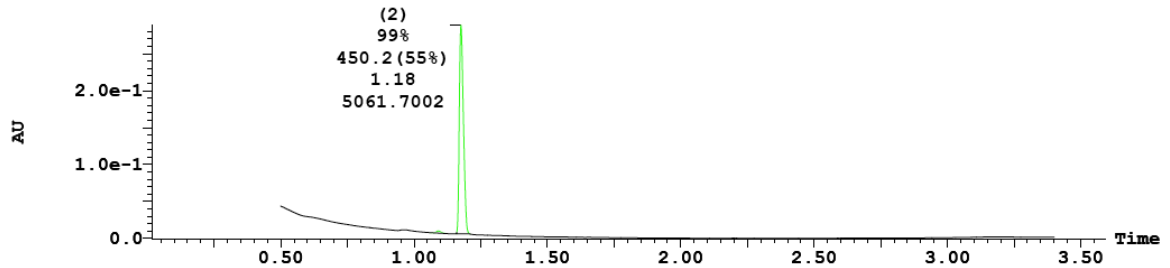
3: UV Detector: 214   5.784e-1
                                                                                              Range: 5.784e-1

```
                                           (3)
                                          100%
                                       492.2(48%)
 4.0e-1                                     1.66
                                        10798.3301
AU
 2.0e-1

 0.0
         0.50    1.00    1.50    2.00    2.50    3.00    3.50      Time
```
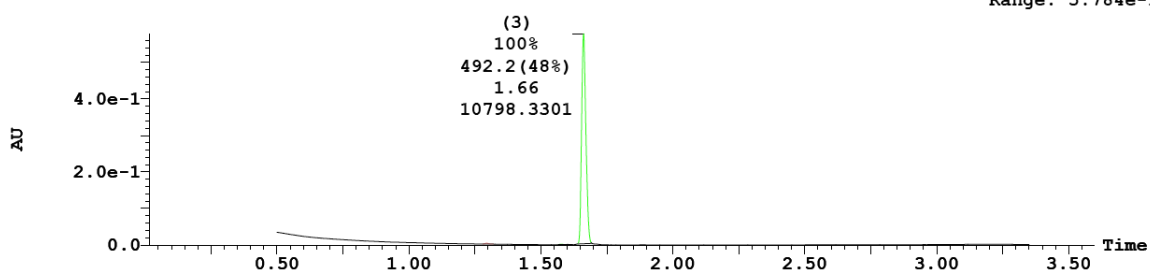
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.29	35	0.32	2020	
2	1.58	12	0.11	900	492.21
3	1.66	10798	99.57	574815	492.21

11{C}

3: UV Detector: 214   4.277e-1
                                                                                              Range: 4.277e-1

```
                                           (3)
                                           98%
                                       528.2(41%)
 3.0e-1                                     1.72
                                        7931.6099
AU  2.0e-1

 1.0e-1

 0.0
         0.50    1.00    1.50    2.00    2.50    3.00    3.50      Time
```
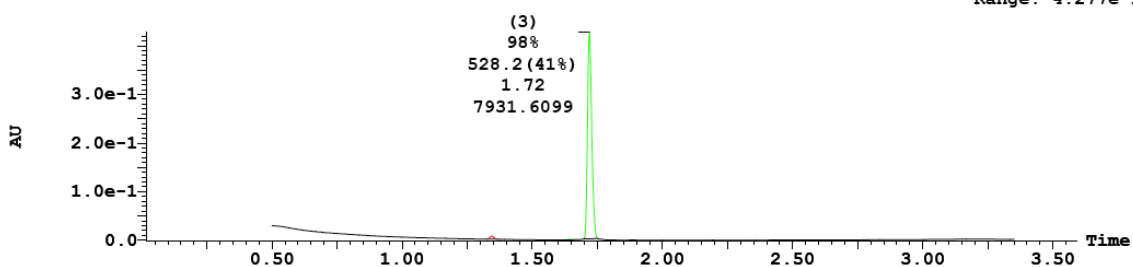
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.34	114	1.41	6270	
2	1.64	28	0.34	1082	528.19
3	1.72	7932	98.25	424711	528.19

11{E}

3: UV Detector: 214   5.408e-1
                                                                                              Range: 5.408e-1

```
                                           (4)
                                           99%
                                       552.2(61%)
 4.0e-1                                     1.67
                                        10103.4004
AU
 2.0e-1

 0.0
         0.50    1.00    1.50    2.00    2.50    3.00    3.50      Time
```
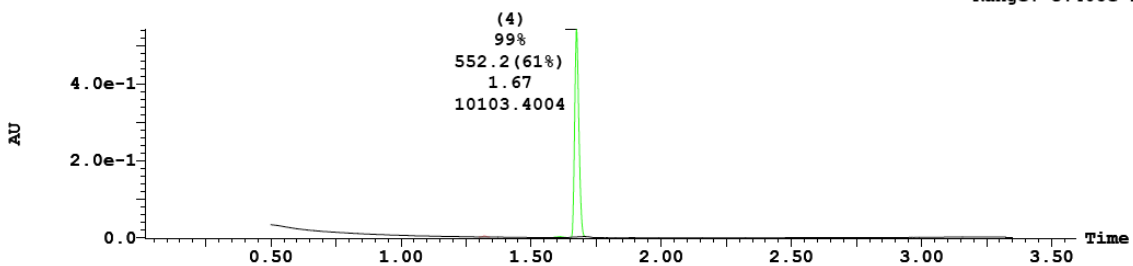
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.32	36	0.35	2048	
3	1.61	66	0.64	2302	552.23
4	1.67	10103	99.01	538142	552.23

177

12{A}

3: UV Detector: 214

3.151e-1
Range: 3.151e-1

```
                          (3)
3.0e-1                    99%
                      390.2(60%)
                          1.24
2.0e-1                 5652.3901

AU

1.0e-1

0.0
          0.50    1.00    1.50    2.00    2.50    3.00    3.50   Time
```
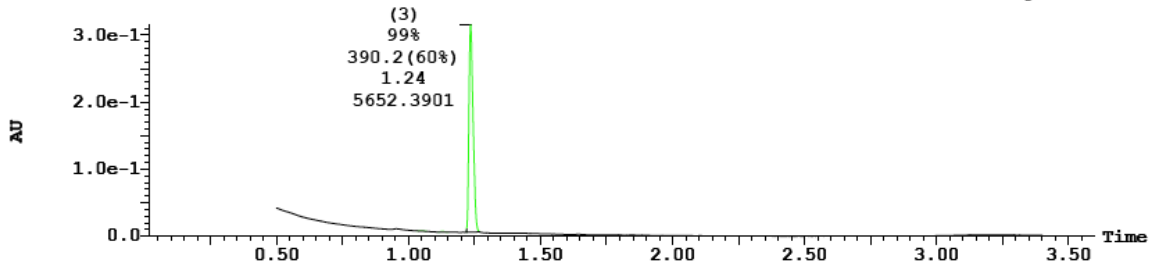
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.04	23	0.40	1242	390.18
2	1.13	18	0.31	986	390.18
3	1.24	5652	99.29	309033	390.18

12{C}

3: UV Detector: 214

2.934e-1
Range: 2.934e-1

```
                          (3)
                          99%
                      408.2(69%)
                          1.28
2.0e-1                 5291.9800

AU

1.0e-1

0.0
          0.50    1.00    1.50    2.00    2.50    3.00    3.50   Time
```
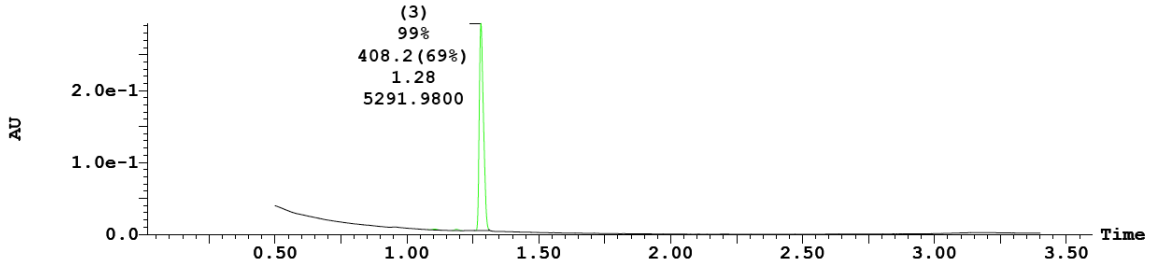
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.10	22	0.41	1206	408.17
2	1.19	30	0.55	1705	408.17
3	1.28	5292	99.04	288058	408.17

12{E}

3: UV Detector: 214

3.54e-1
Range: 3.54e-1

```
                          (2)
                         100%
                      420.2(65%)
3.0e-1                    1.26
                      6383.9302
2.0e-1

AU

1.0e-1

0.0
          0.50    1.00    1.50    2.00    2.50    3.00    3.50   Time
```
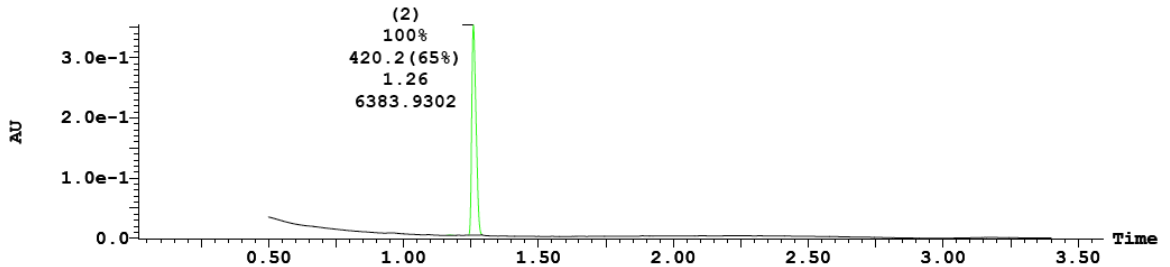
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.17	12	0.19	769	420.19
2	1.26	6384	99.81	348711	420.19

13{A}

2.147e-1
Range: 2.146e-1

(4)
95%
447.2(65%)
1.27
4172.7300

(1)
3%
0.96
135.1900
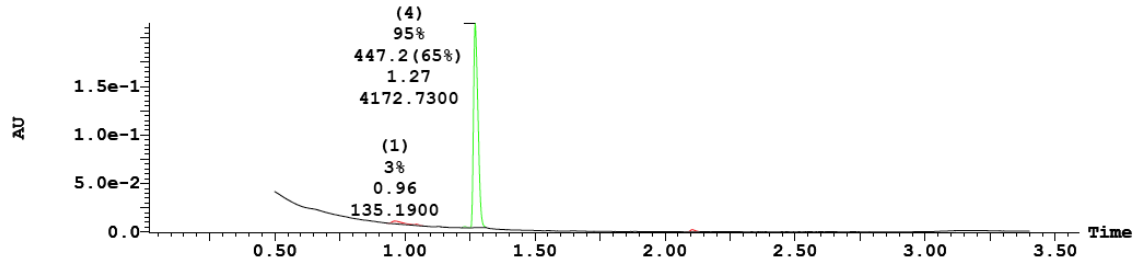
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.96	135	3.07	2723	
2	1.04	26	0.59	1190	
3	1.23	18	0.42	1097	447.24
4	1.27	4173	94.77	210172	447.24
5	2.10	50	1.15	2277	

13{C}

3: UV Detector: 214

2.471e-1
Range: 2.471e-1

(4)
98%
465.2(65%)
1.31
4909.4600
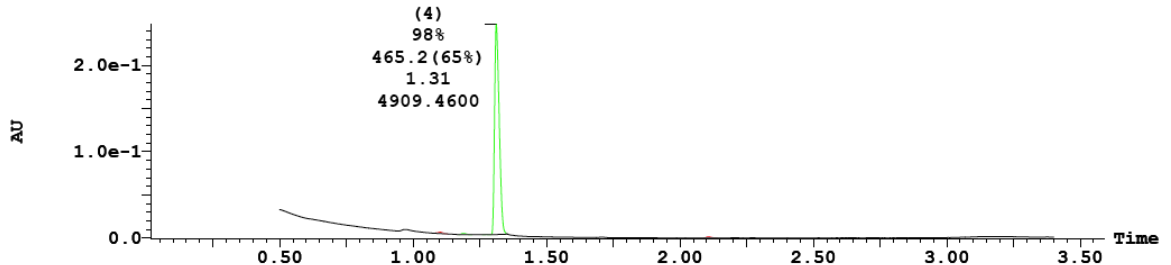
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.10	33	0.66	1550	
2	1.19	30	0.60	1536	465.23
3	1.27	5	0.10	470	465.23
4	1.31	4909	98.01	243082	465.23
6	2.11	31	0.63	1450	

13{E}

3: UV Detector: 214

2.948e-1
Range: 2.947e-1

(6)
96%
477.3(63%)
1.29
5842.6099

(1)
0%
0.77
22.3800
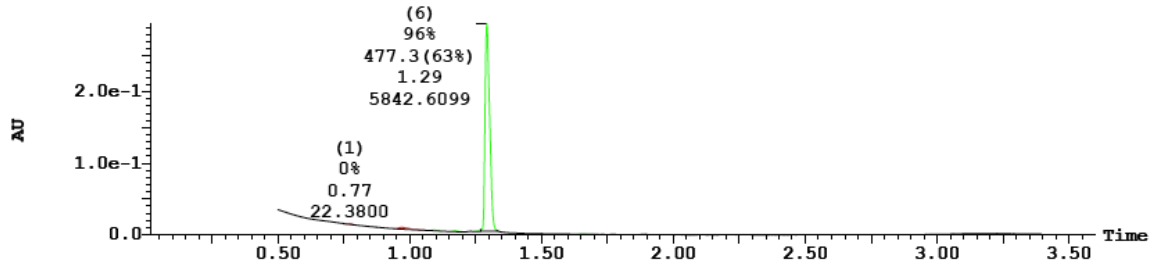
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.77	22	0.37	1236	
2	0.97	109	1.79	2286	
3	1.09	21	0.34	1172	477.25
4	1.17	25	0.41	1209	477.25
5	1.27	33	0.55	2665	477.25
6	1.29	5843	96.32	289780	477.25
7	1.65	13	0.22	656	477.25

14{B}

3: UV Detector: 214

8.785e-2
Range: 8.783e-2

(3)
96%
507.2(44%)
1.48
1816.7600

(2);3%;507.2(44%);1.36;62.0700
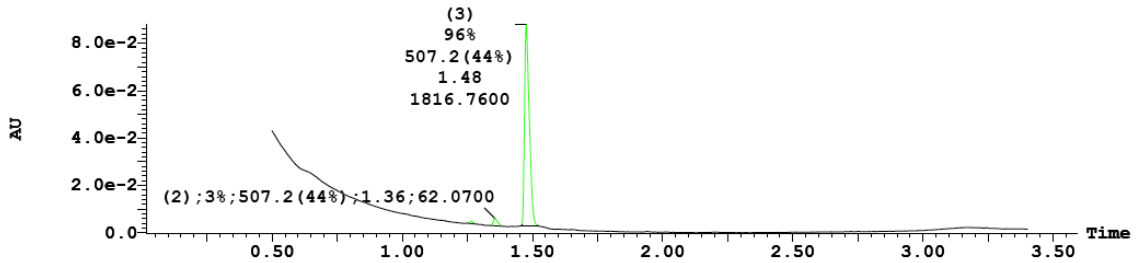
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.27	16	0.86	985	507.22
2	1.36	62	3.27	3024	507.22
3	1.48	1817	95.86	84953	507.22

14{C}

3: UV Detector: 214

1.946e-1
Range: 1.946e-1

(3)
99%
491.2(64%)
1.36
3899.4800
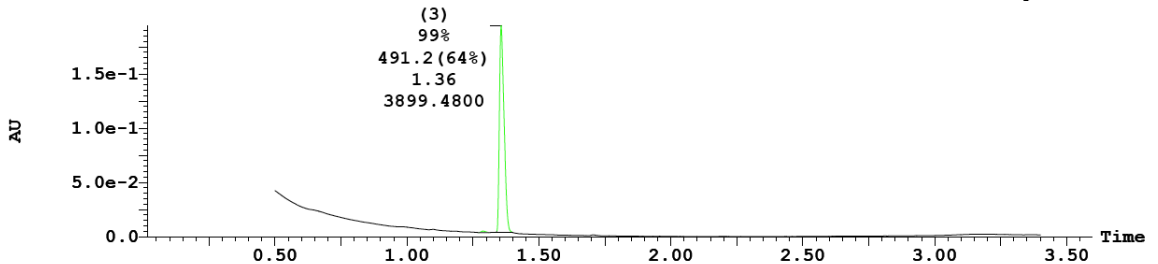
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
2	1.29	24	0.62	1313	491.25
3	1.36	3899	99.38	190661	491.25

14{E}

3: UV Detector: 214

1.98e-1
Range: 1.98e-1

(3)
97%
503.3(60%)
1.34
3965.0100
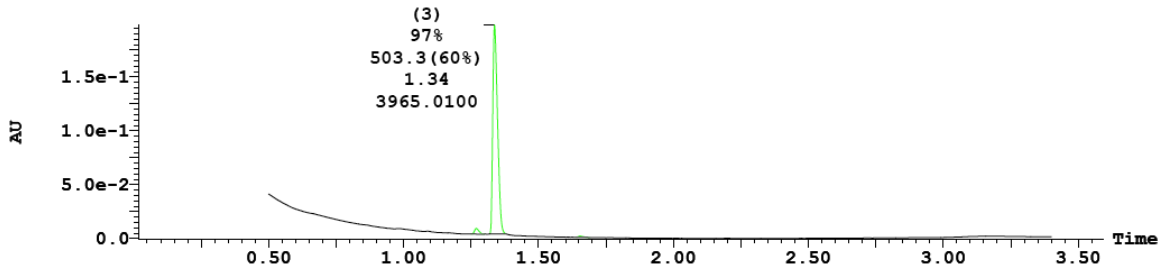
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
2	1.27	97	2.38	5215	503.27
3	1.34	3965	97.01	193738	503.27
5	1.65	25	0.60	1235	503.27

15{A}

3: UV Detector: 214

2.706e-1
Range: 2.706e-1

```
           (4)
           95%
        420.2(50%)
           1.15
        4778.8999
2.0e-1


AU
1.0e-1



0.0
       0.50    1.00    1.50    2.00    2.50    3.00    3.50   Time
```
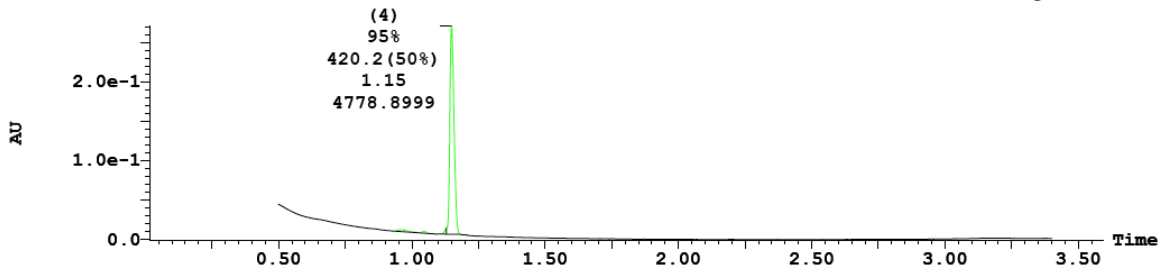
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.96	117	2.33	2369	420.19
2	1.04	43	0.85	2140	420.19
3	1.13	69	1.38	7827	420.19
4	1.15	4779	95.44	263598	420.19

15{C}

3: UV Detector: 214

2.505e-1
Range: 2.505e-1

```
           (2)
           99%
        438.2(64%)
           1.19
        4405.8901
2.0e-1


AU
1.0e-1



0.0
       0.50    1.00    1.50    2.00    2.50    3.00    3.50   Time
```
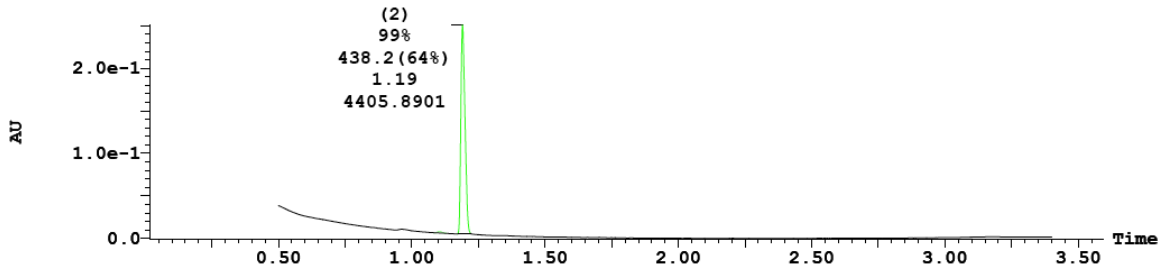
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.10	27	0.61	1373	438.18
2	1.19	4406	99.39	244941	438.18

15{E}

3: UV Detector: 214

2.885e-1
Range: 2.885e-1

```
           (2)
           99%
        450.2(55%)
           1.18
        5061.7002
2.0e-1


AU
1.0e-1



0.0
       0.50    1.00    1.50    2.00    2.50    3.00    3.50   Time
```

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.09	59	1.15	2850	450.20
2	1.18	5062	98.85	282290	450.20

Insilico Analysis

Sketched electronic versions of the library compounds were imported into the Tripos Molecular Spreadsheet [1] wherein standard Lipinski Rule of 5 parameters (molecular weight, ClogP, number of H-acceptors, and number of H-donors[2]) plus the number of rotatable bonds and polar surface area were computed. Lipinski violations were specified according to molecular weight > 500, ClogP > 5.0, number of acceptors > 10, number of donors > 5, and number of rotatable bonds > 5. The structures were then exported into SDF format and coverted into three-dimensional protonated structures via Concord [3]. Absorption, distribution, metabolism and excretion (ADME) profiles of these compounds was then generated via Volsurf [4]. Descriptors were generated using three probes (water, hydrophobic and carbonyl oxygen) with a grid space distribution of 1.0 Å. Predictions were then projected onto internal ADME models at the 5-component level. Finally diversity analysis was carried out using DiverseSolutions [5] using standard H-aware 3D BCUT descriptors. The library was then projected onto a chemical space defined by the following descriptors: gastchrg_invdist2_000.550_K_L, gastchrg_invdist6_000.500_K_H, haccept_invdist2_001.000_K_H, tabpolar_invdist_000.250_K_H, tabpolar_invdist_000.500_K_L and populated (for comparison) by a recent version of the MLSMR screening set (ca. 7/2010; ~330,000 unique chemical structures). Diversity scores (*div(A)*) for our library were then generated for each of our compounds (*A*) according to the expression:

$$div(A) = \frac{pop[Cell(A)]}{\sum_{i \in Occ} pop(i) / N_{occ}}$$

where N_{occ} is the number of cells occupied by PubChem compounds in an evenly distributed

10×10×10×10×10 grid decomposition of the chemistry space, and *pop(i)* is the population of

cell *i*.

Molecule	CLOGP	Mol. Wt	Acceptor	Donor	Rot Bond	LIP_VIOLS	PSA	DIVS	BBB	SOLY	CACO2	SP_S	SP_P	PB	VOLD	HERG	Sol_DMSO	METSTAB
A{1}	2.14	340.44	5	3	4	0	138.91	0.11	-0.42	-3.53	-0.06	0.48	0.17	63.64	-0.39	1.10	2.13	0.08
A{2}	2.14	340.44	5	3	4	0	138.91	0.11	-0.33	-3.66	0.01	0.51	0.13	61.22	-0.43	1.00	1.78	-0.02
A{3}	2.00	354.46	5	3	5	0	139.90	0.11	-0.56	-3.55	-0.01	0.40	0.29	67.93	-0.68	0.93	1.81	-0.03
A{4}	2.00	354.46	5	3	5	0	139.71	0.11	-0.45	-3.88	0.08	0.42	0.19	67.06	-0.58	0.76	1.69	-0.24
A{5}	3.09	353.48	4	3	3	0	92.51	0.11	0.43	-4.22	0.39	0.28	0.39	76.24	-0.31	0.55	1.32	-0.34
A{6}	3.48	356.50	4	2	3	0	115.66	0.11	0.30	-3.81	0.55	0.24	0.62	78.25	-0.74	0.77	0.88	-0.24
A{7}	5.38	443.60	4	3	5	1	89.74	0.11	-0.16	-6.14	0.71	-0.30	0.76	113.09	-0.78	-0.15	1.37	-0.72
A{8}	2.62	328.43	5	3	6	1	144.92	0.11	-0.51	-3.53	-0.05	0.53	0.15	59.93	-0.42	1.05	2.10	-0.02
B{1}	2.14	340.44	5	3	4	0	118.37	0.10	-0.35	-3.39	0.30	0.51	0.37	63.25	-0.42	1.17	2.21	0.03
B{2}	2.14	340.44	5	3	4	0	118.37	0.10	-0.18	-3.65	0.36	0.49	0.33	63.32	-0.35	0.99	2.01	0.00
B{3}	2.00	354.46	5	3	5	0	121.03	0.10	-0.21	-3.99	0.42	0.38	0.44	70.97	-0.53	0.80	1.92	-0.24
B{4}	2.00	354.46	5	3	5	0	119.20	0.10	-0.29	-3.99	0.43	0.38	0.35	65.83	-0.51	0.73	1.84	-0.31
B{5}	3.09	353.48	4	3	3	0	69.05	0.10	0.41	-3.93	0.67	0.28	0.62	69.35	-0.77	0.85	0.85	-0.35
B{6}	3.48	356.50	4	2	3	0	88.85	0.10	0.70	-4.50	0.88	0.23	0.73	80.30	-0.67	0.43	1.04	-0.43
B{7}	5.38	443.60	4	3	5	1	66.28	0.10	0.26	-6.01	1.01	-0.36	0.88	108.06	-1.03	-0.12	0.47	-0.61
B{8}	2.62	328.43	5	3	6	1	121.28	0.10	-0.45	-3.37	0.58	0.30		60.78	-0.15	1.17	2.64	0.28
C{1}	0.68	298.36	5	3	2	0	150.53	0.79	-0.26	-3.07	-0.10	0.62	0.04	59.93	-0.34	1.28	2.12	0.39
C{2}	0.68	298.36	5	3	2	0	150.53	0.79	-0.28	-3.08	-0.08	0.65	-0.05	52.76	-0.41	1.15	1.82	0.24
C{3}	0.55	312.38	5	3	3	0	151.52	0.79	-0.47	-3.13	-0.04	0.51	0.15	64.81	-0.66	1.01	1.83	0.31
C{4}	0.55	312.38	5	3	3	0	151.33	0.79	-0.49	-3.35	-0.02	0.55	0.05	62.62	-0.54	0.86	1.86	0.11
C{5}	1.63	311.40	4	3	1	0	104.13	0.79	0.51	-3.72	0.36	0.42	0.32	75.31	-0.23	0.79	1.46	-0.05
C{6}	2.02	314.42	4	2	1	0	127.28	0.79	0.46	-3.26	0.55	0.36	0.58	78.34	-0.62	1.06	1.09	0.15
C{7}	3.92	401.52	4	3	3	0	101.36	0.79	-0.16	-5.70	0.63	-0.11	0.72	112.54	-0.57	0.20	1.71	-0.47
C{8}	1.16	286.35	5	3	4	0	156.54	0.79	-0.33	-3.25	-0.11	0.66	-0.01	55.56	-0.41	1.11	1.87	0.24
D{1}	0.68	298.36	5	3	2	0	129.99	0.15	-0.13	-3.03	0.27	0.63	0.31	67.78	-0.39	1.20	2.14	0.45
D{2}	0.68	298.36	5	3	2	0	129.99	0.15	-0.05	-3.24	0.31	0.62	0.25	65.89	-0.33	1.00	1.96	0.43
D{3}	0.55	312.38	5	3	3	0	131.30	0.15	-0.01	-3.46	0.37	0.52	0.38	70.74	-0.39	0.83	1.99	0.24
D{4}	0.55	312.38	5	3	3	0	130.82	0.15	-0.20	-3.80	0.38	0.47	0.30	70.03	-0.50	0.72	1.85	0.05
D{5}	1.63	311.40	4	3	1	0	80.67	0.15	0.60	-3.42	0.67	0.39	0.58	70.32	-0.71	0.93	0.89	0.01
D{6}	2.02	314.42	4	2	1	0	100.47	0.02	0.80	-4.20	0.79	0.35	0.66	84.74	-0.56	0.66	1.02	-0.21
D{7}	3.92	401.52	4	3	3	0	79.05	0.27	0.43	-5.39	0.95	-0.22	0.75	101.95	-0.72	0.10	0.67	-0.45
D{8}	1.16	286.35	5	3	4	0	132.90	0.20	-0.24	-3.09	0.14	0.73	0.23	64.99	-0.06	1.23	2.59	0.68
E{1}	2.14	340.44	5	3	4	0	147.35	0.20	-0.32	-3.92	0.06	0.47	0.09	66.79	-0.46	0.88	1.81	0.07
E{2}	2.14	340.44	5	3	4	0	147.42	0.20	-0.32	-3.96	0.06	0.46	0.14	68.83	-0.44	0.92	1.91	0.09
E{3}	2.00	354.46	5	3	5	0	148.65	0.20	-0.49	-3.91	0.08	0.38	0.22	71.13	-0.72	0.76	1.58	-0.03
E{4}	2.00	354.46	5	3	5	0	148.46	0.20	-0.42	-4.25	0.11	0.38	0.24	74.53	-0.52	0.75	1.90	-0.19
E{5}	3.09	353.48	4	3	3	0	100.98	0.20	0.47	-4.64	0.50	0.27	0.36	81.13	-0.32	0.41	1.15	-0.39
E{6}	3.48	356.50	4	2	3	0	124.15	0.20	0.23	-3.99	0.57	0.27	0.61	84.57	-0.69	0.75	1.16	-0.20
E{7}	5.38	443.60	4	3	5	1	98.22	0.13	-0.19	-6.12	0.66	-0.32	0.79	114.83	-0.81	-0.17	1.40	-0.72
E{8}	2.62	328.43	5	3	6	1	152.89	0.13	-0.56	-3.81	0.02	0.51	0.18	67.36	-0.57	0.98	1.91	0.00
F{1}	2.14	340.44	5	3	4	0	126.78	0.13	-0.11	-3.89	0.35	0.44	0.31	73.49	-0.25	0.82	2.17	0.09
F{2}	2.14	340.44	5	3	4	0	126.83	0.13	-0.25	-3.79	0.32	0.45	0.32	73.88	-0.36	1.01	2.19	0.09
F{3}	2.00	354.46	5	3	5	0	128.10	0.13	-0.38	-4.22	0.37	0.32	0.41	78.05	-0.42	0.57	2.23	-0.16
F{4}	2.00	354.46	5	3	5	0	127.93	0.13	-0.49	-4.34	0.35	0.32	0.42	81.45	-0.53	0.75	2.27	-0.24
F{5}	3.09	353.48	4	3	3	0	78.08	0.13	0.30	-4.32	0.67	0.20	0.60	83.06	-0.71	0.63	1.25	-0.35
F{6}	3.48	356.50	4	2	3	0	97.30	0.13	0.71	-5.14	0.85	0.15	0.67	95.95	-0.59	0.22	1.14	-0.62
F{7}	5.38	443.60	4	3	5	1	76.61	0.13	0.56	-6.18	0.97	-0.46	0.89	113.00	-0.90	-0.20	0.47	-0.73
F{8}	2.62	328.43	5	3	6	1	133.03	0.13	-0.17	-3.50	0.32	0.48	0.32	65.94	-0.35	1.03	2.06	0.06
G{1}	0.68	298.36	5	3	2	0	150.53	0.13	-0.21	-3.32	-0.04	0.63	-0.05	54.60	-0.42	1.10	1.68	0.19
G{2}	0.68	298.36	5	3	2	0	150.53	0.29	-0.30	-3.30	-0.03	0.63	0.02	58.36	-0.36	1.21	1.90	0.30
G{3}	0.55	312.38	5	3	3	0	151.52	0.29	-0.46	-3.35	0.02	0.52	0.12	61.91	-0.70	0.92	1.53	0.17
G{4}	0.55	312.38	5	3	3	0	151.33	0.29	-0.50	-3.39	-0.02	0.55	0.16	65.72	-0.46	1.05	2.07	0.19
G{5}	1.63	311.40	4	3	1	0	104.13	0.29	0.56	-3.94	0.44	0.43	0.30	73.40	-0.25	0.71	1.14	-0.14
G{6}	2.02	314.42	4	2	1	0	127.28	0.29	0.37	-3.51	0.64	0.40	0.56	75.02	-0.65	0.97	0.87	0.05
G{7}	3.92	401.52	4	3	3	0	101.36	0.29	-0.19	-5.64	0.62	-0.11	0.73	112.57	-0.58	0.22	1.75	-0.43
G{8}	1.16	286.35	5	3	4	0	156.54	0.29	-0.53	-3.03	-0.14	0.72	0.03	56.16	-0.41	1.22	2.03	0.40
H{1}	0.68	298.36	5	3	2	0	129.98	0.29	-0.03	-3.12	0.30	0.62	0.26	65.92	-0.30	1.00	2.11	0.48
H{2}	0.68	298.36	5	3	2	0	130.01	0.29	-0.13	-3.03	0.27	0.63	0.31	67.80	-0.39	1.20	2.14	0.45
H{3}	0.55	312.38	5	3	3	0	130.95	0.29	-0.06	-3.28	0.36	0.52	0.39	67.90	-0.41	0.83	2.01	0.24
H{4}	0.55	312.38	5	3	3	0	131.10	0.29	-0.20	-3.33	0.32	0.53	0.38	68.86	-0.39	0.84	2.16	0.22
H{5}	1.63	311.40	4	3	1	0	80.68	0.17	0.59	-3.29	0.64	0.40	0.59	70.32	-0.69	0.97	1.02	0.07
H{6}	2.02	314.42	4	2	1	0	100.50	0.17	0.70	-4.01	0.73	0.36	0.66	84.52	-0.63	0.80	1.03	-0.13
H{7}	3.92	401.52	4	3	3	0	79.08	0.17	0.26	-5.47	0.89	-0.28	0.86	106.51	-0.82	0.18	0.80	-0.52
H{8}	1.16	286.35	5	3	4	0	133.18	0.12	-0.26	-2.80	0.20	0.66	0.23	61.75	-0.27	1.13	2.31	0.49
I{1}	2.25	374.45	5	3	4	0	150.53	0.03	-0.34	-4.60	0.18	0.14	0.27	85.37	-0.47	0.55	1.84	0.29
I{2}	2.25	374.45	5	3	4	0	150.53	0.03	-0.40	-4.47	0.19	0.15	0.27	84.22	-0.62	0.57	1.73	0.27
I{3}	2.11	388.48	5	3	5	0	151.52	0.09	-0.55	-4.47	0.20	0.05	0.40	88.49	-0.86	0.45	1.54	0.16
I{4}	2.11	388.48	5	3	5	0	151.33	0.16	-0.52	-4.70	0.23	0.07	0.33	89.10	-0.74	0.39	1.65	0.03
I{5}	3.32	387.50	4	3	3	0	104.14	0.29	0.41	-5.10	0.59	-0.05	0.53	96.20	-0.49	0.23	1.04	-0.19
I{6}	3.59	390.52	4	2	3	0	127.28	0.15	0.15	-4.73	0.74	-0.08	0.74	97.01	-0.86	0.43	0.80	-0.21
I{7}	5.49	477.62	4	3	5	1	101.37	0.15	0.12	-6.79	0.70	-0.56	0.70	121.65	-0.71	-0.60	0.72	-1.27
I{8}	2.73	362.44	5	3	6	1	156.54	0.51	-0.52	-4.38	0.16	0.16	0.29	84.05	-0.62	0.58	2.01	0.27
J{1}	2.25	374.45	5	3	4	0	130.00	0.51	-0.41	-4.62	0.41	0.10	0.56	95.72	-0.50	0.60	2.18	0.31
J{2}	2.25	374.45	5	3	4	0	130.00	0.51	-0.39	-4.62	0.42	0.09	0.54	94.62	-0.52	0.55	2.13	0.29
J{3}	2.11	388.48	5	3	5	0	131.28	0.51	-0.18	-4.97	0.52	0.00	0.61	99.27	-0.58	0.30	1.71	0.03
J{4}	2.11	388.48	5	3	5	0	130.83	0.65	-0.48	-4.88	0.49	-0.03	0.58	95.68	-0.69	0.31	1.95	0.01
J{5}	3.32	387.50	4	3	3	0	80.68	0.65	0.16	-4.80	0.75	-0.13	0.81	98.30	-0.93	0.39	1.00	-0.09
J{6}	3.59	390.52	4	2	3	0	100.47	0.18	0.43	-5.42	0.90	-0.16	0.82	107.46	-0.87	0.14	0.81	-0.41
J{7}	5.49	477.62	4	3	5	1	77.91	0.18	0.41	-6.73	0.88	-0.73	0.78	119.95	-1.04	-0.76	0.00	-1.24
J{8}	2.73	362.44	5	3	6	1	132.91	0.18	-0.37	-4.42	0.29	0.17	0.48	91.81	-0.30	0.70	2.36	0.48
K{1}	2.25	374.45	5	3	4	0	136.88	0.18	-0.47	-4.63	0.26	0.12	0.41	88.25	-0.64	0.59	1.75	0.22
K{2}	2.25	374.45	5	3	4	0	136.88	0.18	-0.41	-4.76	0.26	0.12	0.41	89.25	-0.47	0.56	1.83	0.23

K{3}	2.11	388.48	5	3	5	0	137.87	0.18	-0.49	-4.85	0.29	0.04	0.53	92.07	-0.82	0.49	1.49	-0.02
K{4}	2.11	388.48	5	3	5	0	137.68	0.31	-0.51	-5.01	0.30	0.02	0.49	94.31	-0.68	0.41	1.73	-0.15
K{5}	3.32	387.50	4	3	3	0	90.49	0.31	0.38	-5.30	0.71	-0.09	0.63	98.96	-0.53	0.13	0.97	-0.22
K{6}	3.59	390.52	4	2	3	0	113.63	0.43	0.35	-5.15	0.89	-0.11	0.81	100.52	-0.86	0.25	0.55	-0.35
K{7}	5.49	477.62	4	3	5	1	87.72	0.50	0.18	-6.76	0.81	-0.62	0.75	121.07	-0.76	-0.71	0.47	-1.29
K{8}	2.73	362.44	5	3	6	1	142.89	0.50	-0.74	-4.44	0.21	0.18	0.45	87.79	-0.65	0.68	2.01	0.35
L{1}	2.25	374.45	5	3	4	0	116.33	0.50	-0.15	-4.61	0.50	0.10	0.52	87.31	-0.50	0.48	1.57	0.04
L{2}	2.25	374.45	5	3	4	0	116.37	0.50	-0.15	-4.62	0.48	0.12	0.53	88.29	-0.48	0.55	1.61	0.06
L{3}	2.11	388.48	5	3	5	0	117.30	0.37	-0.15	-4.77	0.55	0.01	0.59	88.54	-0.64	0.27	1.41	-0.17
L{4}	2.11	388.48	5	3	5	0	121.55	0.66	-0.14	-4.78	0.53	0.02	0.60	89.88	-0.63	0.39	1.61	-0.14
L{5}	3.32	387.50	4	3	3	0	67.03	0.38	0.41	-4.85	0.81	-0.09	0.79	92.05	-0.92	0.39	0.42	-0.36
L{6}	3.59	390.52	4	2	3	0	86.86	0.38	0.56	-5.87	1.00	-0.17	0.81	103.10	-0.80	-0.11	0.60	-0.75
L{7}	5.49	477.62	4	3	5	1	64.26	0.38	0.55	-7.29	1.04	-0.77	0.88	122.71	-1.04	-0.85	-0.22	-1.54
L{8}	2.73	362.44	5	3	6	1	124.14	0.38	-0.11	-4.51	0.53	0.07	0.47	86.89	-0.44	0.37	1.88	0.09
A-II-6	4.75	396.57	4	1	5	0	92.64	0.38	0.56	-4.36	0.72	0.16	0.72	88.28	-0.65	0.75	1.03	-0.46
A-II-9	4.74	364.50	4	1	5	0	67.89	0.38	0.75	-4.48	0.82	0.21	0.72	87.18	-0.63	0.60	0.70	-0.58
A-I-6	3.98	370.53	4	1	3	0	93.94	0.15	0.87	-4.98	1.01	0.08	0.78	89.43	-0.61	0.18	0.82	-0.69
A-I-9	3.97	338.46	4	1	3	0	69.17	0.15	0.75	-4.53	1.01	0.13	0.79	86.70	-0.52	0.39	0.86	-0.53
B-II-6	4.75	396.57	4	1	5	0	58.16	0.15	0.66	-3.67	0.70	0.25	0.68	80.88	-0.60	0.86	0.98	-0.14
B-II-9	4.74	364.50	4	1	5	0	38.13	0.15	0.80	-3.77	0.80	0.34	0.68	79.64	-0.57	0.76	0.65	-0.27
B-I-6	3.98	370.53	4	1	3	0	65.76	0.26	0.87	-4.80	1.02	0.20	0.76	91.30	-0.55	0.44	1.09	-0.43
B-I-9	3.97	338.46	4	1	3	0	47.04	0.26	0.93	-4.29	1.02	0.28	0.79	87.92	-0.35	0.56	1.18	-0.29
C-II-6	3.30	354.49	4	1	3	0	91.78	0.04	0.56	-4.42	0.83	0.09	0.75	86.21	-0.72	0.55	0.71	-0.45
C-II-9	3.29	322.42	4	1	3	0	67.03	0.04	0.67	-4.33	0.84	0.14	0.76	87.23	-0.65	0.55	0.78	-0.45
C-I-6	2.52	328.45	4	1	1	0	94.28	0.05	0.67	-5.15	1.01	0.04	0.78	89.86	-0.65	0.14	1.04	-0.72
C-I-9	2.51	296.39	4	1	1	0	69.52	0.05	0.59	-4.70	0.99	0.11	0.79	88.03	-0.55	0.35	1.08	-0.55
D-II-6	3.30	354.49	4	1	3	0	63.30	0.14	0.71	-3.93	0.76	0.29	0.66	79.22	-0.64	0.80	0.53	-0.27
D-II-9	3.29	322.42	4	1	3	0	44.18	0.14	0.63	-3.64	0.72	0.37	0.68	80.38	-0.56	0.85	0.92	-0.22
D-I-6	2.52	328.45	4	1	1	0	67.83	0.14	1.02	-4.38	0.99	0.26	0.76	84.42	-0.54	0.50	0.85	-0.40
D-I-9	2.51	296.39	4	1	1	0	48.70	0.14	1.00	-3.85	1.00	0.34	0.80	81.55	-0.44	0.70	0.95	-0.31
E-II-6	4.75	396.57	4	1	5	0	89.55	0.57	0.19	-5.25	0.87	-0.16	0.83	104.32	-0.81	0.32	0.90	-0.47
E-II-9	4.74	364.50	4	1	5	0	64.77	0.57	0.32	-5.12	0.90	-0.12	0.86	103.89	-0.77	0.32	0.93	-0.45
E-I-6	3.98	370.53	4	1	3	0	93.29	0.57	0.92	-5.75	1.16	-0.23	0.90	106.48	-0.76	-0.12	0.46	-0.67
E-I-9	3.97	338.46	4	1	3	0	68.53	0.57	0.82	-5.26	1.13	-0.17	0.89	101.46	-0.65	0.08	0.51	-0.53
F-II-6	4.75	396.57	4	1	5	0	67.25	0.08	0.44	-5.22	0.90	-0.15	0.83	102.52	-0.81	0.27	0.66	-0.43
F-II-9	4.74	364.50	4	1	5	0	48.13	0.08	0.57	-5.10	0.93	-0.11	0.86	103.01	-0.76	0.26	0.74	-0.40
F-I-6	3.98	370.53	4	1	3	0	67.91	0.08	0.92	-5.87	1.19	-0.26	0.89	109.48	-0.76	-0.13	0.38	-0.67
F-I-9	3.97	338.46	4	1	3	0	48.94	0.08	0.82	-5.43	1.15	-0.19	0.88	106.17	-0.65	0.12	0.45	-0.53
G-II-6	3.30	354.49	4	1	3	0	89.17	0.16	0.52	-4.86	0.83	0.03	0.77	92.34	-0.74	0.54	0.72	-0.66
G-II-9	3.29	322.42	4	1	3	0	64.41	0.16	0.61	-4.75	0.90	0.08	0.79	91.64	-0.68	0.49	0.86	-0.62
G-I-6	2.52	328.45	4	1	1	0	93.69	0.16	0.88	-5.45	1.03	-0.01	0.78	95.54	-0.65	0.07	0.80	-0.93
G-I-9	2.51	296.39	4	1	1	0	68.93	0.16	0.81	-5.40	1.07	0.02	0.78	95.74	-0.49	0.14	1.01	-0.87
H-II-6	3.30	354.49	4	1	3	0	67.48	0.33	0.58	-4.25	0.76	0.20	0.68	81.45	-0.63	0.68	0.74	-0.46
H-II-9	3.29	322.42	4	1	3	0	48.98	0.33	0.68	-4.19	0.82	0.25	0.70	82.68	-0.58	0.60	0.89	-0.44
H-I-6	2.52	328.45	4	1	1	0	67.68	0.33	0.88	-5.00	1.02	0.13	0.75	93.33	-0.65	0.26	1.01	-0.57
H-I-9	2.51	296.39	4	1	1	0	49.30	0.33	0.87	-4.62	1.05	0.19	0.76	90.64	-0.48	0.37	1.12	-0.50
I-II-6	4.86	430.58	4	1	5	0	89.95	0.33	0.47	-4.87	0.84	0.01	0.77	94.30	-0.80	0.49	0.66	-0.63
I-III-9	4.85	398.52	4	1	5	0	69.15	0.33	0.64	-4.82	0.93	0.02	0.79	91.19	-0.79	0.42	0.40	-0.68
I-II-6	4.09	404.55	4	1	3	0	94.86	0.33	0.75	-5.49	1.04	0.01	0.80	97.99	-0.72	0.11	1.03	-0.86
I-II-9	4.08	372.48	4	1	3	0	70.08	0.33	0.73	-5.38	1.07	0.01	0.81	96.61	-0.51	0.17	1.05	-0.83
J-II-6	4.86	430.58	4	1	5	0	58.08	0.14	0.71	-4.18	0.83	0.18	0.69	81.31	-0.70	0.67	0.59	-0.36
J-II-9	4.85	398.52	4	1	5	0	46.00	0.14	0.84	-4.12	0.85	0.23	0.71	83.11	-0.65	0.62	0.66	-0.36
J-I-6	4.09	404.55	4	1	3	0	68.26	0.14	0.85	-4.64	1.02	0.18	0.78	86.26	-0.63	0.36	1.04	-0.59
J-I-9	4.08	372.48	4	1	3	0	49.24	0.14	0.89	-4.22	1.03	0.26	0.80	83.81	-0.45	0.47	1.13	-0.45
K-II-6	4.86	430.58	4	1	5	0	83.82	0.15	0.35	-6.01	1.01	-0.39	0.89	114.99	-0.86	0.09	0.38	-0.58
K-II-9	4.85	398.52	4	1	5	0	59.07	0.15	0.51	-5.50	1.03	-0.26	0.90	105.85	-0.80	0.19	0.57	-0.56
K-I-6	4.09	404.55	4	1	3	0	94.52	0.15	0.60	-6.09	1.07	-0.27	0.90	105.29	-0.79	-0.22	0.59	-1.00
K-I-9	4.08	372.48	4	1	3	0	69.76	0.15	0.33	-5.94	1.14	-0.31	0.92	108.53	-0.78	-0.02	0.68	-0.73
L-II-6	4.86	430.58	4	1	5	0	67.65	0.02	0.06	-5.55	0.89	-0.28	0.88	105.74	-0.86	0.20	0.91	-0.53
L-II-9	4.85	398.52	4	1	5	0	49.20	0.02	0.14	-5.32	0.92	-0.26	0.91	102.70	-0.81	0.21	0.96	-0.51
L-I-6	4.09	404.55	4	1	3	0	68.06	0.02	0.85	-6.26	1.23	-0.40	0.96	115.93	-0.80	-0.23	0.37	-0.79
L-I-9	4.08	372.48	4	1	3	0	49.21	0.02	0.80	-5.86	1.21	-0.35	0.95	110.73	-0.71	-0.02	0.45	-0.76
Averages	2.91	359.14	4.42	2.25	3.58	0.11	103.28	0.25	0.18	-4.50	0.59	0.16	0.56	85.87	-0.60	0.53	1.30	-0.23

4.1.2 Library Production of "4+4" Scaffold via Click-S_NAr

General Procedure A: Cu-catalyzed N-arylation. To a microwave vial charged with solution of sultam **1.12.1** (0.132 mmol, 1.0 equiv.) in EtOH (0.4 mL), was added o-anisidine **1.12.2** (0.330 mmol, 2.5 equiv.), CuI (0.066 mmol, 0.5 equiv.), 1,10-phenanthroline (0.0264 mmol, 0.2 equiv.), and Cs_2CO_3 (0.264 mmol, 2.0 equiv.). The reaction was heated at 100 °C under microwave irradiation for 30 min, which upon completion was quenched with aq., HCl and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and subject to automated column chromatography.

General Procedure B: nucleophilic aromatic substitution (S_NAr). To a microwave vial charged with solution of sultam **1.13.1** (0.315 mmol, 1.0 equiv.) in DMSO (0.3 mL), was added pyrrolidine **1.13.2** (01.575 mmol, 5.0 equiv.), and DBU (0.032 mmol, 0.1 equiv.). The reaction was heated at 180 °C under microwave irradiation for 50 min, which upon completion was diluted with EtOAc and passed through SiO_2 SPE. The resulting mixture was concentrated under reduced pressure, and subject to automated column chromatography.

General Procedure C: one-pot Click/S_NAr. To a microwave vial charged with solution of sultam **1.13.A or 1.13.B** (0.158 mmol, 1.0 equiv.) in DMSO (0.2 mL), was added amine (0.790 mmol, 5.0 equiv.), azide (0.316 mmol, 2.0 equiv.), CuI (0.0474 mmol, 0.3 equiv.)

and DBU (0.0158 mmol, 0.1 equiv.). The reaction was heated at 180 °C under microwave irradiation for 50 min, which upon completion was diluted with EtOAc and passed through SiO$_2$ SPE. The resulting mixture was concentrated under reduced pressure to afford the crude product. The crude product was QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

Comp.	HRMS Expected M/z (M)$^+$	HRMS Found M/z (M+H)$^+$	Mass (mg)	Yield (%)	Purity (%)
1.4.A.FN	569.1708	570.1734	134.5 mg	75 %	99.9 %
1.4.A.DN	601.1429	602.1506	166.6 mg	88 %	99.5 %
1.4.A.CN	598.1974	503.2058	94.0 mg	53 %	99.8 %
1.4.A.EN	692.2193	693.2266	181.1 mg	83 %	100.0 %
1.4.A.GN	573.1658	574.1754	116.4 mg	64 %	99.8 %
1.4.B.GN	574.1658	574.1722	129.4 mg	72 %	99.7 %
1.4.B.HN	571.1865	572.1985	120.5 mg	67 %	99.6 %
1.4.B.IN	595.1501	596.1556	111.1 mg	59 %	98.5 %
1.4.B.DN	601.1429	602.1489	144.8 mg	76 %	98.7 %
1.4.A.FQ	535.1445	536.1111	17.0 mg	20 %	98.4 %
1.4.A.DQ	567.1166	568.0811	54.7 mg	61 %	96.8 %
1.4.A.CQ	564.1710	NA	NA	NA	NA
1.4.A.EQ	658.1929	659.2017	36.1 mg	95 %	98.6 %
1.4.A.GQ	539.1394	540.1498	1.3 mg	2 %	91.9 %
1.4.A.FL	519.1740	520.1812	26.5 mg	32 %	99.6 %
1.4.A.DL	551.1461	552.1535	60.8 mg	70 %	98.3 %
1.4.A.CL	548.2006	NA	NA	NA	NA
1.4.A.EL	642.2225	643.2252	29.5 mg	29 %	98.2 %
1.4.A.GL	523.1689	524.1801	3.2 mg	4 %	98.4 %
1.4.B.GO	573.1658	574.1739	21.7 mg	24 %	92.8 %
1.4.B.HO	571.1865	572.1869	51.1 mg	57 %	91.9 %
1.4.B.IO	595.1501	596.1570	25.8 mg	27 %	99.3 %
1.4.B.JO	587.1814	588.1833	23.8 mg	26 %	95.4 %
1.4.B.DO	601.1429	602.1476	62.7 mg	66 %	97.1 %
1.4.B.GP	573.1658	574.1711	13.4 mg	15 %	97.1 %
1.4.B.HP	571.1865	572.1899	34.2 mg	38 %	93.1 %
1.4.B.IP	595.1501	596.1559	19.2 mg	20 %	99.2 %
1.4.B.JP	587.1814	588.1867	14.2 mg	15 %	96.9 %
1.4.B.DP	601.1429	602.1483	61.2 mg	64 %	97.2 %

1.4.B.JN	587.1814	588.1912	108.9 mg	59 %	98.6 %
1.4.A.FO	569.1708	570.1855	50.6 mg	56 %	97.9 %
1.4.A.DO	601.1429	602.1527	67.6 mg	71 %	99.4 %
1.4.A.CO	598.1974	599.2046	34.0 mg	36 %	99.1 %
1.4.A.EO	692.2193	693.2272	68.2 mg	62 %	99.5 %
1.4.A.GO	573.1658	574.1766	48.5 mg	54 %	99.2 %
1.4.A.FP	569.1708	570.1751	54.5 mg	61 %	98.0 %
1.4.A.DP	601.1429	602.1514	71.9 mg	76 %	99.2 %
1.4.A.CP	598.1974	599.2045	24.0 mg	25 %	99.7 %
1.4.A.EP	692.2193	693.2317	88.9 mg	81 %	99.9 %
1.4.A.GP	573.1658	574.1765	25.3 mg	28 %	99.1 %
1.4.A.FM	519.1740	520.1824	41.6 mg	51 %	98.0 %
1.4.A.DM	551.1461	552.1498	66.4 mg	76 %	98.7 %
1.4.A.CM	548.2006	549.2073	27.5 mg	32 %	99.2 %
1.4.A.EM	642.2225	643.2255	59.8 mg	59 %	99.6 %
1.4.A.GM	523.1690	524.1785	14.0 mg	17 %	99.0 %
1.4.B.GN	573.1658	574.1746	64.9 mg	72 %	97.6 %
1.4.B.HN	571.1865	572.1919	41.4 mg	46 %	98.7 %
1.4.B.IN	595.1501	596.1562	54.3 mg	58 %	99.8 %
1.4.B.JN	587.1814	588.1885	54.5 mg	59 %	87.4 %
1.4.B.DN	601.1429	602.1489	51.0 mg	54 %	99.6 %
1.4.B.GO	523.1690	524.1763	51.4 mg	62 %	98.9 %
1.4.B.HO	521.1897	522.1924	48.2 mg	58 %	99.8 %
1.4.B.IO	545.1533	546.1627	53.2 mg	62 %	99.2 %
1.4.B.JO	537.1846	538.1940	49.9 mg	59 %	98.9 %
1.4.B.DO	551.1461	552.1542	53.4 mg	61 %	98.2 %
1.4.B.GM	523.1690	524.1777	51.0 mg	62 %	99.1 %
1.4.B.HM	521.1897	522.2004	43.9 mg	53 %	100.0 %
1.4.B.IM	545.1533	546.1594	48.3 mg	56 %	98.8 %
1.4.B.JM	537.1846	538.1949	42.5 mg	50 %	97.7 %
1.4.B.DM	551.1461	552.1516	51.1 mg	59 %	98.1 %
1.4.B.GQ	539.1394	540.1457	55.7 mg	65 %	98.9 %
1.4.B.HQ	537.1601	538.1682	50.6 mg	60 %	94.9 %
1.4.B.IQ	561.1238	562.1329	53.0 mg	60 %	99.7 %
1.4.B.JQ	553.1551	554.1635	61.0 mg	70 %	93.1 %
1.4.B.DQ	567.1166	568.1265	58.2 mg	65 %	96.9 %

1.4.A.FN

1.348
Range: 1.348

(3)
100%
569.2(41%)
2.41
22296.8398

AU

1.0—

5.0e-1—

0.0—

Time

0.50   1.00   1.50   2.00   2.50   3.00   3.50

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.26	29	0.13	1639	569.17
3	2.41	22297	99.87	1334866	569.17
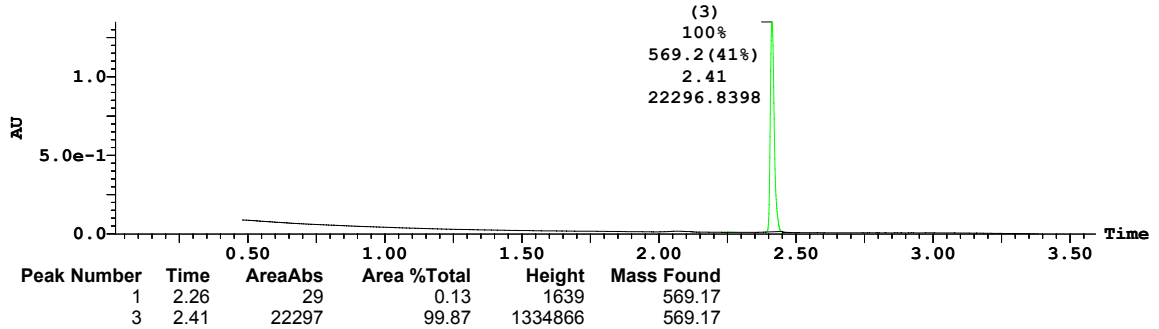
1.4.A.DN

3: UV Detector: 214
1.385
Range: 1.385

(4)
99%
601.1(30%)
2.31
24062.9805

AU

1.0—

5.0e-1—

0.0—

Time

0.50   1.00   1.50   2.00   2.50   3.00   3.50

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.82	45	0.19	2798	
2	2.24	25	0.11	1703	601.14
3	2.26	61	0.25	3140	601.14
4	2.31	24063	99.46	1368486	601.14
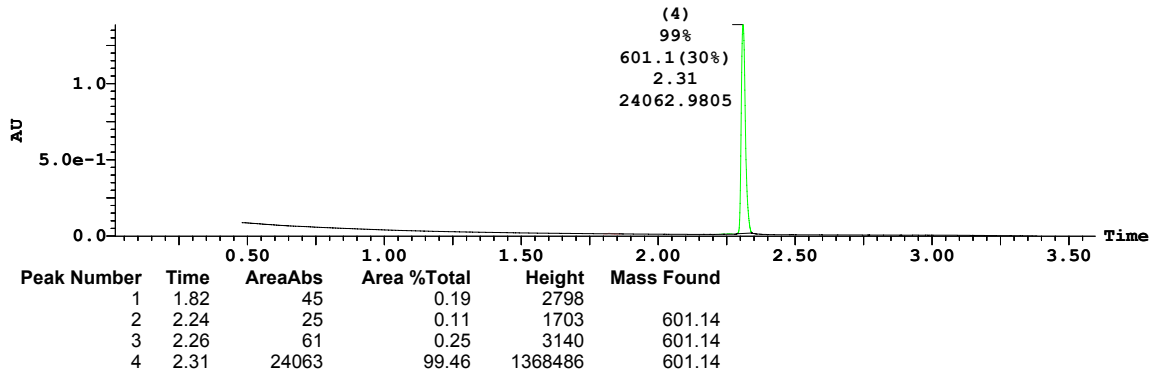
1.4.A.CN

3: UV Detector: 214
1.025
Range: 1.025

(2)
100%
598.2(65%)
2.05
16001.4502

AU

7.5e-1—

5.0e-1—

2.5e-1—

0.0—

Time

0.50   1.00   1.50   2.00   2.50   3.00   3.50

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.90	31	0.19	1663	598.20
2	2.05	16001	99.81	1010951	598.20

188
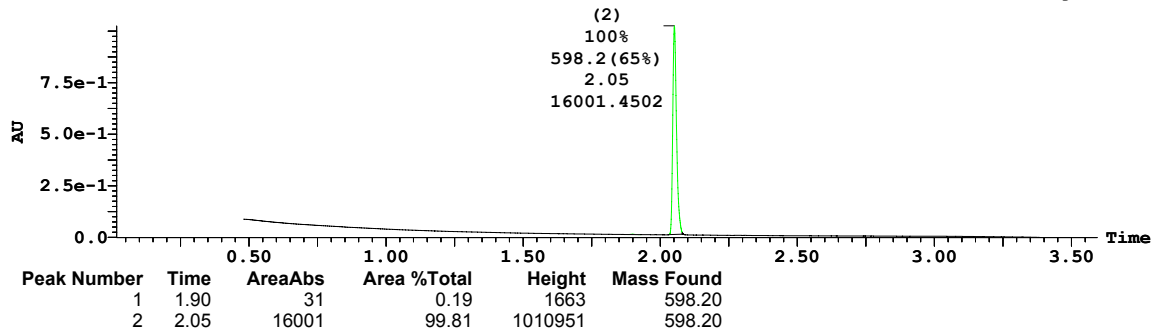
1.4.A.EN

3: UV Detector: 214

1.399
Range: 1.399

(1)
100%
692.2(34%)
2.51
25023.8691

AU

1.0

5.0e-1

0.0

0.50   1.00   1.50   2.00   2.50   3.00   3.50   Time

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.51	25024	100.00	1384910	692.22
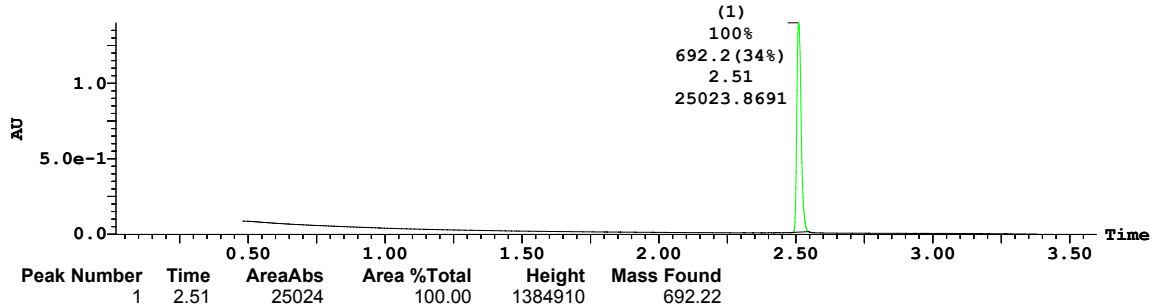
1.4.A.GN

3: UV Detector: 214

1.254
Range: 1.254

(2)
100%
573.2(59%)
1.96
20302.7109

AU

1.0

5.0e-1

0.0

0.50   1.00   1.50   2.00   2.50   3.00   3.50   Time

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.91	41	0.20	2898	573.17
2	1.96	20303	99.80	1235460	573.17
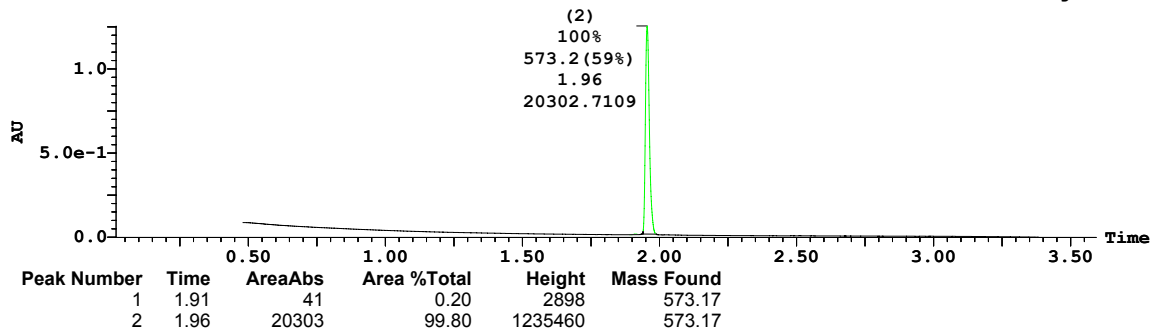
1.4.B.GN

3: UV Detector: 214

1.293
Range: 1.293

(2)
100%
573.2(70%)
2.06
22182.9902

AU

1.0

5.0e-1

0.0

0.50   1.00   1.50   2.00   2.50   3.00   3.50   Time

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.01	66	0.29	2908	573.17
2	2.06	22183	99.71	1278470	573.17

1.4.B.HN

(3)
100%
571.2(46%)
2.57
21364.3809

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.46	61	0.29	4078	571.19
2	2.51	25	0.12	1956	571.19
3	2.57	21364	99.60	1308845	571.19

1.4.B.IN

(5)
99%
595.2(51%)
2.37
21932.6797

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.08	40	0.18	2927	
2	2.22	24	0.11	2140	595.15
3	2.30	127	0.57	7731	595.15
4	2.33	134	0.60	9822	595.15
5	2.37	21933	98.54	1321752	595.15

1.4.B.DN

(3)
99%
601.1(4%)
2.38
8097.3799

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.26	32	0.39	1973	601.14
2	2.34	71	0.87	4207	601.14
3	2.38	8097	98.74	538030	601.14

1.4.A.FQ

3: UV Detector: 214

9.566e-1
Range: 9.566e-1

(5)
98%
535.1(54%)
2.37
14646.2002
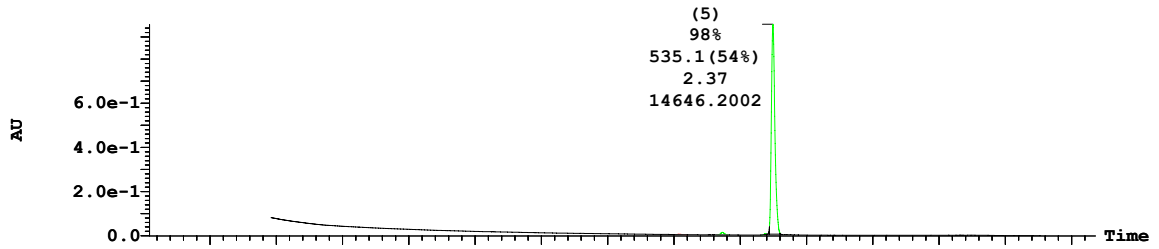
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.02	29	0.20	1725	
2	2.18	179	1.20	11422	535.14
4	2.35	37	0.25	3695	535.14
5	2.37	14646	98.35	949247	535.14

1.4.A.DQ

3: UV Detector: 214

1.054
Range: 1.054

(3)
97%
567.1(41%)
2.28
16228.0898
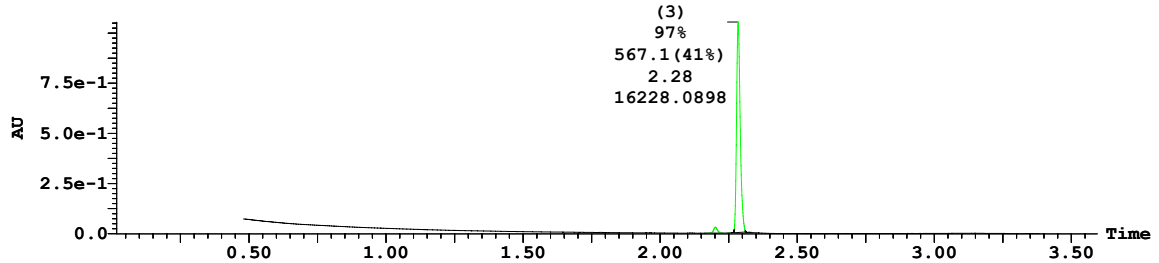
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.20	476	2.84	29341	567.12
2	2.26	20	0.12	1960	567.12
3	2.28	16228	96.80	1048307	567.12
4	2.33	40	0.24	2248	567.12

1.4.A.EQ

3: UV Detector: 214

9.655e-1
Range: 9.655e-1

(4)
99%
658.2(52%)
2.49
15018.5303
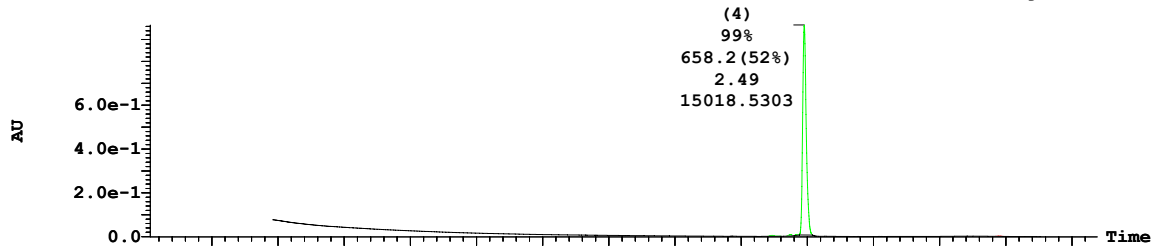
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.37	80	0.52	4408	658.19
2	2.44	75	0.49	5747	658.19
3	2.46	36	0.23	3694	658.19
4	2.49	15019	98.64	957815	658.19
5	3.22	17	0.11	1357	

1.4.A.GQ

3: UV Detector: 214

1.485e-1
Range: 1.484e-1

(5)
92%
539.1(49%)
1.92
2095.9900

1.91
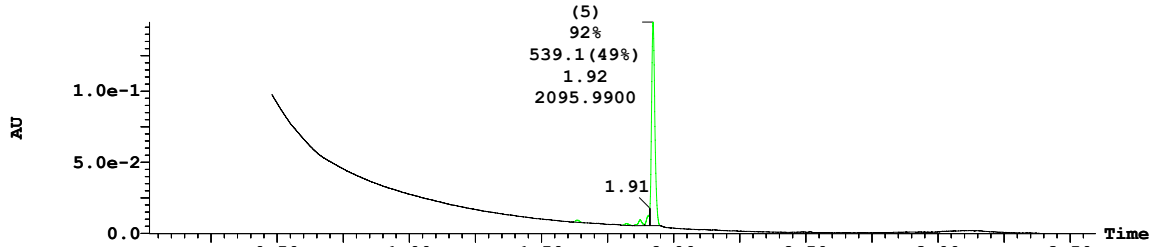
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.64	27	1.18	1592	539.14
2	1.82	22	0.97	1315	539.14
3	1.87	66	2.90	3989	539.14
4	1.91	69	3.05	6912	539.14
5	1.92	2096	91.89	142955	539.14

1.4.A.FL

3: UV Detector: 214

9.507e-1
Range: 9.506e-1

(4)
100%
519.2(48%)
2.27
14611.8799
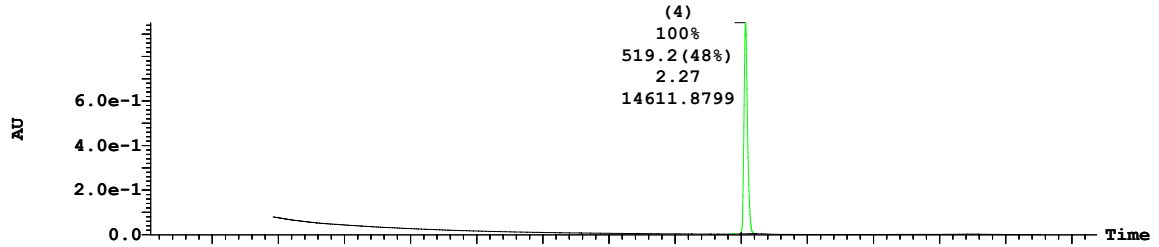
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.91	20	0.14	1322	
3	2.22	38	0.26	2608	519.17
4	2.27	14612	99.60	946656	519.17

1.4.A.DL

3: UV Detector: 214

9.894e-1
Range: 9.894e-1

(2)
98%
551.1(22%)
2.18
14835.7100
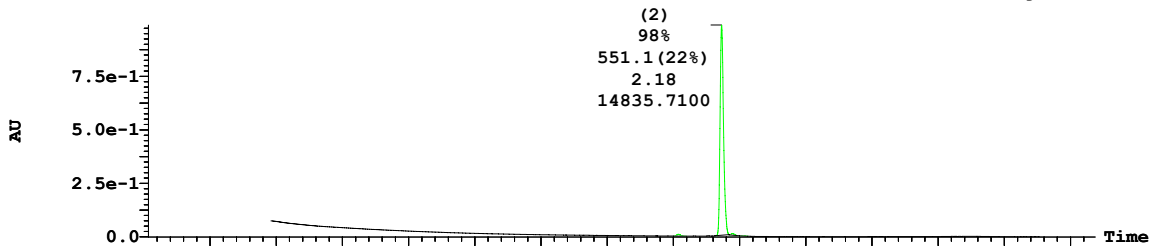
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.02	134	0.88	8634	551.15
2	2.18	14836	98.34	982069	551.15
3	2.22	101	0.67	7617	551.15
4	2.26	17	0.11	1319	551.15

1.4.A.EL

9.376e-1
Range: 9.376e-1

(3)
98%
642.2(64%)
2.39
14373.8203
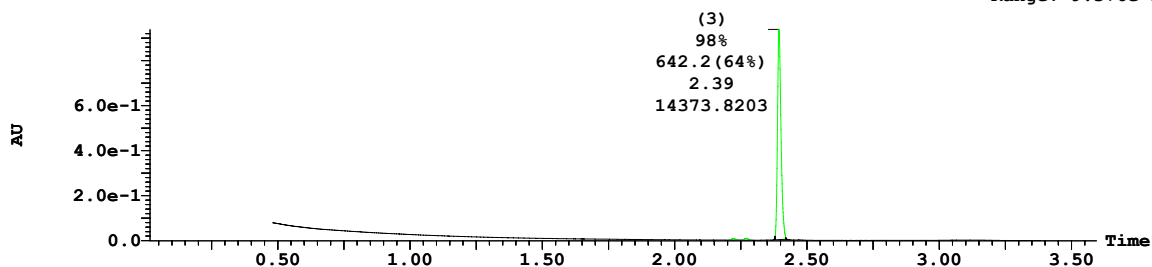
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.22	128	0.88	6872	642.22
2	2.27	138	0.94	8484	642.22
3	2.39	14374	98.18	933030	642.22

1.4.A.GL

3: UV Detector: 214

3.583e-1
Range: 3.583e-1

(3)
98%
523.2(2%)
1.81
4984.8999
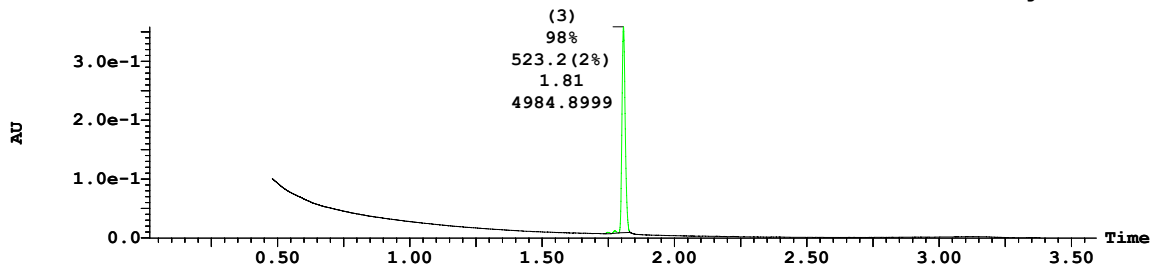
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.75	29	0.58	2408	523.17
2	1.78	52	1.03	4202	523.17
3	1.81	4985	98.39	349410	523.17

1.4.B.GO

3: UV Detector: 214

8.508e-1
Range: 8.508e-1

(6)
93%
573.2(73%)
2.07
12787.2197

(5);5%;573.2(73%);2.03;664.8300
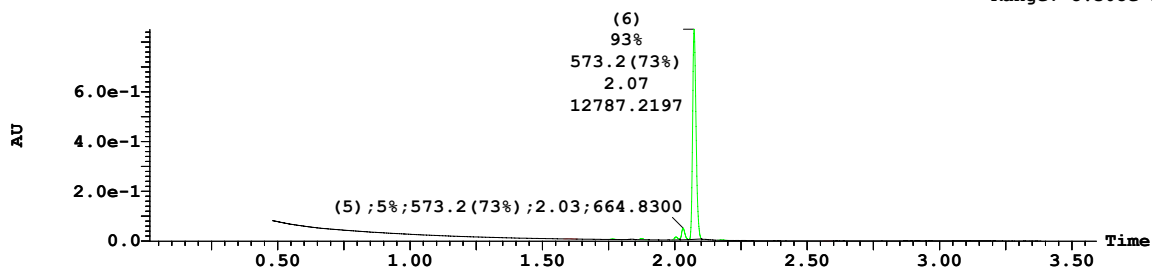
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.60	29	0.21	1524	
2	1.77	31	0.23	1932	573.17
3	1.87	60	0.44	4217	573.17
4	2.01	159	1.15	11582	573.17
5	2.03	665	4.83	46856	573.17
6	2.07	12787	92.84	844091	573.17
7	2.18	28	0.20	1858	573.17
8	2.57	15	0.11	976	

1.4.B.HO

8.813e-1
Range: 8.813e-1

(4)
92%
571.2(60%)
2.55
13813.9004

(3);8%;571.2(60%);2.48;1198.7000
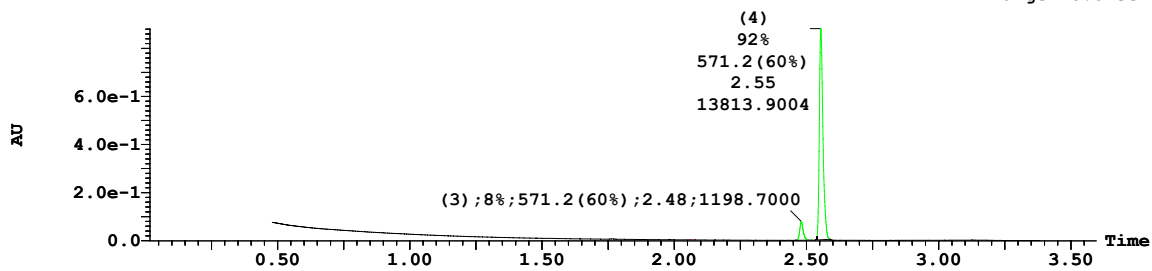
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.06	27	0.18	1604	
3	2.48	1199	7.97	77273	571.19
4	2.55	13814	91.85	877399	571.19

1.4.B.IO

3: UV Detector: 214

1.132
Range: 1.132

(4)
99%
595.2(3%)
2.37
17224.8008
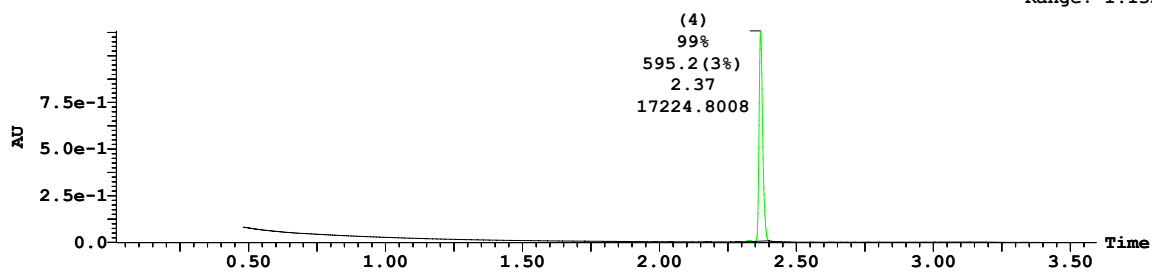
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.09	19	0.11	1273	595.15
2	2.22	24	0.14	1627	595.15
3	2.33	77	0.44	4683	595.15
4	2.37	17225	99.31	1125540	595.15

1.4.B.JO

3: UV Detector: 214

8.504e-1
Range: 8.504e-1

(4)
95%
587.2(64%)
2.19
13681.6299

(3);4%;587.2(64%);2.15;562.3400
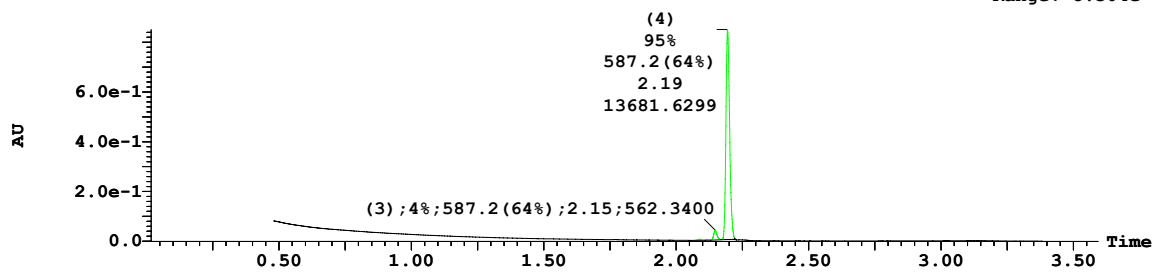
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.09	76	0.53	4706	587.18
2	2.12	18	0.13	1741	587.18
3	2.15	562	3.92	39428	587.18
4	2.19	13682	95.42	843689	587.18

1.4.B.DO

8.413e-1
Range: 8.413e-1

(3)
97%
601.1(65%)
2.37
12646.6299
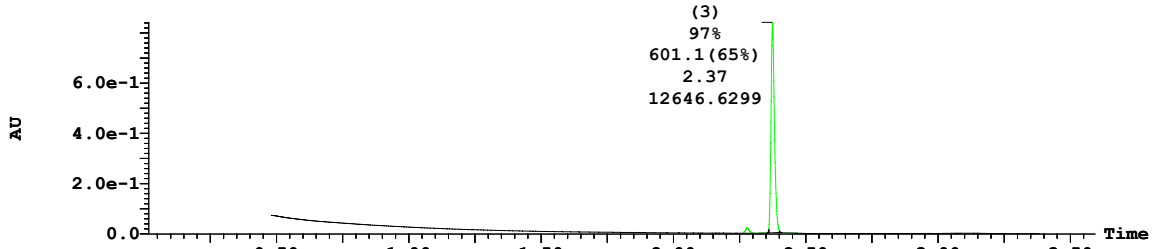
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.28	322	2.47	21359	601.14
2	2.33	32	0.24	2143	601.14
3	2.37	12647	97.08	837081	601.14
4	2.44	27	0.21	1354	601.14

1.4.B.GP

3: UV Detector: 214

6.518e-1
Range: 6.518e-1

(4)
97%
573.2(75%)
2.08
9641.0195
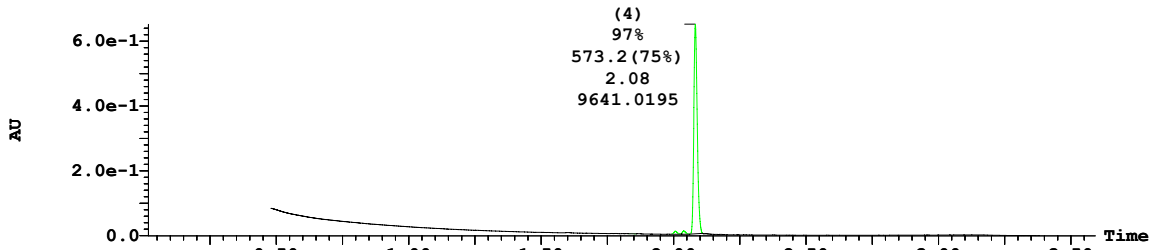
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.84	13	0.13	1033	573.17
2	2.01	133	1.34	9407	573.17
3	2.04	137	1.38	9882	573.17
4	2.08	9641	97.14	646166	573.17

1.4.B.HP

3: UV Detector: 214

8.577e-1
Range: 8.577e-1

(3)
93%
571.2(59%)
2.56
13540.5400

(2);7%;571.2(58%);2.47;974.9500
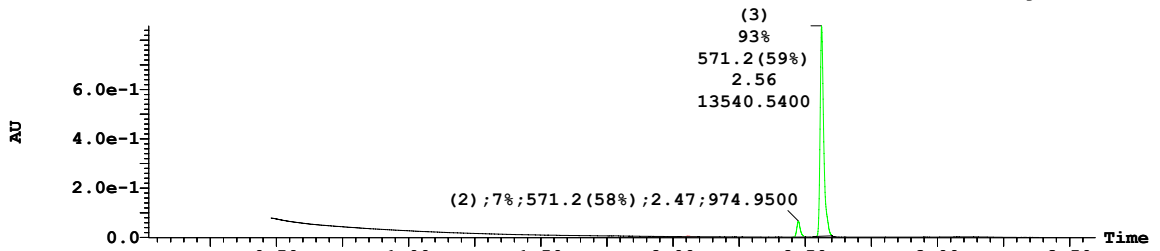
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.06	31	0.21	1804	
2	2.47	975	6.70	63673	571.19
3	2.56	13541	93.09	852811	571.19

195

1.4.B.IP

1.215
Range: 1.215

(5)
99%
595.2(70%)
2.38
18921.0605

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.09	22	0.11	1338	595.15
2	2.23	52	0.27	3546	595.15
3	2.28	25	0.13	2008	595.15
4	2.34	62	0.33	4920	595.15
5	2.38	18921	99.16	1207058	595.15
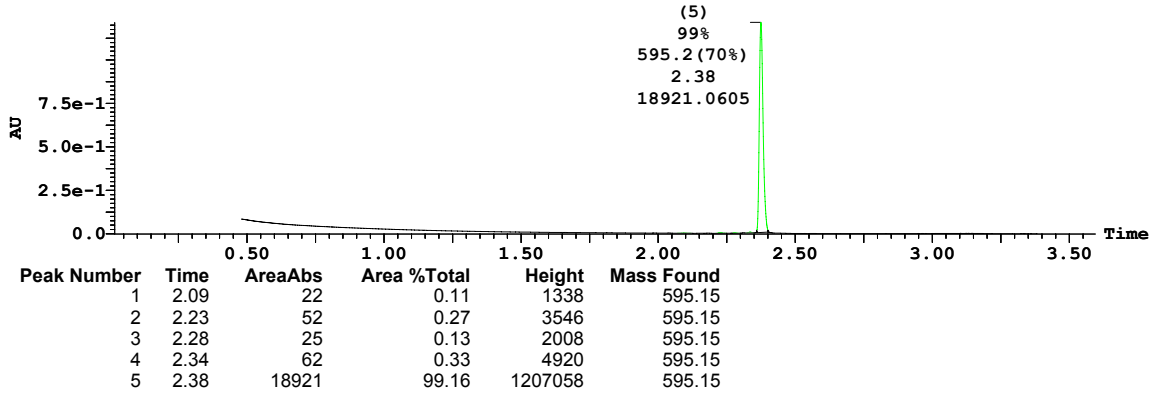
1.4.B.JP

3: UV Detector: 214

6.881e-1
Range: 6.881e-1

(4)
97%
587.2(72%)
2.20
10714.6904

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.10	49	0.44	3687	587.18
2	2.14	34	0.31	2936	587.18
3	2.15	262	2.37	17588	587.18
4	2.20	10715	96.88	682670	587.18
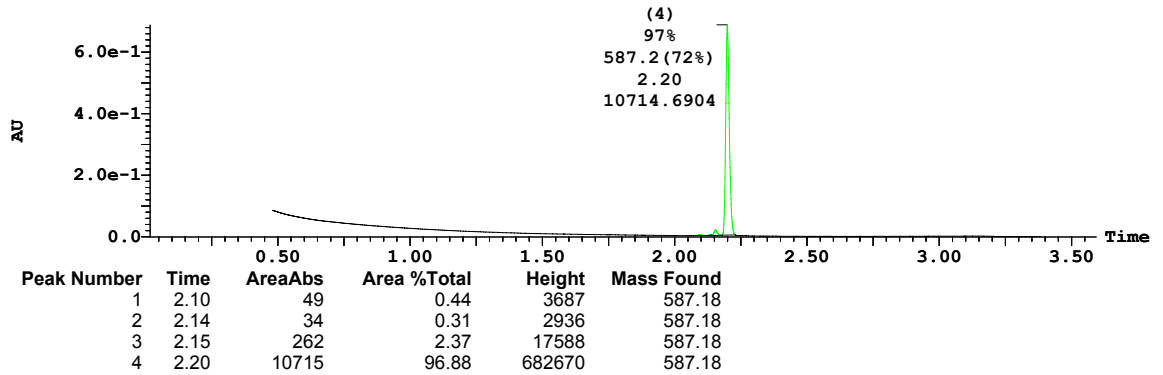
1.4.B.DP

3: UV Detector: 214

1.007
Range: 1.007

(3)
97%
601.1(69%)
2.38
15422.1797

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.28	400	2.52	26119	601.14
2	2.33	41	0.26	2677	601.14
3	2.38	15422	97.22	1000864	601.14

1.4.B.JN

8.914e-1
Range: 8.914e-1

(2)
99%
587.2(5%)
2.18
14013.4502

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.08	125	0.88	8636	587.18
2	2.18	14013	98.64	884185	587.18
3	2.23	69	0.48	4326	587.18
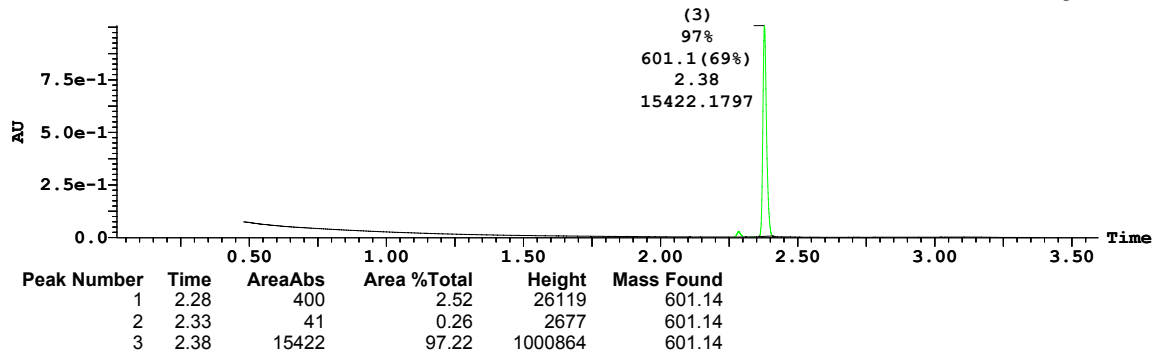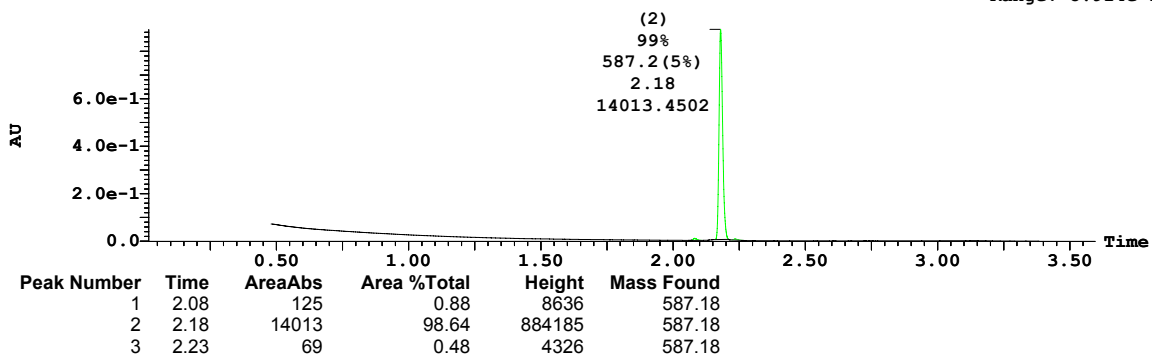
1.4.A.FO

3: UV Detector: 214

9.388e-1
Range: 9.388e-1

(3)
98%
569.2(68%)
2.37
15943.9102

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.99	96	0.59	4876	
2	2.03	253	1.55	14548	569.17
3	2.37	15944	97.86	930767	569.17
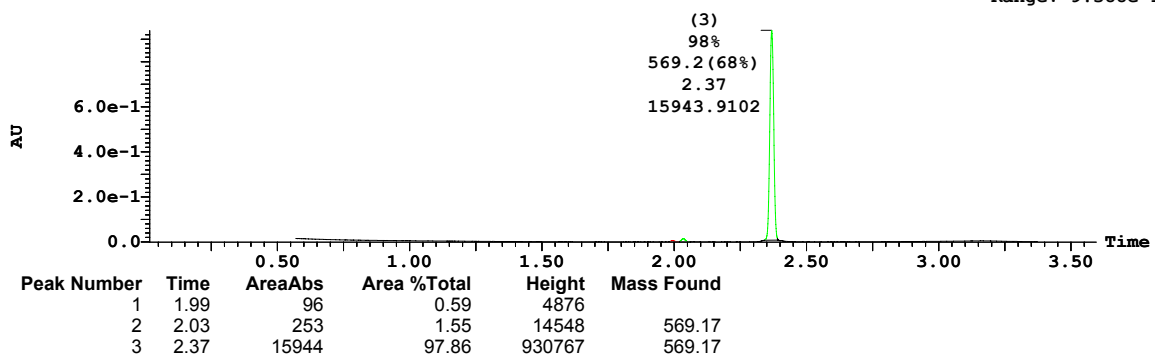
1.4.A.DO

3: UV Detector: 214

8.354e-1
Range: 8.354e-1
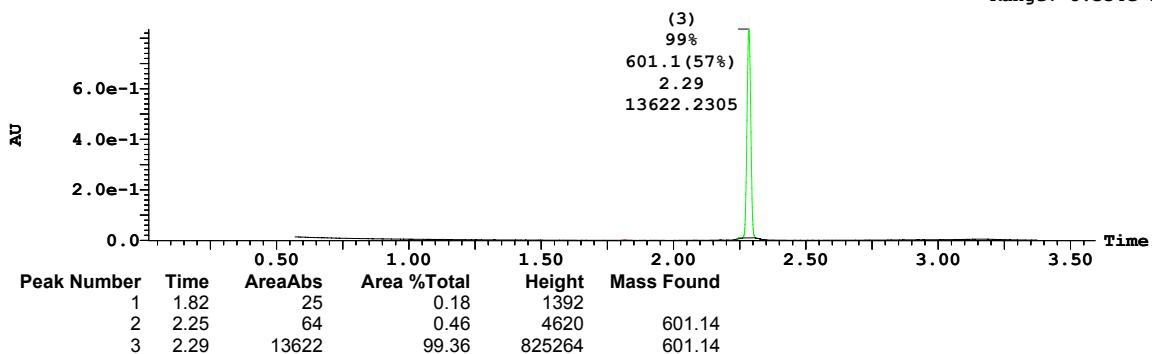
(3)
99%
601.1(57%)
2.29
13622.2305

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.82	25	0.18	1392	
2	2.25	64	0.46	4620	601.14
3	2.29	13622	99.36	825264	601.14

1.4.A.CO

8.888e-1
Range: 8.888e-1

(4)
99%
598.2(63%)
2.04
14182.2402
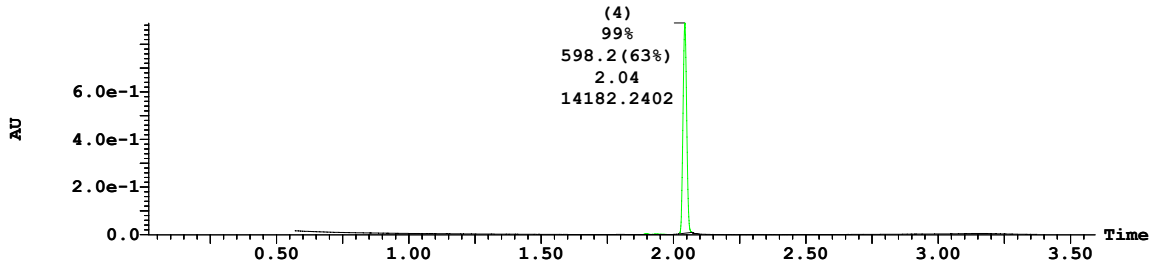
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.90	52	0.37	2861	598.20
2	1.94	53	0.37	2481	598.20
3	1.96	24	0.17	1502	598.20
4	2.04	14182	99.10	882889	598.20

1.4.A.EO

3: UV Detector: 214

8.078e-1
Range: 8.077e-1

(3)
100%
692.2(51%)
2.47
14115.8496
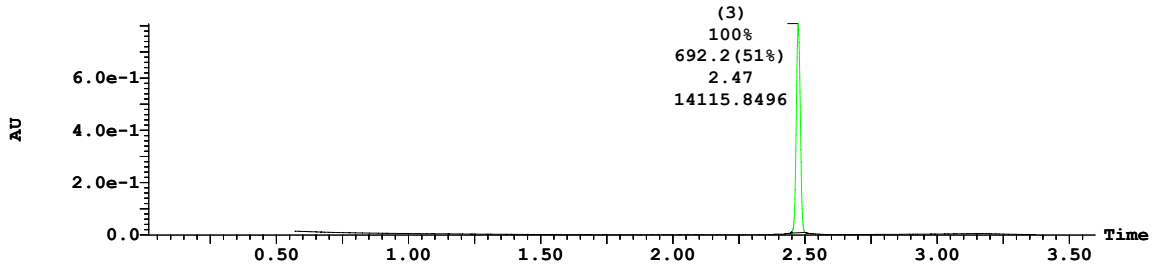
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.90	22	0.15	1224	
2	2.39	48	0.34	2655	692.22
3	2.47	14116	99.51	799716	692.22

1.4.A.GO

3: UV Detector: 214

6.706e-1
Range: 6.706e-1

(3)
99%
573.2(69%)
1.95
10325.8096
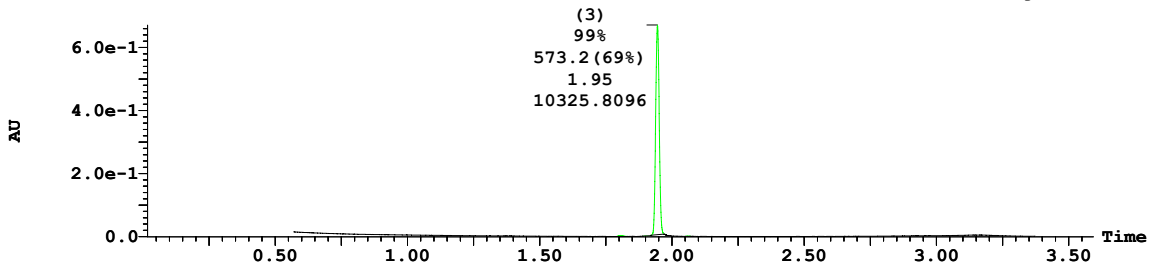
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.81	58	0.56	3169	573.17
2	1.91	13	0.12	941	573.17
3	1.95	10326	99.19	664632	573.17
4	2.06	13	0.13	1022	573.17

1.4.A.FP

3: UV Detector: 214

9.336e-1
Range: 9.336e-1

(3)
98%
569.2(67%)
2.37
15919.2305

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.00	80	0.49	4571	
2	2.04	241	1.48	14008	569.17
3	2.37	15919	98.02	926310	569.17
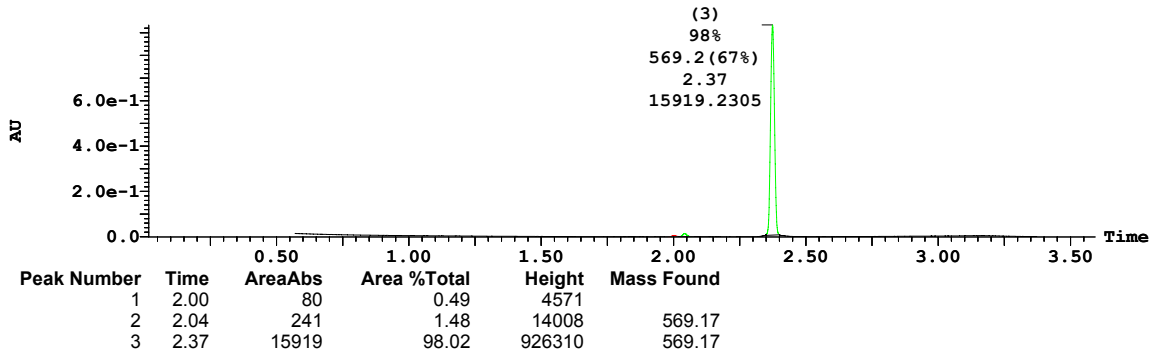
1.4.A.DP

3: UV Detector: 214

9.519e-1
Range: 9.518e-1

(3)
99%
601.1(57%)
2.29
15889.1104

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.82	18	0.11	1285	
2	2.26	107	0.67	6775	601.14
3	2.29	15889	99.22	945456	601.14
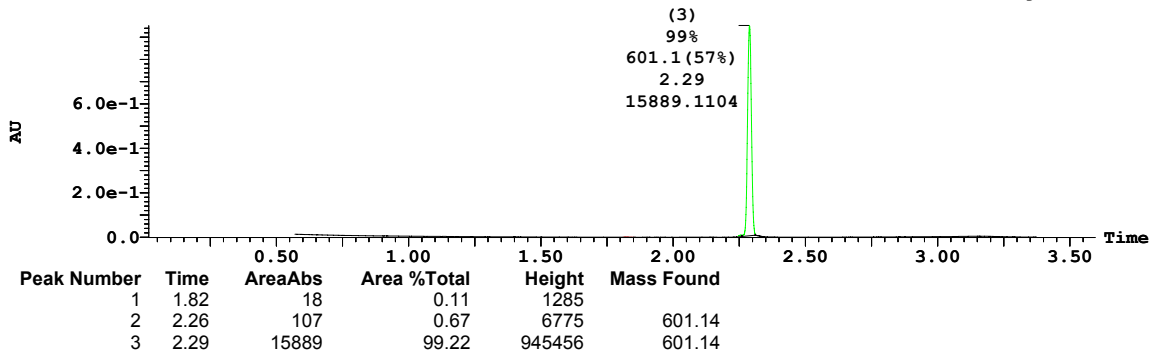
1.4.A.CP

3: UV Detector: 214

9.49e-1
Range: 9.49e-1

(3)
100%
598.2(66%)
2.05
15194.5898

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.90	47	0.31	2791	598.20
3	2.05	15195	99.69	943373	598.20
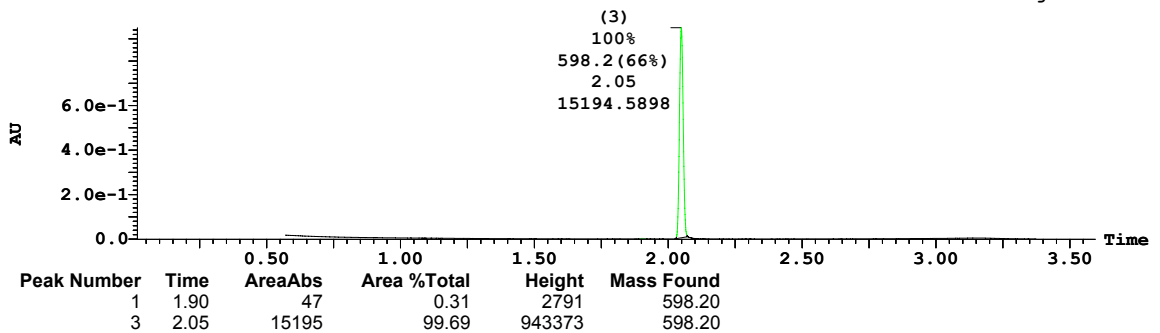
1.4.A.EP

3: UV Detector: 214

9.026e-1
Range: 9.026e-1
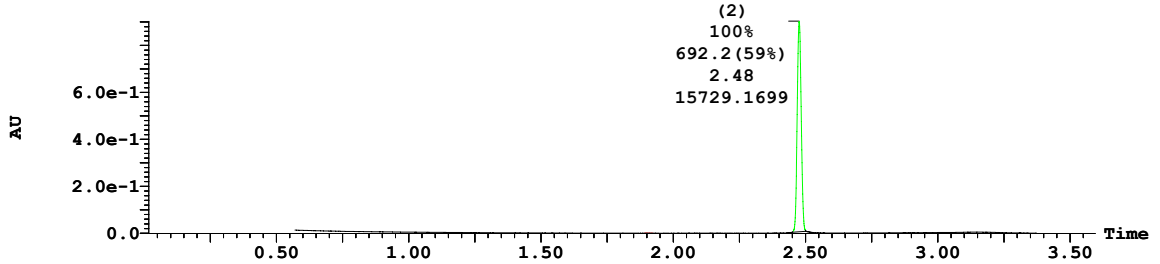
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.90	20	0.13	1265	
2	2.48	15729	99.87	896257	692.22

1.4.A.GP

3: UV Detector: 214

9.625e-1
Range: 9.625e-1
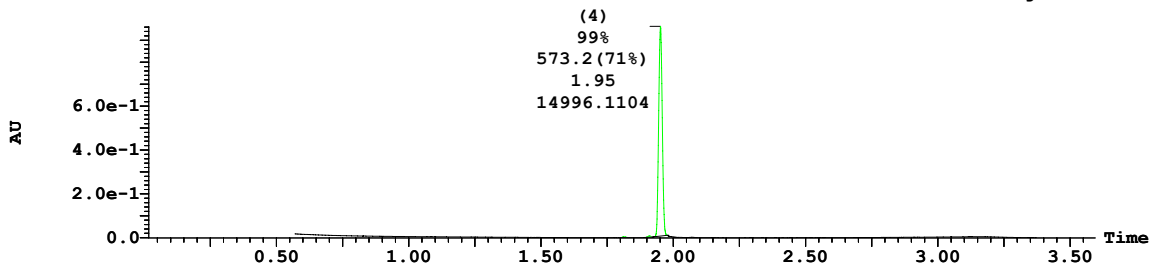
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.81	53	0.35	3222	573.17
3	1.91	77	0.51	5701	573.17
4	1.95	14996	99.14	954682	573.17

1.4.A.FM

3: UV Detector: 214

9.417e-1
Range: 9.416e-1
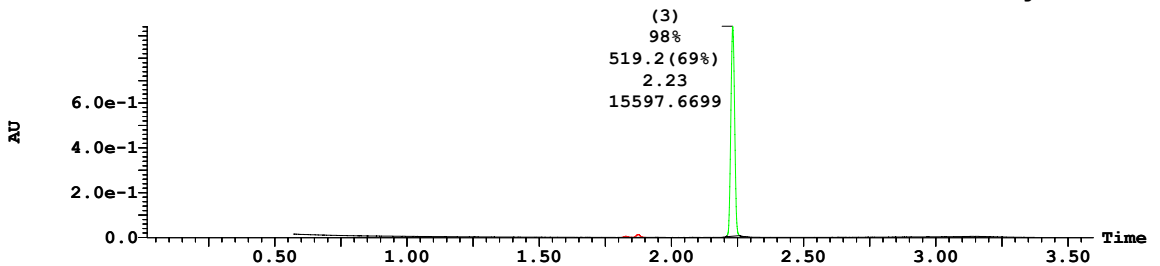
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.83	90	0.56	5111	
2	1.87	223	1.40	12828	
3	2.23	15598	98.04	935649	519.17

1.4.A.DM

3: UV Detector: 214

8.807e-1
Range: 8.806e-1

(3)
99%
551.1(63%)
2.15
14111.0801

AU

6.0e-1

4.0e-1

2.0e-1

0.0

0.50   1.00   1.50   2.00   2.50   3.00   3.50   Time

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.93	23	0.16	1517	551.15
2	2.08	128	0.90	7483	551.15
3	2.15	14111	98.65	872485	551.15
4	2.18	41	0.29	2598	551.15
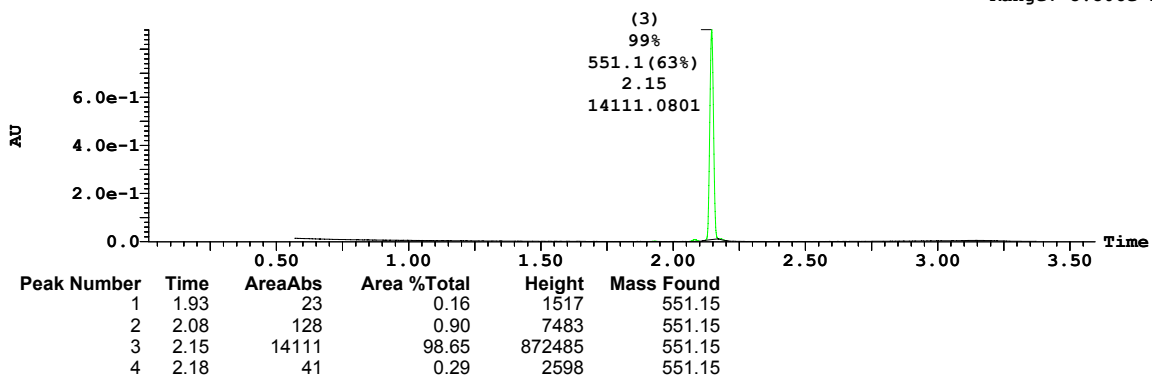
1.4.A.CM

3: UV Detector: 214

8.938e-1
Range: 8.937e-1

(4)
99%
548.2(57%)
1.88
14167.2305

AU

6.0e-1

4.0e-1

2.0e-1

0.0

0.50   1.00   1.50   2.00   2.50   3.00   3.50   Time

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.21	66	0.47	4709	
2	1.73	29	0.20	1648	548.20
4	1.88	14167	99.17	887474	548.20
5	1.99	24	0.17	1451	548.20
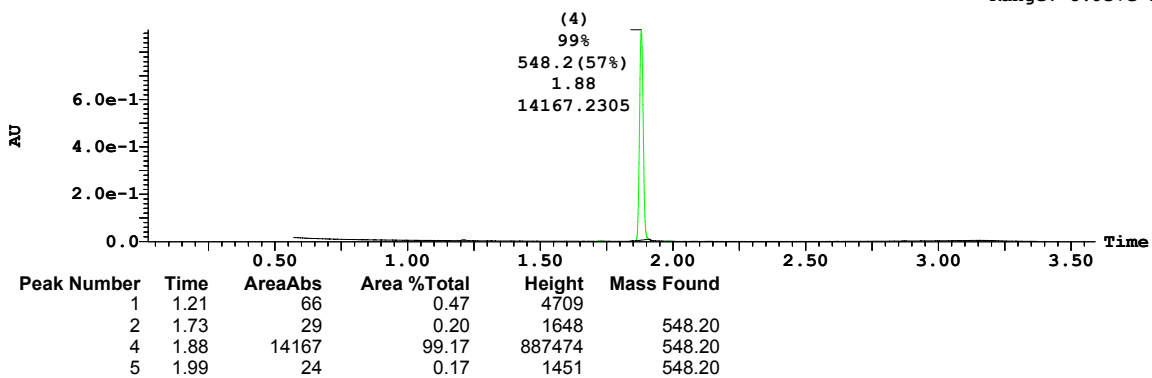
1.4.A.EM

3: UV Detector: 214

8.485e-1
Range: 8.484e-1

(3)
100%
642.2(60%)
2.35
14319.8701

AU

6.0e-1

4.0e-1

2.0e-1

0.0

0.50   1.00   1.50   2.00   2.50   3.00   3.50   Time

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.73	19	0.13	1170	
2	2.19	39	0.27	2085	642.22
3	2.35	14320	99.60	842186	642.22
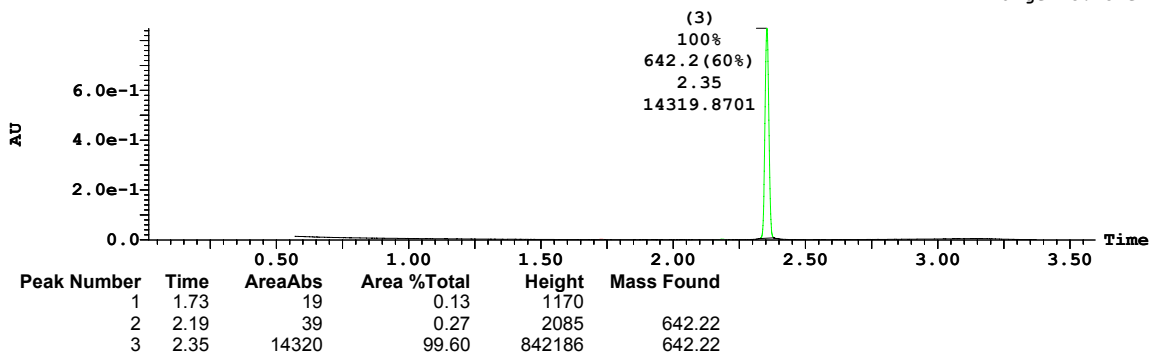
1.4.A.GM

6.582e-1
Range: 6.581e-1
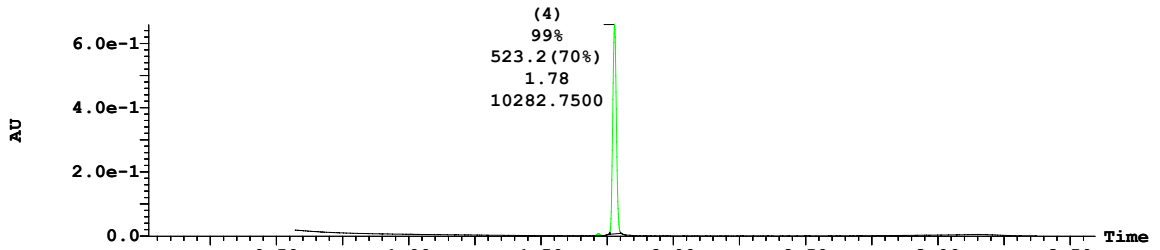
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.01	15	0.14	963	
2	1.63	13	0.13	754	523.17
3	1.72	79	0.76	5337	523.17
4	1.78	10283	98.97	651295	523.17

1.4.B.GN

3: UV Detector: 214

9.488e-1
Range: 9.488e-1
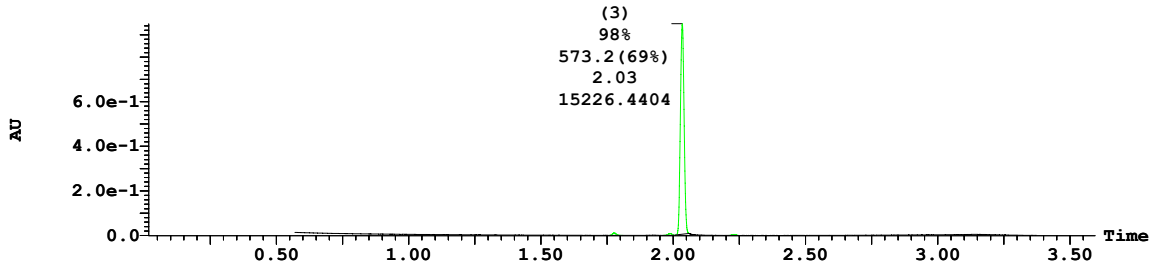
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.78	173	1.11	10648	573.17
2	1.99	131	0.84	7993	573.17
3	2.03	15226	97.58	943099	573.17
5	2.23	73	0.47	4394	573.17

1.4.B.HN

3: UV Detector: 214

8.517e-1
Range: 8.517e-1
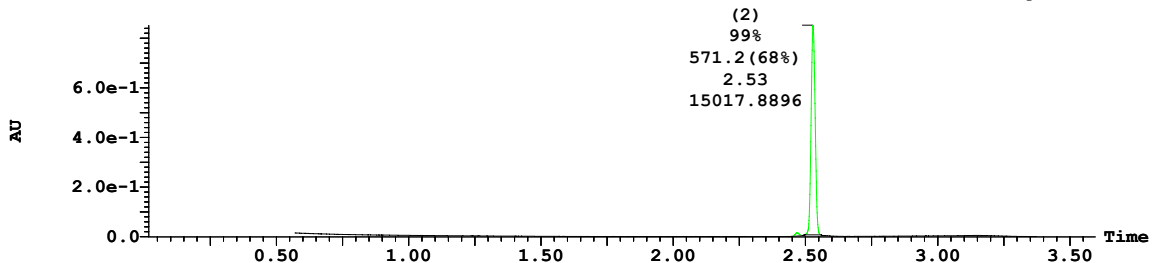
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.47	199	1.31	12483	571.19
2	2.53	15018	98.69	844503	571.19

202

1.4.B.IN

3: UV Detector: 214

1.073
Range: 1.073

(2)
100%
595.2(67%)
2.34
17930.5703

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.14	30	0.17	1821	595.15
2	2.34	17931	99.83	1062637	595.15
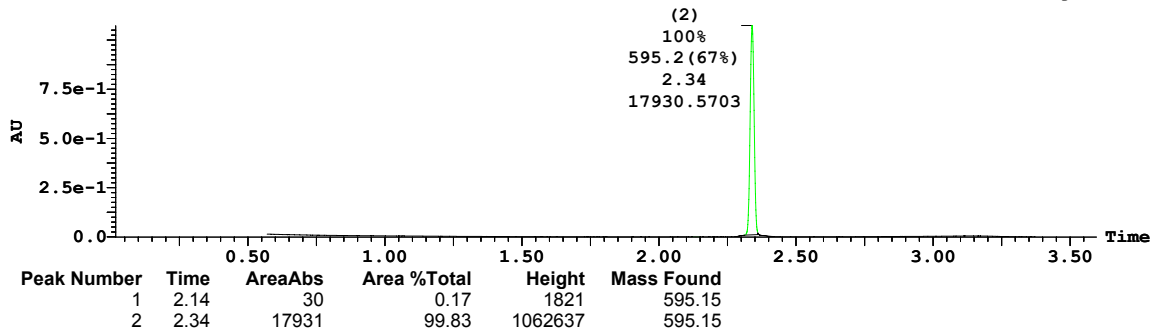
1.4.B.JN

3: UV Detector: 214

7.611e-1
Range: 7.611e-1

(3)
87%
587.2(69%)
2.15
12551.0703

(2);9%;587.2(69%);2.11;1270.1000

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.10	539	3.76	45962	587.18
2	2.11	1270	8.84	77830	587.18
3	2.15	12551	87.40	755170	587.18
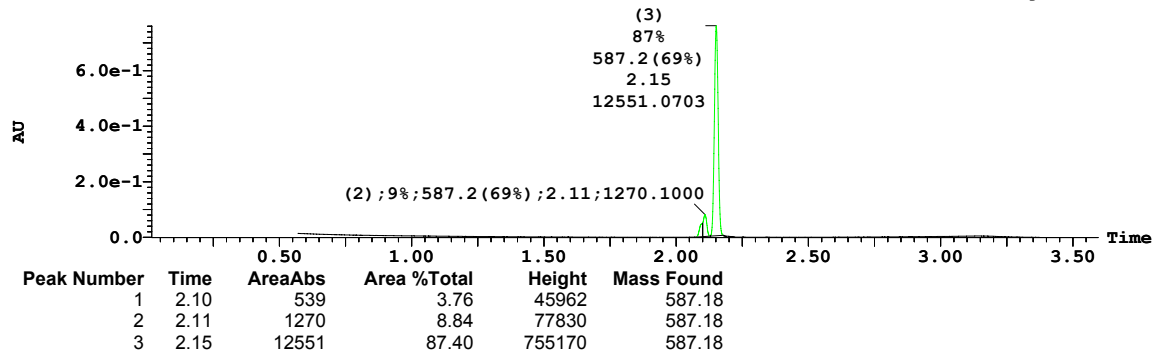
1.4.B.DN

3: UV Detector: 214

3.959e-1
Range: 3.959e-1

(2)
100%
601.1(64%)
2.35
6746.0601

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.32	24	0.36	2479	601.14
2	2.35	6746	99.64	393256	601.14

203

1.4.B.GO

9.585e-1
Range: 9.585e-1

(3)
99%
523.2(68%)
1.88
15404.6201

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
2	1.85	97	0.62	6644	523.17
3	1.88	15405	98.86	950978	523.17
4	2.09	81	0.52	4397	523.17
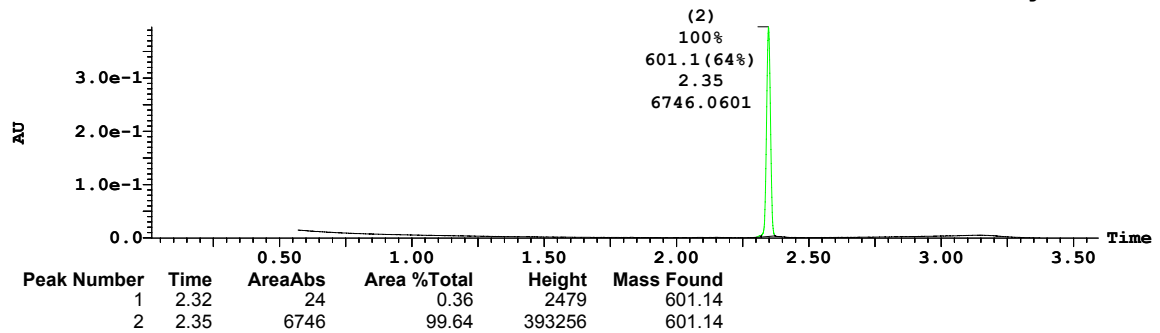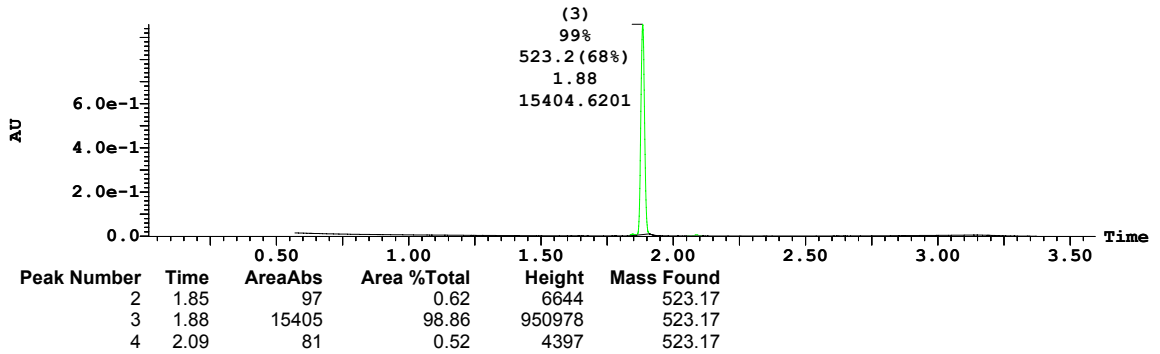
1.4.B.HO

3: UV Detector: 214

9.188e-1
Range: 9.188e-1

(2)
100%
521.2(67%)
2.41
15659.4902

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.21	34	0.22	1929	521.19
2	2.41	15659	99.78	912164	521.19
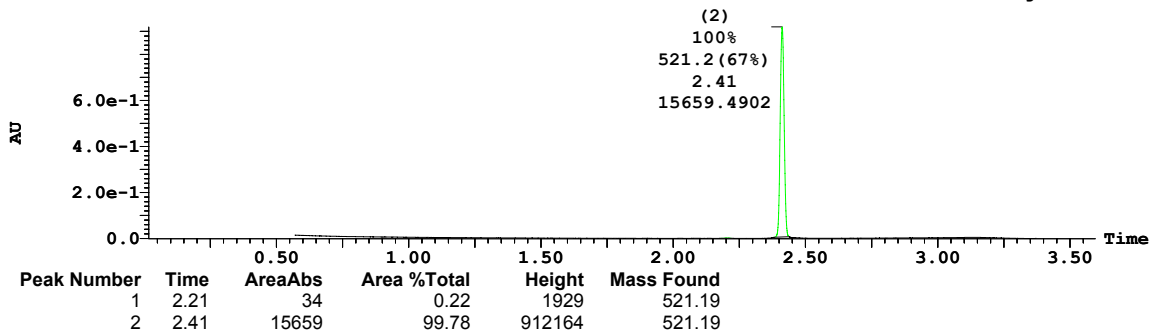
1.4.B.IO

3: UV Detector: 214

1.088
Range: 1.088
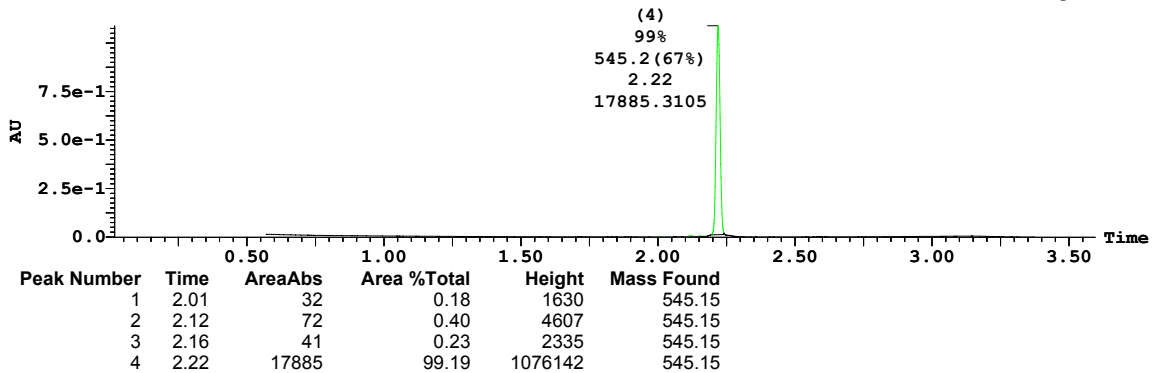
(4)
99%
545.2(67%)
2.22
17885.3105

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.01	32	0.18	1630	545.15
2	2.12	72	0.40	4607	545.15
3	2.16	41	0.23	2335	545.15
4	2.22	17885	99.19	1076142	545.15

1.4.B.JO

8.979e-1
Range: 8.979e-1

(4)
99%
537.2(69%)
2.03
15421.0195
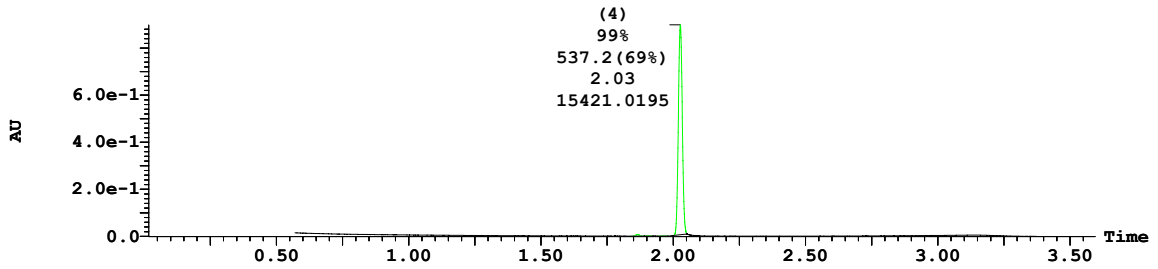
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.87	104	0.67	6494	537.18
2	1.91	36	0.23	2232	537.18
3	1.96	27	0.17	1490	537.18
4	2.03	15421	98.93	891411	537.18

1.4.B.DO

9.422e-1
Range: 9.421e-1

(3)
98%
551.1(62%)
2.21
15978.5596

2.19
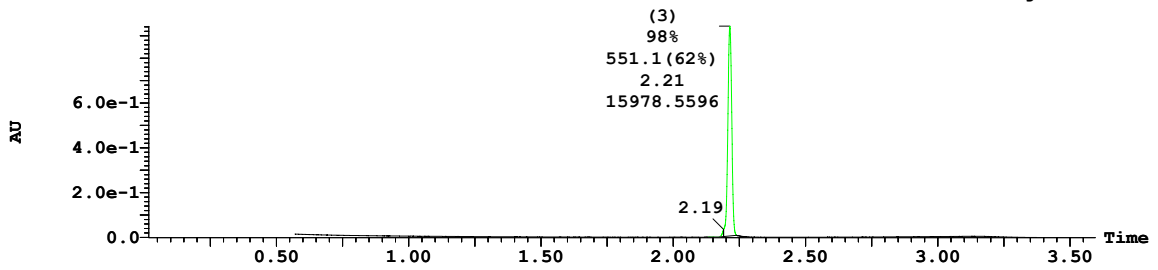
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.15	18	0.11	1127	551.15
2	2.19	280	1.72	40082	551.15
3	2.21	15979	98.17	935646	551.15

1.4.B.GM

9.768e-1
Range: 9.768e-1

(3)
99%
523.2(70%)
1.88
15587.5801
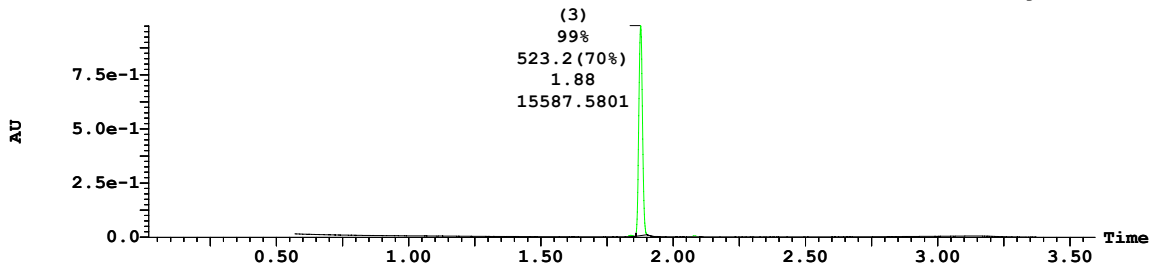
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
2	1.84	82	0.52	5781	523.17
3	1.88	15588	99.06	969490	523.17
4	2.08	66	0.42	3954	523.17

1.4.B.HM

3: UV Detector: 214

9.301e-1
Range: 9.301e-1

(1)
100%
521.2(69%)
2.40
15727.8604

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.40	15728	100.00	922848	521.19
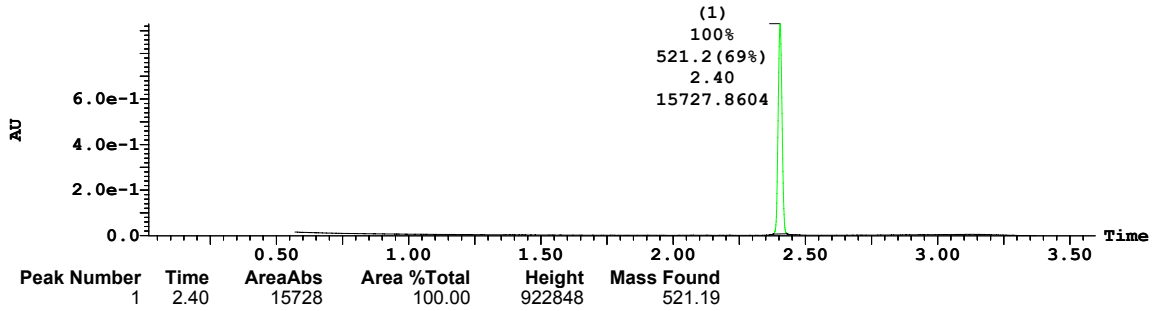
1.4.B.IM

3: UV Detector: 214

1.11
Range: 1.11

(5)
99%
545.2(67%)
2.21
18207.9199

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.87	21	0.11	1282	
2	2.00	31	0.17	1790	545.15
3	2.12	52	0.28	3431	545.15
4	2.15	124	0.67	8627	545.15
5	2.21	18208	98.77	1097910	545.15
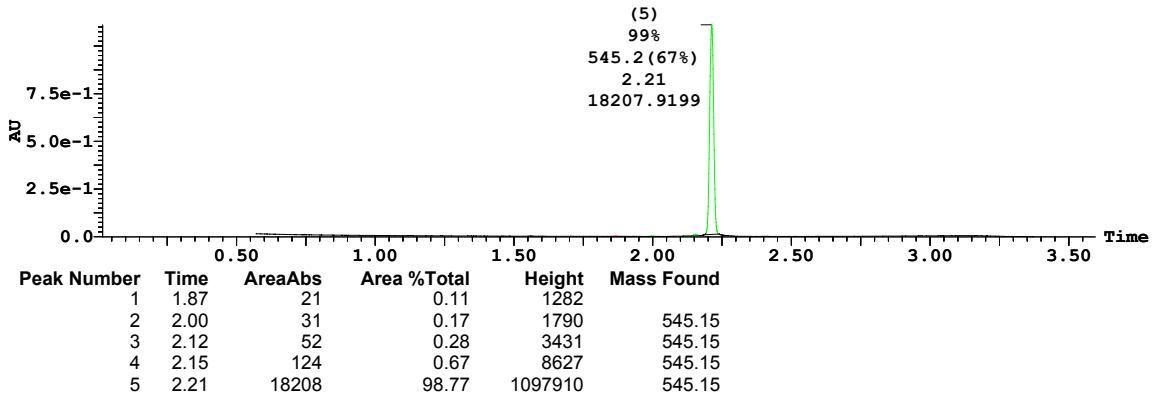
1.4.B.JM

3: UV Detector: 214

9.231e-1
Range: 9.231e-1
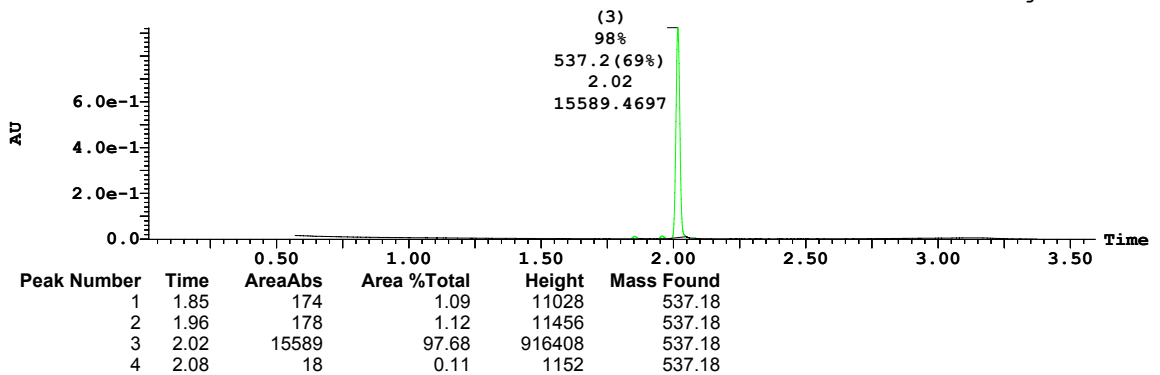
(3)
98%
537.2(69%)
2.02
15589.4697

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.85	174	1.09	11028	537.18
2	1.96	178	1.12	11456	537.18
3	2.02	15589	97.68	916408	537.18
4	2.08	18	0.11	1152	537.18

1.4.B.DM

9.038e-1
Range: 9.037e-1

(4)
98%
551.1(51%)
2.21
14956.1104
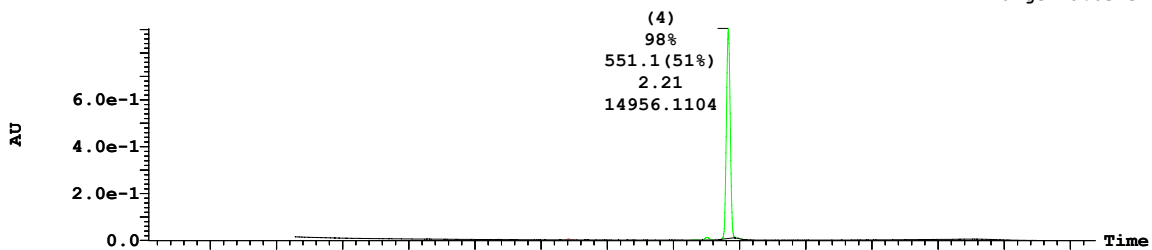
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.60	44	0.29	2941	
2	2.08	27	0.18	1480	551.15
3	2.13	199	1.31	11705	551.15
4	2.21	14956	98.06	895659	551.15
5	2.24	25	0.17	1895	551.15

1.4.B.GQ

1.077
Range: 1.077

(2)
99%
539.1(53%)
2.00
17266.5605
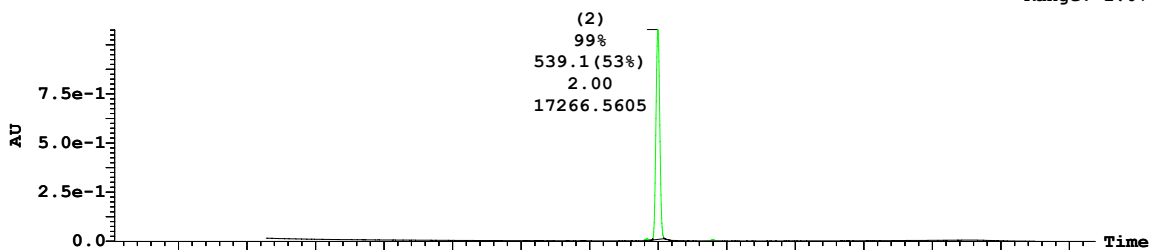
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.96	102	0.59	7217	539.14
2	2.00	17267	98.90	1067426	539.14
3	2.20	90	0.51	5166	539.14

1.4.B.HQ

9.773e-1
Range: 9.772e-1

(4)
95%
537.2(50%)
2.51
17320.2305

(2);3%;537.2(49%);2.37;515.3100
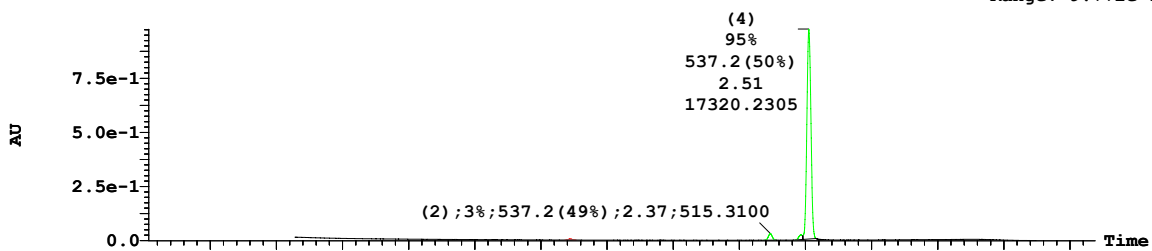
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.61	80	0.44	4707	
2	2.37	515	2.82	30224	537.16
3	2.48	342	1.87	21551	537.16
4	2.51	17320	94.87	970029	537.16

1.4.B.IQ

1.158
Range: 1.158

(3)
100%
561.1(50%)
2.32
19389.3809

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	2.11	30	0.16	1891	561.12
2	2.27	38	0.19	2481	561.12
3	2.32	19389	99.65	1145688	561.12
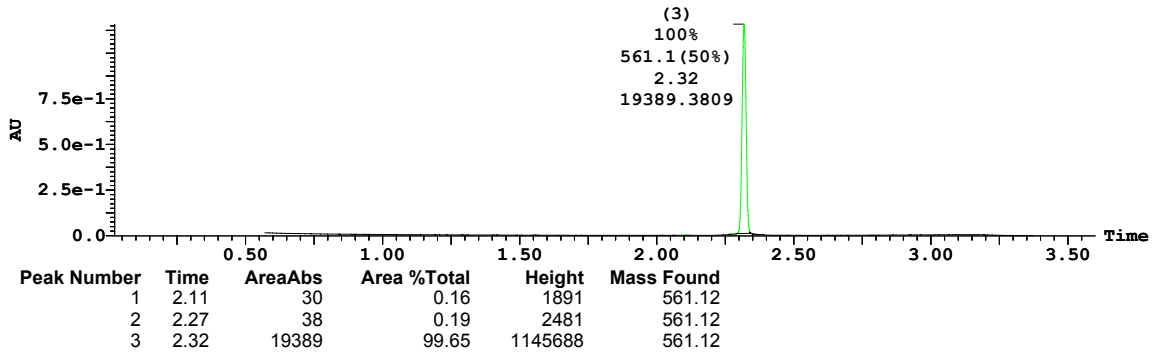
1.4.B.JQ

3: UV Detector: 214

9.273e-1
Range: 9.273e-1

(4)
93%
553.2(52%)
2.13
15813.9297

(2);6%;553.2(52%);2.04;1043.7000

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.61	32	0.19	2050	
2	2.04	1044	6.15	62625	553.15
3	2.08	90	0.53	6054	553.15
4	2.13	15814	93.13	920481	553.15
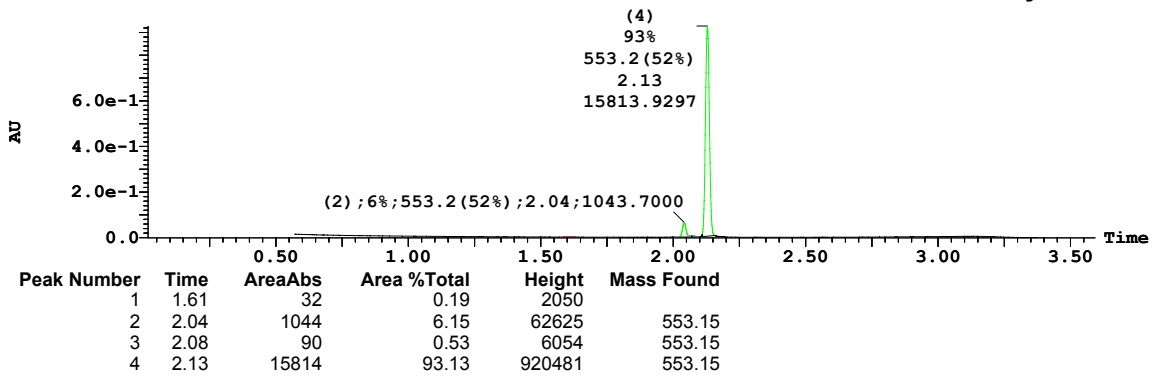
1.4.B.DQ

3: UV Detector: 214

9.446e-1
Range: 9.446e-1

(3)
97%
567.1(5%)
2.32
16001.3896

(2);3%;567.1(5%);2.17;492.6800

Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.79	19	0.11	1463	
2	2.17	493	2.98	29134	567.12
3	2.32	16001	96.90	936938	567.12
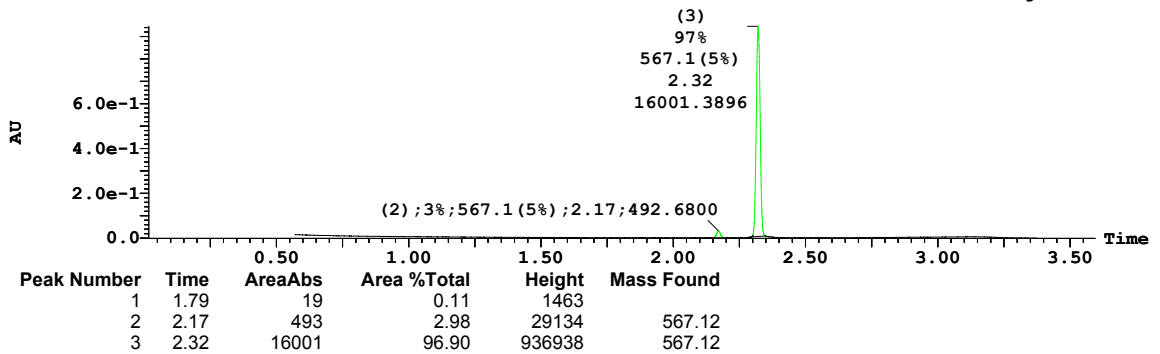
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[1]   SYBYL 8.0, The Tripos Associates, St. Louis MO, 2008.

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[4]   Cruciani, G., Meniconi, M., Carosati, E., Zamora, I., Mannhold, R. VOLSURF: A Tool for Drug ADME-Properties Prediction. In: *Methods and Principles in Medicinal Chemistry*. Eds. van de Waterbeemd, H., Lennernäs, H., Artursson, P. (Wiley-VCH Verlag GmbH & Co., Weinheim, 2003).

[5]   Pearlman, R. S.; Smith, K. M. Metric Validation and the Receptor-Relevant Subspace Concept. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 28-35.

4.2: Experimental for Chapter 2

General Procedure A: preparation of 3-component one-pot sequential reaction (sulfonylation, aza-Michael, and intramolecular S$_N$Ar). To a vigorously stirred solution of amine (0.564 mmol, 1.2 equiv.) and Et$_3$N (0.940 mmol, 2 equiv.) in THF (0.94 mL, 0.5 M) in a microwave vial was added benzenesulfonyl chloride (0.470 mmol, 1 equiv.) at room temperature dropwise, and the reaction was stirred for 1.5 hours. Upon disappearance of sulfonyl chloride, *o*-siloxy benzyl acetate (0.940 mmol, 2 equiv.) and TBAF (1.410 mmol, 3 equiv.) were added to the reaction mixture. The vial was quickly sealed and stirred for 40 minutes under microwave irradiation at 100 °C. Upon completion of the reaction, the reaction was quenched with water and EtOAc, organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried (Na$_2$SO$_4$), concentrated under reduced pressure, subject to column chromatography to afford the product.

General Procedure B: preparation of 4-component one-pot sequential reaction (sulfonylation, aza-Michael, intramolecular S$_N$Ar, and intermolecular S$_N$Ar). To a vigorously stirred solution of amine (0.564 mmol, 1.2 equiv.) and Et$_3$N (0.940 mmol, 2 equiv.) in THF (0.94 mL, 0.5 M) in a microwave vial was added benzenesulfonyl chloride (0.100 g, 0.470 mmol) at room temperature dropwise, and the reaction was stirred for 1.5 hours. Upon disappearance of sulfonyl chloride, *o*-siloxy benzyl acetate (0.264 g, 0.940 mmol) and TBAF (1.410 mmol, 1.41 mL) were added to the reaction mixture. The vial was quickly sealed and stirred for 40 minutes under microwave irradiation at 100 °C. Then the

second amine (2.350 mmol, 5 equiv.) was added to the reaction mixture. The vial was quickly sealed and stirred for 1 hour under microwave irradiation at 100 °C. Upon completion of the reaction, the reaction was quenched with water and EtOAc, organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried (Na$_2$SO$_4$), concentrated under reduced pressure, subject to column chromatography to afford the product.

General Procedure C: preparation of 5-component one-pot sequential reaction (sulfonylation, aza-Michael, intramolecular S$_N$Ar, intermolecular S$_N$Ar, and Click). To a vigorously stirred solution of propargyl amine (0.564 mmol, 1.2 equiv.) and Et$_3$N (0.940 mmol, 2 equiv.) in THF (0.94 mL, 0.5 M) in a microwave vial was added benzenesulfonyl chloride (0.100 g, 0.470 mmol) at room temperature dropwise, and the reaction was stirred for 1.5 hours. Upon disappearance of sulfonyl chloride, *o*-siloxy benzyl acetate (0.264 g, 0.940 mmol) and TBAF (1.410 mmol, 1.41 mL) were added to the reaction mixture. The vial was quickly sealed and stirred for 40 minutes under microwave irradiation at 100 °C. Then the second amine (2.350 mmol, 5 equiv.), azide (0.940 mmol, 2 equiv.), CuI (0.141 mmol, 0.3 equiv.), and DBU (0.047 mmol, 0.1 equiv.) were added to the reaction mixture. The vial was quickly sealed and stirred for 1 hour under microwave irradiation at 100 °C. Upon completion of the reaction, the reaction was quenched with water and EtOAc, organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried (Na$_2$SO$_4$), concentrated under reduced pressure, subject to column chromatography to afford the product.

2-fluoro-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.6)
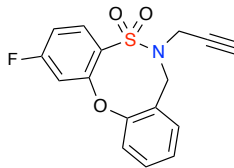
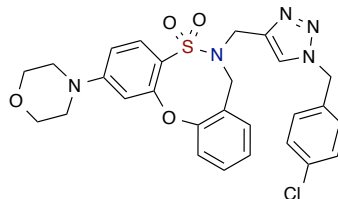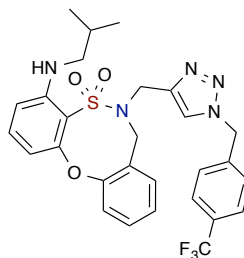According to general procedure **A**, **2.28.6** (148 mg, 99%) was isolated as a yellow solid.

mp 133–136 °C;

FTIR (thin film): 3288, 3095, 2931, 2118, 1916, 1592, 1584, 1489, 1476, 1456, 1418, 1341, 1326, 1269, 1156, 1077, 977, 884, 768, 666 cm^{-1};

^{1}H NMR (500 MHz, CDCl3) δ 7.66 (d, J = 8.50 Hz, 1H), 7.46 (d, J = 7.24 Hz, 1H), 7.35 (m, 2H), 7.16 (m, 1H), 6.63 (d, J = 3.15 Hz, 1H), 6.30 (dd, J = 6.59, 2.22 Hz, 1H), 5.58 (d, J = 15.19 Hz, 1H), 4.19 (d, J = 15.19 Hz, 1H), 4.00 (d, J = 17.84 Hz, 1H), 2.98 (dd, J = 14.73, 2.32 Hz, 1H), 2.24 (t, J = 2.41 Hz, 1H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 159.43, 156.99, 152.20, 131.83, 131.66 (d, $J_{C\text{-}F}$ = 21.22 Hz), 130.24, 129.55, 125.36, 122.40, 118.12, 107.47, 105.93, 47.81, 47.74, 35.29, 25.45;

HRMS calculated for C$_{16}$H$_{12}$FNO$_3$SNa (M+Na)$^+$ 340.0420; found 340.0417 (TOF MS ES$^+$).

6-butyl-2-fluoro-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.7)
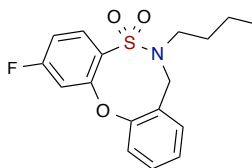
According to general procedure **A**, **2.28.7** (71 mg, 92%) was isolated as a white solid.

FTIR (thin film): 3270, 3130, 2930, 2871, 1591, 1474, 1413, 1334, 1271, 1181, 1158, 1069, 975, 763, 716, 658 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, J = 8.8, 6.3 Hz, 1H), 7.47 (dd, J = 8.2, 1.2 Hz, 1H), 7.41 (td, J = 8.2, 7.7, 2.0 Hz, 1H), 7.31 (dd, J = 9.1, 2.4 Hz, 1H), 6.98 (ddd, J = 8.8, 7.8, 2.5 Hz, 1H), 5.57 (d, J = 15.3 Hz, 1H), 3.95 (d, J = 15.3 Hz, 1H), 2.96 (dtd, J = 13.9, 8.1, 7.4, 1.5 Hz, 1H), 2.25 (ddd, J = 13.6, 8.3, 4.8 Hz, 1H), 1.65 – 1.45 (m, 3H), 1.41 – 1.15 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.59 (d, $^{1}J_{C\text{-}F}$ = 256.0 Hz), 158.98, 156.85 (d, $^{2}J_{C\text{-}F}$ = 11.1 Hz), 132.29 (d, $^{3}J_{C\text{-}F}$ = 10.4 Hz), 131.49, 130.78 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.61, 130.32, 112.55 (d, $^{5}J_{C\text{-}F}$ = 21.7 Hz), 112.25 (d, $^{6}J_{C\text{-}F}$ = 23.7 Hz), 77.16, 47.58, 44.66, 29.75, 19.77, 13.83.

HRMS calculated for C$_{17}$H$_{19}$FNO$_3$S (M+H)$^{+}$ 336.1070; found 336.1019 (TOF MS ES^{+}).

6-benzyl-2-fluoro-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.8)
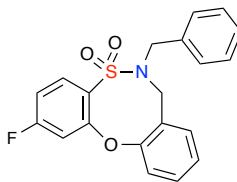
According to general procedure **A**, **2.28.8** (82 mg, 47%) was isolated as a white solid.

mp 149–151 °C;

FTIR (thin film): 3100, 3032, 2933, 1957, 1588, 1471, 1452, 1338, 1272, 1211, 1163, 1143, 1066, 971, 885, 770, 752, 661 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.00 (dd, *J* = 8.8, 6.3 Hz, 1H), 7.52 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.41 – 7.31 (m, 6H), 7.21 (td, *J* = 7.4, 1.2 Hz, 1H), 7.07 – 6.99 (m, 2H), 5.51 (dd, *J* = 15.3, 1.6 Hz, 1H), 4.46 (d, *J* = 14.7 Hz, 1H), 3.72 (d, *J* = 15.4 Hz, 1H), 3.19 (d, *J* = 14.8 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.60 (d, $^1J_{C-F}$ = 256.4 Hz), 159.00, 156.86 (d, $^2J_{C-F}$ = 11.2 Hz), 135.00, 132.07 (d, $^3J_{C-F}$ = 10.4 Hz), 131.73, 130.69 (d, $^4J_{C-F}$ = 3.8 Hz), 130.58, 129.84, 128.77, 128.40, 128.10, 125.85, 122.21, 112.58 (d, $^5J_{C-F}$ = 21.8 Hz), 112.20 (d, $^6J_{C-F}$ = 23.8 Hz), 48.57, 46.81.

HRMS calculated for C$_{20}$H$_{17}$FNO$_3$S (M+H)$^+$ 370.0913; found 370.0878 (TOF MS ES$^+$).

2-fluoro-6-(2-hydroxyethyl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.9)
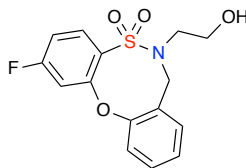
According to general procedure **A**, **2.28.9** (11 mg, 15%) was isolated as a white solid.

mp 165–167 °C;

FTIR (thin film): 3502, 3114, 3081, 2977, 2871, 1925, 1591, 1582, 1473, 1406, 1315, 1270, 1174, 1155, 1063, 995, 971, 892, 852, 793, 717, 661 cm^{-1};

¹H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 8.7, 6.3 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.42 (td, *J* = 8.2, 7.7, 1.9 Hz, 1H), 7.34 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.27 – 7.24 (m, 2H), 7.21 (td, *J* = 7.4, 1.2 Hz, 1H), 7.00 (ddd, *J* = 8.8, 7.8, 2.4 Hz, 1H), 5.62 (d, *J* = 16.2 Hz, 1H), 4.07 (d, *J* = 15.3 Hz, 1H), 3.85 – 3.71 (m, 2H), 2.96 (dddd, *J* = 15.0, 7.0, 4.1, 1.6 Hz, 1H), 2.61 (ddd, *J* = 15.1, 5.6, 3.8 Hz, 1H), 2.18 (dd, *J* = 6.7, 4.2 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 165.81 (d, $^1J_{C\text{-}F}$ = 256.8 Hz), 159.04, 157.05 (d, $^2J_{C\text{-}F}$ = 11.2 Hz), 132.37 (d, $^3J_{C\text{-}F}$ = 10.4 Hz), 132.00, 130.83, 130.12 (d, $^4J_{C\text{-}F}$ = 3.7 Hz), 130.07, 126.15, 122.37, 112.64 (d, $^5J_{C\text{-}F}$ = 21.8 Hz), 112.43 (d, $^6J_{C\text{-}F}$ = 23.8 Hz), 60.97, 49.35, 47.23.

**HRMS** calculated for $C_{15}H_{15}FNO_4S$ (M+H)$^+$ 324.0706; found 324.0691 (TOF MS ES$^+$).
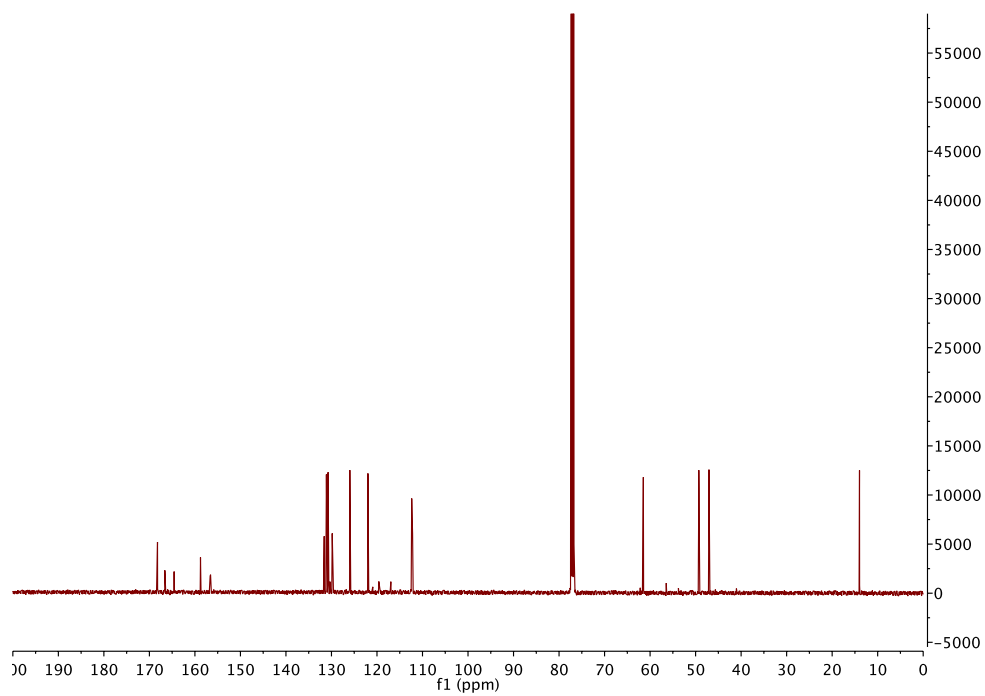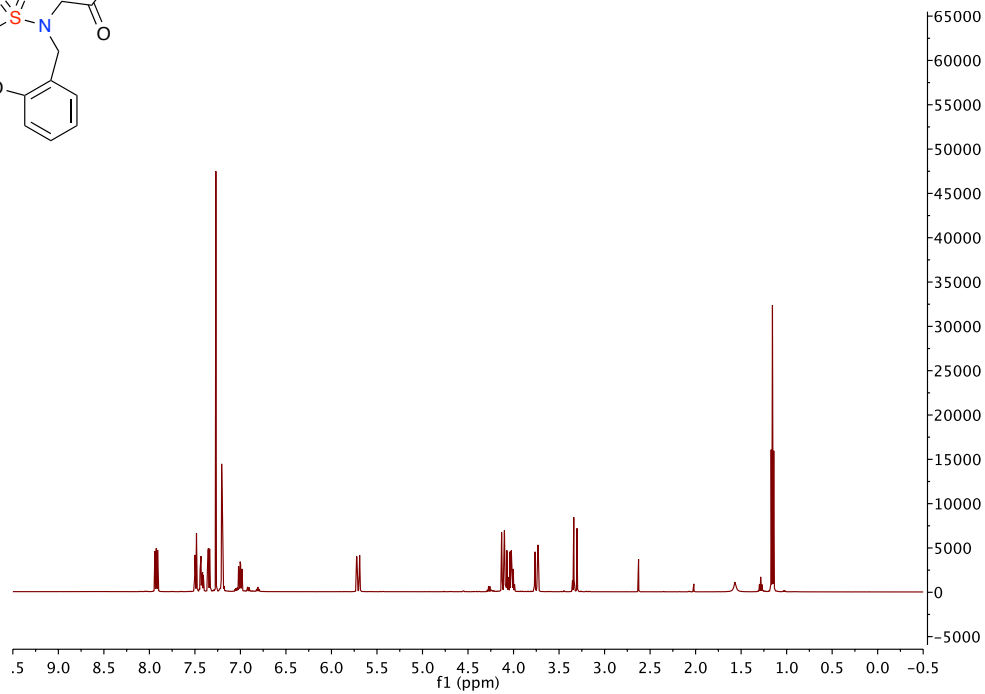

6-cyclopropyl-2-fluoro-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.10)
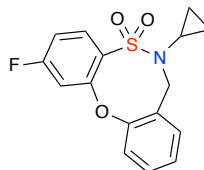
According to general procedure **A**, **2.28.10** (120 mg, 80%) was isolated as yellow solid.

mp 180–183 °C;

FTIR (thin film): 3081, 3024, 2988, 2950, 1934, 1586, 1471, 1412, 1336, 1275, 1212, 1159, 1091, 974, 888, 840, 827, 759, 701, 659 cm^{-1};

¹H NMR (400 MHz, Chloroform-*d*) δ 8.00 (dd, *J* = 8.7, 6.3 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.36 – 7.28 (m, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.01 (td, *J* = 8.3, 2.4

Hz, 1H), 5.57 (d, $J = 14.8$ Hz, 1H), 3.94 (d, $J = 14.8$ Hz, 1H), 1.37 – 1.23 (m, 2H), 0.72 –

0.62 (m, 2H), 0.46 (tt, $J = 7.1$, 3.9 Hz, 1H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 165.86 (d, $J = 256.5$ Hz), 158.95, 157.03 (d, $J =$

11.1 Hz), 133.11 (d, $J = 10.4$ Hz), 132.03, 130.52, 130.26, 129.80 (d, $J = 3.7$ Hz), 126.12,

122.03, 112.77 (d, $J = 21.7$ Hz), 112.27 (d, $J = 23.6$ Hz), 51.12, 27.92, 10.33, 5.38.

HRMS calculated for $C_{16}H_{14}FNO_3SNa$ (M+Na)$^+$ 342.0576; found 342.0556 (TOF MS ES$^+$).

ethyl 2-(2-fluoro-5,5-dioxidodibenzo[*b,g*][1,4,5]oxathiazocin-6(7*H*)-yl)acetate
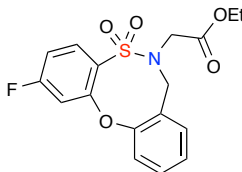
(2.28.11)

According to general procedure **A**, **2.28.11** (15 mg, 9%) was isolated as clear/yellow solid.

mp 180–182 °C;

FTIR (thin film): 3103, 2987, 1746, 1591, 1583, 1474, 1413, 1336, 1206, 1147, 1082, 975,

938, 770, 745, 660 cm^{-1};

¹H NMR (500 MHz, Chloroform-*d*) δ 7.92 (dd, $J = 8.8$, 6.3 Hz, 1H), 7.49 (dd, $J = 8.2$, 0.8

Hz, 1H), 7.45 – 7.40 (m, 1H), 7.34 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.22 – 7.19 (m, 2H), 7.00 (ddd,

$J = 8.8$, 7.7, 2.4 Hz, 1H), 5.71 (dd, $J = 15.4$, 1.5 Hz, 1H), 4.14 – 3.98 (m, 3H), 3.75 (dd, $J =$

17.7, 1.5 Hz, 1H), 3.32 (d, $J = 17.7$ Hz, 1H), 1.16 (t, $J = 7.2$ Hz, 3H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 168.22, 165.59 (d, *J* = 256.6 Hz), 158.77, 156.60 (d, *J* = 11.2 Hz), 131.63 (d, *J* = 10.4 Hz), 131.11, 131.07 (d, *J* = 3.7 Hz), 130.75, 129.83, 125.97, 121.99, 112.46 (d, *J* = 22.1 Hz), 112.28 (d, *J* = 24.1 Hz), 61.48, 49.30, 47.06, 13.99.

HRMS calculated for $C_{17}H_{16}FNNaO_5S$ (M+Na)⁺ 388.0631; found 388.0620 (TOF MS ES⁺).

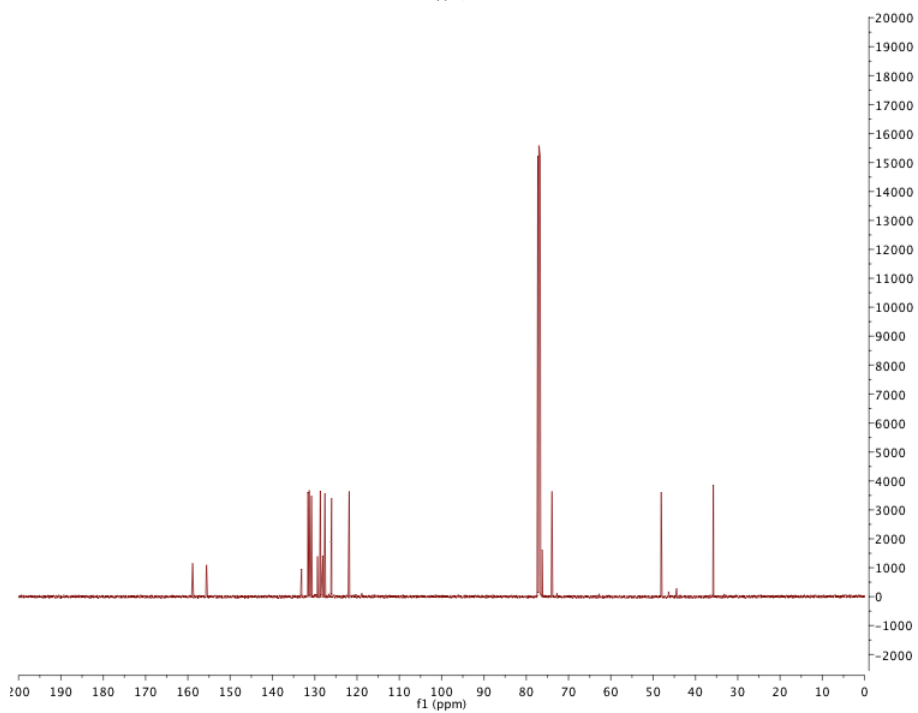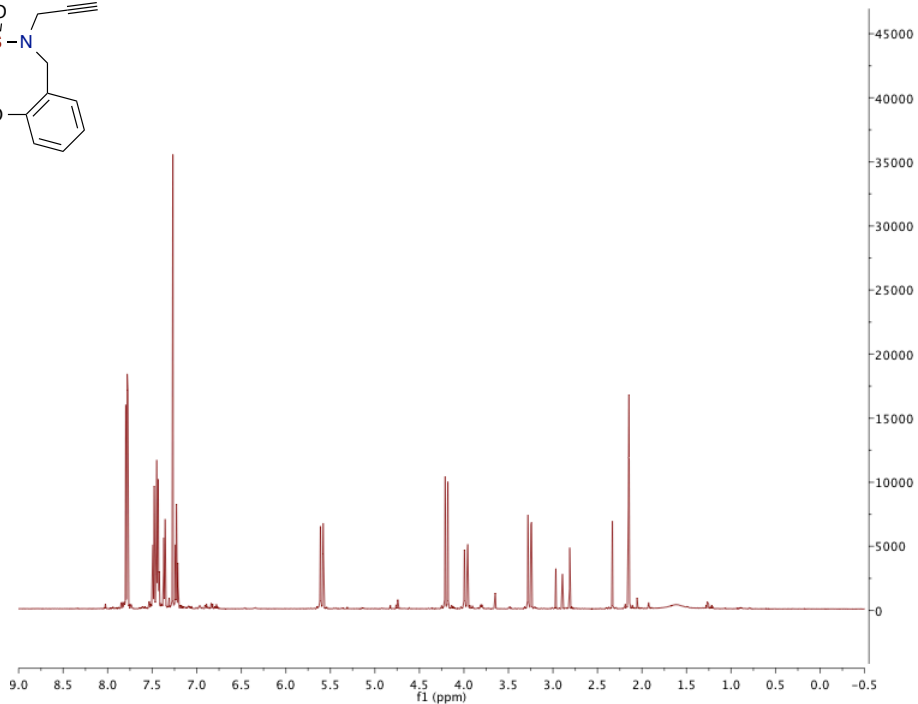**4-fluoro-6-(2-hydroxyethyl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.12)**
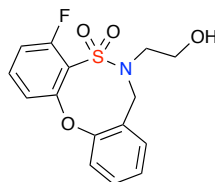
According to general procedure **A**, **2.28.12** (17 mg, 11%) was isolated as yellow oil.

FTIR (thin film): 3526, 3086, 2939, 1600, 1575, 1490, 1456, 1340, 1229, 1156, 1107, 1000, 890, 808, 787, 742, 706, 652 cm⁻¹;

¹H NMR (500 MHz, Chloroform-*d*) δ 7.58 – 7.50 (m, 2H), 7.47 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.42 (td, *J* = 7.8, 1.9 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.21 (td, *J* = 7.4, 1.2 Hz, 1H), 7.05 (ddd, *J* = 9.7, 8.4, 1.2 Hz, 1H), 5.62 (d, *J* = 15.3 Hz, 1H), 4.09 (d, *J* = 15.3 Hz, 1H), 3.88 – 3.77 (m, 2H), 3.12 (dddd, *J* = 15.1, 6.4, 4.4, 1.6 Hz, 1H), 2.67 (ddd, *J* = 15.0, 5.6, 4.1 Hz, 1H), 2.21 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 160.12 (d, $^1J_{C\text{-}F}$ = 262.8 Hz), 158.85, 156.78, 134.36 (d, $^2J_{C\text{-}F}$ = 10.8 Hz), 131.31 , 130.47 , 130.13 , 125.80 , 122.51 (d, $^3J_{C\text{-}F}$ = 11.7 Hz), 121.93 , 119.57 (d, $^4J_{C\text{-}F}$ = 3.7 Hz), 114.66 (d, $^5J_{C\text{-}F}$ = 24.4 Hz), 60.87 , 49.40 , 47.26

**HRMS** calculated for $C_{15}H_{15}FNO_4S$ (M+H)$^+$ 324.0706; found 324.0661 (TOF MS ES$^+$).

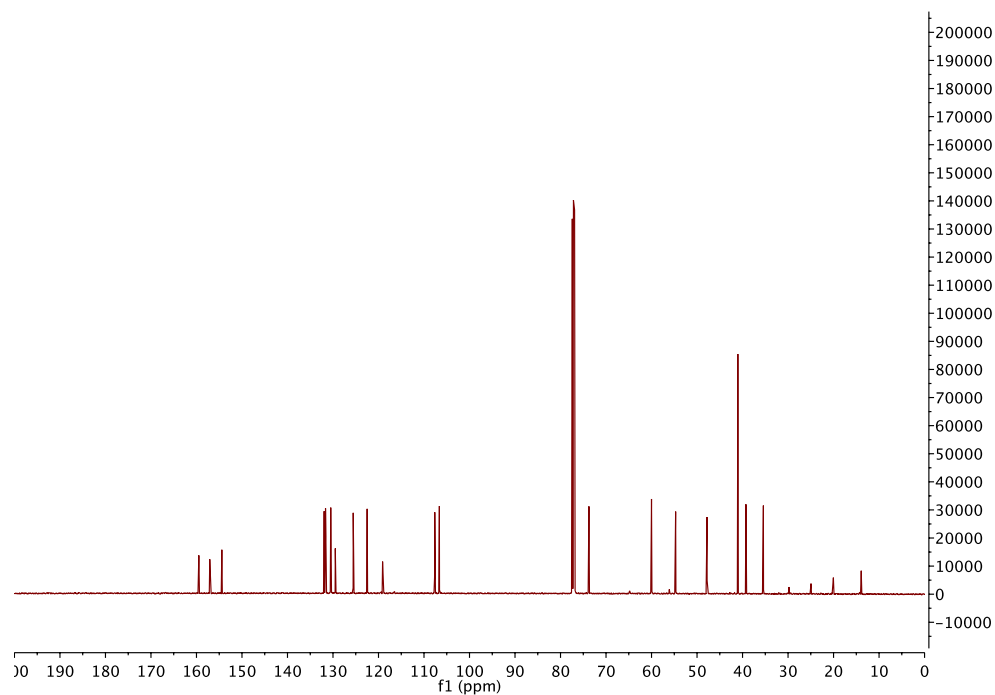**2-bromo-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.13)**
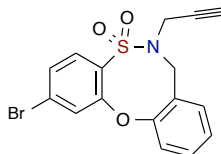
According to general procedure **A**, **2.28.13** (276 mg, 99%) was isolated as white solid.

mp 139–142 °C;

FTIR (thin film): 3092, 3089, 2354, 2334, 2123, 1569, 1452, 1390, 1352, 1344, 1164 cm^{-1}

^{1}H NMR (500 MHz, CDCl3) δ 7.78 (dd, *J* = 5.1, 6.9 Hz, 2H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.44 (ddt, *J* = 2.1, 4.2, 8.3 Hz, 2H), 7.36 (dd, *J* = 1.6, 7.4 Hz, 1H), 7.23 (td, *J* = 1.2, 7.4 Hz, 1H), 5.60 (d, *J* = 15.4 Hz, 1H), 4.20 (d, *J* = 15.3 Hz, 1H), 3.98 (ddd, *J* = 1.3, 2.5, 17.3 Hz, 1H), 3.26 (dd, *J* = 2.5, 17.3 Hz, 1H), 2.15 (t, *J* = 2. Hz, 5, 1H);

^{13}C NMR (126 MHz, CDCl3) δ 158.9, 155.6, 133.1, 131.6, 131.3, 130.8, 129.3, 128.7, 128.1, 127.6, 126.0, 121.8, 76.2, 73.9, 48.1, 35.8;

HRMS calculated for $C_{16}H_{12}BrNO_3SNa$ (M+Na)$^+$ 399.9619; found 399.9618 (TOF MS ES$^+$).
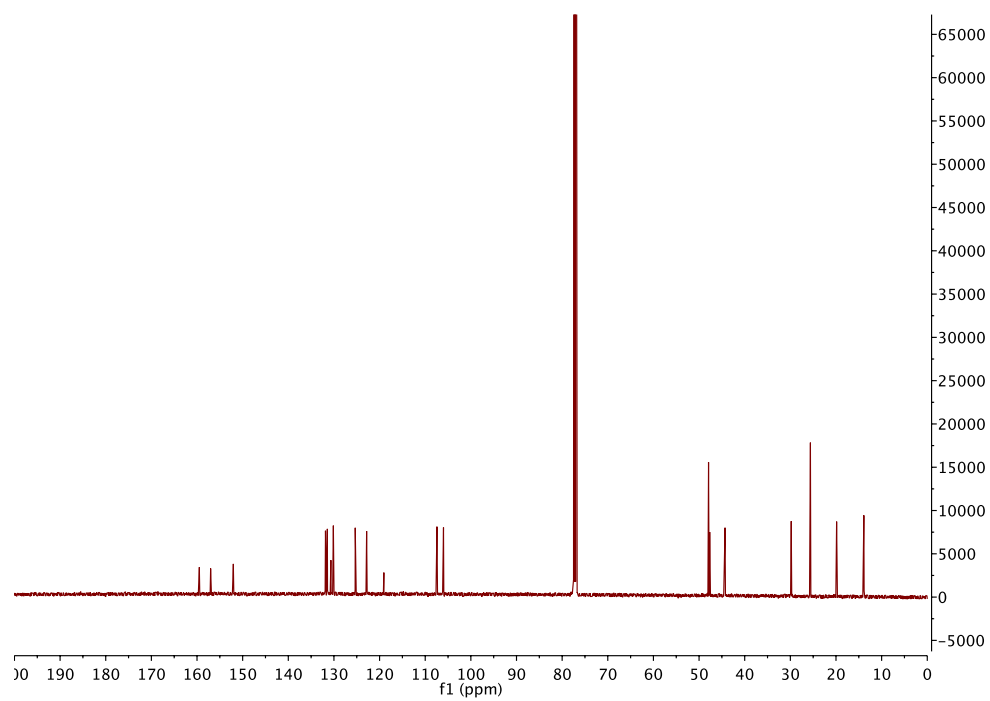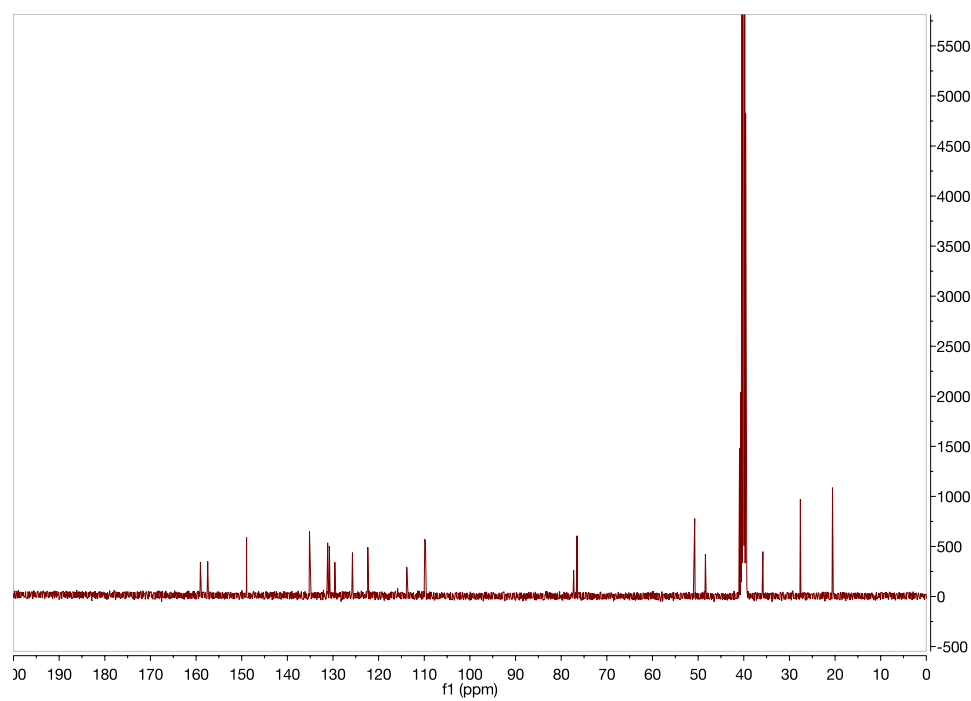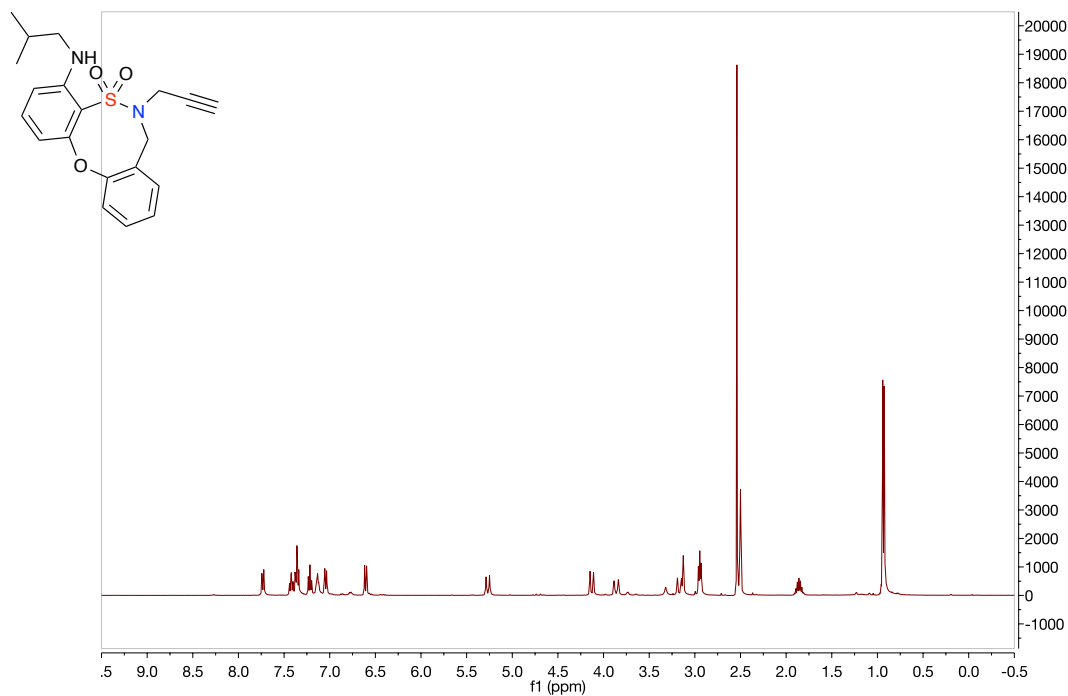
6-(prop-2-yn-1-yl)-2-(pyrrolidin-1-yl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.6)
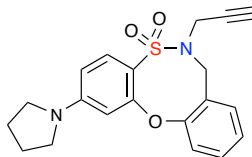
According to general procedure **B**, **2.29.6** (115.6 mg, 67%) was isolated as yellow solid.

mp 203–205 °C;

FTIR (thin film): 3304, 2926, 2871, 1595, 1541, 1512, 1483, 1438, 1393, 1326, 1251, 1218, 1182, 1139, 1076, 1037, 955, 905, 830, 756, 737, 666 cm^{-1};

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 8.9 Hz, 1H), 7.43 (td, *J* = 7.8, 1.8 Hz, 1H), 7.37 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.25 – 7.20 (m, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.39 (dd, *J* = 8.9, 2.3 Hz, 1H), 5.30 (d, *J* = 15.1 Hz, 1H), 4.12 (d, *J* = 15.1 Hz, 1H), 3.86 (dd, *J* = 17.5, 1.5 Hz, 1H), 3.33 (q, *J* = 5.9, 5.5 Hz, 4H), 3.19 (t, *J* = 2.5 Hz, 1H), 2.96 (dd, *J* = 17.5, 2.4 Hz, 1H), 2.01 – 1.92 (m, 4H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.43, 156.99, 152.20, 131.83, 131.66, 130.24, 129.54, 125.36, 122.40, 120.14, 118.11, 116.09, 107.47, 105.93, 73.53, 47.81, 35.29, 25.45.

HRMS calculated for C$_{20}$H$_{21}$N$_2$O$_3$S (M+H)$^+$ 369.1273; found 369.1239

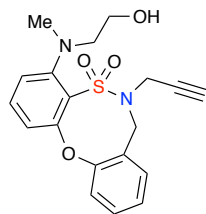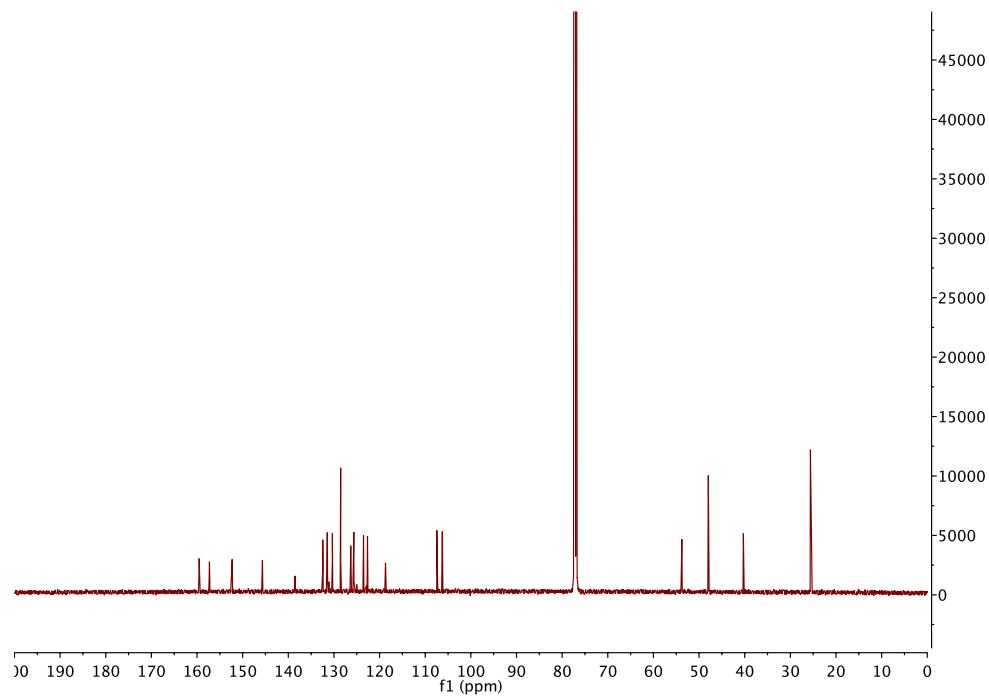**2-morpholino-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.7)**
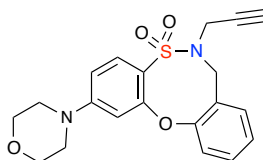
According to general procedure **B**, **2.29.7** (174 mg, 96%) was isolated as yellow solid.

mp 208–210 °C;

FTIR (thin film): 3210, 3025, 2941, 1595, 1487, 1453, 1333, 1269, 1218, 1169, 1117, 1082, 1033, 908, 756 cm^{-1};

^{1}H NMR (500 MHz, CDCl3) δ 7.75 (d, J = 9.00 Hz, 1H), 7.46 (d, J = 8.32 Hz, 1H), 7.40 (m, 2H), 7.21 (t, J = 7.71 Hz, 1H), 7.01 (d, J = 2.47 Hz, 1H), 6.68 (dd, J = 8.63, 2.47 Hz, 1H), 4.22 (d, J = 14.55 Hz, 1H), 4.03 (d, J = 16.98 Hz, 1H), 3.89 (t, J = 5.25 Hz, 4H), 3.33 (t, J = 4.85 Hz, 4H), 3.08 (dd, J = 16.98, 2.83 Hz, 1H), 2.25 (t, J = 2.53 Hz, 1H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 159.30, 156.84, 155.73, 131.87, 131.54, 130.41, 129.52, 125.58, 122.19, 110.05, 109.05, 77.27, 77.22, 77.02, 76.95, 76.77, 73.68, 66.43, 47.79, 47.58, 35.43;

**HRMS** calculated for C$_{20}$H$_{21}$N$_2$O$_4$S (M+H)$^+$ 385.1222; found 385.1191

2-((2-hydroxyethyl)(methyl)amino)-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.8)
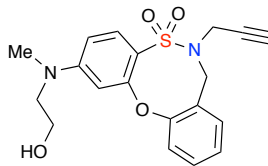
According to general procedure **B**, **2.29.8** (25 mg, 28%) was isolated as white/yellow solid.

mp 148–150 °C;

FTIR (thin film): 3491, 3292, 3260, 2912, 2863, 2131, 1597, 1584, 1435, 1312, 1229, 1182, 1142, 1062, 946, 989, 842, 780, 755, 720 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (dd, J = 8.2, 1.1 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.37 (dd, J = 7.5, 1.8 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.09 (d, J = 2.5 Hz, 1H), 6.55 (dd, J = 9.0, 2.5 Hz, 1H), 5.31 (d, J = 15.0 Hz, 1H), 4.76 (s, 1H), 4.12 (d, J = 15.1 Hz, 1H), 3.87 (ddd, J = 17.4, 2.6, 1.2 Hz, 1H), 3.60 – 3.55 (m, 2H), 3.53 – 3.48 (m, 2H), 3.20 (t, J = 2.5 Hz, 1H), 3.04 (s, 3H), 2.96 (dd, J = 17.4, 2.4 Hz, 1H).

^{13}C NMR (101 MHz, DMSO) δ 158.88, 156.41, 154.10, 131.56, 130.58, 128.88, 125.40, 122.80, 117.49, 107.26, 106.20, 77.31, 76.05, 58.12, 53.94, 47.27, 40.43, 38.98, 34.93.

HRMS calculated for C$_{19}$H$_{21}$N$_2$O$_4$S (M+H)$^+$ 373.1222; found 373.1183

6-butyl-2-morpholino-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.9)
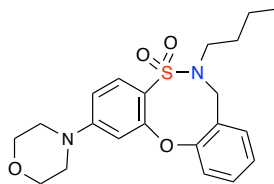
According to general procedure **B**, **2.29.9** (61 mg, 64%) was isolated as yellow oil.

FTIR (thin film): 2959, 2925, 2865, 1595, 1487, 1450, 1431, 1324, 1249, 1189, 1123, 1037, 977, 915, 896, 762, 716, 653 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.8 Hz, 1H), 7.48 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.40 (td, *J* = 7.7, 1.9 Hz, 1H), 7.24 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.19 (td, *J* = 7.3, 1.1 Hz, 1H), 7.02 (d, *J* = 2.5 Hz, 1H), 6.68 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.60 (d, *J* = 15.3 Hz, 1H), 3.94 (d, *J* = 15.3 Hz, 1H), 3.91 – 3.87 (m, 4H), 3.34 – 3.30 (m, 4H), 2.99 (dtd, *J* = 14.1, 8.1, 7.3, 1.4 Hz, 1H), 2.22 (ddd, *J* = 13.5, 8.3, 4.8 Hz, 1H), 1.66 – 1.50 (m, 2H), 1.42 – 1.21 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 159.37, 156.86, 155.57, 131.73, 131.54, 130.59, 130.29, 125.56, 123.44, 122.64, 110.14, 109.26, 66.62, 47.83, 47.61, 44.42, 29.79, 19.83, 13.87.

HRMS calculated for C$_{21}$H$_{27}$N$_2$O$_4$S (M+H)$^+$ 403.1692; found 403.1662 (TOF MS ES$^+$).

6-butyl-2-(pyrrolidin-1-yl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.10)
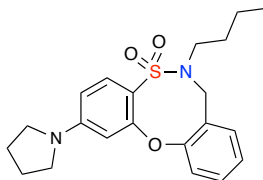
According to general procedure **B**, **2.29.10** (62.0 mg, 68%) was isolated as yellow/brown oil.

FTIR (thin film): 2960, 2921, 2869, 1592, 1487, 1433, 1320, 1251, 1190, 1121, 1036, 977, 914, 895, 762, 716, 653 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 8.8 Hz, 1H), 7.48 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.35 (td, *J* = 7.8, 1.9 Hz, 1H), 7.20 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.14 (td, *J* = 7.4, 1.1 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 5.58 (d, *J* = 15.4 Hz, 1H), 3.91 (d, *J* = 15.3 Hz, 1H), 3.36 (dp, *J* = 9.2, 2.7 Hz, 4H), 2.96 (dddd, *J* = 13.7, 8.7, 7.3, 1.4 Hz, 1H), 2.17 (ddd, *J* = 13.5, 8.3, 4.8 Hz, 1H), 2.07 – 2.03 (m, 6H), 1.64 – 1.43 (m, 3H), 1.39 – 1.13 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.49, 157.02, 152.04, 131.85, 131.45, 130.67, 130.13, 125.33, 122.84, 119.06, 107.43, 106.00, 47.92, 47.67, 44.31, 29.80, 25.60, 19.86, 13.90.

HRMS calculated for C$_{21}$H$_{27}$N$_2$O$_3$S (M+H)$^+$ 387.1742; found 387.1712

4-(isobutylamino)-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.11)
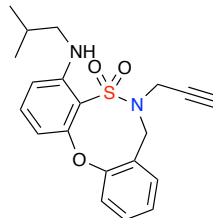
According to general procedure **B**, **2.29.11** (34 mg, 39%) was isolated as yellow/brown oil.

FTIR (thin film): 3395, 3284, 2958, 1602, 1567, 1458, 1335, 1313, 1227, 1179, 1110, 1070, 1042, 902, 800, 770, 729, 673 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.2 Hz, 1H), 7.42 (td, J = 7.8, 1.7 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.25 – 7.19 (m, 1H), 7.13 (t, J = 5.3 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 8.7 Hz, 1H), 5.27 (d, J = 15.2 Hz, 1H), 4.13 (d, J = 15.2 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.21 – 3.14 (m, 1H), 3.14 – 3.11 (m, 1H), 2.95 (t, J = 6.0 Hz, 2H), 1.86 (dp, J = 13.2, 6.5 Hz, 1H), 0.93 (d, J = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, DMSO) δ 159.05, 157.45, 148.94, 135.15, 131.17, 130.79, 129.59, 125.74, 122.38, 113.84, 109.90, 109.74, 77.27, 76.54, 50.75, 48.40, 40.93, 35.82, 27.60, 20.56.

HRMS calculated for C$_{20}$H$_{23}$N$_2$O$_3$S (M+H)$^+$ 371.1429; found 371.1403 (TOF MS ES$^+$).

4-((2-hydroxyethyl)(methyl)amino)-6-(prop-2-yn-1-yl)-6,7-

dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.12)
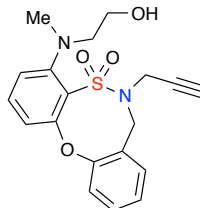
According to general procedure **B**, **2.29.12** (24 mg, 27%) was isolated as brown oil.

FTIR (thin film): 3480, 2923, 2854, 1720, 1595, 1556, 1486, 1423, 1323, 1219, 1165, 1144, 1114, 1040, 1019, 977, 909, 765, 757, 731, 711, 655 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.57 (d, J = 9.0 Hz, 1H), 7.40 (dd, J = 8.1, 1.2 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.10 (td, J = 7.5, 1.2 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.42 (dd, J = 9.0, 2.5 Hz, 1H), 5.49 (d, J = 15.3 Hz, 1H), 4.12 (d, J = 15.1 Hz, 1H), 3.93 (ddd, J = 17.0, 2.6, 1.3 Hz, 1H), 3.78 (t, J = 5.7 Hz, 2H), 3.51 (t, J = 5.7 Hz, 2H), 3.19 (s, 1H), 3.02 (s, 3H), 2.92 (dd, J = 17.0, 2.5 Hz, 1H), 2.19 (t, J = 2.5 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 159.48, 157.08, 154.42, 131.94, 131.64, 130.49, 129.49, 125.55, 122.49, 119.10, 107.63, 106.62, 73.76, 60.00, 54.70, 47.80, 41.03, 39.26, 35.42.

HRMS calculated for C$_{19}$H$_{21}$N$_2$O$_4$S (M+H)$^+$ 373.1222; found 373.1203

2-(pyrrolidin-1-yl)-6-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.6)
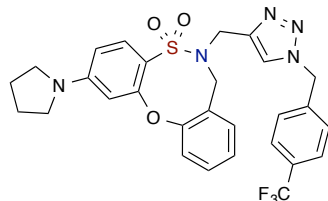
According to general procedure **C**, **2.30.6** (258 mg, 96%) was isolated as a yellow solid.

mp 202–203 °C;

FTIR (thin film): 3144, 2922, 2851, 1598, 1584, 1548, 1486, 1453, 1386, 1251, 1217, 1142, 1041, 913, 834, 759, 714, 690 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 (s, 1H), 7.66 (dd, *J* = 8.4, 4.9 Hz, 3H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.32 (m, 4H), 7.19 (td, *J* = 7.5, 1.2 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.30 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.71 – 5.41 (m, 3H), 4.18 (dd, *J* = 15.9, 1.6 Hz, 1H), 3.84 (d, *J* = 15.2 Hz, 1H), 3.61 (d, *J* = 15.8 Hz, 1H), 3.37 (dq, *J* = 6.9, 3.5 Hz, 4H), 2.06 (td, *J* = 6.3, 3.0 Hz, 4H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.53, 157.27, 152.30, 145.67, 138.51, 132.45, 131.46, 131.24 (d, *J* = 32.6 Hz), 130.34, 130.12, 128.52, 126.33 (q, *J* = 3.7 Hz), 125.64, 123.93 (d, *J* = 272.6 Hz), 123.52, 122.65, 118.70, 107.46, 106.26, 53.78, 47.97, 47.90, 40.29, 25.60.

HRMS calculated for C$_{28}$H$_{27}$F$_3$N$_5$O$_3$S (M+H)$^+$ 570.1787; found 570.1796

6-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-thiomorpholino-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.7)
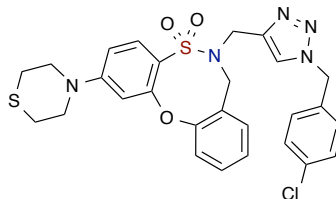
According to general procedure **C**, **2.30.7** (36 mg, 27%) was isolated as yellow/brown oil.

FTIR (thin film): 2915, 1594, 1582, 1486, 1329, 1217, 1183, 1141, 1045, 1016, 945, 909, 777, 756, 729, 702 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.9 Hz, 1H), 7.64 (s, 1H), 7.46 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.42 – 7.35 (m, 4H), 7.26 – 7.24 (m, 2H), 7.22 (td, *J* = 7.4, 1.2 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.62 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.57 – 5.43 (m, 3H), 4.25 – 4.17 (m, 1H), 3.87 (d, *J* = 15.2 Hz, 1H), 3.81 – 3.77 (m, 4H), 3.64 (d, *J* = 15.7 Hz, 1H), 2.78 – 2.71 (m, 4H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 159.29, 157.23, 154.44, 145.04, 134.95, 132.88, 132.46, 131.44, 130.32, 129.95, 129.57, 129.42, 125.69, 123.12, 122.21, 122.01, 110.38, 109.70, 53.60, 50.62, 47.59, 40.26, 25.87.

HRMS calculated for C$_{27}$H$_{27}$ClN$_5$O$_3$S$_2$ (M+H)$^+$ 568.1244; found 568.1234

2-morpholino-6-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.8)
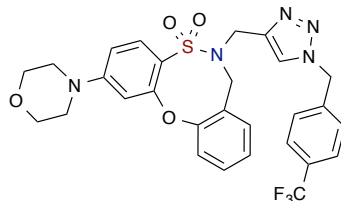
According to general procedure **C**, **2.30.8** (42 mg, 30%) was isolated as yellow solid.

mp 166–168 °C;

FTIR (thin film): 2919, 2851, 1592, 1470, 1454, 1414, 1334, 1265, 1108, 1068, 975, 889, 828, 789, 760, 703, 660 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.9 Hz, 1H), 7.70 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.36 (m, 4H), 7.24 – 7.19 (m, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.67 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.67 – 5.53 (m, 2H), 5.49 (d, *J* = 15.2 Hz, 1H), 4.20 (d, *J* = 15.8 Hz, 1H), 3.89 (d, *J* = 4.3 Hz, 4H), 3.87 (d, *J* = 6.5 Hz, 1H), 3.64 (d, *J* = 15.8 Hz, 1H), 3.34 – 3.30 (m, 4H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.28, 156.98, 155.69, 145.21, 138.33, 132.40, 131.18, 131.12 (q, *J* = 32.8 Hz), 130.37, 129.89, 128.39, 126.20 (q, *J* = 3.7 Hz), 125.71, 123.77 (q, *J* = 271.8 Hz), 123.37, 122.87, 122.30, 109.92, 109.26, 66.44, 53.66, 47.66, 47.59, 40.20.

HRMS calculated for C$_{28}$H$_{27}$F$_3$N$_5$O$_4$S (M+H)$^{+}$ 586.1736; found 586.1728

6-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-morpholino-6,7-

dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.9)

According to general procedure **C**, **2.30.9** (46 mg, 35%) was isolated as yellow solid.

mp 150–152 °C;

FTIR (thin film): 3315, 3223, 3142, 2958, 2920, 2852, 1596, 1556, 1487, 1450, 1329, 1248, 1218, 1189, 1149, 1124, 1080, 1034, 978, 911, 845, 782, 768, 733, 656 cm^{-1};

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.05 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.9 Hz, 1H), 7.50 – 7.43 (m, 4H), 7.38 – 7.33 (m, 2H), 7.28 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.83 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.60 (s, 2H), 5.27 (d, *J* = 15.2 Hz, 1H), 4.15 (d, *J* = 15.4 Hz, 1H), 3.93 (d, *J* = 15.1 Hz, 1H), 3.80 – 3.71 (m, 4H), 3.38 – 3.35 (m, 4H), 3.33 (d, *J* = 3.4 Hz, 1H).

^{13}C NMR (101 MHz, DMSO) δ 158.94, 156.36, 155.58, 142.78, 134.93, 132.84, 131.94, 130.54, 129.91, 129.21, 128.73, 125.43, 123.89, 123.06, 121.20, 109.40, 108.99, 65.76, 51.99, 46.97, 46.83, 40.43.

HRMS calculated for C$_{27}$H$_{27}$ClN$_5$O$_4$S (M+H)$^+$ 552.1472; found 552.1473

4-(isobutylamino)-6-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.10)

According to general procedure **C**, **2.30.10** (45 mg, 34%) was isolated as yellow/brown oil.

FTIR (thin film): 3395, 2960, 1602, 1569, 1460, 1323, 1228, 1161, 1112, 1066, 1044, 1018, 910, 792, 771, 710, 674 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.76 (t, *J* = 6.2 Hz, 3H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.34 (m, 2H), 7.29 – 7.25 (m, 1H), 7.20 (t, *J* = 7.3 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 5.70 (s, 2H), 5.23 (d, *J* = 15.2 Hz, 1H), 4.16 (d, *J* = 15.5 Hz, 1H), 3.93 (d, *J* = 15.3 Hz, 1H), 3.47 (d, *J* = 15.4 Hz, 1H), 2.95 (t, *J* = 5.7 Hz, 2H), 1.85 (dp, *J* = 13.5, 7.4, 6.8 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.10, 157.70, 149.07, 144.84, 138.40, 134.23, 131.17, 131.07 (q, *J* = 32.40 Hz), 130.07, 129.80, 128.36, 126.13 (q, *J* = 3.7 Hz), 125.28, 123.78 (q, *J* = 272.3 Hz), 123.24, 121.90, 114.06, 109.11, 109.08, 53.58, 51.24, 48.12, 40.91, 27.69, 20.46.

HRMS calculated for C$_{28}$H$_{29}$F$_3$N$_5$O$_3$S (M+H)$^+$ 572.1943; found 572.1959

6-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-(pyrrolidin-1-yl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.11)
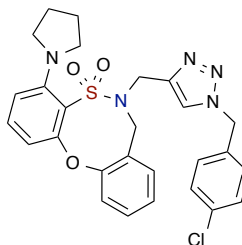
According to general procedure **C**, **2.30.11** (34 mg, 27%) was isolated as red/brown oil.

FTIR (thin film): 3387, 2949, 1593, 1543, 1490, 1474, 1455, 1352, 1326, 1230, 1182, 1109, 1041, 1017, 912, 874, 795, 771, 725, 677 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.49 (m, 2H), 7.41 (td, *J* = 7.7, 1.7 Hz, 1H), 7.35 – 7.32 (m, 2H), 7.28 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.22 – 7.17 (m, 3H), 7.16 – 7.12 (m, 1H), 6.78 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.59 (dd, *J* = 8.7, 1.0 Hz, 1H), 5.50 – 5.31 (m, 3H), 3.92 (dd, *J* = 16.0, 1.7 Hz, 1H), 3.82 (d, *J* = 15.5 Hz, 1H), 3.70 (q, *J* = 10.0, 9.5 Hz, 2H), 3.47 (d, *J* = 15.9 Hz, 1H), 3.34 (dd, *J* = 10.1, 6.7 Hz, 2H), 2.04 (t, *J* = 5.6 Hz, 2H), 1.84 (dd, *J* = 10.7, 7.3 Hz, 2H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 157.92, 157.43, 152.12, 145.07, 134.90, 133.10, 132.02, 130.77, 130.42, 129.64, 129.60, 129.41, 125.84, 123.19, 122.97, 115.39, 110.68, 106.01, 53.55, 53.11, 48.33, 40.75, 25.96.

HRMS calculated for C$_{27}$H$_{27}$ClN$_5$O$_3$S (M+H)$^+$ 536.1523; found 536.1483

2-fluoro-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.6)
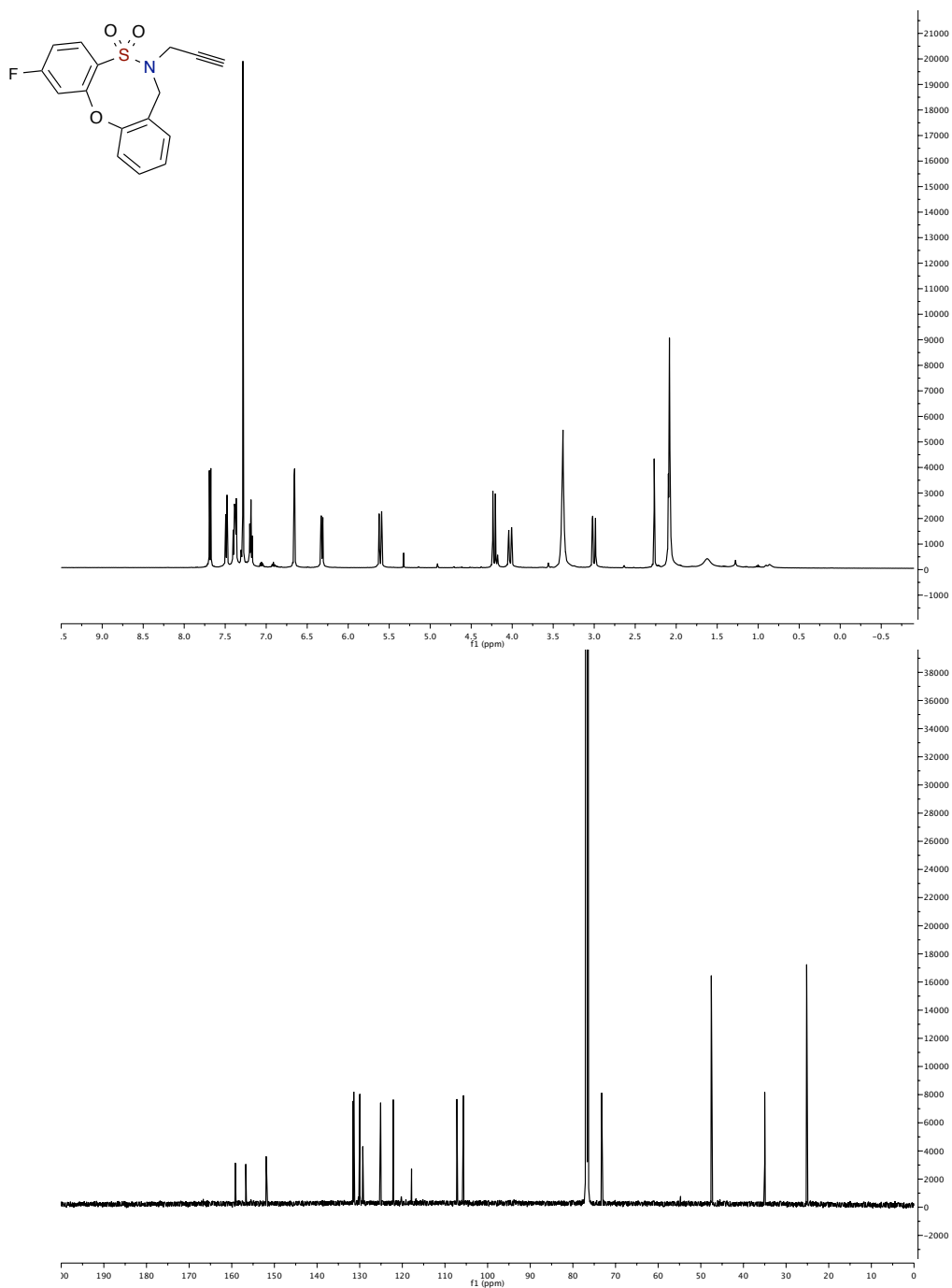
6-butyl-2-fluoro-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.7)
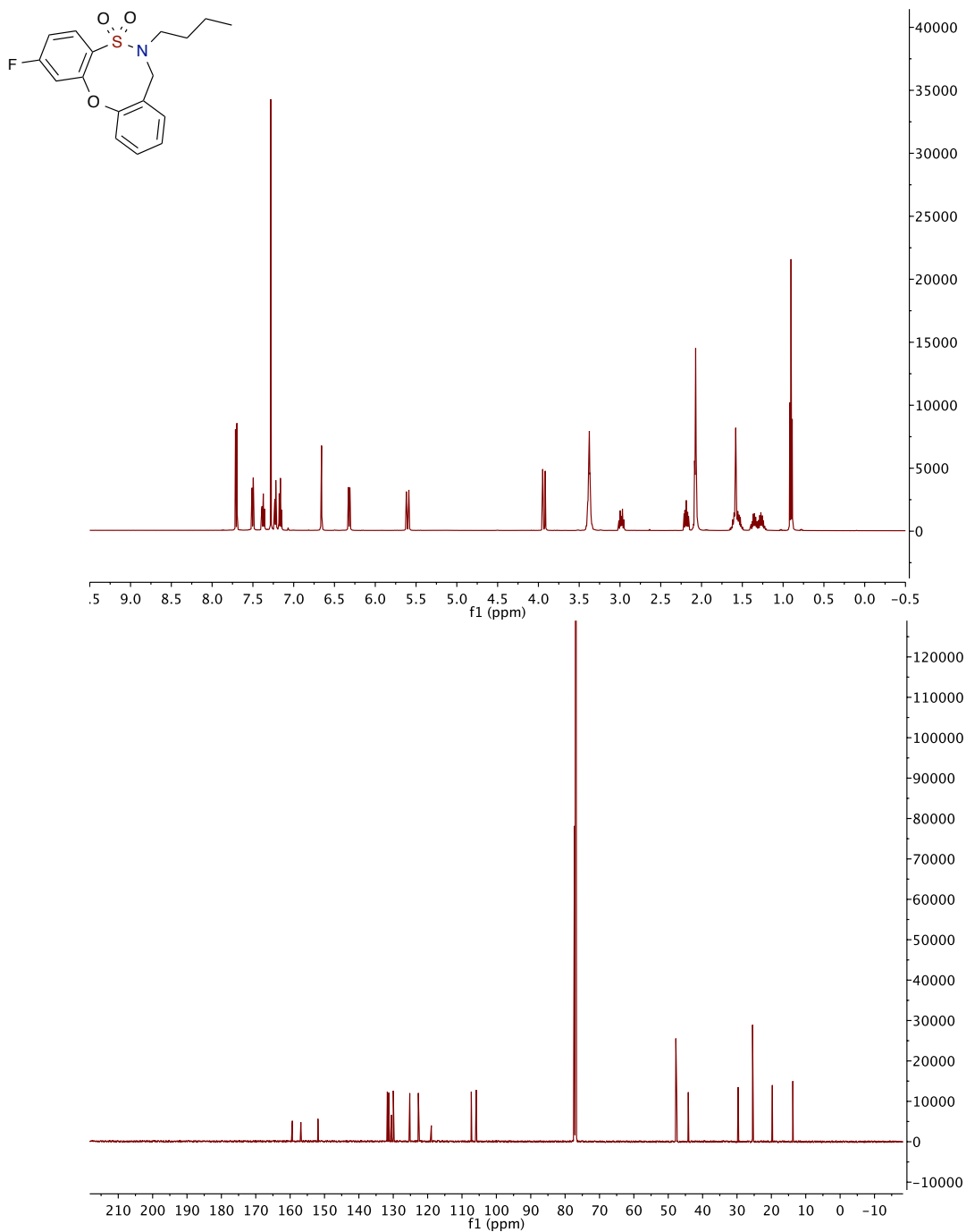
6-benzyl-2-fluoro-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.8)
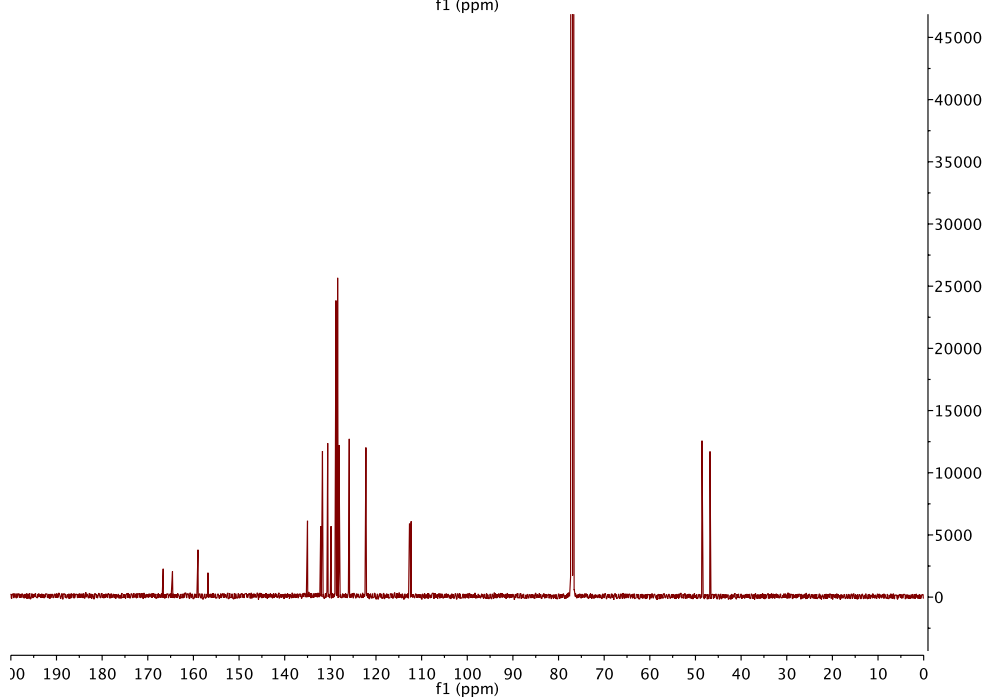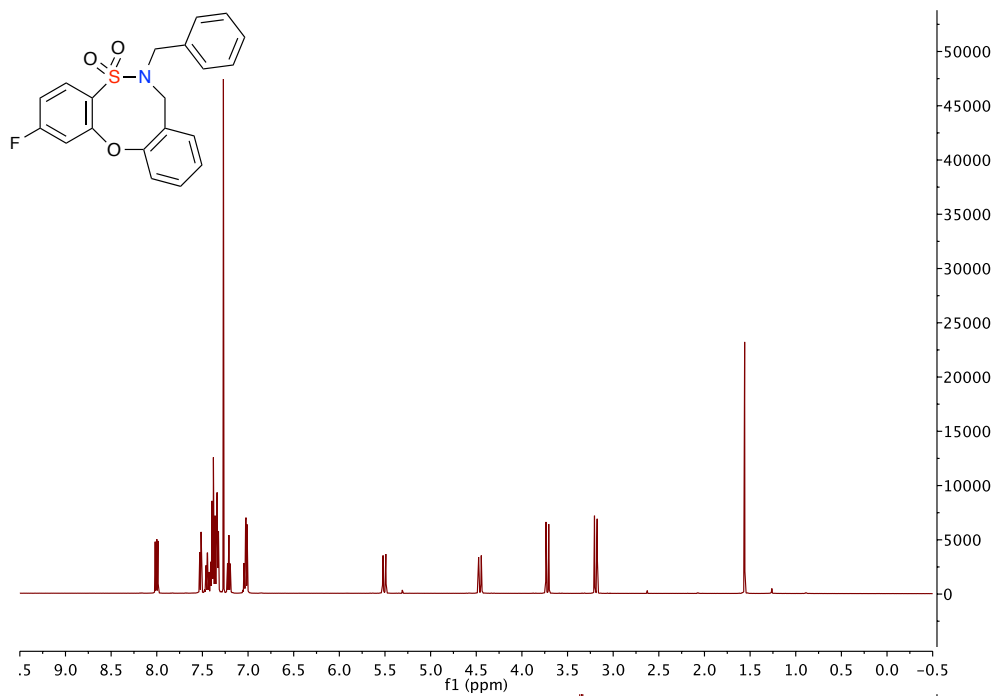
2-fluoro-6-(2-hydroxyethyl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide

(2.28.9)
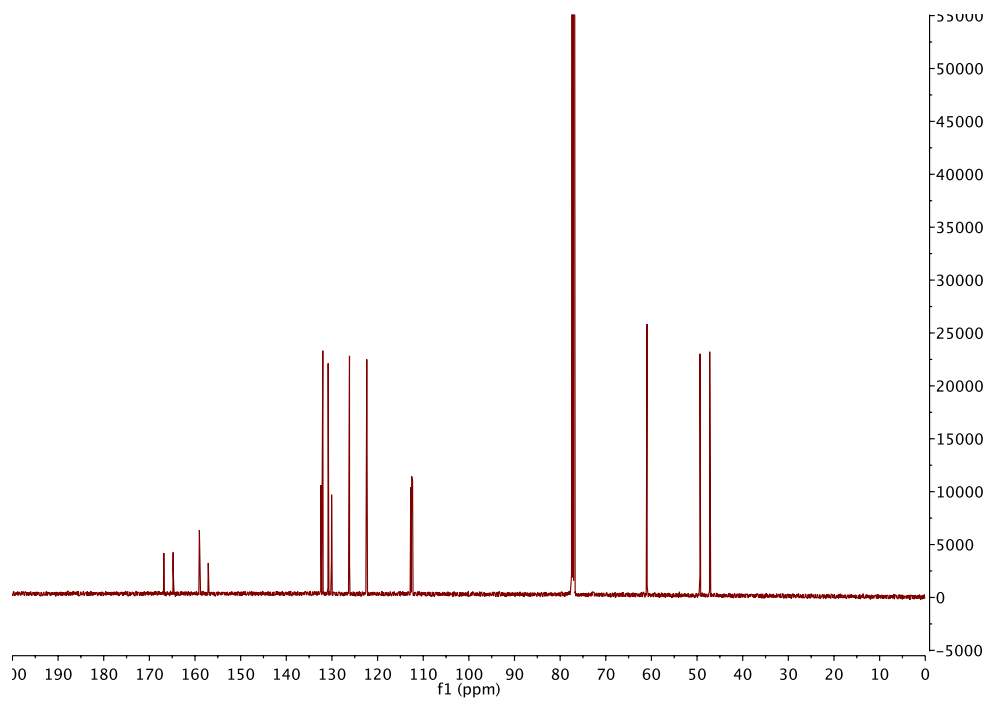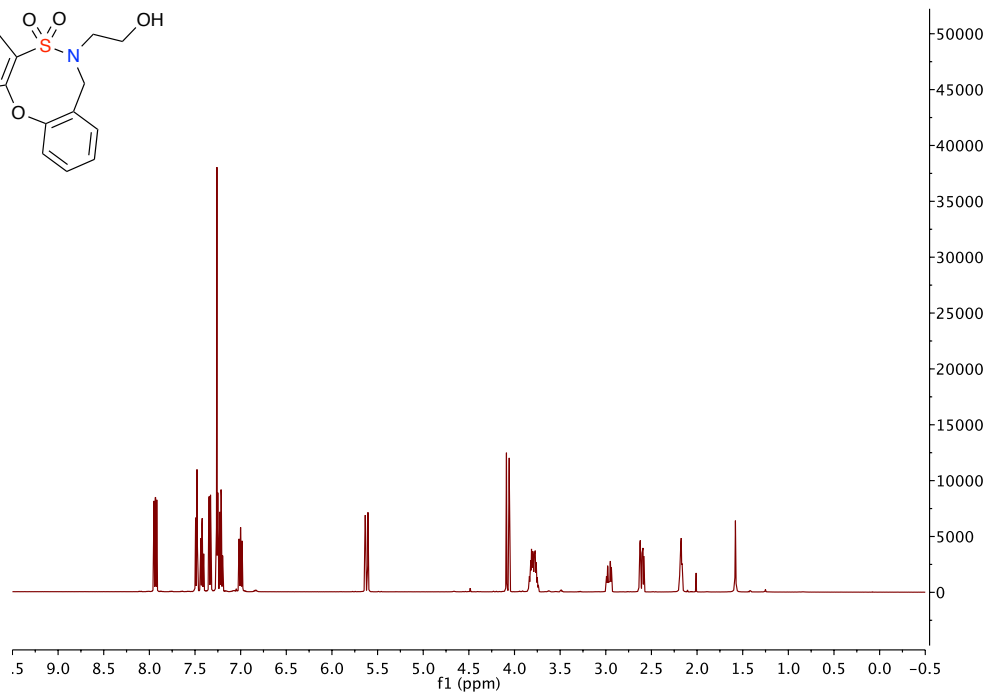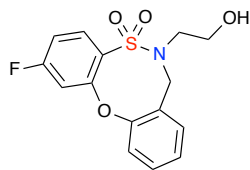
6-cyclopropyl-2-fluoro-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide

(2.28.10)
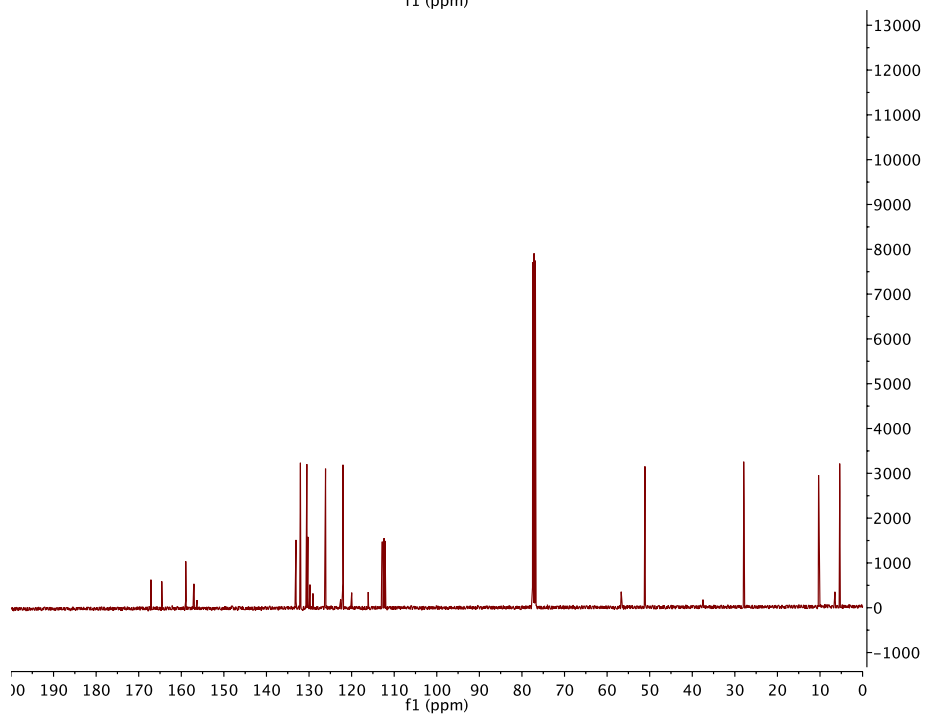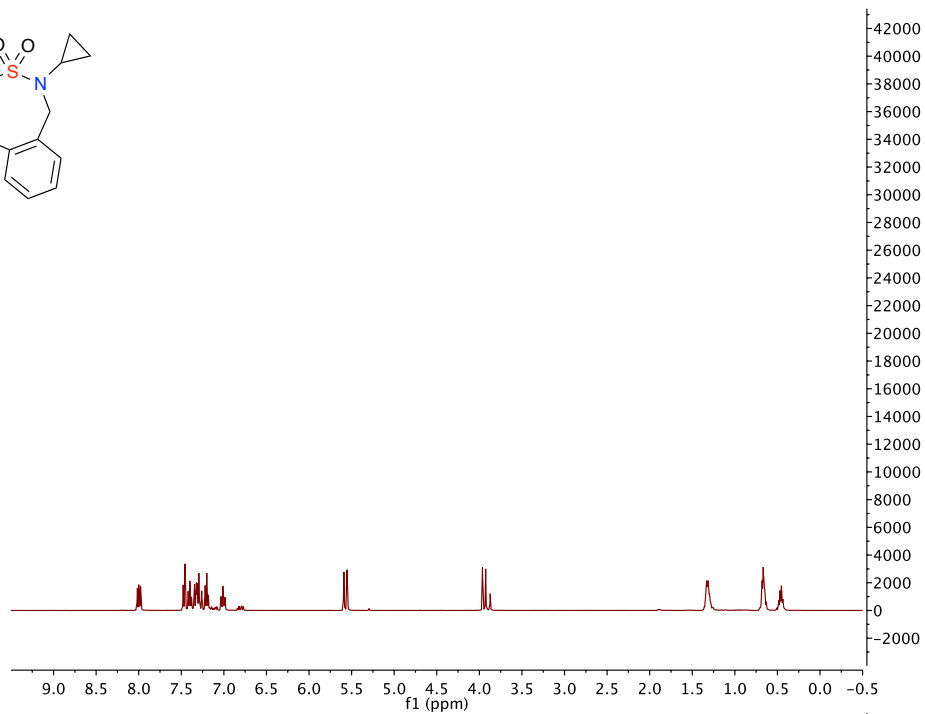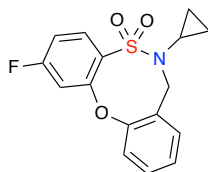
ethyl 2-(2-fluoro-5,5-dioxidodibenzo[*b,g*][1,4,5]oxathiazocin-6(7*H*)-yl)acetate

(2.28.11)
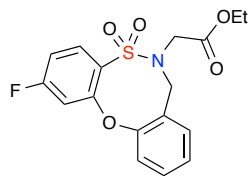
4-fluoro-6-(2-hydroxyethyl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.12)
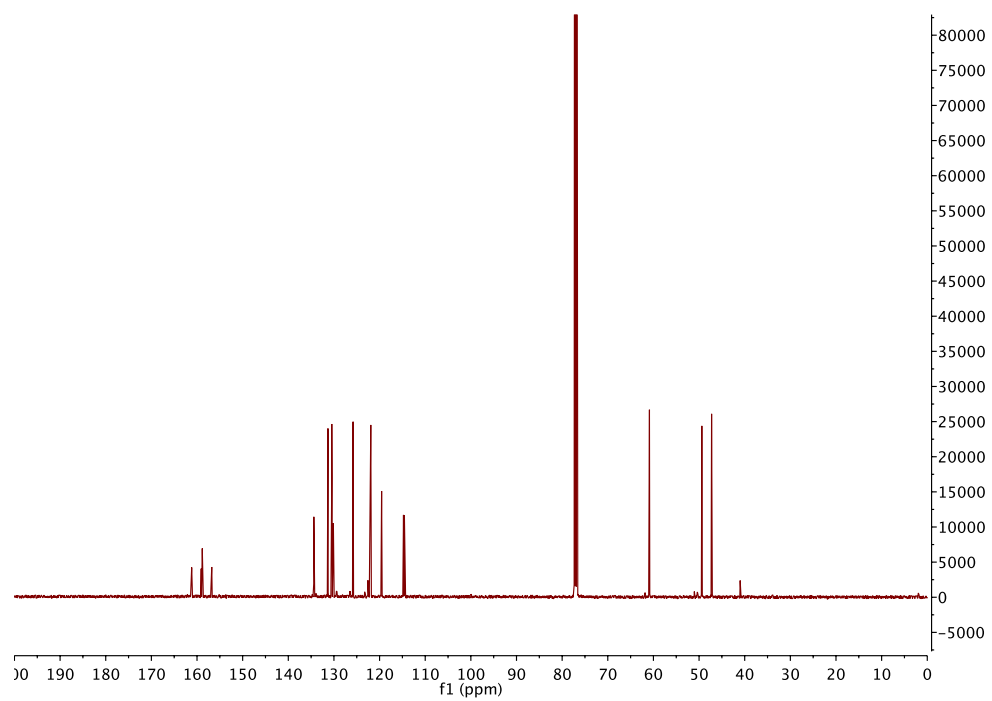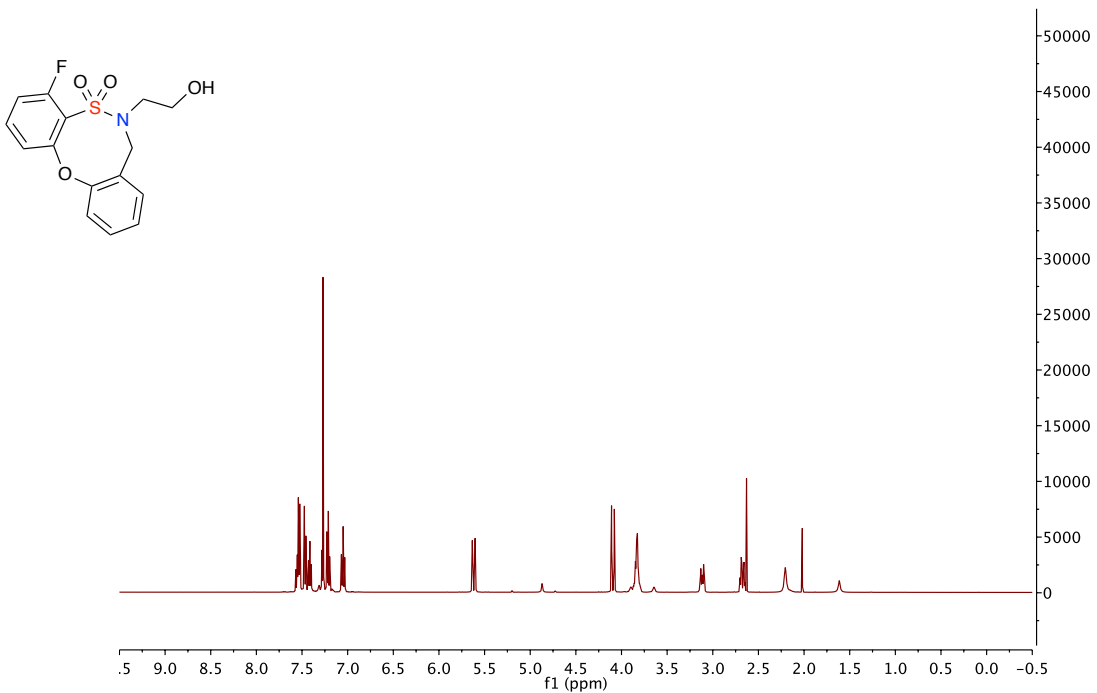
2-bromo-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.28.13)
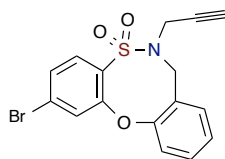
6-(prop-2-yn-1-yl)-2-(pyrrolidin-1-yl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.6)
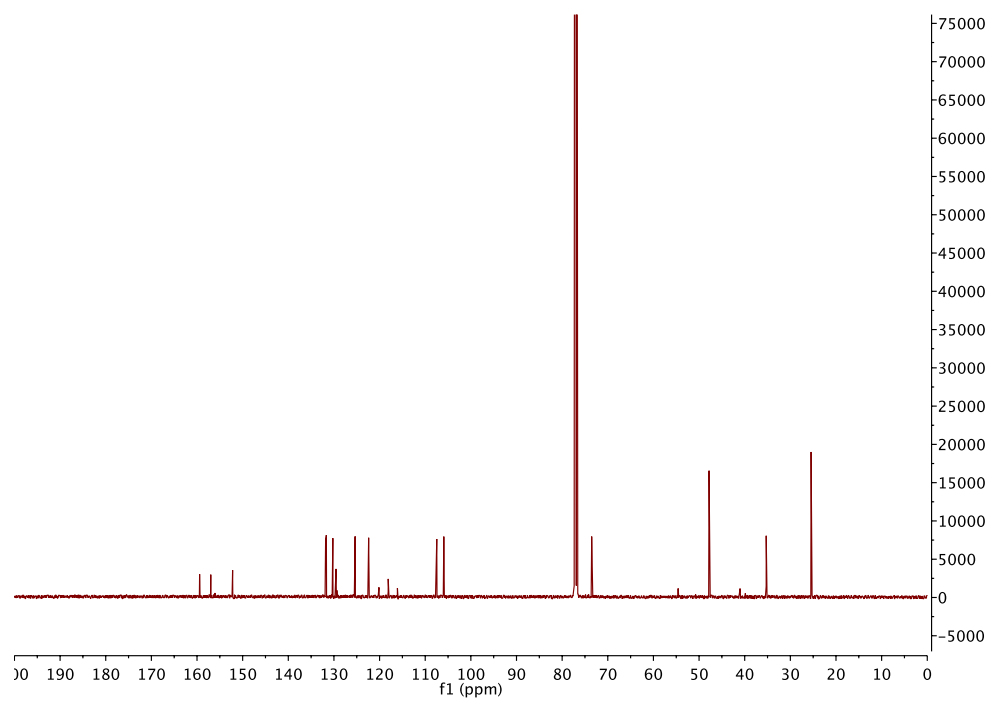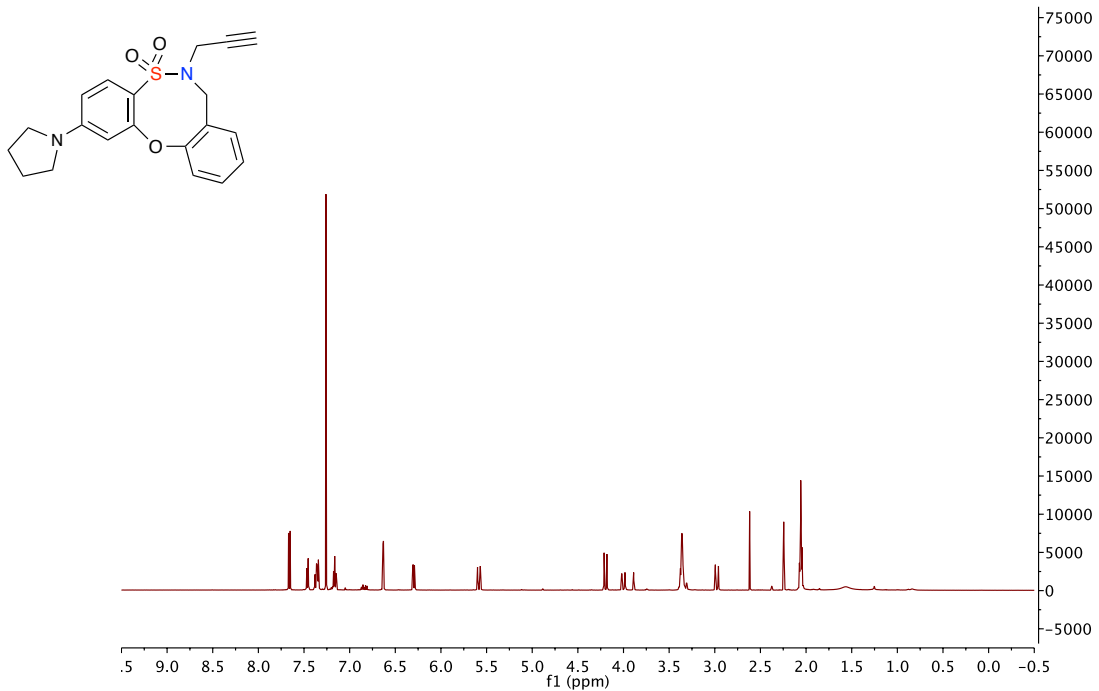
2-morpholino-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.7)
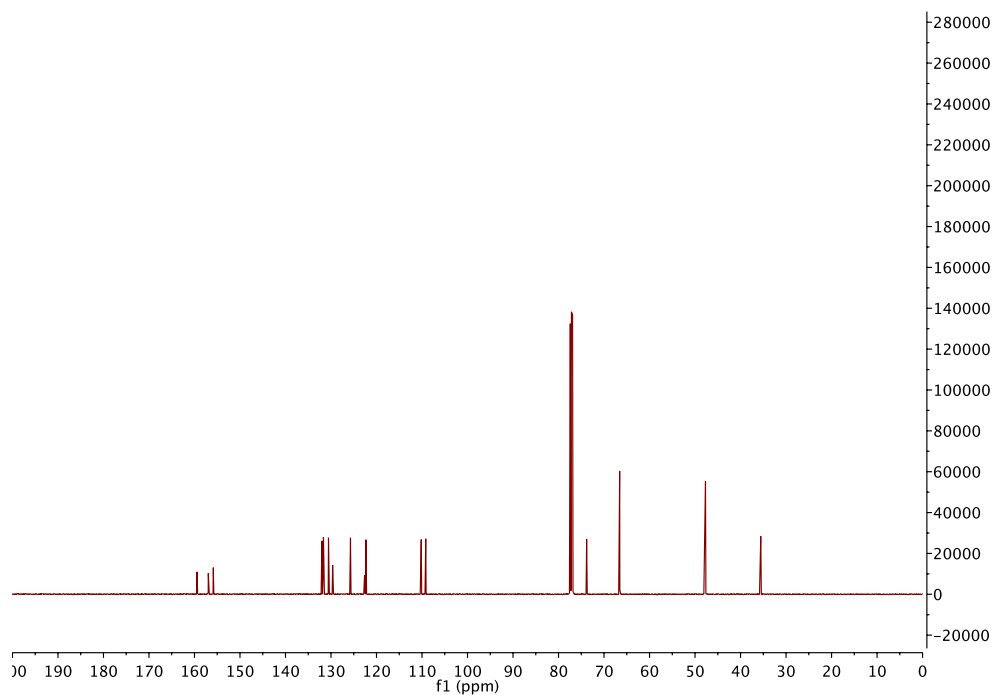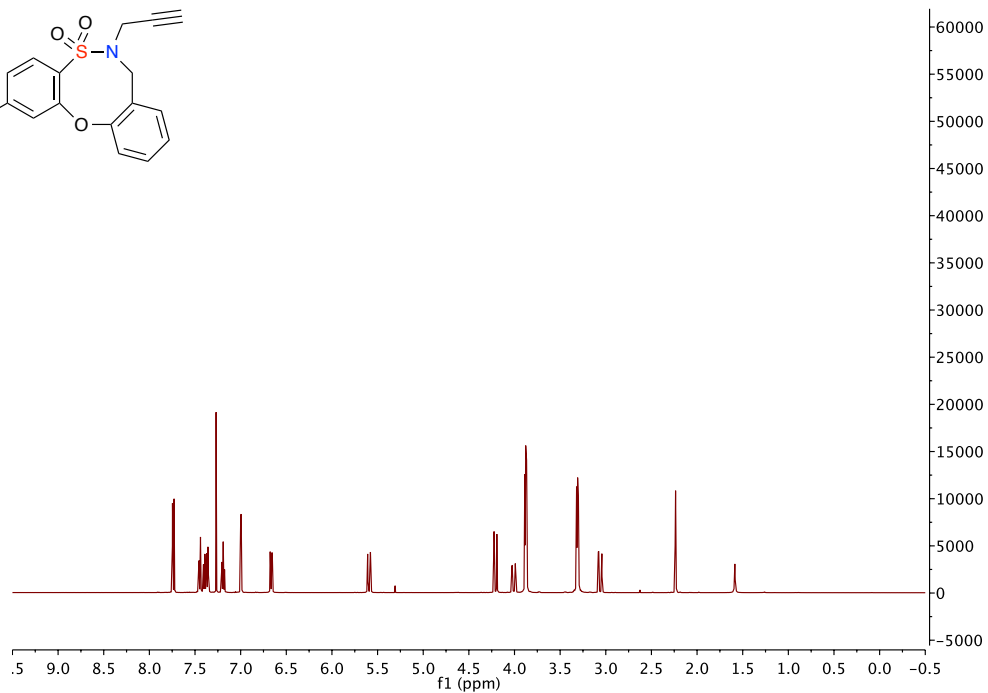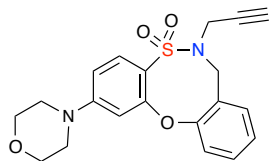
2-((2-hydroxyethyl)(methyl)amino)-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.8)
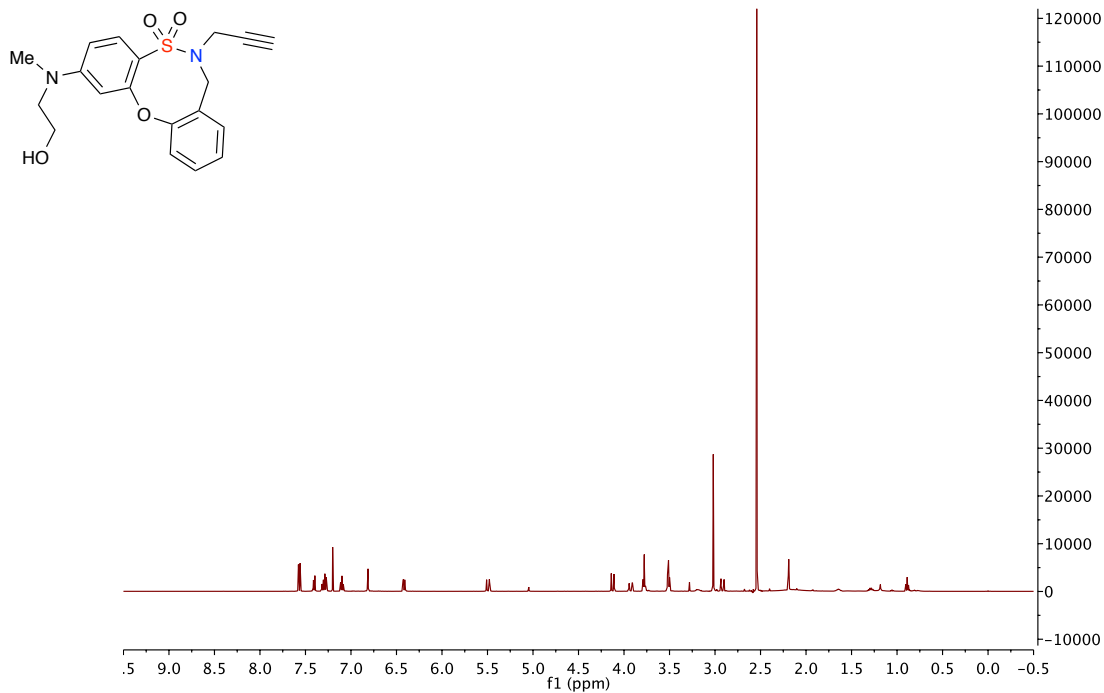
6-butyl-2-morpholino-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide

(2.29.9)
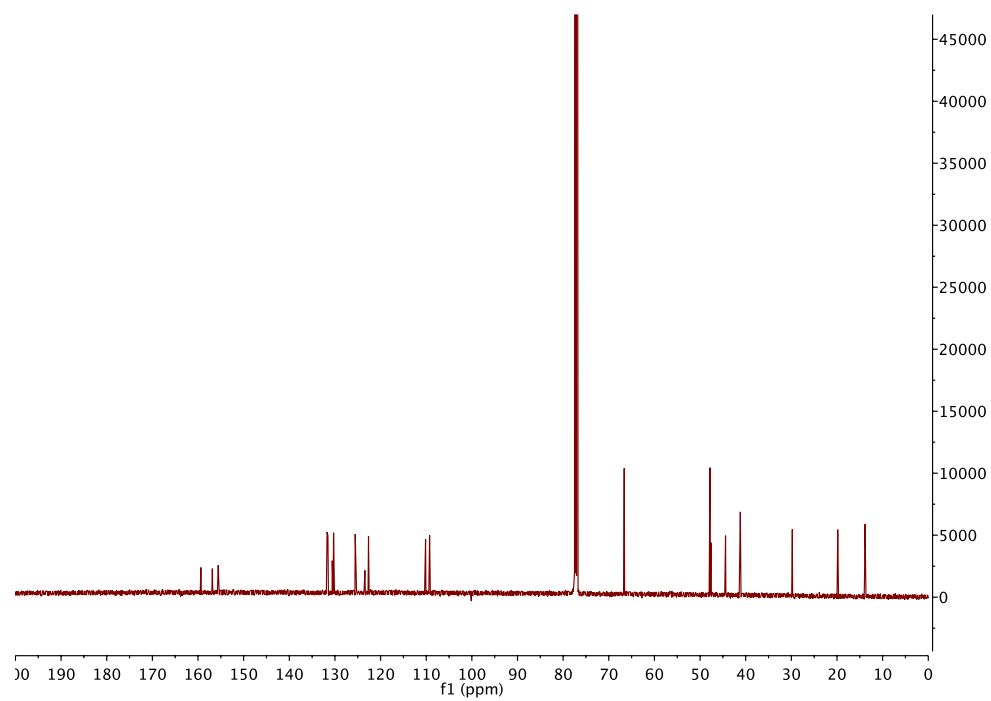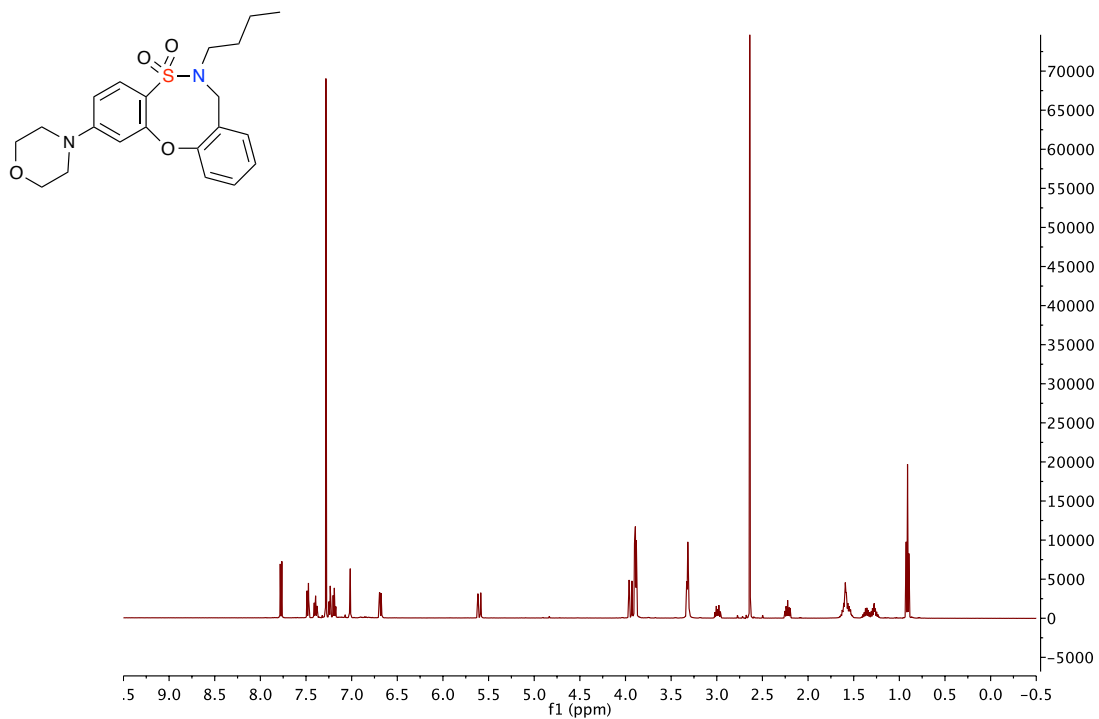
6-butyl-2-(pyrrolidin-1-yl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.10)
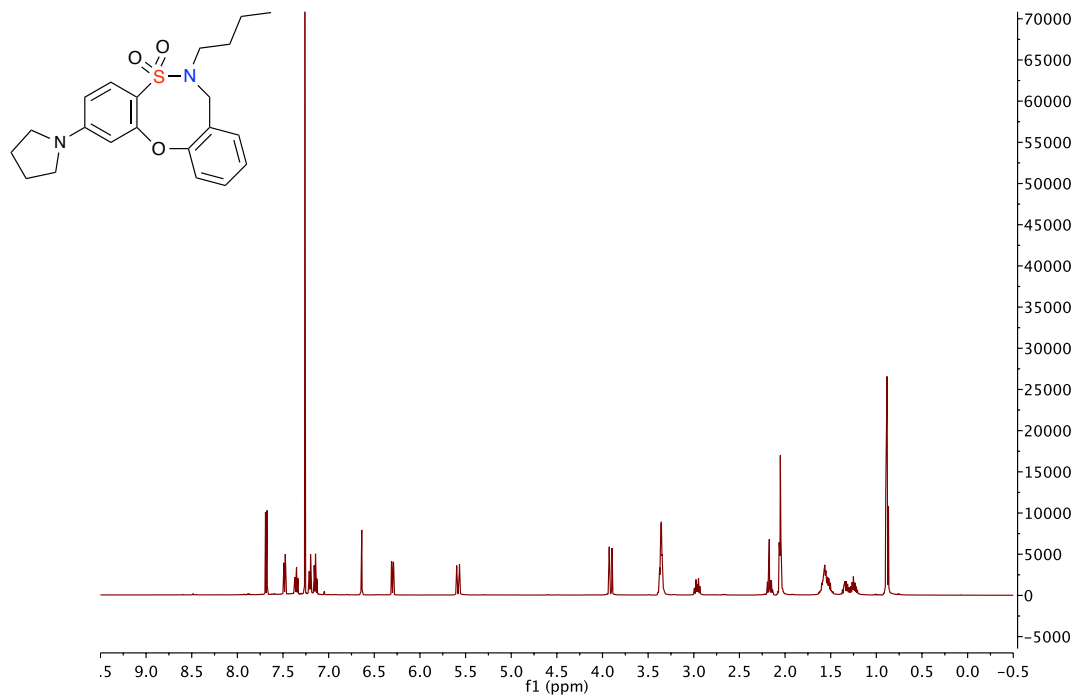
4-(isobutylamino)-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.11)

4-((2-hydroxyethyl)(methyl)amino)-6-(prop-2-yn-1-yl)-6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.29.12)
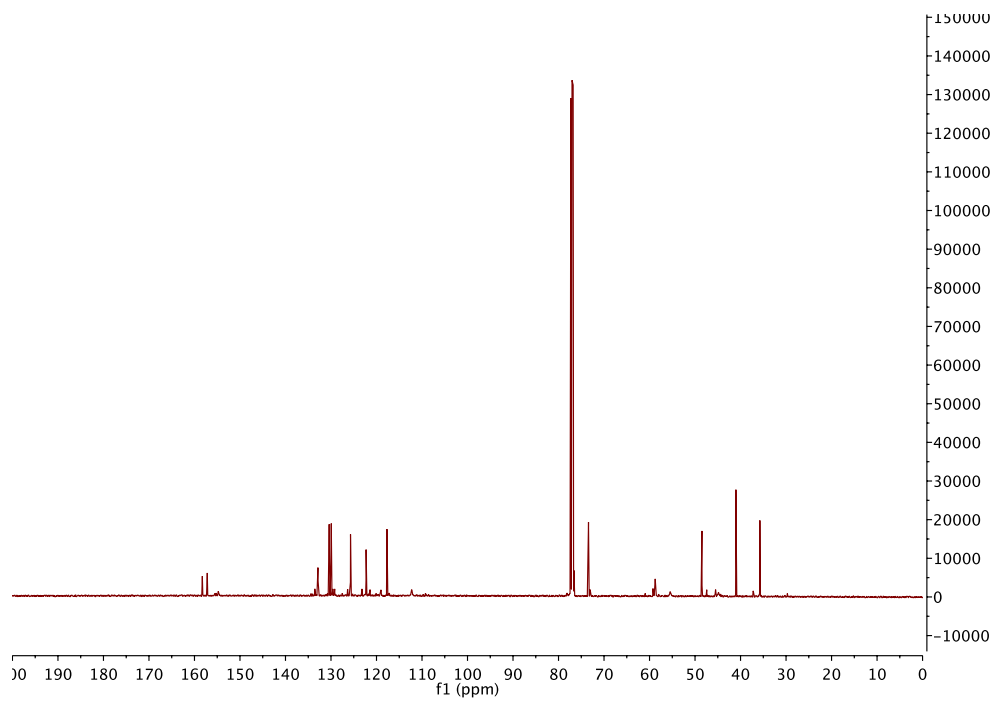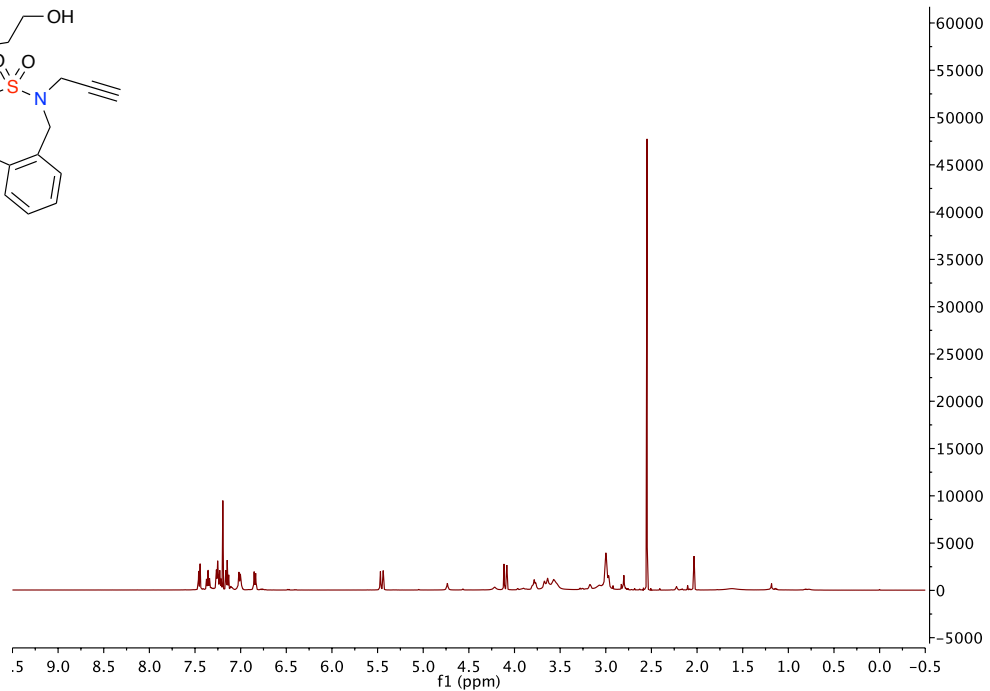
2-(pyrrolidin-1-yl)-6-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.6)
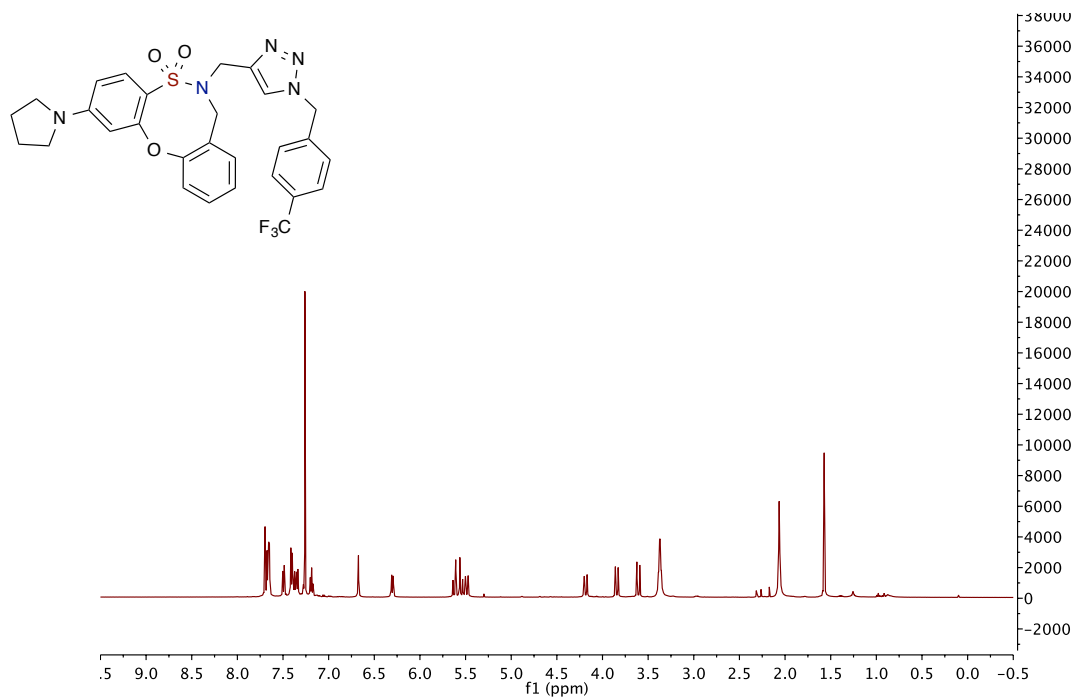
6-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-thiomorpholino-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.7)
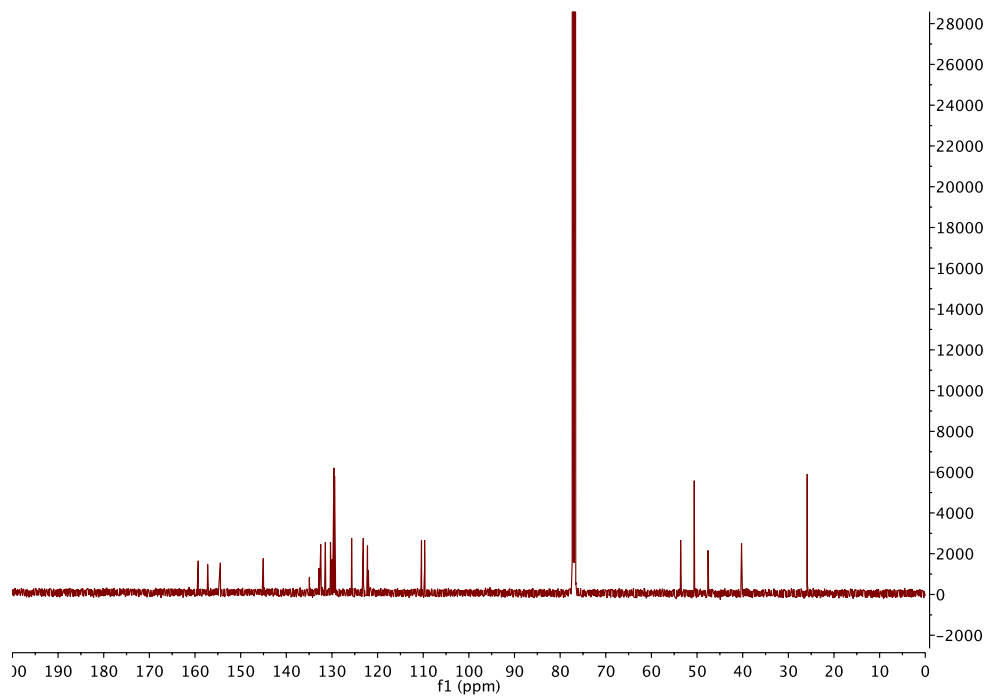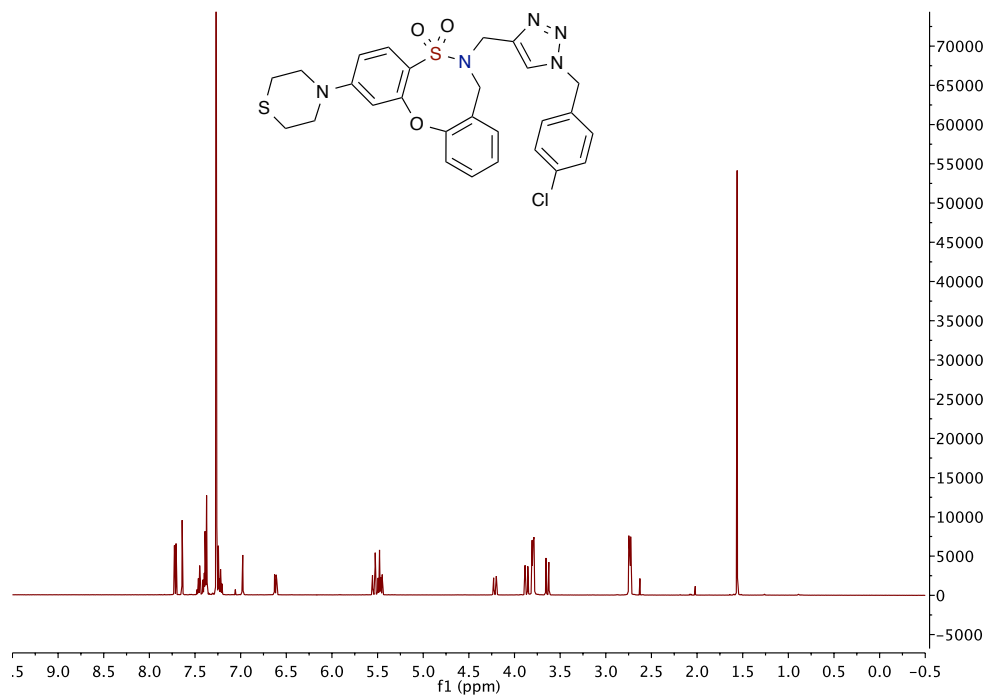
2-morpholino-6-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6,7-

dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.8)
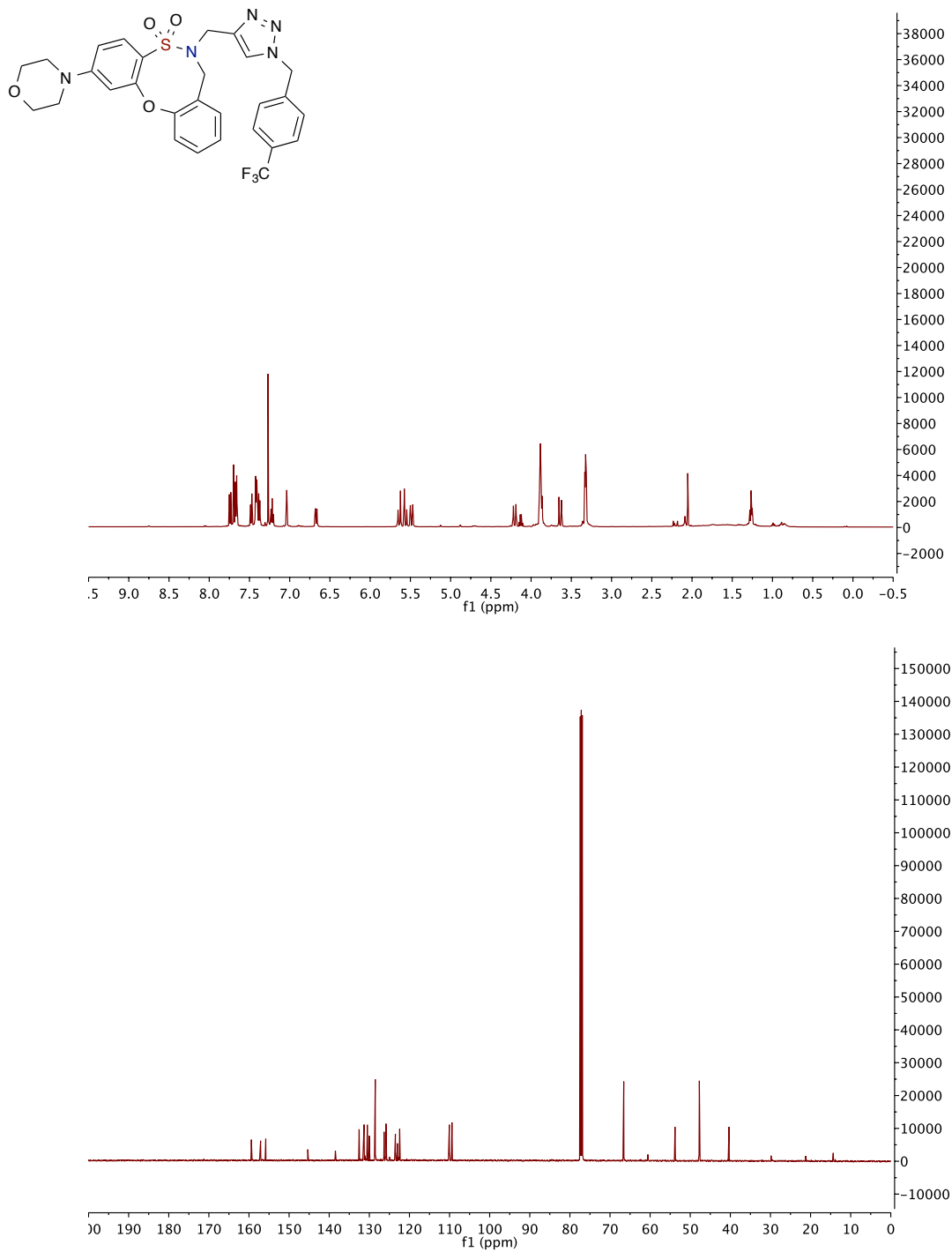
6-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-morpholino-6,7-

dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.9)
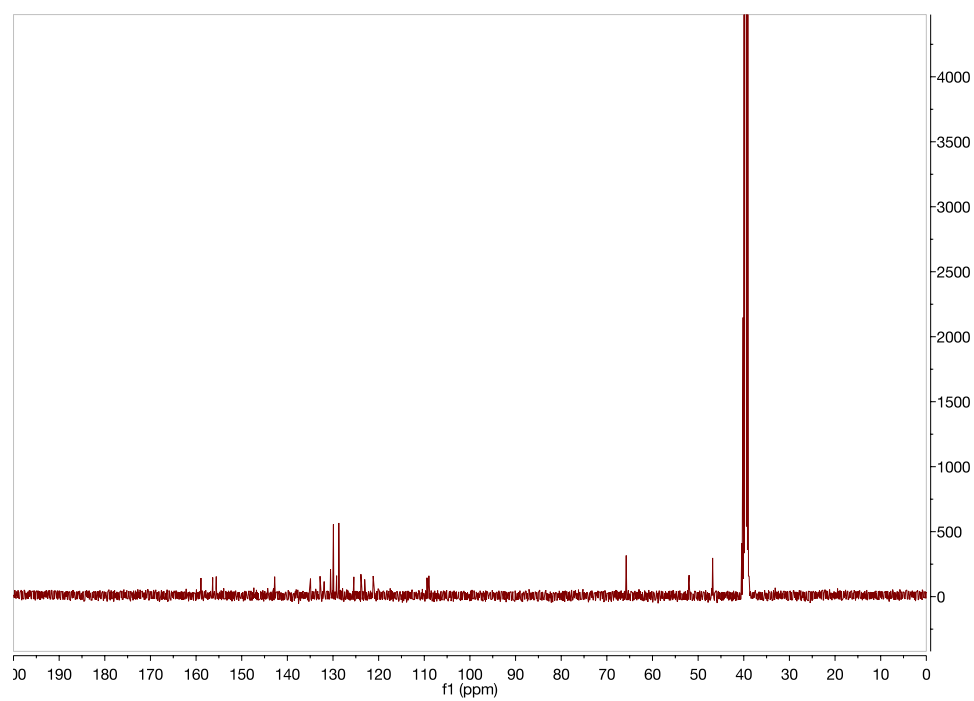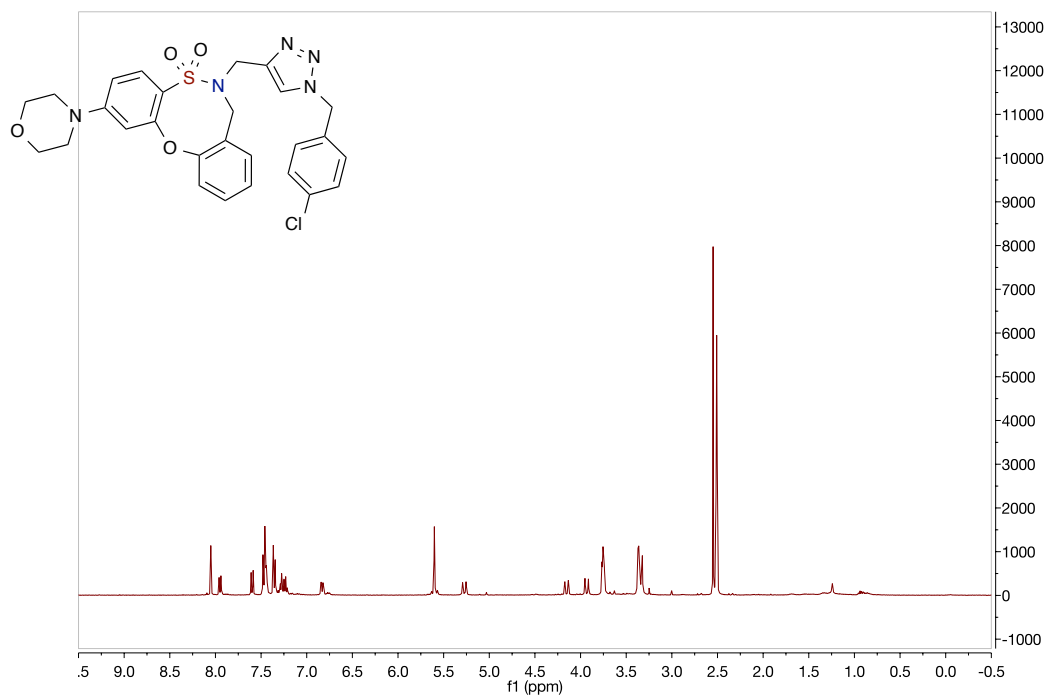
4-(isobutylamino)-6-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.10)
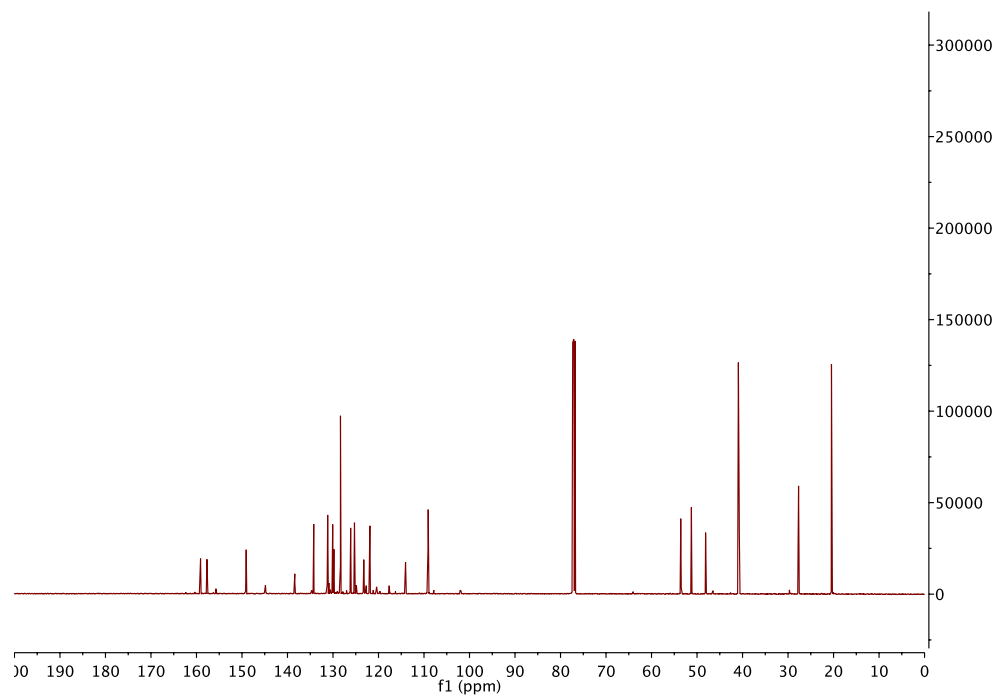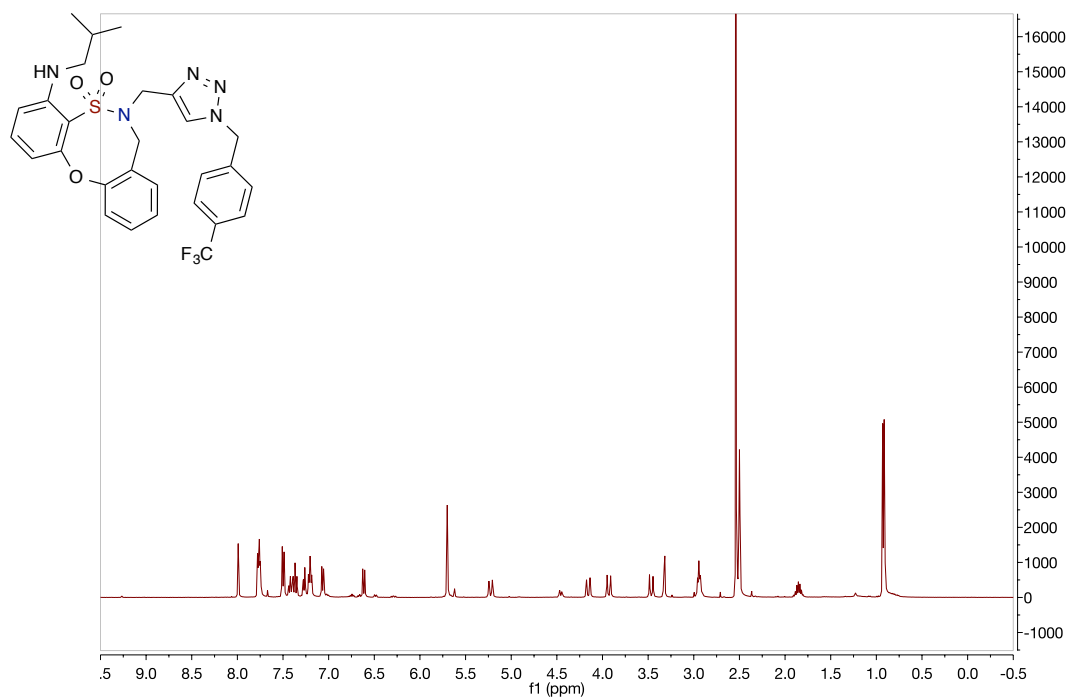
6-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-(pyrrolidin-1-yl)-6,7-dihydrodibenzo[*b,g*][1,4,5]oxathiazocine 5,5-dioxide (2.30.11)
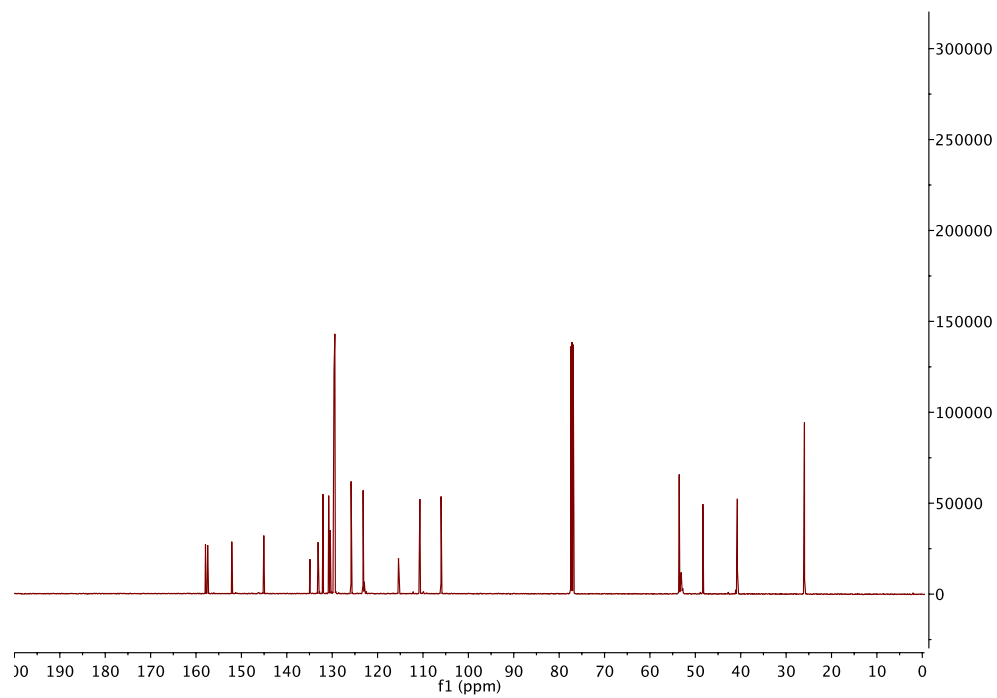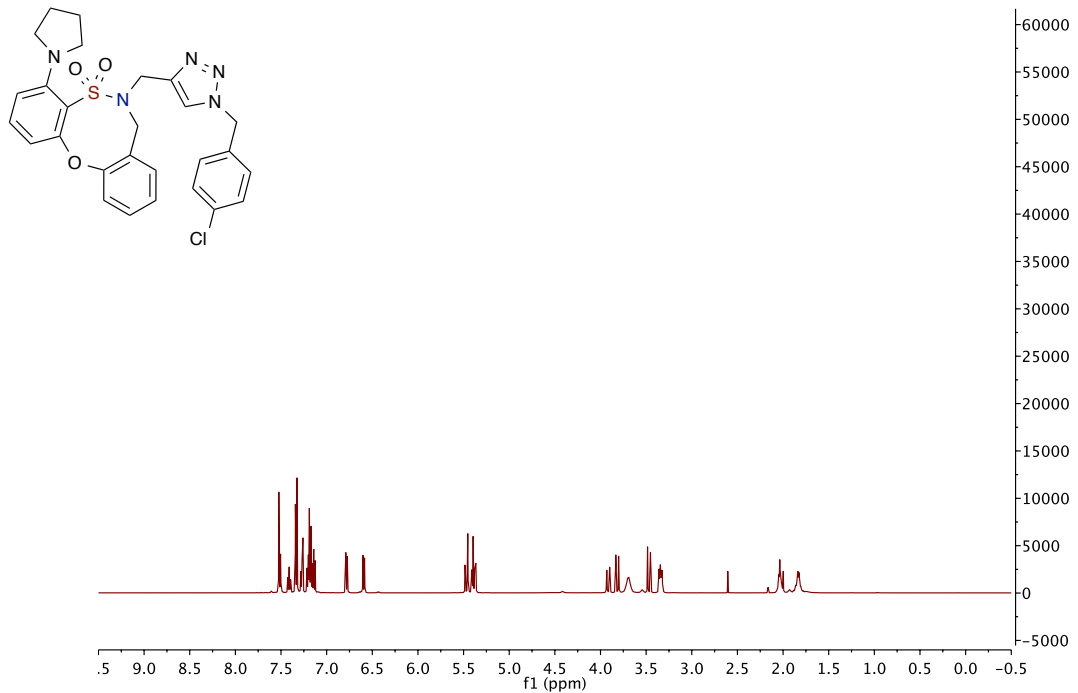
4.3: Experimental for Chapter 3

General Procedure A: preparation of secondary sulfonamide by mesylation of amino esters. A solution of amino ester (4.23 mmol, 1 equiv.) and Et$_3$N (10.76 mmol, 2.5 equiv.) in CH$_2$Cl$_2$ (50 mL, 0.1 M) was cooled to 0 °C. Then methanesulfonyl chloride (6.33 mmol, 1.5 equiv.) was slowly added to the mixture at 0 °C and stirred for 10 minutes, and warmed to room temperature and stirred for 2 hours. Upon completion of the reaction, the mixture was quenched with water and CH$_2$Cl$_2$, organic layer was separated, and aqueous layer was extracted with CH$_2$Cl$_2$ (x3). The combined organic layers were dried (Na$_2$SO$_4$), concentrated under reduced pressure, subject to automated column chromatography to afford the product.

General Procedure B: synthesis of benzylated tertiary sulfonamide via benzylation. To a solution of sulfonamide (3.44 mmol, 1.0 equiv.) and benzyl bromide (5.19 mmol, 1.5 equiv.) in CH$_3$CN (50 mL, 0.1 M), was added K$_2$CO$_3$ (10.32 mmol, 3.0 equiv.). The reaction was stirred and refluxed at 80 °C overnight. Upon completion, the reaction mixture was cooled to room temperature, quenched with EtOAc and water, organic layer was separated, and aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried (Na$_2$SO$_4$), concentrated under reduced pressure, subject to automated column chromatography to afford the product.

General Procedure C: preparation of tetramic acid sultam analog via intramolecular sulfa-Dieckmann cyclization. A solution of sulfonamide (1.01 mmol, 1.0 equiv.) in THF

(100 mL, 0.01M) was cooled to -78 °C in dry ice/acetone bath. Then the solution was treated with LiHMDS (2.0 mmol, 1M in THF) slowly at -78 °C, and stirred for 2 hours. Then the reaction was warmed to room temperature, and quenched with 10% HCl and EtOAc, organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried (Na$_2$SO$_4$), concentrated under reduced pressure, subject to column chromatography to afford the product.

General Procedure D: preparation of 3-carboxamide tetramic acid sultam analogs via addition into isocyanates. To a solution of sultam (0.03 mmol, 1.0 equiv.) and phenyl isocyanate (0.03 mmol, 1.0 equiv.) in CH$_3$CN (2 mL, 0.01 M) in a microwave vial, was added Et$_3$N (0.03 mmol, 1.0 equiv.). The reaction mixture was microwaved at 80 °C for 40 minutes. The resulting mixture was concentrated under reduced pressure and subject to automated column chromatography to afford the product.

(S)-2-benzyl-3-isopropylisothiazolidin-4-one 1,1-dioxide (3.A.1)
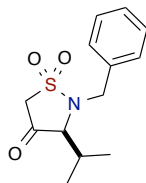
According to general procedure **C**, **3.A.1** (15 mg, 65%) was isolated as golden oil.

$[\alpha]_D^{20}$ = -121.24 (*c* = 1.25, CH$_2$Cl$_2$);

FTIR (neat): 2966, 2933, 2877, 1758, 1604, 1456, 1319, 1205, 1184, 1027, 734, 700 cm^{-1};

¹H NMR (500 MHz, CDCl₃) δ 7.32–7.24 (m, 3H), 7.21–7.17 (m, 2H), 4.90 (s, 1H), 4.69 (s, 1H), 4.07 (ddd, *J* = 7.8, 4.9, 1.1 Hz, 1H), 3.81 (d, *J* = 14.8 Hz, 1H), 3.74 (d, *J* = 16.8 Hz, 1H), 3.58 (dd, *J* = 16.8 Hz, 1.0, 1H), 3.45 (d, *J* = 14.8 Hz, 1H), 3.17 (dd, *J* = 14.2, 4.9 Hz, 1H), 3.10 (dd, *J* = 14.2, 7.8 Hz, 1H), 1.58 (s, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 198.1, 134.39, 128.95, 128.92, 128.43, 73.54, 56.2, 47.7, 29.8, 18.8, 17.1;

HRMS calculated for $C_{13}H_{17}NO_3SNa$ 290.0827 (M+Na)⁺; found 290.0819 (TOF MS ES⁺).

(*S*)-2-(2-fluorobenzyl)-3-isopropylisothiazolidin-4-one 1,1-dioxide (3.A.2)
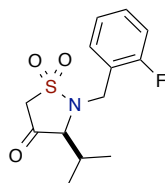
According to general procedure **C**, **3.A.2** (11 mg, 72%) was isolated as reddish brown oil.

$[\alpha]_D^{20}$ = -128.26 (*c* = 1.25, CH₂Cl₂);

FTIR (neat): 2969, 2933, 2358, 2341, 2331, 1758, 1409, 1456, 1323, 1207, 1139, 759 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 7.59 (td, *J* = 7.6, 1.7 Hz, 1H), 7.35 (ddd, *J* = 15.4, 5.3, 1.8 Hz, 1H), 7.20 (td, *J* = 7.5, 1.1 Hz, 1H), 7.13–7.07 (m, 1H), 4.59 (q, *J* = 15.8 Hz, 2H), 3.82–3.70 (m, 2H), 3.63 (dd, *J* = 4.7, 1.2, Hz 1H), 2.25–2.17 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 197.8, 161.8, 159.4, 131.43, 130.3, 115.5, 73.8, 56.2, 41.1, 30.0, 18.8, 17.3;

HRMS calculated for $C_{13}H_{16}FNO_3SH$ 286.0913 (M+H)⁺; found 286.0907 (TOF MS ES⁺).

(*S*)-2-(2-chlorobenzyl)-3-isopropylisothiazolidin-4-one 1,1-dioxide (3.A.3)
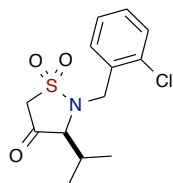
According to general procedure **C**, **3.A.3** (16 mg, 73%) was isolated as golden oil.

$[\alpha]_D^{20}$ = -124.56 (*c* = 1.25, CH$_2$Cl$_2$);

FTIR (neat): 3021, 2967, 2931, 1767, 1413, 1350, 1343, 1196, 1140, 1054, 843 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.62 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.33–7.26 (m, 2H), 4.75 (d, *J* = 16.0 Hz, 1H), 4.52 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 2H), 3.66 (d, *J* = 4.7 Hz, 1H), 2.10 (qd, *J* = 6.9, 2.2 Hz, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 197.8, 133.5, 132.8, 130.8, 129.8, 129.6, 127.4, 75.0, 55.9, 45.0, 30.2, 18.7, 17.1;

HRMS calculated for C$_{13}$H$_{16}$ClNO$_3$SH 302.0618 (M+H)$^+$; found 302.0613 (TOF MS ES$^+$).

(*S*)-3-isopropyl-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide (3.A.4)
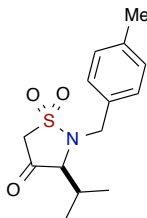
According to general procedure **C**, **3.A.4** (18 mg, 67%) was isolated as brownish oil.

$[\alpha]_D^{20}$ = -125.24 (*c* = 1.25, CH$_2$Cl$_2$);

FTIR (neat): 3016, 2969, 2929, 1758, 1409, 1348, 1323, 1201, 1139, 1054, 854 cm^{-1};

¹H NMR (500 MHz, CDCl₃) δ 7.26 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 4.60 (d, J = 15.4 Hz, 1H), 4.27 (d, J = 15.4 Hz, 1H), 3.72 (d, J = 1.2 Hz, 1H), 3.71 (s, 1H), 3.55 (dd, J = 4.5 Hz, 1.2, 1H), 2.32 (d, J = 7.5 Hz, 3H), 2.16–2.05 (m, 1H), 0.99 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 198.2, 138.1, 131.2, 129.6, 129.0, 73.4, 56.2, 47.2, 30.0, 21.1, 19.0, 17.1;

HRMS calculated for $C_{14}H_{19}NO_3SNa$ 304.0983 (M+Na)⁺; found 304.0983 (TOF MS ES⁺).

(S)-2-(4-bromobenzyl)-3-isopropylisothiazolidin-4-one 1,1-dioxide (3.A.5)
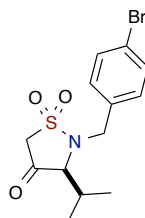
According to general procedure **C**, **3.A.5** (13 mg, 69%) was isolated as golden yellow oil.

$[\alpha]_D^{20}$ = -132.29 (c = 1.25, CH₂Cl₂);

FTIR (neat): 3016, 2969, 2929, 1758, 1409, 1348, 1323, 1201, 1139, 1054, 854 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 7.50–7.46 (m, 2H), 7.27 (d, J = 8.5 Hz, 2H), 4.47 (d, J = 15.8 Hz, 1H), 4.35 (d, J = 15.8 Hz, 1H), 3.76–3.74 (m, 2H), 3.55 (dd, J = 4.2 Hz, 1.0, 1H), 2.10–2.00 (m, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.9, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 197.3, 133.6, 132.0, 130.3, 123.0, 73.8, 56.4, 46.7, 30.3, 18.5, 16.6;

HRMS calculated for $C_{14}H_{16}BrNO_3SH$ 346.0113 (M+H)⁺; found 346.0115 (TOF MS ES⁺).

(*S*)-2-(4-chlorobenzyl)-3-isopropylisothiazolidin-4-one 1,1-dioxide (3.A.6)
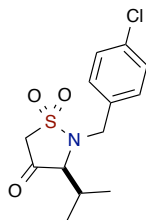
According to general procedure **C**, **3.A.6** (0.110 g, 61%) was isolated as brown oil.

$[\alpha]_D^{20}$ = -15.8 (*c* = 0.55, CH$_3$OH);

FTIR (thin film): 3299, 2938, 1757, 1718, 1598, 1491, 1415, 1316, 1207, 1094, 1051, 1015, 912, 846, 798, 717, 663 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.35 (s, 4H), 4.55–4.36 (m, 2H), 3.78–3.76 (m, 2H), 3.57 (dd, *J* = 4.3, 1.2 Hz, 1H), 2.12–2.03 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 197.75, 134.52, 133.18, 130.31, 129.28, 73.89, 56.41, 46.91, 30.00, 18.87, 16.99.

HRMS calculated for C$_{13}$H$_{17}$ClNO$_3$S (M+H)$^+$ 302.0618; found 302.0583 (TOF MS ES$^+$).

(*S*)-3-isopropyl-2-(4-(trifluoromethyl)benzyl)isothiazolidin-4-one 1,1-dioxide (3.A.7)
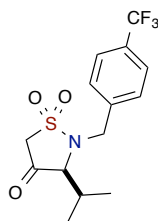
According to general procedure **C**, **3.A.7** (0.170 g, 51%) was isolated as a white solid.

$[\alpha]_D^{20}$ = -1.35 (*c* = 1.63, CH$_3$OH);

mp 95–97 °C;

FTIR (thin film): 2968, 1638, 1621, 1595, 1535, 1447, 1328, 1232, 1117, 1032, 1016, 967, 818 cm^{-1};

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 4.53 (s, 2H), 3.81 (s, 2H), 3.60 (d, *J* = 4.1 Hz, 1H), 2.08 (heptd, *J* = 6.9, 4.4 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 197.46, 139.02 (*d*, J = 1.08 Hz), 130.76 (q, *J* = 32.7 Hz), 129.07, 126.04 (q, *J* = 3.7 Hz), 124.01 (q, *J* = 272.1 Hz), 74.31, 56.35, 47.08, 30.03, 18.84, 16.93;

HRMS calculated for C$_{14}$H$_{16}$F$_3$NO$_3$SNa$^+$ (M+Na) 358.0695; found 358.0701.

(*S*)-2-benzyl-3-isobutylisothiazolidin-4-one 1,1-dioxide (3.A.8)
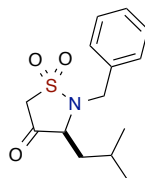
According to general procedure **C**, **3.A.8** (12 mg, 61%) was isolated as golden oil.

$[\alpha]_D^{20}$ = -123.56 (*c* = 1.25, CH$_2$Cl$_2$);

FTIR (neat): 2958, 2933 2358, 1758, 1496, 1456, 1348, 1319, 1203, 1127, 1053, 698 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.60–7.57 (m, 4H), 7.57–7.52 (m, 1H), 4.83 (d, *J* = 15.0 Hz, 1H), 4.52 (d, *J* = 14.9 Hz, 1H), 4.02 (dd, *J* = 17.0, 1.2 Hz, 1H), 3.97–3.92 (m, 2H), 1.94 (tt, *J* = 14.3, 7.2 Hz, 1H), 1.89–1.80 (m, 2H), 0.98 (dd, *J* = 13.2, 6.5 Hz, 6H);

¹³C NMR (126 MHz, CDCl³) δ 199.5, 134.2, 129.0, 128.6, 67.0, 55.4, 47.7, 39.3, 24.5, 22.5, 22.2;

HRMS calculated for $C_{14}H_{19}NO_3SH$ 282.1164 (M+H)⁺; found 282.1154 (TOF MS ES⁺).

(*S*)-2-(2-bromobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide (3.A.9)
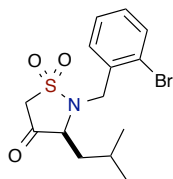
According to general procedure **C**, **3.A.9** (0.080 g, 37%) was isolated as yellow oil.

$[\alpha]_D^{20}$ = +30.4 (*c* = 0.25, CH₃OH);

FTIR (thin film): 2958, 2871, 1759, 1468, 1441, 1318, 1202, 1025, 851, 752, 660 cm⁻¹;

¹H NMR (500 MHz, Chloroform-*d*) δ 7.62–7.52 (m, 2H), 7.39–7.32 (m, 1H), 7.24–7.17 (m, 1H), 4.71 (dd, *J* = 15.6, 2.2 Hz, 1H), 4.53 (dd, *J* = 15.5, 2.3 Hz, 1H), 3.87 (s, 1H), 3.85–3.80 (m, 1H), 1.71–1.61 (m, 3H), 0.79–0.72 (m, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 199.27, 134.28, 133.33, 130.91, 130.06, 128.15, 123.90, 68.19, 55.09, 47.84, 39.60, 24.65, 22.66, 22.08.

HRMS calculated for $C_{14}H_{19}BrNO_3S$ (M+H)⁺ 360.0269; found 360.0255 (TOF MS ES⁺).

(*S*)-3-isobutyl-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide (3.A.10)
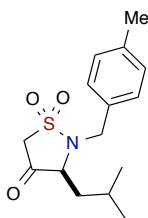
According to general procedure **C**, **3.A.10** (18 mg, 67%) was isolated as brownish oil.

$[\alpha]_D^{20}$ = 129.27 (*c* = 1.25, CH₂Cl₂);

FTIR (neat): 3029, 2940, 2855, 2359, 2335, 1768, 1470, 1321, 1225, 1145, 1127, 729, 711 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 7.24 (t, *J* = 3.6 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.62 (d, *J* = 14.9 Hz, 1H), 4.21 (d, *J* = 14.9 Hz, 1H), 3.78 (dd, *J* = 16.9 Hz, 1.2, 1H), 3.75–3.71 (m, 1H), 3.69 (d, *J* = 16.9 Hz, 1H), 2.32 (d, *J* = 6.7 Hz, 3H), 1.79–1.70 (m, 1H), 1.70–1.58 (m, 2H), 0.78 (dd, *J* = 13.2, 6.5 Hz, 6H);

¹³C NMR (126 MHz, CDCl₃) δ 199.6, 138.4, 131.0, 129.6, 129.0, 66.6, 55.3, 47.7, 39.3, 24.5, 22.5, 22.2, 21.1;

HRMS calculated for $C_{15}H_{21}NO_3SH$ 296.1320 (M+H)⁺; found 296.1315 (TOF MS ES⁺).

(*S*)-3-benzyl-2-(2-methylallyl)isothiazolidin-4-one 1,1-dioxide (3.A.11)
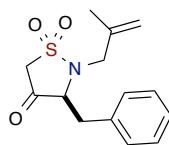
According to general procedure **C**, **3.A.11** (22 mg, 63%) was isolated as yellow oil.

$[\alpha]_D^{20}$ = -104.23 (*c* = 1.25, CH₂Cl₂);

FTIR (neat): 3006, 2956, 2929, 2869, 1758, 1348, 1321, 1201, 1137, 1054, 1020, 811 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 7.32–7.24 (m, 3H), 7.21–7.17 (m, 2H), 4.90 (s, 1H), 4.69 (s, 1H), 4.07 (ddd, *J* = 7.8, 4.9, 1.1 Hz, 1H), 3.81 (d, *J* = 14.8 Hz, 1H), 3.74 (d, *J* = 16.8 Hz, 1H), 3.58 (dd, *J* = 16.8, 1.0 Hz, 1H), 3.45 (d, *J* = 14.8 Hz, 1H), 3.17 (dd, *J* = 14.2, 4.9 Hz, 1H), 3.10 (dd, *J* = 14.2, 7.8 Hz, 1H), 1.58 (s, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 198.7, 138.7, 135.5, 129.6, 128.8, 127.4, 116.8, 76.7, 69.3, 55.4, 55.3, 50.4, 37.1, 19.9;

HRMS calculated for C₁₄H₁₇NO₃SH 280.1007 (M+H)⁺; found 280.0997 (TOF MS ES⁺).

(*S*)-2-allyl-3-benzylisothiazolidin-4-one 1,1-dioxide (3.A.12)
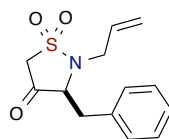
According to general procedure **C**, **3.A.12** (9 mg, 65%) was isolated as golden oil.

$[\alpha]_D^{20}$ = -142.58 (*c* = 1.25, CH₂Cl₂);

FTIR (neat): 3015, 2967, 2935, 2875, 1763, 1351, 1332, 1212, 1141, 1071, 1032, 811 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 7.31 (ddd, *J* = 8.5 Hz, 7.7, 3.6, 3H), 7.22–7.18 (m, 2H), 5.70 (dddd, *J* = 17.0, 10.0, 8.6, 5.3 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 5.11 (d, *J* = 17.1 Hz, 1H), 4.13–4.03 (m, 2H), 3.66 (d, *J* = 16.6 Hz, 1H), 3.46 (ddd, *J* = 23.9 Hz, 16.0, 4.9, 2H), 3.13 (ddd, *J* = 21.5, 14.2, 5.9 Hz, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 198.5, 135.2, 130.9, 129.7, 128.7, 126.7, 121.5, 69.1, 55.8, 47.0, 36.3;

HRMS calculated for C₁₃H₁₅NO₃SNa 288.0670 (M+Na)⁺; found 288.0652 (TOF MS ES⁺).

(*S*)-3-benzyl-2-(4-fluorobenzyl)isothiazolidin-4-one 1,1-dioxide (3.A.13)
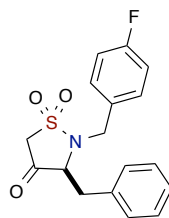
According to general procedure **C**, **3.A.13** (0.131 g, 96%) was isolated as yellow solid.

$[\alpha]_D^{20}$ = +9.00 (c = 0.10, CH$_3$OH);

mp 123–125 °C;

FTIR (thin film): 3010, 2937, 1748, 1604, 1510, 1492, 1329, 1224, 1119, 1035, 841, 745, 699, 681 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-d) δ 7.34–7.29 (m, 3H), 7.16–7.12 (m, 2H), 7.10–7.05 (m, 2H), 7.00–6.94 (m, 2H), 4.66–4.58 (m, 1H), 3.93 (ddd, J = 8.2, 4.3, 1.4 Hz, 1H), 3.83 (d, J = 15.0 Hz, 1H), 3.73–3.54 (m, 2H), 3.17–3.04 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-d) δ 198.03, 162.68 (d, J = 247.9 Hz), 135.52, 130.88 (d, J = 8.2 Hz), 129.62 (d, J = 3.3 Hz), 129.51, 128.90, 127.46, 115.89 (d, J = 21.6 Hz), 68.94, 55.83, 47.28, 37.10.

HRMS calculated for C$_{17}$H$_{17}$FNO$_3$S (M+H)$^+$ 334.0913; found 334.0927 (TOF MS ES$^+$).

(S)-2-(2-fluorobenzyl)-3-methylisothiazolidin-4-one 1,1-dioxide (3.A.14)
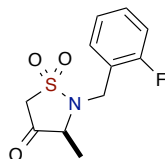
According to general procedure **C**, **3.A.14** (0.049 g, 32%) was isolated as yellow oil.

$[\alpha]_D^{20}$ = +30.0 (c = 0.10, CH$_3$OH);

FTIR (thin film): 2937, 1763, 1618, 1588, 1492, 1456, 1316, 1211, 1138, 1054, 1033, 872, 843, 820, 761, 693 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.55–7.49 (m, 1H), 7.37–7.30 (m, 1H), 7.22–7.16 (m, 1H), 7.12–7.05 (m, 1H), 4.62–4.55 (m, 1H), 4.53–4.46 (m, 1H), 3.90–3.82 (m, 3H), 1.41 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 198.38, 160.95 (d, $^1J_{C-F}$ = 247.0 Hz), 131.35 (d, $^2J_{C-F}$ = 3.5 Hz), 130.38 (d, $^3J_{C-F}$ = 8.1 Hz), 124.77 (d, $^4J_{C-F}$ = 3.6 Hz), 121.72 (d, $^5J_{C-F}$ = 14.1 Hz), 115.72 (d, $^6J_{C-F}$ = 21.5 Hz), 64.32, 55.11, 38.41, 15.05.

HRMS calculated for C$_{11}$H$_{13}$FNO$_3$S (M+H)$^+$ 258.0600; found 258.0582 (TOF MS ES$^+$).

(*S*)-3-((*R*)-*sec*-butyl)-2-(4-fluorobenzyl)isothiazolidin-4-one 1,1-dioxide (3.A.16)
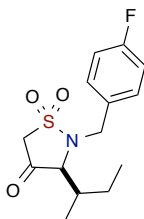
According to general procedure **C**, **3.A.16** (0.119 g, 66%) was isolated as yellow oil.

$[\alpha]_D^{20}$ = -22.9 (*c* = 0.80, CH$_3$OH);

FTIR (thin film): 3104, 2984, 1758, 1606, 1511, 1316, 1222, 1139, 704 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42–7.37 (m, 2H), 7.09–7.04 (m, 2H), 4.56 (d, *J* = 15.7 Hz, 1H), 4.33 (d, *J* = 15.7 Hz, 1H), 3.78–3.75 (m, 2H), 3.67 (dd, *J* = 3.9, 0.9 Hz, 1H), 1.82–1.74 (m, 1H), 1.51 (ddd, *J* = 14.0, 7.5, 6.5 Hz, 1H), 1.39 (dt, *J* = 14.0, 7.5 Hz, 1H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 197.72, 162.64 (d, $^1J_{\text{C-F}}$ = 247.8 Hz), 130.71 (d, $^2J_{\text{C-F}}$ = 8.2 Hz), 130.09 (d, $^3J_{\text{C-F}}$ = 3.2 Hz), 115.87 (d, $^4J_{\text{C-F}}$ = 21.5 Hz), 71.73, 56.54, 45.73, 36.21, 25.68, 13.97, 11.87.

HRMS calculated for $C_{14}H_{19}FNO_3S$ (M+H)$^+$ 300.1070; found 300.1076 (TOF MS ES$^+$).

(*S*)-2-(4-bromobenzyl)-3-((*R*)-*sec*-butyl)isothiazolidin-4-one 1,1-dioxide (3.A.17)
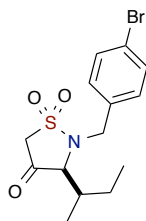
According to general procedure **C**, **3.A.17** (10 mg, 50%) was isolated as golden oil.

$[\alpha]_D^{20}$ = -128.25 (*c* = 1.25, CH_2Cl_2);

FTIR (neat): 2964, 2933, 2358, 2341, 1758, 1488, 1319, 205, 1139, 1070, 1010, 796 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.62–7.47 (m, 2H), 7.41–7.19 (m, 3H), 4.57–4.31 (m, 3H), 3.85–3.77 (m, 2H), 3.69 (dd, *J* = 7.4 Hz, 3.8, 1H), 1.84–1.73 (m, 1H), 1.60–1.48 (m, 1H), 1.47–1.36 (m, 1H), 1.06–1.00 (m, 1H), 0.91 (d, *J* = 6.9, 3H), 0.86–0.77 (m, 4H);

^{13}C NMR (126 MHz, CDCl3) δ 197.6, 132.1, 130.9, 122.5, 77.1, 72.0, 45.9, 36.5, 25.7, 14.4, 11.9;

HRMS calculated for $C_{13}H_{18}BrNO_3SH$ 360.0269 (M+H)$^+$; found 360.0255 (TOF MS ES$^+$).

(*S*)-3-((1*H*-indol-2-yl)methyl)-2-(4-iodobenzyl)isothiazolidin-4-one 1,1-dioxide (3.A.18)
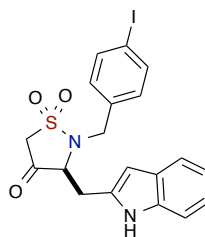
According to general procedure **C**, **3.A.18** (3 mg, 20%) was isolated as golden oil.

$[\alpha]_D^{20}$ = -145.26 (*c* = 1.25, CH$_2$Cl$_2$);

FTIR (neat): 2964, 2933, 2873, 1781, 1485, 1436, 1372, 1292, 1201, 1128, 1171, 1006, 962, 910, 883, 831, 790, 773, 526, 518, cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.01 (s, 1H), 7.47–7.42 (m, 2H), 7.37–7.28 (m, 2H), 7.17–7.13 (m, 1H), 7.08–7.01 (m, 1H), 6.96 (t, *J* = 6.1 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 2H), 4.41 (d, *J* = 15.1 Hz, 1H), 3.98 (t, *J* = 5.6 Hz, 1H), 3.82 (d, *J* = 15.1 Hz, 1H), 3.57 (dt, *J* = 16.7 Hz, 8.9, 2H), 3.20 (dd, *J* = 10.7, 7.1 Hz, 2H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 198.1, 137.4, 135.8, 133.6, 130.8, 126.3, 123.4, 122.6, 119.9, 118.3, 111.2, 108.8, 94.0, 68.3, 55.7, 48.0, 27.2;

HRMS calculated for C$_{19}$H$_{17}$IN$_2$O$_3$SH 481.0083 (M+H)$^+$; found 481.0074 (TOF MS ES$^+$).

(*S*)-tetrahydropyrrolo[1,2-*b*]isothiazol-3(2*H*)-one 1,1-dioxide (3.33.3)
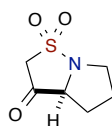
According to general procedure **C**, **3.33.3** (0.149 g, 88%) was isolated as yellow oil.

$[\alpha]_D^{20}$ = -54.7 (*c* = 0.15, CH$_3$OH);

FTIR (thin film): 3009, 2939, 1755, 1462, 1310, 1195, 1126, 1094, 1060, 986, 946, 886, 781 cm^{-1};

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.28 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.83–3.72 (m, 2H), 3.54 (dd, *J* = 17.5, 1.0 Hz, 1H), 3.48 (ddd, *J* = 11.3, 7.9, 6.5 Hz, 1H), 2.39–2.18 (m, 2H), 2.04–1.91 (m, 1H), 1.84–1.70 (m, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 203.83, 72.29, 53.86, 51.12, 30.24, 25.36.

HRMS calculated for C$_6$H$_{10}$NO$_3$S (M+H)$^+$ 176.0381; found 176.0357 (TOF MS ES$^+$).

(3a*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)tetrahydropyrrolo[1,2-*b*]isothiazol-3(2*H*)-one 1,1-dioxide (3.33.4)
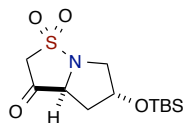
According to general procedure **C**, **3.33.4** (10 mg, 72%) was isolated as pink dense oil.

$[\alpha]_D^{20}$ = -142.31 (*c* = 1.25, CH$_2$Cl$_2$);

FTIR (neat): 2952, 2929, 2856, 2358, 2343, 1762, 1348, 1340, 1201, 1143, 1026, 837, 777 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$) δ 4.46 (t, *J* = 7.5 Hz, 1H), 4.41–4.37 (m, 1H), 3.81–3.76 (m, 2H), 3.68–3.63 (m, 1H), 3.29 (dd, *J* = 11.4, 3.7 Hz, 1H), 2.24–2.11 (m, 2H), 0.84 (s, 9H), 0.03 (s, 6H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 201.6, 71.4, 71.2, 56.7, 53.9, 38.5, 25.6, 18.0;

HRMS calculated for C$_{12}$H$_{23}$NO$_4$SSiH 306.1195 (M+H)$^+$; found 306.1181 (TOF MS ES$^+$).

tetrahydro-2*H*-isothiazolo[2,3-*a*]pyridin-3(3a*H*)-one 1,1-dioxide (3.33.5)
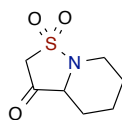
According to general procedure **C**, **3.33.5** (2.121 g, 87%) was isolated as white viscous oil.

FTIR (thin film): 2941, 2863, 1765, 1720, 1432, 1303, 1207, 1135, 1044, 945, 804, 764, 706 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.82–3.76 (m, 1H), 3.76–3.73 (m, 2H), 3.62–3.54 (m, 1H), 2.86 (td, *J* = 12.0, 3.0 Hz, 1H), 2.22 (dqd, *J* = 12.7, 3.3, 1.3 Hz, 1H), 1.99 (dqd, *J* = 13.5, 3.3, 1.2 Hz, 1H), 1.91–1.82 (m, 1H), 1.65–1.53 (m, 1H), 1.52–1.45 (m, 1H), 1.40 (qt, *J* = 13.1, 3.4 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 197.43, 66.40, 54.60, 40.24, 25.66, 23.46, 22.74.

HRMS calculated for C$_7$H$_{12}$NO$_3$S (M+H)$^+$ 190.0538; found 190.0511 (TOF MS ES$^+$).

\textit{tert}-butyl   3-oxohexahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate   1,1-dioxide (3.33.6)
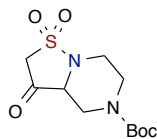
According to general procedure **C**, **3.33.6** (0.345 g, 43%) was isolated as brown oil.

**FTIR (thin film):** 2975, 2867, 2844, 1685, 1414, 1367, 1240, 1132, 1055, 1033, 950, 894, 766, 728 706 cm^{-1};

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.48 (s, 1H), 4.21 (s, 1H), 3.78 (s, 2H), 3.71 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.65 (d, *J* = 9.2 Hz, 1H), 3.05–2.79 (m, 3H), 1.48 (s, 9H).

^{13}**C NMR (101 MHz, CDCl$_3$)** δ 153.97, 81.36, 77.21, 64.24, 54.85, 39.99, 28.30.

HRMS calculated for C$_{11}$H$_{18}$N$_2$O$_5$SNa (M+Na)$^+$ 313.0834; found 313.0851 (TOF MS ES$^+$).

tetrahydroisothiazolo[3,2-*c*][1,4]oxazin-3(2*H*)-one 1,1-dioxide (3.33.7)
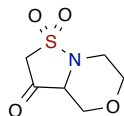
According to general procedure **C**, **3.33.7** (0.024 g, 56%) was isolated as light yellow viscous oil.

FTIR (thin film): 2943, 2859, 1765, 1720, 1432, 1303, 1203, 1130, 1044, 950, 804, 760, 706 cm^{-1};

^{1}**H NMR (400 MHz, Chloroform-*d*)** δ 4.22 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.00 (dt, *J* = 11.7, 2.9 Hz, 1H), 3.92 (dd, *J* = 9.1, 4.0 Hz, 1H), 3.77 (d, *J* = 1.5 Hz, 2H), 3.70–3.61 (m, 2H), 3.56 (dt, *J* = 12.1, 2.7 Hz, 1H), 3.25 (ddd, *J* = 11.9, 10.5, 3.4 Hz, 1H).

^{13}**C NMR (126 MHz, Chloroform-*d*)** δ 195.07, 65.13, 65.10, 63.99, 54.23, 40.87.

HRMS calculated for C$_6$H$_9$NO$_4$SNa (M+Na)$^+$ 214.0150; found 214.0166 (TOF MS ES$^+$).

1-benzyl-4-hydroxy-*N*-phenyl-2-thia-1-azaspiro[4.5]dec-3-ene-3-carboxamide 2,2-dioxide (3.36.5)
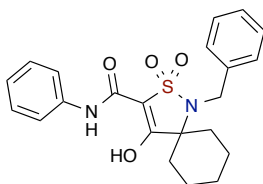
According to general procedure **D**, **3.36.5** (0.030 g, 43%) was isolated as yellow viscous oil.

**FTIR (thin film):** 3399, 2935, 2255, 1748, 1645, 1537, 1444, 1324, 1226, 1135, 1023, 997, 824, 761, 699 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.59–7.38 (m, 4H), 7.35–7.14 (m, 5H), 6.98–6.86 (m, 1H), 4.23 (s, 2H), 2.10–1.93 (m, 2H), 1.64–1.56 (m, 2H), 1.55–1.37 (m, 6H).

^{13}C NMR (126 MHz, DMSO) δ 185.80, 161.42, 140.54, 140.25, 128.72, 127.90, 127.52, 126.45, 121.43, 118.40, 94.75, 64.88, 40.43, 32.29, 24.55, 22.32.

HRMS calculated for C$_{22}$H$_{23}$N$_2$O$_4$S (M-H)$^-$ 411.1379; found 411.1393 (TOF MS ES$^-$).

1-benzyl-4-hydroxy-*N*-(4-methoxyphenyl)-2-thia-1-azaspiro[4.5]dec-3-ene-3-carboxamide 2,2-dioxide (3.36.6)
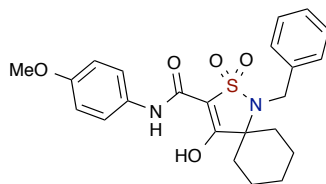
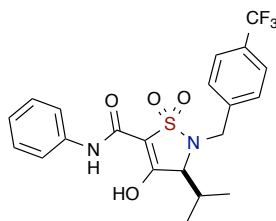According to general procedure **D**, **3.36.6** (0.047 g, 62%) was isolated as yellow viscous oil.

FTIR (thin film): 3420, 2934, 2252, 1643, 1511, 1455, 1415, 1242, 1141, 1052, 1007, 823, 761 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 7.50–7.41 (m, 4H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.24–7.17 (m, 1H), 6.88–6.81 (m, 2H), 4.27 (s, 2H), 3.72 (s, 3H), 2.06–1.87 (m, 2H), 1.70–1.60 (m, 2H), 1.59–1.39 (m, 6H).

^{13}C NMR (126 MHz, DMSO) δ 185.92, 160.89, 154.48, 140.21, 132.89, 127.96, 127.50, 126.57, 120.33, 113.94, 93.65, 65.47, 55.14, 40.43, 32.11, 24.41, 22.26.

HRMS calculated for C$_{22}$H$_{23}$N$_2$O$_4$S (M-H)$^-$ 411.1379; found 411.1393 (TOF MS ES$^-$).

1-benzyl-*N*-(4-fluorophenyl)-4-hydroxy-2-thia-1-azaspiro[4.5]dec-3-ene-3-carboxamide 2,2-dioxide (3.36.7)
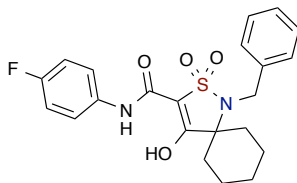
According to general procedure **D**, **3.36.7** (0.035 g, 48%) was isolated as yellow viscous oil.

FTIR (thin film): 3437, 2939, 2251, 2125, 1653, 1206, 1052, 1007, 822, 760 cm^{-1};

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.92 (s, 1H), 7.60–7.52 (m, 2H), 7.47–7.41 (m, 2H), 7.32–7.25 (m, 2H), 7.23–7.16 (m, 1H), 7.11–7.04 (m, 2H), 4.24 (s, 2H), 2.01 (tq, *J* = 12.9, 10.5, 5.4, 4.5 Hz, 2H), 1.61 (d, *J* = 13.7 Hz, 2H), 1.57–1.33 (m, 6H).

^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 185.89, 161.27, 157.12 (d, $^1J_{\text{C-F}}$ = 237.6 Hz), 140.44, 136.52 (d, $^2J_{\text{C-F}}$ = 2.9 Hz), 127.93, 127.52, 126.06, 120.03 (d, $^3J_{\text{C-F}}$ = 7.5 Hz), 115.20 (d, $^4J_{\text{C-F}}$ = 21.8 Hz), 93.66, 65.03, 40.43, 32.24, 24.51, 22.30.

HRMS calculated for C$_{22}$H$_{22}$FN$_2$O$_4$S (M-H)$^-$ 429.1284; found 429.1299 (TOF MS ES$^-$).

1-benzyl-4-hydroxy-*N*-(*p*-tolyl)-2-thia-1-azaspiro[4.5]dec-3-ene-3-carboxamide 2,2-dioxide (3.36.8)
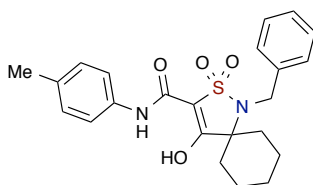
According to general procedure **D**, **3.36.8** (0.046 g, 63%) was isolated as yellow viscous oil.

FTIR (thin film): 3437, 2940, 2250, 2124, 1648, 1052, 1027, 1008, 821, 758 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.47–7.40 (m, 4H), 7.33–7.26 (m, 2H), 7.23–7.17 (m, 1H), 7.10–7.03 (m, 2H), 4.26 (s, 2H), 2.24 (s, 3H), 2.05–1.90 (m, 2H), 1.64 (d, J = 12.9 Hz, 2H), 1.58–1.39 (m, 5H).

^{13}C NMR (126 MHz, DMSO) δ 185.80, 161.07, 140.28, 137.32, 130.70, 129.18, 127.96, 127.51, 126.56, 118.77, 93.14, 65.30, 40.43, 32.14, 24.45, 22.28, 20.46.

HRMS calculated for C$_{23}$H$_{27}$N$_2$O$_4$S (M+H)$^+$ 427.1692; found 427.1686 (TOF MS ES$^+$).

3-hydroxy-*N*-phenyl-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyridine-2-carboxamide 1,1-dioxide (3.36.9)
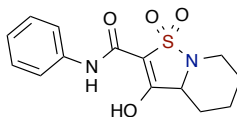
According to general procedure **D**, **3.36.9** (0.083 g) was isolated as brown oil.

FTIR (thin film): 2928, 1641, 1575, 1423, 1360, 1271, 1101, 756, 700 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.49 (dt, J = 8.9, 1.7 Hz, 2H), 7.26–7.18 (m, 2H), 6.90 (t, J = 7.3 Hz, 1H), 3.41 (d, J = 13.4 Hz, 1H), 3.17 (dd, J = 11.6, 3.1 Hz, 1H), 2.57 (td, J = 12.1, 3.0 Hz, 1H), 1.96–1.88 (m, 1H), 1.82 (d, J = 12.7 Hz, 1H), 1.59 (d, J = 12.5 Hz, 1H), 1.49–1.29 (m, 2H), 1.16 (qd, J = 12.4, 3.5 Hz, 1H).

^{13}C NMR (101 MHz, DMSO) δ 161.15, 128.86, 128.66, 121.20, 118.15, 61.32, 50.69, 38.77, 26.75, 23.89, 23.27.

HRMS calculated for C$_{14}$H$_{17}$N$_2$O$_4$S (M+H)$^+$ 309.0909; found 309.0886 (TOF MS ES$^+$).

3-hydroxy-*N*-(*p*-tolyl)-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyridine-2-carboxamide 1,1-dioxide (3.36.10)
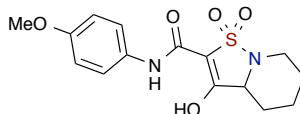
According to general procedure **D**, **3.36.10** (0.095 g, 53%) was isolated as brown oil.

FTIR (thin film): 3274, 2943, 2860, 1727, 1619, 1543, 1415, 1337, 1230, 1129, 1030, 955, 829 cm^{-1};

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.52 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.71 (s, 2H), 3.19–3.11 (m, 1H), 2.58 (t, *J* = 11.9 Hz, 1H), 2.51 (s, 3H), 1.93 (d, *J* = 12.5 Hz, 1H), 1.82 (d, *J* = 12.4 Hz, 1H), 1.64–1.55 (m, 1H), 1.40 (dq, *J* = 23.3, 12.7 Hz, 1H), 1.15 (q, *J* = 11.8 Hz, 1H).

^{13}C NMR (101 MHz, DMSO) δ 154.00, 135.93, 133.67, 119.66, 113.97, 61.34, 55.15, 26.85, 25.51, 23.94, 23.31.

HRMS calculated for C$_{15}$H$_{19}$N$_2$O$_5$S (M+H)$^+$ 339.1015; found 339.0979 (TOF MS ES$^+$).

3-hydroxy-*N*-(*p*-tolyl)-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyridine-2-carboxamide 1,1-dioxide (3.36.12)
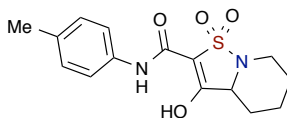
According to general procedure **D**, **3.36.12** (0.051 g, 30%) was isolated as brown oil.

FTIR (thin film): 3336, 3063, 2941, 2852, 1666, 1593, 1535, 1441, 1353, 1222, 1118, 1050, 1008, 943, 814 cm^{-1};

¹H NMR (400 MHz, DMSO-*d₆*) δ 10.37 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 3.44 (d, *J* = 12.9 Hz, 1H), 3.30 (dd, *J* = 11.7, 3.1 Hz, 1H), 3.10 (qd, *J* = 7.1, 4.7 Hz, 2H), 2.62 (td, *J* = 12.1, 3.0 Hz, 1H), 2.23 (s, 3H), 2.00–1.90 (m, 1H), 1.82 (d, *J* = 11.8 Hz, 1H), 1.59 (d, *J* = 11.7 Hz, 1H), 1.49–1.31 (m, 2H).

¹³C NMR (101 MHz, DMSO) δ 160.41, 137.39, 130.45, 129.08, 118.49, 60.62, 45.78, 38.77, 26.89, 23.75, 23.10, 20.36, 8.62.

HRMS calculated for $C_{15}H_{19}N_2O_4S$ (M+H)⁺ 323.1066; found 323.1026 (TOF MS ES⁺).

tert-butyl 3-hydroxy-2-(phenylcarbamoyl)-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (3.36.13)
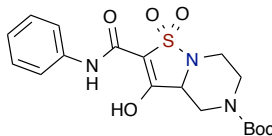
According to general procedure **D**, **3.36.13** (0.059 g, 70%) was isolated as orange viscous oil.

FTIR (thin film): 2981, 2160, 1691, 1630, 1586, 1510, 1416, 1241, 1162, 1130, 1031, 830 cm⁻¹;

¹H NMR (500 MHz, DMSO-*d₆*) δ 10.60 (s, 1H), 7.52–7.47 (m, 2H), 7.27–7.21 (m, 2H), 6.92 (tt, *J* = 7.3, 1.2 Hz, 1H), 4.07 (s, 1H), 3.81 (d, *J* = 12.4 Hz, 1H), 3.46–3.38 (m, 2H), 3.12–3.06 (m, 2H), 2.76 (ddd, *J* = 12.8, 11.5, 3.5 Hz, 1H), 1.42 (s, 9H).

¹³C NMR (126 MHz, DMSO) δ 177.85, 160.91, 153.79, 140.09, 128.77, 121.55, 118.28, 97.77, 79.34, 59.55, 45.76, 40.43, 28.04, 8.66.

HRMS calculated for $C_{18}H_{24}N_3O_6S$ (M+H)⁺ 410.1386; found 410.1380 (TOF MS ES⁺).

***tert*-butyl** 3-hydroxy-2-((4-methoxyphenyl)carbamoyl)-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (3.36.14)
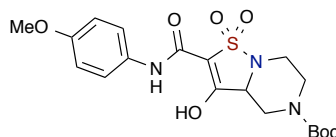
According to general procedure **D**, **3.36.14** (0.054 g, 59%) was isolated as orange viscous oil.

FTIR (thin film): 2985, 2161, 1692, 1634, 1584, 1543, 1512, 1413, 1239, 1166, 1128, 1034, 832 cm^{-1};

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.44 (s, 1H), 7.44–7.38 (m, 2H), 6.86–6.81 (m, 2H), 4.15–3.98 (m, 1H), 3.87–3.77 (m, 1H), 3.70 (s, 3H), 3.46–3.37 (m, 2H), 3.12–3.07 (m, 2H), 2.76 (ddd, *J* = 12.8, 11.5, 3.6 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, DMSO) δ 177.58, 160.73, 154.13, 153.79, 133.28, 119.72, 113.96, 97.59, 79.33, 59.54, 55.11, 45.77, 40.43, 28.04, 8.65.

HRMS calculated for C$_{19}$H$_{26}$N$_3$O$_7$S (M+H)$^+$ 440.1491; found 440.1482 (TOF MS ES$^+$).

***tert*-butyl** 2-((4-fluorophenyl)carbamoyl)-3-hydroxy-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (3.36.15)
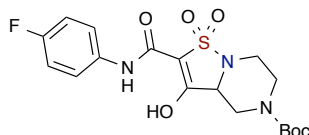
According to general procedure **D**, **3.36.15** (0.061 g, 69%) was isolated as orange viscous oil.

FTIR (thin film): 2979, 1702, 1573, 1514, 1415, 1362, 1240, 1161, 1125, 1031, 901, 812, 760 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.54–7.48 (m, 2H), 7.11–7.05 (m, 2H), 4.15–3.98 (m, 1H), 3.86–3.76 (m, 1H), 3.46–3.38 (m, 2H), 3.11–3.07 (m, 2H), 2.76 (ddd, J = 12.9, 11.5, 3.5 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 177.88, 160.77, 154.91 (d, $^1J_{C-F}$ = 295.1 Hz), 136.40 (d, $^2J_{C-F}$ = 2.4 Hz), 119.74 (d, $^3J_{C-F}$ = 7.6 Hz), 115.19 (d, $^4J_{C-F}$ = 22.0 Hz), 97.53, 79.30, 59.50, 45.71, 40.37, 27.98, 8.60.

HRMS calculated for C$_{18}$H$_{23}$FN$_3$O$_6$S (M+H)$^+$ 428.1292; found 428.1282 (TOF MS ES$^+$).

tert-butyl   3-hydroxy-2-(_p_-tolylcarbamoyl)-3a,4,6,7-tetrahydro-5_H_-isothiazolo[2,3-_a_]pyrazine-5-carboxylate 1,1-dioxide (3.36.16)
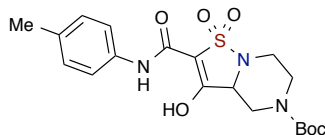
According to general procedure **D**, **3.36.16** (0.025 g, 28%) was isolated as orange viscous oil.

FTIR (thin film): 2977, 1700, 1574, 1516, 1413, 1365, 1238, 1164, 1123, 1032, 902, 811, 759 cm^{-1};

1H NMR (500 MHz, DMSO-d_6) δ 10.51 (s, 1H), 7.40–7.35 (m, 2H), 7.06–7.02 (m, 2H), 4.14–3.97 (m, 1H), 3.86–3.75 (m, 1H), 3.46–3.37 (m, 2H), 3.10–2.85 (m, 2H), 2.75 (ddd, J = 12.9, 11.6, 3.5 Hz, 1H), 2.22 (s, 3H), 1.42 (s, 9H).

13C NMR (126 MHz, DMSO) δ 177.68, 160.83, 153.79, 137.55, 130.28, 129.17, 118.30, 97.71, 79.34, 59.53, 40.43, 38.36, 28.04, 20.40, 8.66.

HRMS calculated for $C_{23}H_{25}N_2O_5S$ (M-H)$^-$ 441.1484; found 441.1499 (TOF MS ES$^-$).

3-hydroxy-*N*-phenyl-3a,4,6,7-tetrahydroisothiazolo[3,2-*c*][1,4]oxazine-2-carboxamide 1,1-dioxide (3.36.17)
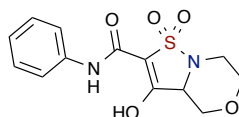
According to general procedure **D**, **3.36.17** (0.030 g, 37%) was isolated as dark brown viscous oil.

FTIR (thin film): 3260, 2940, 2256, 1720, 1680, 1605, 1549, 1346, 1230, 1152, 1112, 954, 830 cm^{-1};

1H NMR (500 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.51–7.47 (m, 2H), 7.24 (dd, J = 8.3, 7.3 Hz, 2H), 6.93 (ddt, J = 8.3, 7.5, 1.4 Hz, 1H), 3.89 (dd, J = 11.1, 4.2 Hz, 1H), 3.70–3.63 (m, 2H), 3.50–3.43 (m, 1H), 3.39–3.34 (m, 1H), 3.30 (t, J = 10.7 Hz, 1H), 3.01–2.93 (m, 1H).

13C NMR (126 MHz, DMSO) δ 171.16, 160.37, 138.48, 128.96, 123.97, 119.18, 67.98, 65.86, 59.13, 55.43, 42.17.

HRMS calculated for $C_{13}H_{15}N_2O_5S$ (M+H)$^+$ 311.0702; found 311.0690 (TOF MS ES$^+$).

3-hydroxy-*N*-(4-methoxyphenyl)-3a,4,6,7-tetrahydroisothiazolo[3,2-*c*][1,4]oxazine-2-carboxamide 1,1-dioxide (3.36.18)
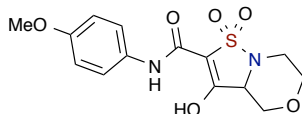
According to general procedure **D**, **3.36.18** (0.021 g, 30%) was isolated as dark brown viscous oil.

FTIR (thin film): 3264, 2937, 2258, 1723, 1680, 1608, 1551, 1348, 1237, 1155, 1110, 1023, 956, 829 cm^{-1};

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.15 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.31–4.25 (m, 2H), 4.22–4.13 (m, 2H), 3.82 (d, *J* = 9.6 Hz, 1H), 3.73 (s, 3H), 3.65 (dd, *J* = 11.7, 3.8 Hz, 1H), 3.50–3.44 (m, 1H).

^{13}C NMR (101 MHz, DMSO) δ 171.11, 159.81, 155.63, 131.59, 120.71, 114.02, 67.92, 65.82, 59.05, 55.17, 42.12, 39.52.

HRMS calculated for C$_{14}$H$_{15}$N$_2$O$_6$S (M-H)$^-$ 339.0651; found 339.0631 (TOF MS ES$^-$).

3-hydroxy-*N*-(*p*-tolyl)-3a,4,6,7-tetrahydroisothiazolo[3,2-*c*][1,4]oxazine-2-carboxamide 1,1-dioxide (3.36.20)
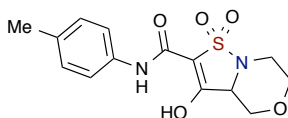
According to general procedure **D**, **3.36.20** (0.018 g, 27%) was isolated as dark brown viscous oil.

FTIR (thin film): 3266, 2931, 2257, 1724, 1683, 1610, 1545, 1514, 1348, 1330, 1223, 1155, 1109, 1048, 1023, 936, 821 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 4.33–4.26 (m, 2H), 4.24–4.13 (m, 2H), 3.85–3.78 (m, 1H), 3.65 (dd, J = 11.6, 3.8 Hz, 1H), 3.50–3.44 (m, 1H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 171.11, 160.07, 135.96, 132.94, 129.27, 119.17, 67.92, 65.82, 59.12, 55.40, 42.13, 20.45.

HRMS calculated for C$_{14}$H$_{15}$N$_2$O$_5$S (M-H)$^-$ 323.0702; found 323.0688 (TOF MS ES$^-$).

(S)-4-hydroxy-3-isopropyl-N-phenyl-2-(4-(trifluoromethyl)benzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide (3.36.21)

According to general procedure **D**, **3.36.21** (0.016 g, 99%) was isolated as a white solid.

$[\alpha]_D^{20}$ = -23.41 (c = 0.44, CH$_3$OH);

mp 103–105 °C;

FTIR (neat): 3393, 2985, 2968, 1626, 1587, 1538, 1448, 1421, 1325, 1233, 1161, 1141, 1098, 1066, 1031, 1016, 966, 820 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.24 (t, J = 7.8 Hz, 2H), 6.92 (t, J = 7.3 Hz, 1H), 4.63 (d,

J = 16.9 Hz, 1H), 4.20 (d, *J* = 17.0 Hz, 1H), 3.39 (d, *J* = 2.3 Hz, 1H), 2.03 (ddt, *J* = 13.9, 7.0,

3.6 Hz, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H);

13C NMR (126 MHz, DMSO) δ 179.51, 160.99, 144.19, 140.22, 128.75, 128.40, 127.40 (q,

J = 31.7 Hz), 125.05 (q, *J* = 3.6 Hz), 124.42 (d, *J* = 271.9Hz), 121.46, 118.30, 97.86, 71.70,

49.30, 30.14, 18.58, 17.28;

HRMS calculated for $C_{21}H_{21}F_3N_2O_4SNa^+$ (M+Na) 477.1066; found 477.1072.

(*S*)-4-hydroxy-3-isopropyl-*N*-(4-methoxyphenyl)-2-(4-(trifluoromethyl)benzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide (3.36.22)
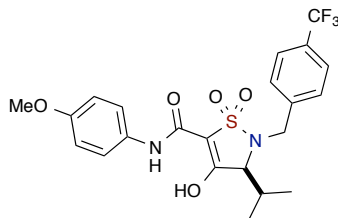
According to general procedure **D**, **3.36.22** (0.160 g, 53%) was isolated as a white solid.

$[\alpha]_D^{20}$ = -9.23 (*c* = 0.26, CH₃OH);

mp >300 °C;

FTIR (neat): 2968, 1625, 1587, 1546, 1514, 1430, 1329, 1235, 1168, 1146, 1096, 1067,

1033, 1015, 918, 825 cm⁻¹

1H NMR (500 MHz, DMSO-*d*₆) δ 10.79 (s, 1H), 7.69 (q, *J* = 8.2 Hz, 4H), 7.44 (d, *J* = 9.0

Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 4.62 (d, *J* = 17.1 Hz, 1H), 4.19 (d, *J* = 16.9 Hz, 1H), 3.71

(s, 3H), 3.36 (d, *J* = 2.5 Hz, 1H), 2.01 (ddd, *J* = 13.2, 6.6, 2.3 Hz, 1H), 0.89 (d, *J* = 6.8 Hz,

3H), 0.82 (d, *J* = 7.0 Hz, 3H);

^{13}**C NMR (126 MHz, DMSO)** δ 179.17, 160.73, 154.01, 144.24, 133.48, 128.39, 127.37 (d, J = 31.7 Hz), 125.03 (q, J = 4.0, 3.5 Hz), 124.42 (d, J = 271.9 Hz), 119.64, 113.93, 97.72, 71.67, 55.09, 49.32, 30.12, 18.60, 17.27;

HRMS calculated for $C_{22}H_{23}F_3N_2O_5SNa^+$ (M+Na) 507.1172; found 507.1177.

(*S*)-*N*-(4-fluorophenyl)-4-hydroxy-3-isopropyl-2-(4-(trifluoromethyl)benzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide (3.36.23)
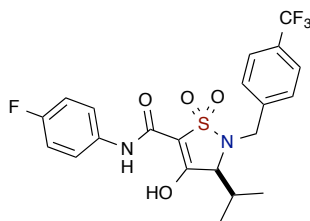
According to general procedure **D**, **3.36.23** (0.202 g, 97%) was isolated as a yellow syrup.

$[\alpha]_D^{20}$ = -6.67 (*c* = 0.90, CH$_3$OH);

FTIR (neat): 2975, 1638, 1579, 1541, 1508, 1412, 1324, 1208, 1117, 1065, 1016, 832, 764, 730 cm^{-1};

^{1}**H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.38 (s, 1H), 8.23 (s, 1H), 7.09 (q, J = 8.2 Hz, 4H), 7.00–6.89 (m, 2H), 6.48 (t, J = 8.7 Hz, 2H), 4.03 (d, J = 16.9 Hz, 1H), 3.60 (d, J = 16.9 Hz, 1H), 2.79 (d, J = 2.5 Hz, 1H), 1.52–1.35 (m, 1H), 0.30 (d, J = 6.8 Hz, 3H), 0.23 (d, J = 7.0 Hz, 3H);

^{13}**C NMR (126 MHz, DMSO)** δ 179.58, 160.86, 157.00 (d, J = 237.8 Hz), 144.18 (d, J = 0.9 Hz), 136.62 (d, J = 2.3 Hz), 128.40, 127.39 (q, J = 31.5 Hz), 125.05 (q, J = 3.7 Hz), 124.42 (d, J = 271.9 Hz), 119.74 (d, J = 7.3 Hz), 115.21 (d, J = 21.9 Hz), 97.72, 71.67, 49.29, 30.14, 18.56, 17.28;

HRMS calculated for $C_{21}H_{20}F_4N_2O_4SNa^+$ (M+Na) 495.0972; found 495.0978.

(S)-4-hydroxy-3-isopropyl-N-(p-tolyl)-2-(4-(trifluoromethyl)benzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide (3.36.24)
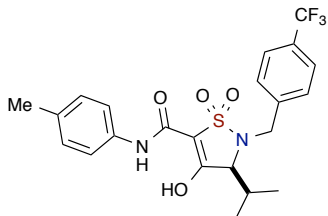
According to general procedure **D**, **3.36.24** (0.078 g, 65%) was isolated as a white solid.

$[\alpha]_D^{20}$ = -40.36 (c = 0.28, CH₃OH);

mp 266-268 °C;

FTIR (neat): 3384, 2968, 1635, 1599, 1561, 1533, 1443, 1421, 1326, 1234, 1157, 1147, 1067, 1017, 1031, 914, 813 cm⁻¹;

¹H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.69 (q, J = 8.4 Hz, 4H), 7.41 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.3 Hz, 2H), 4.62 (d, J = 16.9 Hz, 1H), 4.19 (d, J = 17.1 Hz, 1H), 3.37 (d, J = 2.5 Hz, 1H), 2.23 (s, 3H), 2.02 (td, J = 6.9, 2.5 Hz, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H);

¹³C NMR (126 MHz, DMSO) δ 179.31, 160.86, 144.22, 137.71, 130.12, 129.16, 128.40, 127.38 (d, J = 31.5 Hz), 125.04 (q, J = 3.6 Hz), 124.43 (d, J = 271.9 Hz), 118.27, 97.85, 71.68, 49.33, 30.14, 20.42, 18.61, 17.27;

HRMS calculated for $C_{22}H_{23}F_3N_2O_4SNa^+$ (M+Na) 491.1223; found 491.1228.

(*S*)-2-benzyl-3-isopropylisothiazolidin-4-one 1,1-dioxide (3.A.1)
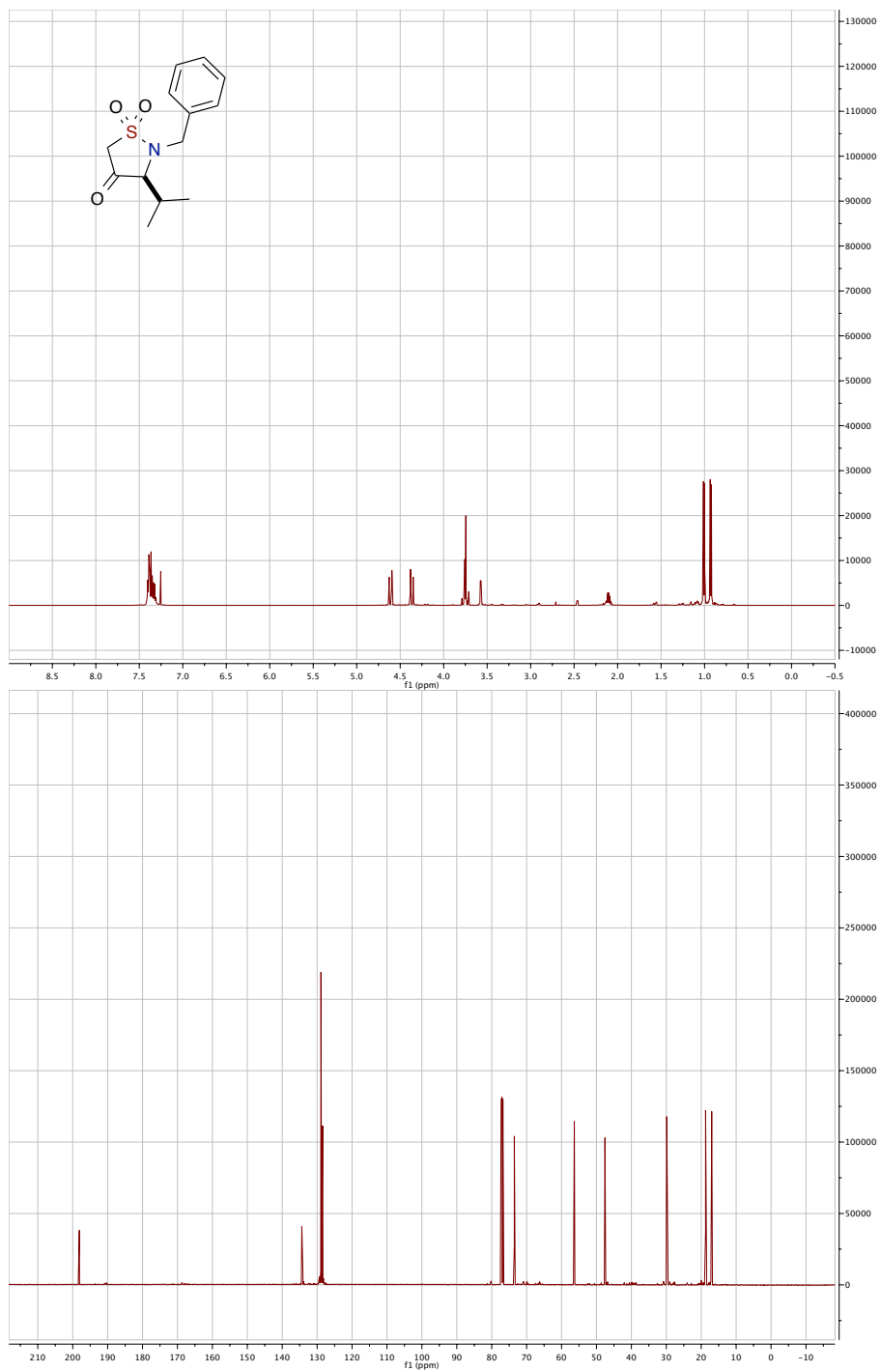
(*S*)-2-(2-fluorobenzyl)-3-isopropylisothiazolidin-4-one 1,1-dioxide (3.A.2)
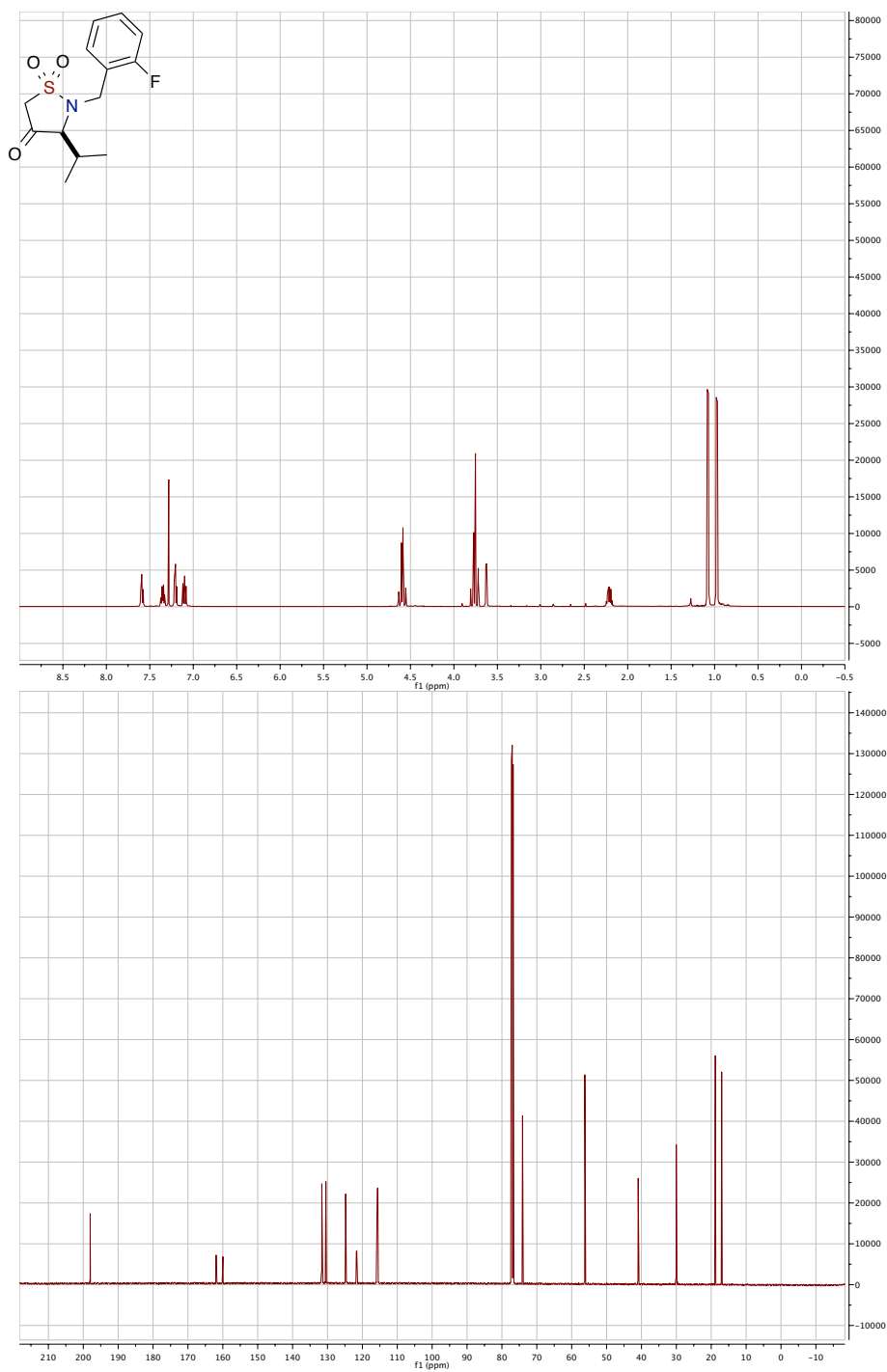
(*S*)-2-(2-chlorobenzyl)-3-isopropylisothiazolidin-4-one 1,1-dioxide (3.A.3)
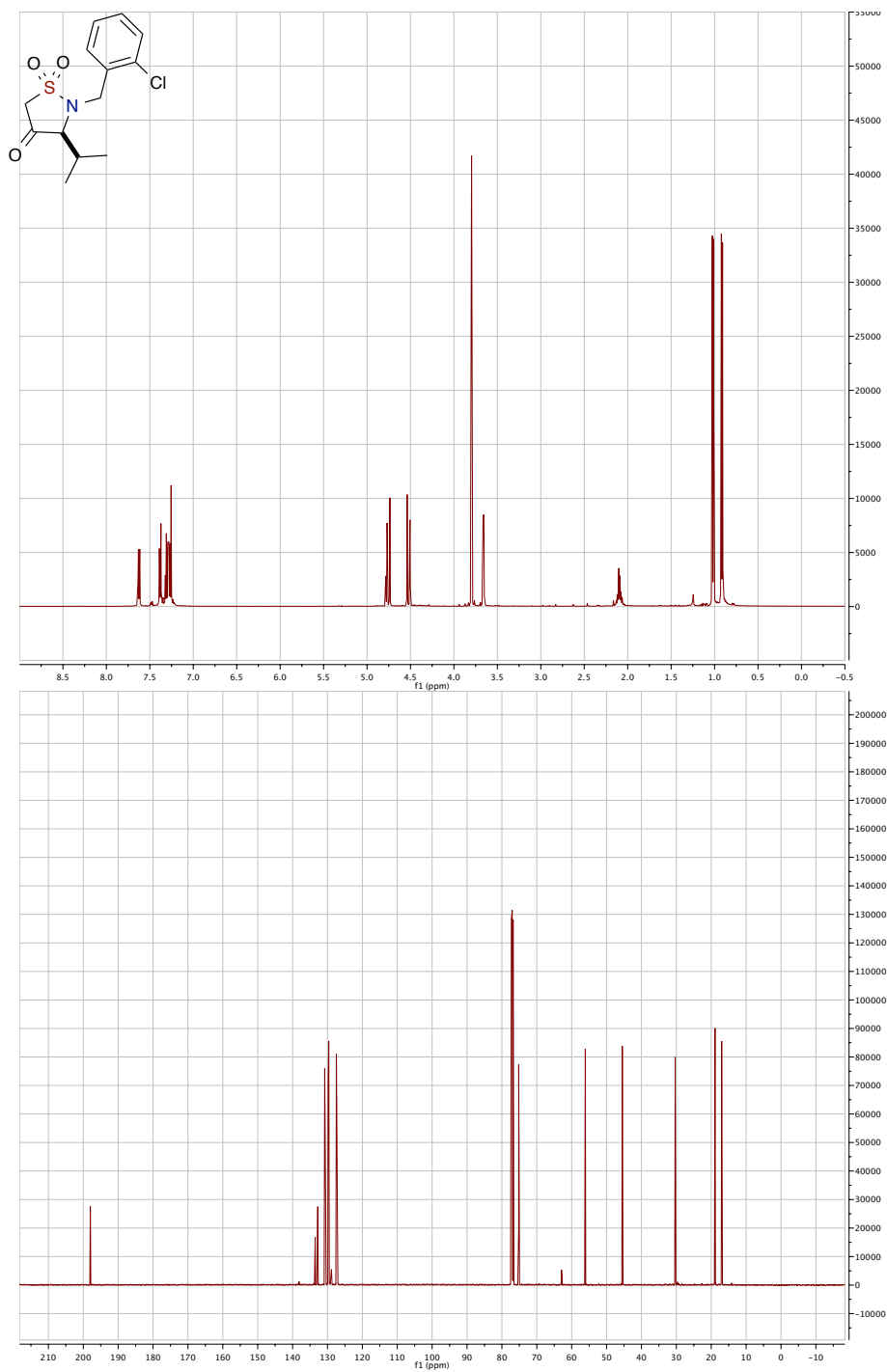
(*S*)-3-isopropyl-2-(4-methylbenzyl)isothiazolidin-4-one 1,1- dioxide (3.A.4)
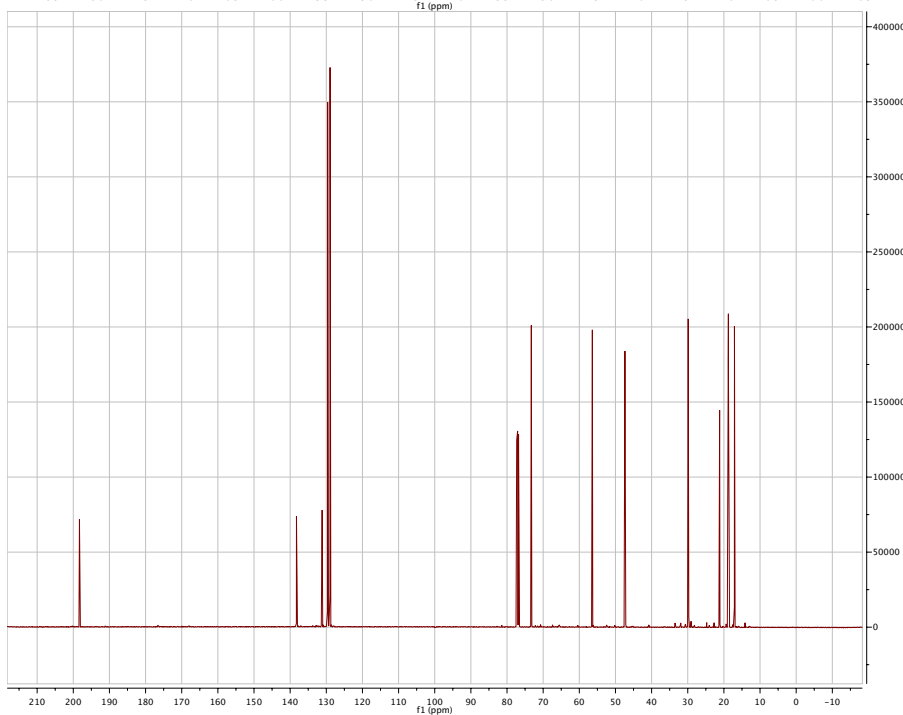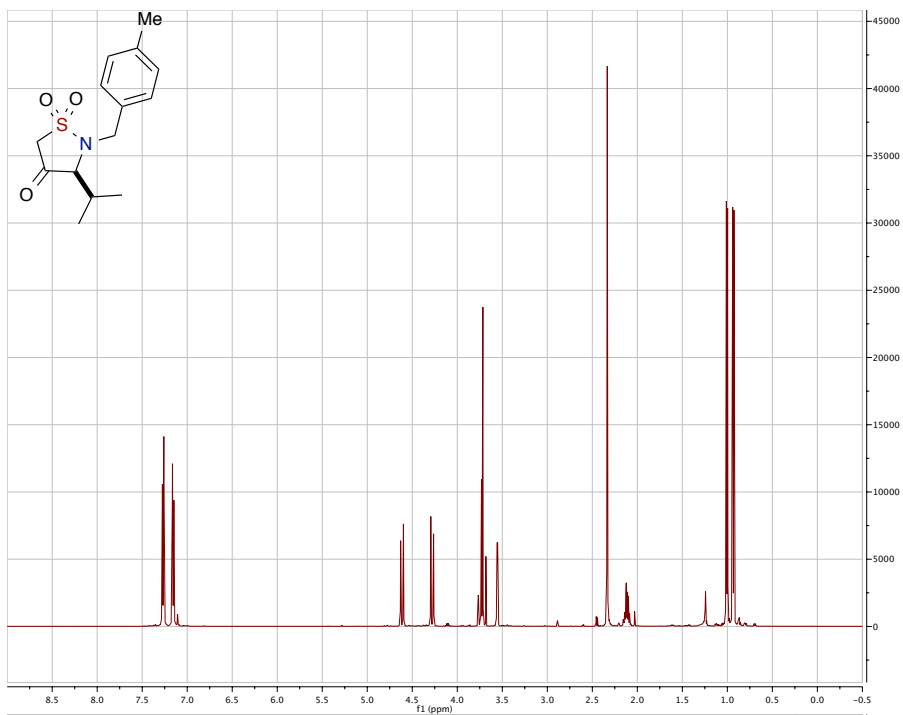
(*S*)-2-(4-bromobenzyl)-3-isopropylisothiazolidin-4-one 1,1- dioxide (3.A.5)
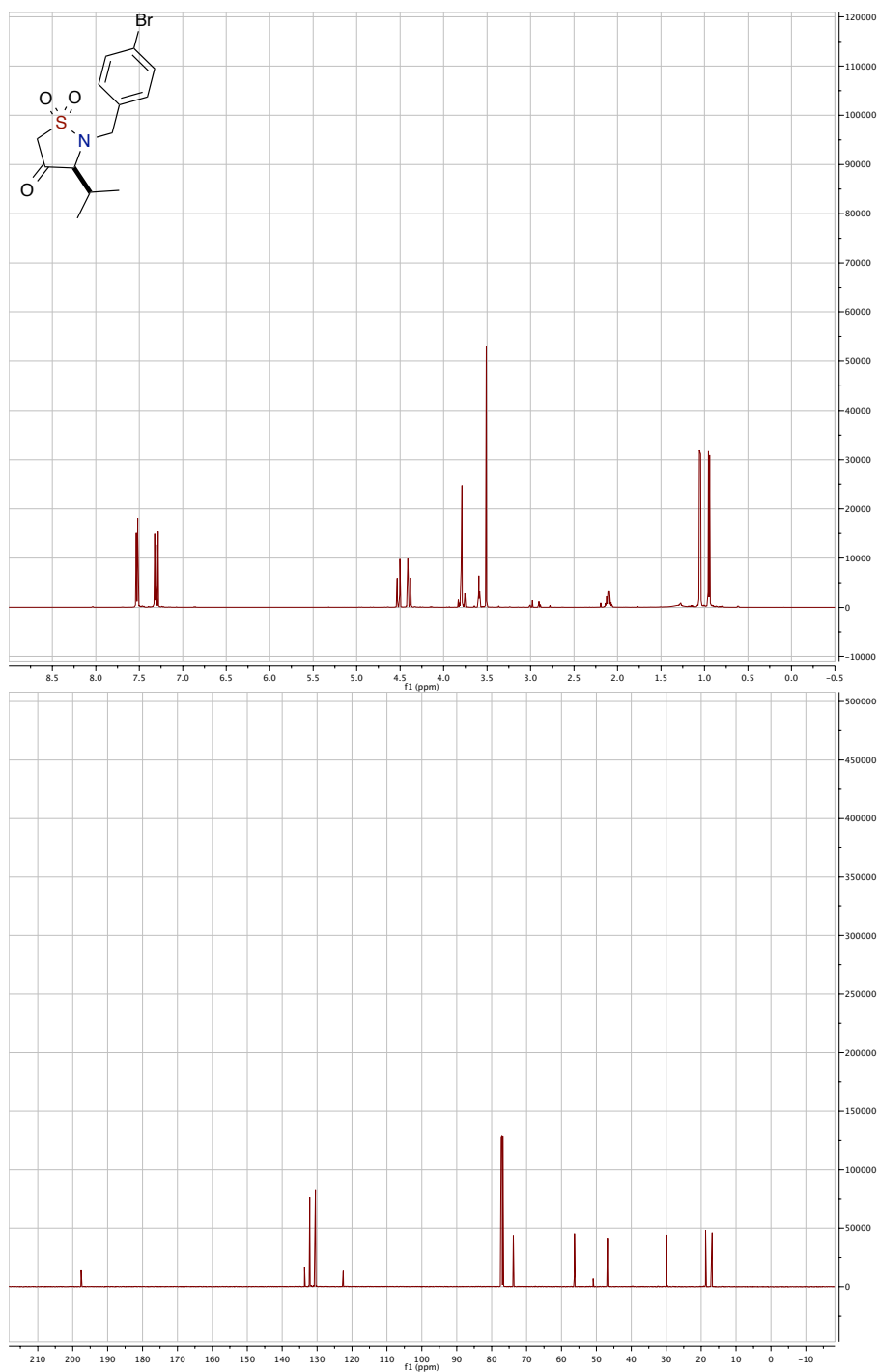
(*S*)-2-(4-chlorobenzyl)-3-isopropylisothiazolidin-4-one 1,1-dioxide (3.A.6)
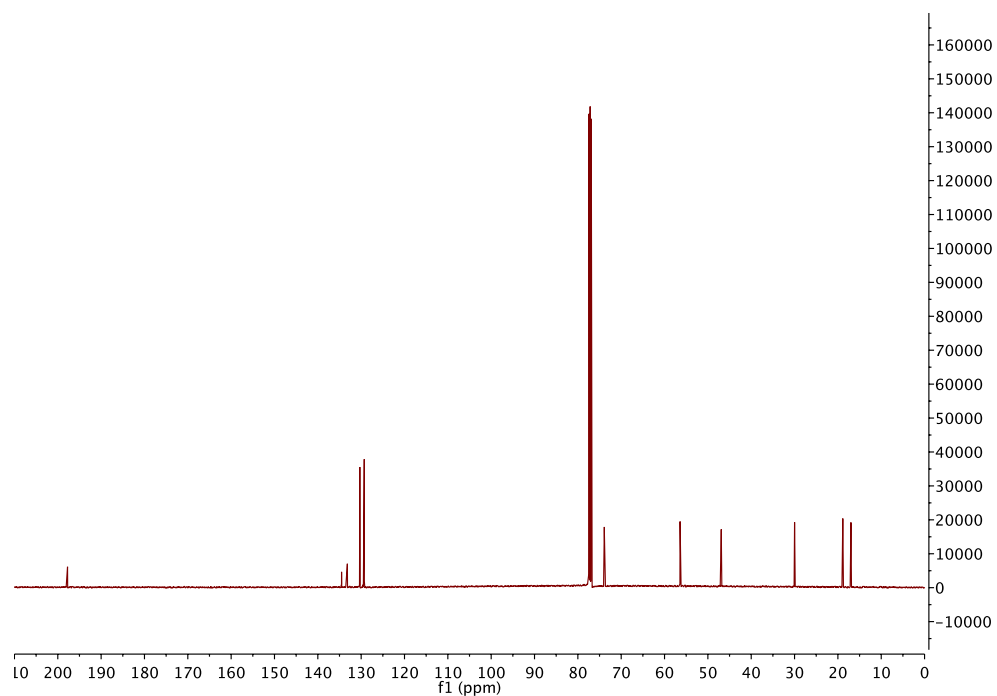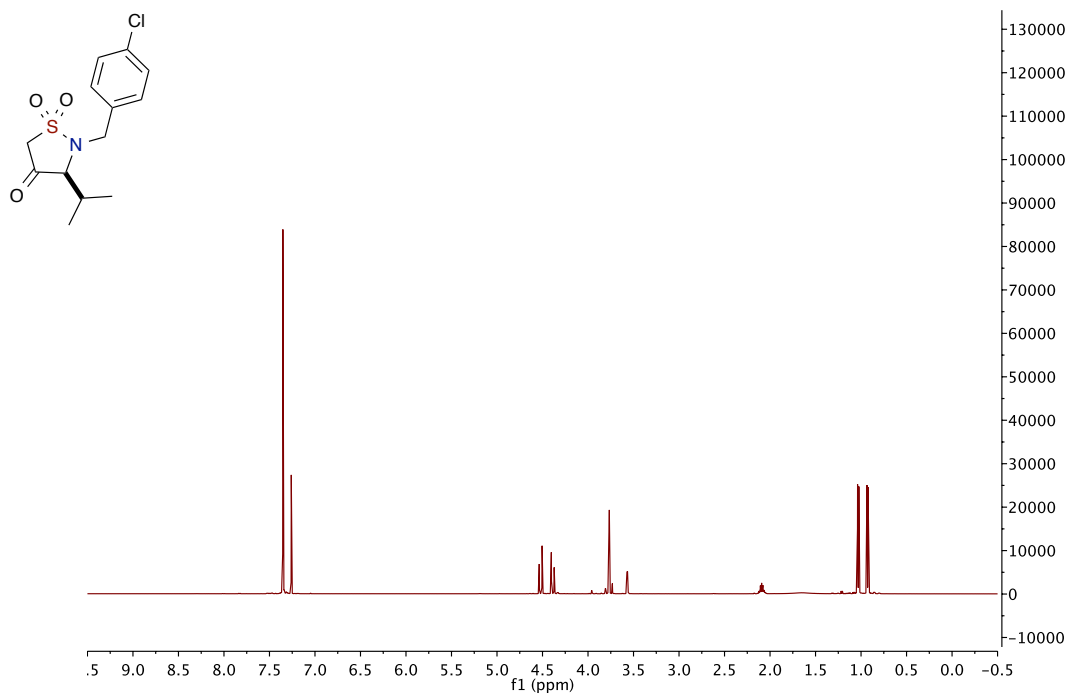
(*S*)-3-isopropyl-2-(4-(trifluoromethyl)benzyl)isothiazolidin-4-one 1,1-dioxide (3.A.7)
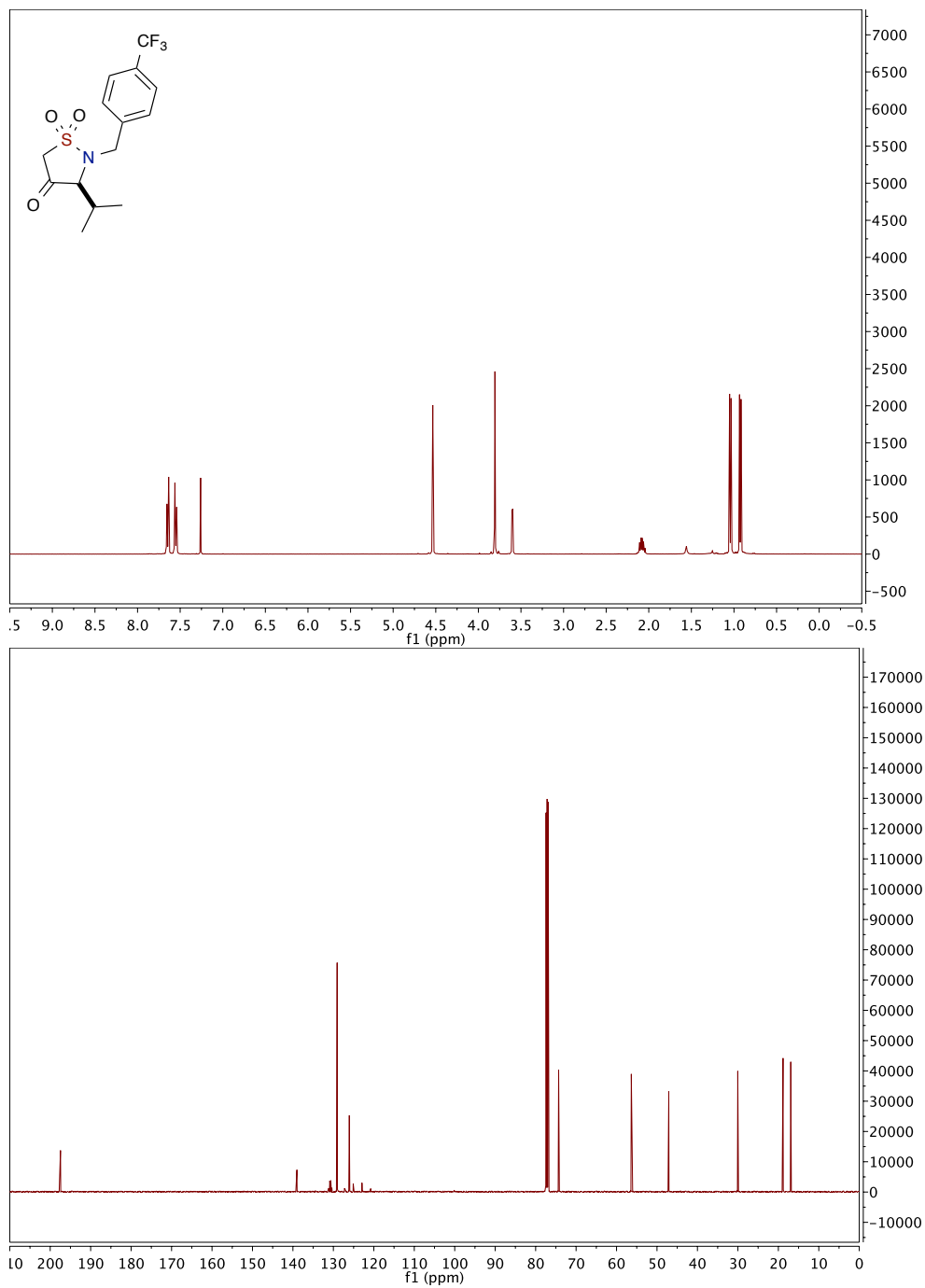
(*S*)-2-benzyl-3-isobutylisothiazolidin-4-one 1,1- dioxide (3.A.8)
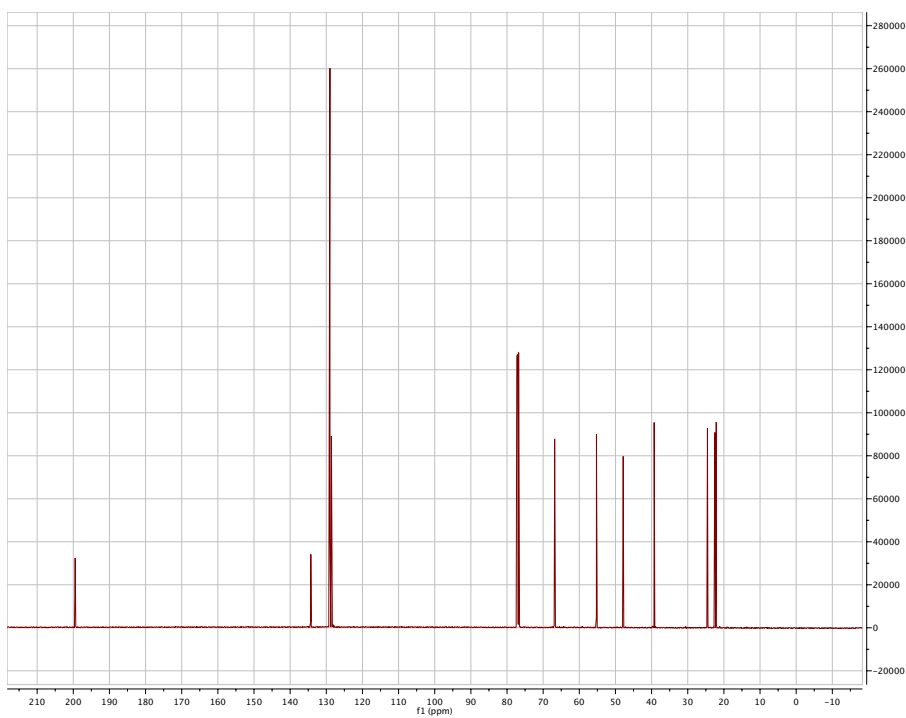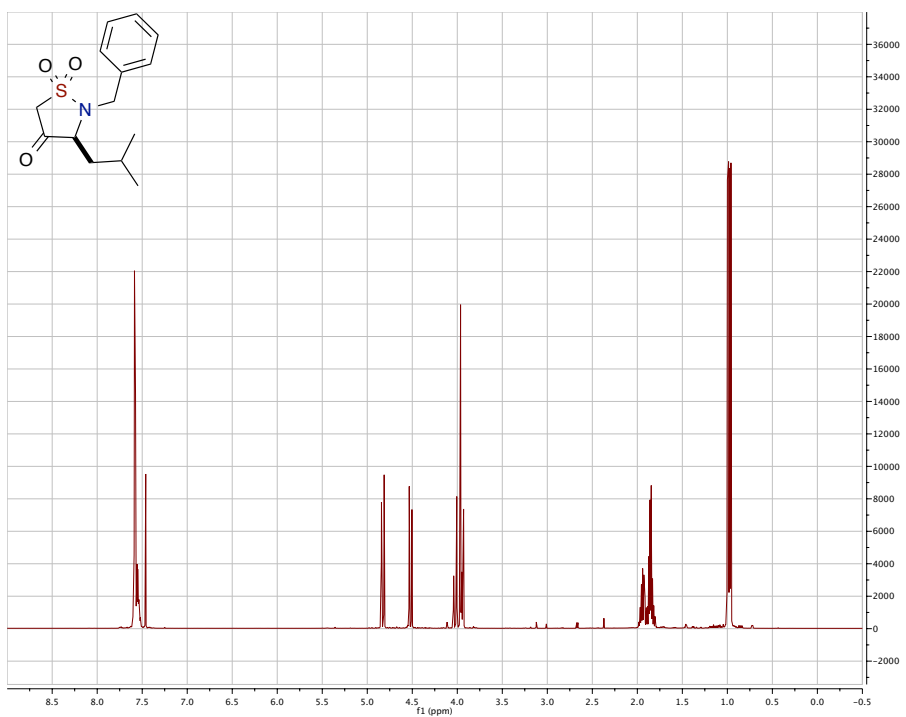
(*S*)-2-(2-bromobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide (3.A.9)
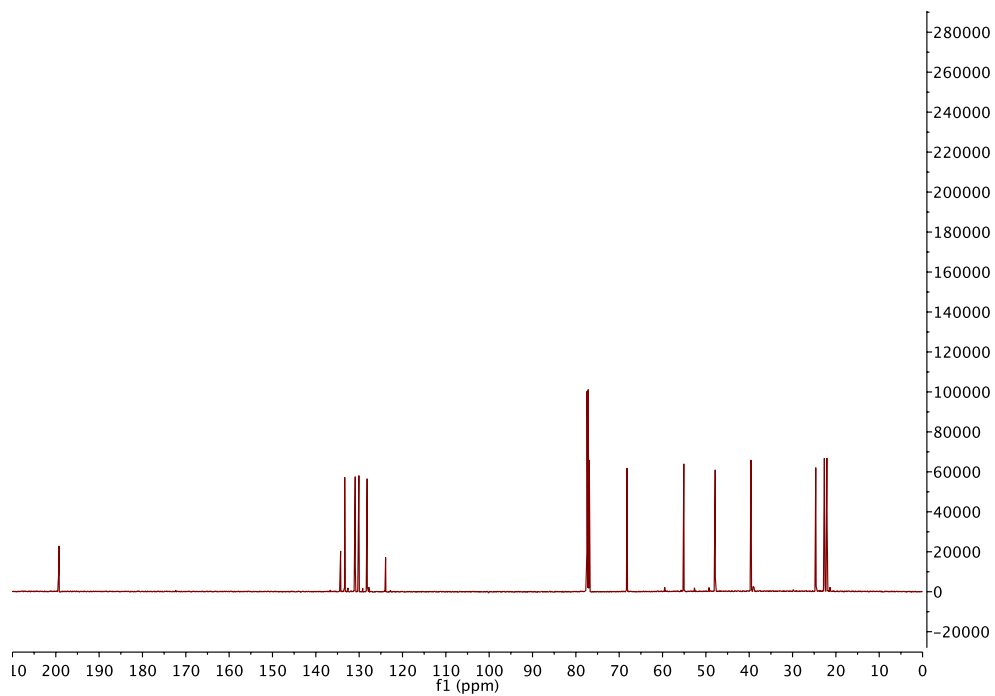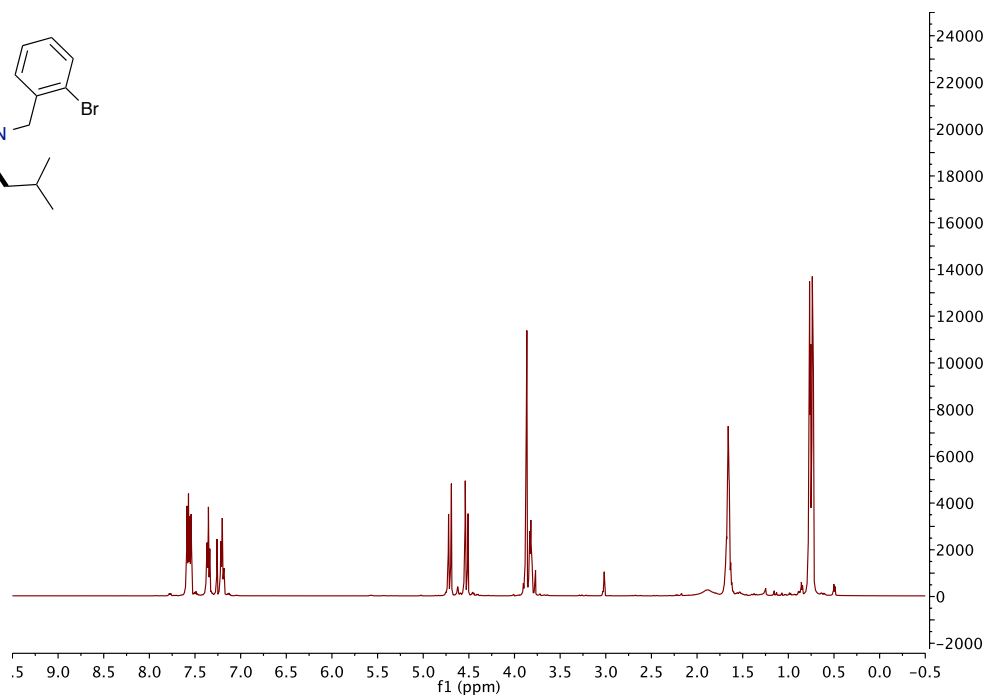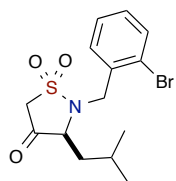
(*S*)-3-isobutyl-2-(4-methylbenzyl)isothiazolidin-4-one 1,1- dioxide (3.A.10)
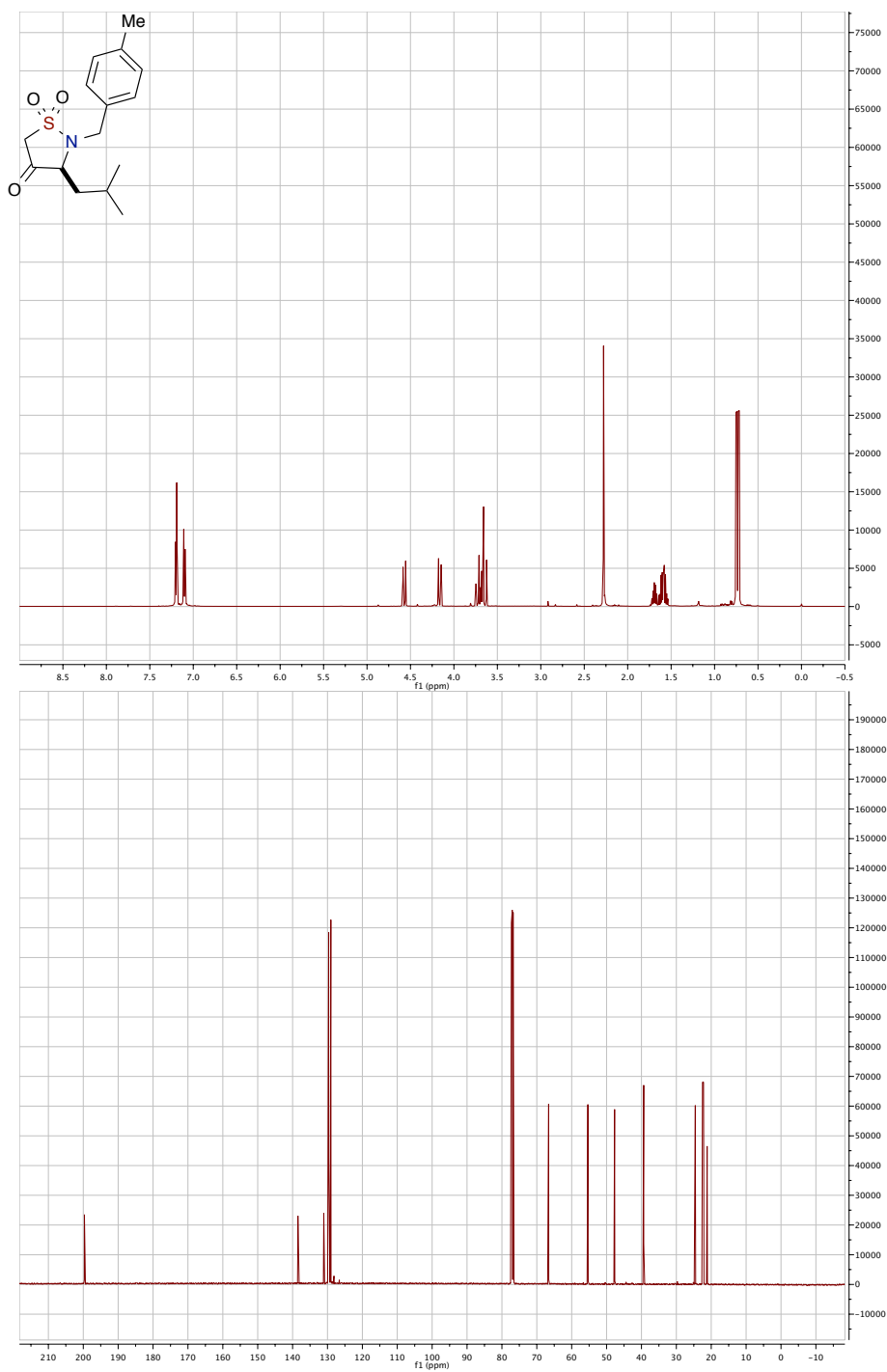
(*S*)-3-benzyl-2-(2-methylallyl)isothiazolidin-4-one 1,1- dioxide (3.A.11)
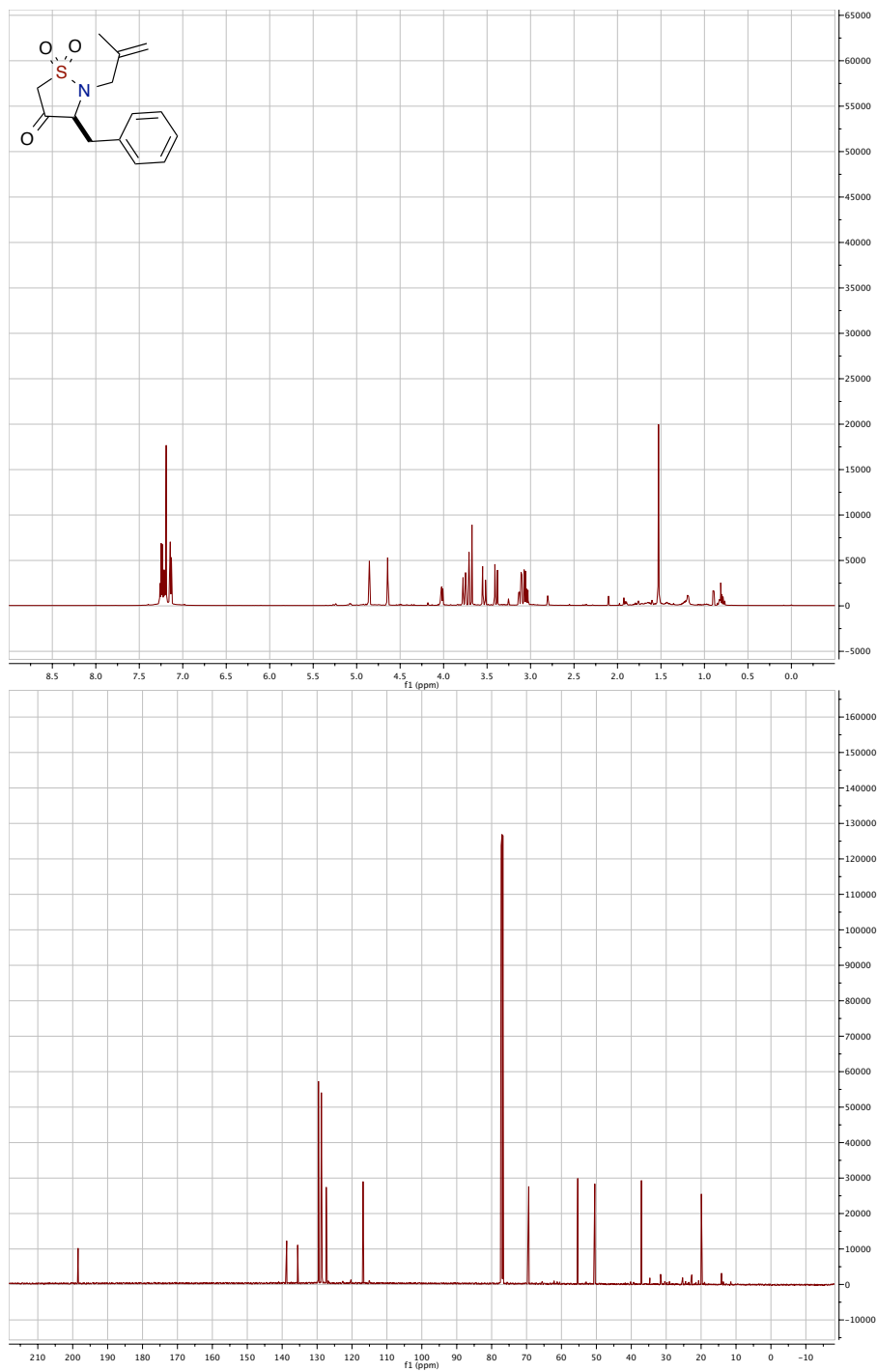
(*S*)-2-allyl-3-benzylisothiazolidin-4-one 1,1-dioxide (3.A.12)
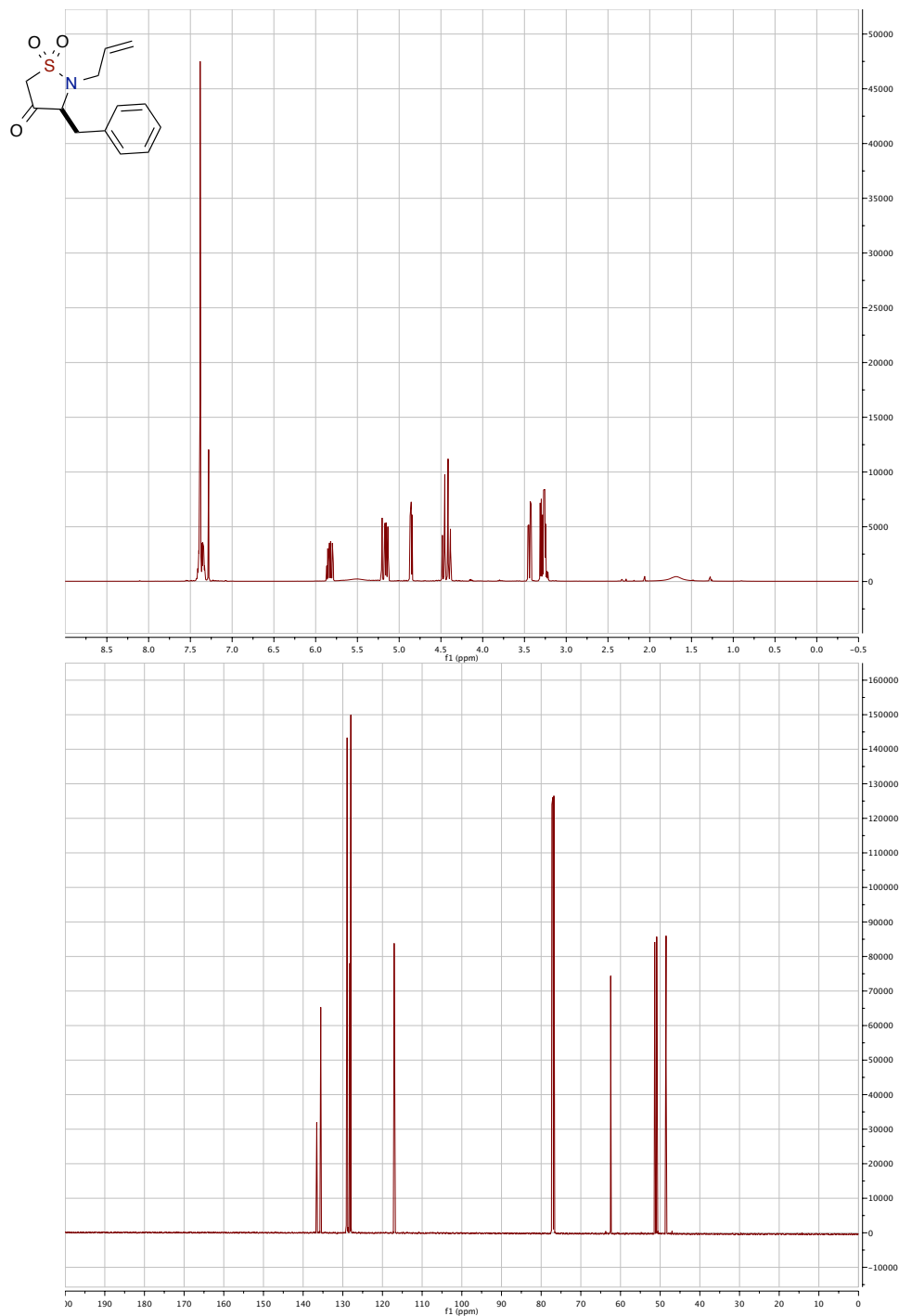
(*S*)-3-benzyl-2-(4-fluorobenzyl)isothiazolidin-4-one 1,1-dioxide (3.A.13)
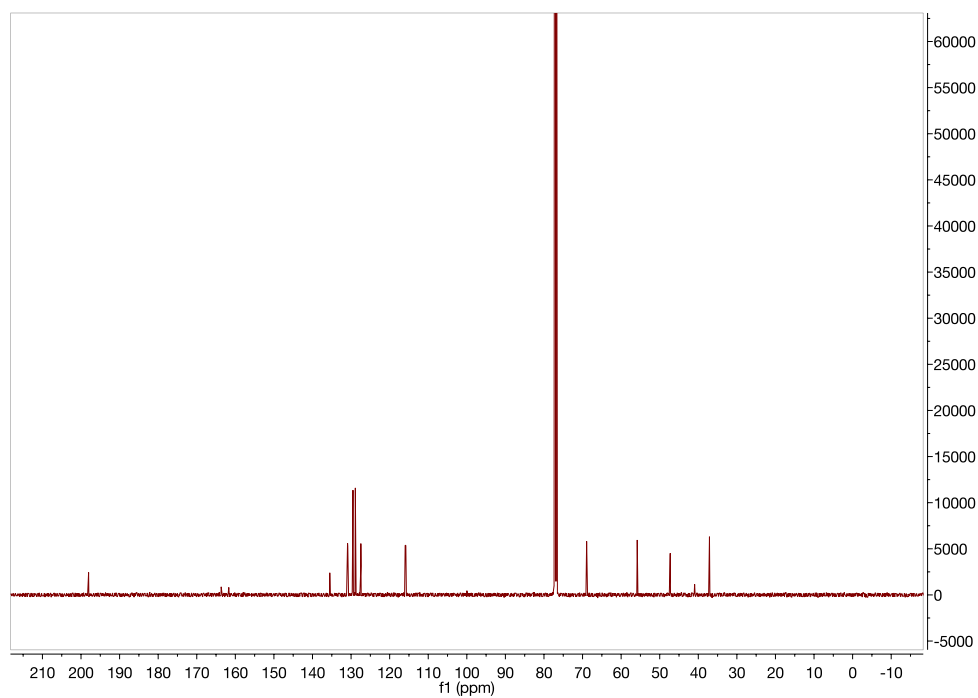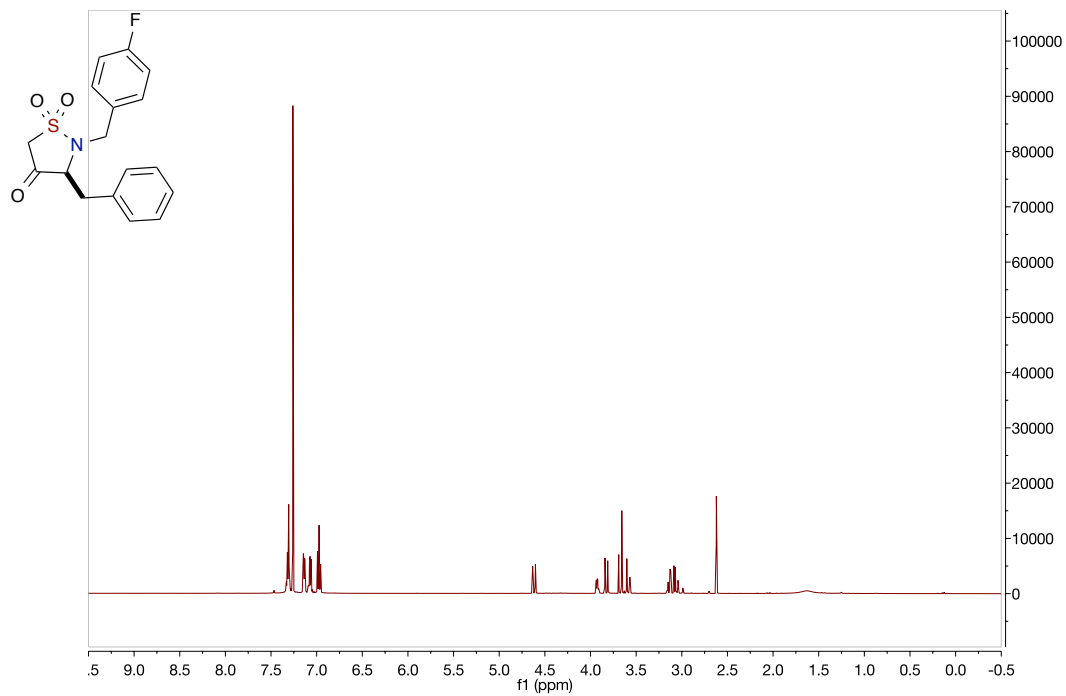
(*S*)-2-(2-fluorobenzyl)-3-methylisothiazolidin-4-one 1,1-dioxide (3.A.14)
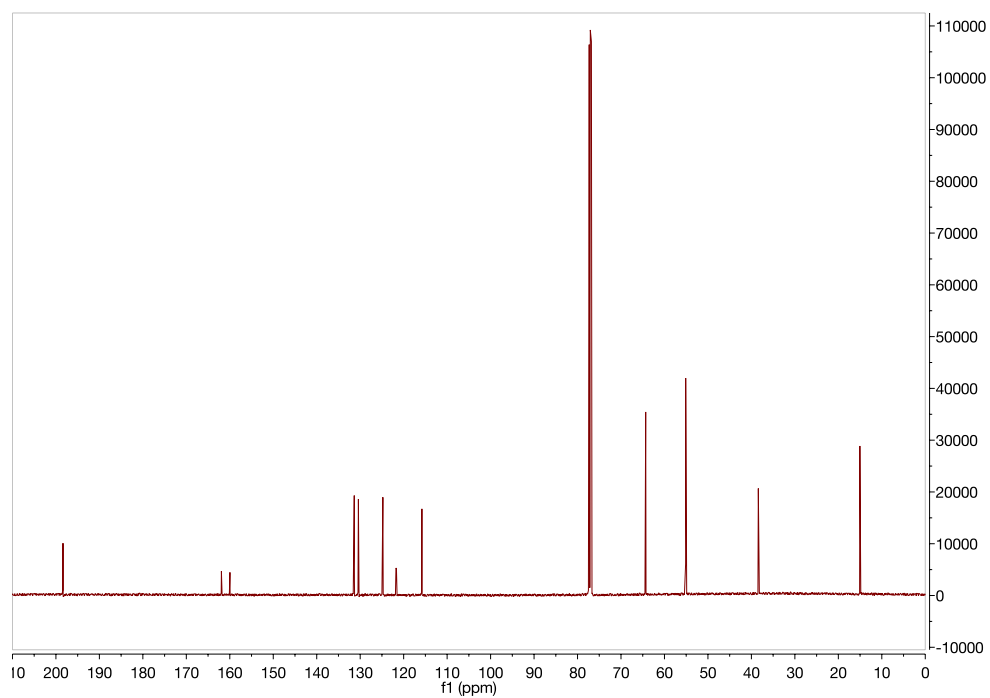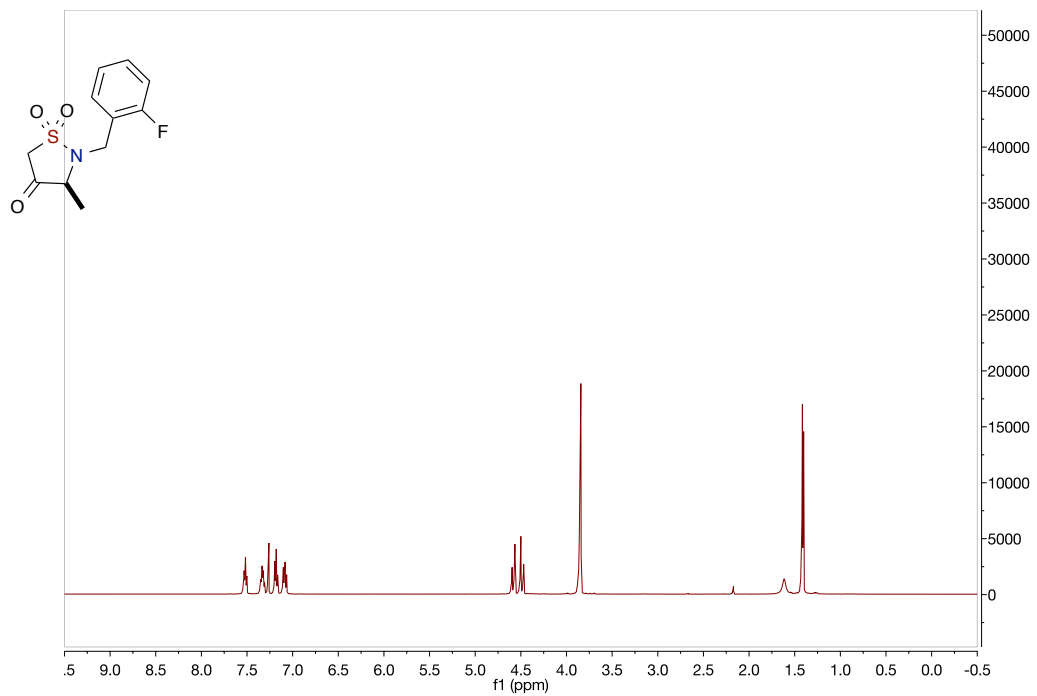
(*S*)-3-((*R*)-*sec*-butyl)-2-(4-fluorobenzyl)isothiazolidin-4-one 1,1-dioxide (3.A.16)
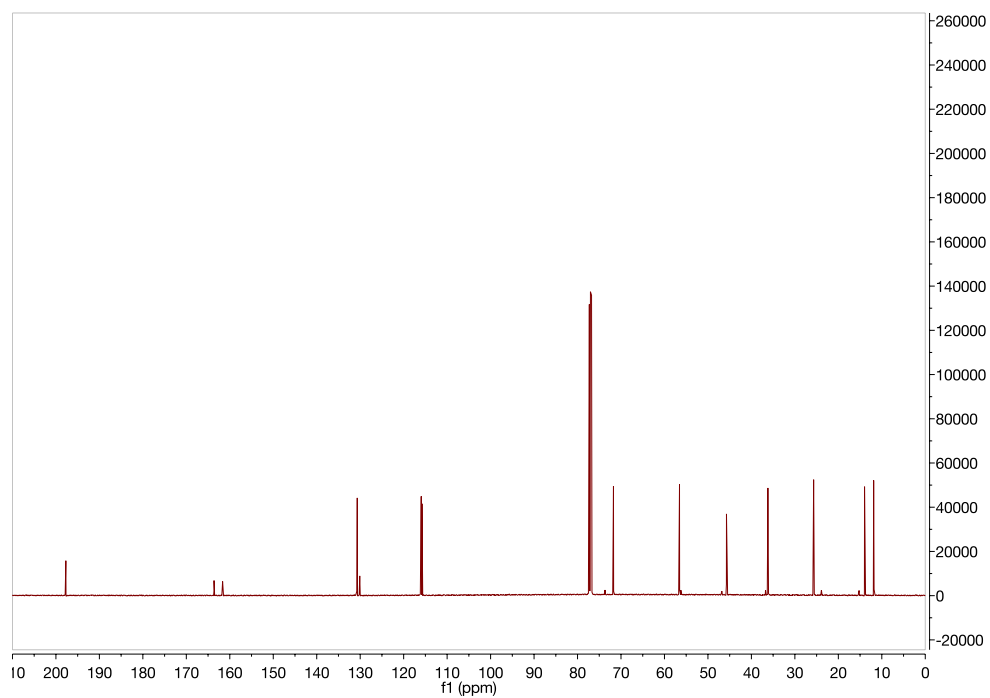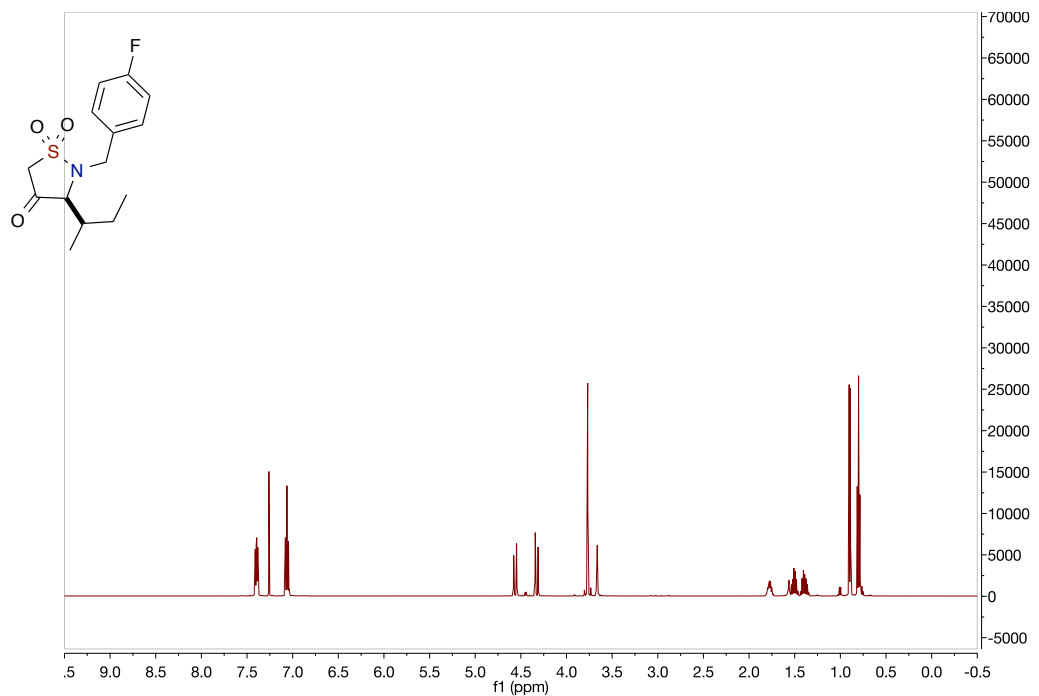
(*S*)-2-(4-bromobenzyl)-3-((*R*)-*sec*-butyl)isothiazolidin-4-one 1,1-dioxide (3.A.17)
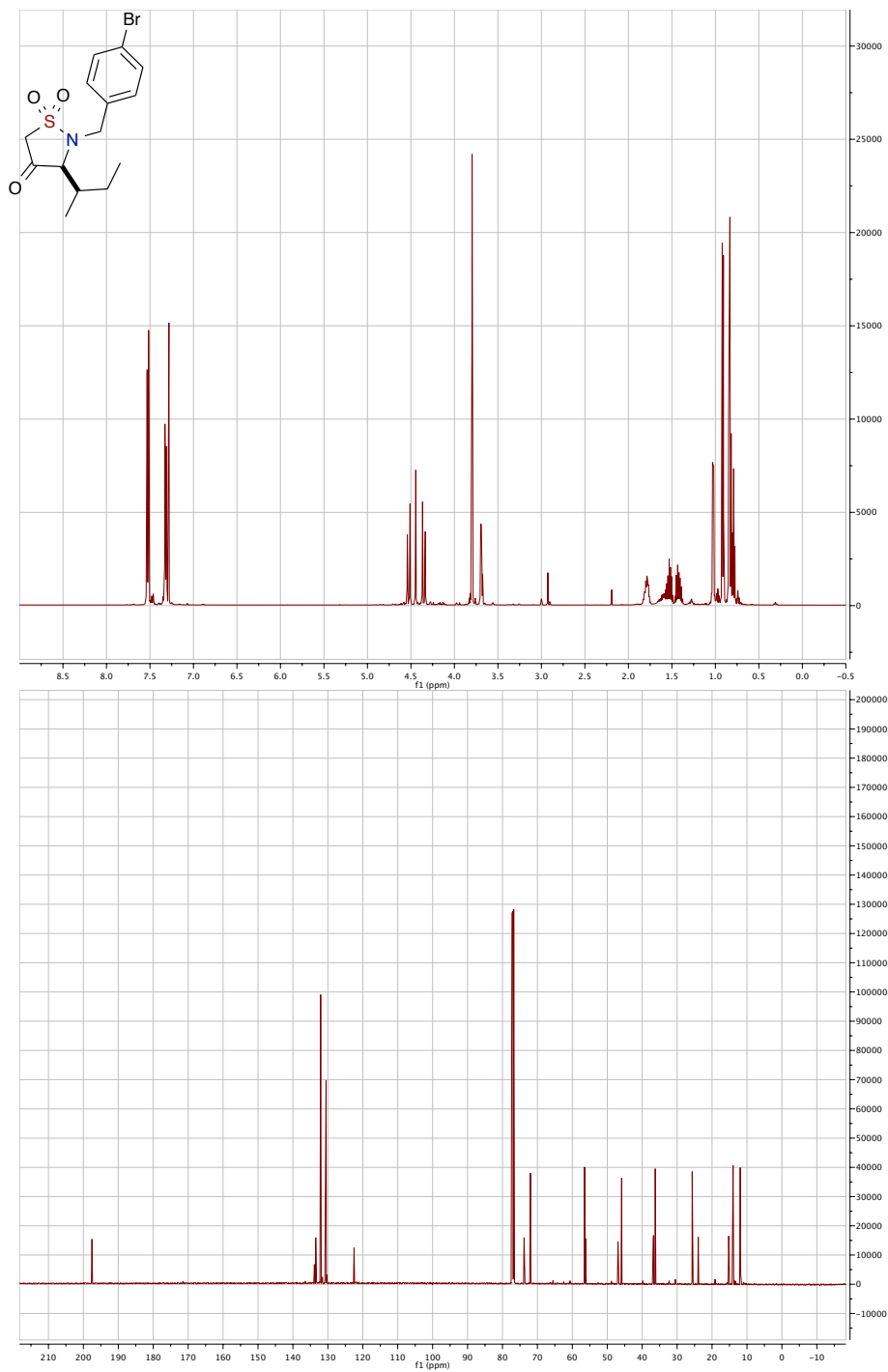
(*S*)-3-((1*H*-indol-2-yl)methyl)-2-(4-iodobenzyl)isothiazolidin-4-one 1,1- dioxide (3.A.18)
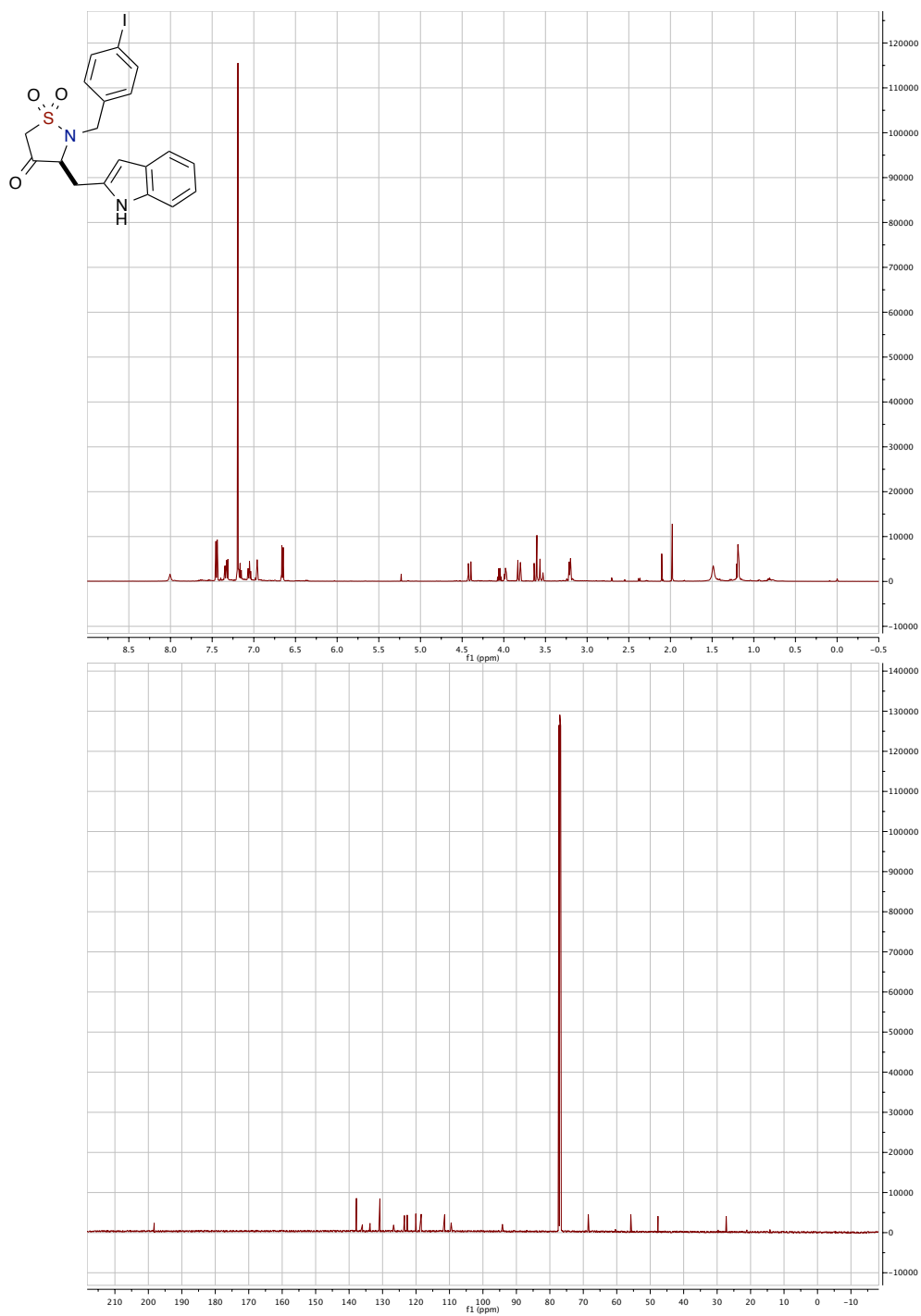
(*S*)-tetrahydropyrrolo[1,2-*b*]isothiazol-3(2*H*)-one 1,1-dioxide (3.33.3)
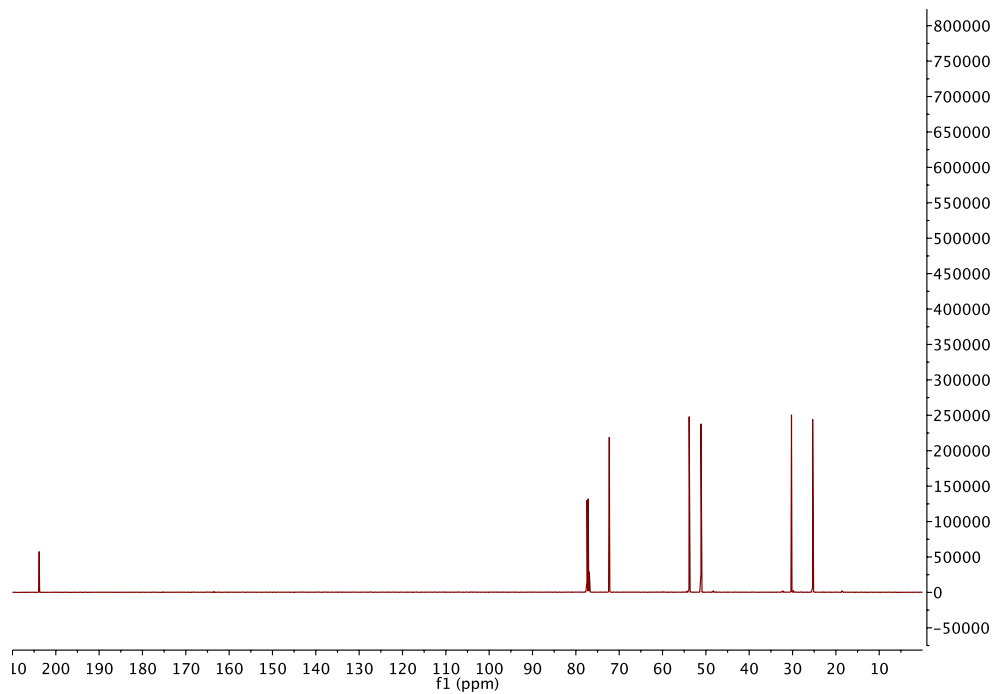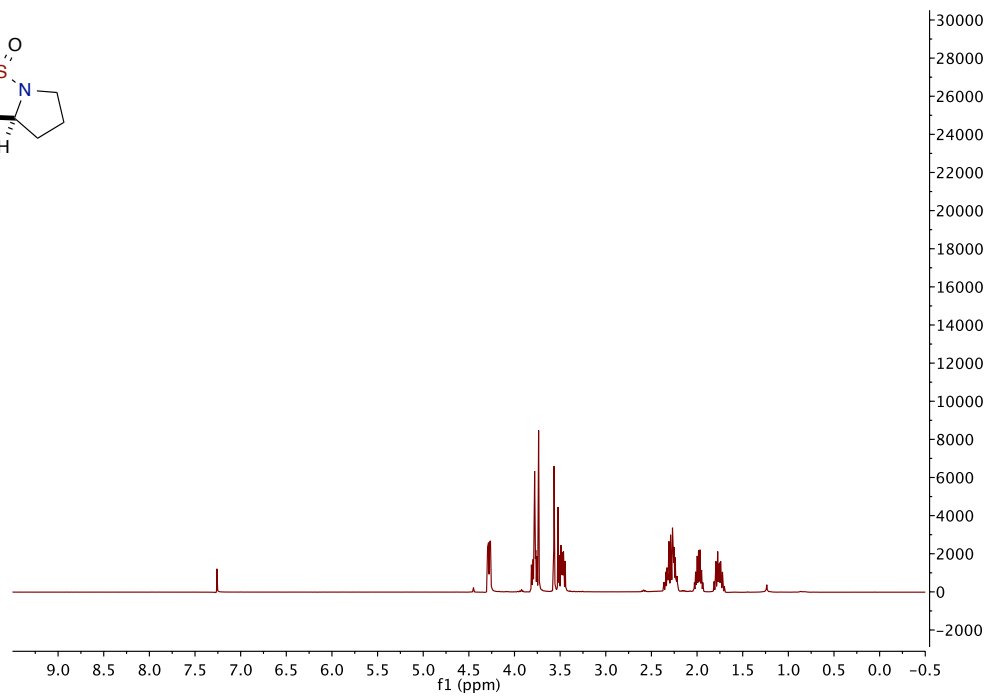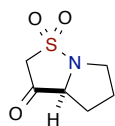
(3aS,5R)-5-((*tert*-butyldimethylsilyl)oxy)tetrahydropyrrolo[1,2-*b*]isothiazol-3(2*H*)-one 1,1-dioxide (3.33.4)
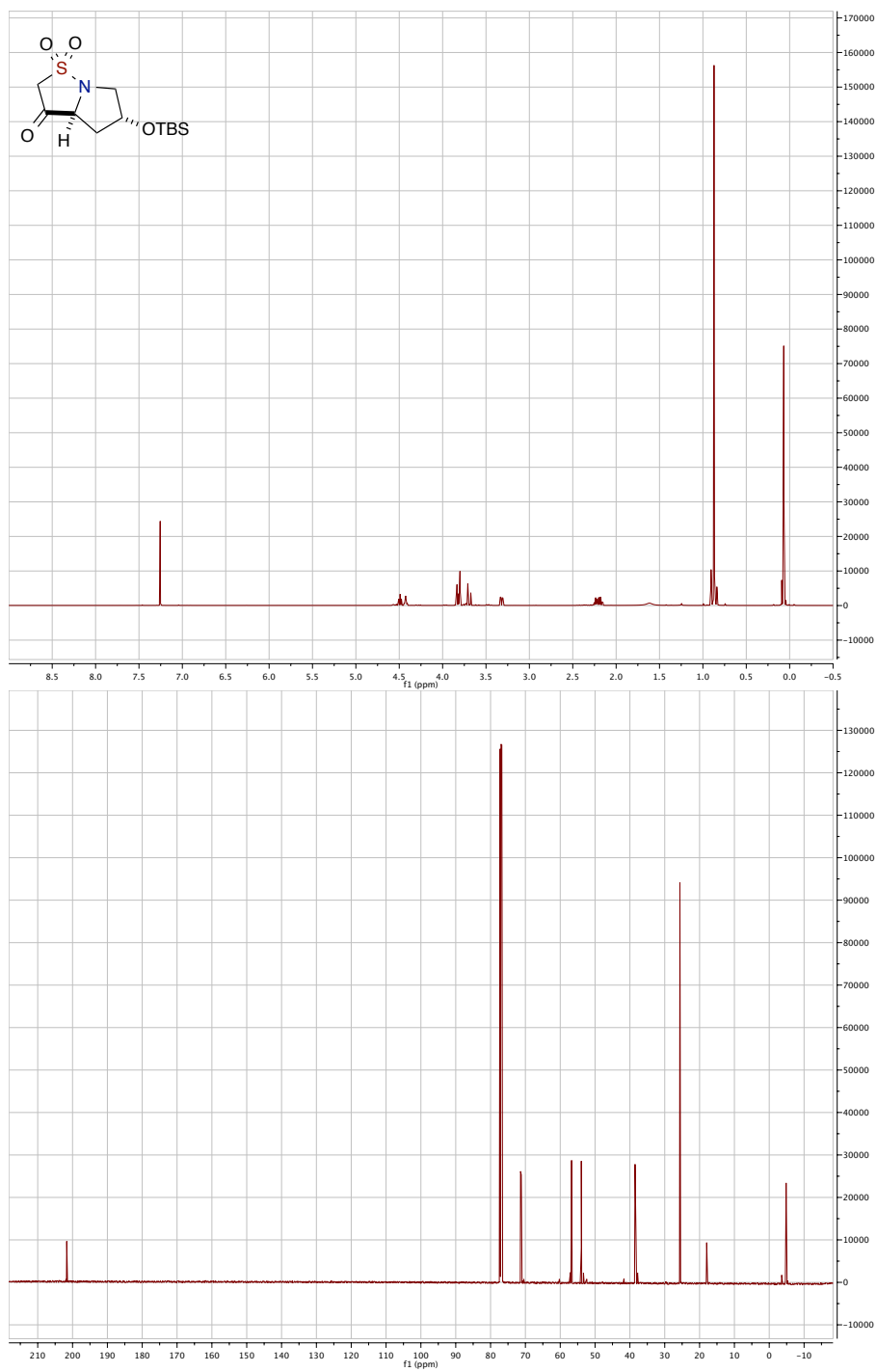
tetrahydro-2*H*-isothiazolo[2,3-*a*]pyridin-3(3a*H*)-one 1,1-dioxide (3.33.5)
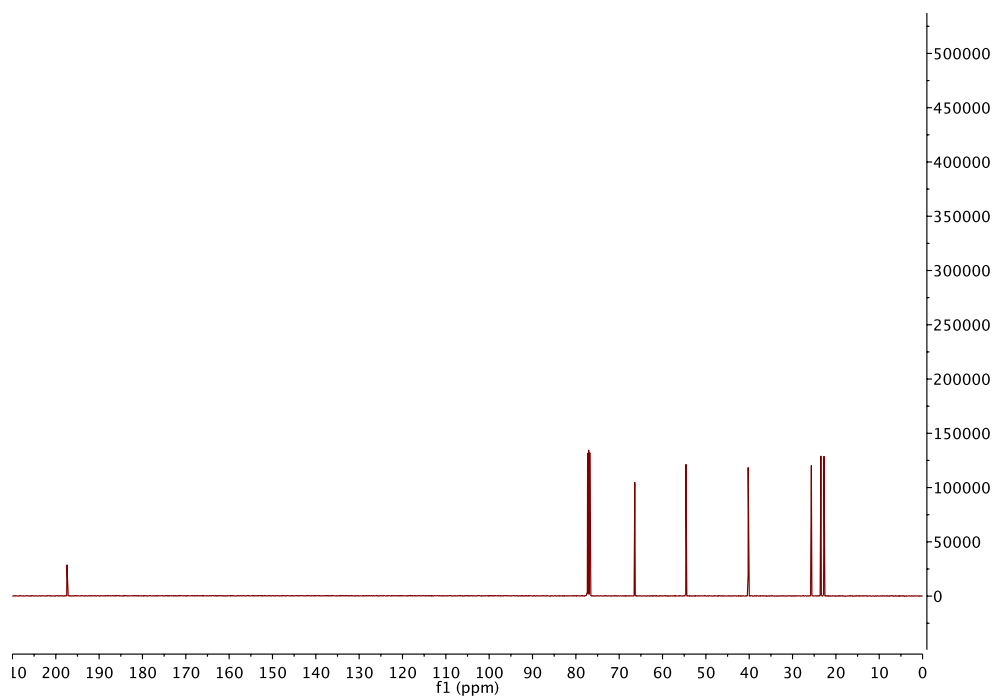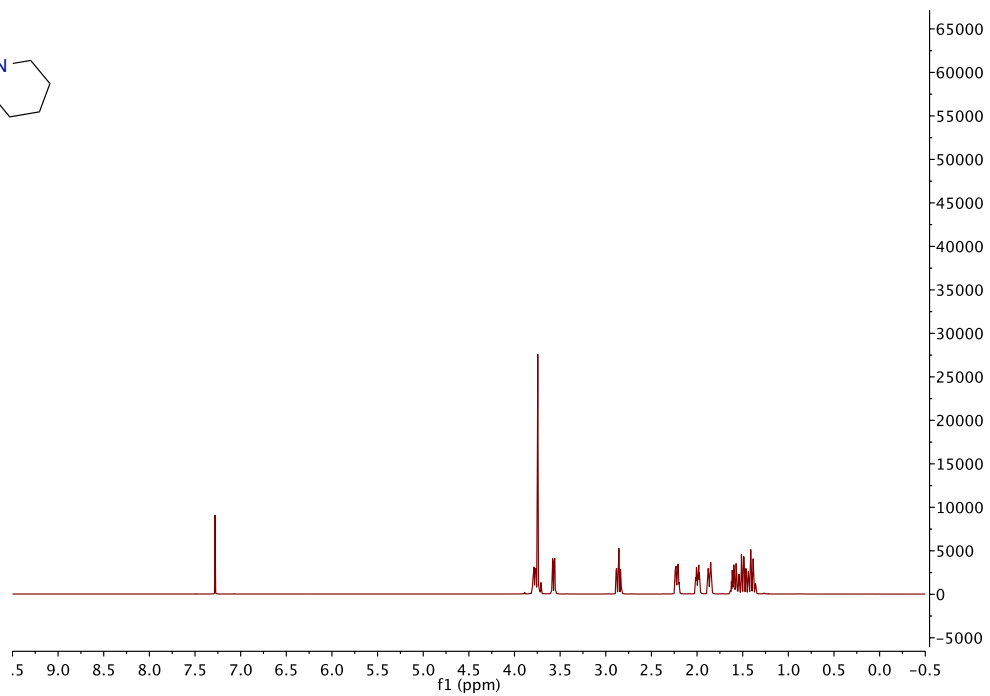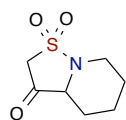
***tert*-butyl 3-oxohexahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (3.33.6)**
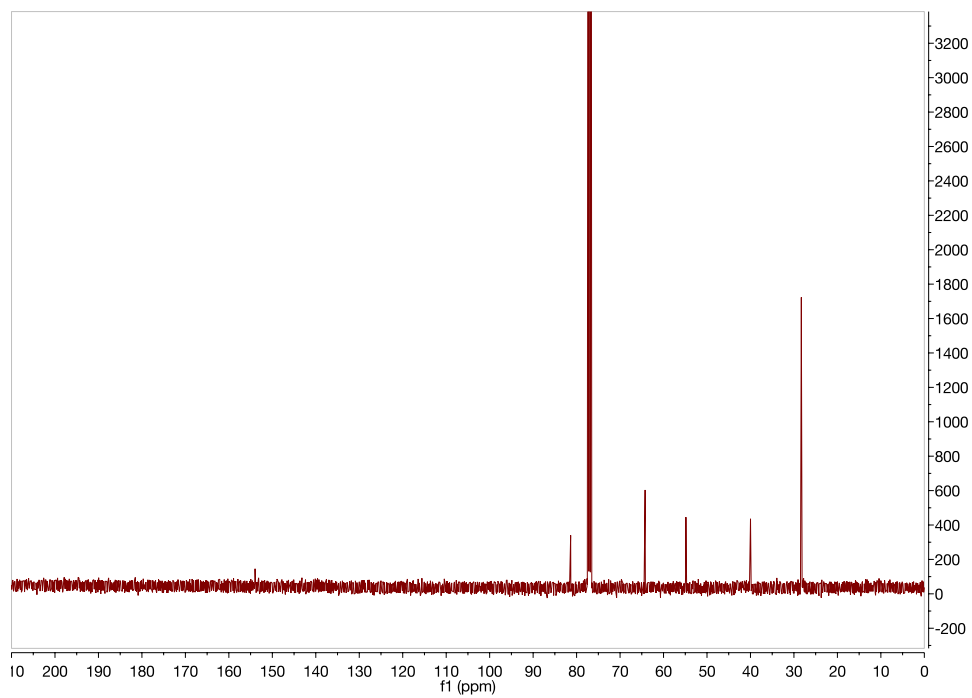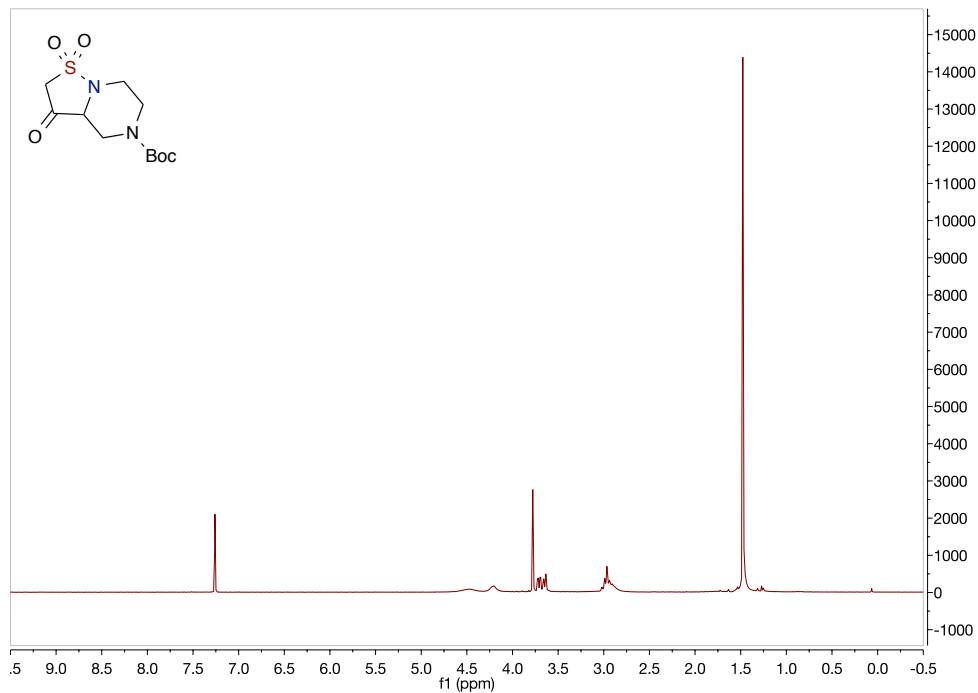
tetrahydroisothiazolo[3,2-*c*][1,4]oxazin-3(2*H*)-one 1,1-dioxide (3.33.7)
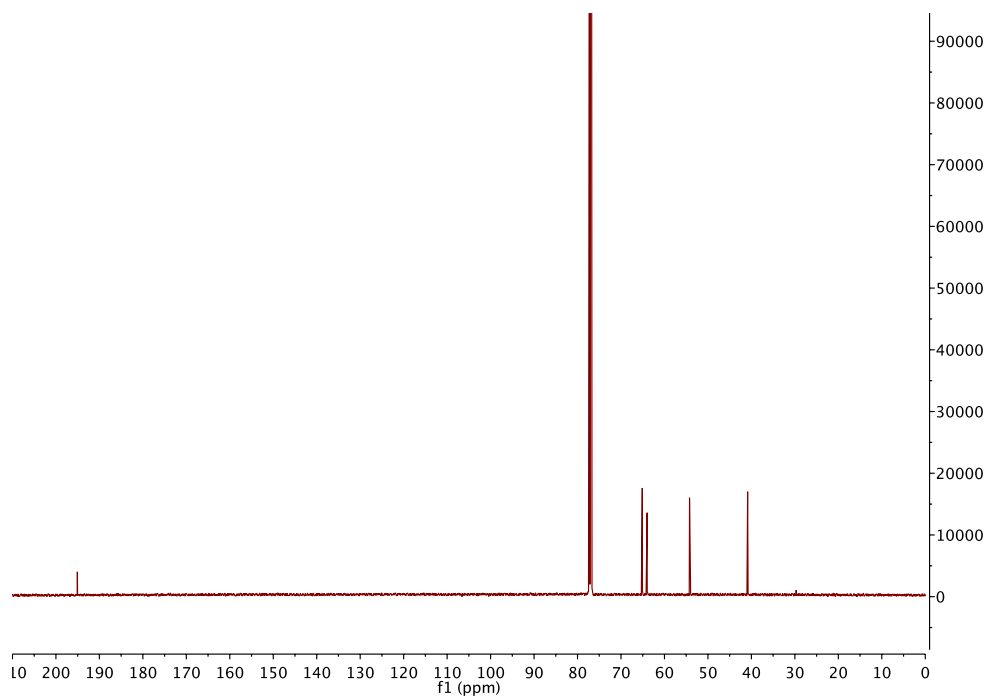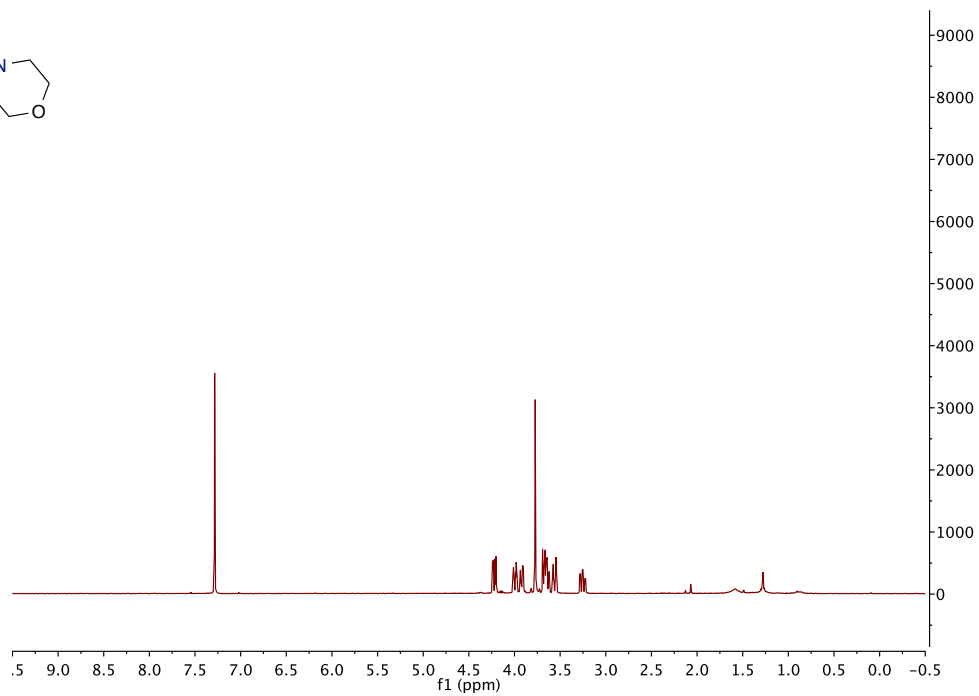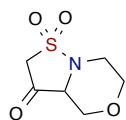
1-benzyl-4-hydroxy-*N*-phenyl-2-thia-1-azaspiro[4.5]dec-3-ene-3-carboxamide 2,2-dioxide (3.36.5)
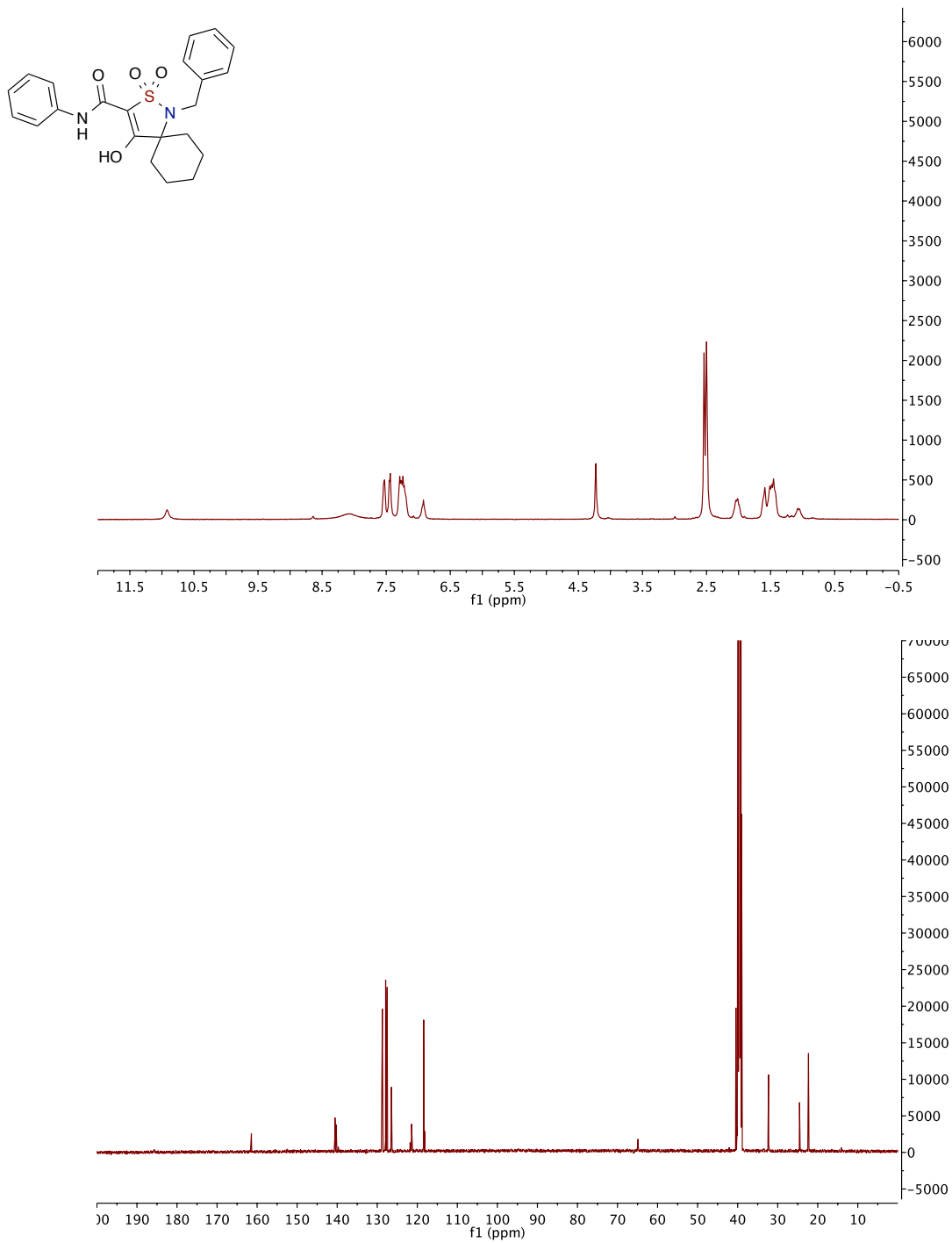
1-benzyl-4-hydroxy-*N*-(4-methoxyphenyl)-2-thia-1-azaspiro[4.5]dec-3-ene-3-carboxamide 2,2-dioxide (3.36.6)
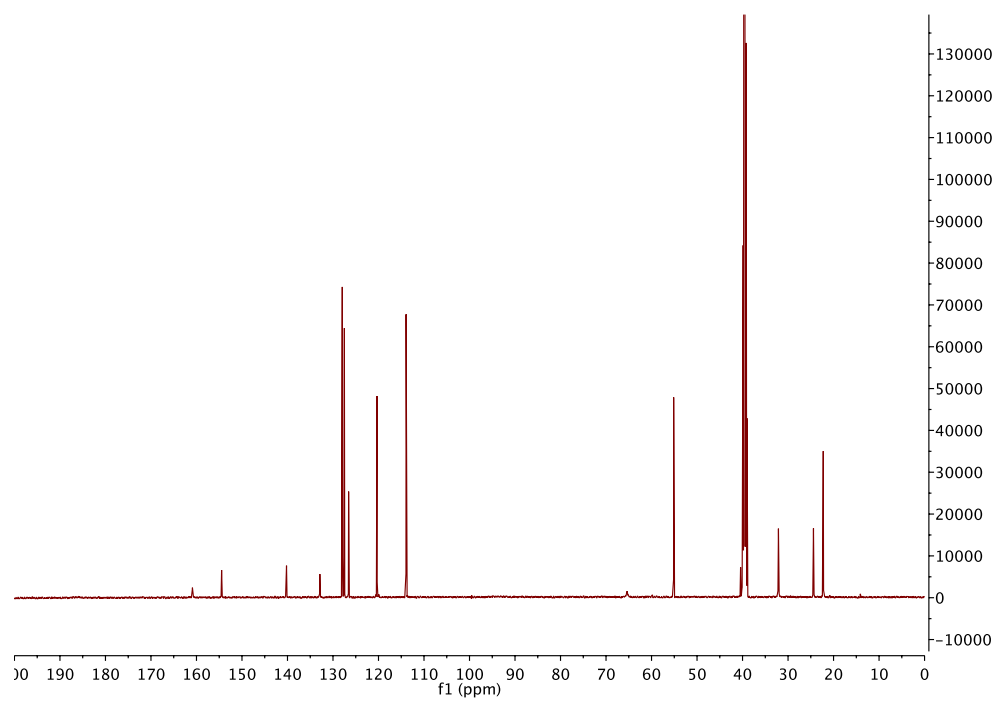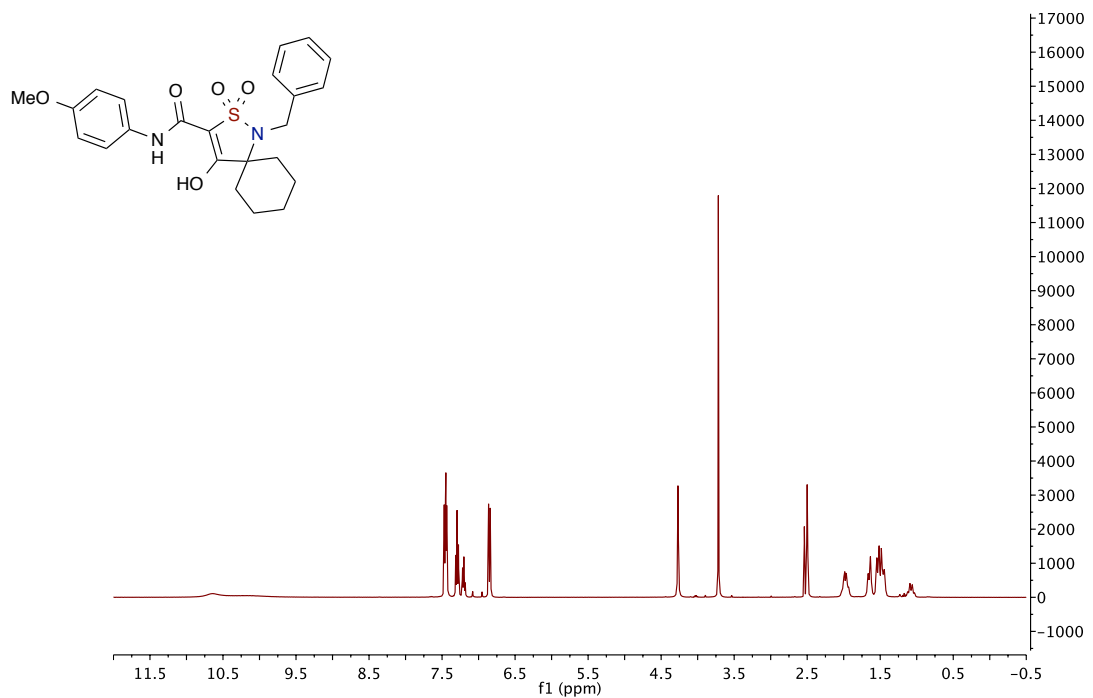
1-benzyl-*N*-(4-fluorophenyl)-4-hydroxy-2-thia-1-azaspiro[4.5]dec-3-ene-3-carboxamide 2,2-dioxide (3.36.7)
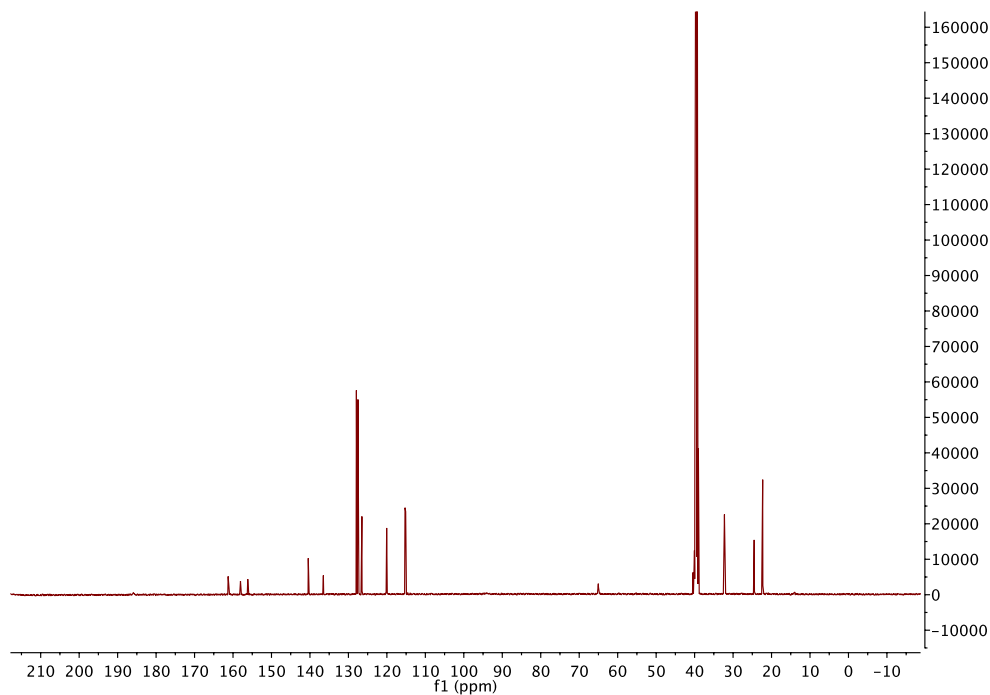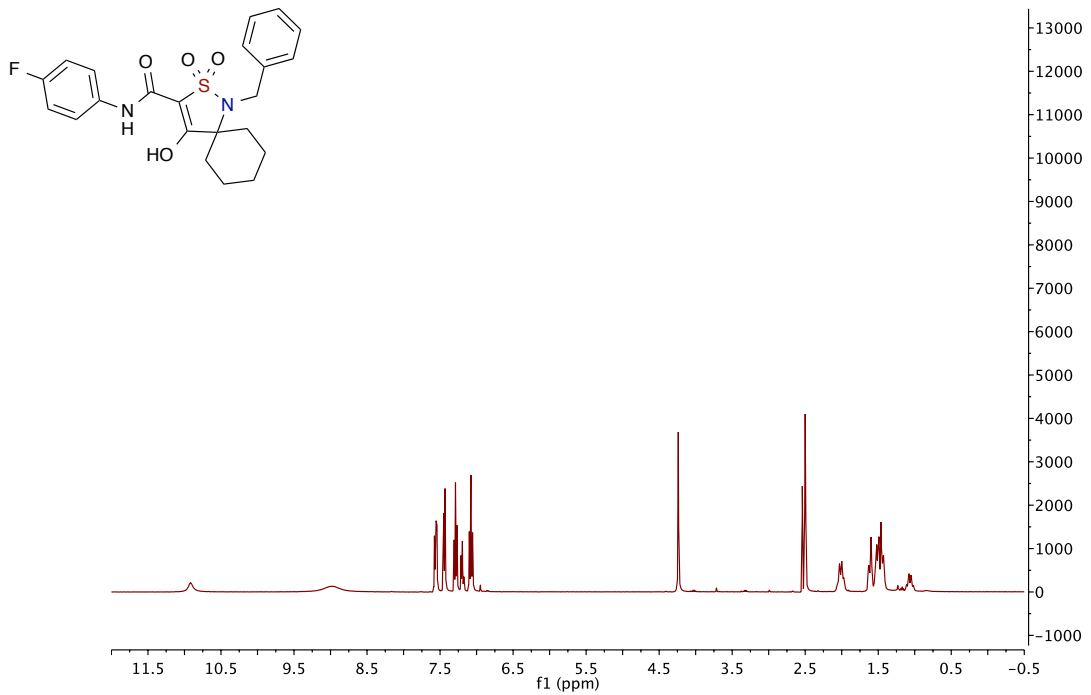
1-benzyl-4-hydroxy-*N*-(*p*-tolyl)-2-thia-1-azaspiro[4.5]dec-3-ene-3-carboxamide 2,2-dioxide (3.36.8)
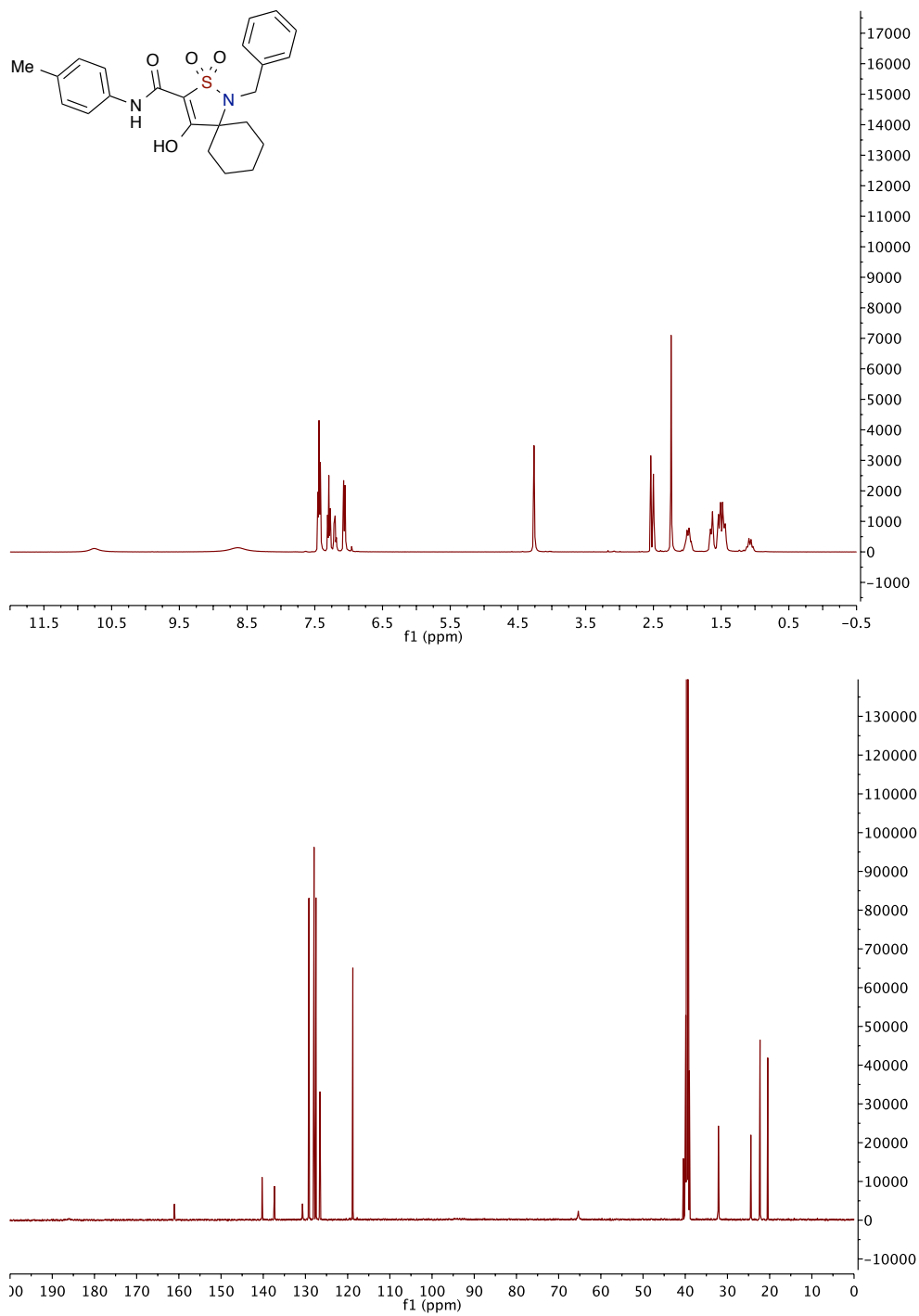
3-hydroxy-*N*-phenyl-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyridine-2-carboxamide 1,1-dioxide (3.36.9)
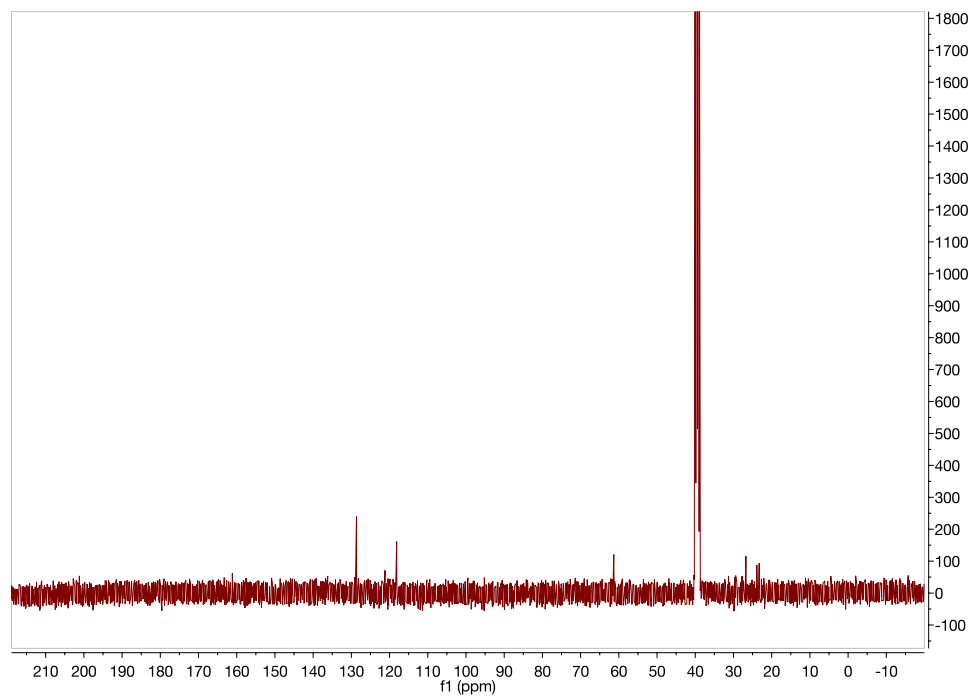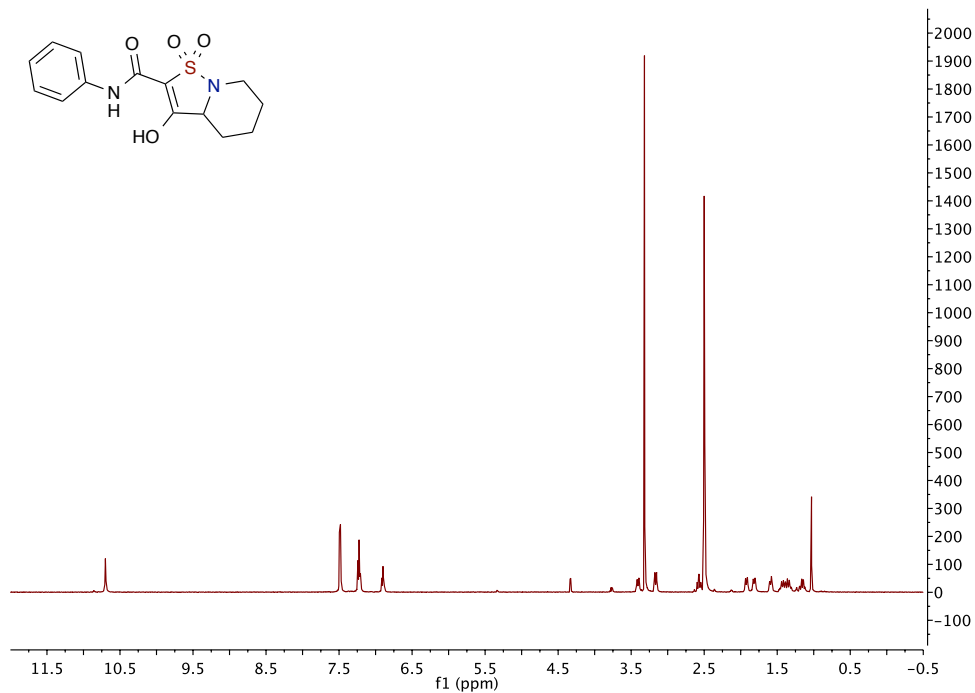
3-hydroxy-*N*-(*p*-tolyl)-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyridine-2-carboxamide 1,1-dioxide (3.36.10)
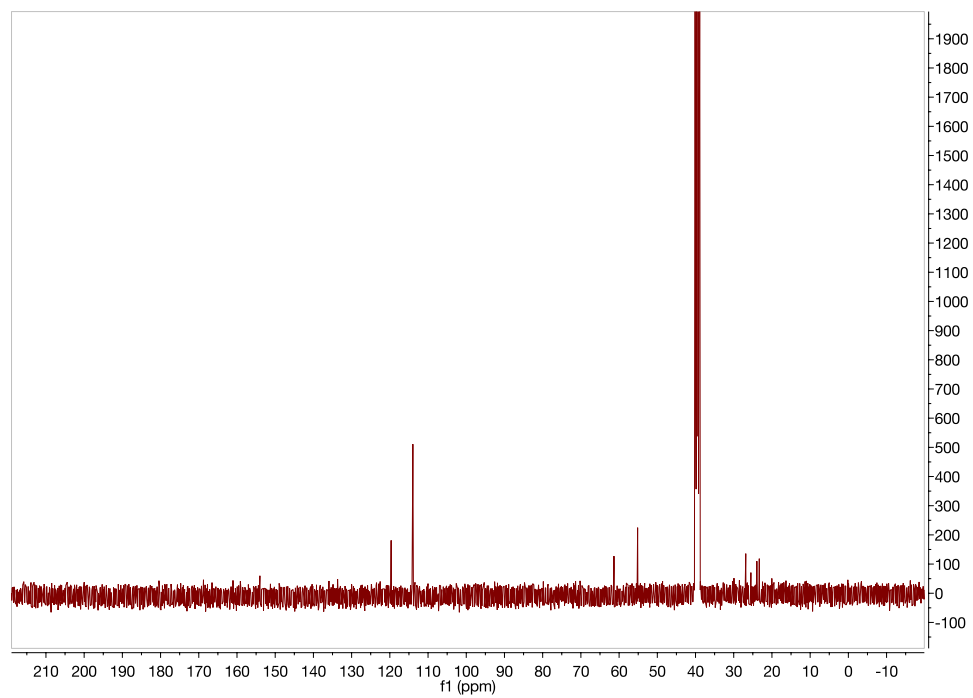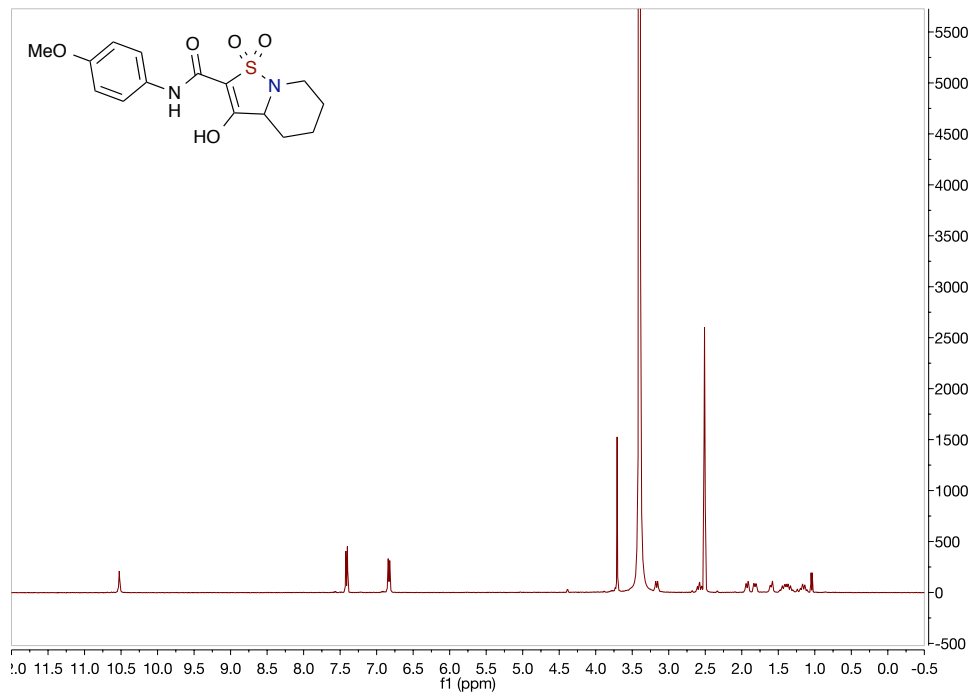
3-hydroxy-*N*-(*p*-tolyl)-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyridine-2-carboxamide 1,1-dioxide (3.36.12)
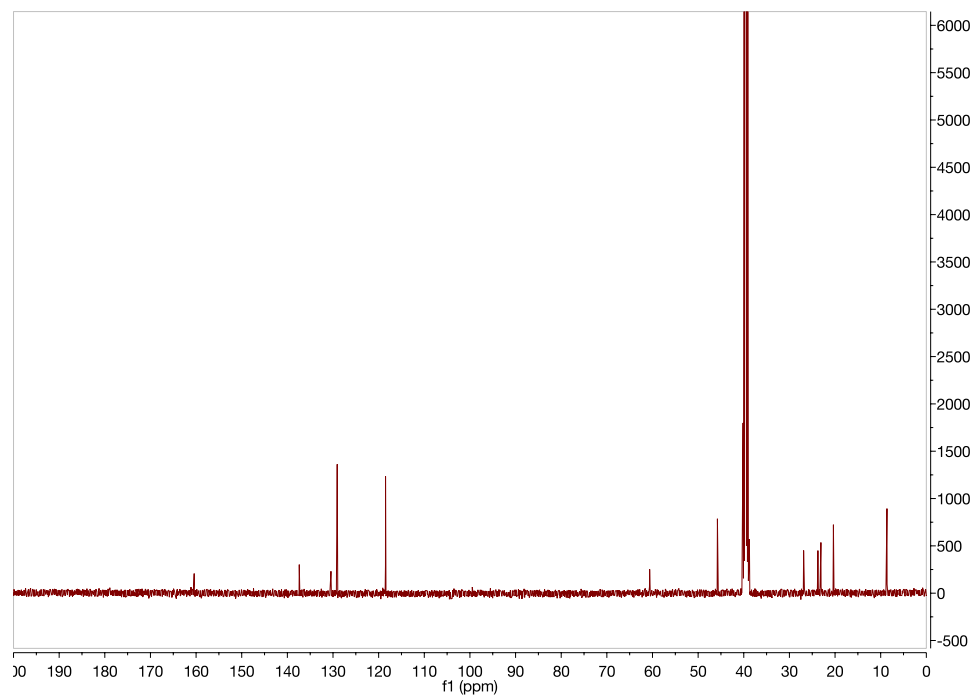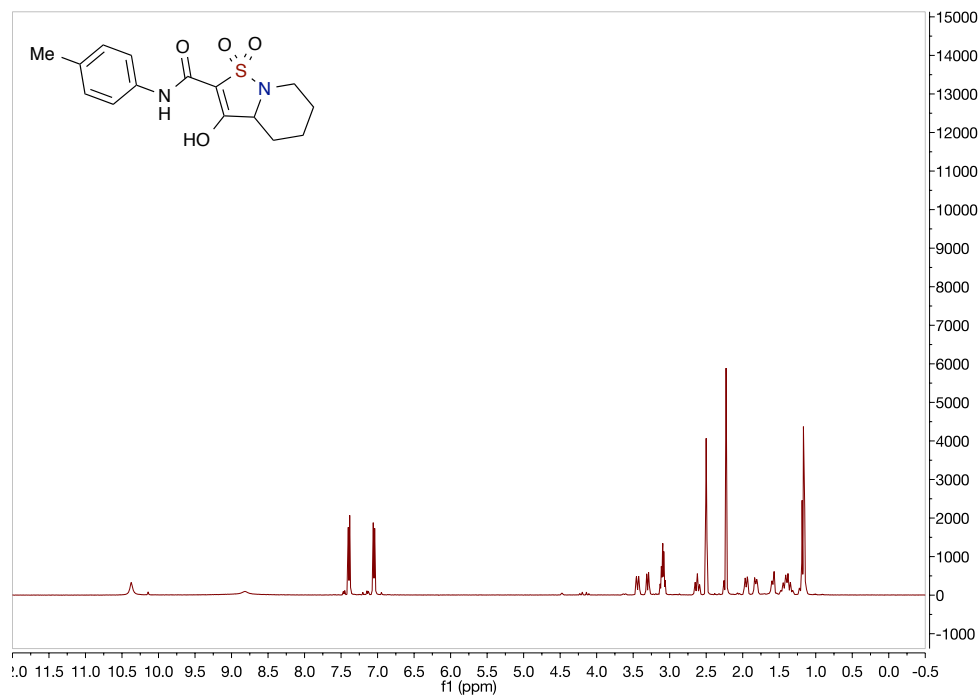
tert-butyl 3-hydroxy-2-(phenylcarbamoyl)-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (3.36.13)
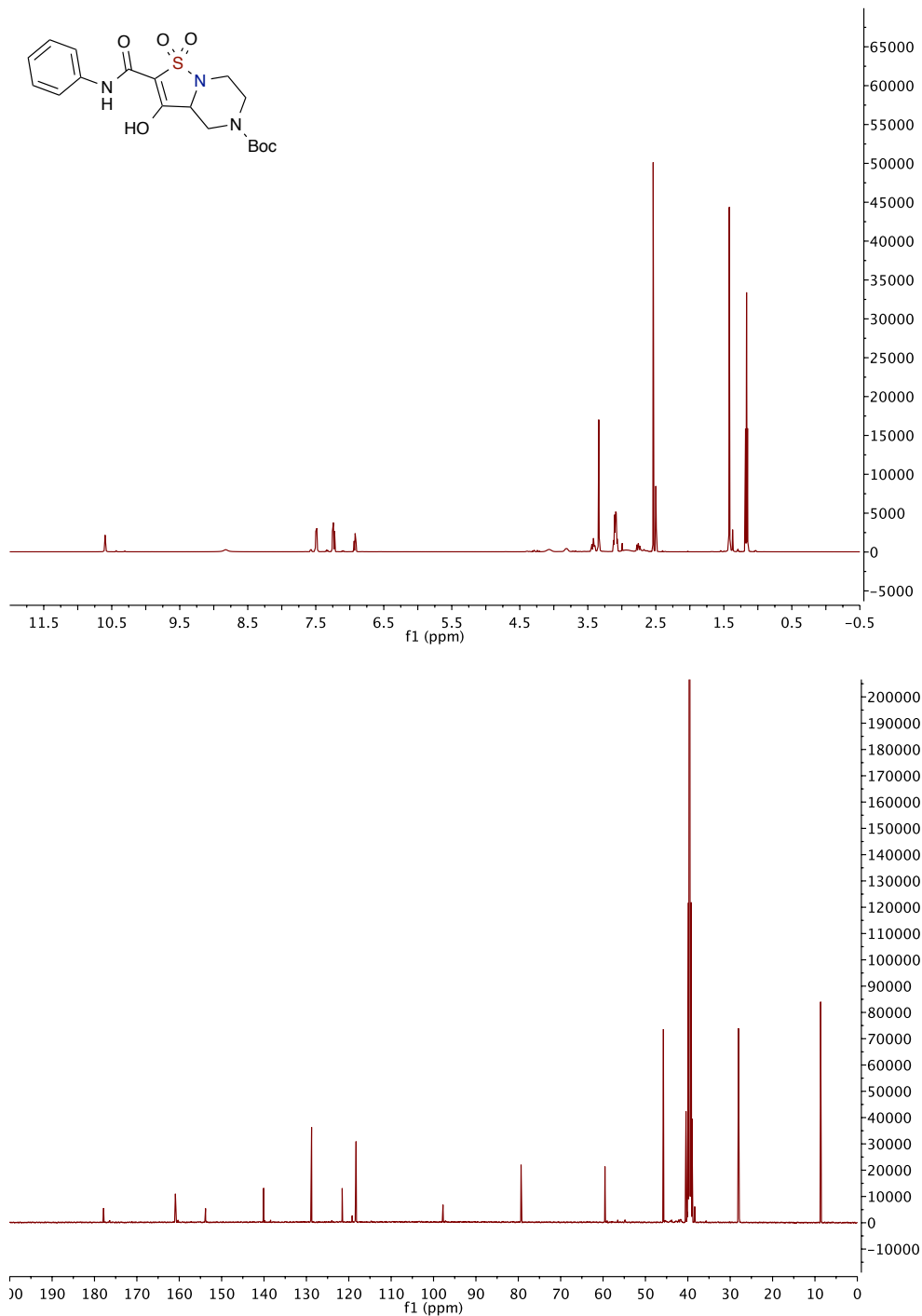
***tert*-butyl 3-hydroxy-2-((4-methoxyphenyl)carbamoyl)-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (3.36.14)**
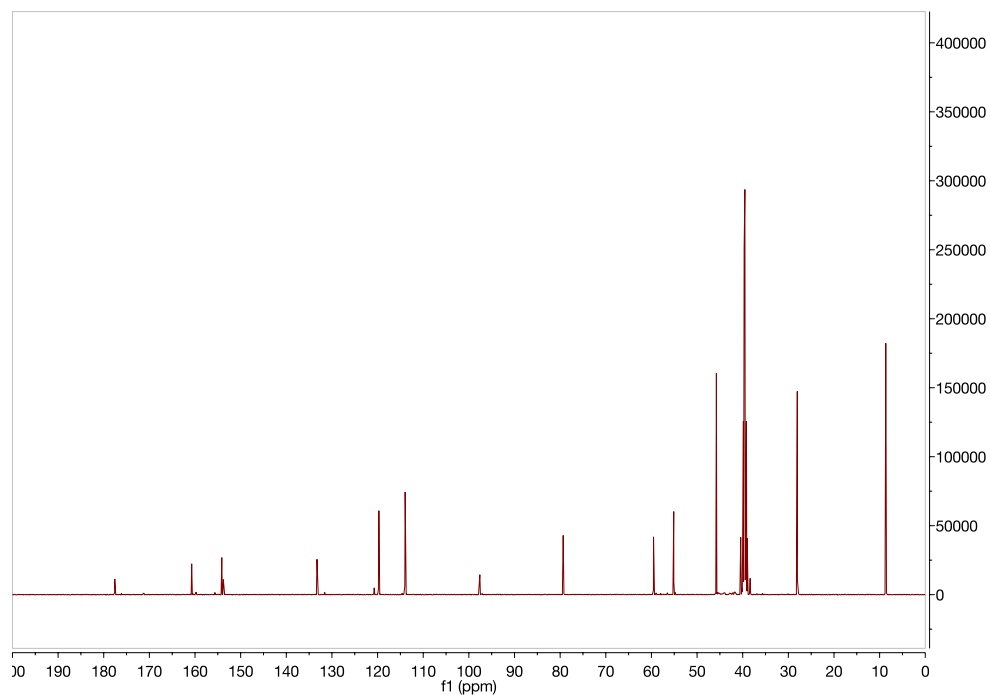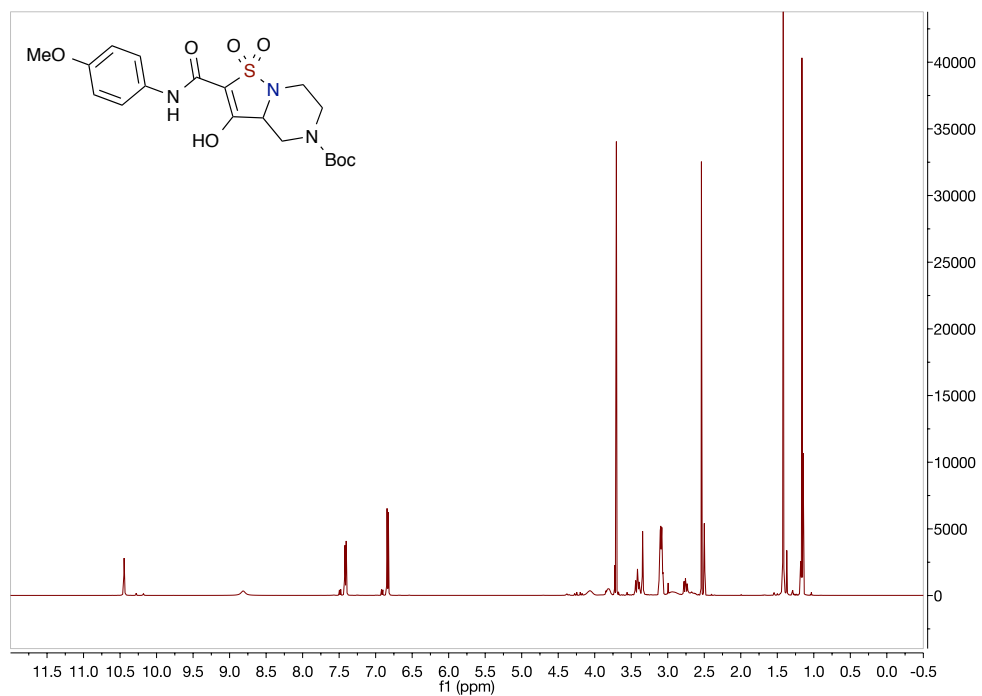
***tert*-butyl** **2-((4-fluorophenyl)carbamoyl)-3-hydroxy-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (3.36.15)**
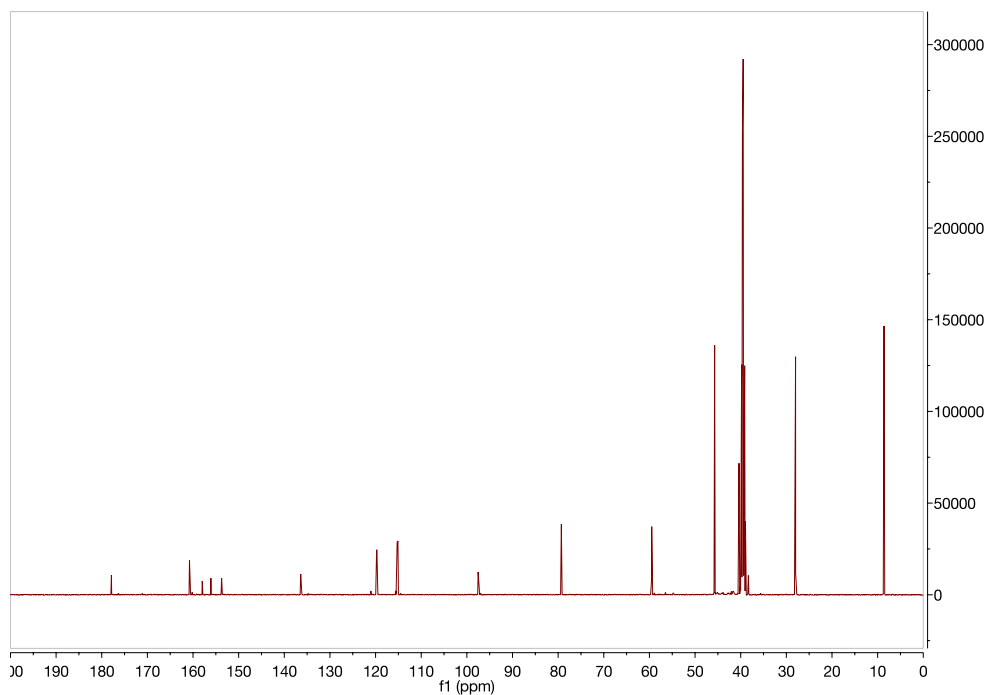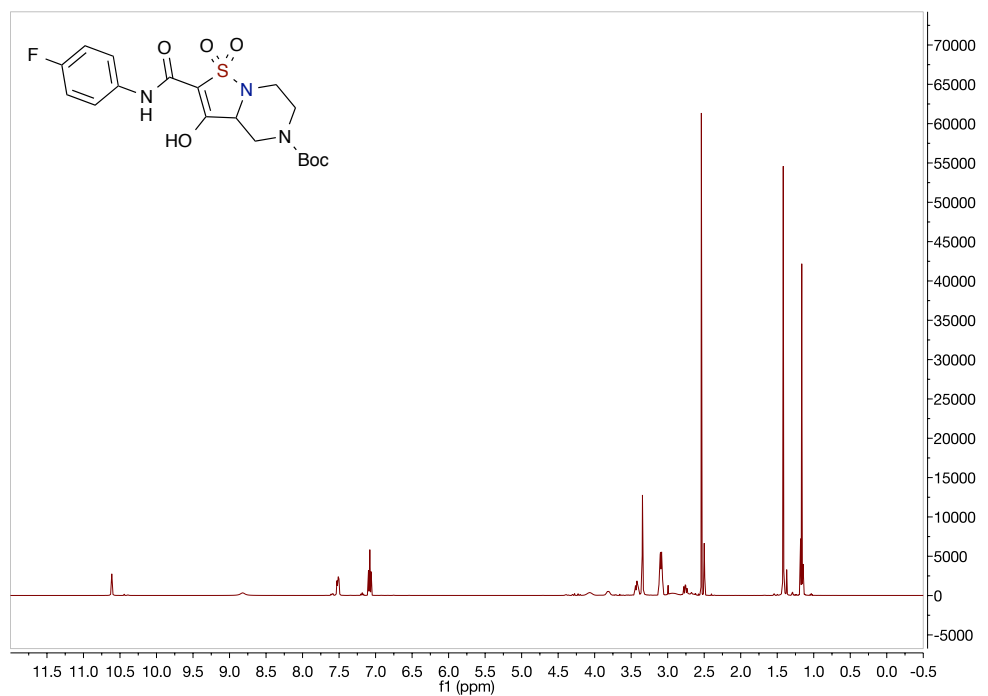
***tert*-butyl 3-hydroxy-2-(*p*-tolylcarbamoyl)-3a,4,6,7-tetrahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (3.36.16)**
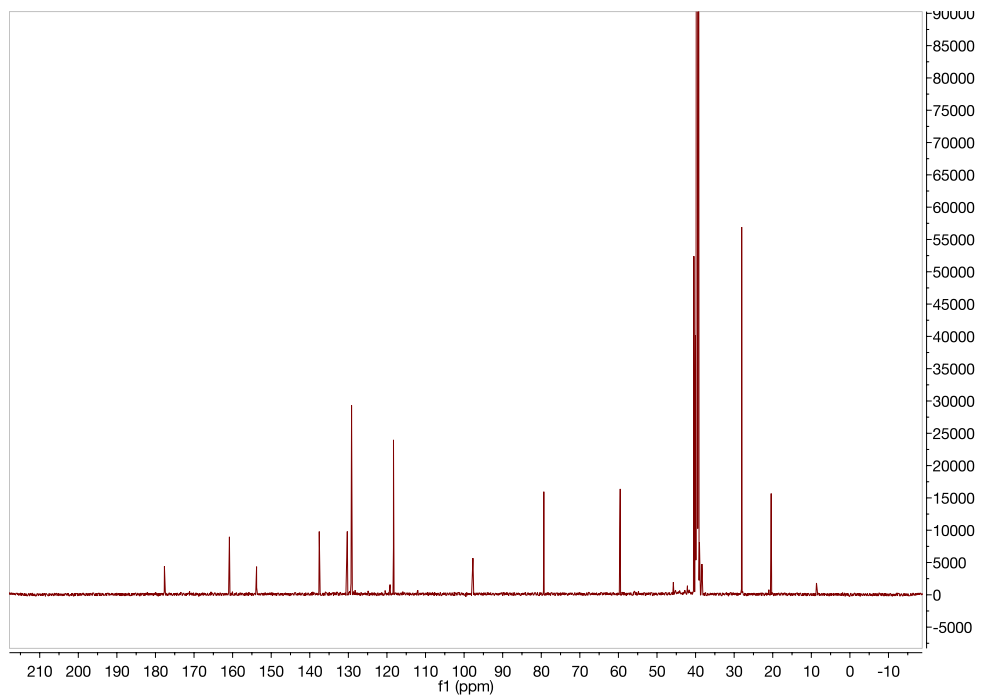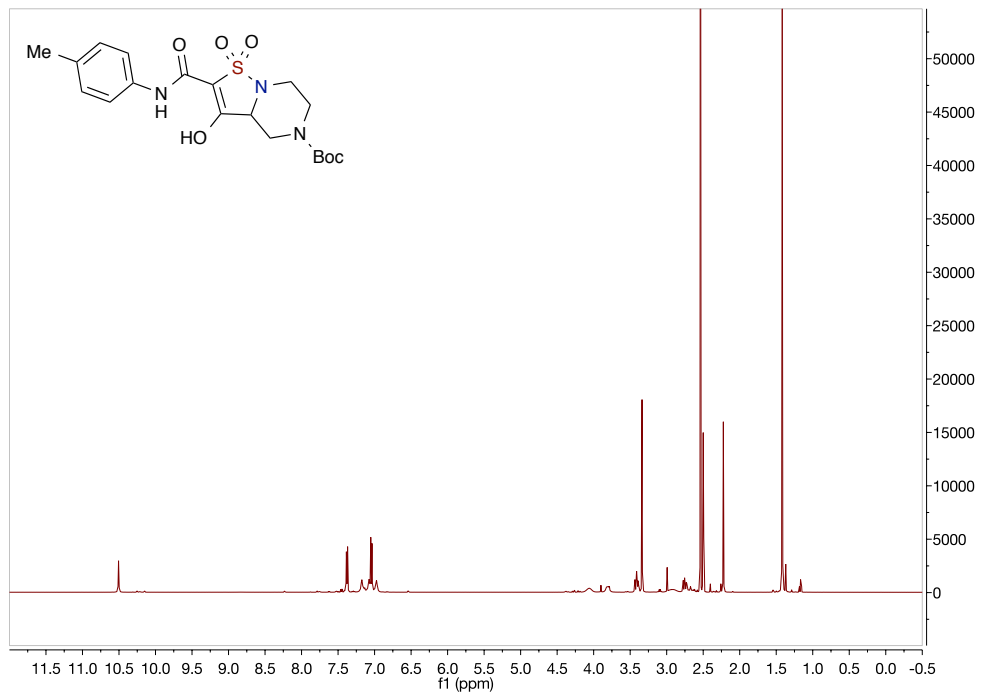
3-hydroxy-*N*-phenyl-3a,4,6,7-tetrahydroisothiazolo[3,2-*c*][1,4]oxazine-2-carboxamide 1,1-dioxide (3.36.17)
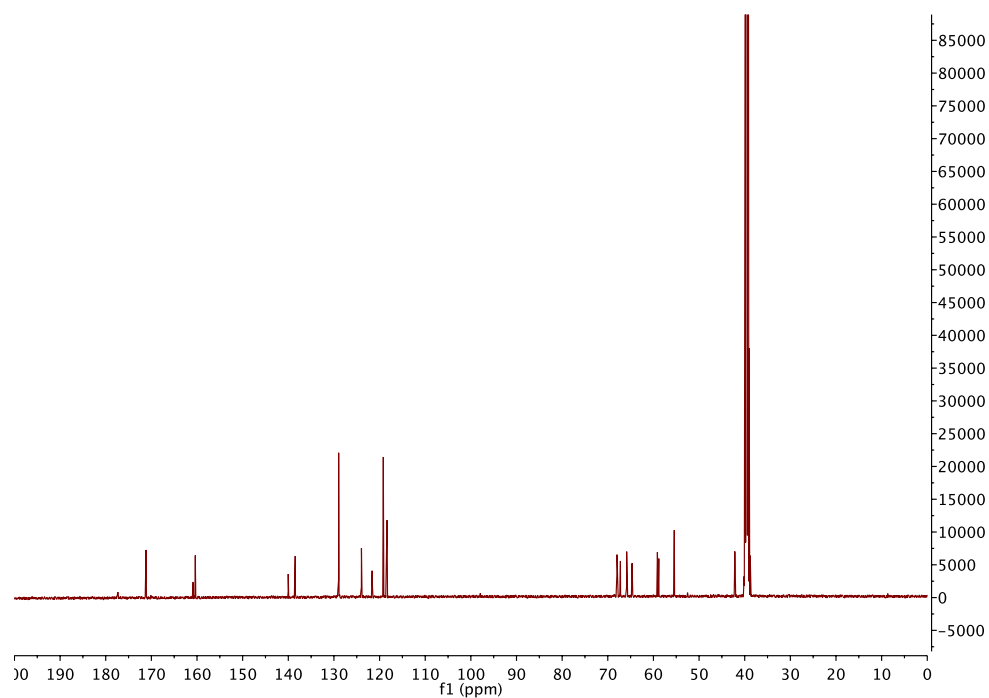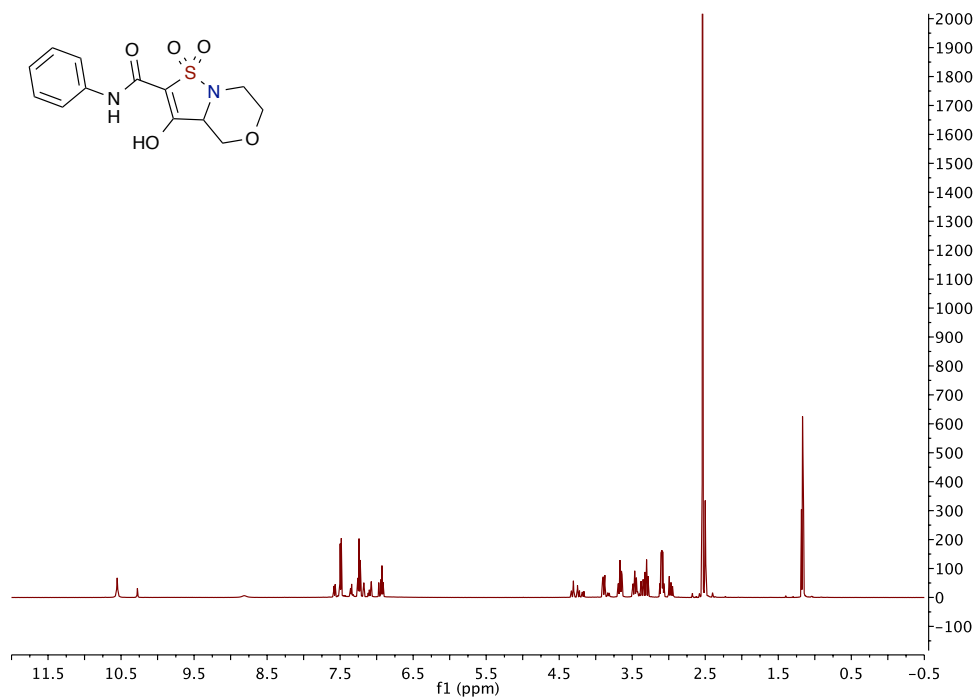
3-hydroxy-*N*-(4-methoxyphenyl)-3a,4,6,7-tetrahydroisothiazolo[3,2-*c*][1,4]oxazine-2-carboxamide 1,1-dioxide (3.36.18)
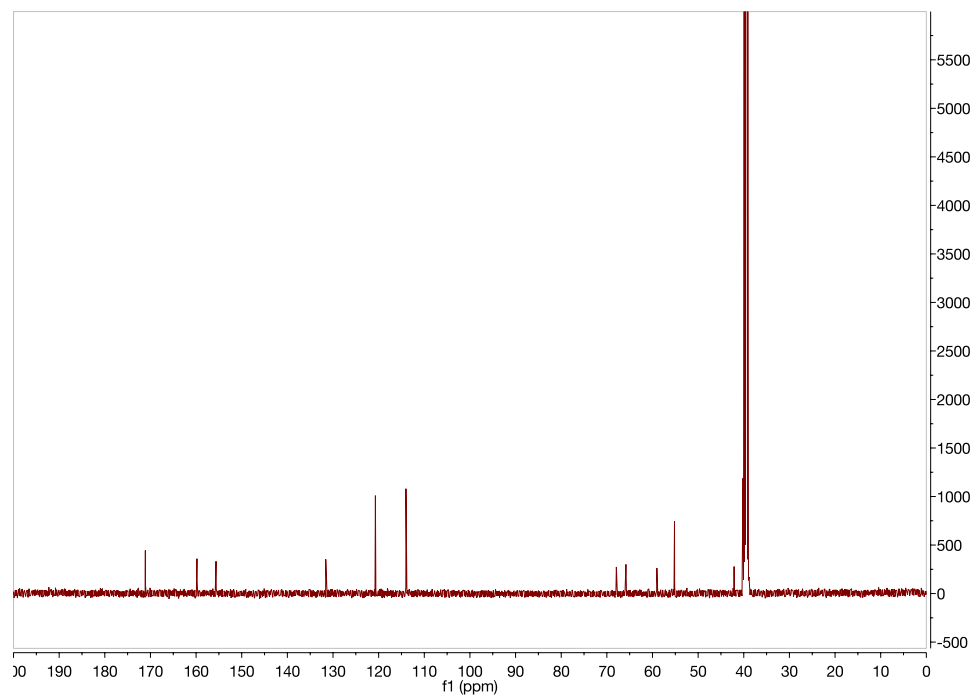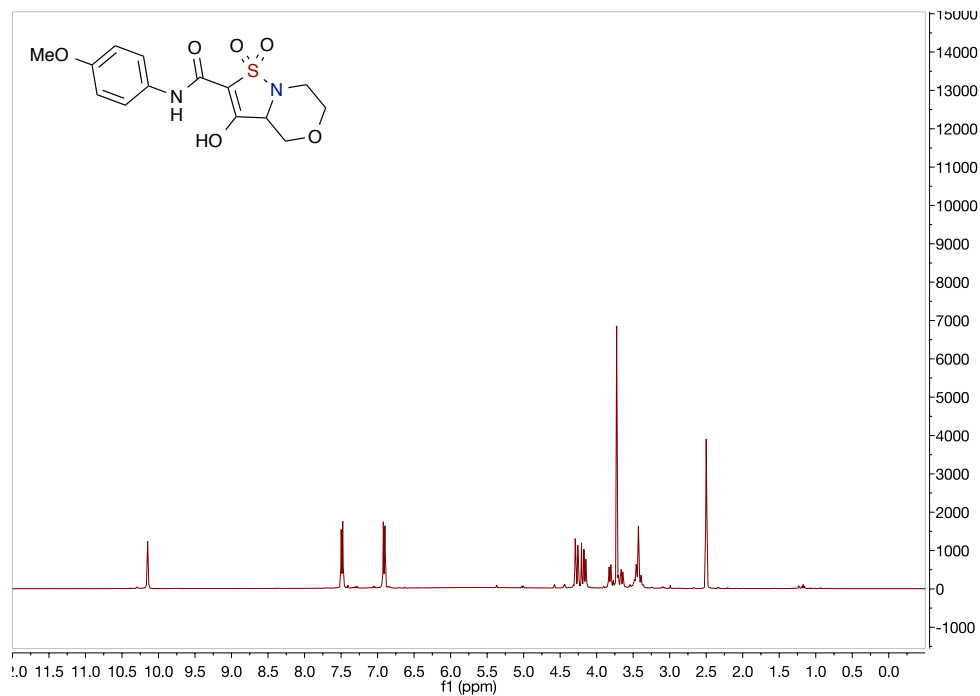
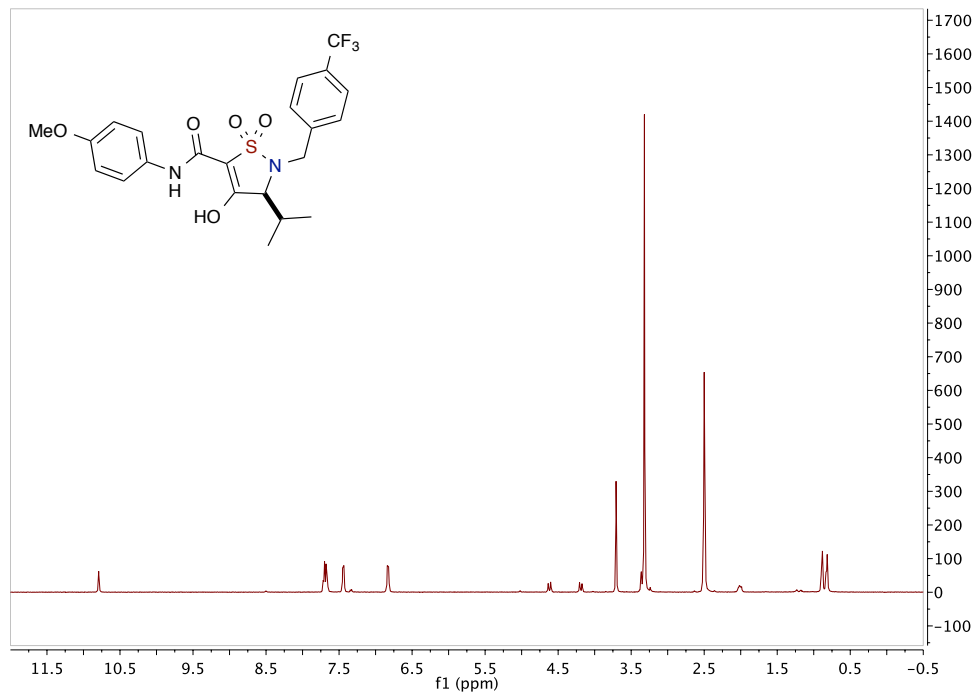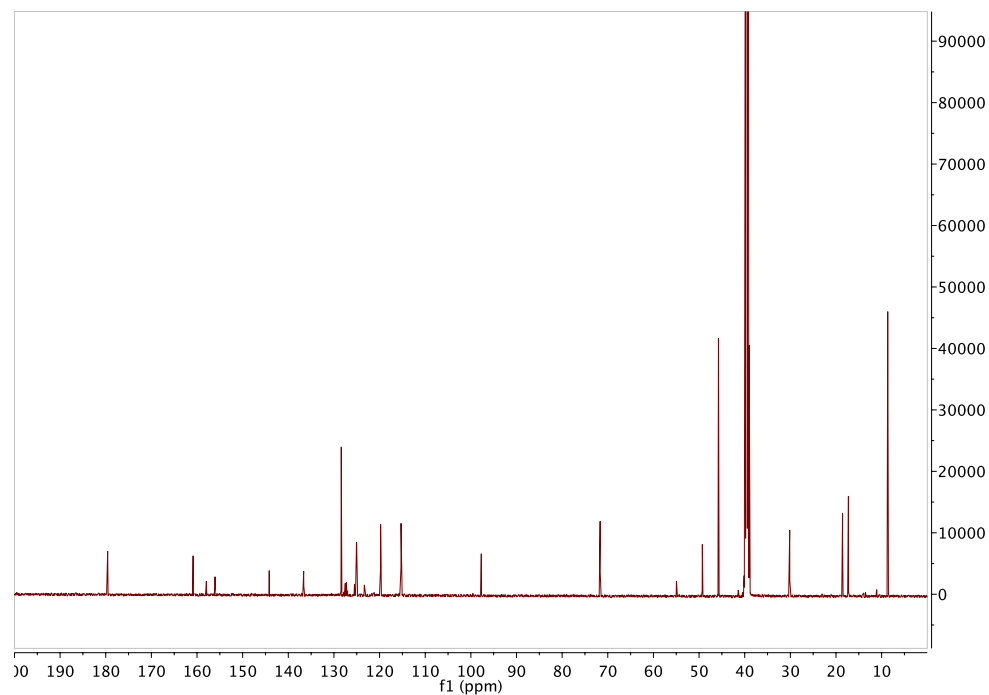# 3-hydroxy-*N*-(*p*-tolyl)-3a,4,6,7-tetrahydroisothiazolo[3,2-*c*][1,4]oxazine-2-carboxamide 1,1-dioxide (3.36.20)
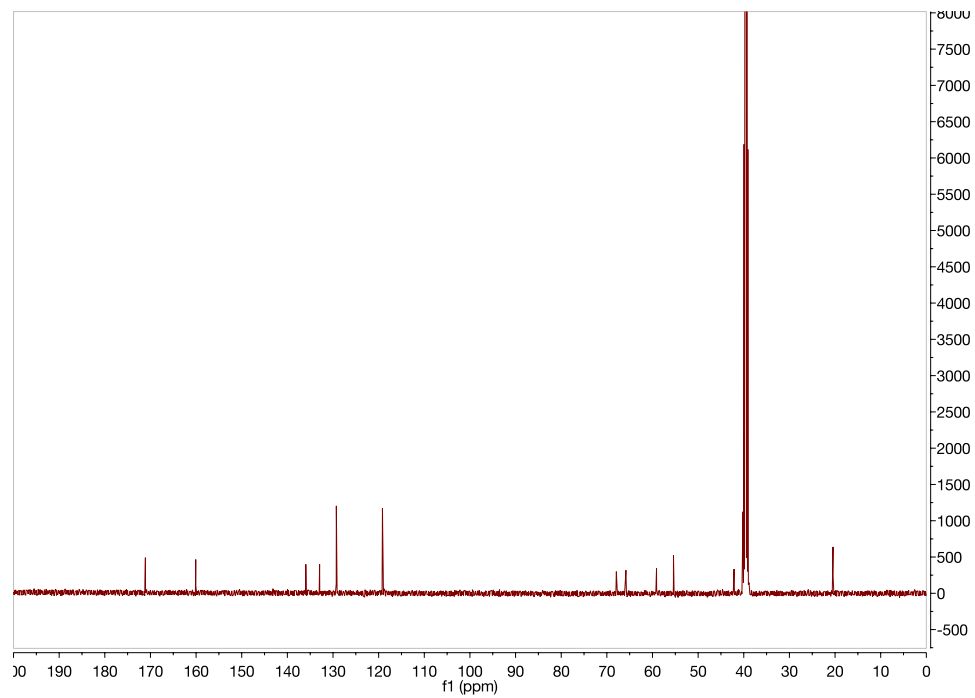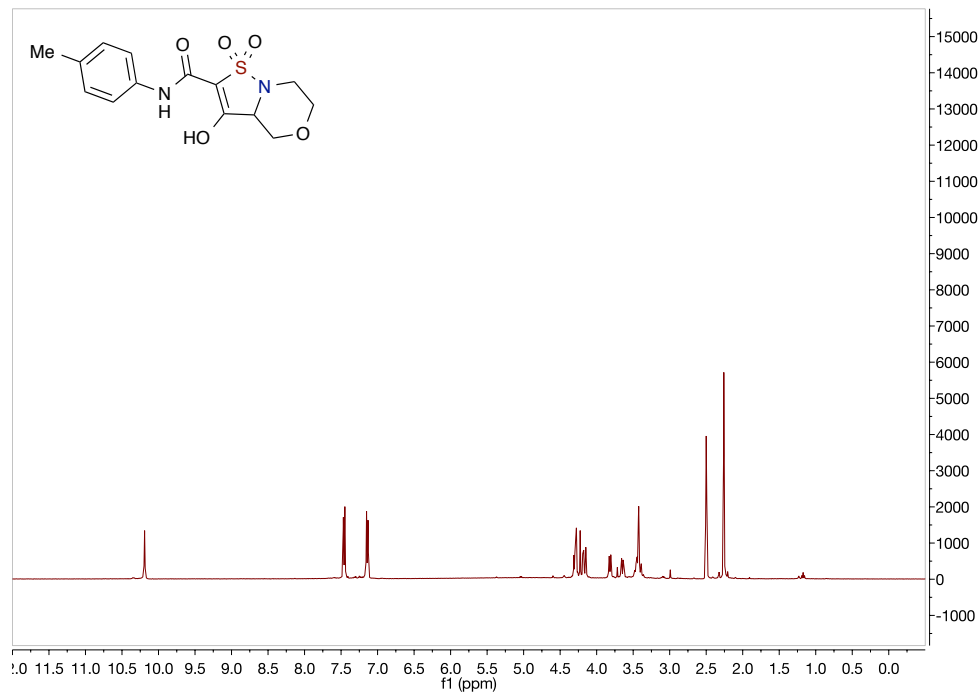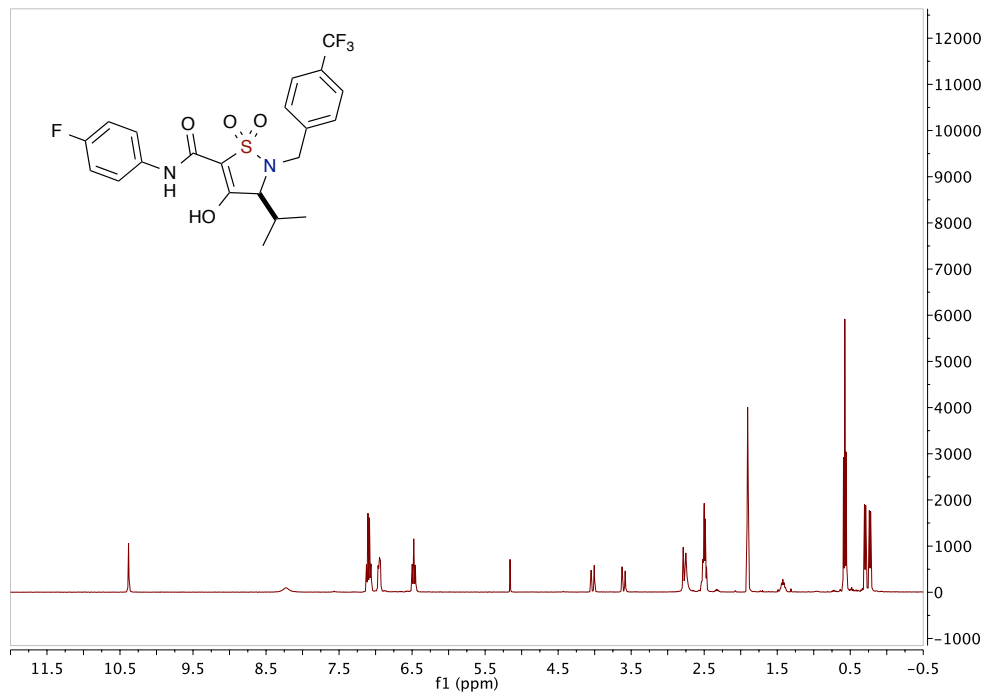
(S)-4-hydroxy-3-isopropyl-N-phenyl-2-(4-(trifluoromethyl)benzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide (3.36.21)
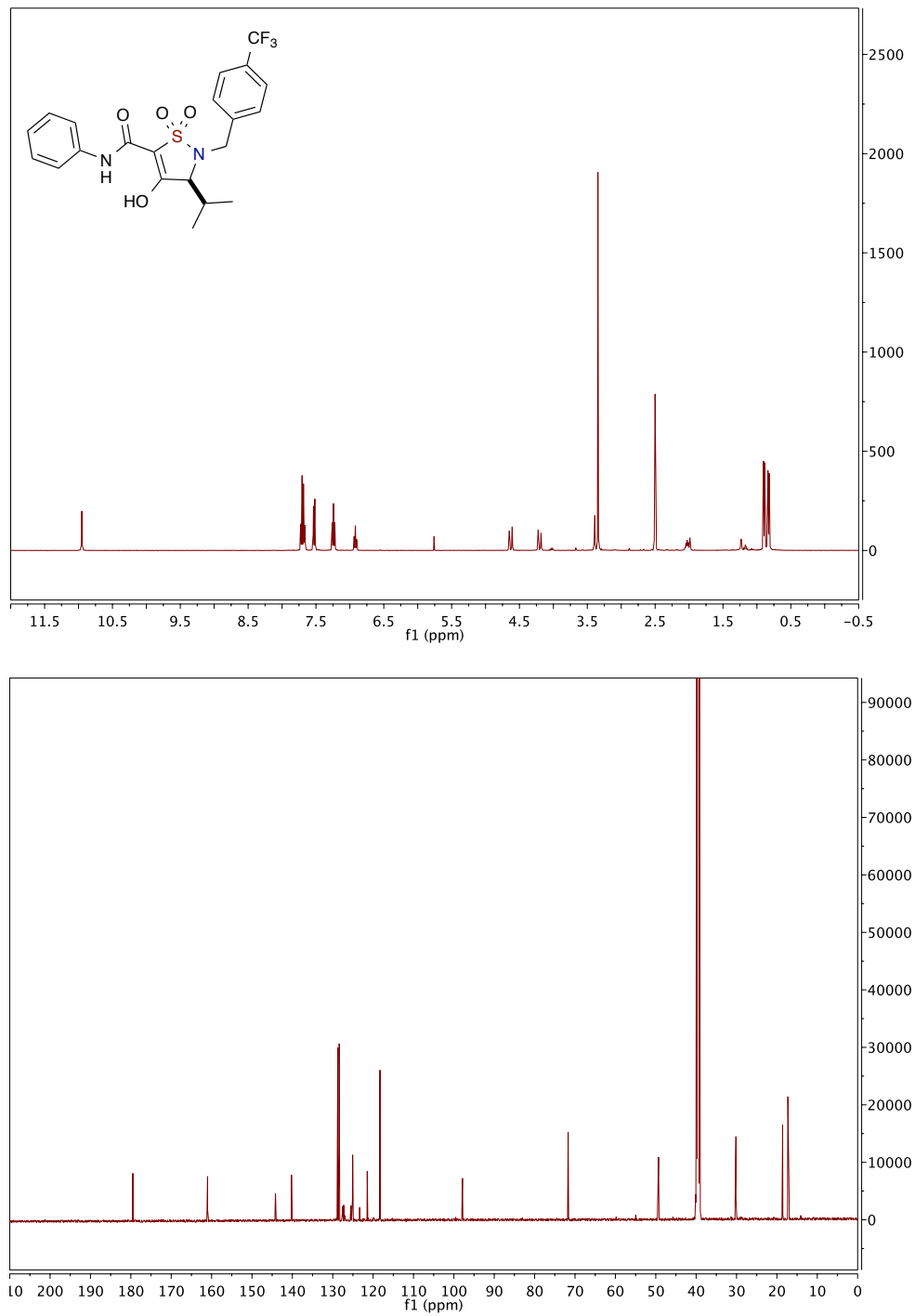
(*S*)-4-hydroxy-3-isopropyl-*N*-(4-methoxyphenyl)-2-(4-(trifluoromethyl)benzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide (3.36.22)
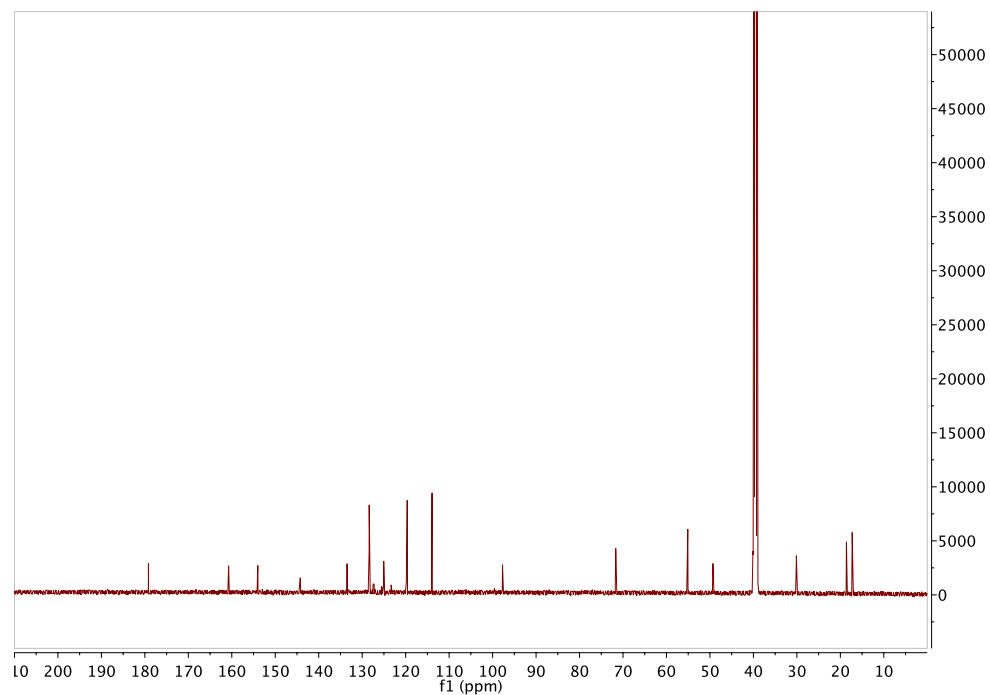
(*S*)-*N*-(4-fluorophenyl)-4-hydroxy-3-isopropyl-2-(4-(trifluoromethyl)benzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide (3.36.23)

(*S*)-4-hydroxy-3-isopropyl-*N*-(p-tolyl)-2-(4-(trifluoromethyl)benzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide (3.36.24)