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Design and Synthesis of Inhibitors of Hypoxia Inducible Factor-1-mediated Functions

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DESIGN AND SYNTHESIS OF INHIBITORS OF HYPOXIA INDUCIBLE FACTOR-1-MEDIATED FUNCTIONS

by

LINGYUN YANG

Under the Direction of Professor Binghe Wang

ABSTRACT

Hypoxia Inducible Factors (HIFs) are very important transcription factors that can respond to low oxygen concentrations in the cellular environment. Inhibition of HIF's transcriptional activity represents a promising approach to new anticancer compounds. Herein, we describe the design and synthesis of a series of HIF-1 inhibitors. Evaluation of these inhibitors using a cell-based luciferase assay led to the discovery compounds with sub-micromolar potency.

INDEX WORDS: Hypoxia, HIF-1, Cancer therapy.

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College of Arts and Sciences

Georgia State University

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DEDICATION

I would like to dedicate this work to my family, especially my parents Xiaoling Chen and Siping Yang. Thanks for their supporting and encouragement through my whole graduate school studying. My mum never questions all decisions, which I have made about academic. I also want to thank my all friends, who always stay around me with love and kindness. Finally, I would like to thank my boyfriend Weiqing Chen, his patient and love gives me the power during this process. I dedicate this work to you.

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you about chemistry and everything else. To Kim and Manjusha, thank you for cheering me up from the beginning. To Zhengnan, thank you for helping me relax when I feel upset, thank you very much. To Dr. Kaili Ji, you were like my sister, thank you for teaching me all biology knowledge; I would remember our friendship forever. To Yueqing, thank you for helping me on operating equipment. To all my friend and lab members I forgot to mention, thank you for being with me and supporting me, you are my hidden treasure and a part of my life. I will forever appreciate all you did for me. Thank you very much.

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HIF-1	Hypoxia Inducible Factor 1
UPP	Ubiquition proteasome pathway
ODD	Oxygen dependent degradation domain
PHD	Prolyl hydroxylase dioxygenase
pVHL	Von Hippel Lindau tumor suppressor prptein
HRE	Hypoxia-responsive element
VEGF	Vascular epidermal growth factor
EPO	Erythropoietin
DMF	Dimethylformamide
K_2CO_3	Potassium carbonate
***n*-BuLi**	*n*-Butyllithium
THF	Tetrahydrofuran
r.t.	Room temperature
Boc_2O	Di-tert-butyl dicarbonate
TsCl	4-Toluenesulfonyl chloride
NEt_3	Triethylamine
NaH	Sodium hydride
NH_4Cl	Ammonium chloride
Luc	Luciferase
SAR	Structure activity relationship
$CDCl_3$	Deuterated chloroform
$MgSO_4$	Magnesium sulfate

1 INTRODUCTION

1.1 Purpose of the Study

A tumor is an abnormal growth of body tissue. Malignant tumors or cancer represent a major threat to human health. Based on the GLOBOCAN database,[1] tens of millions of people are diagnosed with cancer around the world each year, and more than half of them die from it. Cancer is generally considered a name for a class of diseases with varying characteristics. As a result, treatment outcome varies and a cure is an elusive goal.[2] Although there are debates as to whether one can truly summarize certain traits as hallmarks of cancer,[3-4] one thing is true that malignant solid tumors are often accompanied by a state of hypoxic, or low oxygen, conditions, presumably due to their rapid growth and inadequate vascularization.[5] Such hypoxic states activate the expression of genes responsible for malignancy, aggressiveness, metastasis, and treatment-refractory properties.[6]

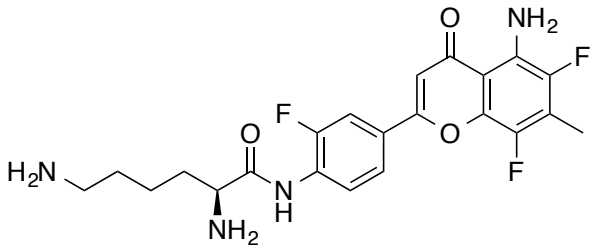
1.2 Hypoxia Inducible Factor-1 Pathway

Hypoxia Inducible Factors (HIF) are a family of transcription factors that regulate hypoxia-driven gene expression.[7-8] HIFs can be activated under hypoxic conditions and induce target genes that regulate adaptive biological processes such as cell motility, anaerobic metabolism and angiogenesis.[9] HIF-1 is the chief regulator in the response of growing tumor to hypoxia.[10] HIF-1 is a heterodimeric protein complex composed of α and β subunits, and HIF-1α plays a role as an oxygen-sensitive transcriptional activator while HIF-1β is constitutively expressed in the cell nucleus.[11-13] In the presence of oxygen, HIF-1α can be destroyed rapidly through the ubiquition-

proteasome pathway (UPP).[14] HIF-1α subunit is dihydroxylated at key proline residues within the oxygen dependent degradation domain (ODD) of HIF-1α. During this process, PHD2, a member of the prolyl hydroxylase family, along with 2-oxoglutarate, oxygen and Fe(II) are required to promote the hydroxylation of HIF-1α.[15-17] Following this process, HIF-1α can bind to the von Hippel Lindau tumor suppressor protein (pVHL) which can polyubiquitinate HIF-1α due to its E3-ubiquitin ligase activity, subsequently signaling degradation via the ubiquition-proteasome pathway (UPP).[18] Under hypoxic conditions, PHD2 activity is inhibited because of the reduction of oxygen, and HIF-1α accumulates rapidly and forms the HIF-1 dimer with HIF-1β, regulating the transcription of many genes in a cell.[19] With the help of cofactor p300, HIF-1 binds to the hypoxia-responsive element (HRE) sequence of DNA, and promotes the expression of a number of target genes such as vascular epidermal growth factor (VEGF) and erythropoietin (EPO), which help hypoxic cells survive.[20-22] Solid tumors need an increased blood supply to grow and spread to other organs and regions of the body, and overexpression of VEGF is able to develop the enhanced blood supply for them.[23] EPO has a role of controlling erythropoiesis or red blood cell production, and it can be used to treat anemia from kidney failure or cancer treatment.[24] Over expression of EPO is a factor that exhibits an anti-apoptotic action on numerous cells, including malignant ones.[25]

1.3 HIF-1 Inhibitors

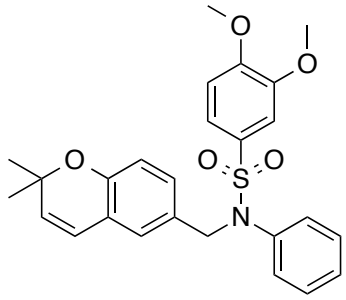
Recently, many anti-cancer compounds have been developed to inhibit the HIF pathway.[26] Some of them have been applied in the clinic successfully. The 2016 Laskar award was given to three scientists: William Kaelin, Jr., Peter Ratcliffe, and Gregg Semenza, for their seminal contributions in oxygen sensing and associated biological implications, further demonstrating the importance of this area. Inhibition of HIF-1 can be achieved in many ways, including decreased HIF-1α mRNA levels, decreased HIF-1α protein synthesis, increased HIF-1α degradation, decreased HIF subunit heterodimerization, decreased HIF binding to DNA, and decreased HIF transcription activity.[27] Many drugs are in clinical trials to treat cancer by inhibition of HIF-1, and they exhibited molecular mechanisms of inhibiting HIF-1 at different steps.[28] For example, the prodrug AFP-464 (Figure **1**) is already applied in phase I cancer trials, and it almost blocks HIF-1α protein expression completely and partially inhibits HIF-1α mRNA expression by decreasing both the stability and translation of HIF-1α mRNA.[29]



AFP-464

Figure 1: Chemical Structure of AFP-464

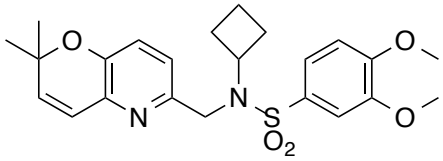
Earlier, KCN1 (Figure **2**) was discovered as a potent HIF-1 inhibitor without any signficant toxicity.[9]



KCN1
IC_{50} = 590 nM

Figure 2: Structure and IC_{50} value of KCN1

Based on KCN1, a new compound SRIV-64b (Figure **3**) was designed and synthesized by our group. Compared to KCN1, IC_{50} of 0.59 μM (Figure **2**), SRIV-64b was determined to have a lower IC_{50} value and was considered the most potent HIF-1 inhibitor of this series synthesized previously.[9]



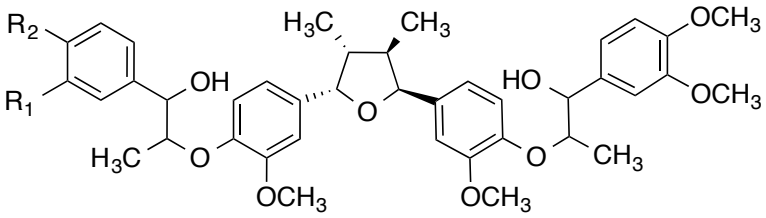
SRIV-64b
IC_{50} = 280 nM

Figure 3: Structure and IC_{50} value of SRIV-64b

1.4 HIF-1 Inhibitors Classes

During the past several years, more than 200 compounds have been synthesized by our group. However, only less than half of the compounds in the library can be considered as potent HIF inhibitors. In order to find more patent HIF inhibitors, new scaffolds were needed.

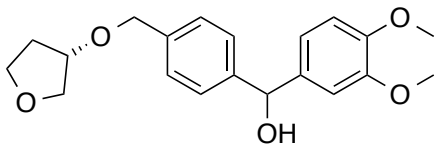
Natural products manassantin A and manassantin B (Figure **4**), isolated from *Saururus cernuus* have been shown to inhibit HIF-1 *in vitro* at nanomolar concentrations.[30-32] With these natural products and our earlier HIF-1 inhibitors in mind,[9] we were interested in designing "hybrid" compounds as a new scaffold of potential HIF-1 inhibitors. As a result, lead compound **2** (Figure **5**) was developed with the goal of achieving manassantin-like activity against HIF, while having a more facile synthetic route than manassantins. Compound **2** was synthesized and shown as a potent HIF inhibitor, and successfully demonstrated HIF inhibition in a luciferase assay in glioblastoma cells. Our goal was to design new analogues by modifying lead compound **2** and to test them for HIF inhibitory activity. Based on substituents at different positions on the phenyl ring, five classes of compounds were designed and synthesized (Figure **6**).



Manassantin A: $R_1=R_2=$-OCH_3
Manassantin B: $R_1=R_2=$-OCH_2O-

1

Figure 4: Manassantin A and B



2

$IC_{50} = 0.58\ \mu M$

Figure 5: Lead compound structure and IC_{50} value

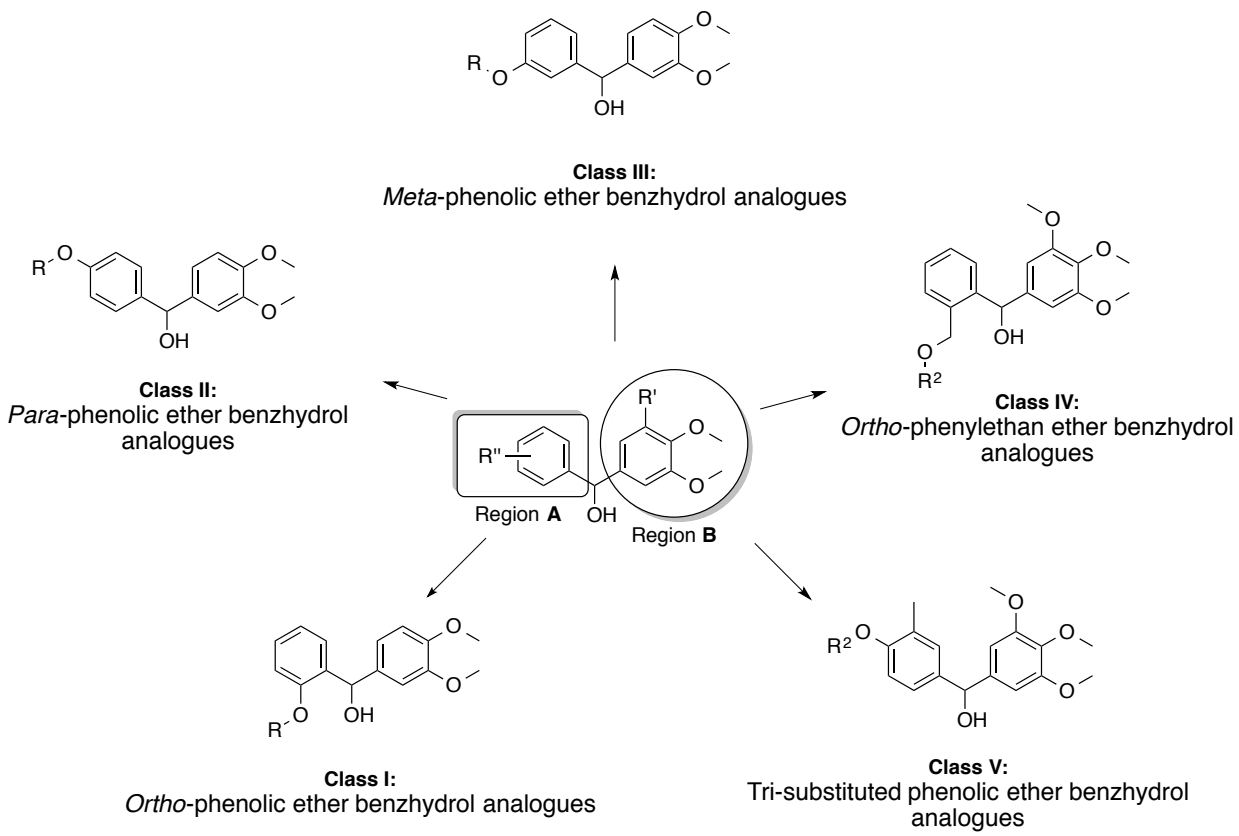


Figure 6: Analogues Designed

2 CHEMISTRY DESIGN AND EXPERIMENTS

This work includes compounds synthesized by Jalisa Ferguson and Marquis Griffin#.*

12a, 14d, 9d, 9g, 19b, 17e and 22a *were synthezied by Dr. Jalisa Holmes Ferguson*.*

14a and 9a *were synthesized by Marquis Griffin#.*

2.1 Design

In Class I, we are interested in exploring the effect of having an ortho-substitution on the phenyl ring of region **A**, while maintaining the methyl-protected catechol structure on the right. In doing so, we expect that the torsional angle defined by

O(hydroxyl)-C-C-C to be slightly perturbed by alkoxy substitution at the ortho position. In this class of compounds, we designed six analogues, and compared their different structures for structure activity relationship study.

In Class II, we are interested in examining the effect of *para*-subtitutions. In this case, the torsional angle defined by O (hydroxyl)-C-C-C is not expected to be perturbed. However, the various substitutions would allow us to explore the favorable and unfavorable interactions between the binding pocket and the *para*-substituents of the phenyl ring. In addition, such substitutions may also perturb the electronic properties of the phenyl ring and to some degree the hydrophobicity of the moiety. The various substituents at the *para*-position may also allow us to explore additional functional group interactions. In Class III, we are interested in examining the effect of substituents at the meta-position while keeping the protected catechol the same on the right side. Similarly, class III can be compared with class II. In Class IV and V, we are interested in changing the protected catechol to protected pyragol, while sampling various substituents on the phenyl ring on the left side. Below are the results of synthesis and biological evaluation.

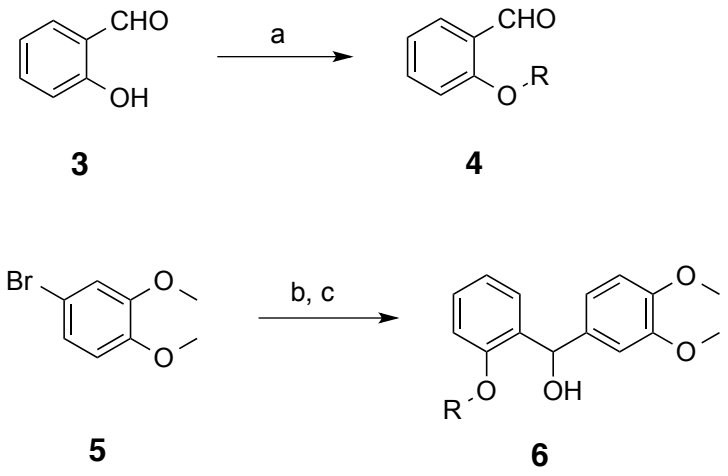
2.2 Chemistry

2.2.1 Class I: *Ortho*-phenolic ether benzhydrol analogues.

Class I analogues were synthesized in two steps: nucleophilic substitution followed by lithium-halogen exchange with subsequent addition to aldehyde. 2-Hydroxybenzaldehyde (**3**) was reacted with the corresponding bromide to generate

compounds (**4a-f**). Compounds (**6a-f**) were generated using a lithium-halogen exchange reaction of bromide of **5** using *n*-butyllithium. The aryllithium generated was used *in situ* in the subsequent addition reaction with aldehydes **4a-f**, yielding final compounds **6a-f**.

Scheme 1: Synthesis of *ortho*-phenolic ether benzhydrol analogues.



R= allyl (**4a, 6a**), isopropyl (**4b, 6b**), propyl (**4c, 6c**), hexyl (**4d, 6d**), methylcyclohexyl (**4e, 6e**), and benzyl (**4f, 6f**).

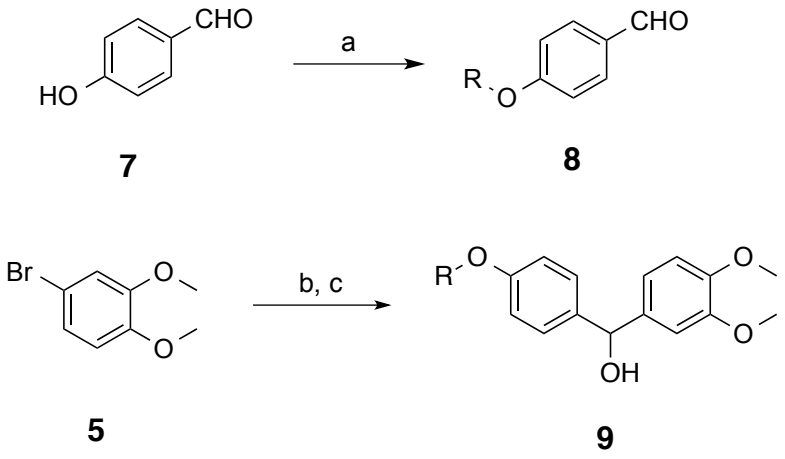
Reagents and Conditions: (a) RBr, K_2CO_3, DMF, 78 °C, overnight, 97-99% yield. (b) *n*-BuLi, THF, -78 °C, 1.5 hours; (c) **4**, 2 hours, 55-69% yield.

2.2.2 Class II: *Para*-phenolic ether benzhydrol analogues

Synthesis of Class II analogues was achieved in either 2 or 4 steps. In Scheme 2, the intermediates **8a-c** were prepared by reaction between 4-hydroxybenzaldehyde (**7**)

and bromide compounds. Next, lithium-halogen exchange of **5** using *n*-BuLi, followed by addition of aldehyde **8,** afforded the final compounds **9a-c.** In Scheme 3, for analogue **9g**, di-*tert*-butyl dicarbonate was reacted with 2-(piperidin-4-yl)ethan-1-ol **10b** under aqueous conditions to yield intermediate **11b**. Tosylation of **11b** with 4-methylbenzenesulfonyl chloride under mild conditions yielded **12***. Next, the intermediates **14a$^{\#}$-d** were prepared by reaction between 4-bromophenol (**13**) and compounds **12*** or bromide compounds. Lastly, lithium-halogen exchange of **14** using *n*-BuLi, followed by addition of 3,4-dimethoxybenzaldehyde, afforded the final compounds **9d$^{\#}$-g*.**

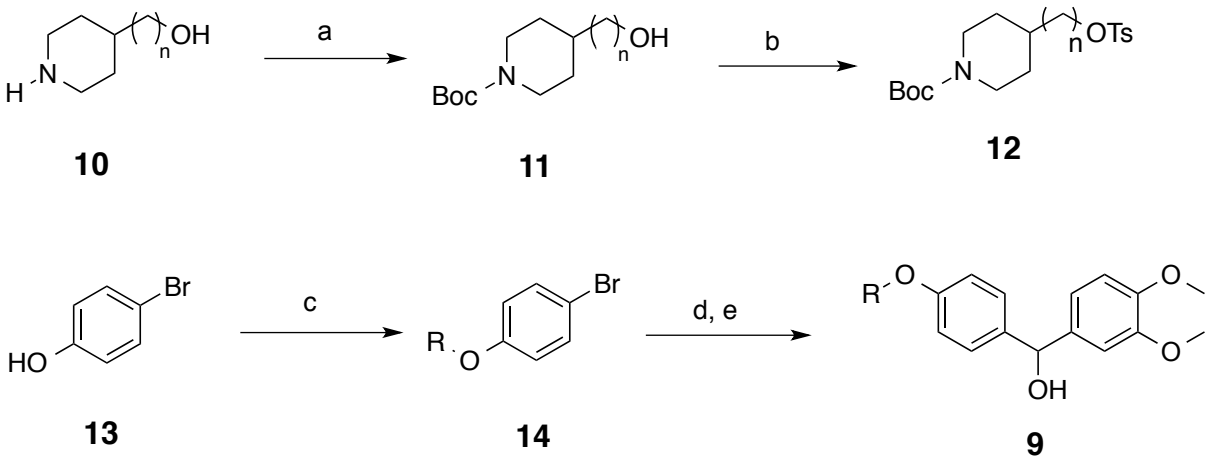
Scheme 2: Synthesis of *Para*-phenolic ether benzhydrol analogues **9a-9c.**



R= isobutyl (**8a, 9a**), hexyl (**8b, 9b**), methylcyclohexyl (**8c, 9c**).

Reagents and Conditions: (a) K_2CO_3, RBr, DMF, 78 °C, overnight, 95-97% yield. (b) *n*-BuLi, THF, -78 °C, 1.5 hours; (c) **8a-c**, 2 hours, 54-71% yield.

Scheme 3: Synthesis of *Para*-phenolic ether benzhydrol analogues **9d[#]-9g***



n=2 (**10b, 11b, 12***)

R= allyl (**14a[#], 9d[#]**), isopropyl (**14b, 9e**), propyl (**14c, 9f**), (1-(*tert*-butoxycarbonyl)piperidin-4-yl)ethyl (**14d[*], 9g***).

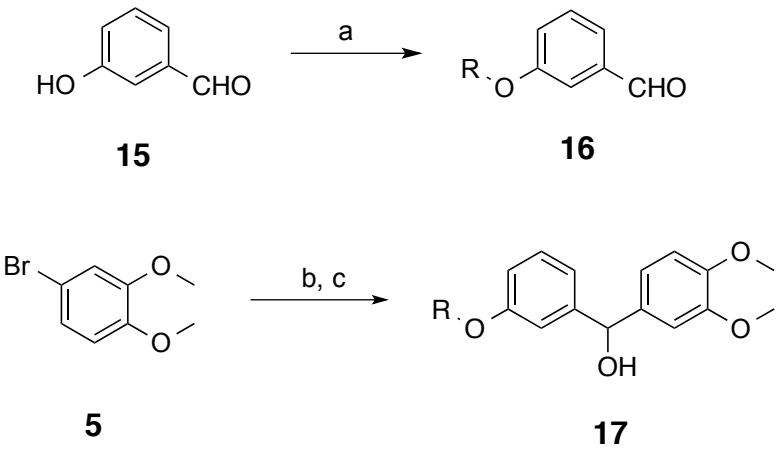
Reagents and Conditions: (a) Boc_2O, H_2O, room temperature, overnight, 96% yield. (b) TsCl, NEt_3, THF, room temperature, overnight, 86% yield. (c) K_2CO_3, **12**; RBr, DMF, 90 °C, 5 hours, 95-97% yield. (d) *n*-BuLi, THF, -78 °C, 1.5 hours; (e) 3,4-dimethoxybenzaldehyde, 2 hours, 54-71% yield.

2.2.3 Class III: *Meta*-phenolic ether benzhydrol analogues

Class III analogues were synthesized as described in Schemes 4 and 5. In Scheme 4, the analogues were synthesized by alkylation of 3-hydroxybenzaldehyde (**15**) using the corresponding bromide to give intermediates **16a-b**. Next, lithium-halogen exchange of **5** using *n*-BuLi, followed by addition of aldehyde **16**, afforded the final compounds **17a-b.** In Scheme 5, for analogues **17c-e,** the intermediates **19a-c**

were prepared by reaction between 3-bromophenol (**18**) and bromide compounds. Next, analogues **17c-e** were synthesized by lithium-halogen exchange as described above.

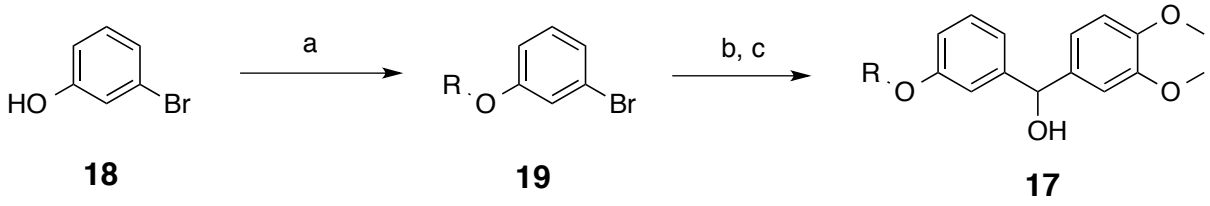
Scheme 4: Synthesis of *Meta*-phenolic ether benzhydrol analogues **17a-17c***.*



R= isobutyl (**16a, 17a**), isopropyl (**16b, 17b**), propyl (**16c, 17c**).

Reagents and Conditions: (a) K_2CO_3, DMF, 78 °C, overnight, 92-96% yield. (b) *n*-BuLi, THF, -78 °C, 1.5 hours; (c) **16a-c**, 2 hours, 67-78% yield.

Scheme 5: Synthesis of *Meta*-phenolic ether benzhydrol analogues **17d** and **17e***.



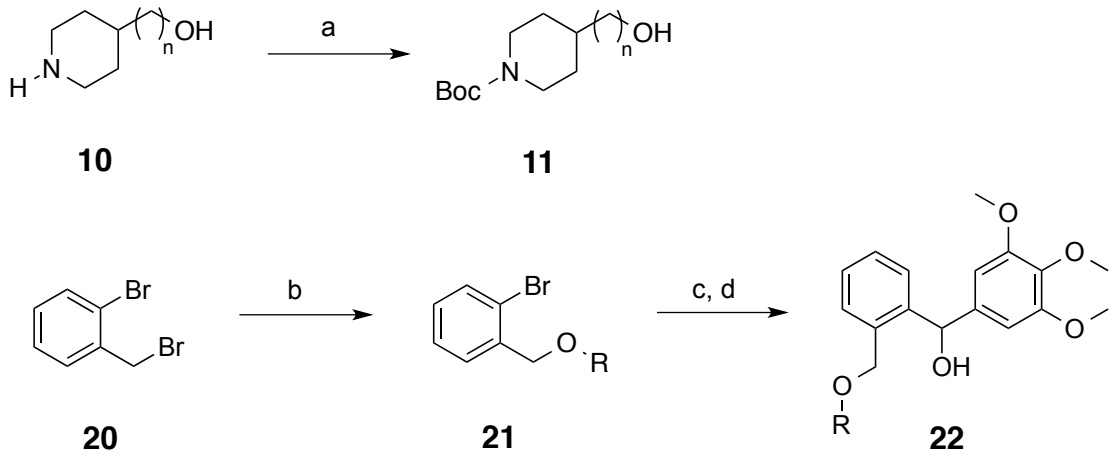
R= allyl (**19a, 17d**), hexyl (**19b, 17e**)*.

Reagents and Conditions: (a) K_2CO_3, DMF, 90 °C, 5 hours, 93-97% yield. (b) *n*-BuLi, THF, -78 °C, 1.5 hours; (c) 3,4-dimethoxybenzaldehyde, 2 hours, 63-69% yield.

2.2.4 Class IV: *Ortho*-benzyl ether benzhydrol analogues.

Synthesis of Class IV analogues was achieved in either 2 or 3 steps. For analogues **22b** and **22c**, intermediates **11a-b** were prepared by the same method as described above (Scheme 3). Benzylic ether intermediates **21** were synthesized by *O*-alkylation with sodium hydride as the base and 2-bromobenzyl bromide (**20**). Final analogues **22a-c** were synthesized using lithium-halogen exchange to generate the arylitihium, followed by addition to trimethoxyphenyl aldehyde.

Scheme 6: Synthesis of *ortho*-benzyl ether benzhydrol analogues.



n=1 (**10a, 11a**), 2 (**10b, 11b**)

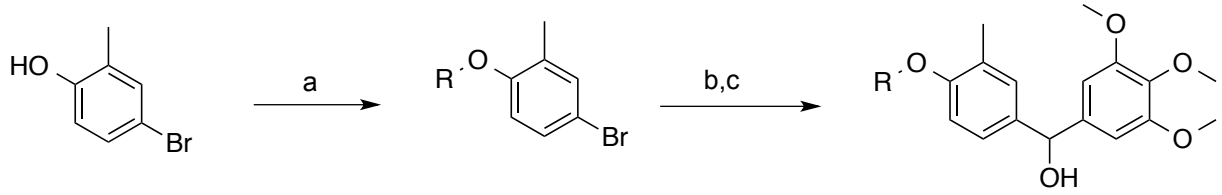
R= phenyl (**21a, 22a***), (1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl (**21b, 22b**), (1-(*tert*-butoxycarbonyl)piperidin-4-yl)ethyl (**21c, 22c**).

Reagents and Conditions: (a) Boc_2O, H_2O, room temperature, overnight, 98-99% yield. (b) ROH; **11a-11b**, NaH, DMF, 0 °C-rt, overnight, 96-98% yield. (c) *n*-BuLi, THF, -78 °C, 1.5 hours; (d) 3,4,5-trimethoxybenzaldehyde, 2 hours, 59-71% yield.

2.2.5 Class V: Tri-substituted phenolic ether benzhydrol analogues.

Class V analogues were synthesized in two steps. 4-Bromo-2-methylphenol (**23**) was reacted with bromide compounds to form the ether intermediates **24a-f** via nucleophilic substitution. Next, analogues **25a-f** were synthesized using lithium-halogen exchange and addition to trimethoxyphenyl aldehyde.

Scheme 7: Synthesis of tri-substituted phenolic ether benzhydrol analogues.



23 **24** **25**

R= allyl (**24a, 25a**), isobutyl (**24b, 25b**), isopropyl (**24c, 25c**), propyl (**24d, 25c**), hexyl (**24e, 25e**), methylcyclohexyl (**24f, 25f**).

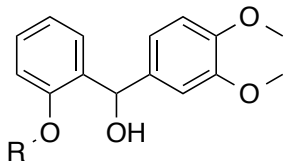
Reagents and Conditions: (a) RBr, K_2CO_3, DMF, 78 °C, overnight, 95%-99% yield. (b) *n*-BuLi, THF, -78 °C, 1.5 hours; (c) 3,4,5-trimethoxybenzaldehyde, 2 hours, 59%-65% yield.

3 BIOLOGY RESULT

All analogues synthesized herein were subsequently tested for their HIF-1 inhibition activity in a luciferase reporter assay performed by our collaborators at Emory University's Winship Cancer Institute, Dr. Erwin Van Meir. This luciferase reporter assay is a tool used to measure expression of gene expression activated by HIF. In this study, the IC_{50} value of each analogue was tested using the HRE of VEGF gene with a luciferase reporter gene. The firefly luciferase reporter gene were encoded by the HIF-responsive luciferase under the control of a promoter and tandem repeats of the hypoxia transcriptional response element (HRE).[33] IC_{50} values over 10 μM for the analogues were considered not potent enough for further evaluation. Therefore, analogues with less than 1 μM of IC_{50} were considered to have sufficient HIF inhibitor activity for further pursual.

3.1 Results for Class I Analogues

Compounds **6a, 6b, 6c, 6d, 6e,** and **6f** in class I were evaluated for their abilities to inhibit the HIF-mediated transcription activity used in the luciferase assay as described above. It was found that the best compound showed IC_{50} of about 3.8 μM (**6c**), while several had IC_{50} values of over 10 μM. Compared to compound **2**, with IC_{50} of 0.58 μM, the *ortho*-modified **6c** was six-fold less potent. Such results suggest that modifications at the *ortho*-position likely twist the molecule due to the disturbance of π-electron overlap and the O (hydroxyl)-C-C-C torsional angle in such a way that disfavors the interactions with the intended target (Table 1).



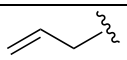
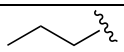
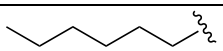
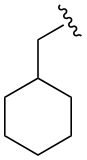
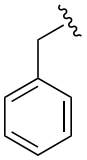
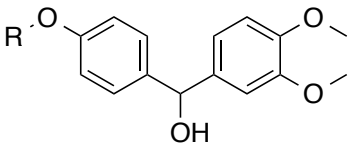
Compounds	R	IC_{50} (μM)
6a		>10
6b		>10
6c		3.8
6d		>10
6e		6.6
6f		>10

Table 1: Class I Analogues

3.2 Results for Class II Analogues

For analogues in class II, **9g*** have IC_{50} value of less 1 μM, and the other analogues (**9a, 9b, 9c)** have a lower IC_{50} value than most compounds in class I. When comparing class II and class I, the result showed that *para*-subtittuions exhibited better

inhibition of HIF-1 activity than those analogues with *ortho*-substitutions. Specifically, **9g*** with a Boc-protected piperidine substitution on the left side inhibited completely HIF-1 activity most effectively with an IC_{50} of 0.89 μM. (Table 2).



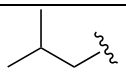
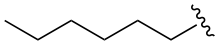
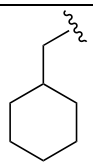
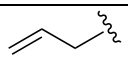
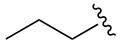
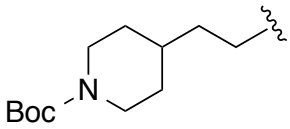
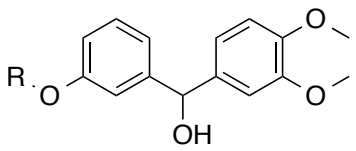
Compounds	R	IC_{50} (μM)
9a		1.1
9b		3.13
9c		4.4
9d[#]		>5
9e		>10
9f		>10
9g*		0.89

Table 2: Class II Analogues

3.3 Results for Class III Analogues

Reviewing Table 3 below and Table 2 above, the analogues of class III were seen to show better IC_{50} values than **9b, 9c and 9d#** in class II. Although there are only minor differences in the structure, *meta*-substituted compounds exhibited lower IC_{50} values than *para*-substituted compounds, especially compound **17d**. The IC_{50} value of **17d** is 0.5 μM, which is lower than the IC_{50} value of compound **2**, but the other compounds were still three- to five-fold less potent compared to compound **2**. Temporarily, class III and class II without **9g*** and **17d** were not considered as potent HIF inhibitors due to the low biology activities.



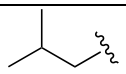
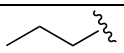
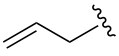
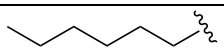
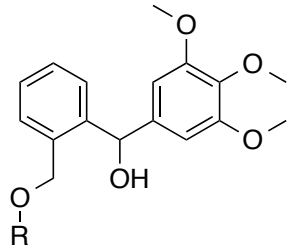
Compounds	R	IC_{50}(μM)
17a		2.12
17b		>10
17c		2.5
17d		0.5
17e*		1.65

Table 3: Class III Analogues.

3.4 Results for Class IV Analogues

Class IV analogues shown in Table 4 can best be compared to Class I analogues except there are two major differences: 1) the use of a protected pyragollol on the right side instead of the protected catechol, and 2) a methylene that separates the oxygen atom of the ether and the phenyl ring on the left side. The IC_{50} values of three compounds in class IV were determined and compared, and it was found that **22c** showed the best inhibitory activity with an IC_{50} value of 2.2 μM (Table 4). In contrast, **22a*** was seen to give IC_{50} over 10 μM. Silimar to class I, the resulting value of this class indicated that *ortho*-modications on the left might twist molecules into a less suitable conformation, unable to inhibit HIF-1 activity.



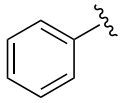
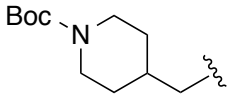
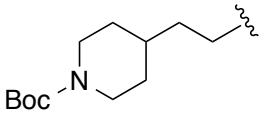
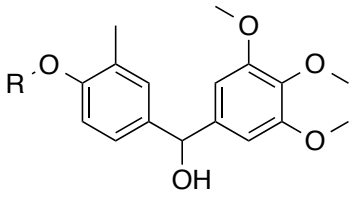
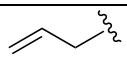
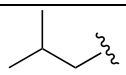
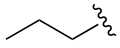
Compounds	R	IC_{50} (μM)
22a*		>10
22b		5.7
22c		2.2

Table 4: Class IV Analogues

3.5 Results for Class V Analogues

The analogues from class V have the best IC_{50} values of all these five classes, listed in Table 5. Notably, **25b** has better IC_{50} value than the lead, **2,** at 0.58 μM. **25d** has the same IC_{50} value as compound **2**; thus it can be considered as the same potent compound. This class of compounds, featuring an additional methyl group on the left ring and a protected pyrogallol ion the right, yields the most active class of compounds, and are likely the best suited for interaction with the HIF-1 target. Following class V, such compounds can be considered as potent inhibitors and evaluated further (Table 5).



Compounds	R	IC_{50} (μM)
25a		0.62
25b		0.4
25c		0.75
25d		0.58

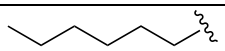
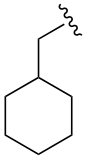
25e		0.7
25f		1.2

Table 5: Class V Analogues.

4 CONCLUSIONS AND FUTURE WORK

4.1 Structure Activity Relationship Study

In conclusion, 27 analogs were synthesized within five different classes. According to the HIF inhibition results from the luciferase assay described above, a structure-activity relationship (SAR) was developed and analyzed. For the right side, protected pyragollol or protected catechol was used on the phenyl ring, and both of them are important to the activity. The different positions substituted on left phenyl ring were compared according to results from the luciferase assay, and the additional methyl group in Class V gave the best results. Otherwise, an important factor in improving inhibitory activity is the substituted *para*-position of Class II. Compared with the *ortho*-substituted analogues were found to be the least potent inhibitors of the three different types of compounds. The results suggest that *ortho*-substituted compounds may twist the molecule unfavorably, resulting in a decrease of activity. However, for the compounds with a Boc-protected piperidine, they exhibited better activity than there comparable analogues, no matter the substitution (Class II and IV).

4.2 Future Work

For future work, more tri-substituted analogs with methyl group of Class V will be synthesized by same method. In this study, class V compounds, especially **25b** were considered to be potent inhibitors. In the future, other similar compounds will be pursued, such as compounds with a methoxy group on 3'-position of the left phenyl ring.

5 EXPERIMENTAL

In this study, all starting materials were purchased from Sigma-Aldrich or Oakwood chemicals without further purification. All intermediates from this study were synthesized by according to literature reports. ^{1}H amd ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker Avance 400 NMR spectrometer. The solvent for dissolving all compounds in this study to record NMR was $CDCl_3$. All mass spectra analyses were obtained by the mass spectratrometry facilities at Georgia State University.

General Procedure for the Synthesis of 4a to 4f. One equivalent of **3** was dissolved in DMF. One equivalent of bromide and 2 equivalents of K_2CO_3 were added. The solution was stirred overnight at 78 ^{o}C, and then ethyl acetate was added. The combined organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography with 100:1 hexane-ethyl acetate as the leuent. **4a-4f** were synthesized by according to literature reports. [34-38]

2-(Allyloxy)benzaldehyde (4a). Yield: 98%, ^{1}H NMR ($CDCl_3$) δ 10.56 (s, 1H), 7.87 (d, 1H), 7.69 (t, *J* = 8Hz, 1H), 7.07-6.99 (m, 2H), 6.13-6.06 (m, 1H), 5.50 (d, *J* = 16Hz, 1H), 5.39 (d, *J* = 12Hz, 1H), 4.68 ppm (d, *J* = 8Hz, 2H).

2-Isopropoxybenzaldehyde (4b). Yield: 99%, ^{1}H NMR ($CDCl_3$) δ 10.52 (s, 1H), 7.84 (d, *J* = 8Hz, 1H), 7.55-7.51 (m, 1H), 7.02-6.99 (m, 2H), 4.71 (t, *J* = 12Hz, 1H), 1.42 ppm (d, *J* = 4Hz, 6H).

2-Propoxybenzaldehyde (4c). Yield: 97%. ^{1}H NMR ($CDCl_3$) δ 10.52 (s, 1H), 7.82-7.80 (m, 1H), 7.49 (t, *J* = 8Hz, 1H), 6.99-6.94 (m, 2H), 4.02 (t, *J* = 12Hz, 2H), 1.88-1.83 (m, 2H), 1.09-1.07 ppm (m, 3H).

2-(Hexyloxy)benzaldehyde (4d). Yield: 98%. ^{1}H NMR ($CDCl_3$) δ 10.51 (d, *J* = 4Hz, 1H), 7.83-7.81 (m, 1H), 7.54-7.49 (m, 1H), 7.01-6.96 (m, 2H), 4.08-4.04 (m, 2H), 1.86-1.81 (m, 2H), 1.49 (s, 2H), 1.26 (s, 4H), 0.92 ppm (t, *J* = 4Hz, 3H).

2-(Cyclohexylmethoxy)benzaldehyde (4e). Yield: 97%. ^{1}H NMR ($CDCl_3$) δ 10.52 (d, *J* = 4Hz, 1H), 7.83-7.81 (m, 1H), 7.54-7.49 (m, 1H), 7.01-6.95 (m, 2H), 4.08-4.04 (m, 2H), 1.86-1.81 (m, 2H), 1.49 (s, 2H), 1.35 (s, 5H), 0.91 ppm (t, *J* = 4Hz, 3H).

2-(Benzyloxy)benzaldehyde (4f). Yield: 99%. ^{1}H NMR ($CDCl_3$) δ 10.59 (s, 1H), 7.90-7.88 (m, 1H), 7.55 (t, *J* = 8Hz, 1H), 7.48-7.38 (m, 5H), 7.08 (t, *J* = 8Hz, 2H), 5.22 ppm (s, 2H).

General Procedure for the Synthesis of 6a to 6f. One equivalent of **5** was dried for half an hour under oil-vacuum pump, and dissolved in dry THF under argon gas. The solution was cooled in a dry ice-acetone bath for 30 minutes, and then 1.1 equivalent of *n*-butyllithium was added. The reaction was stirred for 1.5 hour, followed by the dropwise addition of 1 equivalent of **4** in dry THF under Ar. The reaction was stirred for 2 hours at -78 ^{0}C. Then ethyl acetate was added followed by NH_4Cl. The mixture was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with 100:1 hexane-acetone as the eluent.

(2-(Allyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (6a). Yield: 56%. ^{1}H NMR ($CDCl_3$) δ 7.29-7.26 (m, 3H), 7.00 (t, *J* = 20Hz, 1H), 6.91-6.89 (m, 2H), 6.83 (d, *J* = 8Hz, 1H), 6.08-5.95 (m, 2H), 5.39-5.26 (m, 2H), 4.58-4.56 (m, 2H), 3.87 (d, *J* = 4Hz, 6H), 3.03 ppm (d, *J* = 12Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 155.64, 148.76, 148.13, 136.00, 132.95, 132.49, 128.59,

127.70, 121.02, 118.79, 117.64, 111.97, 110.81, 110.00, 72.02, 68.92, 55.90, 55.82 ppm. HRMS (ESI) *m/z* calculated for $C_{18}H_{20}O_4 + Na^+$: 323.1259, found 323.1261.

(2-Isopropoxyphenyl)(3,4-dimethoxyphenyl)methanol (6b). Yield: 62%. ^{1}H NMR ($CDCl_3$) δ 7.28-7.23 (m, 2H), 7.02 (s, 1H), 6.93-6.81 (m, 4H), 5.97 (s, 1H), 4.65-4.59 (m, 1H), 3.88 (d, *J* = 4Hz, 6H), 3.28 (s, 1H), 1.31 (d, *J* = 4Hz, 3H), 1.27 ppm (d, *J* = 4Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 154.93, 148.70, 148.04, 136.23, 132.90, 128.51, 128.00, 120.44, 118.83, 112.68, 110.74, 109.99, 72.65, 70.01, 55.92, 55.81, 22.16, 21.98 ppm. HRMS (ESI) *m/z* calculated for $C_{18}H_{22}O_4 - OH^-$: 285.1485, found: 285.1473.

(2-Propoxyphenyl)(3,4-dimethoxyphenyl)methanol (6c). Yield: 69%. ^{1}H NMR ($CDCl_3$) δ 7.28-7.23 (m, 2H), 6.97-6.88 (m, 4H), 6.84 (d, *J* = 4Hz, 1H), 6.03 (d, *J* = 4Hz, 1H), 3.99-3.93 (m, 2H), 3.89 (d, *J* = 4Hz, 6H), 3.14 (d, *J* = 8Hz, 1H), 1.81-1.79 (m, 2H), 1.01 ppm (t, *J* = 12Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.21, 148.76, 148.11, 136.02, 132.11, 128.64, 127.73, 120.60, 118.83, 111.45, 110.79, 109.98, 72.37, 69.62, 55.91, 55.81, 22.63, 10.64 ppm. HRMS (ESI^+) *m/z* calculated for $C_{18}H_{22}O_4 + Na^+$: 325.1416, found 325.1426.

(2-(Hexyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (6d). Yield: 61%. ^{1}H NMR ($CDCl_3$) δ 7.28-7.22 (m, 3H), 6.97-6.82 (m, 4H), 4.02-3.97 (m, 2H), 3.93-3.89 (m, 6H), 3.17 (d, *J* = 4Hz, 1H), 1.78-1.74 (m, 2H), 1.33-1.26 (m, 6H), 0.91 ppm (t, *J* = 16Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.24, 148.77, 148.11, 136.04, 132.07, 128.64, 127.76, 120.57, 118.82, 111.44, 110.75, 109.96, 72.44, 68.06, 55.88, 55.79, 31.54, 29.26, 25.76, 22.56, 14.03 ppm. HRMS (ESI^+) *m/z* calculated for $C_{21}H_{28}O_4 + Na^+$: 367.1885, found 367.1877.

(2-(Cyclohexylmethoxy)phenyl)(3,4-dimethoxyphenyl)methanol (6e). Yield: 55%. ^{1}H NMR ($CDCl_3$) δ 7.28-7.19 (m, 4H), 6.99-6.79 (m, 3H), 6.00 (d, *J* = 4Hz, 1H), 3.87-3.85 (m, 4H), 3.79-3.75 (m, 2H), 3.14 (d, *J* = 4Hz, 1H), 1.75-1.71 (m, 6H), 1.26 ppm (t, *J* = 16Hz, 7H). ^{13}C NMR ($CDCl_3$): δ 156.31, 148.79, 148.12, 136.03, 132.05, 128.66, 127.82, 120.49, 118.82, 111.34, 110.83, 109.97, 73.47, 72.42, 55.93, 55.80, 37.77, 29.90, 29.86, 26.40, 26.32, 25.82 ppm. HRMS (ESI^+) *m/z* calculated for $C_{22}H_{28}O_4 + Na^+$: 379.1885, found 379.1886.

(2-(Benzyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (6f). Yield: 64%. ^{1}H NMR ($CDCl_3$) δ 7.33-7.26 (m, 8H), 7.03-6.97 (m, 3H), 6.84-6.80 (m, 2H), 6.05 (d, *J* = 4Hz, 1H), 5.06 (s, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 2.96 (d, *J* = 4Hz, 1H), 1.59 ppm (s, 3H). ^{13}C NMR ($CDCl_3$): δ 155.76, 148.75, 148.11, 136.58, 136.14, 132.45, 128.67, 128.58, 128.09, 127.71,

127.48, 121.09, 118.73, 111.95, 110.84, 110.05, 72.29, 70.18, 55.94, 55.71 ppm. HRMS (ESI^+) *m/z* calculated for $C_{22}H_{22}O_4 + Na^+$: 373.1416, found 373.1398.

General Procedure for the Synthesis of 8a to 8c. One equivalent of **7** was dissolved in DMF. One equivalent of bromide and 2 equivalents of K_2CO_3 were added. The solution was stirred overnight at 78 ^{0}C, and then ethyl acetate was added. The combined organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography with 100:1 hexane-ethyl acetate as the eluent. **8a**-**8c** were synthesized by according to literature reports. [39-40]

4-Isobutoxybenzaldehyde (8a). Yield: 95%. ^{1}H NMR ($CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, *J* = 8Hz, 2H), 7.01 (d, *J* = 8Hz, 1H), 3.82 (d, *J* = 8Hz, 2H), 2.17-2.10 (m, 1H), 1.05 ppm (t, *J* = 8Hz, 6H).

4-(Hexyloxy)benzaldehyde (8b). Yield: 97%. ^{1}H NMR ($CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, *J* = 8Hz, 2H), 7.01 (d, *J* = 8Hz, 1H), 4.06 (t, *J* = 8Hz, 2H), 1.86-1.79 (m, 2H), 1.51-1.36 (m, 6H), 0.95 ppm (t, *J* = 8Hz, 3H).

4-(Cyclohexylmethoxy)benzaldehyde (8c). Yield: 97%. ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1H), 7.84 (d, *J* = 8Hz, 2H), 7.01 (d, *J* = 8Hz, 1H), 3.86 (d, *J* = 4Hz, 2H), 1.91-1.72 (m, 6H), 1.35-1.21 (m, 3H), 1.13-1.07 ppm (m, 2H).

General Procedure for the Synthesis of 9a to 9c. One equivalent of **5** was dried for half an hour under oil-vacuum pump, and dissolved in dry THF under argon gas. The solution was cooled in a dry ice-acetone bath for 30 minutes, and 1.1 equivalent of *n*-butyllithium was added. The reaction was stirred for 1.5 hour, followed by the dropwise addition of 1 equivalent of **8** in dry THF under Ar. The reaction was stirred for another 2 hours at -78 ^{0}C. Then ethyl acetate was added followed by NH_4Cl. The mixture was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with 100:1 hexane-acetone as the eluent.

(4-Isobutoxyphenyl)(3,4-dimethoxyphenyl)methanol (9a). Yield: 66%. ^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J* = 8Hz, 2H), 6.94 (s, 1H), 6.93-6.84 (m, 4H), 5.75 (s, 1H), 3.86 (d, *J* = 4Hz, 6H), 3.72 (d, *J* = 8Hz, 2H), 2.35 (s, 1H), 2.12-2.06 (m, 1H), 1.04 ppm (d, *J* = 4Hz, 6H).

^{13}C NMR ($CDCl_3$): δ 158.72, 148.99, 148.33, 136.85, 136.02, 127.76, 118.79, 114.45, 110.92, 109.70, 75.56, 74.48, 55.92, 55.85, 28.28, 19.28 ppm. HRMS (ESI^+) *m/z* calculated for $C_{19}H_{24}O_4$ – OH^-: 299.1642, found 299.1644.

(4-(Hexyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (9b). Yield: 71%. ^{1}H NMR ($CDCl_3$) δ 7.30-7.27 (m, 3H), 6.95-6.82 (m, 4H), 5.79 (d, *J* = 4Hz, 1H), 3.96 (t, *J* = 8Hz, 2H), 3.88 (d, *J* = 8Hz, 6H), 2.15 (d, *J* = 4Hz, 1H), 1.80-1.75 (m, 2H), 1.49 (t, *J* = 8Hz, 2H), 1.36-1.33 (m, 4H), 0.94-0.91 ppm (m, 3H). ^{13}C NMR ($CDCl_3$): δ 158.63, 149.01, 148.36, 136.79, 135.99, 127.77, 118.78, 114.44, 110.91, 109.68, 75.60, 68.05, 55.93, 55.86, 31.59, 29.25, 25.73, 22.61, 14.04 ppm. HRMS (ESI^+) *m/z* calculated for $C_{21}H_{28}O_4$ – OH^-: 327.1955, found 327.1941.

(4-(Cyclohexylmethoxy)phenyl)(3,4-dimethoxyphenyl)methanol (9c). Yield: 54%. ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 2H), 6.95-6.83 (m, 5H), 5.78 (s, 1H), 3.87 (d, *J* = 4Hz, 6H), 3.76 (d, *J* = 4Hz, 2H), 2.14 (s, 1H), 1.89-1.70 (m, 6H), 1.33-1.20 (m, 3H), 1.10-1.01 ppm (m, 2H). ^{13}C NMR ($CDCl_3$): δ 158.77, 148.99, 148.33, 136.85, 135.97, 127.76, 118.78, 114.43, 110.92, 109.70, 75.57, 73.55, 55.93, 55.85, 37.70, 29.93, 26.54, 25.82 ppm. HRMS (ESI^+) *m/z* calculated for $C_{22}H_{28}O_4$ – OH^-: 339.1955, found 339.1938.

General Procedure for the Synthesis of 11a and 11b. One equivalent of **10** was dissolved in H_2O. Then 1.1 equivalents of Boc_2O was added in solution. The mixture was stirred overnight at room temperature, followed by the addition of ethyl acetate. The mixture was washed with water and brine, dried over $MgSO_4$, and concentrated. **11a-11b** were synthesized by according to literature reports. [41-42]

***Tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (11a).** Yield: 99%. ^{1}H NMR ($CDCl_3$) δ 4.15 (d, *J* = 12Hz, 2H), 3.52 (d, *J* = 8Hz, 2H), 2.75-2.69 (m, 2H), 1.75-1.63 (m, 4H), 1.49 (s, 9H), 1.20 ppm (t, *J* = 12Hz, 2H).

***Tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (11b).** Yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (m, 2H), 3.51-3.48 (m, 2H), 3.16-3.14 (m, 1H), 2.54 (m, 2H), 1.54-1.46 (m, 3H), 1.38-1.34 (m, 4H), 1.30 (s, 9H) 1.00-0.94 (m, 2H) ppm.

General Procedure for the Synthesis of 12*. One equivalent of **11b** was dissolved in THF. Then 1.1 equivalents of TsCl and 1.1 equivalents of NEt_3 were added in solution. The mixture was stirred overnight at room temperature, followed by the addition of ethyl acetate. The solution was washed with water and brine, dried over $MgSO_4$, and concentrated.

***Tert*-butyl 4-(2-(tosyloxy)ethyl)piperidine-1-carboxylate (12*).** Yield: 86%. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, *J* = 8Hz, 2H), 7.28 (d, *J* = 8Hz, 2H), 4.05-3.98 (m, 4H), 2.54 (m, 2H), 2.37 (s, 3H), 1.51-1.44 (m, 5H), 1.38 (s, 9H) 0.99-0.94 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ 170.9, 154.6, 144.8, 132.9, 129.8, 127.8, 79.2, 67.9, 60.2, 43.5, 35.1, 32.1, 31.5, 28.3, 21.5, 20.9 ppm.

General Procedure for the Synthesis of 14a$^{\#}$ to 14d*. One equivalent of **13** was dissolved in DMF. To this solution, one equivalent of bromide or **12** and 2 equivalents of K_2CO_3 were added. The solution was stirred 5 hours at 90 ^{0}C, followed by the addition of ethyl acetate. The combined organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography with 100:1 hexane-ethyl acetate as the leuent. **14a$^{\#}$-14d*** were synthesized by according to literature reports. [43-44]

1-(Allyloxy)-4-bromobenzene (14a$^{\#}$). Yield: 42%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8Hz, 2H), 6.80 (d, *J* = 8Hz, 2H), 6.08-5.98 (m, 1H), 5.40 (d, *J* = 16Hz, 2H), 5.30 (d, *J* = 12Hz, 2H), 4.51 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 132.8, 132.2, 117.9, 116.5, 113.0, 69.0 ppm.

1-Bromo-4-isopropoxybenzene (14b). Yield: 96%. ^{1}H NMR ($CDCl_3$) δ 7.47-7.43 (m, 2H), 6.83-6.79 (m, 2H), 4.52-4.48 (m, 1H), 1.33 ppm (d, *J* = 8Hz, 6H).

1-Bromo-4-propoxybenzene (14c). Yield: 98%. ^{1}H NMR ($CDCl_3$) δ 7.39-7.36 (m, 2H), 6.82-6.79 (m, 2H), 3.90 (t, *J* = 12Hz, 2H), 1.86-1.78 (m, 2H), 1.05 (t, *J* = 16Hz, 3H) ppm.

***Tert*-butyl 4-(2-(4-bromophenoxy)ethyl)piperidine-1-carboxylate (14d*).** Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8Hz, 2H), 6.74 (d, *J* = 8Hz, 2H), 4.07 (m, 2H), 3.95 (t, *J* = 7Hz, 2H), 2.72-2.66 (m, 2H), 1.70-1.67 (m, 5H), 1.44 (s, 9H), 1.18-1.13 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 156.1, 154.9, 132.2, 132.1, 117.3, 116.2, 79.4, 65.6, 44.0, 35.6, 32.9, 32.0, 28.4 ppm.

General Procedure for the Synthesis of 9d$^{\#}$ to 9g*. One equivalent of **14** was dried for half an hour under oil-vacuum pump, and dissolved in dry THF under argon gas. The solution was cooled in a dry ice-acetone bath for 30 minutes, and 1.1 equivalent of *n*-butyllithium was added. The reaction was stirred 1.5 hour, followed by the dropwise addition of 1 equivalent of 3,4-dimethoxybenzaldehyde in dry THF under Ar. The reaction was stirred for another 2 hours at -78 ^{0}C. Then ethyl acetate was added followed by NH_4Cl. The mixture was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with 100:1 hexane-actone as the leuent.

(4-(Allyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (9d$^{\#}$). Yield: 20%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8Hz, 1H), 6.91-6.81 (m, 5H), 6.09-5.99 (m, 1H), 5.76 (s, 1H), 5.40 (d, *J* = 16Hz, 2H), 5.27 (d, *J* = 12Hz, 2H), 4.52 (d, *J* = 8Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.13 (s, 1H). ^{13}CNMR and HRMS are based on MG-1-15.

(4-Isopropoxyphenyl)(3,4-dimethoxyphenyl)methanol (9e). Yield: 57%. ^{1}H NMR ($CDCl_3$) δ 7.24 (d, *J* = 8Hz, 2H), 6.92 (s, 1H), 6.92-6.80 (m, 4H), 5.70 (s, 1H), 4.56-4.51 (m, 1H), 3.84 (d, *J* = 8Hz, 6H), 2.61 (s, 1H), 1.33 ppm (d, *J* = 8Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 157.25, 148.93, 148.25, 136.86, 136.10, 127.84, 118.79, 115.73, 110.87, 109.70, 75.47, 69.89, 55.90, 55.82, 22.06 ppm. HRMS (ESI^+) *m/z* calculated for $C_{18}H_{22}O_4$ – OH^-: 285.1485, found 285.1484.

(4-Propoxyphenyl)(3,4-dimethoxyphenyl)methanol (9f). Yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 4Hz, 2H), 6.91 (d, *J* = 4Hz, 1H), 6.87-6.80 (m, 4H), 5.70 (s, 1H), 3.91 (t, *J* = 12Hz, 2H), 3.89 (d, *J* = 8Hz, 6H), 2.61 (s, 1H), 1.85-1.76 (m, 2H), 1.04 ppm (t, *J* = 16Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 158.52, 148.96, 148.28, 136.92, 136.13, 127.78, 118.80, 114.39, 110.91, 109.73, 75.47, 69.53, 55.90, 55.82, 22.59, 10.54 ppm. HRMS (ESI^+) *m/z* calculated for $C_{18}H_{22}O_4$ – OH^-: 285.1485, found 285.1480.

***Tert*-butyl 4-(2-(4-((3,4-dimethoxyphenyl)(hydroxy)methyl)phenoxy)ethyl)piperidine-1-carboxylate (9g*).**

Yield: 16%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8 Hz, 2H), 6.91 (s, 1H), 6.83-6.79 (m, 4H), 5.74 (s, 1H), 3.99-3.96 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 2.71-2.65 (m, 2H), 2.35 (s, 1H), 1.70-1.68 (m, 5H), 1.44 (s, 9H), 1.16-1.13 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 154.8, 149.0, 148.3, 136.8, 136.2, 127.7, 118.7, 114.3, 110.9, 109.6, 79.2, 76.7, 75.5, 65.3, 60.3, 55.9, 55.8, 35.7, 32.9, 32.0, 28.4, 21.0, 14.2 ppm. HRMS is in Dr. Jalisa Holmes Ferguson's data information

General Procedure for the Synthesis of 16a to 16c. One equivalent of **15** was dissolved in DMF, followed by the addition of one equivalent of bromide and 2 equivalents of K_2CO_3. The reaction was stirred overnight at 78 ^{0}C, followed by the addition of ethyl acetate. The resulting mixture was washed with water and brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by column chromatography with 100:1 hexane-ethyl acetate as the eluent. **16a-16c** were synthesized by according to literature reports. [45-46]

3-Isobutoxybenzaldehyde (16a). Yield: 96%. ^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1H), 7.47-7.40 (m, 3H), 7.21-7.18 (m, 1H), 3.80 (d, *J* = 8Hz, 2H), 2.16-2.10 (m, 1H), 1.05 ppm (t, *J* = 8Hz, 6H).

3-Isopropoxybenzaldehyde (16b). Yield: 95%. ^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1H), 7.45-7.39 (m, 3H), 7.18-7.15 (m, 1H), 4.68-4.62 (m, 1H), 1.38 ppm (d, *J* = 8Hz, 6H).

3-Propoxybenzaldehyde (16c). Yield: 92%. ^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1H), 7.46-7.40 (m, 3H), 7.21-7.18 (m, 1H), 4.00 (t, *J* = 4Hz, 2H), 1.89-1.81 (m, 2H), 1.07 ppm (t, *J* = 8Hz, 3H).

General Procedure for the Synthesis of 17a to 17c. One equivalent of **5** was dried for half an hour under oil-vacuum pump, and dissolved in dry THF under argon gas. The solution was cooled in a dry ice-acetone bath for 30 minutes, followed by the addition of 1.1 equivalent of *n*-butyllithium. The reaction was stirred for 1.5 hour, and then 1 equivalent of **16** in dry THF under Ar was added drop-wise. The reaction was stirred for another 2 hours at -78 ^{0}C, followed by the addition of ethyl acetate to the solution. Then NH_4Cl was added to quench the reaction. The resulting reaction mixture was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with 100:1 hexane-acetone as the eluent.

(3-Isobutoxyphenyl)(3,4-dimethoxyphenyl)methanol (17a). Yield: 68%. ^{1}H NMR ($CDCl_3$) δ 7.28-7.23 (m, 1H), 6.97-6.90 (m, 4H), 6.85-6.81 (m, 2H), 5.76 (s, 1H), 3.87 (d, *J* = 4Hz, 6H), 3.72 (d, *J* = 4Hz, 2H), 2.33 (s, 1H), 2.10-2.07 (m, 1H), 1.04 ppm (d, *J* = 8Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 159.45, 149.04, 148.49, 145.49, 136.48, 129.43, 118.99, 118.57, 113.45, 112.66, 110.95, 109.80, 75.94, 74.39, 55.92, 55.87, 28.32, 19.30 ppm. HRMS (ESI^+) *m/z* calculated for $C_{19}H_{24}O_4$ – OH^-: 299.1642, found 299.1640.

(3-Isopropoxyphenyl)(3,4-dimethoxyphenyl)methanol (17b). Yield: 72%. ^{1}H NMR ($CDCl_3$) δ 7.20 (t, *J* = 16Hz, 1H), 6.92-6.86 (m, 4H), 6.81-6.77 (m, 2H), 5.70 (s, 1H), 4.57-4.51 (m, 1H), 3.88 (d, *J* = 8Hz, 6H), 2.70 (s, 1H), 1.29 ppm (d, *J* = 8Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 157.94, 148.95, 148.36, 145.67, 136.57, 129.45, 118.97, 118.64, 114.62, 114.09, 110.90, 109.75, 75.80, 69.76, 55.89, 55.81, 22.06, 22.04 ppm. HRMS (ESI^+) *m/z* calculated for $C_{18}H_{22}O_4$ – OH^-: 285.1485, found 285.1481.

(3-Propoxyphenyl)(3,4-dimethoxyphenyl)methanol (17c). Yield: 67%. ^{1}H NMR ($CDCl_3$) δ 7.28-7.22 (m, 1H), 6.98-6.84 (m, 4H), 6.82-6.79 (m, 2H), 5.71 (s, 1H), 3.90 (t, *J* = 8Hz, 2H), 3.84 (d, *J* = 8Hz, 2H), 2.66 (d, *J* = 4Hz, 1H), 1.83-1.77 (m, 2H), 1.04 ppm (t, *J* = 8Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 159.26, 149.00, 148.42, 145.61, 136.58, 129.41, 118.98, 118.64, 113.37, 112.68, 110.95, 109.82, 75.83, 69.45, 55.90, 55.84, 22.61, 10.56 ppm. HRMS (ESI^+) *m/z* calculated for $C_{18}H_{22}O_4$ – OH^-: 285.1485, found 285.1483.

General Procedure for the Synthesis of 19a and 19b. One equivalent of **18** was dissolved in DMF. To this solution, one equivalent of bromide and 2 equivalents of K_2CO_3 were added. The solution was stirred 5 hours at 90 ^{0}C, followed by the addition of ethyl acetate. The combined organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography with 100:1 hexane-ethyl acetate as the eluent. **19a-19b*** were synthesized by according to literature reports. [47-48]

1-(Allyloxy)-3-bromobenzene (19a). Yield: 95%. ^{1}H NMR ($CDCl_3$) δ 7.24-7.14 (m, 3H), 6.89-6.86 (m, 1H), 6.14-6.04 (m, 1H), 5.48-5.44 (m, 1H), 5.39-5.35 (m, 1H), 4.55-4.52 ppm (m, 2H).

1-Bromo-3-(hexyloxy)benzene (19b)*. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (t, *J* = 8Hz, 1H), 7.07-7.06 (m, 2H), 6.83 (d, *J* = 8Hz, 2H), 3.93 (t, *J* = 7Hz, 2H), 1.77 (q, 2H),

1.47-1.44 (m, 2H), 1.36-1.34 (m, 4H), 0.93 (t, J = 7Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 130.4, 123.5, 122.8, 117.7, 113.5, 68.2, 31.5, 29.1, 25.7, 22.6, 14.0 ppm.

General Procedure for the Synthesis of 17d and 17e. One equivalent of **19** was dried for half an hour under oil-vacuum pump, and dissolved in dry THF under argon gas. The solution was cooled in a dry ice-acetone bath for 30 minutes, and 1.1 equivalent of *n*-butyllithium was added. The reaction was stirred 1.5 hour, followed by the dropwise addition of 1 equivalent of 3,4-dimethoxybenzaldehyde in dry THF under Ar. The reaction was stirred for another 2 hours at -78 ^{0}C. Then ethyl acetate was added followed by NH_4Cl. The mixture was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with 100:1 hexane-actone as the eluent.

(3-(Allyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (17d). Yield: 64%. ^{1}H NMR ($CDCl_3$) δ 7.27 (t, J = 12Hz, 1H), 6.99-6.89 (m, 4H), 6.84 (d, J = 8Hz, 2H), 6.10-6.03 (m, 1H), 5.78 (s, 1H), 5.44 (d, J = 4Hz, 1H), 5.39 (d, J = 4Hz, 1H), 4.55-4.53 (m, 2H), 3.88 (d, J = 8Hz, 6H), 2.24 ppm (s, 1H). ^{13}C NMR ($CDCl_3$): δ 158.68, 148.99, 148.41, 145.72, 136.56, 133.29, 129.42, 119.00, 118.98, 117.66, 113.56, 112.90, 110.96, 109.82, 75.73, 68.74, 55.90, 55.83 ppm. HRMS (ESI^+) *m/z* calculated for $C_{18}H_{20}O_4$ – OH^-: 283.1329, found 283.1326.

(3-(Hexyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (17e*). Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, J = 8Hz, 1H), 6.93-6.86 (m, 4H), 6.82-6.77 (m, 2H), 5.74 (s, 1H), 3.92 (t, J = 7Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.30 (bs, 1H), 1.75 (p, J = 7Hz, 2H), 1.45-1.40 (m, 2H), 1.34-1.30 (m, 4H), 0.90 (t, J = 7Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 149.1, 148.5, 145.6, 136.5, 129.5, 119.0, 118.6, 113.5, 112.7, 111.0, 109.8, 76.0, 68.0, 56.0, 55.9, 31.7, 29.3, 25.8, 22.7, 14.1 ppm. HRMS is in Dr. Jalisa Holmes Ferguson's data information.

General Procedure for the Synthesis of 21a to 21c. One equivalent of **20** was dissolved in DMF, followed by the addition of 1 equivalent of alcohol and 2 equivalents of NaH. The reaction was stirred overnight at 0 ^{0}C to room temperature. To this solution, ethyl acetate was added. The resulting mixture was washed with water and brine, dried over $MgSO_4$, and

concentrated. The residue was purified by column chromatography with 100:1 hexane-ethyl acetate as the eluent. **21a**-**21c** were synthesized by according to literature reports.[49-51]

1-Bromo-2-(phenoxymethyl)benzene (21a). Yield: 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.65 (m, 2H), 7.43-7.39 (m, 3H), 7.26 (t, *J* = 8Hz, 1H), 7.11-7.07 (m, 3H), 5.23 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 136.4, 132.6, 129.6, 129.2, 128.9, 127.6, 122.3, 121.2, 114.9, 69.3 ppm.

***Tert*-butyl 4-(((2-bromobenzyl)oxy)methyl)piperidine-1-carboxylate (21b).** Yield: 96%. ^{1}H NMR ($CDCl_3$) δ 7.56-7.54 (m, 1H), 7.49-7.47 (m, 1H), 7.33 (t, *J* = 16Hz, 1H), 7.18 (t, *J* = 12Hz, 1H), 4.57 (s, 2H), 3.42 (d, *J* = 8Hz, 2H), 1.80-1.77 (m, 4H), 1.48 (s, 9H), 1.28-1.15 ppm (m, 5H).

***Tert*-butyl 4-(2-((2-bromobenzyl)oxy)ethyl)piperidine-1-carboxylate (21c).** Yield: 96%. ^{1}H NMR ($CDCl_3$) δ 7.56 (d, *J* = 4Hz, 1H), 7.47 (d, *J* = 8Hz, 1H), 7.33 (t, *J* = 16Hz, 1H), 7.17 (t, *J* = 12Hz, 1H), 4.57 (s, 2H), 3.62 (t, *J* = 12Hz, 2H), 1.70-1.59 (m, 6H), 1.47 (t, *J* = 16Hz, 9H), 1.13 ppm (d, *J* = 12Hz, 3H).

General Procedure for the Synthesis of 22a to 22c. One equivalent of **21** was dried for half an hour under oil-vacuum pump, and dissolved in dry THF under argon gas. The solution was cooled in a dry ice-acetone bath for 30 minutes, followed by the addition of 1.1 equivalent of *n*-butyllithium. The reaction was stirred for 1.5 hour, and then 1 equivalent of 3,4,5-trimethoxybenzaldehyde in dry THF under Ar was added drop-wise. The reaction was stirred for another 2 hours at -78 ^{0}C, followed by the addition of ethyl acetate to the solution. Then NH_4Cl was added to quench the reaction. The resulting reaction mixture was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with 100:1 hexane-acetone as the leuent.

(2-(Phenoxymethyl)phenyl)(3,4,5-trimethoxyphenyl)methanol (22a*). Yield: 58%. ^{1}H NMR ($CDCl_3$) δ 7.44 (d, *J* = 4Hz, 1H), 7.33-7.28 (m, 5H), 7.00 (t, *J* = 4Hz, 1H), 6.92-6.90 (m, 2H), 6.55 (s, 2H), 6.07 (d, *J* = 4Hz, 1H), 5.02-4.94 (dd, *J* = 12Hz, 2H), 3.86 (d, *J* = 4Hz, 3H), 3.72 (d, *J* = 4Hz, 6H), 2.92 ppm (d, *J* = 4Hz, 1H). ^{13}C NMR and HRMS are in Dr. Jalisa Holmes Ferguson's data information.

***Tert*-butyl 4-(((2-(hydroxy(3,4,5-trimethoxyphenyl)methyl)benzyl)oxy)methyl)piperidine-1-carboxylate (22b).** Yield: 55%. ^{1}H NMR ($CDCl_3$) δ 7.35-7.23 (m, 4H), 6.61 (s, 2H), 5.95 (d, *J* = 4Hz, 1H), 4.61 (d, *J* = 12Hz, 1H), 4.40 (d, *J* = 12Hz, 1H), 4.17-4.12 (m, 2H), 3.86 (s, 3H), 3.81 (s, 6H), 3.34 (t, *J* = 4Hz, 2H), 2.67 (t, *J* = 8Hz, 2H), 1.79-1.69 (m, 4H), 1.46 (s, 9H), 1.17-1.13 ppm (m, 2H). ^{13}C NMR ($CDCl_3$): δ 154.80, 153.12,143.32, 138.44, 136.98, 135.29, 130.76, 128.94, 128.88, 127.93, 103.57, 79.36, 75.51, 73.81, 72.46, 60.89, 56.09, 43.36, 36.50, 29.07, 28.45 ppm. HRMS (ESI^+) *m/z* calculated for $C_{28}H_{39}NO_7$ – OH^-: 484.2694, found 484.2691.

***Tert*-butyl 4-(2-((2-(hydroxy(3,4,5-trimethoxyphenyl)methyl)benzyl)oxy)ethyl)piperidine-1-carboxylate (22c).** Yield: 59%. ^{1}H NMR ($CDCl_3$) δ 7.36-7.24 (m, 4H), 6.62 (s, 2H), 5.95 (d, *J* = 4Hz, 1H), 4.60 (d, *J* = 8Hz, 1H), 4.39 (d, *J* = 8Hz, 1H), 4.24 (d, *J* = 4Hz, 1H), 4.05 (d, *J* = 8Hz, 2H), 3.87 (s, 3H), 3.79 (s, 6H), 3.34 (t, *J* = 4Hz, 2H), 3.57-3.52 (m, 2H), 2.67 (t, *J* = 12Hz, 2H), 1.71-1.54 (m, 5H), 1.46 (s, 9H), 1.12-1.09 ppm (m, 2H). ^{13}C NMR ($CDCl_3$): δ 154.85, 153.10, 143.45, 138.50, 136.94, 135.39, 130.78, 129.10, 128.91, 127.92, 103.51, 79.26, 73.88, 72.32, 68.15, 60.90, 56.09, 43.81, 36.13, 32.90, 32.06, 28.46 ppm. HRMS (ESI^+) *m/z* calculated for $C_{29}H_{41}NO_7$ – OH^-: 498.2850, found 498.2827.

General Procedure for the Synthesis of 24a to 24f. One equivalent of **23** was dissolved in DMF. To this solution, 1 equivalents of RBr and 2 equivalents of K_2CO_3 were added. The reaction was stirred overnight at 78 ^{0}C, followed by the addition of ethyl acetate. The resulting mixture was washed with water and brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by column chromatography with 100:1 hexane-ethyl acetate. **24a**-**24f** were synthesized by according to literature reports. [52-56]

1-(Allyloxy)-4-bromo-2-methylbenzene (24a). Yield: 97%. ^{1}H NMR ($CDCl_3$) δ 7.29-7.24 (m, 2H), 6.70 (d, *J* = 8Hz, 1H), 6.11-6.04 (m, 1H), 5.47 (d, *J* = 4Hz, 1H), 5.33 (d, *J* = 4Hz, 1H), 4.55-4.53 (m, 2H), 2.26 ppm (s, 3H).

4-Bromo-1-isobutoxy-2-methylbenzene (24b). Yield: 96%. ^{1}H NMR ($CDCl_3$) δ 7.29-7.24 (m, 2H), 6.70 (d, *J* = 8Hz, 1H), 6.11-6.04 (m, 1H), 5.47 (d, *J* = 4Hz, 1H), 5.33 (d, *J* = 4Hz, 1H), 4.55-4.53 (m, 2H), 2.26 ppm (s, 3H).

4-Bromo-1-isopropoxy-2-methylbenzene (24c). Yield: 95%. ^{1}H NMR ($CDCl_3$) δ 7.28-7.25 (m, 2H), 6.69 (d. *J* = 8Hz, 1H), 3.73 (d, *J* = 4Hz, 2H), 2.24 (s, 3H), 2.19-2.09 (m, 1H), 1.08 ppm (d, *J* = 4Hz, 6H).

4-Bromo-2-methyl-1-propoxybenzene (24d). Yield: 97%. ^{1}H NMR ($CDCl_3$) δ 7.25 (d, *J* = 8Hz, 2H), 6.68 (d, *J* = 4Hz, 1H), 3.91 (t, *J* = 8Hz, 2H), 2.21 (s, 3H), 1.90-1.80 (m, 2H), 1.08 ppm (t, *J* = 8Hz, 3H).

4-Bromo-1-(hexyloxy)-2-methylbenzene (24e). Yield: 99%. ^{1}H NMR ($CDCl_3$) δ 7.24 (d, *J* = 4Hz, 2H), 6.69 (d, *J* = 4Hz, 1H), 3.91 (t, *J* = 4Hz, 2H), 2.22 (s, 3H), 1.86-1.79 (m, 2H), 1.52-1.48 (m, 1H), 1.40-1.33 (m, 5H), 0.92 ppm (s, 3H).

4-Bromo-1-(cyclohexylmethoxy)-2-methylbenzene (24f). Yield: 92%. ^{1}H NMR ($CDCl_3$) δ 7.28-7.24 (m, 2H), 6.67 (d, *J* = 4Hz, 1H), 3.73 (d, *J* = 4Hz, 2H), 2.21 (s, 3H), 1.89-1.72 (m, 5H), 1.34-1.23 (m, 4H), 1.11-1.08 ppm (m, 2H).

General Procedure for Synthesis of 25a to 25f. One equivalent of **24** was dried for half an hour under oil-vacuum pump, and dissolved in dry THF under argon gas. The solution was cooled in a dry ice-acetone bath for 30 minutes, followed by the addition of 1.1 equivalent of *n*-butyllithium. The reaction was stirred for 1.5 hour, and then 1 equivalent of 3,4,5-trimethoxybenzaldehyde in dry THF under Ar was added drop-wise. The reaction was stirred for another 2 hours at -78 ^{0}C, followed by the addition of ethyl acetate to the solution. Then NH_4Cl was added to quench the reaction. The resulting reaction mixture was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with 100:1 hexane-acetone as the leuent.

(4-(Allyloxy)-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25a). Yield: 60%. ^{1}H NMR ($CDCl_3$) δ 7.16-7.15 (m, 2H), 6.79 (d, *J* = 4Hz, 1H), 6.63 (s, 2H), 6.12-6.05 (m, 1H), 5.71 (s, 1H), 5.46 (dd, *J* = 8Hz, 1H), 5.31-5.27 (m, 1H), 4.56-4.54 (m, 2H), 3.86-3.85 (m, 9H), 2.26 (s, 3H), 2.21 ppm (s, 1H). ^{13}C NMR ($CDCl_3$): δ 156.35, 153.21, 139.75, 137.11, 135.64, 133.50, 129.16, 127.17, 125.01, 117.00, 111.12, 103.39, 75.97, 68.77, 60.83, 56.11, 16.41 ppm. HRMS (ESI$^+$) *m/z* calculated for $C_{20}H_{24}O_5$ – OH^-: 327.1591, found 327.1592.

(4-Isobutoxy-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25b). Yield: 59%. ^{1}H NMR ($CDCl_3$) δ 7.15-7.13 (m, 2H), 6.77 (d, *J* = 8Hz, 1H), 6.64 (s, 2H), 5.71 (d, *J* = 4Hz, 1H), 3.86 (d, *J* = 4Hz, 9H), 3.73 (d, *J* = 8Hz, 2H), 2.24 (s, 3H), 2.15-2.11 (m, 2H), 1.05 ppm (d, *J* = 8Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 156.84, 153.14, 139.99, 136.99, 135.33, 128.99, 126.94, 125.02, 110.62, 103.38, 75.92, 74.35, 60.80, 56.07, 28.43, 19.33, 16.34 ppm. HRMS (ESI^+) *m/z* calculated for $C_{21}H_{28}O_5$ – OH^-: 343.1904, found 343.1905.

(4-Isopropoxy-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25c). Yield: 43%. ^{1}H NMR ($CDCl_3$) δ 7.16-7.11 (m, 2H), 6.81 (d, *J* = 8Hz, 1H), 6.64 (s, 2H), 5.72 (s, 1H), 4.54-4.51 (m, 1H), 3.86 (t, *J* = 4Hz, 9H), 2.21 (s, 3H), 2.13 (d, *J* = 4Hz, 1H), 1.35 ppm (d, *J* = 4Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 153.21, 139.74, 135.28, 129.27, 124.97, 112.82, 112.50, 104.27, 103.40, 76.04, 70.28, 60.84, 56.12, 56.03, 22.25, 16.56 ppm. HRMS (ESI^+) *m/z* calculated for $C_{20}H_{26}O_5$ – OH^-: 329.1747, found 329.1732.

(3-Methyl-4-propoxyphenyl)(3,4,5-trimethoxyphenyl)methanol (25d). Yield: 69%. ^{1}H NMR ($CDCl_3$) δ 7.13 (t, *J* = 8Hz, 2H), 6.78 (d, *J* = 8Hz, 1H), 6.63 (s, 2H), 5.70 (s, 1H), 3.93 (t, *J* = 8Hz, 2H), 3.88 (s, 9H), 2.34 (s, 1H), 2.23 (s, 3H), 1.86-1.81 (m, 2H), 1.07 ppm (t, *J* = 8Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.65, 153.17, 139.88, 137.04, 135.30, 129.03, 127.02, 125.03, 110.75, 103.38, 75.97, 69.54, 60.82, 56.10, 22.71, 16.33, 10.66 ppm. HRMS (ESI^+) *m/z* calculated for $C_{20}H_{26}O_5$ – OH^-: 329.1747, found 329.1747.

(4-(Hexyloxy)-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25e). Yield: 63%. ^{1}H NMR ($CDCl_3$) δ 7.15-7.13 (m, 2H), 6.78 (d, *J* = 8Hz, 1H), 6.64 (s, 2H), 5.72 (s, 1H), 3.97 (t, *J* = 12Hz, 2H), 3.85 (d, *J* = 4Hz, 9H), 2.23 (s, 3H), 2.19 (s, 1H), 1.83-1.77 (m, 2H), 1.51-1.47 (m, 2H), 1.38-1.34 (m, 4H), 0.92 ppm (t, *J* = 12Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.92, 153.21, 139.79, 137.09, 135.21, 129.02, 127.06, 125.03, 110.72, 103.37, 76.04, 68.05, 60.84, 56.12, 31.57, 29.30, 25.82, 22.62, 16.36, 14.03 ppm. HRMS (ESI^+) *m/z* calculated for $C_{23}H_{32}O_5$ – OH^-: 371.2217, found 371.2219.

(4-(Cyclohexylmethoxy)-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25f). Yield: 62%. ^{1}H NMR ($CDCl_3$) δ 7.15-7.13 (m, 2H), 6.77 (d, *J* = 8Hz, 1H), 6.64 (s, 2H), 5.72 (d, *J* = 4Hz, 1H), 3.89 (s, 9H), 3.76 (d, *J* = 8Hz, 2H), 2.23 (s, 3H), 2.15 (d, *J* = 4Hz, 1H), 1.90-1.74

(m, 6H), 1.25-1.08 ppm (m, 5H). ^{13}C NMR (100 MHz, CDCl3): δ 156.91, 153.14, 139.96, 136.99, 135.26, 128.97, 126.97, 125.01, 110.62, 103.36, 75.94, 73.45, 60.80, 56.08, 37.84, 29.97, 26.57, 25.89, 16.38 ppm. HRMS (ESI$^+$) *m/z* calculated for $C_{24}H_{32}O_5$ – OH^-: 383.2217, found 383.2213.

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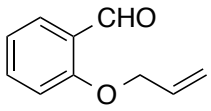
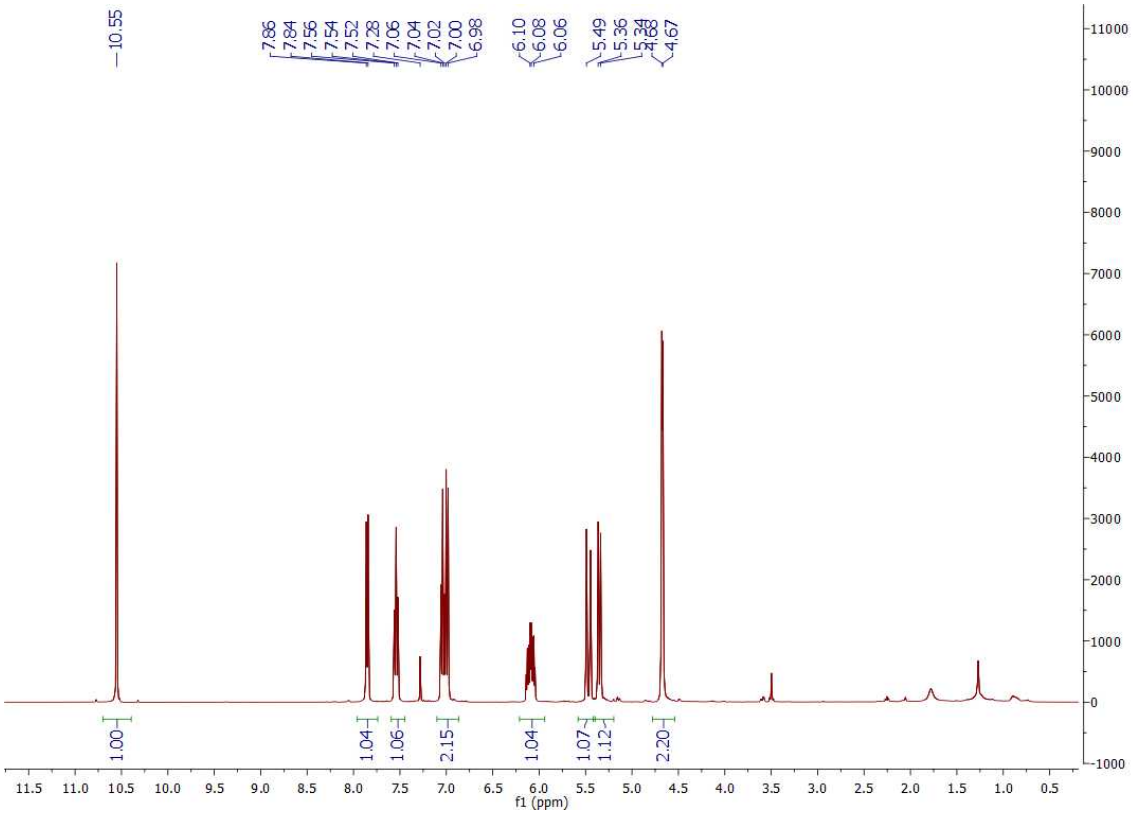
APPENDICES

Spectra

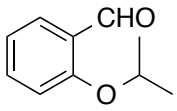
Class I: *Ortho*-phenolic ether benzhydrol analogues

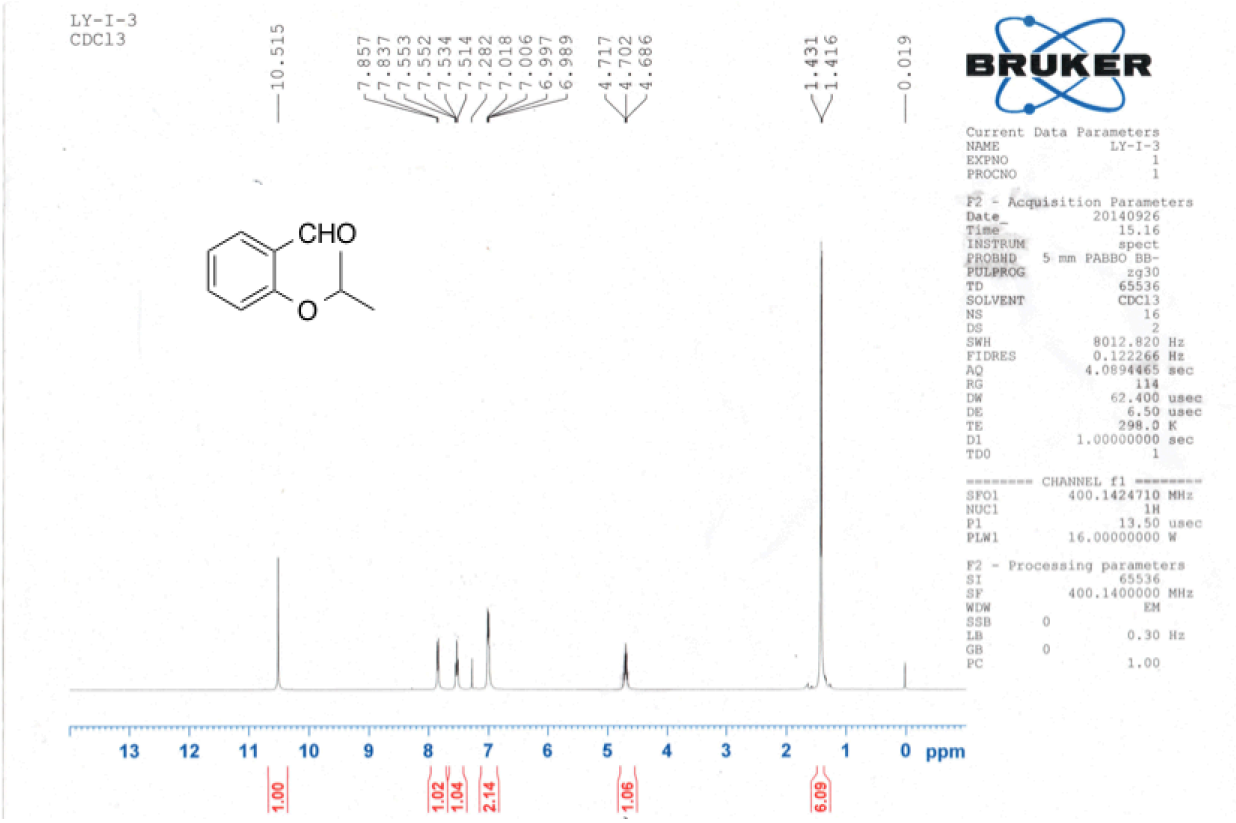
2-(allyloxy)benzaldehyde (4a)



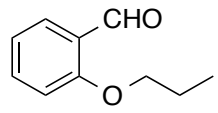


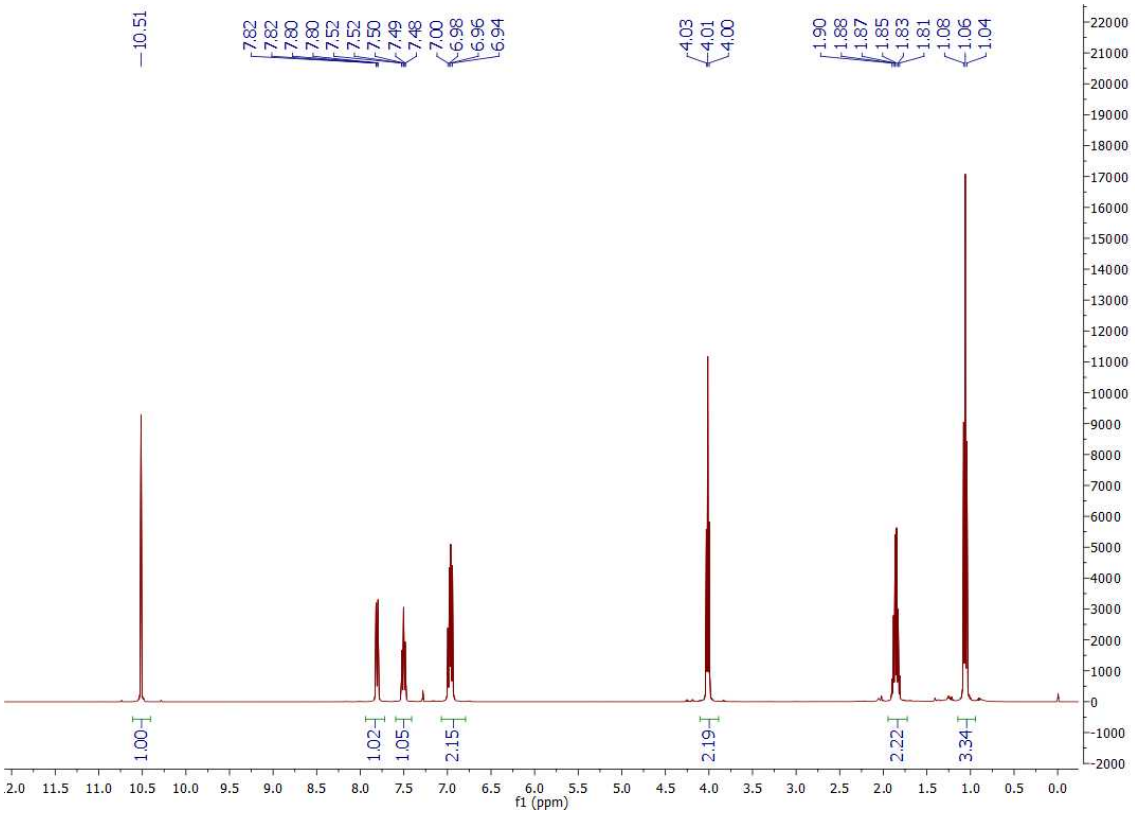
2-isopropoxybenzaldehyde (4b)



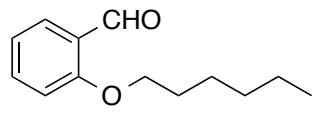


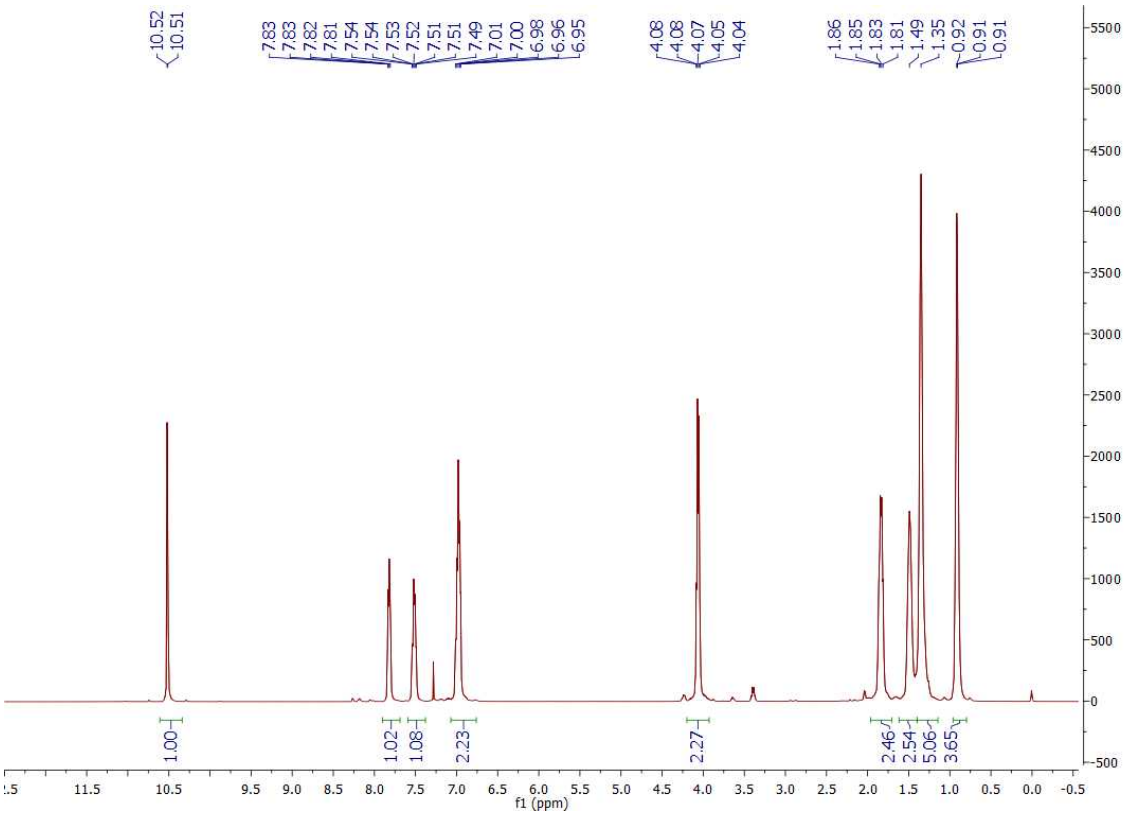
2-propoxybenzaldehyde (4c)



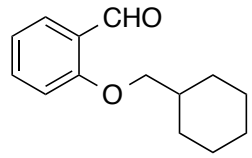


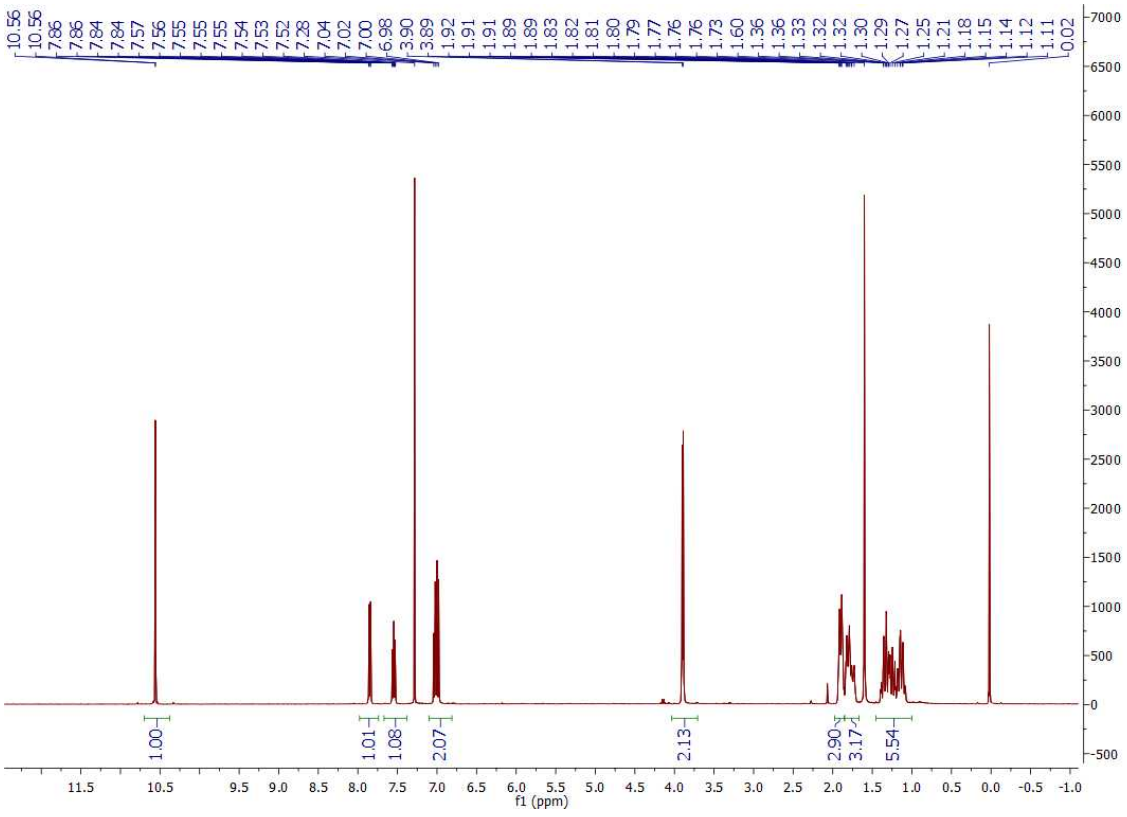
2-(hexyloxy)benzaldehyde (4d).



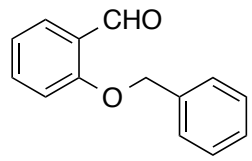


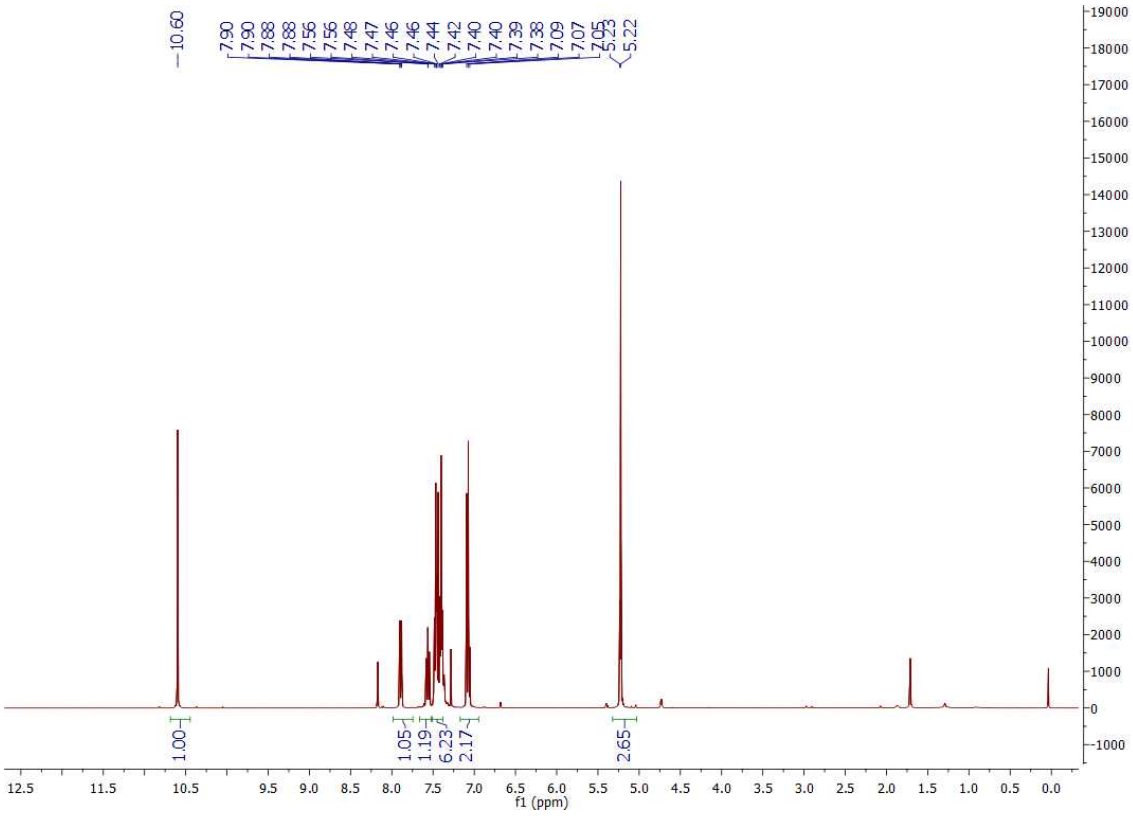
2-(cyclohexylmethoxy)benzaldehyde (4e)


CHO
O

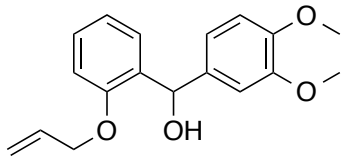

10.56
10.56
7.86
7.86
7.84
7.84
7.57
7.56
7.55
7.55
7.55
7.54
7.53
7.52
7.28
7.04
7.02
7.00
6.98
3.90
3.89
1.92
1.91
1.91
1.89
1.89
1.83
1.82
1.81
1.80
1.79
1.77
1.76
1.76
1.73
1.60
1.36
1.36
1.33
1.32
1.32
1.30
1.29
1.27
1.25
1.21
1.18
1.15
1.14
1.12
1.11
0.02
1.00
1.01
1.08
2.07
2.13
2.90
3.17
5.54
f1 (ppm)

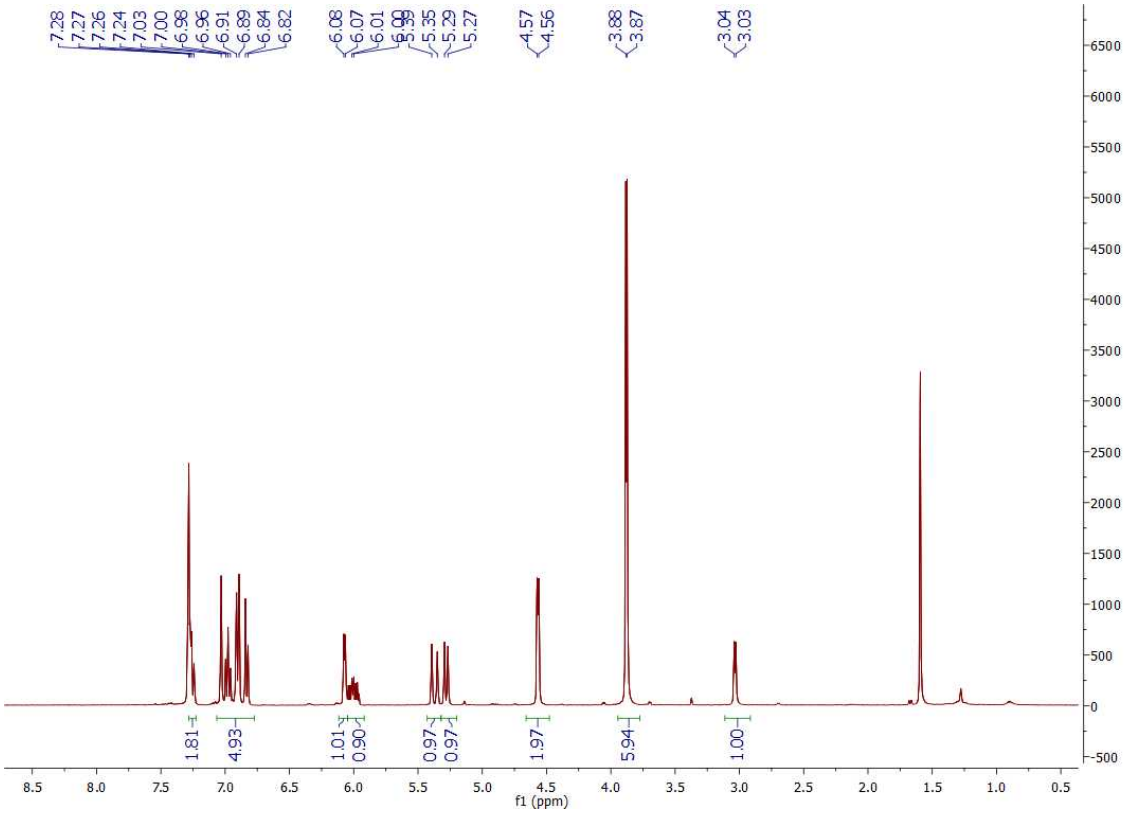
2-(benzyloxy)benzaldehyde (4f)

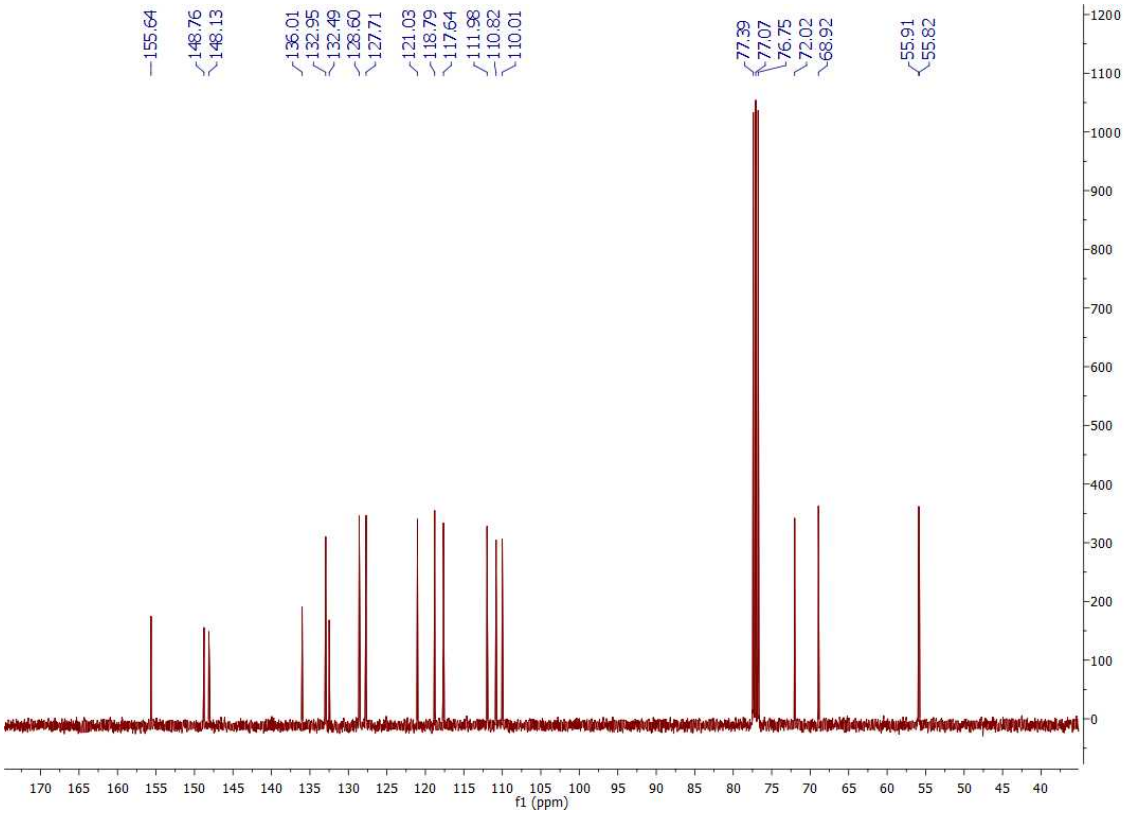


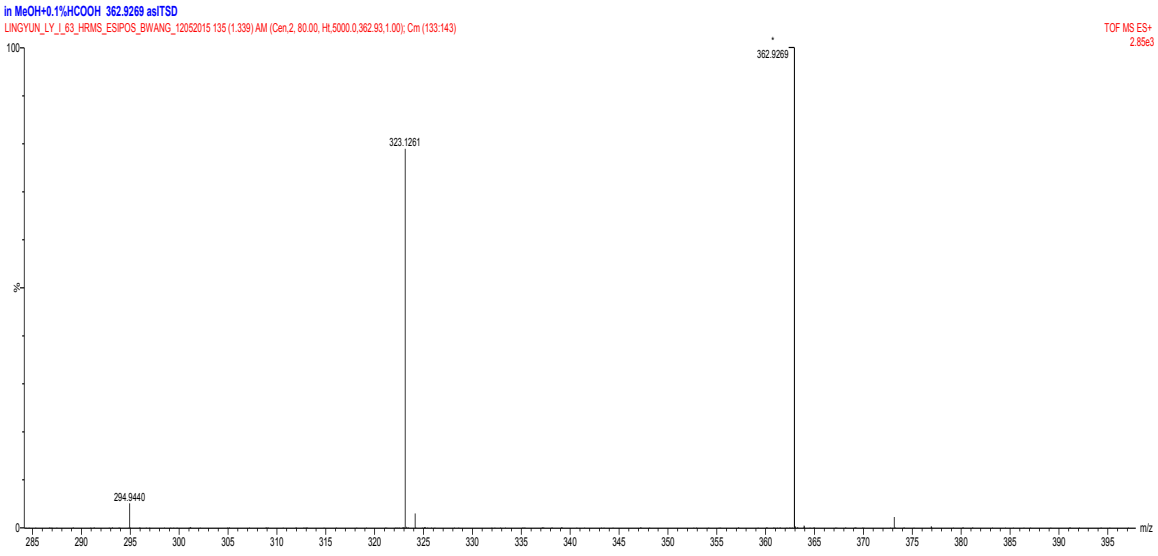


(2-(allyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (6a)

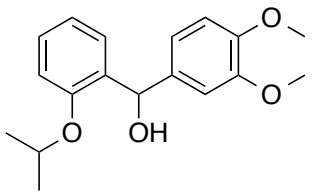


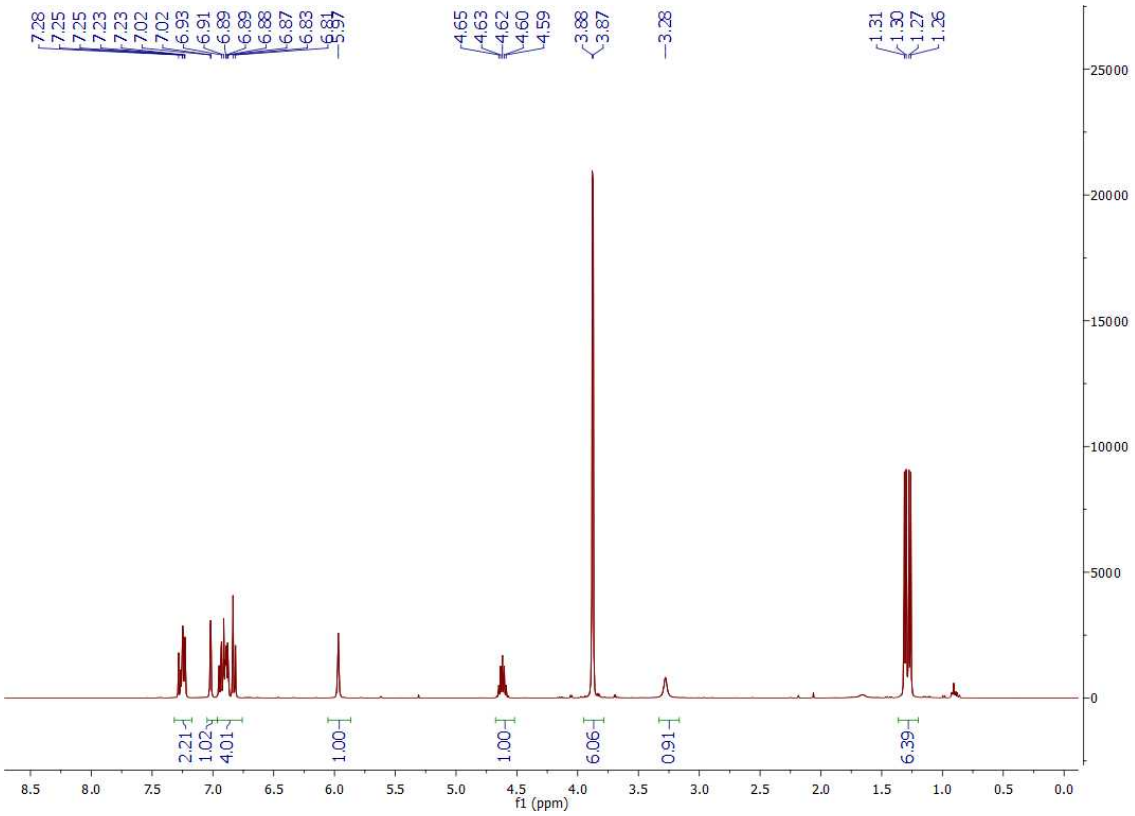


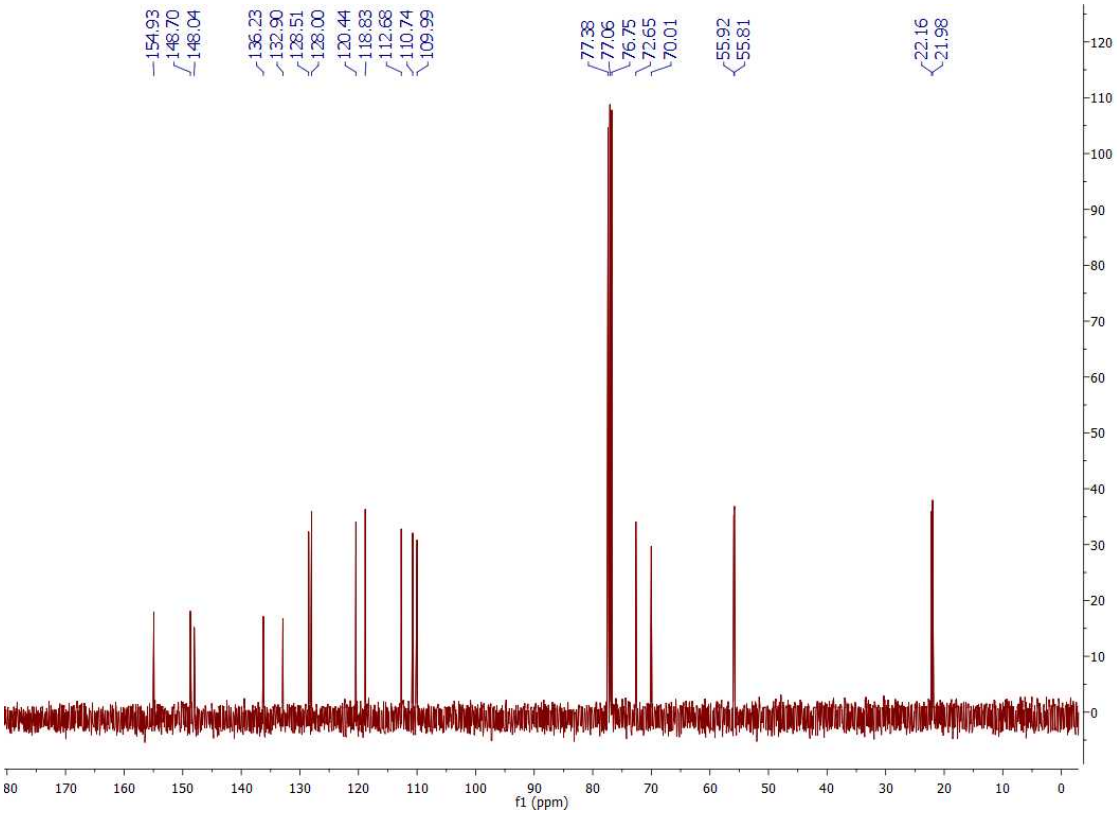


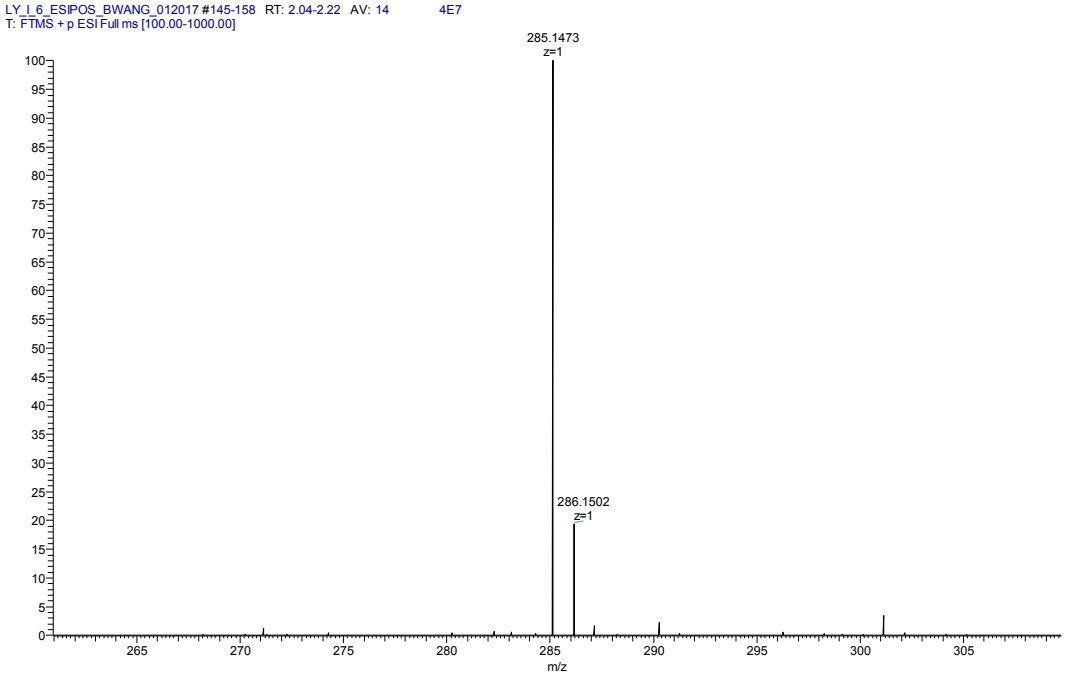


(3,4-dimethoxyphenyl)(2-isopropoxyphenyl)methanol (6b)

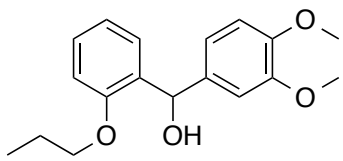

O
O
O
OH

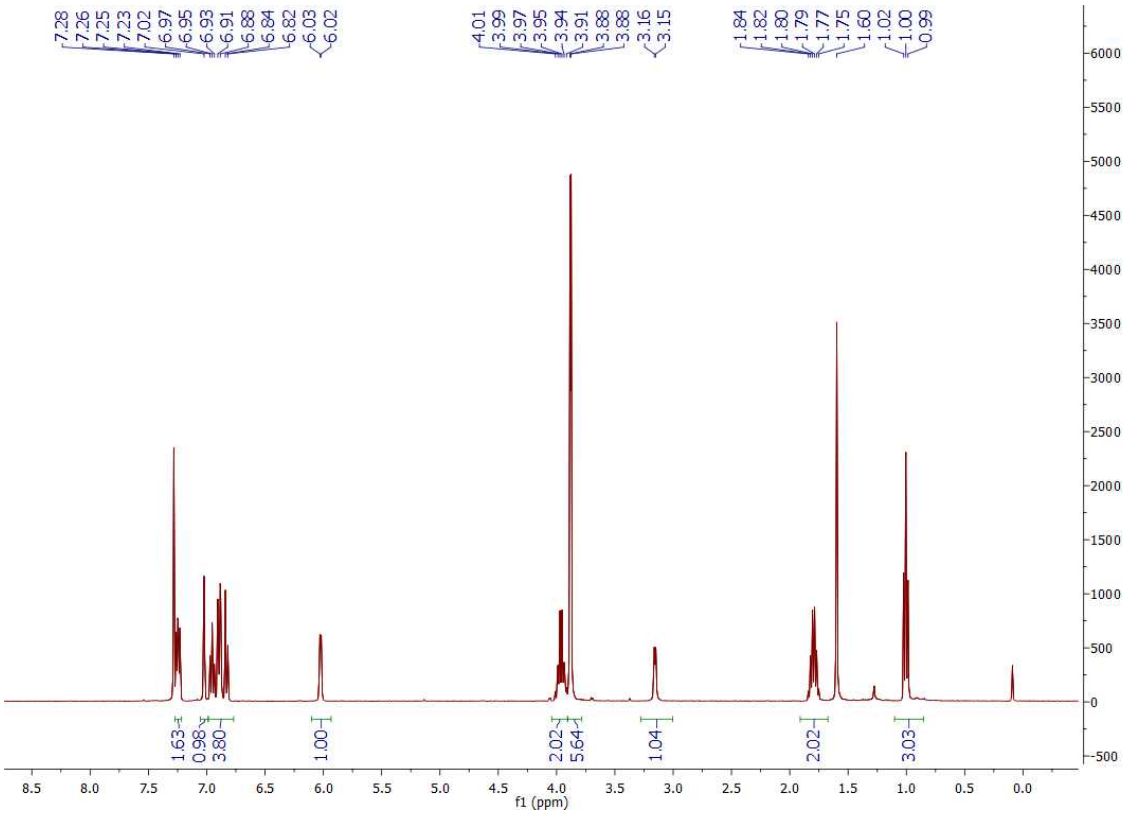

7.28
7.25
7.25
7.23
7.23
7.02
7.02
6.93
6.91
6.89
6.89
6.88
6.87
6.83
6.81
5.97
4.65
4.63
4.62
4.60
4.59
3.88
3.87
3.28
1.31
1.30
1.27
1.26
25000
20000
15000
10000
5000
0
2.21
1.02
4.01
1.00
1.00
6.06
0.91
6.39
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

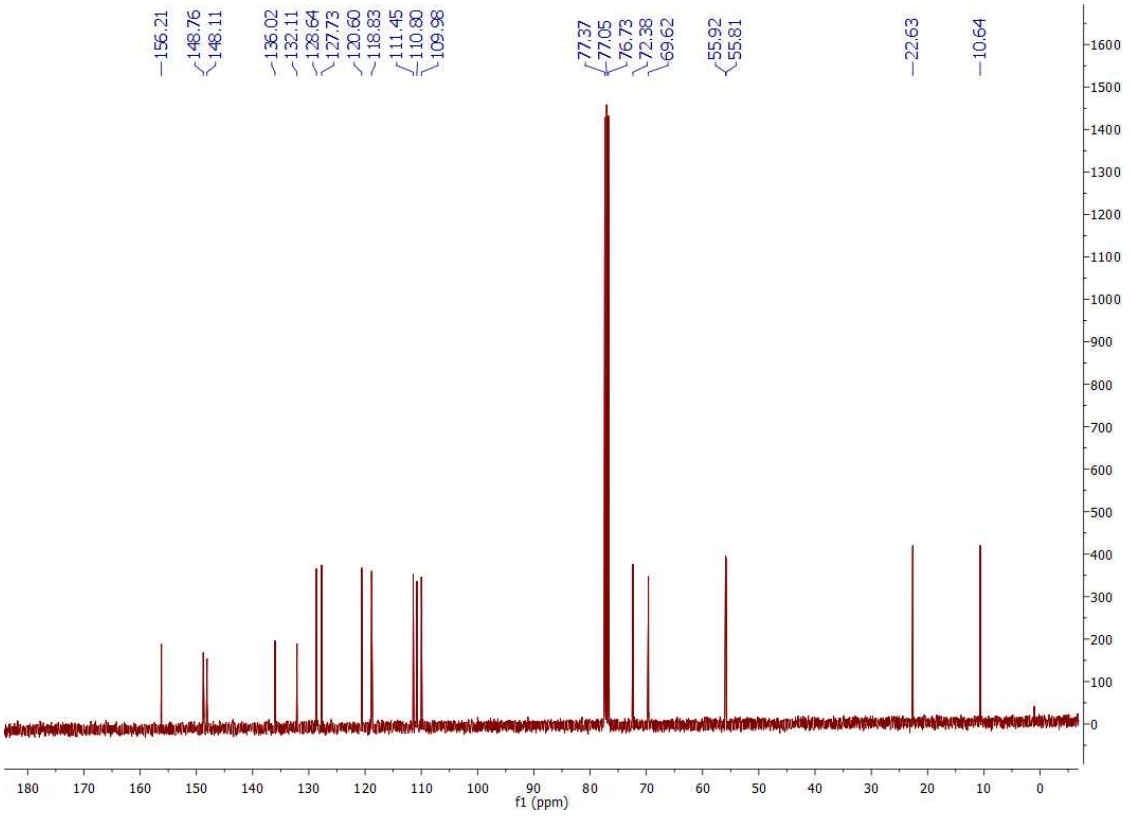

154.93
148.70
148.04
136.23
132.90
128.51
128.00
120.44
118.83
112.68
110.74
109.99
77.38
77.06
76.75
72.65
70.01
55.92
55.81
22.16
21.98
f1 (ppm)

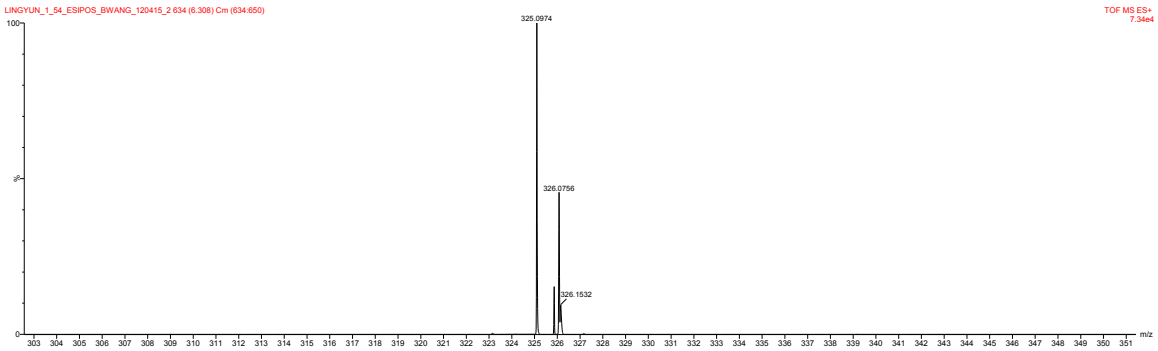

LY_I_6_ESIPOS_BWANG_012017 #145-158 RT: 2.04-2.22 AV: 14 4E7
T: FTMS + p ESI Full ms [100.00-1000.00]
285.1473
z=1
286.1502
z=1
m/z

(3,4-dimethoxyphenyl)(2-propoxyphenyl)methanol (6c)

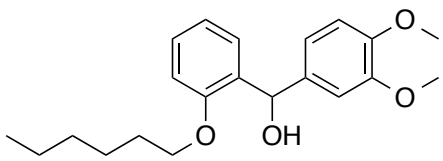


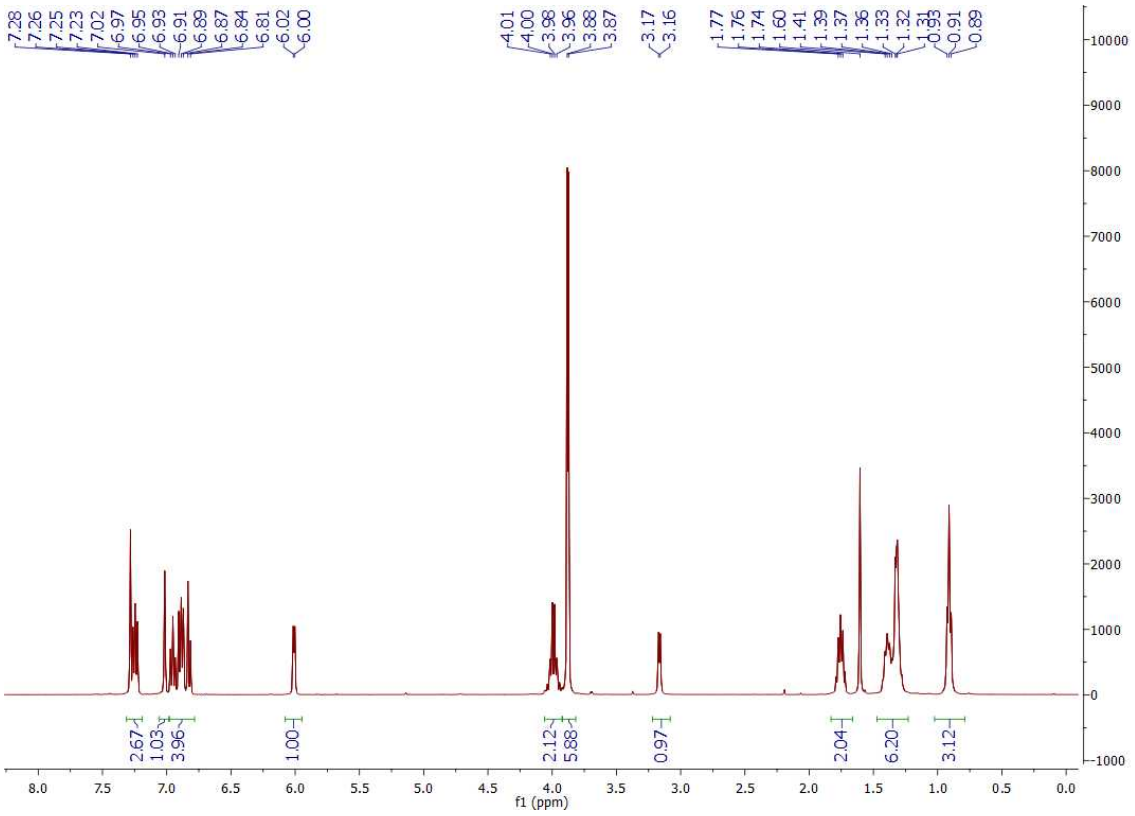


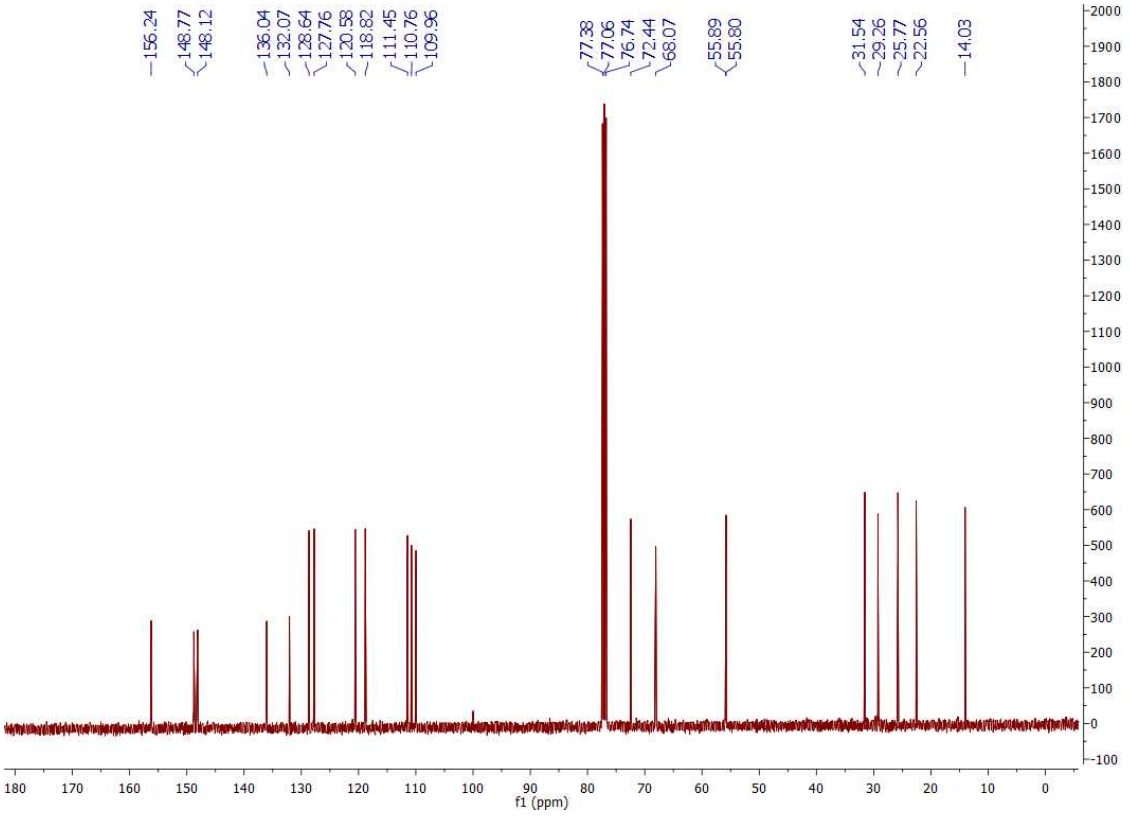

156.21
148.76
148.11
136.02
132.11
128.64
127.73
120.60
118.83
111.45
110.80
109.98
77.37
77.05
76.73
72.38
69.62
55.92
55.81
22.63
10.64
f1 (ppm)

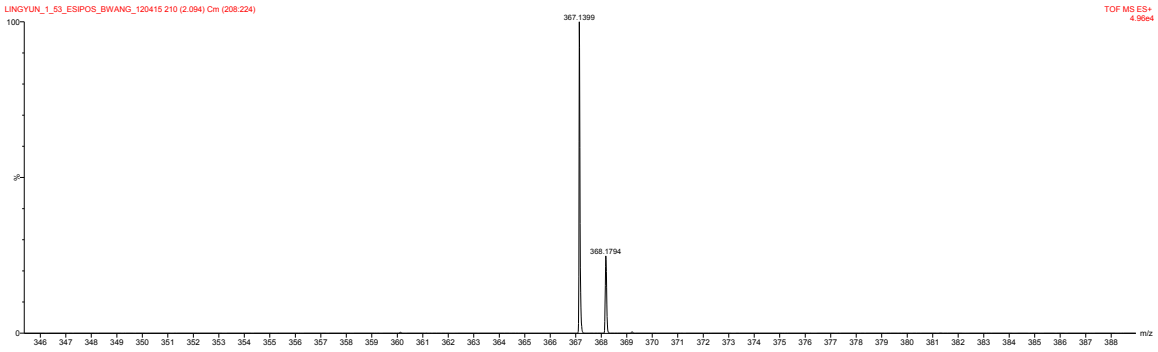

LINGYUN_1_54_ESIPOS_BWANG_120415_2 634 (6.308) Cm (634:650)
TOF MS ES+
7.34e4
325.0974
326.0756
326.1532
m/z

(3,4-dimethoxyphenyl)(2-(hexyloxy)phenyl)methanol (6d)

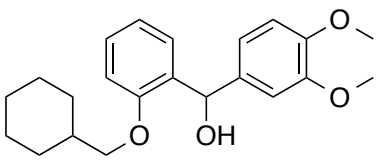


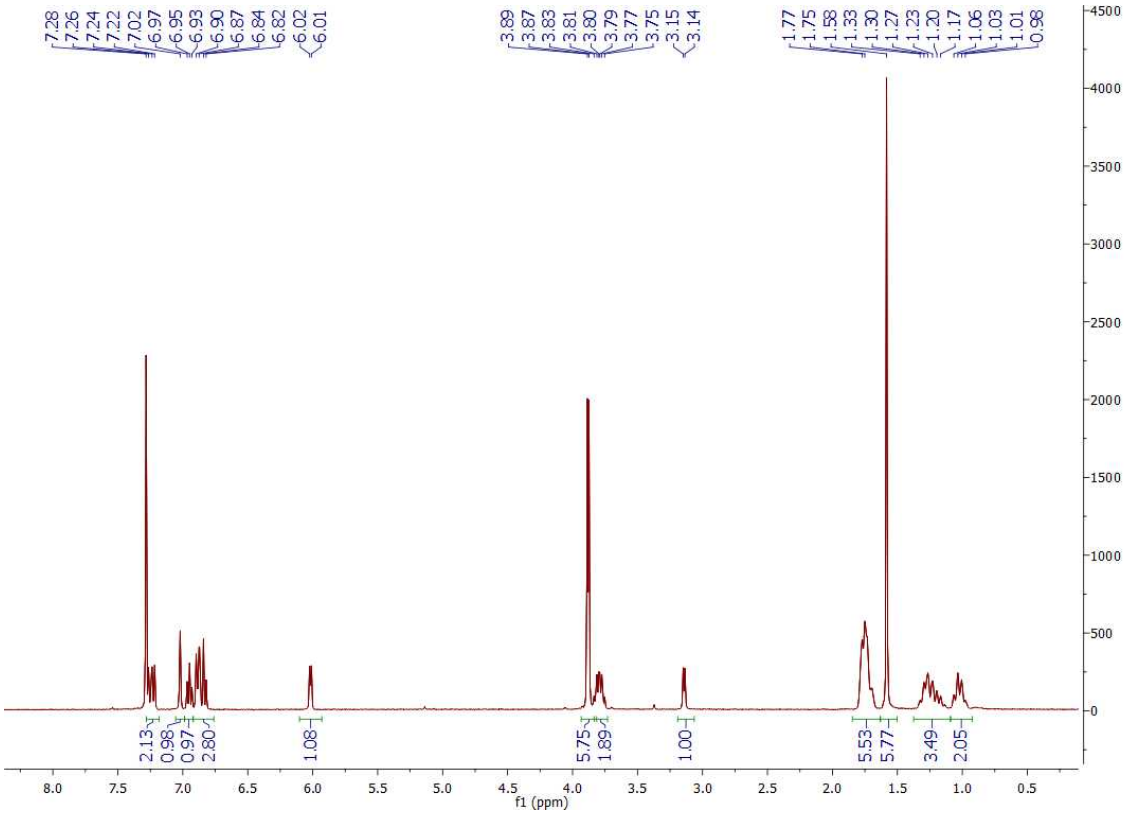


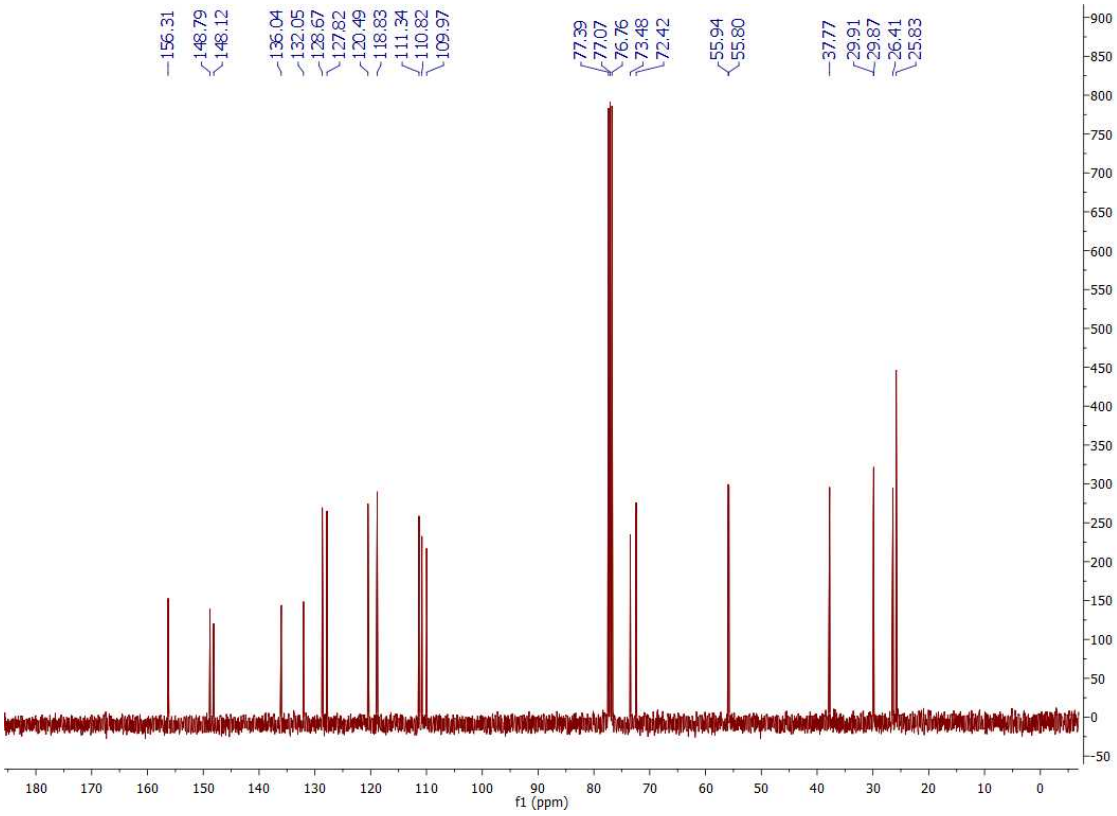

156.24
148.77
148.12
136.04
132.07
128.64
127.76
120.58
118.82
111.45
110.76
109.96
77.38
77.06
76.74
72.44
68.07
55.89
55.80
31.54
29.26
25.77
22.56
14.03
f1 (ppm)

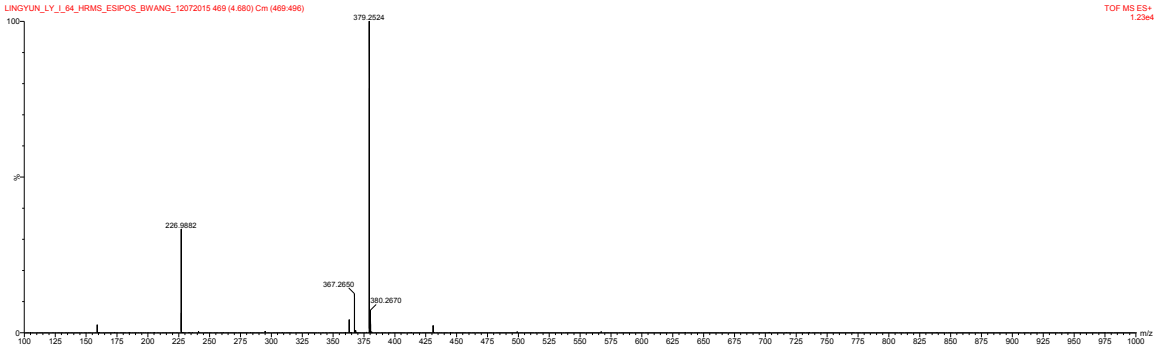

LINGYUN_1_53_ESIPOS_BWANG_120415 210 (2.094) Cm (208:224)
TOF MS ES+
4.96e4
367.1399
368.1794
m/z

(2-(cyclohexylmethoxy)phenyl)(3,4-dimethoxyphenyl)methanol (6e)

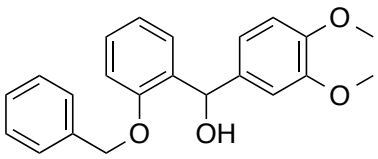


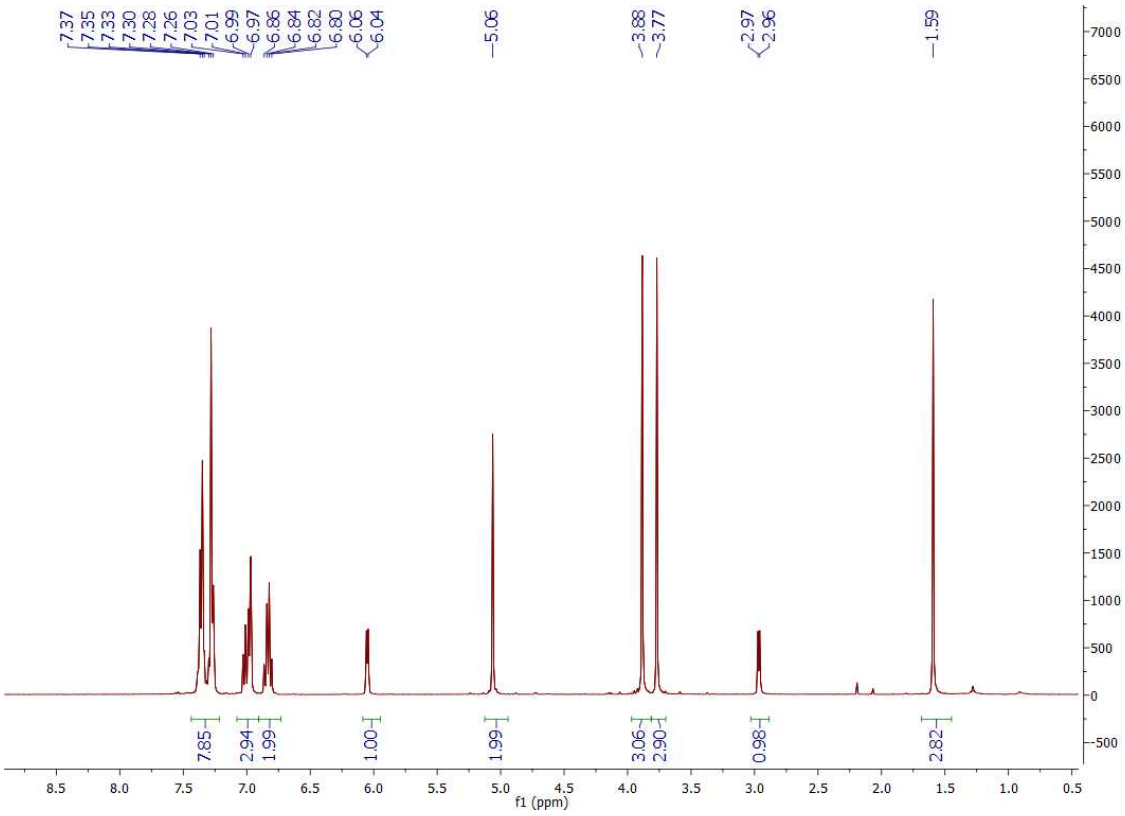


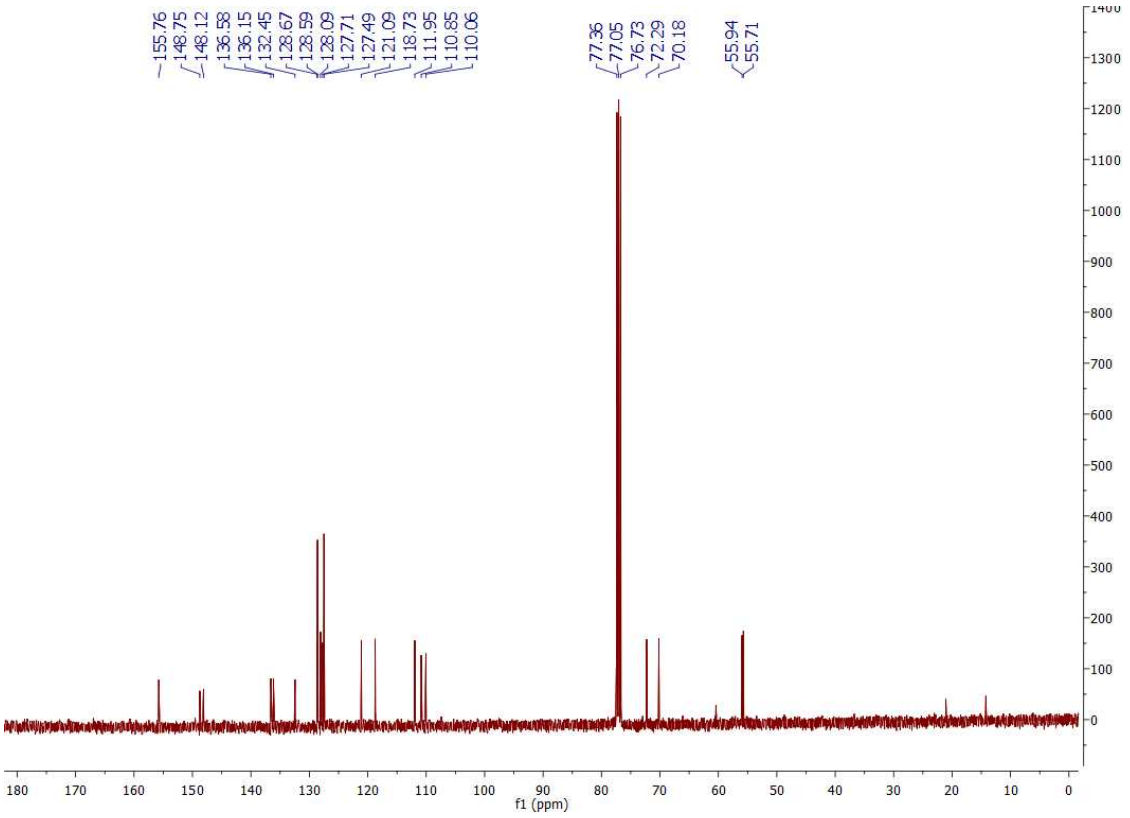

156.31
148.79
148.12
136.04
132.05
128.67
127.82
120.49
118.83
111.34
110.82
109.97
77.39
77.07
76.76
73.48
72.42
55.94
55.80
37.77
29.91
29.87
26.41
25.83
f1 (ppm)

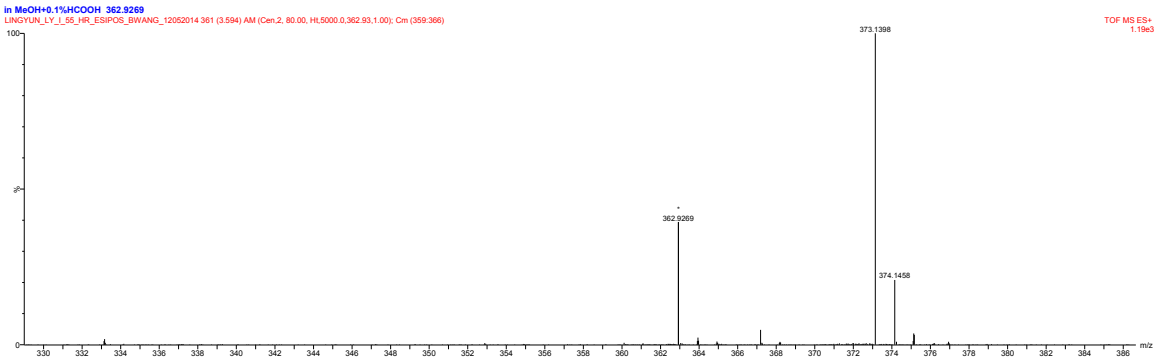

LINGYUN_LY_I_64_HRMS_ESIPOS_BWANG_12072015 469 (4.680) Cm (469:496)
TOF MS ES+
1.23e4
379.2524
226.9882
367.2650
380.2670
%
m/z

(2-(benzyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (6f)



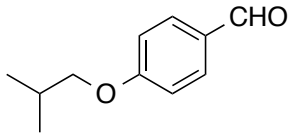


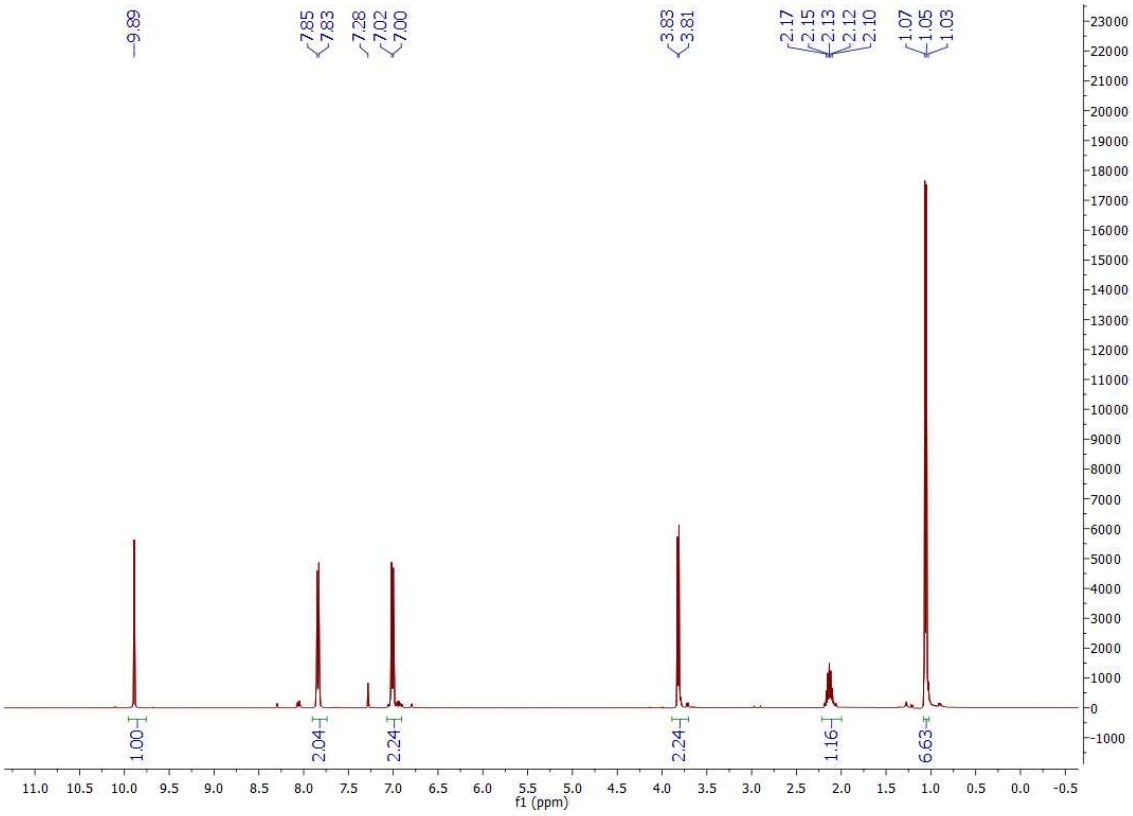

155.76
148.75
148.12
136.58
136.15
132.45
128.67
128.59
128.09
127.71
127.49
121.09
118.73
111.95
110.85
110.06
77.36
77.05
76.73
72.29
70.18
55.94
55.71
f1 (ppm)


in MeOH+0.1%HCOOH 362.9269
LINGYUN_LY_I_55_HR_ESIPOS_BWANG_12052014 361 (3.594) AM (Cen,2, 80.00, Ht,5000.0,362.93,1.00); Cm (359:366)
TOF MS ES+
1.19e3
373.1398
362.9269
374.1458
%
m/z

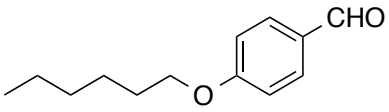
Class II: *Para*-phenolic ether benzhydrol analogues

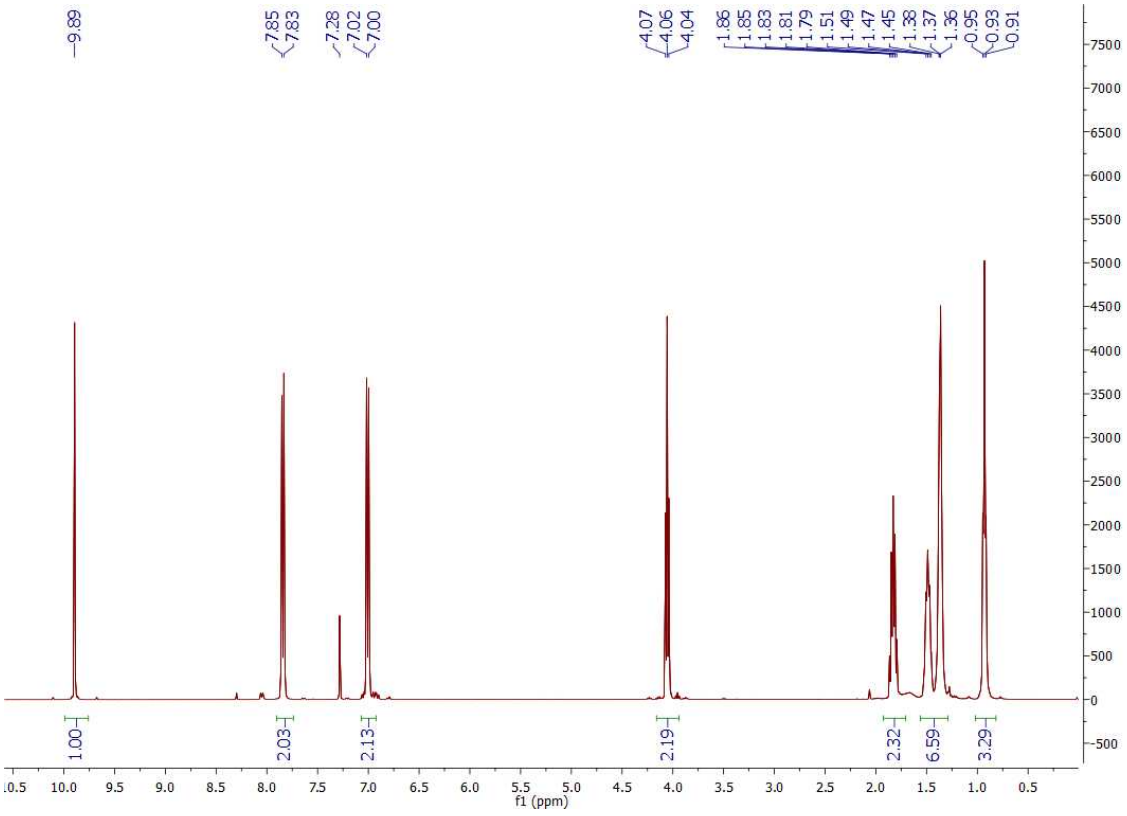
4-isobutoxybenzaldehyde (8a).



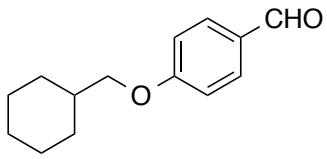


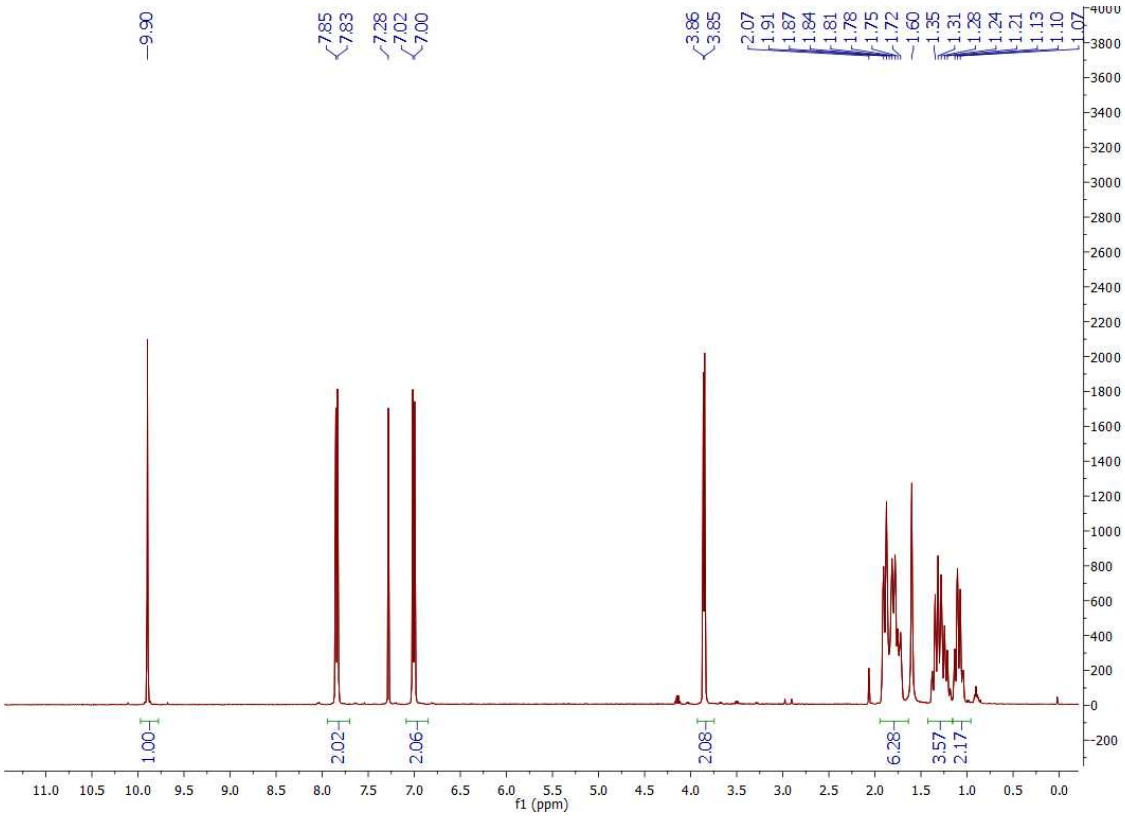
4-(hexyloxy)benzaldehyde (8b)



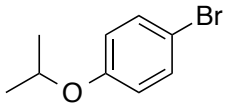


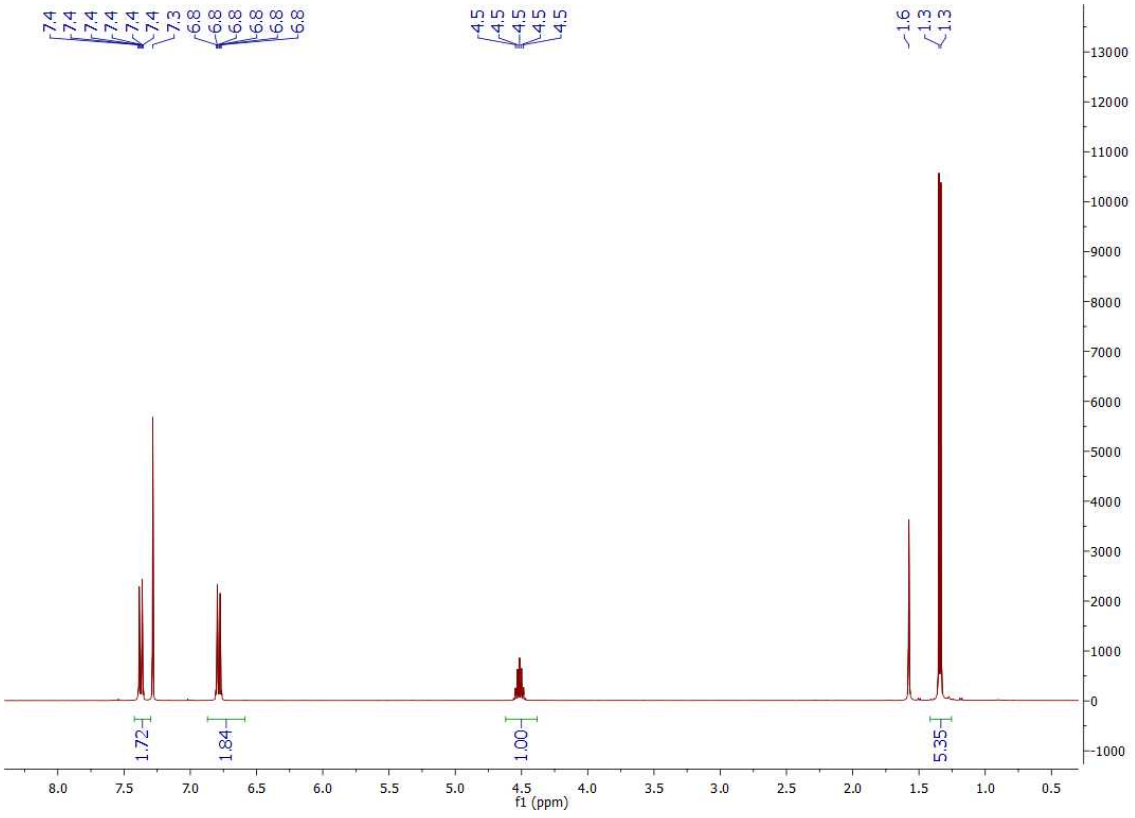
4-(cyclohexylmethoxy)benzaldehyde (8c)



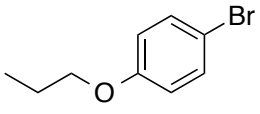


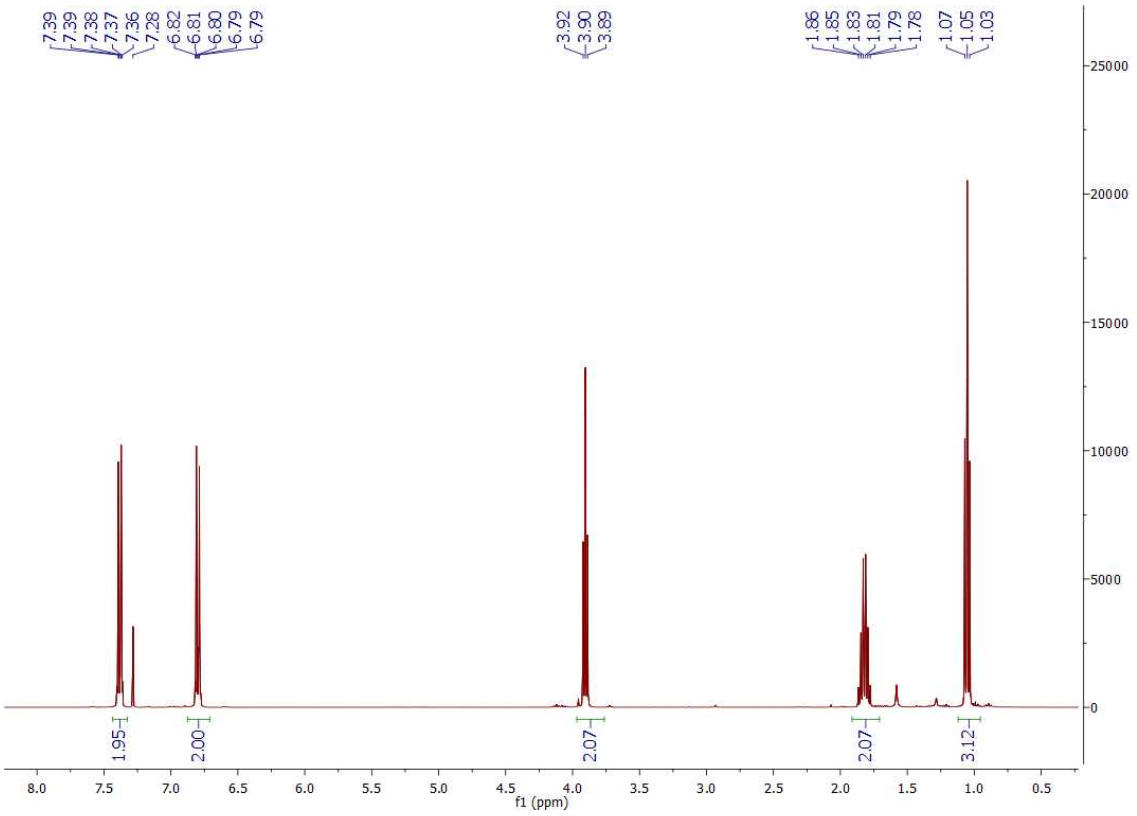
1-bromo-4-isopropoxybenzene (14b)





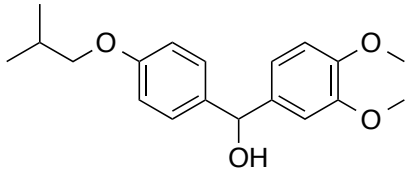
1-bromo-4-propoxybenzene (14c)

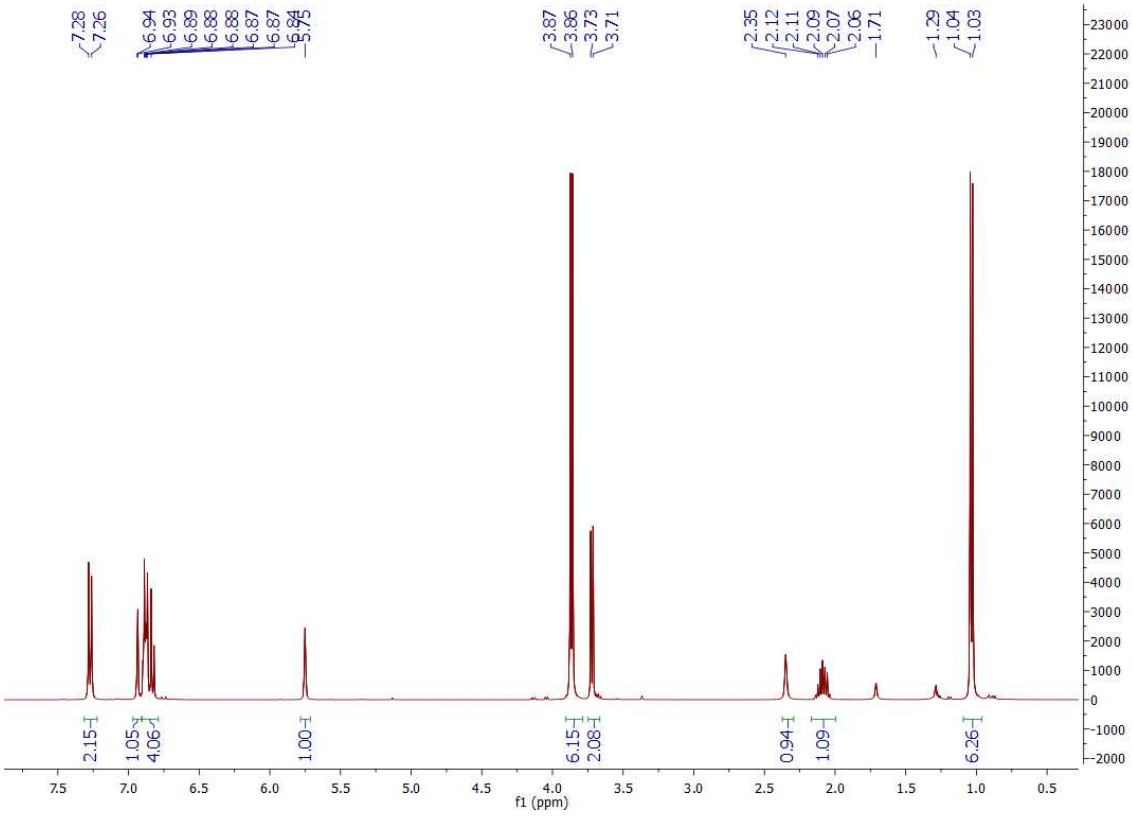


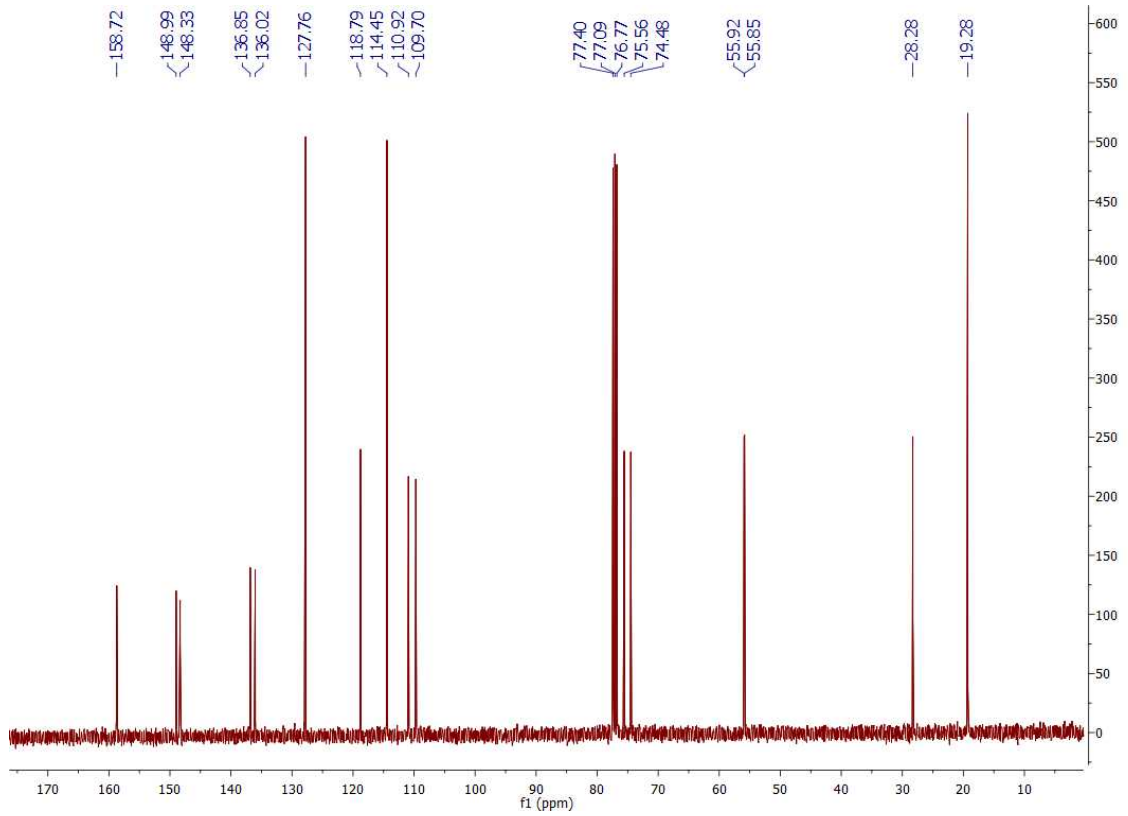


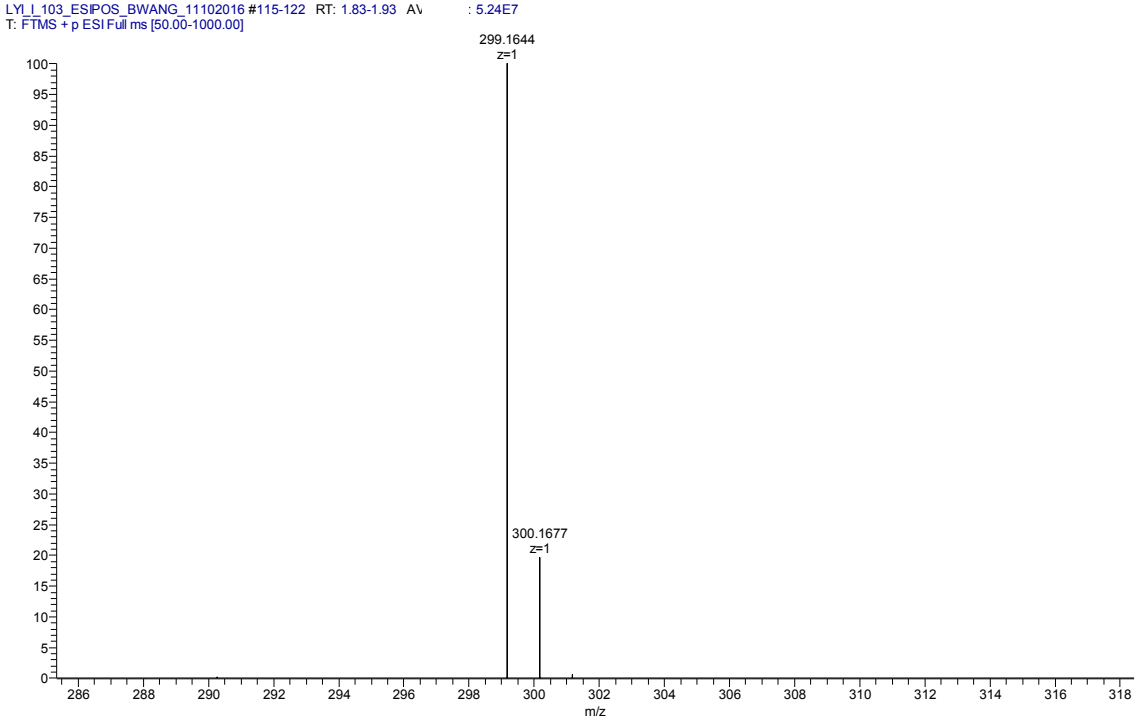
Tert-butyl 4-(2-(4-bromophenoxy)ethyl)piperidine-1-carboxylate (14d)* Spectra will be in Jalisa Ferguson's information.

(3,4-dimethoxyphenyl)(4-isobutoxyphenyl)methanol (9a)

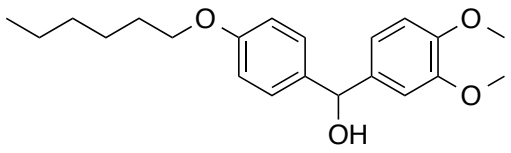


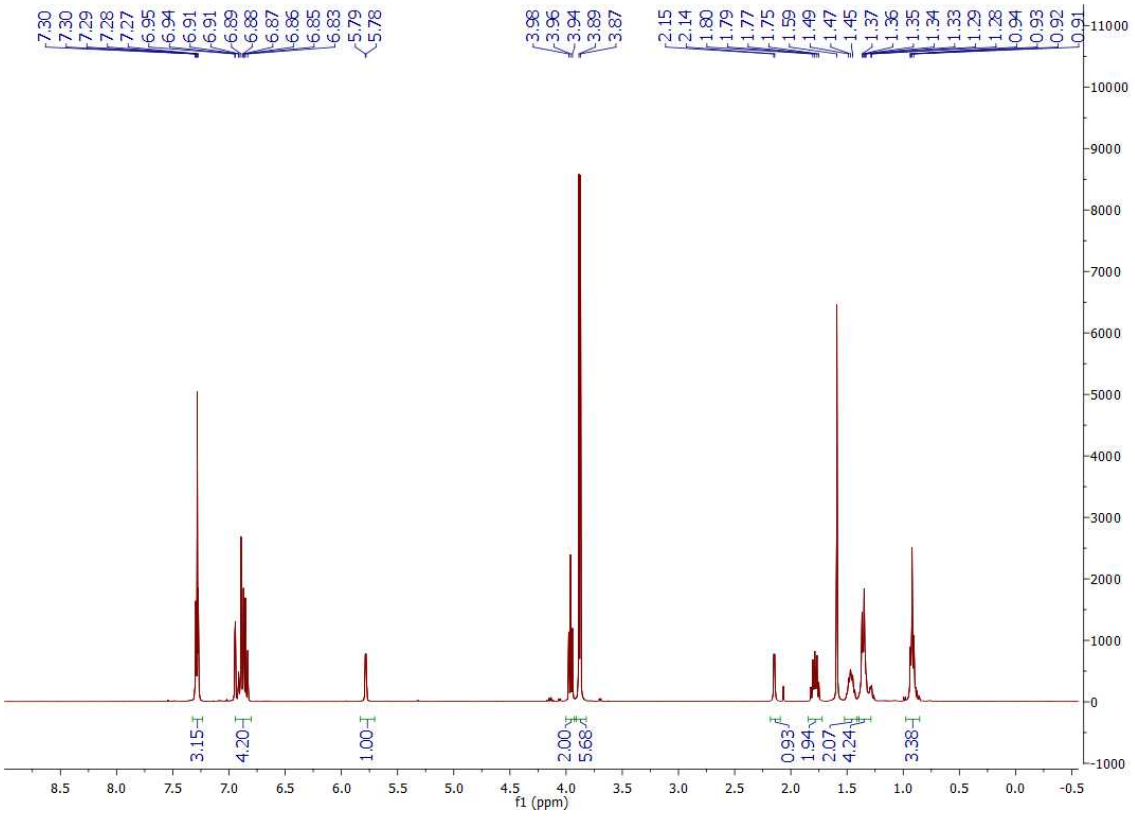


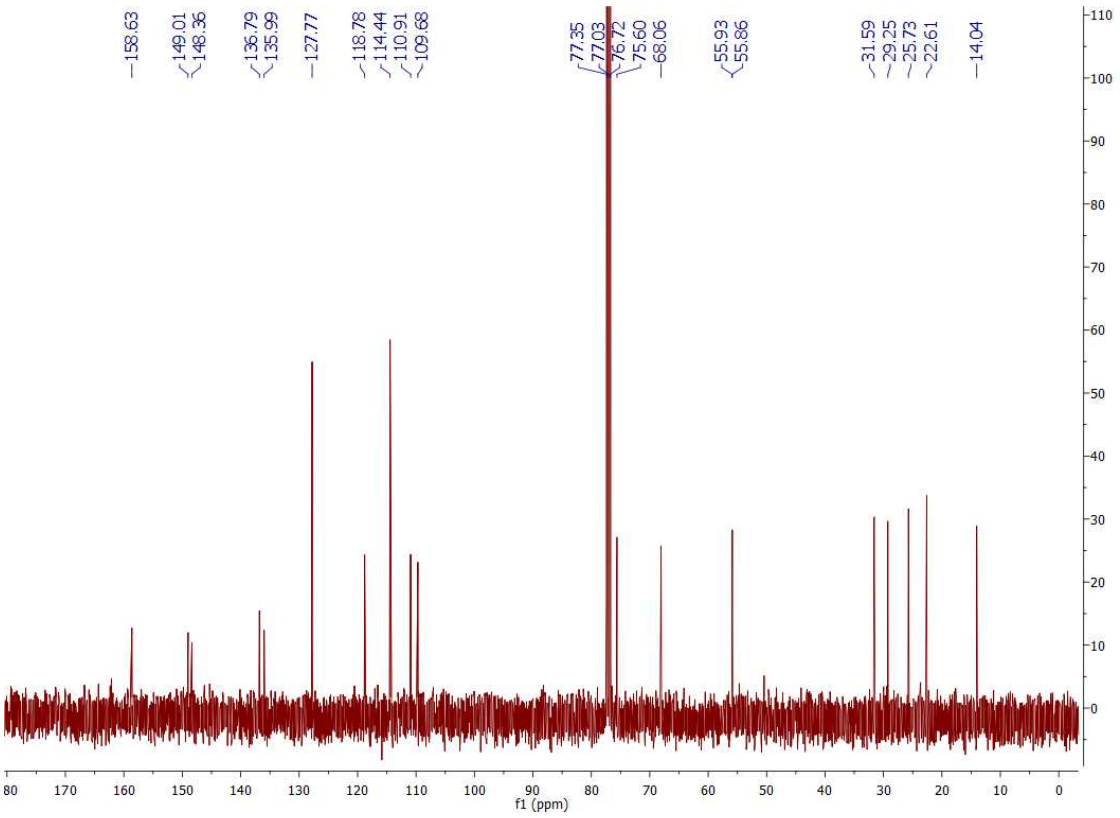

158.72
148.99
148.33
136.85
136.02
127.76
118.79
114.45
110.92
109.70
77.40
77.09
76.77
75.56
74.48
55.92
55.85
28.28
19.28
f1 (ppm)

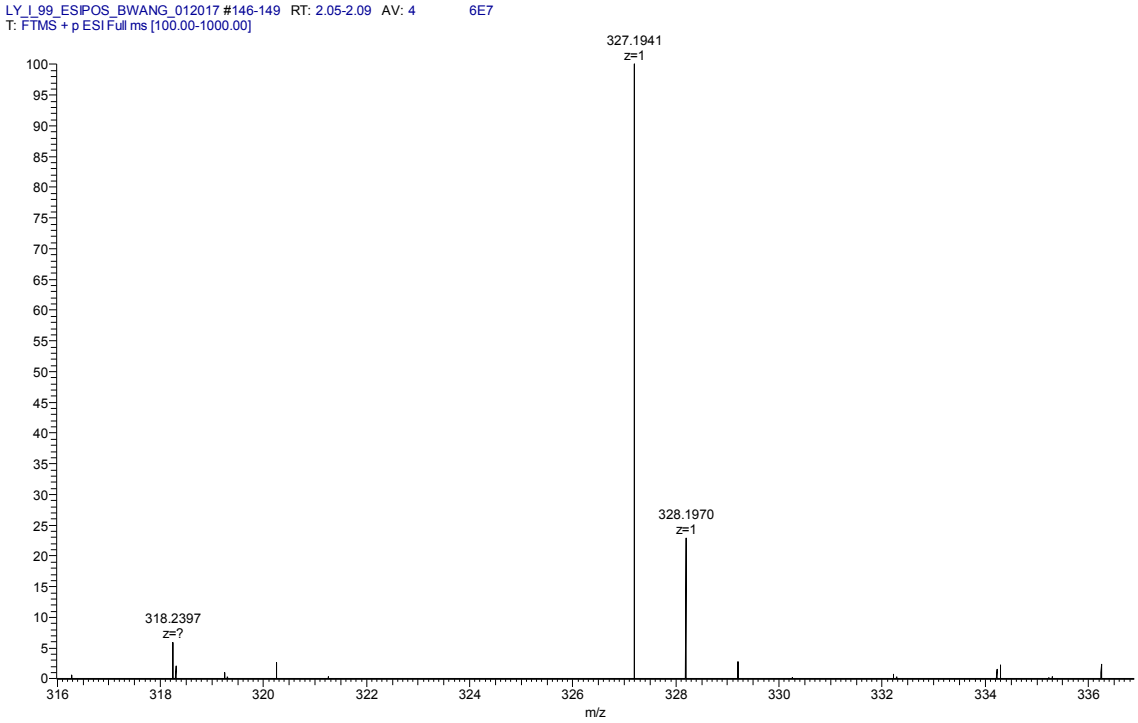

LYI_I_103_ESIPOS_BWANG_11102016 #115-122 RT: 1.83-1.93 AV : 5.24E7
T: FTMS + p ESI Full ms [50.00-1000.00]
299.1644
z=1
300.1677
z=1
m/z

(3,4-dimethoxyphenyl)(4-(hexyloxy)phenyl)methanol (9b)

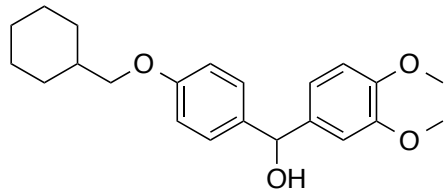


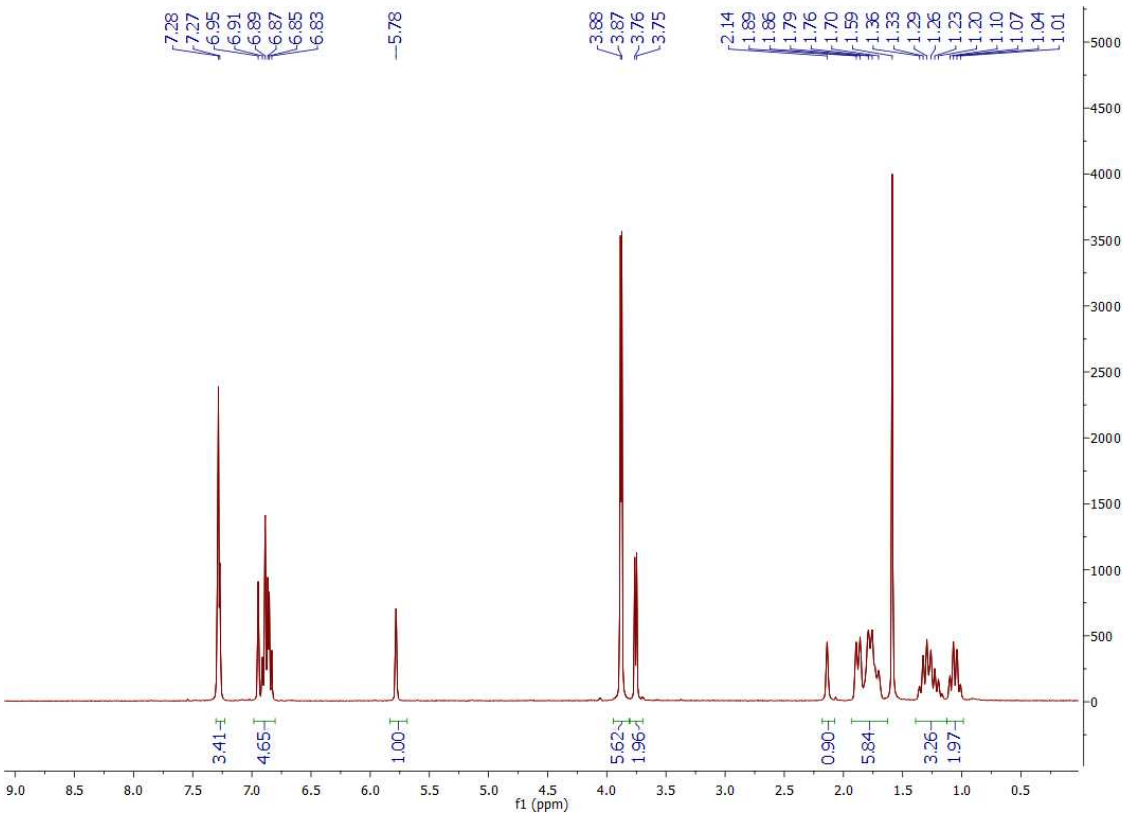


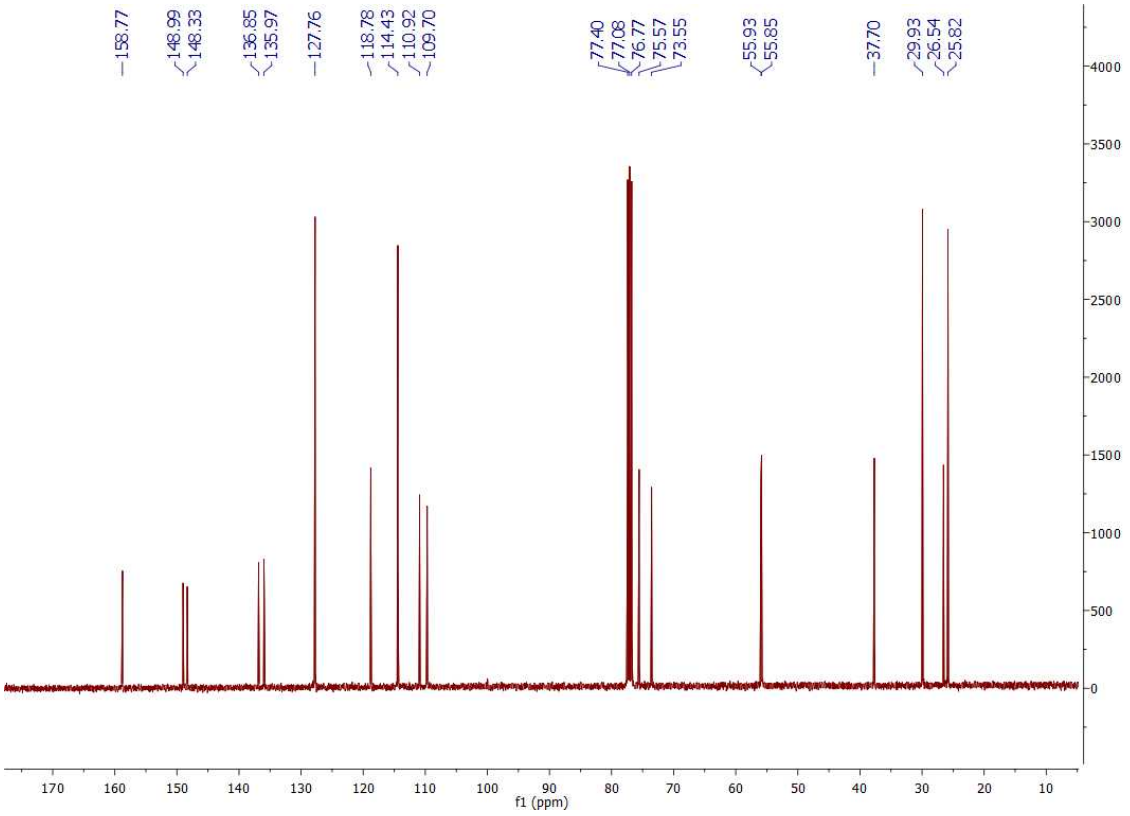

158.63
149.01
148.36
136.79
135.99
127.77
118.78
114.44
110.91
109.68
77.35
77.03
76.72
75.60
68.06
55.93
55.86
31.59
29.25
25.73
22.61
14.04
f1 (ppm)

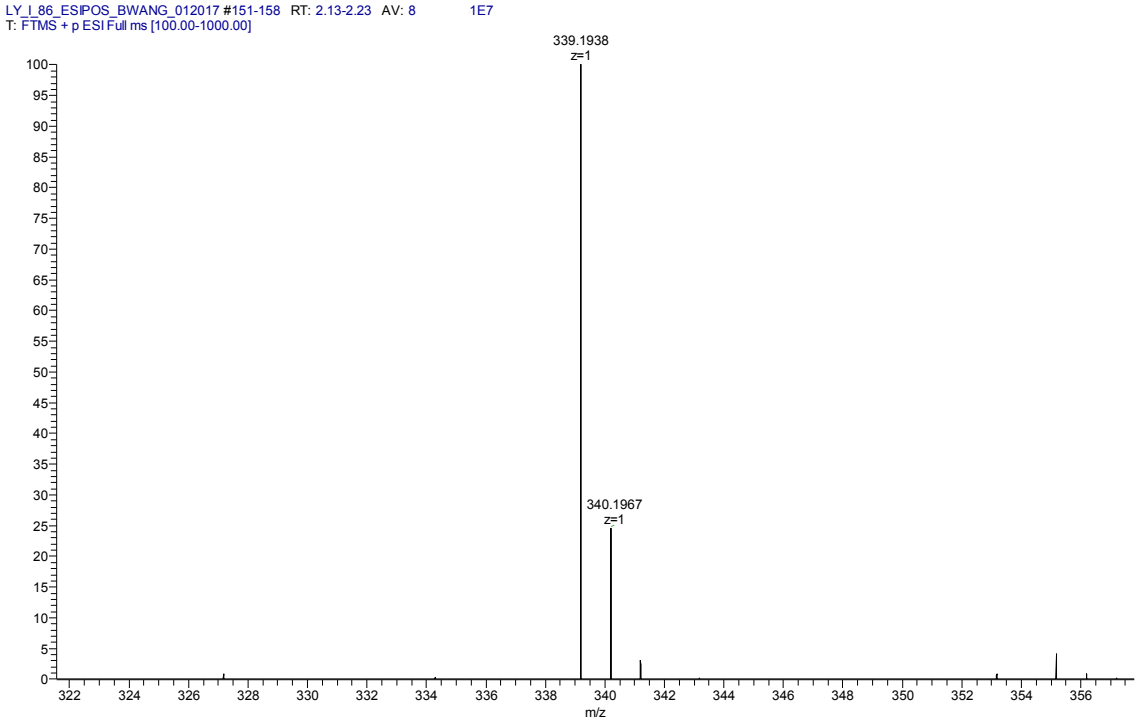

LY_I_99_ESIPOS_BWANG_012017 #146-149 RT: 2.05-2.09 AV: 4 6E7
T: FTMS + p ESI Full ms [100.00-1000.00]
327.1941
z=1
328.1970
z=1
318.2397
z=?
m/z

(4-(cyclohexylmethoxy)phenyl)(3,4-dimethoxyphenyl)methanol (9c)

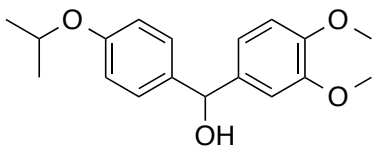


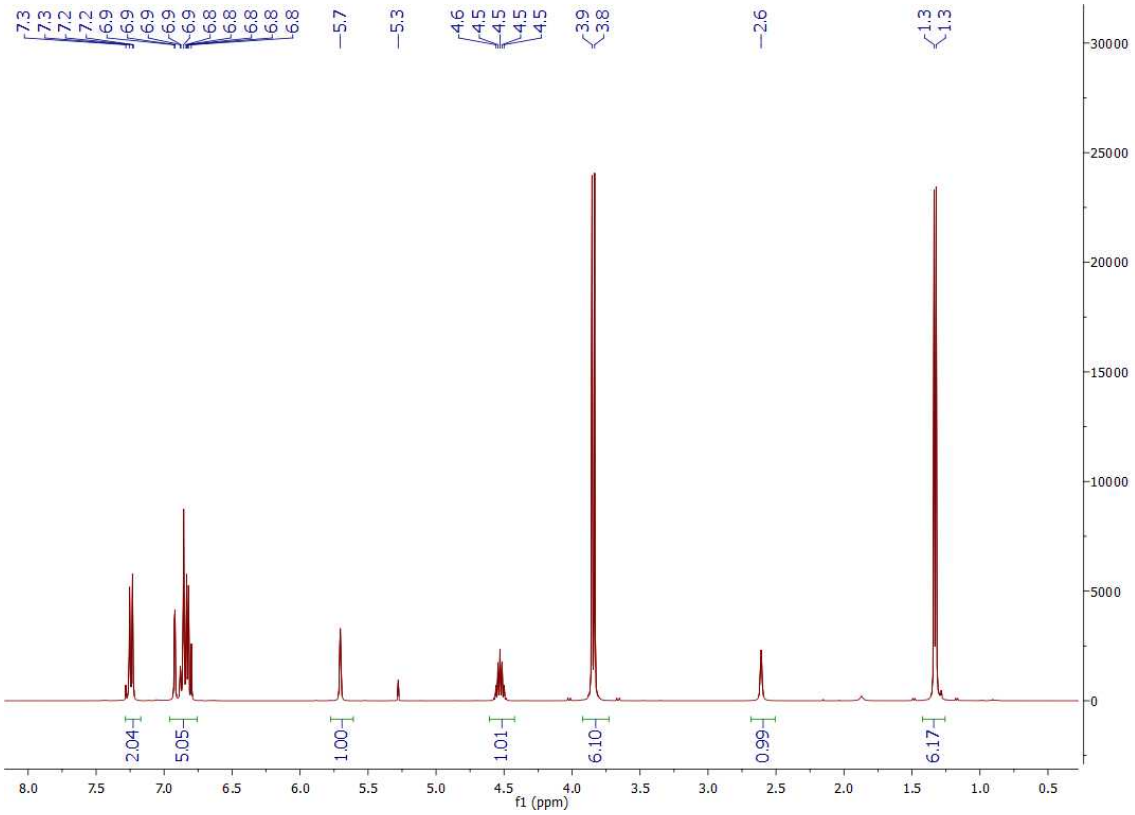


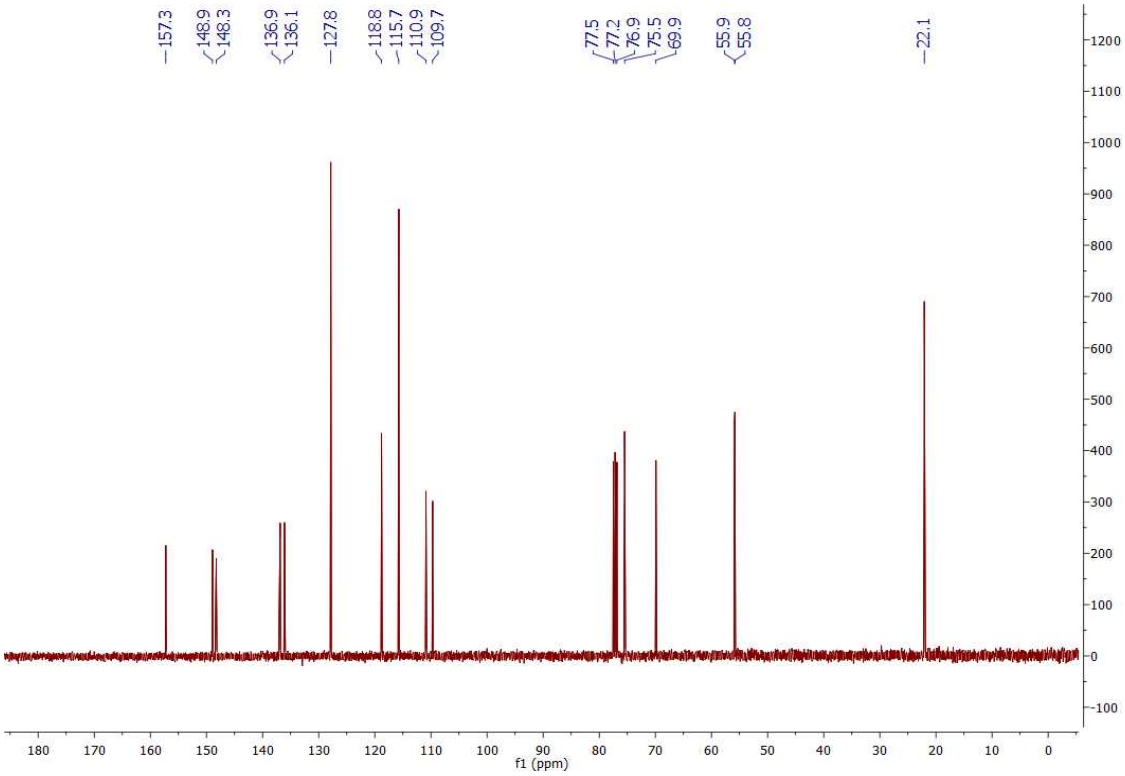

153.77
148.99
148.33
136.85
135.97
127.76
118.78
114.43
110.92
109.70
77.40
77.08
76.77
75.57
73.55
55.93
55.85
37.70
29.93
26.54
25.82
f1 (ppm)

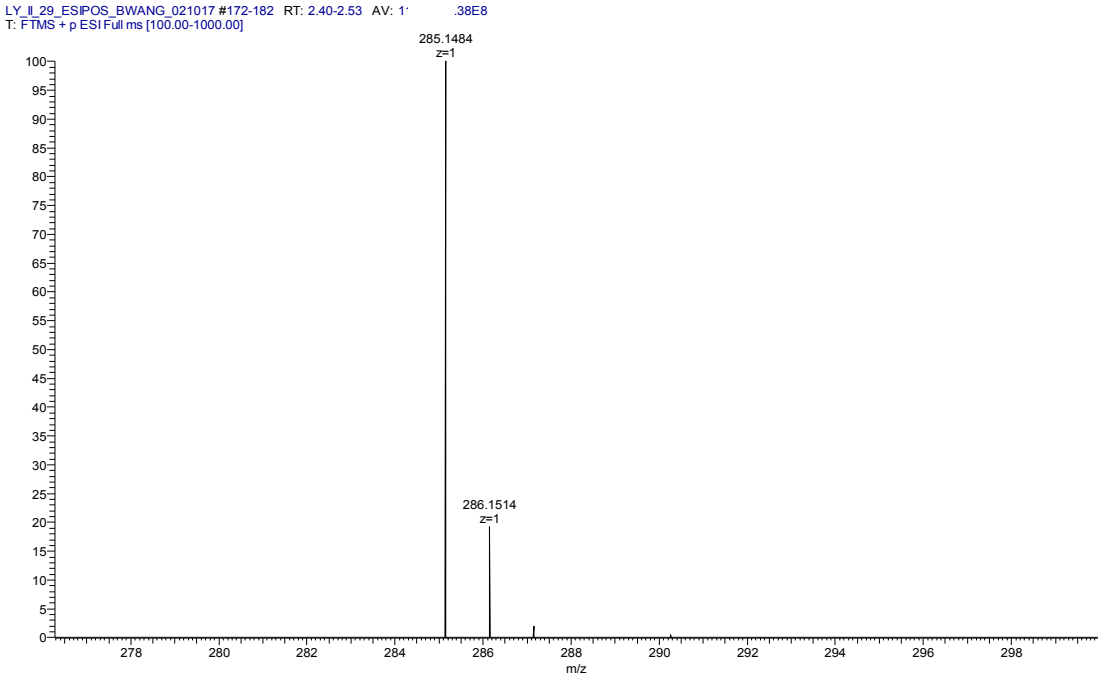

LY_I_86_ESIPOS_BWANG_012017 #151-158 RT: 2.13-2.23 AV: 8 1E7
T: FTMS + p ESI Full ms [100.00-1000.00]
339.1938
z=1
340.1967
z=1
m/z

(3,4-dimethoxyphenyl)(4-isopropoxyphenyl)methanol (9e)

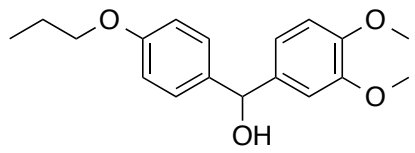


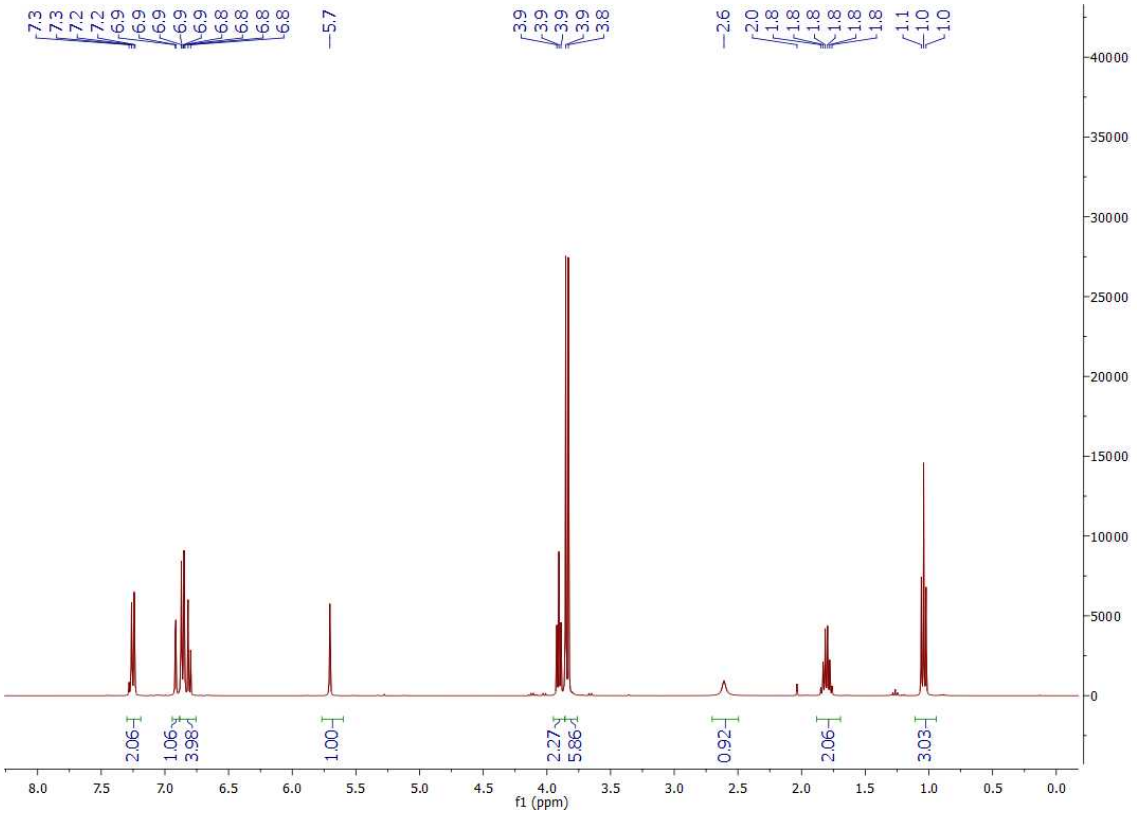


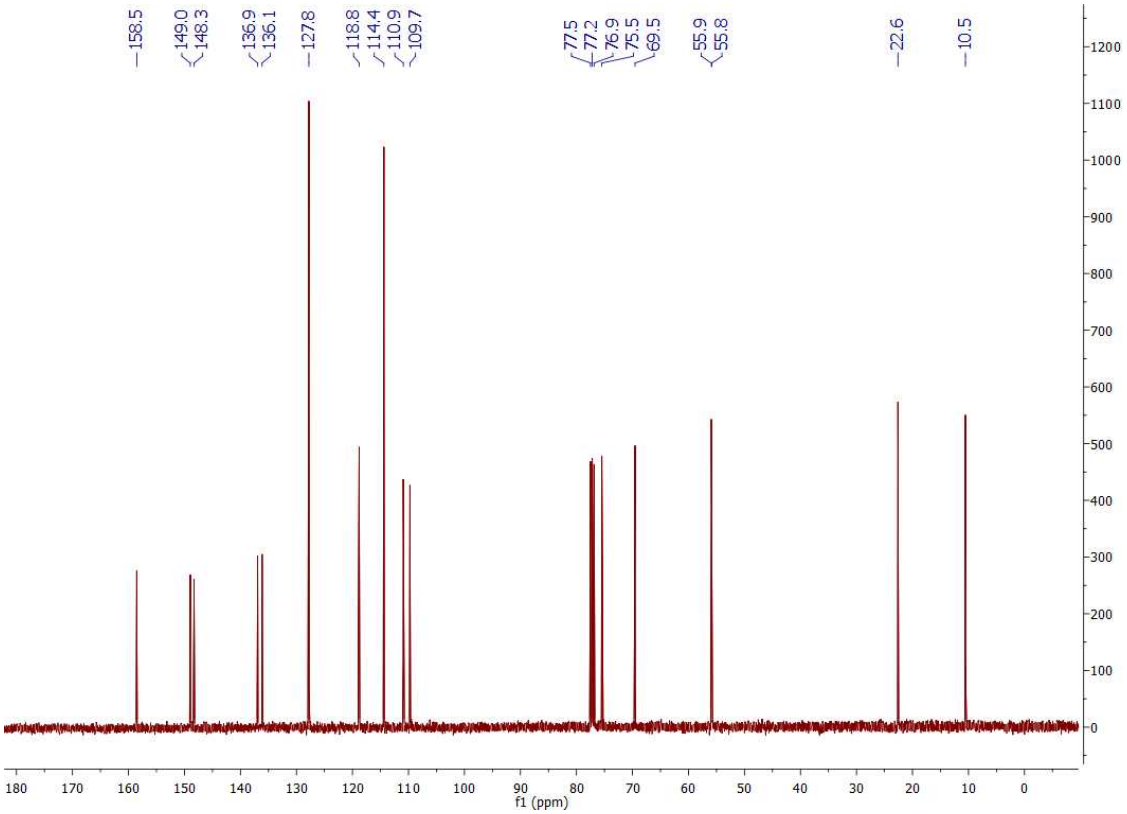

157.3
148.9
148.3
136.9
136.1
127.8
118.8
115.7
110.9
109.7
77.5
77.2
76.9
75.5
69.9
55.9
55.8
22.1
f1 (ppm)

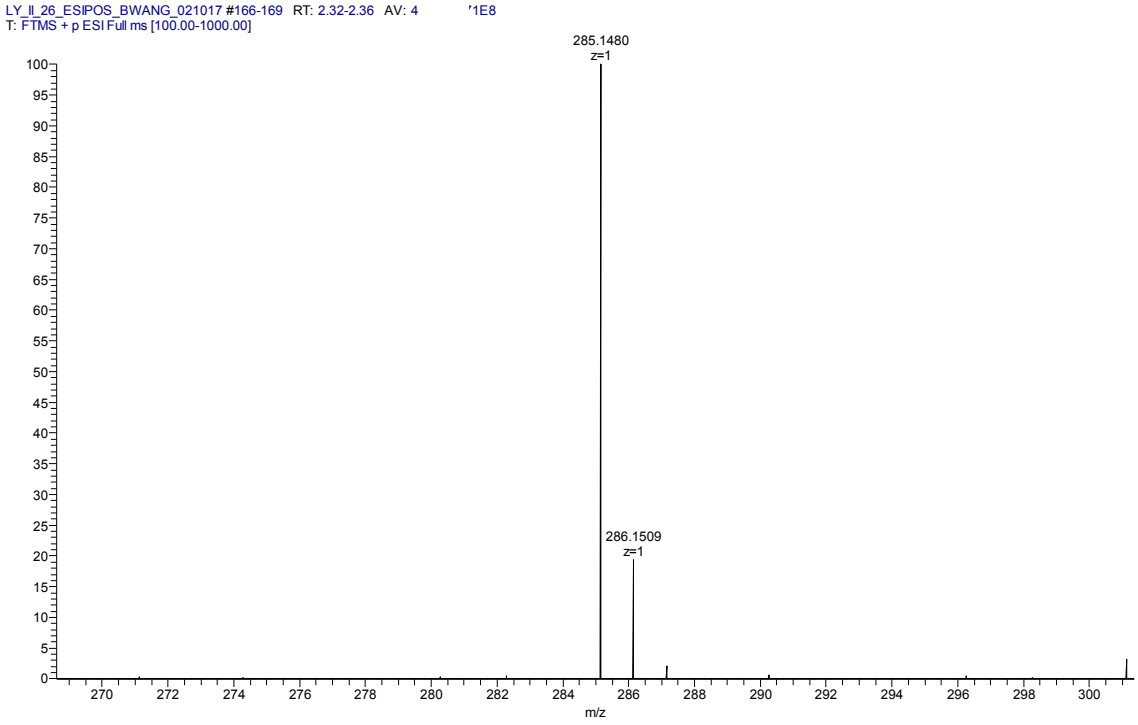

LY_II_29_ESIPOS_BWANG_021017 #172-182 RT: 2.40-2.53 AV: 1
T: FTMS + p ESI Full ms [100.00-1000.00]
285.1484
z=1
286.1514
z=1
m/z

(3,4-dimethoxyphenyl)(4-propoxyphenyl)methanol (9f)





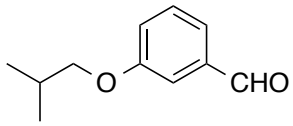

158.5
149.0
148.3
136.9
136.1
127.8
118.8
114.4
110.9
109.7
77.5
77.2
76.9
75.5
69.5
55.9
55.8
22.6
10.5
f1 (ppm)

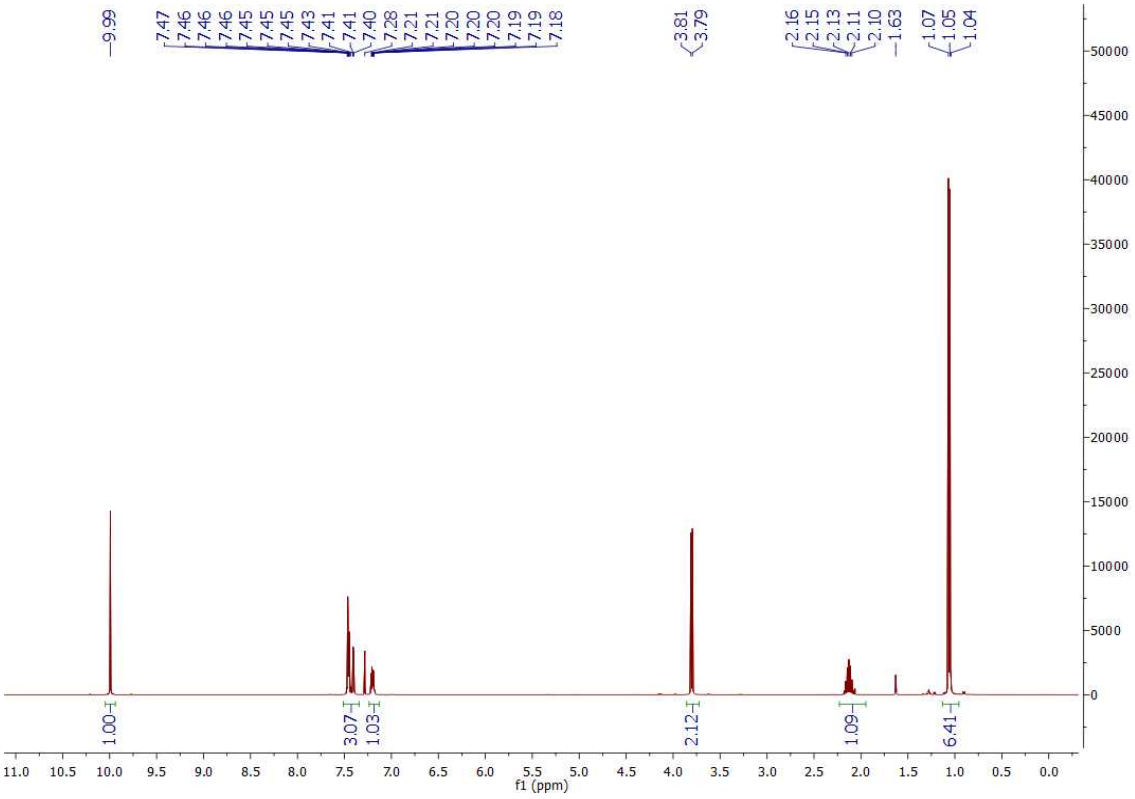

LY_II_26_ESIPOS_BWANG_021017 #166-169 RT: 2.32-2.36 AV: 4
T: FTMS + p ESI Full ms [100.00-1000.00]
285.1480
z=1
286.1509
z=1
m/z

tert*-butyl 4-(2-(4-((3,4-dimethoxyphenyl)(hydroxy)methyl)phenoxy)ethyl)piperidine-1-carboxylate (9g) Spectra will be in Jalisa Ferguson's information.

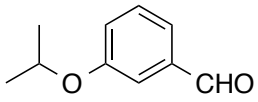
Class III: *Meta*-phenolic ether benzhydrol analogues

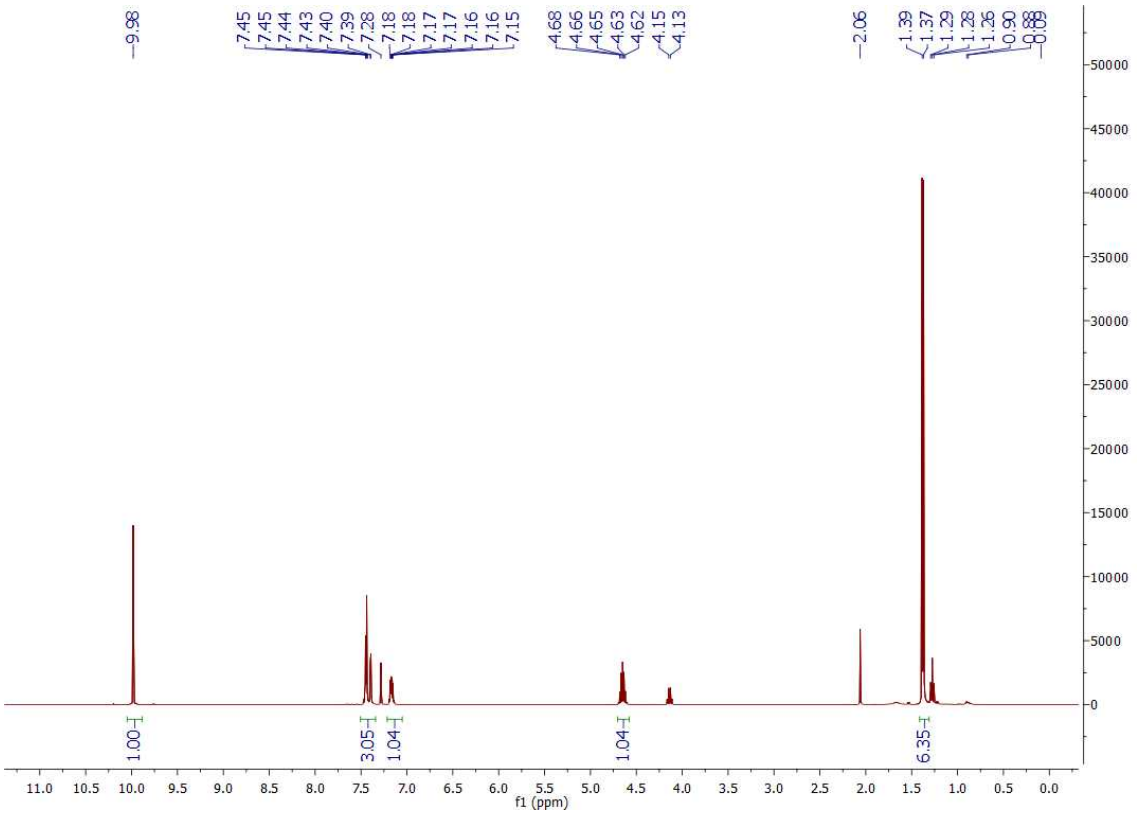
3-isobutoxybenzaldehyde (16a)



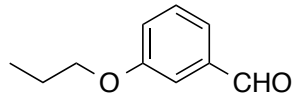


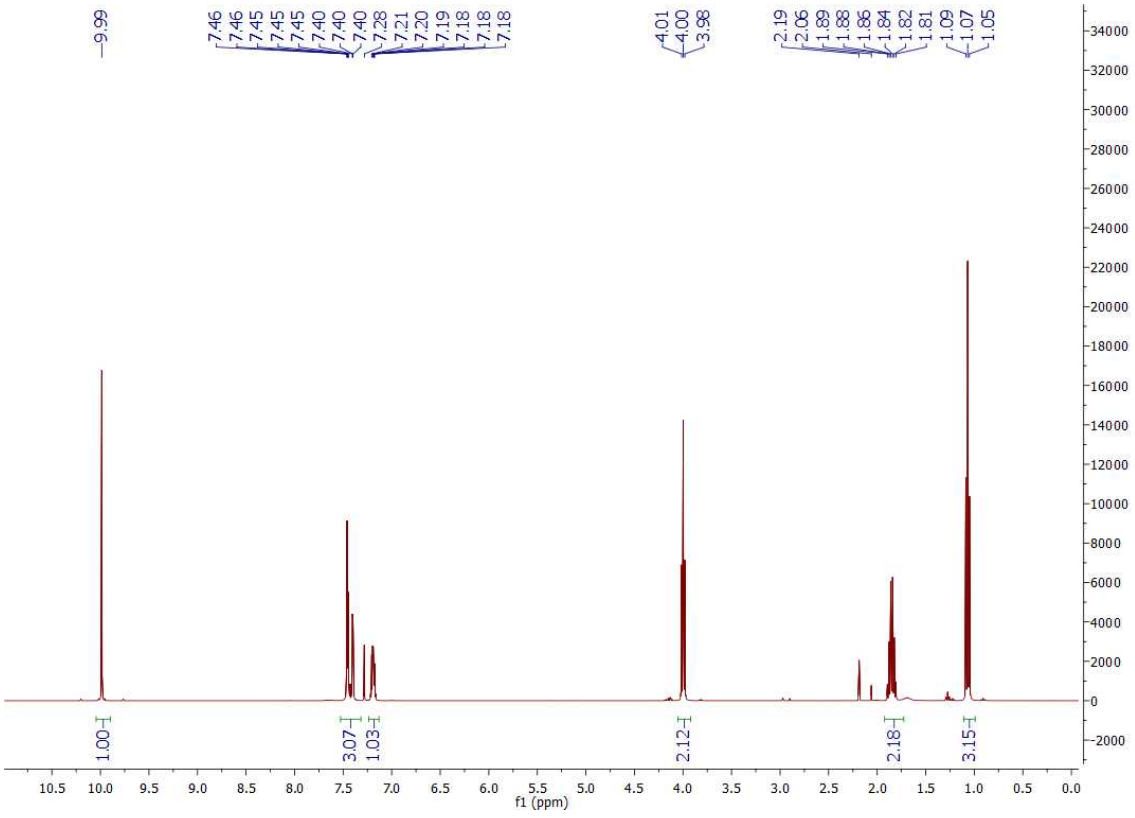
3-isopropoxybenzaldehyde (16b)



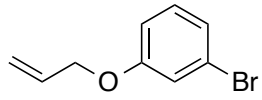


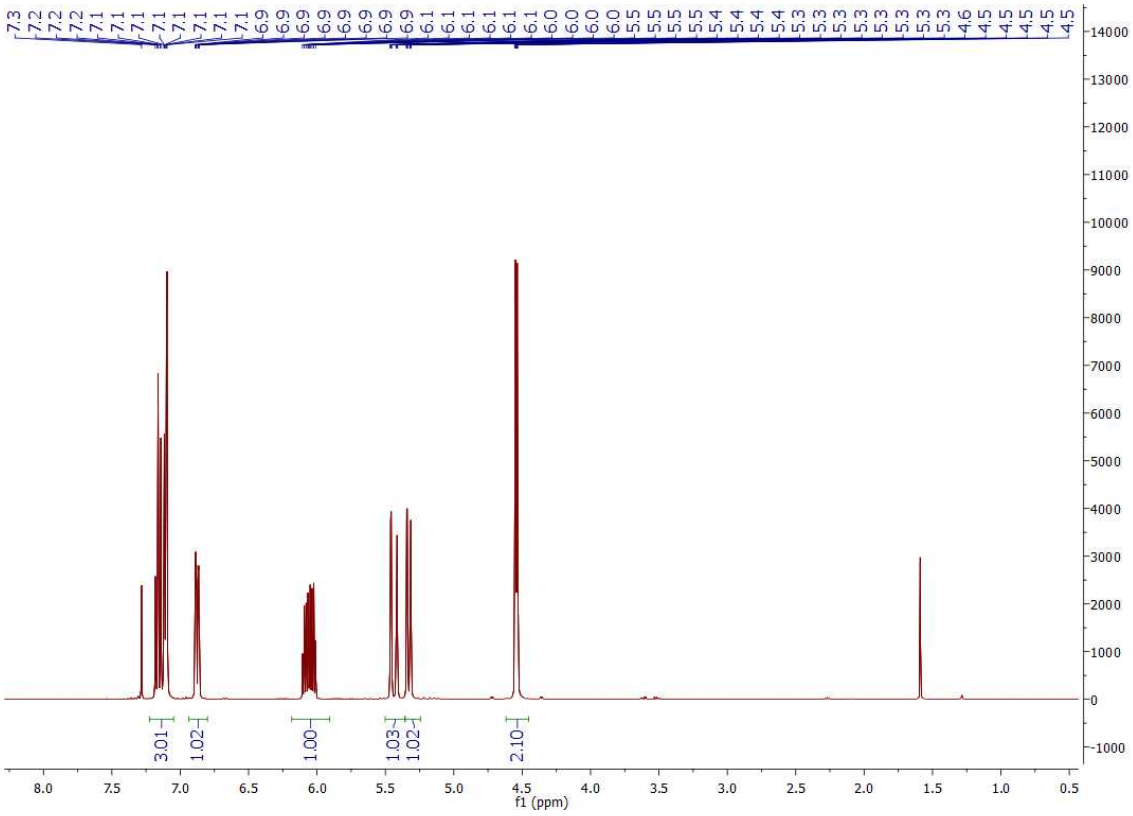
3-propoxybenzaldehyde (16c)





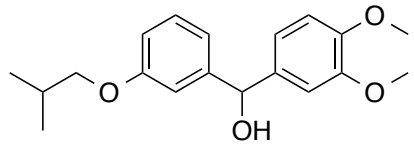
1-(allyloxy)-3-bromobenzene (19a).

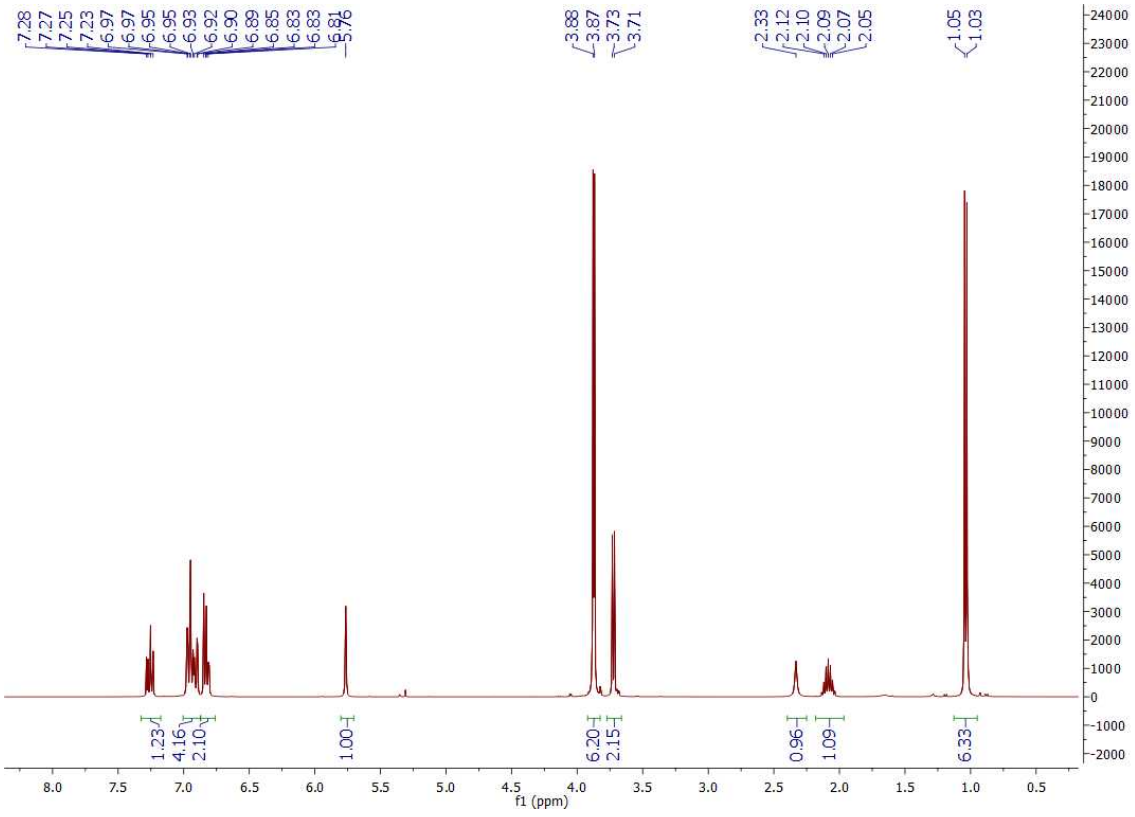


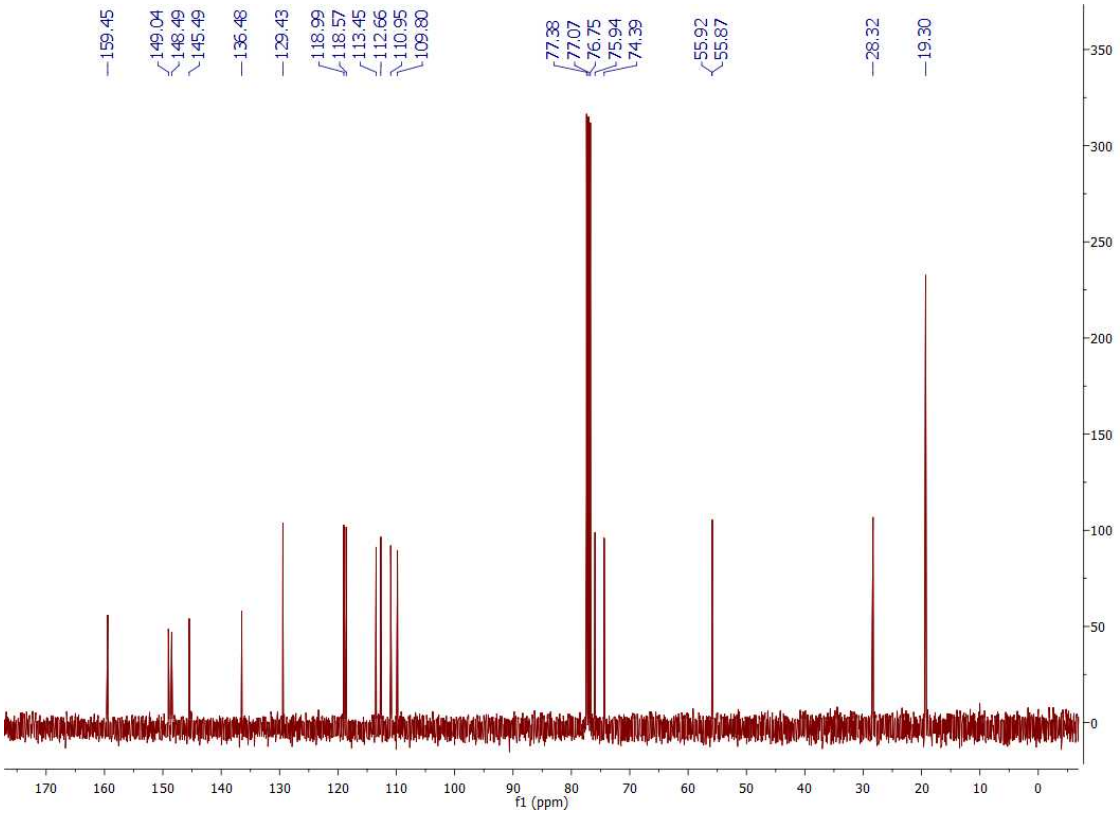


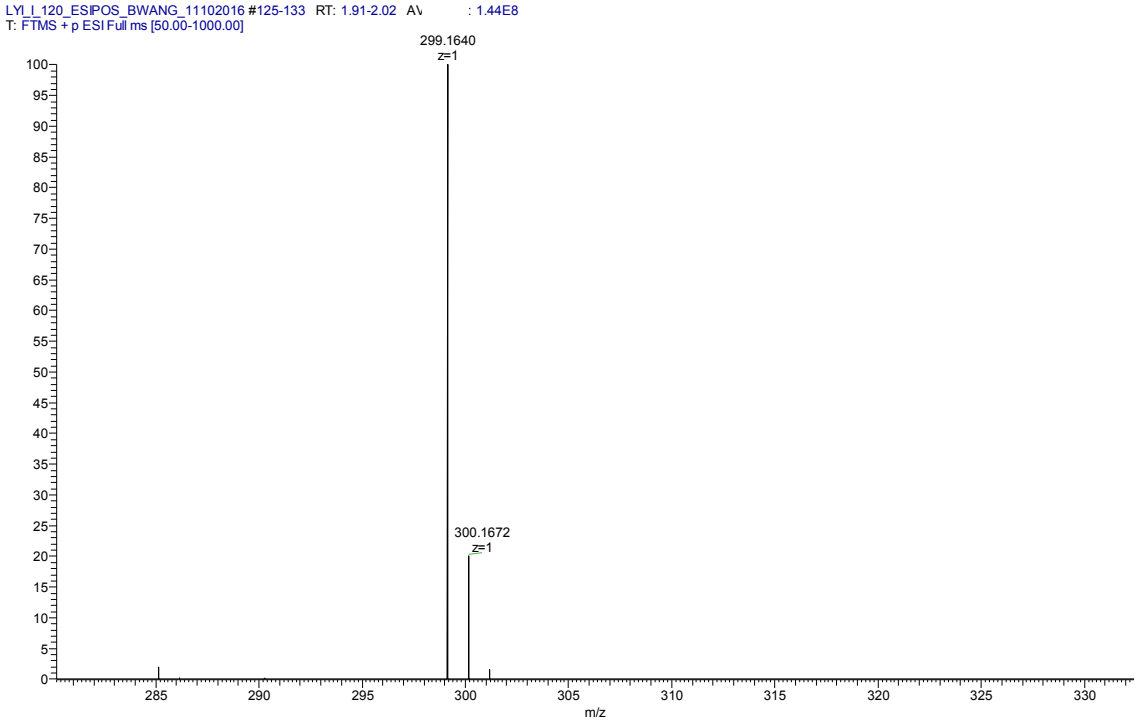
1-bromo-3-(hexyloxy)benzene (19b)*

(3,4-dimethoxyphenyl)(3-isobutoxyphenyl)methanol (17a)

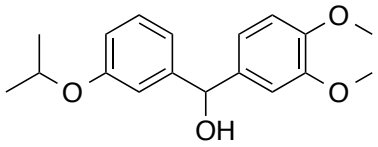


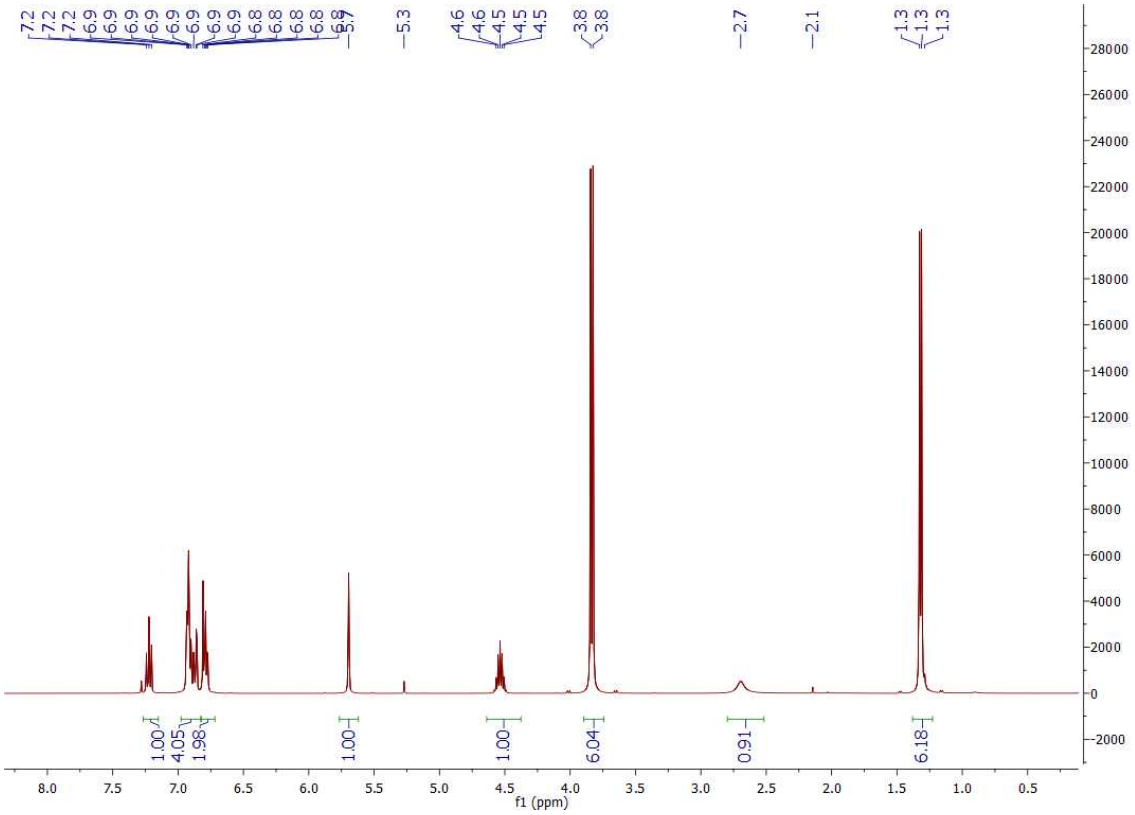


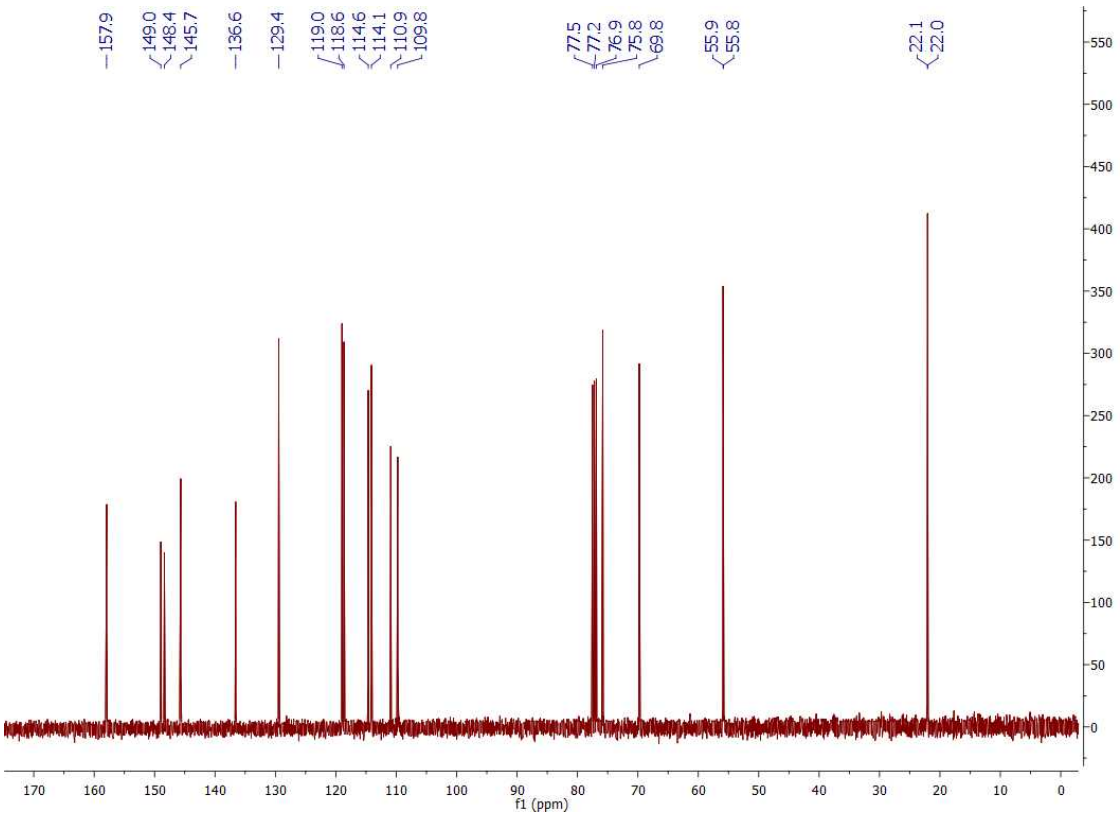

159.45
149.04
148.49
145.49
136.48
129.43
118.99
118.57
113.45
112.66
110.95
109.80
77.38
77.07
76.75
75.94
74.39
55.92
55.87
28.32
19.30
f1 (ppm)

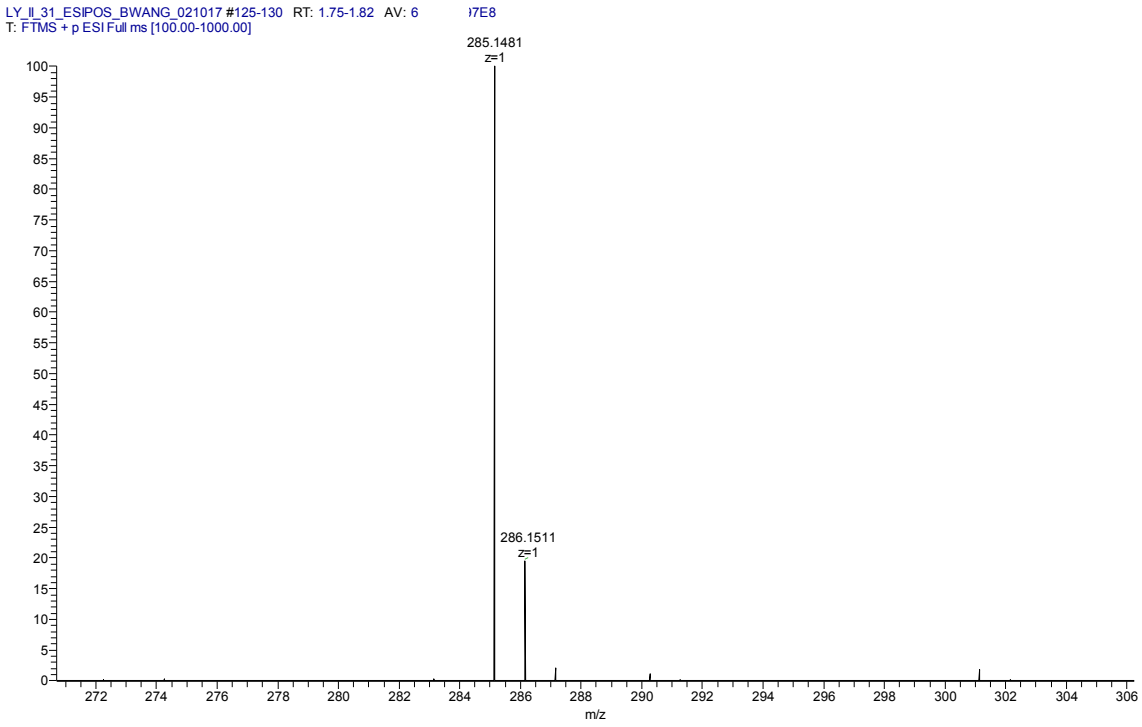

LYI_I_120_ESIPOS_BWANG_11102016 #125-133 RT: 1.91-2.02 AV : 1.44E8
T: FTMS + p ESI Full ms [50.00-1000.00]
299.1640
z=1
300.1672
z=1
m/z

(3,4-dimethoxyphenyl)(3-isopropoxyphenyl)methanol (17b)

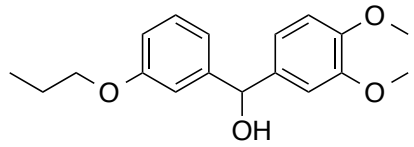


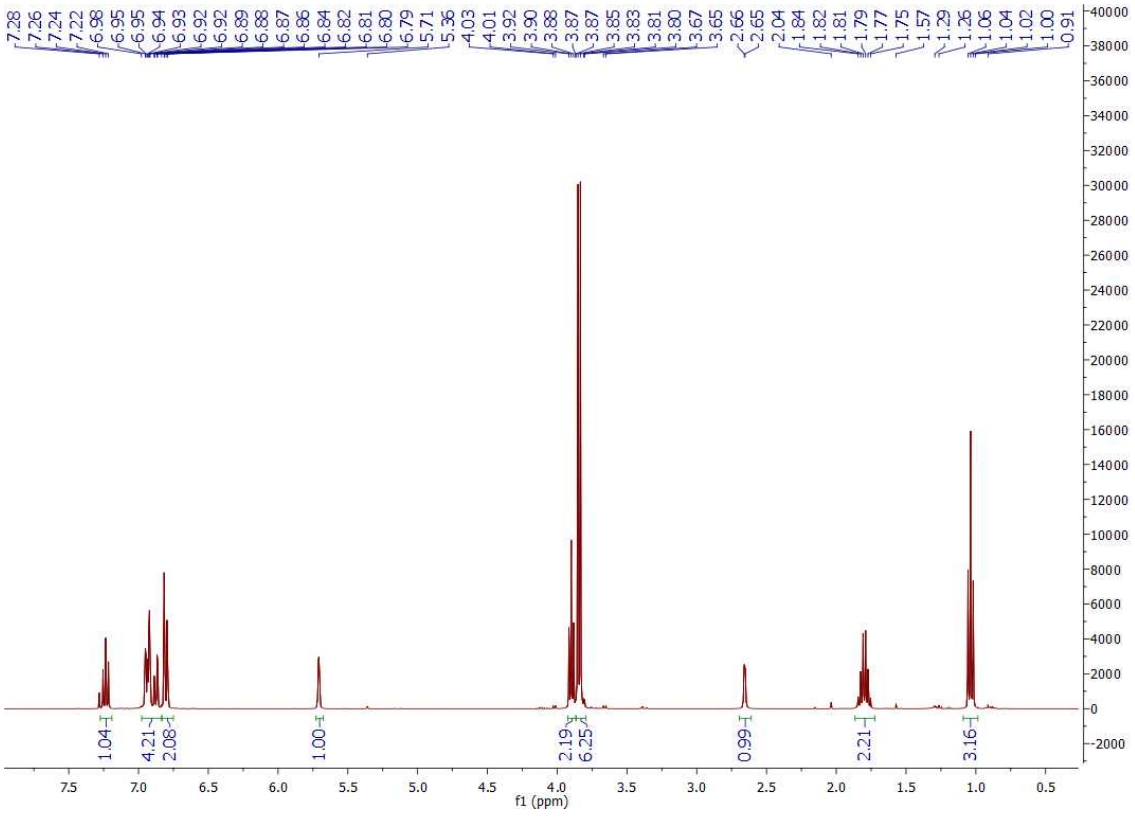


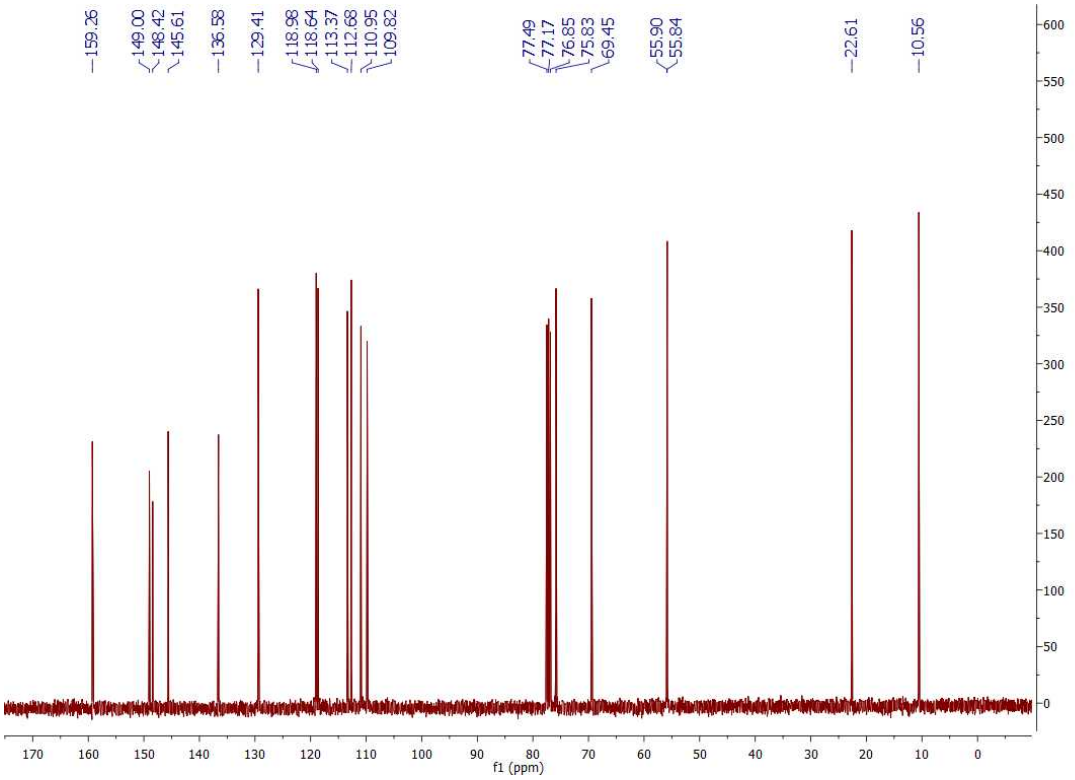

157.9
149.0
148.4
145.7
136.6
129.4
119.0
118.6
114.6
114.1
110.9
109.8
77.5
77.2
76.9
75.8
69.8
55.9
55.8
22.1
22.0
f1 (ppm)

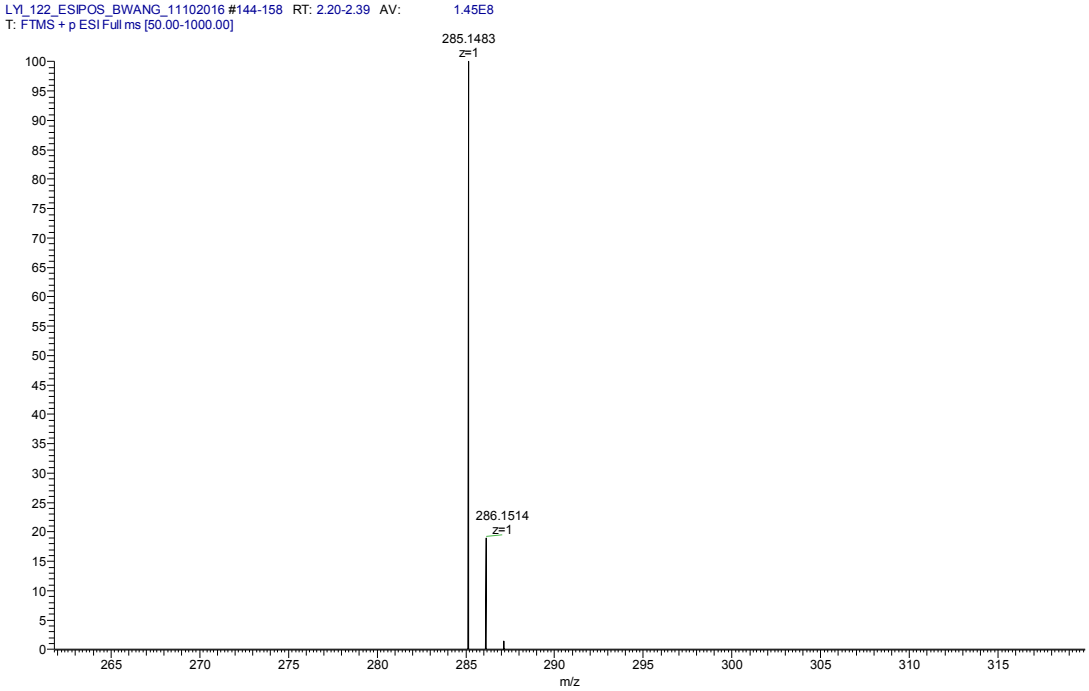

LY_II_31_ESIPOS_BWANG_021017 #125-130 RT: 1.75-1.82 AV: 6
T: FTMS + p ESI Full ms [100.00-1000.00]
285.1481
z=1
286.1511
z=1
m/z

(3,4-dimethoxyphenyl)(3-propoxyphenyl)methanol (17c)

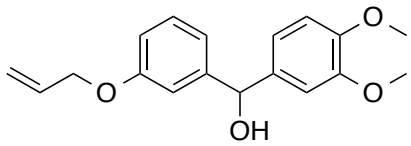


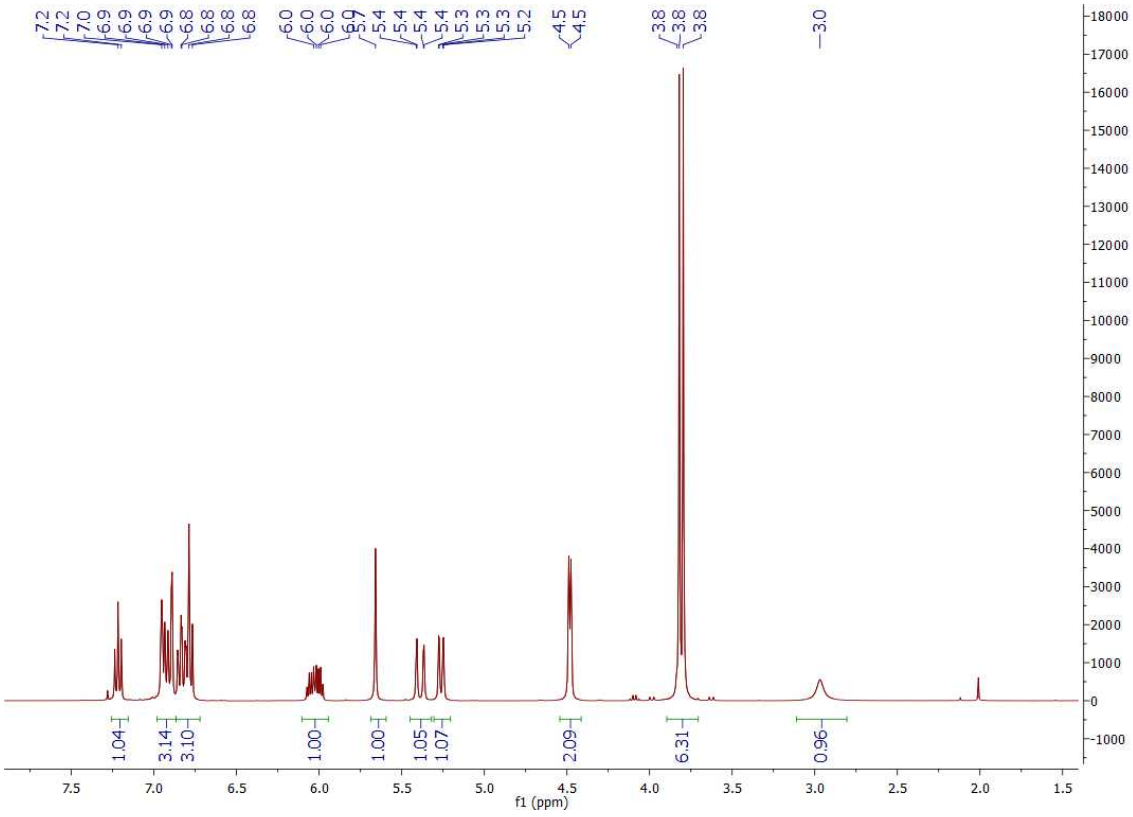


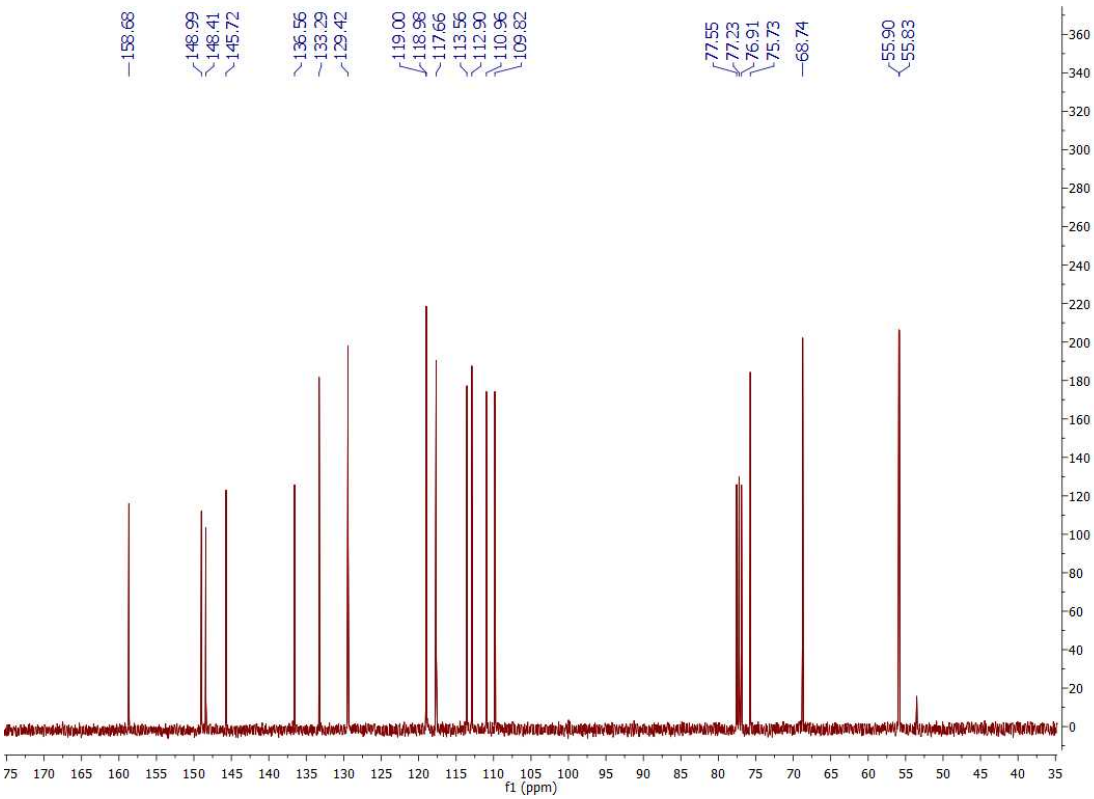

159.26
149.00
148.42
145.61
136.58
129.41
118.98
118.64
113.37
112.68
110.95
109.82
77.49
77.17
76.85
75.83
69.45
55.90
55.84
22.61
10.56
f1 (ppm)

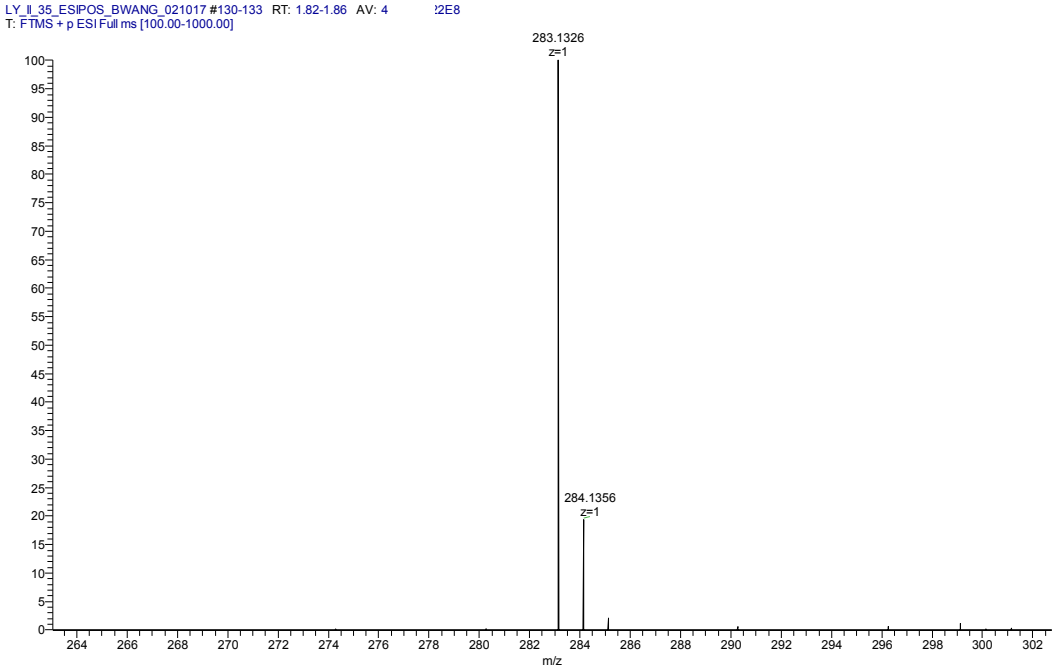

LYI_122_ESIPOS_BWANG_11102016 #144-158 RT: 2.20-2.39 AV: 1.45E8
T: FTMS + p ESI Full ms [50.00-1000.00]
285.1483
z=1
286.1514
z=1
m/z

(3-(allyloxy)phenyl)(3,4-dimethoxyphenyl)methanol (17d)





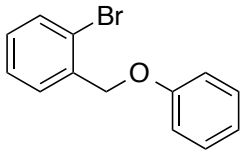

158.68
148.99
148.41
145.72
136.56
133.29
129.42
119.00
118.98
117.66
113.56
112.90
110.96
109.82
77.55
77.23
76.91
75.73
68.74
55.90
55.83
f1 (ppm)

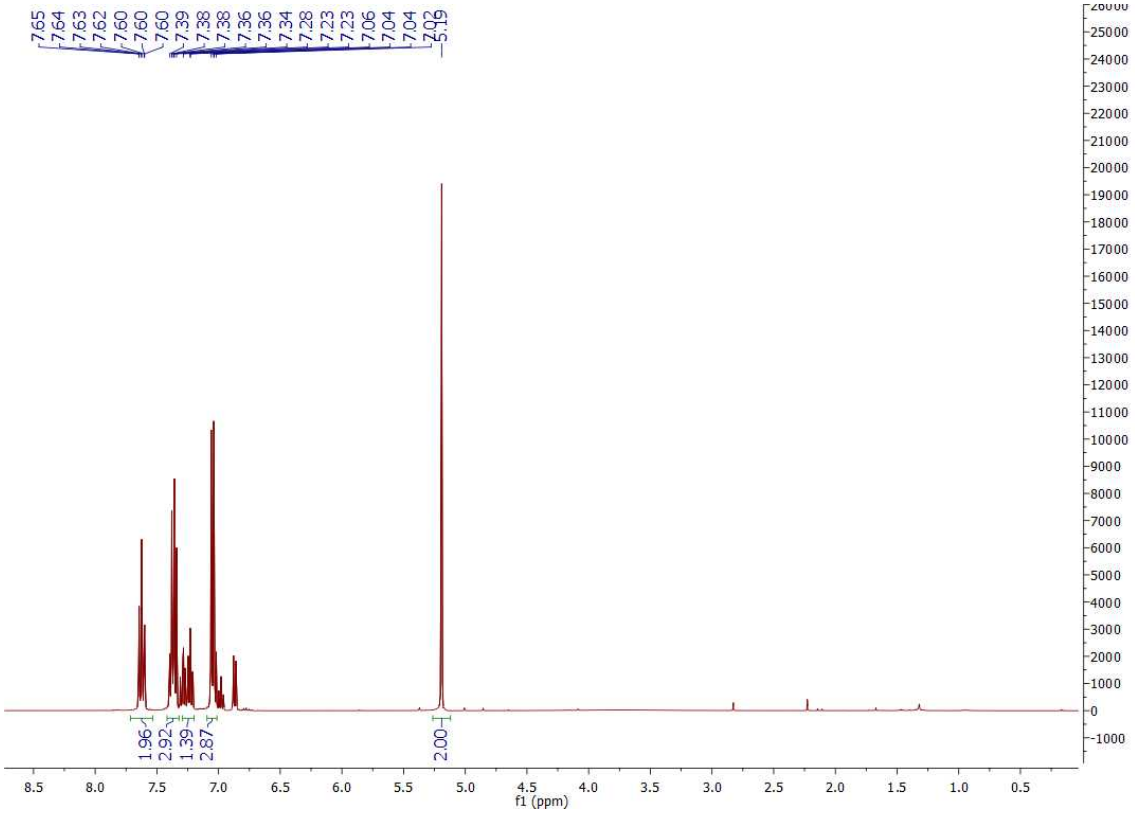

LY_II_35_ESIPOS_BWANG_021017 #130-133 RT: 1.82-1.86 AV: 4
T: FTMS + p ESI Full ms [100.00-1000.00]
283.1326
z=1
284.1356
z=1
m/z

(3,4-dimethoxyphenyl)(3-(hexyloxy)phenyl)methanol (17e)* Spectra will be in Jalisa Ferguson's information.

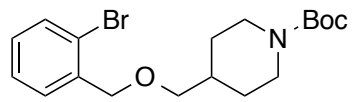
Class IV : *Ortho*-benzyl ether benzhydrol analogues.

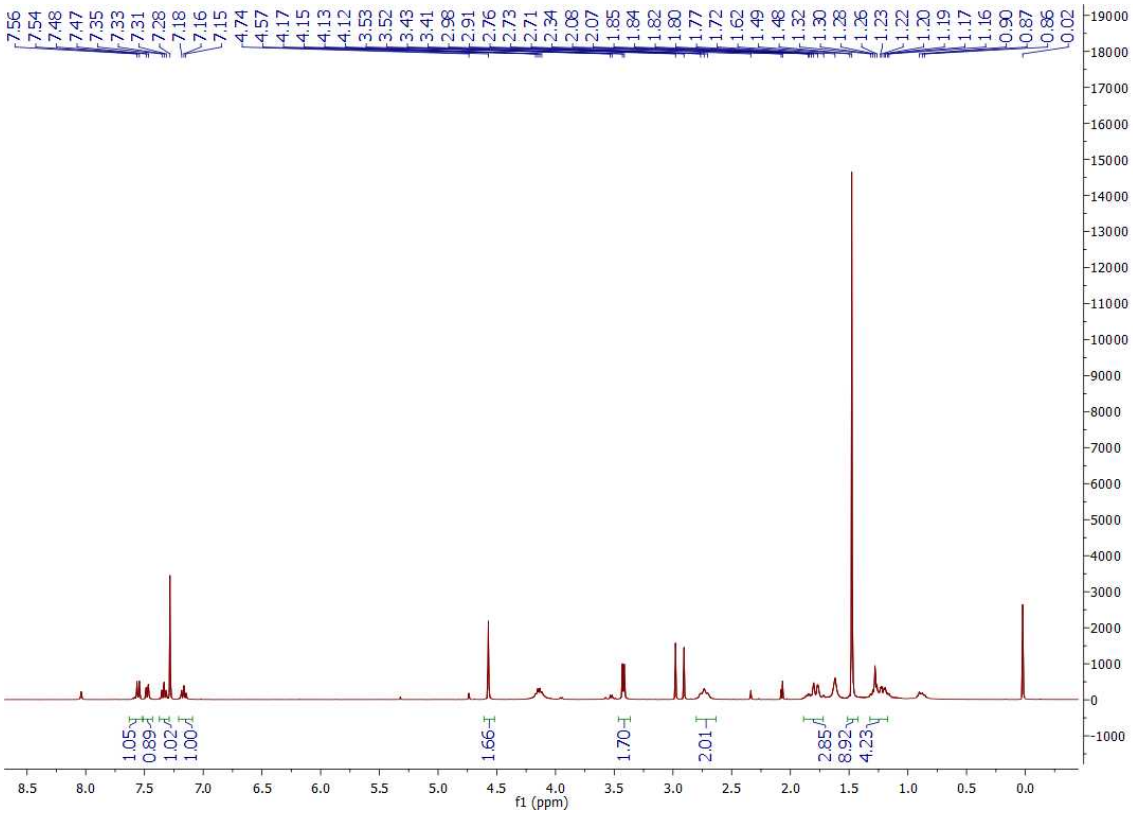
1-bromo-2-(phenoxymethyl)benzene (21a)



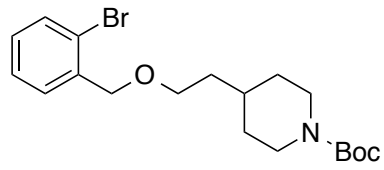


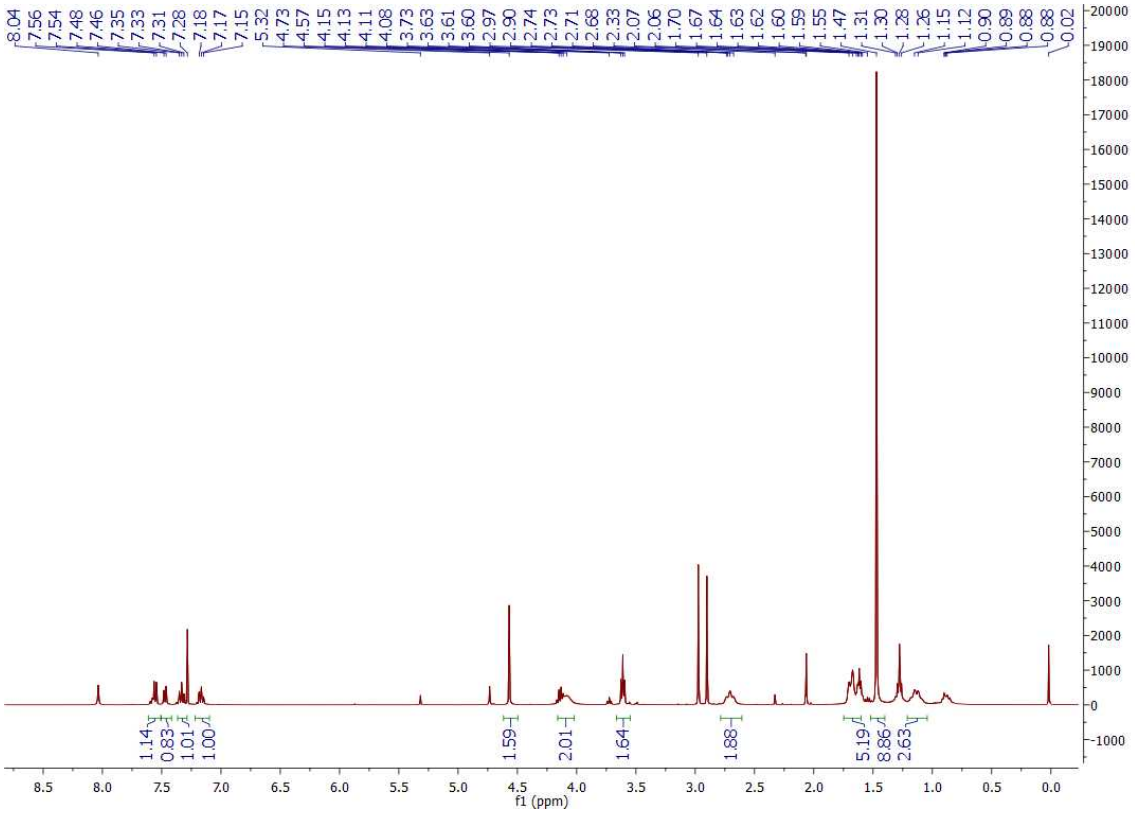
tert-butyl 4-(((2-bromobenzyl)oxy)methyl)piperidine-1-carboxylate (21b)



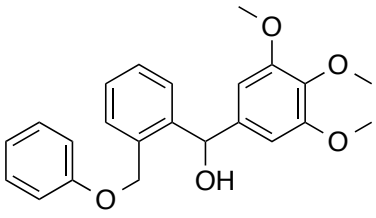


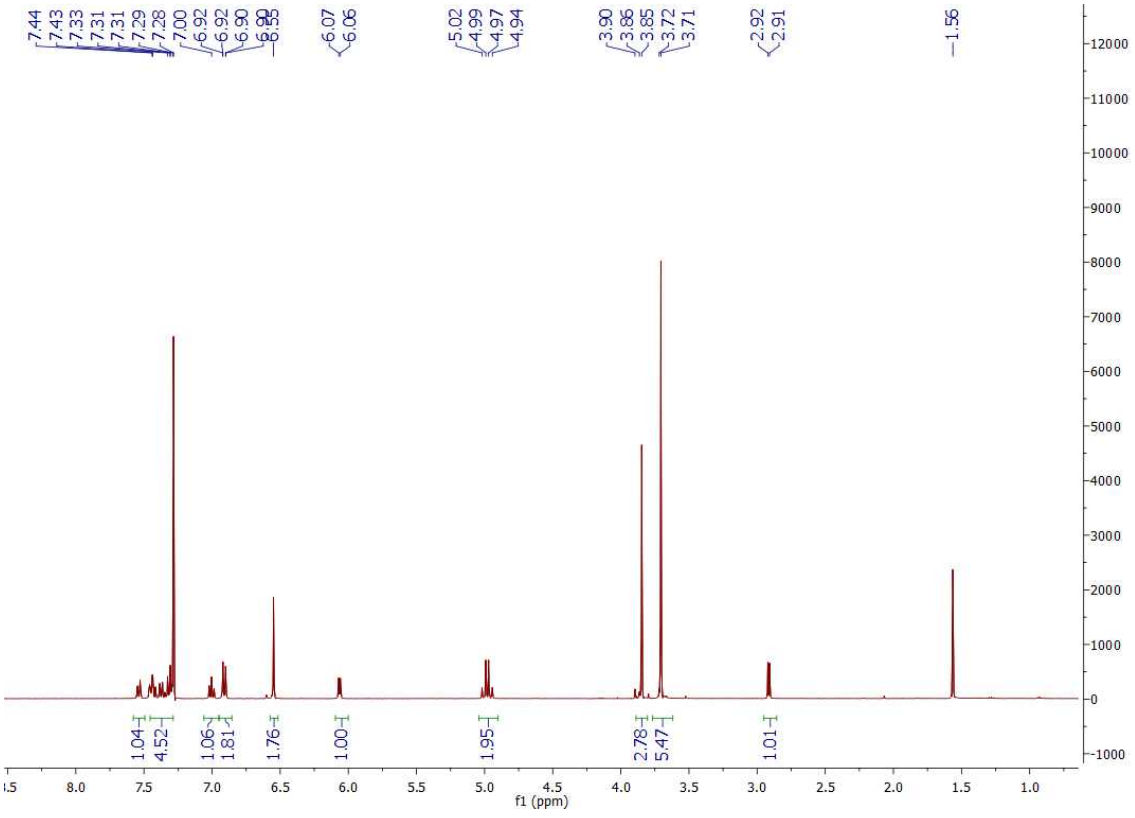
***tert*-butyl 4-(2-((2-bromobenzyl)oxy)ethyl)piperidine-1-carboxylate (21c)**





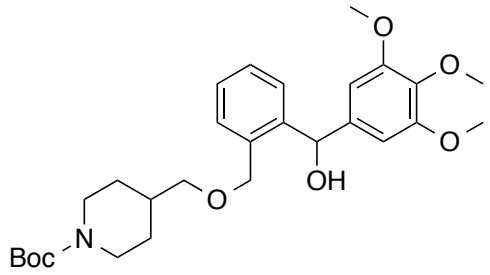
(2-(phenoxymethyl)phenyl)(3,4,5-trimethoxyphenyl)methanol (22a)*

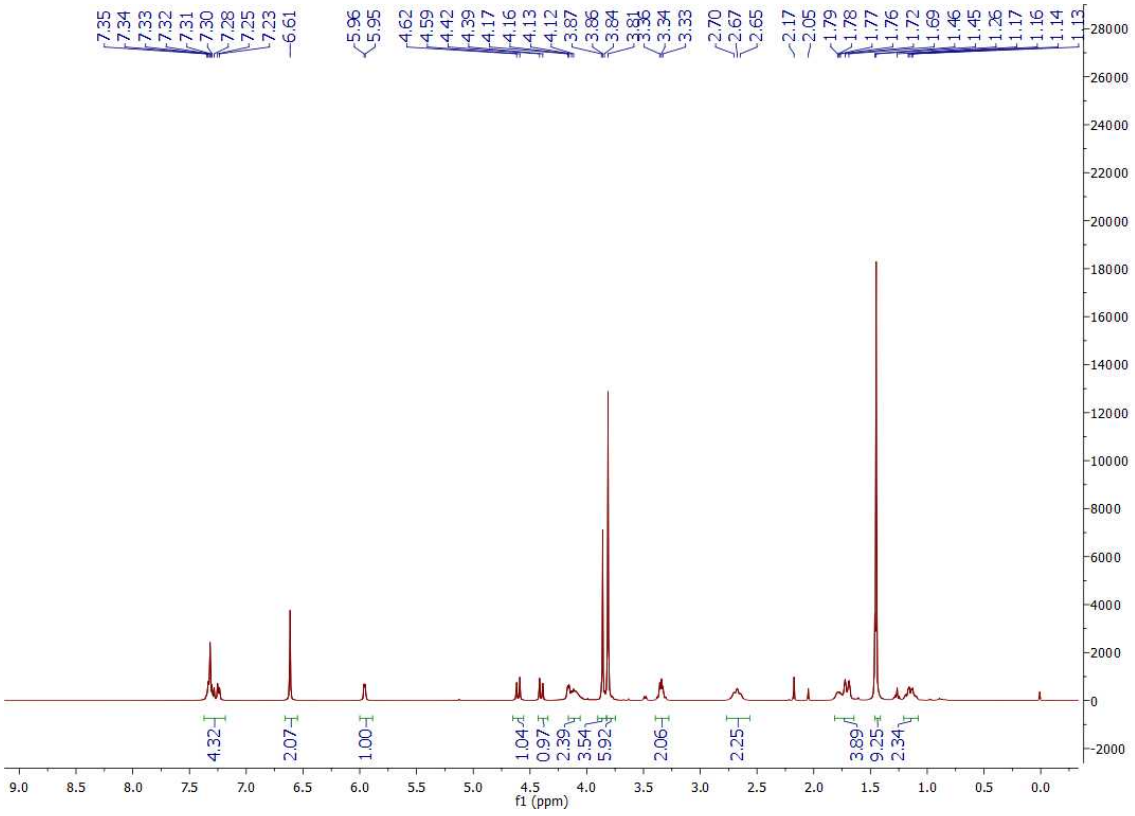


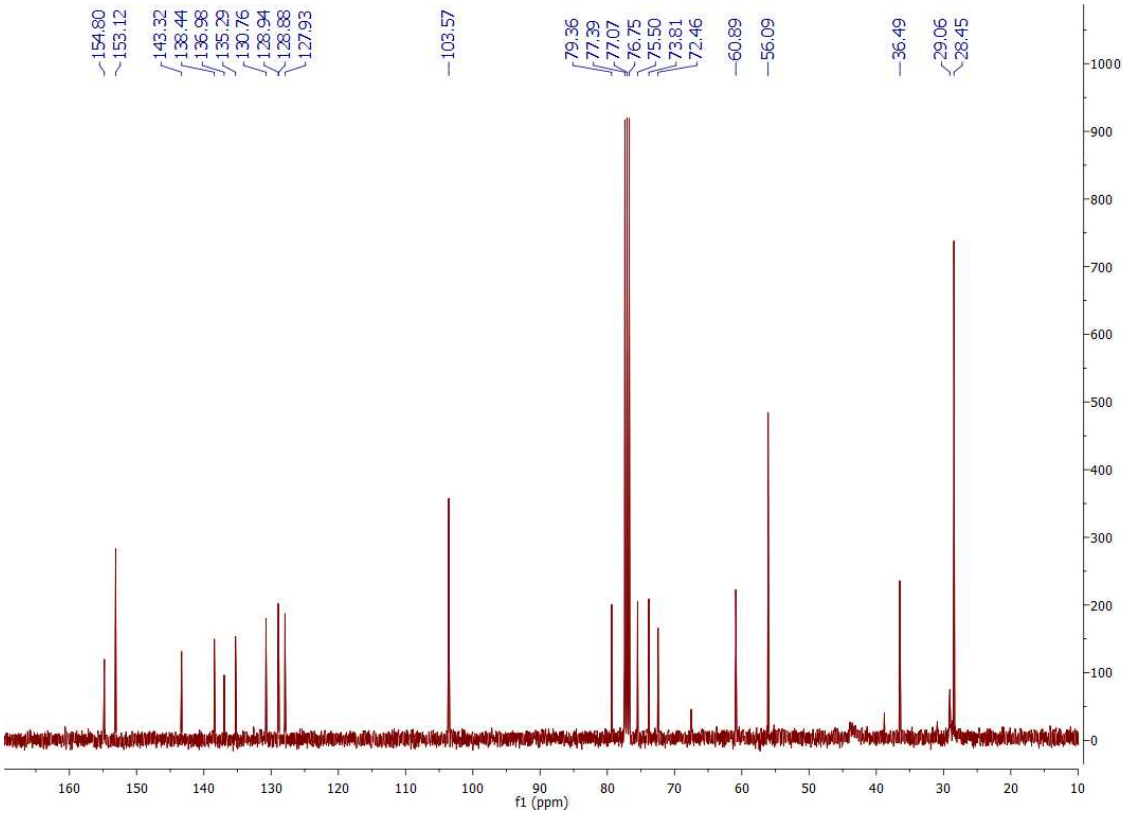


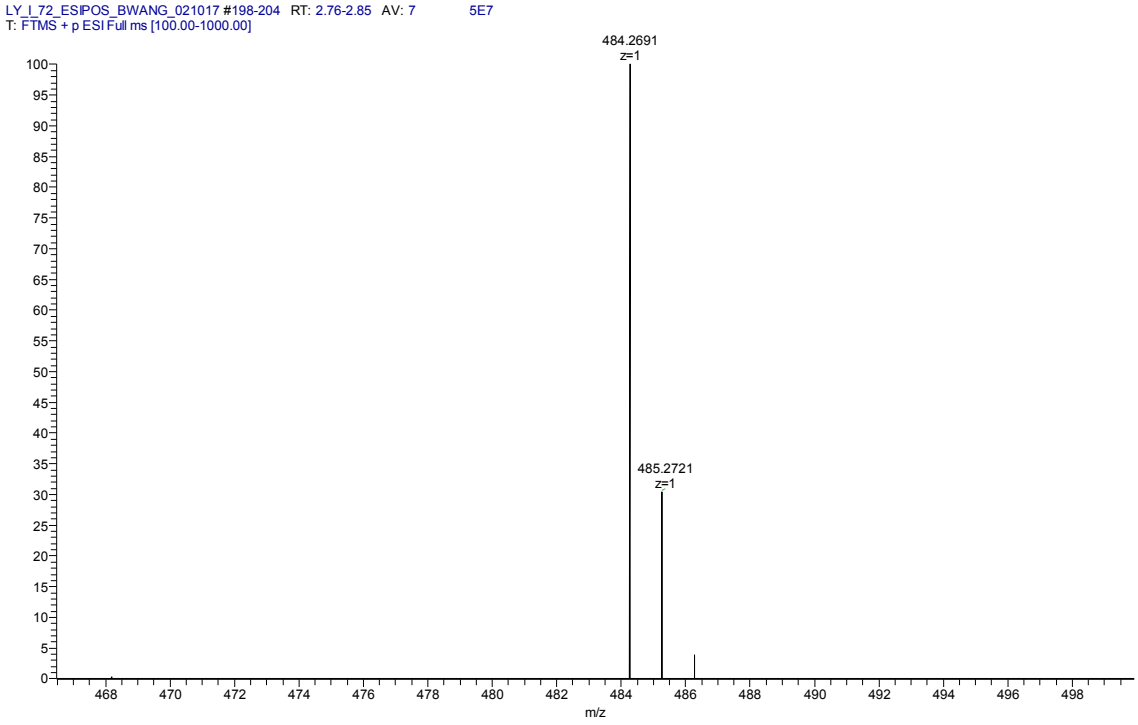
CNMR was obtained from Jalisa Holmes.

***tert*-butyl 4-(((2-(hydroxy(3,4,5-trimethoxyphenyl)methyl)benzyl)oxy)methyl)piperidine-1-carboxylate (22b)**

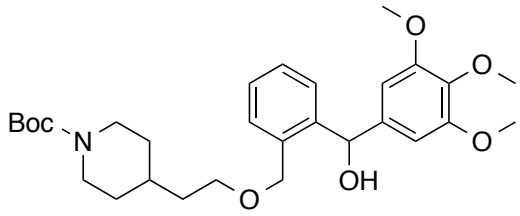


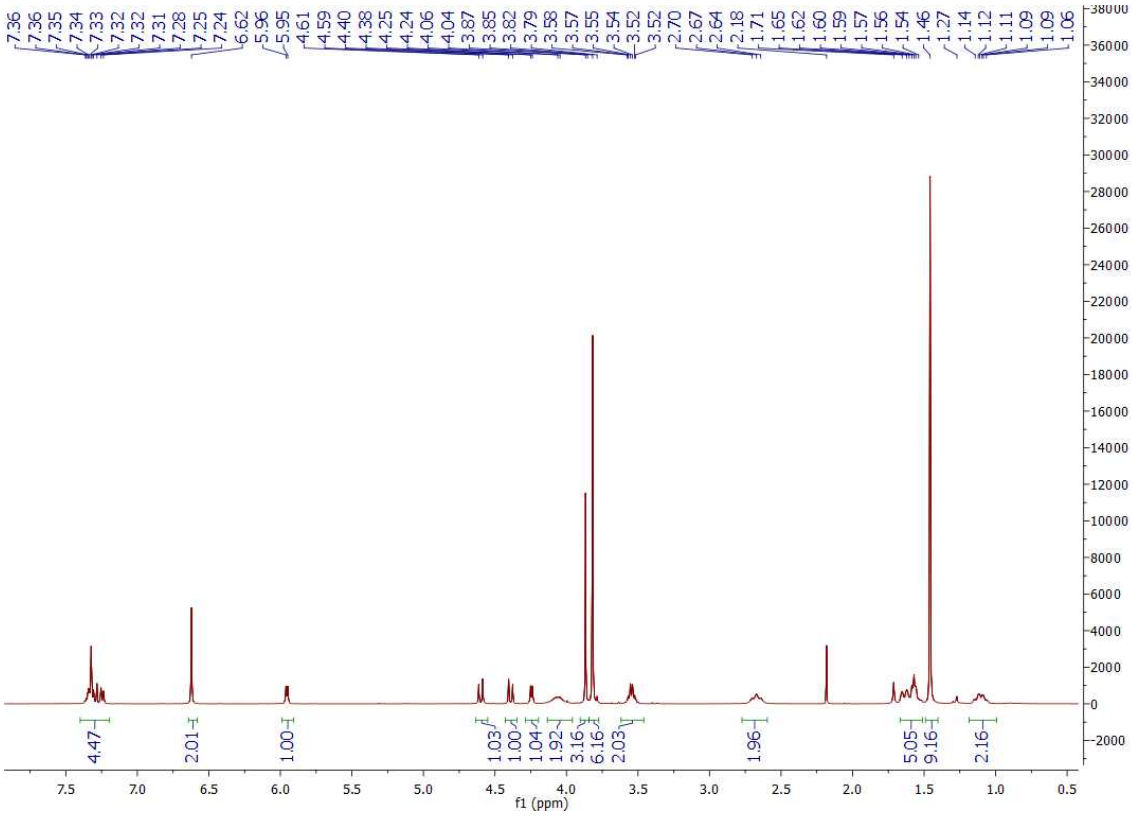


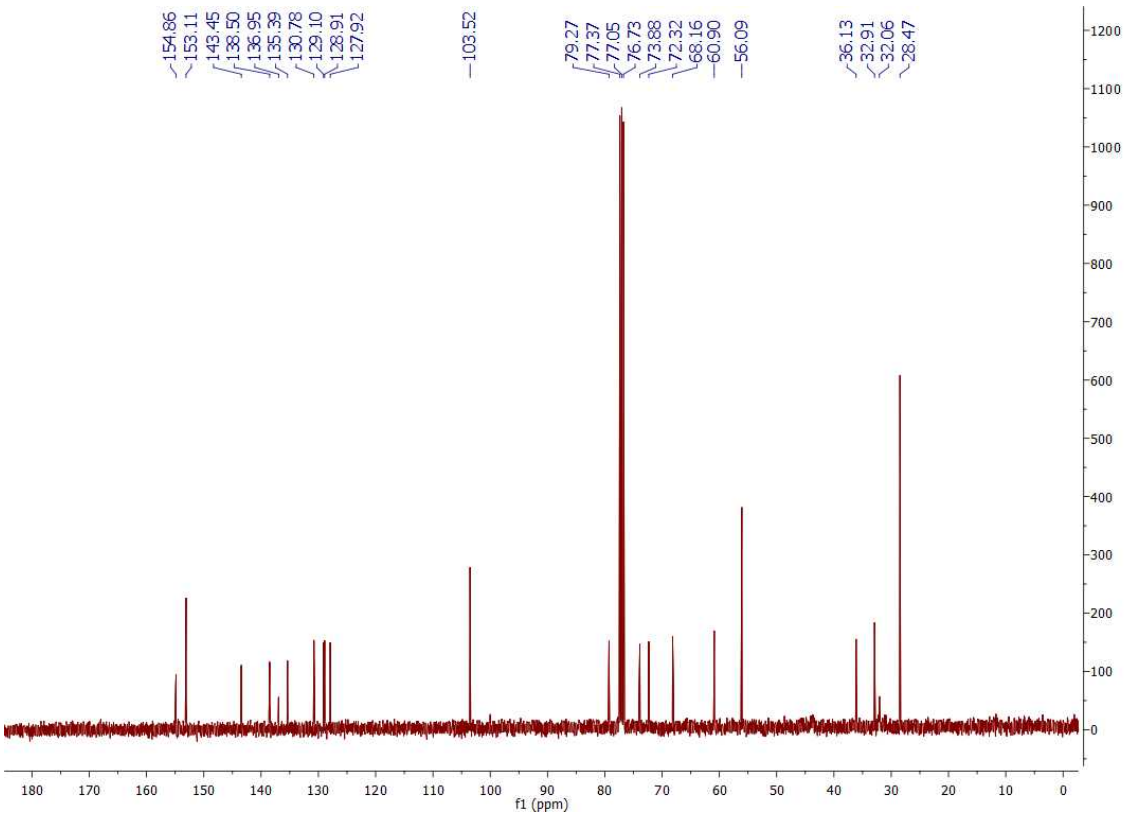

154.80
153.12
143.32
138.44
136.98
135.29
130.76
128.94
128.88
127.93
103.57
79.36
77.39
77.07
76.75
75.50
73.81
72.46
60.89
56.09
36.49
29.06
28.45
f1 (ppm)

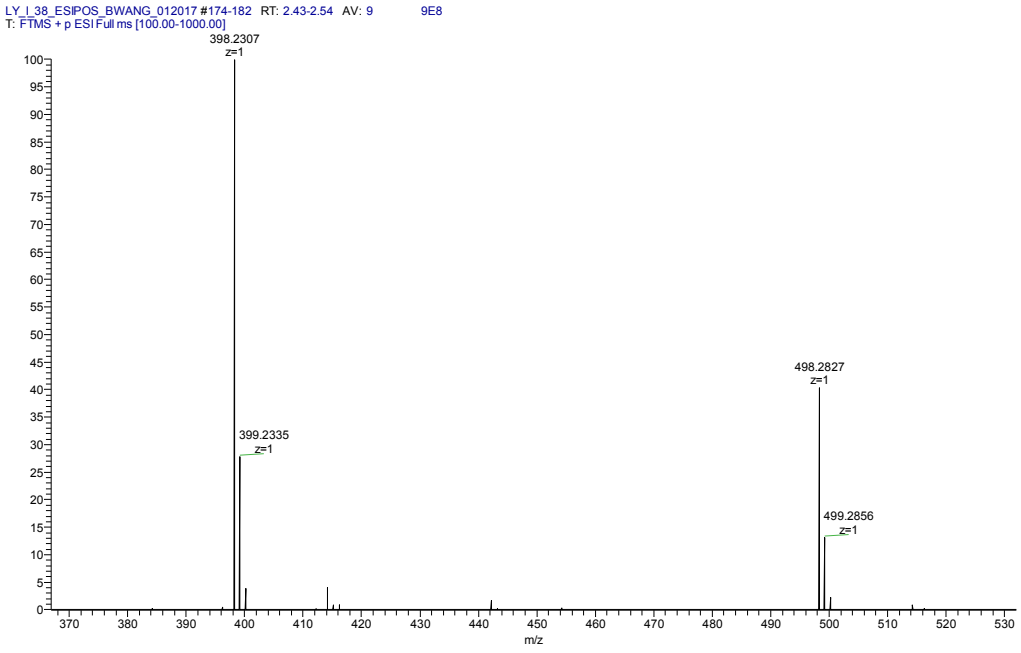

LY_I_72_ESIPOS_BWANG_021017 #198-204 RT: 2.76-2.85 AV: 7 5E7
T: FTMS + p ESI Full ms [100.00-1000.00]
484.2691
z=1
485.2721
z=1
m/z

tert-butyl 4-(2-((2-(hydroxy(3,4,5-trimethoxyphenyl)methyl)benzyl)oxy)ethyl)piperidine-1-carboxylate (22c)



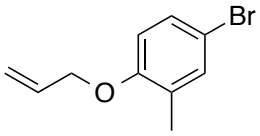


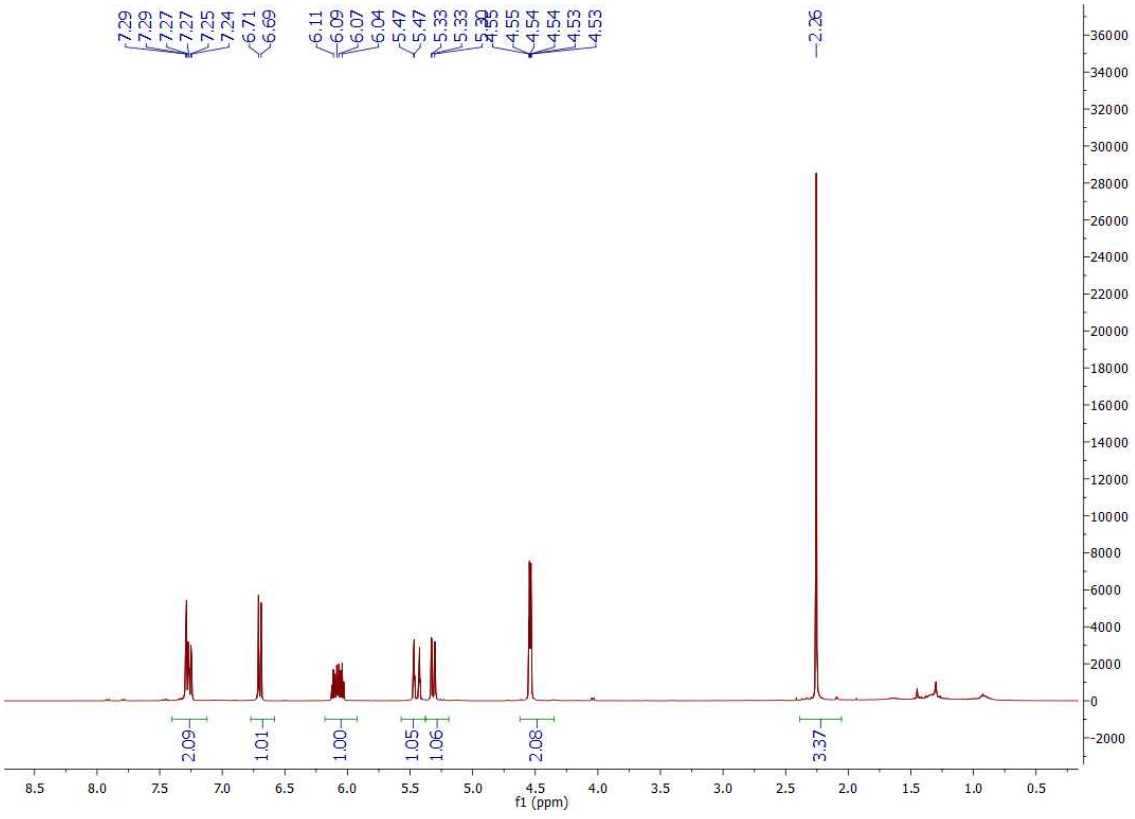

154.86
153.11
143.45
138.50
136.95
135.39
130.78
129.10
128.91
127.92
103.52
79.27
77.37
77.05
76.73
73.88
72.32
68.16
60.90
56.09
36.13
32.91
32.06
28.47
f1 (ppm)


LY_I_38_ESIPOS_BWANG_012017 #174-182 RT: 2.43-2.54 AV: 9 9E8
T: FTMS + p ESI Full ms [100.00-1000.00]
398.2307
z=1
399.2335
z=1
498.2827
z=1
499.2856
z=1
m/z

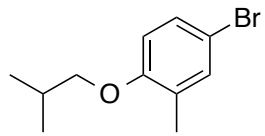
Class V: Tri-substituted phenolic ether benzhydrol analogues

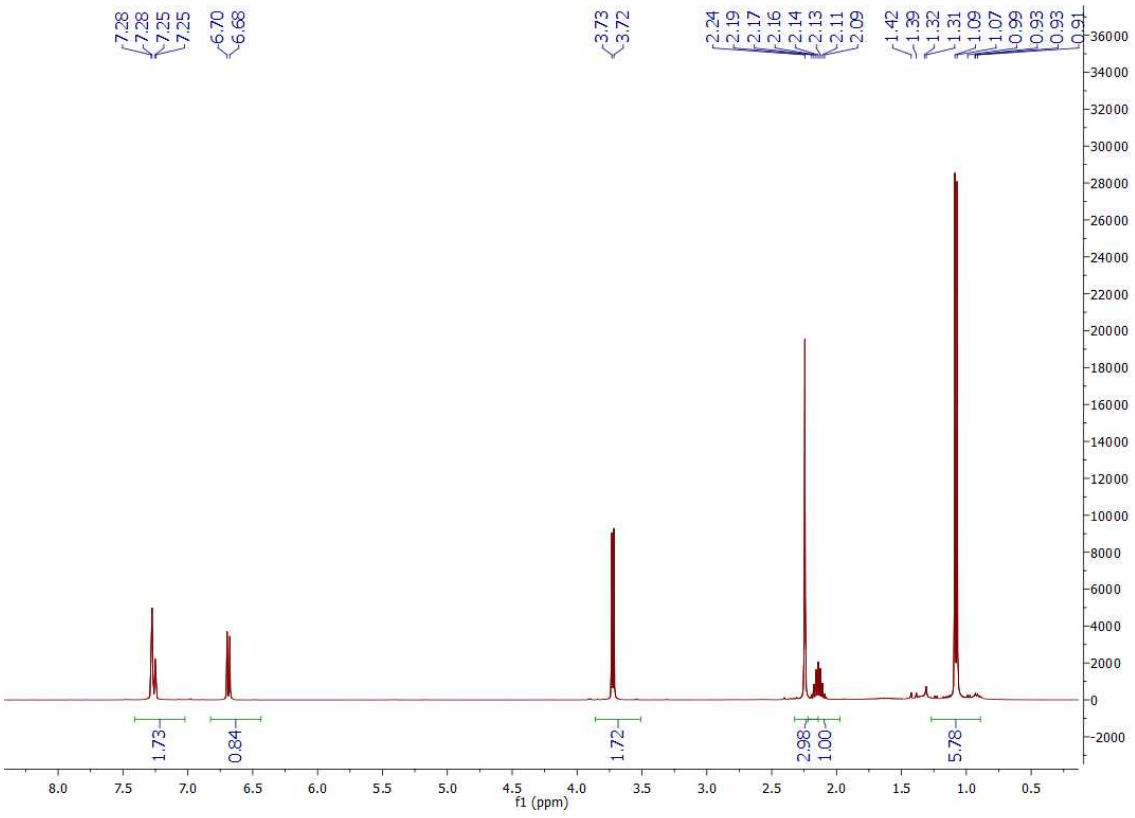
1-(allyloxy)-4-bromo-2-methylbenzene (24a)



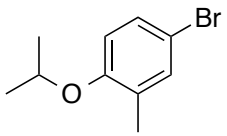


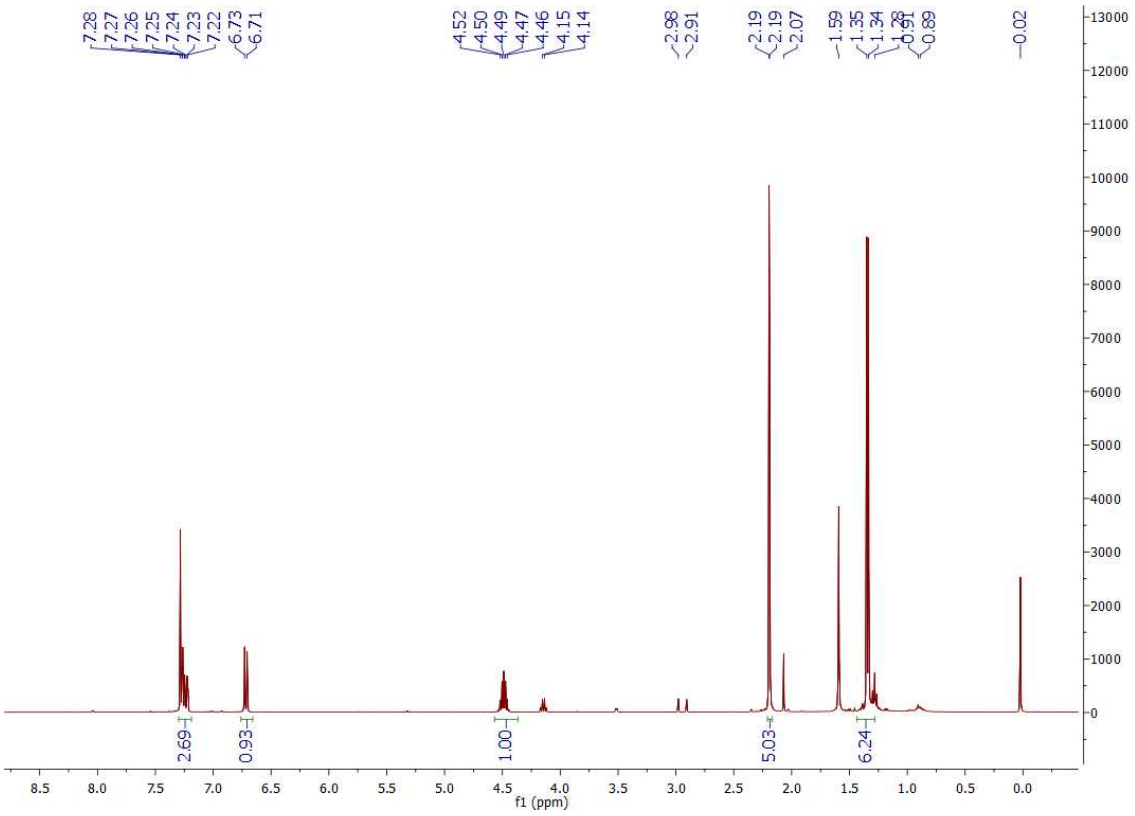
4-bromo-1-isobutoxy-2-methylbenzene (24b)



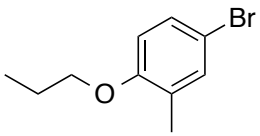


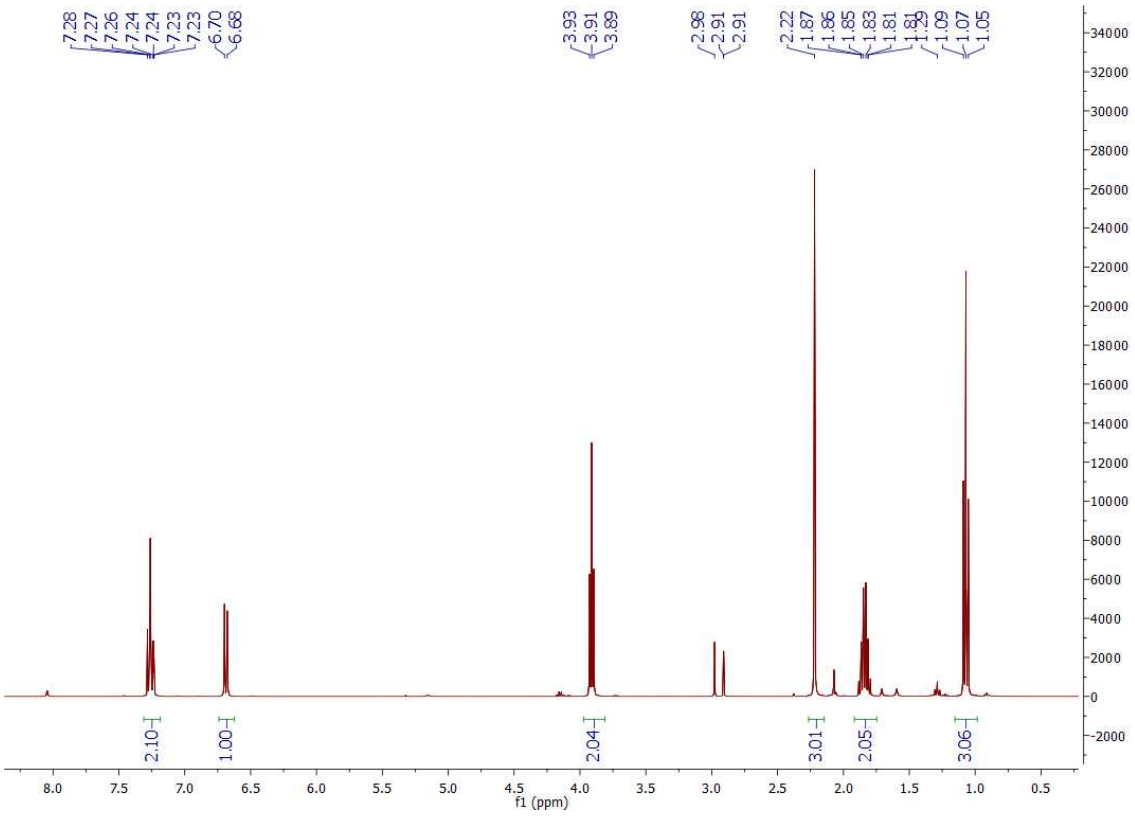
4-bromo-1-isopropoxy-2-methylbenzene (24c)



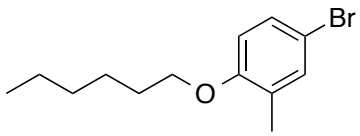


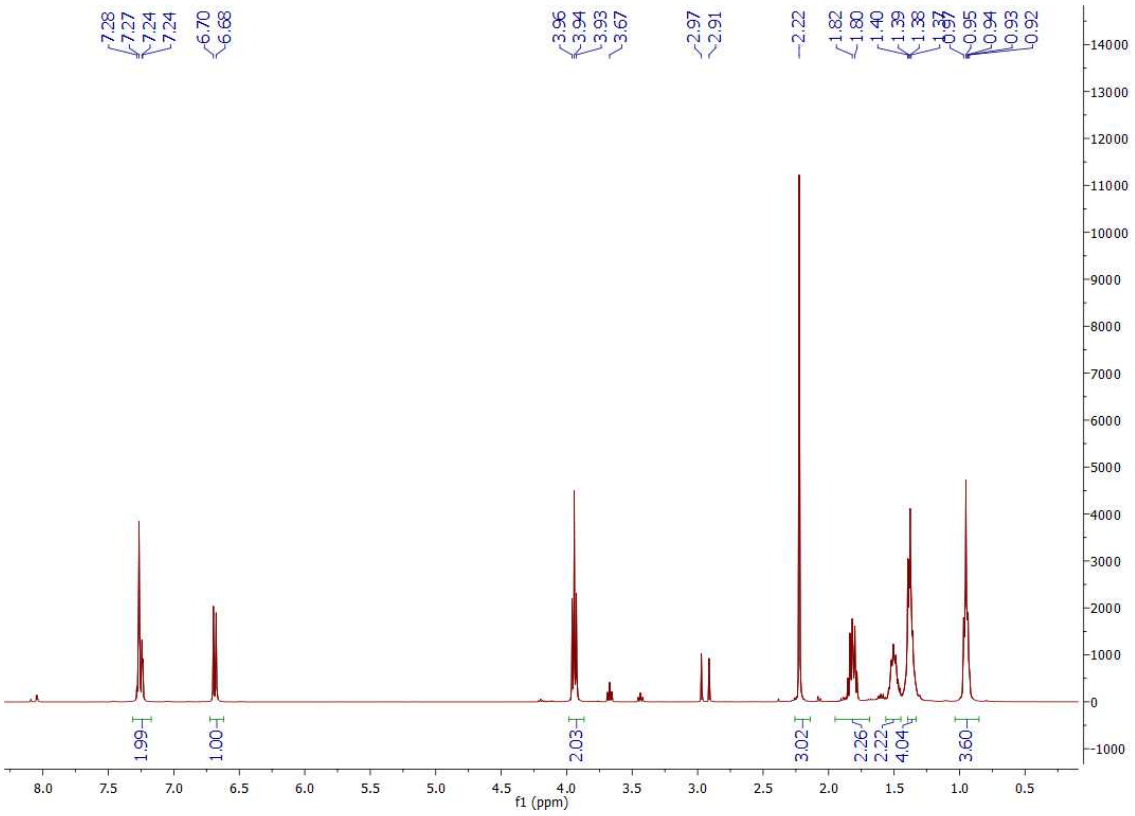
4-bromo-2-methyl-1-propoxybenzene (24d)



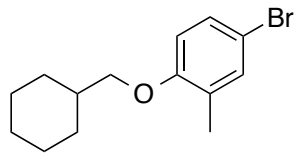


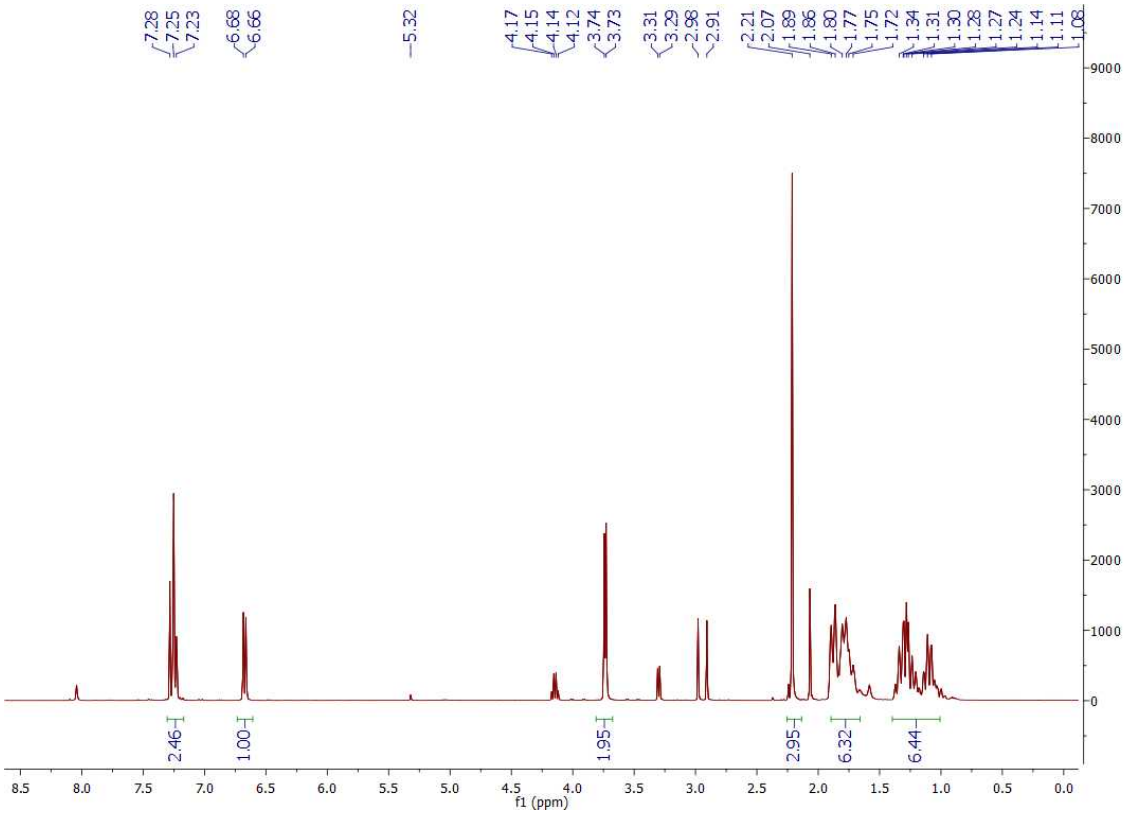
4-bromo-1-(hexyloxy)-2-methylbenzene (24e)



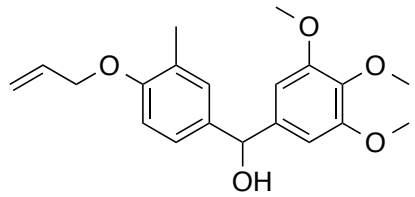


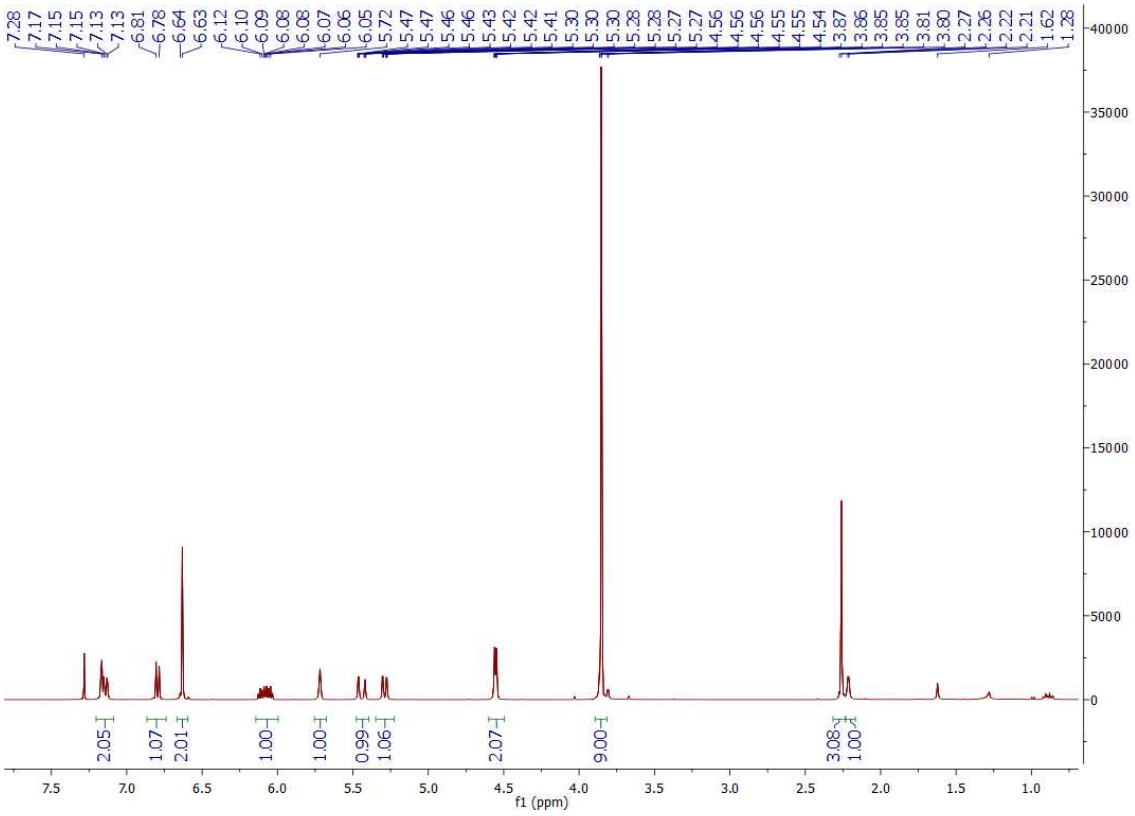
4-bromo-1-(cyclohexylmethoxy)-2-methylbenzene (24f)

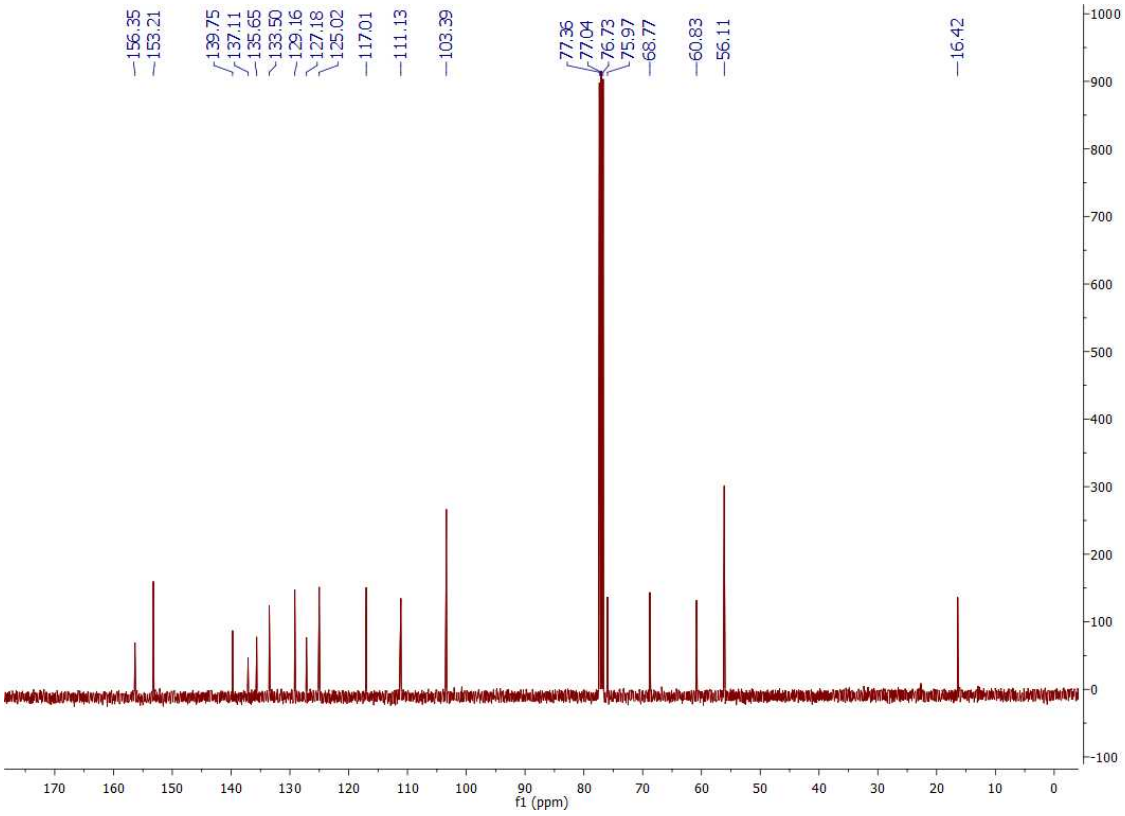


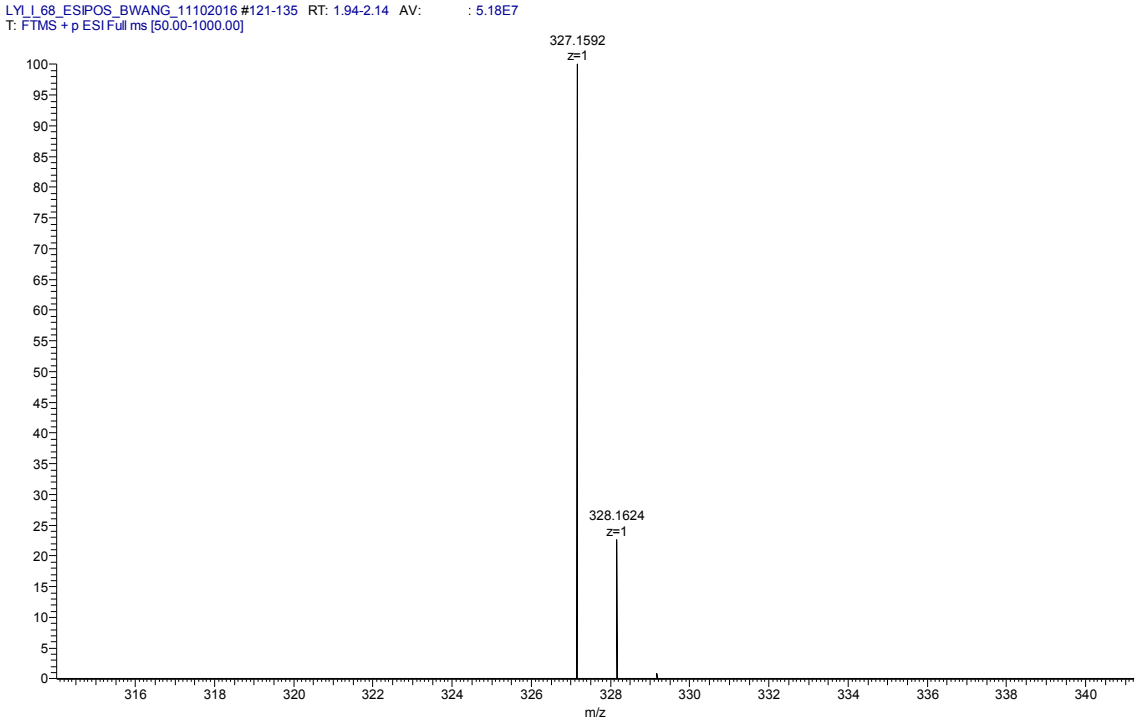


(4-(allyloxy)-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25a)

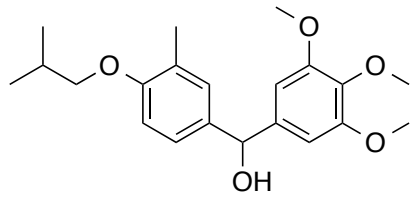


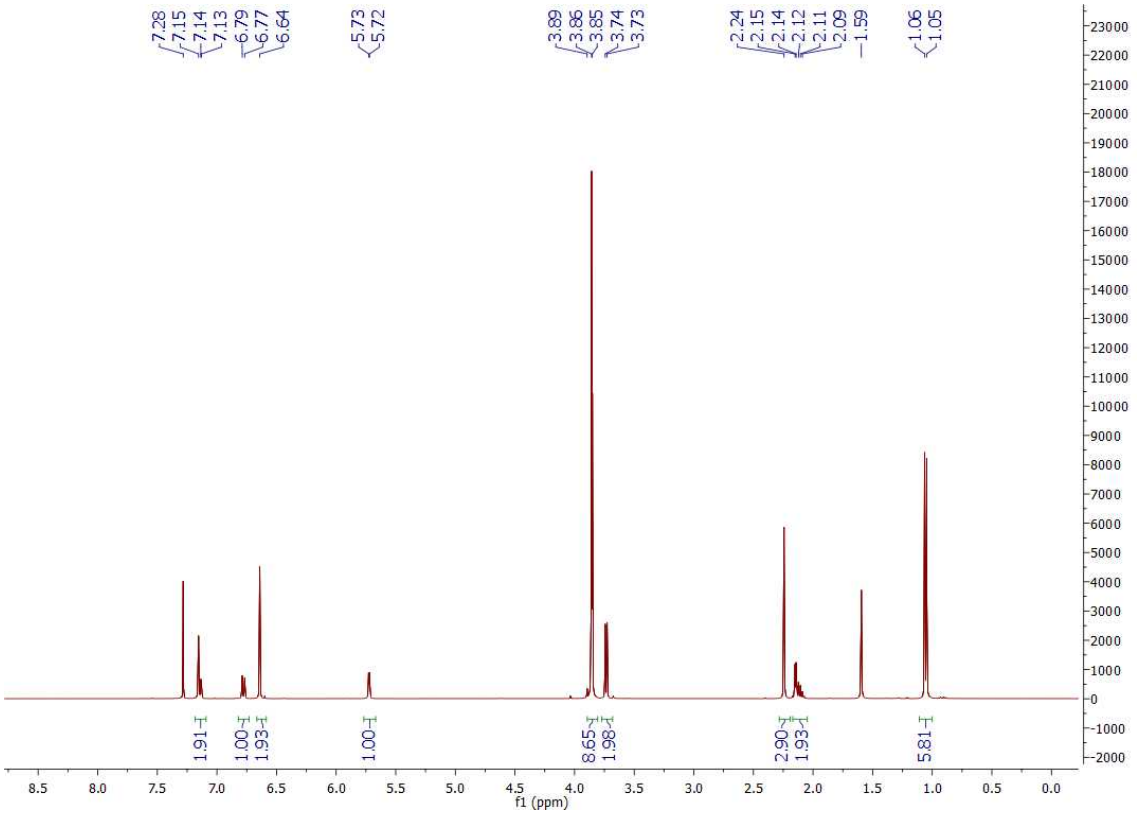


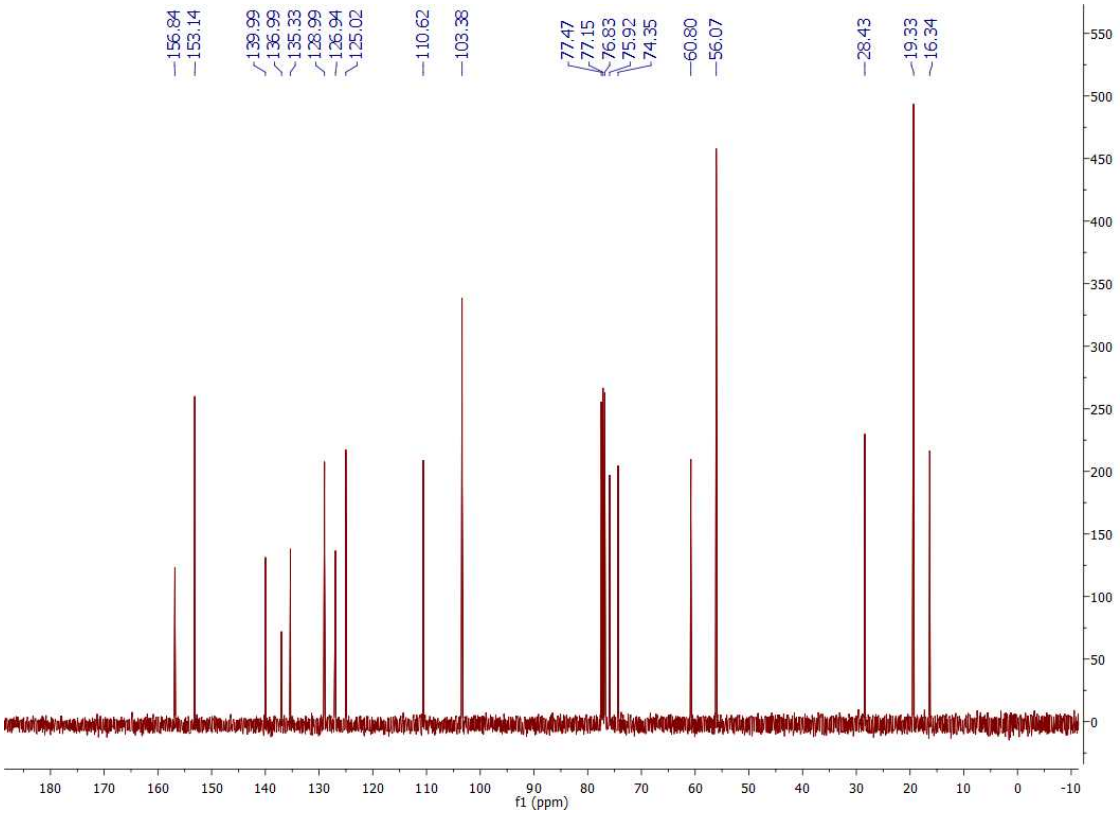

156.35
153.21
139.75
137.11
135.65
133.50
129.16
127.18
125.02
117.01
111.13
103.39
77.36
77.04
76.73
75.97
68.77
60.83
56.11
16.42
f1 (ppm)

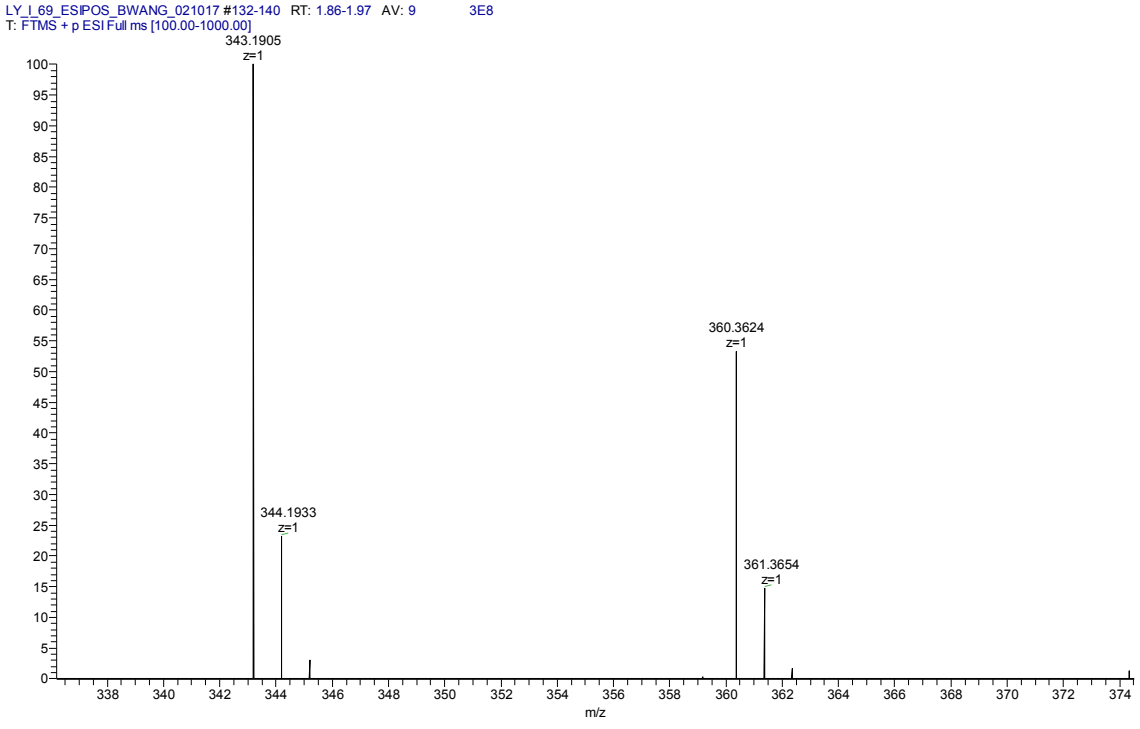

LYI_I_68_ESIPOS_BWANG_11102016 #121-135 RT: 1.94-2.14 AV: : 5.18E7
T: FTMS + p ESI Full ms [50.00-1000.00]
327.1592
z=1
328.1624
z=1
m/z

(4-isobutoxy-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25b)

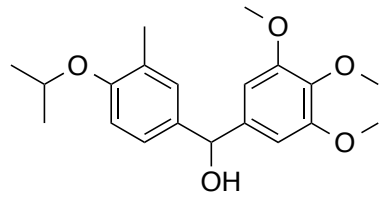


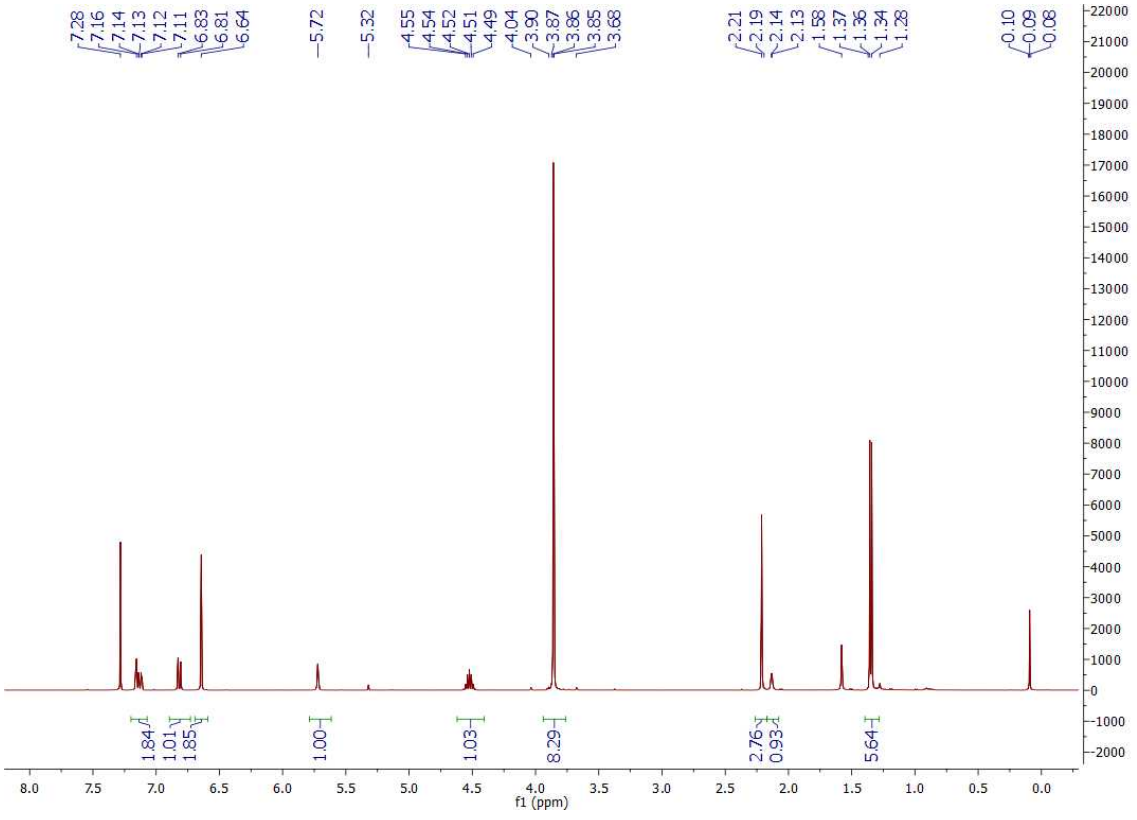


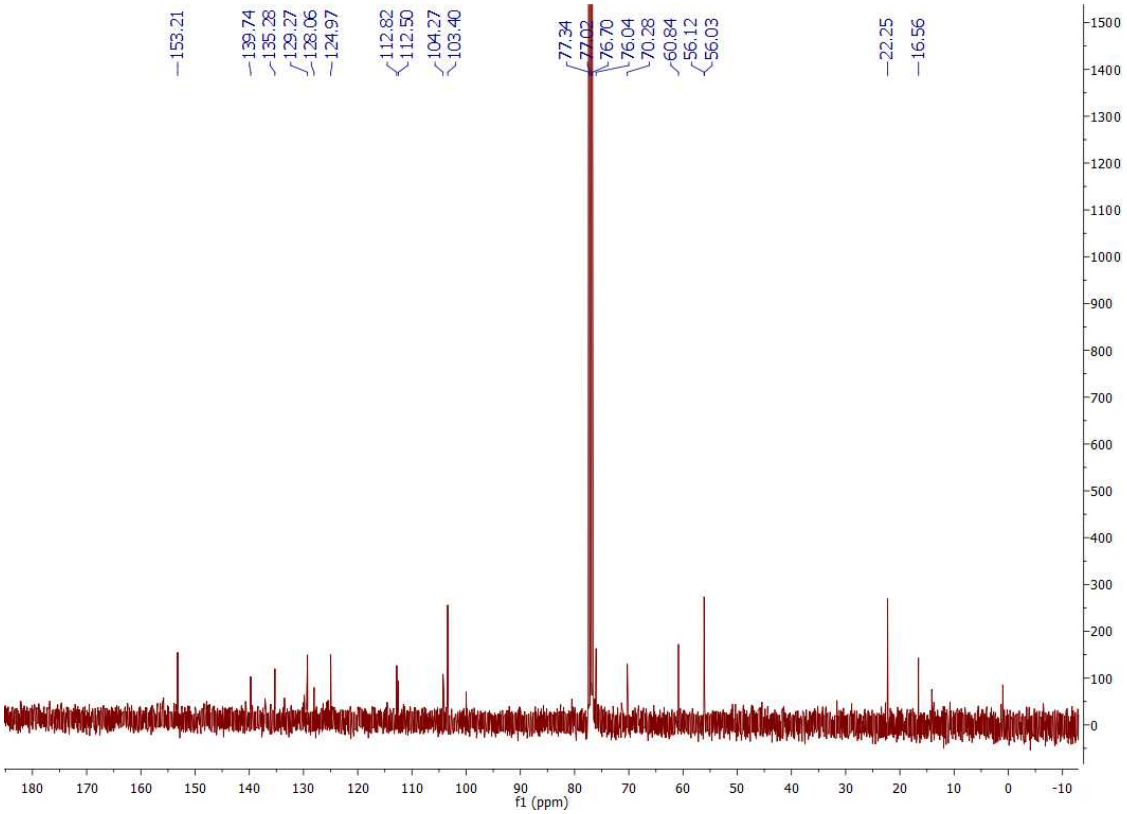

156.84
153.14
139.99
136.99
135.33
128.99
126.94
125.02
110.62
103.38
77.47
77.15
76.83
75.92
74.35
60.80
56.07
28.43
19.33
16.34
f1 (ppm)

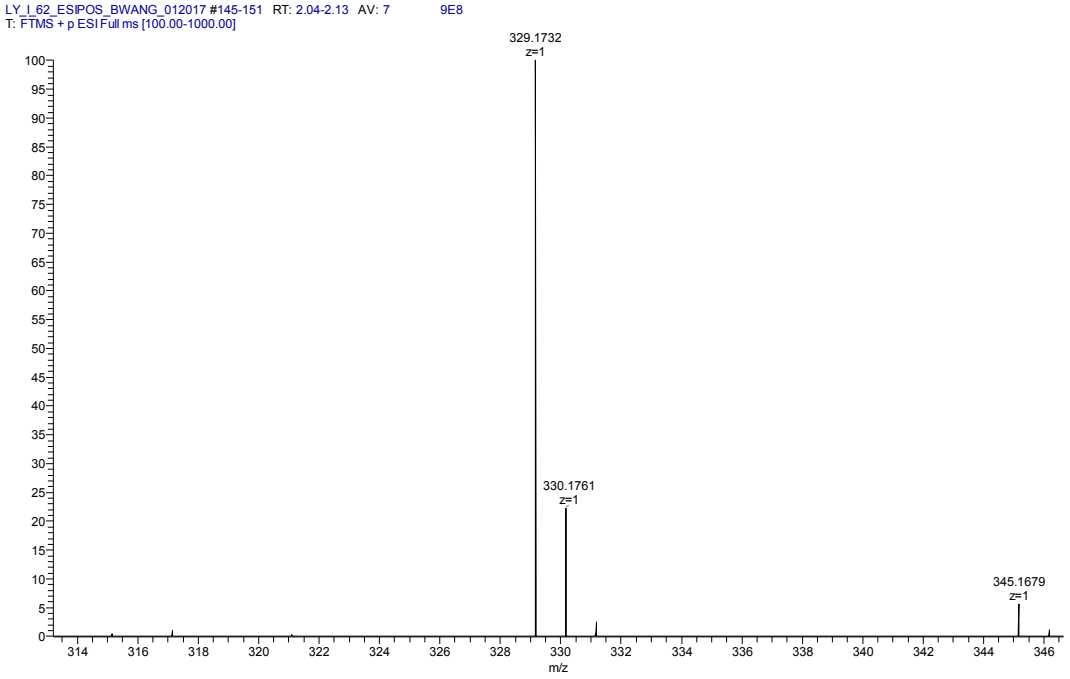

LY_I_69_ESIPOS_BWANG_021017 #132-140 RT: 1.86-1.97 AV: 9 3E8
T: FTMS + p ESI Full ms [100.00-1000.00]
343.1905
z=1
344.1933
z=1
360.3624
z=1
361.3654
z=1
m/z

(4-isopropoxy-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25c)

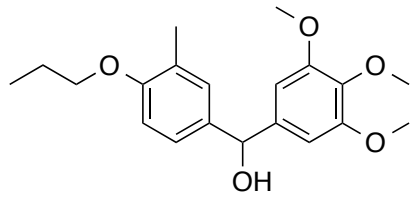


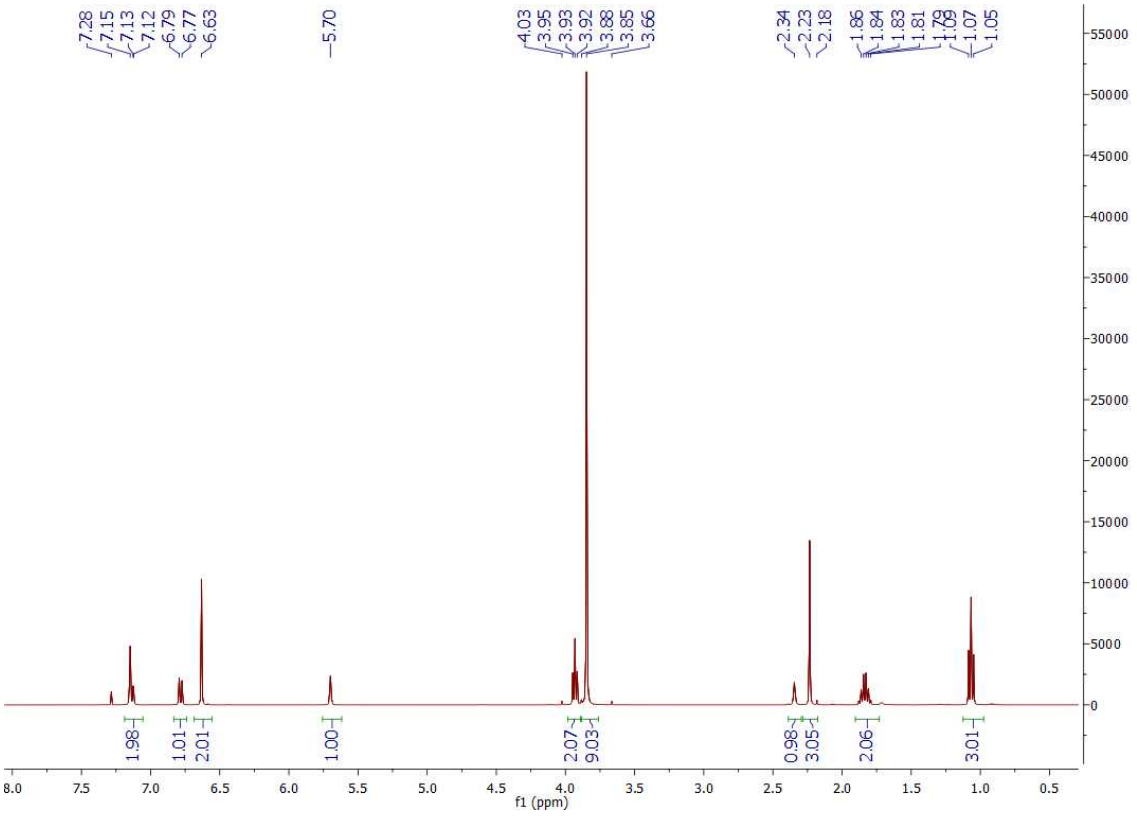


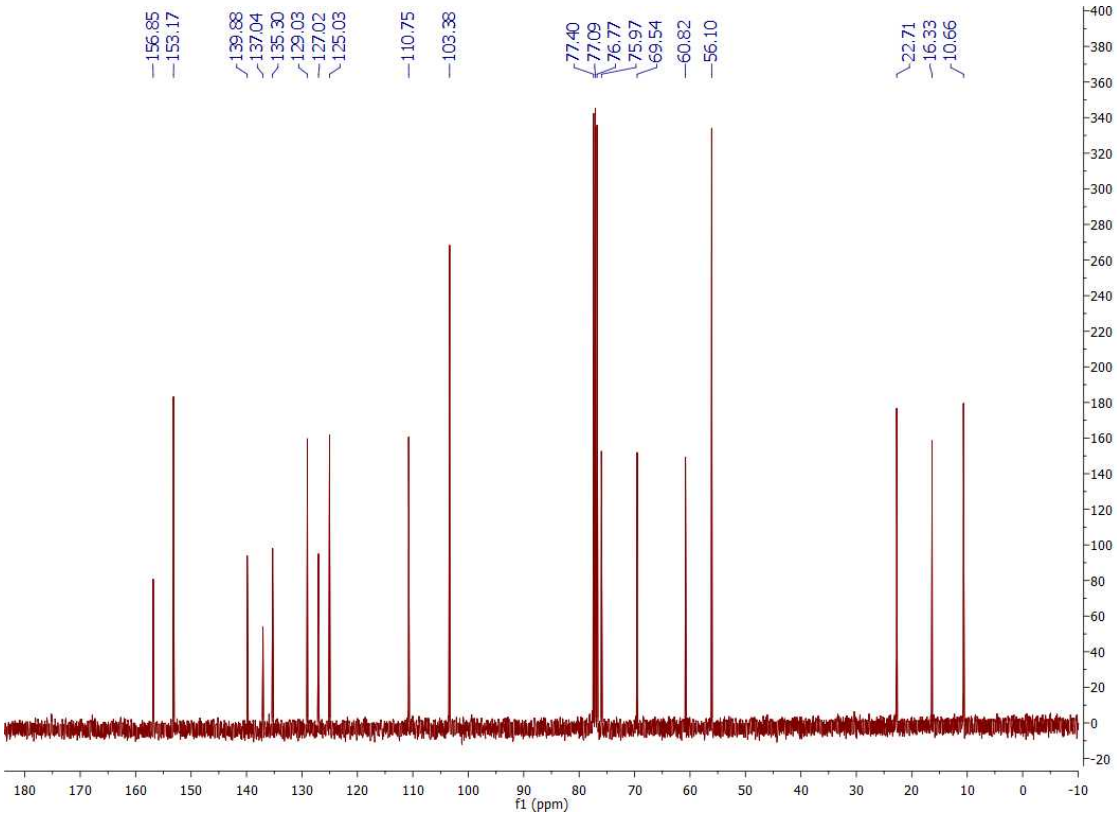

153.21
139.74
135.28
129.27
128.06
124.97
112.82
112.50
104.27
103.40
77.34
77.02
76.70
76.04
70.28
60.84
56.12
56.03
22.25
16.56
f1 (ppm)

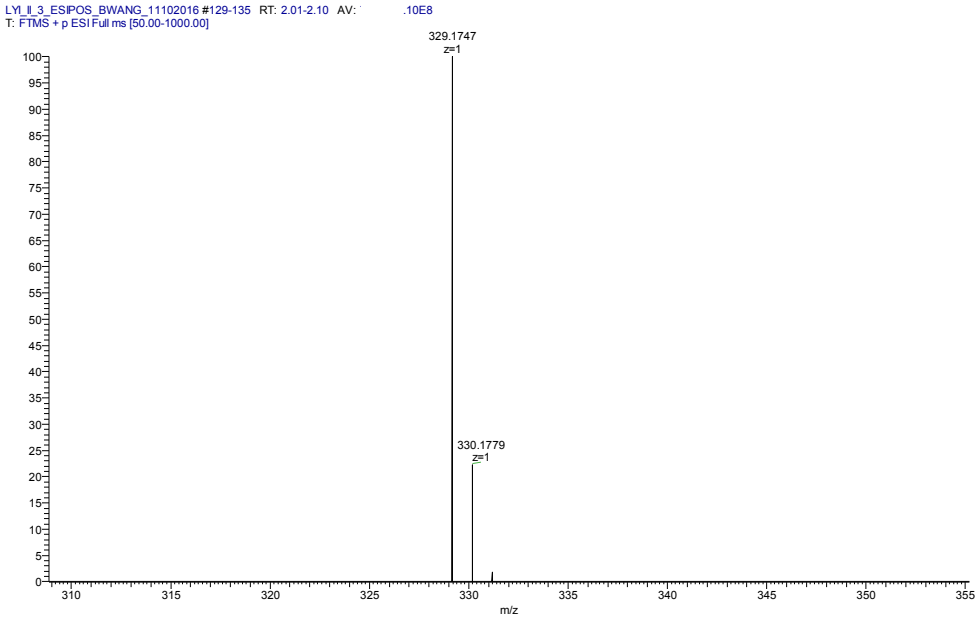

LY_I_62_ESIPOS_BWANG_012017 #145-151 RT: 2.04-2.13 AV: 7 9E8
T: FTMS + p ESI Full ms [100.00-1000.00]
329.1732
z=1
330.1761
z=1
345.1679
z=1
m/z

(3-methyl-4-propoxyphenyl)(3,4,5-trimethoxyphenyl)methanol (25d)

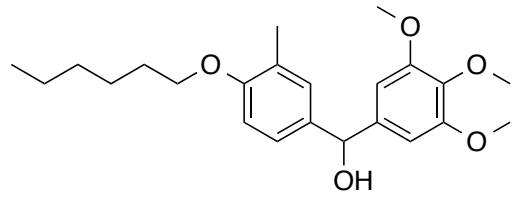


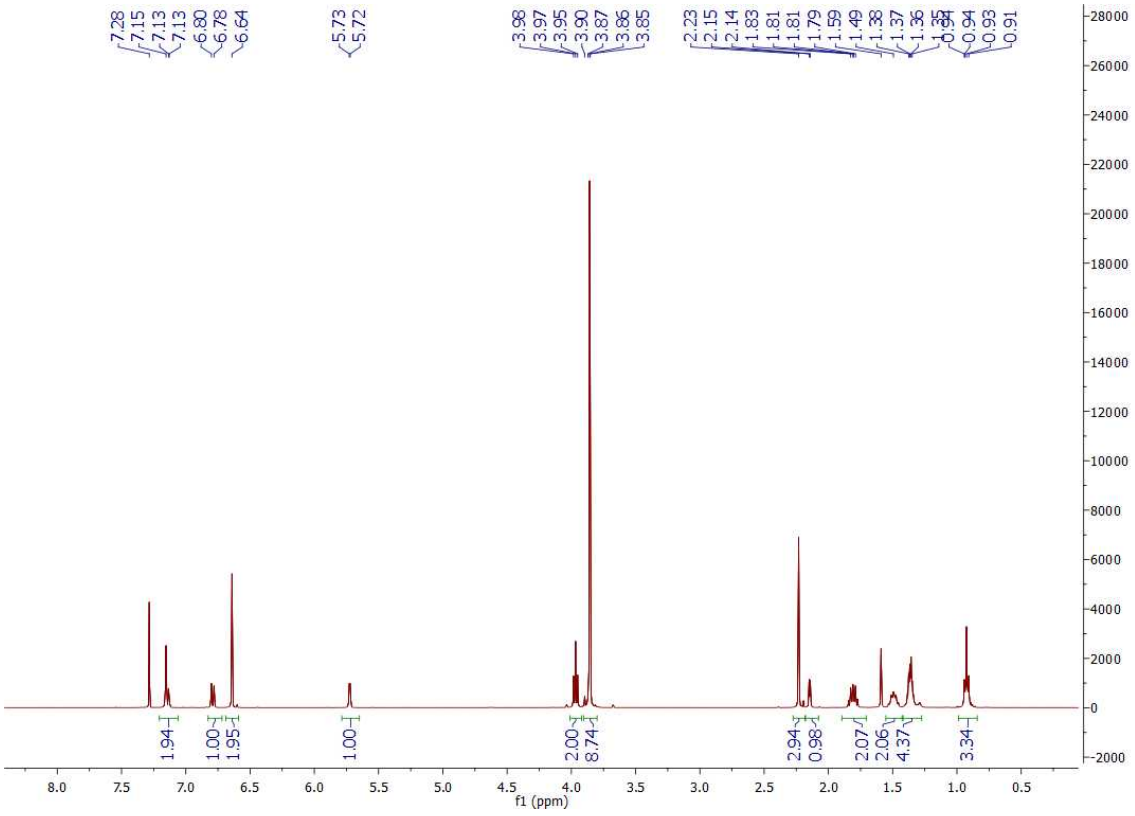


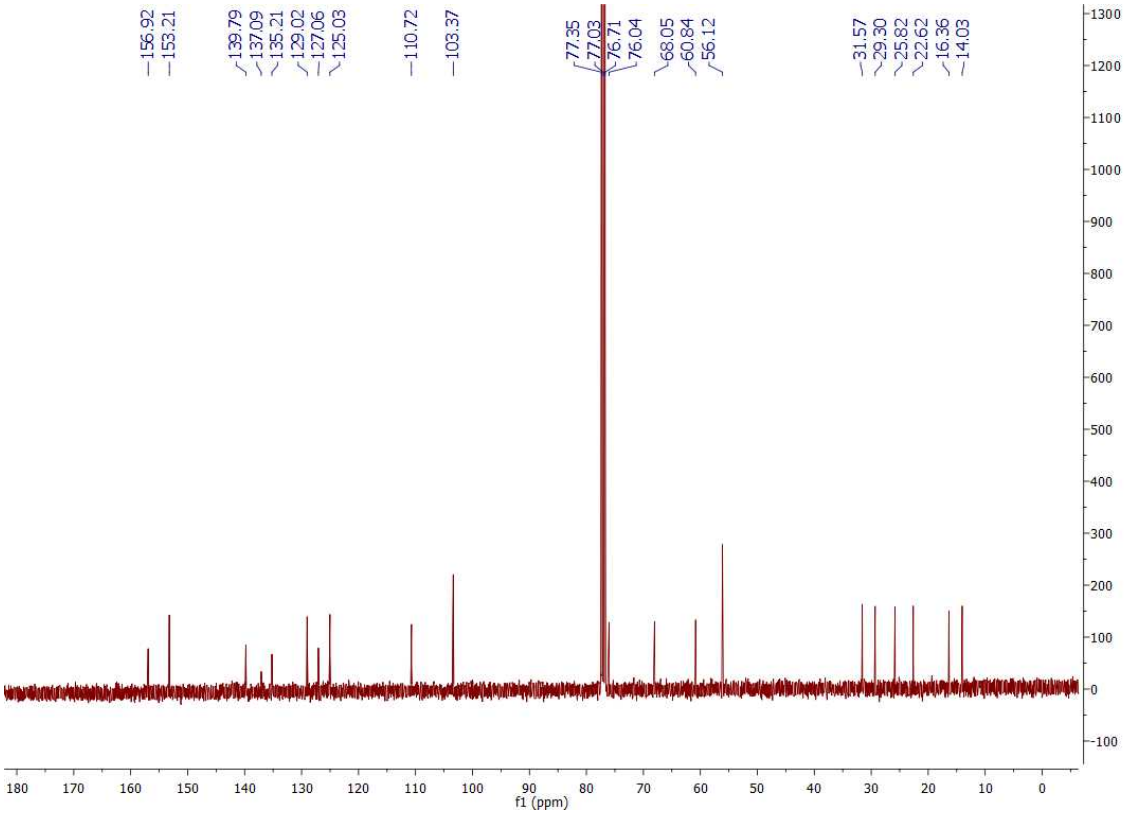

156.85
153.17
139.88
137.04
135.30
129.03
127.02
125.03
110.75
103.38
77.40
77.09
76.77
75.97
69.54
60.82
56.10
22.71
16.33
10.66
f1 (ppm)

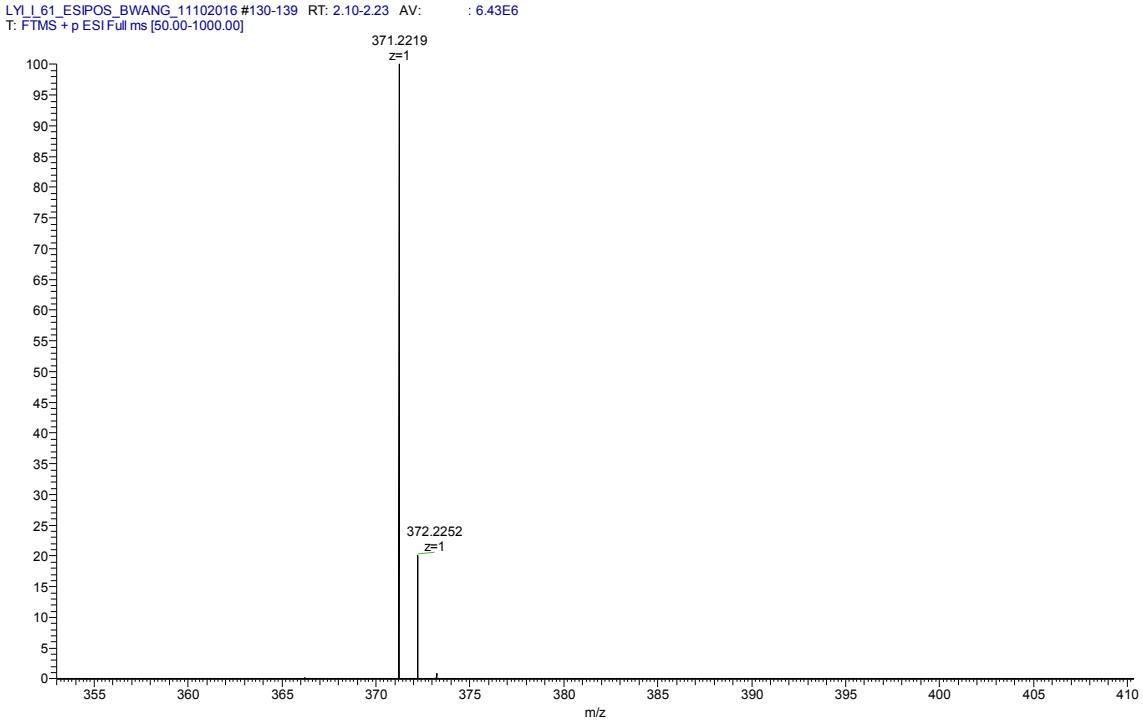

LYI_II_3_ESIPOS_BWANG_11102016 #129-135 RT: 2.01-2.10 AV: .10E8
T: FTMS + p ESI Full ms [50.00-1000.00]
329.1747
z=1
330.1779
z=1
m/z

(4-(hexyloxy)-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25e)

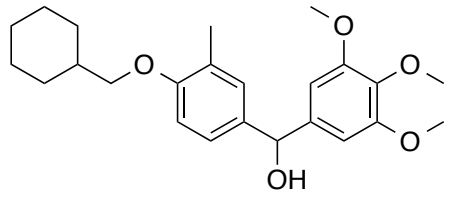


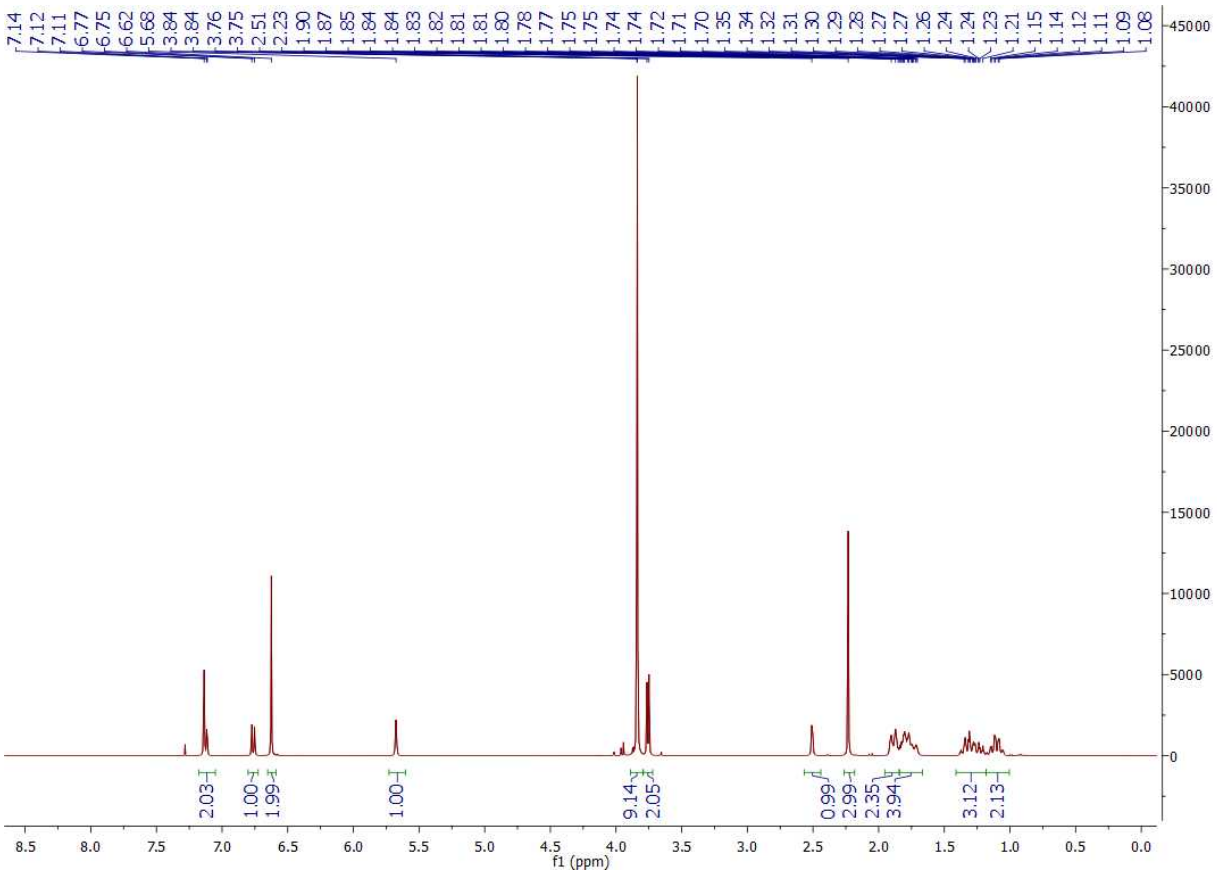


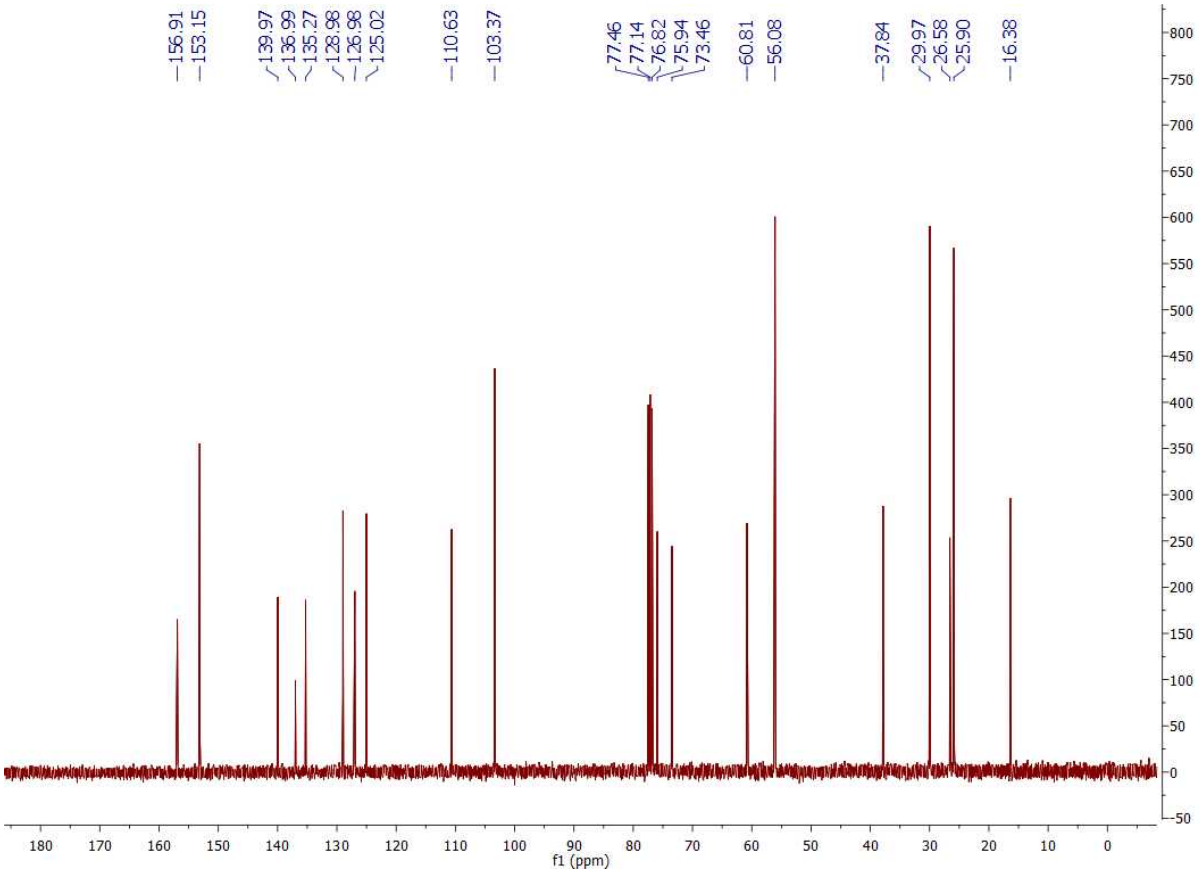

156.92
153.21
139.79
137.09
135.21
129.02
127.06
125.03
110.72
103.37
77.35
77.03
76.71
76.04
68.05
60.84
56.12
31.57
29.30
25.82
22.62
16.36
14.03
f1 (ppm)

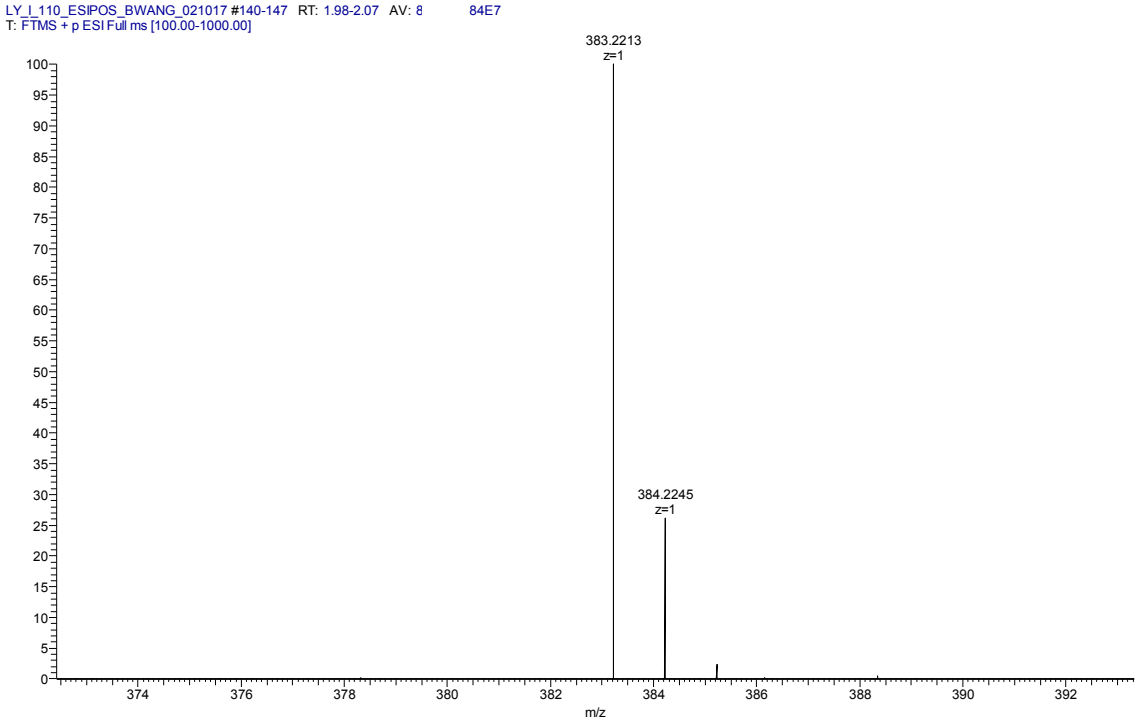

LYI_I_61_ESIPOS_BWANG_11102016 #130-139 RT: 2.10-2.23 AV: : 6.43E6
T: FTMS + p ESI Full ms [50.00-1000.00]
371.2219
z=1
372.2252
z=1
m/z

(4-(cyclohexylmethoxy)-3-methylphenyl)(3,4,5-trimethoxyphenyl)methanol (25f)






156.91
153.15
139.97
136.99
135.27
128.98
126.98
125.02
110.63
103.37
77.46
77.14
76.82
75.94
73.46
60.81
56.08
37.84
29.97
26.58
25.90
16.38
f1 (ppm)


LY_I_110_ESIPOS_BWANG_021017 #140-147 RT: 1.98-2.07 AV: 8 84E7
T: FTMS + p ESI Full ms [100.00-1000.00]
383.2213
z=1
384.2245
z=1
m/z