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Synthesis and characterization of piperazine-substituted dihydrofuran derivatives viaMn(OAc)3 mediated radical cyclizations

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Abstract: The aim of this study is to synthesize novel piperazine-containing dihydrofuran compounds (3a-n)from radical additions and cyclizations of diacyl and alkyl-acyl piperazine derivatives (1a-h) with 1,3-dicarbonyl compounds (2a-c) mediated by $Mn(OAc)_3$ for the first time. From the reactions of 1a-c with dimedone (2a);1a, 1c, and 1d with acetylacetone (2b); and 1a with ethylacetoacetate(2c) ,the dihydrofuran-piperazine compounds 3a-c, 3d-f, and 3g were obtained in medium to high yields (31%–81%), respectively. In addition, dihydrofuran-piperazine compounds 3h-j and 3k-n were prepared at low to medium yields (20%–40%) from the reactions of **1e-g** with **2a** and **1e-h** with **2c**, respectively.

Keywords: Piperazine, dihydrofuran, $Mn(OAc)_3$, radical cyclization

1. Introduction

Heterocycles are important compounds and have gathered much attention due to their biological properties, and many synthetic drugs contain heterocyclic scaffolds [1,2]. Piperazine is considered a privileged scaffold in medicinal chemistry [3], and there are many biological activity studies in the literature for piperazine-bearing compounds such as antibacterial [4], anticonvulsant [5], antituberculosis [6], antiviral [7], anticancer [8], and acetylcholinesterase inhibition [9,10]. Piperazinecan be found in active drug ingredients such as imatinib [11], sildenafil [12], indinavir [13], and gatifloxacin[14]. In addition, there have been anticonvulsant activity [15], monacylglyserine lipase inhibition [16], antimicrobial [17], and antiinflammatory activity studies [18]for cinnamylpiperazines and antimycobacterial [19], antiischemic [20], and antiparasitic activity studies [21] for acrylamide piperazine derivatives.

Dihydrofurans have gathered much attention due to their biological activities and have great potential as building blocks for pharmaceutical agents. Sarcophytoxide [22], clerodin [23], fercoprolone [24], and austocystin [25] are natural bioactive compounds that carry dihydrofuran moieties. Dihydrofurans can be obtained via transition metal salts which are capable of transferring single electrons (Mn^{3+}, Ce^{4+}, Co^{3+}, etc.) to active methylene compounds to form α-carbon radicals. The addition of these radicals to unsaturated systems is used to generate new C-C bonds [26–28]. Manganese (III) acetate [29–33] and cerium(IV) ammonium nitrate (CAN) [34–38] are widely used in these reactions. Our research group has reported radical addition and cyclization reactions with CAN [39–42] and radical cyclization reactions of 1,3-dicarbonyl derivatives with various unsaturated systems, such as conjugated amide derivatives [43–47]and heteroaromatic conjugated alkenes [48–51].

In this work we report new dihydrofuran-containing piperazine compounds (3a-n) via$Mn(OAc)_3$ mediated radical cyclization in medium to high yields. All new compounds were characterized by ^{1}HNMR, ^{13}C NMR, HRMS, and FTIR spectroscopy.

2. Results and discussion

In our previous work [52] diacyl and alkyl-acylpiperazine derivatives were obtained; in this work these compounds (1a-h) were used as starting reagents to synthesize piperazine-containing dihydrofuran molecules.

Novel piperazine–dihydrofuran compounds (3a-n) were synthesized via $Mn(OAc)_3$ mediated oxidative radical cyclization reactions of unsaturated diacyl (1a-d) and alkyl-acyl (1e-h) piperazine derivatives ,as well as 1,3-dicarbonyl compounds such as dimedone (2a), acetylacetone (2b), and ethylacetoacetate (2c). All radical cyclizations were carried out at 1.2:1:2 molar ratios [piperazine derivative:1,3-dicarbonyl:$Mn(OAc)_3$].

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The results of the reactions of 1a-d with 2a-care given in Table 1. The treatment of 1a-c with dimedone (2a) gave dihydrofurans3a (81%), 3b (50%), and 3c (64%), respectively, in moderate-to-good yields. Although compounds 1a and 1b are similar, there is a significant difference in product yields obtained from them (3aand 3b, respectively). The steric hindrance originated through methyl substitution on alkene moiety of 1b caused the relatively low yield of 3b. Compounds 3d (73%), 3e (52%), and 3f (31%) were obtained as a result of reactions between 1a, 1c, and 1d with 2b in moderate-to-good yields, respectively. Through the reaction of 1a with 2c, compound 3g was isolated at a 60% yield. All cyclizations occurred at the aromatic-ring–carrying sides of the piperazines. This is because radical intermediates formed adjacent to aromatic rings have greater stability than those formed adjacent to methacryloyl alpha carbons on carbon atoms (Figure, Intermediate C and F).

The results of the reactions of 1e-hwith 2a are given in Table 2. From the reactions of ally piperazine derivatives (1e-g) with 2a, dihydrofurans 3h (30%), 3i (32%), and 3j (20%) were obtained in low yields. By comparing the yields of 3a (81%) with 3i (32%) and yields of 3c (64%) with 3j (20%) it can be deduced that yields of methacryloyl-piperazine–substituted dihydrofurans are higher than yields of allyl-piperazine–substituted dihydrofurans. Additionally, reactions of 1e-g with 2c formed 3k (25%), 3l (40%), and 3m (20%) in low yields, respectively. Reactions of ally-methacryloyl piperazine (1h) with 2c formed 3n (20%) in low yields.

Radical cyclizations of unsaturated diacyl and allyl-acyl piperazine compounds (except 1h) occurred regioselectively through 3-arylpropenoyl moiety. However, no cyclization product that formed over ally or methacryloyl moiety was isolated (except 3n). This is due to the fact that radical intermediates formed adjacent to the aromatic rings are much more stable than those formed on allyl or methacryloyl moieties. Similarly, since the radical intermediates formed on methacrylic moiety are much more stable than those formed on the ally group, radical cyclization of 1h and 2c occurred through methacryloyl group to form dihydrofuran-piperazine (3n). The ^{1}H NMR spectra of obtained compounds 3a, 3c-e, and 3g-m show that vicinal dihydrofuran couplings are J_{trans} = 5.2–7.6 Hz (in the literature J_{trans} = 2.5–7.6 Hz and J_{cis} = 8–11 Hz) [45,46,48,49,53–56], thus it was determined that these molecules are trans compounds.

The proposed mechanism for the formation of dihydrofuransis is explained in Figure. According to this mechanism, the enol form of dimedone (A) reacts with $Mn(OAc)_3$, and an alpha carbon radical B is formed, while Mn^{3+} reduces to Mn^{2+}. There are two possible pathways for this alpha carbon radical to attach to 1a. Radical intermediate C can be formed by following pathway-*i*, and radical intermediate F can be formed by following pathway-*ii*. On pathway-*i*, oxidation of C to carbocation D with $Mn(OAc)_3$ and intramolecular cyclization of D forms the product E. Similarly, by following pathway-*ii*, product H is formed. However, on the ^{1}H-NMR spectra of the obtained products, the chemical shifts of two terminal alkene peaks of methacryl group were observed in the range of 5.25–5.00 ppm. Additionally, two vicinal proton peaks of dihydrofurans around 6.00 and 4.51 ppm (J_{trans}= 5.2–6.4 Hz) were observed. According to this information, it was determined that the radical cyclization of 1a-d with 2a-c followed the pathway-*i*, and products 3a-g formed; however, the other possible products (H) were not isolated.

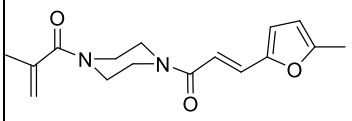
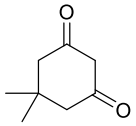
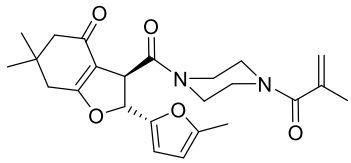
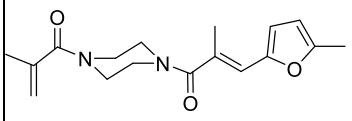
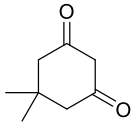
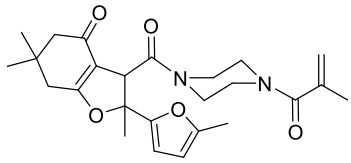
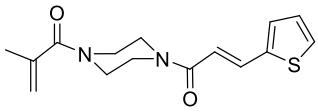
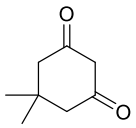
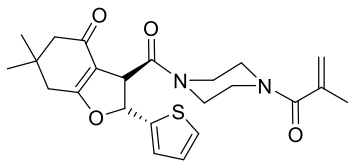
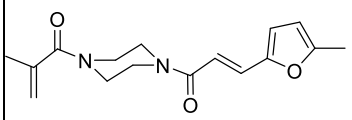
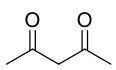
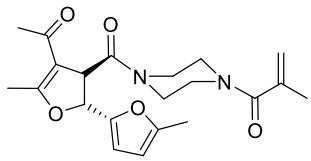
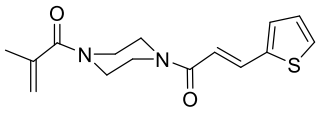
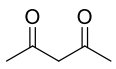
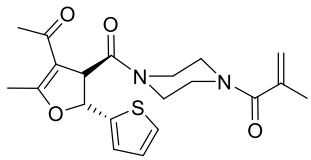
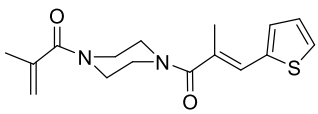
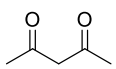
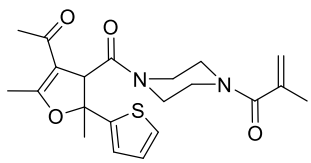
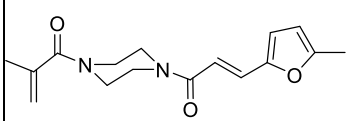
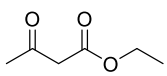
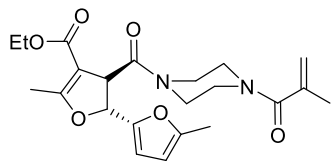
Summarily, reactions of methacryloyl- and 3-arylacryloyl–substituted piperazines (1a-d) with 1,3-dicarbonyls (2a-c) occurs on 3-arylacryloyl sides, regioselectively. However, in reactions of allyl- and acryloyl-substituted (methacryloyl or 3-arylacryloyl) piperazines (1e-h)with 2a or 2c, cyclization occurs at acryloyl moiety, regioselectively, and thus, relevant dihydrofurans (3h-n) were formed. No cyclization occurred on allyl moiety at any reaction.

3. Experimental design

3.1. Chemicals and equipment

Melting points were determined on a Gallenkamp capillary melting point apparatus (Gallenkamp & Co., London, UK) and IR spectra (ATR, PerkinElmer, Inc. Waltham, MA, USA) were obtained with a Bruker Tensor27 spectrophotometer (Bruker Optics GmbH, Ettlingen, Germany) in the 400–4000 cm^{-1} range with 2 cm^{-1} resolutions. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-400 high-performance digital FT-NMR and Varian Oxford NMR300 spectrometers (Varian Medical Systems, Inc., Palo Alto, CA, USA). High resolution mass time-of-flight spectra (TOF) were measured on an Agilent 1200/6210 LC/MS spectrophotometer (AgilentTechnologies, Inc., SantaClara, CA, USA). Thin layer chromatography (TLC) was performed on Merck aluminum-packed silica gel plates (Merck&Co., Inc., Kenilworth, NJ, USA). Purification of products was by column chromatography on silica gel (Merck silica gel 60, 40–60 mm), and preparative TLC was on silica gel from Merck ($PF_{254-366nm}$) (Kenilworth, NJ, USA). All reagents, 1,3-dicarbonyl compounds, and solvents were commercially purchased. Radical oxidant $Mn(OAc)_3$ was synthesized by electrochemical method [57]. Please note that ^{1}H NMR, ^{13}C NMR, and HRMS spectra for all novel compounds can be found as supplementary information.

Table 1. Radical cyclizations of 1a-d with 2a-c.

Entry	Piperazine	1,3-dicarbonyl	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	81
2	 **1b**	 **2a**	 **3b**	50
3	 **1c**	 **2a**	 **3c**	64
4	 **1a**	 **2b**	 **3d**	73
5	 **1c**	 **2b**	 **3e**	52
6	 **1d**	 **2b**	 **3f**	31
7	 **1a**	 **2c**	 **3g**	60

a) Isolated yield based on 1,3-dicarbonyl compounds.

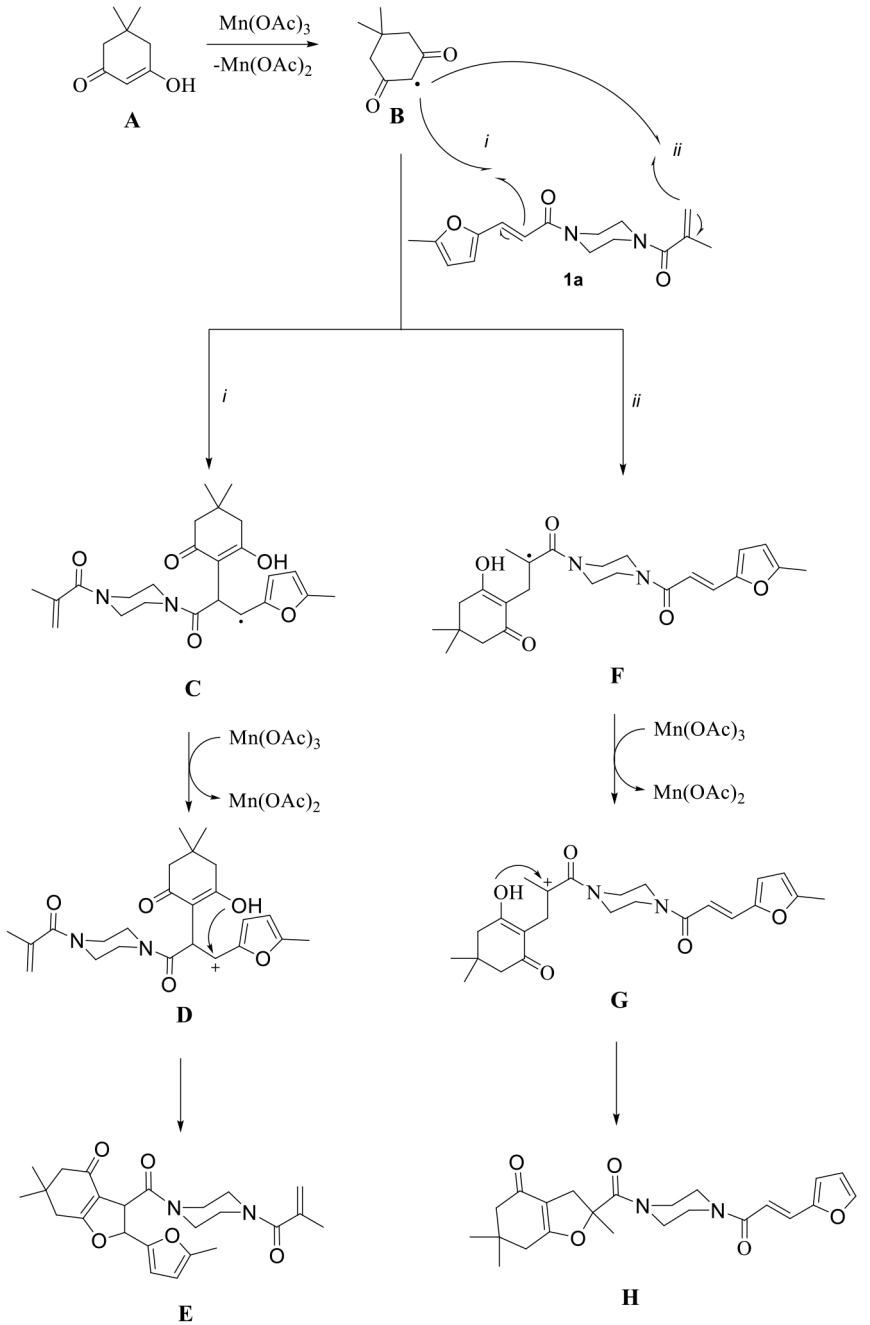
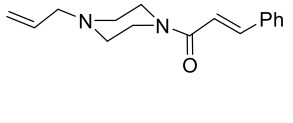
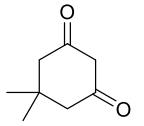
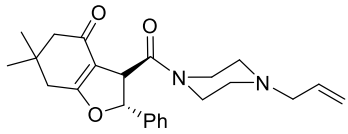
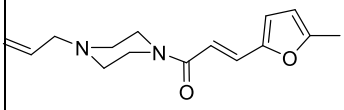
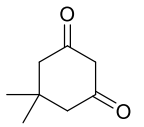
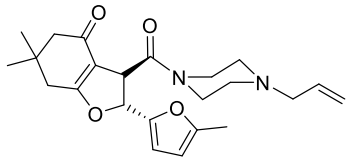
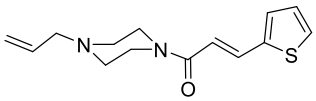
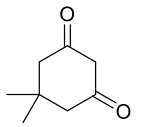
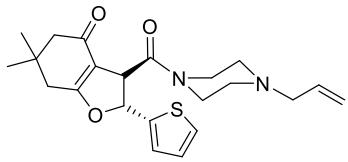
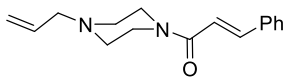
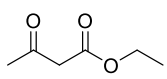
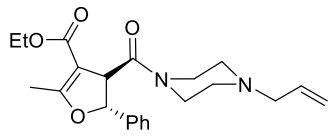
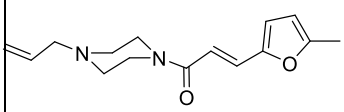
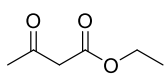
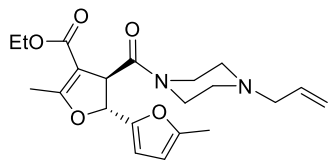
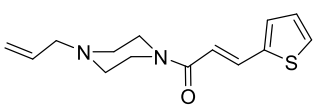
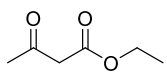
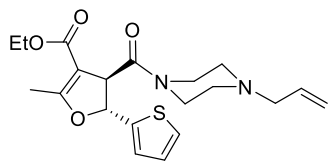
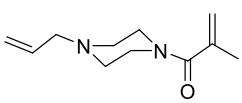
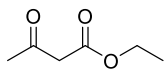
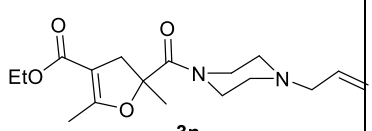


Figure. Proposed mechanism of $Mn(OAc)_3$ mediated radical cyclization.

3.2. General synthesis procedure and spectroscopic data of diacyl (3a-g) piperazine-dihydrofuran compounds

A solution of $Mn(OAc)_3$ (2mmol, 0.53 g) in 15 mL of glacial acetic acid was heated to 80 °C until dissolved. Then, the solution temperature was set to 65 °C. A solution of the corresponding 1,3-dicarbonyl compound (2a-c) (1mmol) and suitable unsaturated piperazine compound (1a-d)(1.2 mmol) in 2 mL of acetic acid was added to $Mn(OAc)_3$ solution. The mixture was stirred, and the disappearance of the dark brown color indicated that the reaction was finished (15–60 min). Water was added, and the crude product was extracted with chloroform (20×3 mL). Combined organic phases were neutralized with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified with column chromatography (silica gel 60, 40–60 mm) using chloroform–acetone (85:15) as eluent. All compounds were further purified by preparative TLC ($PF_{254\text{-}366nm}$) before spectroscopic analyses.

Table 2. Radical cyclizations of **1e-h** with **2a** and **2c**.

Entry	Piperazine	1,3-dicarbonyl	Product	Yield (%)[a]
1	 **1e**	 **2a**	 **3h**	30
2	 **1f**	 **2a**	 **3i**	32
3	 **1g**	 **2a**	 **3j**	20
4	 **1e**	 **2c**	 **3k**	25
5	 **1f**	 **2c**	 **3l**	40
6	 **1g**	 **2c**	 **3m**	20
7	 **1h**	 **2c**	 **3n**	20

a) Isolated yield based on 1,3-dicarbonyl compounds.

***Trans*-3-(4-Methacryloylpiperazine-1-carbonyl)-6,6-dimethyl-2-(5-methylfuran-2-yl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (3a)**

It was obtained as a yellow oil; yield: 81% (0.345 g); IR (ATR) υ_{max} 3000, 2957, 2926, 1720 (C=O), 1618 (C=O), 1606 (C=C), 1197, 1022, 748 (arom. CH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.30 (1H, d, *J* = 3.2 Hz, arom. CH), 6.00 (1H, d, *J* = 5.6 Hz, H-2), 5.96 (1H, d, *J* = 3.2 Hz, arom. CH), 5.21 (1H, s, $H_{olef.}$), 5.04 (1H, s, $H_{olef.}$), 4.51 (1H, d, *J* = 5.6 Hz, H-3), 4.07-3.27 (8H, m), 2.43 (1H, d, *J* = 17.6 Hz), 2.33 (1H, d, *J* = 17.6 Hz), 2.33 (1H, d, *J* = 16.4 Hz), 2.28 (3H, s, $-CH_3$), 2.19 (1H, d, *J* = 16.4 Hz), 1.95 (3H, s, $-CH_3$), 1.13 (3H, s, $-CH_3$), 1.11 (3H, s, $-CH_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm):193.9 (C=O), 177.3 (C=C, C-7a), 171.3 (C=O), 169.9 (C=O), 154.0, 148.6, 140.0 (C=C), 115.9 (C=C), 112.3, 111.1,106.7(C=C, C-3a), 83.6 (C-2), 51.1, 46.6, 45.0 (C-3), 42.2, 37.9, 34.4, 28.9 ($-CH_3$), 28.2 ($-CH_3$), 20.4 ($-CH_3$), 13.6 ($-CH_3$);HRMS (ESI) (m/z) Calcd for $C_{24}H_{30}N_2O_5$427.22275 found 427.22472 $(M+H)^+$.

3-(4-Methacryloylpiperazine-1-carbonyl)-2,6,6-trimethyl-2-(5-methylfuran-2-yl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (3b)

It was obtained as a yellow oil; yield: 50% (0.220 g); IR (ATR) υ_{max}3093, 2956, 2925, 1721 (C=O), 1635 (C=O), 1610 (C=C), 1194, 1020, 728 (arom. CH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):6.24 (1H, d, *J* = 3.2Hz, arom. CH), 5.94 (1H, d, *J* = 3.2 Hz), 5.22 (1H, s, H_{olef}), 5.03 (1H, s, H_{olef}), 4.58 (1H, s, H-3), 3.79-3.52 (8H, m), 2.40 (1H, d, *J* = 17.6 Hz), 2.35 (1H, d, *J* = 17.6 Hz), 2.32 (1H, d, *J* = 16.0 Hz), 2.20 (1H, d , *J* = 16.0 Hz), 2.30 (3H, s, $-CH_3$), 1.94 (3H, s, $-CH_3$), 1.68 (3H, s, $-CH_3$), 1.20 (3H, s, $-CH_3$), 1.11 (3H, s, $-CH_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm): 194.1 (C=O), 175.4 (C=C, C-7a), 171.3 (C=O), 167.8 (C=O), 153.2, 152.8, 139.8 (C=C), 116.1 (C=C), 112.9, 112.5, 106.5 (C=C, C-3a), 88.1 (C-2), 50.7, 49.0 (C-3), 45.9, 42.5, 37.8, 34.6, 28.6 ($-CH_3$), 28.5 ($-CH_3$), 21.1 ($-CH_3$), 20.4 ($-CH_3$), 13.6 ($-CH_3$);HRMS (ESI)(m/z) Calcd for$C_{25}H_{32}N_2O_5$441.23840 found 441.23896 $(M+H)^+$.

***Trans*-3-(4-Methacryloylpiperazine-1-carbonyl)-6,6-dimethyl-2-(thiophen-2-yl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (3c)**

It was obtained as a yellow oil; yield: 64% (0.274 g); IR (ATR) υ_{max}3085, 2956, 2930, 1732 (C=O), 1639 (C=O), 1615 (C=C), 1197, 1026, 726 (arom. CH)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 (1H, d, *J* = 5.2 Hz, arom. CH), 7.06 (1H, d, *J* = 3.6 Hz, arom. CH), 7.00 (1H, dd, *J* = 5.2, 3.6 Hz, arom. CH), 6.32 (1H, d, *J* = 5.2 Hz, H-2), 5.21 (1H, s, H_{olef}), 5.04 (1H, s, H_{olef}), 4.36 (1H, d, *J* = 5.2 Hz, H-3), 4.03-3.28 (8H, m), 2.47 (1H, d, *J* = 17.6 Hz), 2.35 (1H, d, *J* = 17.6 Hz), 2.32 (1H, d, *J* = 16.4 Hz), 2.20 (1H, d, *J* = 16.4 Hz), 1.94 (3H, s, $-CH_3$), 1.14 (3H, s, $-CH_3$), 1.12 (3H, s, $-CH_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm): 193.9 (C=O), 177.0 (C=C, C-7a), 171.2 (C=O), 169.8 (C=O), 141.9, 140.0 (C=C), 115.9 (C=C), 127.1, 126.6, 126.3, 111.9 (C=C, C-3a), 86.1 (C-2), 51.1, 50.0 (C-3), 46.5, 42.2, 37.9, 34.4, 28.9 ($-CH_3$), 28.1 ($-CH_3$), 20.4 ($-CH_3$); HRMS (ESI) (m/z) Calcd for $C_{23}H_{28}N_2O_4S$429.18425 found 429.18588 $(M + H)^+$.

***Trans*-1-(4-(4-Acetyl-5,5'-dimethyl-2,3-dihydro-[2,2'-bifuran]-3-carbonyl)piperazin-1-yl)-2-methylprop-2-en-1-one (3d)**

It was obtained as a yellow oil; yield: 73% (0.282 g); IR (ATR) υ_{max}3009, 2956, 2930, 1732 (C=O), 1652 (C=O), 1612 (C=C), 1193, 1020, 746 (arom. CH)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.29 (1H, d, *J*= 3.2 Hz, arom. CH), 5.95 (1H, d, *J*= 3.2 Hz, arom. CH), 5.52 (1H, d, *J* = 6.4 Hz, H-2), 5.20 (1H, s, H_{olef}), 5.02 (1H, s, H_{olef}), 4.69 (1H, d, *J* = 6.4 Hz, H-3), 3.80-3.66 (8H, m), 2.31 (3H, s, $-CH_3$), 2.30 (3H, s, $-CH_3$), 2.29 (3H, s, $-CH_3$), 1.93 (3H, s, $-CH_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm): 192.8 (C=O), 171.3 (C=C, C-7a), 171.2 (C=O), 167.6 (C=O), 155.5, 153.8, 140.0 (C=C), 116.7 (C=C), 115.9, 110.9, 106.7 (C=C, C-3a), 79.9 (C-2), 49.1 (C-3), 46.2, 42.7, 28.8 ($-CH_3$), 20.4 ($-CH_3$), 15.6 ($-CH_3$), 13.6 ($-CH_3$);HRMS (ESI)(m/z) Calcd for $C_{21}H_{26}N_2O_5$387.19145 found 387.19223 $(M+H)^+$.

***Trans*-1-(4-(4-Acetyl-5-methyl-2-(thiophen-2-yl)-2,3-dihydrofuran-3-carbonyl)piperazin-1-yl)-2-methylprop-2-en-1-one (3e)**

It was obtained as a yellow oil; yield: 52% (0.202g); IR (ATR) υ_{max}3085, 2998, 2917, 1714 (C=O), 1639 (C=O), 1610 (C=C), 1194, 1020, 724 (arom. CH)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.33 (1H, d, *J*= 5.2 Hz, arom. CH), 7.05 (1H, d, *J*= 3.6 Hz, arom. CH), 7.00 (1H, dd, *J*= 5.2, 3.6 Hz, arom. CH), 5.86 (1H, d, *J* = 6.4 Hz, H-2), 5.20 (1H, s, H_{olef}), 5.02 (1H, s, H_{olef}), 4.54 (1H, d, *J* = 6.4 Hz, H-3), 3.81-3.39 (8H, m), 2.34 (3H, s, $-CH_3$), 2.33 (3H, s, $-CH_3$), 1.93 (3H, s, $-CH_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm): 192.8 (C=O), 171.3 (C=C, C-7a), 171.1 (C=O), 167.6 (C=O), 144.6, 140.0 (C=C), 127.1, 126.4, 126.1, 116.6 (C=C), 115.9 (C=C, C-3a), 82.6 (C-2), 53.5 (C-3), 46.5, 42.4, 28.9 ($-CH_3$), 20.4 ($-CH_3$), 15.6 ($-CH_3$)192.9HRMS (ESI)(m/z) Calcd for $C_{20}H_{24}N_2O_4S$389.15295found 389.15460 $(M+H)^+$.

1-(4-(4-Acetyl-2,5-dimethyl-2-(thiophen-2-yl)-2,3-dihydrofuran-3-carbonyl)piperazin-1-yl)-2-methylprop-2-en-1-one (3f)

It was obtained as a yellow oil; yield: 31% (0.125 g); IR (ATR) υ_{max}3117, 2953, 2918, 1734 (C=O), 1648 (C=O), 1615 (C=C), 1191, 1022, 724 (arom. CH)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27 (1H, d, *J*= 6.4 Hz, arom. CH), 6.97-6.95 (2H, m, arom. CH), 5.22 (1H, s, H_{olef}), 5.04 (1H, s, H_{olef}), 4.54 (1H, s, H-3), 3.68-3.32 (8H, m), 2.35 (3H,s, $-CH_3$), 2.30 (3H,s, $-CH_3$), 1.94 (3H,s, $-CH_3$), 1.74 (3H,s, $-CH_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm): 192.9 (C=O), 171.3 (C=C, C-7a),

168.9 (C=O), 166.5 (C=C, C-3a), 149.6, 139.9 (C=C), 126.9, 125.0, 123.0, 116.3 (C=C), 116.0 (C=C, C-3a), 86.4 (C-2), 56.6 (C-3), 46.3, 42.6, 28.7 (-CH_3), 24.0 (-CH_3), 20.4 (-CH_3), 15.4 (-CH_3);HRMS (ESI)(m/z) Calcd for $C_{21}H_{26}N_2O_4S$403.16860 found 403.16968 $(M+H)^+$.

***Trans*-Ethyl 3-(4-methacryloylpiperazine-1-carbonyl)-5,5'-dimethyl-2,3-dihydro-[2,2'-bifuran]-4-carboxylate (3g)**

It was obtained as a yellow oil; yield: 60% (0.250 g); IR (ATR) υ_{max}3080, 2980, 2922, 1701 (C=O), 1641 (C=O), 1619 (C=C), 1194, 1020, 730 (arom. CH)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.30 (1H, d, *J* = 3.2 Hz, arom. CH), 5.95 (1H, d, *J* = 3.2 Hz, arom. CH), 5.55 (1H, d, *J* = 5.6 Hz, H-2), 5.21 (1H, s, H_{olef}), 5.02 (1H, s, H_{olef}), 4.67 (1H, d, *J* = 5.6 Hz, H-3),4.16 (2H, q, *J* = 7.2 Hz, -OC<u>H</u>$_2$$CH_3$), 3.57-3.40 (8H, m), 2.30 (3H, s, -CH_3), 2.25 (3H, s, -CH_3), 1.93 (3H, s, -CH_3), 1.27 (3H, t, *J* = 7.2 Hz, -OCH_2C<u>H</u>$_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm): 171.3 (C=O), 171.2 (C=C, C-7a), 168.8 (C=O), 165.0 (C=O), 153.7, 148.6, 139.9 (C=C), 116.0 (C=C), 110.8, 106.7, 103.8 (C=C, C-3a), 80.2 (C-2), 59.9, 48.7 (C-3), 46.4, 42.6, 20.4 (-CH_3), 14.5 (-CH_3), 14.4 (-CH_3), 13.6 (-CH_3);HRMS (ESI)(m/z) Calcd for $C_{22}H_{28}N_2O_6$417.20201 found 417.20397 $(M+H)^+$.

3.3. General synthesis procedure and spectroscopic data of alkyl-acyl (3h-n) piperazines–dihydrofuran compounds

A solution of $Mn(OAc)_3$ (2mmol, 0.53 g) in 15 mL of glacial acetic acid was heated to 80 °C until dissolved. Then, the solution temperature was set to 65 °C. A solution of the corresponding 1,3-dicarbonyl compound (2a or 2c) (1mmol) and the suitable unsaturated piperazine compound (1e-h) (1.2 mmol) in 2 mL of acetic acid was added to $Mn(OAc)_3$solution. The mixture was stirred, and the disappearance of the dark brown color indicated that the reaction was finished (15–60 min). Water was added, and the crude product was extracted with chloroform (20 × 3 mL). Combined organic phases were neutralized with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified with column chromatography (silica gel 60, 40–60 mm) using chloroform–acetone (85:15) as eluent. All compounds were further purified by preparative TLC ($PF_{254-366nm}$) before spectroscopic analyses.

***Trans*-3-(4-Allylpiperazine-1-carbonyl)-6,6-dimethyl-2-phenyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (3h)**

It was obtained as a yellow oil; yield: 30% (0.118 g); IR (ATR) υ_{max}3067, 2961, 2868, 1730 (C=O), 1632 (C=O), 1612 (C=C), 1197, 1020, 754, 701 (arom. CH)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):7.39-7.31 (3H, m, arom. CH), 7.24-7.22 (2H, m, arom. CH), 6.04 (1H, d, *J* = 5.6 Hz, H-2), 5.83 (1H, ddt, *J* = 16.8, 10, 6.4 Hz, $H_{olef.}$), 5.18 (1H, dd, *J* = 16.8, 1.2 Hz, $H_{olef.}$), 5.14 (1H, dd, *J* = 10.0, 1.2 Hz, $H_{olef.}$), 4.23 (1H, d, *J* = 5.6 Hz, H-3), 3.96-3.84 (2H, m), 3.50-3.39 (2H, m), 3.00 (2H, d, *J* = 6.4 Hz), 2.56-2.44 (4H, m), 2.31 (2H, d, *J* = 16.0 Hz), 2.18 (2H, d, *J* = 16.0 Hz), 1.27 (3H, s, -CH_3), 1.16 (3H, s, -CH_3);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm):193.7(C=O), 177.4 (C=C, C-7a), 169.9 (C=O), 139.9, 134.3 (C=C), 129.0, 128.8, 125.5, 118.5 (C=C), 112.2 (C=C, C-3a), 90.5 (C-2), 61.4,53.1, 52.6, 51.1, 49.7, 46.2, 42.4 (C-3), 34.3, 28.9 (-CH_3), 28.2(-CH_3);HRMS (ESI)(m/z) Calcd for $C_{24}H_{30}N_2O_3$395.23292 found 395.23361 $(M+H)^+$.

***Trans*-3-(4-Allylpiperazine-1-carbonyl)-6,6-dimethyl-2-(5-methylfuran-2-yl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (3i)**

It was obtained as a yellow oil; yield: 32% (0.127 g); IR (ATR) υ_{max}30171, 2961, 2930, 1732 (C=O), 1641 (C=O), 1617 (C=C), 1197, 1002, 734 (arom. CH)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d (ppm):6.28 (1H, δ, *J* = 3.2 Hz, arom. CH), 5.94 (1H, d, *J* = 6.0 Hz, H-2), 5.93 (1H, d, *J* = 3.2 Hz, arom. CH), 5.83 (1H, ddt, *J* = 16.8, 10, 6.8 Hz, H_{olef}), 5.18 (1H, dd, *J* = 16.8, 1.6 Hz, H_{olef}), 5.14 (1H, dd, *J* = 10.0, 1.6 Hz, H_{olef}), 4.49 (1H, d, *J* = 6.0 Hz, H-3), 3.99-3.89 (2H, m), 3.49-3.37 (2H, m), 2.99 (2H, d, *J* = 6.8 Hz), 2.59-2.49 (4H, m), 2.40 (1H, d, *J* = 17.6 Hz), 2.30 (1H, d, *J* = 17.6 Hz), 2.29 (1H, d, *J* = 16.0 Hz), 2.26 (3H, s, -CH_3), 2.17 (1H, d, *J* = 16.0 Hz), 1.12 (3H, s, -CH_3), 1.08 (3H, s, -CH_3);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm):193.8 (C=O), 176.8 (C=C, C-7a), 169.5 (C=O), 153.8, 148.9, 134.3 (C=C), 118.5 (C=C), 112.5, 110.8, 106.6 (C=C, C-3a), 83.5 (C-2), 61.4, 53.0, 52.5, 51.1, 46.2, 45.5, 42.3 (C-3), 37.8, 34.4, 28.9(-CH_3), 28.1(-CH_3), 13.6(-CH_3);HRMS (ESI)(m/z) Calcd for $C_{23}H_{30}N_2O_4$399.22783 found 399.22924 $(M+H)^+$.

***Trans*-3-(4-Allylpiperazine-1-carbonyl)-6,6-dimethyl-2-(thiophen-2-yl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (3j)**

It was obtained as a yellow oil; yield: 20% (0.080 g); IR (ATR) υ_{max}3076, 2955, 2924, 1731 (C=O), 1628 (C=O), 1617 (C=C), 1137, 1000, 750 (arom. CH)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 (1H, d, *J* = 5.2 Hz, arom. CH), 7.06 (1H, d, *J* = 3.6 Hz, arom. CH), 6.99 (1H, dd, *J* = 5.2, 3.6 Hz, arom. CH), 6.28 (1H, d, *J* = 5.2 Hz, H-2), 5.85 (1H,ddt, *J*=16.8, 10.0,6.8 Hz, H_{olef}), 5.20 (1H, dd, *J* = 16.8, 1.6 Hz, H_{olef}), 5.18 (1H, dd, *J* = 10.0, 1.6 Hz, H_{olef}), 4.37(1H,d, *J*=5.2 Hz, H-3), 4.00-3.96 (2H,m), 3.54-3.42 (2H, m), 3.04 (2H,d, *J*=6.8 Hz), 2.58 (4H, s), 2.46 (1H, d, *J* = 17.6 Hz), 2.33 (1H, d, *J* = 17.6 Hz), 2.32 (1H, d, *J* = 16.0 Hz), 2.20 (1H, d, *J* = 16.0 Hz), 1.14 (3H, s, -CH_3), 1.11 (3H, s, -CH_3);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm):193.8 (C=O), 176.7 (C=C, C-7a), 169.3 (C=O), 143.7, 133.9 (C=C), 128.4, 127.0, 126.4, 116.6 (C=C), 112.1 (C=C, C-3a), 86.1 (C-2), 61.3, 53.0, 52.5, 51.1, 49.8, 46.1, 42.2 (C-3), 37.9, 34.4, 28.9 (-CH_3), 28.1 (-CH_3);HRMS (ESI)(m/z) Calcd for $C_{22}H_{28}N_2O_3S$400.23319 found 401.1894 $(M+H)^+$.

***Trans*-Ethyl 4-(4-allylpiperazine-1-carbonyl)-2-methyl-5-phenyl-4,5-dihydrofuran-3-carboxylate (3k)**

It was obtained as a yellow oil; yield: 25% (0.096g); IR (ATR) υ_{max}3080, 2978, 2930, 1701 (C=O), 1659 (C=O), 1619 (C=C), 1203, 969, 730, 692 (arom. CH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40-7.27 (5H, m, arom. CH), 5.81 (1H, ddt, *J*=17.2, 10.4, 6.4 Hz, H_{olef}), 5.61 (1H, d, *J* = 7.2 Hz, H-2), 5.17 (1H, dd, *J* = 16.8, 1.6 Hz, H_{olef}), 5.15 (1H, dd, *J* = 10.4, 1.6 Hz, H_{olef}), 4.33 (1H, d, *J* = 7.2 Hz, H-3), 4.13 (2H, q, *J* = 7.2 Hz, -OC$\underline{H}_2$$CH_3$), 3.84-3.79 (1H, m), 3.64-3.58 (1H, m), 3.48-3.34(2H, m), 2.97 (2H, d, *J* = 6.8 Hz), 2.53-2.36 (4H, m), 2.35 (3H, s, -CH_3), 1.24 (3H, t, *J* = 7.2 Hz, -$OCH_2C\underline{H}_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm):171.2 (C=O), 169.6 (C=C, C-7a), 164.9 (C=O), 140.3, 134.4 (C=C), 128.9, 128.6, 125.4, 118.4 (C=C), 103.6 (C=C, C-3a), 87.3 (C-2), 61.4, 59.7, 53.1, 52.9, 52.8, 42.4 (C-3), 14.4 (-CH_3), 14.3 (-CH_3);HRMS (ESI) (m/z) Calcd for $C_{22}H_{28}N_2O_4$385.21218 found 385.21370 $(M+H)^+$.

***Trans*-Ethyl 3-(4-allylpiperazine-1-carbonyl)-5,5'-dimethyl-2,3-dihydro-[2,2'-bifuran]-4-carboxylate (3l)**

It was obtained as a yellow oil; yield: 40% (0.155 g); IR (ATR) υ_{max}3067, 2982, 2907, 1708 (C=O), 1663 (C=O), 1626 (C=C), 1199, 1100, 732 (arom. CH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.26 (1H, d, *J* = 3.2 Hz, arom. CH), 5.92 (1H, d, *J* = 3.2 Hz, arom. CH), 5.80 (1H, ddt, *J* = 16.8, 10.0, 6.4 Hz, H_{olef}), 5.48 (1H, d, *J* = 7.6 Hz, H-2), 5.14 (1H, dd, *J* = 16.8, 1.6 Hz, H_{olef}), 5.13 (1H, dd, *J* = 10.0, 1.6 Hz, H_{olef}), 4.62 (1H, d, *J* = 7.6 Hz, H-3), 4.12 (2H, q,*J* = 7.2 Hz, -OC$\underline{H}_2$$CH_3$), 3.76-3.71 (1H, m), 3.58-3.49 (2H, m), 3.45-3.40 (1H, m), 2.94 (2H, d, *J* = 6.4 Hz), 2.49-2.13 (4H, m), 2.27 (3H, s, -CH_3), 2.23 (3H, s, -CH_3), 1.22 (3H, t, *J* = 7.2 Hz, -$OCH_2C\underline{H}_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm):170.7 (C=O), 168.7 (C=C, C-7a), 164.9 (C=O), 153.5, 148.9, 134.4 (C=C), 118.4 (C=C), 110.5, 106.5, 103.8 (C=C, C-3a), 80.2 (C-2), 61.4, 59.7, 53.0, 52.6, 48.6, 46.0, 42.3 (C-3), 14.4(-CH_3), 14.3(-CH_3), 13.6(-CH_3);HRMS (ESI)(m/z) Calcd for $C_{21}H_{28}N_2O_5$389.20710 found 389.20877 $(M+H)^+$.

***Trans*-Ethyl 4-(4-allylpiperazine-1-carbonyl)-2-methyl-5-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (3m)**

It was obtained as a yellow oil; yield: 20% (0.078 g); IR (ATR) υ_{max}3075, 2978, 2923, 1701 (C=O), 1652 (C=O), 1628 (C=C), 1197, 1040, 728 (arom. CH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d (ppm): 7.32 (1H, dd, *J* = 5.2 Hz, arom. CH), 7.05 (1H, d, *J* = 3.2 Hz, arom. CH), 6.98 (1H, dd, *J* = 5.2, 3.2 Hz, arom. CH), 5.84 (1H, d, *J* = 6.8 Hz, H-2), 5.81 (1H, ddt, *J* = 16.8, 10.0, 6.4 Hz, H_{olef}), 5.18 (1H, dd, *J* = 16.8, 1.6 Hz, H_{olef}), 5.15 (1H, dd, *J* = 10.0, 1.6 Hz, H_{olef}), 4.48 (1H,d, *J* = 6.8 Hz, H-3), 4.15 (2H, q, *J* = 7.2 Hz, -OC$\underline{H}_2$$CH_3$), 3.83-3.45 (4H, m), 2.98 (2H, d, *J* = 6.4 Hz), 2.52-2.18 (4H, m), 2.29 (3H, s, -CH_3), 1.25 (3H, t, *J* = 7.2 Hz, -$OCH_2C\underline{H}_3$);^{13}C NMR(100 MHz, $CDCl_3$) d (ppm):170.6 (C=O), 168.9 (C=C, C-7a), 164.8 (C=O), 142.5, 134.3 (C=C), 126.9, 126.1, 125.8, 118.5 (C=C), 103.7 (C=C, C-3a), 82.9 (C-2), 61.4, 59.8, 53.1, 53.0, 52.7, 46.1, 42.4 (C-3), 14.5 (-CH_3), 14.4 (-CH_3);HRMS (ESI)(m/z) Calcd for $C_{20}H_{26}N_2O_4S$391.16860 found 391.16985 $(M+H)^+$.

Ethyl 5-(4-allylpiperazine-1-carbonyl)-2,5-dimethyl-4,5-dihydrofuran-3-carboxylate(3n)

It was obtained as a yellow oil; yield: 20% (0.065 g); IR (ATR) υ_{max}3076, 2983, 2930, 1701 (C=O), 1657 (C=O), 1630 (C=C), 1190, 1040cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.84 (1H, ddt, *J* = 16.8, 10, 6.8 Hz, H_{olef}), 5.20 (1H, dd, *J*= 16.8, 1.6 Hz, H_{olef}), 5.17 (1H, dd, *J* = 10.0, 1.6 Hz, H_{olef}), 4.15 (2H, q, *J* = 7.2 Hz, -OC$\underline{H}_2$$CH_3$), 3.81-3.62 (4H, m), 3.58 (1H, d, *J* = 15.2 Hz, Ha-3), 3.00 (2H, d, *J* = 6.8 Hz), 2.70 (1H, d, *J* = 15.2 Hz, Hb-3), 2.44 (4H, m), 2.18 (3H, s, -CH_3), 1.55 (3H, s, -CH_3), 1.26 (3H, t, *J* = 7.2 Hz, -$OCH_2C\underline{H}_3$);^{13}C NMR(100 MHz, $CDCl_3$) δ (ppm):170.1 (C=O), 165.7 (C=C, C-7a), 164.8 (C=O), 134.3 (C=C), 118.5 (C=C), 102.1 (C=C, C-3a), 88.4 (C-2), 61.5, 59.6, 53.1, 52.8, 46.2, 43.2, 41.1 (C-3), 26.0(-CH_3), 14.3(-CH_3), 14.1(-CH_3);HRMS (ESI)(m/z) Calcd for $C_{17}H_{26}N_2O_4$323.19653 found 323.19805 $(M+H)^+$.

4. Conclusion

Summarily, novel piperazines containing dihydrofuran compounds (3a-n) were synthesized by the $Mn(OAc)_3$ mediated radical cyclization from unsaturated diacyl (1a-d) and alkyl-acyl (1e-h) piperazine compounds with 1,3-dicarbonyls (**2a-c**) in low to high yields for the first time. All compounds were characterized by ^{1}HNMR, ^{13}C NMR, HRMS, and FTIR spectroscopy.

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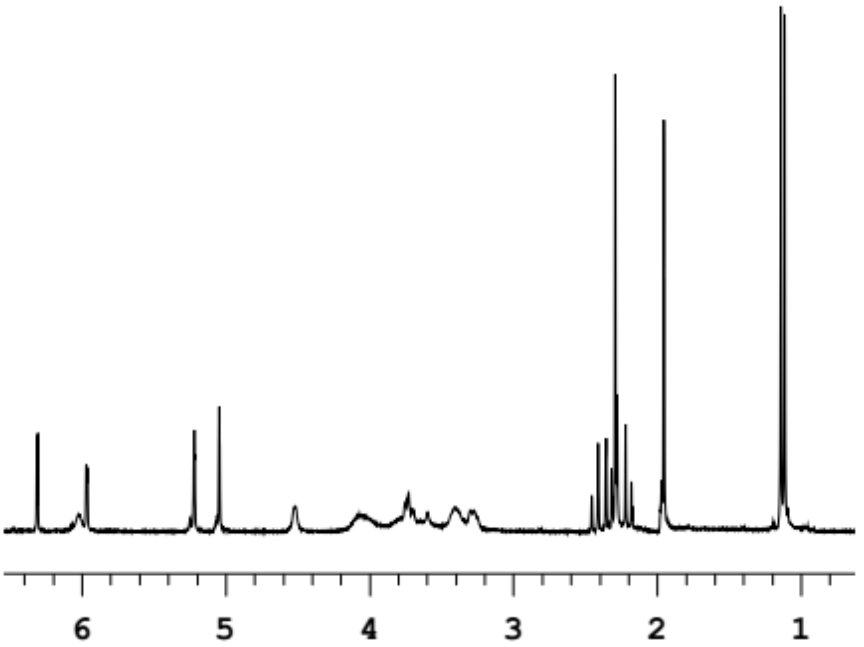
SUPPLEMENTARY INFORMATION

^{1}H NMR and ^{13}C NMR spectra

3a. ^{1}H NMR



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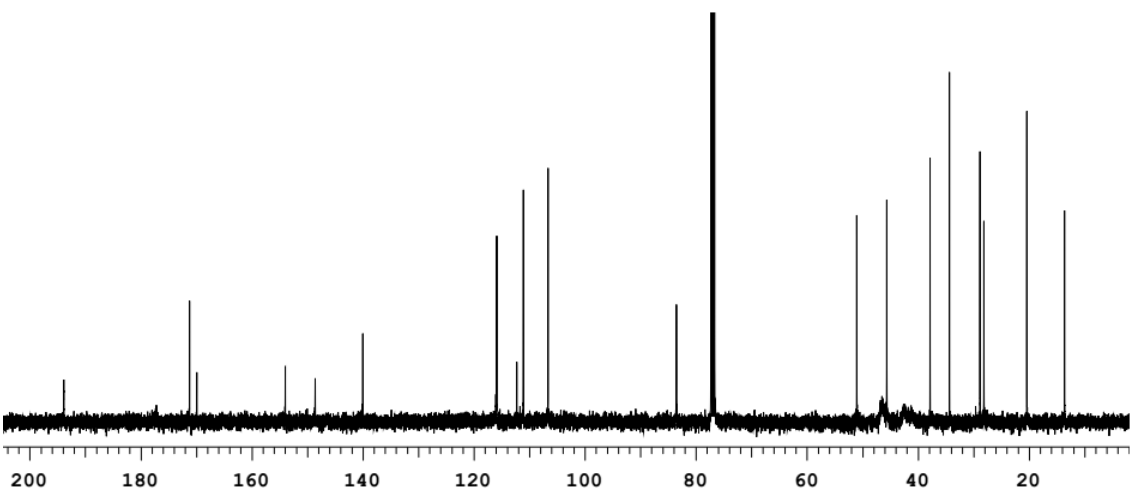

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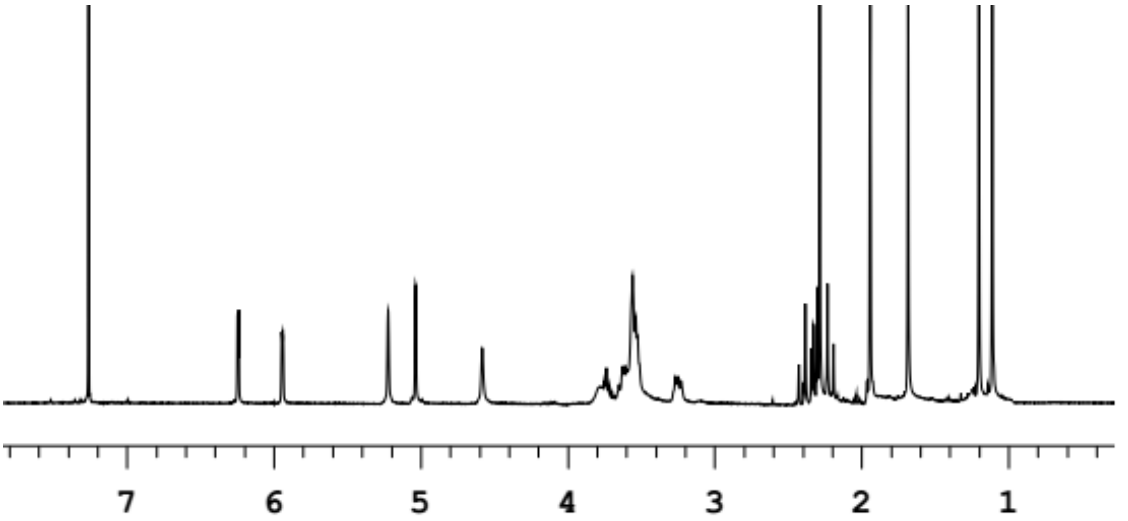

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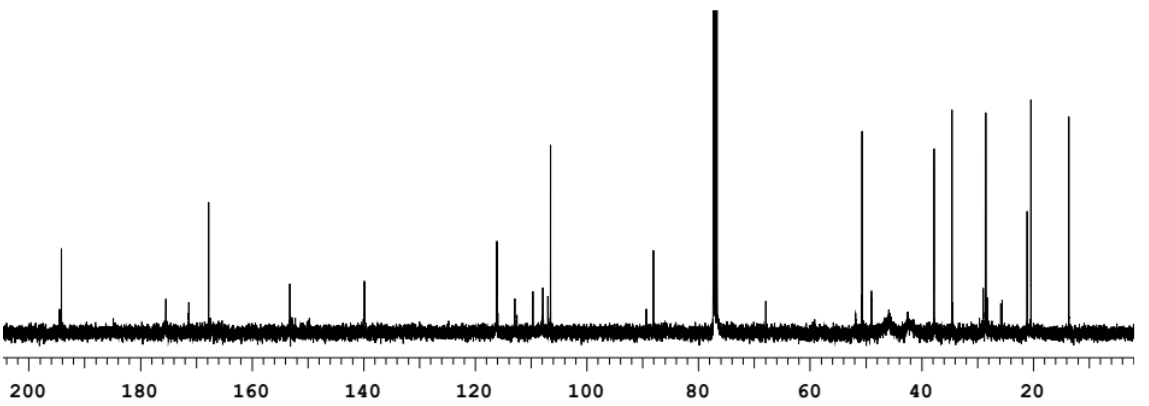

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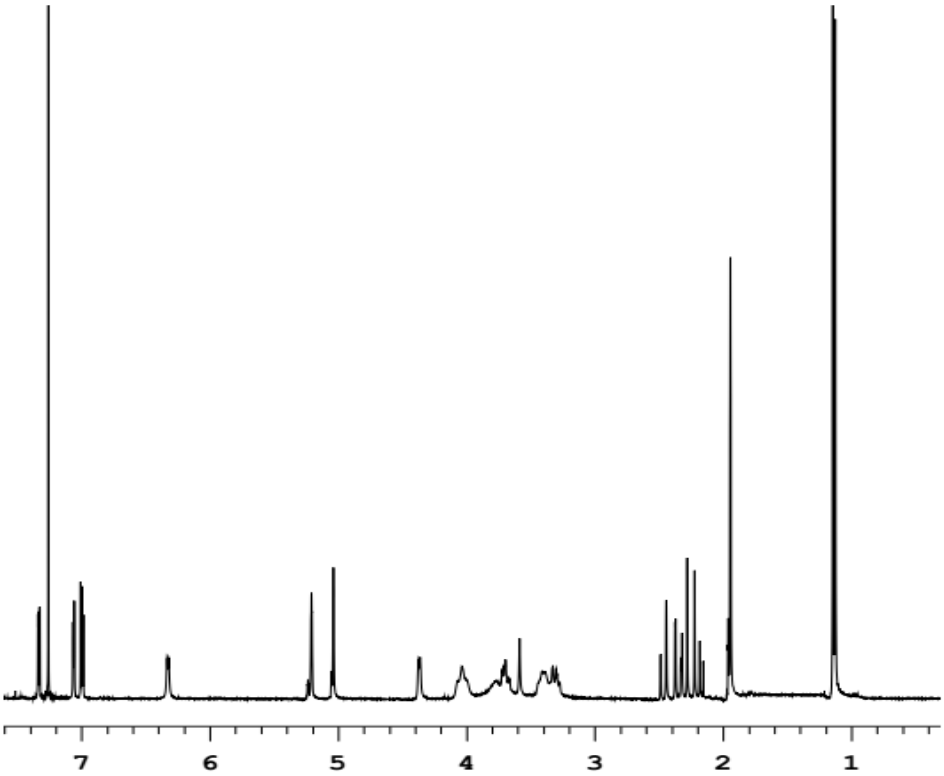

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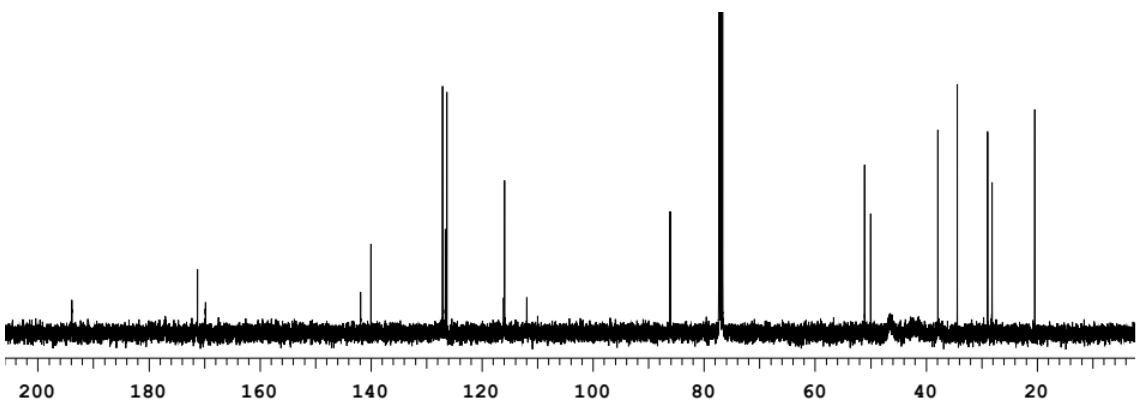
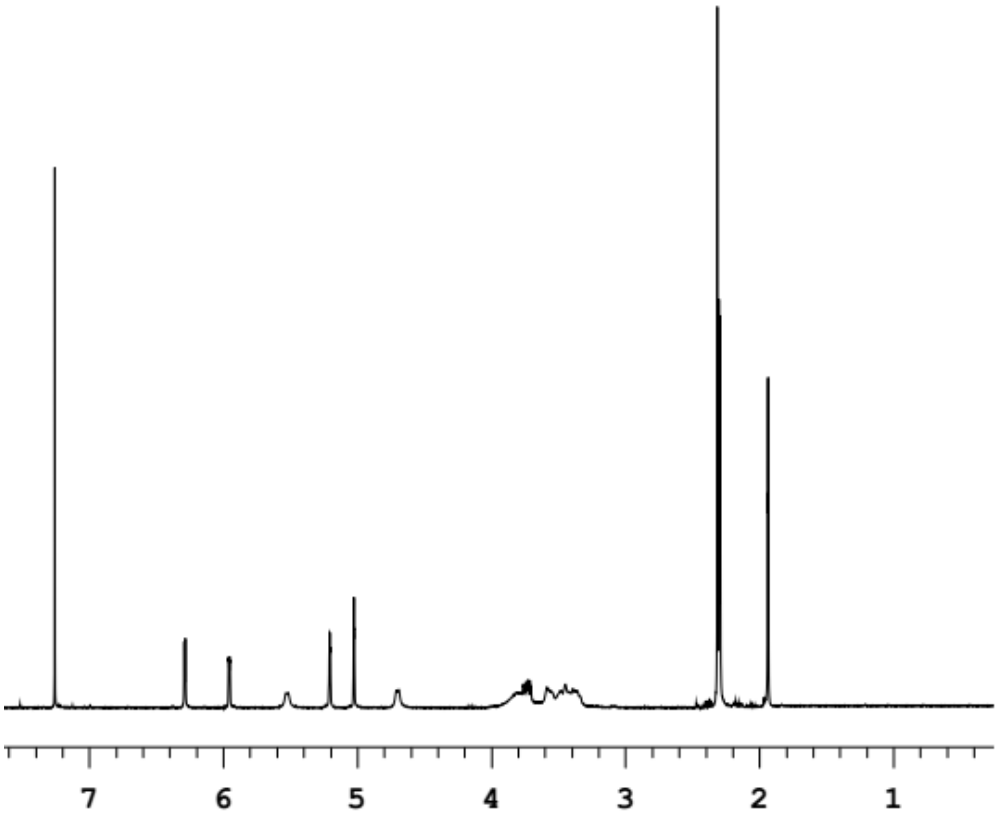
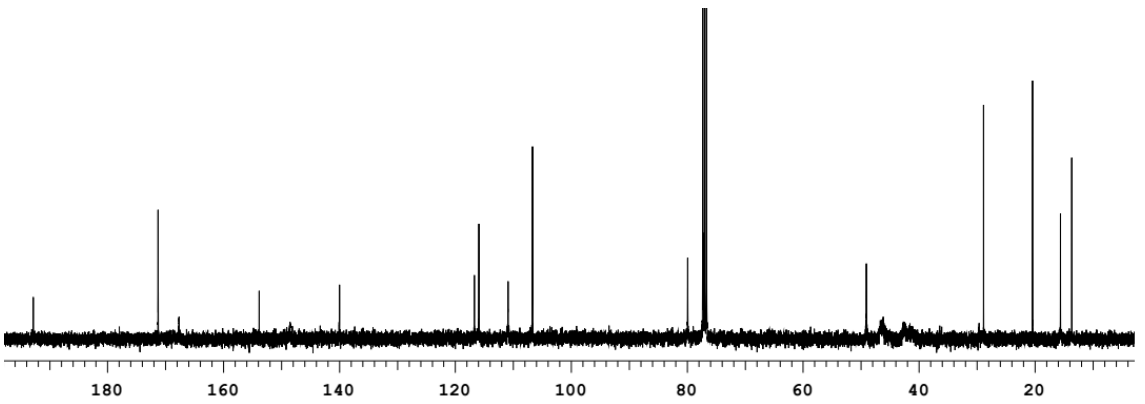


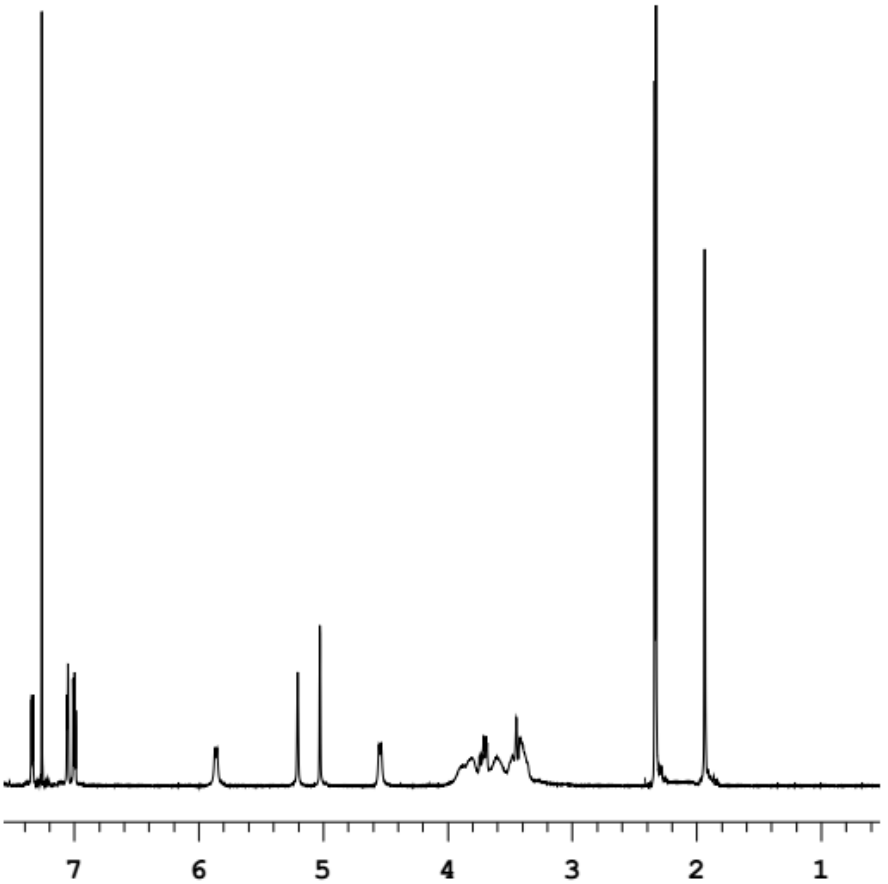
3d. ^{1}H NMR



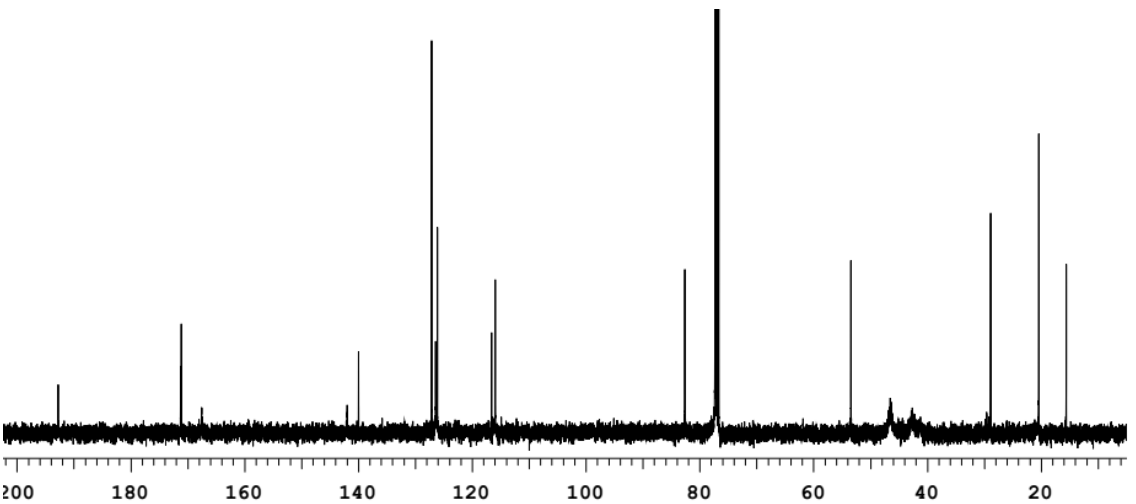
3d. ^{13}C NMR



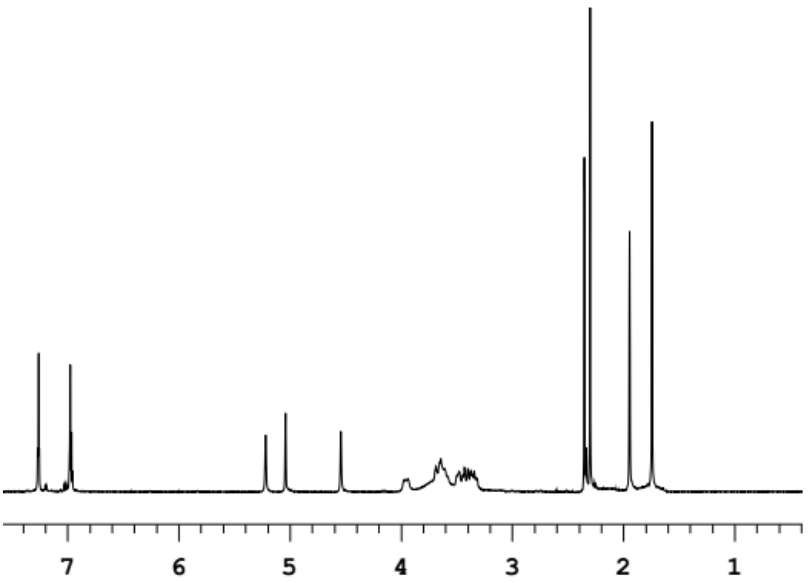
3e. ^{1}H NMR



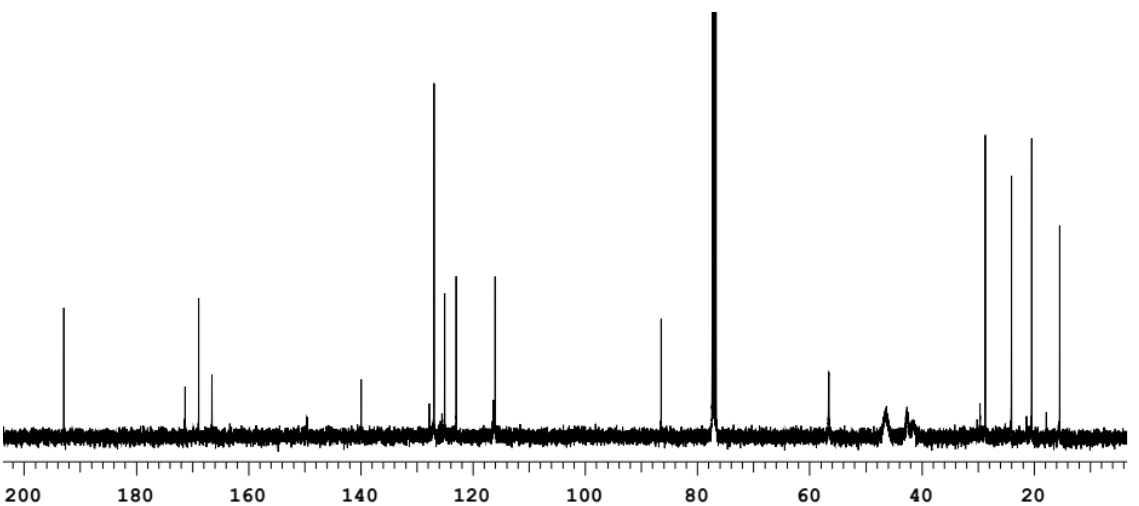
3e. ^{13}C NMR



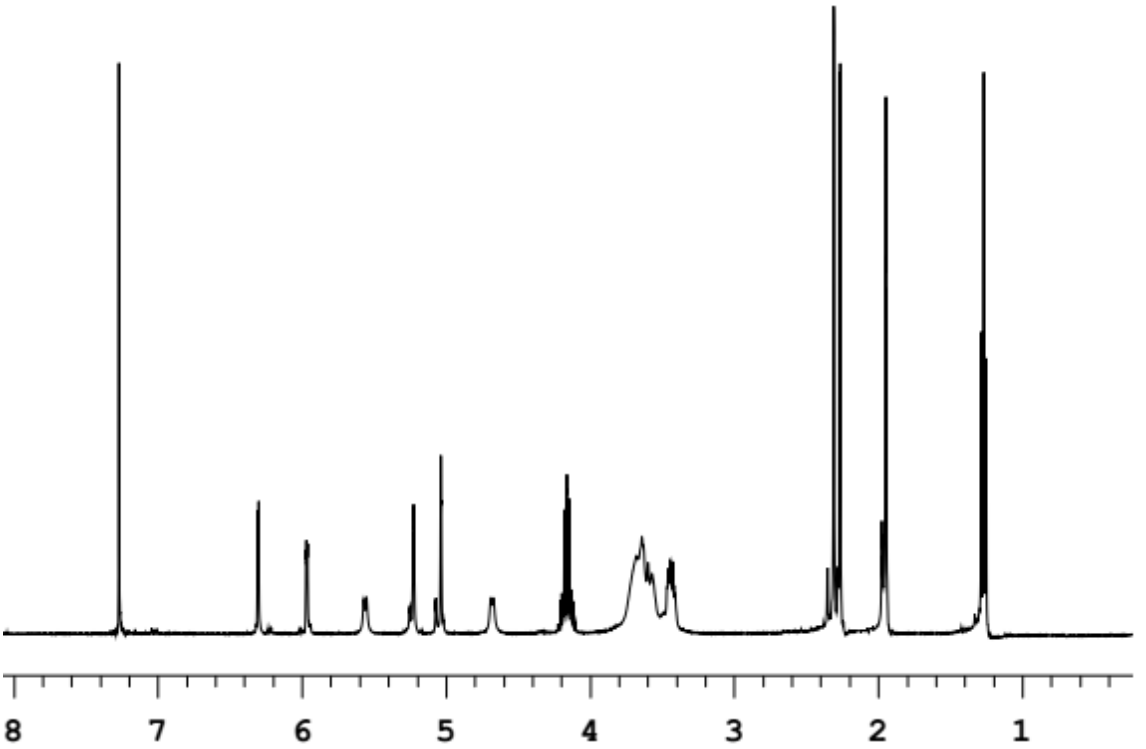
3f. ^{1}H NMR



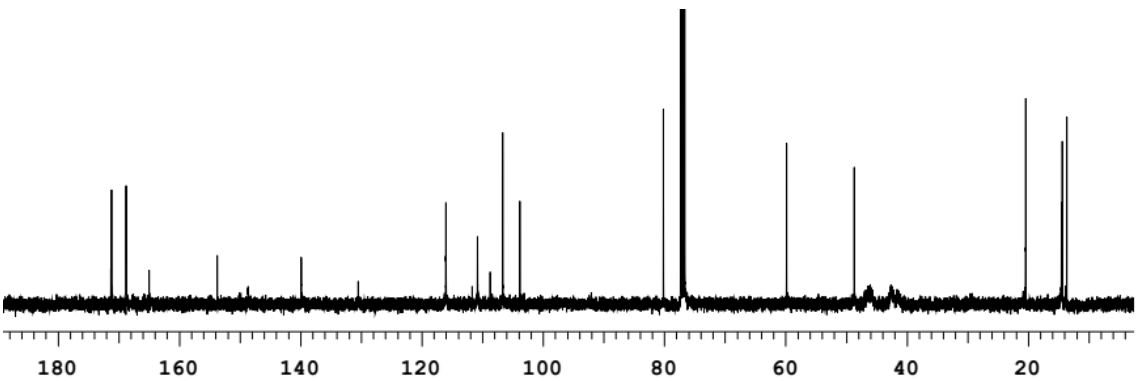
3f. ^{13}C NMR



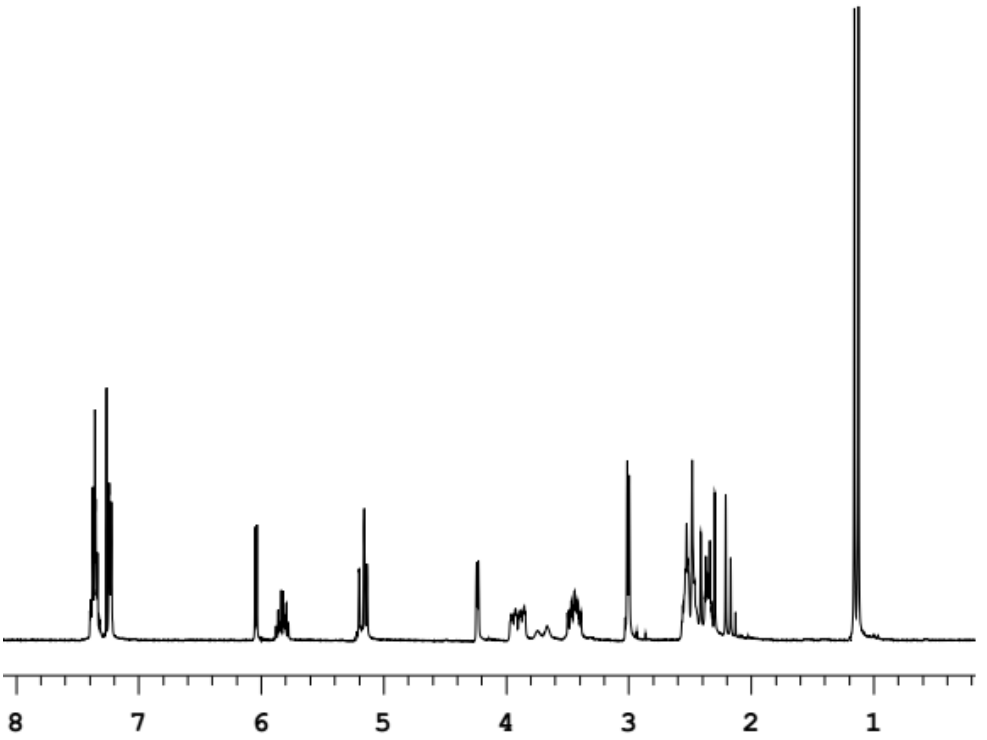
3g. ^{1}H NMR



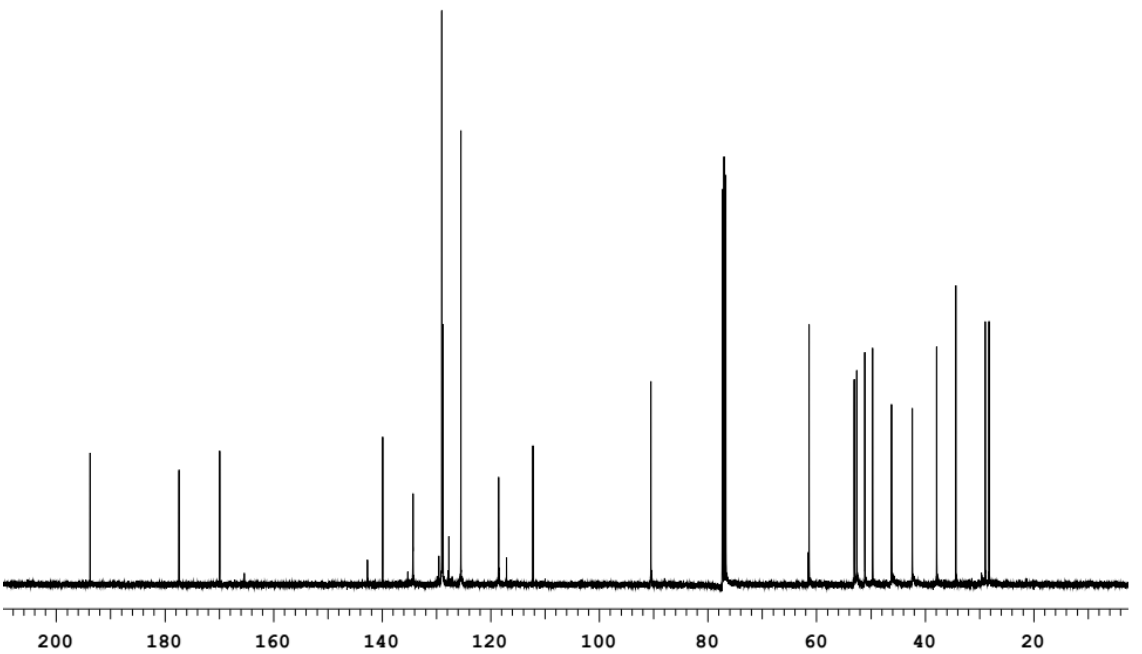
3g. ^{13}C NMR



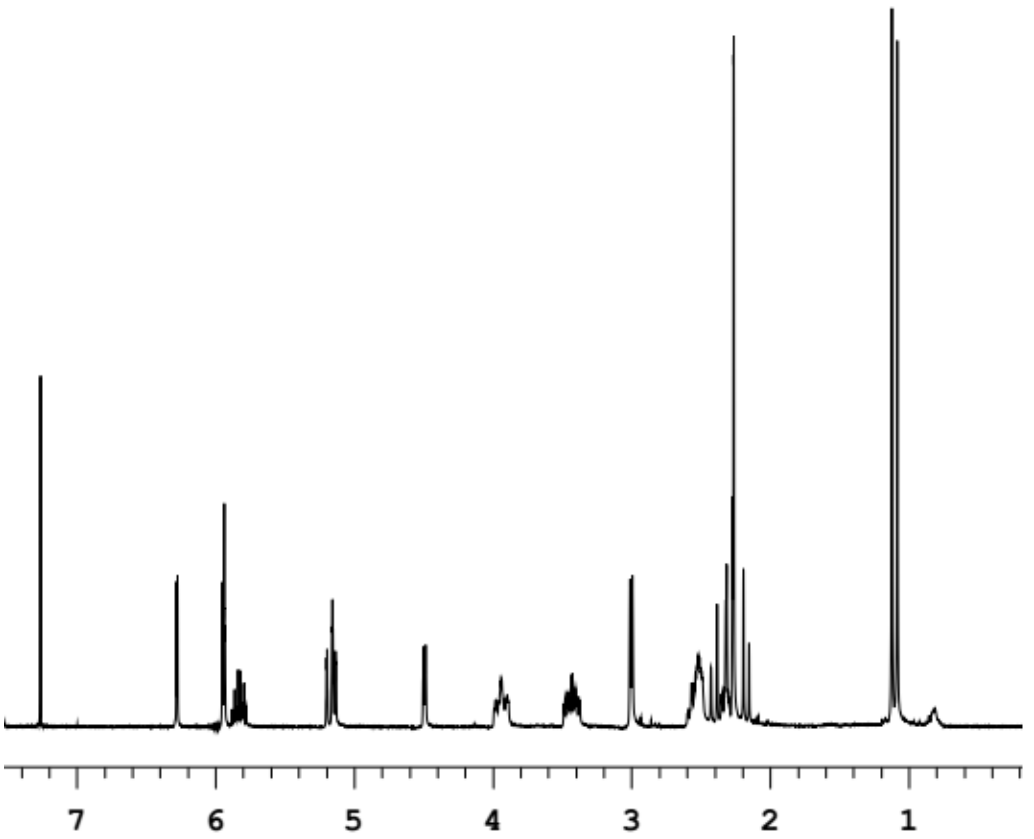
3h. ^{1}H NMR



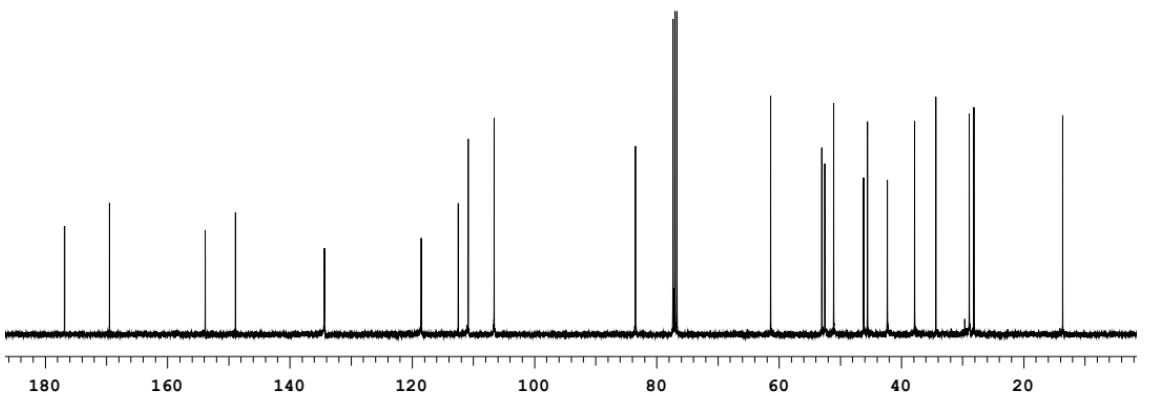
3h. ^{13}C NMR



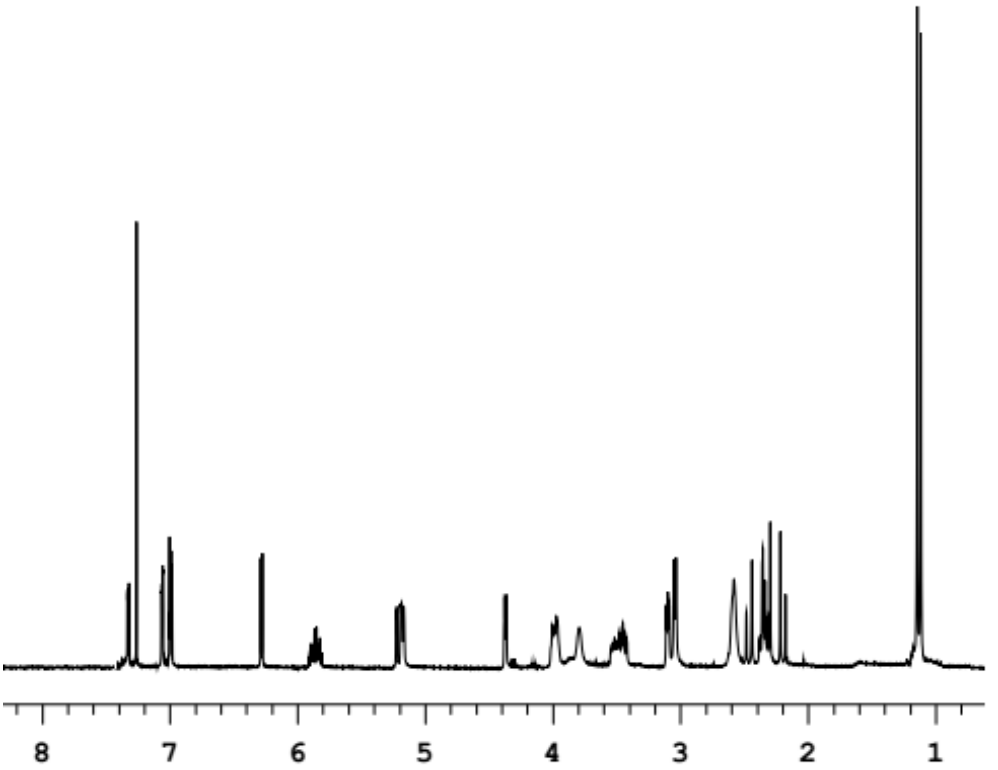
3i. ^{1}H NMR



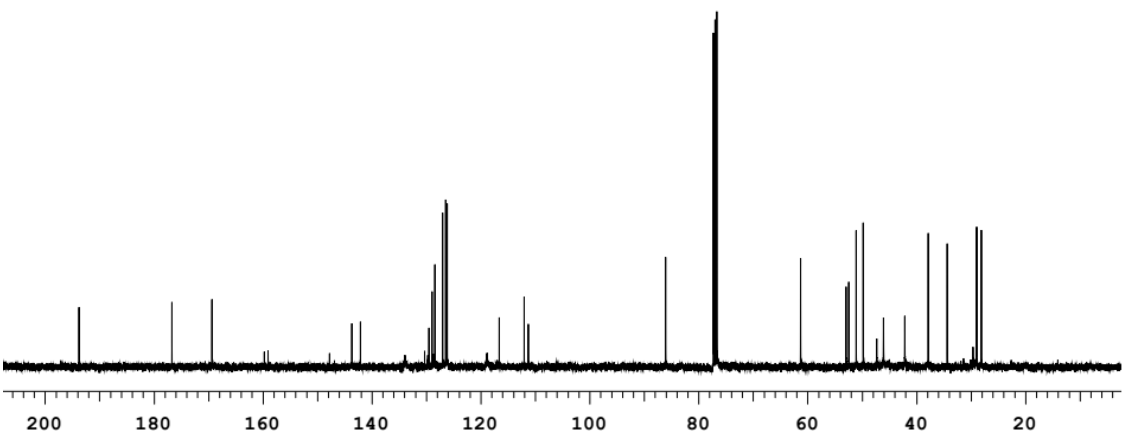
3i. ^{13}C NMR



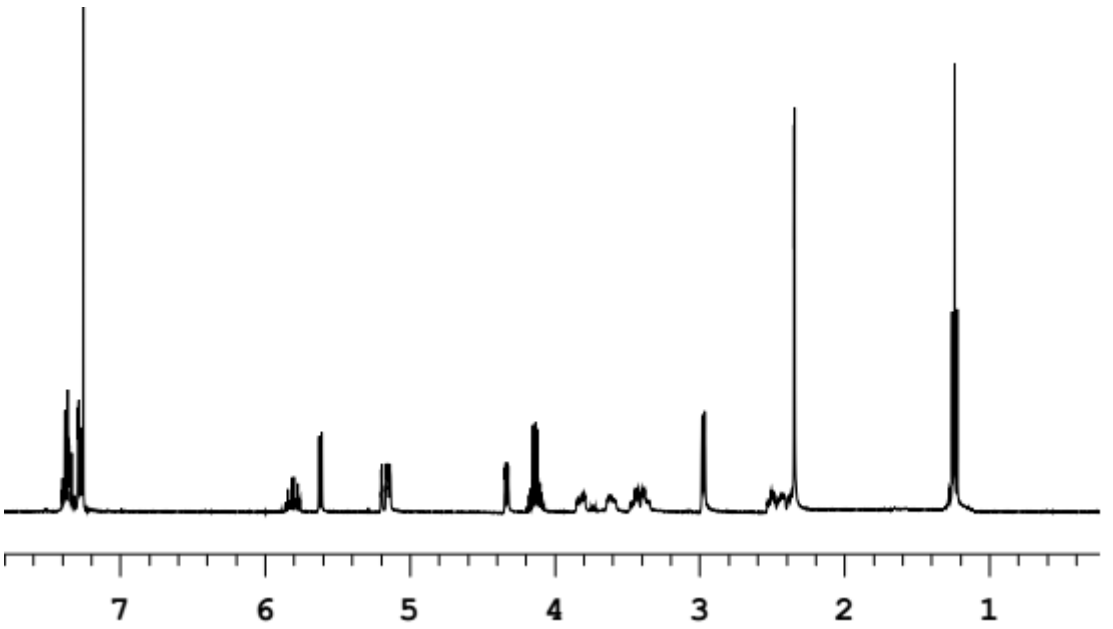
3j. ^{1}H NMR



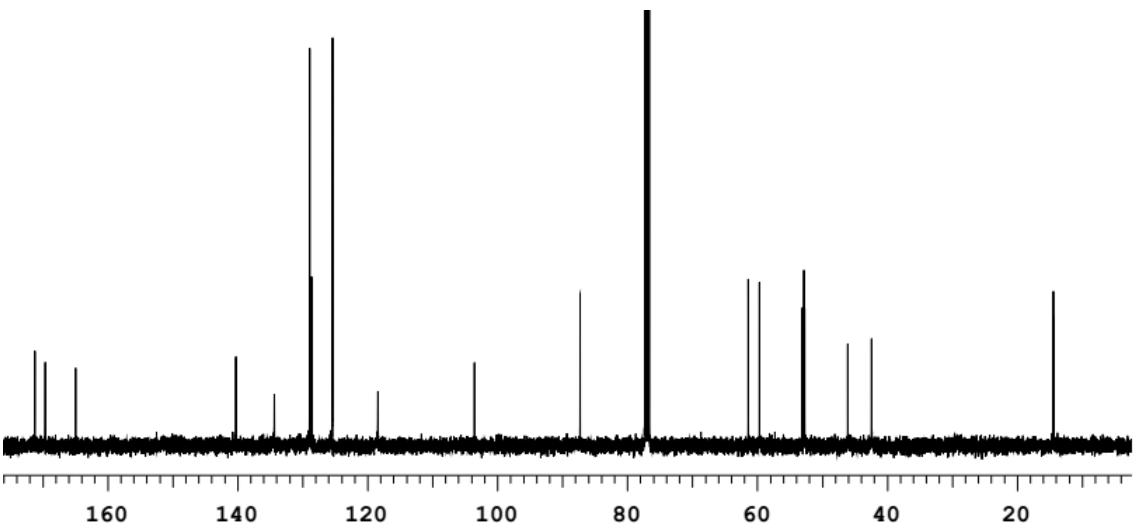
3j. ^{13}C NMR



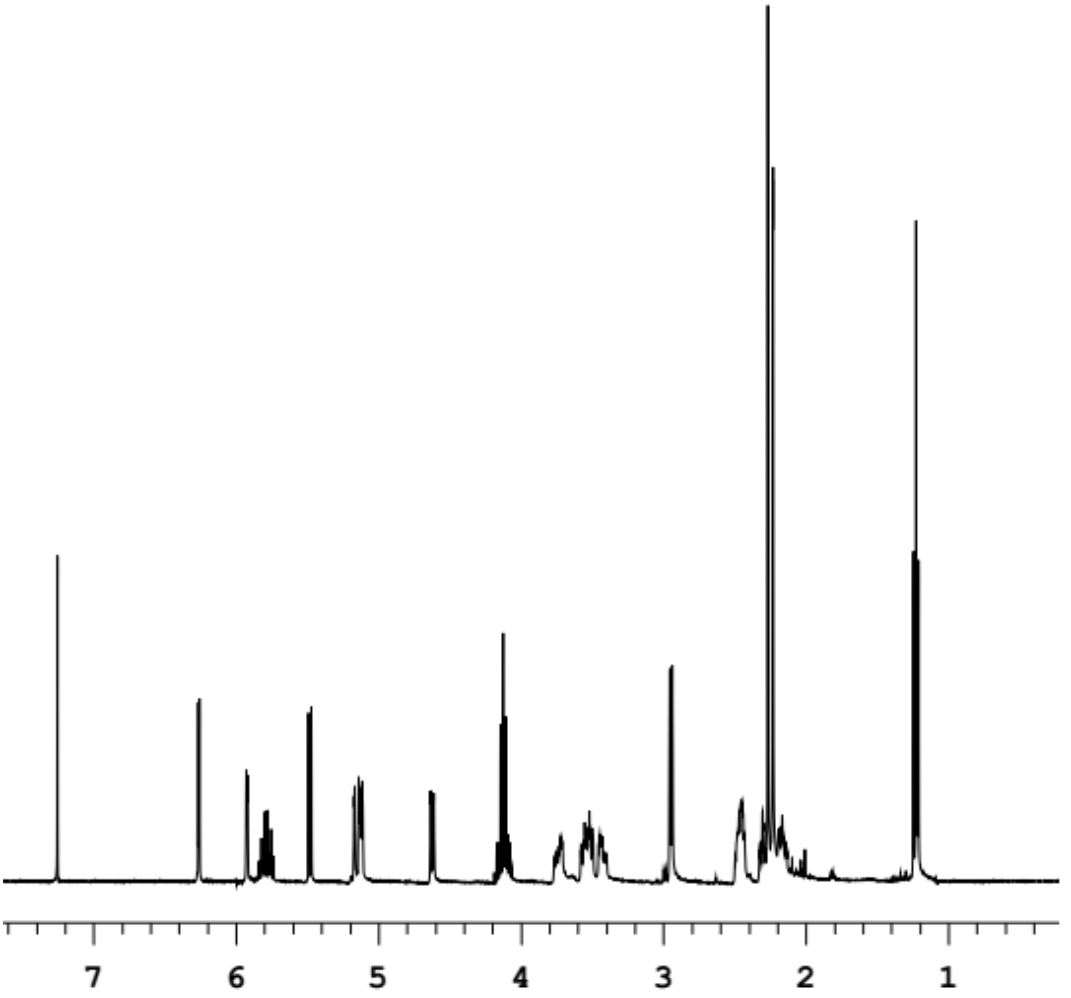
3k. ^{1}H NMR



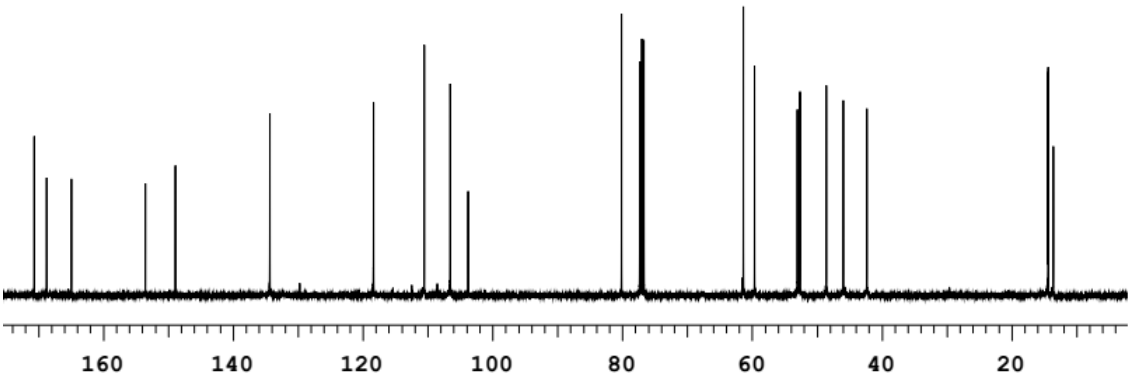
3k. ^{13}C NMR



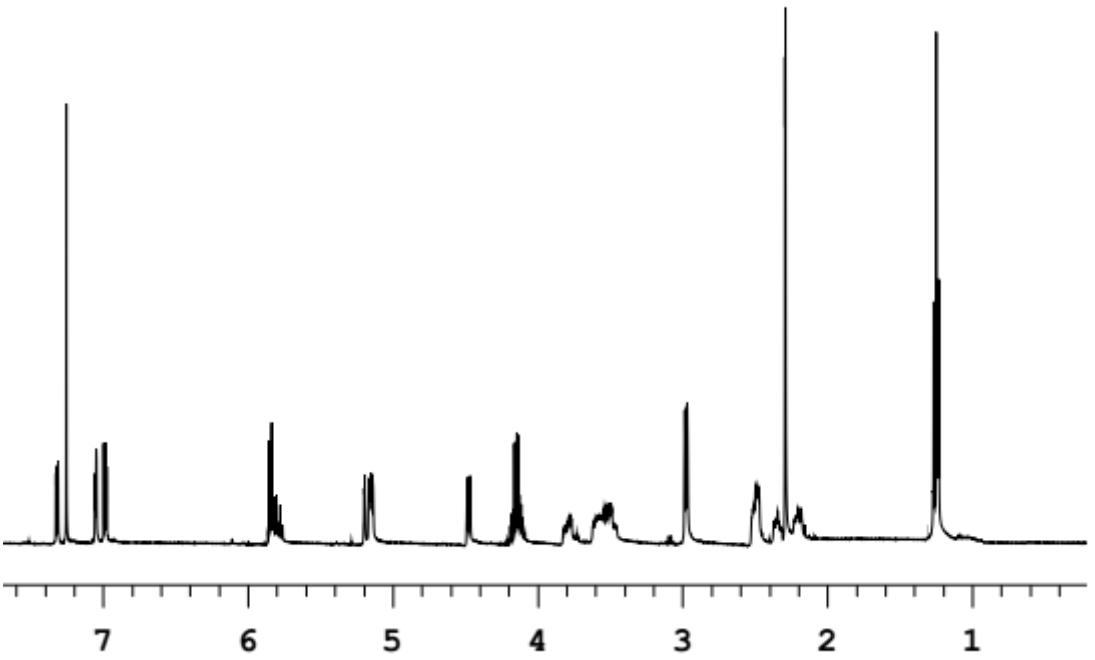
3l. ^{1}H NMR



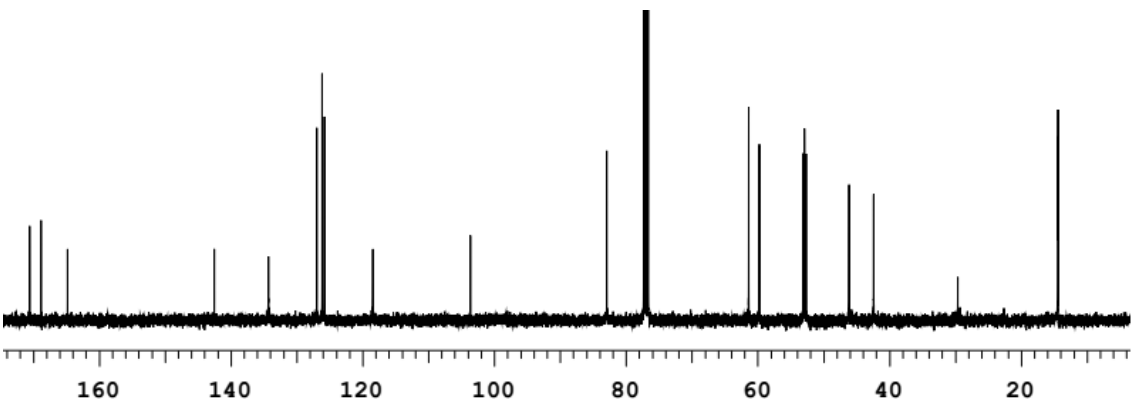
3l. ^{13}C NMR



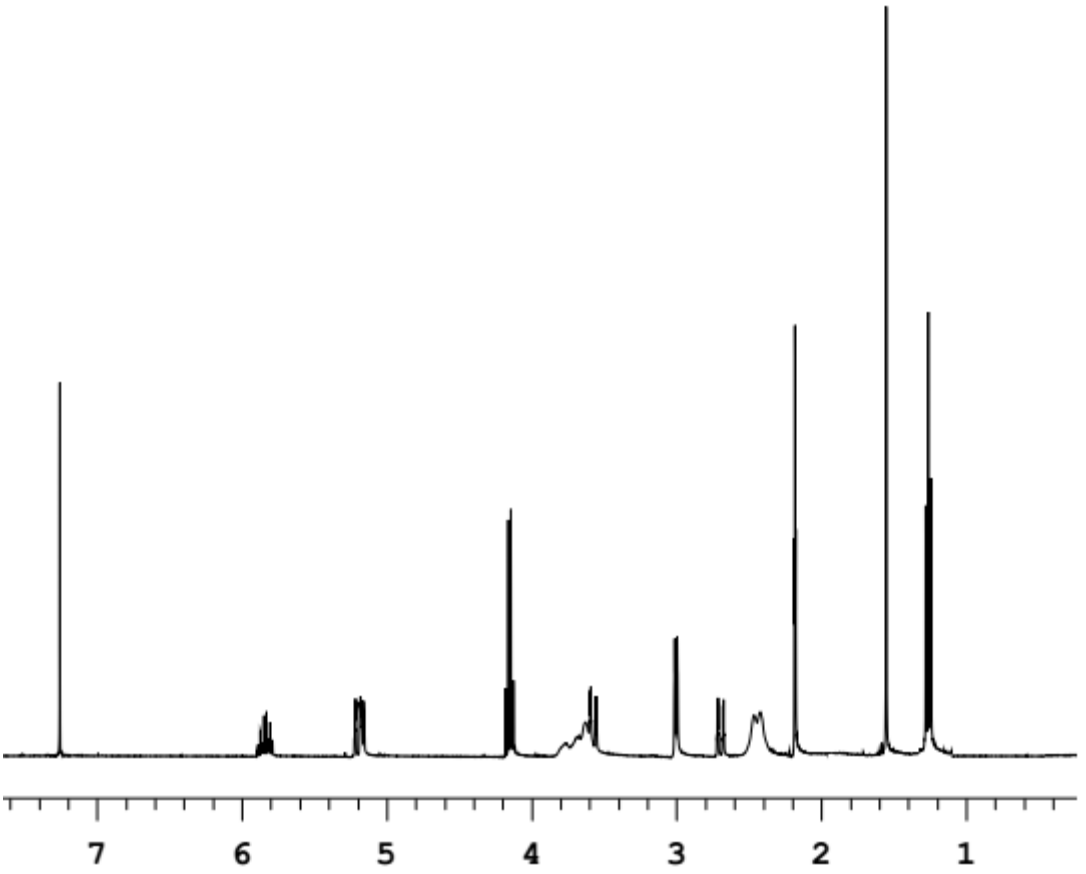
3m. ^{1}H NMR



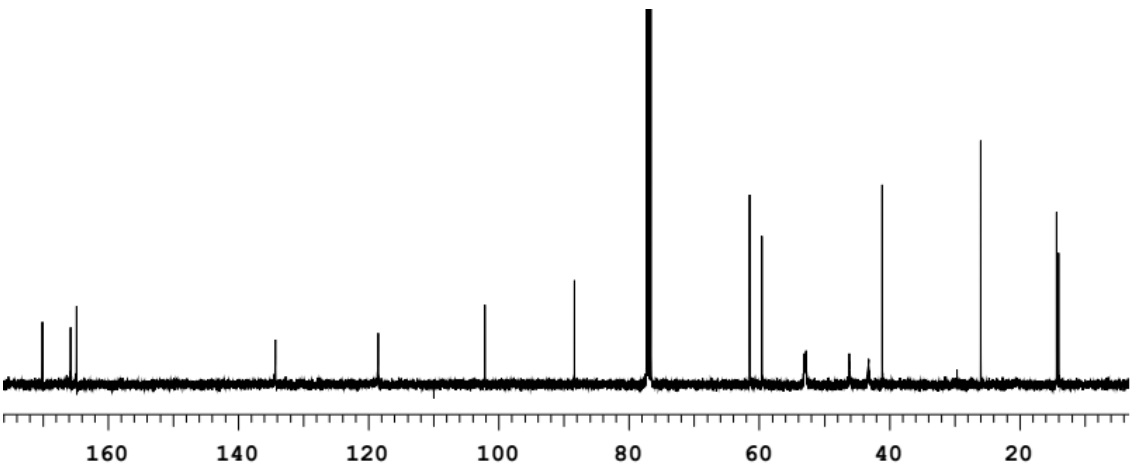
3m. ^{13}C NMR



3n. ^{1}H NMR

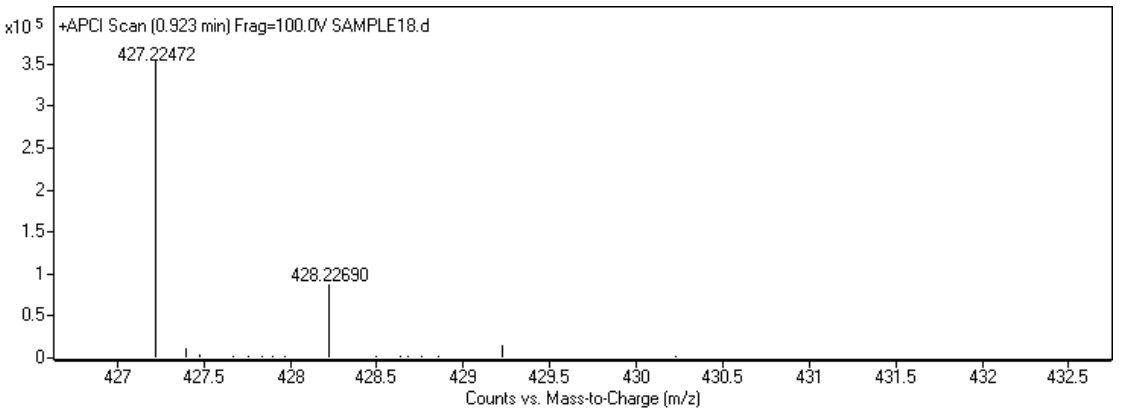


3n. ^{13}C NMR

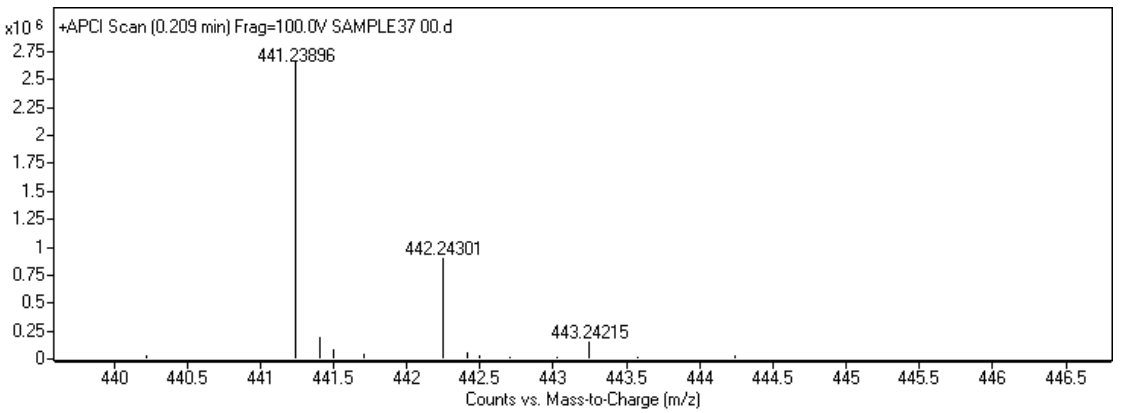


HRMS spectra

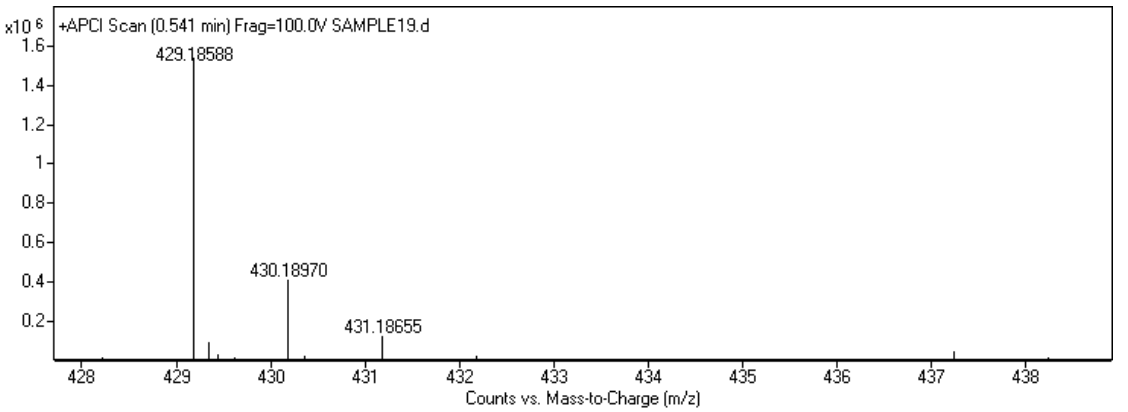
3a



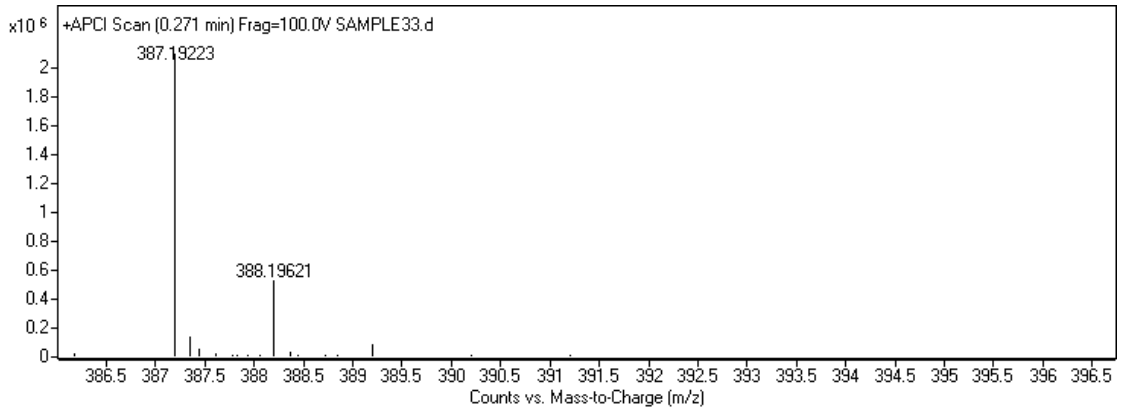
3b



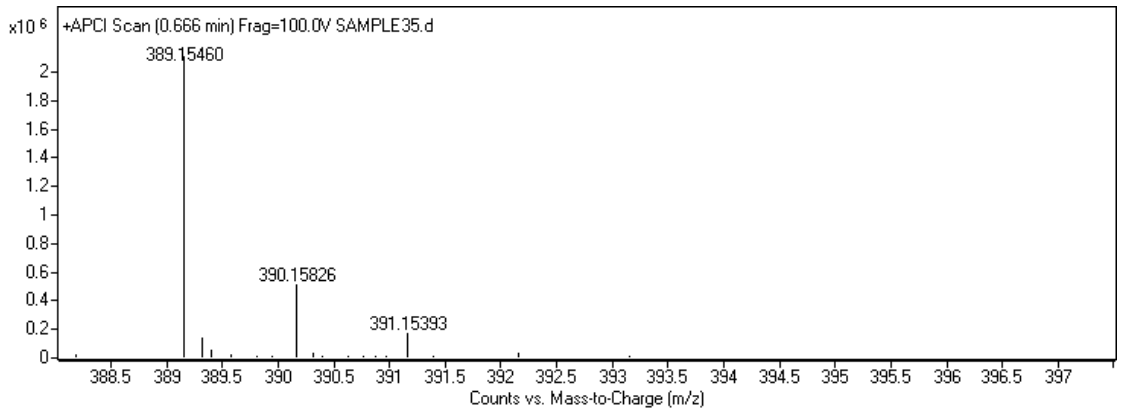
3c



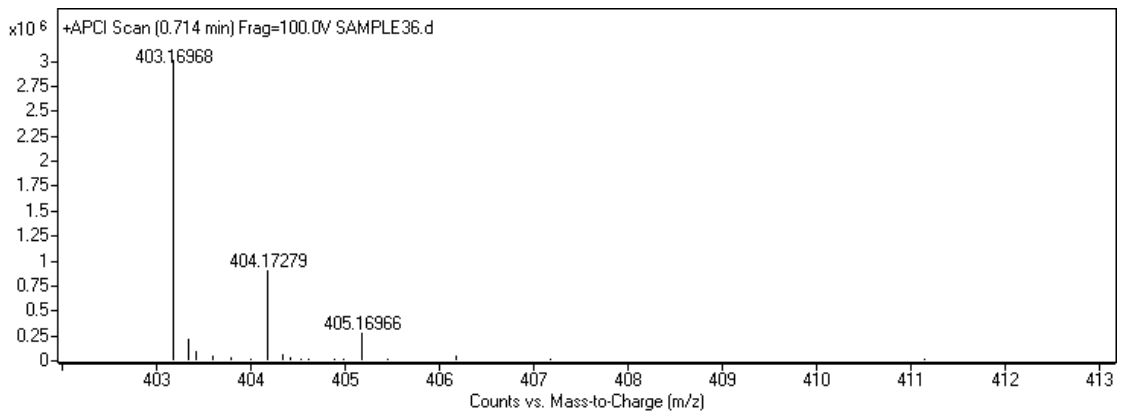
3d


x10 6
+APCI Scan (0.271 min) Frag=100.0V SAMPLE33.d
387.19223
388.19621
Counts vs. Mass-to-Charge (m/z)

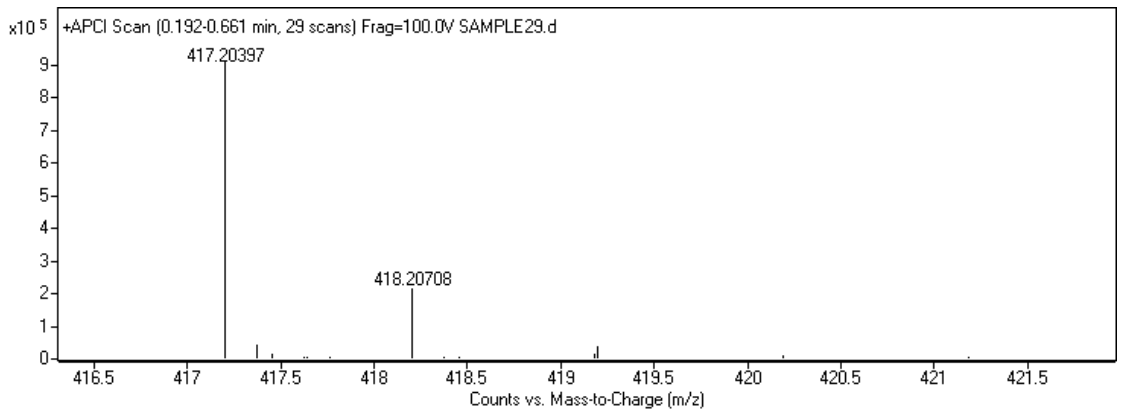
3e


x10 6
+APCI Scan (0.666 min) Frag=100.0V SAMPLE35.d
389.15460
390.15826
391.15393
Counts vs. Mass-to-Charge (m/z)

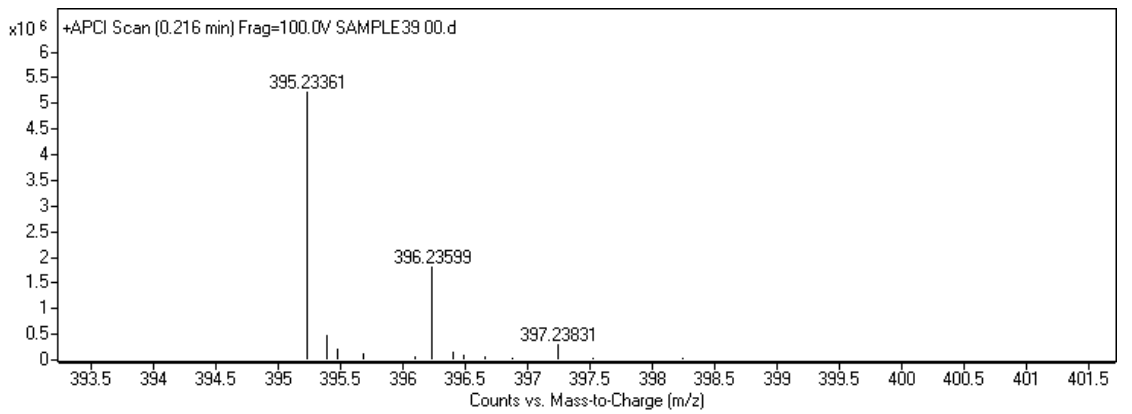
3f


x10 6
+APCI Scan (0.714 min) Frag=100.0V SAMPLE36.d
403.16968
404.17279
405.16966
Counts vs. Mass-to-Charge (m/z)

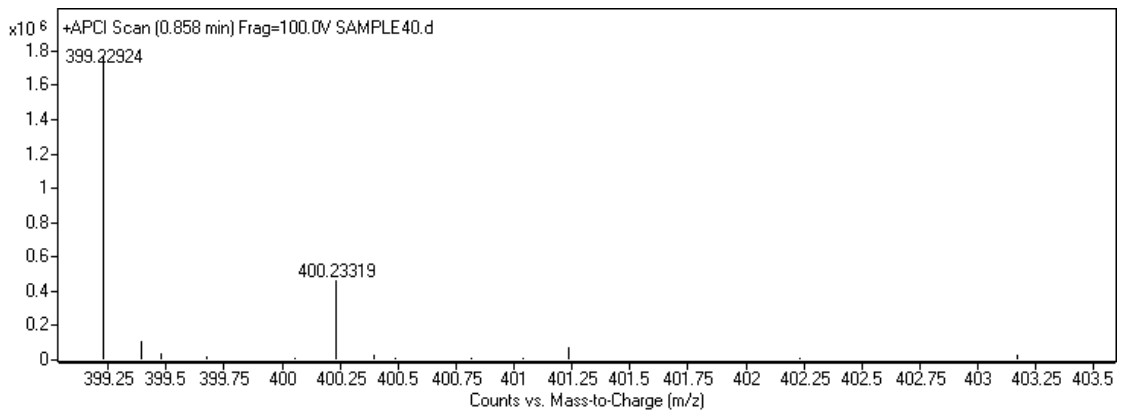
3g


x10 5
+APCI Scan (0.192-0.661 min, 29 scans) Frag=100.0V SAMPLE29.d
417.20397
418.20708
Counts vs. Mass-to-Charge (m/z)

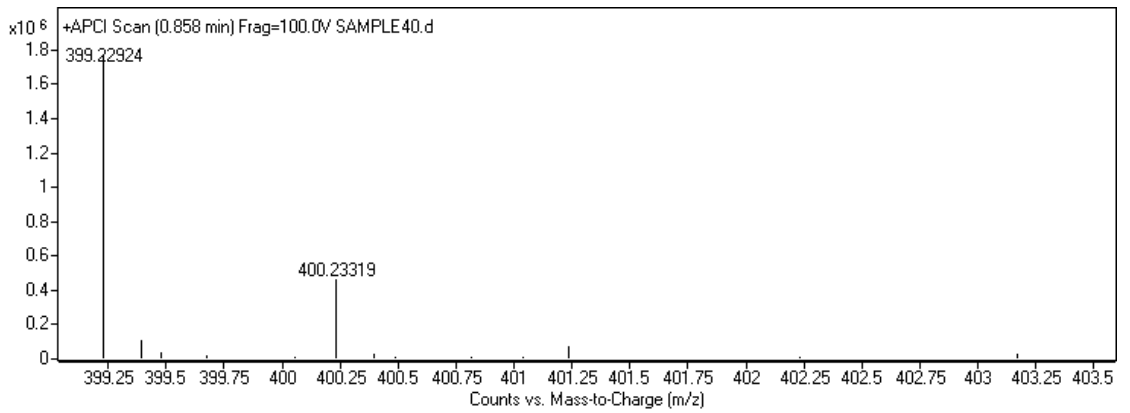
3h


x10 6
+APCI Scan (0.216 min) Frag=100.0V SAMPLE39 00.d
395.23361
396.23599
397.23831
Counts vs. Mass-to-Charge (m/z)

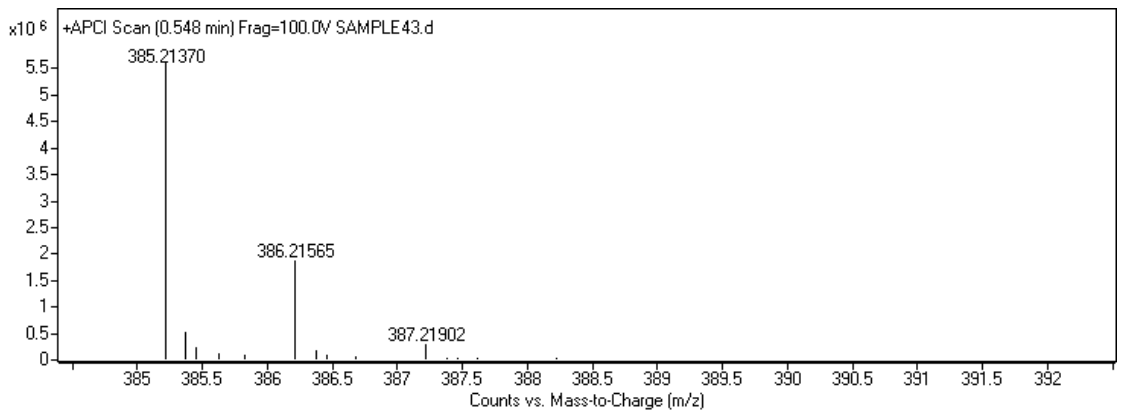
3i


x10 6
+APCI Scan (0.858 min) Frag=100.0V SAMPLE40.d
399.22924
400.23319
Counts vs. Mass-to-Charge (m/z)

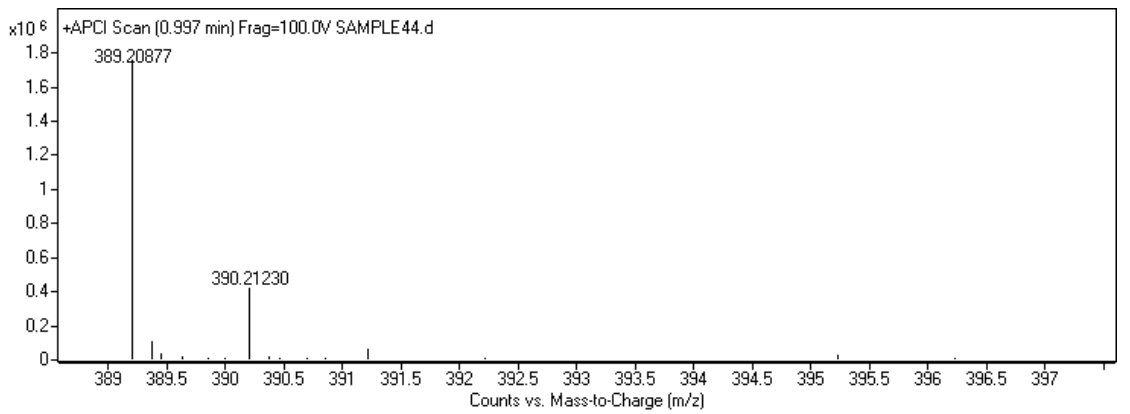
3j


x10 6
+APCI Scan (0.858 min) Frag=100.0V SAMPLE40.d
399.22924
400.23319
Counts vs. Mass-to-Charge (m/z)

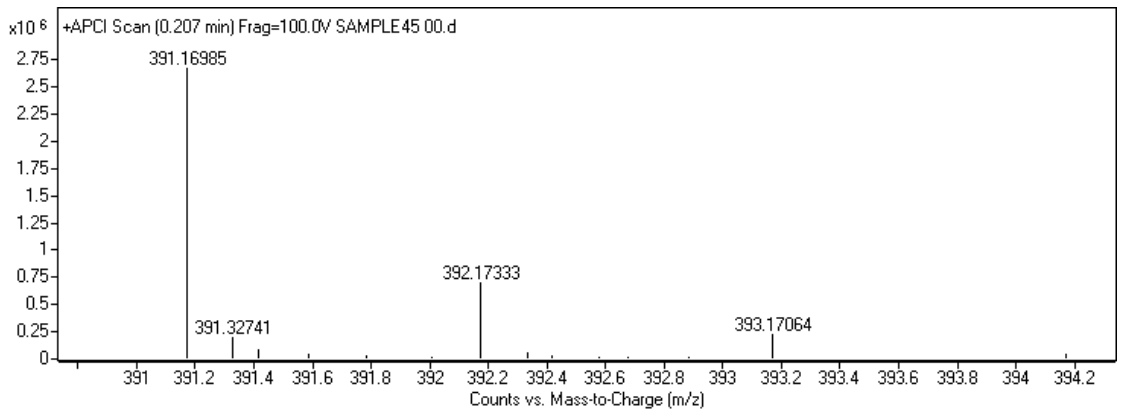
3k


x10 6
+APCI Scan (0.548 min) Frag=100.0V SAMPLE43.d
385.21370
386.21565
387.21902
Counts vs. Mass-to-Charge (m/z)

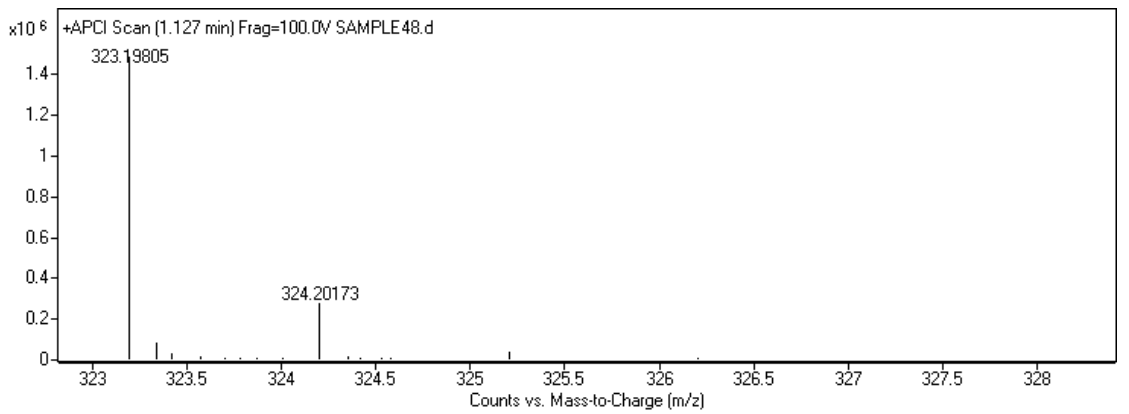
3l


x10 6
+APCI Scan (0.997 min) Frag=100.0V SAMPLE44.d
389.20877
390.21230
Counts vs. Mass-to-Charge (m/z)

3m


x10 6
+APCI Scan (0.207 min) Frag=100.0V SAMPLE45 00.d
391.16985
392.17333
391.32741
393.17064
Counts vs. Mass-to-Charge (m/z)

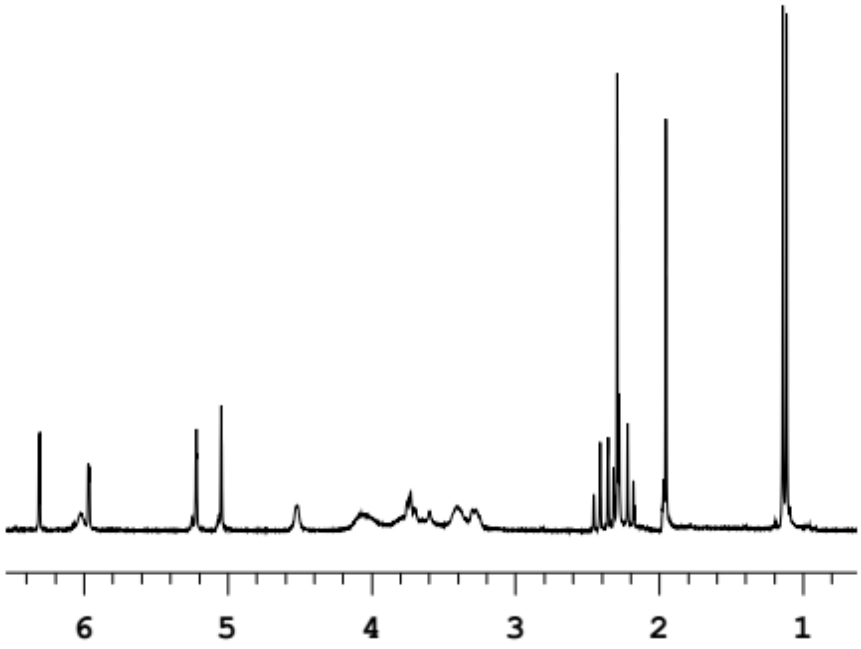
3n


x10 6
+APCI Scan (1.127 min) Frag=100.0V SAMPLE48.d
323.19805
324.20173
Counts vs. Mass-to-Charge (m/z)

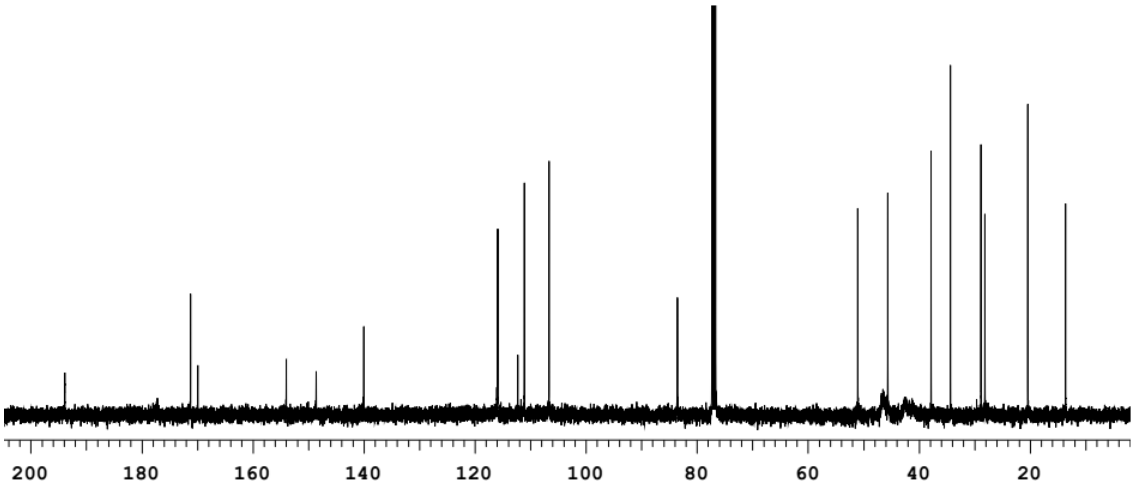
SUPPLEMENTARY INFORMATION

^{1}H NMR and ^{13}C NMR spectra

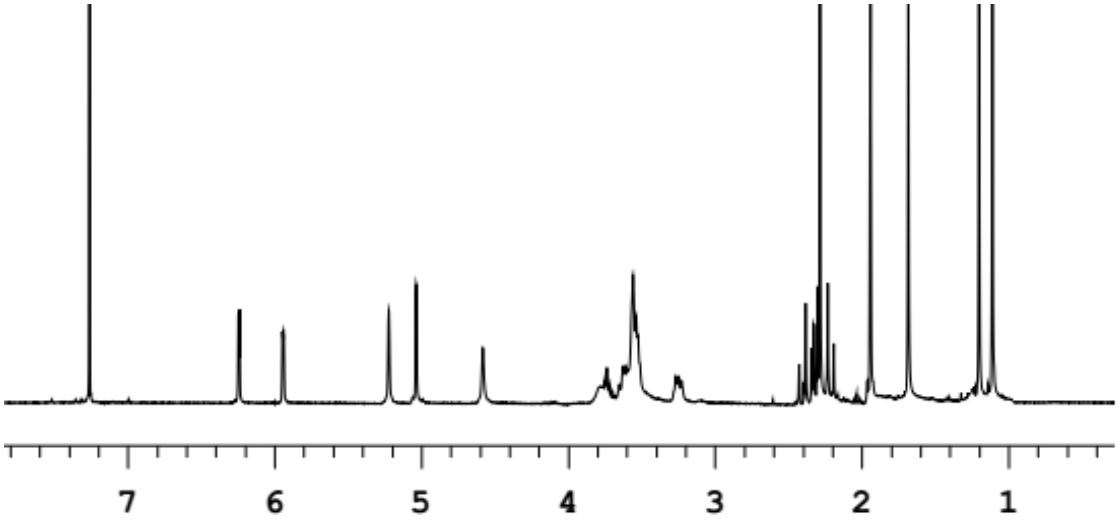
3a. ^{1}H NMR



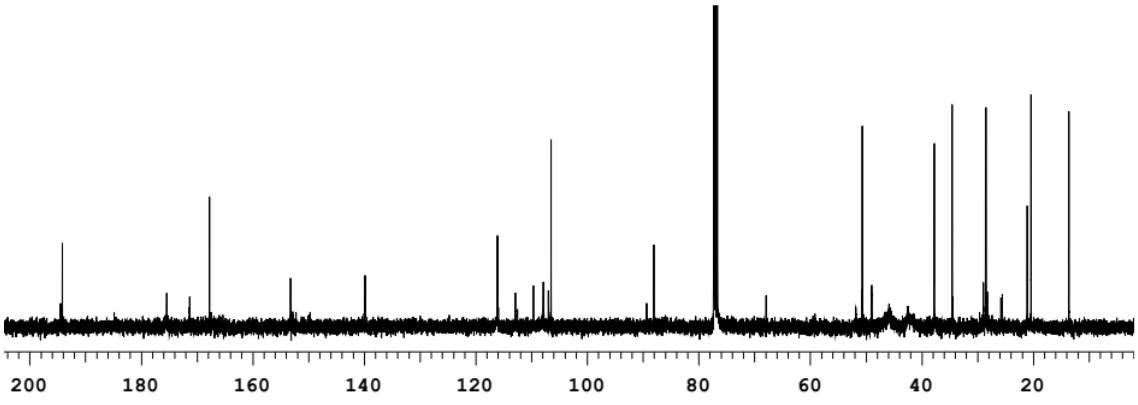
3a. ^{13}C NMR



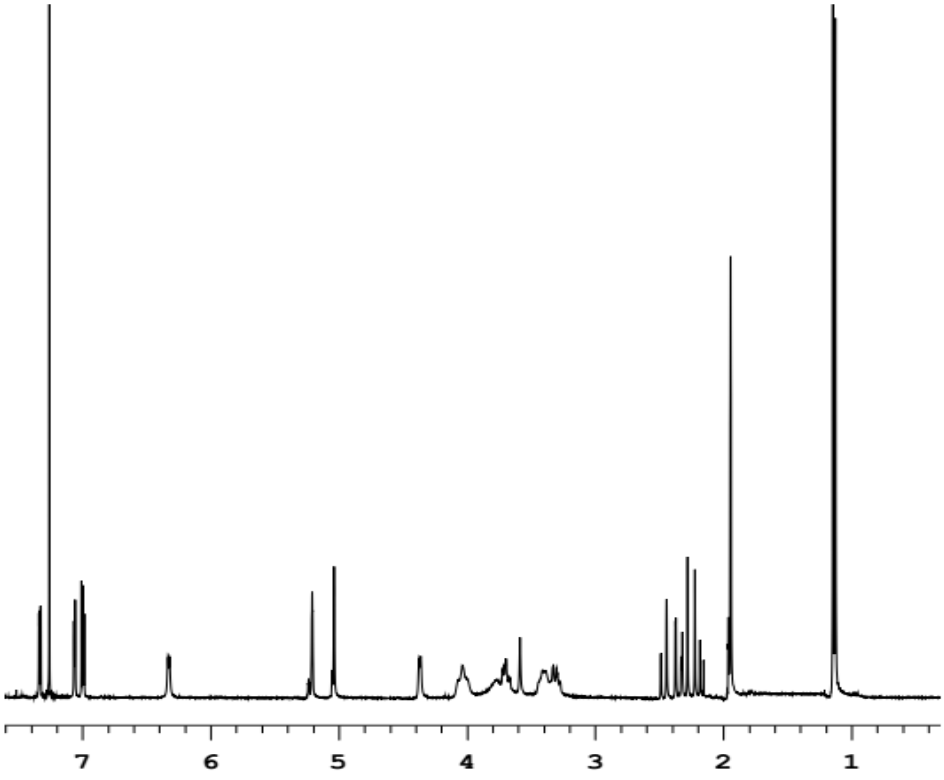
3b. ^{1}H NMR



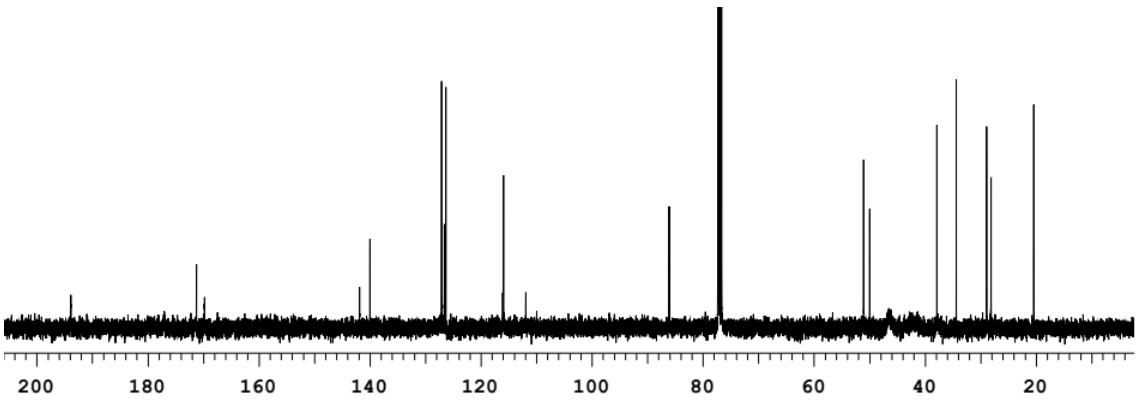
3b. ^{13}C NMR



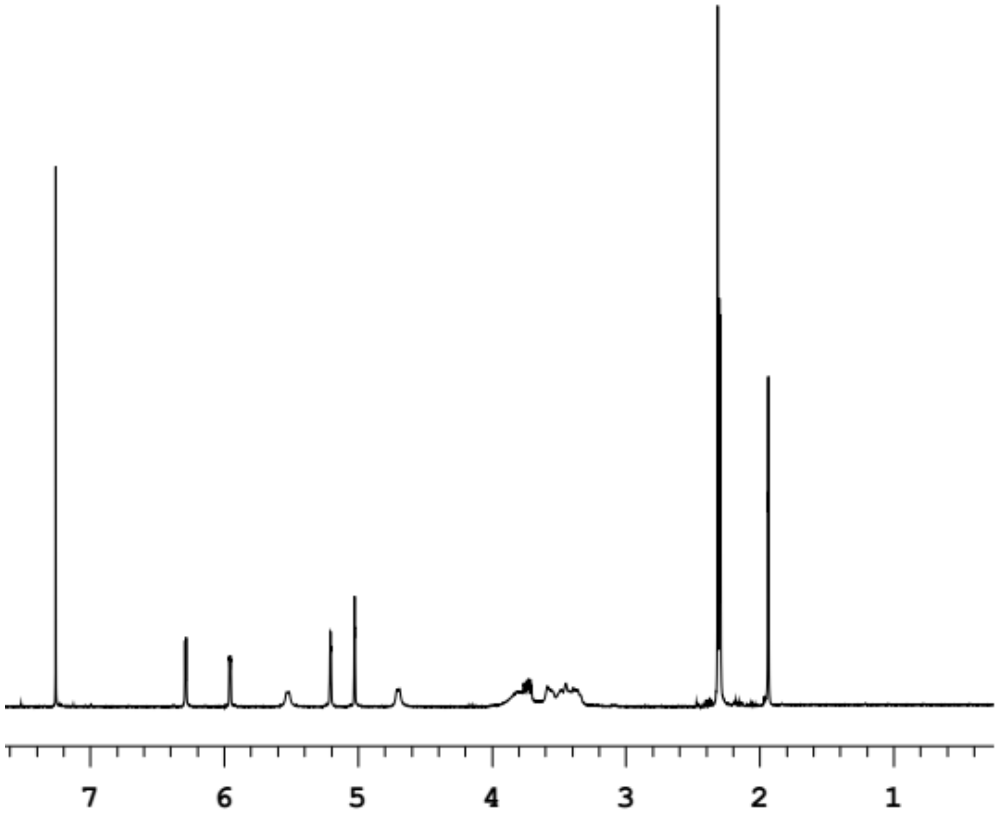
3c. ^{1}H NMR



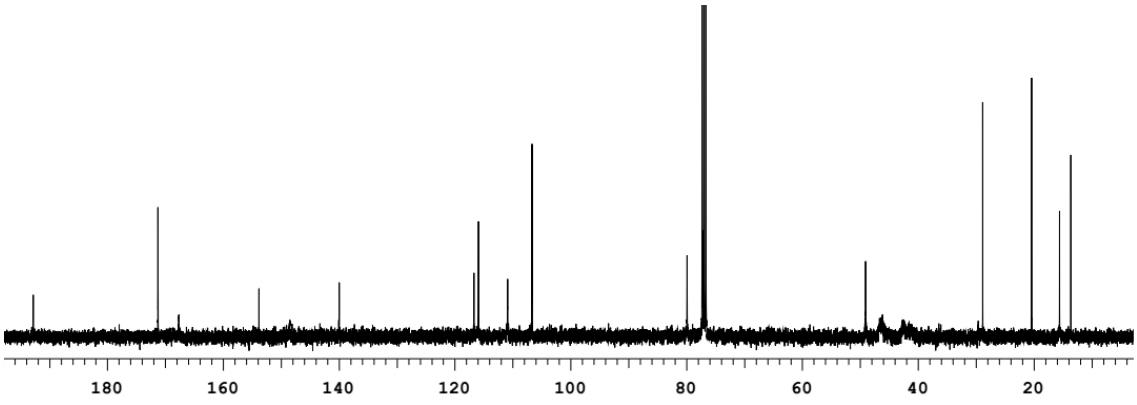
3c. ^{13}C NMR



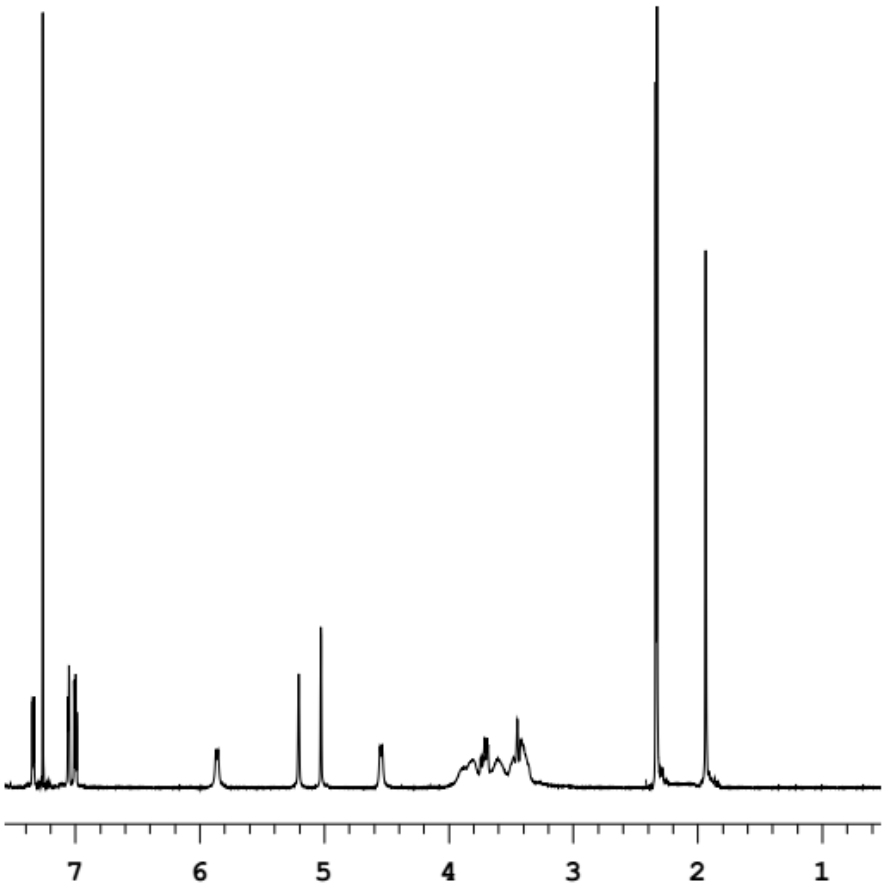
3d. ^{1}H NMR



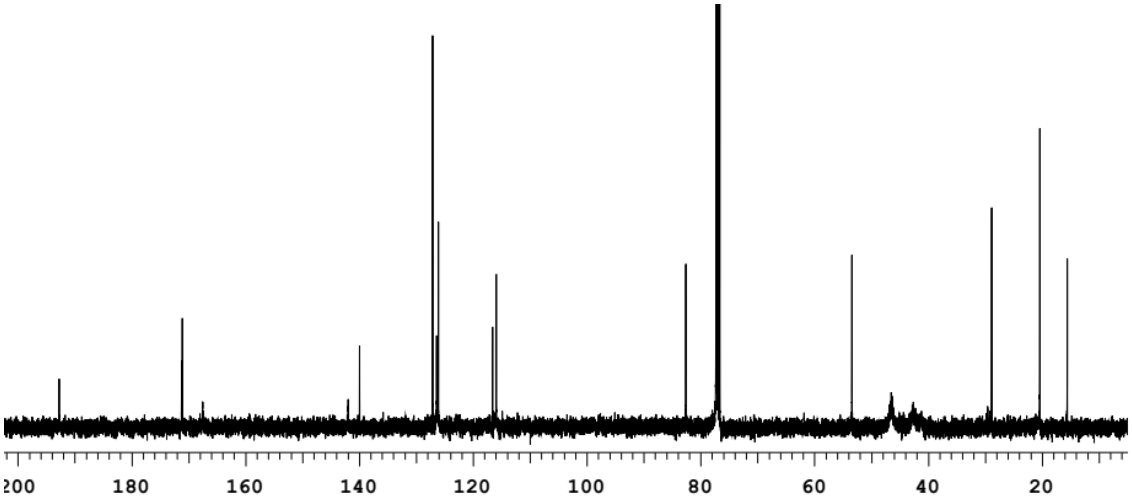
3d. ^{13}C NMR



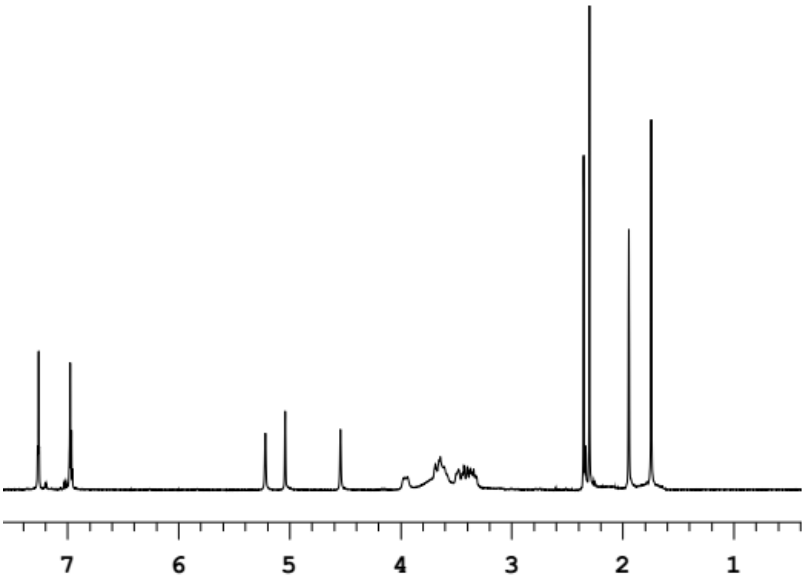
3e. ^{1}H NMR



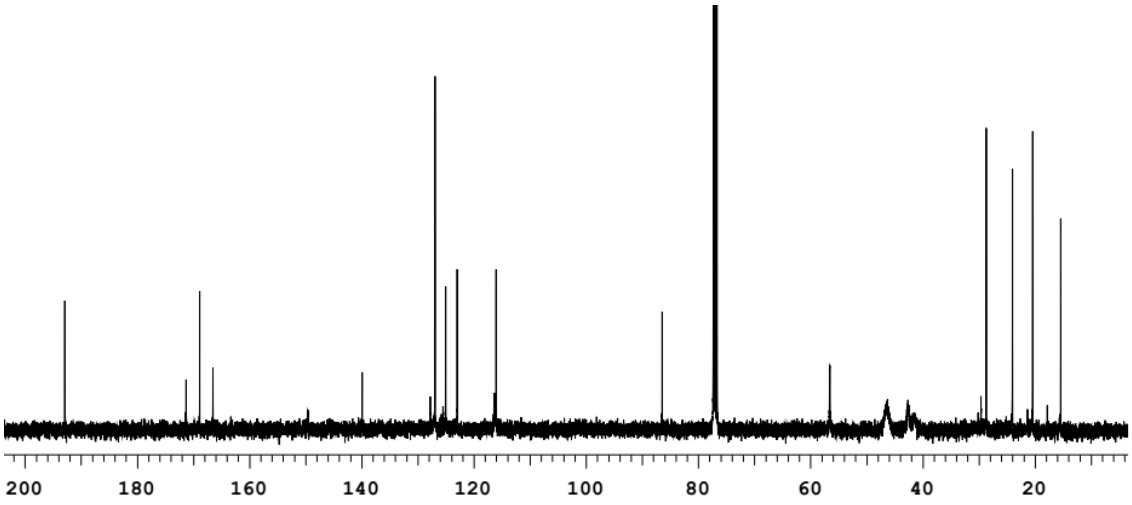
3e. ^{13}C NMR



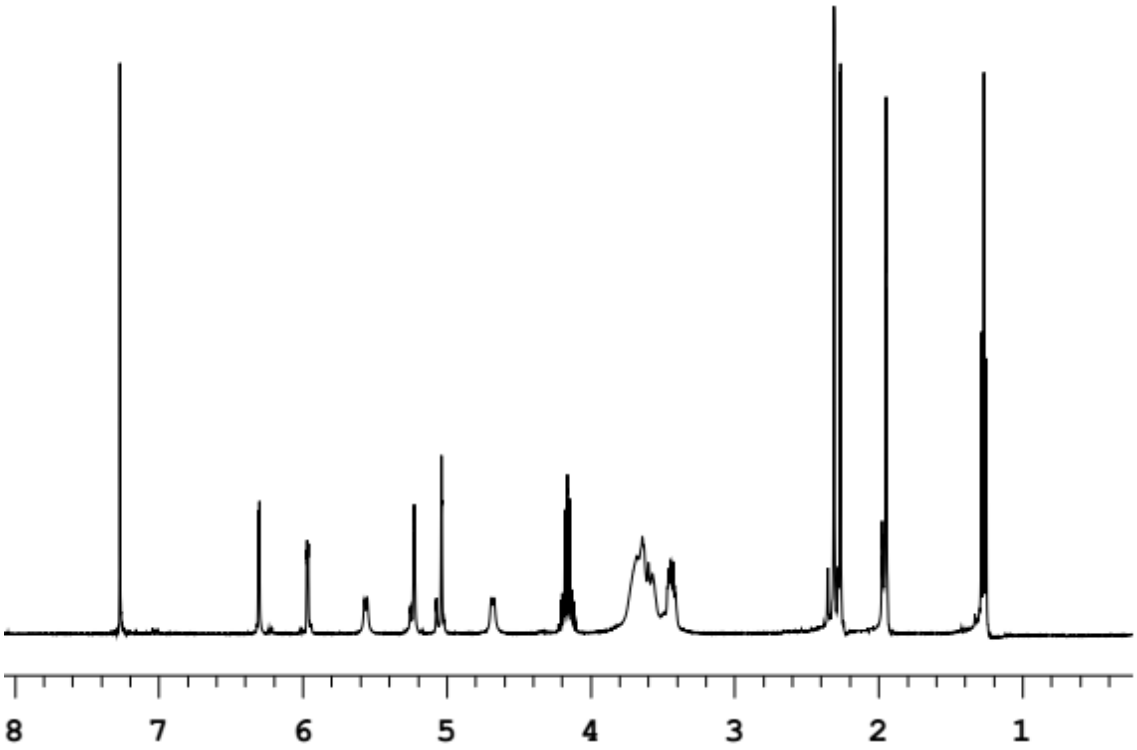
3f. ^{1}H NMR



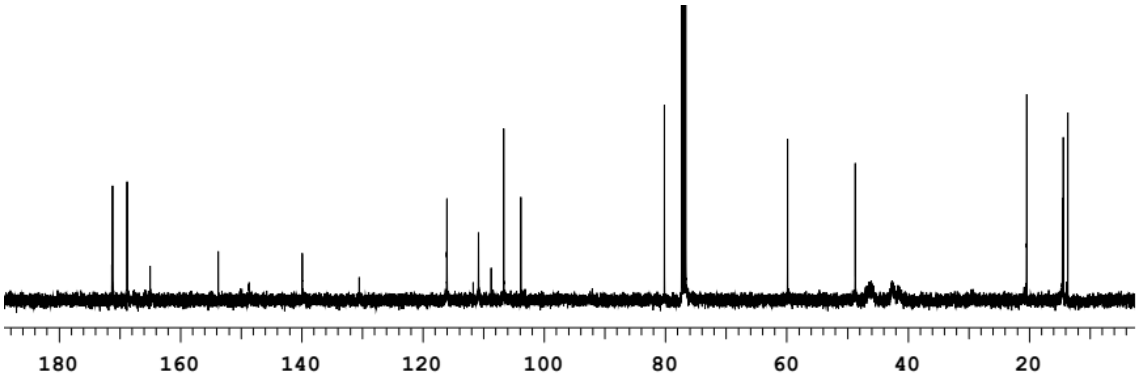
3f. ^{13}C NMR



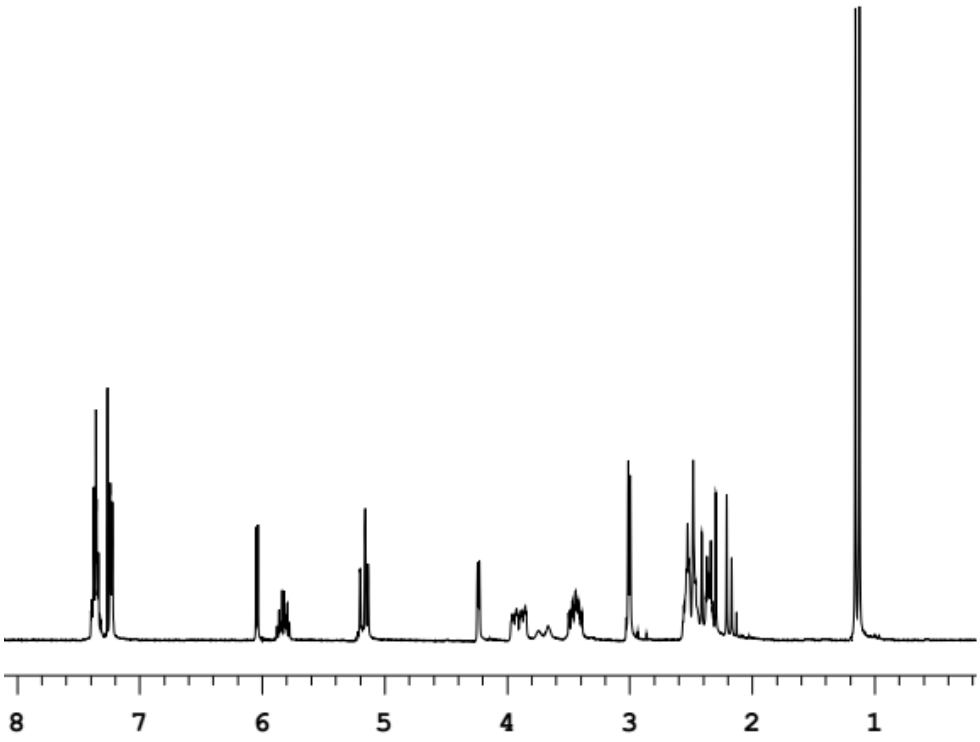
3g. ^{1}H NMR



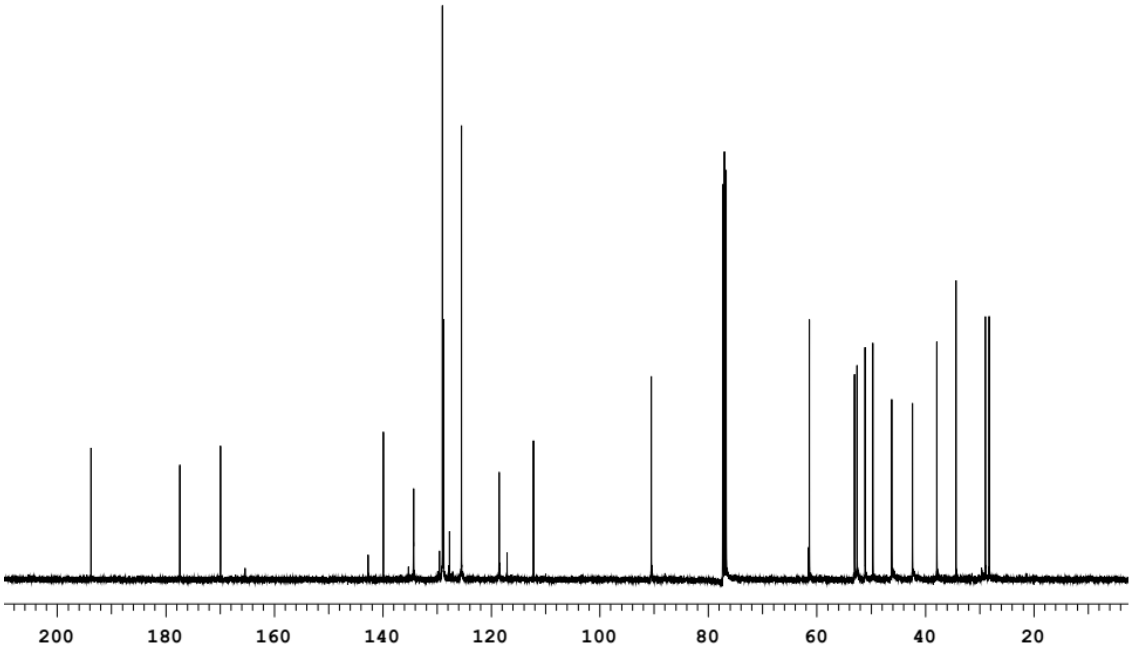
3g. ^{13}C NMR



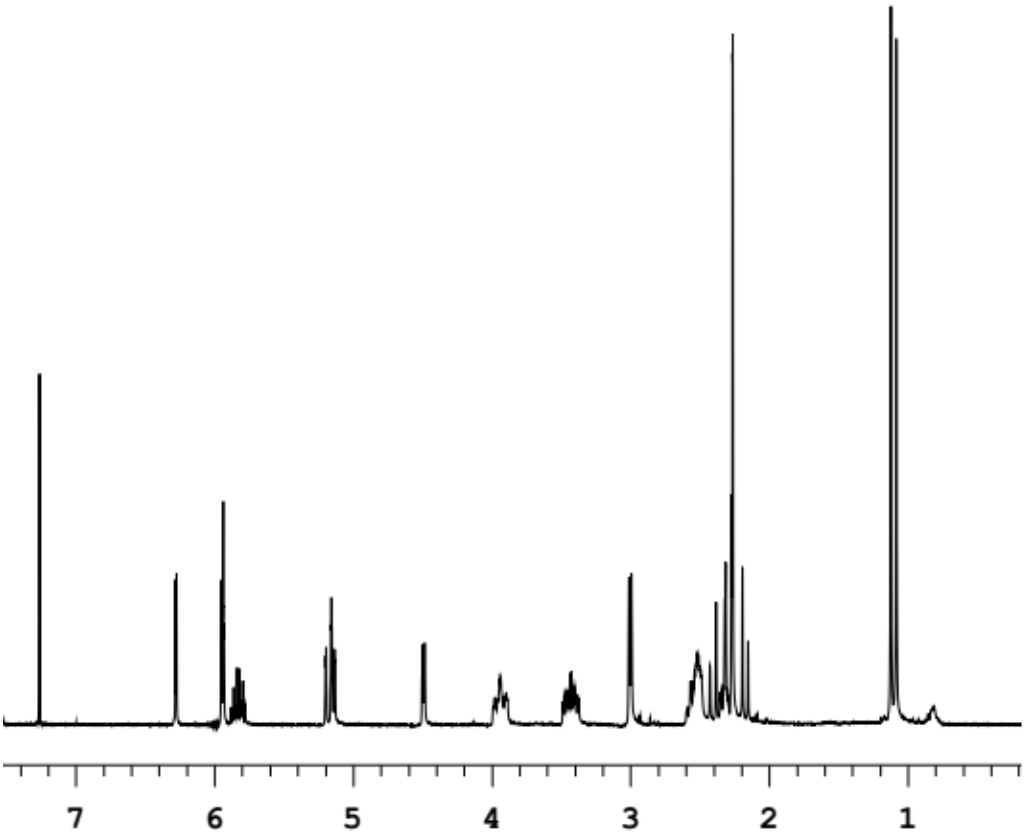
3h. ^{1}H NMR



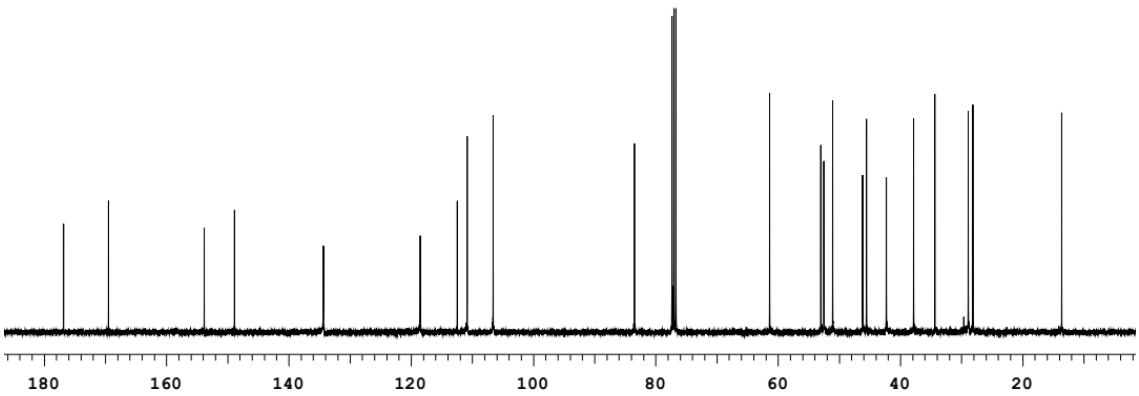
3h. ^{13}C NMR



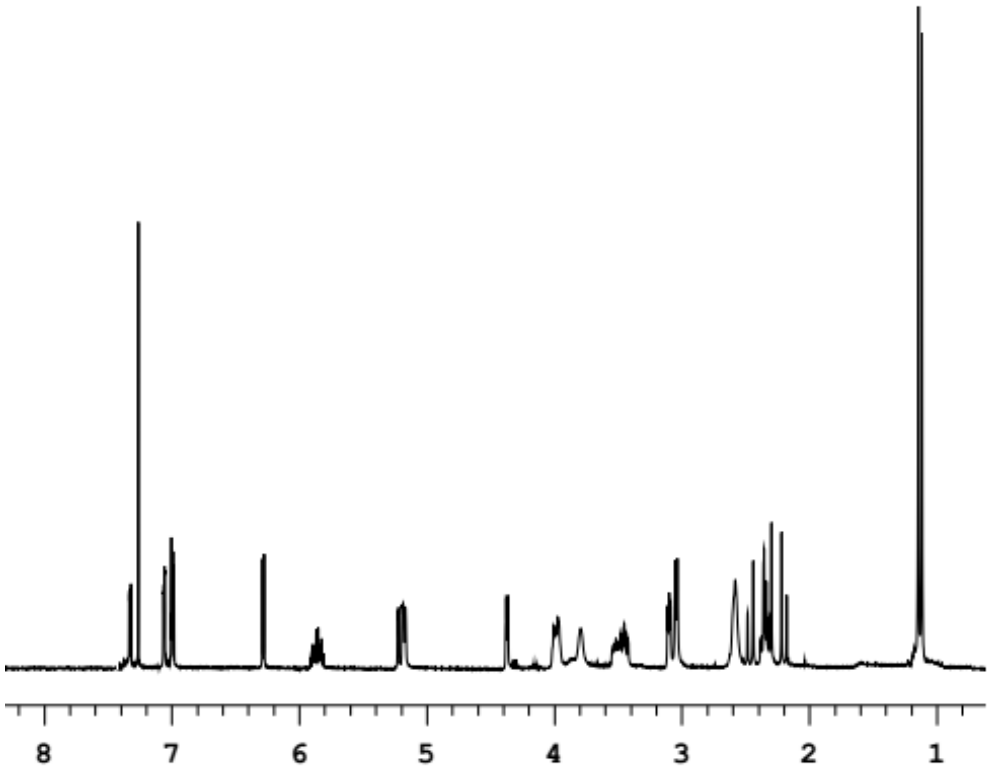
3i. ^{1}H NMR



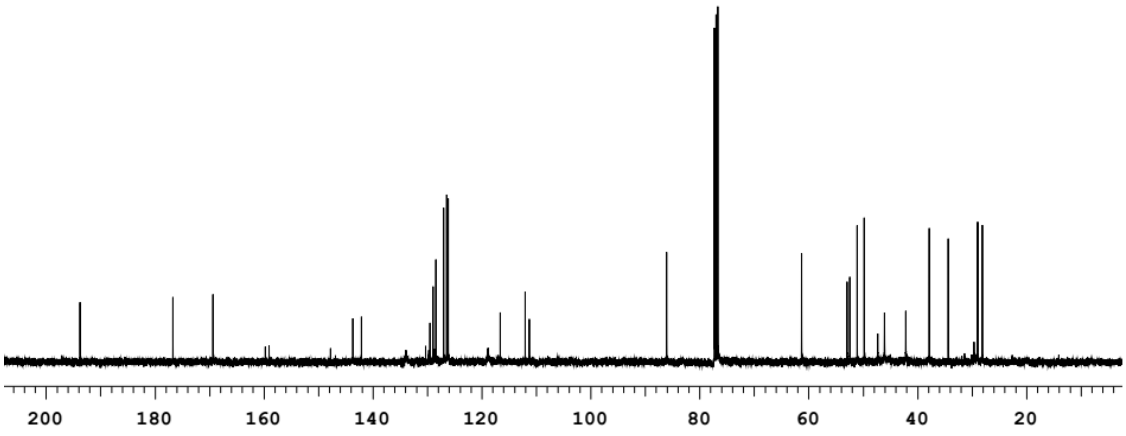
3i. ^{13}C NMR



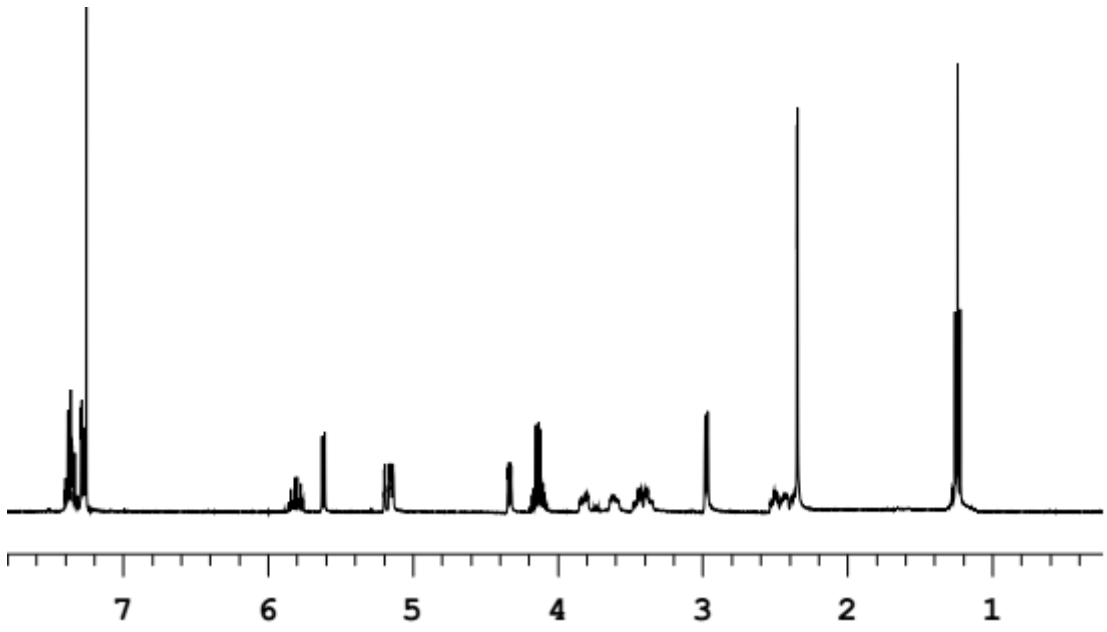
3j. ^{1}H NMR



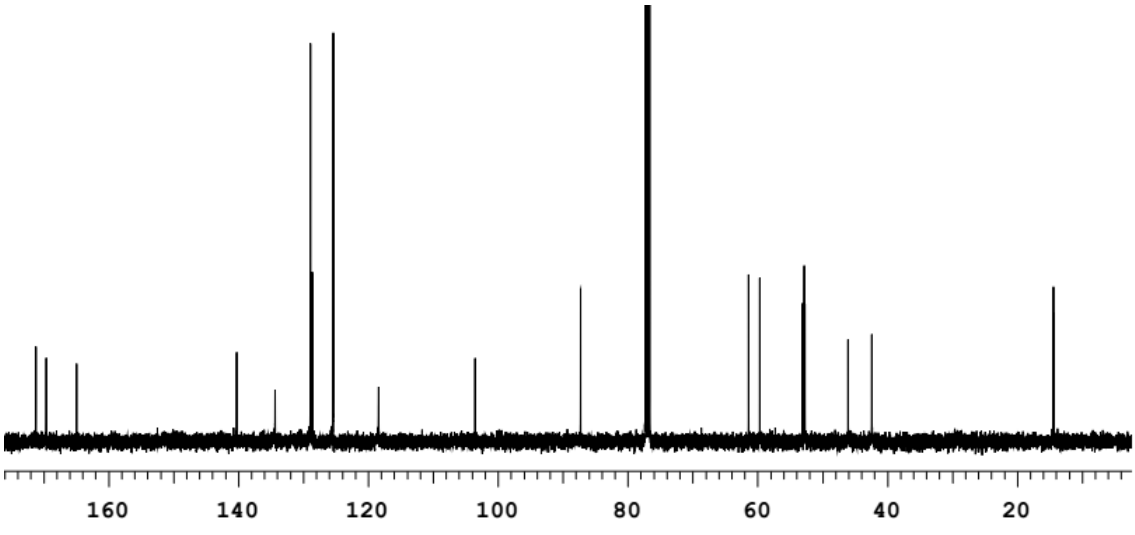
3j. ^{13}C NMR



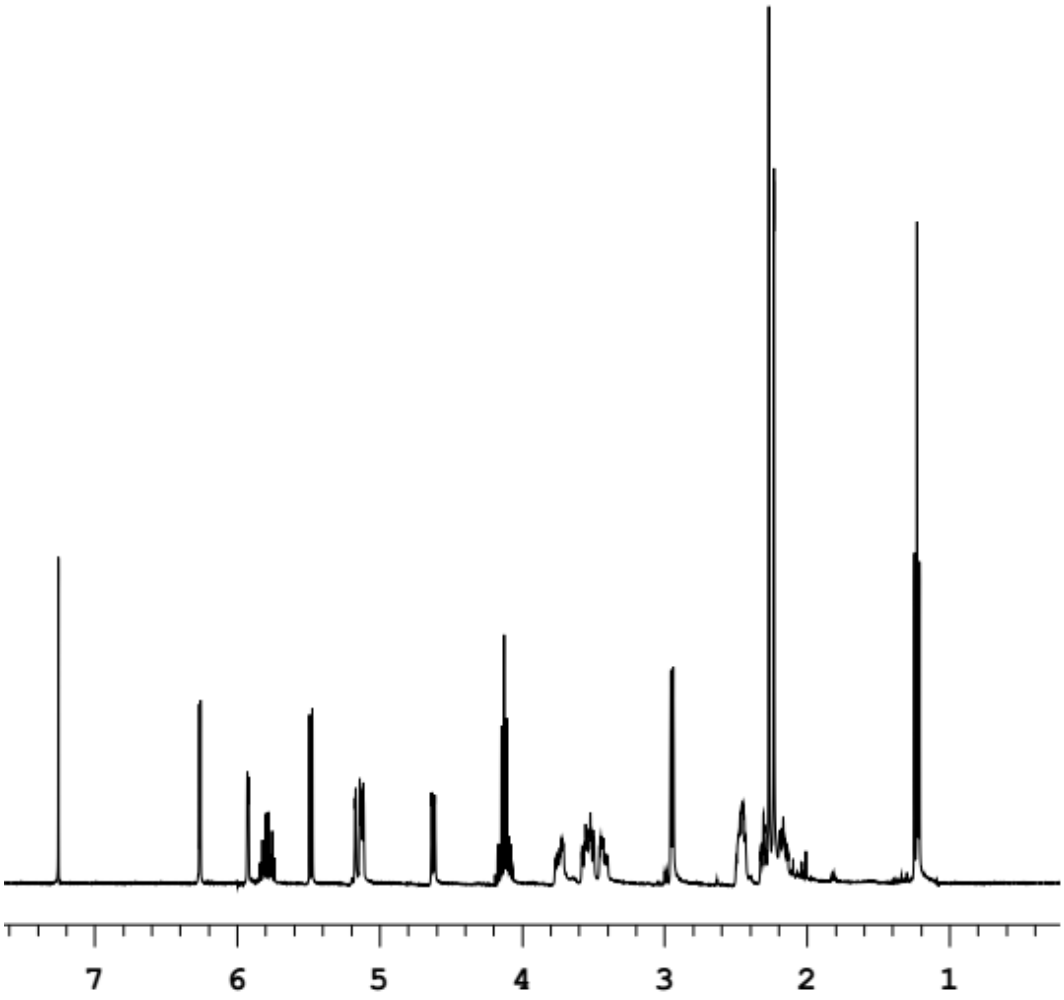
3k. ^{1}H NMR



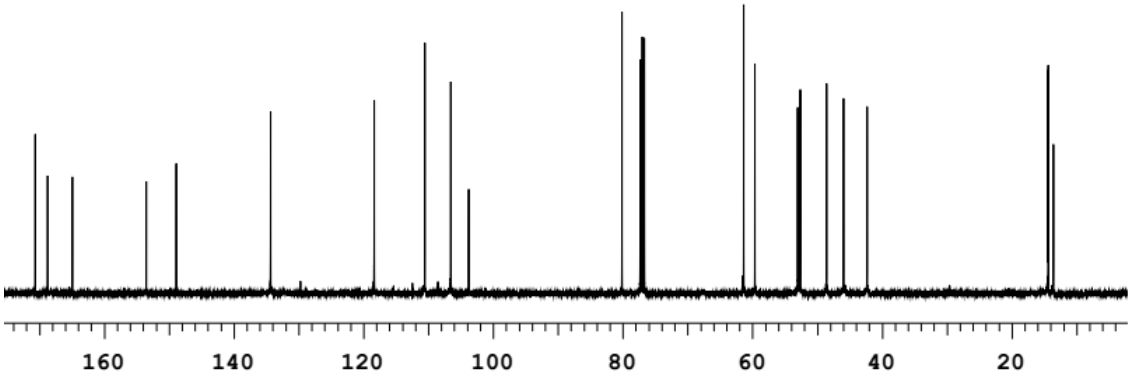
3k. ^{13}C NMR



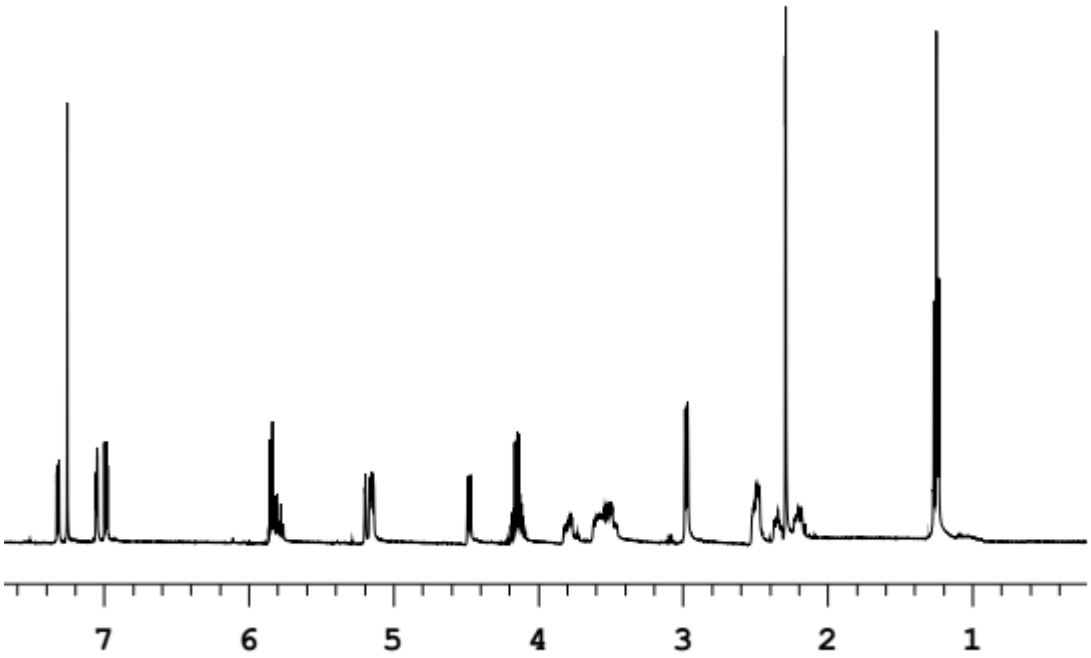
3l. ^{1}H NMR



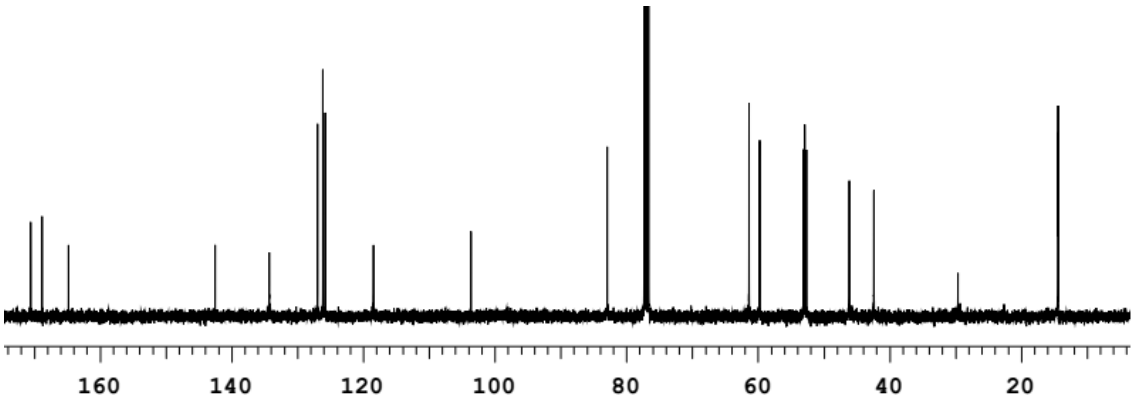
3l. ^{13}C NMR



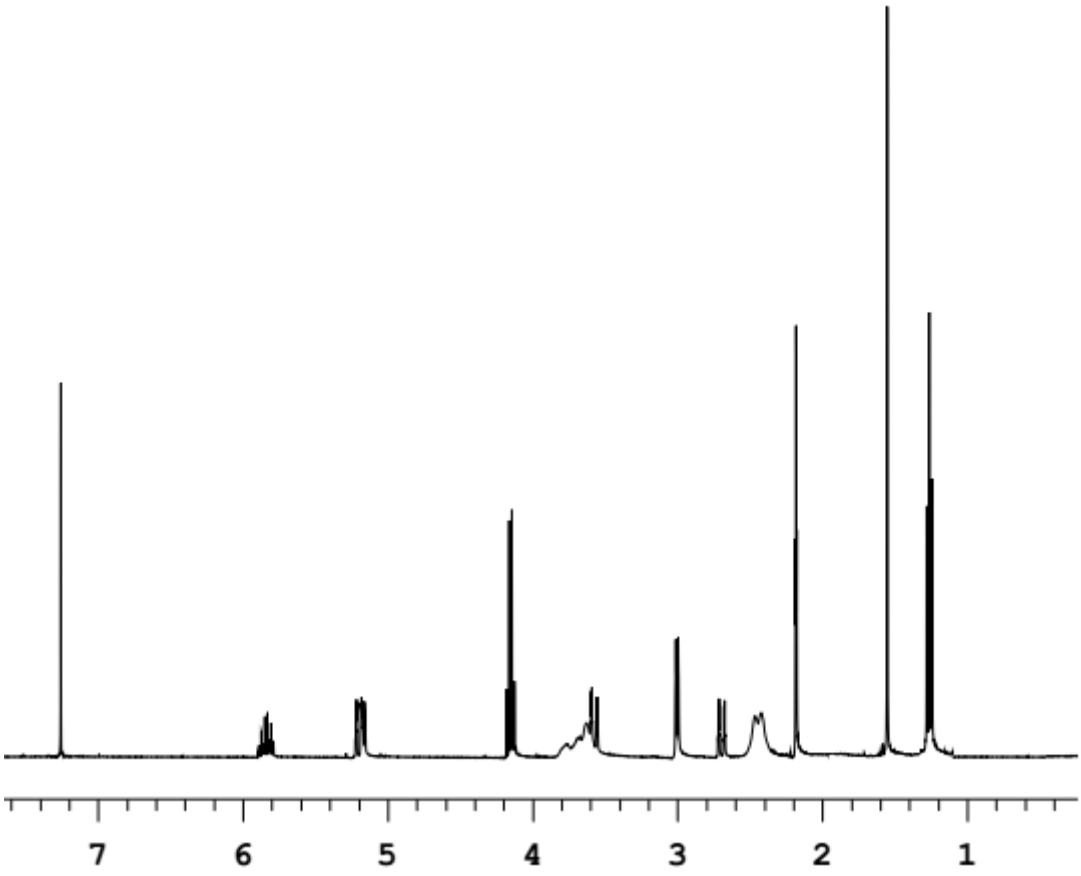
3m. ^{1}H NMR



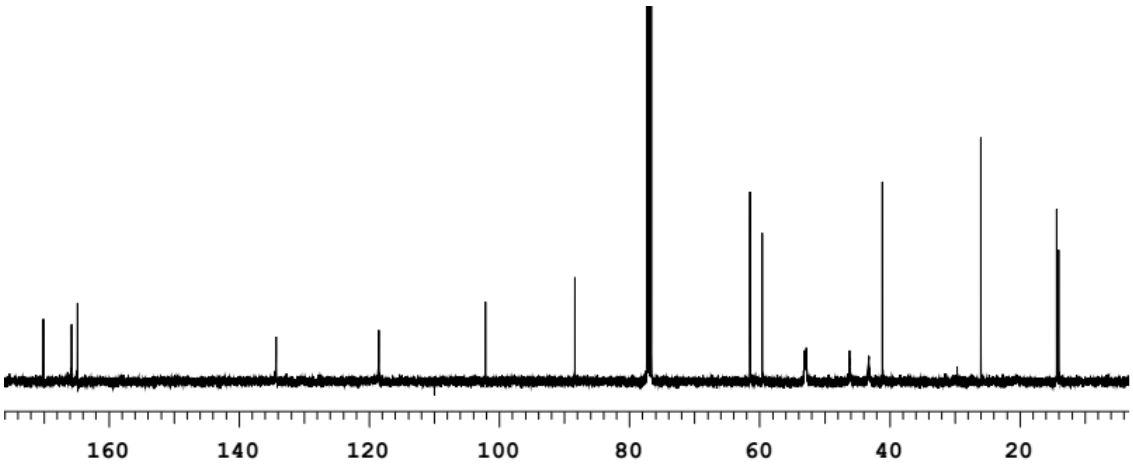
3m. ^{13}C NMR



3n. ^{1}H NMR

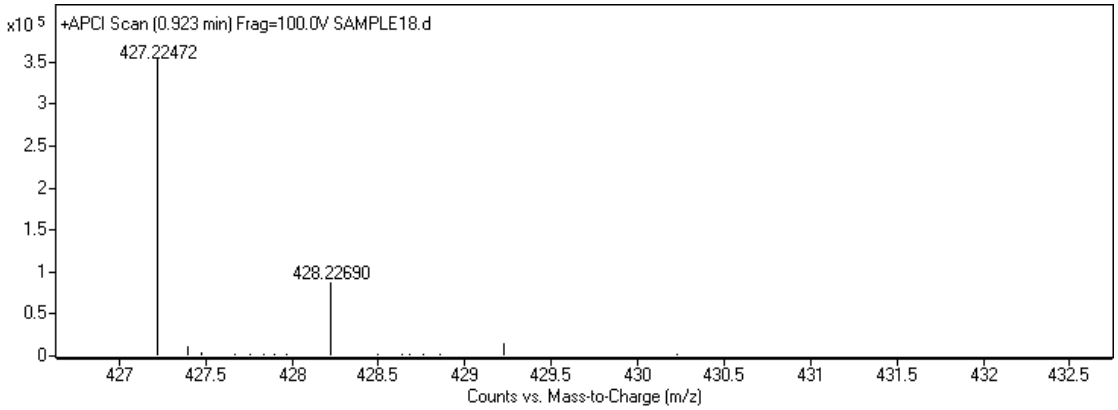


3n. ^{13}C NMR

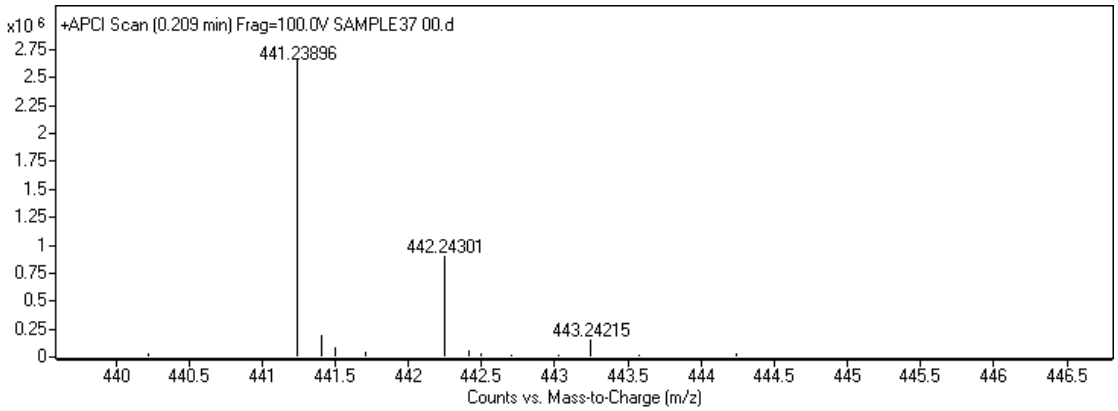


HRMS spectra

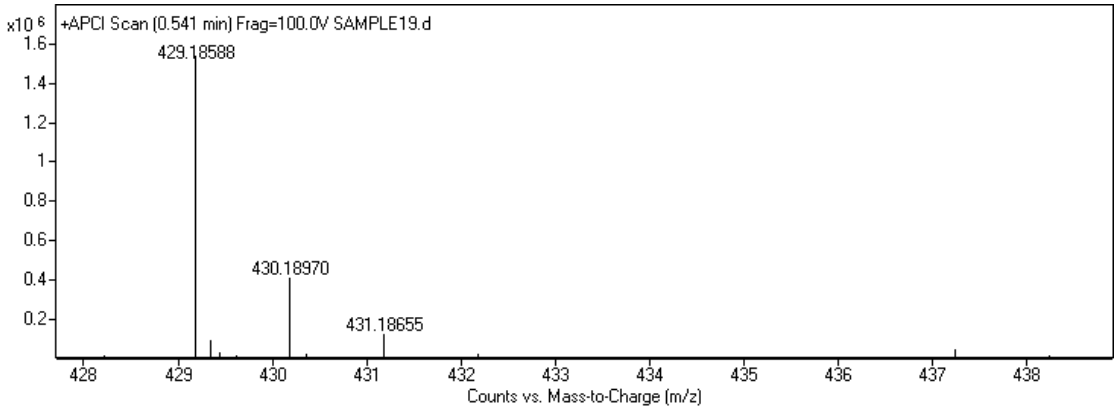
3a



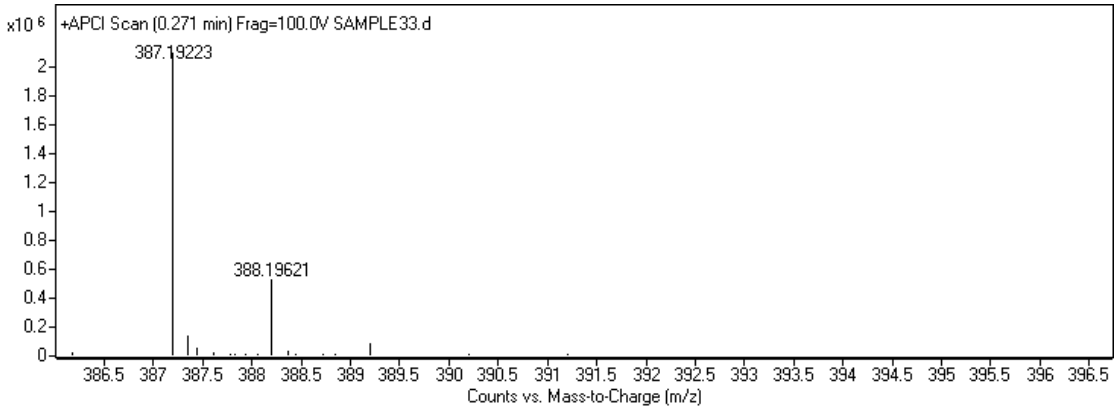
3b



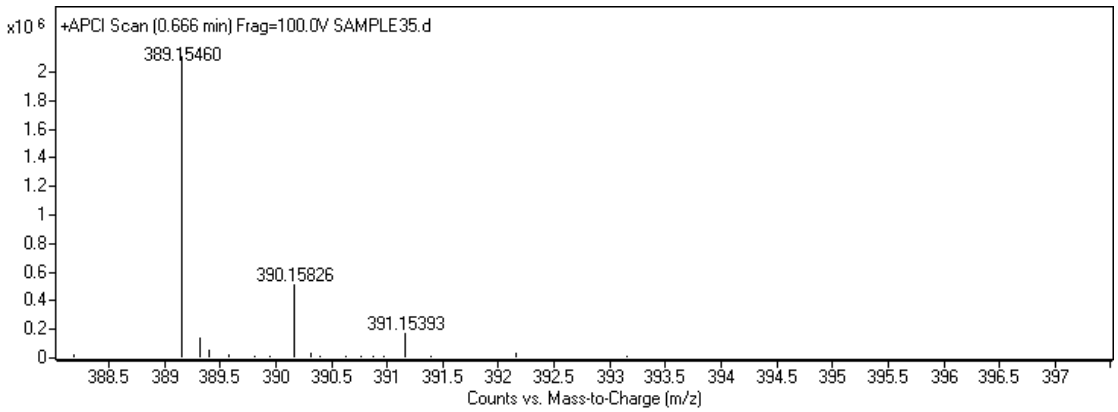
3c



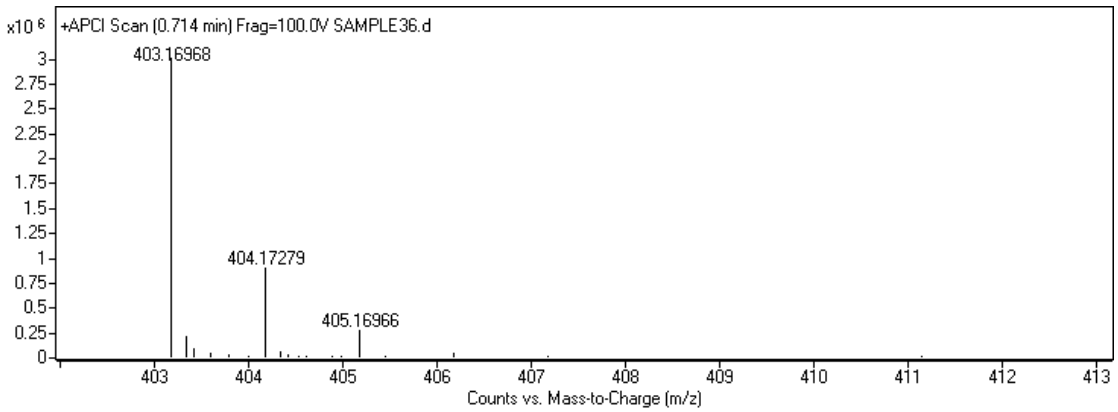
3d


x10 6
+APCI Scan (0.271 min) Frag=100.0V SAMPLE33.d
387.19223
388.19621
Counts vs. Mass-to-Charge (m/z)

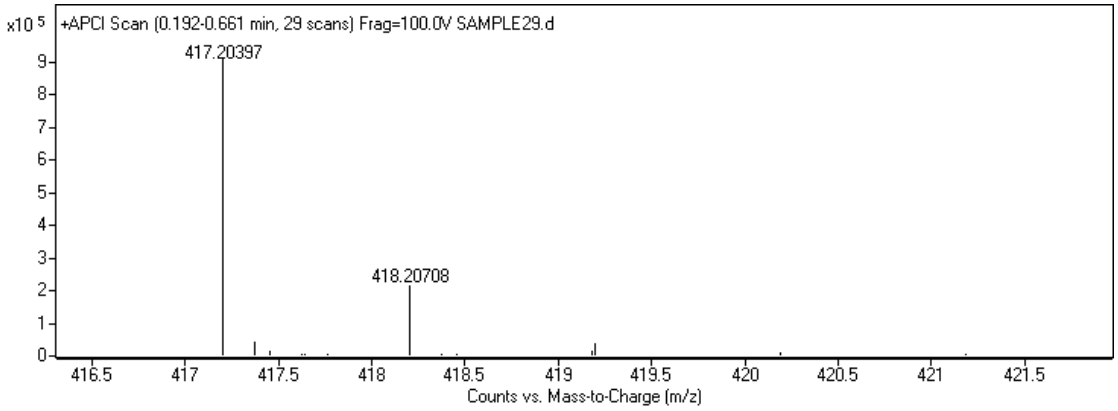
3e


x10 6
+APCI Scan (0.666 min) Frag=100.0V SAMPLE35.d
389.15460
390.15826
391.15393
Counts vs. Mass-to-Charge (m/z)

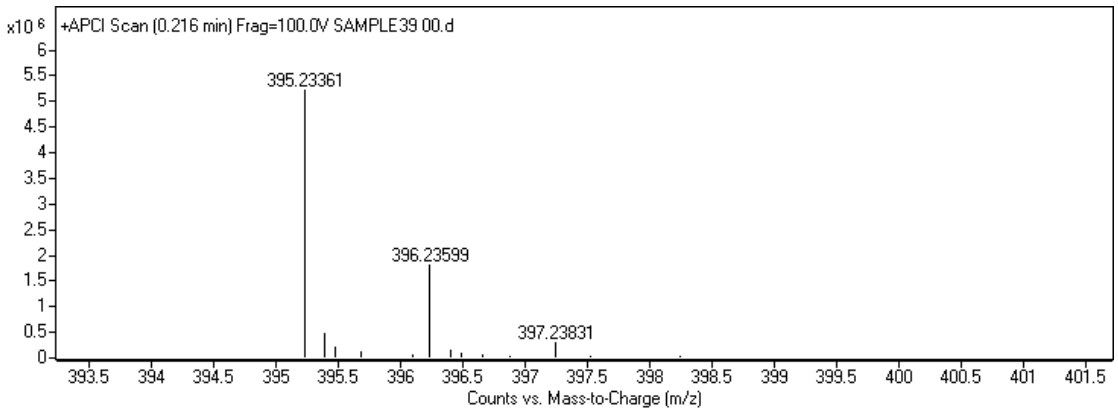
3f


x10 6
+APCI Scan (0.714 min) Frag=100.0V SAMPLE36.d
403.16968
404.17279
405.16966
Counts vs. Mass-to-Charge (m/z)

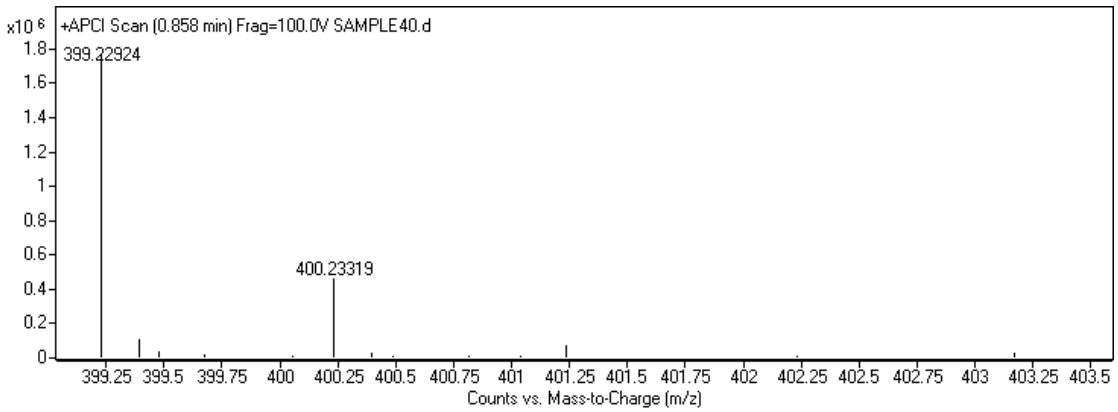
3g


x10 5
+APCI Scan (0.192-0.661 min, 29 scans) Frag=100.0V SAMPLE29.d
417.20397
418.20708
Counts vs. Mass-to-Charge (m/z)

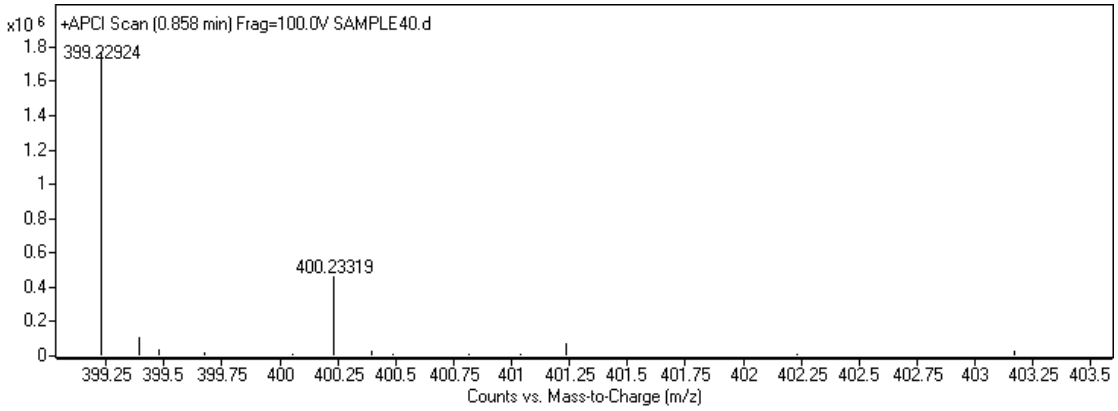
3h


x10 6
+APCI Scan (0.216 min) Frag=100.0V SAMPLE39 00.d
395.23361
396.23599
397.23831
Counts vs. Mass-to-Charge (m/z)

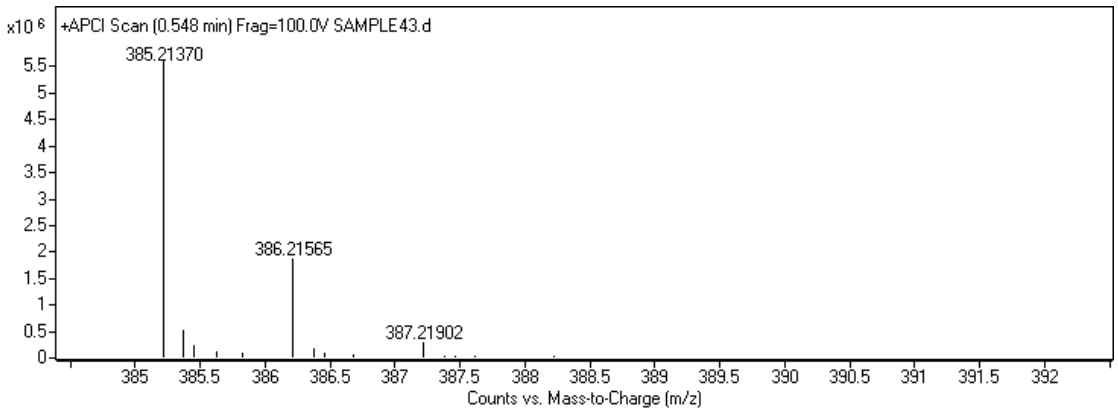
3i


x10 6
+APCI Scan (0.858 min) Frag=100.0V SAMPLE40.d
399.22924
400.23319
Counts vs. Mass-to-Charge (m/z)

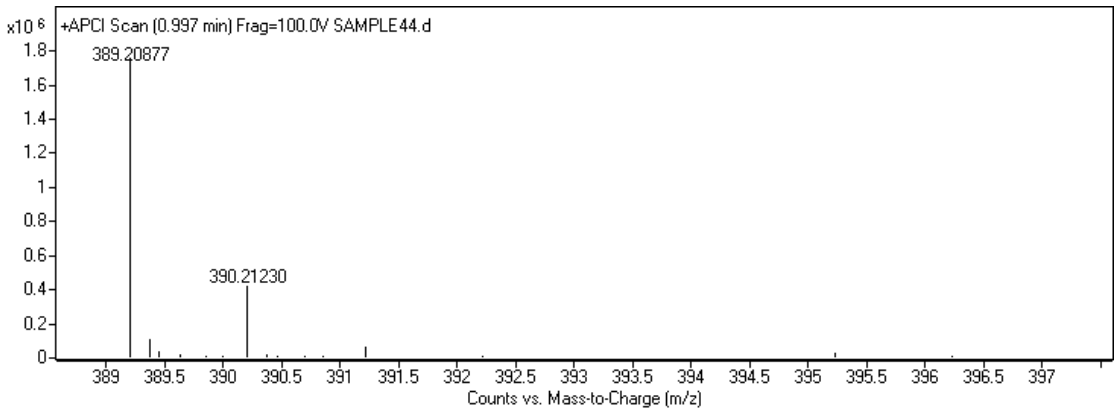
3j


x10 6
+APCI Scan (0.858 min) Frag=100.0V SAMPLE40.d
399.22924
400.23319
Counts vs. Mass-to-Charge (m/z)

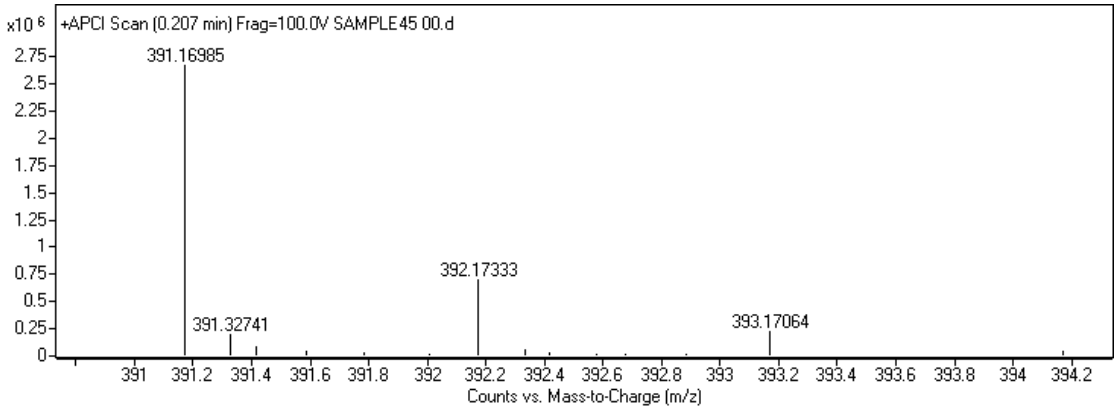
3k


x10 6
+APCI Scan (0.548 min) Frag=100.0V SAMPLE43.d
385.21370
386.21565
387.21902
Counts vs. Mass-to-Charge (m/z)

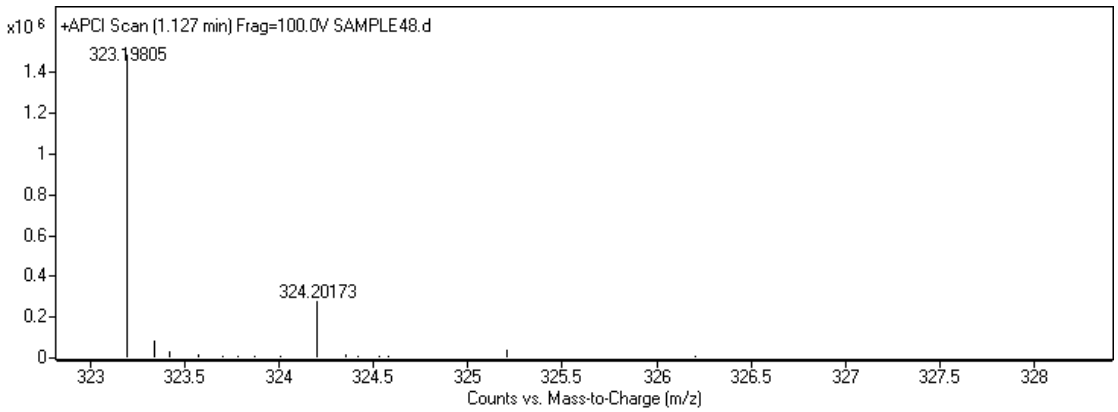
3l


x10 6
+APCI Scan (0.997 min) Frag=100.0V SAMPLE44.d
389.20877
390.21230
Counts vs. Mass-to-Charge (m/z)

3m


x10 6
+APCI Scan (0.207 min) Frag=100.0V SAMPLE45 00.d
391.16985
392.17333
391.32741
393.17064
Counts vs. Mass-to-Charge (m/z)

3n


x10 6
+APCI Scan (1.127 min) Frag=100.0V SAMPLE48.d
323.19805
324.20173
Counts vs. Mass-to-Charge (m/z)