TÜBİTAK

**Turkish Journal of Chemistry**

**http://journals.tubitak.gov.tr/chem/**

**Research Article**

Turk J Chem
(2020) 44: 1303-1313
© TÜBİTAK
doi:10.3906/kim-2003-23

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

**Sait SARI, Mehmet YILMAZ***

Department of Chemistry, Faculty of Arts and Sciences, Kocaeli University, 41380 Umuttepe, Kocaeli, Turkey

**Received:** 12.03.2020 • **Accepted/Published Online:** 14.07.2020 • **Final Version:** 26.10.2020

**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:$Mn(OAc)_3$].

* Correspondence: mehmet.yilmaz@kocaeli.edu.tr

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.

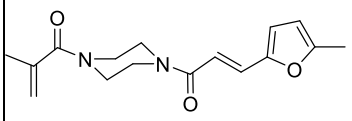
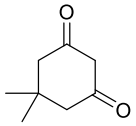
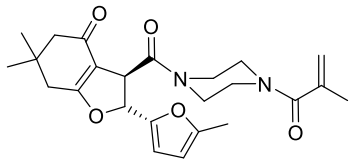
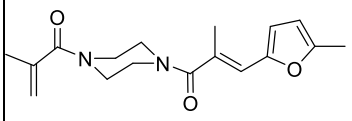
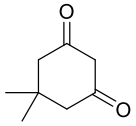
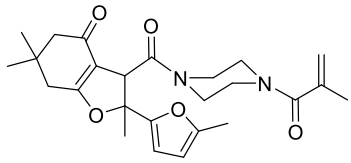
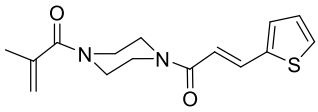
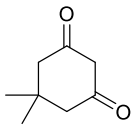
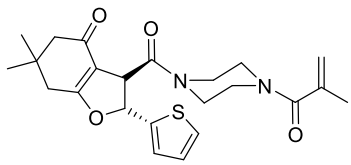
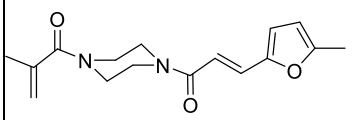
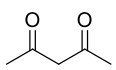
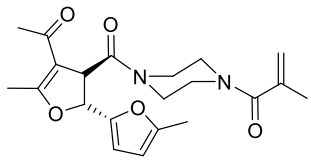
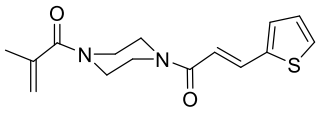
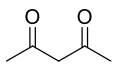
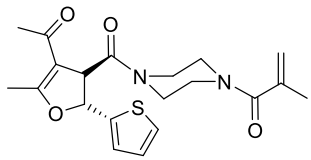
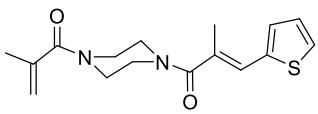
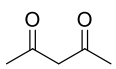
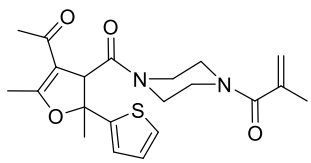
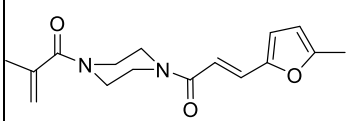
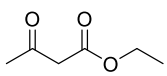
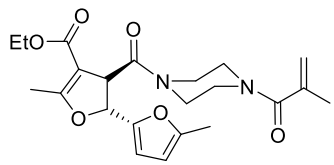
Summarily, reactions of methacryloyl- and 3-arylacryloyl–substituted piperazines (1a-d) with 1,3-dicarbonyls (2a-c) occurs on 3-arylacryloyl sides, regioselectively. However, in reactions of allyl- and acryloyl-substituted (methacryloyl or 3-arylacryloyl) piperazines (1e-h)with 2a or 2c, cyclization 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.

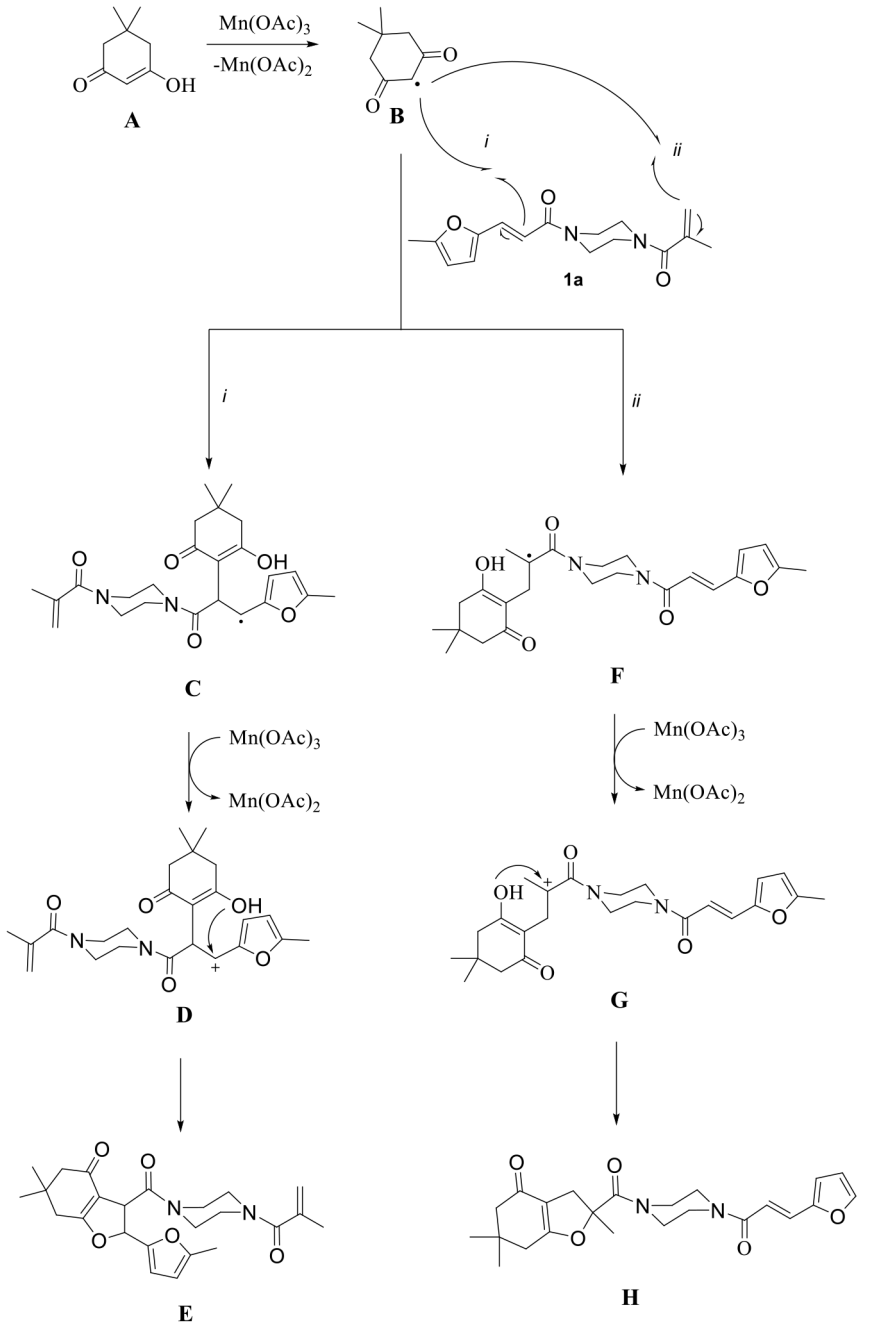
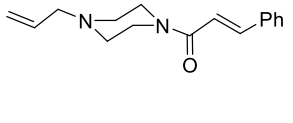
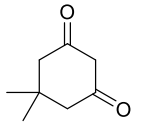
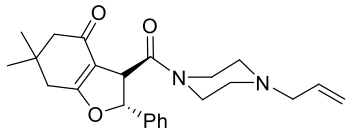
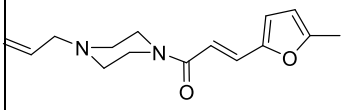
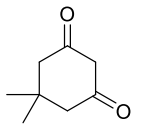
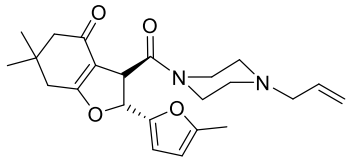
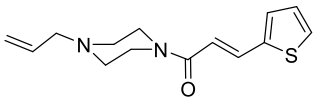
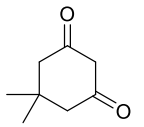
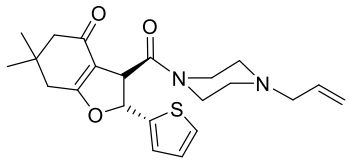
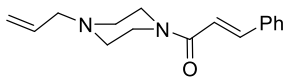
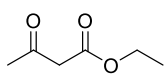
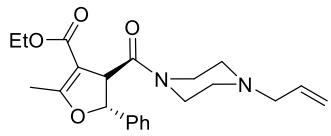
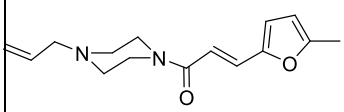
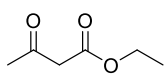
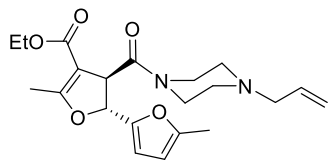
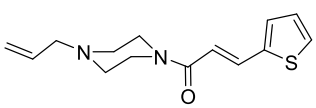
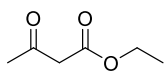
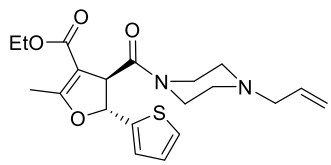
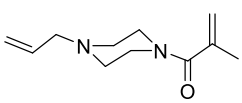
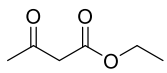
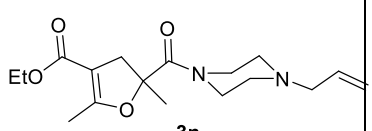



**Figure.** Proposed mechanism of $Mn(OAc)_3$ mediated radical cyclization.

**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) $\upsilon_{max}$ 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) $\upsilon_{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) $\upsilon_{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) $\upsilon_{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) $\upsilon_{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) $\upsilon_{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) $\upsilon_{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_2$C<u>H</u>$_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) $\upsilon_{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) $\upsilon_{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) $\upsilon_{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) $\upsilon_{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) $\upsilon_{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) $\upsilon_{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) $\upsilon_{max}$3076, 2983, 2930, 1701 (C=O), 1657 (C=O), 1630 (C=C), 1190, 1040$cm^{-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.

## Acknowledgments

This study was financially supported by the Scientific and Technological Research Council of Turkey (TÜBİTAK) (TBAG-116Z455). Sait SARI thanks TÜBİTAK for the doctoral fellowship.

## References

1. Dua R, Shrivastava S, Sonwane SK, Shrivastava SK. Pharmacological Significance of Synthetic Heterocycles Scaffold: A Review.Advances in Biological Research 2011;5: 120-144.

2. Rachakonda V, Alla M, Kotipalli SS, Ummani R. Design, diversity-oriented synthesis and structure activity relationship studies of quinolinyl heterocycles as antimycobacterial agents. European Journal of Medicinal Chemistry 2013; 70: 536-547.

3. Szabo M, Herenbrink CK, Christopoulos A, Lane JR, Capuano B. Structure–Activity Relationships of Privileged Structures Lead to the Discovery of Novel Biased Ligands at the Dopamine D2 Receptor. Journal of Medicinal Chemistry2014; 57: 4924–4939.
4. Chaudhary P, Kumar R, Verma AK, Singh D, Yadav V, et al. Synthesis and antimicrobial activity of N-alkyl and N-aryl piperazine derivatives. Bioorganic and Medicinal Chemistry2006; 14: 1819-1826.
5. Harish KP, Mohana KN, Mallesha L, Kumar BNP. Synthesis of novel 1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-piperazine derivatives and evaluation of their in vivo anticonvulsant activity.European Journal of Medicinal Chemistry 2013; 65: 276-283.
6. Patel KN, Telvekar VN. Design, synthesis and antitubercular evaluation of novel series of N-[4-(piperazin-1-yl)phenyl]cinnamamide derivatives. European Journal of Medicinal Chemistry 2014; 75: 43-56.
7. Wang T, Kadow JF, Zhang Z, Yin Z, Gao Q, et al. Inhibitors of HIV-1 attachment. Part 4: A study of the effect of piperazine substitution patterns on antiviral potency in the context of indole-based derivatives. Bioorganic and Medicinal Chemistry Letters 2009; 19: 5140-5145.
8. Tuğrak M, Gül HI, Bandow K, Sakagami H, Gülçin I, et al. Synthesis and biological evaluation of some new mono Mannich bases with piperazines as possible anticancer agents and carbonic anhydrase inhibitors. Bioorganic Chemistry 2019; 90: 103095.
9. Meena P, Nemaysh V, Khatri M, Manral A, Luthra PM, et al. Synthesis, biological evaluation and molecular docking study of novel piperidine and piperazine derivatives as multi-targeted agents to treat Alzheimer's disease. Bioorganic and Medicinal Chemistry 2015; 23: 1135-1148.
10. Piemontese L, Tomás D, Hiremathad A, Capriati Vi, Candeias E, et al. Donepezil structurebased hybrids as potential multifunctional anti-Alzheimer's drug candidates. Journal of Enzyme Inhibition and Medicinal Chemistry 2018;33: 1212-1224.
11. Stegmeier F, Warmuth M, Sellers WR, Dorsch M. Targeted Cancer Therapies in the Twenty-First Century: Lessons From Imatinib. Clinical Pharmacology&Therapautics 2010;87:543-552.
12. Lue TF. Erectile dysfunction. New England Journal of Medicine 2000; 342: 1802-1813.
13. Vacca JP, Dorsey BD, Schleif WA, Levin RB, McDaniel SL et al. L-735,524: an orally bioavailable human immunodeficiency virus type 1 protease inhibitor.Proceedings of the national academy of sciences 1994; 91: 4096-4100.
14. Burka JM, Bower KS, Vanroekel RC, Stutzman RD, Kuzmowych CP et al. The effect of fourth-generation fluoroquinolones gatifloxacin and moxifloxacin on epithelial healing following photorefractive keratectomy. American Journal of Ophthalmology 2005; 140: 83-87.
15. Hu C, Sun ZG, Wei CX, Quan ZS. Synthesis and anticonvulsant activity of some cinnamylpiperazine derivatives. Letters in Drug Design & Discovery 2010; 7(9): 661-664.
16. Kapanda CN, Masquelier J, Labar G, Muccioli GG, Poupaert JH et al. Synthesis and Pharmacological Evaluation of 2,4-Dinitroaryldithiocarbamate Derivatives as Novel Monoacylglycerol Lipase Inhibitors. Journal of Medicinal Chemistry 2012; 55(12): 5774-5783.
17. Srikanth RT, Suryakiran N, Narasimhulu M, Ramesh D, Chinni MK et al. Semi-synthesis and bio-evaluation of polybrominated diphenyl ethers from the sponge Dysidea herbacea. Bioorganic & Medicinal Chemistry Letters 2012; 22(14): 4900-4906.
18. Hatnapure GD, Keche AP, Rodge AH, Birajdar SS, Tale RH et al. Synthesis and biological evaluation of novel piperazine derivatives of flavone as potent anti-inflammatory and antimicrobial agent. Bioorganic & Medicinal Chemistry Letters 2012; 22(20): 6385-6390.
19. Kakwani MD, Suryavanshi P, Ray M, Rajan MGR, Majee S et al. Design, synthesis and antimycobacterial activity of cinnamide derivatives: A molecular hybridization approach. Bioorganic & Medicinal Chemistry Letters 2011; 21: 1997-1999.
20. Zhong Y, Xu Z, Wang Y, Xu Y, Li P et al. Synthesis, Crystal Structure and Anti-ischaemic Activity of (E)-1-{4-[Bis(4-methoxy-phenyl) methyl]piperazin-1-yl}-3-(4-chlorophenyl)-prop-2-en-1-one South African Journal of Chemistry. 2014; 67: 214-217.
21. Saadeh HA, Mosleh IM, Mubarak MS. Synthesis of novel hybrid molecules from precursors with known antiparasitic activity. Molecules 2009; 14: 1483-1494.
22. Chen SP, Chen BW, Dai CF, Sung PJ, Wu YC, et al. Sarcophytonins F and G, New Dihydrofuranocembranoids from a Dongsha Atoll Soft Coral Sarcophyton sp. Bulletin of Chemical Society of Japan. 2012; 85: 920-922.
23. Lallemand JY, Six Y, Ricard LA. Concise Synthesis of an Advanced Clerodin Intermediate through a Vaultier Tandem Reaction. European Journal of Organic Chemistry.2002; 3: 503-513.
24. Appendino G,Cravotto G, Palmisano G,Annunziata R. Synthesis of fercoprolone, a degraded prenylated coumarin. Tetrahedron 1998; 54: 10819-10826.
25. Kornsakulkarn J, Saepua S, Srichomthong K, Supothina S, Thongpanchang C. New mycotoxins from the scale insect fungus Aschersonia coffeae Henn. BCC 28712. Tetrahedron2012; 68: 8480-8486.
26. Melikyan GG. Manganese(III) Mediated Reactions of Unsaturated Systems. Synthesis 1993; 9: 833-850.
27. Snider BB. Manganese(III)-Based Oxidative Free-Radical Cyclizations. Chemical Reviews 1996;96: 339-363.

28. Mondal M, Bora U. Recent advances in manganese(iii) acetate mediated organic synthesis. RSC Advances2013; 3: 18716-18754.

29. Castro S, Fernandez JJ, Fananas FJ, Vicente R, Rodriguez F. Manganese-Mediated C-H Alkylation of Unbiased Arenes Using Alkylboronic Acids. Chemistry A European Journal 2016; 22: 9068-9071.

30. Lofstrand VA, Matsuura BS, Furst L, Narayanam JMR, Stephenson JRC. Formation and trapping of azafulvene intermediates derived from manganese-mediated oxidative malonate coupling. Tetrahedron 2016; 72: 3775-3780.

31. Hyunh TT, Nguyen VH, Nishino H. One-pot synthesis of 2-oxa-7-azaspiro[4.4]nonane-8,9-diones using Mn(III)-based oxidation of 4-acylpyrrolidine-2,3-diones. Tetrahedron Letters2017; 58: 3619-3622.

32. Aslan H, Öktemer A, Dal H, Hökelek T. Synthesis of ferrocene substituted dihydrofuran derivatives via manganese(III) acetate mediated radical addition-cyclization reactions. Tetrahedron 2017; 73: 7223-7232.

33. Zhang PZ, Zhang L, Li JA, Shoberu A, Zou JP, et al. Phosphinoyl Radical Initiated Vicinal Cyanophosphinoylation of Alkenes. Orgamic Letters2017; 19: 5537-5540.

34. Chuang CP, Wu YL. Oxidative free radical reactions of enamino esters. Tetrahedron 2004; 60: 1841-1847.

35. Kobayashi K, Nagase K, Morikawa O, Konishi H. Convenient Synthesis of Furopyranopyrandione Derivatives by the CAN-mediated Furan Ring Formation. Heterocycles 2003; 60: 939-946.

36. Nair V, Mohanan K, Suja TD, Suresh E. Stereoselective synthesis of 3,4-trans-disubstituted pyrrolidines and cyclopentanes via intramolecular radical cyclizations mediated by CAN. Tetrahedron Letters2006; 47: 2803-2806.

37. Sridharan V, Menendez JC. Cerium(IV) Ammonium Nitrate as a Catalyst in OrganicSynthesis. Chemical Reviews2010; 110: 3805–3849.

38. Nair, V, Deepthi A. Cerium(IV) Ammonium NitrateA Versatile Single-Electron Oxidant.Chemical Reviews 2007; 107: 1862–1891.

39. Yılmaz M. Studies on the Radical Cyclization of 3-Oxopropanenitriles and Alkenes withCerium(IV) Ammonium Nitrate in Ether Solvents. Helvetica Chimica Acta 2011; 94: 1335-1342.

40. Yılmaz M, Ustalar A. Synthesis of 2-(2-phenylethenyl) substituted 4,5-dihydrofurans byregioselective addition of 1,3-dicarbonyl compounds to dienespromoted by cerium(IV) ammonium nitrate. Arkivoc 2016; (iii): 202-213.

41. Ustalar A, Yılmaz M, Osmani A, Keçeli SA. Synthesis and antifungal activity of new dihydrofurocoumarins anddihydrofuroquinolines. Turkish Journal of Chemistry 2017; 41: 80-88.

42. Hocaoğlu B, Yılmaz M. Regioselective radical addition of 3-oxopropanenitriles with terminal dienespromoted by cerium(IV) ammonium nitrate andmanganese(III) acetate. Synthetic Communications 2019; 49: 1938-1946.

43. Yilmaz M, Pekel AT. Regioselective Synthesis of 5-Carbamoyl-Dihydrofurans Mediated Manganese (III) Acetate in Acetic Acid. Synthetic Communications2001; 31: 2189-2194.

44. Yilmaz M, Pekel AT. Synthesis of benzofuran derivatives using manganese (III) acetate mediated addition of β-dicarbonyl compounds to alkyne and alkenes – a comparative study. Synthetic Communications 2001; 31: 3871-3876.

45. Burgaz EV, Yılmaz M, Pekel AT, Öktemer A. Oxidative cyclization of 3-oxopropanenitriles with a,b-unsaturated amides by manganese(III) acetate. Regio- and stereoselective synthesis of 4-cyano-2,3-dihydrofuran-3-carboxamides. Tetrahedron 2007; 63: 7229-7239.

46. Yilmaz M, Ustalar A, Uçan B, Pekel AT. Regio- and diastereoselective synthesis of trans-dihydrofuran-3-carboxamides by radical addition of 1,3-dicarbonyl compounds to acrylamides using manganese(III) acetate and determination of exact configuration by X-ray crystallography. Arkivoc 2016; (vi): 79-91.

47. Yılmaz EVB, Yılmaz M, Öktemer A. Radical cyclizations of conjugated esters and amides with3-oxopropanenitriles mediated by manganese(III) acetate. Arkivoc 2011; (ii): 363-376.

48. Yılmaz M, Uzunalioglu N, Pekel AT. Manganese(III) acetate based oxidative cyclizations of 3-oxopropanenitriles with conjugated alkenes and synthesis of 4,5-dihydrofuran-3-carbonitriles containing heterocycles. Tetrahedron 2005; 61: 8860-8867.

49. Yilmaz M. Synthesis of dihydrofurans containing trifluoromethyl ketone and heterocycles by radical cyclization of fluorinated 1,3-dicarbonyl compounds with 2-thienyl and 2-furyl substituted alkenes. Tetrahedron 2011; 67: 8255-8263.

50. Özgür M, Yılmaz M, Nishino H, Avar EÇ, Dal H, et al. Efficient syntheses and antimicrobial activities of new thiophene containing pyranone and quinolinone derivatives using manganese(III) acetate: the effect of thiophene on ring closure–opening reactions. New Journal of Chemistry2019; 43: 5737-5751.

51. Yilmaz M, Bicer E, Ustalar A, Pekel AT. Synthesis of furan-substituted dihydrofuran compounds by radicalcyclization reactions mediated by manganese(III) acetate. Arkivoc 2014;(v): 225-236.

52. Sarı S, Ünalan S, Yılmaz M. Synthesis and characterization of unsaturated diacyl and alkyl-acyl piperazinederivatives. Turkish Journal of Chemistry 2019; 43: 1656-1671.

53. Hagiwara H, Sato K, Nishino D, Hoshi T, Suzuki T, Ando M. Domino Michael–O-alkylation reaction: one-pot synthesis of 2,4-diacylhydrofuran derivatives and its application to antitumor naphthofuran synthesis. Journal of the Chemical Society, Perkin Transactions 1 2001; 22: 2946-2957.

54. Vinoshaa B, Perumal S, Renugaa S, Almansour AI.A facile domino protocol for the stereoselective synthesis of trans-2,3-dihydrobenzofurans and cis-5,6-dihydrofuro[2,3-d]pyrimidines. Tetrahedron Letters.2012; 53: 962–966.

55. Yu H, Han J, Chen J, Deng H, Shao M, Zhang H, Cao W.Preparation of (E )-4-Aryl-1,1,1-trifluoro-3-tosylbut-3-en-2-ones as Fluorinated Building Blocks and Their Application in Ready and Highly Stereoselective Routes to trans -2,3-Dihydrofurans Substituted with Trifluoromethyl and Sulfonyl Groups. European Journal of Organic Chemistry. 2012; 16: 3142-3150.

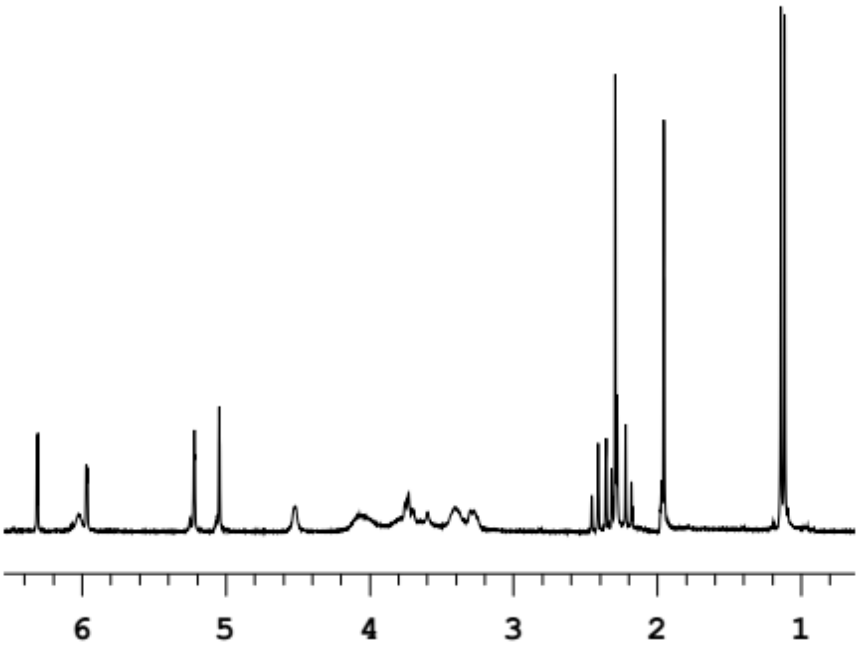
56. S Martinet, AMéou, P Brun. 1H and 13C chemical shifts for some tetrasubstituted 2,5-diaryl di- and tetrahydrofuran derivatives. Magnetic Resonance in Chemistry. 2007; 45: 182-184.

57. Yılmaz M, Yılmaz EVB, Pekel AT. Radical Cyclization of Fluorinated 1,3-Dicarbonyl Compounds with Dienes Using Manganese(III) Acetate and Synthesis of Fluoroacylated 4,5-Dihydrofurans. Helvetica Chimica Acta 2011; 94: 2027-2038.

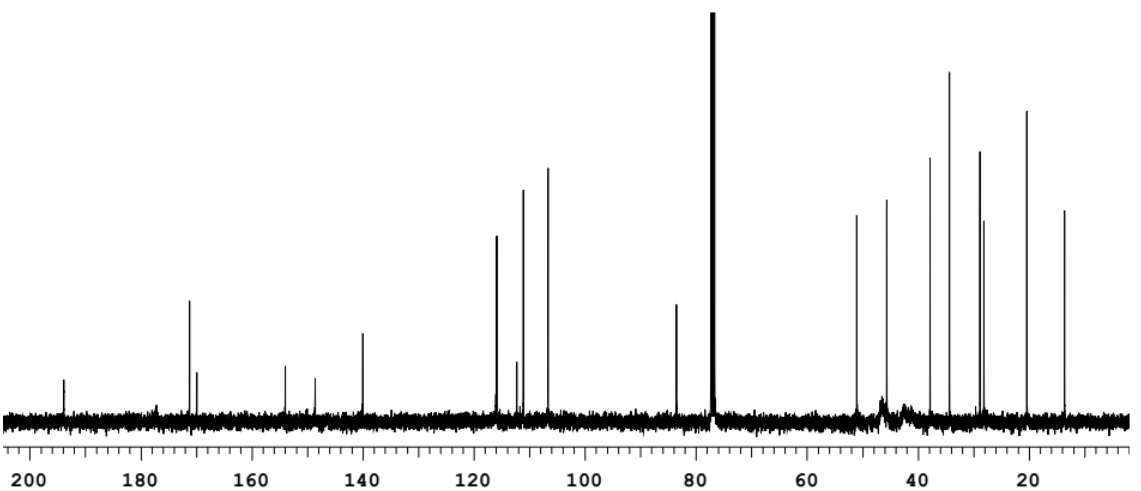
# SUPPLEMENTARY INFORMATION

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

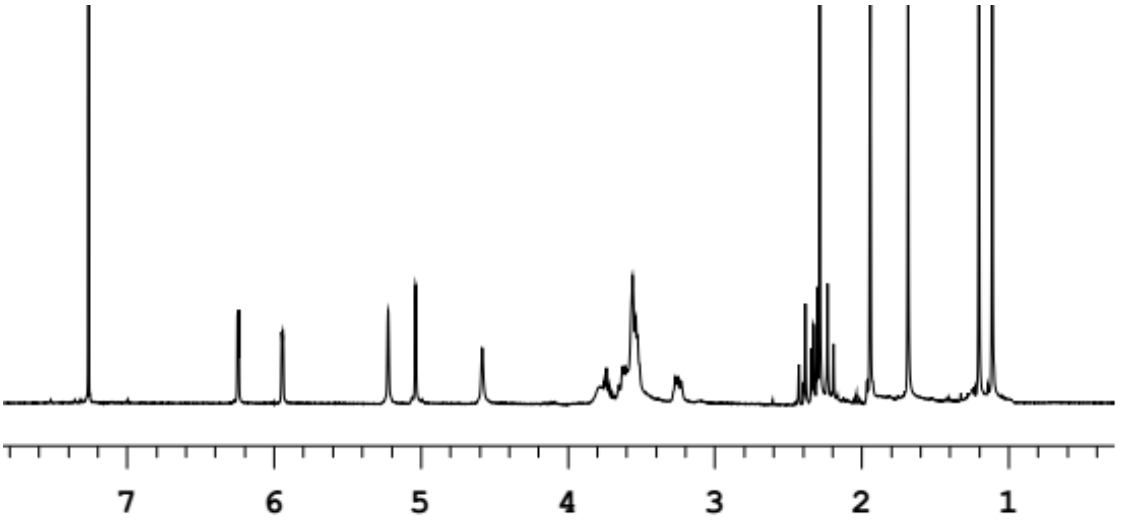
### 3a. $^{1}$H NMR



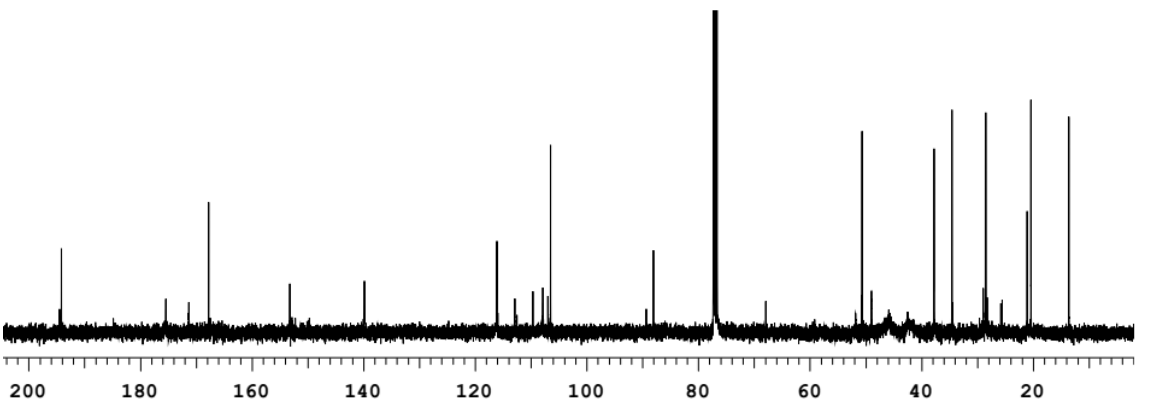

### 3a. $^{13}$C NMR



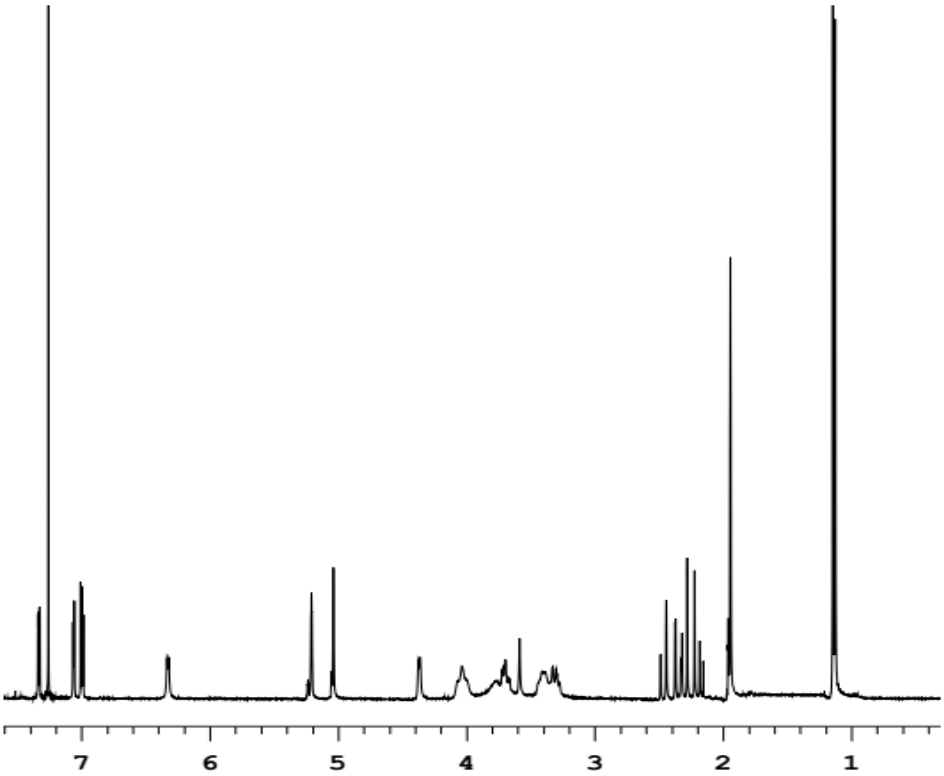
**3b. $^{1}$H NMR**



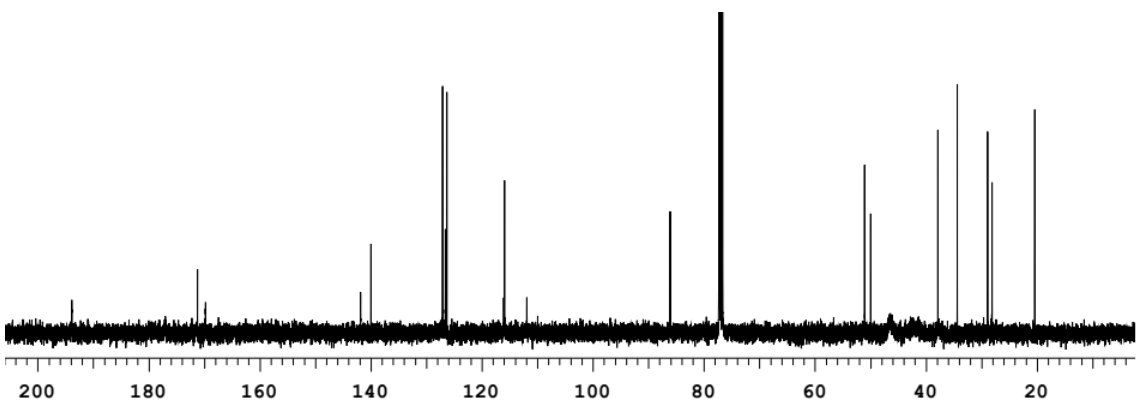

**3b. $^{13}$C NMR**



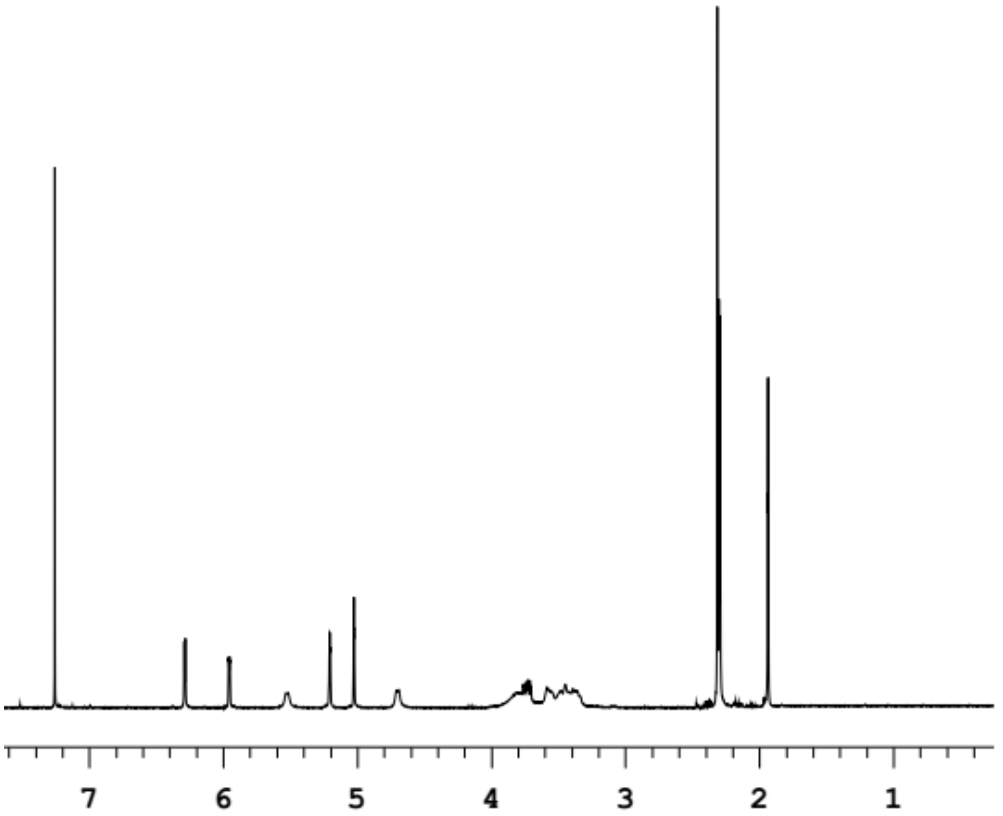
**3c. $^{1}$H NMR**



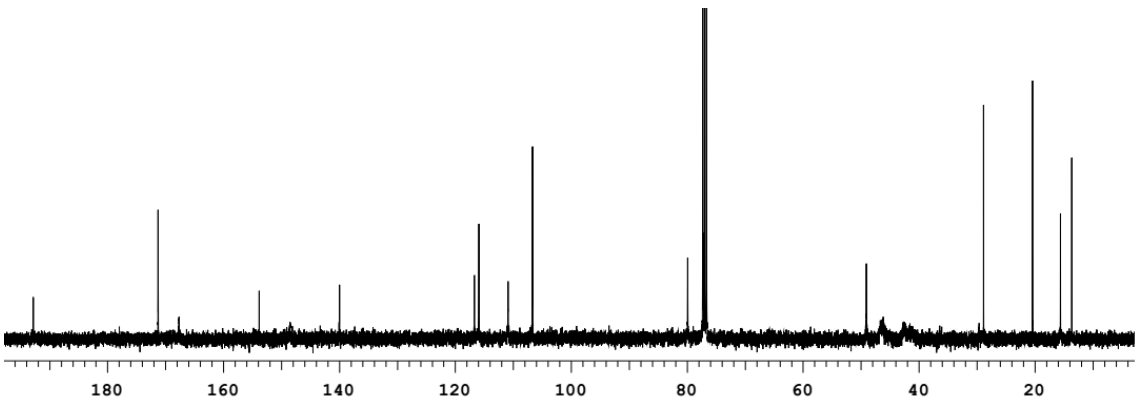

**3c. $^{13}$C NMR**



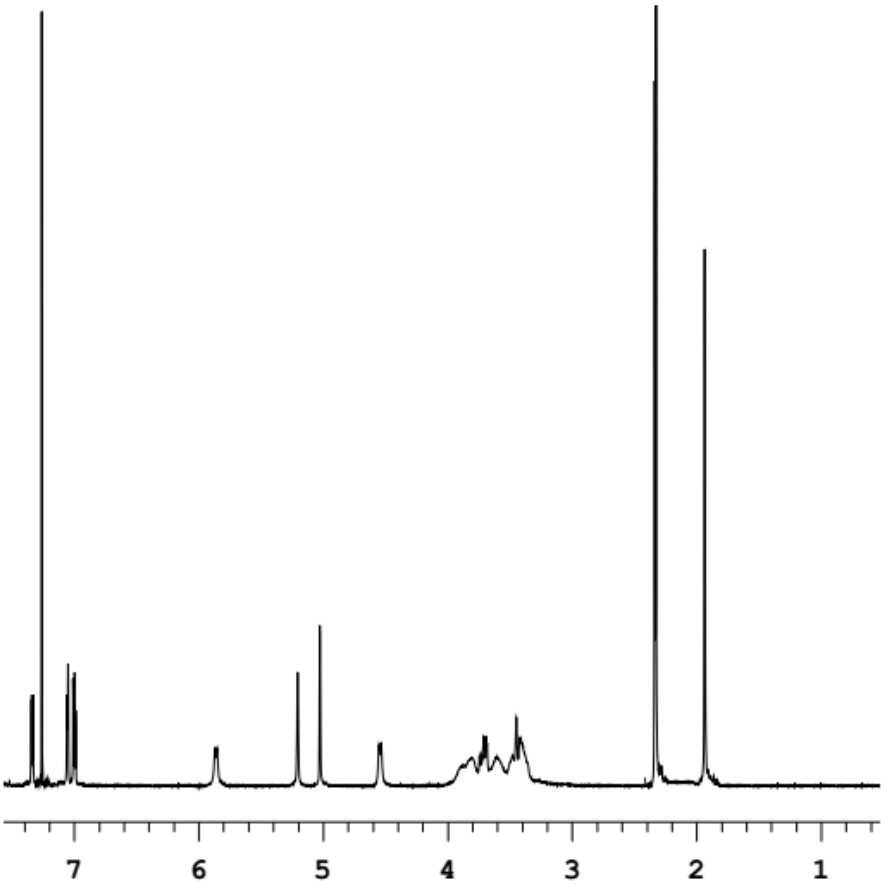
**3d. $^{1}$H NMR**



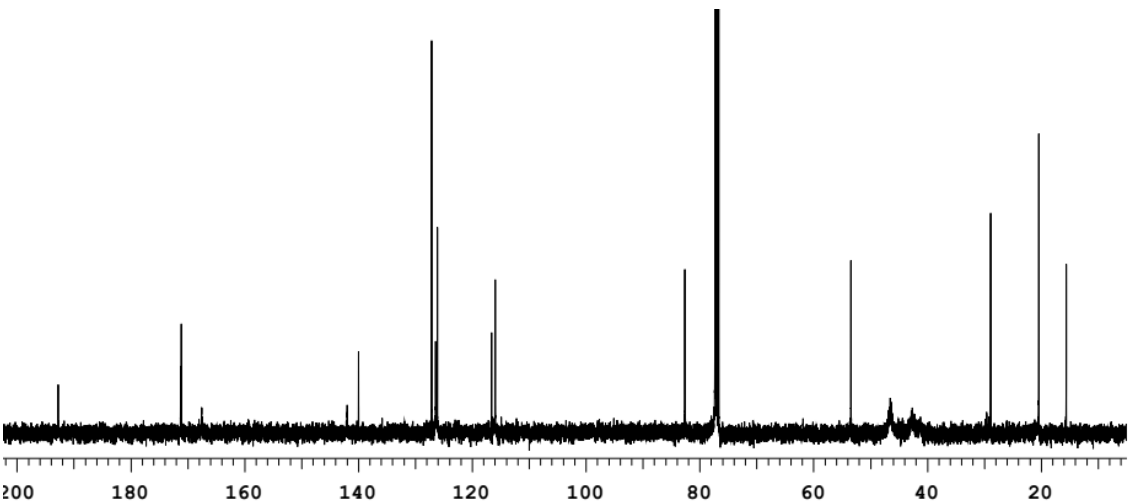

**3d. $^{13}$C NMR**



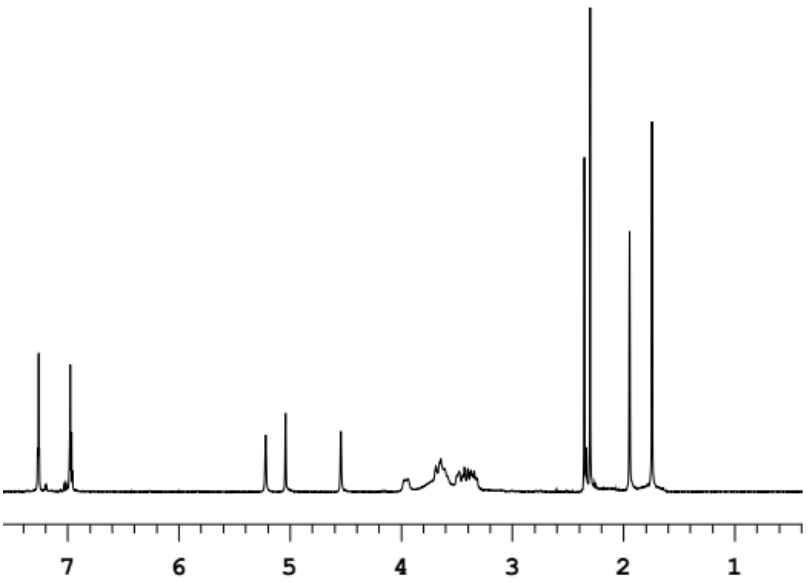
**3e. $^{1}$H NMR**



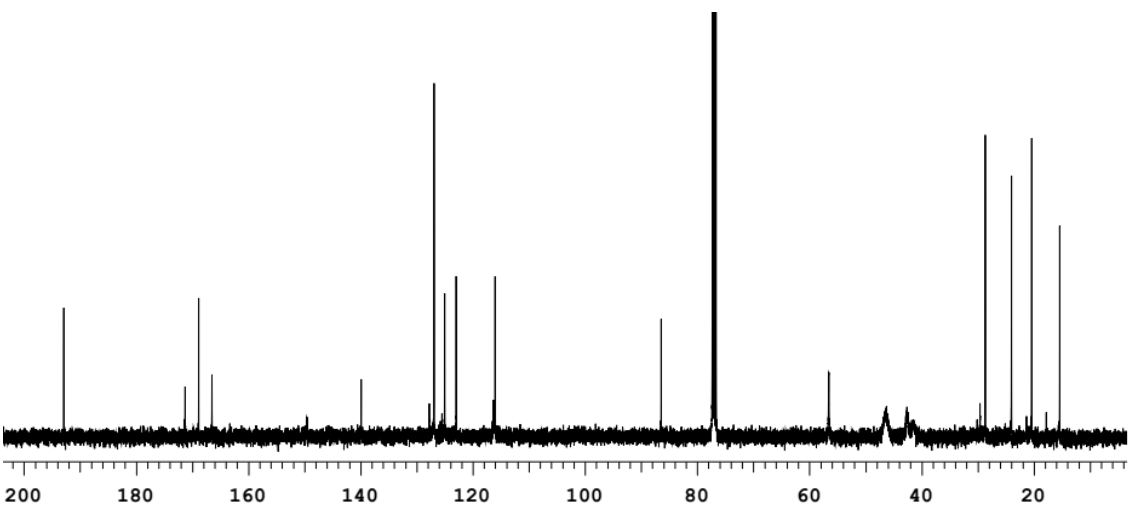

**3e. $^{13}$C NMR**



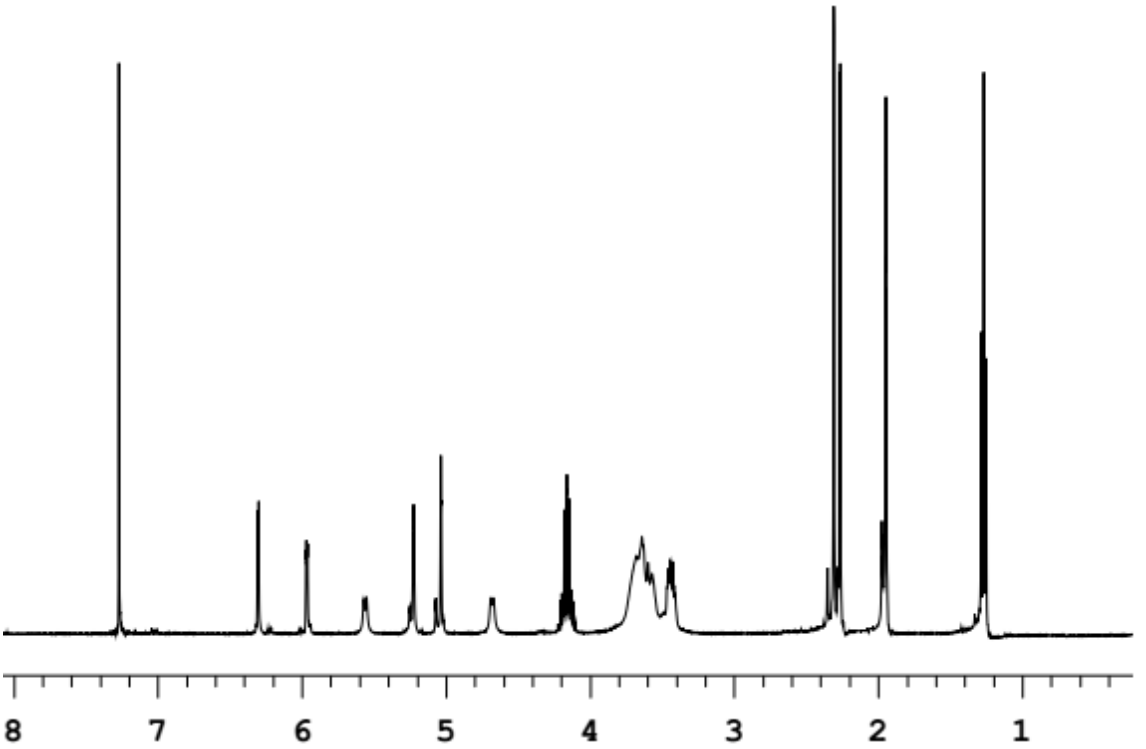
**3f. $^{1}$H NMR**



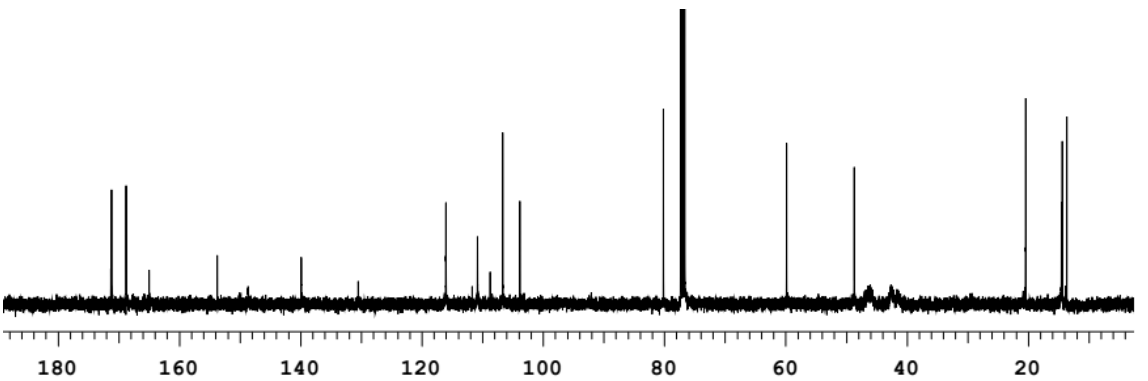

**3f. $^{13}$C NMR**



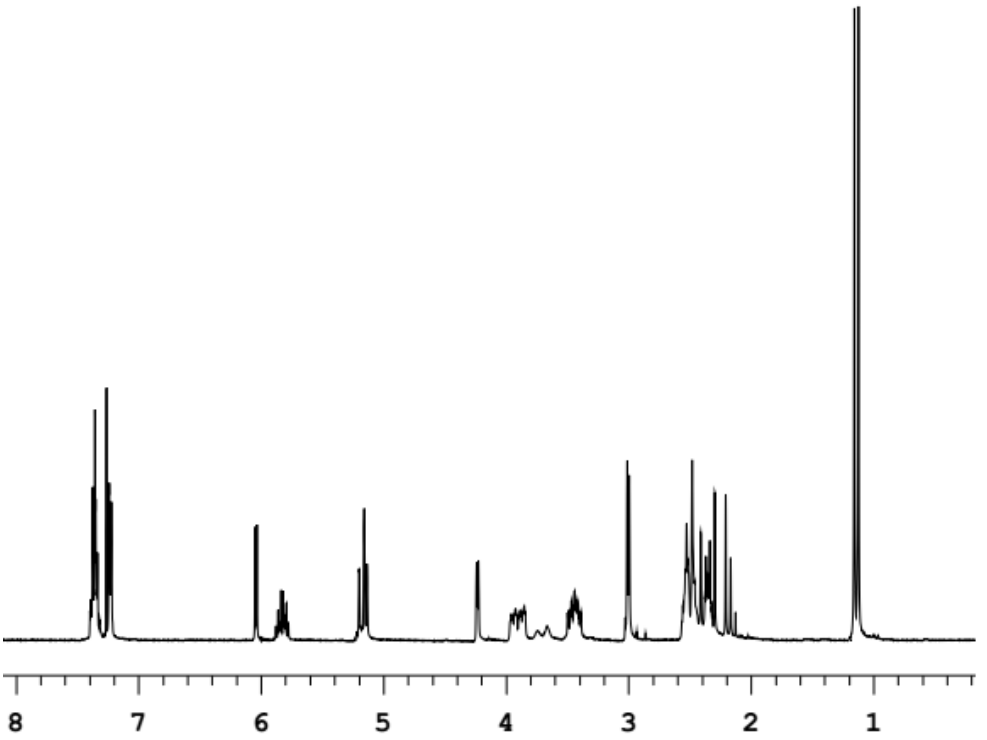
**3g. $^{1}$H NMR**



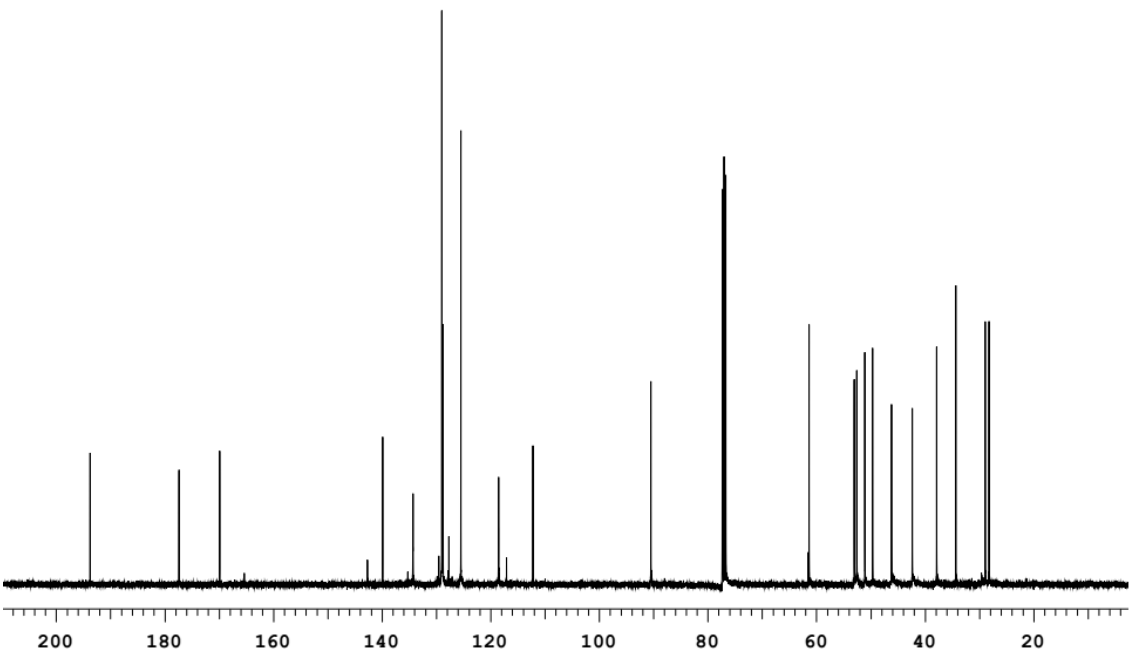

**3g. $^{13}$C NMR**



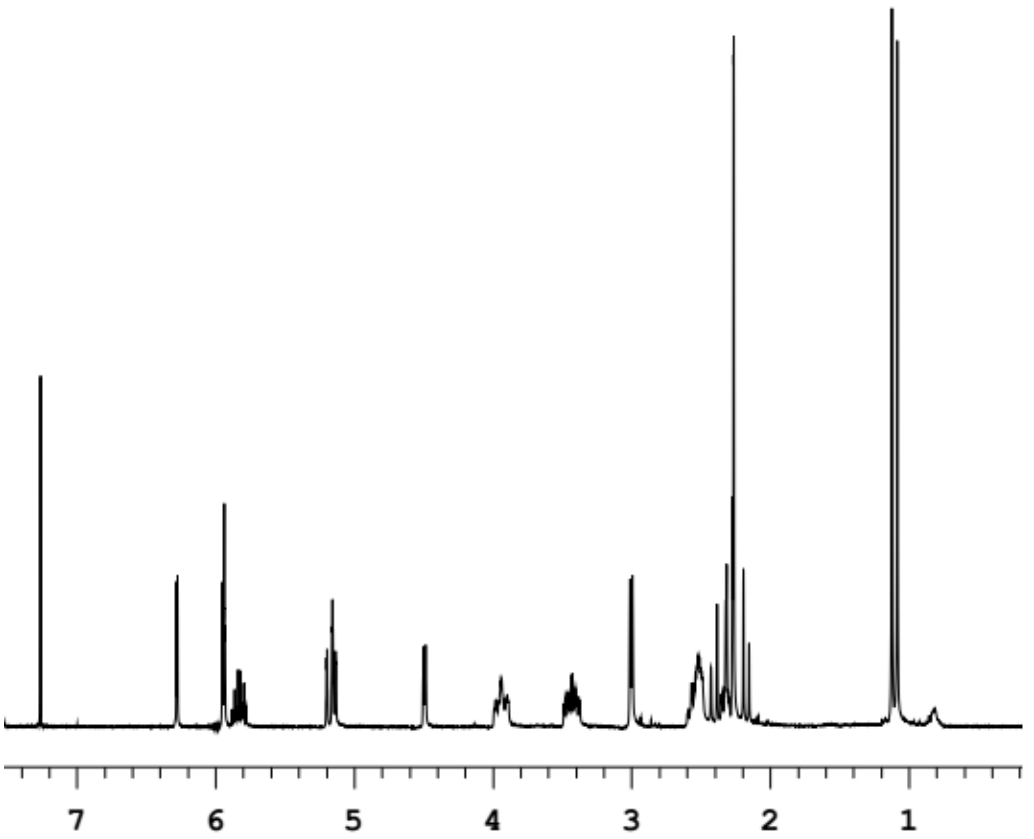
**3h. $^{1}$H NMR**



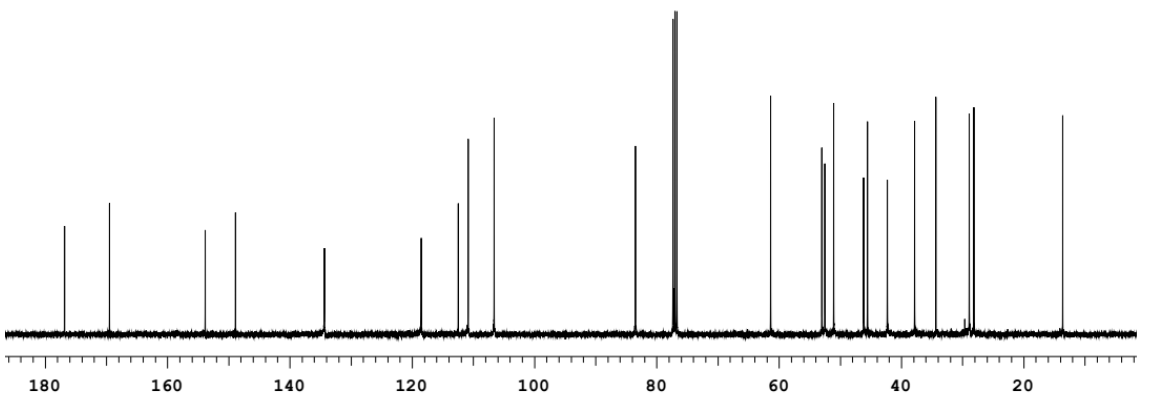

**3h. $^{13}$C NMR**



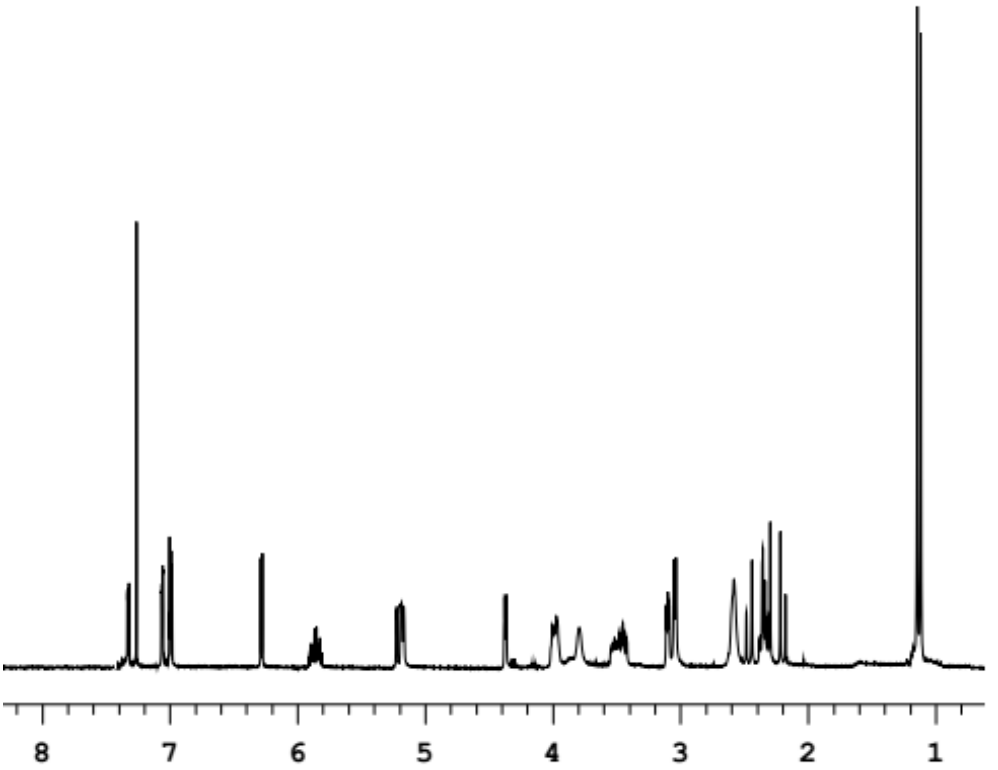
**3i. $^{1}$H NMR**



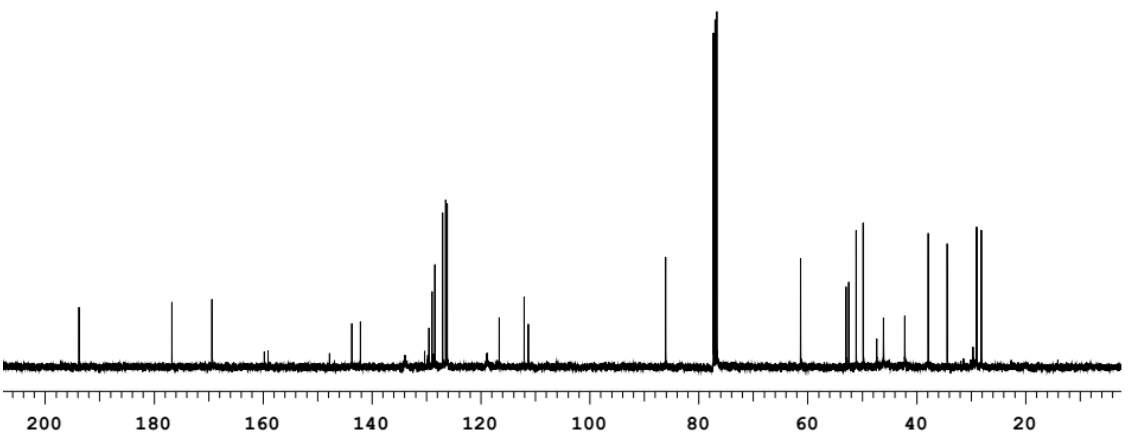

**3i. $^{13}$C NMR**



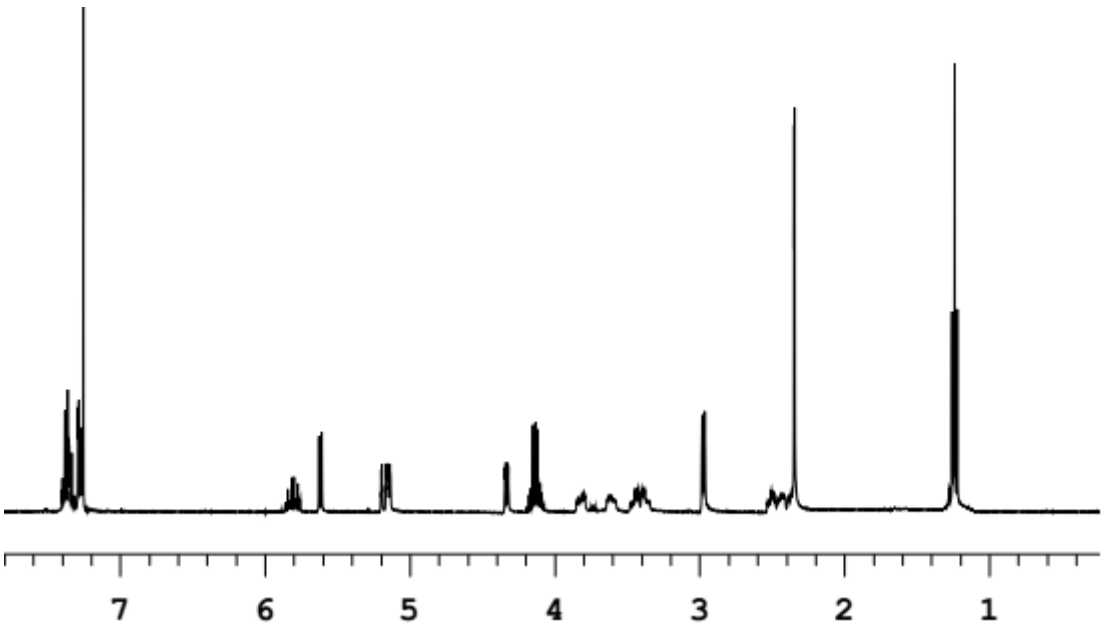
**3j. $^{1}$H NMR**



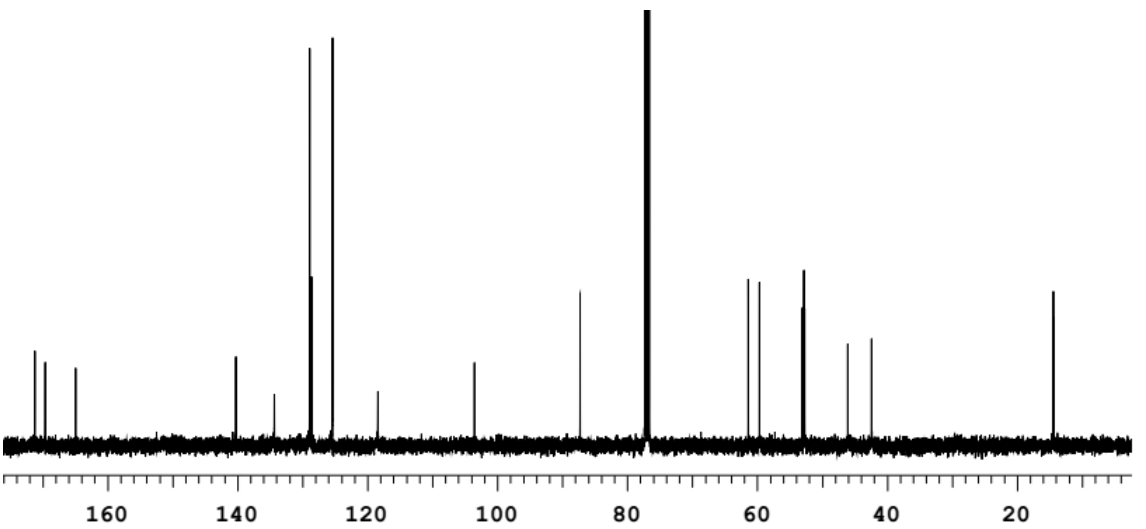

**3j. $^{13}$C NMR**



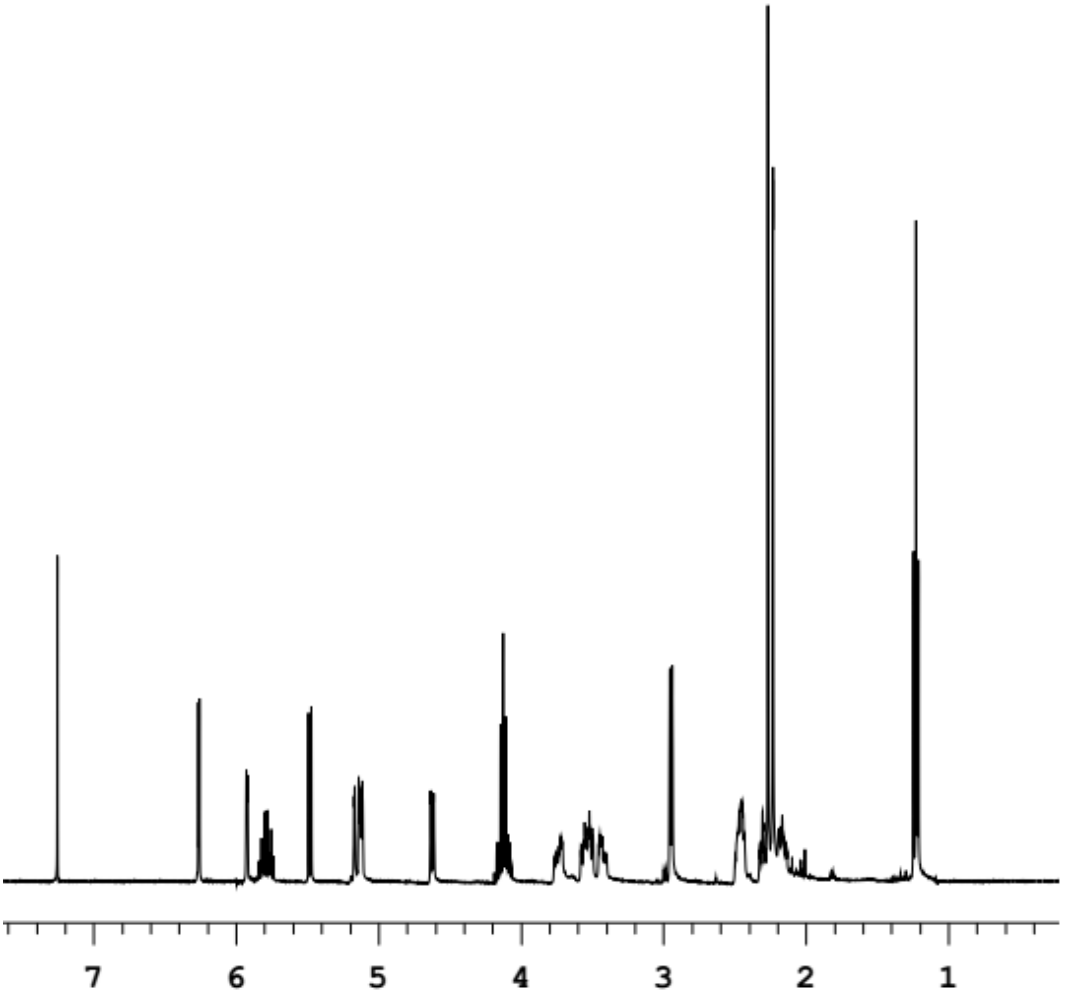
**3k. $^{1}$H NMR**



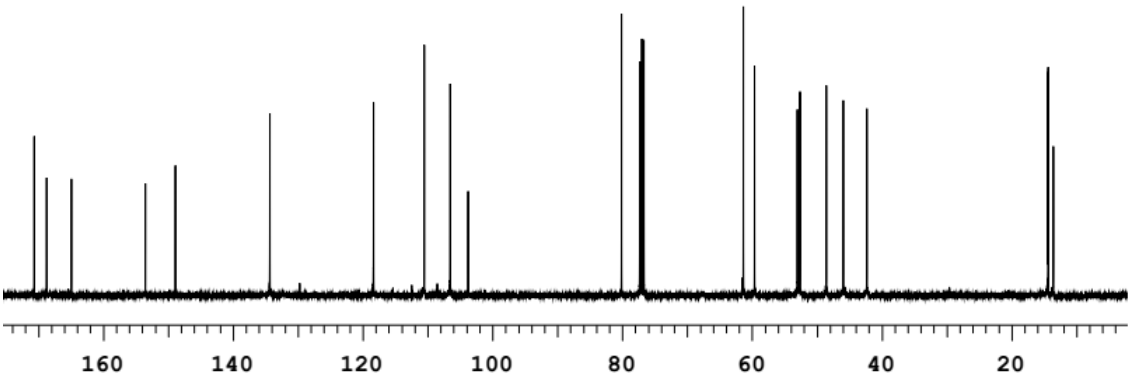

**3k. $^{13}$C NMR**



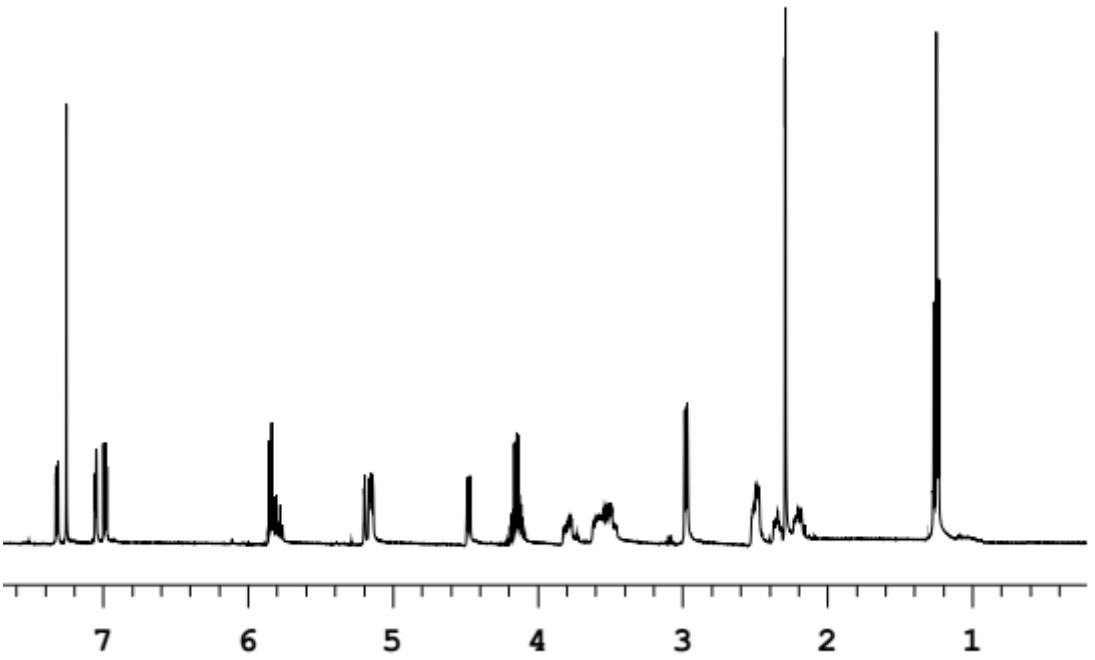
**3l. $^{1}$H NMR**



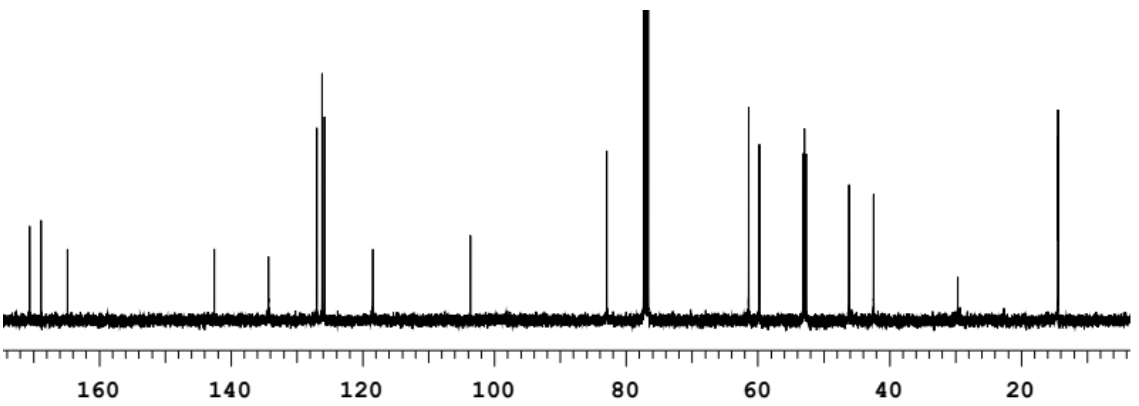

**3l. $^{13}$C NMR**



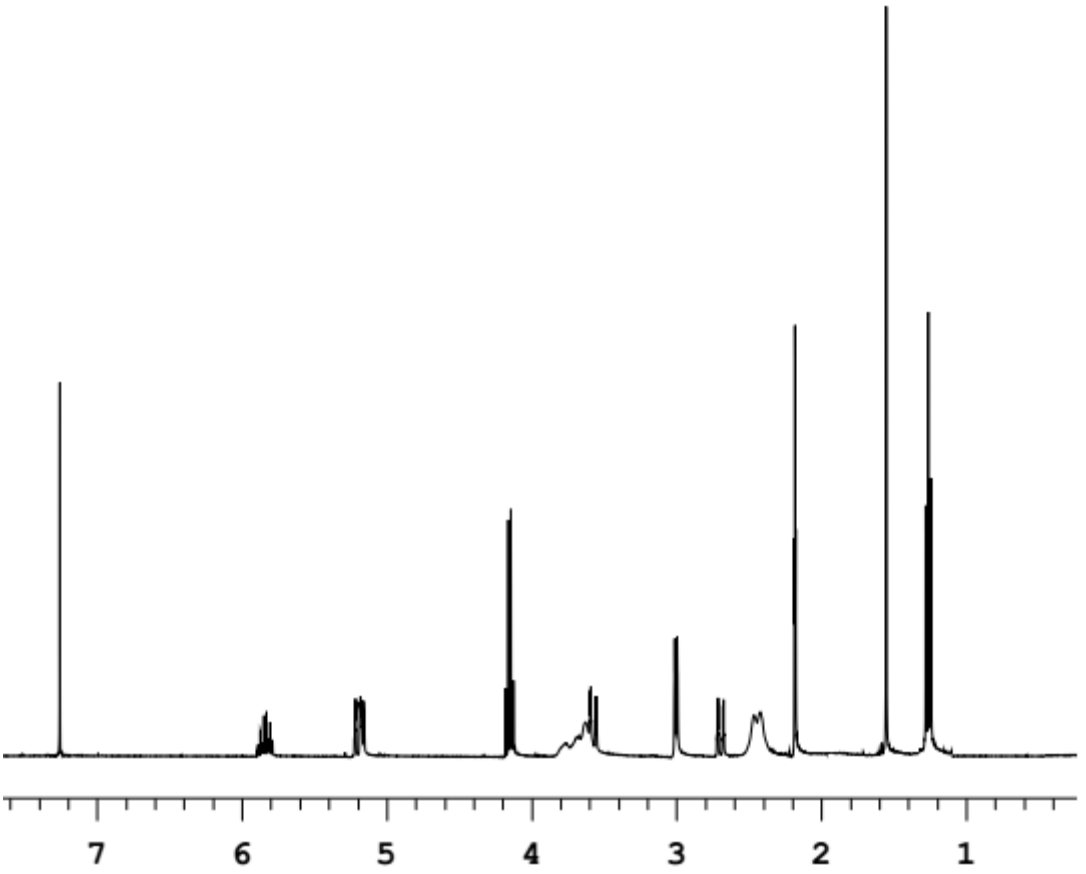
**3m. $^{1}$H NMR**



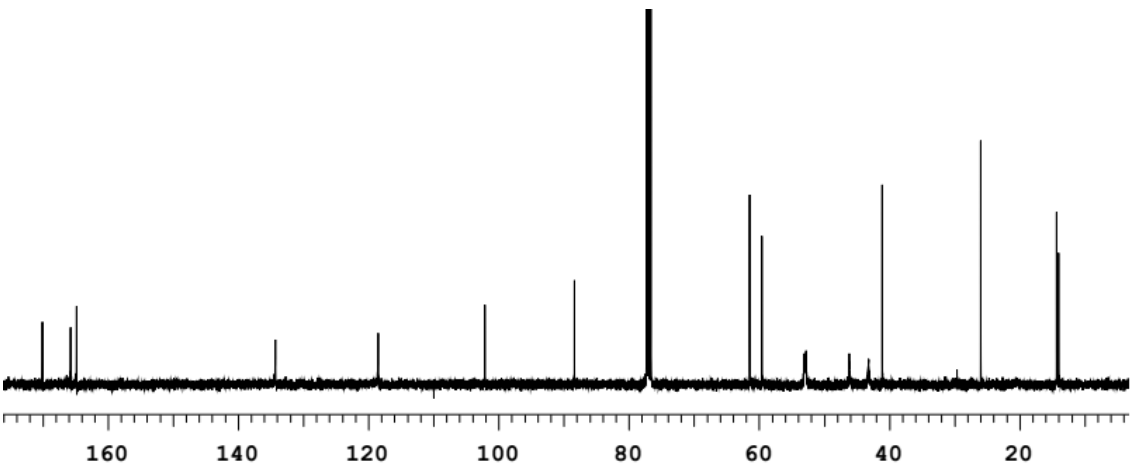

**3m. $^{13}$C NMR**



**3n. $^{1}$H NMR**

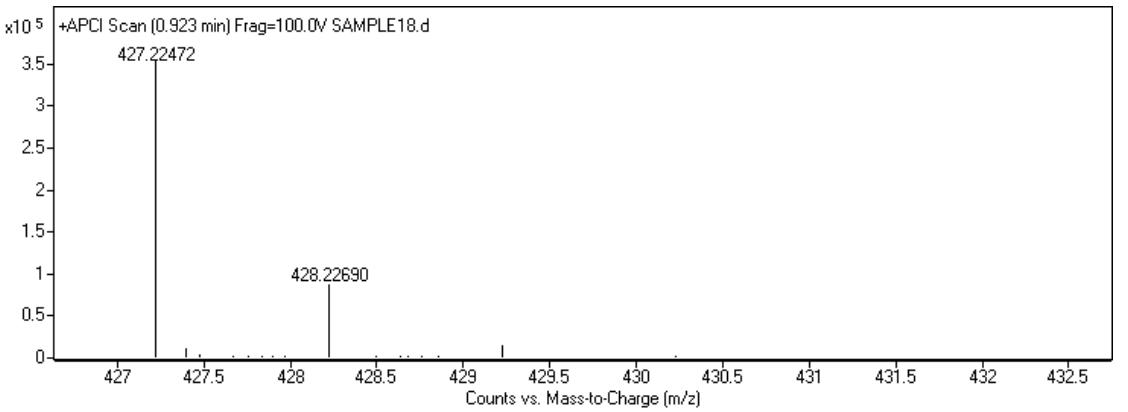



**3n. $^{13}$C NMR**

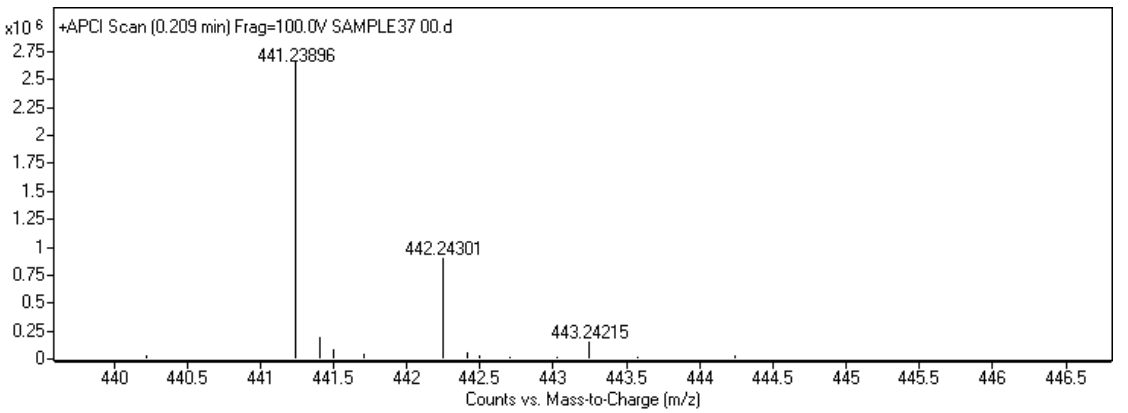


## HRMS spectra

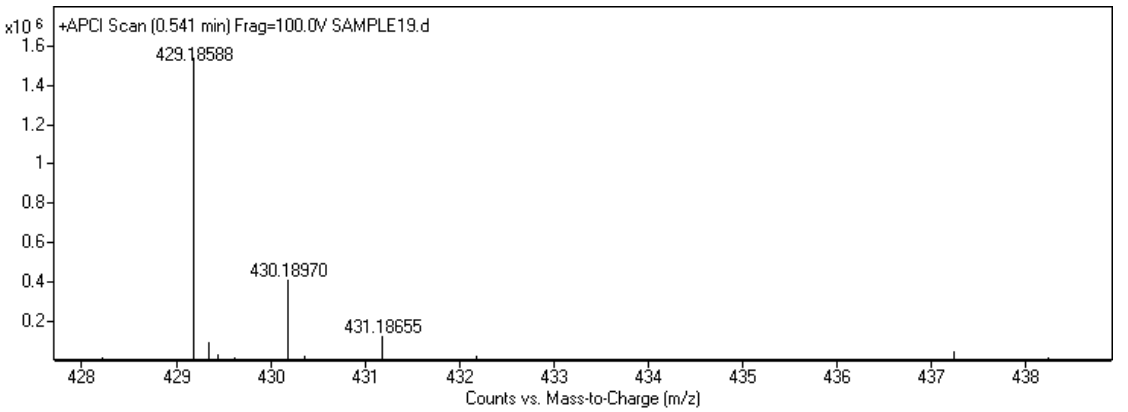
### 3a



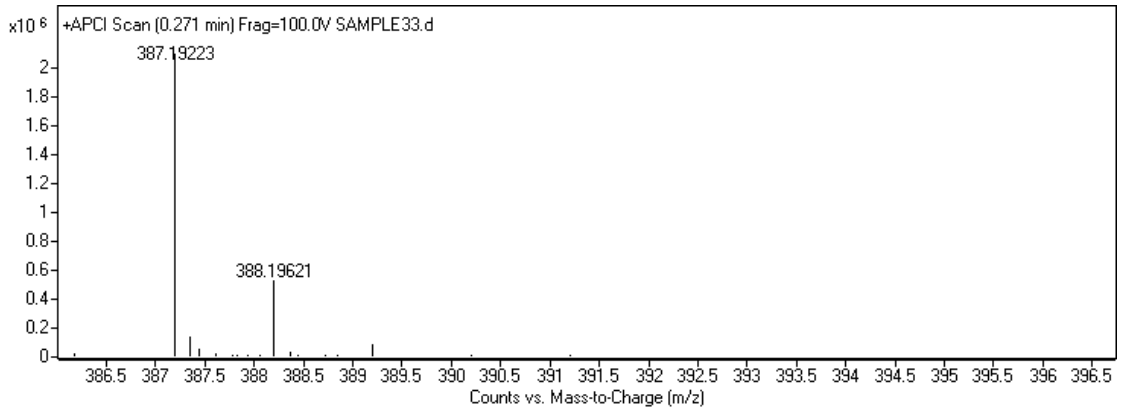

### 3b



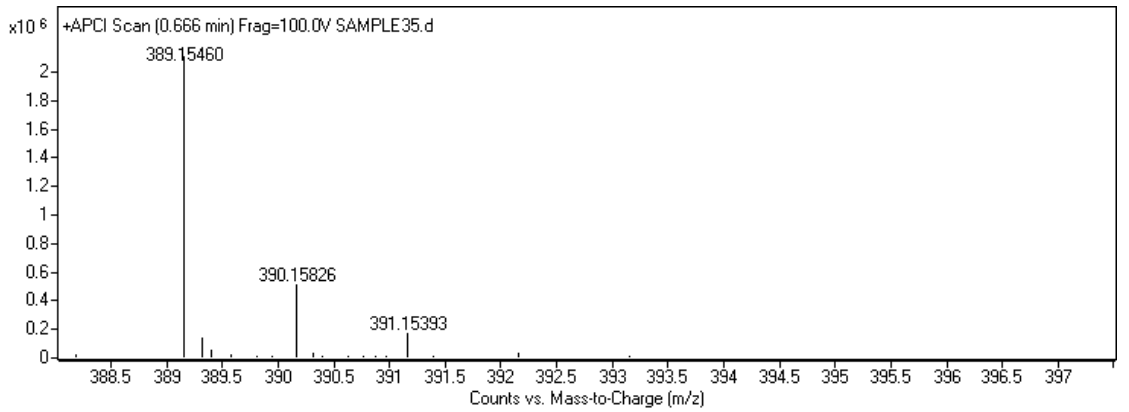

### 3c



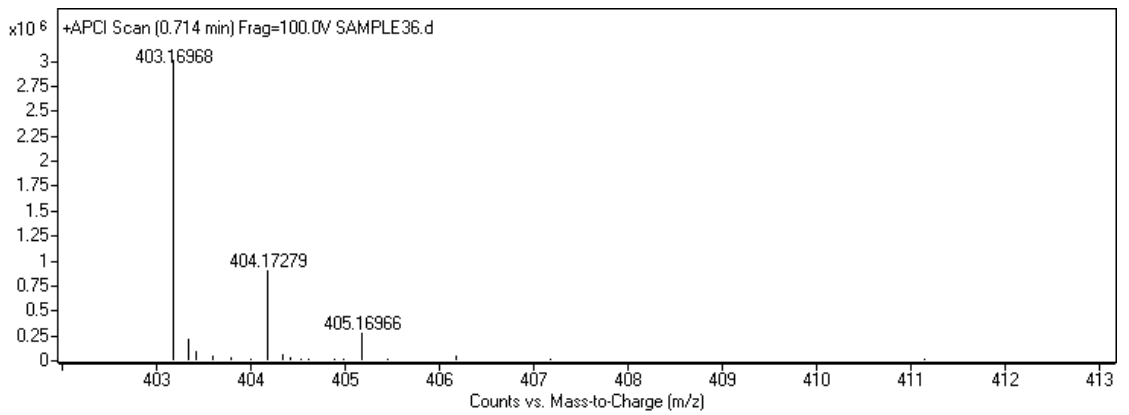
**3d**


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

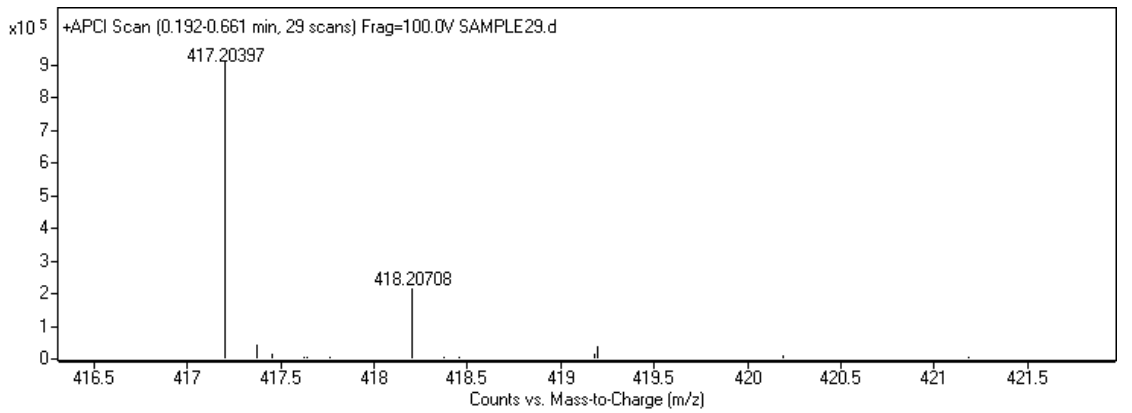
**3e**


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)

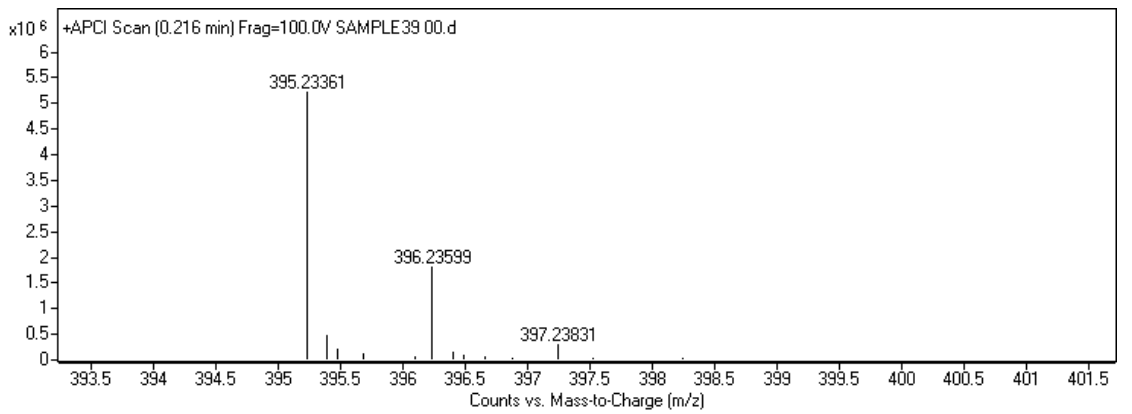
**3f**


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)

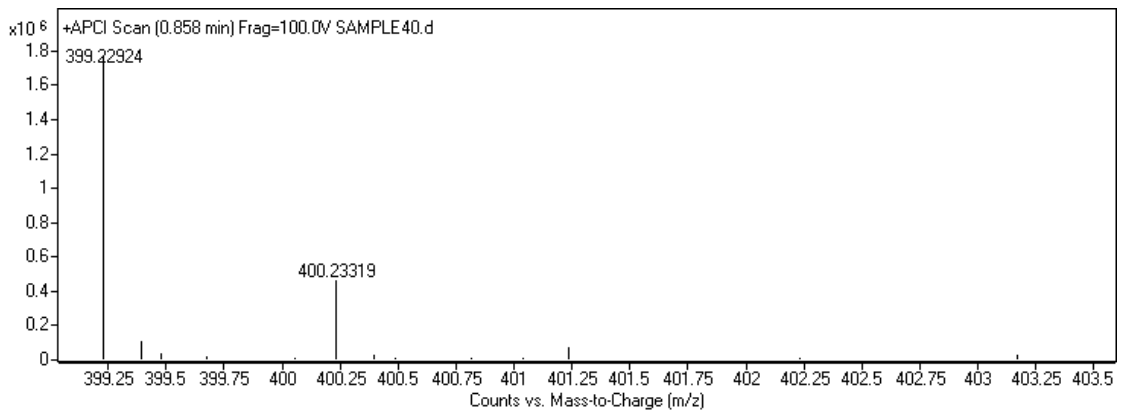
**3g**


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)

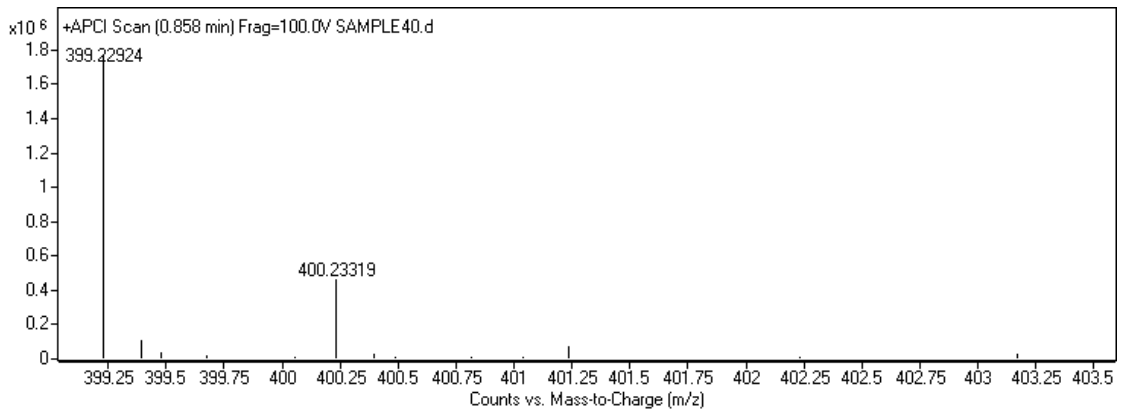
**3h**


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)

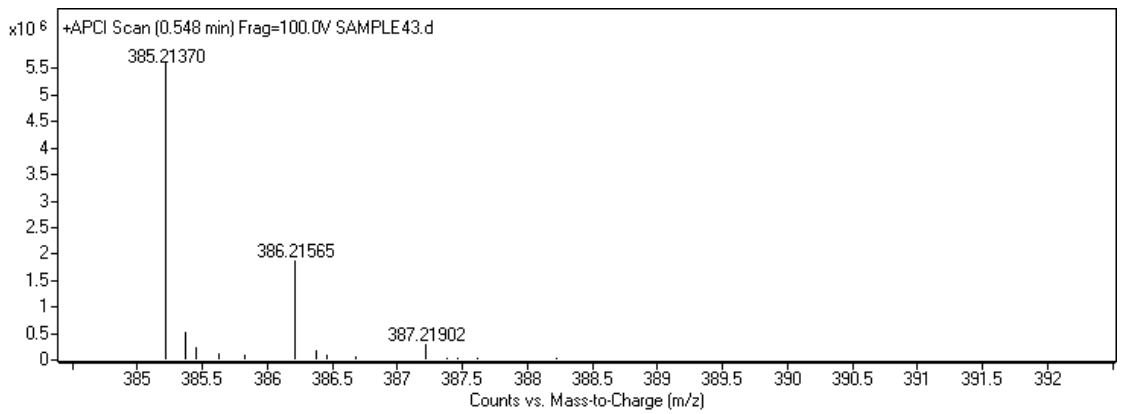
**3i**


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

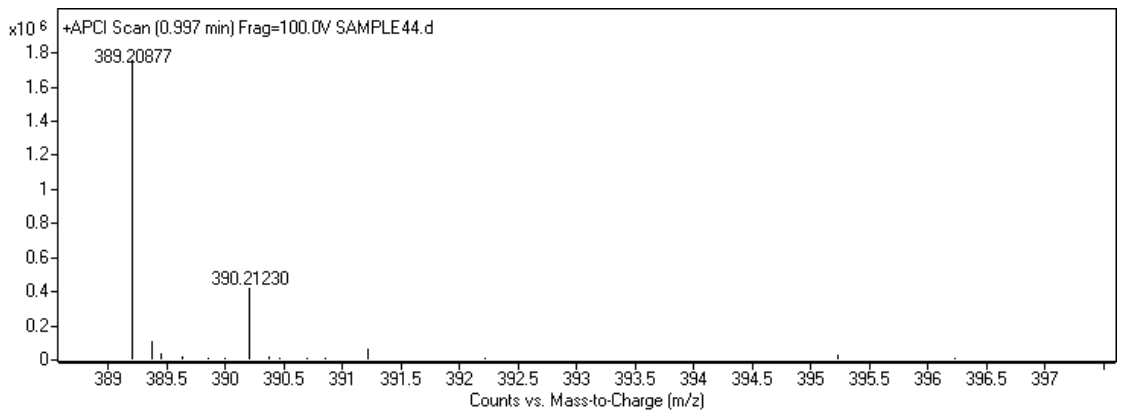
**3j**


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

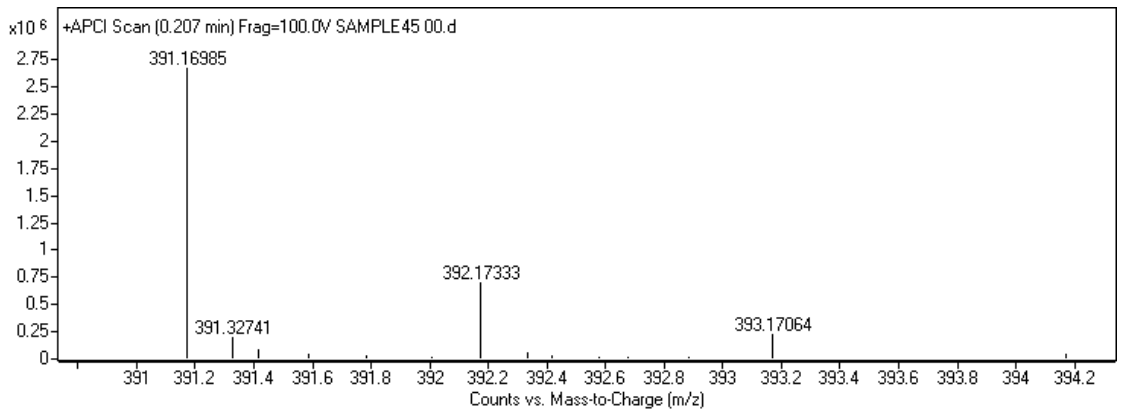
**3k**


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)

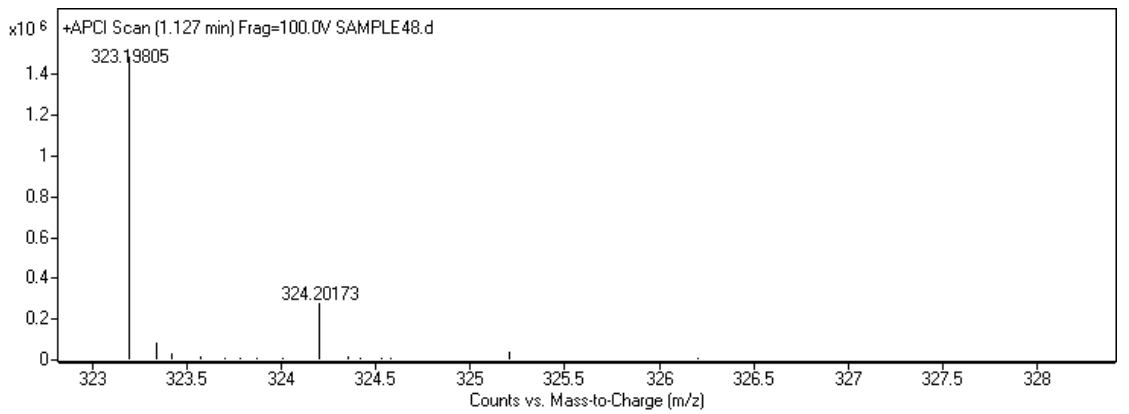
**3l**


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)