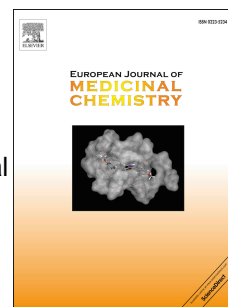


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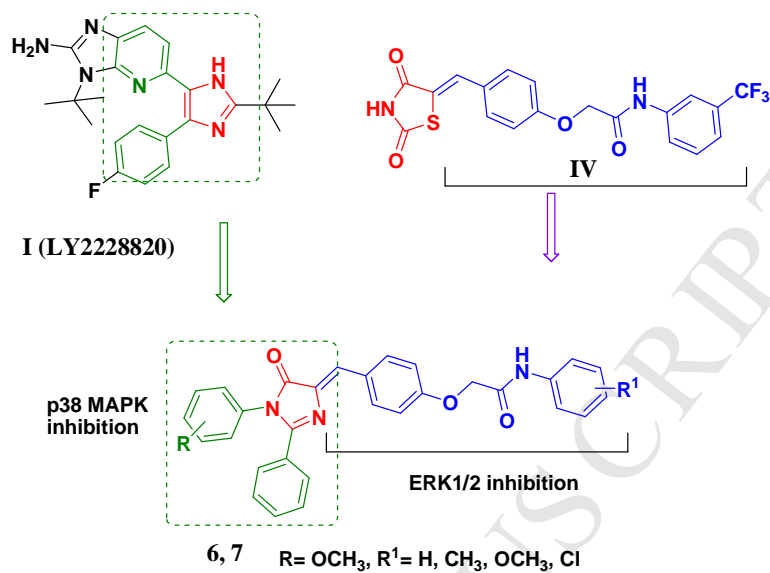
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Graphical abstract:



6d ($R=3\text{-OCH}_3$, $R^1=4\text{-CH}_3$) and **7h** ($R=4\text{-OCH}_3$, $R^1=2\text{-Cl}$) exert inhibitory activity of 4.5 and 4.7 nM against p38 α MAP, 25 and 24 nM against ERK1, and 3.2 and 3.5 nM against ERK2, respectively.

Design and synthesis of potent 1,2,4-trisubstituted imidazolinone derivatives with dual p38 α MAPK and ERK1/2 inhibitory activity

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Abstract.

The synthesis of new 1,2,4-trisubstituted imidazolinone derivatives was described. The new compounds were designed as dual p38 α MAPK and ERK1/2 inhibitors through hybridization of pharmacophoric elements associated with inhibition of these kinases. The kinase inhibition assay revealed excellent activity in the nanomolar range; especially compounds **6d** and **7h** which seemed promising candidates for such dual activity with IC₅₀ values of 4.5 and 4.7 nM against p38 α MAPK, 25.0 and 24.0 nM against ERK1, and 3.2 and 3.5 nM against ERK2, respectively. These compounds were further tested for their antiproliferative activity against nine cancer cell lines, where they elicited high activity in the sub-micromolar range against breast, prostate and melanoma cells.

Keywords: imidazolinones; breast cancer; melanoma; p38 α MAPK; ERK1/2.

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1. Introduction.

The oncogenic process is a result of multiple dysfunctional pathways and pathway genes. Therefore, targeting multiple pathways simultaneously is necessary for sustained tumor remission. Signal transduction in cancer cells is a sophisticated process that involves receptor tyrosine kinases (RTKs) that eventually trigger multiple cytoplasmic kinases, which are often serine/threonine kinases. In clinical trials, highly selective or specific inhibitors of only one of the kinases involved in these signaling pathways has been associated with limited or sporadic responses. Therefore, simultaneous inhibition of several key kinases at the level of receptors and/or downstream serine/threonine kinases may help to optimize the overall therapeutic benefit associated with molecularly targeted anticancer agents [1-3].

Mamalian mitogen-activated protein kinases (MAPKs) are serine/threonine protein kinases that participate in intracellular signaling during proliferation, differentiation, cellular stress responses and apoptosis. Inhibition of MAPKs, including extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38MAPK (having α , β , γ , δ isoforms) and the stress activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK), has been implicated in the activity of numerous chemotherapy and genotoxic drugs [4,5]. p38MAPK regulates production of cytokines by the tumor microenvironment and its activation enables cancer cells to survive in the presence of oncogenic stress, radiation, chemotherapy and targeted therapies [6]. In addition, p38MAPK is implicated in angiogenesis which is required for tumor growth and metastasis, and many new cancer therapies are therefore directed against the tumor vasculature. LY2228820 dimesylate **I** is a highly selective small molecule inhibitor of p38 α and p38 β MAPKs that is currently under clinical investigation for human malignancies [7]. Another example is the potent p38 α MAP kinase inhibitor isoxazole isostere **II** [8] (Figure 1).

On the other hand, upon activation of ERK1/2 by growth factors, cytokines and osmotic stresses, they can phosphorylate and regulate multiple substrates such as cytoskeletal proteins, kinases and transcription factors within various cellular compartments. These events in turn result in gene expression changes and alteration in cell proliferation, differentiation and survival [9]. For this reason, inhibitors of the ERK1/2 are entering clinical trials as potential anticancer agents [10]. The 3,4-diarylsbstituted pyrazole derivative **III** demonstrated potent cytotoxic activity through ERK1/2 inhibition [11] (Figure 1).

Based on these observations, it seemed beneficial to co-target p38 α MAPK and ERK1/2, an approach that might lead to a synergistic effect on inhibiting cell proliferation and on controlling metastasis. Moreover, it was reported that the inhibition of p38MAPK resulted in

stimulation of ERK with subsequent induction of proliferation [12,13]. Therefore, dual targeting of p38MAPK and ERK would prevent activation of ERK following p38MAPK inhibition, and would potentiate the antiproliferative activity of the new compounds.

With the goal of producing new antitumor agents and based on the aforementioned facts, the design of the new target compounds relied on a hybrid pharmacophoric approach in which two molecular fragments were combined. The first was the vicinal diarylsubstituted 5-membered heterocyclic nucleus, which is typical for p38MAPK inhibition, as could be featured in compounds **I** and **II**. Accordingly, the vicinal diarylsubstituted imidazolinone moiety was selected as a core for our target compounds **6** and **7**. On the other hand, it could be observed that the ERK1/2 inhibitor **III** was characterized by a structure extension at position 1 of the pyrazole ring which was believed to contribute to ERK activity. Hence, a second molecular fragment deemed essential to extend the imidazolinone core as to empower ERK inhibition [11]. Searching for a bioactive moiety of interest in the field of chemotherapy, the literature survey revealed the broad spectrum anticancer activity of compound **IV** against lung, prostate, breast cancers and leukemia [14]. Appropriately, the benzylidene tail of the thiazolidinedione derivative **IV** was selected to extend the imidazolinone scaffold with the hope to obtain new compounds with potential activity against many types of cancer cells and acting via inhibition of p38 α MAPK and ERK1/2 (Figure 2).

Herein, we report the synthesis of novel series of diversely substituted imidazolinone derivatives **6a-j** and **7a-j** together with the study of their inhibitory activity against p38 α MAPK and ERK1/2, and their antiproliferative activity toward selected cell lines.

2. Discussion.

2.1. Chemistry:

The synthetic strategy for the preparation of the target compounds **6a-j** and **7a-j** was illustrated in Scheme 1. 4-(4-Hydroxybenzylidene)-2-phenyloxazol-5(4*H*)-one **2** was synthesized according to the literature method [15] via the Erlenmyer reaction of hippuric acid

with 4-hydroxybenzaldehyde and acetic anhydride. Subsequently, 4-(4-hydroxybenzylidene)-1-(3/4-methoxyphenyl)-2-phenyl-1*H*-imidazol-5(4*H*)-ones **3** and **4** were obtained through the reaction of **2** with 3/4-methoxyaniline in glacial acetic acid in the presence of anhydrous sodium acetate. This reaction proceeded through open intermediates which were recycled in the presence of glacial acetic acid to afford the imidazolinones **3** and **4** [16]. IR spectra of compounds **3** and **4** revealed the appearance of bands at 3327 and 3290 cm⁻¹, respectively assigned to the OH group. Also, ¹H NMR showed the exchangeable singlet signal corresponding to OH proton. Reaction of **3**, **4** with 2-chloro-*N*-un/substituted phenylacetamide **5a-j**; previously synthesized according to the literature method [17,18]; afforded the acetamide derivatives **6a-j** and **7a-j** in good yields. IR spectra revealed the presence of an additional carbonyl band assigned to the phenylacetamido function. ¹H NMR revealed the presence of a singlet signal integrated for 2 protons corresponding to the CH₂ protons at 4.67-4.76 ppm and an exchangeable singlet signal corresponding to NH proton mostly at δ 8.16-9.01 ppm. Also, additional singlet signals corresponding to the 3 methyl or 3 methoxy protons resonating at 2.27-2.39 or 3.83-3.90 ppm in case of **6b-d**, **7b-d** or **6e-g**, **7e-g**, respectively, were observed. Moreover, ¹³C NMR showed the characteristic signals of the CH₂ signal at 67.4-67.6 ppm in addition to signals at 17.4-21.4 ppm or 55.4-55.9 ppm for compounds bearing methyl or methoxy groups, respectively.

2.2. Anticancer activity:

2.2.1 *In vitro* kinase inhibitory activity:

The target compounds were evaluated for their potential inhibitory effect on p38 α MAPK and ERK1/2 protein kinases using LanthaScreen Kinase activity assay kits (Invitrogen). The activity was expressed by median growth inhibitory concentration (IC₅₀) and provided in Table 1. Sorafenib was used as reference drug. The results indicated that, the new imidazolinones exhibited potent inhibitory activity against the three kinases at nanomolar level (IC₅₀ ranges: p38 α = 3.7-354, ERK1= 21-95, ERK2= 2.3-89 nM). Moreover, the majority of the tested compounds were more potent against p38 α MAPK and/or ERK2 than ERK1. Several derivatives showed potency higher than sorafenib against p38 α MAPK and ERK2 but all of them were less potent than the reference drug against ERK1. In particular, compounds **6d**, **6f-6j**, **7h** and **7i** displayed excellent kinase suppressive effect at single digit nanomolar concentrations against p38 α MAPK and ERK2 (IC₅₀ range = 3.7-6.5 and 3.4-7.0 nM,

respectively). Compound **6e**, **7g** and **7j** preferentially inhibited ERK2 with IC_{50} = 4.7, 2.3 and 4.5 nM, respectively.

Analysis of p38 α MAPK enzymatic assay results revealed that the inhibitory potency of *N*¹-3-methoxyphenyl imidazolinones **6a-j** and their *N*¹-4-methoxyphenyl analogs **7a-j** was primarily affected by the electronic nature and position of the substituent on the pendant phenyl ring of the aryl acetamide moiety. The inhibitory potency of *N*¹-3-methoxyphenyl imidazolinones **6a-j** was enhanced by grafting electron-withdrawing substituent like 3-methoxy group **6f** (IC_{50} =6.5 nM) or chlorine atom **6h-i** (IC_{50} =3.7-5.6 nM) to the phenyl ring regardless of its position. The potency was also favored by *para*-substitution on the phenyl with 4-methyl **6d** (IC_{50} =4.5 nM) or 4-methoxy group **6g** (IC_{50} = 4.3 nM), (c.f. **6a** R= H, IC_{50} = 35 nM). However, *ortho*- and *meta*-methylphenyl **6b,c** or *ortho*-methoxyphenyl **6e** derivatives were the least active in this series. Considering *N*¹-4-methoxyphenyl imidazolinones **7a-j**, compound **7a**, having unsubstituted phenyl ring, was the least active kinase inhibitor (IC_{50} =354 nM). Similar to the *N*¹-3-methoxyphenyl imidazolinones **6a-j**, compounds with electron-withdrawing 3-methoxy group **7f** (IC_{50} =23 nM) or chloro **7h-i** (IC_{50} =4.5-44 nM) substituent on the pendant phenyl were significantly more potent than those with electron-donating methyl group **7b-d** or 2/4-methoxy group **7e** and **7g** (IC_{50} =34-345 nM). However, substitution at the *para* position (**7d**, **7g** and **7j**) was not well tolerated compared to *ortho* (**7b**, **7e** and **7h**) and *meta* (**7c**, **7f** and **7i**) substituted counterparts.

As per the activity against ERK2, it could be noticed that there was a high degree of homogeneity between the activity of the compounds on p38 α MAPK and ERK2; so that compounds highly effective against p38 α MAPK were similarly effective against ERK2 except for derivatives **6e**, **7g** and **7j** which were more active on ERK2 than p38 α MAPK.

Finally, looking up for our target dual p38 α MAP-ERK1/2 inhibitors, compounds **6d** and **7h** seemed promising candidates for such dual activity; exerting inhibitory activity of 4.5 and 4.7 nM against p38 α MAP, 25 and 24 nM against ERK1, and 3.2 and 3.5 nM against ERK2, respectively.

2.2.2. Antiproliferative activity of compounds **6d** and **7h**:

Constitutive activation of MAPK pathway was found in patient tumor samples in breast, colon, melanoma, lung, blood and thyroid [19,20]. Therefore, the antiproliferative activity of compounds **6d** and **7h** which demonstrated the best overall kinase inhibitory activity was

evaluated against nine human tumor cell lines derived from different cancer types. The growth inhibitory activity of the compounds was evaluated using MTT method [21] and sorafenib was employed as a reference compound. The results were expressed as IC_{50} values and are presented in Table 2. The results revealed that both compounds exhibited potent antiproliferative activity against most of the tested cell lines (IC_{50} range = 0.05-9.40 μ M), but were inactive against leukemia K562. Compounds **6d** and **7h** possessed superior activity at sub-micromolar level, even higher than that of sorafenib, against breast cancer (MCF7 and T47D), melanoma (LOX IMVI and MDA-MB-435) and prostate (PC3) cell lines with IC_{50} ranging from 0.05 to 0.99 μ M. However, unlike sorafenib, the tested compounds were less effective against colon cancer (Colo-205 and HT29) and lung cancer (A549) cell lines (IC_{50} range = 4.50-9.40 μ M).

Comparing the activity of **6d** and **7h** against the sensitive cell lines, revealed that compound **7h** displayed higher potency than **6d** toward breast (MCF7), colon (Colo-205 and HT29), lung (A549) and melanoma (LOX IMVI and MDA-MB-435) cancer cell lines. On the other hand, **6d** was more effective against breast (T47D) and prostate (PC3) cell lines.

To examine the selectivity and hence the safety of compounds **6d** and **7h**, their antiproliferative activity was assessed against normal mammalian cells (Vero cells). The data indicated that the tested compounds had relatively low cytotoxic effect on normal cells (IC_{50} = 17.34 and 13.20 μ M, respectively). The selectivity index calculated in relation to IC_{50} on Vero cells revealed high selectivity toward most tested cancer cells ($SI > 20$) except colon (Colo-205, HT-29) and lung (A-549) cells (Table2).

3. Conclusion.

The design and synthesis of new 1,2,4-trisubstituted imidazolinone derivatives of dual p38 α MAPK and ERK1/2 inhibitory activity was described. The structure of the new compounds featured a vicinal diarylsubstituted imidazolinone core contributing to p38 α MAPK activity and an extended substitution at position 4 of the imidazolinone nucleus that favored the ERK1/2 activity. In vitro kinase activity revealed preferential activity against p38 α MAPK and ERK2 with IC_{50} in the nanomolar level and the activity of some derivatives exceeded that of sorafenib. Generally, the *N*¹-3-methoxyphenyl-imidazolinones were more potent than their *N*¹-4-methoxyphenyl isomers. Compounds **6d** and **7h** exhibited the highest activity against the three tested kinases. Therefore, their antiproliferative activity was assessed against several cell lines belonging to breast, colon, lung, leukemia, melanoma and prostate cancers. These compounds displayed activity in the sub-micromolar range and were found superior to

sorafenib against breast cancer (MCF7 and T47D), melanoma (LOX IMVI and MDA-MB-435) and prostate (PC3) cell lines with IC₅₀ ranging from 0.05 to 0.99 μ M. Also, the compounds were highly selective to the same cancer cell lines as compared to normal Vero cells. Finally, it could be claimed that the rationale behind the design of the target compounds succeeded in achieving dual p38 α MAPK and ERK1/2 inhibition, which in turn secured potent antiproliferative activity against several cancer cell lines.

4. Experimental

4.1. Chemistry:

Melting Points were carried out by open capillary tube method using Stuart SMP3 Melting Point apparatus and they were uncorrected. Elemental Microanalysis was carried out at the Regional Center for Mycology and Biotechnology, Al-Azhar University. Infrared spectra were recorded on Shimadzu Infrared spectrometer IR Affinity-1 (FTIR- 8400S-Kyoto-Japan), and expressed in wave number (cm⁻¹), using potassium bromide discs. NMR spectra were recorded on Bruker Avance III 400 MHz high performance digital FT-NMR spectrophotometer (¹H: 400, ¹³C: 100 MHz) in chloroform-*d*, using TMS as an internal standard. Chemical shifts were expressed in δ units and were related to that of the solvents. All the reactions were followed up by TLC using silica gel F254 plates (Merck), using chloroform: methanol 9:1 or chloroform as eluting system and were visualized by UV-lamp. Compounds **2** [1] and **5a-j** [3,4] were prepared according to reported methods.

4.1. Chemistry

4.1.1. General procedure for the synthesis of compounds (**3**, **4**).

A mixture of **2** (10 mmol, 2.65g), 3/4-methoxyaniline (12 mmol, 1.47g) and freshly prepared anhydrous sodium acetate (0.3g) in glacial acetic acid (10 mL) was heated in a boiling water bath for 3 h. The crystalline product separated on cooling was filtered off, washed with water, dried, and recrystallized from ethanol.

4.1.1.1. 4-(4-Hydroxybenzylidene)-1-(3-methoxyphenyl)-2-phenyl-1H-imidazol-5(4H)-one (**3**).

Yield 87%; m.p. 252-253 °C; IR (KBr, cm⁻¹: 3327 (OH), 3061 (aromatic CH), 2954 (CH aliphatic), 1685 (C=O); ¹H NMR: δ 3.72 (s, 3H, OCH₃), 6.79 (d, 2H, aromatic H, *J*= 7.72 Hz), 6.81 (s, 1H, aromatic H), 6.88 (d, 1H, aromatic H, *J*= 8.60 Hz), 6.91 (s, ex, 1H, OH), 6.99, 7.01 (dd, 1H, *J*= 2.24, 8.30 Hz), 7.20 (s, 1H, CH), 7.33-7.39 (m, 3H, aromatic H), 7.46 (t, 1H, aromatic H, *J*= 7.36 Hz), 7.53 (d, 2H, aromatic H, *J*= 7.16 Hz), 8.24 (d, 2H, aromatic H, *J*=

8.68 Hz); ^{13}C NMR: δ 55.8, 114.2, 114.3, 116.6, 120.4, 125.6, 128.8, 129.1, 129.4, 130.4, 131.5, 135.2, 135.8, 136.3, 158.9, 160.1, 161.2, 169.9. Anal. Calcd. For $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3$ (370.12): C, 74.58; H, 4.90; N, 12.96%. Found: C, 74.69; H, 4.93; N, 7.65%.

4.1.1.2. 4-(4-Hydroxybenzylidene)-1-(4-methoxyphenyl)-2-phenyl-1H-imidazol-5(4H)-one (**4**).

Yield 82%; m.p. 273-274 °C; IR (KBr, cm^{-1}): 3290 (OH), 3062 (aromatic CH), 2960 (CH aliphatic), 1689 (C=O); ^1H NMR: δ 3.76 (s, 3H, OCH_3), 6.89 (d, 2H, aromatic H, J = 8.80 Hz), 6.96 (d, 2H, aromatic H, J = 6.76 Hz), 7.16 (d, 2H, aromatic H, J = 6.96 Hz), 7.18 (s, 1H, CH), 7.34-7.38 (m, 3H, aromatic H), 7.51 (d, 2H, aromatic H, J = 8.52 Hz), 8.24 (d, 2H, aromatic H, J = 8.76 Hz), 10.49 (s, ex, 1H, OH); ^{13}C NMR: δ 55.8, 114.9, 116.4, 127.8, 128.1, 128.8, 129.2, 129.4, 129.5, 131.5, 135.2, 136.1, 159.4, 160.7, 170.4; Anal. Calcd. For $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3$ (370.12): C, 74.58; H, 4.90; N, 12.96%. Found: C, 74.72; H, 4.87; N, 7.68%.

4.1.2. General procedure for the synthesis of compounds (**6a-j**, **7a-j**).

Potassium carbonate (10 mmol, 1.38g) was added to a solution of compound **3**, **4** (10 mmol, 3.70g) in dry DMF (15 mL) and stirred at room temperature for 0.5h. Then, the appropriate 2-chloro-*N*-un/substituted phenylacetamide **5a-j** (10 mmol) was added and heated at 100°C for 8h. The reaction mixture was poured onto ice/water and the precipitated solid was filtered off, washed with water, dried and crystallized from ethanol.

4.1.2.1. 2-(4-((1-(3-Methoxyphenyl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)methyl)phenoxy)-*N*-phenylacetamide (**6a**).

Yield: 82%; m.p. 220-221 °C; IR (KBr, cm^{-1}): 3332 (NH), 3061 (aromatic CH), 2924 (CH aliphatic), 1706, 1685 (C=O); ^1H NMR: δ 3.78 (s, 3H, OCH_3), 4.71 (s, 2H, CH_2), 6.74 (s, 1H, aromatic H), 6.76-6.78 (m, 1H, aromatic H), 6.94, 6.96 (dd, 1H, aromatic H, J = 2.16, 8.40 Hz), 7.09 (d, 2H, aromatic H, J = 8.80 Hz), 7.12 (t, 1H, aromatic H, J = 7.40 Hz), 7.28 (s, 1H, CH), 7.31-7.41 (m, 5H, aromatic H), 7.44 (t, 1H, J = 7.44 Hz), 7.61 (d, 4H, aromatic H, J = 8.40 Hz), 8.25 (s, ex, 1H, NH), 8.34 (d, 2H, aromatic H, J = 8.40 Hz); ^{13}C NMR: δ 55.4, 67.5, 113.0, 114.3, 115.1, 119.6, 120.1, 120.2, 125.0, 128.3, 128.4, 128.6, 129.0, 129.1, 130.0, 131.3, 134.7, 135.7, 136.6, 137.6, 158.5, 160.0, 160.2, 165.6, 170.4. Anal. Calcd. For $\text{C}_{31}\text{H}_{25}\text{N}_3\text{O}_4$ (503.55): C, 73.94; H, 5.00; N, 8.34%. Found: C, 74.02; H, 5.04; N, 8.42%.

4.1.2.2. 2-(4-((1-(3-Methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)-*N*-(*o*-tolyl)acetamide (**6b**).

Yield: 65%; m.p. 159-161°C; IR (KBr, cm^{-1}): 3410 (NH), 3050 (aromatic CH), 2924 (CH aliphatic), 1728, 1693 (C=O); ^1H NMR: δ 2.38 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.68 (s, 2H, CH_2), 6.74 (s, 1H, aromatic H), 6.76-6.78 (m, 1H, aromatic H), 6.93, 6.95 (dd, 1H, aromatic H, $J = 2.24, 8.32$ Hz), 6.99 (t, 1H, aromatic H, $J = 7.50$ Hz), 7.08 (d, 2H, aromatic H, $J = 8.80$ Hz), 7.26 (s, 1H, CH), 7.24-7.48 (m, 7H, aromatic H), 7.61 (d, 2H, aromatic H, $J = 7.32$ Hz), 8.23 (s, ex, 1H, NH), 8.33 (d, 2H, aromatic H, $J = 8.76$ Hz); ^{13}C NMR: δ 21.4, 55.4, 67.5, 113.0, 114.3, 115.1, 117.3, 120.7, 120.8, 125.8, 128.3, 128.4, 128.8, 128.9, 129.0, 129.1, 130.0, 131.3, 134.7, 135.7, 136.6, 137.5, 139.1, 158.5, 159.9, 160.2, 165.6, 170.4. Anal. Calcd. For $\text{C}_{32}\text{H}_{27}\text{N}_3\text{O}_4$ (517.58): C, 74.26; H, 5.26; N, 8.12%. Found: C, 74.34; H, 5.25; N, 8.22%.

4.1.2.3. 2-(4-((1-(3-Methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene) methyl)phenoxy)-N-(m-tolyl)acetamide (**6c**).

Yield: 86%; m.p. 167-169 °C; IR (KBr, cm^{-1}): 3414 (NH), 3066 (aromatic CH), 2924 (CH aliphatic), 1724, 1701 (C=O); ^1H NMR: δ 2.27 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.76 (s, 2H, CH_2), 6.75 (s, 1H, aromatic H), 6.77-6.78 (m, 1H, aromatic H), 6.94, 6.96 (dd, 1H, aromatic H, $J = 1.96, 8.44$ Hz), 7.10 (d, 2H, aromatic H, $J = 8.80$ Hz), 7.13 (d, 1H, aromatic H, $J = 7.72$ Hz), 7.22 (t, 1H, aromatic H, $J = 7.60$ Hz), 7.28 (s, 1H, CH), 7.32 (s, 1H, aromatic H), 7.33-7.37 (m, 3H, aromatic H), 7.44 (t, 1H, aromatic H, $J = 7.44$ Hz), 7.61 (d, 2H, aromatic H, $J = 7.32$ Hz), 7.98 (d, 1H, aromatic H, $J = 7.92$ Hz), 8.22 (s, ex, 1H, NH), 8.35 (d, 2H, aromatic H, $J = 8.80$ Hz); ^{13}C NMR: δ 17.4, 55.4, 67.5, 113.0, 114.3, 115.0, 119.6, 122.4, 125.5, 126.9, 128.3, 128.6, 128.8, 129.0, 129.1, 130.0, 130.5, 131.3, 134.7, 135.7, 137.5, 158.5, 160.0, 160.2, 165.6, 170.4. Anal. Calcd. For $\text{C}_{32}\text{H}_{27}\text{N}_3\text{O}_4$ (517.58): C, 74.26; H, 5.26; N, 8.12%. Found: C, 74.35; H, 5.29; N, 8.25%.

4.1.2.4. 2-(4-((1-(3-Methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene) methyl)phenoxy)-N-(p-tolyl)acetamide (**6d**).

Yield: 84%; m.p. 151-153 °C; IR (KBr, cm^{-1}): 3323 (NH), 3050 (aromatic CH), 2922 (CH aliphatic), 1710, 1683 (C=O); ^1H NMR: δ 2.36 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2), 6.74 (s, 1H, aromatic H), 6.76-6.78 (m, 1H, aromatic H), 6.94, 6.96 (dd, 1H, aromatic H, $J = 2.08, 8.32$ Hz), 7.09 (d, 2H, aromatic H, $J = 8.80$ Hz), 7.18 (d, 2H, aromatic H, $J = 8.24$ Hz), 7.28 (s, 1H, CH), 7.33-7.38 (m, 3H, aromatic H), 7.44-7.50 (m, 3H, aromatic H), 7.61 (d, 2H, aromatic H, $J = 7.32$ Hz), 8.19 (s, ex, 1H, NH), 8.34 (d, 2H, aromatic H, $J = 8.76$ Hz); ^{13}C NMR: δ 20.9, 55.4, 67.5, 113.0, 114.3, 115.1, 119.6, 120.1, 128.3, 128.4, 128.8, 129.0, 129.1, 129.6, 130.0, 131.3, 134.1, 134.7, 135.7, 137.5, 158.5, 160.0, 160.2, 165.5, 170.4. Anal.

Calcd. For $C_{32}H_{27}N_3O_4$ (517.58): C, 74.26; H, 5.26; N, 8.12%. Found: C, 74.39; H, 5.30; N, 8.25%.

4.1.2.5. *N*-(2-Methoxyphenyl)-2-(4-((1-(3-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**6e**).

Yield: 76%; m.p. 172-174 °C -; IR (KBr, cm^{-1}): 3402 (NH), 3060 (aromatic CH), 2924 (CH aliphatic), 1710, 1683 (C=O); 1H NMR: δ 3.78 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 4.72 (s, 2H, CH₂), 6.75 (s, 1H, aromatic H), 6.77-6.78 (m, 1H, aromatic H), 6.91-6.96 (m, 3H, aromatic H), 6.99 (t, 1H, aromatic H, J = 7.52 Hz), 7.10 (d, 2H, aromatic H, J = 8.84 Hz), 7.28 (s, 1H, CH), 7.31-7.37 (m, 3H, aromatic H), 7.44 (t, 1H, J = 7.44 Hz), 7.61 (d, 2H, aromatic H, J = 7.48 Hz), 8.34 (d, 2H, aromatic H, J = 8.76 Hz), 8.41 (d, 1H, aromatic H, J = 7.92 Hz), 8.96 (s, ex, 1H, NH); ^{13}C NMR: δ 55.4, 55.9, 67.6, 110.1, 113.0, 114.3, 115.2, 119.6, 120.0, 121.1, 124.4, 126.6, 128.3, 128.5, 128.8, 129.1, 130.0, 131.3, 134.7, 135.7, 137.4, 148.3, 158.7, 159.9, 160.2, 165.4, 170.4. Anal. Calcd. For $C_{32}H_{27}N_3O_5$ (533.58): C, 72.03; H, 5.10; N, 7.88%. Found: C, 72.19; H, 5.07; N, 8.02%.

4.1.2.6. *N*-(3-Methoxyphenyl)-2-(4-((1-(3-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**6f**).

Yield: 87%; m.p. 137-140°C; IR (KBr, cm^{-1}): 3383 (NH), 3062 (aromatic CH), 2924 (CH aliphatic), 1706, 1676 (C=O); 1H NMR: δ 3.78 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 4.70 (s, 2H, CH₂), 6.73-6.77 (m, 3H, aromatic H), 6.94, 6.96 (dd, 1H, aromatic H, J = 2.20, 8.40 Hz), 7.08-7.11 (m, 3H, aromatic H), 7.25 (s, 1H, aromatic H), 7.28 (s, 1H, CH), 7.33-7.37 (m, 4H, aromatic H), 7.44 (t, 1H, J = 7.40 Hz), 7.61 (d, 2H, aromatic H, J = 7.32 Hz), 8.24 (s, ex, 1H, NH), 8.34 (d, 2H, aromatic H, J = 8.76 Hz); ^{13}C NMR: δ 55.3, 55.4, 67.5, 105.9, 110.8, 112.3, 113.0, 114.3, 115.1, 119.6, 128.3, 128.4, 128.8, 129.0, 129.1, 129.8, 130.0, 131.3, 134.7, 135.7, 137.5, 137.8, 158.5, 160.0, 160.2, 160.3, 165.6, 170.4. Anal. Calcd. For $C_{32}H_{27}N_3O_5$ (533.58): C, 72.03; H, 5.10; N, 7.88%. Found: C, 72.15; H, 5.09; N, 8.02%.

4.1.2.7. *N*-(4-Methoxyphenyl)-2-(4-((1-(3-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**6g**).

Yield: 72%; m.p. 204-206 °C; IR (KBr, cm^{-1}): 3361 (NH), 3055 (aromatic CH), 2927 (CH aliphatic), 1714, 1683 (C=O); 1H NMR: δ 3.83 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 4.70 (s, 2H, CH₂), 6.74 (s, 1H, aromatic H), 6.76-6.79 (m, 1H, aromatic H), 6.91-6.96 (m, 3H, aromatic H), 7.09 (d, 2H, aromatic H, J = 8.48 Hz), 7.28 (s, 1H, CH), 7.31-7.37 (m, 3H, aromatic H), 7.46 (d, 1H, aromatic H, J = 7.76 Hz), 7.50 (d, 2H, aromatic H, J = 8.60 Hz), 7.61

(d, 2H, aromatic H, J = 7.60 Hz), 8.16 (s, ex, 1H, NH), 8.34 (d, 2H, aromatic H, J = 8.52 Hz); ^{13}C NMR: δ 55.4, 55.5, 67.4, 113.0, 114.2, 115.1, 119.6, 122.0, 122.1, 128.3, 128.4, 128.8, 129.0, 129.1, 129.7, 130.0, 131.3, 134.7, 137.5, 156.9, 158.6, 160.0, 160.2, 160.3, 165.6, 170.4. Anal. Calcd. For $\text{C}_{32}\text{H}_{27}\text{N}_3\text{O}_5$ (533.58): C, 72.03; H, 5.10; N, 7.88%. Found: C, 72.13; H, 5.13; N, 7.96%.

4.1.2.8. *N*-(2-Chlorophenyl)-2-(4-((1-(3-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**6h**).

Yield: 78%; m.p. 162-164 °C; IR (KBr, cm^{-1}): 3381 (NH), 3066 (aromatic CH), 2935 (CH aliphatic), 1712, 1685 (C=O), 837 (C-Cl); ^1H NMR: δ 3.77 (s, 3H, OCH_3), 4.71 (s, 2H, CH_2), 6.74 (s, 1H, aromatic H), 6.76-6.78 (m, 1H, aromatic H), 6.93, 6.95 (dd, 1H, aromatic H, J = 2.08, 8.36 Hz), 7.07-7.10 (m, 3H, aromatic H), 7.28 (s, 1H, CH), 7.30-7.41 (m, 5H, aromatic H), 7.43 (t, 1H, aromatic H, J = 7.40 Hz), 7.61 (d, 2H, aromatic H, J = 7.52 Hz), 8.33 (d, 2H, aromatic H, J = 8.72 Hz), 8.46 (d, 1H, aromatic H, J = 8.24 Hz), 9.00 (s, ex, 1H, NH); ^{13}C NMR: δ 55.4, 67.4, 113.0, 114.2, 114.7, 119.6, 121.3, 123.1, 125.2, 127.8, 128.3, 128.4, 128.7, 129.0, 129.1, 130.0, 130.3, 131.0, 131.3, 134.7, 135.7, 137.5, 158.4, 159.9, 160.2, 165.7, 170.4. Anal. Calcd. For $\text{C}_{31}\text{H}_{24}\text{ClN}_3\text{O}_4$ (538.00): C, 69.21; H, 4.50; N, 7.81%. Found: C, 69.30; H, 4.53; N, 7.92%.

4.1.2.9. *N*-(3-Chlorophenyl)-2-(4-((1-(3-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**6i**).

Yield: 74%; m.p. 157-159 °C; IR (KBr, cm^{-1}): 3309 (NH), 3066 (aromatic CH), 2935 (CH aliphatic), 1710, 1685 (C=O), 839 (C-Cl); ^1H NMR: δ 3.77 (s, 3H, OCH_3), 4.68 (s, 2H, CH_2), 6.73 (s, 1H, aromatic H), 6.75-6.77 (m, 1H, aromatic H), 6.93, 6.95 (dd, 1H, aromatic H, J = 2.12, 8.12 Hz), 7.07 (d, 2H, aromatic H, J = 8.76 Hz), 7.14 (d, 1H, aromatic H, J = 8.04 Hz), 7.27 (s, 1H, CH), 7.28-7.29 (m, 3H, aromatic H), 7.31-7.37 (m, 2H, aromatic H), 7.44 (t, 1H, aromatic H, J = 7.66 Hz), 7.61 (d, 2H, aromatic H, J = 7.48 Hz), 7.74 (s, 1H, aromatic H), 8.32 (s, ex, 1H, NH), 8.34 (d, 2H, aromatic H, J = 8.56 Hz); ^{13}C NMR: δ 55.4, 67.4, 113.0, 114.2, 114.7, 115.1, 118.1, 119.6, 120.2, 125.0, 128.3, 128.4, 128.8, 129.1, 130.0, 130.1, 131.3, 134.7, 135.7, 137.6, 137.8, 158.4, 160.0, 160.2, 165.8, 170.4. Anal. Calcd. For $\text{C}_{31}\text{H}_{24}\text{ClN}_3\text{O}_4$ (538.00): C, 69.21; H, 4.50; N, 7.81%. Found: C, 69.33; H, 4.52; N, 7.95%.

4.1.2.10. *N*-(4-Chlorophenyl)-2-(4-((1-(3-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**6j**).

Yield: 75%; m.p. 215-217 °C; IR (KBr, cm^{-1}): 3369 (NH), 3060 (aromatic CH), 2935 (CH aliphatic), 1707, 1674 (C=O), 831 (C-Cl); ^1H NMR: δ 3.78 (s, 3H, OCH_3), 4.69 (s, 2H, CH_2), 6.74 (s, 1H, aromatic H), 6.76-6.77 (m, 1H, aromatic H), 6.93, 6.95 (dd, 1H, aromatic H, $J = 2.16, 8.32$ Hz), 7.07 (d, 2H, aromatic H, $J = 8.80$ Hz), 7.28 (s, 1H, CH), 7.30-7.37 (m, 5H, aromatic H), 7.44 (t, 1H, aromatic H, $J = 7.40$ Hz), 7.57 (d, 2H, aromatic H, $J = 8.76$ Hz), 7.61 (d, 2H, aromatic H, $J = 7.36$ Hz), 8.29 (s, ex, 1H, NH), 8.33 (d, 2H, aromatic H, $J = 8.56$ Hz); ^{13}C NMR: δ 55.4, 67.4, 113.0, 114.2, 114.7, 115.1, 119.6, 121.3, 121.4, 128.3, 128.4, 128.8, 129.1, 129.2, 130.0, 130.1, 131.3, 134.7, 135.3, 135.7, 137.6, 158.4, 160.0, 160.2, 165.7, 170.4. Anal. Calcd. For $\text{C}_{31}\text{H}_{24}\text{ClN}_3\text{O}_4$ (538.00): C, 69.21; H, 4.50; N, 7.81%. Found: C, 69.32; H, 4.53; N, 7.91%.

4.1.2.11. 2-(4-((1-(4-Methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene) methyl)phenoxy)-N-phenylacetamide (**7a**).

Yield: 70%; m.p. 229-230 °C -; IR (KBr, cm^{-1}): 3338 (NH), 3052 (aromatic CH), 2923 (CH aliphatic), 1710, 1689 (C=O); ^1H NMR: δ 3.86 (s, 3H, OCH_3), 4.71 (s, 2H, CH_2), 6.95 (d, 2H, aromatic H, $J = 8.88$ Hz), 7.09 (d, 2H, aromatic H, $J = 6.84$ Hz), 7.13 (d, 2H, aromatic H, $J = 6.84$ Hz), 7.19 (t, 1H, aromatic H, $J = 7.44$ Hz), 7.28 (s, 1H, CH), 7.31-7.48 (m, 5H, aromatic H), 7.61 (d, 4H, aromatic H, $J = 8.36$ Hz), 8.25 (s, ex, 1H, NH), 8.34 (d, 2H, aromatic H, $J = 8.76$ Hz); ^{13}C NMR: δ 55.5, 67.5, 114.7, 115.1, 120.2, 125.0, 127.3, 128.2, 128.3, 128.5, 128.9, 129.1, 129.2, 131.3, 134.7, 136.6, 137.6, 158.4, 159.4, 160.2, 165.6, 170.8. Anal. Calcd. For $\text{C}_{31}\text{H}_{25}\text{N}_3\text{O}_4$ (503.55): C, 73.94; H, 5.00; N, 8.34%. Found: C, 73.98; H, 4.97; N, 8.51%.

4.1.2.12. 2-(4-((1-(4-Methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene) methyl)phenoxy)-N-(o-tolyl)acetamide (**7b**).

Yield: 93%; m.p. 231-233 °C; IR (KBr, cm^{-1}): 3309 (NH), 3062 (aromatic CH), 2960 (CH aliphatic), 1716, 1697 (C=O); ^1H NMR: δ 2.27 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.75 (s, 2H, CH_2), 6.95 (d, 2H, aromatic H, $J = 8.88$ Hz), 7.09-7.14 (m, 4H, aromatic H), 7.21 (t, 1H, aromatic H, $J = 7.28$ Hz), 7.27-7.37 (m, 5H, aromatic H and CH), 7.44 (t, 1H, aromatic H, $J = 7.40$ Hz), 7.61 (d, 2H, aromatic H, $J = 7.31$ Hz), 7.98 (d, 1H, aromatic H, $J = 7.91$ Hz), 8.23 (s, ex, 1H, NH), 8.35 (d, 2H, aromatic H, $J = 8.80$ Hz); ^{13}C NMR: δ 17.4, 55.5, 67.5, 114.7, 115.0, 122.4, 125.5, 126.9, 127.3, 128.1, 128.3, 128.5, 128.6, 128.9, 129.1, 129.2, 130.5, 131.3, 134.7, 134.8, 137.6, 158.4, 159.4, 160.2, 165.6, 170.8. Anal. Calcd. For $\text{C}_{32}\text{H}_{27}\text{N}_3\text{O}_4$ (517.58): C, 74.26; H, 5.26; N, 8.12%. Found: C, 74.35; H, 5.24; N, 8.27%.

4.1.2.13. 2-(4-((1-(4-Methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)-N-(m-tolyl)acetamide (**7c**).

Yield: 87%; m.p. 239-241 °C -; IR (KBr, cm⁻¹): 3350 (NH), 3050 (aromatic CH), 2927 (CH aliphatic), 1710, 1678 (C=O); ¹H NMR: δ 2.39 (s, 3H, CH₃), 3.86 (s, 3H, OCH₃), 4.70 (s, 2H, CH₂), 6.95 (d, 2H, aromatic H, J = 8.84 Hz), 7.00 (d, 1H, aromatic H, J = 7.96 Hz), 7.09-7.13 (m, 4H, aromatic H), 7.28 (m, 1H, CH), 7.25-7.46 (m, 6H, aromatic H), 7.61 (d, 2H, aromatic H, J = 7.40 Hz), 8.19 (s, ex, 1H, NH), 8.34 (d, 2H, aromatic H, J = 8.72 Hz); ¹³C NMR: δ 21.4, 55.5, 67.5, 114.7, 115.1, 117.3, 120.8, 125.8, 127.3, 128.2, 128.3, 128.5, 128.9, 129.0, 129.1, 129.2, 131.3, 134.7, 136.5, 137.6, 139.1, 158.5, 159.4, 160.2, 165.6, 170.8. Anal. Calcd. For C₃₂H₂₇N₃O₄ (517.58): C, 74.26; H, 5.26; N, 8.12%. Found: C, 74.33; H, 5.28; N, 8.25%.

4.1.2.14. 2-(4-((1-(4-Methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)-N-(p-tolyl)acetamide (**7d**).

Yield: 80%; m.p. 244-246 °C; IR (KBr, cm⁻¹): 3361 (NH), 3051 (aromatic CH), 2918 (CH aliphatic), 1716, 1683 (C=O); ¹H NMR: δ 2.36 (s, 3H, CH₃), 3.85 (s, 3H, OCH₃), 4.69 (s, 2H, CH₂), 6.94 (d, 2H, aromatic H, J = 8.84 Hz), 7.01 (d, 2H, aromatic H, J = 8.68 Hz), 7.11 (d, 2H, aromatic H, J = 7.68 Hz), 7.18 (d, 2H, aromatic H, J = 8.24 Hz), 7.28 (s, 1H, CH), 7.30-7.35 (m, 3H, aromatic H), 7.48 (d, 2H, aromatic H, J = 8.36 Hz), 7.59 (d, 2H, aromatic H, J = 7.64 Hz), 8.21 (s, ex, 1H, NH), 8.33 (d, 2H, aromatic H, J = 8.76 Hz); ¹³C NMR: δ 20.9, 55.4, 67.5, 114.6, 115.1, 120.3, 127.3, 128.2, 128.3, 128.5, 128.9, 129.2, 129.3, 129.6, 130.3, 130.8, 131.3, 134.7, 138.0, 158.2, 159.2, 159.4, 165.5, 170.9. Anal. Calcd. For C₃₂H₂₇N₃O₄ (517.58): C, 74.26; H, 5.26; N, 8.12%. Found: C, 74.41; H, 5.29; N, 8.19%.

4.1.2.15. N-(2-Methoxyphenyl)-2-(4-((1-(4-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**7e**).

Yield: 77%; m.p. 188-190 °C; IR (KBr, cm⁻¹): 3367 (NH), 3055 (aromatic CH), 2927 (CH aliphatic), 1710, 1689 (C=O); ¹H NMR: δ 3.85 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 4.72 (s, 2H, CH₂), 6.91-6.99 (m, 4H, aromatic H), 7.01-7.13 (m, 5H, aromatic H), 7.28 (s, 1H, CH), 7.30-7.47 (m, 3H, aromatic H), 7.61 (d, 2H, aromatic H, J = 7.48 Hz), 8.34 (d, 2H, aromatic H, J = 8.60 Hz), 8.41 (d, 1H, aromatic H, J = 7.52 Hz), 8.97 (s, ex, 1H, NH); ¹³C NMR: δ 55.5, 55.7, 67.6, 110.1, 114.7, 115.1, 119.9, 121.1, 127.3, 128.3, 128.4, 128.5, 128.9, 129.1, 129.2, 131.0, 131.2, 134.7, 134.8, 137.5, 148.3, 158.7, 159.4, 160.0, 165.4, 170.9. Anal. Calcd. For C₃₂H₂₇N₃O₅ (533.58): C, 72.03; H, 5.10; N, 7.88%. Found: C, 72.09; H, 5.14; N, 7.96%.

4.1.2.16. *N*-(3-Methoxyphenyl)-2-(4-((1-(4-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**7f**).

Yield: 74%; m.p. 196-197 °C; IR (KBr, cm⁻¹): 3438 (NH), 3062 (aromatic CH), 2938 (CH aliphatic), 1720, 1654 (C=O); ¹H NMR: δ 3.82 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 4.67 (s, 2H, CH₂), 6.09 (s, ex, 1H, NH), 6.59 (d, 1H, aromatic H, *J* = 7.76 Hz), 6.75-6.78 (m, 3H, aromatic H), 6.94 (d, 2H, aromatic H, *J* = 8.48 Hz), 7.08 (d, 2H, aromatic H, *J* = 7.68 Hz), 7.25 (s, 1H, aromatic H), 7.28 (s, 1H, CH), 7.31-7.42 (m, 4H, aromatic H), 7.58 (d, 2H, aromatic H, *J* = 7.16 Hz), 8.31 (d, 2H, aromatic H, *J* = 8.76 Hz); ¹³C NMR: δ 55.3, 55.5, 67.4, 105.9, 110.8, 112.3, 114.7, 115.9, 127.3, 128.2, 128.5, 128.6, 128.8, 129.1, 129.2, 130.2, 131.0, 134.7, 135.9, 137.8, 145.8, 158.5, 159.4, 160.2, 165.6, 170.9. Anal. Calcd. For C₃₂H₂₇N₃O₅ (533.58): C, 72.03; H, 5.10; N, 7.88%. Found: C, 72.11; H, 5.12; N, 7.99%.

4.1.2.17. *N*-(4-Methoxyphenyl)-2-(4-((1-(4-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**7g**).

Yield: 80%; m.p. 239-240 °C; IR (KBr, cm⁻¹): 3332 (NH), 3064 (aromatic CH), 2933 (CH aliphatic), 1712, 1699 (C=O); ¹H NMR: δ 3.84 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 4.70 (s, 2H, CH₂), 6.91 (d, 2H, aromatic H, *J* = 9.08 Hz), 6.95 (d, 2H, aromatic H, *J* = 8.48 Hz), 7.09 (d, 2H, aromatic H, *J* = 8.89 Hz), 7.17 (d, 2H, aromatic H, *J* = 8.84 Hz), 7.28 (s, 1H, aromatic H), 7.31-7.37 (m, 3H, aromatic H), 7.50 (d, 2H, aromatic H, *J* = 8.96 Hz), 7.61 (d, 2H, aromatic H, *J* = 7.60 Hz), 8.15 (s, ex, 1H, NH), 8.34 (d, 2H, aromatic H, *J* = 8.72 Hz); ¹³C NMR: δ 55.5, 55.6, 67.4, 114.2, 114.7, 115.1, 122.1, 125.4, 127.3, 127.7, 128.2, 128.3, 128.6, 129.0, 129.2, 130.0, 131.3, 134.7, 134.8, 137.6, 149.2, 158.5, 159.4, 160.2, 165.6, 170.8. Anal. Calcd. For C₃₂H₂₇N₃O₅ (533.58): C, 72.03; H, 5.10; N, 7.88%. Found: C, 72.14; H, 5.15; N, 7.94%.

4.1.2.18. *N*-(2-Chlorophenyl)-2-(4-((1-(4-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**7h**).

Yield: 94%; m.p. 225-227 °C; IR (KBr, cm⁻¹): 3383 (NH), 3053 (aromatic CH), 2928 (CH aliphatic), 1714, 1710 (C=O), 833 (C-Cl); ¹H NMR: δ 3.85 (s, 3H, OCH₃), 4.74 (s, 2H, CH₂), 6.95 (d, 2H, aromatic H, *J* = 8.84 Hz), 7.09-7.13 (m, 5H, aromatic H), 7.28 (s, 1H, CH), 7.30 (t, 1H, aromatic H, *J* = 7.80 Hz), 7.37-7.45 (m, 4H, aromatic H), 7.61 (d, 2H, aromatic H, *J* = 7.40 Hz), 8.34 (d, 2H, aromatic H, *J* = 8.68 Hz), 8.47 (d, 1H, aromatic H, *J* = 8.20 Hz), 9.01 (s, ex, 1H, NH); ¹³C NMR: δ 55.5, 67.4, 114.7, 115.1, 117.3, 121.3, 125.2, 127.8, 128.2, 128.3, 128.5, 128.9, 129.1, 129.2, 131.0, 131.2, 133.7, 134.5, 134.7, 137.6, 158.3, 159.3, 160.1,

165.7, 170.8. Anal. Calcd. For $C_{31}H_{24}ClN_3O_4$ (538.00): C, 69.21; H, 4.50; N, 7.81%. Found: C, 69.29; H, 4.51; N, 7.89%.

4.1.2.19. *N*-(3-Chlorophenyl)-2-(4-((1-(4-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**7i**).

Yield: 93%; m.p. 267-269 °C; IR (KBr, cm^{-1}): 3375 (NH), 3055 (aromatic CH), 2925 (CH aliphatic), 1708, 1681 (C=O), 832 (C-Cl); 1H NMR: δ 3.86 (s, 3H, OCH₃), 4.71 (s, 2H, CH₂), 6.95 (d, 2H, aromatic H, J = 8.72 Hz), 7.08-7.09 (m, 4H, aromatic H), 7.16 (d, 1H, aromatic H, J = 7.96 Hz), 7.28 (s, 1H, CH), 7.31-7.38 (m, 3H, aromatic H), 7.44-7.48 (m, 2H, aromatic H), 7.61 (d, 2H, aromatic H, J = 7.48 Hz), 7.75 (s, 1H, aromatic H), 8.26 (s, ex, 1H, NH) 8.34 (d, 2H, aromatic H, J = 8.72 Hz); ^{13}C NMR: δ 55.5, 67.4, 114.7, 115.1, 118.1, 120.2, 125.1, 128.1, 128.3, 128.5, 129.2, 130.1, 131.3, 134.7, 134.8, 137.7, 137.8, 158.3, 159.4, 160.1, 165.7, 170.8. Anal. Calcd. For $C_{31}H_{24}ClN_3O_4$ (538.00): C, 69.21; H, 4.50; N, 7.81%. Found: C, 69.31; H, 4.50; N, 7.92%.

4.1.2.20. *N*-(4-Chlorophenyl)-2-(4-((1-(4-methoxyphenyl)-5-oxo-2-phenyl-1,5-dihydro-4H-imidazol-4-ylidene)methyl)phenoxy)acetamide (**7j**).

Yield: 91%; m.p. 276-278 °C; IR (KBr, cm^{-1}): 3354 (NH), 3054 (aromatic CH), 2926 (CH aliphatic), 1714, 1699 (C=O), 831 (C-Cl); 1H NMR: δ 3.86 (s, 3H, OCH₃), 4.70 (s, 2H, CH₂), 6.95 (d, 2H, aromatic H, J = 8.84 Hz), 7.08-7.13 (m, 4H, aromatic H), 7.28 (s, 1H, CH), 7.30-7.37 (m, 4H, aromatic H), 7.44 (t, 1H, aromatic H, J = 7.40 Hz), 7.57 (d, 2H, aromatic H, J = 8.72 Hz), 7.61 (d, 2H, aromatic H, J = 7.48 Hz), 8.24 (s, ex, 1H, NH) 8.32 (d, 2H, aromatic H, J = 8.72 Hz); ^{13}C NMR: δ 55.5, 67.4, 114.7, 115.1, 121.4, 127.3, 128.1, 128.3, 128.5, 128.9, 129.1, 129.2, 130.0, 131.3, 134.7, 135.2, 137.7, 158.3, 159.4, 160.3, 165.7, 170.8. Anal. Calcd. For $C_{31}H_{24}ClN_3O_4$ (538.00): C, 69.21; H, 4.50; N, 7.81%. Found: C, 69.34; H, 4.52; N, 7.94%.

4.2. Anticancer activity screening:

4.2.1. In vitro kinase inhibition:

All kinase reactions were performed using LanthaScreen Kinase activity assay kits (Invitrogen), following the manufacturer's instructions. In summary, kinase reactions were performed in a 10 μ L volume in low-volume 384-well plates. Typically, Corning model 3676 (black) or 3673 (white) plates were used. The concentration of substrate [GFP-ATF2] in the assay was 400 nM, and the kinase reaction buffer consisted of 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl₂, and 1 mM EGTA, plus any additional additives that might be required

for a specific kinase. Kinase reactions were allowed to proceed for 1 hour at room temperature with substrate and ATP in the presence or absence of inhibitor before a 10 μ L preparation of EDTA (20 mM) and Tb-labeled antibody [Tb-pAT F2(pThr71), 4 nM] in TR-FRET dilution buffer were added. The final concentration of the antibody in the assay well was 2 nM, and the final concentration of EDTA was 10 mM. The plate was allowed to incubate at room temperature for at least 30 minutes. The data were generated using a BMG Pherastar plate reader using the LanthaScreen™ filter block available from BMG. Inhibition studies were performed against a dilution series of tested compounds and IC₅₀ values determined from the resulting inhibition curves.

4.2.2. MTT assay for antiproliferative activity:

The cancer cell lines and Vero cells were trypsinized and washed with Ca²⁺/Mg²⁺-free PBS (pH 7.2). Cells were adjusted to 4×10⁴ cells/ml with DMEM supplemented with 10% fetal calf serum (Hyclone, Logan, UT, USA) and plated (50 μ L/well) in 96-well cell culture plate (Corning, Corning, NY, USA) overnight at 37°C with 5% CO₂ and 95% humidity. Fifty microliters of serial 10-fold diluted sterile tested compounds were added to final concentrations of 0-100 μ M. Culture medium was used as negative control. Cultures were incubated for 72 h. Supernatants were discarded, 20 μ L/well of methylthiazolyldiphenyl-tetrazolium bromide (MTT) reagent (Promega, Madison, WI, USA) was added and incubated for 4 h at 37°C with 5% CO₂. Sterile sodium dodecyl sulfate (10% v/v in PBS) was added (25 μ L/well) and the plate was kept at room temperature for 18 h before measuring optical density (OD) at 490 nm. DMEM was used as a blank control. Results from three separate experiments were recorded and the percentage of viable cells was calculated as [(O.D. of cell control–O.D. of treated cells)/(O.D. of cell control–O.D. of initiated cells)] ×100.

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Figure captions:

Figure 1. Structure of some reported inhibitors of p38 α MAPK * and ERK1/2**.

Figure 2. Design of the target compounds **6** and **7**.

Scheme1. Synthesis of the target compounds **6** and **7**.

Table captions:

Table 1. IC₅₀ values (nM) of tested compounds **6a-j** and **7a-j** against p38 α MAPK and ERK1/2.

Table 2. Antiproliferative activity of compounds **6d** and **7h** against different cancer cell lines and normal Vero cells.

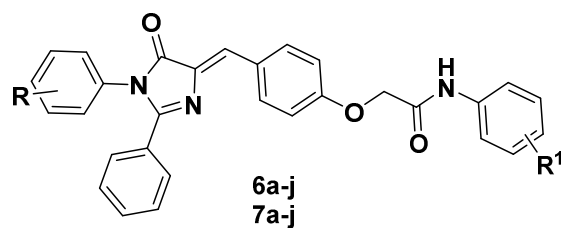


Table 1.

Compound	R	R ¹	IC ₅₀ (nM) ± SEM*		
			P38αMAPK	ERK1	ERK2
6a	3-OCH ₃	H	35.0±2.1	65.0±5.9	54.0±4.3
6b	3-OCH ₃	2-CH ₃	66.0±3.8	43.0±3.2	44.0±3.6
6c	3-OCH ₃	3-CH ₃	87.0±5.2	20.0±1.7	43.0±2.7
6d	3-OCH ₃	4-CH ₃	4.5±0.3	25.0±1.9	3.2±0.32
6e	3-OCH ₃	2-OCH ₃	54.0±3.7	46.0±2.8	4.7±0.45
6f	3-OCH ₃	3-OCH ₃	6.5±0.5	57.0±4.7	5.4±0.27
6g	3-OCH ₃	4-OCH ₃	4.3±0.3	76.0±7.3	4.3±0.34
6h	3-OCH ₃	2-Cl	5.6±0.3	87.0±6.2	5.3±0.41
6i	3-OCH ₃	3-Cl	3.7±0.3	89.0±7.4	3.4±0.30
6j	3-OCH ₃	4-Cl	4.6±0.3	95.0±8.9	4.6±0.3
7a	4-OCH ₃	H	354.0±20.6	23.0±2.4	23.0±2.1
7b	4-OCH ₃	2-CH ₃	56.0±4.1	32.0±2.5	23.0±1.7
7c	4-OCH ₃	3-CH ₃	77.0±5.7	89.0±5.2	78.0±6.3
7d	4-OCH ₃	4-CH ₃	345.0±29.5	23.0±1.6	43.0±3.3
7e	4-OCH ₃	2-OCH ₃	34.0±2.4	43.0±3.8	89.0±6.7
7f	4-OCH ₃	3-OCH ₃	23.0±1.6	21.0±1.2	21.0±1.2
7g	4-OCH ₃	4-OCH ₃	345.0±30.3	23.0±2.0	2.3±0.2
7h	4-OCH ₃	2-Cl	4.7±0.4	24.0±2.1	3.5±0.3
7i	4-OCH ₃	3-Cl	4.5±0.4	35.0±2.3	7.0±0.6
7j	4-OCH ₃	4-Cl	44.0±4.2	47.0±3.1	4.5±0.4
Sorafenib	-	-	37.4±3.5	18.1±1.6	109.5±9.8

*IC₅₀ values were calculated from the mean values of data from three separate experiments

Table 2.

Cancer Type	Cell Line	IC ₅₀ (μM) ± SEM*				
		6d	7h	Sorafenib	SI**(6d)	SI**(7h)
Breast	MCF7	0.37±0.02	0.53±0.05	0.78±0.05	46.86	24.90
	T47D	0.67±0.05	0.50±0.04	0.61±0.04	25.88	26.40
Colon	Colo-205	9.40±0.71	4.50±0.03	0.87±0.07	1.85	2.93
	HT29	5.80±0.05	4.50±0.04	0.39±0.03	2.98	2.93
Leukemia	K562	>100	>100	1.22±0.01	-	-
Lung	A549	6.50±0.05	4.90±0.04	3.19±0.03	2.66	2.69
Melanoma	LOX IMVI	0.76±0.06	0.13±0.01	4.25±0.03	22.81	101.54
	MDA-MB-435	0.23±0.02	0.05±0.003	1.67±0.01	75.39	264.00
Prostate	PC3	0.86±0.08	0.99±0.07	4.13±0.03	20.16	13.33
Vero cells	-	17.34±1.42	13.20±1.20	-	-	-

* IC₅₀ values were calculated from the mean values of data from three separate experiments.

**SI (selectivity index)= IC₅₀ of Vero cells / IC₅₀ of cancer cell. SI > 3 means that the compound is selective to cancer cell.

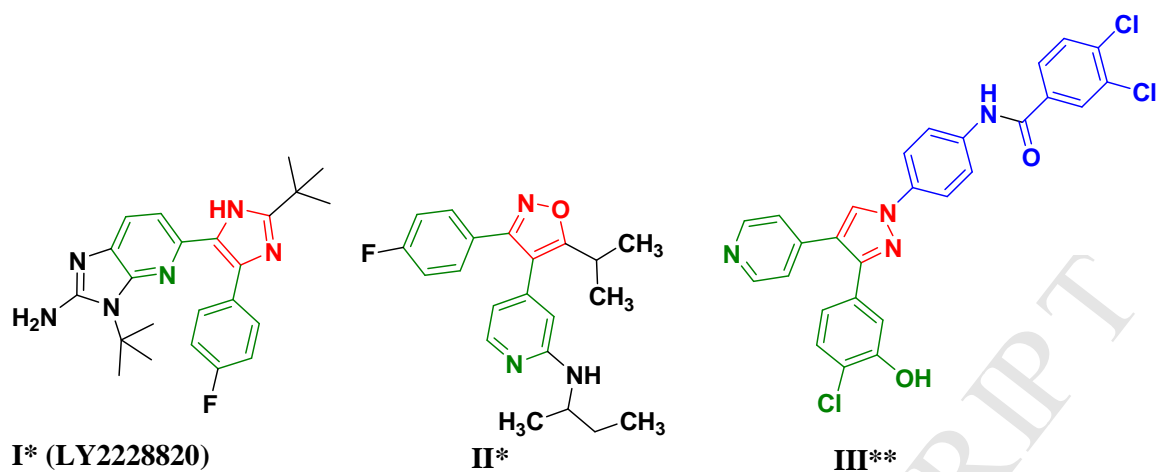


Figure 1.

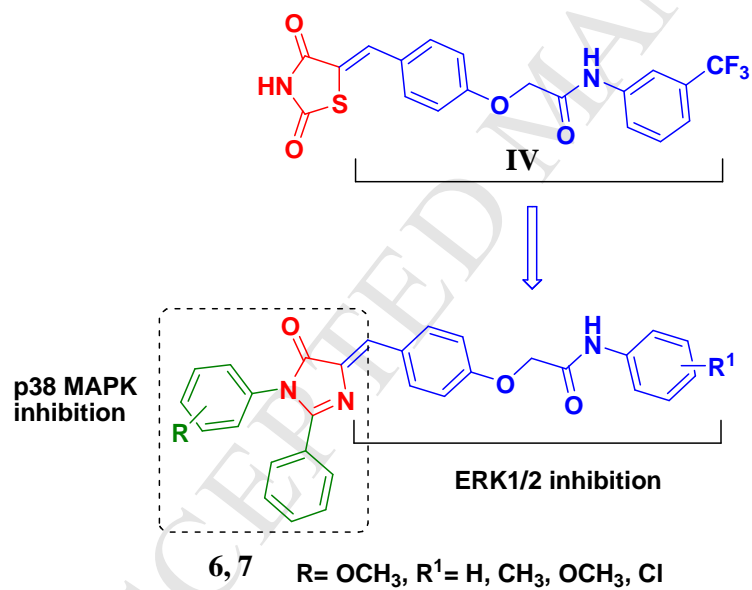
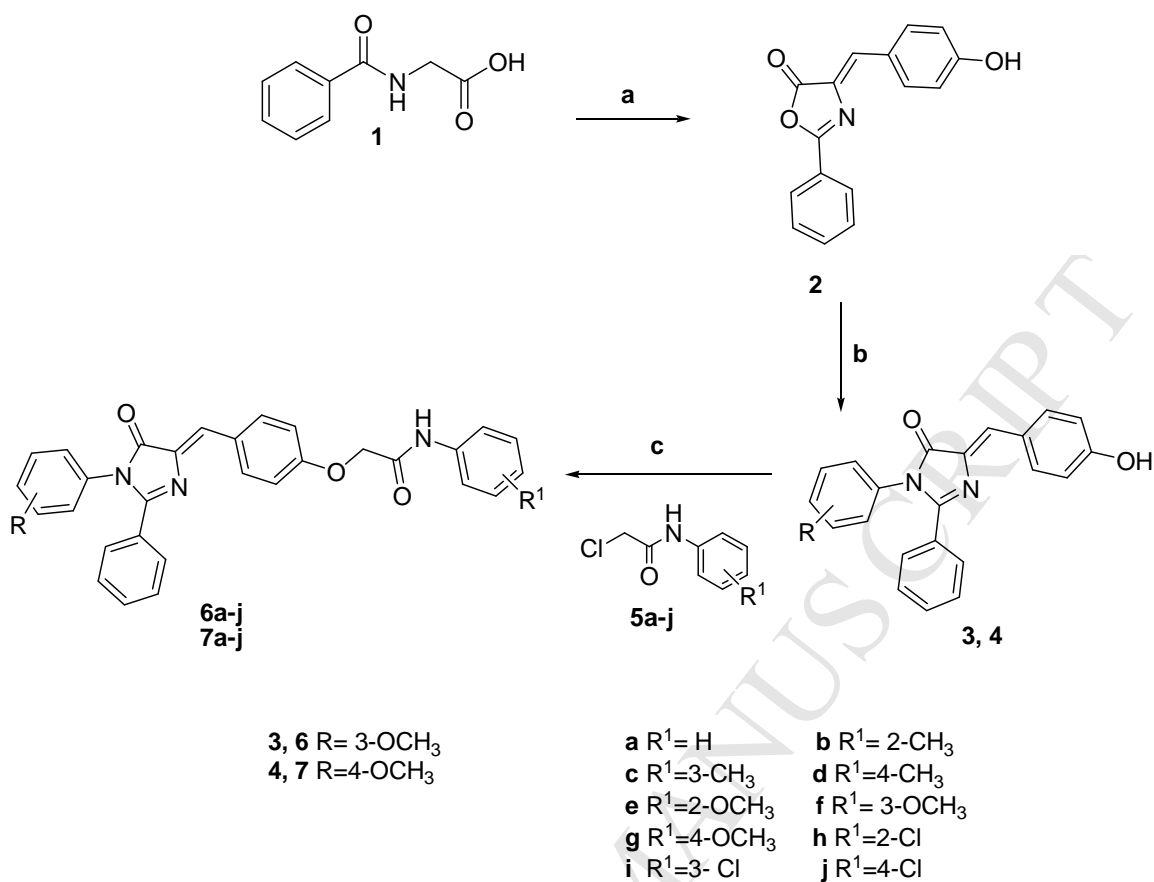


Figure 2.



Scheme1.

Reagents and reaction conditions: **a:** 4-hydroxybenzaldehyde, acetic anhydride, anh. CH₃COONa; **b:** 3/4-methoxyaniline, acetic acid, CH₃COONa; **c:** 2-chloro-*N*-un/substituted phenylacetamide **5a-j**, DMF, K₂CO₃.

Highlights:

- A series of 1,2,4-trisubstituted-imidazolinones was synthesized.
- The new compounds proved active against p38 α MAPK and ERK1/2.
- IC₅₀ of **6d** and **7h** on MDA-MB-435 is 0.23 and 0.05 μ M, respectively.
- IC₅₀ of **6d** against p38 α MAPK and ERK2 = 4.5 and 3.2 nM, respectively.
- Compound **7h** has IC₅₀ against p38 α MAPK and ERK2 = 4.7 and 3.5 nM, respectively.

Compound 6a

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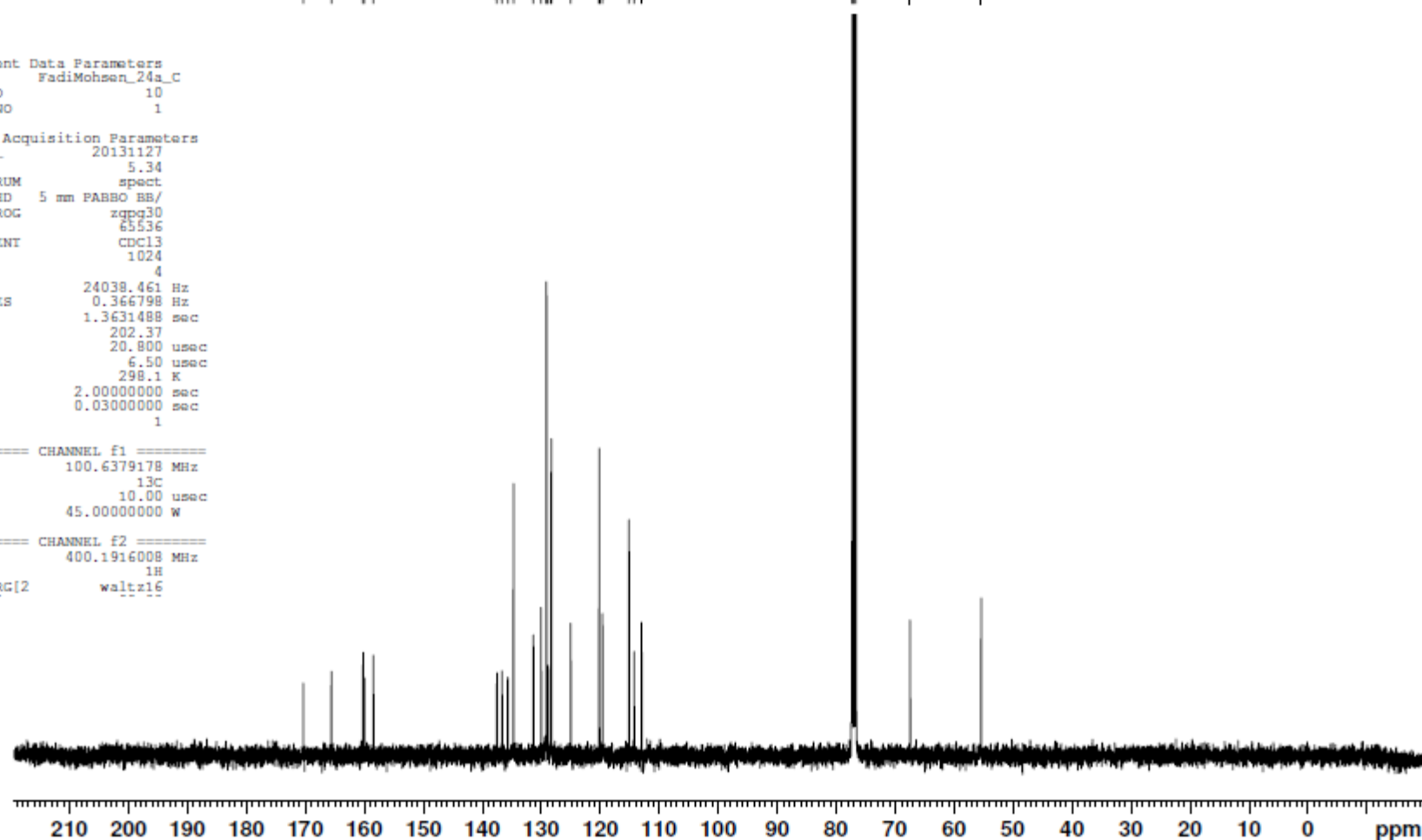
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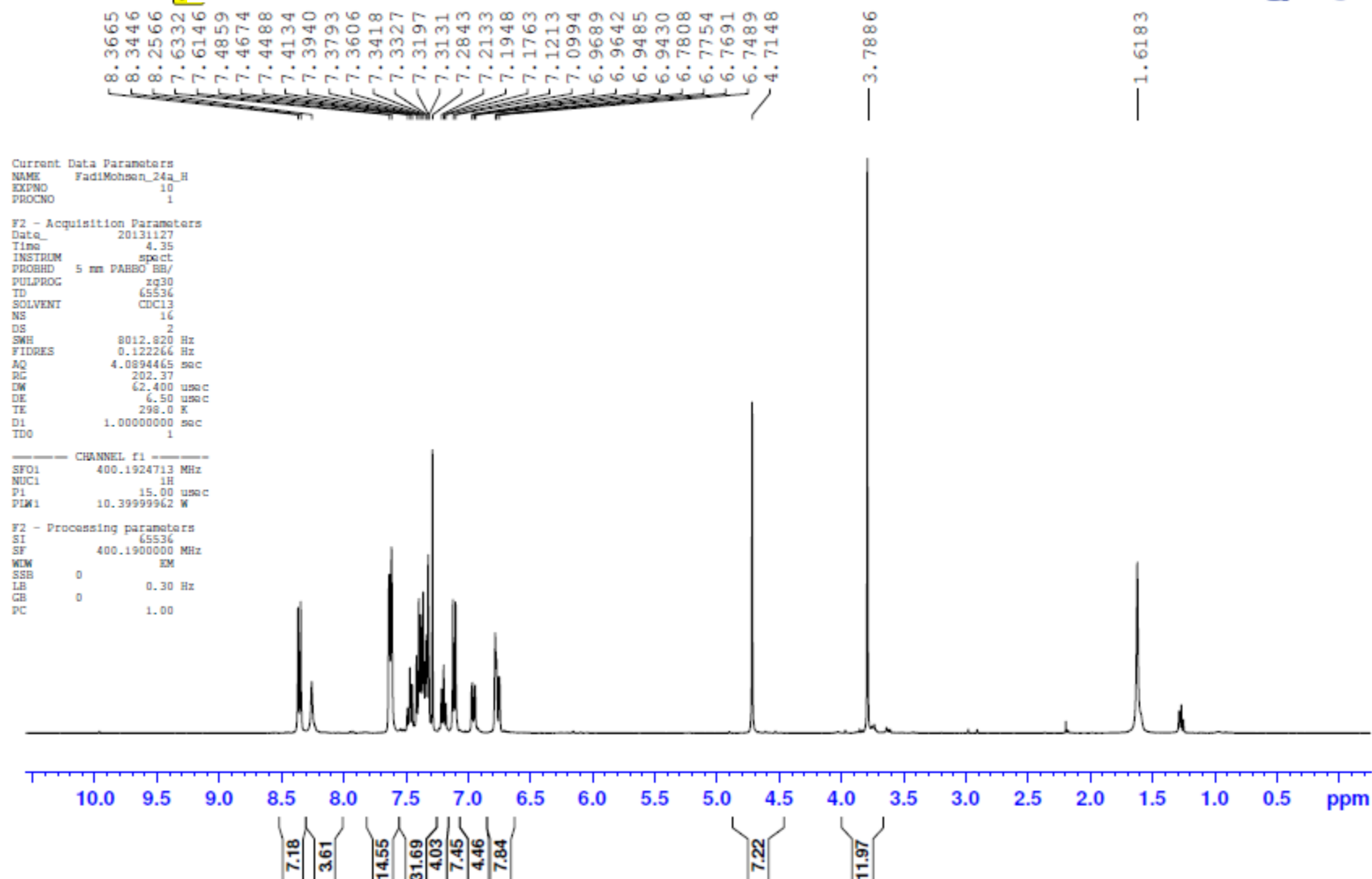
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FadiMohsen

Compound 6a

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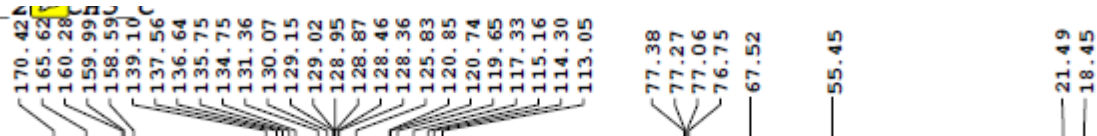


Compound 6b

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Sahar Abo Serei_240CH3_

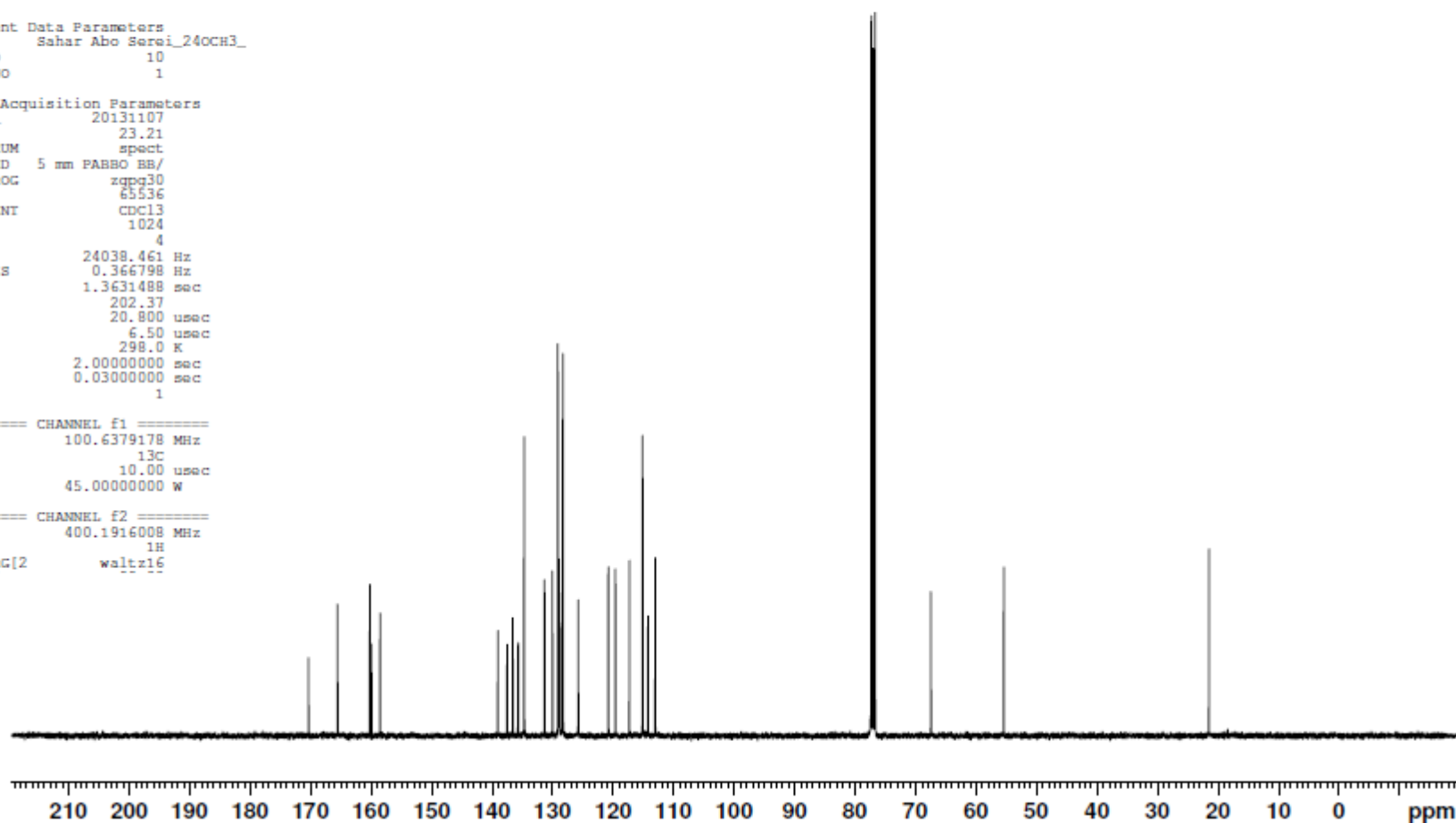


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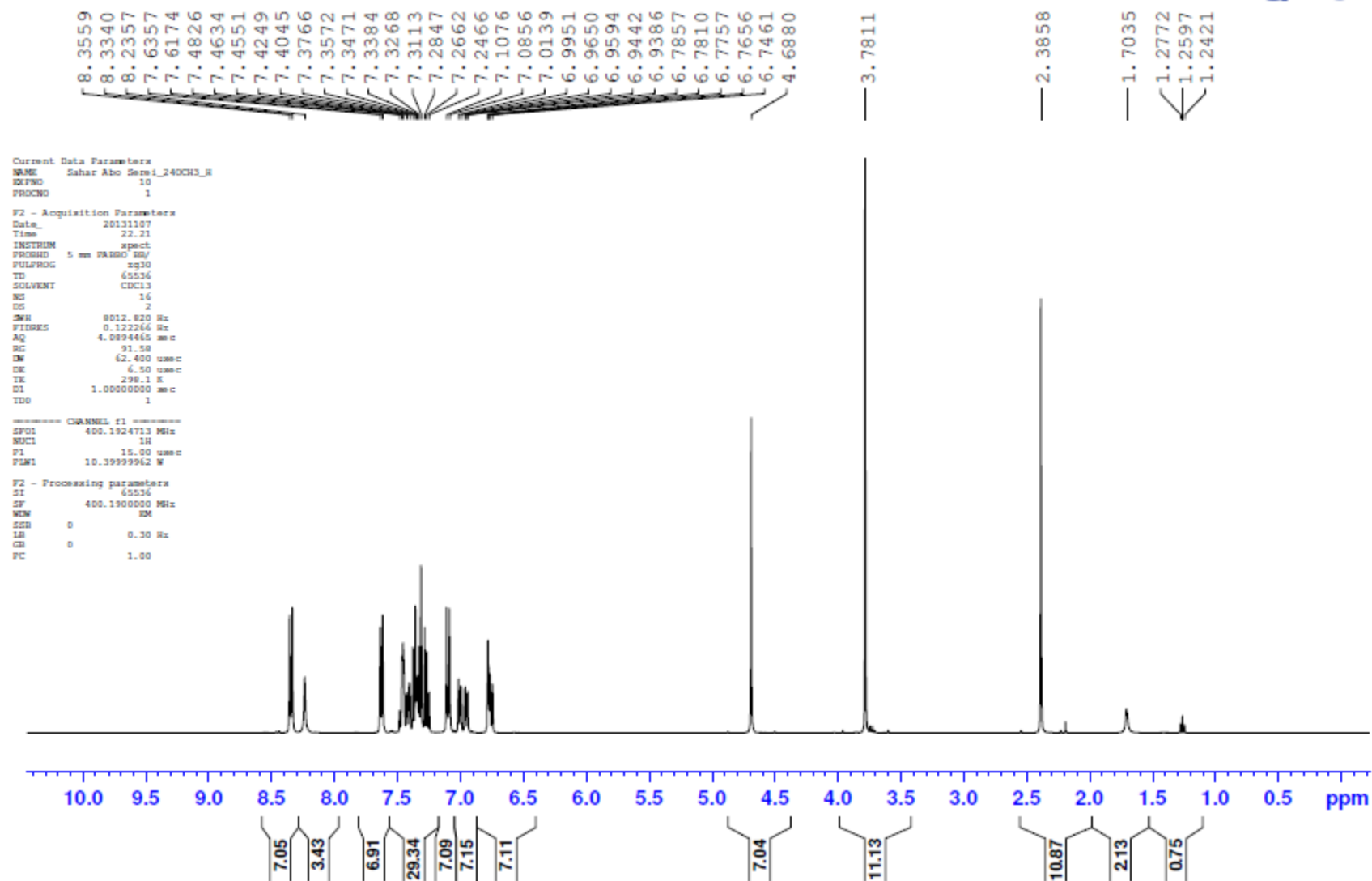
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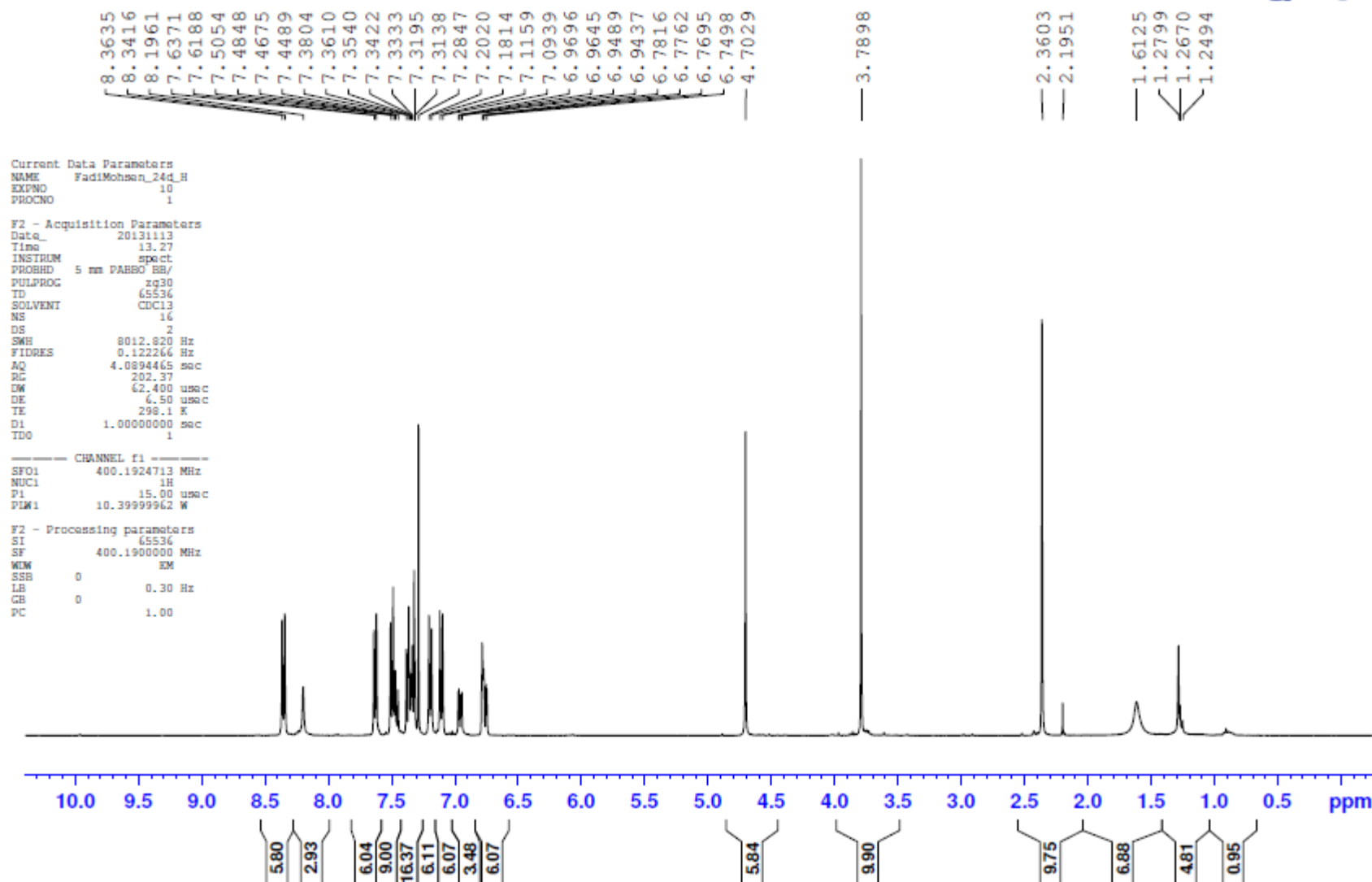
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Compound 6d

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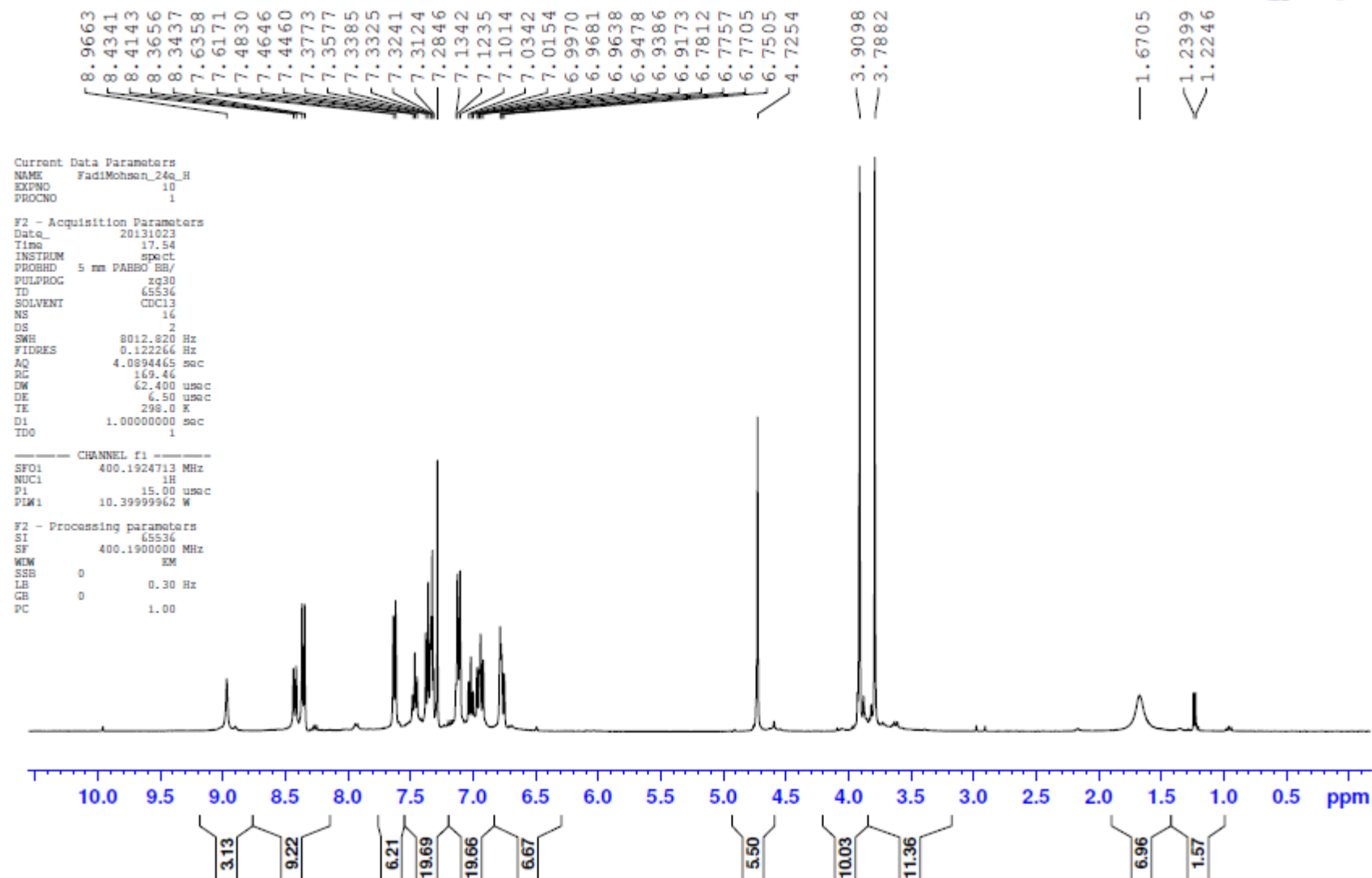
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Compound 6e

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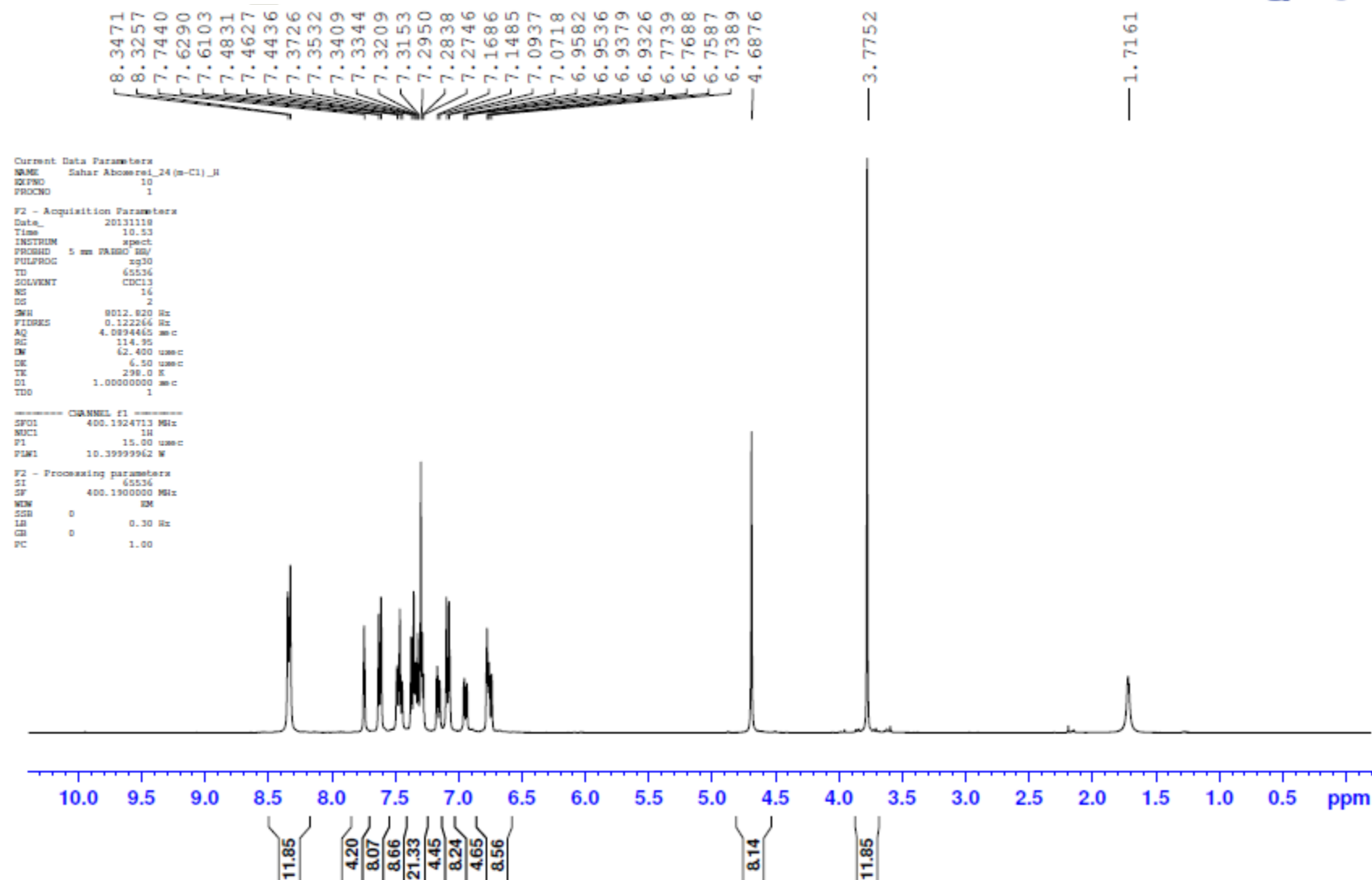
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Sahar Aboseran

Compound 6i

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Compound 7a

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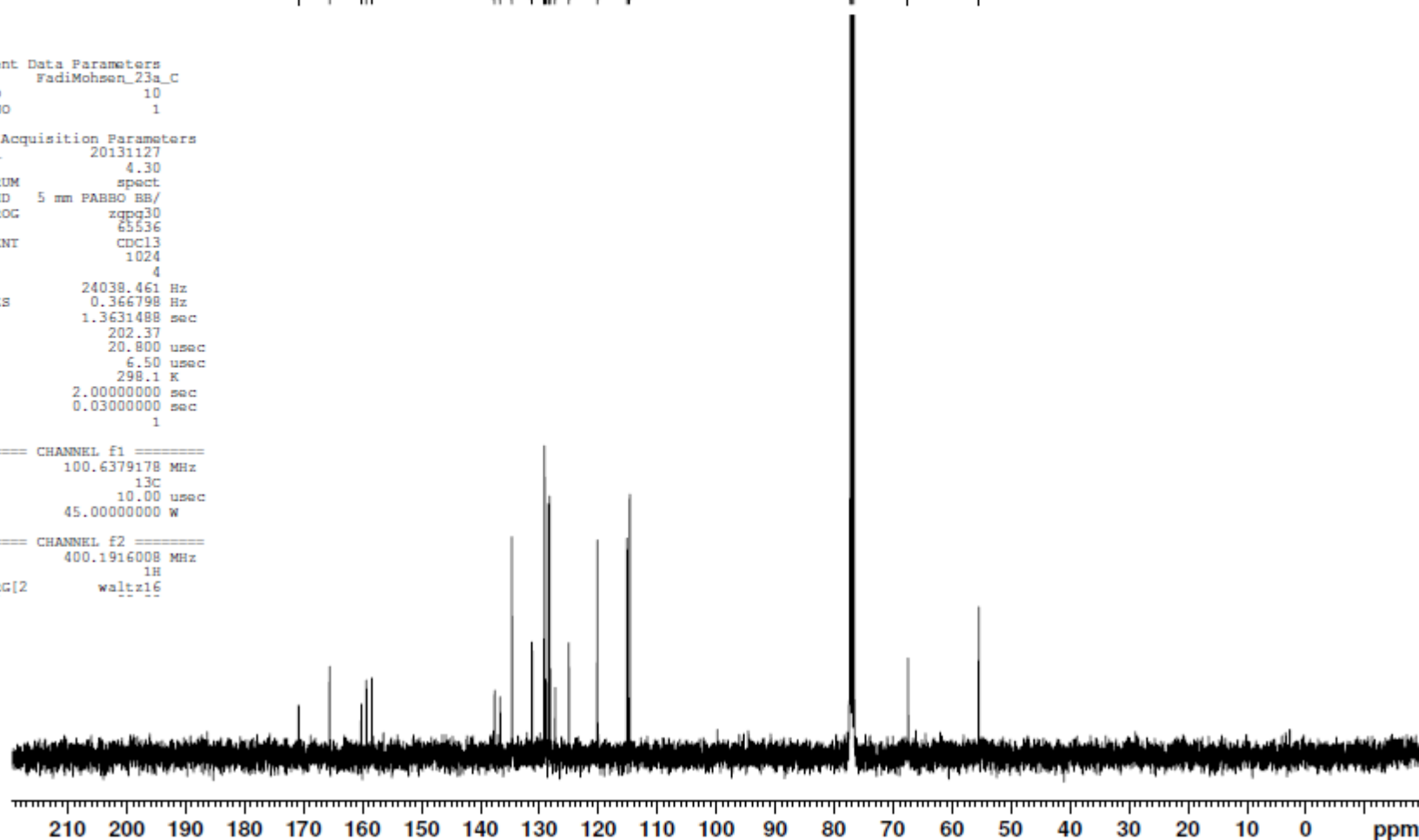
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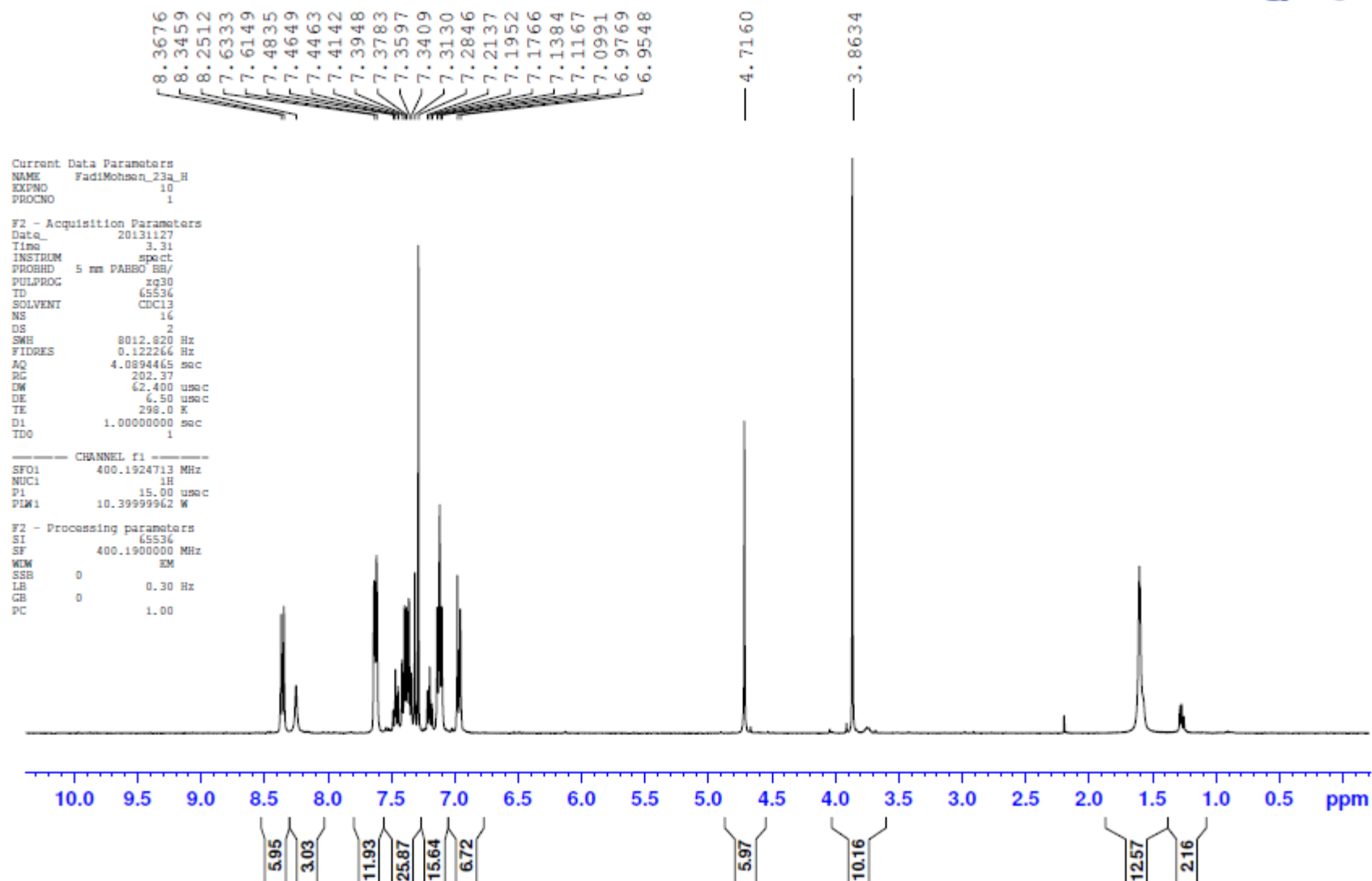


Compound 7a

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FadiMohsen

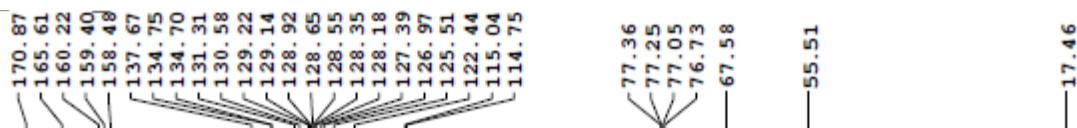


Compound 7b

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SaharAboseri

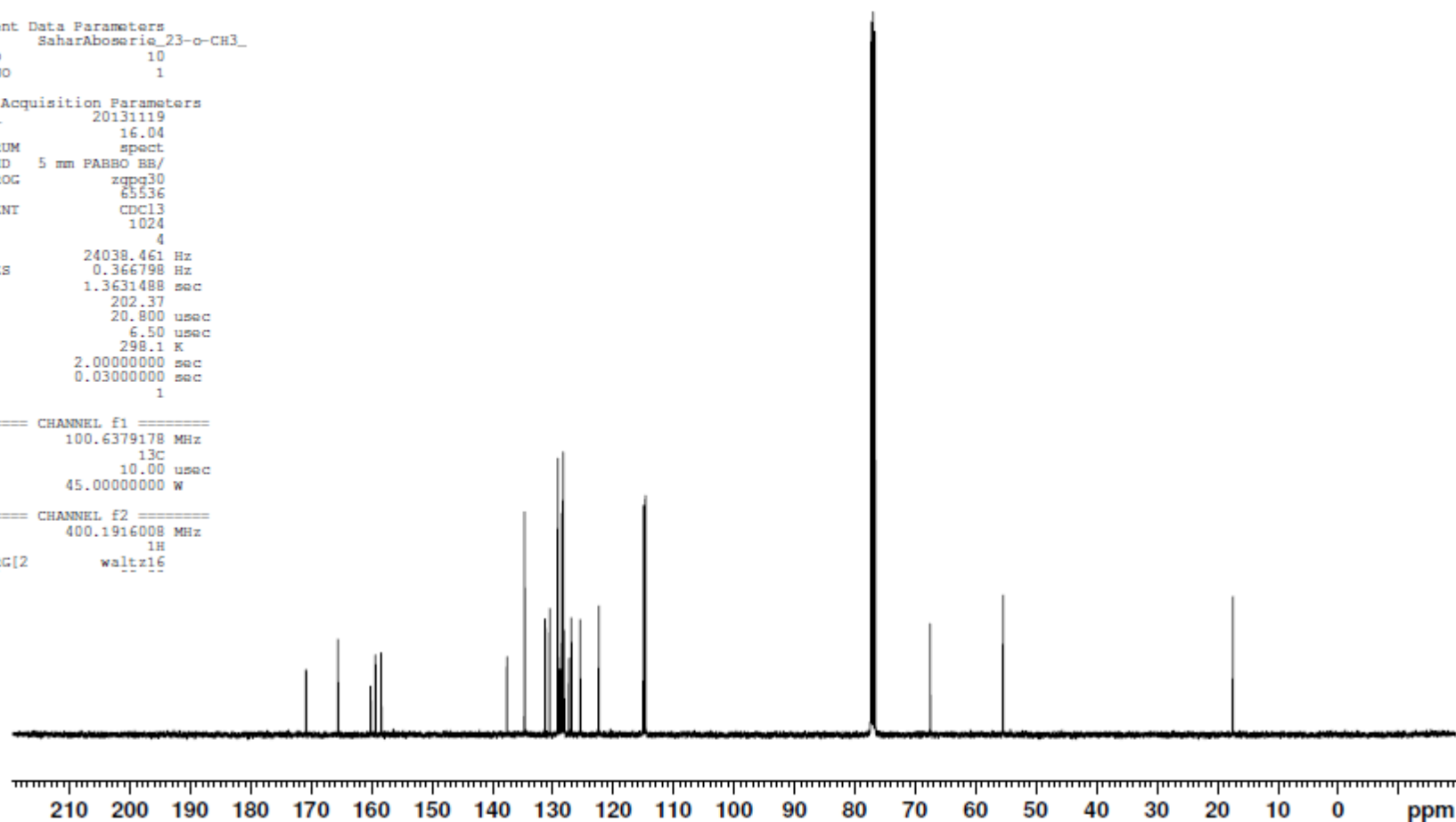


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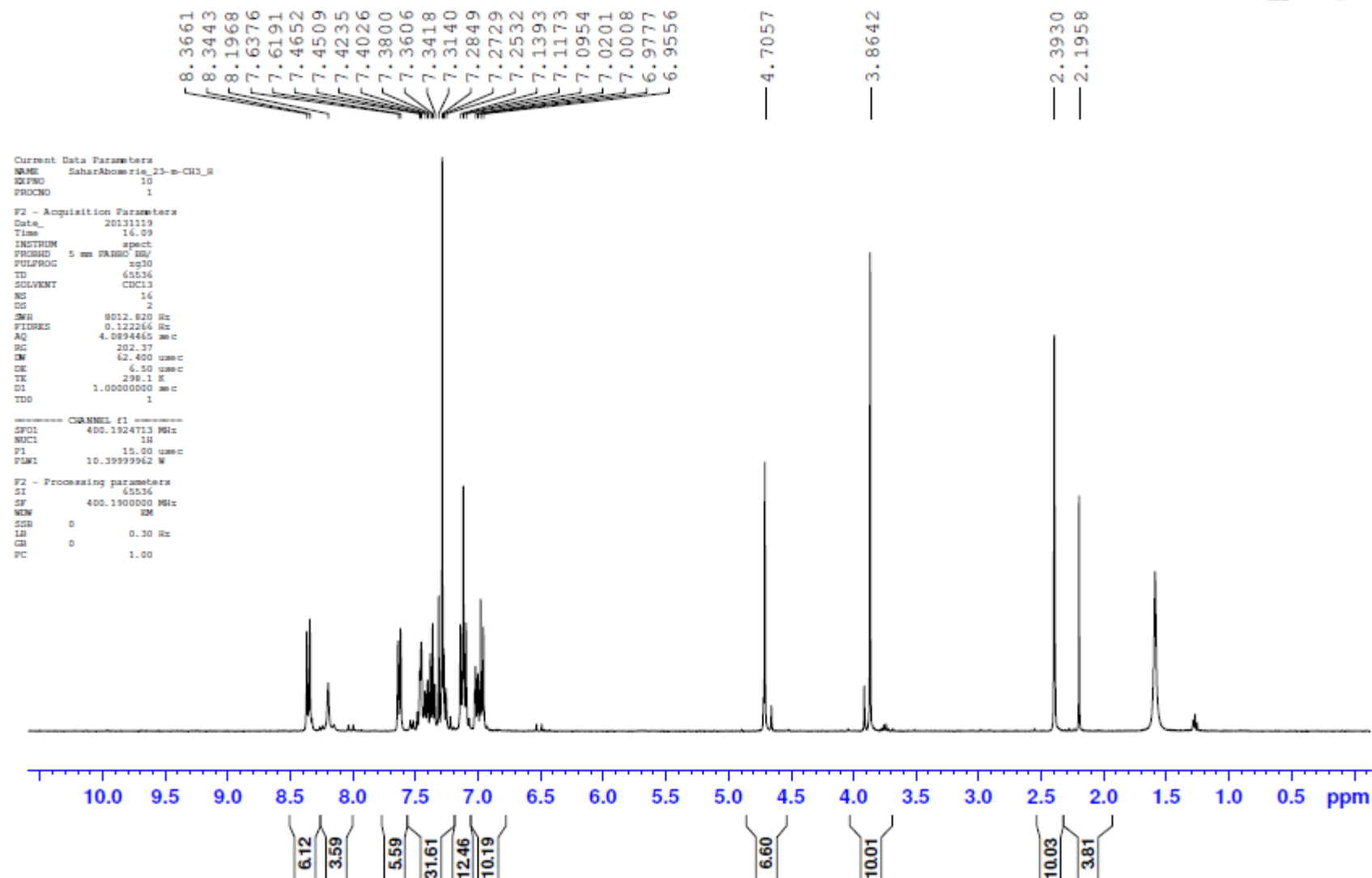
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SaharAboserie

Compound 7c

Microanalytical Unit - FOPCU - NMR laboratory
 www.pharma.cu.edu.eg dir-mau.fopcu@pharma.cu.edu.eg



Compound 7e

Microanalytical Unit - FOPCU - NMR laboratory
www.pharma.cu.edu.eg dir-mau.fopcu@pharma.cu.edu.eg

Fadi Mohsen



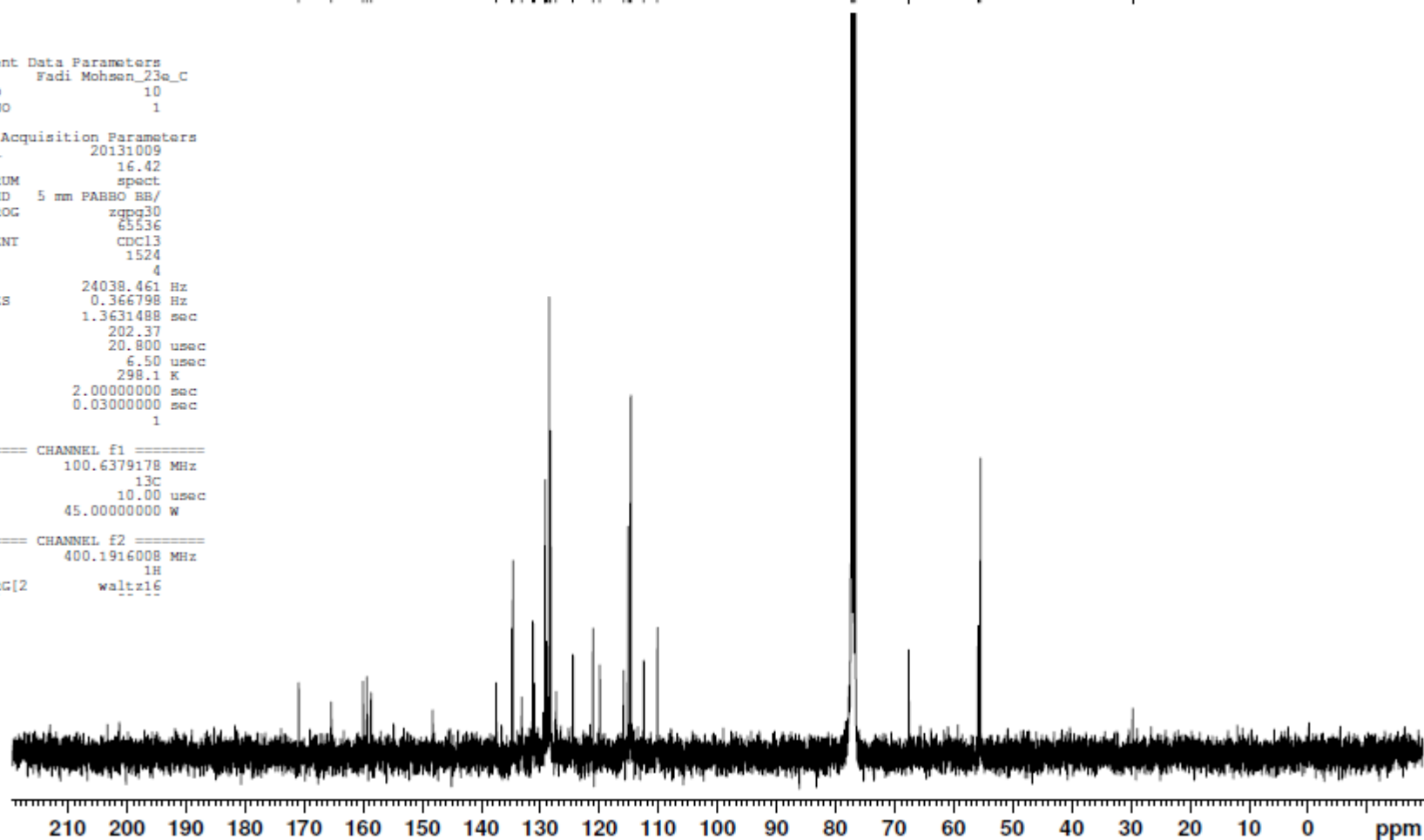
170.95
165.46
160.09
159.40
158.74
137.53
134.88
134.70
133.22
131.28
131.06
129.25
129.21
129.16
128.93
128.56
128.49
128.35
127.39
124.50
121.13
119.95
115.94
115.19
114.76
114.71
112.49
110.19
77.34
77.23
77.03
76.71
67.65
55.90
55.79
55.51
29.71

Current Data Parameters
NAME Fadi Mohsen_23e_C
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20131009
Time 16.42
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1524
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 202.37
DW 20.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

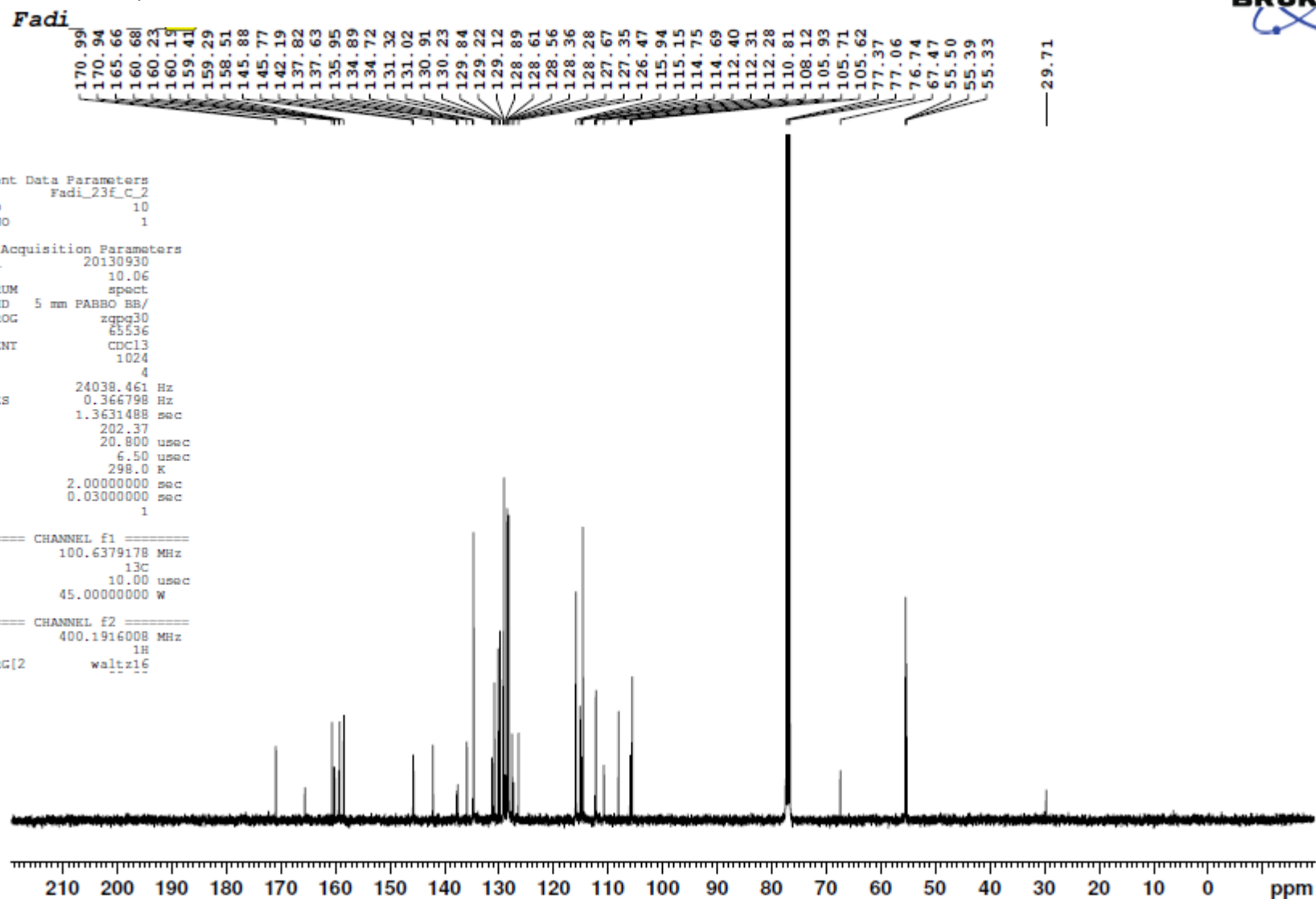
===== CHANNEL f1 =====
SFO1 100.6379178 MHz
NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

===== CHANNEL f2 =====
SFO2 400.1916008 MHz
NUC2 1H
CPDPRG[2] waltz16



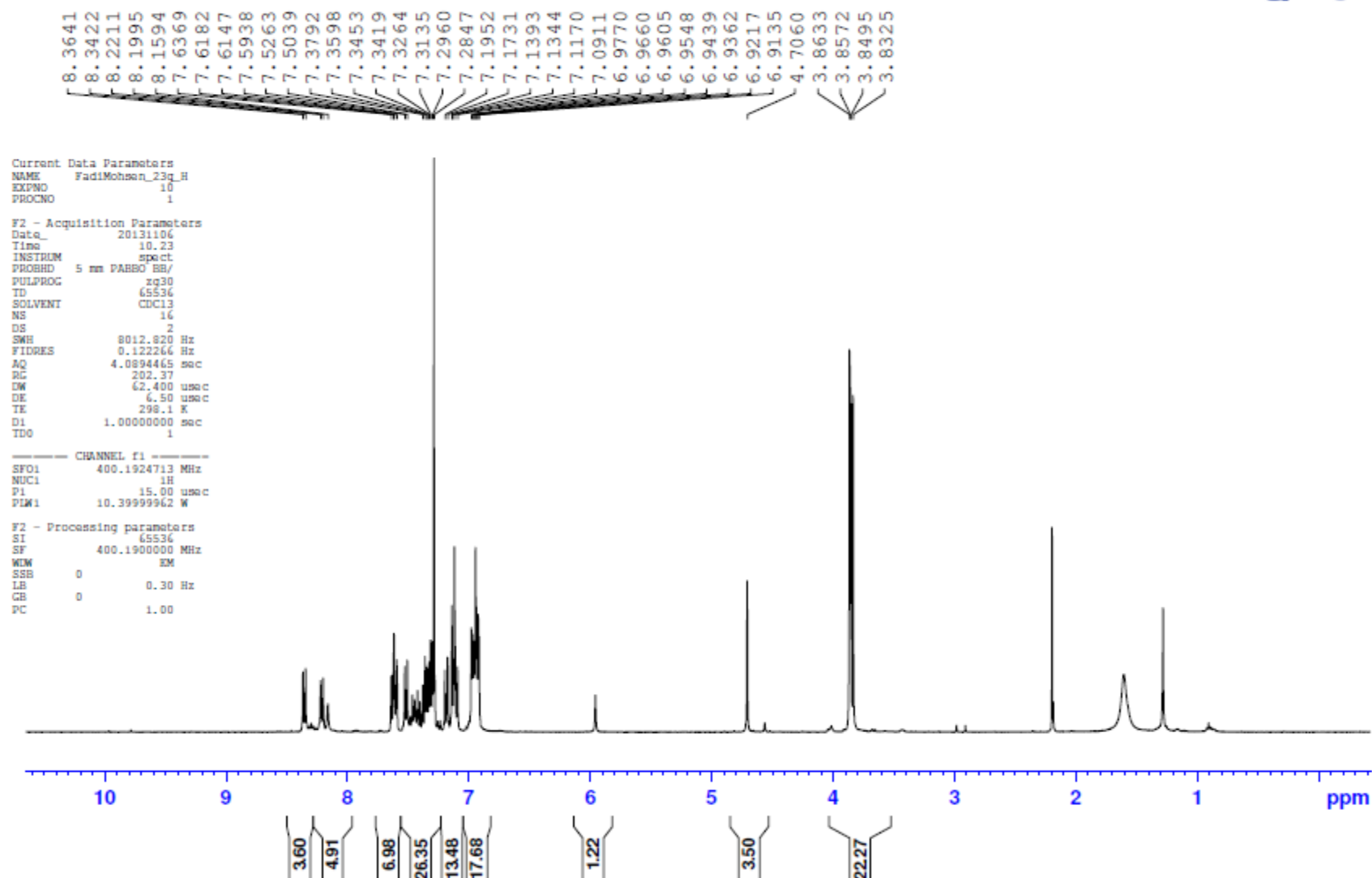
Compound 7f

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FadiMohsen

Compound 7g

Microanalytical Unit - FOPCU - NMR laboratory
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Compound 7h

Microanalytical Unit - FOPCU - NMR laboratory
 www.pharma.cu.edu.eg dir-mau.fopcu@pharma.cu.edu.eg



Sahar Abo Seri

