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Graphic Abstract

Synthesis and anticancer activities of 3-arylflavone-8-acetic acid derivatives

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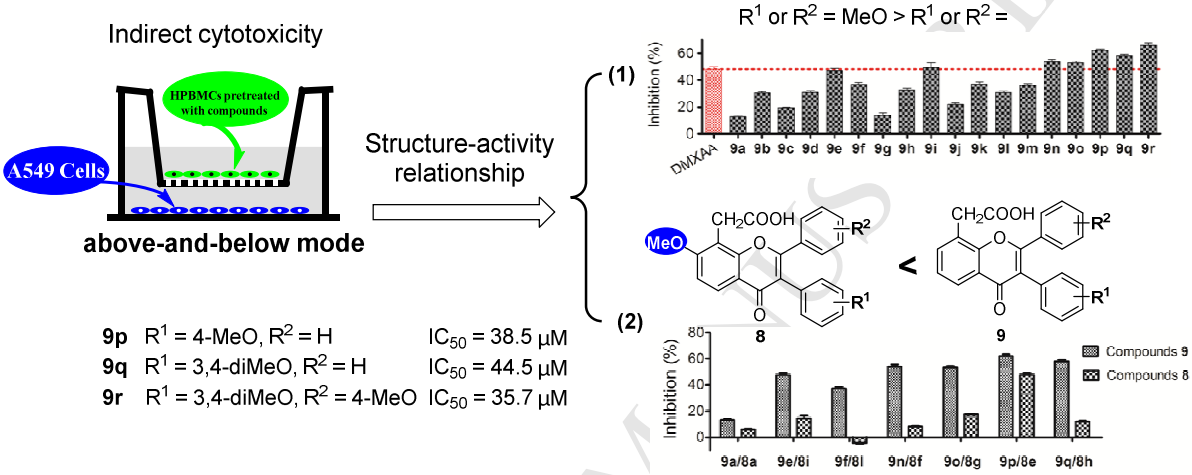

This paper describes the synthesis and antiproliferative activities of eighteen 3-arylflavone-8-acetic acid derivatives **9a**-**r**. Among them, compounds **9p**-**r** bearing methoxy groups showed higher indirect cytotoxicity than DMXAA and could induce TNF-α production in HPBMCs. In addition, the position of a methoxy group on the 3-arylflavone-8-acetic acid was found to have a profound impact on the indirect cytotoxicity.

Synthesis and anticancer activities of 3-arylflavone-8-acetic acid derivatives

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Abstract This paper describes the synthesis and the antiproliferative activities of compounds **9a-r**, 3-aryl analogues of flavone-8-acetic acid that bear diverse subsitiuents on the benzene rings at the 2- and 3-positions of the flavone nucleus. Their direct and indirect cytotoxicities were evaluated against HT-29 human colon adenocarcinoma cell lines, A549 lung adenocarcinoma cell lines and Human Peripheral Blood Mononuclear Cells (HPBMCs). The results indicate that most of the compounds bearing electron-withdrawing substituents (**9b-m**) exhibited moderate direct cytotoxicities. And compounds **9e** and **9i** showed comparable indirect cytotoxicities with 5, 6-dimethylxanthenone-4-acetic acid (DMXAA), and low direct cytotoxicities toward HPBMCs. Interestingly, the compounds **9n-r** bearing methoxy groups at the 2- or 3-position of the flavone nucleus exhibited higher indirect cytotoxicities against A549 cell lines than DMXAA, and lower cytotoxicities against HPBMCs. In addition, compounds **9p-r** were found to be able to induce tumor necrosis factor α (TNF-α) production in HPBMCs.

Key words: 3-Arylflavone-8-acetic acid; Direct cytotoxicity; Indirect cytotoxicity; tumor necrosis factor α;

1. Introduction

Though there has been great advance in the multimodal management of a wide spectrum of human cancers, they remain to be one of the major global killers. The discovery of new anti-cancer drugs represents one of the biggest challenges in modern medicinal chemistry. In

these aspects, nature has proved to be a rich source to provide a variety of molecules that can specifically target cancers [1]. For example, flavonoids, a class of polyphenolic compounds that are widely distributed in plants [2], have been recognized for their high potentials as anti-tumor agents. It has been reported that they function at several stages in cancer progression with distinct structure-activity relationships [3-5]. As a consequence, some flavonoids have been screened in clinical trials for the treatment of cancers [6-8]. For example, it has been reported that 5, 6-dimethylxanthenone-4-acetic acid (DMXAA, **1**, Figure 1), an analogue of flavone acetic acid (FAA, **2**) is a vascular disrupting agent which specifically targets immature and unstable vasculature of solid tumors, leading to thrombosis, hemorrhage and necrosis [9-11]. In addition, it has been shown that DMXAA **1** is safe and well-tolerated in humans [6, 7, 12].

(Please insert Figure 1 here)

On the other hand, substituents on the flavonoids bearing carboxylic groups have a profound impact on the antitumor activity. For example, methyl 6, 7-dimethylflavone-8-carboxylate **3** [13] and 3-nitroflavone-8-acetic acid **4** [14] exhibited extensive direct cytotoxicity against leukemia cell lines. Isoflavone-8-acetic acid **5** was found to have high activity against ovarian carcinoma cells [15]. Azidoxanthenone-4-acetic acid **6** showed 8-fold higher *in vivo* activity than DMXAA [16], but was more toxic to cultured endothelial cells than DMXAA and 10-fold less active in stimulating tumor necrosis factor α (TNF-α) production in cultured splenocytes than DMXAA. In addition, compound **7** bearing a methoxy group at the 3-position of flavone-8-acetic acid skeleton displayed 7-fold higher indirect cytotoxicity toword solid tumor cell lines than DMXAA [17].

In our recent study we have reported the synthesis and the antiprolificative activities of 7-methoxy-3-arylflavone-8-acetic acids **8a-m** (Figure 1) [18]. We have shown that compound **8e** (R^1 = 4-MeO, R^2 = H) exhibited comparable indirect cytotoxicity with DMXAA, but much lower direct cytotoxicity. In contrast, compound **8i** (R^1 = 4-F, R^2 = H) exhibited higher direct but lower indirect activity than DMXAA. With the aim to systematically study the impact of substituents on the antitumor activity, herein we describe the synthesis, direct and indirect

antiproliferative activities of 3-arylflavone-8-acetic acid derivatives **9a-r** (Scheme 1) that bear diverse subsitiuents on the benzene rings at the 2- and 3-positions of flavone nucleus, whereas no methoxy group at the 7-position. Their structure-activity relationships are also briefly discussed.

2. Results and discussion

2.1 Chemistry

The synthetic route for compounds **9a-r** is outlined in Scheme 1. 3-Methyl-2-hydroxy deoxybenzoins **10a-g** were prepared from the microwave-assisted alkali degradation of 3-aryl-4-hydroxycoumarins in water [19], starting from methyl 2-hydroxy-3-methylbenzoate and substituted phenylacetic acids. Then, esterification of compounds **10a-g** with aromatic acyl chlorides **11a-d** and subsequent heating in freshly distilled anhydrous glycerol at 260 °C gave the corresponding 8-methyl-3-arylflavones **13a-r**, which were then brominated, cyanated and hydrolyzed to give compounds **9a-r**. Their structures were confirmed on the basis of MS, NMR (^{1}H and ^{13}C) and elemental analysis data (see experimental section and supporting information).

(Please insert Scheme 1 here)

2.2 Pharmacology

2.2.1 Direct cytotoxicity

The direct antiproliferative activities of compounds **9a-r** were evaluated against HT-29 human colon adenocarcinoma cell lines, A549 human non-small-cell carcinoma cell lines and Human Peripheral Blood Mononuclear Cells (HPBMCs). The obtained IC_{50} values that represent the concentration of each compound resulting in 50% inhibition in cell growth, together with that of DMXAA as a positive control are listed in Table 1. It can be seen that most of the compounds bearing electron-withdrawing groups on the benzene rings exhibited moderate to good direct cytotoxicities toward HT-29 and A549 cells with DMXAA. Among them, compounds **9c**, **9f** and **9j** exhibited higher direct cytotoxicity toward HT-29 cells than

DMXAA, whereas compounds **9i**, **9k** and **9l** showed higher direct cytotoxicity toward A549 cells than DMXAA. In contrast, compounds **9n-r** bearing methoxy groups on the benzene rings at the 2- or 3-position of flavone nucleus exhibited lower direct cytotoxicities toward HT-29 and A549 cells than DMXAA. These results suggest that an electron-withdrawing group on the benzene rings at the 2- or 3-position of flavone nucleus may be favorable. It is worth noting that compounds **9e**, **9i** and **9n-r** displayed lower direct cytotoxicities toward HPBMCs than DMXAA.

(Please insert Table 1 here)

2.2.2 Indirect cytotoxicity

It is reported that the antitumor effects of both DMXAA and FAA are due to their indirect rather than direct cytotoxicities. In other words, they are deeply involved in the induction of apoptosis in tumor vascular endothelial cells [20] and the production of a spectrum of cytokines and chemokines, such as TNF-α [21], interferon-β [22], interferon-inducible protein [23] and inducible nitric oxide synthase (iNOS) [24]. Therefore, we evaluated the indirect cytotoxicities of compounds **9a-r** induced in the HPBMCs (in the top well) toward A549 cells (in the bottom wells) after co-cultured for 24 h in HTS Transwell®-96Well Permeable Support Systems [18]. The indirect cytotoxicities of compounds 9a-r at the concentration of 50 μM are shown in Figure 2. It clearly indicates that compounds **9a-r** could induce indirect cytotoxicities on the HPBMCs toward A549 cells. Among them, most of compounds bearing electron-withdrawing groups exhibited lower indirect cytotoxicities than DMXAA, whereas compounds **9e** and **9i** showed comparable indirect cytotoxicities with DMXAA. Intrestingly, compounds **9n-r** bearing methoxy groups showed higher indirect cytotoxicities than DMXAA.

(Please insert Figure 2 here)

Therefore to gain further insight into the pharmacological activities of compounds **9e**, **9i** and **9n-r**, their IC_{50} value toward A549 cells were measured (Table 2). Interestingly, the indirect cytotoxicities (IC_{50} = 35.7 ~ 92.6 μM) of compounds **9e**, **9i** and **9n-r** are substantially higher than their corresponding direct cytotoxicities (IC_{50} > 239.2 μM, Table 1). This result

suggests that the antitumor activities of these compounds toward solid tumor may be a result of the indirect effects. In addition, compounds **9e** and **9i** exhibited comparable indirect cytotoxicities with DMXAA, whereas compounds **9n-r** showed up to 2.4-fold higher indirect cytotoxicities than DMXAA.

(Please insert Table 2 here)

Careful analysis on the structure-activity relationship of compounds **9a-r** and our previous 3-arylflavone-8-acetic acids **8a-m** [18] reveals that the position of methoxy groups on the 3-arylflavone-8-acetic acid has a profound impact on the indirect cytotoxicity. Firstly, methoxy groups on the benzene rings at the 2- or 3-position of the flavone nucleus are favorable for the indirect cytotoxic activity. For example, compounds **9n-r** showed higher indirect activities than compounds **9a-m**. Secondly, the finding that a 3-arylflavone-8-acetic acid always exhibits higher indirect cytotoxicity than its corresponding analogue with a 7-methoxy group (Figure 3), suggests that a 7-methoxy group is less favorable for the indirect cytotoxicity. This may be because the intramolecular hydrogen bond between the 7-methoxy group and the 8-acetic acid group obstructs the formation of pyrylium-type salts (Figure 4), which was proposed by Kovacic *et al* [25].

(Please insert Figures 3 and 4 here)

*2.2.3 The effects of compounds **9p-r** on TNF-α production*

It is reported that DMXAA induces different cytokines (such as TNF-α, interleukin-6, macrophage inflammatory protein-1a and interferon-c), chemokines (interferon-inducible protein 10), and vasoactive factors (nitric oxide). They interact with tumor endothelial cells resulting in haemorrhagic tumor necrosis [26-28]. As TNF-α plays a critical role in the antitumor activity of DMXAA [29, 30], we investigated the effects of compounds **9p-r** on the TNF-α production by the HPBMCs (Figure 5). Their responses were compared with that obtained with lipopolysaccharide (LPS), a known inducer of TNF-α synthesis [31]. As shown in Figure 5, no cytokine production was stimulated by DMXAA alone at any tested concentration, which is in agreement with the results by Gobbi [17] and Philpott [32]. In

contrast, the level of TNF-α was significantly increased by compounds **9p-r**.

(Please insert Figure 5 here)

3. Conclusion

In summary, a series of novel flavone-8-acetic acid derivatives **9a-r** bearing different substituents on the phenyl rings at the 2- or 3-position of the flavone nuclei, have been synthesized and fully characterized. Except compounds **9b** and **9e**, the derivatives bearing electron-withdrawing groups exhibited comparable direct cytotoxicities with DMXAA. More interestingly, compounds **9n-r** bearing methoxy group showed higher indirect activities against A549 cells than DMXAA, and lower direct cytotoxicities. In addition, compounds **9p-r** could induce TNF-α production in the HPBMCs. Analysis on the structure-activity relationship of compounds **8a-m** and **9a-r** suggests a methoxy group on the benzene rings at the 2- or 3-position of the flavone nucleus is favorable for indirect cytotoxicities, whereas less favorable when it is translocated to the 7-position.

4. Experimental Section

4.1 Chemistry

Melting points were determined in open glass capillaries using an X-5 apparatus and are uncorrected. ESI spectra were measured on a Waters UPLC/Quattro Premier XE mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or d_6-DMSO using a Varian Mercury 400 spectrometer and TMS as an internal reference. Element analyses were carried out on a Vario ELIII CHNSO elemental analyzer.

DMXAA was purchased from Sigma (St. Louis, MO, USA). All the other chemicals were of analytical grade and used without further purification. Compounds (**12-15)a-r** were synthesized using the procedures described in the Supporting Information.

*Synthesis of 3-arylflavone-8-acetic acid derivatives **9a-r***

General procedures: 3-arylflavone-8-acetonitriles **15a-r** (1 mmol) were dissolved in a mixture of acetic acid (9 mL), H_2O (9 mL) and concentrated H_2SO_4 (9 mL). After the mixture was

refluxed for 2 h, water (375 mL) was added. The formed precipitate was collected by filtration and re-crystallized from EtOH to give compounds **9a-r**.

2-(4-Oxo-2,3-diphenyl-4H-chromen-8-yl)acetic acid (9a): Color: White. Yield: 86%. Mp: 222.5–223.0 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.95 (s, 2H), 7.17–7.20 (m, 2H), 7.30–7.34 (m, 5H), 7.38–7.41 (m, 3H), 7.48 (t, J = 7.6 Hz, 1H), 7.78 (dd, J = 7.3, 1.6 Hz, 1H), 8.03 (dd, J = 8.0, 1.6 Hz, 1H), 12.60 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 122.4, 122.9, 124.4, 125.2, 125.6, 127.7, 128.2, 128. 4, 129.5, 130.5, 131.3, 132.9, 133.1, 135.8, 154.1, 160.8, 172.0, 176.4. ESI-MS (*m/z*): 379.3 $[M+Na]^+$, 357.4 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{16}O_4$: C, 77.52; H, 4.53. Found: C, 77.30; H, 4.24.

2-(3-(2-Chlorophenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetic acid (9b): Color: White. Yield: 78%. Mp: 177.7–178.9 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.98 (s, 2H), 7.24–7.32 (m, 2H), 7.36–7.45 (m, 6H), 7.48–7.52 (m, 2H), 7.81 (dd, J = 7.2, 1.6 Hz, 1H), 8.03 (dd, J = 8.0, 1.6 Hz, 1H), 12.61 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 120.6, 122.6, 124.3, 125.4, 125.7, 127.4, 128.5, 128.7, 129.3, 130.1, 130.9, 132.5, 132.7, 133.1, 134.4, 136.1, 154.2, 161.2, 172.0, 175.6. Negative ESI-MS (*m/z*): 389.1 $[M-H]^-$. Anal. Calcd. for $C_{23}H_{15}ClO_4$: C, 70.68; H, 3.87. Found: C, 70.41; H, 3.65.

2-(3-(2-Chlorophenyl)-2-(4-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9c): Color: White. Yield: 94%. Mp: 233.3–235.0 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.98 (s, 2H), 7.27–7.34 (m, 2H), 7.39–7.41 (m, 3H), 7.46 (d, J = 8.8 Hz, 2H), 7.51 (t, J = 9.0 Hz, 2H), 7.82 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 120.7, 122.6, 124.3, 125.5, 125.8., 127.5, 128.7, 129.4, 130.2, 130.5, 131.4, 132.3, 133.1, 134.2, 135.8, 136.1, 154.1, 160.1, 172.0, 175.5. Negative ESI-MS (*m/z*): 423.7 $[M-H]^-$. Anal. Calcd. for $C_{23}H_{14}Cl_2O_4$: C, 64.96; H, 3.32. Found: C, 64.75; H, 3.59.

2-(2-(3-Chlorophenyl)-3-(4-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9d): Color: White. Yield: 86%. Mp: 97.7–99.3 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.99 (s, 2H), 7.29–7.36 (m, 3H), 7.37–7.46 (m, 3H), 7.50–7.55 (m, 3H), 7.83 (dd, J = 7.2, 1.2 Hz, 1H), 8.04 (dd, J = 8.0, 1.6 Hz, 1H), 12.61 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 121.0,

122.5, 124.3, 125.6, 125.8, 127.3, 127.5, 128.5, 129.4, 130.3, 130.5, 130.8, 132.1, 133.1, 133.3, 134.2, 134.4, 136.2, 154.2, 159.5, 172.0, 175.6. ESI-MS (*m/z*): 447.2 $[M+Na]^+$, 425.2 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{14}Cl_2O_4$: C, 64.96; H, 3.32. Found: C, 64.83; H, 3.58.

2-(3-(4-Fluorophenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetic acid (9e): Color: White. Yield: 81%. Mp: 219.8–220.9 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.94 (s, 2H), 7.13–7.24 (m, 4H), 7.34–7.41 (m, 5H), 7.46 (t, J = 7.6 Hz, 1H), 7.78 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 12.64 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 115.1, 115.3, 121.4, 122.8, 124.3, 125.2, 125.7, 128.4, 129.3(d, J = 3.3 Hz), 129.5, 130.5, 132.8, 133.3, 133.4, 135.9, 154.1, 160.5 , 161.0, 162.9, 172.0, 176.4. Negative ESI-MS (*m/z*): 373.6 $[M-H]^-$. Anal. Calcd. for $C_{23}H_{15}FO_4$: C, 73.79; H, 4.04. Found: C, 73.53; H, 4.19.

2-(2-(4-Chlorophenyl)-3-(4-fluorophenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9f): Color: White. Yield: 80%. Mp: 205.1–207.3 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.95 (s, 2H), 7.17 (t, J = 8.8 Hz, 2H), 7.22–7.26 (m, 2H), 7.39–7.50 (m, 5H), 7.79 (dd, J = 7.4, 1.0 Hz, 1H), 8.03 (dd, J = 8.0, 1.6 Hz, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.3, 115.2, 115.4, 121.6, 122.8, 124.3, 125.3, 125.6, 128.6, 129.0 (d, J = 3.2 Hz), 131.4, 131.7, 133.3, 133.4, 135.4, 136.0, 154.1, 159.8, 160.5, 163.0 172.0, 176.3. Negative ESI-MS (*m/z*): 407.4 $[M-H]^-$. Anal. Calcd. for $C_{24}H_{14}ClFO_4$: C, 67.57; H, 3.45. Found: C, 67.62; H, 3.57.

2-(2-(3-Chlorophenyl)-3-(4-fluorophenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9g): Color: White. Yield: 91%. Mp: 156.2–158.3 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.95 (s, 2H), 7.18 (t, J = 8.8 Hz, 2H), 7.24–7.27 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.46–7.51 (m, , 3H), 7.80 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 12.60 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 115.2, 115.4, 116.3, 121.9, 122.8, 124.4, 125.4, 125.7, 128.3, 128.9(d, J = 3Hz) 129.3, 130.3, 130.4, 133.1, 133.3, 136.0, 154.1, 159.2, 160.6, 163.1, 171.9, 176.3. ESI-MS (*m/z*): 409.5 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{14}ClFO_4$: C, 67.57; H, 3.45. Found: C, 67.32; H, 3.56.

2-(3-(2-Chloro-4-fluorophenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetic acid (9h): Color: White. Yield: 73%. Mp: 106.5–107.4 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.97 (s, 2H),

7.18–7.23 (m, 1H), 7.31–7.35 (m, , 1H), 7.37–7.46 (m, 5H), 7.49–7.54 (m, 2H), 7.82 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 12.59 (s, 1H). ^{13}C-NMR (*d*$_6$-DMSO, 100 MHz) *δ* 35.4, 114.7, 114.9, 116.6, 116.9, 119.7, 122.5, 124.3, 125.5, 125.8, 128.6, 128.7, 129.2 (d, *J* = 4 Hz) , 130.9, 132.4, 134.5, 134.6, 135.2, 135.3, 136.1, 154.2, 160.6, 161.5, 163.3, 172.0, 175.6. Negative ESI-MS (*m/z*): 407.4 $[M-H]^-$. Anal. Calcd. for $C_{23}H_{14}ClFO_4$: C, 67.57; H, 3.45. Found: C, 67.40, H, 3.52.

2-(3-(2-Chloro-4-fluorophenyl)-2-(4-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9i): Color: White. Yield: 83%. Mp: 238.6–241.3 °C. ^{1}H-NMR (*d*$_6$-DMSO, 400 MHz) *δ* 3.97 (s, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.34–7.42 (m, 3H), 7.48–7.54 (m, 4H), 7.82 (d, *J* = 6.8Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 12.57 (s, 1H). ^{13}C-NMR (*d*$_6$-DMSO, 100 MHz) *δ* 35.3, 114.8, 115.0, 116.8, 117.0, 119.9, 122.5, 124.3, 125.6, 125.8, 128.8, 130.5, 131.3, 134.5, 134.6, 135.1, 135.2, 135.8, 136.2, 154.2, 160.4, 160.7, 163.2, 172.0, 175.6. ESI-MS (*m/z*): 481.2 $[M+K]^+$, 465.2 $[M+Na]^+$, 443.3 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{13}Cl_2FO_4$: C, 62.32; H, 2.96. Found: C, 62.15; H, 2.85.

2-(3-(2-Chloro-4-fluorophenyl)-2-(3-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9j): Color: White. Yield: 89%. Mp: 98.6–99.5 °C. ^{1}H-NMR (*d*$_6$-DMSO, 400 MHz) *δ* 3.98 (s, 2H), 7.22–7.27 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.37–7.44 (m, 2H), 7.48–7.57 (m, 4H), 7.83 (d, *J* = 6.0 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 12.61 (s, 1H). ^{13}C-NMR (*d*$_6$-DMSO, 100 MHz) *δ* 35.4, 114.8, 115.0, 116.7, 117.0, 120.1, 122.5, 124.3, 125.6, 125.8, 127.4, 128.4, 128.7(d, *J* = 4 Hz), 130.6, 130.9, 133.3, 134.4, 134.6, 134.7, 135.1, 135.2, 136.3,154.2, 159.9, 160.8, 163.2, 172.0, 175.6. ESI-MS (*m/z*): 443.3 $[M+H]^+$ Anal. Calcd. for $C_{23}H_{13}Cl_2FO_4$: C, 62.32; H, 2.96. Found: C, 62.07; H, 2.80.

2-(3-(4-Chlorophenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetic acid (9k): Color: White. Yield: 77%. Mp: 242.5–243.2 °C. ^{1}H-NMR (*d*$_6$-DMSO, 400 MHz) *δ* 3.94 (s, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.35–7.44 (m, 7H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 6.8 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 12.61 (s, 1H). ^{13}C-NMR (*d*$_6$-DMSO, 100 MHz) *δ* 35.4, 121.2, 122.8, 124.4, 125.2, 125.7, 128.3, 128.5, 129.6, 130.6, 132.0, 132.4, 132.7, 133.2, 135.9, 154.1, 161.0, 172.0, 176.2. Negative ESI-MS (*m/z*): 389.5 $[M-H]^-$. Anal. Calcd. for $C_{23}H_{15}ClO_4$: C, 70.68;

H, 3.87. Found: C, 70.51, H, 3.72.

2-(2,3-Bis(4-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9l): Color: White. Yield: 86%. Mp: 221.2–223.5 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.94 (s, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.40–7.42 (m, 4H), 7.45–7.51 (m, 3H), 7.80 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 12.57 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.3, 121.5, 122.8.0, 124.4, 125.4, 125.7, 128.4, 128.6, 131.4, 131.6, 131.7, 132.6, 133.2, 135.5, 136.0, 154.1, 159.9, 172.0, 176.1. ESI-MS (*m/z*): 447.6 $[M+Na]^+$. Anal. Calcd. for $C_{23}H_{14}Cl_2O_4$: C, 64.96; H, 3.32. Found: C, 65.17; H, 3.42.

2-(2-(3-Chlorophenyl)-3-(4-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9m): Color: White. Yield: 83%. Mp: 194.3–195.5 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.95 (s, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.6 Hz, 1H), 7.37-7.42 (m, 3H), 7.48–7.51 (m, 3H), 7.80 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 12.58 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 121.8, 122.8, 124.4, 125.4, 125.7, 128.4, 129.3, 130.3, 130.5, 131.6, 132.7, 133.1, 133.2, 134.7, 136.1, 154.1, 159.4, 171.9, 176.2. ESI-MS (*m/z*): 425.4 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{14}Cl_2O_4$: C, 64.96; H, 3.32. Found: C, 64.81; H, 3.45.

2-(2,3-Bis(4-methoxyphenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9n): Color: White. Yield: 84%. Mp: 225.9–227.4 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.76(s, 3H), 3.77(s, 3H), 3.95 (s, 2H), 6.88–6.91 (m, 4H), 7.10 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.75 (dd, J = 7.2, 1.2 Hz, 1H), 8.00 (dd, J = 8.0, 1.6 Hz, 1H), 12.56 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 55.2, 55.5, 113.9, 121.0, 122.8, 124.3, 124.9, 125.2, 125.3, 125.5, 131.2, 132.4, 135.6, 154.0, 158.7, 160.4, 160.8, 172.1, 176.5. Negative ESI-MS (*m/z*): 415.5 $[M-H]^-$. Anal. Calcd. for $C_{25}H_{20}O_6$: C, 72.11; H, 4.84. Found: C, 71.92; H, 4.61.

2-(2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9o): Color: White. Yield: 77%. Mp: 201.2–202.8 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.53 (s, 3H), 3.77 (s, 6H), 3.97 (s, 2H), 6.90–6.95 (m, 4H), 7.02 (dd, J = 8.6, 2.2 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.76 (dd, J = 7.4, 1.4 Hz, 1H), 8.00 (dd, J = 8.0, 1.6 Hz, 1H), 12.56 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.5, 55.2, 55.3, 55.7, 111.2, 112.8,

114.0, 121.0, 122.8, 122.9, 124.4, 125.0, 125.5, 125.6, 132.3, 135.7, 148.0, 150.5, 154.0, 158.8, 160.2, 172.0, 176.6. Negative ESI-MS *(m/z)*: 445.5 $[M-H]^-$. Anal. Calcd. for $C_{26}H_{22}O_7$: C, 69.95; H, 4.97. Found: C, 70.22; H, 5.19.

2-(3-(4-Methoxyphenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetic acid (9p): Color: White. Yield: 88%. Mp: 224.2–225.7 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.75 (s, 3H), 3.94 (s, 2H), 6.88 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 6.4 Hz, 3H), 7.47 (t, J = 7.6 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 12.57 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 55.2, 113.7, 121.9, 122.8, 124.4, 124.9, 125.1, 125.6, 128.4, 129.5, 130.4, 132.4, 133.2, 135.7, 154.1, 158.7, 160.5, 172.0, 176.6. ESI-MS (*m/z*): 387.8 $[M+H]^+$. Anal. Calcd. for $C_{24}H_{18}O_5$: C, 74.60; H, 4.70. Found: C, 74.33; H, 4.86.

2-(3-(3,4-Dimethoxyphenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetic acid (9q): Color: White. Yield: 79%. Mp: 151.7–153.0 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.58 (s, 3H), 3.74 (s, 3H), 3.94 (s, 2H), 6.65–6.71 (m, 1H), 6.78 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 7.34–7.37 (m, , 2H), 7.39–7.44 (m, 4H),7.77 (d, J = 7.6 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 12.52 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 55.5(6), 55.5(7), 111.6, 115.2, 122.1, 122.9, 123.7, 124.4, 125.0(8), 125.1(2),125.6, 128.4, 129.4, 130.3, 133.2, 135.7, 148.4, 154.1, 160.7, 172.0, 176.5. ESI-MS (*m/z*): 439.8 $[M+Na]^+$, 417.9 $[M+H]^+$. Anal. Calcd. for $C_{25}H_{20}O_6$: C, 72.11; H, 4.84. Found: C, 71.94; H, 5.02.

2-(3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-oxo-4H-chromen-8-yl)acetic acid (9r): Color: White. Yield: 89%. Mp: 114.3–116.0 °C. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.62 (s, 3H), 3.76(s, 3H), 3.77(s, 3H), 3.95 (s, 2H), 6.82 (s, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 3H), 7.38 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 12.54 (s, 1H). ^{13}C-NMR (d_6-DMSO, 100 MHz) δ 35.4, 55.5(1), 55.5(6), 55.6(3), 111.7, 113.8, 115.2, 121.2, 122.8, 123.5, 124.4, 124.9, 125.2, 125.4, 125.6, 131.1, 135.6, 148.3, 148.5, 153.9, 160.5, 160.8, 172.1, 176.5. ESI-MS (*m/z*): 469.7 $[M+Na]^+$, 447.8 $[M+H]^+$. Anal. Calcd. for $C_{26}H_{22}O_7$: C, 69.95; H, 4.97. Found: C, 69.73; H, 4.87.

4.2 Pharmacology

4.2.1 Compounds

Compounds **9a-r** were dissolved in DMSO and stored as stock solutions (100 mM) at -20 °C. For experimental use, all the compounds were prepared from stock solutions, diluted with growth medium and used immediately.

4.2.2 Cell culture

A549 and HT-29 cells were cultured in RPMI 1640, supplemented with 10% fetal bovine serum and 100 U/mL penicillin and 100 μg/mL streptomycin (all from Invitrogen) at 37 °C in a humidified atmosphere of 5% CO_2 and 95% air. HPBMCs were isolated from heparinized whole blood by centrifugation over Ficoll-Paque Plus (TBD Science).

4.2.3 Direct cytotoxicity toward solid tumor cell lines

Cells were seeded for attachment in 96-well microculture plates overnight and then incubated with DMXAA and compounds **9a-r** of varying concentrations for 24 h. Then, the medium was discarded and fresh medium with MTT (0.5 mg/mL) was added to each well, and the cells were further incubated for 3 h. The stained formazan product was determined spectrophotometrically at 570 nm in GENios Pro microplate reader (TECAN).

4.2.4 Indirect cytotoxicity toward A549 cell lines

The indirect cytotoxicity was measured using the proceudres previously described by us [18]. HPBMCs (1×10^6 cells/well) were placed at the top well of a 3 μm 96-transwell plate (CORNING) for attachment overnight, and then activated by DMXAA and compounds **9a-r** of varying concentrations, using triplicate wells per drug dose. After 24 h, the medium was discarded and the A549 cells were seeded at a density of 3×10^3 cells per well in the bottom wells for another 24 h. The cell viability of the A549 cells in the bottom wells was assessed by the MTT assay. The inhibition percentage was calculated according to the following formula.

$$\%\text{inhibition}=\left[1-\frac{\text{OD(A549) of Compounds}}{\text{OD (A549) of Blank Control}}\right]\times 100\%$$

4.2.5 Quantification of TNF-α production

HPBMCs were isolated as described above and treated with culture medium, DMXAA **1** and compounds **9p-r** at the concentrations of 25, 50, and 100 μM. LPS (from E. coli serotype 0127; B8, Sigma) was used as a positive control at the final concentration of 1 μg/mL. After 24 h incubations, the medium was carefully collected and stored at -70 °C for assay. The viability of the cells was assessed by Trypan blue dye exclusion and always higher than 95%. The concentration of TNF-α was determined according to the manufacturer's instructions of the commercially available enzymes-linked immunosorbent assay (ELISA) kits (Sigma).

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Table Captions

Table 1. Direct cytotoxicities of compounds **9a-r**

Table 2. Indirect cytotoxicities of compounds **9e**, **9i** and **9n-r** toward A549 cells

Tables

Table 1. Direct cytotoxicities of compounds **9a-r**

Compound	R^1	R^2	A549	HT-29	HPBMCs
			IC_{50} (μM) [a]	IC_{50} (μM) [a]	CC_{50} (μM) [b]
9a [c]	H	H	>500	>500	ND [d]
9b	2-Cl	H	>500	>500	ND [d]
9c	2-Cl	4-Cl	278.4 ± 48.6	188.6 ± 30.9	ND [d]
9d	2-Cl	3-Cl	311.8 ± 53.0	250.7 ± 49.6	ND [d]
9e	4-F	H	>500	415.5 ± 40.6	> 1000
9f	4-F	4-Cl	337.0 ± 53.3	206.5 ± 53.7	ND [d]
9g	4-F	3-Cl	328.8 ± 51.0	389.0 ± 37.8	ND [d]
9h	2-Cl,4-F	H	314.6 ± 24.8	229.6 ± 41.3	ND [d]
9i	2-Cl,4-F	4-Cl	239.2 ± 36.3	216.7 ± 39.0	> 1000
9j	2-Cl,4-F	3-Cl	290.5 ± 39.2	203.2 ± 28.8	ND [d]
9k	4-Cl	H	250.8 ± 28.4	331.0 ± 36.8	ND [d]
9l	4-Cl	4-Cl	256.4 ± 48.0	270.0 ± 8.3	ND [d]
9m	4-Cl	3-Cl	265.0 ± 61.0	351.5 ± 28.2	ND [d]
9n	4-MeO	4-MeO	377.1 ± 14.1	>500	678.2±48.3
9o	4-MeO	3,4-diMeO	>500	>500	790.7±33.8
9p	4-MeO	H	>500	>500	> 1000
9q	3,4-diMeO	H	>500	>500	881.5±51.5
9r	3,4-diMeO	4-MeO	>500	>500	890.6±56.9
DMXAA	\	\	291.1±14.4	268.4 ± 49.9	648.2±31.5

[a] The IC_{50} value represents the concentration of each compound resulting in 50% inhibition in cell growth after 24 h incubation, and was the mean values of three repeated experiments.

[b] The CC_{50} values represent the 50% cytotoxic concentration, defined as the concentration required to reduce HPBMCs viability by 50% of the control value after 24 h incubation, and was the mean values of three repeated experiments.

[c] Compound **9a** has been previously reported [33].

[d] ND = not determined.

Tables

Table 2. Indirect cytotoxicities of compounds **9e**, **9i** and **9n-r** toward A549 cells

Compound	%Inhibition at 50 μM	IC_{50} (μM) [a]	PR [b]
DMXAA	48.4	84.2±13.5	1.0
9e	47.5	92.6±7.8	0.9
9i	49.5	86.0±10.3	1.0
9n	53.7	61.7±12.2	1.4
9o	53.0	67.4±12.6	1.2
9p	62.9	38.5±7.3	2.2
9q	57.0	44.5±7.7	1.9
9r	66.2	35.7±7.6	2.4

[a] Measured after co-cultured for 24 h and was the mean values of three repeated experiments.

[b] PR denotes the potency ratios (PRs) relative to DMXAA **1**.

Figure Captions

Figure 1. Flavonoids bearing carboxylic groups.

Figure 2. Cytotoxicities of compounds **9a-r** (50 μM) induced in HPBMCs toward A549 cells after co-cultured for 24 h in HTS Transwell®-96 Well Permeable Support Systems.

Figure 3. Pyrylium-type salts formed from compounds **8**.

Figure 4. Indirect inhibitory activities of some 3-arylflavone-8-acetic acids **9** and their corresponding analogues **8** with a 7-methoxy group toward A549 cells at the concentration of 50 μM.

Figure 5. TNF-α released by HPBMC treated with compounds **9p-r** of varying concentrations for 24 h. M represents the medium from unstimulated cells.

Figures

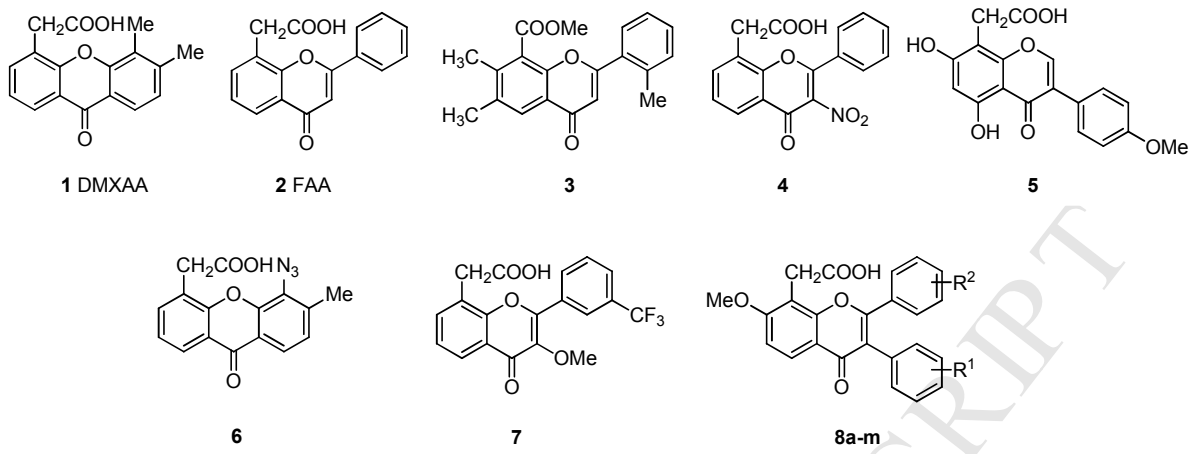


Figure 1.

Figures

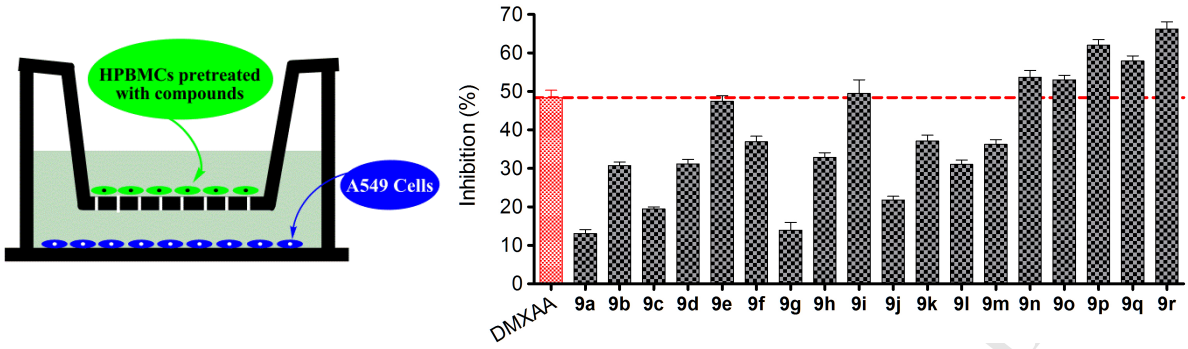


Figure 2.

Figures

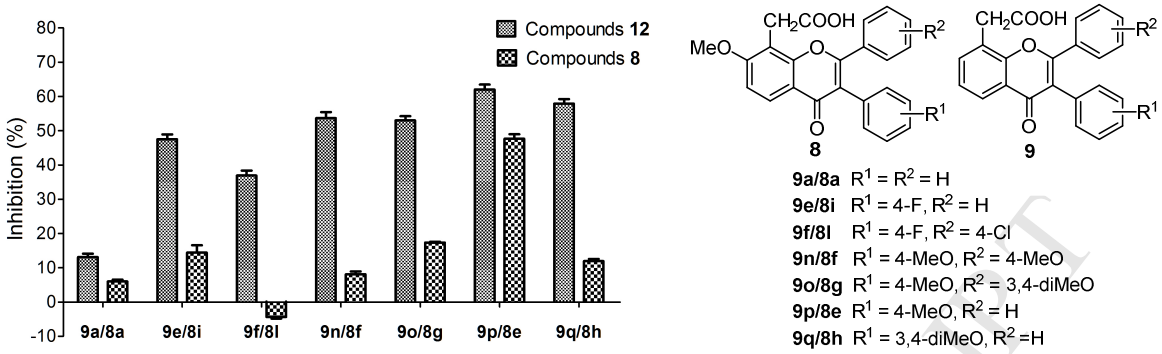


Figure 3.

Figures

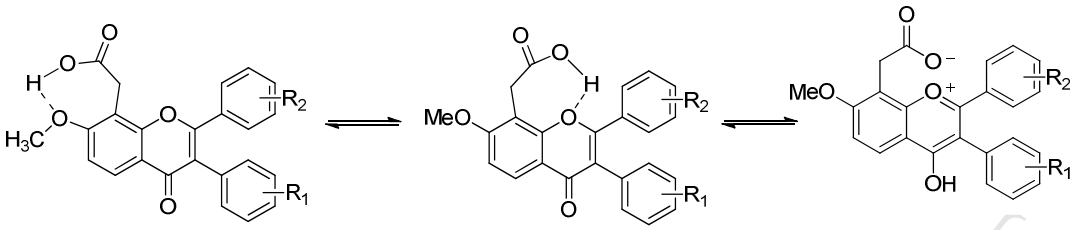


Figure 4.

Figures

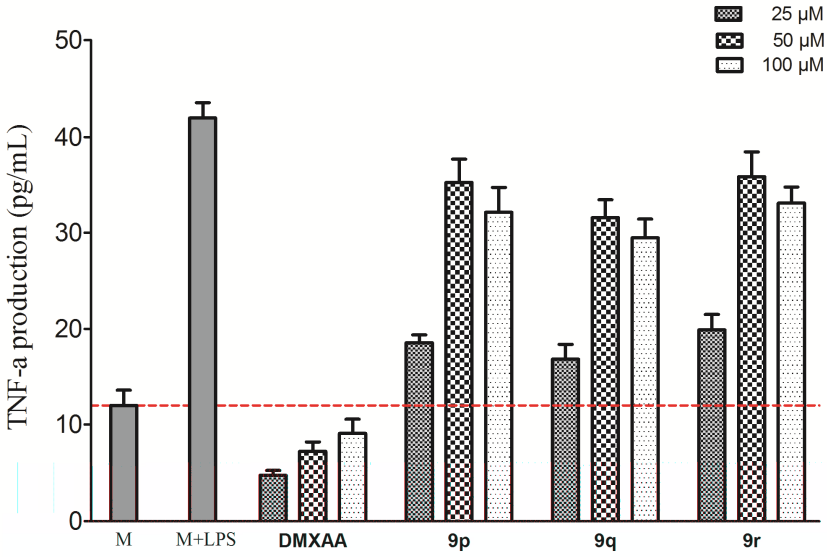
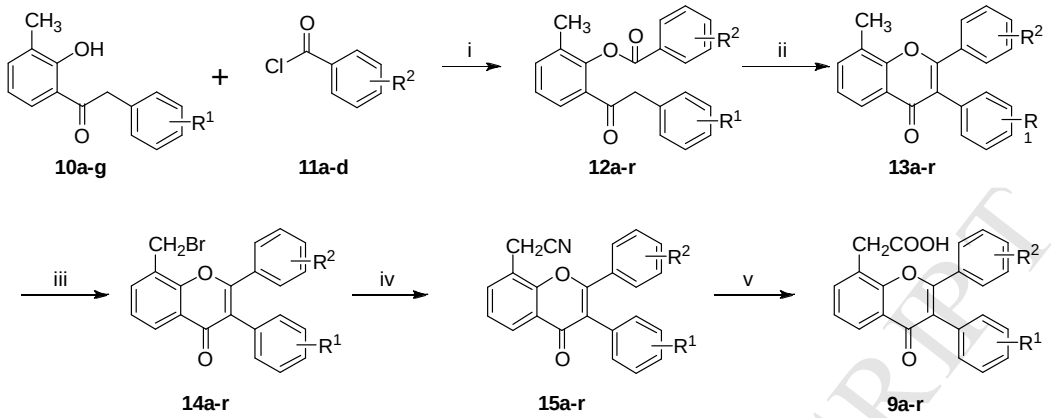


Figure 5.

Scheme



Scheme 1. Synthetic route for compounds **9a**-**r**. Reagents and conditions: (i) pyridine, room temperature; (ii) glycerol, 260 °C, N_2, 2h; (iii) NBS, AIBN, CCl_4, reflux; (iv) Et_4NCN, CH_2Cl_2; (v) H_2SO_4, AcOH, H_2O, 105 °C. Please refer to Table 1 for specific R^1 and R^2.

Research Highlights

- Eighteen 3-arylflavone-8-acetic acid derivatives were synthesized.
- All the compounds bearing methoxy groups showed higher indirect cytotoxicity than DMXAA.
- Compounds **9p-r** were able to induce TNF-α production in HPBMCs.
- A methoxy group at the 7-position of flavones is less favorable for indirect cytotoxicity.
- A methoxy group on the benzene rings is favorable for indirect cytotoxicities.

Synthesis and anticancer activities of 3-arylflavone-8-acetic acid derivatives

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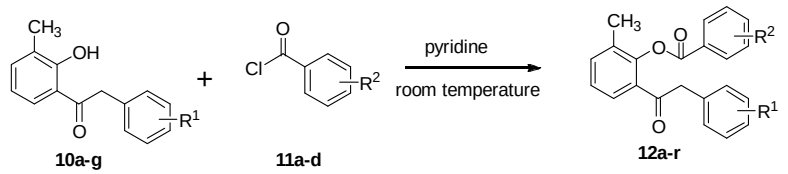
Supporting Information

1. Synthesis of 3-aryl-8-methylflavones 12a-r



General procedures: a solution of compounds **10a-g** (1.0 mmol) and benzoyl chlorides **11a-e** (2.7 mmol) in anhydrous pyridine (5 mL) was stirred at room temperature for 5 h. The reaction mixture was treated with cold diluted HCl (1 M) and then extracted with ether (10 mL×2). The combined organic layer was washed with 5% aqueous HCl (10 mL) and water (10 mL×2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield oily residue. Purification was accomplished by chromatography on a silica gel column, eluted with petroleum ether-acetone (25/l, v/v), to give esters **12a-r**.

2-Methyl-6-(2-phenylacetyl) phenyl benzoate (12a): Yield: 78%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.17 (s, 2H), 7.16–7.22 (m, 3H), 7.24 (d, J = 1.6 Hz, 1H), 7.27 (m, 2H), 7.42 (dd, J = 7.6, 0.8 Hz, 1H), 7.47–7.54 (m, 2H), 7.61–7.65 (m, 2H), 8.20 (d, J = 7.2 Hz, 2H). ESI-MS (*m/z*): 369.3 $[M+K]^+$, 353.4 $[M+Na]^+$.

2-(2-(2-Chlorophenyl)acetyl)-6-methylphenyl benzoate (12b): Yield: 66%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 4.33 (s, 2H), 7.17 (d, J = 2.8 Hz, 3H), 7.27–7.34 (m, 2H), 7.45–7.52 (m, 3H) 7.61–7.65 (m, 1H), 7.72 (dd, J = 7.6, 1.2 Hz, 1H), 8.21 (d, J = 7.2 Hz, 2H). ESI-MS (*m/z*): 403.5 $[M+K]^+$, 387.5 $[M+Na]^+$.

2-(2-(2-Chlorophenyl)acetyl)-6-methylphenyl-4-chlorobenzoate (12c): Yield: 37%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.32 (s, 2H), 7.15–7.21 (m, 3H), 7.28–7.34(m, 2H), 7.44–7.49 (m, 3H), 7.74 (dd, J = 7.7, 0.9 Hz, 1H), 8.12 (d, J = 8.6 Hz, 2H). ESI-MS (*m/z*): 421.3 [M+Na][M+Na]$^+$.

2-(2-(2-Chlorophenyl)acetyl)-6-methylphenyl-3-chlorobenzoate (12d): Yield: 58%. ^{1}H-NMR

(400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.32 (s, 2H), 7.18 (d, *J* = 2.7 Hz, 3H), 7.27–7.35 (m, 2H), 7.44 (dd, *J* = 15.9, 8.0 Hz, 2H), 7.56–7.15 (m, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 8.04–8.09 (m, 1H), 8.13–8.17 (m, 1H). ESI-MS (*m/z*): 421.3 $[M+Na][M+Na]^+$.

2-(2-(4-Fluorophenyl)acetyl)-6-methylphenyl benzoate (12e): Yield: 47%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.14 (s, 2H), 6.90–6. 98 (m, 2H), 7.11–7.13 (m, 2H), 7.42–7.54 (m, 4H), 7.59–7.67 (m, 3H), 8.12 (d, *J* = 7.2 Hz, 1H), 8.19 (d, *J* = 7.2 Hz, 2H). ESI-MS (*m/z*): 371.5 $[M+Na][M+Na]^+$, 349.6 $[M+H]^+$.

2-(2-(4-Fluorophenyl)acetyl)-6-methylphenyl-4-chlorobenzoate (12f): Yield: 75%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 4.14 (s, 2H), 6.95 (t, *J* = 8.7 Hz, 2H), 7.12 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.45–7.49 (m, 3H), 7.64 (d, *J* = 7.0 Hz, 1H), 8.11 (d, *J* = 8.6 Hz, 2H). ESI-MS (*m/z*): 405.6 $[M+Na]^+$, 383.6 $[M+H][M+H]^+$.

2-(2-(4-Fluorophenyl)acetyl)-6-methylphenyl-3-chlorobenzoate (12g): Yield: 53%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.15 (s, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 7.13 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.42–7.47 (m, 2H), 7.59–7.62 (m, 1H), 7.63–7.67 (m, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 8.14 (t, *J* = 1.7 Hz, 1H). ESI-MS (*m/z*): 383.7 $[M+H][M+H]^+$.

2-(2-(2-Chloro-4-fluorophenyl)acetyl)-6-methylphenyl benzoate (12h): Yield: 69%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.27(s, 3H), 4.29 (s, 2H), 6.87–6.92 (m, 1H), 7.08 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.14 (dd, *J* = 8.8, 6.0 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.46–7.53 (m, 3H), 7.59–7.64 (m, 1H), 7.71 (d, *J* =7.6 Hz, 1H), 8.20 (d, *J* = 7.2 Hz, 2H). ESI-MS (*m/z*): 421.3 $[M+K]^+$, 405.4 $[M+Na]^+$, 383.4 $[M+H]^+$.

2-(2-(2-Chloro-4-fluorophenyl)acetyl)-6-methylphenyl-4-chlorobenzoate 12i: Yield: 85%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.28 (s, 2H), 6.88–6.93 (m, 1H), 7.08–7.16 (m, 2H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 3H), 7.73 (d, *J* = 7.7 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 2H). ESI-MS (*m/z*): 439.3 $[M+Na]^+$.

2-(2-(2-Chloro-4-fluorophenyl)acetyl)-6-methylphenyl-3-chlorobenzoate (12j): Yield: 85%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 4.29 (s, 2H), 6.89–6.94 (m, 1H), 7.09 (dd, J = 8.5, 2.6 Hz, 1H), 7.15 (dd, J = 8.5, 6.0 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.42–7.49 (m, 2H), 7.58–7.61(m, 1H), 7.74 (dd, J = 7.8, 1.2 Hz, 1H), 8.05–8.09 (m, 1H), 8.15 (t, J = 1.8 Hz, 1H). ESI-MS (*m/z*): 455.3 $[M+K][M+K]^+$, 439.3 $[M+Na]^+$.

2-(2-(4-Chlorophenyl)acetyl)-6-methylphenyl benzoate (12k): Yield: 74%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 4.14 (s, 2H), 7.09 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.41–7.68 (m, 6H), 8.10–8.19 (dd, J = 28.1, 7.1 Hz, 2H). ESI-MS (*m/z*): 403.6 $[M+K][M+K]^+$, 387.6 $[M+Na]^+$, 365.7 $[M+H]^+$.

2-(2-(4-Chlorophenyl)acetyl)-6-methylphenyl-4-chlorobenzoate (12l): Yield: 63%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 4.14 (s, 2H), 7.09 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 7.7 Hz, 1H), 7.44–7.49 (m, 3H), 7.64 (d, J = 7.7 Hz, 1H), 8.10 (d, J = 8.6 Hz, 2H). ESI-MS (*m/z*): 421.4 $[M+Na]^+$.

2-(2-(4-Chlorophenyl)acetyl)-6-methylphenyl-3-chlorobenzoate (12m): Yield: 41%. ^{1}H-NMR (400 MHz, CDCl3) δ 2.24 (s, 3H), 4.14 (s, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.57–7.62 (m, 1H), 7.62–7.67 (m, 1H), 8.04 (d, J = 7.8 Hz, 1H), 8.13 (t, J = 1.7 Hz, 1H). ESI-MS (*m/z*): 421.4 $[M+Na]^+$.

2-(2-(4-Methoxyphenyl)acetyl)-6-methylphenyl-4-methoxybenzoate (12n): Yield: 36%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.76 (s, 3H), 3.89 (s, 3H), 4.10 (s, 2H), 6.80 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.22 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 8.15 (d, J = 8.5 Hz, 2H). ESI-MS (*m/z*): 429.5 $[M+K]^+$, 413.5 $[M+Na]^+$, 391.5 $[M+H]^+$.

2-(2-(4-Methoxyphenyl)acetyl)-6-methylphenyl-3,4-dimethoxybenzoate (12o): Yield: 37%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.76 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.11 (s, 2H), 6.80 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 7.7 Hz,

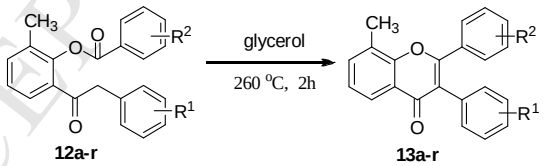
1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.66 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 1H). ESI-MS (*m/z*): 459.5 $[M+K]^+$, 443.5 $[M+Na]^+$, 421.6 $[M+H]^+$.

2-(2-(4-Methoxyphenyl)acetyl)-6-methylphenyl benzoate (12p): Yield: 50%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.75 (d, *J* = 1.5 Hz, 3H), 4.11 (s, 2H), 6.80 (d, *J* = 6.7 Hz, 2H), 7.08 (d, *J* = 6.8 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.48–7.52 (m, 3H), 7.58 (m, 3H), 7.67–2.24 (m, 3H), 8.12 (d, *J* = 7.2 Hz, 1H), 8.19 (d, *J* = 7.2 Hz, 2H). ESI-MS (*m/z*): 383.9 $[M+Na]^+$.

2-(2-(3,4-dimethoxyphenyl)acetyl)-6-methylphenyl benzoate (**12q**): Yield: 52%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.76 (s, 3H), 3.95 (s, 3H), 4.10 (s, 2H), 6.76–6.84 (m, 3H), 7.27–7.38 (m, 4H), 7.43–7.47 (m, 2H), 7.52–7.57 (m, 1H), 8.11–8.16 (m, 1H). ESI-MS (*m/z*): 413.5 $[M+Na]^+$, 391.5 $[M+H]^+$.

2-(2-(3,4-dimethoxyphenyl)acetyl)-6-methylphenyl 4-methoxybenzoate (**12r**): Yield: 27%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.77 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.11 (s, 2H), 6.78–6.85 (m, 5H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.38–7.43 (m, 2H), 7.51–7.54 (m, 1H), 8.10–8.14 (m, 1H). ESI-MS (*m/z*): 444.5 $[M+Na]^+$,421.5 $[M+H]^+$.

2. Synthesis of 3-aryl-8-methylflavones 13a-r



General procedures: Compounds **12a-r** (1.0 mmol) which were obtained at last step were dissolved in freshly distilled anhydrous glycerol (8 mL), and the resulting solution was heated at 260 °C under the atmosphere of nitrogen for 2 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and adjusted to pH 10 with 4 N NaOH. Then, the resulting mixture was stirred at room temperature for 15 min and allowed to stand at 0 °C for 2 d. The formed precipitate was collected by filtration and re-crystallized from EtOH to give

compounds **13a-r**.

8-Methyl-2,3-diphenyl-4H-chromen-4-one (13a): Color: White. Yield: 71%. Mp: 203.8–204.5 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.57 (s, 3H), 7.21–7.24 (m, 2H), 7.27–7.38 (m, 7H), 7.40–7.45 (m, 2H), 7.55 (dd, J = 7.2, 0.8 Hz, 1H), 8.14 (dd, J = 8.0, 1.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 122.7, 123.4, 123.97, 124.7, 127.4, 127.6, 128.1, 128.3, 129.6, 130.0, 131.3, 133.0, 133.5, 134.5, 154. 6, 161.0, 177.7. ESI-MS (*m/z*): 351.6 $[M+K]^+$, 335.6 $[M+Na]^+$, 313.6 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.76; H, 5.21.

3-(2-Chlorophenyl)-8-methyl-2-phenyl-4H-chromen-4-one (13b): Color: White. Yield: 69%. Mp: 174.7–175.2 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.58 (s, 3H), 7.14 (dd, J = 7.6, 2.2 Hz, 1H), 7.18–7.23 (m, 1H), 7.28–7.32 (m, 3H), 7.33–7.40 (m, 2H), 7.42–7.47 (m, 3H), 7.57 (d, J = 7.2 Hz, 1H), 8.14 (d, J = 7.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 121.0, 123.2, 124.0, 124.8, 126.9, 127.5, 128.2, 128.8, 129.4, 129.7, 130.4, 132.7, 132.9, 133.2, 134.7, 135.2, 154.7, 161.6, 176.9. ESI-MS (*m/z*): 385.5 $[M+K]^+$, 369.6 $[M+Na]^+$, 347.6 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{15}ClO_2$: C, 76.19; H, 4.36. Found: C, 76.26; H, 4.32.

3-(2-Chlorophenyl)-2-(4-chlorophenyl)-8-methyl-4H-chromen-4-one (13c): Color: White. Yield: 75%. Mp: 168.0–169.3 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.57 (s, 3H), 7.15 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 7.4 Hz, 1H), 7.27–7.40 (m, 6H), 7.44 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 6.8 Hz, 1H), 8.13 (d, J = 7.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 121.1, 123.1, 124.1, 124.9, 127.1, 127.4, 128.7, 129.7, 129.8, 130.1, 131.6, 132.5, 132.6, 134.8, 135.0, 136.6, 154.6, 160.4, 176.8. ESI-MS (*m/z*): 403.3 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{14}Cl_2O_2$: C, 69.31; H, 3.70. Found: C, 69.55; H, 3.60.

3-(2-Chlorophenyl)-2-(3-chlorophenyl)-8-methyl-4H-chromen-4-one (13d): Color: White. Yield: 78%. Mp: 144.0–145.1 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.58 (s, 3H), 7.14–7.20 (m, 1H), 7.19–7.25 (m, 2H), 7.26–7.27 (m, 1H), 7.28–7.37 (m, 3H), 7.45 (dd, J = 8.0, 1.2 Hz, 1H), 7.48 (t, J = 1.8 Hz, 1H), 7.56–7.59 (m, 1H), 8.13 (dd, J = 8.0, 1.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz)

δ 15.7, 121.4, 123.1, 124.0, 125.0, 127.0, 127.1, 127.4, 128.7, 129.5, 129.7, 129.8, 130.4, 132.3, 132.6, 134.3, 134.9, 134.9, 135.0, 154.6, 159.9, 176.8. ESI-MS (*m/z*): 419.7 $[M+K]^+$, 403.7 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{14}Cl_2O_2$: C, 69.31; H, 3.70. Found: C, 69.35; H, 3.87.

3-(4-Fluorophenyl)-8-methyl-2-phenyl-4H-chromen-4-one (13e): Color: White. Yield: 75%. Mp: 183.5–184.1 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 6.97–7.03 (m, 2H), 7.18–7.22 (m, 2H), 7.28–7.42 (m, 6H), 7.55 (dd, *J* = 7.2, 0.8 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.6, 115.3, 115.5, 121.7, 123.3, 123.9, 124.8, 127.4, 128.3, 128.8 (5), 128.8 (9), 129.5, 130.2, 132.9, 133.0, 133.4, 134.6, 139.5, 142.5, 154.5, 161.2, 163.5, 177.7. ESI-MS (*m/z*): 353.3 $[M+Na]^+$, 331.4 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{15}FO_2$: C, 79.99; H, 4.58. Found: C, 80.26; H, 4.63.

2-(4-Chlorophenyl)-3-(4-fluorophenyl)-8-methyl-4H-chromen-4-one (13f): Color: White. Yield: 69%. Mp: 201.6–202.8 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz,) δ 2.55 (s, 3H), 7.03 (t, *J* = 8.7 Hz, 2H), 7.20 (dd, *J* = 8.7, 5.5 Hz, 2H), 7. 27–7.37 (m, 5H), 7.56 (d, *J* = 7.0 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.6, 115.5, 115.7, 121.8, 123.3, 124.0, 124.9, 127.3, 128.5, 128.6, 128.7, 130.8, 131.8, 132.9, 132.9, 134.8, 136.4, 154.5, 159.9, 161.2 (C-F), 163.6 (C-F), 177.5. ESI-MS (*m/z*): 387.5 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{14}ClFO_2$: C, 72.43; H, 3.87. Found: C, 72.67; H, 3.98.

2-(3-Chlorophenyl)-3-(4-fluorophenyl)-8-methyl-4H-chromen-4-one (13g): Color: Light yellow. Yield: 73%. Mp: 170.2–171.5 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 7.03 (t, *J* = 8.4 Hz, 2H), 7.17–7.24 (m, 4H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.47 (s, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ15.7. 121.1, 123.1, 124.1, 125.0, 127.1, 127.4, 128.7, 129.7, 129.8, 130.1, 131.7, 132.5, 132.6, 134.8, 135.0, 136.6, 154.6, 160.4, 176.8. ESI-MS (*m/z*): 387.5 $[M+Na]^+$, 365.5 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{14}ClFO_2$: C, 72.43; H, 3.87. Found: C, 72.79; H, 3.59.

3-(2-Chloro-4-fluorophenyl)-8-methyl-2-phenyl-4H-chromen-4-one (13h): Color: White.

Yield: 52%. Mp: 168.9–170.3 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.58 (s, 3H), 6.92–6.97 (m, 1H), 7.10–7.14 (m, 1H), 7.18–7.21 (m, 1H), 7.30–7.45 (m, 6H), 7.57 (dd, J = 7.2, 0.8 Hz, 1H), 8.13 (dd, J = 8.0, 0.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 114.3, 114.5, 117.0, 117.3, 120.1, 123.1, 124.0, 124.9, 127.5, 128.4, 128.7, 128.9, 129.0, 130.5, 133.1, 133.7, 133.8, 134.8, 136.0, 136.1, 154.7, 161.1, 161.9, 163.5, 176.9. ESI-MS (*m/z*): 403.2 $[M+K]^+$, 387.3 $[M+Na]^+$, 365.4 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{14}ClFO_2$: C, 72.43; H, 3.87. Found: C, 72.19; H, 3.75.

3-(2-Chloro-4-fluorophenyl)-2-(4-chlorophenyl)-8-methyl-4H-chromen-4-one (13i): Color: Light yellow. Yield: 60%. Mp: 201.1–202.0 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 6.97 (t, J = 8.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.28–7.39 (m, 5H), 7.57 (d, J = 6.8 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 114.5, 114.7, 117.2, 117.5, 120.1, 123.03, 124.0, 125.1, 127.4, 128.5, 128.6, 128.8, 130.0, 131.5, 133.6, 133.7, 135.0 135.8, 136.0, 136.8, 154.65, 160.7, 161.2, 163.7, 176.8. ESI-MS (*m/z*): 421.3 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{13}Cl_2FO_2$: C, 66.18; H, 3.28; 8.01. Found: C, 66.04; H, 3.38.

3-(2-Chloro-4-fluorophenyl)-2-(3-chlorophenyl)-8-methyl-4H-chromen-4-one (13j): Color: Light yellow. Yield: 69%. Mp: 140.0–141.2 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.58 (s, 3H), 6.95–7.00 (m, 1H), 7.11–7.15 (m, 1H), 7.18–7.25 (m, 3H), 7.33–7.39 (m, 2H), 7.47–7.50 (m, 1H), 7.56–7.60 (m, 1H), 8.12 (dd, J = 8.0, 1.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 114.4, 114.7, 117.2, 117.4, 120.5, 123.1, 124.0, 125.1, 126.9, 127.5, 128.4, 128.4, 128.7, 129.6, 130.6, 133.6, 133.7, 134.5, 134.7, 135.0, 135.8, 135.9, 154.6, 160.3, 161.2, 163.7, 176.8.. ESI-MS (*m/z*): 421.7 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{13}Cl_2FO_2$: C, 66.18; H, 3.28. Found: C, 66.20; H, 3.82.

3-(4-Chlorophenyl)-8-methyl-2-phenyl-4H-chromen-4-one (13k): Color: White. Yield: 95%. Mp: 192.9–193.2 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 7.17 (d, J = 8.4 Hz, 2H), 7.27–7.44 (m, 8H), 7.55 (d, J = 7.2 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7. 121.5, 123.3, 123.9, 124.8, 127.4, 128.3, 128.6, 129.6, 130.3, 131.5, 133.2, 132.6, 133.6, 134.7, 154.5, 161.3, 177.5. ESI-MS (*m/z*): 385.5 $[M+K]^+$, 369.5 $[M+Na]^+$, 347.5 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{15}ClO_2$: C, 76.19; H, 4.36. Found: C, 75.92; H, 4.29.

2,3-Bis(4-Chlorophenyl)-8-methyl-4H-chromen-4-one (13l): Color: White. Yield: 79%. Mp: 210.3–212.1 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 7.16 (d, J = 8.4 Hz, 2H), 7.28–7.38 (m, 7H), 7.56 (d, J = 7.2 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 121.7, 123.2, 124.0, 125.0, 127.3, 128.7, 128.8, 130.8, 131.2, 131.6, 132.6, 133.9, 134.8, 136.6, 154.4, 160.0, 177.3. ESI-MS (*m/z*): 403.4 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{14}Cl_2O_2$: C, 69.31; H, 3.70. Found: C, 69.59; H, 3.80.

2-(3-Chlorophenyl)-3-(4-chlorophenyl)-8-methyl-4H-chromen-4-one (13m): Color: Light yellow. Yield: 63%. Mp: 152.9–154.7 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 7.15–7.23 (m, 4H), 7.31 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.50 (s, 1H), 7.57 (d, J = 7.2 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 122.0, 123.2, 124.0, 125.0, 127.4, 127.9, 128.7, 129.3, 129.5, 130.3, 131.0, 132.5, 134.0, 134.5, 134.9, 134.9, 154.4, 159.6, 177.3. ESI-MS (*m/z*): 403.4 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{14}Cl_2O_2$: C, 69.31; H, 3.70. Found: C, 69.50; H, 3.82.

2,3-Bis(4-methoxyphenyl)-8-methyl-4H-chromen-4-one (13n): Color: White. Yield: 54%. Mp: 175.8–177.5 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 6.80 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 7.2 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 55.2, 55.3, 113.6, 114.0, 121.3, 123.3, 123.9, 124.4, 125.5, 125.9, 127.2, 131.2, 132.3, 134.3, 154.4, 159.0, 160.6, 160.8, 177.9. ESI-MS (*m/z*): 395.6 $[M+Na]^+$, 373.6 $[M+H]^+$. Anal. Calcd. for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.37; H, 5.31.

2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-8-methyl-4H-chromen-4-one (13o): Color: White. Yield: 67%. Mp: 166.5–167.3 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.58 (s, 3H), 3.55 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 6.82–6.85 (m, 2H), 6.90 (d, J = 5.6 Hz, 2H), 7.19 (d, J = 5.6 Hz, 2H), 7.23 (s, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.53 (d, J = 6.4 Hz, 1H), 8.12 (d, J = 7.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.8, 55.4, 55.6, 55.9, 110.6, 113.0, 114.2, 121.3, 122.7, 123.3, 124.0, 124.5, 125.8, 125.9, 127.1, 132.4, 134.4, 148.0, 150.4, 154.4, 159.1, 160.3, 178.0. ESI-MS

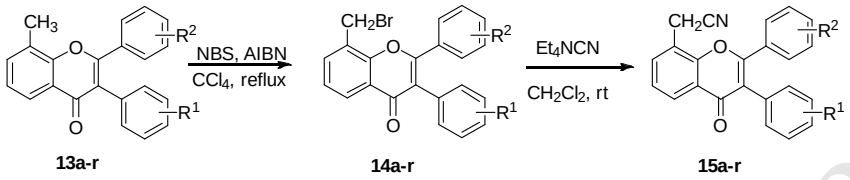
(*m/z*): 425.5 $[M+Na]^+$, 403.6 $[M+H]^+$. Anal. Calcd. for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51. Found: C, 74.45; H, 5.63.

3-(4-Methoxyphenyl)-8-methyl-2-phenyl-4H-chromen-4-one (13p): Color: White. Yield: 66%. Mp: 186.5–187.7 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 3.80 (s, 3H), 6.82–6.88 (m, 2H), 7.13–7.18 (m, 2H), 7.26–7.37 (m, 4H), 7.42–7.46 (m, 2H), 7.51–7.55 (m, 1H), 8.13 (dd, *J* = 8.0, 1.1 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 55.2, 113.9, 122.2, 123.4, 124.0, 124.6, 125.1, 127.3, 128.2, 129.6, 129.9, 132.4, 133.7, 134.4, 154.5, 159.0, 160.7, 178.0. ESI-MS (*m/z*): 381.9 $[M+K]^+$, 343.9 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.25; H, 5.74.

3-(3,4-Dimethoxyphenyl)-8-methyl-2-phenyl-4H-chromen-4-one (13q): Color: Brown. Yield: 74%. Mp: 179.9–181.0 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 3.73 (s, 3H), 3.88 (s, 3H), 6.76–6.84 (m, 3H), 7.27–7.38 (m, 4H), 7.43–7.47 (m, 2H), 7.52–7.57 (m, 1H), 8.11–8.16 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 55.8, 55.8, 111.2, 114.5, 122.3, 123.4, 123.9, 124.0, 124.6, 125.4, 127.4, 128.2, 129.5, 130.0, 133.7, 134.5, 148.6, 148.7, 154.5, 160.9, 177.9. ESI-MS (*m/z*): 411.8 $[M+K]^+$, 373.9 $[M+H]^+$. Anal. Calcd. for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.31; H, 5.31.

3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-8-methyl-4H-chromen-4-one (13r): Color: Yellow. Yield: 52%. Mp: 184.2–185.6 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.57 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 6.78–6.85 (m, 5H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.38–7.43 (m, 2H), 7.51–7.54 (m, 1H), 8.10–8.14 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 55.32 55.8, 55.9, 111.3 113.6, 114.4, 121.4, 123.3, 123.8, 123.9, 124.5, 125.8, 127.2, 131.1, 134.3, 148.5, 148.8, 154.4, 160.7, 160.9, 177.9. ESI-MS (*m/z*): 441.8 $[M+K]^+$, 425.9 $[M+Na]^+$, 403.9 $[M+H]^+$. Anal. Calcd. for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51. Found: C, 74.52; H, 5.74.

3. Synthesis of 3-arylflavone-8-acetonitrile derivatives 15a-r



General procedures: a solution of compounds **13a-r** (1 mmol), NBS (1.1 mmol) and AIBN (0.12 mmol) in anhydrous CCl_4 (40 mL) was refluxed and monitored by TLC. After refluxing for 7 h, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was chromatographed to give 8-bromomethyl-3-arylflavones **14a-r** which were immediately used in the subsequent reaction. Thus, to a solution of compounds **14a-r** in dry CH_2Cl_2 (20 mL) was added tetraethylammonium cyanide (1.05 mmol). The resulting mixture was stirred at room temperature until the starting material disappeared on TLC, and then concentrated under reduced pressure. The obtained residue was re-crystallized from EtOH to give 3-arylflavone-8-acetonitriles **15a-r**.

2-(4-Oxo-2,3-diphenyl-4H-chromen-8-yl)acetonitrile (15a) [1]**:** Yield: 66%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 2H), 7.19–7.24 (m, 2H), 7.28–7.49 (m, 9H), 7.78 (d, J = 7.4 Hz, 1H), 8.30 (dd, J = 8.0, 1.5 Hz, 1H). ESI-MS (*m/z*): 376.2 $[M+K]^+$, 360.3 $[M+Na]^+$, 338.3 $[M+H]^+$.

2-(3-(2-Chlorophenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetonitrile (15b): Yield: 60%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 2H), 7.11 (d, J = 7.2 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.29–7.35 (m, 3H), 7.39 (t, J = 7.4 Hz, 1H), 7.43–7. 51 (m, 4H), 7.80 (d, J = 7.3 Hz, 1H), 8.31 (d, J = 7.6 Hz, 1H). ESI-MS (*m/z*): 394.5 $[M+Na]^+$, 372.5 $[M+H]^+$.

2-(3-(2-Chlorophenyl)-2-(4-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15c): Yield: 77%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 2H), 7.12 (dd, J = 7.6, 1.7 Hz, 1H), 7.23 (td, J = 7.5, 1.3 Hz, 1H), 7.27–7.34 (m, 3H), 7.38–7.42 (m, 2H), 7.43–7.52 (m, 2H), 7.76–7.82 (m, 1H), 8.30 (dd, J = 8.0, 1.6 Hz, 1H). ESI-MS (*m/z*): 428.6 $[M+Na]^+$, 406.7 $[M+H]^+$.

2-(3-(2-Chlorophenyl)-2-(3-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15d): Yield: 69%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 2H), 7.13 (dd, J = 7.5, 1.3 Hz, 1H), 7.21 – 7.26 (m, 2H), 7.28 – 7.33 (m, 2H) 7.34–7.37 (m, 1H), 7.53–7.43 (m, 3H), 7.81 (d, J = 7.2 Hz, 1H), 8.30 (d, J = 7.2 Hz, 1H). ESI-MS (*m/z*): 428.2 $[M+Na]^+$, 406.3 $[M+H]^+$.

2-(3-(4-Fluorophenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetonitrile (15e): Yield: 56%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 2H), 7.01 (t, J = 8.8 Hz, 2H), 7.17–7.23 (m, 2H), 7.30–7.50 (m, 6H), 7.76–7.81 (m, 1H), 8.30 (dd, J = 8.0, 1.2 Hz, 1H). ESI-MS (*m/z*): 394.3 $[M+K]^+$, 378.4 $[M+Na]^+$, 356.4 $[M+H]^+$.

2-(2-(4-Chlorophenyl)-3-(4-fluorophenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15f): Yield: 75%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 2H), 7.04 (t, J = 8.7 Hz, 2H), 7.19 (dd, J = 8.7, 5.4 Hz, 2H), 7.34 (dd, J = 26.9, 8.7 Hz, 4H), 7.47 (t, J = 7.7 Hz, 1H), 7.77 (d, J = 7.3 Hz, 1H), 8.29 (dd, J = 8.0, 1.4 Hz, 1H). ESI-MS (*m/z*): 412.5 $[M+Na]^+$, 390.5 $[M+H]^+$.

2-(2-(3-Chlorophenyl)-3-(4-fluorophenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15g): Yield: 67%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 2H), 7.04 (t, J = 8.7 Hz, 2H), 7.16–7.23 (m, 2H), 7.24–7.25 (m, 2H), 7.35–7.40 (m, 1H), 7.46–7.50 (m, 2H), 7.80 (d, J = 7.3 Hz, 1H), 8.29 (dd, J = 8.0, 1.2 Hz, 1H). ESI-MS (*m/z*): 412.5 $[M+Na]^+$, 390.5 $[M+H]^+$.

2-(3-(2-Chloro-4-fluorophenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetonitrile (15h): Yield: 58%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 2H), 6.94 (td, J = 8.3, 2.6 Hz, 1H), 7.09 (dd, J = 8.6, 6.0 Hz, 1H), 7.20 (dd, J = 8.5, 2.6 Hz, 1H), 7.33–7.51 (m, 6H), 7.78–7.83 (m, 1H), 8.30 (dd, J = 8.0, 1.6 Hz, 1H). ESI-MS (*m/z*): 428.2 $[M+K]^+$, 412.3 $[M+Na]^+$), 390.3 $[M+H]^+$.

2-(3-(2-Chloro-4-fluorophenyl)-2-(4-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15i): Yield: 71%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 2H), 7.12 (dd, J = 7.6, 1.7 Hz, 1H), 7.23 (td, J = 7.5, 1.3 Hz, 1H), 7.27–7.34 (m, 3H), 7.38–7.42 (m, 2H), 7.43–7.52 (m, 2H), 776–7.82 (m, 1H), 8.30 (dd, J = 8.0, 1.6 Hz, 1H). ESI-MS (*m/z*): 446.3 $[M+Na]^+$.

2-(3-(2-Chloro-4-fluorophenyl)-2-(3-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15j): Yield: 71%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 2H), 6.97 (td, J = 8.3, 2.5 Hz, 1H), 7.10 (dd, J = 8.5, 6.0 Hz, 1H), 7.21 (dd, J = 8.5, 2.5 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 7.49 (t, J = 7.7 Hz, 1H), 7.79 (d, J = 7.3 Hz, 1H), 8.29 (dd, J = 8.0, 1.0 Hz, 1H). ESI-MS *m*/*z*: 446.2 $[M+Na]^+$.

2-(3-(4-Chlorophenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetonitrile (15k): Yield: 65%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.27–7.49 (m, 8H), 7.76–7.81 (m, 1H), 8.29 (dd, J = 8.0, 1.6 Hz, 1H). ESI-MS (*m/z*): 394.3 $[M+Na]^+$, 372.4 $[M+H]^+$.

2-(2,3-Bis(4-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15l): Yield: 71%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 2H), 7.13–7.18 (m, 2H), 7.32 (d, J = 8.9 Hz, 4H), 7.36–7.40 (m, 2H), 7.47 (t, J = 7.7 Hz, 1H), 7.75–7.79 (m, 1H), 8.29 (dd, J = 8.0, 1.5 Hz, 1H). ESI-MS *m*/*z*: 444.6 $[M+K]^+$, 428.6 $[M+Na]^+$.

2-(2-(3-Chlorophenyl)-3-(4-chlorophenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15m): Yield: 67%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.21–7.25 (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.38 (dt, J = 7.0, 2.1 Hz, 1H), 7.52–7.46 (m, 2H), 7.80 (d, J = 7.4 Hz, 1H), 8.29 (dd, J = 8.0, 1.1 Hz, 1H). ESI-MS (*m/z*): 428.4 $[M+Na]^+$, 406.5 $[M+H]^+$.

2-(2,3-Bis(4-methoxyphenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15n): Yield: 74%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 6H), 4.01 (s, 2H), 6.82 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 7.39–7.45 (m, 3H), 7.74 (d, J = 7.3 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H). ESI-MS (*m/z*): 436.3 $[M+K]^+$), 420.3 $[M+Na]^+$, 398.4 $[M+H]^+$.

2-(2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-4-oxo-4H-chromen-8-yl)acetonitrile (15o): Yield: 67%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 4.00 (s, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.7 Hz, 3H), 7.18 (d, J = 7.6 Hz, 3H), 7.43 (t, J = 7.6 Hz, 1H), 7.72 (d, J = 7.3 Hz, 1H), 8.29 (d, J = 7.9 Hz, 1H). ESI-MS (*m/z*): 450.3 $[M+Na]^+$, 428.4

$[M+H]^+$.

2-(3-(4-Methoxyphenyl)-4-oxo-2-phenyl-4H-chromen-8-yl)acetonitrile (15p): Yield: 64%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.01 (s, 2H), 6.82–6.88 (m, 2H), 7.11–7.17 (m, 2H), 7.28–7.40 (m, 3H), 7.43–7.47 (m, 3H), 7.74–7.80 (m, 1H), 8.30 (dd, *J* = 8.0, 1.6 Hz, 1H). ESI-MS (*m/z*): 406.8 $[M+K]^+$), 390.8 $[M+Na]^+$, 368.8 $[M+H]^+$.

2-(3-(3,4-Dimethoxyphenyl)-4-oxo-2-phenyl-4H-chromen-8-yl) acetonitrile (15q): Yield: 52%. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.57 (s, 3H), 3.73 (s, 3H), 3.99 (s, 2H), 6.65–6.71 (m, 1H), 6.78 (d, *J* = 1.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 7.34–7.37 (m, , 2H), 7.39–7.44 (m, 4H),7.77 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H). ESI-MS (*m/z*): 420.1 ($[M+Na]^+$), 398.1 $[M+H]^+$.

2-(3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-oxo-4H-chromen-8-yl) acetonitrile (15r): Yield: 54%. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 3.62 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 4.00 (s, 2H), 6.82 (s, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 3H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H). ESI-MS (*m/z*): 450.6 $[M+Na]^+$, 428.5 $[M+H]^+$.

Table 1. Indirect cytotoxicities and selectivity of compounds **9a-r** toward A549 cells

Compound	R^1	R^2	Inhibitor (%) at 50 μM	IC_{50}(μM) [a]	PR[b]
			48.4	84.2 ± 13.5	1.0
9a[c]	H	H	13.1	ND [d]	\
9b	2-Cl	H	30.7	ND [d]	\
9c	2-Cl	4-Cl	19.5	ND [d]	\
9d	2-Cl	3-Cl	31.1	ND [d]	\
9e	4-F	H	47.5	92.6 ± 7.8	0.9
9f	4-F	4-Cl	36.9	ND[d]	\
9g	4-F	3-Cl	13.9	ND [d]	\
9h	2-Cl,4-F	H	32.9	ND [d]	\
9i	2-Cl,4-F	4-Cl	49.5	86.0 ± 10.3	1.0
9j	2-Cl,4-F	3-Cl	21.8	ND[d]	\
9k	4-Cl	H	37.1	ND [d]	\
9l	4-Cl	4-Cl	31.0	ND [d]	\
9m	4-Cl	3-Cl	36.3	ND [d]	\
9n	4-MeO	4-MeO	53.7	61.7 ± 12.2	1.4
9o	4-MeO	3,4-diMeO	53.0	67.4 ± 12.6	1.2
9p	4-MeO	H	62.9	38.5 ± 7.3	2.2
9q	3,4-diMeO	H	57.0	44.5 ± 7.7	1.9
9r	3,4-diMeO	4-MeO	66.2	35.7 ± 7.6	2.4

[a] The IC_{50} value represents the concentration of each compound resulting in 50% inhibition in cell growth after 24 h incubation, and was the mean values of three repeated experiments.

[b] PR denote the potency ratios (PR) relative to DMXAA.

[c] Compound **9a** has been previously reported [1]

[d] ND = not determined.

[1] G. Atassi, P. Briet, J.J. Berthelon, F. Collonges, Synthesis and antitumor activity of some 8-substituted-4-oxo-4H-1-benzopyrans, Eur. J. Med. Chem., 20 (1985) 393-402.

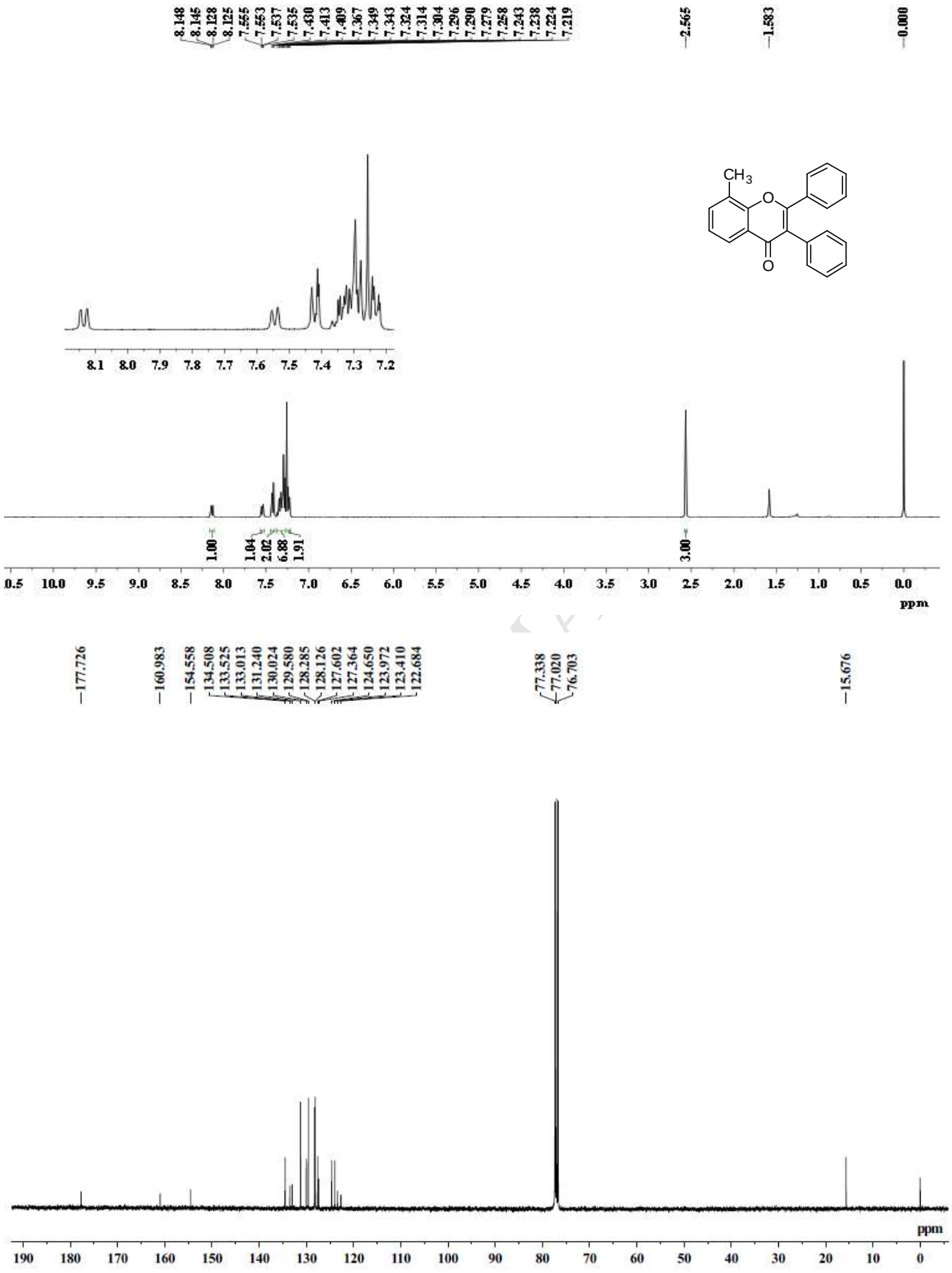


Figure S1. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13a**

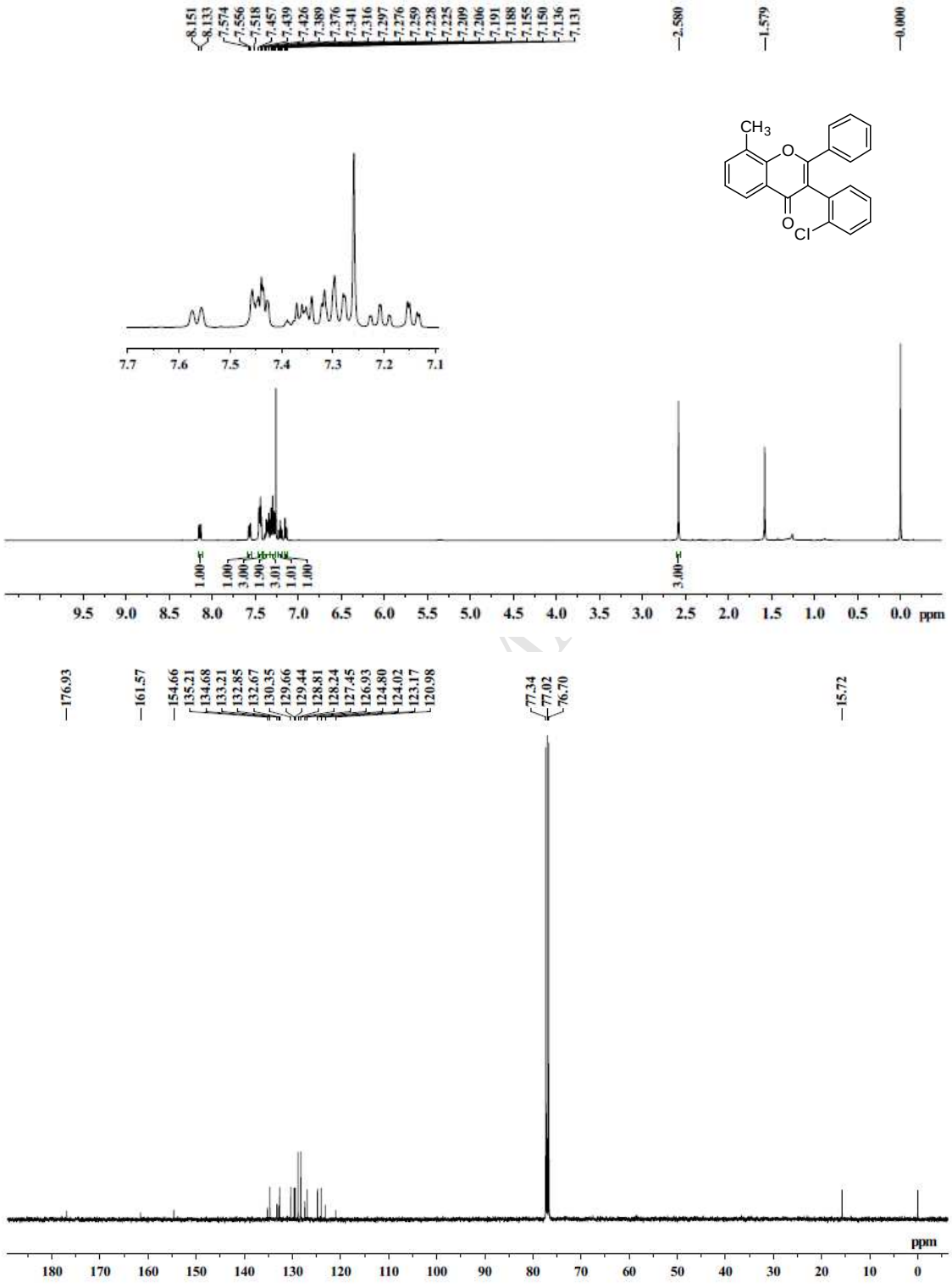


Figure S2. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13b**

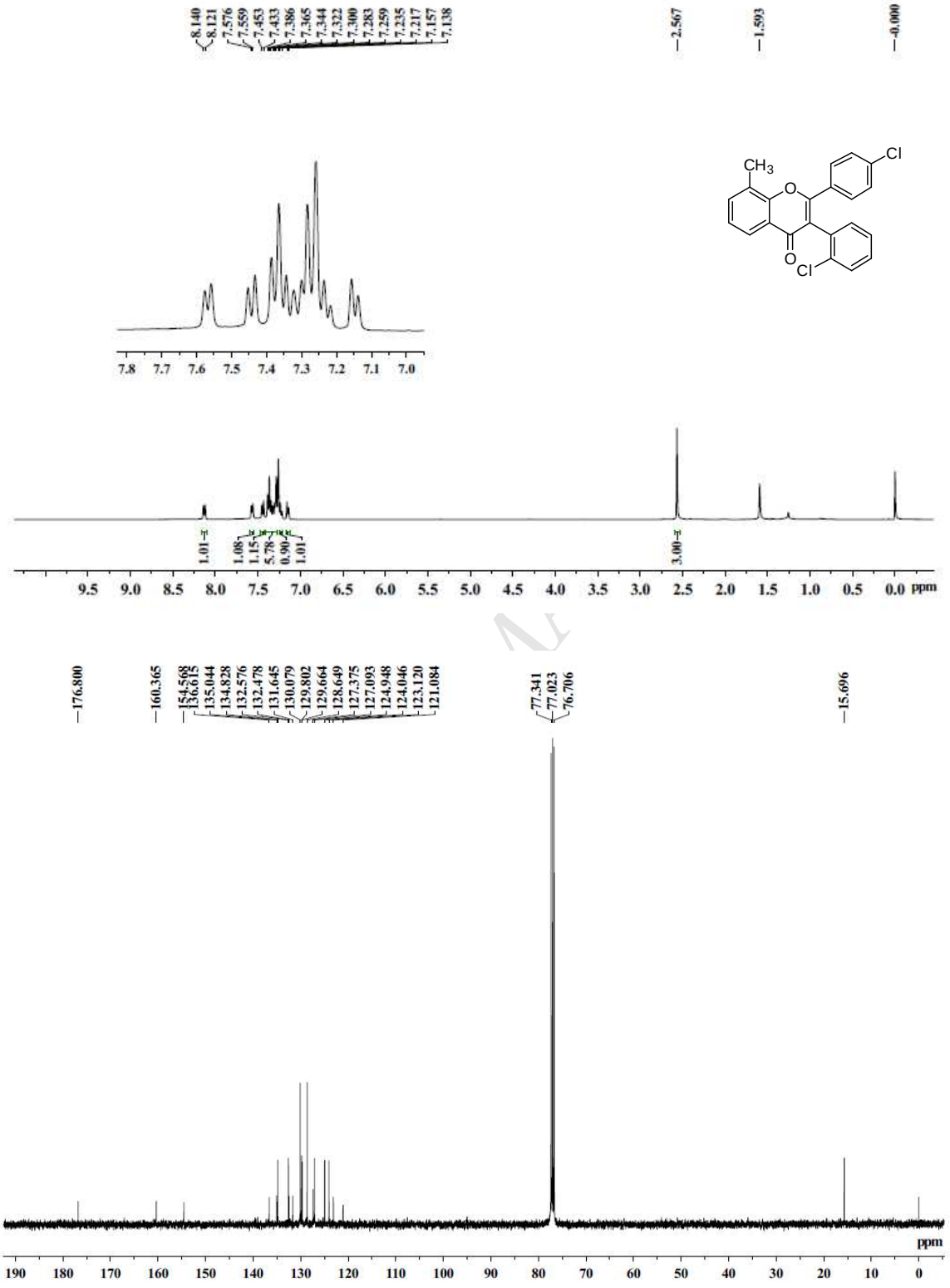


Figure S3. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13c**

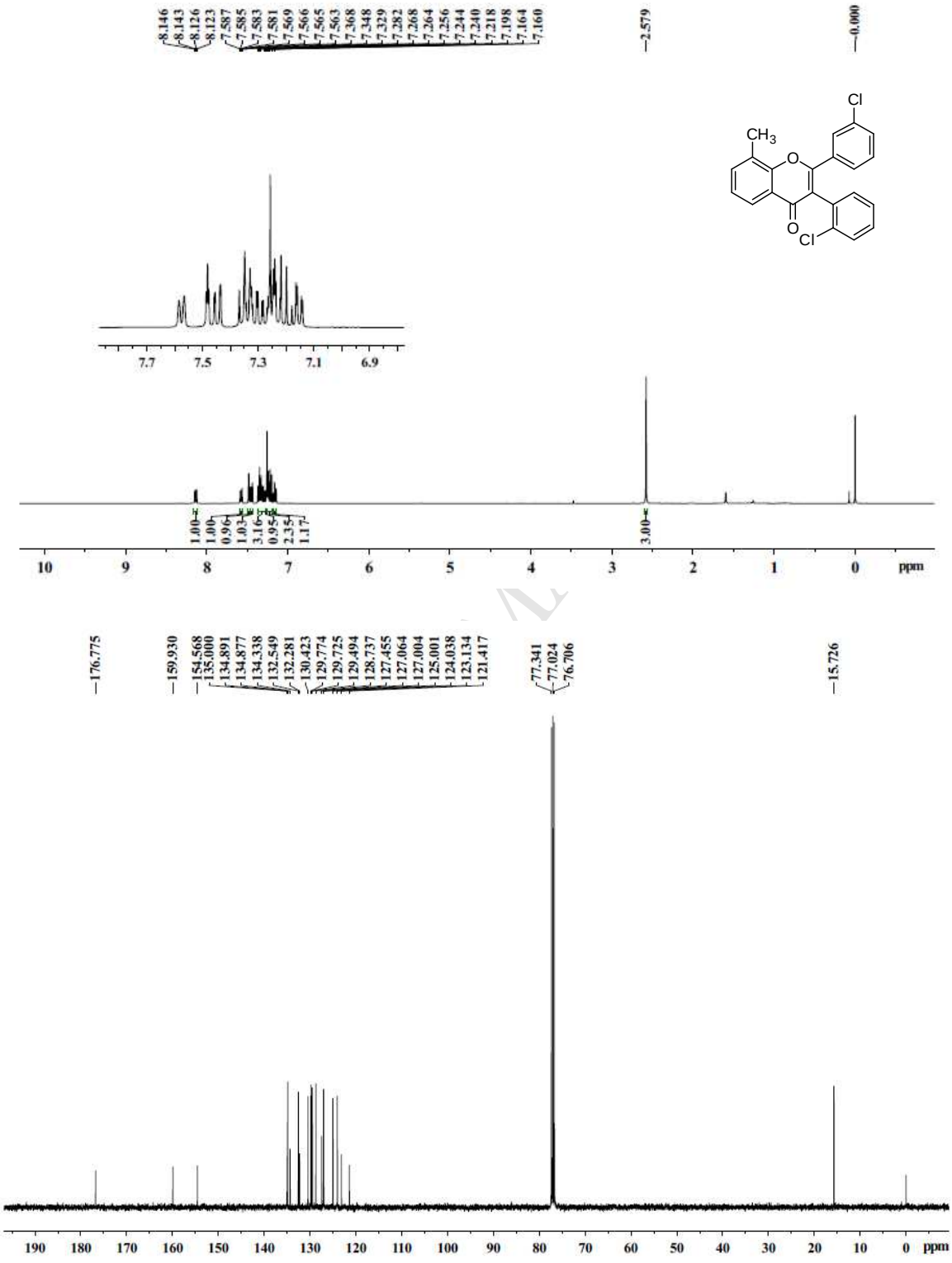


Figure S4. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13d**

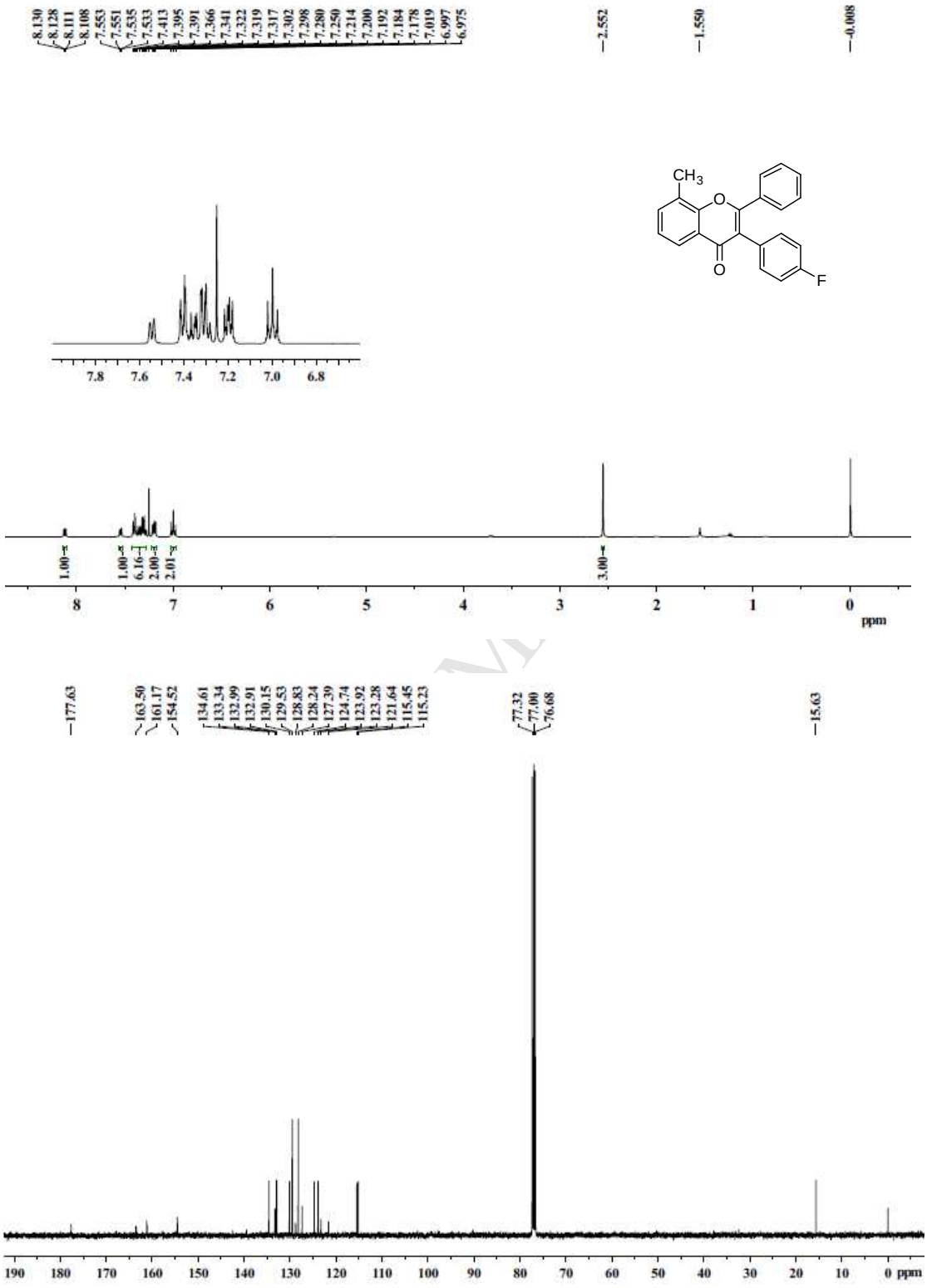


Figure S5. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13e**

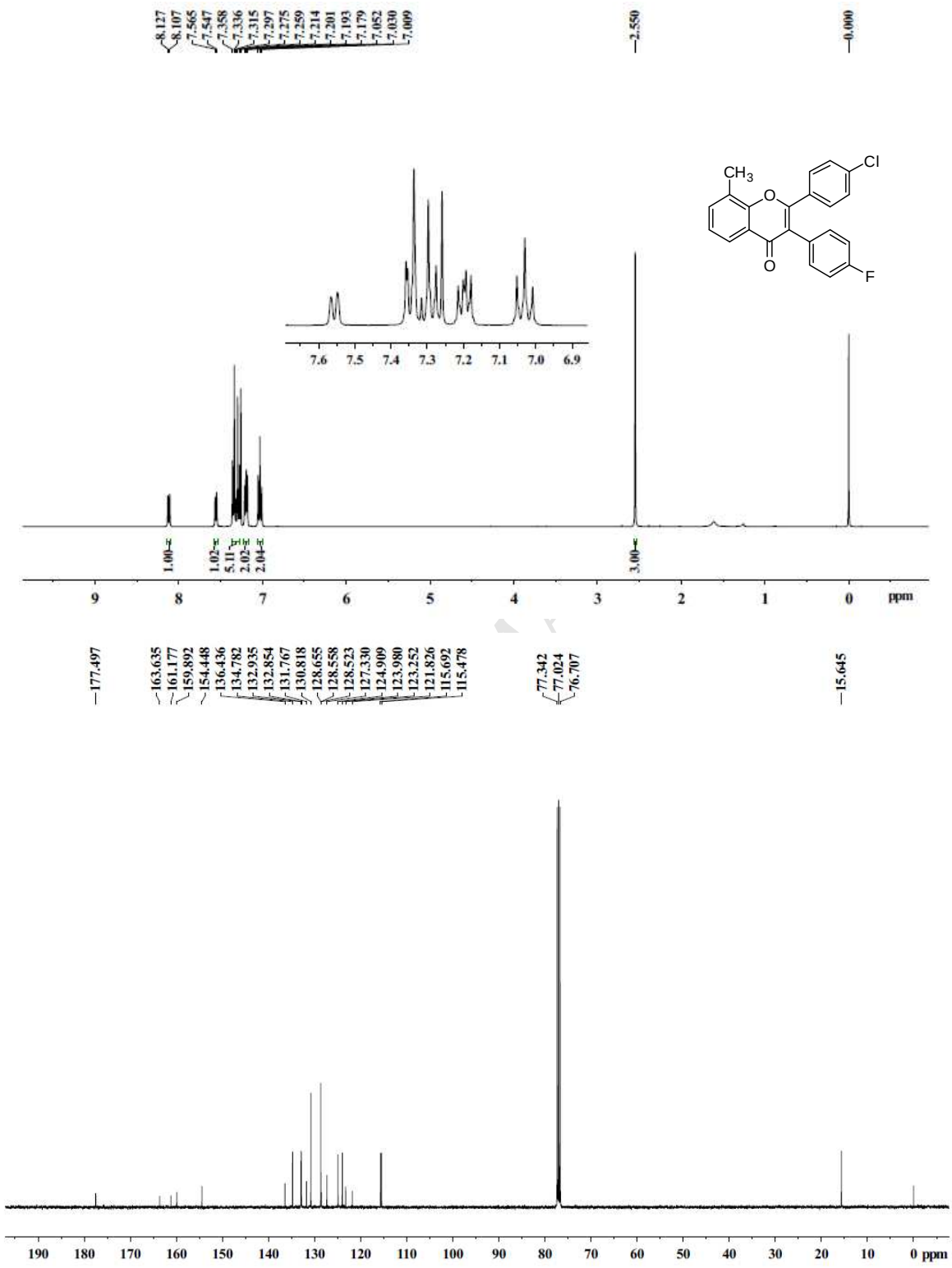


Figure S6. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13f**

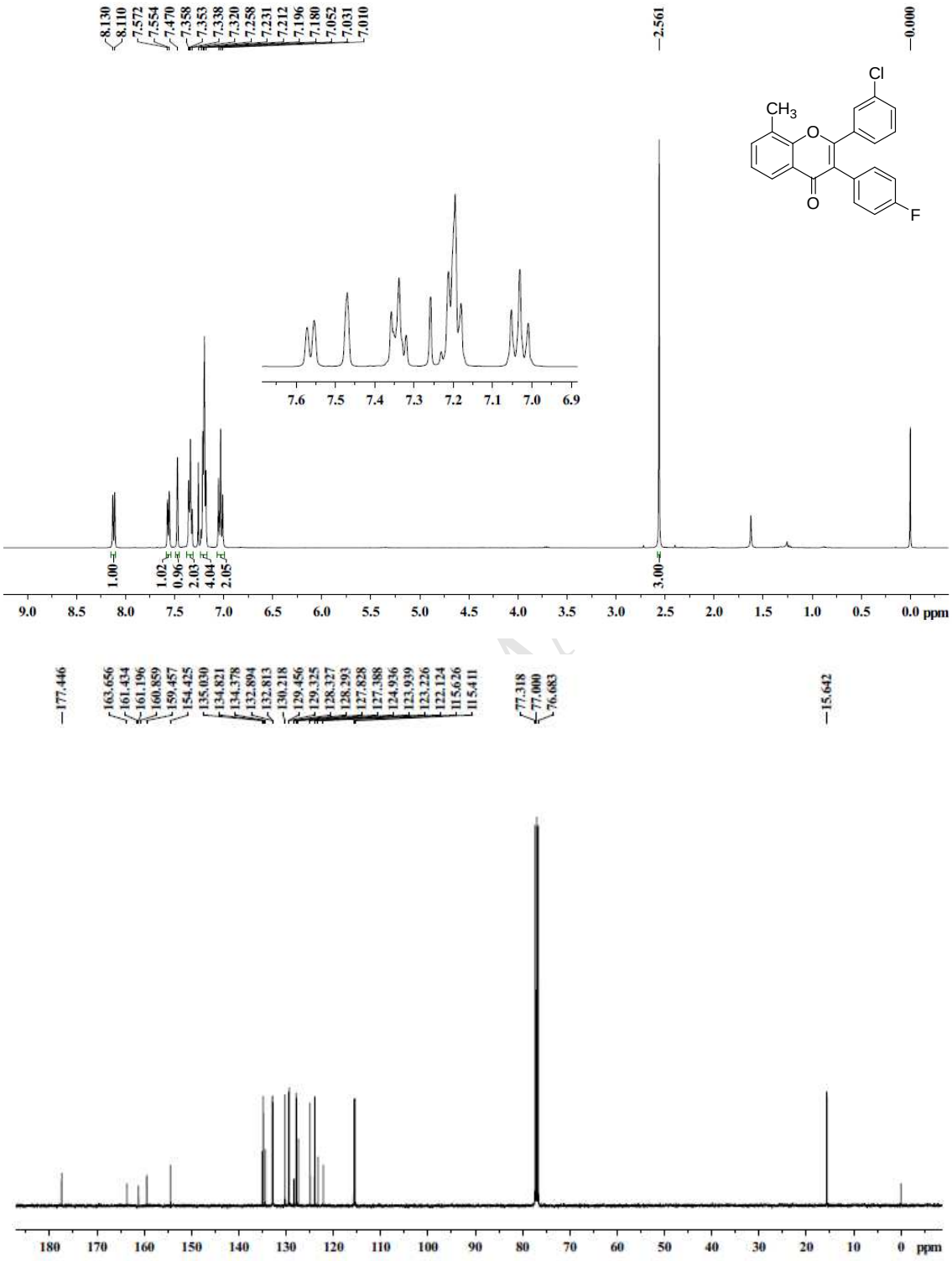


Figure S7. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13g**

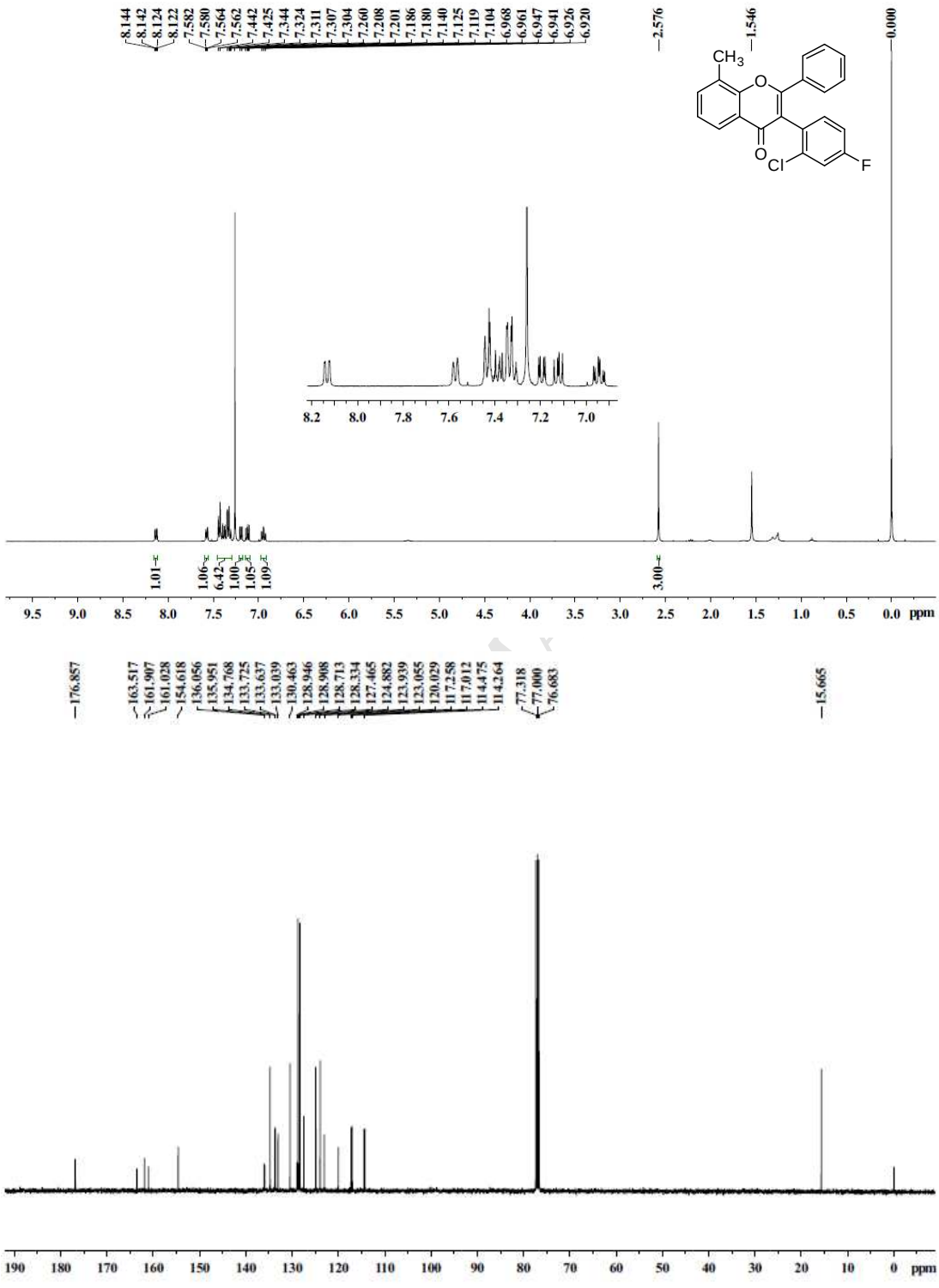


Figure S8. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound 13**h**

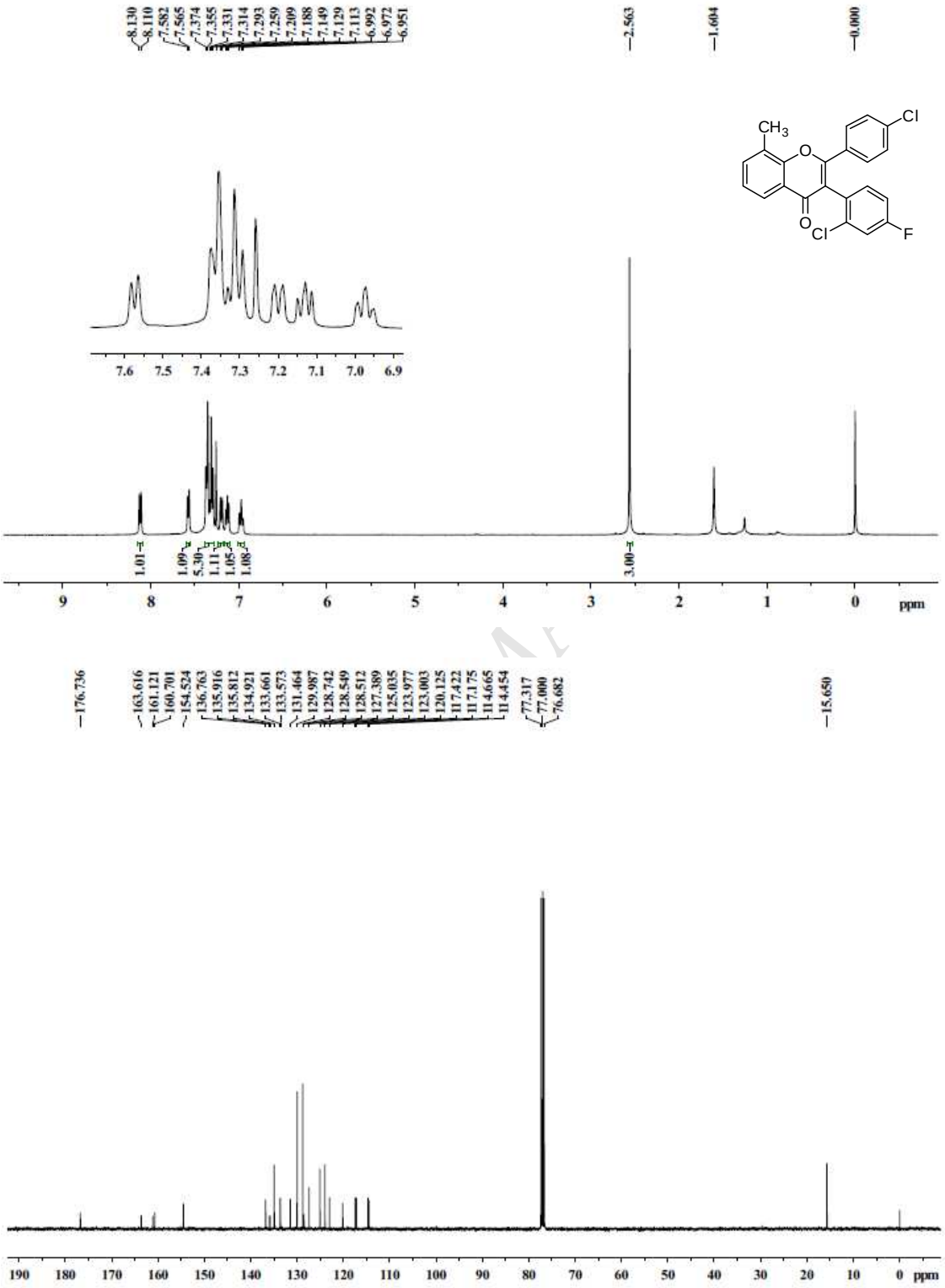


Figure S9. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13i**

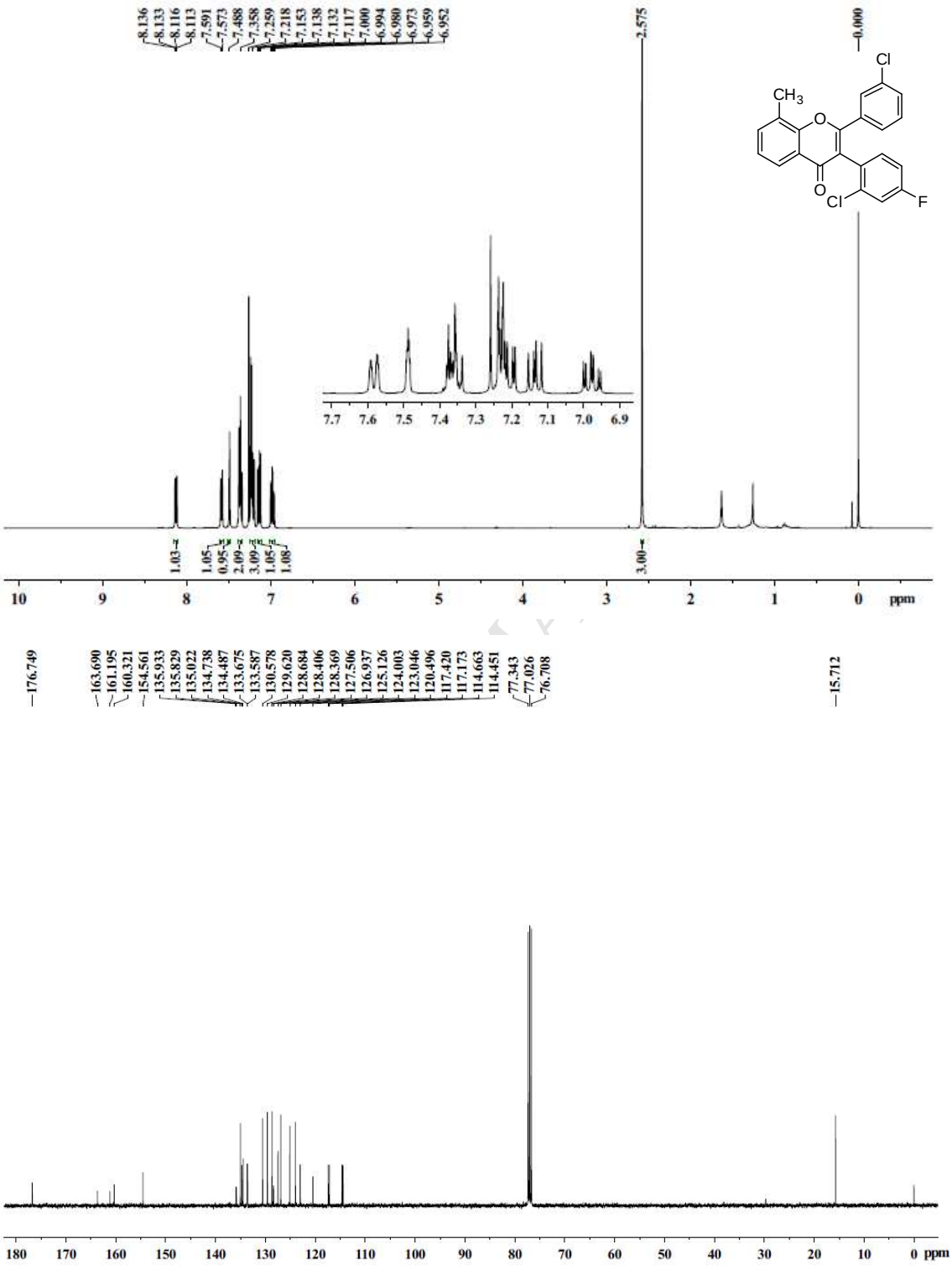


Figure S10. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz)spectra of compound **13j**

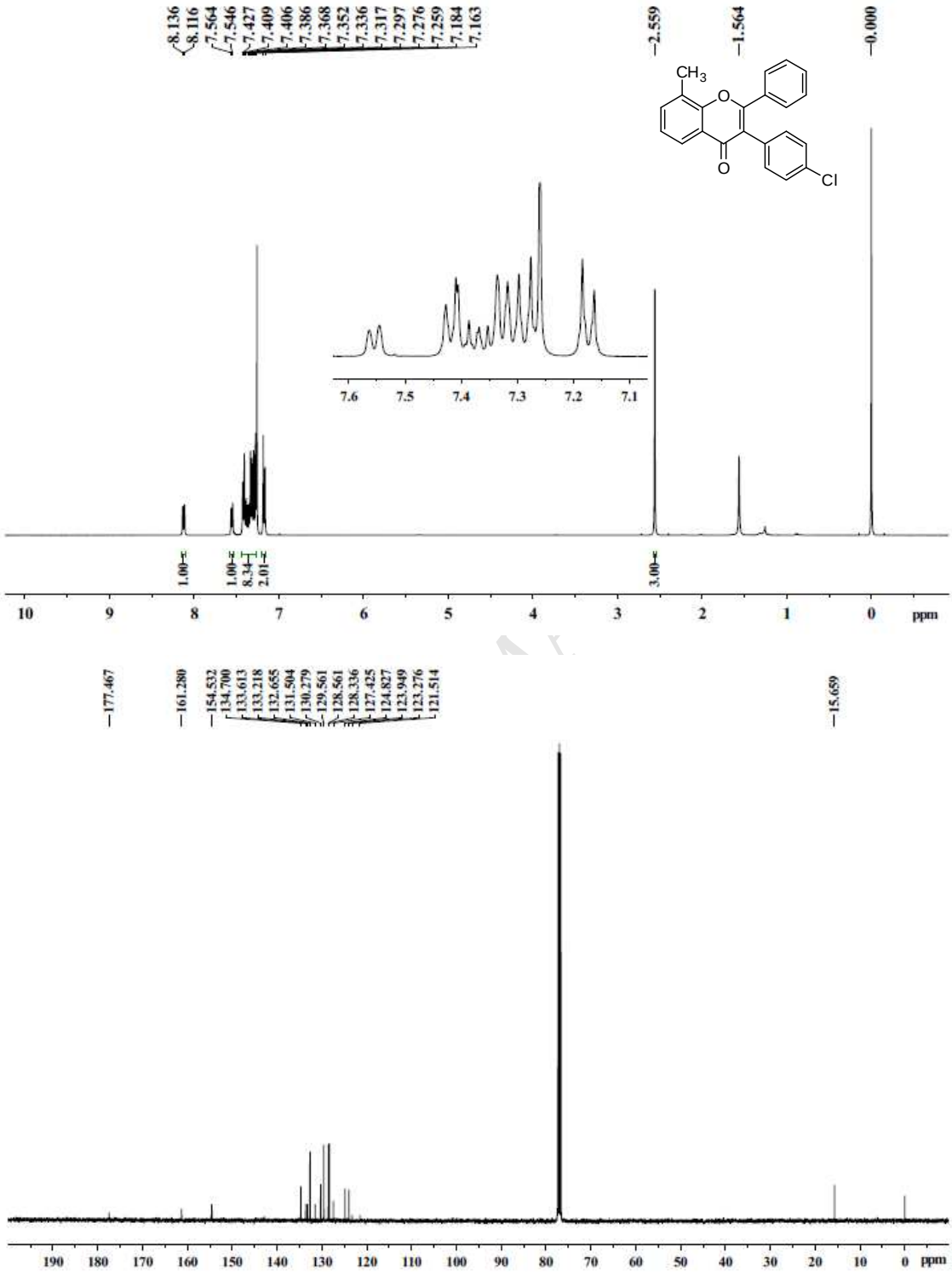


Figure S11. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13k**

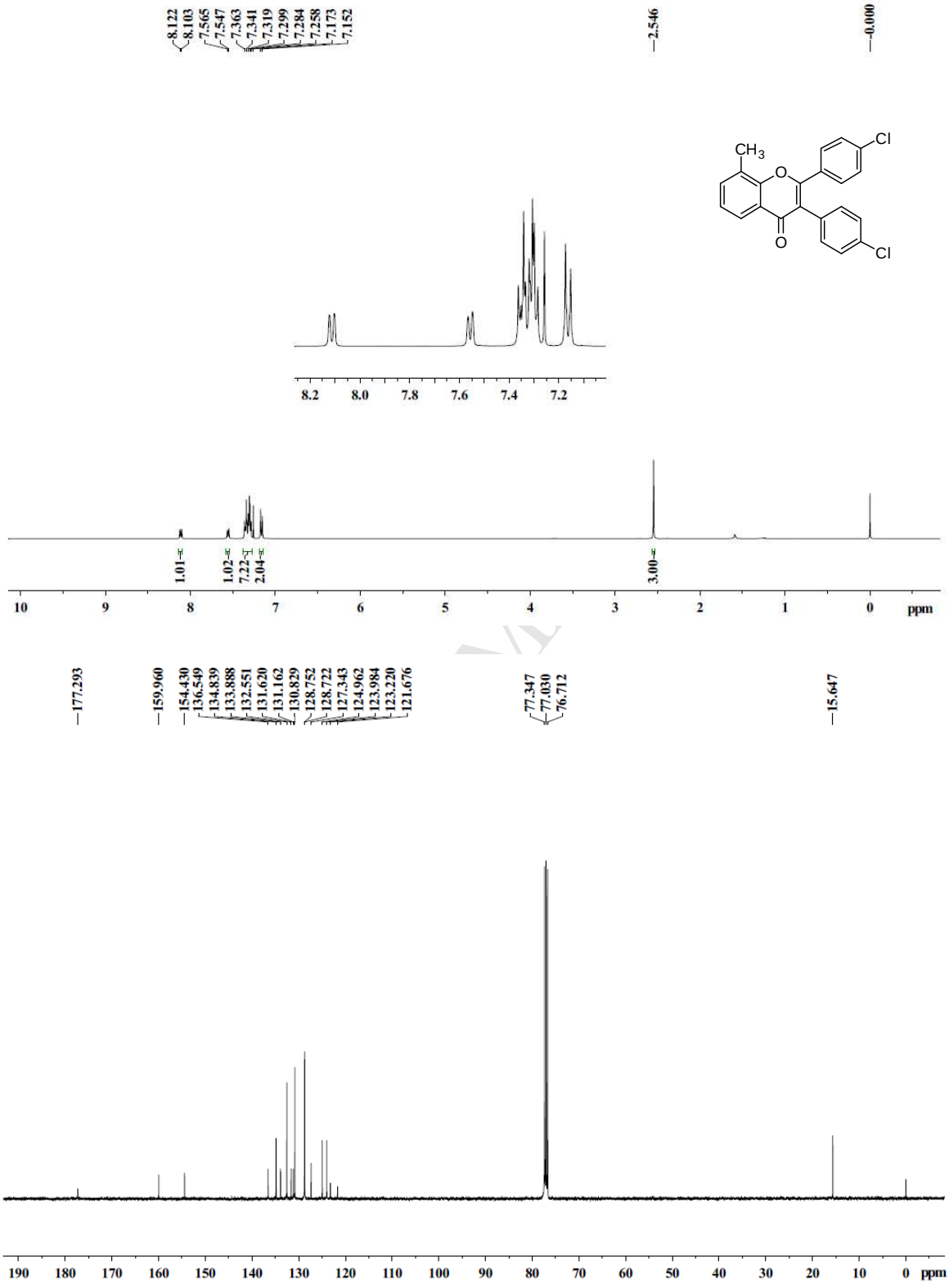


Figure S12. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13l**

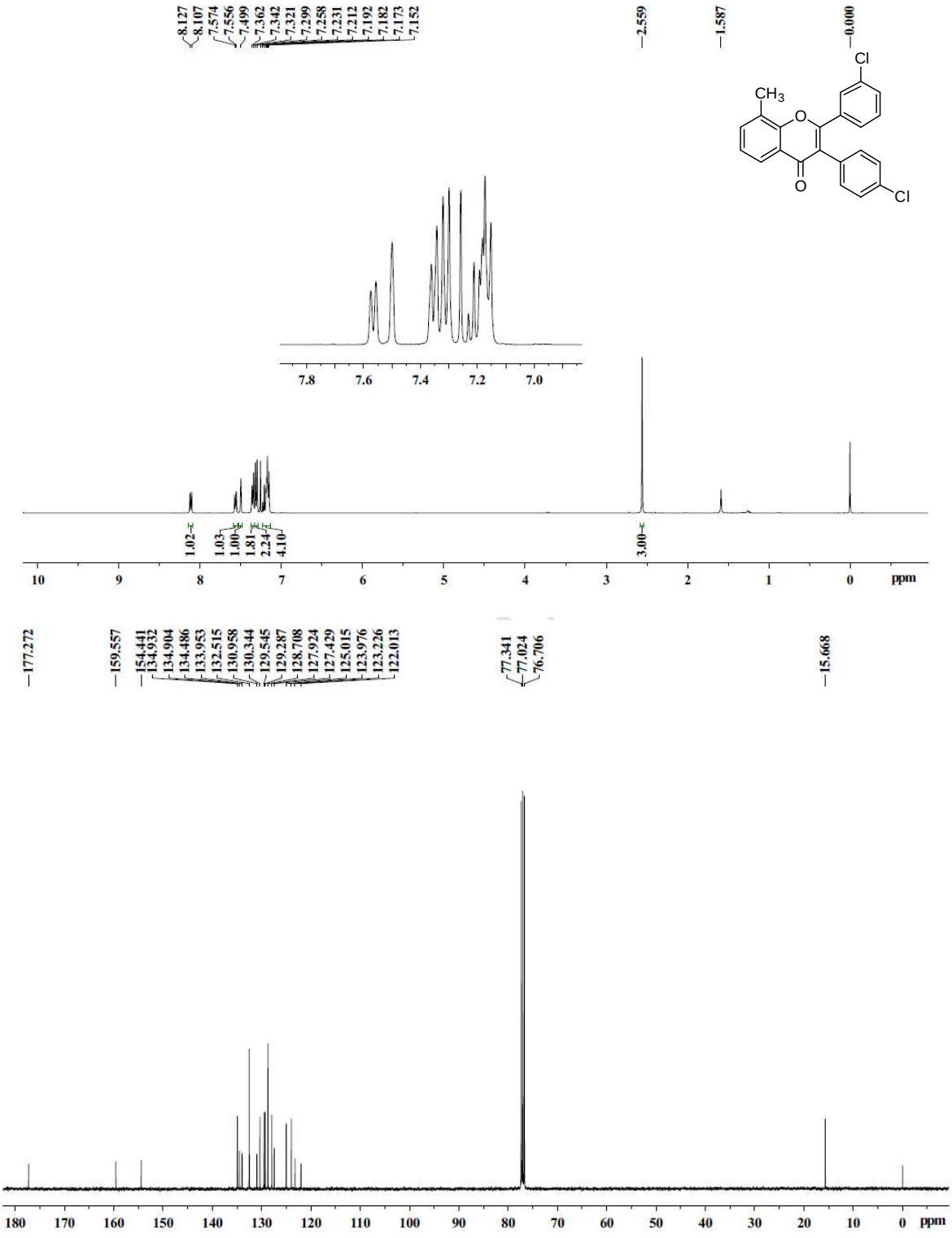


Figure S13. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13m**

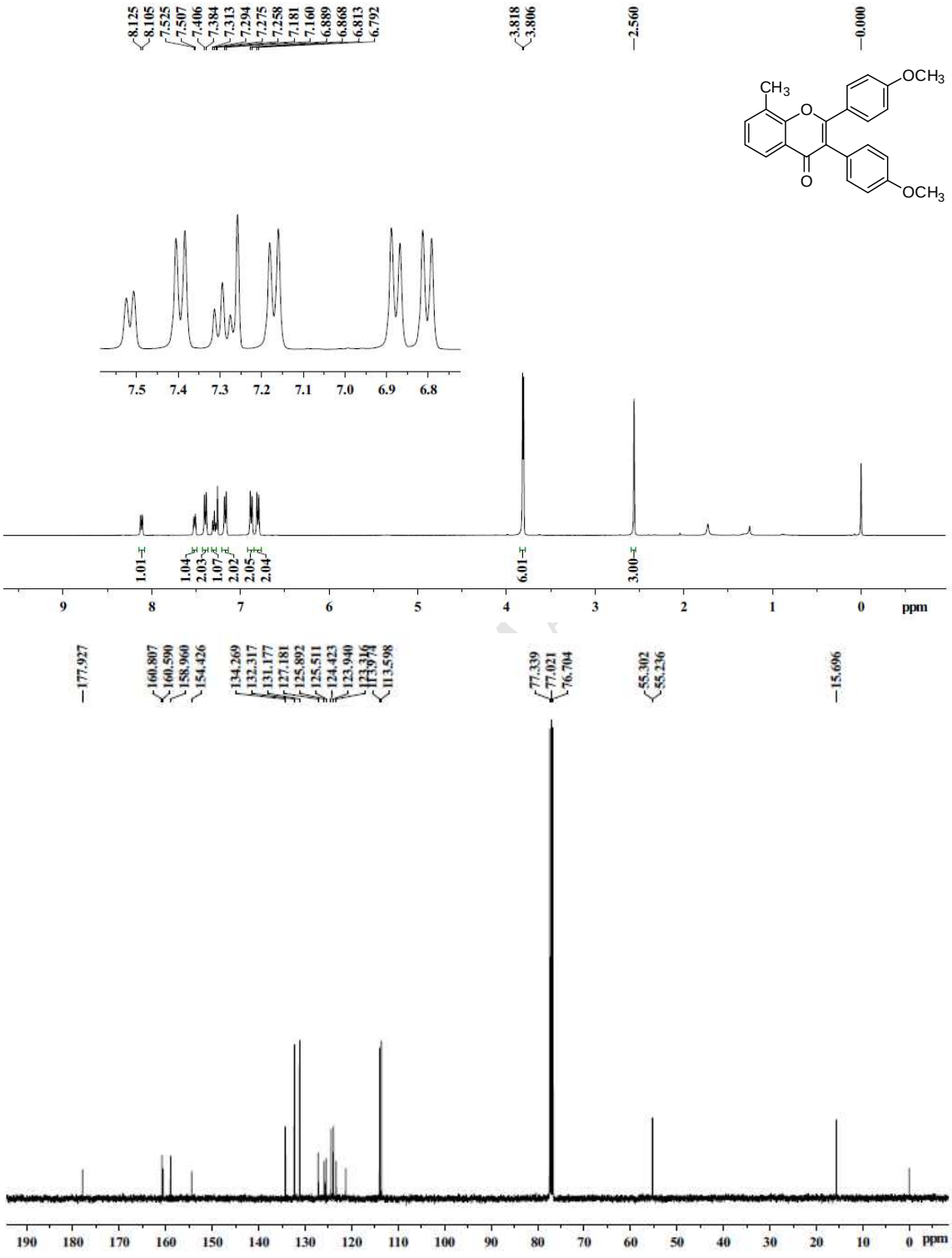


Figure S14. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13n**

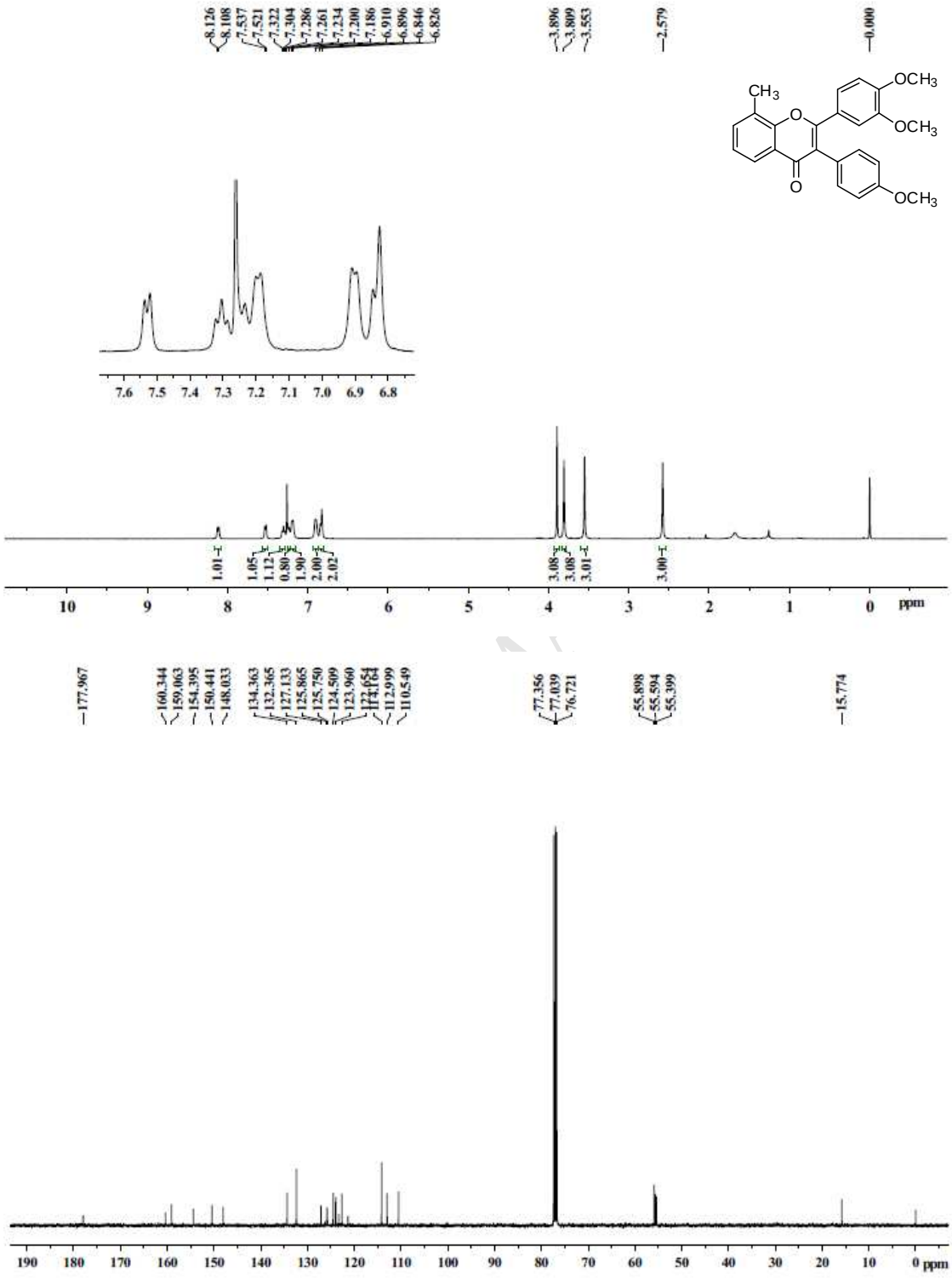


Figure S15. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13o**

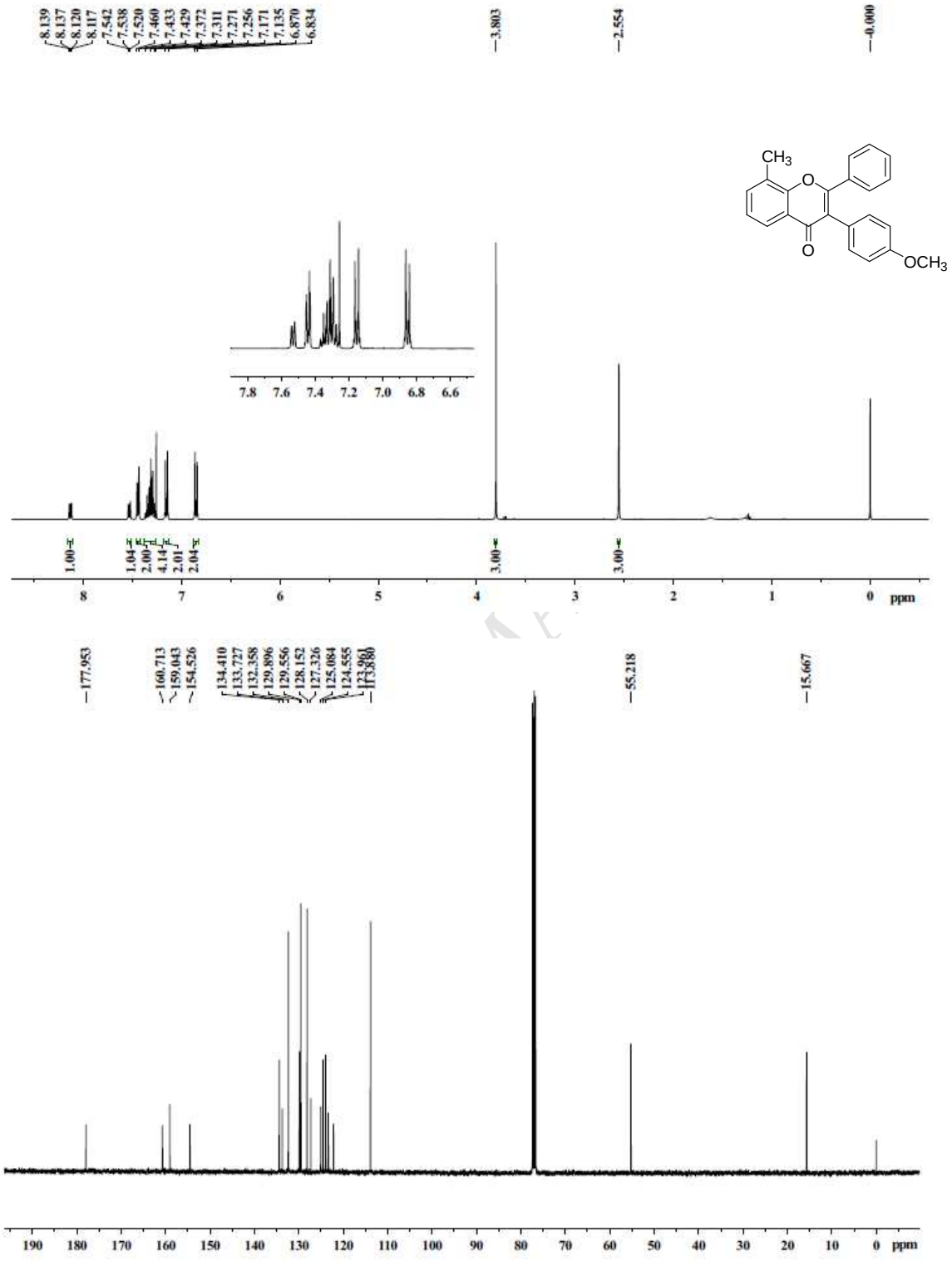


Figure S16. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13p**

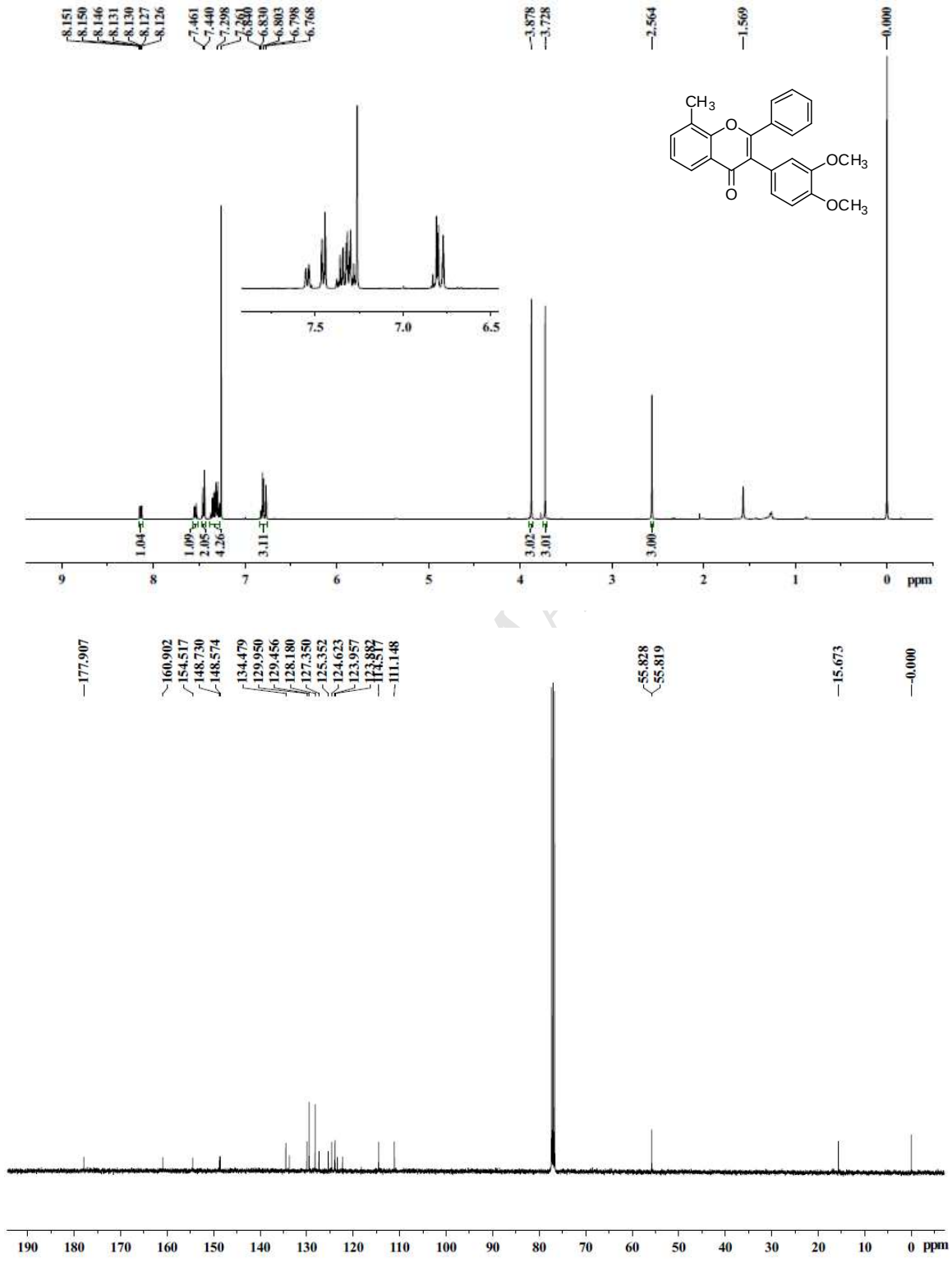


Figure S17. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13q**

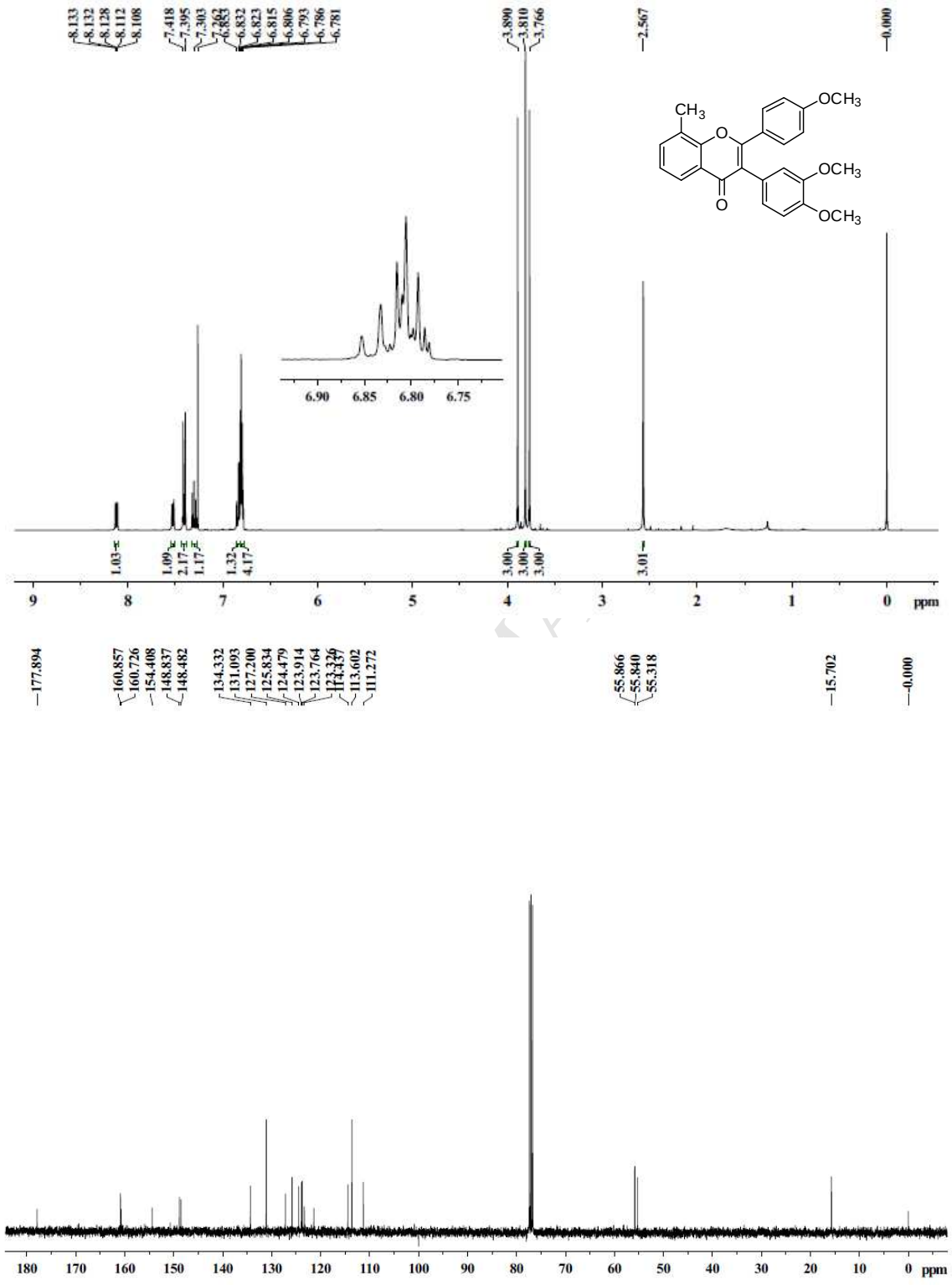


Figure S18. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz) spectra of compound **13r**

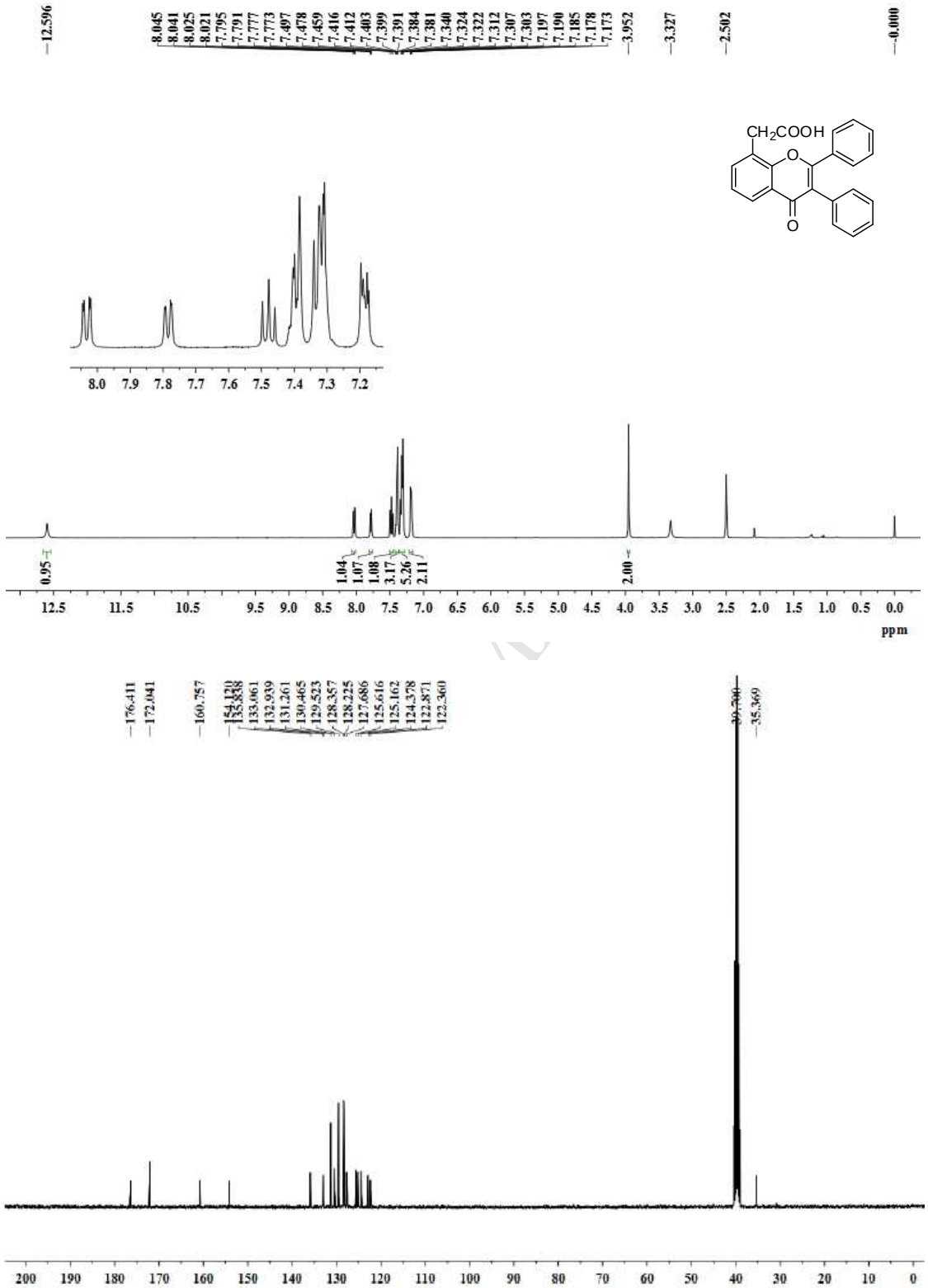


Figure S19. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9a**

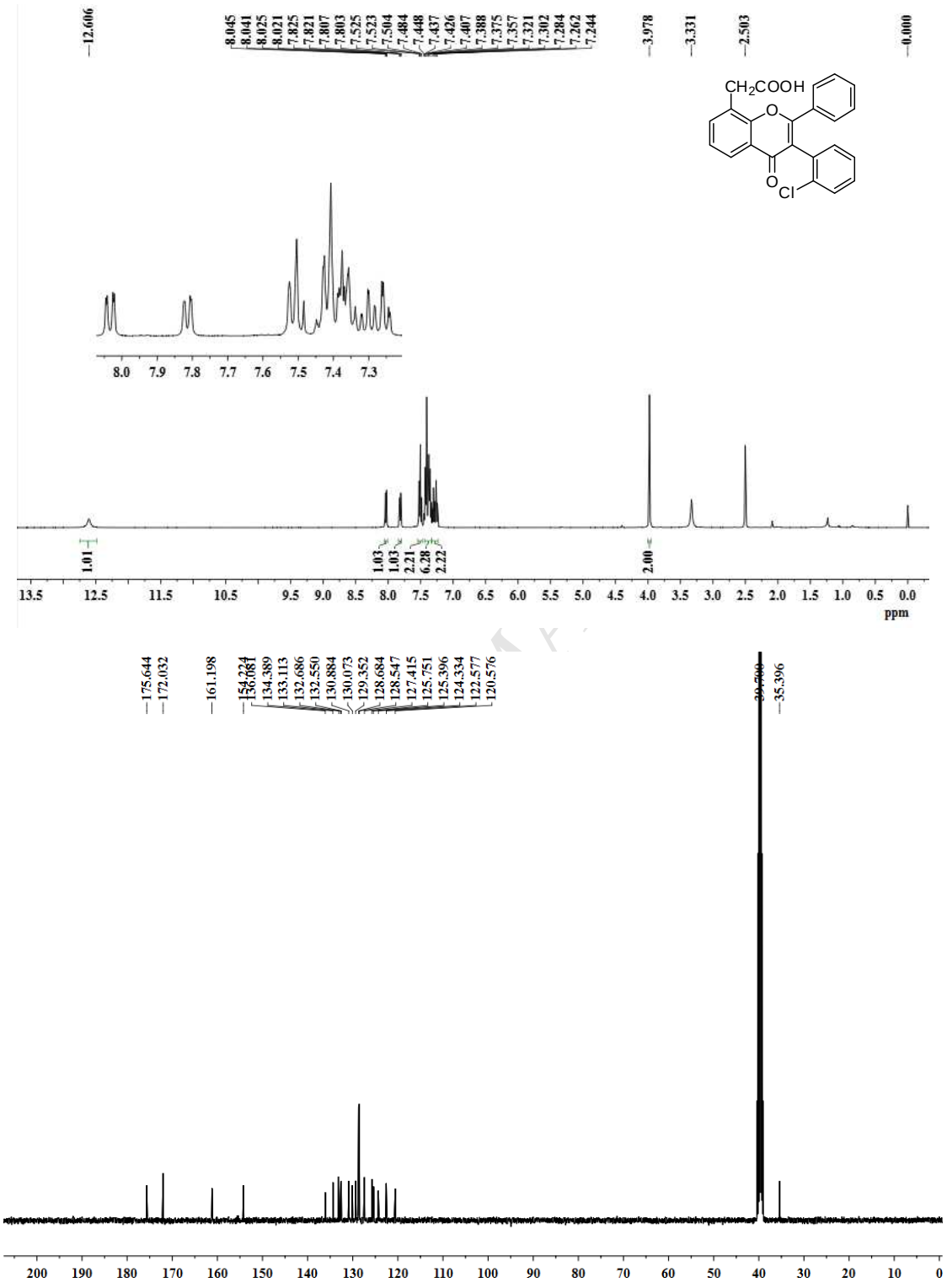


Figure S20. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9b**

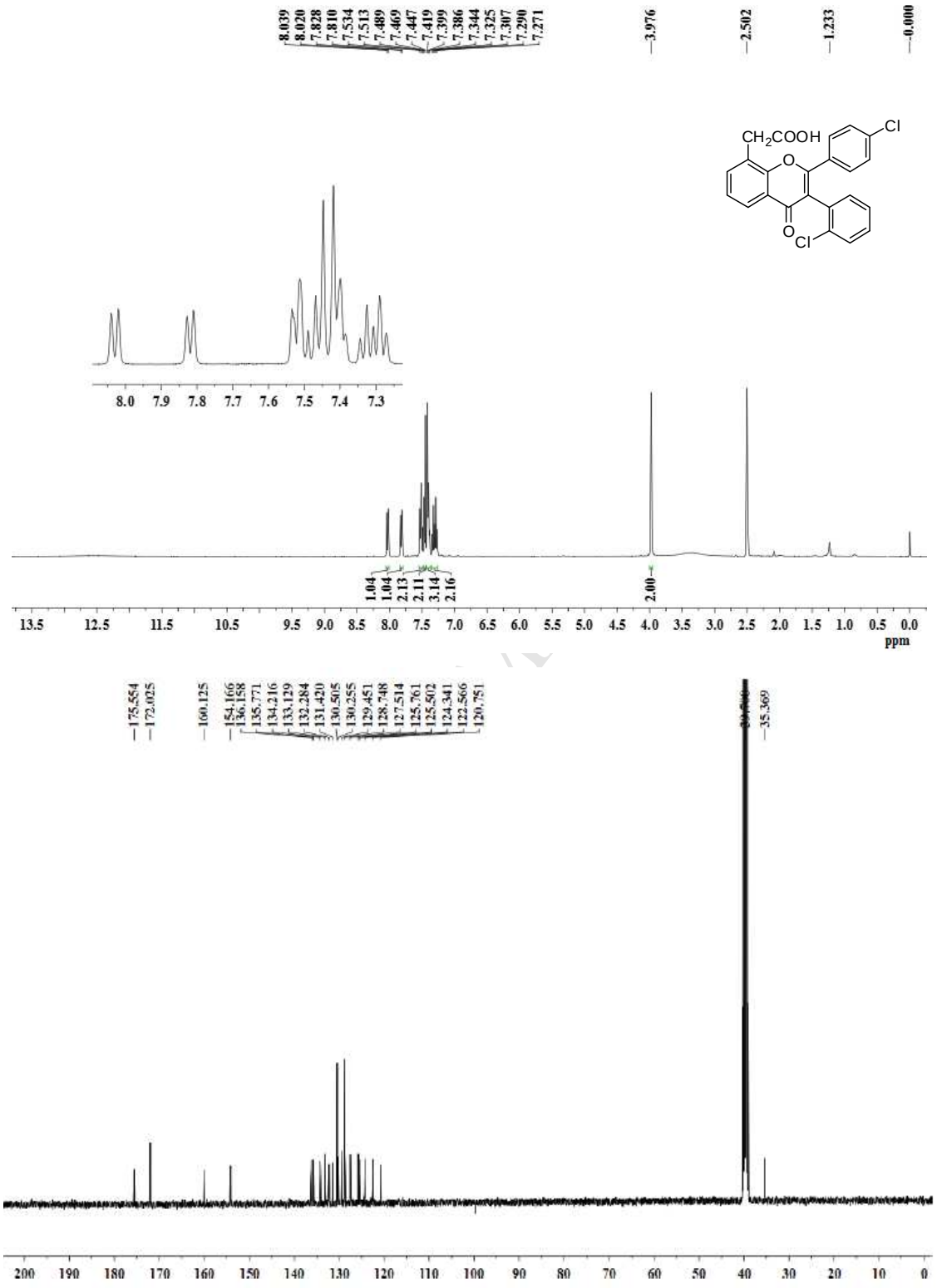


Figure S21. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9c**

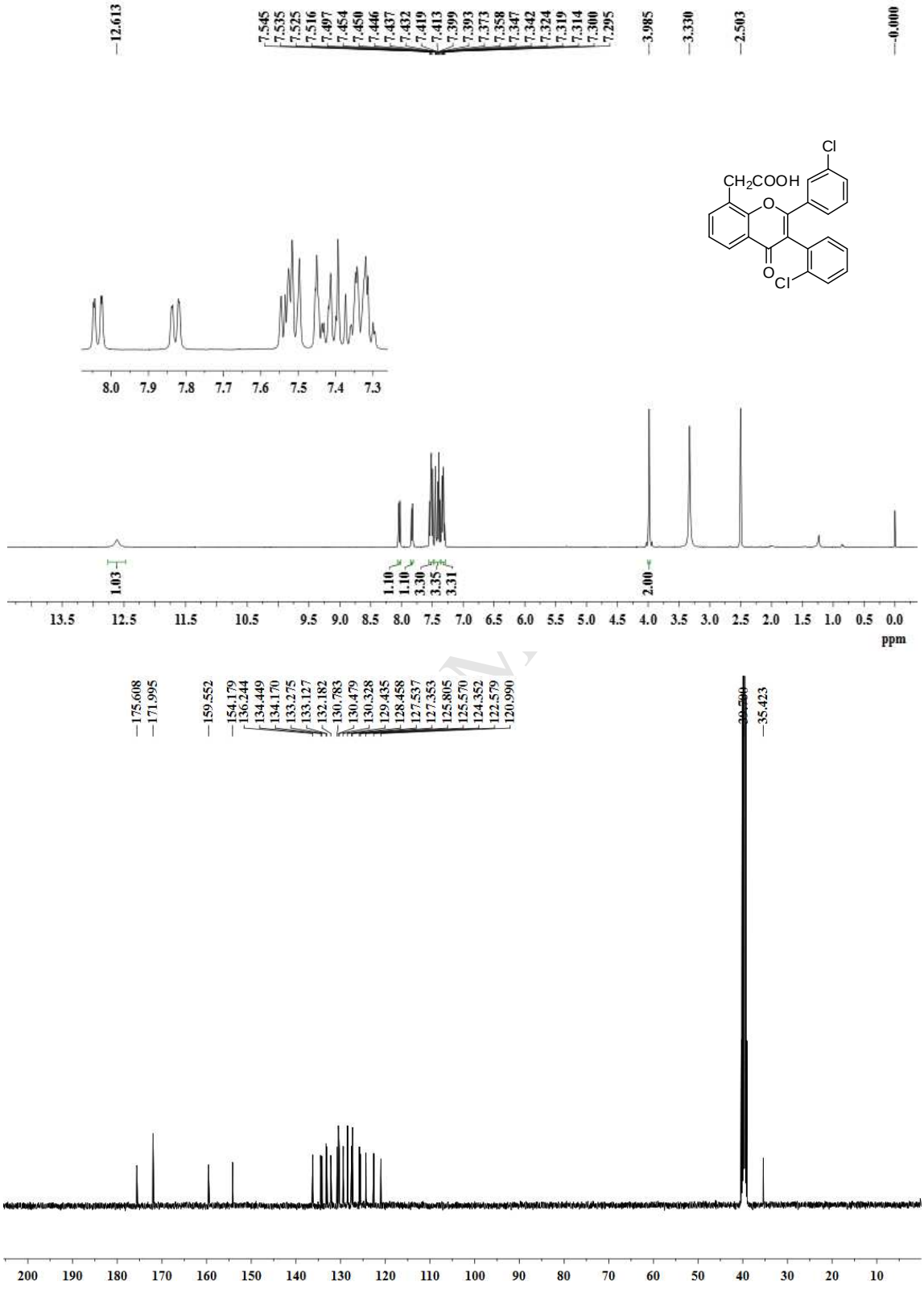


Figure S22. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9d**

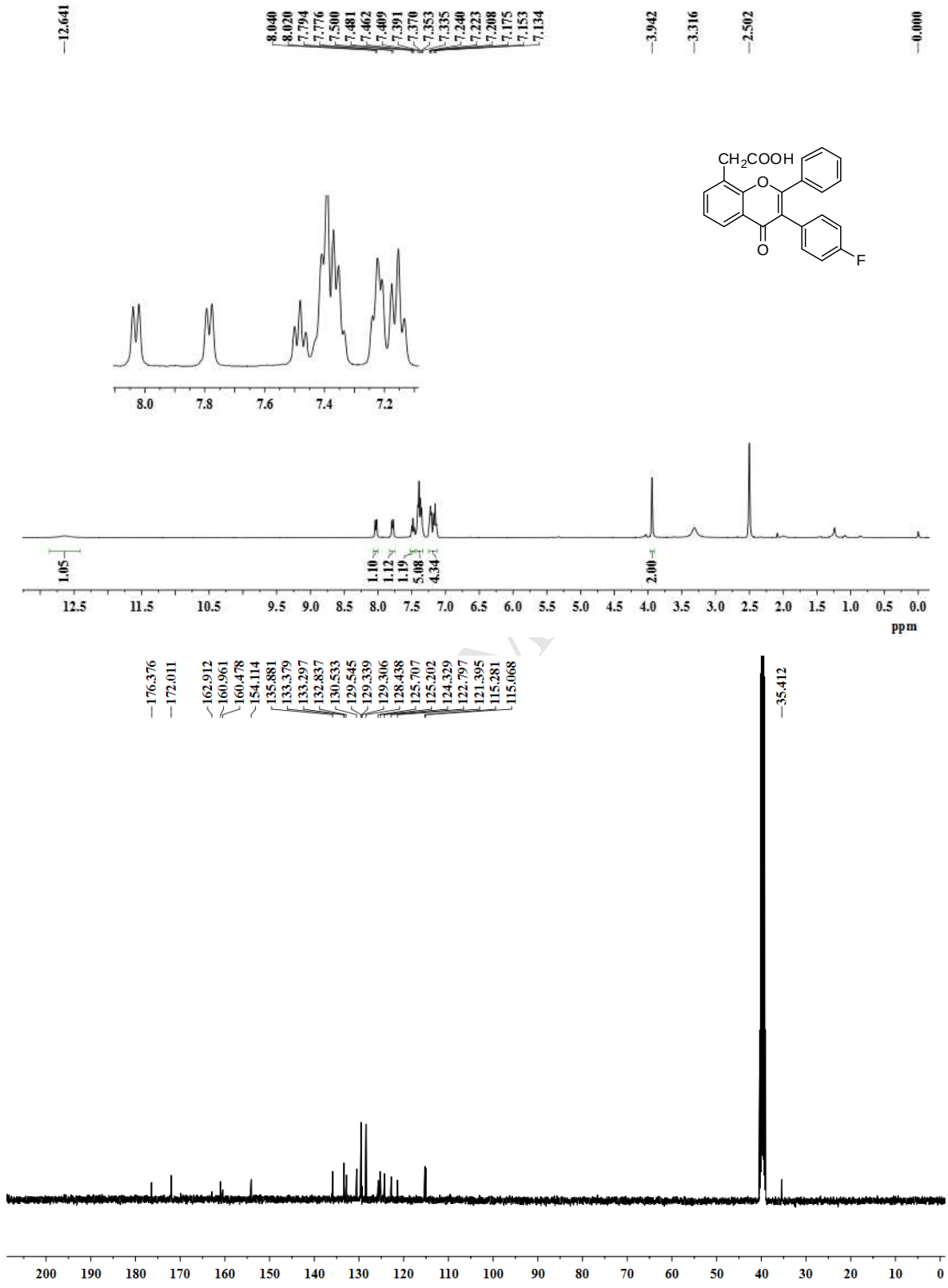


Figure S23. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9e**

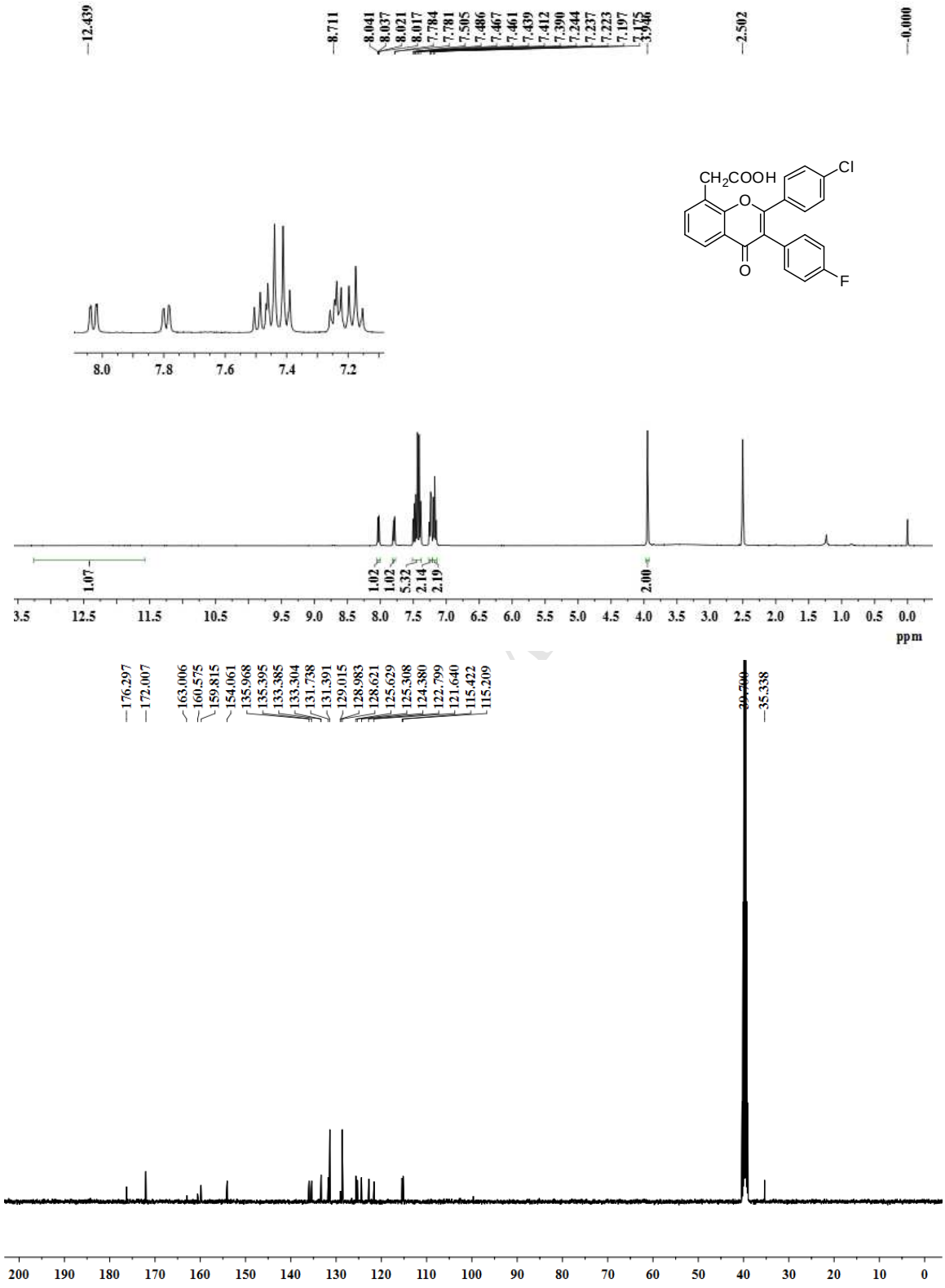


Figure S24. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9f**

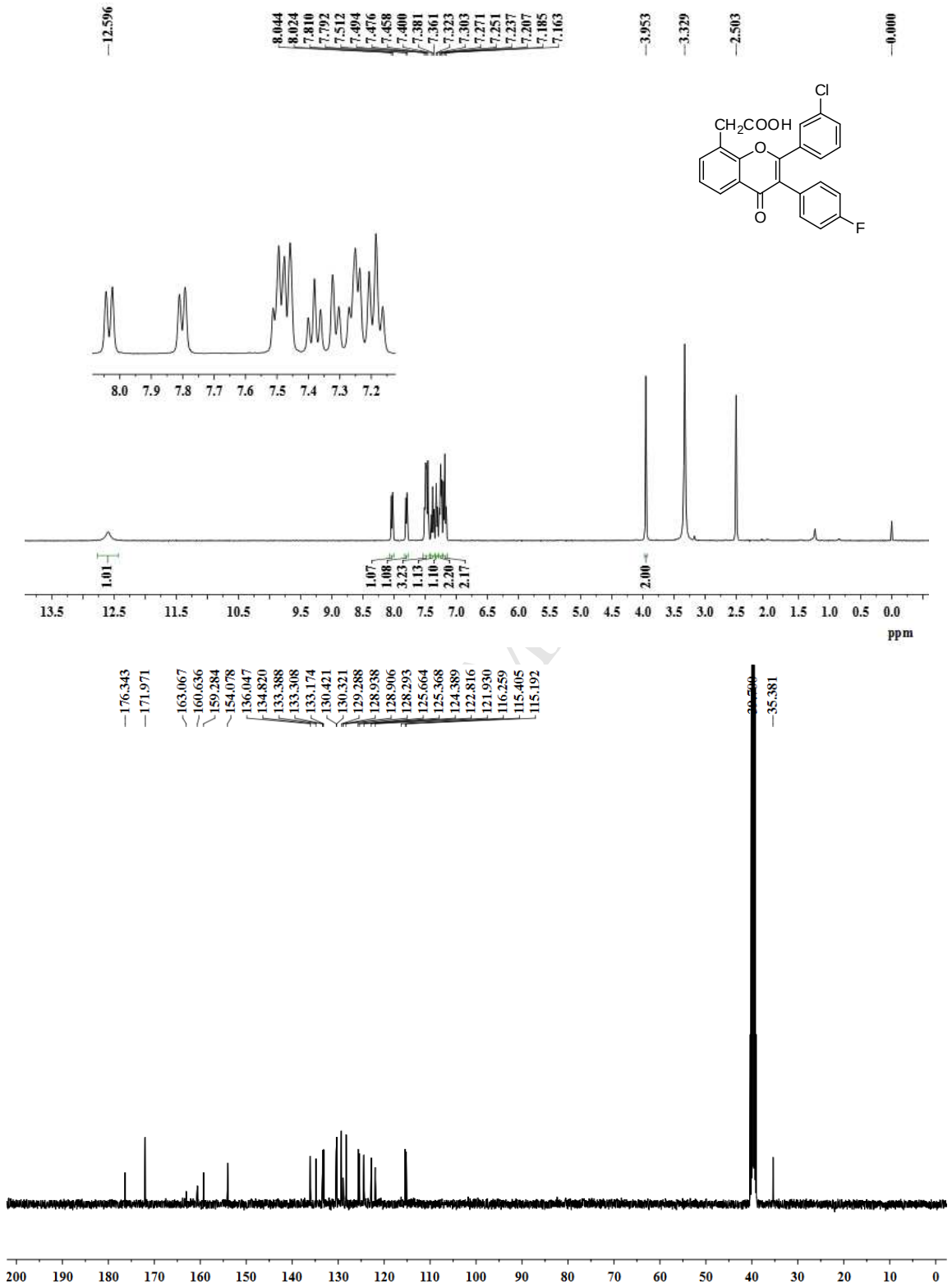


Figure S25. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9g**

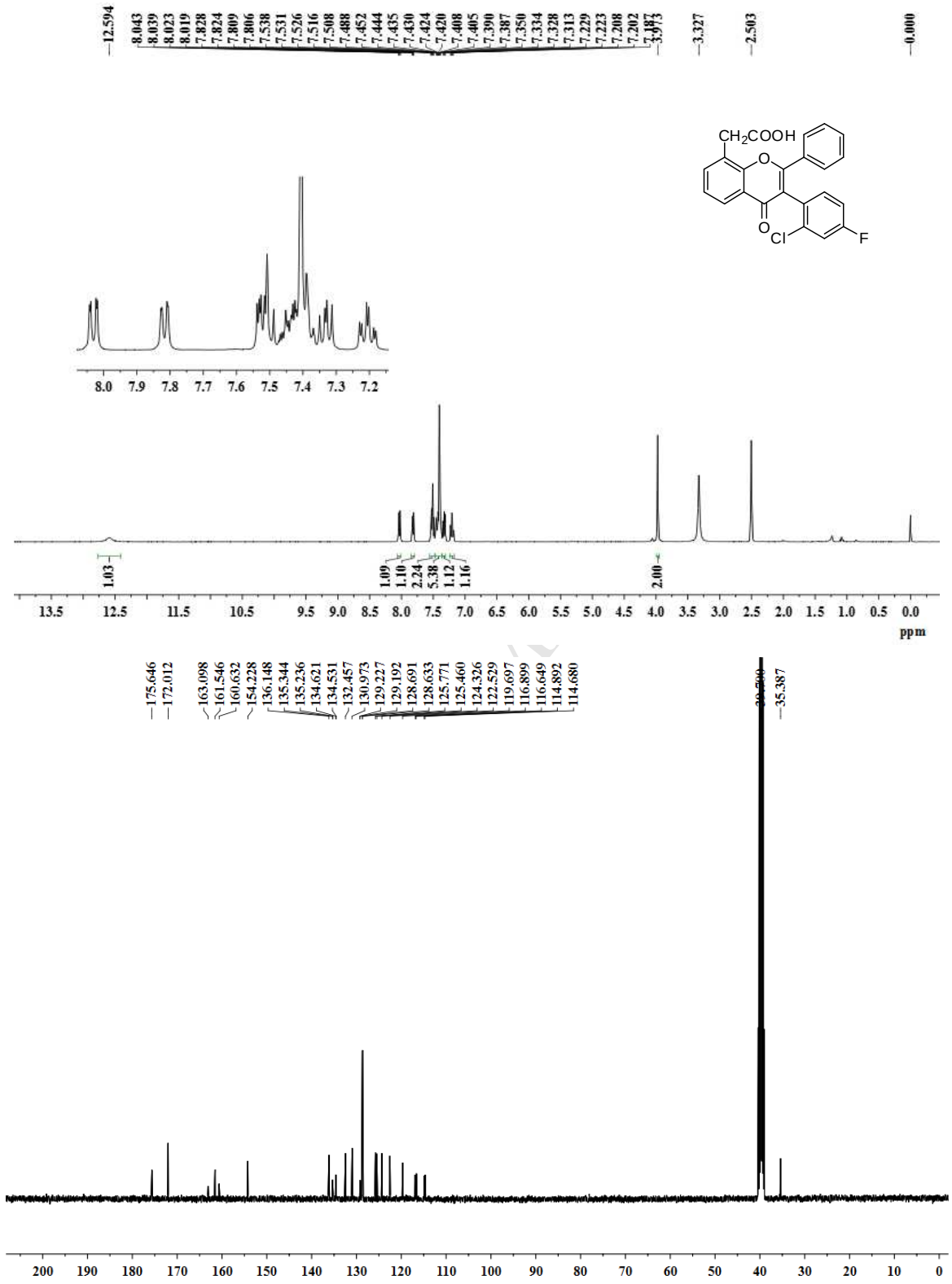


Figure S26. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9h**

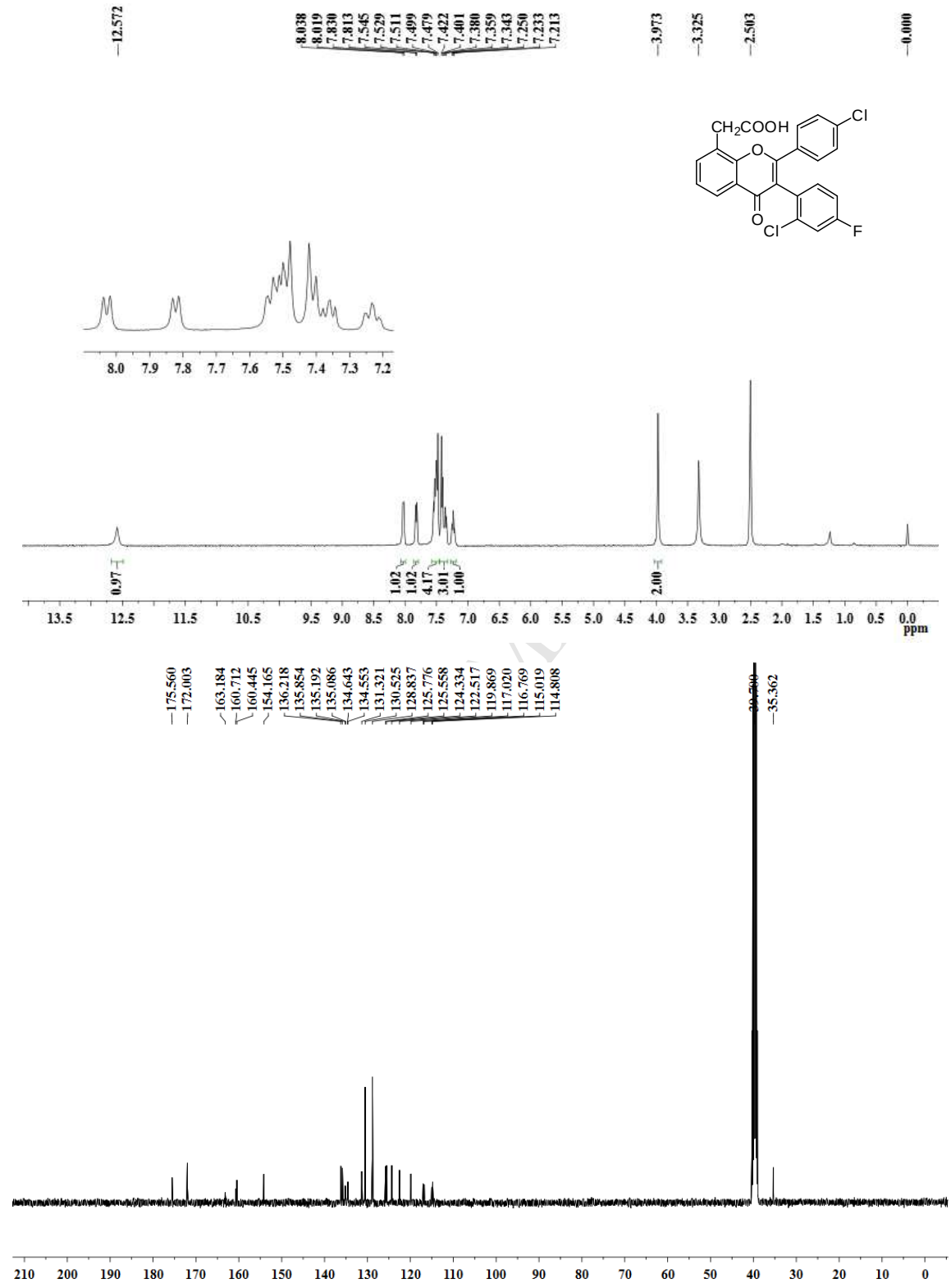


Figure S27. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9i**

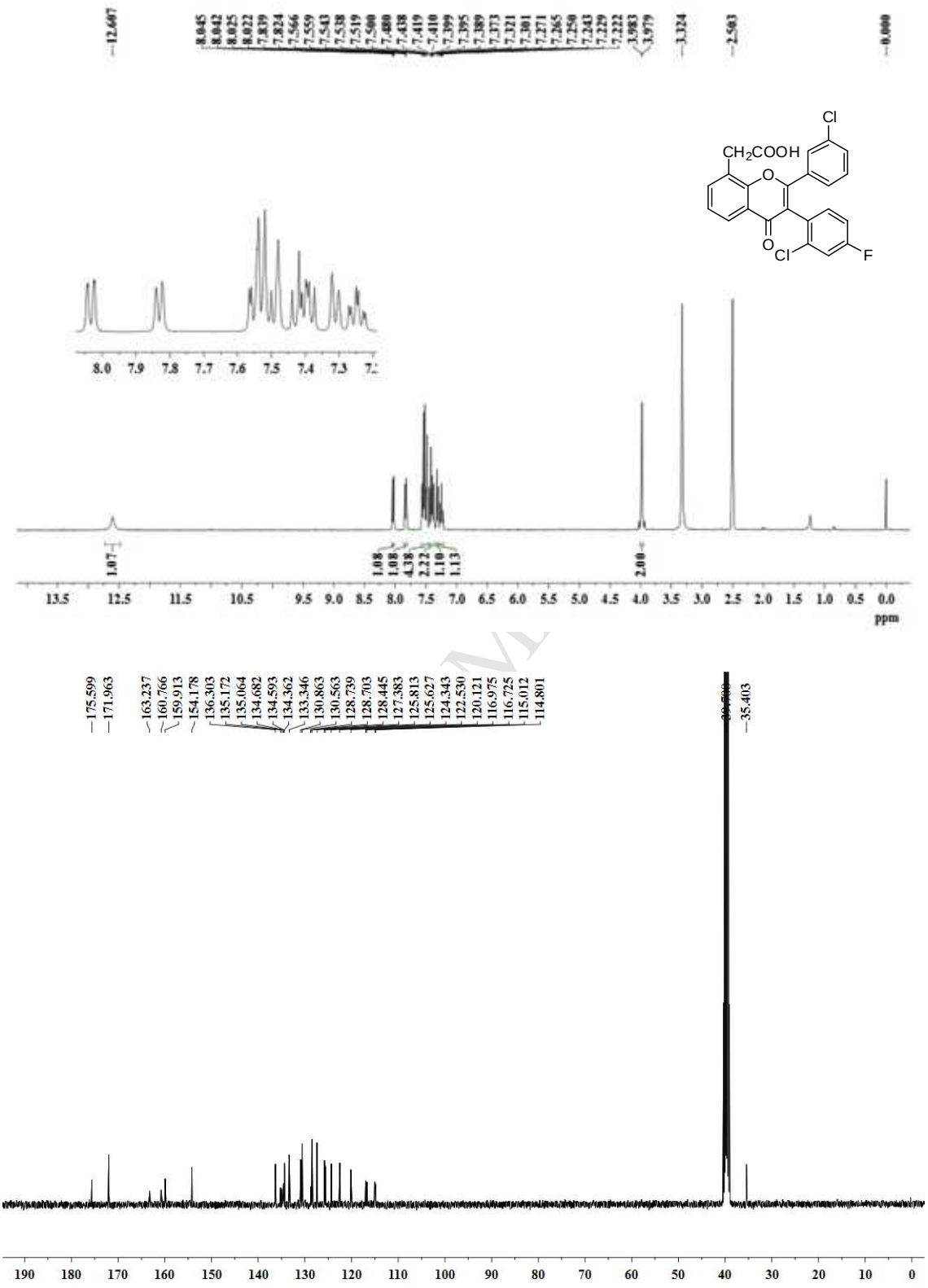


Figure S28. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9j**

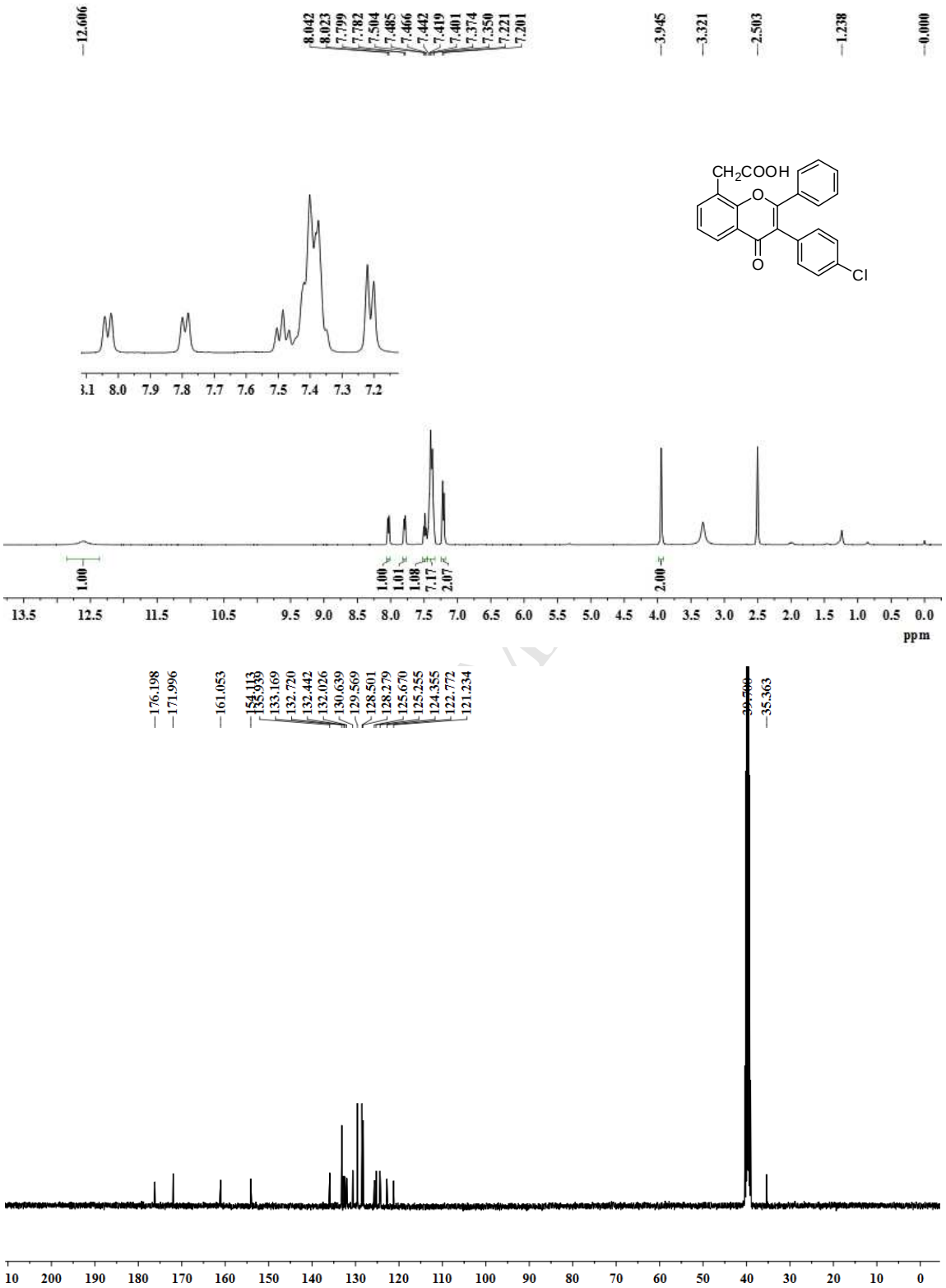


Figure S29. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9k**

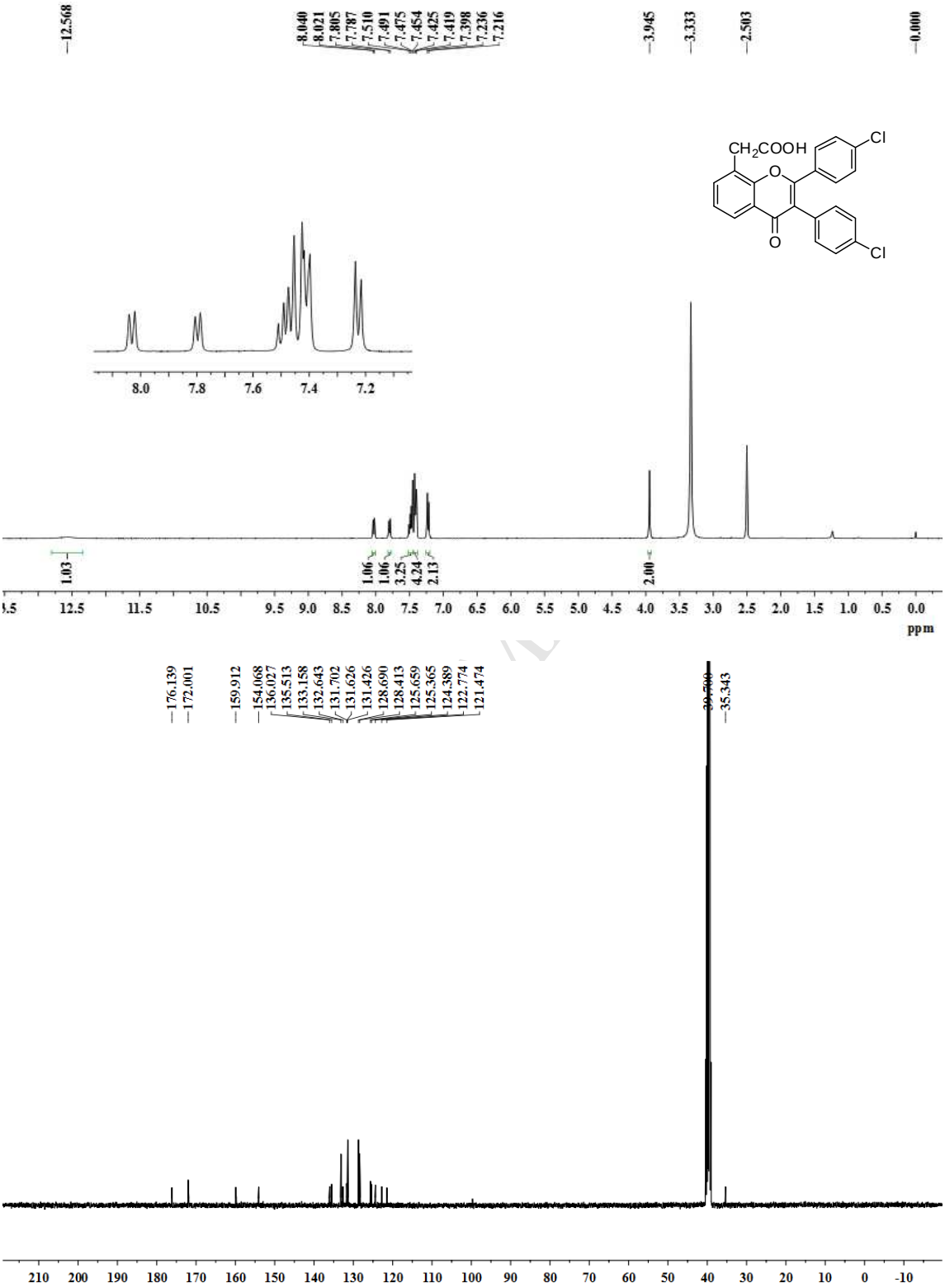


Figure S30. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9l**

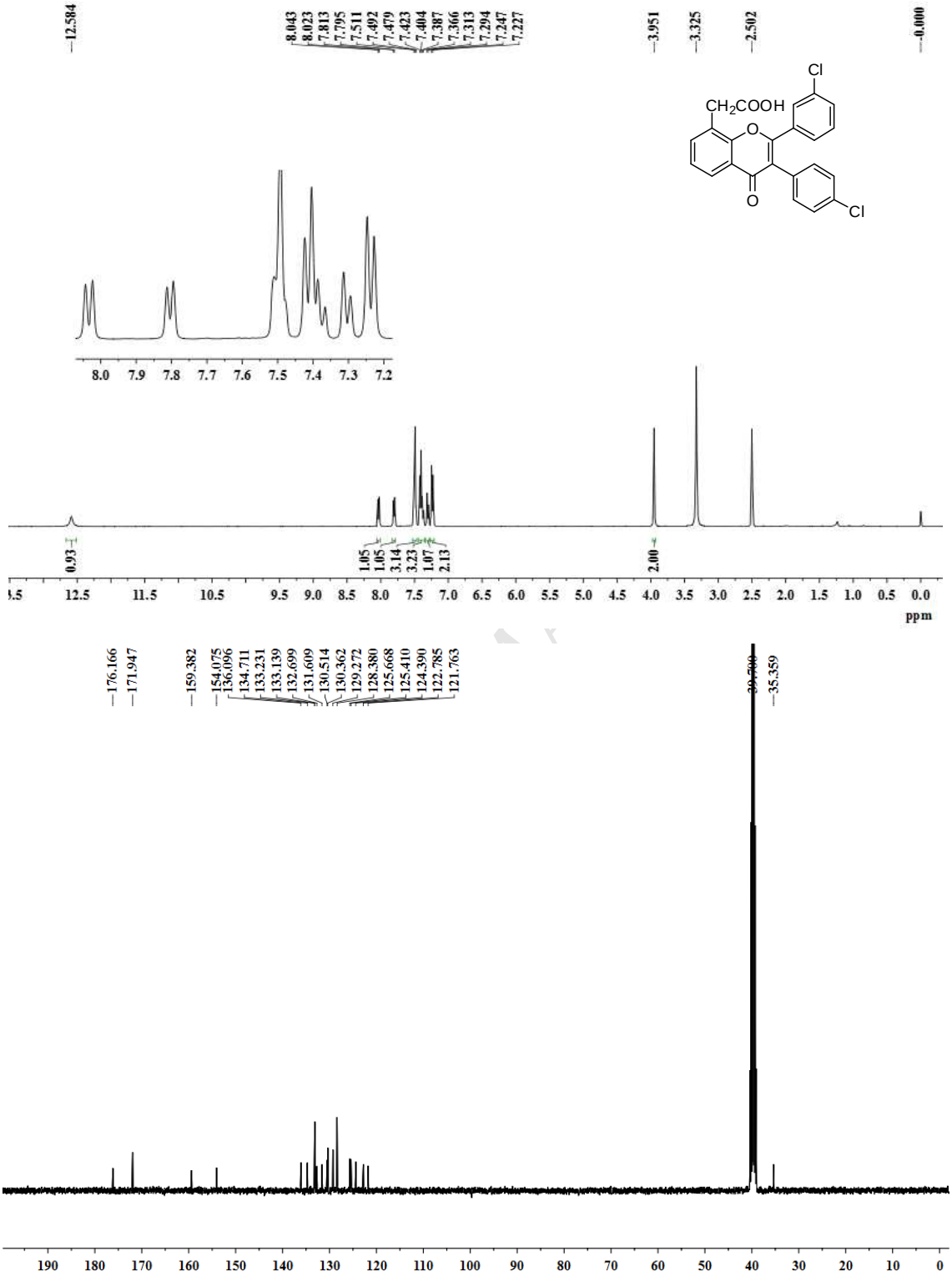


Figure S31. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9m**

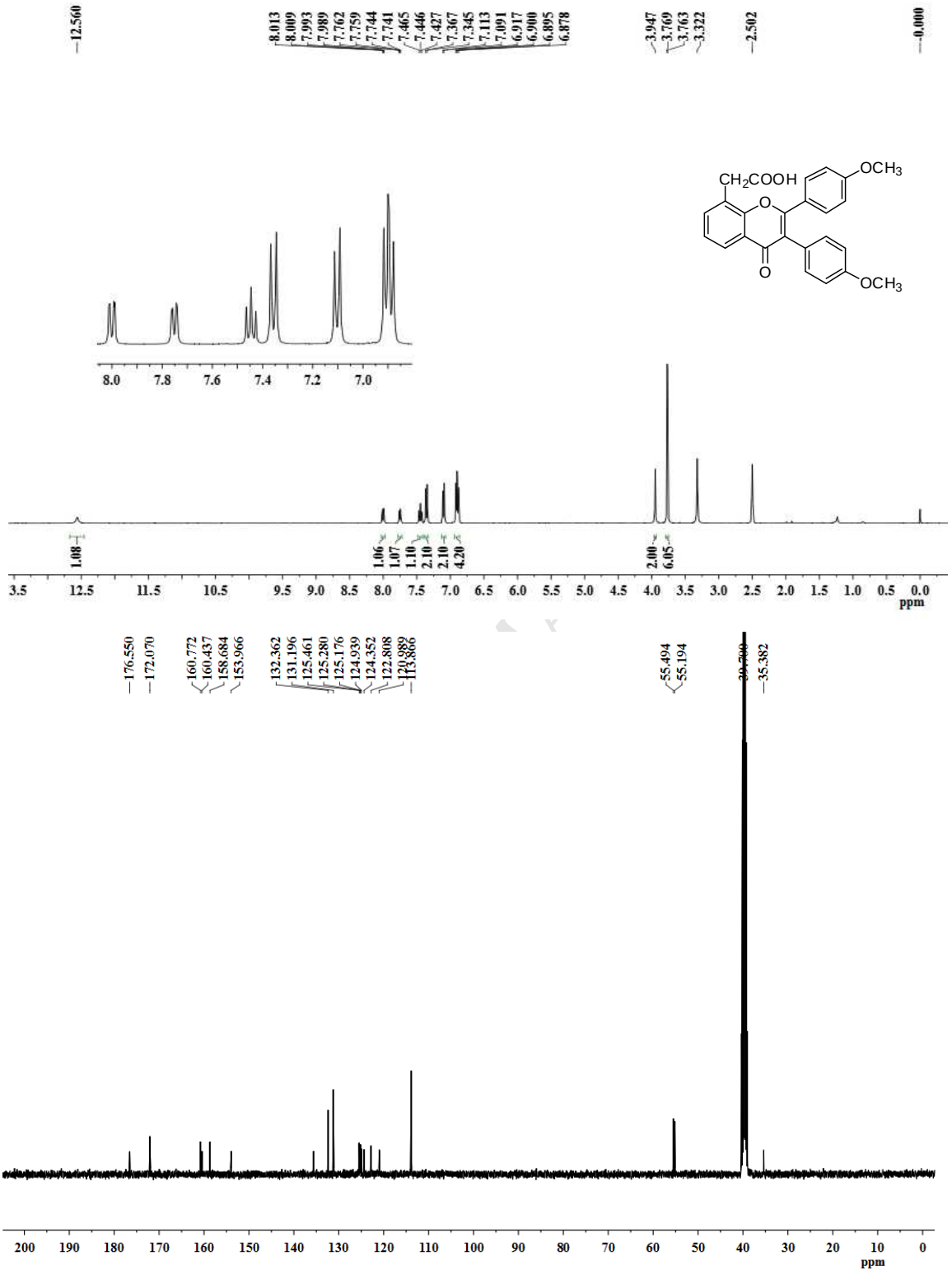


Figure S32. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9n**

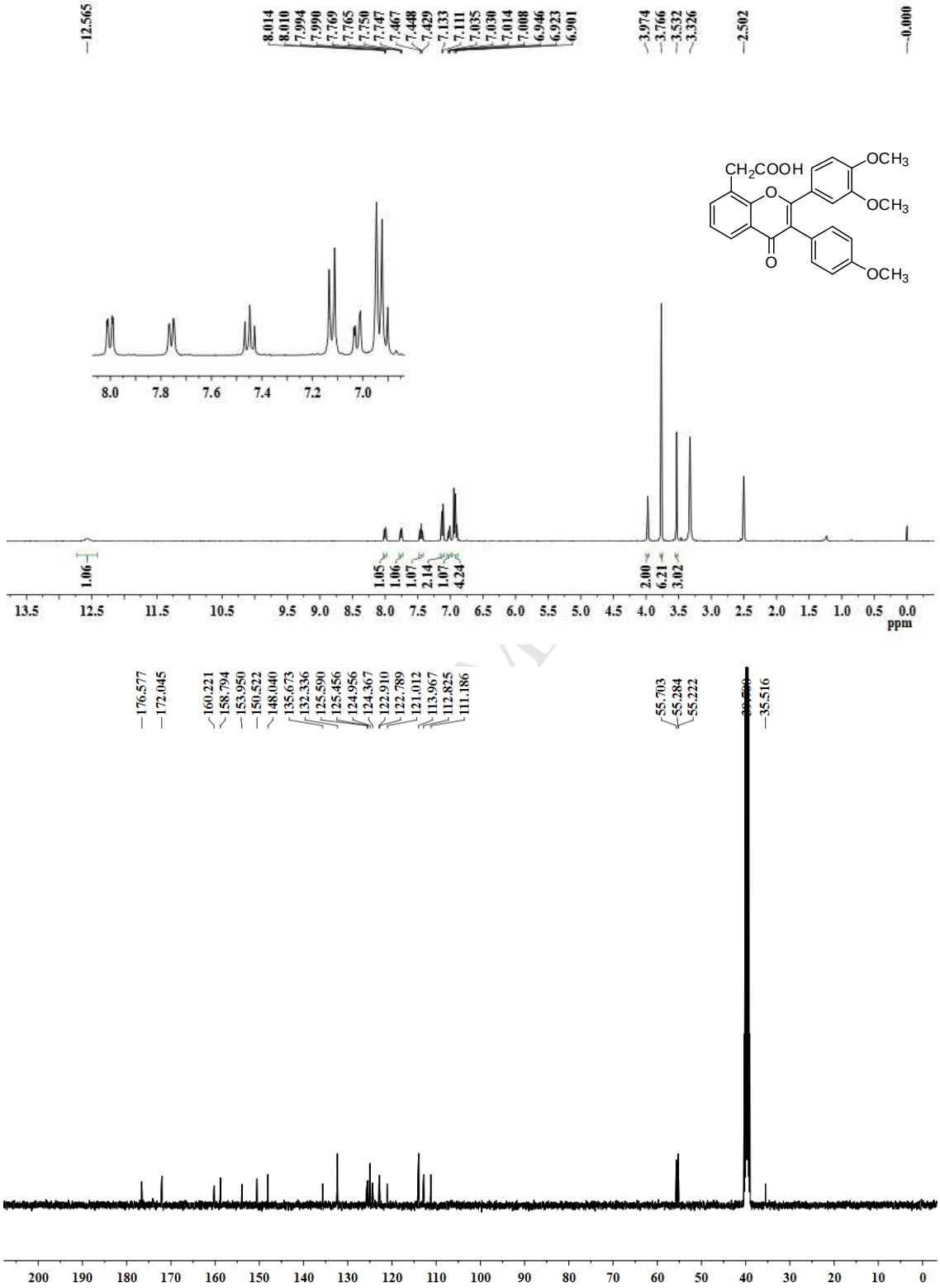


Figure S33. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9o**

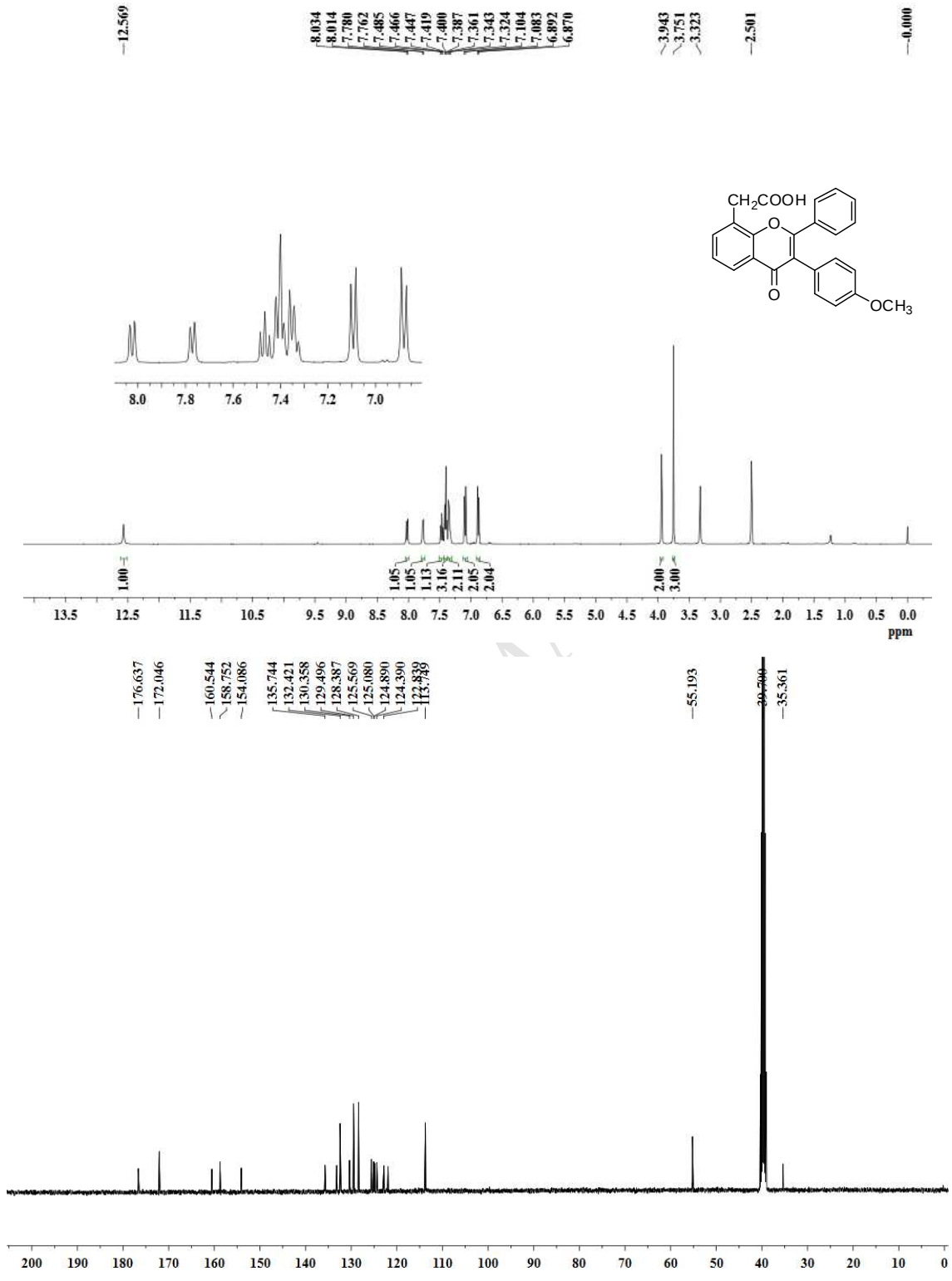


Figure S34. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9p**

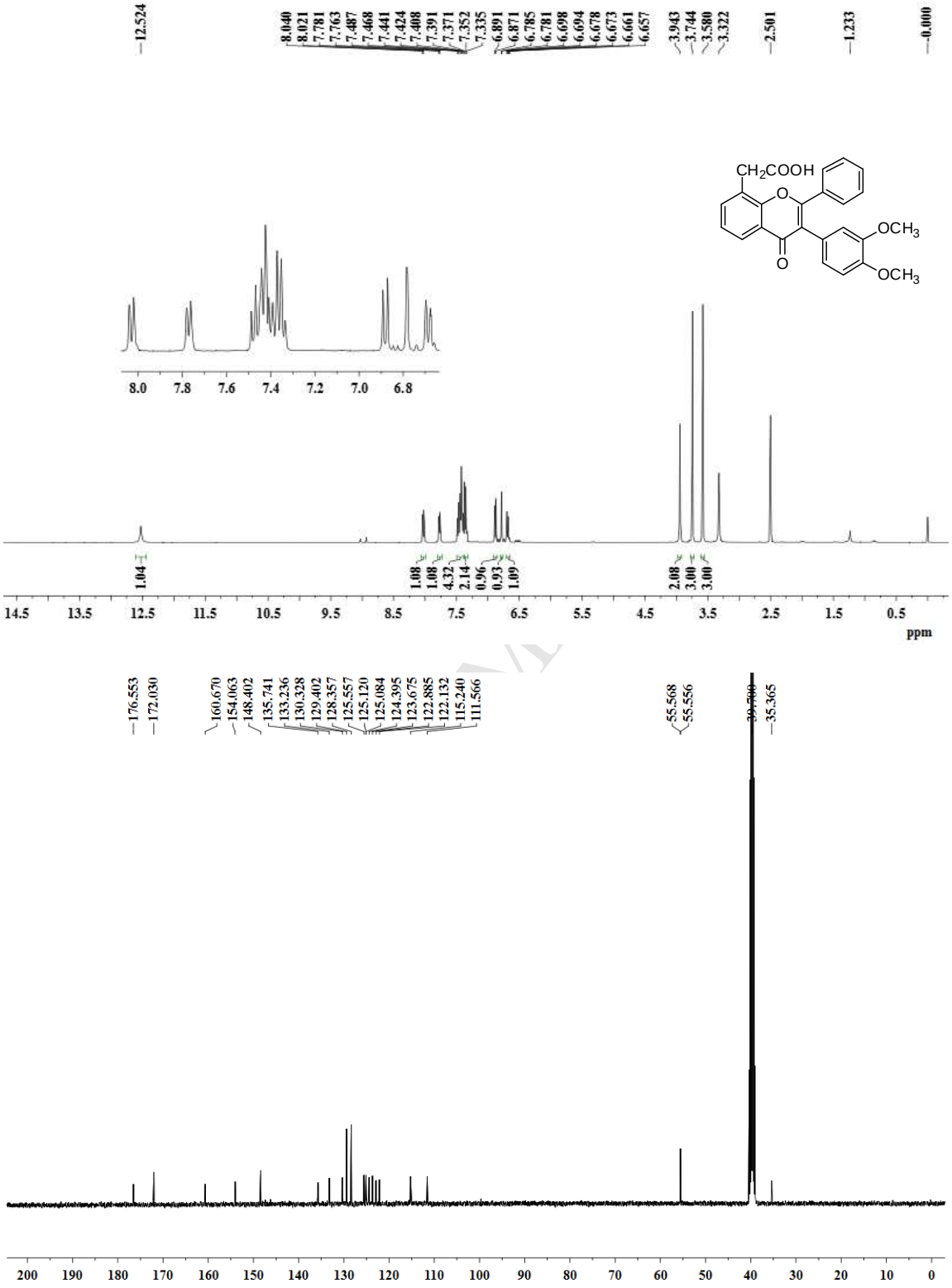


Figure S35. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9q**

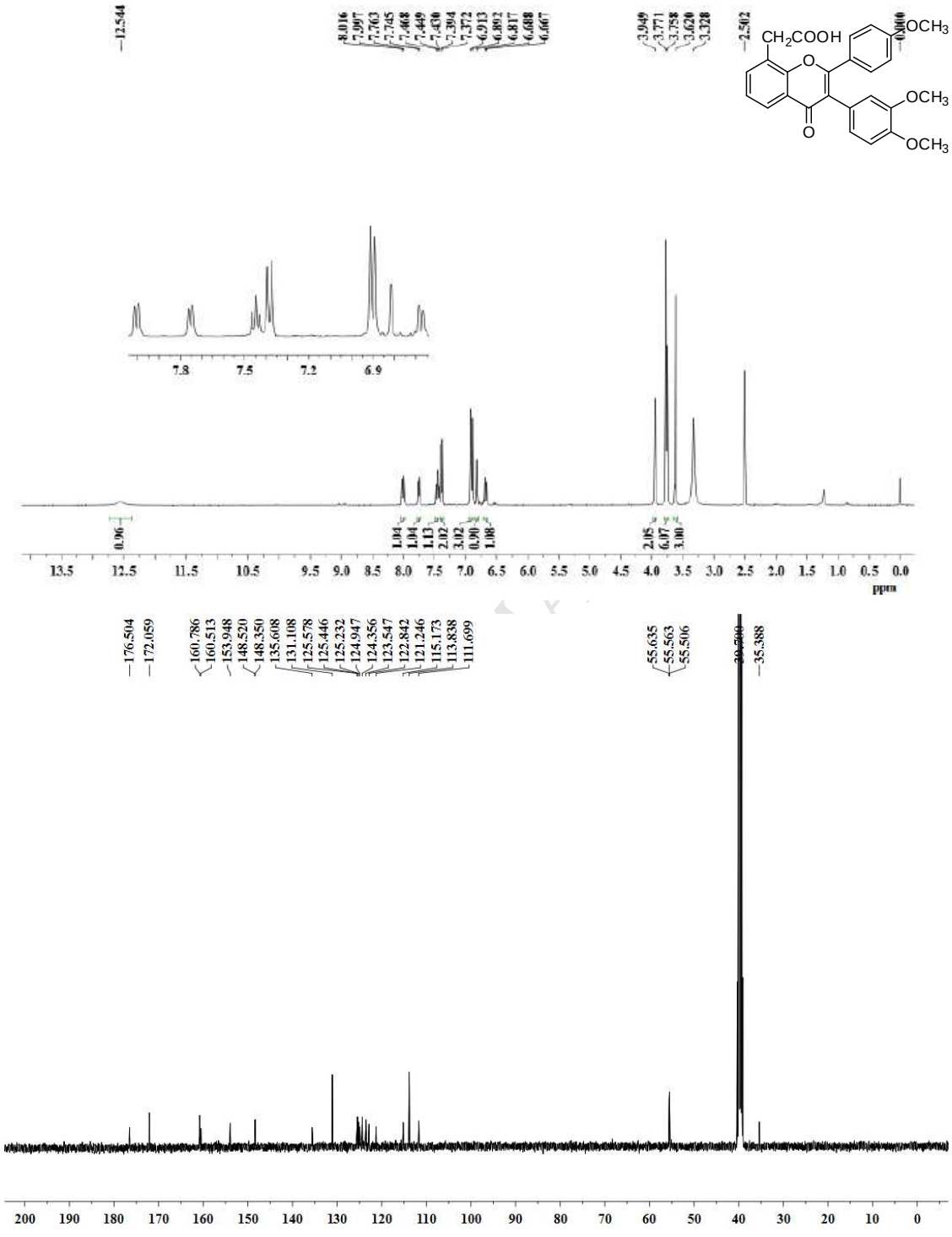


Figure S36. ^{1}H-NMR (d_6-DMSO, 400 MHz) and ^{13}C-NMR (d_6-DMSO, 100 MHz) spectra of compound **9r**