SUPPORTING INFORMATION

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1. Chemistry

Chemistry General considerations. All the commercially available reagents and solvents were used as purchased from vendors without further purification. Dry solvents were purchased from Sigma-Aldrich. Automated column chromatography purifications were done using a Teledyne ISCO apparatus (CombiFlash® Rf) with pre-packed silica gel columns of different sizes (from 4 g up to 24 g) and mixtures of increasing polarity of cyclohexane and ethyl acetate (EtOAc) or dichloromethane (DCM) and methanol (MeOH). NMR experiments were run on a Bruker Avance III 400 system (400.13 MHz for ^{1}H, and 100.62 MHz for ^{13}C), equipped with a BBI probe and Z-gradients. Spectra were acquired at 300 K, using deuterated dimethylsulfoxide (DMSO–*d6*) or deuterated chloroform ($CDCl_3$) as solvents. For 1H-NMR, data are reported as follows: chemical shift, multiplicity (s= singlet, d= doublet, dd= double of doublets, t= triplet, q= quartet, m= multiplet), coupling constants (Hz) and integration. UPLC/MS analyses were run on a Waters ACQUITY UPLC/MS system consisting of a SQD (Single Quadrupole Detector) Mass Spectrometer equipped with an Electrospray Ionization interface and a Photodiode Array Detector. PDA range was 210-400 nm. The analyses were performed on an ACQUITY UPLC BEH C_{18} (50x2.1 mmID, particle size 1.7µm) with a VanGuard BEH C_{18} pre-column (5x2.1 mmID, particle size 1.7 µm) (LogD>1). The mobile phase was 10mM NH_4OAc in H_2O at pH 5 adjusted with AcOH (A) and 10mM NH_4OAc in CH_3CN-H_2O (95:5) at pH 5 (B). Electrospray ionization in positive and negative mode was applied in the mass scan range 100-500Da. Depending on the analysis method used, a different gradient increasing the proportion of mobile phase B was applied. For gradient 1, the mobile-phase B proportion increased from 5 % to 95 % in 3 min. For grandient 2, the mobile-phase B proportion increased from 50 % to 100 % in 3 min. The analysis with the ***gradient 2*** (0 % to 100 % mobile phase B in 3 min) were performed using a different system on Waters ACQUITY UPLC HSS T3 C18 column (50x2.1mmID particle size 1.8µm) with VanGuard HSS T3 C18 pre-column (5x2.1mmID, particle size 1.8µm). Electrospray ionization in positive and negative mode was applied.

.All final compounds displayed ≥ 95% purity as determined by NMR and UPLC/MS analysis.

Accurate mass measurements were performed on a Waters Synapt G2 Quadrupole-Tof Instrument equipped with an ESI ion source. The analyses were run on an ACQUITY UPLC BEH C_{18} column (50x2.1mmID, particle size 1.7µm), using H_2O + 0.1% formic acid (A) and MeCN + 0.1% formic acid as mobile phase.

2. Detailed synthetic methods of compounds 1-17

*General procedure 1: method A for aryl methyl ether cleavage for the synthesis of compounds **1-3**.* The appropriate intermediate **23a-c** (1.0 eq) was added with pyridinium hydrochloride (10.0 eq.). The reaction mixture was heated at 190 °C under argon atmosphere until total conversion of starting material. After reaction completation, reaction mixture was cooled down to room temperature and added with water. The crude product was filtered, washed with water and purified by silica.

*2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-methyl-4H-chromen-4-one **(1)**.* Title compound was synthesized following the general procedure 1 previously described using intermediate **23a** (59 mg, 0.16 mmol) and pyridinium chloride (185 mg, 1.6 mmol). Purification by silica (elution by gradient from 100:0 to 80:20 DCM/MeOH) afforded pure compound **1** (34 mg, 71% yield). UPLC/MS Rt = 1.62 min (gradient 1), MS (ESI) m/z: 301.0 $[M+H]^+$.$[M+H]^+$ calculated for $C_{16}H_{13}O_6$: 301.1. HRMS (AP-ESI) m/z calculated for $C_{16}H_{12}O_6$ $[M+H]^+$ 301.0707, found 301.0712. ^{1}H NMR (400 MHz, DMSO–d_6) δ 13.06 (s, 1H), 7.09 (d, J = 2.2 Hz, 1H), 7.02 (dd, J = 8.2, 2.2 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.30 (d, J = 2.1 Hz, 1H), 6.16 (t, J = 2.6 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO–d_6) δ182.2 (CO), 164.9 (Cq), 161.9 (Cq), 161.8 (Cq), 157.7 (Cq), 148.50 (Cq), 145.7 (Cq), 123.6 (Cq), 121.5 (CH), 116.5 (CH), 115.9 (CH), 113.8 (Cq), 103.1 (Cq), 99.1 (CH), 93.8 (CH), 11.3 (CH_3).

*2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-propyl-4H-chromen-4-one **(2)**.* Title compound was synthesized following the general procedure 1 previously described using intermediate **23b** (54 mg, 0.14 mmol) and pyridinium chloride (185 mg, 1.6 mmol). Purification by silica (elution by gradient from 100:0 to 94:6 DCM/MeOH) afforded pure compound **2** (35 mg, 76% yield). UPLC/MS Rt = 1.93 min (gradient 1), MS (ESI) m/z: 329.0 $[M+H]^+$.$[M+H]^+$ calculated for $C_{18}H_{17}O_6$: 329.1. HRMS (AP-ESI) m/z calculated for $C_{18}H_{16}O_6$ $[M+H]^+$ 329.1017, found 329.1025. ^{1}H NMR (400 MHz, DMSO–d_6) δ 13.09 (s, 1H), 7.02 (d, J = 2.1 Hz, 1H), 6.94 (dd, J = 8.2, 2.1 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.29 (d, J = 2.1 Hz, 1H), 6.17 (d, J = 2.1 Hz, 1H), 2.45 – 2.36 (m, 2H), 1.57 – 1.43 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 182.2 (CO), 164.7 (Cq), 162.8 (Cq), 161.9(Cq), 157.8 (Cq), 148.2 (Cq), 145.7 (Cq), 123.8 (Cq), 120.9 (CH), 118.7 (Cq), 116.2 (CH), 116.0 (CH), 103.5 (Cq), 99.0 (CH), 93.8 (CH), 27.1 (CH_2), 22.2 (CH_2), 14.5 (CH_3).

*3-butyl-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one **(3)**.* Title compound was synthesized following the general procedure 1 previously described using intermediate **23c** (48 mg, 0.12 mmol) and pyridinium chloride (139 mg, 1.2 mmol). Purification by silica (elution by gradient

from 100:0 to 90:10 DCM/MeOH) afforded of pure compound **3** (10 mg, 30% yield). UPLC/MS Rt = 2.07 min (gradient 1), MS (ESI) m/z: 343.2 $[M+H]^+$.$[M+H]^+$ calculated for $C_{19}H_{19}O_6$: 343.1. HRMS (AP-ESI) m/z calculated for $C_{19}H_{18}O_6$ $[M+H]^+$ 343.1167, found 343.1182. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 13.07 (s,1H), 7.00 (d, *J* = 2.1 Hz, 1H), 6.92 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.25 (d, *J* = 2.1 Hz, 1H), 6.13 (d, *J* = 2.1 Hz, 1H), 2.46 – 2.38 (m, 2H), 1.52 – 1.40 (m, 2H), 1.32 – 1.18 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO–*d*$_6$) δ 182.1 (CO), 165.4 (Cq), 162.6 (Cq), 161.9 (Cq), 157.8 (Cq), 148.3 (Cq), 145.7 (Cq), 123.8 (Cq), 120.8 (CH), 118.7 (CH), 116.2 (CH), 116.0 (CH), 103.3 (Cq), 99.2 (CH), 93.8 (CH), 31.0 (CH_2), 24.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

*General procedure 2: benzyl deprotection for the synthesis of compounds **4-6**.* Appropriate benzylated compound of type **28** was dissolved in a 1:1 mixture MeOH/DCM (0.04 M) under an argon atmosphere. Pd/C (20% w/w) and Et_3SiH (3.0 eq. for each benzyl group) were added to the solution. The reaction mixture was stirred at 40°C until complete conversion of starting material. Then, the reaction mixture was filtered over a bed of celite and concentrated under vacuum. The crude product was rised in EtOAc and the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by silica.

*3-butoxy-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one (**4**).* Title compound was synthesized according to general procedure 2 previously described using **28a** (314 mg, 0.5 mmol), Pd/C 20% w\w (50 mg) and, Et_3SiH (0.94 mL, 4.5 mmol) in a 1:1 mixture MeOH/DCM (12.5 mL). Purification by silica (elution by gradient from 100:0 to 50:50 cyclohexane\EtOAc) afforded pure compound **4** (110 mg, 62% yield over two steps). UPLC/MS Rt = 1.64 min (gradient 1), MS (ESI) m/z: 343.1 $[M+H]^+$.$[M+H]^+$ calculated for $C_{19}H_{18}O_6$: 343.1. HRMS (AP-ESI) m/z calculated for $C_{19}H_{18}O_6$ $[M+H]^+$ 343.1167, found 343.1182.^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 12.74 (s, 1H), 7.52 (d, *J* = 2.2 Hz, 1H), 7.44 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.44 – 6.36 (m, 1H), 6.20 – 6.15 (m, 1H), 3.92 (t, *J* = 6.6 Hz, 2H), 1.68 – 1.56 (m, 2H), 1.44 – 1.30 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO–*d*$_6$) δ178.0 (CO), 164.2 (Cq), 161.3 (Cq), 156.4 (Cq), 156.0 (Cq), 148.6 (Cq), 145.2 (Cq), 136.8 (Cq), 121.0 (CH), 120.7 (Cq), 115.6 (CH), 115.6 (CH), 104.2 (Cq), 98.5 (CH), 93.5 (CH), 71.7 (CH_2), 31.5 (CH_2), 18.6 (CH_2), 13.7 (CH_3).

*2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(2-hydroxyethoxy)-4H-chromen-4-one (**5**).* Title compound was synthesized according to general procedure 2 previously described using **28b** (185 mg, 0.3 mmol), Pd/C 20% w\w (50 mg) and, Et_3SiH (0.56 mL, 2.7 mmol) in a 1:1 mixture

MeOH/DCM (7.5 mL). Purification by silica (elution by gradient from 100:0 to 0:100 cyclohexane\EtOAc) afforded pure compound **5** (21 mg, 20% yield over two steps). UPLC/MS Rt = 1.40 min (gradient 1), MS (ESI) m/z: 345.1 $[M-H]^-$.$[M-H]^-$ calculated for $C_{17}H_{14}O_8$: 345.1. HRMS (AP-ESI) m/z calculated for $C_{17}H_{14}O_8$ $[M+H]^+$ 347.0757, found 347.0767. ^{1}H NMR (400 MHz, DMSO–d_6) δ 12.69 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.36 (d, J = 2.1 Hz, 1H), 6.15 (d, J = 2.1 Hz, 1H), 3.99 (t, J = 5.3 Hz, 2H), 3.65 (t, J = 5.3 Hz, 2H). ^{13}C-NMR (101 MHz, DMSO–d_6) δ 177.9 (CO), 164.8 (Cq), 161.2 (Cq), 156.4 (Cq), 155.6 (Cq), 148.8 (Cq), 145.2 (Cq), 136.8 (Cq), 121.1 (CH), 120.9 (Cq), 115.7 (CH), 115.4 (CH), 103.9 (Cq), 98.7 (CH), 93.6 (CH), 73.7 (CH_2), 60.2 (CH_2).

2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(3-hydroxypropoxy)-4H-chromen-4-one ***(6)***. Title compound was synthesized according to general procedure 2 previously described using **28a** (378 mg, 0.6 mmol), Pd/C 20% w\w (70 mg) and, Et_3SiH (0.56 mL, 2.7 mmol) in a 1:1 mixture MeOH/DCM (7.5 mL). Purification by silica (elution by gradient from 100:0 to 40:60 cyclohexane\EtOAc) afforded pure compound **21** (33 mg, 15% yield over two steps). UPLC/MS Rt = 1.40 min (gradient 1), MS (ESI) m/z: 361.1 $[M+H]^+$.$[M+H]^+$ calculated for $C_{18}H_{17}O_8$: 361.1. HRMS (AP-ESI) m/z calculated for $C_{18}H_{16}O_8$ $[M+H]^+$ 361.0923, found 361.0923. ^{1}H NMR (400 MHz, DMSO–d_6) δ 12.72 (s, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.46 (dd, J = 8.4, 2.2 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.39 (d, J = 2.1 Hz, 1H), 6.18 (d, J = 2.1 Hz, 1H), 4.01 (t, J = 6.7 Hz, 2H), 3.49 (t, J = 6.4 Hz, 2H), 1.81 (p, J = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 178.0 (CO), 164.1 (Cq), 161.3 (Cq), 156.4 (Cq), 156.0 (Cq), 148.6 (Cq), 145.2 (Cq), 136.8 (Cq), 121.0 (CH), 120.8 (Cq), 115.6 (CH), 115.5 (CH), 104.2 (Cq), 98.6 (CH), 93.6 (CH), 69.7 (CH_2), 57.7 (CH_2), 32.9 (CH_2).

General procedure 3: method B for aryl methyl ether cleavage for the synthesis of compounds ***7-17***. To a DCM solution (0.05 M) of methylated intermediate **32a-32d**, **39**, **40**, **42a-42c**, **44** or **46** (1.0 equiv), a 1 M solution of BBr_3 was dropwise added at 0°C and reaction mixture was left to react until no starting material was detected by UPLC. The reaction was quenched by slow addition of MeOH. Then, the solvent was evaporated and the residue crude was purified by silica gel chromatography or trituration.

2-(3,4-dihydroxybenzyl)-5-hydroxy-4H-chromen-4-one (7)

Compound 7 was prepared according to generic procedure 3 using intermediate 32a (150 mg, 0.46 mmol), BBr3 (1M in DCM) (2.1 mL, 2.06 mmol) in anhydrous DCM (6 mL). Purification by silica (elution by gradient from 100:0 to 90:10 DCM/EtOAc) afforded desired compound **7** as white

foaming solid (120 mg, 92% yield). UPLC/MS Rt: 1.77 min (gradient 1), MS (ESI) m/z 285.0, $[M+H]^+$. $[M+H]^+$ calculated for $C_{16}H_{13}O_5$: 285.1. ^{1}H NMR (400 MHz, DMSO–d_6) δ 12.60 (s, 1H), 8.81 (s, 1H), 7.61 (t, J = 8.4 Hz, 1H), 6.99 (dd, J = 8.5, 0.9 Hz, 1H), 6.78 (dd, J = 8.3, 0.9 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.60 (dd, J = 8.0, 2.1 Hz, 1H), 6.24 (s, 1H), 3.85 (s, 2H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 183.1 (Cq), 171.2 (Cq), 159.9 (Cq), 156.2 (Cq), 145.4 (Cq), 144.5 (Cq), 135.8 (CH), 125.8 (Cq), 120.0 (CH), 116.4 (CH), 115.8 (CH), 110.9 (CH), 109.7 (Cq), 108.3 (CH), 107.2 (CH), 38.9 (CH_2, recovered from HSQC). HRMS (AP-ESI) m/z calculated for $C_{16}H_{13}O_5$ $[M+H]^+$ 285.0763, found 285.0752.

*2-(1-(3,4-dihydroxyphenyl)ethyl)-5-hydroxy-4H-chromen-4-one (**8**)*

Compound **8** was prepared according to general procedure 3 using intermediate **32b** (28 mg, 0.082 mmol), BBr_3 (1M in DCM) (0.37 mL, 0.37 mmol) in anhydrous DCM (3.1 mL). Purification by silica (elution by gradient from 100:0 to 98:2 DCM/MeOH) afforded desired compound **8** as white foaming solid (19 mg, 78% yield). UPLC/MS Rt: 1.95 min (gradient 1), MS (ESI) m/z 299.0, $[M-H]^+$. $[M-H]^+$ calculated for $C_{17}H_{15}O_5$: 299.1. MS (ESI) m/z 297.2, $[M-H]^-$. $[M-H]^-$ calculated for $C_{17}H_{13}O_5$: 297.1. *See in the main text the characterization by NMR and HRMS.*

*2-(1-(3,4-dihydroxyphenyl)pentyl)-5-hydroxy-4H-chromen-4-one (**9**).*

Compound **9** was prepared according to general procedure 3 using intermediate **32c** (35 mg, 0.092 mmol), BBr_3 (1M in DCM) (0.28 mL, 0.28 mmol) in anhydrous DCM (1.9 mL). Purification by silica (elution by gradient from 100:0 to 98:2 DCM/MeOH) afforded desired compound **9** as white foaming solid (29 mg, 92% yield). UPLC/MS Rt: 1.21 min (gradient 2), MS (ESI) m/z 339.0, $[M-H]^-$. $[M-H]^-$ calculated for $C_{20}H_{19}O_5$: 339.1. ^{1}H NMR (400 MHz, DMSO–d_6) δ 12.59 (s, 1H), 8.88 (s, 2H), 7.61 (t, J = 8.3 Hz, 1H), 7.01 (dd, J = 8.5, 0.9 Hz, 1H), 6.79 – 6.74 (m, 2H), 6.71 – 6.64 (m, 2H), 6.39 (s, 1H), 3.80 (t, J = 7.8 Hz, 1H), 2.11 – 1.97 (m, 1H), 1.93 – 1.80 (m, 1H), 1.37 – 1.26 (m, 2H), 1.25 – 1.14 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 183.2 (Cq), 173.5 (Cq), 159.9 (Cq), 156.2 (Cq), 145.3 (Cq), 144.6 (Cq), 135.9 (CH), 130.6 (Cq), 118.8 (CH), 115.7 (CH), 115.2 (CH), 110.9 (CH), 109.8 (Cq), 107.5 (CH), 107.3 (CH), 48.7 (CH), 31.7 (CH_2), 29.2 (CH_2), 21.9 (CH_2), 13.8 (CH_3, recovered from HSQC). HRMS (AP-ESI) m/z calculated for $C_{20}H_{21}O_5$ $[M+H]^+$ 341.1389, found 341.1393.

*2-(1-(3,4-dihydroxyphenyl)-5,5,5-trifluoropentyl)-5-hydroxy-4H-chromen-4-one (**10**)*

Compound **10** was prepared according to general procedure 3 using intermediate **32d** (35 mg, 0.08 mmol), BBr_3 (1M in DCM) (0.25 mL, 0.25 mmol) in anhydrous DCM (1.4 mL). Purification by silica

(elution by gradient from 100:0 to 99:1 DCM/MeOH) afforded desired compound **10** as white foaming solid (28 mg, 88% yield). UPLC/MS Rt: 1.03 min (gradient 2), MS (ESI) m/z 395.0, $[M-H]^+$. $[M-H]^+$ calculated for $C_{20}H_{18}F_3O_5$: 395.1. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 12.56 (s, 1H), 8.92 (s, 2H), 7.62 (t, J = 8.3 Hz, 1H), 7.00 (dd, J = 8.4, 0.9 Hz, 1H), 6.80 – 6.75 (m, 2H), 6.73 – 6.64 (m, 2H), 6.41 (s, 1H), 3.89 (t, J = 7.8 Hz, 1H), 2.40 – 2.22 (m, 2H), 2.19 – 2.05 (m, 1H), 2.03 – 1.89 (m, 1H), 1.52 – 1.37 (m, 2H). ^{13}C NMR (101 MHz, DMSO–*d*$_6$) δ 183.2 (CH), 172.9 (CH), 159.9 (CH), 156.2 (CH), 145.4 (CH), 144.7 (CH), 135.9 (CH), 130.0 (Cq), 127.6 (q, J = 276.5 Hz) (CF_3), 118.8 (CH), 115.8 (CH), 115.1 (CH), 110.9 (CH), 109.8 (Cq), 107.6 (CH), 107.3 (CH), 48.1 (CH), 32.0 (q, J = 27.3 Hz) (CH_2), 30.8 (CH_2), 19.6 (CH_2, recovered from HSQC). HRMS (AP-ESI) m/z calculated for $C_{20}H_{18}F_3O_5$ $[M+H]^+$ 395.1106, found 395.1098.

*2-(3,4-dihydroxyphenethyl)-5-hydroxy-4H-chromen-4-one (**11**).* Compound **11** was prepared according to general procedure 3 using: intermediate **40** (64 mg, 0.19 mmol), BBr_3 (1M in DCM) (0.86 mL, 0.68 mmol) in anhydrous DCM (3.8 mL). The crude was purified by silica gel (elution by gradient from 100:0 to 85:15 DCM/EtOAc) to yield product **11** (45 mg, 80% yield). UPLC/MS Rt: 1.89 min (gradient 1), MS (ESI) m/z 299.0, $[M+H]^+$. $[M+H]^+$ calculated for $C_{17}H_{15}O_5$: 299.3. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.63 (dd, J = 8.4, 8.4 Hz, 1H), 7.04 (dd, J = 8.5, 0.9 Hz, 1H), 6.78 (dd, J = 8.2, 0.9 Hz, 1H), 6.62 (d, J = 5.1 Hz, 1H), 6.60 (bs, 1H), 6.47 (dd, J = 8.0, 2.1 Hz, 1H), 6.26 (s, 1H), 2.91 (ddd, J = 8.7, 6.8, 1.7 Hz, 2H), 2.84 (ddd, J = 8.4, 6.7 Hz, 1.8 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ 183.0 (Cq), 171.2 (Cq), 159.9 (Cq), 156.3 (Cq), 145.2 (Cq), 143.7 (Cq), 135.8 (CH), 130.6 (Cq), 118.9 (CH), 115.7 (CH), 115.5 (CH), 110.8 (CH), 109.8 (Cq), 108.4 (CH), 107.3 (CH), 35.3 (CH_2), 31.4 (CH_2). HRMS (AP-ESI) m/z calcd for $C_{17}H_{15}O_5$ $[M + H]^+$ 299.0919, found 299.0915.

*(E)-2-(3,4-dihydroxystyryl)-5-hydroxy-4H-chromen-4-one (**12**)*. Compound **12** was prepared according to general procedure 3 using: intermediate **39** (89 mg, 0.26 mmol), BBr_3 (1M in DCM) (1.2 mL, 1.17 mmol) in anhydrous DCM (5.2 mL). The crude was purified by silica gel (elution by gradient from 100:0 to 80:20 DCM/EtOAc) to yield product **12** (53 mg, 66% yield). UPLC/MS Rt: 1.94 min (gradient 1), MS (ESI) m/z 297.0, $[M+H]^+$. $[M+H]^+$ calculated for $C_{17}H_{13}O_5$: 297.3. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.80 (s, 1H), 7.64 (t, J = 8.4 Hz, 1H), 7.59 (d, J = 16.0 Hz, 1H), 7.15 – 7.09 (m, 2H), 7.05 (dd, J = 8.2, 2.0 Hz, 1H), 6.88 (d, J = 16.0 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.47 (s, 1H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 182.8 (Cq), 164.1 (Cq), 159.9 (Cq), 155.7 (Cq), 148.4 (Cq), 145.7 (Cq), 138.6 (CH), 135.7 (CH), 126.4 (Cq), 121.3 (CH),

116.1 (CH), 115.9 (CH), 114.5 (CH), 110.7 (CH), 110.1 (Cq), 107.3 (CH), 107.2 (CH). HRMS (AP-ESI) m/z calcd for $C_{17}H_{13}O_5$ $[M + H]^+$ 297.0763, found 297.0754.

*N-(3,4-dihydroxyphenyl)-5-hydroxy-4-oxo-4H-chromene-2-carboxamide (**13**).* Compound **13** was prepared according to general procedure 3 using: intermediate **42a** (45 mg, 0.13 mmol), BBr_3 (1M in DCM) (0.59 mL, 0.59 mmol) in anhydrous DCM (2.6 mL). The crude was purified by silica (elution by gradient from 100:0 to 98:2 DCM/MeOH) to yield product **13** (16 mg, 40% yield). UPLC/MS Rt:1.65 min (gradient 1), m/z 312.0, $[M-H]^-$. $[M-H]^-$ calculated for $C_{16}H_{10}NO_6$: 312.3. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 12.30 (bs, 1H), 10.48 (bs, 1H), 9.01 (bs, 1H), 7.77 (t, J = 8.4, Hz, 1H), 7.30 (d, J = 2.5 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 8.5, 2.5 Hz, 1H), 6.95 (s, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 183.5 (Cq), 159.7 (Cq), 157.2 (Cq), 156.3 (Cq), 155.4 (Cq), 145.0 (Cq), 142.9 (Cq), 136.7 (CH), 129.2 (Cq), 115.2 (CH), 112.4 (CH), 111.4 (CH), 110.9 (Cq), 109.7 (CH), 109.5 (CH), 108.1 (CH). HRMS (AP-ESI) m/z calcd for $C_{16}H_{12}NO_6$ $[M + H]^+$ 314.0665, found 314.0662.

*3,4-dihydroxyphenyl 5-hydroxy-4-oxo-4H-chromene-2-carboxylate (**14**).* Compound **14** was prepared according to general procedure 3 using: intermediate **42b** (22 mg, 0.062 mmol), BBr_3 (1M in DCM) (0.28 mL, 0.28 mmol) in anhydrous DCM (1.3 mL). The crude was purified by crystallization (EtOAc/pentane) to yield product **14** (0.015 g, 77% yield). UPLC/MS Rt: 1.74 min (gradient 1), MS (ESI) m/z 313.1, $[M-H]^-$. $[M-H]^-$ calculated for $C_{16}H_9O_7$: 313.0. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 12.17 (s, 1H), 9.35 (s, 1H), 9.10 (s, 1H), 7.77 (t, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.16 (s, 1H), 6.91 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 6.58 (dd, *J* = 8.6, 2.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO–*d*$_6$) δ 183.4 (Cq), 159.7 (Cq), 158.6 (Cq), 155.7 (Cq), 153.1 (Cq), 145.8 (Cq), 143.9 (Cq), 142.0 (Cq), 137.2 (CH), 115.3 (CH), 113.4 (CH), 111.7 (CH), 111.4 (Cq), 111.2 (CH), 109.0 (CH), 108.0 (CH, recovered from HSQC). HRMS (AP-ESI) m/z calcd for $C_{16}H_{11}O_7$ $[M + H]^+$ 315.0505, found 315.0498.

*3,4-dihydroxyphenethyl 5-hydroxy-4-oxo-4H-chromene-2-carboxylate (**15**).* Compound **15** was prepared according to general procedure 3 using: intermediate **42c** (60 mg, 0.156 mmol), BBr_3 (1M in DCM) (0.47 mL, 0.47 mmol) in anhydrous DCM (3.1 mL). The crude was washed with MeOH and the resulting yellow solid was filtered off to give desired product (0.045 g, 84% yield). UPLC/MS Rt: 1.82 min (gradient 1), MS (ESI) m/z 341.3, $[M-H]^-$. $[M-H]^-$ calculated for $C_{18}H_{13}O_7$: 341.1. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 12.14 (s, 1H), 8.80 (s, 1H), 8.74 (s, 1H), 7.75 (t, J = 8.4 Hz, 1H), 7.16 (dd, J = 8.5, 0.8 Hz, 1H), 6.92 (s, 1H), 6.89 (dd, J = 8.3, 0.8 Hz, 1H), 6.69 (d, J = 2.1 Hz, 1H), 6.66

(d, J = 8.0 Hz, 1H), 6.55 (dd, J = 8.0, 2.1 Hz, 1H), 4.45 (t, J = 6.9 Hz, 2H), 2.86 (t, J = 6.8 Hz, 2H). ^{13}C NMR (151 MHz, DMSO–*d*$_6$) δ 183.5 (Cq), 159.7 (Cq), 159.3 (Cq), 155.7 (Cq), 153.2 (Cq), 145.2 (Cq), 143.9 (Cq), 137.2 (CH), 128.1 (Cq), 119.7 (CH), 116.3 (CH), 115.6 (CH), 112.7 (CH), 111.7 (Cq), 111.2 (CH), 108.0 (CH), 67.5 (CH_2), 33.5(CH_2, recovered from HSQC). HSQC). HRMS (AP-ESI) m/z calcd for $C_{18}H_{15}O_7$ $[M+H]^+$ 343.0818, found 343.0807.

N-(2-(3,4-dihydroxybenzamido)ethyl)-5-hydroxy-4-oxo-4H-chromene-2-carboxamide ***(16)****.* Compound **16** was prepared according to generic procedure 3 using: intermediate **44** (27 mg, 0.06 mmol), BBr_3 (1M in DCM) (0.27 mL, 0.27 mmol) in anhydrous DCM (3 mL). The crude was purified by trituration with MeOH (1 mL) affording pure compound **16** (19 mg, 78%). UPLC/MS Rt: 2.30 min (gradient 3), MS (ESI) m/z: 383.4 $[M-H]^-$.$[M-H]^-$ Calculated for $C_{19}H_{15}N_2O_7$: 383.3. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.20 (t, J = 5.6 Hz, 1H), 8.52 (t, J = 5.6 Hz, 1H), 7.75 (t, J = 8.4 Hz, 1H), 7.47 (dd, J = 8.3, 2.1 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.63 (s, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.49 – 3.40 (m, 4H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 183.5 (Cq), 166.6 (Cq, 2C), 159.8 (Cq), 158.7 (Cq), 156.8 (Cq), 155.4 (Cq), 148.4 (Cq), 144.8 (Cq), 136.8 (CH), 125.6 (Cq), 119.0 (CH), 115.1 (CH), 114.8 (CH), 111.5 (Cq), 110.8 (CH), 109.4 (CH), 107.9 (CH), 38.5 (CH_2, 2C). HRMS (AP-ESI) m/z calcd for $C_{19}H_{15}N_2O_7$ $[M+H]^+$ 385.1036, found 385.1034.

N-(2-(3-(3,4-dihydroxyphenyl)thioureido)ethyl)-5-hydroxy-4-oxo-4H-chromene-2-carboxamide ***(17)****.* Compound **17** was prepared according to generic procedure 3 using: intermediate **46** (40 mg, 0.09 mmol), BBr_3 (1M in DCM) (0.41 mL, 0.41 mmol) in anhydrous DCM (4 mL). The crude was purified by silica (elution by grandient from 100 to 92/8 $CHCl_3$/EtOH) affording not pure product. So the compound from the chromatographic purification was triturated with cyclohexane/EtOAc 1.1 mixture (1 mL) yielding pure compound **17** (12 mg, 31%). UPLC/MS Rt: 1.48 min (gradient 1), MS (ESI) m/z: 414.3 $[M-H]^-$.$[M-H]^-$ Calculated for $C_{19}H_{16}N_3O_6S$: 414.4. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.27 (s, 1H), 9.30 (s, 1H), 9.26 (t, J = 5.5 Hz, 1H), 9.02 (s, 1H), 8.86 (s, 1H), 7.75 (t, J = 8.3 Hz, 1H), 7.51 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.86 (s, 1H), 6.67 (d, J = 2.5 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 6.52 (dd, J = 8.4, 2.5 Hz, 1H), 3.68 (q, J = 6.0 Hz, 2H), 3.48 (q, J = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 183.5 (Cq), 180.5 (Cq), 159.8 (Cq), 158.7 (Cq), 156.7 (Cq), 155.4 (Cq), 145.3 (Cq), 143.3 (Cq), 136.8 (CH), 129.5 (Cq), 116.0 (CH), 115.4 (CH), 113.0 (CH), 111.5 (CH), 110.8 (Cq), 109.4 (CH), 107.9 (CH), 42.86 (CH_2), 39.13 (CH_2, recovered from HSQC). HRMS (AP-ESI) m/z calcd for $C_{19}H_{15}N_2O_7$ $[M+H]^+$ 416.0916, found 416.0918.

Synthesis of compounds 20-29

*General Procedure 4: Friedel-Craft acylation for the synthesis of compounds **20a-c***. $AlCl_3$ (3.0 eq) was added to a solution of 3,5-dimethoxyphenol **18** (1.0 eq) in anhydrous DCM (0.4 M) and the resulting suspension was stirred at room temperature under an inert atmosphere for 30 minutes. Then, the appropriate acyl chloride **19a-c** (1.1 eq) was slowly added and the reaction mixture was stirred at room temperature. After complete conversion of starting material, the reaction mixture was cooled with an ice-bath and acidified with HCl 1M. Then, organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. Trituration or purification by silica gave the pure compounds **20a-c**.

*1-(2-hydroxy-4,6-dimethoxyphenyl)propan-1-one (**20a**).* Title compound was synthesized according to general procedure 4 using 3,5-dimethoxyphenol **18** (300 mg, 1.95 mmol), $AlCl_3$ (780 mg, 5.85 mmol), and propanoyl chloride **19a** (0.19 mL, 2.14 mmol). Trituration with methanol (3 mL) gave the pure product **20a** (214 mg, 53% yield). UPLC/MS Rt = 2.30 min (gradient 1), MS (ESI) m/z: 211.1 $[M+H]^+$.$[M+H]^+$ calculated for $C_{11}H_{14}O_4$: 211.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.08 (s, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 5.92 (d, *J* = 2.4 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.02 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H).

*1-(2-hydroxy-4,6-dimethoxyphenyl)pentan-1-one (**20b**).* Title compound was synthesized according to general procedure 4 using 3,5-dimethoxyphenol **18** (300 mg, 1.95 mmol), $AlCl_3$ (780 mg, 5.85 mmol), and valeryl chloride **19b** (0.26 mL, 2.14 mmol). Purification by silica (elution by gradient from 100:0 to 90:10 cyclohexane\EtOAc) afforded pure compound **20b** (275 mg, 59% yield). UPLC/MS Rt = 2.64 min (gradient 1), MS (ESI) m/z: 239.0 $[M+H]^+$.$[M+H]^+$ calculated for $C_{13}H_{19}O_4$: 239.1. ^{1}H NMR (400 MHz, DMSO–d_6) δ 13.56 (s, 1H), 6.11 (d, *J* = 2.3 Hz, 1H), 6.08 (d, *J* = 2.3 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.92 (t, *J* = 7.4 Hz, 2H), 1.55 (p, *J* = 7.4 Hz, 3H), 1.40 – 1.25 (m, 3H), 0.90 (t, *J* = 7.3 Hz, 3H).

*1-(2-hydroxy-4,6-dimethoxyphenyl)hexan-1-one (**20c**).* Title compound was synthesized according to general procedure 4 using 3,5-dimethoxyphenol **18** (300 mg, 1.95 mmol), $AlCl_3$ (780 mg, 5.85 mmol), and hexanoyl chloride **19c** (0.19 mL, 2.14 mmol). Purification by silica (elution by gradient from 100:0 to 90:10 cyclohexane\EtOAc) afforded pure compound **20c** (282 mg, 57% yield). UPLC/MS Rt = 1.89 min (method B), MS (ESI) m/z: 253.2 $[M+H]^+$.$[M+H]^+$ calculated for $C_{14}H_{21}O_4$: 253.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.10 (s, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 5.92 (d, *J* = 2.4 Hz, 1H), 3.85 (s,

3H), 3.82 (s, 3H), 3.01 – 2.93 (m, 2H), 1.66 (p, *J* = 7.3 Hz, 2H), 1.39 – 1.29 (m, 4H), 0.95 – 0.87 (m, 3H).

*General Procedure 5: aldol condensation for the synthesis of compounds **22a-22c**.* The appropriate ketone **20a-c** (1.0 eq.) and 3,4-dimethoxybenzaldehyde **21** (1.1 eq) were added to a solution of KOH (20.0 eq.) in MeOH (0.12 M). The reaction mixture was stirred at room temperature. After complete conversion of starting materials, the reaction mixture was acidified to pH=5 with HCl 1M and extracted with EtOAc (3x5 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The product was purified by flash chromatography or trituration with EtOH yielding the pure intermediates **22a-c**.

*(E)-3-(3,4-dimethoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)-2-methylprop-2-en-1-one (**22a**).* Titled compound was synthesized following the general procedure 5 previously described using 1-(2-hydroxy-4,6-dimethoxyphenyl)propan-1-one **20a** (100 mg, 0.48 mmol), 3,4-dimethoxybenzaldehyde **21** (87 mg, 0.53 mmol) and KOH (539 mg, 9.6 mmol) in MeOH (5 mL). Purification by silica (elution by gradient from 100:0 to 80:20 cyclohexane\EtOAc) afforded the pure compound **22a** (80 mg, 47% yield). UPLC/MS Rt = 2.12 min (gradient 1), MS (ESI) m/z: 359.1 $[M+H]^+$.$[M+H]^+$ calculated for $C_{20}H_{23}O_6$: 359.1. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 7.11 (d, *J* = 1.6 Hz, 1H), 7.00 (s, 2H), 6.97 (s, 1H), 6.12 (d, *J* = 2.2 Hz, 1H), 6.07 (d, *J* = 2.1 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 2.09 (d, *J* = 1.3 Hz, 3H).

*(E)-2-(3,4-dimethoxybenzylidene)-1-(2-hydroxy-4,6-dimethoxyphenyl)pentan-1-one (**22b**).* Titled compound was synthesized following the general procedure 5 previously described using 1-(2-hydroxy-4,6-dimethoxyphenyl)pentan-1-one **20b** (105 mg, 0.60 mmol), 3,4-dimethoxybenzaldehyde **21** (101 mg, 0.66 mmol) and KOH (675 mg, 12 mmol) in MeOH (5 mL). Purification by silica (elution by gradient from 100:0 to 30:70 cyclohexane\EtOAc) afforded pure compound **22b** (116 mg, 50% yield). UPLC/MS Rt = 2.40 min (gradient 1), MS (ESI) m/z: 387.2 $[M+H]^+$.$[M+H]^+$ calculated for $C_{22}H_{27}O_6$: 387.1. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 9.70 (s, 1H), 7.04 (s, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.97 – 6.89 (m, 2H), 6.12 (d, *J* = 2.1 Hz, 1H), 6.07 (d, *J* = 2.1 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 1.57 – 1.44 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

*(E)-2-(3,4-dimethoxybenzylidene)-1-(2-hydroxy-4,6-dimethoxyphenyl)hexan-1-one (**22c**).* Titled compound was synthesized following the general procedure 5 previously described using 1-(2-hydroxy-4,6-dimethoxyphenyl)hexan-1-one **20c** (150 mg, 0.6 mmol), 3,4-dimethoxybenzaldehyde **21** (109 mg, 0.66 mmol) and KOH (707 mg, 12.6 mmol) in MeOH (7 mL). Purification by silica

(elution by gradient from 100:0 to 60:40 cyclohexane\EtOAc) afforded pure compound **56c** (81 mg, 35% yield). UPLC/MS Rt = 2.50 min (gradient 1), MS (ESI) m/z: 401.0 $[M+H]^+$.$[M+H]^+$ calculated for $C_{23}H_{29}O_6$: 401.2. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 9.70 (s, 1H), 7.06 – 6.97 (m, 2H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 2.1 Hz, 1H), 6.07 (d, *J* = 2.1 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 2.62 – 2.53 (m, 2H), 1.51 – 1.42 (m, 2H), 1.42 – 1.31 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H).

*General procedure 6: Oxidative cyclization for the synthesis of compounds **23a-c** (Scheme 1).* The appropriate chalcone **22a-c** (1 eq.) was dissolved in DMSO (0.3 M) and heated at 135 °C under argon atmosphere. I_2 (0.05 eq.) was added and the reaction mixture was stirred until full conversion of starting material. After reaction completion, the reaction mixture was cooled to room temperature and $Na_2S_2O_3$ 1N was added to quench the I_2. The crude product was filtered, washed with water and purified by flash chromatography or trituration yielding the pure compounds **23a-c**.

*2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-3-methyl-4H-chromen-4-one (**23a**).* Title compound was synthesized according to general procedure 6 previously described using **22a** (77 mg, 0.22 mmol) and I_2 (2.7 mg, 0.01 mmol) in DMSO (0.7 mL). Trituration with EtOH (1 mL) afforded pure compound **23a** (59 mg, 77% yield). UPLC/MS Rt = 1.96 min (gradient 1), MS (ESI) m/z: 357.0 $[M+H]^+$.$[M+H]^+$ calculated for $C_{20}H_{21}O_6$: 357.1. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 7.28 – 7.20 (m, 2H), 7.14 – 7.08 (m, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 3.87 (s, 3H), 3.86 – 3.80 (m, 9H), 1.96 (s, 3H).

*2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-3-propyl-4H-chromen-4-one (**23b**).* Title compound was synthesized according to general procedure 6 previously described using **22b** (116 mg, 0.30 mmol) and I_2 (4.0 mg, 0.01 mmol) in DMSO (1.0 mL). Purification by silica (elution by gradient from 75:15 to 50:50 cyclohexane\EtOAc) afforded pure compound **23b** (54 mg, 50% yield). UPLC/MS Rt = 2.23 min (gradient 1), MS (ESI) m/z: 385.0 $[M+H]^+$.$[M+H]^+$ calculated for $C_{22}H_{25}O_6$: 385.2. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 7.20 – 7.15 (m, 2H), 7.13 (s, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 2.38 – 2.29 (m, 2H), 1.53 – 1.39 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H).

*3-butyl-2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (**23c**).* Title compound was synthesized according to general procedure 6 previously described using **22c** (81 mg, 0.20 mmol) and I_2 (4 mg, 0.01 mmol) in DMSO (0.7 mL). Trituration with EtOH (1 mL) afforded pure compound **23c** (48 mg, 61% yield). UPLC/MS Rt = 2.38 min (gradient 1), MS (ESI) m/z: 399.0 $[M+H]^+$.$[M+H]^+$

calculated for $C_{23}H_{27}O_6$: 399.2. ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.20 – 7.14 (m, 2H), 7.14 – 7.08 (m, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 6.47 (d, *J* = 2.3 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 2.36 (t, *J* = 7.9 Hz, 2H), 1.42 (p, *J* = 7.5 Hz, 2H), 1.23 (h, *J* = 7.3 Hz, 2H), 0.81 (t, *J* = 7.3 Hz, 3H).

*7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-5-hydroxy-3-(((2R,3S, 4R,5R,6S)-3,4,5-trihydroxy-6-((((2S,3S,4S,5S,6R)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (**25**).* To a solution of rutin **24** (2000 mg, 2.96 mmol) in DMF (20 mL) were added K_2CO_3 (1716 mg, 12.44 mmol) and benzoyl bromide (2.8 mL, 23.68 mmol). The reaction mixture was stirred overnight at room temperature. Then it was diluted with EtOAc (60 mL). The organic phase was divided, washed with water (2x50 mL), dried over $MgSO_4$ and concentrated under vacuum yielding of crude **25**, which was used without further purification for the next step (2000 mg). UPLC/MS Rt = 2.44 min (gradient 1), MS (ESI) m/z: 881.3 $[M+H]^+$.$[M+H]^+$ calculated for $C_{48}H_{49}O_{16}$: 881.3.

*7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3,5-dihydroxy-4H-chromen-4-one (**26**).* Crude intermediate **25** (2000 mg, 2.27 mmol) was dissolved in EtOH (14 mL) and added with HCl 37% (2 mL). The reaction mixture was refluxed for 2 hours. After complete conversion of starting material, the reaction mixture was cooled to room temperature and filtered. The precipitate was washed with water (5 mL) and cold MeOH (5 mL) yielding pure **26** (1394 mg, yield: 82% over two steps). UPLC/MS Rt = 2.55 min (gradient 2), MS (ESI) m/z: 573.2 $[M+H]^+$.$[M+H]^+$ calculated for $C_{36}H_{29}O_7$: 573.2. ^{1}H NMR (400 MHz, DMSO–d_6) δ 11.70 (s, 1H), 7.85 (d, *J* = 2.1 Hz, 1H), 7.77 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.54 – 7.29 (m, 15H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 5.25 (s, 4H), 5.15 (s, 2H).

*General procedure 7: alcohol alkylation for the synthesis of compounds **28a-c**.* K_2CO_3 (3.0 eq) and the appropriate alkyl halide (1.4 eq) were added to a solution of intermediate **26** (1.0 eq) in DMF (0.03-0.06 M). The reaction was stirred at room temperature under an inert atmosphere until full conversion of starting material. Then, the reaction mixture was poured into water (30 mL) and extracted with EtOAc (20 mL x2). Combined organic layer was divided, dried over $MgSO_4$, filtered and concentrated under vacuum yielding crude **28a-c**, that was used for the next step without further purification.

*7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-butoxy-5-hydroxy-4H-chromen-4-one (**28a**).* Title compound was synthesized following the general procedure 7 previously described using intermediate **26** (300 mg, 0.50 mmol), 1-bromobutane (0.07 mL, 0.70 mmol), and K_2CO_3 (207 mg,

1.50 mmol) in DMF (10 mL). UPLC/MS Rt = 2.72 min (gradient 2), MS (ESI) m/z: 629.0 $[M+H]^+$.$[M+H]^+$ calculated for $C_{40}H_{37}O_7$: 629.2.

*7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-5-hydroxy-3-(2-hydroxyethoxy)-4H-chromen-4-one (**28b**).* Title compound was synthesized following the general procedure 7 previously described using intermediate **26** (180 mg, 0.30 mmol), 2-bromoethanol (0.03 mL, 0.45 mmol), and K_2CO_3 (124 mg, 0.90 mmol) in DMF (10 mL). UPLC/MS Rt = 2.58 min (gradient 2), MS (ESI) m/z: 615.0 $[M-H]^-$.$[M-H]^-$ calculated for $C_{38}H_{31}O_8$: 615.2.

*7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-5-hydroxy-3-(3-hydroxypropoxy)-4H-chromen-4-one (**28c**).* Title compound was synthesized following the general procedure 7 previously described using intermediate **26** (350 mg, 0.60 mmol), 3-bromo-1-propanol (0.14 mL, 0.90 mmol), and K_2CO_3 (248 mg, 1.80 mmol) in DMF (10 mL). UPLC/MS Rt = 2.40 min (gradient 2), MS (ESI) m/z: 631.0 $[M+H]^+$.$[M+H]^+$ calculated for $C_{39}H_{35}O_8$: 631.2.

*General procedure 8: α-alkylation of esters for the synthesis of compounds **29b-29d**.* LiHMDS or LDA were added to a THF solution (2M) of starting material metil-2-(3,4-dimethoxyphenyl)acetate **29a** (1.0 eq) at -78°C under argon. After 40 minutes, alkyliodide (2.0 equiv.) was dropwise added and reaction mixture was left to reach room temperature. After no starting material was detected by UPLC, reaction mixture was quenched by slow addition of ice and HCl 2M until pH 6. The mixture was then extracted three times with EtOAc and collected organic layers were dried over Na_2SO_4. After evaporation of solvent, the residual crude was purified by silica gel chromatography.

*Methyl-2-(3,4-dimethoxyphenyl)propanoate (**29b**).* Compound **29b** was synthesized following the general procedure 8 using methyl 2-(3,4-dimethoxyphenyl)acetate **29a** (400 mg, 1.9 mmol), LiHMDS (540 µL, 2.85 mmol), iodomethane (260 µL, 3.8 mmol), THF dry (1.0 mL). Purification by silica (elution by gradient from 100:0 to 75:25 cyclohexane/EtOAc) afforded pure compound **29b** (306 mg, 72% yield). UPLC/MS Rt: 1.74 min (gradient 1), MS (ESI) m/z 225.1, $[M+H]^+$. $[M+H]^+$ calculated for $C_{12}H_{17}O_4$: 225.1. ^{1}H NMR (400 MHz, DMSO–d_6) δ 6.89 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 2.1 Hz, 1H), 6.77 (dd, J = 8.2, 2.1 Hz, 1H), 3.76 – 3.68 (m, 7H), 3.57 (s, 3H), 1.36 (d, J = 7.1 Hz, 3H).

*Methyl-2-(3,4-dimethoxyphenyl)esanoate (**29c**).* Compound **29c** was synthesized following the general procedure 8 using methyl 2-(3,4-dimethoxyphenyl)acetate **29a** (300 mg, 1.43 mmol), LiHMDS (400 µL, 2.14 mmol), 1-iodobutane (2320 µL, 2.85 mmol), THF dry (0.71 mL). Purification by silica (elution by gradient from 100:0 to 85:15 cyclohexane/EtOAc) afforded pure compound **29c** (228 mg, 60% yield). UPLC/MS Rt: 2.27 min (gradient 1), MS (ESI) m/z 267.1, $[M+H]^+$. $[M+H]^+$

calculated for $C_{15}H_{23}O_4$: 267.2. ^{1}H NMR (400 MHz, DMSO–d_6) δ 6.89 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 2.0 Hz, 1H), 6.78 (dd, J = 8.2, 2.0 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.57 (s, 3H), 3.52 (t, J = 7.7 Hz, 1H), 1.99 – 1.85 (m, 1H), 1.71 – 1.58 (m, 1H), 1.33 – 1.06 (m, 4H), 0.82 (t, J = 7.2 Hz, 3H).

*Methyl-2-(3,4-dimethoxyphenyl)-6,6,6-trifluoroesanoate (**29d**).* Compound **29d** was synthesized following the general procedure 8 using methyl 2-(3,4-dimethoxyphenyl)acetate **29a** (400 mg, 1.9 mmol), LDA (1.4 mL, 2.85 mmol), 1,1,1-trifluoro-4-iodobutane (270 µL, 2.09 mmol), THF dry (1.0 mL). Purification by silica (elution by gradient from 100:0 to 80:20 cyclohexane/EtOAc) afforded pure compound **29d** (339 mg, 55% yield). UPLC/MS Rt: 2.35 min (gradient 2), [MS (ESI) m/z 321.1, $[M+H]^+$. $[M+H]^+$ calculated for $C_{15}H_{20}F_3O_4$: 321.1. ^{1}H NMR (400 MHz, DMSO–d_6) δ 6.90 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 2.0 Hz, 1H), 6.79 (dd, J = 8.2, 2.0 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.64 – 3.56 (m, 4H), 2.32 – 2.16 (m, 2H), 2.05 – 1.93 (m, 1H), 1.81 – 1.70 (m, 1H), 1.46 – 1.27 (m, 2H).

Synthesis of compounds 33, 34

*General procedure 9: ester hydrolysis for the synthesis of compounds **33** and **34**.* Corresponding ester **29c**-**29d** (1.0 equiv) was dissolved in a 10:1 mixture of THF/H_2O (0.1 M) and LiOH (2.0 equiv) and reaction mixture was heated up to 50°C for 16 hours. After no starting material was detected by UPLC, reaction mixture was cooled to root temperature and HCl 2M was slowly added until pH <7. The mixture was then extracted three times with EtOAc and collected organic layers were dried over Na_2SO_4. After evaporation of solvent, the residual crude was purified by silica gel chromatography.

*2-(3,4-dimethoxyphenyl)hexanoic acid (**33**).* Compound **33** was synthesized following the general procedure 9 using ester **29c** (330 mg, 1.03 mmol), LiOH (49 mg, 2.06 mmol), THF (9.3 mL), H_2O (1.0 mL). Purification by silica (elution by gradient from 70:30 to 30:70 cyclohexane/DCM, then from 50:50 to 0:100 DCM/EtOAc) afforded pure compound **33** (234 mg, 90% yield). UPLC/MS Rt: 1.85 min (gradient 1), [MS (ESI) m/z 251.2, $[M-H]^-$,253.1, $[M+H]^+$. $[M+H]^+$ calculated for $C_{14}H_{21}O_4$: 253.1. ^{1}H NMR (400 MHz, DMSO–d_6) δ 6.88 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.79 (dd, J = 8.2, 2.1 Hz, 1H), 3.72 (s, 3H), 3.72 (s, 3H), 1.97 – 1.83 (m, 1H), 1.66 – 1.53 (m, 1H), 1.35 – 1.06 (m, 4H), 0.83 (t, J = 7.2 Hz, 3H).

*2-(3,4- dimethoxyphenyl)-6,6,6-trifluorohexanoic acid (**34**).* Compound **34** was synthesized following the general procedure 9 using ester **29d** (330 mg, 1.03 mmol), LiOH (49 mg, 2.06 mmol), THF (9.3 mL), H_2O (1.0 mL). Purification by silica (elution by gradient from 70:30 to 30:70

cyclohexane/DCM, then from 50:50 to 0:100 DCM/EtOAc) afforded pure compound **34** (278 mg, 88% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 6.90 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.80 (dd, J = 8.2, 2.1 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.47 (t, J = 7.7 Hz, 1H), 2.31 – 2.16 (m, 2H), 2.05 – 1.90 (m, 1H), 1.76 – 1.65 (m, 1H), 1.49 – 1.30 (m, 2H).

Synthesis of compounds 31a-31d, 37a, 37b

*General procedure 10: Claisen condensation for the synthesis of compounds **31a**, **31c-31d, 37a.***
Method A. A solution of ketone **30** (1 eq.) in THF dry (0.3 M) was added to a suspension of NaH 60% dispertion in mineral oil (4 eq.) in THF dry (1.2 M) under argon, followed by the addition of appropriate ester (2 eq.) at room temperature. Then reaction mixture stirred at reflux under argon until complete consumption of starting material. The reaction mixture was quenched by pouring into ice and further acidified until pH 6 with HCl 2M aq and then extracted with EtOAc. Collected organic layers were dried over Na2SO4, filtered, and concentrated under vacuum. The crude was used as such without further purification.
Method B. To a THF solution (0.12 M) of ketone **30** (1.0 equiv), LDA (3.0 equiv) was added at -78°C under argon. The reaction mixture was stirred for 30 minutes at the same temperature, then further 30 minutes at 0°C. Next, appropriate ester (1.0 equiv) was dropwise added at -78°C within 15 minutes. After 24 hours at room temperature, reaction mixture was quenched adding slowly H2O and HCl 2M until pH <7. The mixture was then extracted three times with EtOAc and collected organic layers were dried over Na_2SO_4. After evaporation of solvent, the residual crude was purified by silica gel chromatography.
Method B. To a dry DCM solution (0.25 M) of carboxylic acid **33-34** (1.0 equiv) in a septum capped vial under argon atmosphere, SOCl2 (10.0 equiv) was added. The reaction mixture was refluxed for 1 hour. Then, the solvent and SOCl2 reside were evaporated under vacuum obtaining acyl chloride which was dissolved in THF (1.0 mL per 0.4 mmol). Meantime, enolate was prepared in a round-bottomed flask under argon following procedure of previous method B using ketone **30** (1.0 equiv), dry THF (0.12 M), LDA (3.0 equiv). Thus, acyl chloride was dropwise added to that solution and reaction mixture was left to react overnight. The mixture was quenched with H_2O and HCL 2M until pH <7 and extracted with EtOAc. The collected organic layers were dried over Na2SO4 and, after evaporation of solvent, the residual crude was purified by silica gel chromatography.

*4-(3,4-dimethoxyphenyl)-1-(2-hydroxy-6-methoxyphenyl)butane-1,3-dione (**31a**).* Compound **31a** was prepared following general procedure 10 method A using 6′-hydroxy-2′-methoxyacetophenone

30 (200 mg, 1.2 mmol), methyl 2-(3,4-dimethoxyphenyl)acetate **29a** (505, 2.4 mmol), NaH 60% dispersion in mineral oil (192 mg, 4.8 mmol) in THF dry (6 mL). The crude was used as such without further purification. UPLC/MS Rt: 1.85 min (gradient 1); MS (ESI) m/z: 345.0 $[M+H]^+$, $[M+H]^+$ calculated for $C_{19}H_{21}O_6$: 345.4.

*4-(3,4-dimethoxyphenyl)-1-(2-hydroxy-6-methoxyphenyl)pentan-1,3-dione (**31b**).* To a THF solution (2.8 mL, 0.12 M) of ketone **30** (56 mg, 0.34 mmol, 1.0 equiv), LDA (0.51 µL, 1.02 mmol, 3.0 equiv) was added at -78°C under argon. The reaction mixture was stirred for 30 minutes at the same temperature, then further 30 minutes at 0°C. Next, ester **29b** (77 mg, 0.348 mmol, 1.0 equiv) was dropwise added at -78°C within 15 minutes. After 24 hours at room temperature, reaction mixture was quenched adding slowly H_2O and HCl 2M until pH <7. The mixture was then extracted three times with EtOAc and collected organic layers were dried over Na_2SO_4. After evaporation of solvent, the residual crude was filtered on silica (elution by gradient from 90:10 to 70:30 cyclohexane/EtOAc) in order to eliminate super apolar and polar impurities furnishing a more clean crude which was used as such in the next step. UPLC/MS Rt: 2.02 min (gradient 1); MS (ESI) m/z: 359.1 $[M+H]^+$, $[M+H]^+$ calculated for $C_{20}H_{23}O_6$: 359.1.

*4-(3,4-dimethoxyphenyl)-1-(2-hydroxy-6-methoxyphenyl)octan-1,3-dione (**31c**).* Compound **31c** was synthesized following the general procedure 10 method B using **33** (100 mg, 0.396 mmol), $SOCl_2$ (290 μL, 3.96 mmol) dry DCM (1.5 mL), for the formation of acyl chloride, and **30** (60 mg, 0.36 mmol), LDA (0.54 mL, 1,08 mmol) dry THF (3 ml), for the generation of enaolate. The crude was filtered on silica (elution by gradient from 100:0 to 50:50 cyclohexane/EtOAc) in order to eliminate super apolar and polar impurities furnishing a more clean crude which was used as such in the next step. UPLC/MS Rt: 1,67 min (gradient 2); MS (ESI) m/z: 399.2 $[M-H]^-$; 401.1 $[M+H]^+$, $[M+H]^+$ Calculated for $C_{23}H_{29}O_6$: 401.2.

*4-(3,4-dimethoxyphenyl)-8,8,8-trifluoro-1-(2-hydroxy-6-methoxyphenyl)octan-1,3-dione (**31d**).* Compound **31d** was synthesized following the general procedure 10 method B using **34** (138 mg, 0.45 mmol), $SOCl_2$ (330 μL, 4.5 mmol) dry DCM (1.7 mL), for the formation of acyl chloride, and **30** (50 mg, 0.30 mmol), LDA (0.45 mL, 0.90 mmol) dry THF (4.9 ml), for the generation of enaolate. The crude was filtered on silica (elution by gradient from 100:0 to 50:50 cyclohexane/EtOAc) in order to eliminate super apolar and polar impurities furnishing a more clean crude which was used as such in the next step. UPLC/MS Rt: 1,48 min (gradient 2); MS (ESI) m/z: 453.3 $[M-H]^-$, 455.1 [M+H]+, $[M+H]_+$ Calculated for $C_{23}H_{26}F_3O_6$: 455.2.

*1-(2-hydroxy-6-methoxyphenyl)butane-1,3-dione (**37a**).* Compound **37a** was prepared according to general procedure 10 method A using: 6′-hydroxy-2′-methoxyacetophenone **30** (1 mL, 8.3 mmol), NaH 60% dispersion in mineral oil (1328 mg, 33.2 mmol) in a 5:1 mixture THF/EtOAc (24 mL). The obtained crude was used as such, without further purifications. UPLC/MS Rt: 1.42 min (gradient 1), MS (ESI) m/z 285.0, [M−H]−. [M−H]− calculated for $C_{11}H_{11}O_4$: 207.2.

*ethyl 5-methoxy-4-oxo-4H-chromene-2-carboxylate (**37b**).* NaOEt (210 mg, 3 mmol) was dissolved in absolute EtOH (4 mL). A mixture of diethyl oxalate (310 mg, 2.1 mmol) and 2-Hydroxy-6-methoxyacetophenone 30 (100 mg, 0.6 mmol) in absolute EtOH (2 mL) was slowly added to NaOEt solution. The solution stirred at reflux for 2 hours until complete consumption of starting material. Then the mixture was allowed to cool to room temperature and neutralized with HCl (2M)aq. The mixture was extracted with EtOAc (3 x 5 mL), collected organic layer were dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification by silica (elution by gradient from 100:0 to 75:25 Cyclohexane/EtOAc) afforded pure title compound **37b** (120 mg, 79%). UPLC/MS Rt: 1.65 min (gradient 1), MS (ESI) m/z 249.0, [M+H]+. [M+H]+ calculated for C17H15O5: 249.3. ^{1}H NMR (400 MHz, CDCl3) δ 7.60 (t, J = 8.4 Hz, 1H), 7.16 (dd, J = 8.5, 0.9 Hz, 1H), 7.00 (s, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H).

Synthesis of compounds 32a-32d, 38a

General procedure 11: dehydrative cyclization

Method A. Dikeetone **31a** and **37a** (1 eq.) were treated with a 8:1 mixture MeOH/HCl 37% (0.15 M). Reaction mixture stirred at room temperature until complete consumption of starting material. Then the solvent was removed under vacuum, the residue was rised with EtOAc and washed with NaHCO3 sat. sol. Organic layer was divided, dried over Na2SO4, filtered and concentrated under vacuum. Purification by typical silica afforded the pure desired product.

Method B. To a solution of crude **31b-31d** in CH_3COOH (0.12 M), H_2SO_4 conc (0.25 mL per 4.0 mmol of starting material) was added and reaction mixture was heated up to 100°C. After no starting material was detected by UPLC the solvent was evaporated, H2O was added and extracted three times with EtOAc. The collected organic layers were dried over Na_2SO_4 and, after evaporation of solvent, the residual crude was purified by silica gel chromatography.

*2-(3,4-dimethoxybenzyl)-5-methoxy-4H-chromen-4-one (**32a**).* Compound **32a** was prepared following general procedure 11 method A using crude **31a** (412 mg), HCl 37% (1 mL) in MeOH (7 mL). Reaction mixture stirred at room temperature for 20 hours. Purification by silica (elution by gradient from 100:0 to 50:50 dichlorometane/EtOAc) afforded the pure title compound **32a** as white powder (145 mg, yield 37 % over 2 steps). UPLC/MS Rt: 1.80 min (gradient 1), MS (ESI) m/z 327.1, $[M+H]^+$. $[M+H]^+$ calculated for $C_{19}H_{19}O5$: 327.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 8.41 Hz, 1H), 6.96 (d, J = 8.35 Hz, 1H), 6.83 (bs, 2H), 6.79-6.77 (m, 2H), 6.06 (s, 1H), 3.95 (s, 3H), 3.97 (s, 3H), 3.86 (s, 3H), 3.48 (s, 2H).

*2-(1-(3,4-dimethoxyphenyl)ethyl)-5-methoxy-4H-chromen-4-one (**32b**).* Compound **32b** was synthesized following the general procedure 11 method B using intermediate **31b** (34 mg, 0.095 mmol), CH_3COOH (0.45 mL), H_2SO_4 (2 drops). Purification by silica (elution by gradient from 60:40 to 0:100 cyclohexane/EtOAc) afforded pure compound **32b** (28 mg, 88% yield after 2 steps). UPLC/MS Rt: 1.93 min (gradient 1), MS (ESI) m/z 299.0, $[M-H]^+$. $[M-H]^+$ calculated for $C_{17}H_{14}O_5$: 299.1.0. MS (ESI) m/z 297.2, $[M-H]^-$. $[M-H]^-$ calculated for $C_{17}H_{14}O_5$: 297.1 ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.61 (t, J = 8.4 Hz, 1H), 6.99 (dd, J = 8.5, 0.9 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.63 (dd, J = 8.1, 2.1 Hz, 1H), 6.33 (s, 1H), 4.01 (q, J = 7.2 Hz, 1H), 1.53 (d, J = 7.1 Hz, 3H).

*2-(1-(3,4-dimethoxyphenyl)pentyl)-5-methoxy-4H-chromen-4-one (**32c**).* Compound **32c** was synthesized following the general procedure 11 method B using intermediate **31b** (65 mg, 0.15 mmol), CH_3COOH (0.50 mL), H_2SO_4 (2 drops). Purification by silica (elution by gradient from 90:10 to 0:100 cyclohexane/EtOAc) afforded pure compound **32c** (40 mg, 29% yield after 3 steps). UPLC/MS Rt: 1.21 min (gradient 2), MS (ESI) m/z 383.1, $[M+H]^+$. $[M+H]^+$ calculated for $C_{23}H_{27}O_5$: 383.2. ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.61 (t, J = 8.4 Hz, 1H), 7.08 (dd, J = 8.5, 0.9 Hz, 1H), 6.99 (d, J = 1.6 Hz, 1H), 6.95 – 6.88 (m, 3H), 6.13 (s, 1H), 3.84 – 3.77 (m, 4H), 3.75 (s, 3H), 3.72 (s, 3H), 2.13 – 2.01 (m, 1H), 1.96 – 1.84 (m, 1H), 1.38 – 1.26 (m, 2H), 1.26 – 1.15 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H).

*2-(1-(3,4-dimethoxyphenyl)-5,5,5-trifluoropentyl)-5-methoxy-4H-chromen-4-one (**32d**).* Compound **32d** was synthesized following the general procedure 11 method B using intermediate **31d** (70 mg, 0.154 mmol), CH_3COOH (0.60 mL), H_2SO_4 (2 drops). Purification by silica (elution by gradient from 80:20 to 0:100 cyclohexane/EtOAc) afforded pure compound **32d** (32 mg, 24% yield after 3 steps). UPLC/MS Rt: 1.03 min (gradient 2), MS (ESI) m/z 435.2 $[M-H]^-$; 437.1, $[M+H]^+$. $[M+H]^+$ calculated

for $C_{23}H_{24}F_3O_5$: 437.2. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 7.62 (t, J = 8.4 Hz, 1H), 7.06 (dd, J = 8.5, 0.9 Hz, 1H), 7.00 (s, 1H), 6.97 – 6.91 (m, 3H), 6.15 (s, 1H), 3.89 (t, J = 7.8 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 2.40 – 2.23 (m, 2H), 2.20 – 2.08 (m, 1H), 2.07 – 1.94 (m, 1H).

*5-methoxy-2-methyl-4H-chromen-4-one (**38a**).* Compound **38a** was prepared according to general procedure 11 method A using: crude of compound **37a** (1480 g), HCl 37% (1 mL), in MeOH (20 mL). Purification by typical silica gel (elution by gradient from 100:0 to 75:25 cyclohexane/EtOAc) afforded the pure title compound **38b** as white powder (1.18 g, yield 84 % over 2 steps). UPLC/MS Rt: 1.43 min (gradient 1), MS (ESI) m/z 190.9, $[M+H]^+$. $[M+H]^+$ calculated for $C_{11}H_{11}O_3$: 191.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, J = 8.4 Hz, 1H), 6.98 (dd, J = 8.5, 1.0 Hz, 1H), 6.78 (dd, J = 8.4, 1.0 Hz, 1H), 6.10 (d, J = 0.9 Hz, 1H), 3.97 (s, 3H), 2.31 (d, J = 0.7 Hz, 3H).

Synthesis of compounds 38b-46

*5-methoxy-4-oxo-4H-chromene-2-carboxylic acid (**38b**)*. K_2CO_3 (100 mg, 0.60 mmol) was added to a solution of intermediate **37b** (100 mg, 0.40 mmol) in a 3:1 mixture THF/EtOH (4 mL). Reaction mixture stirred for 6h at 50°C until complete consumption of starting material, then HCl (2M)aq was added until pH=5, and the mixture was extracted with EtOAc (3x4 mL). Collected organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to yield pure compound **38b** (70 mg, 79% yield). UPLC/MS Rt:0.80 min (gradient 1), MS (ESI) m/z 220.9, $[M+H]^+$. $[M+H]^+$ calculated for $C_{11}H_9O_5$: 221.2. ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 7.72 (t, J = 8.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 3.86 (s, 3H).

*(E)-2-(3,4-dimethoxystyryl)-5-methoxy-4H-chromen-4-one (**39**).* Sodium ethoxide (55 mg, 0.31 mmol) was added to a solution of compound **38a** (100 mg, 0.62 mmol) in EtOH (2 mL), followed by addition of a solution of 3,4-dimethoxybenzaldehyde (110 mg, 0.62 mmol) in EtOH (1 mL). Reaction mixture stirred at 50°C for 2 hours. After that, HCl (2M)aq was added to reaction mixture until pH=4, the resulted precipitate was filtered and washed with water (0.5 mL) and dried under vacuum to afford pure title compound **39** (140 mg, 74% yield). UPLC/MS Rt: 1.97 min (gradient 1), MS (ESI) m/z 339.0, $[M+H]^+$. $[M+H]^+$ calculated for $C_{20}H_{19}O_5$: 338.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, J = 8.4 Hz, 1H), 7.51 (d, J = 16.0 Hz, 1H), 7.15 (dd, J = 8.4, 2.0 Hz, 1H), 7.10 (dd, J = 8.4, 1.0 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.82 (dd, J = 8.4, 0.9 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 6.38 (s, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H).

*2-(3,4-dimethoxyphenethyl)-5-methoxy-4H-chromen-4-one (**40**).* Ammonium formate (21 mg, 0.30 mmol) and $Pd(OH)_2/C$ (0.015 g, 15% p/p) were added to a solution of intermediate **39** (100 mg, 0.29 mmol) in MeOH (3 mL). Reaction mixture stirred at 80°C for 4 h. After that the mixture was filtered over a pad of celite, rised with MeOH (10 mL), and concentrated under vacuum. Purification by silica (elution by gradient DCM/EtOAc from 100:0 to 60:40) afforded pure title compound **40** (64 mg, 63%). UPLC/MS Rt: 1.89 min (gradient 1), MS (ESI) m/z 341.0, $[M+H]^+$. $[M+H]^+$ calculated for $C_{20}H_{21}O_5$: 341.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 8.4, 8.4 Hz, 1H), 6.99 (dd, J = 8.4, 0.9 Hz, 1H), 6.81 – 6.76 (m, 2H), 6.75 – 6.69 (m, 2H), 6.08 (s, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 2.97 (dd, J = 9.4, 7.3 Hz, 2H), 2.84 (dd, J = 9.3, 7.2 Hz, 2H).

*2-(3,4-dimethoxyphenyl)ethan-1-ol (**41c**).* To a THF solution of ester **29a**, a 2 M THF solution of $LiAlH_4$ (0.57 mL, 1.14 mmol, 2.0 equiv) was dropwise slowly added at 0°C under inert atmosphere and reaction mixture was left to stir at the same temperature for 1 hour and 30 minutes. Then, very slowly, water was dropwise added maintaining the solution cold with ice bath. When no effervescence was detected, HCl 2M was added until pH <7 and the mixture was extracted three times with 15 mL of EtOAc. Collected organic layers were dried over Na_2SO_4, solvent was evaporated affording pure compound **41c** (104 mg, quantitative yield) which was used as such in the next step. UPLC/MS Rt = 1.20 min (gradient 1), MS (ESI) m/z: 183.0 $[M+H]^+$.$[M+H]^+$ calculated for $C_{10}H_{15}O_3$: 183.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.70 (dd, J = 8.1, 2.0 Hz, 1H), 4.59 (t, J = 5.2 Hz, 1H), 3.56 (td, J = 7.2, 5.2 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H).

*N-(3,4-dimethoxyphenyl)-5-methoxy-4-oxo-4H-chromene-2-carboxamide (**42a**).* HATU (170 mg, 0.43 mmol) and DIPEA (0.23 mL, 1.3 mmol) were sequentially added to a solution of intermediate **38b** (60 mg, 0.29 mmol) in a 3:1 mixture DMF/DCM (4 mL) under argon. Reaction mixture stirred at room temperature for 15 minutes, after that 3,4-dimethoxyaniline **41a** (44 mg, 0.29 mmol) was added and reaction mixture stirred for other 4 hours until complete consumption of starting material. Water (1mL) and HCl (2M)aq were added until pH=7, the mixture was extracted with DCM (3 x 3 mL), collected organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica (elution by gradient from 100:0 to 55:45 DCM/EtOAc) afforded pure title compound **42a** (92 mg, 90%). UPLC/MS Rt: 1.66 min (gradient 1), MS (ESI) m/z 356.0, $[M+H]^+$. $[M+H]^+$ calculated for $C_{19}H_{18}NO_6$: 356.3. ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.78 (t, J = 8.4 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.36 (dd, J = 8.6, 2.4 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 6.76 (s, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.76.

*General procedure 12: Steglich esterification for the synthesis of compounds **42b-42c.*** To a DCM solution (0.36 M) of alcohol **41b-c** (1.0 equiv), DMAP (0.1 equiv), DCC (1.0 equiv) and carboxylic acid **38b** (1.0 equiv) were added at 0°C. After no starting material was detected by UPLC, reaction mixture was filtered to eliminate suspended solid. The evaporation of solvent gives a crude that was purified by silica gel chromatography.

*3,4-dimethoxyphenyl 5-methoxy-4-oxo-4H-chromene-2-carboxylate (**42b**).* Compound **42b** was synthesized following the general procedure 12 using 3,4-dimethoxyphenol **41b** (44 mg, 0.286 mmol) dry DCM (0.75 mL), carboxylic acid **38b** (63 mg, 0.286 mmol), DCC (59 mg, 0.286 mmol), and DMAP (3.5 mg, 0.0286 mmol). Purification by silica (elution by gradient from 100:0 to 70:30 DCM/EtOAc) afforded not pure desired compound **42b**, which was cystrallized by precipitation in DCM with pentane (25 mg, 25% yield). UPLC/MS Rt: 1.76 min (gradient 1), MS (ESI) m/z 357.0, $[M+H]^+$. $[M+H]^+$ calculated for $C_{19}H_{17}O_7$: 357.1. ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.78 (t, *J* = 8.4 Hz, 1H), 7.26 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 7.05 – 7.00 (m, 2H), 6.96 (s, 1H), 6.87 (dd, *J* = 8.7, 2.7 Hz, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H).

*3,4-dimethoxyphenethyl 5-methoxy-4-oxo-4H-chromene-2-carboxylate (**42c**).* Compound **42c** was synthesized following the general procedure 12 using 3,4-dimethoxyphenol **41c** (66 mg, 0.363 mmol) dry DCM (1 mL), carboxylic acid **38b** (80 mg, 0.363 mmol), DCC (75 mg, 0.363 mmol), and DMAP (4.4 mg, 0.0363 mmol). Purification by silica (elution by gradient from 100:0 to 10:90 cyclohexane/EtOAc) afforded pure desired compound **42c** as white-off solid (62 mg, 44% yield). UPLC/MS Rt: 1.84 min (gradient 1), MS (ESI) m/z 385.1, $[M+H]^+$. $[M+H]^+$ calculated for $C_{21}H_{20}O_7$: 385.1. ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.74 (t, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.5, 0.9 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.82 (dd, J = 8.1, 1.9 Hz, 1H), 6.71 (s, 1H), 4.49 (t, J = 6.7 Hz, 2H), 3.86 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 2.96 (t, J = 6.7 Hz, 2H).

*tert-butyl (2-(5-methoxy-4-oxo-4H-chromene-2-carboxamido)ethyl)carbamate (**42d**).* DIPEA (0.52 mL, 3 mmol), PyBOP (780 mg, 1.5 mmol), N-Boc-ethylenediamine **41d** (0.24 mL, 1.5 mmol) were sequentially added to a suspension of compound 21 (220 mg, 1 mmol) in a 4:1 mixture DCM/DMF (10 mL) under argon at 0°C. The reaction mixture was allowed warming to room temperature. After 30 minutes conversion of starting material was complete. Resulted precipitate was filtered, water and DCM were added to filtered, aqueous layer was extracted with DCM (5 mL x 2), and combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The product was purified by silica (elution by gradient from 100/0 to 94/6 DCM/MeOH) yielding the pure

intermediate **42d** (252 mg, 79% yield). UPLC/MS Rt: 1.52 min (gradient 1), MS (ESI) m/z: 363.1 $[M+H]^+$.$[M+H]^+$ Calculated for $C_{18}H_{23}N_2O_6$: 363.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.01 (s, 1H), 7.59 (t, J = 8.4 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.01 (s, 1H), 6.83 (dd, J = 8.4, 0.9 Hz, 1H), 3.97 (s, 3H), 3.56 (q, J = 5.2 Hz, 2H), 3.42 (m, 2H), 1.43 (s, 11H).

*N-(2-aminoethyl)-5-methoxy-4-oxo-4H-chromene-2-carboxamide hydrochloride(**43**).* HCl (4M in 1,4 dioxane) (0.7 mL, 2.82 mmol) was dropwise added to a solution of intermediate **42d** (170 mg, 0.46 mmol) in 1.4-dioxane dry (2.8 mL) under argon. Reaction mixture stirred for 2h, after that the solvent was removed under vacuum. Trituration with Et_2O (1 mL) yielded desire intermediate **43** (122 mg, 87% yield). UPLC/MS Rt: 1.45 min (gradient 1), MS (ESI) m/z: 263.1 $[M+H]^+$.$[M+H]^+$ Calculated for $C_{13}H_{15}N_2O_4$: 263.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (t, J = 5.8 Hz, 1H), 8.08 (s, 3H), 7.76 (t, J = 8.4 Hz, 1H), 7.29 (dd, J = 8.5, 0.9 Hz, 1H), 7.03 (dd, J = 8.4, 1.0 Hz, 1H), 6.67 (s, 1H), 3.87 (s, 3H), 3.56 (q, J = 6.0 Hz, 2H), 3.02 (q, J = 5.9 Hz, 2H).

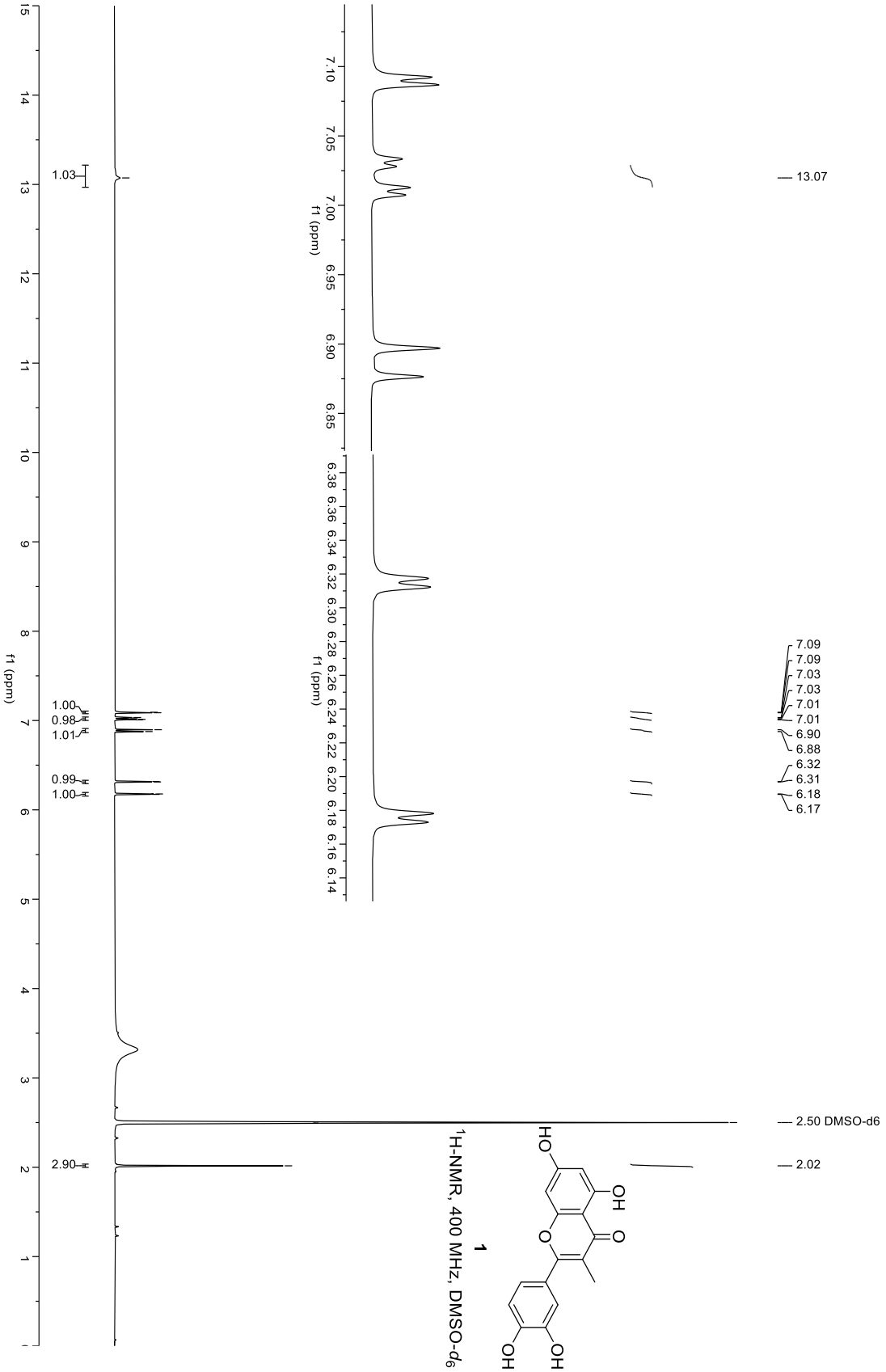
*N-(2-(3,4-dimethoxybenzamido)ethyl)-5-methoxy-4-oxo-4H-chromene-2-carboxamide (**44**).* DIPEA (0.11 mL, 0.6 mmol), and PyBOP (157 mg, 0.30 mmol) were added to a solution of 3,4-dimethoxybenzoic acid (0.24 mL, 0.20 mmol) in a DCM/DMF 4:1 mixture (3 mL) under argon at 0°C. The reaction mixture was allowed warming to room temperature. After 5 minutes a solution of compound **43** in DIPEA/DMF 1:1 mixture (0.22 mL) was dropwise added to the reaction mixture at 0°C under argon. The reaction mixture was allowed warming to room temperature. After 30 minutes conversion of starting material was complete. Brine was added and aqueous layer was extracted with DCM (5 mL x 2), and combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The product was purified by silica (elution by gradient from 100/0 to 94/6 DCM/MeOH) yielding the pure intermediate **44** (57 mg, 66% yield). UPLC/MS Rt: 1.37 min (gradient 1), MS (ESI) m/z: 425.3 $[M-H]^-$.$[M-H]^-$ Calculated for $C_{22}H_{21}N_2O_7$: 425.4 ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (t, J = 5.6 Hz, 1H), 8.52 (t, J = 5.6 Hz, 1H), 7.75 (t, J = 8.4 Hz, 1H), 7.47 (dd, J = 8.3, 2.1 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.63 (s, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.49 – 3.40 (m, 4H).

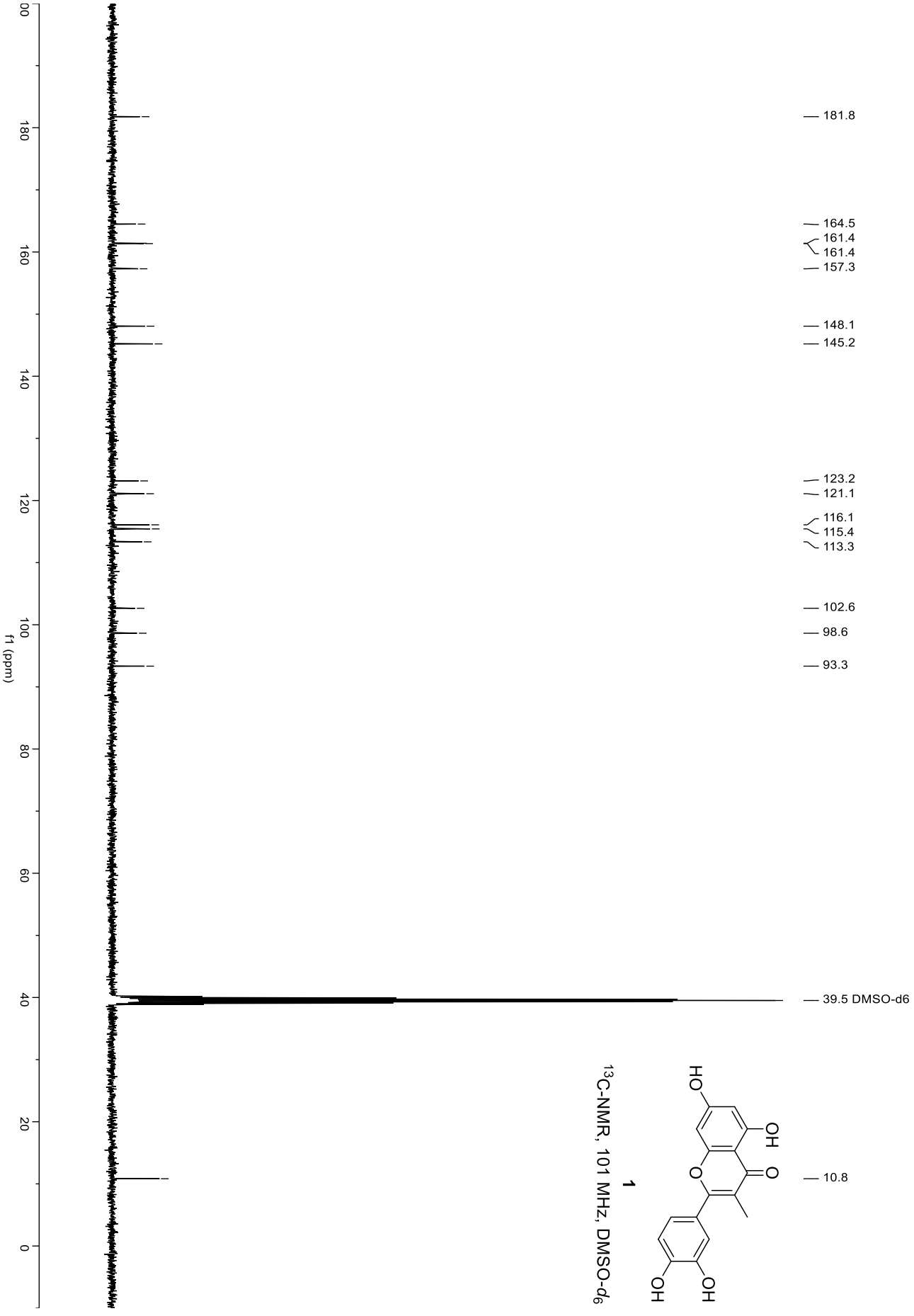
*4-isothiocyanato-1,2-dimethoxybenzene (**45**).* A solution of 3,4-dimethoxyaniline **41a** (300 mg, 1.95 mmol) in $CHCl_3$ dry (2 mL) was added dropwise to a solution of TCDI (384 mg, 2.15 mmol) in $CHCl_3$ (4 mL) under argon. Reaction mixture stirred for 1h at 40°C. After that, solvent was removed under vacuum and the crude was purified by silica (elution by gradient from 100 to 85/15 cyclohexane/EtOAc) yielding compound **45** (216 mg, 42% yield). UPLC/MS Rt: 2.14 min (gradient

1), no ionization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dd, J = 8.6, 2.2 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149. (Cq), 148.7 (Cq), 123.9 (Cq), 118.3 (CH), 111.4 (CH), 109.3 (CH), 56.3 (CH_3), 56.2 (CH_3).

*N-(2-(3-(3,4-dimethoxyphenyl)thioureido)ethyl)-5-methoxy-4-oxo-4H-chromene-2-carboxamide (**46**).* DIPEA (0.18 mL, 1.00 mmol) and a solution of compound **45** (39 mg, 0.20 mmol) in EtOH (1 mL) were sequentially added to a solution of compound **43** (60 mg, 0.20 mmol) in EtOH (1 mL) under argon. Reaction mixture stirred at reflux for 15 minutes. After that, the solvent was removed under vacuum. Crude was purified by trituration with DCM/MeOH 8:2 mixture (1 mL) yielding pure product **46** (44 mg, 49% yield). UPLC/MS Rt: 1.44 min (gradient 1), MS (ESI) m/z: 458.1 $[M+H]^+$.$[M+H]^+$ Calculated for $C_{22}H_{24}N_3O_6S$: 458.5. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 9.14 (t, J = 5.6 Hz, 1H), 7.76 (t, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.77 (dd, J = 8.5, 2.4 Hz, 1H), 6.63 (s, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.68 (m, 2H), 3.65 (s, 3H), 3.49 (q, J = 5.7 Hz, 2H).

3. Representative ^{1}H and ^{13}C NMR Spectra

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123.2
121.1
116.1
115.4
113.3
102.6
98.6
93.3
39.5 DMSO-d6
10.8
f1 (ppm)
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20
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80
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120
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180
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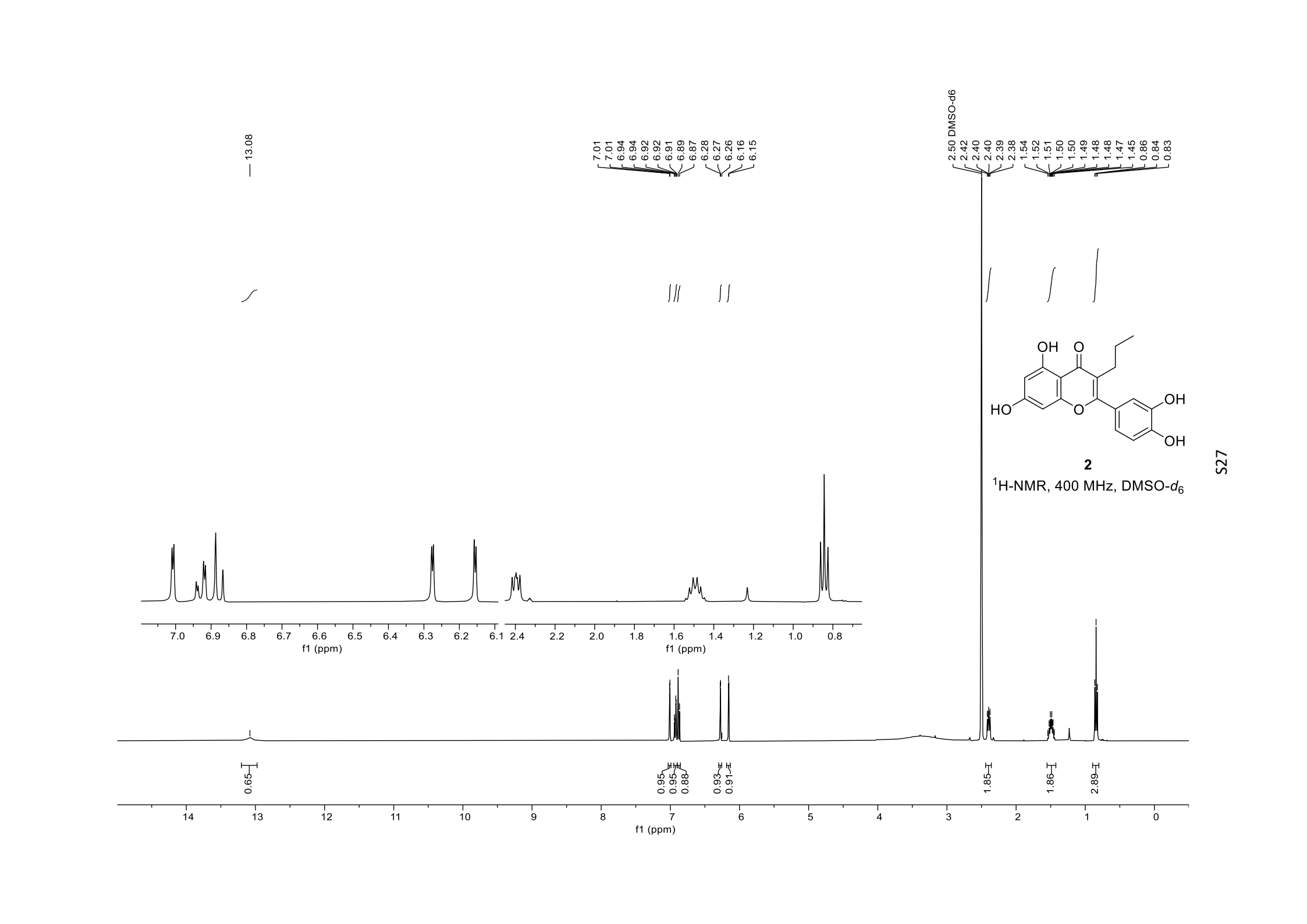
O
O
OH
OH
1
13C-NMR, 101 MHz, DMSO-d6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6.26
6.16
6.15
2.50 DMSO-d6
2.42
2.40
2.40
2.39
2.38
1.54
1.52
1.51
1.50
1.50
1.49
1.48
1.48
1.47
1.45
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0.84
0.83
OH
O
HO
O
OH
OH
2
1H-NMR, 400 MHz, DMSO-d6
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0.95
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0.93
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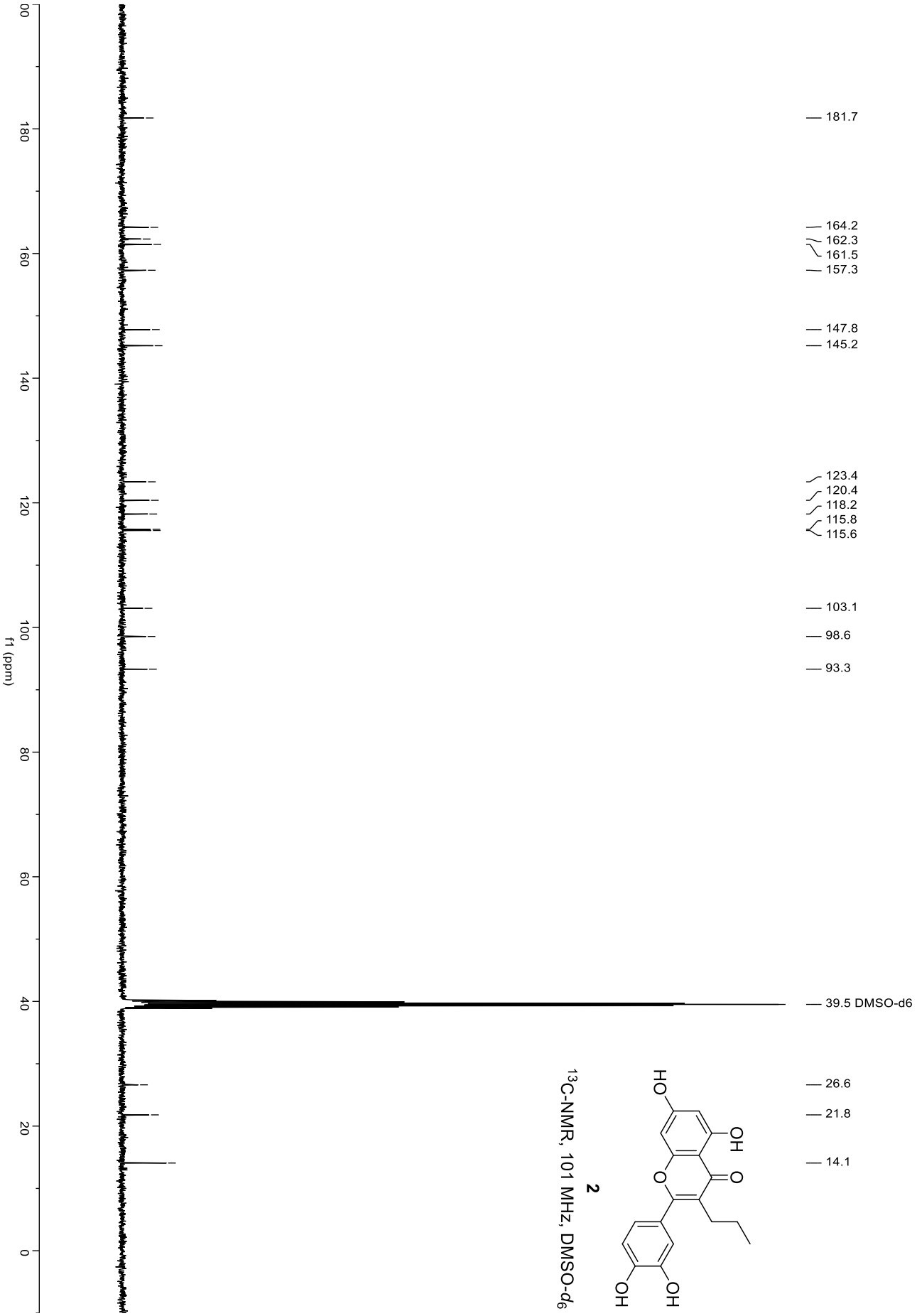
1.85
1.86
2.89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39.5 DMSO-d6
26.6
21.8
14.1
f1 (ppm)
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180
160
140
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OH
O
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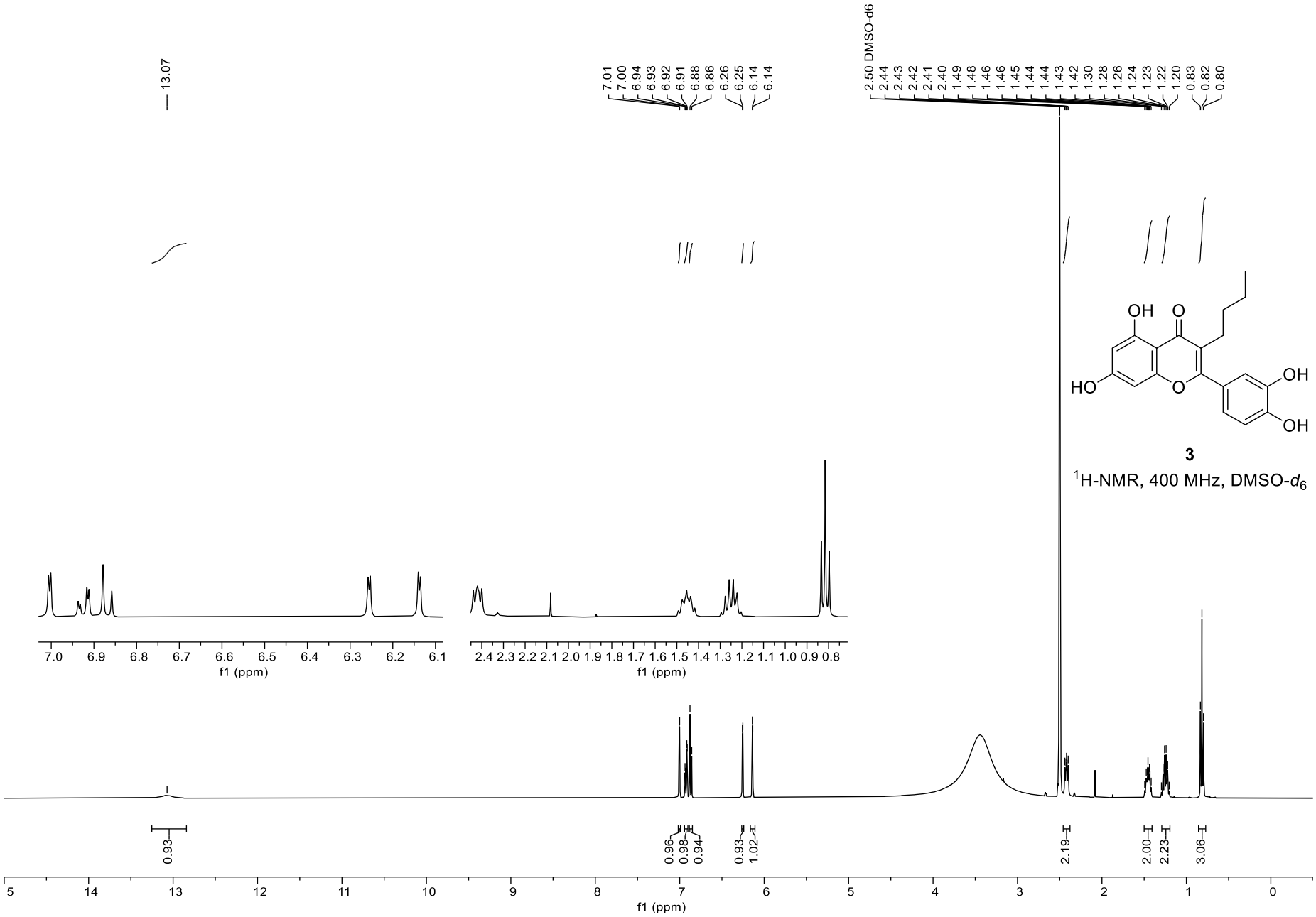
OH
OH
2
^{13}C-NMR, 101 MHz, DMSO-d_6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6.88
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2.50 DMSO-d6
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1.44
1.44
1.43
1.42
1.30
1.28
1.26
1.24
1.23
1.22
1.20
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0.80
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HO
O
OH
OH
3
1H-NMR, 400 MHz, DMSO-d6
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0.94
0.93
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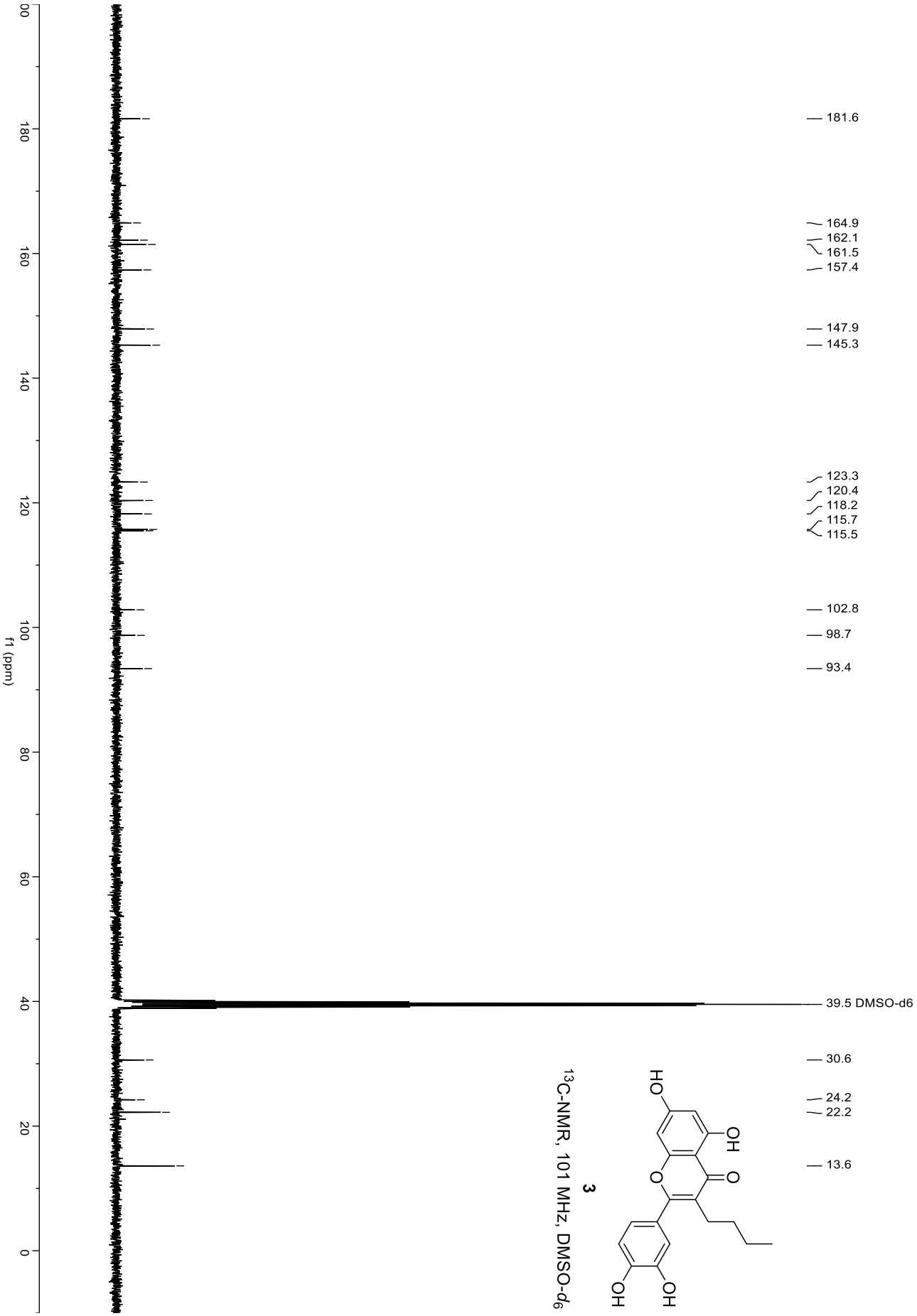
2.00
2.23
3.06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f1 (ppm)
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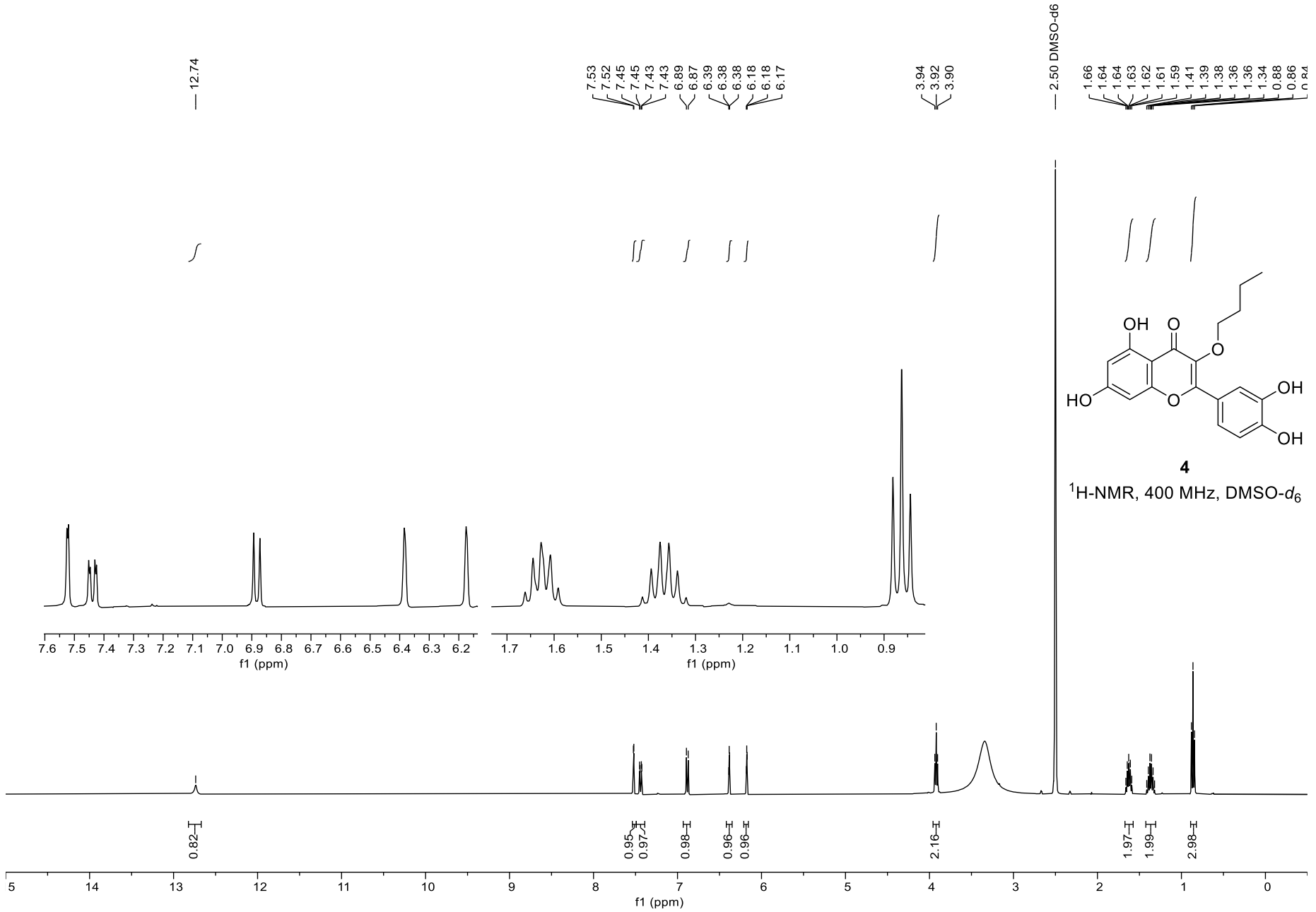
13C-NMR, 101 MHz, DMSO-d6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3.90
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1.64
1.63
1.62
1.61
1.59
1.41
1.39
1.38
1.36
1.36
1.34
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0.86
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HO
O
OH
OH
4
1H-NMR, 400 MHz, DMSO-d6
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0.98
0.96
0.96
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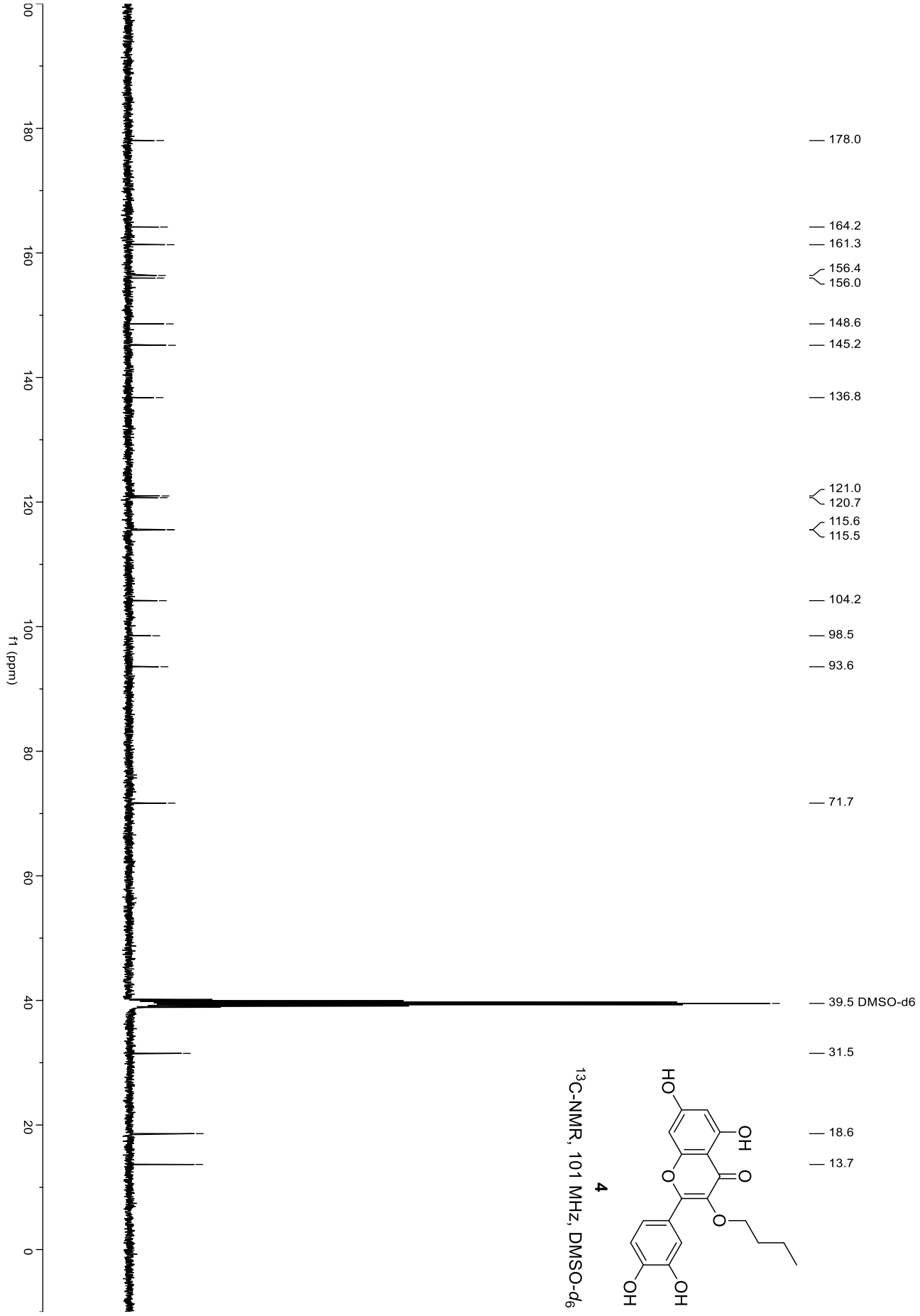
1.97
1.99
2.98
f1 (ppm)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145.2
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120.7
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104.2
98.5
93.6
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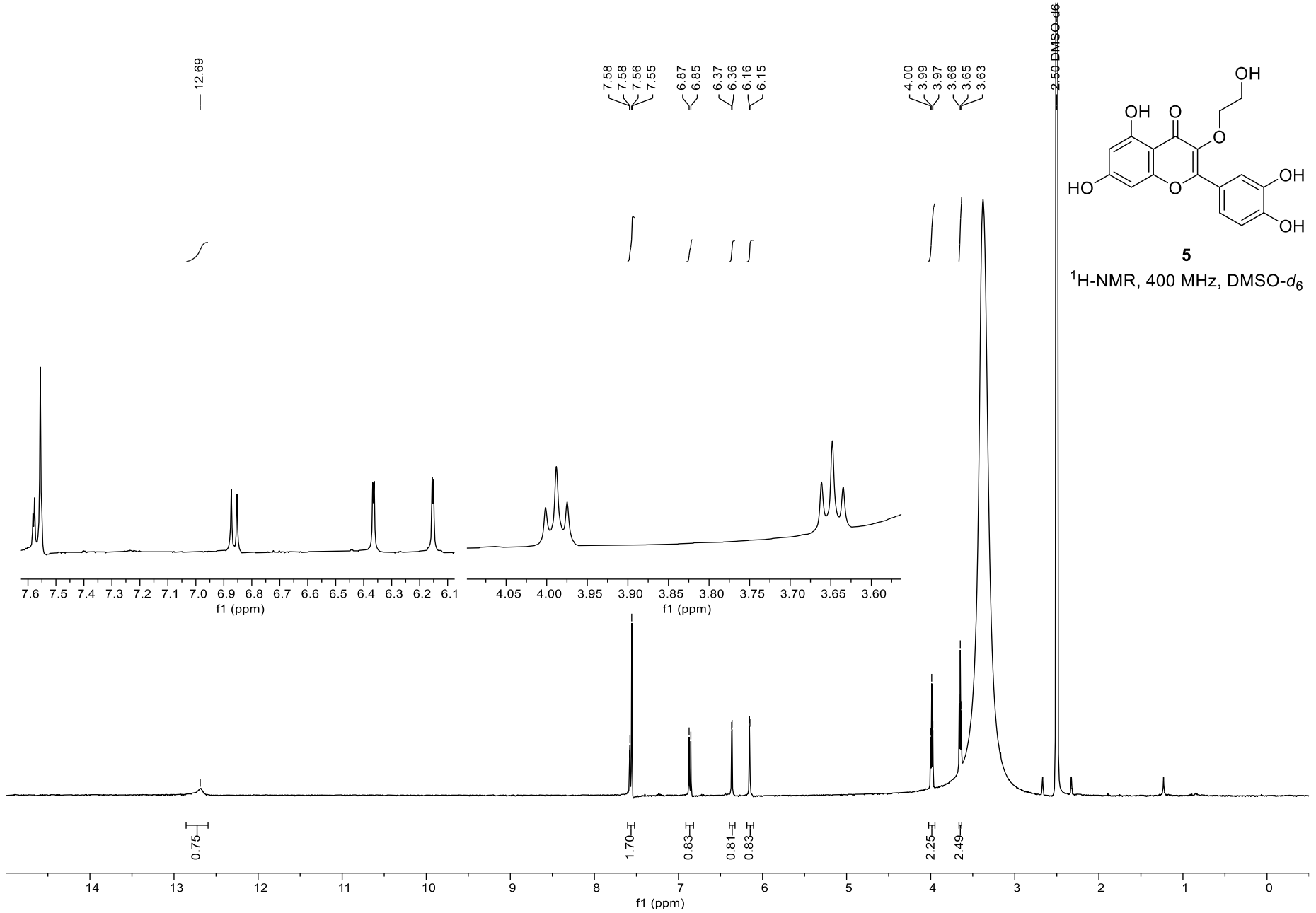
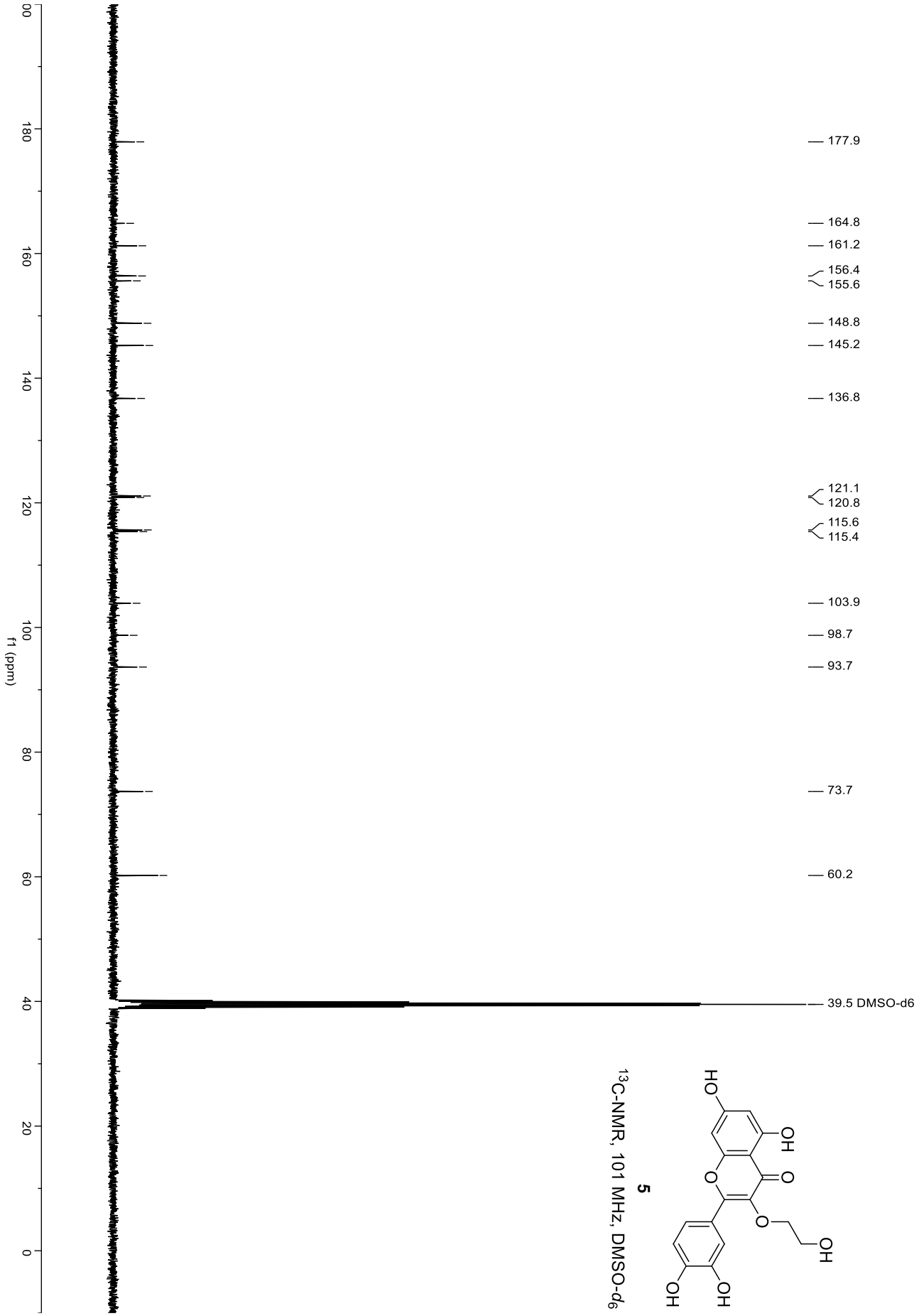
13.7
f1 (ppm)
4
^{13}C-NMR, 101 MHz, DMSO-d_6



5

^{1}H-NMR, 400 MHz, DMSO-d_6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98.7
93.7
73.7
60.2
39.5 DMSO-d6
f1 (ppm)
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60
80
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OH
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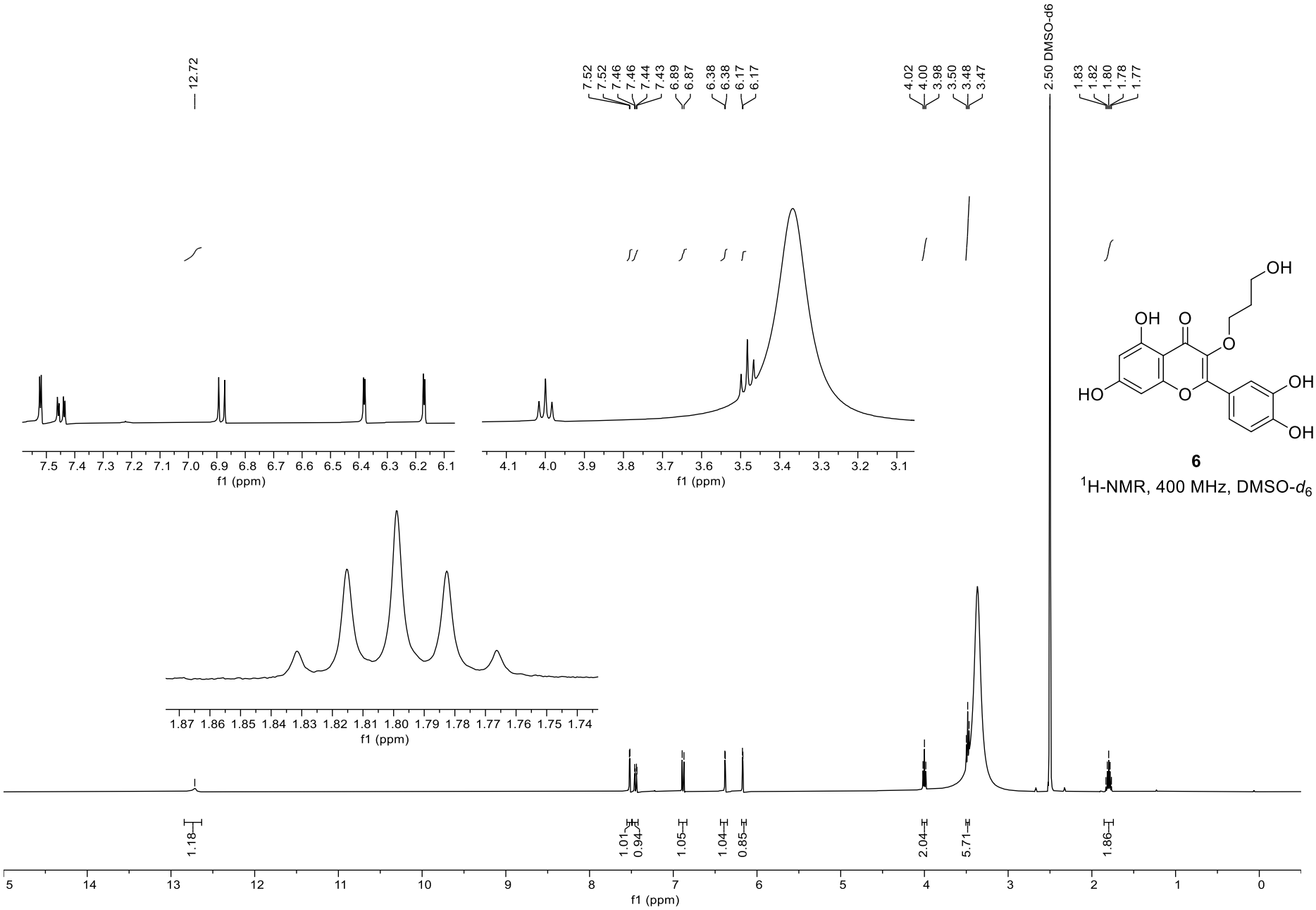
^{13}C-NMR, 101 MHz, DMSO-d_6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3.48
3.47
2.50 DMSO-d6
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1.82
1.80
1.78
1.77
f1 (ppm)
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1.04
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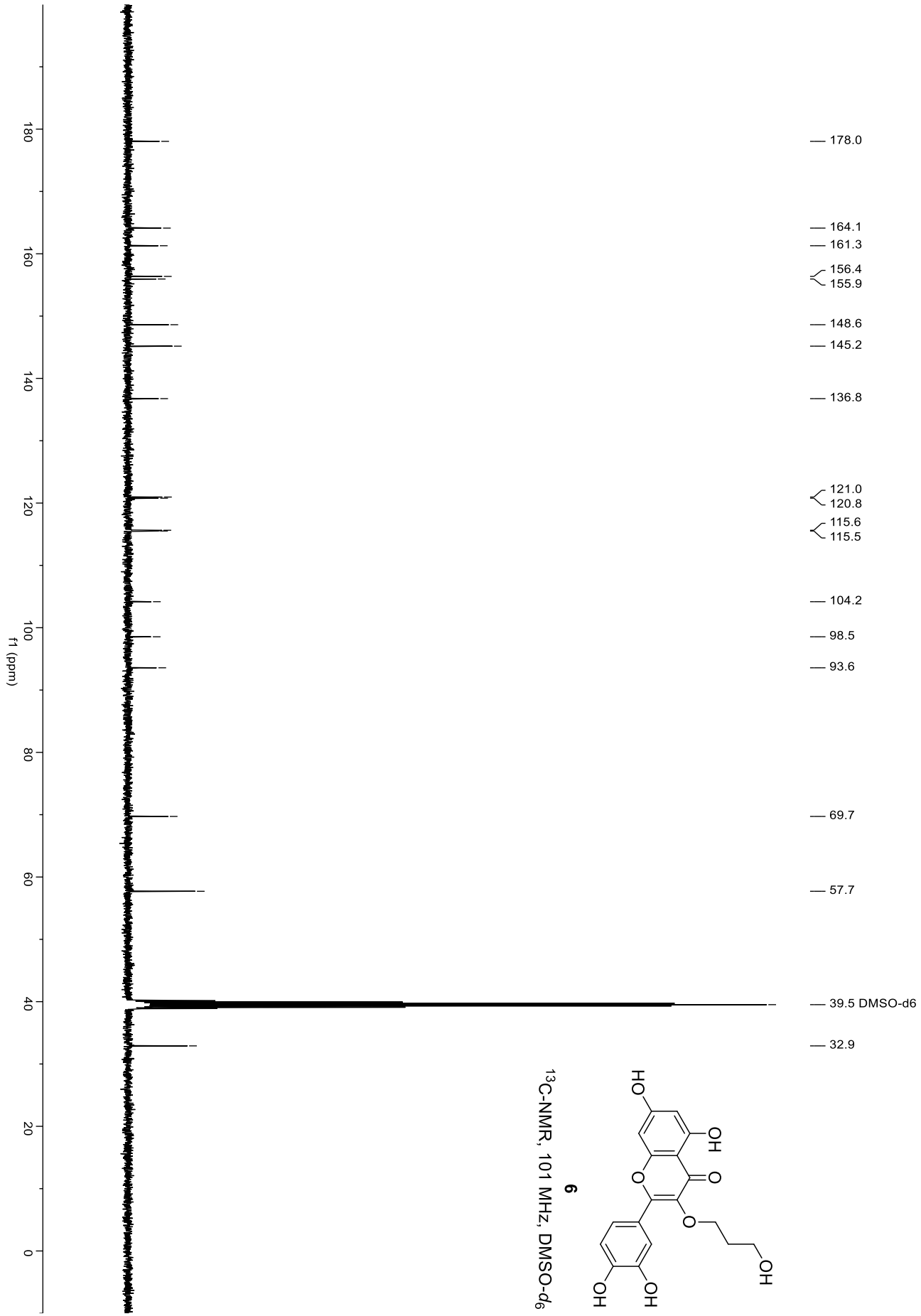
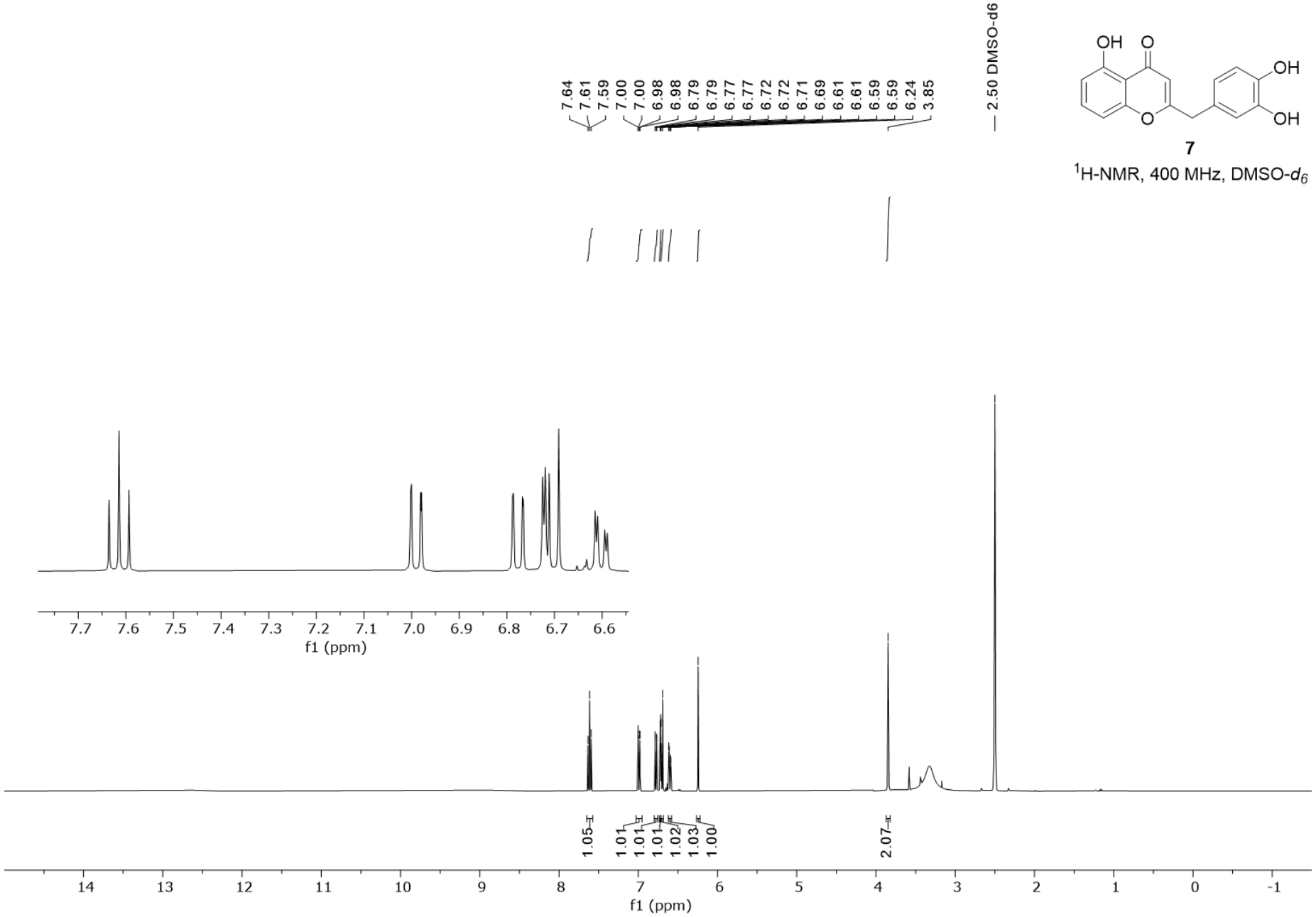
1H-NMR, 400 MHz, DMSO-d6



6

^{13}C-NMR, 101 MHz, DMSO-d_6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7.00
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6.72
6.71
6.69
6.61
6.61
6.59
6.59
6.24
3.85
2.50 DMSO-d6
OH
O
OH
OH
O
7
1H-NMR, 400 MHz, DMSO-d6
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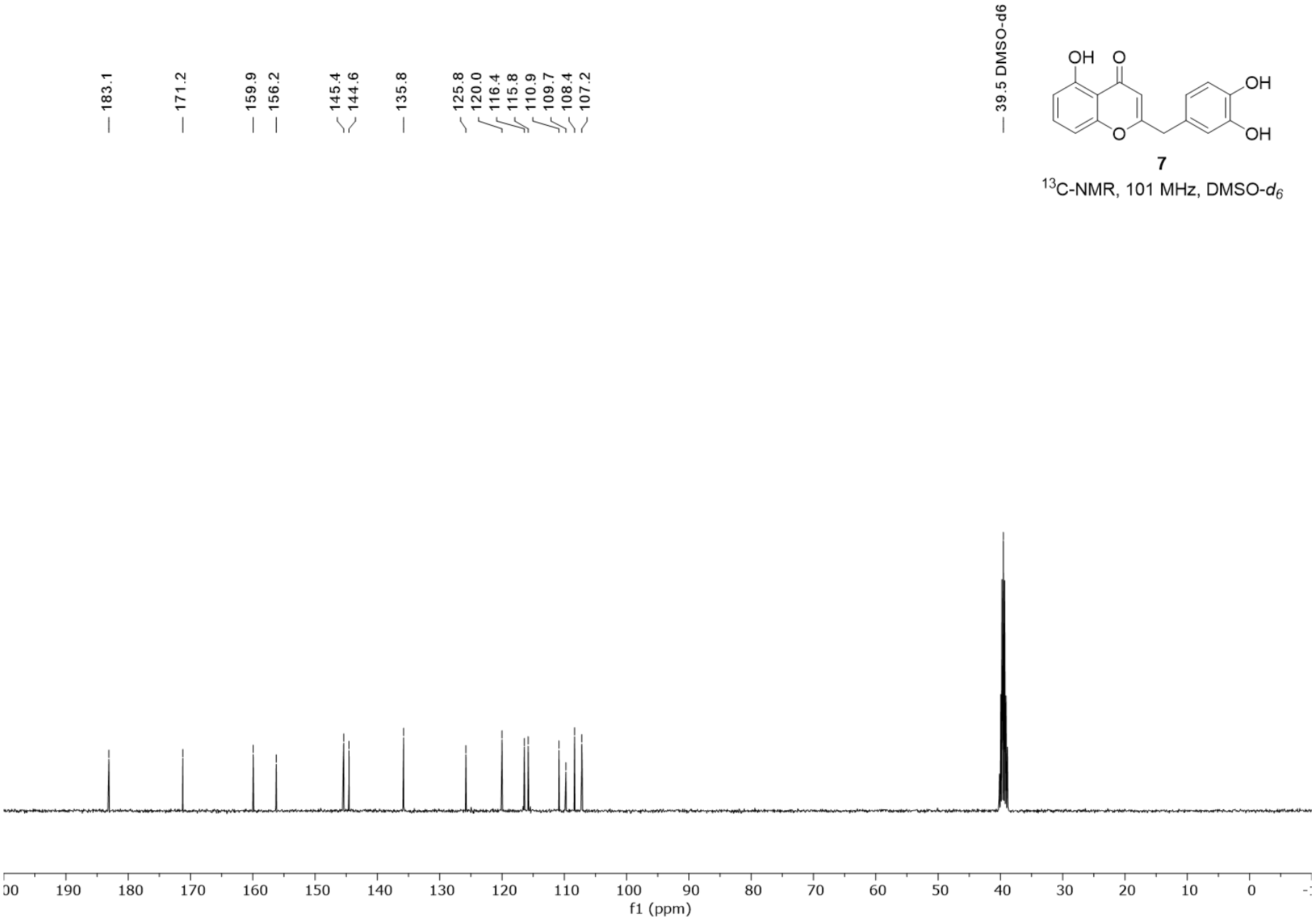
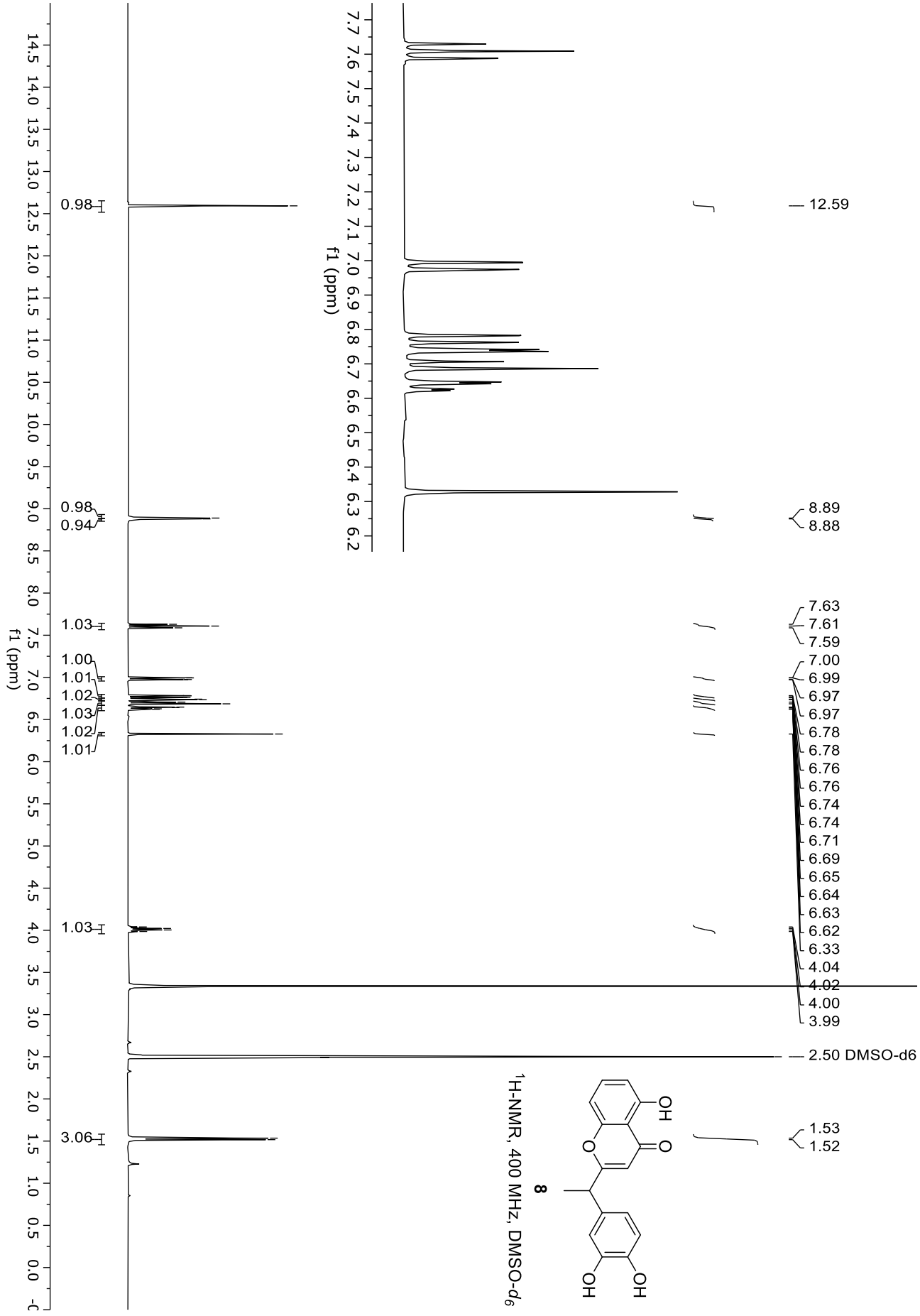
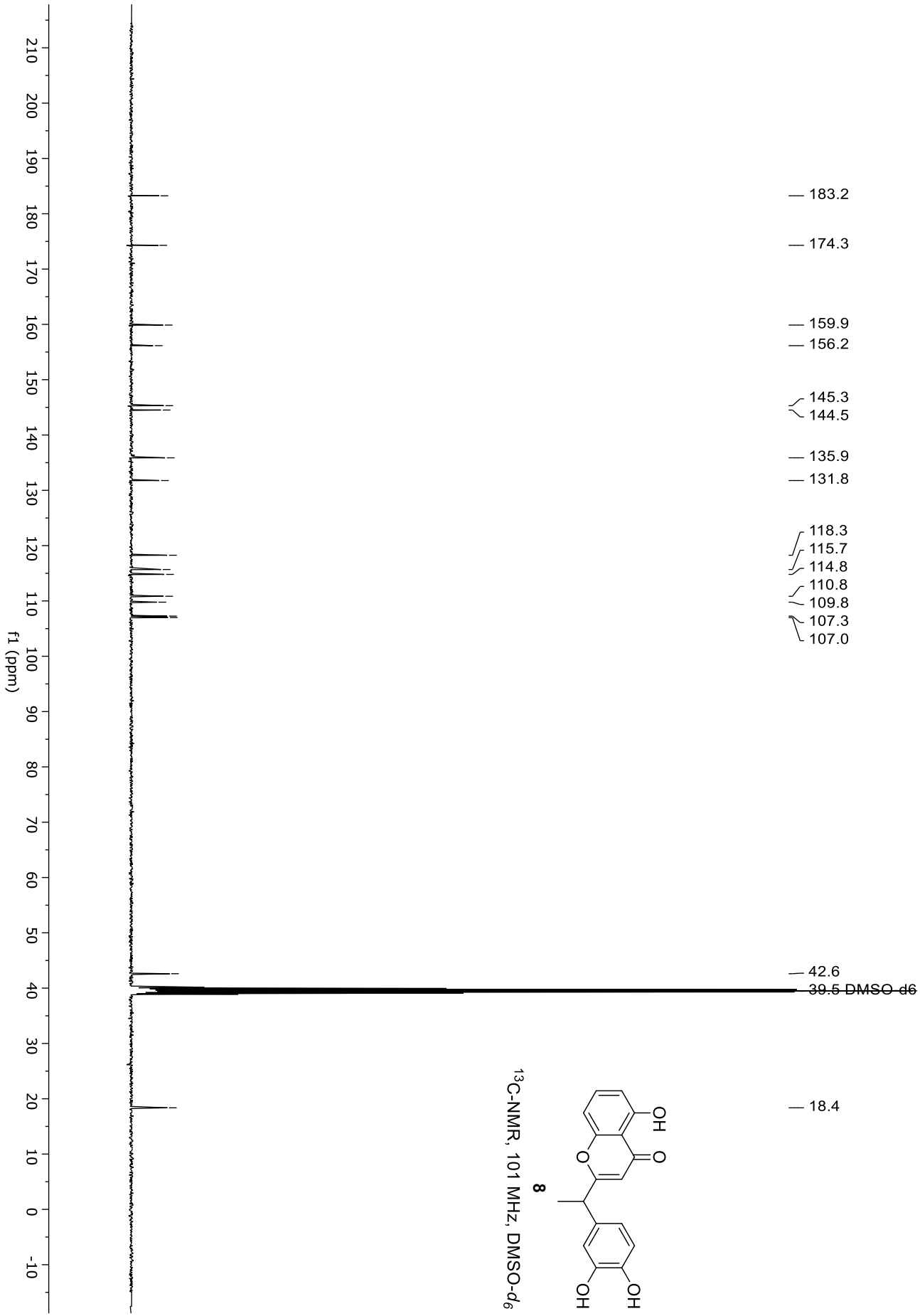
1.01
1.01
1.02
1.03
1.00
2.07
f1 (ppm)



7

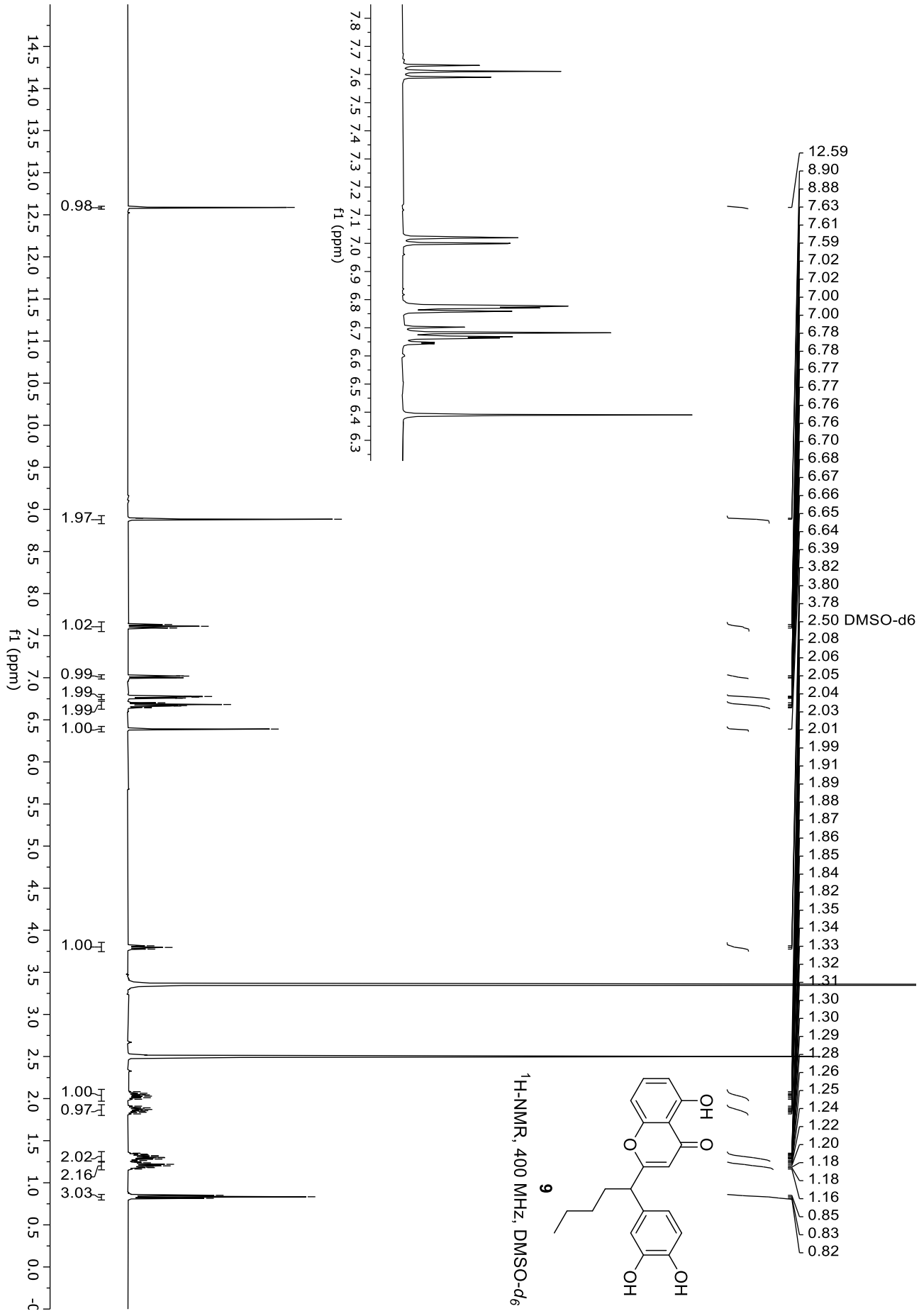
^{13}C-NMR, 101 MHz, DMSO-d_6

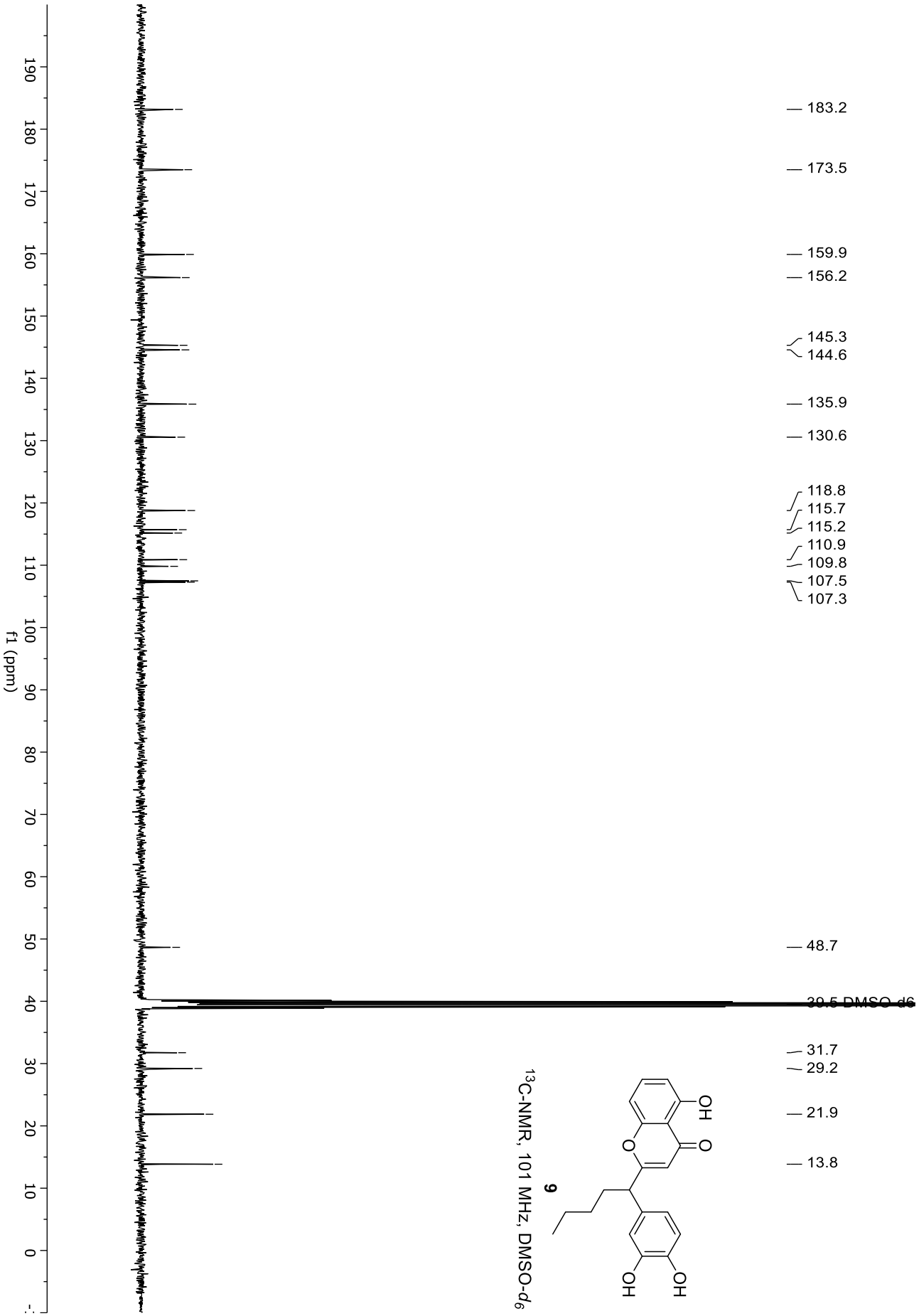

f1 (ppm)
0.98
0.98
0.94
1.03
1.00
1.01
1.02
1.03
1.02
1.01
1.03
3.06
12.59
8.89
8.88
7.63
7.61
7.59
7.00
6.99
6.97
6.97
6.78
6.78
6.76
6.76
6.74
6.74
6.71
6.69
6.65
6.64
6.63
6.62
6.33
4.04
4.02
4.00
3.99
2.50 DMSO-d6
1.53
1.52
OH
O
O
OH
OH
8
^{1}H-NMR, 400 MHz, DMSO-d_6

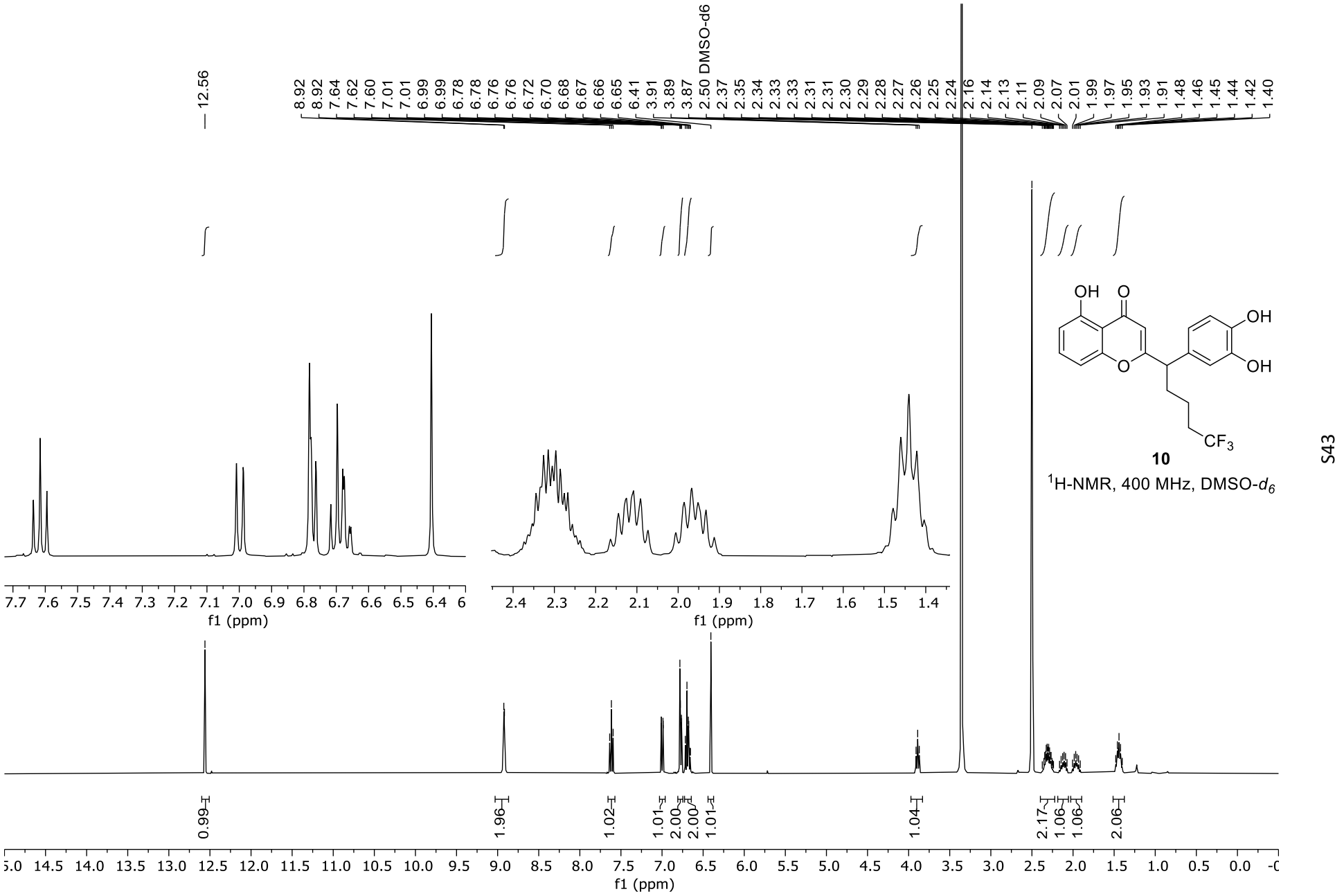


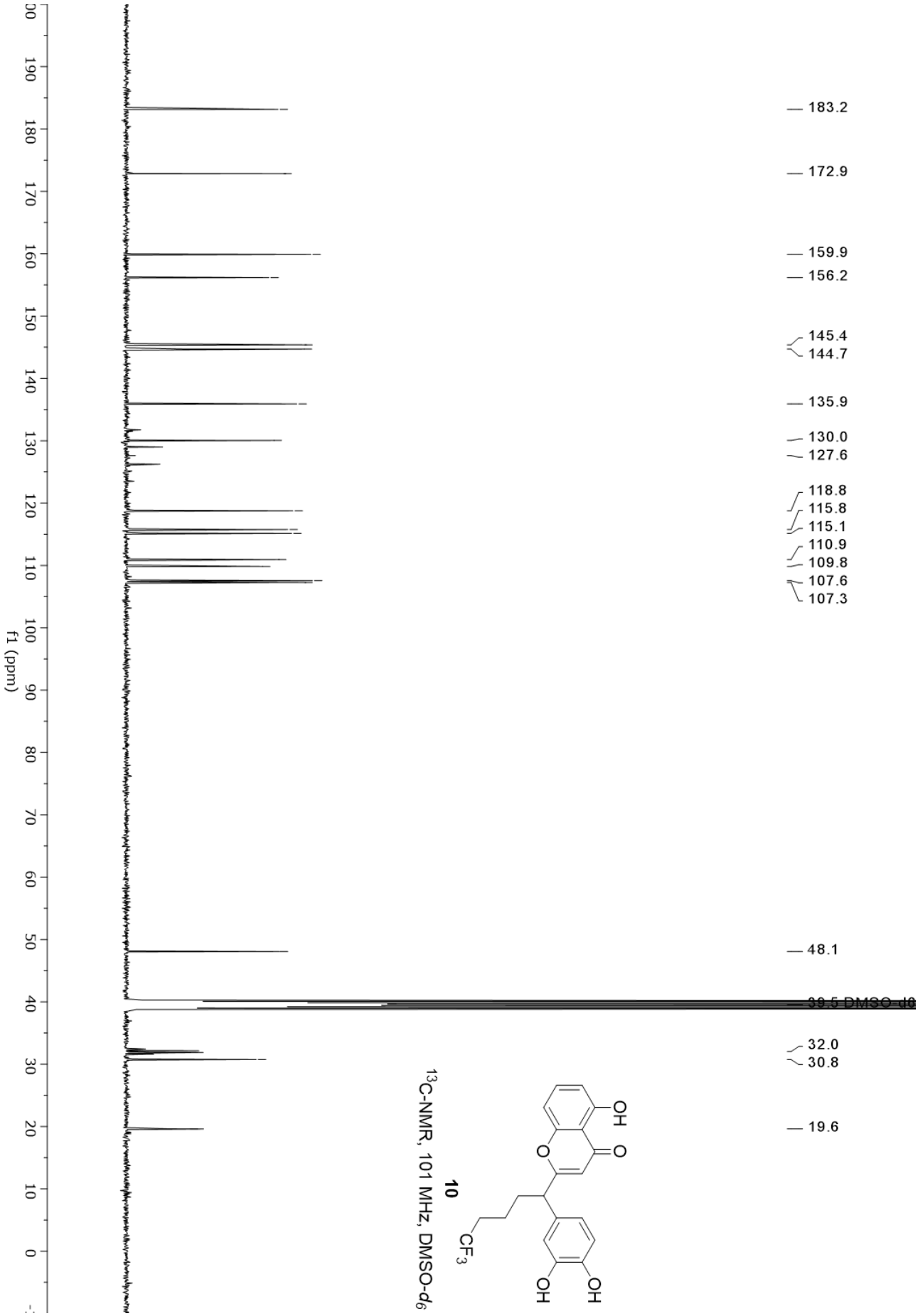
^{13}C-NMR, 101 MHz, DMSO-d_6

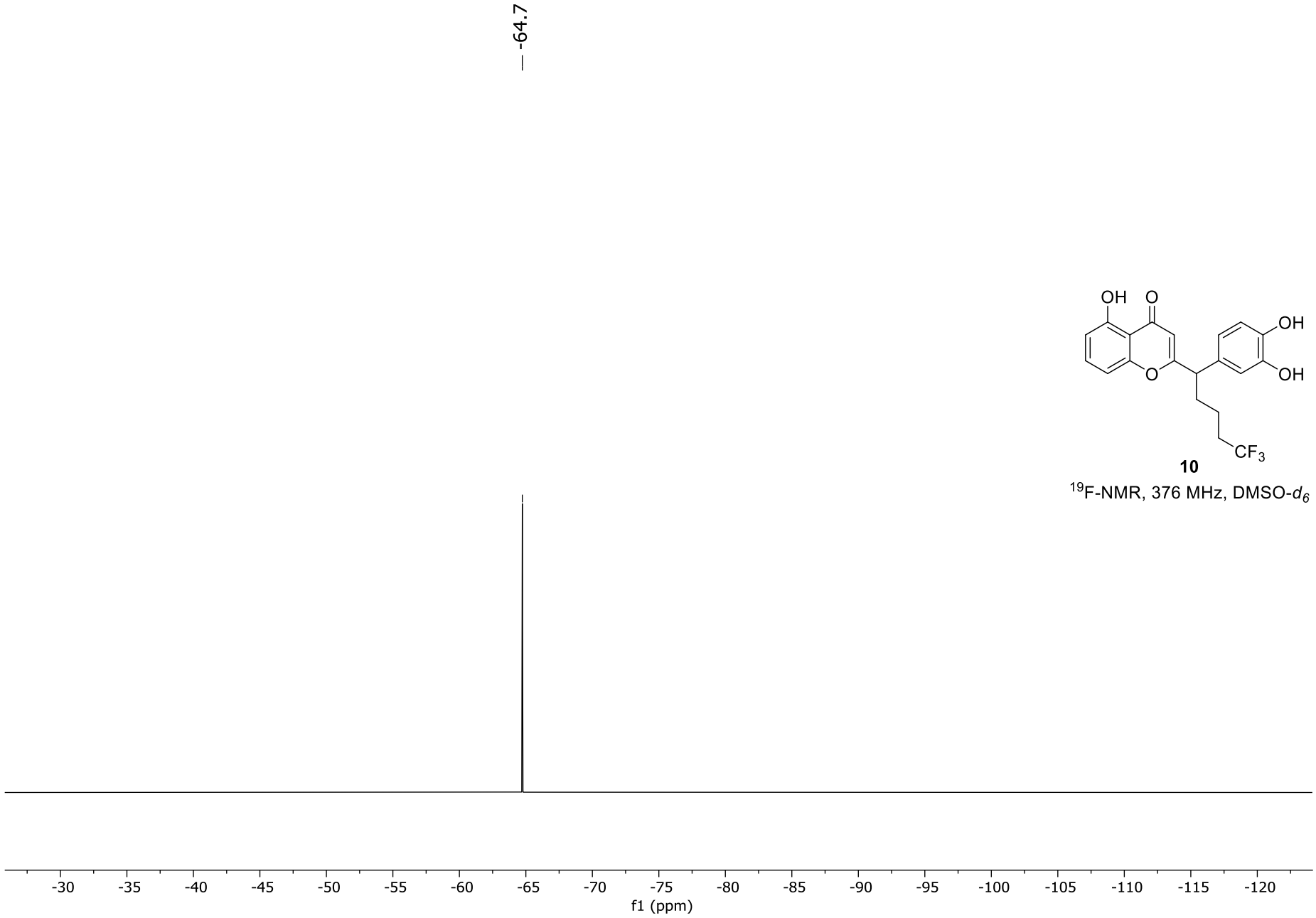
8


f1 (ppm)
0.98
1.97
1.02
0.99
1.99
1.99
1.00
1.00
1.00
0.97
2.02
2.16
3.03
12.59
8.90
8.88
7.63
7.61
7.59
7.02
7.02
7.00
7.00
6.78
6.78
6.77
6.77
6.76
6.76
6.70
6.68
6.67
6.66
6.65
6.64
6.39
3.82
3.80
3.78
2.50 DMSO-d6
2.08
2.06
2.05
2.04
2.03
2.01
1.99
1.91
1.89
1.88
1.87
1.86
1.85
1.84
1.82
1.35
1.34
1.33
1.32
1.31
1.30
1.30
1.29
1.28
1.26
1.25
1.24
1.22
1.20
1.18
1.18
1.16
0.85
0.83
0.82
OH
O
O
OH
OH
9
^{1}H-NMR, 400 MHz, DMSO-d_6


183.2
173.5
159.9
156.2
145.3
144.6
135.9
130.6
118.8
115.7
115.2
110.9
109.8
107.5
107.3
48.7
39.5 DMSO-d6
31.7
29.2
21.9
13.8
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
OH
O
O
OH
OH
6
13C-NMR, 101 MHz, DMSO-d6

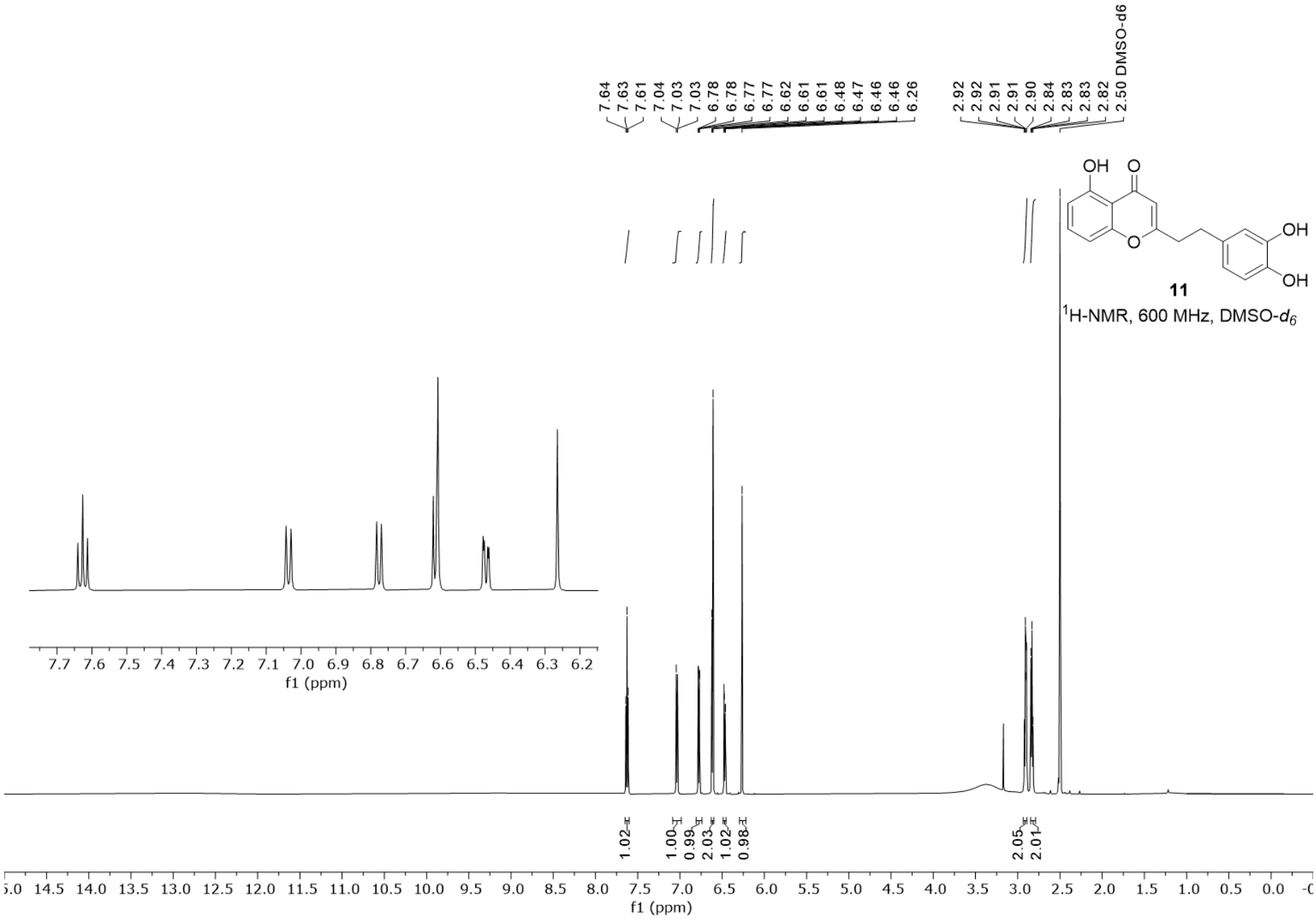

12.56
8.92 8.92 7.64 7.62 7.60 7.01 7.01 6.99 6.99 6.78 6.78 6.76 6.76 6.72 6.70 6.68 6.67 6.66 6.65 6.41 3.91 3.89 3.87 2.50 DMSO-d6 2.37 2.35 2.34 2.33 2.33 2.31 2.31 2.30 2.29 2.28 2.27 2.26 2.25 2.24 2.16 2.14 2.13 2.11 2.09 2.07 2.01 1.99 1.97 1.95 1.93 1.91 1.48 1.46 1.45 1.44 1.42 1.40
OH O OH OH O CF3
10
1H-NMR, 400 MHz, DMSO-d6
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6
f1 (ppm)
2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4
f1 (ppm)
0.99 1.96 1.02 1.01 2.00 2.00 1.01 1.04 2.17 1.06 1.06 2.06
f1 (ppm)

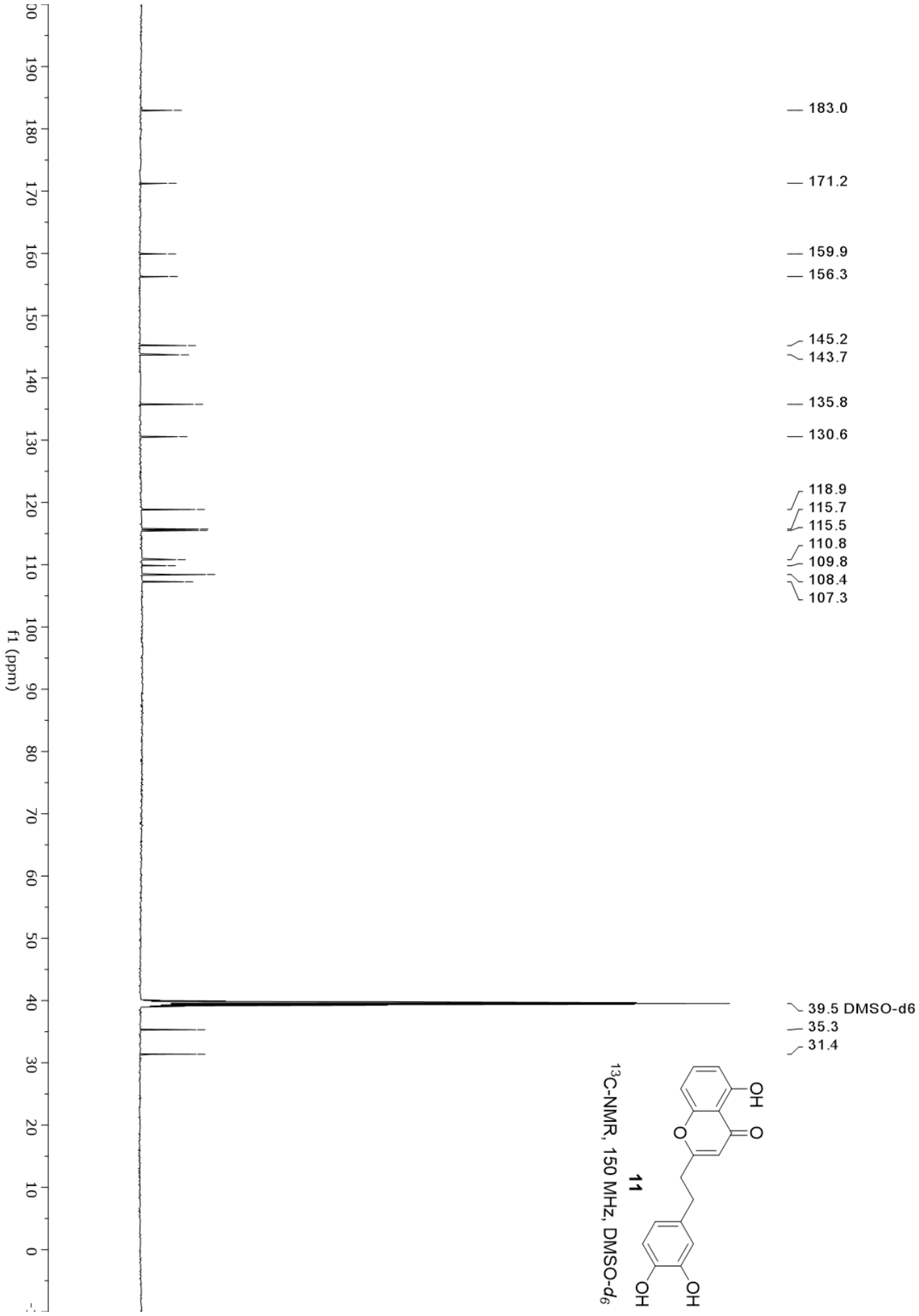

183.2
172.9
159.9
156.2
145.4
144.7
135.9
130.0
127.6
118.8
115.8
115.1
110.9
109.8
107.6
107.3
48.1
39.5 DMSO-d6
32.0
30.8
19.6
f1 (ppm)
13C-NMR, 101 MHz, DMSO-d6
10
CF3
OH
O
OH
OH

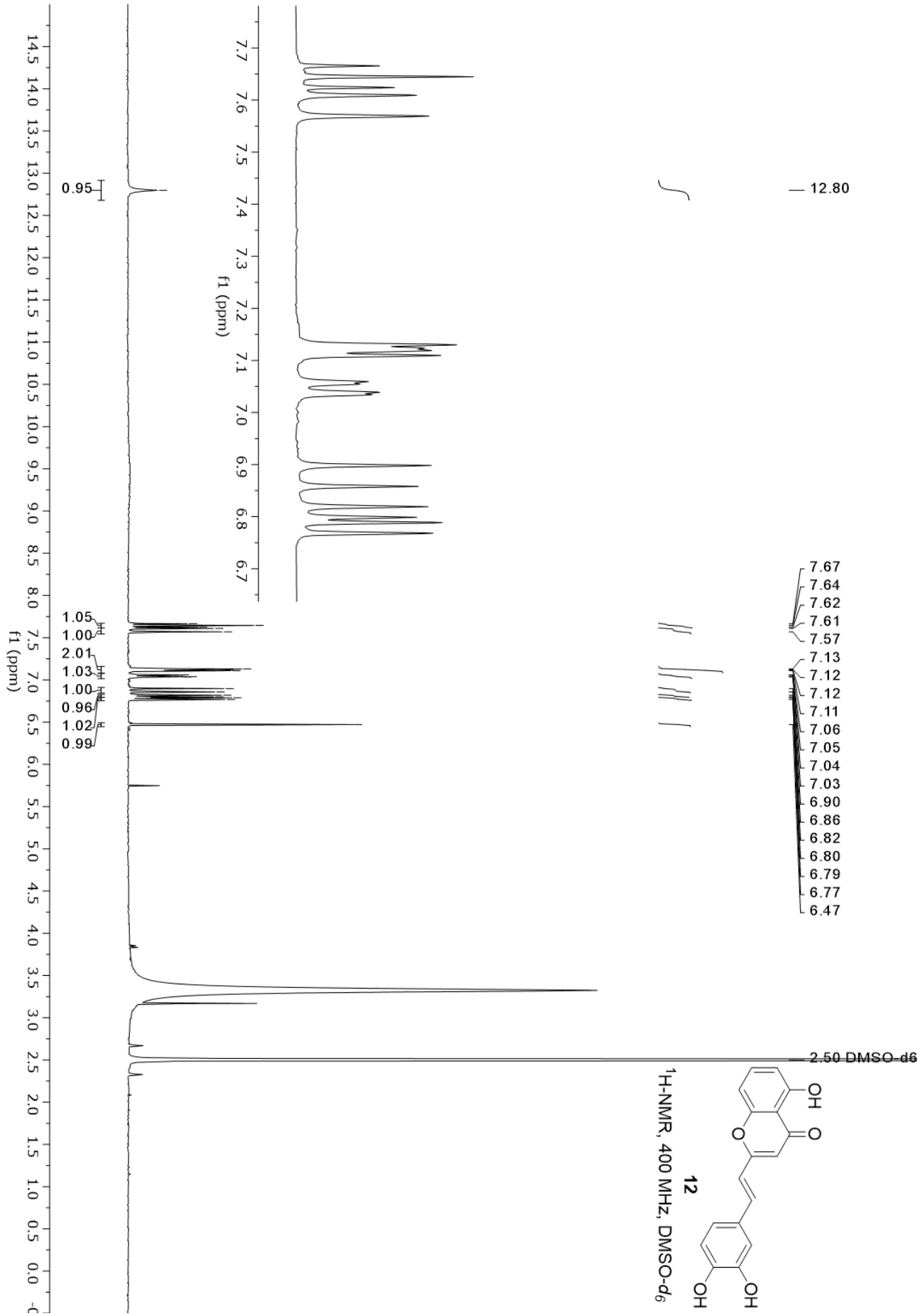


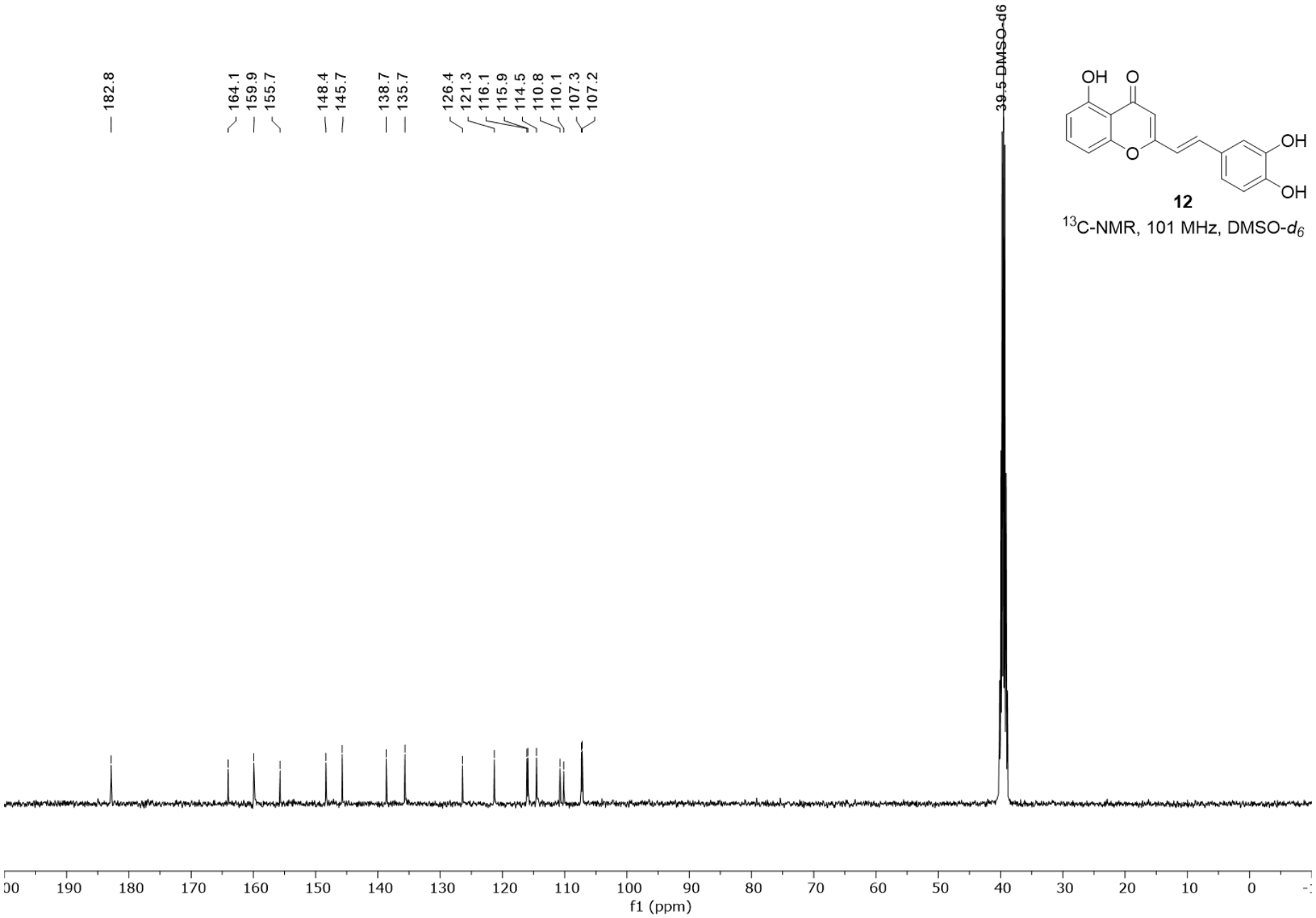
10

^{19}F-NMR, 376 MHz, DMSO-d_6


7.64
7.63
7.61
7.04
7.03
7.03
6.78
6.78
6.77
6.77
6.62
6.61
6.61
6.48
6.47
6.46
6.46
6.26
2.92
2.92
2.91
2.91
2.90
2.84
2.83
2.83
2.82
2.50 DMSO-d6
OH
O
O
OH
OH
11
1H-NMR, 600 MHz, DMSO-d6
1.02
1.00
0.99
2.03
1.02
0.98
2.05
2.01
f1 (ppm)
f1 (ppm)

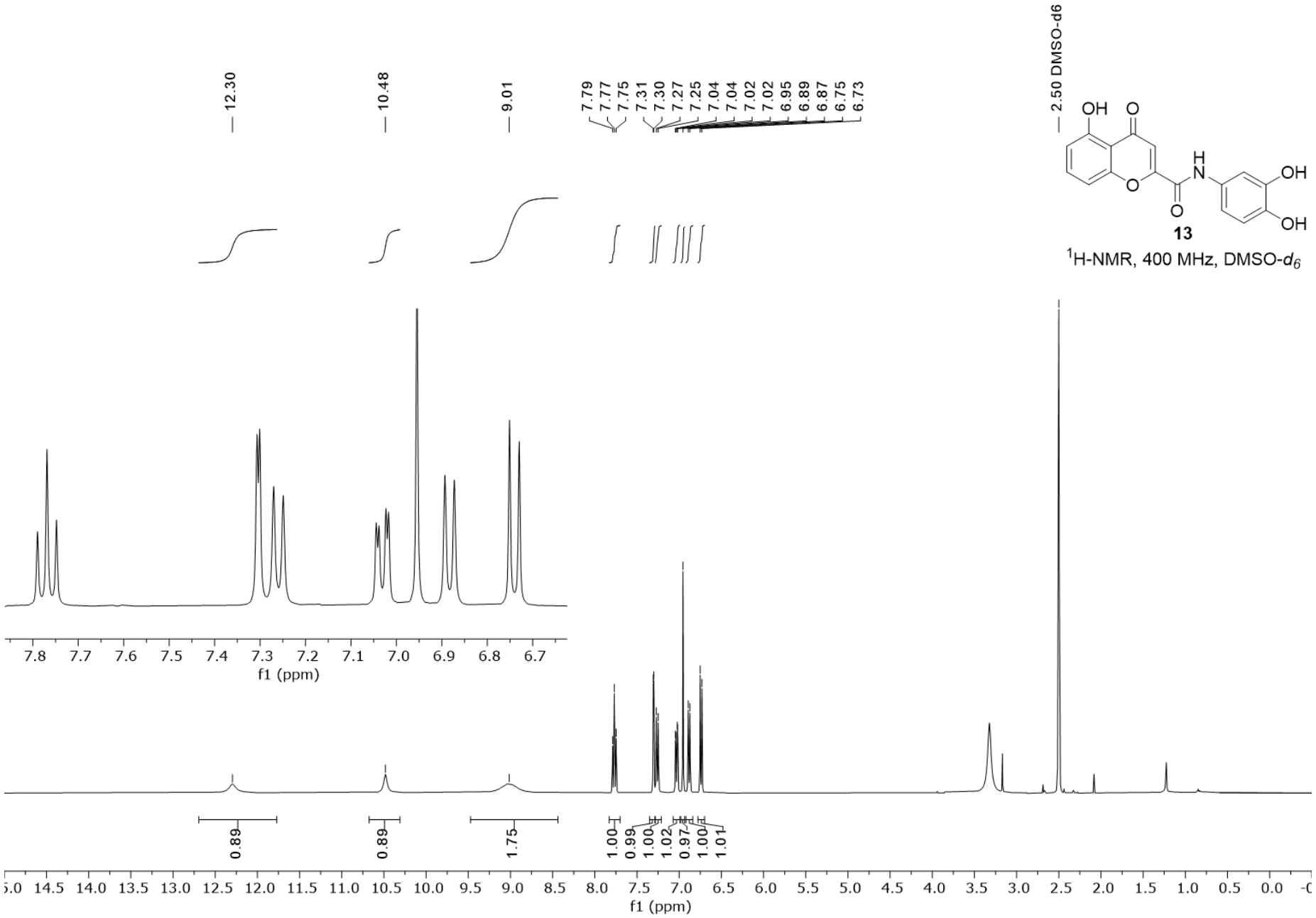

183.0
171.2
159.9
156.3
145.2
143.7
135.8
130.6
118.9
115.7
115.5
110.8
109.8
108.4
107.3
39.5 DMSO-d6
35.3
31.4
f1 (ppm)
11
13C-NMR, 150 MHz, DMSO-d6

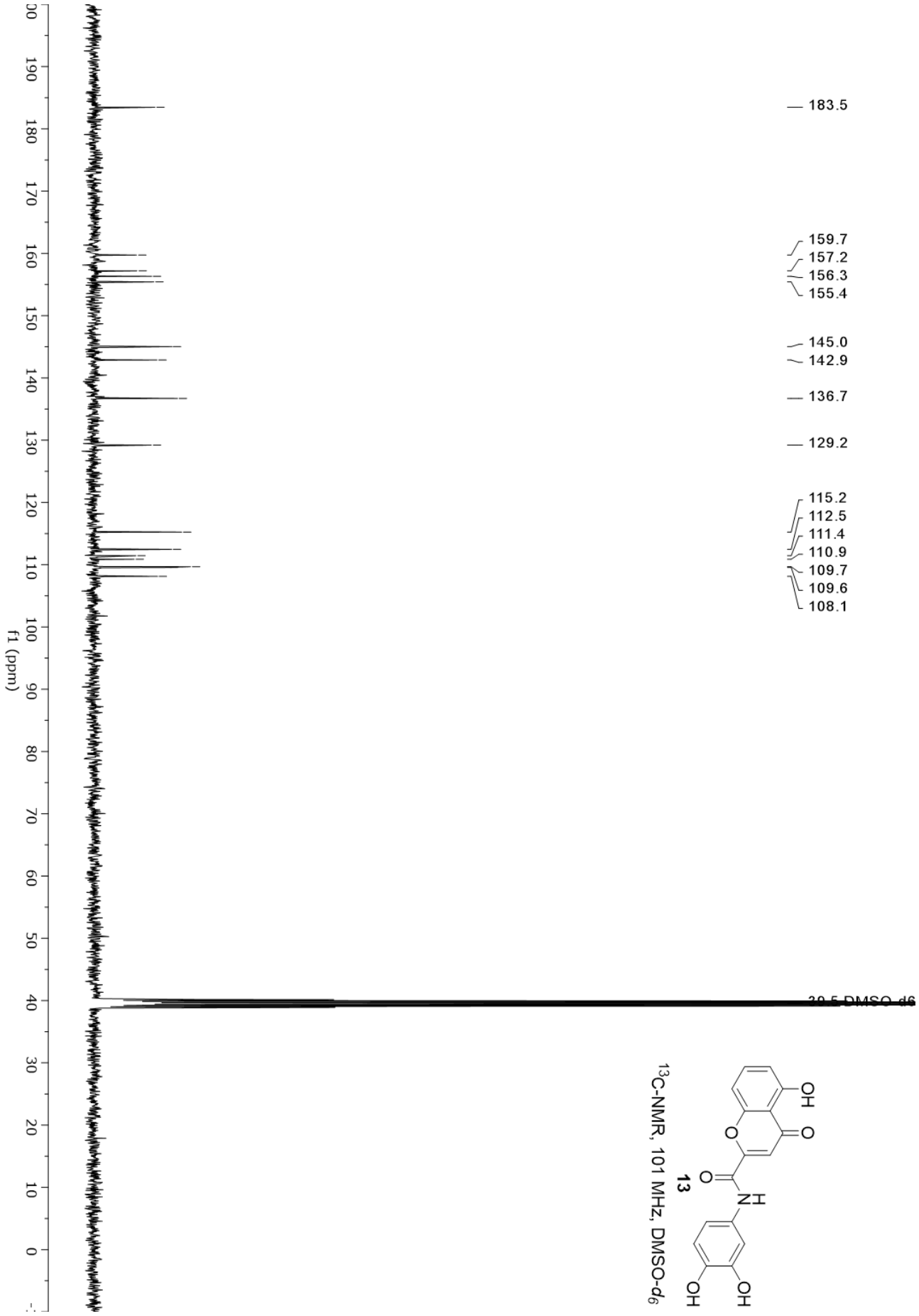

12
^{1}H-NMR, 400 MHz, DMSO-d_6
12.80
7.67
7.64
7.62
7.61
7.57
7.13
7.12
7.12
7.11
7.06
7.05
7.04
7.03
6.90
6.86
6.82
6.80
6.79
6.77
6.47
2.50 DMSO-d6
0.95
1.05
1.00
2.01
1.03
1.00
0.96
1.02
0.99
f1 (ppm)
f1 (ppm)
OH
O
O
OH
OH

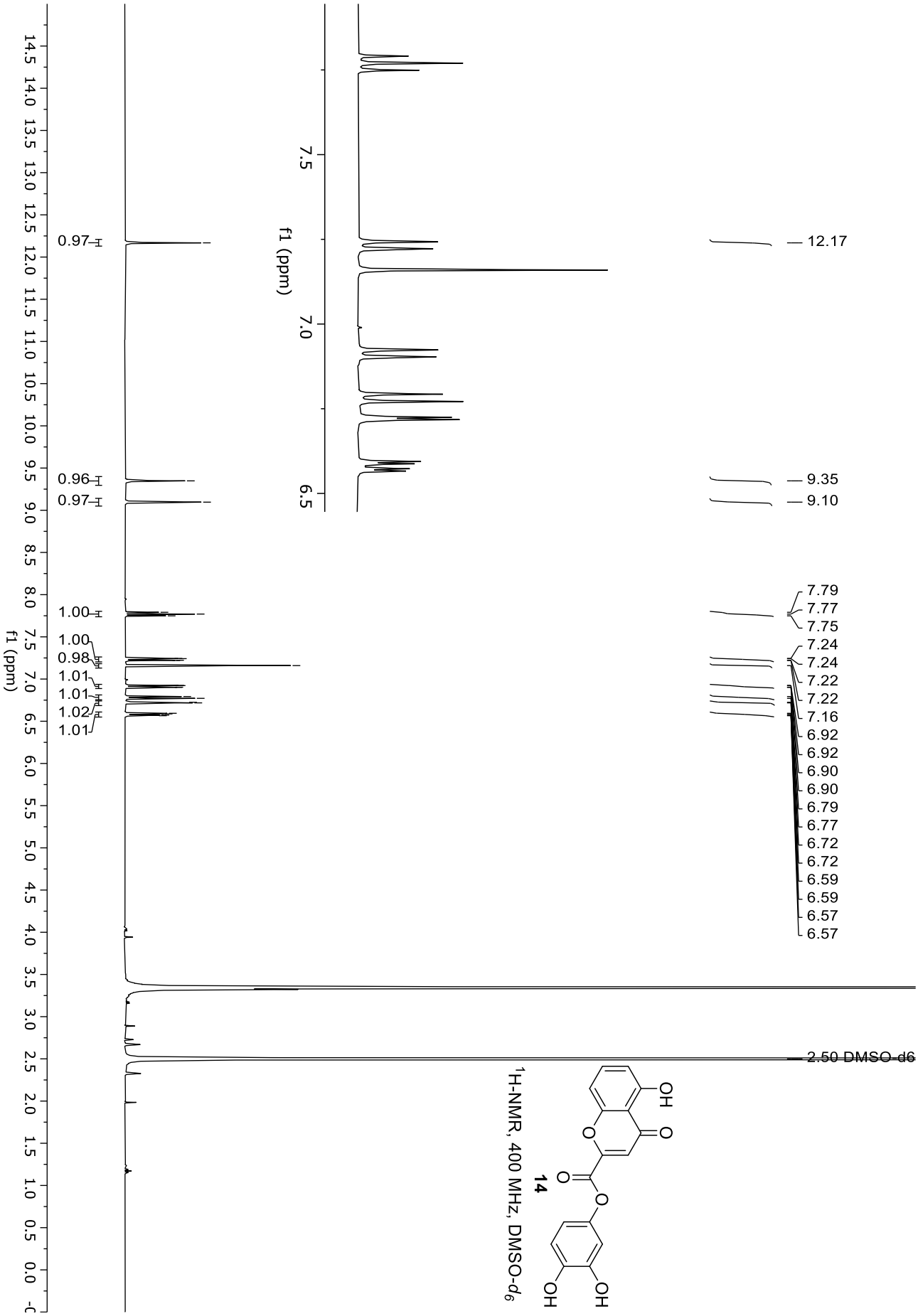


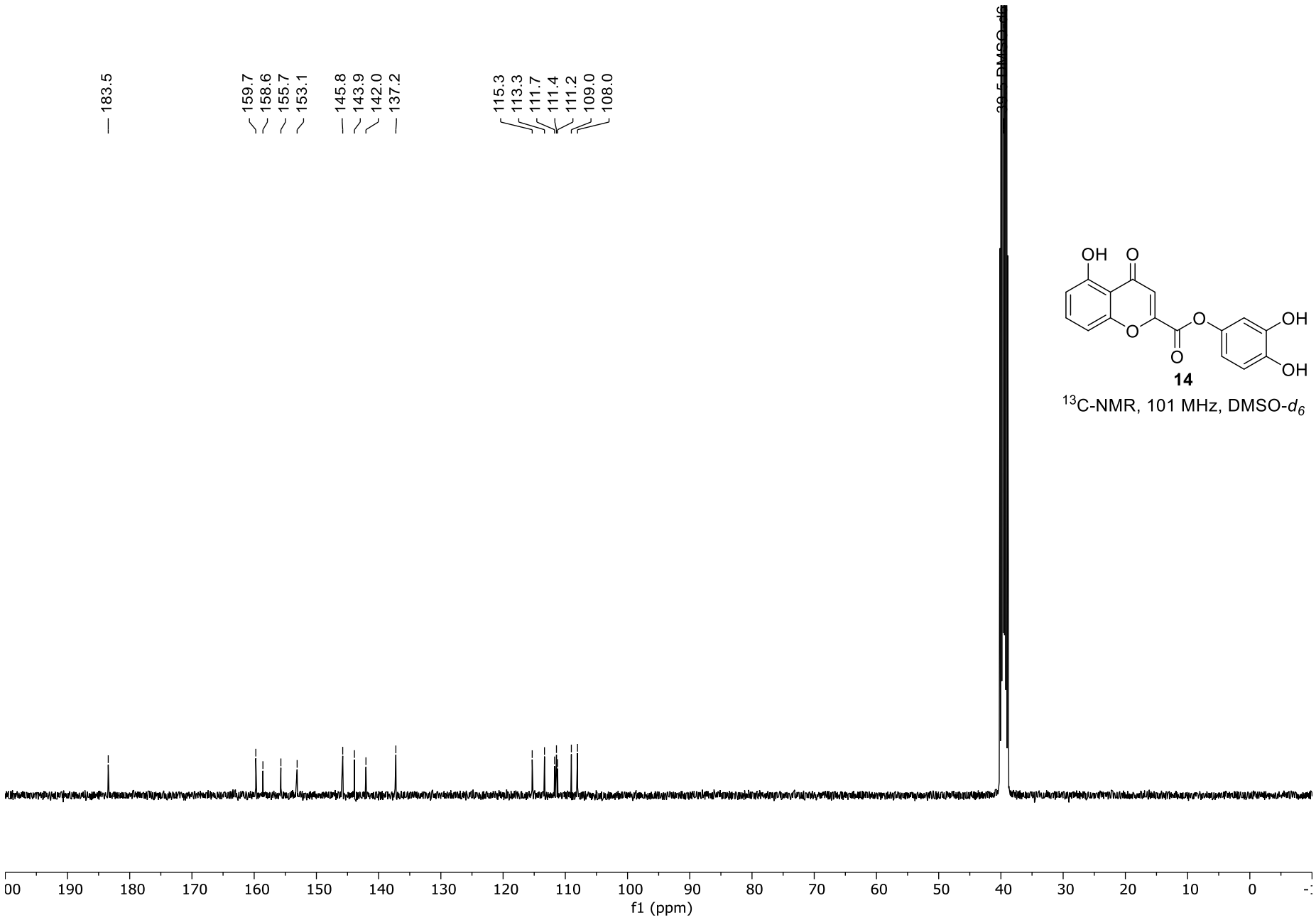
12

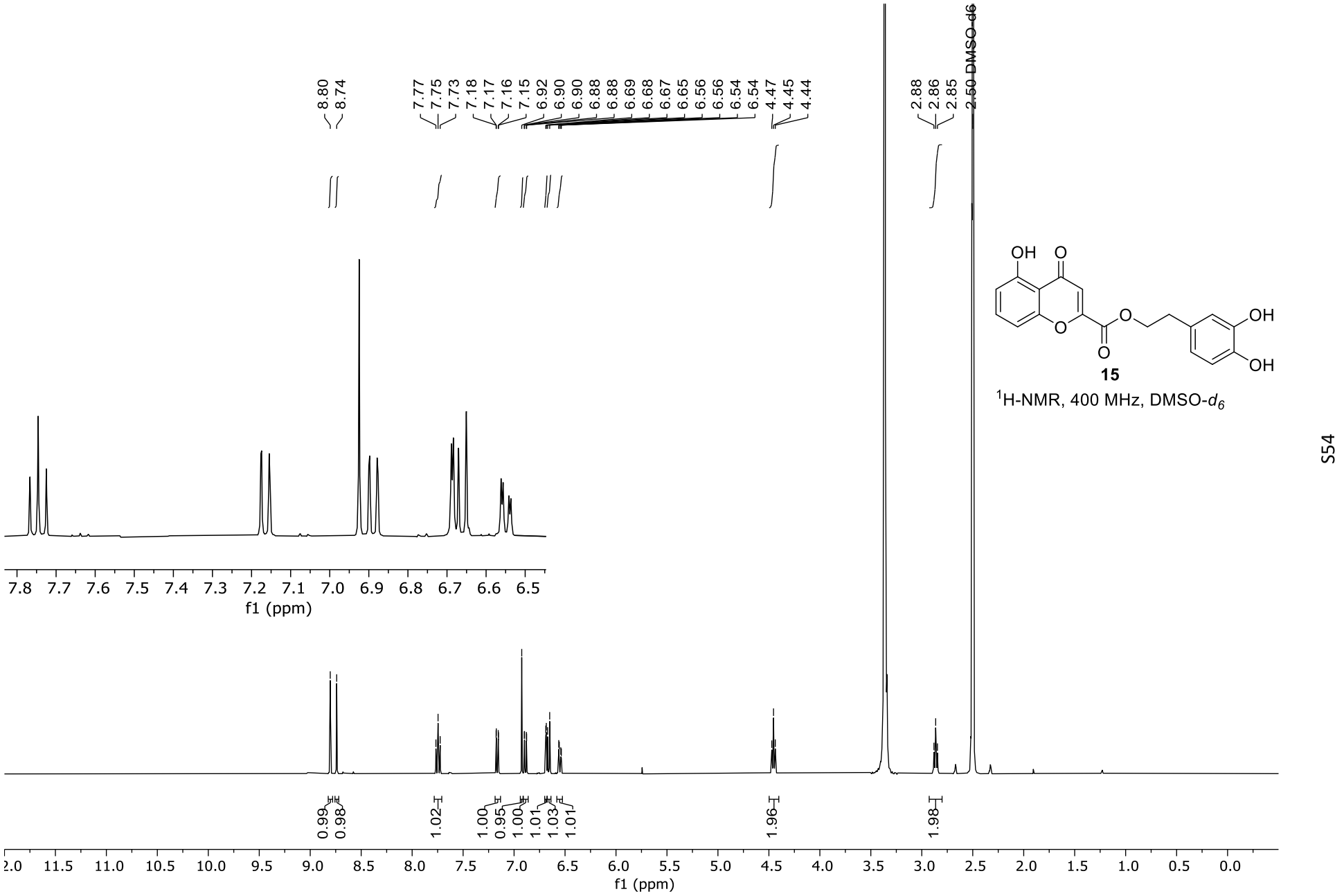
^{13}C-NMR, 101 MHz, DMSO-d_6

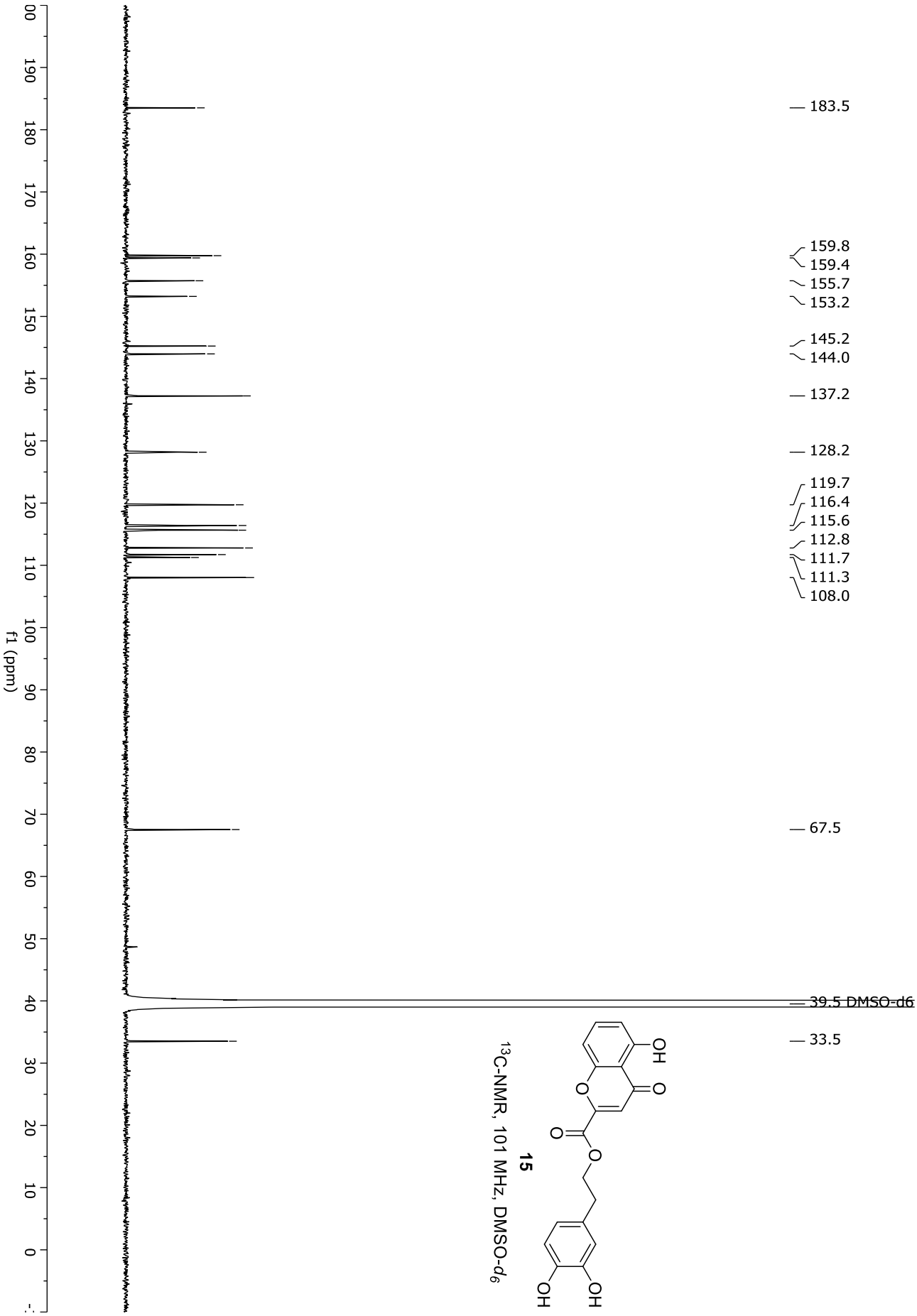

12.30
10.48
9.01
7.79
7.77
7.75
7.31
7.30
7.27
7.25
7.04
7.04
7.02
7.02
6.95
6.89
6.87
6.75
6.73
2.50 DMSO-d6
OH
O
H
N
O
O
OH
OH
13
1H-NMR, 400 MHz, DMSO-d6
0.89
0.89
1.75
1.00
0.99
1.00
1.02
0.97
1.00
1.01
f1 (ppm)

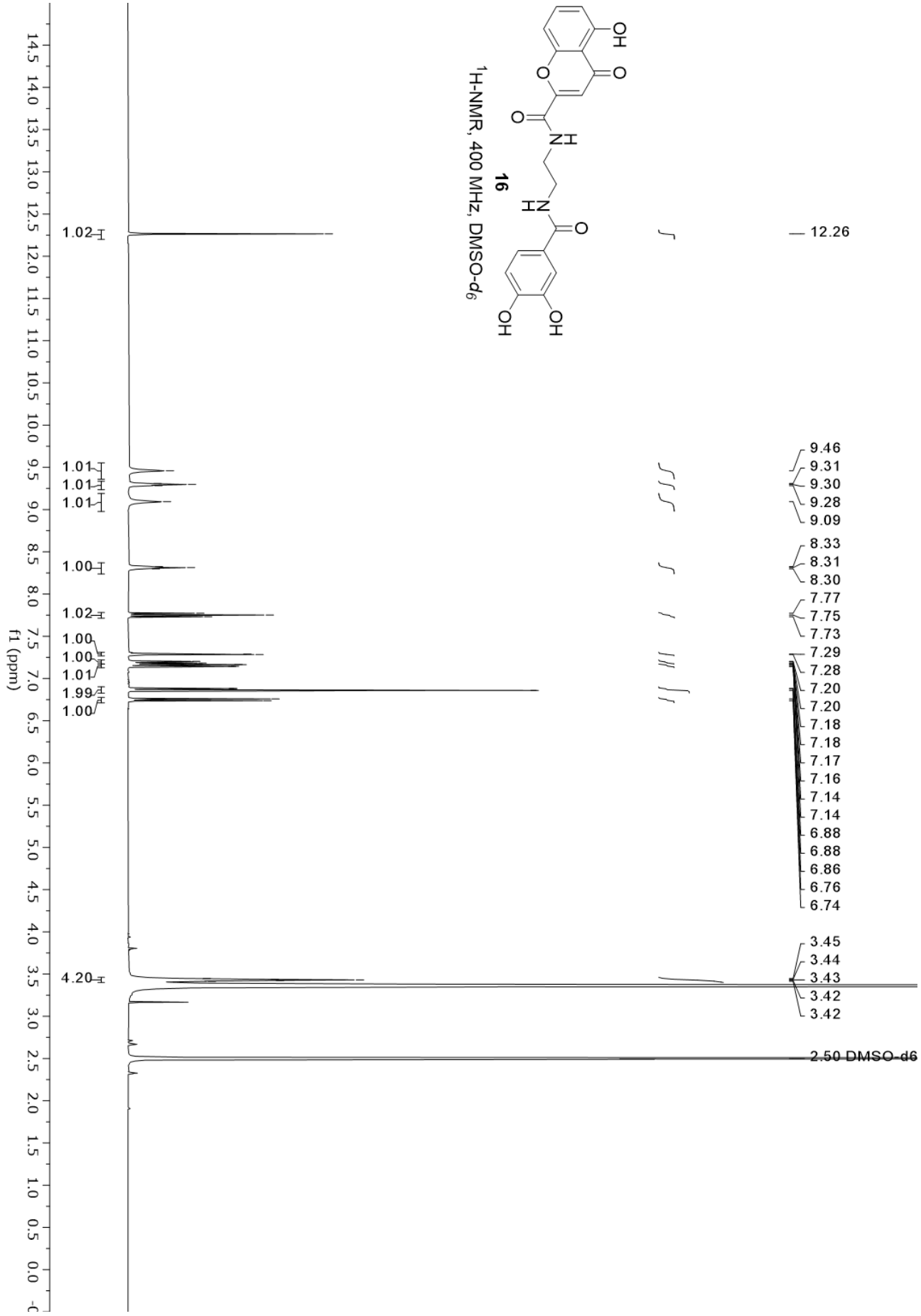

183.5
159.7
157.2
156.3
155.4
145.0
142.9
136.7
129.2
115.2
112.5
111.4
110.9
109.7
109.6
108.1
39.5 DMSO-d6
f1 (ppm)
13
13C-NMR, 101 MHz, DMSO-d6

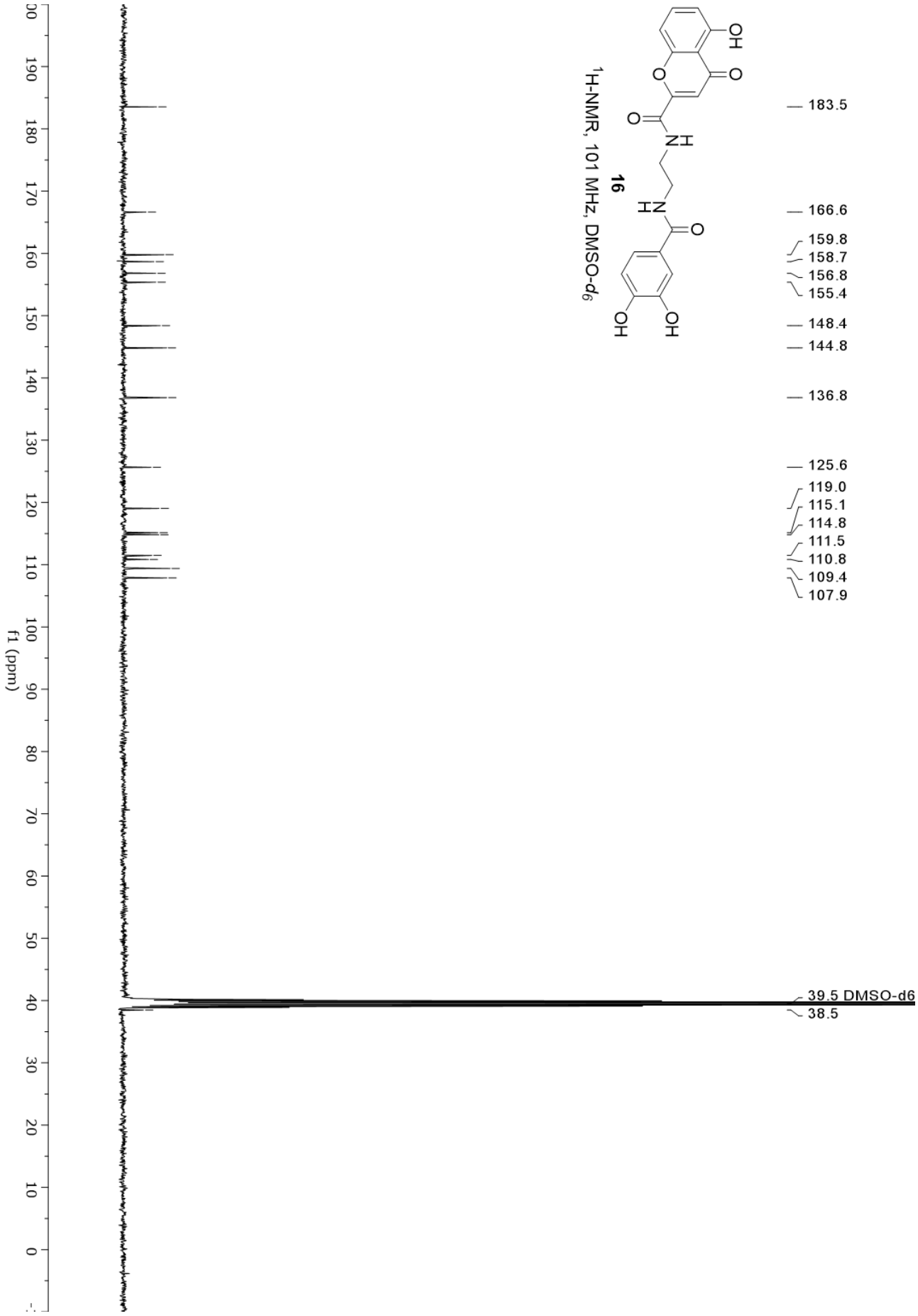

f1 (ppm)
0.97
0.96
0.97
1.00
1.00
0.98
1.01
1.01
1.02
1.01
12.17
9.35
9.10
7.79
7.77
7.75
7.24
7.24
7.22
7.22
7.16
6.92
6.92
6.90
6.90
6.79
6.77
6.72
6.72
6.59
6.59
6.57
6.57
2.50 DMSO-d6
14
^{1}H-NMR, 400 MHz, DMSO-d_6

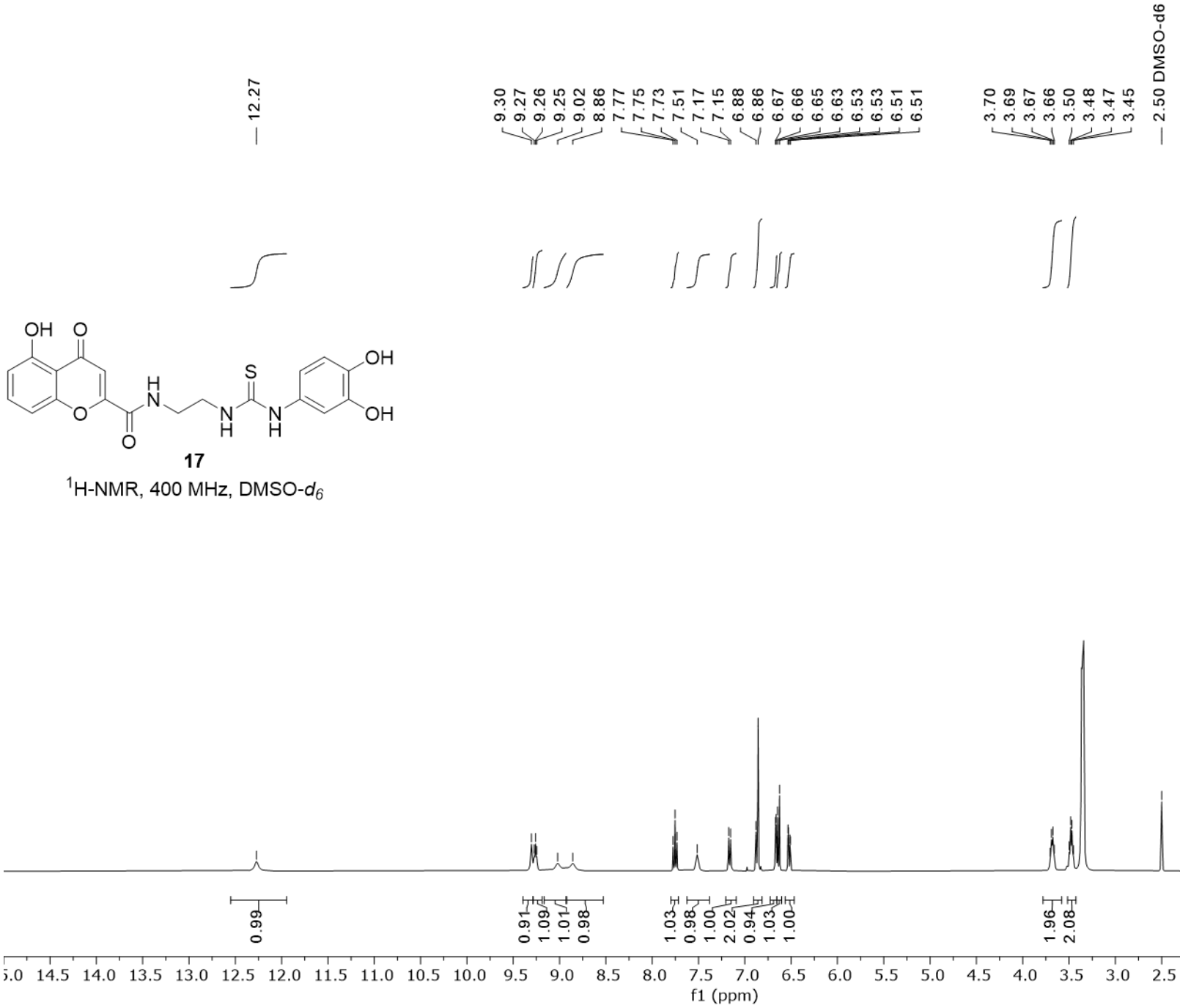

183.5
159.7
158.6
155.7
153.1
145.8
143.9
142.0
137.2
115.3
113.3
111.7
111.4
111.2
109.0
108.0
39.5 DMSO-d6
OH
O
O
O
O
OH
OH
14
13C-NMR, 101 MHz, DMSO-d6
f1 (ppm)


8.80
8.74
7.77
7.75
7.73
7.18
7.17
7.16
7.15
6.92
6.90
6.90
6.88
6.88
6.69
6.68
6.67
6.65
6.56
6.56
6.54
6.54
4.47
4.45
4.44
2.88
2.86
2.85
2.50 DMSO-d6
OH
O
O
O
O
OH
OH
15
1H-NMR, 400 MHz, DMSO-d6
7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5
f1 (ppm)
0.99
0.98
1.02
1.00
0.95
1.00
1.01
1.03
1.01
1.96
1.98
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


183.5
159.8
159.4
155.7
153.2
145.2
144.0
137.2
128.2
119.7
116.4
115.6
112.8
111.7
111.3
108.0
67.5
39.5 DMSO-d6
33.5
f1 (ppm)
15
13C-NMR, 101 MHz, DMSO-d6
OH
O
O
O
O
OH
OH

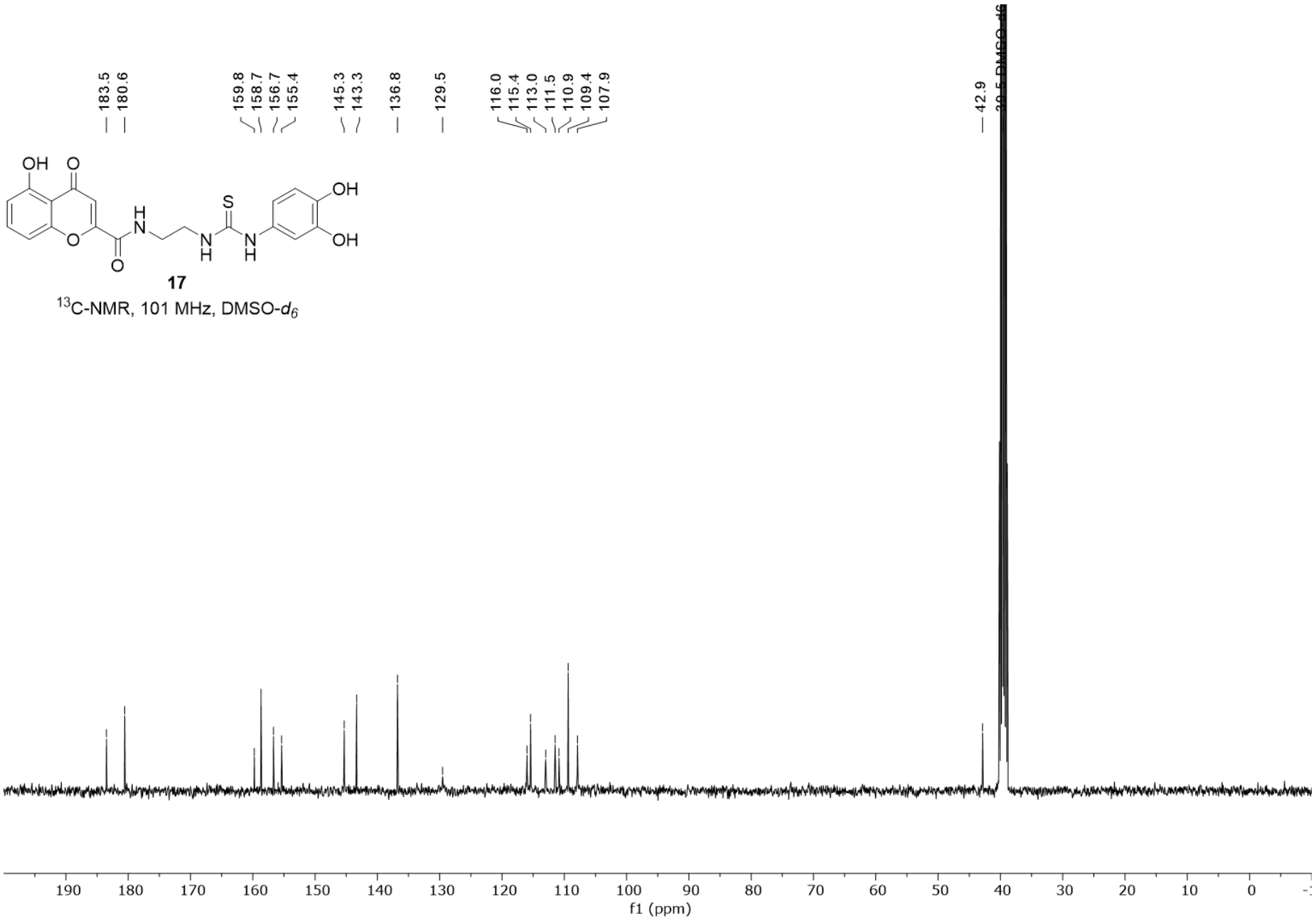

16
1H-NMR, 400 MHz, DMSO-d6
f1 (ppm)
1.02
1.01
1.01
1.01
1.00
1.02
1.00
1.00
1.01
1.99
1.00
4.20
12.26
9.46
9.31
9.30
9.28
9.09
8.33
8.31
8.30
7.77
7.75
7.73
7.29
7.28
7.20
7.20
7.18
7.18
7.17
7.16
7.14
7.14
6.88
6.88
6.86
6.76
6.74
3.45
3.44
3.43
3.42
3.42
2.50 DMSO-d6


16
^{1}H-NMR, 101 MHz, DMSO-d_6
183.5
166.6
159.8
158.7
156.8
155.4
148.4
144.8
136.8
125.6
119.0
115.1
114.8
111.5
110.8
109.4
107.9
39.5 DMSO-d6
38.5
f1 (ppm)



17

^{1}H-NMR, 400 MHz, DMSO-d_6

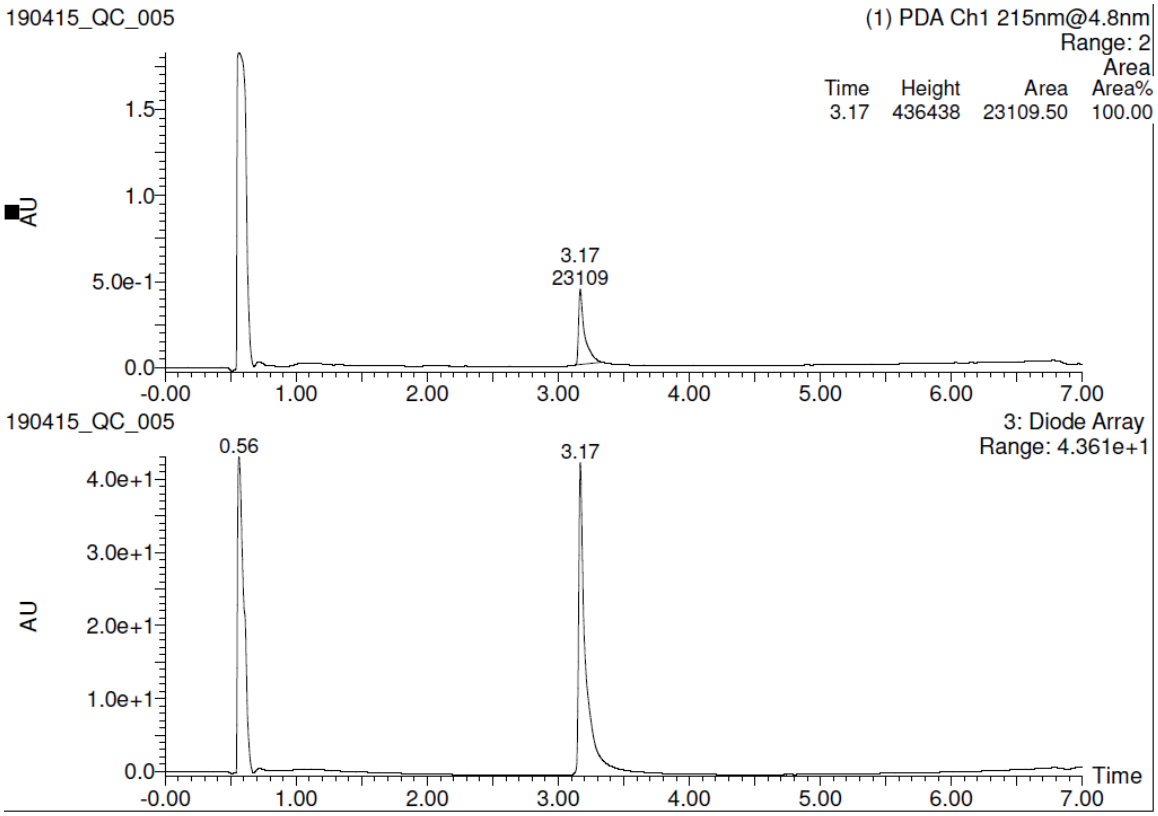

183.5
180.6
159.8
158.7
156.7
155.4
145.3
143.3
136.8
129.5
116.0
115.4
113.0
111.5
110.9
109.4
107.9
42.9
39.5 DMSO-d6
OH
O
O
H
N
O
S
N
H
N
H
OH
OH
17
13C-NMR, 101 MHz, DMSO-d6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

4. Chromatography analysis of key compounds

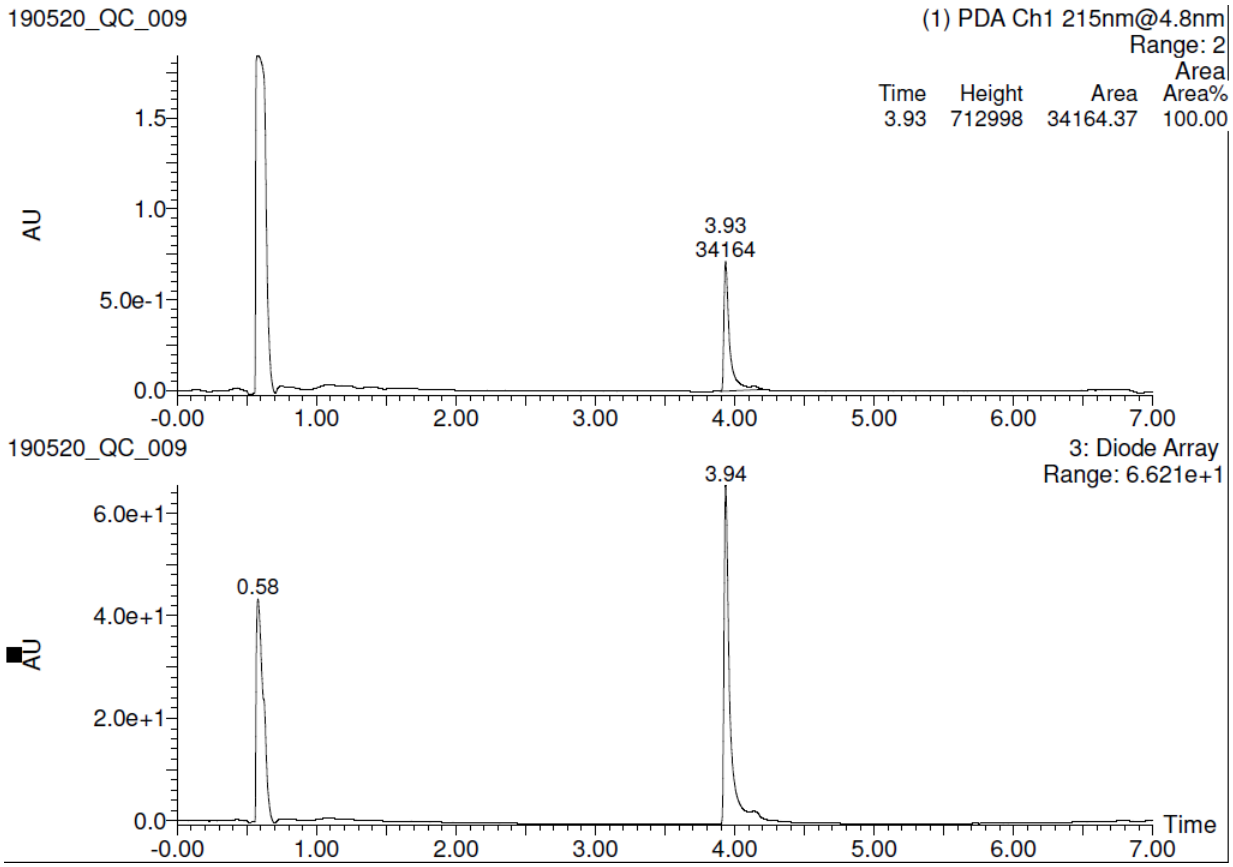
10mM stock solution of test compound was prepared in DMSO-d_6 and further diluted 20-fold with CH_3CN-H_2O (1:1) for analysis. The QC analyses were performed on a Waters ACQUITY UPLC/MS system consisting of a SQD (Single Quadrupole Detector) Mass Spectrometer equipped with an Electrospray Ionization interface and a Photodiode Array Detector. Electrospray ionization in positive and negative mode was applied in the mass scan range 100-500Da. The PDA range was 210-400nm. The analyses were run on an ACQUITY UPLC BEH C_{18} column (100x2.1mmID, particle size 1.7µm) with a VanGuard BEH C_{18} pre-column (5x2.1mmID, particle size 1.7µm). The mobile phase was 10mM NH_4OAc in H_2O at pH 5 adjusted with AcOH (A) and 10mM NH_4OAc in CH_3CN-H_2O (95:5) at pH 5 (B) with 0.5mL/min as flow rate. A linear gradient was applied: 0-0.2min: 10%B, 0.2-6.2min: 10-90%B, 6.2-6.3min: 90-100%, 6.3-7.0min: 100%B. All final compounds displayed ≥95% purity as determined by UPLC/MS analysis (unless otherwise indicated).

For compound **17** we used quantitative 1H NMR spectra analysis to evaluate the purity of the final compound: Quantitative 1H spectra (qNMR). qNMR was acquired with 64 transients, after an automatic 90°degree pulse length optimization,1 by using 65536 digit points, 30 s of interpulses delay, and the receiver gain fixed (64), the spectral width was 22.55 ppm with the offset positioned at 6.17 ppm. An apodization esponential function equivalent to 0.3Hz was applied to FIDs before Fourier transform. Spectra were phased, and baseline corrected, automatically. For purity evaluation by NMR assay (qNMR), the signal of final compound (10 mM solution in DMSO-d6), was compared to the peak of an equimolar external standard solution of maleic acid (TraceCERT, 99.99%, Sigma-Aldrich, Milan, Italy), after the normalization for the number of protons genearating such signals, by using the PULCON method.

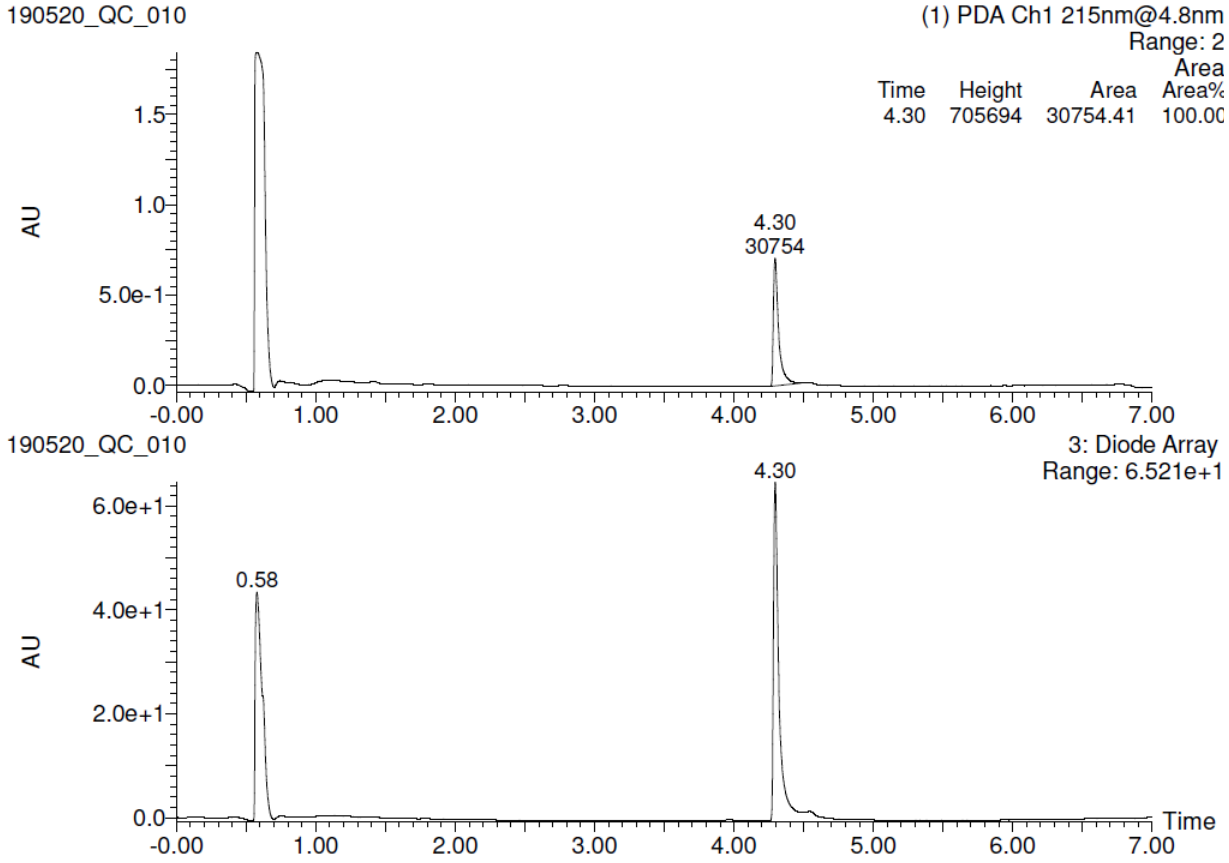
Compound **1**.



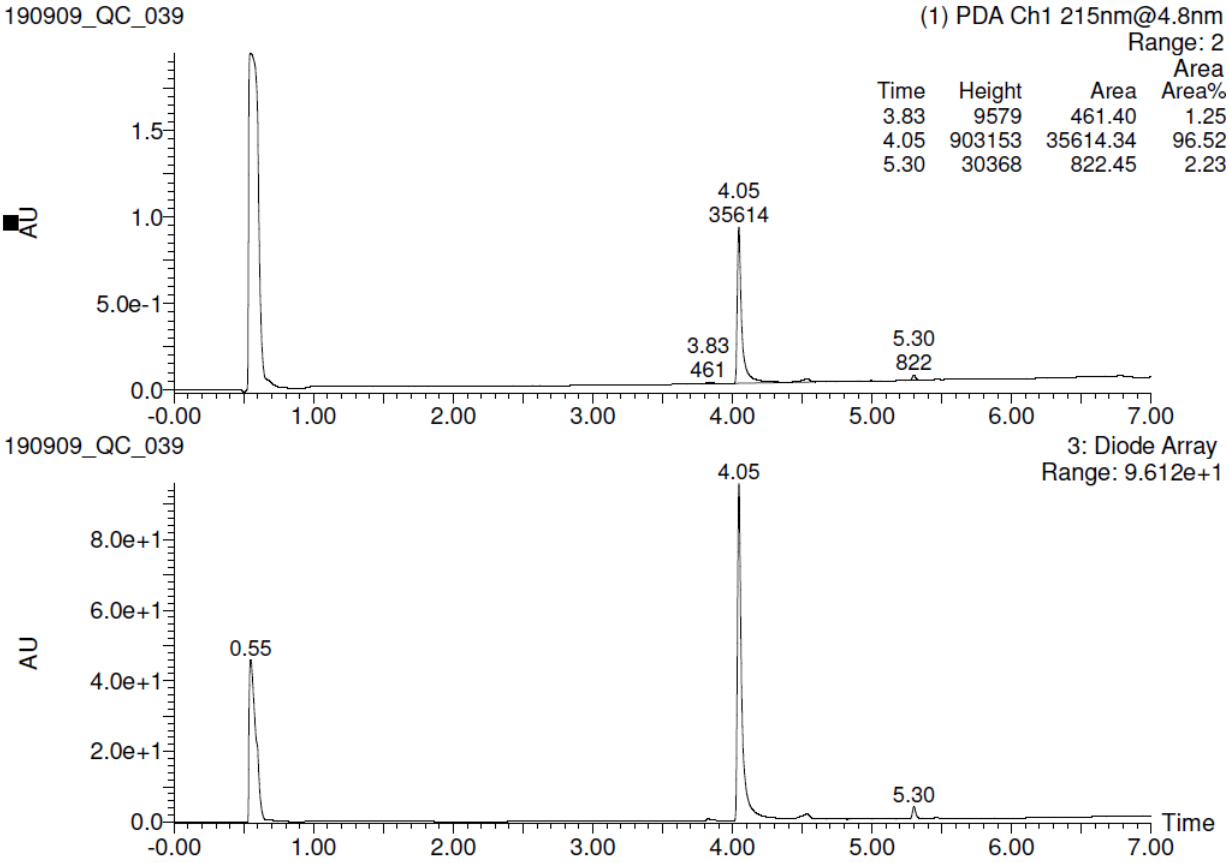
Compound **2**.



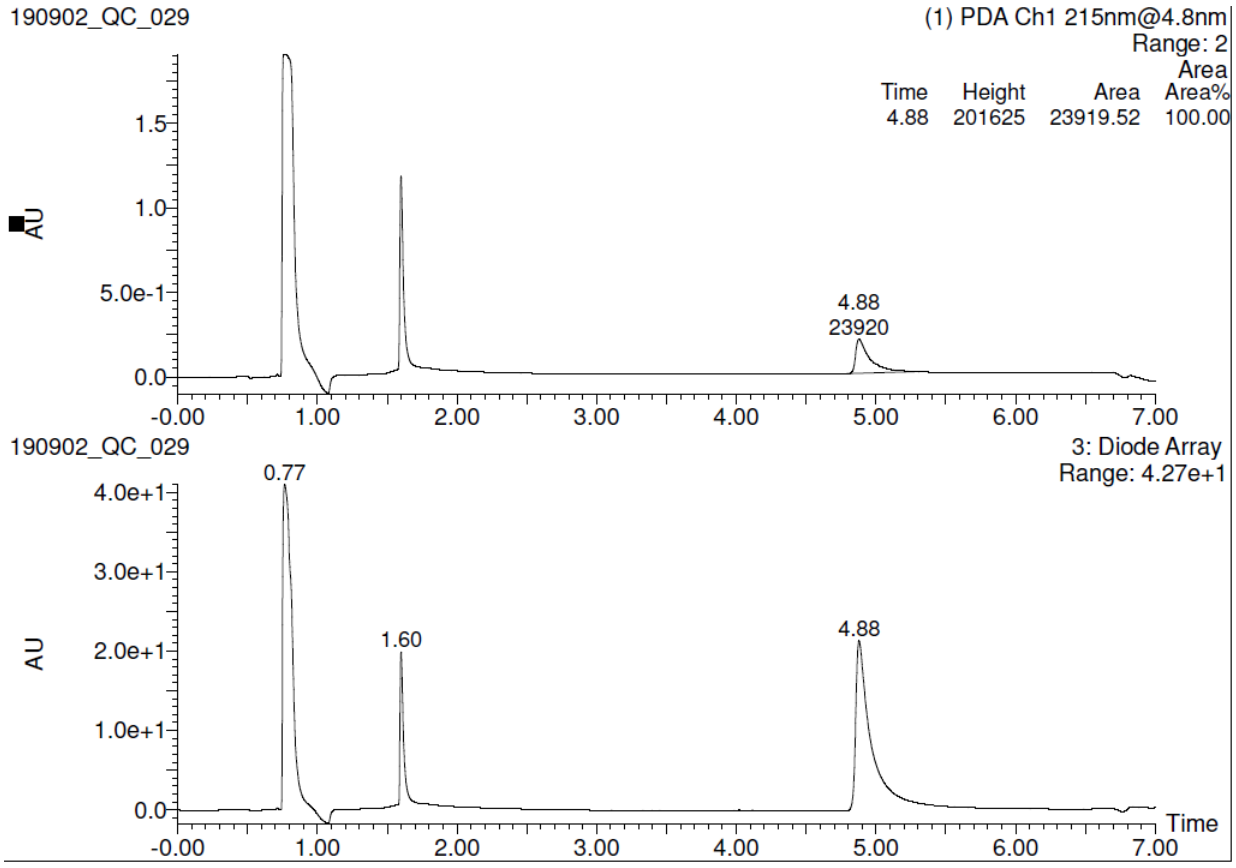
Compound **3**.



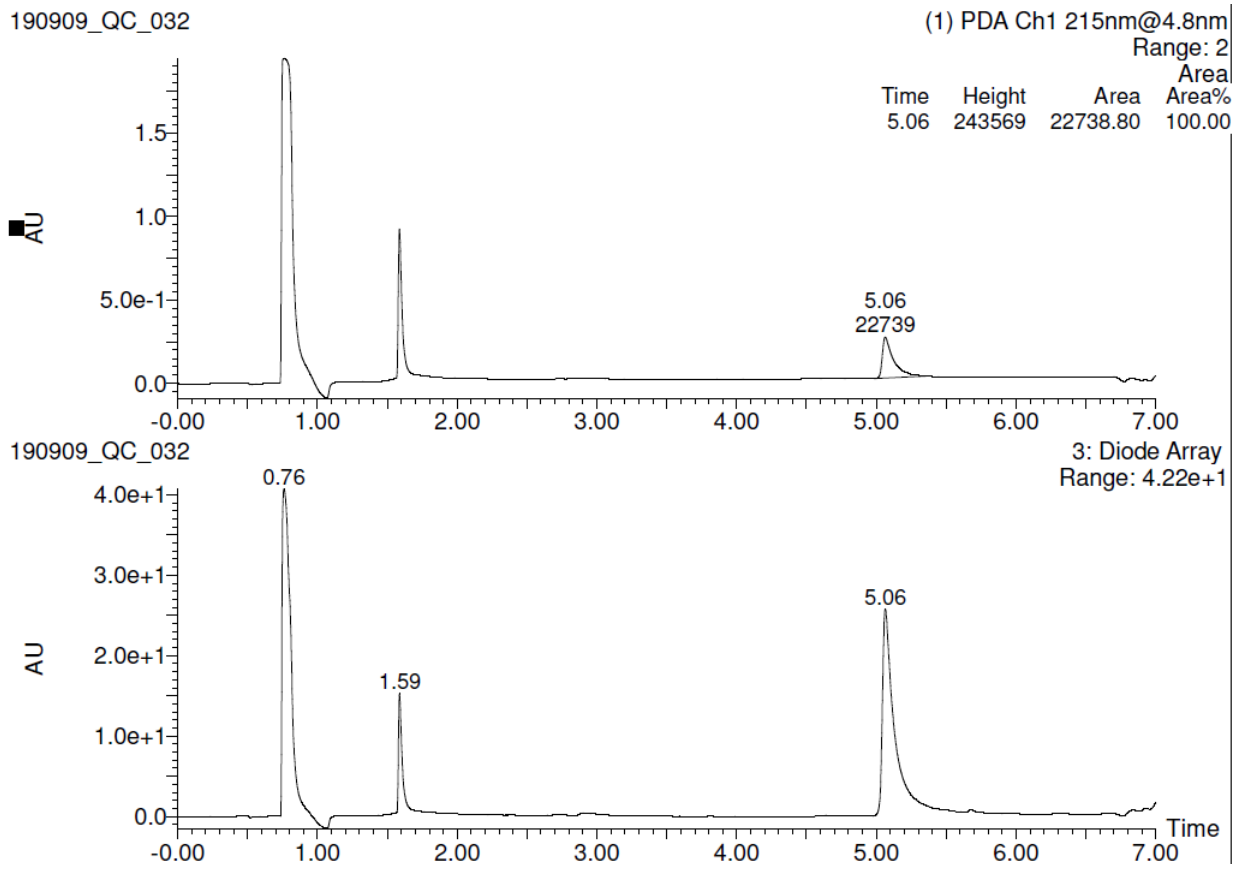
Compound **4**.



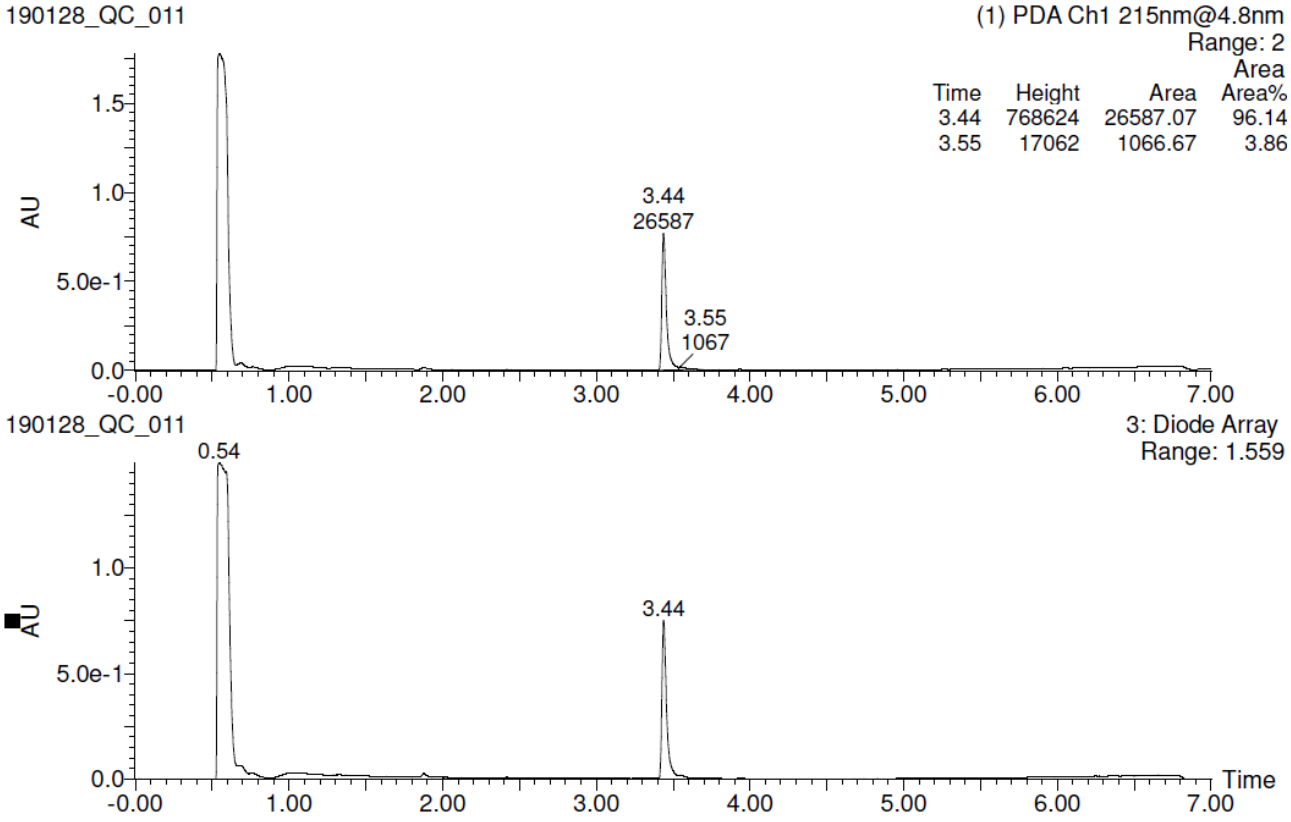
Compound **5**.



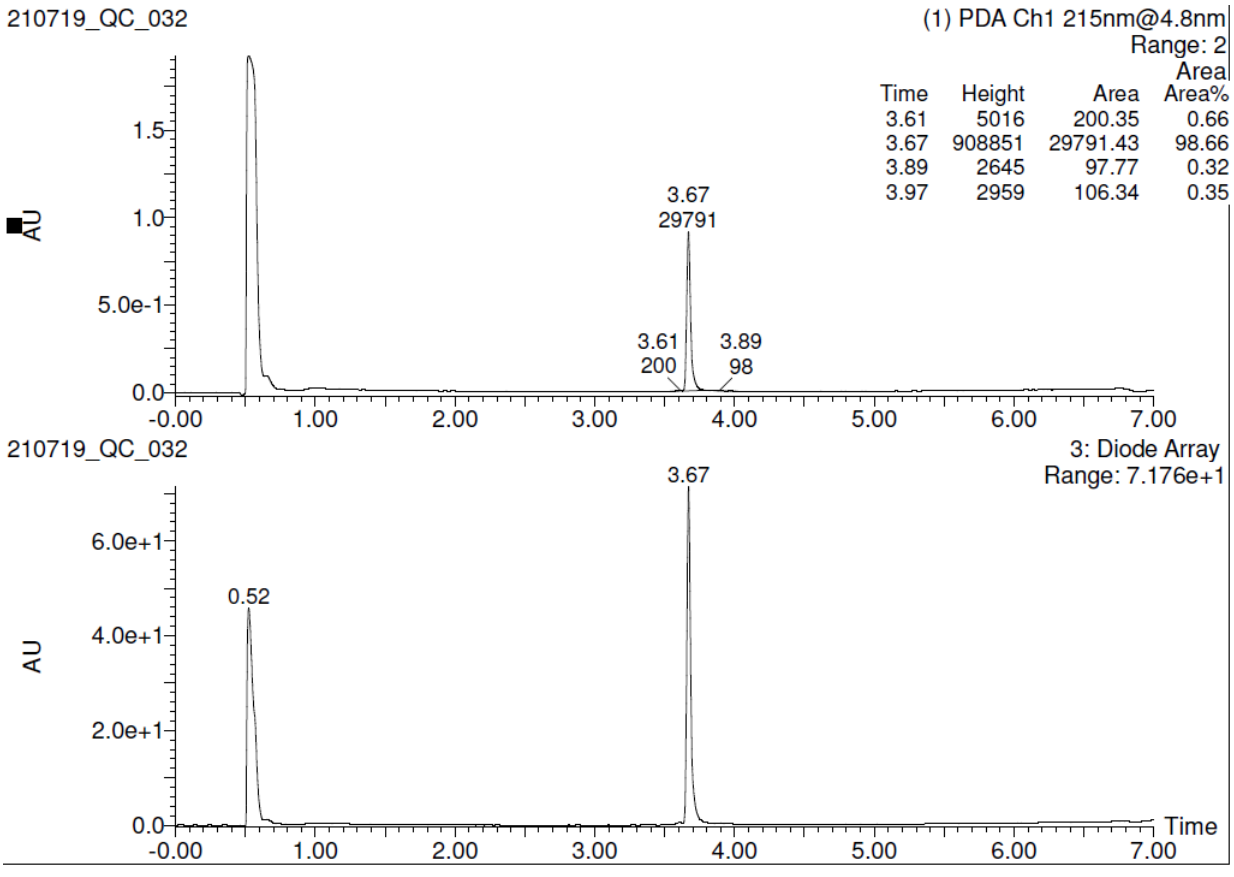
Compound **6**.



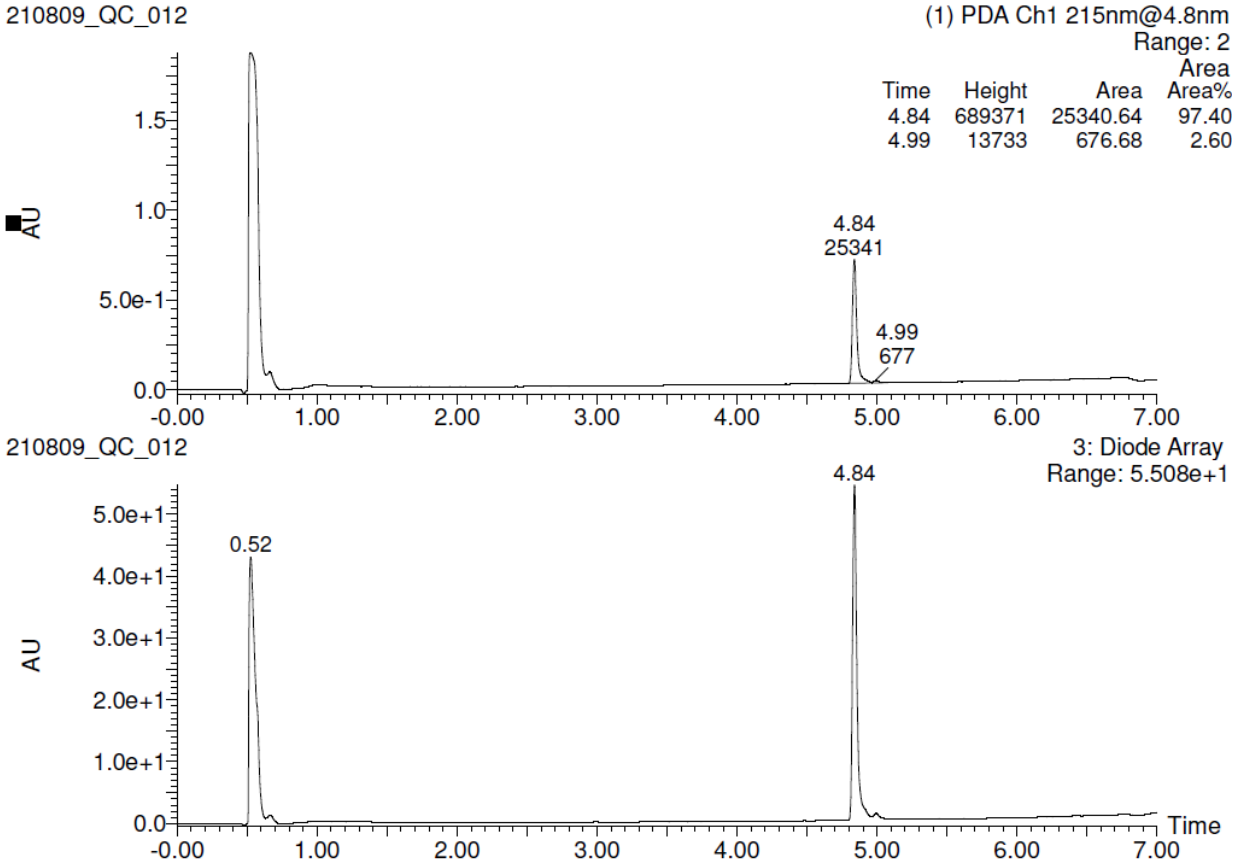
Compound **7**.



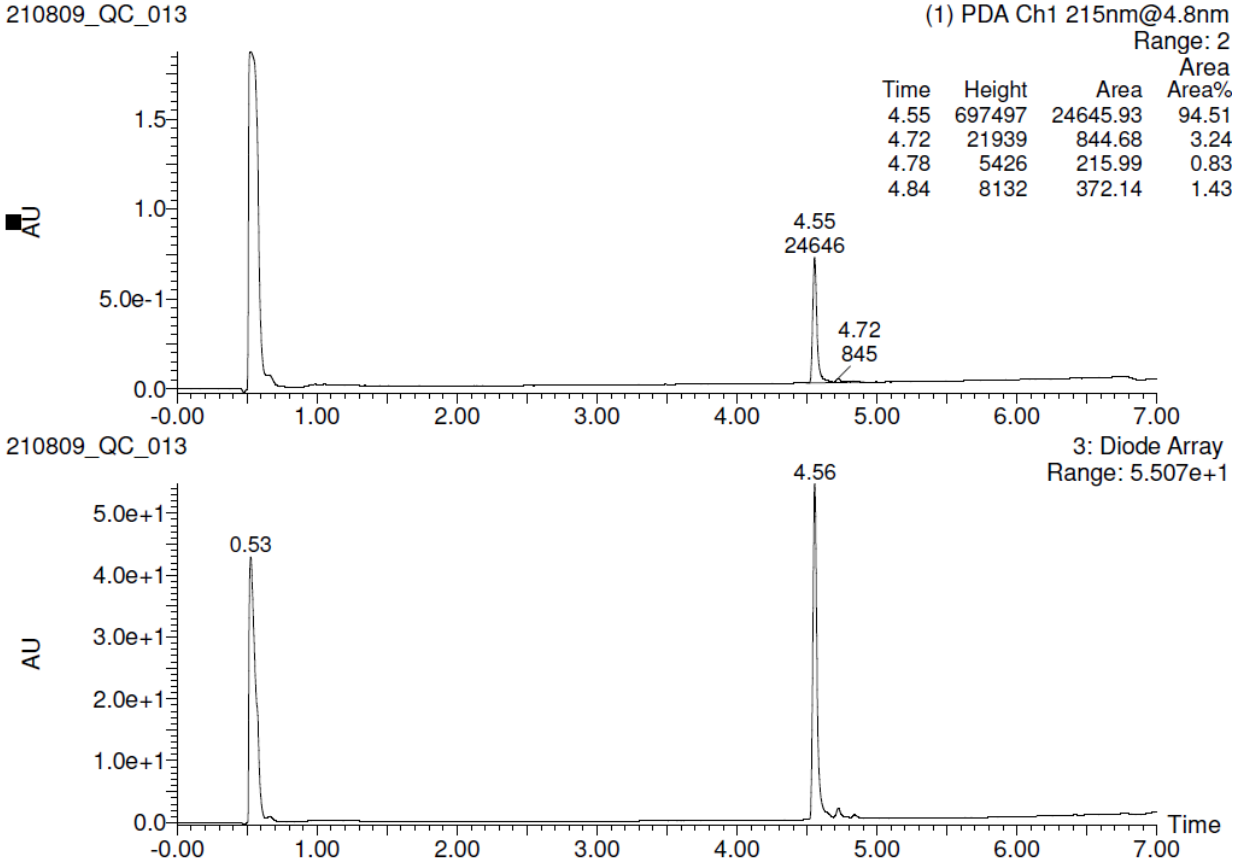
Compound **8**.



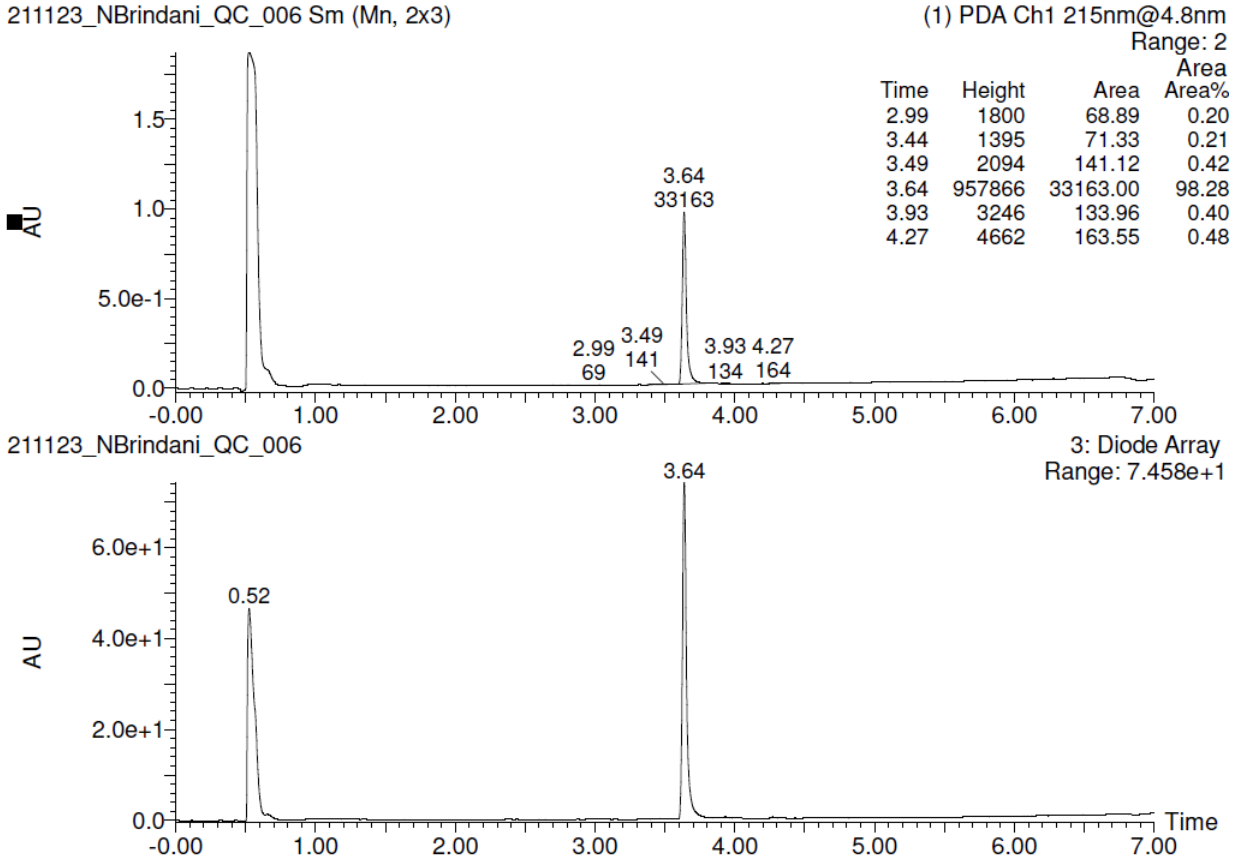
Compound **9**.



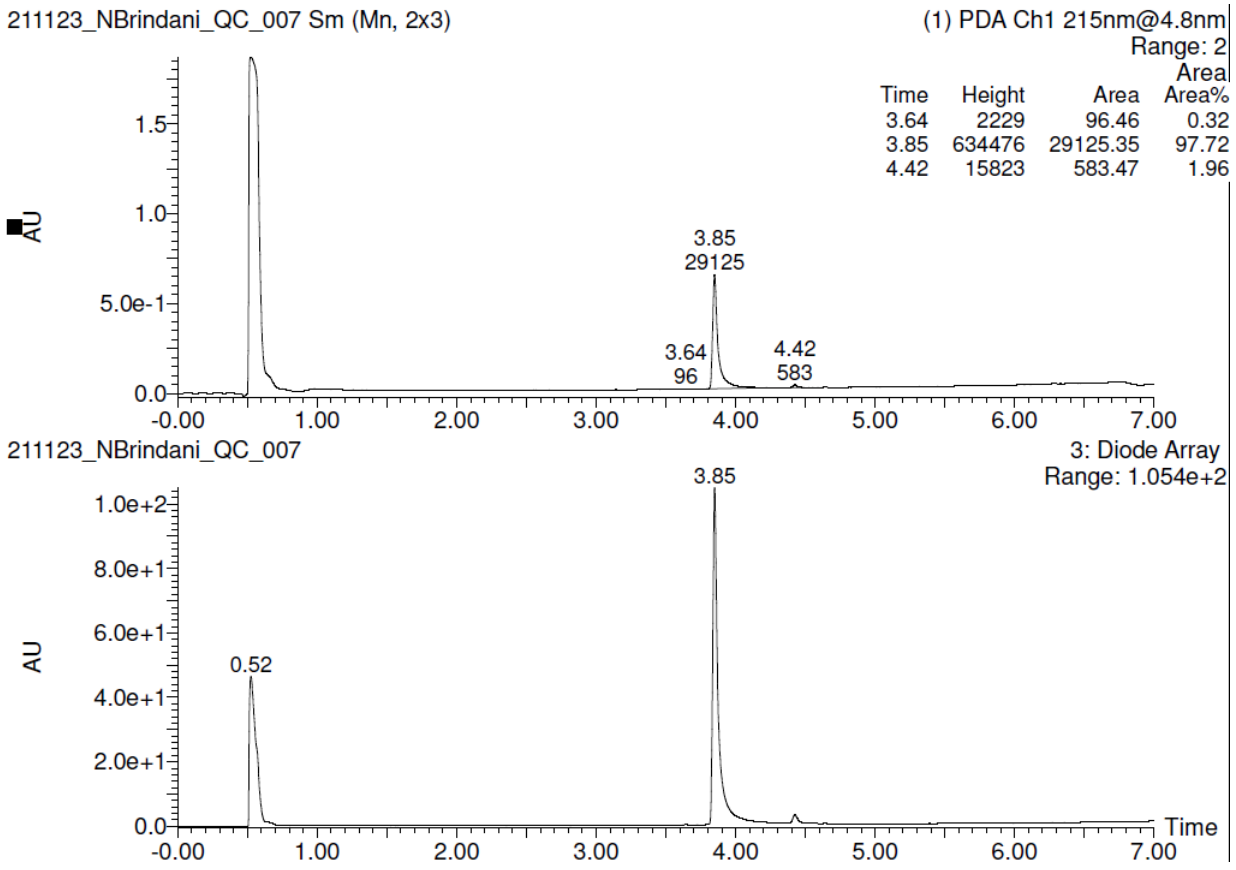
Compound **10**.



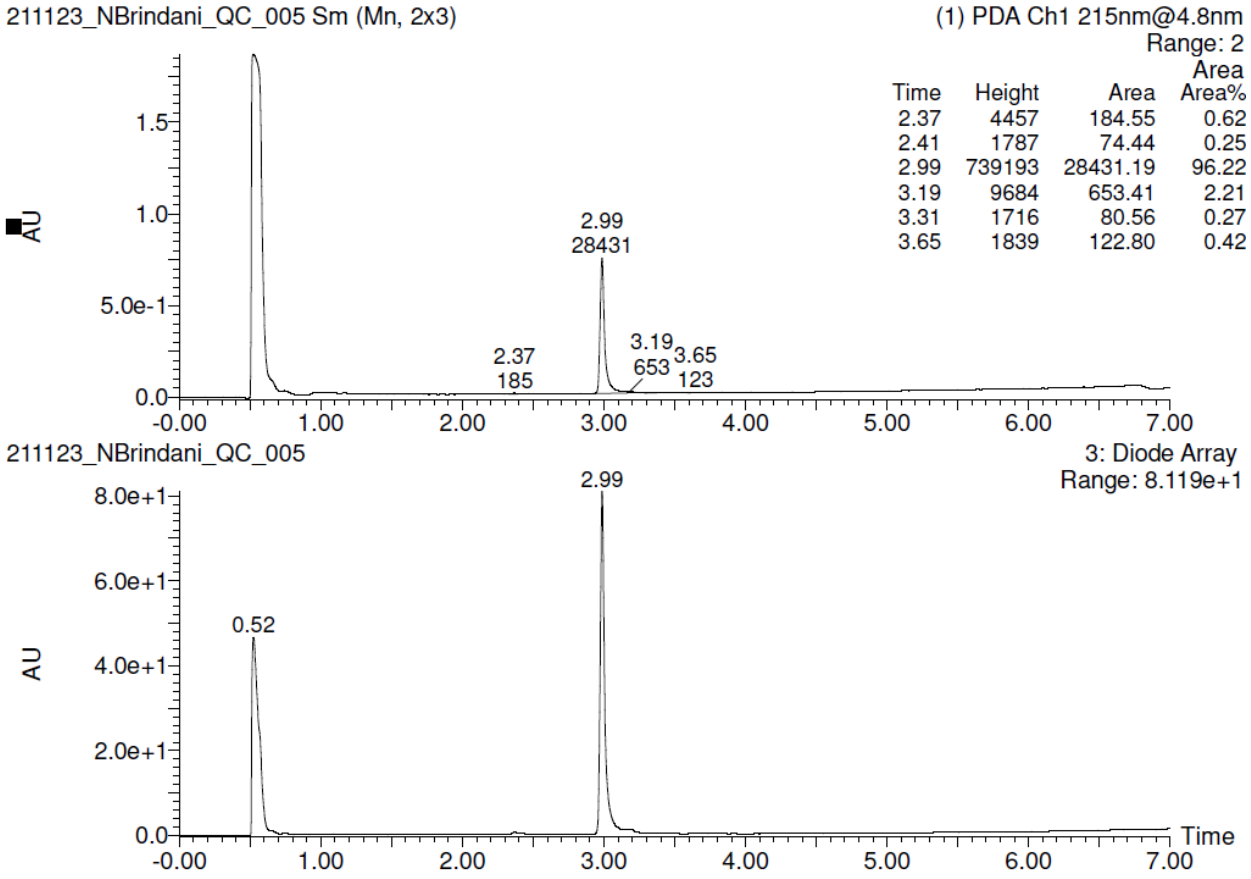
Compound **11**.



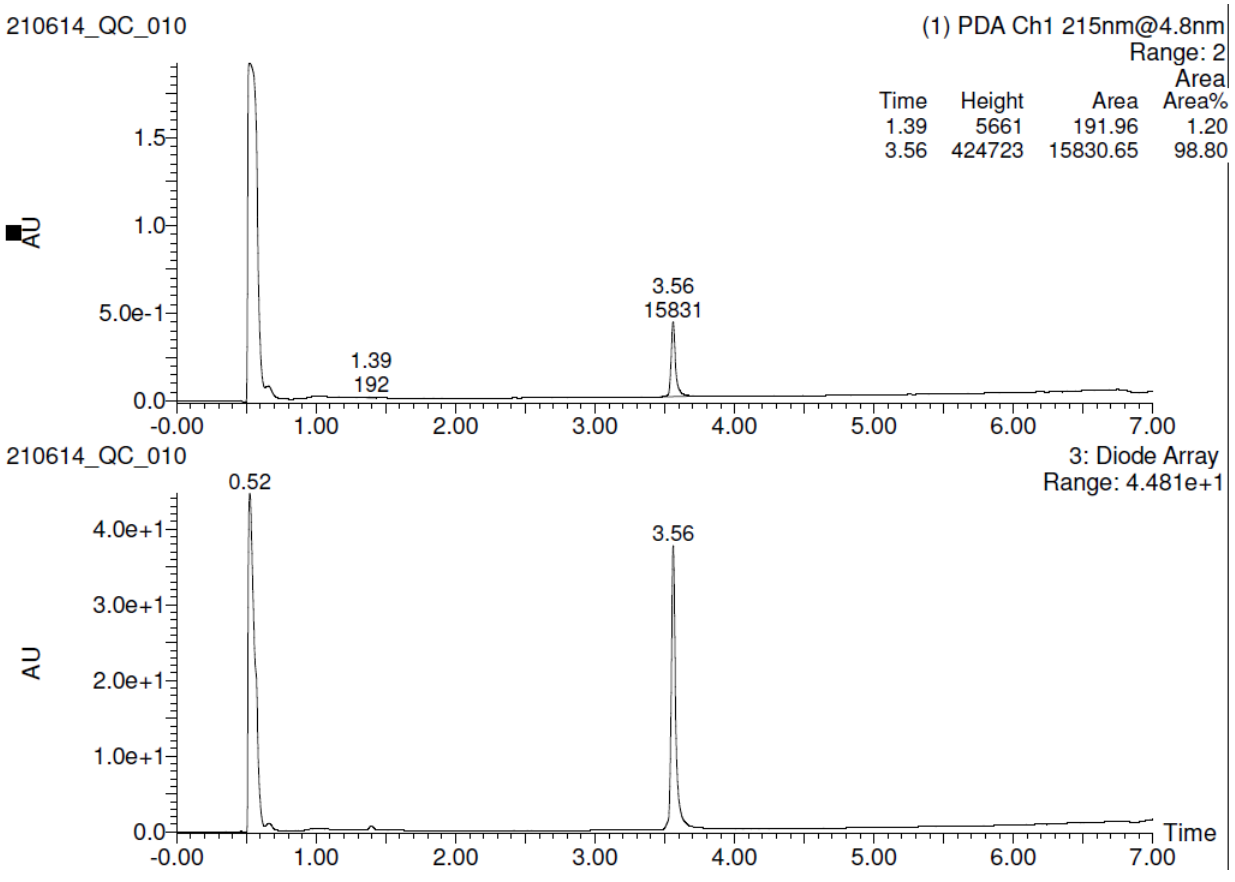
Compound **12**.



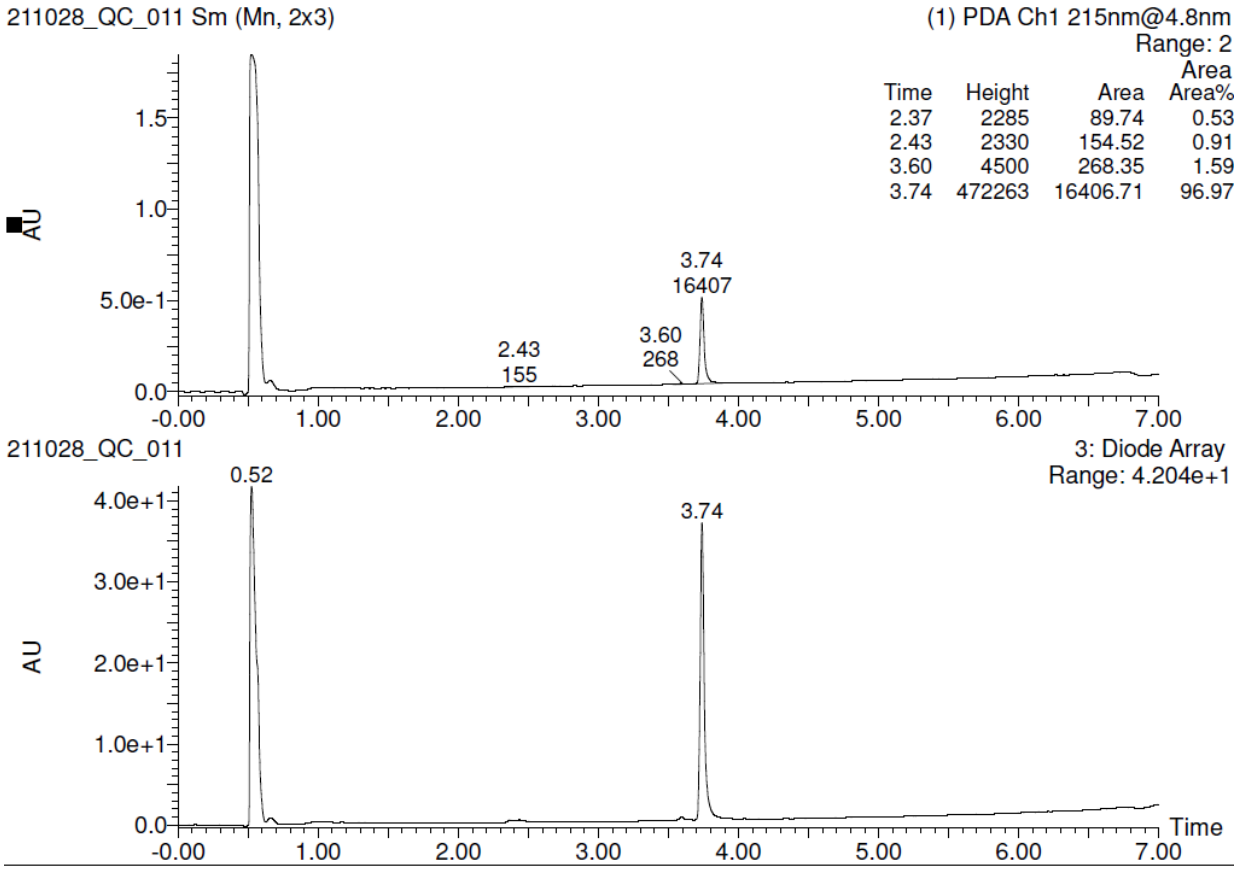
Compound **13**.



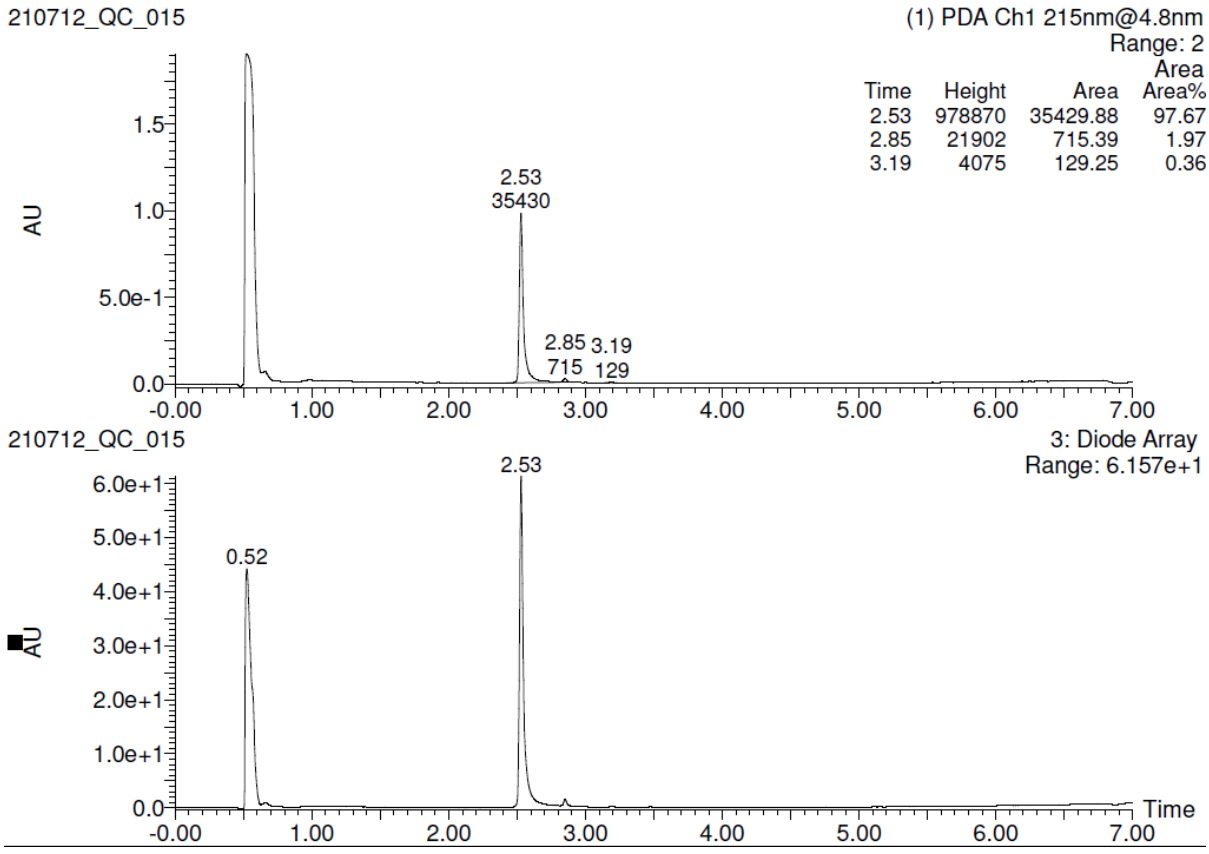
Compound **14**.



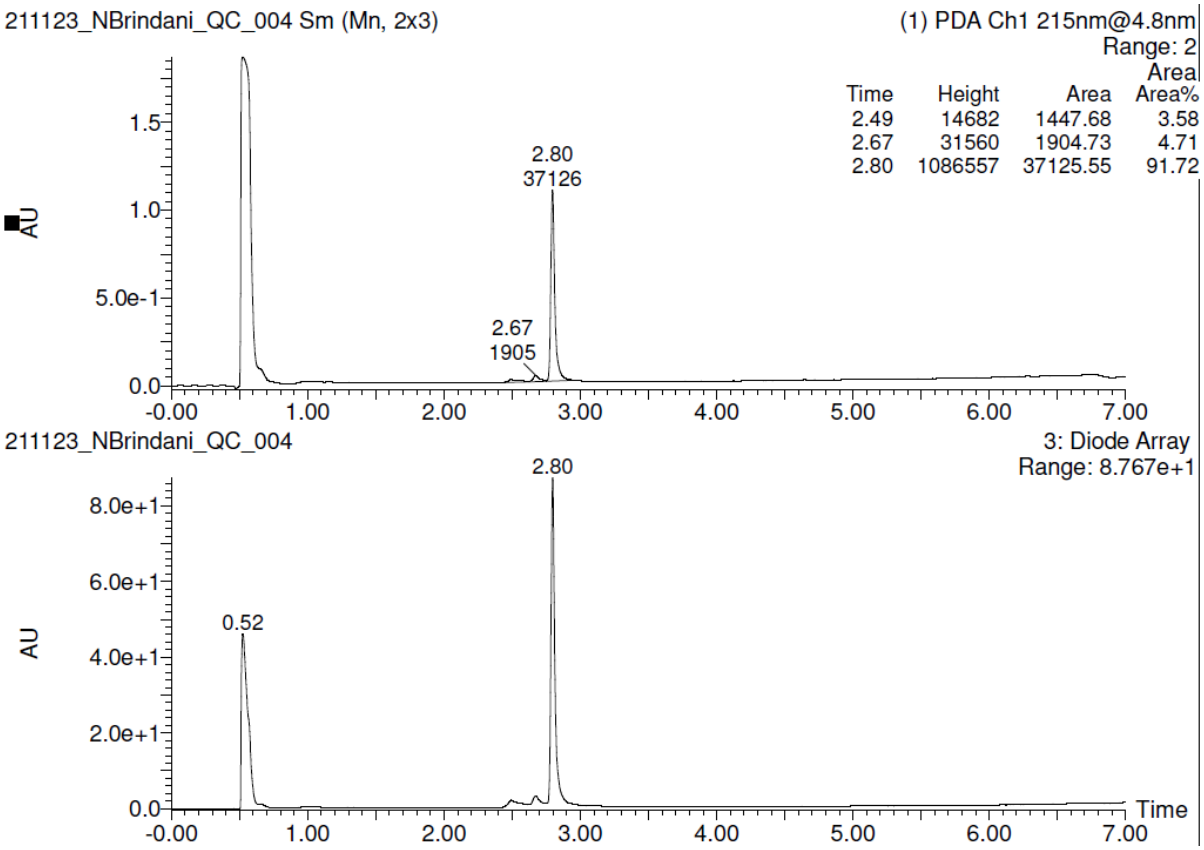
Compound **15**.



Compound **16**.



Compound **17** displayed 92% purity by UPLC due to its instability in the UPLC columns, but QC by NMR showed 95% purity.



5. Table S1

B_{RNA} binding site			B_{NTP} binding site	
Compound	**GScore**		**Compound**	**GScore**
15	-7,655		16	-7,139
16	-6,905		17	-6,627
Quercetin	-5,955		12	-5,631
5	-5,884		Quercetin	-5,576
11	-5,703		5	-5,571
6	-5,624		4	-5,535
2	-5,563		14	-5,455
17	-5,501		1	-5,062
7	-5,407		13	-4,964
3	-5,243		9(S)	-4.76
13	-5,128		Luteolin	-4,747
1	-5,101		11	-4,646
12	-4,965		6	-4,556
14	-4,914		9(R)	-4,479
4	-4,893		8(S)	-4.37
8(R)	-4,694		2	-4,327
9(R)	-4,566		10(R)	-4,291
10(S)	-4,486		7	-4,186
10(R)	-4,436		3	-4,213
8(S)	-4,044		10(S)	-4,086
9(S)	-3.86		8(R)	-3,846
Luteolin	-3,449		15	-3,375

Table S1. Docking scores of all 22 compounds (i.e. 1-17 including the enantiomers of derivatives 8-10, in addition to luteolin and quercetin), obtained from XP Glide for both binding pockets (i.e. B_{RNA} and B_{NTP}). In red compounds **9** and **10**, corresponding to low and absent inhibitory activity.

6. Figure S1-S3

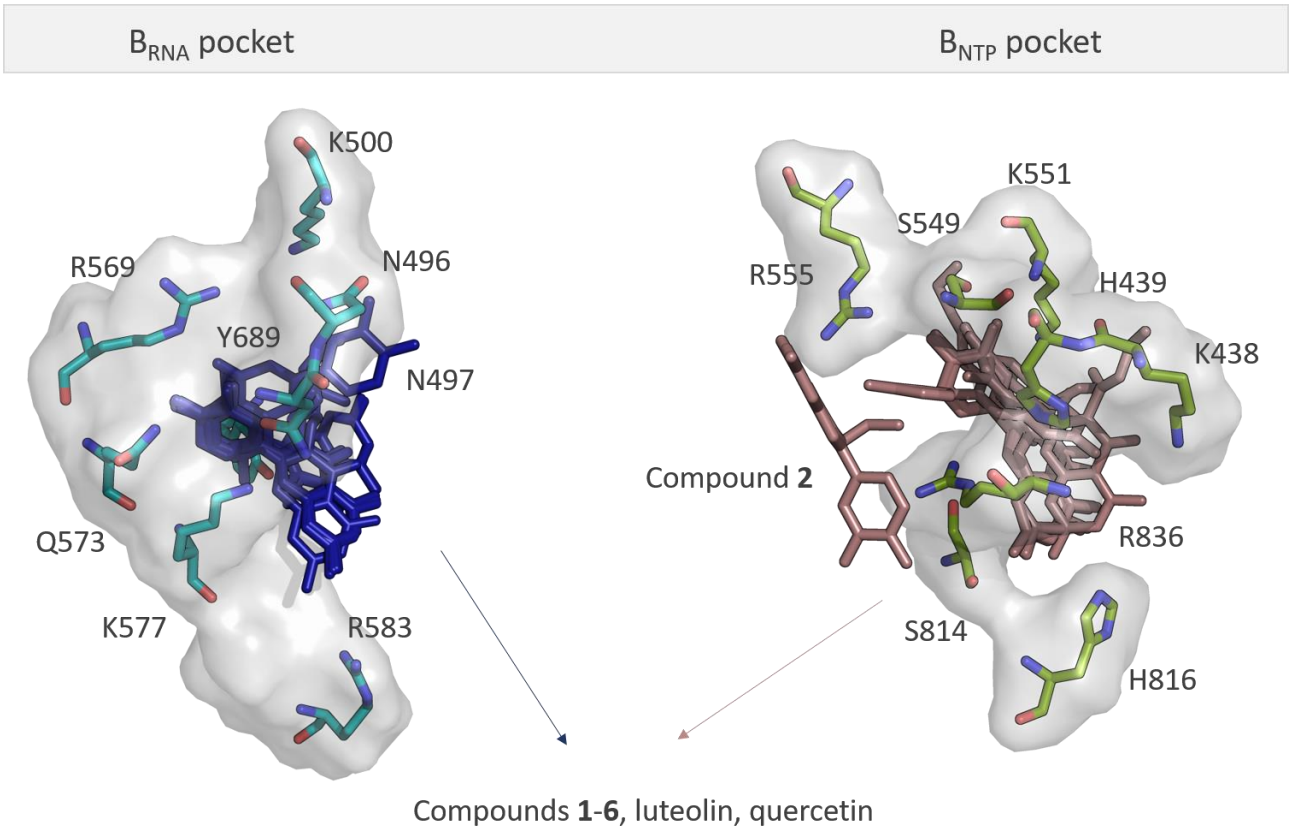


Figure S1. Docking poses of the first subset of derivatives (i.e. compounds **1**-**6**) in addition to luteolin and quercetin, in both B_{RNA} (on the left) and B_{NTP} (on the right) pockets. Interacting residues from each pocket are shown in licorice.

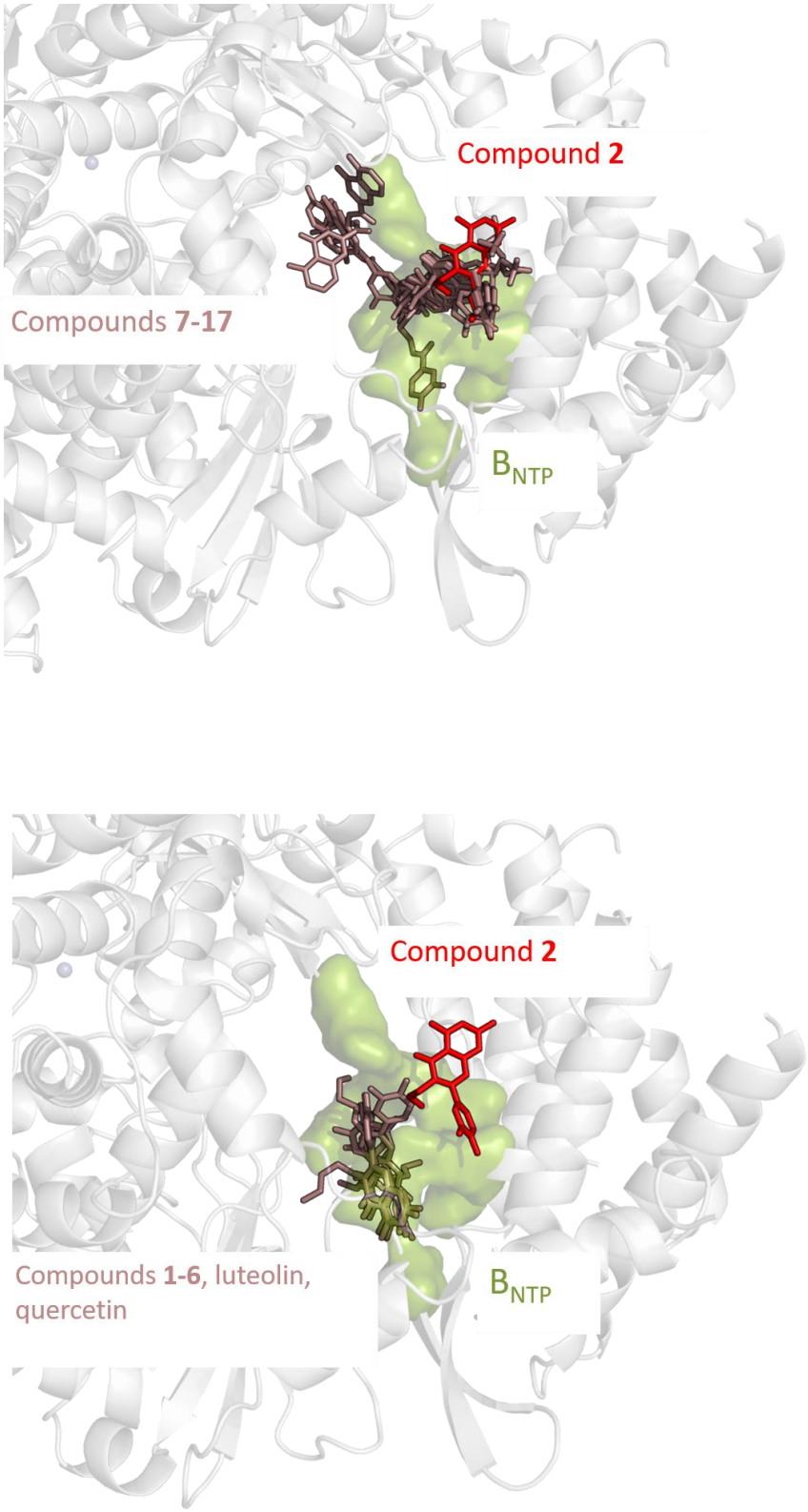


Figure S2. (Top) Superposition of the docking poses of compound **2** (in red licorice) and the second subset of derivatives (i.e. compounds **7-17**) in the B_{NTP} pocket. (Bottom) Superposition of the docking poses of compound **2** (in red licorice) and the first subset of derivatives (i.e. compounds **1-6**) in addition to luteolin and quercetin in the B_{NTP} pocket.

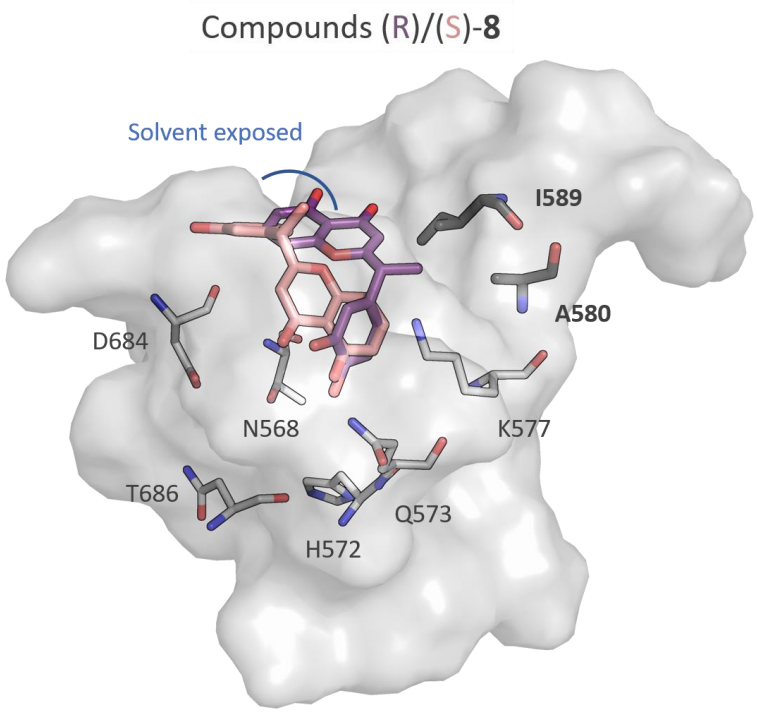
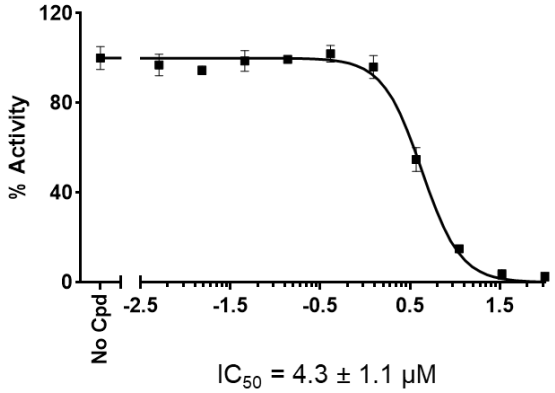


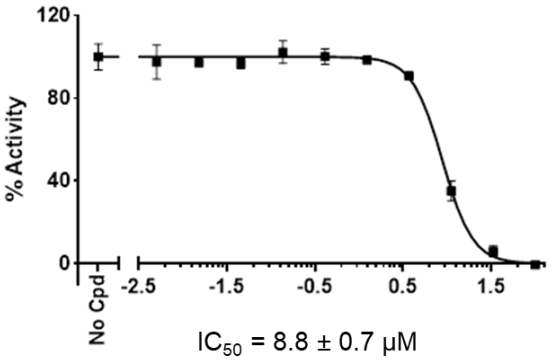
Figure S3. Docking poses of both (S)-8 (in pink licorice) and (R)-8 (in purple licorice) enantiomers in the B_{RNA} pocket. Polar residues defining the small cleft are represented in white licorice, while the lipophilic residues interacting with the methyl group in (R)-8 are represented in dark grey licorice.

7. Dose response curve of inhibitory activity



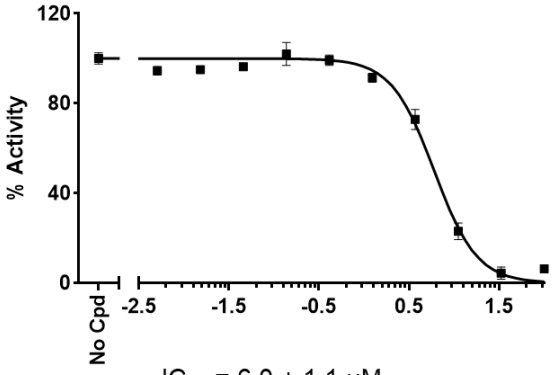
IC_{50} = 4.3 ± 1.1 μM

compound **1** **(Log [μM])**



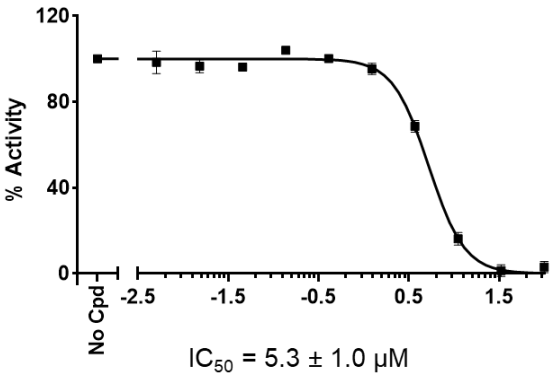
IC_{50} = 8.8 ± 0.7 μM

compound **2** **(Log [μM])**



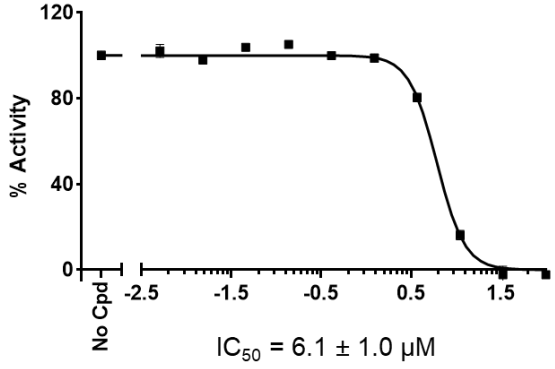
IC_{50} = 6.0 ± 1.1 μM

compound **3** **(Log [μM])**



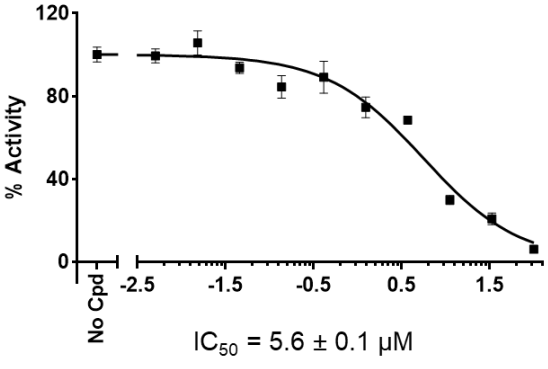
IC_{50} = 5.3 ± 1.0 μM

compound **4** **(Log [μM])**



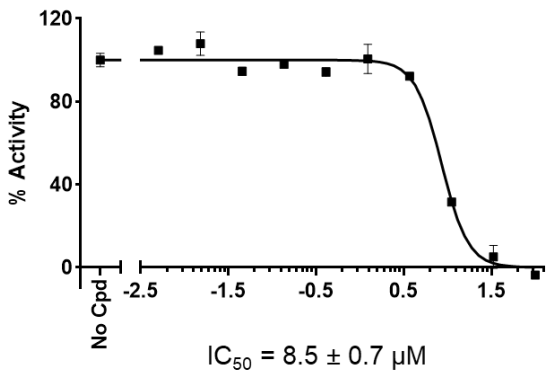
IC_{50} = 6.1 ± 1.0 μM

compound **5** **(Log [μM])**



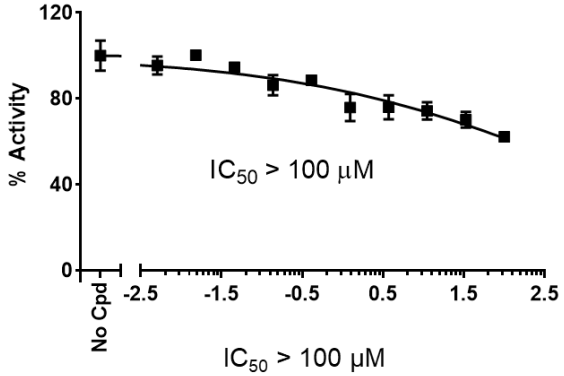
IC_{50} = 5.6 ± 0.1 μM

compound **6** **(Log [μM])**



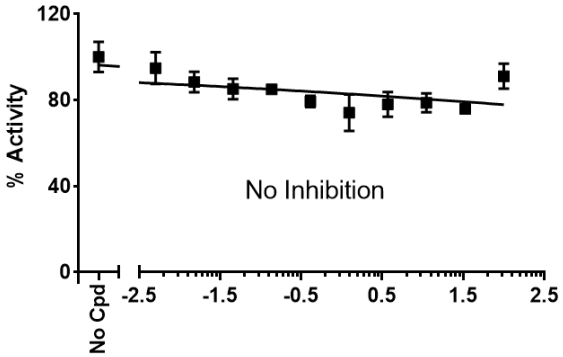
IC_{50} = 8.5 ± 0.7 μM

compound **7** **(Log [μM])**

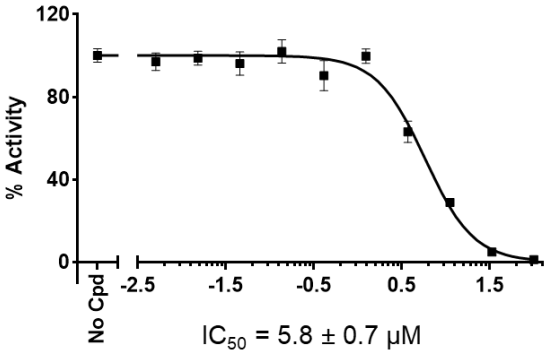


IC_{50} > 100 μM

compound **9** **(Log [μM])**

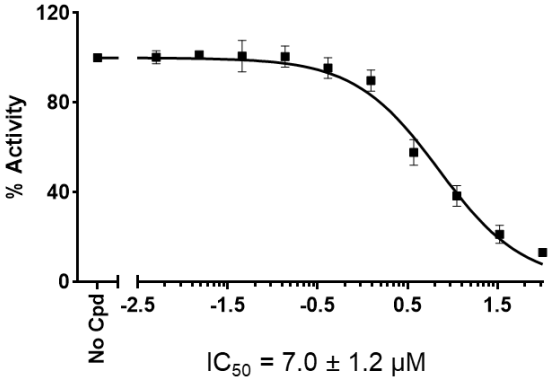


compound **10** **(Log [μM])**



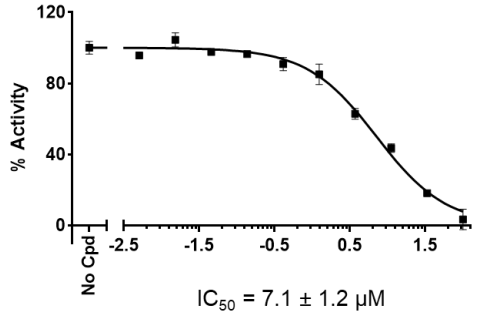
IC_{50} = 5.8 ± 0.7 μM

compound **11** **(Log [μM])**



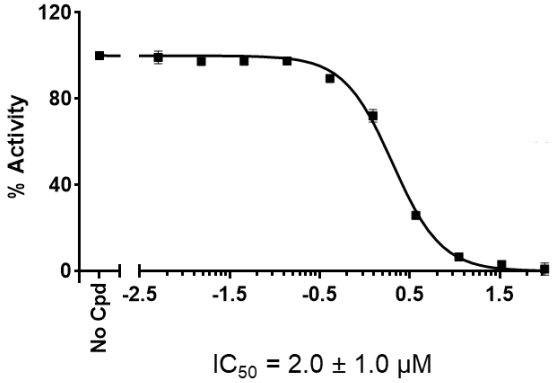
IC_{50} = 7.0 ± 1.2 μM

compound **12** **(Log [μM])**



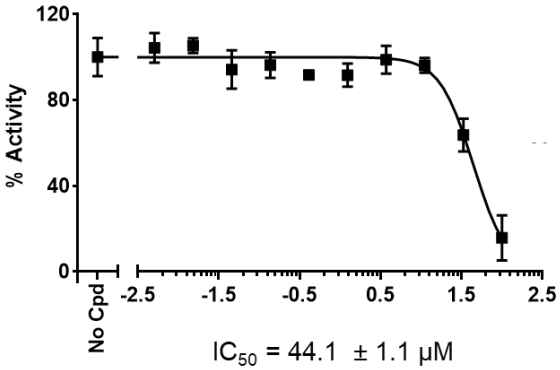
IC_{50} = 7.1 ± 1.2 μM

compound **13** **(Log [μM])**



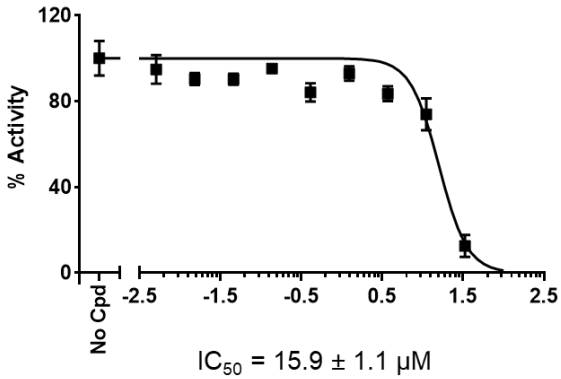
IC_{50} = 2.0 ± 1.0 μM

compound **14** **(Log [μM])**



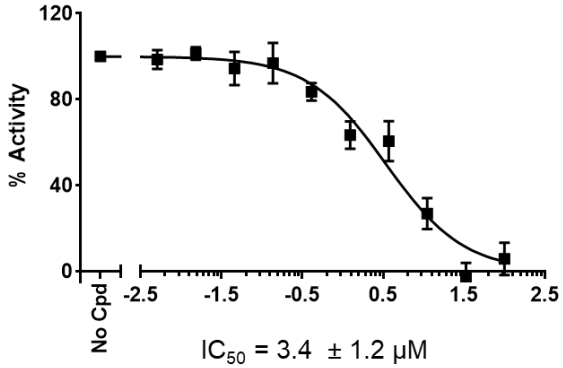
IC_{50} = 44.1 ± 1.1 μM

compound **15** **(Log [μM])**



IC_{50} = 15.9 ± 1.1 μM

compound **16** **(Log [μM])**



IC_{50} = 3.4 ± 1.2 μM

compound **17** **(Log [μM])**

8. Cell viability of compounds 4, 5, 6.