Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.

Hypoxia-activated prodrugs of phenolic olaparib analogues for tumour-selective chemosensitisation.

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Key Structures

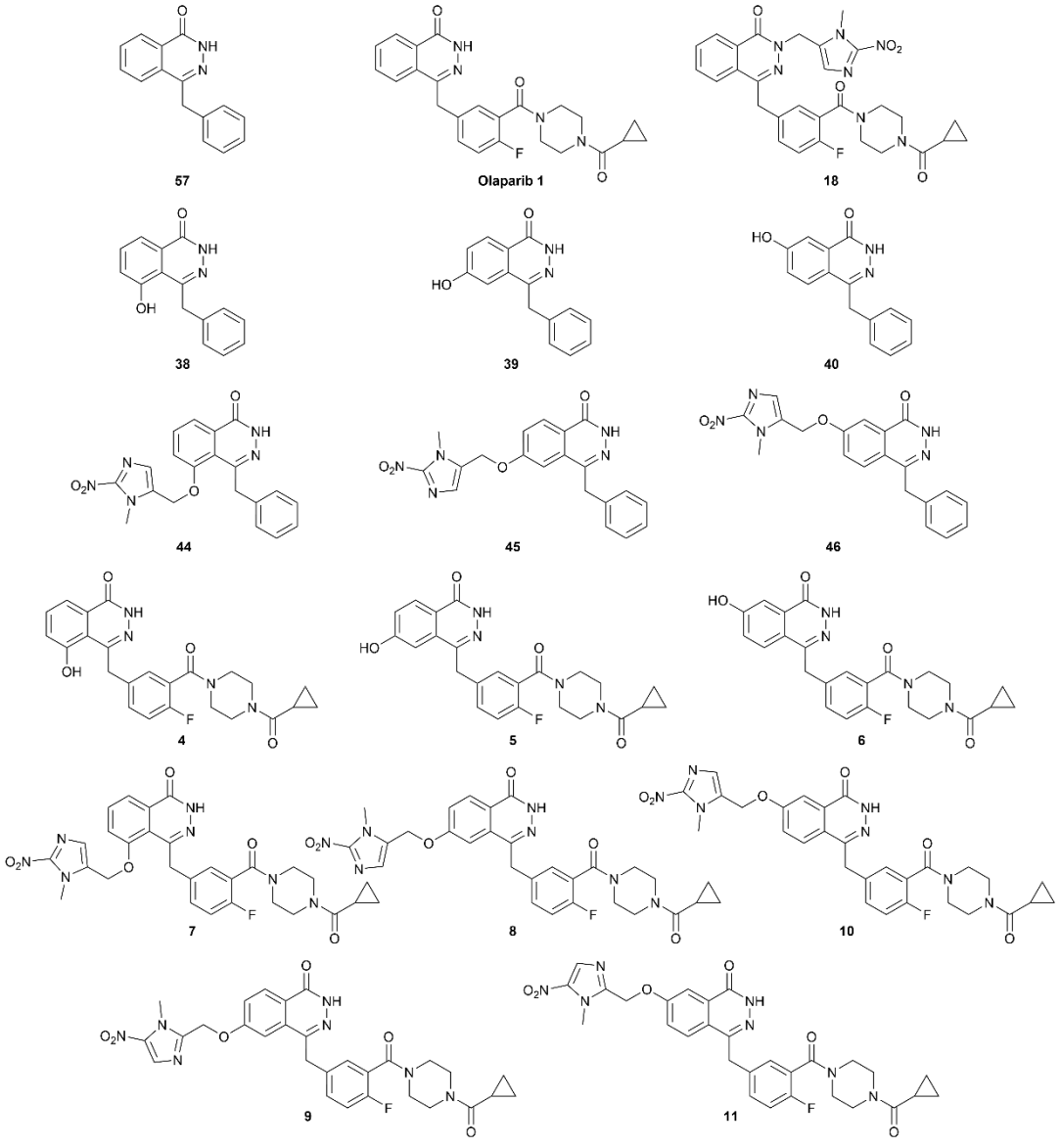


Figure S1: Structures of key compounds included in biochemical and cellular analyses.

General Information

DCM, DMF, MeCN and THF were purchased pre-dried and stored over molecular sieves from Acros Organics. All other reaction solvents were analytical grade. For lithiation reactions analytical grade THF was pre-dried over sodium, then distilled from sodium benzophenone ketyl prior to use. Non-aqueous reactions were carried out under a nitrogen atmosphere unless otherwise noted. Commercial reagents were used without purification. Flash column chromatography was carried out on a silica gel solid phase (Merck 230 – 400 mesh) using distilled laboratory grade solvents. Thin layer chromatography was carried out using Merck 60 F_{254} aluminium plates pre-coated with silica. Compounds were identified using UV fluorescence and/or staining with either ninhydrin in ethanol/glacial acetic acid (95:5) (with heating), or iodine on silica gel. Melting points were determined on an Electrothermal 2300 Melting Point Apparatus. High resolution mass spectra (HRMS) were measured on an Agilent Technologies 6530 Accurate-Mass Quadrupole Time of Flight (Q-TOF) LC/MS interfaced with an Agilent Jet Stream Electrospray Ionisation (ESI) source allowing positive or negative ions detection. Low-resolution mass spectra (LRMS) were gathered by direct injection of methanolic solutions into an Agilent 6120 mass spectrometer using atmospheric pressure chemical ionization (APCI) mode with a fragmentor voltage of 50 V and a drying gas temperature of 250 °C. NMR spectra were recorded on a Bruker Avance 400 spectrometer (^{1}H nuclei, 400 MHz; ^{13}C nuclei, 100MHz) in $(CD_3)_2SO$ unless specified. All chemical shift (δ) values are reported in parts per million (ppm) relative to the residual ^{1}H resonance from the deuterated solvent, coupling constants are reported in Hertz (Hz). ^{13}C spectral assignments were made *via* interpretation of HSQC, HMBC and APT experiments. Final products were analysed by reverse-phase HPLC (Agilent Zorbax Eclipse XDB C8 5 µm column, 150 mm × 4.6 mm; or Alltech Altima C8 5 µm column, 150 mm × 2.1;) using an Agilent HP1100 equipped with a photodiode array detector. Mobile phases were gradients of 80% CH_3CN/20% H_2O (v/v) in 45 mM ammonium formate at pH 3.5 and 0.5 – 1.0 mL/min. Purity was determined by monitoring at 330 ± 50 nm. AcOH refers to acetic acid, DCM refers to dichloromethane, DIPEA refers to diisopropylethylamine, DMF refers to dimethylformamide, Et_2O refers to diethylether, EtOAc refers to ethyl acetate, EtOH refers to ethanol, LiHMDS refers to lithium hexamethyldisilazide, MeOH refers to methanol, MeCN refers to acetonitrile, NEt_3 refers to triethylamine, PhMe refers to toluene, THF refers to tetrahydrofuran, X4 refers to petroleum ether, boiling fraction 40 – 60 °C.

Assignment of alkene stereochemistry

For alkenes where both isomers were isolated it was possible to organise the products into two distinct groups based on the ^{1}H and ^{13}C signals of the olefinic CH (Table S1). The groupings could be defined as Group A: δ_H 6.86 – 7.06 ppm; δ_C 108.0 – 113.3 ppm and Group B: δ_H 6.39 – 7.00 ppm; δ_C 102.4 – 109.2 ppm. The ^{13}C signal is more diagnostic as there is significant overlap in the ^{1}H signal range, however in cases where the ^{13}C signal leaves ambiguity the ^{1}H signal can in some cases resolve this. Miura *et al*.[1] reported the *Z*-isomer of alkene **34**, with assignment provided by analysis of NOE enhancements and based on this we tentatively assigned Group A as the *E*-isomer and Group B as the *Z*-isomer. A NOESY experiment for alkene **50** (Figure S1, Figure S2) supported this assignment and all other alkene stereochemistry has been assigned on this basis. In all except one instance (benzofuranone **55**) when only a single isomer was isolated it was the *E*-isomer.

Table S1: Alkene isomer 1H and 13C shifts ($(CD_3)_2SO$ unless specified) for olefinic CH

	Group A (*E*)		Group B (*Z*)	
Compound	**Alkene ^{1}H (ppm)**	**Alkene ^{13}C (ppm)**	**Alkene ^{1}H (ppm)**	**Alkene ^{13}C (ppm)**
33	6.99	112.4	6.85	109.2
34	6.90[1]	112.8[1]	6.39[1]	107.0[1]
35	6.92	110.8	6.80	105.3
36	6.95	112.4	6.81	106.2
37	n.i.	n.i.	6.70[1]	104.3[1]
41	n.i.	n.i.	6.79	110.4
42	7.06	113.3	6.96	106.9
43	n.i.	n.i.	6.84	105.7
47	6.98	110.5	6.87	107.2
48	7.01	111.2	7.00	104.8
49	6.89	109.0	6.84	103.3
50	6.93	110.5	6.85	104.3
51	6.86	108.0	6.76	102.4
52	6.90	112.0	6.81	108.9
53	n.i.	n.i.	6.99	105.0
54	n.i.	n.i.	6.88	103.7
55	7.02	112.0	n.i.	n.i.
56	6.93	109.5	6.88	103.7

n.i.: Not isolated. [1]From $CDCl_3$ spectrum.

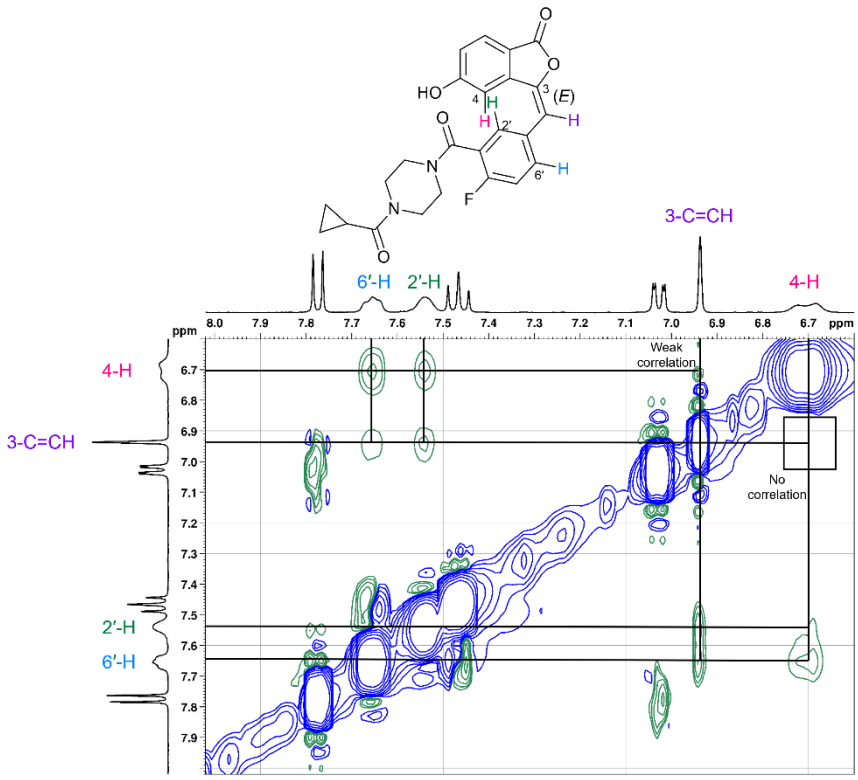


Figure S2: (*E*)-**50** NOESY experiment key correlations. Through space correlations between 6′-H and 3-C=CH, and 2′-H and 3-C=CH support assignment as *E*. Weak correlation between 4-H and 3-C=CH is only present on one axis and is likely an artifact, providing further support to assignment as *E*.

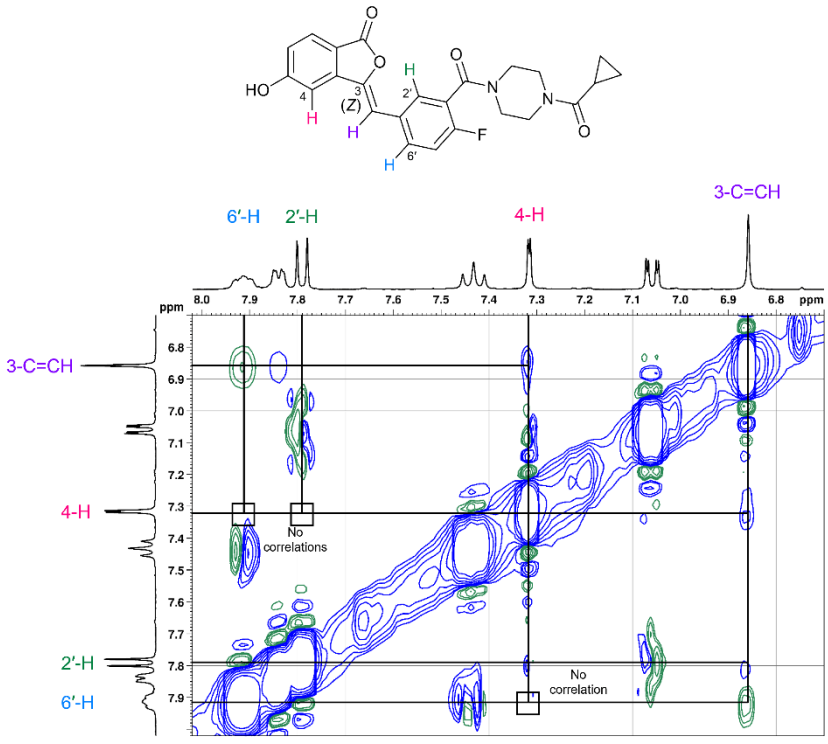


Figure S3: (*Z*)-**50** NOESY experiment key correlation. Correlation between 4-H and 3-C=CH is present on both axes supporting assignment as *Z*. Single weak correlation between 2′-CH and 4-H on one axis is likely an artifact, and there are no correlations between 4-H and 6′-CH providing further support to assignment as *Z*.

Synthesis of Compounds

General Procedure B – Ring expansion (benzyl sidechain)

Benzofuranone (10 mg/mL) in 1:1 EtOH/hydrazine hydrate (aq.) was stirred at 50 °C for 18 h then volatiles were removed *in vacuo* to give the crude product.

General Procedure C – Trigger installation

To phenol in DMF (25 mg/mL) was added K_2CO_3 (1.5 – 3 eq.), followed by chloromethyl nitroimidazole (1.1 eq.) then the mixture was stirred 7 - 18 h at room temperature or 50 °C, then diluted with water. Product was collected by filtration, or extracted from the aqueous fraction with EtOAc, dried (Na_2SO_4) and solvent was removed *in vacuo*.

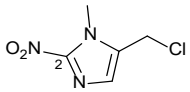
General Procedure D – Horner-Wadsworth-Emmons olefination

To a solution of phosphonate in THF (20 mg/mL) at -78 °C was added a 1M solution of LiHMDS in THF (1.1 eq.) dropwise and the resulting solution was stirred for 1 h. A solution of aldehyde in THF (30 mg/mL, 1.05 eq.) was added dropwise and the resulting mixture stirred a further 1 h at -78 °C, quenched with saturated aqueous NH_4Cl, allowed to warm to room temperature and diluted with 1 M HCl. The aqueous fractions were extracted with EtOAc, dried (Na_2SO_4) and solvent was removed *in vacuo*.

General Procedure E – Demethylation

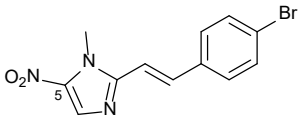
To a solution of aryl ether in DCM (20 mg/mL) at 0 °C was added a 1 M solution of BBr_3 in DCM (6 eq.) and the mixture was stirred at room temperature for 18 h. The reaction was cooled to 0 °C and quenched by portionwise addition of ice, then the mixture was allowed to return to room temperature and extracted with DCM. The combined organic fractions were dried (Na_2SO_4) and solvent was removed *in vacuo*.

5-(chloromethyl)-1-methyl-2-nitro-1*H*-imidazole (16)



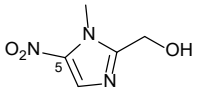
To alcohol **12** (1.0 g, 6.4 mmol) in THF (20 mL) was added DIPEA (1.3 mL, 7.6 mmol), and methanesulfonyl chloride (0.60 mL, 7.6 mmol). The resulting mixture was stirred 0.5 h, diluted with EtOAc (40 mL), washed with 1 M HCl (40 mL), dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with a gradient (30-100%) of EtOAc/X4 to give the title compound (1.1 g, 98%) as a yellow solid: mp 99 – 100 °C (lit.[2] mp 94–96 °C). δ_H ($CDCl_3$) 7.19 (1H, s, 4-H), 4.63 (2H, s, CH_2), 4.08 (3H, s, CH_3). LRMS 176.1 (100%, M^{35}+H), 178.1 (36%, M^{37}+H). These data are in good agreement with literature values.[2]

(*E*)-2-(4-Bromostyryl)-1-methyl-5-nitro-1*H*-imidazole (15)



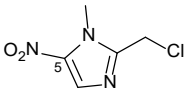
To EtOH (200 mL) was added sodium (2.0 g, 89 mmol) portionwise, with stirring until all sodium was consumed. 1,2-Dimethyl-5-nitro-1*H*-imidazole (5.0 g, 35 mmol) was added portionwise then the mixture was stirred for 0.5 h, and 4-bromobenzaldehyde added. The mixture was heated to 65 °C for 18 h, cooled to room temperature and partitioned between DCM (200 mL) and water (100 mL). The organic phase was collected and the aqueous fraction extracted twice more with DCM (200 mL), the combined organic fractions were washed with brine, dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with EtOAc/X4 (33%) to give the title compound (3.6 g, 33%) as a yellow solid: mp 238 – 240 °C. δ_H ($CDCl_3$) 8.09 (1H, s, 4-CH), 7.82 (1H, d, *J* = 15.8 Hz, 2-CC*H*), 7.55 (2H, d, *J* = 8.5 Hz, 3′-H, 5′-H), 7.44 (2H, d, *J* = 8.4 Hz, 2′-H, 6′-H), 6.87 (1H, d, *J* = 15.8 Hz, 1′-CC*H*), 4.06 (3H, s, NCH_3). LRMS (M+H) 308.9 (100%), 310.0 (100%). These data are consistent with literature values.[3]

(1-Methyl-5-nitro-1*H*-imidazol-2-yl)methanol (13)



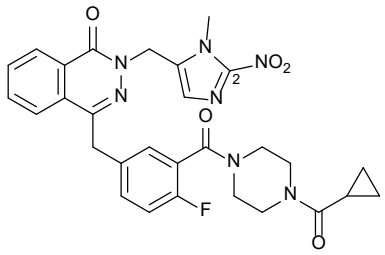
Ozone was bubbled through a solution of alkene **15** (0.6 g, 2.0 mmol) in DCM/MeOH (1:1, 54 mL) at -78 °C for 0.5 h with the headspace vented into a 10% aqueous solution of NaI. The ozone feed was switched with O_2 for 5 minutes, then N_2 for 30 minutes as the mixture was warmed to -40 °C. A solution of $NaBH_4$ (70 mg, 2.0 mmol) in EtOH (6 mL) was added dropwise over 0.5 h and the mixture was slowly warmed to room temperature, then a further portion of $NaBH_4$ (70 mg, 2.0 mmol) was added and the reaction stirred for 3 h, treated with AcOH (2.5 mL) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with EtOAc to give the title product (0.23 g, 74%) as a tan solid: mp 111 – 113 °C (lit.[4] 115 – 116 °C). δ_H 8.01 (1H, s, 4-CH), 5.68 (1H, t, *J* = 5.7 Hz, OH), 4.58 (2H, d, *J* = 5.6 Hz, CH_2), 3.91 (3H, s, NCH_3). LRMS (M+H) 158.2 (100%).

2-(Chloromethyl)-1-methyl-5-nitro-1*H*-imidazole (17)



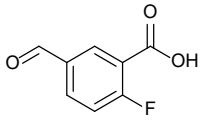
To alcohol **13** (0.10 g, 0.64 mmol) in THF (2 mL) was added DIPEA (0.13 mL, 0.76 mmol) and methanesulfonyl chloride (0.060 mL, 0.76 mmol). The resulting mixture was stirred for 0.5 h, diluted with EtOAc (10 mL), washed with 1M HCl (10 mL), dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with 50% EtOAc/X4, to give the title compound (94 mg, 86%) as a beige solid: mp 39 – 40 °C (lit.[4] 43.5 – 44 °C). δ_H ($CDCl_3$) 7.96 (1H, s, 4-H), 4.68 (2H, s, CH_2), 4.05 (3H, s, NCH_3). LRMS (M+H) 176.1 (100%), 178.1 (32%). These data are in good agreement with literature values.[4]

4-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-2-((1-methyl-2-nitro-1H-imidazol-5-yl)methyl)phthalazin-1(2H)-one (18)



To olaparib (0.30 g, 0.69 mmol) in DMF (5 mL) was added Cs_2CO_3 (0.45 g, 1.4 mmol) followed by chloride **16** (0.18 g, 1.5 mmol) and the resulting mixture was stirred for 25 h. The mixture was diluted with water (25 mL), filtered and the resulting solid collected by filtration. The crude compound was purified by semi-preparative HPLC (MeCN, NH_4CO_2H) to give the title compound (0.08 g, 20%) as a colourless solid: mp 122 – 125 °C. δ_H 8.32 (1H, dd, *J* = 7.7, 1.2 Hz, 8-H), 8.03 (1H, br d, *J* = 7.6 Hz, 5-H), 7.93 (1H, br dd, *J* = 8.3, 1.2 Hz, 6-H), 7.87 (1H, td, *J* = 7.9, 1.2 Hz, 7-H), 7.45 – 7.40 (1H, m, 6′-H), 7.35 (1H, br d, *J* = 5.1 Hz 2′-H), 7.21 (1H, t, *J* = 9.0 Hz, 5′-H), 7.15 (1H, s, 4‴-H), 5.43 (2H, s, 2-NCH_2), 4.35 (2H, s, 4-CC*H*$_2$), 3.94 (3H, s, NCH_3), 3.85 – 3.10 (8H, m, 2″-CH_2, 3″-CH_2, 5″-CH_2, 6″-CH_2), 2.07 – 1.86 (1H, m, 1‴-CH), 0.78 – 0.67 (4H, m, 2‴-CH_2, 3‴-CH_2). δ_C 171.8 (4″-NC=O), 164.5 (1″-NC=O), 158.5 (1-C=O), 156.8 (4′-C, $J_{C\text{-}F}$ = 244.7 Hz), 146.1 (4-C, 2‴-C), 134.8 (1′-C, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.1 Hz), 134.4 (5‴-C), 134.2 (6-CH), 132.6 (7-CH), 132.4 (6′-CH, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.0 Hz), 129.5 (2′-CH, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.7 Hz), 129.1 (4a-C), 128.9 (4‴-CH), 127.8 (8a-C), 127.0 (8-CH), 126.1 (5-CH), 124.1 (3′-C, $J_{C\text{-}C\text{-}F}$ = 18.1 Hz), 116.3 (5′-CH, $J_{C\text{-}C\text{-}F}$ = 21.6 Hz), 47.5 - 44.8 and 42.5 – 41.4 (m, 2″-CH_2, 3″-CH_2, 5″-CH_2, 6″-CH_2), 44.0 (NCH_2), 36.8 (4-C*C*H_2), 34.9 (NCH_3), 10.8 (1‴-CH), 7.6 (2‴-CH_2, 3‴-CH_2). HRMS calcd for $C_{29}H_{29}FN_7O_5$ (M+H) *m/z* 564.2209, found 574.2203 (-1.02 ppm). HPLC purity 99.7%

2-Fluoro-5-formylbenzoic acid (22)



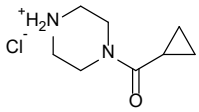
5-(Diethoxymethyl)-2-fluorobenzonitrile

To 2-fluoro-5-formylbenzonitrile (5.0 g, 34 mmol) and NH_4Cl (0.36 g, 6.7 mmol) in EtOH (45 mL) at 0 °C was added triethyl orthoformate (8.4 mL, 50 mmol) and the mixture was warmed to room temperature and stirred for 18 h. Solvent was removed *in vacuo*, residual solids were separated by filtration, washing with EtOAc, then solvent was removed *in vacuo* and the crude product was purified by chromatography, eluting with 30% EtOAc/X4 to give the title compound (6.3 g, 84%) as a colourless oil. δ_H ($CDCl_3$) 7.77 (1H, dd, *J* = 6.1, 2.1 Hz, 6-H), 7.71 (1H, ddd, *J* = 8.7, 5.2, 2.2 Hz, 4-H), 7.20 (1H, t, *J* = 8.7 Hz, 3-H) 5.49 (1H, s, 5-CCH), 3.64 – 3.48 (4H, m, 2 × CH_2), 1.25 (6H, t, *J* = 7.1 Hz, 2 × CH_3). These data are in good agreement with literature values.[5]

2-Fluoro-5-formylbenzoic acid

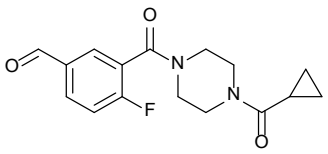
3 M NaOH (32 mL) was added to 5-(diethoxymethyl)-2-fluorobenzonitrile (6.0 g, 27 mmol) and this slurry was heated to 90 °C for 3 h. The resulting solution was cooled to 0 °C, the pH was adjusted to 2 with 6M HCl and the resulting precipitate collected by filtration. Refiltration of the mother liquor after standing produced a second crop. Combination of crops gave the title compound (4.3 g, 95%) as a white solid: mp 160 – 163 °C. δ_H ($CDCl_3$) 10.00 (1H, s, CHO), 8.57 (1H, dd, *J* = 6.9, 2.2 Hz, 6-H), 8.16 (1H, ddd, *J* = 8.6, 4.6, 2.2 Hz, 4-H), 7.36 (1H, dd, *J* = 10.0, 8.6 Hz, 3-H), CO_2H not observed. These data are in good agreement with literature values.[5] LRMS (M-H) 167.1 (100%).

4-(Cyclopropanecarbonyl)piperazin-1-ium chloride (20)



Piperazine (4.6 g, 52 mmol) was dissolved in acetic acid (50 mL) at 40 °C and the resulting solution was cooled to room temperature. Cyclopropanecarbonyl chloride (5.2 mL, 58 mmol) was added dropwise, then the resulting mixture was stirred for 18 h, and the resulting precipitate was collected by filtration. The filtrate was suspended in PhMe (25 mL) and evaporated to dryness twice, then suspended again in PhMe (30 mL) and stirred overnight, the precipitate was collected by filtration and dried *in vacuo* to give the title compound (8.2 g, 82%) as white crystals. δ_H 9.05 (2H, br s, $NH_2^+Cl^-$), 4.00 – 3.56 (4H, m, 2 × NCH_2), 3.22 – 2.98 (4H, m, 2 × NCH_2), 2.03 – 1.95 (1H, m, 1′-H), 0.80 – 0.70 (4H, m, 2′-CH_2, 3′-CH_2). LRMS (M+) 155.2 (100%)

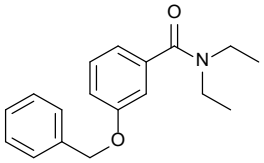
3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzaldehyde (19)



To aldehyde **22** (4.0 g, 24 mmol) in PhMe (100 mL) was added thionyl chloride (17.3 mL, 238 mmol) and the resulting solution was heated to reflux for 1 h, allowed to cool and volatiles removed by vacuum distillation. The crude residue was taken up in DCM (70 mL) and amide **20** (5.0 g, 26 mmol) was added as a solution in MeCN/NEt_3 (30/7 mL). The resulting mixture was stirred 18 h at room temperature, diluted with saturated $NaHCO_3$ (30 mL), the aqueous layer extracted with EtOAc (2 × 30 mL), the combined organic fractions washed with water (30 mL), brine (30 mL), dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with EtOAc (100%) to give the title compound (4.7 g, 65%) as a white foam.

δ_H 10.01 (1H, s CHO), 8.12 – 7.98 (2H, m, H-2, H-6), 7.57 (1H, t, *J* = 9.0 Hz, H-5), 3.93 – 3.13 (8H, m, 4 × NCH_2), 2.11 – 1.81 (1H, m, 1″-H), 0.83 – 0.62 (4H, m, 2″-CH_2, 3″-CH_2). δ_C 191.3 (CHO), 171.3 (4′-NC=O), 163.1 (1′-NC=O), 161.0 (4-C, $J_{C\text{-}F}$ 254.7 Hz), 133.2 (1-C, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 2.8 Hz), 132.7 (6-CH, $J_{C\text{-}C\text{-}C\text{-}F}$ = 10.0 Hz), 131.0 (2-CH, $J_{C\text{-}C\text{-}C\text{-}F}$ = 5.6 Hz), 124.8 (3-C, $J_{C\text{-}C\text{-}F}$ = 19.4 Hz), 117.2 (5-CH, $J_{C\text{-}C\text{-}F}$ = 22.8 Hz), 46.9 – 46.1, 45.1 – 44.3 and 42.1 – 41.0 (m, 4 × NCH_2), 10.4 (2″-CH_2, 3″-CH_2), 7.13 (1″-CH). HRMS calcd for $C_{16}H_{18}FN_2O_3$ (M+H) *m/z* 305.1296, found 305.1293 (-0.86 ppm).

3-(Benzyloxy)-*N,N*-diethylbenzamide (26)



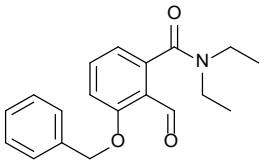
N,N-Diethyl-3-hydroxybenzamide

To 3-hydroxybenzoic acid (6.0 g, 43 mmol) was added thionyl chloride (24 mL, 330 mmol) followed by two drops of DMF (~0.1 mL) and the resulting mixture was stirred at reflux for 1 h. Thionyl chloride was evaporated *in vacuo*, the residue was dissolved in PhMe (100 mL) and the solution once more evaporated to dryness. The residue was dissolved in THF (50 mL) and cooled to 0 °C, then diethylamine (13.5 mL, 130 mmol) was added slowly and the mixture stirred for 18 h at room temperature. Solvent was removed *in vacuo*, the residue dissolved in DCM (50 mL) and the organic layer washed with water (50 mL), $NaHCO_3$ (50 mL) and brine (50 mL) then solvent was removed *in vacuo* to give the title compound (4.0 g, 48%) as a brown solid: mp 74 – 77 °C (lit. 84 °C[6]). δ_H ($CDCl_3$) 7.76 (1H, br s OH), 7.17 (1H, t, *J* = 7.8, 7.8 Hz, 5-H), 6.90 (1H, m, 2-H), 6.81 – 6.77 (2H, m, 4-H, 6-H), 3.61 – 3.49 (2H, m, CH_2), 3.34 – 3.21 (2H, m, CH_2), 1.25 (3H, t, 6.6 Hz, CH_3), 1.10 (3H, t, 6.6 Hz, CH_3). These data are in good agreement with literature values.[6] LRMS (M+H) 194.2, (M-H) 192.2

3-(Benzyloxy)-N,N-diethylbenzamide

To *N,N*-diethyl-3-hydroxybenzamide (0.50 g, 2.6 mmol) in acetone (25 mL) at 0 °C was added K_2CO_3 (0.72 g, 5.2 mmol), KI (0.04 g, 0.26 mmol) and benzyl bromide (0.34 mL, 2.9 mmol), then the mixture was stirred at room temperature for 18 h. Volatiles were removed *in vacuo* and the residue was partitioned between water (25 mL) and EtOAc (25 ml). The organic fraction was collected and the aqueous fraction was washed with EtOAc (2 × 25 mL), then the combined organic fractions were washed with brine, dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with 30% EtOAc/X4 to give the title compound (0.73 g, quant.) as a golden oil. δ_H ($CDCl_3$) 7.45 – 7.27 (6H, m, Ar-H), 7.03 – 6.92 (3H, m, Ar-H), 5.08 (2H, s, CH_2), 3.63 – 3.43 (2H, m, CH_2), 3.33 – 3.12 (2H, m, CH_2), 1.31 – 0.98 (6H, m, 2 × CH_3). These data are in good agreement with literature values.[7] LRMS (M+H) 284.2.

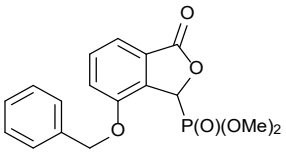
3-(Benzyloxy)-*N,N*-diethyl-2-formylbenzamide (27)



To THF (50 mL) at -78 °C under an atmosphere of N_2 was added ^{t}BuLi in pentane (1.6 M, 10.1 mL, 16.2 mmol) followed by a solution of benzamide **26** (2.0 g, 7.0 mmol) in THF (20 mL) dropwise. The solution was stirred at -78 °C for 1 h, then DMF (1.1 mL, 14.1 mmol) was added dropwise and the mixture allowed to warm to room temperature, After stirring a further 15 min, the reaction was quenched

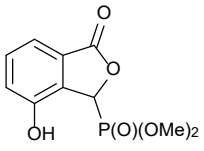
with saturated aqueous NH_4Cl (10 mL) and the aqueous fraction was extracted with EtOAc (2 × 50 mL). The combined organic fractions were washed with water (50 mL), dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with 60% EtOAc/X4, to give the title compound (1.2 g, 56%) as a yellow oil. δ_H ($CDCl_3$) 10.56 (1H, s, CHO), 7.52 (1H, t, *J* = 8.0 Hz, 5-H), 7.48 – 7.33 (5H, m, Ar-H), 7.06 (1H, d, *J* = 8.0 Hz, 4-H), 6.85 (1H, d, *J* = 7.5 Hz 6-H), 5.21 (2H, s, OCH_2), 3.59 (2H, q, *J* = 8.0 Hz, NCH_2), 3.07 (2H, q, *J* = 7.15 Hz, NCH_2), 1.32 (3H, t, *J* = 7.1 Hz, CH_3), 1.01 (3H, t, *J* = 7.1 Hz, CH_3). δ_C ($CDCl_3$) 189.5 (HC=O), 170.0 (1-C*C*=O), 161.6 (3-C), 139.6 (1-C), 135.9 (Ar-C), 135.7 (5-CH), 129.0 (2 × Ar-CH), 128.6 (Ar-CH), 127.6 (2 × Ar-CH), 121.8 (2-C), 119.7 (6-CH), 113.4 (4-CH), 71.1 (OCH_2), 42.7, 38.9 (2 × NCH_2), 13.7, 12.4 (2 × CH_3). LRMS (M+H) 312.2.

Dimethyl (7-(benzyloxy)-3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (28)



To *tert*-butyldimethylsilyl dimethyl phosphite (2.4 g, 11 mmol) in benzene (30 mL) was added a solution of benzamide **27** (1.7 g, 5.5 mmol) in benzene (8 mL) and the resulting mixture was stirred 18 h at room temperature. Volatiles were removed *in vacuo* and the residue dissolved in MeOH (25 mL), then methanesulfonic acid (0.75 mL, 11 mmol) in MeOH (12 mL) was added slowly. The resulting mixture was stirred at room temperature for 12 h, then volatiles removed *in vacuo*, the slurry diluted with water (25 mL), the aqueous fraction was extracted with DCM (3 × 25 mL) and the combined organic fractions were washed with $NaHCO_3$ (25 mL), brine (25 mL), dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with 50% EtOAc/X4, to give the title compound (1.1 g, 56%) as a golden oil that solidified on standing: mp 81 – 83 °C. δ_H ($CDCl_3$) 7.56 – 7.47 (4H, m, Ar-H), 7.43 – 7.33 (3H, m, Ar-H), 7.21 (1H, m, 6-H), 5.78 (1H, d, *J* = 9.8 Hz, 1-H), 5.22 (2H, OCH_2), 3.73 (3H, d, *J* = 10.7 Hz, OCH_3), 3.69 (3H, d, *J* = 10.9 Hz, OCH_3). δ_C ($CDCl_3$) 169.7 (C=O, d, *J* = 2.2 Hz), 156.7 (7a-C), 154.0 (7-C, d, $J_{C\text{-}C\text{-}C\text{-}P}$ = 3.5 Hz), 135.9 (Ar-C), 132.2 (3a-C, d, $J_{C\text{-}C\text{-}C\text{-}P}$ = 4.5 Hz), 131.9 (4-CH, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}P}$ = 2.4 Hz), 128.9 (2 × Ar-CH), 128.6 (Ar-CH), 127.7 (2 × Ar-CH), 118.3 (5-CH, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}P}$ = 1.5 Hz), 117.3 (6-CH, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}P}$ = 2.2 Hz), 75.4 (1-CH, $J_{C\text{-}P}$ = 168.1 Hz), 70.9 (CH_2), 54.8 (CH_3, $J_{C\text{-}O\text{-}P}$ = 6.6 Hz) 54.3 (CH_3, $J_{C\text{-}O\text{-}P}$ = 7.2 Hz). LRMS (M+H) 349.1.

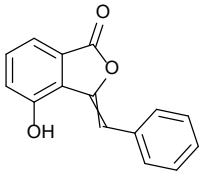
Dimethyl (7-hydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (23)



To phosphonate **28** (0.88 g, 2.9 mmol) in MeOH (25 mL) was added 5% w/w Pd/C (0.09 g) and the resulting slurry was stirred under 1 atm. H_2 for 18 h, filtered through diatomaceous earth and solvent was removed *in vacuo*. The crude material was purified by chromatography, eluting with a gradient (1 – 2%) of MeOH/DCM to give the title compound (0.55 g, 85%) as a white solid: mp 151 – 154 °C. δ_H ($CDCl_3$) 9.08 (1H, br s, OH), 7.56 – 7.48 (2H, m, 4-H, 5-H), 7.28 (1H, dd, *J* = 7.4, 1.8 Hz, 6-H), 5.73

(1H, d, *J* = 8.5 Hz, 1-H), 4.04 (3H, d, *J* = 10.9 Hz, OCH_3), 3.58 (3H, d, *J*= 10.5 Hz, OCH_3). δ_C ($CDCl_3$) 169.6 (C=O, d, $J_{C\text{-}O\text{-}C\text{-}P}$ = 3.1 Hz), 152.4 (7-C, d, $J_{C\text{-}C\text{-}C\text{-}P}$ = 2.9 Hz), 132.3 (5-CH, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}P}$ = 2.1 Hz), 128.2 (3a-C, d, $J_{C\text{-}C\text{-}C\text{-}P}$ = 3.7 Hz), 126.2 (7a-C, d, $J_{C\text{-}C\text{-}P}$ = 4.2 Hz), 124.1 (6-CH, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}P}$ = 2.1 Hz), 118.4 (4-CH, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}P}$ = 1.5 Hz), 73.6 (1-CH, *J* = 163.7 Hz), 55.7 (CH_3, $J_{C\text{-}O\text{-}P}$ = 7.4 Hz), 55.3 (CH_3, $J_{C\text{-}O\text{-}P}$ = 7.2 Hz). LRMS (M+H) 259.1.

3-Benzylidene-4-hydroxyisobenzofuran-1(*3H*)-one (33)

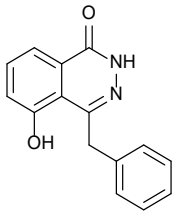


To a solution of phosphonate **23** (0.20 g, 0.77 mmol) in THF (10 mL) at -78 °C was added a 1 M solution of LiHMDS in THF (1.7 mL, 1.7 mmol) dropwise and the resulting solution was stirred 1 h. A solution of benzaldehyde (0.08 mL, 0.8 mmol) in THF (30 mL) was added dropwise and the resulting mixture stirred a further 1 h at -78 °C, then stirred at room temperature for 18 h, quenched with saturated aqueous NH_4Cl, and diluted with 1 M HCl. The aqueous fractions were extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with 33% EtOAc/X4, to give the title product (0.13 g, 72%) as a cream solid. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 10.85 (1H, br s, OH), 7.51 (1H, t, *J* = 7.7 Hz, 6-H), 7.39 (1H, dd, *J* = 7.4, 0.7 Hz, 7-H), 7.36 – 7.24 (5H, m, Ar-H), 7.14 (1H, d, *J* = 8.1 Hz, 5-H), 6.99 (1H, s, 3-C=CH). δ_C 166.1 (C=O), 153.6 (4-C), 144.4 (3-C), 133.8 (Ar-C), 132.2 (6-CH), 130.7 (2 × Ar-CH), 127.7 (7a-C), 127.1 (Ar-CH), 126.8 (2 × Ar-CH), 122.8 (3a-C), 121.5 (5-CH), 115.4 (7-CH), 112.4 (3-C=*C*H)

***Z*:** δ_H 11.30 (1H, br s, OH), 7.79 (2H, d, *J* = 8.2 Hz, 2 × Ar-CH), 7.54 – 7.37 (4H, m, 6-H, 7-H, 2 × Ar-CH), 7.37 – 7.21 (2H, m, 5-H, Ar-CH), 6.85 (1H, s, 3-C=CH). δ_C 166.5 (C=O), 153.4 (4-C), 143.7 (3-C), 133.8 (Ar-C), 131.6 (6-CH), 129.7 (2 × Ar-CH), 128.8 (2 × Ar-CH), 128.0 (Ar-CH), 125.5 (3a-C), 124.4 (7a-C), 121.2 (5-CH), 115.7 (7-CH), 109.2 (3-C=*C*H). LRMS (M+H) 239.2.

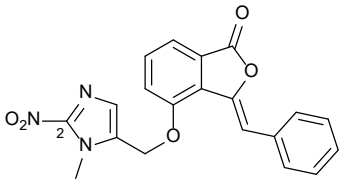
4-Benzyl-5-hydroxyphthalazin-1(*2H*)-one (38)



The reaction was carried out according to General Procedure B with benzofuranone **33** (44 mg, 0.19 mmol) to give the title product (47 mg, quant.) as a white solid: mp 222 – 224 °C. δ_H 12.43 (1H, s, NH), 10.84 (1H, br s, OH), 7.70 (1H, dd, *J* = 7.8, 1.2 Hz, 8-H), 7.58 (1H, t, *J* = 7.9 Hz, 7-H), 7.27 – 7.11 (6H, m, 6-H, Ar-H), 4.42 (2H, s, CH_2). δ_C 159.0 (C), 155.0 (5-C), 144.2 (4-C), 139.9 (Ar-C), 132.3 (7-CH), 129.7 (8a-C), 128.4 (2 × Ar-CH), 128.1 (2 × Ar-CH), 125.7 (Ar-CH), 119.6 (8-CH), 118.2 (4a-C), 116.3

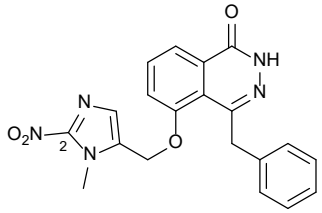
(6-CH), 59.7 (CH_2). HRMS calcd for $C_{15}H_{13}N_2O_2$ (M+H) *m*/*z* 253.0972, found 253.0963 (-3.45 ppm). HPLC purity 99.2%.

(*Z*)-3-Benzylidene-4-((1-methyl-2-nitro-1*H*-imidazol-5-yl)methoxy)isobenzofuran-1(*3H*)-one (41)



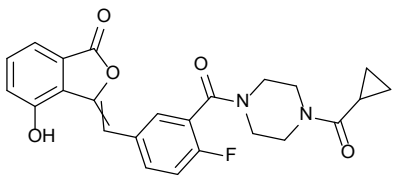
The reaction was carried out according to General Procedure C with benzofuranone **33** (54 mg, 0.23 mmol), K_2CO_3 (0.10 g, 0.69 mmol) and chloride **16** (44 mg, 0.25 mmol) stirring for 7 h at 50 °C. The crude product was collected by extraction and purified by chromatography, eluting with 70% EtOAc/X4 to give the title product (47 mg, 52%) as a white solid: mp 221 – 224 °C. δ_H 7.79 – 7.73 (3H, m, 5-H, 2′-H, 6′-H), 7.67 (1H, t, *J* = 7.8 Hz, 6-H), 7.62 – 7.58 (1H, m, 7-CH), 7.50 – 7.42 (3H, m, 3′-H, 5′-H, 4″-H), 7.37 – 7.31 (1H, m, 4′-H), 6.79 (1H, s, 3-C=C*H*), 5.62 (2H, s, OCH_2), 4.06 (3H, s, CH_3). δ_C 166.0 (1-C=O), 152.6 (4-C), 146.5 (2″-C), 143.0 (3-C), 133.4 (1′-C), 132.4 (5″-C), 131.9 (6-CH), 129.9 (2′-CH, 6′-CH), 129.0 (4″-CH), 128.9 (3′-CH, 5′-CH), 128.4 (4′-CH), 127.2 (3a-C), 124.7 (7a-C), 118.5 (5-CH), 117.8 (7-CH), 110.4 (3-C=*C*H), 59.8 (OCH_2), 34.5 (NCH_3). LRMS (M-H) 376.9, (M- M-$C_5H_6N_3O_2$) 237.2.

4-Benzyl-5-((1-methyl-2-nitro-1H-imidazol-5-yl)methoxy)phthalazin-1(*2H*)-one (44)



The reaction was carried out according to General Procedure B with benzofuranone **41** (50 mg, 0.13 mmol) to give the title product (43 mg, 84%) as a white solid: mp 280 – 283 °C. δ_H 12.66 (1H, s, NH), 7.94 (1H, dd, *J* = 7.9, 1.0 Hz, 8-H), 7.82 (1H, t, *J* = 8.0 Hz, 7-H), 7.64 (1H, dd, *J* = 8.2, 0.9 Hz, 6-H), 7.24 (1H, s, 4'-H), 7.10 – 7.03 (3H, m, Ar-H), 6.76 – 6.71 (2H, m, Ar-H), 5.27 (2H, s, OCH_2), 4.26 (2H, s, CH_2), 3.60 (3H, s, CH_3). δ_C 158.7 (1-C=O), 154.2 (5-C), 146.0 (2′-C), 142.5 (4-C), 139.7 (Ar-C), 132.5 (7-CH), 132.4 (5′-C), 129.8 (8a-C), 129.1 (4′-CH), 127.9 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.5 (Ar-CH), 119.9 (4a-C), 118.6 (8-CH), 116.4 (6-CH), 59.6 (OCH_2), 41.7 (4-C*C*H_2), 33.8 (NCH_3). HRMS calcd for $C_{20}H_{17}N_5NaO_4$ (M+Na) *m*/*z* 414.1173, found 414.1174 (0.4 ppm). HPLC purity 98.6%

3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-4-hydroxyisobenzofuran-1(*3H*)-one (47)

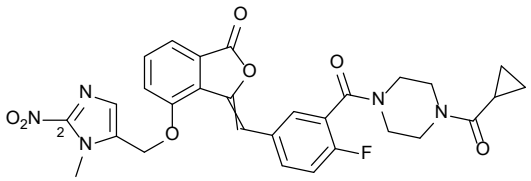


The reaction was carried out according to General Procedure D with phosphonate **23** (0.50 g, 1.94 mmol), LiHMDS (4.1 mL) and aldehyde **19** (0.62 g, 1.1 mmol). The crude product was purified by chromatography, eluting with 80% EtOAc/X4 to give the title product (0.58 g, 68%) as a yellow foam. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 10.84 (1H, br s, OH), 7.53 (1H, t, *J* = 7.7 Hz, 6-H), 7.43 – 7.36 (2H, m, 7-H, 6'-H), 7.32 – 7.25 (2H, m, 2'-H, 5'-H), 7.16 (1H, br d, 7.5 Hz, 5-H), 6.98 (1H, s, 3-C=CH), 3.82 – 3.22 (8H, m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.07 – 1.85 (1H, m, 1‴-CH), 0.81 – 0.66 (4H, m, 2"'-CH_2, 3"'-CH_2). δ_C 171.3 (4"-NC=O), 166.0 (1-C=O), 164.0 (1"-NC=O) 156.9 (4'-C, d, $J_{C\text{-}F}$ = 245.8 Hz), 153.4 (4-C), 145.3 (3-C), 133.3 (6'-CH, m), 132.5 (6-CH), 131.0 (1'-C, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.1 Hz), 130.4 (2'-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 2.9 Hz), 127.7 (3a-C), 122.6 (7a-C), 122.4 (3'-C, d, $J_{C\text{-}C\text{-}F}$ = 18.4), 121.6 (5-CH), 115.7 (7 -CH), 114.4 (5′-CH, $J_{C\text{-}C\text{-}F}$ = 21.8 Hz), 110.5 (3-C=*C*H), 10.39 (1‴-CH), 7.12 (2‴-CH_2, 3‴-CH_2), 4 × CH_2 not observed. LRMS (M+H) 437.2 (100%), (M-H) 435.1 (100%).

***Z*:** δ_H 11.38 (1H, br s, OH), 7.97 – 7.89 (1H, m, 6'-H), 7.86 (1H, dd, *J* = 6.4, 1.9 Hz, 2'-H), 7.51 (1H, t, *J* = 7.7 Hz, 6-H), 7.46 – 7.38 (2H, m, 7-H, 5'-H), 7.30 (1H, dd, *J* = 8.0, 0.61 Hz 5-H), 6.87 (1H, s, 3-C=CH), 3.87 – 3.22 (8H, m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.09 – 1.87 (1H, m, 1‴-CH), 0.80 – 0.65 (4H, m, 2"'-CH_2, 3"'-CH_2). δ_C 171.3 (4"-NC=O), 166.3 (1-C=O), 163.8 (1"-NC=O), 156.8 (4'-C, d, $J_{C\text{-}F}$ = 250.3 Hz), 153.4 (4-C), 144.0 (3-C), 132.7 (6'-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.4 Hz), 131.9 (6-CH), 130.9 (1'-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.3 Hz), 129.9 (2'-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.2 Hz), 125.2 (3a-C), 124.4 (7a-C), 124.3 (3'-C, d, $J_{C\text{-}C\text{-}F}$ = 18.3 Hz), 121.3 (5-CH), 116.5 (5'-CH, d, $J_{C\text{-}C\text{-}F}$ = 22.0 Hz), 115.9 (7-CH), 107.2 (3-C=*C*H), 10.37 (1‴-CH), 7.13 (2‴-CH_2, 3‴-CH_2), 4 × CH_2 not observed. LRMS (M+H) 437.2 (100%), (M-H) 435.1 (100%).

3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-4-((1-methyl-2-nitro-*1H*-imidazol-5-yl)methoxy)isobenzofuran-1(*3H*)-one (52)



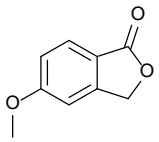
The reaction was carried out according to General Procedure C with benzofuranone **47** (90 mg, 0.21 mmol), K_2CO_3 (44 mg, 0.32 mmol) and chloride **16** (40 mg, 0.23 mmol) stirring for 18 h at room temperature. The crude product was collected by filtration and triturated with MeOH to give the title product (70 mg, 58%) as a yellow solid. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 7.79 – 7.66 (2H, m, 5-H, 6-H), 7.63 (1H, br d, *J* = 7.1 Hz, 6-H), 7.34 – 7.29 (1H, m, 6′-H), 7.25 – 7.20 (1H, m, 2′-H), 7.06 (1H, s, 4‴-H), 7.05 (1H, s, 3-C=C*H*), 6.90 (1H, t, *J* = 9.0 Hz, 5′-CH), 5.18 (2H, s, OCH_2), 3.85 – 3.13 (8H, m, 2″-CH_2, 3″-CH_2, 5″-CH_2, 6″-CH_2), 3.48 (3H, s, NCH_3), 2.09 – 1.86 (1H, m, 1‴-CH), 0.80 – 0.65 (4H, m, 2‴-CH_2, 3‴-CH_2). δ_C 171.8 (4″-NC=O), 165.6 (1-C=O), 163.8 (1″-NC=O), 157.0 (4′-C, d, $J_{C\text{-}F}$ = 242.9 Hz), 152.6 (4-C), 146.0 (2‴-C), 144.3 (3-C), 132.9 (6-CH), 132.7 (6′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 6.6 Hz), 131.6 (5‴-C), 130.7 (2′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.5 Hz), 130.5 (1′-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.8 Hz),

128.7 (4′′′′-CH), 128.0 (7*a*-C), 124.7 (3a-C), 122.4 (3′-C, d, $J_{C\text{-}C\text{-}F}$ = 15.4 Hz), 118.5 (5-CH), 117.7 (7-CH), 114.2 (5′-CH, d, $J_{C\text{-}C\text{-}F}$ = 22.2 Hz), 112.0 (3-C=*C*H), 59.9 (OCH_2), 33.8 (NCH_3), 10.36 (2′′′-CH_2, 3′′′-CH_2), 7.12 (1′′′-CH), 4 × CH_2 not observed. LRMS (M+H) 576.2 (24%), (M-$C_5H_6N_3O_2$) 435.2 (100%).

***Z*:** δ_H 7.93 – 7.86 (1H, m, 6′-H), 7.86 – 7.81 (1H, m, 2′-H), 7.77 (1H, d, *J* = 8.1 Hz, 5-H), 7.68 (1H, t, *J* = 7.8 Hz, 6-H), 7.60 (1H, d, *J* =7.3 Hz, 7-H), 7.47 (1H, s, 4′′′′-H), 7.42 (1H, t, *J* = 9.0 Hz, 5′-H), 6.81 (1H, s, 3-C=C*H*), 5.62 (2H, s, OCH_2), 4.05 (3H, s, NCH_3), 3.87 – 3.19 (8H, m, 2′′-CH_2, 3′′-CH_2, 5′′-CH_2, 6′′-CH_2), 2.10 – 1.86 (1H, m, 1′′′-CH), 0.80 – 0.67 (4H, m, 2′′′-CH_2, 3′′′-CH_2). δ_C 171.8 (4′′-NC=O), 166.3 (1-C=O), 164.2 (1′′-NC=O), 157.4 (4′-C, d, $J_{C\text{-}F}$ = 249.2 Hz), 153.2 (4-C), 147.0 (2′′′′-C), 143.8 (3-C), 133.6 (6′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.2 Hz), 132.9 (5′′′′-C), 132.6 (6-CH), 131.1 (1′-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.5 Hz), 130.6 (2′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.1 Hz), 129.6 (4′′′′-CH), 127.4 (3a-C), 125.2 (7a-C), 124.8 (3′-CH, $J_{C\text{-}C\text{-}F}$ = 18.7 Hz), 119.1 (5-CH), 118.4 (7-CH), 117.0 (5′-CH, d, $J_{C\text{-}C\text{-}F}$ = 22.1 Hz), 108.9 (3-C=*C*H), 60.3 (OCH_2), 35.0 (NCH_3), 10.9 (2′′′-CH_2, 3′′′-CH_2), 7.60 (1′′′-CH), 4 × CH_2 not observed. LRMS (M+H) 576.2 (24%), (M-$C_5H_6N_3O_2$) 435.2 (100%).

5-Methoxyisobenzofuran-1(*3H*)-one (29)



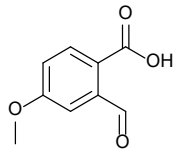
5-Methoxyisobenzofuran-1,3-dione

A solution of 4-methoxyphthalic acid (5.0 g, 26 mmol) in acetic anhydride (50 mL) was heated to reflux for 1 h, cooled and volatiles removed *in vacuo*. The crude residue was dissolved in EtOAc (100 mL) and evaporated to dryness to give the title compound (4.5 g, quant.) as a white solid: mp 91 – 93 °C. δ_H 8.00 (1H, d, *J* = 8.4 Hz, 6-H), 7.59 (1H, d, *J* = 2.2 Hz, 4-H), 7.49 (1H, dd, *J* = 8.4, 2.3 Hz, 6-H), 3.97 (3H, s, OCH_3). These data are in good agreement with literature values.[8] LRMS (M-CH_3) 163.1.

5-Methoxyisobenzofuran-1(*3H*)-one

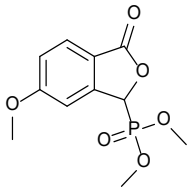
To $NaBH_4$ (0.96 g, 25 mmol) in THF (40 mL) at 0 °C was added dropwise a solution of 5-methoxyisobenzofuran-1,3-dione (4.5 g, 25 mmol) in THF (50 mL). The resulting mixture was stirred for 1.5 h at room temperature, then cooled to 0 °C, acidified to pH 1 with 6 M HCl, and the aqueous fraction was extracted with Et_2O (5 × 50 mL), then solvent was removed *in vacuo*. The resulting residue was taken up in 6 M HCl (50 mL) and stirred at reflux for 18 h, then cooled to room temperature and the aqueous fraction extracted with EtOAc (5 × 50 mL), the combined organic fractions were washed with brine and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with DCM to give the title compound (3.3 g, 80%) as a white solid: mp 114 – 116 °C (lit.[9] 110 – 111 °C). δ_H ($CDCl_3$) 7.83 (1H, d, *J* = 8.5 Hz, 7-H), 7.04 (1H, dd, *J* = 8.5, 2.2 Hz, 6-H), 6.92 (1H, d, *J* = 2.0 Hz, 4-H), 5.25 (2H, s, CH_2), 3.91 (3H, s, OCH_3). These data are in good agreement with literature values.[9] LRMS (M+H) 165.2.

2-Formyl-4-methoxybenzoic acid (31)



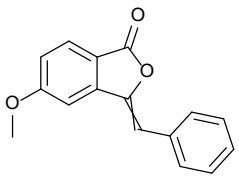
To benzofuranone **30** (7.7 g, 47 mmol) in chlorobenzene (100 mL) was added *N*-bromosuccinimide (9.2 g, 52 mmol) and azobisisobutyronitrile (0.77 g, 4.7 mmol), then the mixture was heated to 85 °C for 2 h. Water (100 mL) was added and the reaction heated to reflux for 18 h, then the mixture was cooled to room temperature and extracted with EtOAc (3 × 100 mL), dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was dissolved in 2M NaOH (50 mL), stirred for 2 h then cooled to 0 °C, acidified and the resulting solid collected by filtration to give the title compound (5.3 g, 63%) as a yellow solid: mp 128 – 130 °C. δ_H 8.12 (1H, br s, CO_2H), 7.74 (1H, d, *J* = 8.3 Hz, 6-H), 7.24 – 7.12 (2H, m, 3-H, 5-H), 6.57 (1H, br s, 2-CHO), 3.89 (3H, s, CH_3). δ_C 168.0 (C=O), 164.5 (4-C), 150.3 (2-C), 126.2 (6-CH), 118.7 (1-C), 117.8 (5-CH), 107.7 (3-CH), 97.3 (CHO), 55.9 (CH_3). LRMS (M+H) 181.2 (100%), (M-H) 179.1 (100%).

Dimethyl (6-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (24)



To acid **31** (6.0 g, 28 mmol) in THF (150 mL) was added dimethyl phosphite (2.9 mL, 31 mmol) dropwise followed by K_2CO_3 (11.5 g, 83.3 mmol) portionwise and the resulting mixture was stirred for 18 h at room temperature, then cooled to 0 °C and methanesulfonic acid (6.4 mL, 97 mmol) was added dropwise. The resulting mixture was stirred for 2 h at room temperature, then solvent was removed *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (100 mL), the organic fraction was separated and the aqueous fraction extracted with EtOAc (2 × 100 mL). The combined organic fractions were dried (Na_2SO_4) and solvent was removed *in vacuo* to give the crude product which was purified by chromatography, eluting with 70% EtOAc/X4, to give the title compound (6.8 g, 89%) as a colourless semi-solid. δ_H ($CDCl_3$) 7.84 (1H, d, *J* = 8.5 Hz, 4-H), 7.19 (1H, br s, 3-H), 7.10 (1H, dt, *J* = 8.5, 1.5 Hz, 5-H), 5.64 (1H, d, *J* = 11.0 Hz, 1-H), 3.95 (3H, d, *J* = 10.9 Hz, $POCH_3$), 3.93 (3H, s, OCH_3), 3.62 (3H, d, *J* = 10.6 Hz, $POCH_3$). These data are in good agreement with literature values.[10] LRMS (M+H) 273.1, (M-H) 271.1.

3-Benzylidene-5-methoxyisobenzofuran-1(*3H*)-one (34)

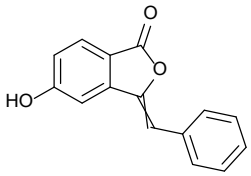


The reaction was carried out according to General Procedure D with phosphonate **24** (0.50 g, 1.8 mmol), LiHMDS (2.02 mL) and benzaldehyde (0.19 mL, 1.9 mmol). The crude product was purified by chromatography, eluting with 10% EtOAc/X4, to give the title product (0.46 g, quant.) as a colourless oil. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H ($CDCl_3$) 7.81 (1H, d, *J* = 8.6 Hz, 7-H), 7.51 – 7.38 (5H, m, Ar-H), 7.03 (1H, dd, *J* = 8.5, 2.2 Hz, 6-H), 6.90 (1H, s, 3-C=CH), 6.86 (1H, d, 2.2 Hz, 4-H), 3.66 (3H, s, OCH_3). δ_C ($CDCl_3$) 166.7 (C=O), 164.6 (5-C), 146.8 (3-C), 140.3 (3a-C), 133.4 (Ar-C), 129.5 (2 × Ar-CH), 129.0 (2 × Ar-CH), 128.7 (Ar-CH), 127.0 (7-CH), 119.0 (7a-C), 118.5 (6-CH), 112.8 (3-C=*C*H), 106.5 (4-CH), 55.7 (CH_3). LRMS (M+H) 253.1.

***Z*:** δ_H ($CDCl_3$) 7.87 – 7.82 (3H, m, 7-H, 2 × Ar-H), 7.44 – 7.39 (2H, m, 2 × Ar-H), 7.35 – 7.29 (1H, m, Ar-H), 7.16 (1H, d, *J* = 2.0 Hz, 4-H), 7.88 (1H, dd, *J* = 8.5, 2.1 Hz, 6-H), 6.39 (1H, s, 3-C=CH), 3.97 (3H, s, OCH_3). δ_C ($CDCl_3$) 167.0 (C=O), 165.3 (5-C), 144.8 (3-C), 143.5 (3a-C), 133.2 (Ar-C), 130.3 (2 × Ar-CH), 129.0 (2 × Ar-CH), 128.6 (Ar-CH), 127.3 (7-CH), 118.5 (6-CH), 116.4 (7a-C), 107.0 (3-C=*C*H), 102.9 (4-CH), 56.2 (CH_3). LRMS (M+H) 253.1. These data are in good agreement with literature values.[1]

3-Benzylidene-5-hydroxyisobenzofuran-1(*3H*)-one (36)



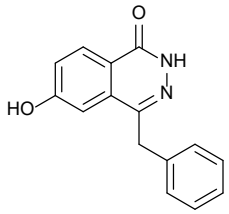
The reaction was carried out according to General Procedure E with benzofuranone **34** (0.20 g, 0.79 mmol) and BBr_3 (4.8 mL, 4.8 mmol). The crude product was purified by chromatography, eluting with 20% EtOAc/X4, to give the title product (0.13 g, 68%) as a yellow solid. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 10.82 (1H, br s, OH), 7.76 (1H, d, *J* = 8.4 Hz, 7-CH), 7.54 – 7.41 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 7.00 (1H, dd, *J* = 8.4, 2.0 Hz, 6-CH), 6.95 (1H, s, 3-C=C*H*), 6.87 (1H, d, *J* = 1.9 Hz, 4-CH). δ_C 165.7 (1-C), 163.5 (5-C), 145.7 (3-C), 139.4 (3a-C), 132.7 (1′-C), 129.1 (2′-CH, 6′-CH), 128.8 (3′-CH, 5′-CH), 128.4 (4′-CH), 127.1 (7-CH), 119.4 (6-CH), 116.0 (7a-C), 112.4 (3-C=*C*H), 108.0 (4-CH).

***Z*:** δ_H 10.97 (1H, br s, OH), 7.83 – 7.76 (3H, m, 7-H, 2′-H, 6′-H), 7.48 – 7.43 (2H, m, 3′-H, 5′-H), 7.37 – 7.33 (2H, m, 4-H, 4′-H), 7.05 (1H, dd, *J* = 8.4, 2.0 Hz, 6-CH), 6.81 (1H, s, 3-C=CH). δ_C 166.0 (1-C=O), 164.0 (5-C), 144.2 (3-C), 143.0 (3a-C), 133.3 (1′-C), 129.7 (2′-CH, 6′-CH), 128.8 (3′-CH, 5′-CH), 128.2 (4-CH), 127.2 (7-CH), 119.0 (6-CH), 113.4 (7a-C), 106.2 (3-C=*C*H), 105.9 (4′-CH).

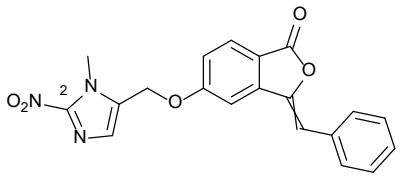
LRMS (M+H) 239.1, (M-H) 237.2.

4-Benzyl-6-hydroxyphthalazin-1(*2H*)-one (39)



The reaction was carried out according to General Procedure B with benzofuranone **36** (50 mg, 0.21 mmol) and the crude product was triturated in water, then isolated by filtration to give the title product (53 mg, quant.) as a white solid: mp 218 – 221 °C. δ_H 12.30 (1H, s, NH), 10.69 (1H, br s, OH), 8.08 (1H, d, *J* = 8. 7 Hz, 8-H), 7.33 – 7.24 (4H, m, 2′-H, 3′-H, 5′-H, 6′-H), 7.23 – 7.16 (2H, m, 4′-H, 7-H), 7.08 (1H, d, *J* = 2.2 Hz, 5-H), 4.18 (2H, s, 4-CCH_2). δ_C 162.2 (6-C), 159.3 (1-C=O), 144.4 (4-C), 138.2 (1′-C), 131.4 (4a-C), 128.5 (2′-C, 6′-C), 128.42 (3′-C, 5′-C), 128.39 (8-CH), 126.4 (4′-CH), 120.7 (7-CH), 119.8 (8a-C), 109.4 (5-CH), 37.9 (CH_2). HRMS calcd for $C_{15}H_{12}N_2O_2$ (M+H) *m*/*z* 253.9872, found 253.0971 (-0.1 ppm). LRMS (M+H) 253.2, (M-H) 251.1. HPLC purity 93.8%.

3-Benzylidene-5-((1-methyl-2-nitro-1*H*-imidazol-5-yl)methoxy)isobenzofuran-1(*3H*)-one (42)

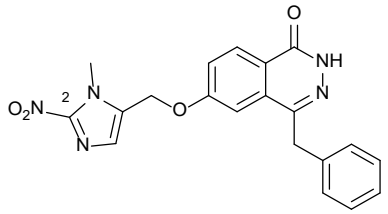


The reaction was carried out according to General Procedure C with benzofuranone **36** (50 mg, 0.21 mmol), K_2CO_3 (90 mg, 0.63 mmol) and chloride **16** (40 mg, 0.23 mmol) stirring for 7 h at 50 °C. The crude product was collected by extraction and triturated with 1:1 EtOAc/X4 to give the title product (33.0 mg, 37%) as a yellow solid. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 7.93 (1H, d, *J* =8.6 Hz, 7-H), 7.59 – 7.52 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 7.37 (1H, dd, *J* = 8.6, 2.2 Hz, 6-H), 7.15 (1H, s, 4″-H), 7.06 (1H, s, 3-C=C*H*), 7.05 (1H, d, *J* = 2.1 Hz, 4-CH), 5.25 (2H, s, OCH_2), 3.88 (3H, s, NCH_3).δ_C 165.4 (1-C=O), 162.4 (5-C), 146.3 (2″-C), 145.4 (3-C), 139.0 (3a-C), 132.5 (1′-C), 132.3 (5″-C), 129.2 (2′-CH, 6′-CH), 128.8 (3′-CH, 5′-CH), 128.7 (4′-CH, 4″-CH), 127.2 (7-CH), 118.8 (6-CH), 118.5 (7a-C), 113.3 (3-C=*C*H), 107.5 (4-CH), 59.6 (OCH_2), 34.3 (NCH_3). LRMS (M+H) 378.2, (M-$C_5H_6N_3O_2$) 237.1.

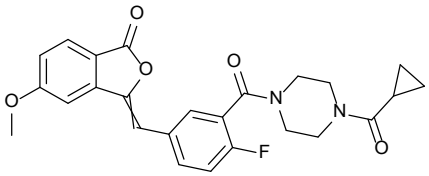
***Z*:** δ_H 7.93 – 7.88 (2H, m, 7-H, 4′-H), 7.83 – 7.78 (2H, m, 2′-H, 6′-H), 7.52 – 7.46 (2H, m, 3′-H, 5′-H), 7.46 (1H, s, 4″-H), 7.40 – 7.34 (1H, m, 4-H), 7.30 (1H, dd, *J* = 8.6, 2.1 Hz, 6-H), 6.96 (1H, s, 3-C=C*H*), 5.48 (2H, s, OCH_2), 3.99 (3H, s, NCH_3). δ_C 165.8 (1-C=O), 163.2 (5-C), 146.3 (2″-C), 144.0 (3-C), 142.8 (3a-C), 133.2 (1′-C), 132.6 (5″-C), 129.7 (2′-CH, 6′-CH), 129.0 (4-CH), 128.8 (3′-CH, 5′-CH), 128.4 (4″-CH), 127.0 (7-CH), 119.3 (6-CH), 115.6 (7a-C), 106.9 (3-C=*C*H), 105.1 (4′-CH), 59.5 (OCH_2), 34.4 (NCH_3). LRMS (M+H) 378.2, (M-$C_5H_6N_3O_2$) 237.1.

4-Benzyl-6-((1-methyl-2-nitro-1*H*-imidazol-5-yl)methoxy)phthalazin-1(*2H*)-one (45)



The reaction was carried out according to General Procedure B with benzofuranone **42** (32 mg, 0.085 mmol) to give the title product (25 mg, 76%) as a white solid: mp 232 – 235 °C. δ_H 12.47 (1H, s, NH), 8.21 (1H, d, *J* = 8.8 Hz, 8-H), 7.51 (1H, dd, *J* = 8.8, 2.4 Hz, 7-H), 7.47 (1H, d, *J* = 2.4 Hz, 5-H), 7.35 – 7.28 (4H, m, Ar-H), 7.27 (1H, s, 4'-H), 7.23 – 7.17 (1H, m, Ar-H), 5.41 (2H, s, OCH_2), 4.30 (2H, s, 4-CCH_2), 3.94 (3H, s, CH_3). δ_C 161.4 (6-C), 159.5 (C=O), 146.8 (2'-C), 145.3 (4-C), 138.6 (Ar-C), 133.2 (5'-C), 131.6 (4a-C), 129.2 (4'-CH), 129.1 (2 × Ar-CH), 129.0 (2× Ar-CH), 128.9 (8-CH), 126.9 (Ar-CH), 122.5 (8a-C), 120.7 (7-C), 109.5 (5-CH), 60.1 (OCH_2), 37.9 (4-C*C*H_2), 34.8 (CH_3). HRMS calcd for $C_{20}H_{18}N_5O_4$ (M+H) *m*/*z* 392.1353, found 392.1343 (-2.67 ppm). LRMS (M+H) 392.2. HPLC purity 99.8%.

3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-5-methoxyisobenzofuran-1(*3H*)-one (48)



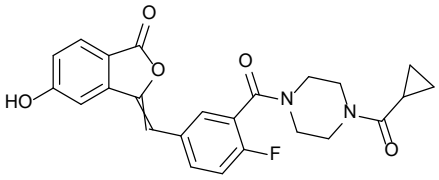
The reaction was carried out according to General Procedure D with phosphonate **24** (2.5 g, 9.2 mmol), LiHMDS (10.1 mL) and aldehyde **19** (2.8 g, 9.2 mmol). The crude product was purified by chromatography, eluting with a gradient (33% - 40%) of EtOAc/DCM, to give the title product (3.8 g, 92%) as a white foam. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 7.88 (1H, d, *J* = 8.6 Hz, 7-H), 7.72 – 7.63 (2H, m, 2'-H, 6'-H), 7.47 (1H, t, *J* = 8.9 Hz 5'-H), 7.24 (1H, dd, *J* = 8.6, 2.2 Hz, 6-H), 7.01 (1H, s, 3-C=CH), 6.94 (1H, s, 4-H), 3.78 (3H, s, OCH_3), 3.76 – 3.22 (8H, br m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.06 – 1.87 (1H, br m, 1‴-CH), 0.79 – 0.66 (4H, br m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4″-NC=O), 165.4 (1-C=O), 164.3 (5-C), 163.6 (1″-NC=O), 157.2 (4'-C, d, J_{C-F} = 248.2 Hz), 146.1 (3-C), 139.1 (3a-C), 132.6 (6'-CH, d, $J_{C-C-C-F}$ = 8.2 Hz), 129.7 (2'-C, d, $J_{C-C-C-F}$ = 4.2 Hz), 129.5 (1'-C, d, $J_{C-C-C-C-F}$ = 3.3 Hz), 127.1 (7-CH), 124.5 (3'-C, d, J_{C-C-F} = 19.1 Hz), 118.8 (6-CH), 117.8 (7a-C), 116.6 (5'-CH, d, J_{C-C-F} = 22.2 Hz), 111.2 (3-C=*C*H), 106.1 (4-C), 55.8 (OCH_3), 10.37 (1"'-CH), 7.11 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M+H) 451.2, (M-CH_3) 435.1.

***Z*:** δ_H 7.91 – 7.82 (3H, m, 7-H, 2'-H, 6'-H), 7.65 (1H, d, *J* = 2.0 Hz, 4-H), 7.45 (1H, t, *J* = 9.0 Hz, 5'-H), 7.24 – 7.18 (1H, m, 6-H), 7.00 (1H, s, 3-C=CH), 3.95 (3H, s, OCH_3), 3.86 – 3.23 (8H, br m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.07 – 1.87 (1H, br m, 1‴-CH), 0.79 – 0.66 (4H, br m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4″-NC=O), 165.8 (1-C=O), 165.2 (5-C), 163.8 (1″-NC=O), 156.9 (4'-C, d, J_{C-F} = 248.9 Hz), 144.4 (3-C), 142.8 (3a-C), 132.8 (6'-C, d, $J_{C-C-C-F}$ = 8.3 Hz), 130.4 (1'-C, d, $J_{C-C-C-C-F}$ = 3.4 Hz), 129.9 (2'-CH, d, $J_{C-C-C-F}$ = 3.1 Hz), 127.2 (7-CH), 126.9 (7-CH), 124.4 (3'-C, d, J_{C-C-F} = 18.8 Hz), 119.0 (6-CH), 114.9 (7a-C),

104.8 (3-C=*C*H), 103.9 (4-CH), 56.3 (OCH_3), 10.38 (1‴-CH), 7.13 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M+H) 451.2, (M-CH_3) 435.1.

3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-5-hydroxyisobenzofuran-1(*3H*)-one (50)

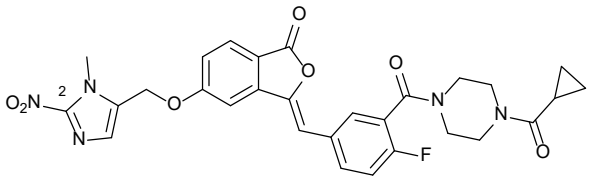


The reaction was carried out according to General Procedure E with benzofuranone **48** (0.20 g, 0.44 mmol) and BBr_3 (2.7 mL, 2.7 mmol). The crude product was purified by chromatography, eluting with 100% EtOAc to give the title product (0.14 g, 74%) as a white foam. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 10.90 (1H, br s, OH), 7.77 (1H, d, *J* = 8.4 Hz, 7-H), 7.69 – 7.61 (1H, m, 6′-H), 7.60 – 7.50 (1H, m, 2′-H), 7.46 (1H, t, *J* = 9.1 Hz, 5′-H), 7.02 (1H, dd, *J* = 8.4, 2.0 Hz, 6-H), 6.93 (1H, s, 3-C=C*H*), 6.76 – 6.62 (1H, m, 4-H), 3.86 – 3.22 (8H, m, 2″-CH_2, 3″-CH_2, 4″-CH_2, 5″-CH_2), 2.05 – 1.82 (1H, m, 1‴-CH), 0.81 – 0.64 (4H, m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4″-NC=O), 165.6 (1-C=O), 163.6 (1″-NC=O), 163.4 (5-C), 157.4 (4′-C, d, $J_{C\text{-}F}$ = 247.7 Hz), 146.3 (3-C), 139.4 (3a-C), 132.3 (6′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 7.9 Hz), 129.7 (1′-C, 2′-CH, m), 127.3 (7-CH), 124.5 (3′-C, $J_{C\text{-}C\text{-}F}$ = 18.9 Hz), 119.4 (6-CH), 116.6 (5′-CH, $J_{C\text{-}C\text{-}F}$ = 22.0 Hz), 11.6.0 (7a-C), 110.5 (3-C=*C*H), 108.1 (4-CH), 10.37 (1‴-CH), 7.10 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M+H) 437.2 (100%), (M-H) 435.1 (100%).

***Z*:** δ_H 11.05 (1H, br s, OH), 7.96 – 7.87 (1H, m, 6′-H), 7.84 (1H, dd, *J* = 6.5, 2.0 Hz, 2′-H), 7.78 (1H, d, *J* = 8.4 Hz, 7-H), 7.43 (1H, t, *J* = 9.0 Hz, 5′-H), 7.31 (1H, d, *J* = 1.8 Hz, 4-H), 7.06 (1H, dd, *J* = 8.4, 2.0 Hz, 6-CH), 6.85 (1H, s, 3-C=C*H*), 3.92 – 3.19 (8H, m, 2″-CH_2, 3″-CH_2, 4″-CH_2, 5″-CH_2), 2.10 – 1.84 (1H, m, 1‴-CH), 0.82 – 0.63 (4H, m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4″-NC=O), 165.9 (1-C=O), 164.2 (5-C), 163.8 (1″-NC=O), 156.8 (5′-C, d, $J_{C\text{-}F}$ = 248.7 Hz), 144.5 (3-C), 142.8 (3a-C), 132.8 (6′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.2 Hz), 130.5 (1′-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.4 Hz), 129.9 (2′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 4.6 Hz), 127.3 (7-CH), 124.3 (3′-CH, d, $J_{C\text{-}C\text{-}F}$ = 18.7 Hz), 119.2 (6-CH), 116.6 (5′-CH, d, $J_{C\text{-}C\text{-}F}$ = 22.1 Hz), 113.3 (7a-C), 105.9 (4-CH), 104.3 (3-C=*C*H), 10.37 (1‴-CH), 7.13 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M+H) 437.2 (100%), (M-H) 435.1 (100%).

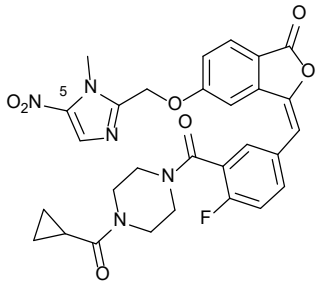
(*Z*)-3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-5-((1-methyl-2-nitro-1*H*-imidazol-5-yl)methoxy)isobenzofuran-1(*3H*)-one (53)



The reaction was carried out according to General Procedure C with benzofuranone **50** (90 mg, 0.21 mmol), K_2CO_3 (44 mg, 0.32 mmol) and chloride **16** (40 mg, 0.23 mmol) stirring for 18 h at room

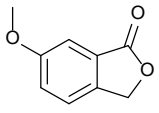
temperature. The crude product was collected by filtration and purified by chromatography, eluting with a gradient (1 – 2%) MeOH/DCM to give the title product (45 mg, 38%) as a tan foam. δ_H 7.97 – 7.80 (4H, m, 4-H, 7-H, 2′-H, 6′-H), 7.52 – 7.42 (2H, m, 6′-H, 4‴-H), 7.33 (1H, dd, *J* = 8.5, 2.0 Hz), 6.99 (1H, s, 3-C=C*H*), 5.47 (2H, s, OCH_2), 3.99 (3H, s, NCH_3), 3.89 – 3.22 (8H, m, 2″-CH_2, 3″-CH_2, 5″-CH_2, 6″-CH_2), 2.12 – 1.81 (1H, m, 1‴-CH), 0.83 – 0.63 (4H, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4″-NC=O), 165.6 (5-C), 163.7 (1″-NC=O), 163.2 (1-C=O), 157.0 (4′-C, d, $J_{C\text{-}F}$ = 249.0 Hz), 146.4 (2‴-C), 144.4 (3-C), 142.6 (3a-C), 132.9 (6′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.3 Hz), 132.5 (5‴-C), 130.3 (1′-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.3 Hz), 129.9 (2′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.4 Hz), 128.9 (4‴-CH), 127.1 (7-CH), 124.4 (3′-C, d, $J_{C\text{-}C\text{-}F}$ = 18.8 Hz), 119.3 (6-CH), 116.7 (5′-CH, d, $J_{C\text{-}C\text{-}F}$ = 22.0 Hz), 115.6 (7a-C), 105.3 (4-CH), 105.0 (3-C=*C*H), 59.9 (OCH_2), 34.4 (NCH_3), 10.4 (1‴-CH), 7.13 (2‴-CH_2, 3‴-CH_2), , 4 × CH_2 not observed. LRMS (M+H) 576.1 (8%), (M-$C_5H_6N_3O_2$) 435.0 (80%).

(*E*)-3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-5-((1-methyl-5-nitro-1*H*-imidazol-2-yl)methoxy)isobenzofuran-1(*3H*)-one (55)



The reaction was carried out according to General Procedure C with benzofuranone **50** (90 mg, 0.21 mmol), K_2CO_3 (44 mg, 0.32 mmol) and chloride **17** (40 mg, 0.23 mmol) stirring for 18 h at room temperature. The crude product was collected by filtration and purified by chromatography, eluting with a gradient (1 – 2%) of MeOH/DCM to give the title product (34 mg, 28%) as a yellow gum. δ_H 8.01 (1H, s, 4‴-H), 7.91 (1H, d, *J* = 8.6 Hz, 7-CH), 7.71 – 7.63 (2H, m, 6′-CH, 2′-CH), 7.46 (1H, t, *J* = 9.3 Hz, 5′-CH), 7.35 (1H, dd, *J* = 8.6, 2.1 Hz, 6-CH), 7.17 (1H, d, *J* = 2.0 Hz, 4-CH), 7.02 (1H, s, 3-C=CH), 5.36 (2H, s, OCH_2), 3.89 (3H, s, NCH_3), 3.88 – 3.26 (8H, m, 2″-CH_2, 3″-CH_2, 5″-CH_2, 6″-CH_2), 2.07 – 1.85 (1H, br m, 1‴-CH), 0.79 – 0.65 (4H, br m, 2‴-CH_2, 3‴-CH_2). δ_C 171.9 (4″-C=O), 165.8 (1-C=O), 164.2 (5-C), 162.9 (1″-C=O), 157.7 (4′-C, d, $J_{C\text{-}F}$ = 248.5 Hz), 147.3 (2‴-C), 146.4 (3-C), 140.1 (5‴-C), 139.3 (3a-C), 133.0 (6′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.6 Hz), 131.9 (4‴-CH), 130.3 (2′-CH, m), 129.9 (1′-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.5 Hz), 127.6 (7-CH), 124.8 (3′-C, d, $J_{C\text{-}C\text{-}F}$ = 19.0 Hz), 119.9 (6-CH), 119.0 (7a-C), 117.2 (5′-CH, d, $J_{C\text{-}C\text{-}F}$ = 21.8 Hz), 112.0 (3-C=*C*H), 107.9 (4-CH), 62.8 (OCH_2), 34.0 (NCH_3), 10.8 (1‴-CH), 7.60 (2‴-CH_2, 3‴-CH_2), 4 × CH_2 not observed. LRMS (M+H) 576.2 (20%), (M-$C_5H_6N_3O_2$) 435.2 (100%).

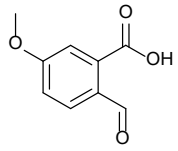
6-Methoxyisobenzofuran-1(3H)-one (30)



To 3-methoxybenzoic acid (10 g, 64 mmol) in AcOH (33 mL) was added conc. HCl (48 mL) and formaldehyde (19.2 mL) and the resulting mixture was stirred at 100 °C for 1 h. The reaction was cooled

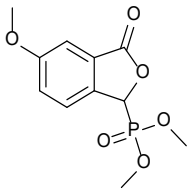
to room temperature, neutralised with saturated $NaHCO_3$ and solvent was removed *in vacuo*. The crude residue was dissolved in boiling X4, residual solid filtered off and the mother liquor was evaporated to give the title compound (6.8 g, 64%) as a white solid: mp 97 – 100 °C (lit. 107.6 °C[11]). δ_H 7.56 (1H, dd, *J* = 8.4, 0.6 Hz, 5-H), 7.35 (1H, dd, 8.4, 2.4 Hz, 4-H), 7.32 (1H, d, *J* = 2.3 Hz, 7-H), 5.34, (2H, s, CH_2), 3.85 (3H, s, OCH_3). These data are in good agreement with literature values.[11] LRMS (M+H) 165.2.

2-Formyl-5-methoxybenzoic acid (32)



To benzofuranone **30** (8.6 g, 54 mmol) in chlorobenzene (170 mL) was added *N*-bromosuccinimide (9.8 g, 55 mmol) and the resulting mixture was heated to 85 °C. Azobisisobutyronitrile (0.086 g, 0.52 mmol) was suspended in chlorobenzene (10 mL) and 2 mL of this suspension was added to the reaction mixture, followed by the remainder after the resulting exotherm subsided. The mixture was stirred for 2 h at 85 °C, cooled to 0 °C and filtered to remove insoluble material, washing the filter cake with chlorobenzene (10 ml). The mother liquor was evaporated *in vacuo*, and the residue partitioned between 2 M NaOH (50 mL) and DCM (50 mL). The organic fraction was collected, and the aqueous fraction washed with DCM (2 × 50 mL). The aqueous residue was acidified with conc. HCl, extracted with EtOAc (3 × 50 mL) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with 50% EtOAc/X4, and the resulting solid recrystallised from EtOAc to give pure product (3.4 g, 36%) as a white solid: mp 131 – 133 °C (lit.[11] 166.2 °C). δ_H 8.01 (1H, br s, OH), 7.61 (1H, t, *J* = 7.8 Hz, 4-H), 7.39 – 7.35 (2H, m, 3-H, 6-H), 6.66 (1H, s, CHO), 3.89 (3H, s, OCH_3). These data are in good agreement with literature values.[11] LRMS (M-H) 179.2 (100%).

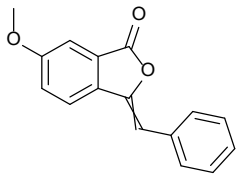
Dimethyl (5-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (25)



To acid **32** (3.3 g, 18mmol) in THF (100 mL) was added dimethyl phosphite (1.9 mL, 20 mmol), followed by K_2CO_3 (3.8 g, 28 mmol) portionwise and the resulting mixture was stirred at room temperature for 48 h. A further portion of K_2CO_3 (2.5 g, 18 mmol) was added and the mixture stirred a further 24 hours, cooled to 0 °C and methanesulfonic acid (3.9 mL, 60 mmol) was added. The mixture was stirred for 1 h at room temperature, then solvent was removed *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (100 mL), the organic layer was separated, and the aqueous residue was extracted with EtOAc (6 × 200 mL). The organic fractions were combined, dried (Na_2SO_4) and solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with 70% EtOAc/X4 to give the title compound (2.3 g, 46%) as a yellow oil that solidified on standing: mp 75 – 77 °C. δ_H ($CDCl_3$)

7.64 (1H, dt, *J* = 8.5, 0.8 Hz, 7-H), 7.37 (1H, d, *J* = 2.4 Hz, 4-H), 7.29 (1H, dd, *J* = 8.5, 2.4 Hz, 6-H), 5.66 (1H, dd, *J* = 9.9, 0.6 Hz, 1-CH), 3.92 (3H, d, *J* = 10.9 Hz, P(OCH_3)) 3.89 (3H, OCH_3), 3.61 (3H, d, *J* = 10.6 Hz, P(OCH_3)). δ_C ($CDCl_3$) 169.9 (3-C=O, $J_{C\text{-}O\text{-}P}$ = 2.3 Hz), 161.5 (5-C, $J_{C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}P}$ = 2.2 Hz), 135.9 (7a-C, $J_{C\text{-}C\text{-}P}$ = 4.4 Hz), 126.8 (3a-C, $J_{C\text{-}C\text{-}C\text{-}P}$ = 4.6 Hz), 124.6 (7-CH, $J_{C\text{-}C\text{-}C\text{-}P}$ = 2.6 Hz), 123.7 (6-CH, $J_{C\text{-}C\text{-}C\text{-}C\text{-}P}$ = 2.8 Hz), 108.1 (4-CH, $J_{C\text{-}C\text{-}C\text{-}C\text{-}P}$ = 1.3 Hz), 75.2 (1-CH, $J_{C\text{-}P}$ = 166.2 Hz), 56.1 (5-CO*C*H_3), 54.8 ($POCH_3$, $J_{C\text{-}O\text{-}P}$ = 6.9 Hz), 54.4 ($POCH_3$, $J_{C\text{-}O\text{-}P}$ = 7.2 Hz). LRMS (M+H) 273.1 (100%), (M-H) 271.1 (100%).

3-Benzylidene-6-methoxyisobenzofuran-1(*3H*)-one (35)

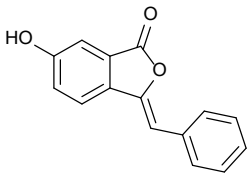


The reaction was carried out according to General Procedure D with phosphonate **25** (0.50 g, 1.8 mmol), LiHMDS (2.0 mL) and benzaldehyde (0.19 mL, 1.9 mmol). The crude product was purified by chromatography, eluting with 10% EtOAc/X4 to give the title product (0.45 g, 98%) as a white solid. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 7.55 – 7.39 (7H, m, 4-H, 7-H, 4 × Ar-H), 7.28 (1H, dd, *J* = 8.7, 2.5 Hz, 5-H), 6.92 (1H, s, 3-C=CH), 3.87 (3H, s, OCH_3). δ_C 165.8 (C=O), 161.4 (6-C), 145.7 (3-C), 132.8 (Ar-C), 129.7 (3a-C), 129.1 (2 × Ar-CH), 128.9 (2 × Ar-CH), 128.3 (Ar-CH), 127.2 (7a-C), 123.7 (4-CH), 123.3 (5-CH), 110.8 (3-C=*C*H), 107.5 (7-CH), 56.0 (OCH_3). LRMS (M+H) 253.1.

***Z*:** δ_H 8.03 (1H, d, *J* = 8.6 Hz 4-H), 7.80 – 7.75 (2H, m, 2 × Ar-H), 7.49 – 7.40 (4H, m, 7-H, 4–H, 2 × Ar-H), 7.33 (1H, dddd, *J* = 7.4, 6.8, 1.2, 1.2 Hz, Ar-H), 6.80 (1H, s, 3-C=CH), 3.90 (3H, s, OCH_3). δ_C 166.3 (C=O), 161.2 (6-C), 144.2 (3-C), 133.5 (Ar-C), 133.0 (3a-C), 129.5 (2 × Ar-CH), 128.8 (2 × Ar-CH), 128.0 (Ar-CH), 124.1 (7a-C), 124.0 (5-CH), 122.2 (4-CH), 107.1 (7-CH), 105.3 (3-C=*C*H), 56.0 (OCH_3). LRMS (M+H) 253.1.

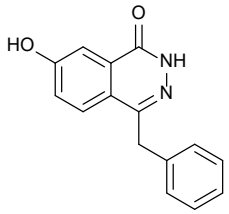
(*Z*)-3-Benzylidene-6-hydroxyisobenzofuran-1(*3H*)-one (37)



The reaction was carried out according to General Procedure E with benzofuranone **35** (0.38 g, 1.5 mmol) and BBr_3 (9.0 mL, 9.0 mmol). The crude product was purified by chromatography, eluting with 50% EtOAc/X4, to give the title product (0.35 g, 97%) as a yellow solid: mp 205 – 208 °C. δ_H ($CDCl_3$) 7.83 – 7.80 (2H, m, Ar-H), 7.67 (1H, d, *J* = 8.4 Hz, 4-H), 7.43 – 7.38 (2H, m, Ar-H), 7.34 – 7.27 (2H, m, Ar-H), 7.26 – 7.23 (1H, dd, *J* = 8.5, 2.3 Hz, 5-H), 6.70 (1H, s, 3-C=CH), 5.84 (1H, br s, OH). δ_H 10.54 (1H, br s, OH), 7.94 (1H, dd, *J* = 8.5, 0.4 Hz, 4-H), 7.76 (2H, dd, *J* = 8.3, 1.0 Hz, 2'-H, 6'-H), 7.47 – 7.42 (2H, m, 3'-H, 5'-H), 7.34 – 7.30 (1H, m , 4'-H), 7.28 (1H, dd, *J* = 8.5, 2.2 Hz, 5-H), 7.18 (1H, dd, *J* = 2.2,

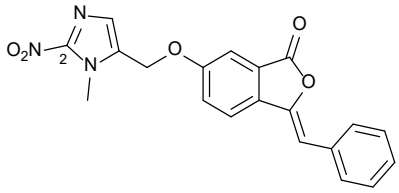
0.4 Hz, 7-H). 6.70 (1H, s, 3-C=CH). δ_C 166.4 (1-C=O), 159.7 (7a-C), 144.5 (3-C), 133.6 (1'-C), 131.4 (3a-C), 129.6 (2'-CH, 6'-CH), 128.8 (3'-CH, 5'-CH), 127.7 (4'-CH), 124.6 (6-C), 123.8 (5-CH), 122.4 (4-CH), 109.4 (7-CH), 104.3 (3-C=*C*H). LRMS (M+H) 239.2, (M-H) 237.1.

4-Benzyl-7-hydroxyphthalazin-1(*2H*)-one (40)



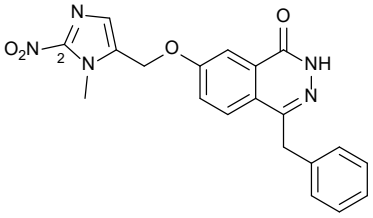
The reaction was carried out according to General Procedure B with benzofuranone **33** (50 mg, 0.21 mmol) and the crude product was triturated in water, then isolated by filtration to give the title product (47 mg, 89%) as a white solid: mp 303 – 306 °C. δ_H 12.34 (1H, s, NH), 10.69 (1H, br s, OH), 7.79 (1H, d, *J* = 8.9 Hz, 5-H), 7.51 (1H, d, *J* = 2.6 Hz, 8-H), 7.31 – 7.26 (4H, m, Ar-H), 7.24 (1H, dd, *J* = 8.8, 2.6 Hz, 6-H), 7.21 – 7.15 (1H, m, Ar-H), 4.20 (2H, s, CH_2). δ_C 160.2 (7-C), 159.3 (C=O), 145.0 (4-C), 138.5 (Ar-C), 130.0 (8a-C), 128.5 (4 × Ar-CH), 128.0 (5-CH), 126.3 (Ar-CH), 122.4 (6-CH), 121.8 (4a-CH), 109.6 (8-CH), 37.6 (CH_2). HRMS calcd for $C_{15}H_{13}N_2O_2$ (M+H) *m*/*z* 253.0972, found 253.0964 (-3.10 ppm). HPLC purity 97.9%

(*Z*)-3-Benzylidene-6-((1-methyl-2-nitro-1*H*-imidazol-5-yl)methoxy)isobenzofuran-1(*3H*)-one (43)



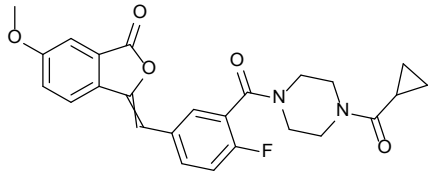
The reaction was carried out according to General Procedure C with benzofuranone **33** (50 mg, 0.21 mmol), K_2CO_3 (90 mg, 0.63 mmol) and chloride **16** (40 mg, 0.23 mmol) stirring for 7 h at 50 °C. The crude product was collected by filtration and triturated with EtOAc to give the title product (40 mg, 44%) as a yellow solid: mp 266 – 269 °C. δ_H 8.08 (1H, d, *J* = 8.6 Hz, 4-H), 7.79 (2H, d, *J* = 7.6 Hz, Ar-H), 7.67 (1H, d, *J* = 2.2 Hz, 7-H), 7.57 (1H, dd, *J* = 8.6, 2.2 Hz, 5-H), 7.47 (2H, t, *J* = 7.6 Hz, Ar-H), 7.37 (1H, s, 4'-H), 7.34 (1H, t, *J* = 7.3 Hz, Ar-H), 6.84 (1H, s, 3-C=CH), 5.44 (2H, s, CH_2), 3.97 (3H, s, CH_3). δ_C 166.2 (C=O), 159.3 (6-C), 146.3 (2′-CH), 144.1 (3-C), 133.8 (3a-C), 133.4 (Ar-C), 132.9 (5′-C), 129.5 (2 × Ar-CH), 128.9 (2 × Ar-CH), 128.6 (4′-CH), 128.1 (Ar-CH), 124.6 (5-CH), 124.0 (7a-C), 122.4 (4-CH), 108.7 (7-CH), 105.7 (3-C=*C*H), 60.0 (OCH_2), 34.4 (NCH_3). LRMS (M+H) 378.2.

4-Benzyl-7-((1-methyl-2-nitro-1*H*-imidazol-5-yl)methoxy)phthalazin-1(*2H*)-one (46)



The reaction was carried out according to General Procedure B with benzofuranone **43** (38 mg, 0.10 mmol) to give the title product (26 mg, 67%) as a white solid: mp 227 – 230 °C. δ_H 12.55 (1H, s, NH), 7.90 (1H, d, *J* = 9.0 Hz, 5-H), 7.84 (1H, d, *J* = 2.8 Hz, 8-H), 7.51 (1H, dd, *J* = 9.0, 2.8 Hz, 6-H), 7.35 (1H, s, 4'-H), 7.32 – 7.25 (4H, m, Ar-H), 7.22 – 7.16 (1H, m, Ar-H), 5.46 (2H, s, OCH_2), 4.27 (2H, CH_2Ph), 3.94 (3H, s, CH_3). δ_C 160.0 (7-C), 159.7 (C=O), 146.8 (2'-C), 145.4 (4-C), 138.8 (Ar-C), 133.4 (5'-C), 130.4 (8a-C), 129.2 (4'-CH), 129.0 (2 × Ar-CH), 128.9 (2 × Ar-CH), 128.5 (5-CH), 126.9 (Ar-CH), 124.2 (4a-C), 123.2 (6-CH), 108.8 (8-CH), 60.1 (OCH_2), 38.1 (4-C*C*H_2), 34.8 (CH_3). HRMS calcd for $C_{20}H_{18}N_5O_4$ (M+H) *m*/*z* 392.1353, found 392.1342 (-3.00 ppm). HPLC purity 98.4%

3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-6-methoxyisobenzofuran-1(*3H*)-one (49)

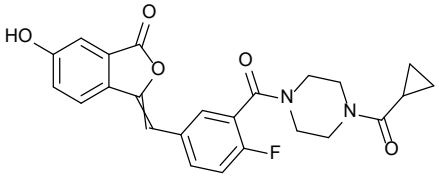


The reaction was carried out according to General Procedure D with phosphonate **25** (0.40 g, 1.5 mmol), LiHMDS (1.62 mL) and aldehyde **19** (0.45 g, 1.5 mmol). The crude product was purified by chromatography, eluting with 70% EtOAc/X4 to give the title product (0.60 g, 91%) as a white foam. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 7.69 – 7.63 (1H, m, 6'-H), 7.60 – 7.55 (1H, m, 2'-H), 7.49 – 7.37 (3H, m, 5'-H, 5-H, 7-H), 7.30 (1H, d, *J* = 7.2 Hz, 4-H), 6.89 (1H, s, 3-C=CH), 3.88 (3H, s, OCH_3), 3.81 – 3.27 (8H, br m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.05 – 1.89 (1H, br m, 1‴-CH), 0.78 – 0.67 (4H, m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4"-NC=O), 165.7 (1-C=O), 163.6 (1"-NC=O), 161.6 (6-C), 157.3 (4'-C, d, *J* = 247.8), 146.3 (3-C), 132.3 (6'-CH, d, *J* = 8.3 Hz), 129.9 (1'-C, d, *J* = 3.5 Hz), 129.7 (2'-CH, d, *J* = 4.2 Hz), 129.4 (3a-C), 127.3 (7a-C), 124.5 (3'-C, d, *J* = 19.4 Hz), 123.8 (5-CH), 123.3 (4-CH), 116.7 (5'-CH, d, *J* = 22.5 Hz), 109.0 (3-C=*C*H), 107.6 (7-CH), 56.1 (OCH_3), 10.4 (1‴-CH), 7.2 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M+H) 451.2 (100%)

***Z*:** δ_H 7.99 (1H, d, *J* = 8.4 Hz, 4-H), 7.90 – 7.84 (1H, m, 6'-H), 7.81 (1H, dd, *J* = 6.5, 1.9 Hz, 2'-H), 7.48 (1H, dd, *J* = 8.5, 2.4 Hz, 5-H), 7.46 – 7.39 (2H, m, 5'-H, 7-H), 6.84 (1H, s, 3-C=CH), 3.91 (3H, s, OCH_3), 3.86 – 3.22 (8H, br m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.09 – 1.85 (1H, br m, 1‴-CH), 0.82 – 0.67 (4H, m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4"-NC=O), 166.1 (1-C=O), 163.8 (1"-NC=O), 161.4 (6-C), 156.8 (4'-C, d, *J* = 248.3 Hz), 144.5 (3-C), 132.8 (3a-C), 132.5 (6'-CH, d, *J* = 8.2 Hz), 130.7 (1'-C, d, *J* = 3.5 Hz), 129.7 (2'-CH, d, *J* = 2.9 Hz), 124.3 (3'-C, d, *J* = 18.9 Hz), 124.2 (7a-C), 124.1 (5-CH), 122.2 (4-CH), 116.6 (5'-CH, d, *J* = 23.3 Hz), 107.3 (7-CH), 103.3 (3-C=*C*H), 56.1 (OCH_3), 10.4 (1‴-CH), 7.1 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M+H) 451.2 (100%)

3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-6-hydroxyisobenzofuran-1(*3H*)-one (51)

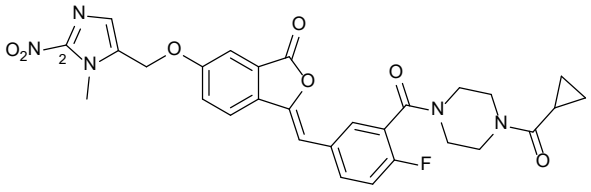


The reaction was carried out according to General Procedure E with benzofuranone **49** (0.20 g, 0.44 mmol) and BBr_3 (2.66 mL, 2.66 mmol). The crude product was purified by chromatography, eluting with 100% EtOAc to give the title product (0.14 g, 74%) as a yellow foam. Further chromatography prepared samples of the alkene isomers for analysis.

***E*:** δ_H 10.67 (1H, s, OH), 7.72 – 7.66 (1H, m, 6'-H), 7.64 – 7.56 (1H, m, 2'-H), 7.48 (1H, t, *J* = 9.0 Hz, 5'-H), 7.40 (1H, d, *J* = 8.35 Hz, 4-H), 7.22 (1H, d, *J* = 2.2 Hz, 7-H), 7.16 (1H, d, *J* = 7.6 Hz, 5-H), 6.86 (1H, s, 3-C=CH), 3.86 – 3.30 (8H, br m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.10 – 1.91 (1H, br m, 1‴-CH), 0.82 – 0.71 (4H, m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4"-NC=O), 165.9 (1-C=O), 163.6 (1"-NC=O), 160.1 (6-C), 157.1 (4'-CH, d, $J_{C\text{-}F}$ = 247.1 Hz), 146.5 (3-C), 132.2 (6'-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.5 Hz), 130.0 (1'-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.1 Hz), 129.6 (2'-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.5 Hz), 127.8 (3a-C), 127.3 (7a-C), 124.5 (3'-C, d, $J_{C\text{-}C\text{-}F}$ = 19.2 Hz), 124.1 (4-CH), 123.2 (5-CH), 116.6 (5'-CH, d, $J_{C\text{-}C\text{-}F}$ = 22.1 Hz), 109.8 (7-CH), 108.0 (3-C=*C*H), 10.38 (1‴-CH), 7.12 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M+H) 437.2 (100%), (M-H) 435.1 (100%).

***Z*:** δ_H 10.60 (1H, s, OH), 7.91 (1H, d, *J* = 8.5 Hz, 4-H), 7.89 – 7.83 (1H, m, 6'-H), 7.82 – 7.77 (1H, m, 2'-H), 7.42 (1H, t, *J* = 9.1 Hz, 5'-H), 7.30 (1H, dd, *J* = 8.5, 2.2 Hz, 5-H), 7.20 (1H, d, *J* = 2.2 Hz, 7-H), 6.76 (1H, s, 3-C=CH), 3.86 – 3.24 (8H, br m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.11 – 1.88 (1H, br, m, 1‴-CH), 0.82 – 0.67 (4H, br m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4"-NC=O), 166.2 (1-C=O), 163.9 (1"-NC=O), 159.9 (6-C), 156.7 (4'-C, d, $J_{C\text{-}F}$ = 249.5 Hz), 144.8 (3-C), 132.4 (6'-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.2 Hz), 131.1 (3a-C), 130.8 (1'-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.2 Hz), 129.5 (2'-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.2 Hz), 124.3 (3'-C, d, $J_{C\text{-}C\text{-}F}$ = 18.1 Hz), 124.2 (7a-C), 123.9 (5-CH), 122.4 (4-CH), 116.6 (5'-CH, d, $J_{C\text{-}C\text{-}F}$ = 21.8 Hz), 109.5 (7-CH), 102.4 (3-C=*C*H), 10.37 (1‴-CH), 7.14 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M+H) 437.2 (100%), (M-H) 435.1 (100%).

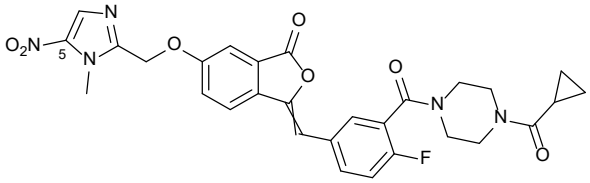
(*Z*)-3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-6-((1-methyl-2-nitro-1H-imidazol-5-yl)methoxy)isobenzofuran-1(3H)-one (54)



The reaction was carried out according to General Procedure C with benzofuranone **51** (90 mg, 0.21 mmol), K_2CO_3 (44 mg, 0.32 mmol) and chloride **16** (40 mg, 0.23 mmol) stirring for 18 h at room temperature. The crude product was collected by filtration and triturated with MeOH to give the title product (60 mg, 50%) as a cream solid: mp 234 - 237 °C.

δ_H 8.04 (1H, d, *J* = 8.6 Hz, 5-H), 7.91 – 7.85 (1H, m, 6'-H), 7.85 – 7.80 (1H, m, 2'-H), 7.68 (1H, d, *J* = 2.2 Hz, 7-H), 7.58 (1H, dd, *J* = 8.6, 2.3 Hz, 5-H), 7.44 (1H, d, *J* = 9.0 Hz, 5'-H), 7.37 (1H, s, 4⁗-H), 6.88 (1H, s, 3-C=CH), 5.44 (2H, s, OCH_2), 3.97 (3H, s, NCH_3), 3.87 – 3.24 (8H, br m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.09 – 1.86 (1H, br m, 1‴-CH), 0.81 – 0.67 (4H, br m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4"-NC=O), 166.0 (1"-NC=O), 163.8 (1-C=O), 159.5 (6-C), 156.8 (4'-C, d, $J_{C\text{-}F}$ = 248.6 Hz), 146.3 (2⁗-C), 144.4 (3-C), 133.5 (3a-C), 132.9 (5⁗-C), 132.6 (6'-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 7.9 Hz), 130.6 (1'-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.4 Hz), 129.7 (2'-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 2.3 Hz), 128.6 (4⁗-CH), 124.7 (5-CH), 124.3 (3'-C, d, $J_{C\text{-}C\text{-}F}$ = 18.7 Hz), 124.1 (7a-C), 122.4 (4-CH), 116.3 (5'-CH, d, $J_{C\text{-}C\text{-}F}$ = 22.3 Hz), 108.9 (7-CH), 103.7 (3-C=*C*H), 60.0 (OCH_2), 34.4 (NCH_3), 10.37 (1‴-CH), 7.13 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M+H) 576.2 (24%), (M-$C_5H_6N_3O_2$) 435.2 (100%)

3-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzylidene)-6-((1-methyl-5-nitro-1*H*-imidazol-2-yl)methoxy)isobenzofuran-1(*3H*)-one (56)



The reaction was carried out according to General Procedure C with benzofuranone **51** (90 mg, 0.21 mmol), K_2CO_3 (44 mg, 0.32 mmol) and chloride **17** (40 mg, 0.23 mmol) stirring for 18 h at room temperature. The crude product was collected by filtration and triturated with MeOH to give the title product (50 mg, 42%) as a white foam. Further chromatography prepared samples of the alkene isomers for analysis

***E*:** δ_H 8.09 (1H, s, 4⁗-H), 7.71 – 7.63 (2H, m, 7-H, 6′-H), 7.61 – 7.53 (1H, m, 5-H), 7.45 (1H, t, *J* = 9.1Hz, 5′-H), 7.42 – 7.37 (2H, m, 4-H, 2′-H), 6.93 (1H, s, 3-C=CH), 5.48 (2H, s, OCH_2), 3.93 (3H, s, NCH_3), 3.84 – 3.39 (8H, br m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.05 – 1.87 (1H, br m, 1‴-H), 0.79 – 0.66 (4H, br m, 2‴-CH_2, 3‴-CH_2).δ_C 171.3 (4″-NC=O), 165.6 (1-C=O), 163.6 (1″-NC=O), 159.7 (6-C), 157.2 (4′-C, d, $J_{C\text{-}F}$ = 248.0 Hz), 147.2 (2⁗-C), 146.1 (3-C), 139.7 (5⁗-C), 132.3 (6′-CH, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.2 Hz), 131.5 (4⁗-CH), 130.3 (3a-C) 129.8 (1′-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.2 Hz), 129.7 (5-CH), 127.1 (7a-C), 124.5 (3′-C, d, $J_{C\text{-}C\text{-}F}$ = 18.1 Hz), 124.0 (4-CH), 123.9 (2′-C, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 6.6 Hz), 116.7 (5′-C, d, $J_{C\text{-}C\text{-}F}$ = 23.0 Hz), 109.5 (3-C=*C*H), 109.2 (7-CH), 62.6 (OCH_2), 33.6 (NCH_3), 10.4 (1‴-CH), 7.12 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M-$C_5H_6N_3O_2$) 435.1 (100%).

***Z*:** δ_H 8.11 (1H, s, 4⁗-H), 8.03 (1H, d, *J* = 8.6 Hz, 4-H), 7.91 – 7.85 (1H, m, 6'-H), 7.82 (1H, dd, *J* = 6.4, 1.8 Hz, 2'-H), 7.69 (1H, d, *J* = 2.3 Hz, 7-H), 7.56 (1H, dd, *J* = 8.6, 2.4 Hz, 5-H), 7.44 (1H, t, *J* = 9.1 Hz, 5'-H), 6.88 (1H, s, 3-C=CH), 5.49 (2H, s, OCH_2), 3.97 (3H, s, NCH_3), 3.86 – 3.24 (8H, br m, 2"-CH_2, 3"-CH_2, 5"-CH_2, 6"-CH_2), 2.08 – 1.86 (1H, br m, 1‴-H), 0.79 – 0.67 (4H, br m, 2‴-CH_2, 3‴-CH_2). δ_C 171.3 (4″-NC=O), 166.0 (1-C), 163.8 (1″-NC=O), 159.5 (6-C), 156.8 (4′-C, d, $J_{C\text{-}F}$ = 248.6 Hz), 147.2 (2⁗-C), 144.4 (3-C), 139.7 (5⁗-C), 133.6 (3a-C), 132.6 (6′-C, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.5 Hz), 131.5 (4⁗-CH), 130.5 (1′-C, d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 2.9 Hz), 129.7 (2′-C, d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.7 Hz), 127.1 (7a-C), 124.6 (5-CH), 124.3 (3′-C, d, $J_{C\text{-}C\text{-}F}$ = 19.4 Hz), 122.3 (4-CH), 116.6 (5′-CH, d, $J_{C\text{-}C\text{-}F}$ = 22.1 Hz), 108.9 (7-CH), 103.7 (3-C=*C*H), 62.7

(OCH_2), 33.6 (NCH_3), 10.4 (1‴-CH), 7.13 (2 × CH_2), 4 × NCH_2 not observed. LRMS (M-$C_5H_6N_3O_2$) 435.1 (100%).

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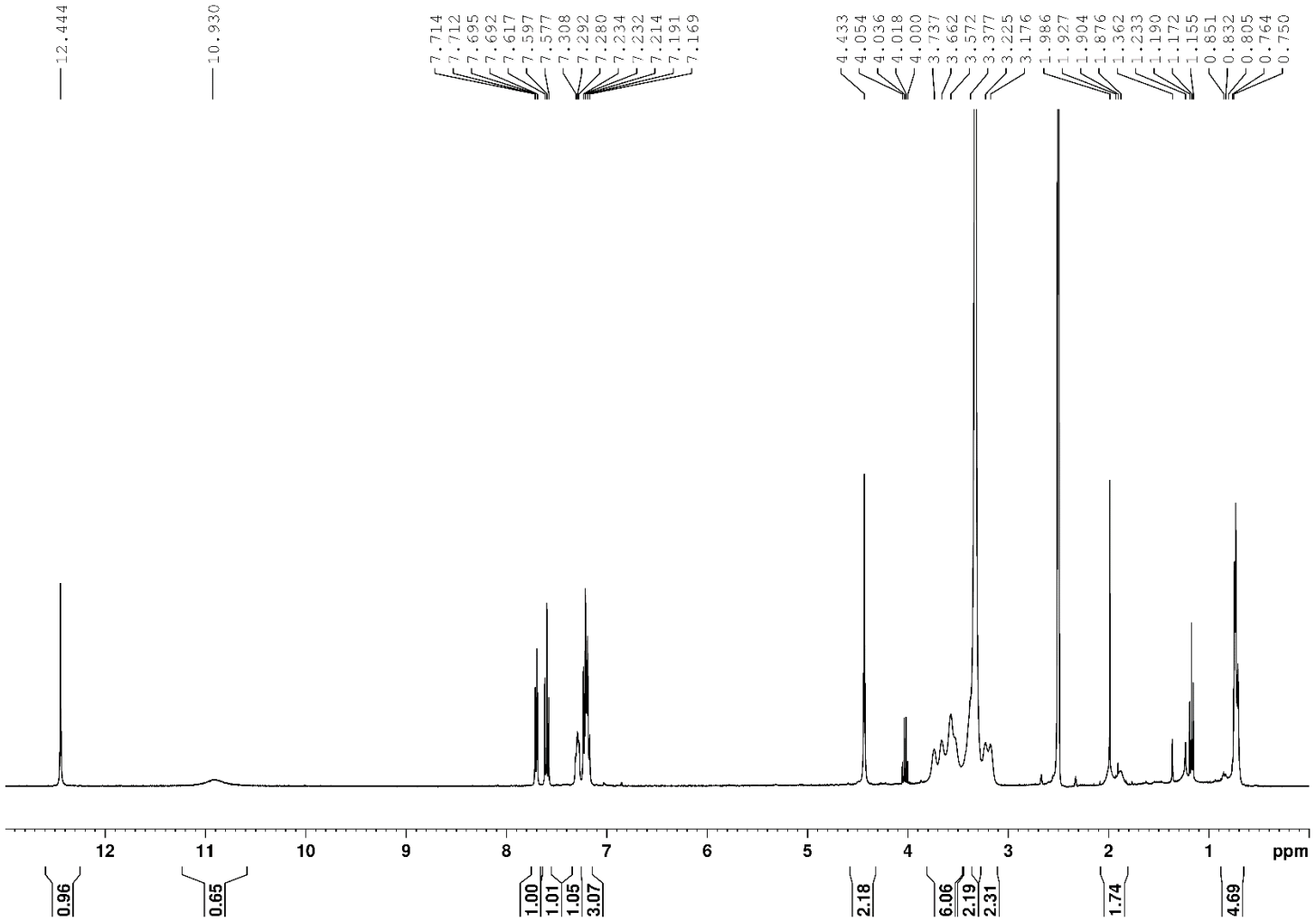
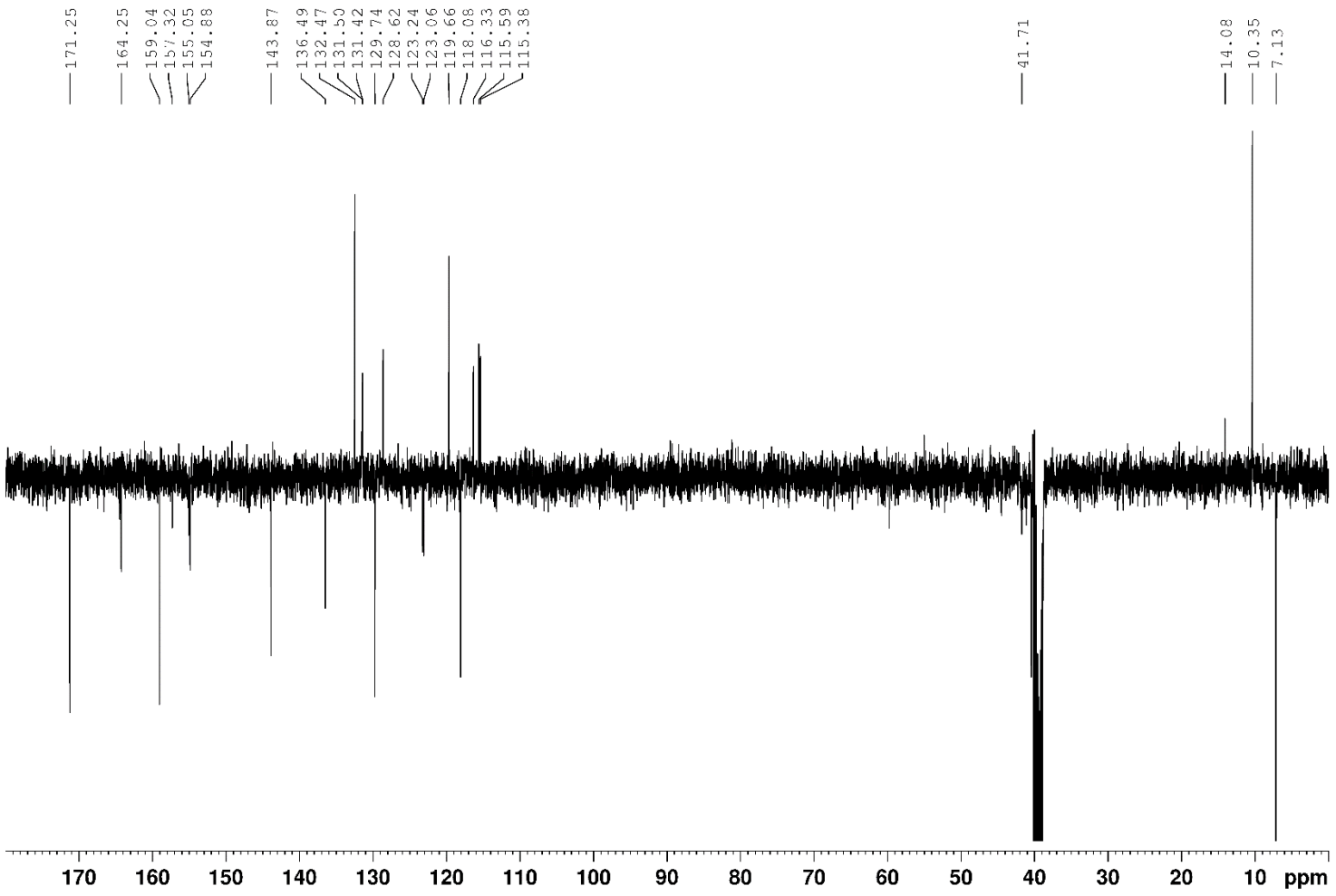
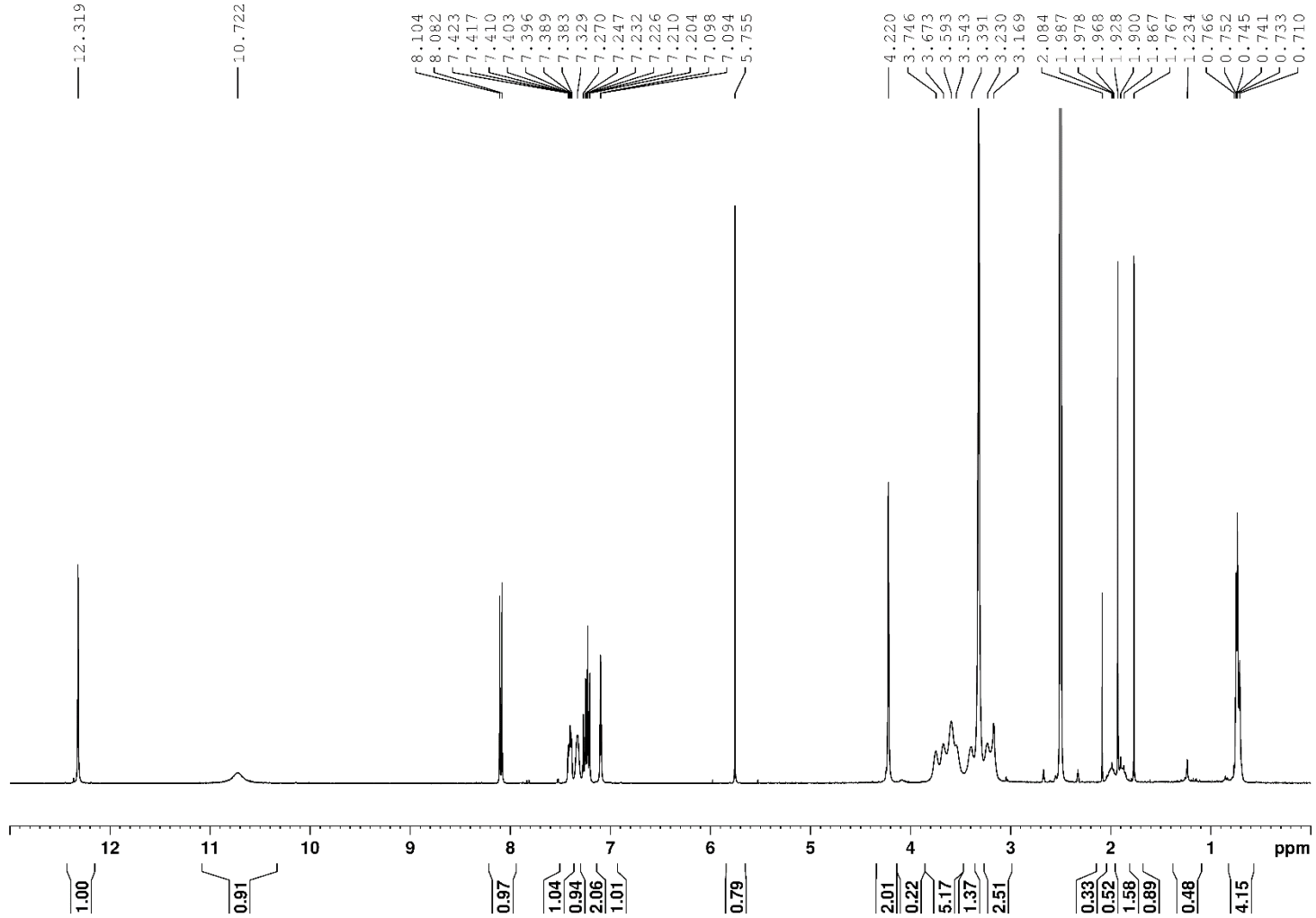
^{1}H NMR Compound 4



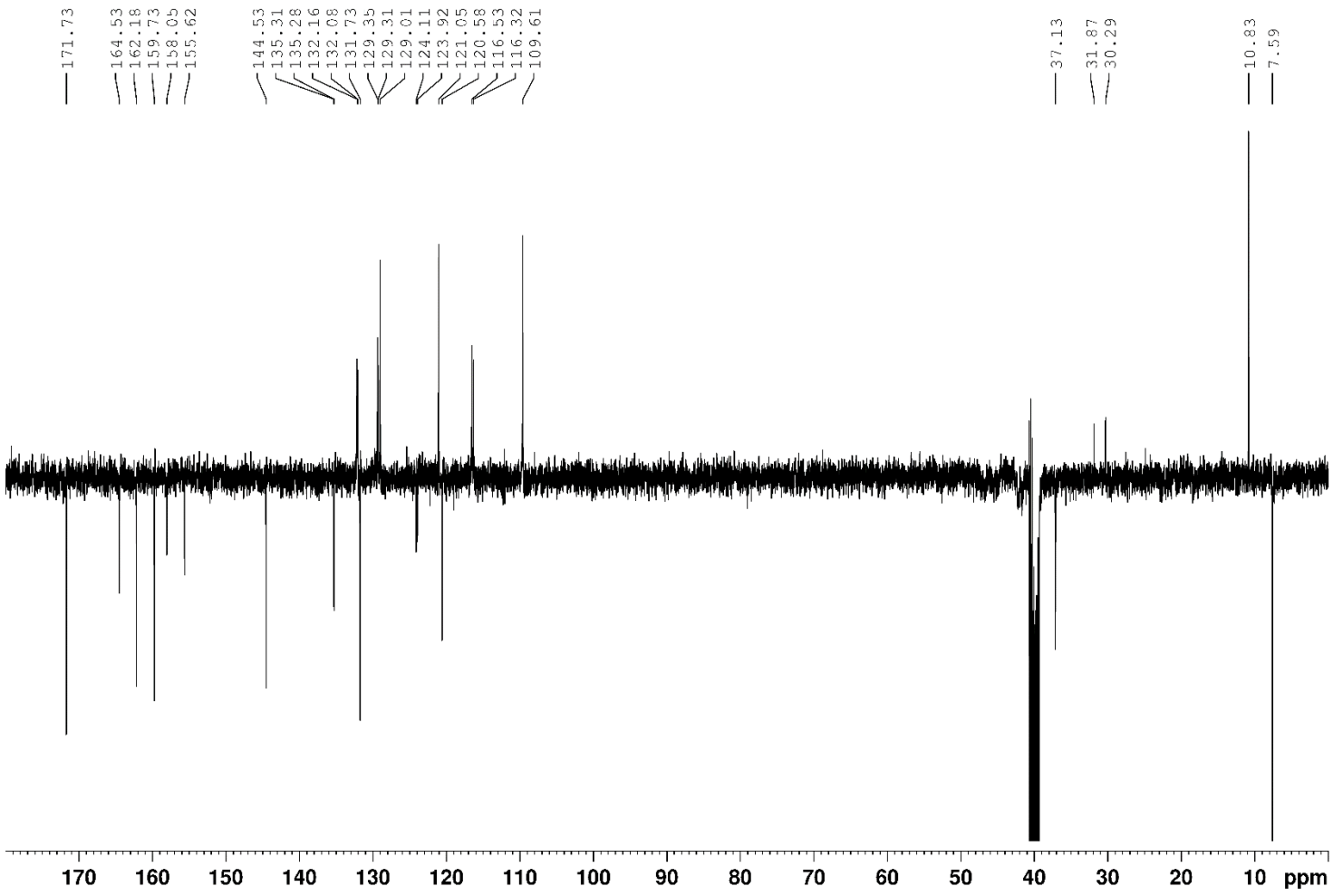
^{13}C NMR (APT) Compound 4



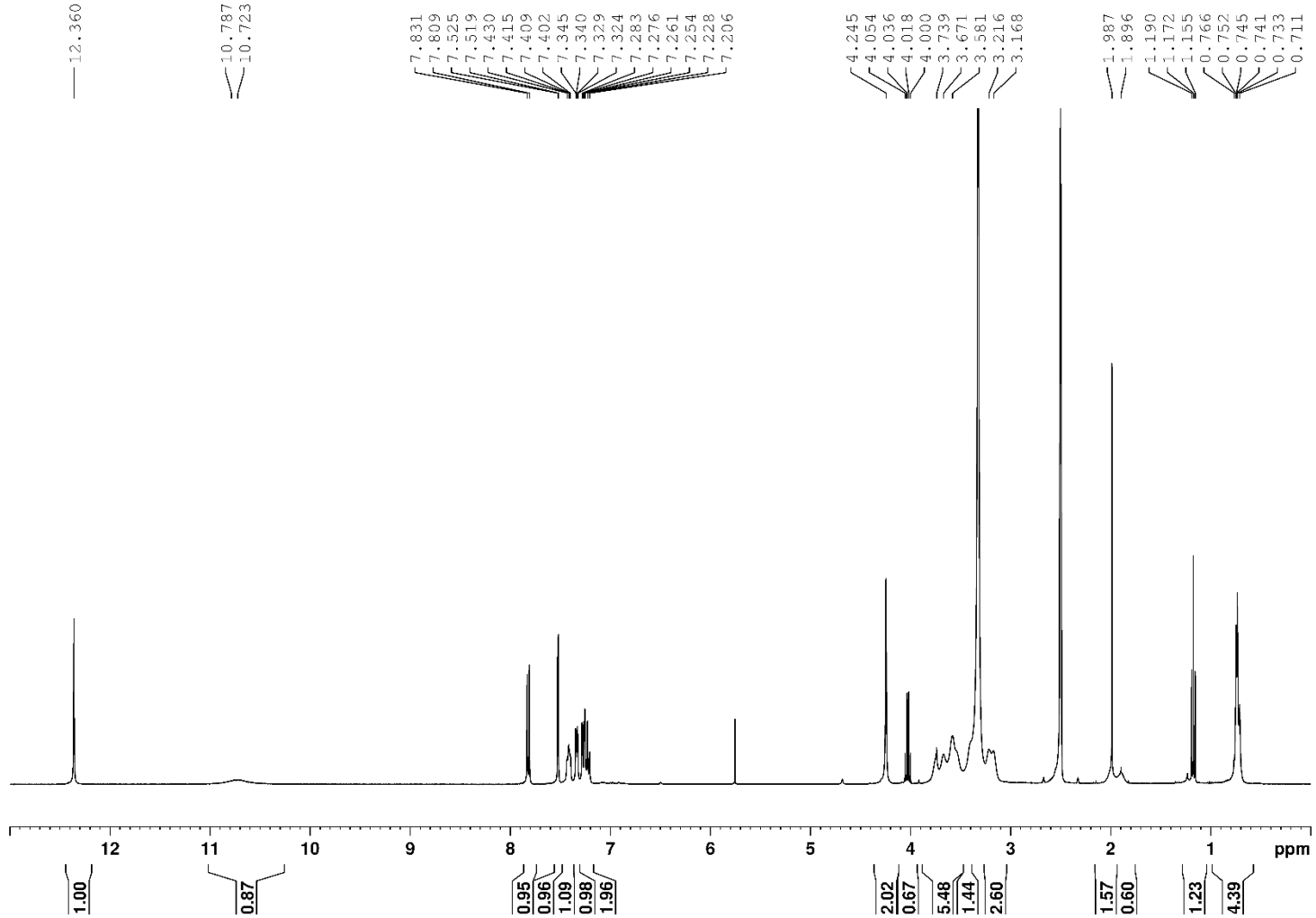
^{1}H NMR Compound 5



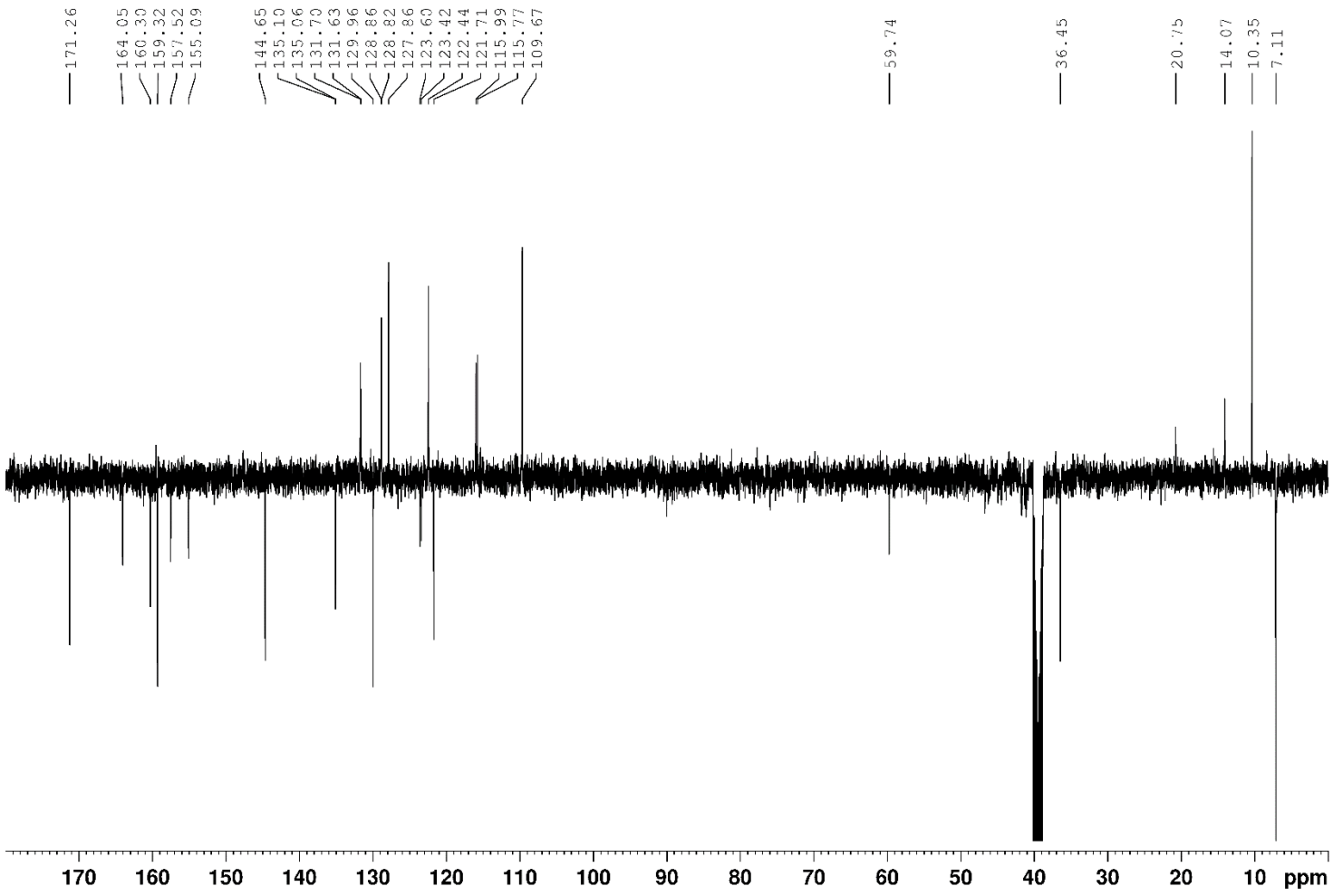
^{13}C NMR (APT) Compound 5



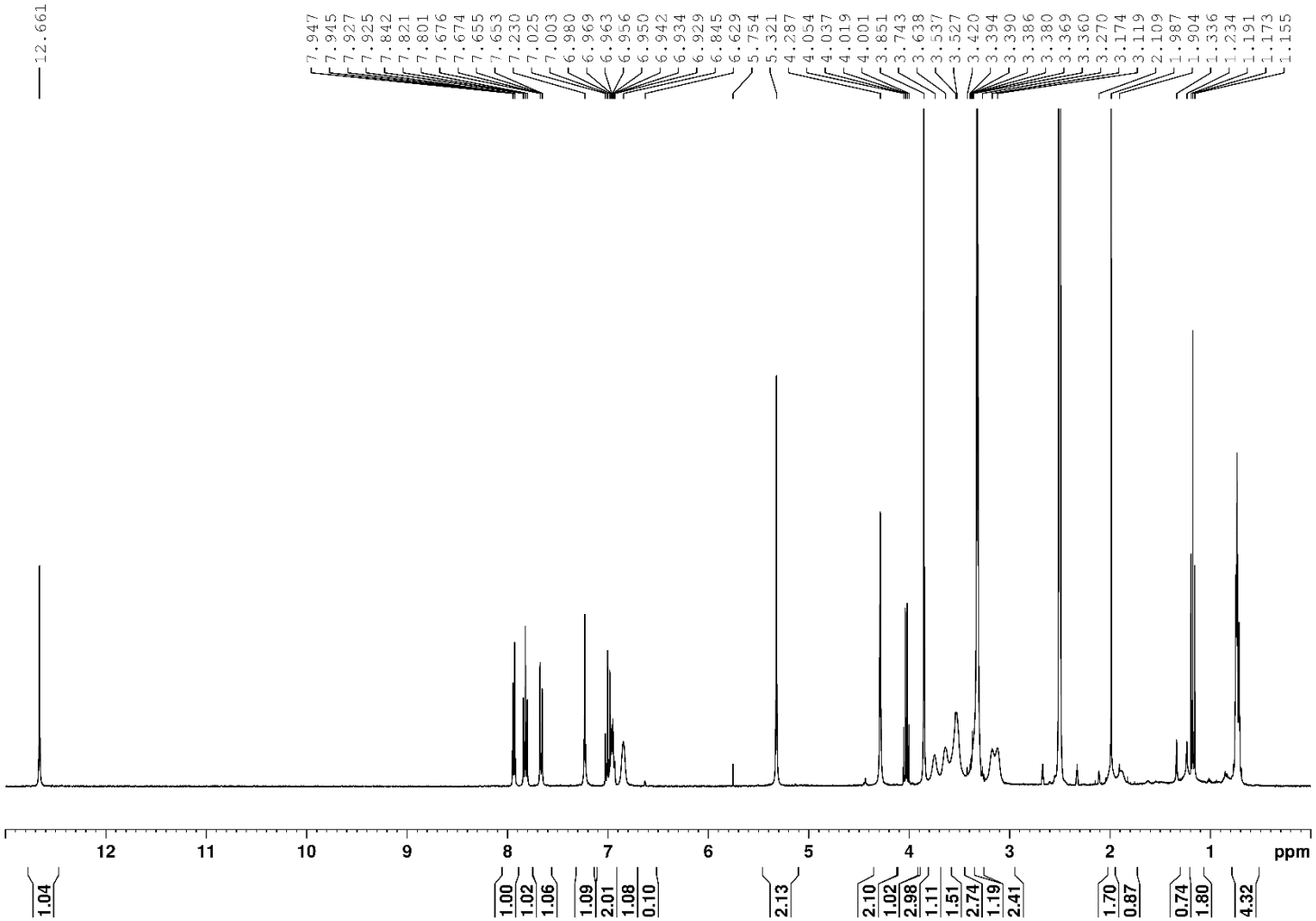
^{1}H NMR Compound 6



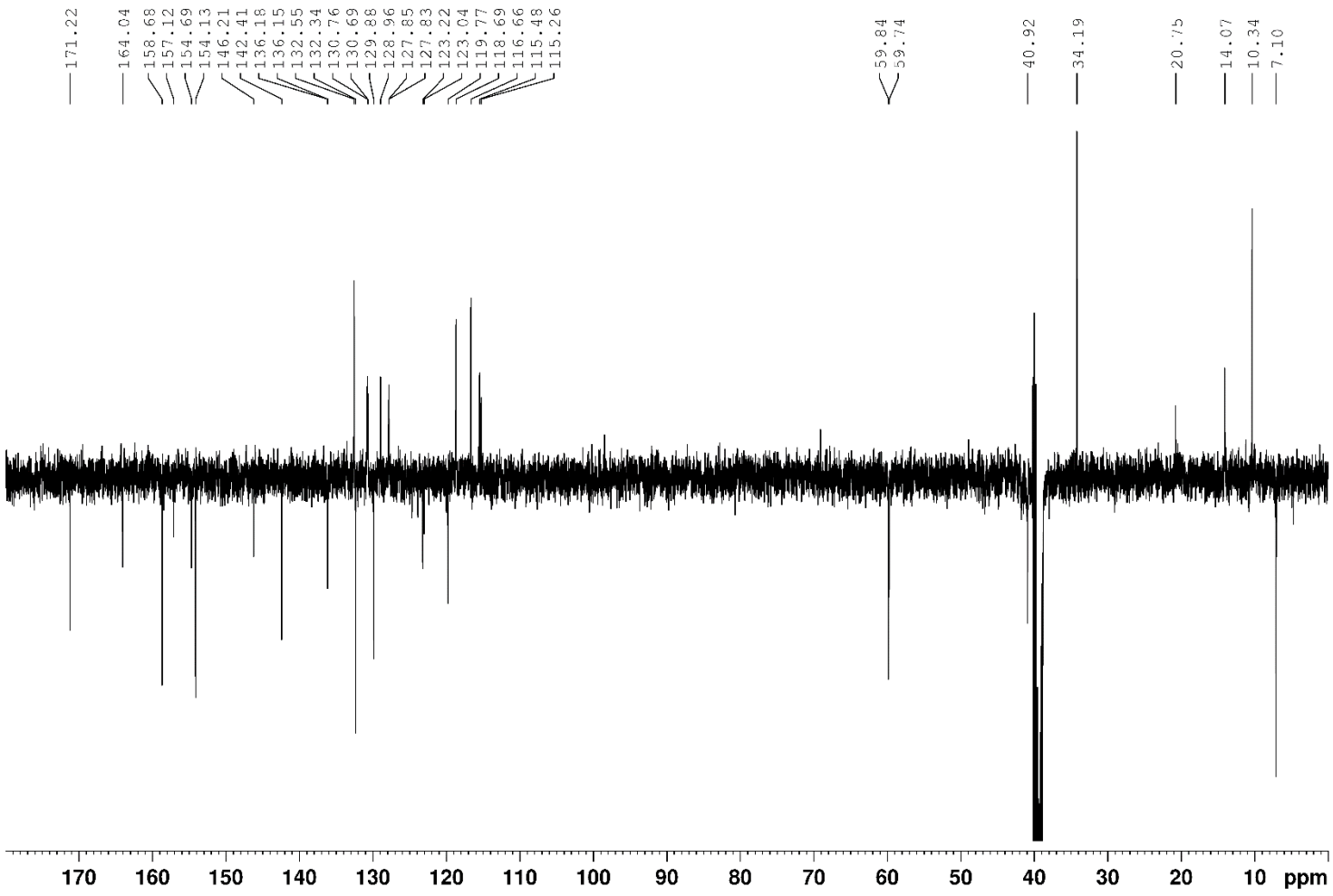
^{13}C NMR (APT) Compound 6



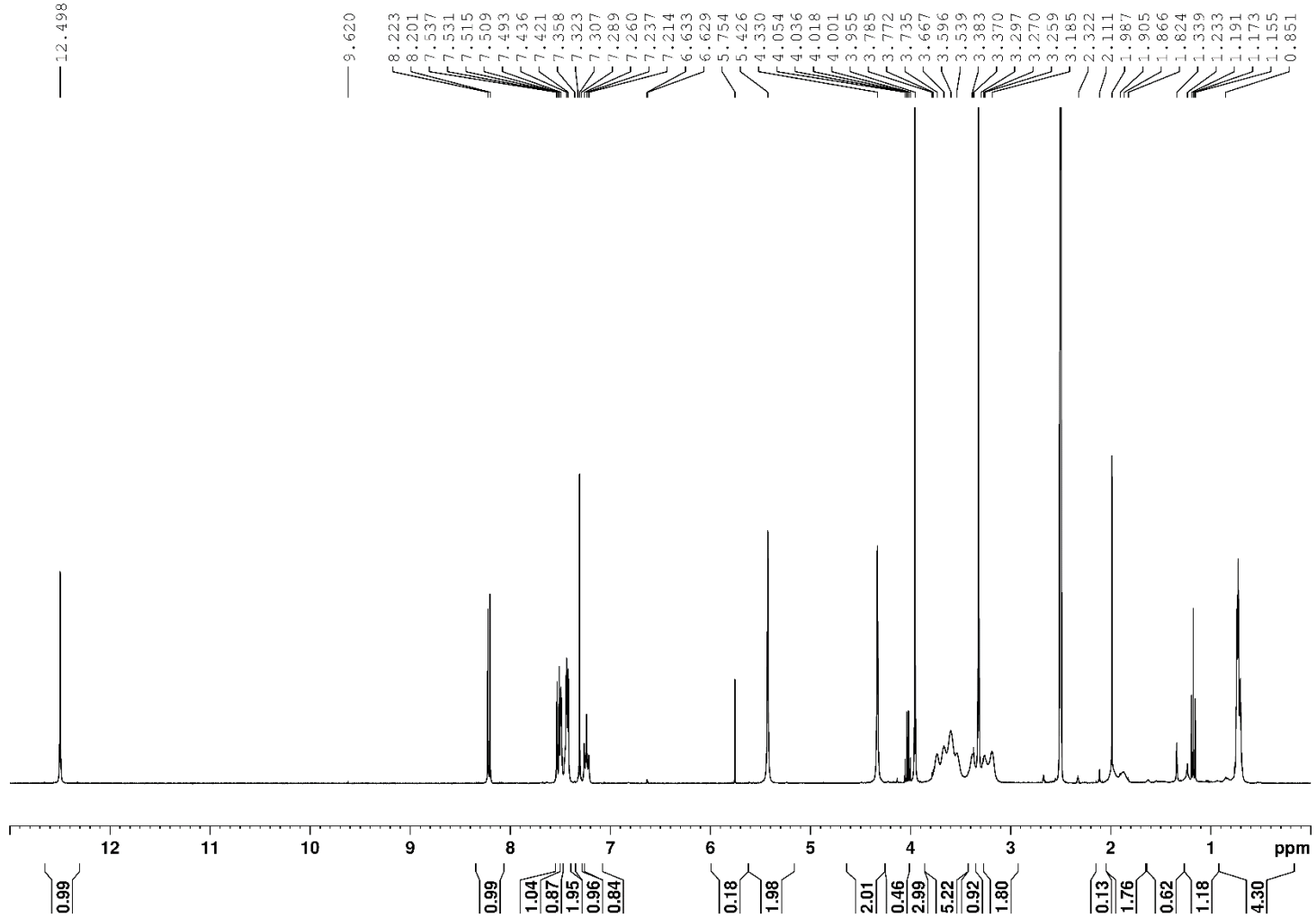
^{1}H NMR Compound 7



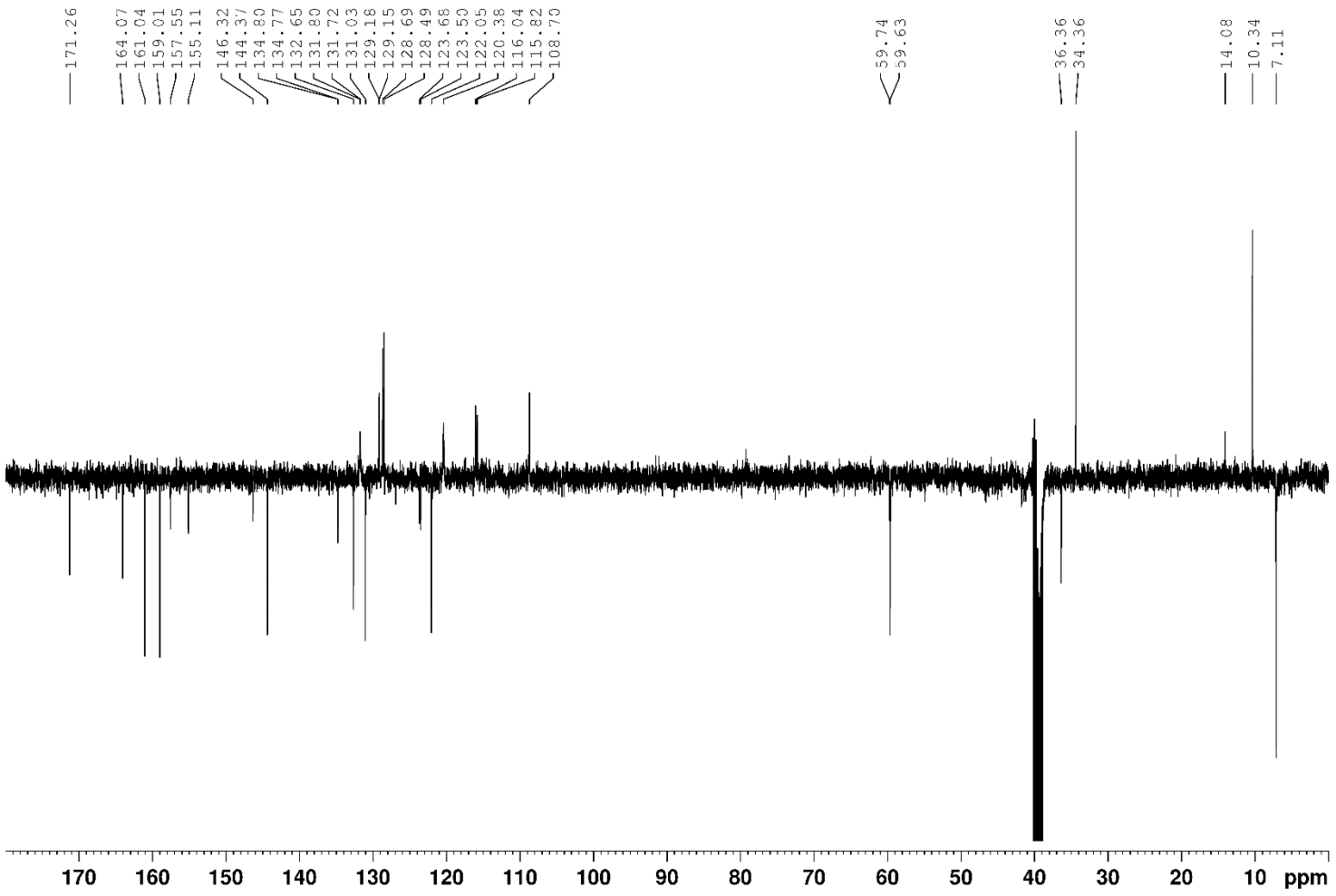
^{13}C NMR (APT) Compound 7



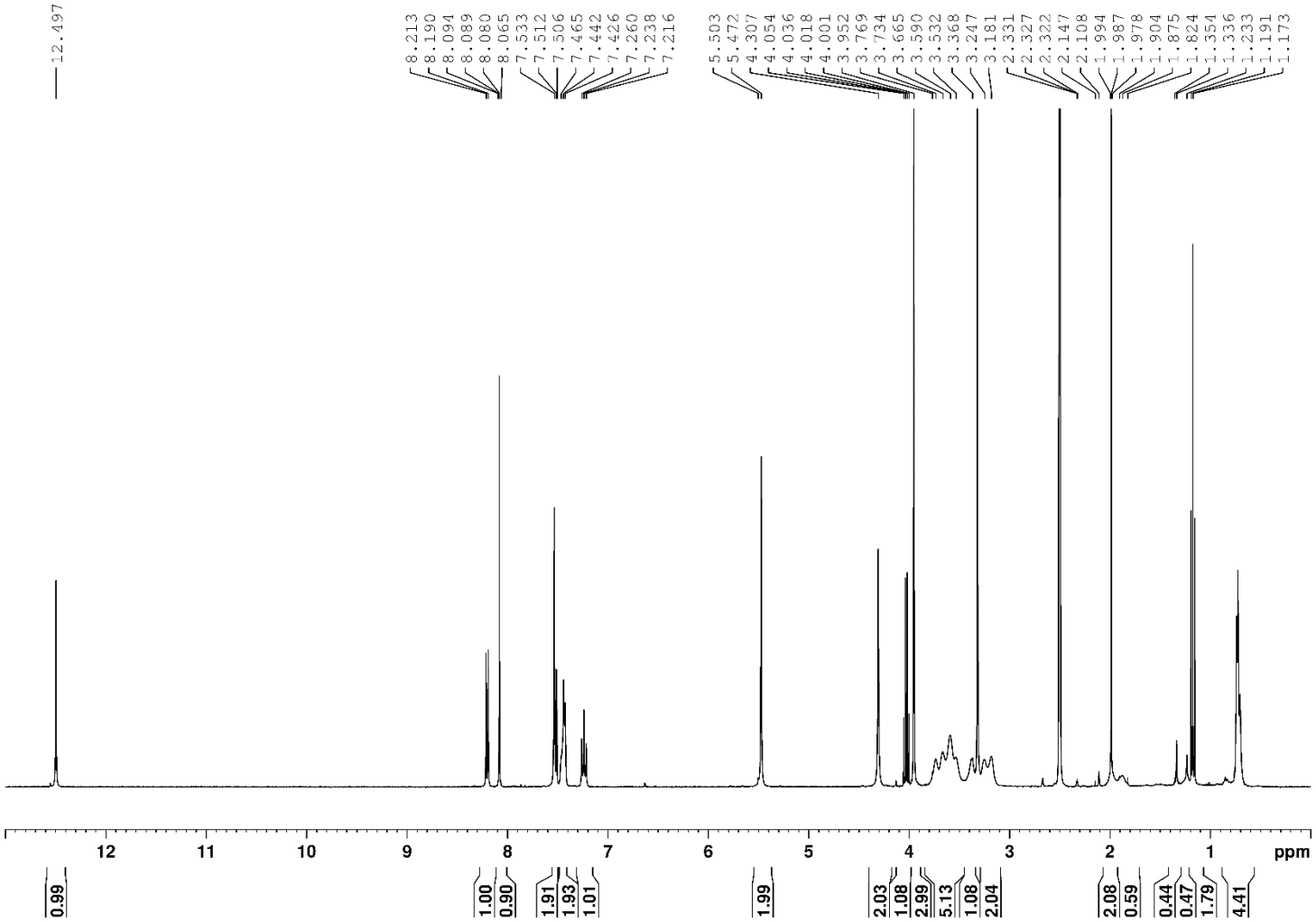
^{1}H NMR Compound 8



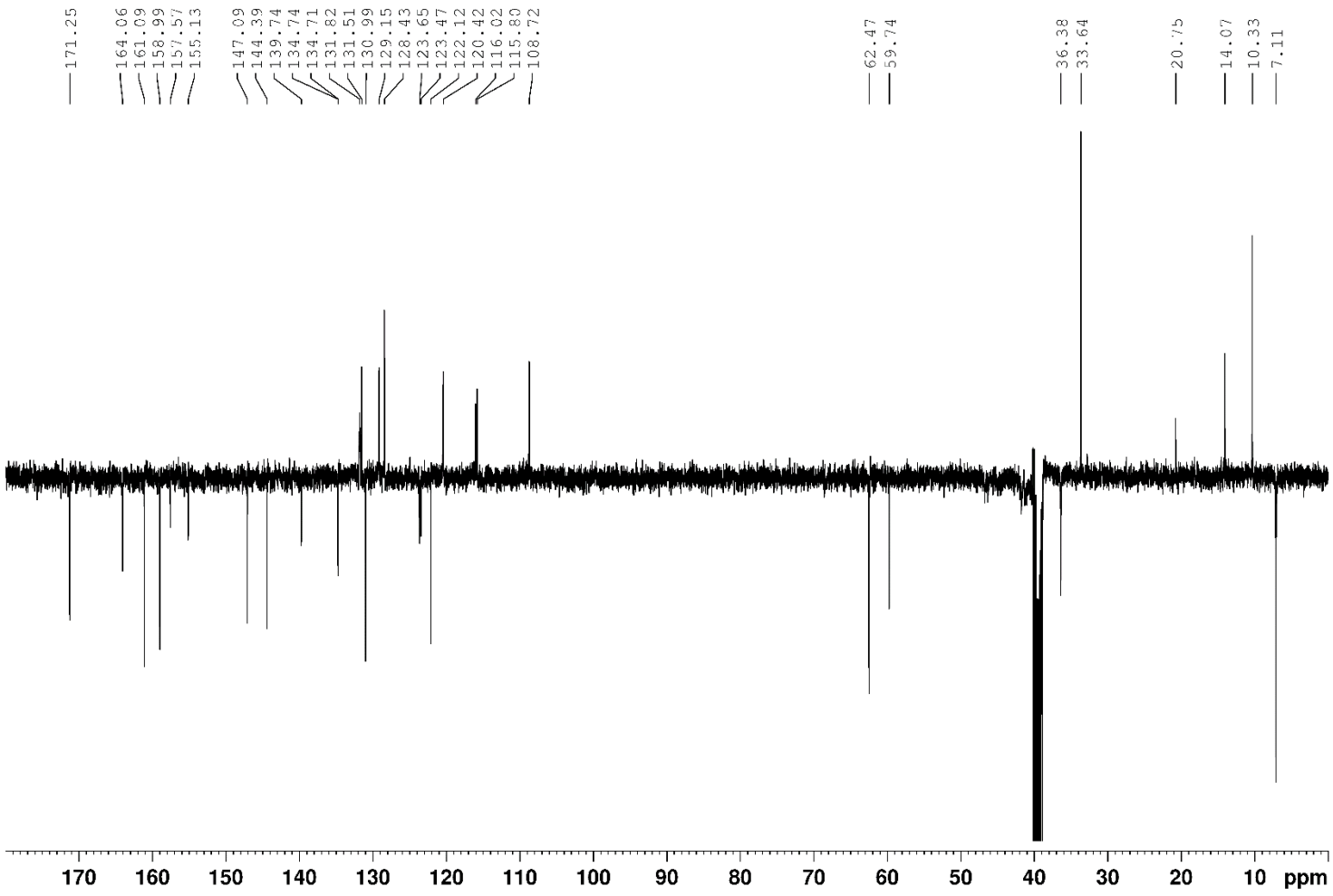
^{13}C NMR (APT) Compound 8



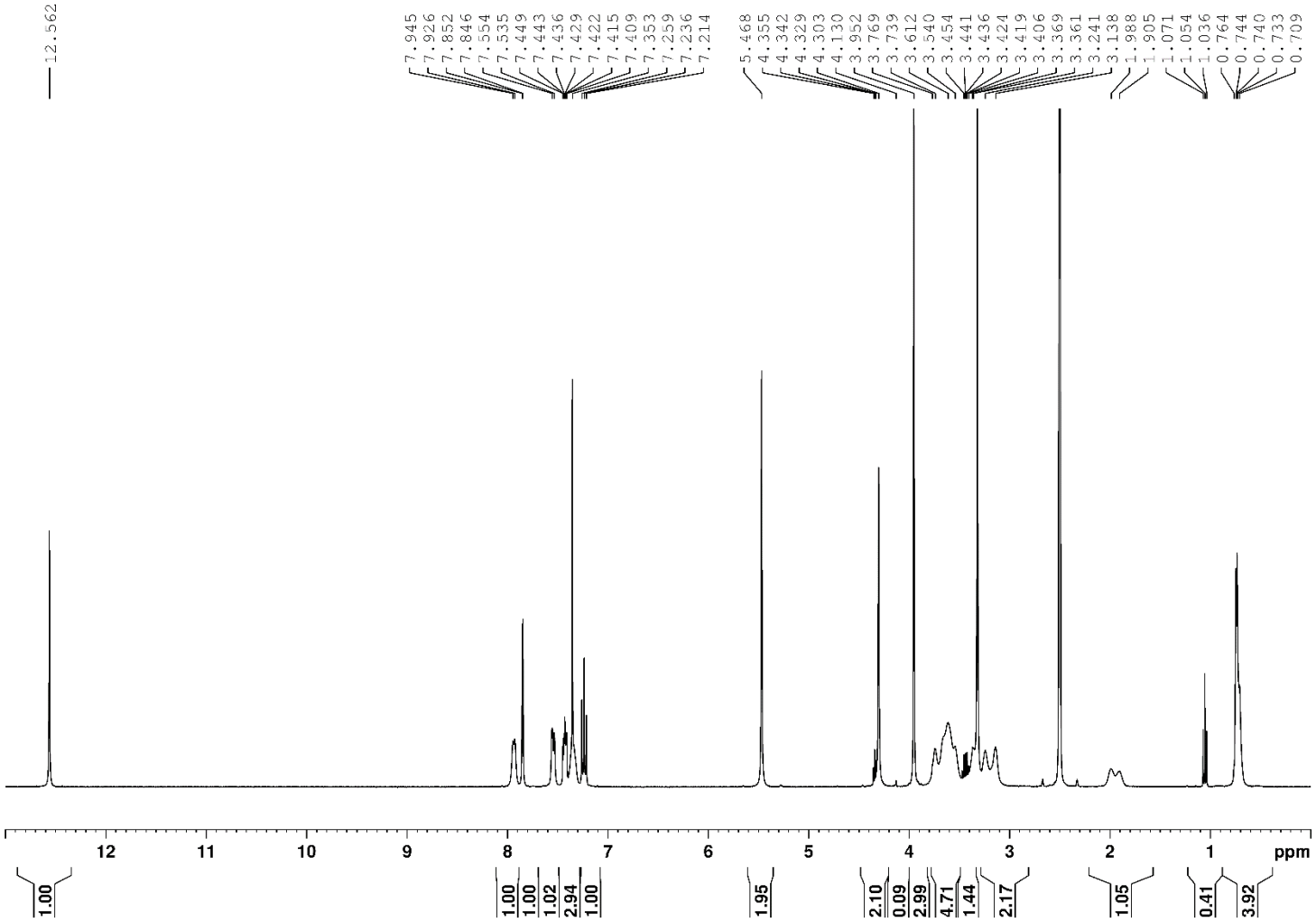
^{1}H NMR Compound 9



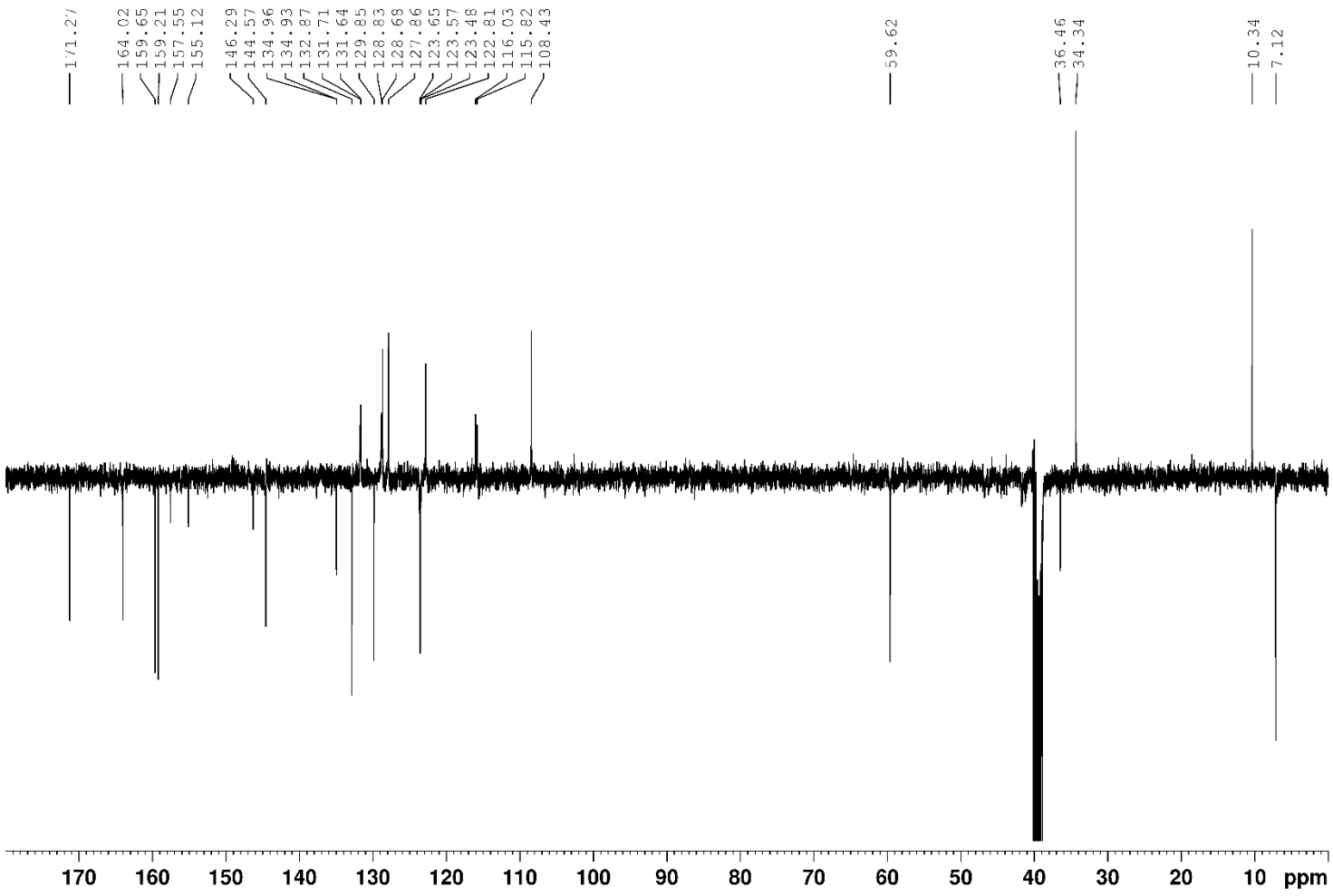
^{13}C NMR (APT) Compound 9



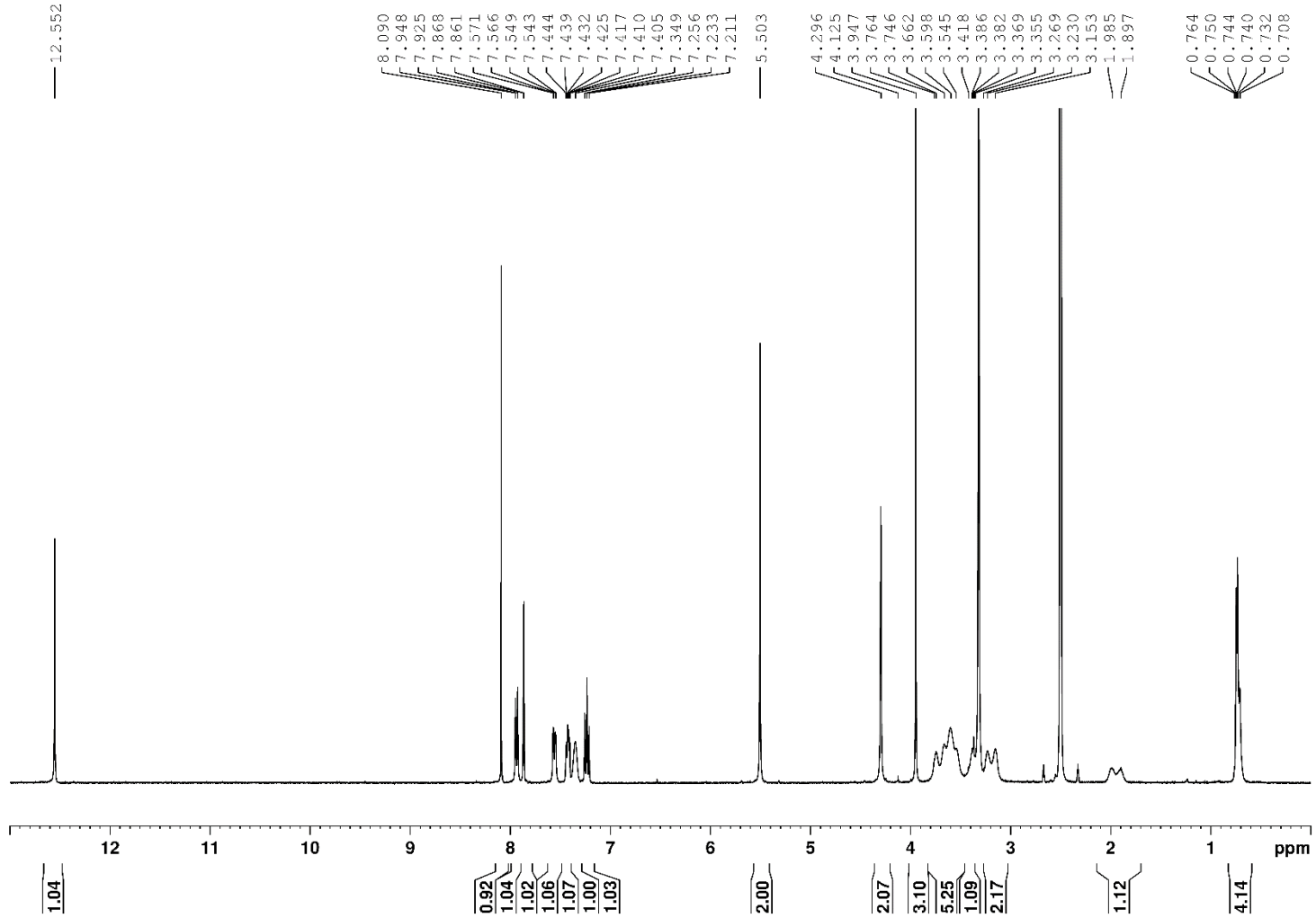
^{1}H NMR Compound 10



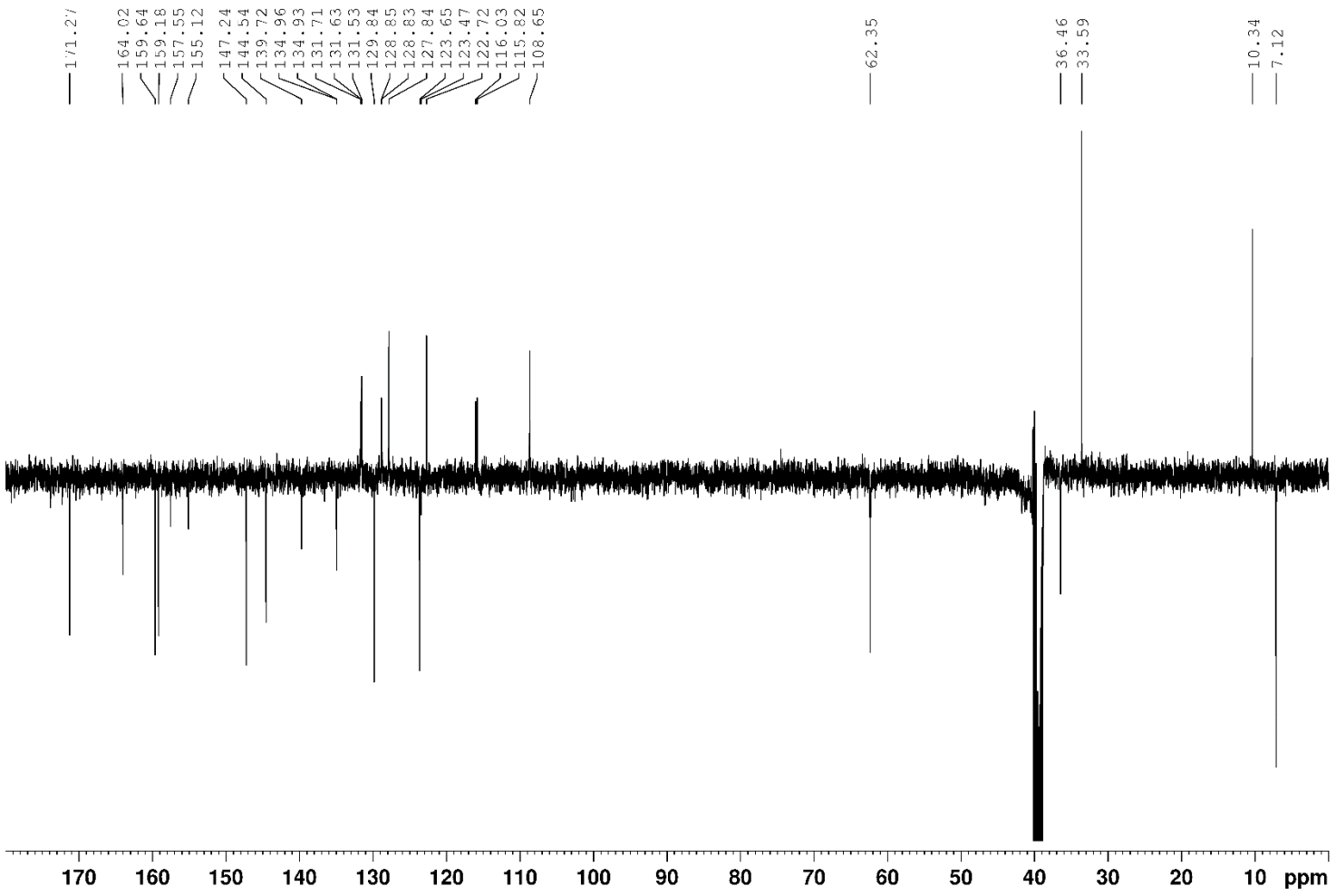
^{13}C NMR (APT) Compound 10



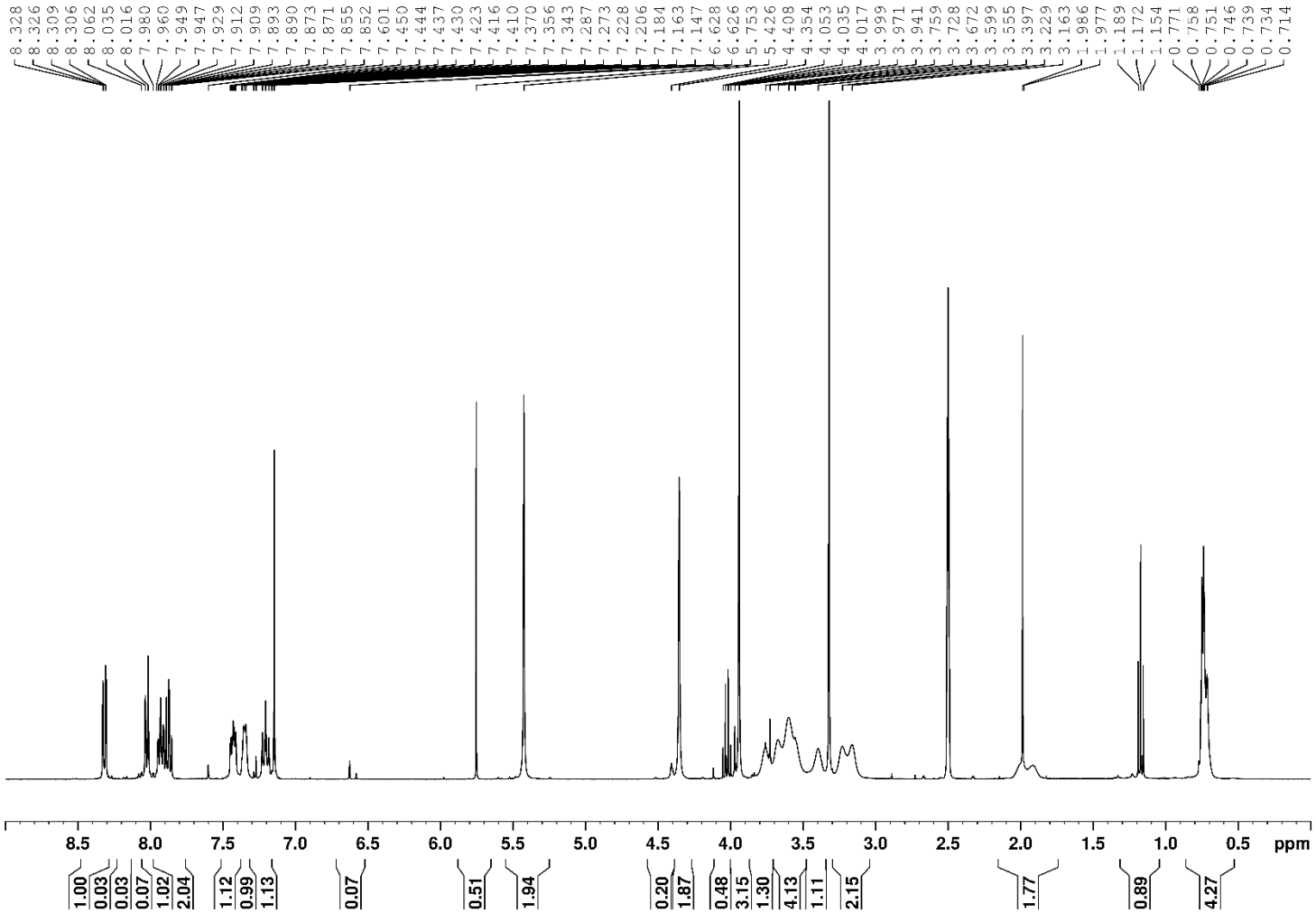
^{1}H NMR Compound 11



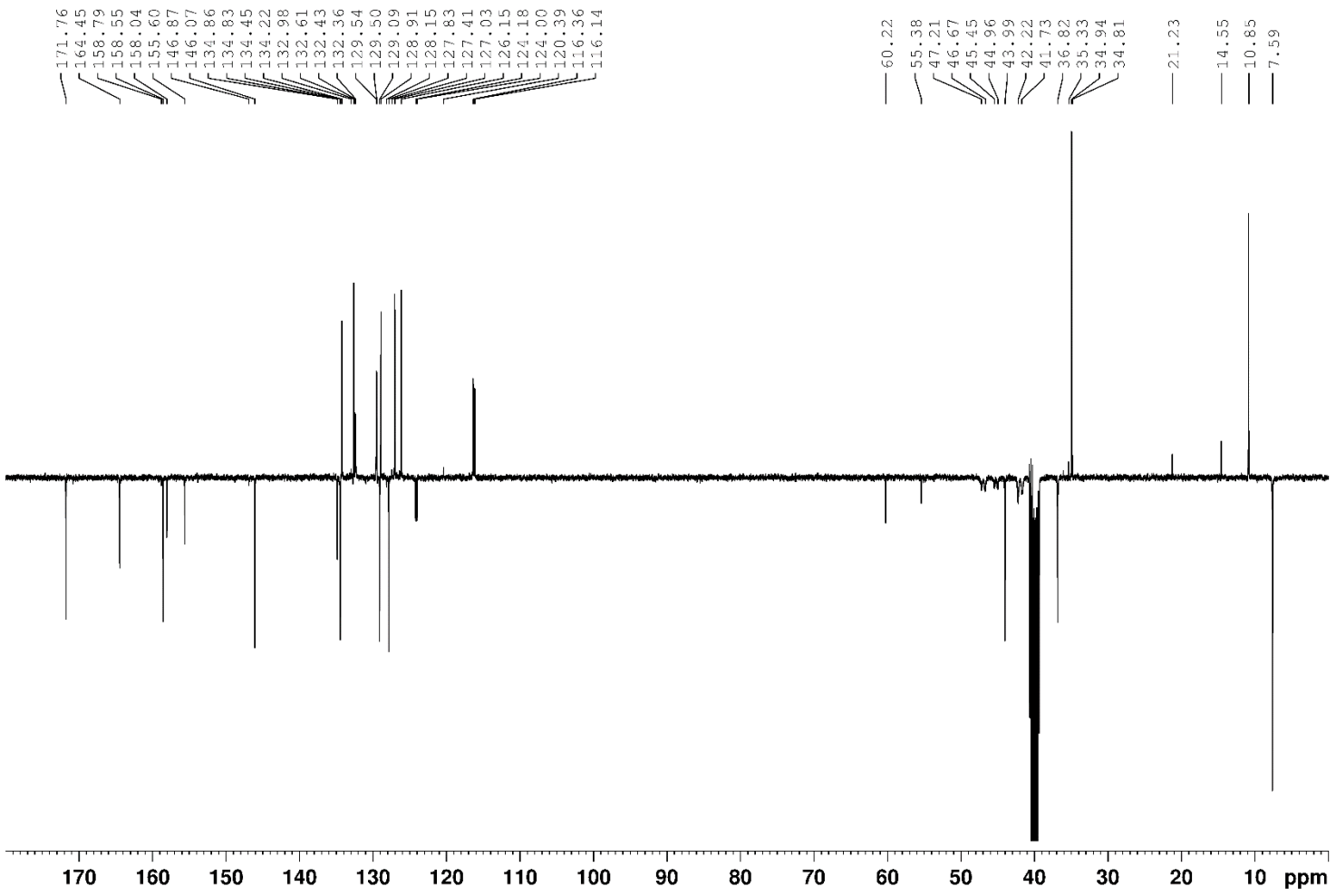
^{13}C NMR (APT) Compound 11



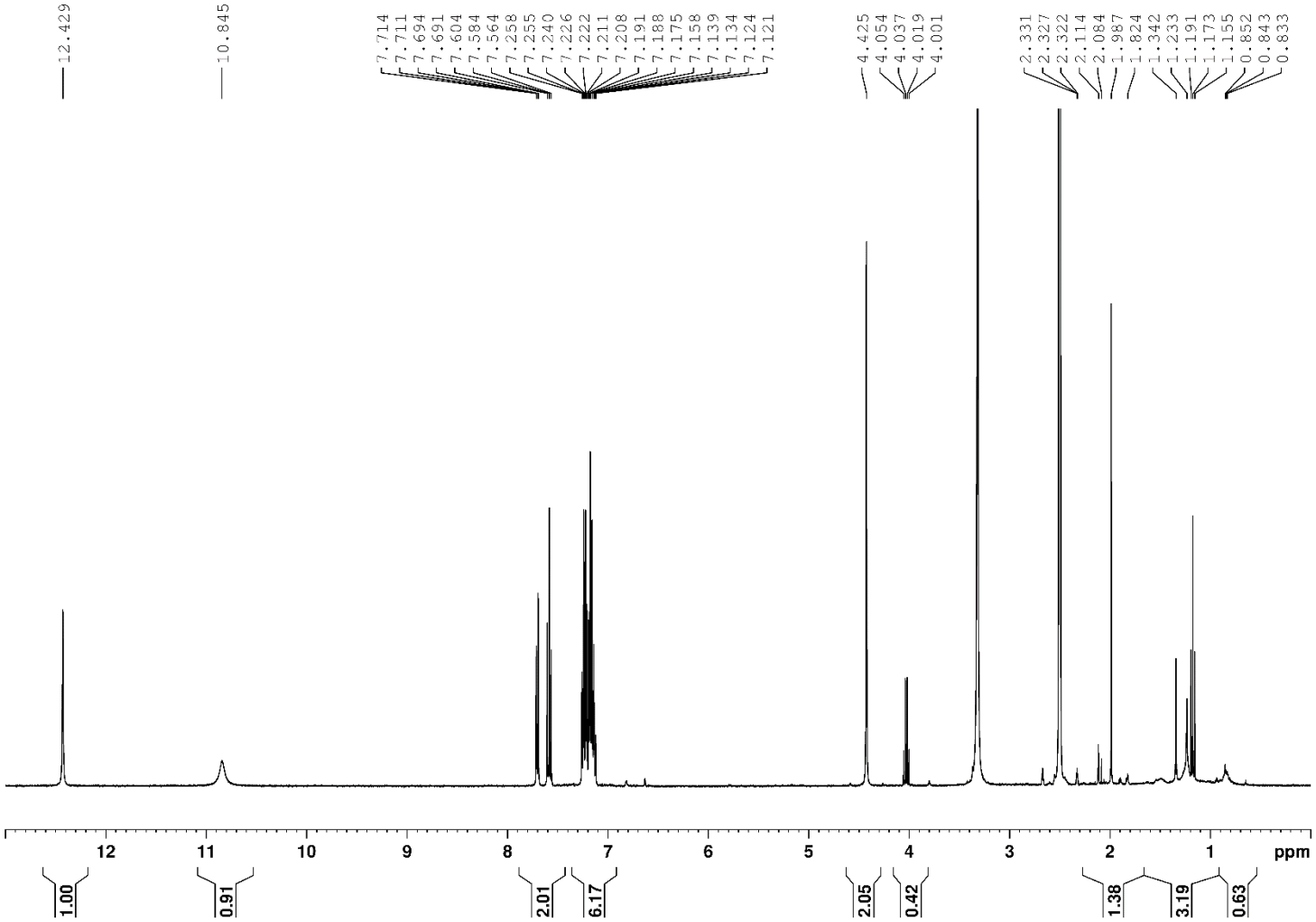
^{1}H NMR Compound 18



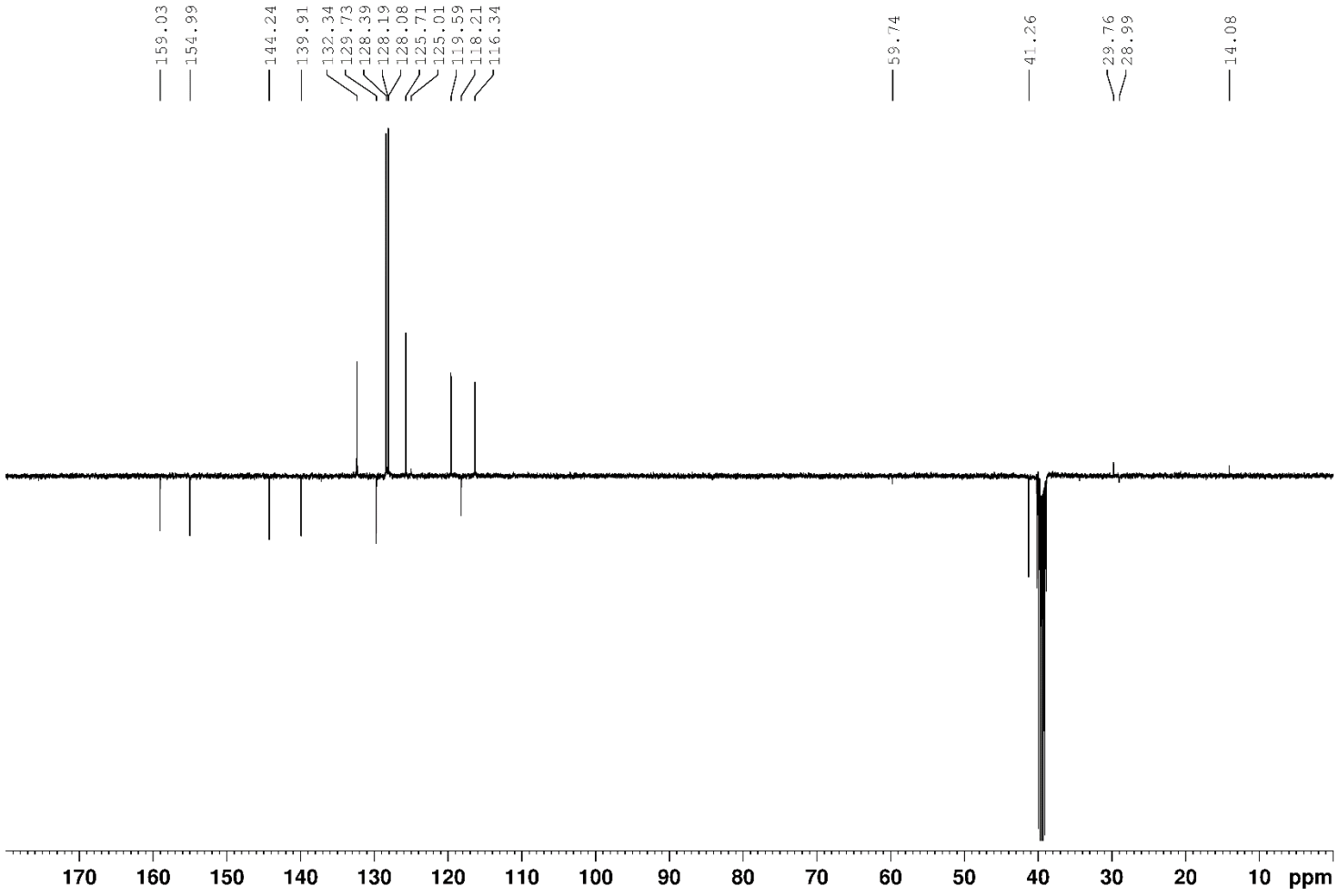
^{13}C NMR (APT) Compound 18



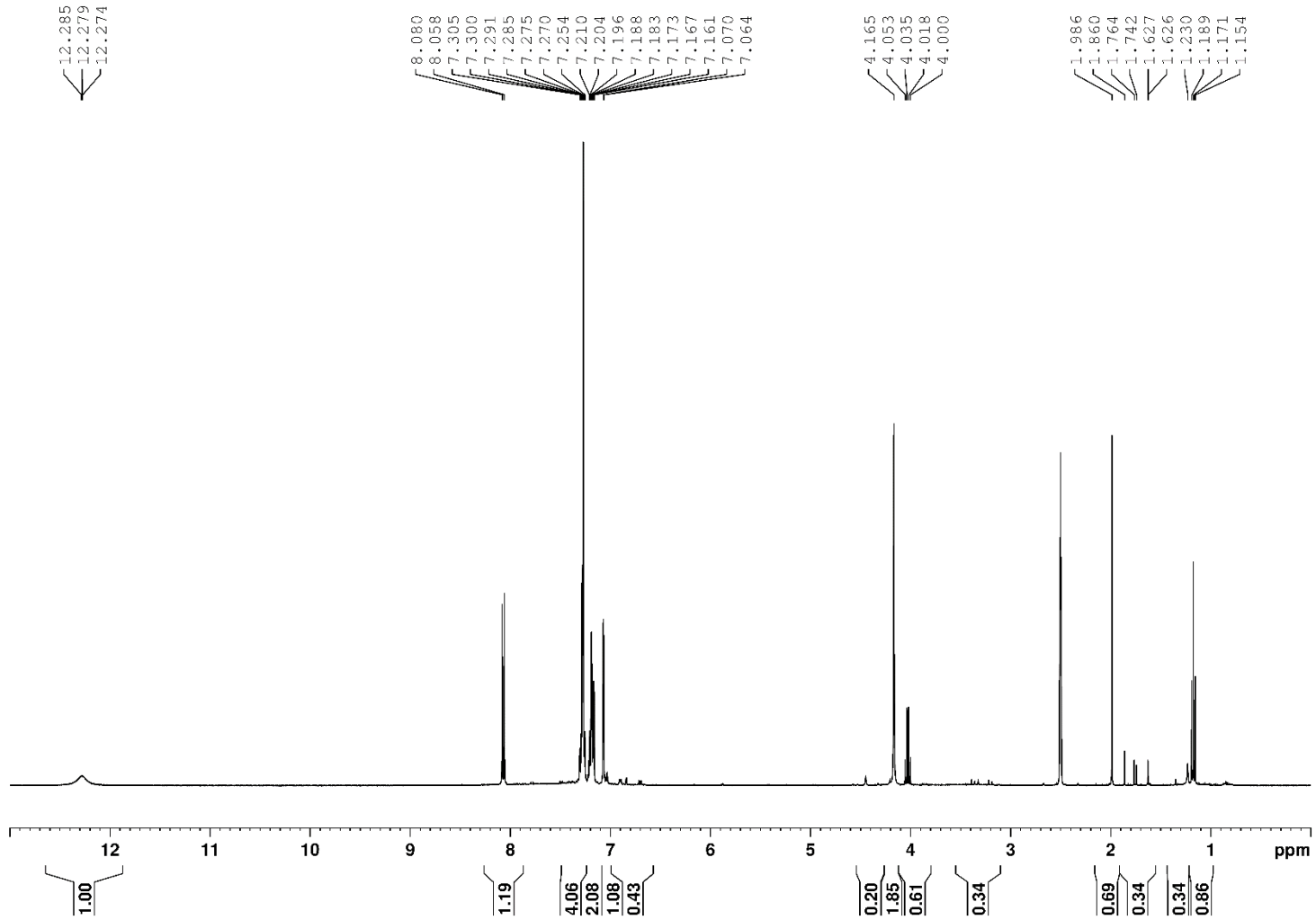
^{1}H NMR Compound 38



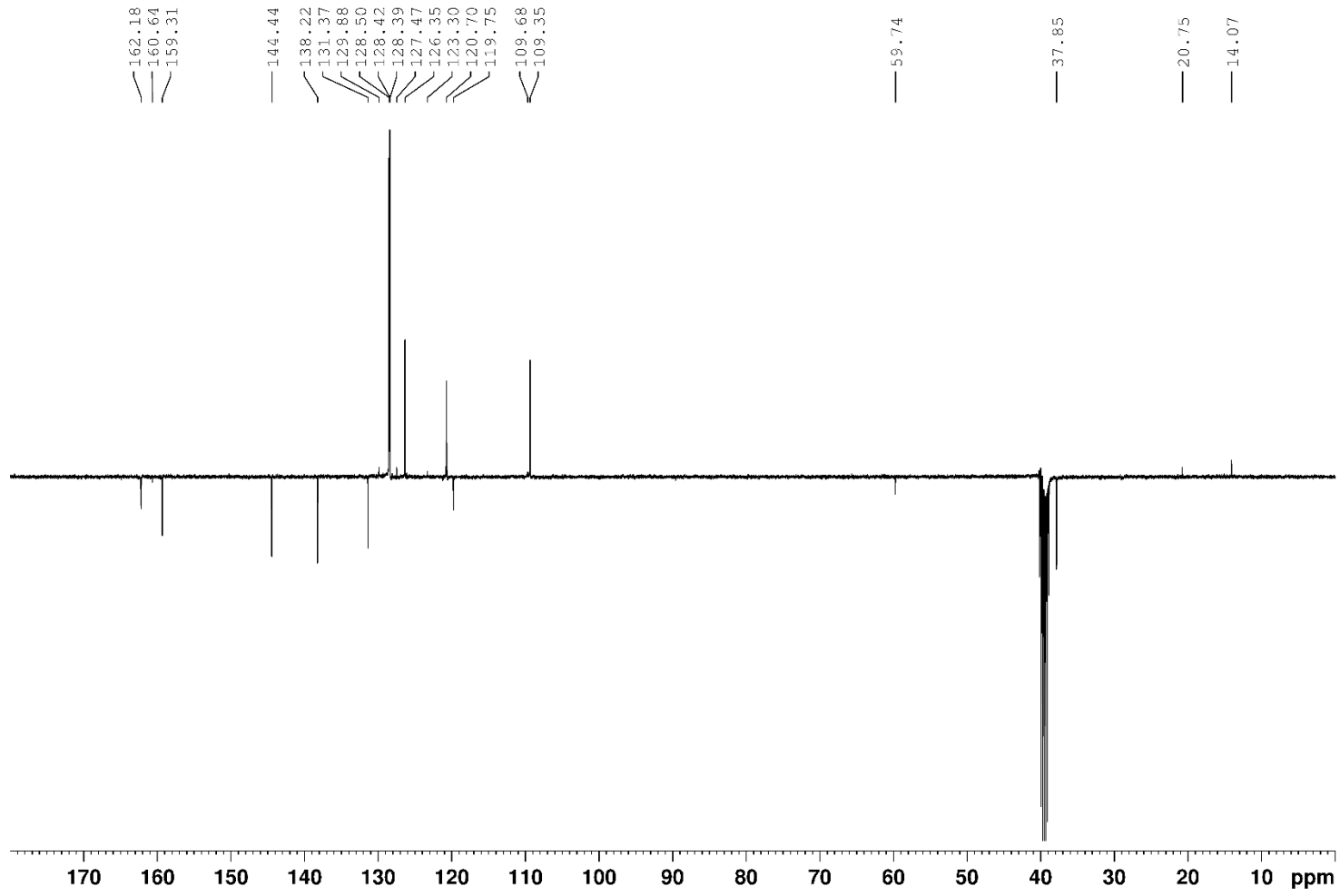
^{13}C NMR (APT) Compound 38



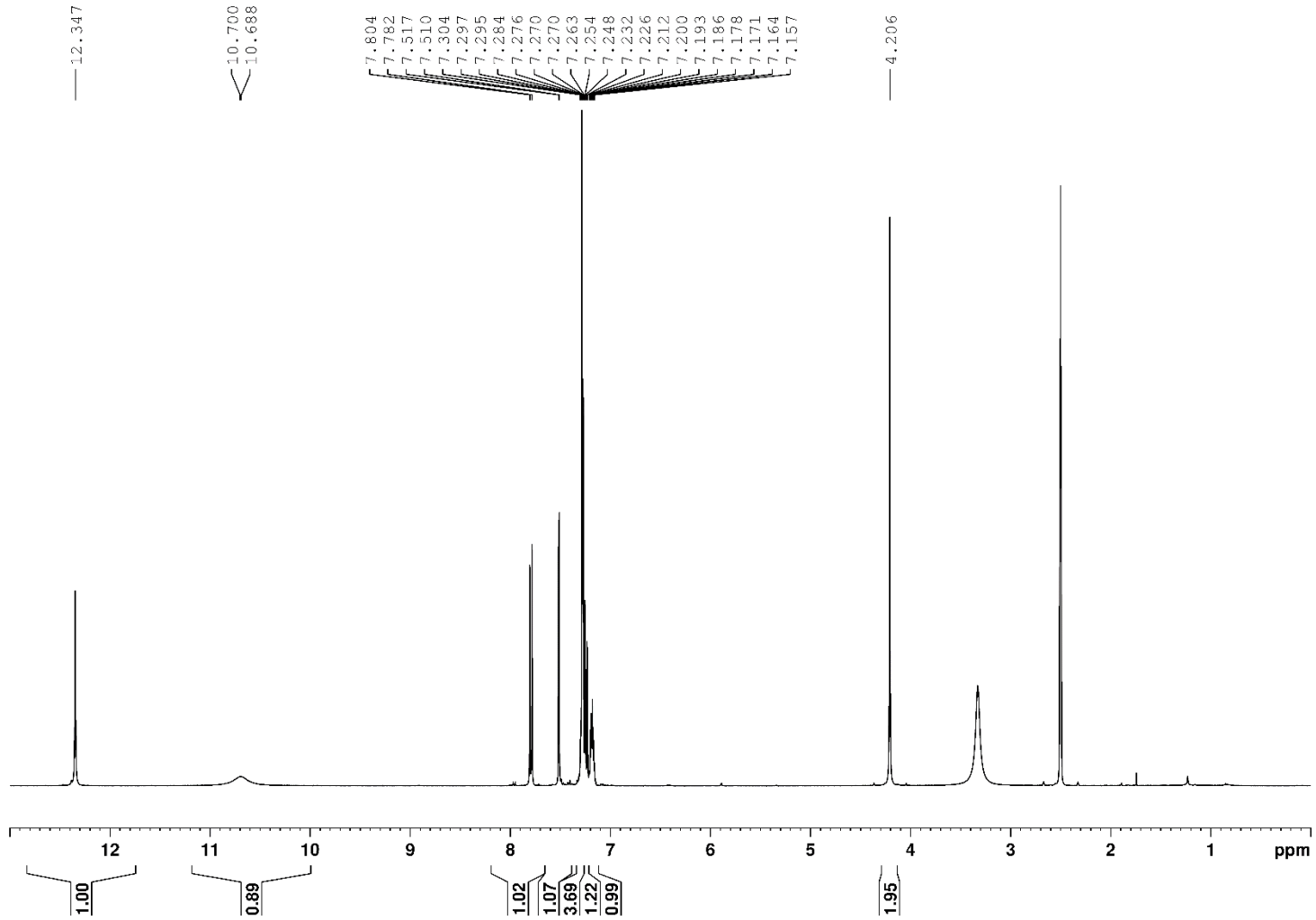
^{1}H NMR Compound 39



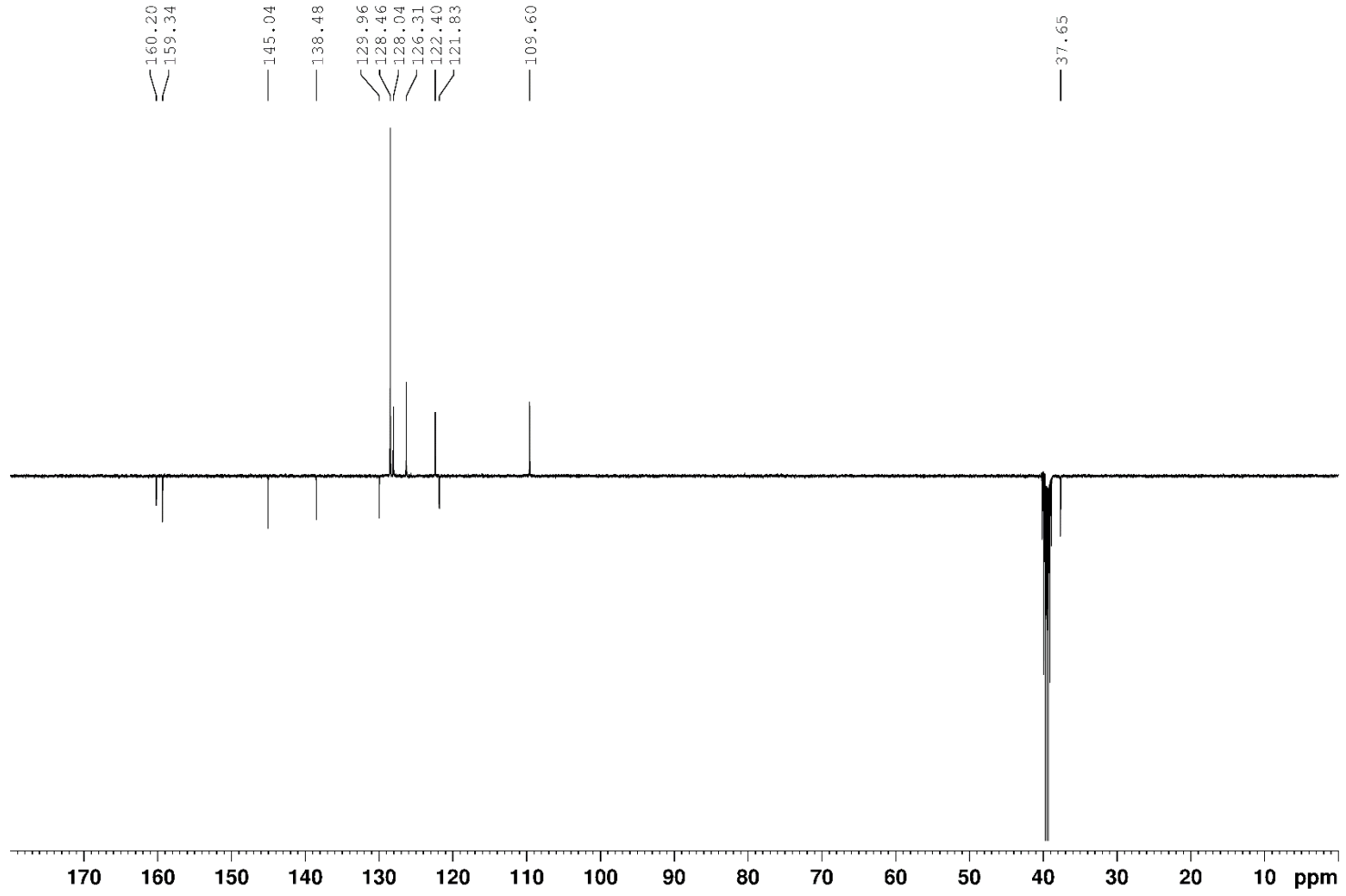
^{13}C NMR (APT) Compound 39



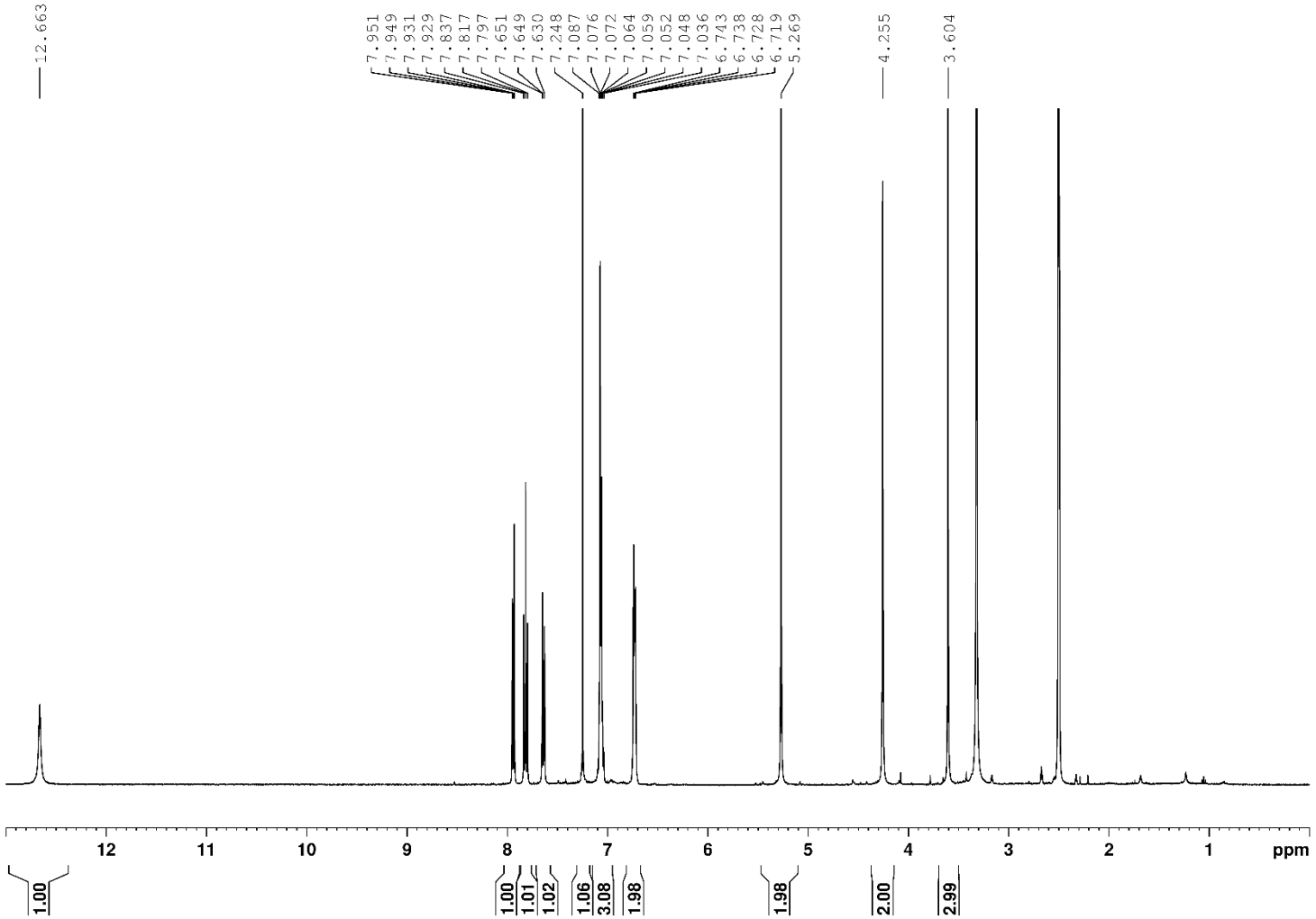
^{1}H NMR Compound 40



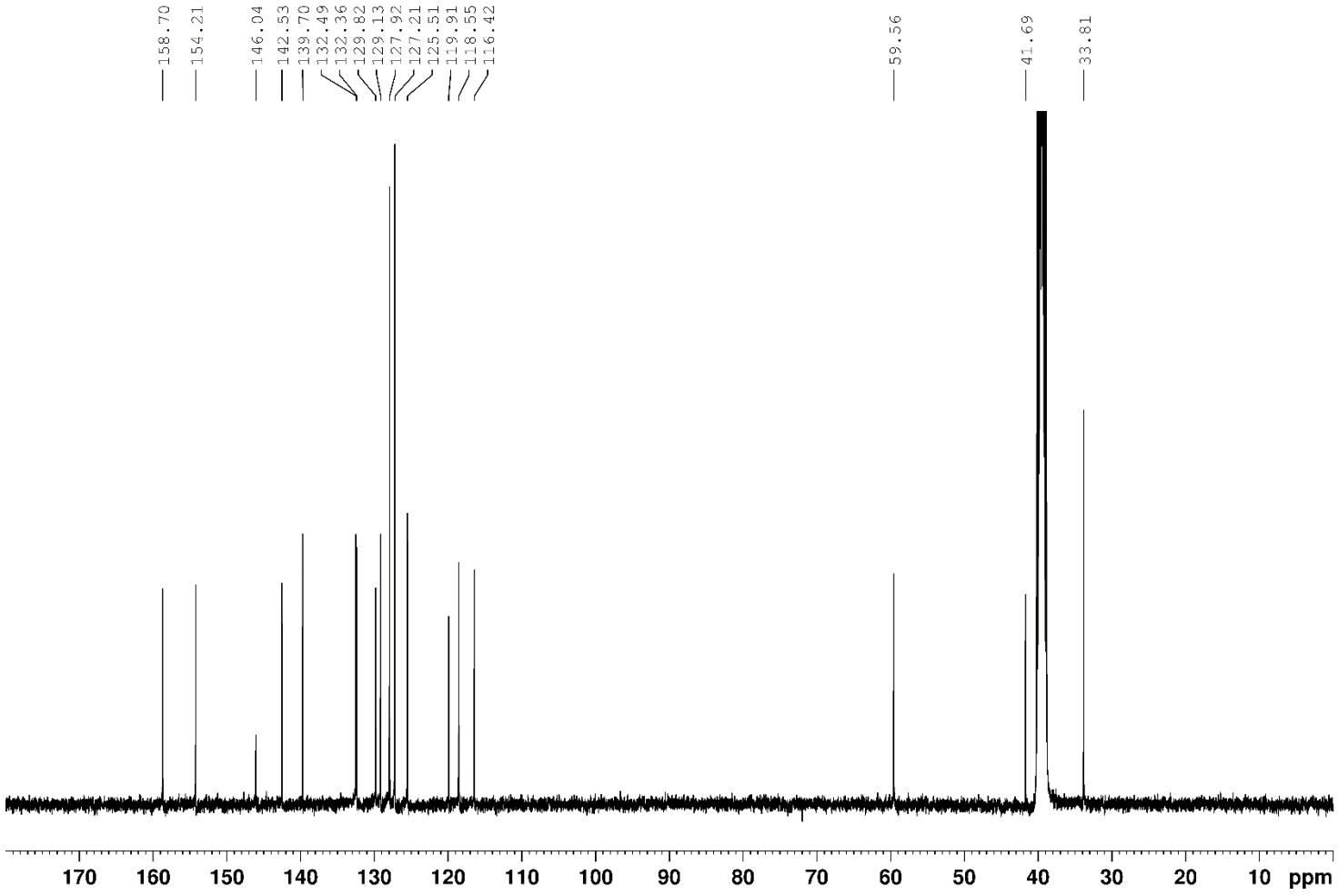
^{13}C NMR (APT) Compound 40



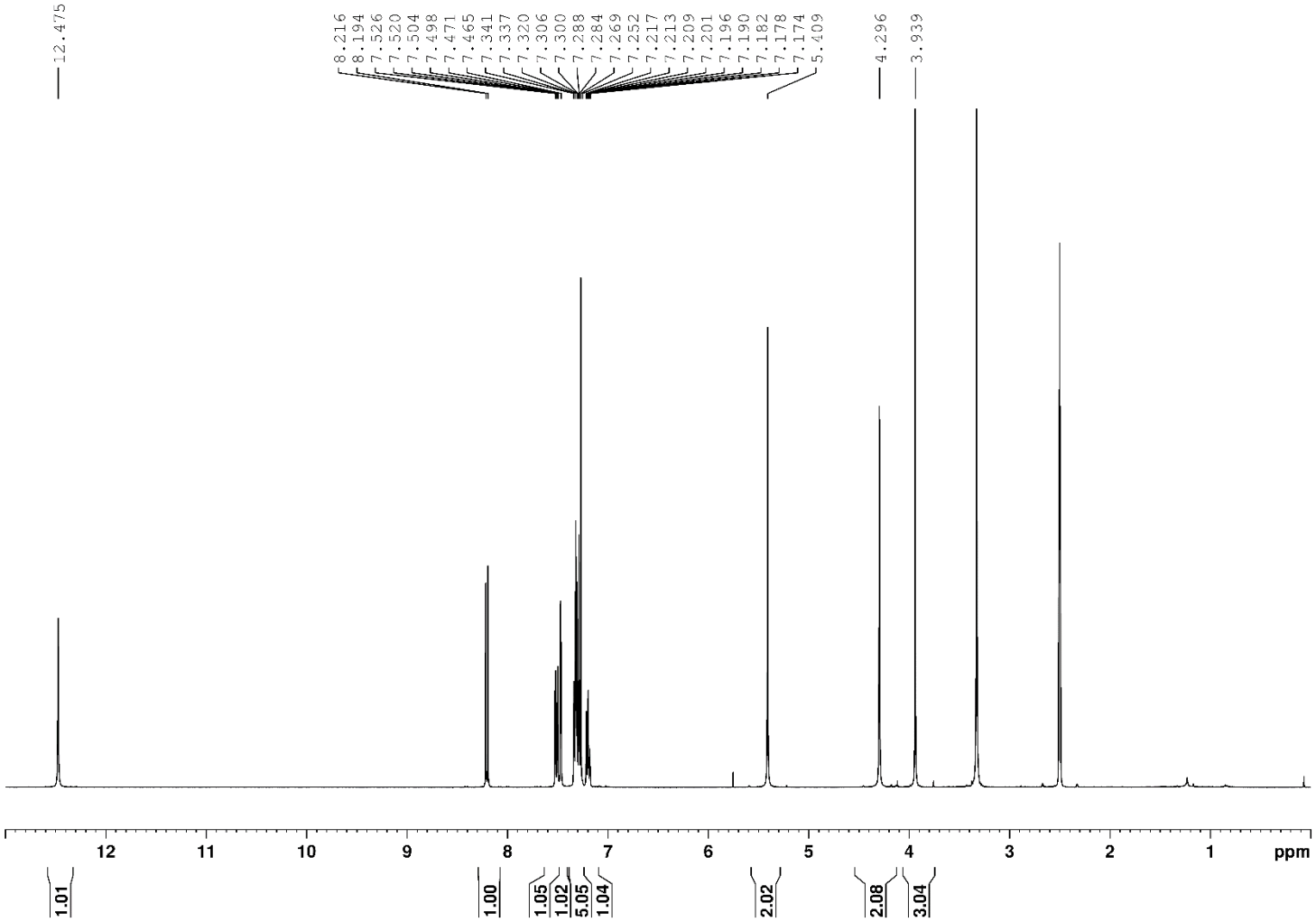
^{1}H NMR Compound 44



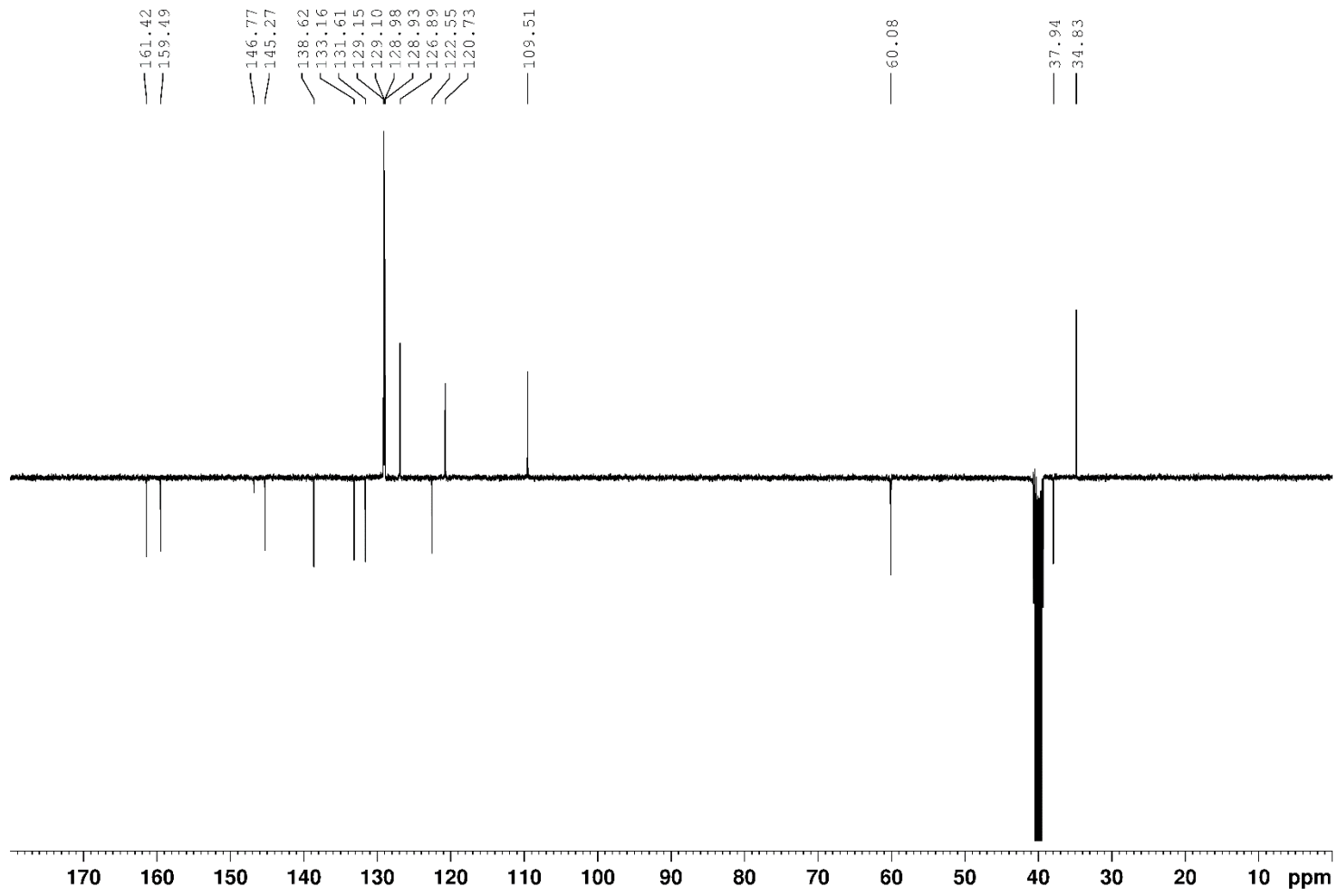
^{13}C NMR Compound 44



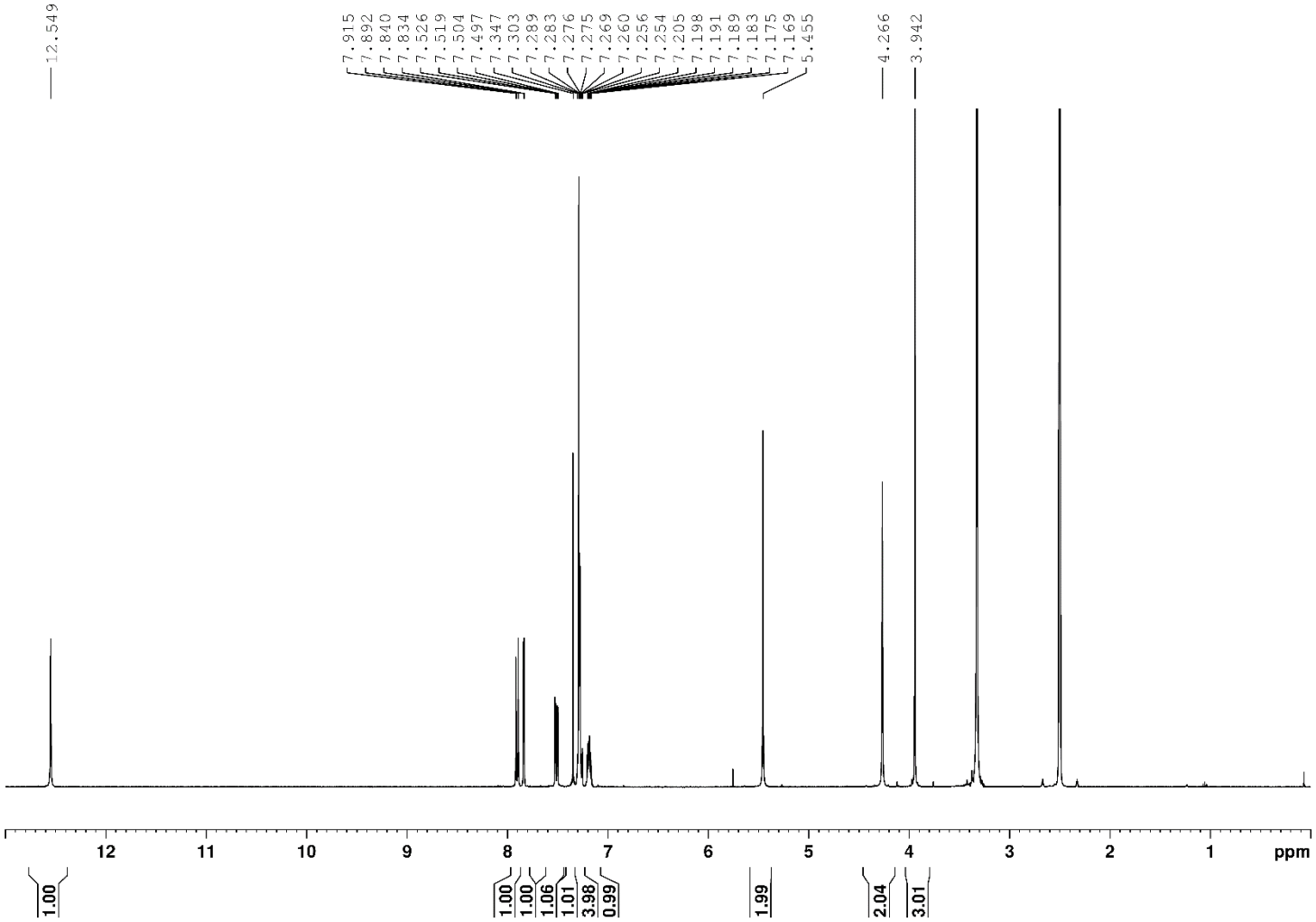
^{1}H NMR Compound 45



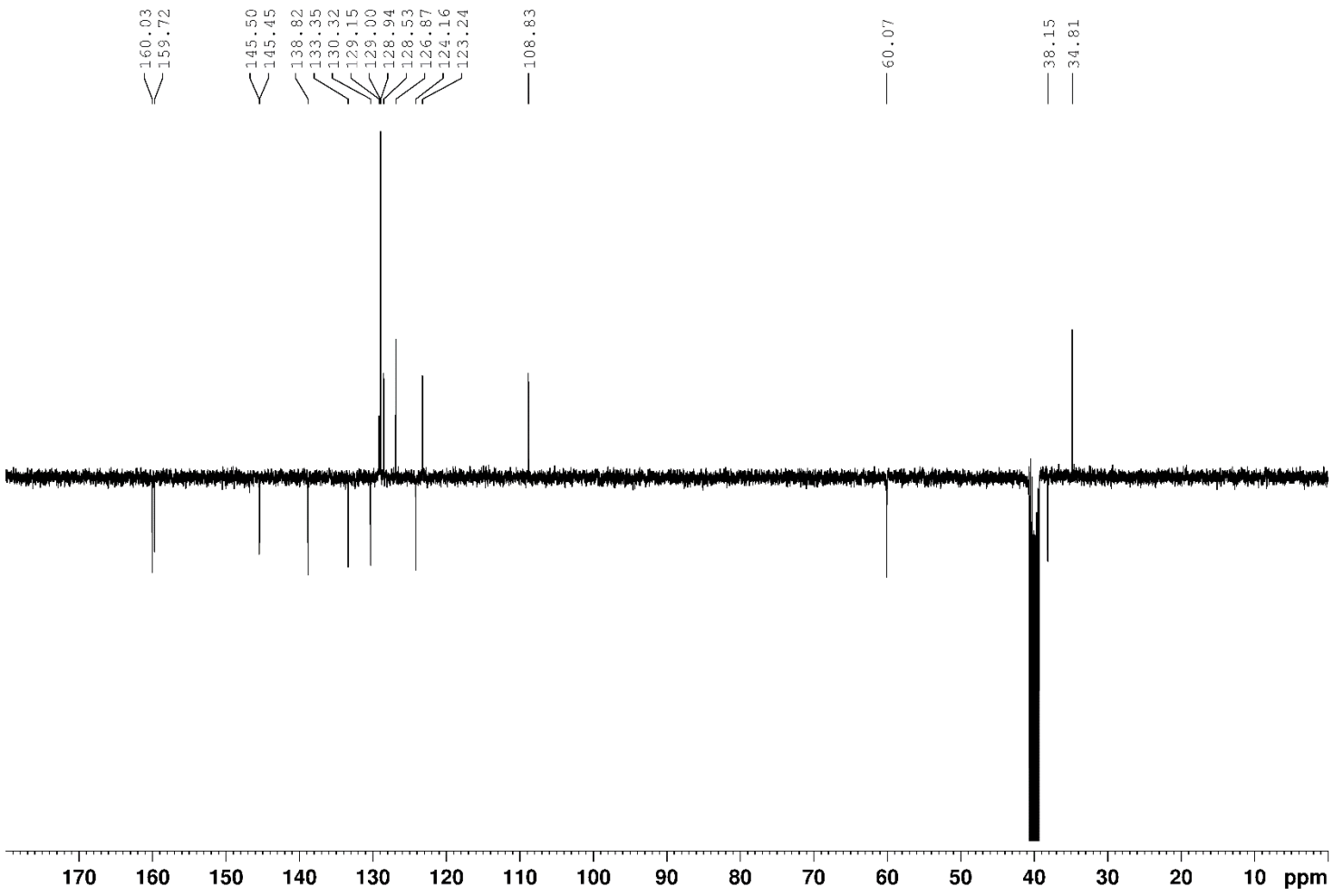
^{13}C NMR (APT) Compound 45



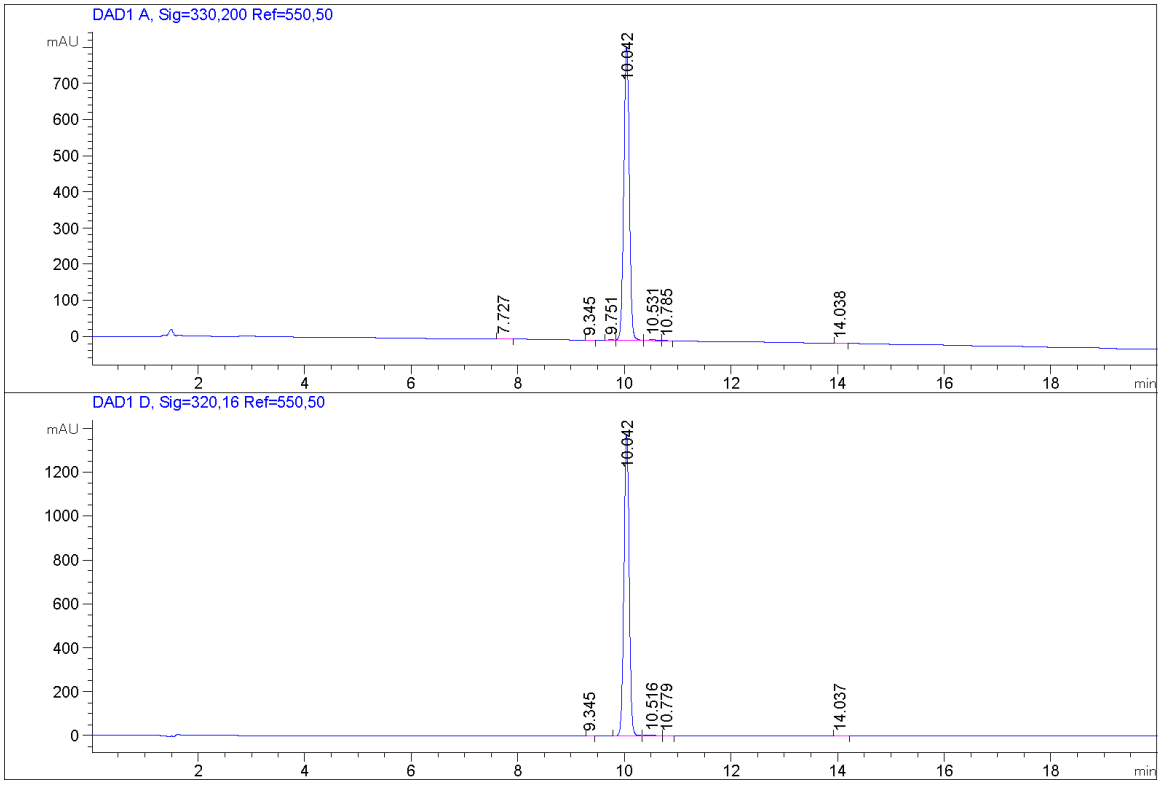
^{1}H NMR Compound 46



^{13}C NMR (APT) Compound 46



HPLC Compound 4



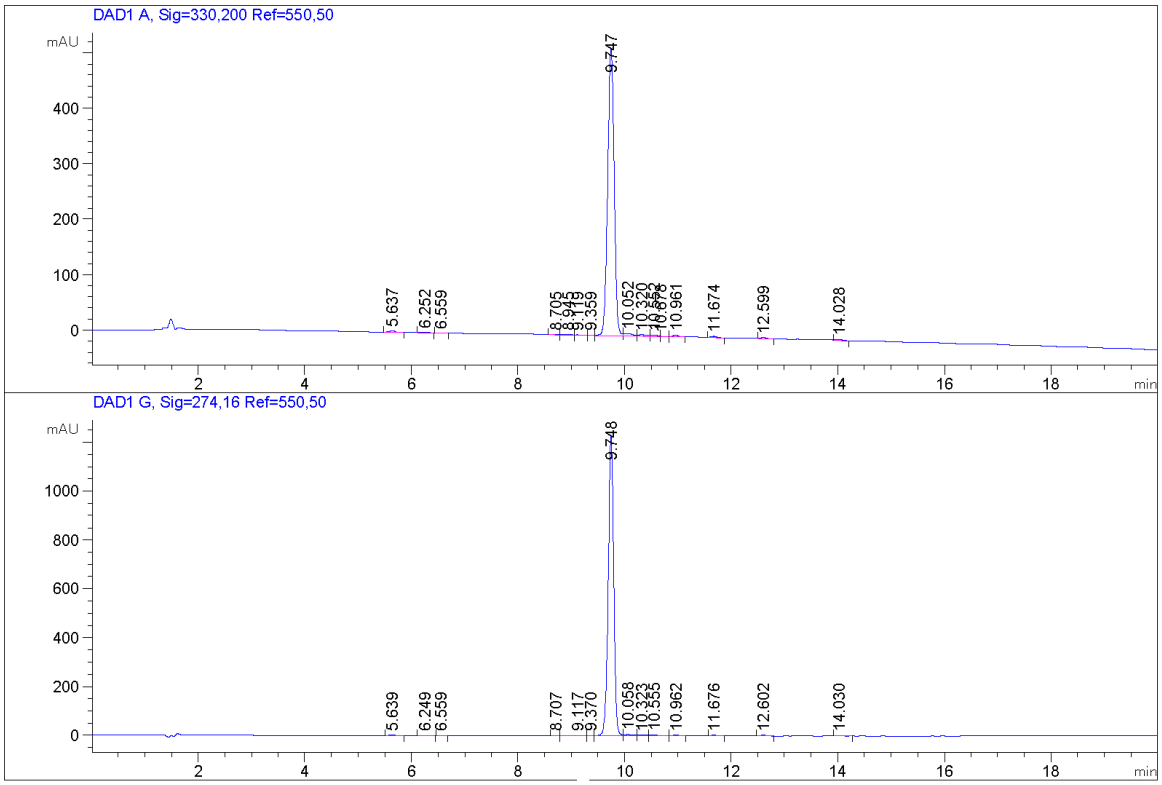
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.727	BB	0.1075	11.75733	1.72611	0.2005
2	9.345	MM	0.0965	1.81819	3.13892e-1	0.0310
3	9.751	MF	0.1037	12.87006	2.06860	0.2195
4	10.042	FM	0.1183	5795.53711	816.48138	98.8360
5	10.531	FM	0.1721	34.71669	3.36196	0.5921
6	10.785	FM	0.1344	2.44897	3.03666e-1	0.0418
7	14.038	MM	0.1091	4.64618	7.09625e-1	0.0792
Totals :				5863.79452	824.96523	

Signal 2: DAD1 D, Sig=320,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.345	MM	0.0761	1.07070	2.34443e-1	0.0115
2	10.042	FM	0.1116	9257.09277	1382.00073	99.2618
3	10.516	FM	0.2158	58.51730	4.52041	0.6275
4	10.779	FM	0.1402	2.82679	3.35930e-1	0.0303
5	14.037	BB	0.1016	6.42618	1.01804	0.0689
Totals :				9325.93374	1388.10956	

HPLC Compound 5



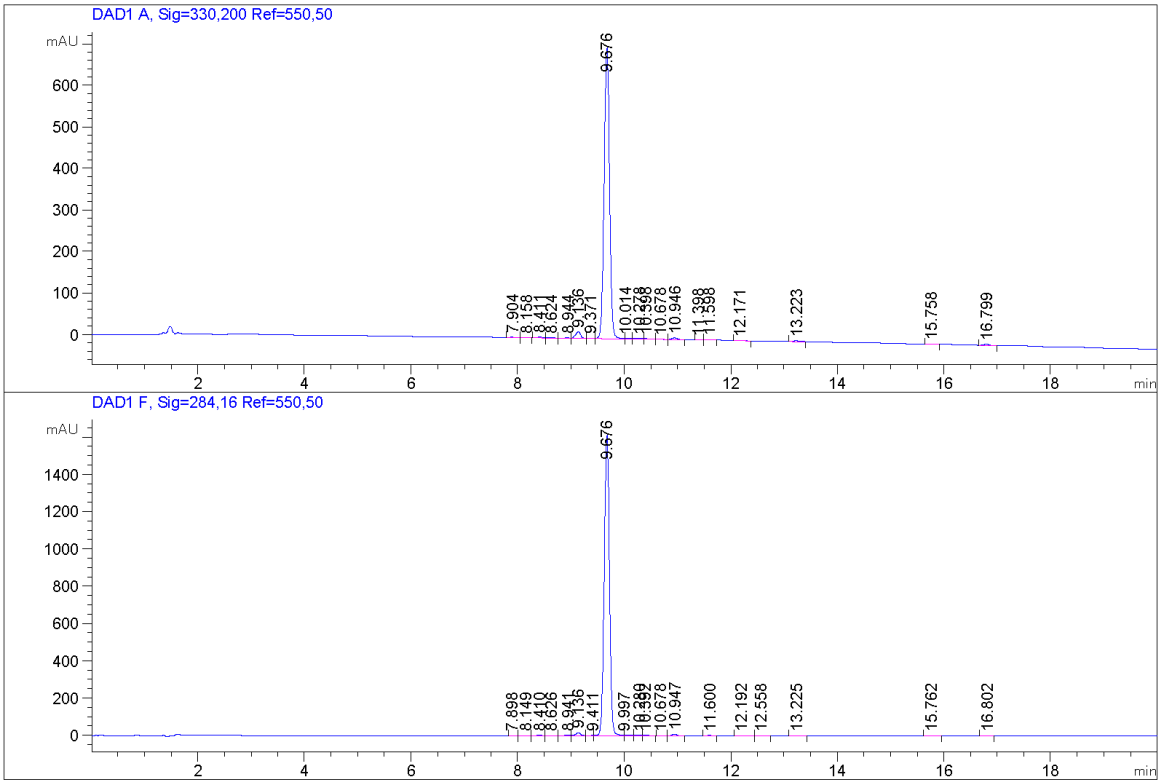
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.637	BB	0.1198	18.18447	2.31092	0.3966
2	6.252	MM	0.1170	2.55232	3.63564e-1	0.0557
3	6.559	MM	0.1160	1.52749	2.19373e-1	0.0333
4	8.705	MF	0.1096	4.48760	6.82128e-1	0.0979
5	8.945	FM	0.2010	8.43796	6.99805e-1	0.1840
6	9.119	FM	0.1943	7.88025	6.75934e-1	0.1719
7	9.359	FM	0.1193	4.00252	5.59142e-1	0.0873
8	9.747	FM	0.1399	4368.44580	520.47461	95.2774
9	10.052	FM	0.1808	50.56490	4.66221	1.1028
10	10.320	FM	0.1718	31.27438	3.03397	0.6821
11	10.552	FM	0.1269	20.68893	2.71728	0.4512
12	10.678	FM	0.1035	3.70106	5.95917e-1	0.0807
13	10.961	FM	0.1119	21.59909	3.21784	0.4711
14	11.674	BB	0.1031	15.15764	2.35580	0.3306
15	12.599	BB	0.1033	13.79095	2.13716	0.3008
16	14.028	VB	0.1035	12.67939	1.86152	0.2765
Totals :				4584.97476	546.56716	

Signal 2: DAD1 G, Sig=274,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.639	BB	0.1209	17.07057	2.24046	0.1890
2	6.249	BB	0.1169	9.17972	1.20413	0.1016
3	6.559	MM	0.1083	1.30608	2.00913e-1	0.0145
4	8.707	MF	0.1043	4.55193	7.27149e-1	0.0504
5	9.117	FM	0.3173	26.93488	1.41493	0.2982
6	9.370	FM	0.1256	6.65056	8.82820e-1	0.0736
7	9.748	FM	0.1180	8754.33398	1236.17505	96.9103
8	10.058	FM	0.1932	68.84543	5.94036	0.7621
9	10.323	FM	0.1521	34.15041	3.74257	0.3780
10	10.555	FM	0.1516	40.50114	4.45409	0.4483
11	10.962	FM	0.1165	25.91370	3.70673	0.2869
12	11.676	BB	0.1026	16.95728	2.65300	0.1877
13	12.602	BB	0.1042	16.34636	2.50260	0.1810
14	14.030	VB	0.1008	10.69770	1.62559	0.1184
Totals :				9033.43974	1267.47039	

HPLC Compound 6



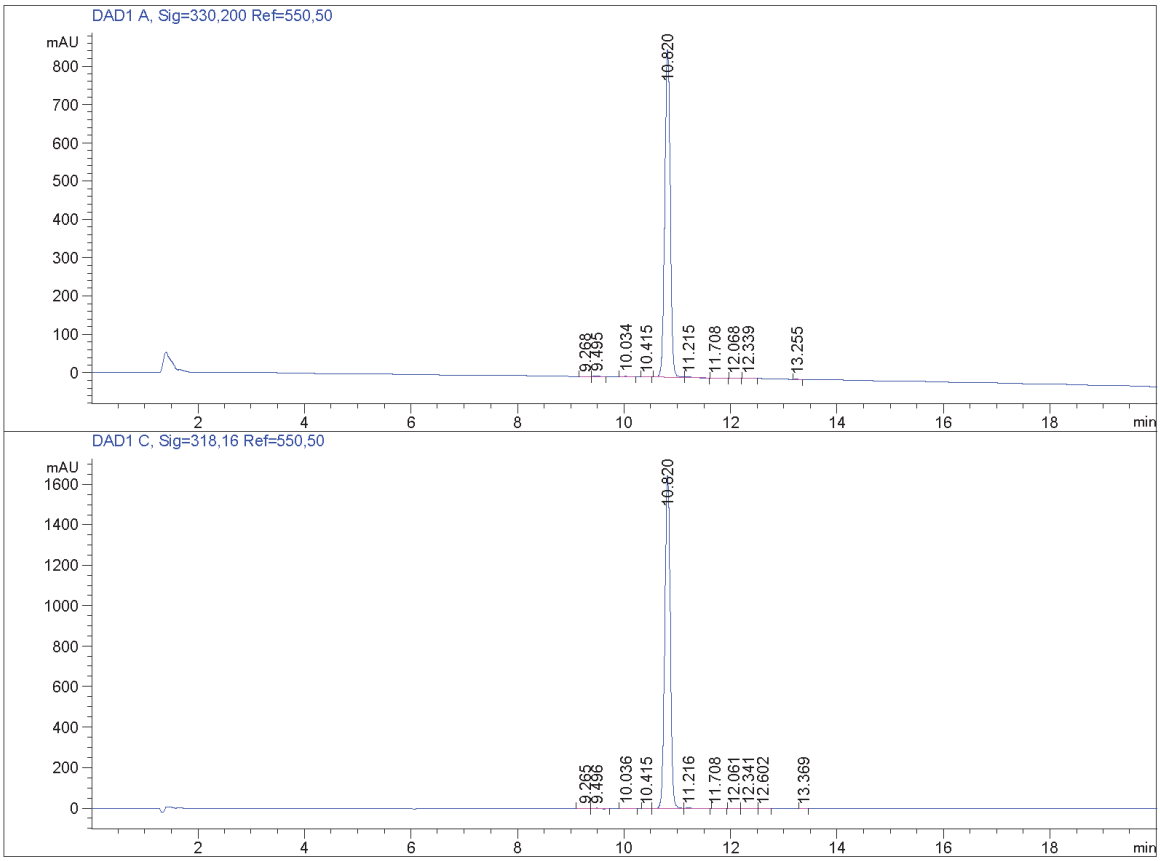
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.904	MM	0.1058	3.56522	5.61768e-1	0.0687
2	8.158	MM	0.0890	1.69985	3.18470e-1	0.0328
3	8.411	MF	0.1062	9.62270	1.50996	0.1855
4	8.624	MF	0.1403	7.09010	8.42230e-1	0.1367
5	8.944	MF	0.1677	9.22324	9.16861e-1	0.1778
6	9.136	MF	0.1090	102.09525	15.60889	1.9683
7	9.371	MF	0.1487	6.69319	7.50134e-1	0.1290
8	9.676	MF	0.1169	4938.46582	704.11267	95.2086
9	10.014	MF	0.1146	8.69852	1.26477	0.1677
10	10.278	MF	0.1619	13.22692	1.36150	0.2550
11	10.398	MF	0.1015	5.62420	9.23731e-1	0.1084
12	10.678	FM	0.1073	2.05109	3.18719e-1	0.0395
13	10.946	MM	0.1055	26.32039	4.15735	0.5074
14	11.398	MF	0.1065	1.04640	1.63762e-1	0.0202
15	11.598	MF	0.1069	8.37694	1.30620	0.1615
16	12.171	MM	0.1441	5.03327	5.81958e-1	0.0970
17	13.223	BB	0.1137	19.45991	2.64942	0.3752
18	15.758	MM	0.1121	4.08571	6.07180e-1	0.0788
19	16.799	BB	0.1133	14.61656	1.99864	0.2818
Totals :				5186.99528	739.95421	

Signal 2: DAD1 F, Sig=284,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.898	MF	0.0950	2.81639	4.93872e-1	0.0249
2	8.149	MF	0.1041	4.76618	7.62986e-1	0.0422
3	8.410	MF	0.1038	18.66243	2.99531	0.1651
4	8.626	MF	0.1598	15.93376	1.66199	0.1409
5	8.941	MF	0.1805	22.94137	2.11889	0.2029
6	9.136	MF	0.1159	105.27835	15.13420	0.9311
7	9.411	MF	0.1278	11.91934	1.55384	0.1054
8	9.676	MF	0.1128	1.09623e4	1619.64441	96.9532
9	9.997	MF	0.1059	23.70437	2.70946	0.2096
10	10.280	MF	0.1462	22.48327	2.56251	0.1988
11	10.392	FM	0.1194	15.94146	2.22541	0.1410
12	10.678	MM	0.0987	4.42833	7.47463e-1	0.0392
13	10.947	MM	0.1084	49.07473	7.54863	0.4340
14	11.600	FM	0.1045	14.59027	2.32761	0.1290
15	12.192	MF	0.1632	6.09994	6.23080e-1	0.0539
16	12.558	FM	0.1201	1.60356	2.22454e-1	0.0142
17	13.225	BB	0.1241	11.58981	1.40744	0.1025
18	15.762	BB	0.1117	7.97025	1.11108	0.0705
19	16.802	MM	0.1120	4.68887	6.97820e-1	0.0415
Totals :				1.13068e4	1666.54845	

HPLC Compound 7



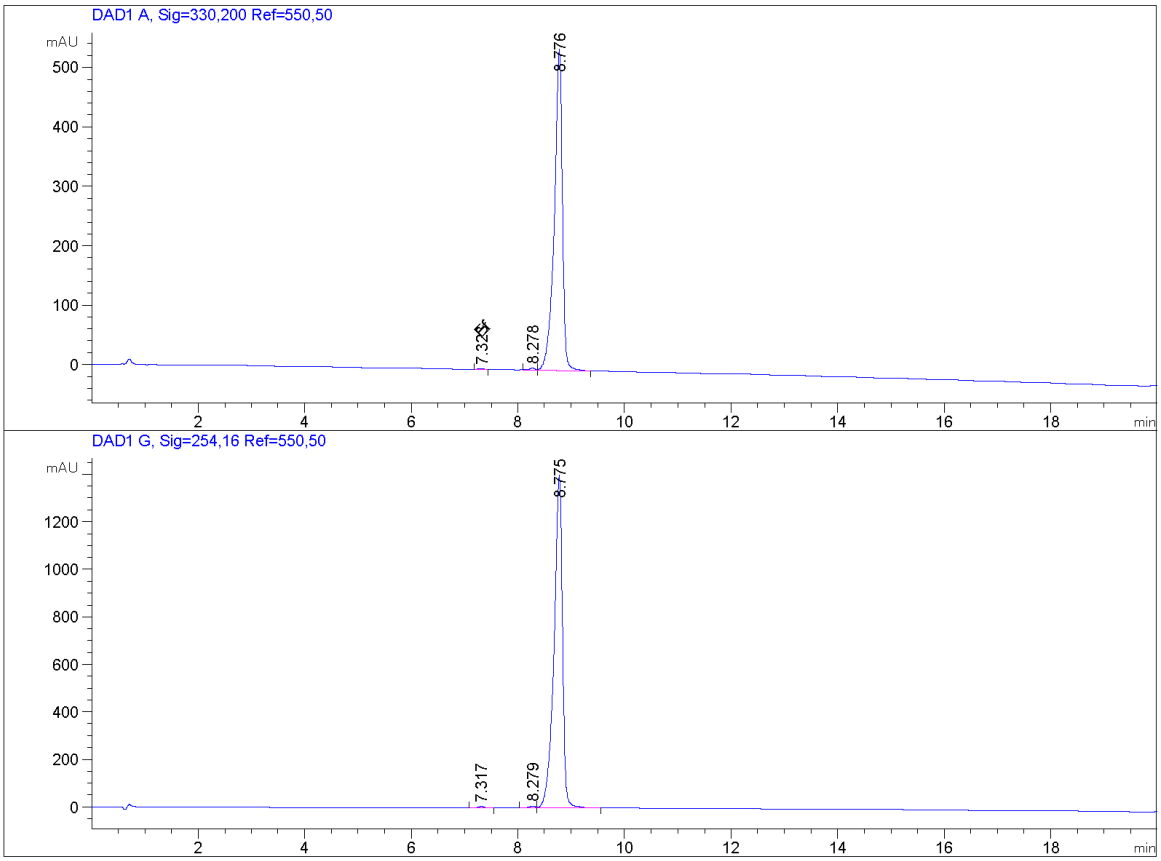
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.268	MF	0.1311	1.72087	2.18778e-1	0.0282
2	9.495	FM	0.1061	10.38393	1.63179	0.1703
3	10.034	BB	0.1015	11.63047	1.75014	0.1907
4	10.415	MM	0.0966	1.62253	2.79957e-1	0.0266
5	10.820	MF	0.1167	6040.02783	862.69769	99.0406
6	11.215	FM	0.1497	18.45611	2.05527	0.3026
7	11.708	MM	0.1856	1.94787	1.74941e-1	0.0319
8	12.068	MM	0.1110	2.32211	3.48555e-1	0.0381
9	12.339	MM	0.1139	8.85413	1.29591	0.1452
10	13.255	MM	0.0949	1.57108	2.75791e-1	0.0258
Totals :				6098.53694	870.72882	

Signal 2: DAD1 C, Sig=318,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.265	MF	0.1260	3.46477	4.58295e-1	0.0295
2	9.496	FM	0.1083	19.66725	3.02642	0.1672
3	10.036	BB	0.1017	14.86017	2.23210	0.1264
4	10.415	MM	0.0908	1.63078	2.99336e-1	0.0139
5	10.820	MF	0.1170	1.16548e4	1660.62476	99.1099
6	11.216	FM	0.1527	34.59153	3.77521	0.2942
7	11.708	MM	0.1854	2.65404	2.38527e-1	0.0226
8	12.061	MF	0.1158	4.50979	6.48891e-1	0.0384
9	12.341	MF	0.1215	18.07388	2.48013	0.1537
10	12.602	MF	0.1768	3.25558	3.06947e-1	0.0277
11	13.369	MM	0.1004	1.96588	3.26457e-1	0.0167
Totals :				1.17595e4	1674.41707	

HPLC Compound 8



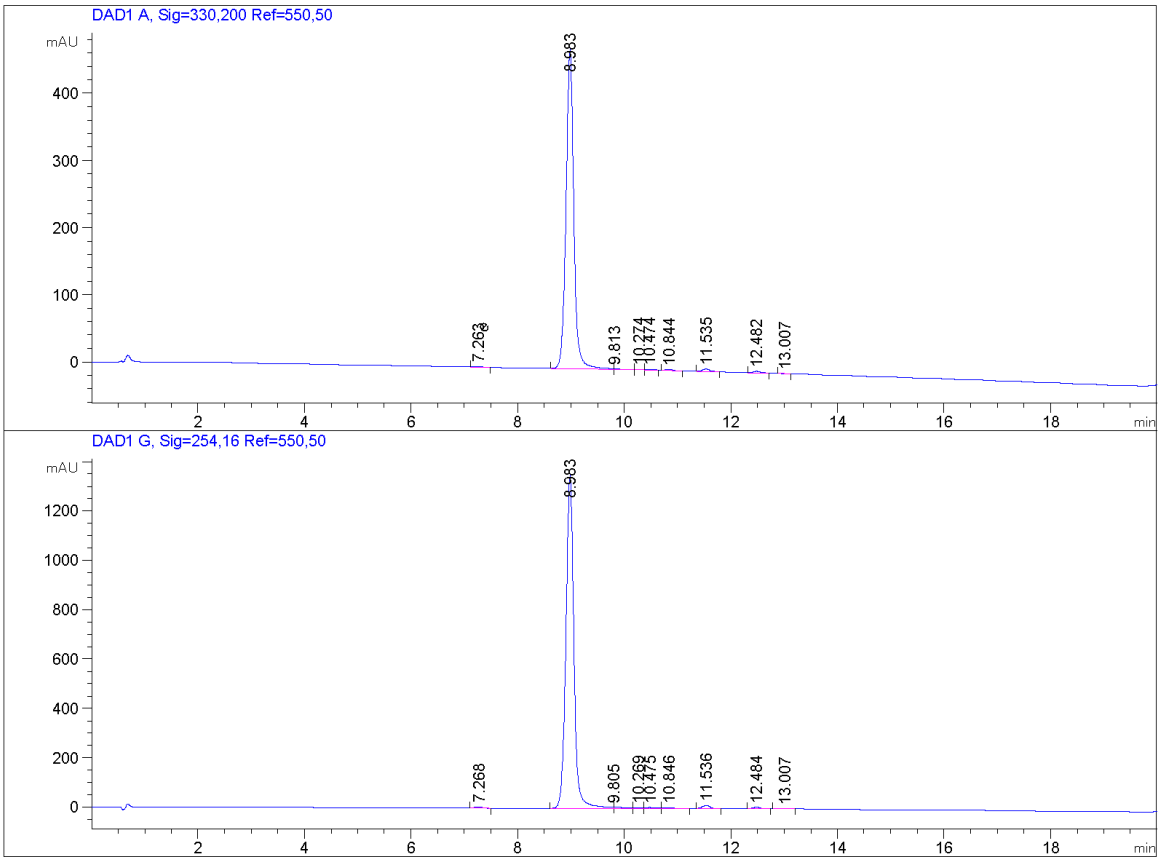
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.323	MM	0.1189	9.33224	1.30863	0.1622
2	8.278	BV	0.1316	28.16499	3.17270	0.4896
3	8.776	VB	0.1554	5714.62744	540.30011	99.3481
Totals :				5752.12467	544.78144	

Signal 2: DAD1 G, Sig=254,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.317	BB	0.1328	60.44975	6.72714	0.3852
2	8.279	BV	0.1316	74.70703	8.09972	0.4761
3	8.775	VB	0.1655	1.55569e4	1401.67444	99.1387
Totals :				1.56920e4	1416.50129	

HPLC Compound 9



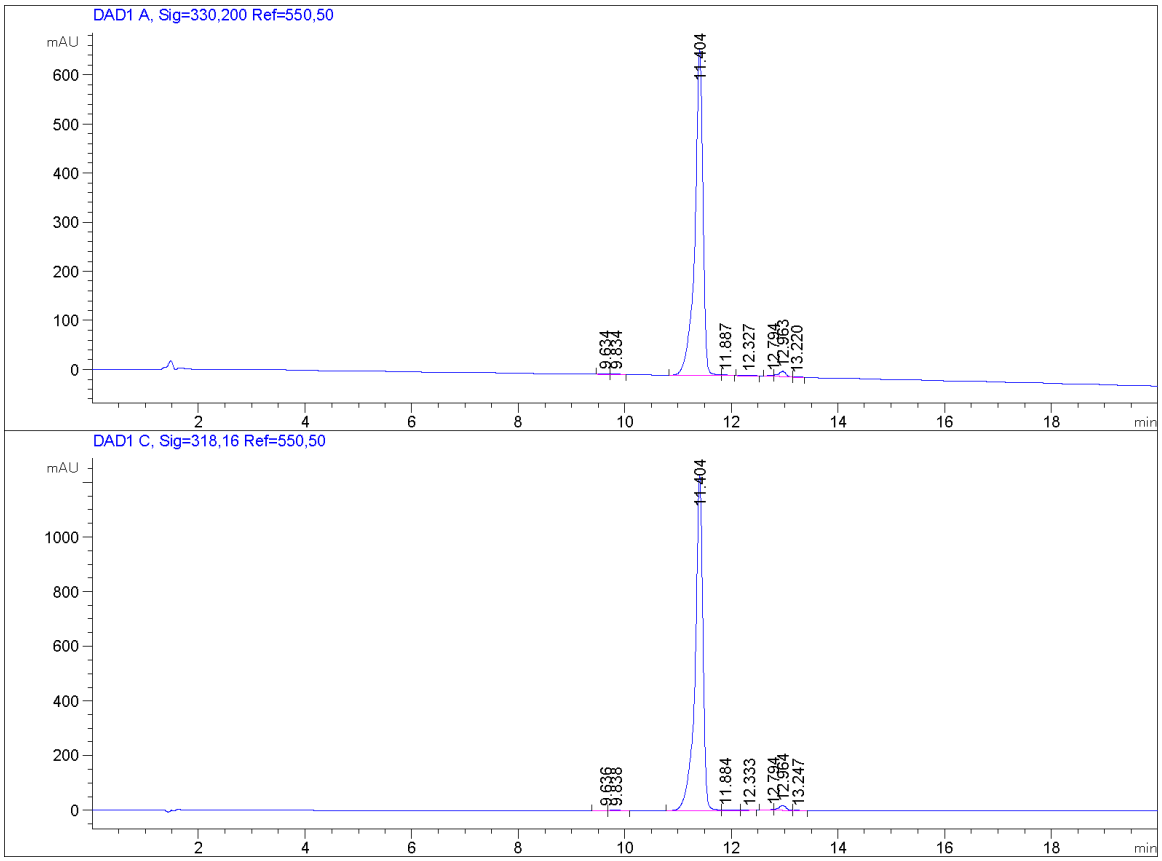
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.263	BB	0.1295	8.96987	1.07332	0.1820
2	8.983	MF	0.1688	4828.12061	476.62775	97.9373
3	9.813	FM	0.2027	12.75467	1.04896	0.2587
4	10.274	FM	0.1529	5.84979	6.37674e-1	0.1187
5	10.474	FM	0.1540	5.93827	6.42651e-1	0.1205
6	10.844	BB	0.1257	9.83322	1.22485	0.1995
7	11.535	BB	0.1407	37.63882	4.03996	0.7635
8	12.482	BB	0.1380	19.66622	2.16490	0.3989
9	13.007	MM	0.1230	1.03492	1.40201e-1	0.0210
Totals :				4929.80637	487.60025	

Signal 2: DAD1 G, Sig=254,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.268	BB	0.1308	40.44790	4.77439	0.2817
2	8.983	MF	0.1722	1.39697e4	1352.39001	97.2977
3	9.805	FM	0.2368	59.56230	4.19212	0.4148
4	10.269	FM	0.1895	29.30147	2.57722	0.2041
5	10.475	FM	0.2293	42.92558	3.11965	0.2990
6	10.846	FM	0.2061	33.09069	2.67655	0.2305
7	11.536	BB	0.1409	120.07300	12.86047	0.8363
8	12.484	BB	0.1385	56.24610	6.16137	0.3917
9	13.007	MM	0.1886	6.34873	5.60905e-1	0.0442
Totals :				1.43577e4	1389.31268	

HPLC Compound 10



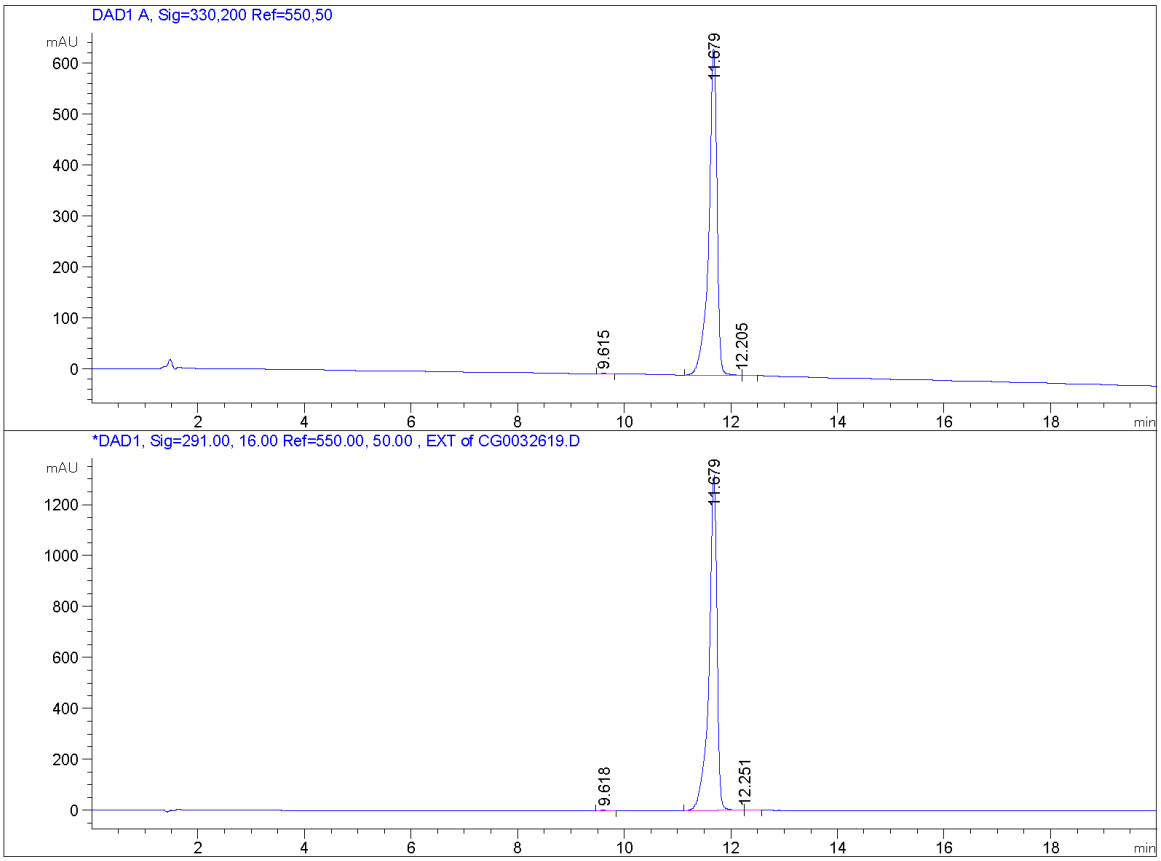
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.634	MF	0.1572	8.22762	8.72504e-1	0.1158
2	9.834	FM	0.1465	11.18903	1.27318	0.1575
3	11.404	MF	0.1740	6942.24268	665.11871	97.7168
4	11.887	FM	0.1536	13.24840	1.43800	0.1865
5	12.327	MM	0.2014	8.13280	6.73106e-1	0.1145
6	12.794	MF	0.0899	15.13313	2.80692	0.2130
7	12.963	FM	0.1577	102.22871	10.80432	1.4389
8	13.220	FM	0.1293	4.05084	5.22011e-1	0.0570
Totals :				7104.45321	683.50876	

Signal 2: DAD1 C, Sig=318,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.636	MF	0.1534	9.40972	1.02234	0.0741
2	9.838	FM	0.1651	23.41307	2.36302	0.1843
3	11.404	MF	0.1681	1.24302e4	1232.57166	97.8354
4	11.884	FM	0.1780	33.52730	3.13985	0.2639
5	12.333	FM	0.1605	6.23373	6.47303e-1	0.0491
6	12.794	MF	0.1031	28.55816	4.61488	0.2248
7	12.964	FM	0.1543	170.28780	18.39075	1.3403
8	13.247	FM	0.1138	3.58803	5.25305e-1	0.0282
Totals :				1.27052e4	1263.27511	

HPLC Compound 11



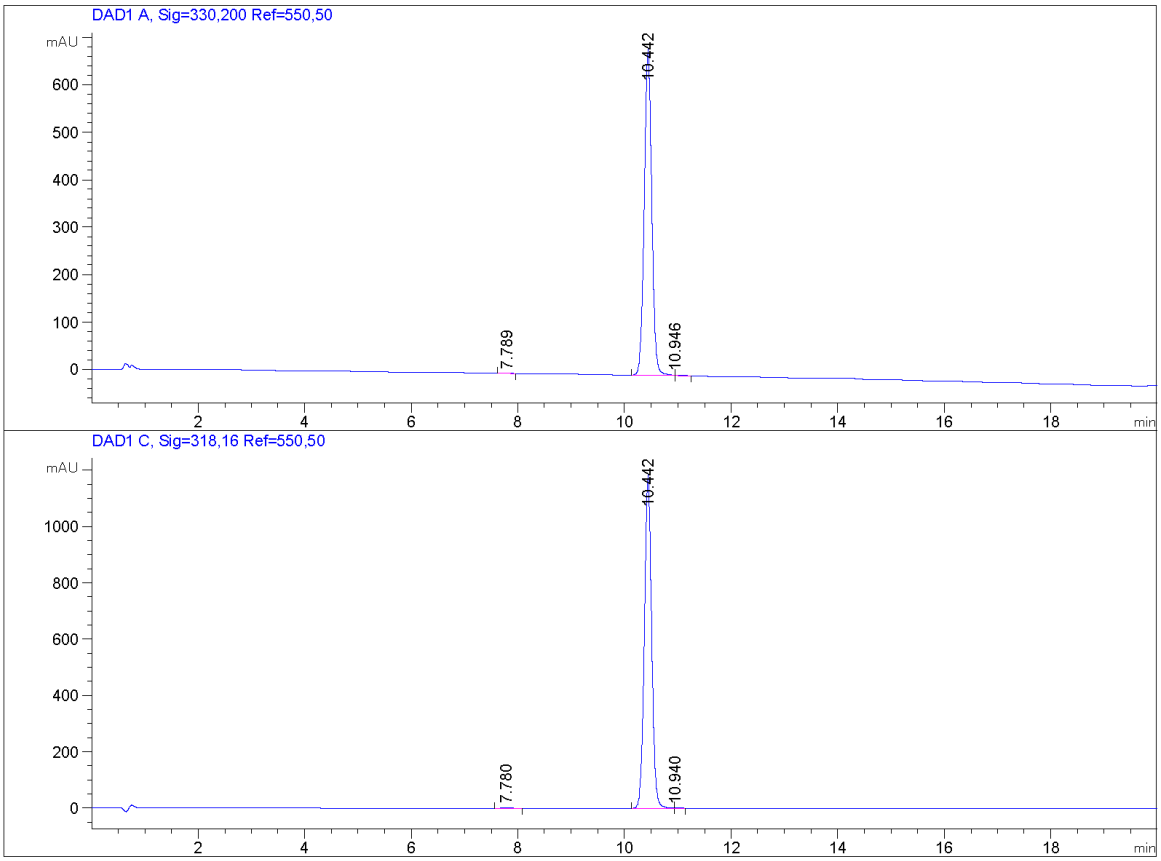
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.615	BB	0.1243	9.36506	1.13425	0.1371
2	11.679	MF	0.1767	6812.16553	642.65698	99.7393
3	12.205	FM	0.1469	8.43945	9.57526e-1	0.1236
Totals :				6829.97004	644.74876	

Signal 2: DAD1, Sig=291.00, 16.00 Ref=550.00, 50.00 , EXT

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.618	BB	0.1260	13.92036	1.72773	0.1021
2	11.679	MF	0.1693	1.36119e4	1340.29089	99.8311
3	12.251	FM	0.1198	9.11127	1.26757	0.0668
Totals :				1.36349e4	1343.28619	

HPLC Compound 18



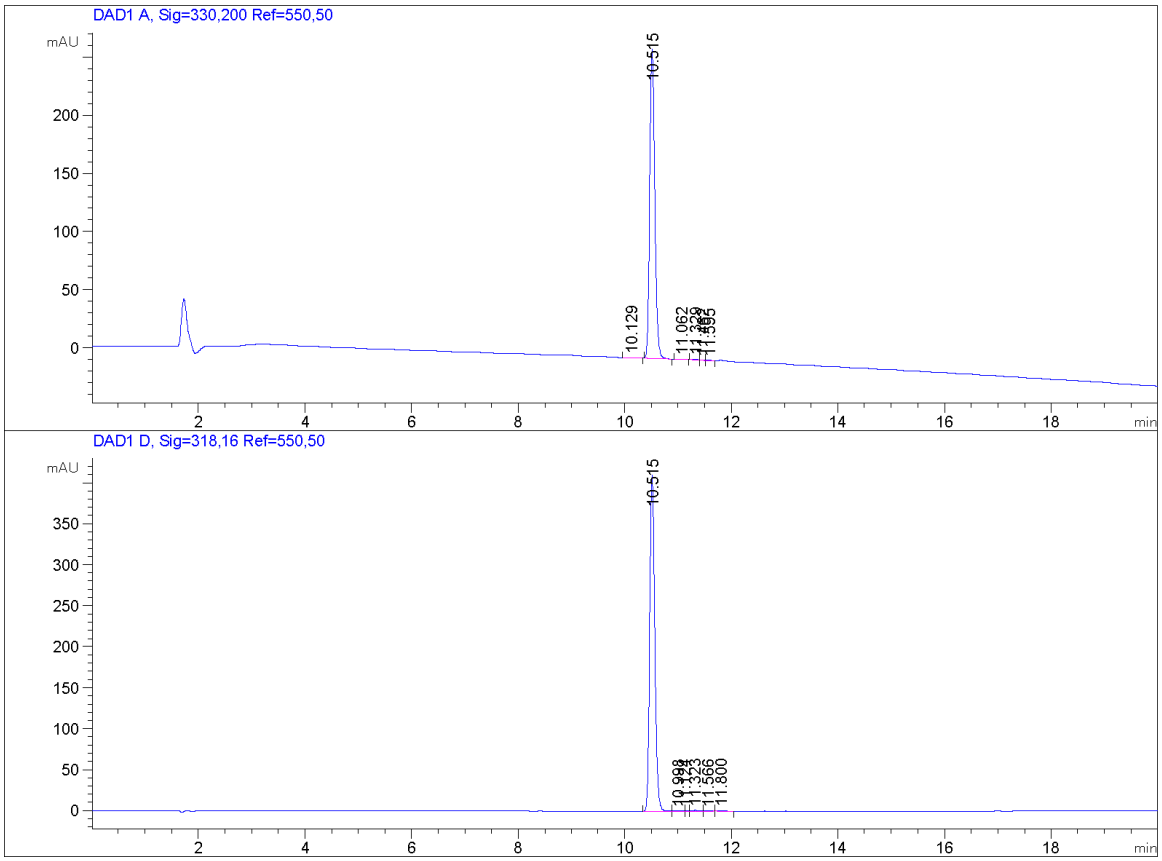
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.789	MM	0.1835	9.03691	8.21007e-1	0.1332
2	10.442	MF	0.1636	6761.18408	688.59430	99.6827
3	10.946	FM	0.1363	12.48178	1.52576	0.1840
Totals :				6782.70277	690.94107	

Signal 2: DAD1 C, Sig=318,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.780	BB	0.1738	40.69121	3.54754	0.3585
2	10.442	MF	0.1585	1.12943e4	1187.36853	99.5164
3	10.940	FM	0.1463	14.18865	1.61590	0.1250
Totals :				1.13492e4	1192.53197	

HPLC Compound 38



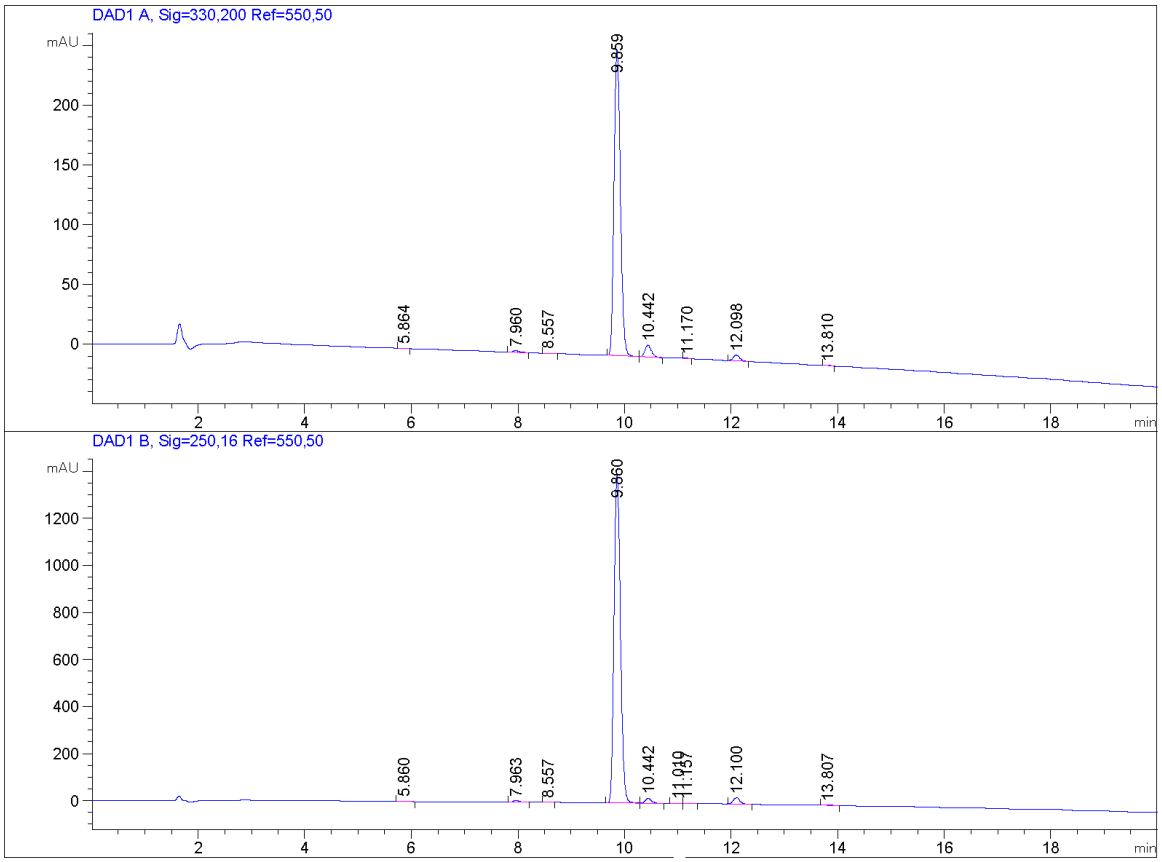
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.129	MM	0.1912	3.01423	2.62811e-1	0.1699
2	10.515	MM	0.1098	1759.11926	267.06094	99.1550
3	11.062	MM	0.1535	2.49148	2.70486e-1	0.1404
4	11.329	MF	0.1030	4.45789	7.21103e-1	0.2513
5	11.462	MF	0.1073	1.93765	3.01009e-1	0.1092
6	11.595	FM	0.1050	3.08968	4.90312e-1	0.1742
Totals :				1774.11019	269.10666	

Signal 2: DAD1 D, Sig=318,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.515	MF	0.1096	2707.84473	411.59457	99.1490
2	10.998	FM	0.1913	4.78554	4.16963e-1	0.1752
3	11.124	FM	0.0805	1.12226	2.32425e-1	0.0411
4	11.323	FM	0.1206	9.17852	1.26862	0.3361
5	11.566	FM	0.1069	3.25396	5.07408e-1	0.1191
6	11.800	MM	0.1068	4.90164	7.64929e-1	0.1795
Totals :				2731.08664	414.78491	

HPLC Compound 39



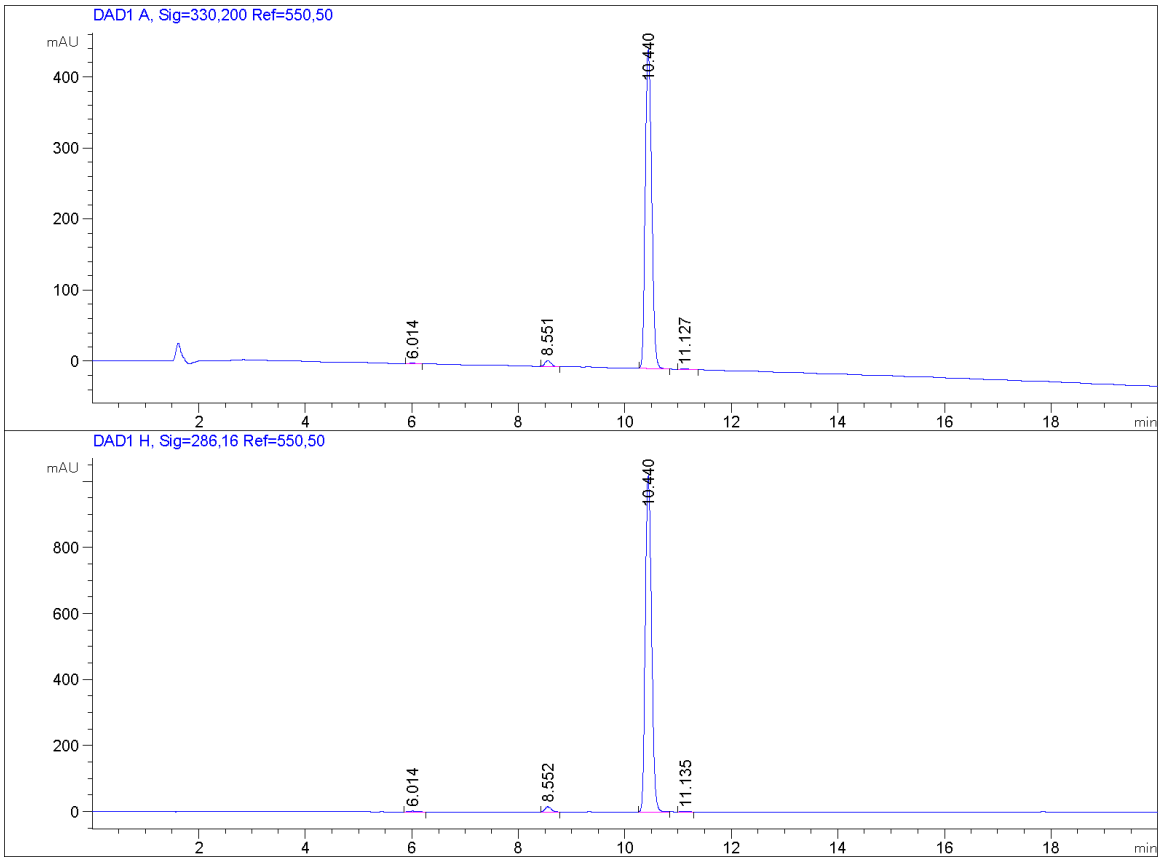
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.864	MM	0.1141	1.00763	1.47135e-1	0.0447
2	7.960	MM	0.1354	10.89578	1.34153	0.4832
3	8.557	MM	0.1359	1.90896	2.34164e-1	0.0847
4	9.859	MF	0.1367	2114.14819	257.71332	93.7519
5	10.442	FM	0.1384	83.43619	10.05059	3.7000
6	11.170	FM	0.1014	1.19145	1.95883e-1	0.0528
7	12.098	BB	0.1282	40.29640	4.88599	1.7869
8	13.810	MM	0.1217	2.16050	2.95928e-1	0.0958
Totals :				2255.04511	274.86454	

Signal 2: DAD1 B, Sig=250,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.860	BB	0.1407	9.77839	1.01236	0.0812
2	7.963	BB	0.1250	56.95283	7.14178	0.4731
3	8.557	MM	0.1303	3.17456	4.06126e-1	0.0264
4	9.860	MF	0.1377	1.15466e4	1397.05493	95.9148
5	10.442	FM	0.1400	169.84541	20.22128	1.4109
6	11.010	MF	0.1326	7.47281	9.39391e-1	0.0621
7	11.157	FM	0.1336	5.86704	7.31655e-1	0.0487
8	12.100	BB	0.1281	223.90973	27.17718	1.8600
9	13.807	BB	0.1335	14.79097	1.70021	0.1229
Totals :				1.20383e4	1456.38492	

HPLC Compound 40



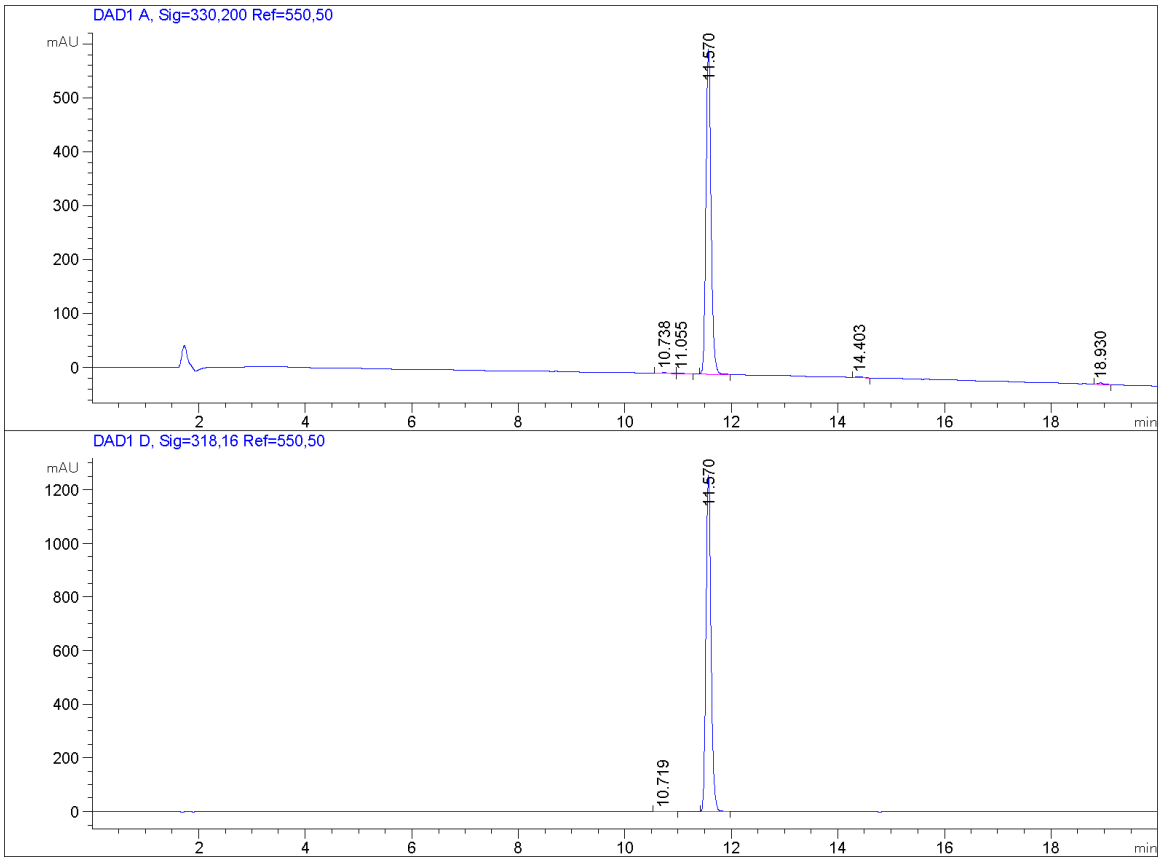
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.014	MM	0.1306	6.53320	8.33988e-1	0.1726
2	8.551	BB	0.1242	62.63586	7.92926	1.6547
3	10.440	BB	0.1323	3706.57666	449.04364	97.9204
4	11.127	BB	0.1450	9.55159	1.02226	0.2523
Totals :				3785.29732	458.82915	

Signal 2: DAD1 H, Sig=286,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.014	BB	0.1382	15.91976	1.74943	0.1912
2	8.552	BB	0.1258	127.24166	15.83137	1.5283
3	10.440	BB	0.1295	8175.51563	1020.15442	98.1973
4	11.135	MM	0.1324	6.92784	8.72410e-1	0.0832
Totals :				8325.60489	1038.60762	

HPLC Compound 44



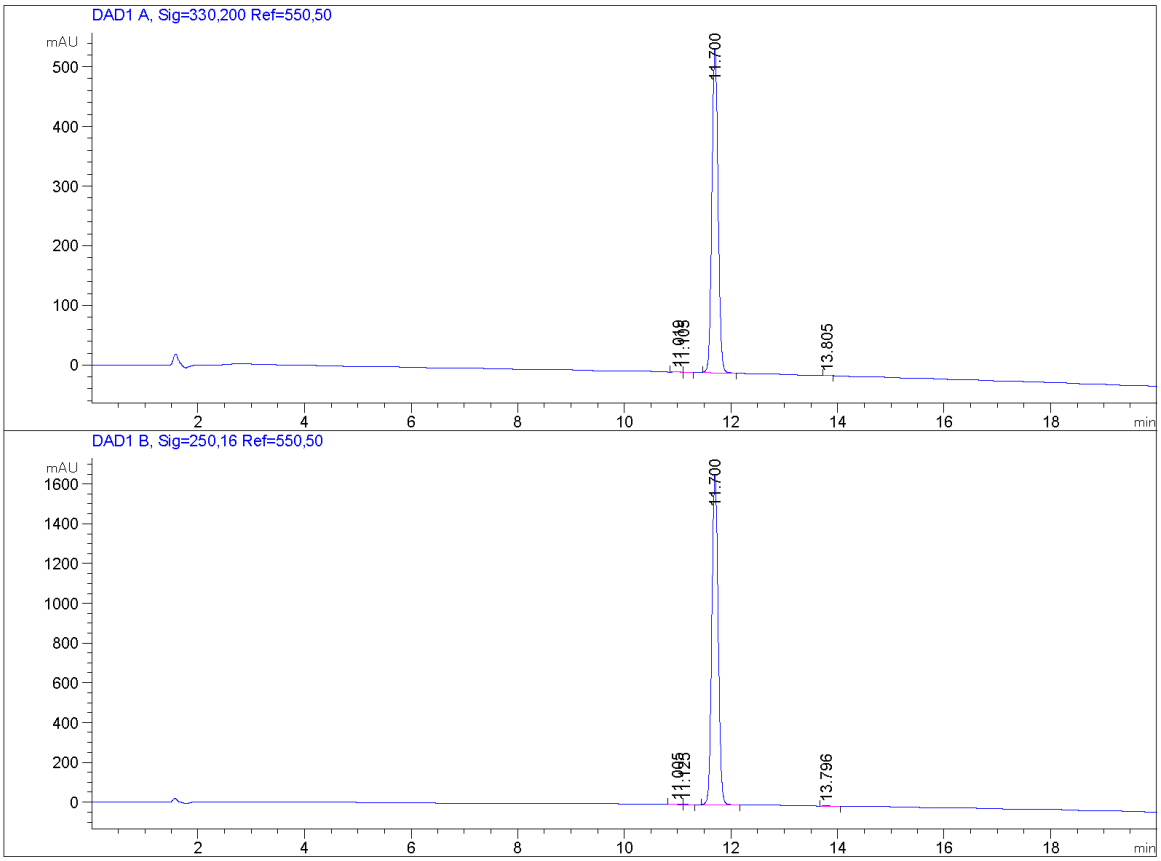
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.738	BV	0.1842	13.73168	1.11107	0.3399
2	11.055	VB	0.1324	10.05269	1.08206	0.2488
3	11.570	BB	0.1009	3983.40625	604.05237	98.5988
4	14.403	BB	0.1095	16.17840	2.31659	0.4005
5	18.930	BB	0.1063	16.64522	2.47948	0.4120
Totals :				4040.01423	611.04157	

Signal 2: DAD1 D, Sig=318,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.719	BB	0.1509	16.44027	1.51152	0.1980
2	11.570	BB	0.1007	8284.79102	1259.61780	99.8020
Totals :				8301.23129	1261.12932	

HPLC Compound 45



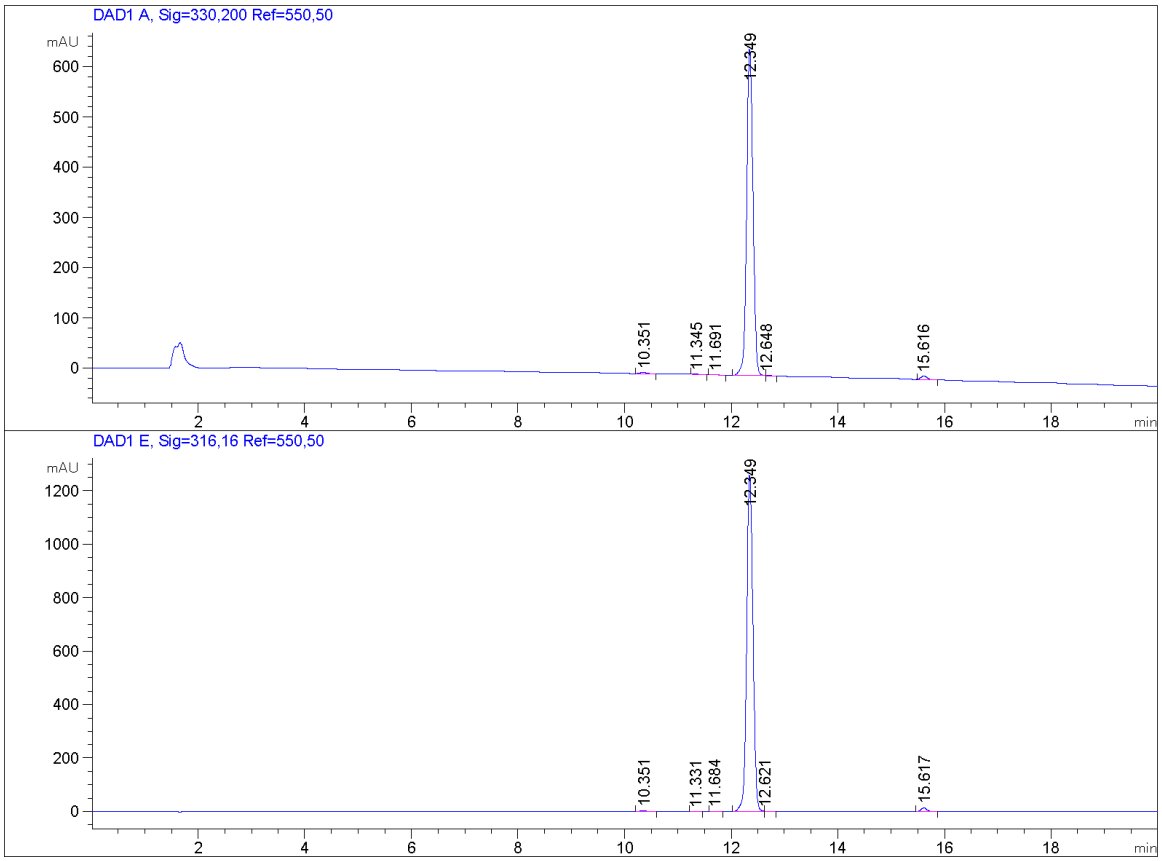
Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.019	MF	0.1765	4.36887	4.12618e-1	0.1010
2	11.105	FM	0.0960	2.32950	4.04262e-1	0.0538
3	11.700	BB	0.1250	4319.02441	541.99005	99.8167
4	13.805	MM	0.1079	1.23456	1.90627e-1	0.0285
Totals :				4326.95734	542.99756	

Signal 2: DAD1 B, Sig=250,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.005	MF	0.1760	12.86699	1.21813	0.0947
2	11.125	FM	0.0962	5.44487	9.43734e-1	0.0401
3	11.700	BB	0.1314	1.35531e4	1657.98474	99.7759
4	13.796	BB	0.1476	12.12931	1.26824	0.0893
Totals :				1.35835e4	1661.41485	

HPLC Compound 46



Signal 1: DAD1 A, Sig=330,200 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.351	BB	0.1358	16.43426	1.84768	0.3023
2	11.345	MM	0.1272	2.36062	3.09312e-1	0.0434
3	11.691	MM	0.1261	4.27950	5.65829e-1	0.0787
4	12.349	MF	0.1366	5348.98633	652.49316	98.4046
5	12.648	FM	0.0740	4.09503	9.22236e-1	0.0753
6	15.616	BB	0.1281	59.55434	7.22788	1.0956
Totals :				5435.71008	663.36611	

Signal 2: DAD1 E, Sig=316,16 Ref=550,50

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.351	BB	0.1345	31.43723	3.57756	0.3019
2	11.331	MM	0.1145	2.49630	3.63414e-1	0.0240
3	11.684	MM	0.1239	4.87090	6.55346e-1	0.0468
4	12.349	MF	0.1348	1.02498e4	1266.81738	98.4281
5	12.621	FM	0.1038	12.07526	1.93933	0.1160
6	15.617	BB	0.1284	112.80532	13.65660	1.0833
Totals :				1.04134e4	1287.00964	