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Supporting Information

From *in vitro* to *in cellulo*: Structure-activity relationship and biochemical evaluation of (2-nitrophenyl)methanol derivatives as inhibitors of PqsD in *Pseudomonas aeruginosa*

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1. Synthesis and analytical data of all tested compounds

(2-Nitrophenyl)(phenyl)methanol (3)[1] The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and benzaldehyde according to general method A. Purification via flash chromatography (petroleum ether/ethyl acetate 1:1) gave **3** (681 mg, 70 %) as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (s, 1H), 7.27-7.32 (m, 1H), 7.33-7.34 (m, 4H), 7.44-7.47 (m, 1H), 7.62-7.65 (m, 1H), 7.73-7.75 (m, 1H), 7.93 (dd, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.7, 124.9, 127.1, 128.2, 128.7, 128.7, 129.6, 133.6, 138.6, 141.7. R_t = 9.75 min; purity ≥ 97 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 212.07060, found 212.07037. Mp: 54-55°C (Lit. 59-60°C).[2]

***tert*-Butyl phenylcarbamate (5)**[3] To a solution of aniline (3.42 ml, 37.50 mmol) in 35 ml THF was added di-*tert*-butyl dicarbonate (9.48 ml, 41.25 mmol) and the mixture was refluxed for 3 h. The solvent was removed in vacuo and 75 ml ethyl acetate were added. The solution was washed with 1 M citric acid and brine, dried and concentrated under reduced pressure. Crystallization from hexane yielded **5** (5.013 g, 69 %) as a white solid. ^{1}H NMR (500 MHz, acetone-d_6) δ 1.48 (s, 9H), 6.98 (t, J = 7.4, 1H), 7.24-7.29 (m, 2H), 7.55 (d, J = 7.9, 2H). ^{13}C NMR (125 MHz, acetone-d_6) δ 28.5, 79.9, 119.0, 123.0, 123.0, 129.5. Mp: 135°C (Lit. 137°C).[2]

***tert*-Butyl (2-(hydroxy(phenyl)methyl)phenyl)-carbamate (6)**[3] A solution of *tert*-butyl phenylcarbamate **5** (1.200 g, 6.20 mmol) in 10 ml THF was cooled to -60°C and 8.76 ml of a *tert*-butyllithium solution (1.7 M in pentane, 14.89 mmol) were added slowly. The solution was stirred at -60°C for 15 min followed by 2 h at -20°C. A solution of benzaldehyde (0.63 ml, 6.20 mmol) in 5 ml THF was added and the mixture was stirred for 2 h at -20°C. The reaction was quenched with a saturated solution of NH_4Cl (10 ml) and the aqueous phase was extracted with ethyl acetate (three times). The combined organic layers were washed with brine, dried, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 8:1) to yield **6** (653 mg, 35 %) as a

white solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.41 (s, 9H), 5.88 (s, 1H), 7.07 (td, J = 7.6, J = 1.3, 1H), 7.19-7.34 (m, 7H), 7.60 (d, J = 7.6, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 28.6, 75.4, 81.0, 124.8, 127.3, 128.1, 129.1, 129.1, 129.4, 137.9, 144.2, 155.3. MS (ESI) *m/z*: 267.2 (M-O^{t}Bu)$^+$. Mp: 135-137°C (Lit. 141-142°C).[2]

4-Phenyl-1H-benzo[*d*][1,3]oxazin-2(4H)-one (7) To a solution of **6** (200 mg, 0.67 mmol) in 4 ml of dry dichloromethane at 0°C were added 0.8 ml TFA and the mixture was stirred at room temperature for 1 h. The solvent and TFA were removed in vacuo, DCM was added and the pH was adjusted to 7 using a saturated solution of sodium bicarbonate. The solution was extracted three times with ethyl acetate and the combined organic phase was dried, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 3:1) to give **7** (117 mg, 78 %) as a brownish solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (s, 1H), 6.86 (d, J = 7.6, 1H), 6.92 (dd, J = 7.9, J = 0.6, 1H), 7.02 (td, J = 7.6, J = 0.9, 1H), 7.26-7.30 (m, 1H), 7.35-7.42 (m, 5H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 81.4, 114.5, 121.1, 123.5, 126.0, 127.9, 128.9, 129.3, 129.6, 135.5, 153.1. R_t = 9.46 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: (M+H)$^+$ calculated 226.08626, found 226.08576. Mp: 57-60°C.

(2-Aminophenyl)(phenyl)methanol (8) To a solution of **7** (200 mg, 0.89 mmol) in 5 ml methanol a solution of potassium hydroxide (2.00 g) in 5 ml H_2O was added. The mixture was refluxed for 18 h, methanol was removed under reduced pressure and the phases were separated. The aqueous phase was extracted twice with ethyl acetate and the combined organic phase was dried, filtered and concentrated in vacuo. The crude product was purifed by flash chromatography (petroleum ether/ethyl acetate 4:1) to give **8** (30 mg, 17 %) as a yellowish solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 5.82 (s, 1H), 6.66 (t, J = 7.3, 1H), 6.72 (d, J = 7.9, 1H), 6.99 (d, J = 7.6, 1H), 7.04 (td, J = 7.6, J = 1.3, 1H), 7.25 (t, J = 7.3, 1H), 7.32 (t, J = 7.6, 2H), 7.38 (d, J = 7.6, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 74.6, 117.8, 118.9, 127.9, 128.2, 129.1, 129.2, 129.3, 129.7, 144.3, 146.6. R_t = 6.16 min; purity ≥ 97 % (UV). HRMS (ESI)

m/z: $(M+H)^+$ calculated 200.10699, found 200.10644. Mp: 118-120°C (Lit. 115-116°C).[4]

3-Phenylisobenzofuran-1(3H)-one (10) The title compound was prepared according to the general method B using methyl 2-iodobenzoate (2.00 g, 7.63 mmol) and purified by column chromatography (petroleum ether/ethyl acetate 6:1) to yield **10** (1.007 g, 63 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.73 (s, 1H), 7.30-7.34 (m, 2H), 7.37-7.43 (m, 3H), 7.45 (d, J = 7.6, 1H), 7.63 (t, J = 7.6, 1H), 7.76 (t, J = 7.6, 1H), 7.93 (d, J = 7.3, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 81.8, 123.2, 124.6, 125.0, 126.8, 128.9, 129.0, 129.5, 134.7, 136.9, 149.9, 169.9. R_t = 10.70 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 226.07536, found 211.07491. Mp: 116-117°C (Lit. 115-117°C).[5]

Sodium 2-(hydroxy(phenyl)methyl)benzoate (11) To a solution of **10** (400 mg, 1.90 mmol) in 20 ml MeOH an aqueous solution of sodium hydroxide (20 ml, 1M) was added. The mixture was stirred for 2 h at room temperature followed by 2 h at 50°C. The solvent was evaporated and **11** was isolated by preparative HPLC to afford 199 mg (39 %) as a white solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.10 (s, 1H), 7.16-7.21 (m, 2H), 7.23-7.30 (m, 4H), 7.36 (d, J = 7.9, 2H), 7.66 (d, J = 7.3, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 75.7, 127.6, 127.6 128.1, 128.8, 129.4, 129.9, 130.6. 140.8, 143.4, 145.2, 177.5. R_t = 8.80 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M-OH)^+$ calculated 211.07536, found 211.07512. IR (ATR) ν_{max} 3288, 3061, 3028, 1557 (ν_{as} COO^-) , 1385 (ν_s COO^-), 1015, 739, 699 cm^{-1}. Mp: 67-71°C.

Phenyl(2-(trifluoromethyl)phenyl)methanol (14) The title compound was prepared according to the general method B using 2-iodobenzotrifluorid (1.00 g, 3.68 mmol) and purified by column chromatography (petroleum ether/ethyl acetate 10:1) to yield **14** (665 mg, 71 %) as a colorless oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.21 (s, 1H), 7.22 (t, J = 7.6, 1H), 7.27-7.32 (m, 4H), 7.41 (t, J = 7.6, 1H), 7.58 (t, J = 7.6, 1H), 7.68 (d, J = 7.9, 1H), 7.70 (d, J = 7.9, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ

71.5, 126.0 (q, J = 273), 126.3 (q, J = 6), 127.7, 128.3, 128.5 (q, J = 30), 128.7, 129.2, 130.8, 133.4, 144.4, 145.0. R_t = 11.74 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 235.07291, found 235.07263.

2-(Hydroxy(phenyl)methyl)benzonitrile (15) The title compound was prepared according to the general method B using 2-iodobenzonitril (1.00 g, 4.36 mmol) and purified by column chromatography (petroleum ether/ethyl acetate 1:1) to yield **15** (426 mg, 47 %) as a yellowish solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.52 (s, 1H), 7.26-7.30 (m, 3H), 7.33-7.39 (m, 3H), 7.52-7.56 (m, 1H), 7.59 (td, J = 7.6, J = 1.3, 1H), 7.95-7.97 (m, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 86.5, 123.9, 124.7, 126.6, 127.9, 129.4, 129.9, 130.1, 130.2, 134.0, 139.5, 149.1. R_t = 6.58 min; purity ≥ 96 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 210.09143, found 210.09094. Mp: 86-91°C.

(2-Chlorophenyl)(phenyl)methanol (21) The title compound was prepared according to the general method C using 2-chlorobenzaldehyde (0.40 ml, 3.56 mmol) and purified by column chromatography (petroleum ether/ethyl acetate 10:1) to yield **21** (450 mg, 58 %) as a grey solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.16 (s, 1H), 7.20-7.25 (m, 2H), 7.27-7.31 (m, 2H), 7.31-7.36 (m, 4H), 7.65-7.67 (m, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 73.1, 128.1, 128.2, 128.4, 129.2, 129.6, 130.3, 133.5, 143.2, 144.3. R_t = 11.07 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 201.04655, found 201.04627. Mp: 64-66°C (Lit. 64-66°C).[6]

(2-Bromophenyl)(phenyl)methanol (22) The title compound was prepared according to the general method C using 2-bromobenzaldehyde (0.63 ml, 5.41 mmol) and purified by column chromatography (petroleum ether/ethyl acetate 10:1) to yield **22** (516 mg, 36 %) as a yellowish solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.12 (s, 1H), 7.17 (td, J = 7.7, J = 1.9, 1H), 7.22 (tt, J = 8.2, J = 1.4, 1H), 7.27-7.31 (m, 2H), 7.34-7.398 (m, 3H), 7.54 (dd, J = 8.2, J = 1.3, 1H), 7.64 (dd, J = 7.9, J = 1.6, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 75.3, 128.3, 128.4, 129.2, 129.6, 130.0, 133.7, 144.3,

144.7. R_t = 11.13 min; purity ≥ 96 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 244.99604, found 244.99585. Mp: 56-58°C (Lit. 56°C).[7]

Phenyl(*o*-tolyl)methanol (23) The title compound was prepared according to the general method C using 2-methylbenzaldehyde (0.42 ml, 3.67 mmol) and purified by column chromatography (petroleum ether/ethyl acetate 8:1) to yield **23** (700 mg, 92 %) as a white solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 2.22 (s, 3H), 5.96 (s, 1H), 7.10-7.25 (m, 4H), 7.27-7.31 (m, 4H), 7.47 (d, J = 7.6, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 19.5, 73.9, 126.8, 127.5, 128.2, 128.4, 129.2, 131.3, 136.5, 143.3, 144.8. R_t = 10.90 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 181.10118, found 181.10078. Mp: 90-91°C (Lit. 90-91°C).[8]

2-Methoxyphenyl)(phenyl)methanol (24) To a solution of 14.20 ml 2-methoxy-magnesium bromide (1M in TFH, 14.3 mmol) in 35 ml THF at -40°C was slowly added benzaldehyde (1.73 ml, 17.03 mmol). After 3 h at -40°C the reaction was quenched with a saturated solution of NH_4Cl (10 ml) and diluted with water (10 ml). The workup was carried out as described in method A. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 8:1) to give the desired product (2.098 g, 69 %). ^{1}H NMR (500 MHz, MeOH-d_4) δ 3.76 (s, 3H), 6.12 (s, 1H), 6.91-6.96 (m, 2H), 7.18 (tt, J = 7.3, J = 1.3, 1H) 7.20-7.23 (m, 1H), 7.24-7.27 (m, 2H), 7.32-7.35 (m, 2H), 7.44 (dd, J = 7,6, J = 1.9, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 55.8, 70.8, 111.6, 121.5, 127.8, 127.9, 129.0, 129.4, 134.0, 145.7, 157.7. R_t = 10.48 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 197.09609, found 197.09576. Mp: 37-38°C (Lit. 38-39°C).[9]

2-(Hydroxy(phenyl)methyl)phenol (25) The title compound was prepared according to the general method C using 2-hydroxybenzaldehyde (0.87 ml, 8.19 mmol) and 2.5 eq phenylmegnesium chloride (10.23 ml, 20.47 mmol). The crude product was purified by column chromatography (petroleum ether/ethyl acetate 6:1) to yield **25** (1.160 g, 70 %) as a white solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.11 (s,

1H), 6.76 (dd, J = 8.2, J = 0.9, 1H), 6.80 (tt, J = 7.6, J = 1.3, 1H), 7.05-7.09 (m, 1H), 7.19 (tt, J = 6.6, J = 1.9, 1H), 7.23 (dd, J = 7.6, J = 1.8, 1H), 7.25-7.29 (m, 2H), 7.37-7.40 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 72.3, 120.4, 127.7, 127.9, 128.4, 129.0, 129.2, 131.5, 145.6, 155.8. R_t = 9.00 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 183.08044, found 183.08003. Mp: 136-137°C (Lit. 84-86°C).[10]

(3-Nitrophenyl)(phenyl)methanol (28) The title compound was prepared according to the general method D using *meta*-nitrobenzaldehyde **26** to yield **28** (102 mg, 7 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 5.88 (s, 1H), 7.26 (tt, J = 7.3, J = 1.3, 1H), 7.32-7.35 (m, 2H), 7.37-7.40 (m, 2H), 7.54 (t, J = 7.9, 1H), 7.73-7.76 (m, 1H), 8.08-8.11 (m, 1H), 8.27-8.28 (m, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 75.8, 122.1, 122.9, 127.8, 128.7, 129.6, 130.5, 133.9, 148.7. R_t = 10.26 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 212.07060, found 212.07028.

(4-Nitrophenyl)(phenyl)methanol (29) The title compound was prepared according to the general method D using *para*-nitrobenzaldehyde **27** to yield **29** (176 mg, 12 %) as a green-brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 5.87 (s, 1H), 7.25 (t, J = 7.6, 2H), 7.36-7.39 (m, 2H), 7.62 (d, J = 8.8, 2H), 8.16-8.19 (m, 2H), 7.73-7.76 (m, 1H), 8.08-8.11 (m, 1H), 8.27-8.28 (m, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 76.1, 124.4, 127.8, 128.4, 128.7, 129.6, 145.0, 148.4, 153.7. R_t = 10.25 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 230.08117, found 230.08099. Mp: 58-59°C (Lit. 52-53°C).[11]

(4-Chloro-2-nitrophenyl)(phenyl)methanol (33) The title compound was prepared from phenylmagnesium chloride (0.67 ml, 2M in THF, 1.35 mmol) and 4-chloro-2-nitrobenzaldehyde (259 mg, 1.35 mmol) using the procedure described in the general method D. Pure **33** (174 mg, 49 %) was obtained as brown oil by flash chromatography (petroleum ether/ethyl acetate 8:1). ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.34 (s, 1H), 7.25-7.32 (m, 5H), 7.71 (dd, J = 8.5, J = 2.2, 1H), 7.86 (d, J = 8.5, 1H),

7.92 (d, J = 2.2, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 71.3 125.1, 128.3, 128.8, 129.4, 131.5, 134.0, 134.7, 139.1, 143.6. R_t = 12.14 min; purity ≥ 96 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 246.03163, found 246.03135.

(5-Chloro-2-nitrophenyl)(phenyl)methanol (34) The title compound was prepared from phenylmagnesium chloride (2.69 ml, 2M in THF, 5.39 mmol) and 5-chloro-2-nitrobenzaldehyde (1.00 g, 5.39 mmol) using the procedure described in the general method D. Pure **34** (0.792 mg, 56 %) was obtained as brown oil by flash chromatography (petroleum ether/ethyl acetate 12:1). ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.40 (s, 1H), 7.23-7.27 (m, 3H), 7.29-7.32 (m, 2H), 7.50 (dd, J = 8.8, J = 2.2, 1H), 7.89-7.92 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 71.5, 127.3, 128.4, 128.9, 129.3, 129.5, 129.7, 140.4, 142.8, 143.3. R_t = 11.29 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 246.03163, found 246.03134.

(2,4-Dinitrophenyl)(phenyl)methanol (35) The title compound was prepared from phenylmagnesium chloride (1.27 ml, 2M in THF, 2.55 mmol) and 2,4-dinitrobenzaldehyde (0.50 g, 5.39 mmol) using the procedure described in the general method D. Pure **35** (141 mg, 20 %) was obtained as brown oil by flash chromatography (petroleum ether/ethyl acetate 6:1). ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.44 (s, 1H), 7.24-7.32 (m, 5H), 8.21 (dd, J = 8.8, 1H), 8.53 (dd, J = 8.8, J = 2.2, 1H), 8.69 (d, J = 2.2, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 71.7, 120.8, 128.1, 128.5, 129.1, 129.6, 131.4, 143.0, 147.0, 148.4, 149.5. R_t = 10.82 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 257.05568, found 257.05544.

(4-Methyl-2-nitrophenyl)(phenyl)methanol (39) The title compound was synthesized from 4-iodo-3-nitro-toluene **37** (2.00 g, 7.60 mmol) and benzaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 8:1) gave **39** (765 mg, 41 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 2.41 (s, 3H), 6.34 (s, 1H), 7.21-7.30 (m, 5H), 7.45-7.51 (m, 1H), 7.68-7.71 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 20.6, 71.5, 125.4, 128.3, 128.6,

129.3, 129.8, 134.7, 137.2, 140.1, 144.2, 149.7. R_t = 11.20 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 226.08626, found 226.08597.

(5-Methyl-2-nitrophenyl)(phenyl)methanol (40) The title compound was synthesized from 3-iodo-4-nitro-toluene **38** (1.00 g, 3.80 mmol) and benzaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 8:1) gave **40** (383 mg, 42 %) as a yellow-brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 2.45 (s, 3H), 6.42 (s, 1H), 7.21-7.30 (m, 6H), 7.70-7.71 (m, 1H), 7.81 (d, J = 8.2, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 21.6, 71.6, 125.5, 128.4, 128.6, 129.3, 129.7, 130.2, 140.4, 144.1, 145.6, 147.5. R_t = 11.09 min; purity ≥ 96 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 226.08626, found 226.08598.

(4-Methoxy-2-nitrophenyl)(phenyl)methanol (43) A solution of 4-iodo-3-nitroanisol **41** (1.00 g, 3.59 mmol) in 25 ml THF was cooled to -40°C and a solution of 4-methoxyphenylmagnesium chloride (3.94 ml, 1M in THF, 3.94 mmol) was added drop-wise. The solution was stirred for 1 h at -20°C. Then, benzaldehyde (0.39 ml, 3.59 mmol) was added at -40°C and the mixture was stirred for further 90 min at constant temperature. The workup was carried out as described in method A. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 8:1) to give the desired product (192 mg, 21 %).^{1}H NMR (500 MHz, MeOH-d_4) δ 3.86 (s, 3H), 6.30 (s, 1H), 7.21-7.31 (m, 6H), 7.40 (d, J = 2.5, 1H), 7.69 (d, J = 8.8, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 56.4, 71.3, 110.1, 112.0, 128.2, 128.5, 129.3, 131.1, 132.0, 144.3, 160.6. R_t = 10.57 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 226.08117, found 226.08092.

(5-Methoxy-2-nitrophenyl)(phenyl)methanol (44) A solution of 3-iodo-4-nitroanisol **42** (1.00 g, 3.59 mmol) in 25 ml THF was cooled to -40°C and a solution of 4-methoxyphenylmagnesium chloride (3.94 ml, 1M in THF, 3.94 mmol) was added drop-wise. The solution was stirred for 1 h at -20°C. Then, benzaldehyde (0.39 ml, 3.59 mmol) was added at -40°C and the mixture was stirred for further 90 min at

constant temperature. The workup was carried out as described in method A. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 6:1) to give the desired product (298 mg, 68 %). ^{1}H NMR (500 MHz, MeOH-d_4) δ 3.91 (s, 3H), 6.53 (s, 1H), 6.98 (dd, J = 9.1, J = 2.8, 1H), 7.21-7.30 (m, 5H), 7.48 (d, J = 2.8, 1H), 8.01 (d, J = 8.8, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 56.5 72.0, 113.8, 114.7, 128.5, 128.7, 129.3, 143.9, 165.0. R_t = 10.32 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 242.08117, found 226.08099.

1-(2-Nitrophenyl)ethanol (47)[13] To a solution of 1-(2-nitrophenyl)ethanone **46** (400 mg, 2.42 mmol) in methanol (6 ml) sodium borohydride (366 mg, 9,69 mmol) was slowly added at 5°C. The reaction mixture was stirred for 16 h at room temperature, the solvent was evaporated and water was added. The solution was extracted three times with ethyl acetate and the combined organic phase was dried, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 4:1) to give **47** (252 mg, 62 %) as a brownish oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.49 (d, J = 6.3, 3H), 5.31 (q, J = 6.3, 1H), 7.45 (td, J = 7.7, J = 1.3, 1H), 7.69 (td, J = 7.7, J = 1.3, 1H), 7.84-7.87 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 25.1, 66.0, 124.8, 128.6, 129.0, 134.3, 142.8, 149.3. R_t = 8.21 min; purity ≥ 96 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 168.06552, found 168.06508. Mp: 26-28°C (Lit. 40-41°C).[12]

1-(2-Nitrophenyl)propan-1-ol (48) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and propionaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 6:1) gave **48** (398 mg, 55 %) as a brown oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.01 (t, J = 7.3, 3H), 1.62-1.71 (m, 1H), 1.76-1.84 (m, 1H), 5.07 (dd, J = 8.2, J = 3.8, 1H), 7.43-7.46 (m, 1H), 7.70 (d, J = 7.6, J = 1.3, 1H), 7.81 (dd, J = 7.9, J = 1.3, 1H), 7.85 (dd, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 10.8, 32.8, 71.0, 124.9, 129.0, 129.1, 134.1, 141.8, 149.5. R_t = 9.45 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 164.09609, found 164.07060.

1-(2-nitrophenyl)butan-1-ol (49) The title compound was synthesized from 2-iodonitrobenzene **36** (498 mg, 2.00 mmol) and butyraldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 8:1) gave **49** (398 mg, 55 %) as a brown oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.97 (t, J = 7.6, 3H), 1.41-1.50 (m, 1H), 1.52-1.62 (m, 1H), 1.70-1.82 (m, 2H), 5.25 (dd, J = 7.9, J = 4.1, 1H), 7.39-7.42 (m, 1H), 7.61-7.64 (m, 1H), 7.80 (dd, J = 7.9, J = 1.3, 1H), 7.89 (dd, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 19.3, 40.2, 69.2, 124.3, 128.0, 128.1, 133.4, 140.24, 148.0. R_t = 10.36 min; purity ≥ 98 % (UV). MS (EI) *m/z*: 152.0* $(M\text{-}C_3H_7^{\bullet})^+$, 135.0* $(M\text{-}C_3H_8O^{\bullet})^+$.

1-(2-nitrophenyl)pentan-1-ol (50) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and pentanal according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 9:1) gave **50** (312 mg, 37 %) as a brownish solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 0.92 (t, J = 6.9, 3H), 1.33-1.45 (m, 3H), 1.45-1.56 (m, 1H), 1.61-1.68 (m, 1H), 1.71-1.78 (m, 1H), 5.14 (dd, J = 8.5, J = 3.8, 1H), 7.44 (t, J = 7.9, 1H), 7.67 (t, J = 7.6, 1H), 7.82 (d, J = 7.9, 1H), 7.85 (d, J = 8.2, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 14.4, 23.5, 29.4, 39.7, 69.6, 124.8, 128.9, 129.0, 134.1, 142.2, 149.4. R_t = 10.95 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 210.11247, found 210.11189. Mp: 28-32°C.

1-(2-nitrophenyl)hexan-1-ol (51) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and hexanal according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 9:1) gave **51** (349 mg, 39 %) as a brownish solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 0.91 (t, J = 6.9, 3H), 1.28-1.38 (m, 4H), 1.39-1.47 (m, 1H), 1.50-1.59 (m, 1H), 1.60-1.67 (m, 1H), 1.70-1.77 (m, 1H), 5.14 (dd, J = 8.5, J = 3.8, 1H), 7.42-7.46 (m, 1H), 7.70 (td, J = 7.3, J = 1.3, 1H), 7.81 (dd, J = 7.9, J = 1.3, 1H), 7.85 (dd, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 14.4, 23.6, 26.8, 32.7, 39.9, 69.9, 124.8, 128.9, 129.9, 134.1,

142.2, 149.4. R_t = 12.07 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 206.11756, found 206.11725. Mp: 26-29°C.

3-Methyl-1-(2-nitrophenyl)butan-1-ol (52) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and 3-methylbutanal according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 8:1) gave **52** (417 mg, 50 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 0.95 (d, J = 6.6, 3H), 1.01 (d, J = 6.6, 3H), 1.42-1.48 (m, 1H), 1.57-1.63 (m, 1H), 1.90-1.98 (m, 1H), 5.25 (dd, J = 9.8, J = 2.8, 1H), 7.43 (td, J = 7.7, J = 1.3, 1H), 7.67 (td, J = 7.6, J = 0.9, 1H), 7.84 (td, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 21.6, 24.1, 26.1, 67.8, 124.8, 128.8, 129.0, 134.2, 143.0, 149.2. R_t = 11.05 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 192.10191, found 192.10154.

3,3-Dimethyl-1-(2-nitrophenyl)butan-1-ol (53) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and 3,3-dimethylbutanal according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 12:1) gave **53** (447 mg, 50 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.04 (s, 9H), 1.51-1.64 (m, 2H), 5.34 (dd, J = 9.5, J = 2.2, 1H), 7.41-7.44 (m, 1H), 7.64-7.68 (m, 1H), 7.81 (dd, J = 8.2, J = 1.3, 1H), 7.83 (dd, J = 7.9, J = 1.3, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 30.7, 31.7, 53.1, 67.6, 124.7, 128.7, 129.3, 134.1, 143.4, 149.0. R_t = 11.91 min; purity ≥ 97 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 206.11756, found 206.11724.

Cyclopentyl(2-nitrophenyl)methanol (54) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and cyclopentanecarbaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 7:1) gave **54** (574 mg, 51 %) as a brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.25-1.32 (m, 1H), 1.40-1.74 (m, 7H), 2.21-2.29 (m, 1H), 5.02 (d, J = 8.2, 1H), 7.41-7.45 (m, 1H), 7.63-7.66 (m, 1H), 7.77- 7.80 (m, 2H). ^{13}C NMR (125

MHz, MeOH-d_4) δ 26.4, 26.4, 29.5, 30.1, 72.3, 124.6, 129.0, 129.8, 133.7, 140.8, 150.3. R_t = 11.23 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 204.10191, found 206.10162.

Cyclohexyl(2-nitrophenyl)methanol (55) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and cyclohexanecarbaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 8:1) gave **55** (279 mg, 29 %) as a yellow-brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.09-1.23 (m, 5H), 1.35-1.37 (m, 1H), 1.57-1.65 (m, 1H), 1.74-1.77 (m, 1H), 1.81-1.85 (m, 1H), 4.95 (d, J = 6.3, 1H), 7.42-7.46 (m, 1H), 7.63-7.67 (m, 1H), 7.75 (dd, J = 7.9, J = 1.6, 1H), 7.80 (dd, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 27.2, 27.4, 27.5, 30.9, 46.2, 73.5, 124.7, 128.9, 129.9, 133.5, 140.3, 150.3. R_t = 12.10 min; purity ≥ 99 % (UV). MS (EI) *m/z*: 152.1* $(M\text{-}C_6H_{11}^{\bullet})^+$. Mp: 64-65°C.

Adamantan-1-yl(2-nitrophenyl)methanol (56) The title compound was synthesized from 2-iodonitrobenzene **36** (0.61 g, 2.44 mmol) and 1-adamantylcarboxaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 10:1) gave **56** (290 mg, 42 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.42 (d, J = 12.0, 3H), 1.57 (t, J = 12.0, 6H), 1.68 (d, J = 12.0, 3H), 1.91 (s, 3H), 5.03 (s, 1H), 7.42-7.45 (m, 1H), 7.60-7.63 (m, 1H), 7.71-7.74 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 29.8, 38.9, 39.3, 75.6, 124.4, 128.9, 131.4, 132.4, 136.9, 151.4. R_t = 13.74 min; purity ≥ 95 % (UV). MS HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 270.14886, found 270.14863.

1-(2-Nitrophenyl)-2-phenylethanol (57) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and phenylacetaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 6:1) gave **57** (331 mg, 32 %) as a brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 2.84-2.89 (m, 1H), 3.07-3.10 (m, 1H), 5.42 (dd, J = 8.5, J = 3.8, 1H), 7.17-7.19 (m.

1H), 7.22-7.26 (m, 4H), 7.43-7.47 (m, 1H), 7.64-7.68 (m, 1H), 7.83 (dd, J = 7.9, J = 1.6, 1H), 7.87 (dd, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 46.2, 71.1, 124.9, 127.3, 129.1, 129.1, 129.4, 130.6, 134.2, 139.8, 141.6. R_t = 11.10 min; purity ≥ 97 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 244.09682, found 244.09712.

1-(2-Nitrophenyl)-3-phenylpropan-1-ol (58) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and 3-phenylpropanal according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 6:1) gave **58** (331 mg, 32 %) as a brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.88-1.96 (m, 1H), 2.01-2.08 (m, 1H), 2.70-2.76 (m, 1H), 2.84-2.90 (m, 1H), 5.16 (dd, J = 8.8, J = 3.5, 1H), 7.12-7.16 (m, 1H), 7.18-7.20 (m, 2H), 7.22-7.26 (m, 2H), 7.42-7.46 (m, 1H), 7.66-7.69, 7.84-7.87 (m, 2H) ^{13}C NMR (125 MHz, MeOH-d_4) δ 33.6, 41.8, 69.3, 124.9, 126.8, 129.0, 129.1, 129.4, 129.4, 134.2, 141.9, 143.0. R_t = 11.55 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M-OH)^+$ calculated 240.10191, found 240.11247.

Naphthalen-1-yl(2-nitrophenyl)methanol (59) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and 1-naphthaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 6:1) gave **59** (302 mg, 27 %) as a brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.19 (d, J = 6.9, 1H), 7.23 (s, 1H), 7.35-7.38 (m, 1H), 7.47-7.53 (m, 3H), 7.62-7.65 (m, 1H), 7.69-7.71 (m, 1H), 7.81 (d, J = 8.2, 1H), 7.87-7.89 (m, 1H), 7.96 (dd, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 68.8, 124.8, 125.4, 125.6, 126.1, 127.3, 129.6, 129.6, 129.7, 130.5, 132.7, 134.0, 135.4, 139.4, 139.8, 150.1. R_t = 11.39 min; purity ≥ 97 % (UV). HRMS (ESI) *m/z*: $(M-OH)^+$ calculated 262.08626, found 262.08606. Mp: 74-75°C (Lit. 68-70°C).[14]

Naphthalen-2-yl(2-nitrophenyl)methanol (60) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and 2-naphthaldehyde according to general method A. Purification by flash chromatography (petroleum

ether/ethyl acetate 6:1) gave **60** (969 mg, 86 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.56 (s, 1H), 7.42 (dd, J = 8.5, J = 1.6, 1H), 7.43-7.45 (m, 2H), 7.47-7.50 (m, 1H), 7.68-7.71 (m, 1H), 7.73-7.74 (m, 1H), 7.77-7.81 (m, 1H), 7.88 (dd, J = 8.2, J = 1.0, 1H), 7.90 (dd, J = 8.2, J = 1.6, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 71.7, 125.2, 126.5, 126.9, 127.1, 127.2, 128.6, 129.1, 129.1, 129.4, 130.0, 134.1, 134.3, 134.6, 140.0, 141.4, 150.0. R_t = 11.58 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 262.08626, found 262.08591.

(2-Nitrophenyl)(thiophen-2-yl)methanol (61) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and thiophen-2-carboxaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 5:1) gave **61** (514 mg, 54 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.64 (s, 1H), 6.83-6.91 (m, 2H), 7.30 (d, J = 4.1, 1H), 7.50 (t, J = 7.3, 1H), 7.71 (t, J = 7.3, 1H), 7.91 (d, J = 7.9, 1H), 7.97 (d, J = 7.9, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 67.5, 125.2, 126.2, 126.3, 127.4, 129.4, 129.6, 134.3, 140.2, 148.2, 149.3. R_t = 9.74 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 218.02703, found 218.02672.

(2-Nitrophenyl)(thiophen-3-yl)methanol (62) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and thiophene-3-carboxaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 5:1) gave **62** (584 mg, 62 %) as a green-brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.45 (s, 1H), 7.01 (dd, J = 5.0, J = 1.3, 1H), 7.14-7.15 (m, 1H), 7.32 (dd, J = 5.0, J = 2.8, 1H), 7.48 (t, J = 7.8, 1H), 7.69 (t, J = 7.6, 1H), 7.87-7.90 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 67.9, 123.2, 125.1, 126.8, 127.8, 129.4, 129.6, 134.2, 140.3, 145.4, 149.6. R_t = 9.79 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 218.02703, found 218.02670. Mp: 62-64°C.

Furan-2-yl(2-nitrophenyl)methanol (63) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and furan-2-carboxaldehyde

according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 5:1) gave **63** (391 mg, 44 %) as a red-brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.01 (dt, J = 3.2, J = 0.6, 1H), 6.31 (dd, J = 3.2, J = 1.9, 1H), 6.44 (s, 1H), 7.42 (dd, J = 1.9, J = 0.7, 1H), 7.53 (td, J = 7.7, J = 1.6, 1H), 7.73 (td, J = 7.6, J = 1.3, 1H), 7.93-7.97 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 65.7, 108.3, 111.2, 125.3, 129.7, 129.8, 134.2, 137.9, 143.7, 149.4, 156.5. R_t = 8.97 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 202.04955, found 202.04987. Mp: 52-53°C.

Furan-3-yl(2-nitrophenyl)methanol (64) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and furan-3-carboxaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 7:1) gave **64** (412 mg, 47 %) as a brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.34 (s, 1H), 6.34-6.35 (m, 1H), 7.29-7.30 (m, 1H), 7.40 (t, J = 1.6, 1H), 7.47-7.05 (m, 1H), 7.70 (t, J = 7.6, 1H), 7.89 (dd, J = 8.2, J = 0.9, 1H), 7.93 (dd, J = 7.9, J = 0.9, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 64.8, 110.4, 125.1, 129.3, 129.4, 129.4, 134.2, 140.1, 141.2, 144.4. R_t = 8.90 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 202.04987, found 202.04947. Mp: 35-36°C.

(2-Nitrophenyl)(pyridin-2-yl)methanol (65) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and pyridine-2-carboxaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 3:1; TEA 0,1 %) gave **65** (410 mg, 44 %) as a brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.47 (s, 1H), 7.27-7.29 (m, 1H), 7.48-7.51 (m, 2H), 7.67 (td, J = 7.9, J = 1.3, 1H), 7.76 (dd, J = 7.9, J = 1.6, 1H), 7.80 (td, J = 7.6, J = 1.6, 1H), 7.92 (dd, J = 8.2, J = 1.3, 1H), 8.42-8.43 (m, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 72.5, 123.0, 124.0, 125.3, 129.6, 130.4, 134.1, 138.6, 139.0, 149.6, 150.1, 162.6. R_t = 4.92 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 231.07642, found 231.07510. Mp: 71°C.

(2-Nitrophenyl)(pyridin-3-yl)methanol (66) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and pyridine-3-carboxaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 3:1; TEA 0.1 %) gave **66** (602 mg, 65 %) as a orange-brown solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.42 (s, 1H), 7.38 (dd, J = 7.9, J = 4.7, 1H), 7.52-7.56 (m, 1H), 7.73-7.78 (m, 2H), 7.94-7.98 (m, 2H), 8.42 (dd, J = 4.7, J = 1.6, 1H), 8.50 (d, J = 1.9, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 69.7, 125.1, 125.5, 129.8, 129.9, 134.6, 137.0, 139.4, 140.7, 149.0, 149.2, 149.5. R_t = 4.86 min; purity ≥ 99 % (UV).). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 231.07642, found 231.07549. Mp: 78°C (Lit. 105-106).[15]

(2-Nitrophenyl)(pyridin-4-yl)methanol (67) The title compound was synthesized from 2-iodonitrobenzene **36** (1.00 g, 4.02 mmol) and pyridine-4-carboxaldehyde according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 1:1; TEA 0.1 %) gave **67** (553 mg, 60 %) as a brownish powder. ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.37 (s, 1H), 7.40-7.41 (m, 1H), 7.41-7.42 (m, 1H), 7.52-7.56 (m, 1H), 7.71-7.74 (m, 1H), 7.81-7.83 (m, 1H), 7.95 (dd, J = 8.2, J = 1.3, 1H), 8.46-8.48 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 70.3, 123.6, 125.4, 130.0, 130.0, 134.6, 139.0, 149.8, 150.1, 154.5. R_t = 4.79 min; purity ≥ 99 % (UV).). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 231.07642, found 231.07542. Mp: 158-160°C (Lit. 169-170°C).[15]

2-(3-Hydroxy-3-(2-nitrophenyl)propyl)isoindoline-1,3-dione (68) The title compound was synthesized from 2-iodonitrobenzene **36** (4.00 g, 16.06 mmol) and aldehyde **68i** according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 2:1) gave **68** (2.25 g, 43 %) as a yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.82-1.89 (m, 1H), 1.96-2.02 (m, 1H), 3.72-3.78 (m, 1H), 3.81-3.86 (m, 1H), 5.01-5.04 (m, 1H), 5.66 (dd, J = 4.4, J = 1.1, 1H), 7.45-7.50 (m, 1H), 7.71-7.74 (m, 1H), 7.82-7.89 (m, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 35.0, 36.8, 65.8, 122.9, 123.9, 128.0, 128.1, 131.7, 133.5, 134.3, 140.7, 147.0, 167.9.

R_t = 10.45 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 327.09755, found 327.09695. Mp: 154-155°C.

2-(4-Hydroxy-4-(2-nitrophenyl)butyl)isoindoline-1,3-dione (69) The title compound was synthesized from 2-iodonitrobenzene **36** (2.49 g, 10.00 mmol) and aldehyde **69i** according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 5:2) gave **69** (2.89 g, 85 %) as a yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.56-1.61 (m, 1H), 1.63-1.72 (m, 2H), 1.78-1.86 (m, 1H), 3.58-3.61 (m, 2H), 4.93-4.96 (m, 1H), 5.54 (d, J = 4.7, 1H), 7.46-7.49 (m, 1H), 7.70 (td, J = 7.3, J = 1.3, 1H), 7.76 (dd, J = 7.9, J = 1.3, 1H), 7.82-7.87 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.0, 35.7, 37.4, 67.3, 123.0, 123.6, 128.0, 131.6, 133.2, 134.3, 140.6, 147.5, 167.9. R_t = 10.86 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 341.11320, found 341.11214. Mp: 169°C.

2-(5-Hydroxy-5-(2-nitrophenyl)pentyl)isoindoline-1,3-dione (70) The title compound was synthesized from 2-iodonitrobenzene **36** (4.00 g, 16.06 mmol) and aldehyde **70i** according to general method A. Purification by flash chromatography (petroleum ether/ethyl acetate 2:1) gave **70** (2.29 g, 40 %) as a yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33-1.42 (m, 1H), 1.44-1.50 (m, 1H), 1.52-1.70 (m, 4H), 3.57 (t, J = 7.3, 1H), 4.93 (m, 1H), 5.49 (d, J = 4.7, 1H), 7.50-7.48 (m, 1H), 7.68-7.71 (m, 1H), 7.77 (dd, J = 7.9, J = 1.3, 1H), 7.82-7.87 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.0, 27.6, 37.4, 38.0, 67.2, 123.0, 123.6, 127.9, 128.1, 131.6, 133.2, 134.3, 141.0, 147.7, 167.9. R_t = 11.63 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 355.12885, found 355.12828. Mp: 120-122°C.

1-(5-Methyl-2-nitrophenyl)propan-1-ol (71) The title compound was synthesized from 3-iodo-4-nitro-toluene **38** (500 mg, 1.90 mmol) and propionaldehyde according to general method A. Purification by column chromatography (hexane/ethyl acetate 8:1) gave **71** (244 mg, 55 %) as an orange solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.01 (t, J = 7.3, 3H), 1.57-1.83 (m, 2H), 2.45 (s, 3H), 4.47 (d, J = 4.5, 1H), 5.16-5.22

(m, 1H), 7.29 (dd, J = 5.7, J = 1.6, 1H), 7.70 (s, 1H), 7.80 (d, J = 8.2, 1H). ^{13}C NMR (75 MHz, acetone-d_6) δ 10.9, 21.5, 32.7, 70.4, 124.9, 129.1, 129.4, 142.4, 145.0, 146.7. R_t = 11.06 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 196.09646, found 196.09682. Mp: 72-74°C.

(5-Methyl-2-nitrophenyl)(thiophen-2-yl)methanol (72) The title compound was synthesized from 3-iodo-4-nitro-toluene **38** (500 mg, 1.90 mmol) and thiophen-2-carboxaldehyde according to general method A. Purification by column chromatography (hexane/ethyl acetate 8:1) gave **72** (54 mg, 11 %) as an orange solid. ^{1}H NMR (500 MHz, acetone-d_6) δ 2.47 (s, 3H), 5.45 (s, 1H), 6.72 (s, 1H), 6.85-6.87 (m, 1H), 6.91 (dd, J = 5.09, J = 3.5, 1H), 7.34 (dd, J = 5.05, J = 1.2, 1H), 7.37 (dd, J = 8.1, J = 1.6, 1H), 7.84 (m, 1H), 7.88 (d, J = 8.3, 1H). ^{13}C NMR (125 MHz, acetone-d_6) δ 21.6, 67.1, 125.3, 125.6, 126.0, 127.2, 129.6, 129.8, 140.3, 145.5, 146.6, 148.6. R_t = 11.78 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M-OH)^+$ calculated 232.04268, found 232.04251. Mp: 93-96°C.

(5-Methyl-2-nitrophenyl)(thiophen-3-yl)methanol (73) The title compound was synthesized from 3-iodo-4-nitro-toluene **38** (500 mg, 1.90 mmol) and thiophene-3-carboxaldehyde according to general method A. Purification by column chromatography (hexane/ethyl acetate 8:1) gave **73** (127 mg, 27 %) as a yellow oil. ^{1}H NMR (500 MHz, acetone-d_6) δ 2.45 (s, 3H), 5.13 (d, J = 4.7, 1H), 6.52 (d, J = 4.8, 1H), 7.06 (dd, J = 5.1, J = 1.3, 1H), 7.21-7.22 (m, 1H), 7.33 (dd, J = 7.6, J = 1.3, 1H), 7.36 (dd, J = 5, J = 3, 1H), 7.78 (m, 1H), 7.83 (d, J = 8.2, 1H). ^{13}C NMR (125 MHz, acetone-d_6) δ 21.6, 67.5, 122.6, 125.1, 126.5, 127.7, 129.5, 129.9, 142.5, 145.3, 145.8, 146.8. R_t = 12.26 min; purity ≥ 95 % (UV). HRMS (ESI) *m/z*: $(M-OH)^+$ calculated 232.04268, found 232.04242.

Furan-2-yl(5-methyl-2-nitrophenyl)methanol (74) The title compound was synthesized from 3-iodo-4-nitro-toluene **38** (500 mg, 1.90 mmol) and furan-2-carboxaldehyde according to general method A. Purification by column

chromatography (hexane/ethyl acetate 8:1) gave **74** (244 mg, 44 %) as a red-brown oil. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.50 (s, 3H), 5.29 (s, 1H), 6.03 (d, J = 3.3, 1H), 6.32 (dd, J = 3.3, J = 1.9, 1H), 6.53 (s, 1H), 7.39 (d, J = 8.4, 1H), 7.45 (dd, J = 1.9, J = 0.9, 1H), 7.87 (s, 1H), 7.91 (d, J = 8.3, 1H). ^{13}C NMR (75 MHz, acetone-d_6) δ 21.6, 65.3, 107.7, 111.0, 125.3, 129.8, 130.0, 138.0, 143.2, 145.4, 146.6, 156.8. R_t = 10.90 min; purity ≥ 96 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 216.06522, found 216.06552.

2-(3-Hydroxy-3-(5-methyl-2-nitrophenyl)propyl)isoindoline-1,3-dione (75) The title compound was synthesized from 3-iodo-4-nitro-toluene **38** (500 mg, 1.90 mmol) and aldehyde **68i** according to general method A. Purification by semi-preparative HPLC gave **75** (100 mg, 15 %) as a yellow crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82-1.93 (m, 1H), 2.19-2.30 (m, 1H), 2.44 (s, 3H), 3.90-3.97 (m, 1H), 4.02-4.12 (m, 1H), 5.27 (dd, J = 9.7, J = 2.8, 1H), 7.17 (dd, J = 8.7, J = 1.9, 1H), 7.67 (s, 1H), 7.73-7.77 (m, 2H), 7.85-7.89 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 35.0, 37.7, 66.6, 123.6, 125.0, 128.4, 128.8, 132.2, 134.3, 140.0, 144.8, 145.4, 169.2. R_t = 11.91 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 341.11320, found 341.11255. Mp: 130-132°C.

2-(4-Hydroxy-4-(5-methyl-2-nitrophenyl)butyl)isoindoline-1,3-dione (76) The title compound was synthesized from 3-iodo-4-nitro-toluene **38** (500 mg, 1.90 mmol) and aldehyde **69i** according to general method A. Purification by semi-preparative HPLC gave **76** (168 mg, 25 %) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75-2.02 (m, 4H), 2.44 (s, 3H), 2.59 (s, 1H), 3.79 (t, J = 6.4, 2H), 5.32 (dd, J = 7.6, J = 3.2, 1H), 7.19 (dd, J = 8.6, J = 2.0, 1H), 7.59 (d, J = 1.6, 1H), 7.68-7.74 (m, 2H), 7.81-7.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 25.8, 35.2, 37.9, 69.4, 123.4, 125.0, 128.6, 128.9, 132.6, 134.1, 140.2, 145.1, 145.6, 168.7. R_t = 12.40 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 355.12848, found 355.12885.

3-Amino-1-(2-nitrophenyl)propan-1-ol (77) The title product was prepared according to method E to yield **77** (89 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-

d_4) δ 1.77-1.84 (m, 1H), 1.91-1.97 (m, 1H), 2.81-2.91 (m, 2H), 5.26 (dd, J = 9.0, J = 3.2, 1H), 7.44-7.48 (m, 1H), 7.68-7.71 (m, 1H), 7.86-7.80 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 40.1, 42.3, 68.6, 125.0, 129.1, 129.2, 134.3, 142.1, 149.1. R_t = 1.60 min; purity ≥ 97 % (UV).§ HRMS (ESI) *m/z*: $(M\text{-}OH)^+$ calculated 197.09167, found 197.09207.

4-Amino-1-(2-nitrophenyl)butan-1-ol (78) The title product was prepared according to method E to yield **78** (62 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.63-1.76 (m, 3H), 1.77-1.87 (m, 1H), 2.67-2.77 (m, 2H), 5.17 (dd, J = 7.9, J = 3.5, 1H), 7.45 (m, 1H), 7.67-7.70 (m, 1H), 7.85 (dd, J = 7.9, J = 1.6, 1H), 7.87 (dd, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 30.0, 37.3, 42.1, 69.4, 125.0, 129.0, 129.1, 134.2, 142.1, 149.3. R_t = 5.24 min; purity ≥ 98 % (UV).§ HRMS (ESI) *m/z*: $(M+H)^+$ calculated 211.10772, found 211.10738.

5-Amino-1-(2-nitrophenyl)pentan-1-ol (79) The title product was prepared according to method E to yield **79** (86 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.44-1.61 (m, 4H), 1.63-1.70 (m, 1H), 1.73-1.80 (m, 1H), 2.60-2.68 (m, 2H), 5.16 (dd, J = 8.5, J = 3.5, 1H), 7.43-7.47 (m, 1H), 7.66-7.70 (m, 1H), 7.83 (dd, J = 7.9, J = 1.6, 1H), 7.86 (dd, J = 8.2, J = 1.3, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 24.5, 33.4, 39.7, 42.4, 69.5, 124.9, 129.0, 129.1, 134.2, 142.2, 149.3. R_t = 7.04 min; purity ≥ 99 % (UV).§ HRMS (ESI) *m/z*: $(M+H)^+$ calculated 225.12307, found 225.12337.

5-(Dimethylamino)-*N*-(3-hydroxy-3-(2-nitrophenyl)propyl)naphthalene-1-sulfonamide (80) To a solution of the amine **77** (150 mg, 0.765 mmol) in dry DCM (40 ml) a solution of dansyl chloride (200 mg, 0.803 mmol) in dry DCM and TEA (0.158 ml, 1.137 mmol) were added. After stirring for 24 h at room temperature, the solution was washed with water and the aqueous phase was extracted twice with DCM. The combined organic layers were dried and the solvent was evaporated under reduced pressure. The crude product was purified by semi-preparative HPLC to yield

80 (147 mg, 45 %) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69-1.74 (m, 1H), 1.92-1.98 (m, 1H), 2.60 (d, J = 3.8, 1H), 2.89 (s, 6H), 3.02-3.09 (m, 1H), 3.19-3.26 (m, 1H), 5.25-5.27 (m, 1H), 5.46 (dd, J = 7.6, J = 3.5, 1H), 7.19 (dd, J = 7.6, J = 0.6, 1H), 7.36-7.39 (m, 1H), 7.51-7.55 (m, 2H), 7.57-7.62 (m, 2H), 7.88 (dd, J = 8.2, J = 1.3, 1H), 8.26 (dd, J = 7.3, J = 1.3, 1H), 8.32-8.34 (m, 1H), 8.53-8.55 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.9, 41.3, 45.6, 68.4, 115.4, 118.9, 123.4, 124.6, 128.1, 128.4, 128.6, 129.7, 130.0, 130.1, 130.6, 133.9, 134.6, 139.6, 147.3, 152.2. R_t = 8.77 min; purity ≥ 96 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 430.14312, found 430.14242. Mp: 53-56°C.

5-(Dimethylamino)-*N*-(4-hydroxy-4-(2-nitrophenyl)butyl)naphthalene-1-sulfonamide (81) Synthesis of **81** was carried out following the procedure described for **80** using **78** (85 mg, 0.404 mmol), dansyl chloride (106 mg, 0.424 mmol) and TEA (0.10 ml, 0.687 mmol). **81** (52 mg, 29 %) was obtained as a as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57-1.73 (m, 4H), 2.58 (s, 1H), 2.87 (s, 6H), 2.90-3.02 (m, 2H), 5.07-5.10 (m, 1H), 5.16 (t, J = 6.0, 1H), 7.15 (d, J = 7.6, 1H), 7.35-7.39 (m, 1H), 7.49-7.59 (m, 3H), 7.65 (dd, J = 7.9, J = 1.6, 1H), 7.86 (dd, J = 8.2, J = 1.3, 1H), 8.23 (dd, J = 7.3, J = 1.3, 1H), 8.27-8.30 (m, 1H), 8.50-8.53 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 35.1, 43.1, 45.5, 69.0, 115.3, 118.8, 123.3, 124.5, 128.0, 128.2, 128.5, 129.7, 129.8, 130.0, 130.5, 133.8, 134.8, 140.2, 147.6, 152.1. R_t = 10.18 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 444.15877, found 444.15416. Mp: 47-48°C.

5-(Dimethylamino)-*N*-(5-hydroxy-5-(2-nitrophenyl)pentyl)naphthalene-1-sulfonamide (82) Synthesis of **82** was carried out following the procedure described for **80** using **81** (150 mg, 0.669 mmol), dansyl chloride (175 mg, 0.702 mmol) and TEA (0.158 ml, 1.137 mmol). **82** (126 mg, 41 %) was obtained as a as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31-1.50 (m, 4H), 1.52-1.60 (m, 1H), 1.62-1.68 (s, 1H), 2.25 (d, J = 4.1, 1H), 2.88 (s, 6H), 2.90-2.94 (m, 2H), 4.70 (t, J = 6.3, 1H), 5.06-5.09 (m, 1H), 7.18 (dd, J = 7.6, J = 0.9, 1H), 7.38-7.41 (m, 1H), 7.51-7.56 (m, 2H),

7.59-7.63 (m, 1H), 7.72 (dd, J = 7.9, J = 1.3, 1H), 7.88 (dd, J = 8.2, J = 1.3, 1H), 8.25 (dd, J = 7.3, J = 1.3, 1H), 8.28-8.30 (m, 1H), 8.52-8.54 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1, 29.2, 37.5, 43.2, 45.5, 69.1, 115.3, 118.8, 123.4, 124.5, 128.1, 128.2, 128.6, 129.8, 129.9, 130.6, 133.7, 134.8, 140.2, 152.2. R_t = 9.51 min; purity ≥ 98 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 458.17442, found 458.17363. Mp: 50-51°C.

4-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)-1-(2-nitrophenyl)butan-1-ol (83) At 0°C, 4-chlor-7-nitrobenzofurazan (100 mg, 0.499 mmol) and $NaHCO_3$ (126 mg, 1.497 mmol) were added to a solution of **78** (105 mg, 0.499 mmol) in 8 ml of methanol. The mixture was stirred for 30 min at 0°C, followed by 90 min at room temperature and, finally, another 90 min at 50°C. After extraction with ethyl acetate (three times) the combined organic layers were dried and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 1:2) to give **83** (74 mg, 40 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.76-1.83 (m, 1H), 1.91-1.99 (m, 2H), 2.00-2.06 (m, 1H), 3.59 (s, 2H), 5.23 (dd, J = 8.5, J = 2.8, 1H), 6.33 (d, J = 8.8, 1H), 7.43-7.47 (m, 1H), 7.66-7.70 (m, 1H), 7.51-7.87 (m, 2H), 8.49 (d, J = 7.9, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 14.4, 26.0, 37.0, 61.5, 69.4, 125.0, 129.1, 129.1, 134.4, 138.5, 142.0, 149.2. R_t = 10.82 min; purity ≥ 96 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 374.10951, found 574.10908.

***N*-(4-Hydroxy-4-(2-nitrophenyl)butyl)-3-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)propanamide (84)** To a solution of **78** (200 mg, 0.951 mmol) in 12 ml of acetonitrile **84i** (240 mg, 0.951 mmol), *N*-methylmorpholine (0.52 ml, 4.755 mmol), *N*-hydroxy-benzotriazole (HOBt) hydrate (231 mg, ~1.510 mmol) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) hydro-chloride (328 mg, 1.712 mmol) were added. After stirring for 20 h at room temperature water was added and the mixture was extracted with ethyl acetate (three times). The combined organic layers were washed with brine, dried, and concentrated in vacuo. The crude product

was purified by flash chromatography (100 % ethyl acetate) to give **84** (133 mg, 32 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.56-1.64 (m, 2H), 1.71-1.76 (m, 2H), 2.65 (t, J = 6.9, 2H), 3.19-3.27 (m, 2H), 3.83 (s, 2H), 5.09 (dd, J = 8.2, J = 2.7, 1H), 6.40 (d, J = 8.8, 1H), 6.41-6.45 (m, 1H), 7.64-7.67 (m, 1H), 7.77 (dd J = 7.9, J = 1.3, 1H), 7.82 (dd, J = 8.2, J = 1.3, 1H), 8.50 (d, J = 8.8, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 27.0, 37.0, 40.2, 69.3, 77.3, 118.0, 124.9, 129.0, 129.0, 134.3, 142.0, 149.1, 173.1. R_t = 9.22 min; purity ≥ 99 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 445.14662, found 445.14667.

***N*-(4-Hydroxy-4-(2-nitrophenyl)butyl)-6-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)hexanamide (85)** Synthesis of **85** was carried out following the procedure described for **84** using **78** (130 mg, 0.618 mmol), **85i** (182 mg, 0.618 mmol), *N*-methylmorpholine (0.340 ml, 3.092 mmol), HOBt hydrate (150 mg, ~0.980 mmol) and EDC hydrochloride (213 mg, 1.113 mmol) in 6 ml of aceto nitrile. The crude product was purified by preparative HPLC to yield **85** (117 mg, 46 %) as a brown oil. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.43-1.50 (m, 2H), 1.62-1.71 (m, 4H), 1.43-1.82 (m, 4H), 2.21 (t, J = 7.4, 2H), 3.20-3.23 (m, 2H), 3.51 (s, 2H), 5.13-5.15 (m, 1H), 6.33 (d, J = 8.8, 1H), 7.41-7.45 (m, 1H), 7.66 (td, J = 7.6, J = 1.3, 1H), 7.81-7.85 (m, 2H), 8.50 (d, J = 8.5, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 14.4, 26.6, 27.2, 27.5, 36.9, 37.2, 40.1, 69.4, 125.0, 129.0, 129.1, 134.3, 138.5, 142.1, 149.2, 155.3, 176.0. R_t = 13.75 min; purity ≥ 96 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 487.19357, found 487.19290.

1-(3',6'-dihydroxy-3-oxo-3H-spiro[isobenzofuran-1,9'-xanthen]-5-yl)-3-(4-hydroxy-4-(2-nitrophenyl)butyl)thiourea (86) Fluorescein isothiocyanate (111 mg, 0.285 mmol) was added to a solution of **78** (60 mg, 0.285 mmol) and DIEA (0.348 ml, 1.998 mmol) in 5 ml of DMF and the mixture was stirred for 18 h at room temperature. The solvent was evaporated under reduced pressure and the crude product was purified by preparative HPLC to give **86** (61 mg, 36 %) as an orange solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 1.71-1.96 (m, 4H), 3.49 (s, 2H), 5.21 (dd, J =

8.5, J = 2.8, 1H), 6.53 (dd, J = 8.8, J = 2.2, 2H), 6.67-6.68 (m, 4H), 7.14 (d, J = 8.2, 1H), 7.43-7.46 (m, 1H), 7.66-7.69 (m, 1H), 7.74 (dd, J = 8.2, J = 1.6, 1H), 7.85-7.89 (m, 2H), 8.19 (d, J = 1.9, 1H). ^{13}C NMR (125 MHz, MeOH-d_4) δ 26.8, 37.1, 69.5, 103.5, 111.5, 113.7, 125.0, 129.1, 129.1, 130.3, 134.3, 142.1, 149.2, 154.2, 171.2. R_t = 9.98 min; purity ≥ 97 % (UV). HRMS (ESI) *m/z*: $(M+H)^+$ calculated 600.14351, found 600.14344. Mp: 168-174°C.

2. Experiment procedure for HPLC, HRMS, and MS

The retention time R_t and purity of every compound tested in the biological assays were determined using HPLC according to the following procedure:

A SpectraSystems® LC system consisting of a pump, an autosampler, and a PDA detector was employed. The system was operated by the standard software Xcalibur®. An RP-C18 NUCLEODUR® 100-5 (125x3 mm) column (Macherey-Nagel GmbH, Düren, Germany) was used as stationary phase. All solvents were HPLC grade.
In a gradient run, the percentage of acetonitrile (containing 0.1 % trifluoroacetic acid; TFA) in an aqueous solution of 0.1 % TFA was increased from an initial concentration of 0 % at 0 min to 100 % at 15 min and kept at 100 % for 5 min. RT values determined without the use of trifluoroacetic acid are marked by a paragraph (§). The injection volume was 10 µL and flow rate was set to 800 µL/min. Chromatograms were recorded at 254 nm for the UV trace.

HRMS values were determined by the following procedure:

Measurements were performed on a Dionex Ultimate 3000 RSLC system using a Waters BEH C18, 50 x 2.1 mm, 1.7 µm dp column by injection of two µl methanolic sample. Separation was achieved by a linear gradient with (A) H2O + 0.1 % FA to (B) ACN + 0.1 % FA at a flow rate of 600 µL/min and 45 °C. The gradient was initiated by a 0.33 min isocratic step at 5 % B, followed by an increase to 95 % B in 9 min to end up with a 1 min flush step at 95 % B before reequilibration under the initial conditions. UV and MS detection were performed simultaneously. Coupling the HPLC to the MS was supported by an Advion Triversa Nanomate nano-ESI system attached to a Thermo Scientific Orbitrap. Mass spectra were acquired in centroid mode ranging from 100 – 2000 m/z at a resolution of R = 30000.

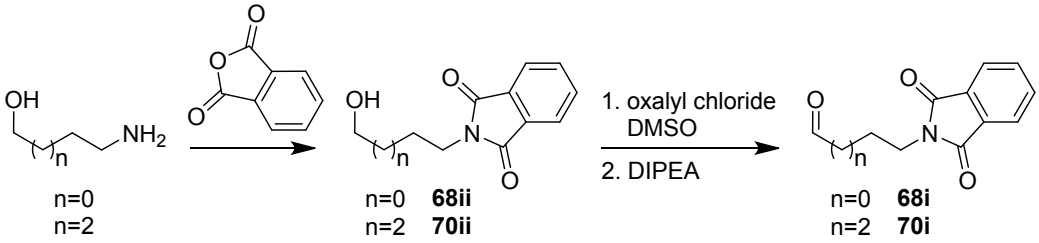
In two cases (**49** and **55**), m/z values were generated by a DSQII electron ionization analyzer (ThermoFisher, Dreieich, Germany). These values are marked by an asterisk (*).

For intermediates, m/z values were measured on an MSQ® electro spray mass spectrometer (ThermoFisher, Dreieich, Germany). A spray voltage of 3800 V, a capillary temperature of 350°C, and a source CID of 10 V was applied. MS spectra were acquired in positive mode.

3. Synthesis and analytical data of synthetic intermediates

3.1 Phthalimide aldehydes used for synthesis of 68-70

*a) Synthesis and Analytical Data of Intermediates **68i** and **70i**[16]*



2-(3-Hydroxypropyl)isoindoline-1,3-dione (68ii)

Phthalic anhydride (9.9 g, 67 mmol) was added to a solution of 3-aminopropan-1-ol (5.0 g, 67 mmol) and TEA (9.3 ml, 67 mmol) in 100 ml of toluene. The mixture was stirred for 3 h at 125°C and water was removed using a Dean-Stark apparatus. After cooling to room temperature the solvent was evaporated under reduced pressure to yield the desired product **68ii** (13.5 g, 99 %), which was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.71-1.76 (m, 2H), 3.43-3.46 (m, 2H), 3.63 (t, J = 7.3, 2H), 4.49 (s, 1H), 7.81-7.86 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 31.2, 35.2, 58.5, 122.9, 131.7, 134.3, 167.9. MS (ESI) *m/z*: 206.3 $(M+H)^+$.

2-(5-Hydroxypentyl)isoindoline-1,3-dione (70ii)

Following the procedure described for **68ii** using phthalic anhydride (16.1 g, 109 mmol), 5-aminopentan-1-ol (11.2 g, 109 mmol) and TEA (15.2 ml, 109 mmol) in 140 ml of toluene, the desired product **70ii** (25.1 g, 99 %) was obtained, which was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.25-1.32 (m, 2H), 1.40-1.46 (m, 2H), 1.56-1.62 (m, 2H), 3.34-3.38 (m, 2H), 3.56 (t, J = 7.1, 2H), 4.33 (s, 1H), 7.82-7.87 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.8, 27.8, 32.0, 37.4, 60.4, 122.9, 131.6, 134.3, 167.9. MS (ESI) *m/z*: 234.2 $(M+H)^+$.

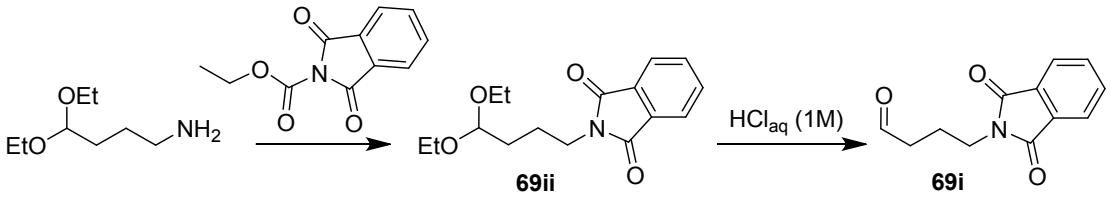
3-(1,3-Dioxoisoindolin-2-yl)propanal (68i)

Oxalyl chloride (8.4 ml, 99 mmol) was added to 30 ml of dry DCM and the mixture was cooled to -78°C. Dry DMSO (21.1 ml, 297 mmol) was added drop-wise and the solution was stirred for 30 min. A solution of **68ii** (13.5 g, 66 mmol) in 25 ml of dry DCM was added drop-wise and the solution was stirred for 30 min. DIPEA (56.1 ml, 330 mmol) was added and the mixture was stirred for another 30 min at -78°C. The mixture was warmed to room temperature and a solution of NaH_2PO_4 (11.9 g, 99 mmol) in 20 ml of water was added. The aqueous layer was extracted three times with DCM and the combined organic layers were washed with 1 M HCl, saturated $NaHCO_3$ and brine. The solvent was removed under reduced pressure to yield **68i** (13.4 g, 100 %), which was sufficient pure for use in the next step. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.81 (td, J = 6.8, J = 1.6, 2H), 3.86 (t, J = 3.9, 2H), 7.82-7.87 (m, 4H), 9.67 (t, J = 1.6, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 31.4, 41.5, 123.0, 131.6, 134.3, 167.7.

5-(1,3-Dioxoisoindolin-2-yl)pentanal (70i)

Following the procedure described for **68i** using oxalyl chloride (13.7 ml, 162 mmol) in 30 ml of DCM, DMSO (34.5 ml, 486 mmol), **70ii** (25.1 g, 108 mmol) in 20 ml of DCM, DIPEA (91.8 ml, 540 mmol) and a solution of NaH_2PO_4 (19.4 g, 162 mmol) in 30 ml of water, the desired product **70i** (20.1 g, 80 %) was obtained in sufficient purity for use in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.49-1.54 (m, 2H), 1.56-1.62 (m, 2H), 2.46 (td, J = 7.3, J = 1.6, 2H), 3.57 (t, J = 6.6, 2H), 7.78-7.87 (m, 4H), 9.64 (t, J = 1.4, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.8, 27.4, 37.1, 42.4, 122.9, 131.6, 134.3, 167.9. MS (ESI) *m/z*: 232.3 $(M+H)^+$.

b) Synthesis and Analytical Data of Intermediate ***69i***[17]



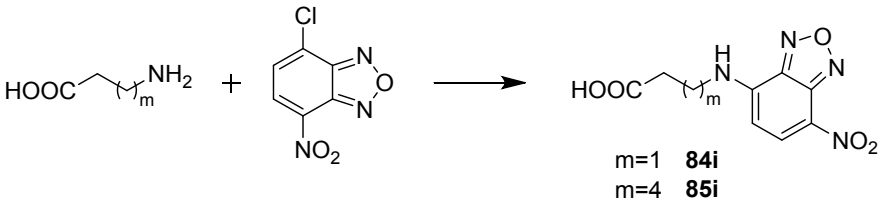
2-(4,4-Diethoxybutyl)isoindoline-1,3-dione (69ii)

N-Carbethoxyphthalimide (13.0 g, 59 mmol) and 4-aminobutyraldehyde diethyl acetal (10.3 g, 59 mmol) were dissolved in THF (90 ml) and TEA (8.4 ml, 59 mmol) was added. After stirring for 20 h at room temperature the solvent was evaporated under reduced pressure and the remaining oil was purified by flash chromatography (*n*-hexane/ethyl acetate 8:1) to yield the title compound **69i** (15.4 g, 88 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, J = 7.0, 6H), 1.62-1.67 (m, 2H), 1.72-1.78 (m, 2H), 3.44-3.50 (m, 2H), 3.58-3.64 (m, 2H), 3.70 (t, J = 7.3, 2H), 4.49 (t, J = 5.5, 1H), 7.69 (dd, J = 5.5, J = 3.0, 2H), 7.82 (dd, J = 5.5, J = 3.0, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.4, 24.1, 31.1, 37.9, 61.4, 102.5, 123.3, 132.3, 134.0, 168.5. MS (ESI) *m/z*: 246.2 $(M\text{-}OEt)^+$.

4-(1,3-Dioxoindolin-2-yl)butanal (69i)

A mixture of 2-(4,4-diethoxybutyl)isoindoline-1,3-dione **69ii** (15.4 g, 53 mmol) and 1 M aqueous HCl (101 ml) in acetone (108 ml) was heated under reflux for 2 h. The solvent was removed in vacuo and the residue was extracted with ether (three times). The combined organic extracts were washed with water, dried, filtered, and concentrated in vacuo to yield the title compound **69i** (11.1 g, 97 %) as a white solid, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (m, 2H), 2.53 (td, J = 7.3, J = 0.9, 2H), 3.74 (t, J = 6.7, 2H), 7.72 (dd, J = 5.5, J = 3.0, 2H), 7.84 (dd, J = 5.5, J = 3.0, 2H), 9.77 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 37.3, 41.2, 123.4, 132.2, 134.2, 168.5, 200.9. MS (ESI) *m/z*: 218.1 $(M+H)^+$.

3.2 NBD containing carboxylic acids for synthesis of 84 and 85



3-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)propanoic acid (84i)

At 0°C, 4-chlor-7-nitrobenzofurazan (300 mg, 1.503 mmol) and $NaHCO_3$ (379 mg, 4.509 mmol) were added to a solution of 3-aminopropanoic acid (134 mg, 1.503 mmol) in 30 ml of methanol. The mixture was stirred for 30 min at 0°C, followed by 90 min at room temperature and another 90 min at 50°C. The pH was adjusted to 2-3 by addition of 0.1 M aqueous HCl. After extraction with ethyl acetate (three times) the combined organic layers were dried and concentrated under reduced pressure. The crude product was purified by flash chromatography (8 % methanol/DCM) to give the title compound **84i** (211 mg). The identity of **84i** (211 mg) was proven by LC/MS (ESI) *m/z*: 253.22 $(M+H)^+$, indicating 72 % purity (UV). The product was used in the next step without further purification.

6-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)hexanoic acid (85i)[18]

Following the procedure described for **84i** using 3-aminopropanoic acid (198 mg, 1.503 mmol), 4-chlor-7-nitrobenzofurazan (300 mg, 1.503 mmol) and $NaHCO_3$ (379 mg, 4.509 mmol) in 20 ml of methanol, the crude product was recrystallized from methanol to give 383 mg of the title compound **85i** (87 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.35-1.41 (m, 2H), 1.52-1.58 (m, 2H), 1.65-1.71 (m, 2H), 2.22 (t, J = 7.3, 2H), 3.43-3.48 (m, 2H), 6.40 (d, J = 8.8, 1H) 8.49 (d, J = 8.7, 1H), 9.52 (s, 1H), 11.98 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.1, 25.9, 27.3, 43.2, 48.6, 99.1, 120.5, 137.9, 144.2, 144.4, 145.2, 174.4. MS (ESI) *m/z*: 295.01 $(M+H)^+$.

4. Synthesis of substrates used in the enzyme inhibition assay

Synthesis of anthraniloyl-S-CoA thioester[19]

Anthraniloyl-CoA (ACoA) was synthesized from isatoic anhydride and coenzyme A (CoA) using a previously described method. ACoA was purified by HPLC (Agilent 1200 series consisting of a quaternary pump, a fraction collector and an MWD; Agilent Technologies, USA) after freeze drying of the aqueous reaction mixture (25 mL) and resuspending of the dried residue in 3 mL of a mixture of 50 % methanol and water. A 10 μm RP C18 150-30 column (30 x 100 mm, Agilent) was used along with a mobile phase consisting of water containing 1‰ TFA (A) and acetonitrile containing 1‰ TFA (B) with a flow rate of 5 mL/min. The following gradient was used: 0-35 min, linear gradient 10 % - 100 % B; 35-42 min, 100 % B; 42-43 min, 10 % B (initial conditions). ACoA containing fractions were pooled and freeze dried.

Synthesis of β-ketodecanoic acid[20]

Ethyl 3-oxodecanoate (300 mg, 1.4 mmol, 1.0 eq) was stirred with NaOH (56 mg, 1.4 mmol, 1.0 eq) in water (2 ml) overnight. Any remaining ester was removed by washing with Et_2O (10 ml). The aqueous layer was cooled and acidified with 32 % HC1 to pH = 6. After filtration the 3-oxodecanoic acid was dried *in vacuo* and obtained as white solid (100 mg, 0.54 mmol, 38 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0, 3H), 1.25-1.29 (m, 8H), 1.58 (quintet, J = 7.0, 2H), 2.54 (t, J = 7.5, 2H), 3.49 (s, 2H). LC/MS (ESI) no ionization, 99 % (UV).

Synthesis of ethyl 3-oxodecanoate[21]

To a THF solution of 2M LDA (20 ml, 40 mmol 2.4 eq) was added ethyl acetoacetate (2.16 g, 16.6 mmol, 1.0 eq) at 0°C. The deep yellow clear solution was stirred at 0°C for 1 h. To this solution the 1-iodohexane was added (4.20 g, 19.81 mmol, 1.2 eq) at -78°C. The temperature was allowed to reach an ambient temperature over 14 h and the solution was stirred at room temperature for 2 h. To the solution was added 10 % HCl (200 ml) and the mixture was extracted with Et_2O (4 × 250 ml). The combined

organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/ethyl acetate, 30/1) to give ethyl 3-oxodecanoate as a yellow oil (1.98 g, 9.24 mmol, 55 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, J = 7.0, 3H), 1.23-1.28 (m, 11H), 1.54 (quintet, J = 7.0, 2H), 2.49 (t, J = 7.0, 2H), 3.39 (s, 2H), 4.16 (m, 2H).

5. Mutagenicity assay

The *S. typhimurium* derivatives TA100, TA1535 and TA102 were used as bacterial strains. These were provided by B. N. Ames (University of California, Berkeley, USA) or Trinova Biochem (Gießen, Germany).

The standard *S. typhimurium* plate incorporation assay was carried out.[22] All mutagenicity assays were performed with and without S9 mix. S9, prepared from livers of male rats pre-treated with Aroclor 1254 (500 mg/kg), was provided by Trinova Biochem GmbH (Gießen, Germany). The concentrations of cofactors in the S9 mix (before adding them to the overlay) were 33 mM KCl, 8 mM $MgCl_2$, 5 mM glucose-6-phosphate, 4 mM NADP, 100 mM phosphate buffer (pH=7.4), and 5 % S9.

In absence of S9 mix sodium azide was used as positive control in TA100 (1 µg/plate) and TA1535 (2 µg/plate), whereas Mitomycin D (0.3 µg/plate) was used for TA102. When the assay was carried out with S9 mix, 2-aminoanthracen (1.5 µg/plate for TA100 and TA1535, respectively, and 8.0 µg/plate for TAS102) were added as positive control. The compound and positive controls were dissolved in DMSO was used as negative control. Doses of compound **3** for each strain with and without S9 mix were 5, 16, 50, 160, 500, 1600, and 5000 µg/plate (3 plates per dose level).

6. Effects on *P. aeruginosa* wild-type

Cultivation of *P. aeruginosa* PA14 wild-type

For determination of extracellular HHQ and PQS levels, cultivation was performed in the following way: cultures of *P. aeruginosa* PA14 wild-type cells (initial OD_{600} = 0.02) were incubated with or without inhibitor (final DMSO concentration 1 %, *v/v*) at 37°C, 200 rpm and a humidity of 75 % for 16 h in 24-well Greiner Bio-One Cellstar plates (Frickenhausen, Germany) containing 1.5 ml medium per well. Cultures were generally grown in PPGAS medium (20 mM NH_4Cl, 20 mM KCl, 120 mM Tris-HCl, 1.6 mM $MgSO_4$, 0.5 % (*w*/*v*) glucose, 1 % (*w*/*v*) Bacto$_{TM}$ Tryptone). Exceptionally, LB medium (86 mM NaCl, 0.5 % (*w*/*v*) yeast extract; 1 % (*w*/*v*) peptone from casein) was used for PQS quantification. For each sample, cultivation and sample work-up were performed in triplicates.

Determination of extracellular HHQ and PQS levels

Extracellular levels of HHQ were determined according to the method of Lépine *et al*. with the following modifications.[23] An aliquot of 500 µl of bacterial cultures were supplemented with 50 µl of a 10 µM methanolic solution of the internal standard (IS) 5,6,7,8-tetradeutero-2-heptyl-4(1*H*)-quinolone (HHQ-d_4) and extracted with 1 ml of ethyl acetate by vigorous shaking. After centrifugation, 400 µl of the organic phase were evaporated to dryness in LC glass vials. The residue was re-dissolved in methanol. UHPLC-MS/MS analysis was performed as described in detail recently.[24] The following ions were monitored (mother ion [m/z], product ion [m/z], scan time [s], scan width [m/z], collision energy [V], tube lens offset [V]): HHQ: 244, 159, 0.5, 0.01, 30, 106; HHQ-*d4* (IS): 248, 163, 0.1, 0.01, 32, 113. Xcalibur software was used for data acquisition and quantification with the use of a calibration curve relative to the area of the IS. Quantification of PQS produced by *P. aeruginosa* PA14 was performed as described by Maurer and colleagues.[25]

Results: Effects on *P. aeruginosa* wild-type

We selected three structurally divers compounds with good inhibitory potency in the *pqsH*$^-$ mutant to examine their effects on *P. aeruginosa* PA14 wild-type. Since HHQ is not fully converted into PQS, both signal molecules had to be quantified to gain a full insight into inhibition of signal molecule production. All three compounds **3**, **48** and **62** were potent inhibitors of both signal molecules, whereas the most pronounced effects were exerted by **62** (Table S2). This is in accordance to the data observed in the *pqsH*$^-$ mutant, which validates the latter as appropriate simplified test system to measure PqsD inhibition by quantification of only a singular reporter molecule.

Table S2 Effects of PqsD inhibitors on HHQ and PQS production in *P. aeruginosa* PA14 wild-type.

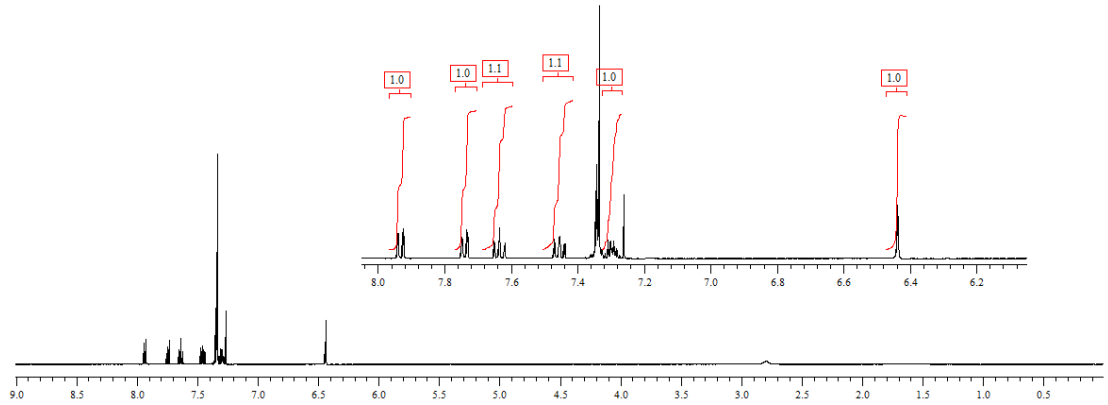
Compound	% HHQ inhibition[a]	% PQS inhibition[a]
3	38 ± 6[b]	37 ± 6[b]
48	33 ± 6	60 ± 11
62	49 ± 1	68 ± 1

[a] Planctonic *P. aeruginosa* PA14. Inhibitor concentration 250 μM. Percentage of inhibition was normalized regarding OD600.

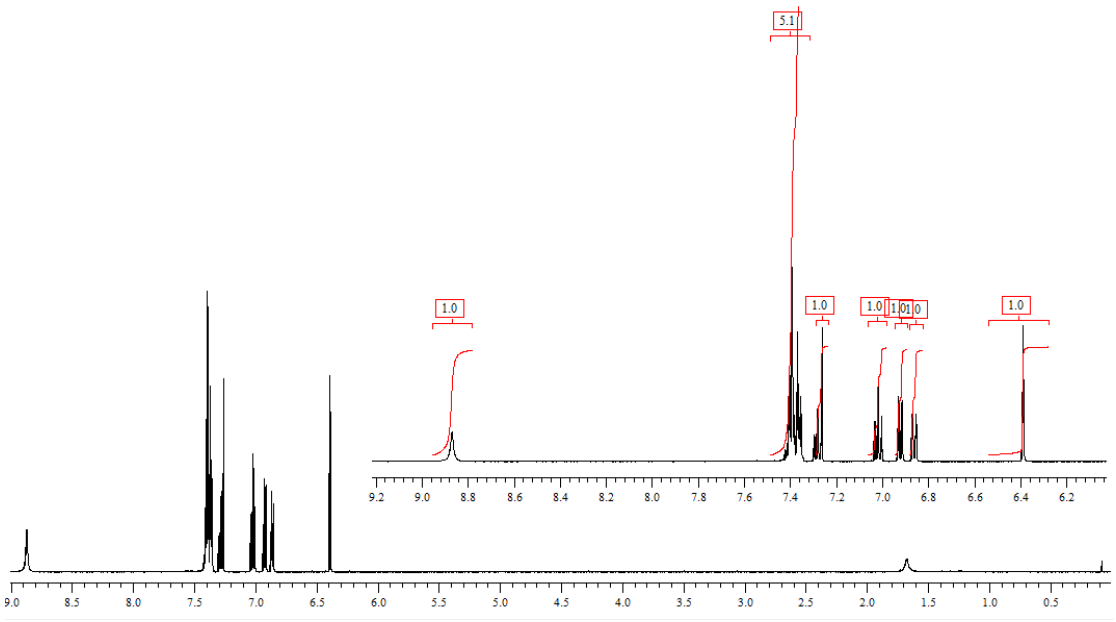
[b] Values differ from ref. 12 due to improvements of the assay procedures.

7. ^{1}H NMR spectra of all tested compounds

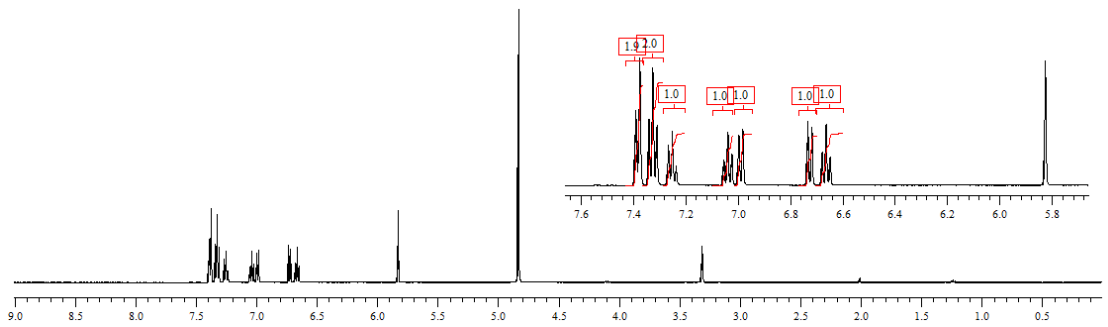
Compound 3



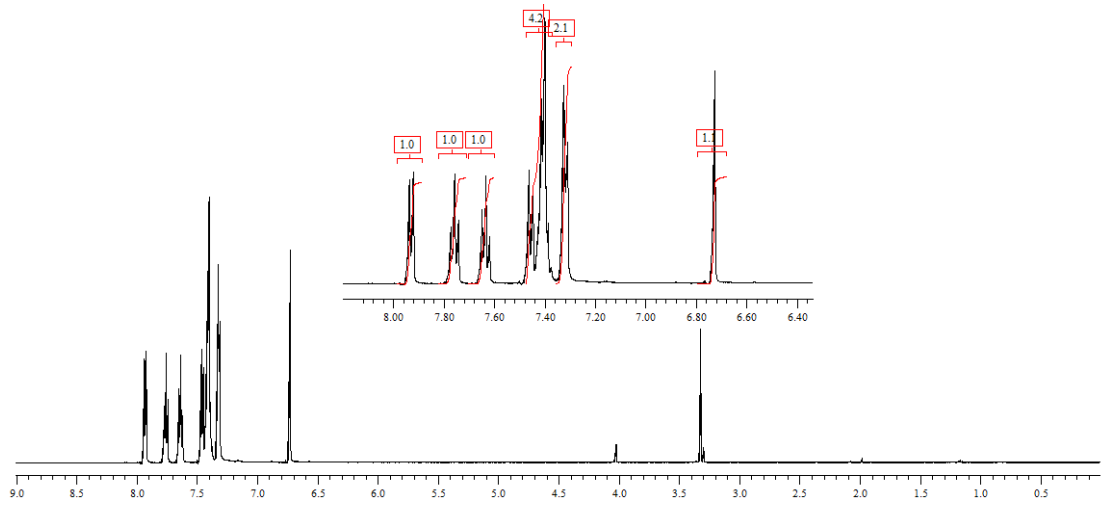
Compound 7



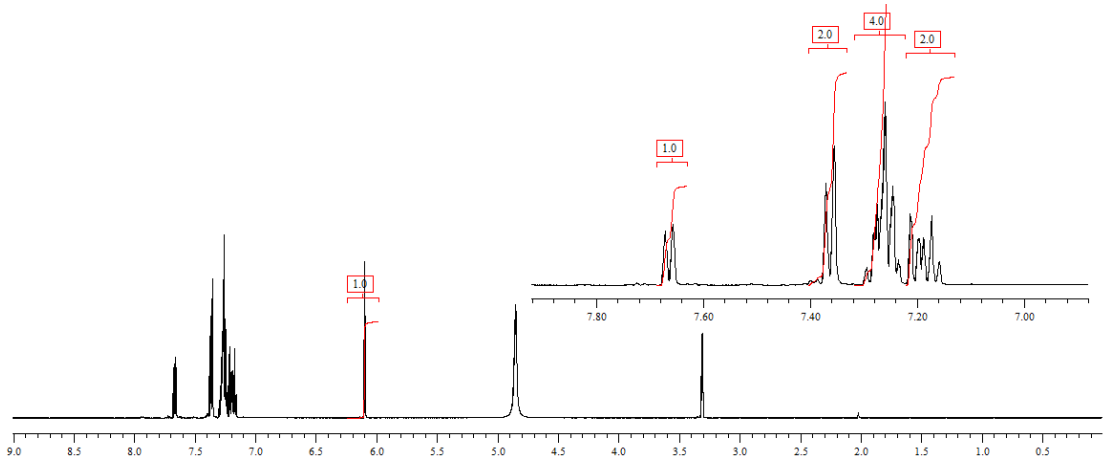
Compound 8



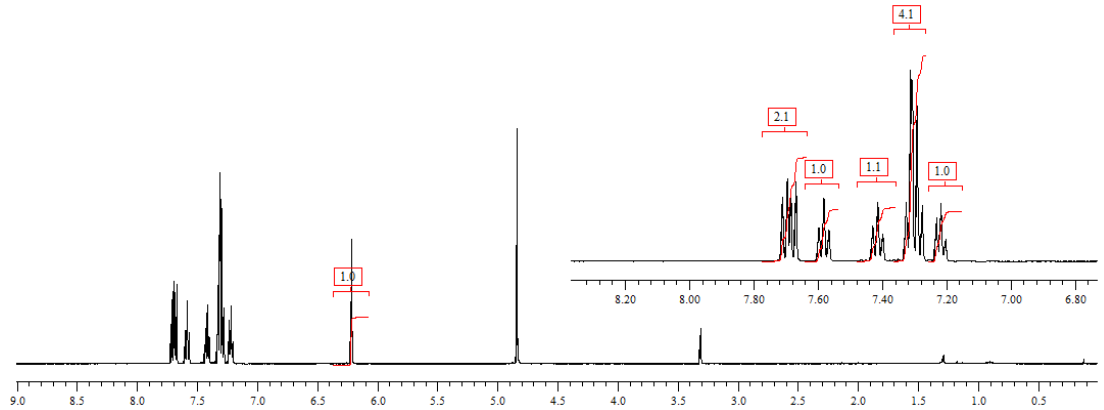
Compound 10



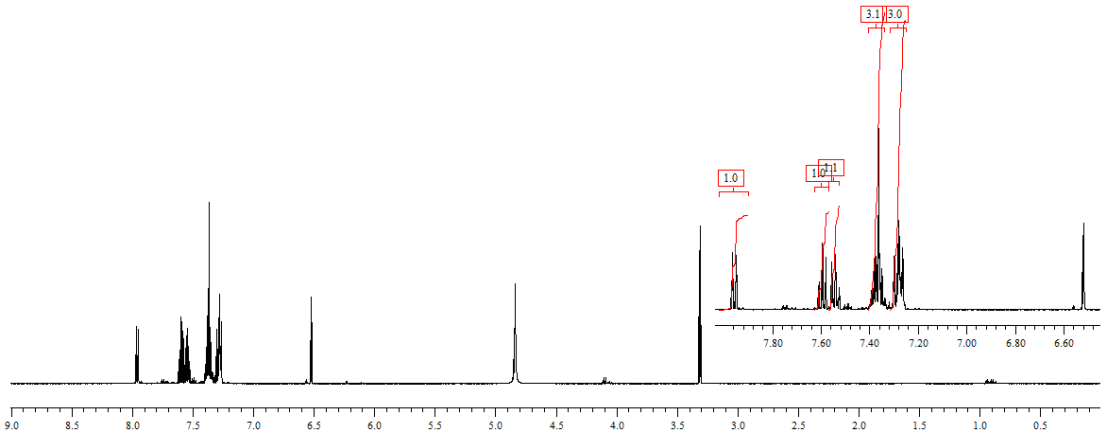
Compound 11



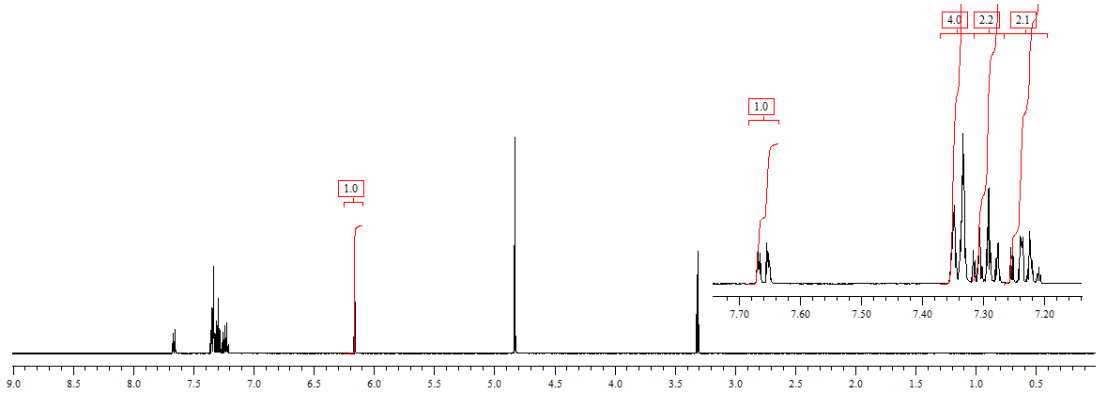
Compound 14



Compound 15



Compound 21



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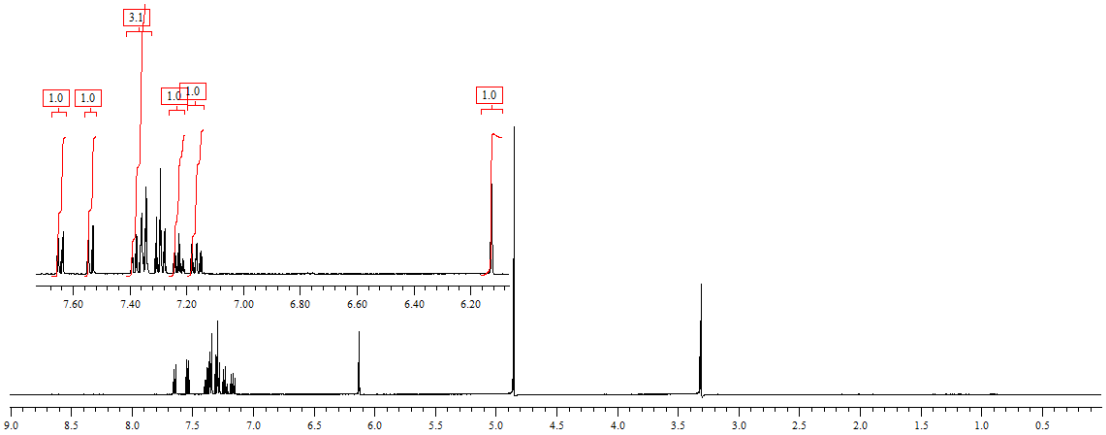
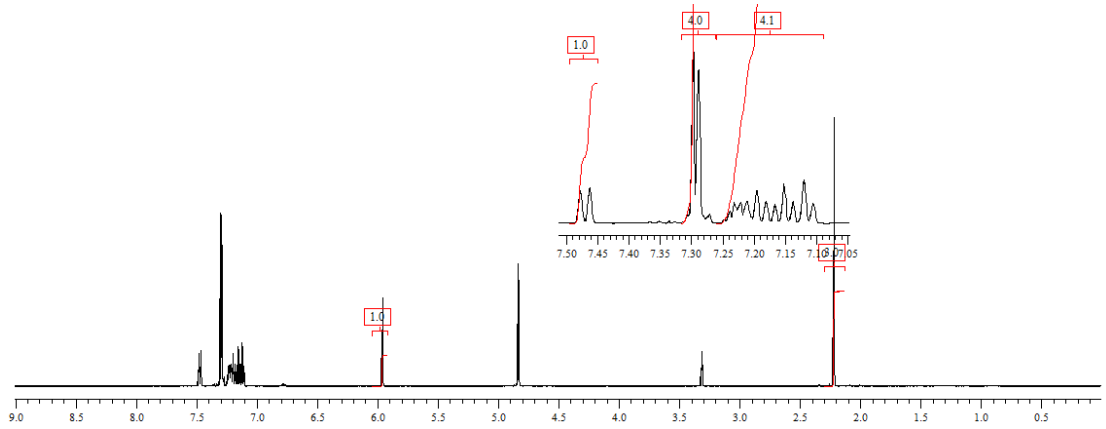
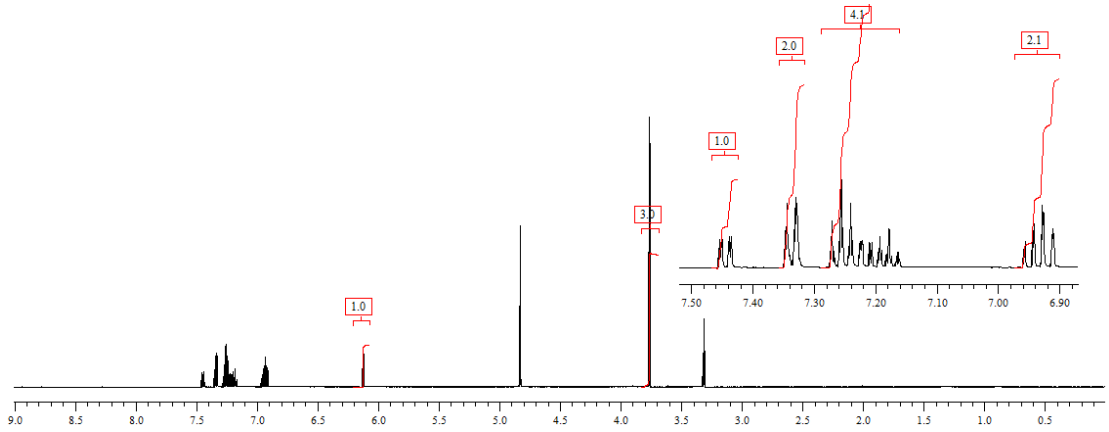


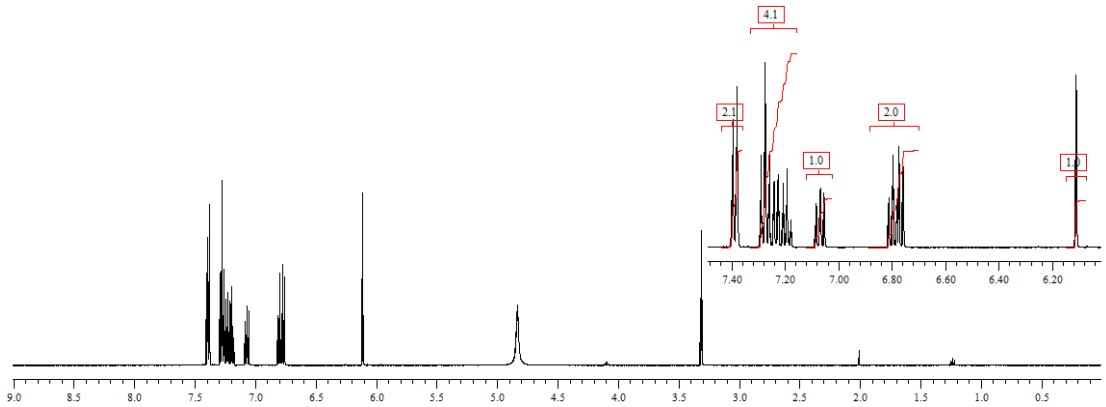
Compound 23



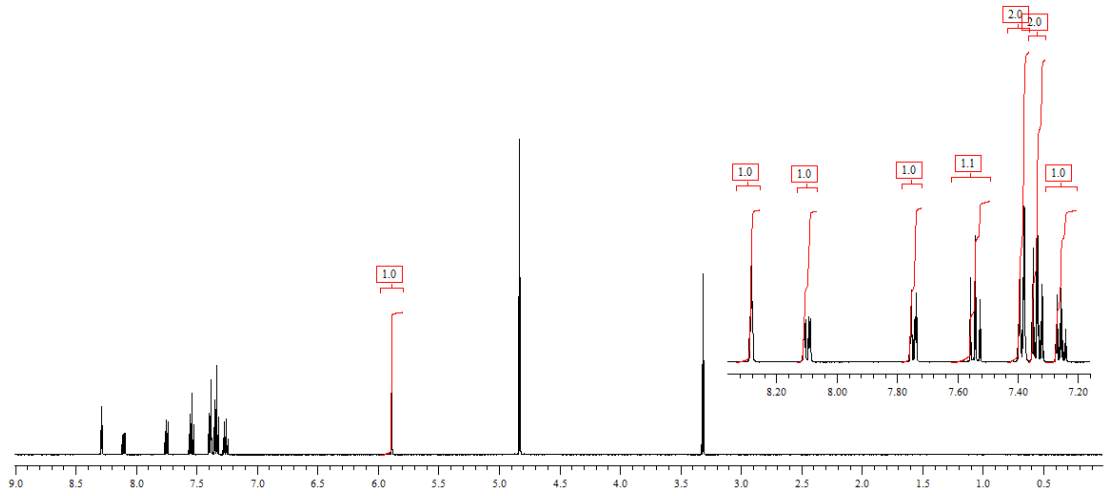
Compound 24



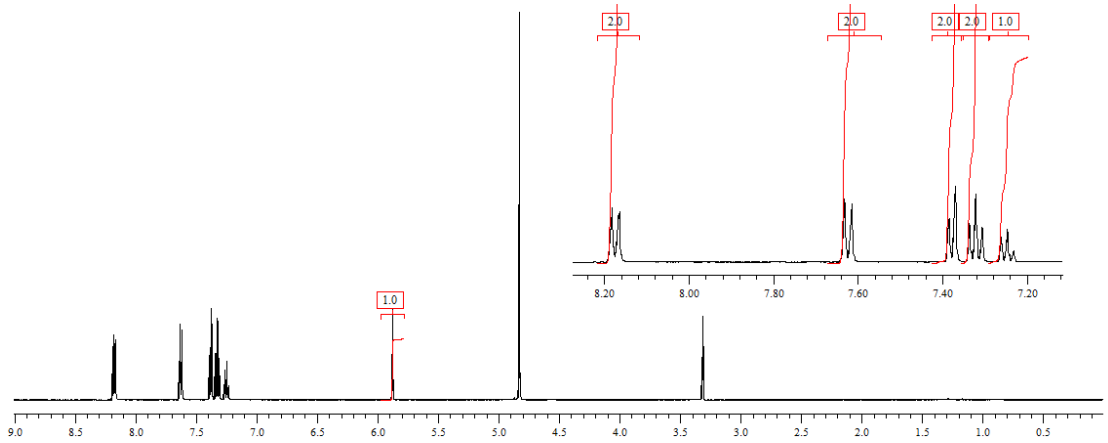
Compound 25



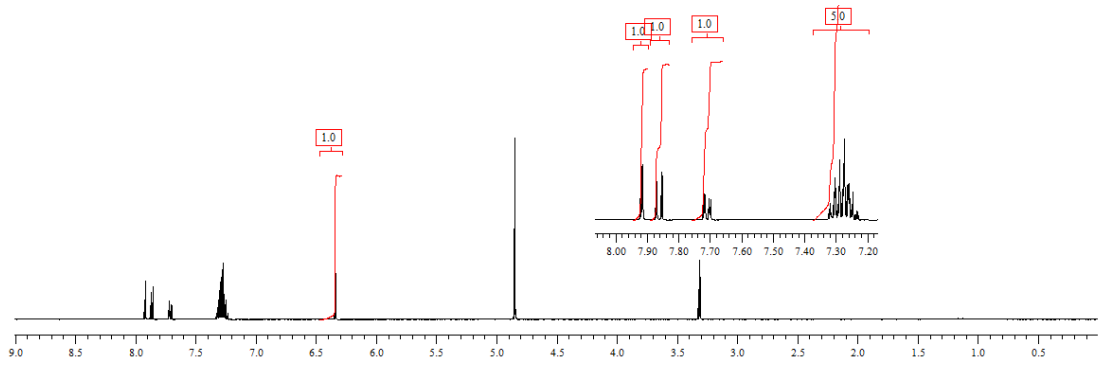
Compound 28



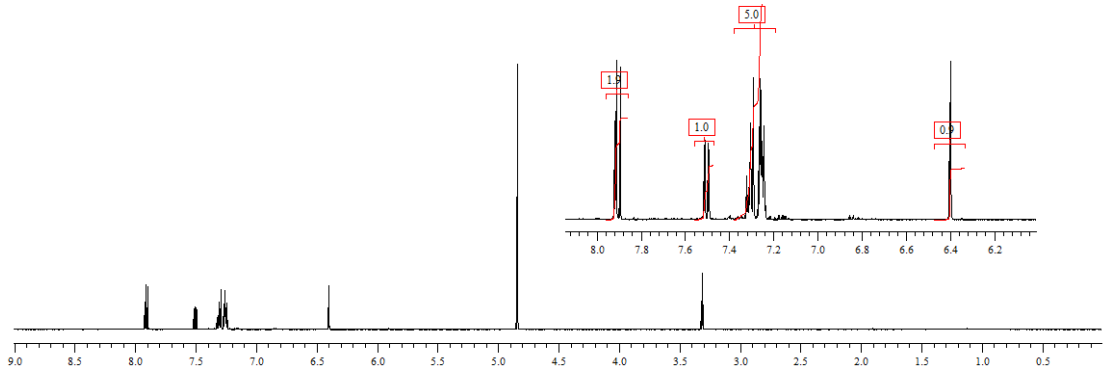
Compound 29



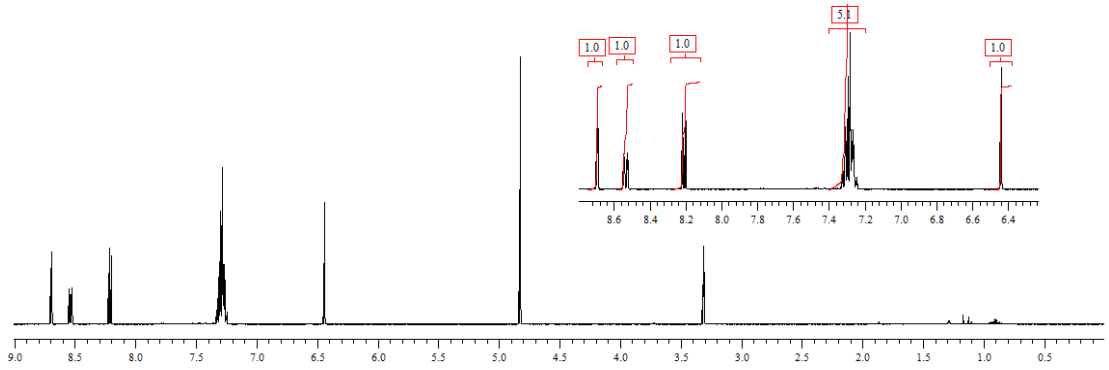
Compound 33



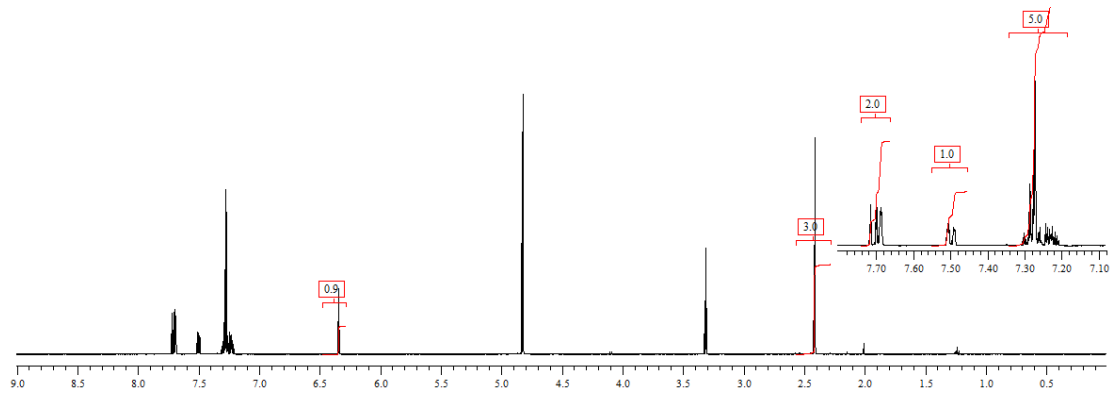
Compound 34



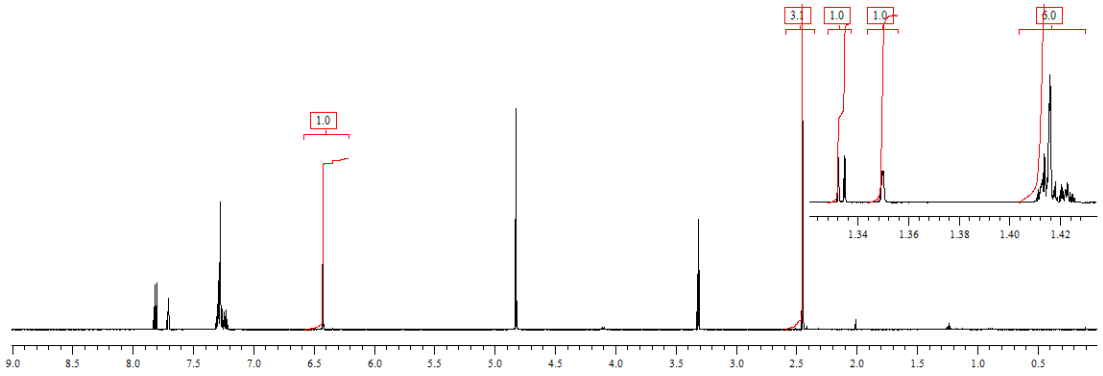
Compound 35



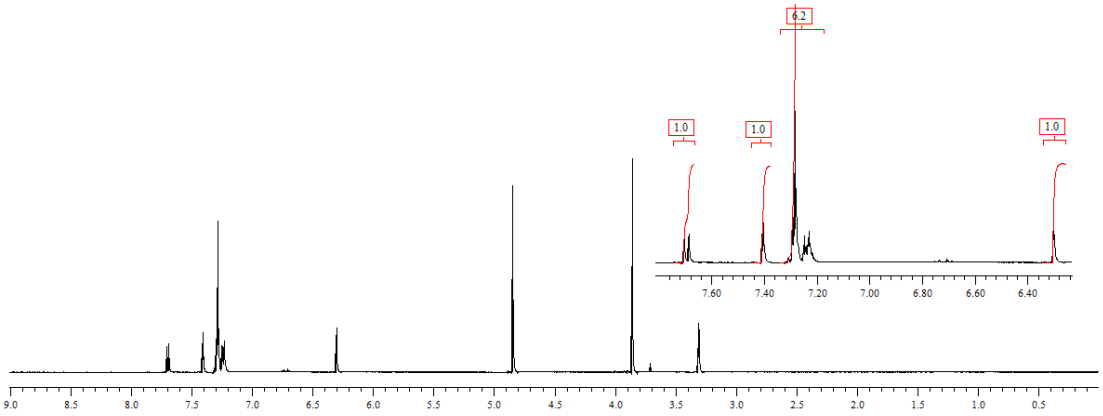
Compound 39



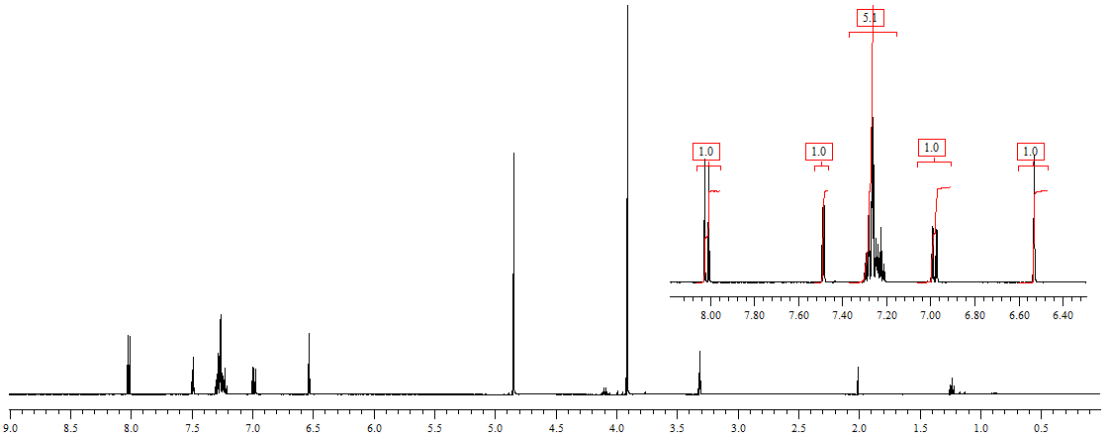
Compound 40



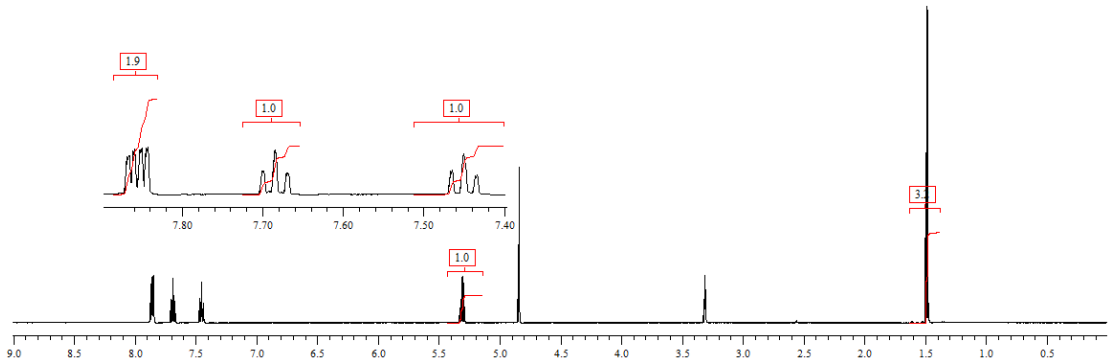
Compound 43



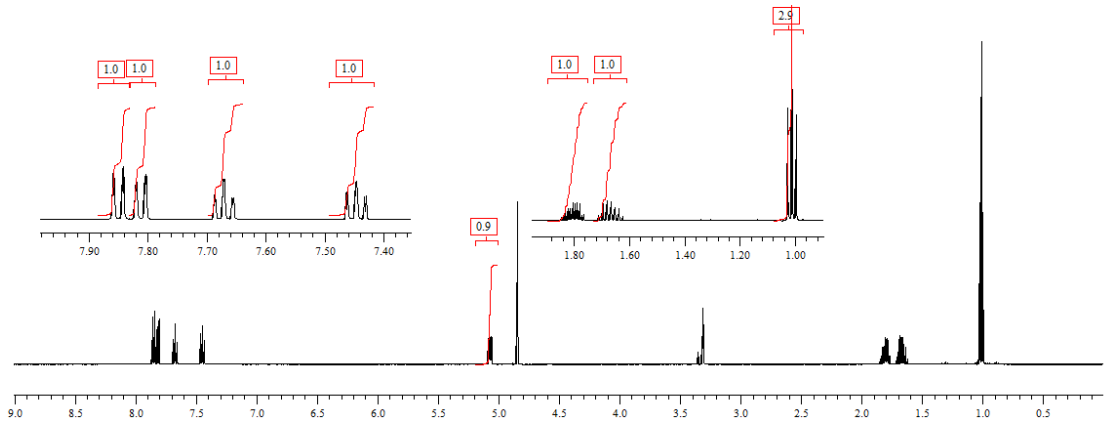
Compound 44



Compound 47



Compound 48



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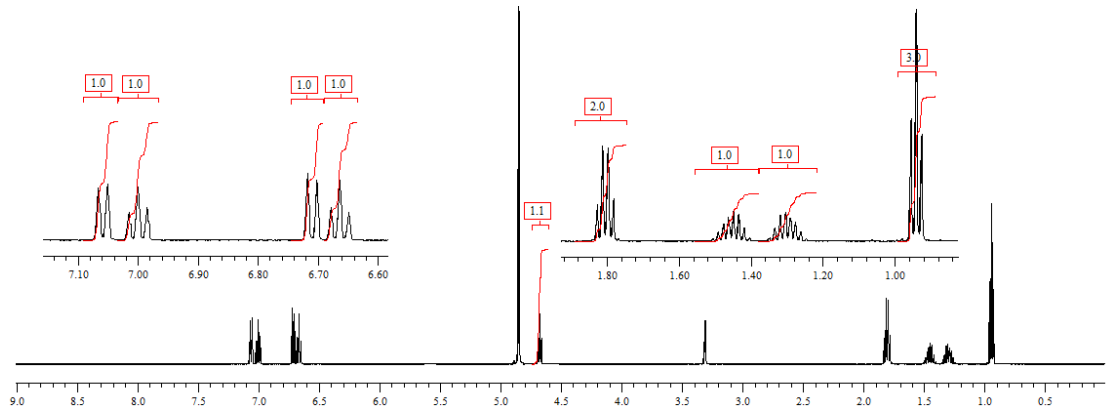
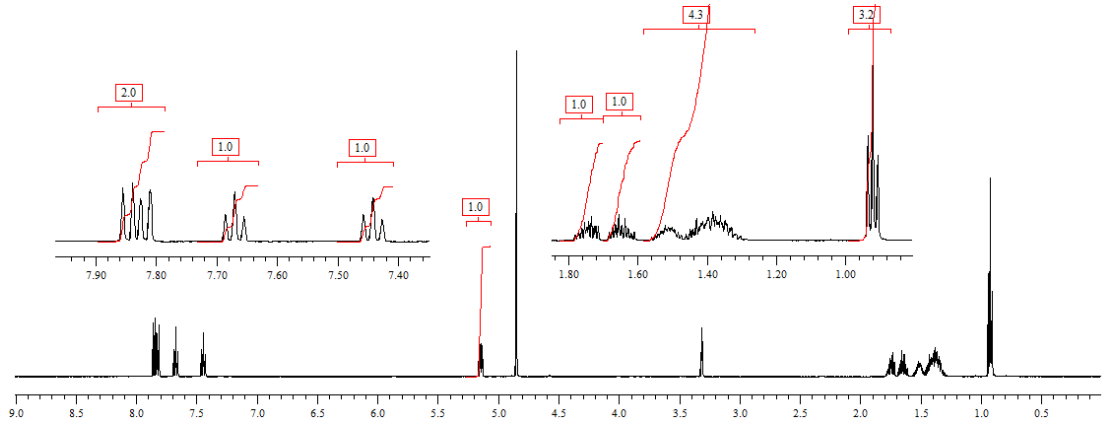
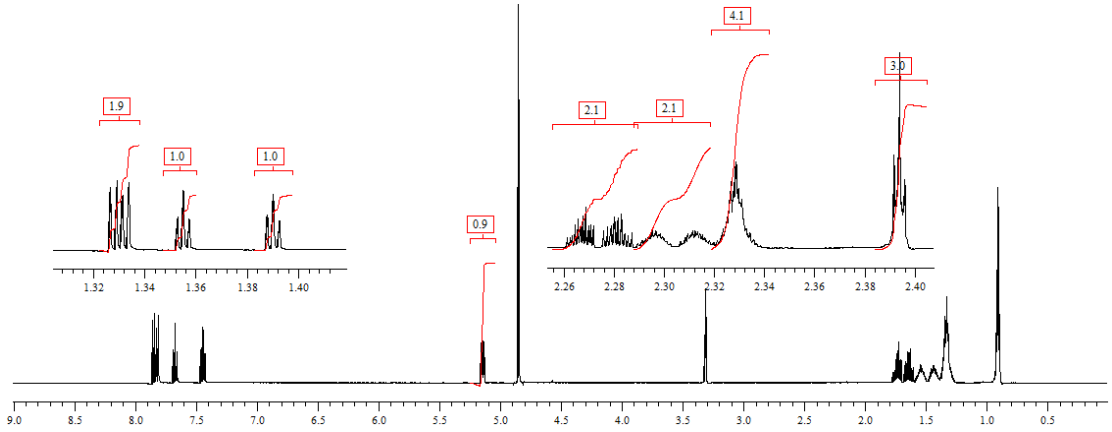


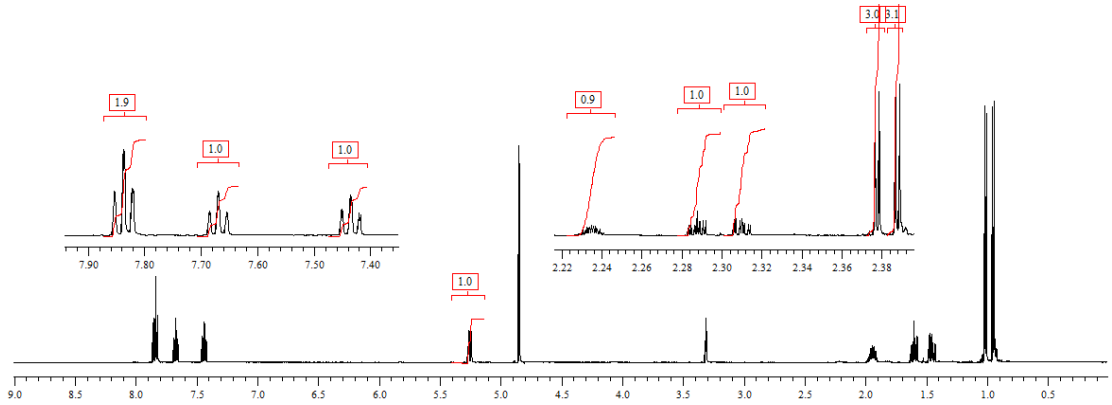
Compound 50



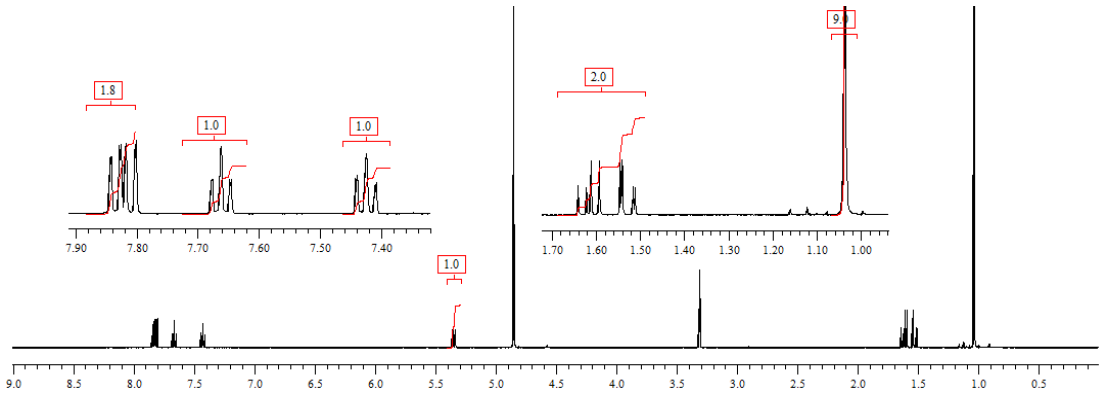
Compound 51



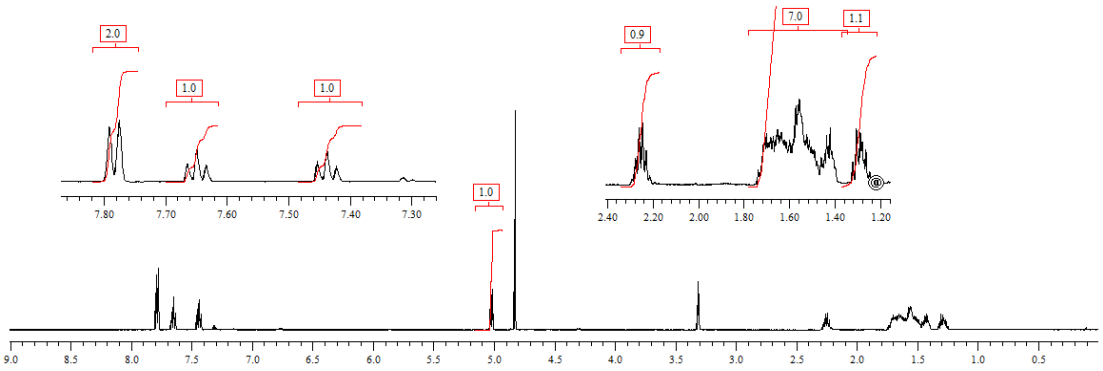
Compound 52



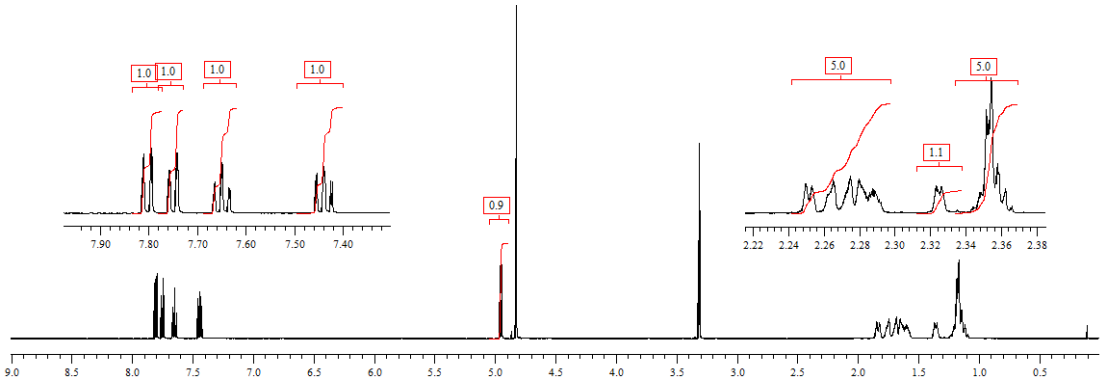
Compound 53



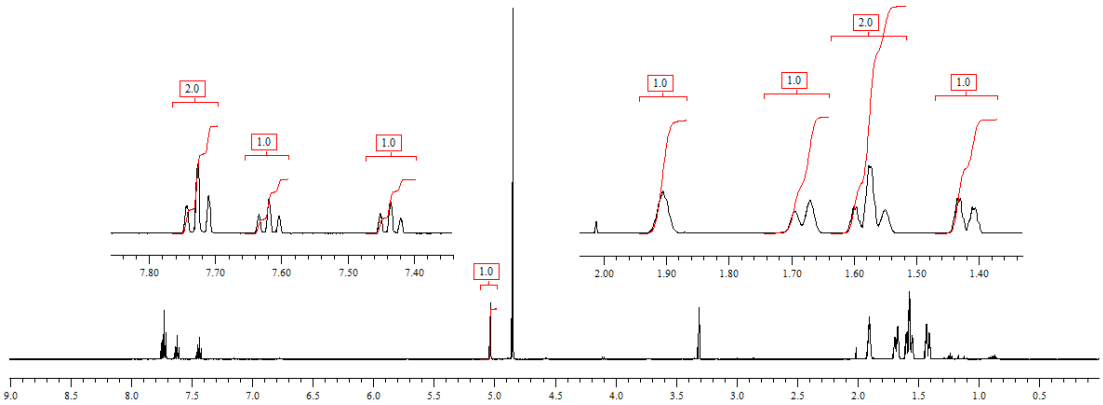
Compound 54



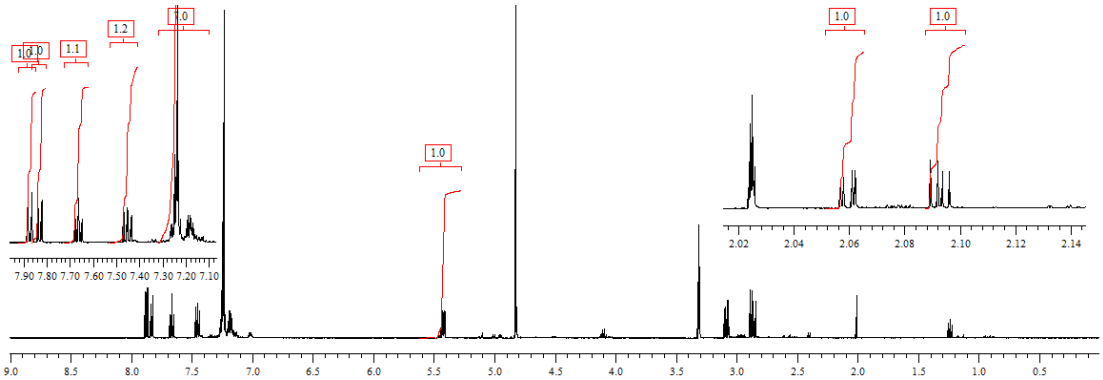
Compound 55



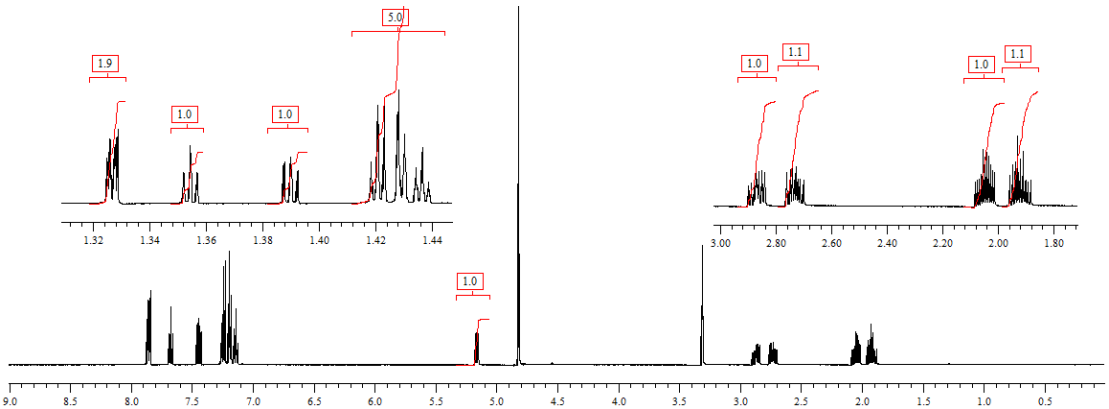
Compound 56



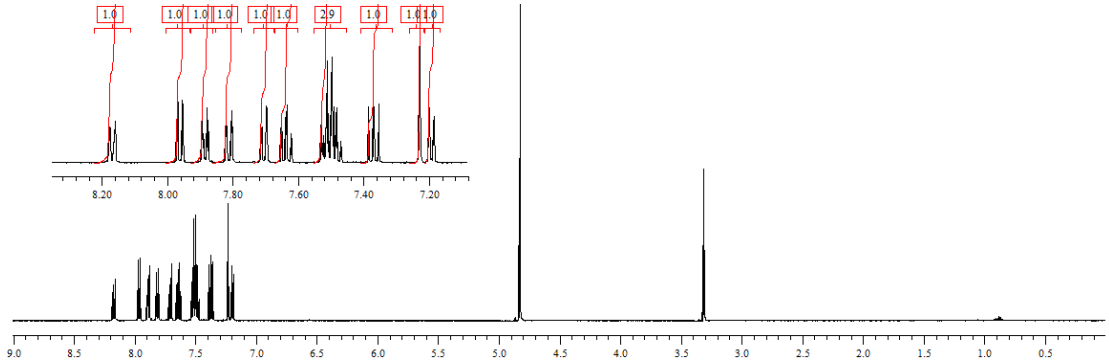
Compound 57



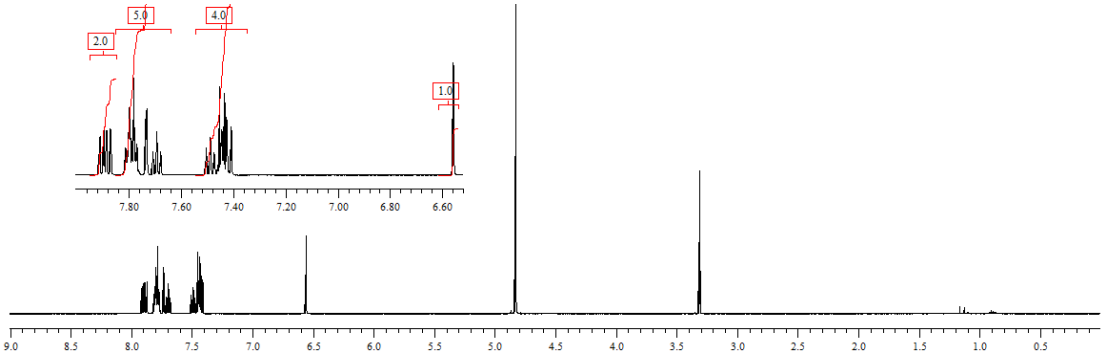
Compound 58



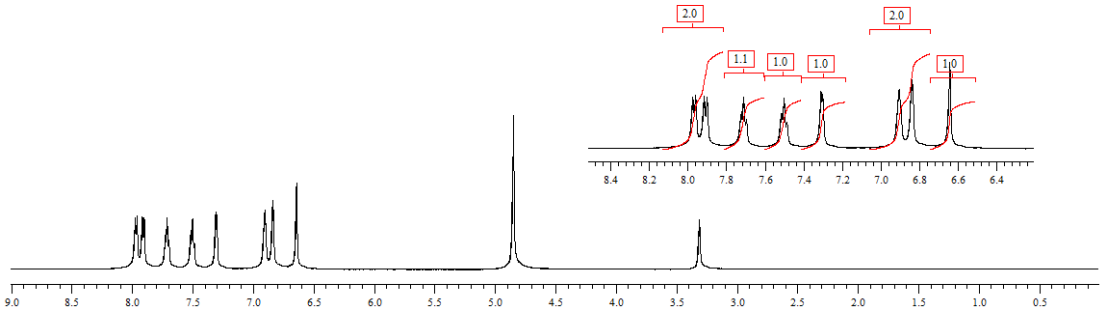
Compound 59



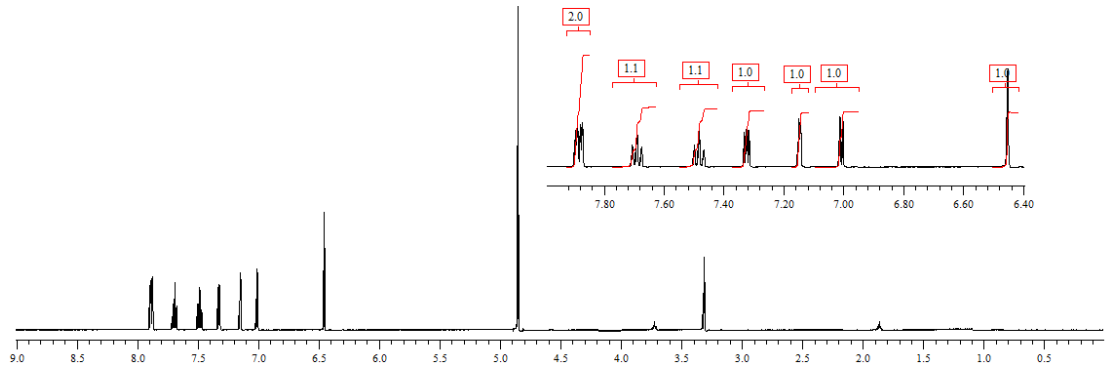
Compound 60



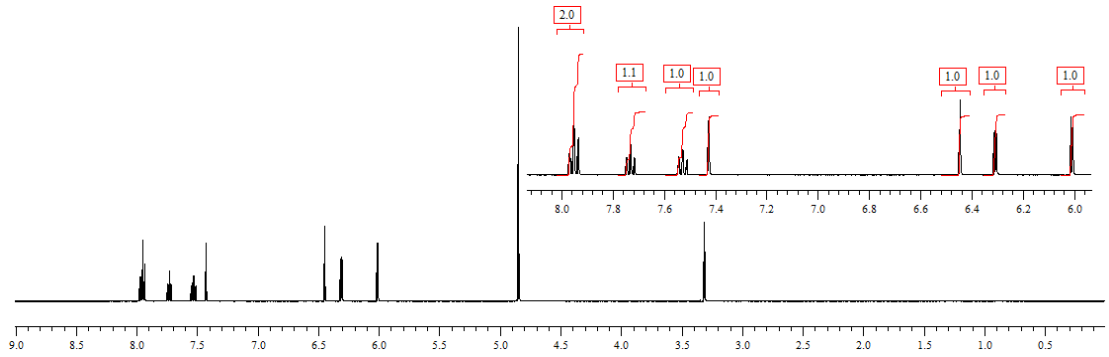
Compound 61



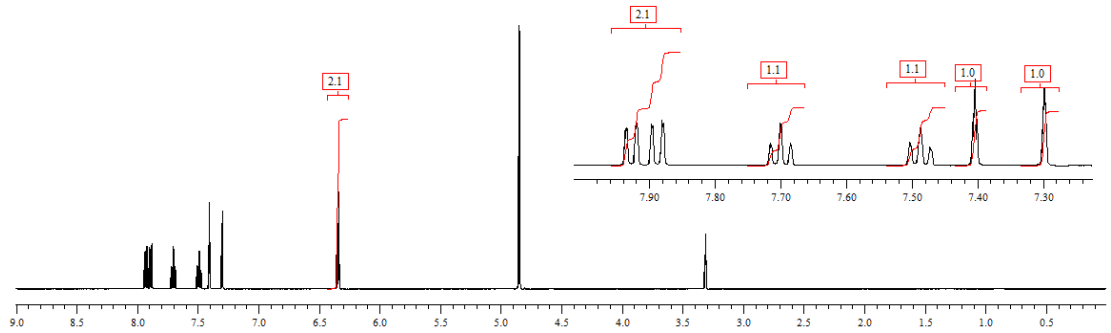
Compound 62



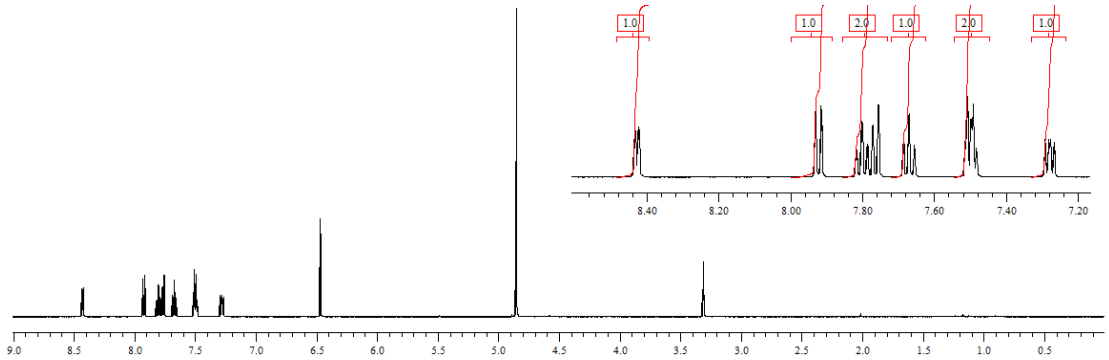
Compound 63



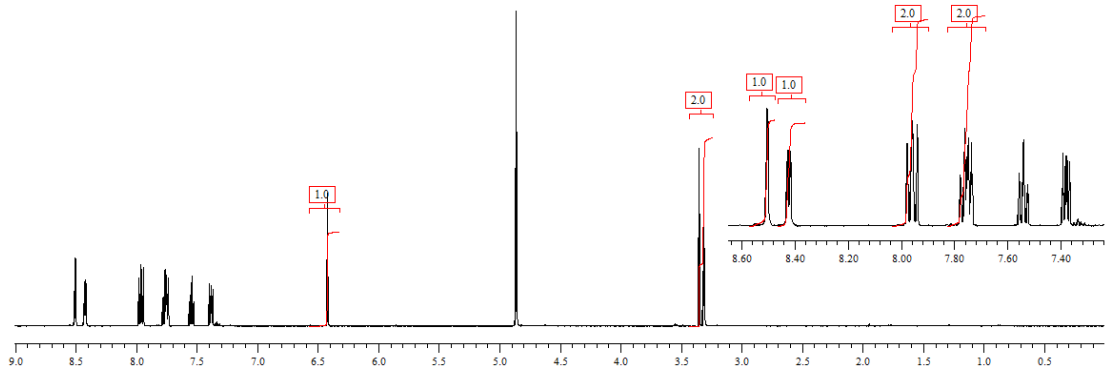
Compound 64



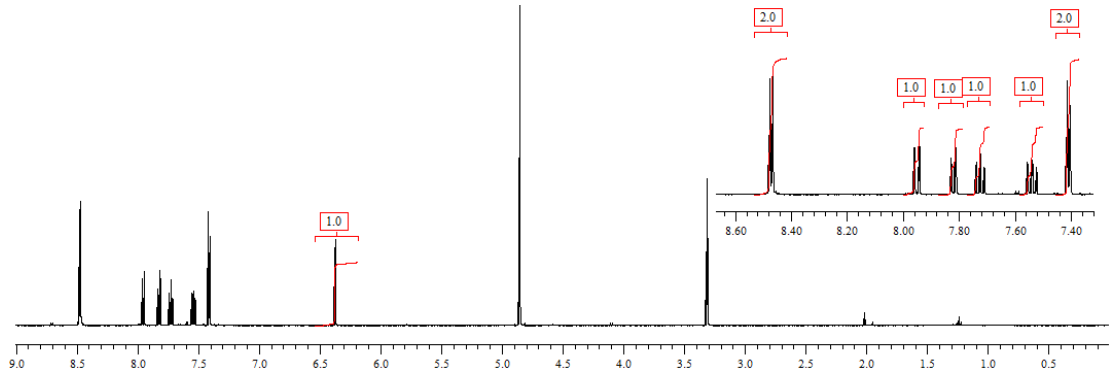
Compound 65



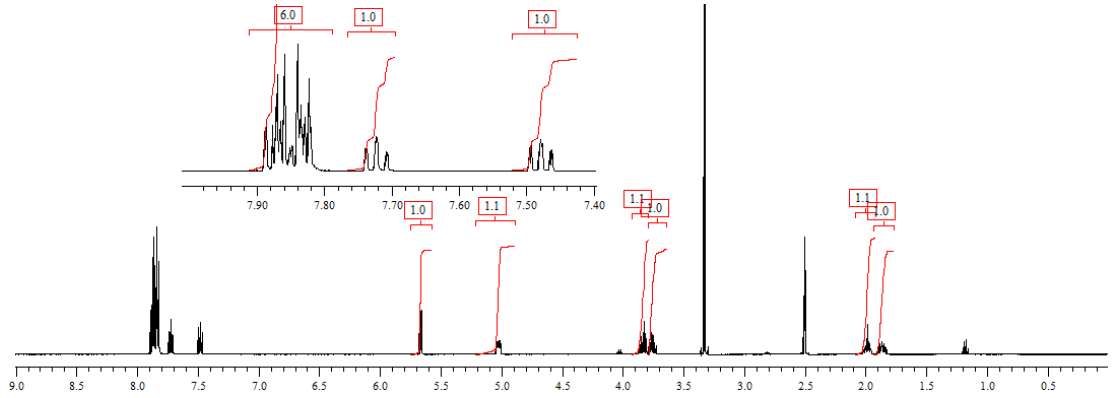
Compound 66



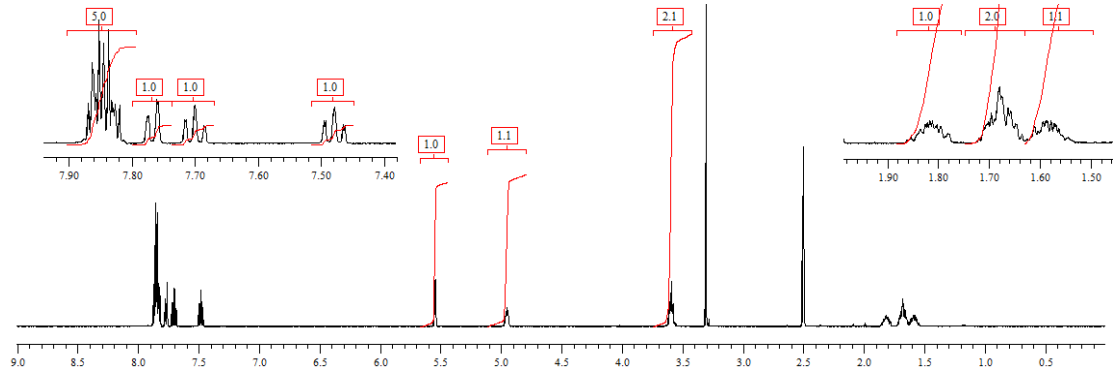
Compound 67



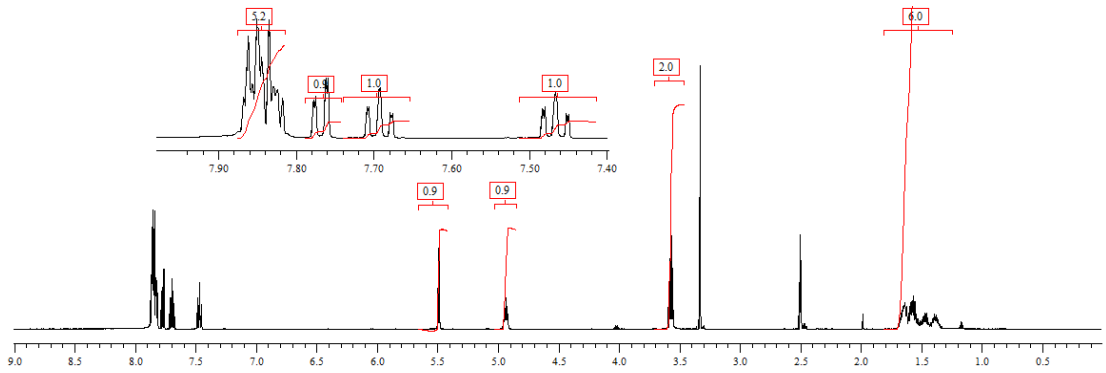
Compound 68



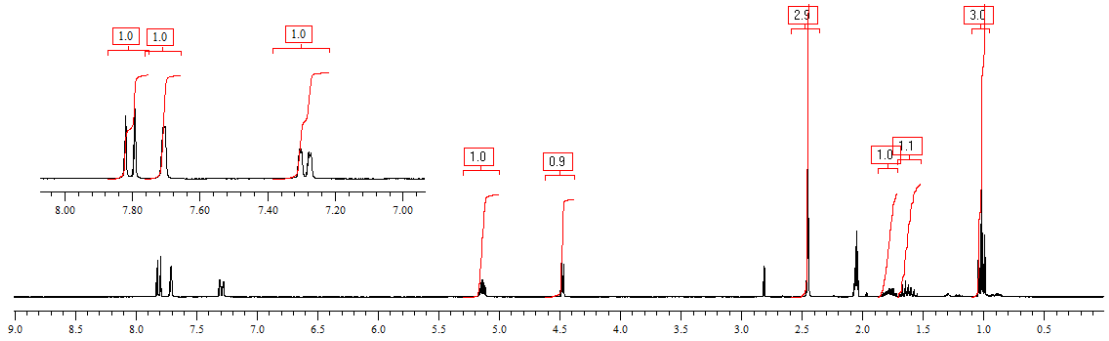
Compound 69



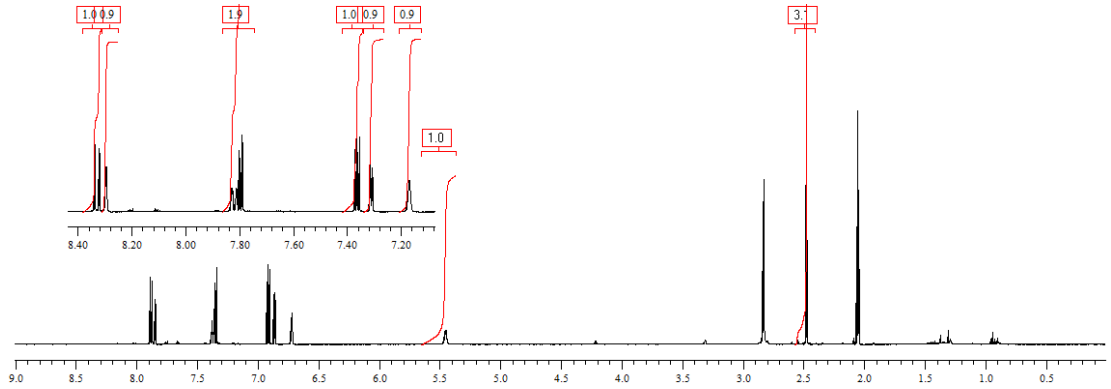
Compound 70



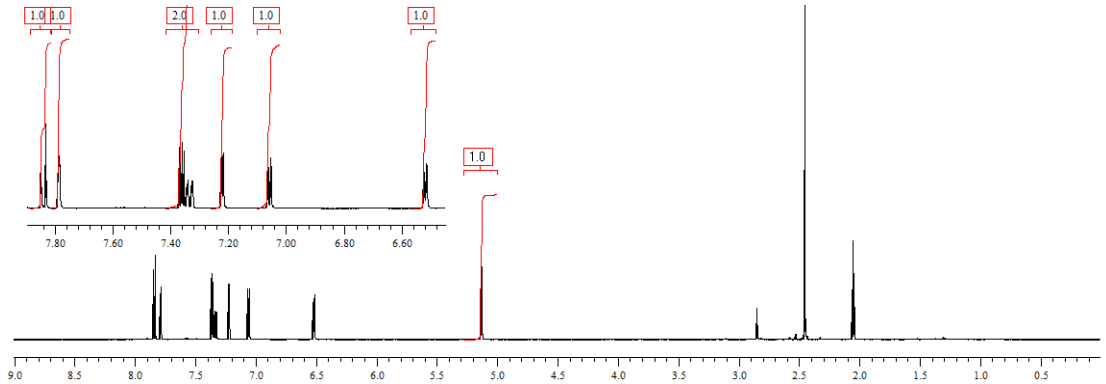
Compound 71



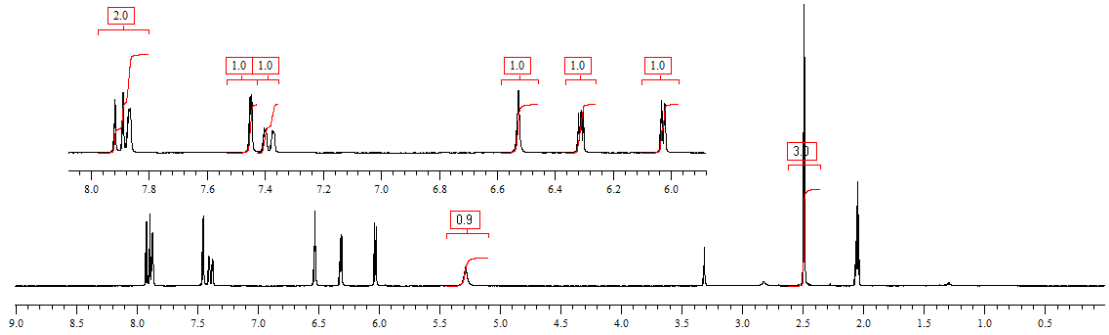
Compound 72



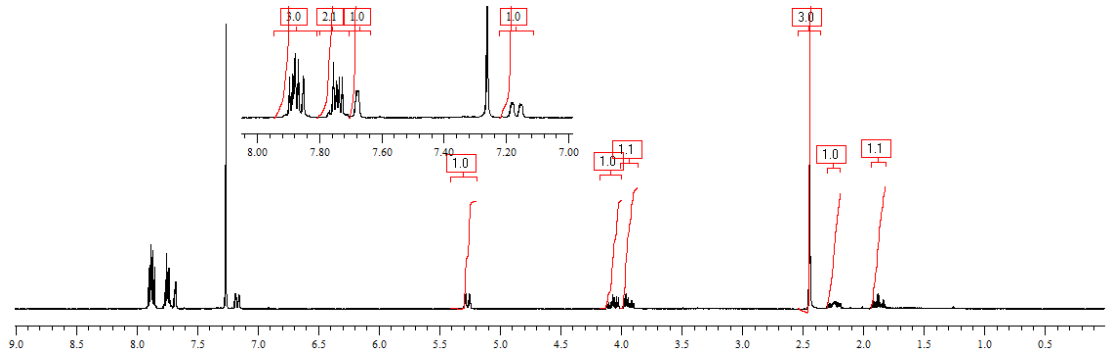
Compound 73



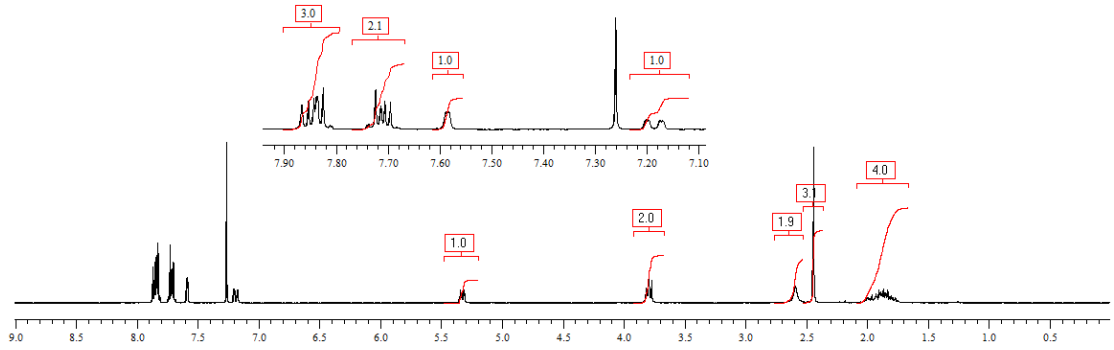
Compound 74



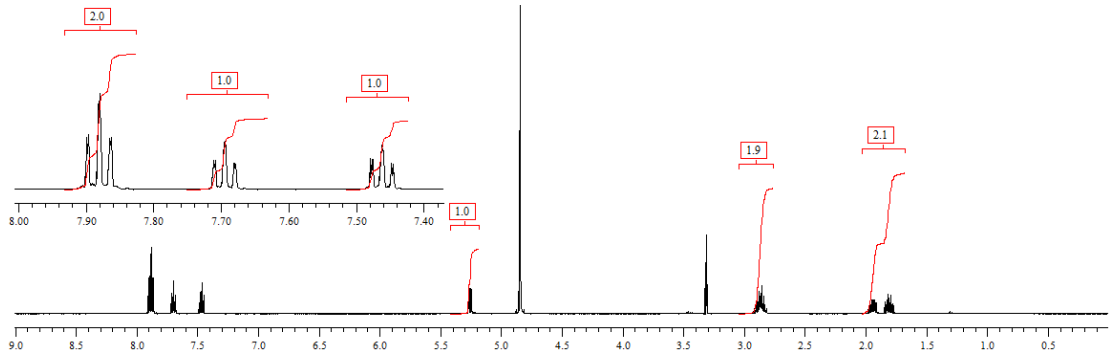
Compound 75



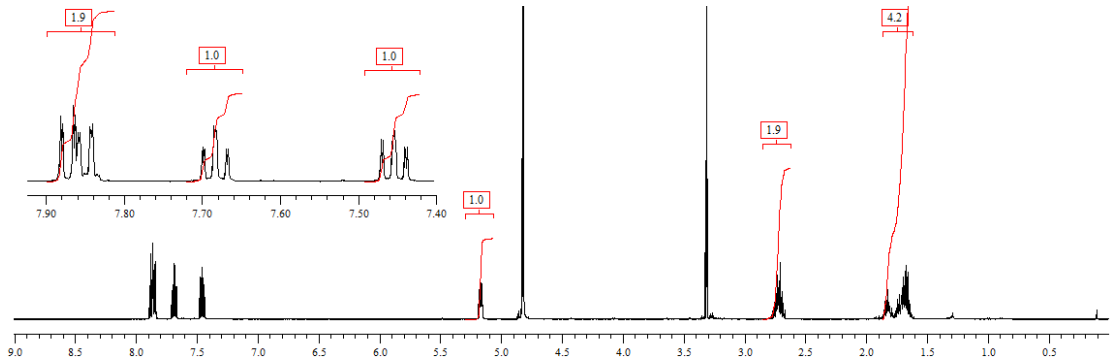
Compound 76



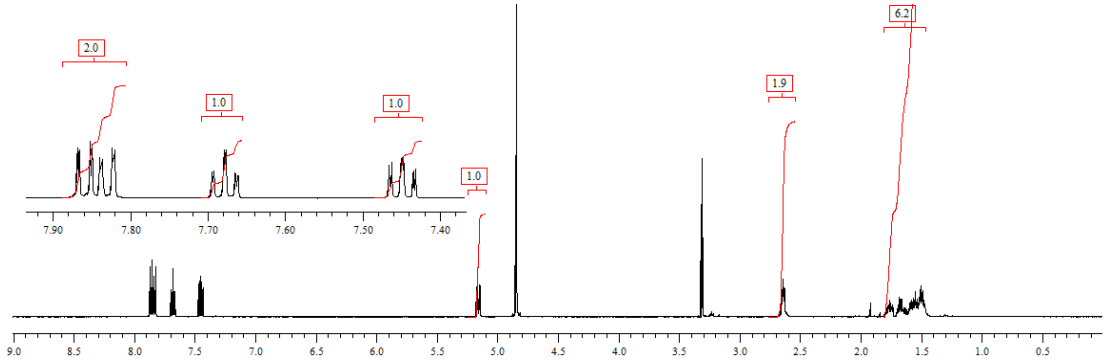
Compound 77



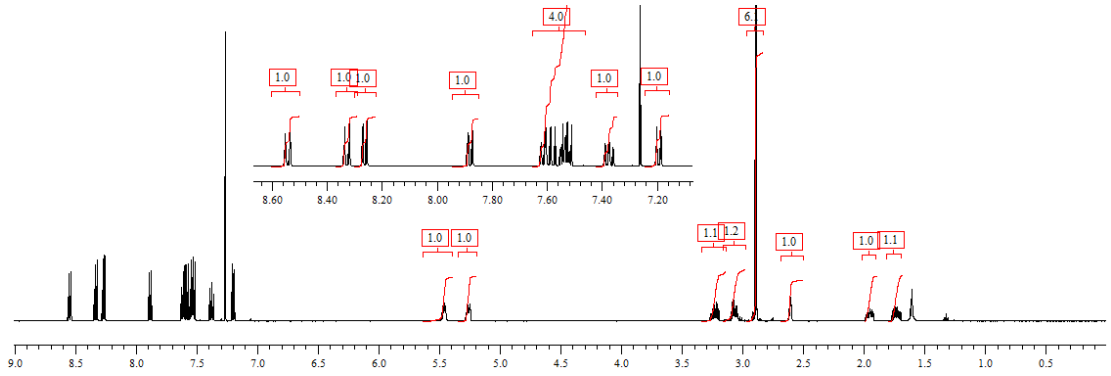
Compound 78



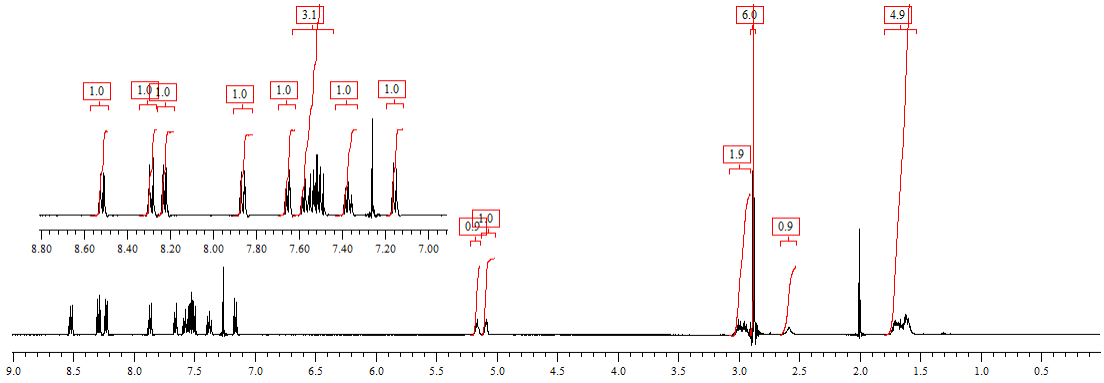
Compound 79



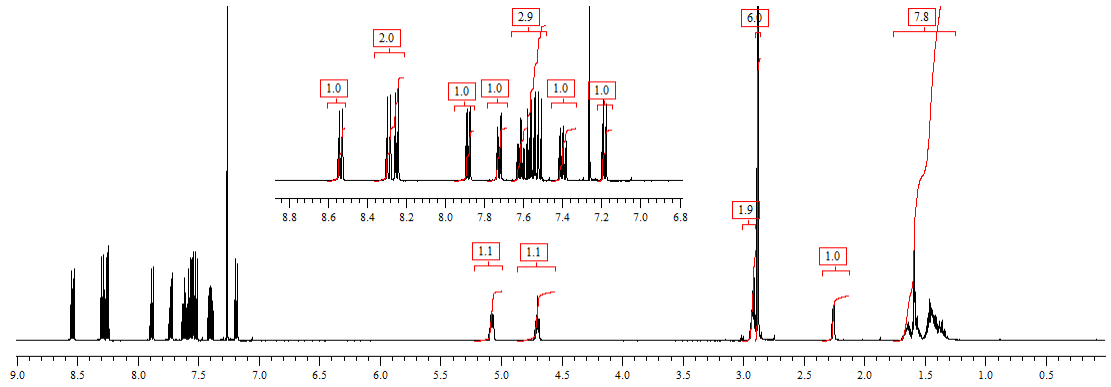
Compound 80



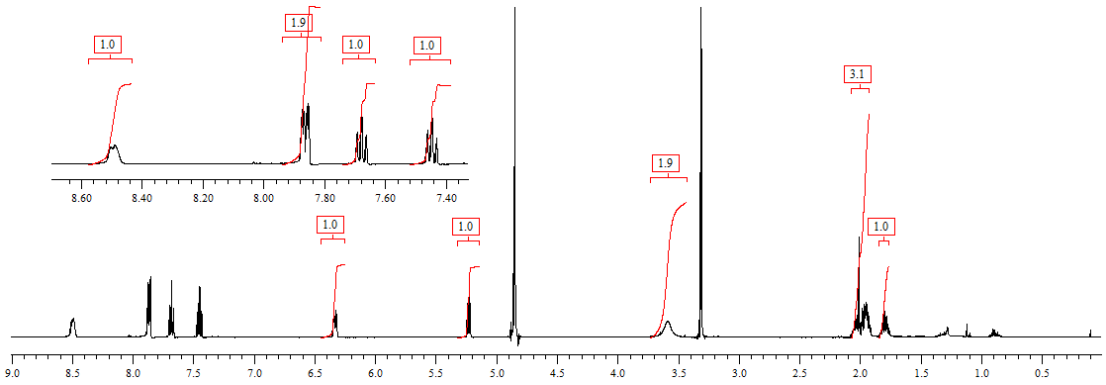
Compound 81



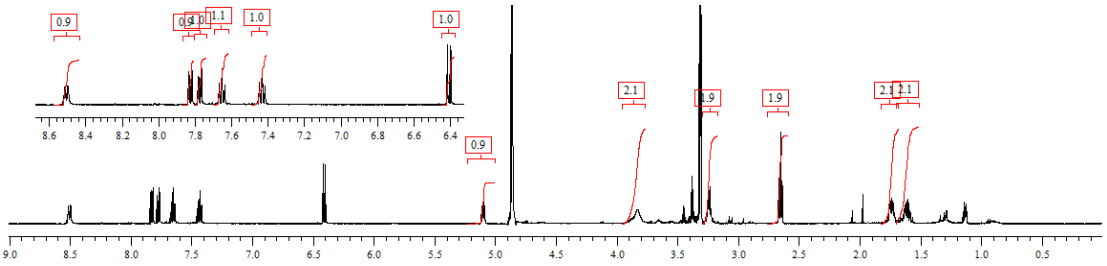
Compound 82



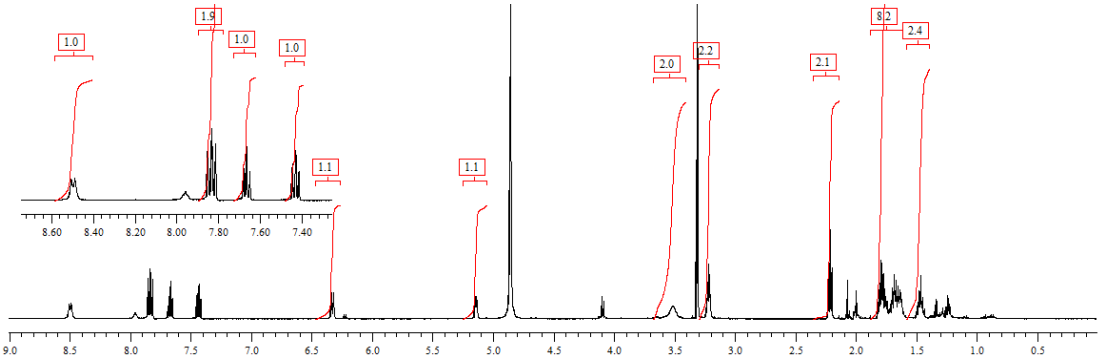
Compound 83



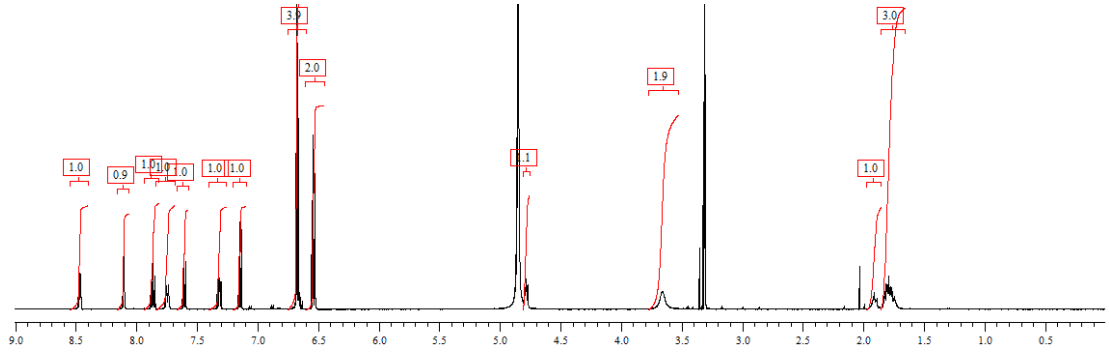
Compound 84



Compound 85



Compound 86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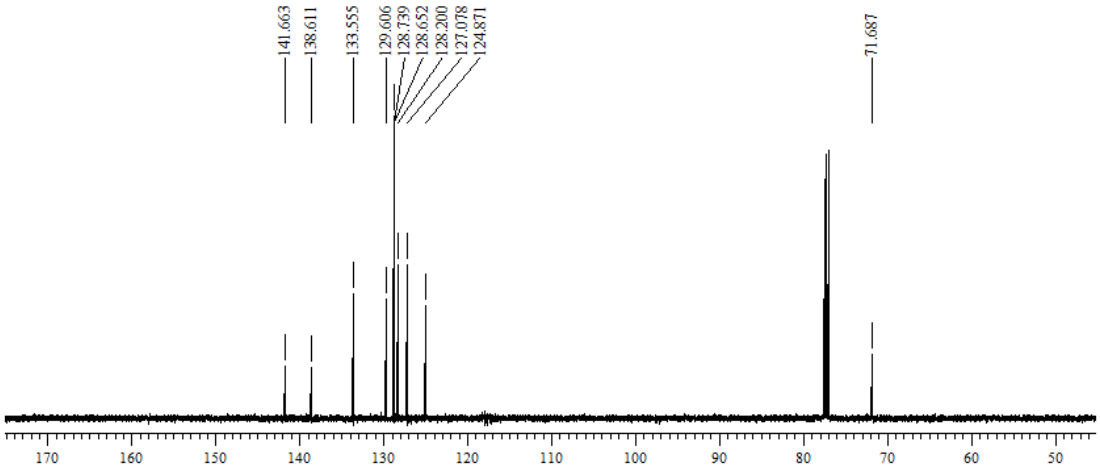
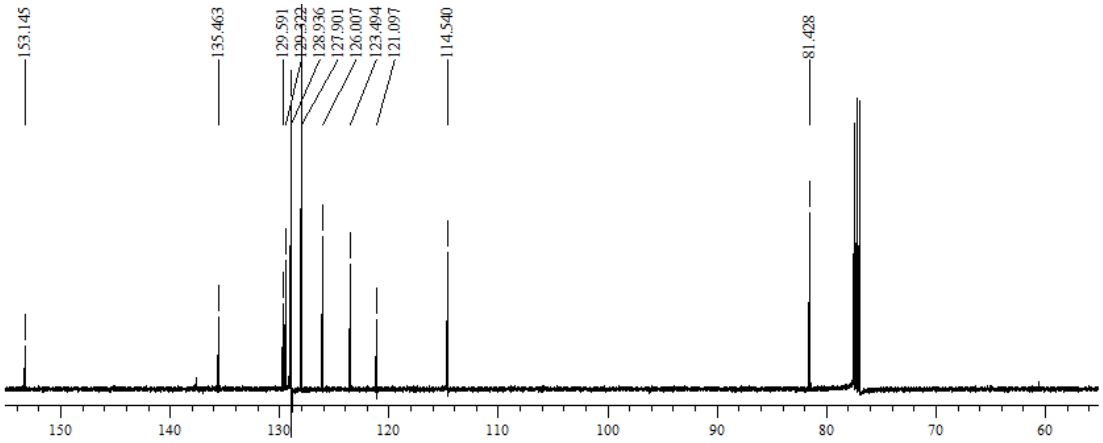
1.0
1.0
1.1
1.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

8. ^{13}C NMR spectra of all tested compounds

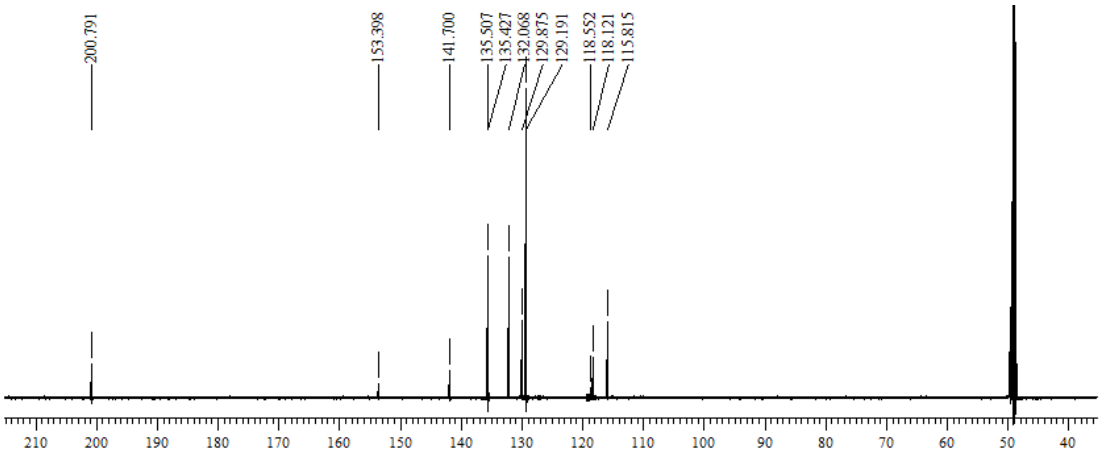
Compound 3



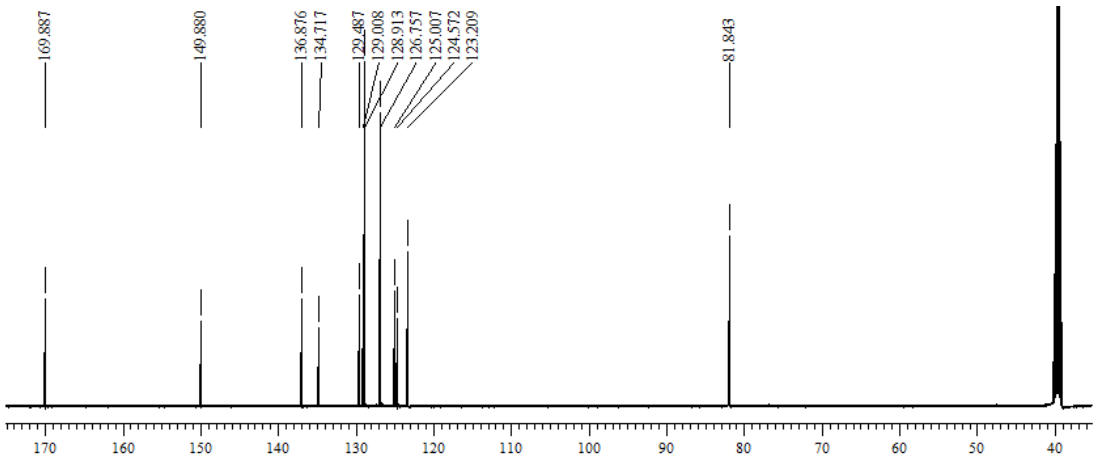
Compound 7



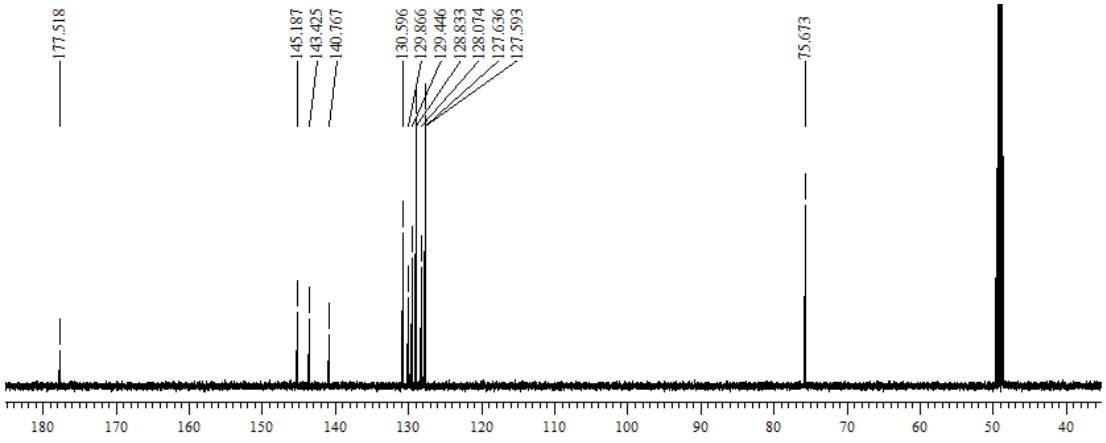
Compound 8



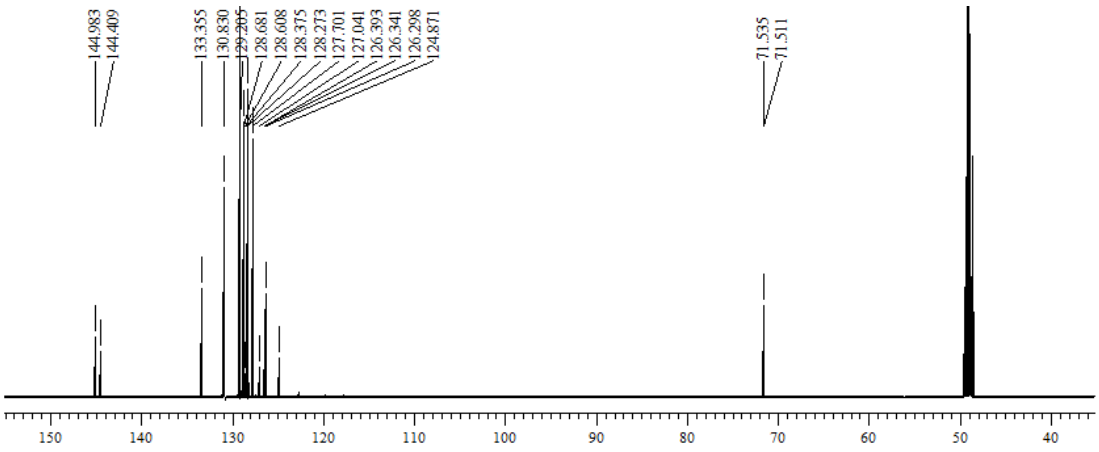
Compound 10



Compound 11



Compound 14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129.205
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128.608
128.375
128.273
127.701
127.041
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126.341
126.298
124.871
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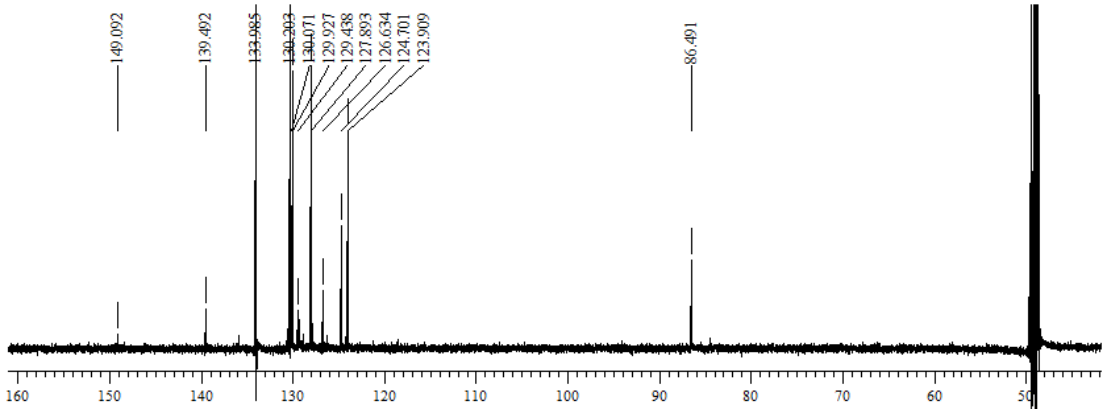
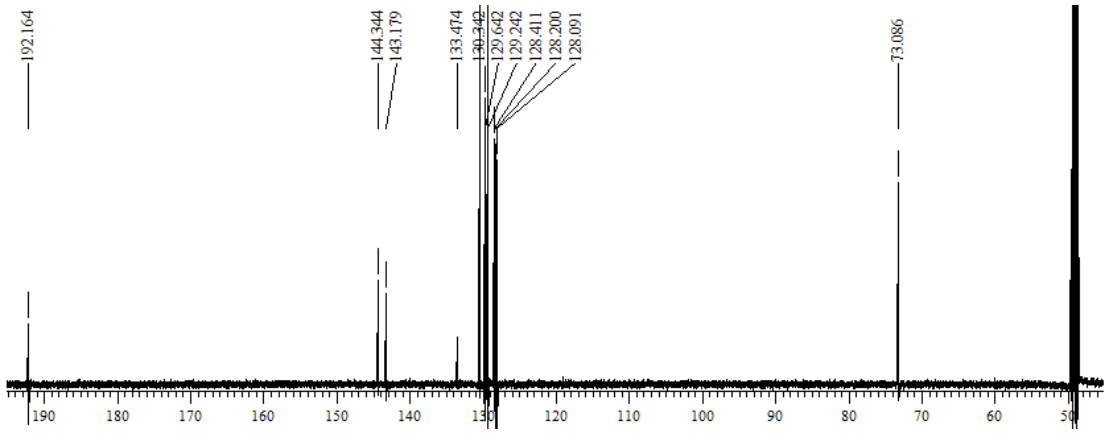
71.511
150
140
130
120
110
100
90
80
70
60
50
40

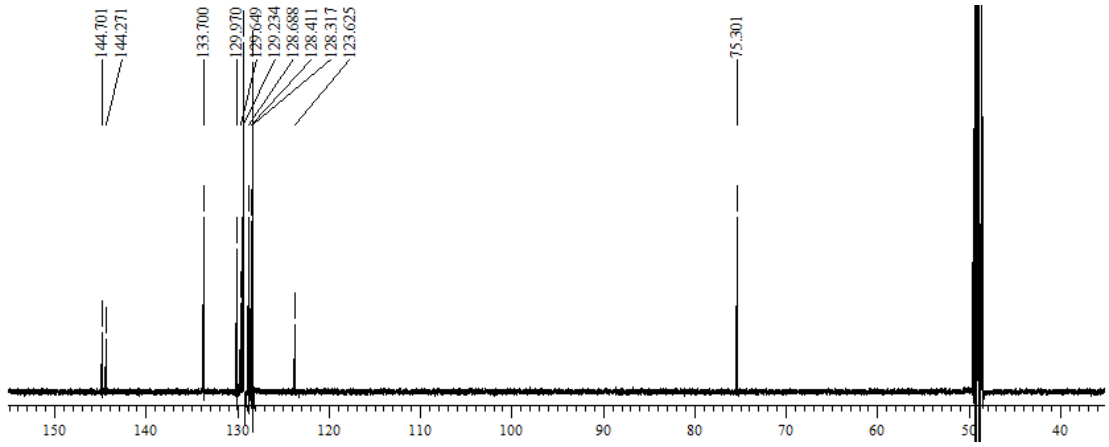
Compound 15



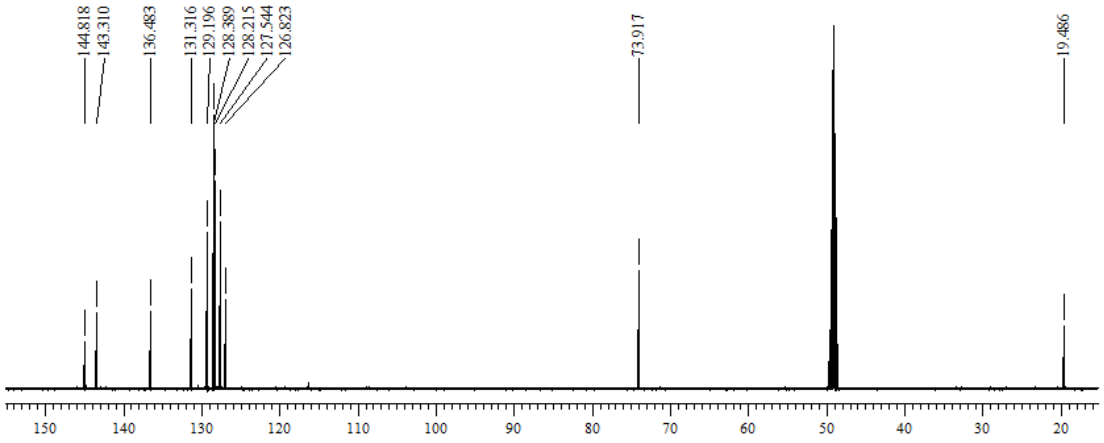
Compound 21



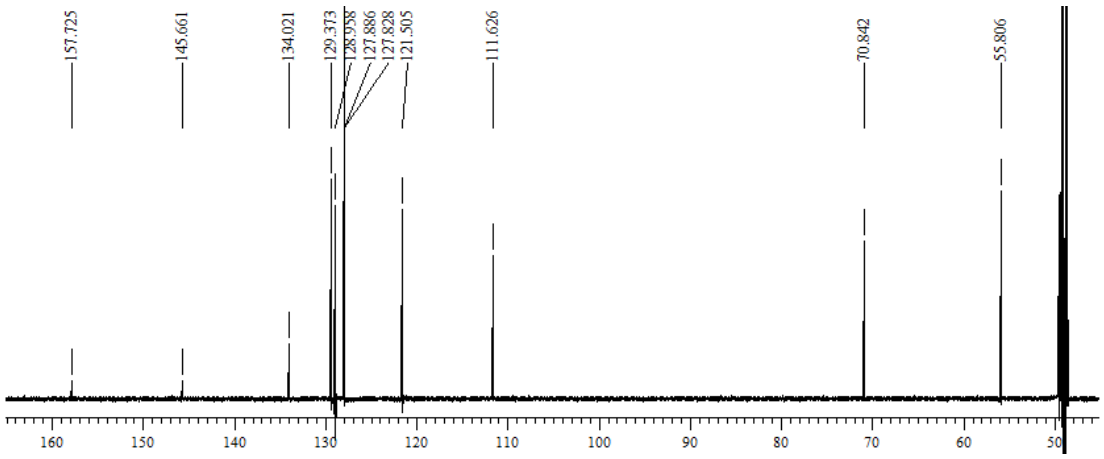
Compound 22



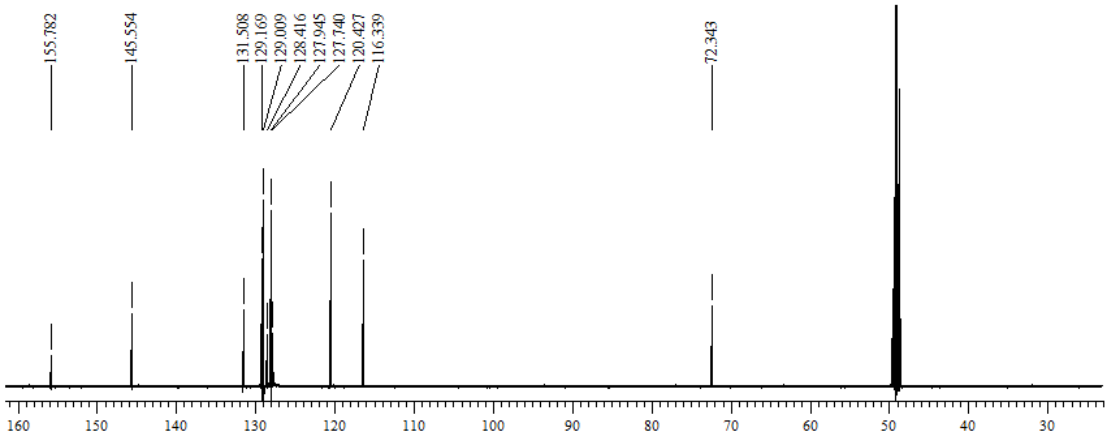
Compound 23



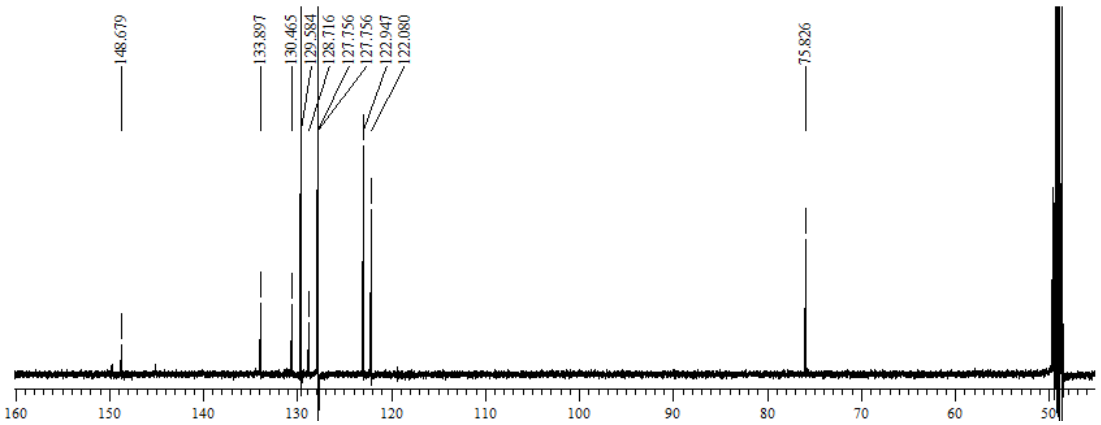
Compound 24



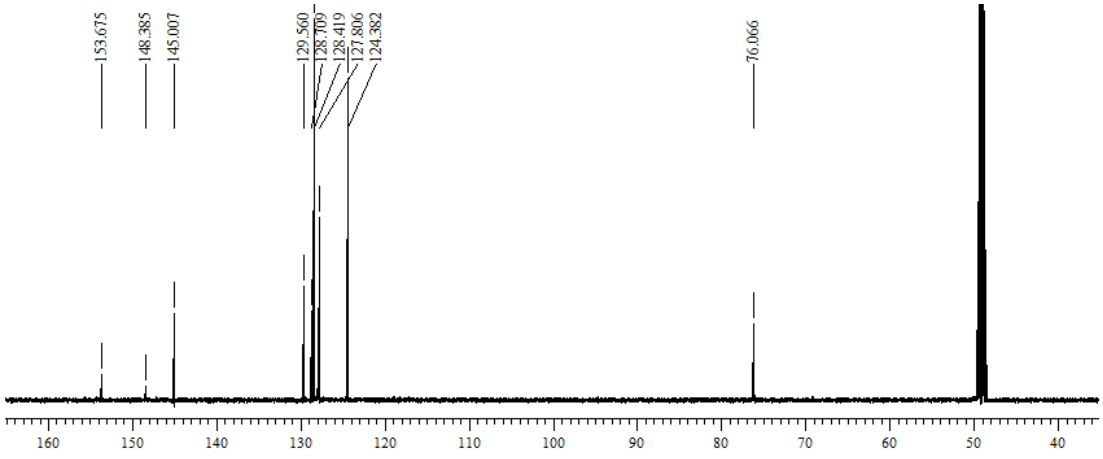
Compound 25



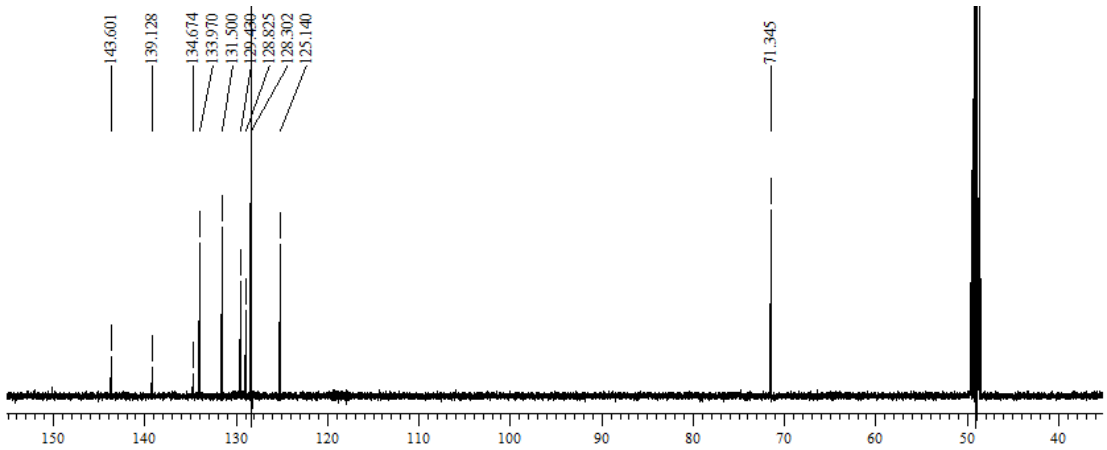
Compound 28



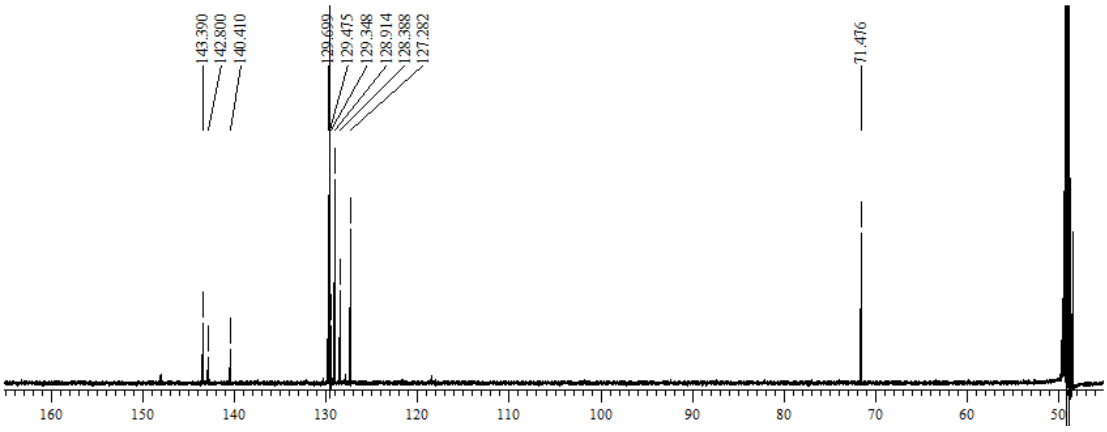
Compound 29



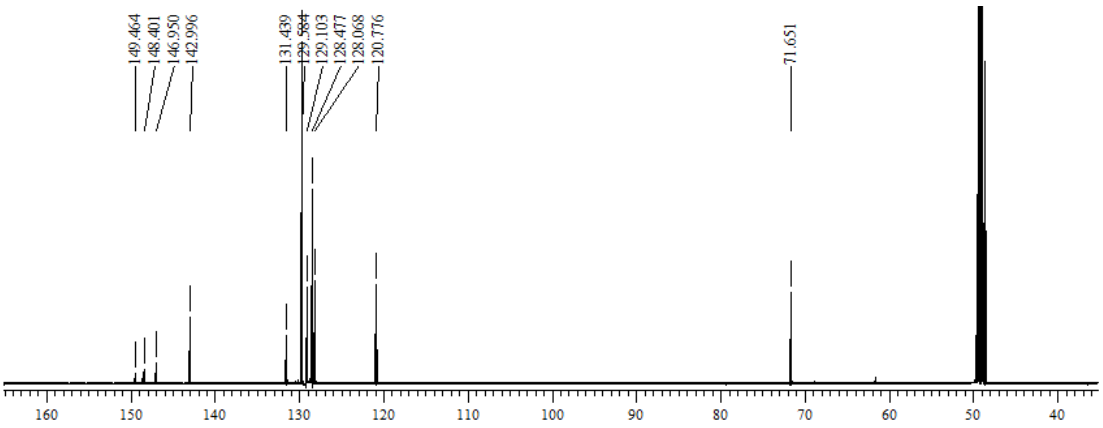
Compound 33



Compound 34



Compound 35



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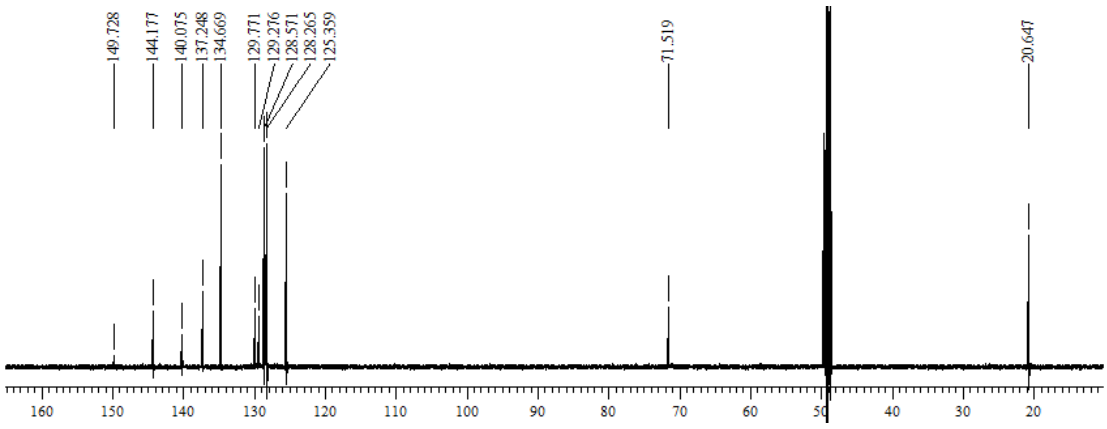

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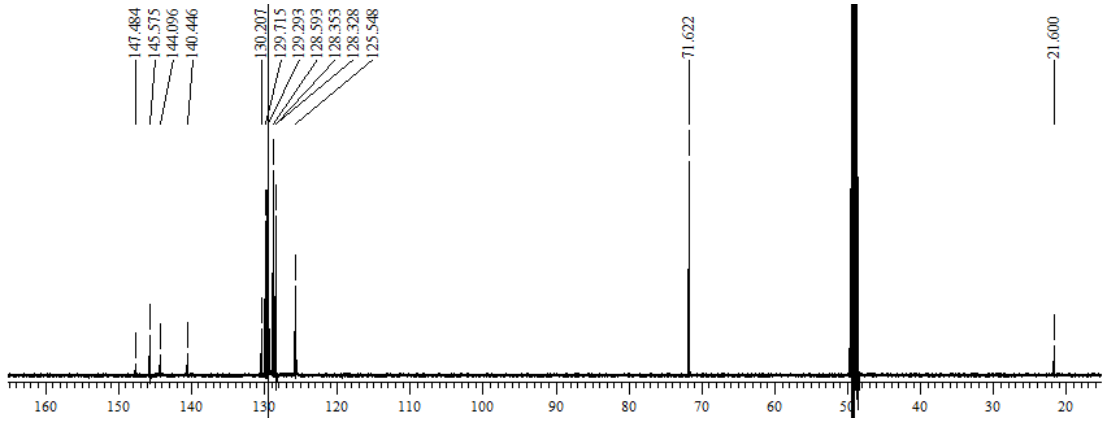
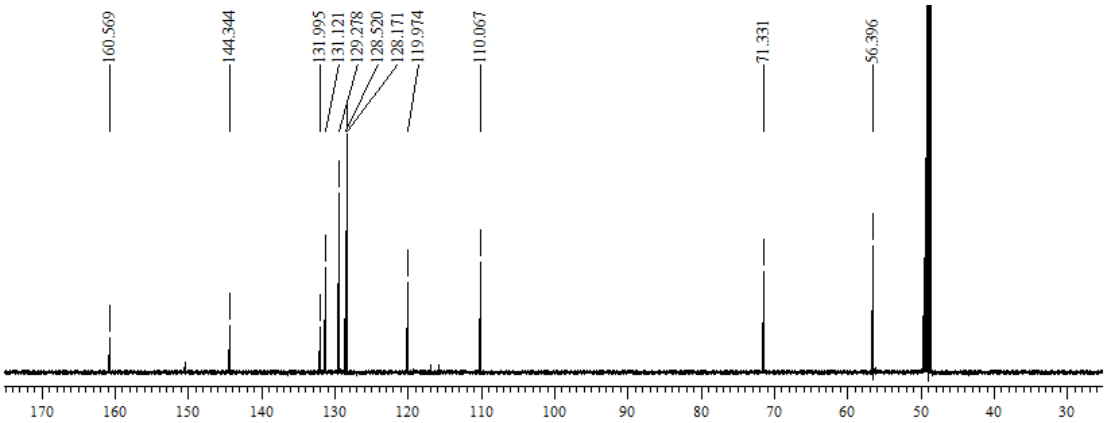
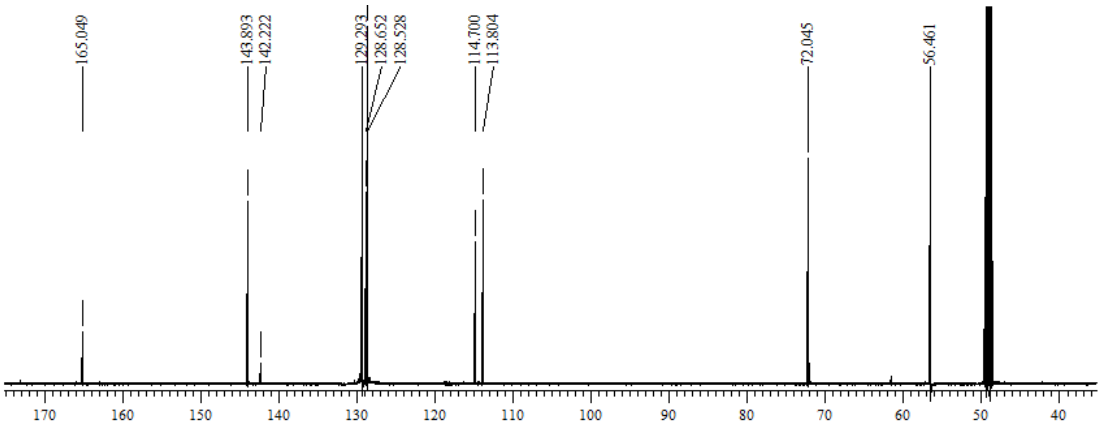


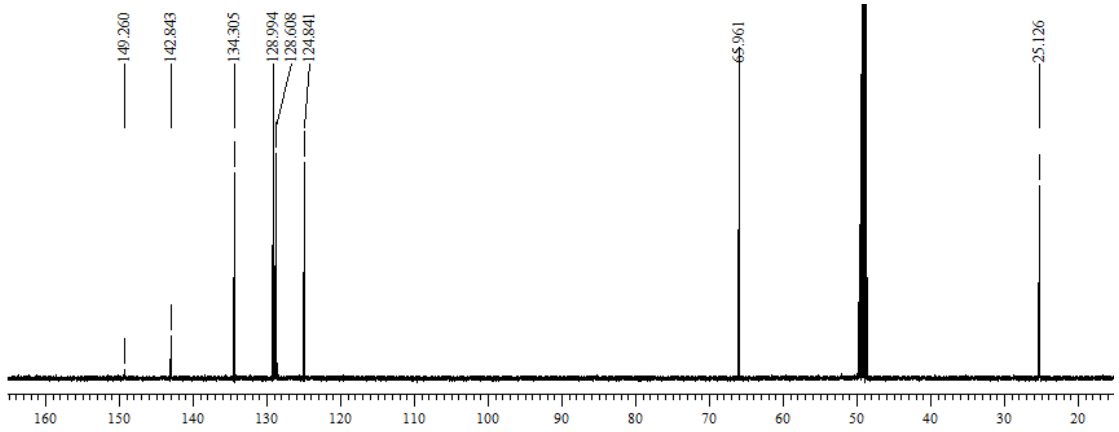
Compound 43



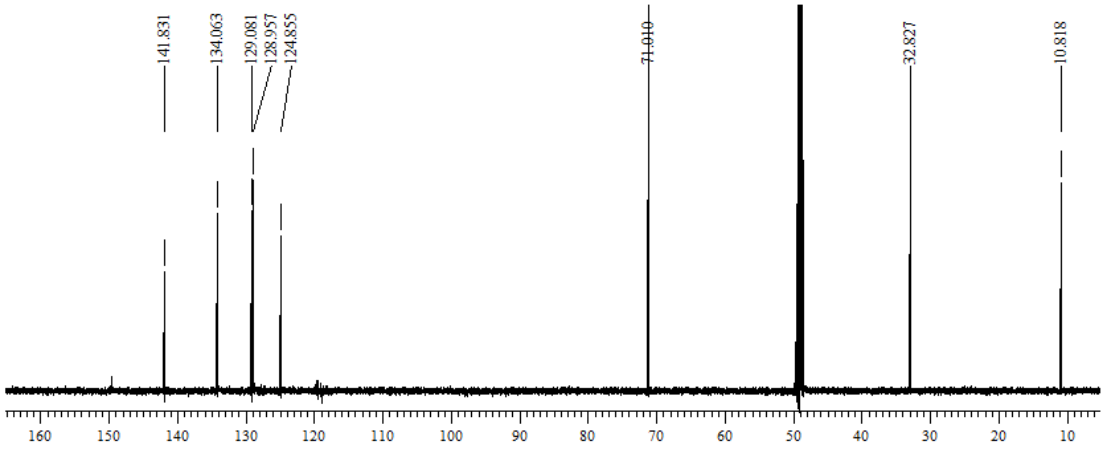
Compound 44



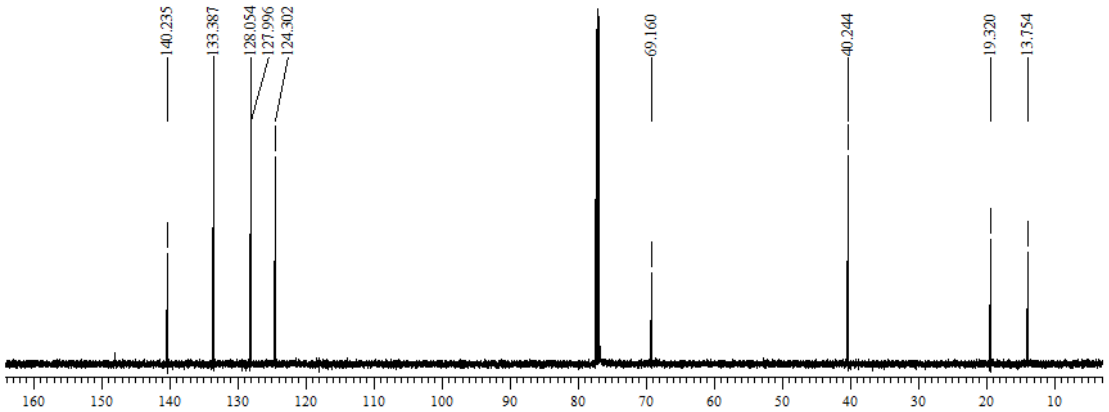
Compound 47



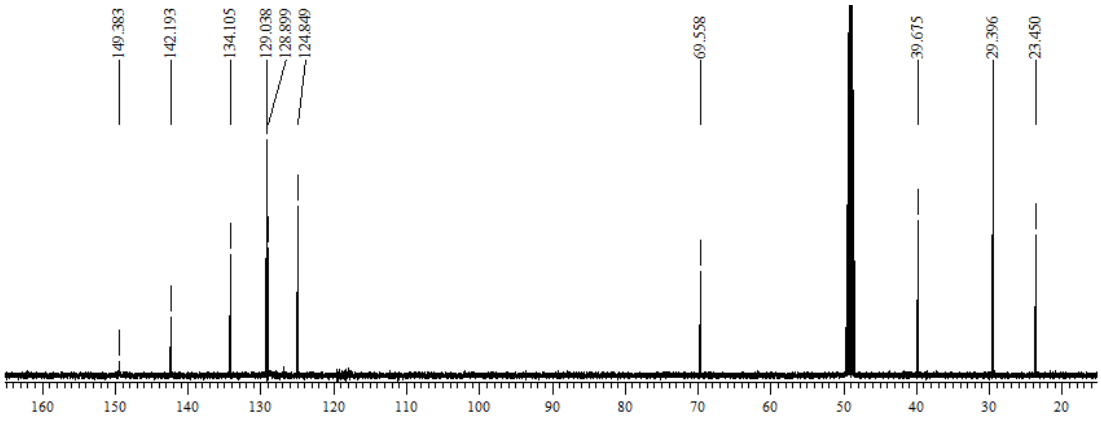
Compound 48



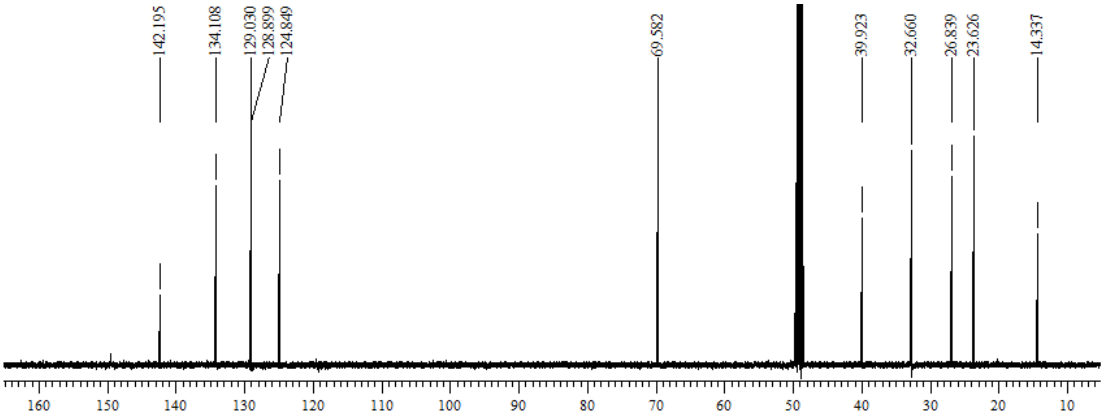
Compound 49



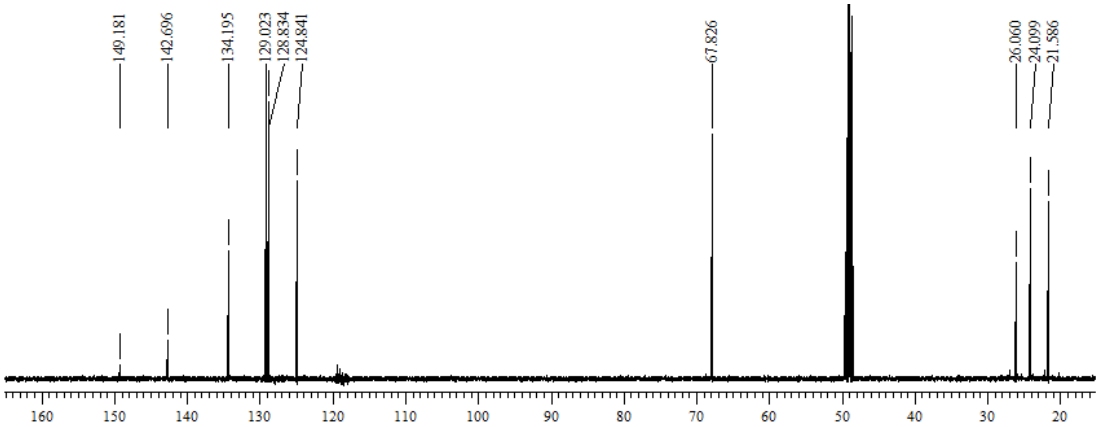
Compound 50



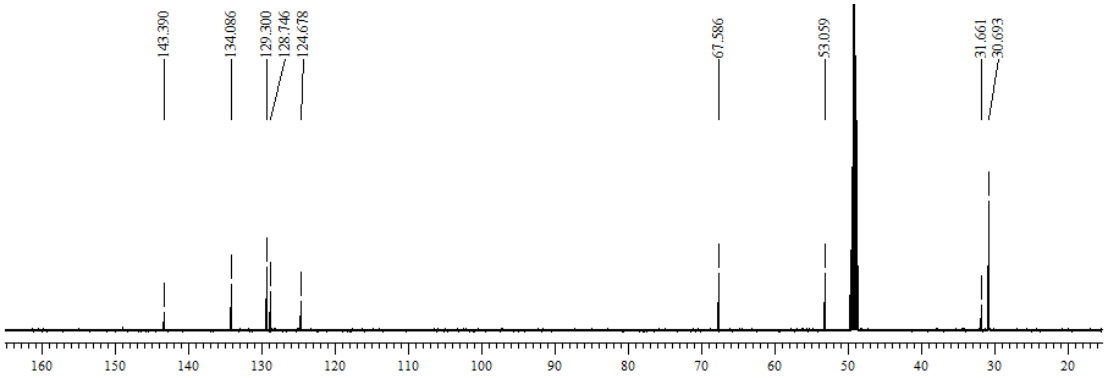
Compound 51



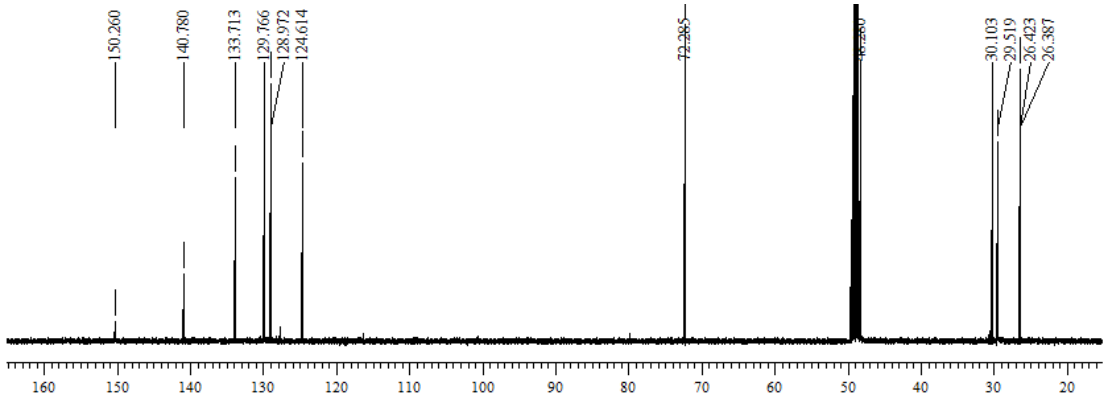
Compound 52



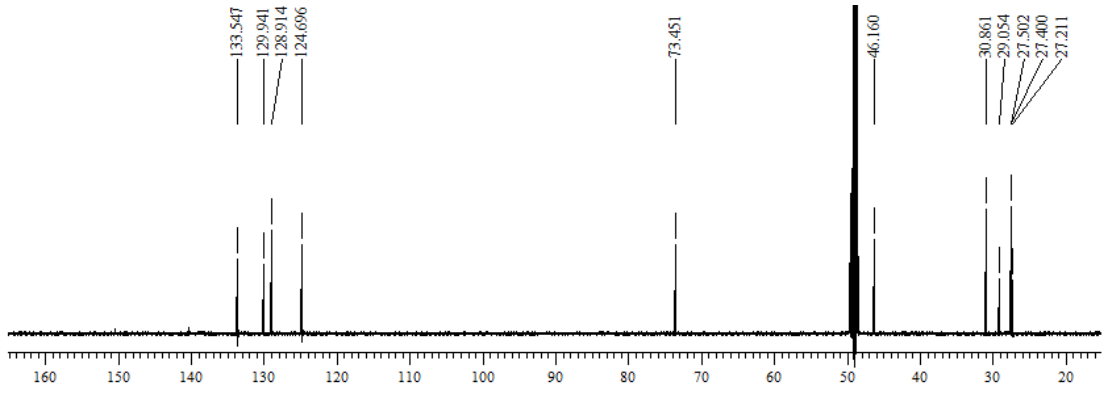
Compound 53



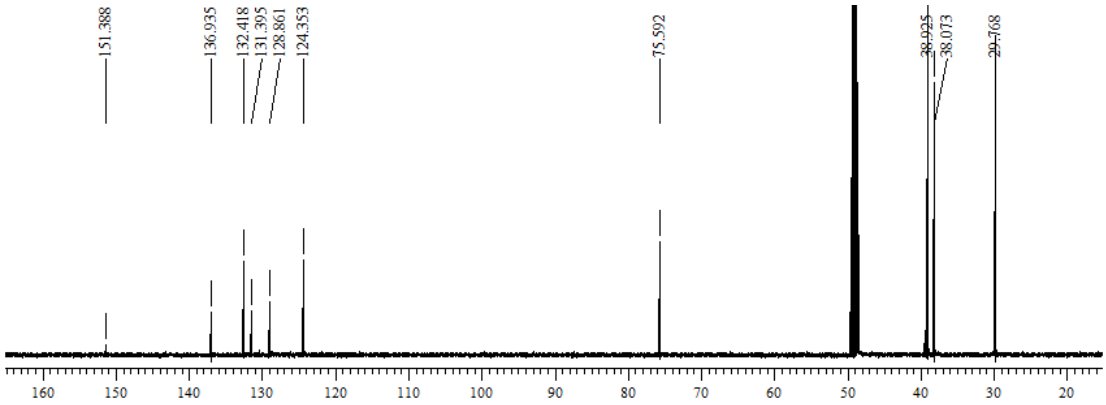
Compound 54



Compound 55



Compound 56



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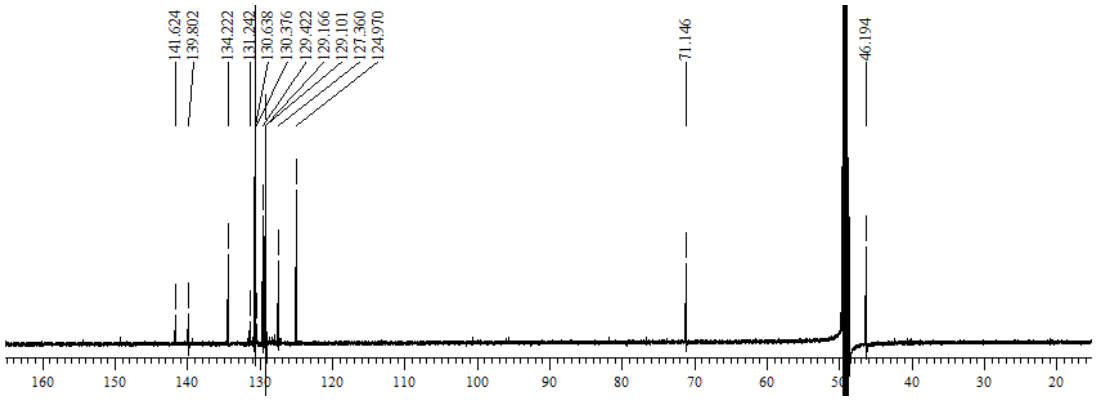
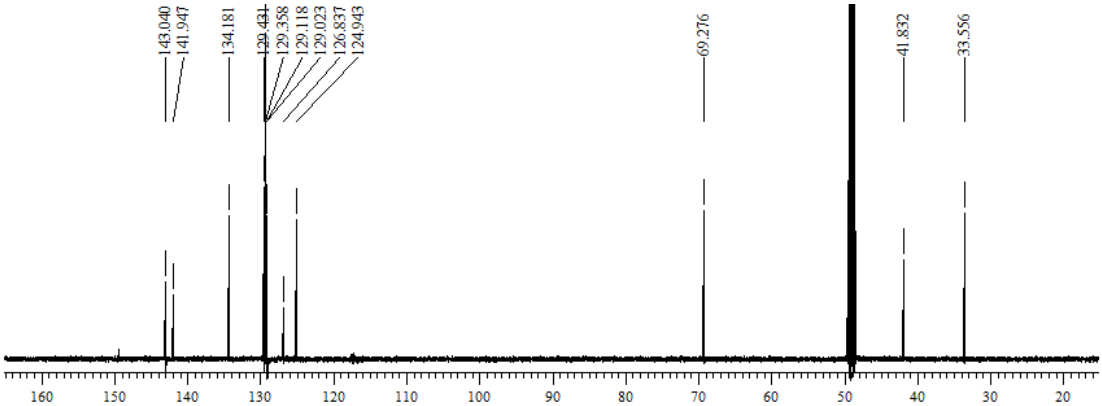
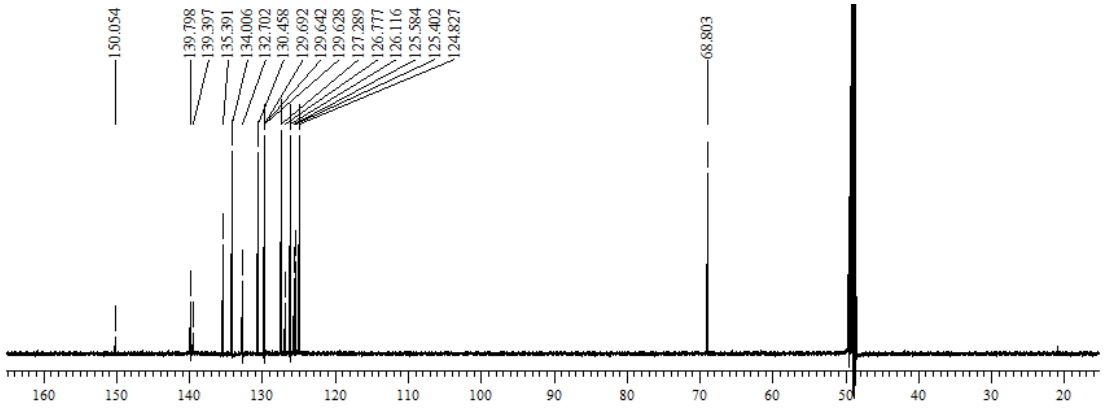


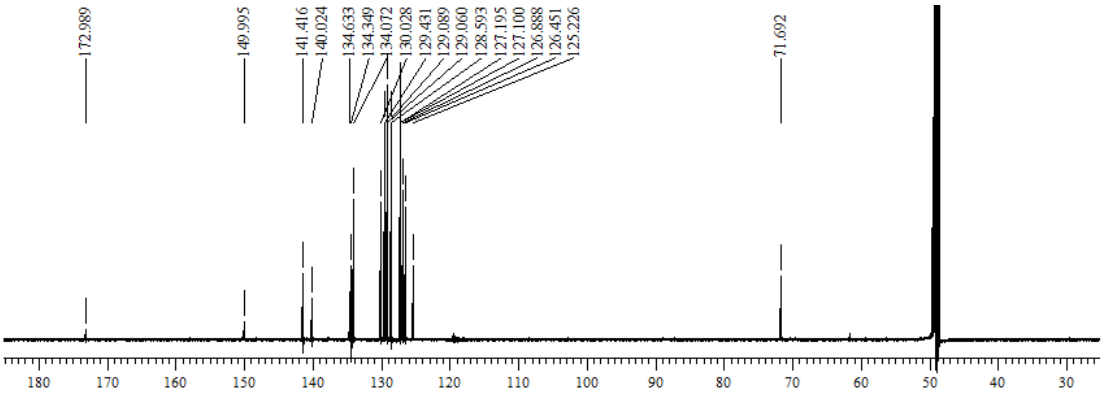
Compound 58



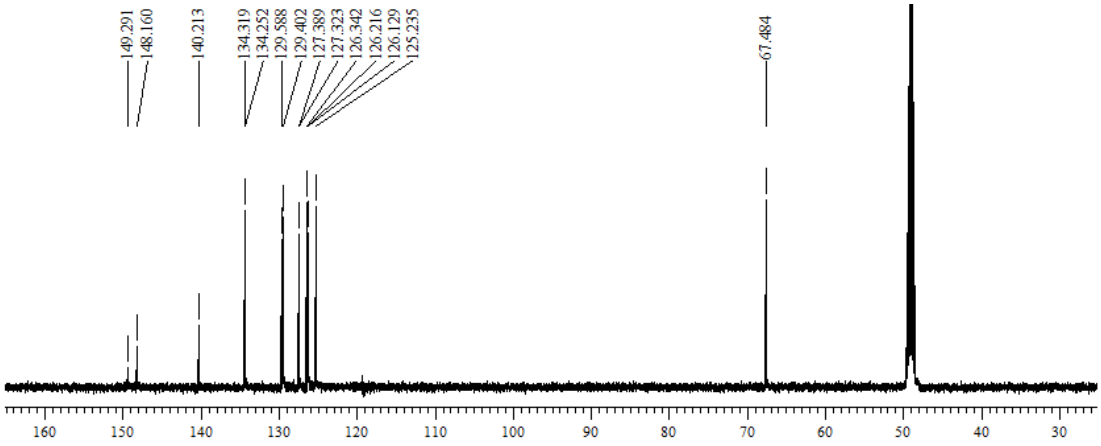
Compound 59



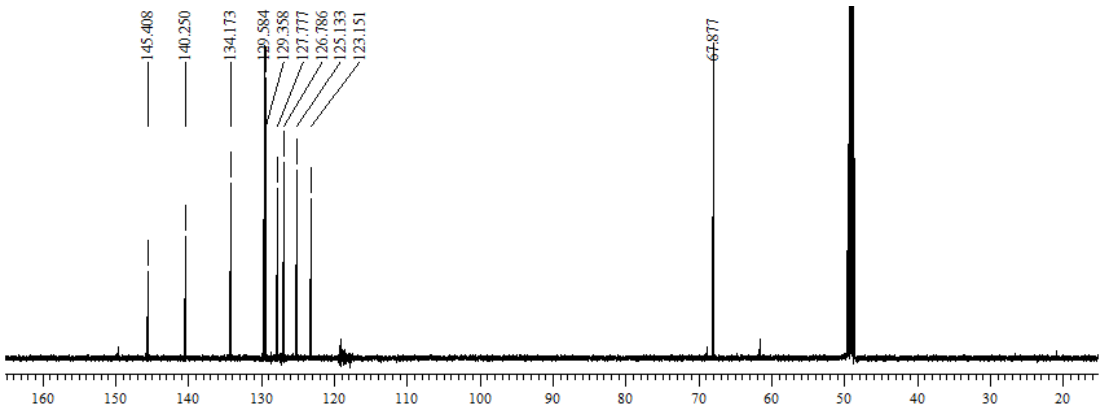
Compound 60



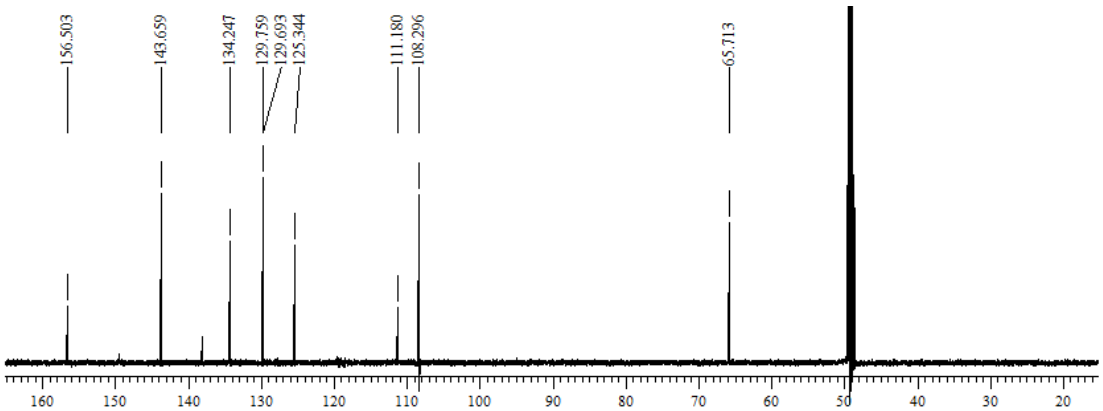
Compound 61



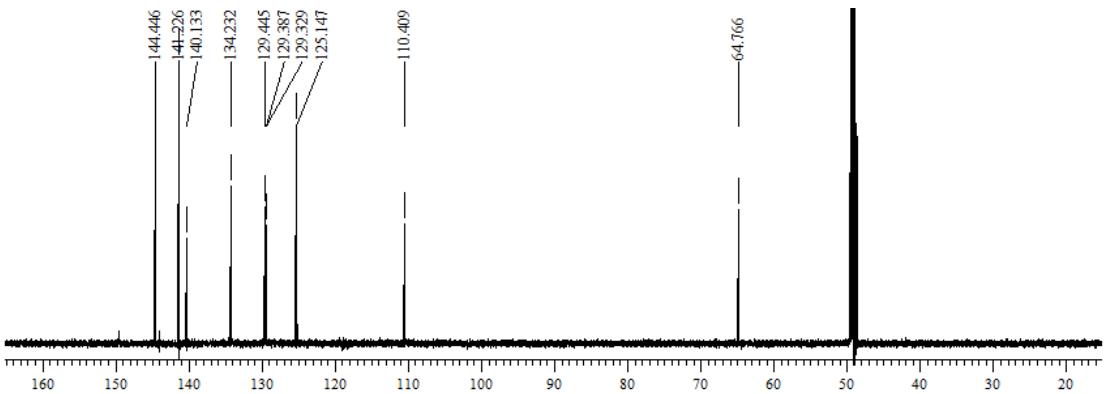
Compound 62



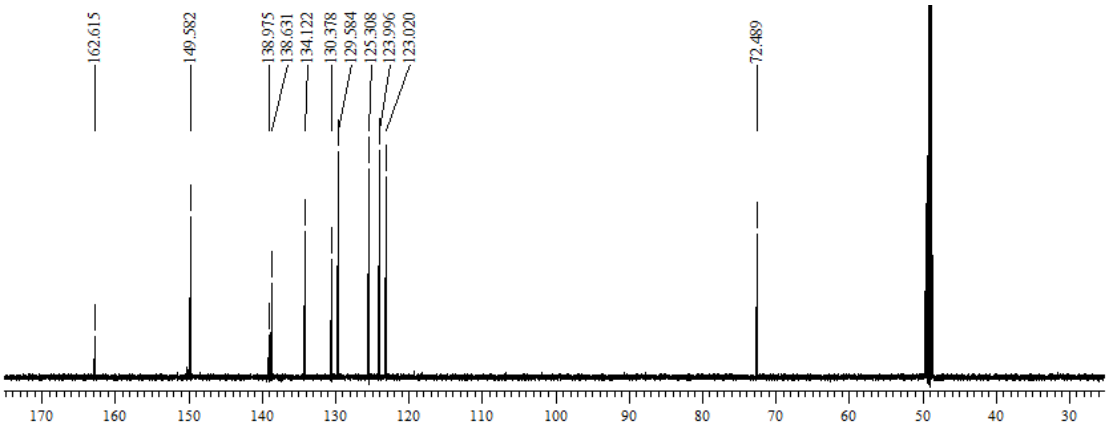
Compound 63



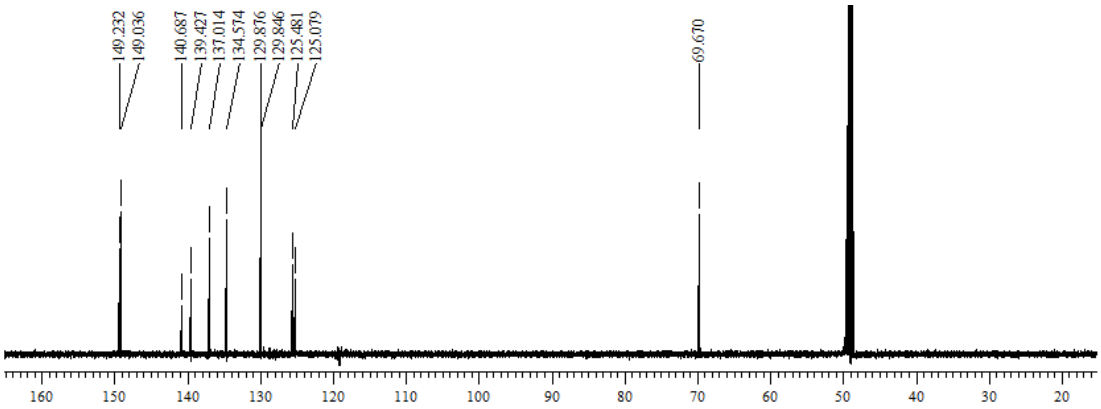
Compound 64



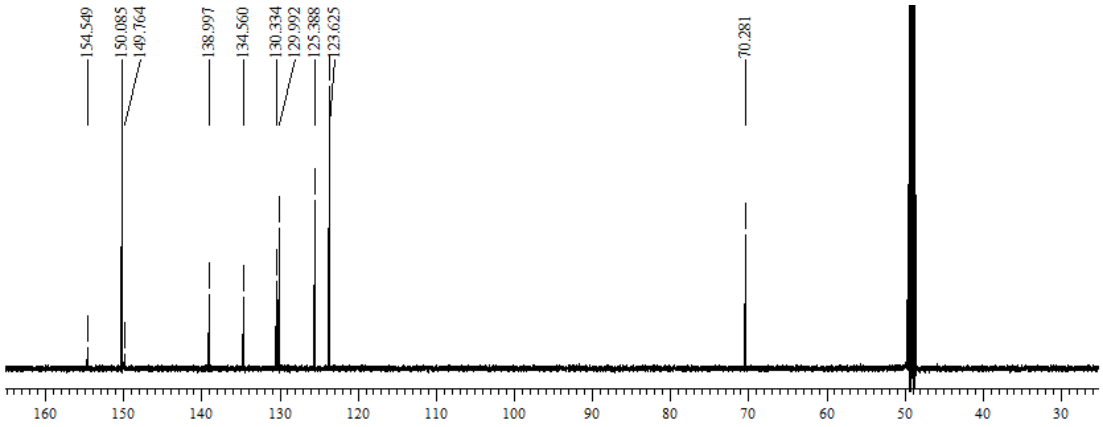
Compound 65



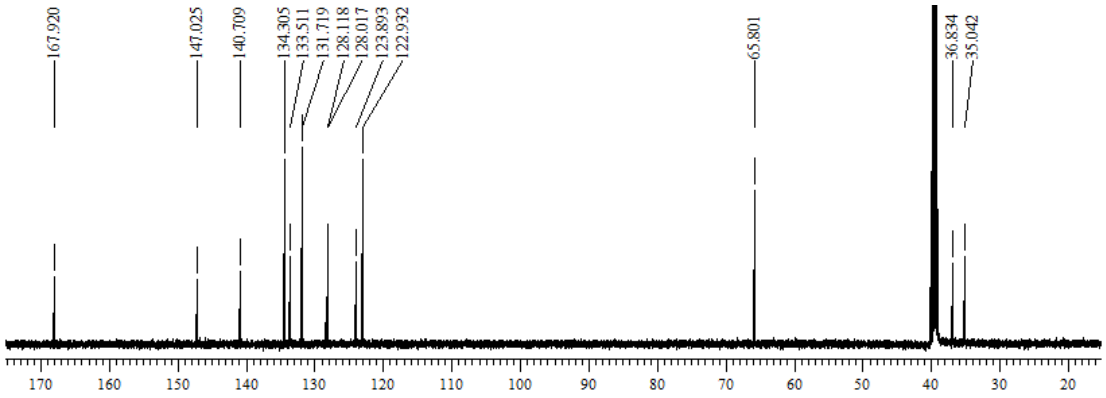
Compound 66



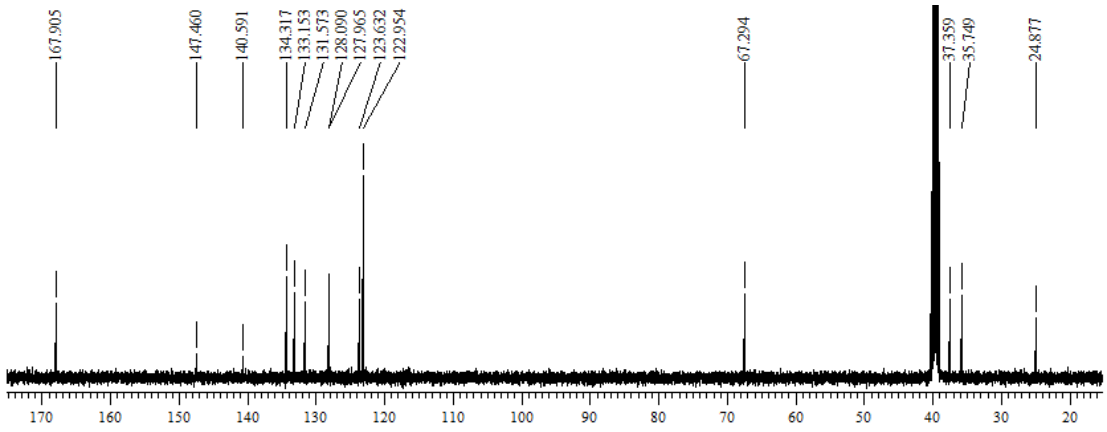
Compound 67



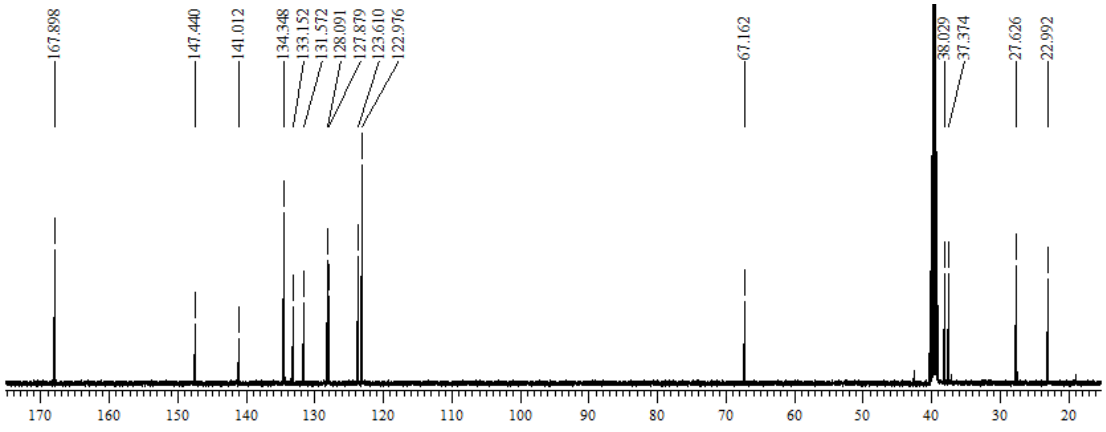
Compound 68



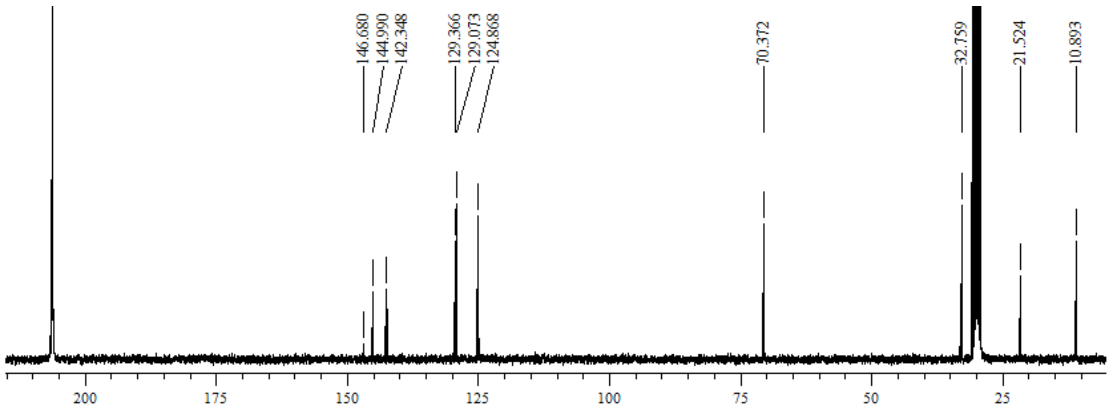
Compound 69



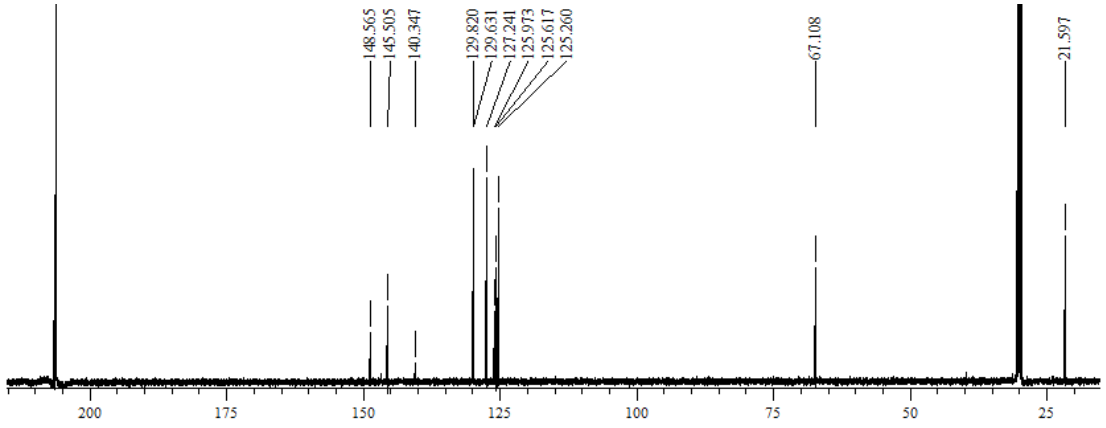
Compound 70



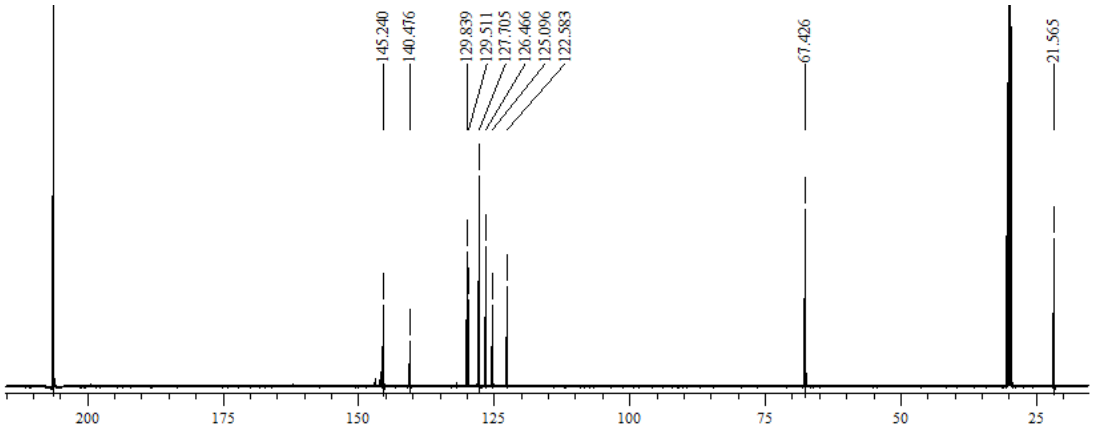
Compound 71



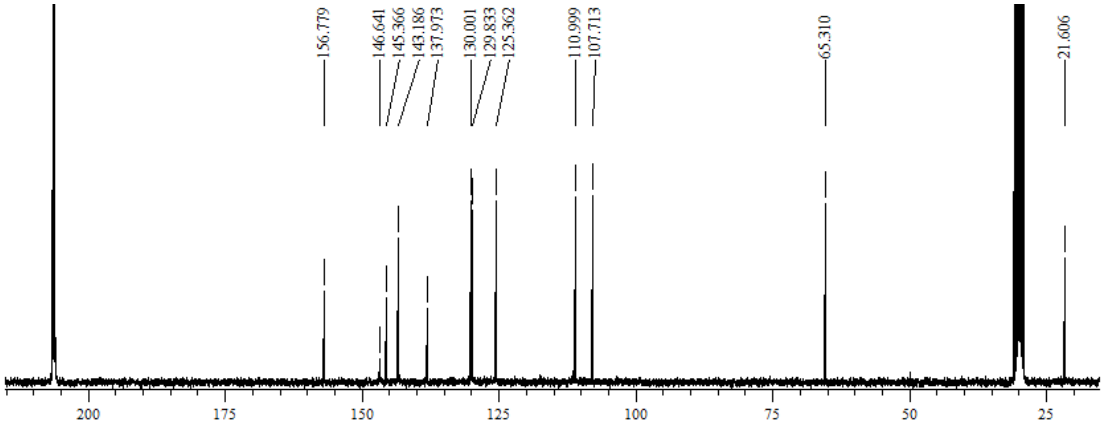
Compound 72



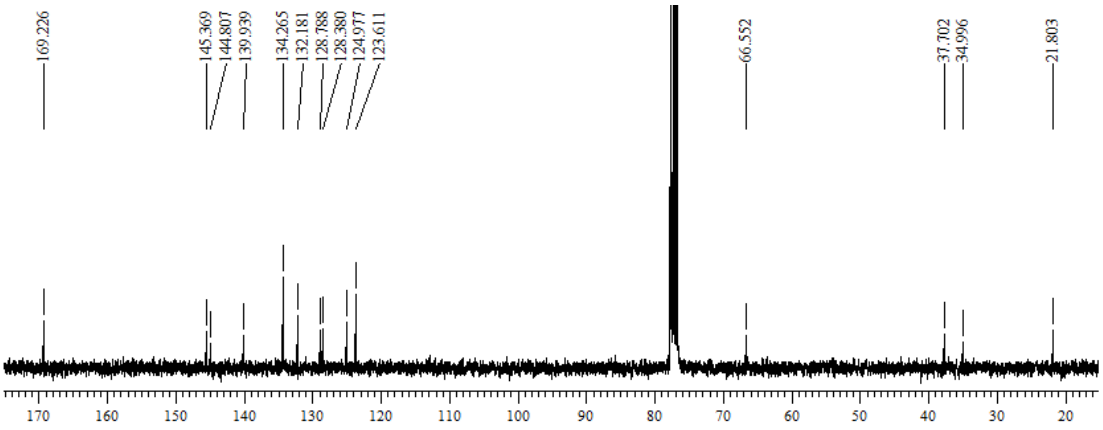
Compound 73



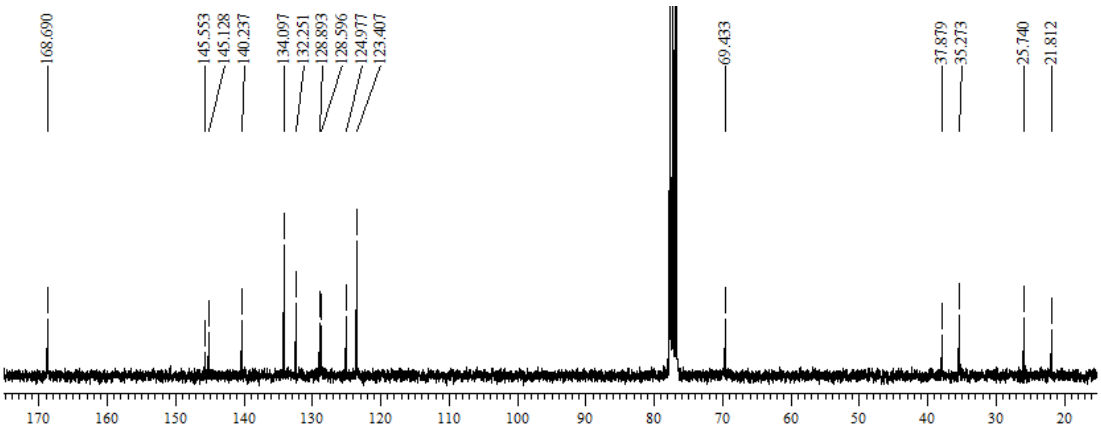
Compound 74



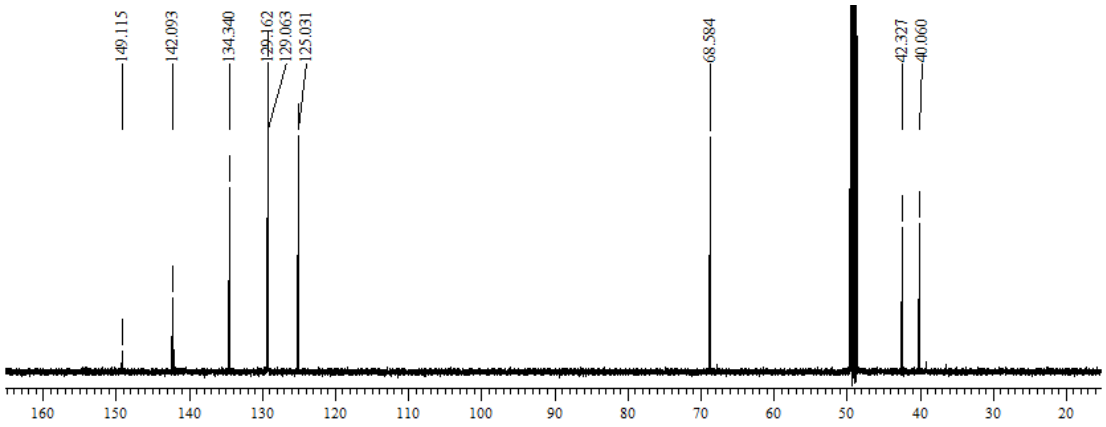
Compound 75



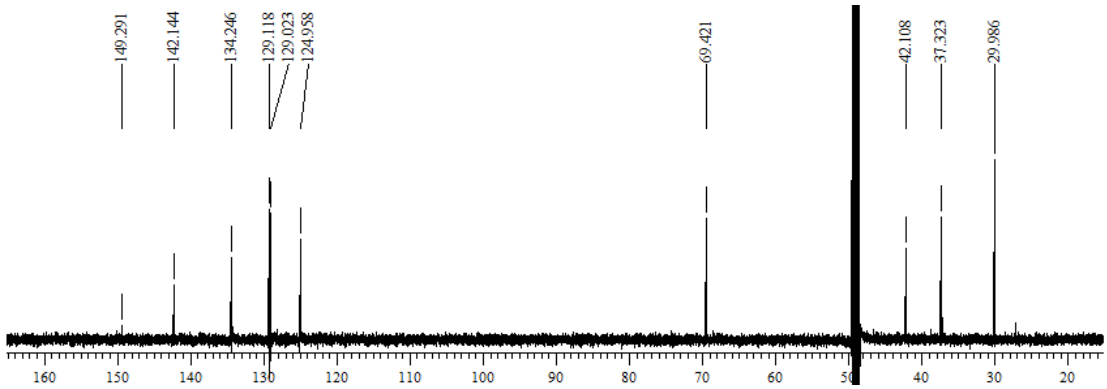
Compound 76



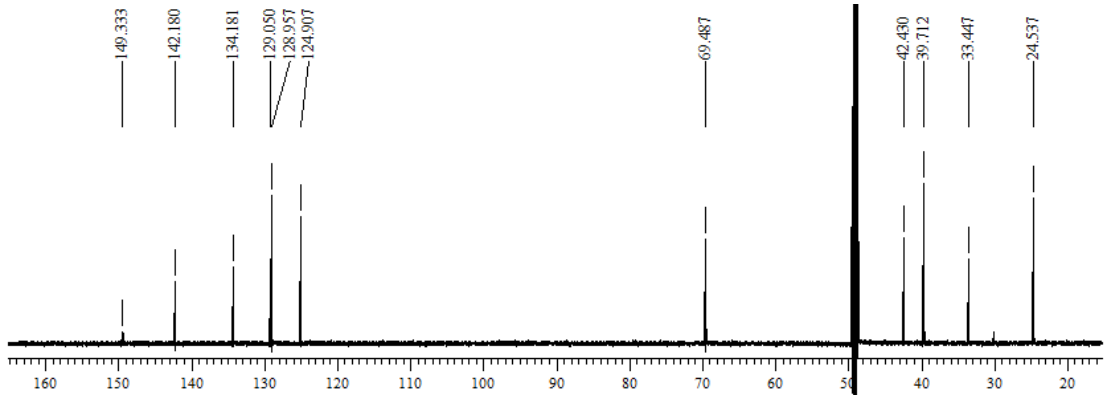
Compound 77



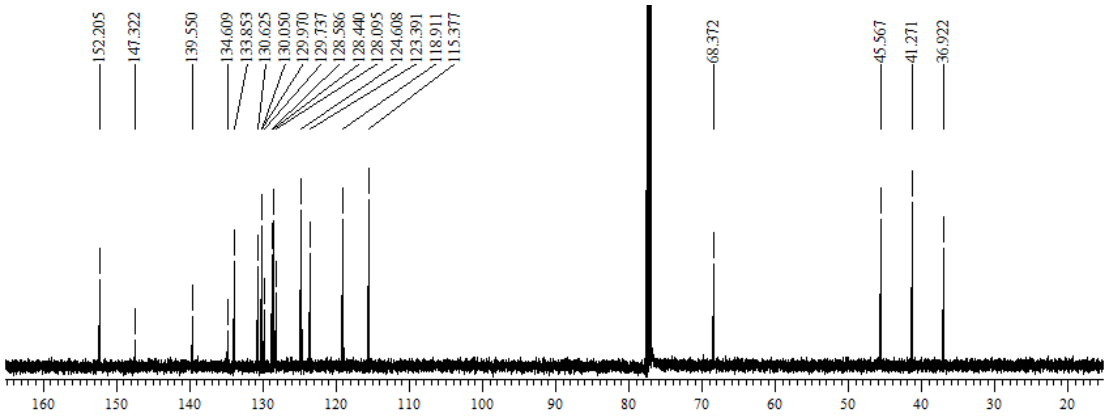
Compound 78



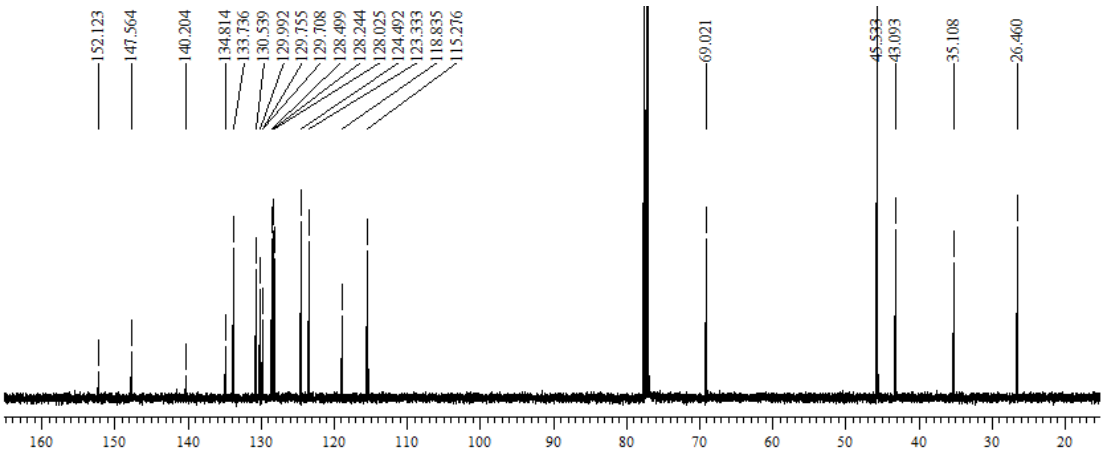
Compound 79



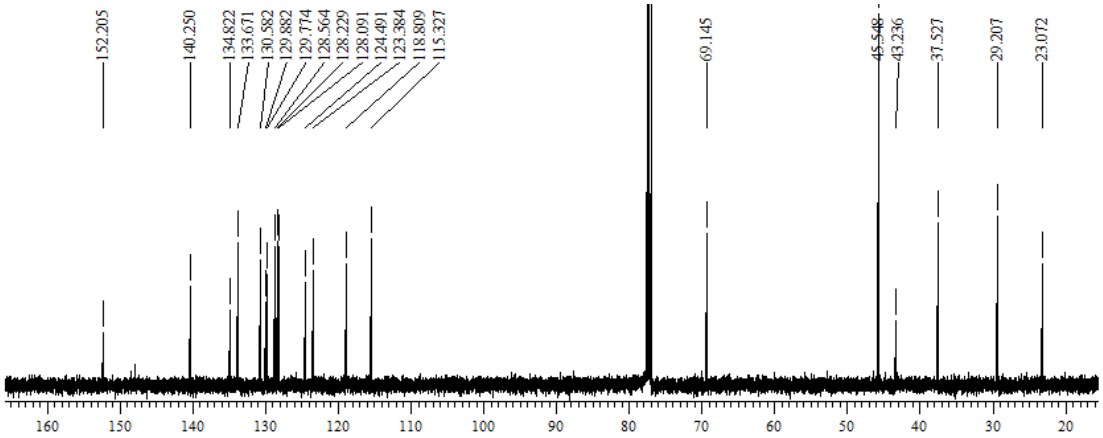
Compound 80



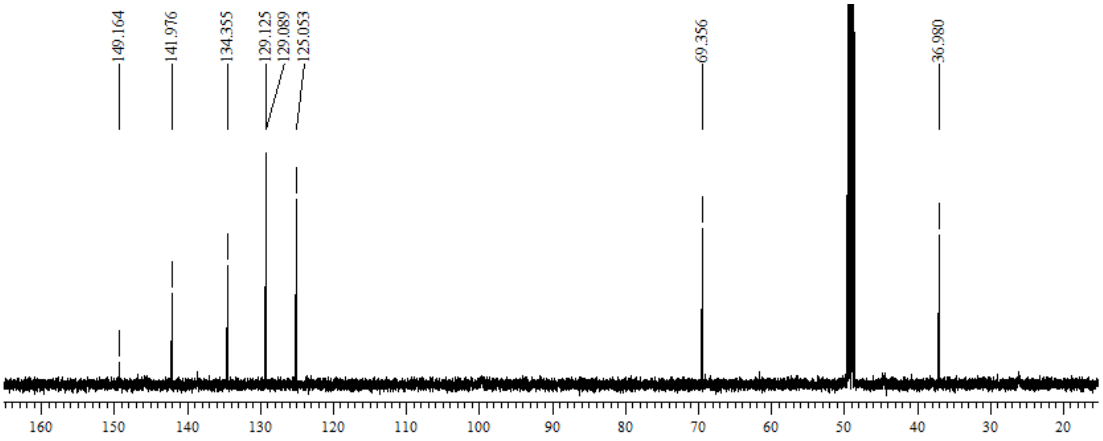
Compound 81



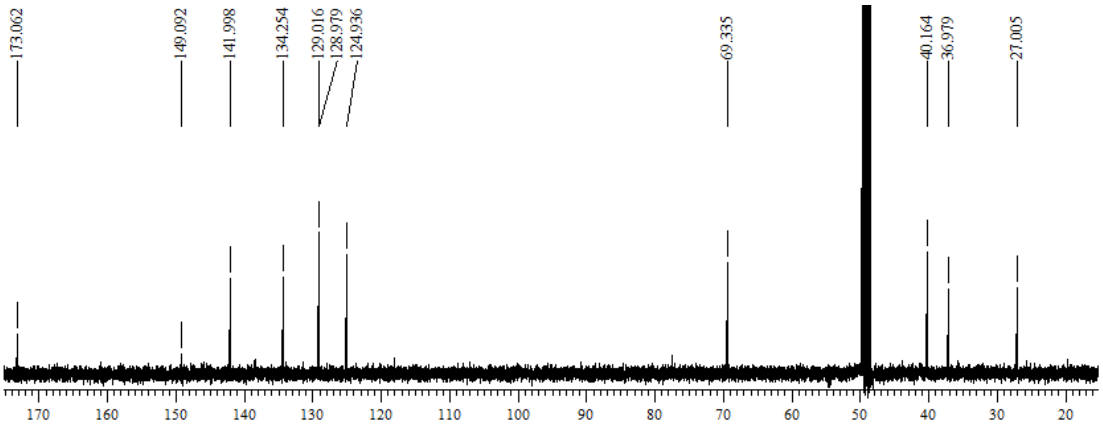
Compound 82



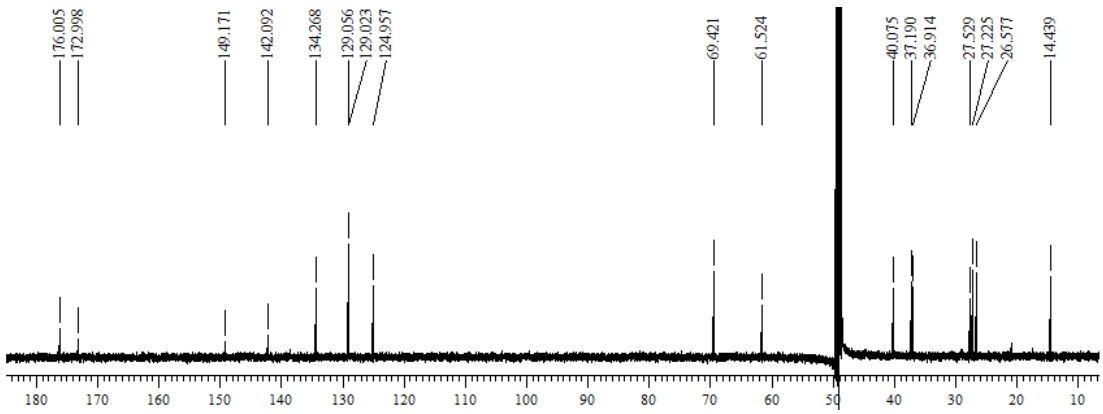
Compound 83



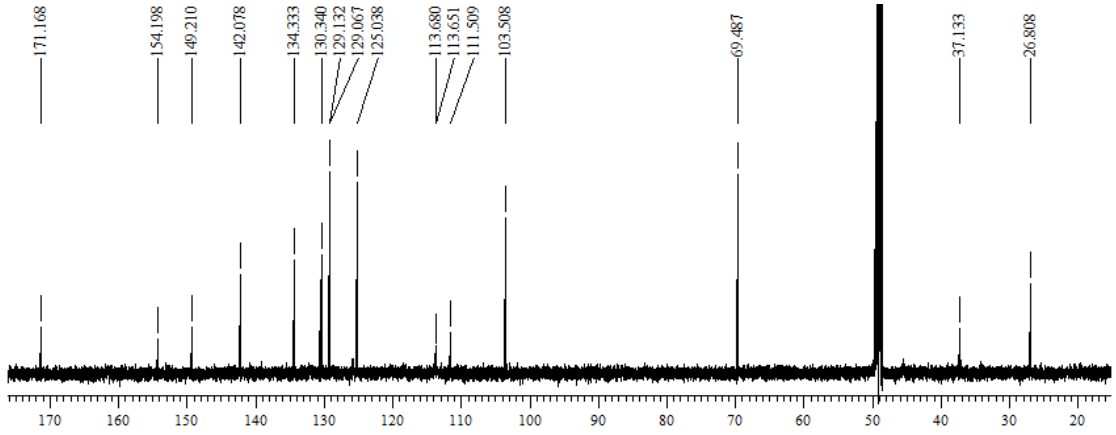
Compound 84



Compound 85



Compound 86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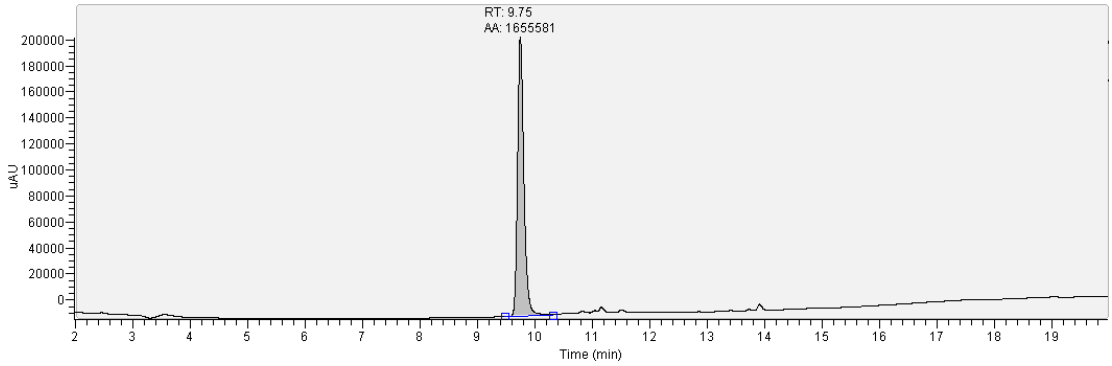
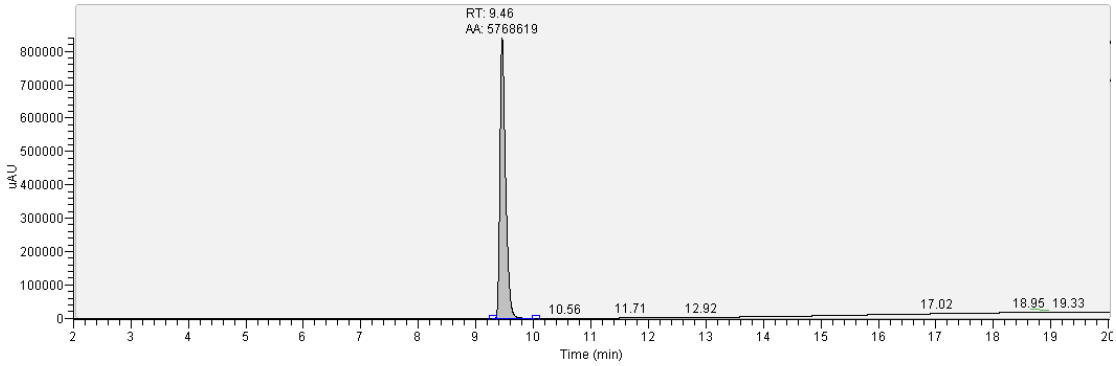
154.198
149.210
142.078
134.333
130.340
129.132
129.067
125.038
113.680
113.651
111.509
103.508
69.487
37.133
26.808
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

9. HPLC spectra of all tested compounds

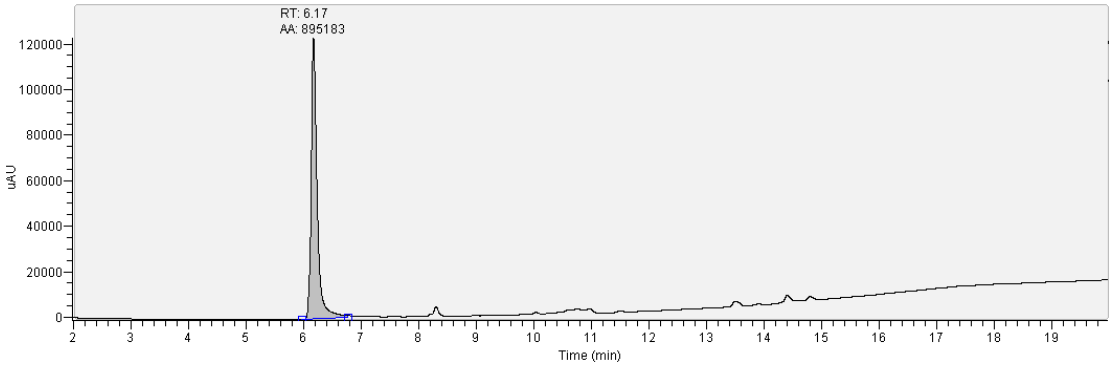
Compound 3



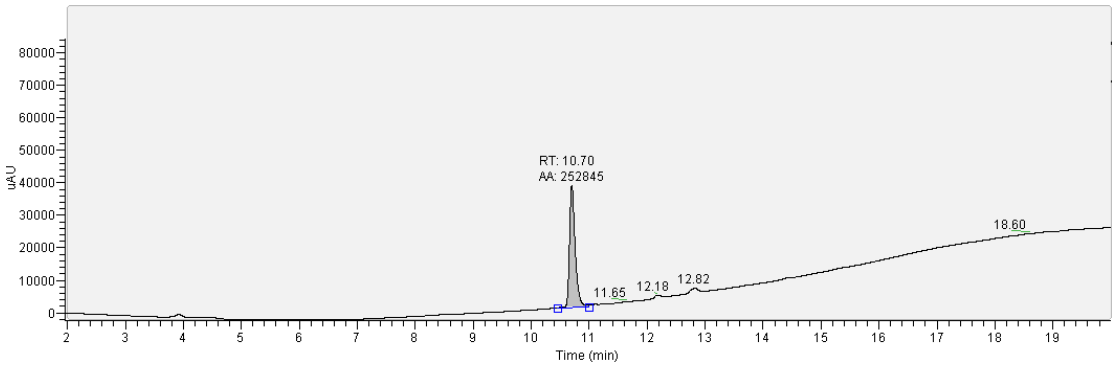
Compound 7



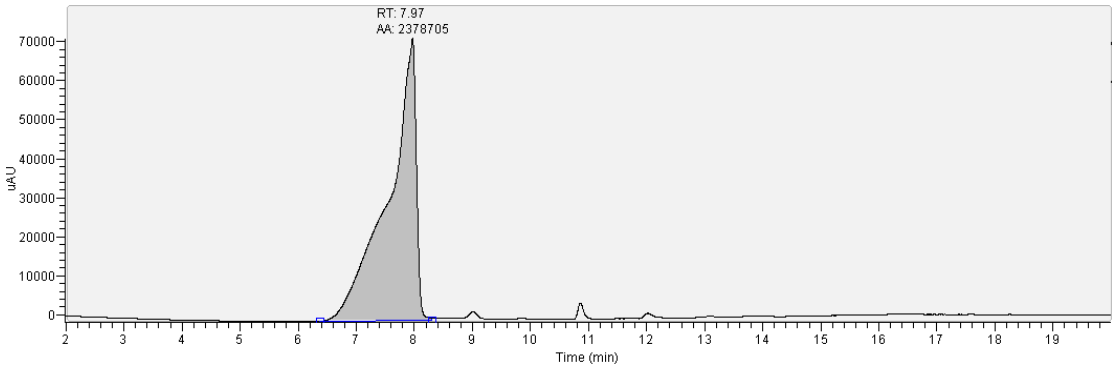
Compound 8



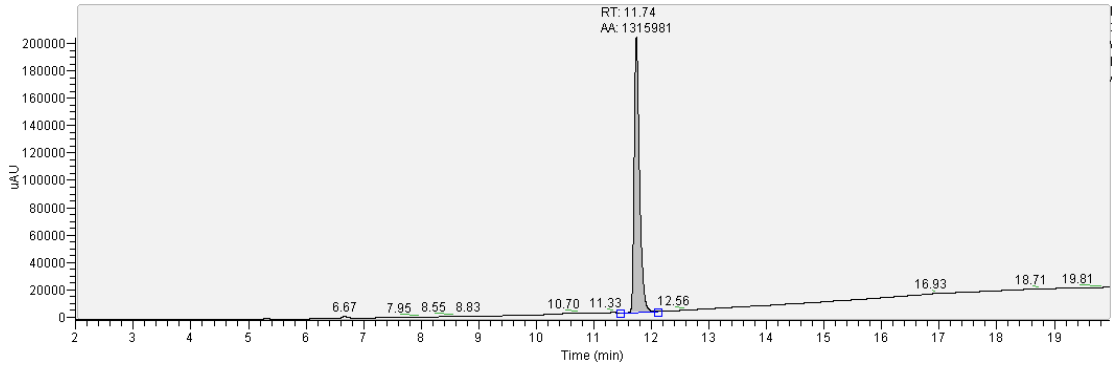
Compound 10



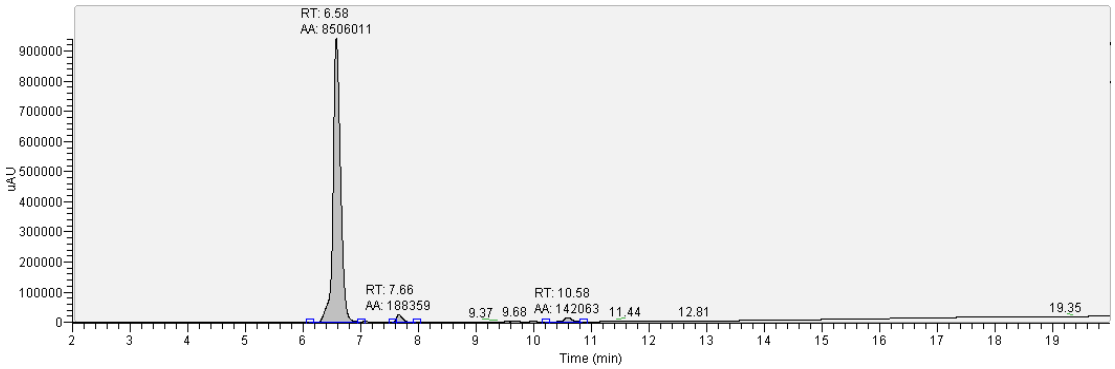
Compound 11



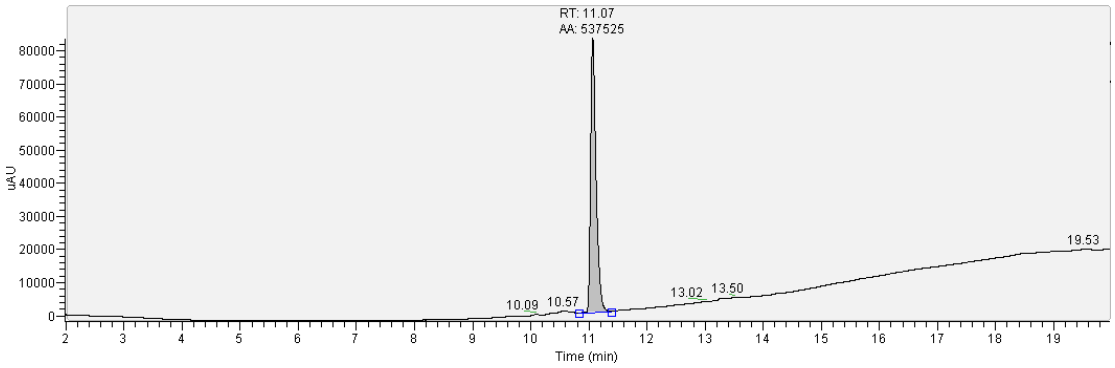
Compound 14



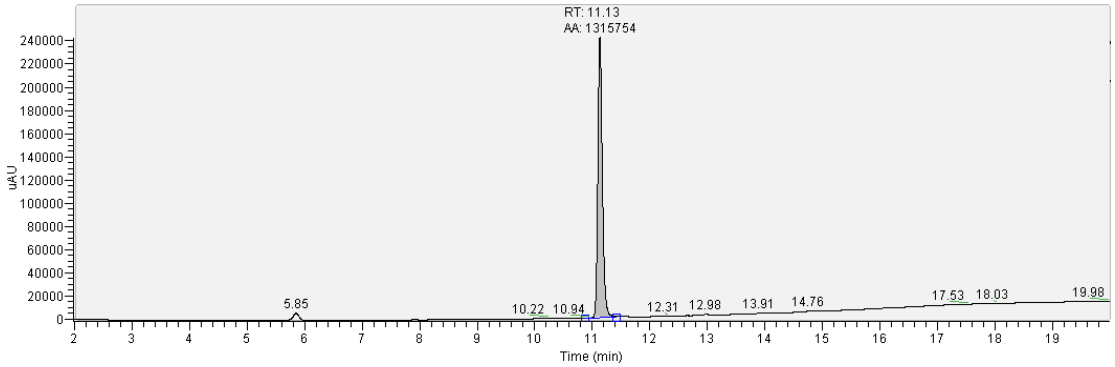
Compound 15



Compound 21



Compound 22



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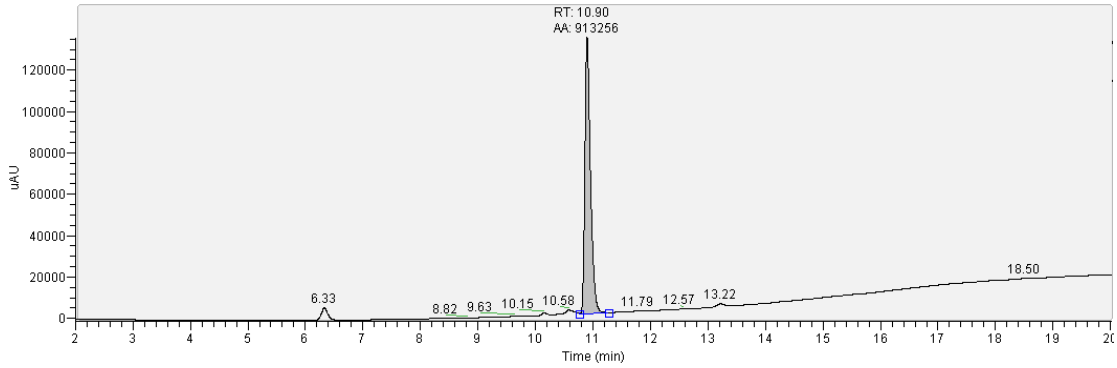

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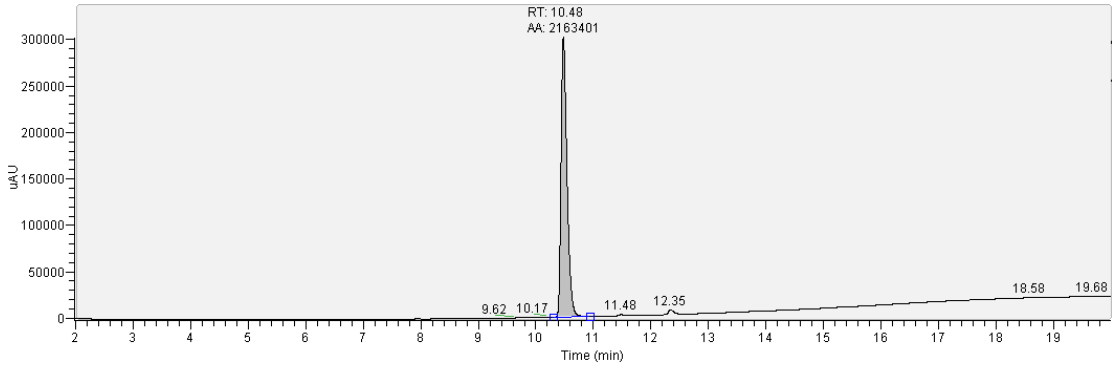

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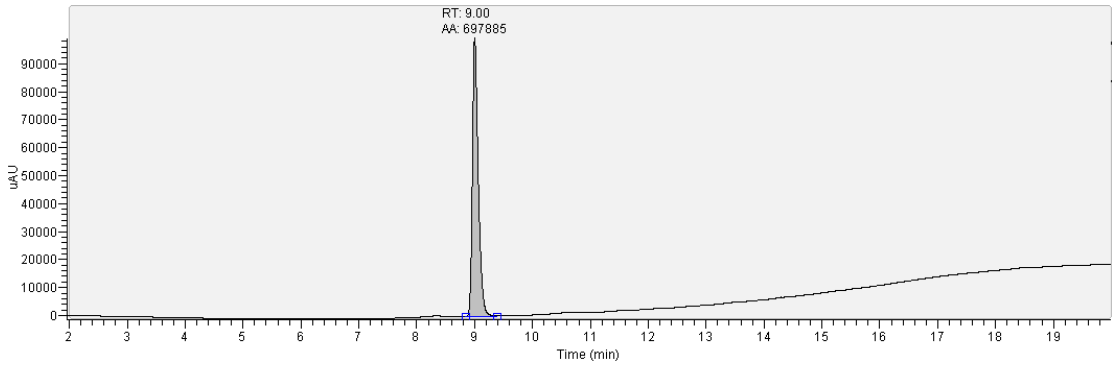

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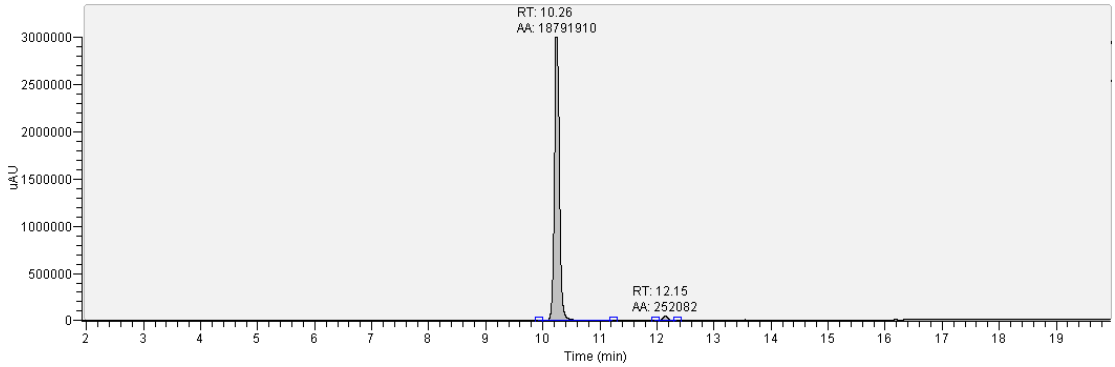

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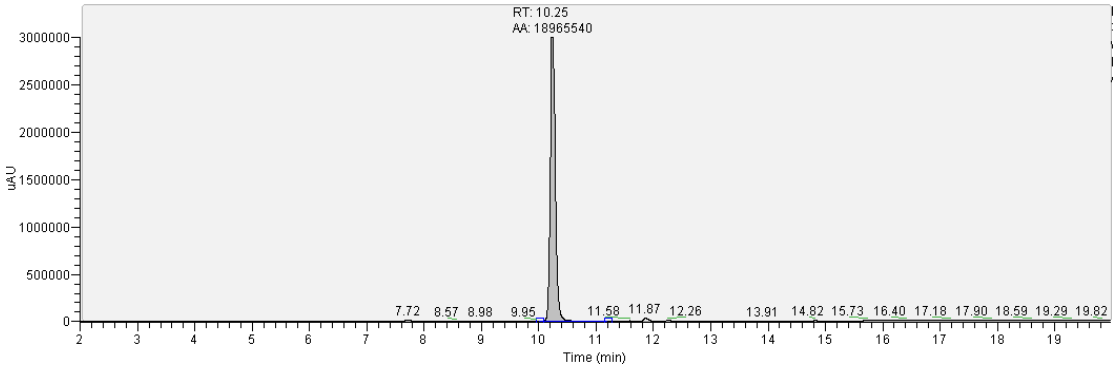

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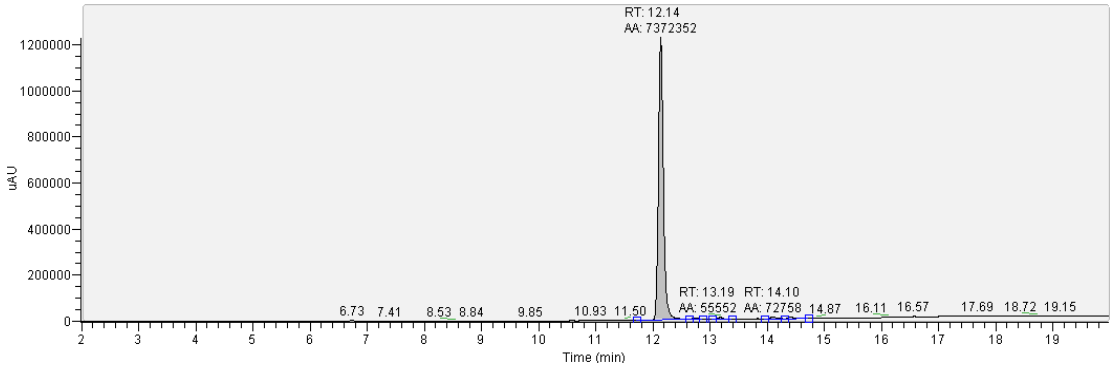

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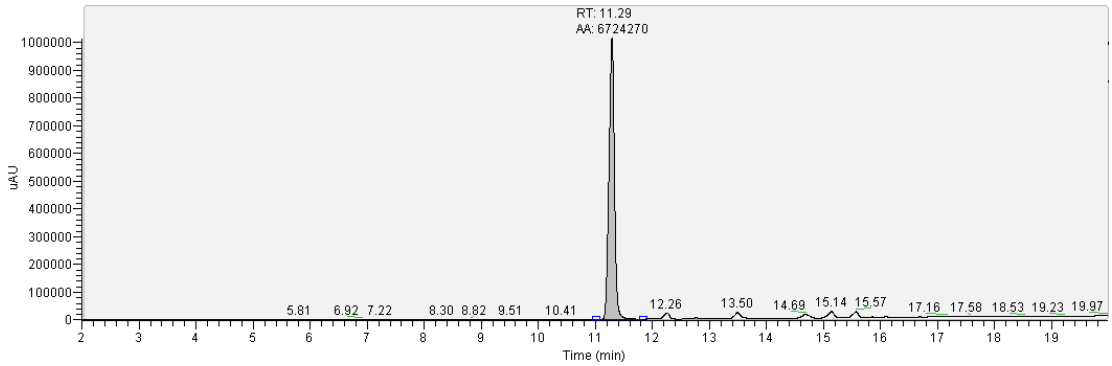

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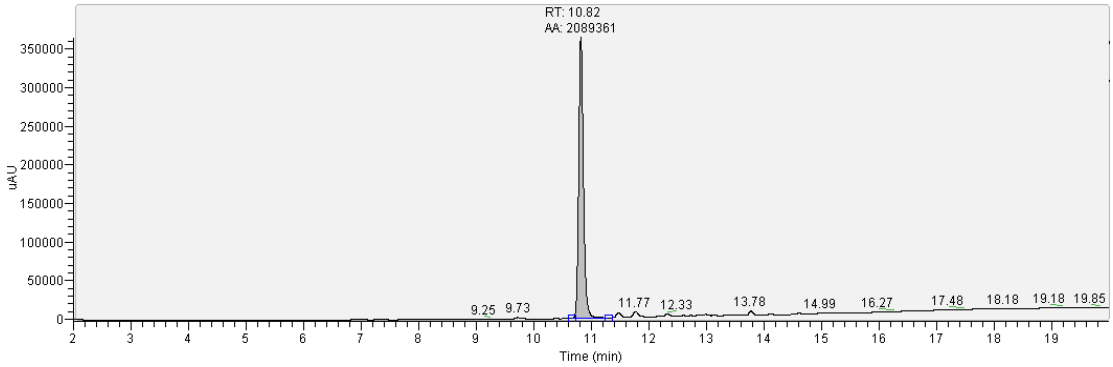

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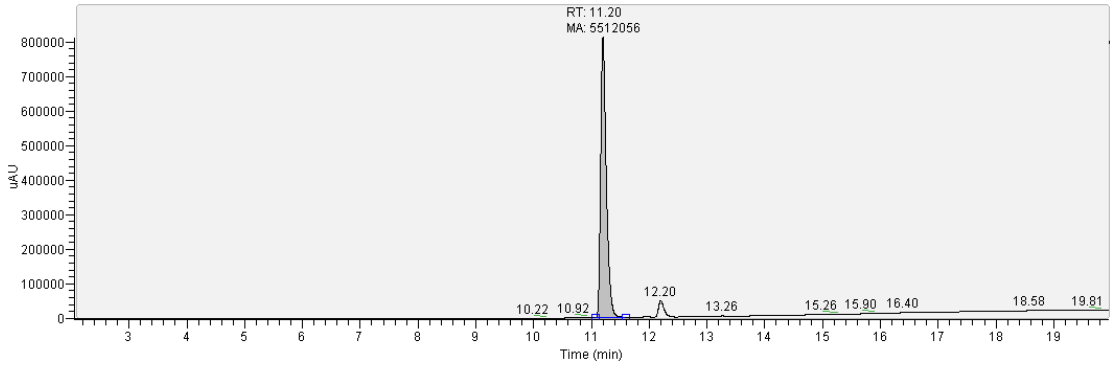

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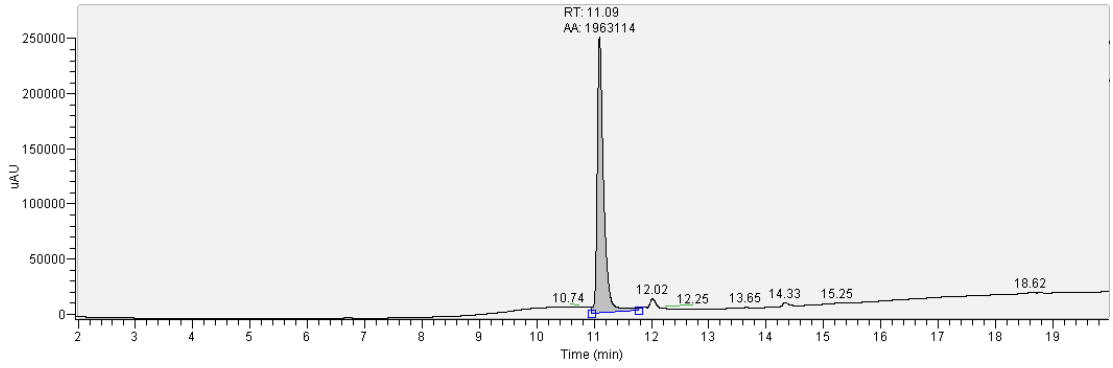

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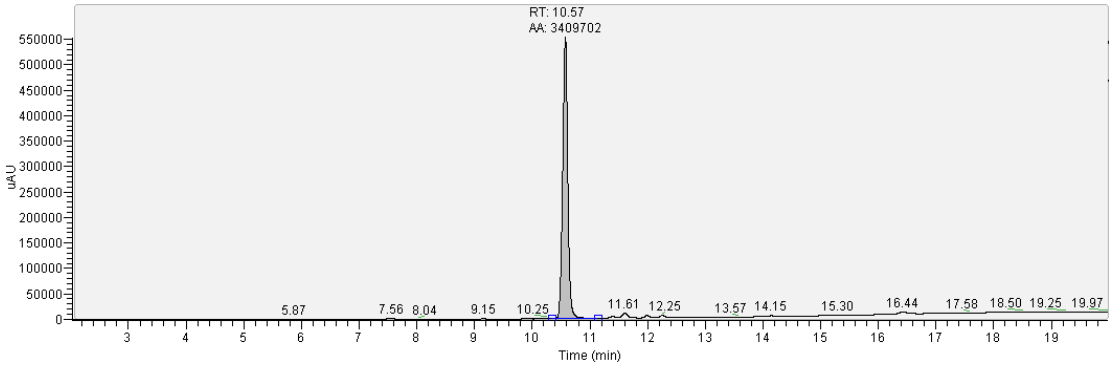

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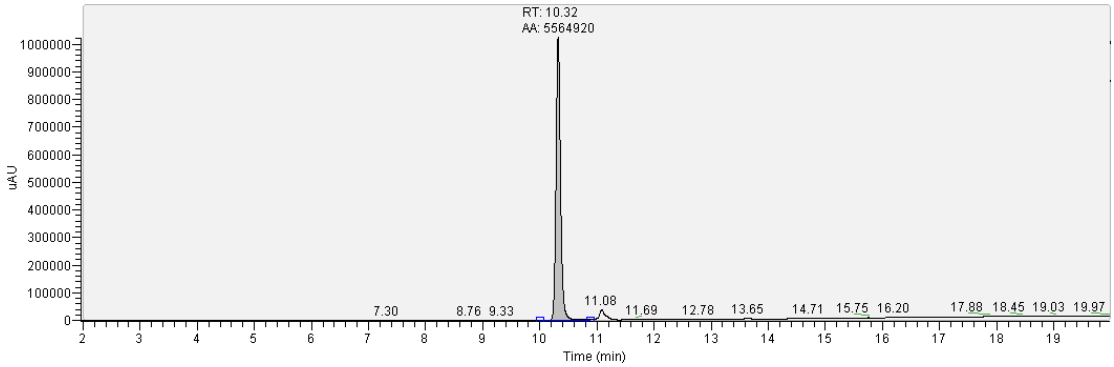

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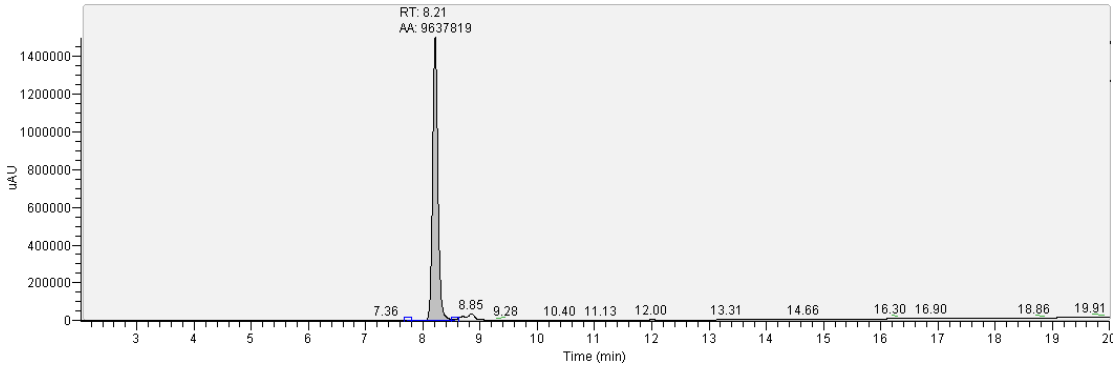

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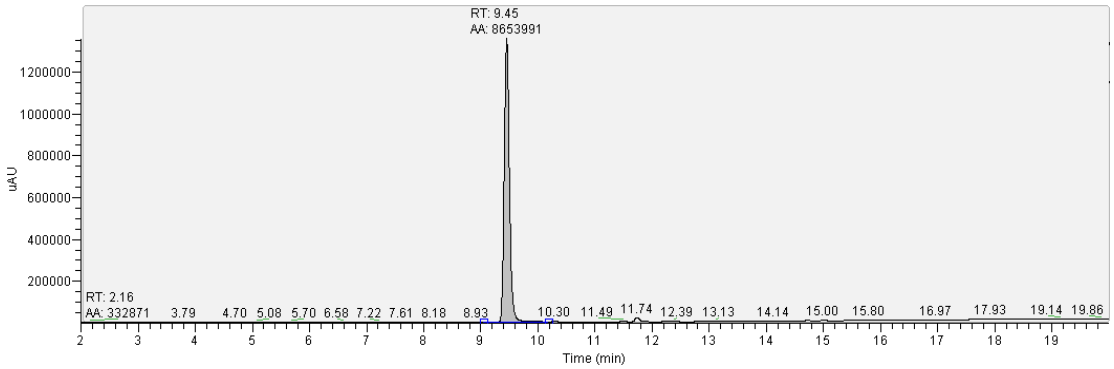

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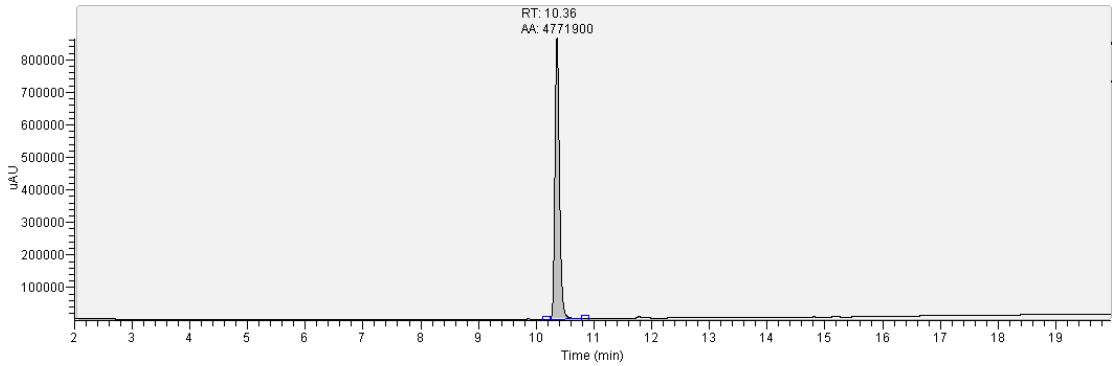

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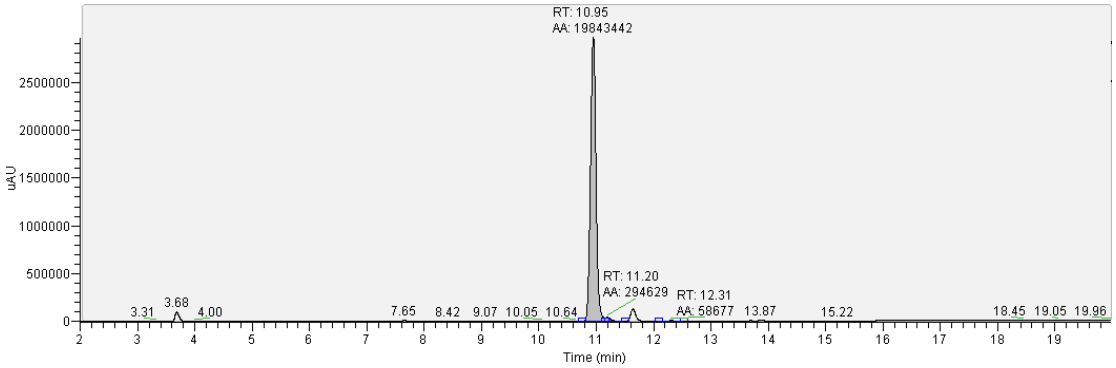

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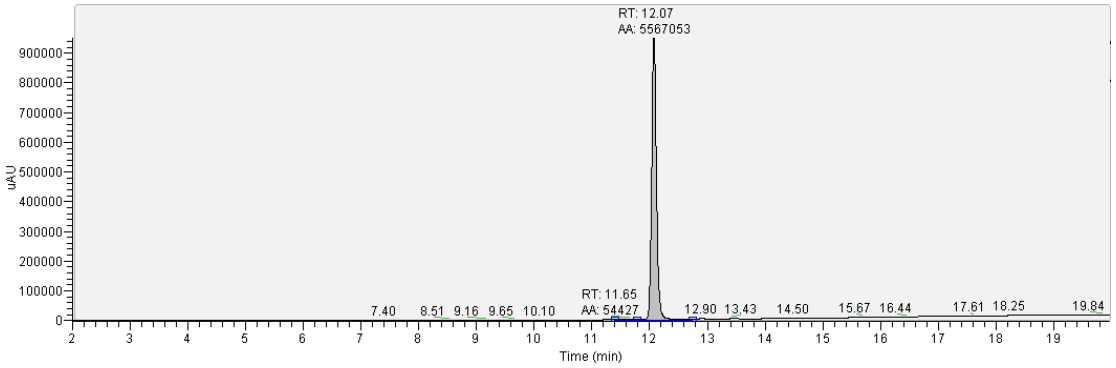

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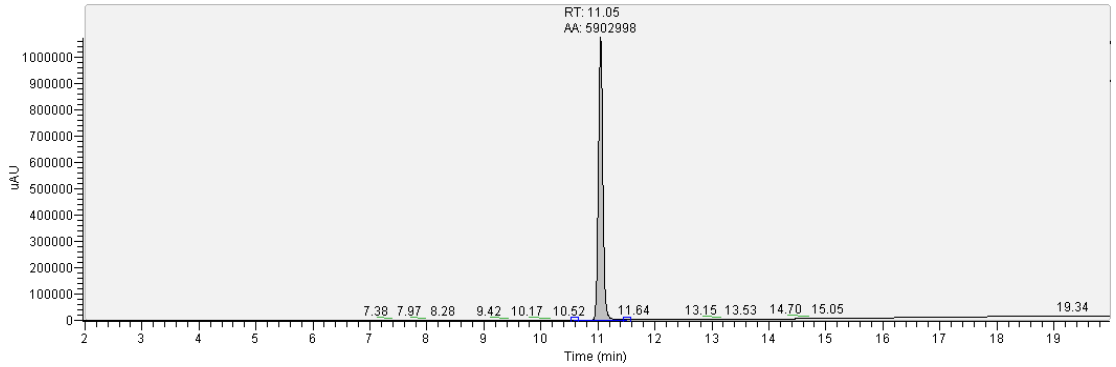

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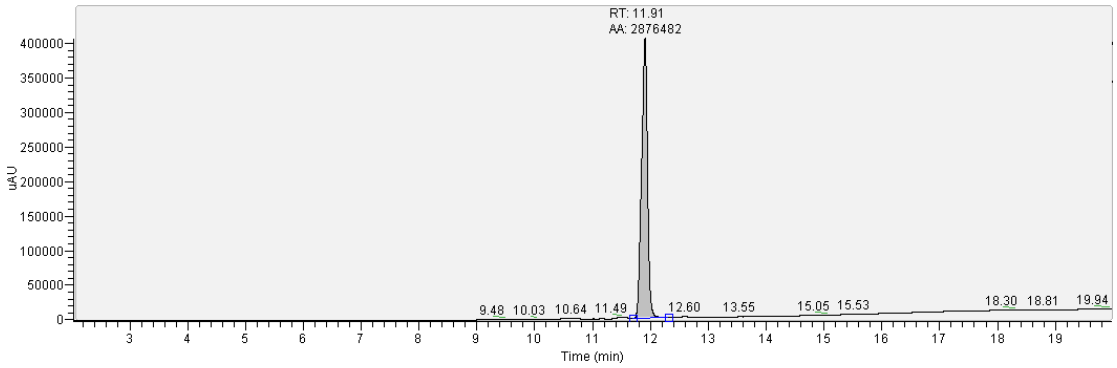

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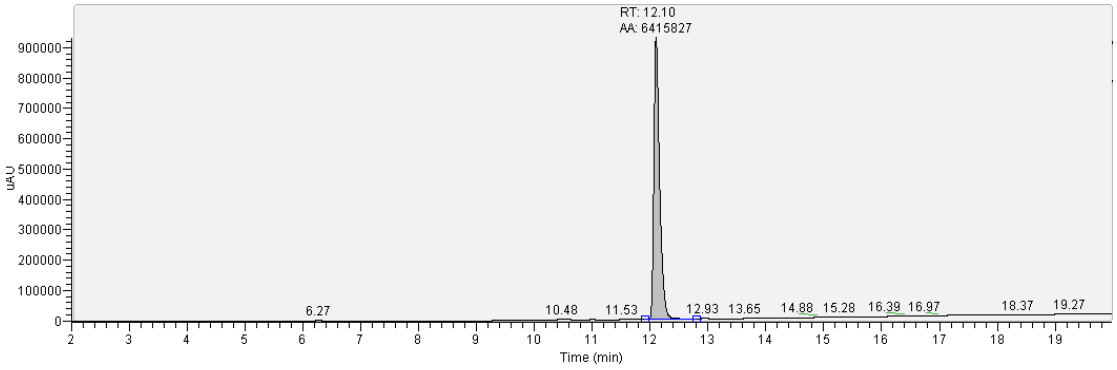

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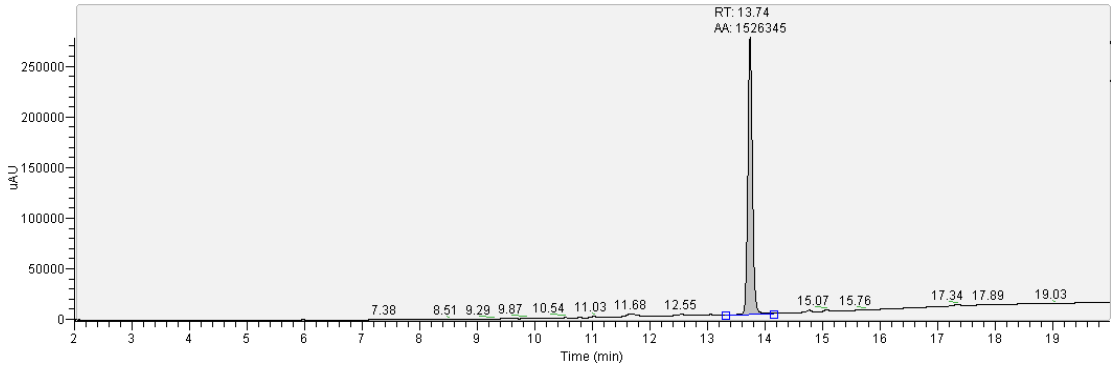

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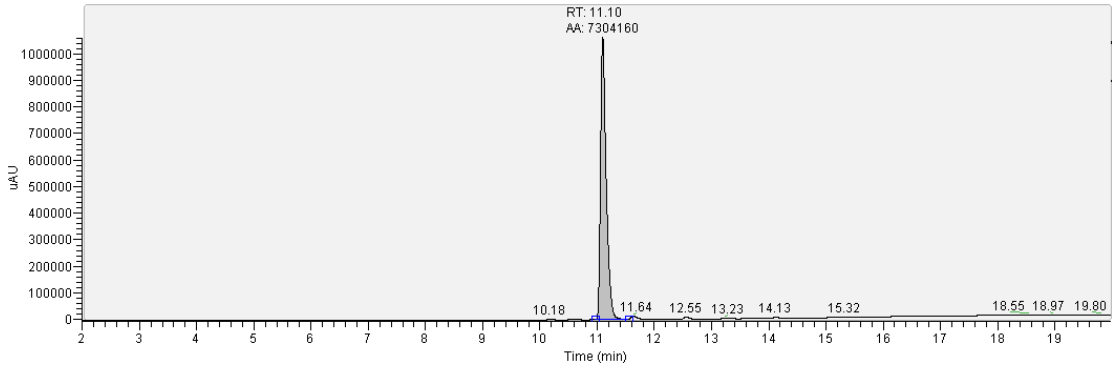

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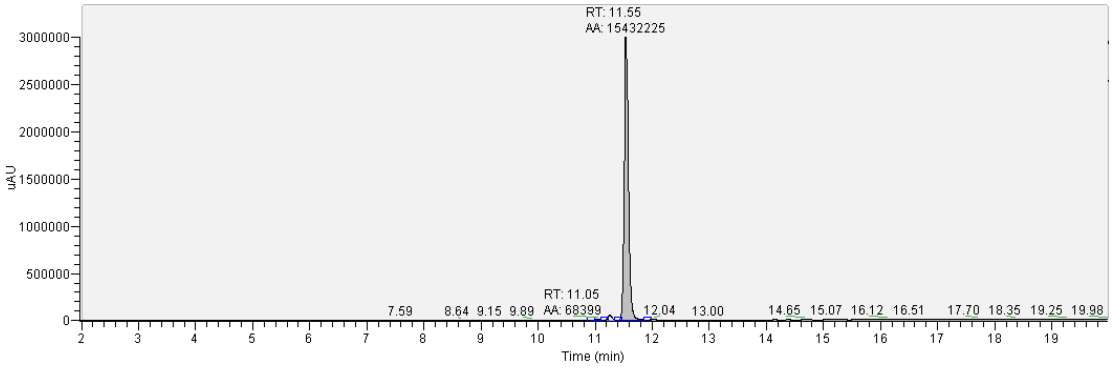

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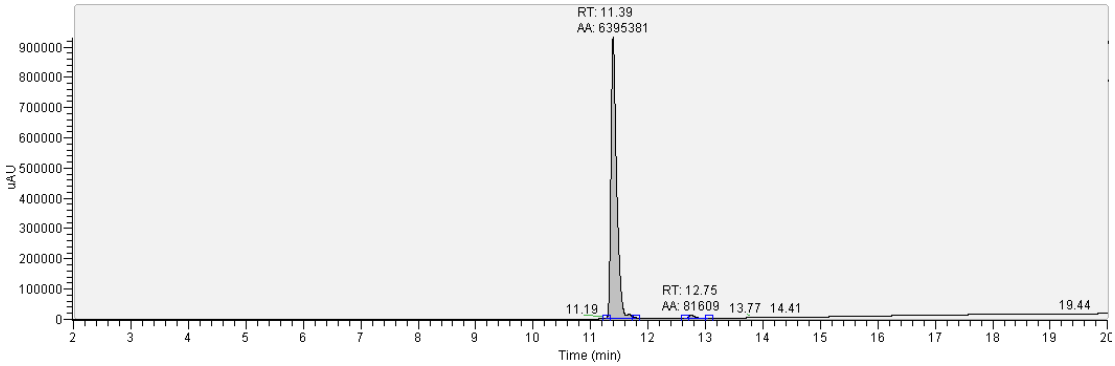

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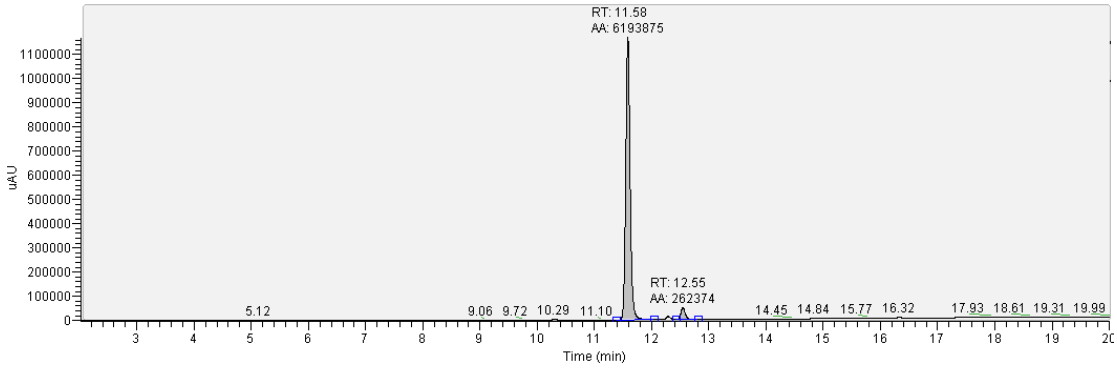

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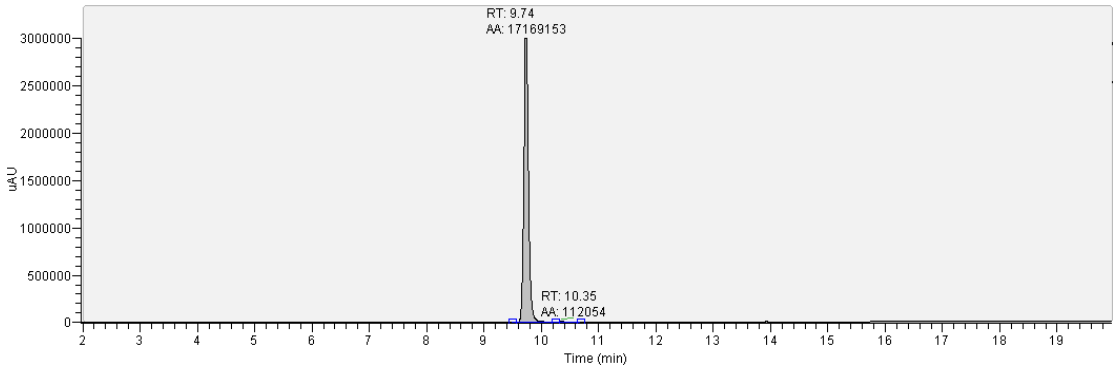

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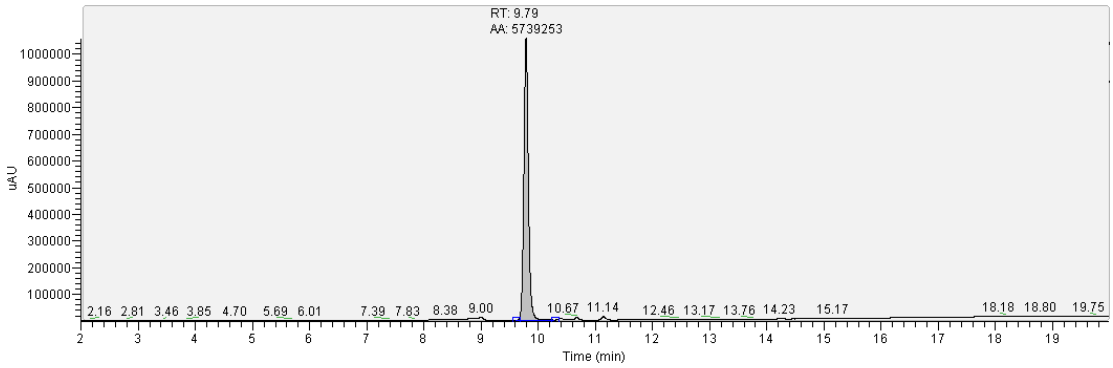

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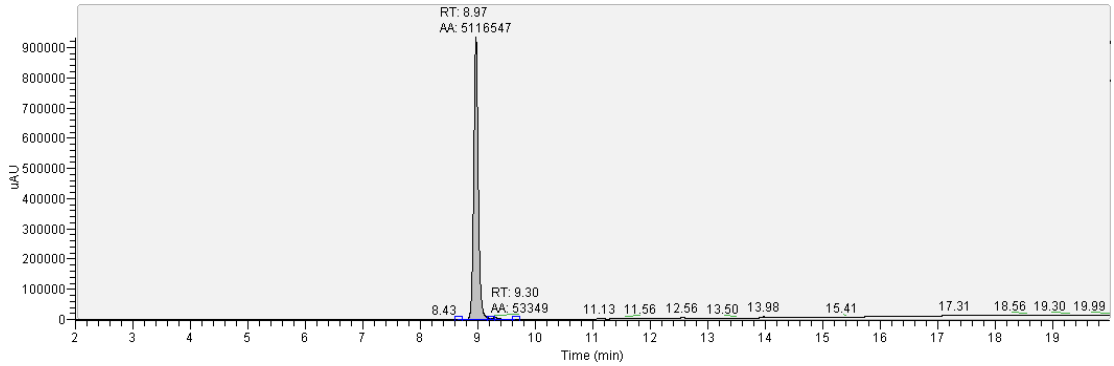

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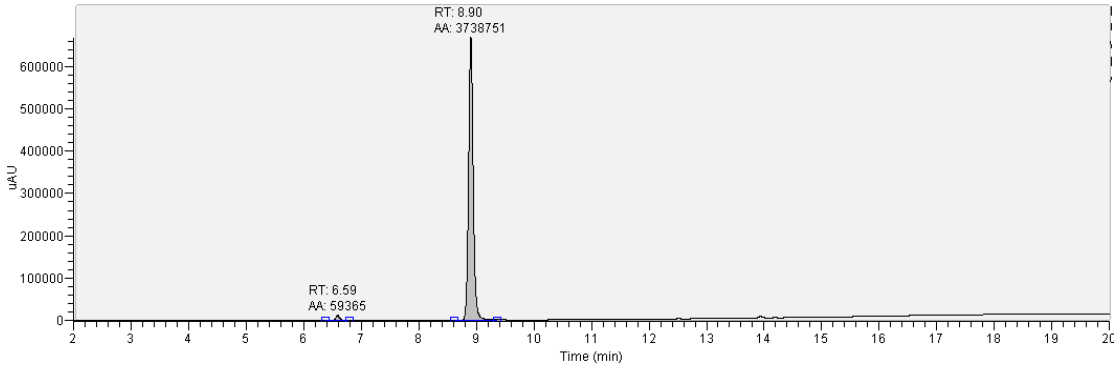

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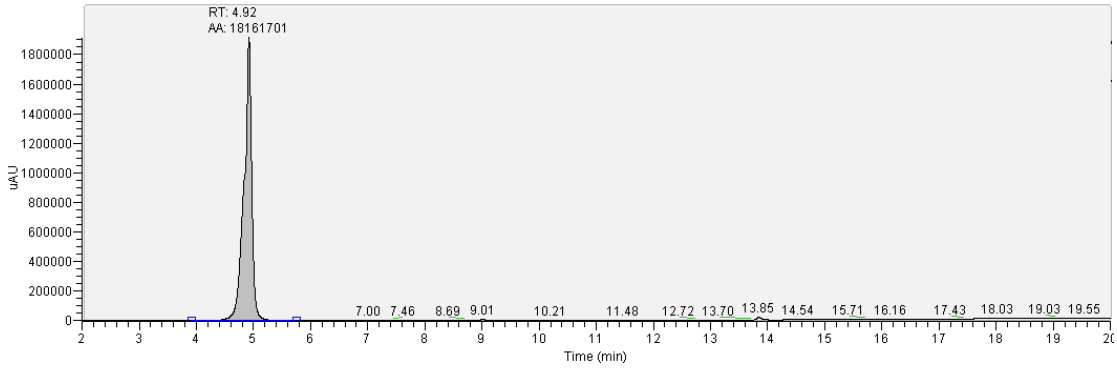

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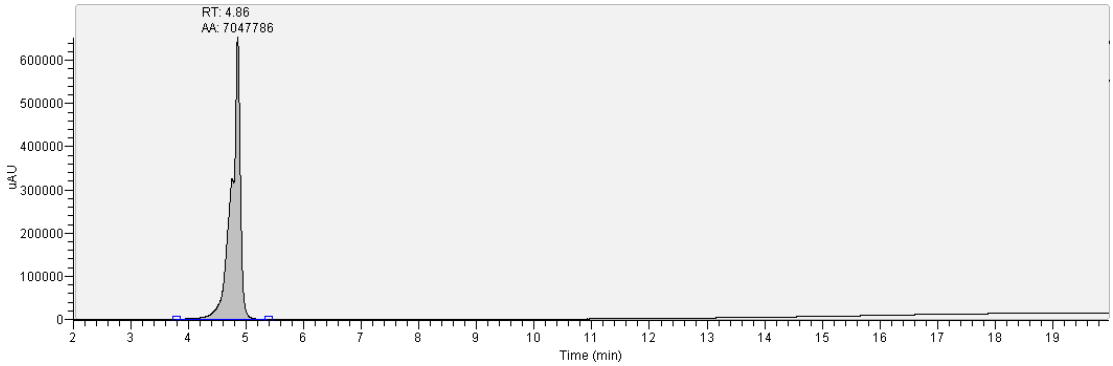

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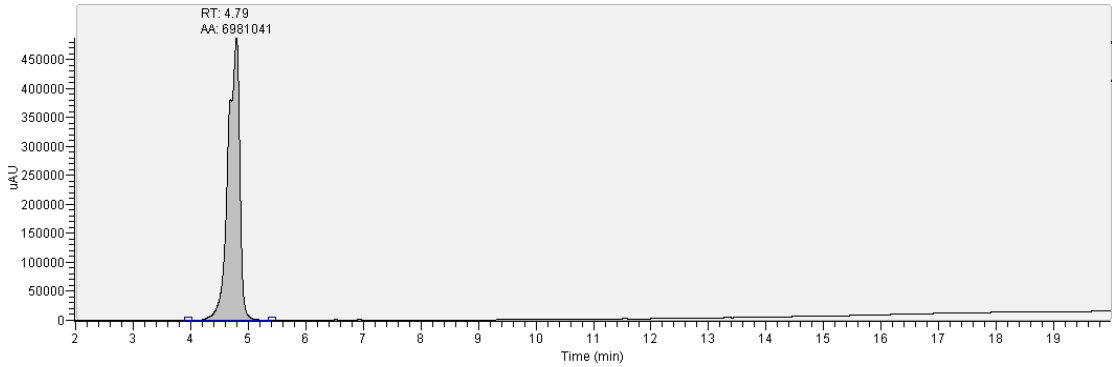

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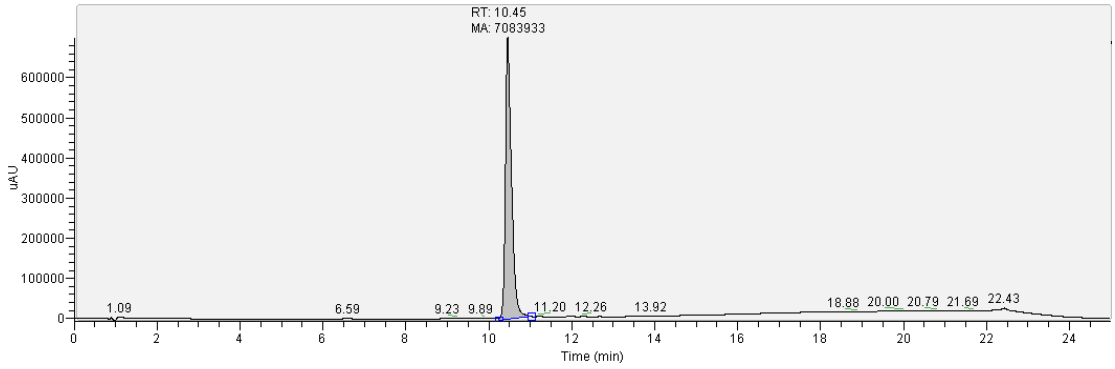

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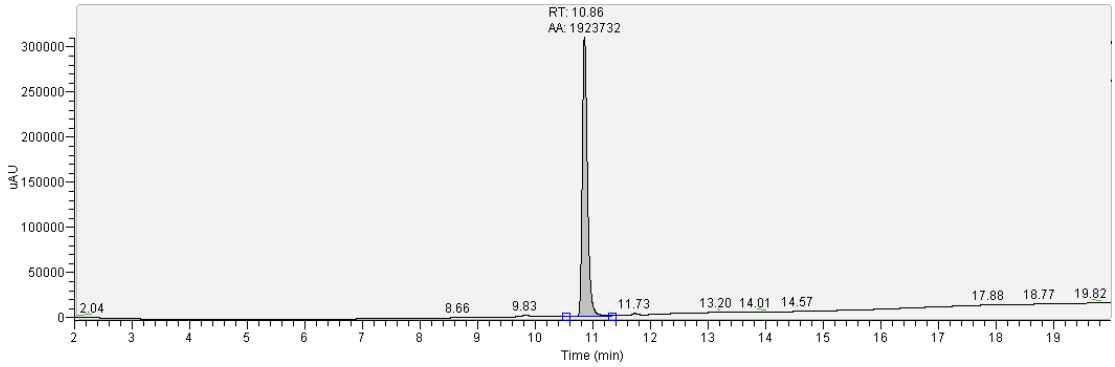

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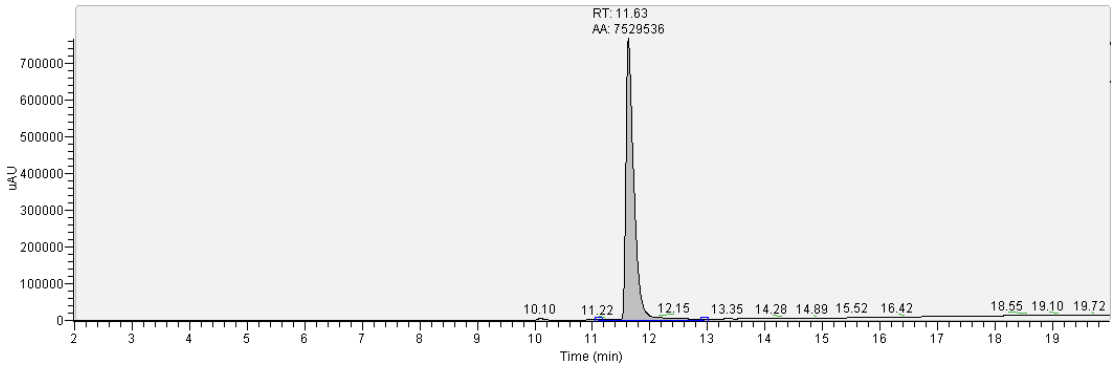

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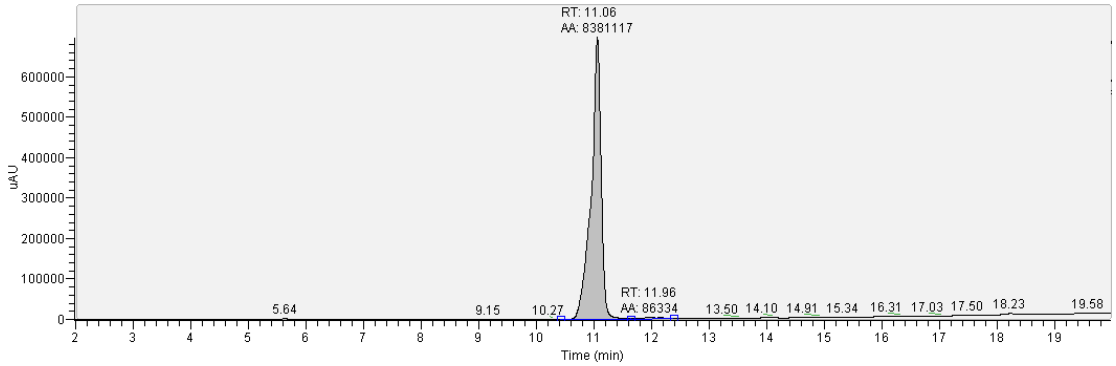

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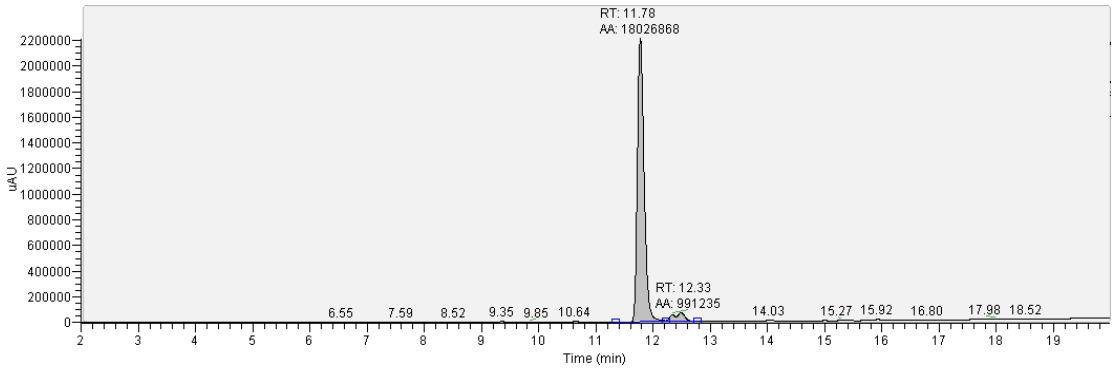

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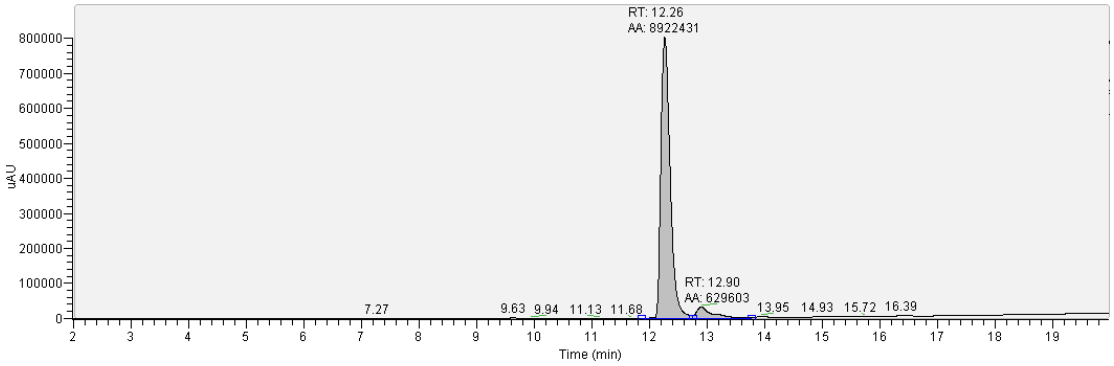

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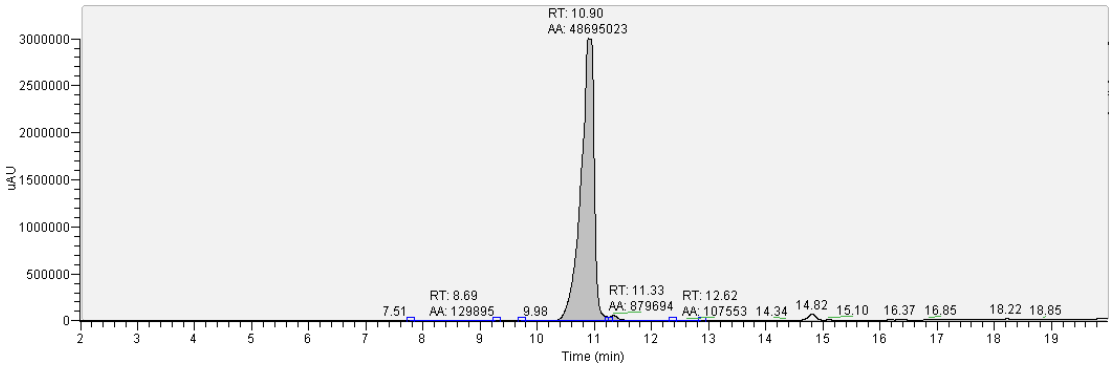

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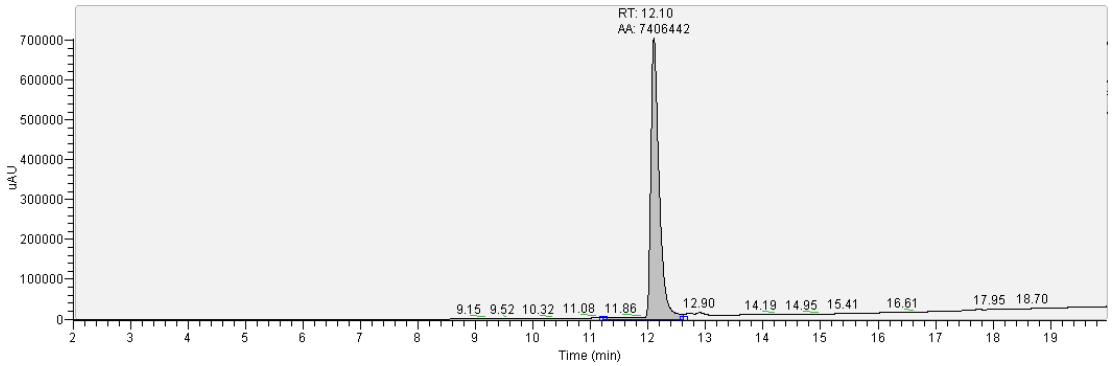

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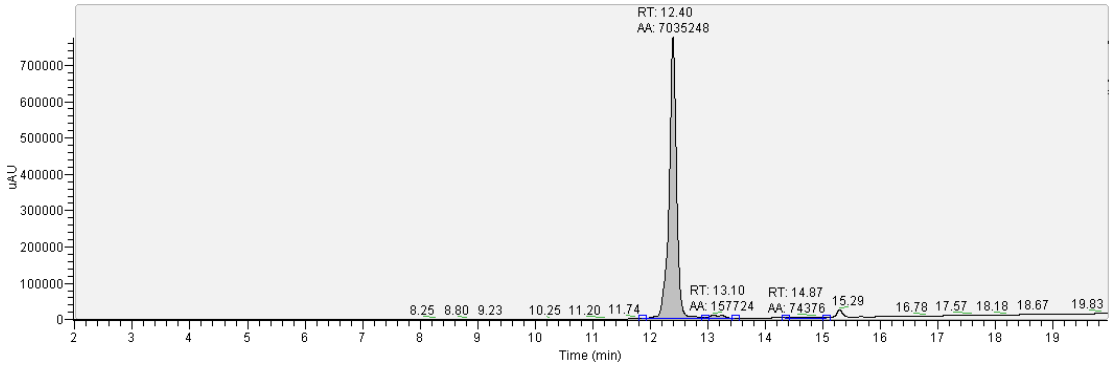

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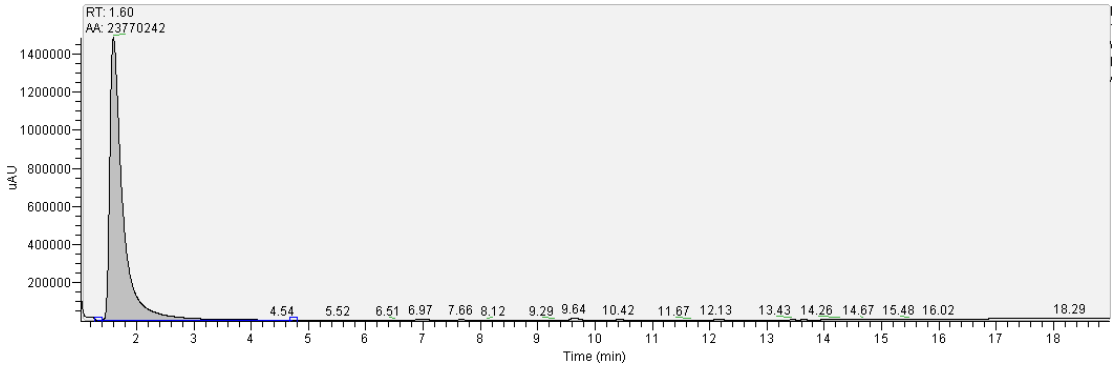

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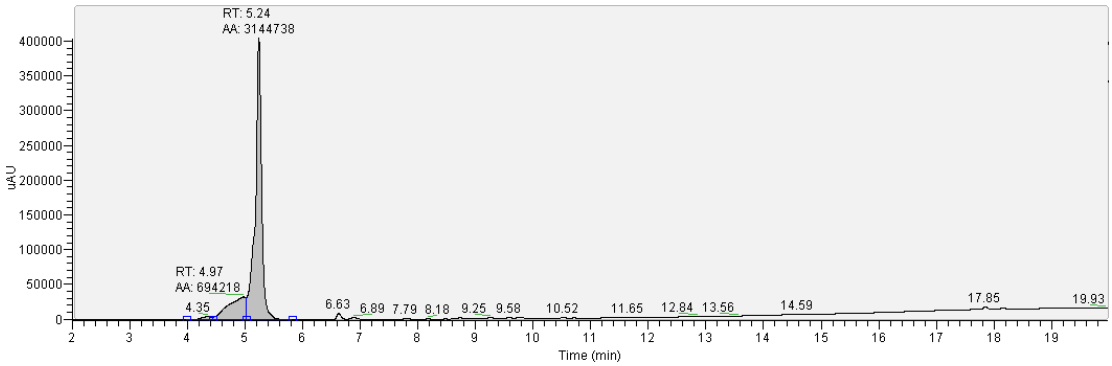

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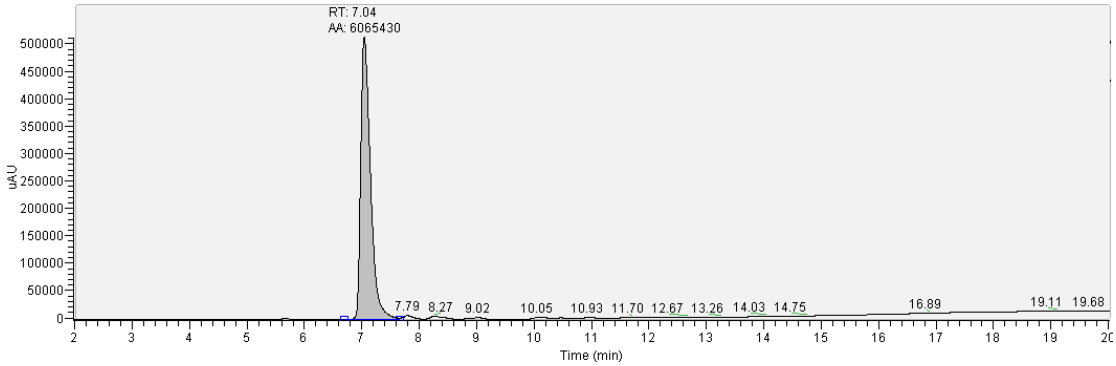

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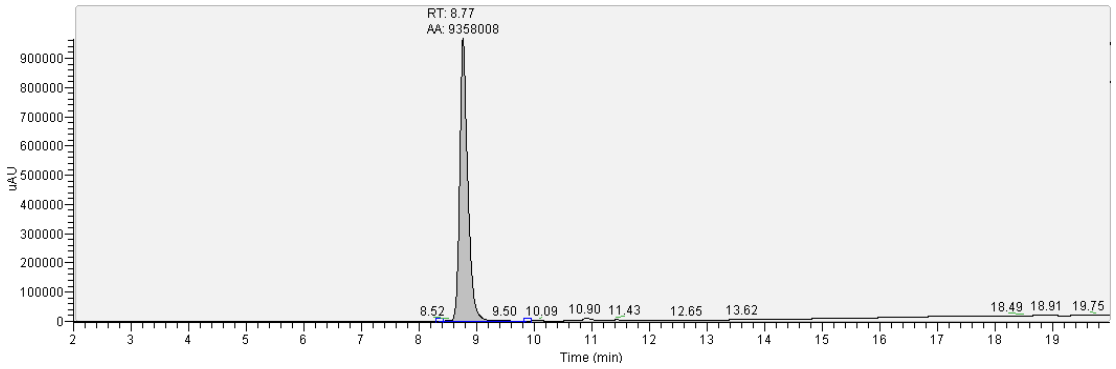

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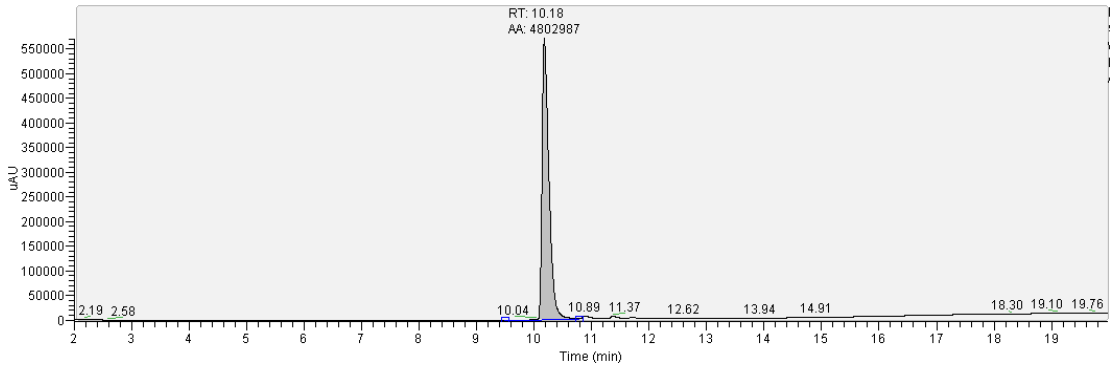

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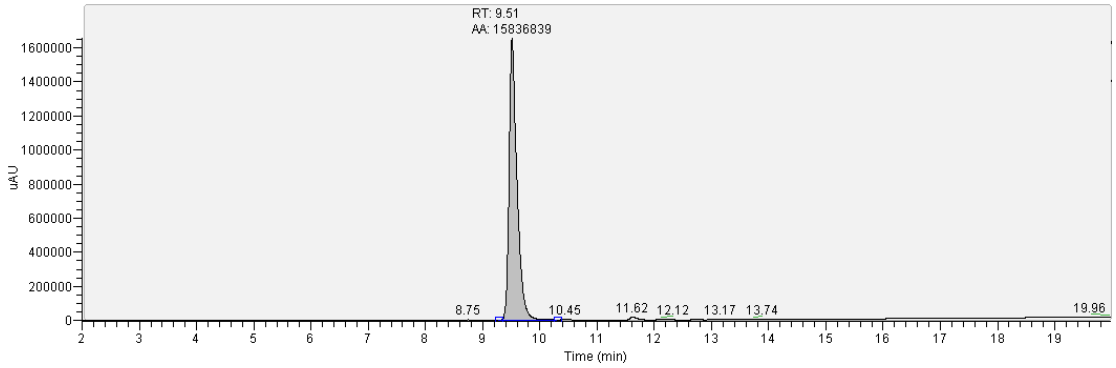

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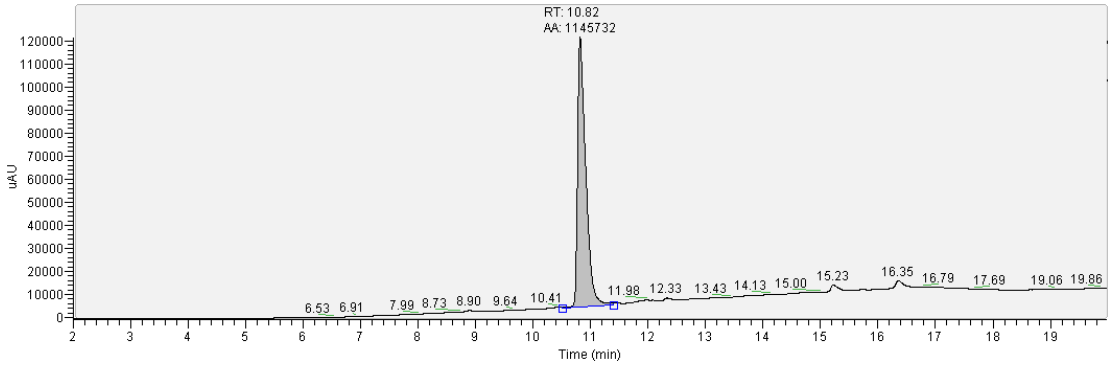

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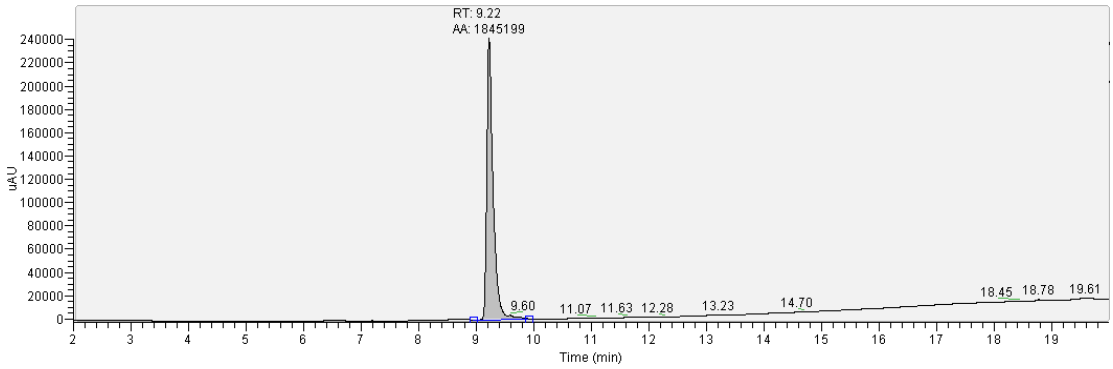

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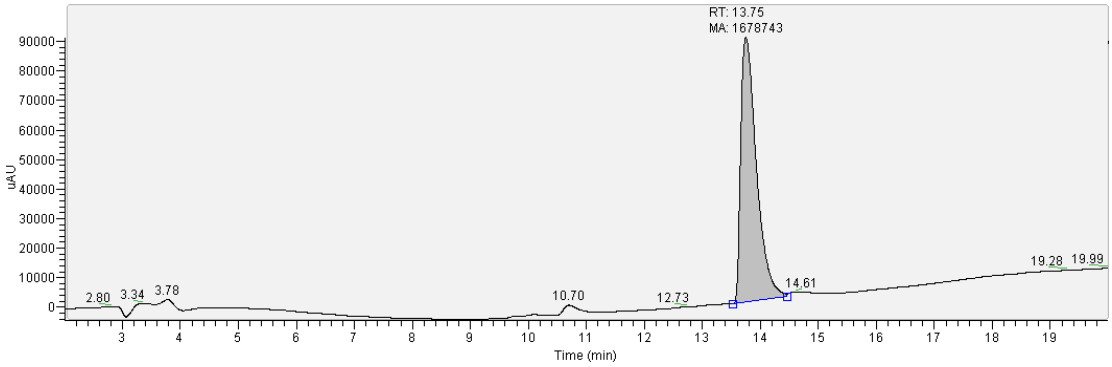

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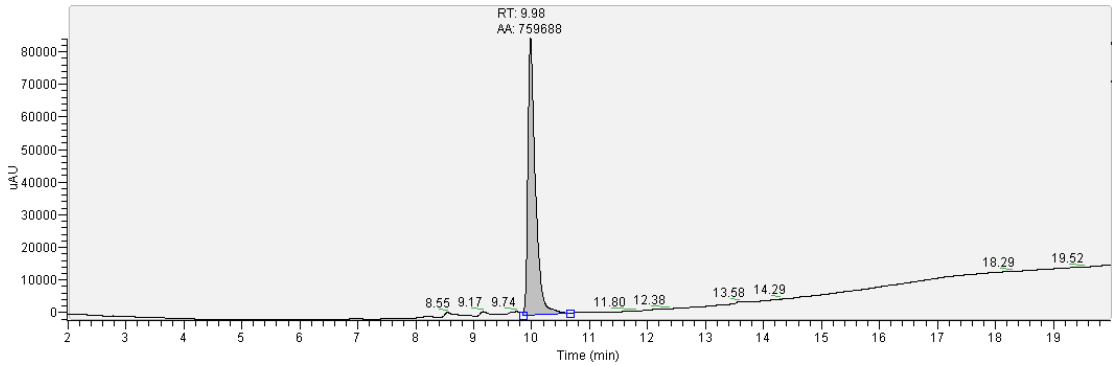
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Time (min)

10. References

(1) Sapountzis, I.; Knochel, P.; General preparation of functionalized *o*-nitroarylmagnesium halides through an iodine–magnesium exchange. *Angew. Chem. Int. Ed.* 2002, **41**, 1610.

(2) Hey, D. H.; Mulley, R. D.; Internuclear cyclization V. The cyclization of derivatives of diphenylmethane, benzophenone, and N-methyldiphenylamine. *J. Chem. Soc.* 1952, 2276.

(3) Muchowski, J. M.; Venuti, M. C.; Ortho functionalization of N-(tert-butoxycarbonyl)aniline. *J. Org. Chem.* 1980, **45**, 4798.

(4) Toyoda, T; Sasakura, X.; Sugasaw, T.; Aminoraloboran in organic sysnthesis. VIII. A one-step synthesis of 2-Aminobenzhydrols from anilines. *Tetrahedron Letters* 1980, **21**, 173.

(5) Krasovskiy, A; Knochel, P.; A LiCl-mediated Br/Mg exchange reaction for the Ppreparation of functionalized aryl- and heteroarylmagnesium compounds from organic bromides. *Angew. Chem. Int. Ed.* 2004, *43*, 3333.

(6) Winthrop, S. O.; Sybulski, S.; Gavin, G.; Gran, G. A.; New analeptics: 1-Benzhydryl-2-alkyl-2-thiopseudo-ureas. *J. Am. Chem. Soc.* 1957, **79**, 3496.

(7) Koopal, S. A.; Molecular transposition in the α-glycols. *Recl. Trav. Chim. Pays-Bas* 1915, **34**, 115.

(8) Kuriyama, M.; Shimazawa, R.; Enomoto, T.; Shirai, R.; Palladium-catalyzed 1,2-addition of potassium aryl- and alkenyltrifluoroborates to aldehydes using thioether-imidazolinium carbine ligands. *J. Or. Chem.* 2008, **73**, 6939.

(9) Rybakova, M. N.; Reactions of alkoxydiarylcarbinolates with esters. *Zh. Obsh. Khim,* 1966, **2**, 470.

(10) Fan, J.; Wang, Z.; Facile construction of functionalized 4H-chromene via tandem benzylation and cyclization. *Chem. Comm.* 2008, **42**, 5381.

(11) Kuriyama, M.; Ishiyama, N.; Shimazawa, R.; Onomura, O.; Palladium-imidazolinium carbine-catalyzed arylation of aldehydes with arylboronic acids in water. *Tetrahedron* 2010, **66**, 6814.

(12) Markees, D. G.; Reaction of benzyl methyl esters with bromine and N-bromosuccinimide. J. Org. Chem. 1958, **23**, 1490.

(3) Barros-Filho, B. B.; de Oliveira, M. C. F.; Lemos, T. L. G.; de Matos, M. C.; de Gonzalo, G.; Gotor-Fernández, V.; Gotor, V.; *Lentinus strigellus*: a new versatile stereoselective biocatalyst for the bioreduction of prochiral ketones. *Tetrahedron: Asymmetry* 2009, **9**, 1057.

(14) Qin, C.; Wu, H.; Cheng, J.; Chen, X.; Liu, M.; Zhang, W.; Su, W.; Ding, J.; The pallium-catalyzed addition of aryl- and heteroarylboronic acids to aldehydes. *J. Org. Chem.* 2007, **72**, 4102.

(15) Carde, R. N.; Hayes P. C.; Jones, G.; Cliff, C. J.; Intramolecular nitrene insertions into aromatic and heteroaromatic systems. Part 7. Insertions into electron-deficient rings. J. Chem. Soc., Perkin Trans. 1, 1981, 1132.

(16) Joossens, J.; Van der Veken, P.; Lambeir, A.-M.; Augustyns, K.; Haemers, A; Development of Irreversible Diphenyl Phosphonate Inhibitors for Urokinase Plasminogen Activator. *J. Med. Chem.* 2004, **47**, 2411.

(17) Li, A.-H.; Moro, S., Forsyth, N; Melman, N.; Ji, X.-D.; Jacobson, K. A.; Synthesis, CoMFA analysis, and receptor docking of 3,5-diacyl-2,4-dialkylpyridine derivatives as selective A_3 adenosine receptor antagonists. *J. Med. Chem.* 1999*,* **42***,* 706-721.

(18) Novotný. J.; Pospěchová. K.; Hrabálek, A.; Čáp, R.; Vávravá, K.; Synthesis of fluorescent C_{24}-ceramide: Evidence for acyl chain length dependent differences in penetration of exogenous NBD-ceramides into human skin. *Bioorg. Med. Chem. Lett.* 2009, **19**, 6975-6977.

(19) Simon, E. J.; Shemin, D. The preparation of S-succinyl coenzyme. A.; *J. Am. Chem. Soc.* 1953, **75**, 2520.

(20) Cook, L.; Ternai, B.; Ghosh, P. Inhibition of human sputum elastase by substituted 2-pyrones. *J. Med. Chem.* 1987, **30**, 1017.

(21) Synthesized according to: Nguyen, V. T. H.; Bellur, E.; Appel, B.; Langer, P.; Synthesis of 4-alkyl- and 4-(ω-chloroalkyl)-3-hydroxy-5-alkylidenebutenolides based

on cyclizations of 4-alkyl- and 4-(ω-chloroalkyl)-1,3-bis(trimethylsilyloxy) buta-1,3-dienes with oxalyl chloride. *Synthesis* 2006, **17**, 2865.

(22) Maron, D. M.; Ames, B. N.; Revised methods for the *Salmonella* mutagenicity test. *Mutat. Res.* 1983, **113**, 173.

(23) Lépine, F.; Déziel, F. E.; Milot, S.; Rahme, L. G.; A stable isotope dilution assay for the quantification of the *Pseudomonas* Quinolone Signal in *Pseudomonas aeruginosa* cultures. *Biochim. Biophys. Acta,* 2003, **1622***,* 36.

(24) Storz, M. P.; Maurer, C. K.; Zimmer, C.; Wagner, N.; Brengel, C.; de Jong, J. C.; Lucas, S.; Müsken, M.; Häussler, S.; Steinbach, A.; Hartmann, R. W.; Validation of PqsD as an anti-biofilm target in *Pseudomonas aeruginosa* by development of small-molecule inhibitors. *J. Am. Chem. Soc.* 2012*,* **134**, 16143.

(23) Maurer, C. K.; Steinbach, A.; Hartmann, R. W.; Development and validation of a UHPLC-MS/MS procedure for quantification of the *Pseudomonas* Quinolone Signal in bacterial culture after acetylation for characterization of new *quorum sensing* inhibitors. *J. Pharm. Biomed. Anal.* 2013, **86**, 127.