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Supporting Information

Efficient Synthesis of Benzothiazinone Analogues with Activity against Intracellular *Mycobacterium tuberculosis*

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Synthetic materials and methods All chemicals were purchased from Sigma Aldrich, Alfa Aesar, VWR, Carl Roth, Fisher Scientific or Acros Organics and were used without further purification. All organic solvents, piperidine, 2,6- dimethylpiperidine, TEA (triethylamine), and DIPEA (*N*,*N*-diisopropylethylamine) were distilled prior use and stored with molecular sieve 3 Å. All solids were dried in a glass oven (Büchi TO-51, Büchi Labortechnik, Flawil, Switzerland) at 60 °C, 20 mbar for 60-120 min prior to use. The notation hexane in the description of the syntheses refers to n-hexane. Column chromatography was carried out using Merck silica gel 60 (63-200 µm). Flash chromatography was performed on a puriFlash® 430 instrument (Interchim, Montluçon, France). Prepacked columns with silica gel (30 µm) were used. The maximum compound load per column was 5 % (m/m) of the silica gel quantity. NMR spectra were recorded on an Agilent Technologies VNMRS 400 MHz spectrometer. Chemical shifts are reported relative to the residual solvent signal ($CDCl_3$ δ_H = 7.26 ppm; δ_C = 77.10 ppm; CD_3OD δ_H = 3.31 ppm; DMSO-d_6 δ_H = 2.50 ppm). Abbreviations: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, m = multiplet. ESI mass spectra were measured on a Thermo Finnigan LCQ Classic spectrometer and high-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Scientific LTQ Orbitrap XL mass spectrometer. APCI mass spectra were measured with an Advion expression^S compact mass spectrometer. Electron impact (EI) mass spectra were recorded on an AMD 402 of AMD Intectra GmbH. Final compounds were confirmed to be of >95% purity based on HPLC. Purity was measured by UV absorbance at 254 nm. The HPLC consists of an XTerra RP18 column (3.5 µm, 3.9 mm × 100 mm) from the manufacturer Waters (Milford, MA, USA) and two LC-10AD pumps, a SPD-M10A VP PDA detector, and a SIL-HT autosampler, all from the manufacturer Shimadzu (Kyoto, Japan). The mobile phase was a gradient of methanol/ water (starting at 95% water going to 5% water) with 0.05 % TFA.

General procedure A - Synthesis of aromatic carboxylic acid chlorides The aromatic carboxylic acid is dissolved in toluene and after addition of $SOCl_2$ (2 eq.) heated for 2 h under reflux. The solvent is then removed under vacuum and the carboxylic acid chloride produced is used for the next reaction step without further work-up.

General procedure B - Synthesis of thioureas with thiocarbonyldiimidazole Thiocarbonyldiimidazole is dissolved in THF in a single-neck flask, the amine is added as solution in THF. The reaction mixture is stirred for 2 h at room temperature, followed by heating to 55 °C for 1 h. After the reaction is complete, 2/3 of the THF volume is removed under vacuum, 2 M ammonia solution in MeOH (2-5 eq. ammonia) is added and the flask is sealed tightly. After 15 h reaction at room temperature, the addition of the 2 M ammonia (2-5 eq. ammonia) solution is repeated and the mixture is heated to 50 °C for 8 h. The solvent is removed under vacuum and the thiourea can be purified by column chromatography or by recrystallisation from isopropanol/diisopropyl ether (1:1).

General procedure C - Synthesis of benzothiazinones by the thiourea pathway The thiourea prepared according to general procedure B is added to toluene in a multi-neck flask and the suspension is heated to 70 °C whereby the thiourea dissolves. The carboxylic acid chloride, prepared according to general procedure A, is also dissolved in toluene and this solution is slowly added to the warm solution of thiourea by a dropping funnel. After complete addition of the acid chloride, heat the reaction mixture for 1 h under reflux and leave it overnight at room temperature.

General procedure D - Synthesis of piperazine monoamides Piperazine (3-5 eq.) and PyBOP® (1.15 eq.) are dissolved in DMF and slowly added to a solution of the corresponding carboxylic acid in DMF. The reaction mixture is stirred overnight, then the solvent is removed under vacuum.

General procedure E Synthesis of thioureas with NaSCN Dry NaSCN was suspended in acetone and cooled to 5 °C. An equimolar amount of benzoylchloride was dissolved in acetone and added dropwise. Subsequently, the mixture was stirred for 2 h at 5 °C. Equimolar amounts of the corresponding amine were dissolved in acetone, added dropwise at approx. 10 °C and the mixture stirred for 2 h at rt. After evaporation of the solvent, the residue was suspended in a small amount (approx. 4-8 eq.) of conc. HCl and heated to 90 °C for 1 h. After carefully neutralizing the mixture with conc. NH_3, the product was collected after precipitation via setting aside the mixture for 48 h at 8 °C or extracting the mixture with chloroform and subsequent flash chromatography of the combined organic layers.

General procedure F Synthesis of thioureas with trimethylsilylisothiocyanate To a solution of the secondary (1 eq.) amine in dried THF trimethylsilylisothiocyanate (2 eq.) was added and stirred for 48 h. The solvent was removed under vacuum and a 2-propanol/water mixture (9:1) was added to the residue. The reaction mixture was boiled for a few seconds and the hot solution mixture was filtered. The flask and filter were washed twice with acetone. The filtrate was evaporated and the product was recrystallized from isopropanol/ diisopropyl ether (1:2).

tert-Butylpiperazine-1-carboxylate (**1a**) For the synthesis of **1a**, piperazine (2000 mg, 23.26 mmol, 1.0 eq.) and triethylamine (4.837 ml, 34.90 mmol, 1.5 eq.) are dissolved in MeOH (20 ml), to which di-tert-butyl dicarbonate (2028 mg, 9.30 mmol, 0.4 eq.) is added slowly. The reaction mixture is then stirred at room temperature overnight. After completion of the reaction, the solvent is removed at the rotary evaporator and the crude product is purified by column chromatography (chloroform/MeOH 9:1). After purification the title compound is isolated as a colourless oil (1486 mg, 86 %).^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.36 (t, C**H₂**-N(CO)-C**H₂**, ^{2}J = 5.1 Hz, 4H), 2.78 (t, C**H₂**-NH-C**H₂**, ^{2}J = 5.1 Hz, 4H), 1.74 (bs, C**H₂**-NH-C**H₂**, 1H), 1.44 (s, t-butyl, 9H) MS (ESI) *m/z* 187.36 [M+H^{+}]

4-Carbamothioylpiperazine-1-carboxylate (**1b**) Compound **1b** is prepared by general procedure B, using tert-butylpiperazine-1-carboxylate (**1a**) (0.341 g, 1.83 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.376 g, 2.11 mmol, 1.15 eq.). Purification is carried out by MPLC (chloroform/MeOH gradient) and the title compound is isolated as a white solid (310 mg 69 %). ^{1}H-NMR (400 MHz, CD_3OD) δ 3.83 (m, C**H2**-N-C**H2**, 4H), 3.48 (m, C**H2**-NH-C**H2**, 4H), 1.47 (s, t-butyl, 9H) MS (ESI) *m/z* 268.41 [M+Na^{+}]

tert-Butyl 4-[8-nitro-4-oxo-6-(trifluoromethyl)-4H-1,3-benzothiazin-2-yl]piperazin-1-carboxylate (**1c**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (2.250 g, 8.4 mmol, 1.1 eq.) by general procedure A. **1c** is synthesised by general procedure C, using 4-carbamothioylpiperazine-1-carboxylate (**1b**) (1.863 g, 7.6 mmol, 1.0 eq.)and adding DIPEA (3.878 ml, 22.8 mmol, 3.0 eq.). Purification is carried out by MPLC (Puriflash system, EtAc/heptane gradient). The title compound is isolated as yellow solid (3000 mg 86 %, HPLC purity 99.9 %, t_R = 14.3 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.09 (d, Ar-**H**, ^{4}J = 2.2 Hz, 1H), 8.76 (d, Ar-**H**, ^{4}J = 2.2 Hz, 1H), 4.01 (bs, C**H₂**-N-C**H₂**, 4H), 3.61 (bs, C**H₂**-N-C**H₂**, 4H), 1.49 (s, t-butyl, 9H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ

166.1, 162.5, 154.2, 143.8, 133.7, 133.3 (q, $^{3}J_{C,F}$ = 3.8 Hz), 129.7 (q, $^{2}J_{C,F}$ = 35.9 Hz), 126.6, 126.0 (q, $^{3}J_{C,F}$ = 3.8 Hz), 122.1 (q, $^{1}J_{C,F}$ = 273.1 Hz), 80.9, 46.1, 43.0, 28.5 HRMS *m/z* calc for $C_{18}H_{20}F_3N_4O_5S$ [M+H$^+$], 461.1103; found, 461.1079, calc for $C_{18}H_{19}F_3N_4O_5SNa$ [M+Na$^+$], 483.0921; found, 483.0896.

8-Nitro-2-(piperazin-1-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**1d**) Compound (**1c**) (150 mg, 0.33 mmol, 1.0 eq.) is dissolved in a mixture of 0.5 ml DCM and 0.5 ml TFA and stirred for 1 h at room temperature. The solvent is removed under vacuum and the reaction mixture is co-evaporated three times each with toluene and chloroform. Compound **1d** is isolated as a pale-yellow solid (106 mg 91 %)) and used for the next reaction step without further purification. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.88 (s, Ar-**H**, 1H), 8.84 (s, Ar-**H**, 1H), 4.29 (bs, C**H$_2$**-N-C**H$_2$**, 4H), 3.49 (t, C**H$_2$**-NH_2^+-C**H$_2$**, ^{3}J = 5.3 Hz, 4H) MS (ESI) *m/z* 361.63 [M+H$^+$]

8-Nitro-2-(4-octanoylpiperazin-1-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-on **(1e)** For the synthesis of **1e**, caprylic acid (0.048 g, 0.33 mmol, 1.0 eq.) is dissolved in 10 ml DCM. DIPEA (0.166 ml, 0.98 mmol, 3.0 eq.), PyBOP® (0.198 g, 0.38 mmol, 1.15 eq.) and 8-nitro-2-(piperazin-1-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**1d**) (0.117 g, 0.33 mmol, 1.0 eq.) dissolved in 5 ml DCM are added to the reaction mixture. The mixture is then left overnight at room temperature and the solvent is removed *in vacuo*. Purification is carried out by MPLC (EtAc/Heptane gradient) and the title compound is isolated as a yellow solid (106 mg 59 %, HPLC purity 98.9 %, t_R = 15.2 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.08 (d, Ar-**H**, ^{4}J = 2.0 Hz, 1H), 8.76 (d, Ar-**H**, ^{4}J = 2.0 Hz, 1H), 4.03 (m, C**H$_2$**-N-C**H$_2$**, 4H), 3.81 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 3.65 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 2.36 (t, CO-C**H$_2$**, ^{3}J = 7.6 Hz, 2H), 1.64 (m, C**H$_2$**, 2H), 1.30 (m, C**H$_2$**, 8H), 0.88 (m, C**H$_3$**-CH_2, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0, 166.2, 162.7, 143.9, 133.6, 133.5 (q, $^{3}J_{C,F}$ = 3.8 Hz), 130.0 (q, $^{2}J_{C,F}$ = 35.1 Hz), 126.6, 126.1 (q, $^{3}J_{C,F}$ = 3.8 Hz), 122.2 (q, $^{1}J_{C,F}$ = 273.1 Hz), 46.2, 46.0,

44.7, 40.8, 33.2, 31.7, 29.3, 29.0, 25.1, 22.6, 14.0 HRMS *m/z* calc for $C_{21}H_{26}F_3N_4O_4S$ [M+H$^+$], 487.1622; found, 487.1594.

8-(Nitro-2-(4-octadecanoylpiperazin-1-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**2a**) For the synthesis of **2a**, stearic acid (0.062 g, 0.22 mmol, 1.0 eq.) is dissolved in 10 ml DCM. DIPEA (0.110 ml, 0.65 mmol, 3.0 eq.), PyBOP® (0.130 g, 0.25 mmol, 1.15 eq.) and 8-nitro-2-(piperazin-1-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**1d**) (0.078 g, 0.22 mmol, 1.0 eq.), dissolved in 5 ml DCM, are added to the reaction mixture. The mixture is then left overnight at room temperature and the solvent is removed *in vacuo*. Purification is carried out by MPLC (EtAc/Heptane gradient) and the titel compound is isolated as a yellow solid (71 mg 52 %, HPLC purity 94.7 %, t_R = 19.2 min). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.10 (d, Ar-**H**, ^4J = 2.0 Hz, 1H), 8.78 (d, Ar-**H**, ^4J = 2.0 Hz, 1H), 4.05 (m, C**H$_2$**-N-C**H$_2$**, 4H), 3.82 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 3.66 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 2.37 (t, CO-C**H$_2$**, ^3J = 7.6 Hz, 2H), 1.65 (m, C**H$_2$**, 2H), 1.29 (m, C**H$_2$**, 28H), 0.87 (m, C**H$_3$**-CH_2, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.2, 166.3, 162.8, 143.9, 133.6, 133.5 (q, $^3J_{C,F}$ = 3.8 Hz), 130.0 (q, $^2J_{C,F}$ = 35.1 Hz), 126.5, 126.2 (q, $^3J_{C,F}$ = 3.8 Hz), 122.2 (q, $^1J_{C,F}$ = 273.1 Hz), 46.2, 46.0, 44.7, 40.8, 33.2, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 25.1, 22.6, 14.1 HRMS *m/z* calc for $C_{31}H_{46}F_3N_4O_4S$ [M+H$^+$], 627.3187; found, 627.3177, calc for $C_{31}H_{45}F_3N_4O_4SNa$ [M+Na$^+$], 649.3007; found, 649.2996.

1-(Piperazin-1-yl)-2-propylpentan-1-on (**3a**) The synthesis of **3a** is carried out according to general procedure D. For this, sodium valproate (0.100 g, 0.60 mmol, 1.0 eq.) and PyBOP® (0.359 g, 0.69 mmol, 1.15 eq.) are dissolved in DMF (10 ml). Then a solution of piperazine (0.259 g, 3.01 mmol, 5.0 eq.) in DMF (5 ml) is added. After 16 h at RT, the solvent is removed in vacuo and the product is purified by column chromatography (chloroform/MeOH/ammonia lsg. 36 % 90:10:1). The titel compound is isolated as colourless oil (106 mg 84 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.58 (m, C**H$_2$**-N-C**H$_2$**, 2H), 3.47 (m, C**H$_2$**-N-C**H$_2$**, 2H), 2.78 (m, C**H$_2$**-N-C**H$_2$**, 4H),

2.60 (m, CO-C**H**-$(CH_2)_2$, 1H), 2.00 (bs, N**H**, 1H), 1.58 (m, CH-C**H₂**, 2H), 1.32 (m, CH-C**H₂**, 2H), 1.20 (m, C**H₂**-CH_3, 4H), 0.82 (t, CH_2-C**H₃**, ^3J = 7.3 Hz, 6H) MS (APCI) *m/z* 213.2 [M+H^+].

4-(2-Propylpentanoyl)piperazin-1-thiourea (**3b**) **3b** is prepared by general procedure B, using 1-(piperazin-1-yl)-2-propylpentan-1-one (**3a**) (0.106 g, 0.50 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.102 g, 0.58 mmol, 1.15 eq.). Purification is carried out by MPLC (heptane gradient) and the product is isolated as a white solid (98 mg 72 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.23 (bs, N**H₂**, 2H), 4.03 (bs, C**H₂**-N-C**H₂**, 2H), 3.73 (bs, C**H₂**-N-C**H₂**, 4H), 3.66 (bs, C**H₂**-N-C**H₂**, 2H), 2.62 (m, CO-C**H**-$(CH_2)_2$, 1H), 1.58 (m, CH-C**H₂**, 2H), 1.38 (m, CH-C**H₂**, 2H), 1.22 (m, C**H₂**-CH_3, 4H), 0.86 (t, CH_2-C**H₃**, ^3J = 7.2 Hz, 6H) MS (APCI) *m/z* 272.2 [M+H^+].

*8-Nitro-2-[4-(2-propylpentanoyl)piperazin-1-yl]-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (***3c***)* 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.055 g, 0.20 mmol, 1.1 eq.) by general procedure A. **3c** is synthesised by general procedure C, using 4-(2-propylpentanoyl)piperazine-1-thiourea (**3b**) (0.050 g, 0.19 mmol, 1.0 eq.). Purification is carried out by MPLC (EtAc/heptane gradient) and the title compound is isolated as a yellow amorphous substance (84 mg 91 % HPLC purity 95.2 %, t_R = 14.8 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.09 (d, Ar-**H**, ^4J = 2.2 Hz, 1H), 8.77 (d, Ar-**H**, ^4J = 2.2 Hz, 1H), 4.07 (bs, C**H₂**-N-C**H₂**, 2H), 3.98 (bs, C**H₂**-N-C**H₂**, 2H), 3.86 (bs, C**H₂**-N-C**H₂**, 2H), 3.74 (bs, C**H₂**-N-C**H₂**, 2H), 2.67 (m, CH_2-C**H**-CH_2, 1H), 1.65 (m, CH-C**H₂**, 2H), 1.43 (m, CH-C**H₂**, 2H), 1.27 (m, C**H₂**-CH_3, 4H), 0.89 (t, CH_2-C**H₃**, ^3J = 7.2 Hz, 6H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.2, 166.2, 162.7, 143.9, 133.6, 133.5 (q, $^3J_{C,F}$ = 3.8 Hz), 130.0 (q, $^2J_{C,F}$ = 35.1 Hz), 126.6, 126.1 (q, $^3J_{C,F}$ = 3.8 Hz), 122.3 (q, $^1J_{C,F}$ = 273.1 Hz), 46.4, 46.2, 44.8, 41.0, 40.7, 35.2, 20.8, 14.2 HRMS *m/z* calc for $C_{31}H_{45}F_3N_4O_4SNa$ [M+Na^+], 509.1445; found, 509.1450.

Ethyl-1-(piperazin-1-yl)hexan-1-on (**4a**) The synthesis of **4a** is carried out according to general procedure D. For this, 2-ethylhexanoic acid (0.300 g, 2.08 mmol, 1.0 eq.) and PyBOP® (1.244

g, 2.39 mmol, 1.15 eq.) are dissolved in DMF (20 ml). Then a solution of piperazine (0.537 g, 6.25 mmol, 3.0 eq.) in DMF (10 ml) is added. After 16 h at room temperature, the solvent is removed in vacuo and the product is purified by column chromatography (chloroform/MeOH/ammonia 36 % 90:10:1) and the title compound is isolated as colourless oil (284 mg 69 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.57 (t, C**H$_2$**-N-C**H$_2$**, ^3J = 4.9 Hz, 2H), 3.46 (t, C**H$_2$**-N-C**H$_2$**, ^3J = 4.9 Hz, 2H), 2.76 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.49 (m, CH_2-C**H**-CH_2, 1H), 2.02 (bs, N**H**, 1H), 1.57 (m, CH-C**H$_2$**, 2H), 1.37 (m, CH-C**H$_2$**, 2H), 1.16 (m, C**H$_2$**-C**H$_2$**, 4H), 0.79 (m, CH_2-C**H$_3$**, 6H) MS *m/z* (APCI) 213.2 [M+H$^+$].

4-(2-Ethylhexanoyl)piperazin-1-thiourea (**4b**) **4b** is prepared according general procedure B, using Ethyl-1-(piperazin-1-yl)hexan-1-on (**4a**) (0.170 g, 0.80 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.164 g, 0.92 mmol, 1.15 eq.). Purification is carried out by MPLC (EtAc/heptane gradient) and the title compound is isolated as a white solid (132 mg 61 %). ^{1}H-NMR (400 MHz, CD_3OD) δ 3.95 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 3.81 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 3.74 (m, C**H$_2$**-N-C**H$_2$**, 2H), 3.71 (m, C**H$_2$**-N-C**H$_2$**, 2H), 2.76 (m, CH_2-C**H**-CH_2, 1H), 1.60 (m, CH-C**H$_2$**, 2H), 1.48 (m, CH-C**H$_2$**, 2H), 1.27 (m, C**H$_2$**-CH_3, 4H), 0.90 (t, CH_2-C**H$_3$**, ^3J = 7.0 Hz, 3H), 0.88 (t, CH_2-C**H$_3$**, ^3J = 7.4 Hz, 3H) MS *m/z* (APCI) 272.3 [M+H$^+$].

2-[4-(2-Ethylhexanoyl)piperazin-1-yl]-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**4c**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.109 g, 0.41 mmol, 1.1 eq.) by general procedure A. **4c** is synthesised by general procedure C, using 4-(2-ethylhexanoyl)piperazine-1-thiourea (**4b**) (0.100 g, 0.37 mmol, 1.0 eq.). Thet title compound is isolated by MPLC (EtAc/heptane gradient) (175 mg 97 %, HPLC purity 95.9 %, t_R = 14.8 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.06 (d, Ar-**H**, ^4J = 1.8 Hz, 1H), 8.75 (d, Ar-**H**, ^4J = 1.8 Hz, 1H), 4.07 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 3.97 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 3.86 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 3.73 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 2.56 (m, CH_2-C**H**-CH_2, 1H), 1.65 (m, CH-C**H$_2$**,

2H), 1.47 (m, CH-C**H₂**, 2H), 1.23 (m, C**H₂**-CH_3, 4H), 0.87 (m, CH_2-C**H₃**, 6H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.1, 166.2, 162.7, 143.9, 133.6, 133.4 (q, $^3J_{C,F}$ = 3.1 Hz), 130.0 (q, $^2J_{C,F}$ = 35.1 Hz), 126.6, 126.1 (q, $^3J_{C,F}$ = 3.1 Hz), 122.3 (q, $^1J_{C,F}$ = 273.1 Hz), 46.4, 46.2, 44.8, 42.7, 41.0, 32.8, 29.8, 25.8, 22.8, 13.9, 12.0 HRMS *m/z* calc for $C_{21}H_{26}F_3N_4O_4S$ [M+H$^+$], 487.1623; found, 487.1603, calc for $C_{21}H_{25}F_3N_4O_4SNa$ [M+Na$^+$], 509.1442; found, 509.1420.

tert-Butyl (S)-(4-methyl-1-oxo-1-(piperazin-1-yl)pentan-2-yl)carbamate (**5a**) The synthesis of **5a** is carried out according to general procedure D. t-Boc-leucine (0.233 g, 1.01 mmol, 1.0 eq.) and PyBOP® (0.604 g, 1.16 mmol, 1.15 eq.) are dissolved in DMF (15 ml). Then a solution of piperazine (0.260 g, 3.02 mmol, 3.0 eq.) in DMF (5 ml) is added. After 16 h at room temperature, the solvent is removed in vacuo and the product is purified by column chromatography (chloroform/MeOH/ammonia 36 % 90:10:1). The title compound is a colourless oil (251 mg 84 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.31 (d, N**H**, ^3J = 9.0 Hz, 1H), 4.60 (m, CO-C**H**-NH, 1H), 4.33 (bs, N**H**/H_2O, 2H), 3.75 (m, C**H₂**-N-C**H₂**, 1H), 3.62 (m, C**H₂**-N-C**H₂**, 1H), 3.52 (m, C**H₂**-N-C**H₂**, 2H), 2.95 (m, C**H₂**-N-C**H₂**, 2H), 2.90 (m, C**H₂**-N-C**H₂**, 2H), 1.68 (m, CH_3-C**H**-CH_3, 1H), 1.43 (m ,CH-C**H₂**-CH, 2H), 1.40 (s, C-(C**H₃**)$_3$, 9H), 0.94 (d, C**H₃**-CH-CH_3, ^3J = 6.7 Hz, 3H), 0.89 (d, CH_3-CH-C**H₃**, ^3J = 6.7 Hz, 3H) MS *m/z* (APCI) 300.3 [M+H$^+$].

tert-Butyl (S)-(1-(4-carbamothioylpiperazin-1-yl)-4-methyl-1-oxopentan-2-yl)carbamate (**5b**) Compound **5b** is prepared by general procedure B, using tert-butyl N-[4-methyl-1-oxo-1-(piperazin-1-yl)pentan-2-yl]carbamate (**5a**) (0.202 g, 0.68 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.138 g, 0.78 mmol, 1.15 eq.). The product is purified by column chromatography (chloroform/MeOH 95:5) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.25 (m, N**H₂**, 2H), 5.25 (m, N**H**, 1H) ,4.57 (m, CO-C**H**-NH, 1H), 4.07 (bs, C**H₂**-N-C**H₂**, 1H), 3.80 (bs, C**H₂**-N-C**H₂**, 5H), 3.55 (bs, C**H₂**-N-C**H₂**, 1H), 1.68 (m, CH_3-C**H**-CH_3, 1H), 1.45 (m , CH-C**H₂**-CH, 2H),

1.39 (s, C-(C**H₃**)₃, 9H), 0.94 (d, C**H₃**-CH-CH₃, ^3J = 6.5 Hz, 3H), 0.90 (d, CH₃-CH-C**H₃**, ^3J = 6.6 Hz, 3H) MS *m/z* (ESI) 381.53 [M+Na⁺].

tert-Butyl (S)-(4-methyl-1-(4-(8-nitro-4-oxo-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-2-yl)piperazin-1-yl)-1-oxopentan-2-yl)carbamate (**5c**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.114 g, 0.42 mmol, 1.1 eq.) by general procedure A. AR160 is synthesised by general procedure C, using tert-butyl N-[1-(4-carbamothioylpiperazin-1-yl)-4-methyl-1-oxopentan-2-yl]carbamate (**5b**) (0.138 g, 0.39 mmol, 1.0 eq.). Purification of the title compound is done by column chromatography (chloroform/MeOH 98:2) (170 mg 76 %, HPLC purity 99.2 %, t_R = 14.8 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.08 (d, Ar-**H**, ^4J = 2.2 Hz, 1H), 8.76 (d, Ar-**H**, ^4J = 2.2 Hz, 1H), 5.15 (d, N**H**, ^3J = 9.0 Hz, 1H), 4.64 (m, CO-C**H**-NH, 1H), 4.25 (bs, C**H₂**-N-C**H₂**, 2H), 4.04 (m, C**H₂**-N-C**H₂**, 1H), 3.94 (bs, C**H₂**-N-C**H₂**, 2H),3.85 (m, C**H₂**-N-C**H₂**, 1H), 3.59 (m, C**H₂**-N-C**H₂**, 2H), 1.70 (m, CH₃-C**H**-CH₃, 1H), 1.51 (m, CH-C**H₂**-CH, 1H), 1.42 (s, C-(CH₃)₃, 9H), 1.39 (m, CH-C**H₂**-CH, 1H), 0.97 (d, CH₃-CH-C**H₃**, ^3J = 6.5 Hz, 3H), 0.93 (d, C**H₃**-CH-CH₃, ^3J = 6.5 Hz, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0, 166.2, 162.7, 155.6, 143.9, 133.6, 133.5 (q, $^3J_{C,F}$ = 3.8 Hz), 130.0 (q, $^2J_{C,F}$ = 35.9 Hz), 126.6, 126.1 (q, $^3J_{C,F}$ = 3.8 Hz), 122.3 (q, $^1J_{C,F}$ = 273.1 Hz), 80.0, 48.4, 46.0, 44.8, 42.4, 41.5, 28.3, 24.7, 23.2, 22.0 HRMS *m/z* calc for $C_{24}H_{30}F_3N_5O_6SNa$ [M+Na⁺], 596.1763; found, 596.1735.

2-(4-(L-Leucyl)piperazin-1-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (**5d**) (47 mg, 0.08 mmol, 1.0 eq.) is dissolved in a mixture of 1 ml DCM and 1 ml TFA and left for 1 h at room temperature. The solvent is removed under vacuum and the reaction mixture is co-evaporated three times each with toluene and chloroform. The crude product is purified by column chromatography (chloroform/MeOH/ammonia 36 % 95:5:1) and the title compound is a yellow amorphous substance (31 mg 80 %, HPLC purity 97.4 %, t_R = 13.7 min). ^{1}H-NMR

(400 MHz, $CDCl_3$): δ = 9.09 (d, Ar-**H**, ^4J = 2.0 Hz, 1H), 8.77 (d, Ar-**H**, ^4J = 2.2 Hz, 1H), 4.04 (m, C**H₂**-N-C**H₂**, 5H), 3.76 (m, C**H**-NH_2, 1H), 3.73 (bs, C**H₂**-N-C**H₂**, 2H), 3.64 (bs, C**H₂**-N-C**H₂**, 1H), 1.86 (m, CH_3-C**H**-CH_3, 1H), 1.40 (m, CH-C**H₂**, 2H), 0.96 (dd, C**H₃**-CH-C**H₃**, ^3J = 6.7 Hz, 6H) ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.6, 166.2, 162.8, 143.9, 133.6, 133.5 (q, $^3J_{C,F}$ = 3.8 Hz), 129.1 (q, $^2J_{C,F}$ = 35.1 Hz), 126.6, 126.2 (q, $^3J_{C,F}$ = 3.8 Hz), 122.3 (q, $^1J_{C,F}$ = 273.1 Hz), 49.7, 46.0, 44.8, 44.4, 41.4, 24.7, 23.5, 21.6 HRMS *m/z* calc for $C_{19}H_{23}F_3N_5O_4S$ [M+H^+], 474.1419; found, 474.1413.

4-{[(tert-Butoxy)carbonyl]amino}butanoic acid (**6a**) For the synthesis of **6a**, γ-aminobutyric acid (1000 mg, 9.70 mmol, 1.0 eq.) and di-tert-butyl dicarbonate (2538 mg, 11.64 mmol, 1.2 eq.) are dissolved in THF (10 ml). To this solution a solution of $NaHCO_3$ (1076 mg, 12.80 mmol, 1.32 eq.) in water (10 ml) is added under ice cooling. The reaction mixture is then left at room temperature overnight. For work-up, the pH of the mixture is adjusted to 2 with 1 N HCl and the product is extracted with DCM (twice). The organic phases are collected and, after drying, concentrated over Na_2SO_4 in vacuo. The product - colourless oil - obtained is used without further purification (1453 mg 94 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.68 (bs, COO**H**, 1H), 3.75 (m, N**H**, 1H), 3.18 (bs, NH-C**H₂**H), 2.39 (t, CO-C**H₂**, ^3J = 7.4 Hz, 2H), 1.82 (m, CH_2-C**H₂**-CH_2, 2H), 1.52 (s, C**H₃**, 9H) MS *m/z* (ESI) 202.30 [M-H^+].

tert-Butyl N-[4-oxo-4-(piperazin-1-yl)butyl]carbamate (**6b**) The synthesis of **6b** is carried out according to general procedure D by dissolving 4-{[(tert-butoxy)carbonyl]amino}butanoic acid (**6a**) (1.453 g, 7.16 mmol, 1.0 eq.) and PyBOP® (4.282 g, 8.23 mmol, 1.15 eq.) in DMF (25 ml). Then a solution of piperazine (1.850 g, 21.47 mmol, 3.0 eq.) in DMF (10 ml) is added. After 16 h at room temperature the solvent is removed *in vacuo* and the product – a colourless oil - is purified by column chromatography (chloroform/MeOH/ammonia 36 % 90:10:1) (450 mg 23 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.90 (bs, N**H**, 1H), 3.56 (m, C**H₂**-N-C**H₂**, 2H), 3.41 (m, C**H₂**-N-C**H₂**, 4H), 3.12 (q, NH-C**H₂**, ^3J = 6.5 Hz, 2H), 2.83 (m, C**H₂**-N-C**H₂**, 4H), 2.77 (bs, N**H**, 1H), 2.32 (t,

CO-C**H₂**, ^{3}J = 7.2 Hz, 2H), 1.78 (qi, CH_2-C**H₂**-CH_2, ^{3}J = 7.0 Hz, 2H), 1.39 (s, C**H₃**, 9H) MS *m/z* (ESI) 294.18 [M+Na^+].

tert-Butyl N-[4-(4-carbamothioylpiperazin-1-yl)-4-oxobutyl]carbamate (**6c**) Compound **6c** is prepared by general procedure B, using tert-butyl N-[4-oxo-4-(piperazin-1-yl)butyl]carbamate (**6b**) (0.420 g, 1.55 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.318 g, 1.78 mmol, 1.15 eq.). The product - a white solid - is purified by column chromatography (chloroform/MeOH 9:1) (359 mg 70 %) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.85 (bs, N**H₂**, 2H), 4.72 (bs, N**H**, 1H), 4.05 (bs, C**H₂**-N-C**H₂**, 2H), 3.75 (bs, C**H₂**-N-C**H₂**, 4H), 3.61 (bs, C**H₂**-N-C**H₂**, 2H), 3.18 (t, NH-C**H₂**, ^{3}J = 6.6 Hz, 2H), 2.38 (t, CO-C**H₂**, ^{3}J = 7.1 Hz, 2H), 1.85 (qi, CH_2-C**H₂**-CH_2, ^{3}J = 6.8 Hz, 2H), 1.43, (s, C**H₃**, 9H) MS *m/z* (ESI) 353.66 [M+Na^+].

tert-Butyl N-(4-{4-[8-nitro-4-oxo-6-(trifluoromethyl)-4H-1,3-benzothiazin-2-yl]piperazin-1-yl}-4-oxobutyl)carbamate (**6d**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.436 g, 1.62 mmol, 1.1 eq.) by general procedure A. **6d** is synthesised by general procedure C, using tert-butyl N-[4-(4-carbamothioylpiperazin-1-yl)-4-oxobutyl]carbamate (**6c**) (0.138 g, 0.39 mmol, 1.0 eq.). Purification is carried out by MPLC (chloroform/MeOH gradient) and the title compound is isolated as a yellow solid (195 mg 24 %, HPLC purity 95.4 %, t_R = 13.7 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.08 (d, Ar-**H**, ^{4}J = 2.2 Hz, 1H), 8.76 (d, Ar-**H**, ^{4}J = 2.2 Hz, 1H), 4.73 (bs, N**H**, 1H), 4.04 (m, C**H₂**-N-C**H₂**, 4H), 3.82 (bs, C**H₂**-N-C**H₂**, 2H), 3.65 (bs, C**H₂**-N-C**H₂**, 2H), 3.18 (q, NH-C**H₂**, ^{3}J = 6.5 Hz, 2H), 2.41 (t, CO-C**H₂**, ^{3}J = 7.1 Hz, 2H), 1.83 (qi, CH_2-C**H₂**-CH_2, ^{3}J = 6.8 Hz, 2H), 1.42, (s, C**H₃**, 9H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.3, 166.1, 162.7, 156.1, 143.9, 133.6, 133.6 (q, $^{3}J_{C,F}$ = 3.1 Hz), 129.9 (q, $^{2}J_{C,F}$ = 35.9 Hz), 126.5, 126.1 (q, $^{3}J_{C,F}$ = 3.8 Hz), 122.3 (q, $^{1}J_{C,F}$ = 273.1 Hz), 79.2, 46.1, 45.9, 44.6, 40.9, 40.1, 30.2, 28.4, 25.3 HRMS *m/z* calc for $C_{22}H_{26}F_3N_5O_6SNa$ [M+Na^+], 568.1449; found, 568.1442.

(S)-N-(4-(Methylthio)-1-oxo-1-(piperazin-1-yl)butan-2-yl)acetamide (**7a**) The synthesis of **7a** is carried out according to general procedure D. For this, N-acetylcysteine (0.244 g, 1.50 mmol, 1.0 eq.) and PyBOP® (0.897 g, 1.73 mmol, 1.15 eq.) are dissolved in DMF (15 ml). Then a solution of piperazine (0.388 g, 4.50 mmol, 3.0 eq.) in DMF (5 ml) is added. After 16 h at room temperature, the solvent is removed *in vacuo* and the product is purified by column chromatography (chloroform/MeOH/ammonia 36 % 90:10:1). The title compound is isolated as a colourless oil (159 mg 41 %) ^{1}H-NMR (400 MHz, CD_3OD) δ 6.67 (d, NH, ^3J = 8.0 Hz, 1H), 5.05 (m, CO-C**H**-NH, 1H), 3.56 (m, C**H$_2$**-N-C**H$_2$**, 1H), 2.85 (m, C**H$_2$**-N-C**H$_2$**, 1H), 2.47 (m, CH_2-C**H$_2$**-S, 2H), 2.06 (s, -C**H$_3$**, 3H), 1.98 (s, -C**H$_3$**, 3H), 1.95 (m, CH-C**H$_2$**-CH_2, 1H), 1.79 (m, CH-C**H$_2$**-CH_2, 1H) MS *m/z* (ESI) 260.64 [M+H$^+$], 283.15 [M+Na$^+$].

(S)-N-(1-(4-Carbamothioylpiperazin-1-yl)-4-(methylthio)-1-oxobutan-2-yl)acetamide (**7b**) Compound **7b** is prepared by general procedure B, using N-[4-(methylsulfanyl)-1-oxo-1-(piperazin-1-yl)butan-2-yl]acetamide (**7a**) (0.159 g, 0.61 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.126 g, 0.71 mmol, 1.15 eq.). The purification is carried out by recrystallisation from DCM/hexane 1:1 and the title compond is a white solid (116 mg 60 %). ^{1}H-NMR (400 MHz, CD_3OD) δ 4.98 (m, CO-C**H**-NH, 1H), 4.03 (m, C**H$_2$**-N-C**H$_2$**, 1H), 3.94 (m, C**H$_2$**-N-C**H$_2$**, 1H), 3.86 (m, C**H$_2$**-N-C**H$_2$**, 2H), 3.75 (m, C**H$_2$**-N-C**H$_2$**, 3H), 3.55 (m, C**H$_2$**-N-C**H$_2$**, 1H), 2.53 (m, CH_2-C**H$_2$**-S, 2H), 2.10 (s, -C**H$_3$**, 3H), 1.99 (m, CH-C**H$_2$**-CH_2, 1H), 1.97 (s, -C**H$_3$**, 3H), 1.90 (m, CH-C**H$_2$**-CH_2, 1H) MS *m/z* (ESI) 341.50 [M+Na$^+$].

(S)-N-(4-(Methylthio)-1-(4-(8-nitro-4-oxo-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-2-yl)piperazin-1-yl)-1-oxobutan-2-yl)acetamide (**7c**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.093 g, 0.35 mmol, 1.1 eq.) by general procedure A. **7c** is synthesised by general procedure C, using N-[1-(4-carbamothioylpiperazin-1-yl)-4-(methylsulfanyl)-1-oxobutan-2-yl]acetamide (**7b**) (0.100 g,

0.31 mmol, 1.0 eq.). Purification is carried out by MPLC (EtAc/MeOH gradient) and the title compound is isolated as a yellow amorphous substance (73 mg 44 %, HPLC purity 100.0 %, t_R = 12.3 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.04 (s, Ar-**H**, 1H), 8.74 (s, Ar-**H**, 1H), 6.66 (d, N**H**, ^3J = 7.2 Hz, 1H), 5.10 (m, CO-C**H**-NH, 1H), 4.18 (bs, C**H$_2$**-N-C**H$_2$**, 2H), 3.98 (m, C**H$_2$**-N-C**H$_2$**,4H), 3.76 (m, C**H$_2$**-N-C**H$_2$**, 1H), 3.61 (m, C**H$_2$**-N-C**H$_2$**, 1H), 2.51 (m, C**H$_2$**-S, 2H), 2.07 (s, -C**H$_3$**, 3H), 1.99 (s, -C**H$_3$**, 3H), 1.98 (m, CH-C**H$_2$**-CH_2, 1H), 1.87 (m, C**H$_2$**-S, 1H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.1, 166.2, 162.7, 143.9, 133.6, 133.4 (q, $^3J_{C,F}$ = 3.1 Hz), 130.0 (q, $^2J_{C,F}$ = 35.1 Hz), 126.6, 126.1 (q, $^3J_{C,F}$ = 3.1 Hz), 122.3 (q, $^1J_{C,F}$ = 273.1 Hz), 46.4, 46.2, 44.8, 42.7, 41.0, 32.8, 29.8, 25.8, 22.8, 13.9, 12.0 HRMS *m/z* calc for $C_{20}H_{23}F_3N_5O_5S_2$ [M+H$^+$], 534.1089; found, 534.1062, calc for $C_{20}H_{22}F_3N_5O_5S_2Na$ [M+Na$^+$], 556.09118; found, 556.0881.

2-[4-rac-(2-Methylpropyl)phenyl]-1-(piperazin-1-yl)propan-1-on (**8a**) The synthesis of **8a** is carried out according to general procedure D by dissolving 2-[4-(2-methylpropyl)phenyl]propanoic acid (0.500 g, 2.42 mmol, 1.0 eq.) and PyBOP® (1.450 g, 2.79 mmol, 1.15 eq.) in DMF (10 ml). Then a solution of piperazine (0.626 g, 7.27 mmol, 3.0 eq.) in DMF (10 ml) is added. After 16 h at room temperature the solvent is removed *in vacuo* and the product is purified by column chromatography (chloroform/MeOH/ammonia 36 % 90:10:1) as a colourless oil (534 mg 80 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.06 (m, Ar-**H**, 4H), 6.88 (bs, N**H**, 1H), 3.94 (bs, C**H$_2$**-N-C**H$_2$**, 1H) 3.76 (q, CO-C**H**, ^3J = 6.8 Hz, 1H), 3.47 (m, C**H$_2$**-N-C**H$_2$**, 3H), 3.04 (bs, C**H$_2$**-N-C**H$_2$**, 1H), 2.85 (m, C**H$_2$**-N-C**H$_2$**, 2H), 2.40 (d, C**H$_2$**, ^3J = 7.2 Hz, 2H), 2.34 (bs, C**H$_2$**-N-C**H$_2$**, 1H), 1.80 (n, CH_2-C**H**-(CH_3)$_2$, ^3J = 6.8 Hz, 1H), 1.38 (d, C**H$_3$**-CH, ^3J = 6.8 Hz, 3H), 0.85 (d, C**H$_3$**-CH-C**H$_3$**, ^3J = 6.7 Hz, 6H) MS *m/z* (APCI) 275.2 [M+H$^+$].

4-{2-[4-rac-(2-Methylpropyl)phenyl]propanoyl}piperazin-1-thiourea (**8b**) Compound **8b** is prepared by general procedure B, using 2-[4-(2-methylpropyl)phenyl]-1-(piperazin-1-yl)propan-1-one (**8a**) (0.534 g, 1.94 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.397 g, 2.23

mmol, 1.15 eq.). The product is recrystallised from isopropanol/diisopropyl ether (1:1) and the title compound is a white solid (407 mg 63 %). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.17 (d, Ar-**H**, ^{3}J = 8.2 Hz, 2H), 7.12 (d, Ar-**H**, ^{3}J = 8.2 Hz, 2H), 4.04 (q, CO-C**H**, ^{3}J = 6.8 Hz, 1H), 3.85 (m, C**H₂**-N-C**H₂**, 3H), 3.52 (m, C**H₂**-N-C**H₂**, 2H), 3.16 (m, C**H₂**-N-C**H₂**, 1H), 2.45 (d, C**H₂**, ^{3}J = 7.2 Hz, 2H), 1.83 (n, CH_2-C**H**-$(CH_3)_2$, ^{3}J = 6.8 Hz, 1H), 1.38 (d, C**H₃**-CH, ^{3}J = 6.8 Hz, 3H), 0.88 (d, C**H₃**-CH-C**H₃**, ^{3}J = 6.7 Hz, 6H) MS *m/z* (ESI) 356.86 [$M+H^+$].

2-(4-{2-rac-[4-(2-Methylpropyl)phenyl]propanoyl}piperazin-1-yl)-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**8c**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.133 g, 0.50 mmol, 1.1 eq.) by general procedure A. Compound **8c** is synthesised by general procedure C, using 4-{2-[4-(2-methylpropyl)phenyl]propanoyl}piperazine-1-thiourea (**8b**) (0.138 g, 0.39 mmol, 1.0 eq.). Purification is carried out by MPLC (EtAc/heptane gradient) and the title compound is isolated as a yellow solid (207 mg 84 %, HPLC purity 98.9 %, t_R = 15.9 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.07 (d, Ar-**H**, ^{4}J = 2.0 Hz, 1H), 8.76 (d, Ar-**H**, ^{4}J = 2.0 Hz, 1H), 7.14 (d, Ar-**H**, ^{3}J = 8.4 Hz, 2H), 7.11 (d, Ar-**H**, ^{3}J = 8.4 Hz, 2H), 4.15 (bs, C**H₂**-N-C**H₂**, 3H), 3.84 (q, CO-C**H**, ^{3}J = 6.8 Hz, 1H), 3.60 (m, C**H₂**-N-C**H₂**, 2H), 3.48 (m, C**H₂**-N-C**H₂**, 2H), 3.06 (bs, C**H₂**-N-C**H₂**, 1H), 2.44 (d, C**H₂**, ^{3}J = 7.2 Hz, 2H), 1.84 (n, CH_2-C**H**-$(CH_3)_2$, ^{3}J = 6.8 Hz, 1H), 1.47 (d, C**H₃**-CH, ^{3}J = 6.8 Hz, 3H), 0.88 (dd, C**H₃**-CH-C**H₃**, ^{3}J = 6.5 Hz, 6H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.5, 166.1, 162.5, 143.9, 140.8, 138.5, 133.6, 133.4 (q, $^{3}J_{C,F}$ = 3.8 Hz), 130.0, 129.9 (q, $^{2}J_{C,F}$ = 35.1 Hz), 126.8, 126.6, 126.1 (q, $^{3}J_{C,F}$ = 3.8 Hz), 122.3 (q, $^{1}J_{C,F}$ = 273.1 Hz), 46.1, 45.6, 44.9, 44.8, 43.4, 41.4, 30.1, 22.3, 20.5 HRMS *m/z* calc for $C_{26}H_{28}F_3N_4O_4S$ [$M+H^+$], 549.1779; found, 549.1764, calc for $C_{26}H_{26}F_3N_4O_4SNa$ [$M+Na^+$], 571.1599; found, 571.1583.

2-{4-[(2S)-2-[4-(2-Methylpropyl)phenyl]propanoyl]piperazin-1-yl}-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**9a**) For the synthesis of **9a**, (2S)-2-[4-(2-

methylpropyl)phenyl]propanoic acid (0.068 g, 0.33 mmol, 1.0 eq.) is dissolved in 10 ml DCM. DIPEA (0.166 ml, 0.98 mmol, 3.0 eq.), PyBOP® (0.198 g, 0.38 mmol, 1.15 eq.) and 8-nitro-2-(piperazin-1-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**1d**) (0.117 g, 0.33 mmol, 1.0 eq.) dissolved in 5 ml DCM are added to the reaction mixture. The mixture is then left overnight at room temperature and the solvent is removed *in vacuo*. Purification is carried out by MPLC (EtAc/Heptane gradient). The title compound is a yellow solid (164 mg 91 %, HPLC purity 97.4 %, t_R = 15.9 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.06 (d, Ar-**H**, ^4J = 2.0 Hz, 1H), 8.75 (d, Ar-**H**, ^4J = 2.0 Hz, 1H), 7.14 (d, Ar-**H**, ^3J = 8.2 Hz, 2H), 7.11 (d, Ar-**H**, ^3J = 8.2 Hz, 2H), 4.15 (m, C**H₂**-N-C**H₂**, 3H), 3.84 (q, CO-C**H**, ^3J = 6.8 Hz, 1H), 3.61 (m, C**H₂**-N-C**H₂**, 2H), 3.48 (m, C**H₂**-N-C**H₂**, 2H), 3.06 (bs, C**H₂**-N-C**H₂**, 1H), 2.43 (d, C**H₂**, ^3J = 7.2 Hz, 2H), 1.84 (n, CH_2-C**H**-$(CH_3)_2$, ^3J = 6.8 Hz, 1H), 1.46 (d, C**H₃**-CH, ^3J = 6.8 Hz, 3H), 0.87 (d, C**H₃**-CH-C**H₃**, ^3J = 6.7 Hz, 6H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.5, 166.1, 162.5, 143.9, 140.8, 138.5, 133.6, 133.4 (q, $^3J_{C,F}$ = 3.8 Hz), 130.0, 129.9 (q, $^2J_{C,F}$ = 35.1 Hz), 126.8, 126.6, 126.1 (q, $^3J_{C,F}$ = 3.8 Hz), 122.2 (q, $^1J_{C,F}$ = 273.1 Hz), 46.0, 45.6, 44.9, 44.8, 43.4, 41.4, 30.1, 22.3, 20.5 HRMS *m/z* calc for $C_{26}H_{28}F_3N_4O_4S$ [M+H$^+$], 549.1779; found, 549.1783, calc for $C_{26}H_{27}F_3N_4O_4SNa$ [M+Na$^+$], 571.1599; found, 571.1600.

1-(4-Methylbenzensulfonyl)piperazine (**10a**) p-Toluenesulfonic acid chloride (0.500 g, 2.62 mmol, 1.0 eq.) is taken up in DMF (10 ml), added to a solution of piperazine (1.552 g, 13.05 mmol, 5.0 eq.) in DMF (20 ml) and stirred overnight (inert gas). The solvent is removed under vacuum and the crude product is purified by column chromatography (chloroform/MeOH/ammonia 36 % 90:10:1). The title compound is isolated as a colourless oil (458 mg 73 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, Ar-**H**, ^3J = 8.4 Hz, ^4J = 2.0 Hz 2H), 7.25 (d, Ar-**H**, ^3J = 8.4 Hz, 2H), 2.87 (m, C**H₂**-N-C**H₂**, 8H), 2.36 (s, C**H₃**, 3H) MS *m/z* (APCI) 241.1 [M+H$^+$].

4-(4-methylbenzensulfonyl)piperazin-1-thiourea (**10b**) Compound **10b** is prepared by general procedure B, using 1-(4-methylbenzenesulfonyl)piperazine (**10a**) (0.400 g, 1.66 mmol, 1.0 eq.)

and thiocarbonyldiimidazole (0.341 g, 1.19 mmol, 1.15 eq.). The product is recrystallised as a white solidfrom isopropanol/diisopropyl ether (1:1) (172 mg 35 %). ^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.63 (d, Ar-**H**, ^3J = 8.2 Hz, 2H)7.49 (bs, N**H$_2$**, 2H) 7.46 (d, Ar-**H**, ^3J = 8.0 Hz, 2H), 3.84 (bs, C**H$_2$**-N-C**H$_2$**, 4H), 2.84 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.41 (s, C**H$_3$**, 3H) MS *m/z* (ESI) 322.70 [M+Na$^+$].

2-[4-(4-Methylbenzensulfonyl)piperazin-1-yl]-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**10c**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.149 g, 0.55 mmol, 1.1 eq.) by general procedure A. **10c** is synthesised by general method 3, using 4-{24-(4-methylbenzenesulfonyl)piperazine-1-thiourea (**10b**) (0.150 g, 0.50 mmol, 1.0 eq.). Purification is carried out by MPLC (EtAc/Heptane gradient). The title compound is isolated as a yellow solid (213 mg 86 %, HPLC purity 98.9 % , t_R = 14.0 min) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.04 (d, Ar-**H**, ^4J = 2.2 Hz, 1H), 8.74 (d, Ar-**H**, ^4J = 2.2 Hz, 1H), 7.64 (d, Ar-**H**, ^3J = 8.4 Hz, 2H), 7.34 (d, Ar-**H**, ^3J = 8.4 Hz, 2H), 4.11 (bs, C**H$_2$**-N-C**H$_2$**, 4H), 3.17 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.42 (s, C**H$_3$**, 3H) ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ 165.7, 162.5, 144.8, 144.4, 134.6, 132.3, 131.8 (q, $^3J_{C,F}$ = 3.8 Hz), 130.4, 128.0, 127.9 (q, $^2J_{C,F}$ = 34.3 Hz),126.7 (q, $^3J_{C,F}$ = 3.8 Hz), 126.5, 123.0 (q, $^1J_{C,F}$ = 273.7 Hz), 45.8, 45.6, 21.4 HRMS *m/z* calc for $C_{20}H_{18}F_3N_4O_5S_2$ [M+H$^+$], 515.0667; found, 515.0665, calc for $C_{20}H_{17}F_3N_4O_5S_2Na$ [M+Na$^+$], 537.0486; found, 537.0483.

1-(Heptane-1-sulfonyl)piperazine (**11a**) Sodium-1-heptanesulfonate (1.50 g, 6.81 mmol, 1.0 eq.) is mixed with $POCl_3$ (4.66 ml, 51.19 mol, 7.5 eq.) in a round bottom flask and heated to 100 °C for 1 h with vigorous stirring. Then cool the reaction mixture to 0 °C, add 10 ml toluene and 25 ml water. The organic phase is separated, washed twice with water and concentrated in vacuo after drying over $NaSO_4$. The acid chloride is taken up without further purification in DMF (15 ml), added to a solution of piperazine (4.05 g, 34.05 mmol, 5.0 eq.) in DMF (35 ml) and stirred overnight (inert gas). The solvent is removed under vacuum and the crude product

is worked up by column chromatography (chloroform/MeOH/ammonia 36 % 90:10:1). The product is isolated as a colourless oil (880 mg 65 %) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.23 (m, C**H₂**-N-C**H₂**, 4H), 2.91 (m, C**H₂**-N-C**H₂**, 4H), 2.86 (m, SO_2-C**H₂**, 2H), 2.34 (bs, N**H**, 1H), 1.78 (m, C**H₂**, 2H), 1.38 (m, C**H₂**, 2H), 1.26 (m, C**H₂**, 6H), 0.86 (m, C**H₃**, 3H) MS *m/z* (APCI) 249.2 [$M+H^+$].

4-(heptane-1-sulfonyl)piperazin-1-thiourea (**11b**) Compound **11b** is prepared by general procedure B, using 1-(heptane-1-sulfonyl)piperazine (**11a**) (0.300 g, 1.21 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.248 g, 1.39 mmol, 1.15 eq.). Purification is carried out by MPLC (chloroform /MeOH gradient). The product is a white compound (311 mg 84 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.92 (bs, N**H₂**, 1H) 3.93 (m, C**H₂**-N-C**H₂**, 4H), 3.37 (t, C**H₂**-N-C**H₂**, ^{3}J = 5.1 Hz, 4H), 2.92 (m, SO_2-C**H₂**, 2H), 1.79 (m, C**H₂**, 2H), 1.41 (m, C**H₂**, 2H), 1.29 (m, C**H₂**, 6H), 0.88 (m, C**H₃**, 3H) MS *m/z* (ESI) 330.85 [$M+Na^+$].

2-[4-(Heptane-1-sulfonyl)piperazine-1-yl]-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**11c**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.145 g, 0.54 mmol, 1.1 eq.) by general procedure A. Compound **11c** is synthesised by general procedure C, using 4-(heptane-1-sulfonyl)piperazine-1-thiourea (**11b**) (0.150 g, 0.49 mmol, 1.0 eq.). Purification is carried out by MPLC (EtAc/heptane gradient). The title compound is slightly yellow (234 mg 91 %, HPLC purity 99.5 %, t_R = 15.1 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.09 (d, Ar-**H**, ^{4}J = 2.2 Hz, 1H), 8.78 (d, Ar-**H**, ^{4}J = 2.2 Hz, 1H), 4.12 (bs, C**H₂**-N-C**H₂**, 4H), 3.47 (m, C**H₂**-N-C**H₂**, 4H), 2.95 (m, SO_2-C**H₂**, 2H), 1.81 (m, C**H₂**, 2H), 1.42 (m, C**H₂**, 2H), 1.29 (m, C**H₂**, 6H), 0.88 (m, C**H₃**, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.3, 162.7, 143.9, 133.5 (q, $^{3}J_{C,F}$ = 3.8 Hz), 133.4, 130.1 (q, $^{2}J_{C,F}$ = 35.9 Hz), 126.6, 126.2 (q, $^{3}J_{C,F}$ = 3.8 Hz), 122.3 (q, $^{1}J_{C,F}$ = 273.1 Hz), 50.4, 46.5, 45.4, 31.4, 28.7, 28.3, 23.1, 22.5, 14.0 HRMS *m/z* calc for $C_{20}H_{26}F_3N_4O_5S_2$ [$M+H^+$], 523.1292; found, 523.1279, calc for $C_{20}H_{25}F_3N_4O_5SNa$ [$M+Na^+$], 545.1112; found, 545.1098.

Pyrrolidine-1-thiourea (**12a**) Compound **12a** is prepared by general procedure B, using pyrrolidine (0.450 g, 6.33 mmol, 1.0 eq.) and thiocarbonyldiimidazole (1.300 g, 7.28 mmol, 1.15 eq.). The crude product is worked up by column chromatography (chloroform/MeOH 98:2). The title compound is a white solid (187 mg 21 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.71 (bs, N**H₂**, 2H), 3.82 (bs, N-C**H₂**, 2H), 3.38 (bs, N-C**H₂**, 2H), 2.07 (bs, C**H₂**-C**H₂**, 2H), 1.95 (bs, C**H₂**-C**H₂**, 2H) MS *m/z* (APCI) 131.1 [M+H$^+$].

8-Nitro-2-(pyrrolidine-1-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**12b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.210 g, 0.77 mmol, 1.1 eq.) by general procedure A. Compound **12b** is synthesised by general procedure C, using pyrrolidine-1-thiourea (**12a**) (0.100 g, 0.70 mmol, 1.0 eq.). The crude product is worked up by column chromatography (LM chloroform) and washed with diisopropyl ether. The title compound is isolated a yellow solid (85 mg 34 %, HPLC purity 99.1 %, t_R = 13.5 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.17 (d, Ar-**H**, ^{4}J = 2.2 Hz, 1H), 8.77 (d, Ar-**H**, ^{4}J = 2.2 Hz, 1H), 3.93 (t, C**H₂**-N-CH_2, ^{3}J = 6.9 Hz, 2H), 3.70 (t, CH_2-N-C**H₂**, ^{3}J = 6.9 Hz, 2H), 2.19 (qi, C**H₂**-CH_2, ^{3}J = 6.9 Hz, 2H), 2.06 (bs, CH_2-C**H₂**, ^{3}J = 6.9 Hz, 2H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9, 160.3, 143.5, 134.6, 133.7 (q, $^{3}J_{C,F}$ = 3.8 Hz), 129.5 (q, $^{2}J_{C,F}$ = 35.9 Hz), 126.9, 125.8 (q, $^{3}J_{C,F}$ = 3.8 Hz), 122.4 (q, $^{1}J_{C,F}$ = 273.1 Hz), 50.4, 47.4, 25.5, 24.1 HRMS *m/z* calc for $C_{13}H_{11}F_3N_3O_3S$ [M+H$^+$], 346.0469; found, 346.0461.

Piperidine-1-thiourea (**13a**)

Synthesis by procedure B Compound **13a** is prepared by general procedure B, using piperidine (1.000 g, 11.74 mmol, 1 eq.) and thiocarbonyldiimidazole (2.406 g, 13.50 mmol, 1.15 eq.). The crude product is purified by column chromatography (chloroform/MeOH 98:2) and the title compound is isolated as a white solid (723 mg 43 %).

Synthesis by procedure E Synthesis according to general procedure E, starting from piperidine (4.95 ml, 50 mmol). Work-up after neutralization: the mixture was kept at 8 °C for 48 h, the brown oil which settled on the bottom of the flask was separated and purified by flash chromatography twice (eluent chloroform). The fractions containing the product were combined, the solvent evaporated and the remaining crude product treated with a few ml of toluene. A white precipitate formed, which was filtered off and dried (611 mg 9 %).

Synthesis by procedure F Synthesis according to general procedure F, starting from piperidine (49 mg, 0.57 mmol, 1 eq.). Compound **13a** was isolated as a slightly brownish solid (30 mg, 36 %)

^{1}H-NMR (400 MHz, CD_3OD) δ 3.78 (bs, C**H$_2$**-N-C**H$_2$**, 4H), 1.67 (m, C**H$_2$**, 2H), 1.61 (m, C**H$_2$**, 4H) MS *m/z* (ESI) 145.09 [M+H$^+$].

8-Nitro-2-(piperidine-1-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**13b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (1.116 g, 4.14 mmol, 1.0 eq.) by general procedure A. Compound **13b** is synthesised by general procedure C, using piperidine-1-thiourea (**13a**) (0.597 g, 4.14 mmol, 1.0 eq.). The crude product is processed by column chromatography (chloroform) and the titel compound appears as a yellow solid (1105 mg 74 %, HPLC purity 96.2 %, t_R = 14.1 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.09 (d, Ar-**H**, ^4J = 2.5 Hz, 1H), 8.74 (d, Ar-**H**, ^4J = 2.5 Hz, 1H), 3.97 (bs, N-C**H$_2$**, 4H), 1.77 (m, C**H$_2$**-C**H$_2$**-C**H$_2$**, 6H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 161.5, 143.9, 134.3, 133.3 (q, $^3J_{C,F}$ = 3.5 Hz), 129.5 (d, $^2J_{C,F}$ = 35.3 Hz), 126.7, 125.9 (q, $^3J_{C,F}$ = 3.6 Hz), 122.4 (q, $^1J_{C,F}$ = 272.5 Hz), 47.9, 26.0, 24.3 MS *m/z* (APCI) 360.2 [M+H$^+$].

2-(2,6-Dimethylpiperidin-1-yl)-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**14a**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.500 g, 1.86 mmol, 1.0 eq.) by general procedure A. The 2-

chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is dissolved in acetone (5 ml) and added to a suspension of KSCN (0.181 g, 1.86 mmol, 1.0 eq.) in acetone (10 ml) at 5 °C under inert gas. The reaction mixture is stirred for 2 h at 5-10 °C. Dimethylpiperidine (0.210 g, 1.86 mmol, 1 eq.) is then dissolved in acetone (5 ml) and added via a dropping funnel. After the addition is completed, the temperature is kept at 5-10 °C for another 2 h. Subsequently, solvent is removed *in vacuo* and the reaction product is worked up by column chromatography (DCM). The title compound appears as a yellow solid (340 mg 47 %, HPLC purity 100.0 %, t_R = 15.0 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.09 (s, Ar-**H**, 1H), 8.73 (s, Ar-**H**, 1H), 5.48, (bs, C**H**-CH_3, 1H), 4.61 (bs, C**H**-CH_3, 1H), 1.95 (m, C$\mathbf{H_2}$, 1H), 1.77 (bs, C**H**-CH_3, 4H), 1.66 (bs, C**H**-CH_3, 1H), 1.41 (bs, CH-C$\mathbf{H_3}$, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 161.9, 144.0, 134.7, 133.2 (q, $^3J_{C,F}$ = 3.5 Hz), 129.4 (q, $^2J_{C,F}$ = 35.4 Hz), 126.9, 125.8 (q, $^3J_{C,F}$ = 3.8 Hz), 122.5 (q, $^1J_{C,F}$ = 273.6 Hz), 50.0, 49.0, 30.5, 29.76, 20.5, 19.9, 14.1. HRMS *m/z* calc for $C_{16}H_{17}F_3N_3O_3S$ [M+H$^+$], 388.0938; found, 388.0933.

4-Hydroxypiperidin-1-thiourea (**15a**) Compound **15a** is prepared by general procedure B, using 3-hydroxypiperidine (0.285 g, 2.82 mmol, 1 eq.) and thiocarbonyldiimidazole (0.580 g, 3.25 mmol, 1.15 eq.). The crude product is worked up column chromatographically (chloroform/MeOH 9:1) and the final compound is isolated as a white solid (206 mg 52 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.41 (m, cyclohexyl, 1H), 4.09 (m, cyclohexyl, 1H), 3.66 (m, cyclohexyl, 1H), 3.33 (m, cyclohexyl, 1H), 3.14 (m, cyclohexyl, 1H), 1.98 (m, cyclohexyl, 1H), 1.80 (m, cyclohexyl, 1H), 1.51 (m, cyclohexyl, 2H) MS *m/z* (ESI) 159.15 [M-H$^+$].

2-(4-Hydroxypiperidine-1-yl)-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**15b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (AR96) (0.168 g, 0.63 mmol, 1.0 eq.) by general procedure A. Compound **15b** is prepared by general procedure C, using 4-hydroxypiperidine-1-thiourea

(**15a**) (0.100 g, 0.63 mmol, 1 eq.). The crude product is worked up by column chromatography (chloroform/MeOH 9:1) and recrystallised from EtAc/hexane (1:1). The title compound is isolated as a yellow solid (120 mg 51 %, HPLC purity 100.0 %, t_R = 12.5 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.06 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 8.74 (s, Ar-**H**, 1H), 4.05 (m, cyclohexyl, O**H**, 5H), 2.66 (s, C**H**, 1H), 2.02 (m, cyclohexyl, 2H), 1.82 (m, cyclohexyl, 1H), 1.68 (m, cyclohexyl, 1H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.7, 162.9, 143.9, 134.3, 133.2, 129.6 (q, $^2J_{C,F}$ = 35.9 Hz), 126.5, 126.0, 122.3 (q, $^1J_{C,F}$ = 273.1 Hz), 65.9, 52.9, 47.5, 31.9, 22.0. HRMS *m/z* calc for $C_{14}H_{13}F_3N_3O_4S$ [M+H$^+$], 376.0575; found, 376.0575.

Thiomorpholin-4-thiourea (**16a**) Dried NaSCN (389 mg, 4.80 mmol, 1.0 eq.) is suspended in acetone (10 ml), placed under argon and cooled to 5 °C. Benzoyl chloride (0.675 ml, 4.80 mmol, 1.0 eq.) is added slowly and the reaction mixture is stirred for 3 h at 5 °C. Thiomorpholine (500 mg, 4.80 mmol, 1.0 eq.) dissolved in acetone (5 ml) is then added at 12 °C, after which the reaction mixture is stirred at RT for 4 h. After the reaction, the solvent is removed *in vacuo* and the residue is dissolved in 36 % HCl (7.0 ml) and heated to 95 °C for 1.5 h. The aqueous solution is then mixed with acetone (7.0 ml) and solution is then neutralised with ammonia 36 % and extracted three times with DCM. The organic phases are collected, dried with $MgSO_4$ and the evaporated on a rotary evaporator. The crude product is purified by column chromatography (EtAc/Heptane 1:1). The title compound is a white solid (270 mg 35 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.48 (bs, N**H$_2$**, 2H), 4.11 (s,C**H$_2$**-N-C**H$_2$**, 4H), 2.74 (m,C**H$_2$**-S-C**H$_2$**, 4H) MS *m/z* (APCI) 163.0 [M+H$^+$].

8-Nitro-2-(thiomorpholin-4-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**16b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.332 g, 1.23 mmol, 1.0 eq.) by general procedure A. **16b** is synthesised by general procedure C, using thiomorpholine-4-thiourea (**16a**) (0.200 g, 1.23

mmol, 1.0 eq.). The crude product is purified by recrystallisation from acetone (260 mg 56 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.10 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 8.77 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 4.31 (bs,C**H₂**-N-C**H₂**, 4H), 2.81 (m,C**H₂**-S-C**H₂**, 4H) MS *m/z* (APCI) 378.1 [M+H$^+$].

8-Nitro-2-(1-oxo-1λ⁴,4-thiomorpholin-4-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**16c**) $NaIO_4$ (0.06 mg, 0.28 mmol, 1.05 eq.) is dissolved in 15 ml water and cooled to 0 °C with the aid of an ice bath. Now 8-nitro-2-(thiomorpholin-4-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**16b**) dissolved in 5 ml MeOH is added, the reaction mixture is left at 0 °C for 4 h and then kept in the refrigerator for 65 h. Subsequently the aqueous phase is extracted three times with chloroform, the organic phases are collected, dried with $MgSO_4$ and the solvent is removed *in vacuo*. The crude product is purified by column chromatography (chloroform/MeOH 95:5). The title compound appears as a yellow solid (67 mg 64 %, HPLC purity 99.9 %, t_R = 11.0 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.11 (d, Ar-**H**, ^4J = 2.2 Hz, 1H), 8.80 (d, Ar-**H**, ^4J = 2.2 Hz, 1H), 4.59 (bs,C**H₂**-N-C**H₂**, 4H), 3.04 (m,C**H₂**-S-C**H₂**, 2H), 2.81 (m,C**H₂**-S-C**H₂**, 2H) ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.3, 162.4, 144.0, 133.6 (q, $^2J_{C,F}$ = 3.8 Hz), 133.3, 130.3 (q, $^2J_{C,F}$ = 35.3 Hz), 126.8, 126.4 (q, $^3J_{C,F}$ = 3.8 Hz), 121.4 (q, $^1J_{C,F}$ = 273.7 Hz), 45.4, 37.4. HRMS *m/z* calc for $C_{13}H_{11}F_3N_3O_4S_2$ [M+H$^+$], 394.0139; found, 394.0143, *m/z* calc for $C_{13}H_{10}F_3N_3O_4S_2Na$ [M+Na$^+$] 415.9958; found, 415.9958.

4-[8-Nitro-4-oxo-6-(trifluoromethyl)-4H-1,3-benzothiazin-2-yl]-1λ⁶,4-thiomorpholin-1,1-dione (**16d**) 8-Nitro-2-(1-oxo-1λ⁴,4-thiomorpholin-4-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**16b**) (0.100 mg, 0.265 mmol, 1.0 eq.) is dissolved in 5 ml DCM and cooled to 0 °C. A solution of meta-chloroperbenzoic acid (m-CPBA) 65 % (0.165 mg, 0.624 mmol, 2.4 eq.) in 5 ml DCM is slowly added, the reaction mixture is slowly warmed to RT and left overnight at RT. Solvent is then removed under vacuum, the residue is dissolved in EtAc and washed twice with $NaHCO_3$ solution. The organic phase is dried over $MgSO_4$ and concentrated *in vacuo*.

Purification is carried out by recrystallisation from diisopropyl ether. The title compound appears as a white solid (55 mg 51 %, HPLC purity 99.8 %, t_R = 10.8 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.12 (d, Ar-**H**, ^4J = 2.0 Hz, 1H), 8.83 (d, Ar-**H**, ^4J = 2.0 Hz, 1H), 4.52 (bs,C**H$_2$**-N-C**H$_2$**, 4H), 3.23 (m,C**H$_2$**-S-C**H$_2$**, 4H) ^{13}C-NMR (125 MHz, Aceton D_6) δ 165.4, 163.1, 144.7, 134.2, 131.9 (q, $^2J_{C,F}$ = 3.8 Hz), 128.7 (q, $^2J_{C,F}$ = 35.3 Hz), 126.7, 126.1 (q, $^3J_{C,F}$ = 3.8 Hz), 122.7 (q, $^1J_{C,F}$ = 271.8 Hz), 51.1, 44.6. HRMS *m/z* calc for $C_{13}H_{10}F_3N_3O_5S_2Na$ [M+Na$^+$], 431.9908; found, 431.9906.

3-Hydroxyazetidine-1-thiourea (**17a**) Compound **17a** is prepared according general procedure B, using 3-hydroxyazetidine*HCl (0.100 g, 0.92 mmol, 1 eq.) and thiocarbonyldiimidazole (0.189 g, 1.06 mmol, 1.15 eq.). The crude product is purified by column chromatography (chloroform/MeOH 95:5). The title compound is a white solid (45 mg 37 %) ^{1}H-NMR (500 MHz, CD_3OD) δ 4.51 (m, C**H**, 1H), 4.27 (bs, C**H$_2$**, 2H), 3.85 (bs, C**H$_2$**, 2H) MS *m/z* (APCI) 133.1 [M+H$^+$].

2-(3-hydroxyazetidin-1-yl)-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**17b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.045 g, 0.16 mmol, 1.1 eq.) by general procedure A. **17b** is prepared by general procedure C, using 3-hydroxyazetidine-1-thiourea (**17a**) (0.020 g, 0.15 mmol, 1 eq.). The crude product is purified by column chromatography (chloroform/MeOH 9:1). The title compound appears as a yellow solid (18 mg 35 %, HPLC purity 99.2 %, t_R = 14.9 min). ^{1}H-NMR (400 MHz, CD_3OD) δ 8.99 (s, Ar-**H**, 1H), 8.87 (s, Ar-**H**, 1H), 4.78 (bs, C**H**, 1H), 4.60 (bs, C**H$_2$**, 2H), 4.14 (m, C**H$_2$**, 2H) ^{13}C-NMR (100 MHz, CD_3OD) δ 166.7, 162.9, 144.0, 134.6, 132.1, 128.7 (q, $^2J_{C,F}$ = 35.3 Hz), 126.2, 125.8, 122.7 (q, $^1J_{C,F}$ = 271.8 Hz), 61.7, 61.5, 60.0 HRMS *m/z* calc for $C_{12}H_9F_3N_3O_4S$ [M+H$^+$], 348.0262; found, 348.0260, calc for $C_{12}H_8F_3N_3O_4SNa$ [M+Na$^+$], 370.0081; found, 370.0079.

Morpholine-4-thiourea (**18a**)

Synthesis by procedure B Compound **18a** is prepared by general procedure B, using morpholine (0.450 g, 5.17 mmol, 1 eq.) and thiocarbonyldiimidazole (1.058 g, 5.94 mmol, 1.15 eq.). The crude product is purified by recrystallisation from isopropanol/diisopropyl ether (1:1). The title compound is isolated as a white solid (515 mg 68 %).

Synthesis by procedure E Synthesis according to general procedure E, starting from morpholine (4.35 ml, 50 mmol, 1 eq). Work-up after neutralization: the mixture was kept at 8 °C for 48 h, the precipitate filtered off, washed with a small amount of chloroform and dried. The title compound is isolated as a white solid (1.09 g, 15 %).

Synthesis by procedure F Synthesis according to general procedure F, starting from morpholine (166 mg, 1.91 mmol, 1 eq.). Compound 18a was isolated as a slightly brownish solid (115 mg, 41 %)

^{1}H-NMR (400 MHz, CD_3OD) δ 3.80 (m, C**H$_2$**, 4H), 3.67 (m, C**H$_2$**, 4H) MS *m/z* (ESI) 146.98 [M+H$^+$].

2-(Morpholin-4-yl)-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**18b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.050 g, 0.18 mmol, 1.1 eq.) by general procedure A. Compound **18b** is prepared by general procedure C using morpholine-4-thiourea (**18a**) (0.034 g, 0.23 mmol, 1 eq.). The crude product is purified by column chromatography (chloroform/MeOH 9:1). The title compound appears as a yellow solid (49 mg 75 %, HPLC purity 100.0 %, t_R = 12.4 min). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.08 (d, 1H, Ar-**H**, ^{4}J = 1.5 Hz), 8.75 (d, 1H, Ar-**H**, ^{4}J = 1.5 Hz), 4.01 (m, 4H, C**H$_2$**-N-C**H$_2$**), 3.82 (m, 4H, C**H$_2$**-O-C**H$_2$**) ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.3, 162.6, 143.9, 133.7, 133.5 (q, $^{3}J_{C,F}$ = 3.7 Hz), 129.9 (q, $^{2}J_{C,F}$ = 35.9 Hz), 126.8, 126.1 (q, $^{3}J_{C,F}$ = 3.7 Hz), 122.3 (q, $^{1}J_{C,F}$ = 272. 5 Hz), 66.3, 46.7 HRMS *m/z* calc for $C_{13}H_{10}F_3N_3O_4SNa$ [M+Na$^+$], 384.0237; found, 384.0239.

4-[4-(Trifluoromethoxy)phenoxy]piperidine-1-thiourea (**19a**) Compound **19a** is prepared by general procedure B, using 4-[4-(trifluoromethoxy)phenoxy]piperidine (0.100 g, 0.38 mmol, 1 eq.) and thiocarbonyldiimidazole (0.078 g, 0.44 mmol, 1.15 eq.). The crude product is purified by column chromatography (chloroform/MeOH 9:1). The tittle compound is a white solid (68 mg 56 %). 1H-NMR (400 MHz, CD3OD) δ 7.18 (m, Ar-H, 2H), 7.03 (m, Ar-H, 2H), 4.65 (m, C-H, 1H), 4.05 (m, cyclohexyl, 2H), 3.82 (m, cyclohexyl, 2H), 2.01 (m, cyclohexyl, 2H), 1.78 (m, cyclohexyl, 2H) MS *m/z* (ESI) 319.15 [M-H^+].

8-Nitro-2-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**19b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.049 g, 0.18 mmol, 1.1 eq.) by general procedure A. **19b** is prepared by general procedure C, using 4-[4-(trifluoromethoxy)phenoxy]piperidine-1-thiourea (**19a**) (0.050 g, 0.16 mmol, 1 eq.). The crude product is purified by column chromatography (chloroform/MeOH 95:5). The title compound is a beige coloured solid (52 mg 60 %, HPLC purity 100.0 %, t_R = 13.9 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.10 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 8.75 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 7.17 (m, Ar-**H**, 2H), 6.93 (m, Ar-**H**, 2H) 4.68 (m, C-**H**, 1H), 4.51 (bs, cyclohexyl, 1H), 3.98 (m, cyclohexyl, 3H), 2.06 (s, cyclohexyl, 4H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.5, 161.9, 155.2, 143.9, 143.3, 134.0, 133.4, 129.7 (q, $^2J_{C,F}$ = 36.4 Hz), 126.7, 126.0, 122.4 (q, $^1J_{C,F}$ = 272.8 Hz), 120.5 (q, $^1J_{C,F}$ = 255.6 Hz), 116.8, 70.8, 42.9, 30.3 HRMS *m/z* calc for $C_{21}H_{16}F_6N_3O_5S$ [M+H^+], 536.0711; found, 536.0707, calc for $C_{21}H_{15}F_6N_3O_5SNa$ [M+Na^+], 558.0527; found, 558.0534.

6-Methoxy-1,2,3,4-tetrahydroisoquinoline-2-thiourea (**20a**) Compound **20a** is prepared by general procedure B, using 6-methoxy-1,2,3,4-tetrahydroisoquinoline (0.358 g, 2.20 mmol, 1 eq.) and thiocarbonyldiimidazole (0.450 g, 2.52 mmol, 1.15 eq.). The crude product is purified by column chromatography (LM chloroform/MeOH 95:5) and title compound appears as a

white solid (339 mg 62 %). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.08 (m, Ar-**H**, 1H), 6.79 (m, Ar-**H**, 2H), 4.83 (m, C**H$_2$**, 2H, close to solvent signal), 3.95 (m, C**H$_2$**, 2H), 3.79 (s, C**H$_3$**, 3H), 2.91 (t, C**H$_2$**, ^2J = 5.9 Hz, 2H) MS *m/z* (ESI) 223.06 [M+H$^+$].

2-(6-Methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**20b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.399 g, 1.49 mmol, 1.1 eq.) by general procedure A. Compound **20b** is prepared by general method 3, using 6-methoxy-1,2,3,4-tetrahydroisoquinoline-2-thiourea (**20a**) (0.300 g, 1.35 mmol, 1 eq.). The crude product is purified by column chromatography (chloroform/MeOH 99:1). The title compound is a yellow solid (545 mg 92 %, HPLC purity 95.2 %, t_R = 15.0 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.13 (d, Ar-H, ^4J = 1.6 Hz, 1H), 8.76 (d, Ar-H, ^4J = 1.6 Hz, 1H), 7.14 (d, Ar-H, ^3J = 8.4 Hz, 1H), 6.81 (m, Ar-H, 1H), 6.75 (s, Ar-H, 1H), 5.01 (m, CH_2, 2H), 4.15 (m, CH_2, 2H), 3.80 (s, CH_3, 3H), 3.02 (m, CH_2, 2H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.1, 162.3, 159.0, 143.9, 134.2, 133.5, 129.7 (q, $^2J_{C,F}$ = 36.2 Hz), 127.7, 126.9, 126.0, 122.4 (q, $^1J_{C,F}$ = 272.8 Hz), 113.0, 55.4, 47.8, 44.5, 29.0 HRMS *m/z* calc for $C_{19}H_{15}F_3N_3O_4S$ [M+H$^+$], 438.0731; found, 438.0735, calc for $C_{19}H_{14}F_3N_3O_4SNa$ [M+Na$^+$], 460.0551; found, 460.0553.

7-Methoxy-1,2,3,4-tetrahydroisoquinoline-2-thiourea (**21a**) Compound **21a** is prepared by general procedure B, using 7-methoxy-1,2,3,4-tetrahydroisoquinoline (0.073 g, 0.45 mmol, 1 eq.) and thiocarbonyldiimidazole (0.092 g, 0.51 mmol, 1.15 eq.). The crude product is purified by column chromatography (LM chloroform/MeOH/ammonia 36 % 98:2:1). The title compound appears as a white solid (76 mg 76 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.08 (d, Ar-**H**, ^3J = 8.4 Hz, 1H), 6.77 (dd, Ar-**H**, ^3J = 8.2 Hz,^4J = 2.5 Hz, 1H), 6.71 (d, Ar-**H**, ^4J = 2.5 Hz, 1H), 5.95 (bs, N**H$_2$**, 2H), 4.89 (bs, C**H$_2$**, 2H), 3.90 (bs, C**H$_2$**, 2H), 3.77 (s, C**H$_3$**, 3H), 2.88 (t, C**H$_2$**, ^3J = 5.9 Hz, 2H) MS *m/z* (ESI) 221.25 [M-H$^+$].

2-(7-Methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**21b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.026 g, 0.10 mmol, 1.1 eq.) by general procedure A. Compound **21b** is prepared by general procedure C, using 7-methoxy-1,2,3,4-tetrahydroisoquinoline-2-thiourea (**21a**) (0.020 g, 0.09 mmol, 1 eq.). The crude product is worked up by column chromatography (chloroform/MeOH 98:2) and recrystallised from EtAc/hexane (1:1). The title compound appears as a yellow solid (14 mg 36 %, HPLC purity 100.0 %, t_R = 15.1 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.14 (s, Ar-**H**, 1H), 8.77 (s, Ar-**H**, 1H), 7.13 (d, Ar-**H**, ^3J = 8.4 Hz, 1H), 6.82 (d, Ar-**H**, ^3J = 8.4 Hz, 1H), 6.77 (s, Ar-**H**, 1H), 5.05 (m, C**H$_2$**, 2H), 4.16 (m, C**H$_2$**, 2H), 3.81 (s, C**H$_3$**, 3H), 3.00 (m, C**H$_2$**, 2H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.1, 162.4, 158.7, 143.9, 134.1, 133.6 (q, $^3J_{C,F}$ = 3.8 Hz), 129.8 (q, $^2J_{C,F}$ = 35.1 Hz), 129.0, 126.9, 126.3, 126.0 (q, $^3J_{C,F}$ = 3.8 Hz), 121.4 (q, $^1J_{C,F}$ = 273.9 Hz), 113.8, 111.3, 55.4, 48.4, 45.0, 28.0 0 HRMS *m/z* calc for $C_{19}H_{15}F_3N_3O_4S$ [M+H$^+$], 438.0731; found, 438.0731.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-thiourea (**22a**) Compound **22a** is prepared by general procedure B, using 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.721 g, 3.73 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.765 g, 4.29 mmol, 1.15 eq.). The crude product is purified by column chromatography (chloroform/MeOH/ammonia 36 % 98:2:1). The title compound appears as a white solid (218 mg 23 %) ^{1}H-NMR (400 MHz, CD_3OD) δ 6.78 (s, Ar-**H**, 1H), 6.74 (s, Ar-**H**, 1H), 4.84 (bs, N-C**H$_2$**, 2H, Wasser Signal), 3.95 (m, N-C**H$_2$**, 2H), 3.80 (s, O-C**H$_3$**, 3H), 3.79 (s, O-C**H$_3$**, 3H), 2.84 (t, C**H$_2$**, , ^3J = 5.9 Hz, 2H) MS *m/z* (APCI) 253.1 [M+H$^+$].

2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**22b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.229 g, 0.85 mmol, 1.1 eq.) by general procedure A. Compound **22b** is synthesised by general procedure C, using 6,7-

dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-thiourea (**22a**) (0.194 g, 0.77 mmol, 1.0 eq.). The crude product is purified by column chromatographically (chloroform) and re-crystallised from EtOH. The title compound apears as a yellow solid (137 mg 38 %, HPLC purity 97.7 %, t_R = 14.5 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.13 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 8.77 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 6.71 (s, Ar-**H**, 1H), 6.68 (s, Ar-**H**, 1H), 5.02 (m, N-C**H$_2$**, 2H), 4.19 (m, N-C**H$_2$**, 2H), 3.87 (s, O-C**H$_3$**, 6H), 2.98 (m, C**H$_2$**, 2H) ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.2, 162.2, 148.3, 143.9, 134.2, 133.5 (q, $^3J_{C,F}$ = 3.8 Hz), 129.8 (q, $^2J_{C,F}$ = 35.8 Hz), 126.9, 126.0 (q, $^3J_{C,F}$ = 3.8 Hz),125.3, 123.8, 122.4 (q, $^1J_{C,F}$ = 273.1 Hz), 111.2, 109.4, 56.2, 56.0, 48.0, 44.7, 28.1 HRMS *m/z* calc for $C_{20}H_{17}F_3N_3O_5S$ [M+H$^+$], 468.0837; found, 468.0841, calc for $C_{20}H_{16}F_3N_3O_5SNa$ [M+Na$^+$], 490.0657; found, 490.0661.

1,2,3,4-Tetrahydroisoquinoline-2-thiourea (**23a**) Compound **23a** is prepared by general procedure B, using 1,2,3,4-tetrahydroisoquinoline (0.750 g, 5.63 mmol, 1.0 eq.) and thiocarbonyldiimidazole (1.154 g, 6.48 mmol, 1.15 eq.). The crude product is recrystallised from diisopropyl ether/isopropanol 1:1. The title compound appears as a white solid (610 mg 56 %) ^{1}H-NMR (400 MHz, CD_3OD) δ 7.18 (m, Ar-**H**, 4H), 4.89 (bs, N-C**H$_2$**, 2H),3.95 (bs, N-C**H$_2$**, 2H), 2.91 (t, C**H$_2$**, ^3J = 5.9 Hz, 2H) MS *m/z* (ESI) 191.21 [M-H$^+$].

8-Nitro-2-(1,2,3,4-tetrahydroisoquinolin-2-yl)-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**23b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.463 g, 1.72 mmol, 1.1 eq.) by general procedure a. **23b** is synthesised by general procedure C, using 1,2,3,4-tetrahydroisoquinoline-2-thiourea (**23a**) (0.300 g, 1.56 mmol, 1.0 eq.). The crude product is purified by column chromatography (chloroform). The final product appears as a yellow solid (438 mg 69 %, HPLC purity 99.1 %, t_R = 15.0 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.13 (d, Ar-**H**, ^4J = 2.0 Hz, 1H), 8.77 (d, Ar-**H**, ^4J = 2.0 Hz, 1H), 7.25 (m, Ar-**H**, 4H), 5.08 (m, N-C**H$_2$**, 2H), 4.17 (m, N-C**H$_2$**, 2H), 3.07 (m, C**H$_2$**, 2H) ^{13}C-

NMR (125 MHz, $CDCl_3$) δ 166.1, 162.3, 143.9, 134.6, 134.1, 133.7, 133.5 (q, $^3J_{C,F}$ = 3.8 Hz), 131.8, 129.7 (q, $^2J_{C,F}$ = 35.8 Hz), 128.7, 128.0, 127.7, 127.2, 126.6, 126.8, 126.0 (q, $^3J_{C,F}$ = 3.8 Hz), 122.4 (q, $^1J_{C,F}$ = 273.1 Hz), 48.2, 44.6, 28.7 HRMS *m/z* calc for $C_{18}H_{12}F_3N_3O_3SNa$ [M+Na^+], 430.0445; found, 430.0438.

4-(Piperidin-1-yl)piperidine-1-thiourea (**24a**) Compound **24a** is prepared by general procedure B, using 4-(piperidin-1-yl)piperidine (0.100 g, 0.59 mmol, 1 eq.) and thiocarbonyldiimidazole (0.121 g, 0.68 mmol, 1.15 eq.). The crude product is purified by column chromatography (chloroform/MeOH/ammonia 36 % 90:10:1). The title compound appears as a white solid (24 mg 18 %) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.76 (s, N**H₂**, 2H), 4.53 (s, C**H**, 1H), 3.06 (m, cyclohexyl, 2H), 2.51 (m, cyclohexyl, 5H), 1.88 (m, cyclohexyl, 2H), 1.60 (m, cyclohexyl, 7H), 1.43 (m, cyclohexyl, 2H) MS *m/z* (ESI) 228.13 [M+H_+].

8-Nitro-2-[4-(piperidin-1-yl)piperidin-1-yl]-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**24b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.024 g, 0.09 mmol, 1.1 eq.) by general procedure A. **24b** is prepared by general procedure C, using 4-(piperidin-1-yl)piperidin-1-thiourea (**24a**) (0.018 g, 0.08 mmol, 1 eq.). The crude product is worked up by column chromatography (chloroform/MeOH/ammonia 36 % 98:2:1). The title compound appears as a yellow solid (20 mg 57 %, HPLC purity 99.4 %, t_R = 12.4 min) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.10 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 8.74 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 5.22 (bs, cyclohexyl, 1H), 4.42 (bs, cyclohexyl, 1H), 3.18 (m, cyclohexyl, 2H), 2.65 (m, C**H**, 1H), 2.52 (m, cyclohexyl, 4H), 2.03 (m, cyclohexyl, 2H), 1.63 (m, cyclohexyl, 6H), 1.45 (m, cyclohexyl, 2H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.5, 161.6, 143.9, 134.2, 133.3, 129.6 (q, $^2J_{C,F}$ = 35.1 Hz), 126.7, 125.9, 126.0, 122.4 (q, $^1J_{C,F}$ = 273.1 Hz), 61.8, 50.3, 46.1 28.1 26.2, 24.5 HRMS *m/z* calc for $C_{19}H_{22}F_3N_4O_3S$ [M+H^+], 443.1361; found, 443.1357, calc for $C_{19}H_{21}F_3N_4O_3SNa$ [M+Na^+], 465.1180; found, 465.1176.

5-Benzyl-octahydropyrrolo[3,4-c]pyrrole-2-thiourea (**25a**) Compound **25a** is prepared by general procedure B, using 2-benzyl-octahydropyrrolo[3,4-c]pyrrole (0.100 g, 0.49 mmol, 1 eq.) and thiocarbonyldiimidazole (0.101 g, 0.57 mmol, 1.15 eq.). The crude product is purified by column chromatography (chloroform/MeOH 98:2) and the title compound is a white solid (58 mg 45 %) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (m, Ar-**H**, 5H), 5.67 (bs, N**H$_2$**, 2H), 3.87 (bs, Octahydropyrrolo[3,4-c]pyrrole, 2H), 3.59 (s, C**H$_2$**, 2H), 3.42 (bs, octahydropyrrolo[3,4-c]pyrrole, 2H), 2.94 (bs, octahydropyrrolo[3,4-c]pyrrole, 2H), 2.60 (m, octahydropyrrolo[3,4-c]pyrrole, 2H), 2.53 (m, octahydropyrrolo[3,4-c]pyrrole, 2H) MS *m/z* (ESI) 262.12 [M+H$^+$].

2-{5-Benzyl-octahydropyrrolo[3,4-c]pyrrol-2-yl}-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**25b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.045 g, 0.17 mmol, 1.1 eq.) by general procedure A. **25b** is prepared by general procedure C, using 5-benzyl-octahydropyrrolo[3,4-c]pyrrole-2-thiourea (**25a**) (0.040 g, 0.15 mmol, 1 eq.). The crude product is purified by column chromatography (chloroform/MeOH 98:2). The title compound appears as a light yellow solid (50 mg 69 %, HPLC purity 94.9 %, t_R = 12.9 min) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.15 (s, Ar-**H**, 1H), 8.76 (s, Ar-**H**, 1H), 7.28 (m, Ar-**H**, 5H), 4.18 (m, Octahydropyrrolo[3,4-c]pyrrole, 1H), 3.94 (m, Octahydropyrrolo[3,4-c]pyrrole, 2H), 3.62 (bs, C**H$_2$**, 2H), 3.60 (m, Octahydropyrrolo[3,4-c]pyrrole, 1H), 3.11 (bs, Octahydropyrrolo[3,4-c]pyrrole, 1H), 2.99 (bs, Octahydropyrrolo[3,4-c]pyrrole, 1H), 2.70 (m, Octahydropyrrolo[3,4-c]pyrrole, 2H), 2.58 (m, Octahydropyrrolo[3,4-c]pyrrole, 2H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9, 159.8, 143.6, 138.4, 134.6, 133.7 (q, $^{3}J_{C,F}$ = 3.8 Hz), 129.6 (q, $^{2}J_{C,F}$ = 35.8 Hz), 128.5, 128.4, 127.2, 126.8, 125.8 (q, $^{3}J_{C,F}$ = 3.8 Hz), 122.4 (q, $^{1}J_{C,F}$ = 273.1 Hz), 59.7, 59.6, 59.1, 56.3, 53.3, 41.8, 40.0 HRMS *m/z* calc for $C_{22}H_{20}F_3N_4O_3S$ [M+H$^+$], 477.1204; found, 477.1206.

tert-Butyl 6-thiourea-octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (**26a**) Compound **26a** is prepared by general procedure B, using tert-butyloctahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (0.500 g, 2.21 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.453 g, 2.54 mmol, 1.15 eq.). For better solubility of tert-butyloctahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate 3 ml MeOH are added to the reaction mixture. The crude product is purified by column chromatography (EtAc). The title compound appears as a white solid (397 mg 63 %). ^{1}H-NMR (400 MHz, CD_3OD) δ 4.69 (bs, 2,8-diazabicyclo[4.3.0]nonane, 1H), 3.90 (m, 2,8-diazabicyclo[4.3.0]nonane, 2H), 3.56 (m, 2,8-diazabicyclo[4.3.0]nonane, 2H), 3.35 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.81 (bs, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.26 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 1.75 (m, 2,8-diazabicyclo[4.3.0]nonane, 2H), 1.47 (s, t-Boc, 9H), 1.36 (m, 2,8-diazabicyclo[4.3.0]nonane, 2H) MS *m/z* (ESI) 285.99 [M+H$^+$], 303.03 [M+Na$^+$].

tert-Butyl 6-[8-nitro-4-oxo-6-(trifluoromethyl)-4H-1,3-benzothiazin-2-yl]-octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (**26b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.215 g, 0.80 mmol, 1.1 eq.) by general procedure A. **26b** is synthesised by general procedure C, using tert-butyl-6-thiourea octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (**26a**) (0.205 g, 0.72 mmol, 1.0 eq.). The crude product is purified by column chromatography (EtAc/heptane 1:1). The title compound appears as a yellow solid (180 mg 50 %, HPLC purity 98.6 %, t_R = 15.0 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.06 (m, Ar-**H**, 1H), 8.69 (d, Ar-**H**, ^{4}J = 1.7 Hz, 1H), 4.83 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H),4.02 (m, 2,8-diazabicyclo[4.3.0]nonane, 2H), 3.77 (m, 2,8-diazabicyclo[4.3.0]nonane, 0.5H), 3.72 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 3.58 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 3.48 (m, 2,8-diazabicyclo[4.3.0]nonane, 0.5H), 2.71 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.34 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 1.83 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 1.70 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 1.44 (s, t-Boc,

5H), 1.42 (m, 2,8-diazabicyclo[4.3.0]nonane, 2H), 1.41 (s, t-Boc, 4H) ^{13}C-APT-NMR (100 MHz, $CDCl_3$) δ 165.9, 161.6, 154.8, 143.6, 134.2, 133.8 (q, $^3J_{C,F}$ = 3.1 Hz), 129.7, 126.8, 125.9 (q, $^3J_{C,F}$ = 3.1 Hz), 122.4 (q, $^1J_{C,F}$ = 273.1 Hz), 80.7, 54.7, 52.3, 50.9, 47.0, 44.1, 38.7, 35.3, 33.9, 28.3, 25.3, 23.8 HRMS *m/z* calc for $C_{21}H_{24}F_3N_4O_5S$ [M+H$^+$], 501.1415; found, 501.1411.

8-Nitro-2-{octahydro-1H-pyrrolo[3,4-b]pyridin-6-yl}-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**26c**) tert-butyl 6-[8-nitro-4-oxo-6-(trifluoromethyl)-4H-1,3-benzothiazin-2-yl]-octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (**26b**) (0.273 g, 0.55 mmol, 1.0 eq.) is dissolved in a mixture of 2 ml DCM and 2 ml TFA and stirred at room temperature for 1.5 h. The solvent is removed under vacuum and the reaction mixture is co-evaporated three times each with toluene and chloroform. The crude product purified by column chromatography (chloroform/MeOH/ammonia 36 % 95:5:1). The title compound appears as a yellow amorphous substance (164 mg 75 %, HPLC purity 96.0 %, t_R = 13.5 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.05 (m, Ar-**H**, 1H), 8.66 (m, Ar-**H**, 1H), 3.71 (m, 2,8-diazabicyclo[4.3.0]nonane, 4H), 3.40 (m, N**H**, 1H), 2.94 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.62 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.52 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.39 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 1.68 (m, 2,8-diazabicyclo[4.3.0]nonane, 4H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.7, 161.0, 143.4, 134.1, 133.5, 129.4, 126.8, 125.7, 122.4 (q, $^1J_{C,F}$ = 273.1 Hz), 57.9, 56.1, 54.9, 54.6, 51.4, 48.1, 45.2, 44.9, 37.3, 35.5, 22.8, 22.7, 21.1, 20.8 HRMS *m/z* calc for $C_{16}H_{16}F_3N_4O_3S$ [M+H$^+$], 401.0891; found, 401.0879.

2-{1-Benzyl-octahydro-1H-pyrrolo[3,4-b]pyridin-6-yl}-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**26d**) 8-Nitro-2-{octahydro-1H-pyrrolo[3,4-b]pyridin-6-yl}-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**26c**) (0.020 g, 0.05 mmol, 1.0 eq.) is dissolved in a mixture of equal parts DCM and saturated aqueous Na_2CO_3 solution. To this solution is added benzyl bromide (0.011 g, 0.06 mmol, 1.24 eq.) and the reaction mixture is left at room

temperature for 12 h. The aqueous phase is then extracted three times with DCM. The oragnic phases are collected, dried with $MgSO_4$ and the solvent is removed *in vacuo*. Further purification is carried out by column chromatography (chloroform/ammonia 36 % 99:1). The title compound as a yellow solid (18 mg 72 %, HPLC purity 99.5%, t_R = 12.4 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.17 (m, Ar-**H**, 1H), 8.76 (m, Ar-**H**, 1H), 7.25 (m, Ar-**H**, 5H), 3.82 (m, 2,8-diazabicyclo[4.3.0]nonane, N-C**H$_2$**-Ar, 4H), 3.51 (m, N-C**H$_2$**-Ar, 1H), 3.34 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.72 (bs, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.52 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.31 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 1.66 (m, 2,8-diazabicyclo[4.3.0]nonane, 5H) ^{13}C-APT-NMR (100 MHz, $CDCl_3$) δ 165.9, 161.0, 143.6, 138.6, 134.5, 133.7, 129.5 (q, $^2J_{C,F}$ = 35.9 Hz), 128.8, 128.4, 128.3, 128.2, 127.1, 126.9, 125.8, 122.4 (q, $^1J_{C,F}$ = 273.1 Hz), 61.9, 60.2, 59.6, 59.5, 52.6, 51.6, 50.4, 50.0, 49.7, 48.4, 37.7, 36.1, 23.6, 22.1 HRMS *m/z* calc for $C_{23}H_{22}F_3N_4O_3S$ [M+H$^+$], 491.1361; found, 491.1346.

6-Benzyl-octahydro-1H-pyrrolo[3,4-b]pyridine-1-thiourea (**27a**)Compound **27a** is prepared by general procedure B, using 6-benzyl-octahydro-1H-pyrrolo[3,4-b]pyridine (0.140 g, 0.64 mmol, 1.0 eq.) and thiocarbonyldiimidazole (0.131 g, 0.73 mmol, 1.15 eq.). The crude product is processed by column chromatography (chloroform/MeOH/ammonia 36 % 90:10:1). The title compound appears as a white solid (95 mg 54 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (m, Ar-**H**, 5H), 5.97 (bs, N**H$_2$**, 2H), 5.15 (bs, 2,8-diazabicyclo[4.3.0]nonane, 1H), 4.19 (bs, 2,8-diazabicyclo[4.3.0]nonane, 1H), 3.68 (d, N-C**H$_2$**-Ar, ^2J = 13.1 Hz, 1H), 3.60 (d, N-C**H$_2$**-Ar, ^2J = 13.1 Hz, 1H), 3.12 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.98 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.78 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 2.58 (t, 2,8-diazabicyclo[4.3.0]nonane, ^3J = 6.8 Hz, 1H), 2.52 (dd, 2,8-diazabicyclo[4.3.0]nonane, ^3J = 9.2 Hz, ^4J = 2.0 Hz, 1H), 2.36 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 1.86 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 1.70 (m, 2,8-

diazabicyclo[4.3.0]nonane, 1H), 1.57 (m, 2,8-diazabicyclo[4.3.0]nonane, 2H) MS *m/z* (ESI) 276.10 [M+H$^+$].

2-{6-Benzyl-octahydro-1H-pyrrolo[3,4-b]pyridin-1-yl}-8-nitro-6-(trifluoromethyl)-4H-1,3-benzothiazin-4-one (**27b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.102 g, 0.38 mmol, 1.1 eq.) by general method 1. **27b** is synthesised by general procedure C, using tert-6-benzyl-octahydro-1H-pyrrolo[3,4-b]pyridine-1-thiourea (**27a**) (0.095 g, 0.34 mmol, 1.0 eq.). The crude product is purified by column chromatography (chloroform/ammonia 36 % 99:1). The title compound is a yellow solid (54 mg 32 %, HPLC purity 99.0 %, t_R = 14.1 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.07 (d, Ar-**H**, ^4J = 1.6 Hz, 1H), 8.72 (m, Ar-**H**, ^4J = 1.6 Hz, 1H), 7.28 (m, Ar-**H**, 5H), 5.66 (bs, 2,8-diazabicyclo[4.3.0]nonane, 0.5H), 5.02 (bs, 2,8-diazabicyclo[4.3.0]nonane, 0.5H), 4.80 (bs, 2,8-diazabicyclo[4.3.0]nonane, 0.5H), 4.12 (bs, 2,8-diazabicyclo[4.3.0]nonane, 0.5H), 3.74 (bs, C**H$_2$**-Ar, 1H) 3.65 (m, C**H$_2$**-Ar, 1H), 3,41 (bs, 2,8-diazabicyclo[4.3.0]nonane, 0.5H), 3.09 (bs, 2,8-diazabicyclo[4.3.0]nonane, 0.5H), 3.02 (t, 2,8-diazabicyclo[4.3.0]nonane, ^4J = 9.5 Hz, 1H), 2.69 (m, 2,8-diazabicyclo[4.3.0]nonane, 3H) 2.42 (m, 2,8-diazabicyclo[4.3.0]nonane, 1H), 1.94 (m, 2,8-diazabicyclo[4.3.0]nonane, 4H) ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.2, 162.9, 143.9, 138.6, 134.3, 133.3 (q, $^3J_{C,F}$ = 3.8 Hz), 129.6 (q, $^2J_{C,F}$ = 35.3 Hz),128.5, 128.3, 127.1, 126.8, 125.9 (q, $^3J_{C,F}$ = 3.8 Hz), 122.4 (q, $^1J_{C,F}$ = 272.8 Hz), 60.0, 58.7, 56.1, 55.0, 54.4, 43.4, 36.4, 35.9, 26.4, 25.7, 22.9, 22.1 HRMS *m/z* calc for $C_{23}H_{22}F_3N_4O_3S$ [M+H$^+$], 491.1360; found, 491.1354.

1-(Cyclohexylmethyl)piperazine (**28a**) N-formylpiperazine (1.32 ml, 12.8 mmol, 1.0 eq.), cyclohexylmethyl bromide (1.97 ml, 14.1 mmol, 1.1 eq.), KI (0.026 g, 0.18 mmol, 0.014 eq.) and K_2CO_3 (2.13 g, 15.4 mmol, 1.2 eq.) are dissolved in a round bottom flask in 10 ml acetonitrile. After 23 h heating under reflux the reaction mixture is filtered and the filtrate is concentrated on the rotary evaporator. After dissolving the residue in 5 N NaOH solution (5.0

ml) and EtOH (9.3 ml), it is heated for 14 h under reflux. After the reaction is complete, the EtOH is removed under vacuum, distilled water is added to the residue and extracted three times with DCM. The organic layers are collected, dried over $MgSO_4$ and the solvent removed under vacuum. The crude product is purified by column chromatography chloroform/MeOH/ammonia 36 %. (9:1:0.1). The title compound is a colourless oil (1.83 g 79 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.76 (bs, N-H, 1H), 2.95 (t, C**H$_2$**-N-C**H$_2$**, ^{3}J=4.9 Hz, 4H), 2.43 (bs, C**H$_2$**-N-C**H$_2$**, 4H), 2.11 (d, N-C**H$_2$**-CH, ^{3}J=7.2 Hz, 2H), 1.70 (m, Cyclohexyl, 5H), 1.46 (m, CH_2-C**H**-$(CH_2)_2$, 1H), 1.18 (m, Cyclohexyl, 3H), 0.86 (m, Cyclohexyl, 2H) MS *m/z* (ESI) 183.30 [M+H$^+$].

4-(Cyclohexylmethyl)piperazin-1-thiourea (**28b**) Compound **28b** is prepared by general procedure B, using 3-cyclohexylmethylpiperazine (**28a**) (0.190 g, 1.04 mmol, 1 eq.) and thiocarbonyldiimidazole (0.214 g, 1.20 mmol, 1.15 eq.). The crude product is purified by column chromatography (LM chloroform/MeOH 98:2). The title compound appears as a brownish solid (118 mg 52 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.85 (m, N**H$_2$**, 2H), 3.83 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.47 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.17 (d, N-C**H$_2$**-CH, ^3J = 7.2 Hz, 2H), 1.71 (m, cyclohexyl, 5H), 1.47 (m, N-CH_2-C**H**, 1H), 1.19 (m, cyclohexyl, 3H), 0.88 (m, cyclohexyl, 2H) MS *m/z* (ESI): 242.12 [M+H$^+$].

Macozinone 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.282 g, 1.04 mmol, 1.0 eq.) according to general procedure A. The synthesis of the benzothiazinone is carried out according to general procedure C. The precipitated product is isolated by filtration and recrystallised from acetone. The title compound is light yellow solid (293 mg 68 %, HPLC purity 100.0 %, t_R = 12.5 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.09 (d, Ar-**H**, ^4J = 2.0, 1H), 8.75 (d, Ar-**H**, ^4J = 2.0, 1H), 3.98 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.56 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.20 (m, N-C**H$_2$**-CH, 2H), 1.74 (m, cyclohexyl, 5H), 1.51 (m, N-CH_2-C**H**, 1H), 1.22 (m, cyclohexyl, 3H), 0.89 (m, cyclohexyl, 2H) ^{13}C-NMR (100 MHz,

$CDCl_3$) δ 166.4, 162.0, 143.9, 134.1, 133.4 (q, $^3J_{C,F}$ = 3.4 Hz), 129.7 (q, $^2J_{C,F}$ = 35.5 Hz), 126.8, 126.0 (q, $^3J_{C,F}$ = 3.8 Hz), 122.4 (q, $^1J_{C,F}$ = 273.1 Hz), 65.1, 53.1, 46.6, 35.0, 31.7, 26.7, 26.0 HRMS *m/z* calc for $C_{23}H_{22}F_3N_4O_3S$ [M+H$^+$], 457.15217; found, 457.1512.

(2S)-2-Methyl-1,4-dioxa-8-azaspiro[4.5]decane (**29a**) 4-Piperidone monohydrate (995 mg, 6.57 mmol, 1 eq.) and (2S)-propane-1,2-diol (0.500 mg, 6.57 mmol, 1 eq.) are dissolved in anisole (50 ml). After addition of p-toluenesulfonic acid monohydrate (0.125 mg, 0.66 mmol, 0.1 eq.) the reaction mixture is boiled for 4 h on the water separator. Then the anisole is removed on the rotary evaporator and the crude product obtained is suspended in brine. After addition of NaOH solution (2 N, pH 12) the product is extracted from the aqueous phase with diethyl ether (six times). The ether phases are combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. The product appears as a colourless oil (186 mg 15 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.22 (m, CH_2-C**H**-CH_3, 1H), 4.05 (dd, C**H$_2$**-CH-CH_3, ^2J = 7.8 Hz, 1H), 3.44 (t, C**H$_2$**-CH-CH_3, ^2J = 7.8 Hz, 1H), 2.92 (m, C**H$_2$**-N-C**H$_2$**, 4H), 1.87 (bs, N-**H**, 1H), 1.67 (m, C**H$_2$**-C-C**H$_2$**, 4H), 1.27 (d, C**H$_3$**, , ^3J = 6.0 Hz, 3H) MS *m/z* (APCI) 158.2 [M+H$^+$].

(2S)-2-Methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-thiourea (**29b**) Dried NaSCN (338 mg, 4.16 mmol, 1.0 eq.) is suspended in acetone (10 ml), placed under inert gas and cooled to 5 °C. Benzoyl chloride (0.480 ml, 4.16 mmol, 1.0 eq.) is added slowly and the reaction mixture is stirred for 3.5 h at 5 °C. This is followed by the addition of (2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]decane (**29a**) (186 mg, 4.16 mmol, 1.0 eq.) dissolved in acetone (5 ml) at 12 °C, then the reaction mixture is stirred at room temperature overnight. After the reaction, the solvent is removed under vacuum and the residue is dissolved in 19 ml MeOH/water mixture (3:1) and K_2CO_3 (1152 mg, 8.34 mmol, 1.0 eq.) is added .The reaction mixture is heated under reflux for 24 h .After the reaction is complete, the solid is removed by filtration and the solvent is concentrated *in vacuo*. The crude product is suspended in brine and the aqueous phase is

extracted with EtAc (three times). The organic layers are collected, dried ($MgSO_4$) and concentrated. The crude product is purified by column chromatography (TBME). The product is a white solid (111 mg 43 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.07 (bs, N-**H**, 2H), 4.23 (m, CH_2-C**H**-CH_3, 1H), 4.06 (dd, CH_2-C**H**-CH_3, ^2J = 8.0 Hz, 1H), 3.88 (m, C**H$_2$**-N-C**H$_2$**, 4H), 3.44 (t, C**H$_2$**-CH-CH_3, ^2J = 7.8 Hz, 1H), 1.76 (m, C**H$_2$**-C-C**H$_2$**, 4H), 1.26 (d, C**H$_3$**, ^3J = 6.1 Hz, 3H) MS *m/z* (APCI) 217.1 [M+H$^+$].

BTZ043 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.57 g, 0.21 mmol, 1.0 eq.) by general procedure A, replacing toluene with anisole. **BTZ043** is synthesised by general procedure C in anisole in place of toluene, using (2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-thiourea (**29b**) (0.47 g, 0.21 mmol, 1.0 eq.). The crude product is purified chromatographically (LM TBME). The title compound appears as a yellow solid (66 mg 73 %, HPLC purity 100.0 %, t_R = 14.2 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.08 (d, Ar-**H**, ^3J = 1.6 Hz, 1H), 8.74 (d, Ar-**H**, ^3J = 1.8 Hz, 1H), 4.29 (m, CH_2-C**H**-CH_3, 1H), 4.11 (dd, C**H$_2$**-CH-CH_3, ^2J = 8.0 Hz, 1H), 4.05 (m, C**H$_2$**-N-C**H$_2$**, 4H), 3.50 (t, C**H$_2$**-CH-CH_3, ^2J = 8.0 Hz, 1H), 1.85 (m, C**H$_2$**-C-C**H$_2$**, 4H), 1.31 (d, C**H$_3$**, ^3J = 6.1 Hz, 3H) ^{13}C-NMR (125 Hz, $CDCl_3$) δ 166.5, 161.8, 143.9, 134.1, 133.3, 129.6 (q, $^2J_{C,F}$ = 35.1 Hz), 126.6, 125.9, 122.4 (q, $^1J_{C,F}$ = 273.1 Hz), 106.3, 72.5, 70.9, 44.6, 36.4, 35.2, 18.3 HRMS *m/z* calc for $C_{17}H_{17}F_3N_3O_5S$ [M+H$^+$], 432.0837; found, 432.0829, calc for $C_{17}H_{16}F_3N_3O_5SNa$ [M+Na$^+$], 454.0656; found, 454.0646.

Morpholine-4-carboxamide (**30a**) 1.0 g (16.70 mmol) urea were dissolved in 20 ml morpholine and refluxed for 40 h, until release of ammonia stopped. The amine was removed under reduced pressure and the resulting oily residue recrystallized from hexane:chloroform (approx. 1:2 (V/V)). Pale yellow crystals were collected and dried (1.64 g 76 %). ^{1}H-NMR

(500 MHz, $CDCl_3$) δ 4.53 (bs, 2H, N**H₂**), 3.69 (m, 4H, C**H₂**-O-C**H₂**), 3.38 (m, 4H, C**H₂**-N-C**H₂**) MS *m/z* (EI) 130 (M).

2-(Morpholin-4-yl)-8-nitro-6-(trifluoromethyl)-4H-1,3-benzoxazin-4-one (**30b**) Synthesis of 2-chloro-3-nitro-5-(trifluoromethyl)benzoylchloride according to general procedure A from 250 mg (0.93 mmol) 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid. 151 mg (1.16 mmol) morpholine-4-carboxamide (**30a**) and 158 µl (0.93 mmol) DIPEA were dissolved in 30 ml toluene and heated to 70 °C. 2-chloro-3-nitro-5-(trifluoromethyl)benzoylchloride was dissolved in 4 ml toluene and added dropwise. Upon complete addition, the mixture was refluxed for 2.5 h. After cooling, the solvent was removed under reduced pressure and the crude product purified by flash chromatography (eluent TBME). The title compound appears as a pale-yellow solid (111 mg 35 %, HPLC purity 99.3 %, t_R = 11.1 min). ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 8.71 (d, 1H, Ar-**H**, ^4J = 2.3 Hz), 8.59 (d, 1H, Ar-**H**, ^4J = 2.3 Hz), 3.93 (m, 4H, C**H₂**-N-C**H₂**), 3.83 (m, 4H, C**H₂**-O-C**H₂**) ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 162.9, 155.4, 148.5, 136.3, 131.1 (q, $^3J_{C,F}$ = 3.4 Hz), 127.8 (q, $^2J_{C,F}$ = 35.9 Hz), 127.1 (q, $^3J_{C,F}$ = 3.4 Hz), 122.1 (q, $^1J_{C,F}$ = 273.1 Hz), 120.3, 66.2, 66.1, 45.4, 45.0 HRMS *m/z* calc for $C_{13}H_{11}F_3N_3O_5$ [M+H$^+$], 346.0650; found, 346.0649, calc for $C_{13}H_{10}F_3N_3O_5Na$ [M+Na$^+$], 368.0466; found, 368.0467.

1,2,3,4-Tetrahydroisoquinoline-2-carboxamide (**31a**) Tetrahydroisoquinoline (1.000 g, 7.51 mmol, 2 eq.) and urea (0.225 g, 3.76 mmol, 1 eq.) are heated in a flask for 42 h at 120 °C (clear brown colouration). The crude product is worked up by recrystallisation from chloroform/hexane (1:1). The title compound appears as a brownish solid (479 mg 72 %). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.13 (m, Ar-**H**, 4H), 6.00 (bs, N**H₂**, 2H), 4.45 (s, N-C**H₂**, 2H), 3.50 (t, N-C**H₂**, ^3J = 5.9 Hz, 2H), 2.74 (t, C**H₂**, ^3J = 5.9 Hz, 2H) MS *m/z* (APCI) 177.1 [M+H$^+$].

8-Nitro-2-(1,2,3,4-tetrahydroisoquinolin-2-yl)-6-(trifluoromethyl)-4H-1,3-benzoxazin-4-one (**31b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-

nitro-5-(trifluoromethyl)benzoic acid (0.337 g, 1.25 mmol, 1.25 eq.) by general procedure A. 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is dissolved in toluene (5 ml) and slowly added to a solution of 1,2,3,4-tetrahydroisoquinoline-2-carboxamide (**31a**) (0.200 g, 1.13 mmol, 1.0 eq.) and DIPEA (0.438 ml, 3.39 mmol, 3 eq.) in toluene at 70 °C. After 1 h reflux, the reaction is cooled overnight and the solvent was removed under vacuum. Purification is carried out by flash chromatography with the solvent chloroform. Subsequently, the reaction product is recrystallised from EtAc/hexane (1:1). The title compound appears as a pale yellowish solid (227 mg 58 %, HPLC purity 98.1 %, t_R = 14.3 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.74 (s, Ar-**H**, 1H), 8.61 (s, Ar-**H**, 1H), 7.23 (m, Ar-**H**, 4H), 5.03 (d, C**H$_2$**, ^2J = 8.0 Hz, 2H), 4.13 (m, C**H$_2$**, 2H), 3.80 (s, C**H$_3$**, 3H), 3.06 (m, C**H$_2$**, 2H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.1, 162.9, 155.6, 155.5, 148.6, 136.3, 133.8, 133.4, 131.3, 131.1 (q, $^3J_{C,F}$ = 3.8 Hz), 130.9, 128.7, 128.4, 127.6, 127.5 (q, $^2J_{C,F}$ = 36.2 Hz), 127.4, 127.1, 127.0(q, $^3J_{C,F}$ = 3.8 Hz), 126.9, 126.5, 126.4, 122.2 (q, $^1J_{C,F}$ = 272.8 Hz), 120.3, 47.1, 46.4, 43.6, 42.8, 28.6, 28.0 HRMS *m/z* calc for $C_{18}H_{13}F_3N_3O_4$ [M+H$^+$], 392.0854; found, 392.0858.

Nitro-2-(1,2,3,4-tetrahydroisoquinolin-2-yl)-6-(trifluoromethyl)-1,4-dihydrochinazolin-4-one

(**32a**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.098 g, 0.36 mmol, 1.1 eq.) by general procedure A. **32a** is synthesised by general procedure C, using 1,2,3,4-tetrahydroisoquinoline-2-guanidine hydroiodide (0.100 g, 0.33 mmol, 1.0 eq.). For a complete reaction, diazabicycloundecene (DBU) (0.039 g, 0.27 mmol, 0.82 eq.) is added as auxiliary base and the reaction is boiled for 3 h in toluene under reflux. The crude product is purified by flash chromatography (chloroform/MeOH 99:1). The title compound appears as a yellow solid (10 mg 8 %, HPLC purity 100.0 %, t_R = 15.3 min). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55 (s, Ar-**H**, 1H), 8.29(s, Ar-**H**, 1H), 7.26 (m, Ar-**H**, 4H), 4.99 (bs, N-C**H$_2$**, 2H), 4.07 (t, N-C**H$_2$**, ^3J = 5.7 Hz, 2H), 3.08 (t, C**H$_2$**, ^3J = 5.7 Hz,

2H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.4, 151.3, 134.2, 131.7 (q, $^3J_{C,F}$ = 3.1 Hz), 128.7, 128.4, 127.6, 127.0, 126.6 (q, $^3J_{C,F}$ = 3.8 Hz), 126.4, 123.4, 122.9 (q, $^1J_{C,F}$ = 271.6 Hz),122.8, 118.6, 46.6, 42.9, 28.5 HRMS *m/z* calc for $C_{18}H_{14}F_3N_4O_3$ [M+H$^+$], 391.1013; found, 391.1002, calc for $C_{18}H_{13}F_3N_4O_3Na$ [M+Na$^+$], 413.0833; found, 413.0821.

4-(Cyclohexylmethyl)piperazine-1-carboxamide (**33a**) Cyclohexylmethylpiperazine (0.500 g, 2.73, 2 eq.) and urea (0.082 g, 1.37 mmol, 1 eq.) are added to a flask and heated to 120 °C for 42 h (clear brown colouration). The crude product was purified up by flash chromatography with the eluent chloroform/MeOH/ammonia 36 % (95:5:1). The title compound appears as a brownish solid (308 mg 100 %). ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 4.55 (m, N**H$_2$**, 2H), 3.37 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.36 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.11 (d, N-C**H$_2$**-CH, ^3J = 7.0 Hz, 2H), 1.70 (m, cyclohexyl, 5H), 1.47 (m, N-CH_2-C**H**, 1H), 1.18 (m, cyclohexyl, 3H), 0.86 (m, cyclohexyl, 2H)

2-[4-(Cyclohexylmethyl)piperazin-1-yl]-8-nitro-6-(trifluoromethyl)-4H-1,3-benzoxazin-4-one (**33b**) 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid chloride is prepared from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (0.266 g, 0.98 mmol, 1.0 eq.) by general procedure A. The carboxylic acid chloride is dissolved in toluene (5 ml) and slowly added to a solution of 4-(cyclohexylmethyl)piperazine-1-carboxamide (**33a**) (0.200 g, 0.89 mmol, 0.9 eq.) and DIPEA (0.499 ml, 2.94 mmol, 3 eq.) in toluene at 70 °C. After refluxing for 1 h, the reaction cooled overnight. The purification was carried out column chromatographically with the solvent medium chloroform/MeOH (98:2). The title compound appears as a brownish solid (162 mg 41 %, HPLC purity 95.8 %, t_R = 11.3 min). ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 8.58 (d, Ar-**H**, ^4J = 2.3, 1H), 8.45 (d, Ar-**H**, ^4J = 2.2, 1H), 3.81 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.41 (m, C**H$_2$**-N-C**H$_2$**, 4H), 2.06 (m, N-C**H$_2$**-CH, 2H), 1.60 (m, cyclohexyl, 5H), 1.38 (m, N-CH_2-C**H**, 1H) 1.08 (m, cyclohexyl, 3H), 0.75 (m, cyclohexyl, 2H) ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.0, 155.2, 148.6, 136.2, 131.0 (q, $^3J_{C,F}$ = 3.8 Hz), 127.5 (q, $^2J_{C,F}$ = 35.3 Hz), 127.0 (q, $^3J_{C,F}$ = 3.8 Hz), 122.1 (q, $^1J_{C,F}$ = 273.3 Hz), 120.3,

65.1, 53.0, 52.5, 45.2, 44.7, 34.9, 31.7, 26.6, 26.0 HRMS *m/z* calc for $C_{20}H_{23}F_3N_4O_4$ [M+H$^+$], 441.1745; found, 441.1740

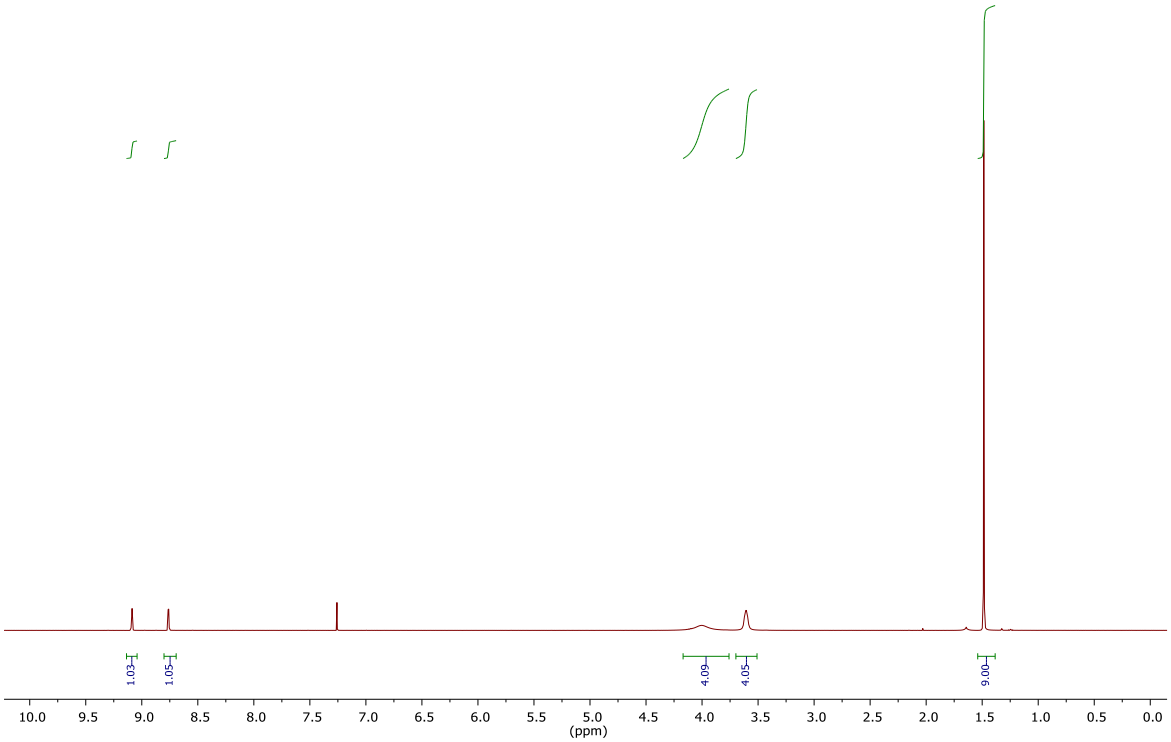


*Figure S1A ^{1}H-NMR (400 MHz) of **1c** in $CDCl_3$.*

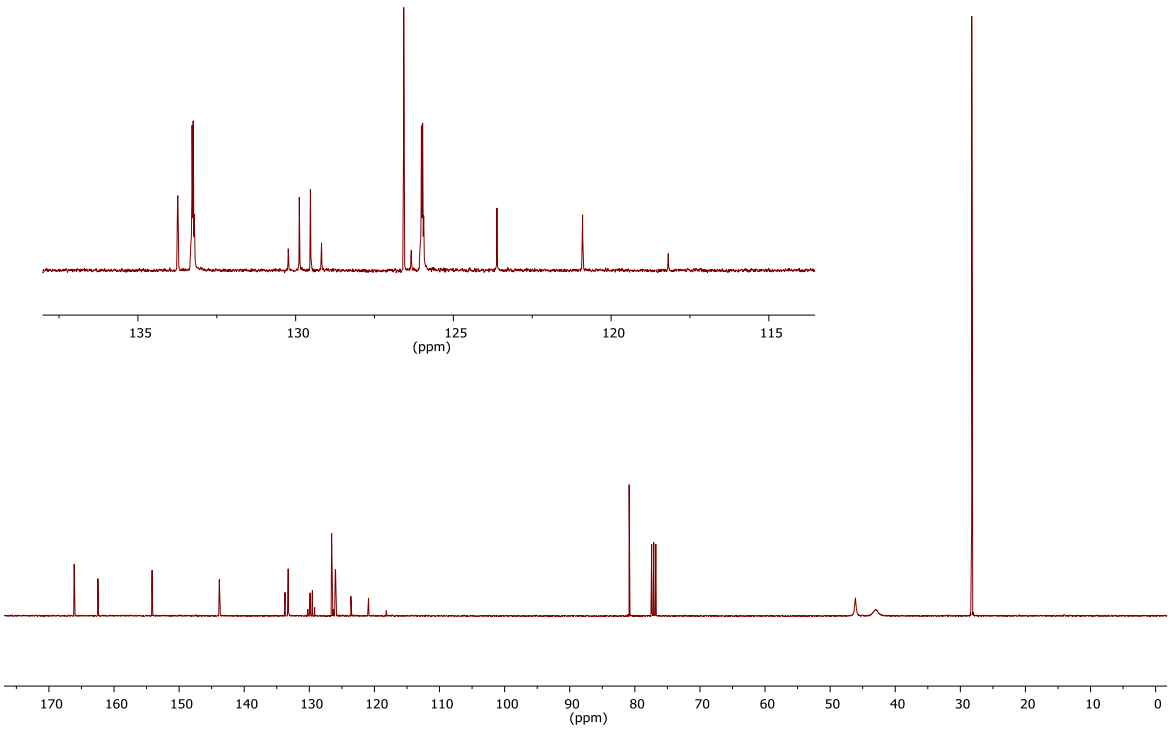
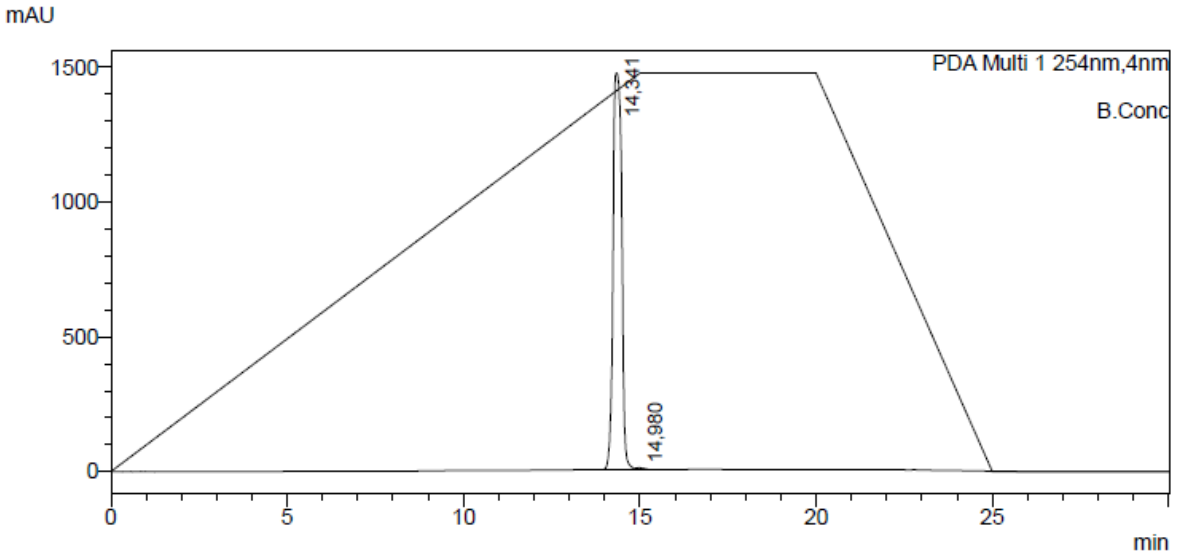


*Figure S1B ^{13}C-NMR (100 MHz) of **1c** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 12
Injection Volume	: 5
Data File	: AR210.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 18:56:13
Date Processed	: 17.05.2021 19:26:15



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	14,341	25137137	1470453	99,861
2	14,980	34897	3878	0,139
Total		25172034	1474330	100,000

*Figure S1C HPLC chromatogram of **1c**.*

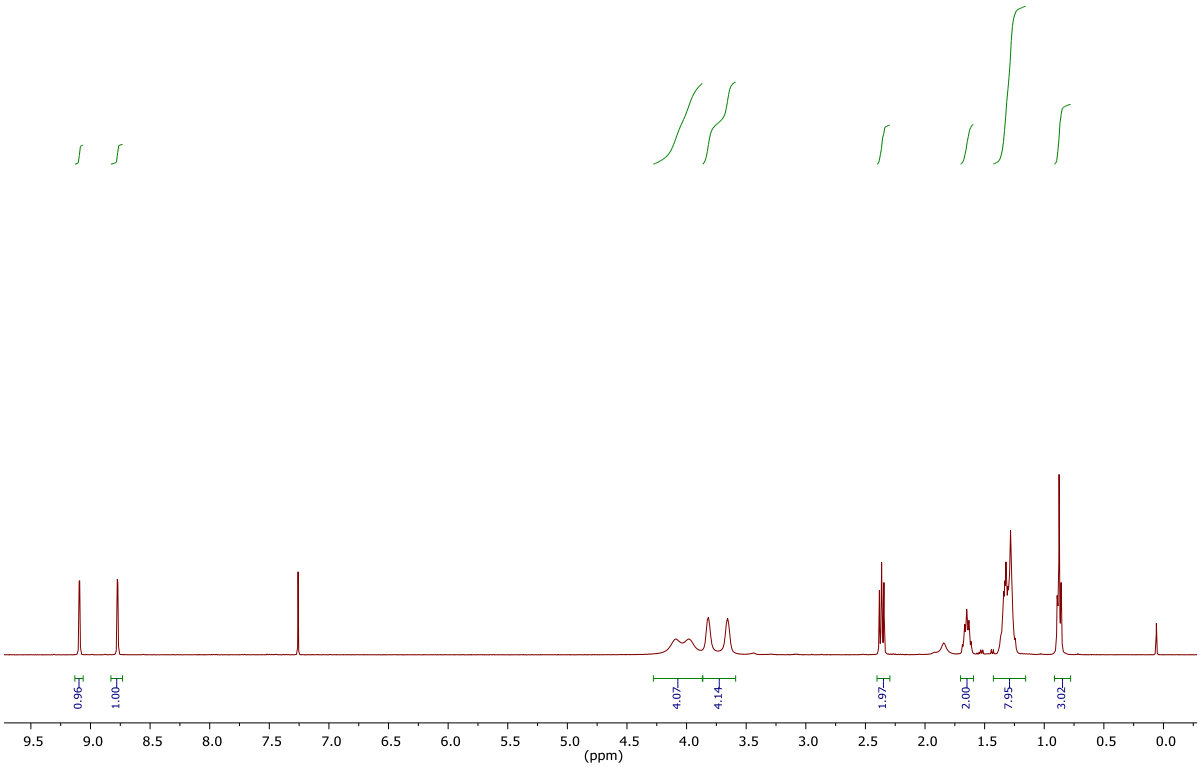


*Figure S2A ^{1}H-NMR (400 MHz) of **1e** in $CDCl_3$.*

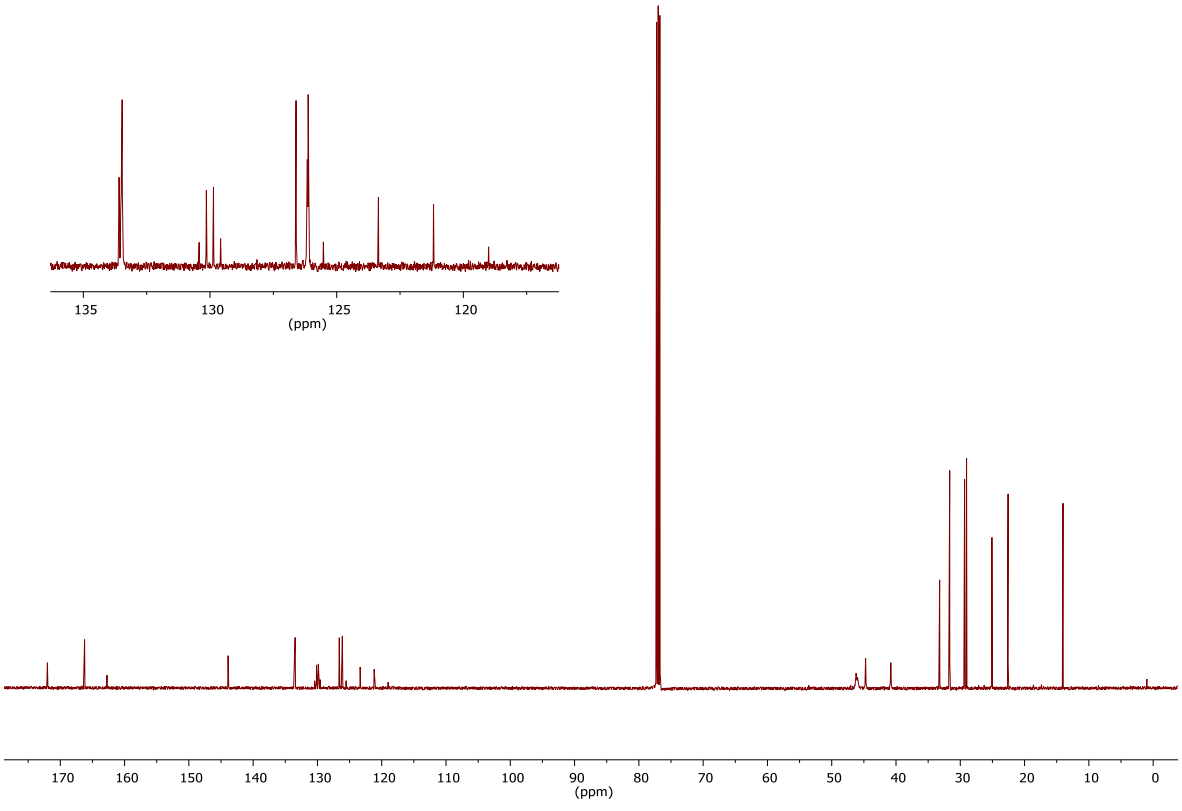
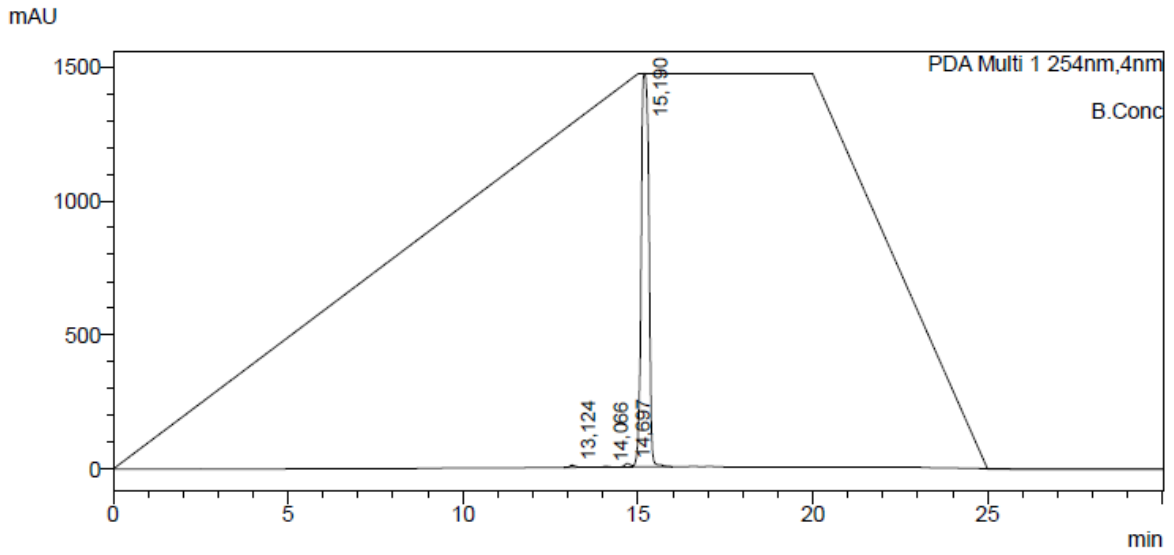


*Figure S2B ^{13}C-NMR (100 MHz, $CDCl_3$) of **1e** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 7
Injection Volume	: 5
Data File	: AR213.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 16:23:32
Date Processed	: 17.05.2021 16:53:34



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	13,124	84765	7719	0,376
2	14,066	37343	2946	0,166
3	14,697	138160	12527	0,613
4	15,190	22291013	1464792	98,846
Total		22551281	1487985	100,000

*Figure S2C HPLC chromatogram of **1e**.*

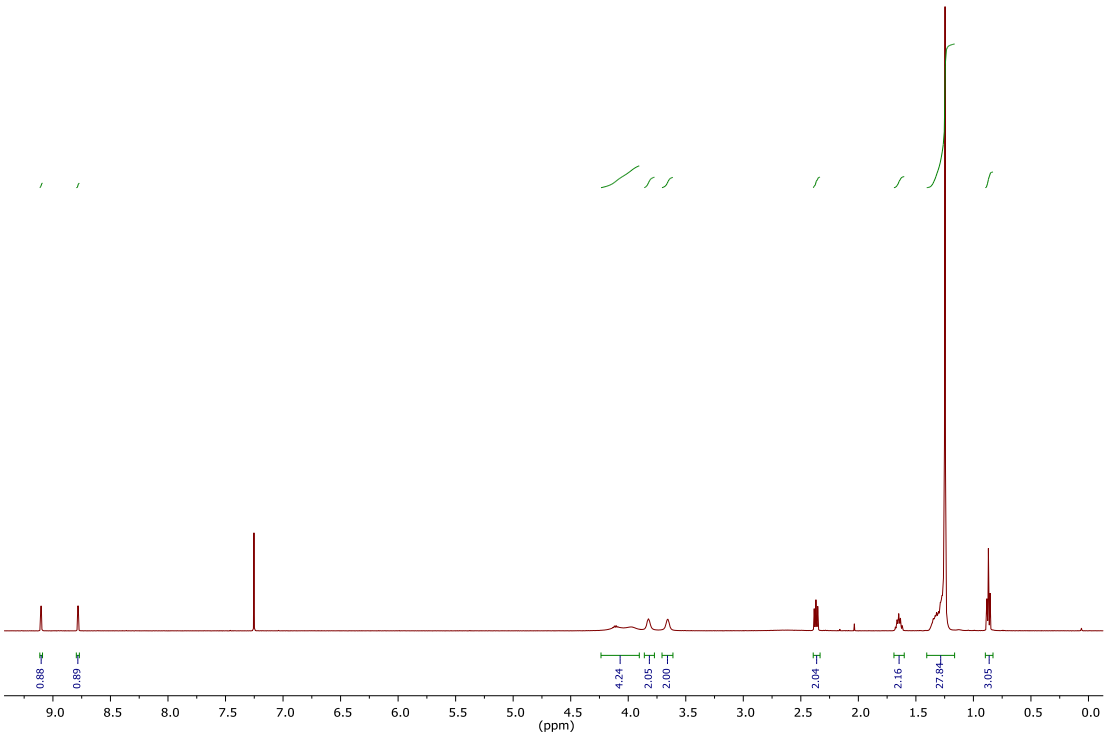


*Figure S3A ^{1}H-NMR (500 MHz) of **2a** in $CDCl_3$.*

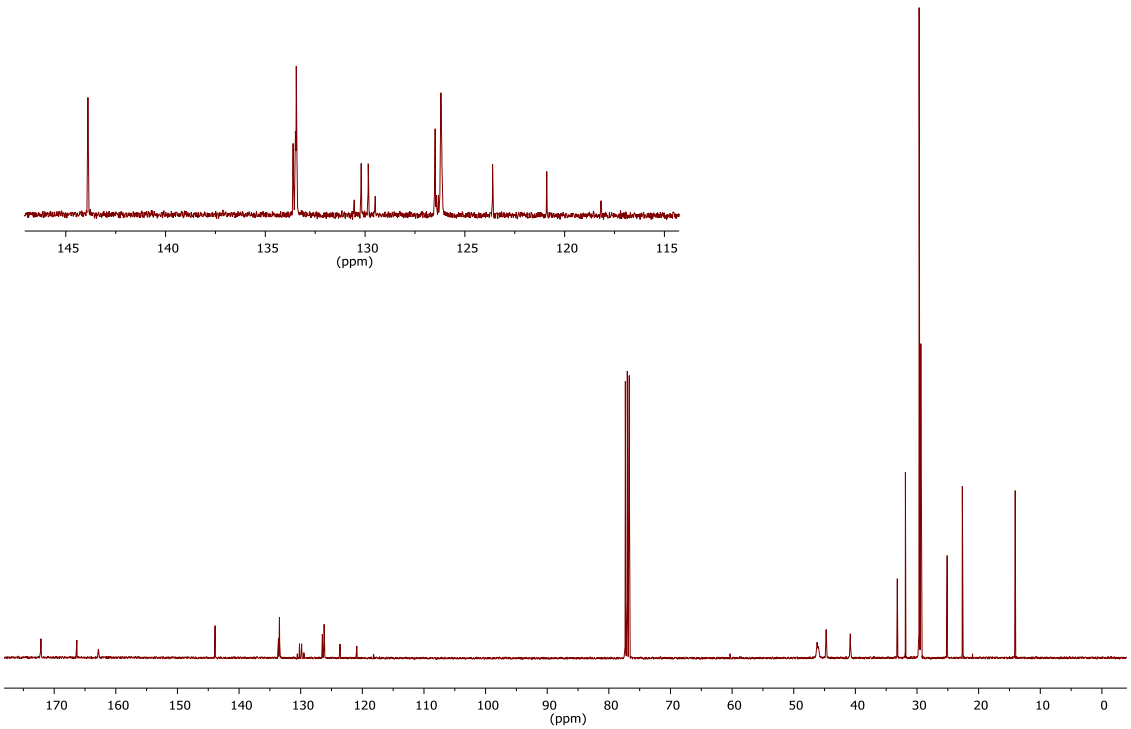
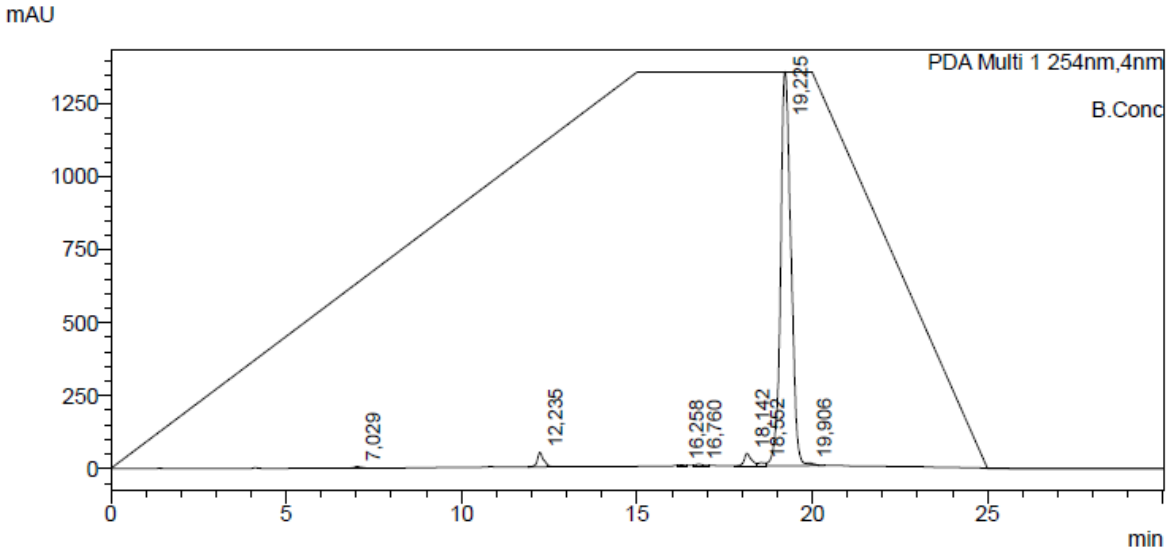


*Figure S3B ^{13}C-NMR (100 MHz) of **2a** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 9
Injection Volume	: 5
Data File	: AR214.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 17:24:35
Date Processed	: 17.05.2021 17:54:38



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	7,029	61048	5607	0,207
2	12,235	610495	49008	2,075
3	16,258	45379	3848	0,154
4	16,760	81057	5442	0,276
5	18,142	602920	42867	2,049
6	18,552	139963	10605	0,476
7	19,225	27850638	1348642	94,661
8	19,906	29829	3075	0,101
Total		29421329	1469094	100,000

*Figure S3C HPLC chromatogram of **2a**.*

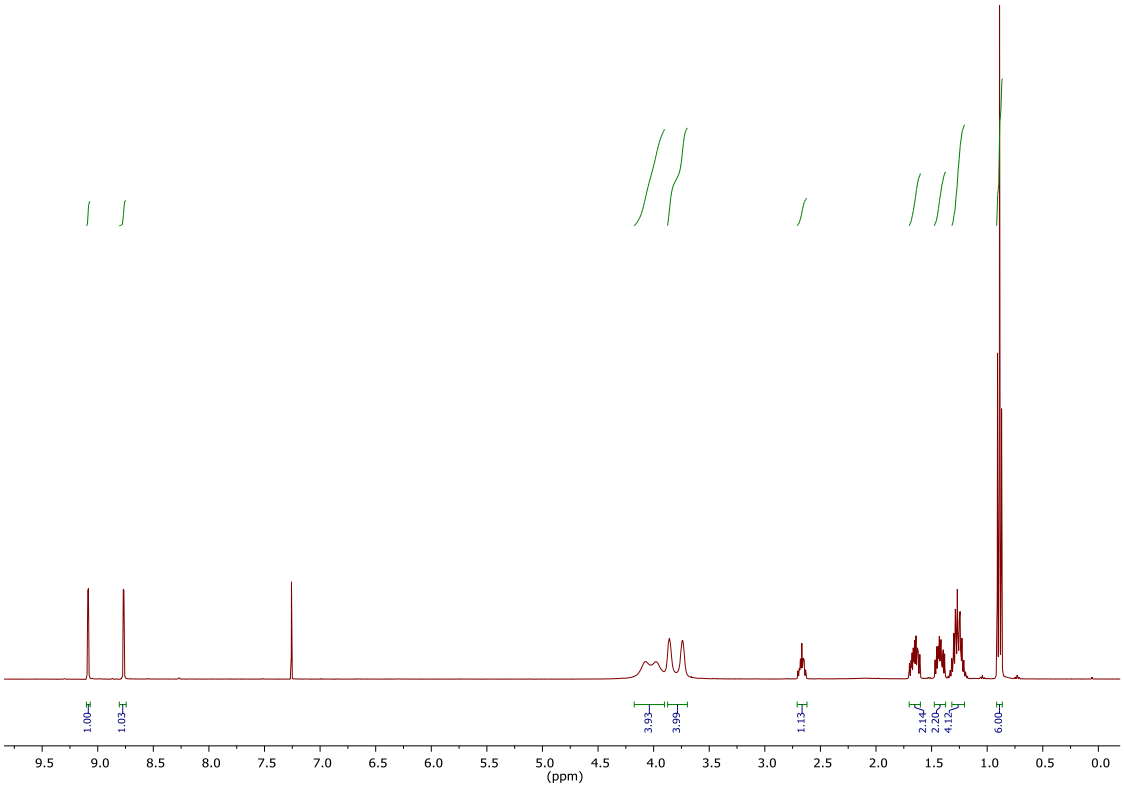


*Figure S4A ^{1}H-NMR (400 MHz) of **3c** in $CDCl_3$.*

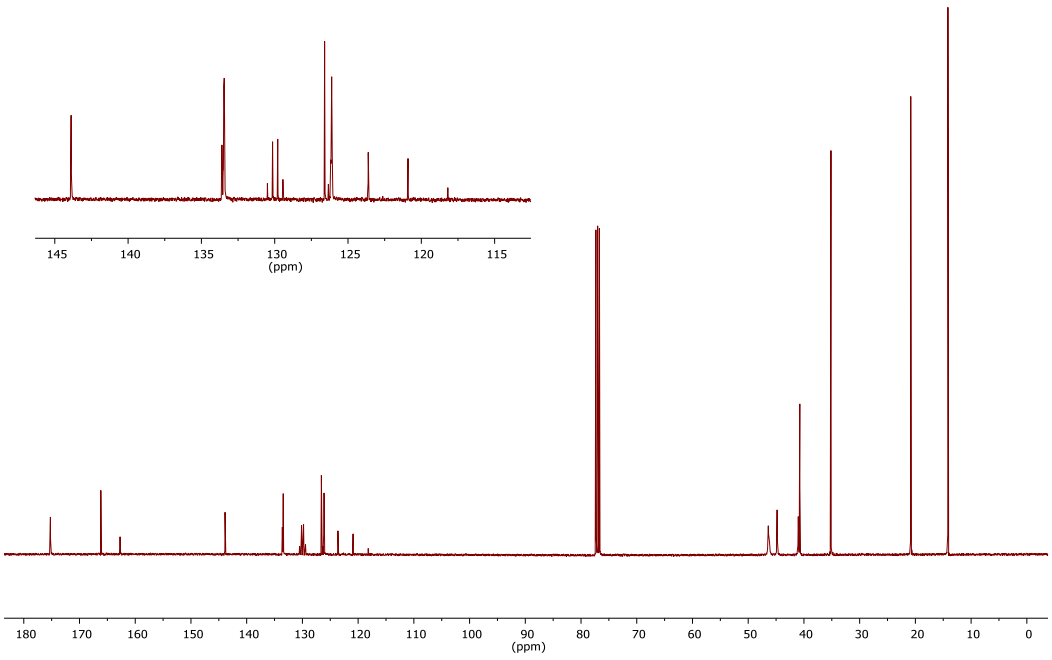
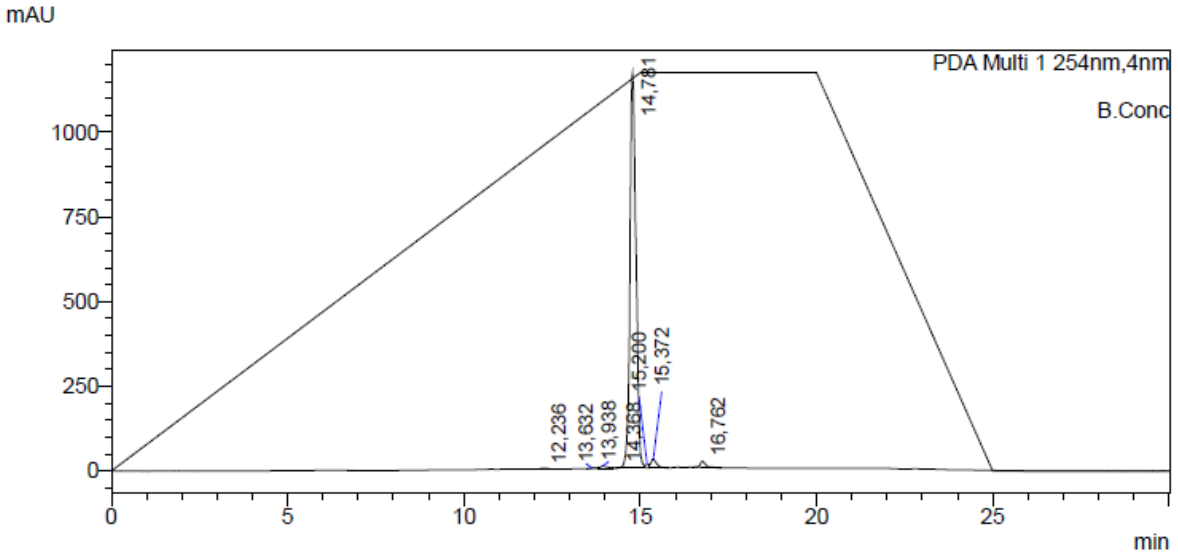


*Figure S4B ^{13}C-NMR (100 MHz) of **3c** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 10
Injection Volume	: 5
Data File	: AR154.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 17:55:07
Date Processed	: 17.05.2021 18:25:10



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,236	34631	2418	0,238
2	13,632	15776	1423	0,109
3	13,938	89297	6815	0,614
4	14,368	20797	2273	0,143
5	14,781	13833400	1166841	95,190
6	15,200	64034	9523	0,441
7	15,372	281308	25621	1,936
8	16,762	193110	18173	1,329
Total		14532354	1233086	100,000

*Figure S4C HPLC chromatogram of **3c**.*

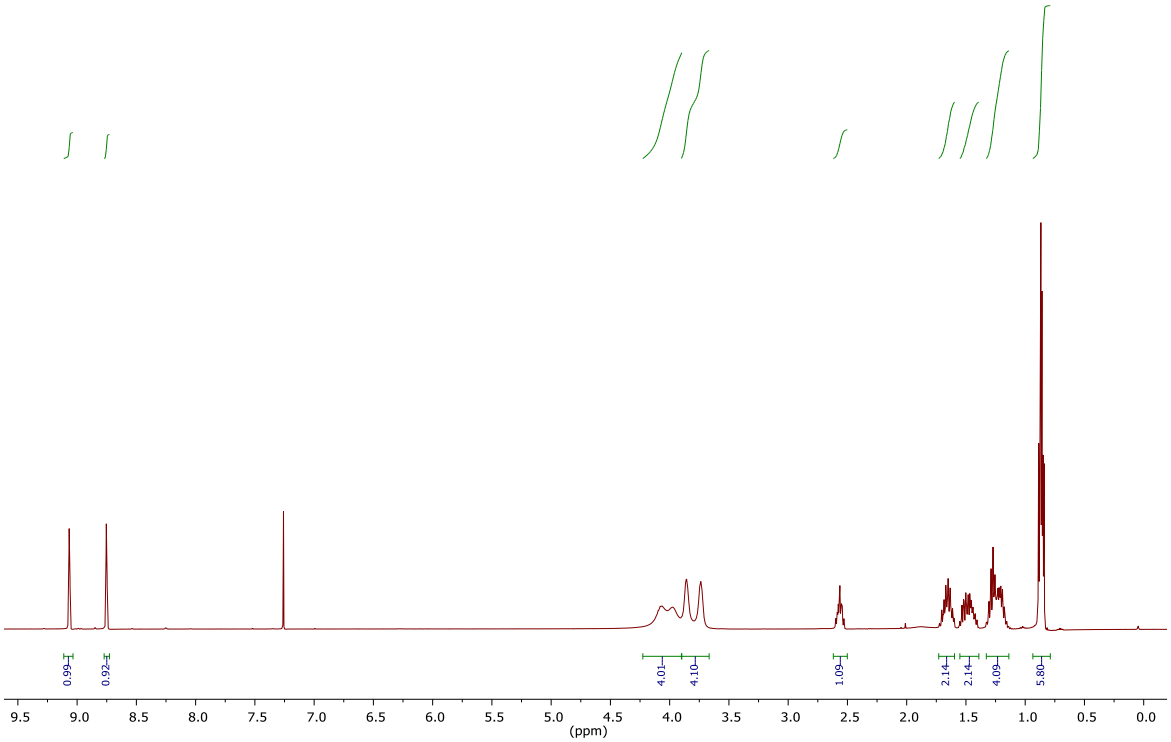


*Figure S5A ^{1}H-NMR (400 MHz) of **4c** in $CDCl_3$.*

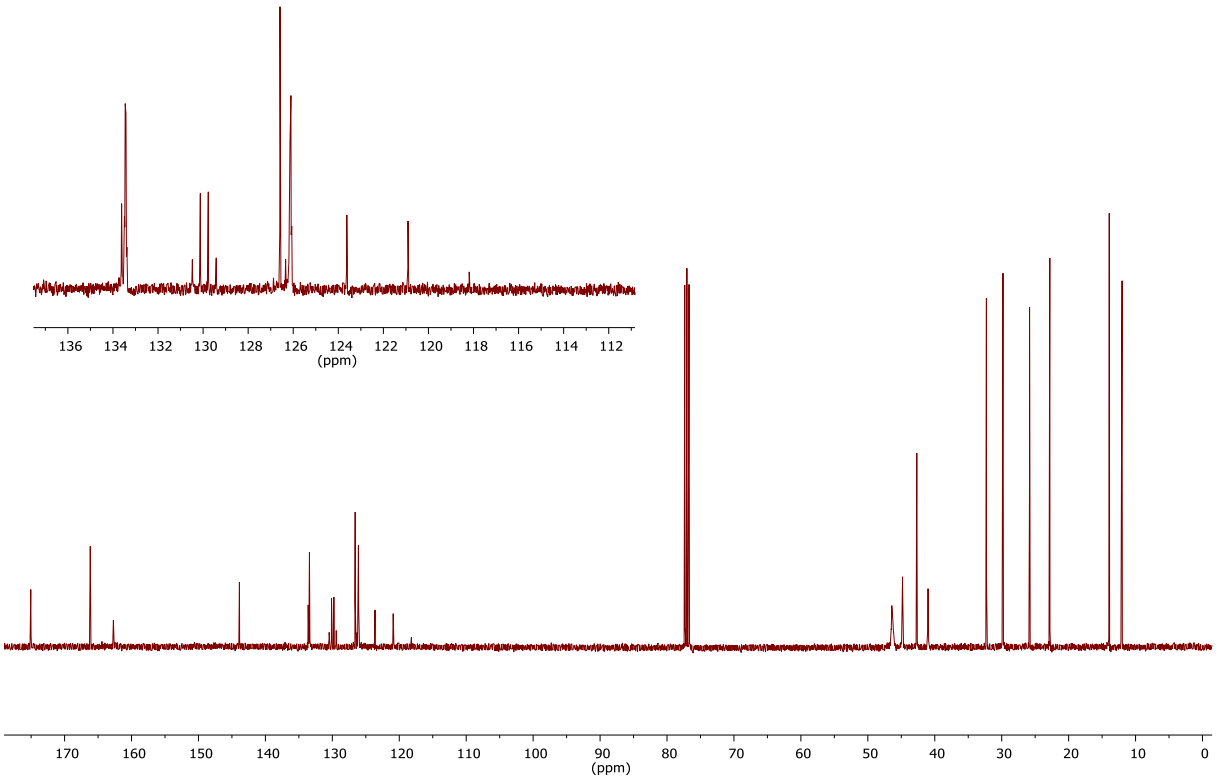
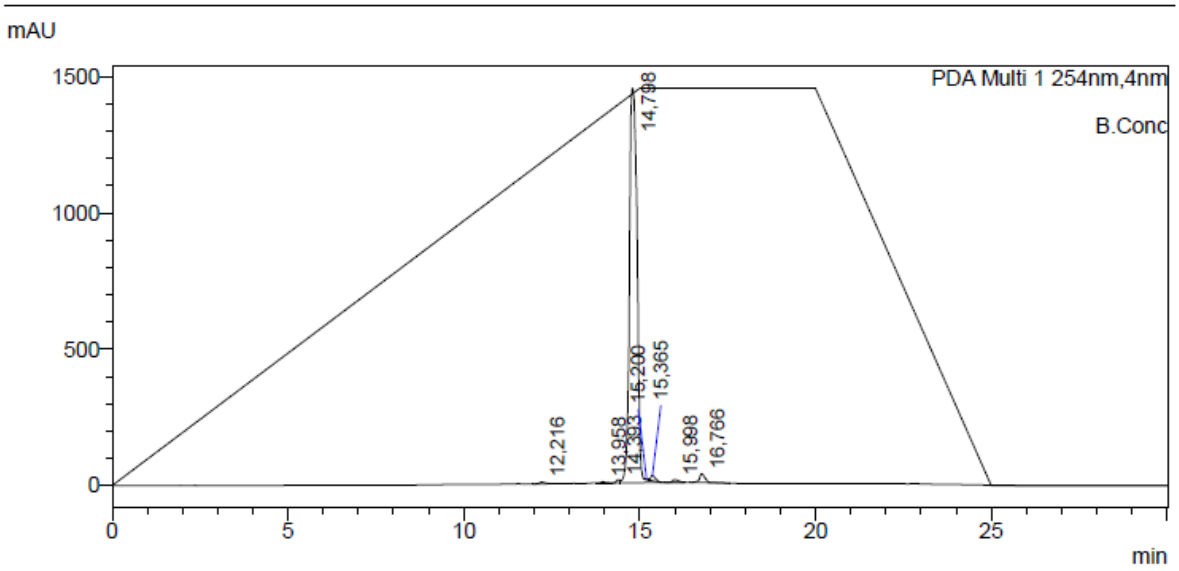


*Figure S5B ^{13}C-NMR (100 MHz) of **4c** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 21
Injection Volume	: 5
Data File	: AR158.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 23:30:55
Date Processed	: 18.05.2021 00:00:57



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,216	85894	7013	0,379
2	13,958	60433	4854	0,267
3	14,393	96290	11703	0,425
4	14,798	21754324	1446670	95,943
5	15,200	5220	1305	0,023
6	15,365	176274	19463	0,777
7	15,998	121540	10375	0,536
8	16,766	374279	32909	1,651
Total		22674254	1534293	100,000

*Figure S5C HPLC chromatogram of **4c**.*

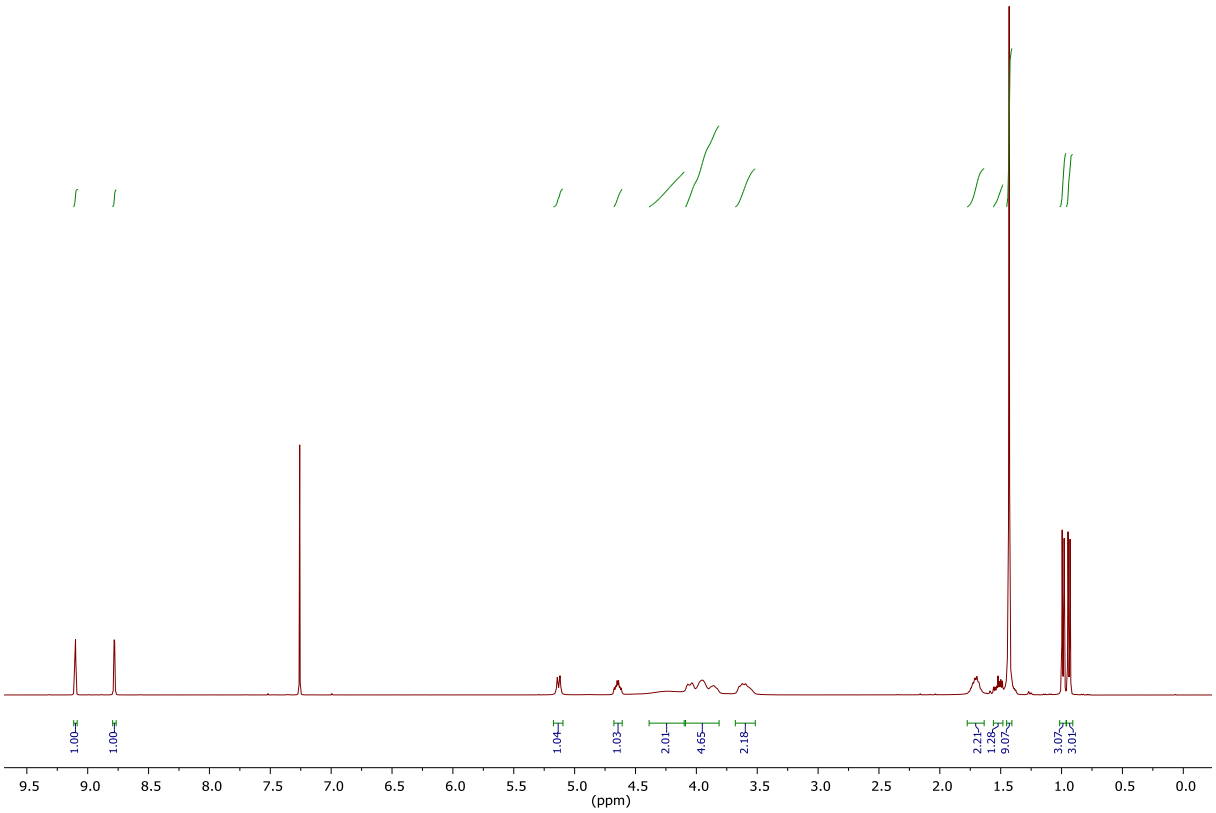


*Figure S6A ^{1}H-NMR (400 MHz) of **5c** in $CDCl_3$.*

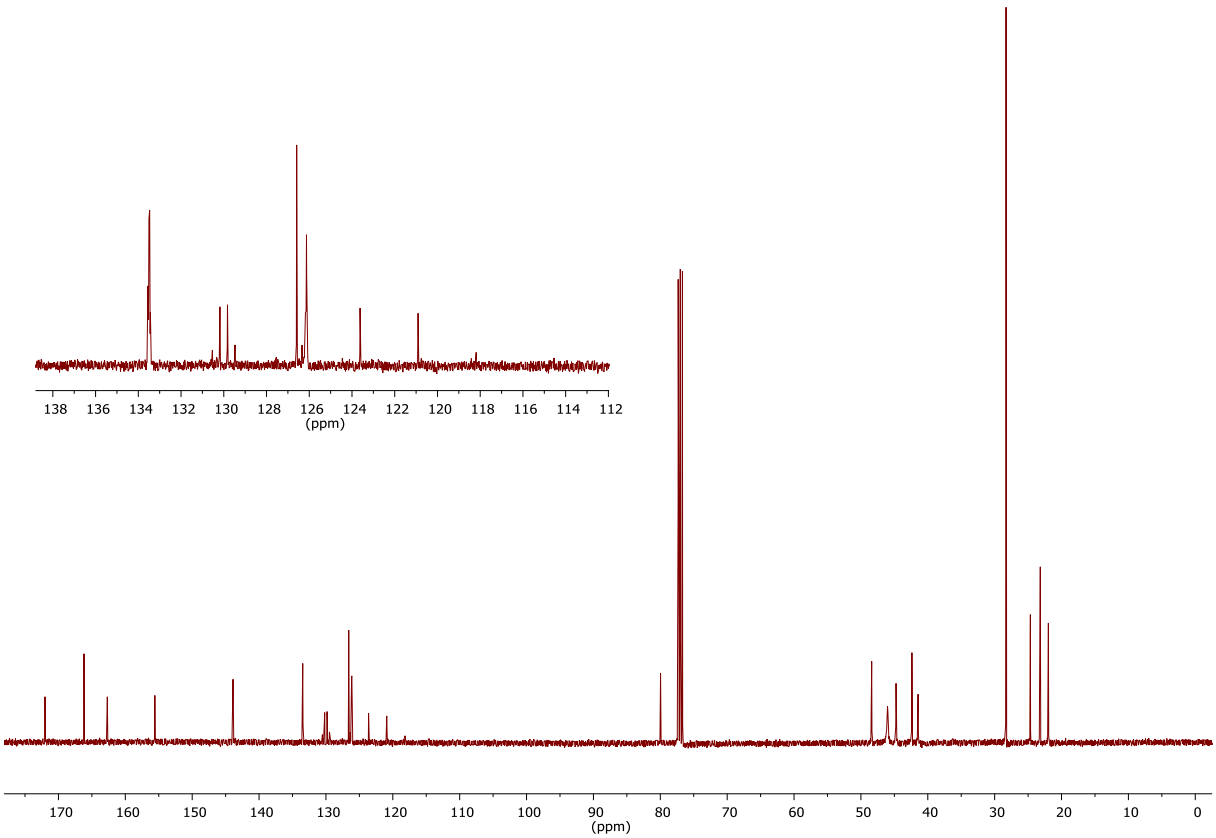
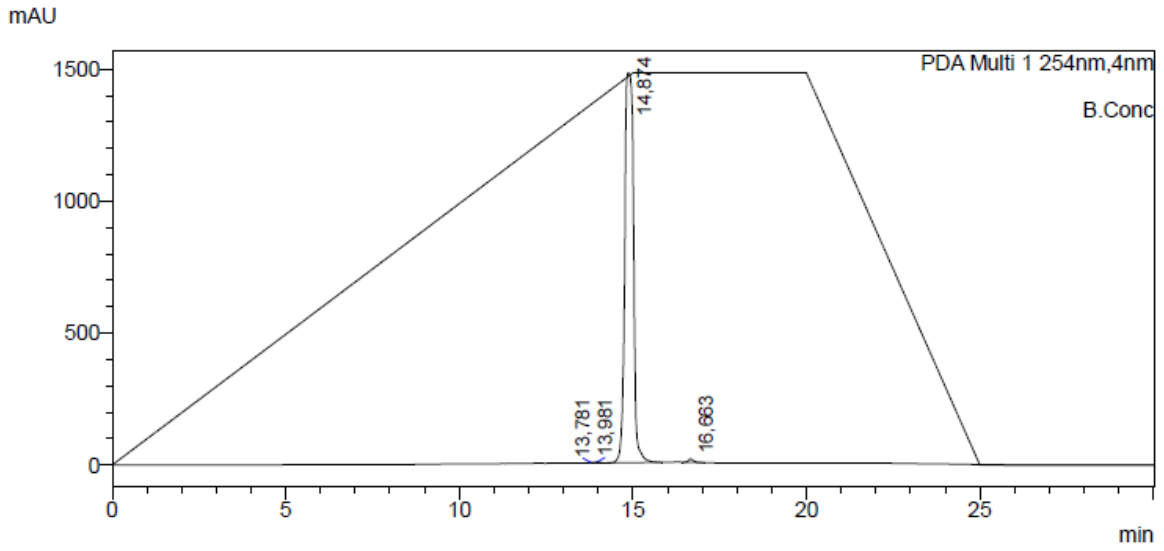


*Figure S6B ^{13}C-NMR (100 MHz) of **5c** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 24
Injection Volume	: 5
Data File	: AR160.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 01:02:29
Date Processed	: 18.05.2021 01:32:31



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	13,781	36919	2031	0,141
2	13,981	43633	4145	0,167
3	14,874	25935138	1477303	99,212
4	16,663	125320	12864	0,479
Total		26141011	1496343	100,000

*Figure S6C HPLC chromatogram of **5c**.*

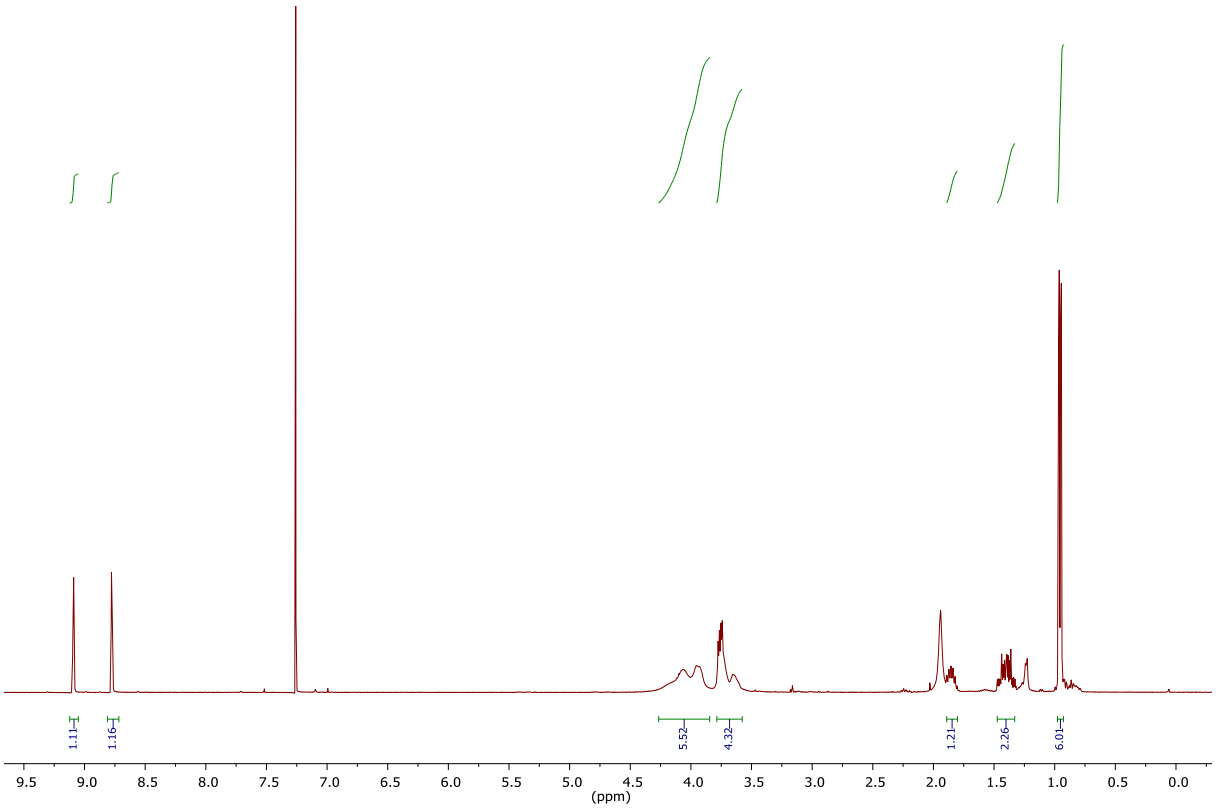


*Figure S7A ^{1}H-NMR (400 MHz) of **5d** in $CDCl_3$.*

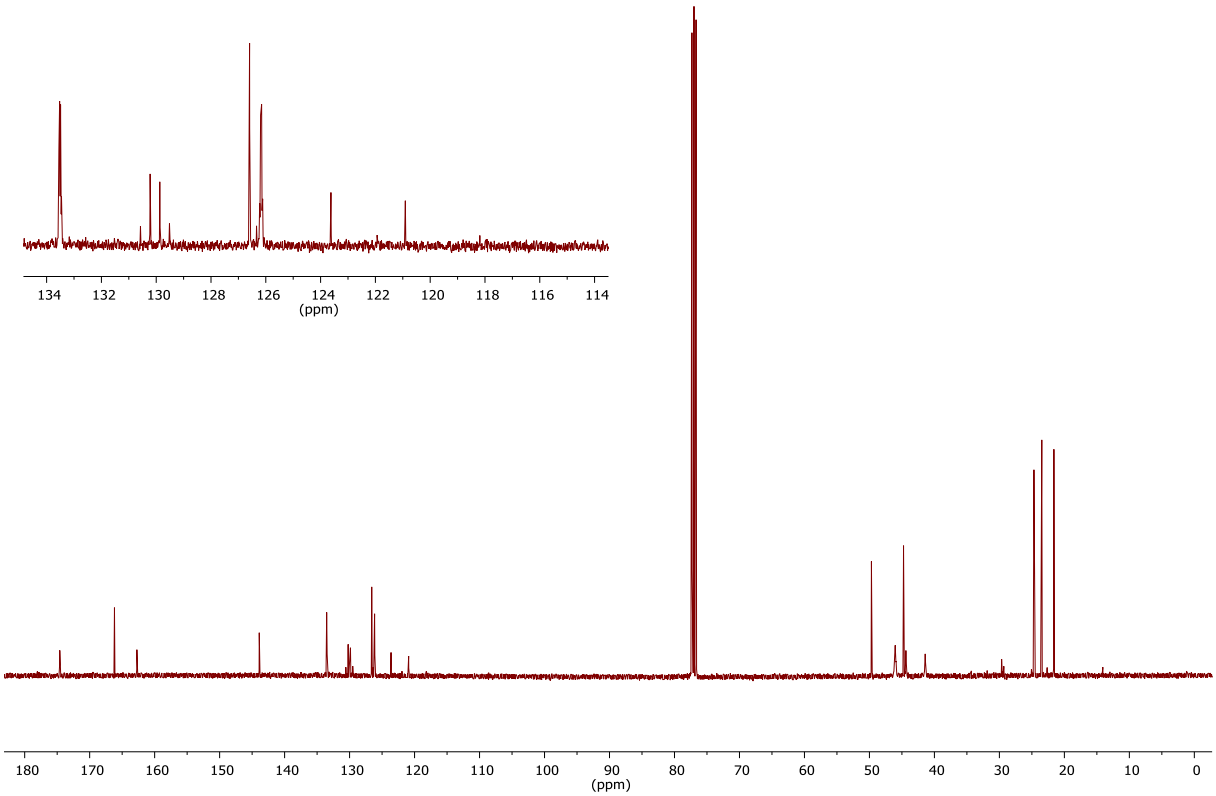
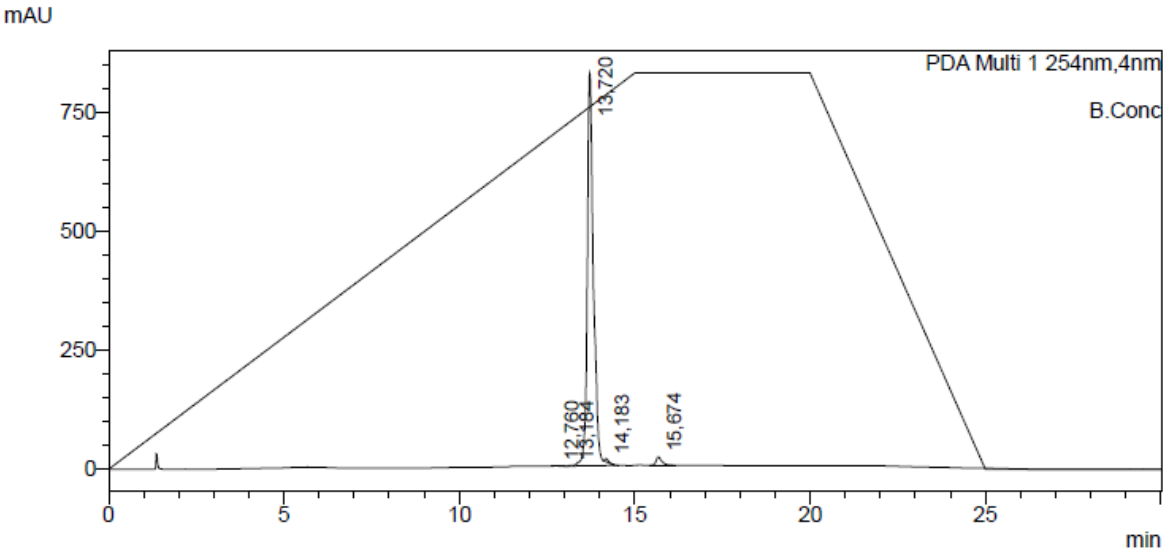


*Figure S7B ^{13}C-NMR (100 MHz) of **5d** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 2
Injection Volume	: 20
Data File	: AR 162.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch040621_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 04.06.2021 09:41:13
Date Processed	: 04.06.2021 10:11:15



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,760	10534	1338	0,101
2	13,184	14190	1370	0,137
3	13,720	10111887	824970	97,351
4	14,183	42583	6579	0,410
5	15,674	207835	17635	2,001
Total		10387029	851892	100,000

*Figure S7C HPLC chromatogram of **5d**.*

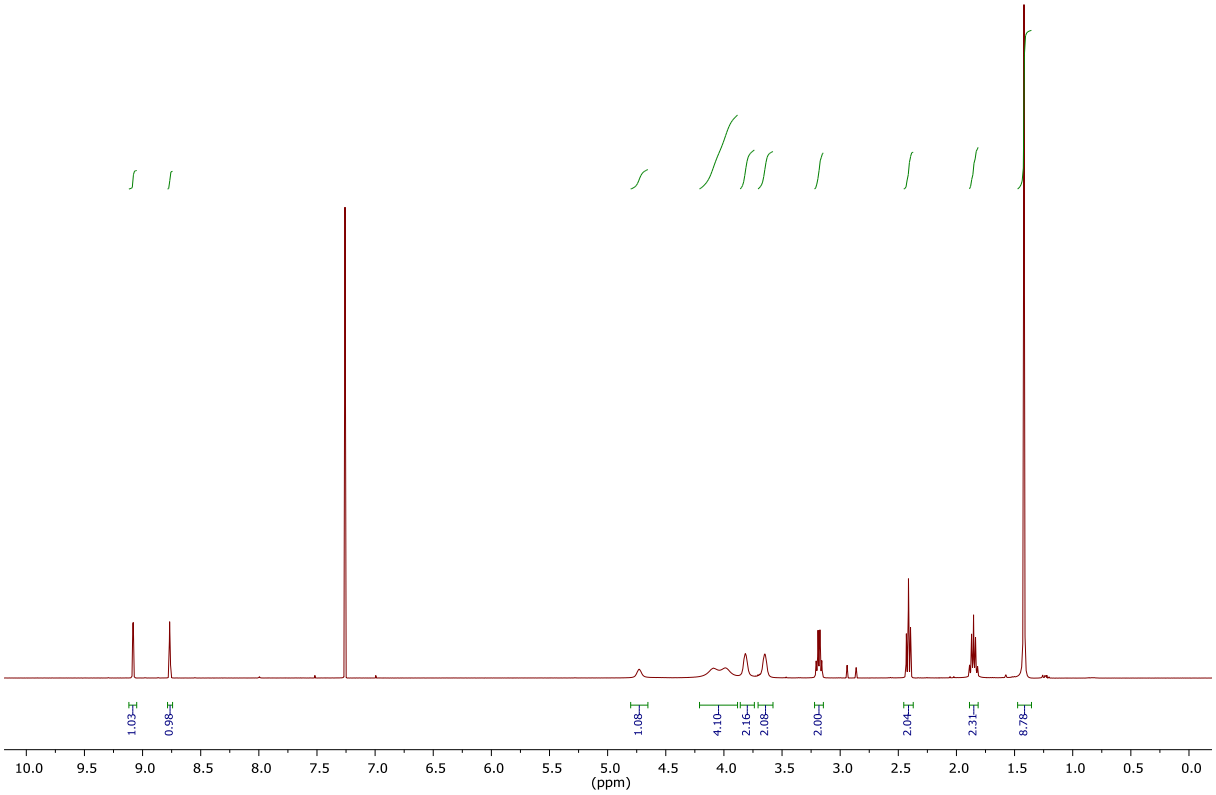


*Figure S8A ^{1}H-NMR (400 MHz) of **6d** in $CDCl_3$.*

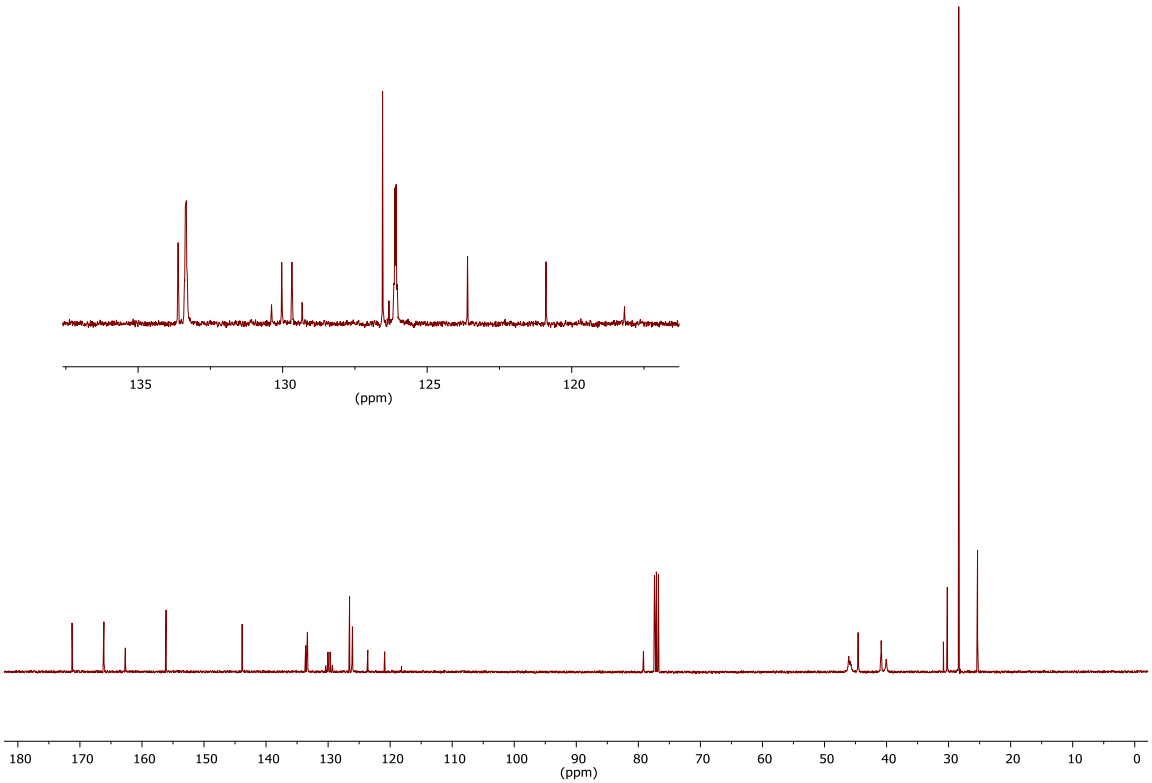
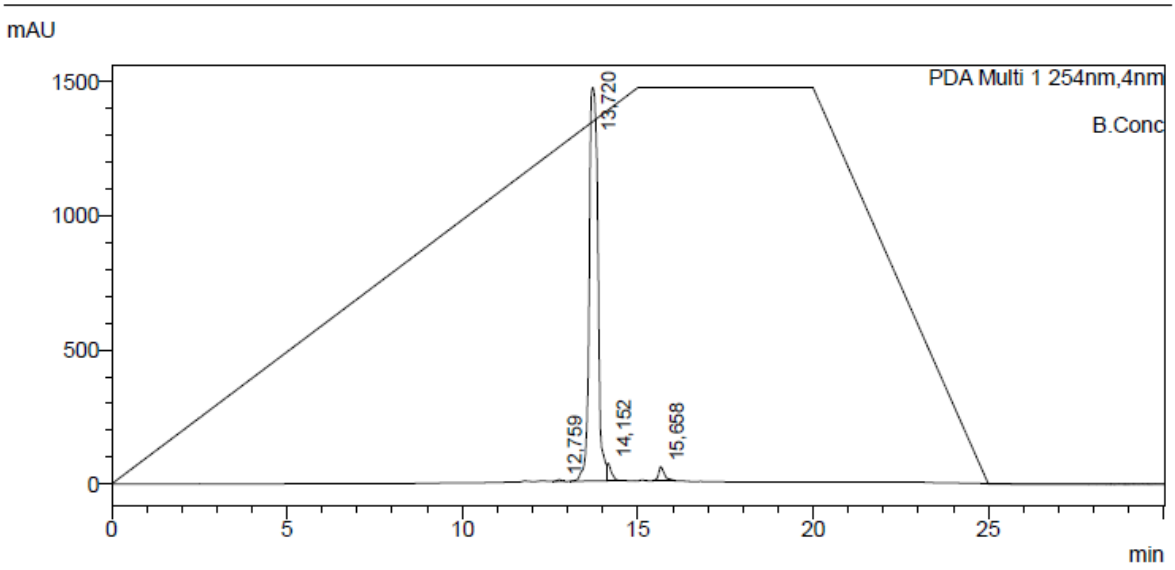


*Figure S8B ^{13}C-NMR (100 MHz) of **6d** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 16
Injection Volume	: 5
Data File	: AR164.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 20:58:20
Date Processed	: 17.05.2021 21:28:22



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,759	38977	4984	0,148
2	13,720	25128998	1464975	95,420
3	14,152	562009	64280	2,134
4	15,658	605033	51639	2,297
Total		26335017	1585878	100,000

*Figure S8C HPLC chromatogram of **6d**.*

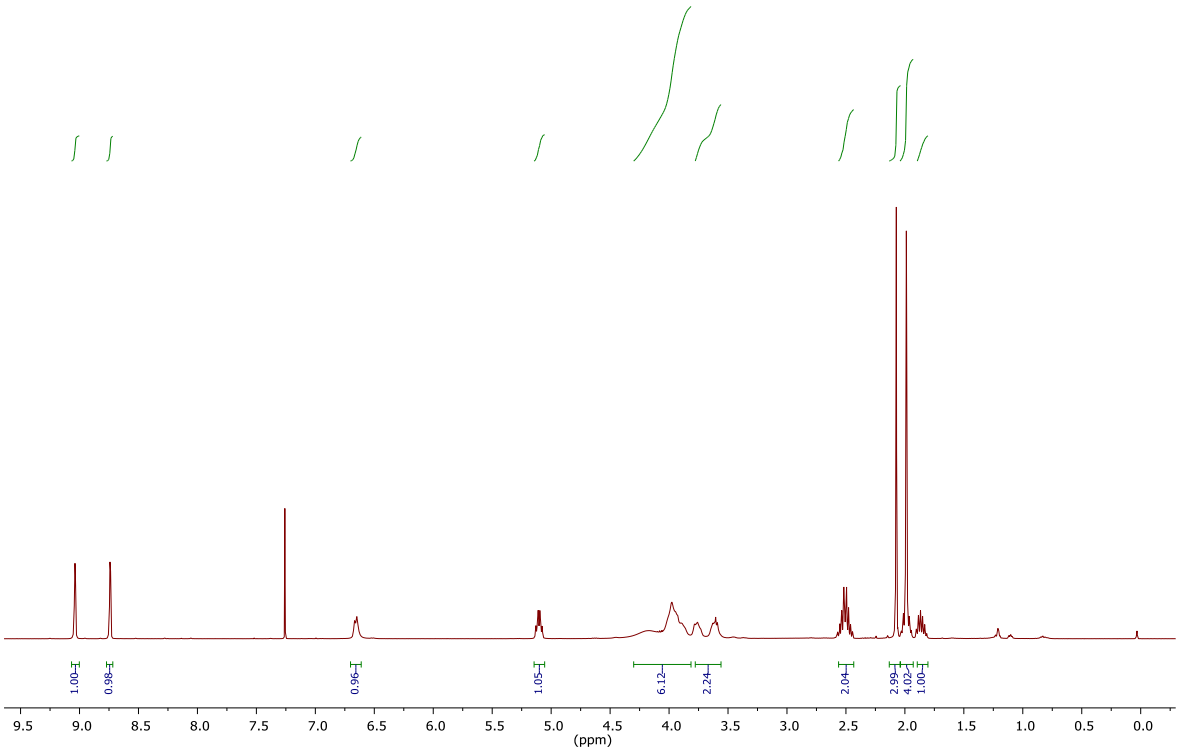


*Figure S9A [1]H-NMR (400 MHz) of **7c** in $CDCl_3$.*

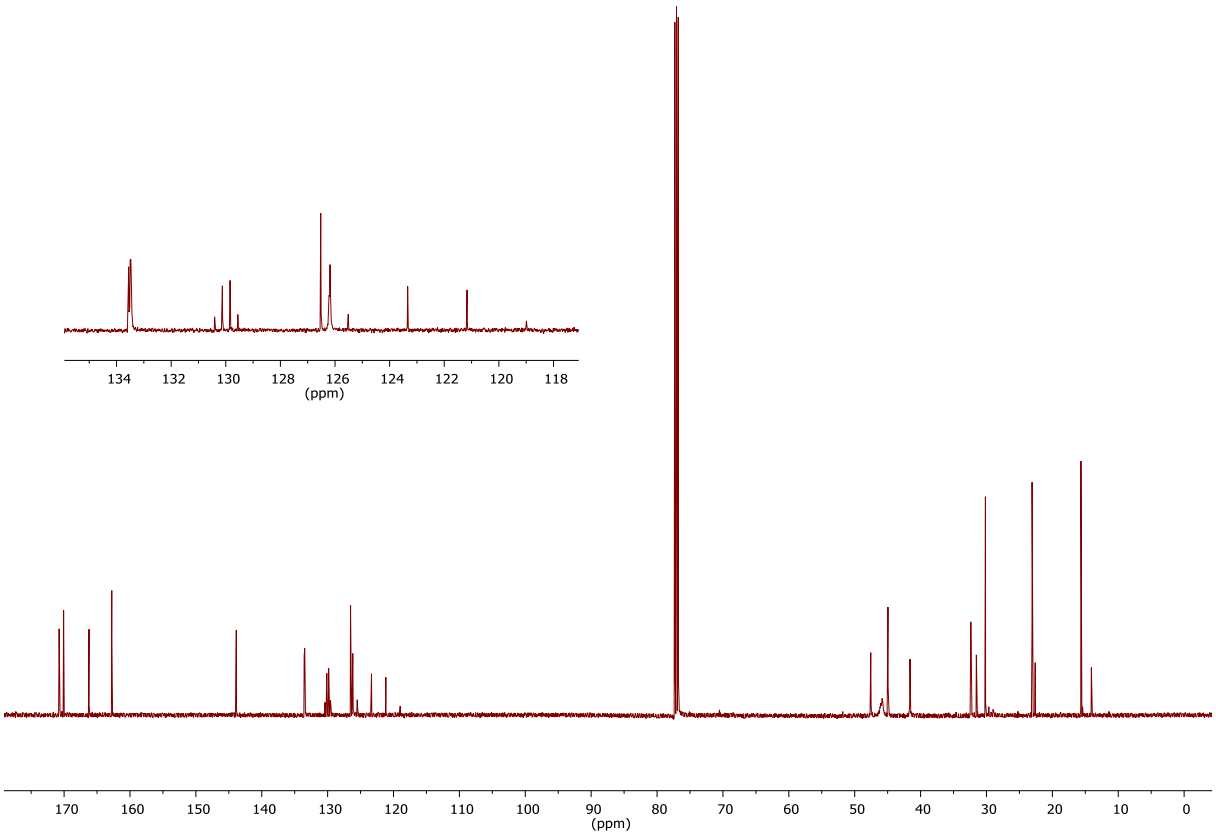
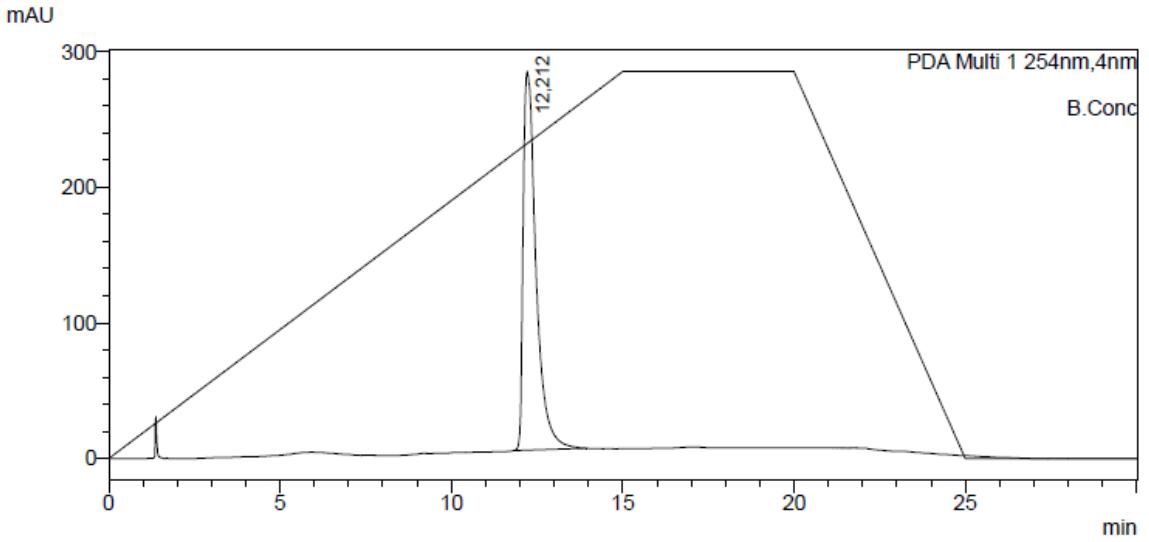


*Figure S9B [13]C-NMR (100 MHz) of **7c** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 3
Injection Volume	: 20
Data File	: AR 153_040621.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch040621_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 04.06.2021 08:09:39
Date Processed	: 04.06.2021 08:39:42



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,212	7298063	279211	100,000
Total		7298063	279211	100,000

*Figure S9C HPLC chromatogram of **7c**.*

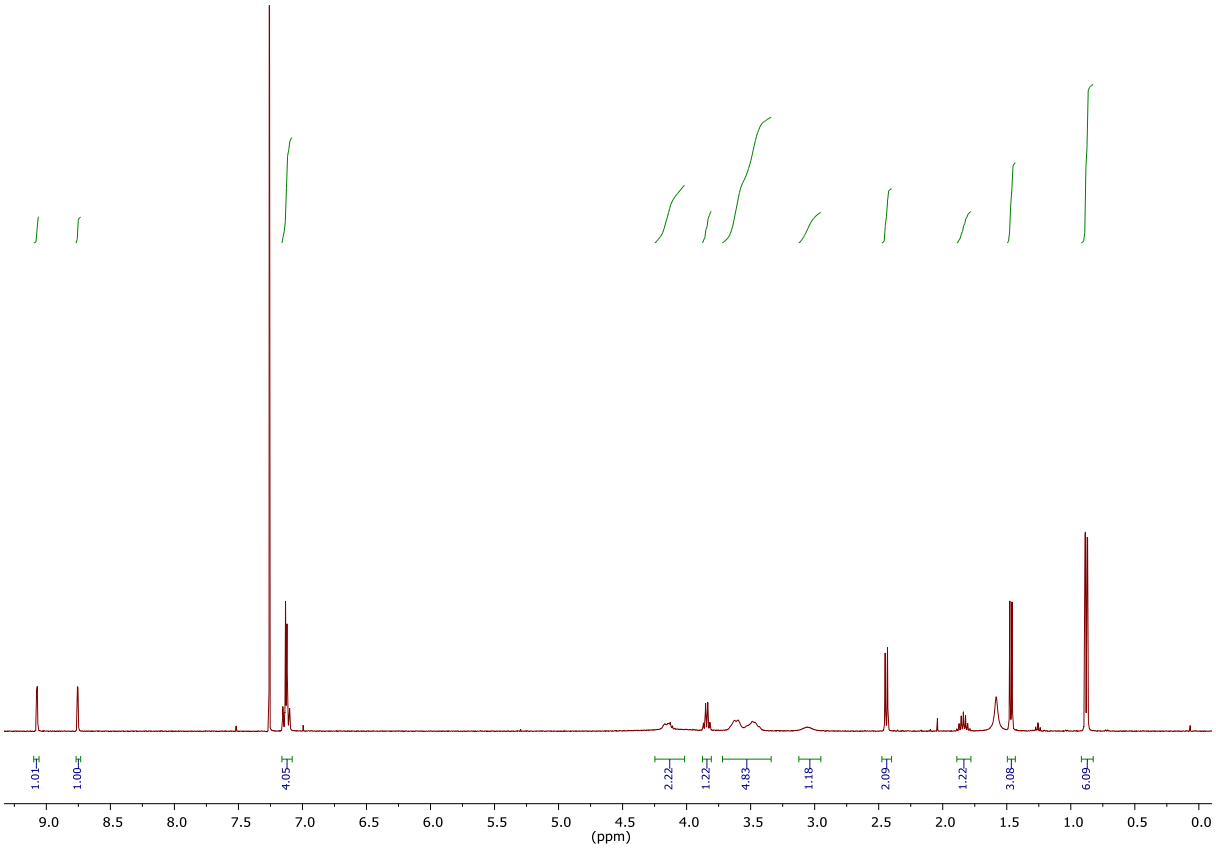


*Figure S10A [1]H-NMR (400 MHz) of **8c** in $CDCl_3$.*

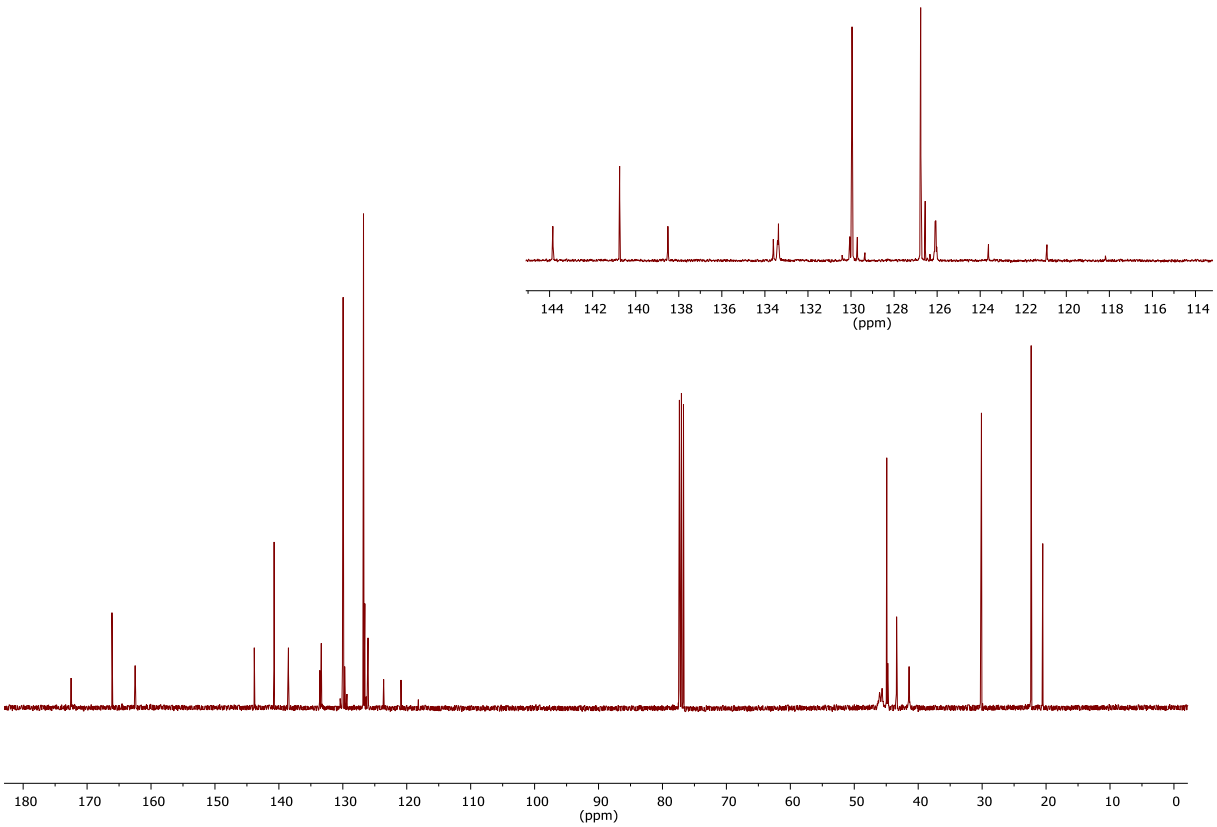
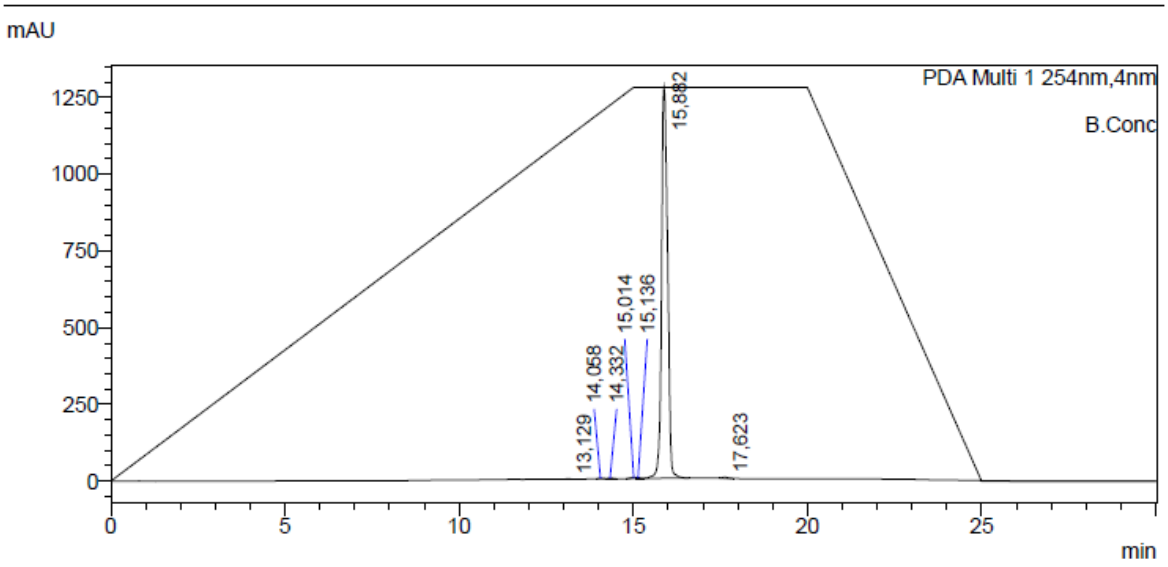


*Figure S10B [13]C-NMR (100 MHz) of **8c** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 25
Injection Volume	: 5
Data File	: AR168.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 01:33:00
Date Processed	: 18.05.2021 02:03:03



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	13,129	18827	1659	0,121
2	14,058	24230	2337	0,156
3	14,332	24993	2384	0,161
4	15,014	37622	4012	0,243
5	15,136	27282	3355	0,176
6	15,882	15338115	1272360	98,922
7	17,623	34198	3576	0,221
Total		15505267	1289683	100,000

*Figure S10C HPLC chromatogram of **8c**.*

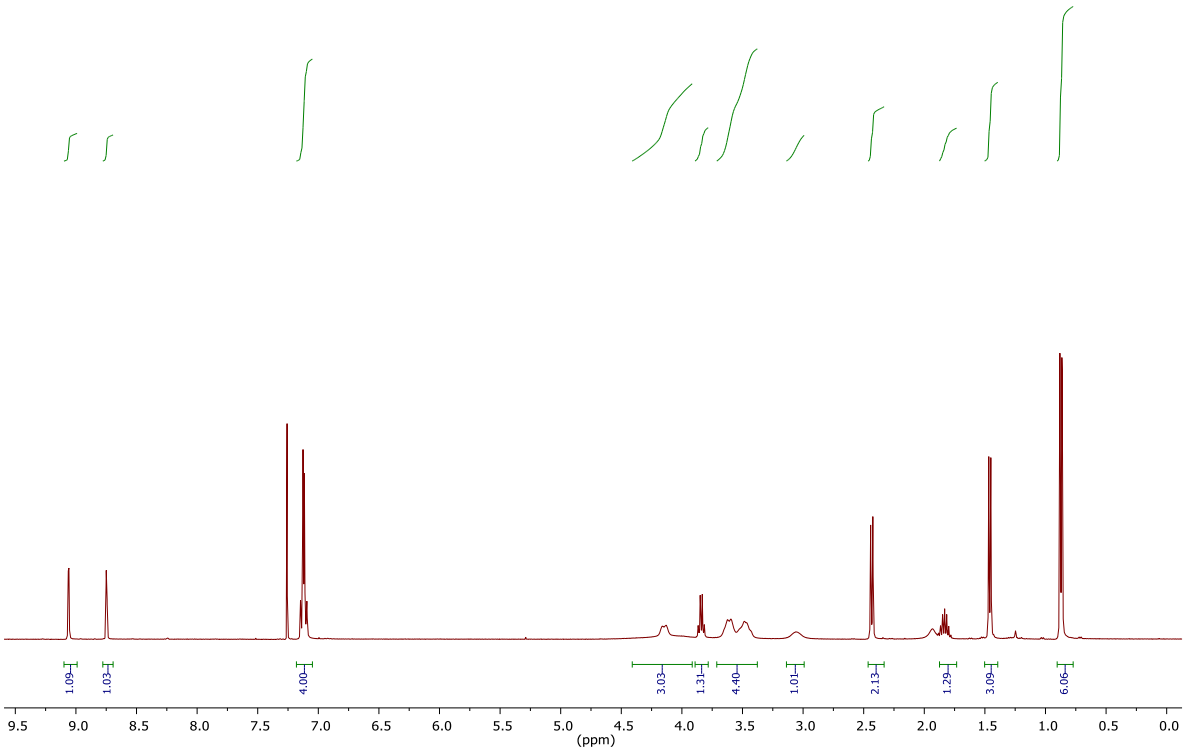


*Figure S11A [1]H-NMR (400 MHz) of **9a** in $CDCl_3$.*

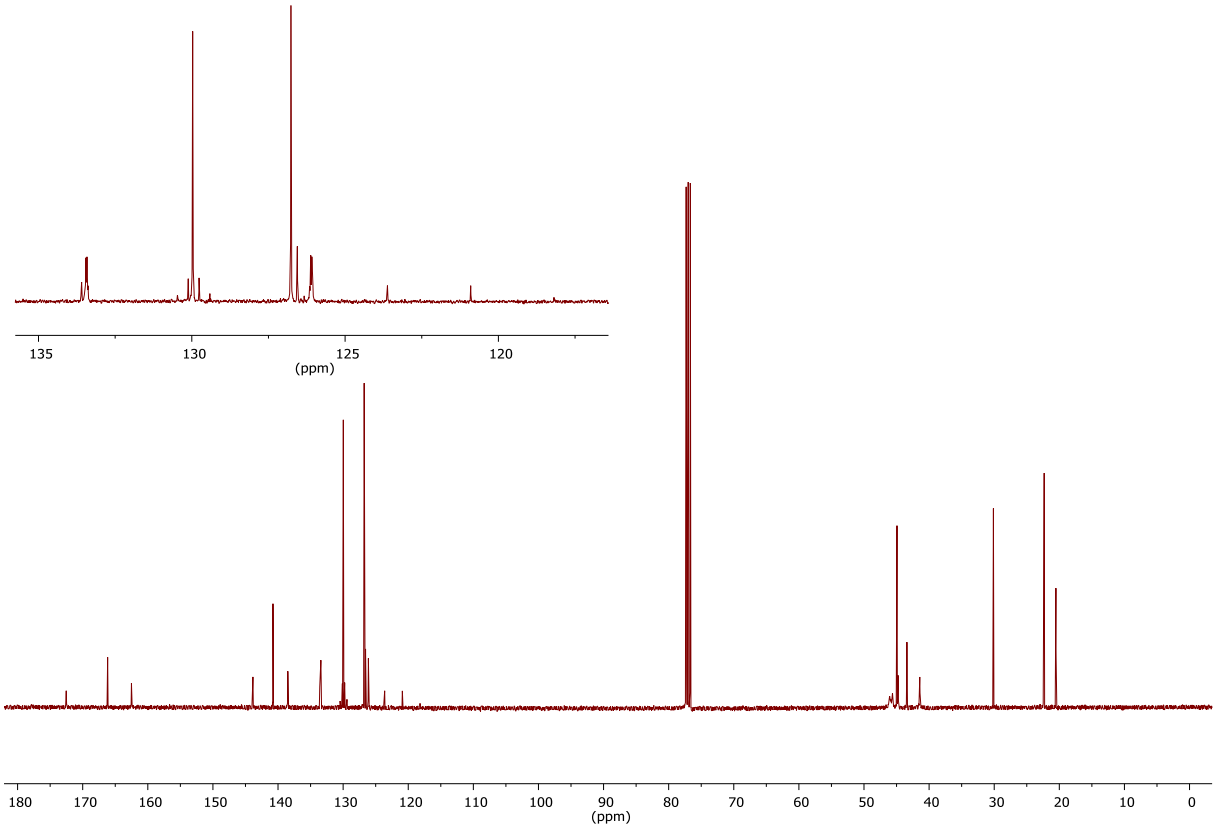
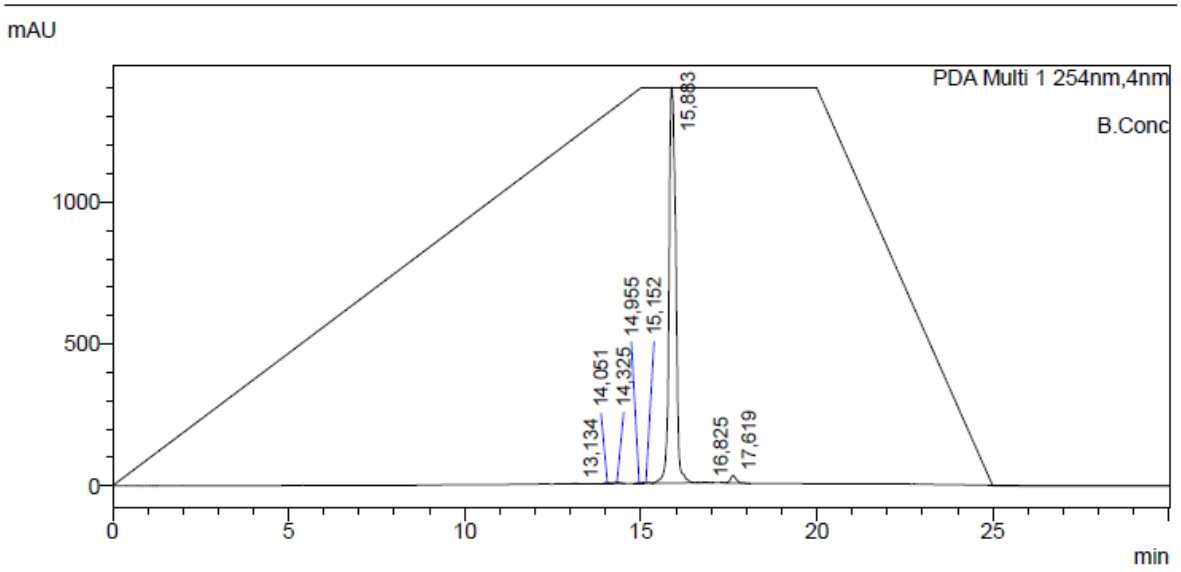


*Figure S11B [13]C-NMR (100 MHz) of **9a** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 26
Injection Volume	: 5
Data File	: AR212.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 02:03:33
Date Processed	: 18.05.2021 02:33:36



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	13,134	27386	2550	0,144
2	14,051	45016	4063	0,236
3	14,325	53819	5441	0,282
4	14,955	21414	2035	0,112
5	15,152	30845	2878	0,162
6	15,883	18562379	1391444	97,402
7	16,825	21439	1538	0,112
8	17,619	295253	26573	1,549
Total		19057552	1436521	100,000

*Figure S11C HPLC chromatogram of **9a**.*

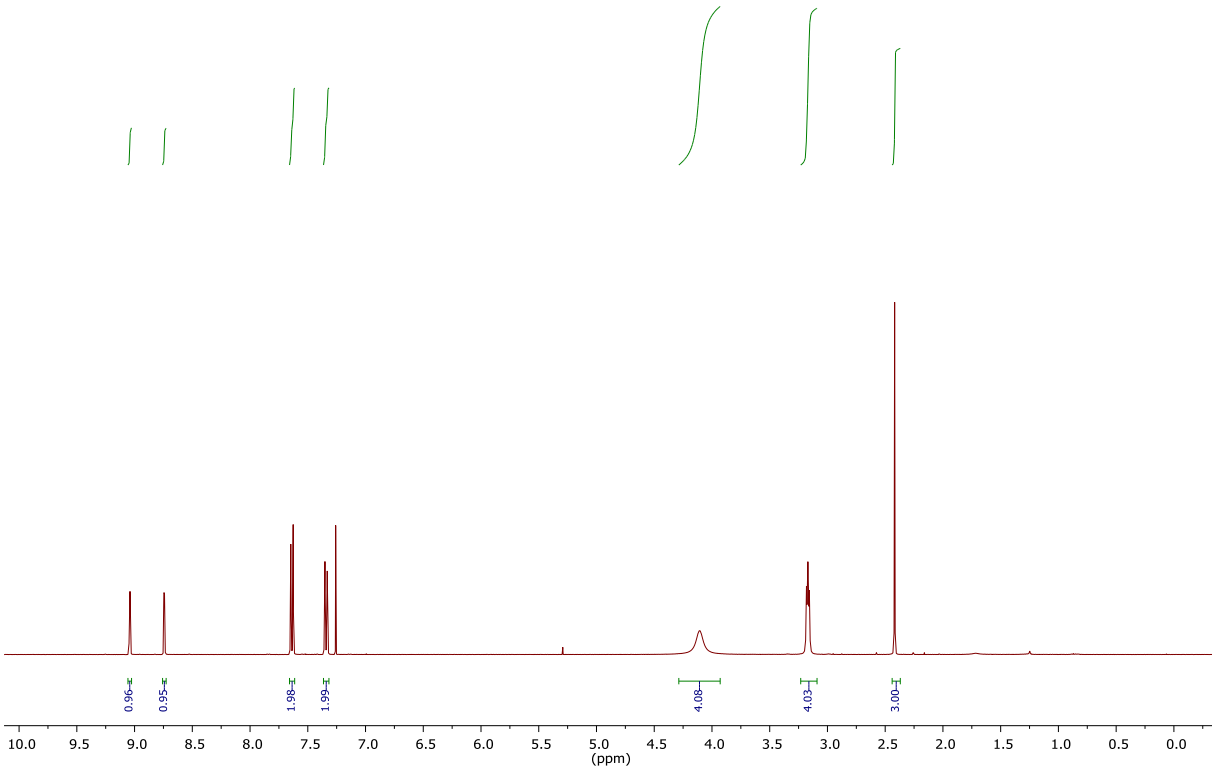


*Figure S12A [1]H-NMR (400 MHz) of **10c** in $CDCl_3$.*

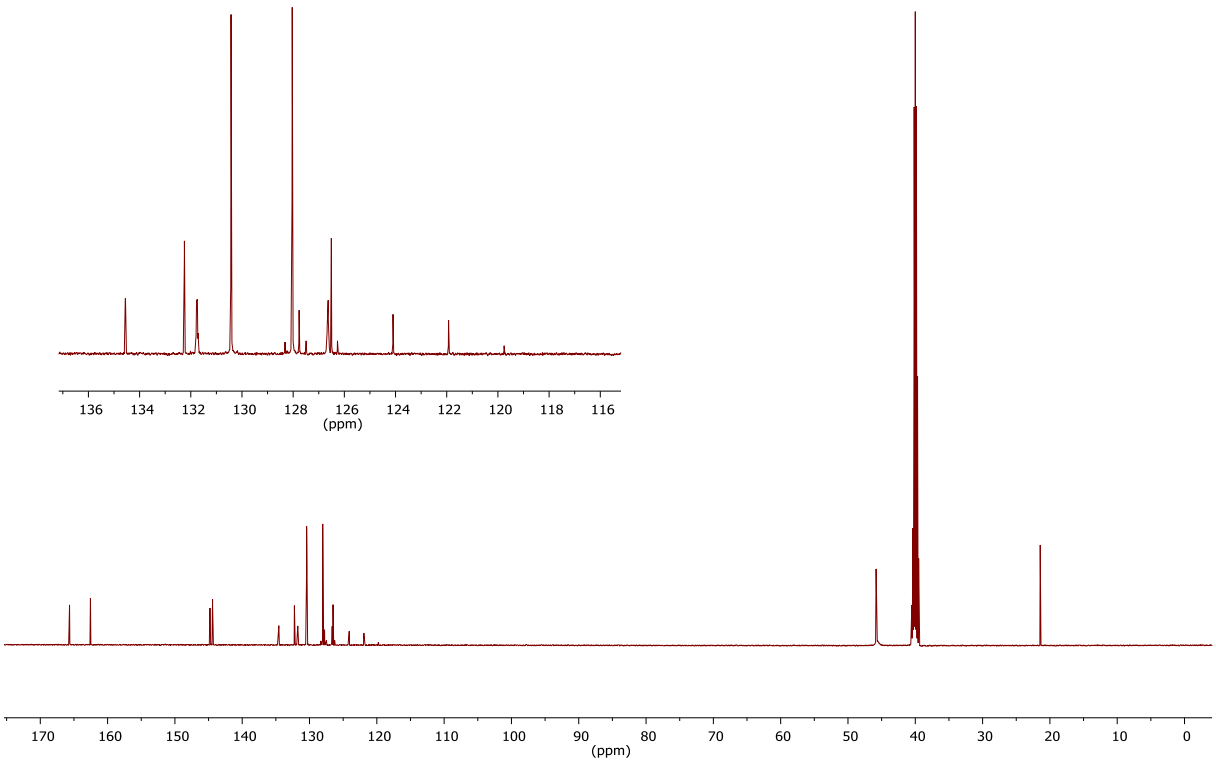
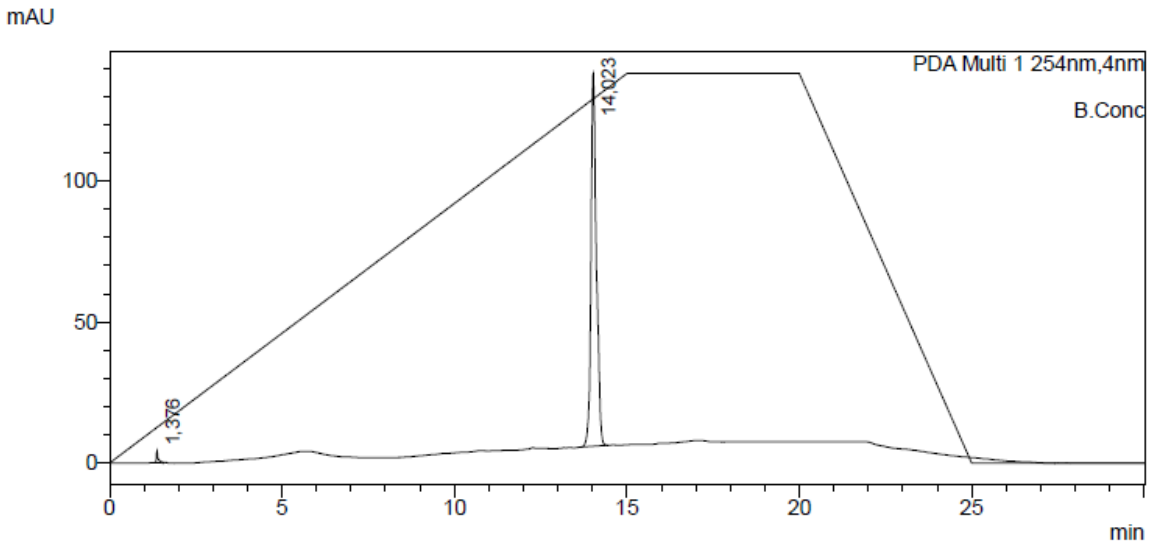


*Figure S13B [13]C-NMR (100 MHz) of **10c** in DMSO-d_6.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 8
Injection Volume	: 10
Data File	: AR172_200521.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch190521_1.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 20.05.2021 23:01:05
Date Processed	: 20.05.2021 23:31:07



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	1,376	16338	4169	1,120
2	14,023	1442010	132279	98,880
Total		1458347	136448	100,000

*Figure S12C HPLC chromatogram of **10c**.*

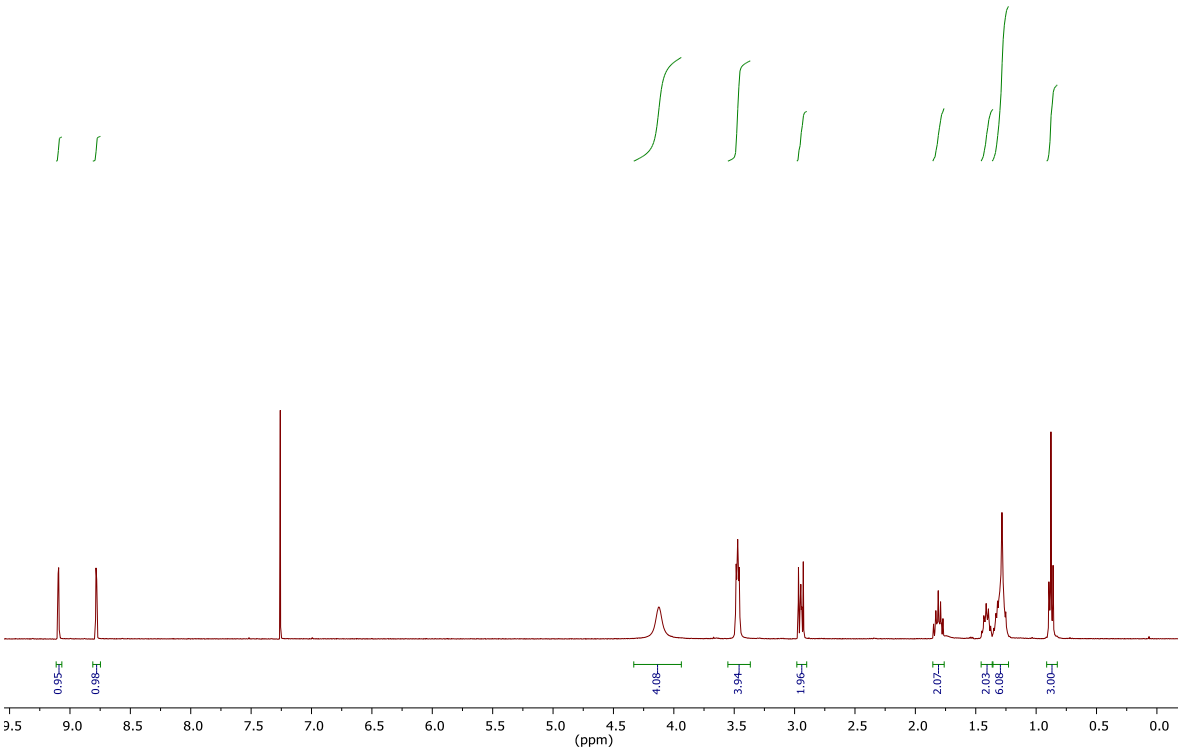


*Figure S13A [1]H-NMR (400 MHz) of **11c** in $CDCl_3$.*

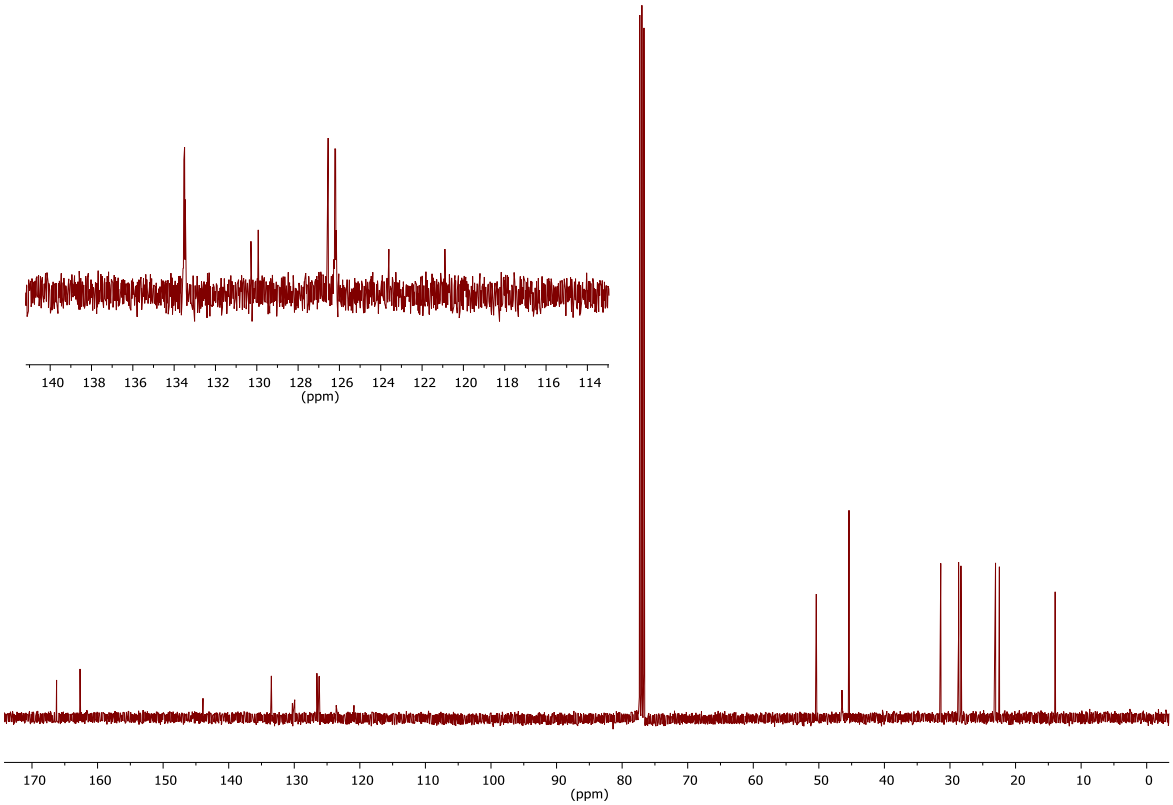
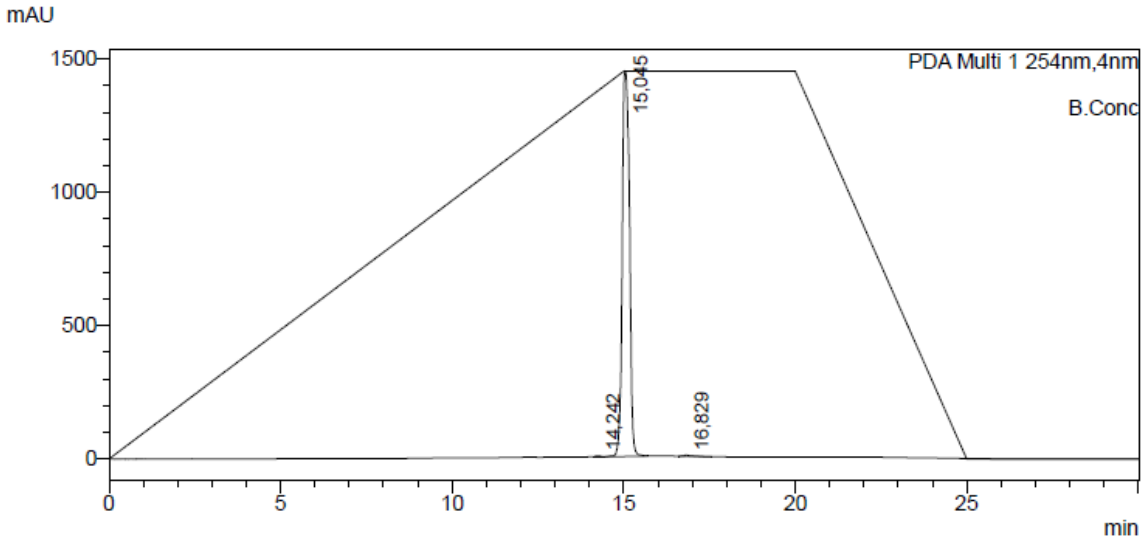


*Figure S13B [13]C-NMR (100 MHz) of **11c** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 13
Injection Volume	: 5
Data File	: AR175.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 19:26:45
Date Processed	: 17.05.2021 19:56:47



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	14,242	39777	4002	0,186
2	15,045	21242103	1444526	99,493
3	16,829	68525	4440	0,321
Total		21350405	1452968	100,000

*Figure S13C HPLC chromatogram of **11c**.*

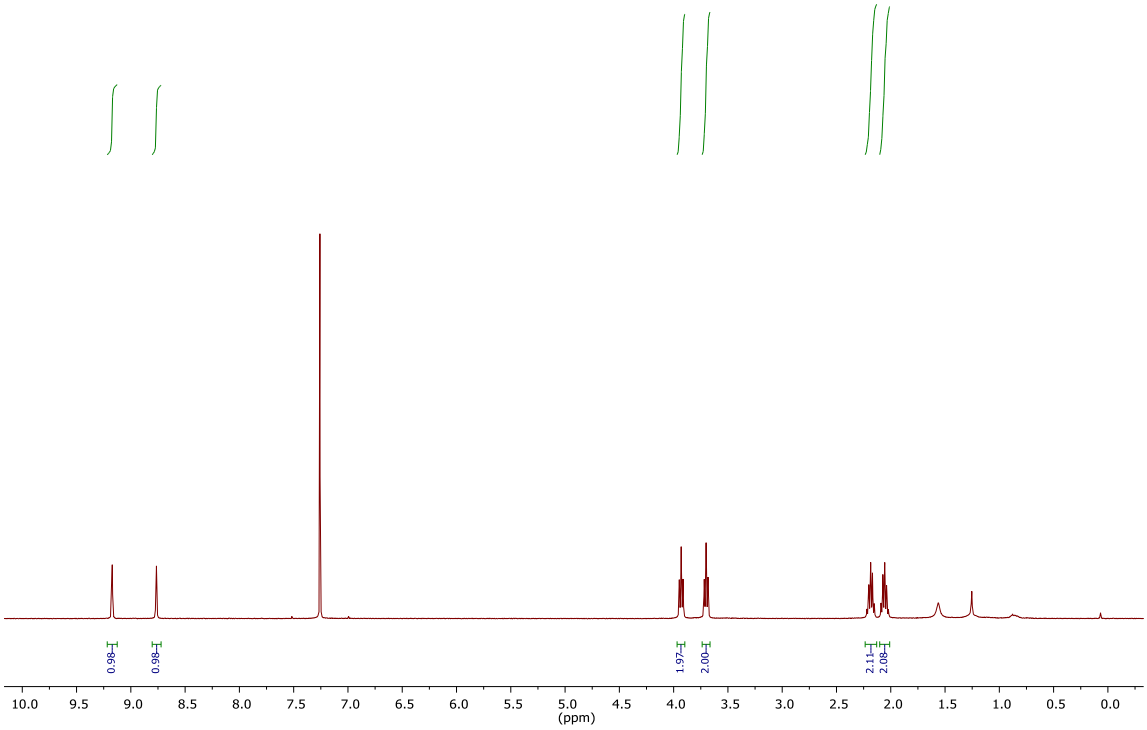


*Figure S14A [1]H-NMR (400 MHz) of **12b** in $CDCl_3$.*

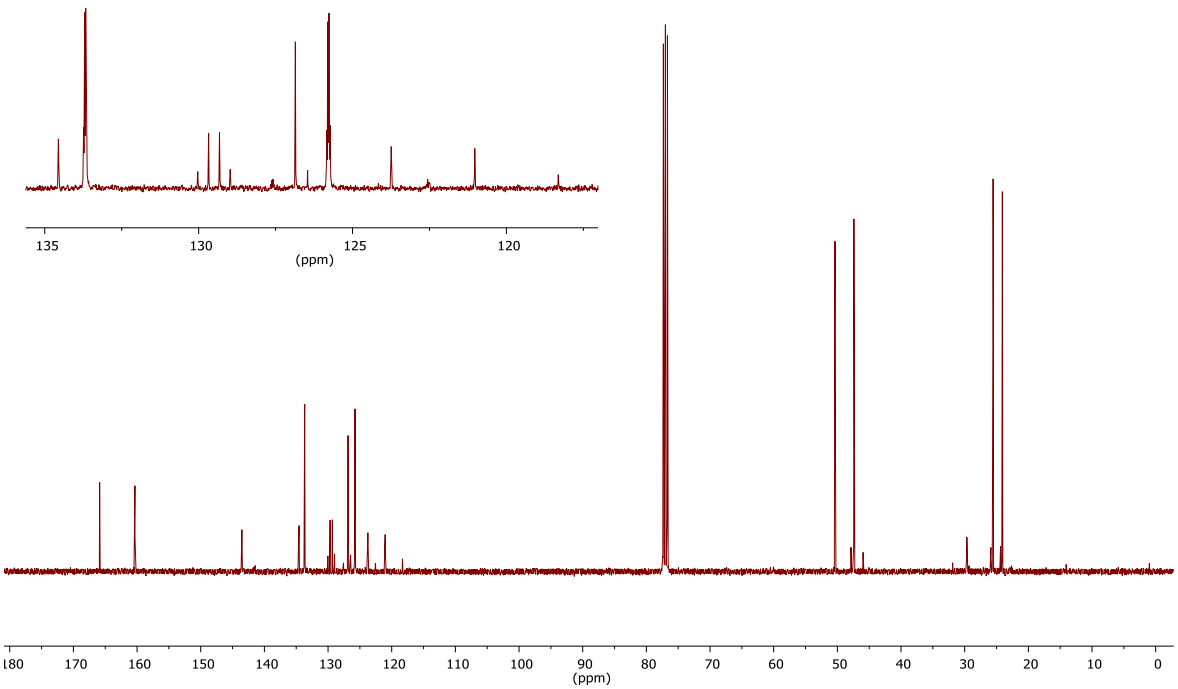
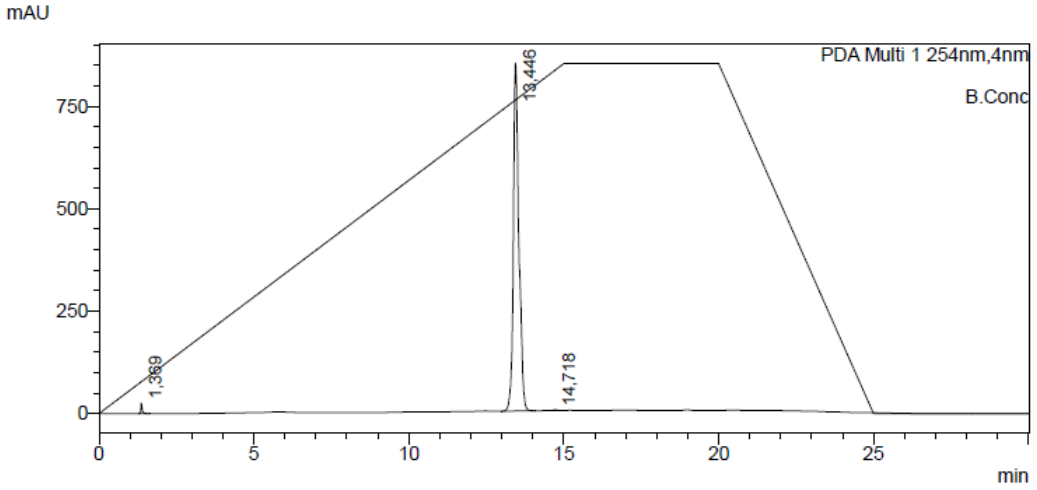


*Figure S14B [13]C-NMR (100 MHz) of **12b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 9
Injection Volume	: 20
Data File	: IF265_250521.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch250521_1.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 25.05.2021 17:41:22
Date Processed	: 25.05.2021 18:11:24



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	1,369	80183	24783	0,754
2	13,446	10535814	847120	99,129
3	14,718	12443	1375	0,117
Total		10628440	873277	100,000

Figure S14C HPLC chromatogram of ***12b****.*

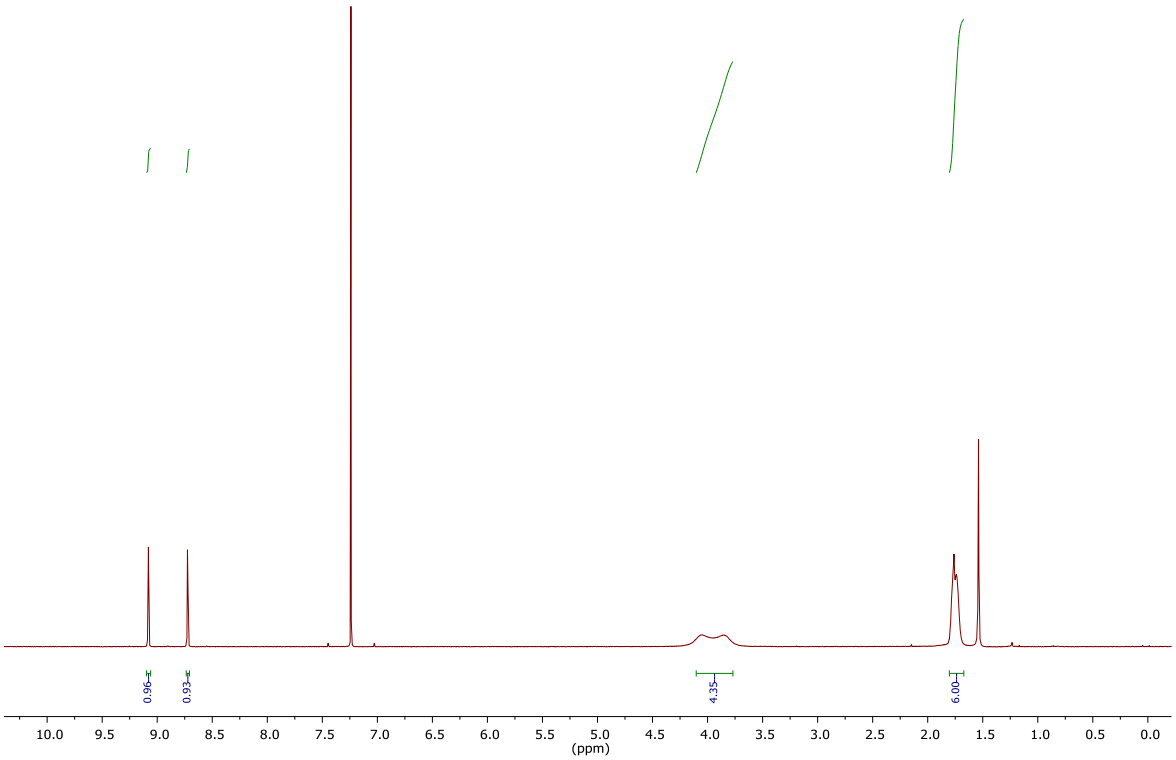


*Figure S15A ^{1}H-NMR (400 MHz) of **13b** in $CDCl_3$.*

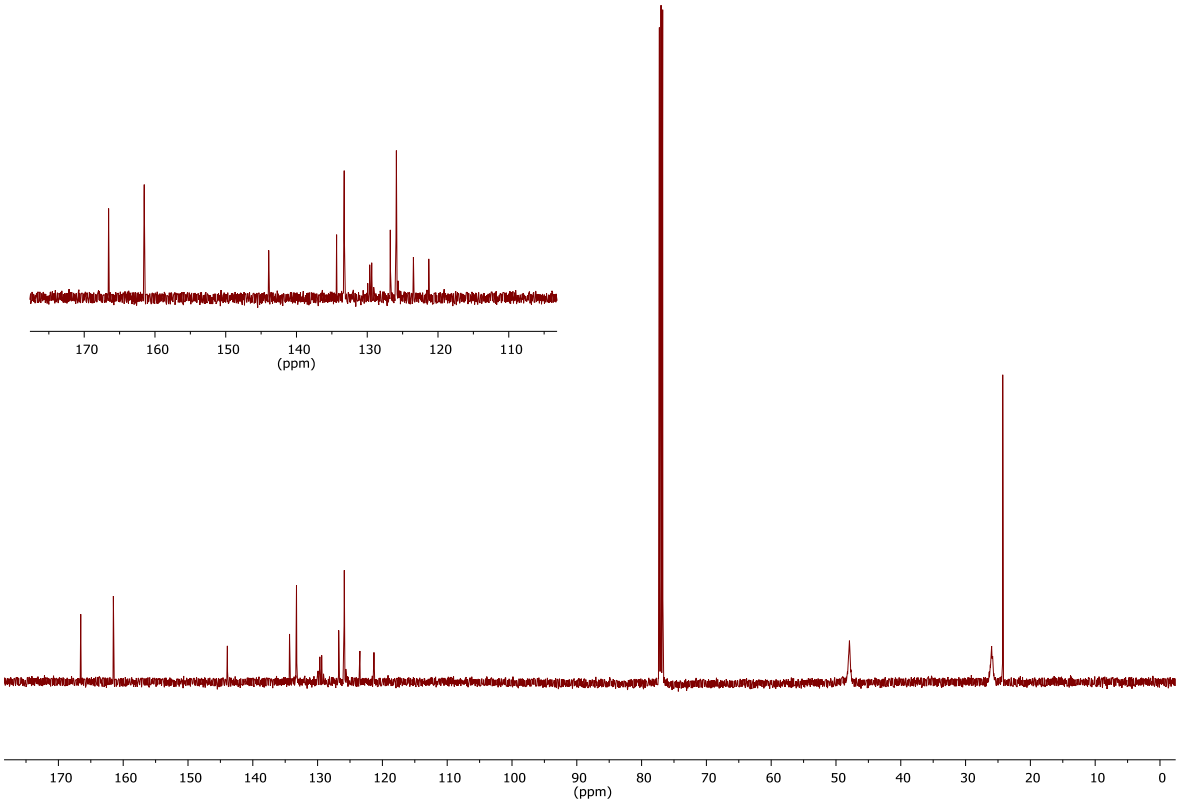
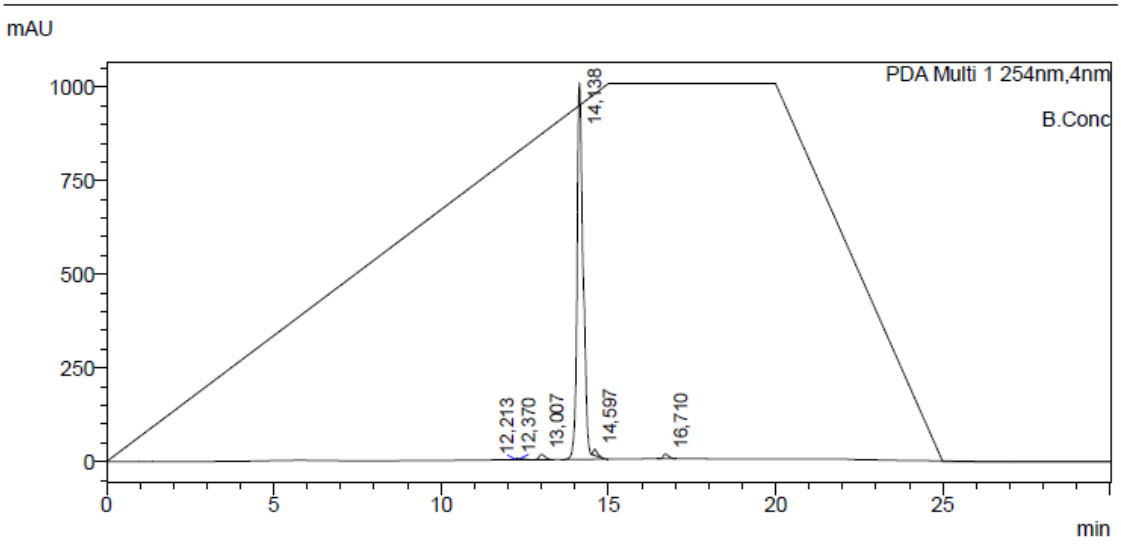


*Figure S15B ^{13}C-NMR (100 MHz) of **13b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 2
Injection Volume	: 5
Data File	: AR187_WDH.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch190521_1.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 20.05.2021 08:46:10
Date Processed	: 20.05.2021 09:16:13



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,213	19637	2290	0,147
2	12,370	45595	3613	0,341
3	13,007	169252	14284	1,265
4	14,138	12873608	1002787	96,201
5	14,597	139113	15998	1,040
6	16,710	134757	12511	1,007
Total		13381962	1051483	100,000

*Figure S15C HPLC chromatogram of **13b**.*

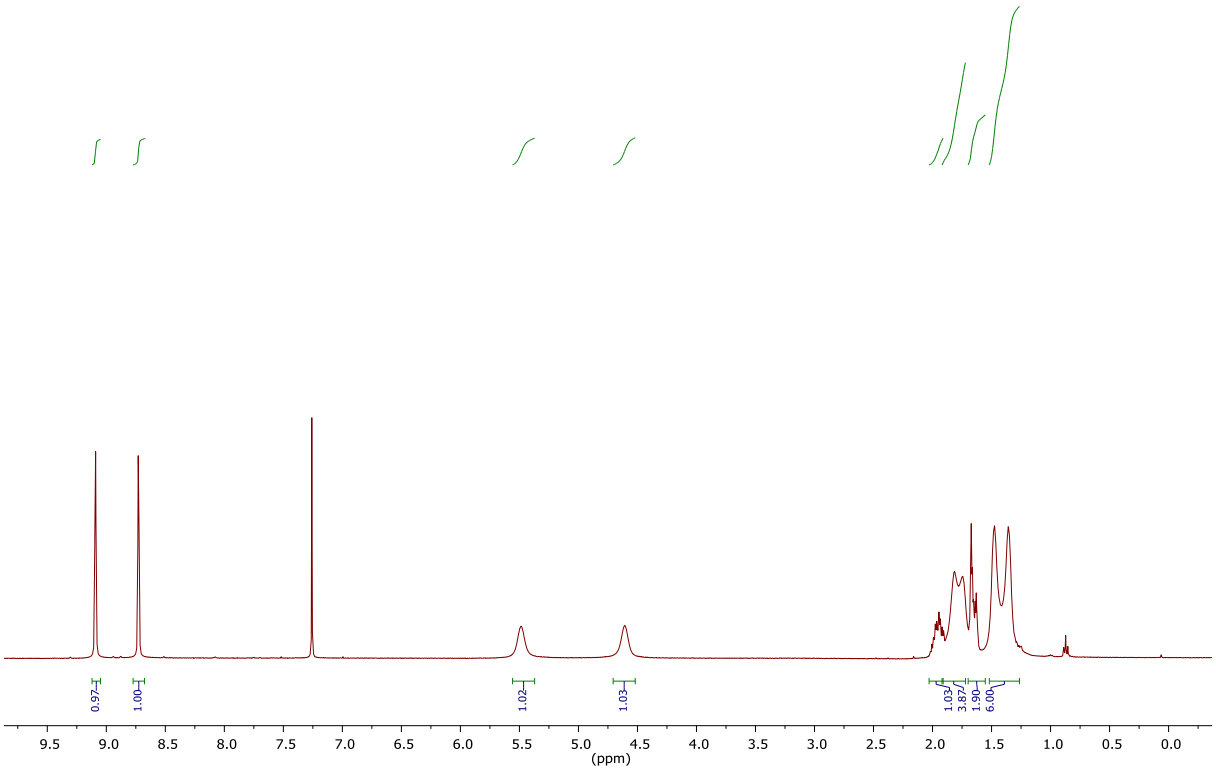


*Figure S16A ^{1}H-NMR (400 MHz) of **14a** in $CDCl_3$.*

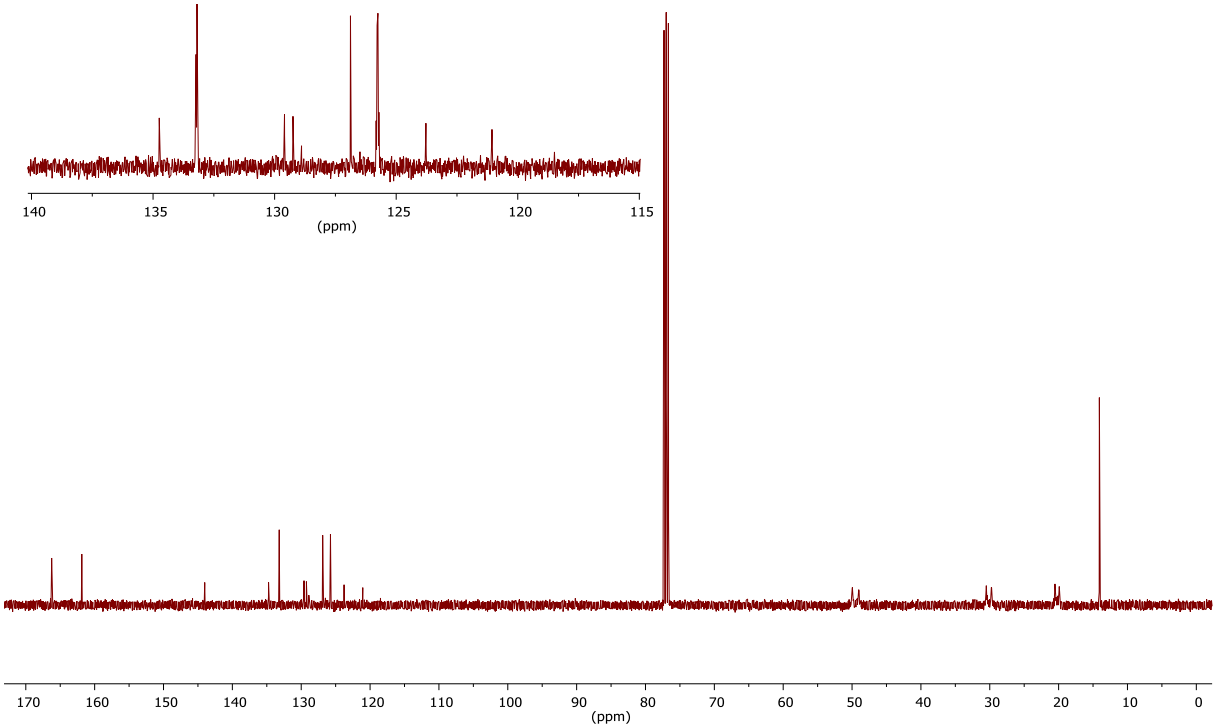
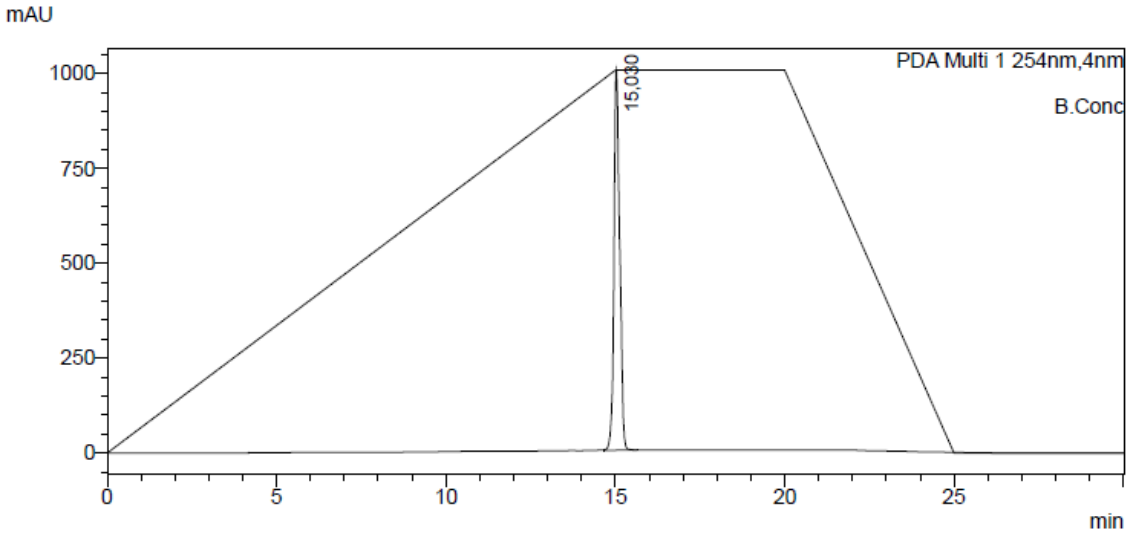


*Figure S16B ^{13}C-NMR (100 MHz) of **14a** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 23
Injection Volume	: 5
Data File	: AR120.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 00:31:57
Date Processed	: 18.05.2021 01:02:00



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	15,030	11795376	1000470	100,000
Total		11795376	1000470	100,000

*Figure S16C HPLC chromatogram of **14a**.*

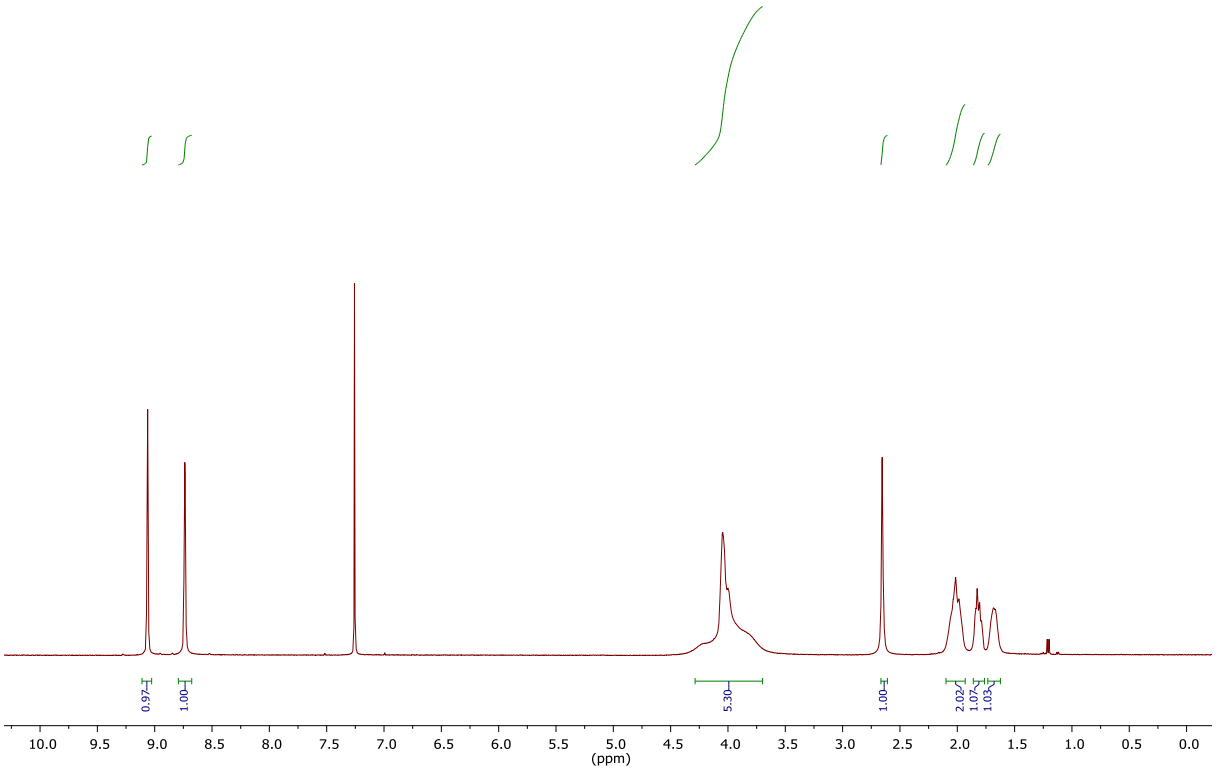


*Figure S17A ^{1}H-NMR (400 MHz) of **15b** in $CDCl_3$.*

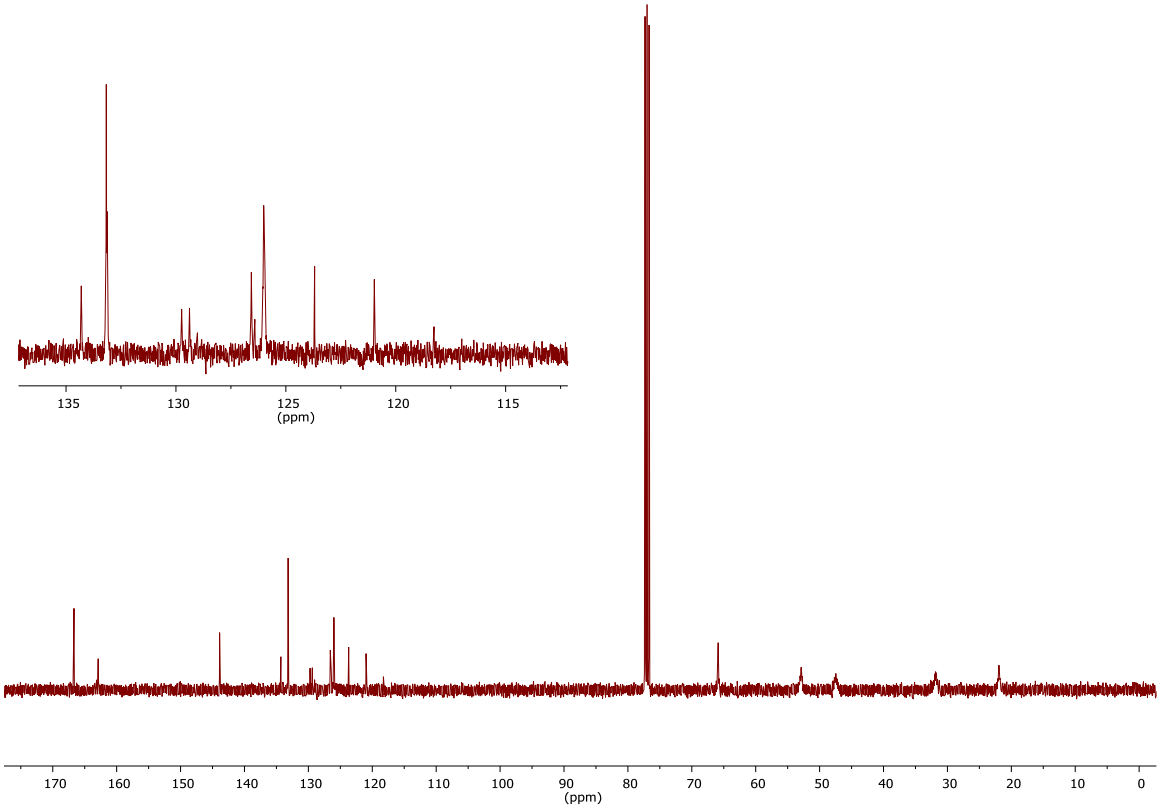
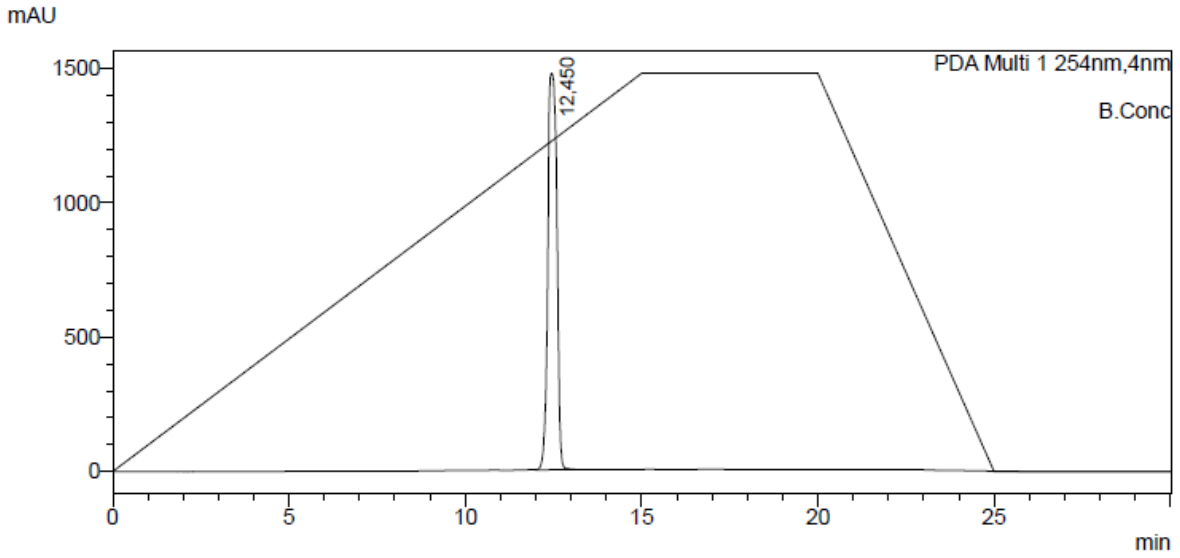


*Figure S17B ^{13}C-NMR (100 MHz) of **15b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 6
Injection Volume	: 5
Data File	: AR110.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 15:53:00
Date Processed	: 17.05.2021 16:23:02



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,450	26349511	1475139	100,000
Total		26349511	1475139	100,000

*Figure S17C HPLC chromatogram of **15b**.*

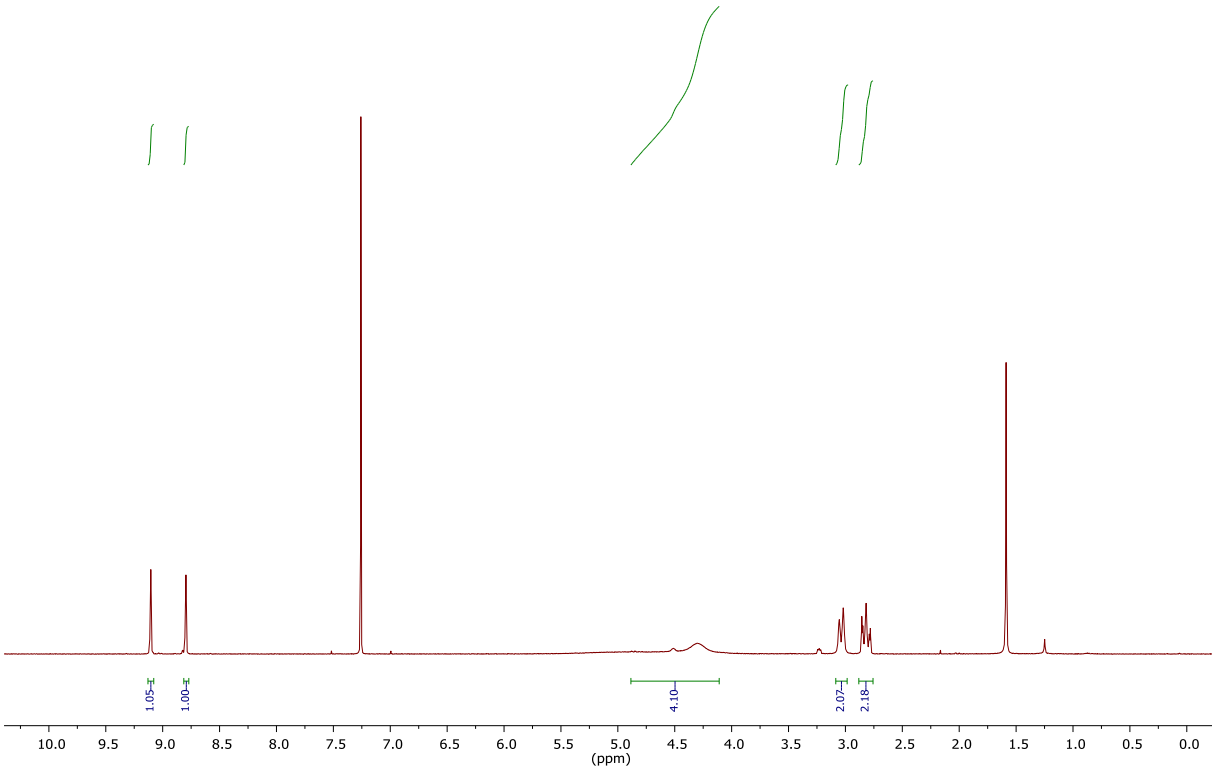


*Figure S18A ^{1}H-NMR (400 MHz) of **16c** in $CDCl_3$.*

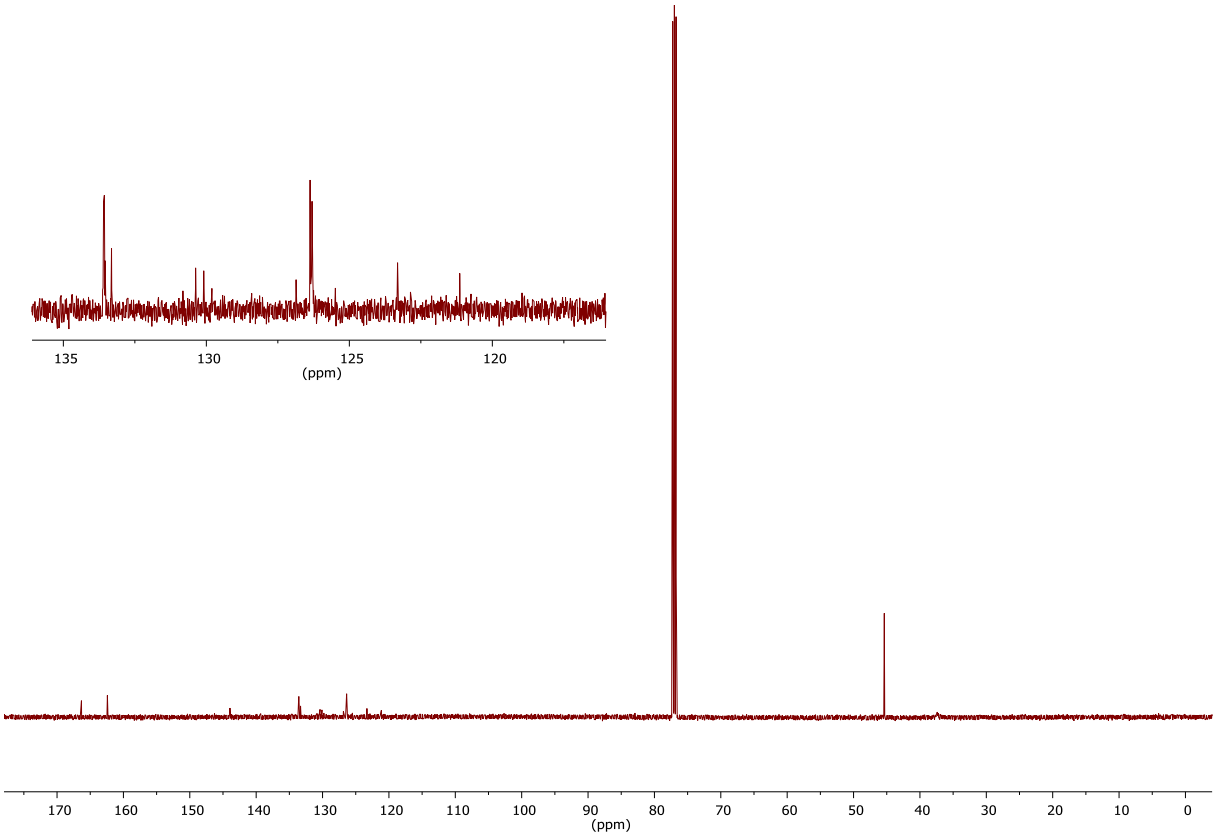
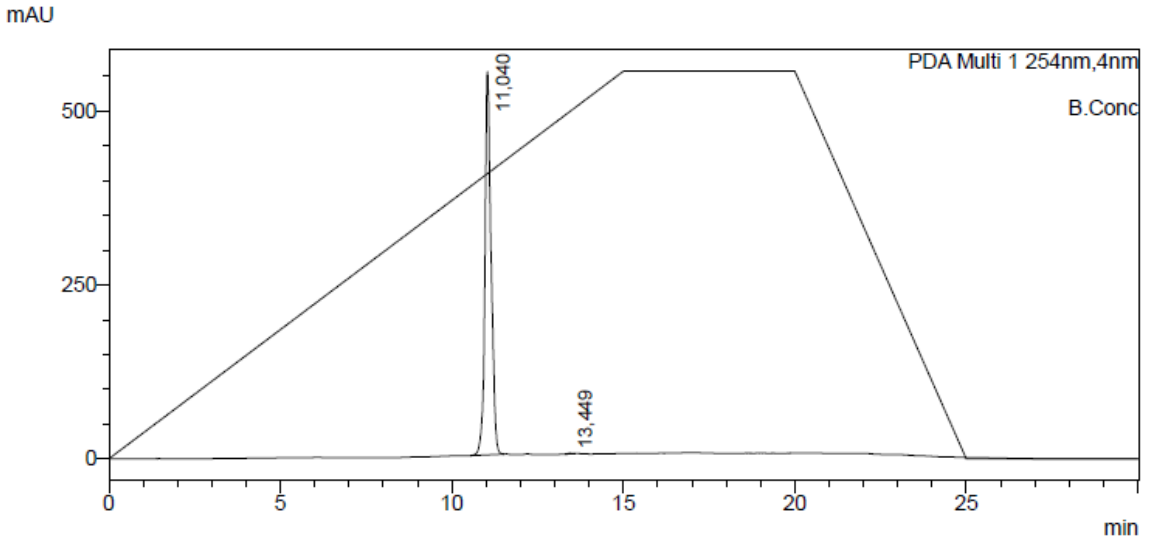


*Figure S18B ^{13}C-NMR (100 MHz) of **16c** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 28
Injection Volume	: 5
Data File	: AR185.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 03:04:37
Date Processed	: 18.05.2021 03:34:39



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	11,040	6887676	551521	99,875
2	13,449	8615	1106	0,125
Total		6896291	552627	100,000

*Figure S18C HPLC chromatogram of **16c**.*

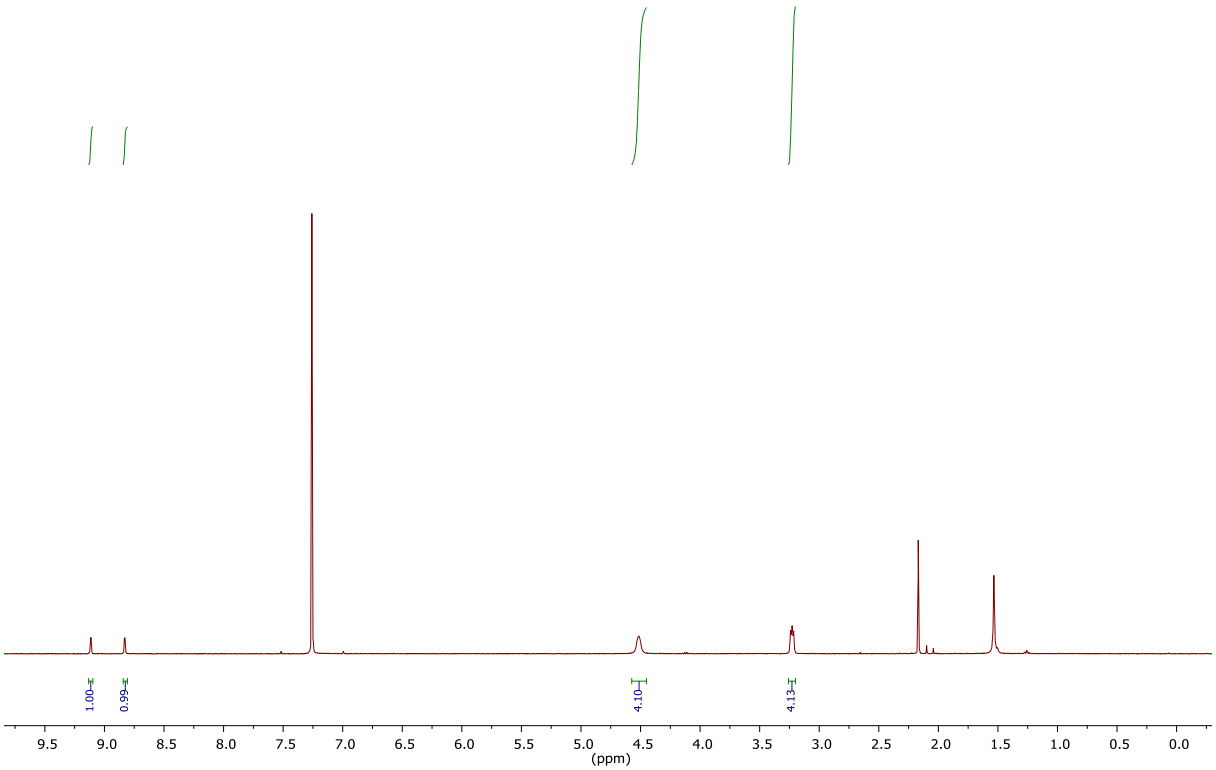


*Figure S19A ^{1}H-NMR (400 MHz) of **16d** in $CDCl_3$.*

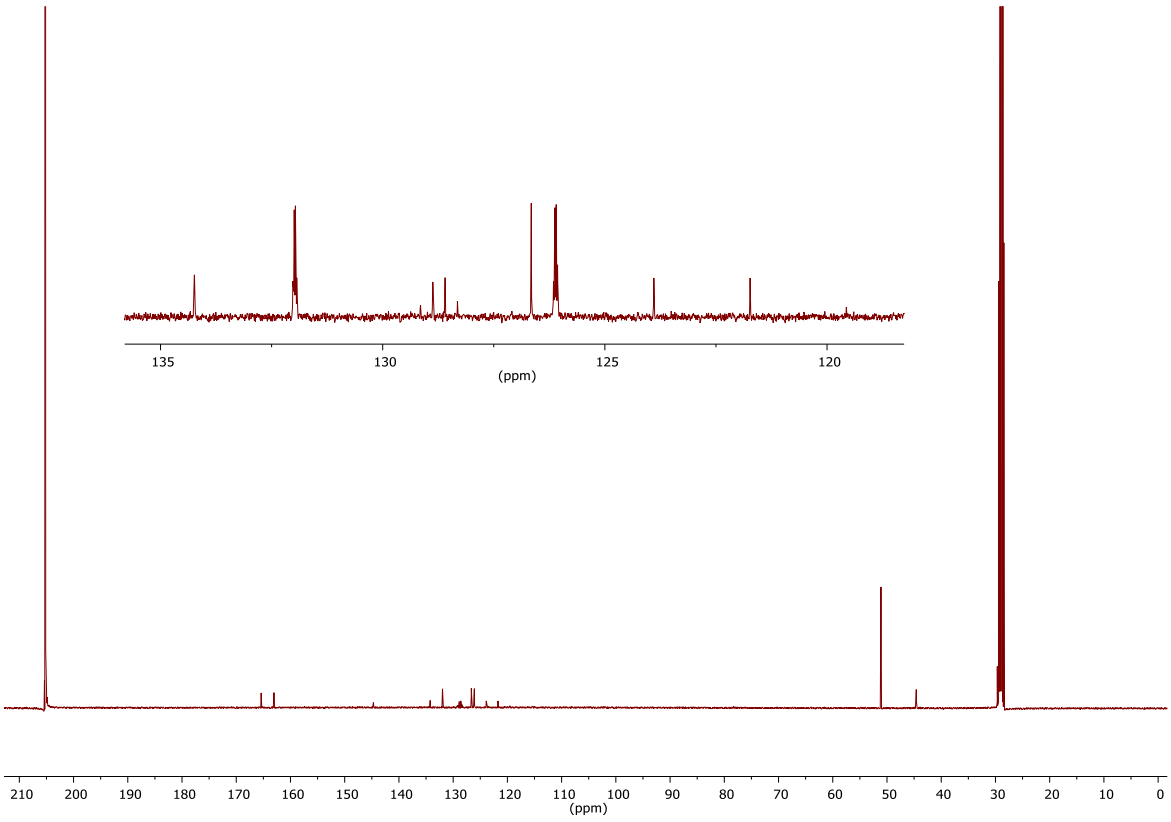
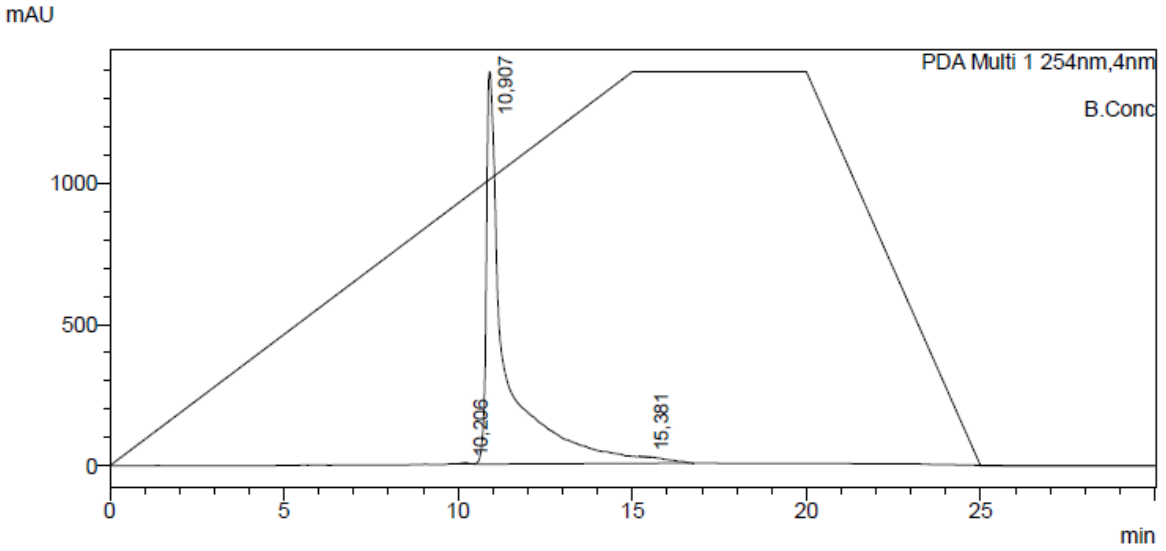


*Figure S19B ^{13}C-NMR (125 MHz) of **16d** in Acetone d_6.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 36
Injection Volume	: 5
Data File	: IF242.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 07:08:51
Date Processed	: 18.05.2021 07:38:54



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	10,206	96170	5599	0,179
2	10,907	53711942	1386031	99,801
3	15,381	10925	1276	0,020
Total		53819037	1392905	100,000

Figure S19C HPLC chromatogram of ***16d****.*

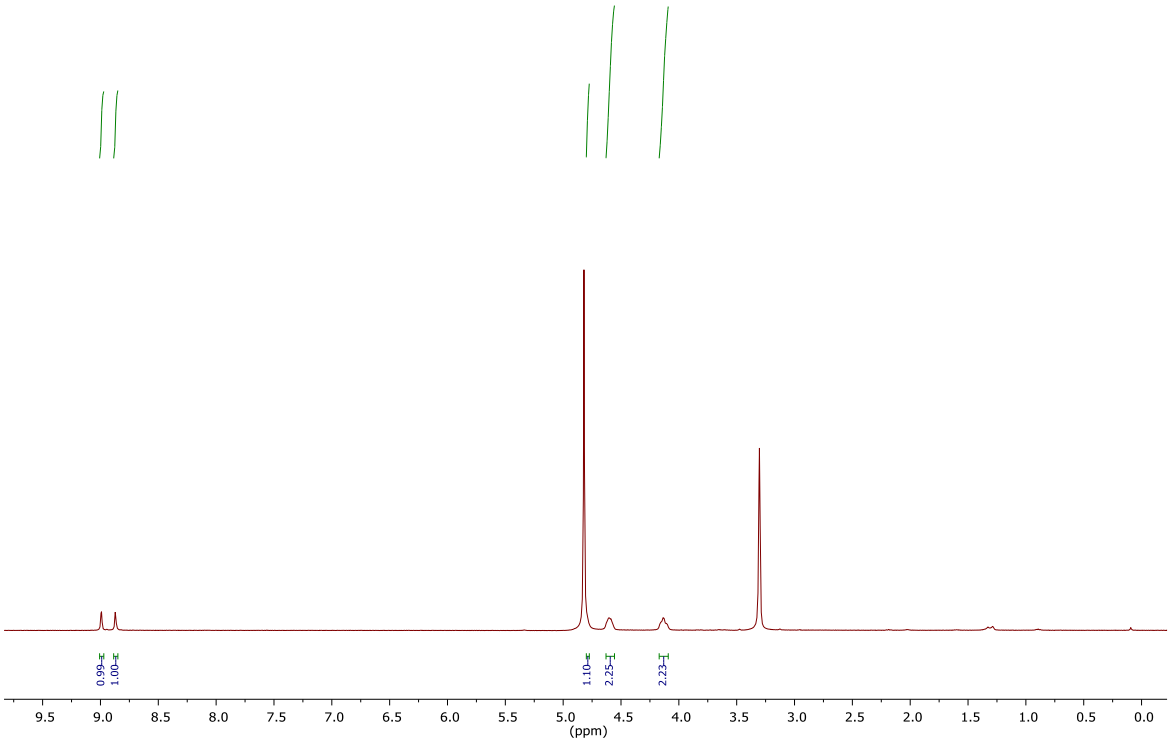


*Figure S20A [1]H-NMR (400 MHz) of **17b** in CD_3OD.*

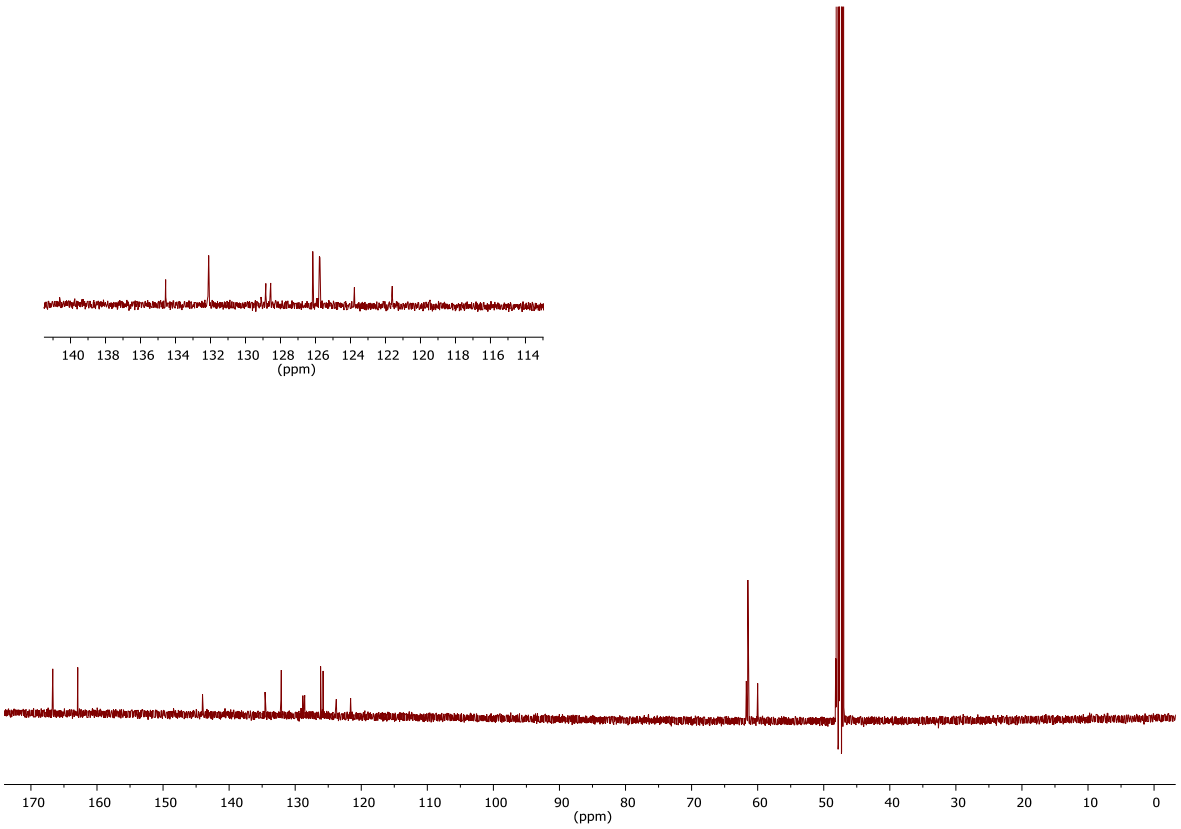
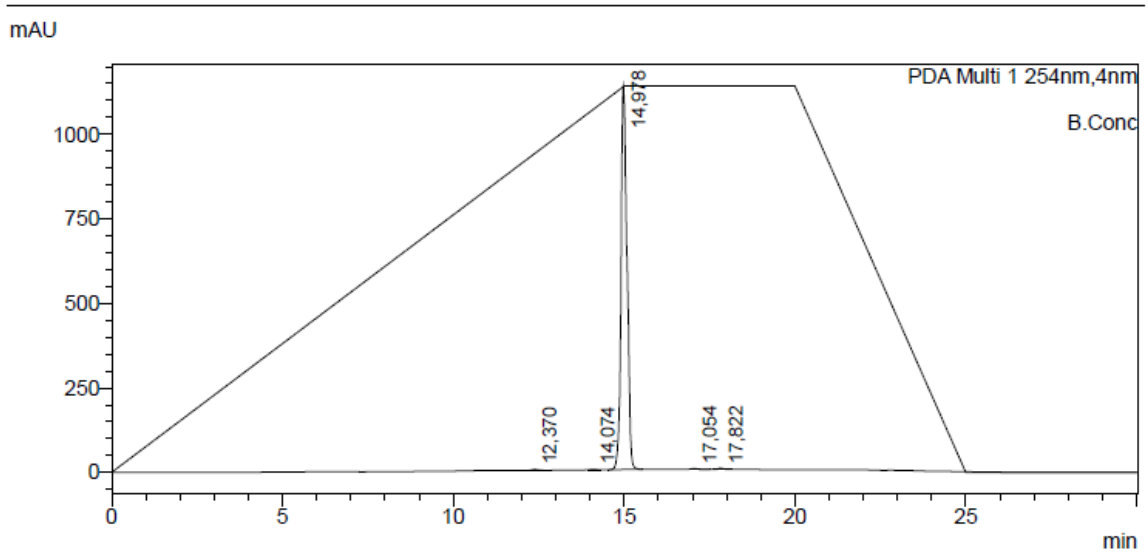


*Figure S20B [13]C-NMR (100 MHz) of **17b** in CD_3OD.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 20
Injection Volume	: 5
Data File	: AR100.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 23:00:23
Date Processed	: 17.05.2021 23:30:26



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,370	28376	2417	0,205
2	14,074	17833	1784	0,129
3	14,978	13710356	1133975	99,230
4	17,054	17220	1632	0,125
5	17,822	43024	3773	0,311
Total		13816810	1143582	100,000

*Figure S20C HPLC trace of **17b**.*

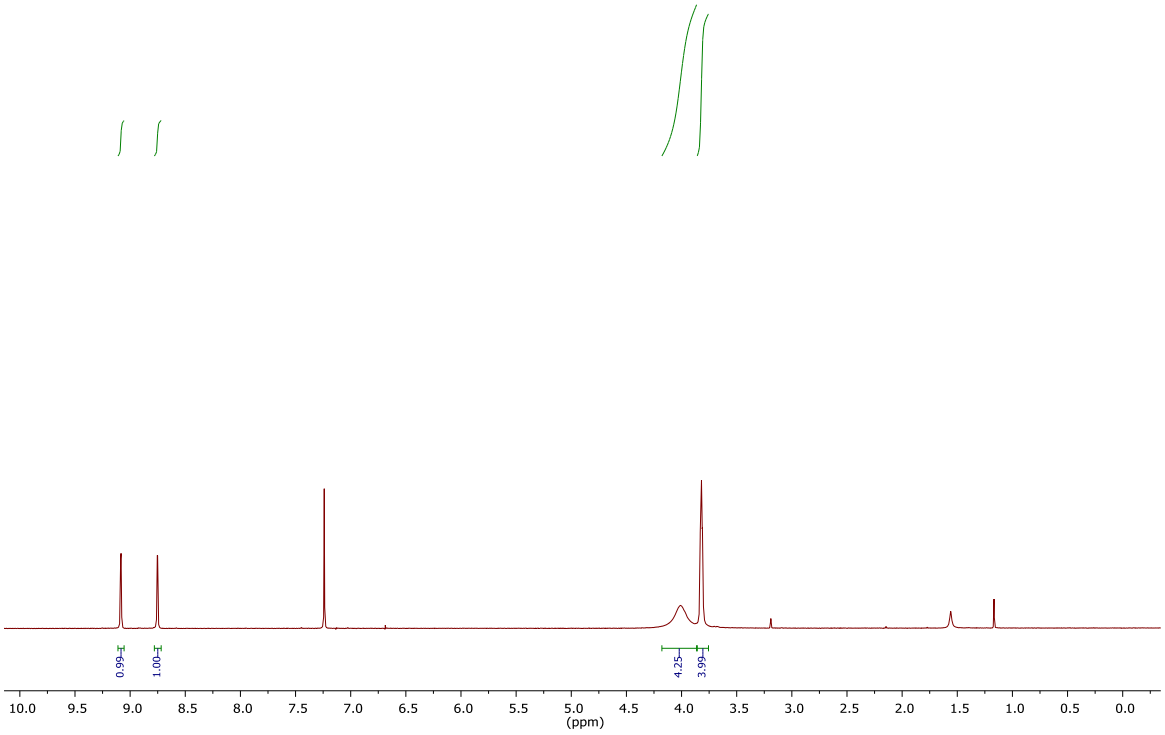


*Figure S21A ^{1}H-NMR (400 MHz) of **18b** in $CDCl_3$.*

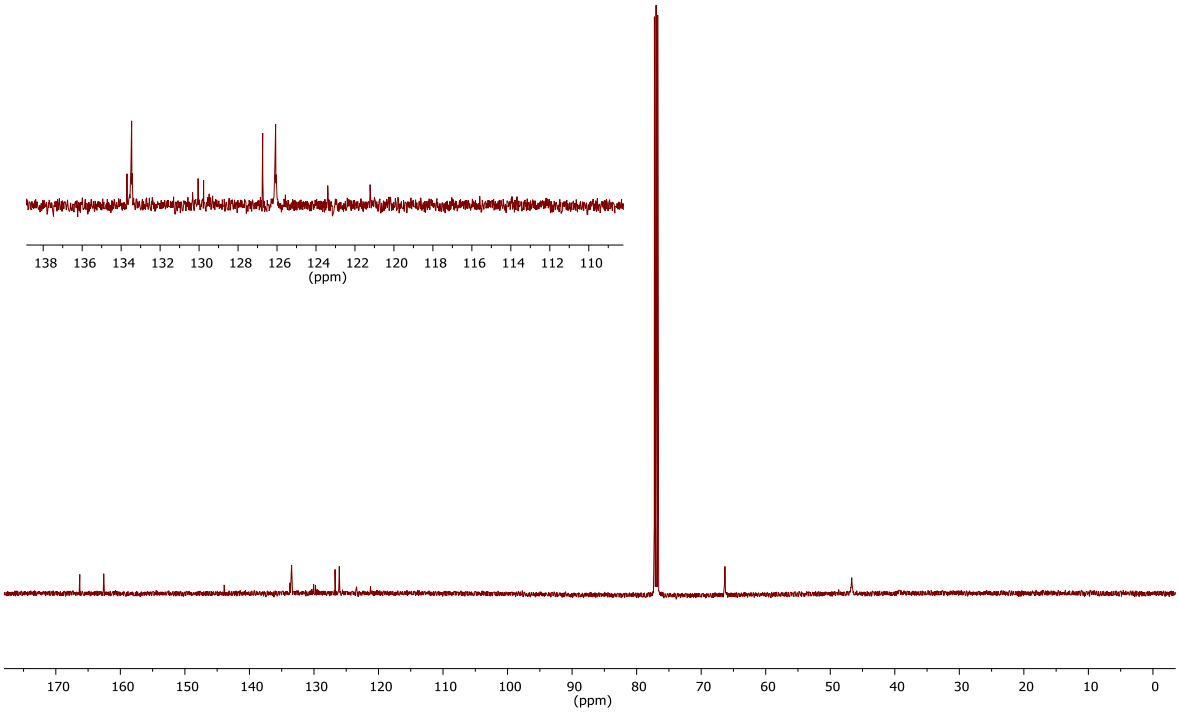
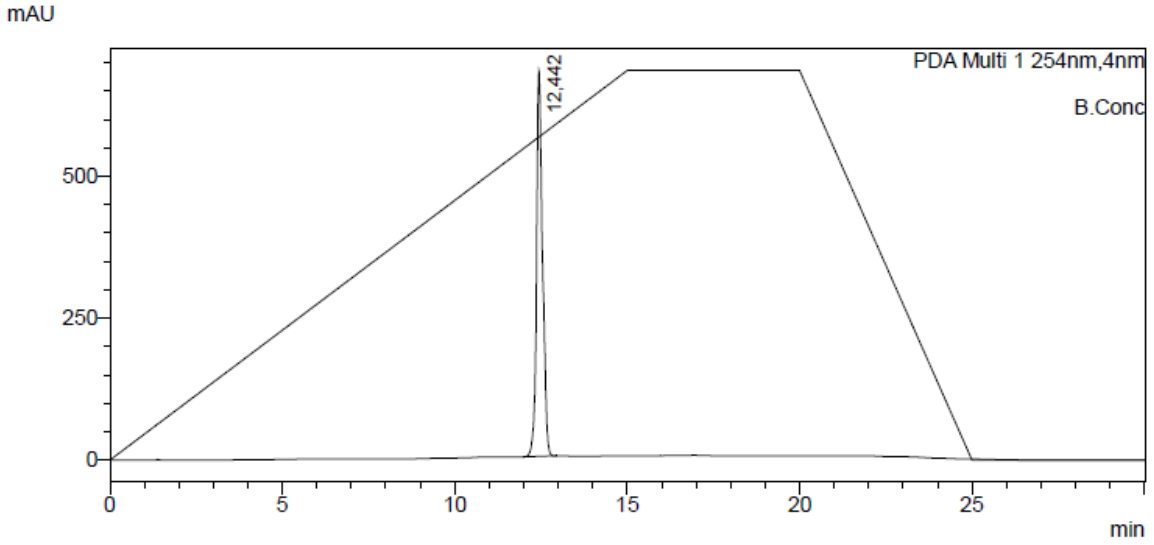


*Figure S21B ^{13}C-NMR (100 MHz) of **18b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 35
Injection Volume	: 10
Data File	: IR58_WDH.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 09:41:29
Date Processed	: 18.05.2021 10:11:32



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,442	8255951	679591	100,000
Total		8255951	679591	100,000

*Figure S21C HPLC chromatogram of **18b**.*

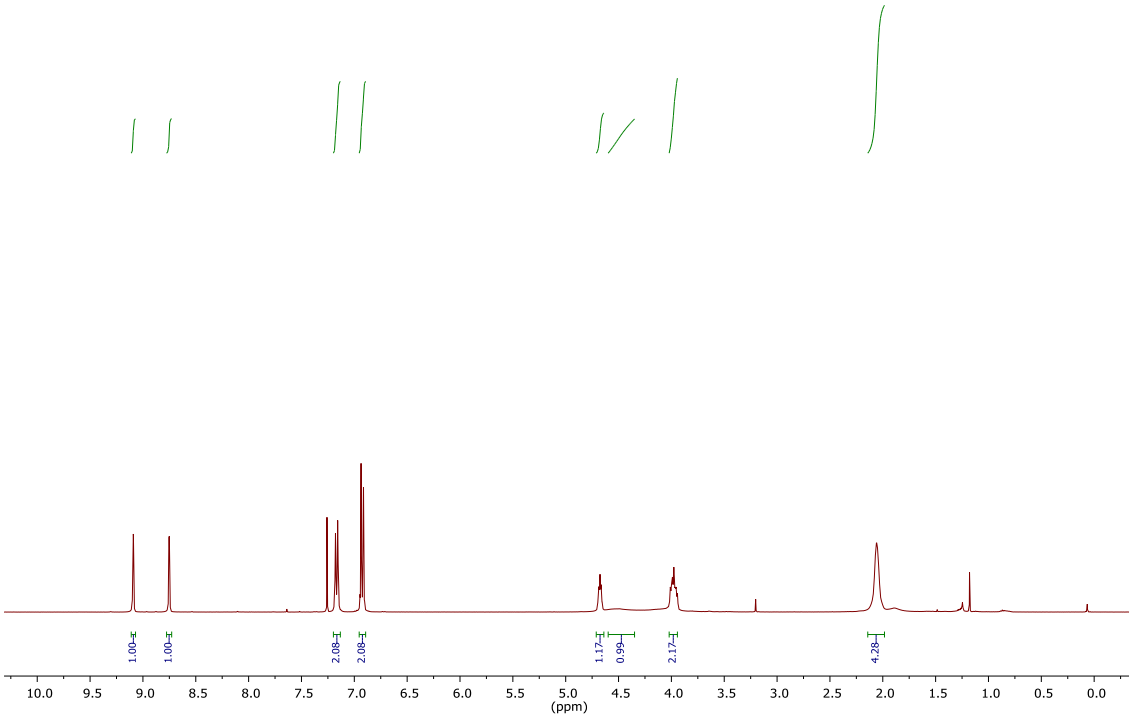


*Figure S22A ^{1}H-NMR (400 MHz) of **19b** in $CDCl_3$.*

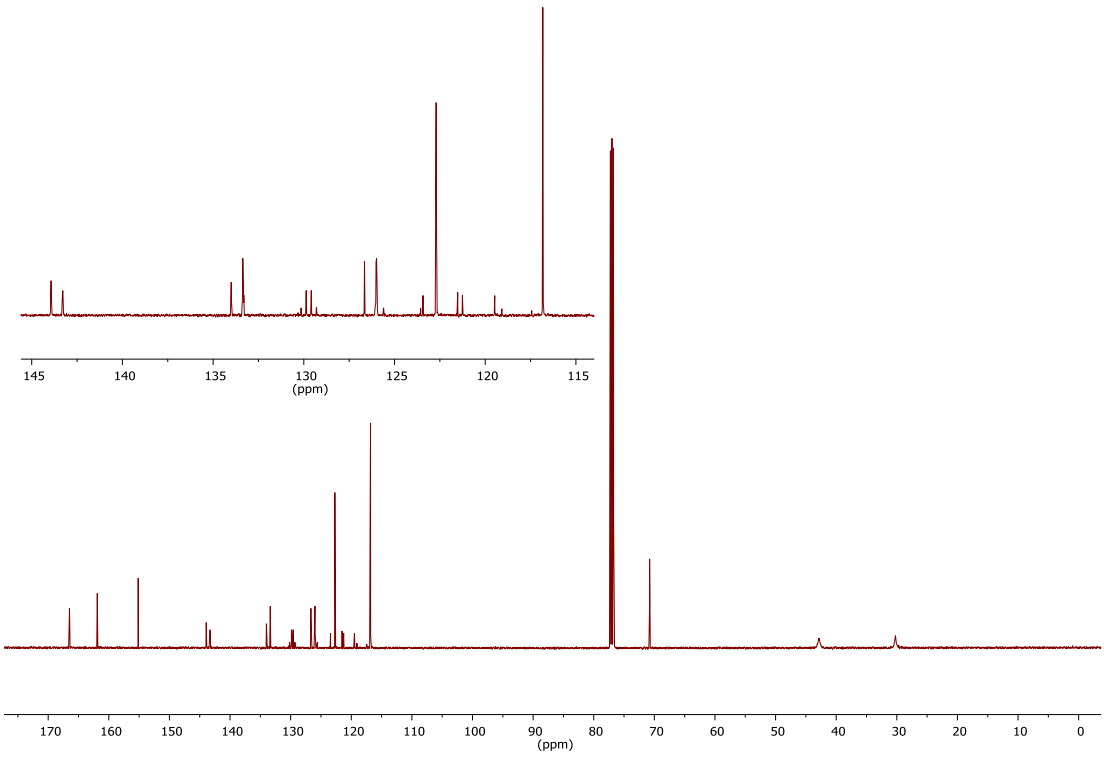
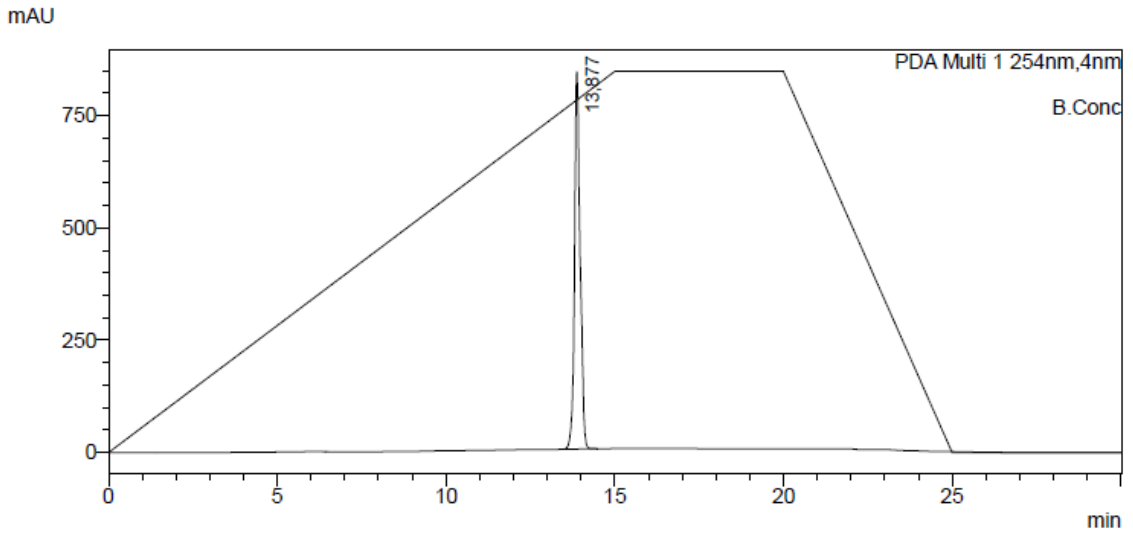


*Figure S22B ^{13}C-NMR (100 MHz) of **19b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 32
Injection Volume	: 5
Data File	: AR106.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 05:06:48
Date Processed	: 18.05.2021 05:36:49



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	13,877	9735294	840298	100,000
Total		9735294	840298	100,000

*Figure S22C HPLC chromatogram of **19b**.*

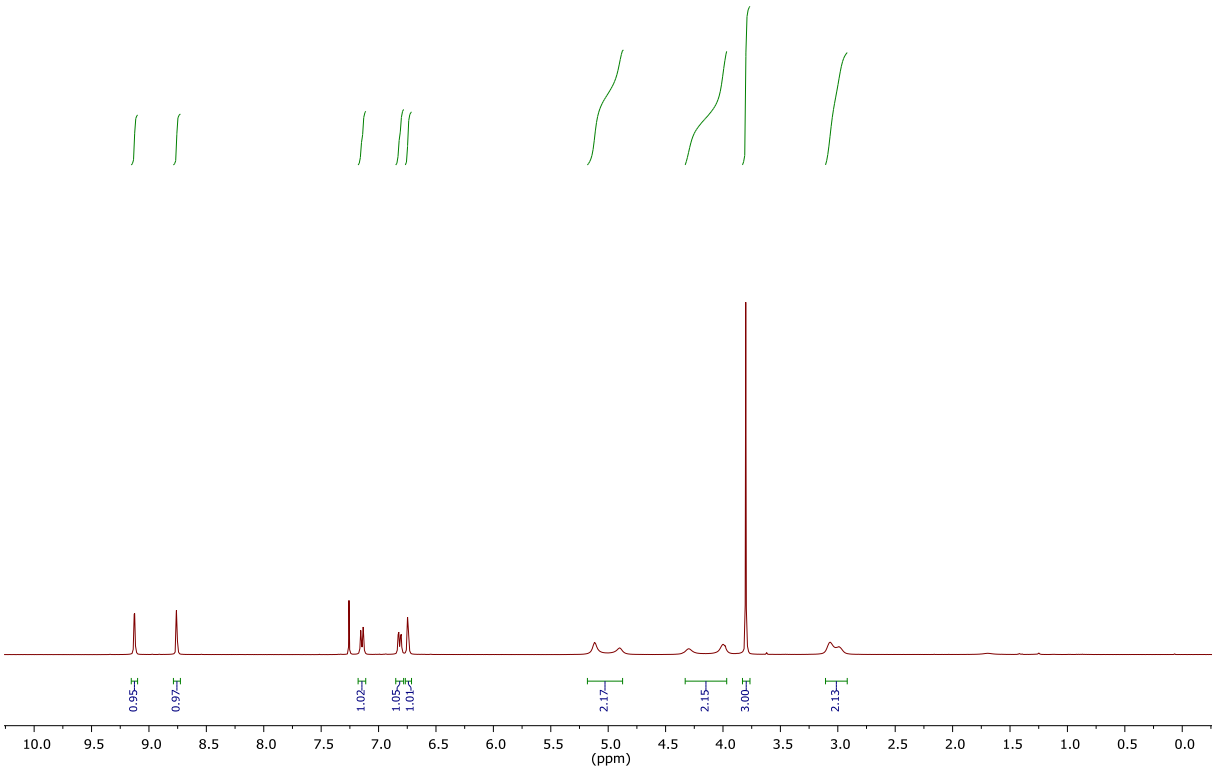


*Figure S23A ^{1}H-NMR (400 MHz) of **20b** in $CDCl_3$.*

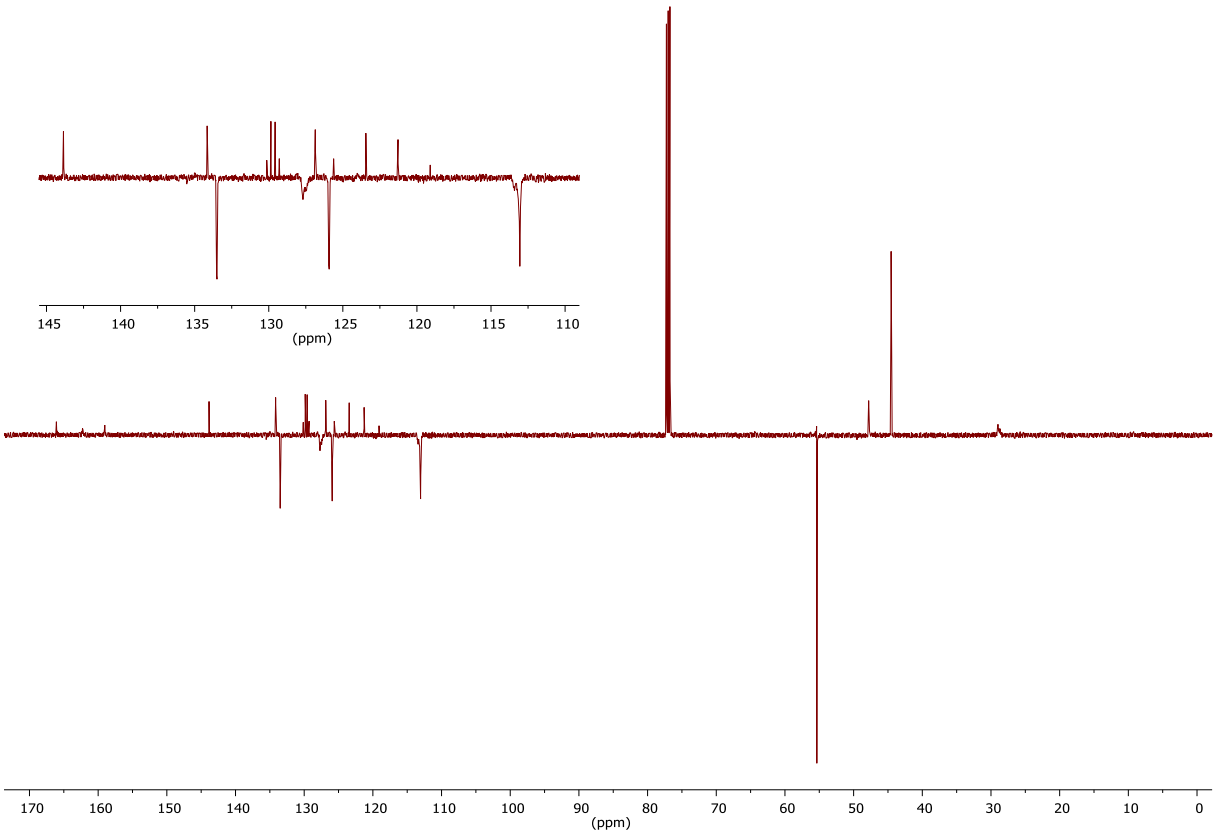
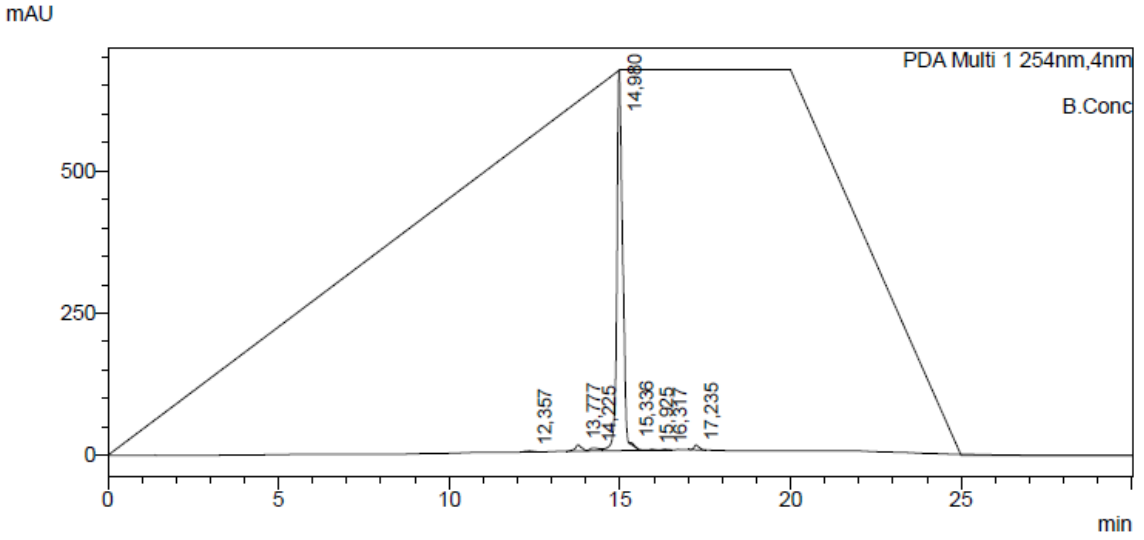


*Figure S23B ^{13}C-NMR (100 MHz) of **20b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 27
Injection Volume	: 5
Data File	: AR112.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 02:34:06
Date Processed	: 18.05.2021 03:04:08



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,357	28911	1980	0,348
2	13,777	145028	11014	1,745
3	14,225	100643	5364	1,211
4	14,980	7910461	669598	95,166
5	15,336	20315	2841	0,244
6	15,925	12270	1226	0,148
7	16,317	9693	1105	0,117
8	17,235	84927	8409	1,022
Total		8312247	701538	100,000

*Figure S23C HPLC chromatogram of **20b**.*

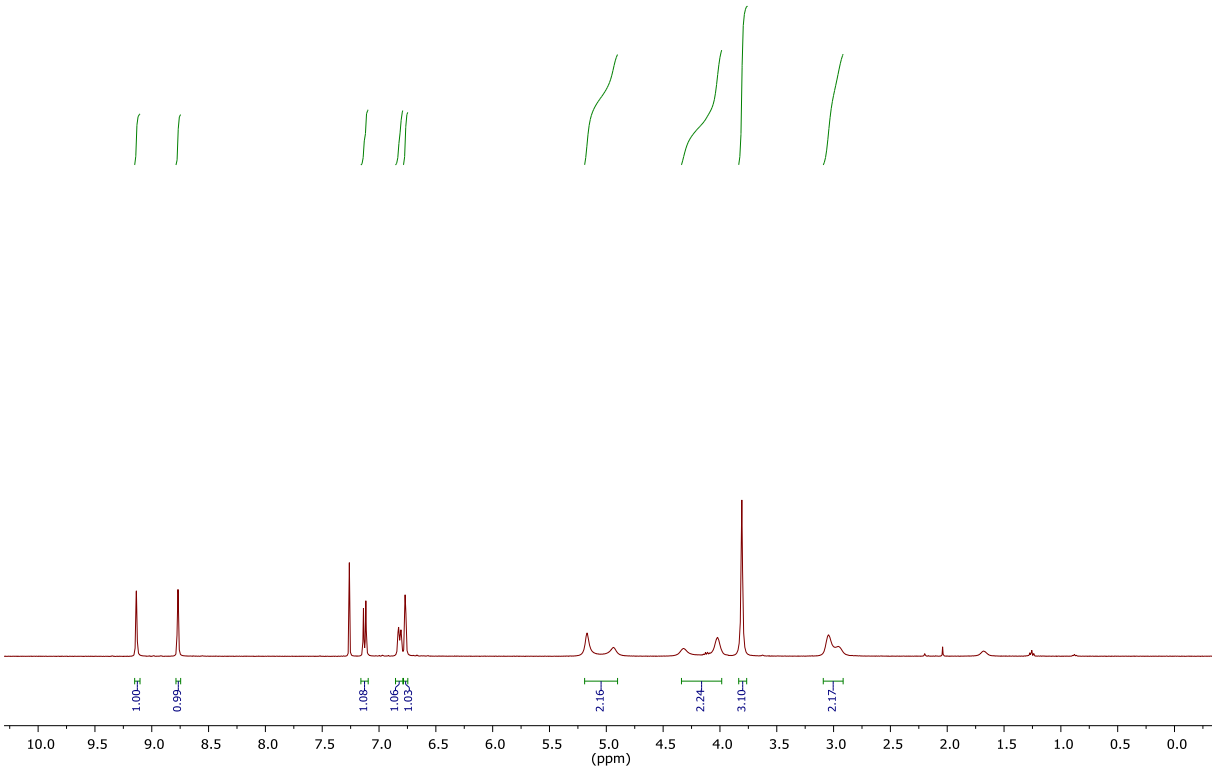


*Figure S24A ^{1}H-NMR (400 MHz) of **21b** in $CDCl_3$.*

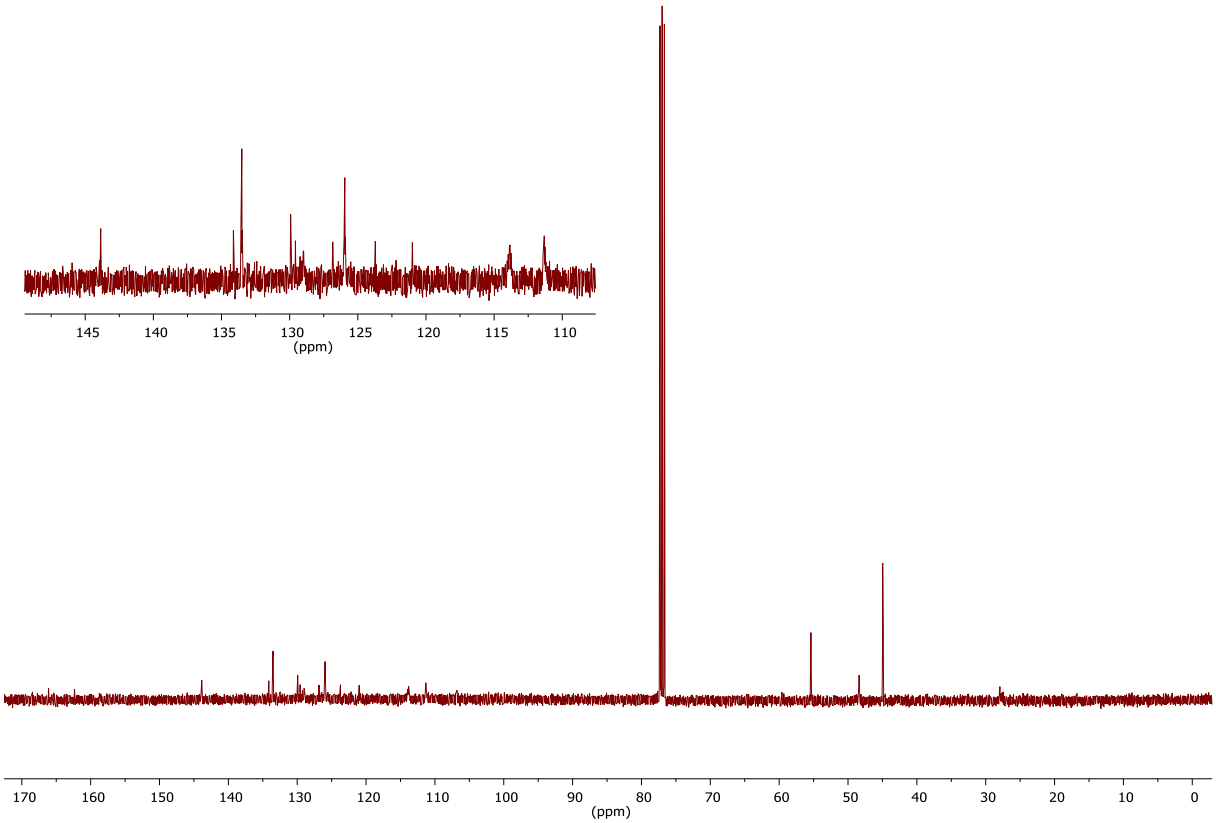
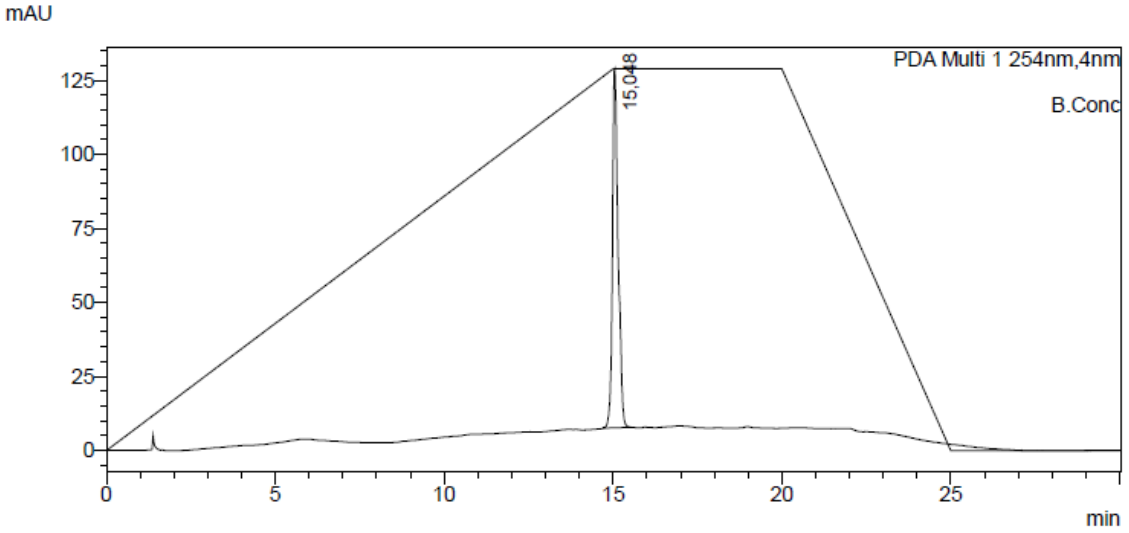


*Figure S24B ^{13}C-NMR (100 MHz) of **21b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 4
Injection Volume	: 10
Data File	: AR130_270521.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch270521_1.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 27.05.2021 10:20:39
Date Processed	: 27.05.2021 10:50:44



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	15,048	1414410	121218	100,000
Total		1414410	121218	100,000

*Figure S24C HPLC chromatogram of **21b**.*

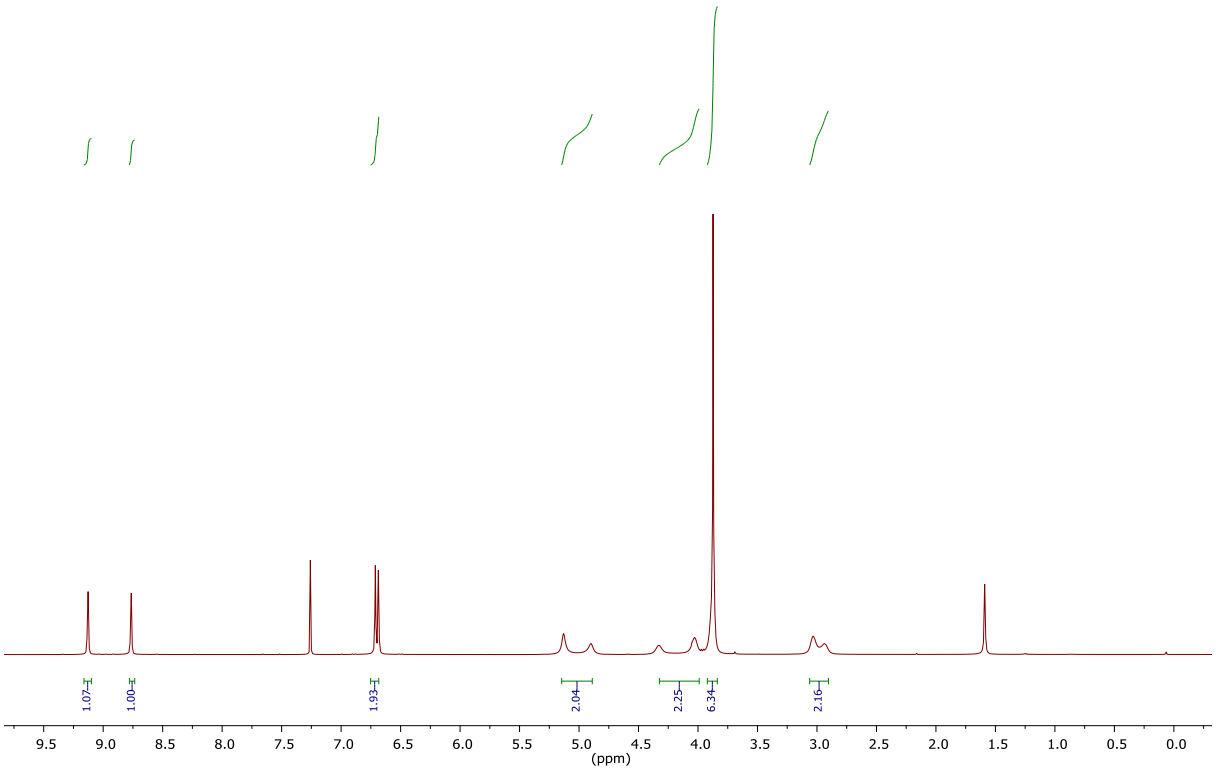


*Figure S25A ^{1}H-NMR (400 MHz) of **22b** in $CDCl_3$.*

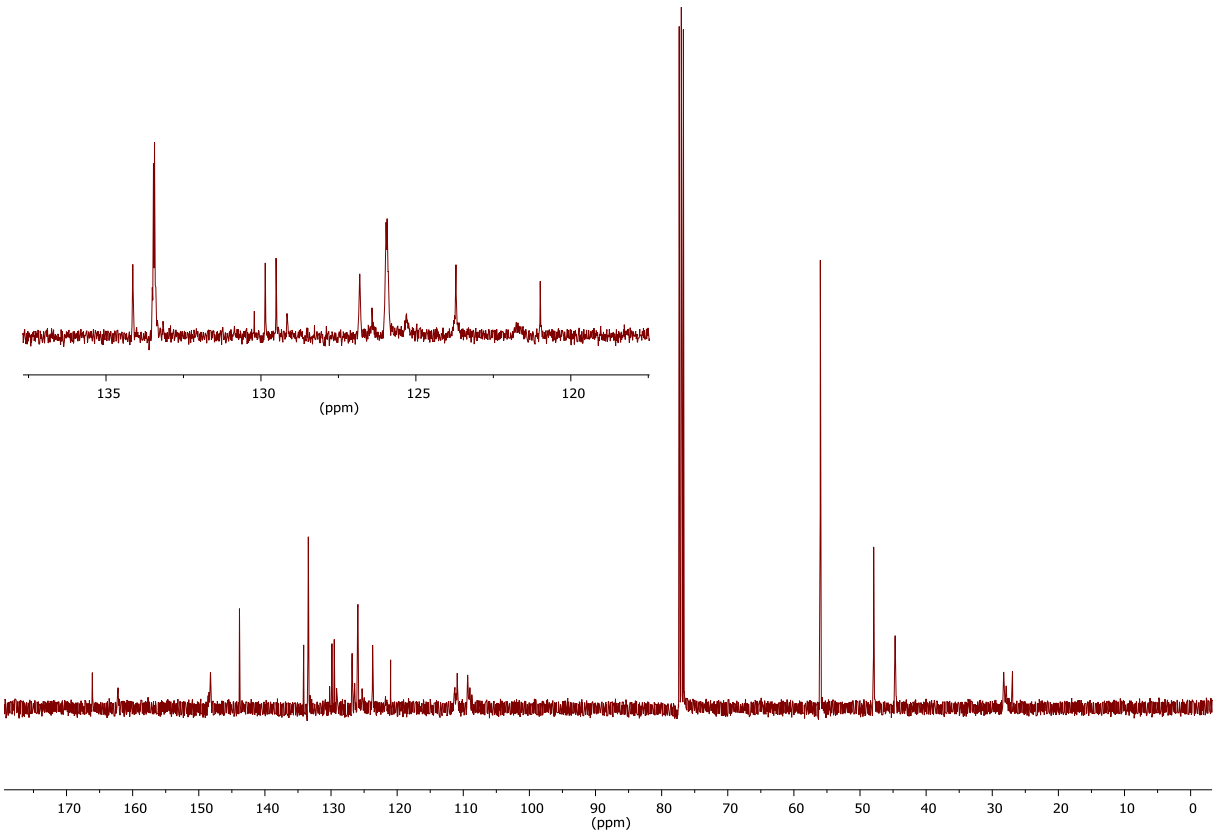
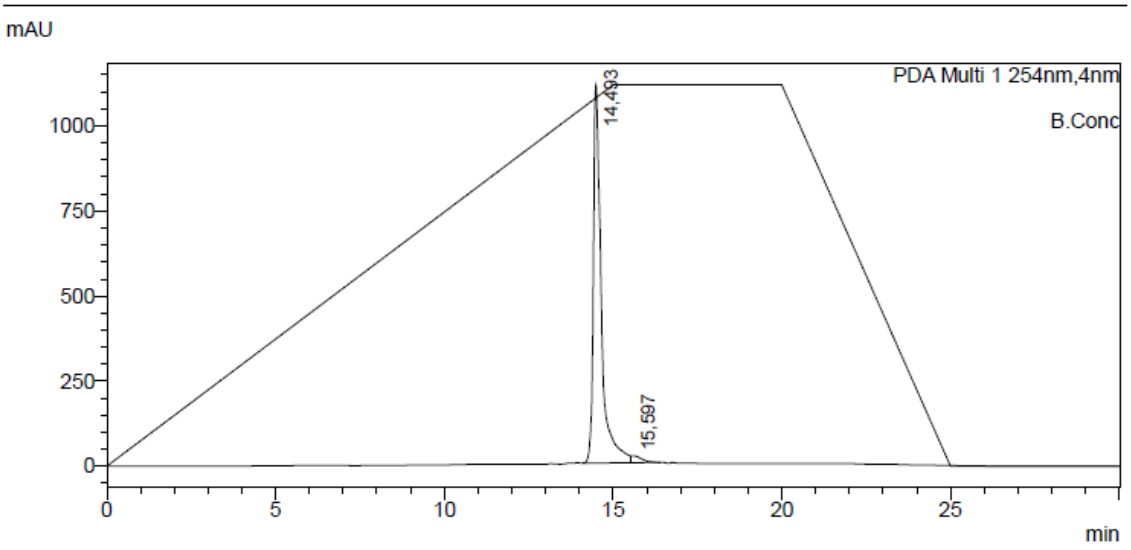


*Figure S25B ^{13}C-NMR (100 MHz) of **22b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 29
Injection Volume	: 5
Data File	: AR204.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 03:35:09
Date Processed	: 18.05.2021 04:05:12



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	14,493	18243079	1110956	97,734
2	15,597	423013	20462	2,266
Total		18666092	1131418	100,000

*Figure S25C HPLC chromatogram of **22b**.*

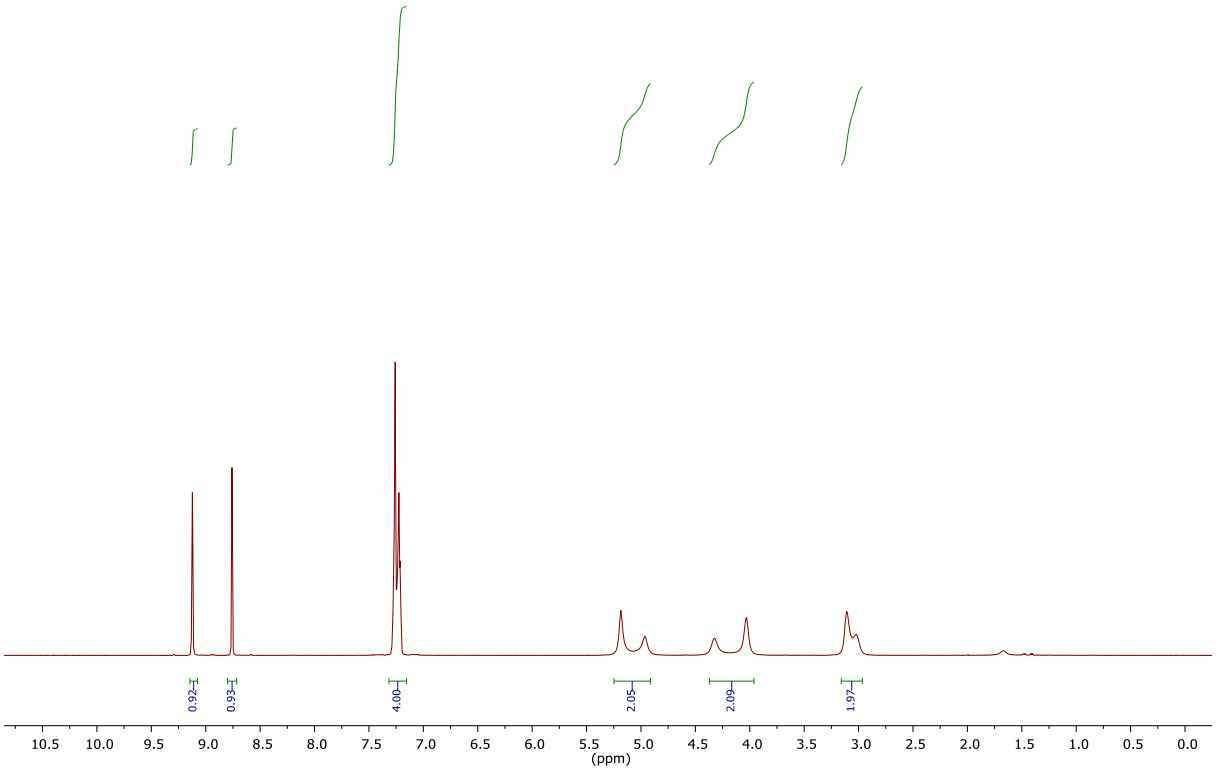


*Figure S26A [1]H-NMR (400 MHz) of **23b** in $CDCl_3$.*

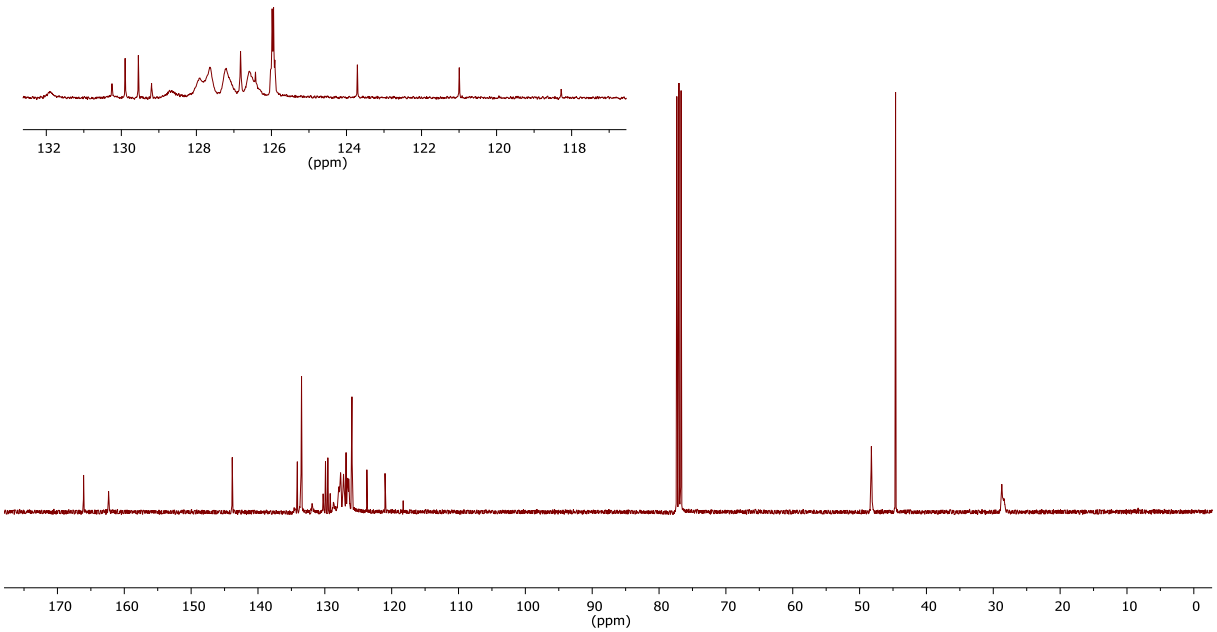
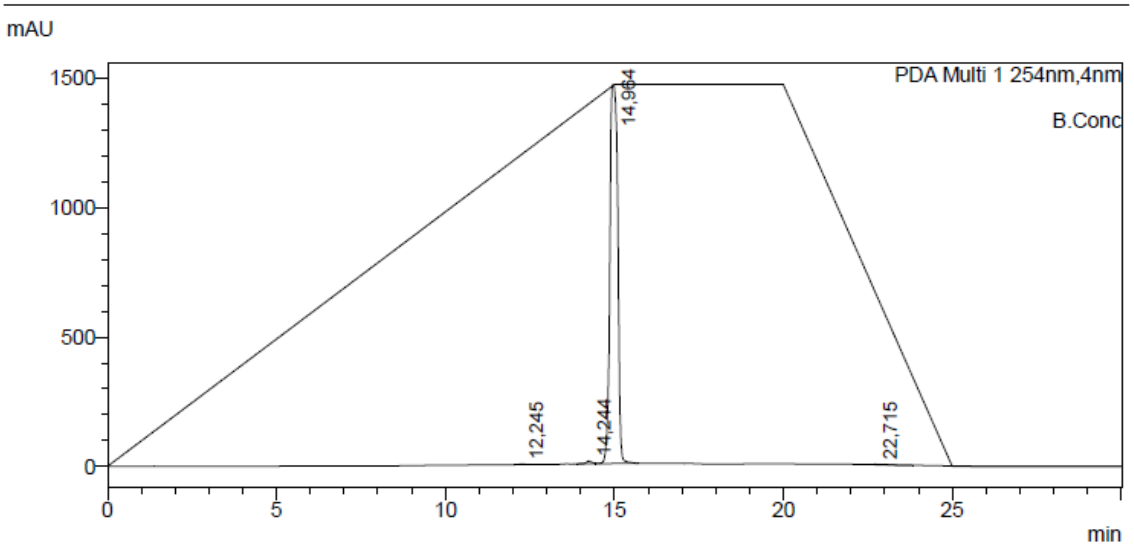


*Figure S26B [13]C-NMR (100 MHz) of **23b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 4
Injection Volume	: 10
Data File	: AR196.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 14:51:56
Date Processed	: 18.05.2021 06:41:44



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,245	38932	2735	0,164
2	14,244	128647	9891	0,541
3	14,964	23581511	1464831	99,141
4	22,715	36829	1770	0,155
Total		23785919	1479227	100,000

*Figure S26C HPLC trace of **23b**.*

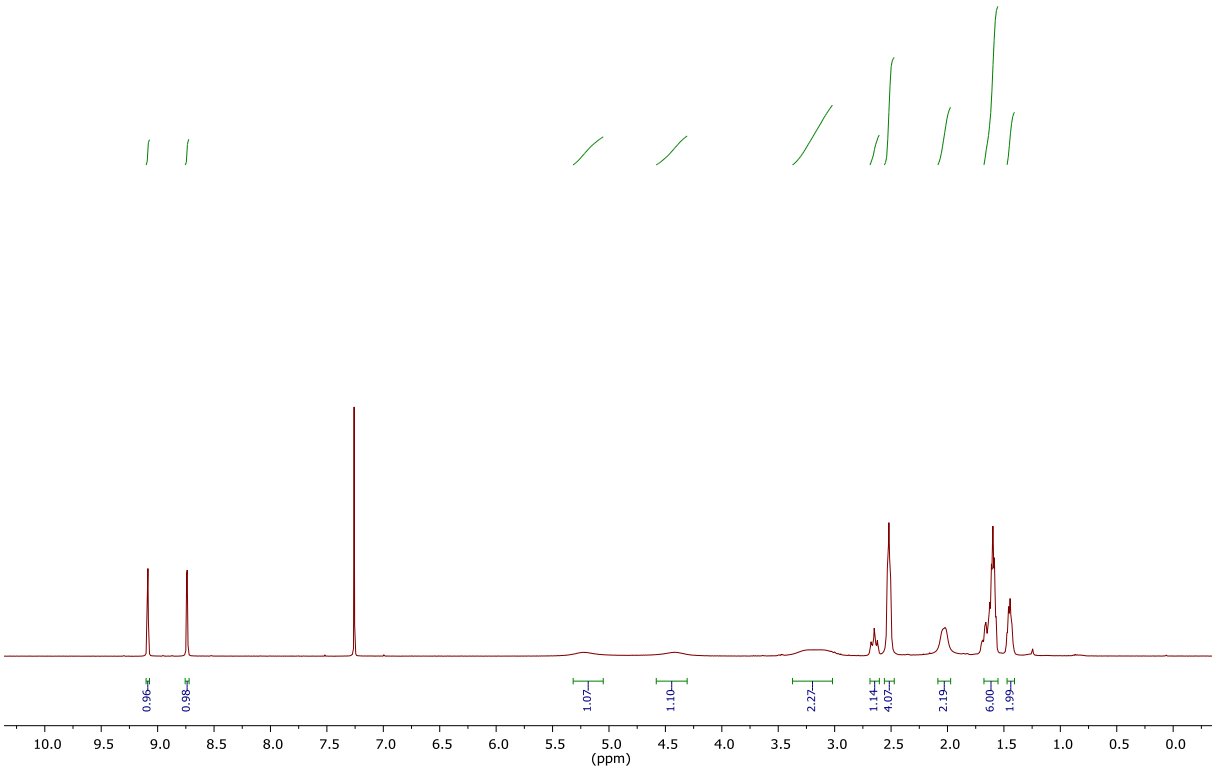


*Figure S27A ^{1}H-NMR (400 MHz) of **24b** in $CDCl_3$.*

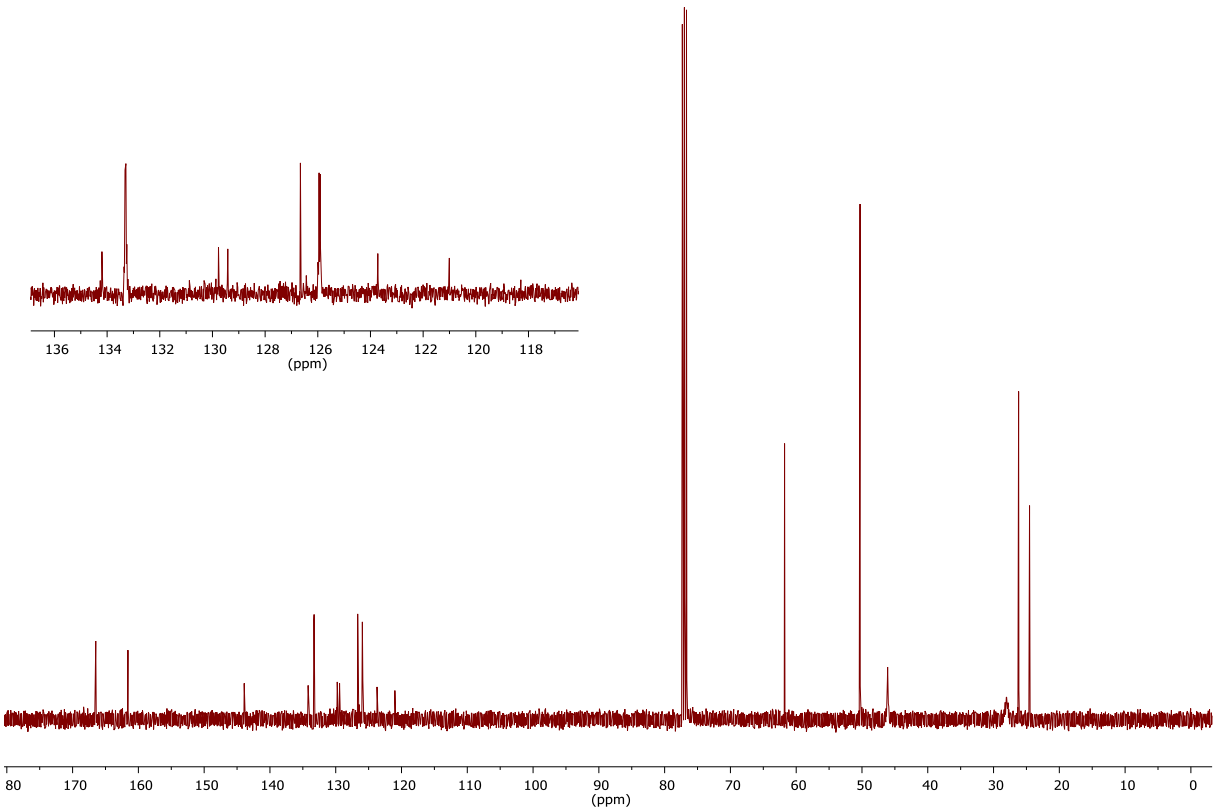
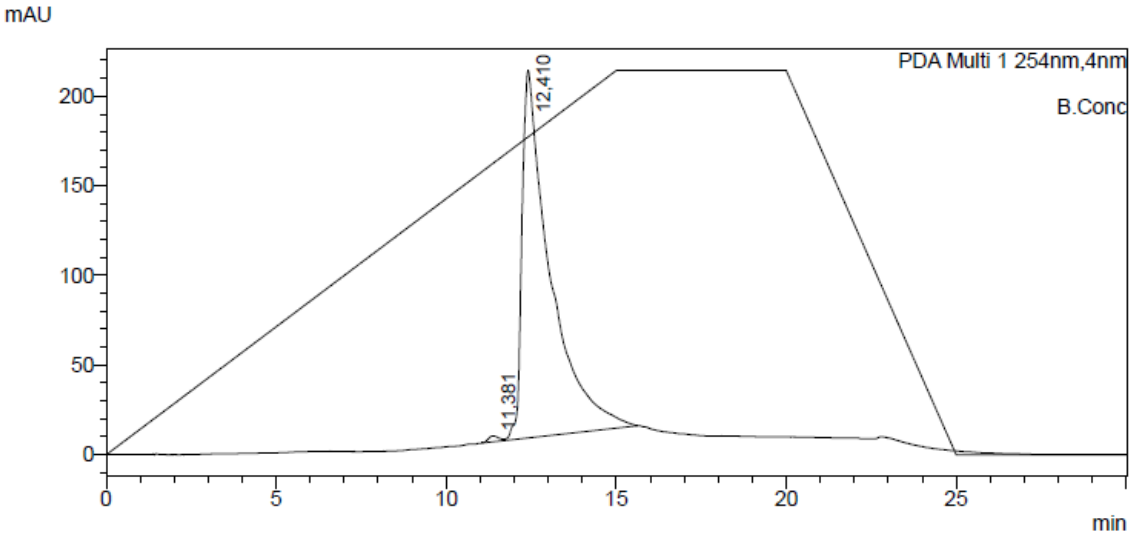


*Figure S27B ^{13}C-NMR (100 MHz) of **24b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 33
Injection Volume	: 5
Data File	: AR107.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 05:37:18
Date Processed	: 18.05.2021 06:07:20



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	11,381	68461	3277	0,575
2	12,410	11830837	204963	99,425
Total		11899297	208240	100,000

*Figure S27C HPLC chromatogram of **24b**.*

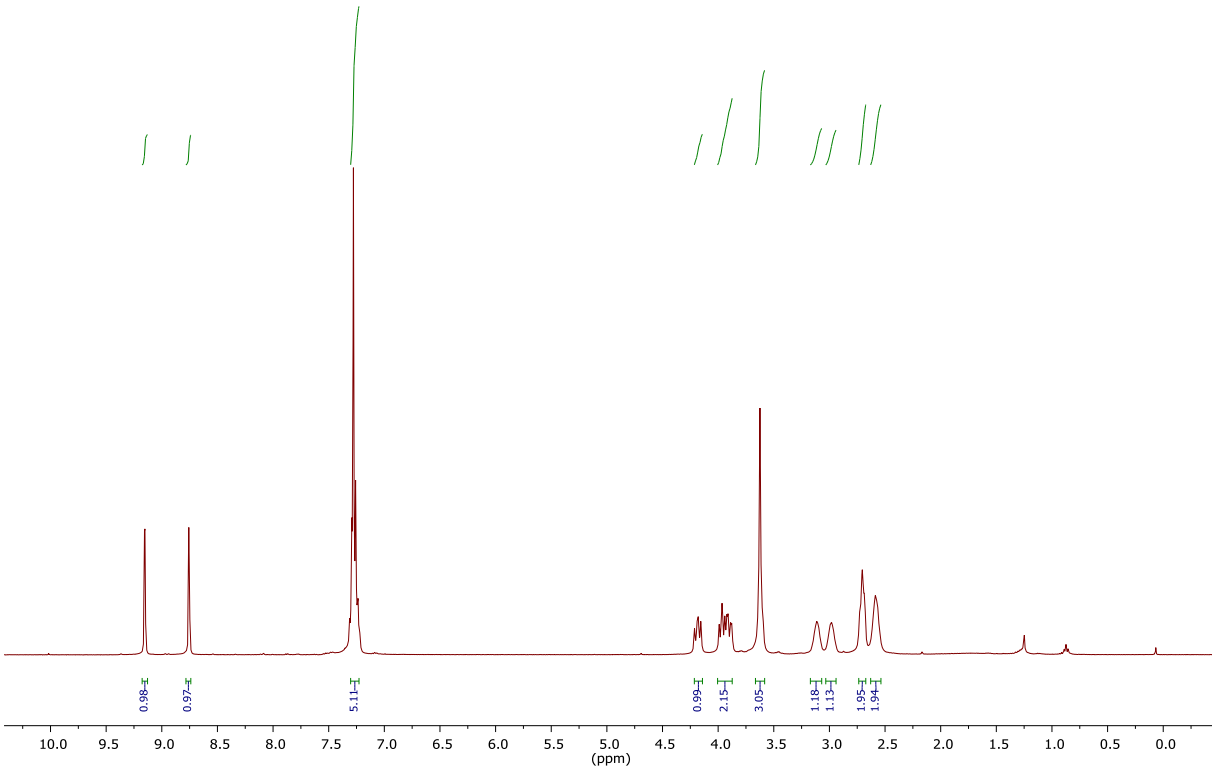


*Figure S28A ^{1}H-NMR (400 MHz) of **26b** in $CDCl_3$.*

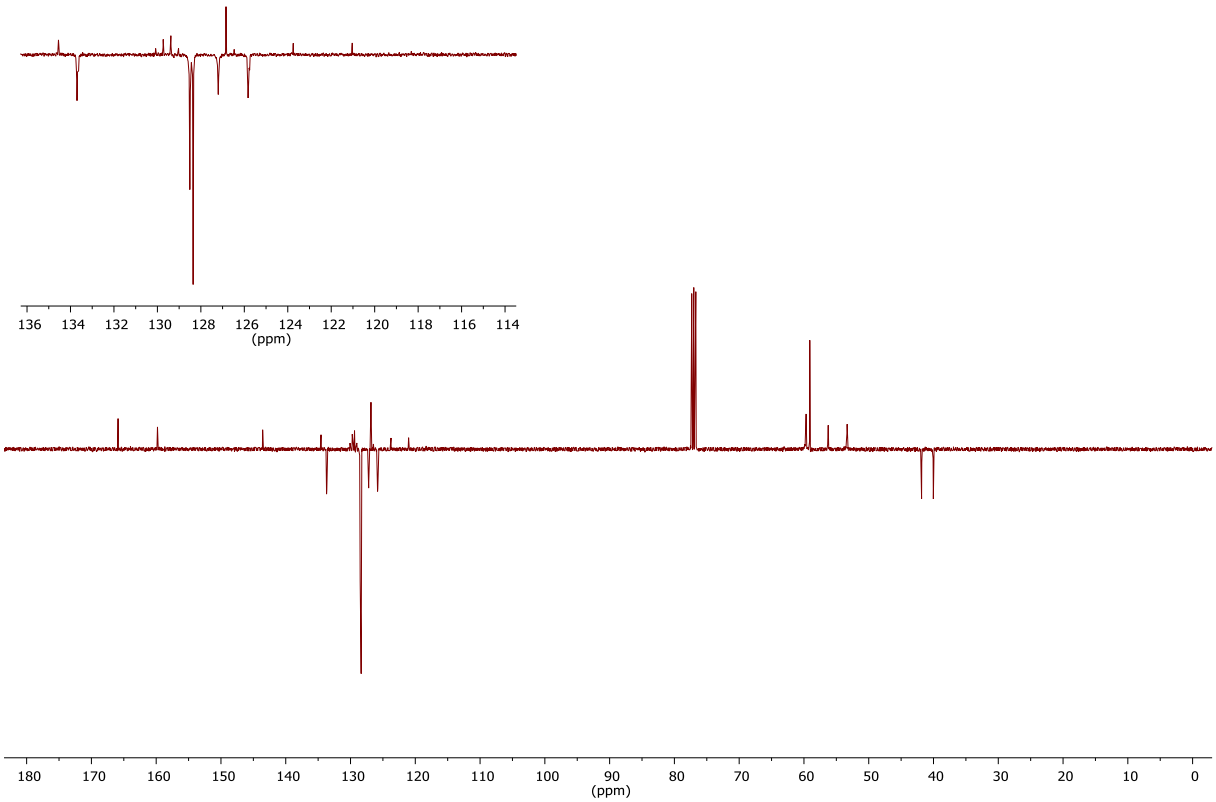
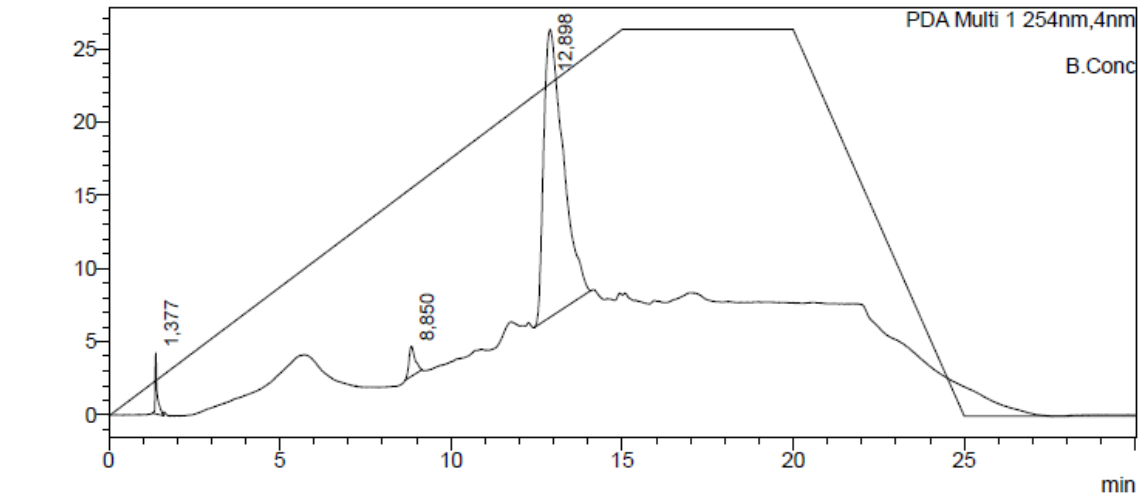


*Figure S28B ^{13}C-NMR (100 MHz) of **26b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 10
Injection Volume	: 10
Data File	: AR115_200521.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch190521_1.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 21.05.2021 00:02:09
Date Processed	: 21.05.2021 00:32:11



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	1,377	16295	4188	1,985
2	8,850	25700	2052	3,130
3	12,898	778981	19632	94,885
Total		820976	25871	100,000

*Figure S28C HPLC chromatogram of **25b**.*

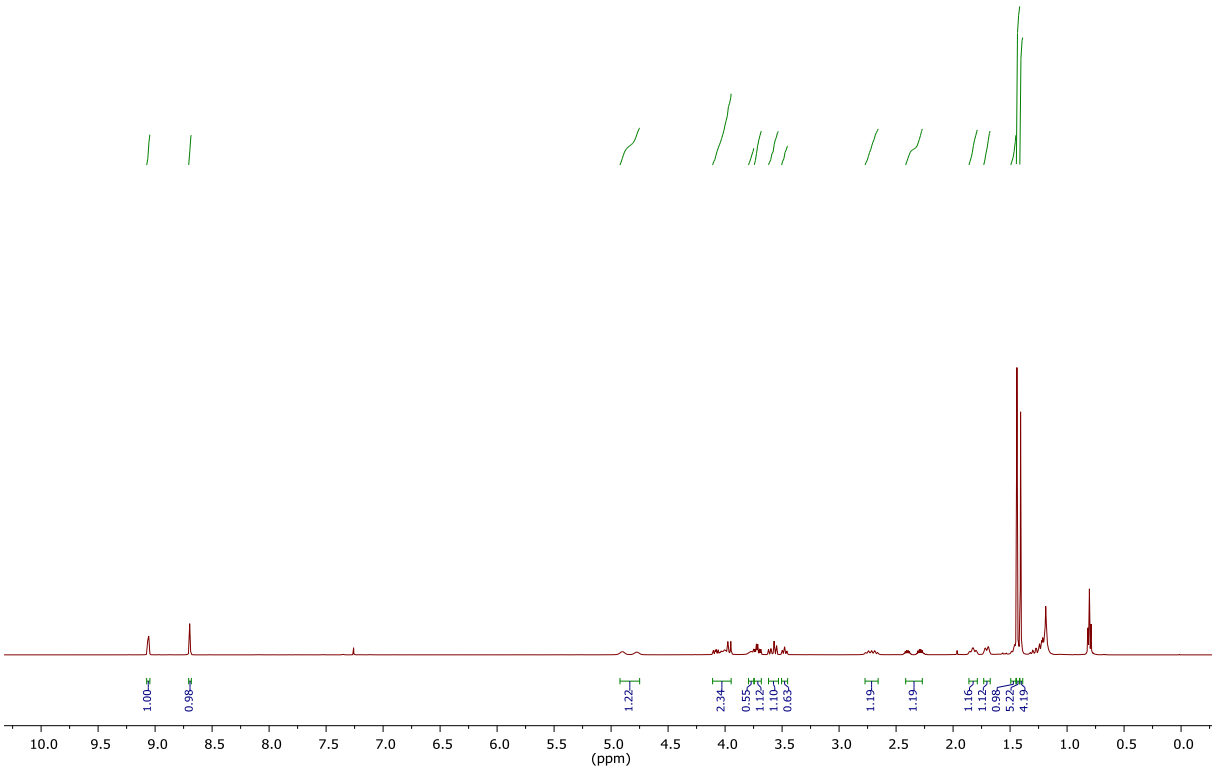


*Figure S29A ^{1}H-NMR (400 MHz) of **26b** in $CDCl_3$.*

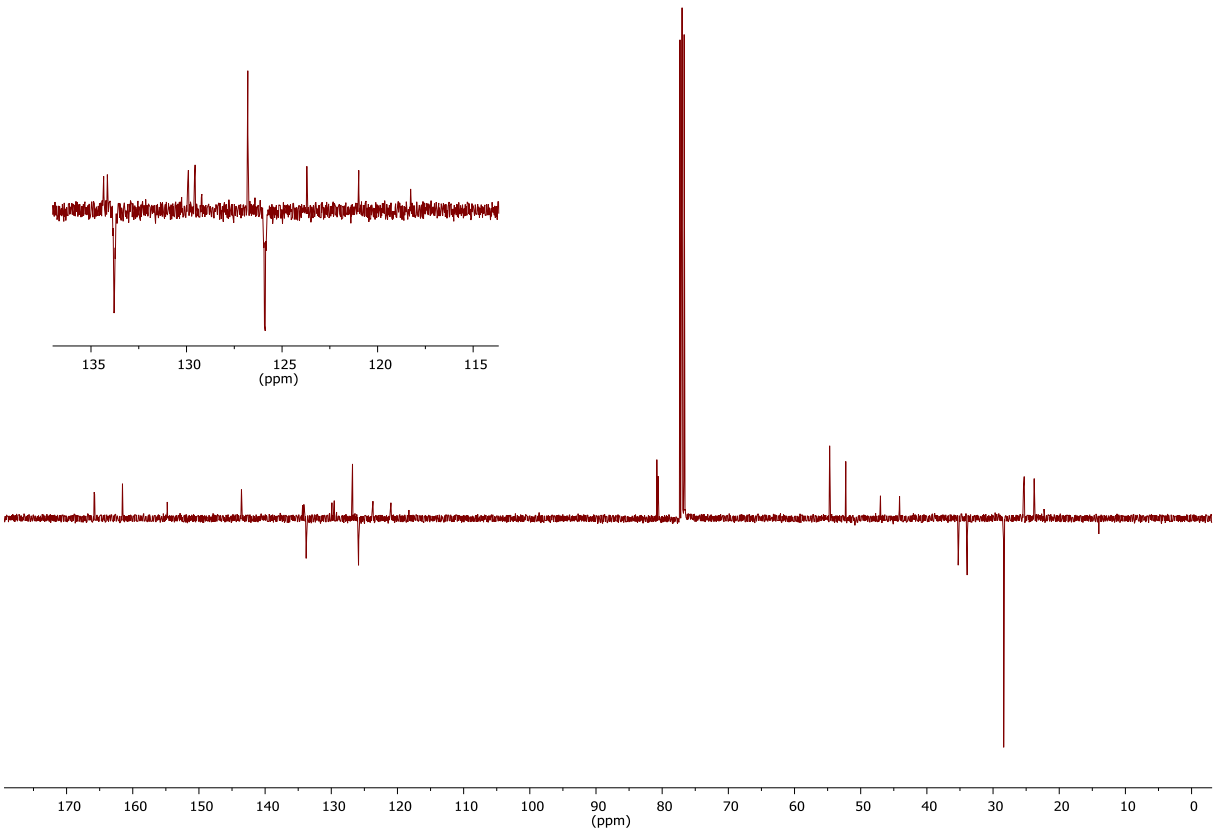
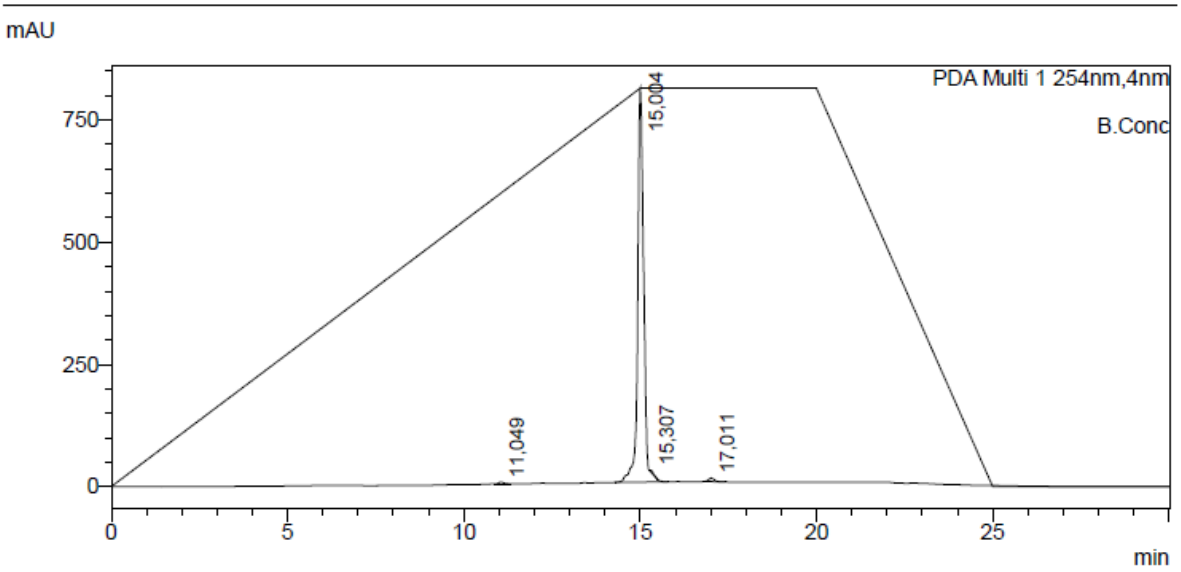


*Figure S29B ^{13}C-APT-NMR (100 MHz) of **26b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 5
Injection Volume	: 5
Data File	: AR190.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 15:22:28
Date Processed	: 17.05.2021 15:52:31



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	11,049	36949	3284	0,380
2	15,004	9576331	806130	98,579
3	15,307	21170	4165	0,218
4	17,011	79911	7314	0,823
Total		9714361	820894	100,000

*Figure S29C HPLC chromatogram of **26b**.*

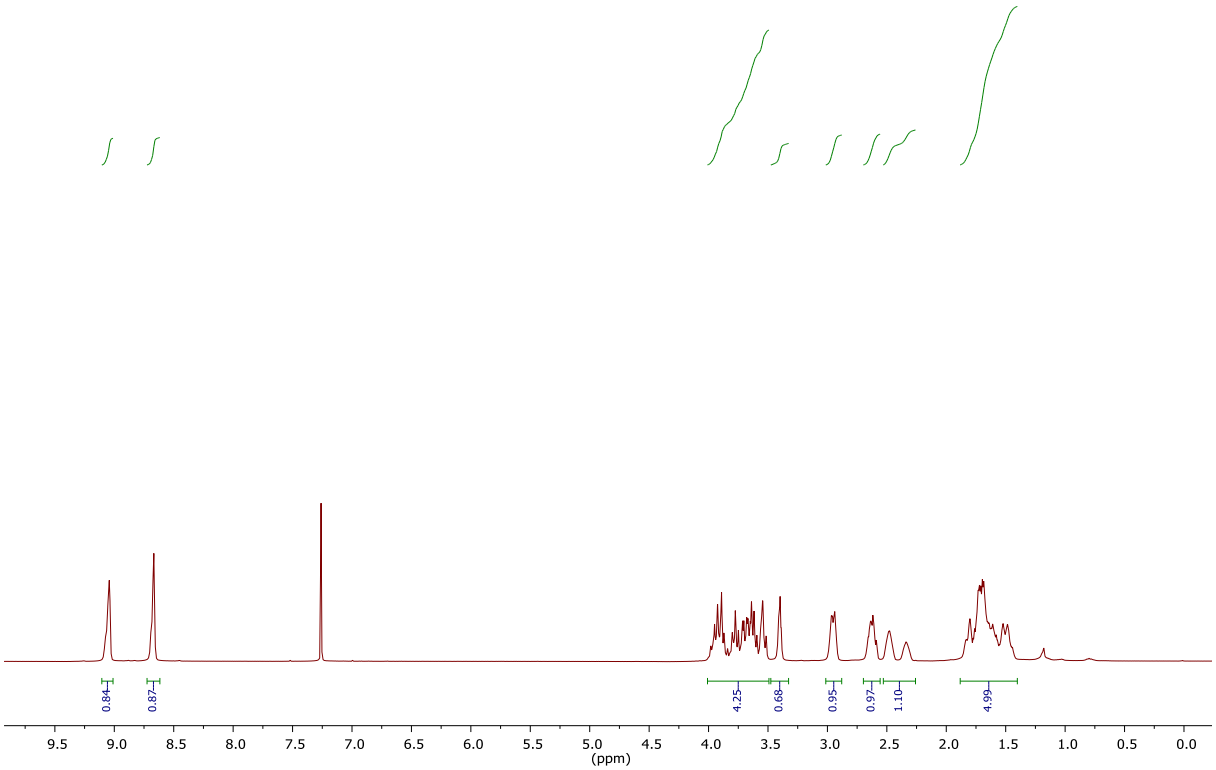


*Figure S30A [1]H-NMR (400 MHz) of **26c** in $CDCl_3$.*

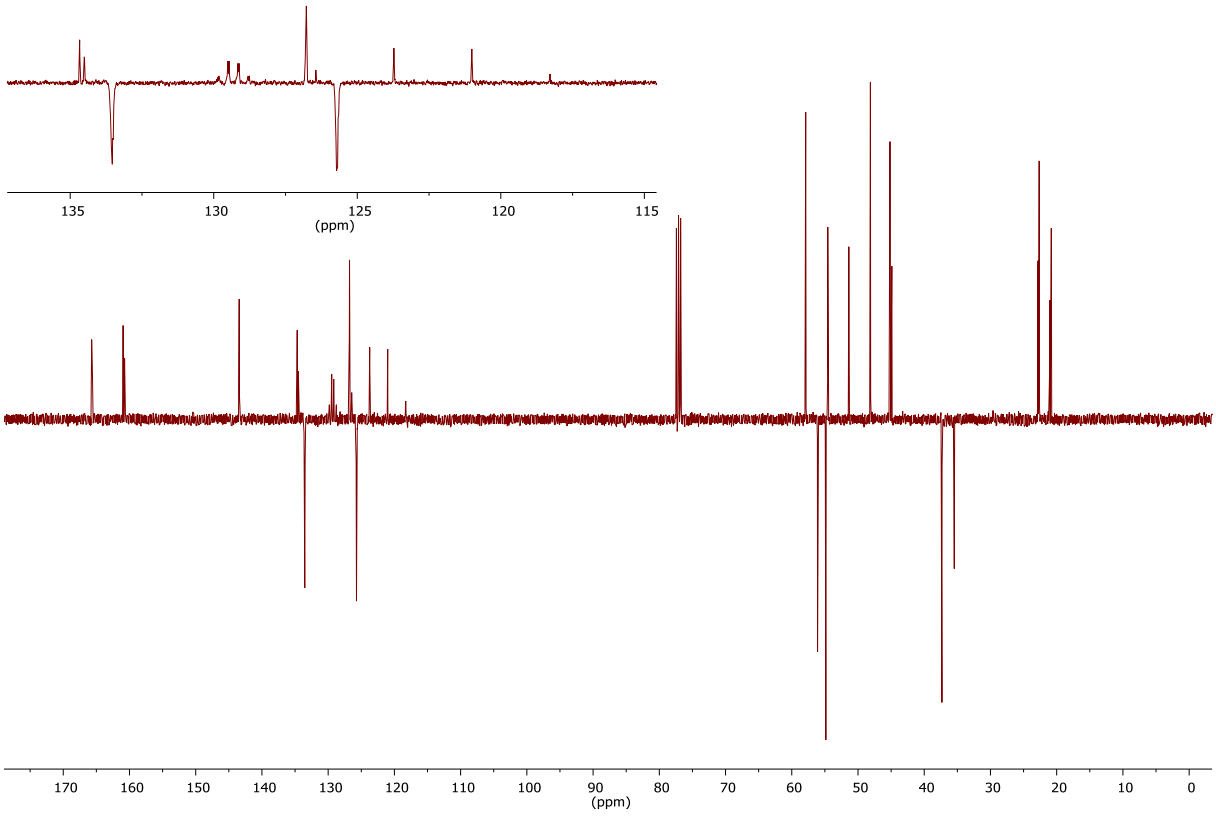
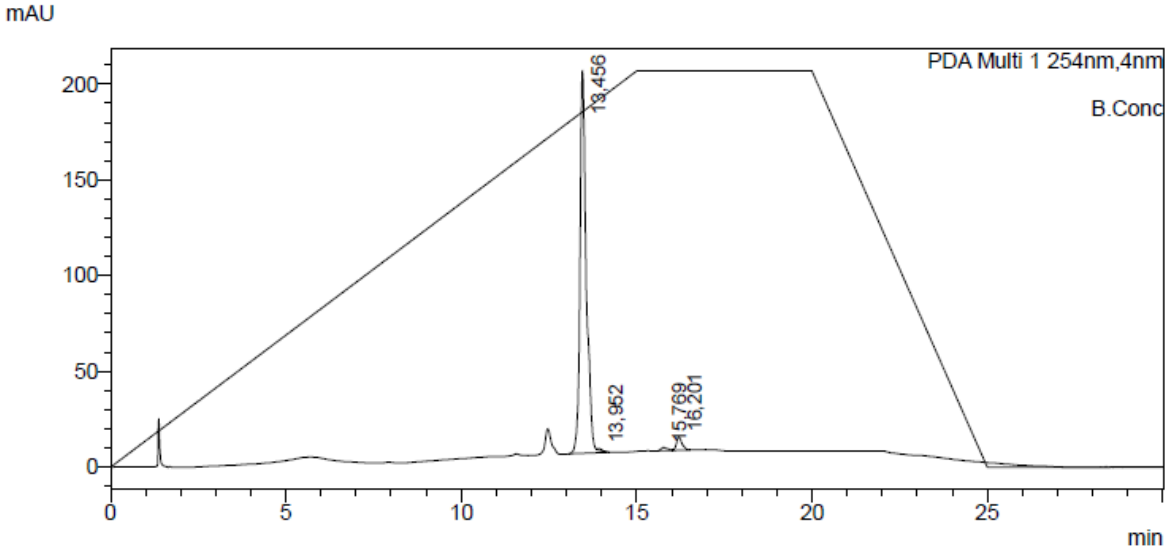


*Figure S30B [13]C-APT-NMR (100 MHz) of **26c** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 4
Injection Volume	: 20
Data File	: AR 191_070621.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch070621_1.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 07.06.2021 09:28:34
Date Processed	: 07.06.2021 09:58:36



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	13,456	2502547	199602	95,972
2	13,952	3977	625	0,153
3	15,769	22872	1775	0,877
4	16,201	78176	6989	2,998
Total		2607572	208990	100,000

*Figure S30C HPLC chromatogram of **26c**.*

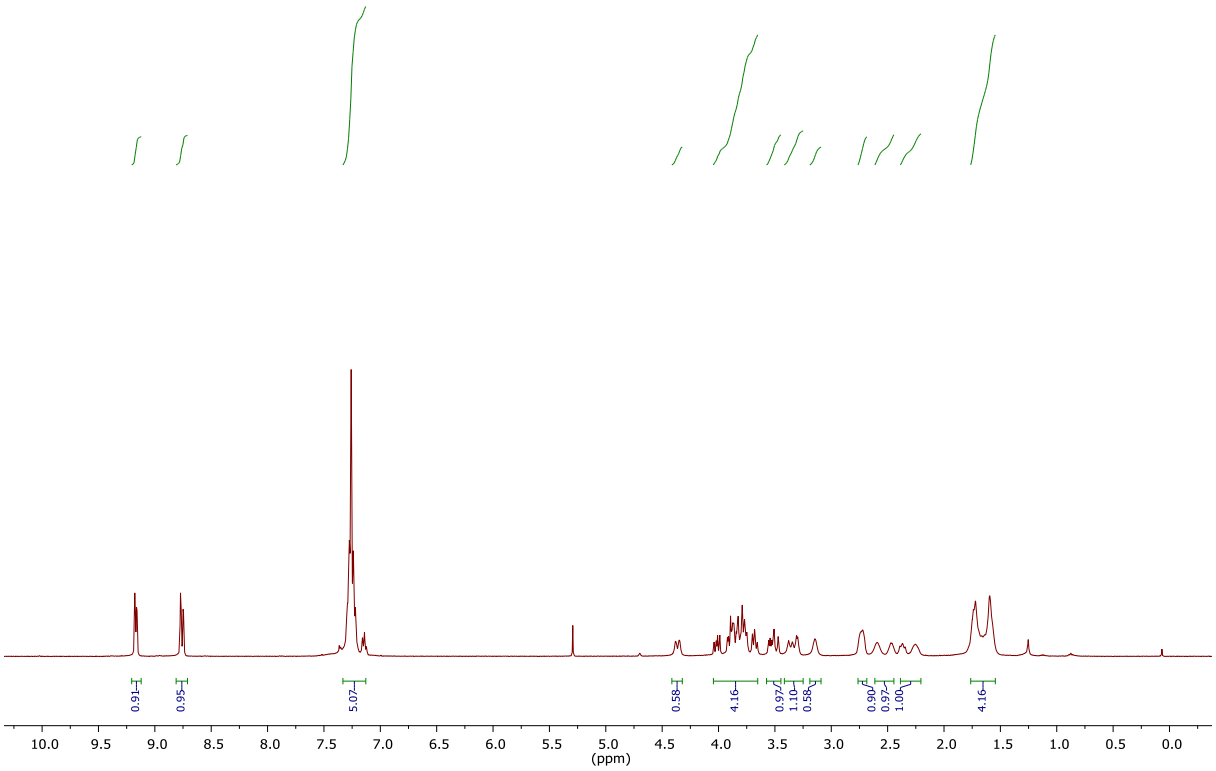


*Figure S31A ^{1}H-NMR (400 MHz) of **26d** in $CDCl_3$.*

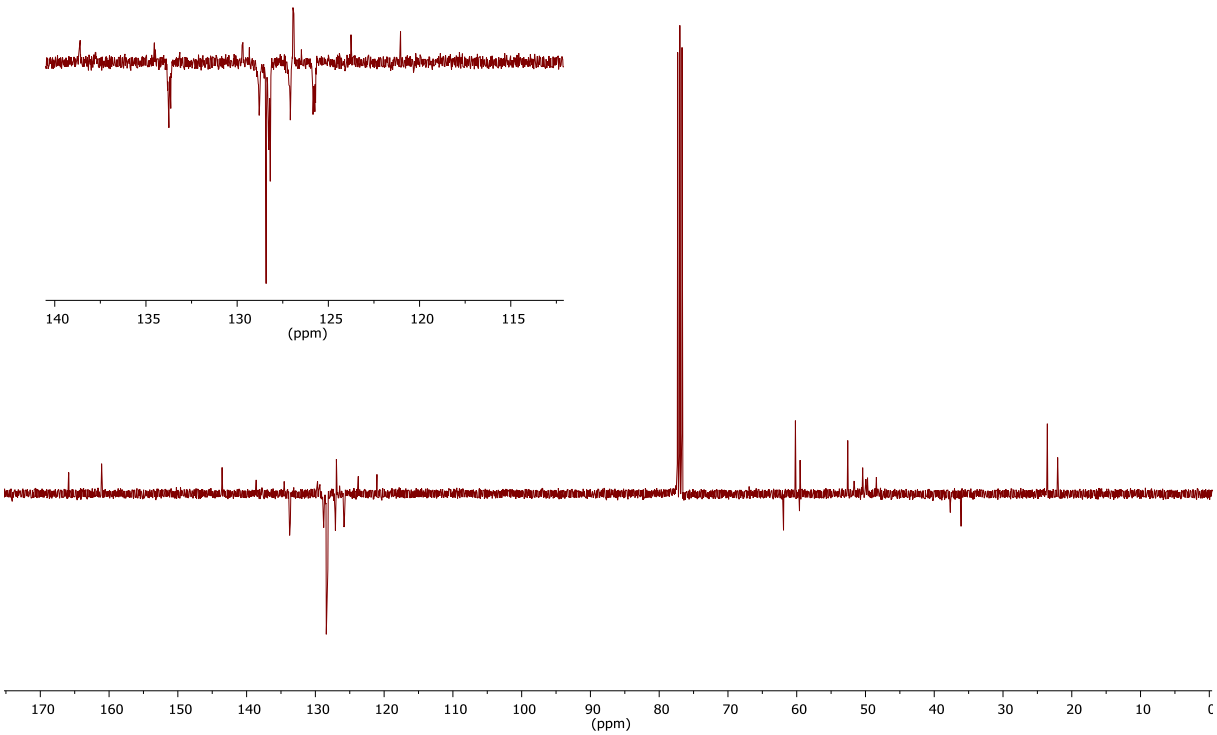
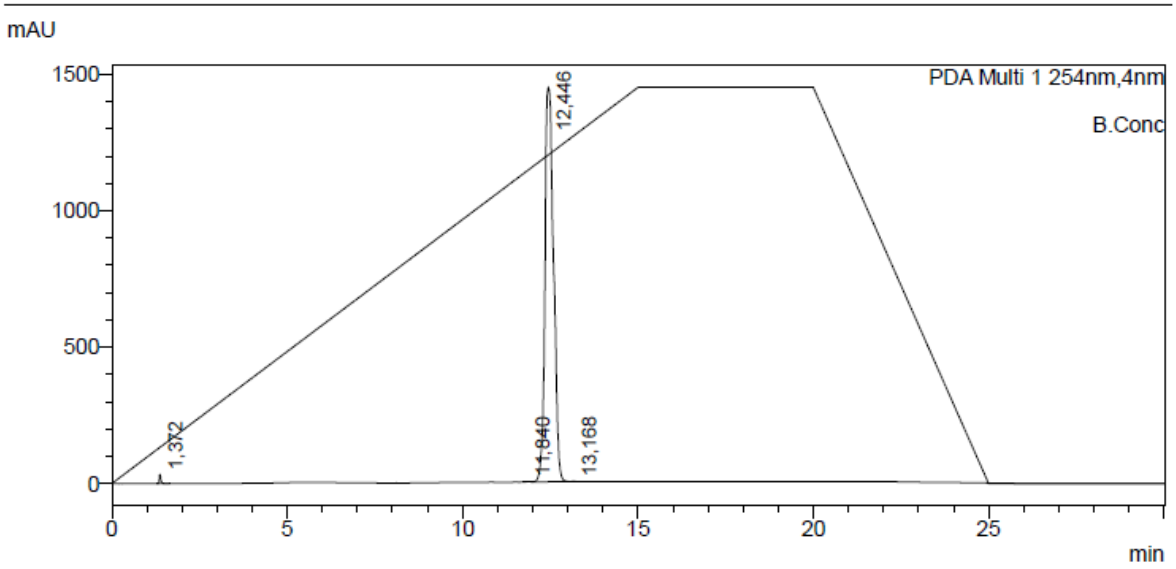


*Figure S31B ^{13}C-APT-NMR (100 MHz) of **26d** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 1
Injection Volume	: 20
Data File	: AR 194.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch040621_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 04.06.2021 09:10:43
Date Processed	: 04.06.2021 09:40:44



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	1,372	103147	32228	0,415
2	11,840	12083	1204	0,049
3	12,446	24748293	1446069	99,510
4	13,168	6698	894	0,027
Total		24870220	1480395	100,000

*Figure S31C HPLC trace of **26d**.*

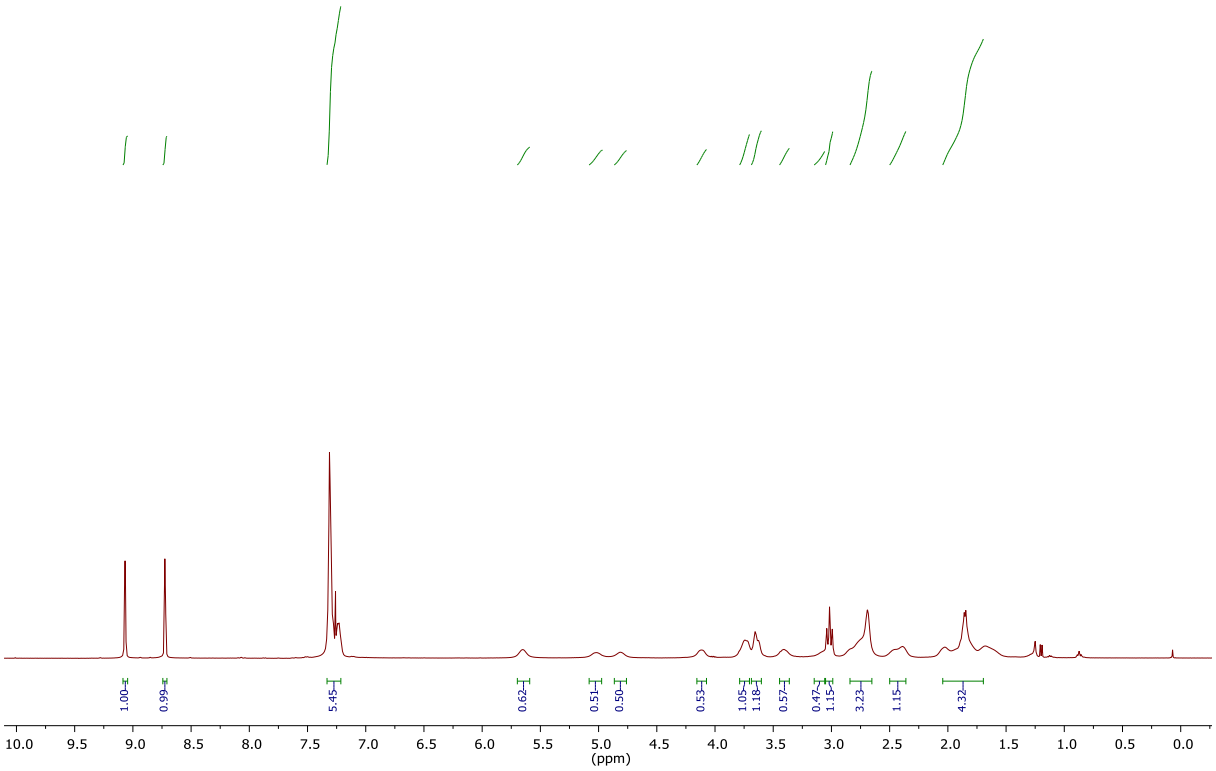


*Figure S32A [1]H-NMR (400 MHz) of **27b** in $CDCl_3$.*

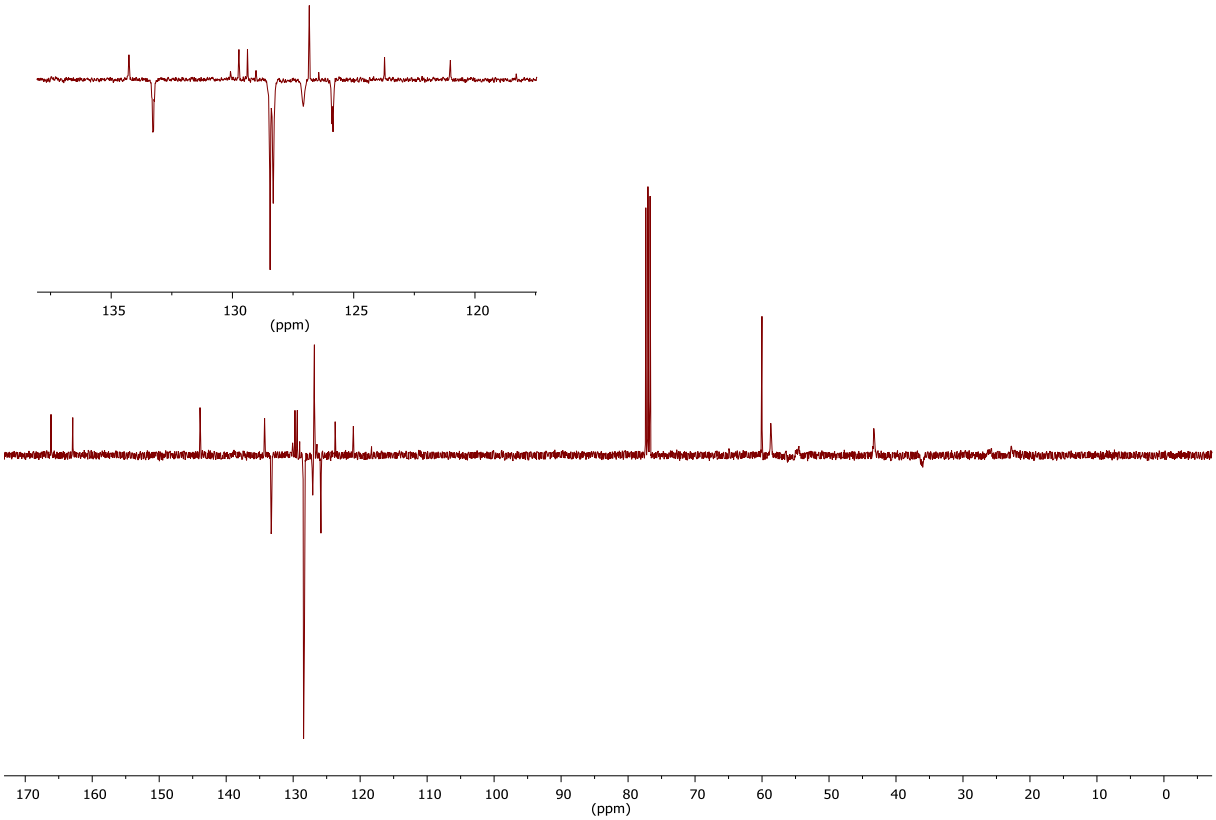
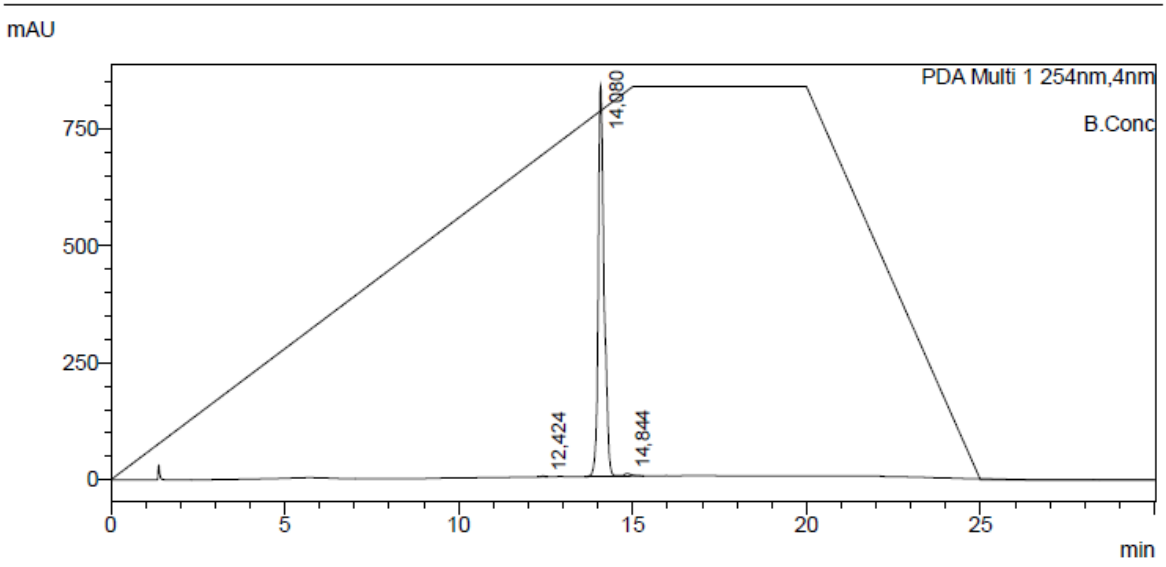


*Figure S32B [13]C-APT-NMR (125 MHz) of **27b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 0
Vial#	: 5
Injection Volume	: 20
Data File	: AR 192_070621.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch070621_1.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 07.06.2021 09:59:06
Date Processed	: 07.06.2021 10:29:08



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,424	10870	1365	0,110
2	14,080	9792401	832575	99,028
3	14,844	85240	5657	0,862
Total		9888511	839596	100,000

*Figure S32C HPLC chromatogram of **27b**.*

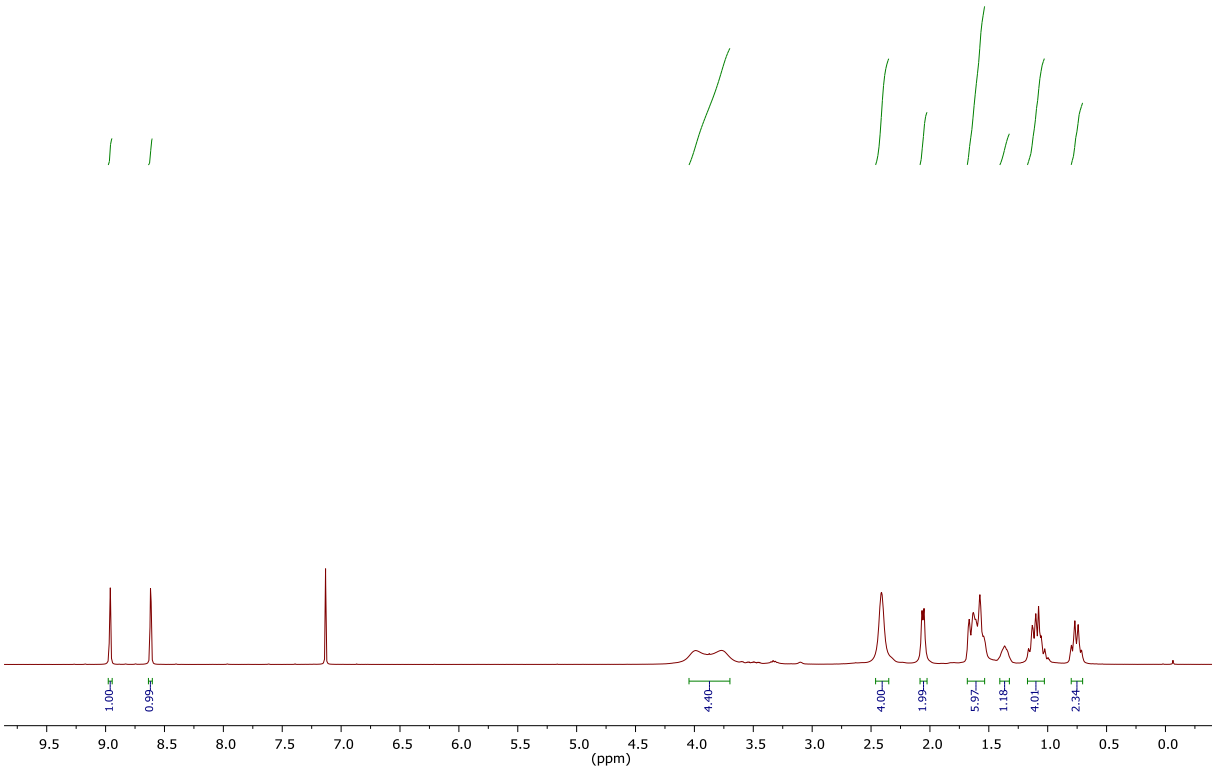


*Figure S33A ^{1}H-NMR (400 MHz) of **macozinone** in $CDCl_3$.*

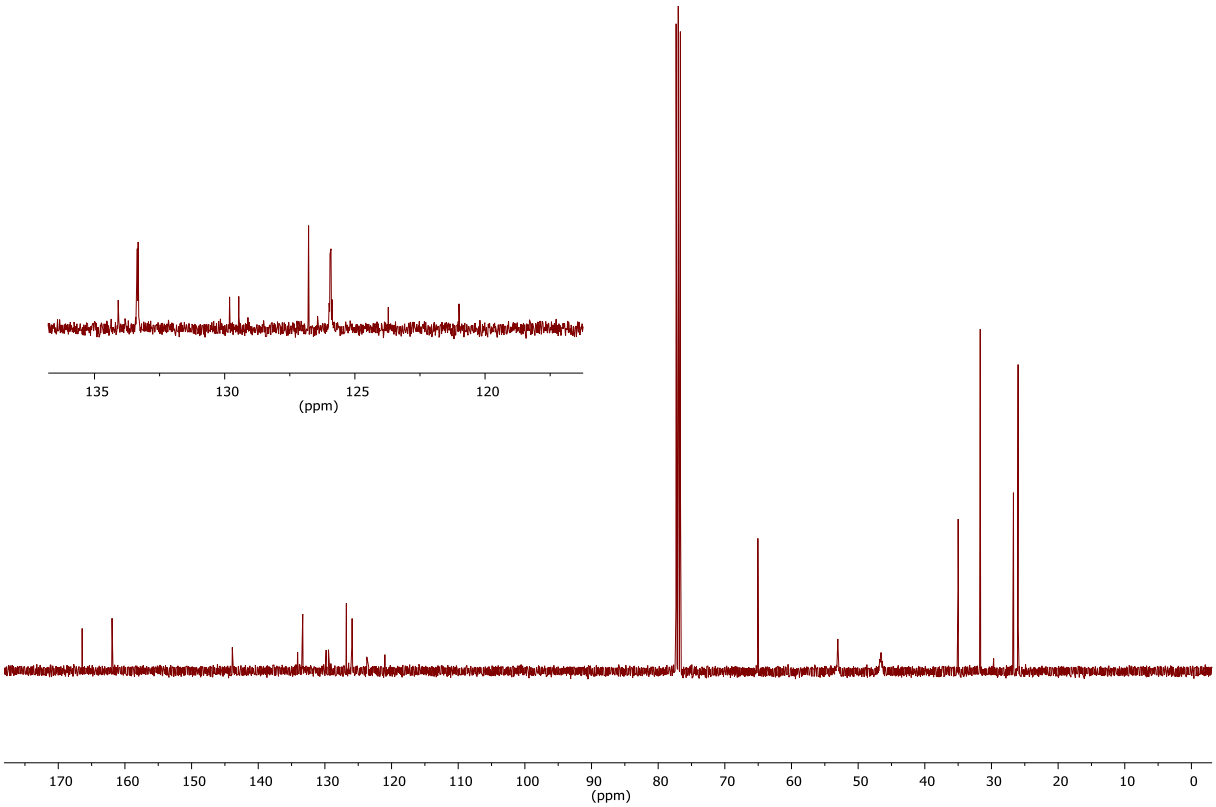
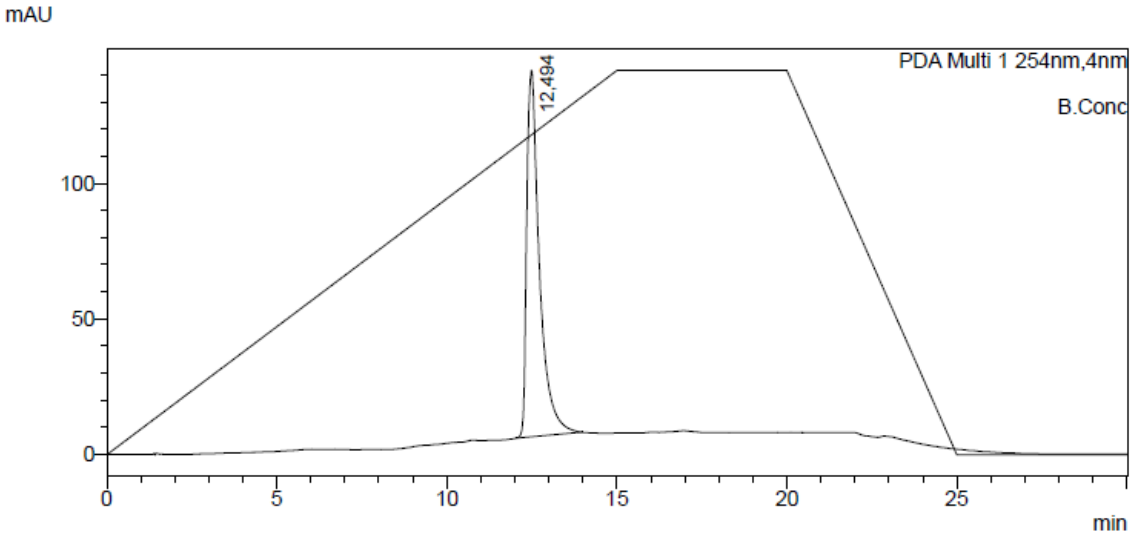


*Figure S33B ^{13}C-NMR (100 MHz) of **macozinone** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 40
Injection Volume	: 5
Data File	: macozinone.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 09:10:57
Date Processed	: 18.05.2021 09:41:00



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,494	3525842	135066	100,000
Total		3525842	135066	100,000

Figure S33C HPLC trace of ***macozinone****.*

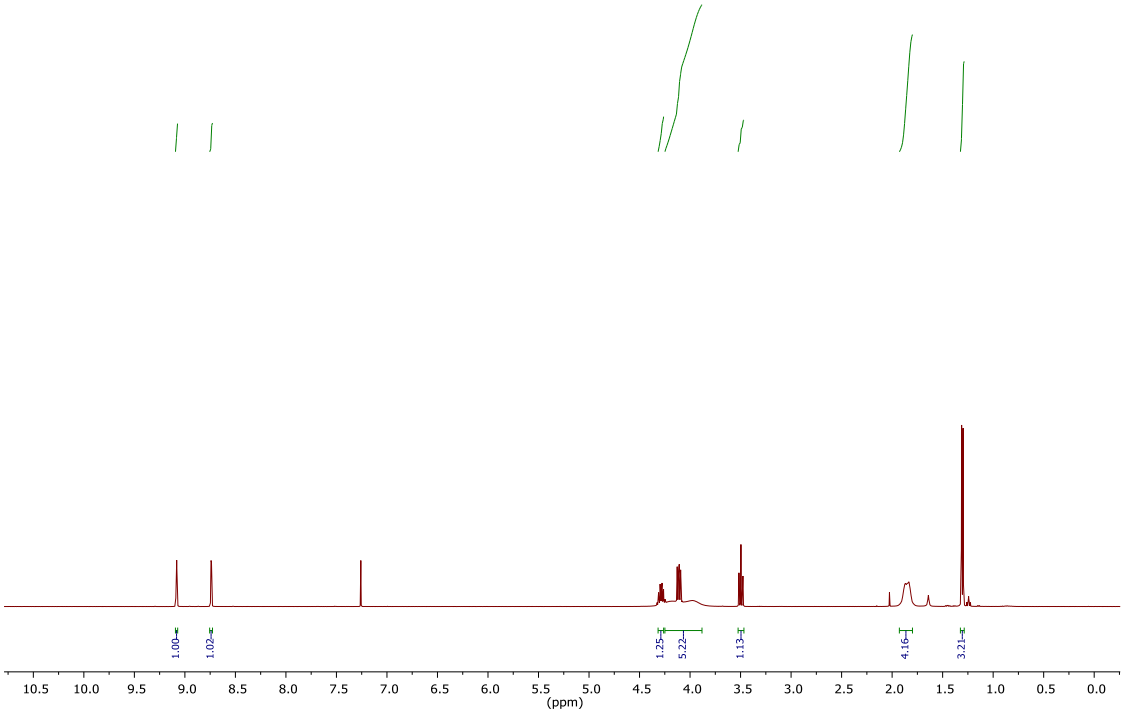


*Figure S34A ^{1}H-NMR (400 MHz) of **BTZ043** in $CDCl_3$.*

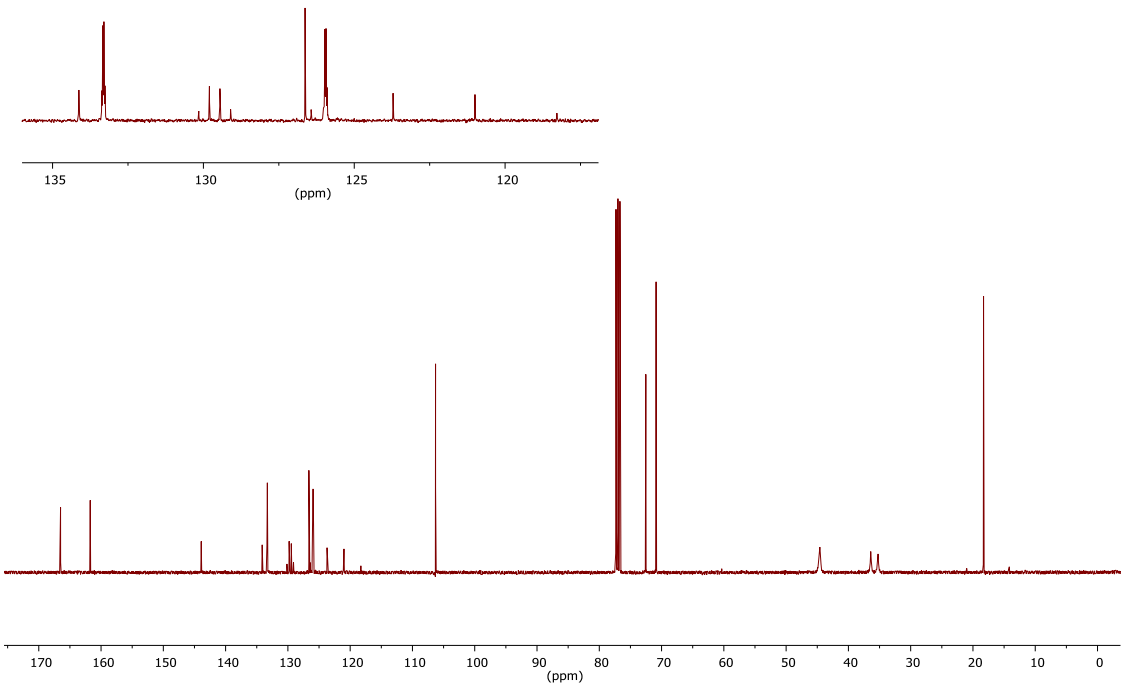
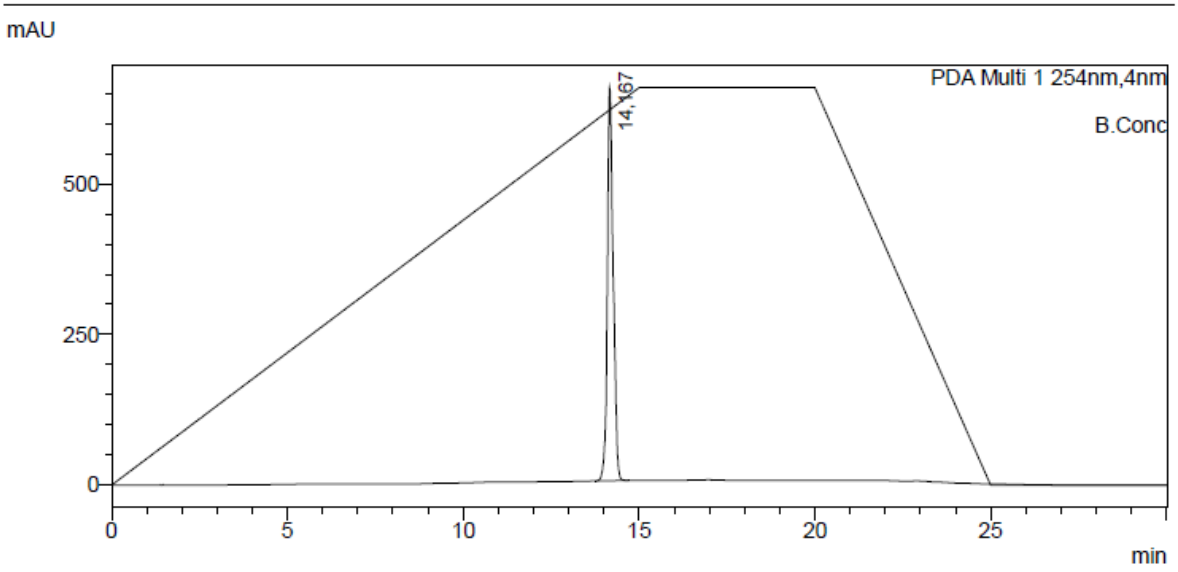


*Figure S34B ^{13}C-NMR (100 MHz) of **BTZ043** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 39
Injection Volume	: 5
Data File	: BTZ043.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 08:40:24
Date Processed	: 18.05.2021 09:10:28



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	14,167	7587509	652404	100,000
Total		7587509	652404	100,000

*Figure S34C HPLC trace of **BTZ043**.*

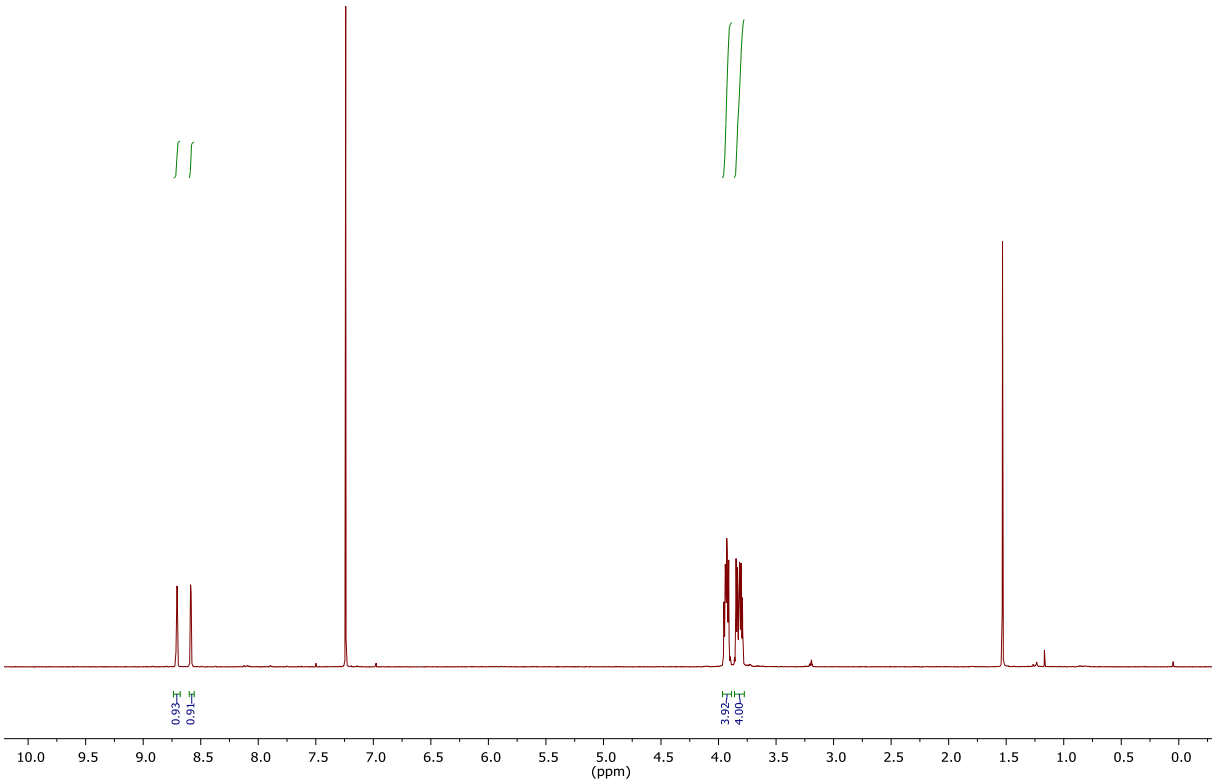


*Figure S35A ^{1}H-NMR (400 MHz) of **30b** in $CDCl_3$.*

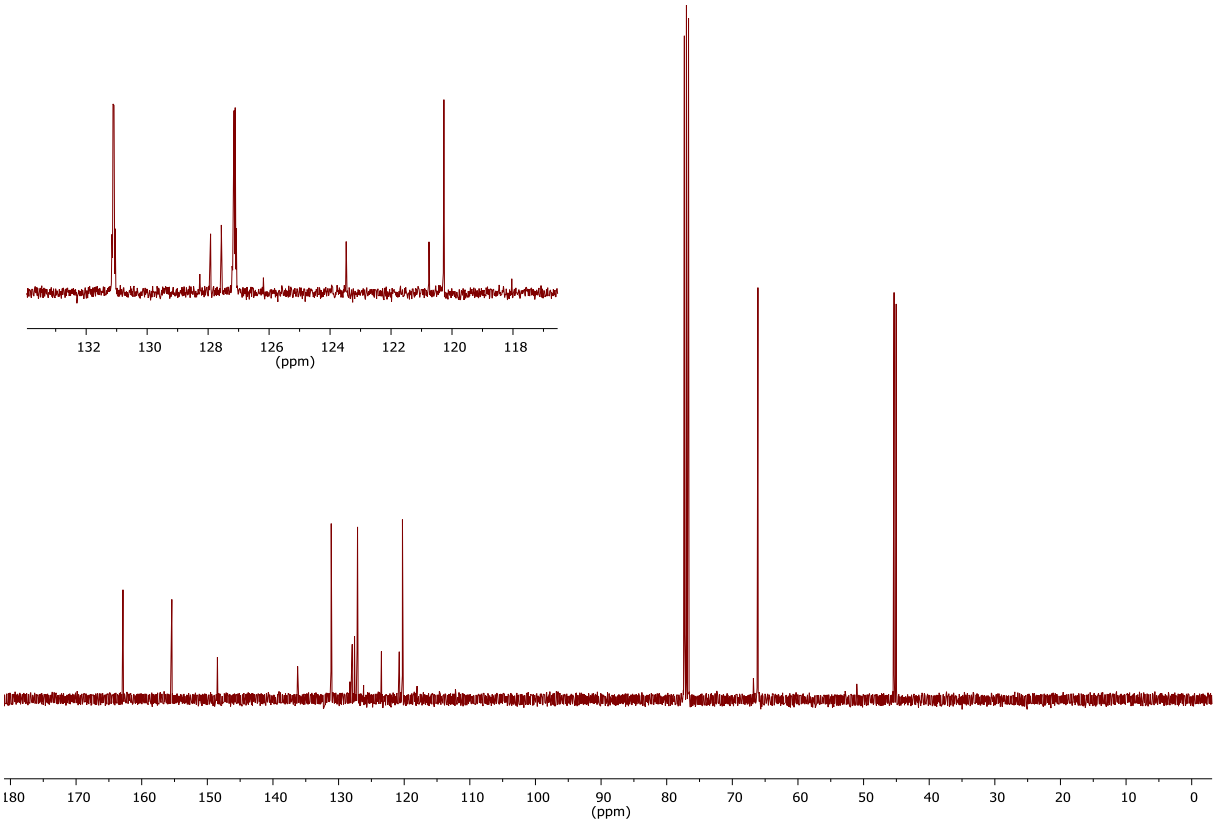
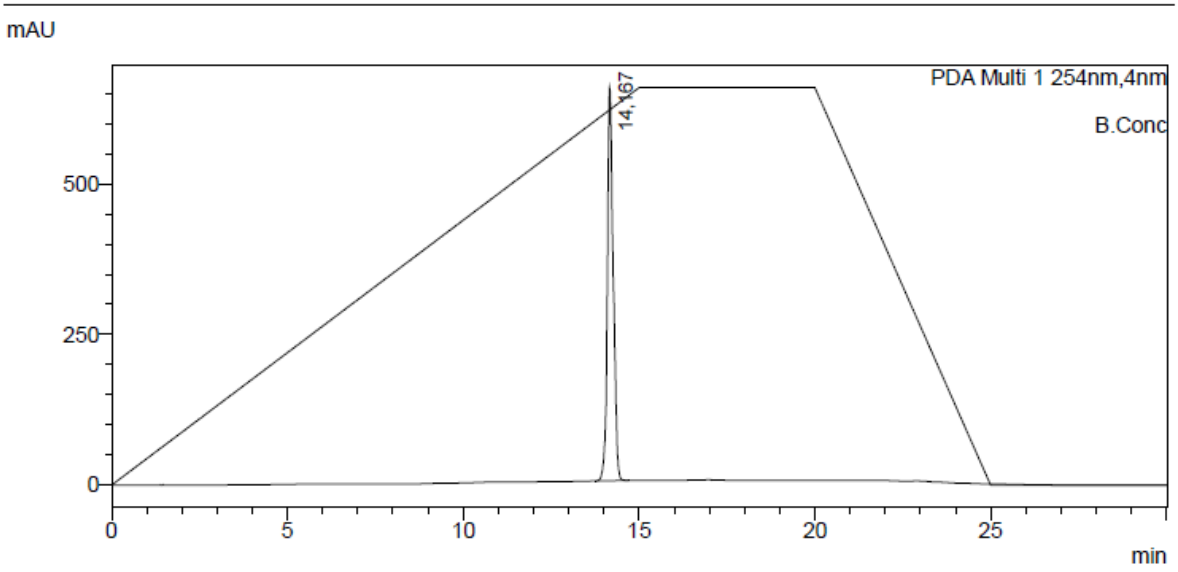


*Figure S35B ^{13}C-NMR (100 MHz) of **30b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 39
Injection Volume	: 5
Data File	: BTZ043.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 18.05.2021 08:40:24
Date Processed	: 18.05.2021 09:10:28



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	14,167	7587509	652404	100,000
Total		7587509	652404	100,000

*Figure S35C HPLC chromatogram of **30b**.*

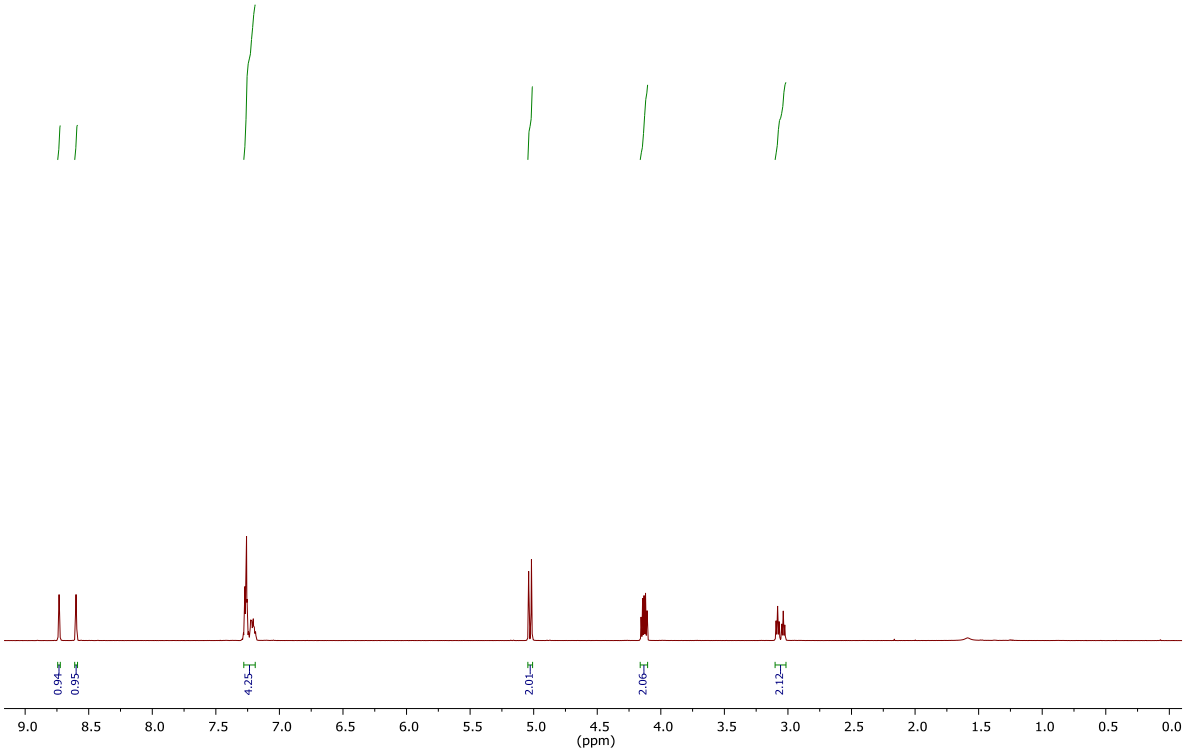


*Figure S36A [1]H-NMR (400 MHz) of **31b** in $CDCl_3$.*

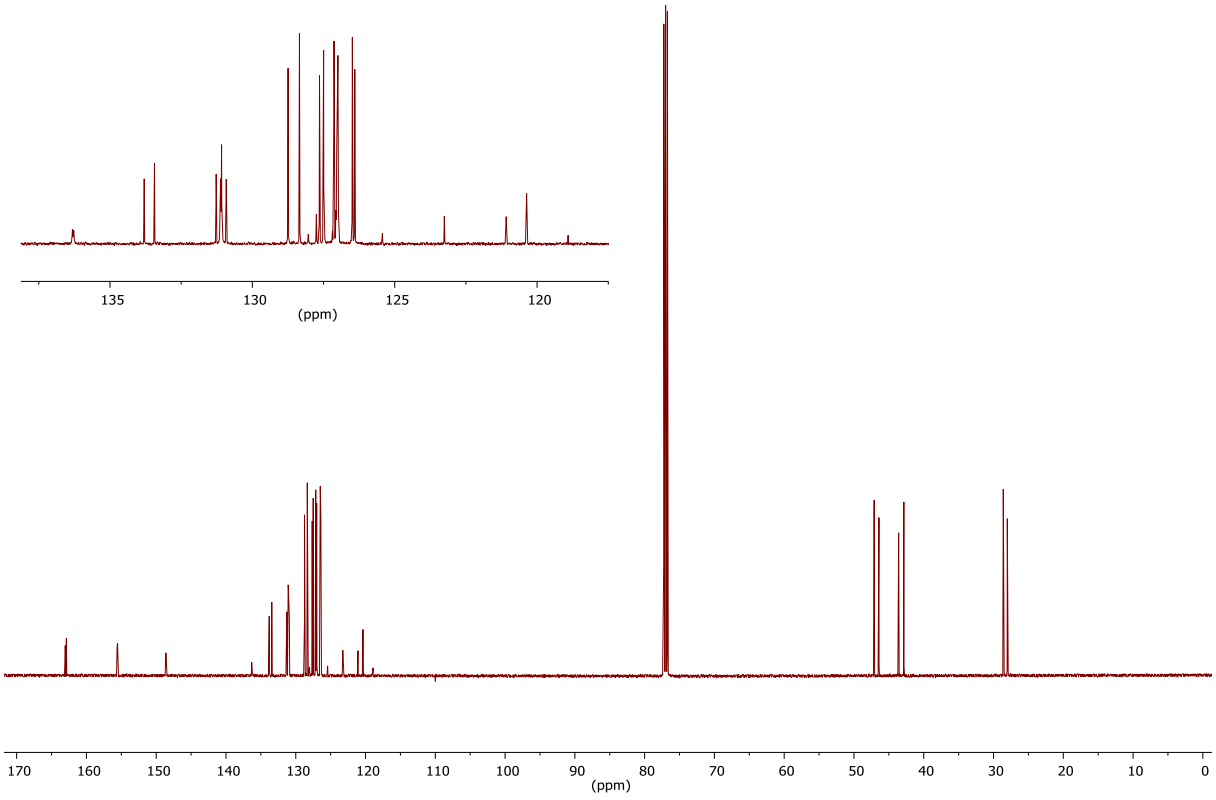


*Figure S36B [13]C-NMR (100 MHz) of **31b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 8
Injection Volume	: 5
Data File	: AR125.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 16:54:03
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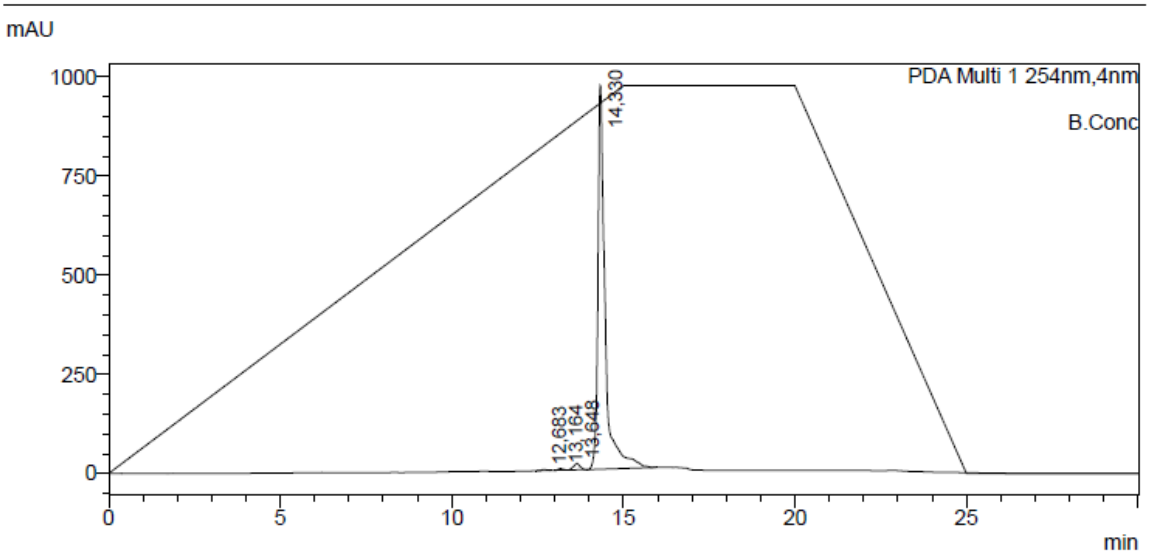

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	12,683	21919	2130	0,151
2	13,164	36265	3754	0,250
3	13,648	216198	16547	1,490
4	14,330	14238048	967103	98,109
Total		14512430	989534	100,000

*Figure S36C HPLC trace of **31b**.*

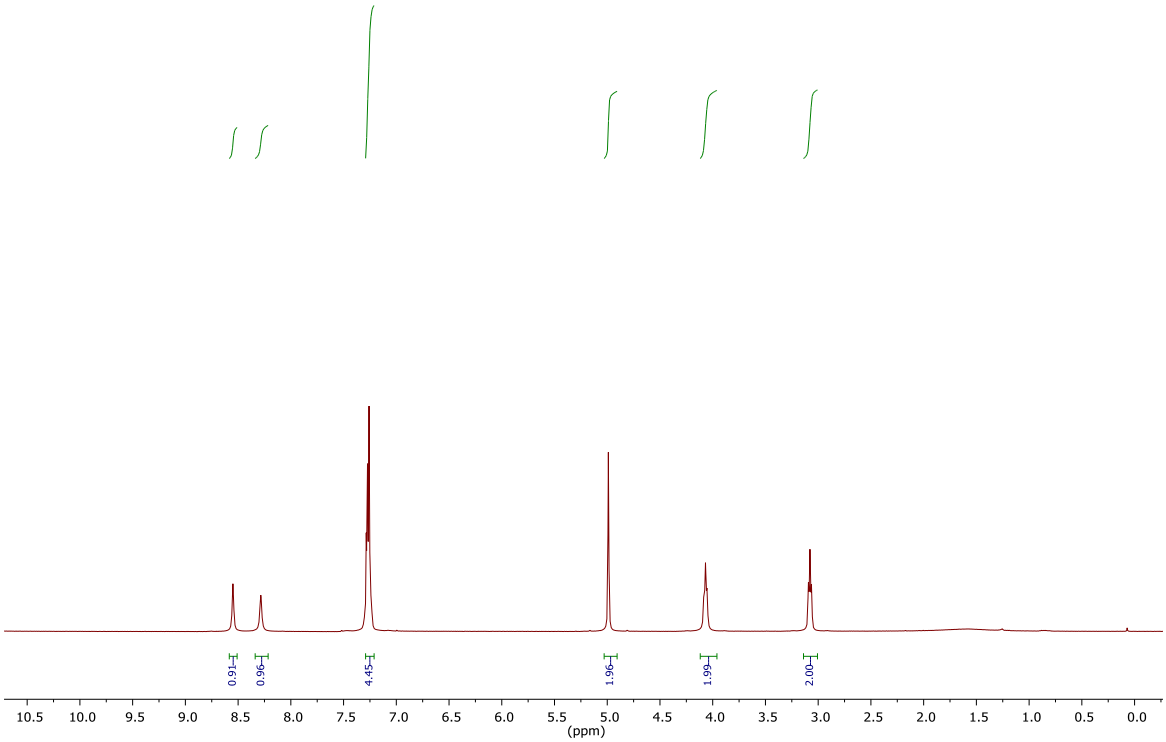

*Figure S37A [1]H-NMR (400 MHz) of **32a** in $CDCl_3$.*

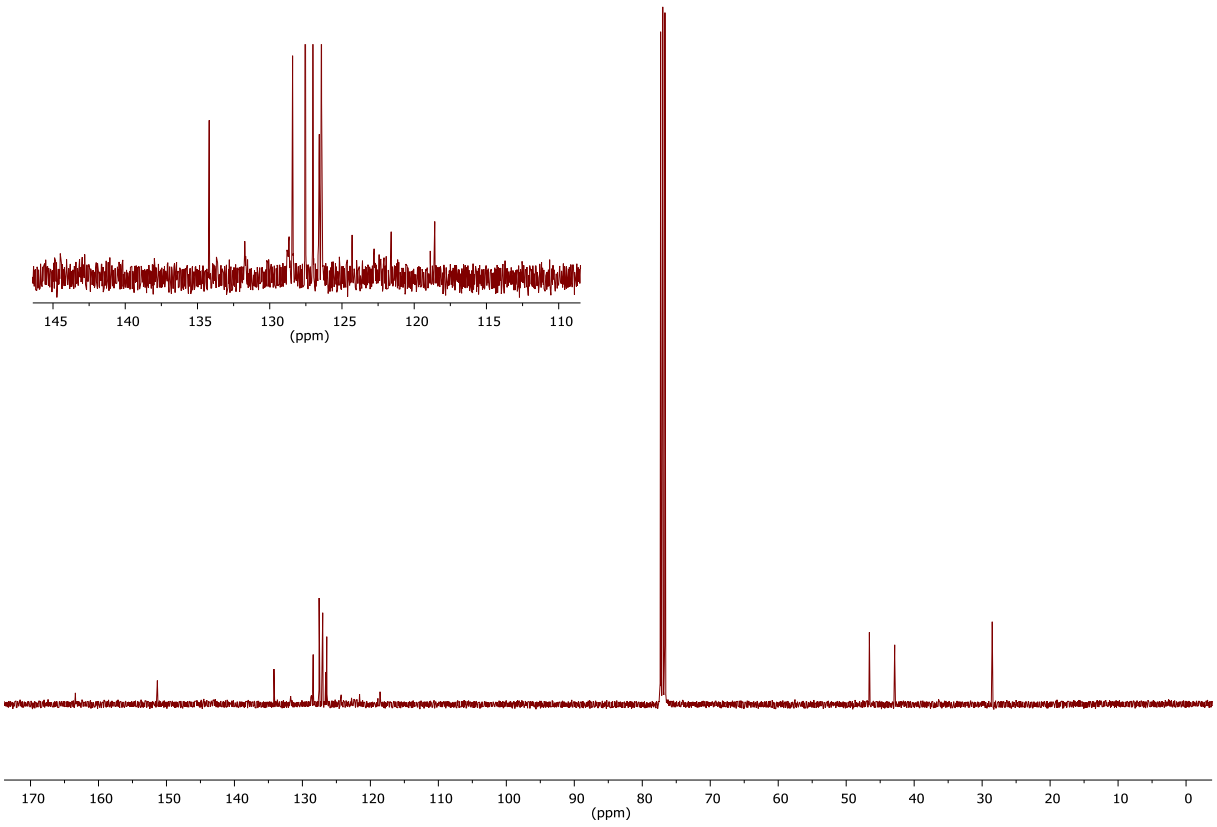

*Figure S37B [13]C-NMR (100 MHz) of **32a** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 18
Injection Volume	: 5
Data File	: AR199.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
Date Acquired	: 17.05.2021 21:59:22
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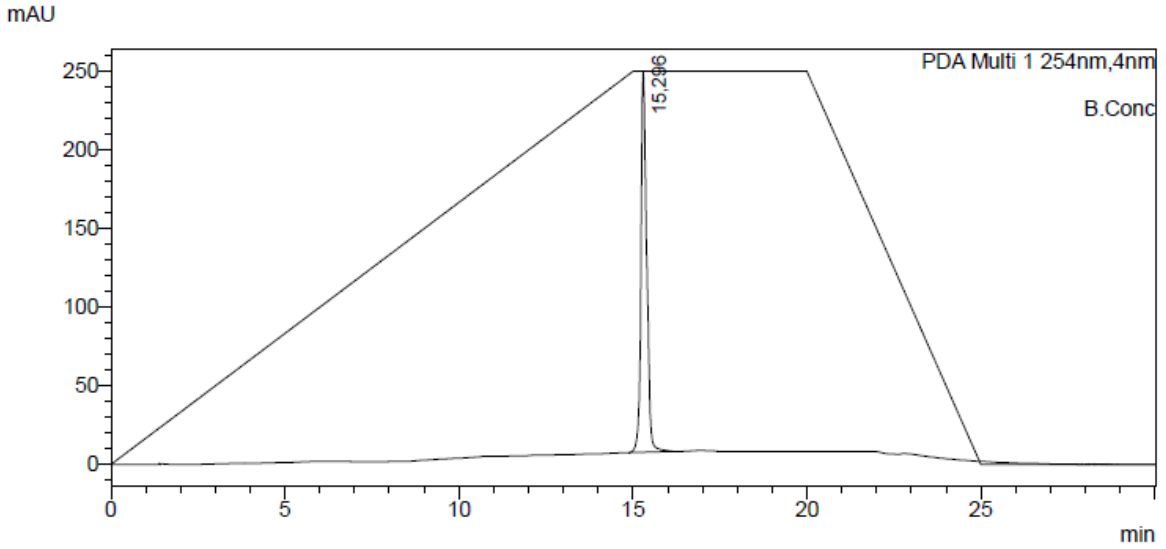

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	15,296	2779372	242101	100,000
Total		2779372	242101	100,000

*Figure S37C HPLC chromatogram of **32a**.*

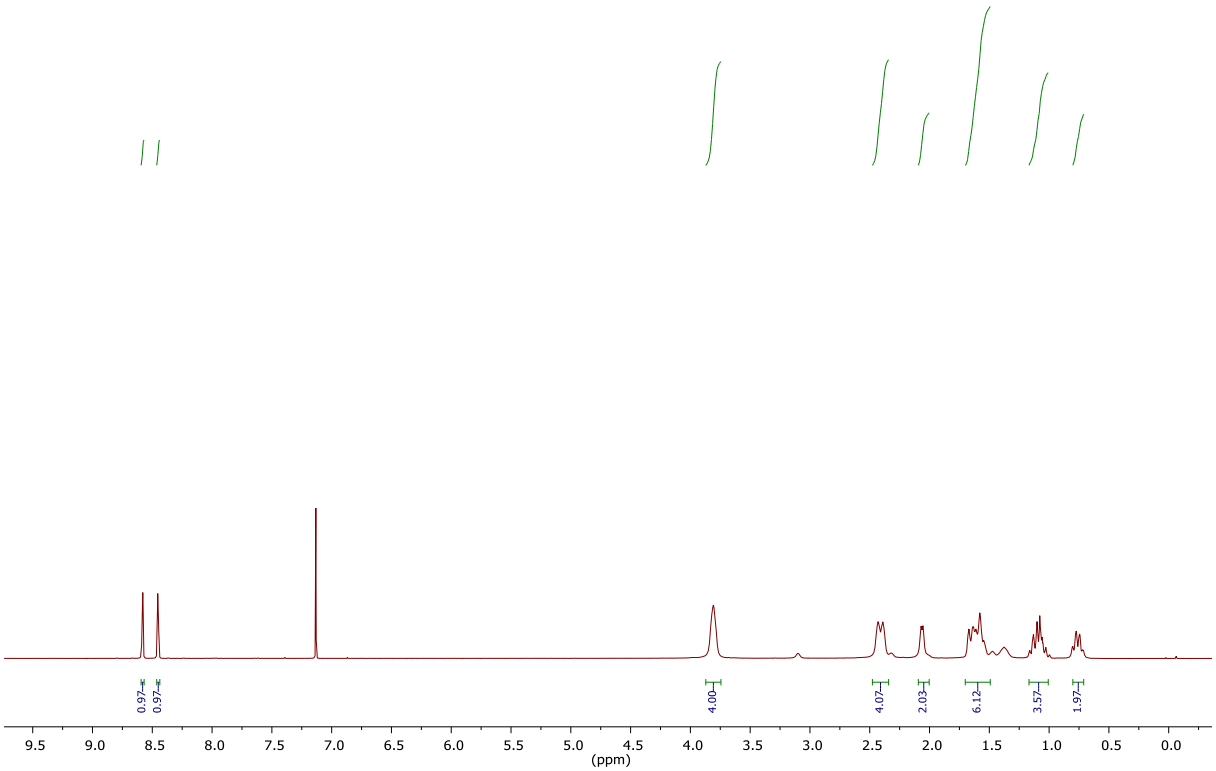

*Figure S38A [1]H-NMR (400 MHz) of **33b** in $CDCl_3$.*

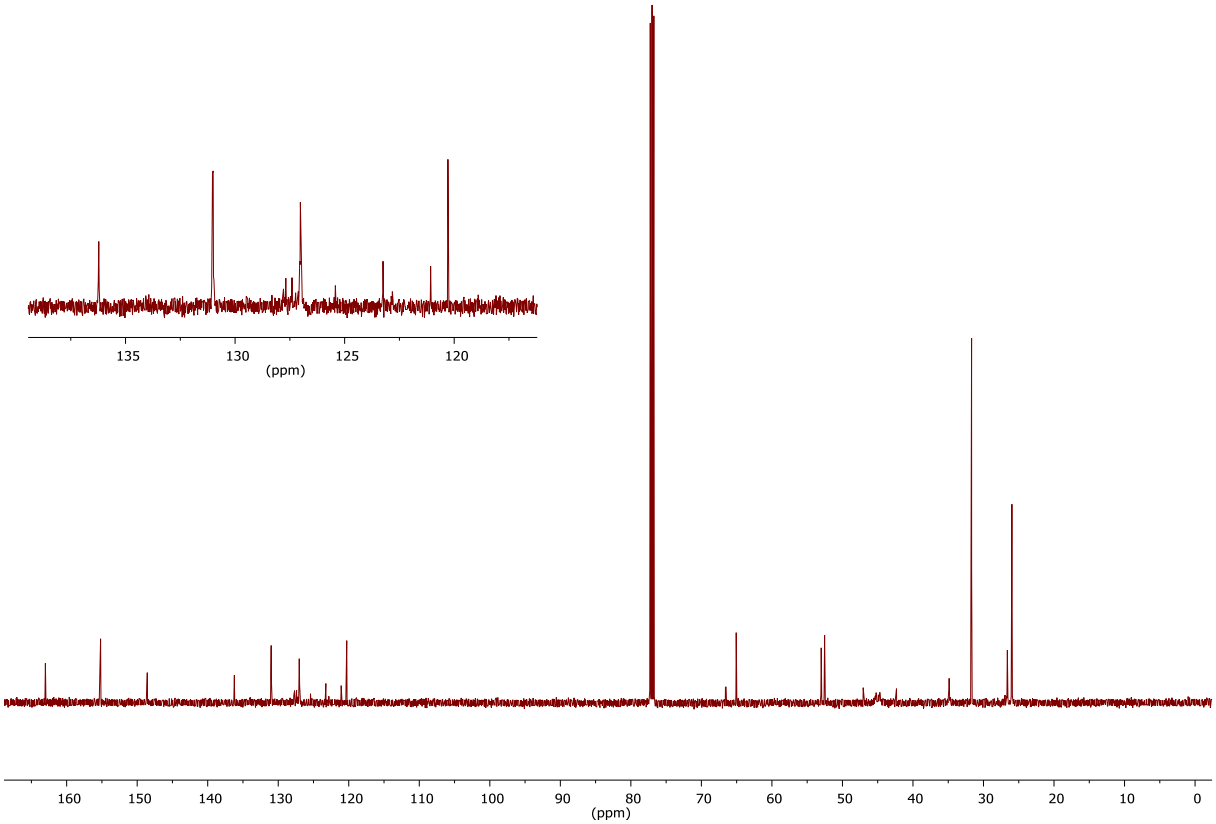

*Figure S38B [13]C-NMR (125 MHz) of **33b** in $CDCl_3$.*

Sample Information

Sample Name	:
Tray#	: 1
Vial#	: 17
Injection Volume	: 5
Data File	: AR79.lcd
Method File	: MSP5-95_30min_1.0.lcm
Batch File	: Batch170521_2.lcb
Report Format File	: Reportformat1.lsr
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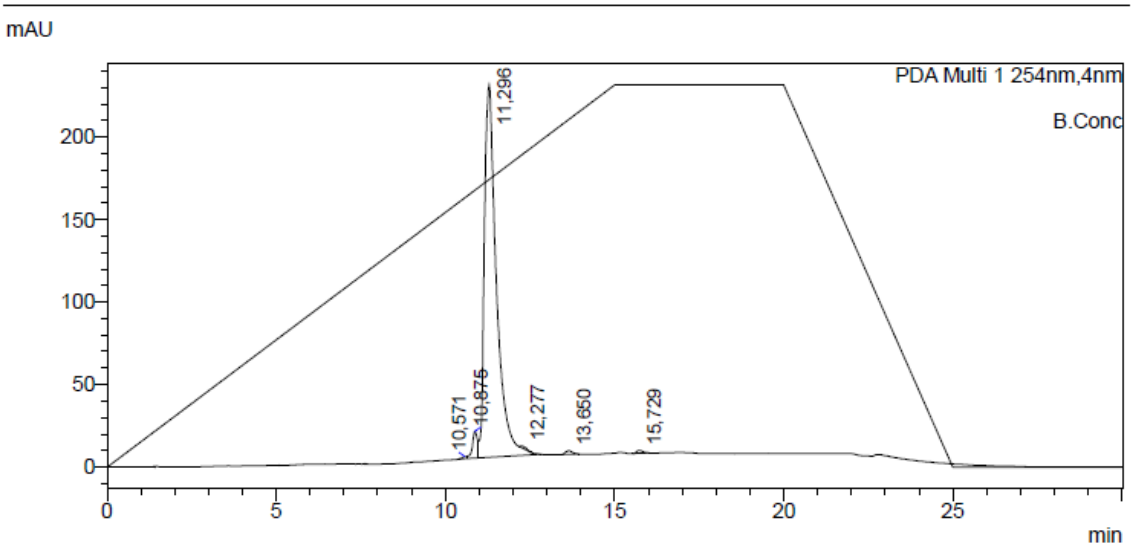
Date Processed	: 17.05.2021 21:58:53



PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	10,571	13749	1309	0,235
2	10,875	167610	16245	2,866
3	11,296	5599146	225774	95,754
4	12,277	13785	1212	0,236
5	13,650	30701	2196	0,525
6	15,729	22423	1809	0,383
Total		5847414	248545	100,000

*Figure S38C HPLC chromatogram of **33b**.*

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) ipds5968

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: ipds5968

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               alpha=80.347(4)   beta=82.041(4)   gamma=87.310(4)
Temperature:   170 K
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	Calculated	Reported
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Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C18 H19 F3 N4 O5 S	C18 H19 F3 N4 O5 S
Sum formula	C18 H19 F3 N4 O5 S	C18 H19 F3 N4 O5 S
Mr	460.43	460.43
Dx,g cm-3	1.524	1.524
Z	2	2
Mu (mm-1)	0.228	0.228
F000	476.0	476.0
F000’	476.54	
h,k,lmax	8,12,23	8,12,23
Nref	5428	5359
Tmin,Tmax	0.909,0.934	0.745,1.328
Tmin’	0.894	

```
Correction method= # Reported T Limits: Tmin=0.745 Tmax=1.328
AbsCorr = MULTI-SCAN

Data completeness= 0.987          Theta(max)= 29.201

R(reflections)= 0.0476( 4802)     wR2(reflections)= 0.1311( 5359)

S = 1.040                 Npar= 293
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

```
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ......      2.086 Check
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L=    0.600         29 Report
PLAT913_ALERT_3_C Missing # of Very Strong Reflections in FCF ....          9 Note
```

Alert level G

```
PLAT002_ALERT_2_G Number of Distance or Angle Restraints on AtSite          8 Note
PLAT003_ALERT_2_G Number of Uiso or Uij Restrained non-H Atoms ...          6 Report
PLAT154_ALERT_1_G The s.u.'s on the Cell Angles are Equal ..(Note)      0.004 Degree
PLAT171_ALERT_4_G The CIF-Embedded .res File Contains EADP Records          3 Report
PLAT176_ALERT_4_G The CIF-Embedded .res File Contains SADI Records          3 Report
PLAT186_ALERT_4_G The CIF-Embedded .res File Contains ISOR Records          1 Report
PLAT230_ALERT_2_G Hirshfeld Test Diff for    F1'      --C9       .       20.5 s.u.
PLAT230_ALERT_2_G Hirshfeld Test Diff for    F2'      --C9       .        5.2 s.u.
PLAT230_ALERT_2_G Hirshfeld Test Diff for    F3'      --C9       .        6.7 s.u.
PLAT242_ALERT_2_G Low    'MainMol' Ueq as Compared to Neighbors of         C9 Check
PLAT301_ALERT_3_G Main Residue  Disorder ..............(Resd  1  )        10% Note
PLAT860_ALERT_3_G Number of Least-Squares Restraints .............         81 Note
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min).          1 Note
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600         40 Note
PLAT933_ALERT_2_G Number of OMIT Records in Embedded .res File ...          2 Note
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ...........        2.7 Low
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.         11 Info
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   3 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  17 ALERT level G = General information/check it is not something unexpected

   1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   8 ALERT type 2 Indicator that the structure model may be wrong or deficient
   7 ALERT type 3 Indicator that the structure quality may be low
   4 ALERT type 4 Improvement, methodology, query or suggestion
   0 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica, Journal of Applied Crystallography, Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 13/07/2021; check.def file version of 13/07/2021

Datablock ipds5968 - ellipsoid plot