

Supplementary Material

Facilitating Biomimetic Syntheses of Borrerine Derived Alkaloids by Means of Flow-Chemical Methods

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1. General information

Solvents and reagents:

All flow reactions were carried out with reagent grade solvents. All batch reactions were carried out with anhydrous solvents and with oven dried glassware. Reagents were purchased from commercial suppliers and used as received.

Flow Equipment:

Flow reactions were performed on a Vapourtec R series Flow chemistry system, equipped with standard Knauer HPLC pumps (flow rates from 0.010 to 9.99 mL/min, pressures up to 42 bar) and a standard column reactor, i.e. the column was housed inside an insulated glass manifold which was heated by hot air. The temperature was measured at the column wall. Glass Omnifit[®] columns (10.0 mm i.d. × 100.0 mm length) were used to contain the solid-supported reagents. Standard PTFE tubing (i.d. 1.0 mm) was used. Standard PTFE tubing connectors were used to connect tubing to inputs and outputs.

Back pressure regulators (BPR) were obtained from Upchurch and were adjusted prior to use. The flow direction through the solid-supported reagent was against gravity (input at the bottom of the column, output at the top) to negate any gravitational effects.

Melting points:

Melting points were performed on a Stanford Research Systems MPA100 (OptiMelt) automated melting point system and are uncorrected.

NMR spectroscopy:

¹H-NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer with the residual solvent peak as the internal reference (CDCl₃ = 7.26 ppm, DMSO-*d*⁶ = 2.50 ppm, MeOH-*d*⁴ = 3.31 ppm). ¹H resonances are reported to the nearest 0.01 ppm. ¹³C-NMR spectra were recorded on the same spectrometer with the central resonance of the solvent peak as the internal reference (CDCl₃ = 77.16 ppm, DMSO-*d*⁶ = 39.52 ppm, MeOH-*d*⁴ = 49.00 ppm). All ¹³C resonances are reported to the nearest 0.01 ppm. DEPT 135, COSY, HMQC, and HMBC experiments were used to aid structural determination and spectral assignment. The multiplicity of ¹H signals are indicated as: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, m = multiplet, m_c = centered multiplet, br. = broad, or combinations thereof. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz.

IR spectroscopy:

Infrared spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories.

Elemental analysis:

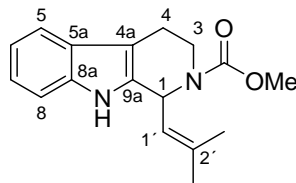
Elemental analyses were determined by the microanalysis laboratories at the Department of Chemistry, University of Cambridge/UK.

High resolution mass:

High resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT Premier™ spectrometer using time of flight with positive electrospray ionization (EI).

2. Experimental Procedures

Methyl 1-(2-methylprop-1-enyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (**12**)¹



Molecular sieves 3Å (previously dried at 140°C for 18 h, 60 g) was added to a solution of tryptamine (5.13 g, 32.0 mmol) and 3-methyl-2-butenal (3.36 mL, 2.96 g, 35.2 mmol, 1.1 equiv.) in CH₂Cl₂ (160 mL) at room temp. After stirring for 12 h the mixture was cooled to 0°C. Pyridine (10.4 mL, 10.1 g, 128 mmol, 4.0 equiv.) and methyl chloro formate (5.44 mL, 6.65 g, 70.4 mmol, 2.2 equiv.) were added consecutively, and the reaction mixture was allowed to warm to room temp. After 5 h at room temperature the mixture was filtered over a pad of celite and the filtrate was washed with aqueous HCl (1 M, 2 × 100 mL) and brine (100 mL). The organic phase was dried over Na₂SO₄. Evaporation of the solvent gave a dark brown foam. To remove remaining aldehyde the material was pulverized, suspended in hexane/Et₂O (90:10 v/v, 100 mL), vigorously stirred for 30 min. and afterwards filtered and dried *in vacuo* to yield **12** (8.10 g, 89%) as a brownish solid which was reduced to **2** in the next step without further purification.

12 for use in flow experiments was purified by column chromatography (5.0 cm × 10 cm, CH₂Cl₂ → CH₂Cl₂/MeOH 100:1) to give a white, analytically pure solid.

R_f (CH₂Cl₂) = 0.13.

Melting point: 183°C.

¹H NMR (400 MHz, CDCl₃): δ = 1.82 and 2.03 (2 × s, 6H, 2 × 3'-CH₃), 2.77-2.93 (m, 2H, 4-H₂), 3.24-3.32 (m, 1H, 3-H¹), 3.81 (s, 3H, OCH₃), 4.49 (br. s, 1H, 3-H²), 5.42 (m_c, *J*_{1',1} = 9.6 Hz visible, 1H, 1'-H), 5.99 (br. s, 1H, 1-H), 7.15 (ddd, 1H, *J*_{6,5} = *J*_{6,7} = 7.2 Hz, *J*_{6,8} = 1.1 Hz, 6-H), 7.20 (ddd, 1H, *J*_{7,6} = *J*_{7,8} = 7.1 Hz, *J*_{7,5} = 1.3 Hz, 7-H), 7.33 (d, *J*_{8,7} = 7.5 Hz, *J*_{8,6} not visible, 1H, 8-H), 7.54 (d, *J*_{5,6} = 7.6 Hz, *J*_{5,7} not visible, 1H, 5-H), 7.99 ppm (br. s, 1H, NH).

¹³C NMR (100 MHz, CDCl₃): δ = 18.45 (C-3¹), 21.57 (C-4), 25.98 (C-3^{II}), 39.36 (C-3), 49.82 (C-1), 52.77 (OCH₃), 108.73 (C-4a), 110.95 (C-8), 118.23 (C-5), 119.53 (C-6), 121.85 (C-7), 122.38 (C-1'), 127.04 (C-5a), 133.82 (C-9a), 136.29 (C-8a), 156.15 ppm (C=O).

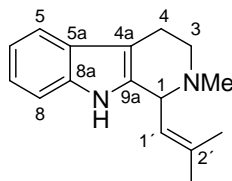
Elemental analysis: 71.77% C, 7.08% H, 9.86% N; calc. for C₁₇H₂₀N₂O₂: 71.81% C, 7.09% H, 9.85% N.

HRMS (ESI): *m/z* calcd. for C₁₇H₂₁N₂O₂ [M+H]⁺: 285.1603; found: 285.1615 (Δ = 4.2 ppm).

¹ R. Vallakati, J. A. May, *J. Am. Chem. Soc.* **2012**, *134*, 6936-6939.

IR (neat): $\tilde{\nu}$ = 3400, 2907, 1683, 1444, 1407, 1360, 1296, 1265, 1240, 1211, 1167, 1112, 1096, 1029, 999, 932, 910, 839, 805, 765, 751, 737, 691, 666 cm^{-1} .

2-Methyl-1-(2-methylprop-1-enyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (1)¹



LiAlH_4 (3.42 g, 90.0 mmol, 6.0 equiv.) was added to a solution of carbamate **12** (4.27 g, 15.0 mmol) in THF (200 mL) at room temp. in small portions. After complete hydride addition the reaction mixture was heated under reflux for 5 h. The reaction mixture was cooled to -78°C and was quenched by successive addition of H_2O (10 mL), aqueous NaOH (1M, 20 mL) and H_2O (10 mL). The mixture was allowed to warm to room temp. and was afterwards filtered over a pad of celite. THF was removed under reduced pressure, and the aqueous phase was extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were washed with brine (150 mL) and dried over Na_2SO_4 . Evaporation of the solvent and purification of the residue by column chromatography (5.0 cm \times 15 cm, 60 mL, $\text{CH}_2\text{Cl}_2/\text{MeOH} = 30:1 \rightarrow 20:1$) gave borrerine **1** (#7-54, g, %) as a pale yellow solid.

R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 30:1$) = 0.18.

Melting point: 106°C .

¹H NMR (400 MHz, CDCl_3): δ = 1.93 (d, $J_{3',1'} = 1.2$ Hz, 3H, $3'-\text{CH}_3^{\text{I}}$), 1.94 (d, $J_{3''\text{II},1'} = 1.2$ Hz, 3H, $3'-\text{CH}_3^{\text{II}}$), 2.51 (s, 3H, NMe), 2.70 (m_c, 1H, $4-\text{H}^{\text{I}}$), 2.80-2.85 (m, 1H, $3-\text{H}^{\text{I}}$), 3.03 (m_c, 1H, $4-\text{H}^{\text{II}}$), 3.25 (m_c, 1H, $3-\text{H}^{\text{II}}$), 4.14 (br. d, $J_{1,1'} = 9.6$ Hz, 1H, 1-H), 5.30 (m_c, $J_{1',1} = 9.6$ Hz visible, 1H, $1'-\text{H}$), 7.13-7.21 (m, 2H, 6-H, 7-H), 7.33 (m_c, 1H, 8-H), 7.55 (br. d, $J_{5,6} = 7.5$ Hz, 1H, 5-H), 7.66 ppm (br. s, 1H, NH).

¹³C NMR (100 MHz, CDCl_3): δ = 18.59 (C-3^A), 21.63 (C-4), 26.17 (C-3^B), 43.38 ($\text{CH}_3\text{-N}$), 53.20 (C-3), 59.97 (C-1), 108.01 (C-4a), 110.79 (C-8), 118.21 (C-5), 119.31 (C-7)^a, 121.34 (C-6)^a, 124.61 (C-1'), 127.63 (C-5a), 134.52 (C-2'), 136.11 (C-9a), 137.35 (C-8a) ppm.

Elemental analysis: 79.72% C, 8.43% H, 11.68% N; calc. for $\text{C}_{16}\text{H}_{20}\text{N}_2$: 79.96% C, 8.39% H, 11.66% N.

HRMS (ESI): m/z calcd. for $\text{C}_{16}\text{H}_{21}\text{N}_2$ [$\text{M}+\text{H}$]⁺: 241.1705; found: 241.1707 ($\Delta = 0.8$ ppm).

IR (neat): $\tilde{\nu}$ = 3392, 2908, 1445, 1369, 1309, 1263, 1222, 1166, 1111, 1060, 1038, 967, 919, 800, 741 cm^{-1} .

^a Assignment interchangeable.

Polyvinylpolypyrrolidone-boron trifluoride complex (PVPP-BF₃)²

Polyvinyl(polypyrrolidone) (12.0 g) was suspended in CH₂Cl₂ (100 mL). At room temp. a solution of BF₃·OEt₂ (20.0 mL, 22.4 g, 158 mmol) in CH₂Cl₂ (60 mL) was added dropwise within 10 min, and the reaction mixture was stirred for 1 h at room temp. Afterwards the solid was filtered off, washed with CH₂Cl₂ (3 × 40 mL) and dried *in vacuo* over night.

Silica-supported BF₃ (Silica-BF₃)³

Silica gel (20 g, pre-dried at 140°C for 14 h) was suspended in MeOH (70 mL). At room temp. BF₃·2H₂O (5.1 mL, 8.3 g, 80 mmol) was added dropwise within 10 min, and the reaction mixture was stirred for 2 h at room temp. Afterwards the solvent was removed under reduced pressure.

General experimental procedures for the flow reactions

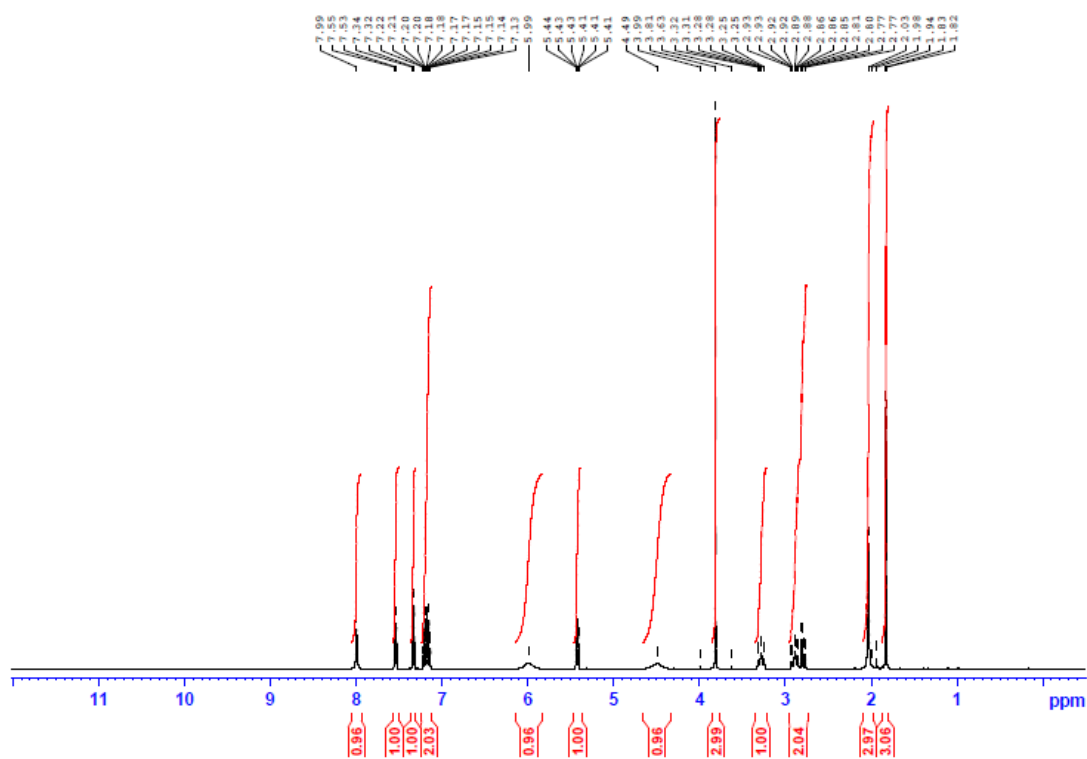
A solution of the substrate (preloaded in a 5 mL loop, 0.2 mmol, c = 0.04 M, if not otherwise stated) in the stated solvent was pumped through a glass column (Omnifit[®], 10.0 mm i.d. × 100.0 mm length) packed with the solid supported reagent (1.8 g for silica-supported BF₃, 0.8 g for all other solid-supported reagents) and heated to the stated temperature. A 100 psi back pressure regulator was placed after the reactor. The solution obtained was concentrated *in vacuo*. To isolate the free amine the solution was washed with saturated NaHCO₃ solution (10 mL) prior to concentration.

² M. M. Lakouraj, M. Mokhtary, *Monatsh. Chem.* **2009**, *140*, 53-56.

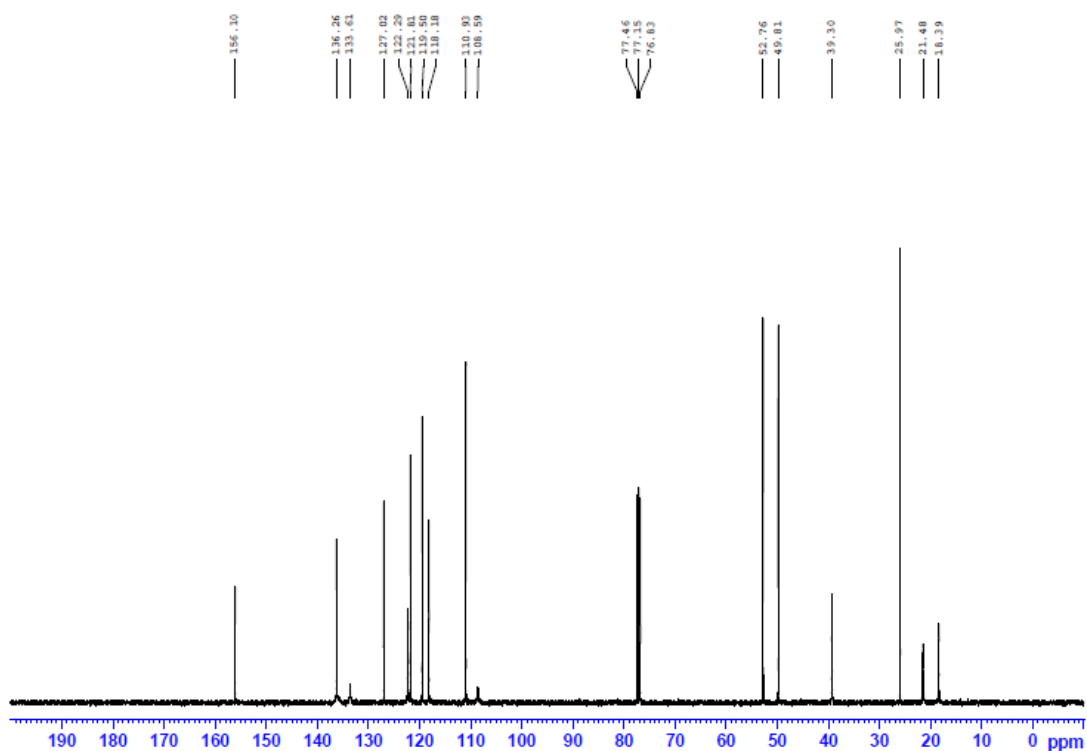
³ C. R. Quinn, J. H. Clark, S. J. Tavener, K. Wilson, *Green Chem.* **2003**, *5*, 602-605.

3. NMR spectra of 12, 1, 2, and 13

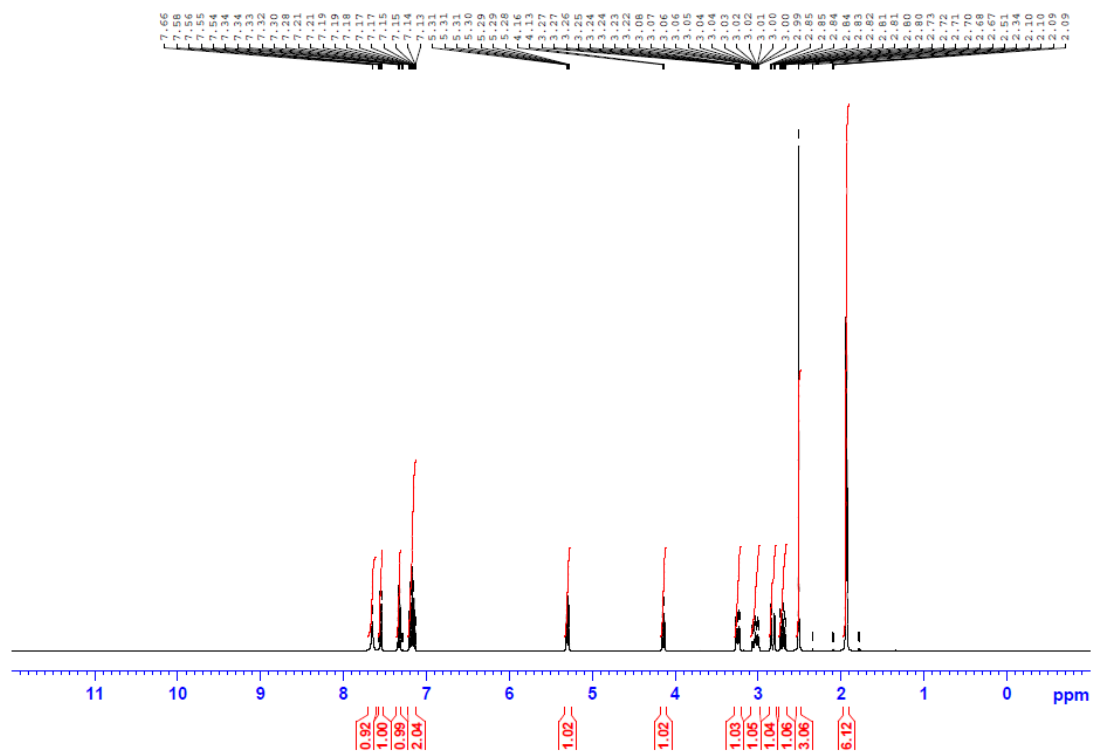
^1H NMR spectrum of **12** (400 MHz, CDCl_3):



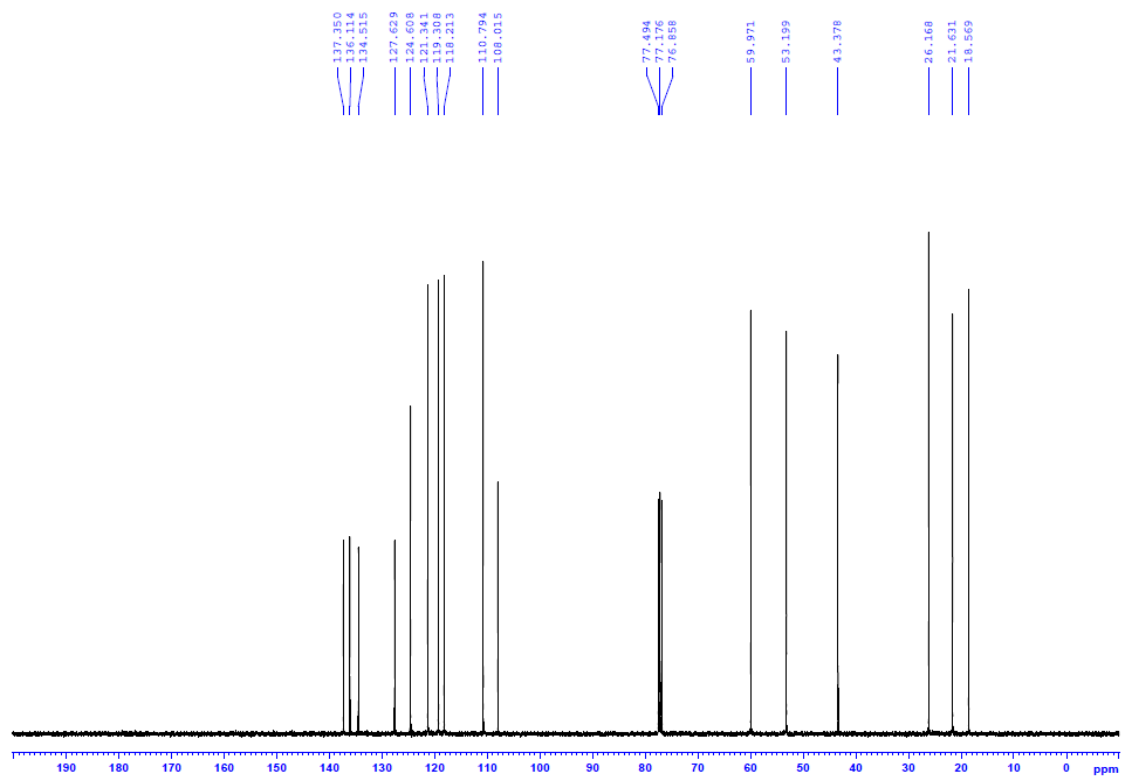
^{13}C NMR spectrum of **12** (100 MHz, CDCl_3):



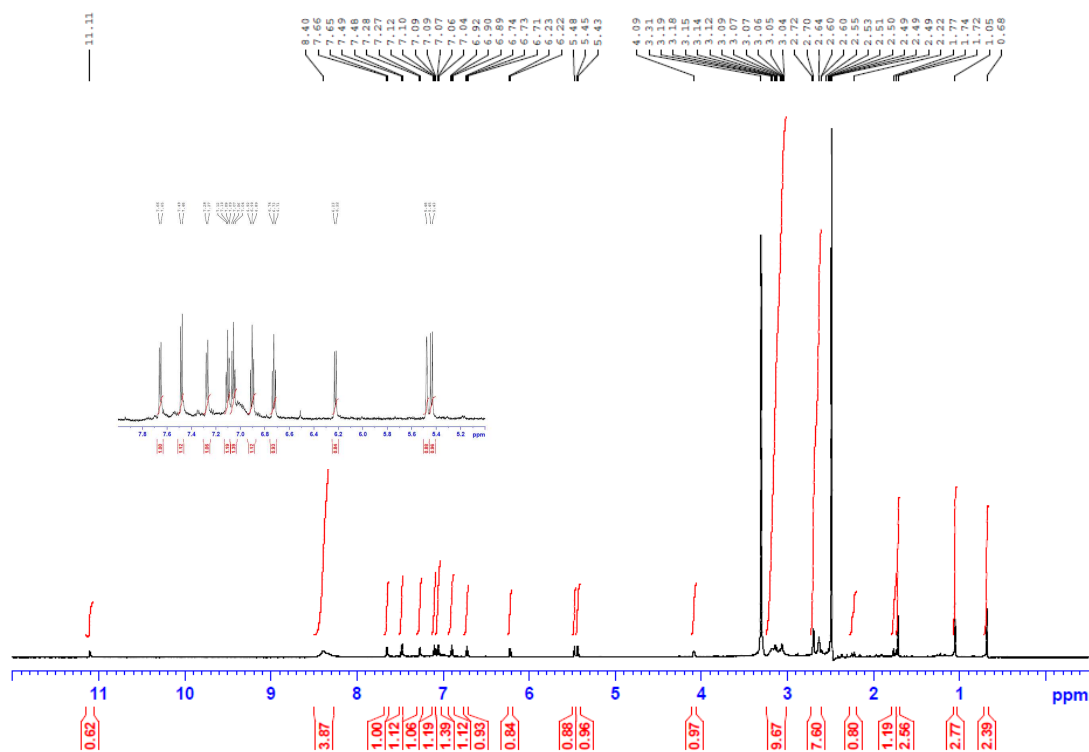
^1H NMR spectrum of **1** (400 MHz, CDCl_3):



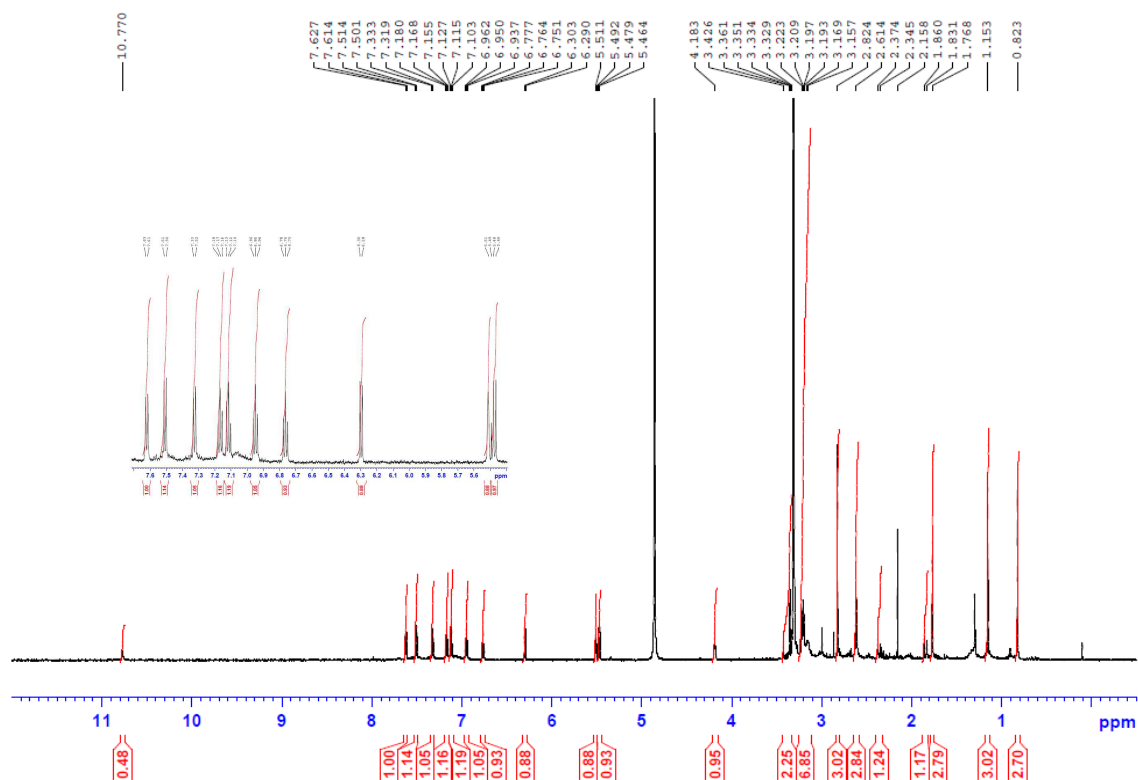
^{13}C NMR spectrum of **1** (100 MHz, CDCl_3):



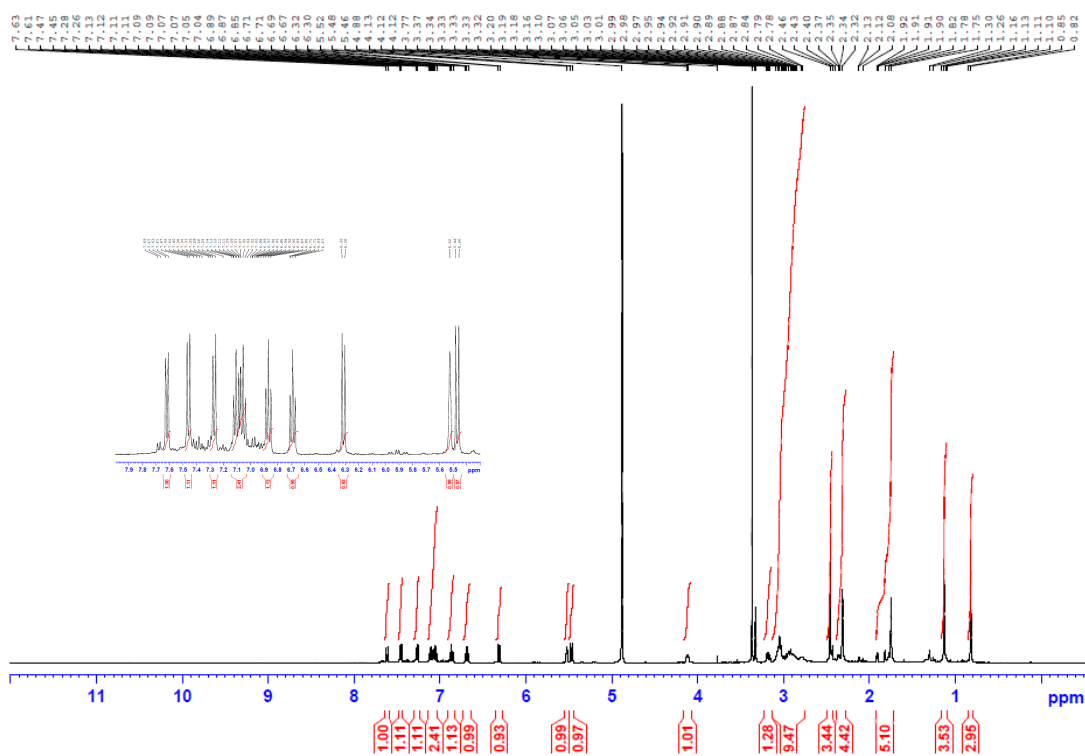
^1H NMR spectrum of $2 \cdot \text{BF}_4$ (400 MHz, $\text{DMSO}-d^6$):



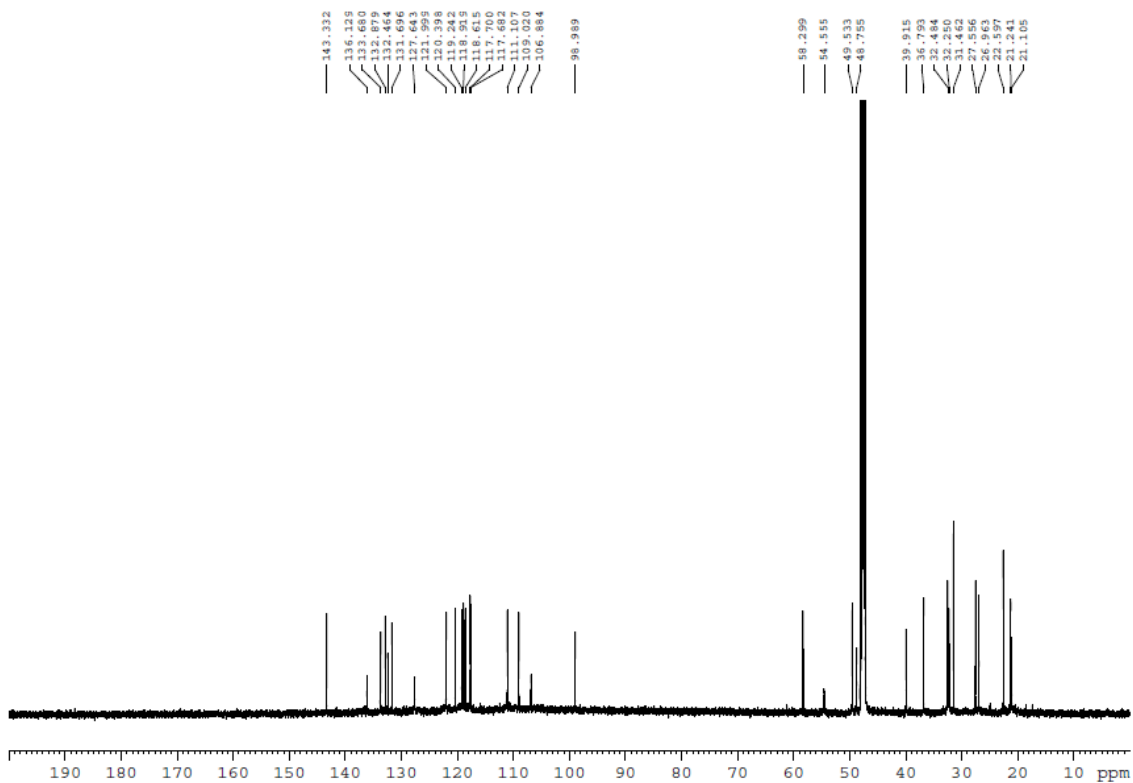
^1H NMR spectrum of $2 \cdot \text{BF}_4$ (600 MHz, $\text{MeOH}-d^4$):



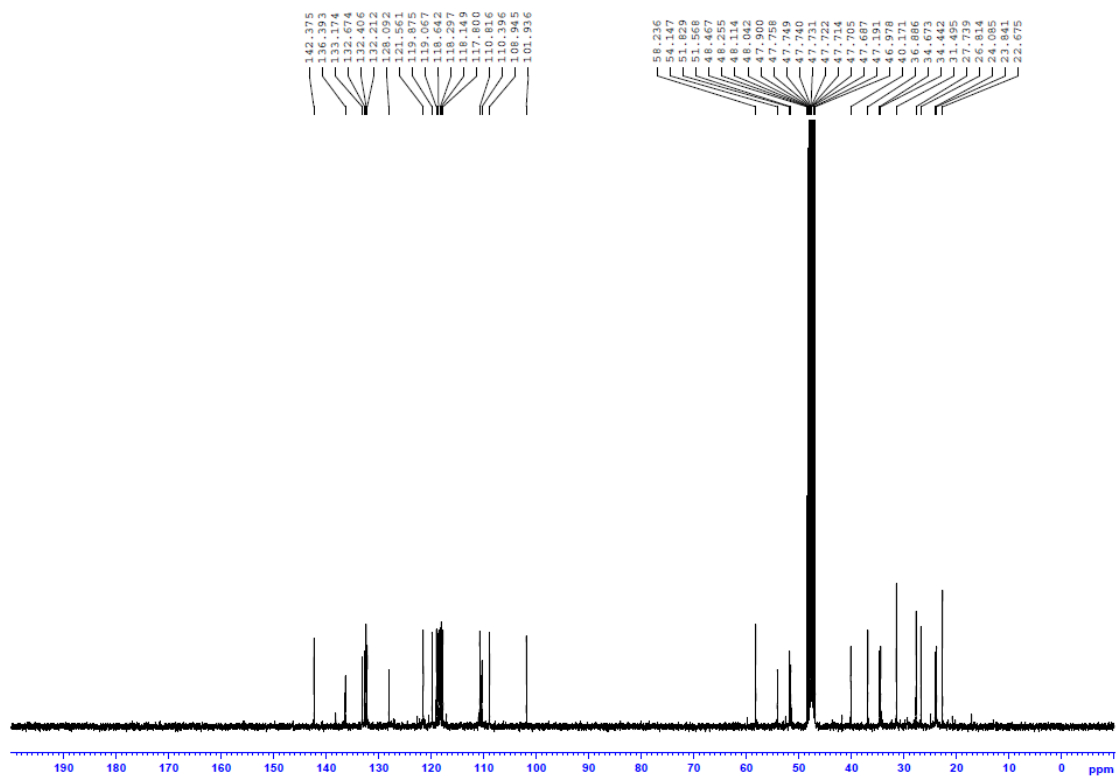
^1H NMR spectrum of **2** (400 MHz, $\text{MeOH-}d^4$):



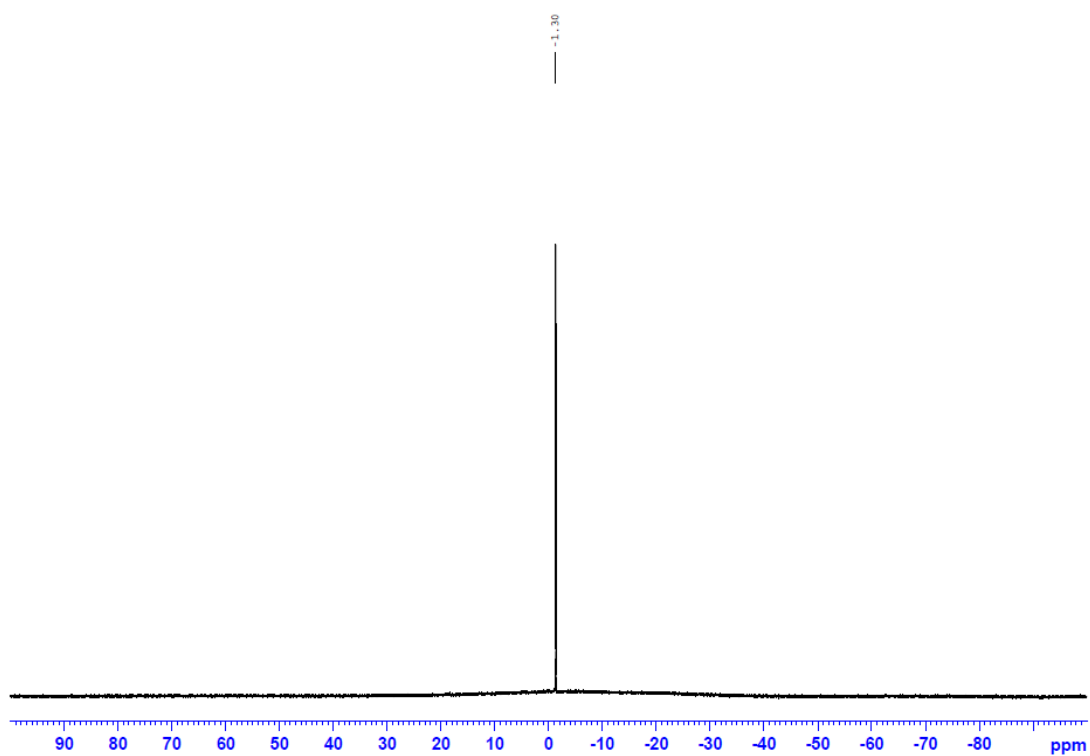
^{13}C NMR spectrum of **2**· BF_4 (151 MHz, $\text{MeOH-}d^4$):



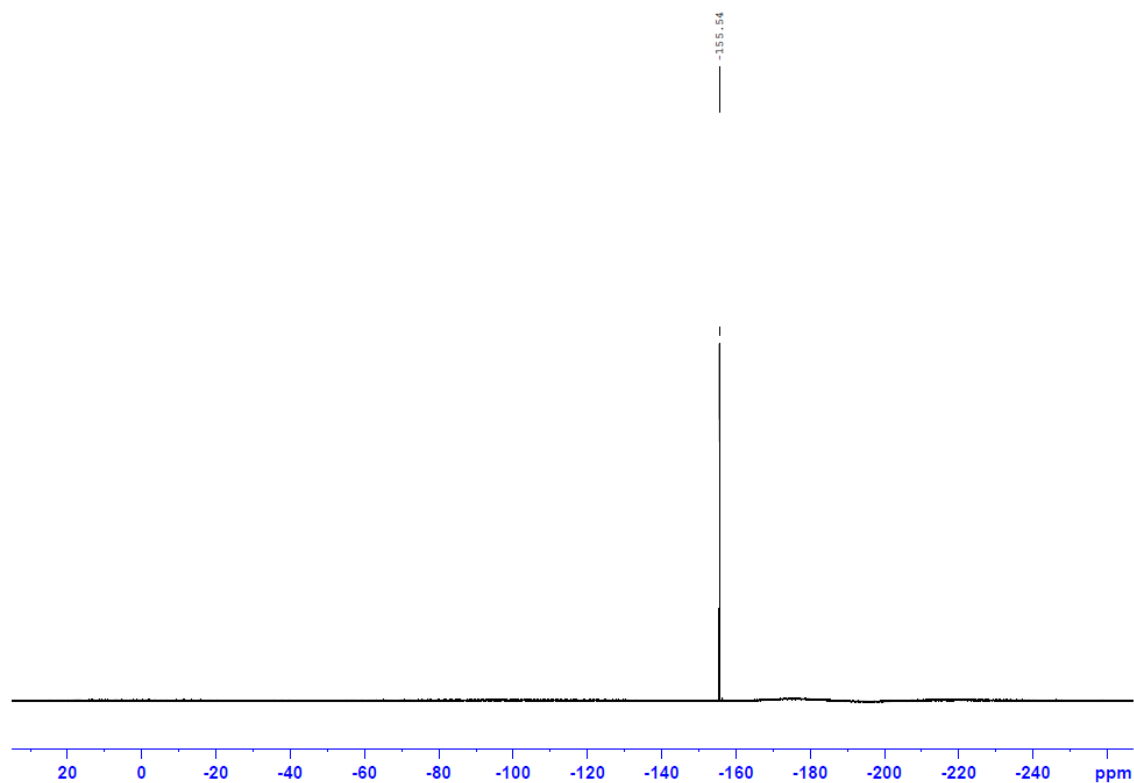
^{13}C NMR spectrum of **2** (100 MHz, $\text{MeOH-}d^4$):



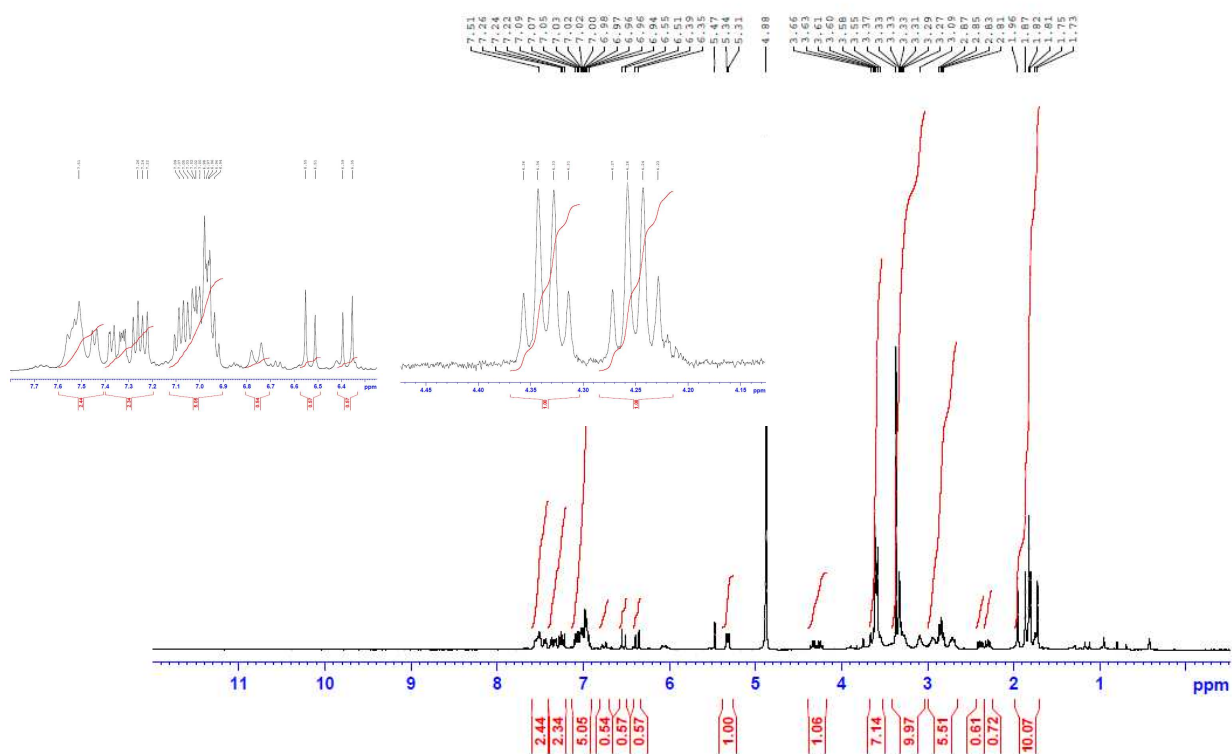
^{11}B NMR spectrum of **2**· BF_4 (128 MHz, $\text{MeOH-}d^4$):



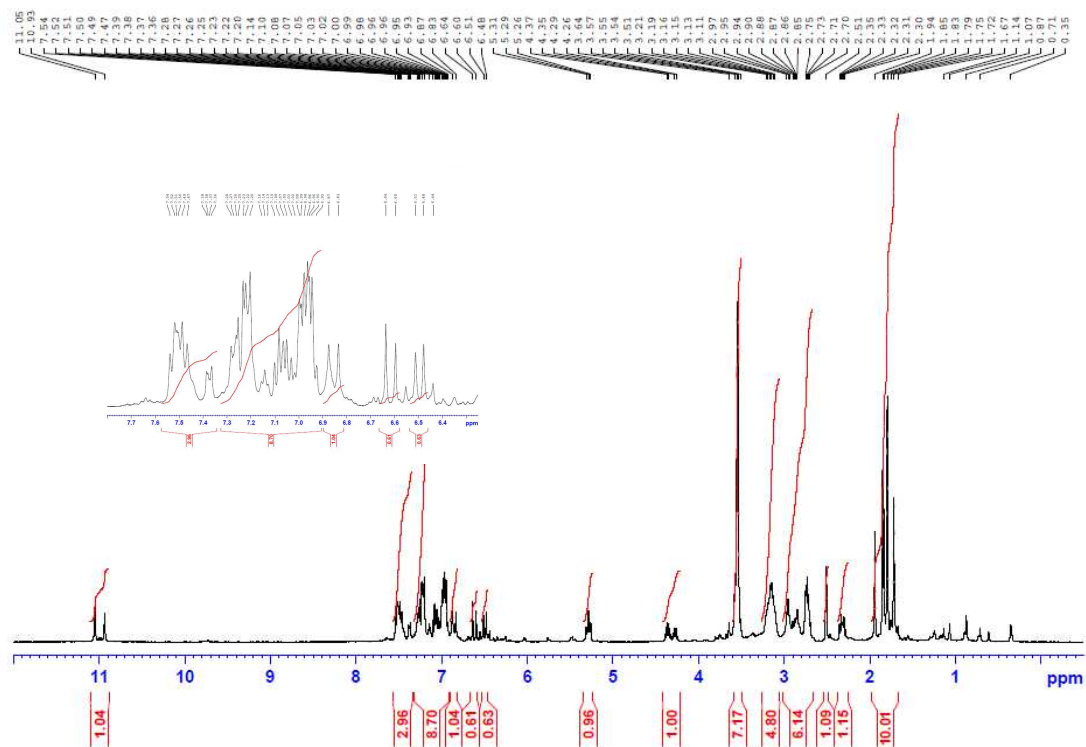
^{19}F NMR spectrum of $2 \cdot \text{BF}_4$ (376 MHz, $\text{MeOH-}d^4$):



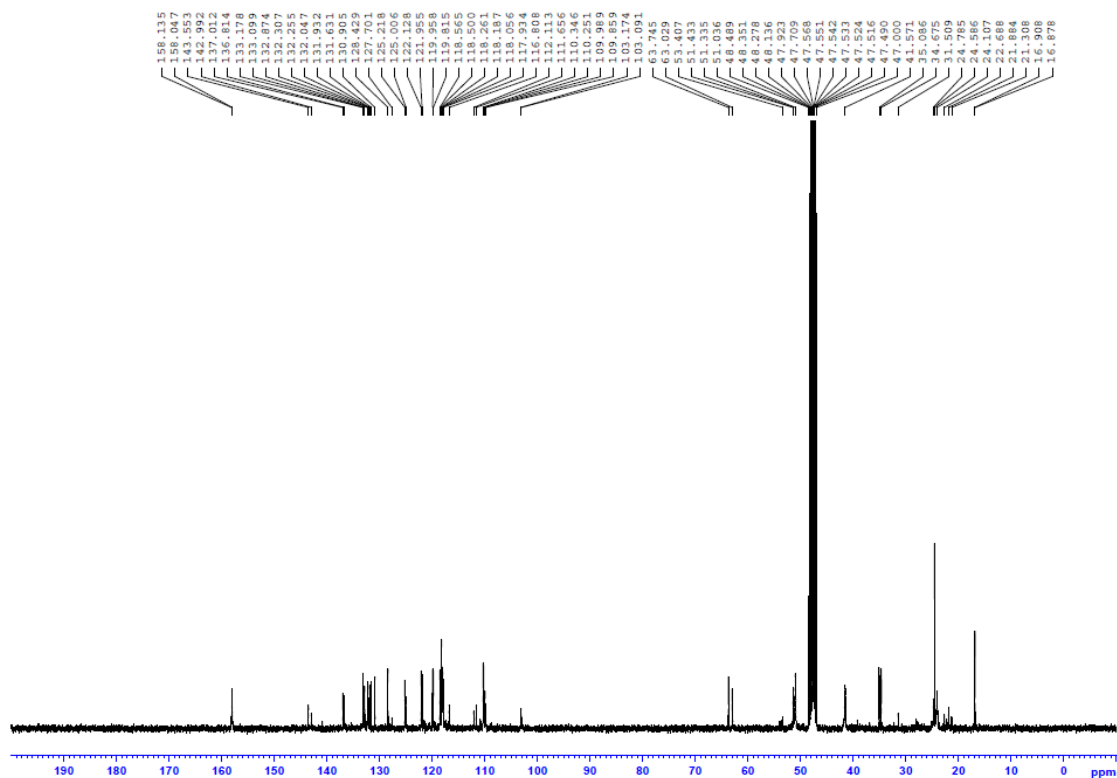
^1H NMR spectrum of $13 \cdot \text{BF}_4$ (400 MHz, $\text{MeOH-}d^4$):



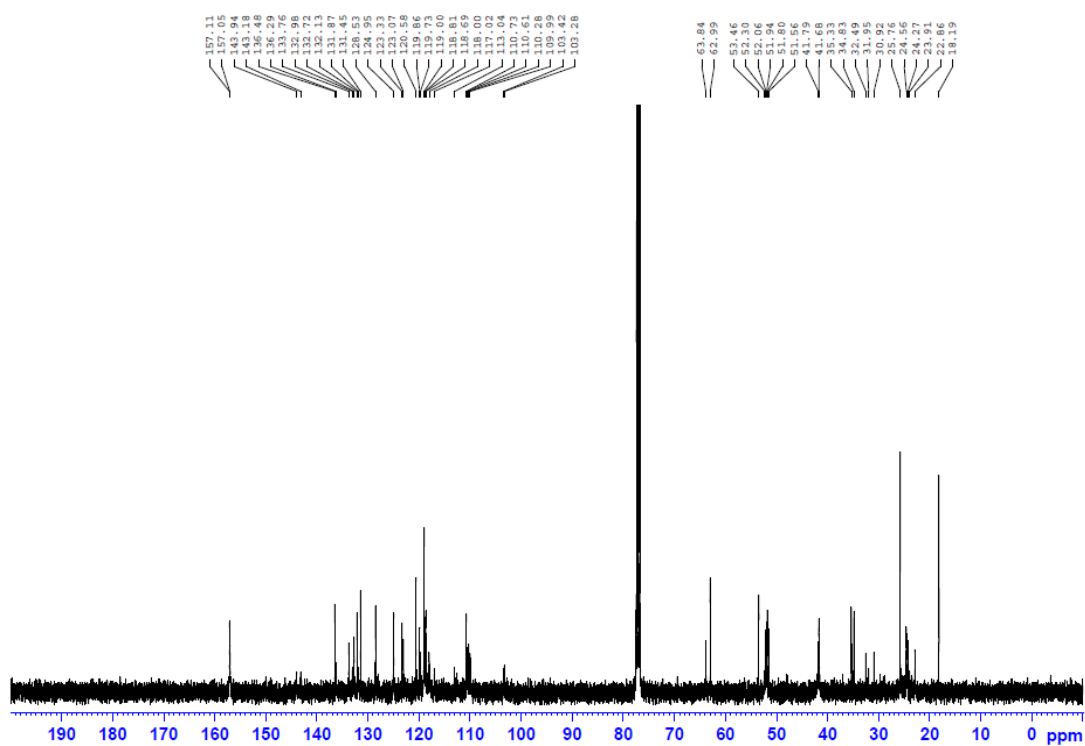
^1H NMR spectrum of **13** (400 MHz, $\text{DMSO-}d_6$):



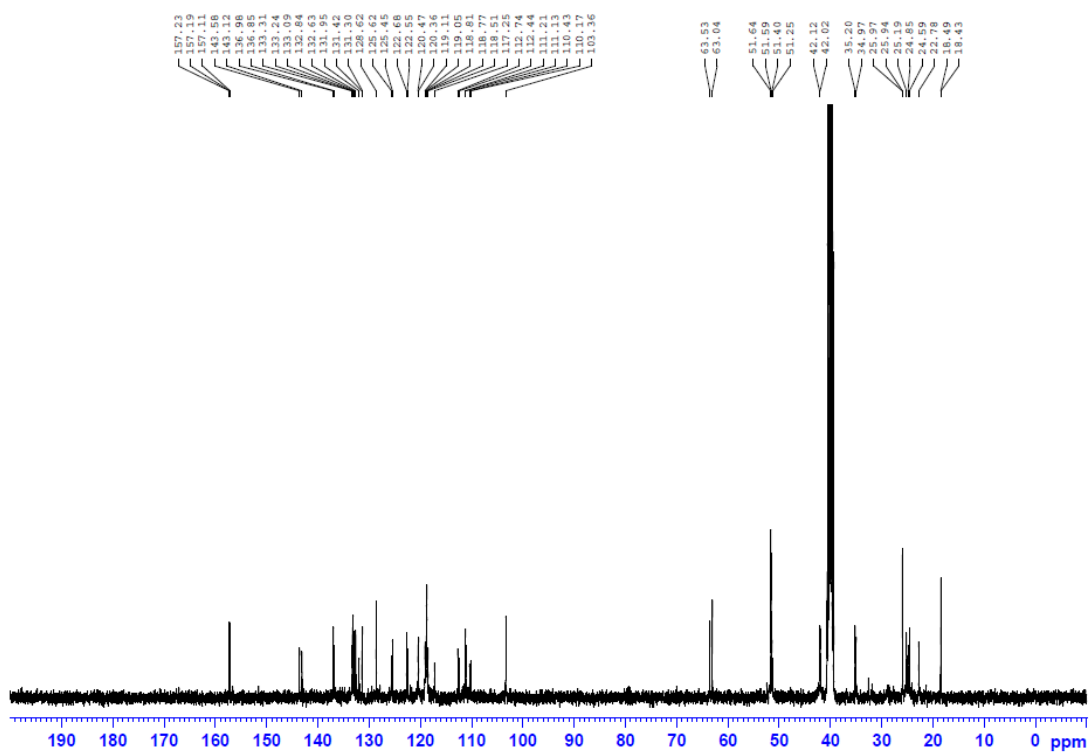
^{13}C NMR spectrum of **13**· BF_4 (100 MHz, $\text{MeOH-}d_4$):



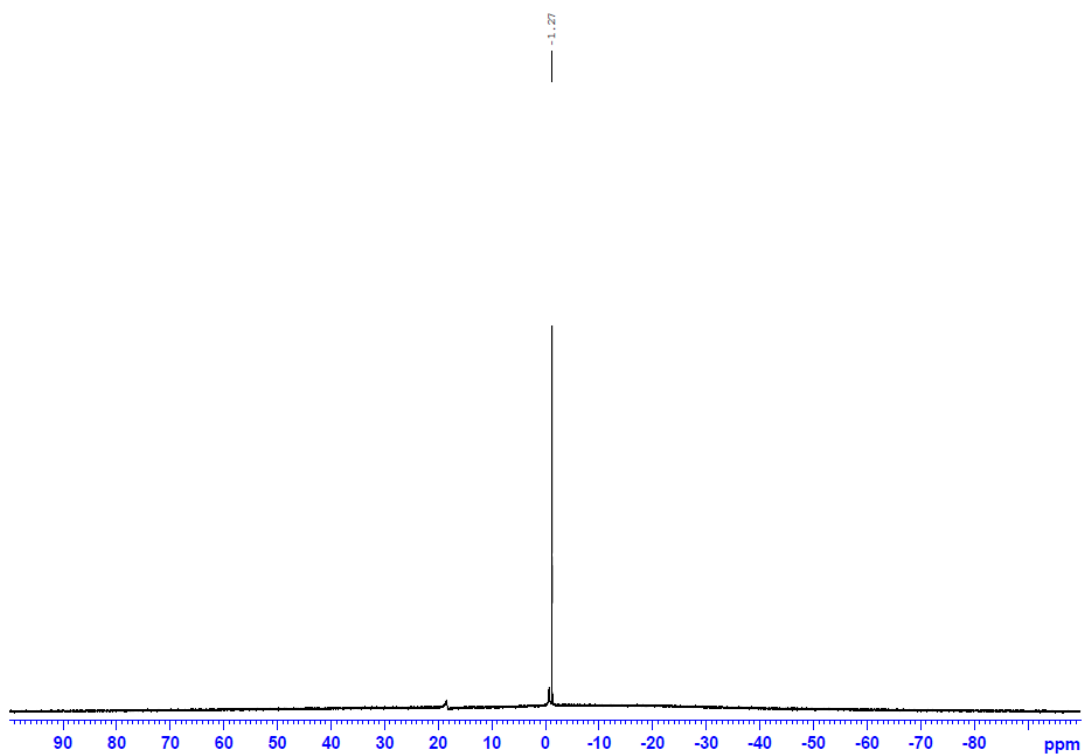
^{13}C NMR spectrum of **13** (100 MHz, CDCl_3):



^{13}C NMR spectrum of **13** (100 MHz, $\text{DMSO}-d_6$):



^{11}B NMR spectrum of $\mathbf{13}\cdot\text{BF}_4$ (128 MHz, $\text{MeOH-}d^4$):



^{19}F NMR spectrum of $\mathbf{13}\cdot\text{BF}_4$ (376 MHz, $\text{MeOH-}d^4$):

