

New Journal of Chemistry

Supporting Information

Title : Practical Synthesis of Thio-Noscapinoid

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Supplementary information

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1. Material and Methods :

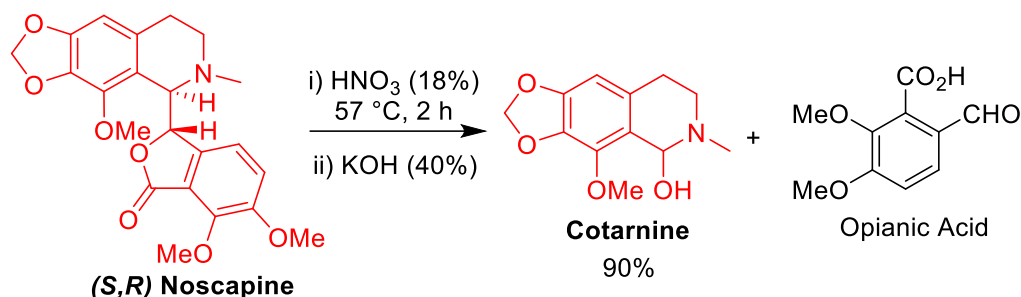
All reactions were performed under ambient conditions unless otherwise specified. Methanol and ethanol (99.9%) were purchased from Sigma-Aldrich. (S,R)-Noscapine, with 97% purity, was obtained from Sigma-Aldrich France. All thiophenols were sourced from Sigma, TCI, and BLD Pharma. Thin-layer chromatography (TLC) was used to monitor reactions (0.25 mm silica gel 60-F plates), and visualization was achieved under UV light. Flash chromatography was performed on silica gel (320-400 mesh) when necessary. Yields were calculated by simple filtration or after column. ¹H NMR spectra were recorded at 400 MHz, and ¹³C NMR spectra at 100 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the residual solvent peak (CDCl₃) as an internal reference, with coupling constants given in Hertz. Melting points were determined using a Visualize melting point apparatus, EI model – 2935

2. Synthesis of Starting Material :

Synthesis of Cotarnine :

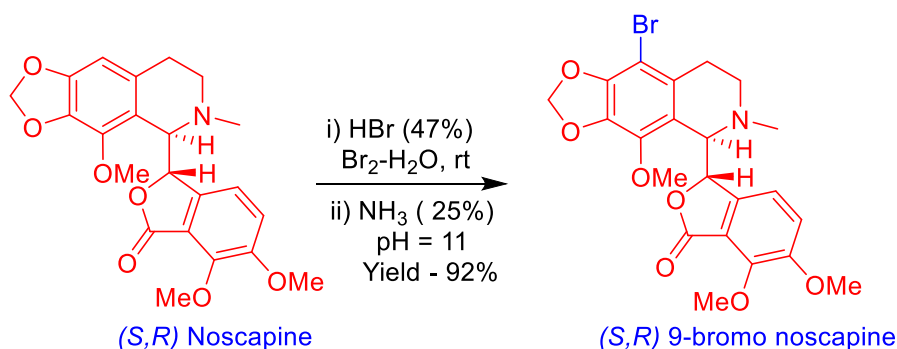
A 250 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with (S,R)-noscapine (20 g, 24.2 mmol). Over the course of 5 minutes, 18% HNO₃ (150 mL) was added dropwise with gentle stirring at room temperature. The resulting mixture was then transferred to an oil bath and heated to 55°C for 2 hours. After 2 hours, once no more precipitate formed, the reaction was removed from the oil bath and allowed to cool at room temperature for 10 minutes. The mixture was then filtered through a Buchner funnel under vacuum to obtain

opianic acid. The yellow filtrate was neutralized gradually with 40% KOH while shaking continuously until a yellow precipitate formed (pH = 11). The precipitate was filtered, washed with cold distilled water (5 mL), and dried to yield cotarnine **I** as a yellow solid^[1,2] (10 g, 90% yield).



Synthesis of 9-Bromo Noscapine :

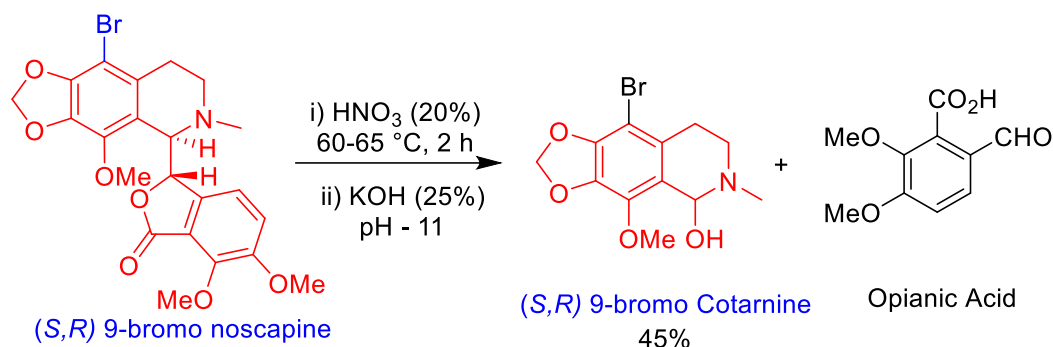
To a flask containing noscapine (4 g, 12.1 mmol); 4 ml of 47% HBr solution is added and stirred for 5 minute. To the reaction mixture freshly prepared bromine water (3% Br₂, Br₂- H₂O, 30-40 ml) was added dropwise until an orange precipitate appeared. The reaction mixture was then stirred at room temperature for 30 min. The above mixture was neutralized by 25% NH₃ and was added till pH=11 to afford white precipitate^[1,2]. The solid precipitate was filtered, dried and recrystallized with ethanol to afford 9-bromo noscapine in 92% yield (5.5 g).



Synthesis of 9-Bromo Cotarnine :

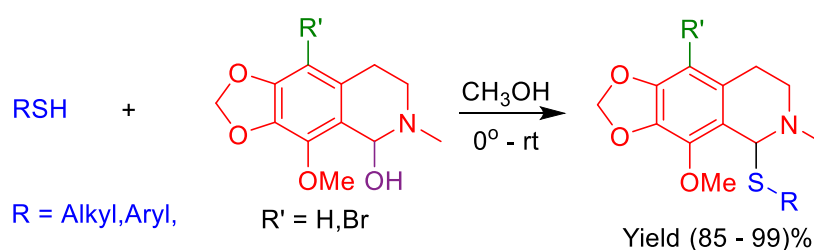
An oven-dried, 100 mL round bottom flask equipped with a magnetic stir bar was charged with 9-bromo-(S,R)-noscapine (3.5 g, 7.12 mmol). 20% HNO₃ (15mL) was added carefully and drop wise for 5 min with slow stirring at room temperature. The resulting mixture was transferred to an oil bath and heated to 62°C for 2 h. After 2 h, the reaction mixture was cooled at room temperature. The mixture was then extracted with 25 ml of dichloromethane. The water layer was then neutralized with 25% KOH with continuous shaking until yellowish precipitate

was formed (pH=11). The precipitate was filtered, washed with cold distilled water (5 mL), and dried to give 9-bromo-cotarnine^[1,2] 1b as a yellowish solid product (1g, 45%)

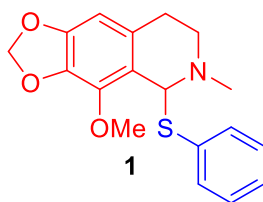


3. General Procedure for synthesis :

An oven dried 10ml RB was charged with cotarnine (2mmol, 474mg) and stirrer bar then put at 0 °C at 200rpm. Then cooled methanol previously stored at fridge added dropwise for complete soluble of cotarnine (400-500 μl) followed by thiol (2mmol) are added simultaneously. Then the product comes out with a precipitation formed and filtered using whattmann-42 filter paper. Then washed with chilled methanol and dried at room temperature. The ppt so collected send NMR analysis and melting point checked with visual melting point apparatus (EI model-2936).



4. Characterization of new Product :

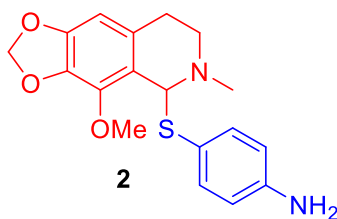


4-methoxy-6-methyl-5-(phenylthio)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (1) : Brown White Solid, Yield 604mg (92%), M.P.: 89 °C

¹H NMR (400 MHz, CDCl₃) δ 7.65 – 7.57 (m, 2H), 7.26 – 7.21 (m, 2H), 7.19 – 7.10 (m, 1H), 6.25 (s, 1H), 5.83 (d, *J* = 13.1 Hz, 3H), 4.03 (s, 3H), 2.88 (t, *J* = 6.4 Hz, 2H), 2.72 (t, *J* = 6.4 Hz, 2H), 2.30 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 148.87, 139.24, 134.32, 131.95, 128.79, 127.67, 126.17, 121.57, 102.23, 100.75, 59.20, 45.58, 43.55, 28.27.

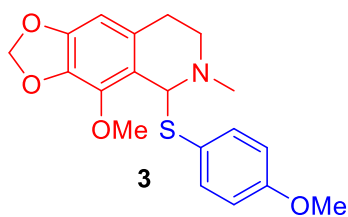
HRMS : TOF MS ESI, C₁₈H₁₉NO₃S: *m/e* = 329.1058; Calculated for [M-PhSH] C₁₂H₁₄NO₃; *m/e* Calculated = 220.0937, Found = 220.1023



4-((4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)thio)aniline (2) : White Solid, Yield – 592mg (86%), M.P.: 120 °C.

¹H NMR (400 MHz, CDCl₃) δ 7.60 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 6.28 (s, 1H), 5.86 (d, *J* = 22.1 Hz, 3H), 4.08 (s, 3H), 2.95 (t, *J* = 5.9 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.40 (s, 3H).

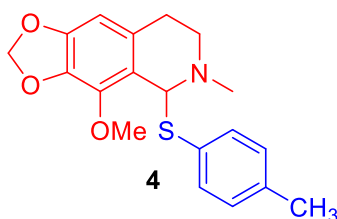
¹³C NMR (101 MHz, CDCl₃) δ 162.92, 160.48, 149.07, 139.25, 134.59 – 134.13, 127.79, 115.85, 115.63, 102.23, 101.51 (d, *J* = 145.7 Hz), 59.21, 45.62, 43.66, 28.18.



4-methoxy-5-((4-methoxyphenyl)thio)-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (3) : White Solid, Yield 688 mg (96%), M.P: 113 °C

¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.27 (s, 1H), 5.88 (s, 3H), 4.10 (s, 3H), 3.80 (s, 3H), 2.94 (s, 2H), 2.75 (t, *J* = 6.1 Hz, 2H), 2.39 (s, 3H).

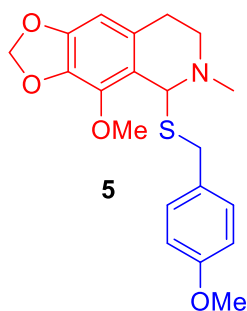
¹³C NMR (101 MHz, CDCl₃) δ 158.58, 148.94, 139.30, 134.56, 134.27, 132.67, 129.91, 127.74, 121.48, 114.62, 114.32, 102.22, 100.73, 59.23, 55.33 (d, *J* = 7.5 Hz), 45.58, 43.70, 28.22.



4-methoxy-6-methyl-5-(p-tolylthio)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (4): White Solid, Yield – 644mg (94%), M.P.: 116 °C

¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.28 (s, 1H), 5.84 (d, *J* = 33.0 Hz, 3H), 4.08 (s, 3H), 2.92 (s, 2H), 2.76 (d, *J* = 6.2 Hz, 2H), 2.33 (t, *J* = 6.3 Hz, 6H).

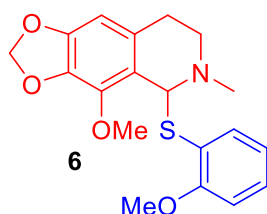
¹³C NMR (101 MHz, CDCl₃) δ 132.28, 129.78, 129.54, 128.59, 102.22, 100.71, 77.23, 59.19, 45.58 (d, *J* = 3.6 Hz), 43.60 (d, *J* = 4.1 Hz), 28.25, 21.04 (d, *J* = 3.0 Hz).



4-methoxy-5-((4-methoxybenzyl)thio)-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (5) : White Solid, Yield 676 mg (91%) , M.P: 86 °C

¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.25 (s, 1H), 5.86 (d, *J* = 11.5 Hz, 2H), 5.25 (s, 1H), 4.03 (s, 3H), 3.88 (d, *J* = 1.7 Hz, 2H), 3.79 (s, 3H), 2.88 (dd, *J* = 9.7, 5.6 Hz, 2H), 2.74 – 2.48 (m, 2H), 2.38 (s, 3H).

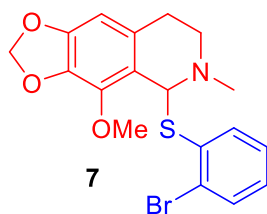
¹³C NMR (101 MHz, CDCl₃) δ 158.48, 148.41, 131.68, 130.52, 130.03, 127.16, 122.53, 113.82 (d, *J* = 15.7 Hz), 102.22, 100.63, 70.71, 59.23, 55.29, 45.91, 42.73 (d, *J* = 9.3 Hz), 38.28, 28.01.



4-methoxy-5-((2-methoxyphenyl)thio)-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (6) : White Solid, Yield 648 mg (90%), M.P.: 110 °C

¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.27 (s, 1H), 5.97 (s, 1H), 5.86 (s, 2H), 4.02 (s, 3H), 3.89 (s, 3H), 2.97 (t, *J* = 6.1 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.32 (s, 3H).

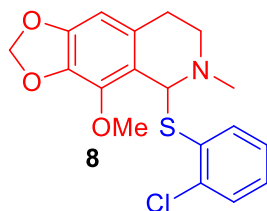
¹³C NMR (101 MHz, CDCl₃) δ 157.52, 148.80, 139.37, 134.30, 133.05, 127.82, 127.71 – 127.65 (m), 127.50 (d, *J* = 22.2 Hz), 121.56, 121.35, 121.15, 110.78, 110.51, 102.24, 100.70, 75.77, 59.21, 55.86 (d, *J* = 7.9 Hz), 45.49, 42.84, 28.19.



5-((2-bromophenyl)thio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (7) : White Solid, Yield 720 mg (88%), M.P – 109 °C

¹H NMR (400 MHz, CDCl₃) δ 7.88 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 11.2, 4.0 Hz, 1H), 7.08 – 6.95 (m, 1H), 6.30 (s, 1H), 5.96 (s, 1H), 5.89 (s, 2H), 4.06 (s, 3H), 2.96 (t, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 6.4 Hz, 2H), 2.27 (s, 3H).

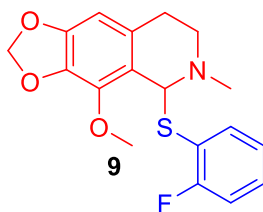
¹³C NMR (101 MHz, CDCl₃) δ 149.14, 141.14, 139.34, 134.34, 132.98 (d, *J* = 9.6 Hz), 132.37, 128.01 (dd, *J* = 24.8, 14.1 Hz), 127.00, 125.49, 120.71, 102.33, 100.84, 78.63, 59.25, 45.58, 43.12, 28.15.



5-((2-chlorophenyl)thio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (8) : White Solid, Yield -620 mg (85%), M.P. : 102 °C

¹H NMR (400 MHz, CDCl₃) δ 7.87 (dd, *J* = 7.9, 1.5 Hz, 5H), 7.35 (dd, *J* = 7.9, 1.4 Hz, 7H), 7.24 – 7.19 (m, 6H), 7.10 (td, *J* = 7.7, 1.5 Hz, 7H), 6.30 (s, 5H), 5.96 (s, 5H), 5.89 (s, 11H), 4.06 (s, 14H), 2.95 (t, *J* = 6.5 Hz, 10H), 2.78 (t, *J* = 6.4 Hz, 10H), 2.27 (s, 14H).

¹³C NMR (101 MHz, CDCl₃) δ 149.14, 139.34, 134.39, 132.80, 131.89, 129.69 (d, *J* = 5.4 Hz), 127.82, 127.58, 127.18 (d, *J* = 12.6 Hz), 126.73, 102.32, 100.78 (d, *J* = 8.5 Hz), 59.23, 45.55, 43.00, 28.15.

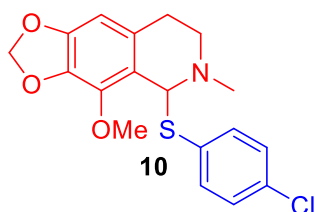


5-((2-fluorophenyl)thio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (9) : White Solid; Yield 576 mg (83%), M.P.: 92 °C

¹H NMR (700 MHz, CDCl₃) δ 7.74 (td, *J* = 7.6, 1.1 Hz, 1H), 7.23 – 7.15 (m, 1H), 7.09 (dd, *J* = 10.9, 4.0 Hz, 1H), 7.01 (t, *J* = 8.7 Hz, 1H), 6.28 (s, 1H), 5.90 (d, *J* = 28.5 Hz, 3H), 4.06 (s, 3H), 2.96 (t, *J* = 6.5 Hz, 2H), 2.77 (t, *J* = 6.4 Hz, 2H), 2.35 (s, 3H).

¹³C NMR (176 MHz, CDCl₃) δ 161.78, 160.40, 149.07, 139.27, 134.74, 134.21, 128.22 (d, *J* = 8.0 Hz), 127.93, 124.46 (d, *J* = 3.6 Hz), 120.95, 115.60, 115.47, 102.22, 100.76, 59.20, 45.45, 43.03, 28.17.

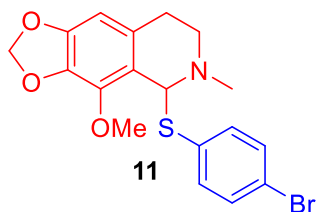
¹⁹F NMR (377 MHz, CDCl₃) δ -107.05 (s), -109.95 (s).



5-((4-chlorophenyl)thio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (10) : White Solid, Yield – 624mg (86%), M.P.: 110 °C

¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.32 – 7.17 (m, 2H), 6.28 (s, 1H), 5.87 (d, *J* = 14.7 Hz, 3H), 4.06 (s, 3H), 2.92 (t, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.37 (s, 3H).

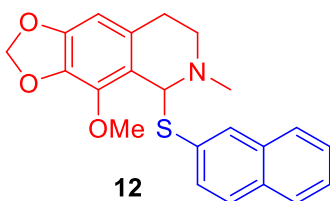
¹³C NMR (101 MHz, CDCl₃) δ 149.12, 139.24, 138.22, 134.25, 133.40, 132.08, 129.33 (d, *J* = 3.7 Hz), 128.87, 127.80, 121.01, 102.24, 100.81, 59.20, 45.65, 43.64, 28.19.



5-((4-bromophenyl)thio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (11) : White Solid, Yield – 744mg (91%), M.: 109 °C

¹H NMR (400 MHz, CDCl₃) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.28 (s, 1H), 5.86 (d, *J* = 20.6 Hz, 3H), 4.06 (s, 3H), 2.91 (t, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 6.3 Hz, 2H), 2.36 (s, 3H).

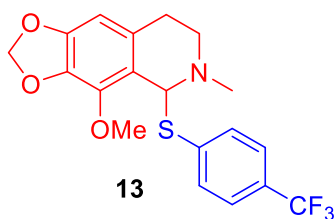
¹³C NMR (101 MHz, CDCl₃) δ 149.00, 139.09 (d, *J* = 12.9 Hz), 135.74, 134.25, 133.63, 132.23, 131.79, 129.42, 127.71, 121.56, 121.11, 119.99, 102.23, 100.79, 59.18, 45.61, 43.58, 28.22.



4-methoxy-6-methyl-5-(naphthalen-2-ylthio)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (12): White Solid, 712mg (94%), M.P.: 110 °C

¹H NMR (400 MHz, CDCl₃) δ 8.11 (s, 2H), 7.84 – 7.74 (m, 9H), 7.50 – 7.40 (m, 5H), 6.30 (s, 2H), 5.94 (d, *J* = 41.6 Hz, 6H), 4.11 (s, 6H), 2.96 (t, *J* = 6.3 Hz, 4H), 2.78 (t, *J* = 6.3 Hz, 4H), 2.36 (s, 6H).

¹³C NMR (176 MHz, CDCl₃) δ 134.38, 134.24, 133.47, 132.49, 129.01, 127.79, 127.48, 126.77, 126.51, 126.27, 125.64, 101.40, 100.75, 97.71, 77.25, 77.07, 76.89, 59.17, 44.92, 30.67.

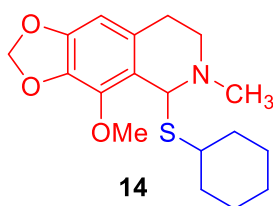


4-methoxy-6-methyl-5-((4-(trifluoromethyl)phenyl)thio)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (13) : White Solid, Yield – 674 mg (85%) , M.P.: 89 °C

¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 6.30 (s, 1H), 5.91 (d, *J* = 18.9 Hz, 3H), 4.03 (s, 3H), 2.91 (t, *J* = 6.3 Hz, 2H), 2.77 (t, *J* = 6.3 Hz, 2H), 2.34 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 149.13, 145.22, 139.18, 134.26 , 131.11, 128.29 (d, *J* = 7.9 Hz), 128.04 – 127.51 (m), 127.29, 126.60, 126.47 – 125.40, 122.93, 120.88, 120.23, 102.24, 100.83, 59.14, 45.70, 43.47, 28.20.

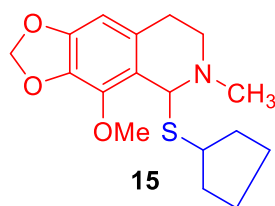
¹⁹F NMR (377 MHz, CDCl₃) δ -62.37 (s).



5-(cyclohexylthio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (14) : Gummy solid, Yield 568 mg (85%)

¹H NMR (400 MHz, CDCl₃) δ 6.24 (s, 1H), 5.84 (d, *J* = 16.8 Hz, 1H), 5.28 (s, 1H), 4.04 (s, 3H), 3.02 (td, *J* = 11.8, 4.8 Hz, 1H), 2.95 – 2.80 (m, 2H), 2.60 (ddd, *J* = 20.9, 13.8, 5.9 Hz, 2H), 2.49 (s, 3H), 2.20 (d, *J* = 12.4 Hz, 1H), 2.00 (d, *J* = 10.8 Hz, 1H), 1.76 (d, *J* = 11.3 Hz, 2H), 1.59 (d, *J* = 8.8 Hz, 1H), 1.52 – 1.43 (m, 1H), 1.30 (dt, *J* = 20.9, 11.1 Hz, 4H).

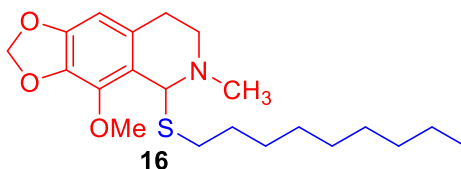
¹³C NMR (101 MHz, CDCl₃) δ 148.33, 138.93 (s), 133.97, 127.12, 122.77, 102.15, 100.52, 68.74, 59.03, 46.37, 45.54, 42.96, 35.06, 34.58, 32.86, 27.88, 26.45 (d, *J* = 14.1 Hz), 25.84 .



5-(cyclopentylthio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (15): Gummy solid, Yield 520 mg (81%)

¹H NMR (400 MHz, CDCl₃) δ 6.24 (s, 1H), 5.85 (d, *J* = 15.6 Hz, 2H), 5.29 (s, 1H), 4.05 (s, 3H), 3.37 – 3.23 (m, 1H), 3.03 (td, *J* = 11.8, 4.9 Hz, 1H), 2.94 – 2.81 (m, 1H), 2.70 – 2.54 (m, 2H), 2.52 (s, 3H), 2.19 – 1.96 (m, 2H), 1.83 – 1.67 (m, 3H), 1.53 (ddd, *J* = 16.0, 13.2, 7.3 Hz, 3H).

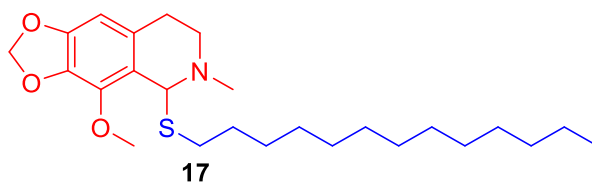
¹³C NMR (101 MHz, CDCl₃) δ 148.35, 139.02, 127.11, 122.70, 102.19, 100.56, 77.33, 77.01, 76.70, 69.89, 59.10, 46.82, 45.53, 43.09, 34.91 (d, *J* = 7.2 Hz), 27.96, 24.80 (d, *J* = 2.8 Hz).



4-methoxy-6-methyl-5-(octylthio)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (16)
: Gummy solid, Yield 640 mg (84%)

¹H NMR (400 MHz, CDCl₃) δ 6.25 (s, 1H), 5.85 (d, *J* = 13.3 Hz, 2H), 5.17 (s, 1H), 4.05 (s, 3H), 2.91 (dq, *J* = 18.2, 11.9 Hz, 2H), 2.80 – 2.53 (m, 4H), 2.49 (s, 3H), 1.70 – 1.58 (m, 2H), 1.44 – 1.17 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 148.35, 139.17, 134.26, 126.96, 122.84, 102.19, 100.61, 71.28, 59.20, 45.74, 42.85, 35.26, 31.84, 30.66, 29.39 – 29.00(m), 28.11, 22.66, 14.09.

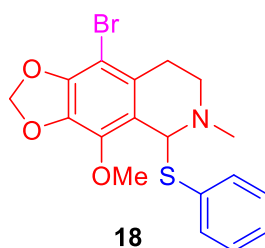


4-methoxy-6-methyl-5-(tridecylthio)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline

(17): Yellow solid; Yield 740 mg (85%) M.P.: 45 °C

¹H NMR (400 MHz, CDCl₃) δ 6.25 (s, 1H), 5.85 (d, *J* = 12.9 Hz, 2H), 5.17 (s, 1H), 4.05 (s, 3H), 3.02 – 2.81 (m, 2H), 2.74 (ddd, *J* = 15.1, 8.8, 5.8 Hz, 2H), 2.69 – 2.50 (m, 3H), 2.49 (s, 3H), 1.62 (dd, *J* = 14.2, 6.9 Hz, 4H), 1.42 – 1.26 (m, 14H), 0.88 (t, *J* = 6.7 Hz, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 148.36, 139.17, 134.26, 126.96, 122.85, 102.20, 100.62, 77.35, 77.03, 76.71, 71.28, 59.2, 45.74, 42.86, 35.28, 34.07, 31.92, 30.67, 29.45(ddd, *J* = 44.7, 17.3, 7.5 Hz), 28.39, 28.11, 24.67, 22.69, 14.12.

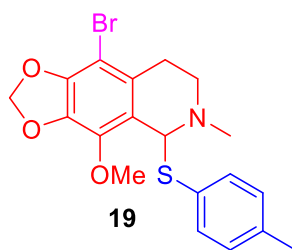


9-bromo-4-methoxy-6-methyl-5-(phenylthio)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (18) : White Solid, Yield 736 mg (90%), M.P.: 104 °C

¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, *J* = 7.4 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 5.98 (s, 2H), 5.86 (s, 1H), 4.05 (s, 3H), 2.97 (s, 2H), 2.72 (t, *J* = 5.9 Hz, 2H), 2.36 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 139.19, 134.64, 131.93, 129.06, 128.83, 127.55, 126.94, 126.34, 101.17, 95.70, 59.33, 45.47, 43.34, 28.36.

HRMS : TOF MS ESI, C₁₈H₁₈BrNO₃S: *m/e* = 407.0190, Calculated for [M-PhSH] For C₁₂BrH₁₃NO₃; *m/e* Calculated =298.0079

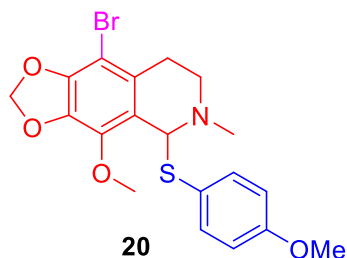


9-bromo-4-methoxy-6-methyl-5-(p-tolylthio)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (19) : White Solid, Yield 768 mg (91%), M.P.: 111 °C

¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 5.99 (s, 2H), 5.74 (s, 1H), 4.07 (s, 3H), 2.97 (s, 2H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.36 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 137.46, 133.89, 129.78, 128.56, 125.89, 122.54, 103.67, 101.10, 99.50, 77.23, 77.02, 76.70, 71.22, 60.95, 59.25, 44.81, 29.69, 21.04.

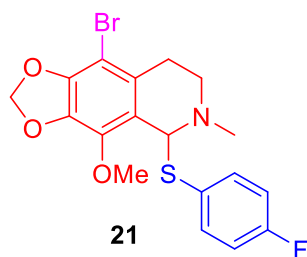
HRMS : TOF MS ESI, MF C₁₈H₁₉NO₃S, *m/e* Calculated - 298.0079 Found : 298.0085



9-bromo-4-methoxy-5-((4-methoxyphenyl)thio)-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (20): White Solid, Yield 832 mg (95%), M.P.: 125 °C

¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.98 (s, 2H), 5.67 (s, 1H), 4.08 (s, 3H), 3.80 (s, 3H), 3.26 – 2.60 (m, 4H), 2.36 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 158.58, 134.56, 134.27, 132.67, 114.62, 114.32, 102.22, 101.12, 100.73, 77.34, 77.02, 76.70, 59.29, 55.33, 45.58, 43.71, 28.31.

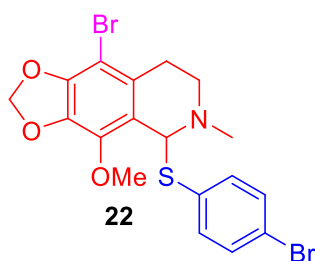


9-bromo-5-((4-fluorophenyl)thio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (21): White Solid, Yield – 699mg (82%), M.P.: 125 °C

¹H NMR (400 MHz, CDCl₃) δ 7.52 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.91 (t, *J* = 8.7 Hz, 2H), 5.92 (s, 2H), 5.67 (s, 1H), 4.00 (s, 3H), 2.90 (s, 2H), 2.64 (t, *J* = 6.5 Hz, 2H), 2.30 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 163.86, 143.44, 135.90, 131.30 (d, *J* = 8.3 Hz), 122.52, 116.40, 116.18, 103.70, 101.11, 99.50, 71.22, 60.92, 59.26, 48.60, 44.82, 29.69.

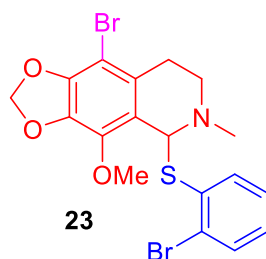
¹⁹F NMR (377 MHz, CDCl₃) δ -113.49 (s), -115.43 (s).



9-bromo-5-((4-bromophenyl)thio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (22): White Solid, Yield 837mg (86%), M.P.: 118 °C

¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 5.99 (s, 2H), 5.78 (s, 1H), 4.04 (s, 3H), 2.94 (t, *J* = 6.3 Hz, 2H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.34 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 135.82 (d, *J* = 14.8 Hz), 132.23, 129.43, 121.56, 101.11, 99.51, 77.23, 71.22, 59.26, 44.82, 29.69.



9-bromo-5-((2-bromophenyl)thio)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (23) : White Solid, Yield 827mg (85%), M.P.: 111 °C

¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.06 (dt, *J* = 15.4, 7.6 Hz, 1H), 6.09 (s, 1H), 6.01 (s, 2H), 4.05 (s, 3H), 3.05 (t, *J* = 6.3 Hz, 2H), 2.77 (t, *J* = 6.5 Hz, 2H), 2.36 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 138.80, 134.66, 133.11, 132.20, 127.86, 127.28 (d, *J* = 16.4 Hz), 101.27, 95.79, 59.41, 45.52, 42.98, 29.69, 28.22.

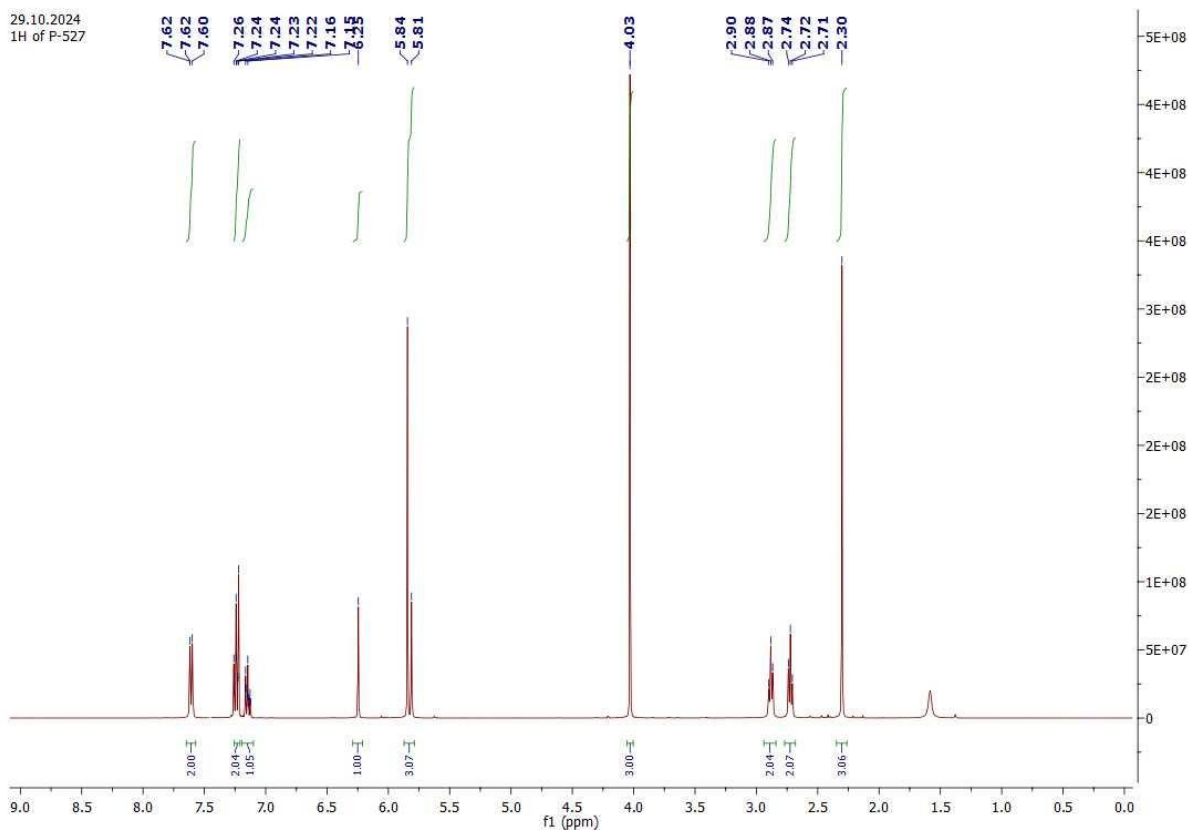
Reference:

1. Metal-Free Activation of a C(sp)-H Bond of Aryl Acetylenes , Laxmidhar Rout, Dr. Dr. Jean-Claude Florent, Dr. Ludger Johannes, Santosh Kumar Choudhury, Joe Scanlon and Emmanuel Bertounesque *Chem. - A Europ. J.* 2016, **22**, 14812–14815.
2. Metal Free Activation of C(SP³)-H Bond, Practical and Rapid Synthesis of Privileged 1-Substituted-1,2,3,4-Tetrahydroisoquinolines, S. K. Choudhury, P. Rout, J-C. Florent, L. Johannes, E. Bertounesque, Prof. Laxmidhar Rout, *Eur J. Org. Chem.* 2017, **35**, 5275-5292.

5. ^1H (proton) and ^{13}C (carbon) NMR spectra

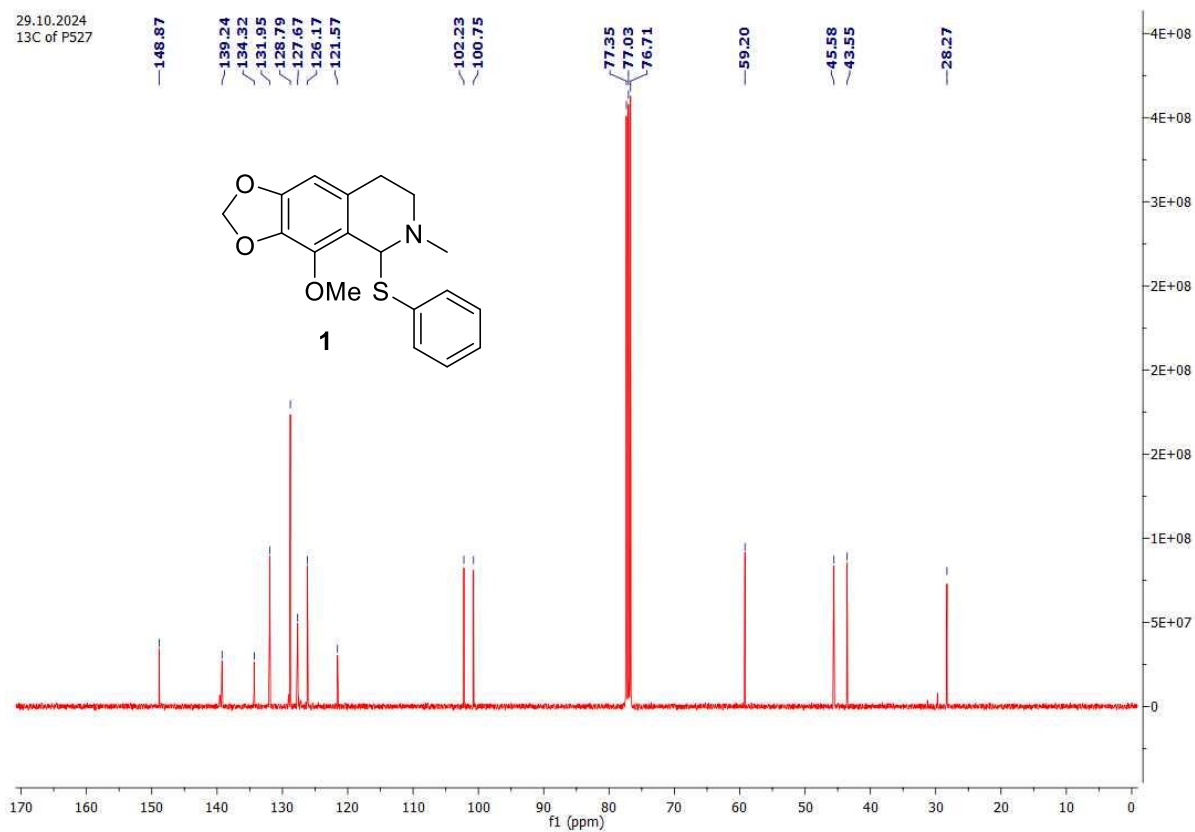
¹H NMR of Compound (1)

29.10.2024
1H of P-527

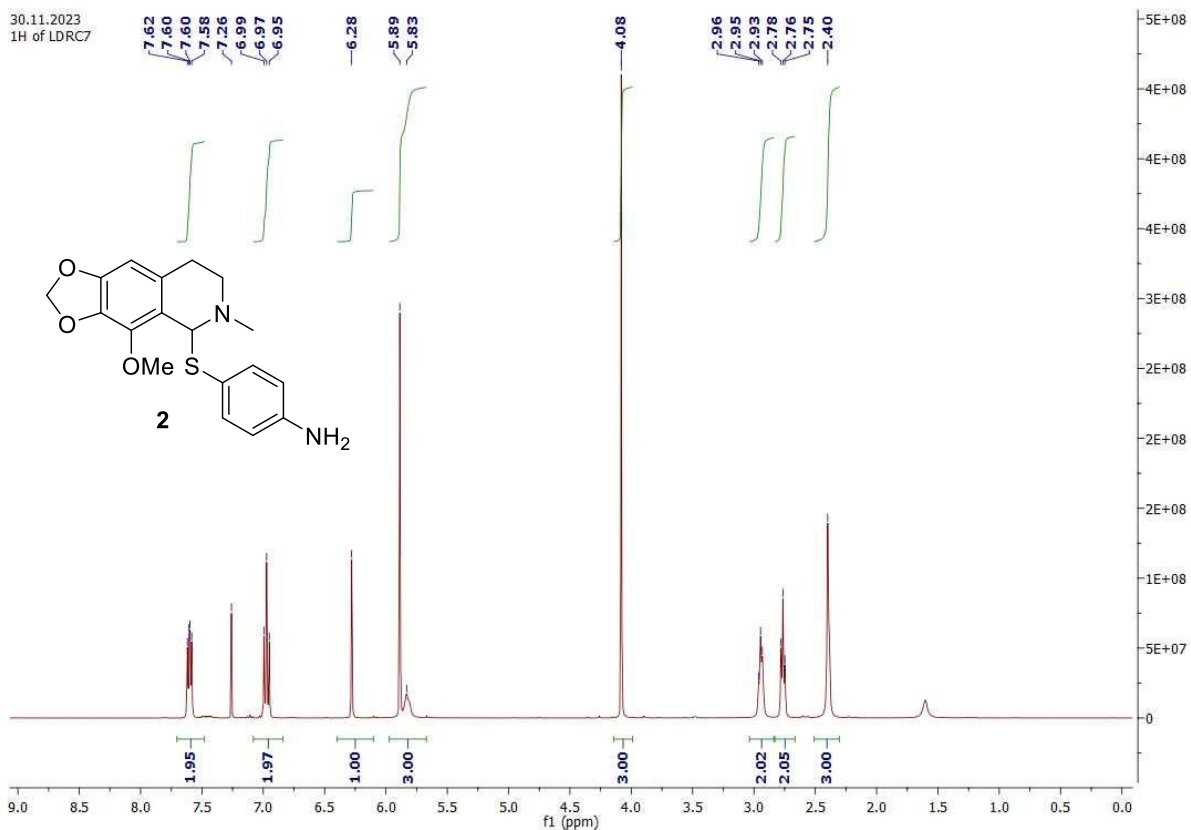


¹³C NMR of Compound (1)

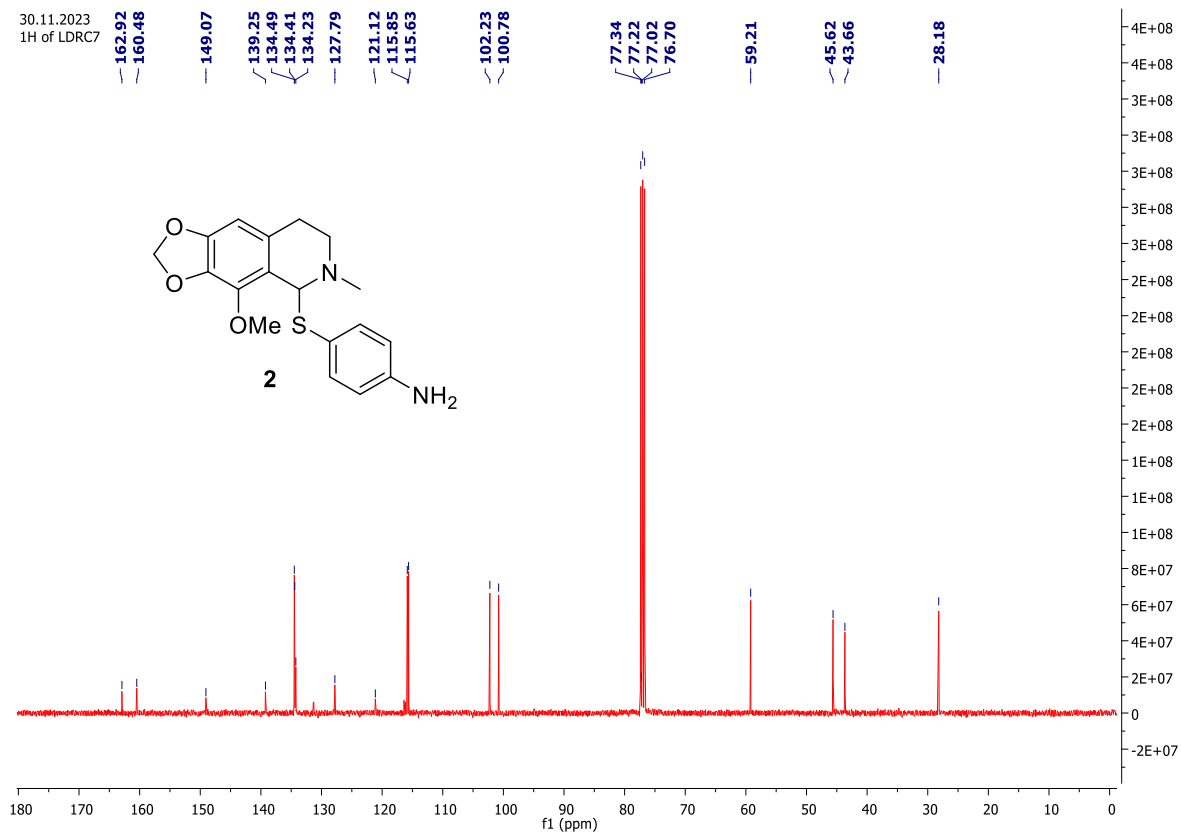
29.10.2024
13C of P527



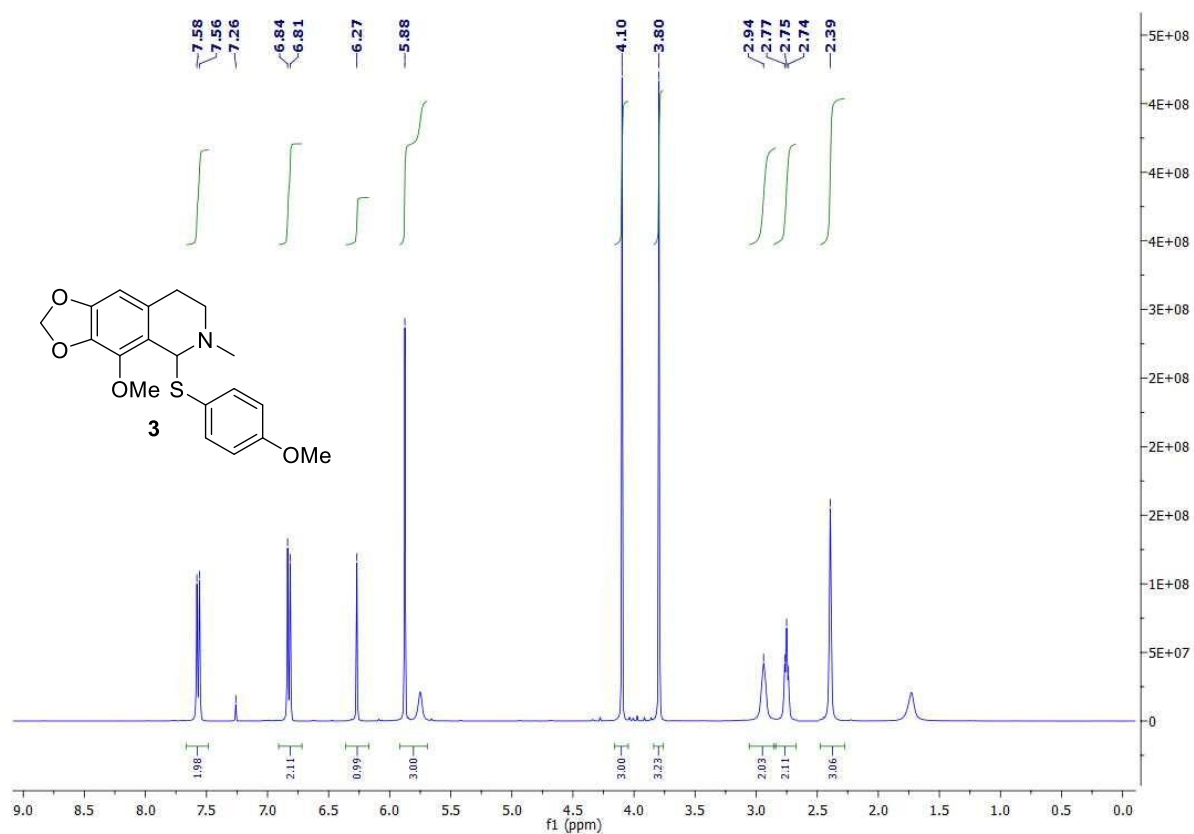
¹H NMR of Compound (2)



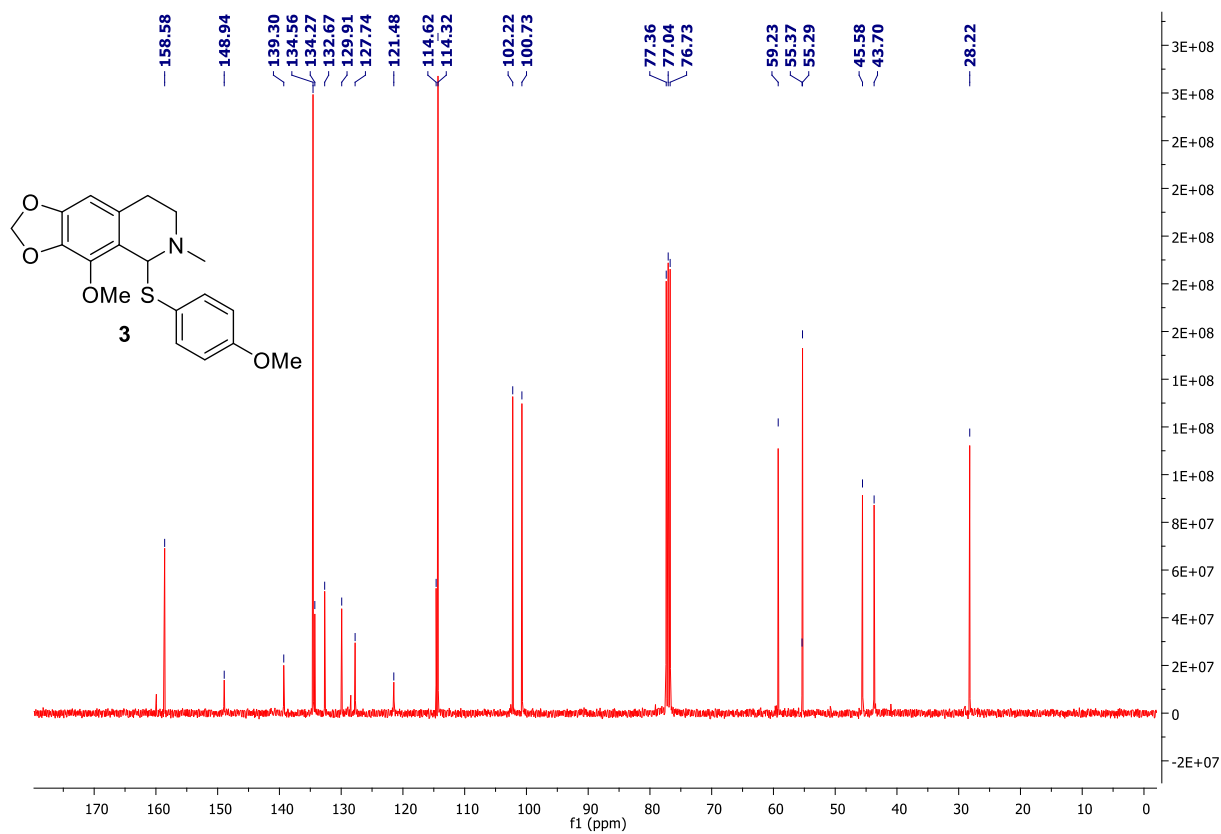
¹³C NMR of Compound (2)



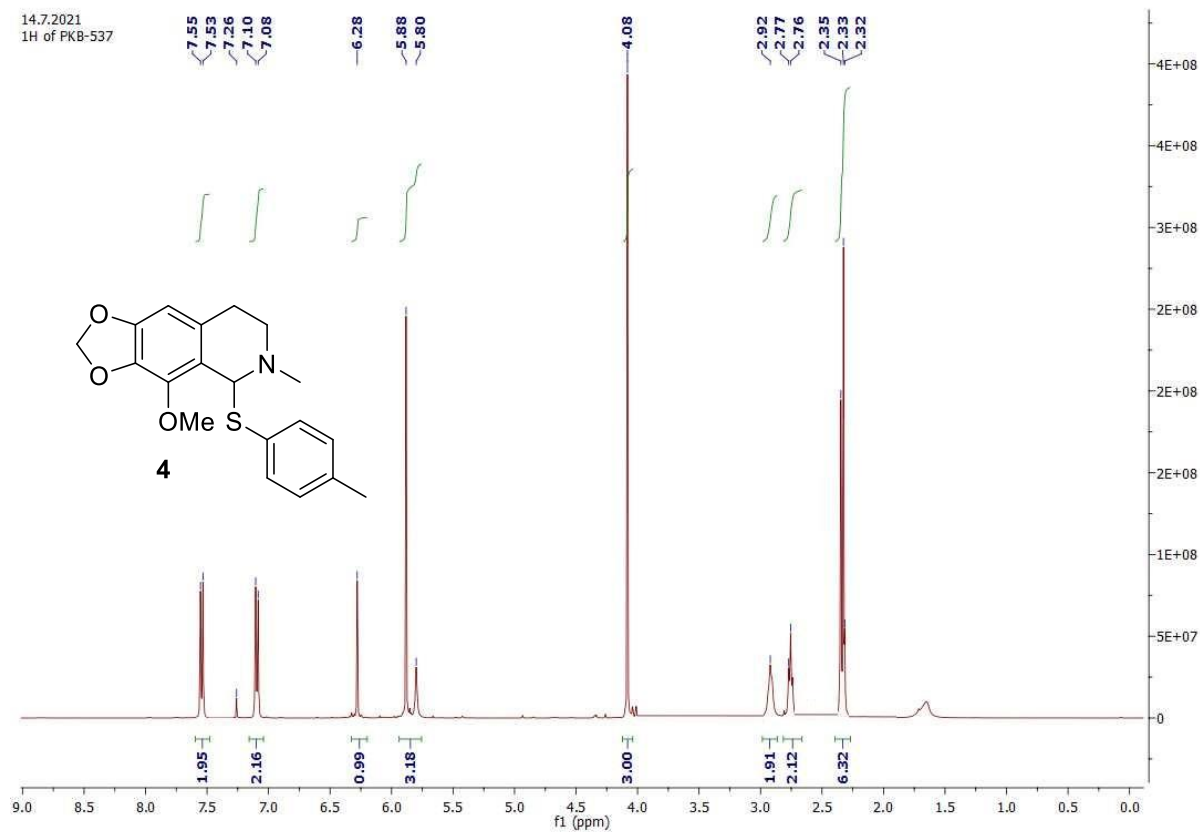
¹H NMR of Compound (3)



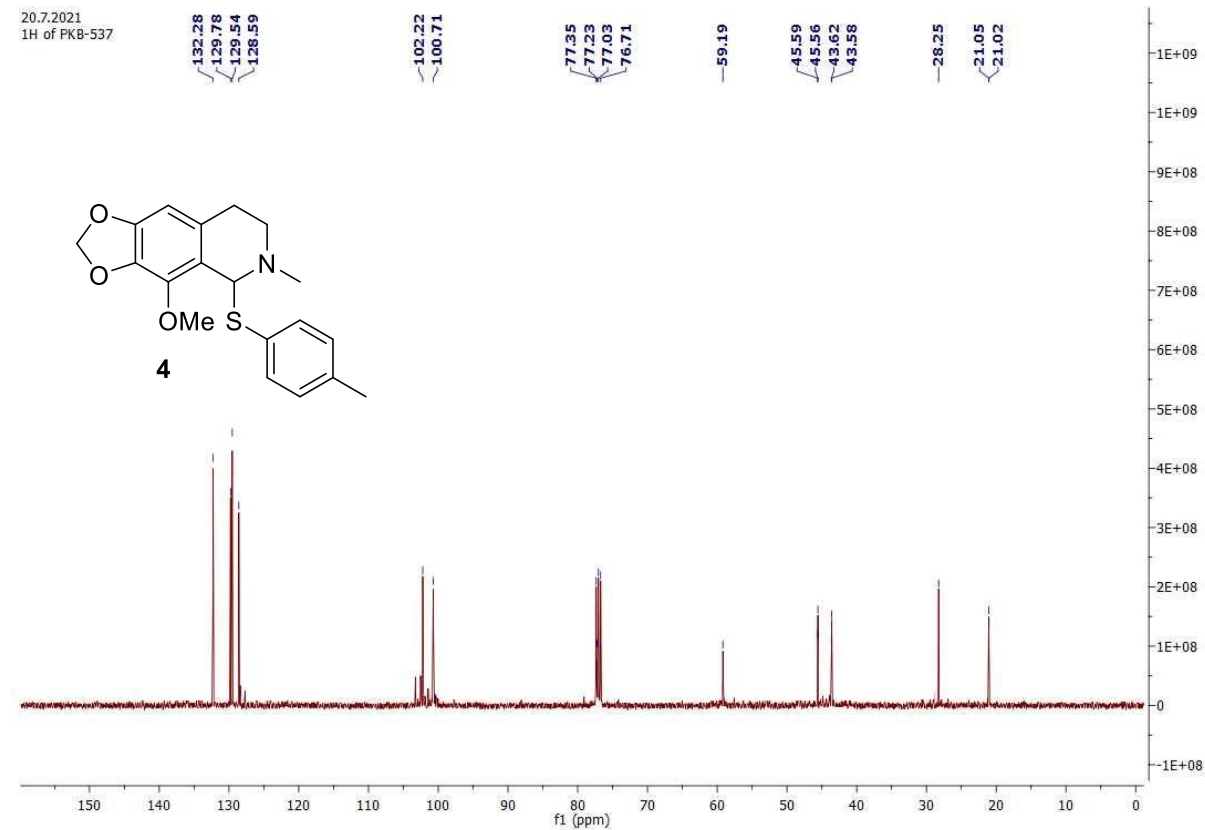
¹³C NMR of Compound (3)



¹H NMR of Compound (4)

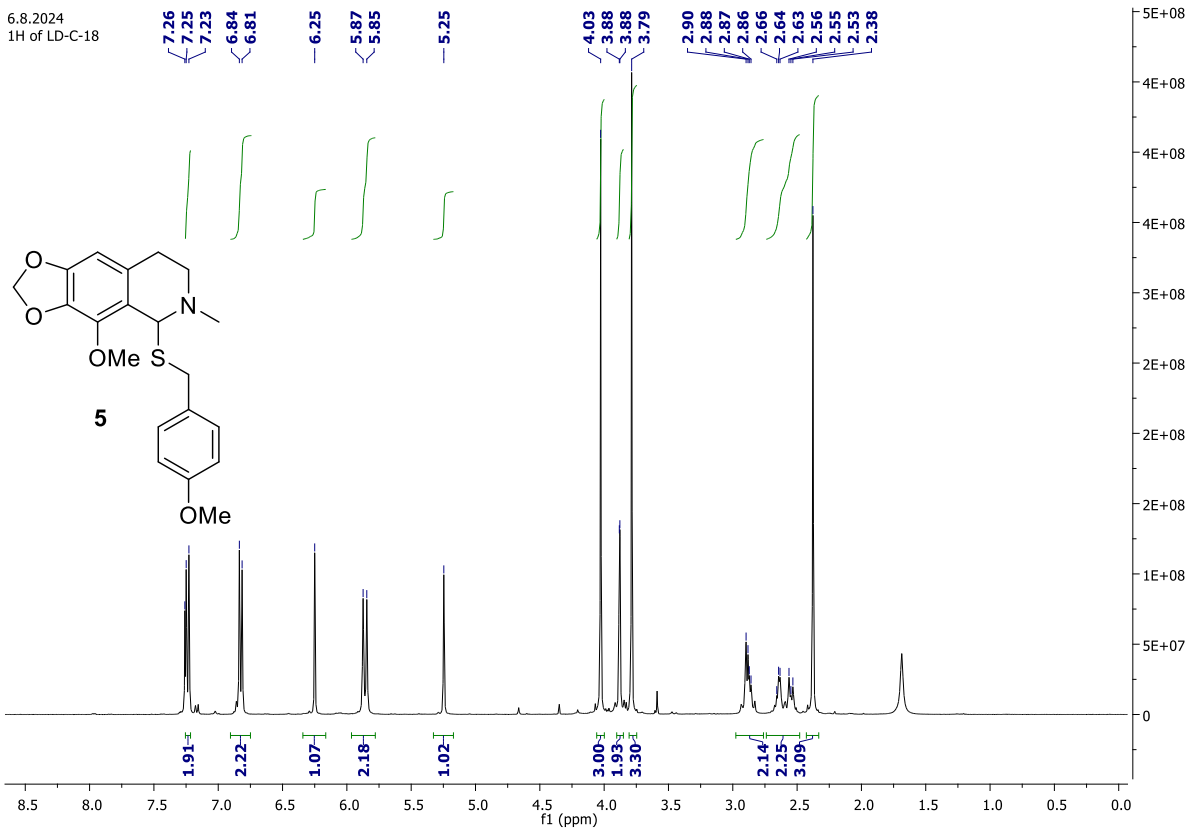


¹³C NMR of Compound (4)



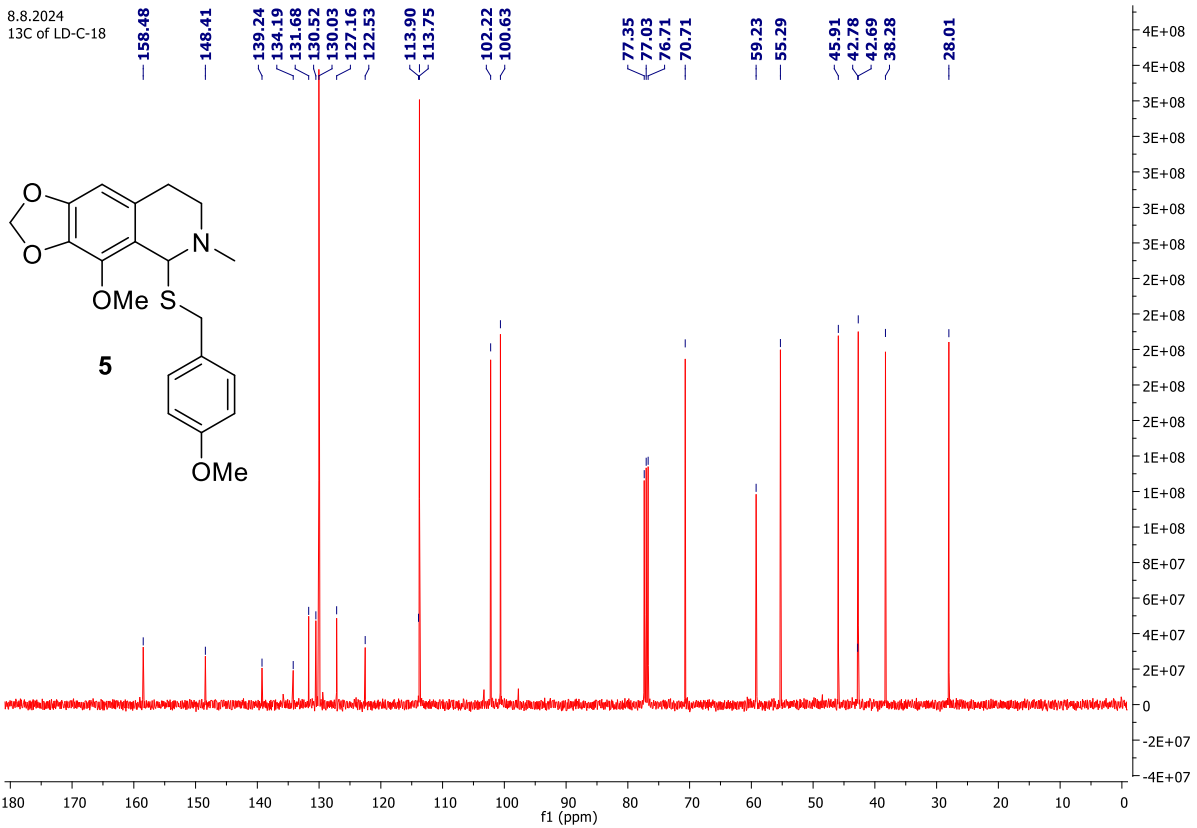
¹H NMR of Compound (5)

6.8.2024
1H of LD-C-18

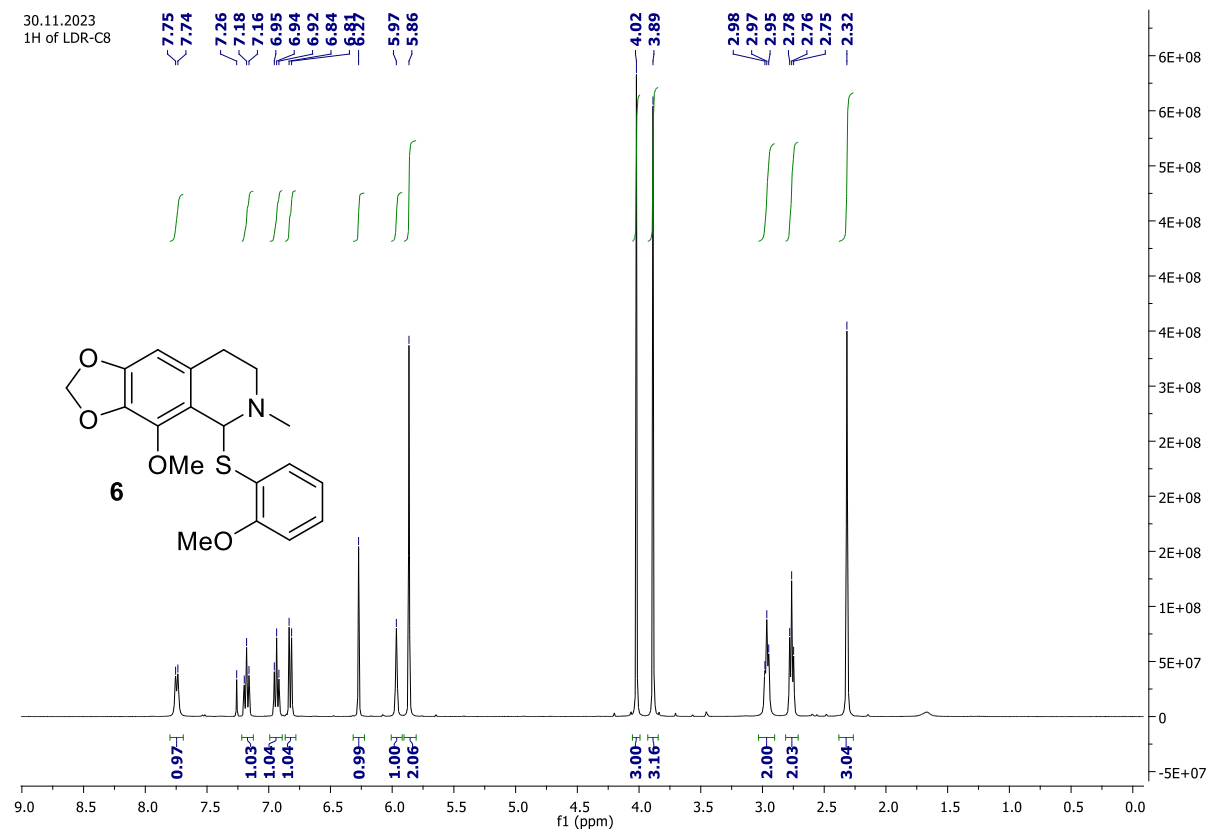


¹³C NMR of Compound (5)

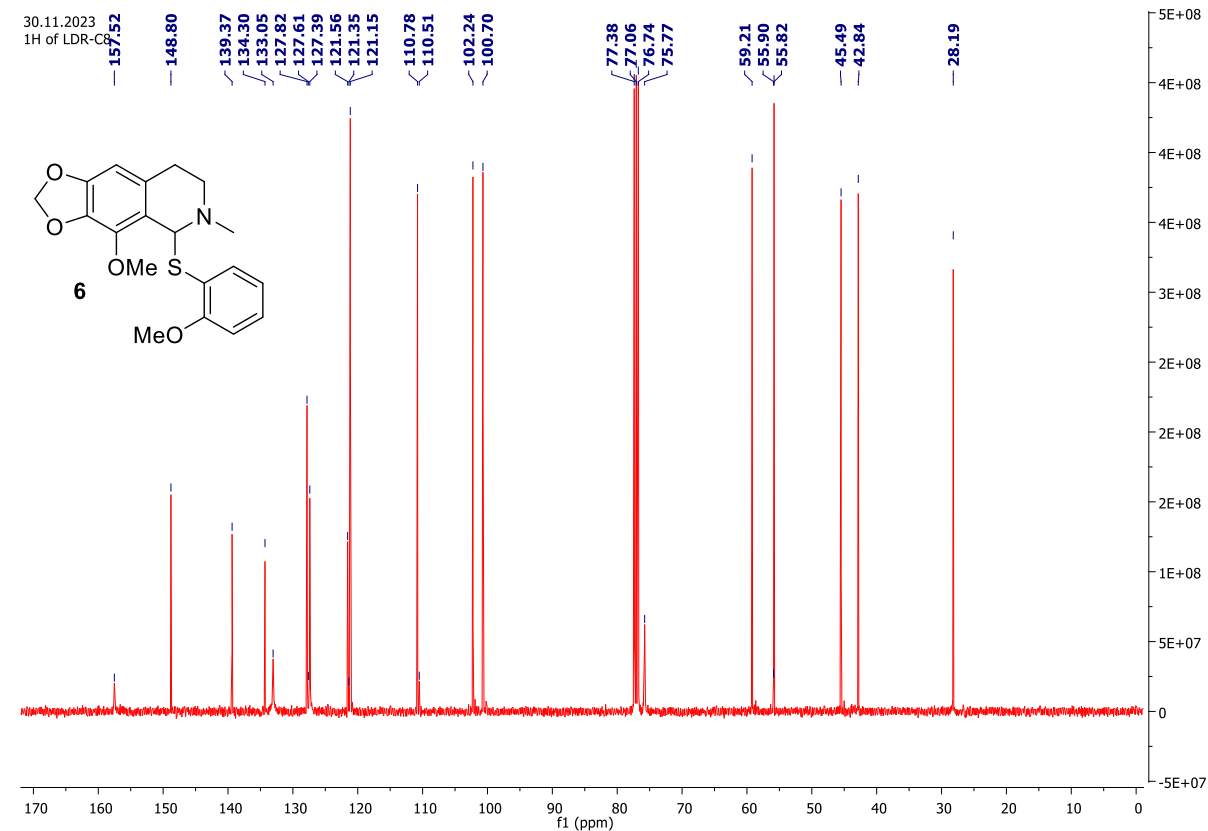
8.8.2024
13C of LD-C-18



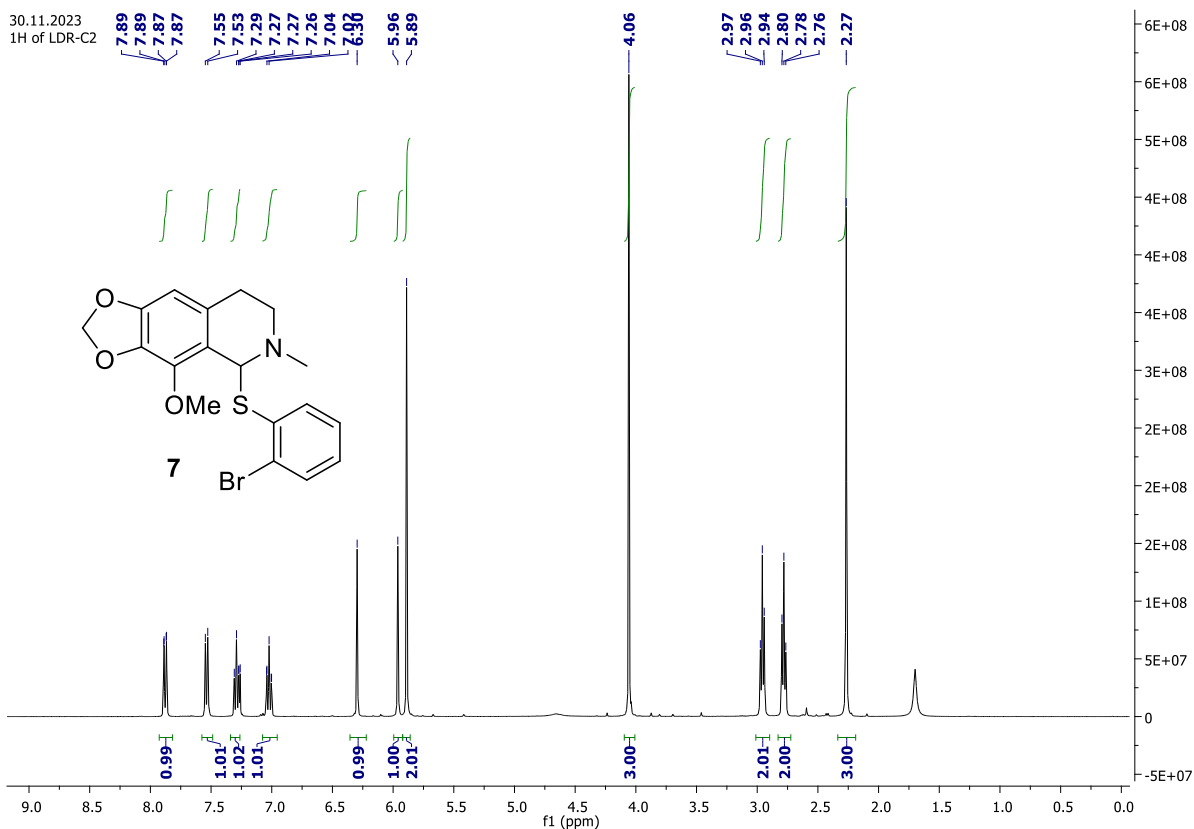
¹H NMR of Compound (6)



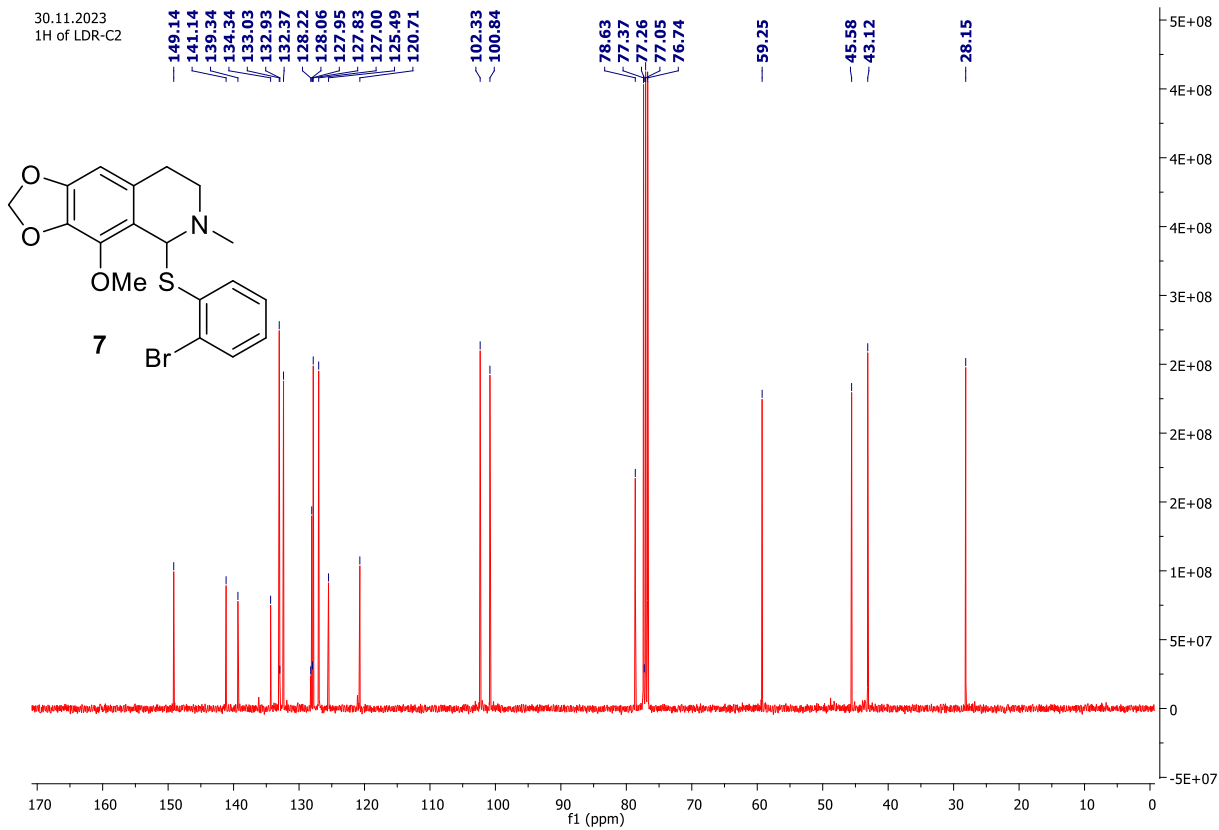
¹³C NMR of Compound (6)



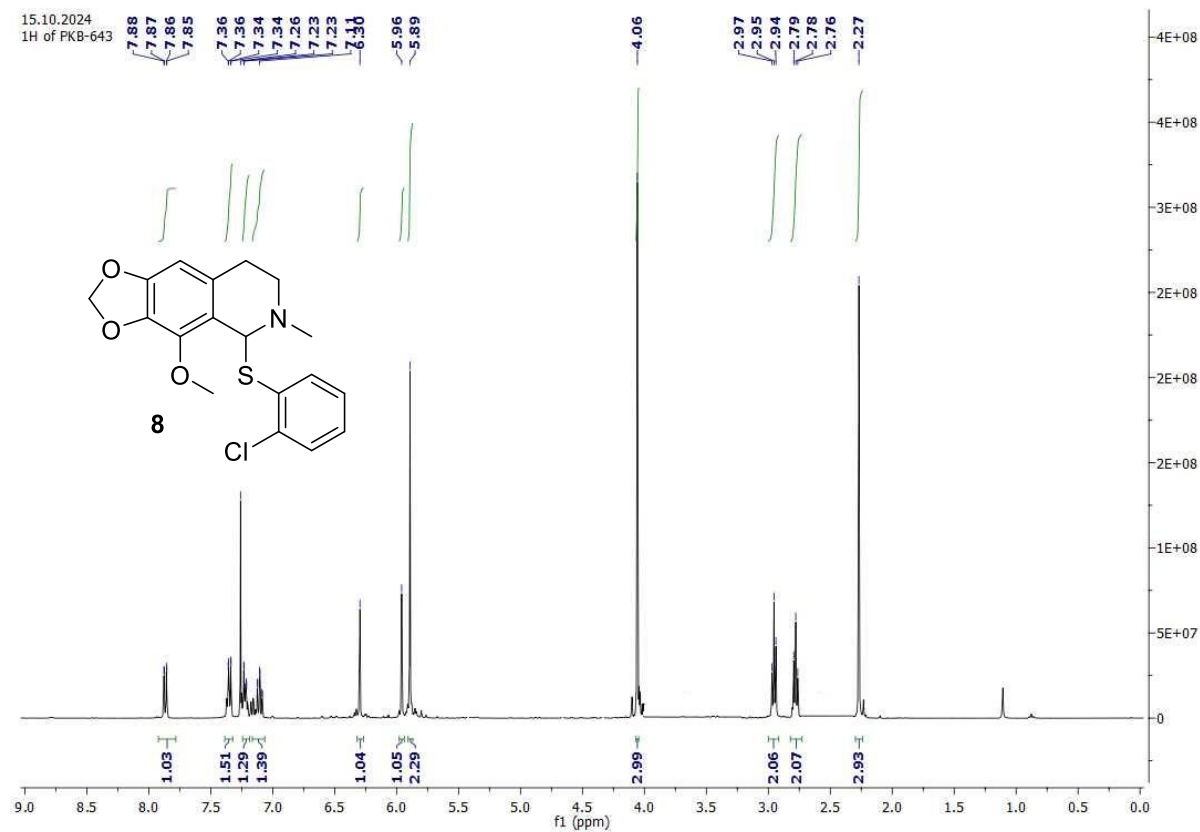
¹H NMR of Compound (7)



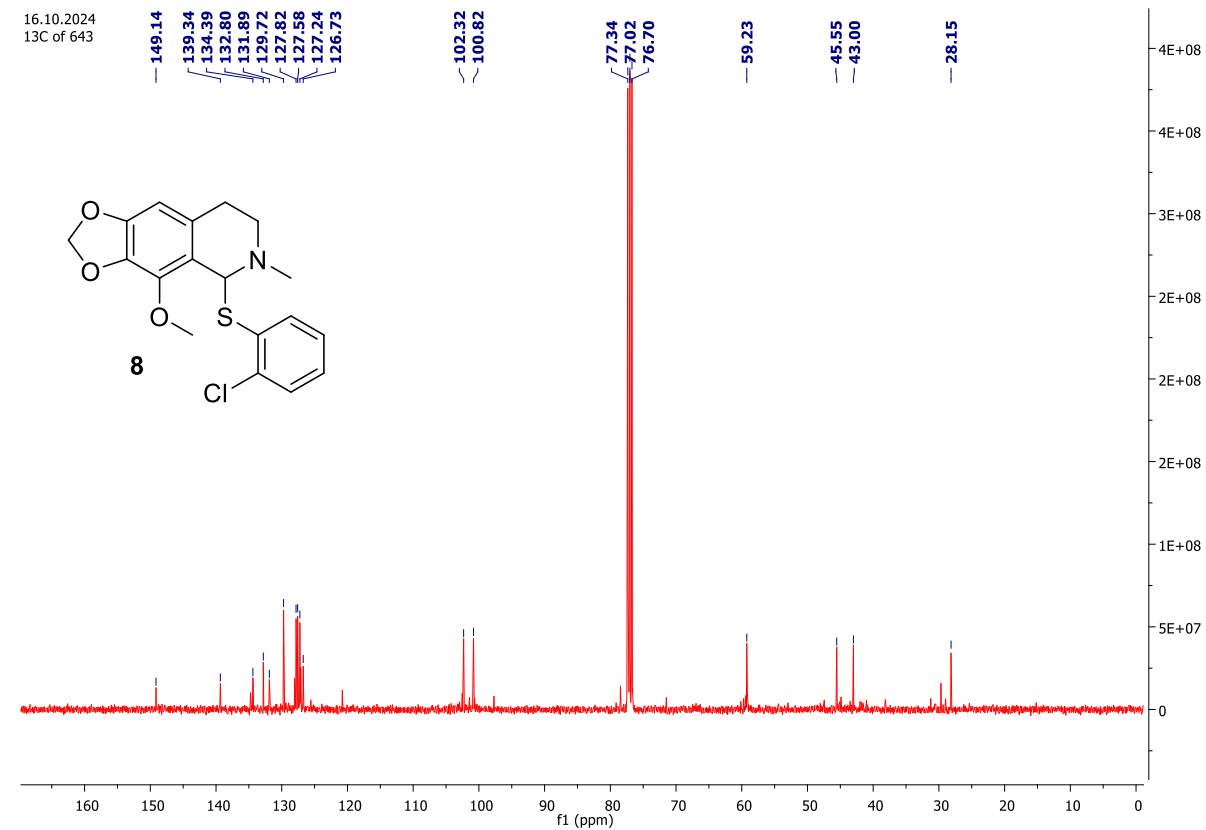
¹³C NMR of Compound (7)



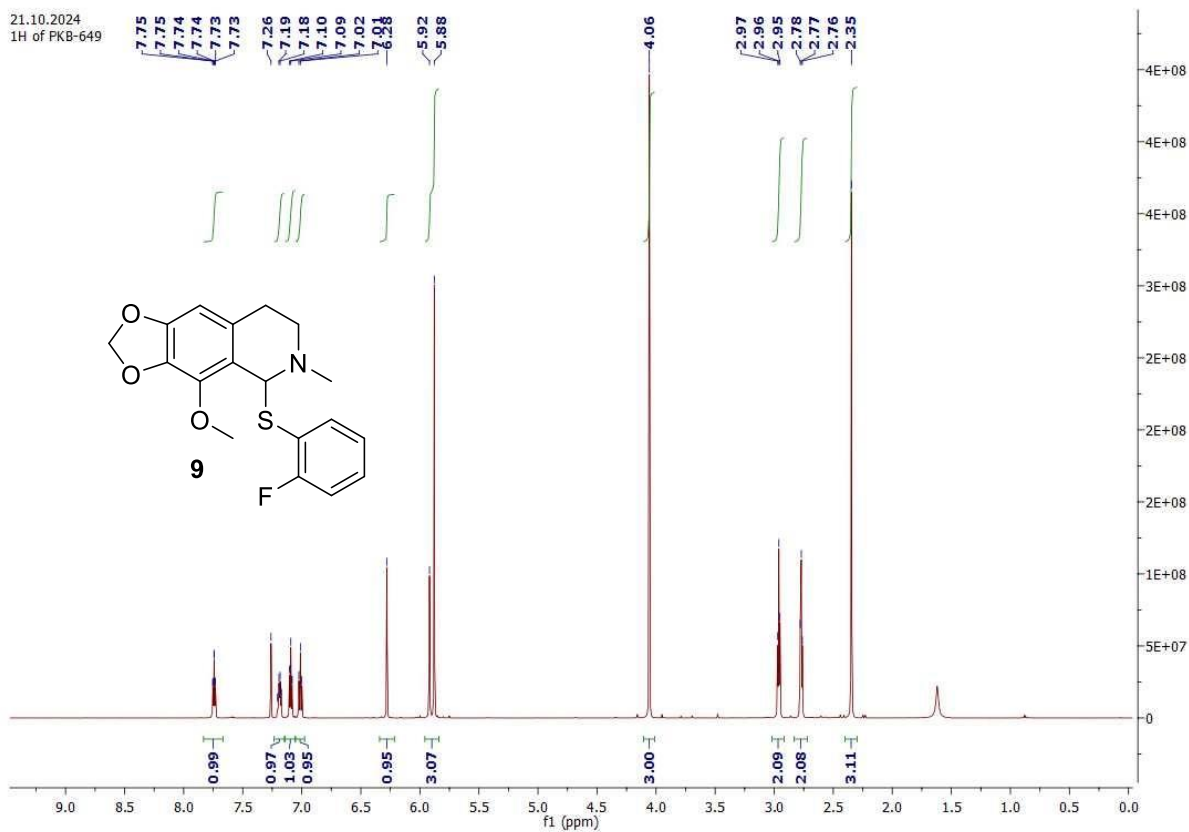
¹H NMR of Compound (8)



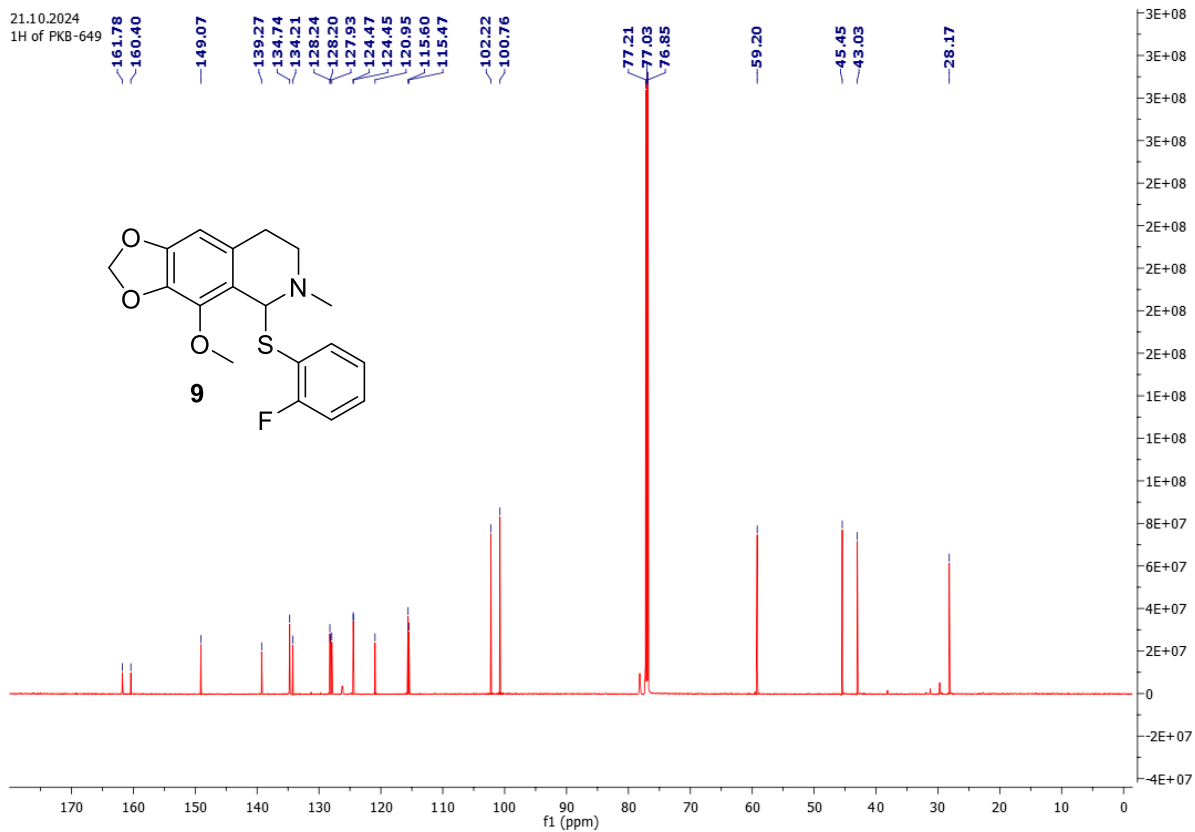
¹³C NMR of Compound (8)



¹H NMR of Compound (9)

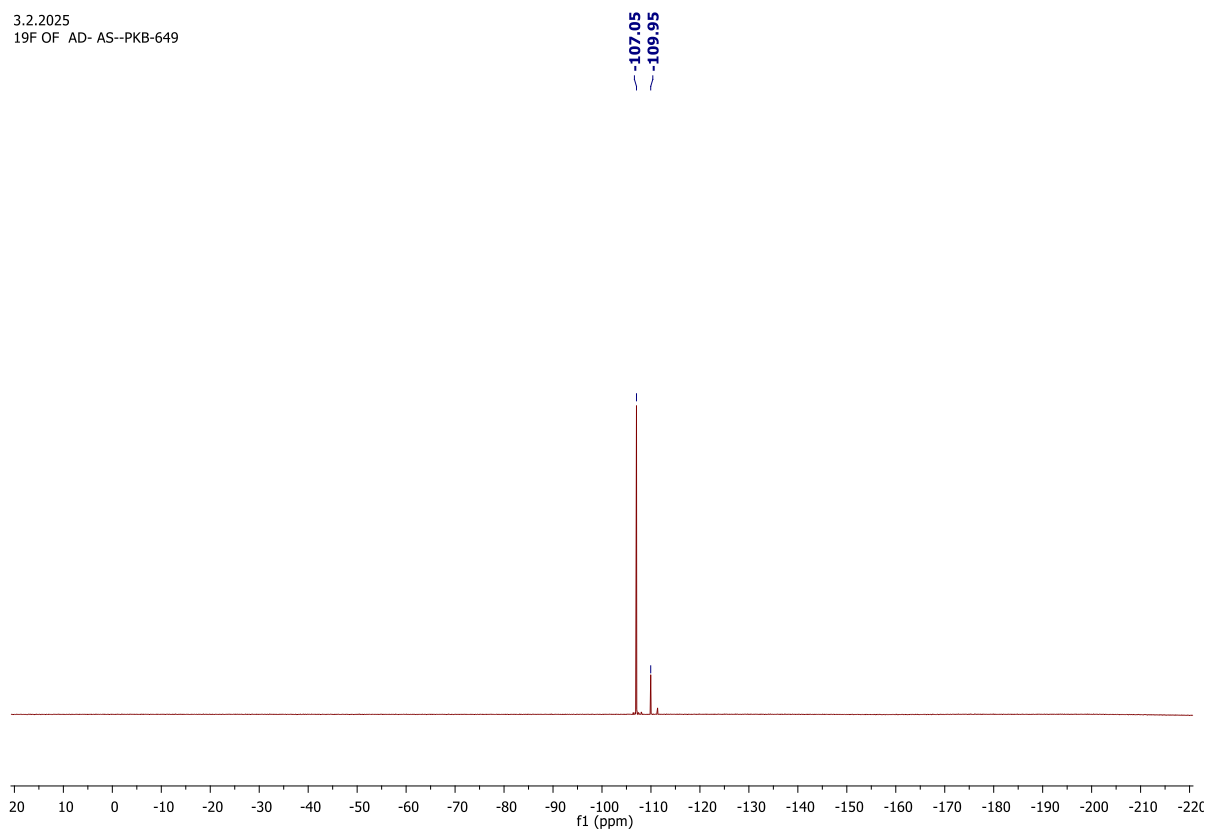


¹³C NMR of Compound (9)



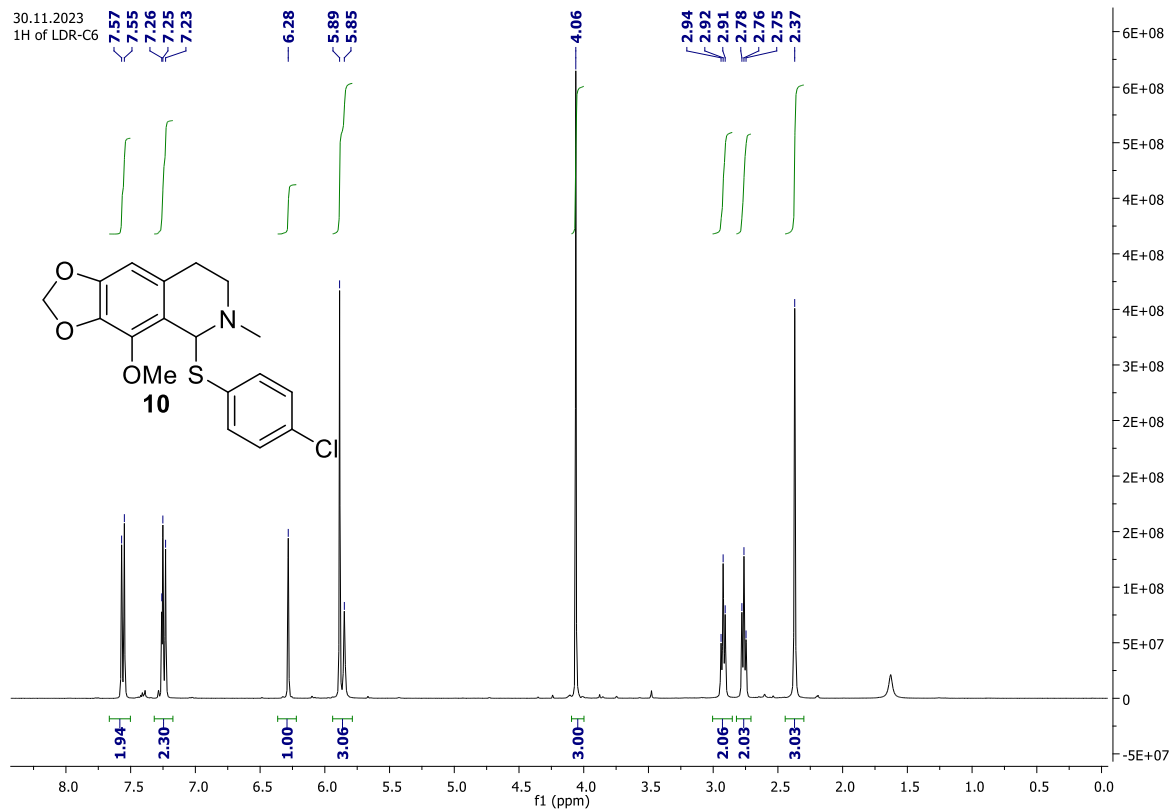
¹⁹F NMR of Compound (9)

3.2.2025
19F OF AD- AS--PKB-649

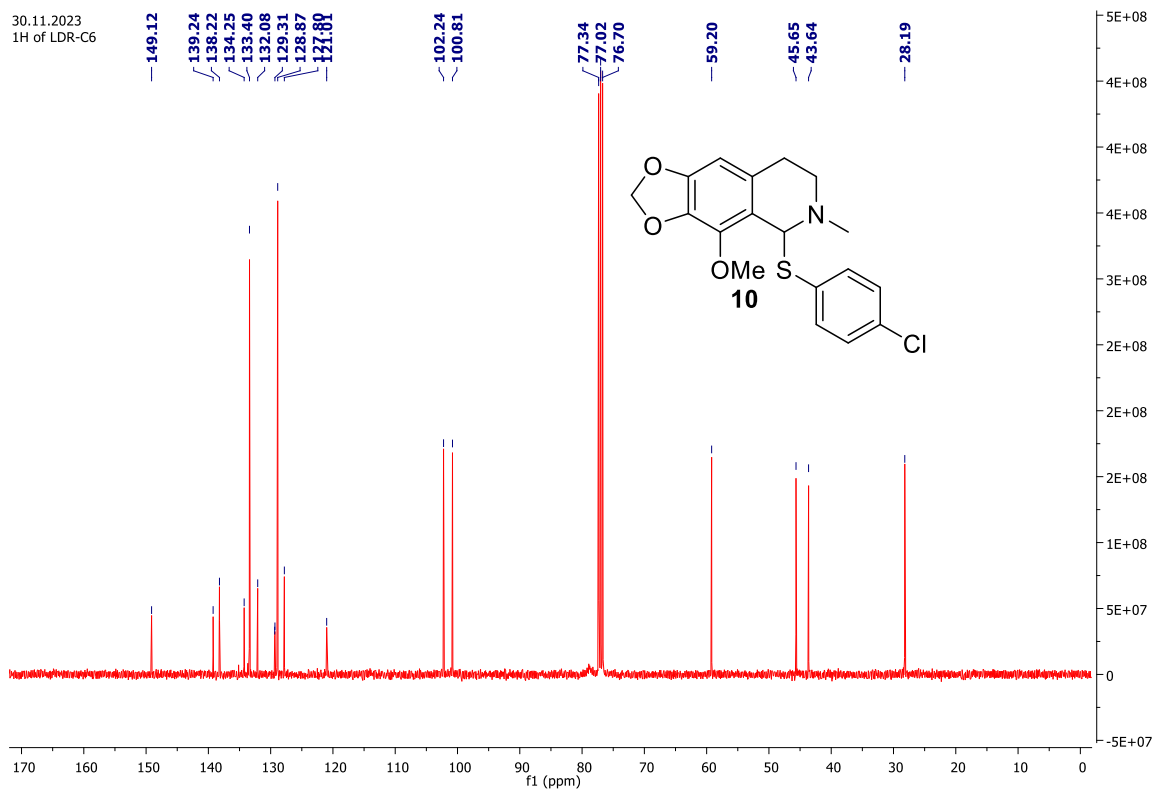


¹H NMR of Compound (10)

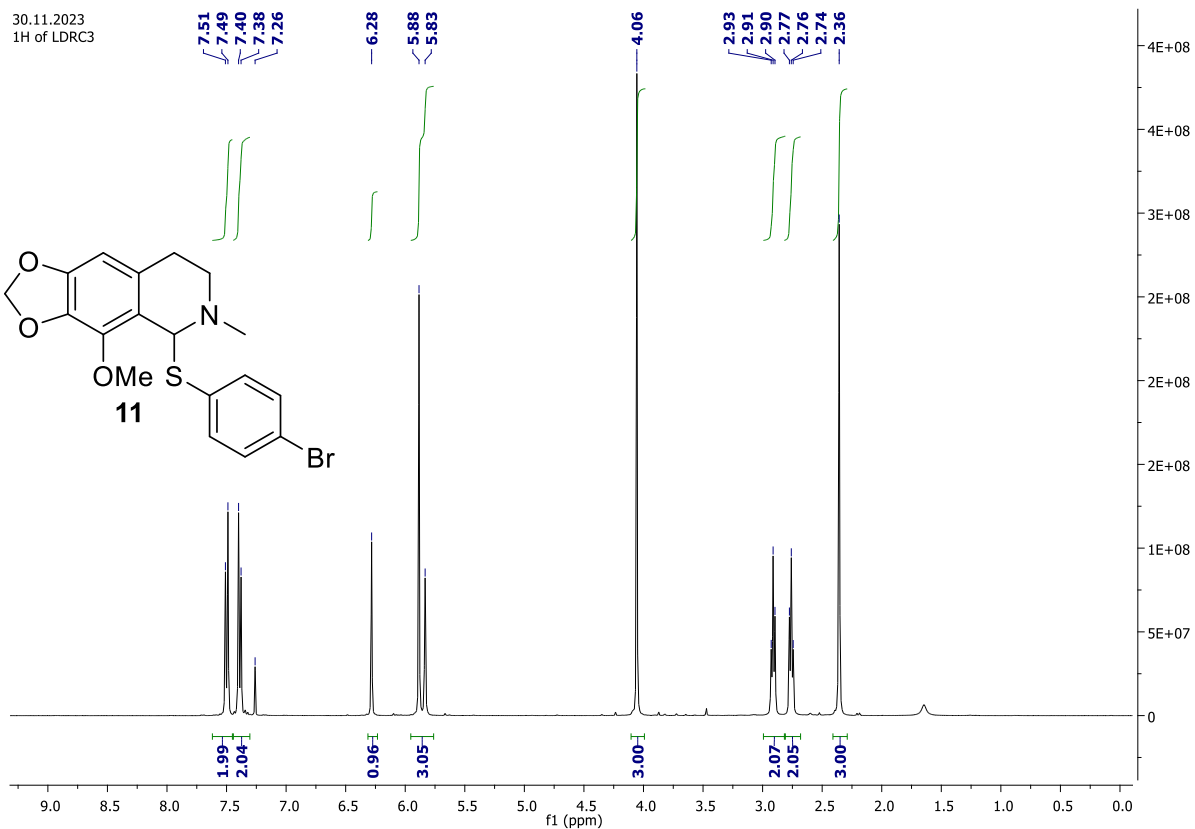
30.11.2023
1H of LDR-C6



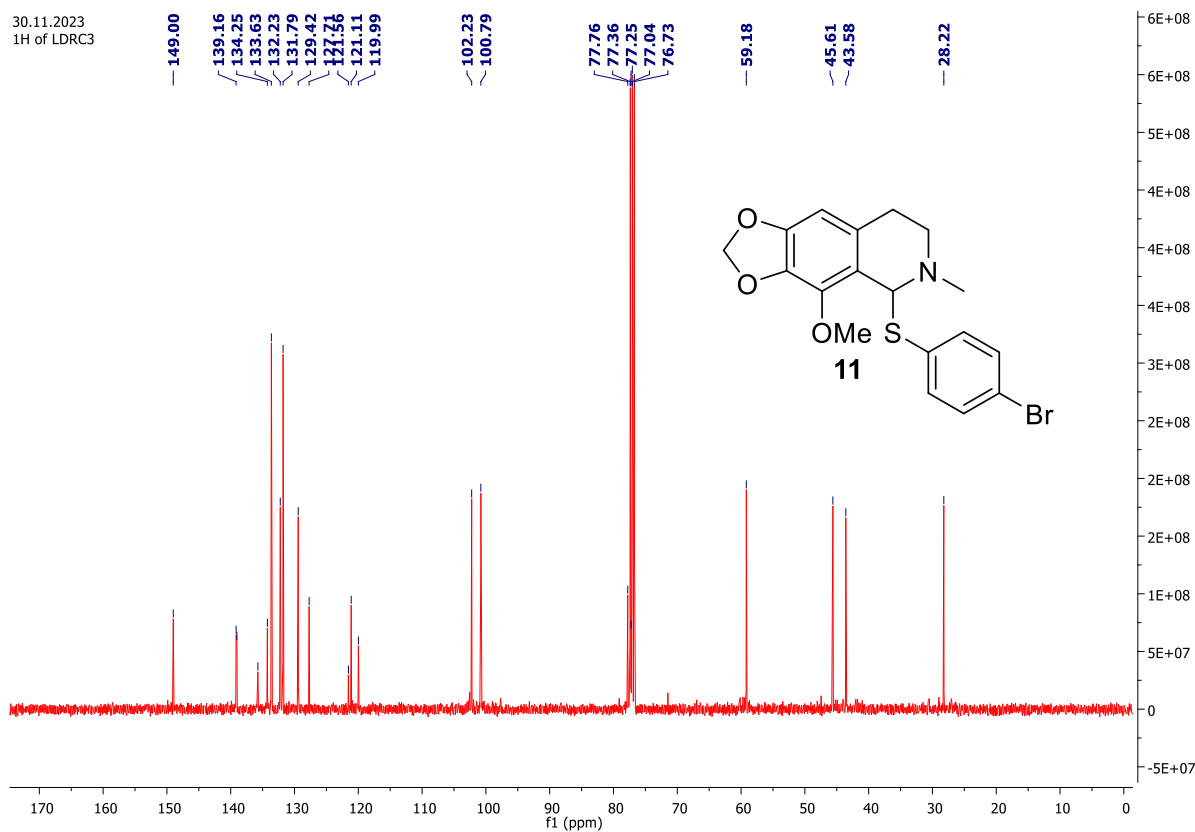
¹³C NMR of Compound (10)



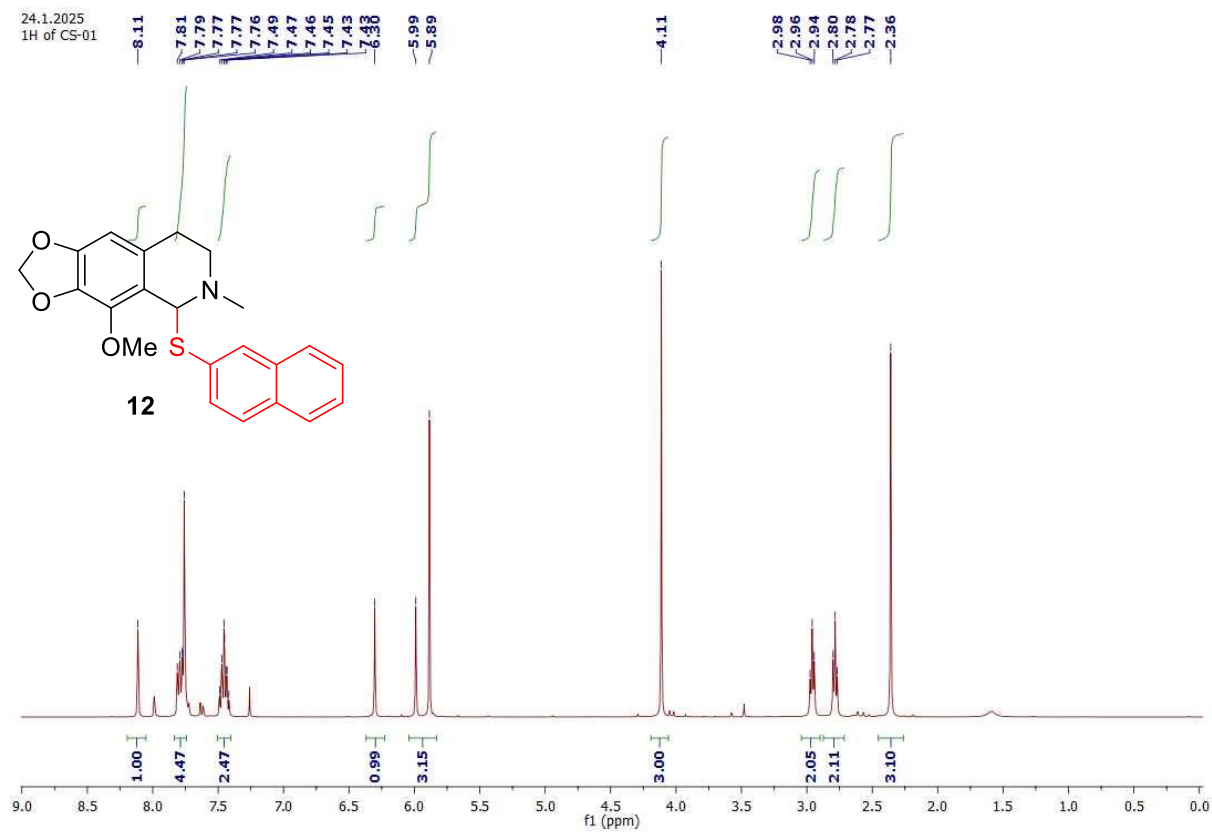
¹H NMR of Compound (11)



¹³C NMR of Compound (11)

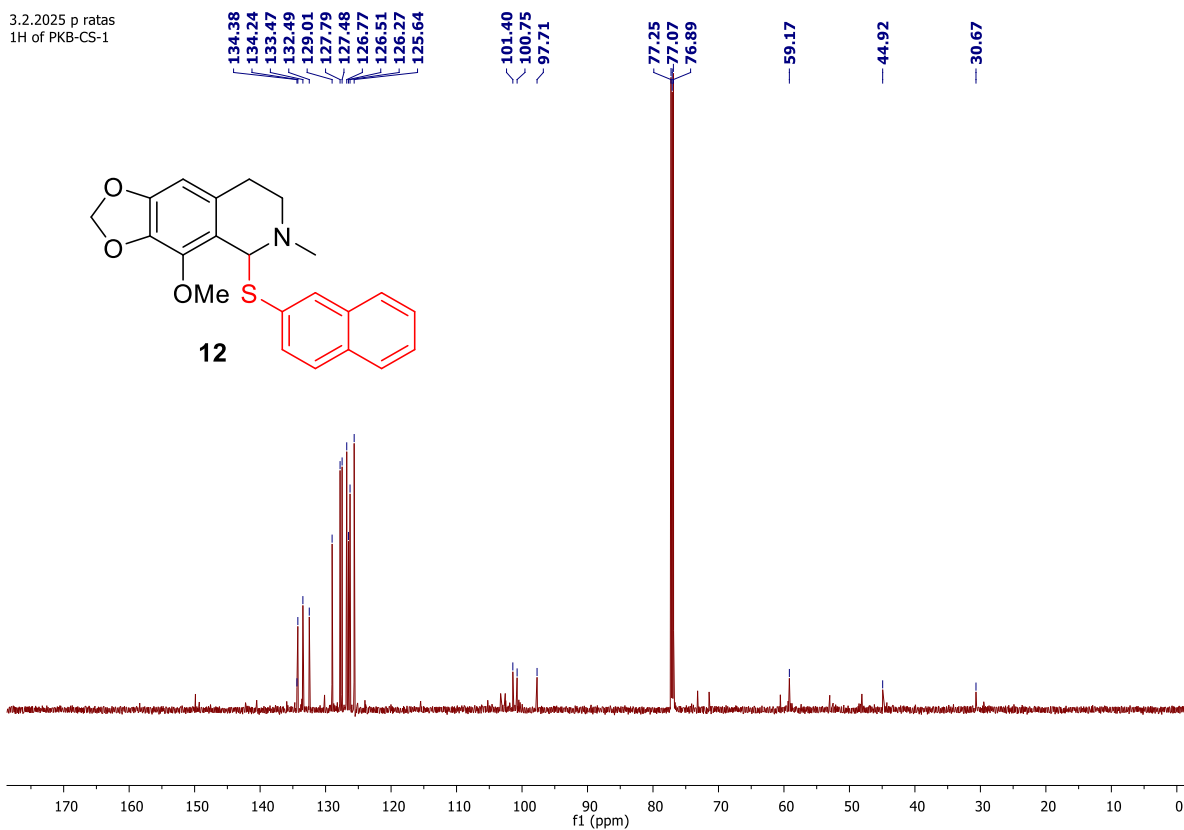


¹H NMR of Compound (12)



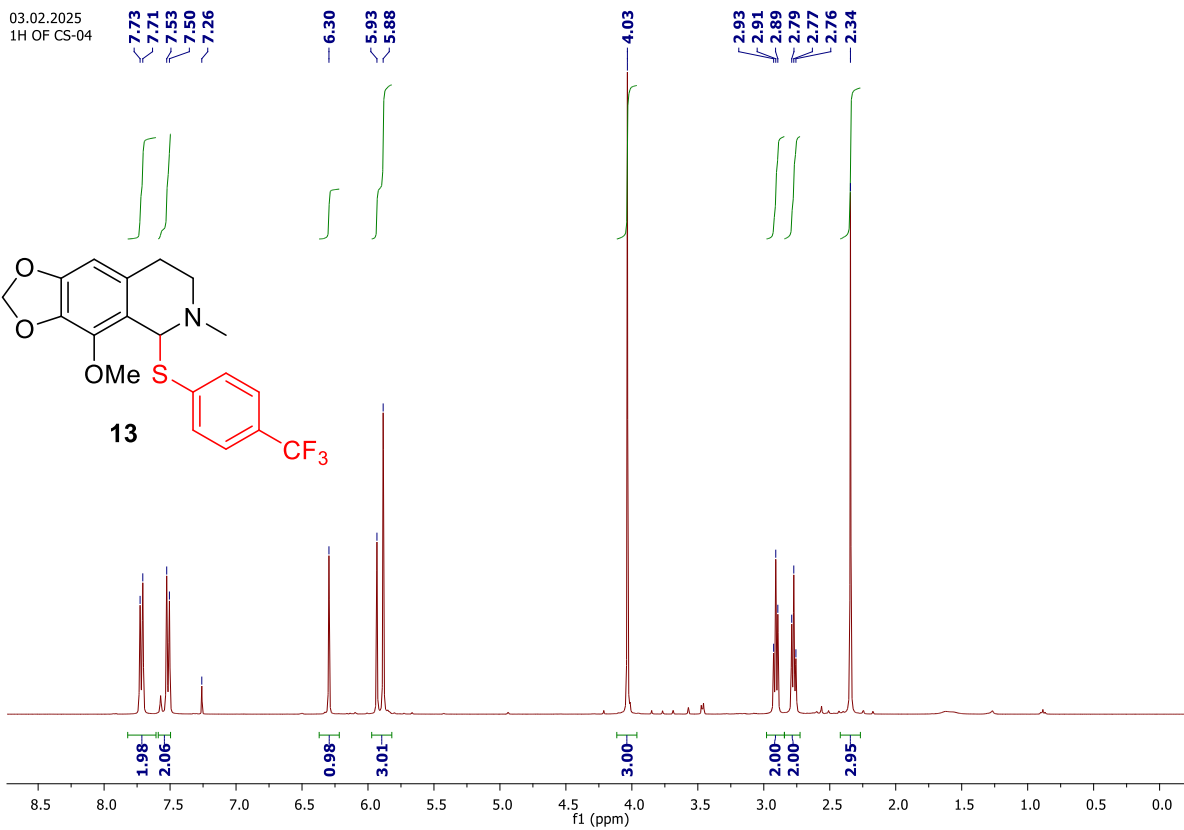
¹³C NMR of Compound (12)

3.2.2025 p ratas
1H of PKB-CS-1



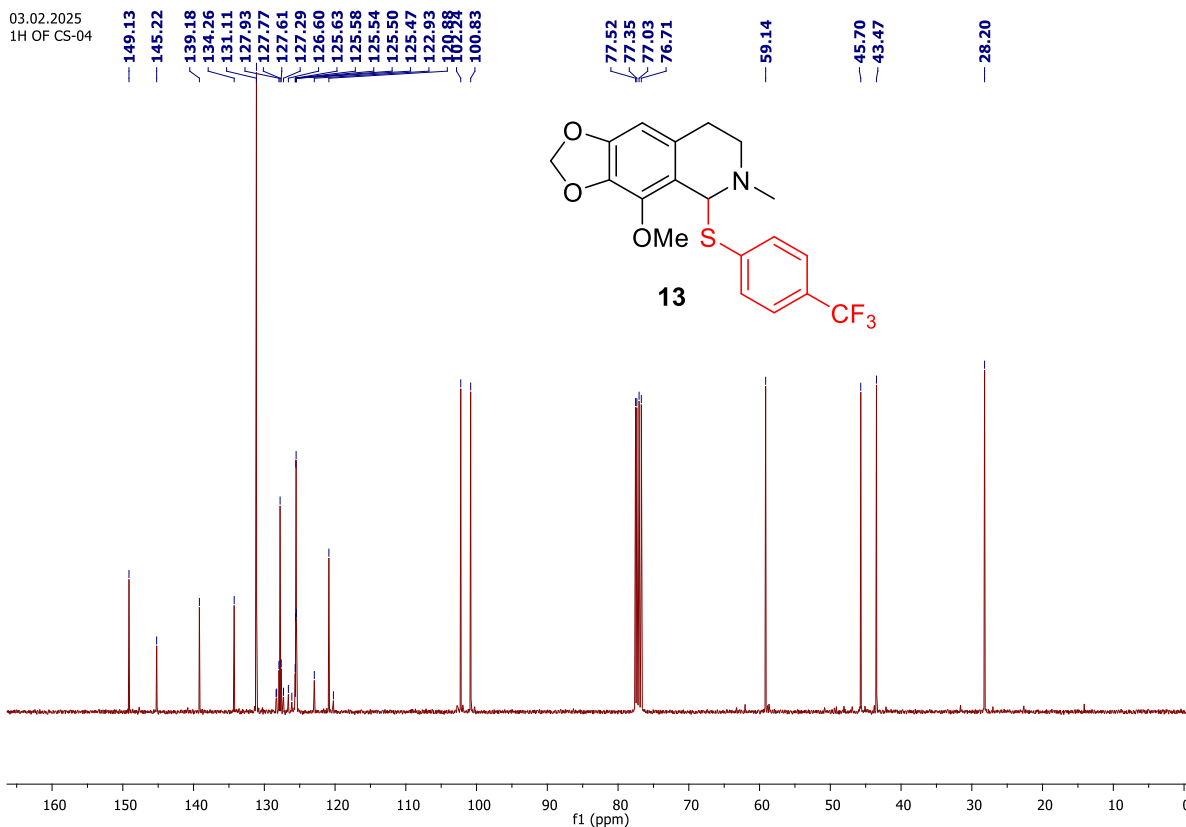
¹H NMR of Compound (13)

03.02.2025
1H OF CS-04



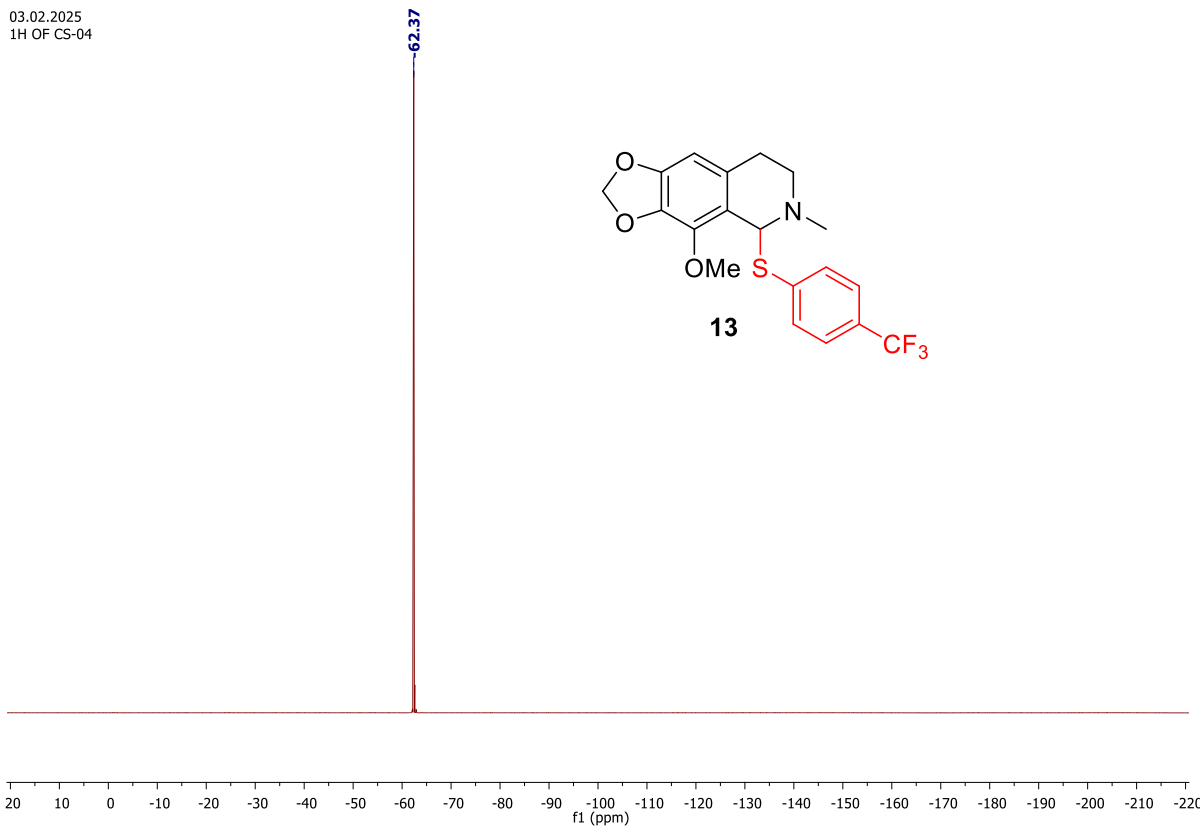
¹³C NMR of Compound (13)

03.02.2025
1H OF CS-04



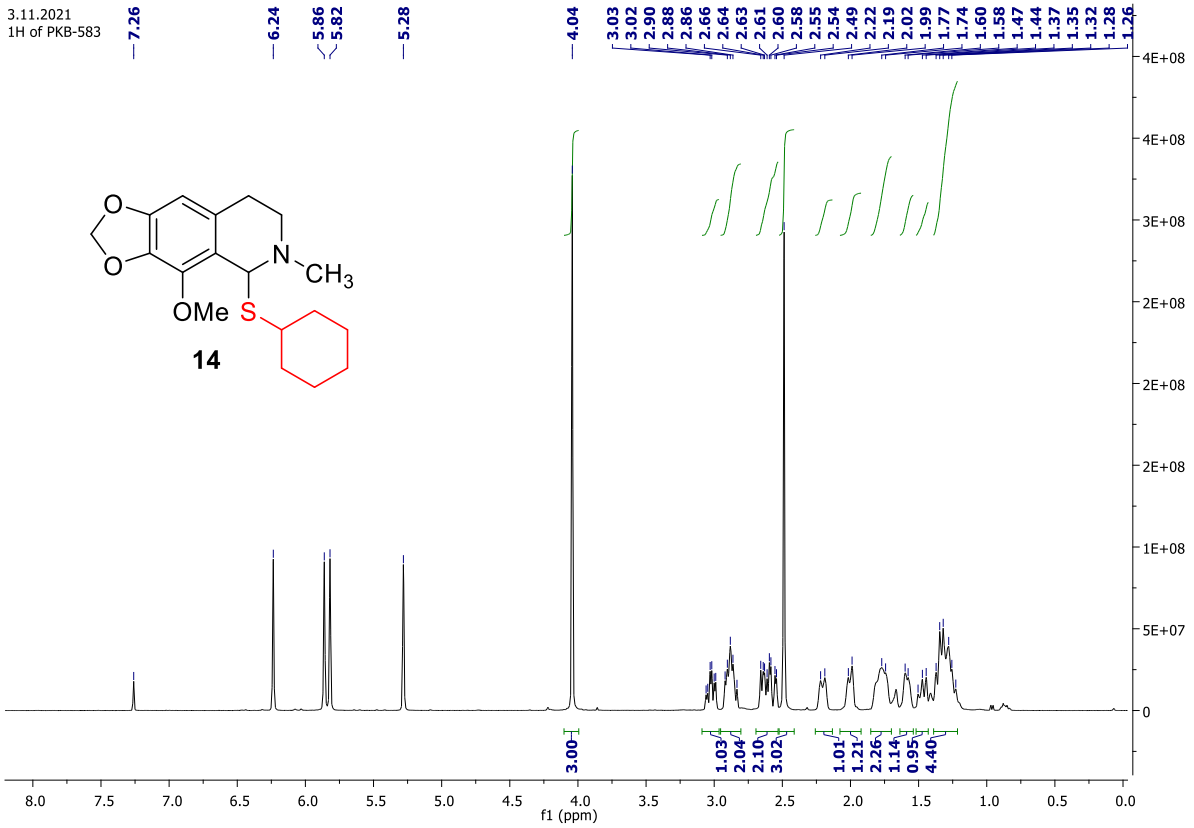
¹⁹F NMR of Compound (13)

03.02.2025
1H OF CS-04



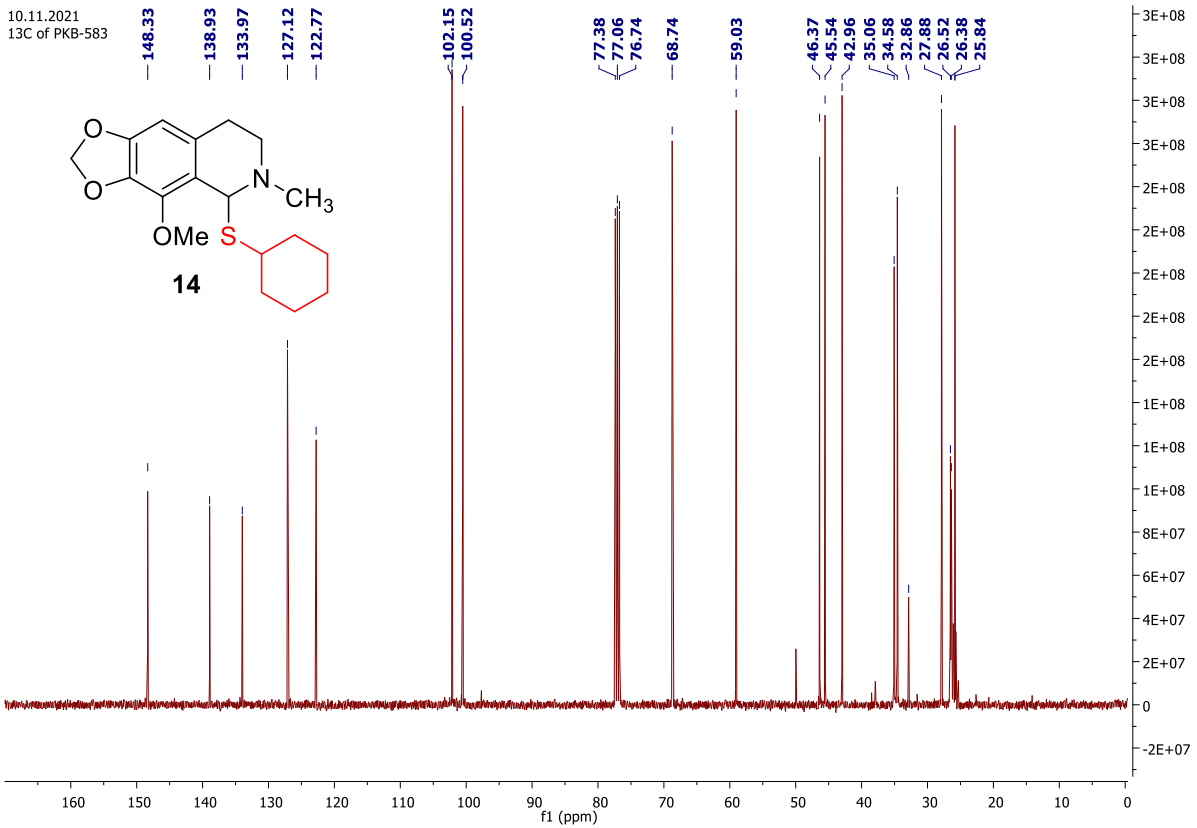
¹H NMR of Compound (14)

3.11.2021
1H of PKB-583



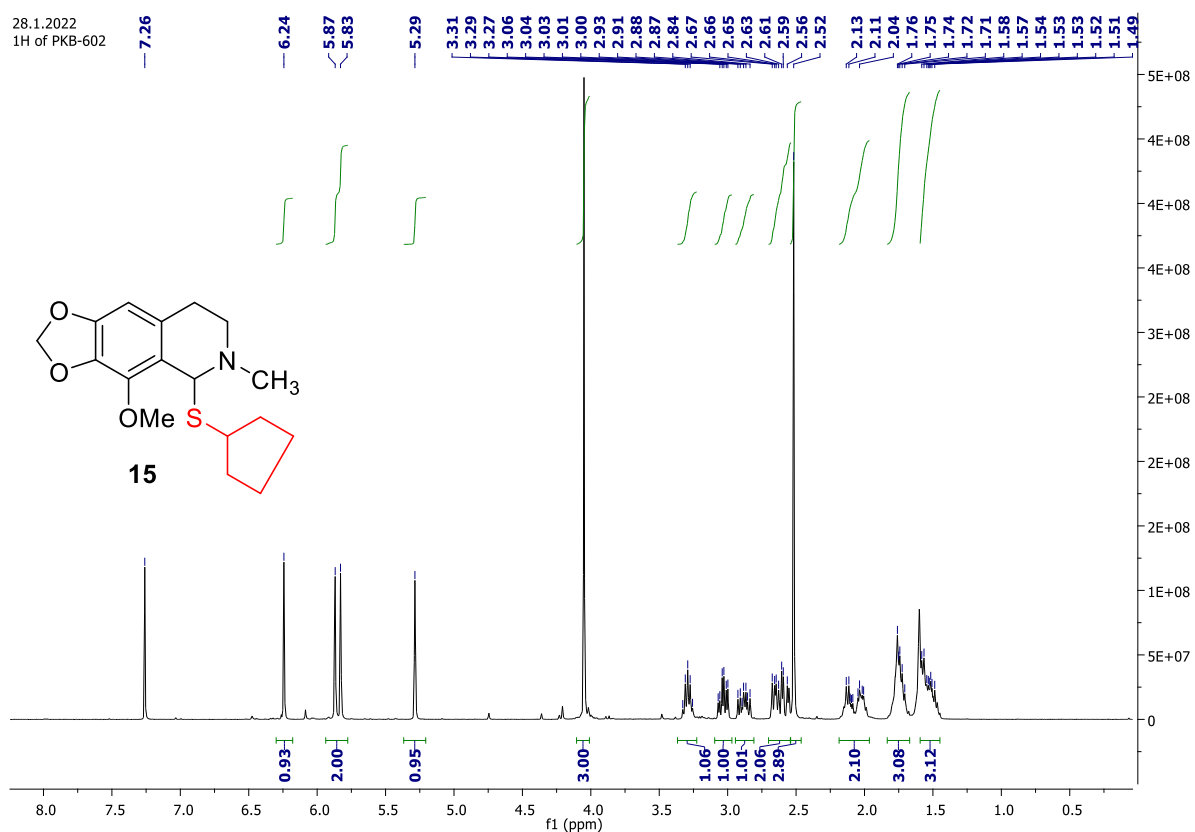
¹³C NMR of Compound (14)

10.11.2021
13C of PKB-583

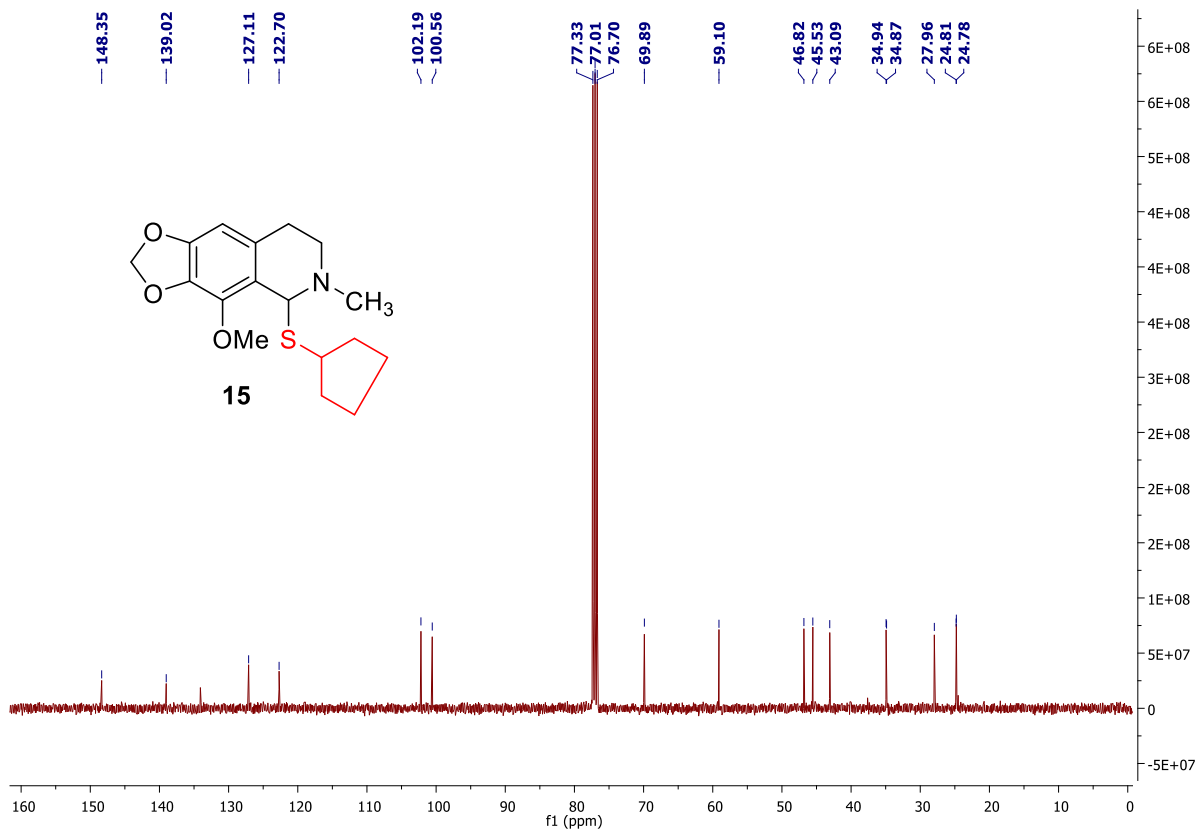


¹H NMR of Compound (15)

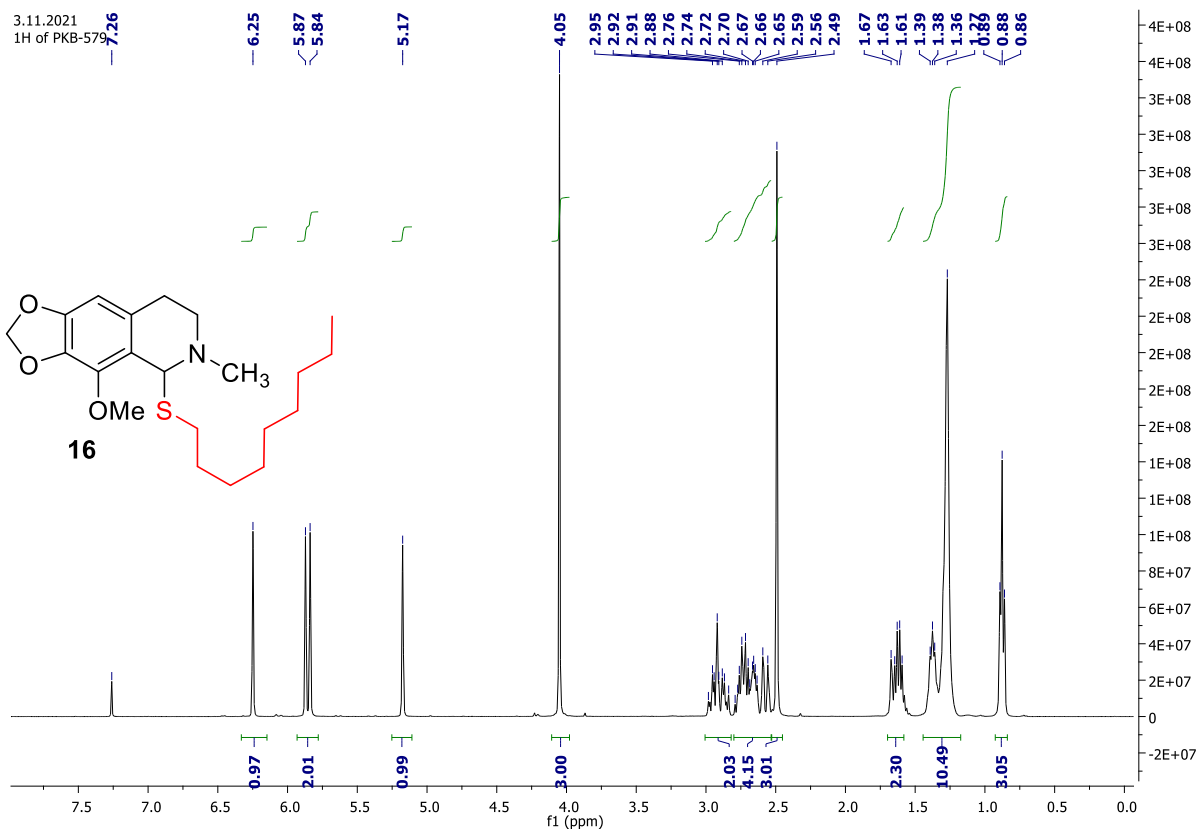
28.1.2022
1H of PKB-602



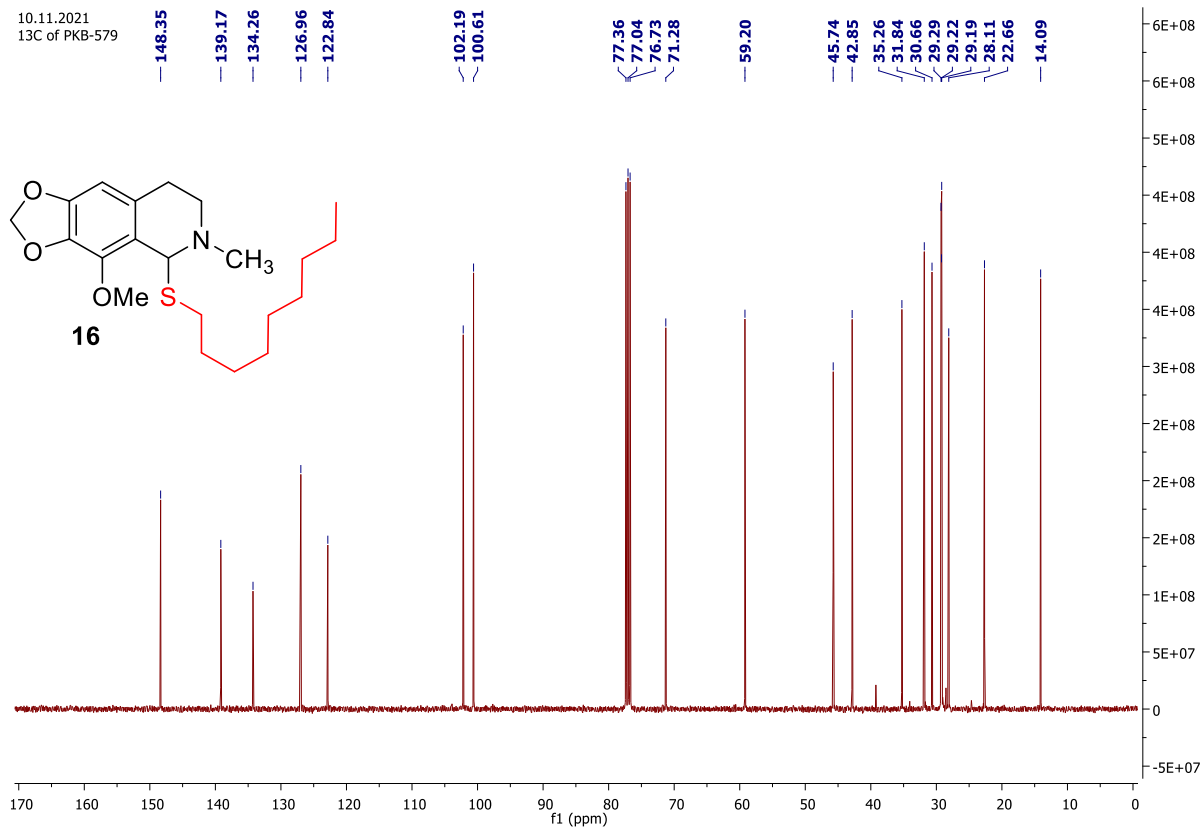
¹³C NMR of Compound (15)



¹H NMR of Compound (16)

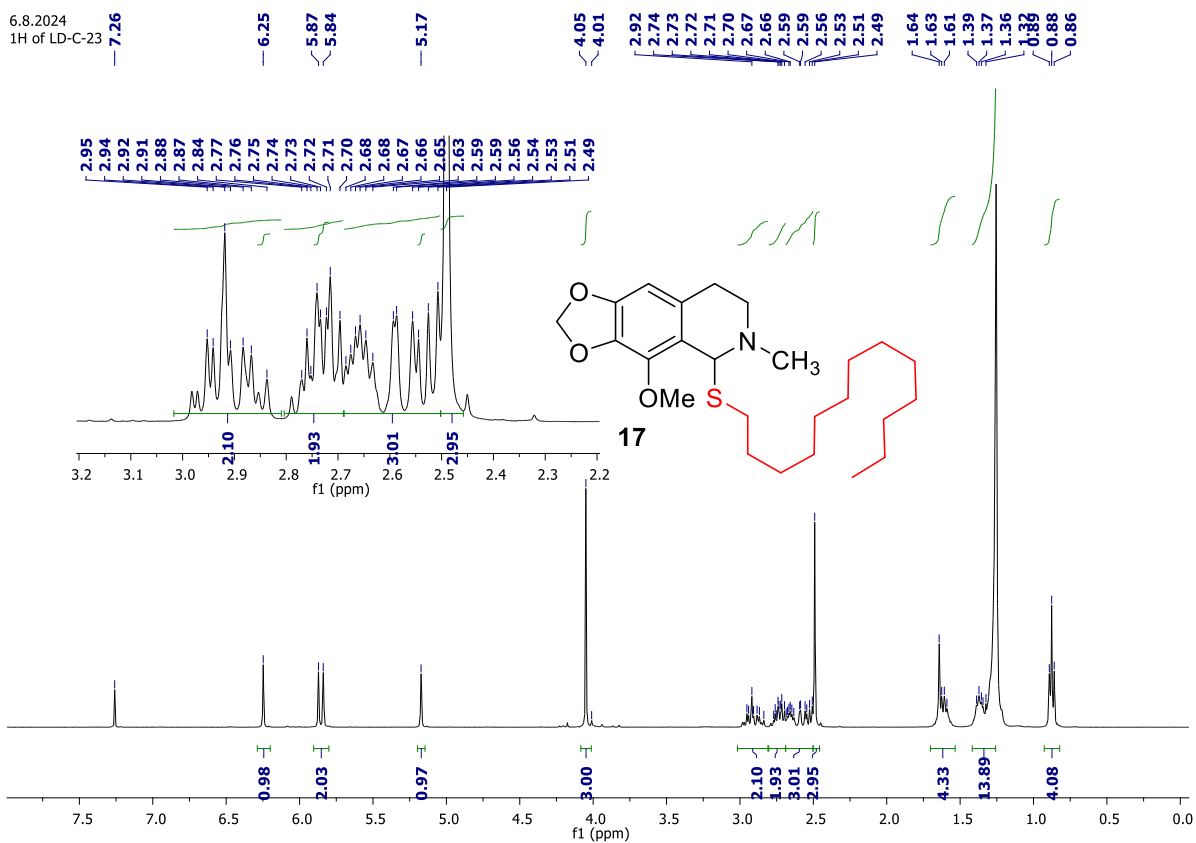


¹³C NMR of Compound (16)



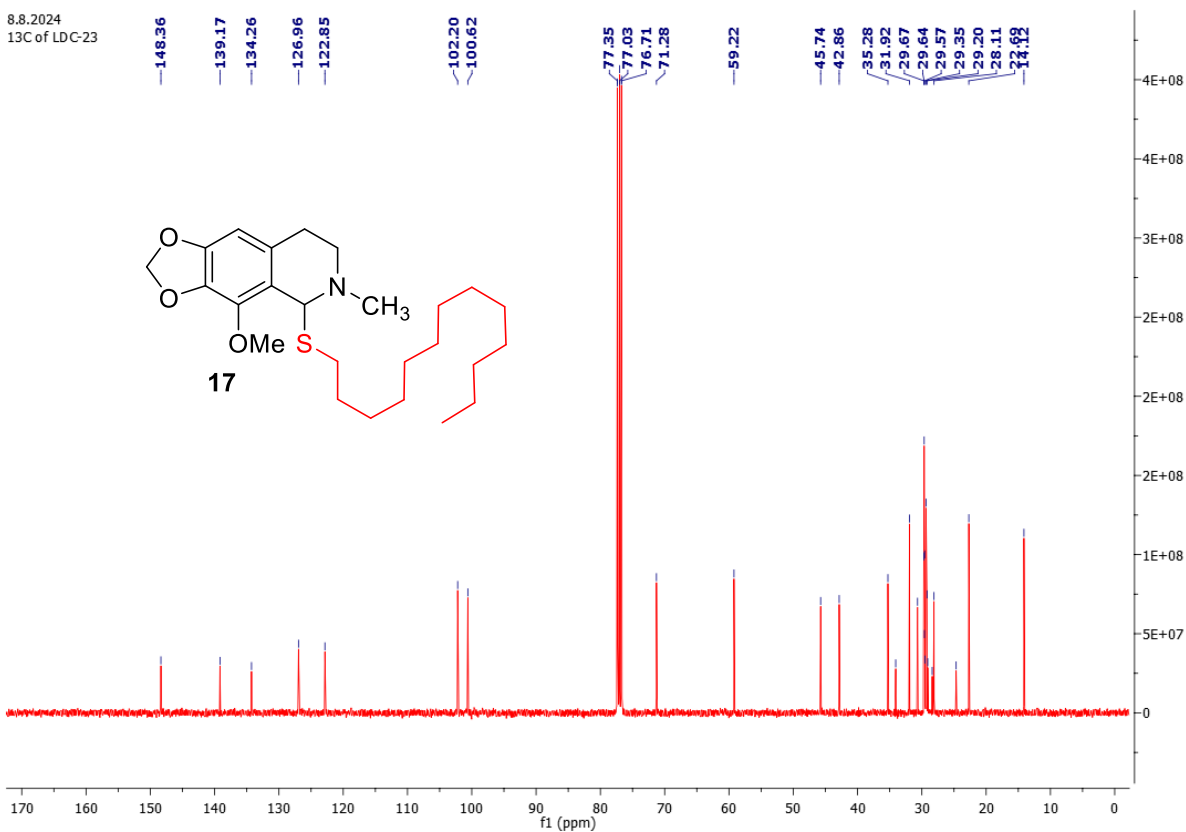
¹H NMR of Compound (17)

6.8.2024
1H of LD-C-23



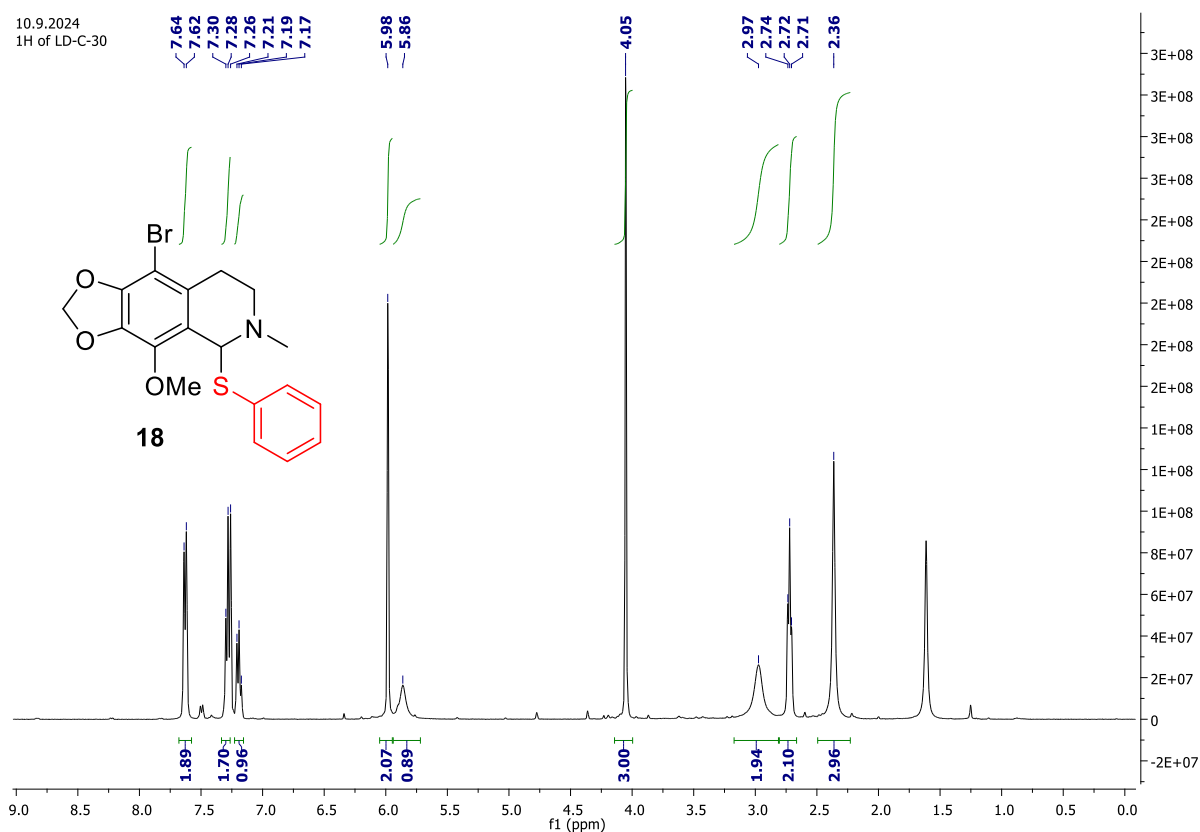
¹³C NMR of Compound (17)

8.8.2024
13C of LDC-23



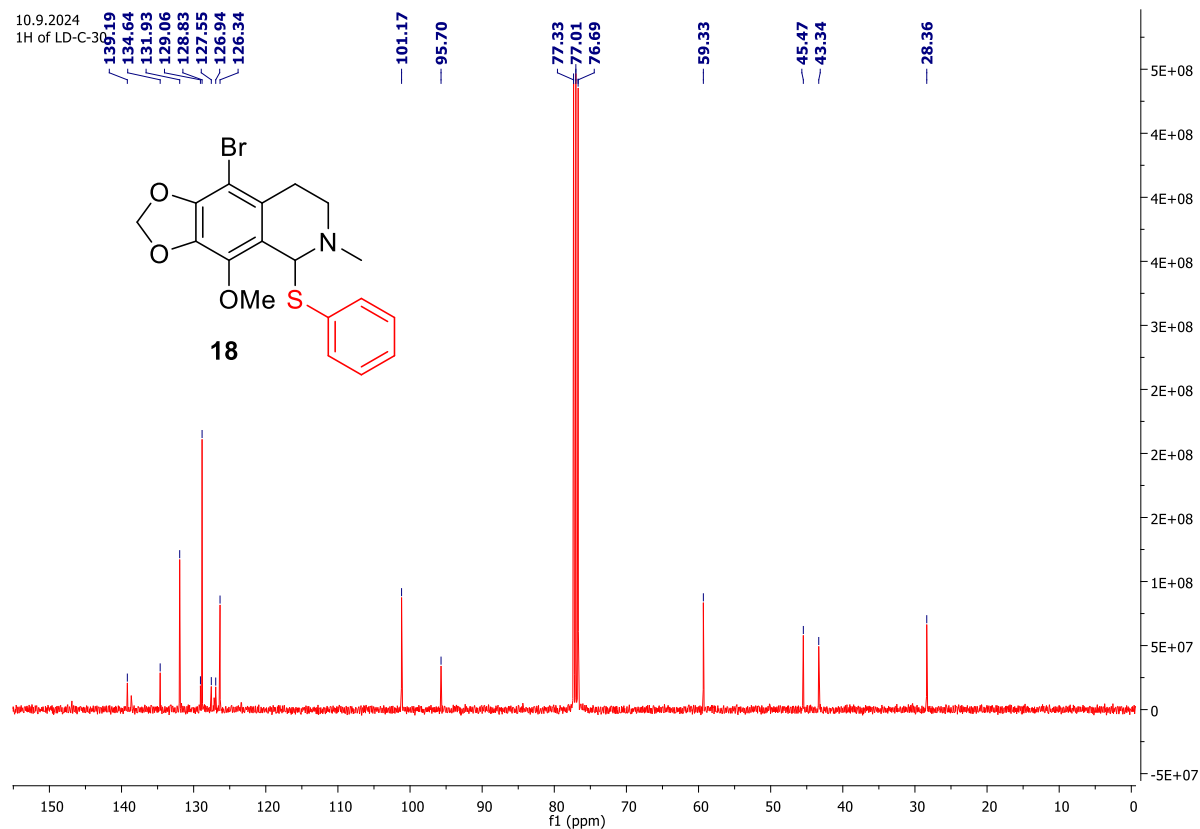
¹H NMR of Compound (18)

10.9.2024
1H of LD-C-30

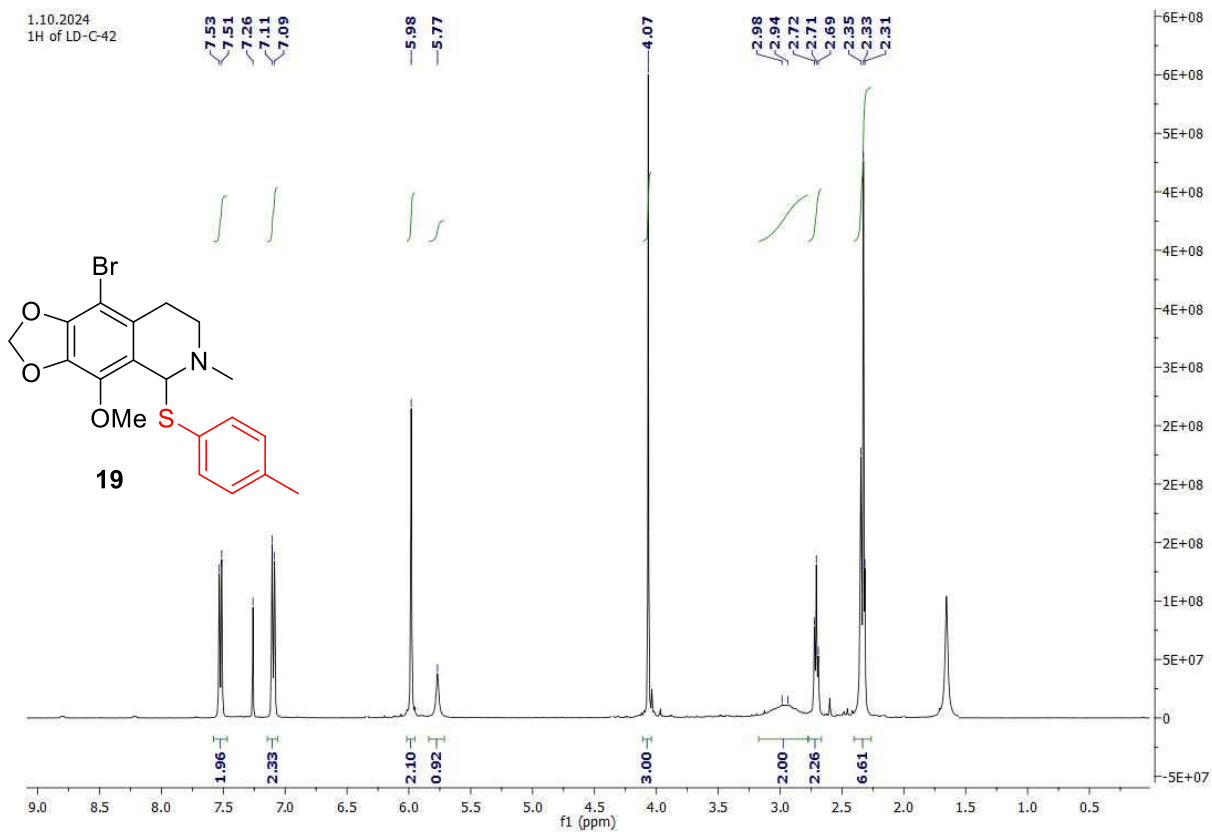


¹³C NMR of Compound (18)

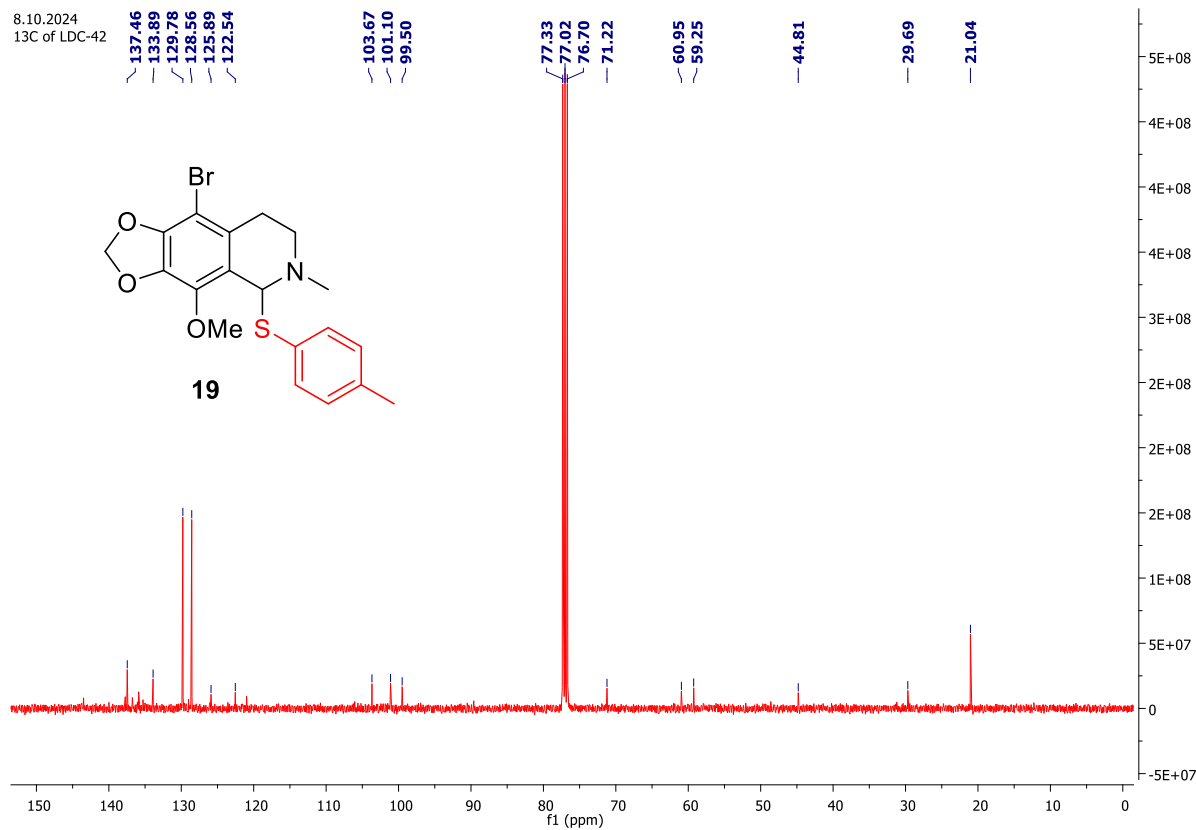
10.9.2024
1H of LD-C-30



¹H NMR of Compound (19)

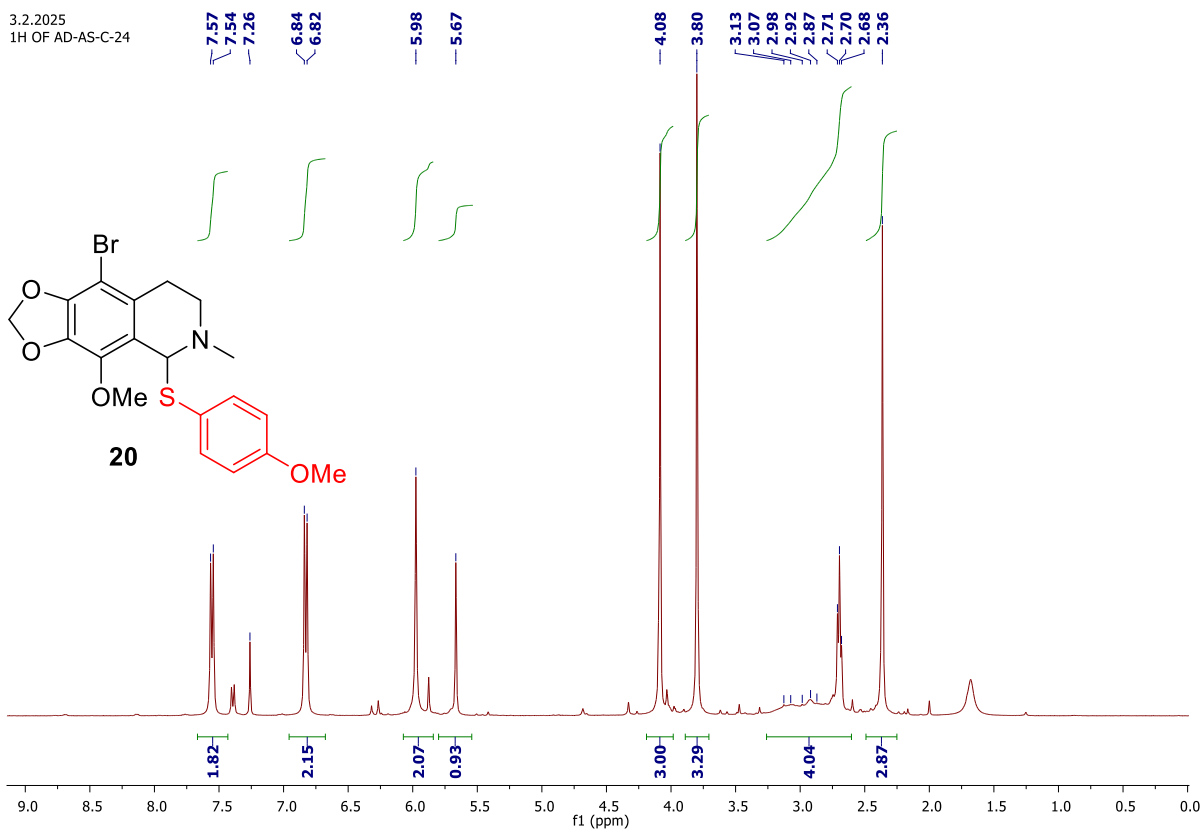


¹³C NMR of Compound (19)



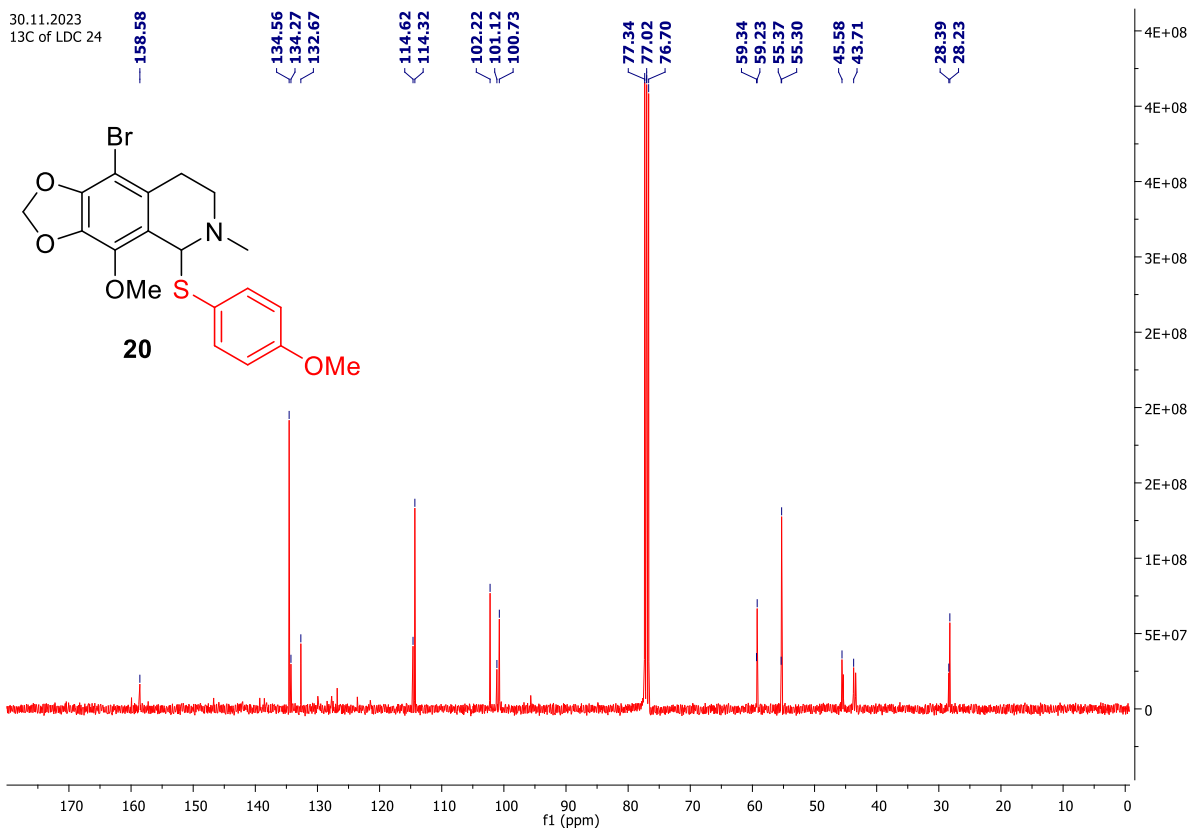
¹H NMR of Compound (20)

3.2.2025
1H OF AD-AS-C-24

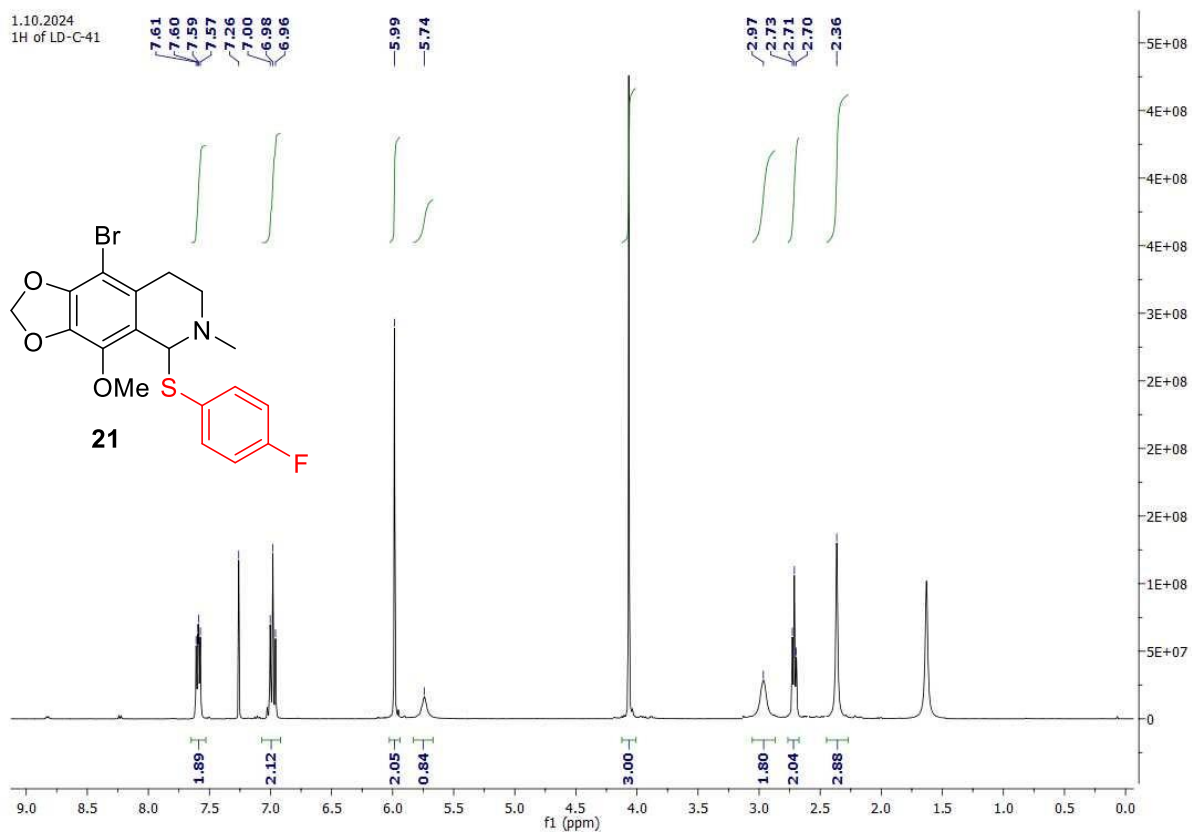


¹³C NMR of Compound (20)

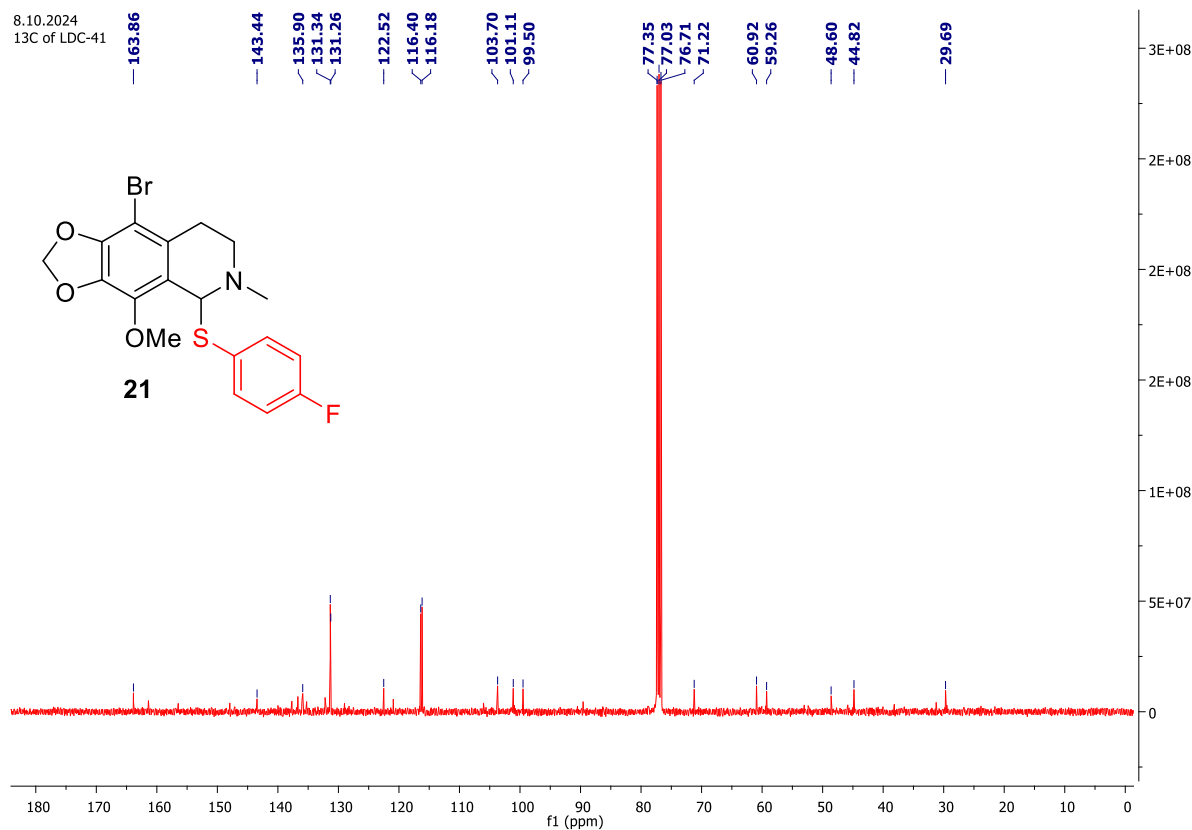
30.11.2023
13C of LDC 24



¹H NMR of Compound (21)

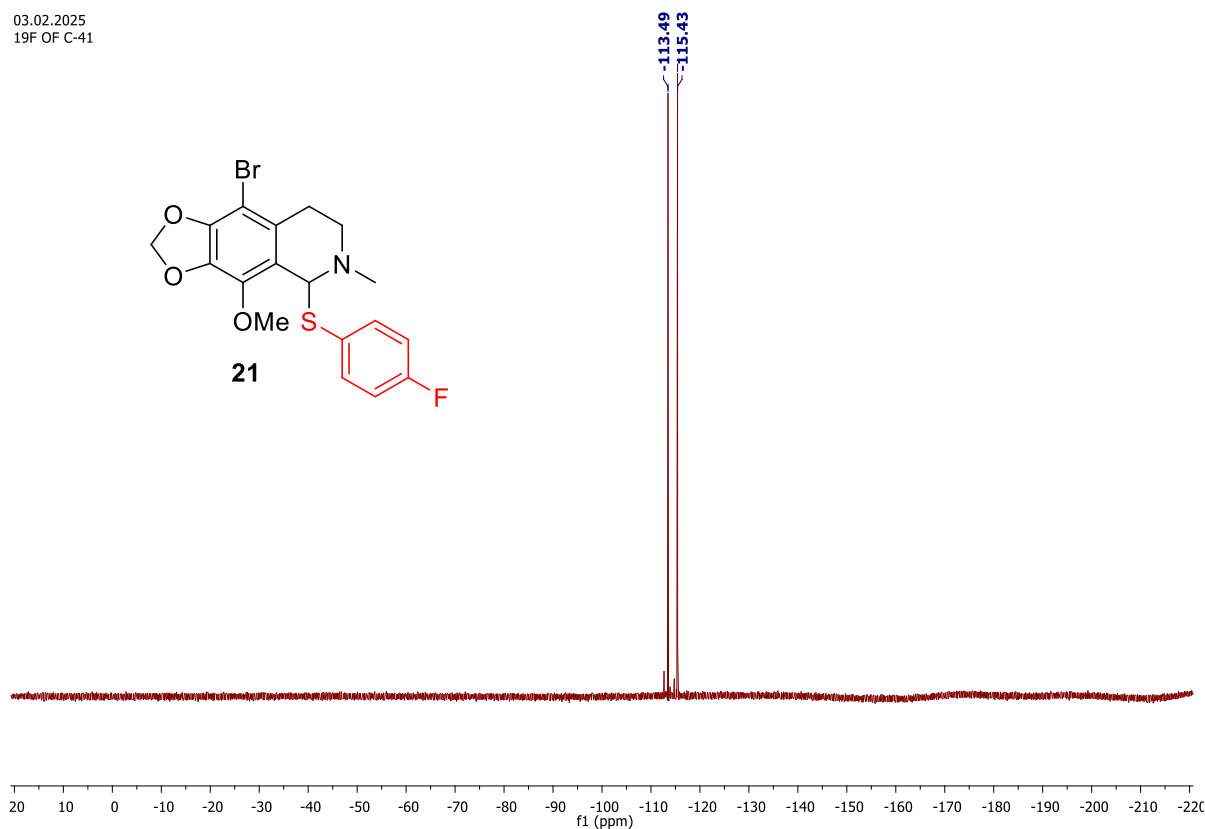


¹³C NMR of Compound (21)



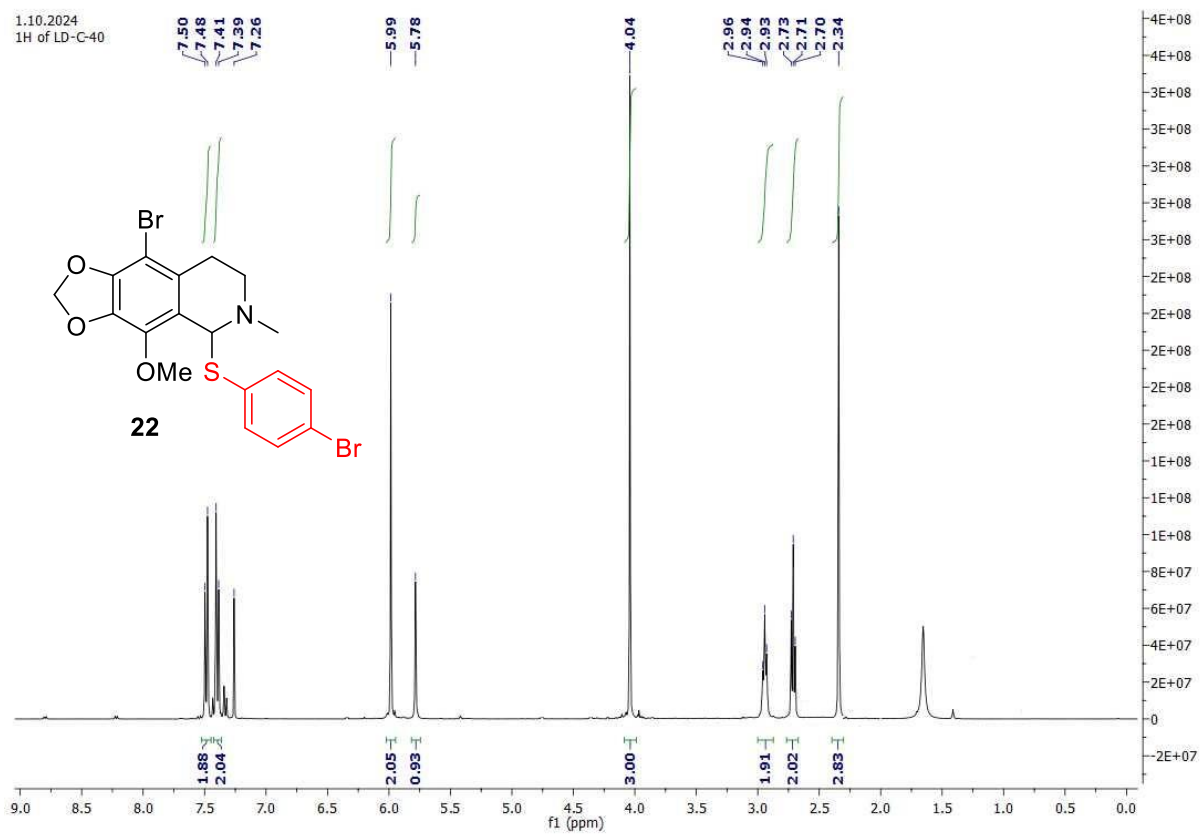
¹⁹F NMR of Compound (21)

03.02.2025
19F OF C-41

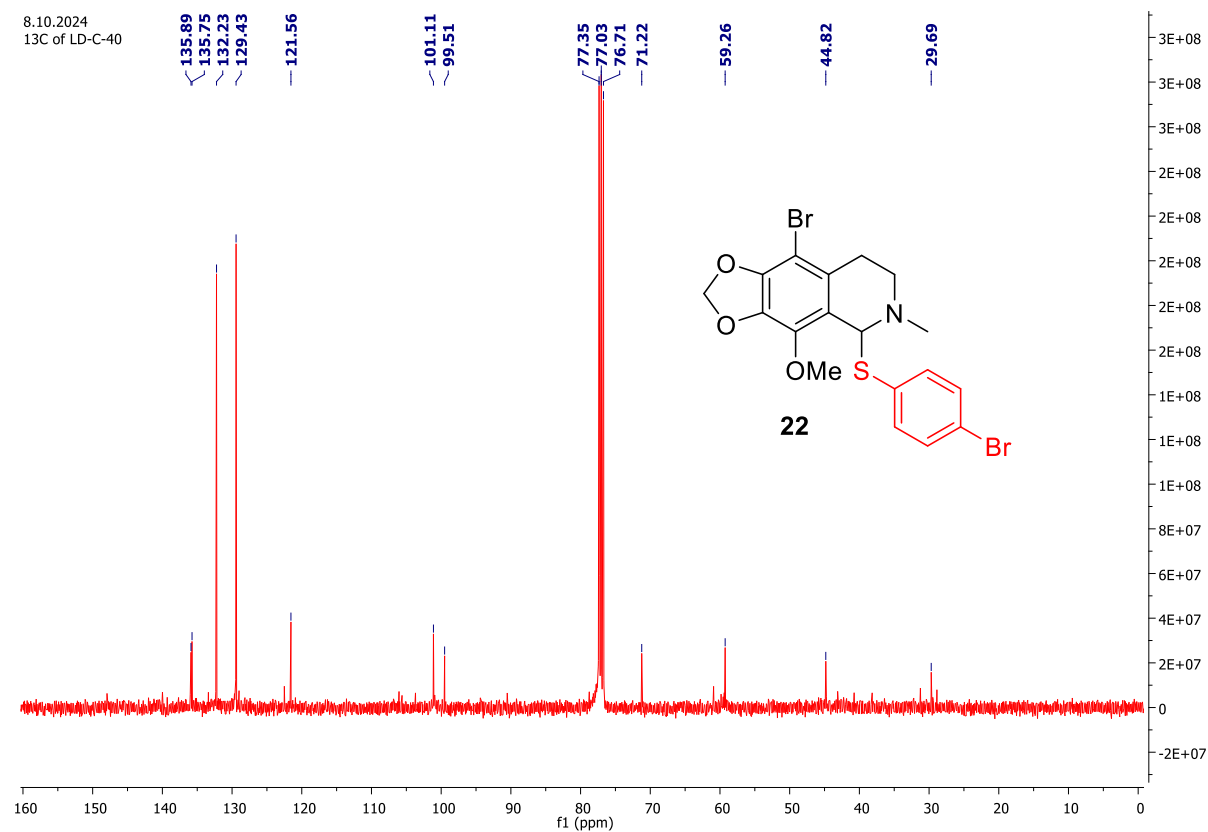


¹H NMR of Compound (22)

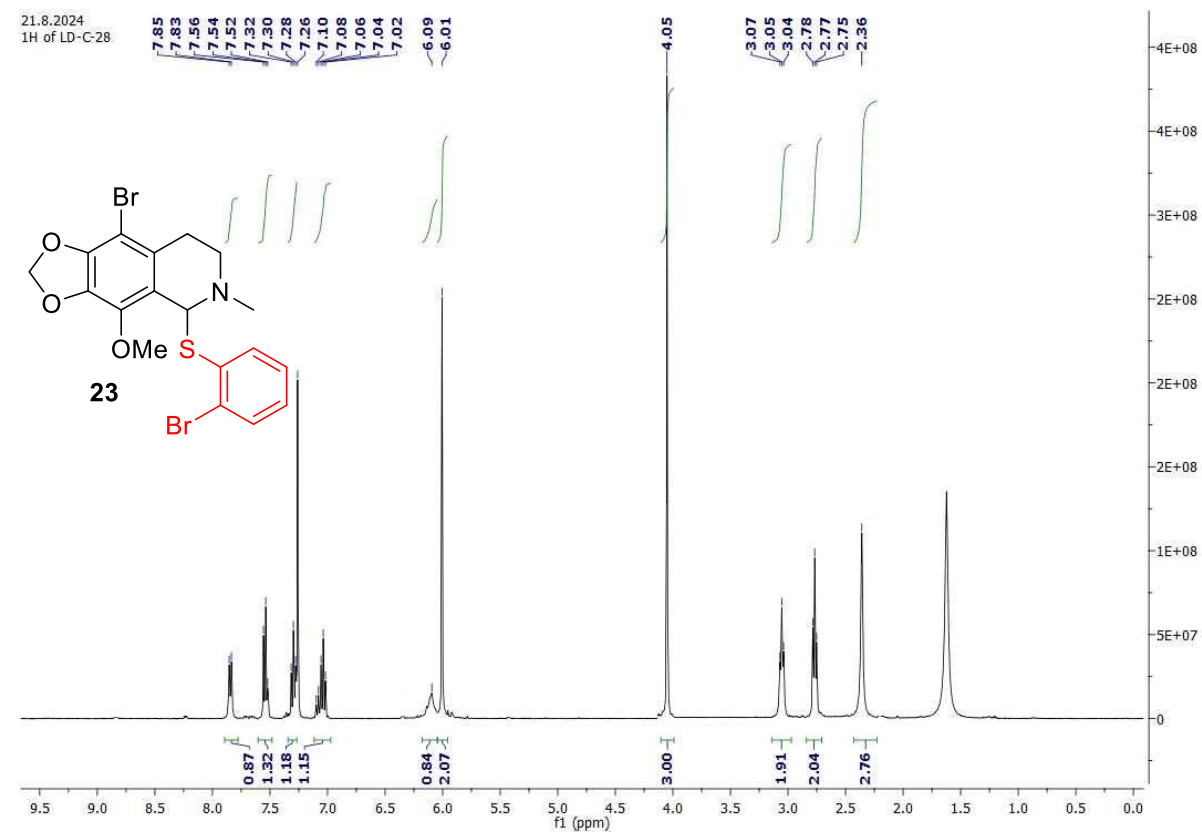
1.10.2024
1H of LD-C-40



¹³C NMR of Compound (22)

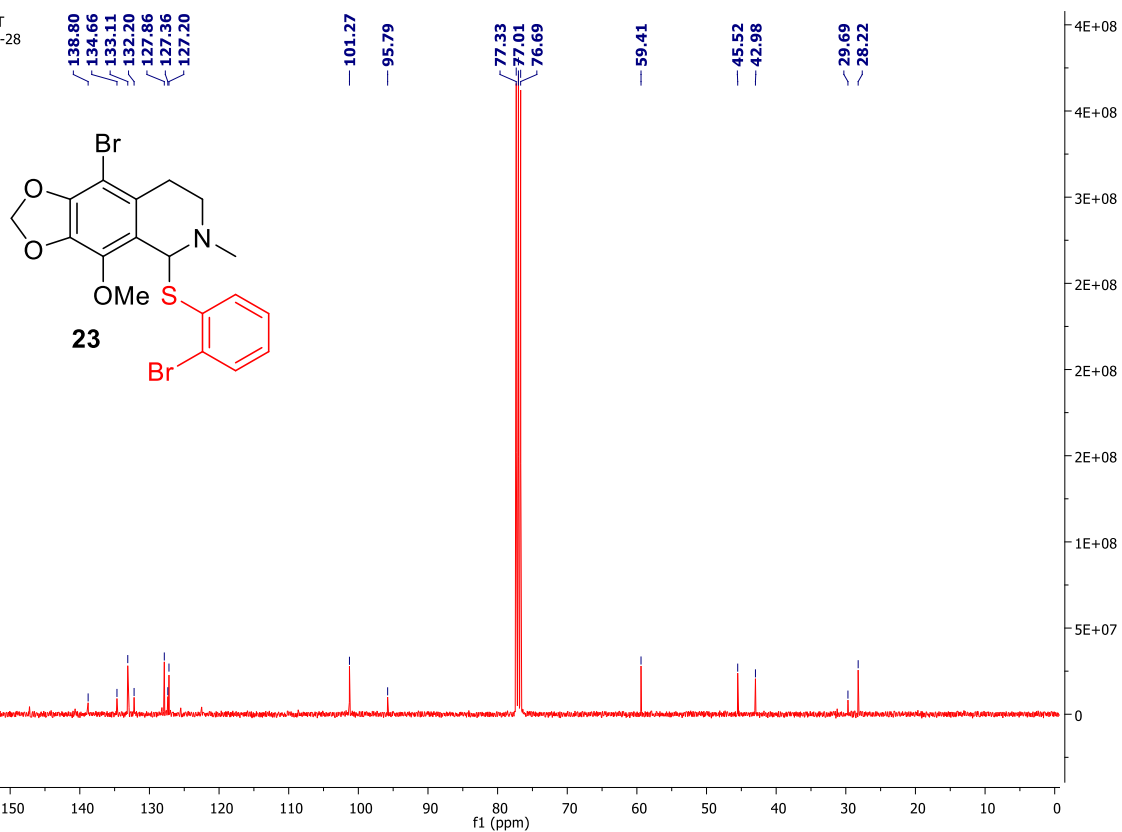


¹H NMR of Compound (23)



¹³C NMR of Compound (23)

12.10.24T
13C OF C-28



6. Crystallographic Data :

Compound 1 : ORTEP Diagram

Light Brown Crystal,

Empirical Formula - $C_{18}H_{19}NO_3S$, M = 329.41

Crystal System – Monoclinic,

Mo Ka ($\lambda = 0.71073 \text{ \AA}$)

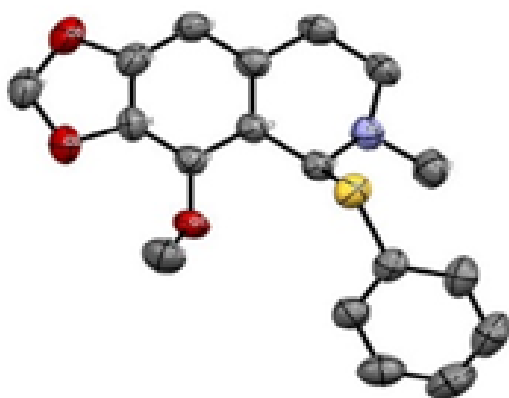
Space group P- 1, a = 10.9365(5) \AA , b = 7.9877(3) \AA c = 19.0534(9) \AA V = 1664.29 (13)

T = 299K. $\theta_{\text{max}} = 27.525$.

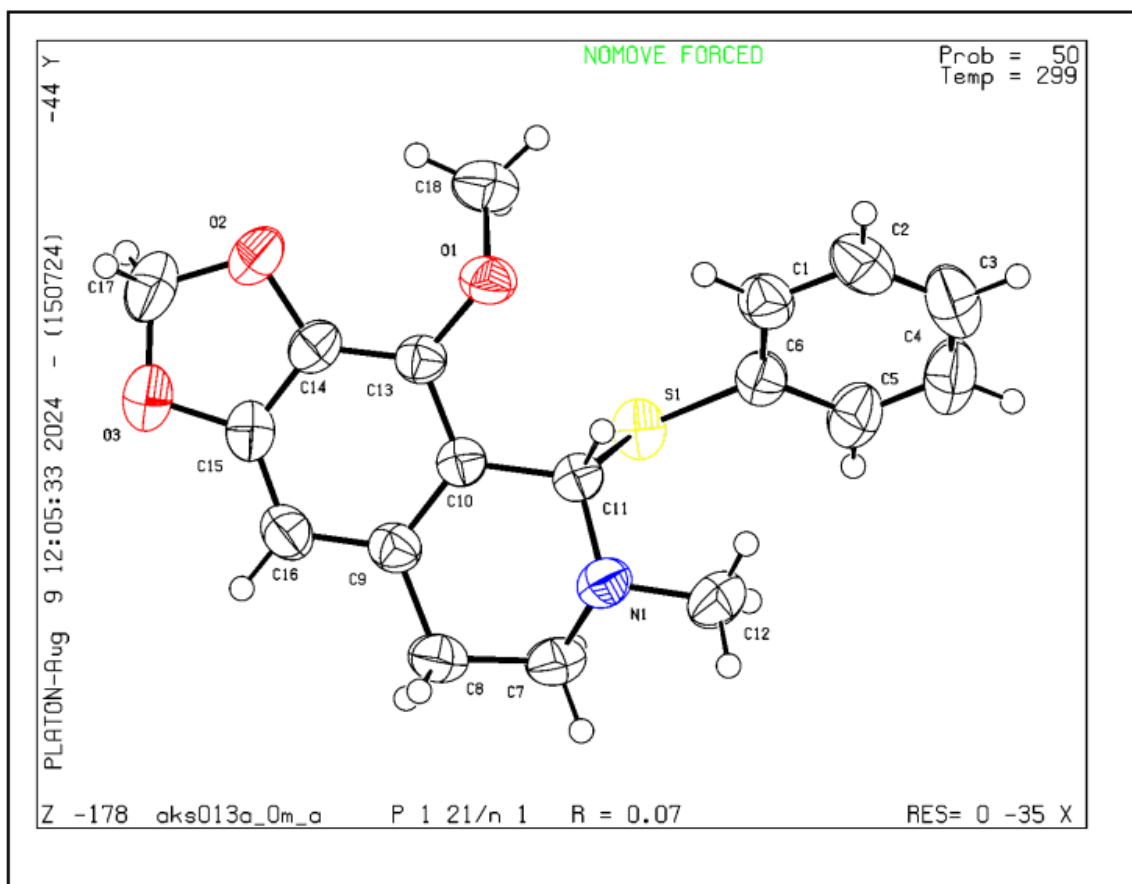
Refinement of 210 parameter on 3154 independent reflection.

$R_1 = 0.0739$ $wR_2 = 0.1827$ and S = 1.251

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 2377839)



Datablock aks013a_0m_a - ellipsoid plot



No syntax errors found.
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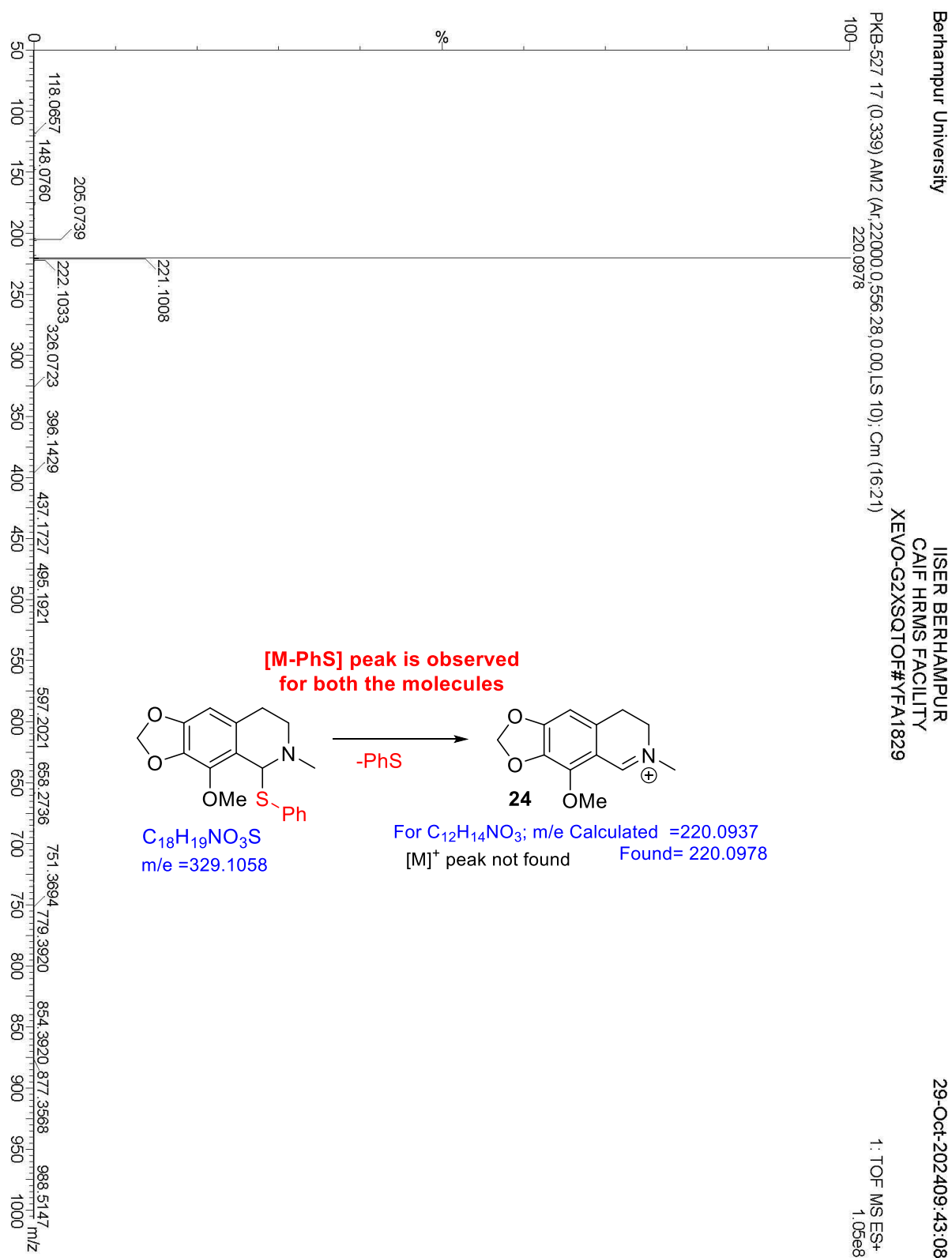
[CIF dictionary](#)
[Interpreting this report](#)

Datablock: aks013a_0m_a

Bond precision:	C-C = 0.0029 Å	Wavelength=0.71073
Cell:	a=10.9365(5) b=7.9877(3) c=19.0534(9)	alpha=90 beta=90.804(2) gamma=90
Temperature:	299 K	
Volume	Calculated 1664.29(13)	Reported 1664.29(13)
Space group	P 21/n	P 1 21/n 1
Hall group	-P 2yn	-P 2yn
Moiety formula	C18 H19 N O3 S	C18 H19 N O3 S
Sum formula	C18 H19 N O3 S	C18 H19 N O3 S
Mr	329.40	329.40
Dx, g cm ⁻³	1.315	1.315
Z	4	4
Mu (mm ⁻¹)	0.209	0.209
F000	696.0	696.0
F000'	696.80	
h,k,lmax	14,10,24	14,10,24
Nref	3842	3838
Tmin,Tmax	0.985,0.992	0.664,0.746
Tmin'	0.983	
Correction method=	# Reported T Limits: Tmin=0.664 Tmax=0.746	
AbsCorr =	NONE	
Data completeness=	0.999	Theta(max)= 27.525
R(reflections)=	0.0739(3154)	wR2(reflections)= 0.1827(3838)
S =	1.251	Npar= 210

7. HRMS Data:

CHNS Analysis (Compound 1): C₁₂H₁₄NO₃⁺; Mass - **220.0978**; Elemental Composition:
C - 65.44; H - 6.41; N - 6.36; O - 21.79.



CHNS Analysis (Compound 17): C₁₂H₁₃BrNO₃⁺ ; Mass - **298.0085**; Elemental Composition: C, 48.18; H, 4.38; Br, 26.71; N, 4.68; O, 16.04

