Expedient, regioselective C–H chalcogenation of 3,4-dihydro-1,4-benzoxazines using palladium-copper catalyst.

Ram Sunil Kumar Lalji[a, b] Monika[a], Mohit Gupta[a, c], Sandeep Kumar[a], Ray J. Butcher and Brajendra Kumar Singh[a*]

a .Bio-Organic Research Laboratory, Department of Chemistry, University of Delhi, Delhi-110007, India.

b .Department of Chemistry, Kirori Mal College, University of Delhi, Delhi-110007, India.

c. Department of Chemistry, L.N.M.S. College, Birpur, Supaul, Bihar-8543340 , India.

d. Inorganic & Structural Chemistry, Howard University Washington DC 20059, USA.

Supporting Information

Content

1. General Information S2

2. Experimental Section

2.1 General procedure for the synthesis of compounds **3a**-**3q**. S2

2.2 General procedure for the synthesis of compounds **5a**-**5h.** S3

2.3 Gram Scale Symthesis. S3

2.4 Procedure for late-stage modification to afford compound **6.** S4

2.5 Procedure to afford compound **8.** S4

2.6 Procedure to afford compound **9.** S5

2.7 Procedure for deuteration compound 1a for affording compound **1a[D_1].** S5

3. Analytical data S7-S18

4. Copies of ^{1}H NMR and ^{13}C NMR Spectra S19-S47

5. Single Crystal data S48-49

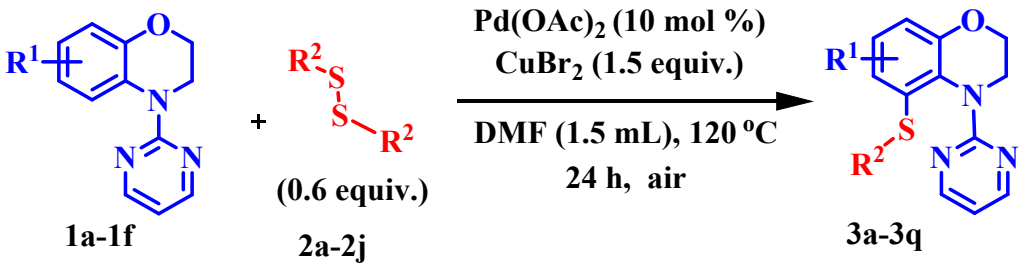
6. References S50

1. General Information

All the experiments were carried out in an oven-dried 50 mL round botton flask under conventional heating. Commercial reagents were purchased from Sigma-Aldrich, Alfa Aeser, Acros, TCI and other commercial suppliers and used as received without further purification. The analytical TLC was performed using 0.20 mm silica gel 60F plates with a 254 nm fluorescent indicator. The TLC plates were visualised by using ultra-violet light. Column chromatography was done using 150-230 mesh silica gel. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on JEOL ECX-400P NMR or Brucker at 400 MHz and 100 MHz respectively using TMS as the internal standard and are reported as chemical shifts (δ) in parts per million (ppm). The spectra were measured in $CDCl_3$ (TMS, ^{1}H δ = 0; $CDCl_3$, ^{1}H δ = 7.26, ^{13}C δ = 77.16) or DMSO-d_6 (TMS, ^{1}H δ = 0; DMSO-d_6, ^{1}H δ = 2.50, ^{13}C δ = 39.52). The coupling constants (*J*) are reported in Hz. The following abbreviations are used for explaining the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS (m/z) were recorded using an Agilent Technology 6530, Accurate mass, Q-TOF LCMS spectrometer. Melting points were recorded on a Buchi M-560 melting point apparatus and are uncorrected. Single crystal was recorded in a Bruker Kappa APEC2 CCD Diffractometer with MoKα radiation. The structures were solved by SHELXT and refined with SHELX. Unless otherwise stated the benzoxazines were prepared following the literature procedure.[1]

2. Experimental Section

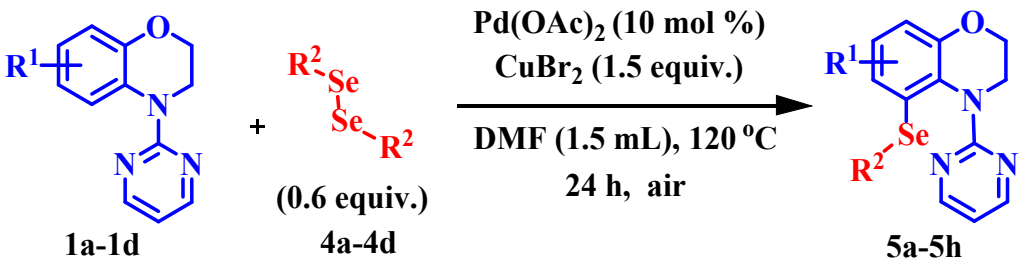
2.1 General procedure for the synthesis of compounds 3a – 3q.



In an oven-dried 50 mL round bottom flask, with a stirring bar was charged with a mixture of 4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **1a** (0.328 mmol), diphenyl disulfides **2a** (0.197 mmol, 0.6 equiv.), $Pd(OAc)_2$ (0.0328 mmol, 10 mol%), $CuBr_2$ (1.5 equiv. 0.492 mmol) and 1.5 mL DMF as solvent in air. The round bottom flask was kept for stirring in an oil bath by heating at 120 °C (oil bath temperature). The progress of the reaction was monitored using TLC. After 24 h, the reaction was stopped, and the reaction mixture was

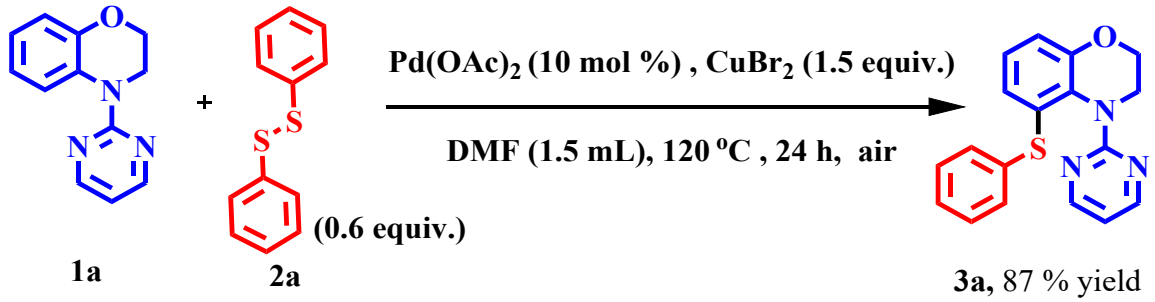
cooled to the ambient temperature. The reaction mixture was extracted with (3 x 10 mL) ethyl acetate . The combined organic layer was dried over anhydrous sodium sulfate and purified by column chromatography (ethyl acetate and *n*-hexane) to afford the targeted products **3a-3q**.

2.2 General procedure for the synthesis of compounds 5a–5h.



In an oven-dried 50 mL round bottom flask, with a stirring bar was charged with a mixture of 4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **1a** (0.328 mmol), diphenyl diselenides **4a** (0.197 mmol, 0.6 equiv.), $Pd(OAc)_2$ (0.0328 mmol, 10 mol%), $CuBr_2$ (1.5 equiv. 0.492 mmol) and 1.5 mL DMF as solvent in air. The round bottom flask was kept for stirring in an oil bath by heating at 120 °C (oil bath temperature). The progress of the reaction was monitored using TLC. After 24 h, the reaction was stopped, and the reaction mixture was cooled to ambient temperature. The reaction mixture was extracted with (3 x 10 mL) ethyl acetate . The combined organic layer was dried over anhydrous sodium sulfate and purified by column chromatography (ethyl acetate and *n*-hexane) to afford the targeted products **5a-5h**.

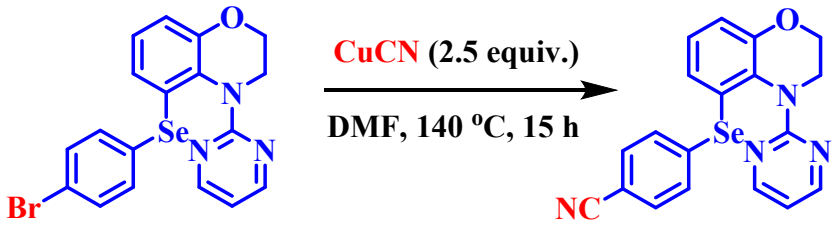
2.3 Gram Scale Synthesis



In an oven-dried 50 mL round bottom flask, with a stirring bar was charged with a mixture of 4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **1a** (1000mg, 4.69 mmol, 1 equiv.), diphenyl disulfides **2a** (614.35 mg, 2.81 mmol, 0.6 equiv.), $Pd(OAc)_2$ (315.87 mg, 0.469 mmol, 10 mol%), $CuBr_2$ (1571 mg, 7.035 mmol) and 15 mL DMF as solvent in air. The round bottom flask was kept for stirring in an oil bath by heating at 120 °C (oil bath temperature). The progress of the reaction was monitored using TLC. After 24 h, the reaction was stopped, and the reaction mixture was cooled to the ambient temperature. The reaction mixture was extracted

with (3 x 30 mL) ethyl acetate . The combined organic layer was dried over anhydrous sodium sulfate and purified by column chromatography (ethyl acetate and *n*-hexane) to afford the targeted products **3a** in 87% yield (1311 mg).

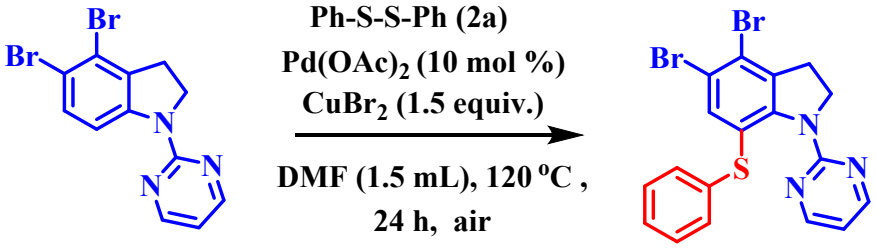
2.4 Procedure for late-stage modification of 5d to afford compound 6[2].



5d **6**, 79% yield

In an oven-dried, 50 mL round bottom flask with a stirring bar was charged with a mixture of 5-((4-bromophenyl)selanyl)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **5d** 0.1006 mmol) and CuCN (2.5 equiv., 0.251 equiv.) in DMF as solvent. The round bottom flask was kept for stirring in an oil bath by heating at 140 °C (oil bath temperature). The progress of the reaction was monitored using TLC. After 15 h, the reaction was stopped, and the reaction mixture was cooled to ambient temperature. The reaction mixture was extracted with (3 x 10 mL) ethyl acetate . The combined organic layer was dried over anhydrous sodium sulfate and purified by column chromatography (10% ethyl acetate and *n*-hexane) to afford the targeted product **6** in 79% yield.

2.5 Procedure to afford compound 8.

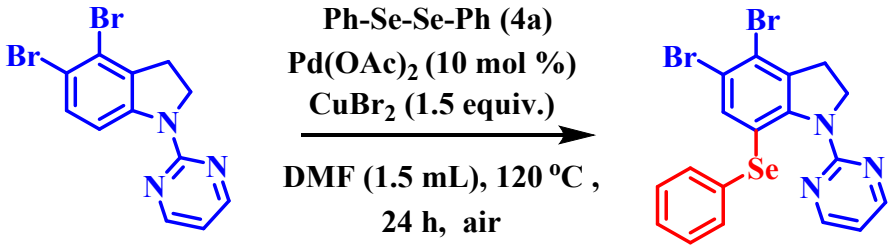


7 **8**, 78% yield

In an oven-dried 50 mL round bottom flask, with a stirring bar was charged with a mixture of 5,6-dibromo-1-(pyrimidin-2-yl)indoline **7** (0.142 mmol), diphenyl disulfides **2a** (0.085 mmol, 0.6 equiv.), $Pd(OAc)_2$ (0.0142 mmol, 10 mol%), $CuBr_2$ (0.213 mmol, 1.5 equiv.) and 1.5 mL DMF as solvent in air. The round bottom flask was kept for stirring in an oil bath by heating at 120 °C (oil bath temperature). The progress of the reaction was monitored using TLC. After

24 h, the reaction was stopped, and the reaction mixture was cooled to ambient temperature. The reaction mixture was extracted with (3 x 10 mL) ethyl acetate . The combined organic layer was dried over anhydrous sodium sulfate and purified by column chromatography (10% ethyl acetate and *n*-hexane) to afford the targeted product **8** in 78% product yield.

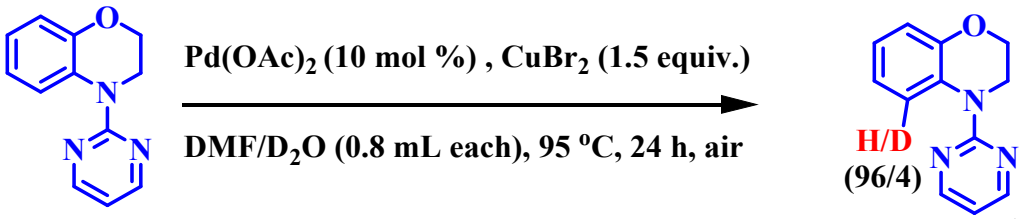
2.6 Procedure to afford compound 9.



7 **9**, 88% yield

In an oven-dried 50 mL round bottom flask, with a stirring bar was charged with a mixture of 5,6-dibromo-1-(pyrimidin-2-yl)indoline **7** (0.142 mmol), diphenyl diselenide **4a** (0.085 mmol, 0.6 equiv.), $Pd(OAc)_2$ (0.0142 mmol, 10 mol%), $CuBr_2$ (0.213 mmol, 1.5 equiv.) and 1.5 mL DMF as solvent in air. The round bottom flask was kept for stirring in an oil bath by heating at 120 °C (oil bath temperature). The progress of the reaction was monitored using TLC. After 24 h, the reaction was stopped, and the reaction mixture was cooled to ambient temperature. The reaction mixture was extracted with (3 x 10 mL) ethyl acetate . The combined organic layer was dried over anhydrous sodium sulfate and purified by column chromatography (10% ethyl acetate and *n*-hexane) to afford the targeted product **9** in 88% product yield.

2.7 Procedure for deuteration of compound 1a for affording compound 1a[D_1][3].



1a **1a** 86 % recovered

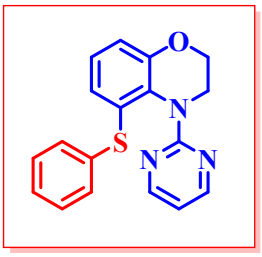
1a[D_1] 4% Deuterated

In an oven-dried, 50 mL round bottom flask with a stirring bar was charged with a mixture of 4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **1a** (0.328 mmol), $Pd(OAc)_2$ (0.0328 mmol, 10 mol%), $CuBr_2$ (1.5 equiv. 0.492 mmol) , 0.8 mL each of DMF and D_2O as solvents in air. The round bottom flask was kept for stirring in an oil bath by heating at 95 °C (oil bath temperature). The progress of the reaction was monitored using TLC. After 24 h, the reaction

was stopped, and the reaction mixture was cooled to the ambient temperature. The reaction mixture was extracted with (3 x 10 mL) ethyl acetate . The combined organic layer was dried over anhydrous sodium sulfate and purified by column chromatography (10% ethyl acetate and *n*-hexane). However, the 86% of the compound **1a** was recovered with 4% deuteration.

3. Analytical data

3.1 5-(phenylthio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine. (1a)



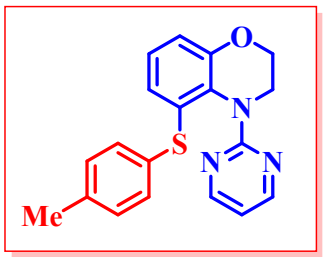
Colour and physical state: Pale yellow solid

Yield: 96%

Melting point: 103-105 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 4.8 Hz, 2H), 7.24-7.20 (m, 4H), 7.19-7.15 (m, 1H), 7.01 (t, *J* = 7.9 Hz, 1H), 6.94 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.73 (t, *J* = 4.8 Hz, 1H), 4.35-4.25 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.16, 157.92, 148.77, 138.03, 134.31, 130.85, 128.96, 128.42, 126.59, 126.21, 125.42, 116.33, 113.17, 66.33, 43.72. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{15}N_3OS$ $[M+H]^+$: 322.1009; found: 322.1019.

3.2 4-(pyrimidin-2-yl)-5-(p-tolylthio)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3b)



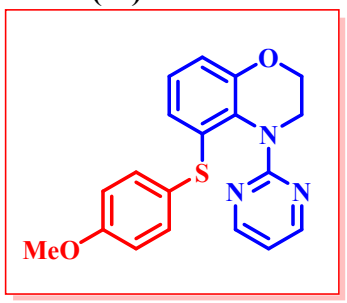
Colour and physical state: Pale yellow solid

Yield: 90%

Melting point: 88-90 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 4.7 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.97 (t, *J* = 8.0 Hz, 0H), 6.85 – 6.80 (m, 1H), 6.74 (t, *J* = 4.8 Hz, 1H), 4.39-4.20 (m, 4H), 2.30 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.15, 157.98, 148.63, 137.04, 135.53, 133.73, 132.01, 129.85, 127.78, 126.15, 124.35, 115.71, 113.15, 66.34, 43.79, 21.23. **HRMS** (ESI+) m/z: calculated for $C_{19}H_{17}N_3OS$ $[M+H]^+$: 336.1165; found: 336.1154.

3.3 5-((4-methoxyphenyl)thio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine (3c)



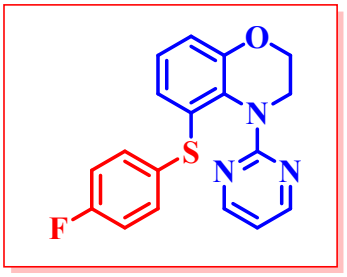
Colour and physical state: Yellow solid

Yield: 82%

Melting point: 118-120 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 4.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.84 – 6.69 (m, 5H), 4.31 (m, 4H), 3.79 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.61, 159.08, 158.08, 148.21, 136.21, 134.40, 134.37, 127.28, 126.22, 125.62, 122.63, 114.98, 114.79, 113.46, 65.79, 55.23, 43.42. **HRMS** (ESI+) m/z: calculated for $C_{19}H_{17}N_3O_2S$ $[M+H]^+$: 352.1114; found: 352.1116.

3.4 5-((4-fluorophenyl)thio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3d)

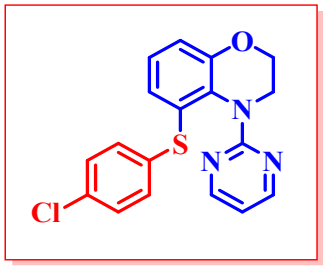


Colour and physical state: Pale yellow semi-solid

Yield: 73%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 4.9 Hz, 2H), 7.28-7.23 (m, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.96-6.91 (m, 2H), 6.86-6.82 (m, 2H), 6.75 (t, *J* = 4.8 Hz, 1H), 4.37-4.21 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 162.51, 160.61, 160.07, 158.05, 148.40, 134.20, 133.05, 132.96, 129.53, 128.31, 127.20, 125.94, 124.40, 116.39, 116.17, 115.95, 113.55, 65.84, 43.22. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}FN_3OS$ $[M+H]^+$: 340.0914; found: 340.0916.

3.5 5-((4-chlorophenyl)thio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3e)



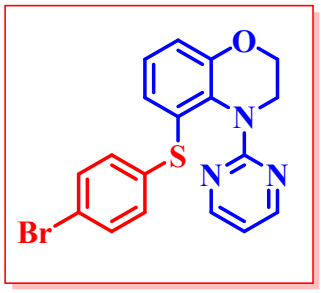
Colour and physical state: White solid

Yield: 72%

Melting point: 113-115 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, *J* = 4.8 Hz, 2H), 7.16 (q, *J* = 8.7 Hz, 4H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.90 (Hz, 2H), 6.74 (t, *J* = 4.8 Hz, 1H), 4.31 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.61, 158.05, 148.52, 137.02, 132.73, 131.21, 131.06, 129.10, 128.94, 126.12, 125.44, 116.66, 113.63, 65.86, 43.16. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}ClN_3OS$ $[M+H]^+$: 356.0619; found: 356.0623.

3.6 5-((4-bromophenyl)thio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3f)



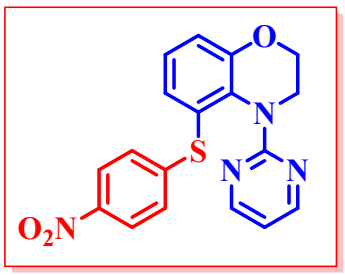
Colour and physical state: White solid

Yield: 70%

Melting point: 162-164 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 4.7 Hz, 2H), 7.56-7.54 (m, 1H), 7.34-7.30 (m, 1H), 7.27-7.19 (m, 2H), 7.08-7.00 (m, 2H), 6.95-6.87 (m, 1H), 6.83-6.72 (m, 1H), 4.41-4.19 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.13, 157.95, 148.85, 137.65, 133.54, 132.01, 128.63, 126.37, 125.66, 120.36, 116.82, 113.30, 66.32, 43.66. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}BrN_3OS$ $[M+H]^+$: 400.0114; found: 400.0121.

3.7 5-((4-nitrophenyl)thio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3g)



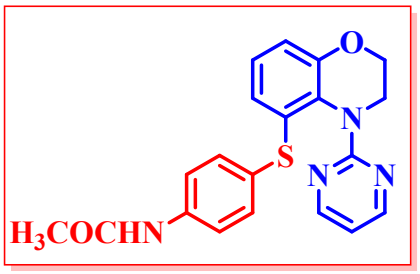
Colour and physical state: Yellow solid

Yield: 89%

Melting point: 104-106 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 4.8 Hz, 2H), 8.04 – 7.97 (m, 2H), 7.17-7.08 (m, 4H), 7.04 (dd, *J* = 7.5, 2.2 Hz, 1H), 6.74 (t, *J* = 4.8 Hz, 1H), 4.36-4.22 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.02, 157.88, 149.94, 149.28, 145.19, 130.01, 129.68, 127.77, 127.14, 126.79, 123.94, 118.80, 113.57, 66.30, 43.48. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}N_4O_3S$ $[M+H]^+$: 367.0859; found: 367.0881.

3.8 N-(4-((4-(primidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-5-yl)thio)phenyl) acetamide (3h)



Colour and physical state: Yellow solid

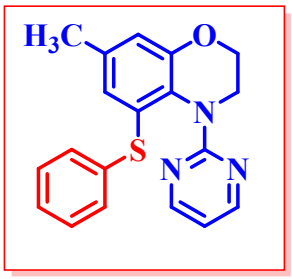
Yield: 73%

Melting point: 87-89 °C

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.51 (d, *J* = 4.8 Hz, 2H), 7.53-7.48 (m, 2H), 7.20-7.14 (m, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 4.8 Hz, 1H), 6.80 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.67 (dd, *J* = 7.8, 1.4 Hz, 1H), 4.33-4.11 (m, 4H), 2.02 (s, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 168.77, 160.78, 158.21, 148.45, 138.77, 135.30, 132.57,

129.87, 127.93, 125.91, 123.65, 119.94, 115.46, 113.66, 65.96, 43.52, 24.10. **HRMS** (ESI+) m/z: calculated for $C_{20}H_{18}N_4O_2S$ $[M+H]^+$: 379.1223; found: 379.1248.

3.9 7-methyl-5-(phenylthio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3i)



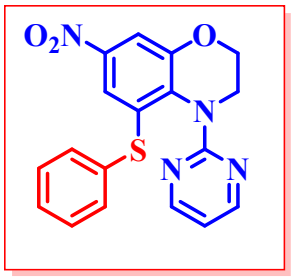
Colour and physical state: Yellow solid

Yield: 88%

Melting point: 128-130 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, *J* = 4.8 Hz, 2H), 7.22 – 7.18 (m, 4H), 7.17 – 7.12 (m, 1H), 6.79 (d, *J* = 1.9 Hz, 1H), 6.73 – 6.67 (m, 2H), 4.34 – 4.23 (m, 4H), 2.20 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.30, 157.92, 148.41, 138.26, 136.35, 133.37, 130.47, 128.94, 126.38, 125.98, 117.11, 113.01, 66.25, 43.83, 21.17. **HRMS** (ESI+) m/z: calculated for $C_{19}H_{17}N_3OS$ $[M+H]^+$: 336.1165; found: 336.1173.

3.10 7-nitro-5-(phenylthio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3j)



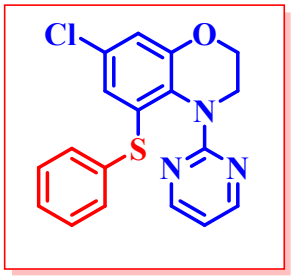
Colour and physical state: Yellow solid

Yield: 86%

Melting point: 124-126 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 (d, *J* = 4.7 Hz, 2H), 7.72-7.66 (m, 2H), 7.36-7.22 (m, 5H), 6.84 (t, *J* = 4.8 Hz, 1H), 4.38-4.29 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.52, 158.16, 148.50, 145.08, 137.03, 135.35, 133.42, 132.44, 129.55, 128.19, 118.99, 114.31, 111.07, 66.37, 43.64. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}N_4O_3S$ $[M+H]^+$: 367.0859; found: 367.0859.

3.11 7-chloro-5-(phenylthio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine (3k)



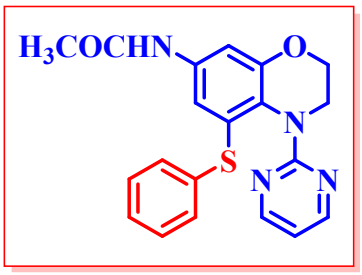
Colour and physical state: Yellow solid

Yield: 91%

Melting point: 122-124 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 4.8 Hz, 2H), 7.29-7.26 (m, 4H), 7.25-7.21 (m, 1H), 6.87-6.80 (m, 2H), 6.76 (t, *J* = 4.8 Hz, 1H), 4.39-4.17 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.97, 158.04, 149.08, 136.54, 136.35, 131.88, 131.10, 129.28, 127.47, 126.60, 123.97, 116.13, 113.45, 66.38, 43.60. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}ClN_3OS$ $[M+H]^+$: 356.0619; found: 356.0647.

3.12 N-(5-(phenylthio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl) acetamide (3l)



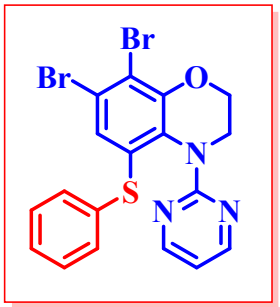
Colour and physical state: Pale yellow solid

Yield: 72%

Melting point: 251-253 °C

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 9.20 (s, 1H), 8.85-8.74 (m, 1H), 8.31 (s, 1H), 7.68-7.55 (m, 2H), 7.44-7.33 (m, 3H), 7.29 (s, 1H), 7.05 (t, 1H), 4.42-4.27 (m, 4H), 2.00 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 168.20, 159.58, 157.89, 148.53, 136.87, 136.16, 131.78, 129.29, 129.13, 126.54, 125.96, 123.52, 112.85, 109.40, 66.23, 42.01, 24.90. **HRMS** (ESI+) m/z: calculated for $C_{20}H_{18}N_4O_2S$ $[M+H]^+$: 379.1223; found: 379.1223.

3.13 7,8-dibromo-5-(phenylthio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine (3m)



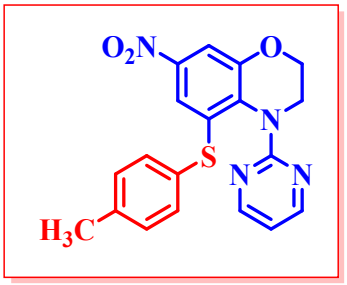
Colour and physical state: White solid

Yield: 79%

Melting point: 163-165 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (s, 2H), 7.28-7.24 (m, 5H), 6.98 (dd, *J* = 17.1, 2.2 Hz, 2H), 4.36-4.18 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 159.11, 158.33, 149.31, 136.56, 136.08, 131.70, 129.36, 127.56, 126.90, 126.80, 119.15, 118.99, 110.21, 66.38, 43.82. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{13}Br_2N_3OS$ $[M+H]^+$: 477.9212; found: 477.9241.

3.14 7-nitro-4-(pyrimidin-2-yl)-5-(p-tolylthio)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3n)



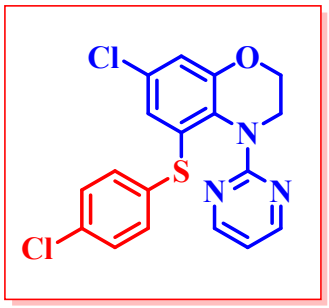
Colour and physical state: Yellow solid

Yield: 78%

Melting point: 149-151 °C

^{1}H NMR ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 4.8 Hz, 2H), 7.60 – 7.50 (m, 2H), 7.21 – 7.14 (m, 2H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.78 (t, *J* = 4.8 Hz, 1H), 4.31 (m, 4H), 2.26 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.52, 158.20, 148.39, 145.09, 138.76, 138.14, 133.37, 132.78, 131.08, 130.45, 118.06, 114.26, 110.57, 66.36, 43.72, 21.33. **HRMS** (ESI+) m/z: calculated for $C_{19}H_{16}N_4O_3S$ $[M+H]^+$: 381.1016; found: 381.1037.

3.15 7-chloro-5-((4-chlorophenyl)thio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3o)



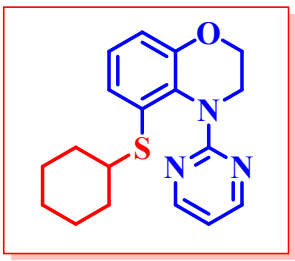
Colour and physical state: White solid

Yield: 80%

Melting point: 108-110 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 4.8 Hz, 2H), 7.25-7.21 (m, 2H), 7.21-7.18 (m, 2H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.77 (t, *J* = 4.8 Hz, 1H), 4.36-4.19 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.93, 158.03, 149.15, 135.92, 135.22, 133.43, 132.88, 131.18, 129.42, 126.79, 124.11, 116.50, 113.53, 66.35, 43.52. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{13}Cl_2N_3OS$ $[M+H]^+$: 390.0229; found: 390.0228.

3.16 5-(cyclohexylthio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3p)



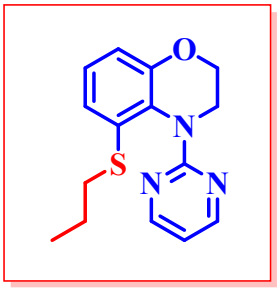
Colour and physical state: Light brown semi-solid

Yield: 61%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 4.8 Hz, 2H), 7.11 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.08-7.03 (m, 1H), 6.86-6.79 (m, 1H), 6.70 (t, *J* = 4.8 Hz, 1H), 4.32-4.22 (m, 4H), 3.06-2.97 (m, 1H), 1.86-1.78 (m, 2H), 1.72-1.65 (m, 2H), 1.35-1.25 (m,

6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.30, 158.18, 157.90, 148.65, 133.91, 125.86, 124.50, 115.75, 112.98, 66.28, 47.79, 43.86, 33.52, 33.30, 29.84, 26.25, 25.92. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{21}N_3OS$ $[M+H]^+$: 328.1478; found: 328.1495.

3.17 5-(propylthio)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (3q)

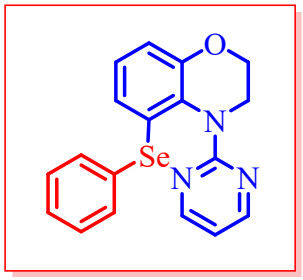


Colour and physical state: Light brown semi-solid

Yield: 57%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 4.7 Hz, 2H), 7.08-7.02 (m, 2H), 6.80 (dd, *J* = 7.6, 2.0 Hz, 1H), 6.72 (t, *J* = 4.8 Hz, 1H), 4.34-4.21 (m, 4H), 2.80 (t, 2H), 1.54-1.50 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.49, 158.12, 149.55, 127.62, 126.62, 124.22, 121.39, 116.23, 113.94, 65.85, 43.93, 35.74, 21.92, 13.13. **HRMS** (ESI+) m/z: calculated for $C_{15}H_{17}N_3OS$ $[M+H]^+$: 288.1165; found: 288.1169.

3.18 5-(phenylselanyl)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (5a)



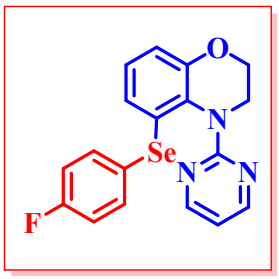
Colour and physical state: Pale yellow solid

Yield: 91%

Melting point: 110-112 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 4.8 Hz, 2H), 7.46-7.38 (m, 2H), 7.25-7.18 (m, 3H), 7.03 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.95 (t, *J* = 7.9 Hz, 1H), 6.86 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.74 (t, *J* = 4.8 Hz, 1H), 4.70-3.93 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.12, 158.03, 148.52, 133.92, 133.48, 131.96, 129.14, 128.64, 127.17, 126.44, 126.41, 116.29, 113.13, 66.33, 43.35. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{15}N_3OSe$ $[M+H]^+$: 370.0453; found: 370.0466.

3.19 5-((4-fluorophenyl)selanyl)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine (5b)



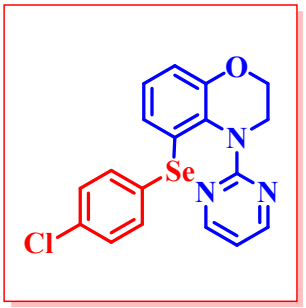
Colour and physical state: White solid

Yield: 86%

Melting point: 98-100 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 4.8 Hz, 2H), 7.42 (dd, *J* = 8.6, 5.6 Hz, 2H), 6.96-6.89 (m, 4H), 6.87-6.81 (m, 1H), 6.75 (t, *J* = 4.8 Hz, 1H), 4.71-3.87 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 163.75, 161.30, 161.10, 158.08, 148.52, 136.09, 136.01, 132.42, 128.36, 128.27, 128.24, 126.45, 125.81, 116.46, 116.24, 116.22, 113.20, 77.48, 76.84, 66.32, 43.34. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}FN_3OSe$ $[M+H]^+$: 388.0351; found: 388.0359.

3.20 5-((4-chlorophenyl)selanyl)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine (5c)



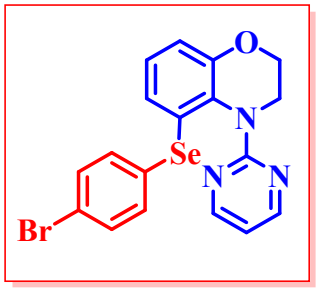
Colour and physical state: White solid

Yield: 94%

Melting point: 134-136 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.36 (d, *J* = 4.7 Hz, 2H), 7.28-7.21 (m, 2H), 7.11-7.08 (m, 2H), 6.93-6.83 (m, 2H), 6.79 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 4.46-4.00 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.05, 158.01, 148.54, 134.65, 133.25, 132.40, 131.61, 129.27, 128.67, 126.52, 126.38, 116.56, 113.21, 66.28, 43.25. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}ClN_3OSe$ $[M+H]^+$: 404.0090; found: 404.0078.

3.21 5-((4-bromophenyl)selanyl)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine (5d)



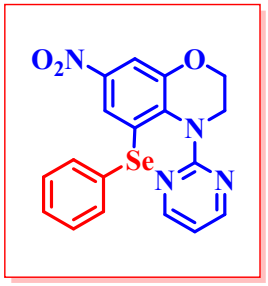
Colour and physical state: White solid

Yield: 91%

Melting point: 200-202 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 4.8 Hz, 2H), 7.37-7.31 (m, 2H), 7.30-7.25 (m, 2H), 7.04-6.94 (m, 2H), 6.89 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.77 (t, *J* = 4.8 Hz, 1H), 4.61-3.99 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.09, 158.05, 148.57, 134.85, 133.22, 132.21, 131.47, 128.75, 126.57, 126.51, 121.33, 116.65, 113.25, 66.32, 43.27. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}BrN_3OSe$ $[M+H]^+$: 447.9558; found: 447.9547.

3.22 7-nitro-5-(phenylselanyl)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine (5e)



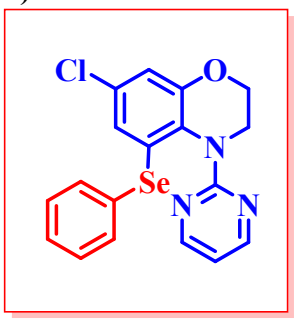
Colour and physical state: Yellow solid

Yield: 84%

Melting point: 136-138 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 (d, *J* = 4.8 Hz, 2H), 7.81 (d, *J* = 2.6 Hz, 1H), 7.68 (d, *J* = 2.6 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.31-7.24 (m, 3H), 6.85 (t, *J* = 4.8 Hz, 1H), 4.42-4.29 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.38, 158.27, 148.18, 144.93, 134.49, 134.03, 133.76, 132.02, 129.65, 128.42, 120.54, 114.25, 111.36, 66.37, 43.16. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}CN_4O_3Se$ $[M+H]^+$: 415.0304; found: 415.0305.

3.23 7-chloro-5-(phenylselanyl)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine (5f)



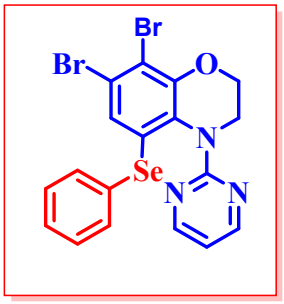
Colour and physical state: White solid

Yield: 89%

Melting point: 150-152 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 4.7 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.26 (t, *J* = 2.6 Hz, 3H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.76 (t, *J* = 4.8 Hz, 1H), 4.51-4.09 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.02, 158.13, 148.88, 134.10, 133.64, 132.76, 131.21, 129.43, 127.83, 127.22, 125.42, 116.32, 113.41, 66.37, 43.27. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{14}ClN_3OSe$ $[M+H]^+$: 404.0063; found: 404.0068.

3.24 7,8-dibromo-5-(phenylselanyl)-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*] [1,4] oxazine (5g)



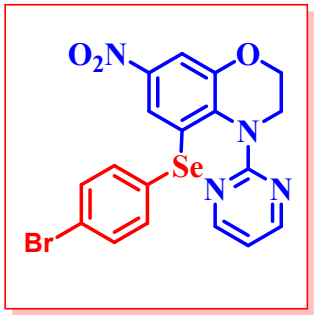
Colour and physical state: White solid

Yield: 71%

Melting point: 170-172 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (s, 2H), 7.45-7.40 (m, 2H), 7.29-7.24 (m, 3H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 2.2 Hz, 1H), 4.62-3.95 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.16, 158.40, 149.10, 133.92, 133.58, 132.42, 129.50, 128.29, 127.92, 127.38, 119.33, 119.18, 110.11, 66.33, 43.55. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{13}Br_2N_3OSe$ $[M+H]^+$: 477.9219; found: 477.9241.

3.25 5-((4-bromophenyl)selanyl)-7-nitro-4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*] [1,4]oxazine (5h)



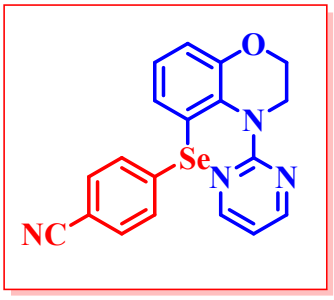
Colour and physical state: Pale yellow solid

Yield: 92%

Melting point: 126-128 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (d, *J* = 4.8 Hz, 2H), 7.82 (d, *J* = 2.6 Hz, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.41-7.36 (m, 2H), 7.33-7.28 (m, 2H), 6.86 (t, *J* = 4.8 Hz, 1H), 4.41-4.30 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.43, 158.28, 148.31, 145.07, 135.78, 134.24, 133.13, 132.78, 131.34, 122.82, 120.78, 114.35, 111.76, 66.40, 43.10. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{13}BrN_4O_3Se$ $[M+H]^+$: 492.9409; found: 492.9412.

3.26 4-((4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-5-yl)selanyl) benzonitrile (compound 6)



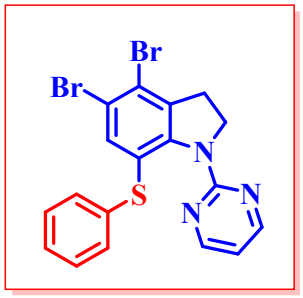
Colour and physical state: White solid

Yield: 79%

Melting point: 134-136 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 4.8 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.16-7.11 (m, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.98 – 6.94 (m, 1H), 6.75 (t, *J* = 4.7 Hz, 1H), 4.45-4.14 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.05, 157.97, 148.86, 143.42, 132.29, 131.15, 129.64, 129.10, 127.95, 126.93, 119.07, 117.94, 113.45, 109.49, 66.31, 43.15. **HRMS** (ESI+) m/z: calculated for $C_{19}H_{14}N_4OSe$ $[M+H]^+$: 395.0406; found: 395.0436.

3.27 4,5-dibromo-7-(phenylthio)-1-(pyrimidin-2-yl)indoline (8)



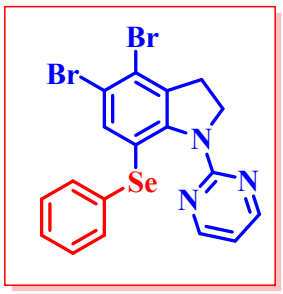
Colour and physical state: Pale yellow solid

Yield: 78%

Melting point: 184-186 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (s, 2H), 7.28-7.27 (m, 1H), 7.26-7.26 (m, 3H), 7.25-7.22 (m, 1H), 7.21-7.15 (m, 2H), 4.41 (t, *J* = 7.9 Hz, 2H), 3.13 (t, *J* = 7.9 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.92, 157.81, 142.70, 136.96, 136.82, 133.39, 131.78, 129.29, 128.44, 127.52, 126.21, 116.93, 109.71, 52.89, 29.60. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{13}Br_2N_3S$ $[M+H]^+$: 461.9270; found: 461.9296.

3.28 4,5-dibromo-7-(phenylselanyl)-1-(pyrimidin-2-yl)indoline (compound 9)



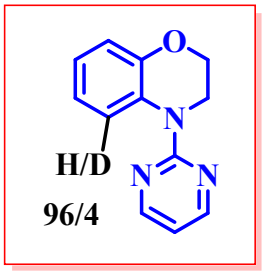
Colour and physical state: White solid

Yield: 88%

Melting point: 139-141 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (s, 2H), 7.47 (dd, *J* = 7.3, 2.2 Hz, 2H), 7.29 – 7.25 (m, 3H), 7.19 (s, 2H), 4.43 (t, *J* = 8.0 Hz, 2H), 3.13 (t, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 158.85, 157.89, 143.11, 136.45, 134.42, 134.24, 133.57, 129.48, 128.05, 126.15, 124.73, 117.05, 109.44, 52.07, 29.42. **HRMS** (ESI+) m/z: calculated for $C_{18}H_{13}Br_2N_3Se$ $[M+H]^+$: 509.8714; found: 509.8719.

3.29 4-(pyrimidin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-5-*d* (compound 1a[D_1] and 1a)



Colour and physical state: White solid

Yield: 86%

Melting point: 135-137 °C

^{1}H NMR (77a[D$_1$]) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 4.7 Hz, 2H), 8.01 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.02-6.97 (m, 1H), 6.95-6.89 (m, 2H), 6.72 (t, *J* = 4.7 Hz, 1H), 4.33 (t, 2H), 4.28 (t, 2H). **^{1}H NMR (77a)** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 4.7 Hz, 2H), 8.01 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.03-6.96 (m, 1H), 6.94-6.89 (m, 2H), 6.72 (t, *J* = 4.7 Hz, 1H), 4.32 (t, 2H), 4.28 (t, 2H).

HRMS (ESI+) m/z **77a[D$_1$]**: calculated for $C_{12}H_{10}DN_3O$ $[M+H]^+$: 214.0975; found: 214.0983.

HRMS (ESI+) m/z **77a**: calculated for $C_{12}H_{11}N_3O$ $[M+H]^+$: 215.1038; found: 215.1037.

4. Copies of ^{1}H NMR and ^{13}C NMR Spectra

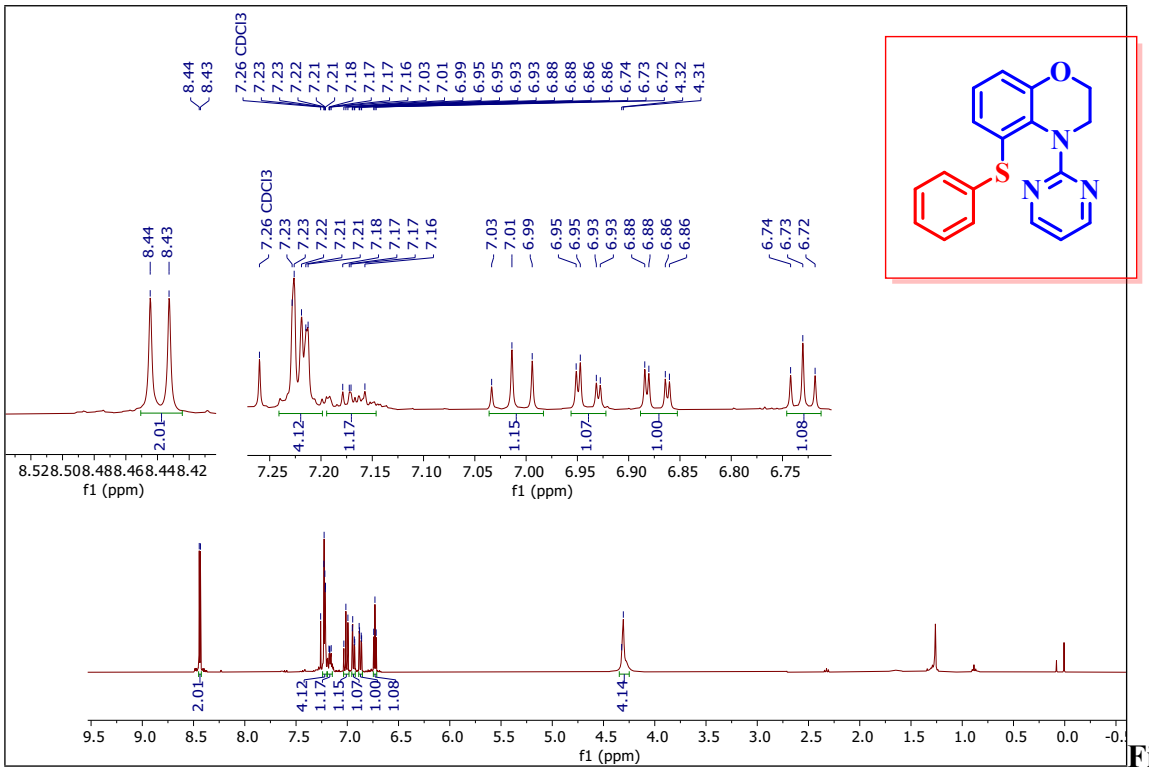


Figure 1: ^{1}H NMR spectrum of compound **3a** ($CDCl_3$, 400 MHz)

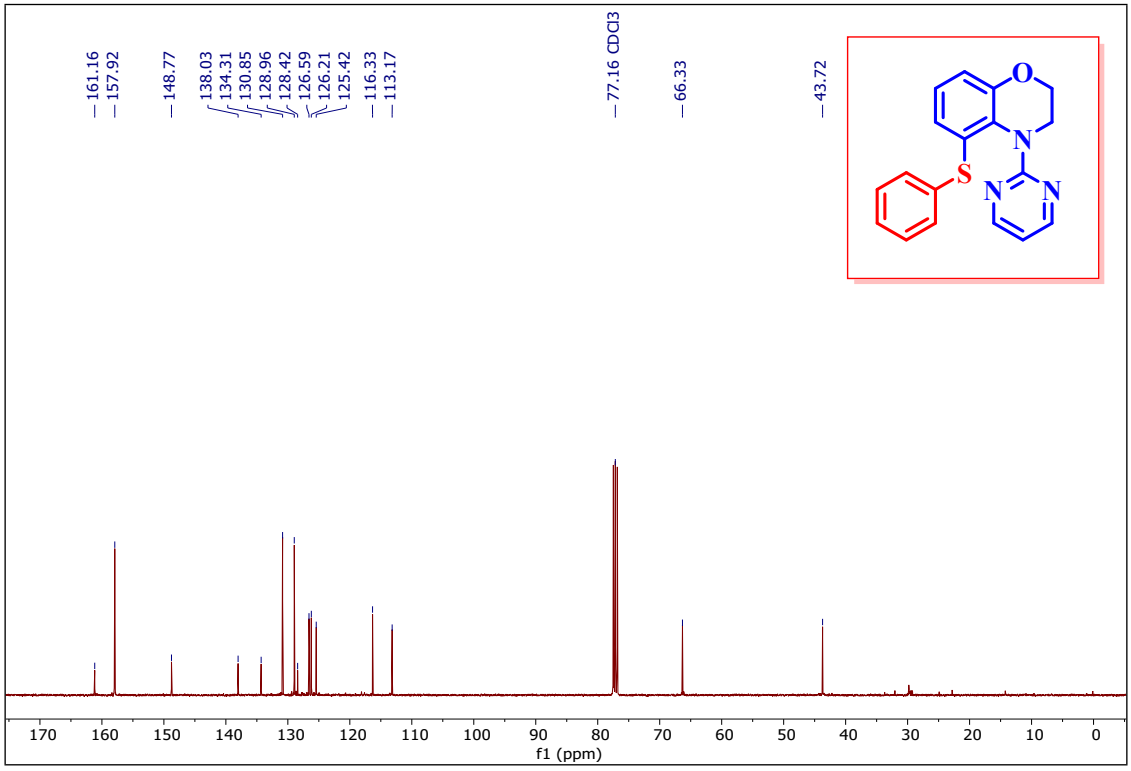


Figure 2: ^{13}C NMR spectrum of compound **3a** ($CDCl_3$, 100 MHz)

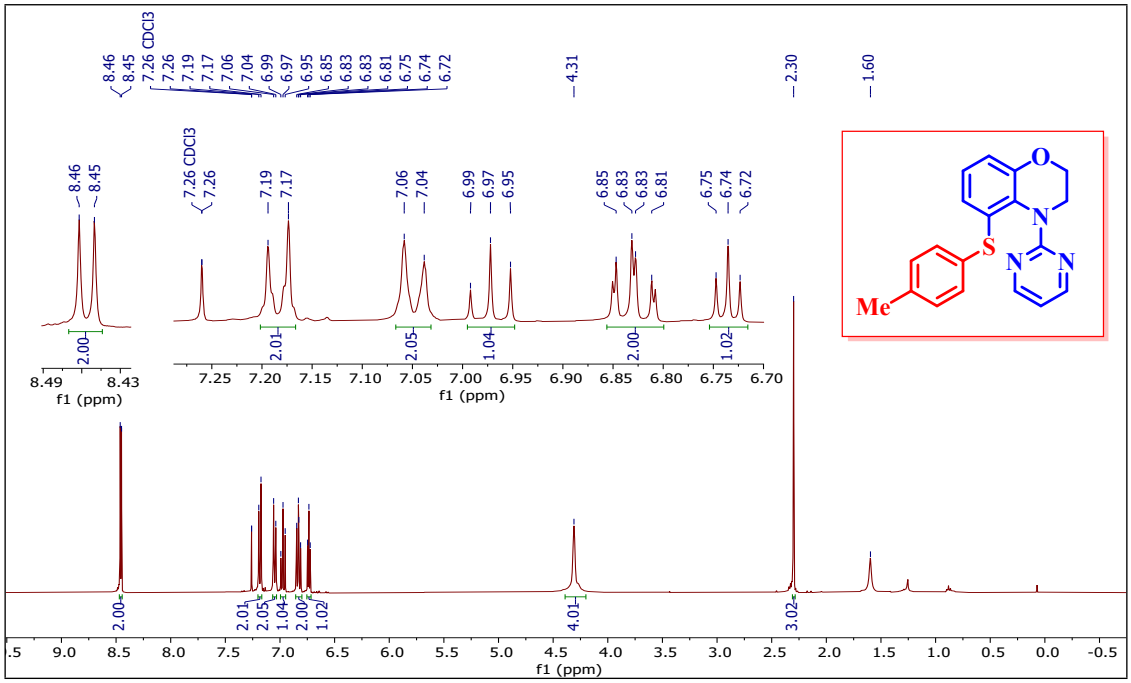


Figure 3: ^{1}H NMR spectrum of compound **3b** ($CDCl_3$, 400 MHz)

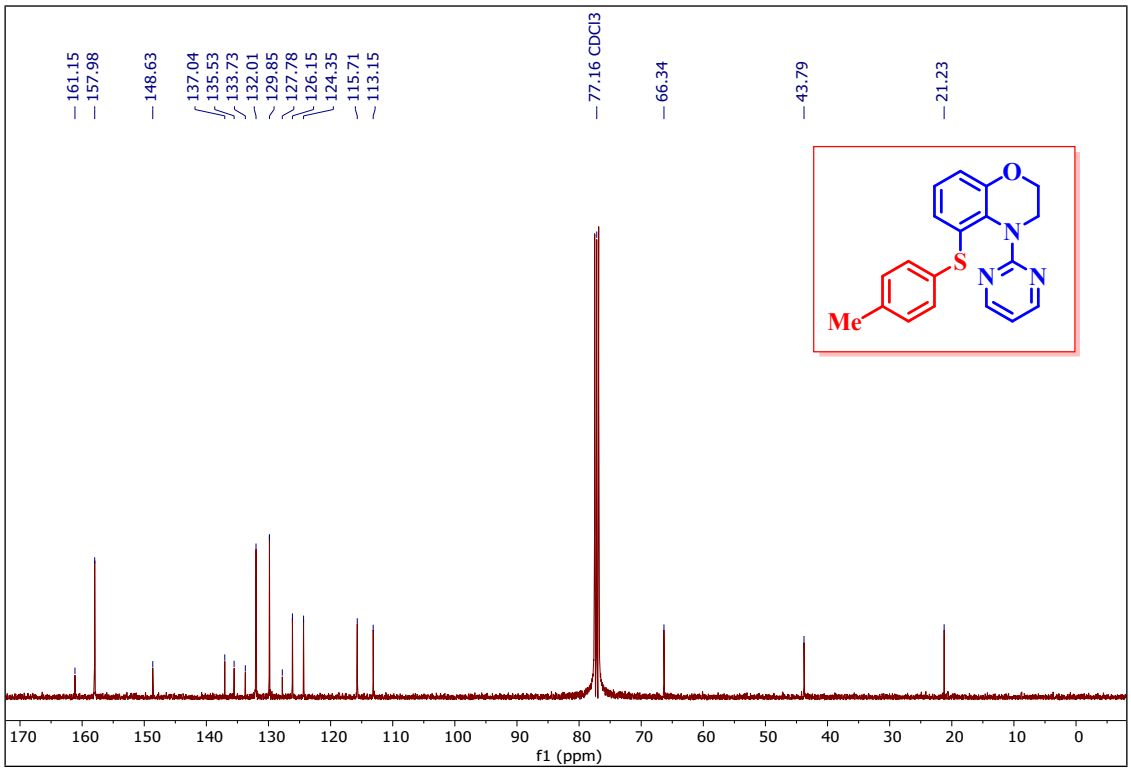


Figure 4: ^{13}C NMR spectrum of compound **3b** ($CDCl_3$, 100 MHz)

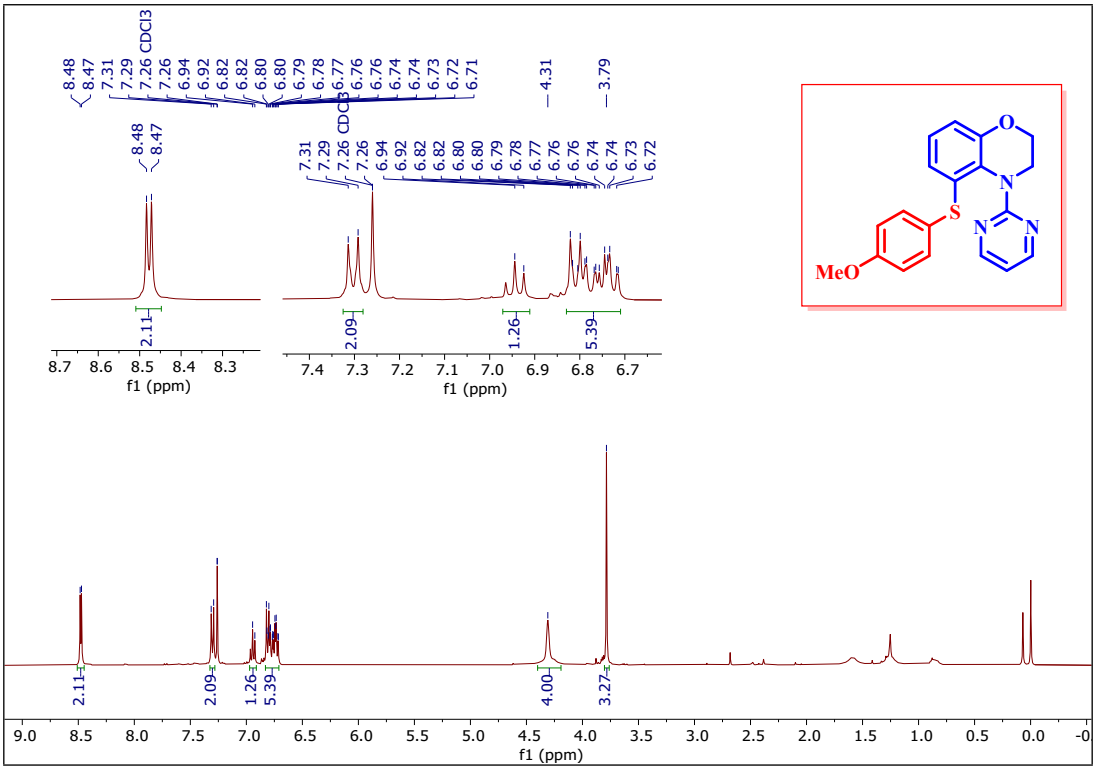


Figure 5: ^{1}H NMR spectrum of compound **3c** ($CDCl_3$, 400 MHz)

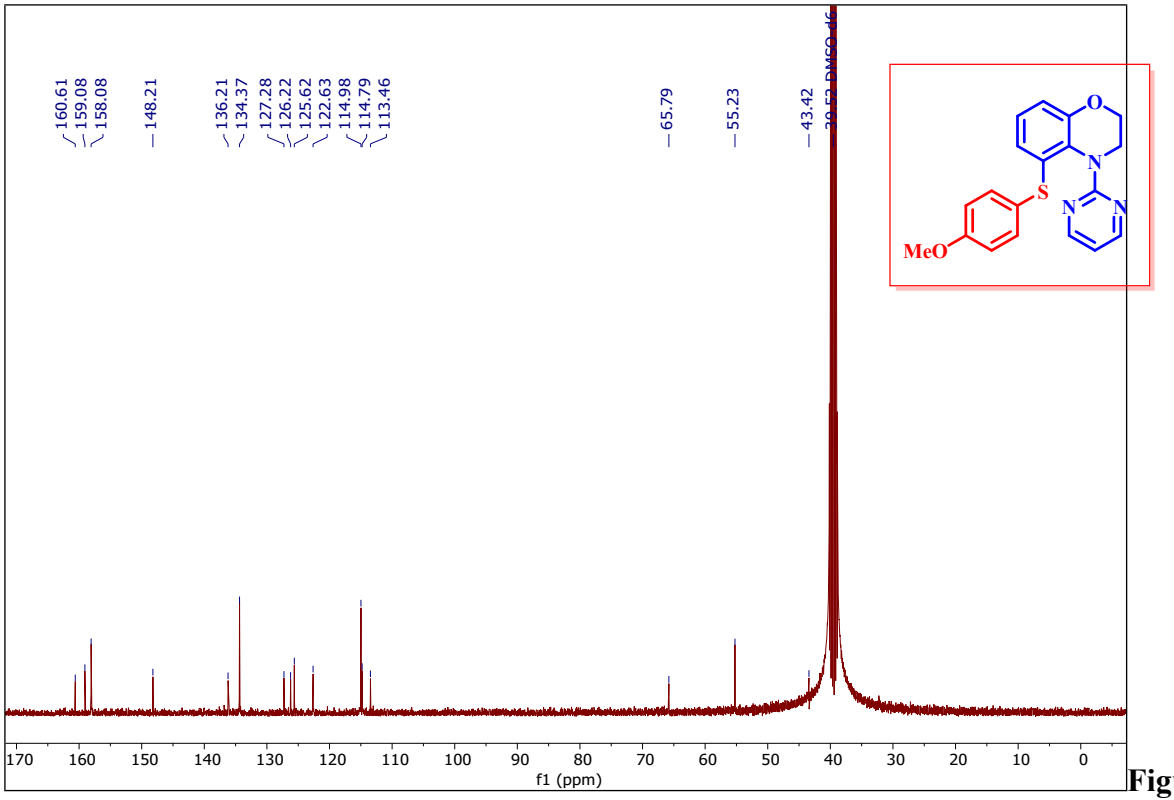
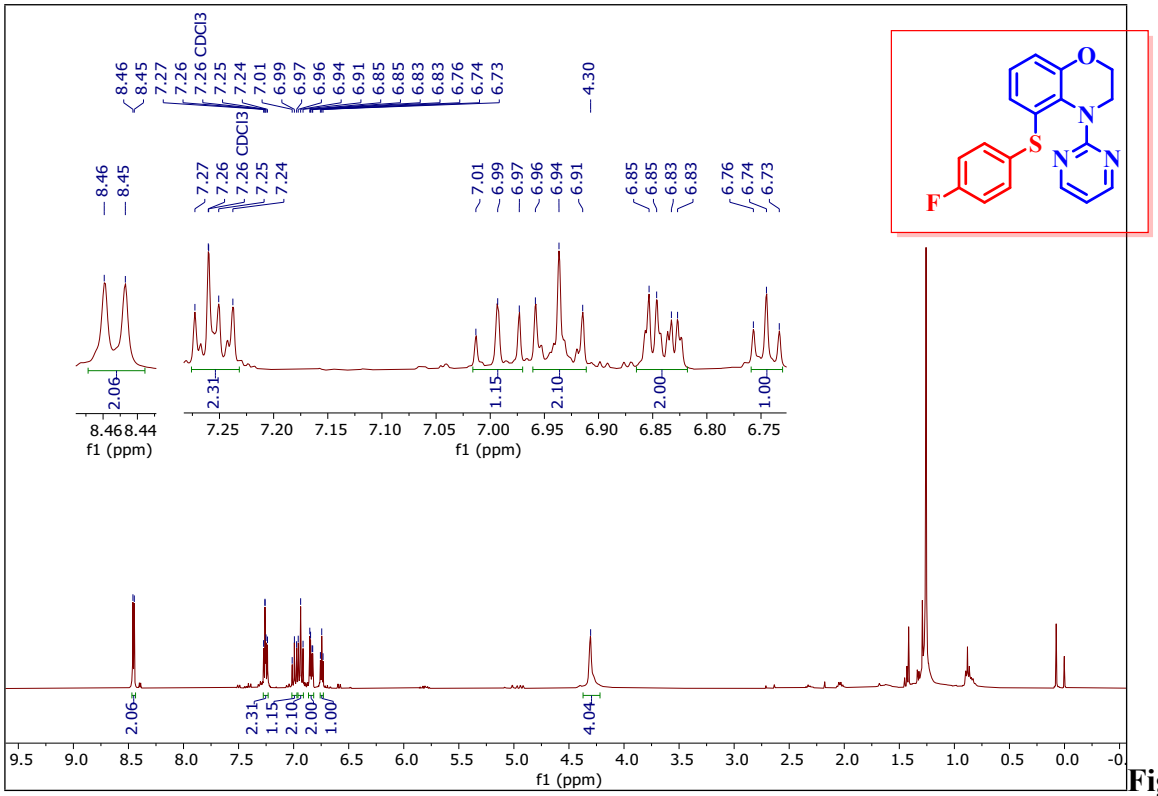
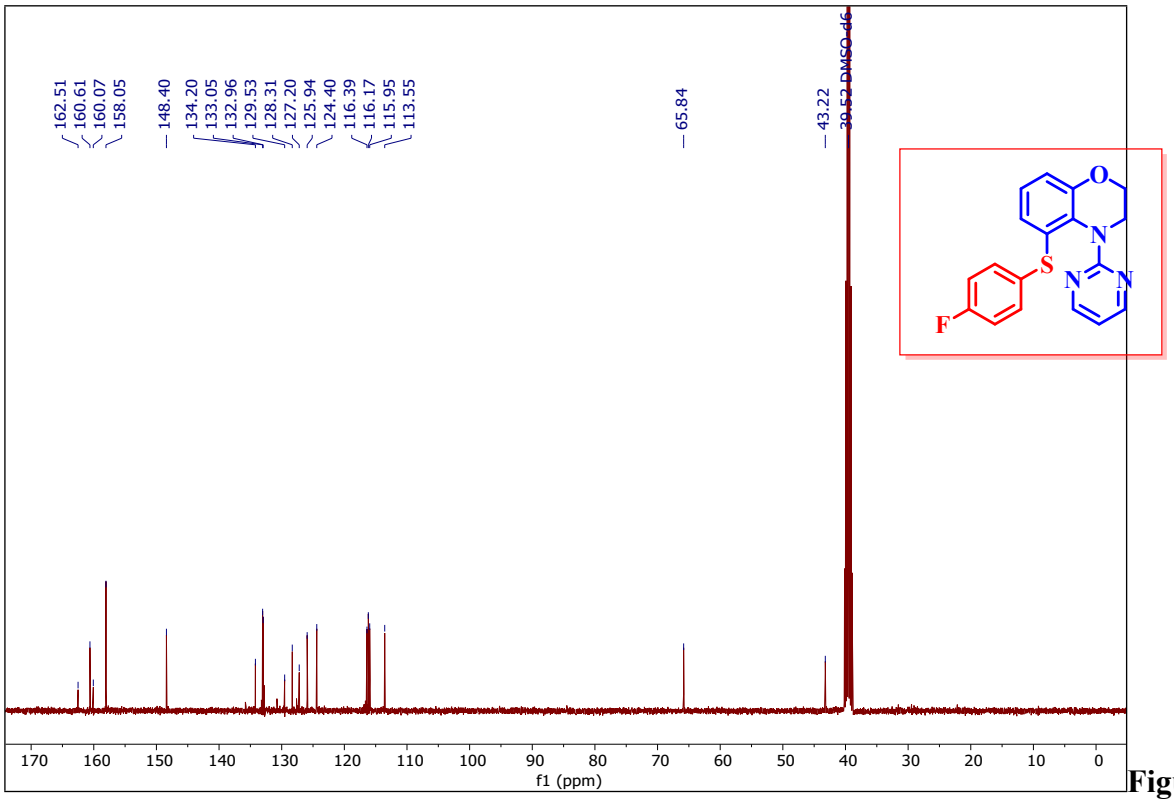


Figure 6: ^{13}C NMR spectrum of compound **3c** ($CDCl_3$, 100 MHz)



Figur

e 7: ^{1}H NMR spectrum of compound **3d** ($CDCl_3$, 400 MHz)



Figur

e 8: ^{13}C NMR spectrum of compound **3d** ($CDCl_3$, 100 MHz)

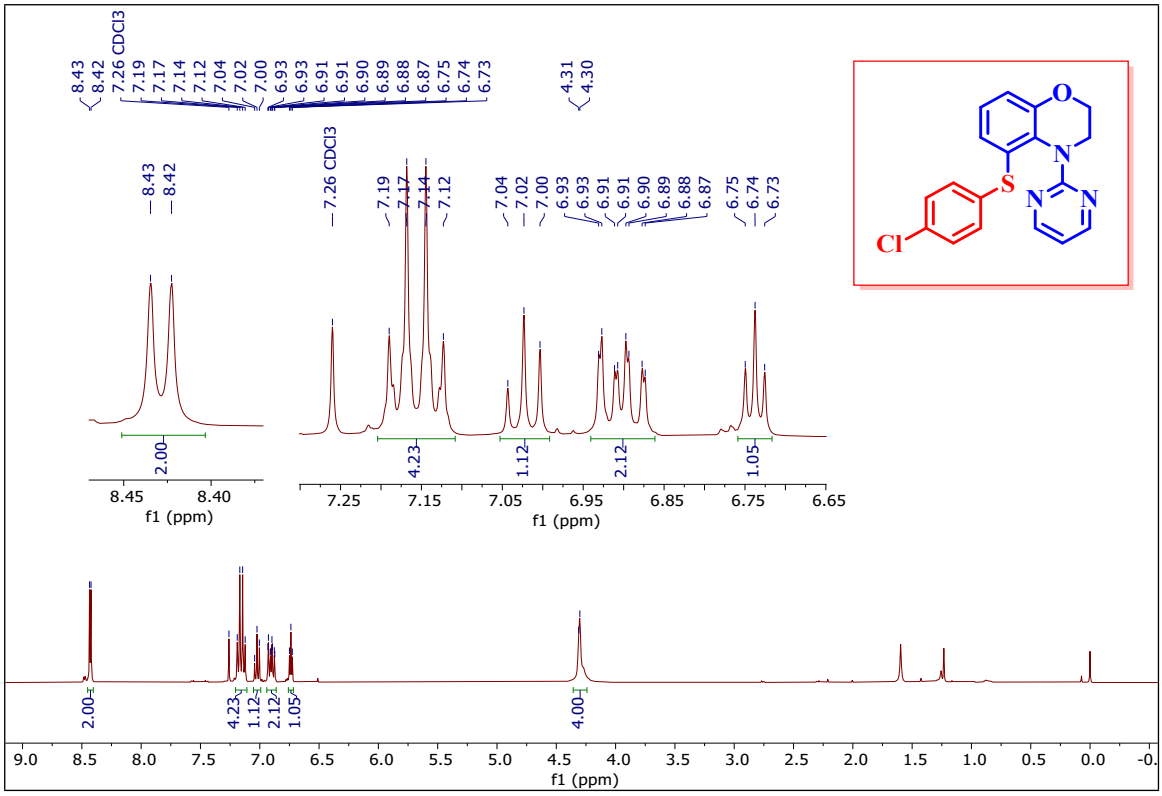


Figure 9: ^{1}H NMR spectrum of compound **3e** ($CDCl_3$, 400 MHz)

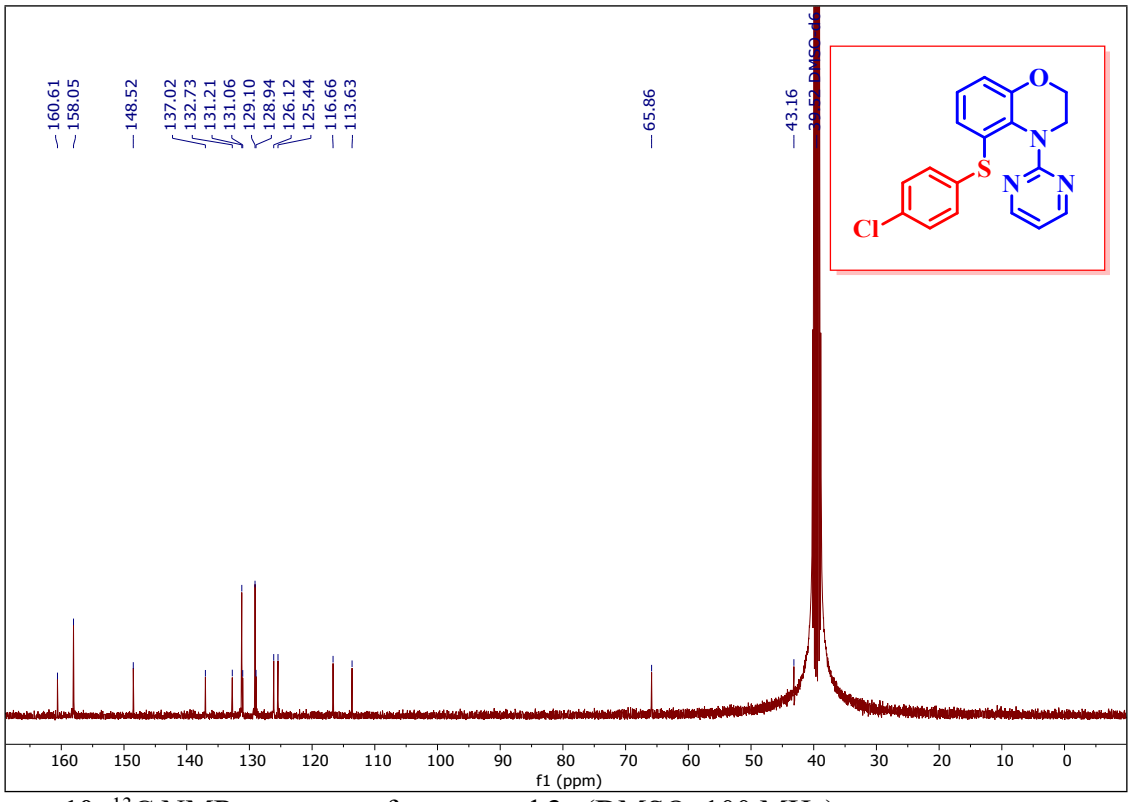


Figure 10: ^{13}C NMR spectrum of compound **3e** (DMSO, 100 MHz)

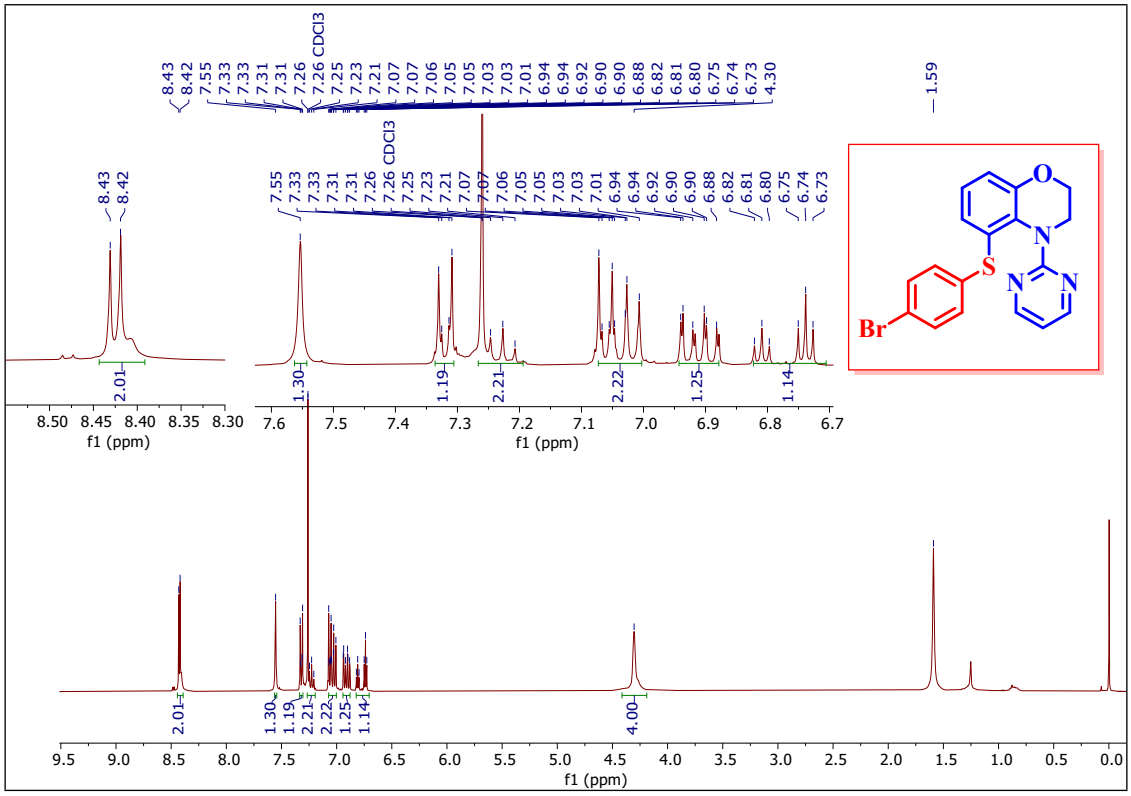


Figure 11: ^{1}H NMR spectrum of compound **3f** ($CDCl_3$, 400 MHz)

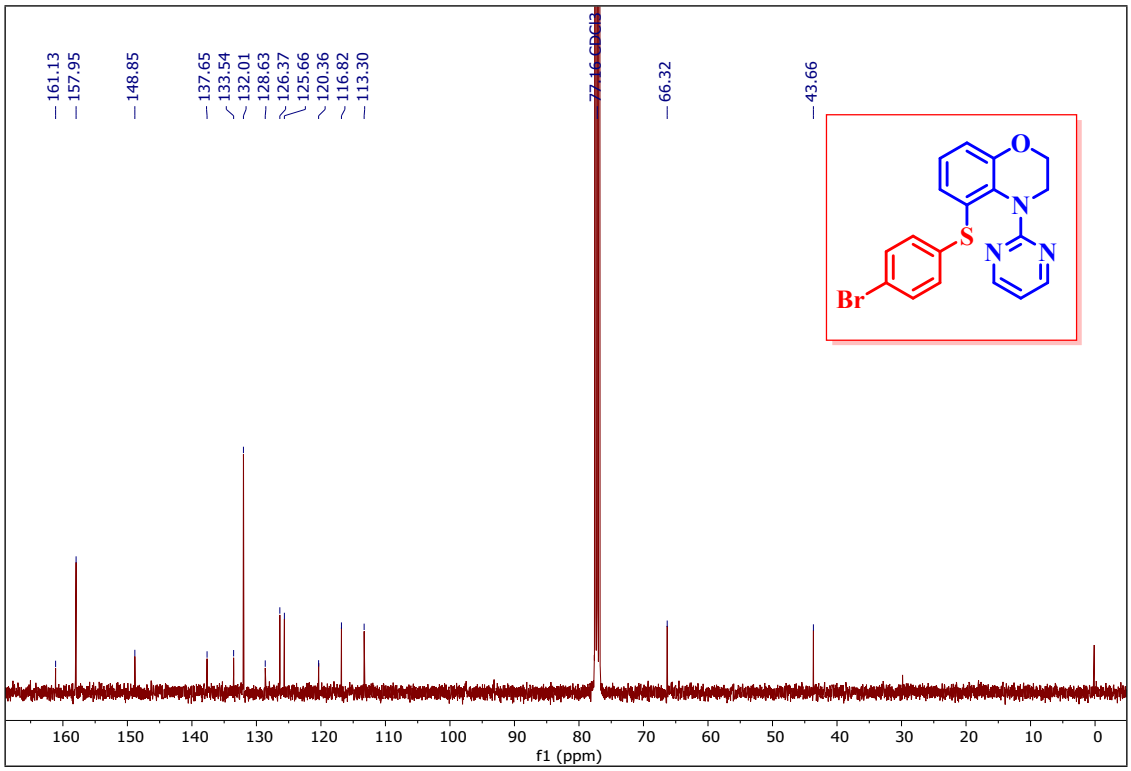


Figure 12: ^{13}C NMR spectrum of compound **3f** ($CDCl_3$, 100 MHz)

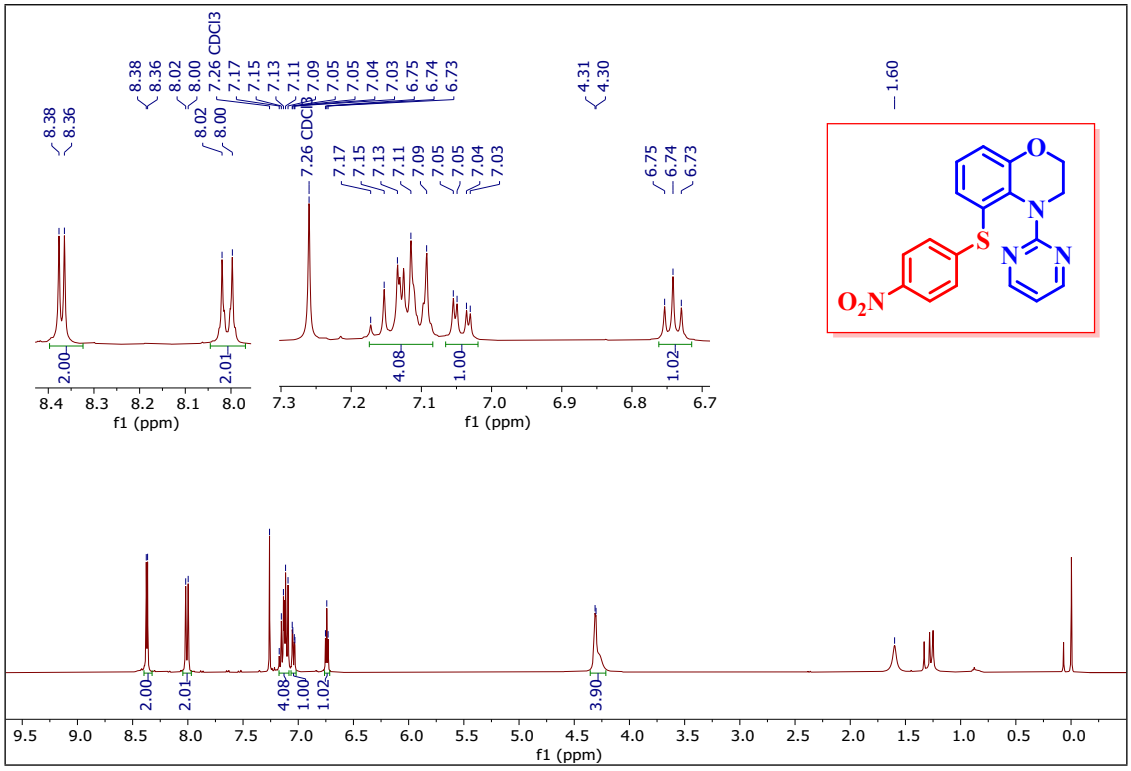


Figure 13: ^{1}H NMR spectrum of compound **3g** ($CDCl_3$, 400 MHz)

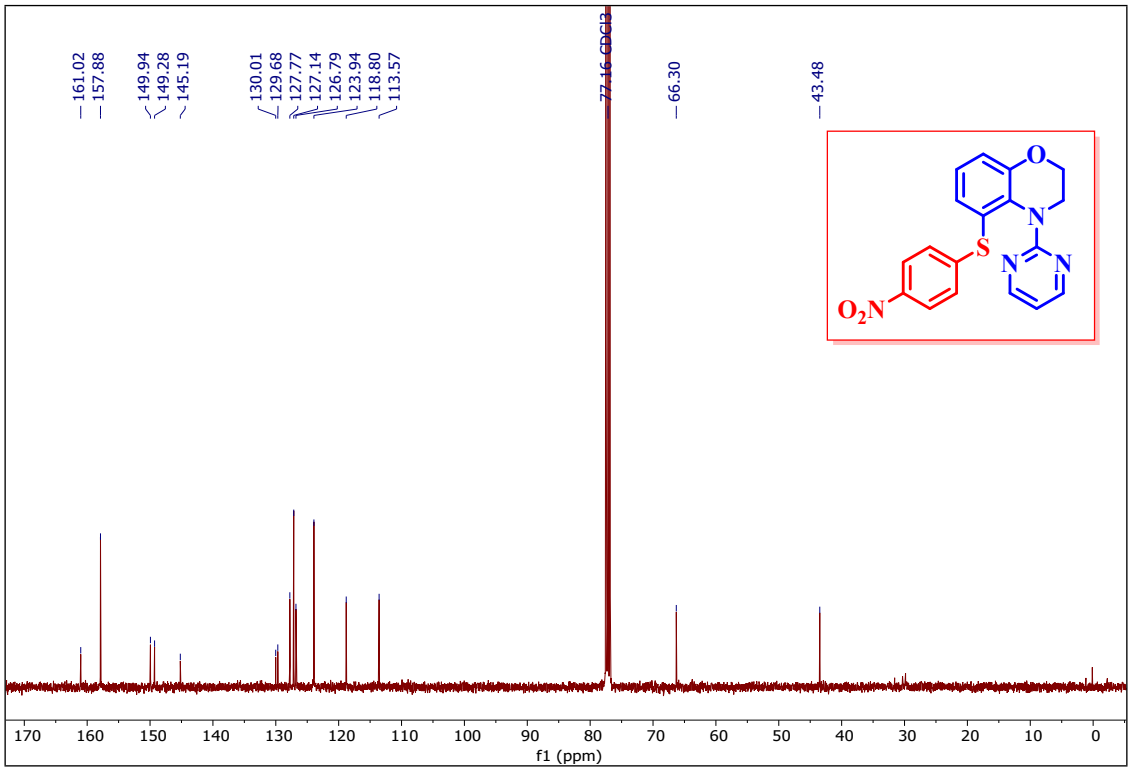


Figure 14: ^{13}C NMR spectrum of compound **3g** ($CDCl_3$, 100 MHz)

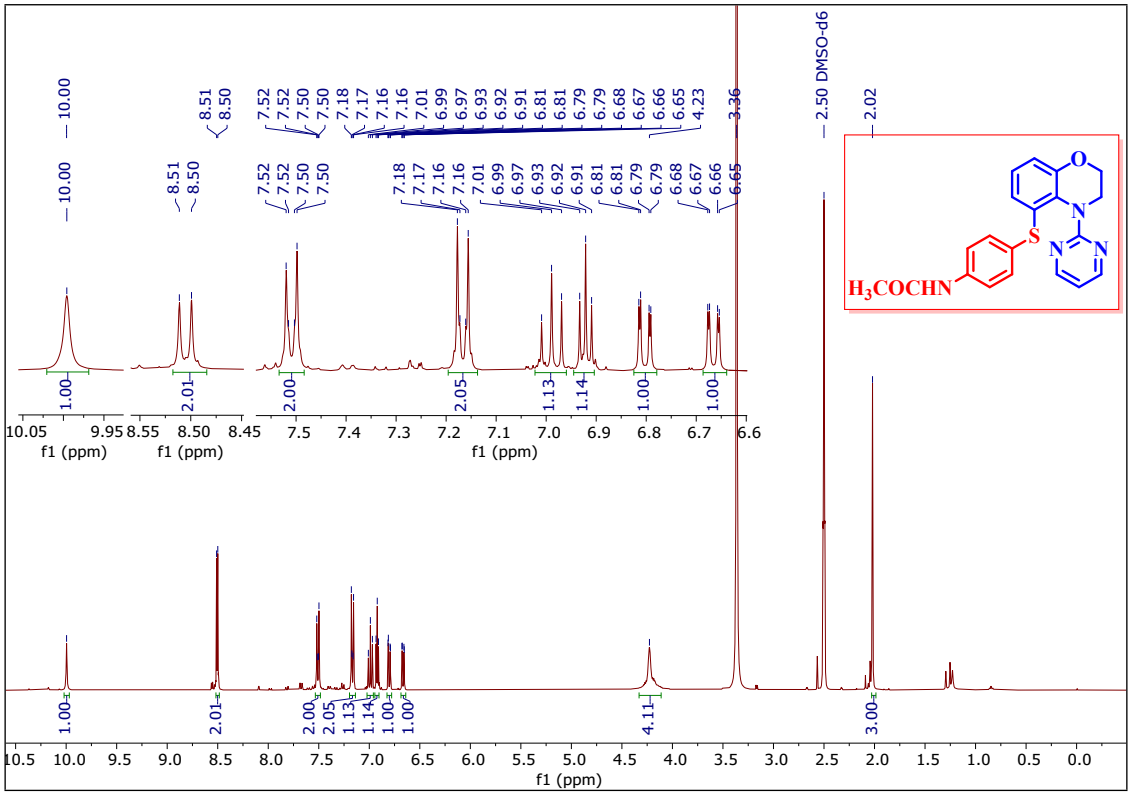
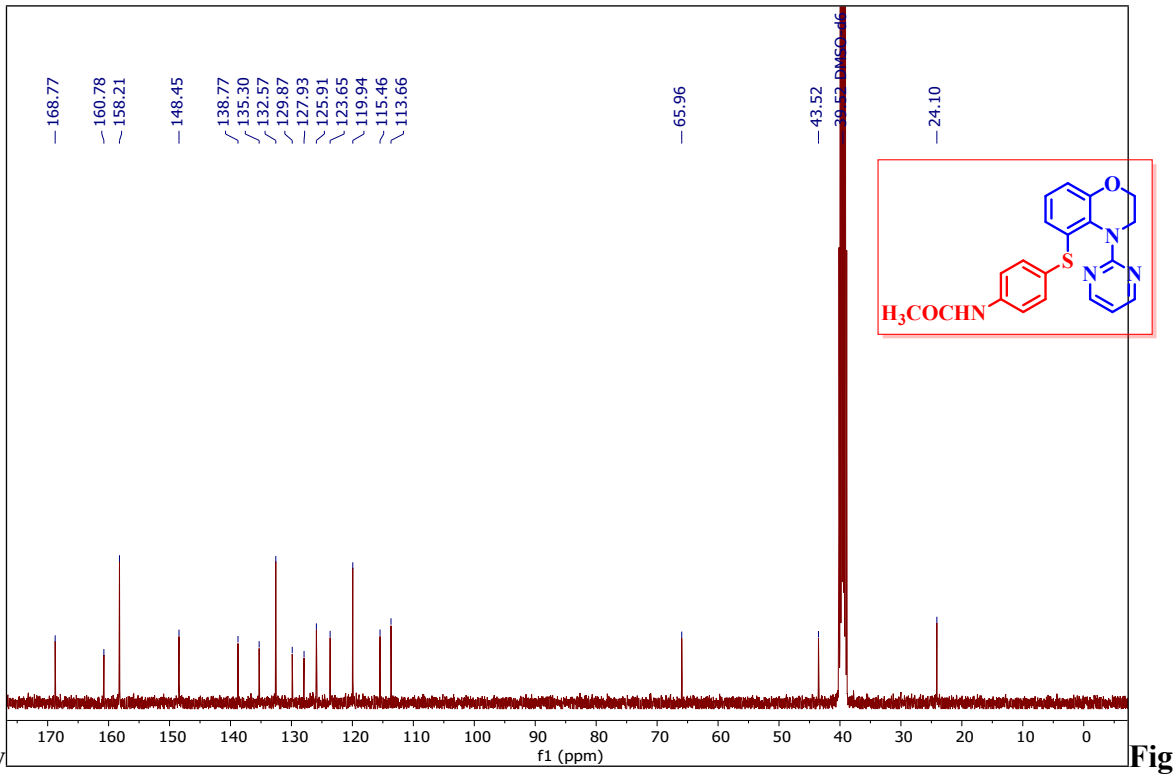


Figure 15 [1]H NMR spectrum of compound **3h** (DMSO, 400 MHz)



W**Figure 16**: [13]C NMR spectrum of compound **3h** (DMSO, 100 MHz)

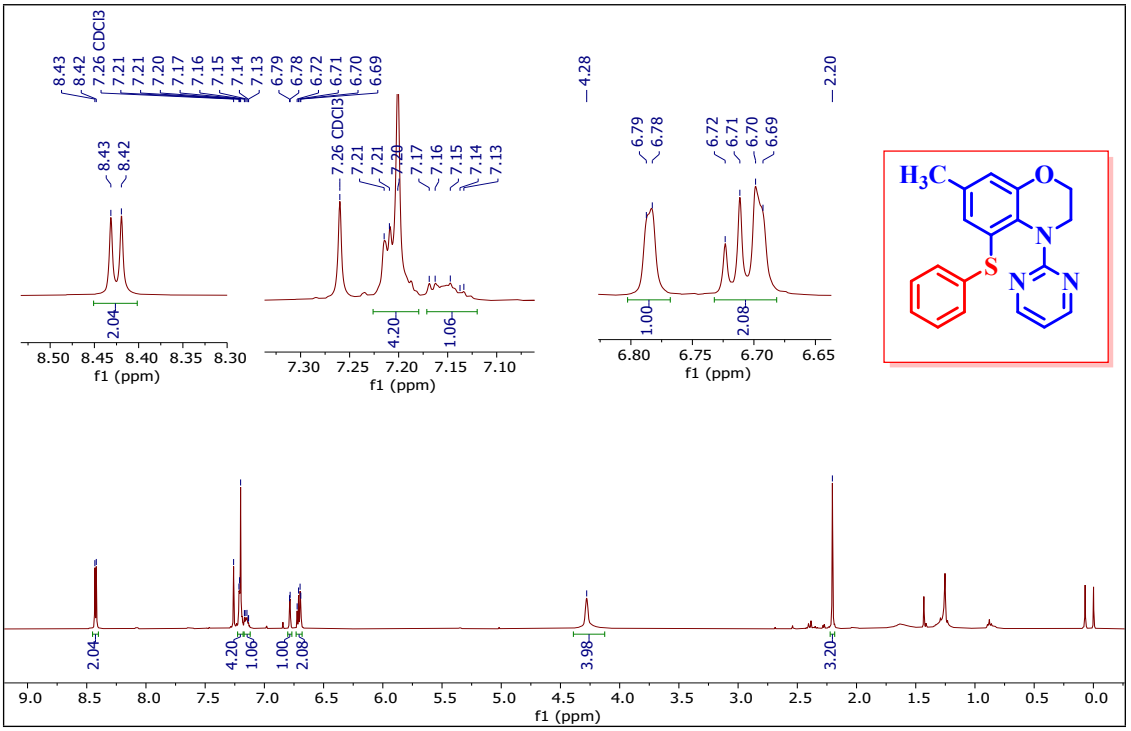


Figure 17: ^{1}H NMR spectrum of compound **3i** ($CDCl_3$, 400 MHz)

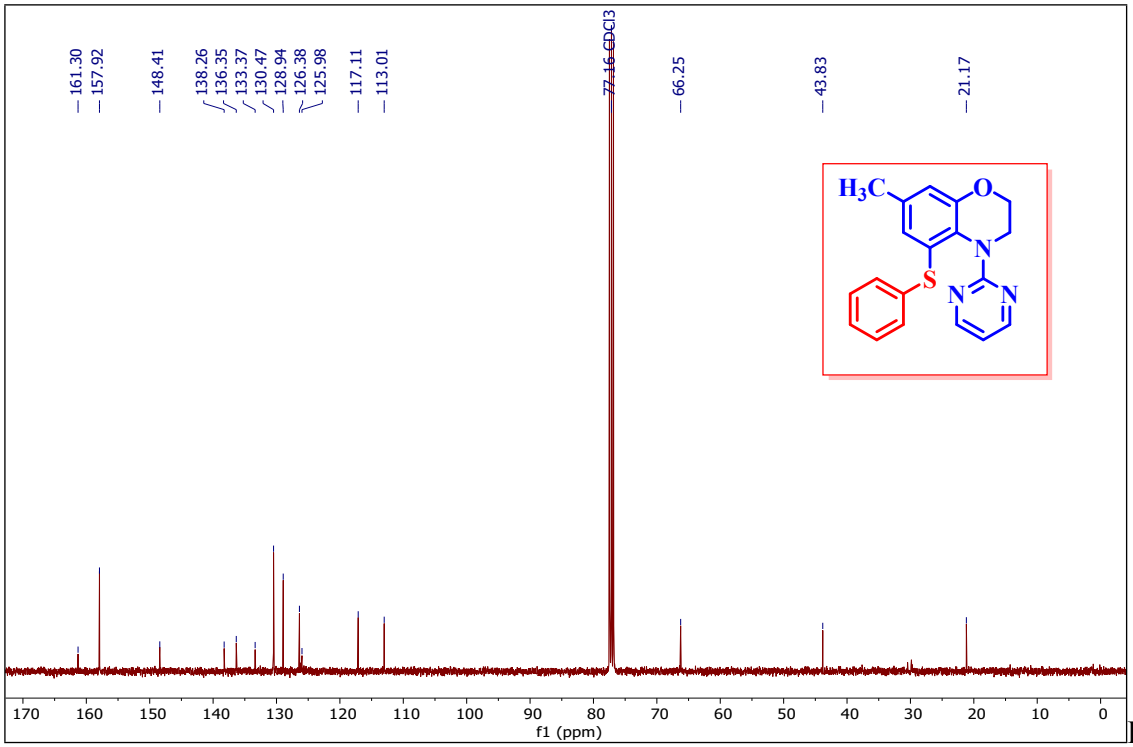


Figure 18: ^{13}C NMR spectrum of compound **3i** ($CDCl_3$, 100 MHz)

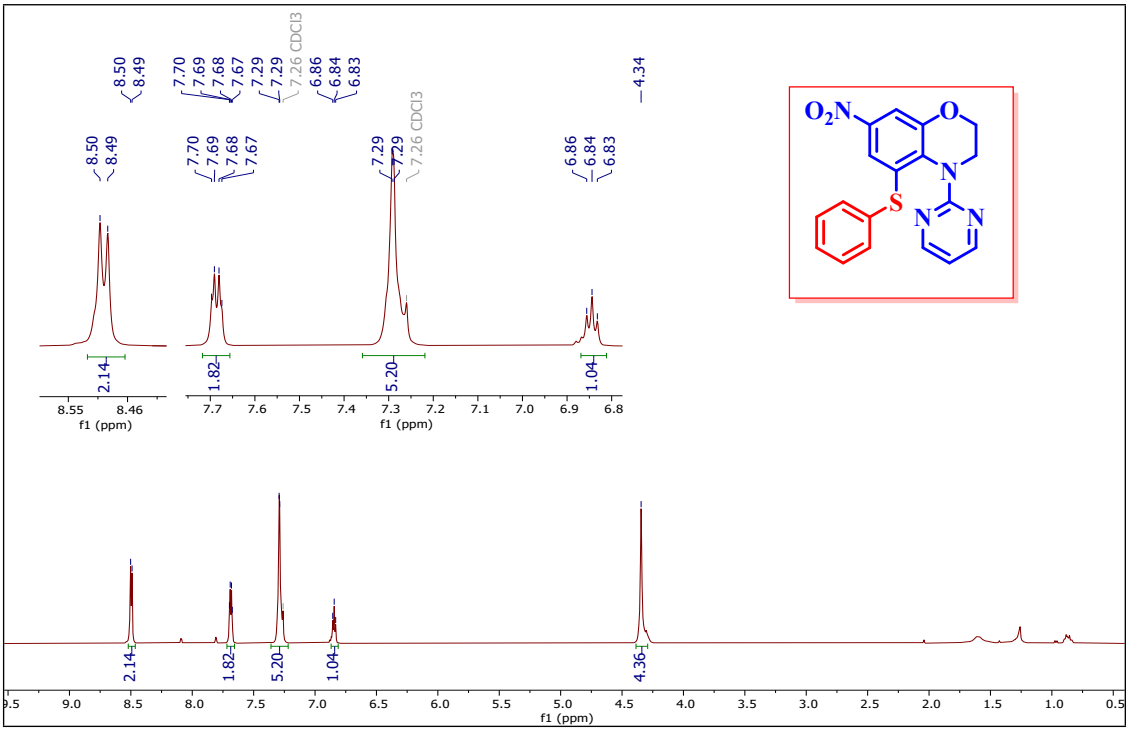


Figure 19: ^{1}H NMR spectrum of compound **3j** ($CDCl_3$, 400 MHz)

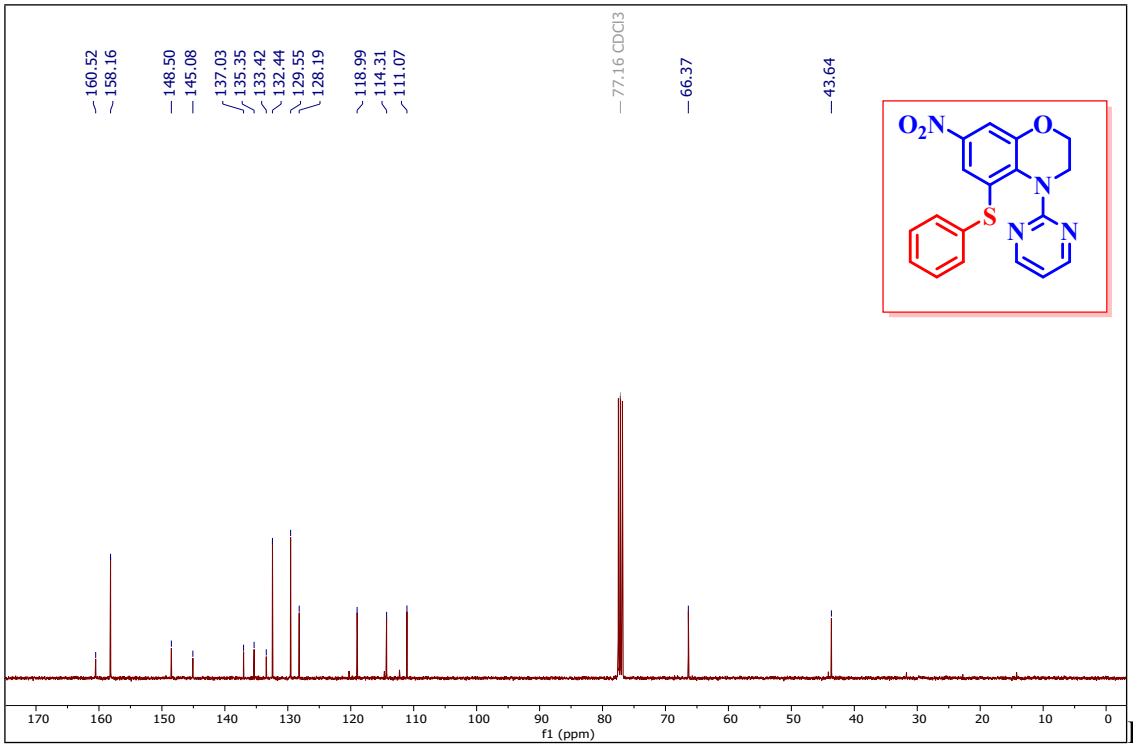


Figure 20: ^{13}C NMR spectrum of compound **3j** ($CDCl_3$, 100 MHz)

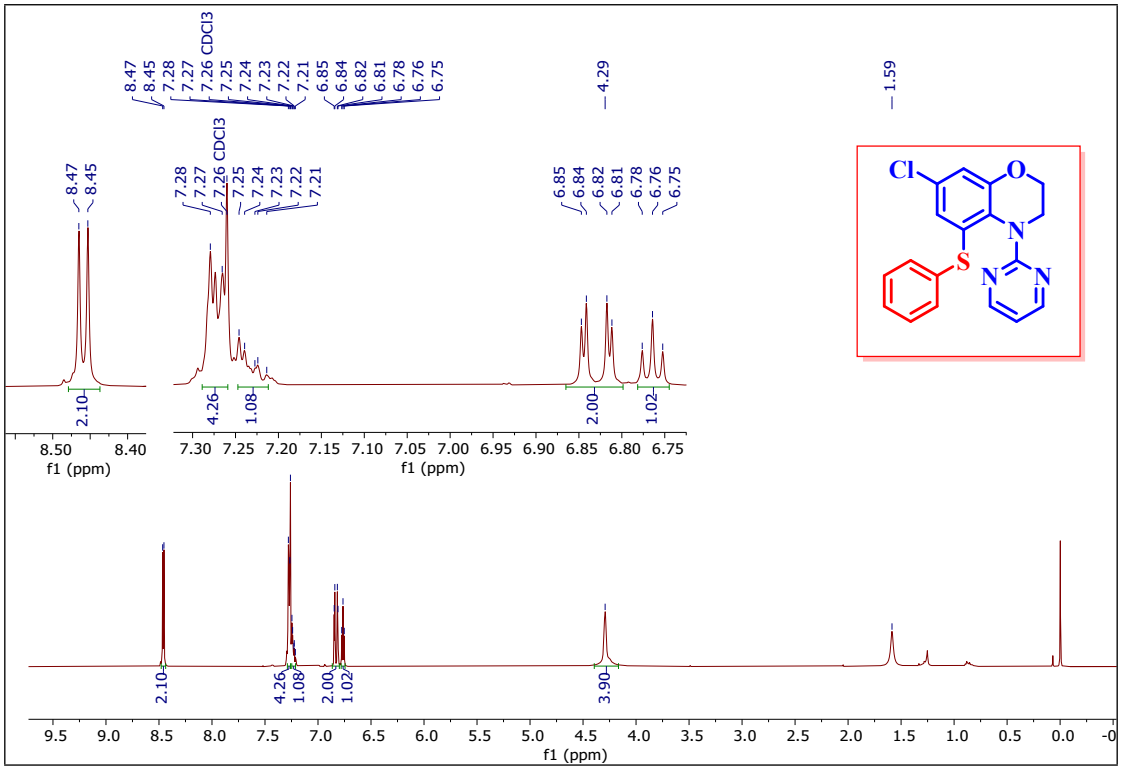


Figure 21: ^{1}H NMR spectrum of compound **3k** ($CDCl_3$, 400 MHz)

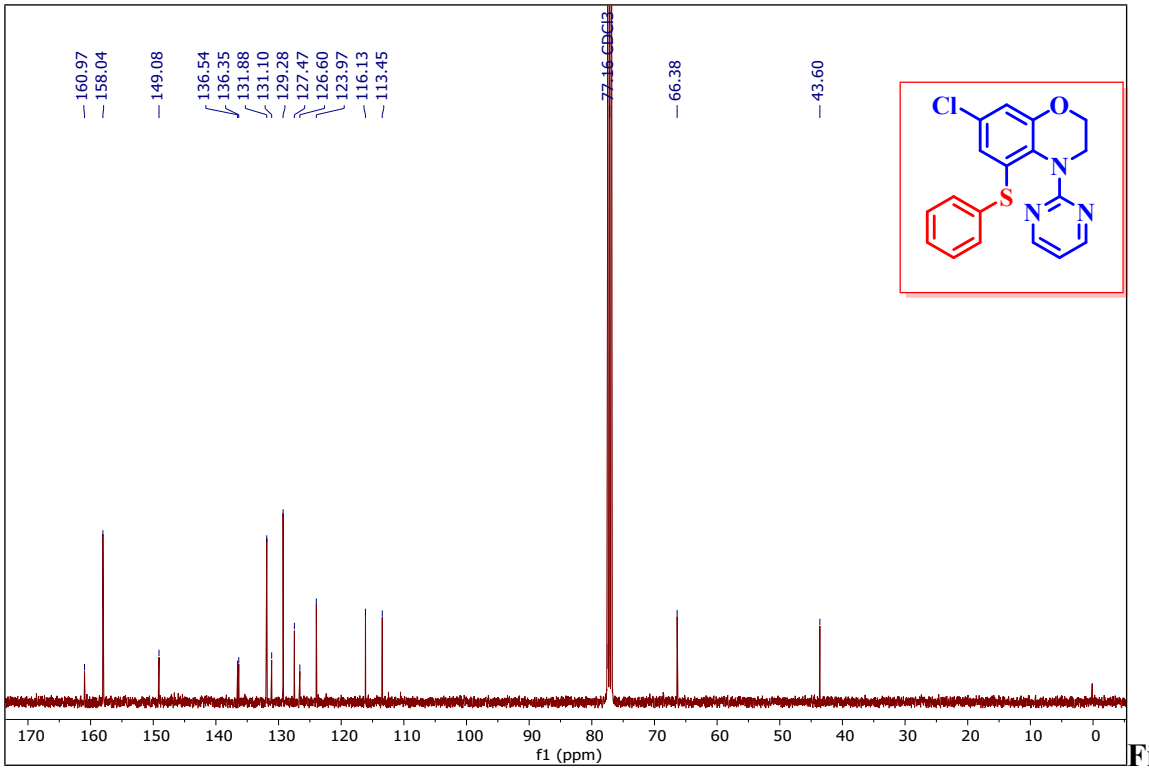
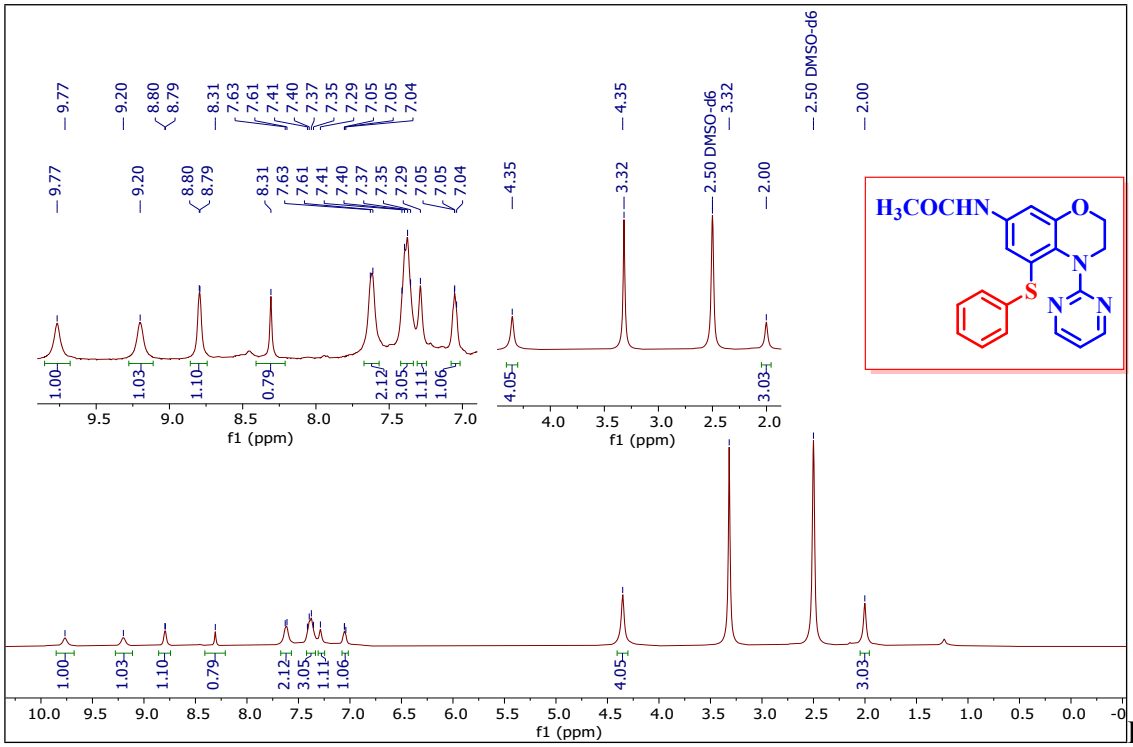
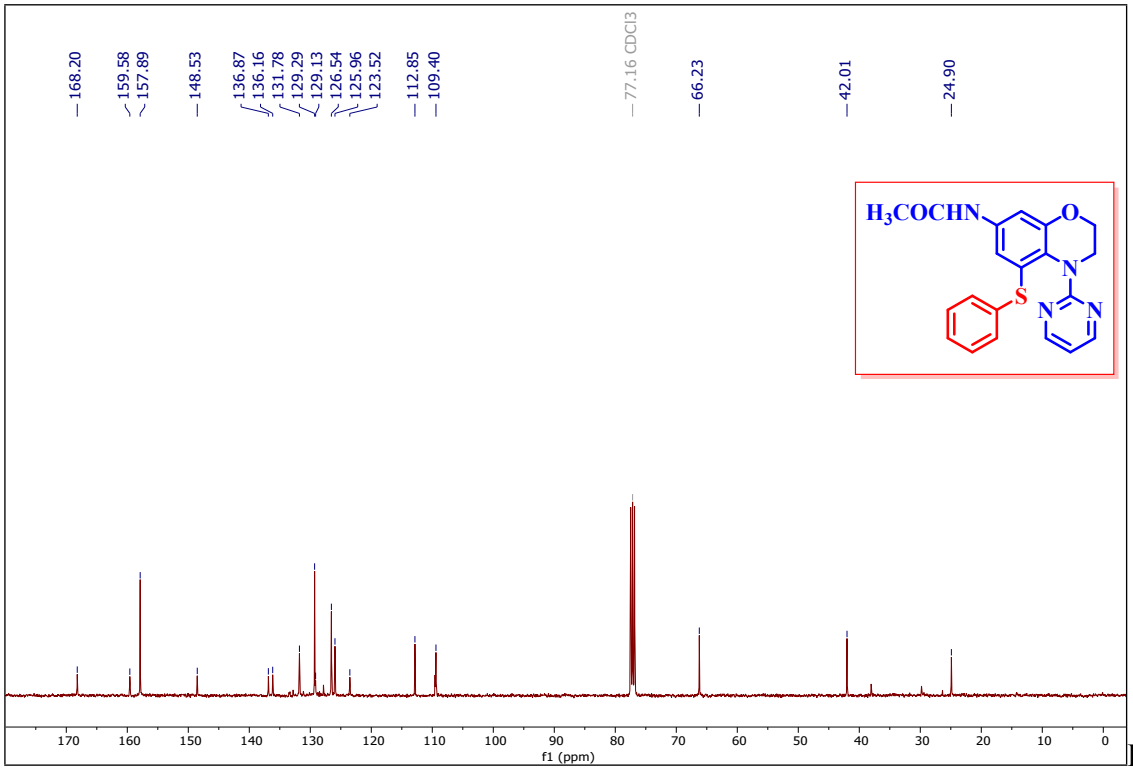


Figure 22: ^{13}C NMR spectrum of compound **3k** ($CDCl_3$, 100 MHz)



Figur e 23: ^{1}H NMR spectrum of compound **3l** (DMSO, 400 MHz)



Figur e 24: ^{13}C NMR spectrum of compound **3l** (CDCl3, 100 MHz)

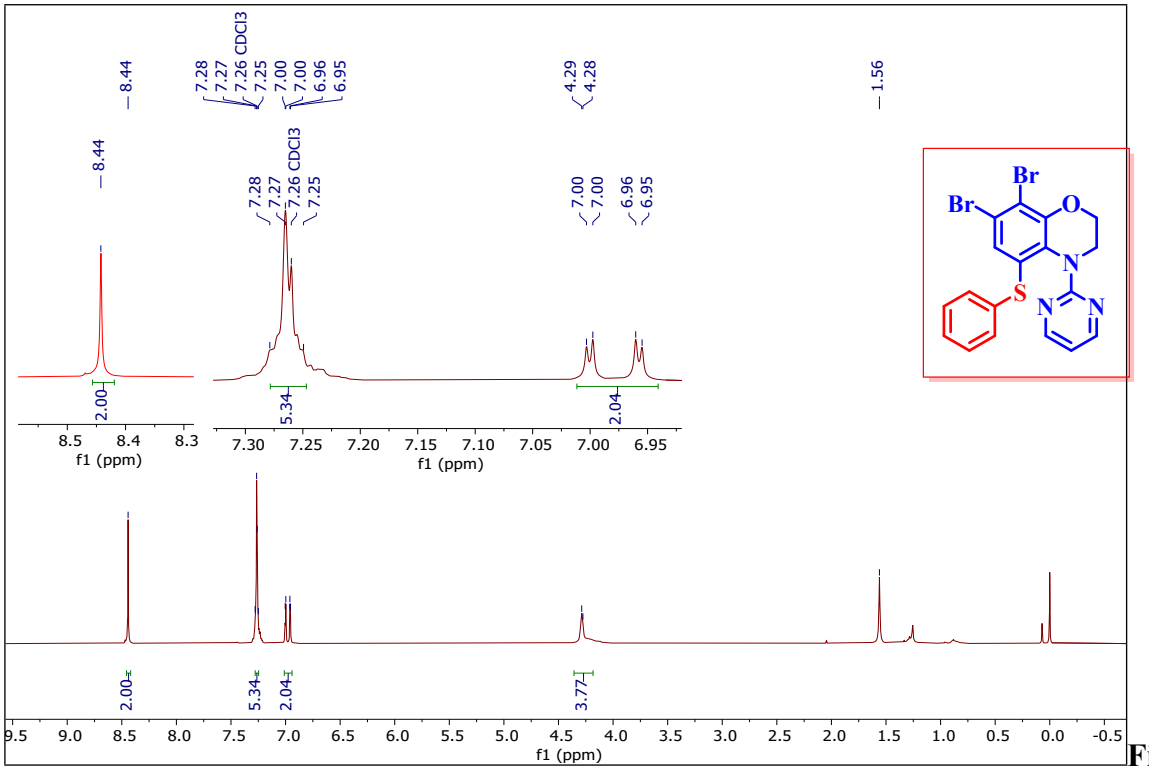


Figure 25: ^{1}H NMR spectrum of compound **3m** ($CDCl_3$, 400 MHz)

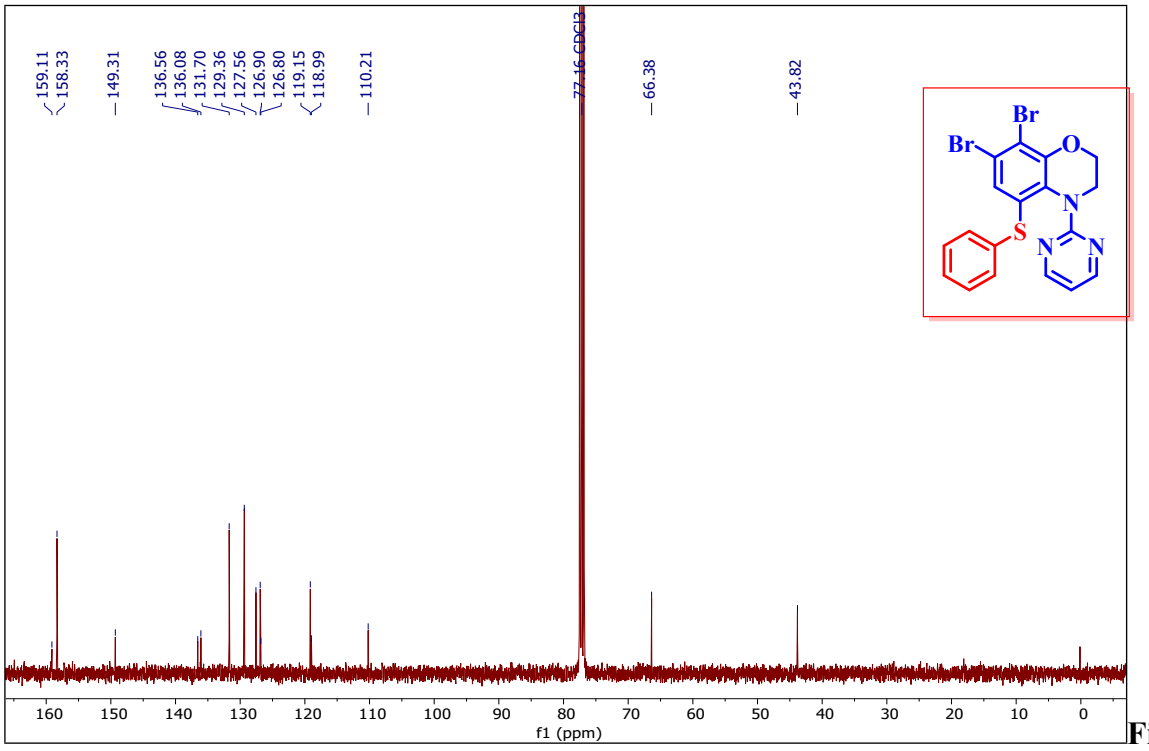


Figure 26: ^{13}C NMR spectrum of compound **3m** ($CDCl_3$, 100 MHz)

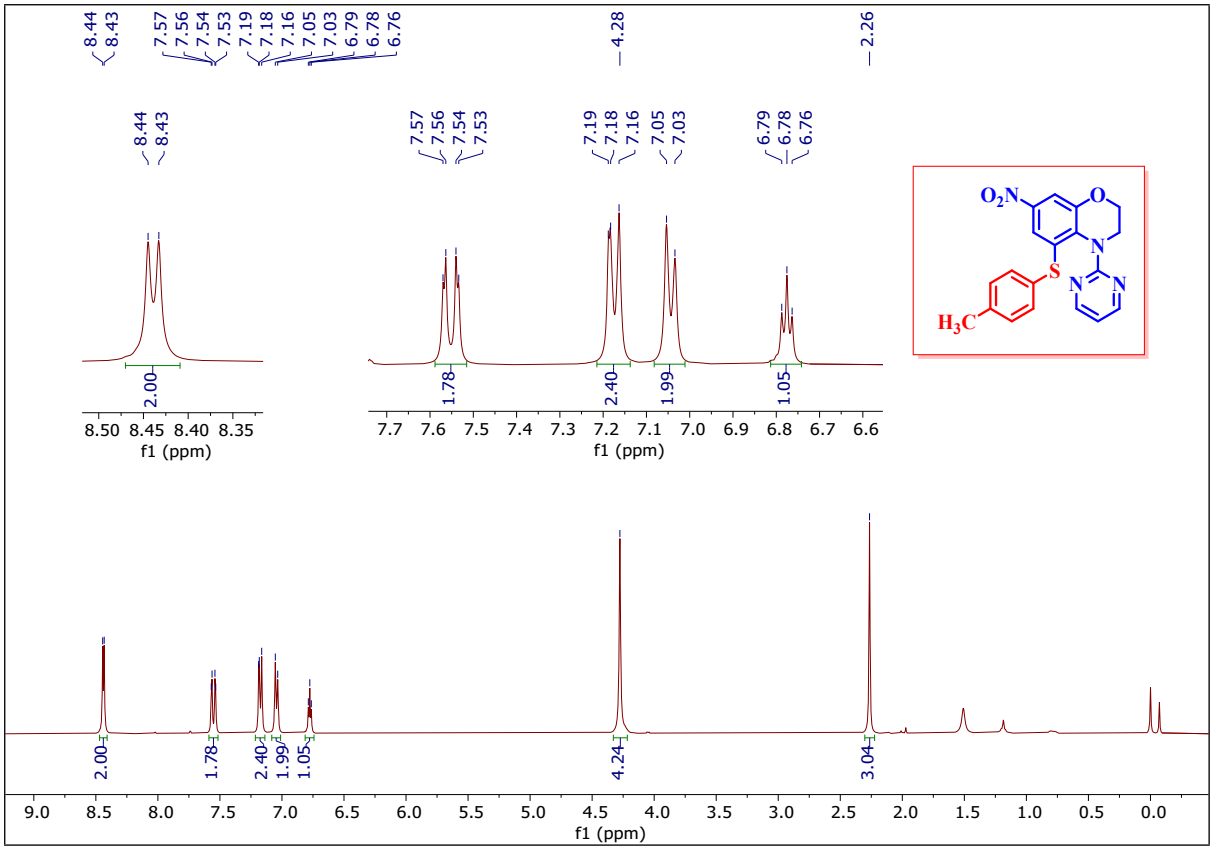


Figure 27: ^{1}H NMR spectrum of compound **3n** ($CDCl_3$, 400 MHz)

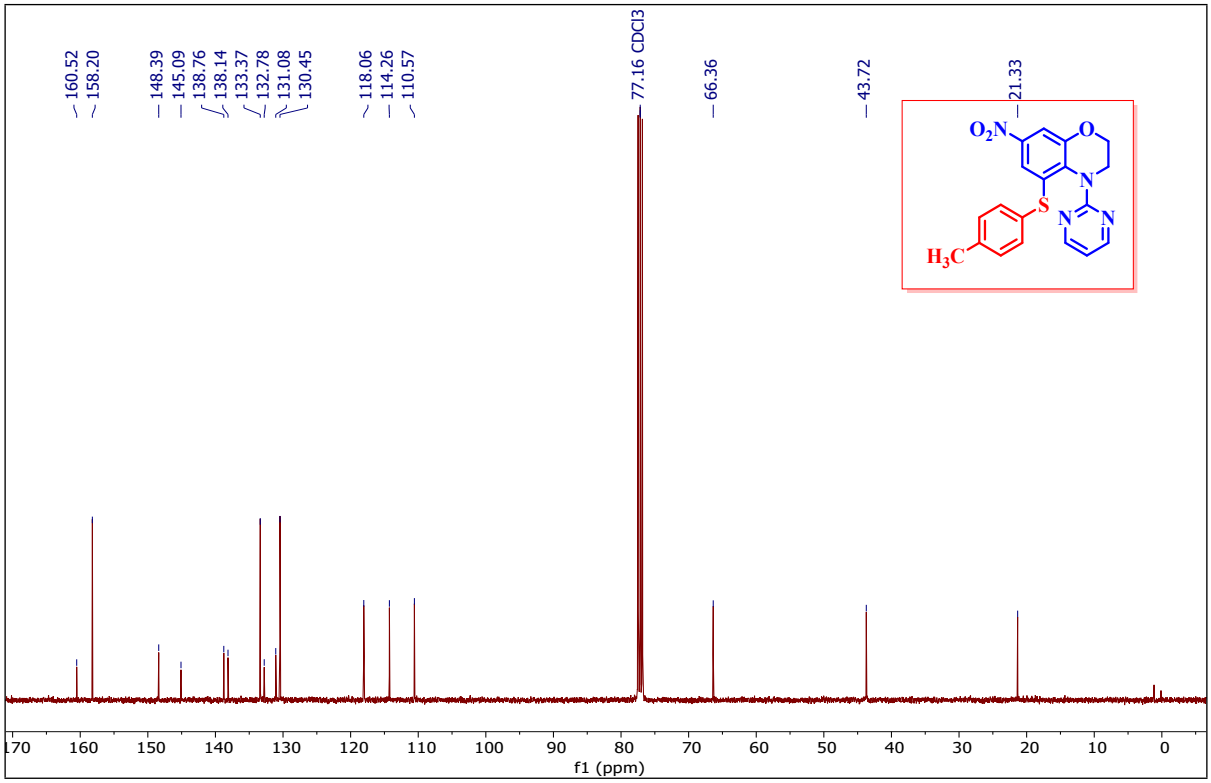


Figure 28: ^{13}C NMR spectrum of compound **3n** (CDCl3, 100 MHz)

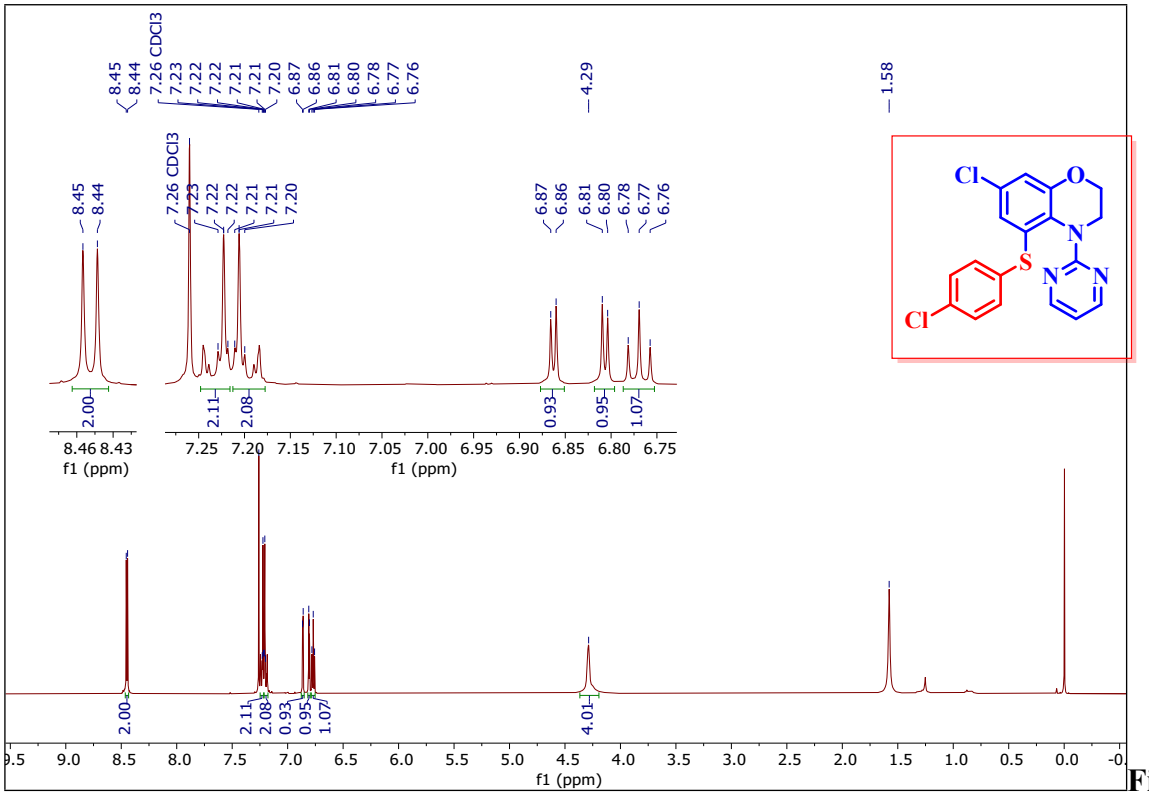


Figure 29: ^{1}H NMR spectrum of compound **3o** ($CDCl_3$, 400 MHz)

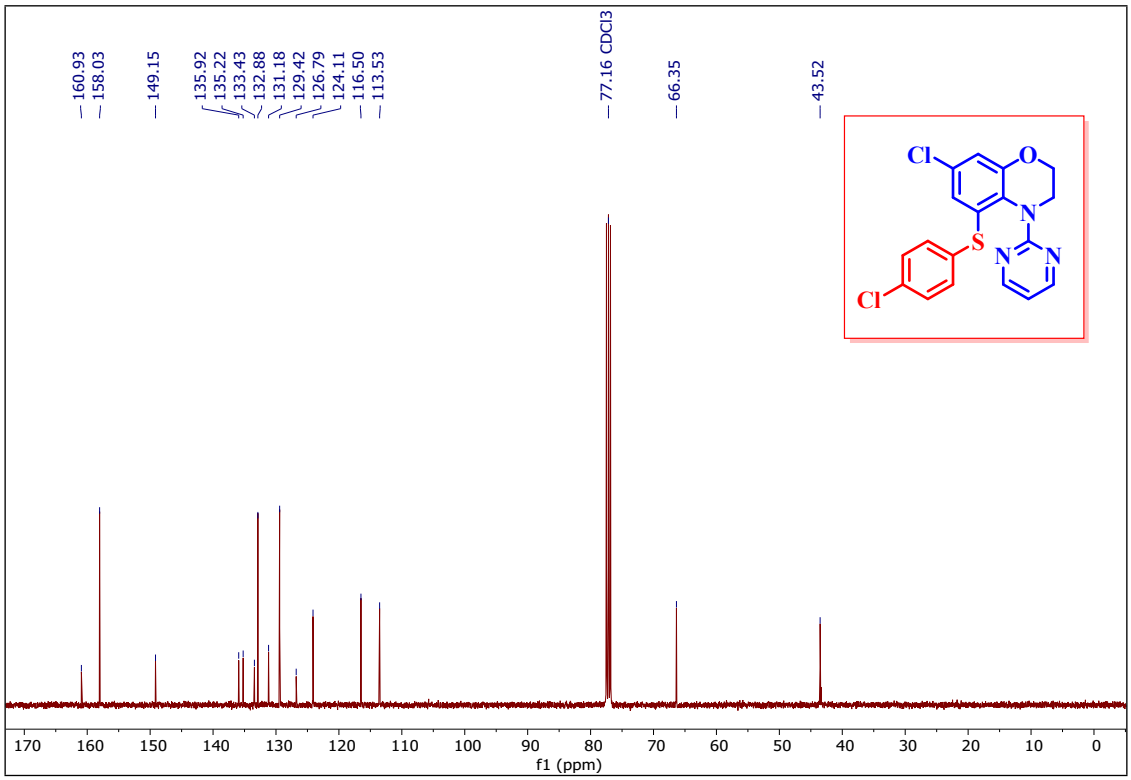


Figure 30: ^{13}C NMR spectrum of compound **3o** ($CDCl_3$, 100 MHz)

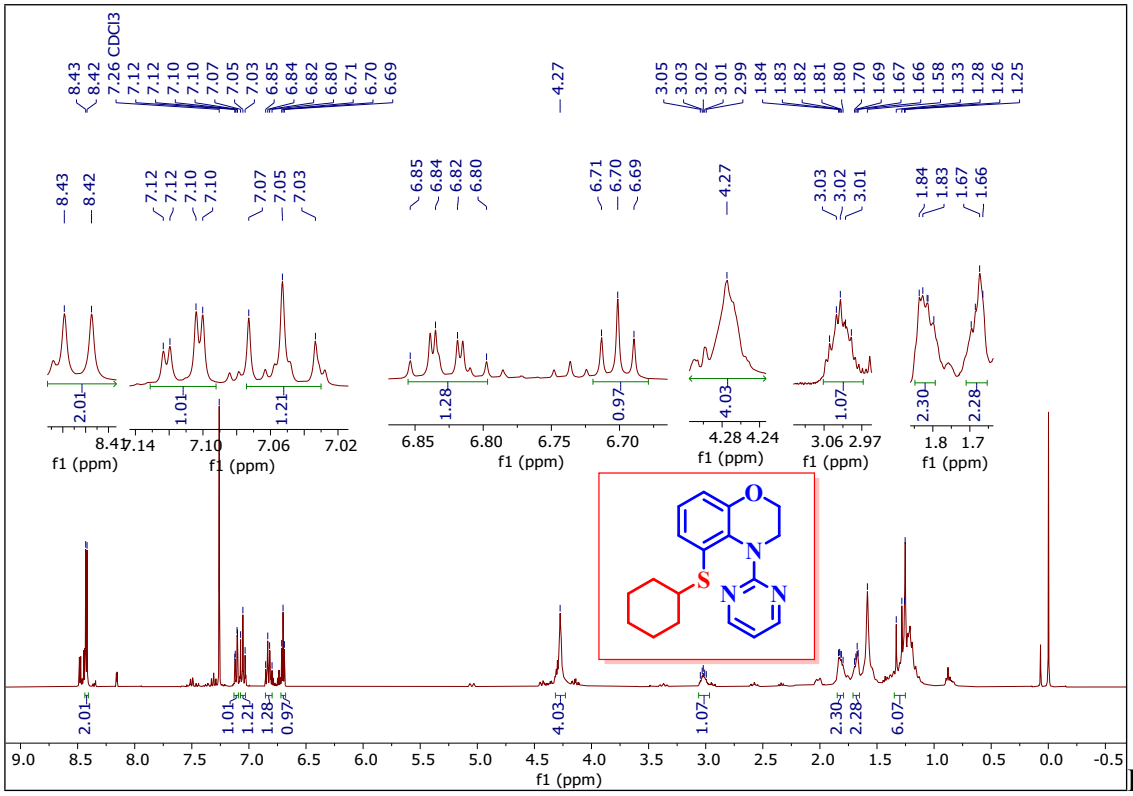


Figure 31: ^{1}H NMR spectrum of compound **3p** ($CDCl_3$, 400 MHz)

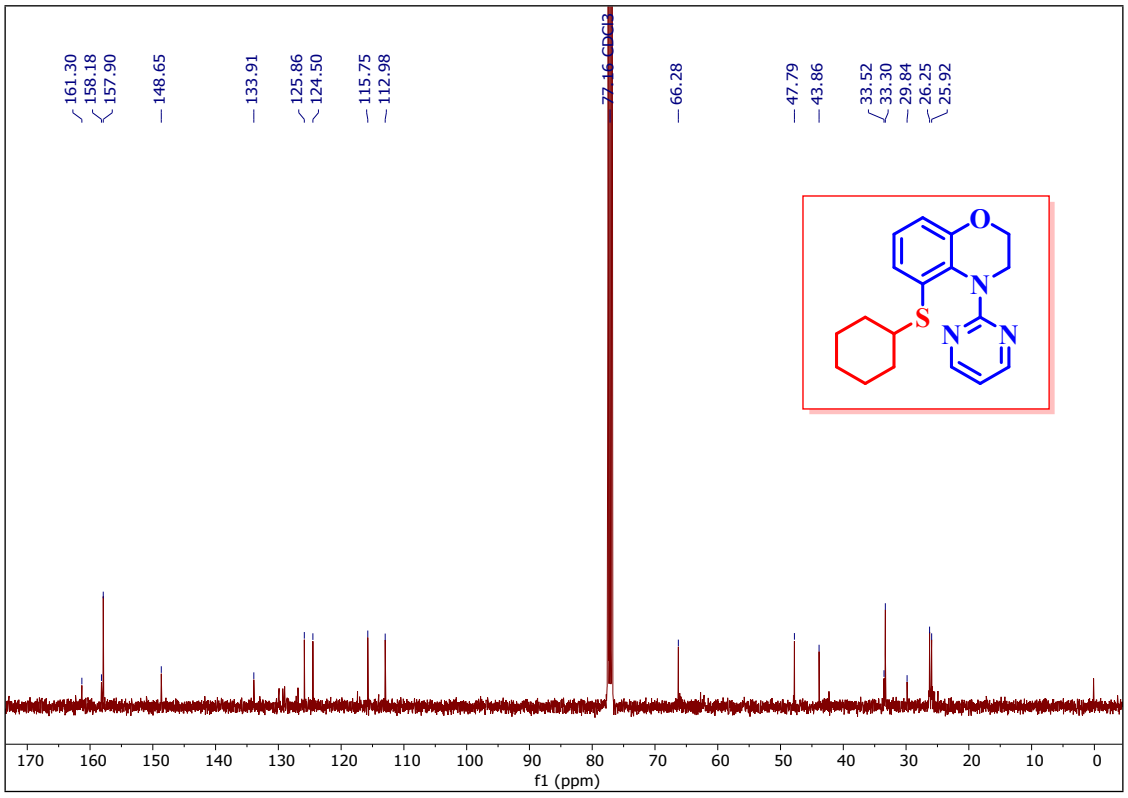
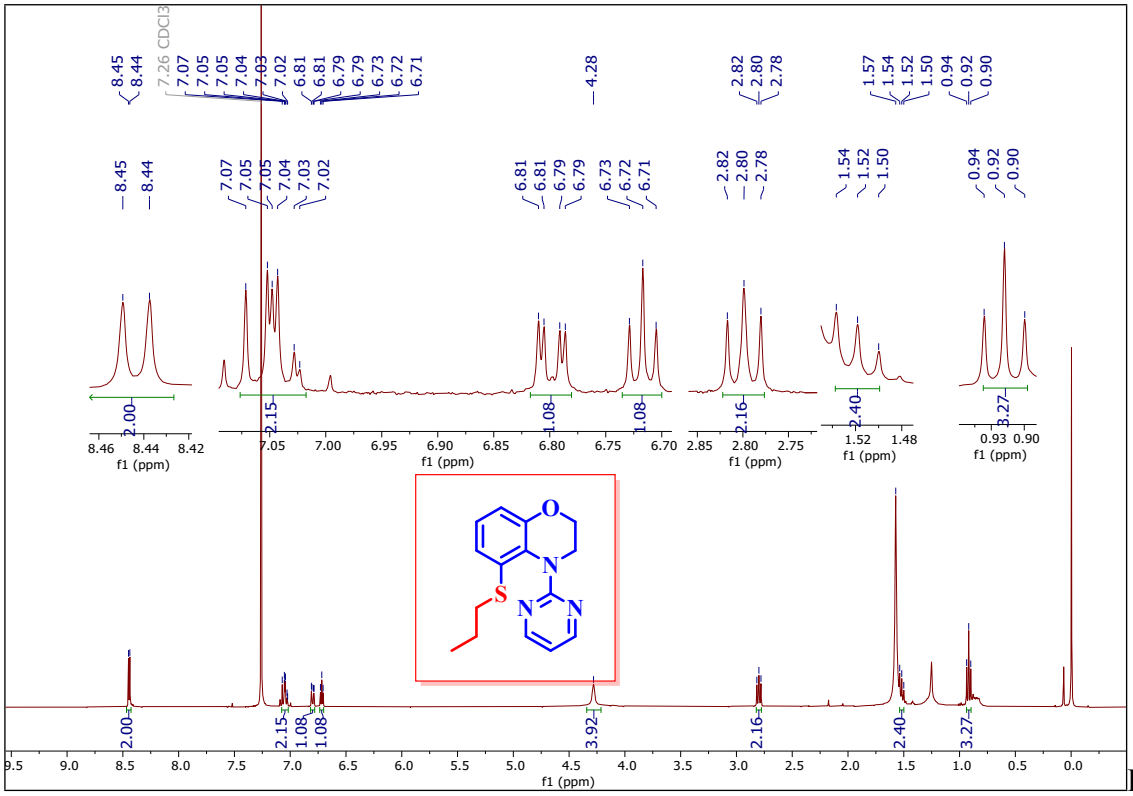
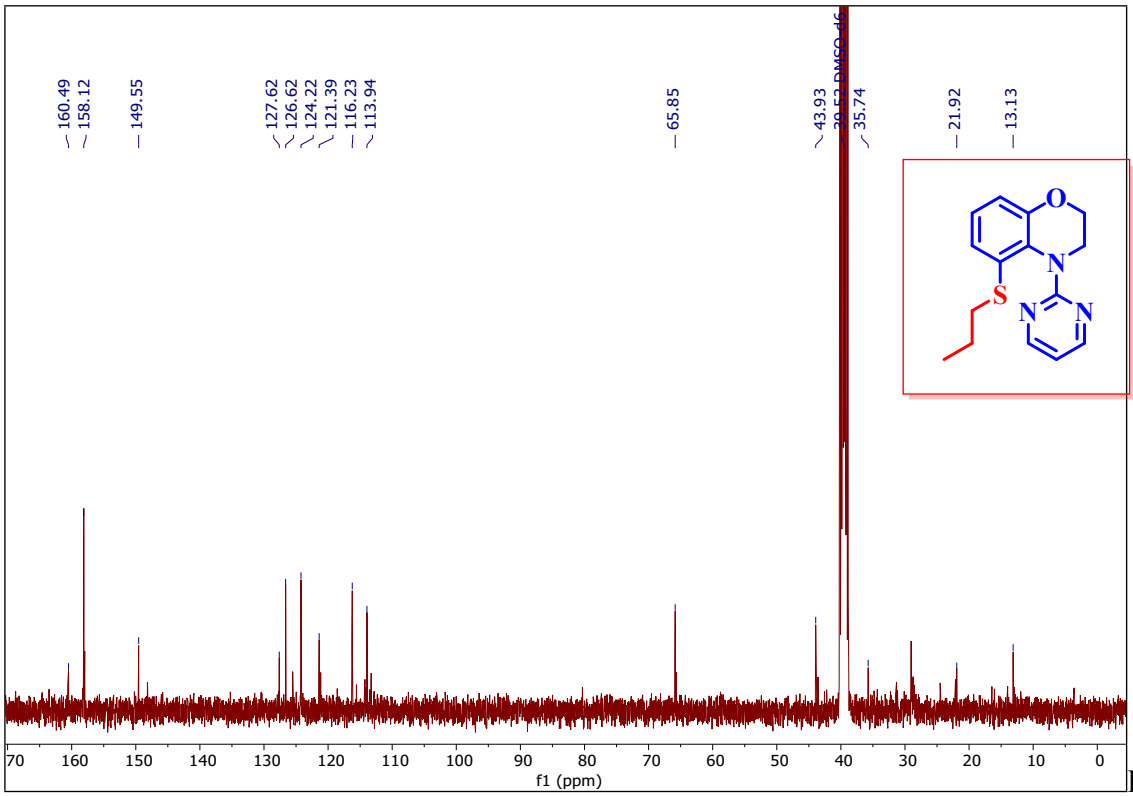


Figure 32: ^{13}C NMR spectrum of compound **3p** ($CDCl_3$, 100 MHz)



Figur e 33: ^{1}H NMR spectrum of compound **3q** ($CDCl_3$, 400 MHz)



Figur e 34: ^{13}C NMR spectrum of compound **3q** (DMSO, 100 MHz)

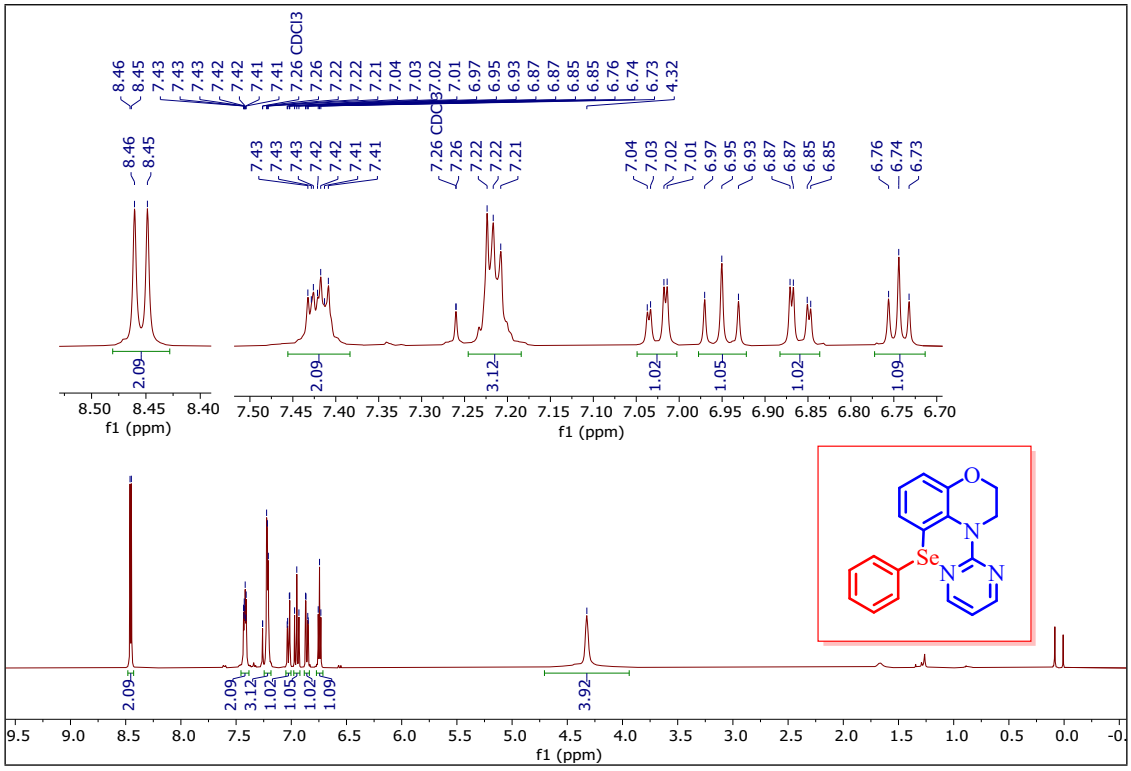


Figure 35: ^{1}H NMR spectrum of compound **5a** ($CDCl_3$, 400 MHz)

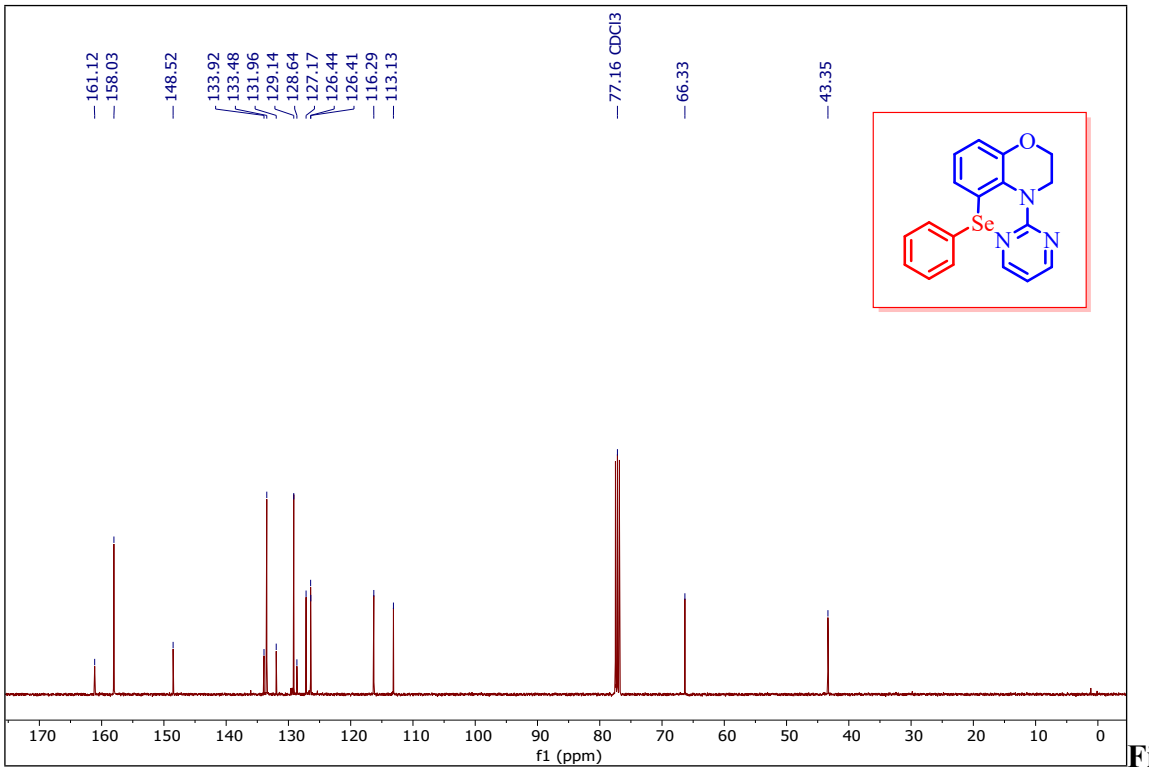
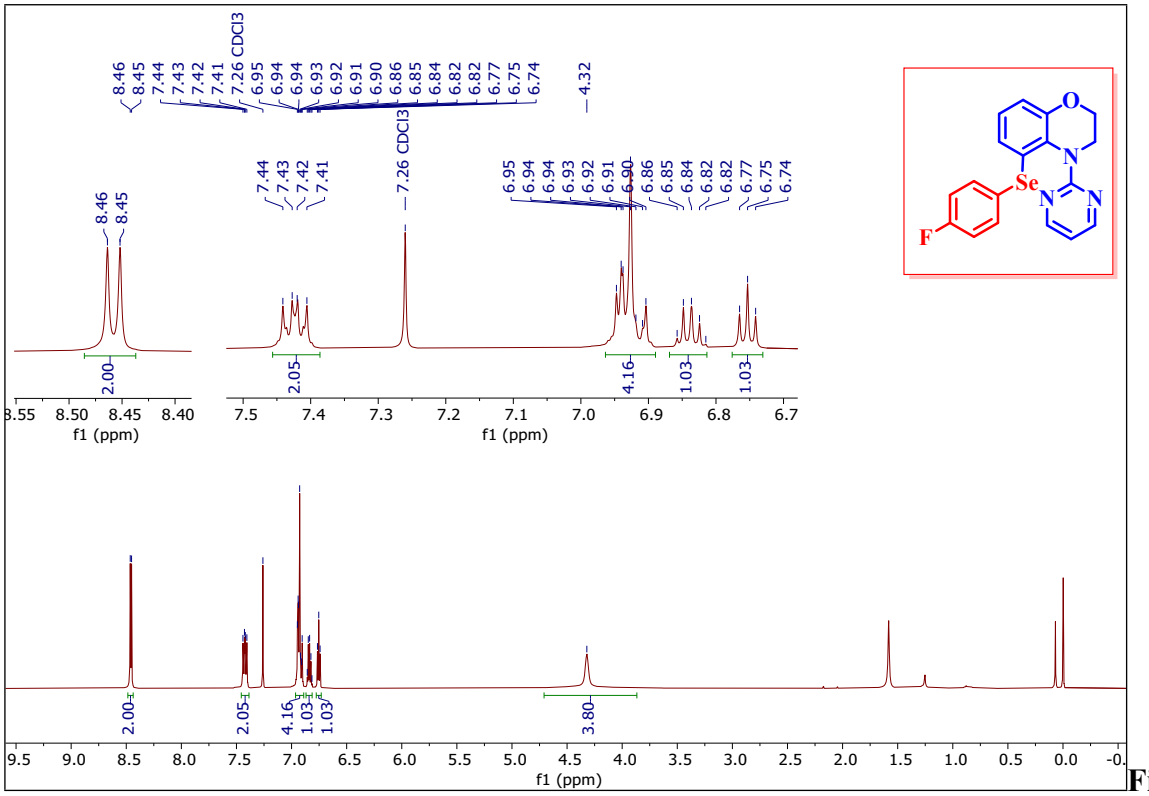
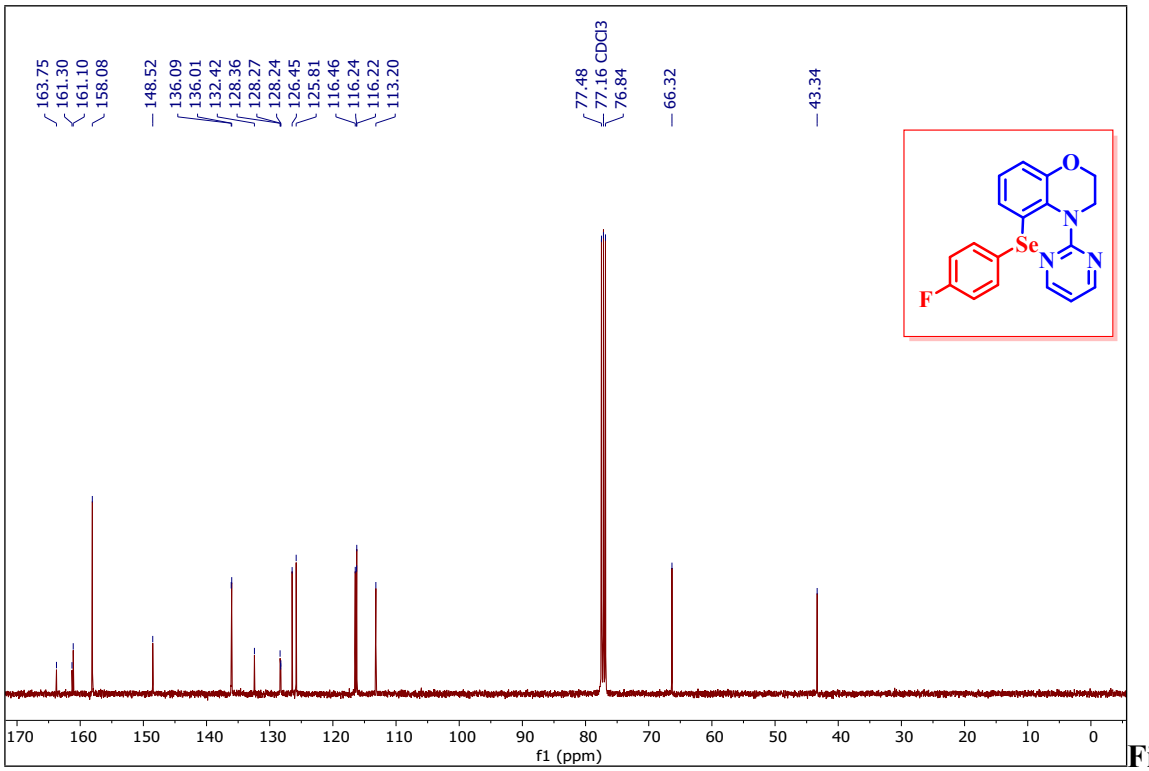


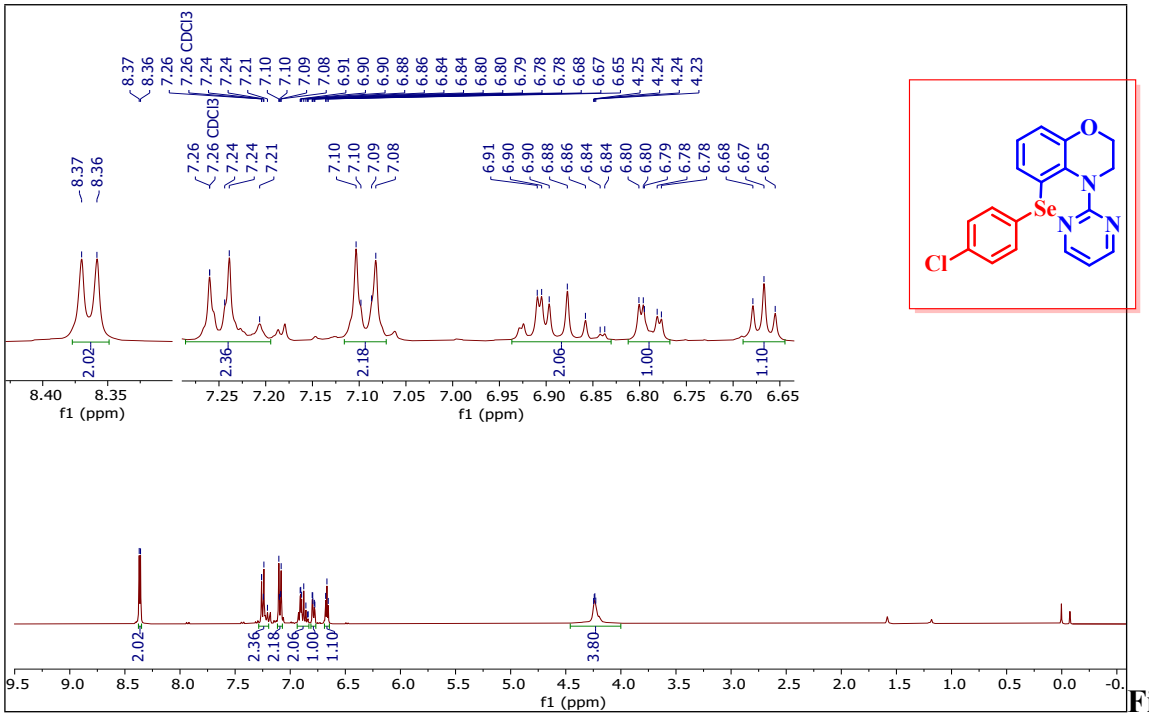
Figure 36: ^{13}C NMR spectrum of compound **5a** ($CDCl_3$, 100 MHz)



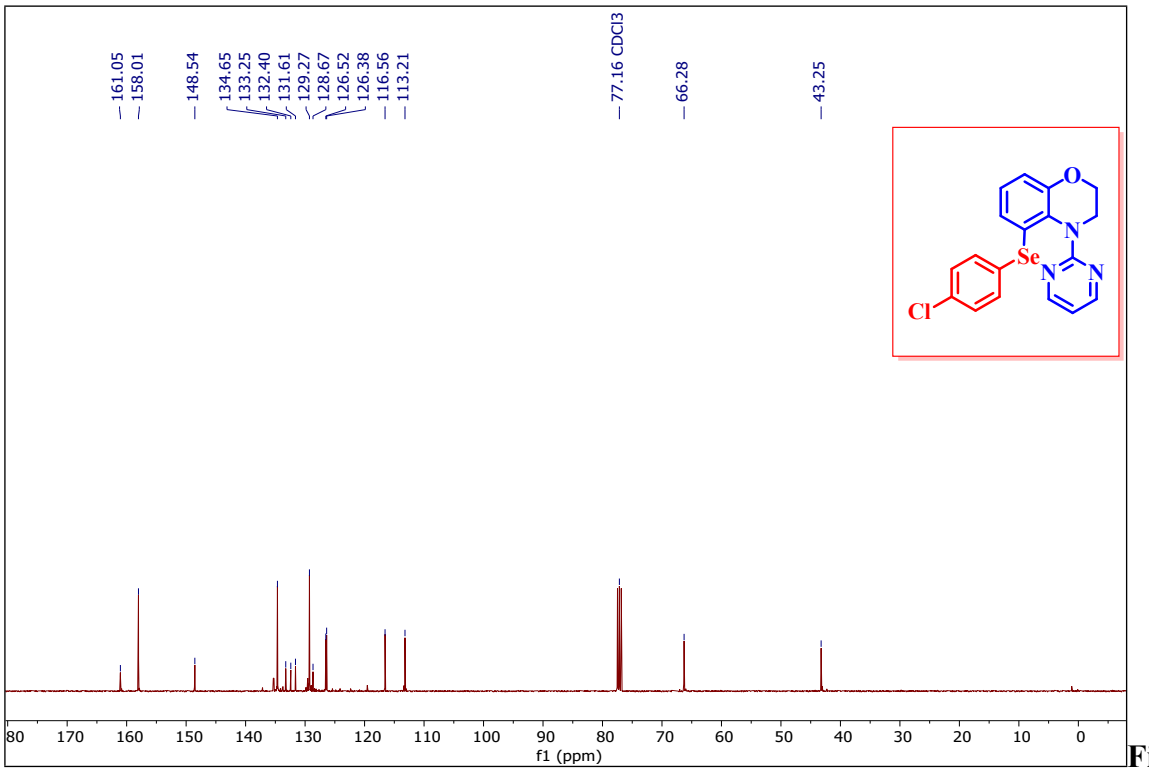
Figur e 37: ^{1}H NMR spectrum of compound **5b** ($CDCl_3$, 400 MHz)



Figur e 38: ^{13}C NMR spectrum of compound **5b** ($CDCl_3$, 100 MHz)



Figur e 39: ^{1}H NMR spectrum of compound **5c** ($CDCl_3$, 400 MHz)



Figur e 40: ^{13}C NMR spectrum of compound **5c** ($CDCl_3$, 100 MHz)

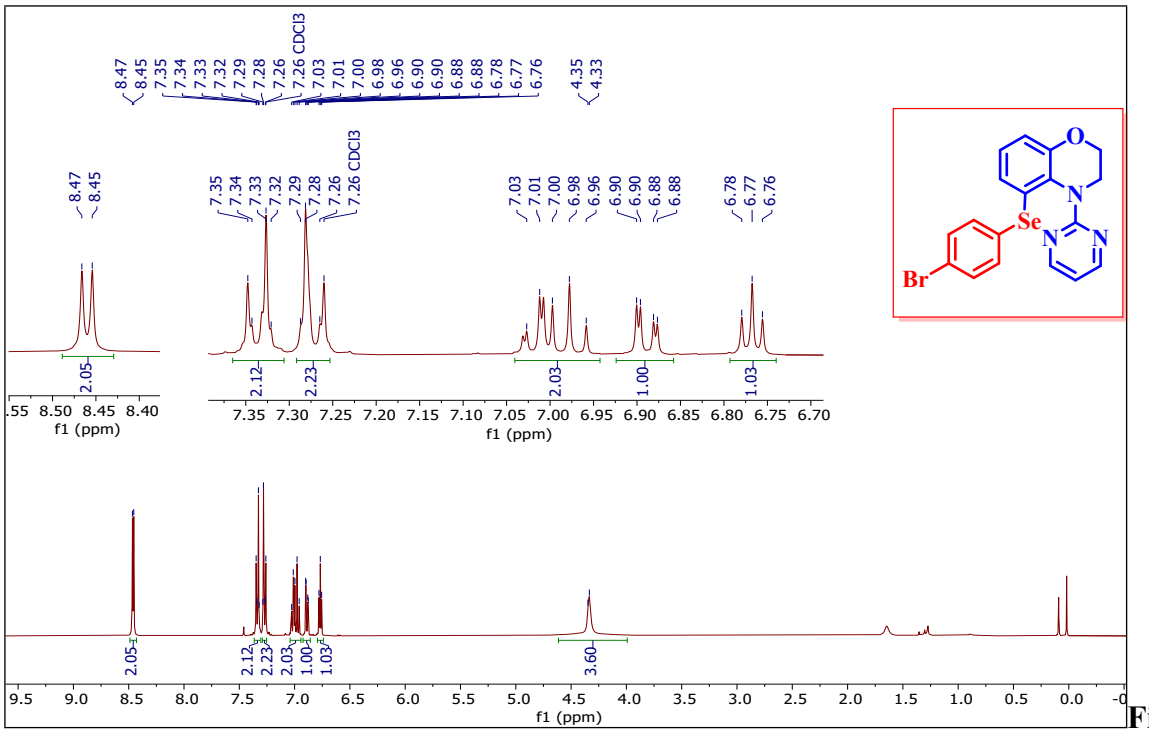


Figure 41: ^{1}H NMR spectrum of compound **5d** ($CDCl_3$, 400 MHz)

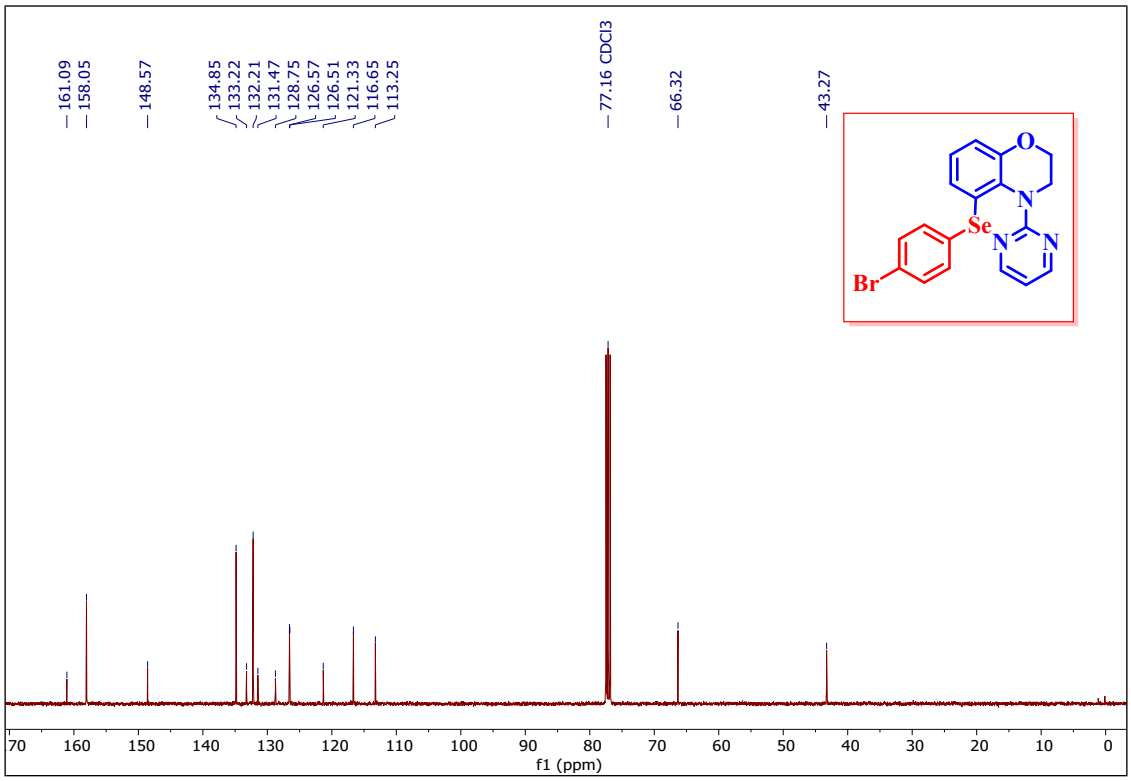
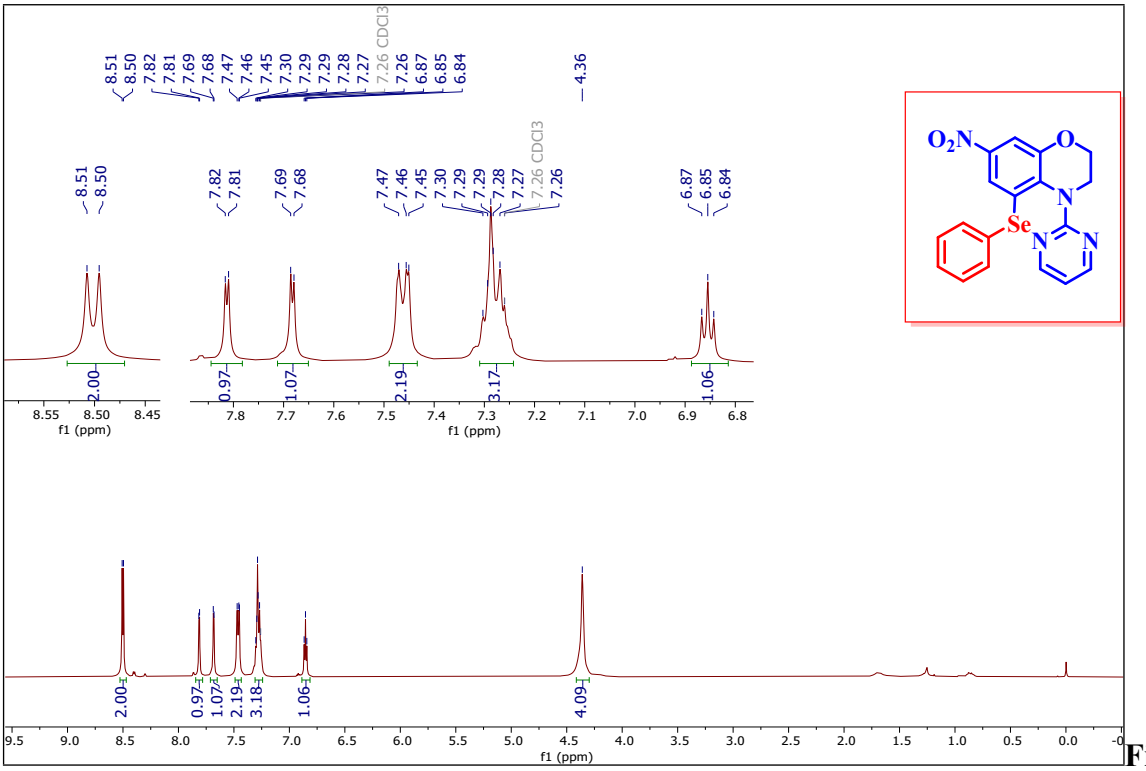
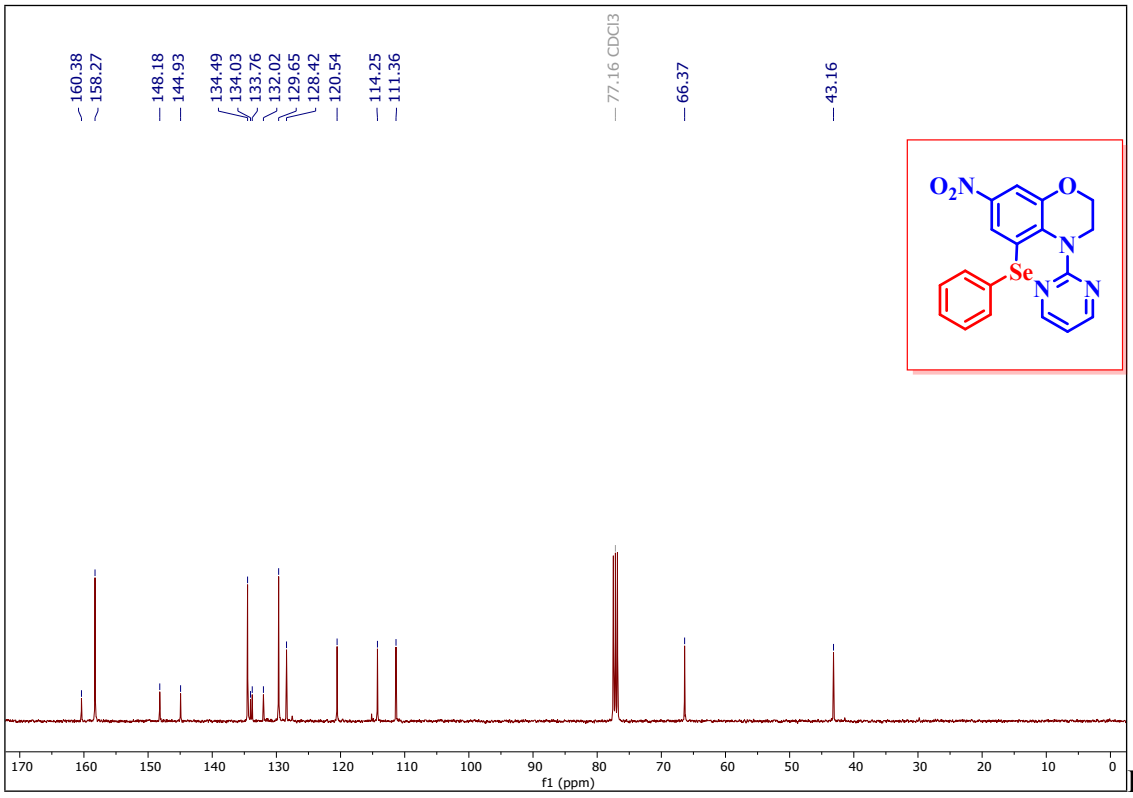


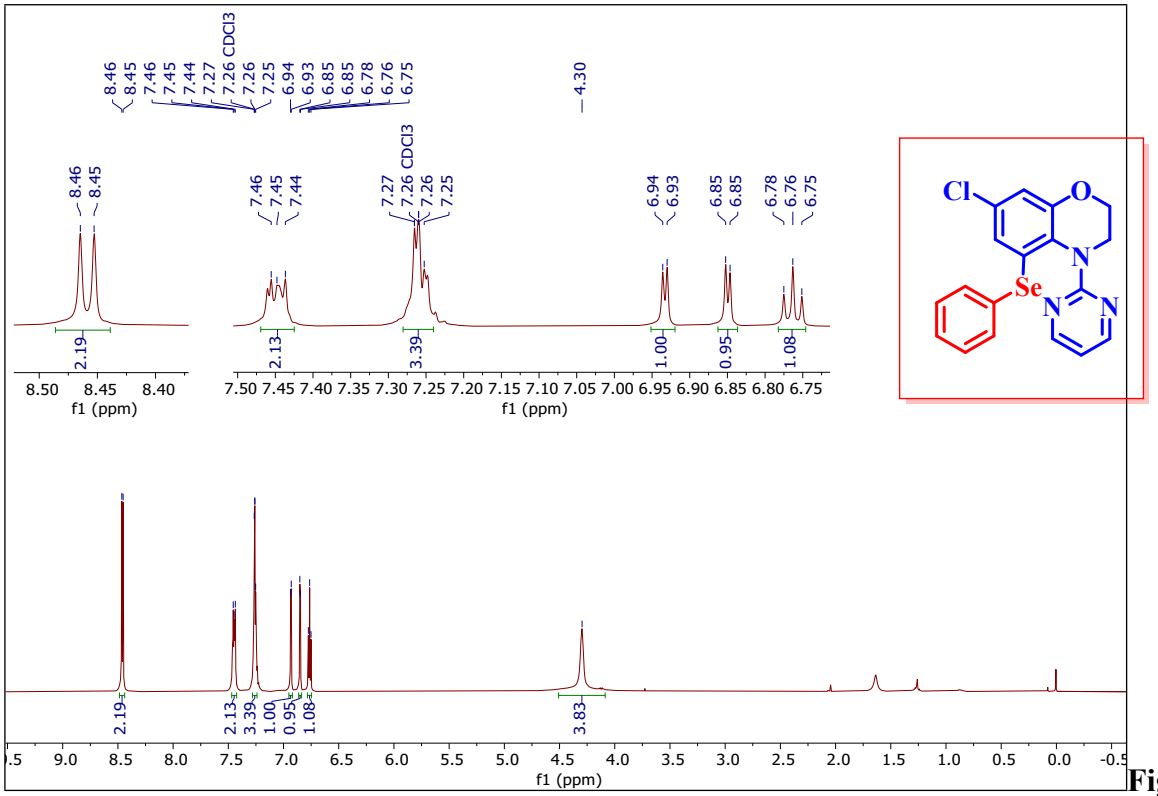
Figure 42: ^{13}C NMR spectrum of compound **5d** ($CDCl_3$, 100 MHz)



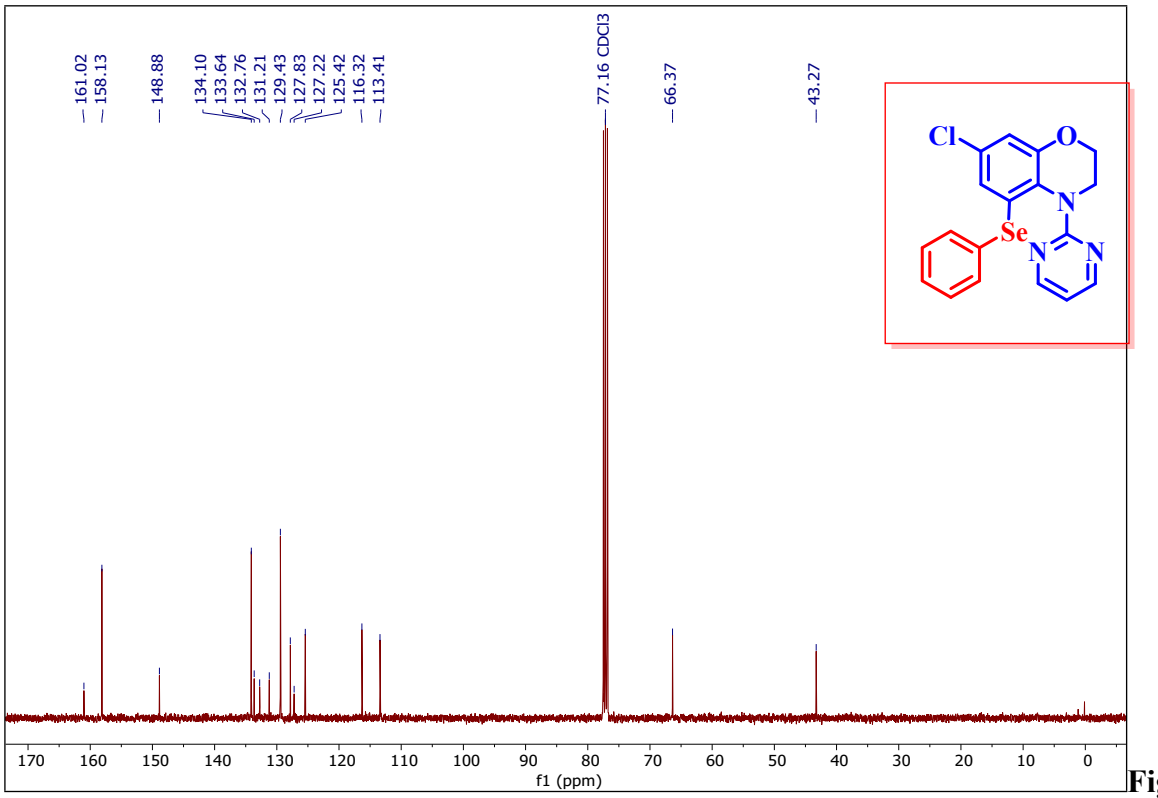
Figur e 43: ^{1}H NMR spectrum of compound **5e** ($CDCl_3$, 400 MHz)



Figur e 44: ^{13}C NMR spectrum of compound **5e** ($CDCl_3$, 100 MHz)



Figur e 45: ^{1}H NMR spectrum of compound **5f** ($CDCl_3$, 400 MHz)



Figur e 46: ^{13}C NMR spectrum of compound **5f** ($CDCl_3$, 100 MHz)

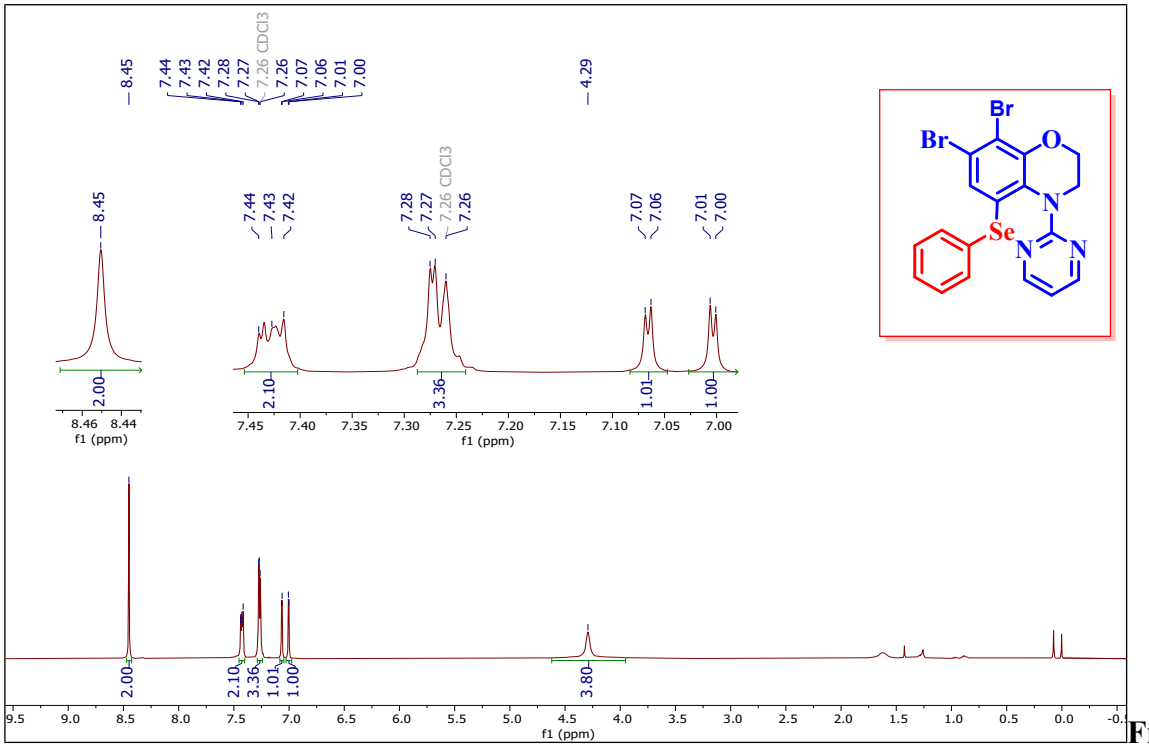


Figure 47: ^{1}H NMR spectrum of compound **5g** ($CDCl_3$, 400 MHz)

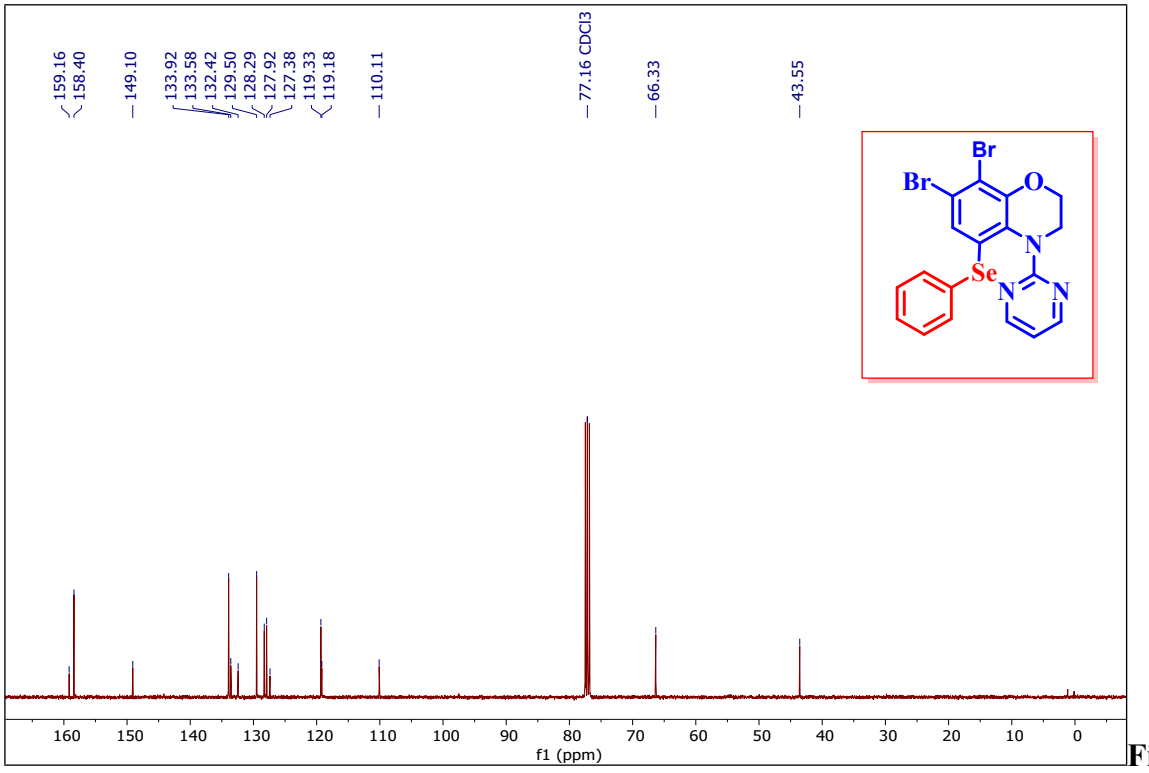


Figure 48: ^{13}C NMR spectrum of compound **5g** ($CDCl_3$, 100 MHz)

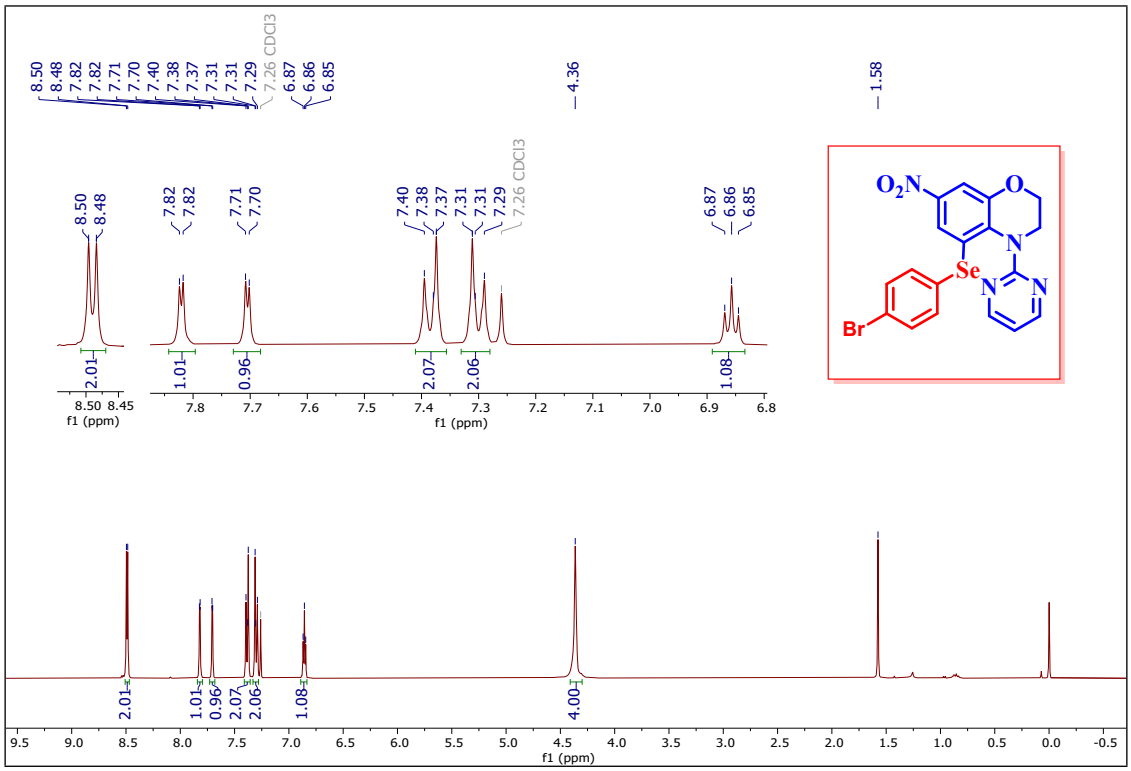


Figure 49: ^{1}H NMR spectrum of compound **5h** ($CDCl_3$, 400 MHz)

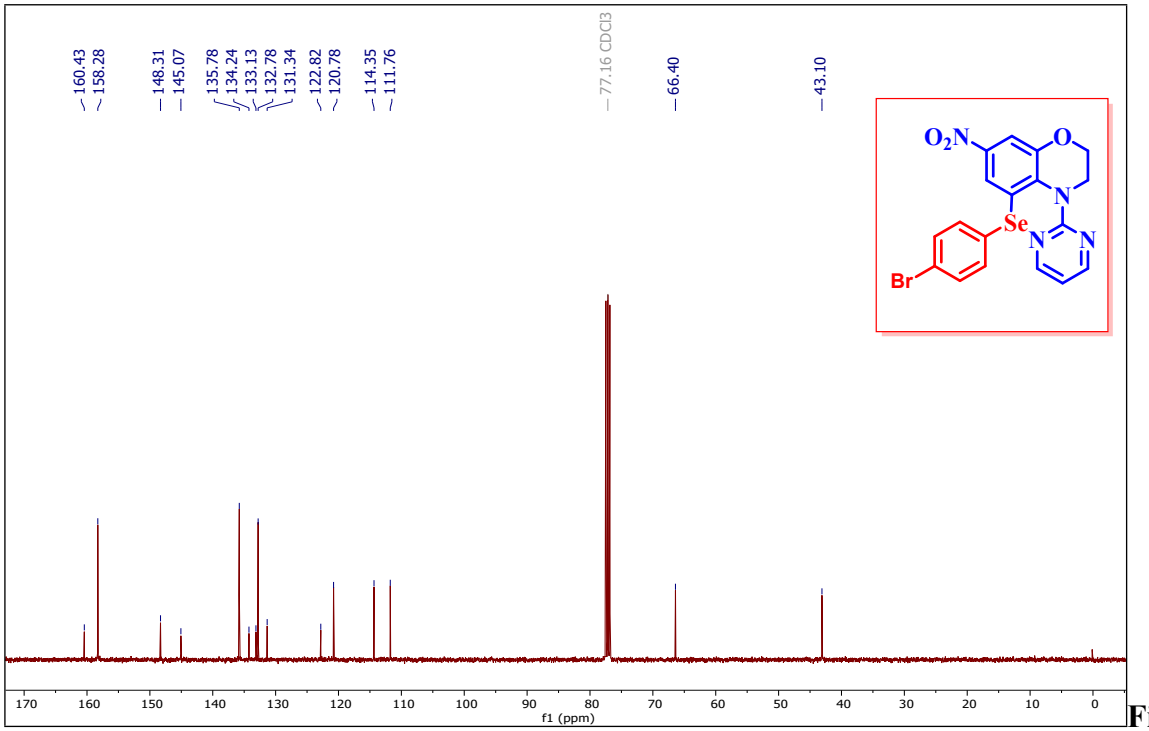
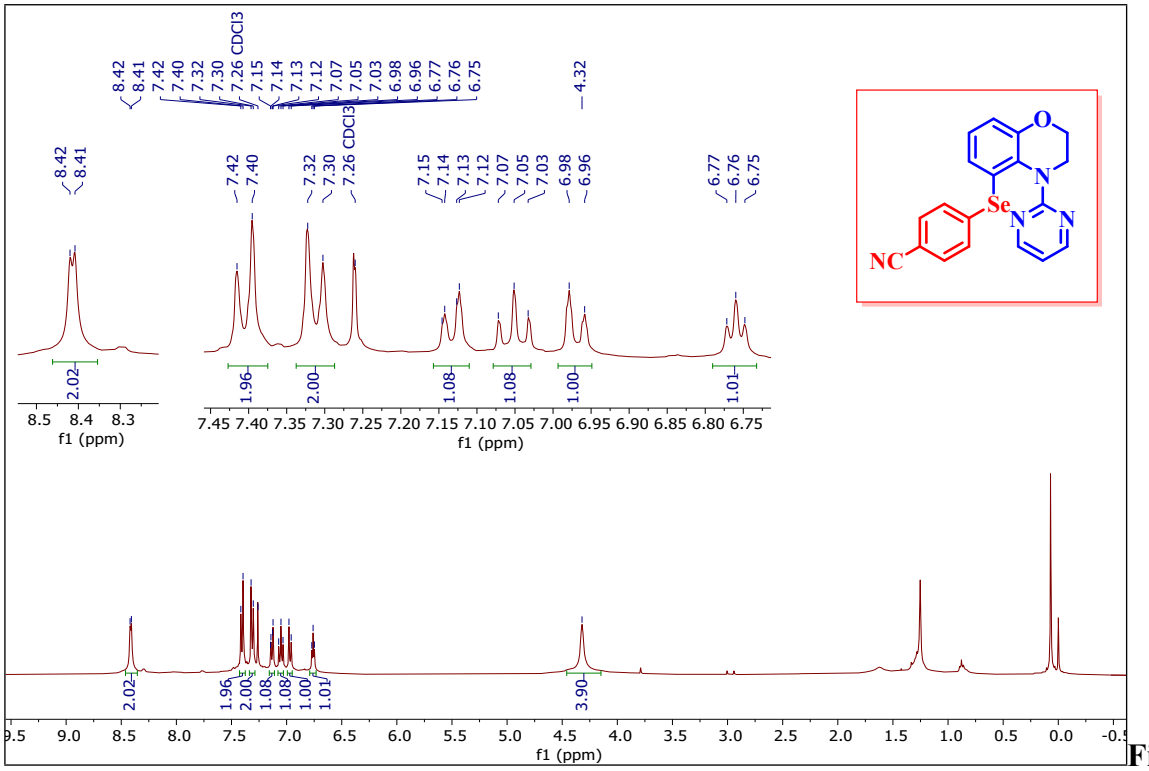
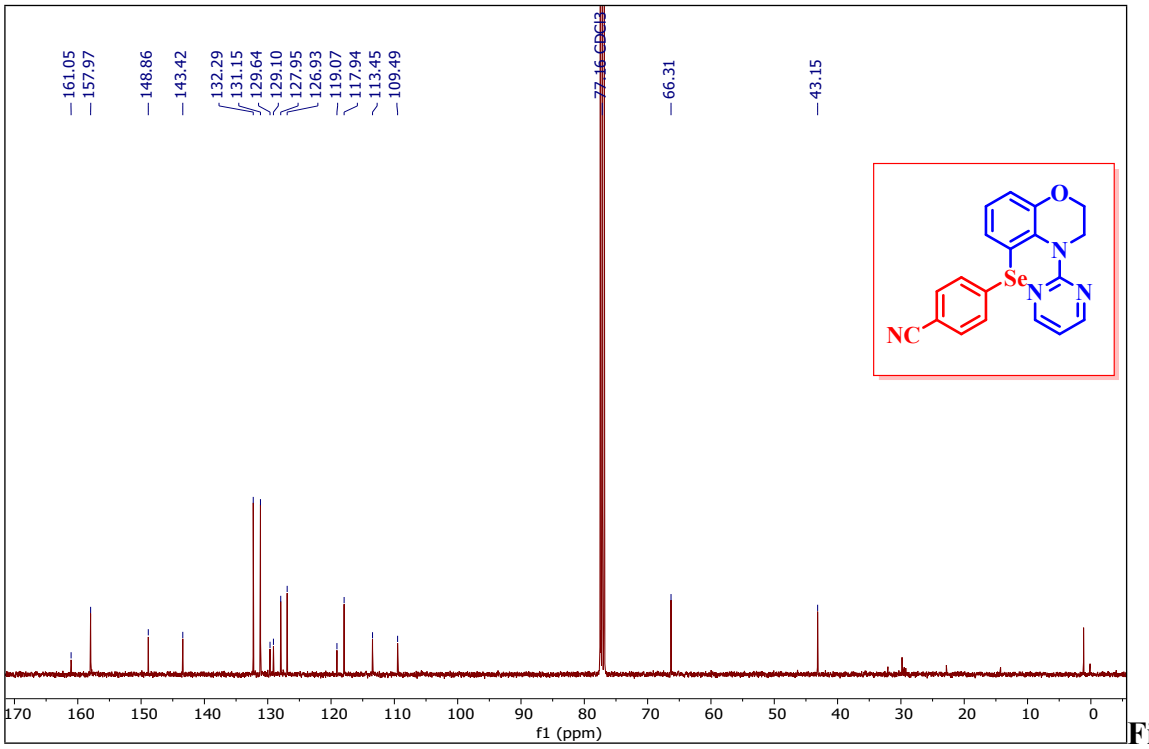


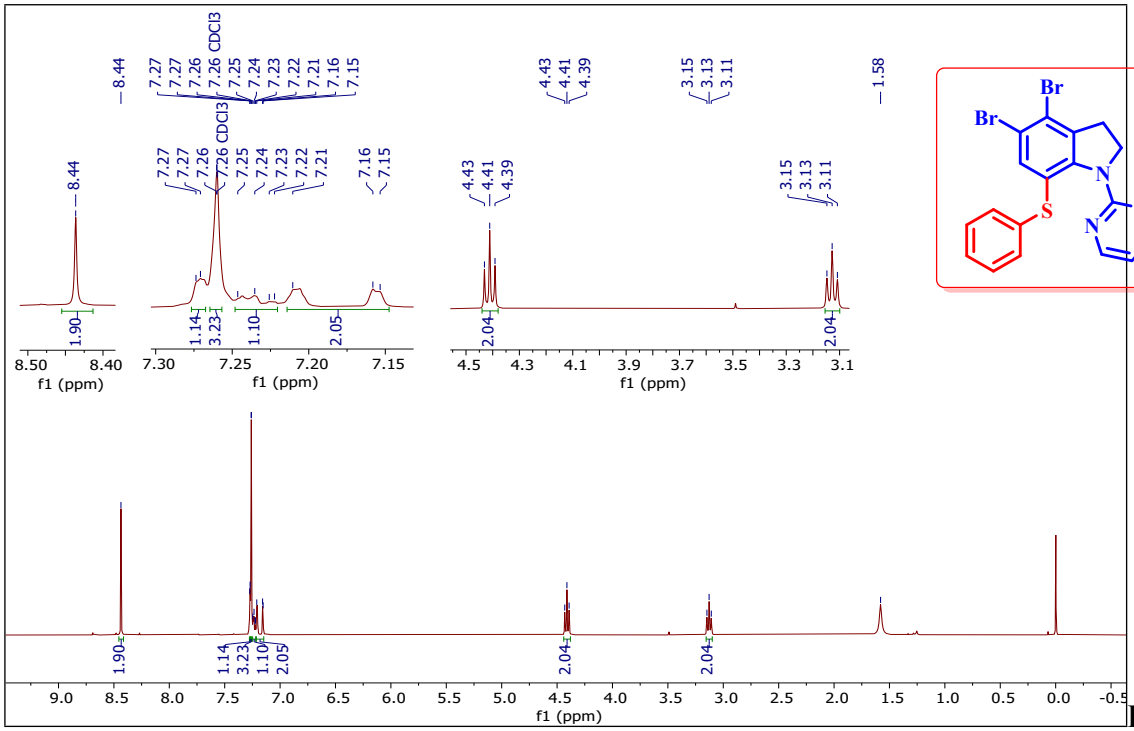
Figure 50: ^{13}C NMR spectrum of compound **5h** ($CDCl_3$, 100 MHz)



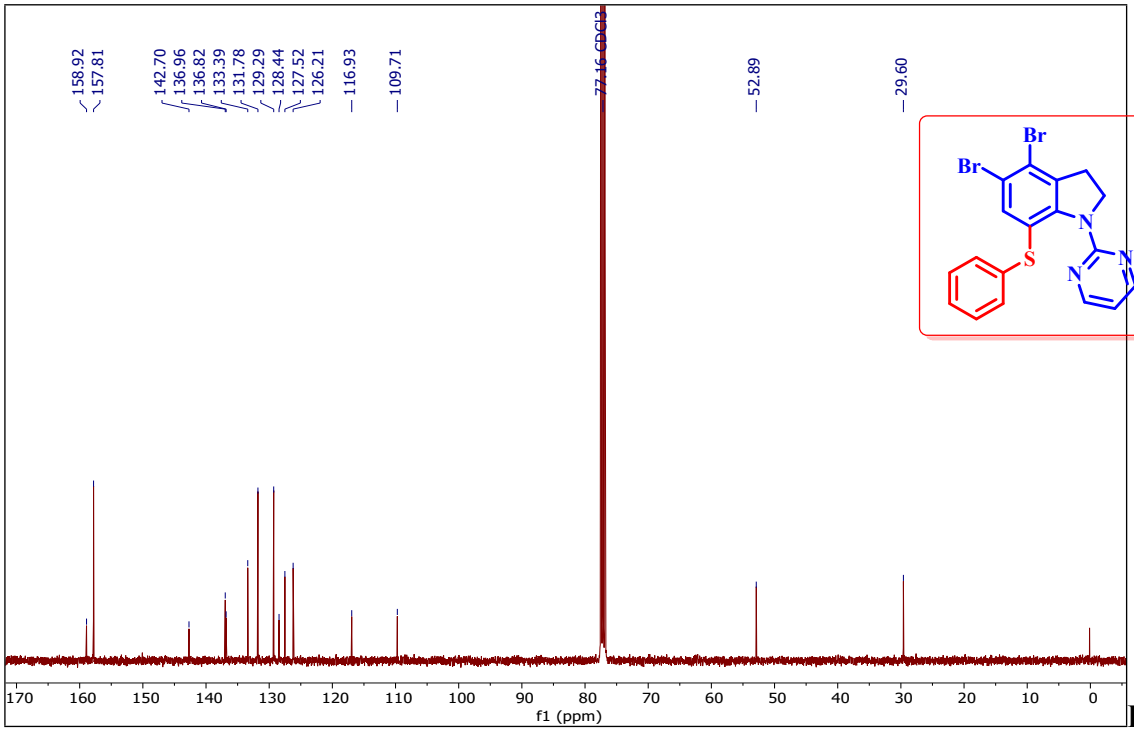
Figur e 51: ^{1}H NMR spectrum of compound compound **6** ($CDCl_3$, 400 MHz)



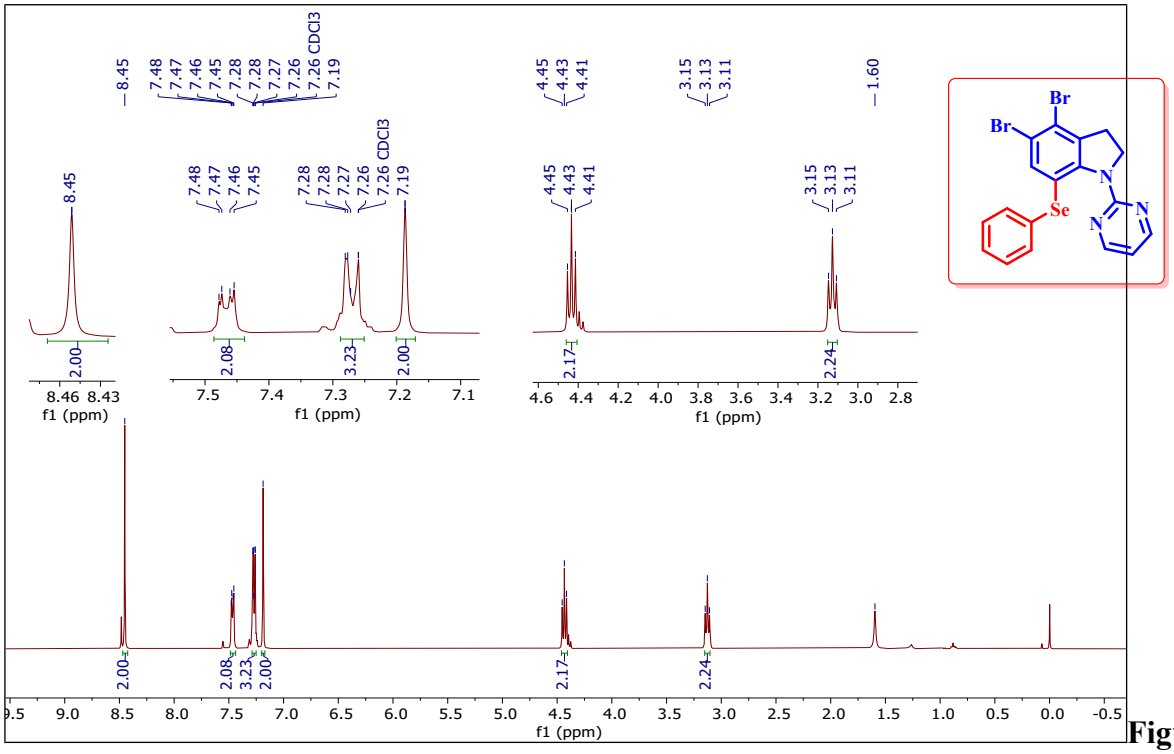
Figur e 52: ^{13}C NMR spectrum of compound compound **6** ($CDCl_3$, 100 MHz)



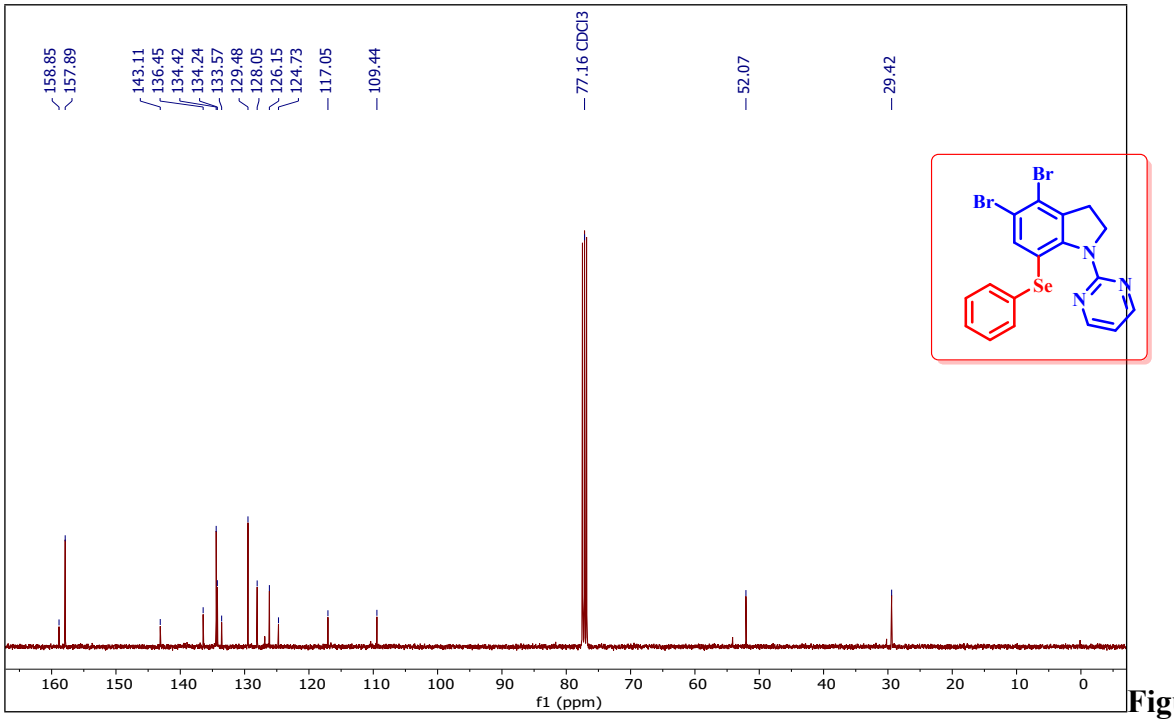
Figur e 53: ^{1}H NMR spectrum of compound **8** ($CDCl_3$, 400 MHz)



Figur e 54: ^{13}C NMR spectrum of compound **8** ($CDCl_3$, 100 MHz)



Figur e 55: ^{1}H NMR spectrum of compound **9** ($CDCl_3$, 400 MHz)



Figur e 56: ^{13}C NMR spectrum of compound **9** ($CDCl_3$, 100 MHz)

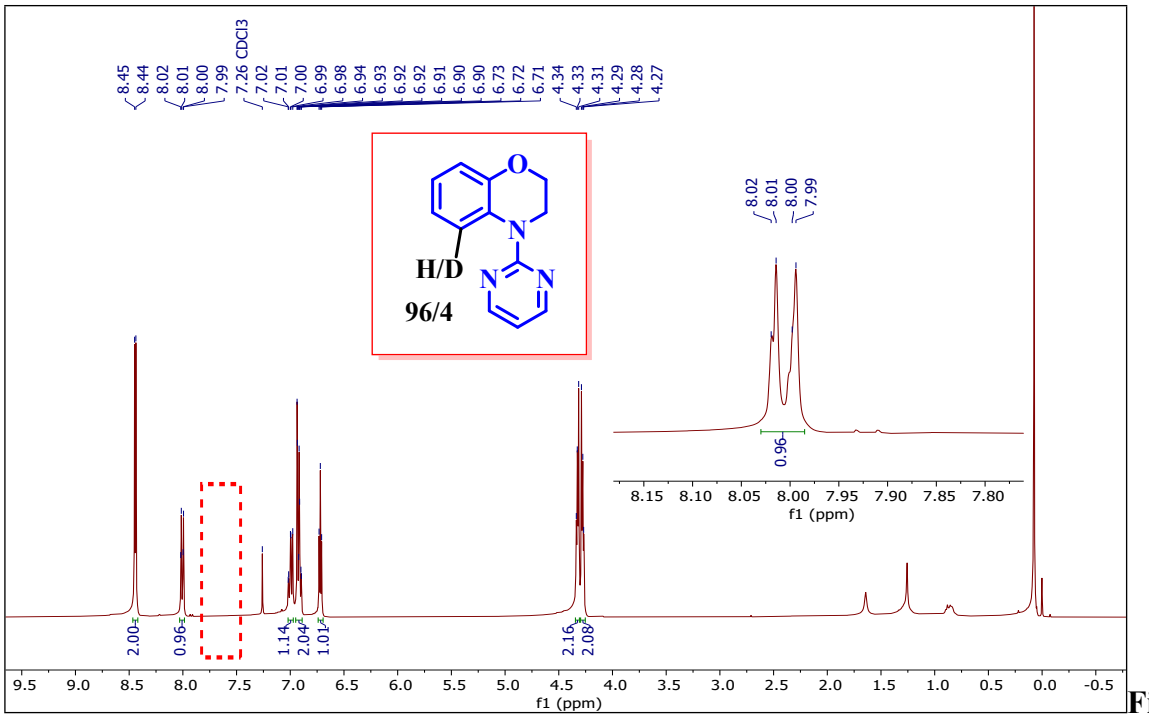


Figure 57: ^{1}H NMR spectrum of compound **1a [D_1]** ($CDCl_3$, 400 MHz) with 4% deuteration

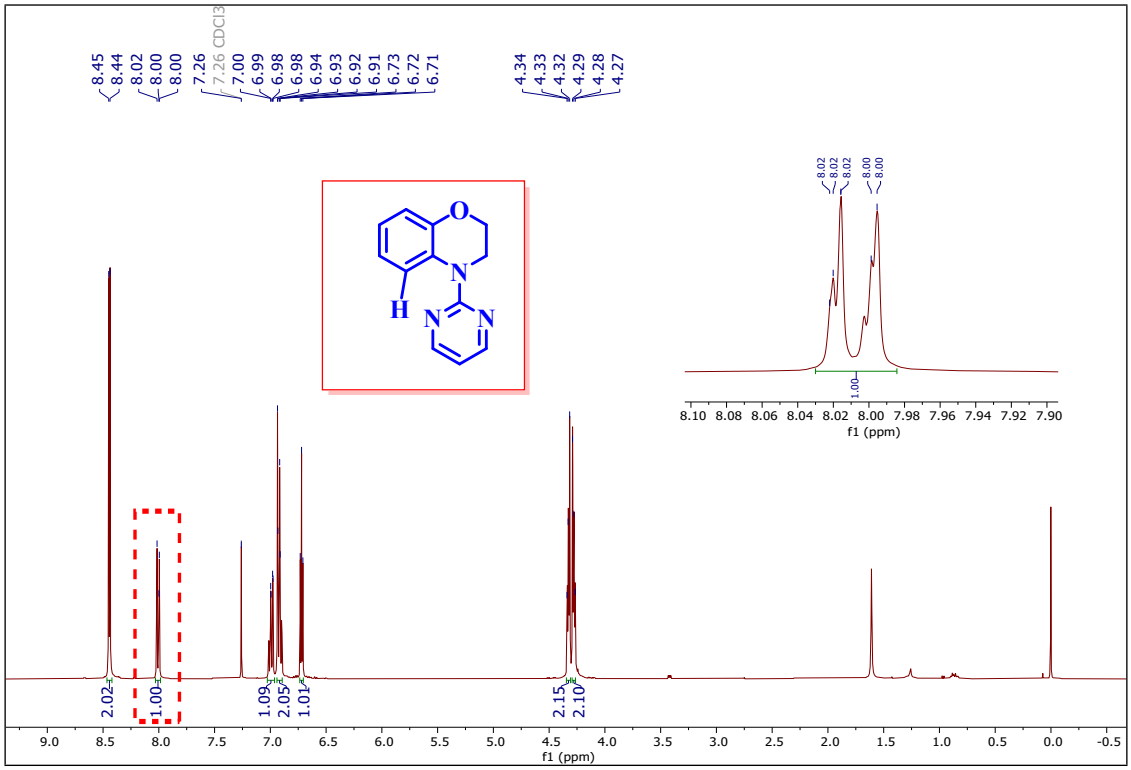


Figure 58: ^{1}H NMR spectrum of compound **1a** ($CDCl_3$, 400 MHz)

5. X-ray Structure of 5h[4, 5, 6]

The single crystals were grown by slow evaporation at room temperature using ethyl acetate for compounds **5h**. The data for X-ray intensity were collected at room temperature (110 K) on Bruker CCD diffractometer and MoKα radiation having wavelength 0.71073 was used. The structures were solved by SHELXL. All the non-hydrogens were refined by full matrix least square on F2 using SHELXL-2019/3. The ORTEP diagrams were generated using Mercury (**Figure 57**). The CCDC number is **2299902** for compound **5h**. The supplementary crystallographic data can be obtained *via* CCDC www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

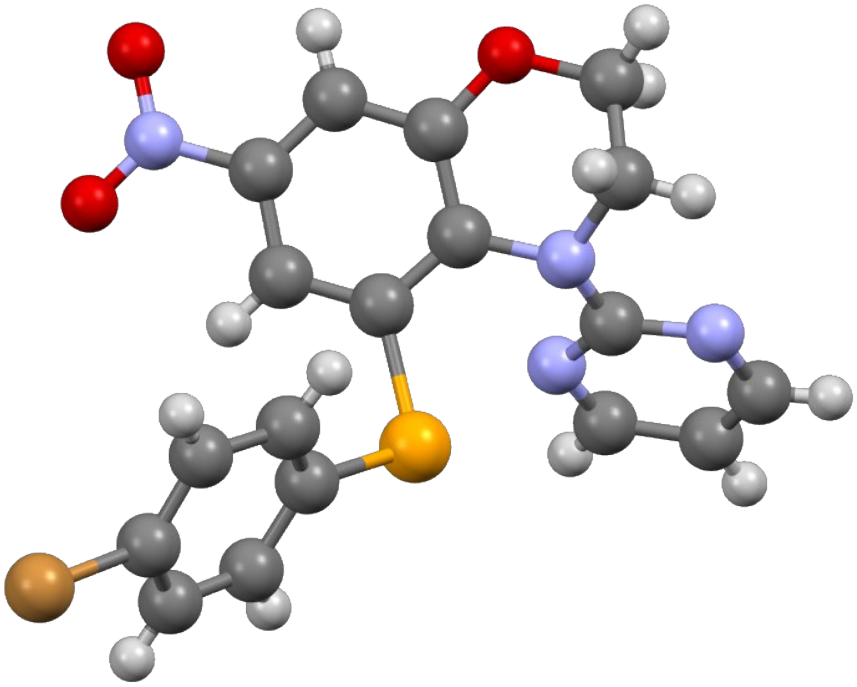


Figure 59. ORTEP diagram of the compound **5h (CCDC 2299902).**

Table 1: Crystal data and structure refinement for **5h, CCDC** 2299902**.**

Identification code	**5h**
Emperical Formula	C_{18} H_{13} Br N_4 O_3 Se
Formula weight	492.19
Temperature	110 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimentions	a/Å = 6.0959(3) Å b/Å = 14.8987(6) Å c/Å = 19.7130(7) Å α/° = 90 β/° = 90 γ/° = 90
volume	1790.35(13) $Å^3$
Z	4
Density (calculated)	1.826 Mg/m3
Absorption coefficient	4.357 mm^{-1}
F(000)	968
Crystal size	0.331 x 0.070 x 0.044 mm^3
Theta ranges	3.389°. to 30.832°.
Reflections collected	11746
Independent Reflections	4337 [R(int) = 0.0442]
Index ranges	-6≤ h≤ 8 -19 ≤ k ≤ 21 -26≤ l≤ 22
Completeness of data	99.5%
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraint/parameters	4337/956/417
Goodness of fit on F^2	1.059
Final R indices [I>2sigma(I)]	R1=0.0710, wR2=0.1816
R indices (all data)	R1=0.0800, wR2=0.1869
Absolute structure parameter	0.52(4)
Largest diff. peak and hole [e $Å^{-3}$]	1.651 and -1.585 e.$Å^{-3}$

6. References

1. (a) M. Gupta, S. Kumar, P. Kumar, A. K. Singh, A., V. Bahadur, & B. K. Singh, *ChemistrySelect*, 2019, **4**, 13992, (b) C. Chen, Y. Pan, H. Zhao, X. Xu, Z. Luo, L.Cao, & L. Xu, *Org. Lett.*, 2018, **20**, 6799.
2. (a) J.H. Chu, S.T. Chen, M. F. Chiang, & M.J. Wu, *Organometallics*, 2015, **34**, 953. (b) E. M. Simmons, & J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2012, **51**, 3066.
3. F. Koelsch, & A. G. Whitney, *J. Org. Chem.*, 1941, **6**, 795.
4. L. J. Farrugia, *J. Appl. Crystallogr.* 1999, **32**, 837.
5. G. M. Sheldrick, *Acta Crystallogr.,* 2015, *C71*, 3.
6. C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler, J. van de Steek, J. *Appl. Crystallogr.* 2006, **39**, 453.