Supporting Information

Synthesis and electrochemical and antioxidant properties of chalcogenocyanateoxadiazole and 5-heteroarylchalcogenomethyl-1H-tetrazole derivatives †

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Materials and Methods

Proton nuclear magnetic resonance spectra (^{1}H NMR) spectra were obtained at 400 MHz in Brucker Avance III HD NMR spectrometer. Spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ) expressed in ppm, multiplicity (s = singlet, d = doublet, m = multiplet), and coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained either at 100 MHz in AVANCE III HD NMR spectrometer. Spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or DMSO-d_6. Samples were diluted in 1:1 (v/v) acetonitrile:water mixture, containing 0.1% of formic acid. Analyses were performed by infusion mode in an ACQUITY^{TM} UPLC system from Waters Corp. (Milford, MA, USA) equipped with sampler manager and quadrupole time of flight (Q-TOF) MS detector. The Xevo G2 Q-TOF mass spectrometer was equipped with an electrospray ionization source (ESI). Detections were performed in positive ion mode and high resolution. Optimized MS conditions were: capillary voltage 2.50 kV, cone voltage 15 V, extractor cone 3.30 V, desolvation gas 300 L/h, cone gas 10 L/h, desolvation temperature 300 °C, and source temperature 150 °C. Acquisition mass range was monitored from 50 to 1000 Da. System control and data acquisition were performed using MassLynx V 4.1 software. Column chromatography was performed using Merck Silica Gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF_{254} (0.25 mm thickness). For visualization, TLC plates were placed under ultraviolet light (254 nm) and then soaked in acidic vanillin, followed by heating. The product yields included in all Tables refer to isolated yields. Cyclic voltametric measurements were performed using an AutoLabgalvanostat/potentiostat PGSTAT 302N Eco Chemie. In all electrochemical studies a three-electrode system was used, consisting of a glassy carbon working electrode, a platinum wire auxiliary electrode and a platinum pseudo-reference electrode (ferrocene was used as internal standard; Fc/Fc^+ couple in acetonitrile; $E_{1/2}$ = 0.403 V). All electrochemical experiments were carried out under an argon atmosphere at room temperature using dry CH_3CN solution of compounds containing 0.1 M tetrabutylammoniumhexafluorophosphate ($TBAPF_6$) as the supporting electrode.

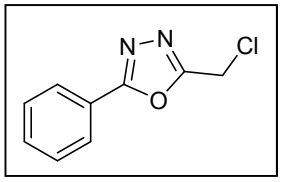
Experimental section

General procedure for the synthesis of 2-aryl-5-(chloromethyl)-1,3,4-oxadiazoles (3a-e)

In a two neck round-bottom flask the appropriate aryl hidrazide **2a-e** (10 mmol) was dissolved in DCM (25 mL). After the base was added, Et_3N (2.0 equiv / 20 mmol) and under stirred the reaction remained for a few minutes, then the temperature system was taken at 0 °C and the choroacetylchloride **1** (1.5 equiv / 15 mmol) was slowly dripped in a flask. The mixture remained at ambient temperature for 4 h approximately, and the intermediate was obtained, without isolation.

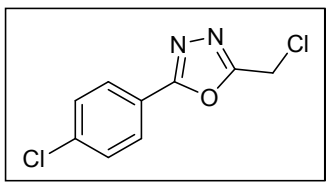
In the same flask, were added triphenylphosphine (1.57 equiv / 15.7 mmol), carbon tetra-chloride (5 equiv / 50 mmol), triethylamine (1.57 equiv / 15.7 mmol), and the mixture was heated to reflux for 12 h. Then the mixture was cooled to room temperature, poured into water (15 mL) and extracted with DCM (3 x 15 mL). Combined organic layers were dried over $MgSO_4$, the solvent evaporated under reduced pressure. The residue was purified on a silica flash column with hexane/ethyl acetate (90:10) as eluent to yield 1,3,4-oxadiazoles **3a-e**.

2-(chloromethyl)-5-phenyl-1,3,4-oxadiazole (3a)



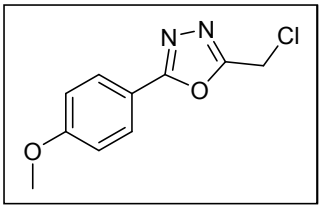
Yield 86%. Light Yellow solid; mp: 108-110 °C (lit.[1] 118°C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.04 (d, J = 6.8 Hz, 2H), 7.45-7.55 (m, 3H), 4.77 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 162.1, 132.0, 129.0, 126.9, 123.2, 32.9. MS (EI): *m/z* (%) = 194 [M^+] (22), 159 (22), 105 (95), 89 (24), 77 (100), 63 (23), 51 (34).

2-(chloromethyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (3b)



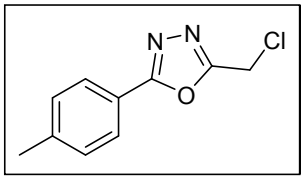
Yield 82%. Pale Yellow solid; mp: 80-81 °C (lit.[2] 80.5 – 81°C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.98 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 4.78 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.1, 162.2, 138.4, 129.4, 128.2, 121.7, 32.9. MS (EI): *m/z* (%) = 228 [M^+] (19), 193 (22), 139 (100), 111 (59), 75 (65) 50 (25).

2-(chloromethyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (3c)



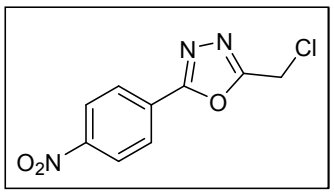
Yield 73%. Pale Yellow solid; mp: 86-88 °C (lit.[1] 88.5 – 90°C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.99 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 4.76 (s, 2H), 3.88 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.9, 162.7, 161.6, 128.9, 115.8, 114.6, 55.4, 33.0. MS (EI): *m/z* (%) = 224 [M^+•, Cl_{35}] (27), 226 [M^+•, Cl_{37}] (9)189 (27), 135 (100), 133 (27), 77 (27).

2-(chloromethyl)-5-(*p*-tolyl)-1,3,4-oxadiazole (3d)



Yeld 87%. Pale Yellow solid; mp: 115-117 °C (lit.[3] 119 – 121°C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.96 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.78 (s, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.1, 161.8, 142.8, 129.8, 127.0, 120.5, 33.0, 21.6. MS (EI): *m/z* (%) = 208 [M^+] (29), 173 (24), 119 (100), 91 (53), 89 (20), 77 (19), 65 (23).

2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (3e)



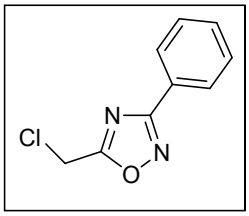
Yield 67%. Pale Yellow solid; mp: 125-127 °C (lit.[3] 134 – 135°C).^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.38 (d, J = 9.1 Hz, 2H), 8.27 (d, J = 9.1 Hz, 2H), 4.81 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.3, 163.3, 150.0, 128.7, 128.1, 124.5, 32.8. MS (EI): *m/z* (%) = 239 [M^+] (87), 204 (59), 190 (28), 150 (100), 120 (23), 104 (48), 90 (26), 76 (62), 69 (38), 57 (31), 43 (46).

General procedure for the synthesis of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (5a).

In a two neck round-bottom flask the appropriate benzamidoxime **4a** (5 mmol) was dissolved in DCM (25 mL). After the base was added, Et_3N (1.2 equiv / 6 mmol) and under stirred the reaction remained for a few minutes, then the temperature system was taken at 0 °C and the choroacetylchloride **1** (1.5 equiv / 7.5 mmol) was slowly dripped in a flask. The mixture remained at ambient temperature for 6 h approximately, the solvent was removed under reduced pressure and the intermediate was obtained, without isolation.

In the same flask, were added toluene (10 mL) and the mixture was heated to reflux for 12 h. Then the mixture was cooled to room temperature, poured into water (15 mL) and extracted with DCM (3 x 15 mL). Combined organic layers were dried over $MgSO_4$, the solvent evaporated under reduced pressure. The residue was purified on a silica flash column with hexane/ethyl acetate (95:5) as eluent to yield 1,2,4-oxadiazole **5a**.

5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (5a)

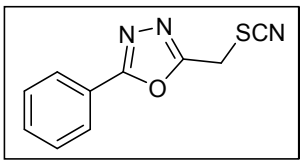


Yield 99%. White solid; mp: 38-39 °C (lit.[4] 39 – 40 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07 (d, J = 6.3 Hz, 2H), 7.44-7.51 (m, 3H), 4.72 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.3, 168.8, 131.5, 129.0, 127.5, 126.2, 33.3. MS (EI): *m/z* (%) = 194 [M^+] (39), 119 (100), 91 (28), 77 (13), 64 (14), 51 (11).

General procedure for the synthesis of 2-aryl-5-(chalcogenocyanatomethyl)-1,3,4-oxadiazole (7aa-eb) and 3-phenyl-5-(chalcogenocyanatomethyl)-1,2,4-oxadiazole (8aa-ab).

A mixture of 2-aryl-5-(chloromethyl)-1,3,4-oxadiazoles **(3a-e)** or 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **(4a)** (1.0 mmol), TBAB (0.5 equiv), KSCN **(6a)** or KSeCN **(6b)** (1.5 equiv) in MeCN (8 mL) was placed in a flask and stirred at heated (82 °C) for the 4 h. On completion of the reaction, followed by TLC examination, the mixture allowed to be cold and the MeCN was removed under reduced pressure, water (15 mL) was poured about crude and extracted with DCM (3 x 15 mL). Combined organic layers were dried over $MgSO_4$, the solvent evaporated under reduced pressure. The residue was purified on a silica flash column with hexane/ethyl acetate (75:25) as eluent to yield thiocyanatomethyl and selenocyanatomethyloxadiazoles (**7** and **8**).

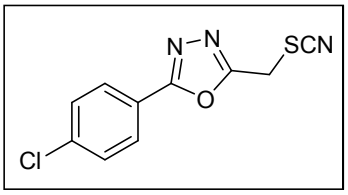
2-phenyl-5-(thiocyanatomethyl)-1,3,4-oxadiazole (7aa)



Yield 87%. Yellow solid; mp: 149-151 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.10 (d, J = 6.7 Hz, 2H), 7.50-7.60 (m, 3H), 4.45 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.3, 160.8,

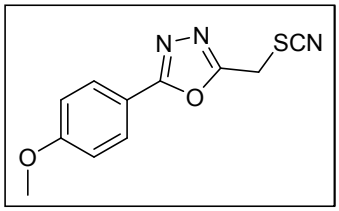
132.3, 129.2, 127.1, 123.1, 109.7, 27.0. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_7N_3OS$ $[M + H]^+$: 218.0388, Found: 218.0379.

2-(4-chlorophenyl)-5-(thiocyanatomethyl)-1,3,4-oxadiazole (7ba)



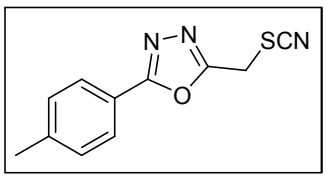
Yield 89%. White solid; mp: 122-123 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.01 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 4.45 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.4, 161.0, 138.8, 129.6, 128.4, 121.5, 109.6, 26.9. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_6ClN_3OS$ $[M + H]^+$: 251.9998, Found: 252.0006.

2-(4-methoxyphenyl)-5-(thiocyanatomethyl)-1,3,4-oxadiazole (7ca)



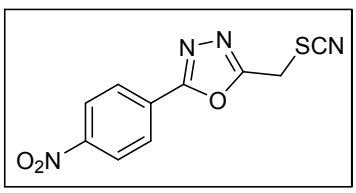
Yield 90%. White solid; mp: 101-102 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.03 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 4.43 (s, 2H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.2, 162.9, 160.2, 129.0, 115.5, 114.7, 109.7, 55.5, 27.0. HRMS-ESI(+) *m/z* Calculated for $C_{11}H_9N_3O_2S$ $[M + Na]^+$: 270.0313, Found: 270.0305.

2-(thiocyanatomethyl)-5-(*p*-tolyl)-1,3,4-oxadiazole (7da)



Yield 92%. White solid; mp: 149-151 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.97 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.44 (s, 2H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.4, 160.5, 134.0, 129.9, 127.1, 120.3, 109.7, 27.0, 21.6. HRMS-ESI(+) *m/z* Calculated for $C_{11}H_9N_3OS$ $[M + Na]^+$: 254.0364, Found: 254.0364.

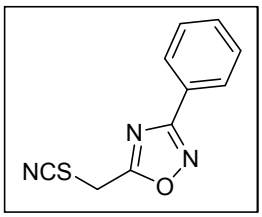
2-(4-nitrophenyl)-5-(thiocyanatomethyl)-1,3,4-oxadiazole (7ea)



Yield 83%. Light yellow solid; mp: 119-121 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.42 (d, J = 9.1 Hz, 2H), 8.22 (d, J = 9.1 Hz, 2H), 4.83 (s, 2H).^{13}C NMR (DMSO-d_6, 100 MHz): δ = 164.1, 164.0, 149.9, 128.9, 128.5, 125.2,

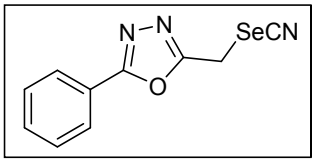
112.5, 26.9. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_6N_4O_3S$ $[M + H]^+$: 263.0239, Found: 263.0245.

3-phenyl-5-(thiocyanatomethyl)-1,2,4-oxadiazole (8aa)



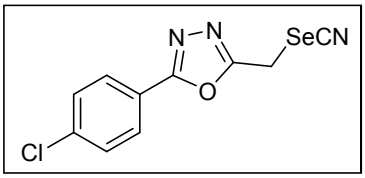
Yield 92%. Yellow solid; mp: 120-122 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11 (d, J = 7.9 Hz, 2H), 7.49-7.55 (m, 3H), 4.40 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.0, 169.1, 131.7, 129.0, 127.6, 126.0, 109.4, 27.4. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_7N_3OS$ $[M + H]^+$: 218.0388, Found: 218.0395.

2-phenyl-5-(selenocyanatomethyl)-1,3,4-oxadiazole (7ab)



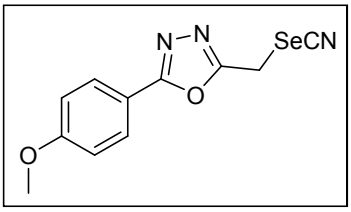
Yield 89%. Red solid; mp: 149-151 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.00 (d, J = 6.2 Hz, 2H), 7.60-7.70 (m, 3H), 4.60 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.2, 164.5, 132.6, 130.0, 127.0, 123.7, 104.3, 19.9. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_7N_3OSe$ $[M + Na]^+$: 287.9652; Found: 287.9658.

2-(4-chlorophenyl)-5-(selenocyanatomethyl)-1,3,4-oxadiazole (7bb)



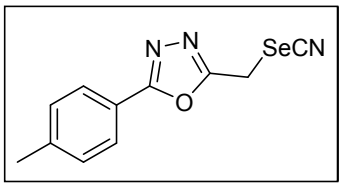
Yield 90%. Brown solid; mp: 168-170 °C.^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.99 (d, J = 8.4 Hz,2H), 7.49 (d, J = 8.4 Hz,2H), 4.34 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 164.7, 164.4, 137.5, 130.2, 128.8, 122.5, 104.3, 19.8. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_6ClN_3OSe$ $[M + H]^+$: 299.9443; Found: 299.9441

2-(4-methoxyphenyl)-5-(selenocyanatomethyl)-1,3,4-oxadiazole (7cb)



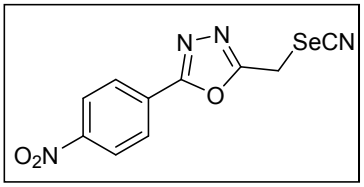
Yield 83%. Brown solid; mp: 130-133 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.92 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.9 Hz, 2H), 4.55 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.0, 164.0, 162.7, 128.8, 115.9, 115.5, 104.8, 56.0, 19.9. HRMS-ESI(+) *m/z* Calculated for $C_{11}H_9N_3O_2Se$ $[M + H]^+$: 295.9938, Found: 295.9966.

2-(selenocyanatomethyl)-5-(*p*-tolyl)-1,3,4-oxadiazole (7db)



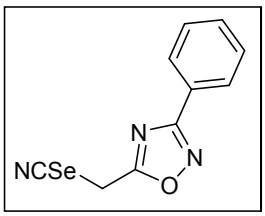
Yield 89%. Brown solid; mp: 159-162 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.88 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 4.56 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.2, 164.4, 142.9, 130.6, 126.9, 120.8, 104.9, 21.6, 19.9. HRMS-ESI(+) *m/z* Calculated for $C_{11}H_9N_3OSe$ [M + Na]$^+$: 301.9809, Found: 301.9810.

2-(4-nitrophenyl)-5-(selenocyanatomethyl)-1,3,4-oxadiazole (7eb)



Yield 69%. Brown solid; mp: 126-128 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.45 (d, J = 8.9 Hz, 2H), 8.24 (d, J = 8.9 Hz, 2H), 4.61 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.7, 163.8, 149.9, 129.1, 128.4, 125.2, 104.7, 19.8. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_6N_4O_3Se$ [M + H]$^+$: 310.9683, Found: 310.9698.

3-phenyl-5-(selenocyanatomethyl)-1,2,4-oxadiazole (8ab)



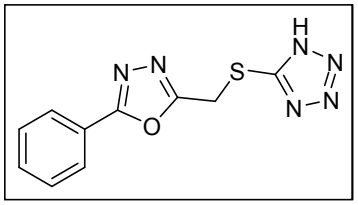
Yield 92%. Brown solid; mp: 131-132 °C ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.10 (d, J = 8.6 Hz, 2H), 7.48-7.55 (m, 3H), 4.43 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.0, 169.1, 131.6, 129.0, 127.6, 126.1, 99.0, 18.9. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_7N_3OSe$ [M + H]$^+$: 265.9833, Found: 265.9840.

General procedure for the synthesisof 2-{[(1*H*-tetrazol-5-yl)chalcogeno]methyl}-5-aryl-1,3,4-oxadiazole (9aa-eb) and 5-{[(1*H*-tetrazol-5-yl)chacogeno]methyl}-3-phenyl-1,2,4-oxadiazole (10aa-ab).

A 50 mL two-necked flask equipped with a reflux condenser was charged with a suspension of triethylamine hydrochloride (1.25 equiv / 1.25 mmol) in 10 mL of toluene. Sodium azide (1.25 equiv / 1.25 mmol) was added in portions under stirring, and a solution of thio and selenocianatomethyloxadiazoles (**7-8**) (1.0 mmol) in 10 mL of toluene was then slowly added. The mixture was stirred for 5 minutes, and after heated for 12 h (**7**) or 24 h (**8**), under reflux. The mixture was cooled, 20 mL of distilled water was added, the aqueous layer was separated; and the toluene layer was washed with

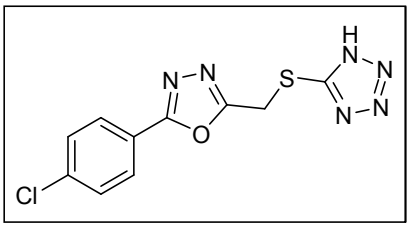
water (3 × 10 mL). The aqueous phase was combined with the aqueous extracts (≈ pH 8) and acidified to pH 5.5 using HCl 1N under stirring for 10 min. The 1*H*-tetrazoles (**9-10**) were obtained by recrystallization using a mixture of hexane/DCM (9:1).

2-{[(1*H*-tetrazol-5-yl)thio]methyl}-5-phenyl-1,3,4-oxadiazole (9aa)



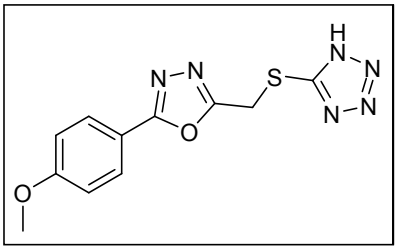
Yield 93%. Yellow solid; mp: 127-129 °C. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ = 7.99 (d, J = 6.5 Hz, 2H), 7.55-7.65 (m, 3H), 4.84 (s, 2H). ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ = 164.9, 163.7, 153.5, 132.5, 129.8, 126.8, 123.5, 26.6. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_8N_6OS$ [M + Na]$^+$: 283.0378, Found: 283.0374.

2-{[(1*H*-tetrazol-5-yl)thio]methyl}-5-(4-chlorophenyl)-1,3,4-oxadiazole (9ba)



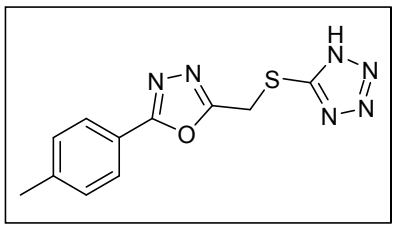
Yield 98%. White solid; mp: 177-179 °C. ^{1}H NMR (DMSO-d$_6$,400 MHz): δ = 7.92 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 4.83 (s, 2H). ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ = 164.2, 163.9, 153.4, 137.4, 130.1, 128.6, 122.4, 26.5. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_7ClN_6OS$ [M + H]$^+$: 295.0169, Found: 295.0153.

2-{[(1*H*-tetrazol-5-yl)thio]methyl}-5-(4-methoxyphenyl)-1,3,4-oxadiazole (9ca)



Yield 99%. Light yellow solid; mp: 141-143 °C. ^{1}H NMR (DMSO-d$_6$,400 MHz): δ = 7.84 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 4.80 (s, 2H), 3,84 (s, 3H). ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ = 164.9, 163.1, 162.6, 153.4, 128.7, 115.8, 115.3, 55.9, 26.6. HRMS-ESI(+) *m/z* Calculated for $C_{11}H_{10}N_6O_2S$ [M + H]$^+$: 291.0664, Found: 291.0664.

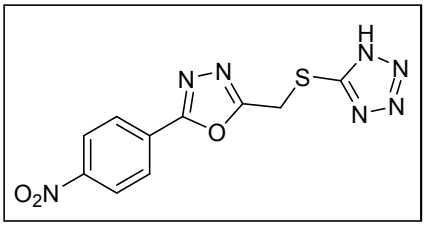
2-{[(1*H*-tetrazol-5-yl)thio]methyl}-5-(*p*-tolyl)-1,3,4-oxadiazole (9da)



Yield 99%. Yellow solid; mp: 156-158 °C. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ = 7.78 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 4.82 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ = 165.0, 163.4, 153.5,

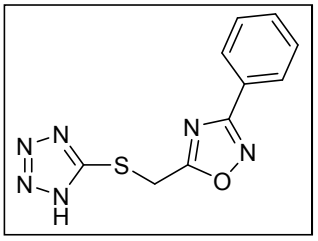
142.8, 130.4, 126.8, 120.8, 26.6, 21.5. HRMS-ESI(+) *m/z* Calculated for $C_{11}H_{10}N_6OS$ $[M + H]^+$: 275.0715, Found: 275.0720.

2-{[(1*H*-tetrazol-5-yl)thio]methyl}-5-(4-nitro)-1,3,4-oxadiazole (9ea)



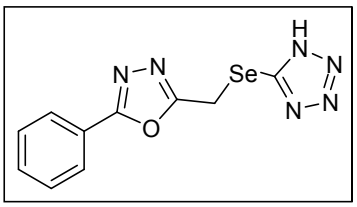
Yield 99%. Yellow solid; mp: 174-175 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.40 (d, J = 8.3 Hz, 2H), 8.17 (d, J = 8.3 Hz, 2H), 4.88 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 164.8, 163.7, 153.5, 149.7, 129.0, 128.3, 125.1, 26.6. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_7N_7O_3S$ $[M + H]^+$: 306.0409, Found: 306.0413.

5-{[(1*H*-tetrazol-5-yl)thio]methyl}-3-phenyl-1,2,4-oxadiazole (10aa)



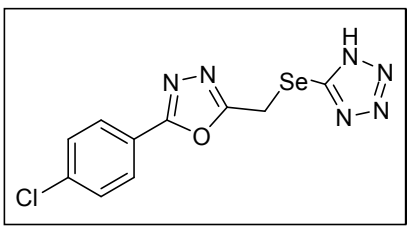
Yield 52%. White solid; mp: 138-139 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.96 (d, J = 8.2 Hz, 2H), 7.53-7.60 (m, 3H), 4.92 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 177.0, 168.4, 153.9, 132.2, 129.7, 127.5, 126.4, 27.3. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_8N_6OS$ $[M + Na]^+$: 283.0378, Found: 283.0373.

2-{[(1*H*-tetrazol-5-yl)seleno]methyl}-5-phenyl-1,3,4-oxadiazole (9ab)



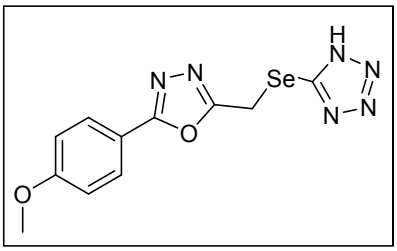
Yield 75%. Dark Brown solid; mp: 148-150 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.86 (d, J = 8.0 Hz, 2H), 7.50-7.60 (m, 3H), 4.65 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 164.8 (2C), 144.9, 132.5, 129.9, 126.8, 123.6, 18.8. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_8N_6OSe$ $[M + H]^+$: 309.0003, Found: 308.9992.

2-{[((1*H*-tetrazol-5-yl)seleno]methyl}-5-(4-chloro)-1,3,4-oxadiazole (9bb)



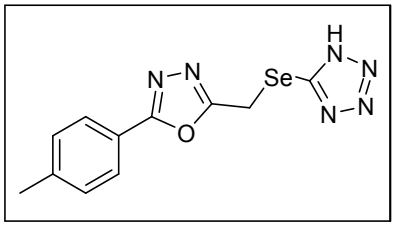
Yield 80%. Brown solid; mp: 132-134 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.86 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 4.64 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.0, 164.0, 144.9, 137.3, 130.1, 128.6, 122.5, 18.8. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_7ClN_6OSe$ $[M + Na]^+$: 364.9443, Found: 364.9441.

2-{[(1*H*-tetrazol-5-yl)seleno]methyl}-5-(4-methoxy)-1,3,4-oxadiazole (9cb)



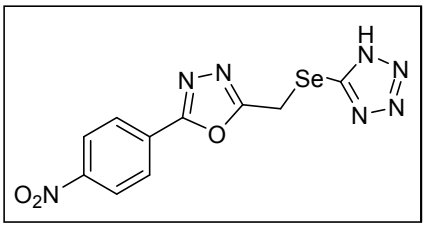
Yield 89%. Brown solid; mp: 159-161 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.78 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 4.61 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 164.7, 164.2, 162.6, 144.9, 128.7, 115.9, 115.3, 56.0, 18.8. HRMS-ESI(+) *m/z* Calculated for $C_{11}H_{10}N_6O_2Se$ [M + H]$^+$: 339.0109, Found: 339.0108.

2-{[(1*H*-tetrazol-5-yl)seleno]methyl}-5-(*p*-tolyl)-1,3,4-oxadiazole (9db)



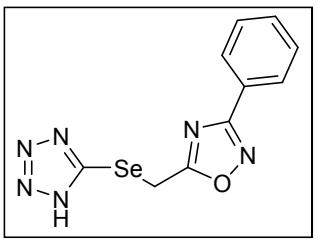
Yield 88%. Dark Brown solid; mp: 152-154 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.73 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 4.63 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 164.9, 164.5, 144.9, 142.8, 130.4, 126.8, 120.8, 21.6, 18.8. HRMS-ESI(+) *m/z* Calculated for $C_{11}H_{10}N_6OSe$ [M + H]$^+$: 323.0160, Found: 323.0168.

2-{[(1*H*-tetrazol-5-yl)seleno]methyl}-5-(4-nitro)-1,3,4-oxadiazole (9eb)



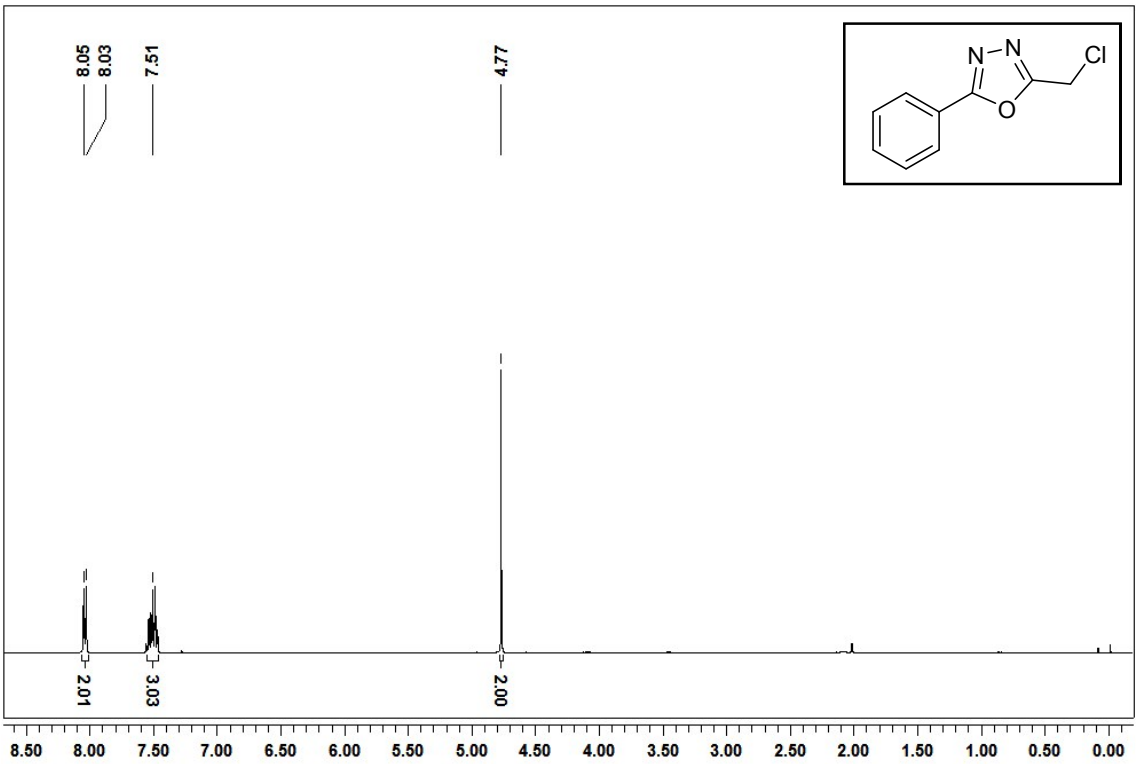
Yield 81%. Brown solid; mp: 177-179 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.41 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H), 4.69 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 165.9, 163.5, 149.7, 145.0, 129.1, 128.2, 125.1, 18.7. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_7N_7O_3Se$ [M + H]$^+$: 353.9854, Found: 353.9859.

5-{[(1*H*-tetrazol-5-yl)seleno]methyl}-3-phenyl-1,2,4-oxadiazole (10ab)

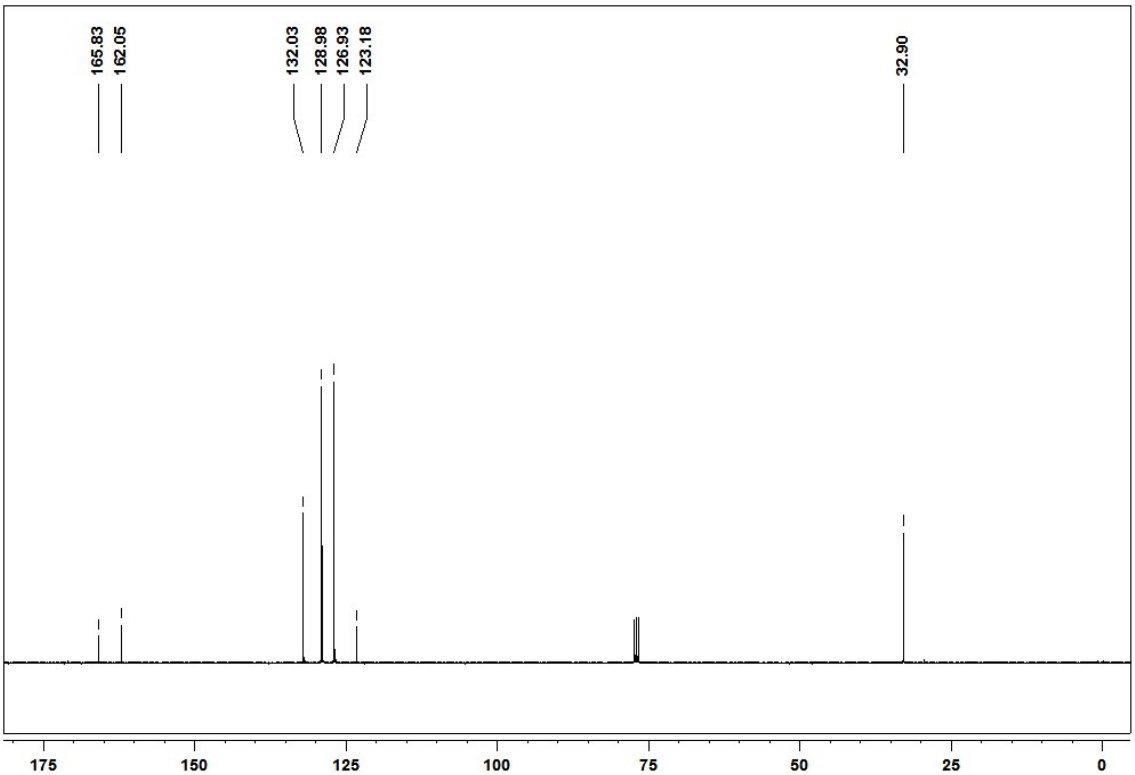


Yield 49%. Brown solid; mp: 190-191 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.93 (d, J = 8.2 Hz, 2H), 7.53-7.60 (m, 3H), 4.69 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 178.0, 168.3, 145.2, 132.1, 129.7, 127.4, 126.5, 19.3. HRMS-ESI(+) *m/z* Calculated for $C_{10}H_9N_6OSe$ [M + Na]+: 330.9823, Found: 330.9804

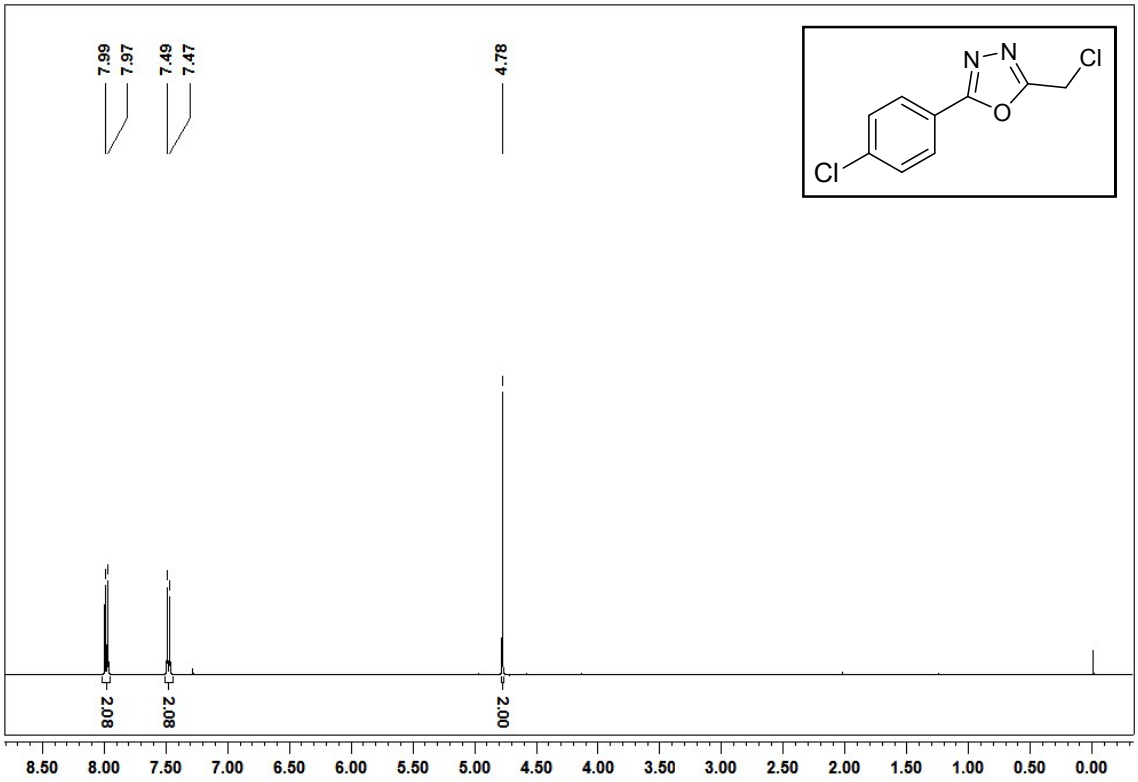
^{1}H, ^{13}C-NMR Spectrum of Synthesized Compounds



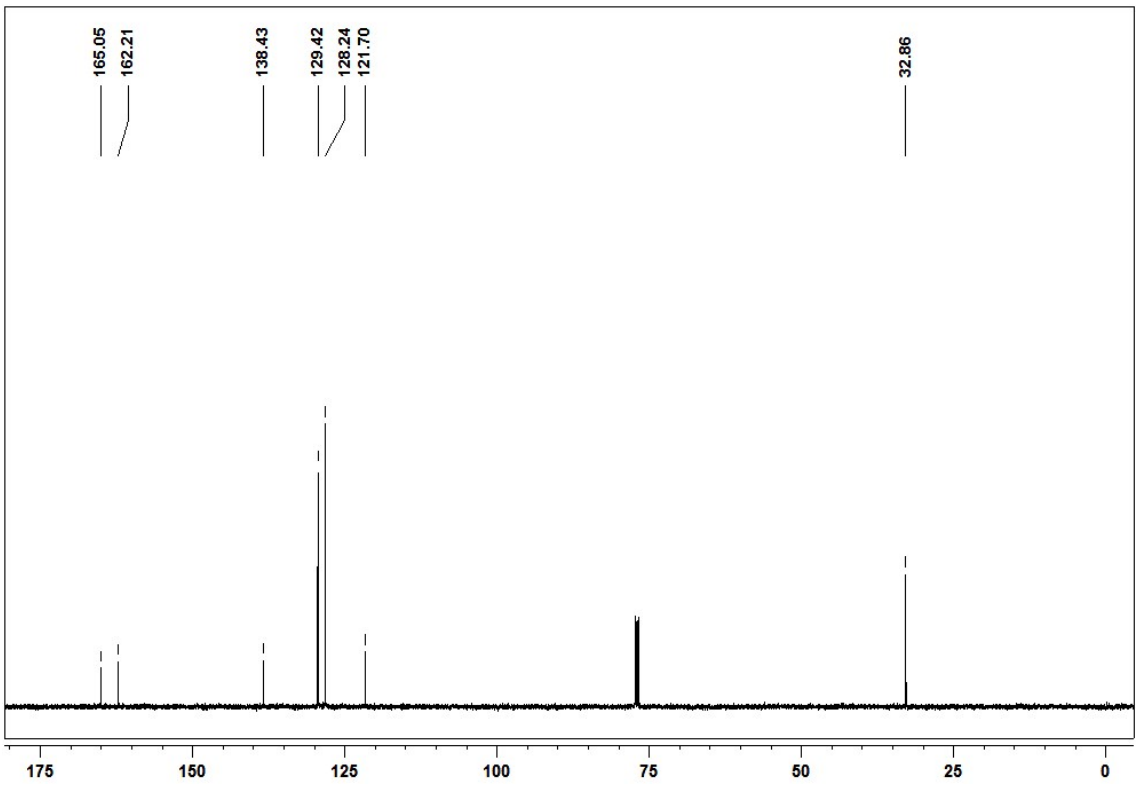
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **4a**.



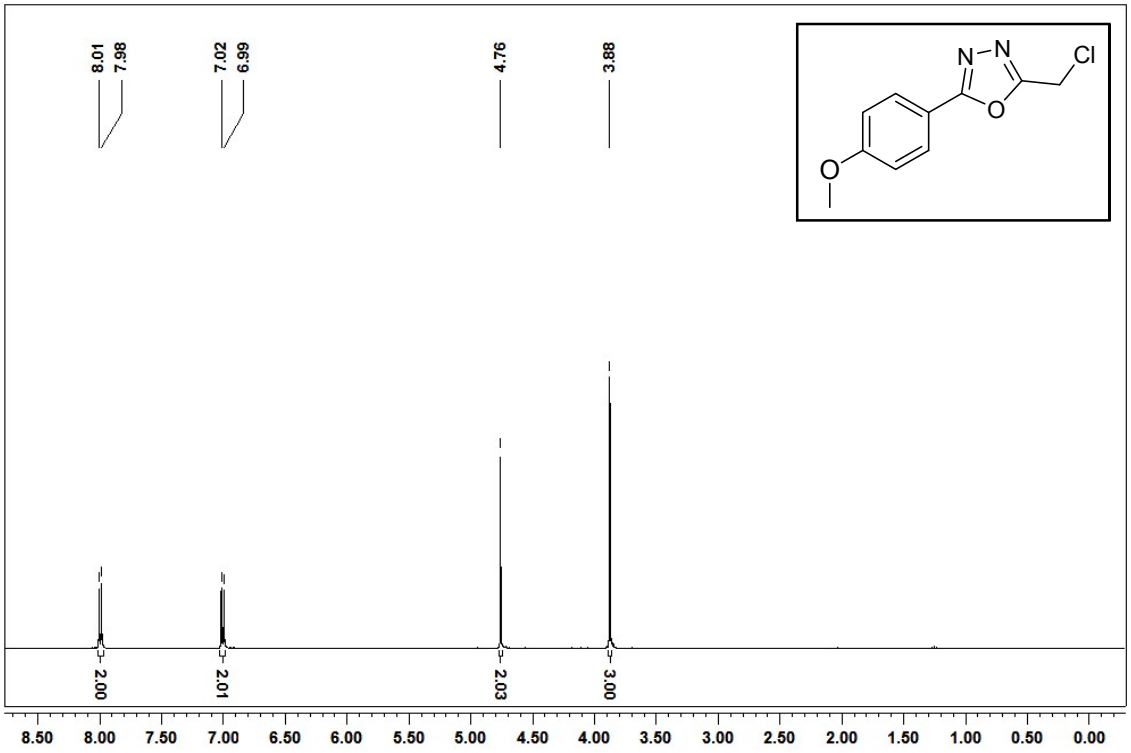
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **4a**.



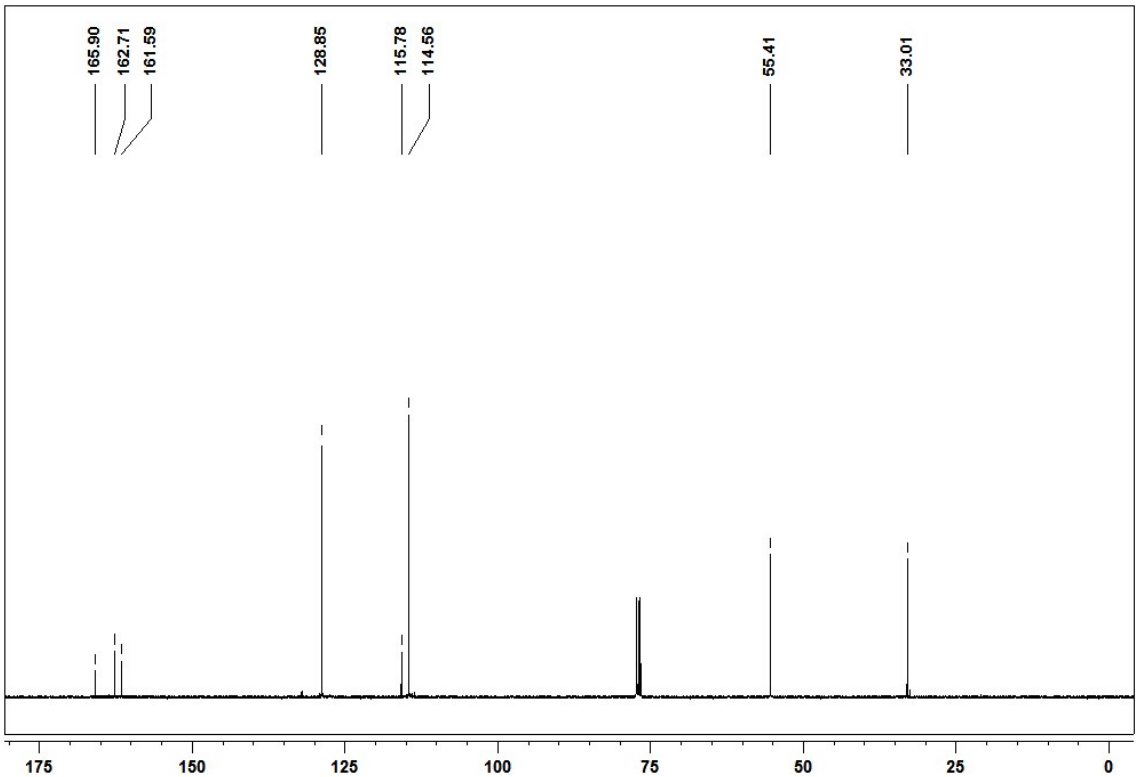
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **4b**.



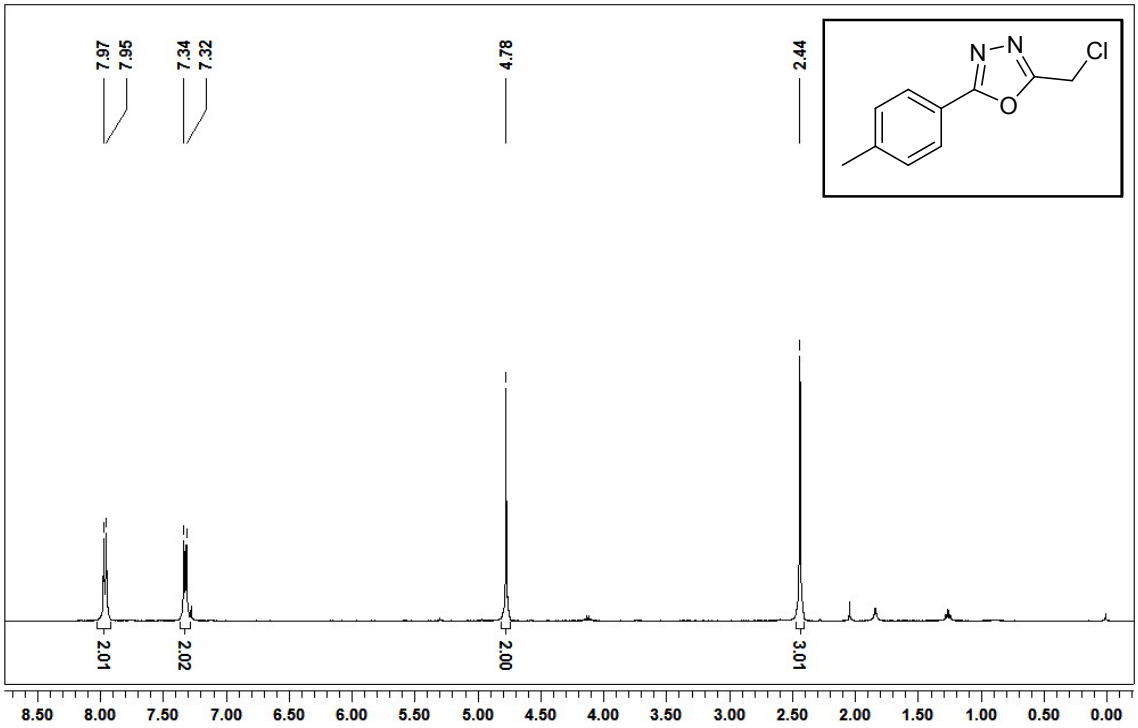
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **4b**.



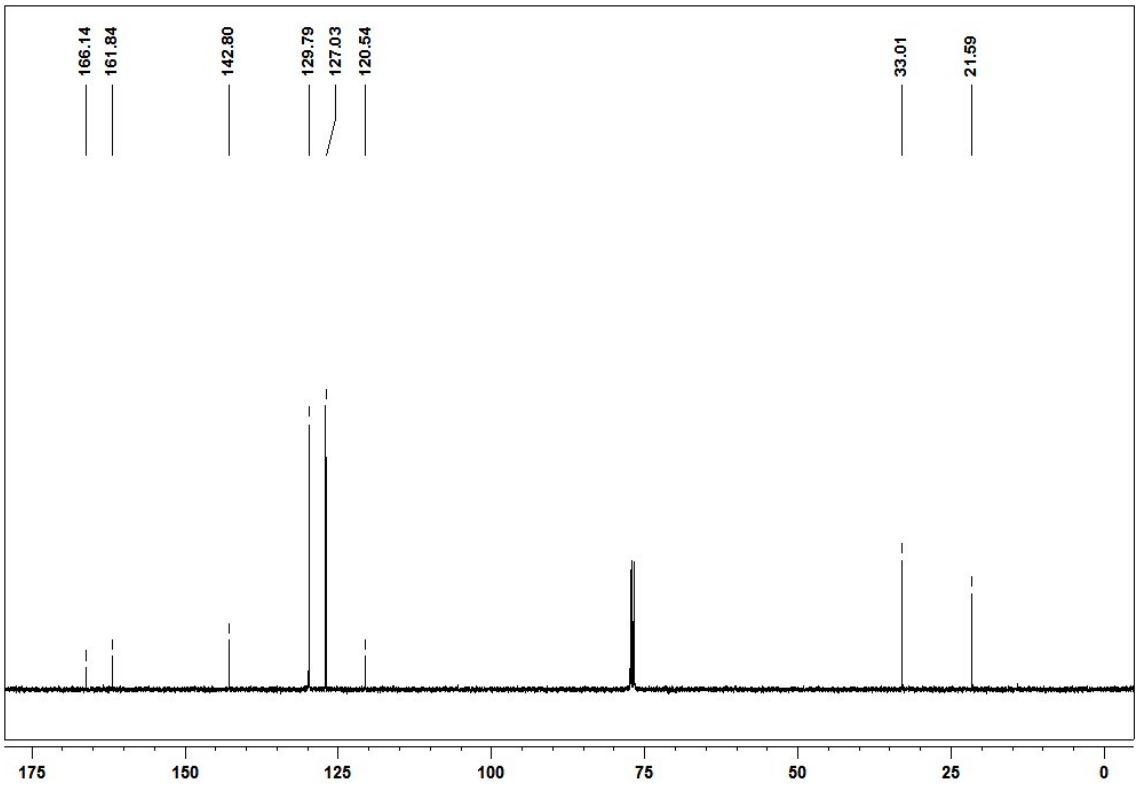
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **4c**.



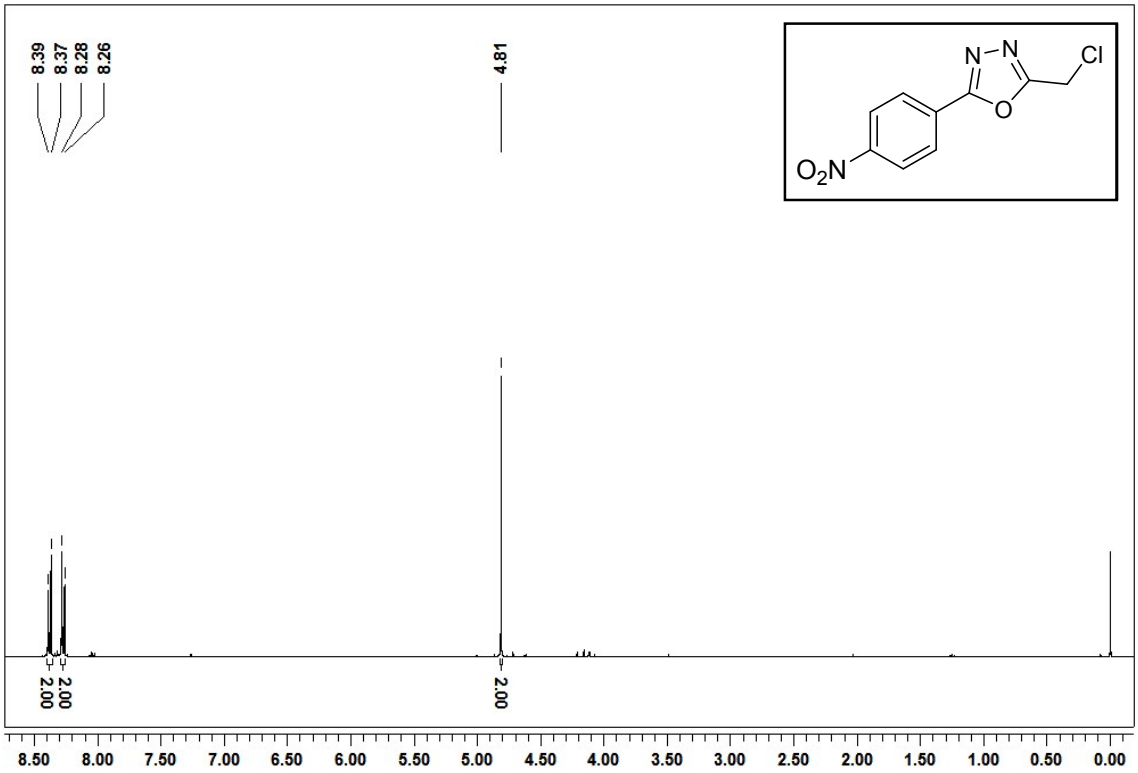
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **4c**.



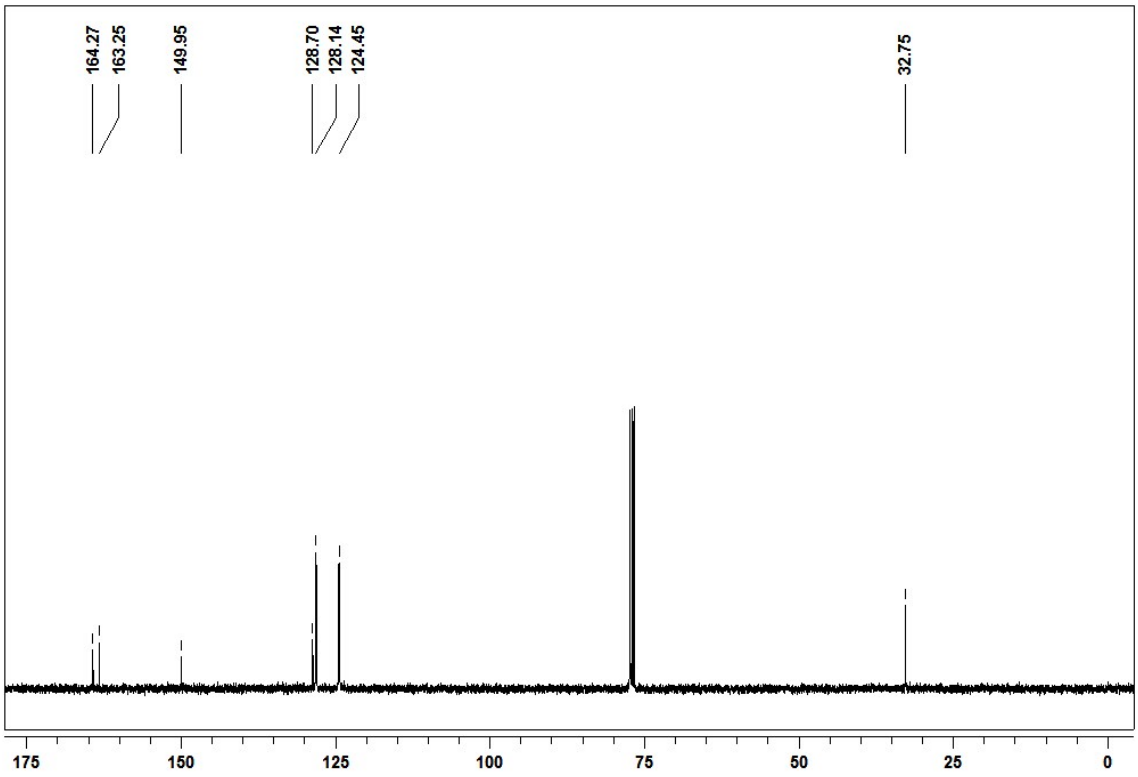
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **4d**.



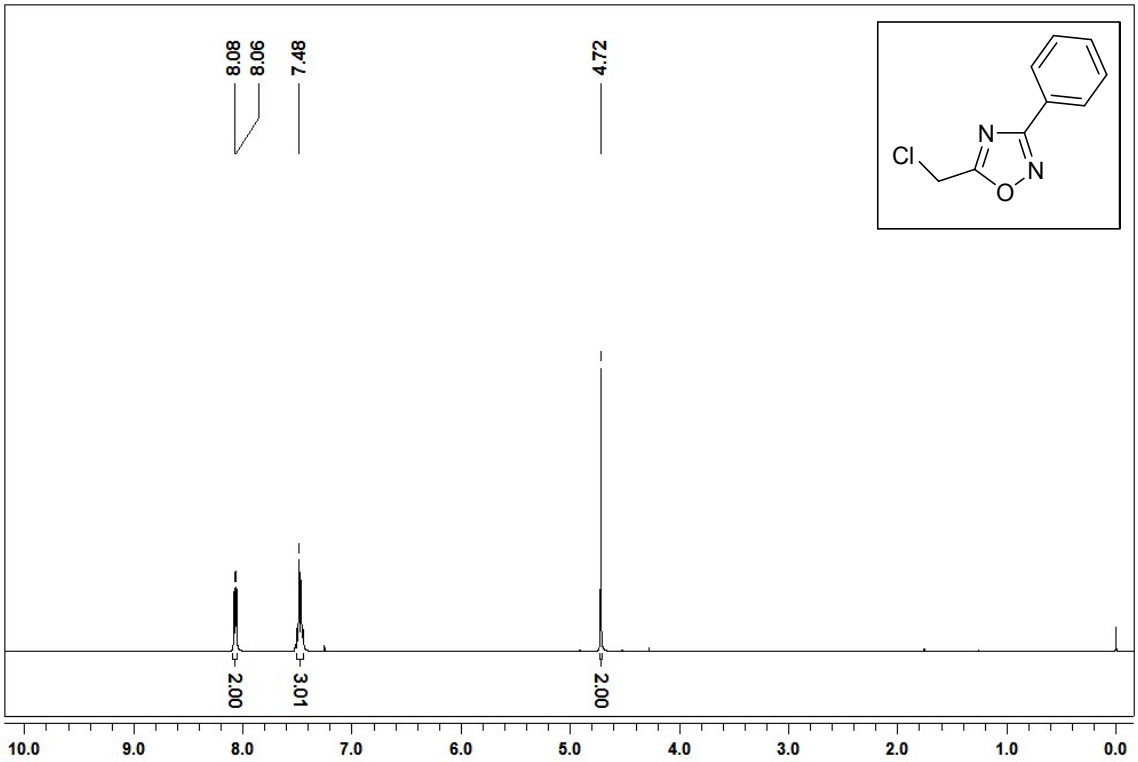
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **4d**.



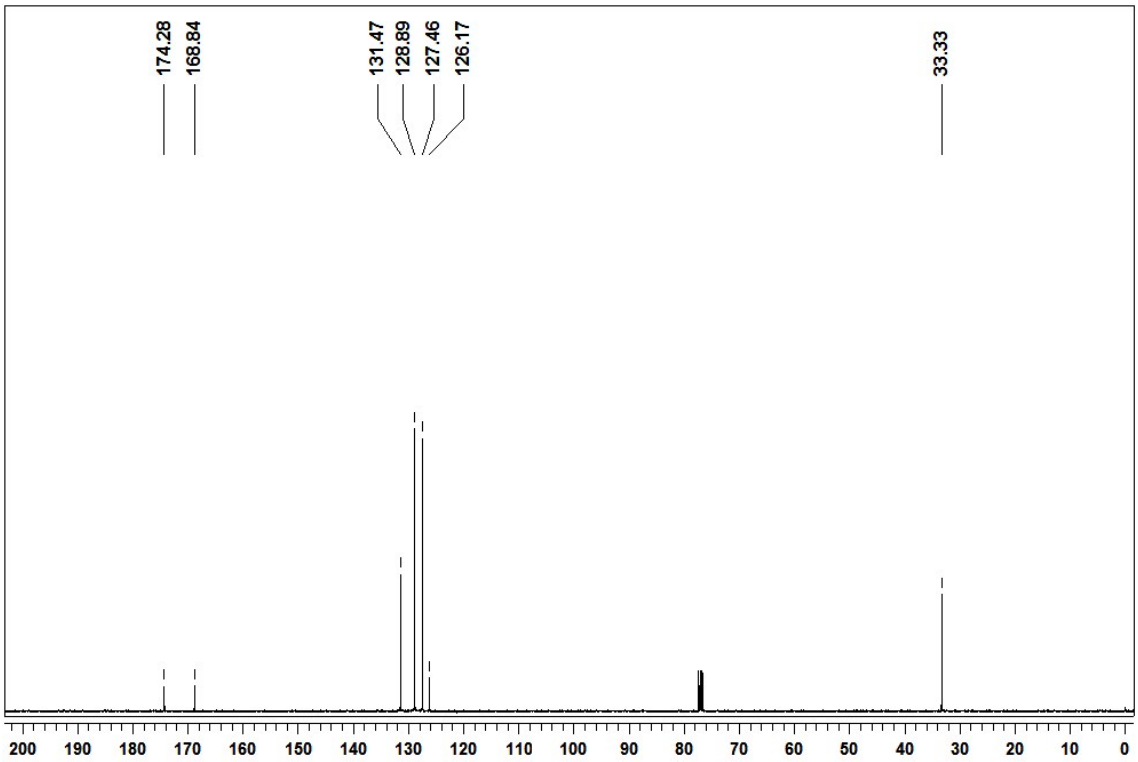
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **4e**.



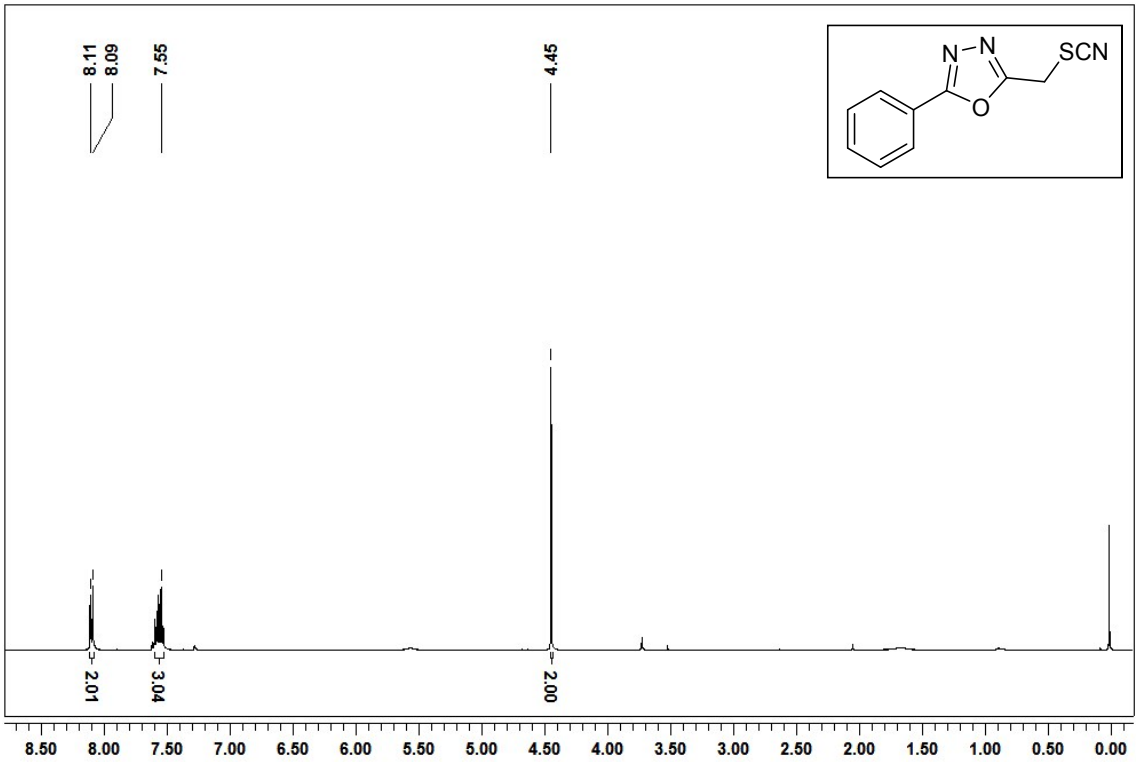
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **4e**.



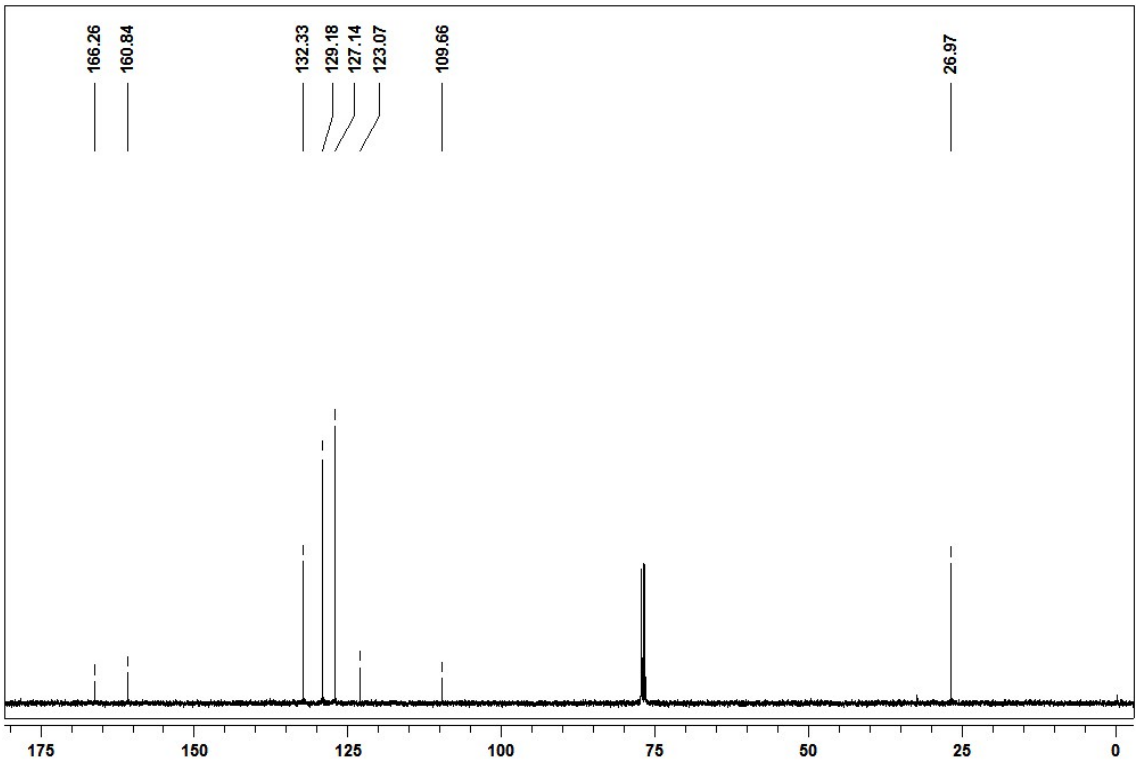
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **5a**.



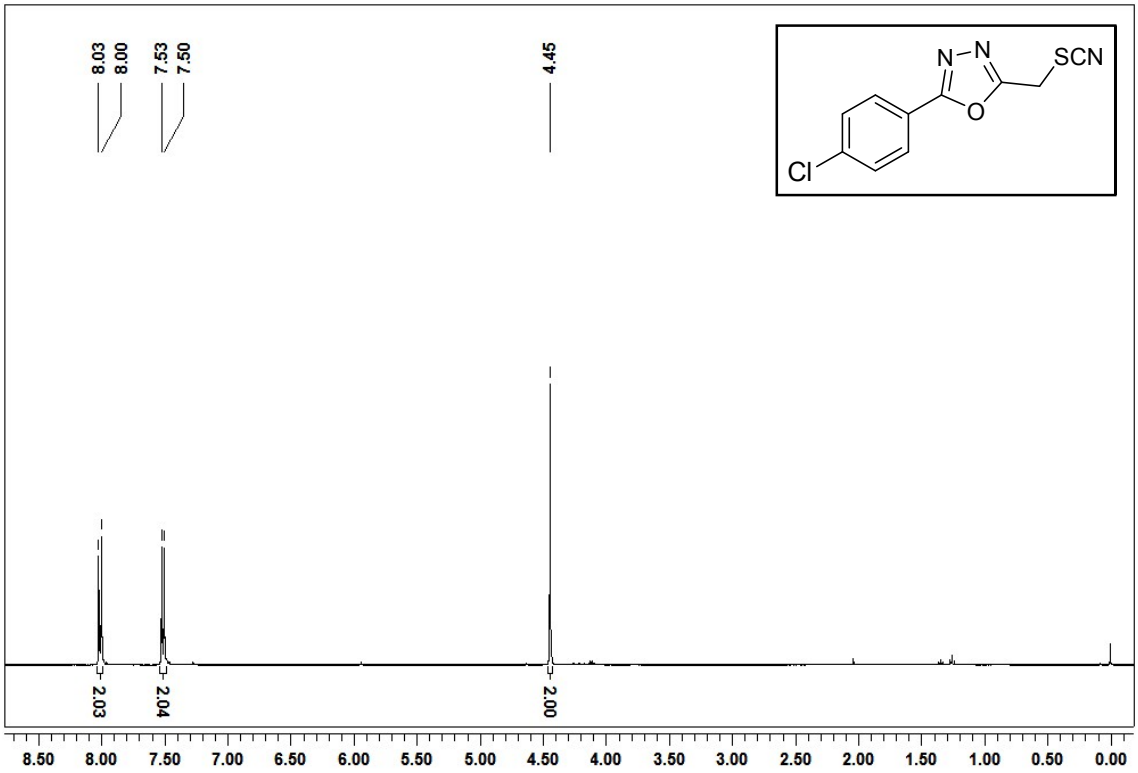
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **5a**.



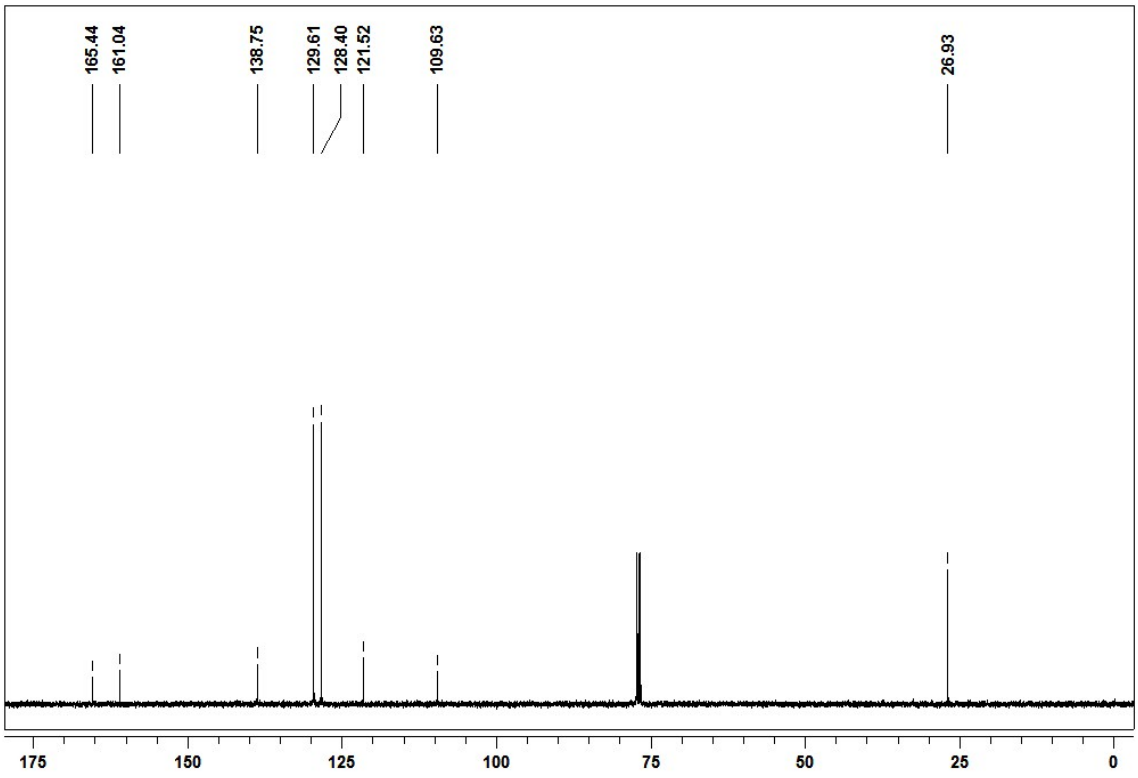
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **7aa**.



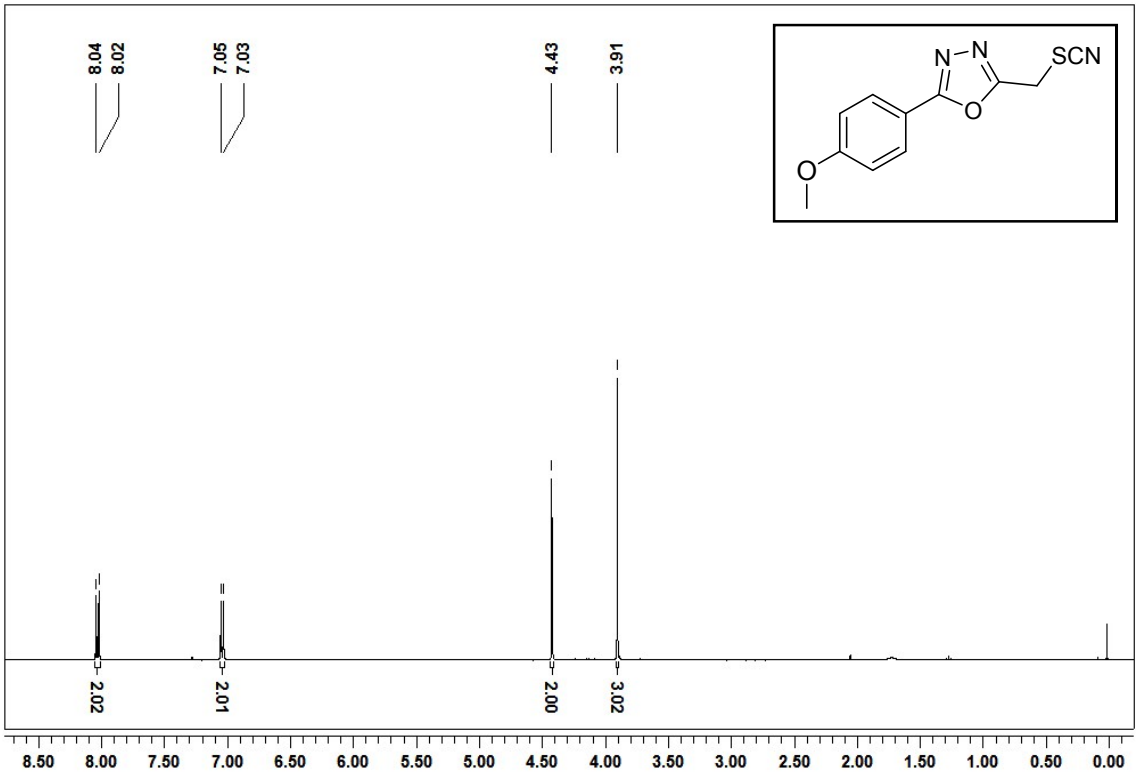
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **7aa**.



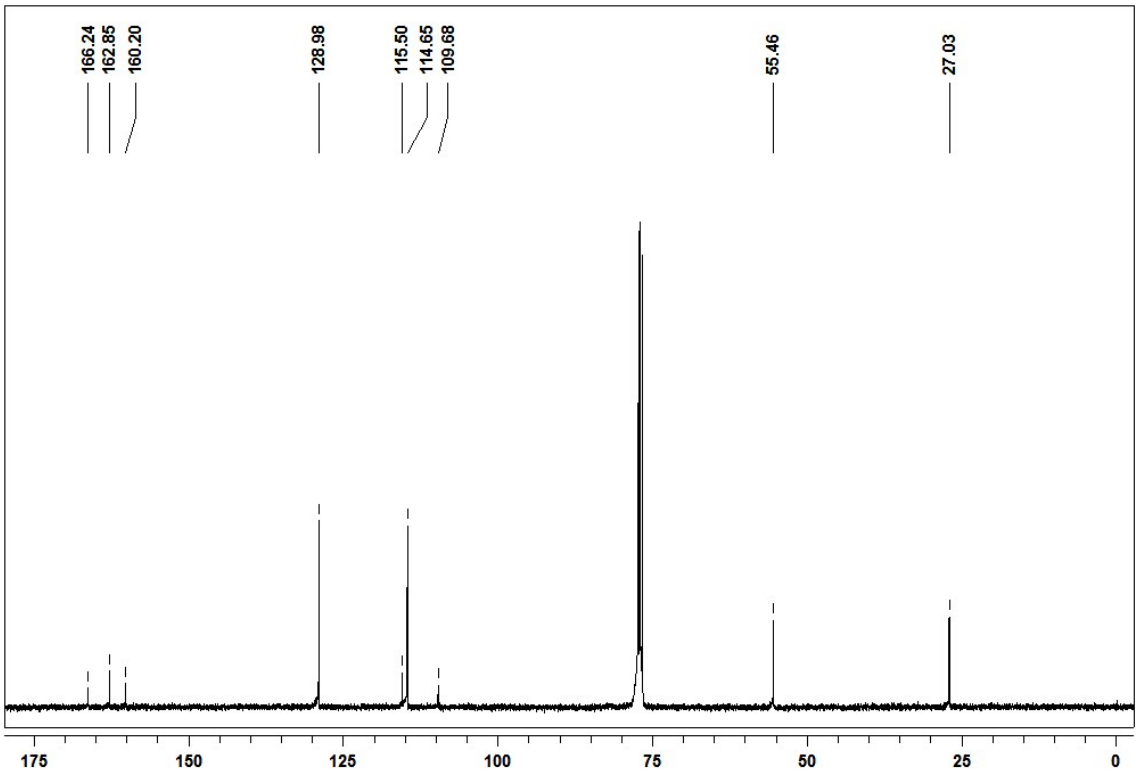
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **7ba**.



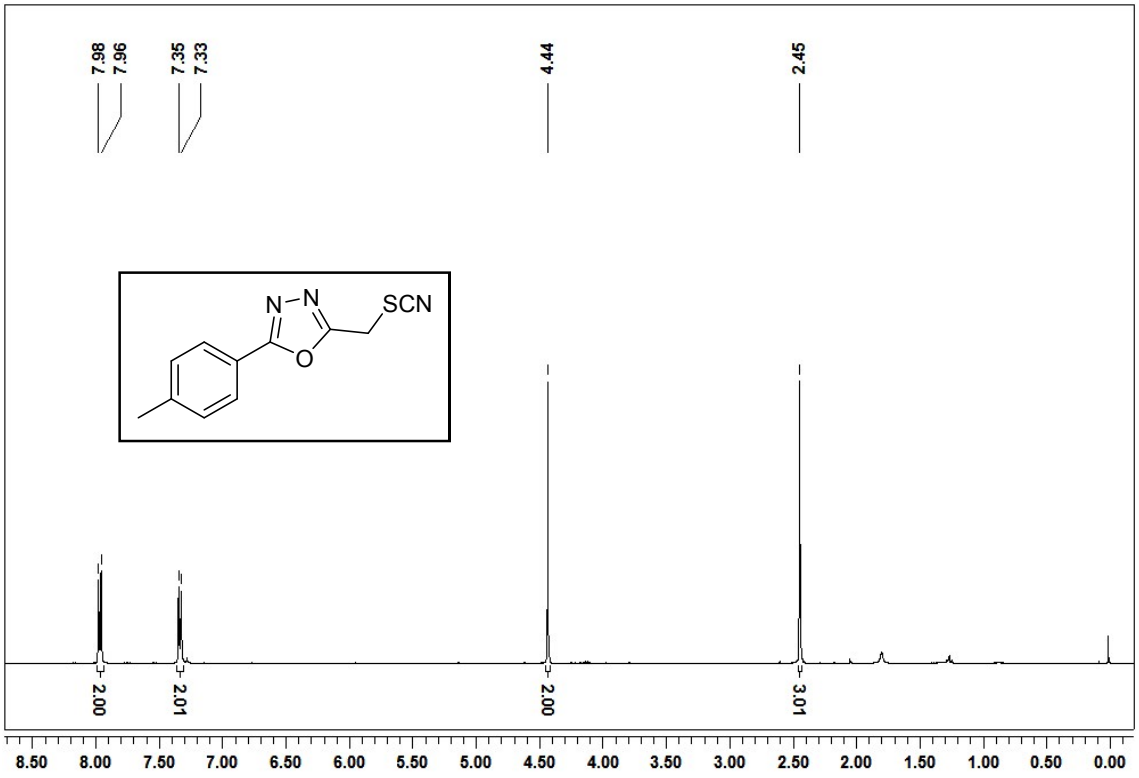
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **7ba**.



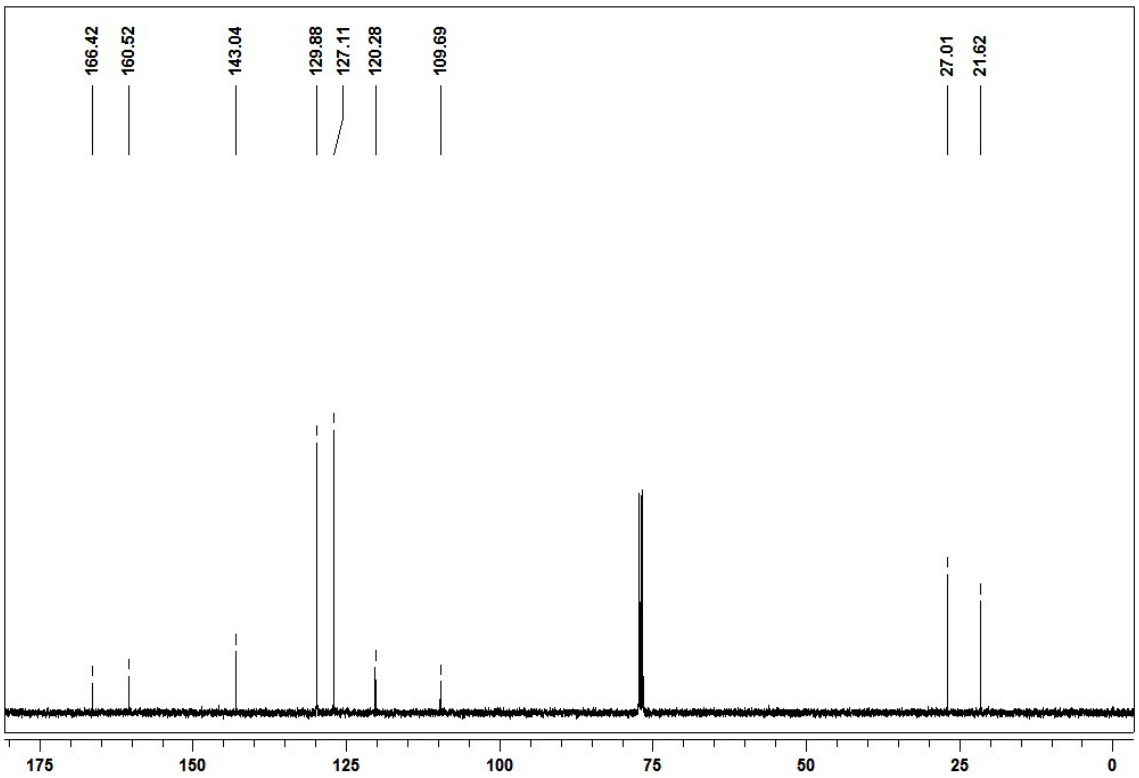
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **7ca**.



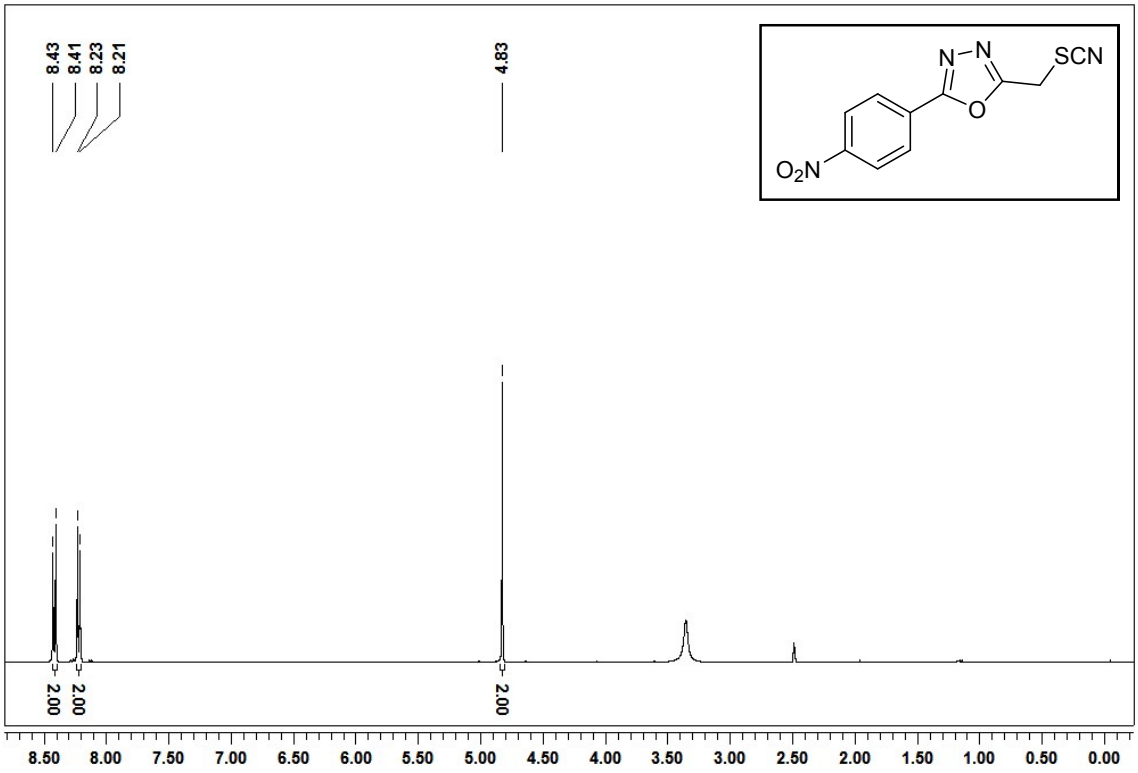
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **7ca**.



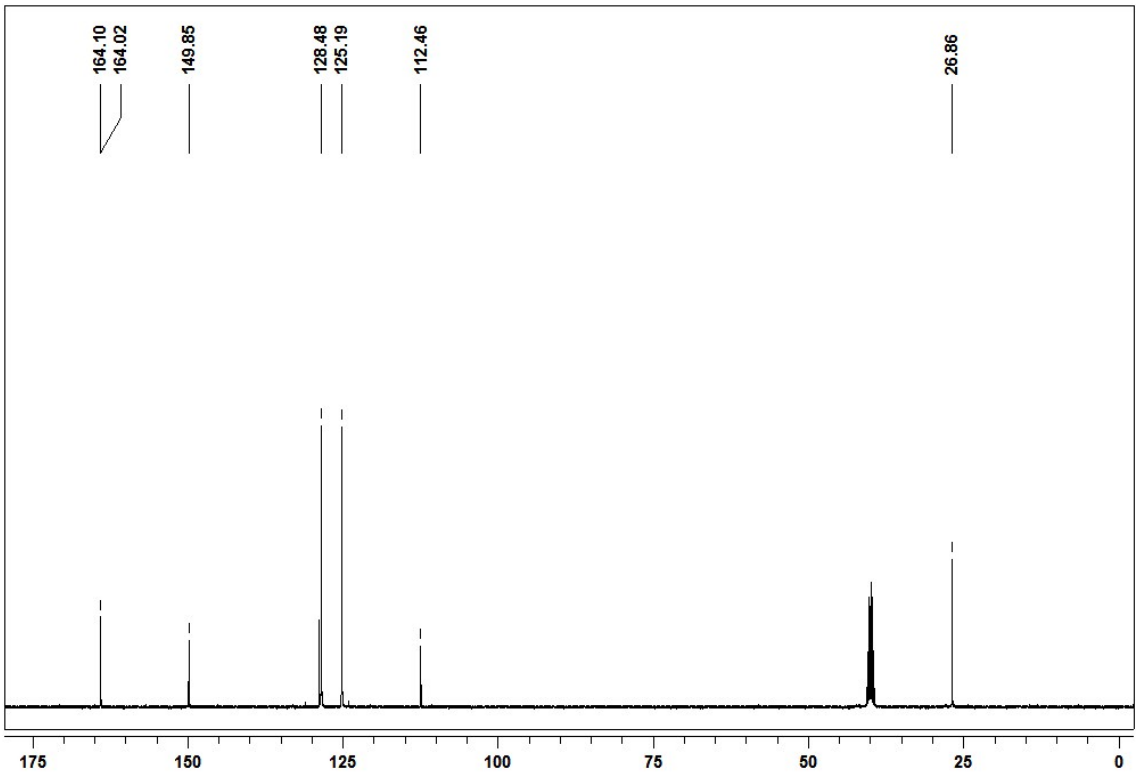
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **7da**.



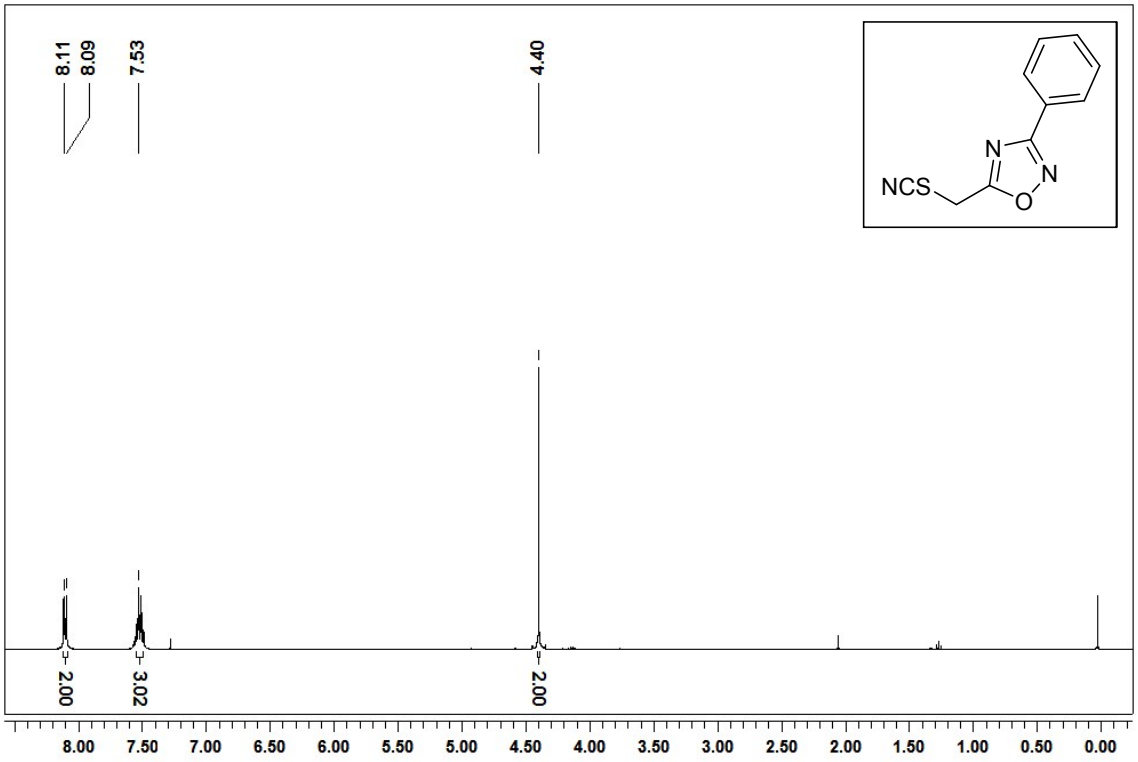
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **7da**.



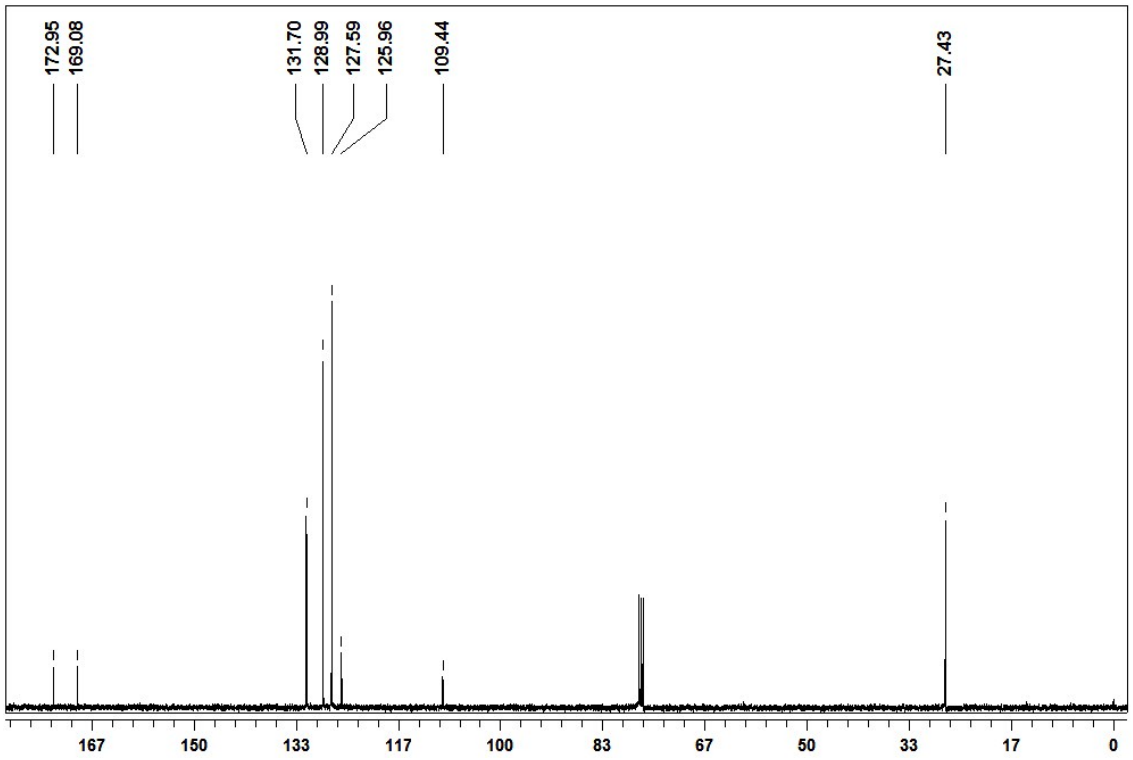
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **7ea**.



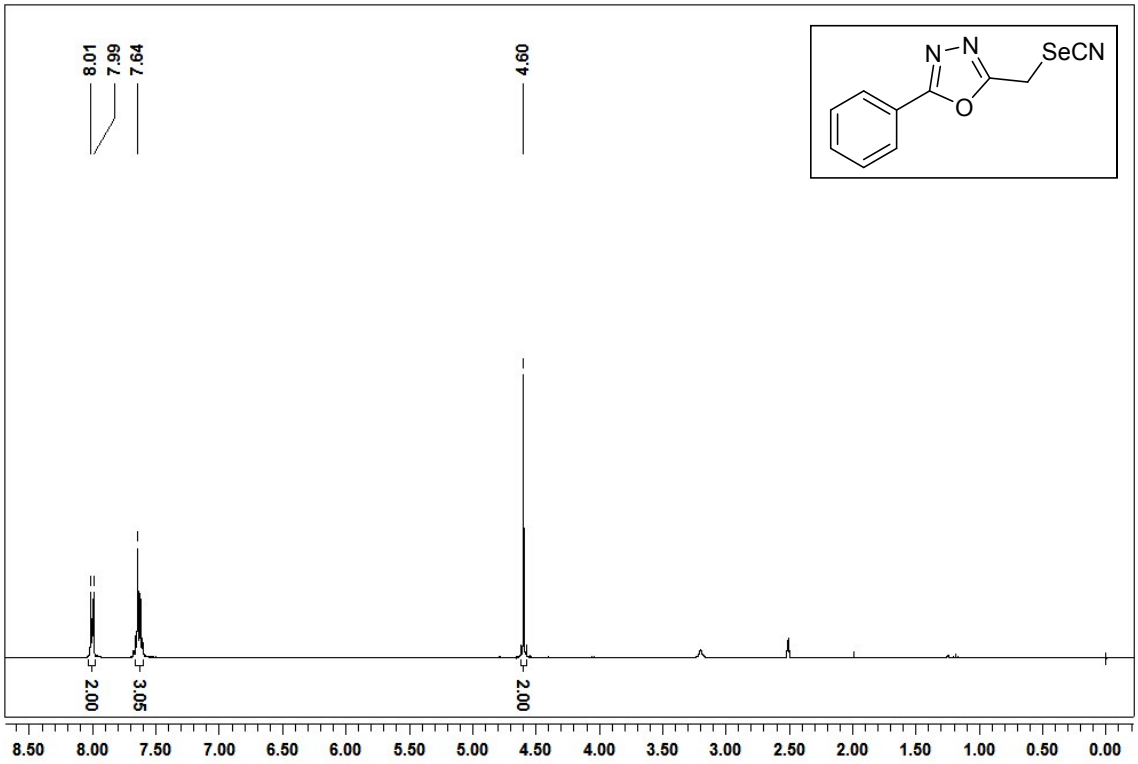
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **7ea**.



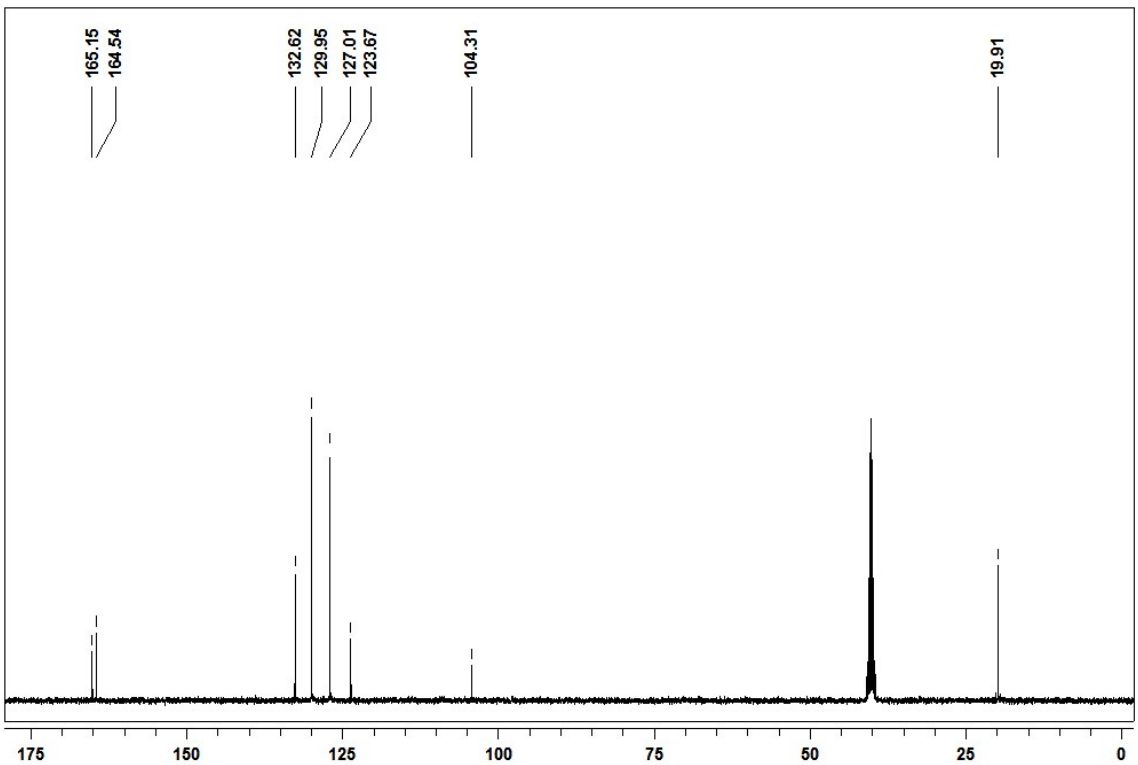
^{1}H NMR spectrum ($CDCl_3$ at 400 MHz) of compound **8aa**.



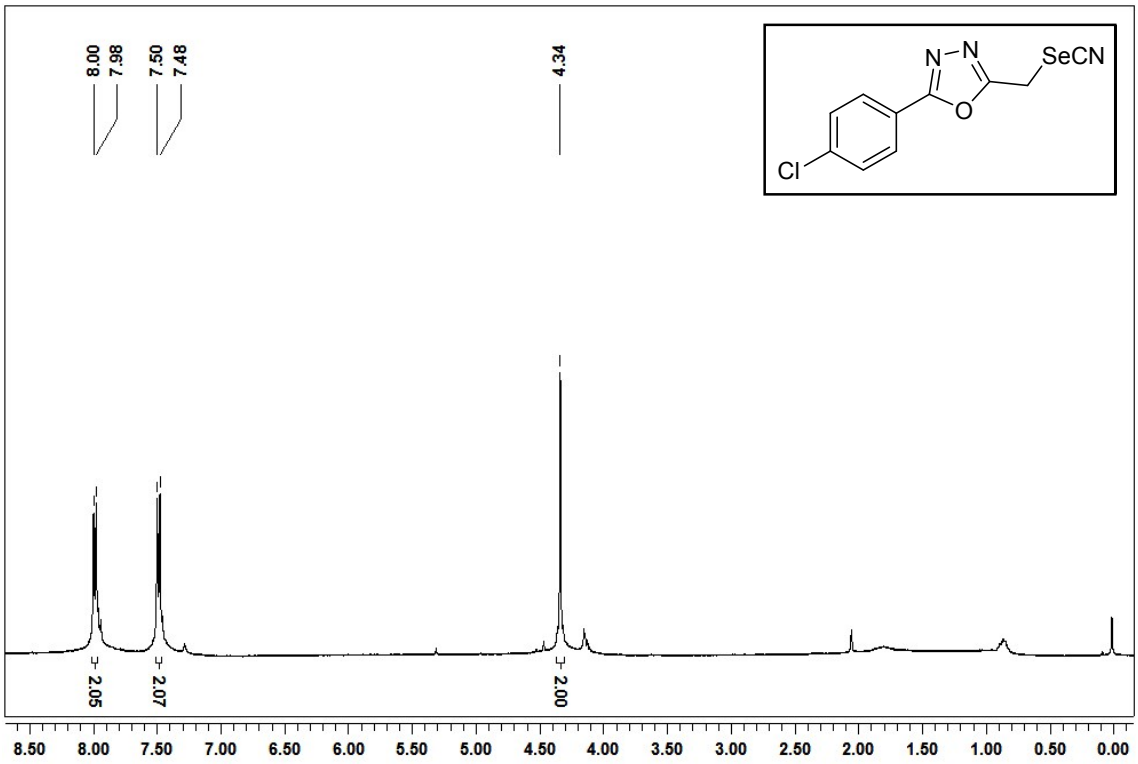
^{13}C NMR spectrum ($CDCl_3$ at 100 MHz) of compound **8aa**.



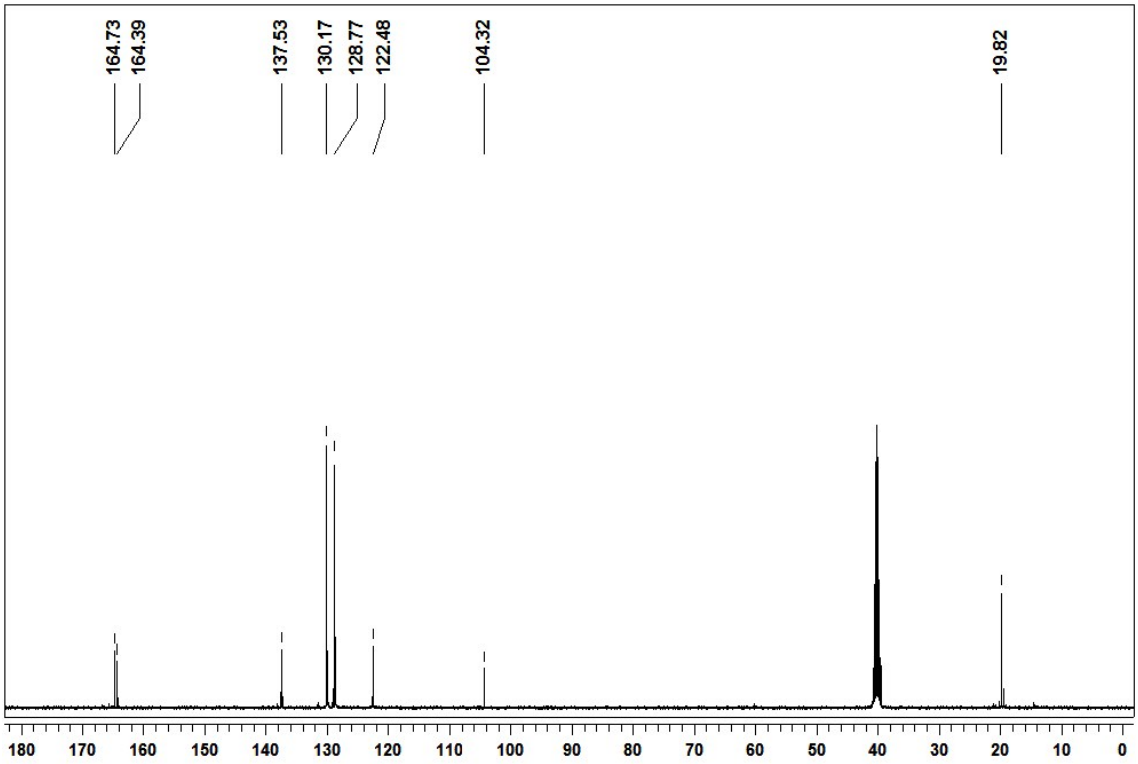
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **7ab**.



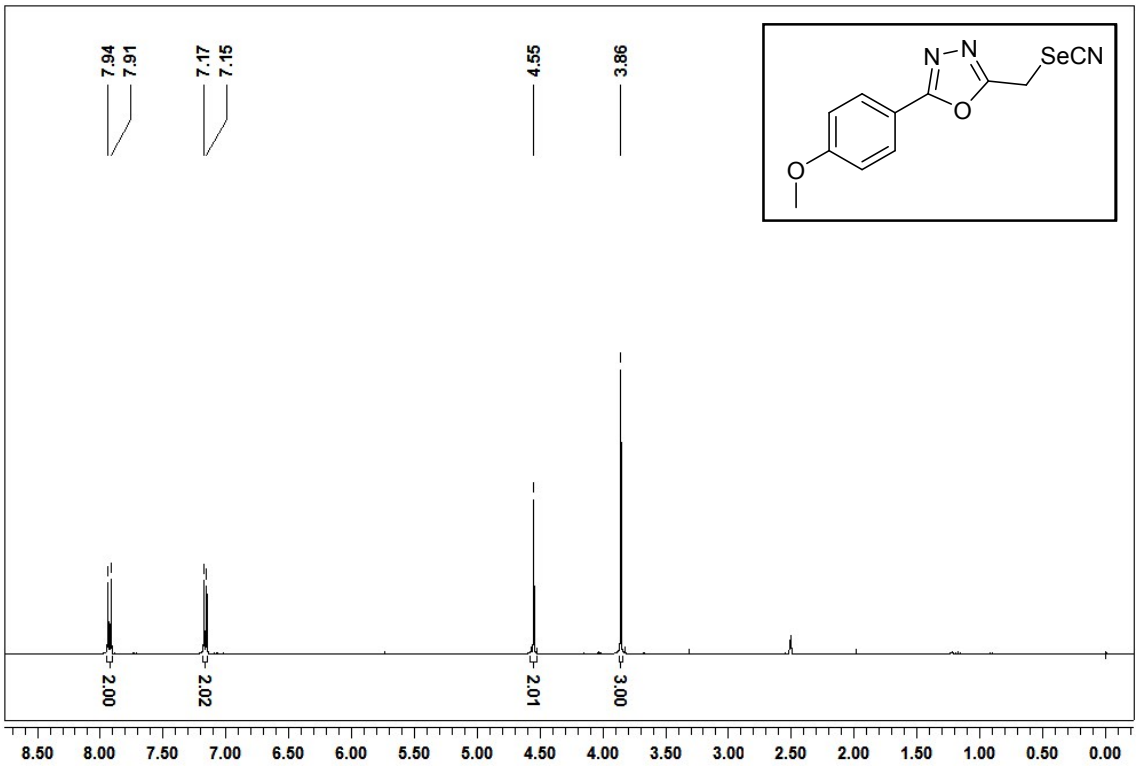
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **7ab**.



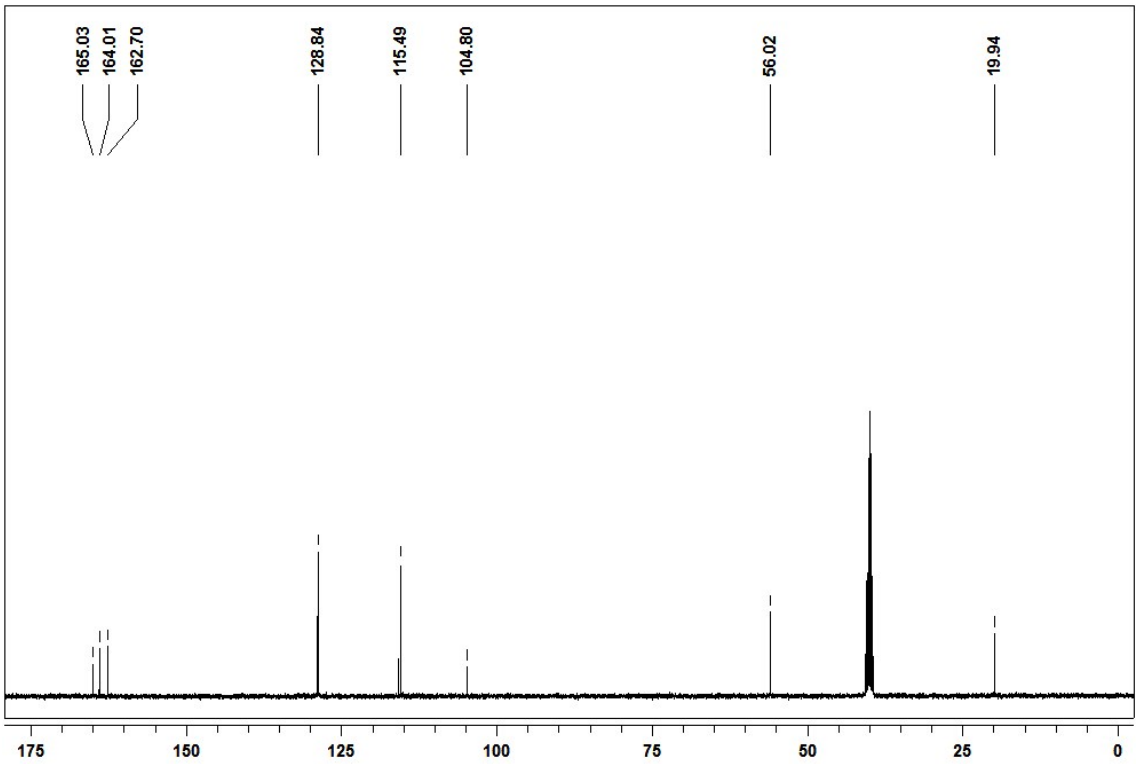
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **7bb**.



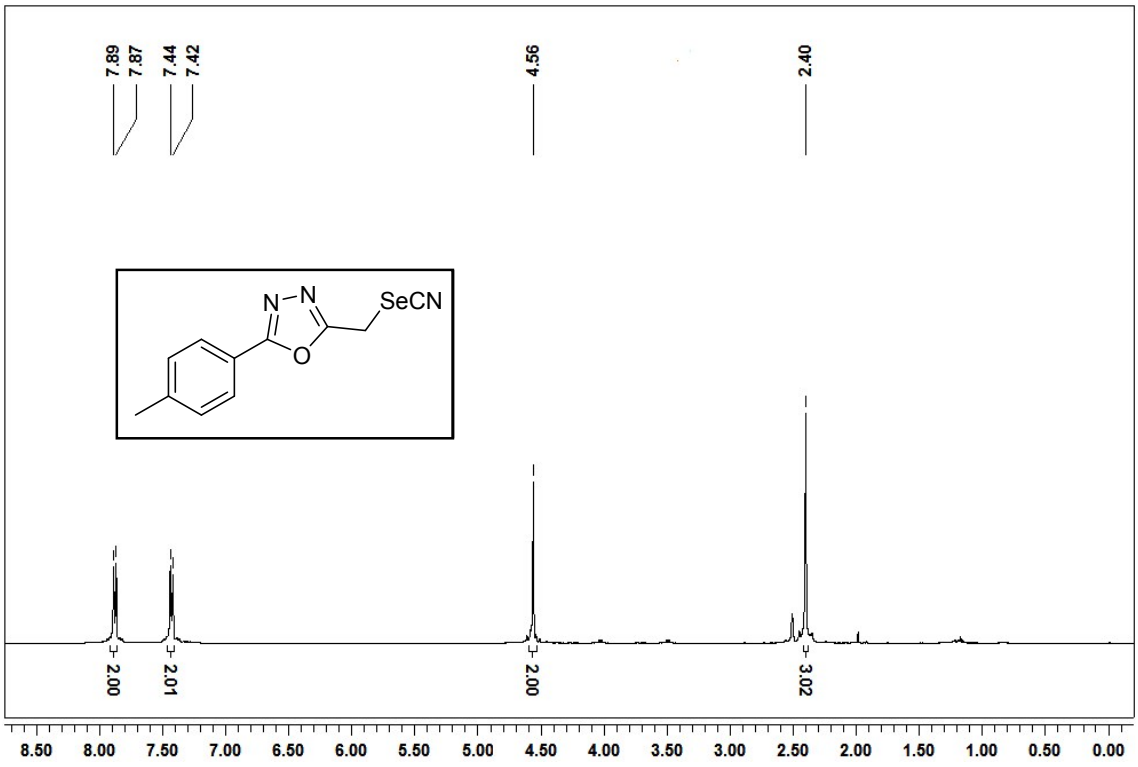
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **7bb**.



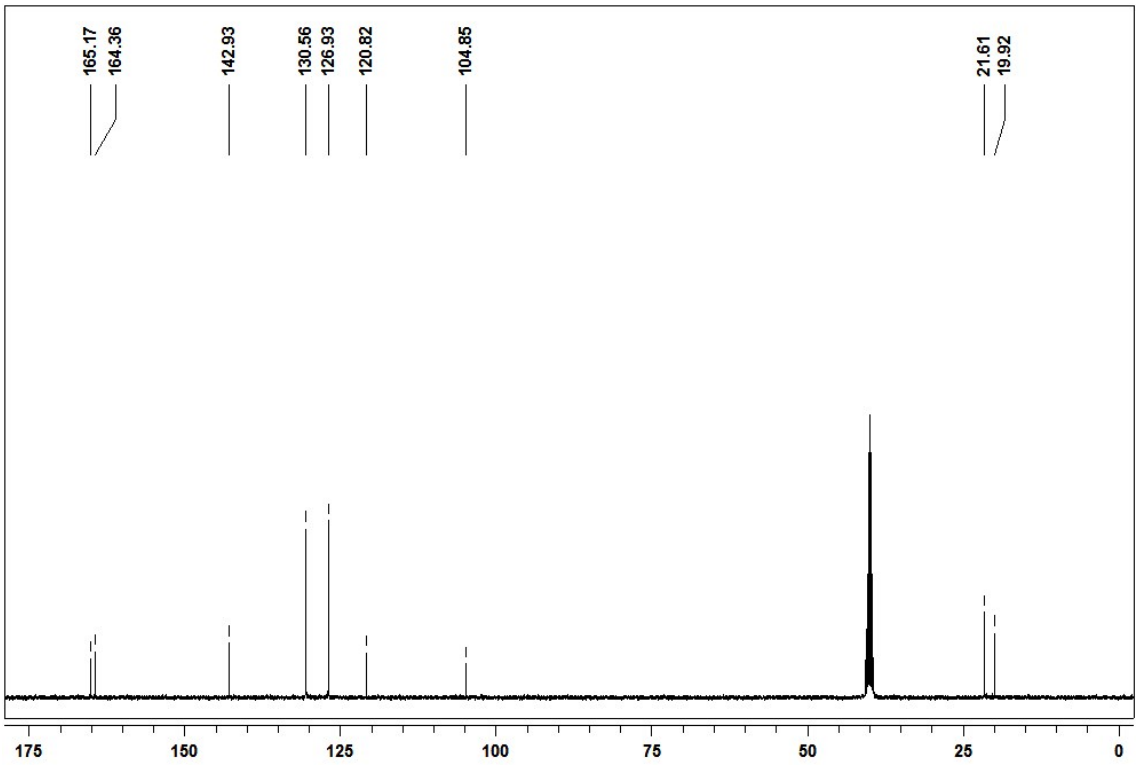
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **7cb**.



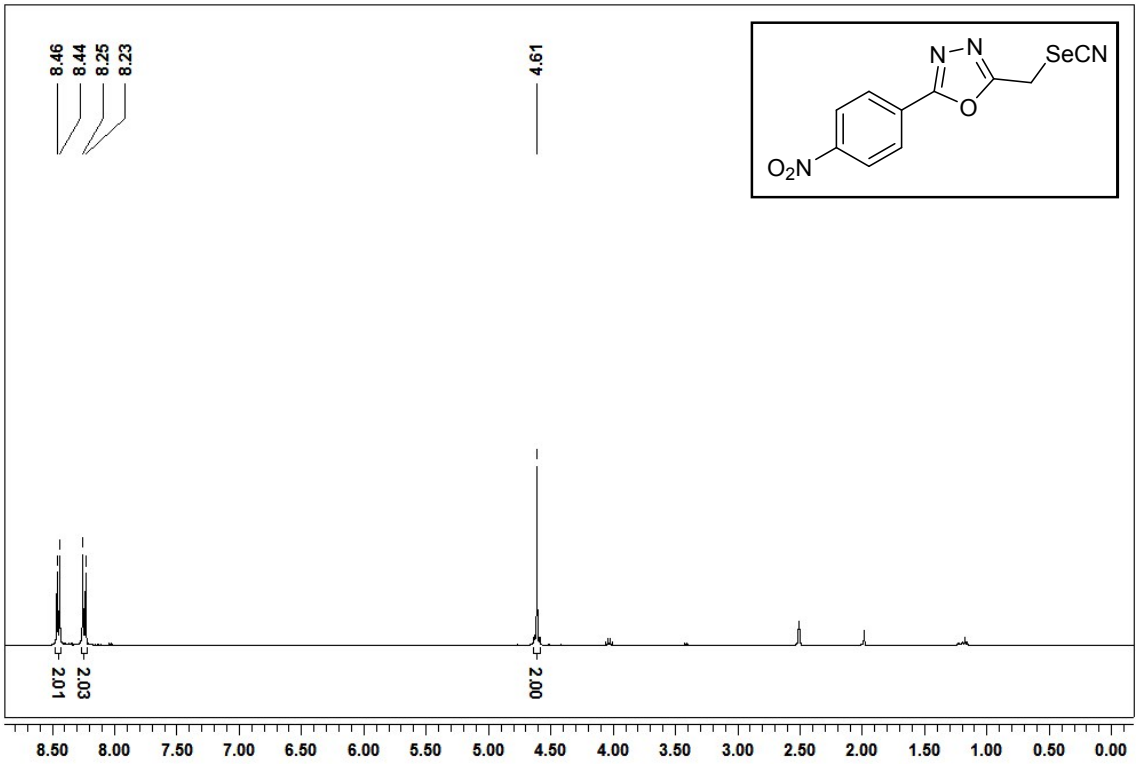
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **7cb**.



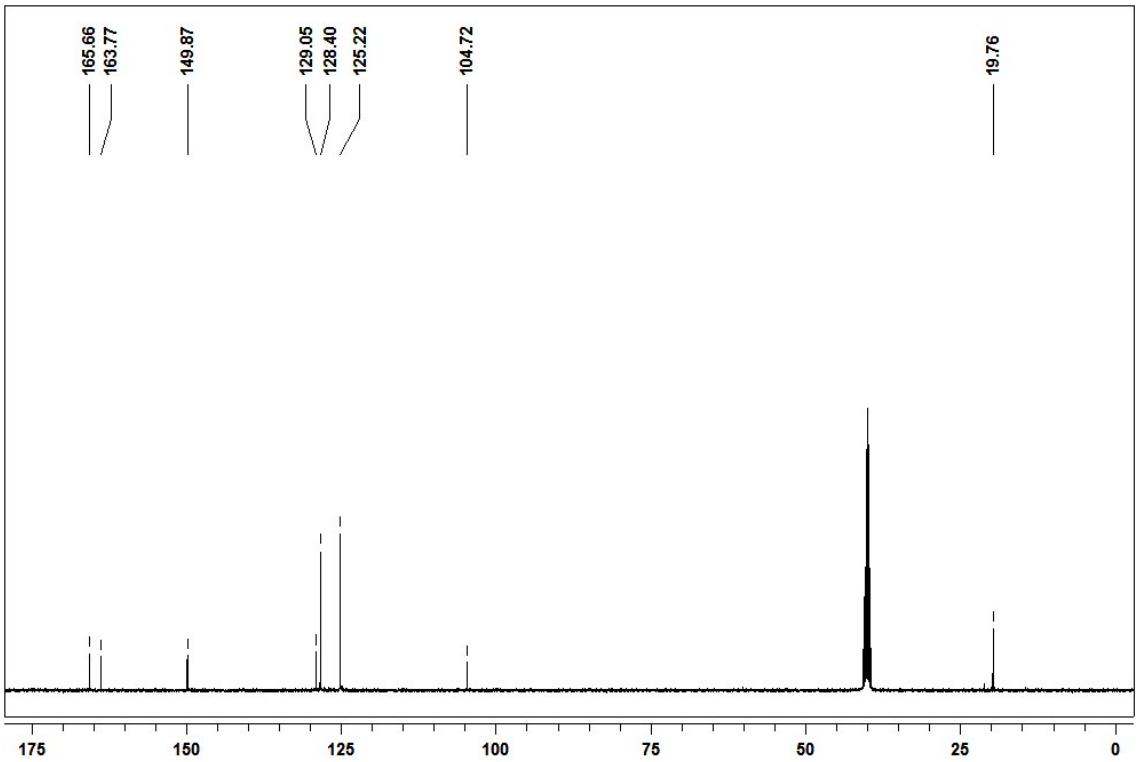
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **7db**.



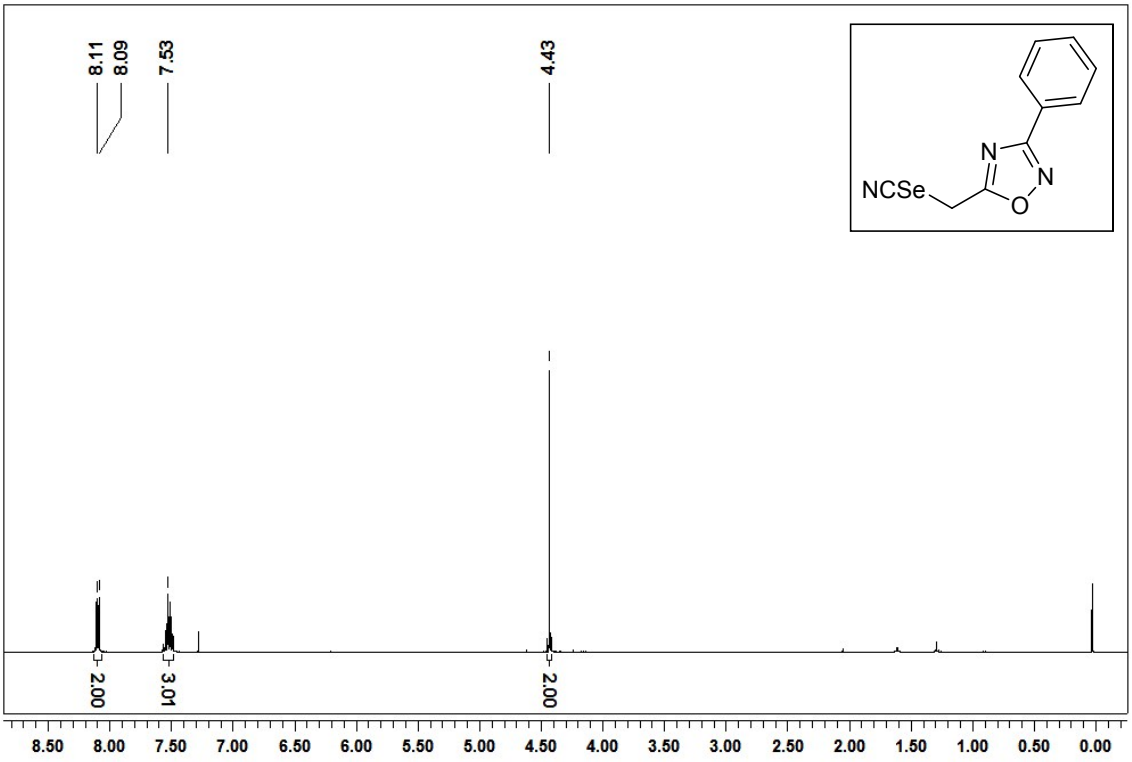
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **7db**.



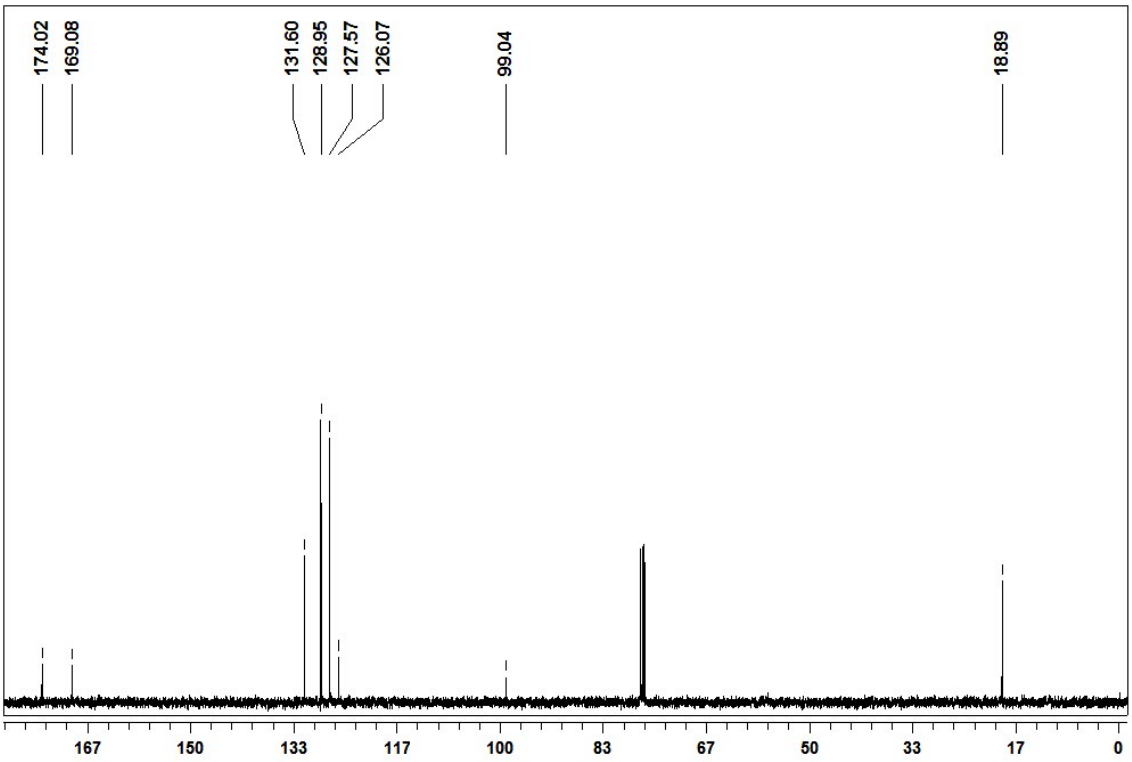
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **7eb**.



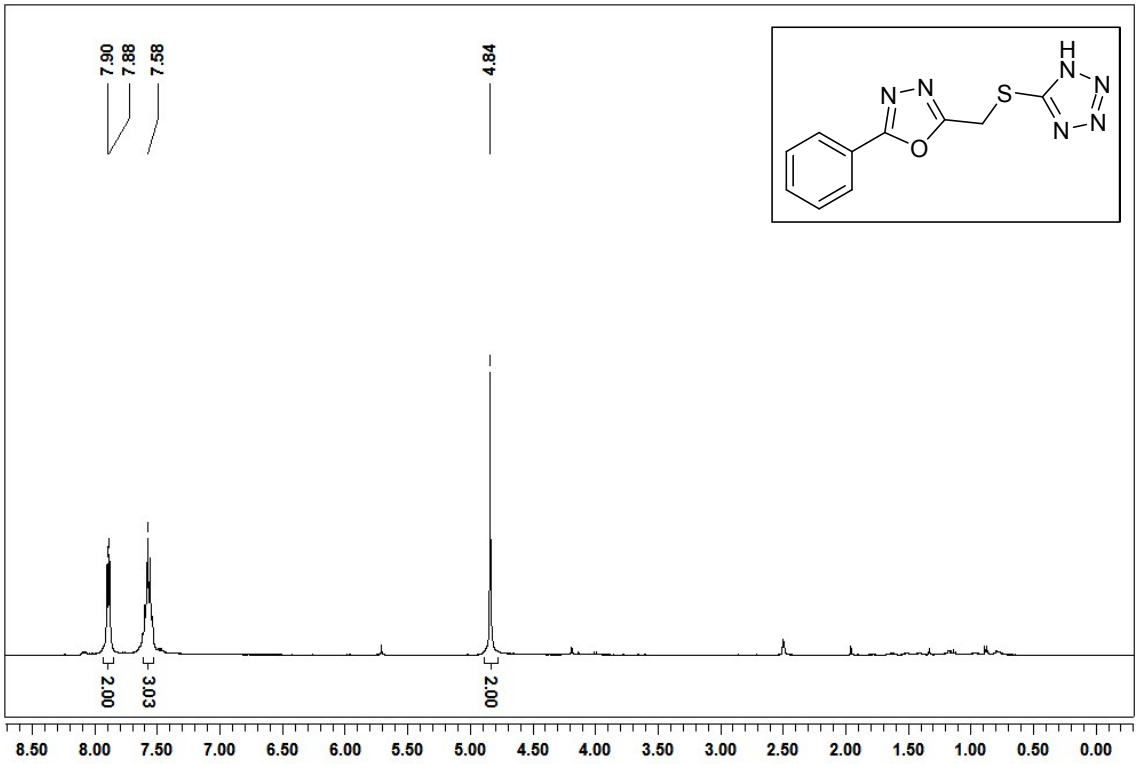
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **7eb**.



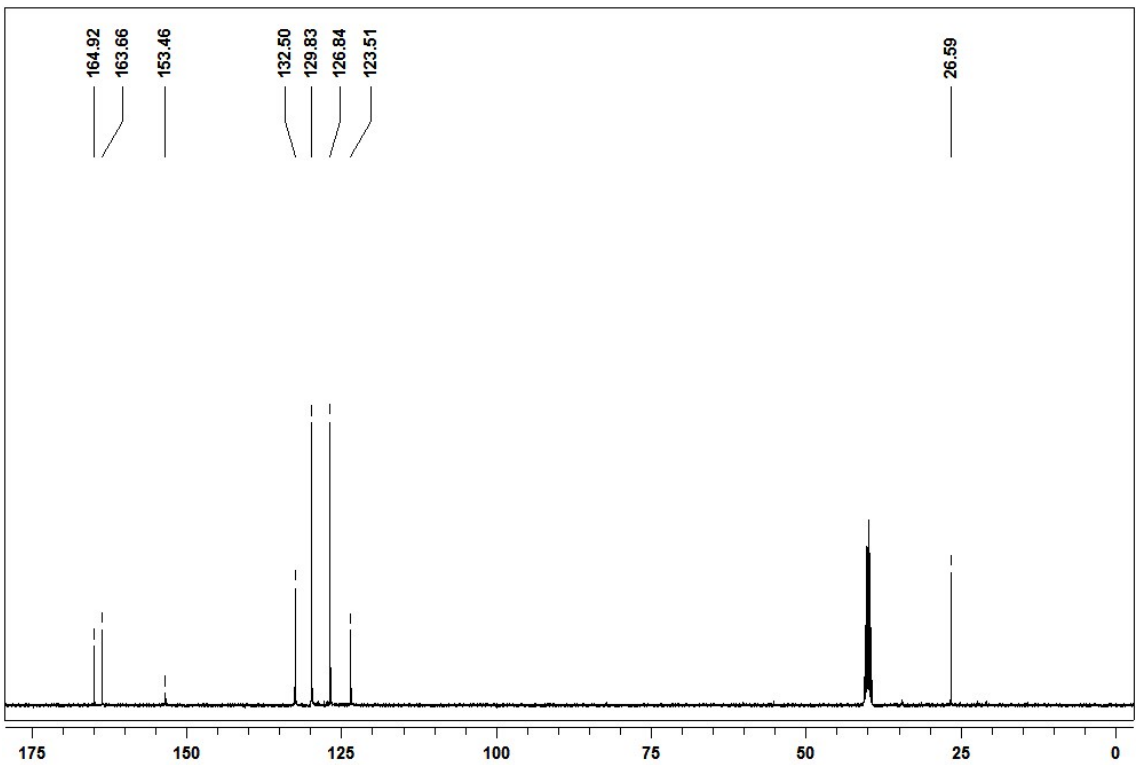
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **8ab**.



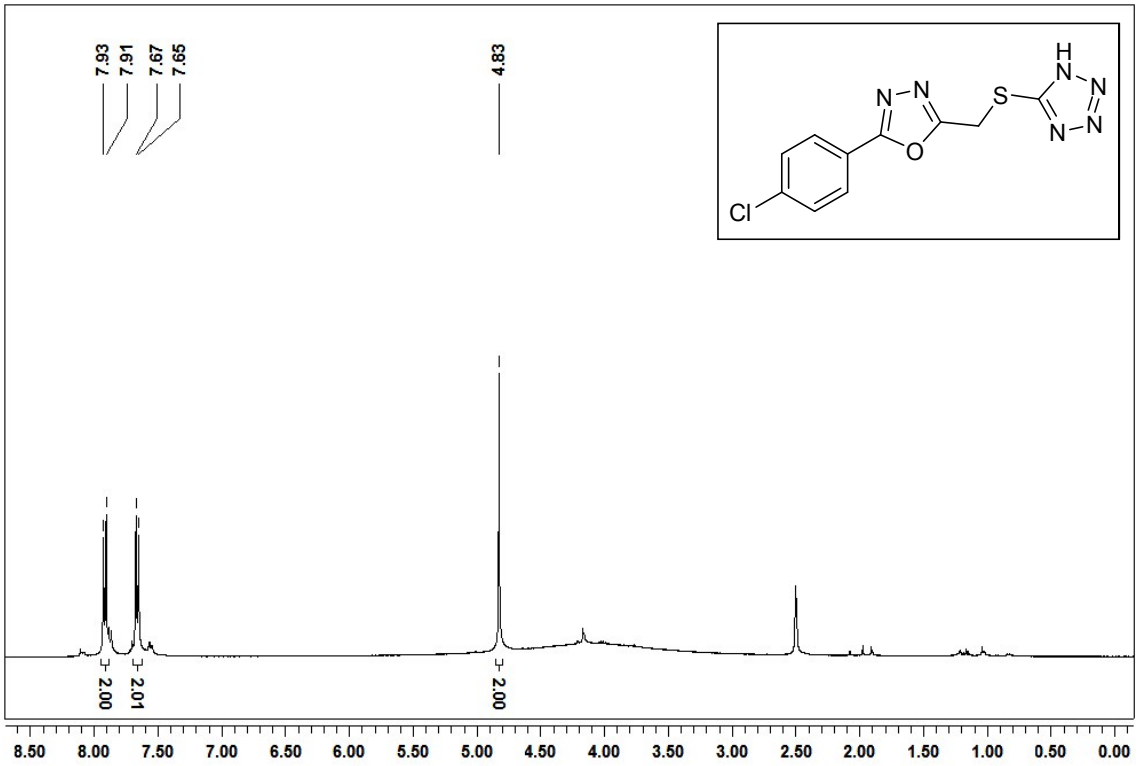
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **8ab**.



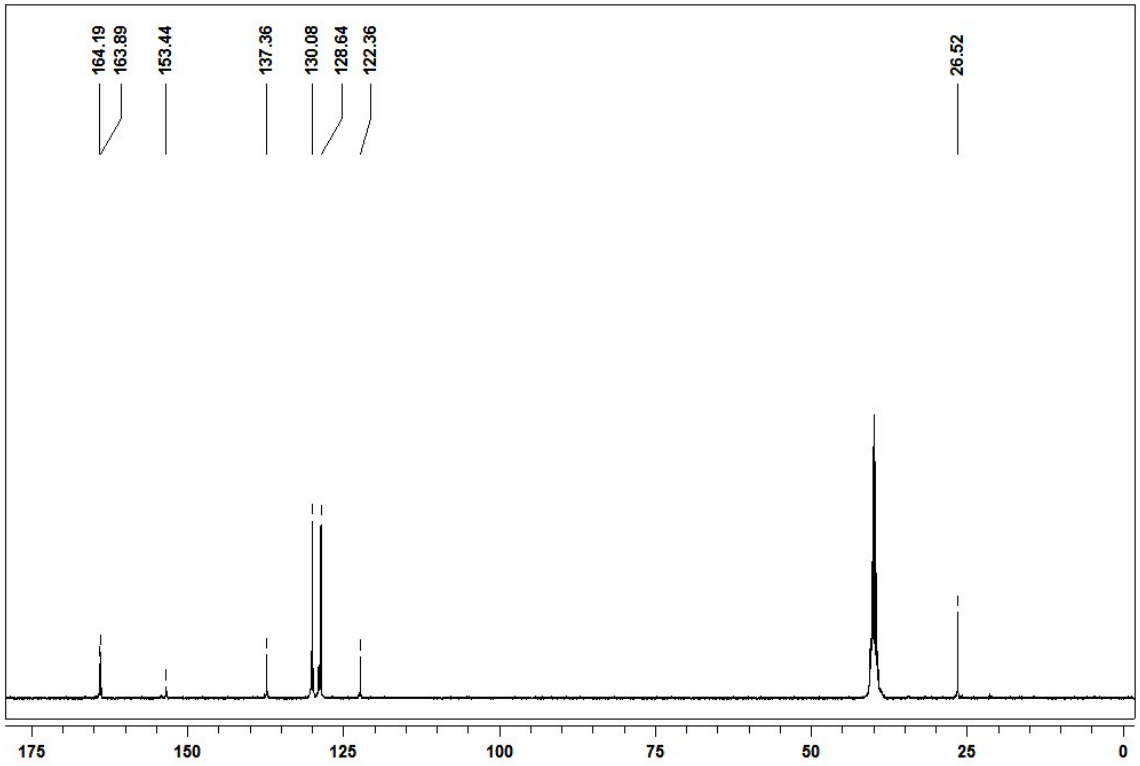
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9aa**.



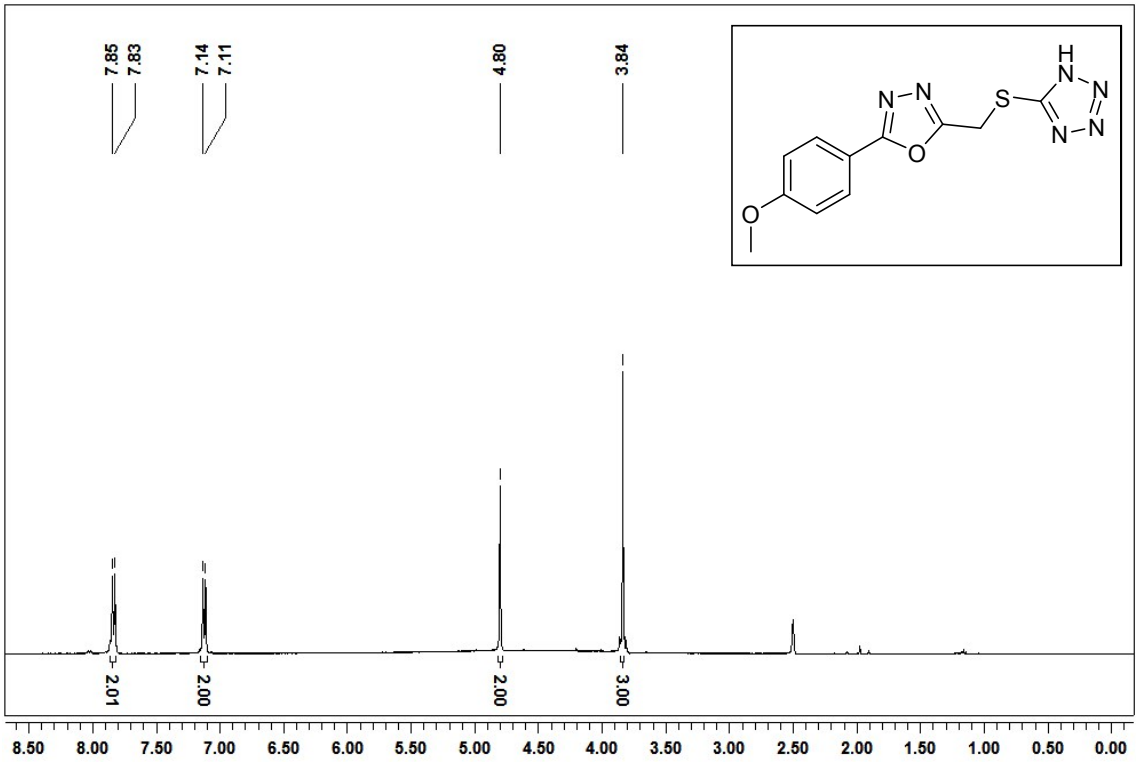
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9aa**.



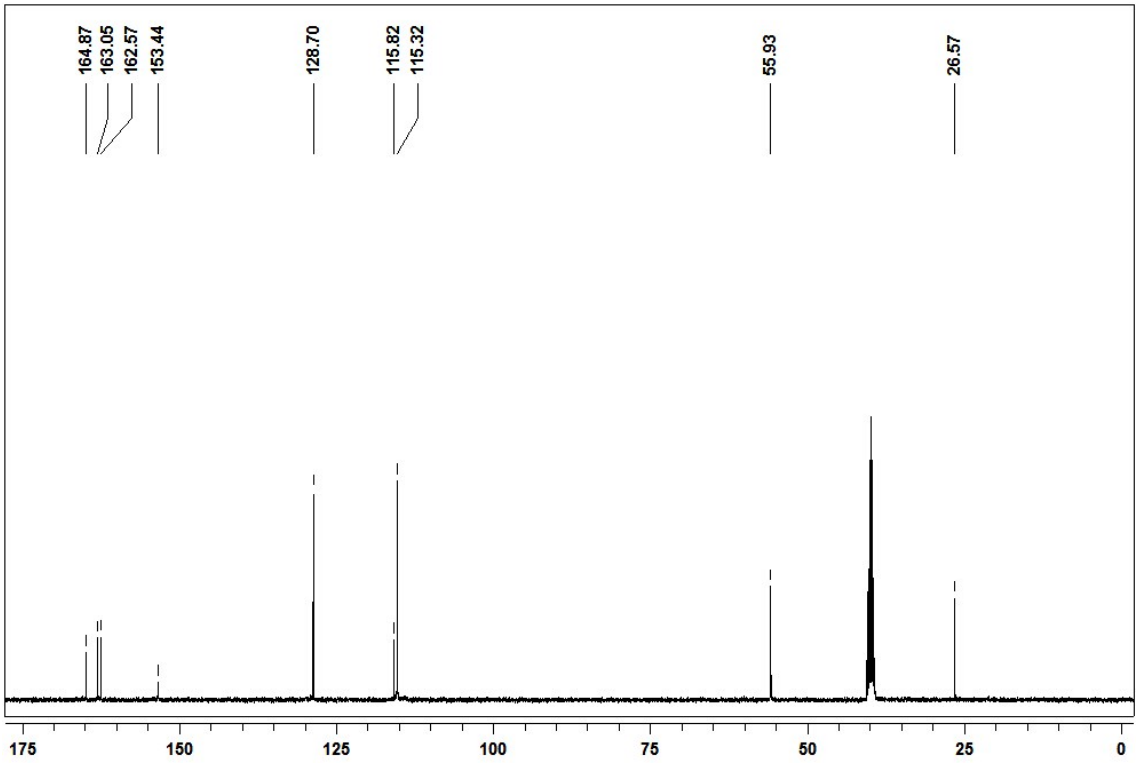
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9ba**.



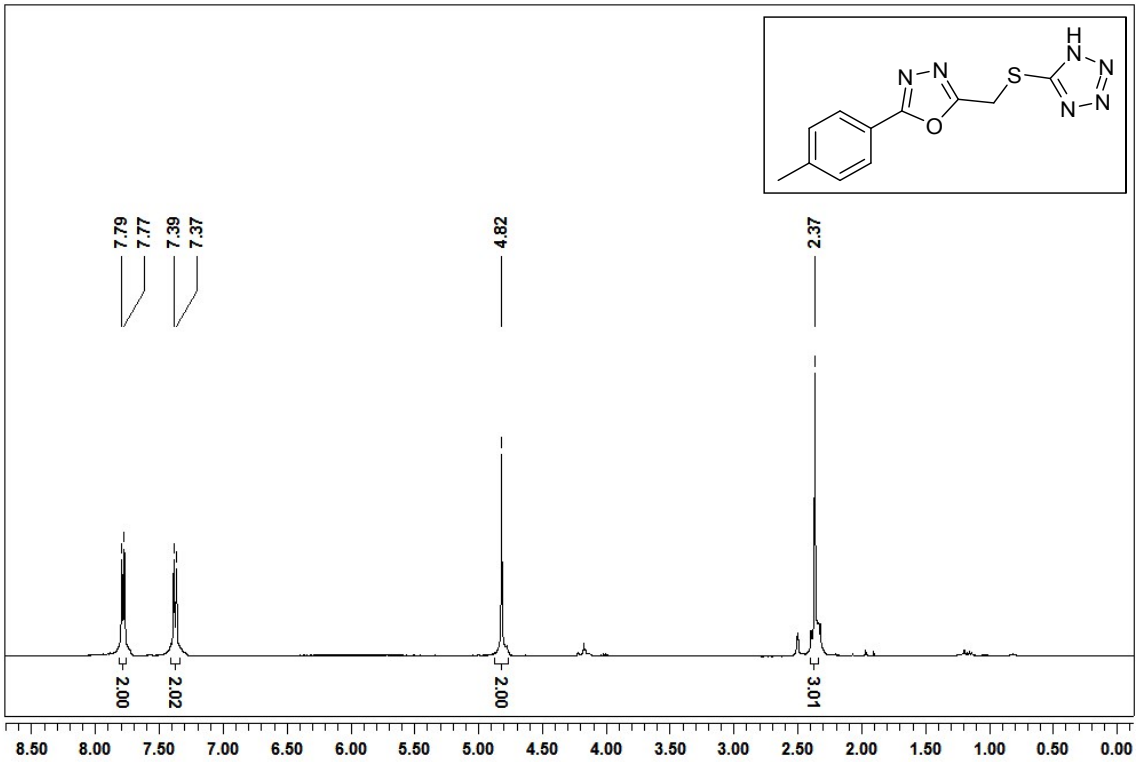
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9ba**.



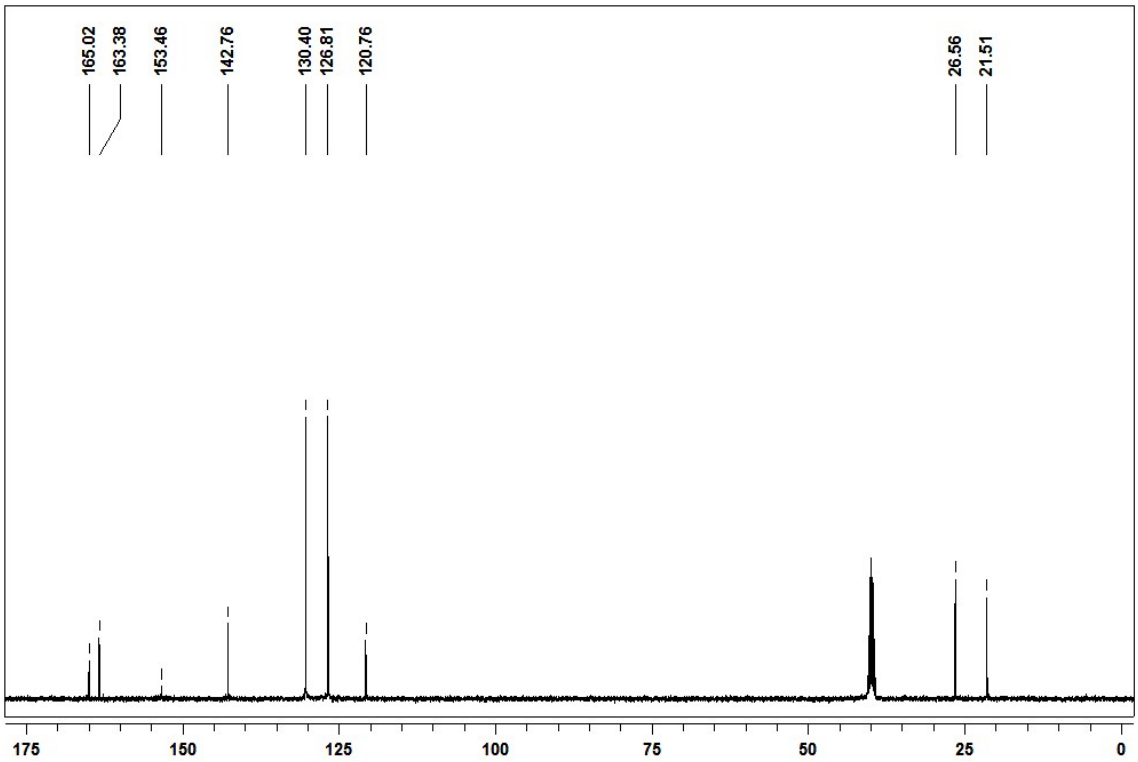
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9ca**.



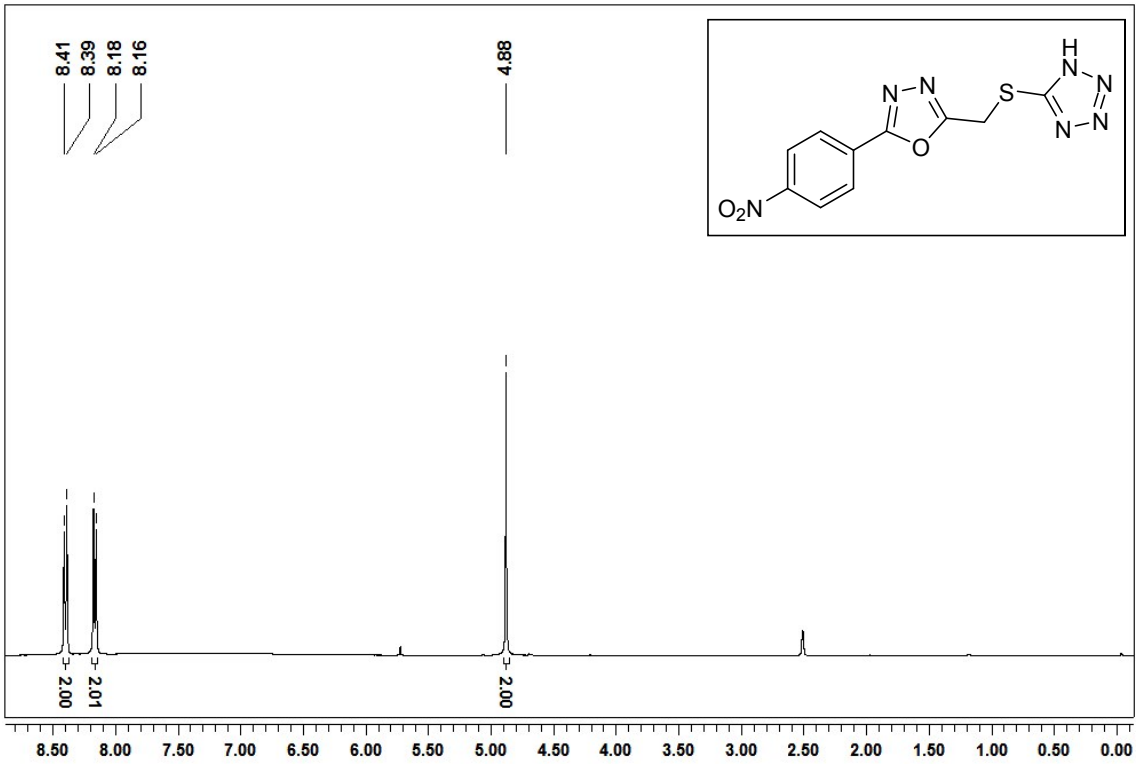
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9ca**.



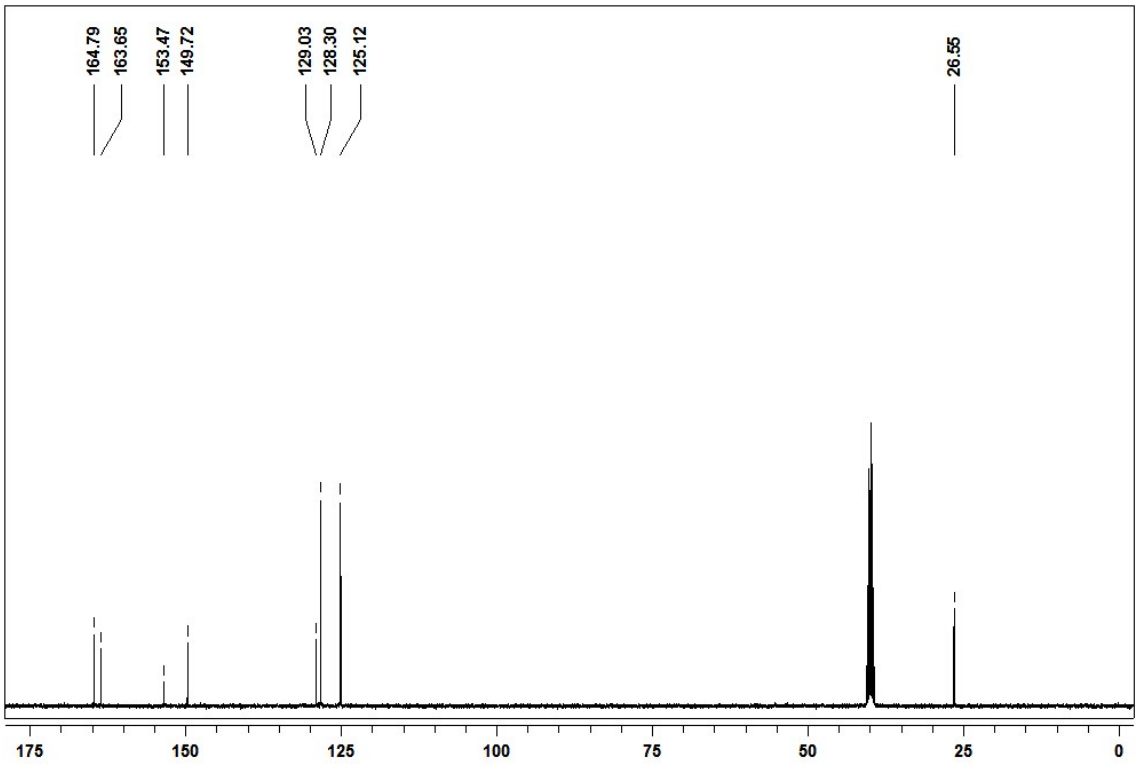
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9da**.



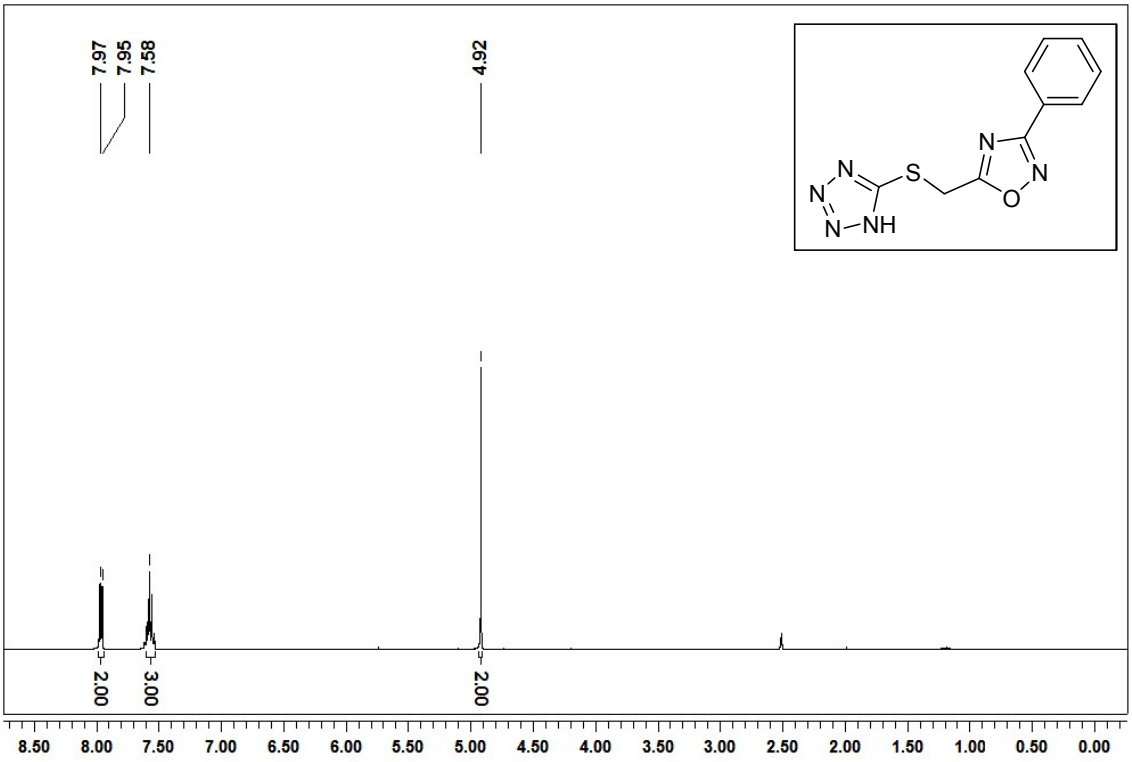
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9da**.



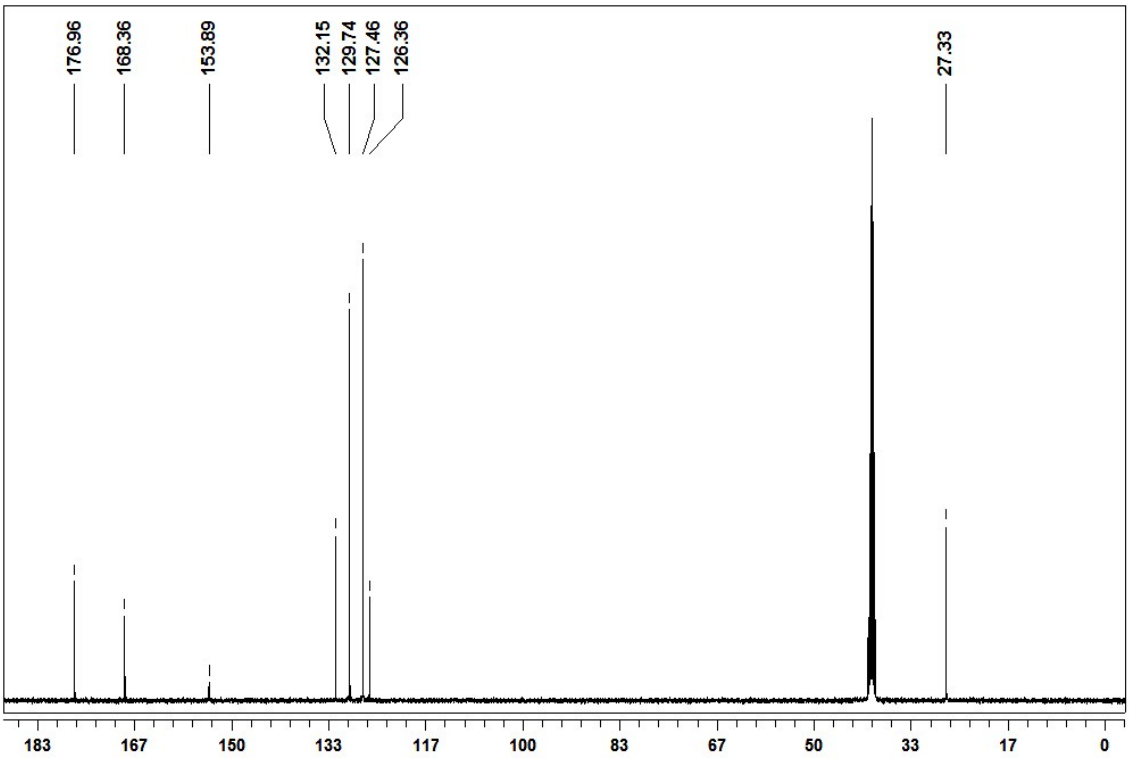
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9ea**.



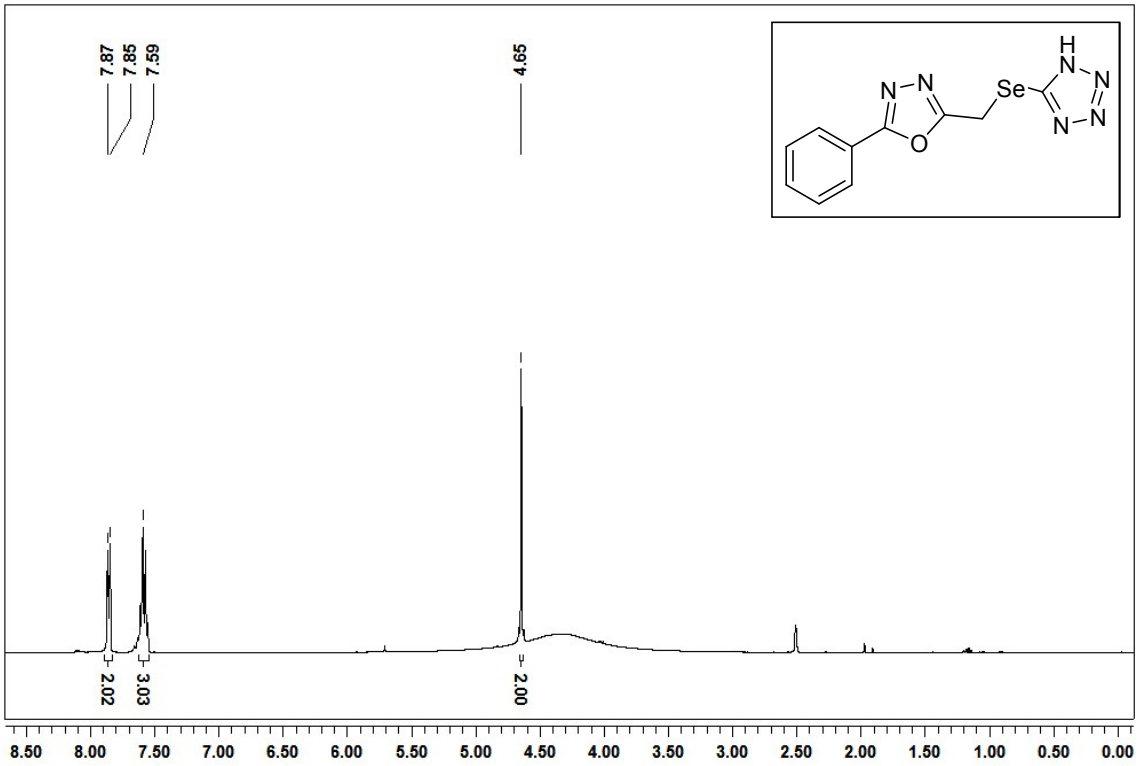
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9ea**.



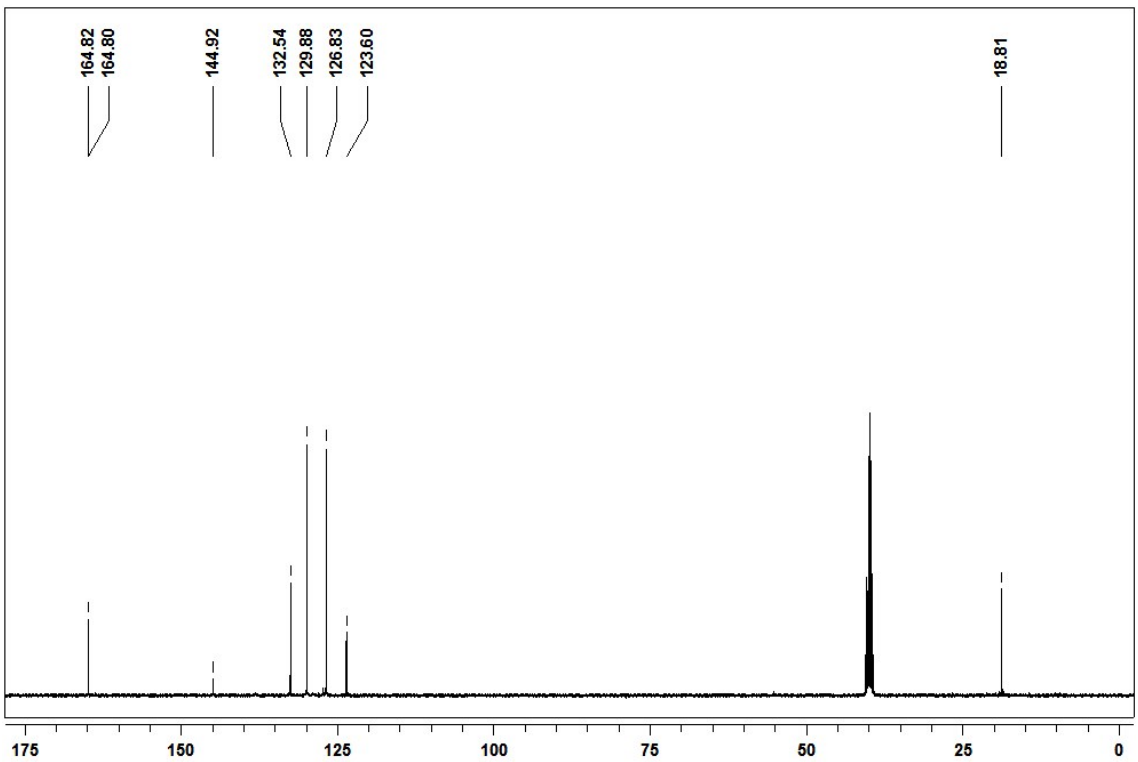
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **10aa**.



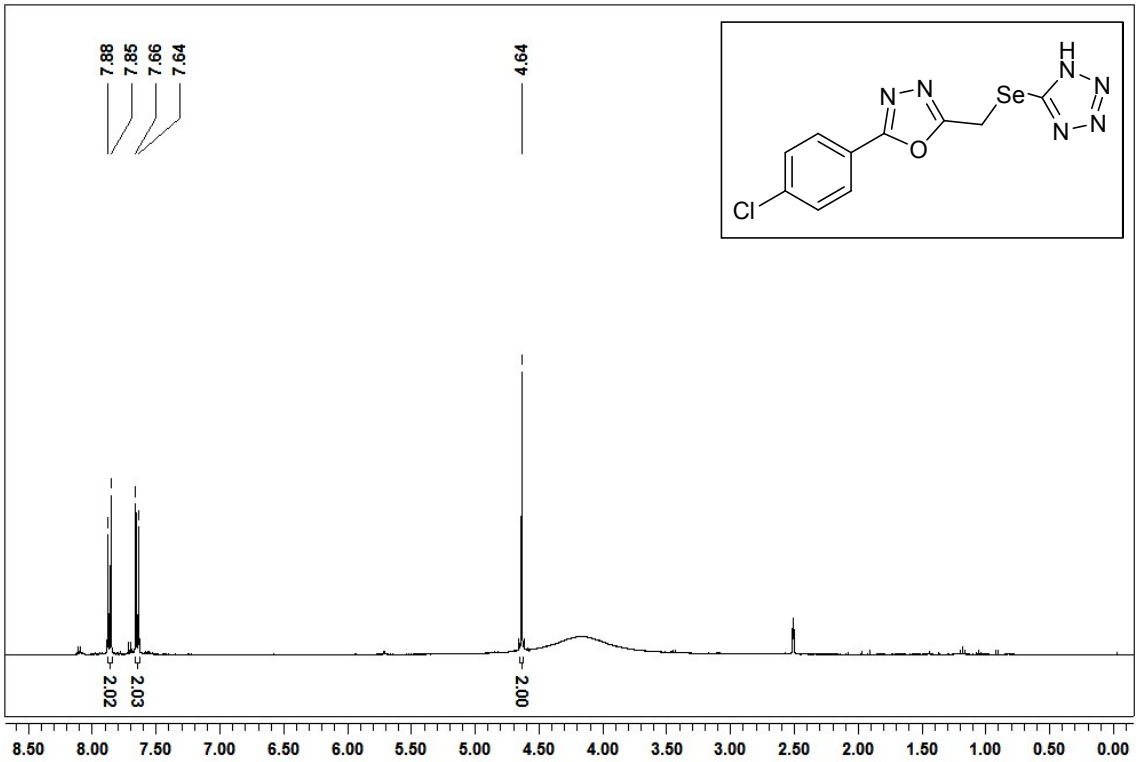
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **10aa**.



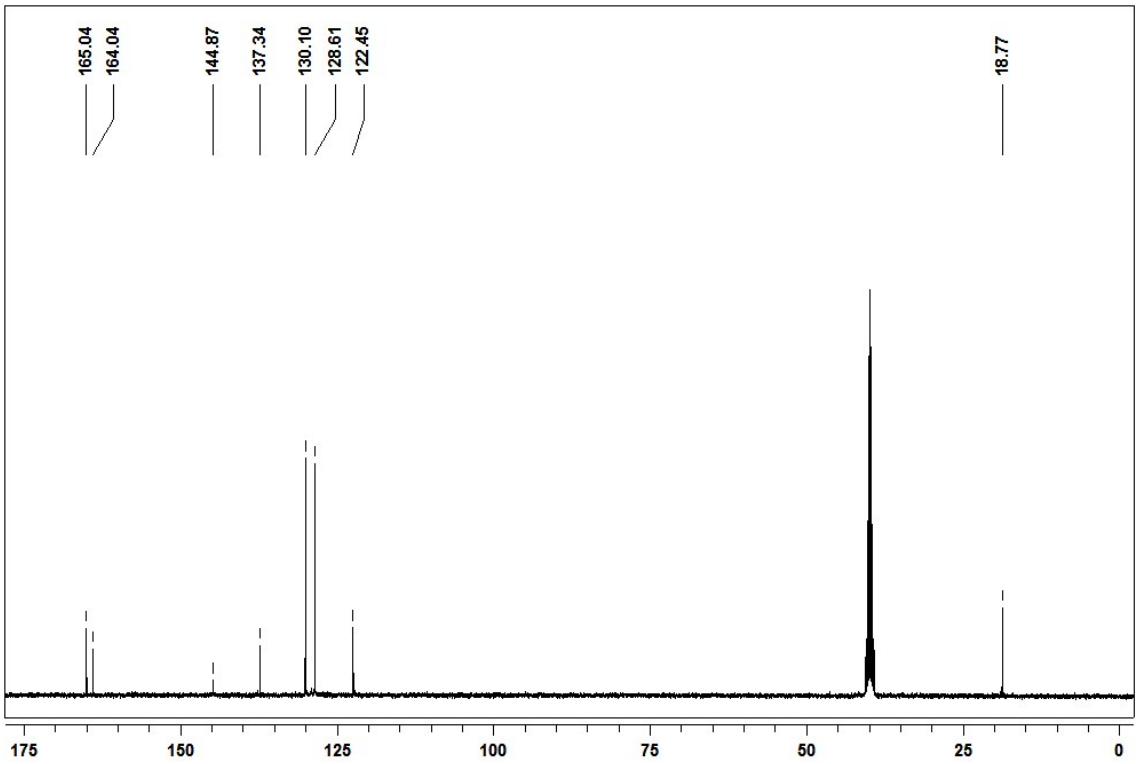
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9ab**.



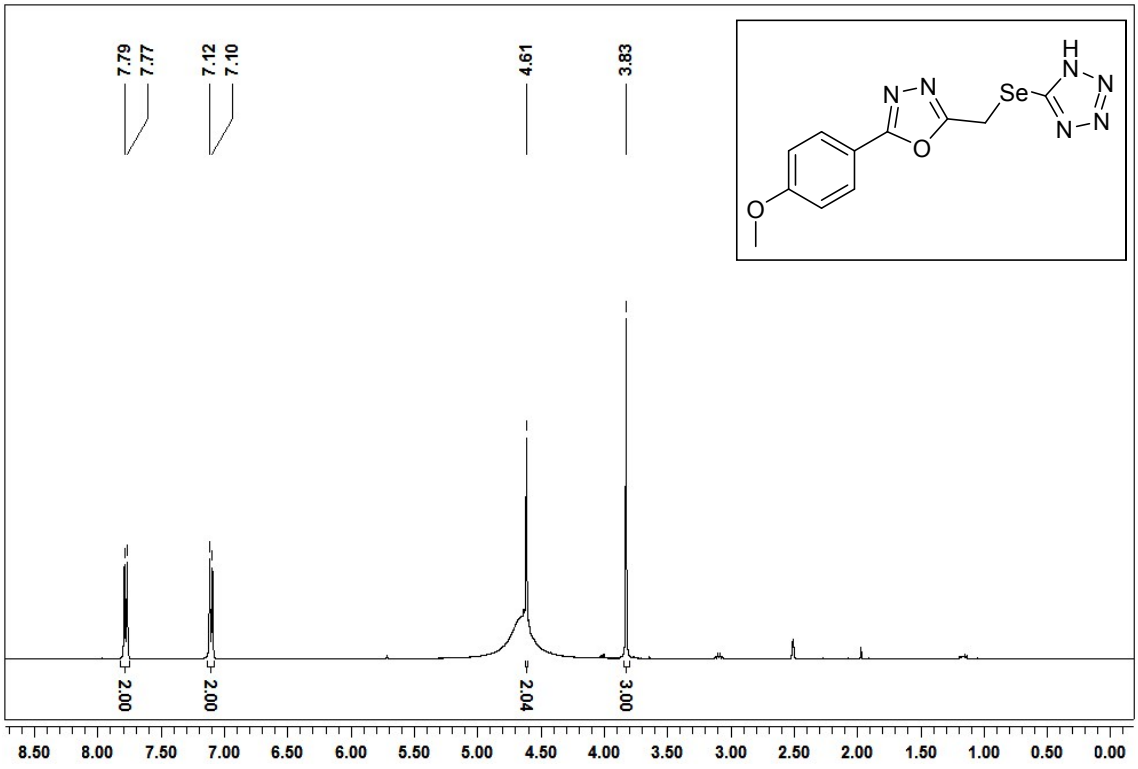
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9ab**.



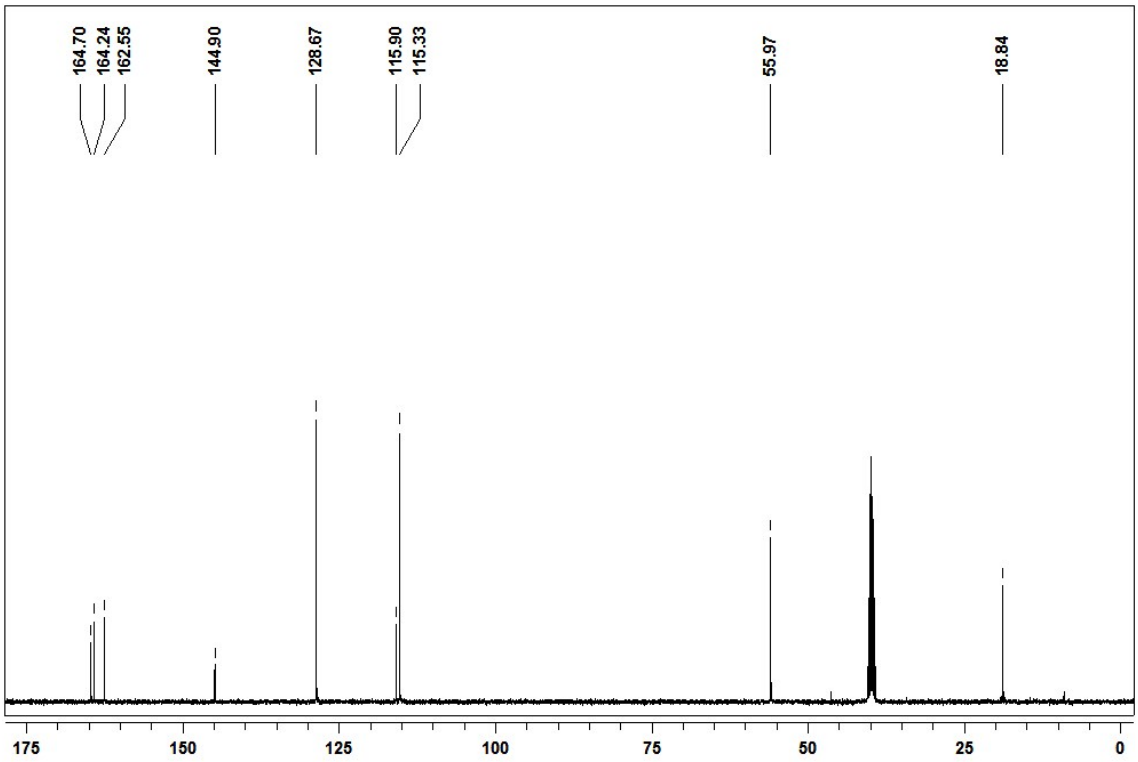
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9bb**.



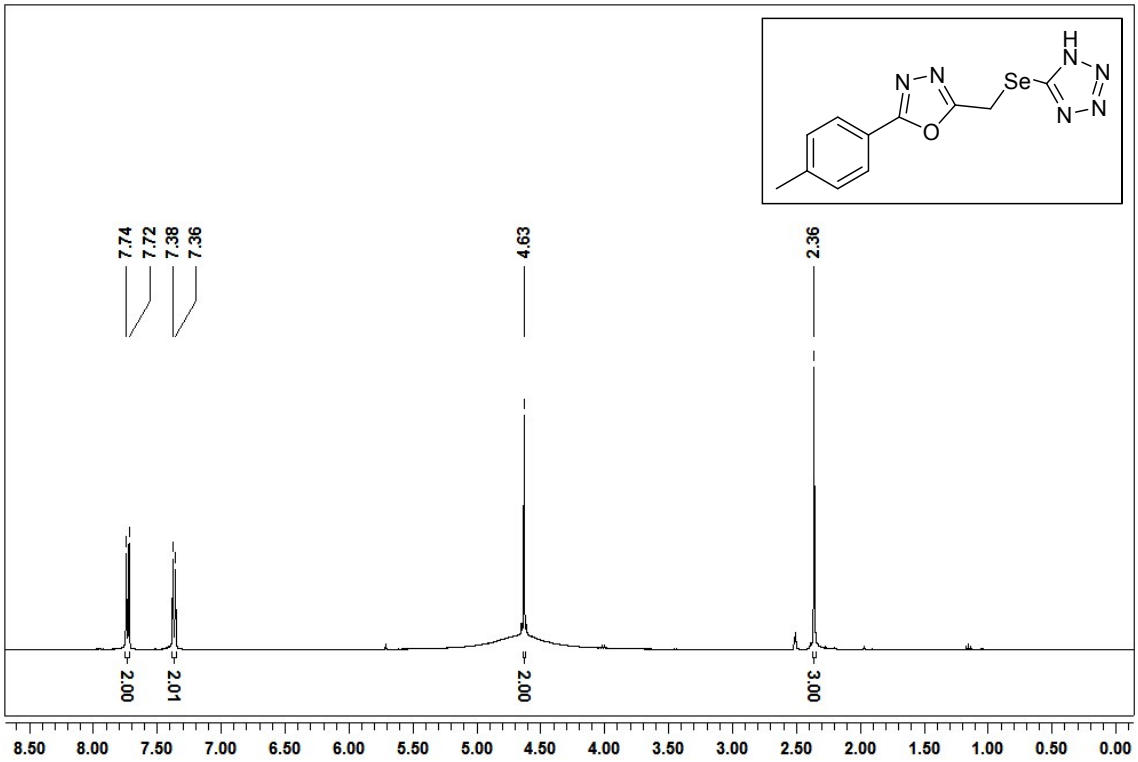
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9bb**.



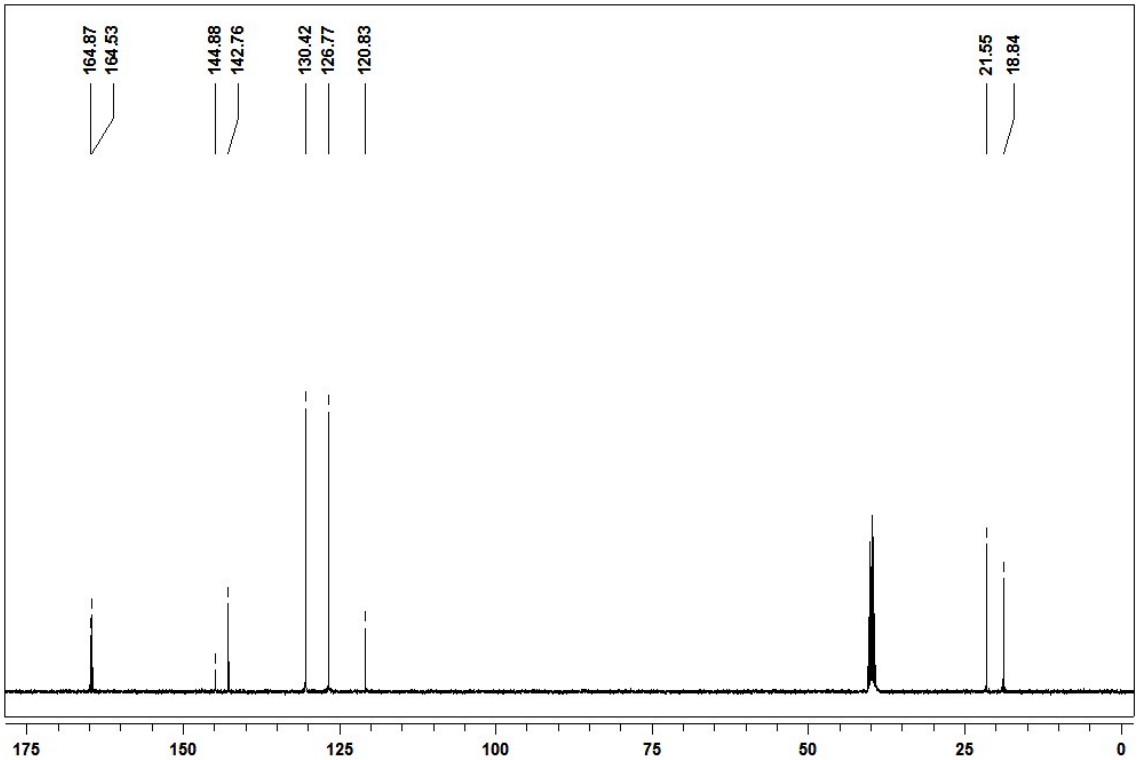
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9cb**.



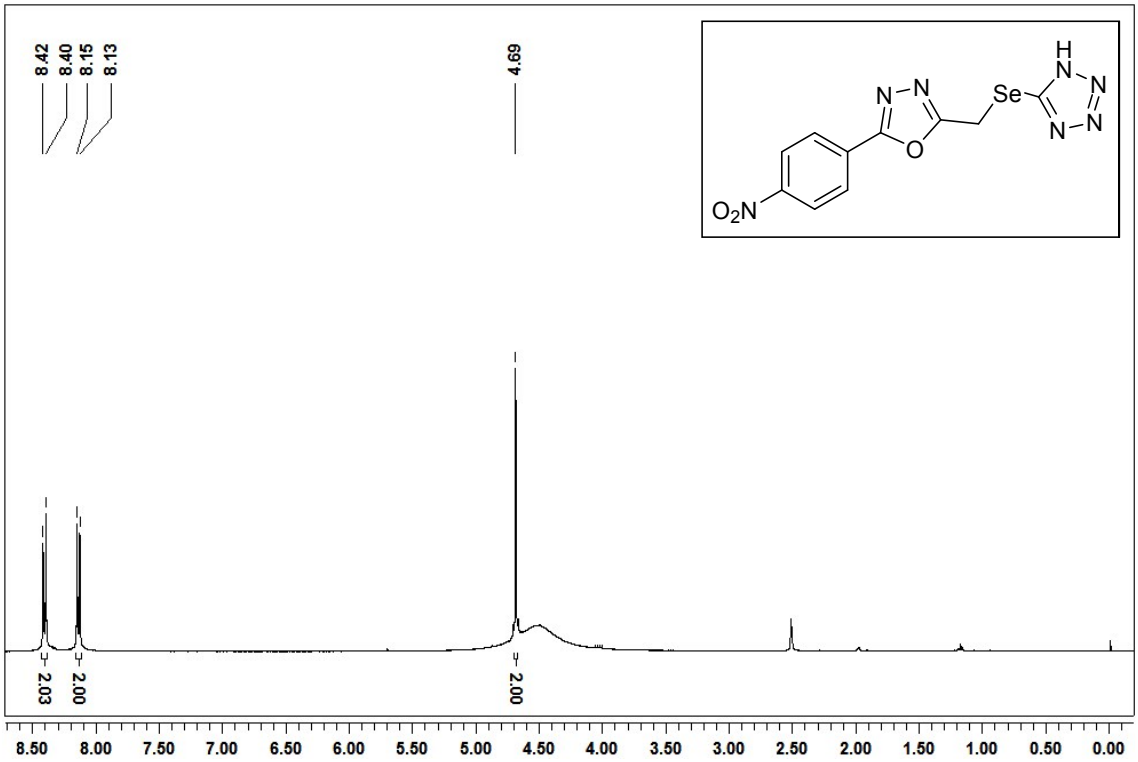
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9cb**.



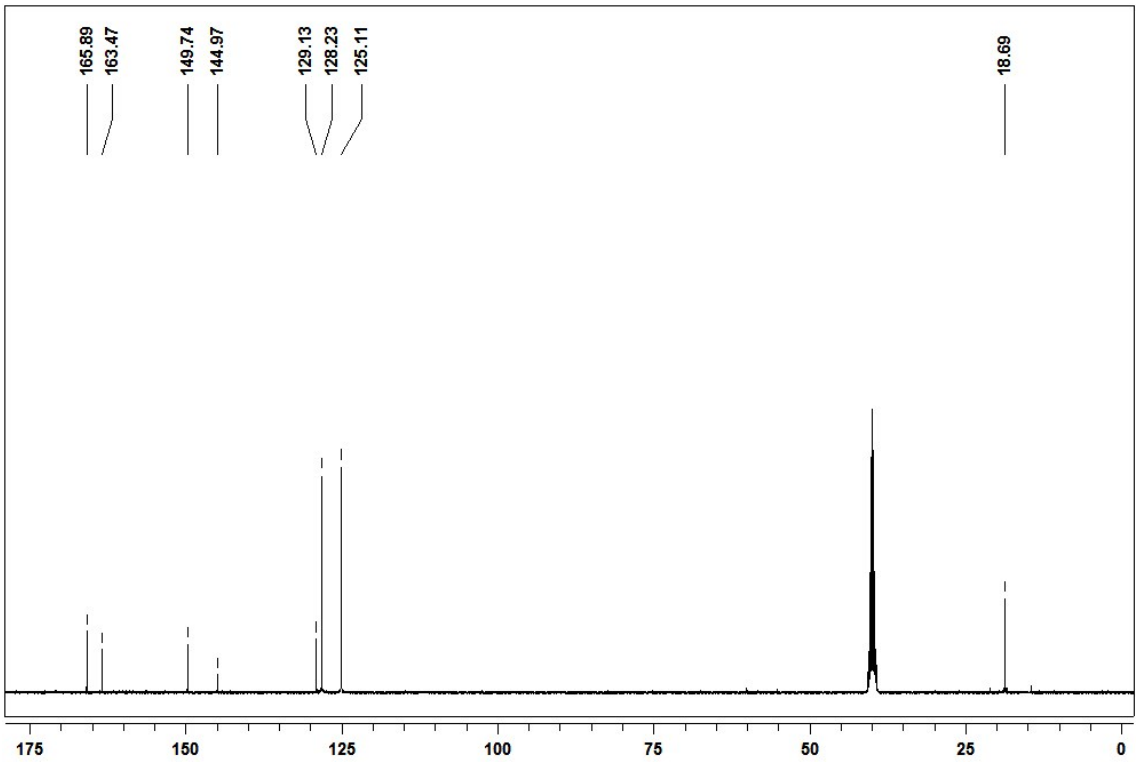
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9db**.



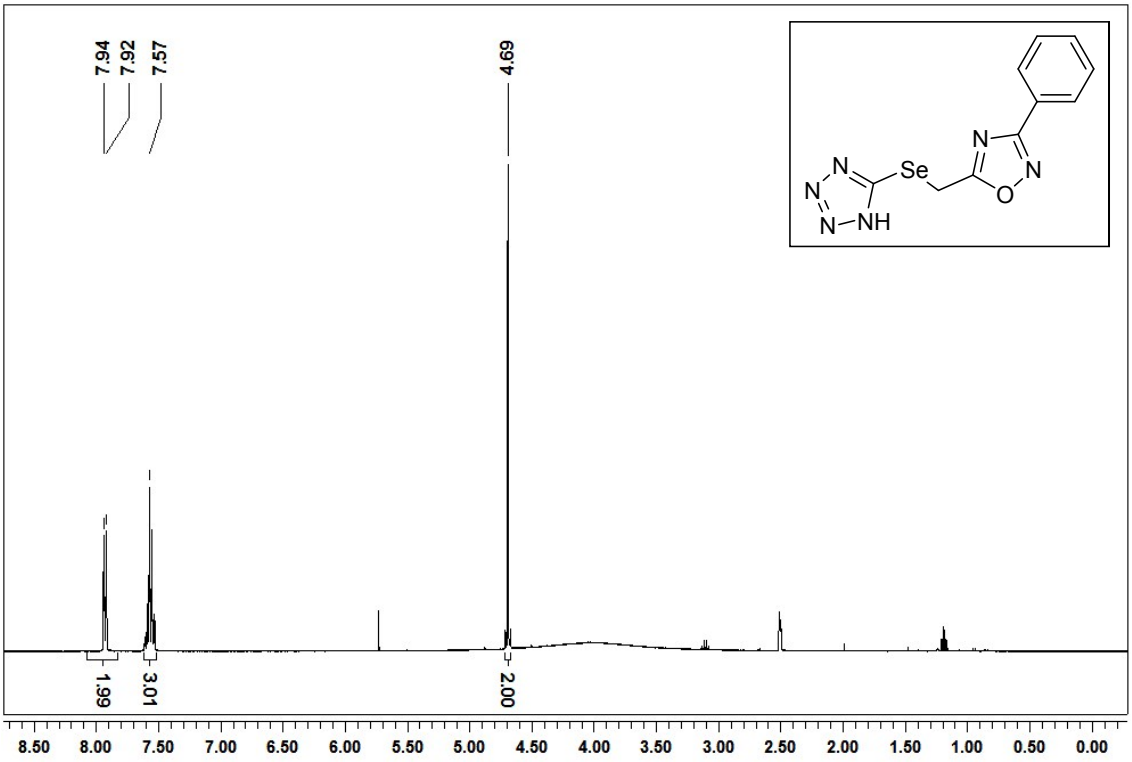
^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9db**.



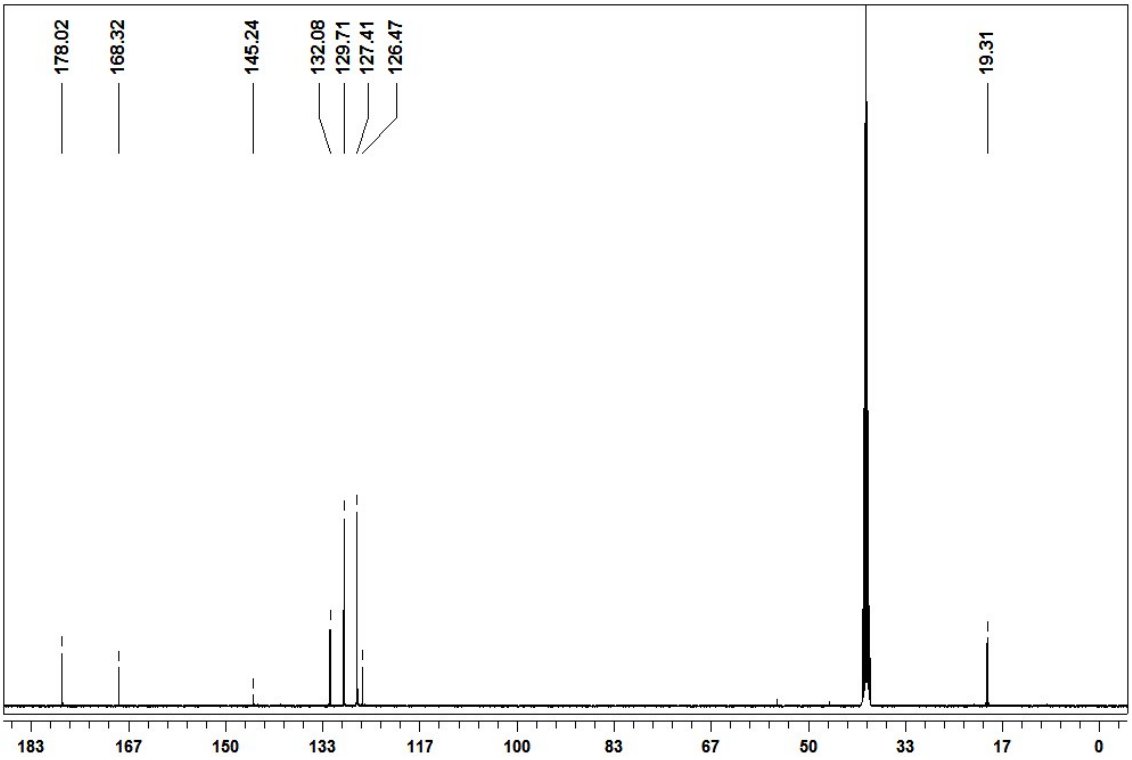
^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **9eb**.



^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **9eb**.



^{1}H NMR spectrum (DMSO-d_6 at 400 MHz) of compound **10ab**.



^{13}C NMR spectrum (DMSO-d_6 at 100 MHz) of compound **10ab**.

X-ray crystallography

Data were collected on a Bruker D8 QUEST Photon 100 diffractometer equipped with an Incoatec IμS high brilliance MoKα X-ray (0.71073 Å) tube with two dimensional Montel micro-focusing optics. The structure was solved by direct methods using SHELXS.[5] Subsequent Fourier-difference map analyses yielded the positions of the non-hydrogen atoms. Refinements were carried out with the SHELXL package.[5] All refinements were made by full-matrix least-squares on F2 with anisotropic displacement parameters for all non–hydrogen atoms. Hydrogen atoms were included in the refinement in calculated positions but the atoms (hydrogen) that are commenting performing special bond were located in the Fourier map. Drawings were done using ORTEP-3[6] and DIAMOND.[7] Crystal data and more details of the data collection and refinement of the compound **9db** are presented in Table S1.

Table S1. Crystal data and details of the refinement of the crystal sctructure of **9db**.

Bond precision:	C-C = 0.0041 A	Wavelength=0.71073
Cell:	a=6.246(2)	b=23.899(7) c=8.301(2)
	alpha=90	beta=97.582(13) gamma=90
Temperature:	100 K	
	Calculated	Reported
Volume	1228.3(6)	1228.3(7)
Space group	P 21/n	P21/n
Hall group	-P 2yn	-P2yn
Moiety formula	C11 H10 N6 O Se	C11 H10 N6 O Se
Sum formula	C11 H10 N6 O Se	C11 H10 N6 O Se
Mr	321.21	321.21
Dx,g cm-3	1.737	1.737
Z	4	4
Mu (mm-1)	3.059	3.059
F000	640.0	640.0
F000'	639.81	
h,k,lmax	8,33,11	8,33,11
Nref	3469	3453
Tmin,Tmax	0.359,0.714	0.374,0.730
Tmin'	0.283	

Correction method= # Reported T Limits: Tmin=0.374 Tmax=0.730
AbsCorr = MULTI-SCAN

Data completeness= 0.995 Theta(max)= 29.630

R(reflections)= 0.0386(2966) wR2(reflections)= 0.1436(3453)

S = 1.167 Npar= 172

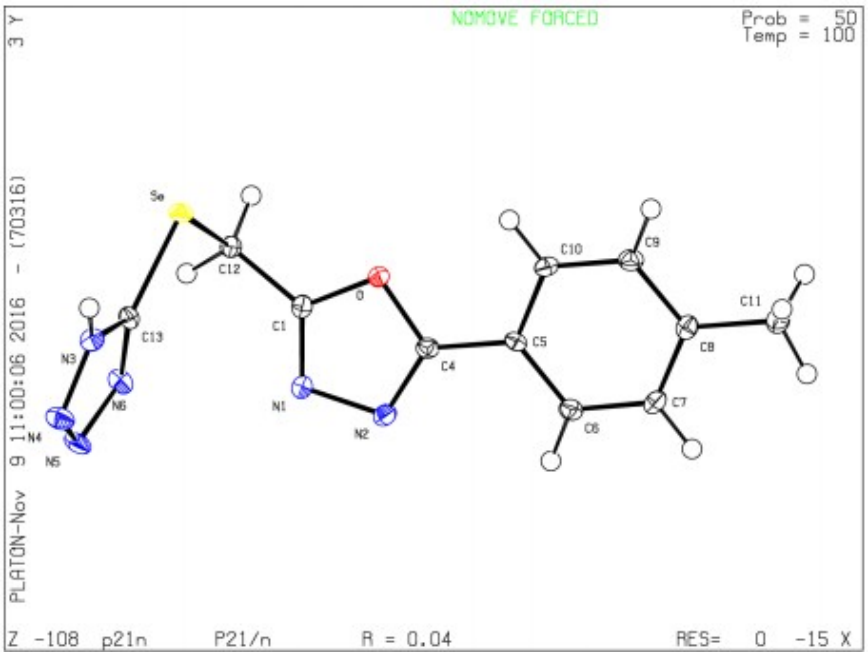


Figure S1. ORTEP representation of the X-Ray crystal structure for compound **9db**.

Antioxidant Potential Evaluation

DPPH$^{\bullet}$ radical scavenging assay

The radical scavenging activities of the compounds were determined as previously described.[8] Each compound was tested at 1, 10, 100 and 1000 µg mL^{-1}. Butylatedhydroxytoluene (BHT) was used as antioxidant standard and was tested at the same concentrations cited before. 2,2-diphenyl-1-picryl-hydrazil radical (DPPH) was added to final concentration of 0.3 mM and allowed to react at room temperature for 30 min in dark conditions. The absorbance was measured at 518 nm using Spectra Max Plate Reader® M2 (Molecular Devices), Sunnyvale, California, USA.

Total antioxidant capacity assay

The total antioxidant potential compounds were evaluated by the phosphomolybdenum method.[9] The compounds and BHT (positive control) was tested at 1, 10, 100 and 1000 µg mL^{-1}. The vials were capped and incubated in a water bath at 95 ºC for 90 min. After cooling the mixture to room temperature, the absorbance was

measured at 695 nm using Spectra Max Plate Reader® M2 (Molecular Devices), Sunnyvale, California, USA.

Table S2. Calculated half maximal effective concentration (EC_{50}) of compounds on scavenging activity of DPPH radical.[a]

Compounds	EC_{50} (µg mL^{-1})
BHT	549.20
7eb	965.89
9ba	873.63
8ab	663.87

[a] The EC_{50} of the remaining compounds were estimate as higher than 1000 µg ml^{-1}.

Cyclic Voltammograms

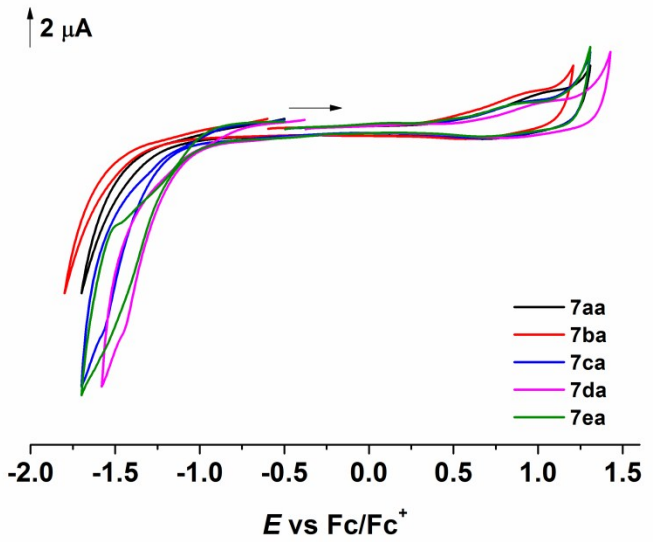


Figure S2. Cyclic voltammogram of compounds **7aa**, **7ba**, **7ca**, **7da** and **7ea** measured in dry acetonitrile solution, using $TBAPF_6$ as supporting electrolyte, at scan rate 100 mV/s, respectively.

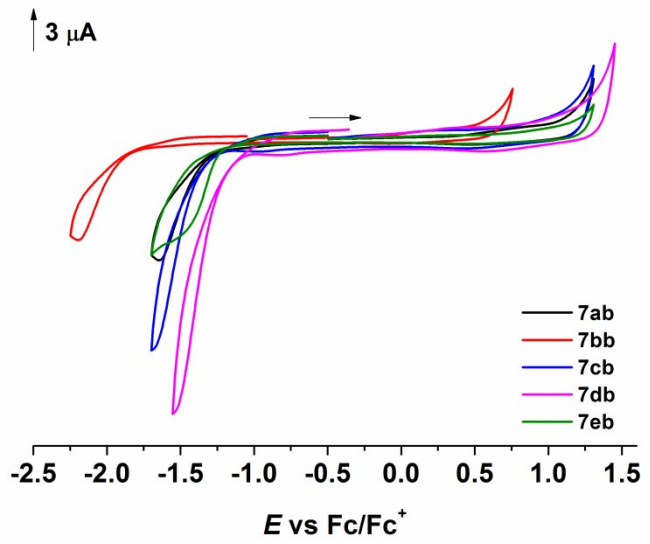


Figure S3. Cyclic voltammogram of compounds **7ab**, **7bb**, **7cb**, **7db** and **7eb** measured in dry acetonitrile solution, using $TBAPF_6$ as supporting electrolyte, at scan rate 100 mV/s, respectively.

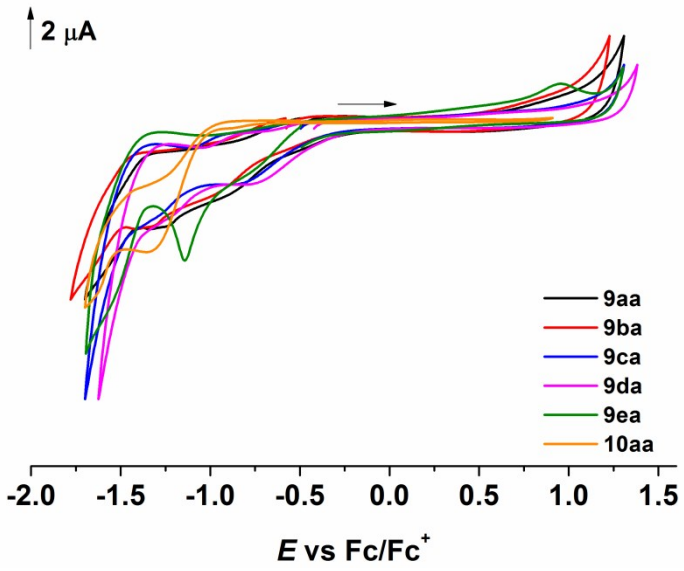


Figure S4. Cyclic voltammogram of compounds **9aa**, **9ba**, **9ca**, **9da**, **9ea** and **10aa** measured in dry acetonitrile solution, using $TBAPF_6$ as supporting electrolyte, at scan rate 100 mV/s, respectively.

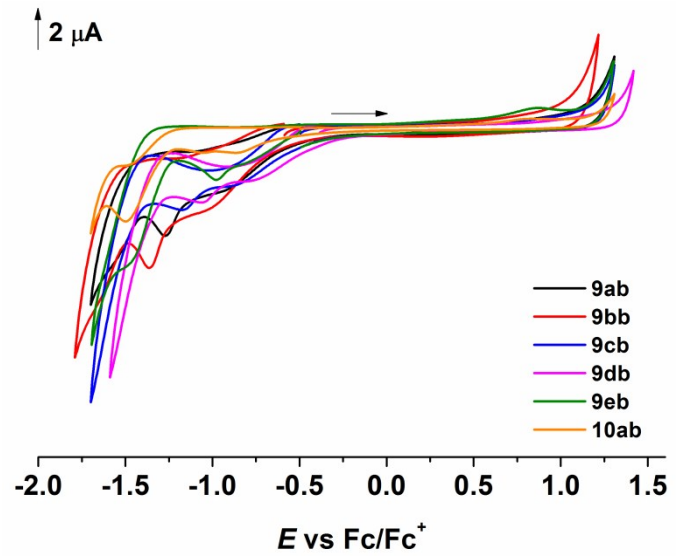


Figure S5. Cyclic voltammogram of compounds **9ab**, **9bb**, **9cb**, **9db**, **9eb** and **10ab** measured in dry acetonitrile solution, using $TBAPF_6$ as supporting electrolyte, at scan rate 100 mV/s, respectively.

References

1. J. Balsells, L. DiMichele, J. Liu, M. Kubryk, K. Hansen and J. D. Armstrong, *Org. Lett.*, 2005, **7**, 1039.
2. A. Kiss-Szikszai, T. Patonay and J. Jekő, *ARKIVOC*, 2001, 40.
3. N. B. Patel and S. D. Patel, *Chem. Biol. Interface*, 2012, **2**, 183.
4. Y. Dürüst, H. Karakuş, M. Kaiser and D. Tasdemir, *Eur. J. Med. Chem.*, 2012, **48**, 296.
5. G. M. Sheldrick, *Acta Cryst. A*, 2008, **64**, 112.
6. L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.
7. DIAMOND 3.1a. 1997–2005, Version 1.1a . K. Brandenburg, Crystal Impact GbR, Bonn, Germany.
8. W. Brand-Williams, M. E. Cuvelier and C. Berset, *LWT - Food Sci. Technol.*, 1995, **28**, 25.
9. P. Prieto, M. Pineda and M. Aguilar, *Anal. Biochem.*, 1999, **269**, 337.