

SUPPLEMENTARY MATERIAL

1,2,4-Oxadiazole/2-imidazoline hybrids: Multi-target-directed compounds for the treatment of infectious diseases and cancer

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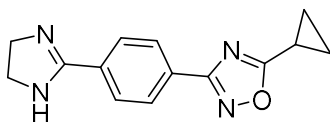
S1. General information

All reagents and solvents were obtained from commercial sources and were used without purification. DMSO was dried over molecular sieves (4 Å). Reactions were monitored by analytical thin layer chromatography (TLC) using Macherey-Nagel TLC sheets (Silufol UV-254) and the developed sheets were visualized under UV light. NMR spectra were recorded on Bruker AVANCE DPX 400 at 400 MHz and 101 MHz for ^1H and ^{13}C , respectively. Chemical shifts are reported as parts per million (δ , ppm) and were referenced to the residual solvent peaks at 7.26 and 2.50 ppm for ^1H in CDCl_3 and $\text{DMSO-}d_6$ respectively, and 39.52 and 77.16 ppm for ^{13}C in $\text{DMSO-}d_6$ and CDCl_3 respectively. Multiplicities are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants, J , are reported in Hertz (Hz). Melting points were determined in open capillary tubes with an Electrothermal IA 9300 series Digital Melting Point Apparatus. High-resolution mass spectra (HRMS) were recorded with a Bruker maXis HRMS-ESI-QTOF (ESI mode).

S2. Synthesis and characterization of 1,2,4-oxadiazoles

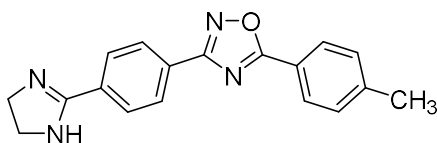
General procedure for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles (3a-h, 5a-t)

To a solution of the amidoxime (2 mmol) and the appropriate carboxylic ester (2 mmol) in DMSO (1 mL), 120 mg (3 mmol) powdered NaOH was rapidly added. The reaction mixture was stirred at room temperature for the required time (TLC or precipitation of the product). The reaction mixture was diluted with cold water (30–50 mL). The resulting precipitate was collected by filtration, washed with water (30 mL), dried and purified by column chromatography (eluent: 5% methanol / 95% chloroform).



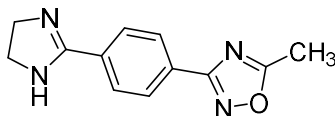
5-Cyclopropyl-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (3a)

White solid, 89 % (391 mg) yield, m.p. 170–172 °C. ^1H NMR (DMSO- d_6 , 300 MHz): δ 7.99 (q, $J_1 = 8.6$ Hz, $J_2 = 14.9$ Hz, 2H), 7.36 – 7.04 (br s, 1H), 3.64 (s, 4H), 2.46 – 2.37 (m, 1H), 1.26–1.33 (m, 2H), 1.23 – 1.16 (m, 2H). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 182.5, 167.6, 163.4, 133.7, 128.3, 128.1, 127.3, 50.0, 10.5, 7.7. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 255.1240, found 255.1253.



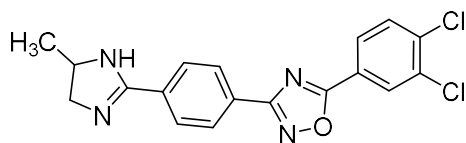
3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-p-tolyl-1,2,4-oxadiazole (3b)

White solid, 77 % yield, m.p. 184–186 °C. ^1H NMR (DMSO- d_6 , 300 MHz): δ 8.11 (dd, $J_1 = 7.8$ Hz, $J_2 = 16.4$ Hz, 4H), 8.03 (d, $J = 7.8$ Hz, 2H), 7.48 (d, $J = 7.3$ Hz, 2H), 7.05 (s, 1H), 3.89 – 3.79 (m, 2H), 3.39–3.49 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 179.2, 175.0, 156.8, 142.6, 130.5, 130.2, 130.1, 127.4, 127.0, 126.9, 124.8, 119.5, 55.9, 32.0. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 305.1397, found 305.1387.



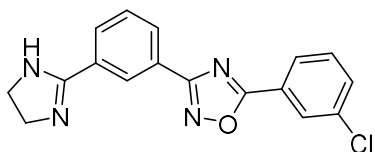
3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-methyl-1,2,4-oxadiazole (3c)

White solid, 63 % (156 mg) yield, m.p. 168–170 °C. ^1H NMR (DMSO- d_6 , 300 MHz): δ 8.06 – 7.95 (m, 4H), 7.06 (s, 1H), 3.63 (s, 4H), 2.67 (s, 3H). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 178.1, 167.7, 163.4, 133.8, 128.3, 128.2, 127.3, 55.6, 12.5. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{12}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 229.1084, found 229.1093.



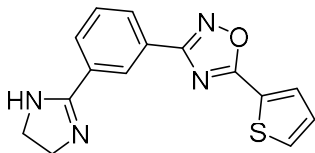
5-(3,4-Dichlorophenyl)-3-(4-(5-methyl-4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (3d)

White powder, 52 % (195 mg) yield, m.p. 190–192 °C. ¹H NMR (400 MHz, DMSO) δ 8.18 (m, 3H), 8.05 (d, *J* = 8.4 Hz, 2H), 8.00 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 4.09–3.99 (m, 1H), 3.85 – 3.77 (m, 1H), 3.24 (dd, *J* = 12.1, 7.9 Hz, 1H), 1.20 (d, *J* = 6.3 Hz, 3H). ¹³C NMR (101 MHz, DMSO) δ 175.8, 167.1, 161.7, 135.4, 134.9, 132.7, 132.2, 129.1, 128.5, 128.3, 127.5, 127.0, 124.7, 58.0, 57.0, 22.3. HRMS (ESI) calcd for C₁₈H₁₄Cl₂N₄O [*M*+*H*]⁺ 373.0617, found 373.0633.



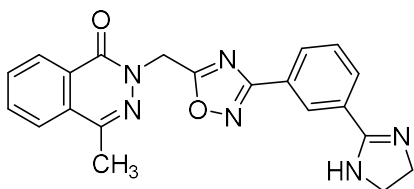
5-(3-Chlorophenyl)-3-(3-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (3e)

White powder, 78 % (271 mg) yield, m.p. 210–211 °C. ¹H NMR (400 MHz, DMSO) δ 8.58 (s, 1H), 8.16 (m, 3H), 8.05 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 7.1 Hz, 1H), 7.72–7.63 (m, 7.6 Hz, 2H), 6.87 (s, 1H), 3.68 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 174.9, 168.8, 163.4, 134.8, 133.5, 132.4, 131.9, 130.6, 129.6, 129.1, 127.9, 127.1, 126.6, 126.5, 125.9. HRMS (ESI) calcd for C₁₇H₁₃ClN₄O [*M*+*H*]⁺ 325.0851, found 325.0874.



3-(3-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(thiophen-2-yl)-1,2,4-oxadiazole (3f)

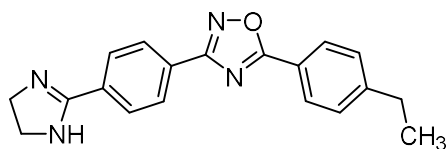
White solid, 79 % (302 mg) yield, m.p. 215–217 °C. ¹H NMR (400 MHz, DMSO) δ 8.53 (s, 1H), 8.16 – 8.10 (m, 3H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.44 – 7.33 (m, 1H), 7.26 (s, 1H), 3.65 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 171.7, 168.3, 163.4, 134.7, 133.4, 132.0, 130.6, 129.8, 129.2, 126.4, 126.4, 125.7, 124.9, 50.0. HRMS (ESI) calcd for C₁₅H₁₂N₄OS [*M*+*H*]⁺ 297.0805, found 297.0807.



2-((3-(3-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-methylphthalazin-1(2H)-one (3g)

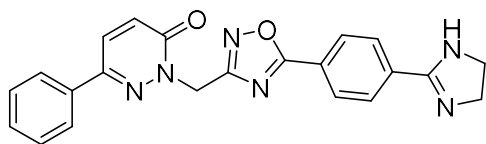
White powder, 57 % (230 mg) yield, m.p. 151–153 °C. ¹H NMR (400 MHz, DMSO) δ 8.44 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 8.08 – 7.95 (m, 4H), 7.94 – 7.88 (m, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 5.71 (s, 2H), 3.64 (s,

4H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 176.4, 168.2, 163.4, 159.0, 145.1, 134.3, 132.6, 132.4, 130.5, 130.1, 129.6, 129.0, 127.3, 126.8, 126.5, 126.4, 126.3, 47.2, 41.3, 18.8. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{18}\text{N}_6\text{O}_2$ $[\text{M}+\text{H}]^+$ 387.1564, found 387.1589.



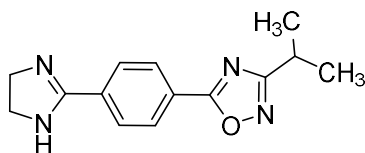
3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(4-ethylphenyl)-1,2,4-oxadiazole (3h)

White powder, 34 % (216 mg) yield, m.p. 196–198 °C. ^1H NMR (400 MHz, DMSO) δ 8.14 (m, 4H), 8.04 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.07 (br s, 1H), 3.66 (s, 4H), 2.75 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 176.1, 168.3, 163.4, 150.4, 133.9, 129.5, 128.5, 128.4, 128.1, 127.4, 121.3, 28.7, 15.5. HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 319.1553, found 319.1573.



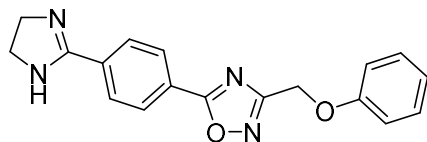
2-((5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazol-3-yl)methyl)-6-phenylpyridazin-3(2H)-one (5a)

Light brown solid, 82 % (256 mg) yield, m.p. 216–218 °C. ^1H NMR (DMSO- d_6 , 300 MHz): δ 8.13 (dd, J = 6.16 Hz, J = 8.8 Hz, 3H), 8.02 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 6.6 Hz, 2H), 7.53 – 7.42 (m, 3H), 7.16 (d, J = 9.8 Hz, 1H), 5.59 (s, 2H, CH_2), 3.64 (s, 4H). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 175.7, 167.7, 163.2, 159.2, 144.8, 135.5, 134.7, 131.9, 130.4, 130.0, 129.3, 128.6, 128.2, 126.4, 124.9, 50.3, 47.5. Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_6\text{O}_2$ (398.43): C, 66.32; H, 4.55; N, 21.09; found: C, 66.12; H, 4.56; N, 20.99.



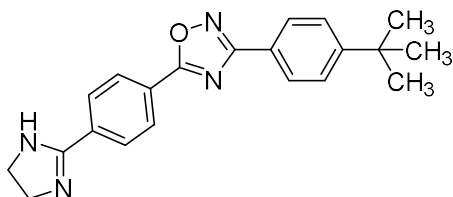
5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-isopropyl-1,2,4-oxadiazole (5b)

White solid, 77 % (337 mg) yield, m.p. 164–166 °C. ^1H NMR (DMSO- d_6 , 300 MHz): δ 8.12 (d, J = 8.3 Hz, 2H), 8.03 (d, J = 8.3 Hz, 2H), 3.64 (s, 4H), 3.19 – 3.08 (m, 1H), 1.32 (d, J = 7.1 Hz, 6H). ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 175.8, 174.8, 163.2, 135.0, 128.5, 128.1, 125.2, 50.2, 26.6, 20.8. Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}$ (256.31): C, 65.61; H, 6.29; N, 21.86; found: C, 65.41; H, 6.30; N, 21.75.

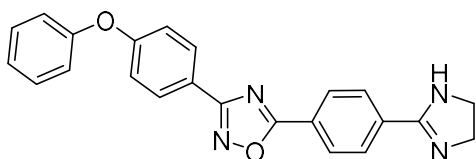


5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-(phenoxymethyl)-1,2,4-oxadiazole (5c)

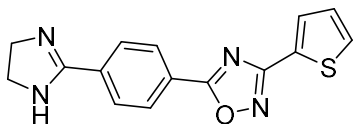
White solid, 64 % (278 mg) yield, m.p. 190–192 °C. ¹H NMR (DMSO-*d*₆, 300 MHz): δ 8.18 (d, *J* = 7.8 Hz, 2H), 8.05 (d, *J* = 7.3 Hz, 2H), 7.38 – 7.28 (m, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.95–7.04 (m, 1H), 5.36 (s, 2H), 3.92 – 3.73 (br s, 2H), 3.36–3.55 (br s, 2H). ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 175.6, 168.1, 163.2, 158.1, 135.4, 130.1, 128.6, 128.3, 124.8, 124.7, 122.0, 115.3, 61.2. Anal. Calcd for C₁₈H₁₆N₄O₂ (320.35): C, 67.49; H, 5.03; N, 17.49; found: C, 67.29; H, 5.04; N, 17.58.

**3-(4-*Tert*-butylphenyl)-5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (5d)**

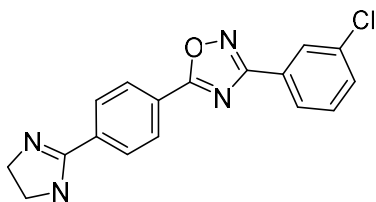
White solid, 79 % (338 mg) yield, m.p. 196–198 °C. ¹H NMR (DMSO-*d*₆, 300 MHz): δ 8.23 (d, *J* = 8.3 Hz, 2H), 8.10 – 8.00 (m, 4H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.12 (s, 1H), 3.91 – 3.79 (m, 2H), 3.40–3.51 (m, 2H), 1.33 (s, 9H). ¹³C NMR (DMSO-*d*₆, 100 MHz): δ 175.3, 168.7, 163.2, 155.0, 135.3, 128.6, 128.3, 127.4, 126.6, 125.1, 123.8, 55.2, 35.2, 31.4. Anal. Calcd for C₂₁H₂₂N₄O (346.44): C, 72.81; H, 6.40; N, 16.17; found: C, 72.59; H, 6.41; N, 16.09.

**5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-(4-phenoxyphenyl)-1,2,4-oxadiazole (5e)**

White powder, 74 % (363 mg) yield, m.p. 241–242 °C. ¹H NMR (400 MHz, DMSO) δ 8.41 (d, *J* = 8.4 Hz, 2H), 8.34 (d, *J* = 8.4 Hz, 2H), 8.11 (d, *J* = 8.7 Hz, 2H), 7.48 (t, *J* = 7.9 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.17 (dd, *J* = 11.9, 8.4 Hz, 4H), 4.05 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 174.6, 168.5, 164.4, 160.5, 155.8, 130.8, 130.3, 129.8, 129.0, 128.5, 126.6, 125.1, 120.9, 120.3, 118.8, 45.0. HRMS (ESI) calcd for C₂₃H₁₈N₄O₂ [M+H]⁺ 383.1503, found 383.1505.

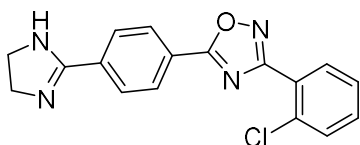
**5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-(thiophen-2-yl)-1,2,4-oxadiazole (5f)**

White powder, 84 % (320 mg) yield, m.p. 182–184 °C. ¹H NMR (400 MHz, DMSO) δ 8.07 (m, 6H), 7.37 (t, *J* = 4.1 Hz, 1H), 3.67 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 171.8, 168.4, 163.5, 134.4, 134.2, 133.2, 129.6, 128.4, 127.9, 127.4, 125.1, 50.3. HRMS (ESI) calcd for C₁₅H₁₂N₄OS [M+H]⁺ 297.0805, found 297.0806.



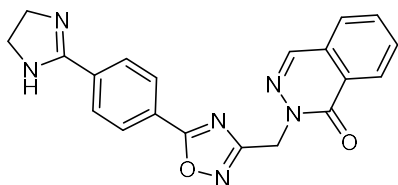
3-(3-Chlorophenyl)-5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (5g)

White solid, 62 % (258 mg) yield, m.p. 187–188 °C. ¹H NMR (400 MHz, DMSO) δ 8.25 (d, *J* = 8.3 Hz, 1H), 8.15 – 7.99 (m, 2H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 3.66 (s, 2H). ¹³C NMR (101 MHz, DMSO) δ 179.6, 175.8, 173.8, 167.8, 135.3, 134.5, 134.3, 134.1, 131.9, 128.6, 128.5, 127.2, 126.3, 125.1, 50.1. HRMS (ESI) calcd for C₂₀H₁₆N₆O₂ [M+H]⁺ 325.0851, found 325.0856.



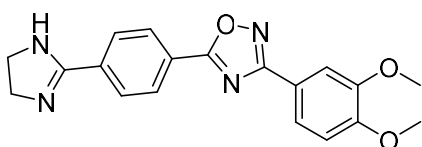
3-(2-Chlorophenyl)-5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (5h)

White powder, 79 % (329 mg) yield, m.p. 179–181 °C. ¹H NMR (400 MHz, DMSO) δ 8.24 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 6.4 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 6.9 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.13 (s, 1H), 3.84 (s, 1H), 3.46 (s, 1H). ¹³C NMR (101 MHz, DMSO) δ 175.0, 167.7, 163.2, 135.4, 133.2, 132.7, 132.3, 131.3, 128.6, 128.4, 128.2, 125.9, 124.8, 40.9. HRMS (ESI) calcd for C₁₇H₁₃ClN₄O [M+H]⁺ 325.0851, found 325.0849.



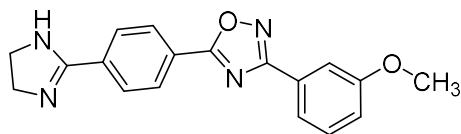
2-((5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazol-3-yl)methyl)phthalazin-1(2H)-one (5i)

White solid, 87 % (361 mg) yield, m.p. 229–230 °C. ¹H NMR (400 MHz, DMSO) δ 8.46 (s, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.97 (t, *J* = 2.7 Hz, 2H), 7.93 – 7.87 (m, 1H), 6.85 (s, 1H, NH), 5.58 (s, 2H, CH₂), 3.65 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 175.6, 168.1, 163.2, 159.0, 139.1, 135.6, 134.3, 132.7, 130.1, 128.5, 128.2, 127.5, 126.4, 124.9, 46.5. HRMS (ESI) calcd for C₂₀H₁₆N₆O₂ [M+H]⁺ 322.1408, found 321.1307.



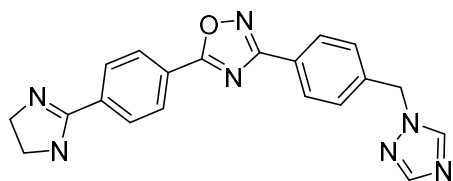
5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (5j)

White solid, 59 % (223 mg) yield, m.p. 194–195 °C. ¹H NMR (400 MHz, DMSO) δ 8.21 (d, *J* = 8.0 Hz, 2H), 8.06 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.55 (s, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 3.87 - 3.76 (m, 8H), 3.46 (s, 2H). ¹³C NMR (75 MHz, DMSO) δ 175.1, 168.6, 163.2, 152.1, 149.5, 135.2, 128.5, 128.3, 125.1, 121.0, 118.8, 112.4, 110.2, 56.1, 55.2, 45.0. HRMS (ESI) calcd for C₁₉H₁₈N₄O₃ [M+H]⁺ 351.1452, found 351.1454.



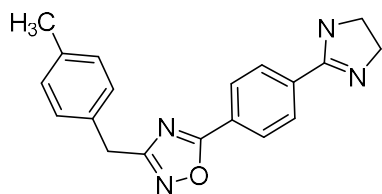
5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-(3-methoxyphenyl)-1,2,4-oxadiazole (5k)

White solid, 72 % (296 mg) yield, m.p. 194–195 °C. ¹H NMR (400 MHz, DMSO) δ 8.22 (d, *J* = 8.1 Hz, 2H), 8.09 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 2.6 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.19 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.89 (s, 1H), 3.68 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 190.3, 175.6, 168.9, 163.2, 160.4, 135.6, 130.9, 128.6, 128.3, 128.0, 125.1, 120.0, 118.1, 112.9, 56.0, 47.4. HRMS (ESI) calcd for C₁₈H₁₆N₄O₂ [M+H]⁺ 321.1346, found 321.1349.



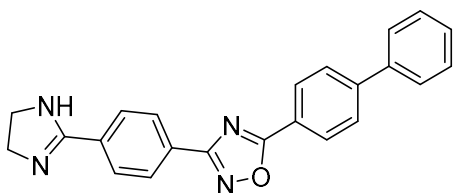
3-(4-((1H-1,2,4-Triazol-1-yl)methyl)phenyl)-5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (5l)

White powder, 33 % (130 mg) yield, m.p. 243–245 °C. ¹H NMR (400 MHz, DMSO) δ 8.65 (s, 1H), 8.22 (d, *J* = 8.3 Hz, 2H), 8.09 (d, *J* = 8.2 Hz, 4H), 7.99 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 5.54 (s, 2H), 3.70 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 175.6, 168.7, 163.3, 152.3, 144.9, 140.3, 135.2, 129.0, 128.6, 128.3, 128.0, 126.4, 125.3, 52.4, 50.1. HRMS (ESI) calcd for C₂₀H₁₇N₇O [M+H]⁺ 372.1567, found 372.1579.



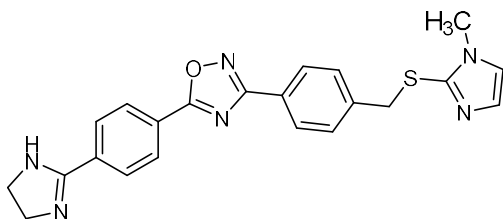
5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-(4-methylbenzyl)-1,2,4-oxadiazole (5m)

White powder, 65 % (225 mg) yield, m.p. 181–183 °C. ¹H NMR (400 MHz, DMSO) δ 8.11 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 4.12 (s, 2H), 3.69 (s, 4H), 2.29 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 175.1, 170.7, 163.3, 136.5, 134.8, 133.1, 129.6, 129.2, 128.6, 128.1, 125.4, 50.0, 31.6, 21.0. HRMS (ESI) calcd for C₁₉H₁₈N₄O [M+H]⁺ 319.1554, found 319.1544.



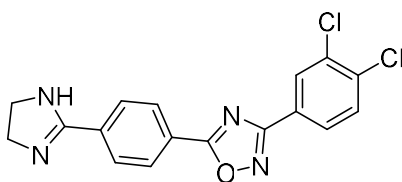
5-([1,1'-Biphenyl]-4-yl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (5n)

White solid, 82 % (385 mg) yield, m.p. 238–240 °C. ¹H NMR (400 MHz, DMSO) δ 8.44 (d, *J* = 6.3 Hz, 2H), 8.36 (d, *J* = 5.9 Hz, 2H), 8.20 (d, *J* = 6.9 Hz, 2H), 7.92 (d, *J* = 6.7 Hz, 2H), 7.77 (d, *J* = 5.8 Hz, 2H), 7.61 – 7.48 (m, 2H), 7.45 (d, *J* = 6.1 Hz, 1H), 4.07 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 172.0, 164.8, 161.4, 130.3, 129.9, 129.5, 129.3, 129.2, 129.0, 128.7, 128.6, 128.3, 128.0, 127.3, 125.4, 45.2. HRMS (ESI) calcd for C₂₃H₁₈N₄O[M+H]⁺ 367.1554, found 367.1555.



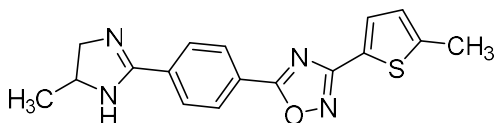
5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-(4-(((1-methyl-1H-imidazol-2-yl)thio)methyl)phenyl)-1,2,4-oxadiazole (5o)

White powder, 54 % (293 mg) yield, m.p. 166–168 °C. ¹H NMR (400 MHz, DMSO) δ 8.23 (d, *J* = 8.3 Hz, 2H), 8.08 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.23 (s, 1H), 7.00 (s, 1H), 4.26 (s, 2H), 3.67 (s, 4H), 3.39 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 175.4, 168.6, 163.2, 142.6, 139.4, 135.2, 130.1, 129.4, 128.6, 128.3, 127.6, 125.3, 125.0, 124.0, 38.6, 33.3. HRMS (ESI) calcd for C₂₂H₂₀N₆OS [M+H]⁺ 417.1492, found 417.1507.



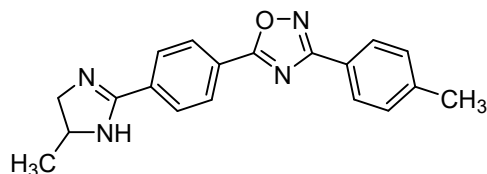
5-(3,4-Dichlorophenyl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (5p)

Light brown crystal, 64 % (299 mg) yield, m.p. 271–273 °C. ¹H NMR (400 MHz, DMSO) δ 8.25 (d, *J* = 7.3 Hz, 2H), 8.12 – 7.99 (m, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.20 (s, 1H), 3.66 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 175.4, 168.6, 163.3, 142.6, 139.4, 134.5, 134.1, 130.1, 129.4, 128.7, 128.4, 127.6, 125.3, 124.0, 49.8. HRMS (ESI) calcd for C₁₇H₁₂Cl₂N₄O [M+H]⁺ 359.0461, found 359.0461.

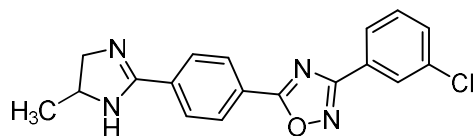


5-(4-(5-Methyl-4,5-dihydro-1H-imidazol-2-yl)phenyl)-3-(5-methylthiophen-2-yl)-1,2,4-oxadiazole (5q)

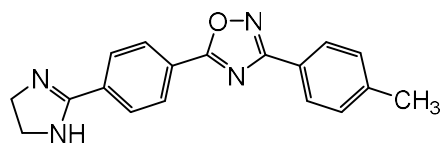
Pale powder, 61 % (201 mg) yield, m.p. 159–161 °C. ¹H NMR (400 MHz, DMSO) δ 8.18 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 3.6 Hz, 1H), 7.19 (s, 1H), 6.99 (dd, *J* = 3.7, 1.4 Hz, 1H), 4.18 – 3.65 (m, 2H), 2.56 – 2.52 (m, 3H), 1.18 (d, *J* = 6.0 Hz, 3H). ¹³C NMR (101 MHz, DMSO) δ 175.2, 164.8, 161.7, 145.3, 135.5, 130.9, 128.5, 128.3, 127.5, 125.2, 124.8, 51.8, 22.4, 15.6. HRMS (ESI) calcd for C₁₇H₁₆N₄O [M+H]⁺ 325.1118, found 325.1119.

**5-(4-(5-Methyl-4,5-dihydro-1H-imidazol-2-yl)phenyl)-3-(p-tolyl)-1,2,4-oxadiazole (5r)**

Pale powder, 59 % (330 mg) yield, m.p. 89–90 °C. ¹H NMR (400 MHz, DMSO) δ 8.23 (d, *J* = 8.4 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.22 (br s, 1H), 4.09 – 3.98 (m, 1H), 3.81 (t, *J* = 11.1 Hz, 1H), 3.24 (dd, *J* = 11.8, 7.9 Hz, 1H), 1.20 (d, *J* = 6.3 Hz, 3H). ¹³C NMR (101 MHz, DMSO) δ 175.3, 168.8, 161.7, 142.1, 135.3, 130.3, 128.5, 128.3, 127.5, 125.0, 123.8, 22.4, 21.6. HRMS (ESI) calcd for C₁₉H₁₈N₄O [M+H]⁺ 319.1553, found 319.1555.

**3-(3-chlorophenyl)-5-(4-(5-methyl-4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (5s)**

White powder, 36 % (243 mg) yield, m.p. 139–141 °C. ¹H NMR (400 MHz, DMSO) δ 8.16 (m, 4H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 7.18 (br s, 1H), 4.09 – 3.96 (m, 1H), 3.81 (t, *J* = 11.0 Hz, 1H), 3.23 (dd, *J* = 11.8, 7.9 Hz, 1H), 1.20 (d, *J* = 6.3 Hz, 3H). ¹³C NMR (101 MHz, DMSO) δ 174.8, 168.4, 161.9, 134.7, 134.1, 133.7, 132.1, 128.4, 127.9, 127.7, 127.4, 127.1, 125.7, 57.6, 56.9, 22.4. HRMS (ESI) calcd for C₁₈H₁₅ClN₄O [M+H]⁺ 339.1007, found 339.1028.

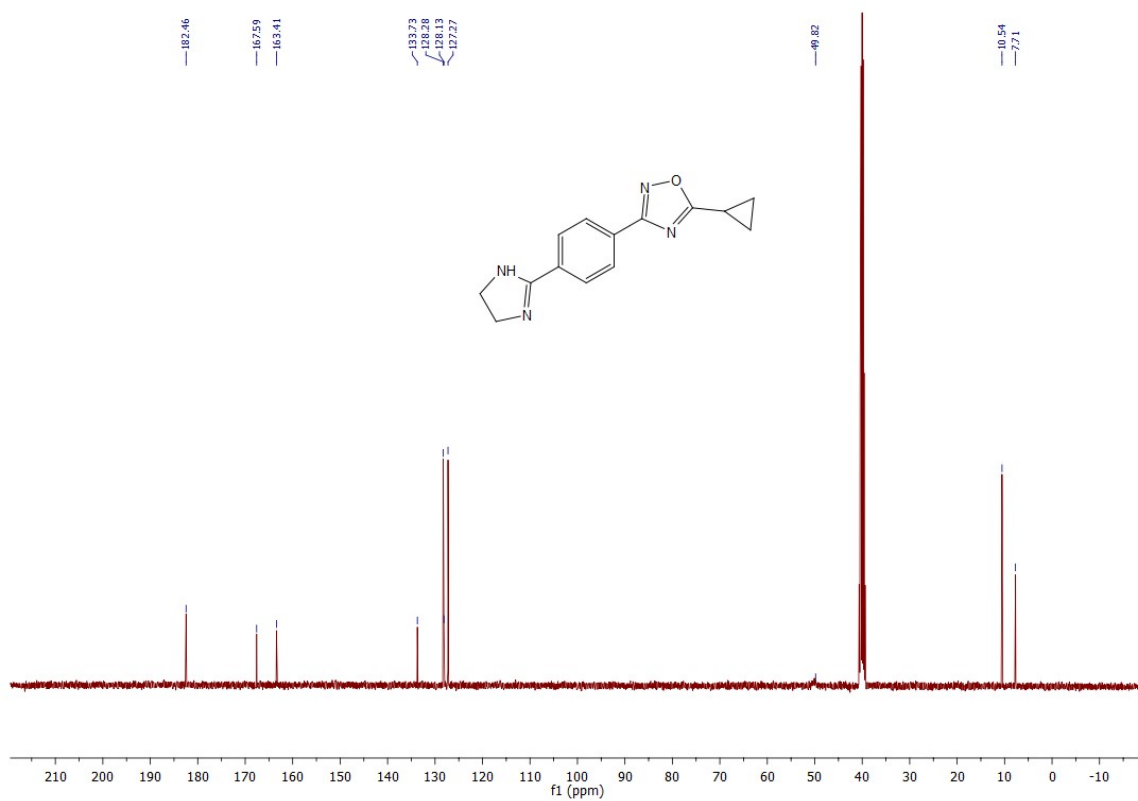
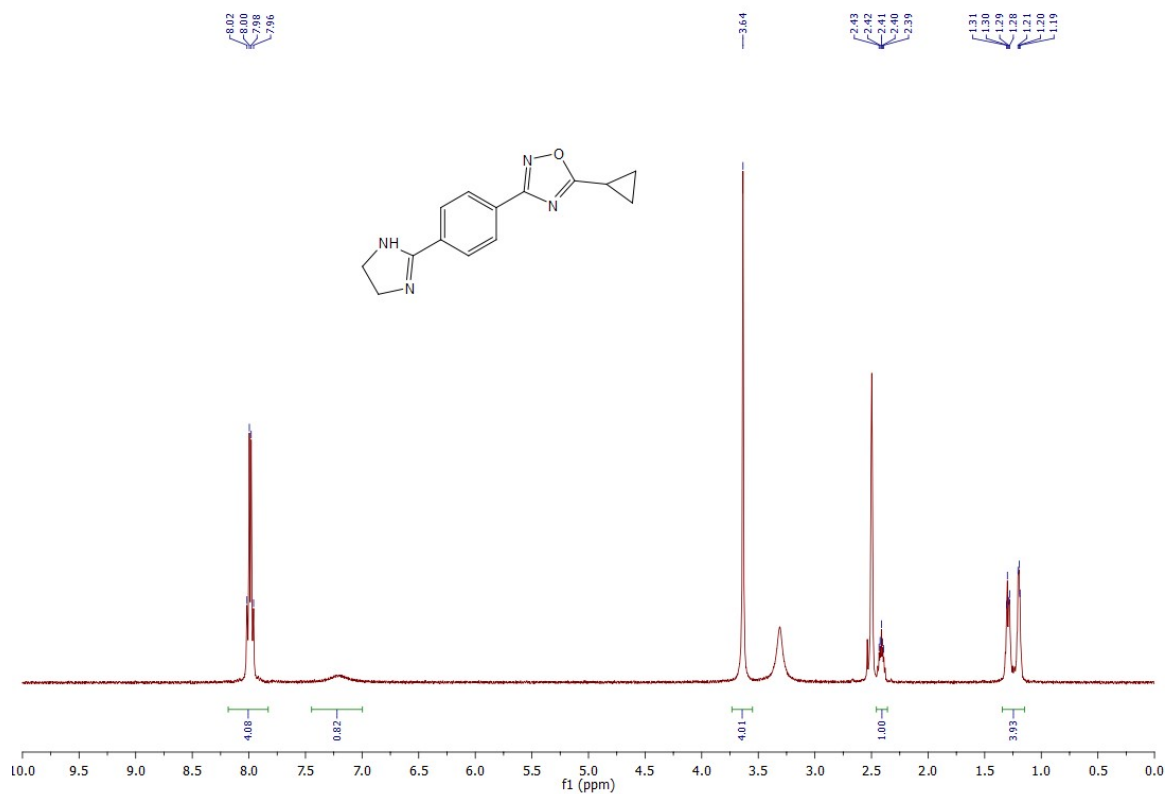
**5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-3-(p-tolyl)-1,2,4-oxadiazole (5t).**

White powder, 39 % (240 mg) yield, m.p. 246–247 °C. ¹H NMR (400 MHz, DMSO) δ 8.25 (d, *J* = 8.3 Hz, 2H), 8.09 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.12 (s, 1H), 3.88 (br. s, 2H), 3.47 (br s, 2H), 2.42 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 175.5, 169.0, 163.3, 142.1, 135.6, 130.2, 128.6, 128.2, 127.6, 125.3, 124.1, 21.5, 21.4. HRMS (ESI) calcd for C₁₆H₁₈N₄O [M+H]⁺ 305.1397, found 305.1386.

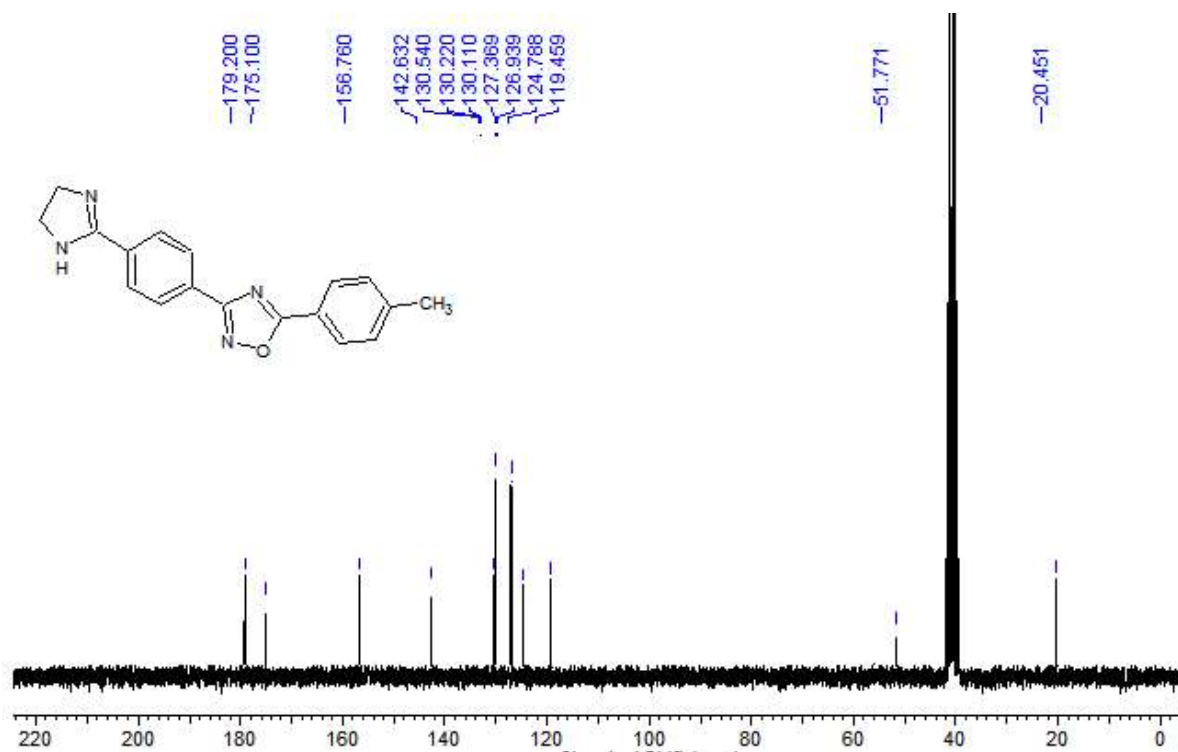
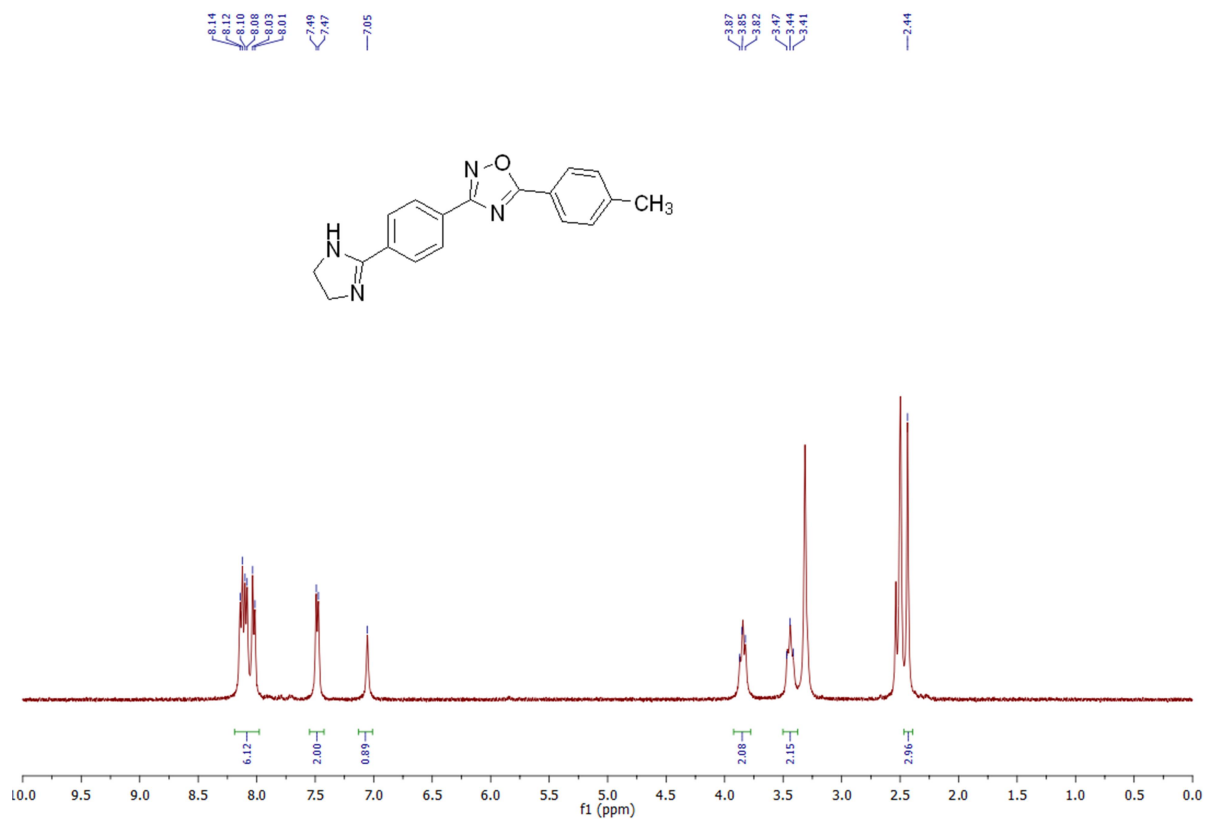
S3. Copies of ^1H and ^{13}C NMR spectra

^1H and ^{13}C NMR spectra of 5-cyclopropyl-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole

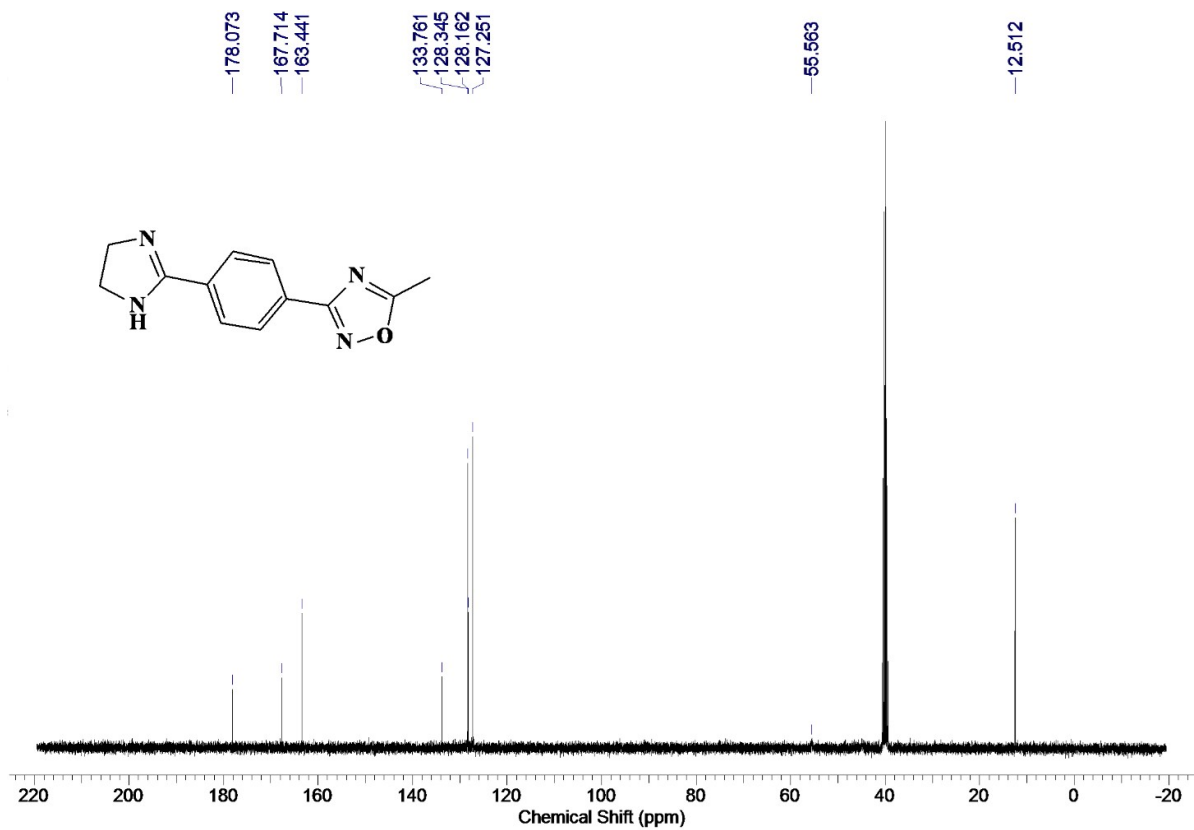
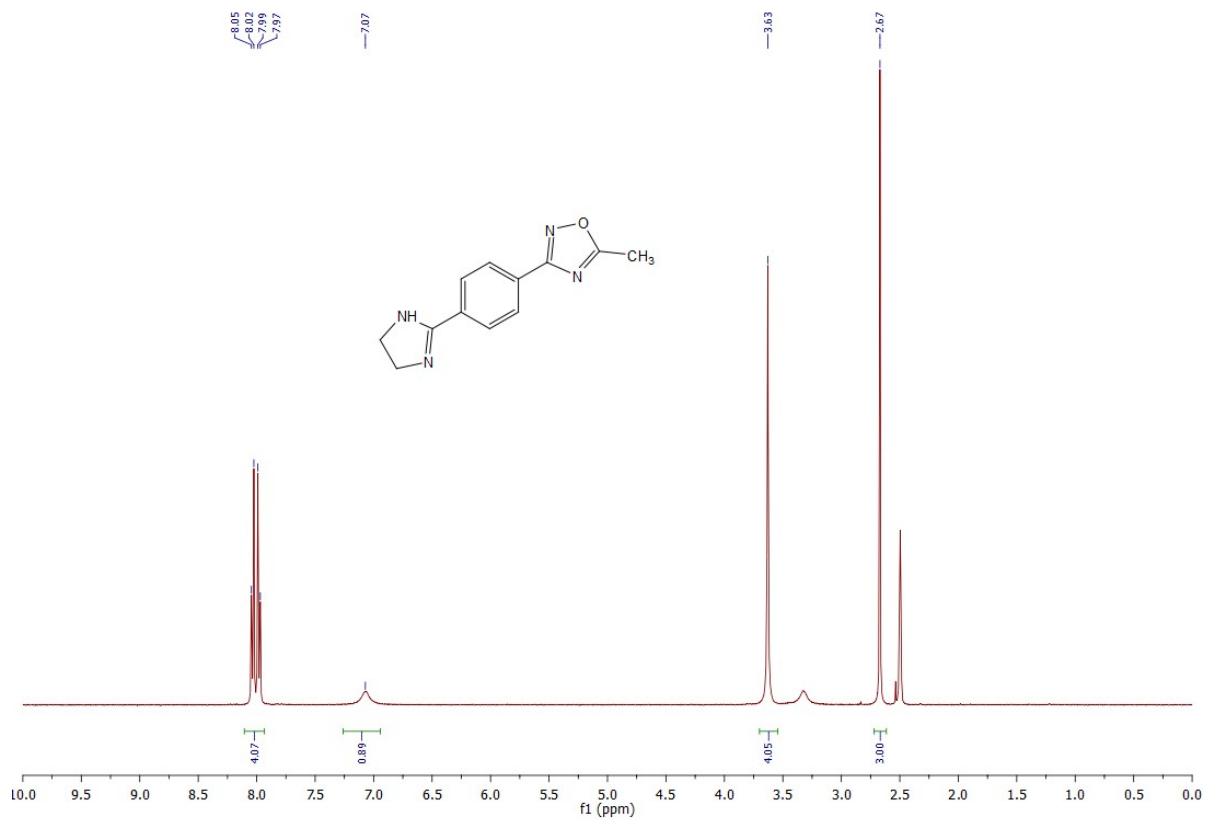
(3a)



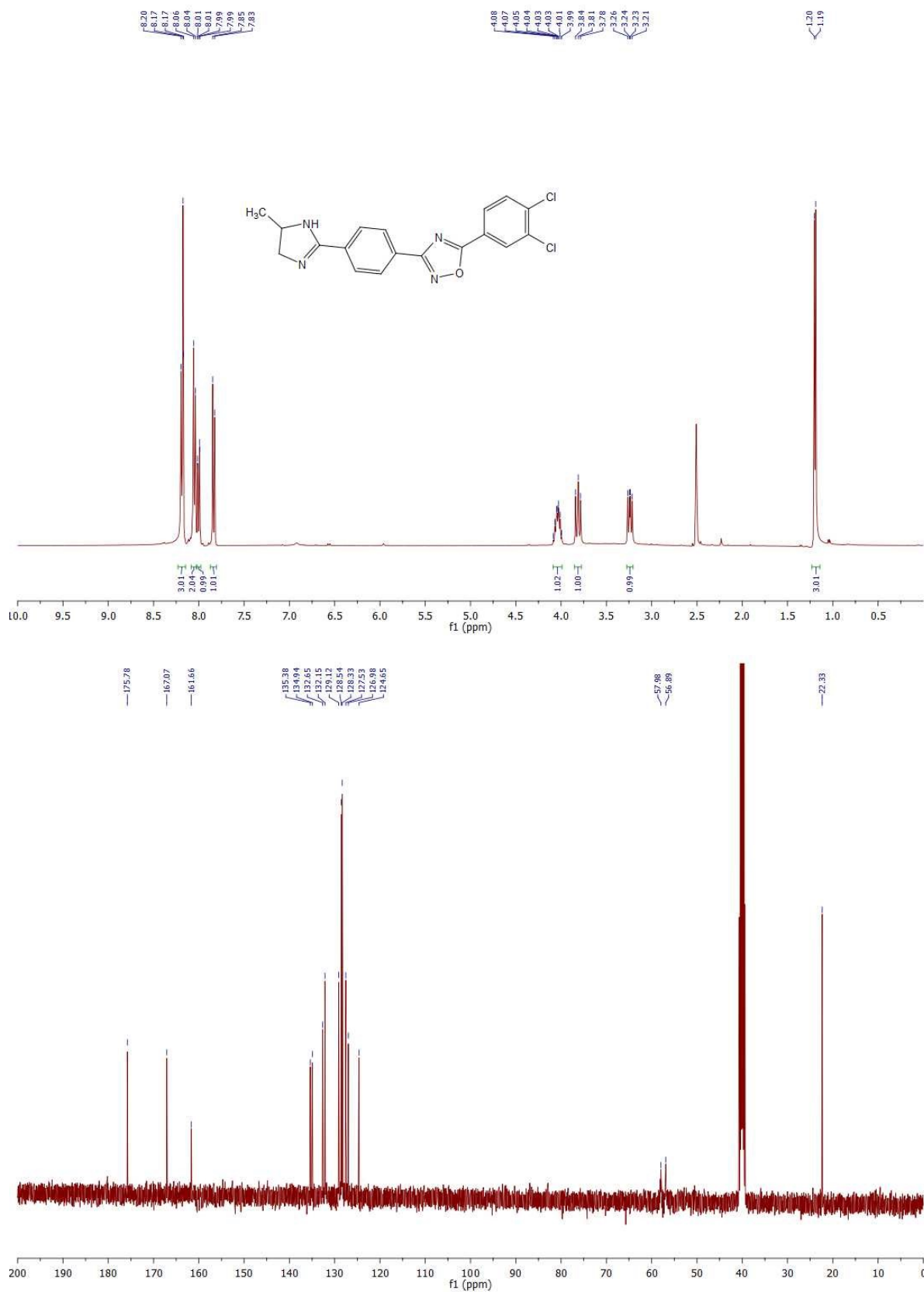
^1H and ^{13}C NMR spectra of 3-(4-(4,5-Dihydro-1*H*-imidazol-2-yl)phenyl)-5-p-tolyl-1,2,4-oxadiazole (**3b**)



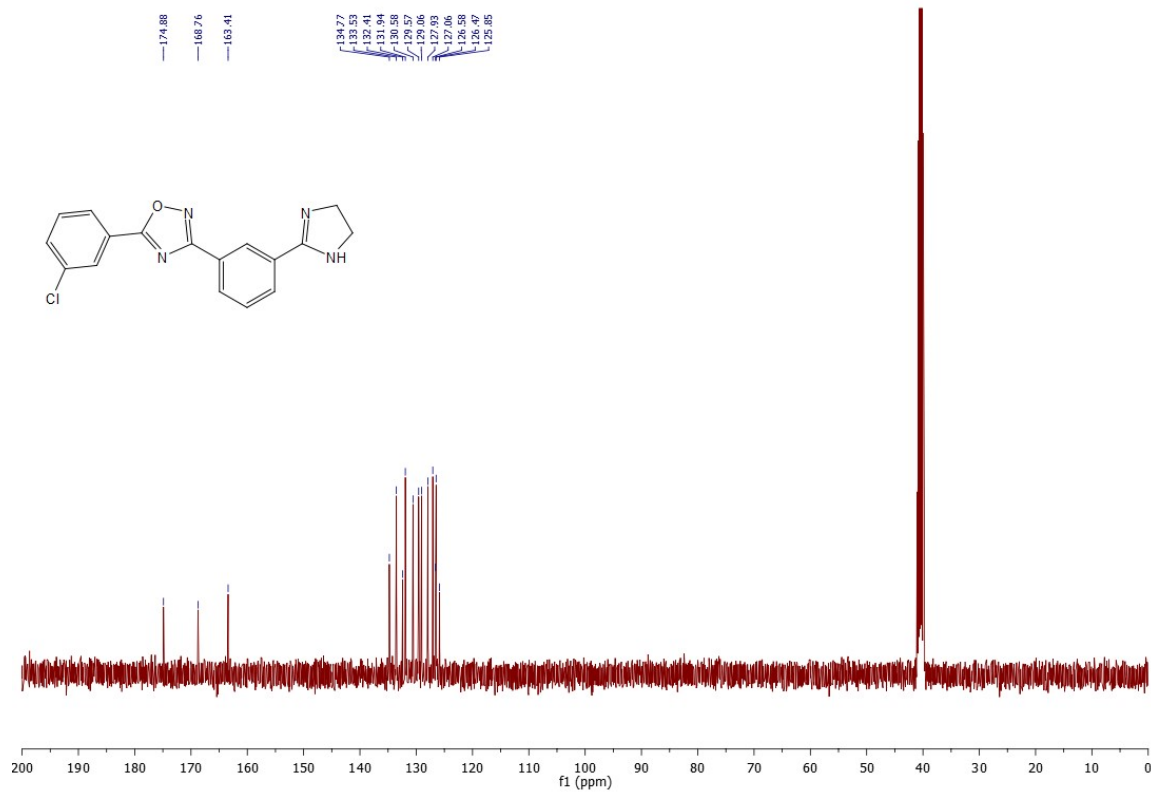
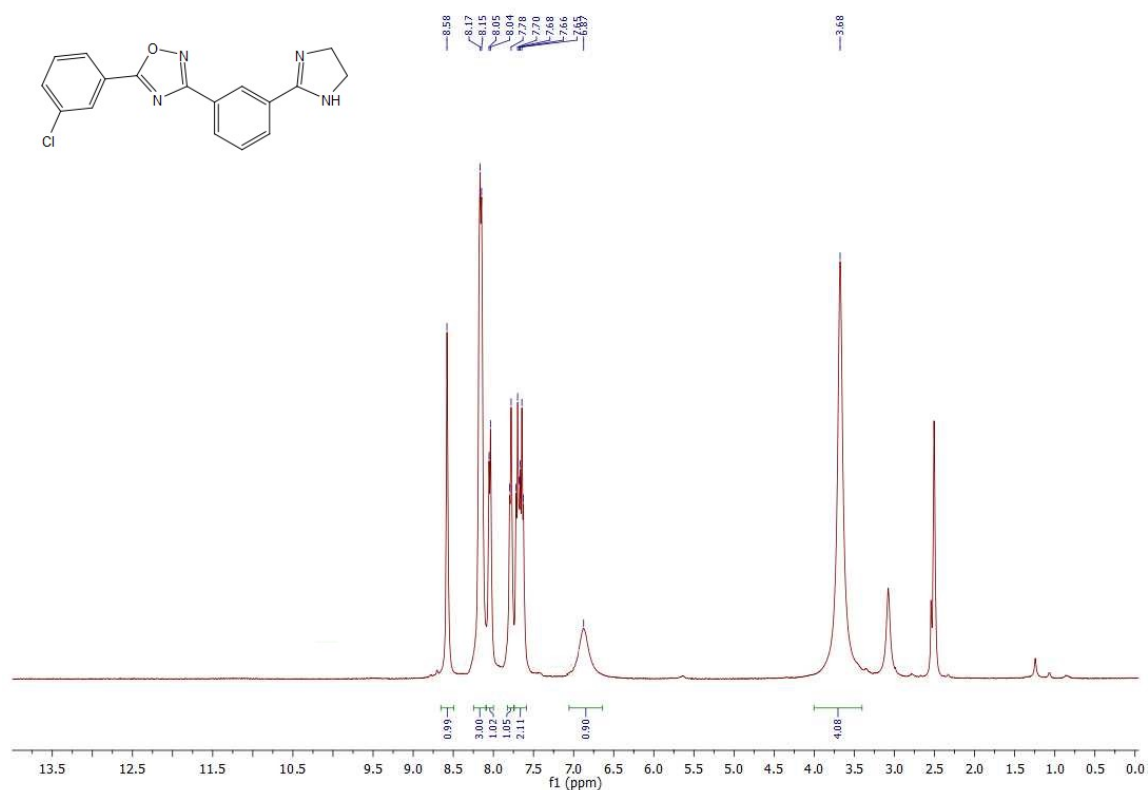
^1H and ^{13}C NMR spectra of 3-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-5-methyl-1,2,4-oxadiazole (**3c**)



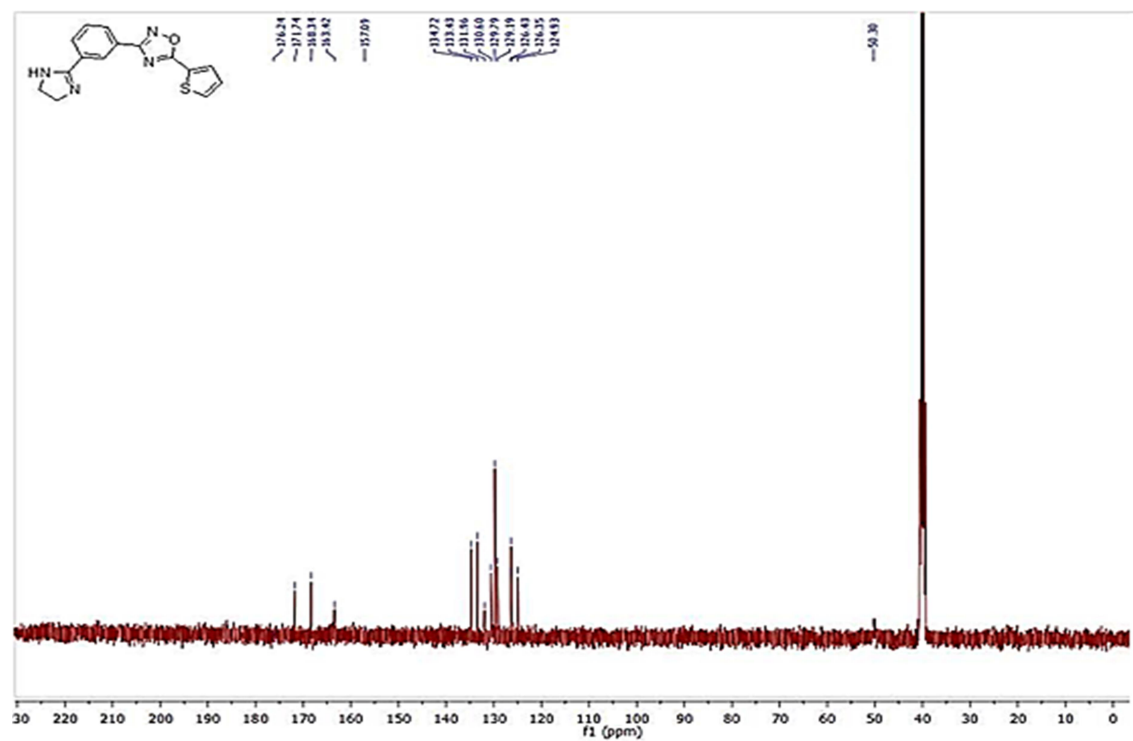
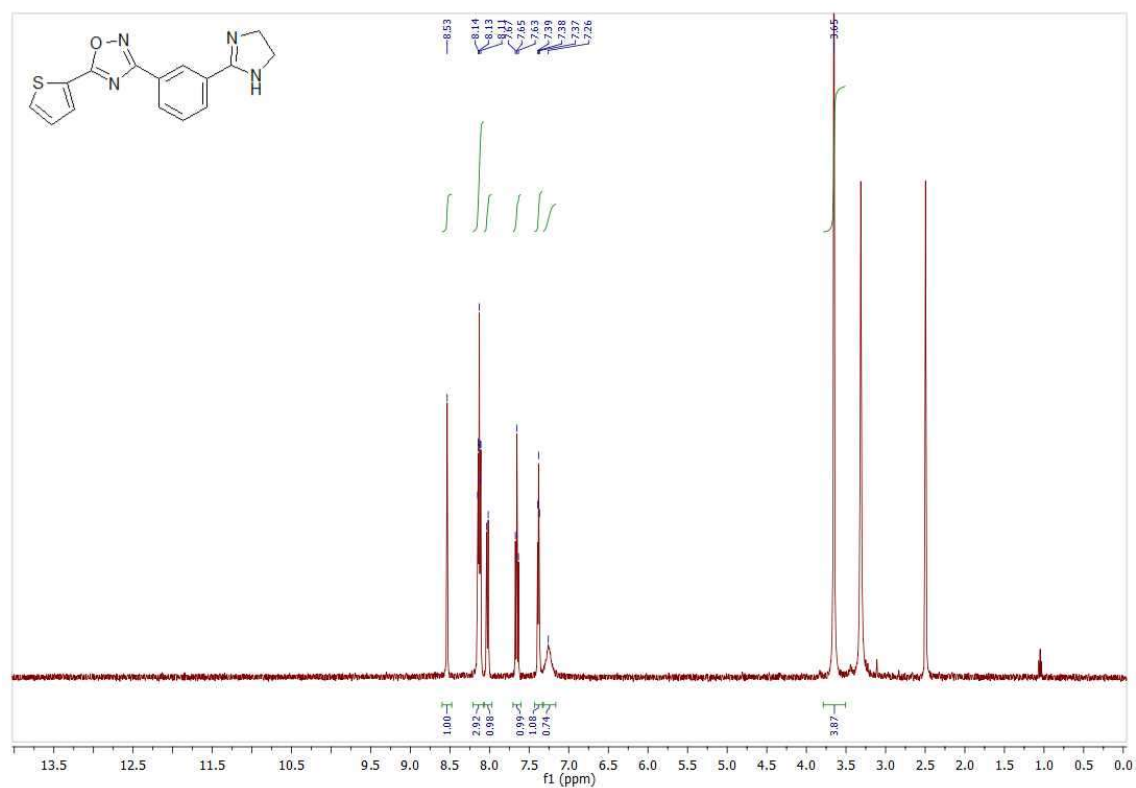
^1H and ^{13}C NMR spectra of 5-(3,4-dichlorophenyl)-3-(4-(5-methyl-4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (**3d**)



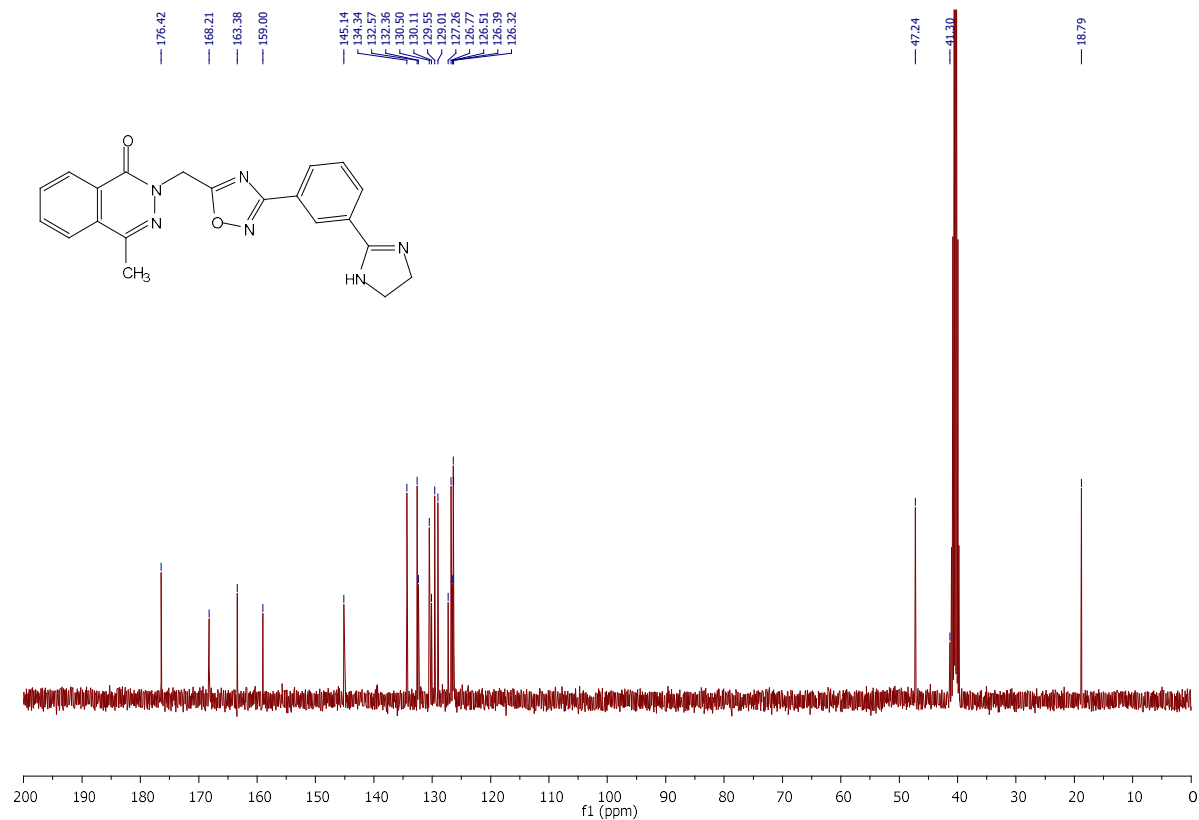
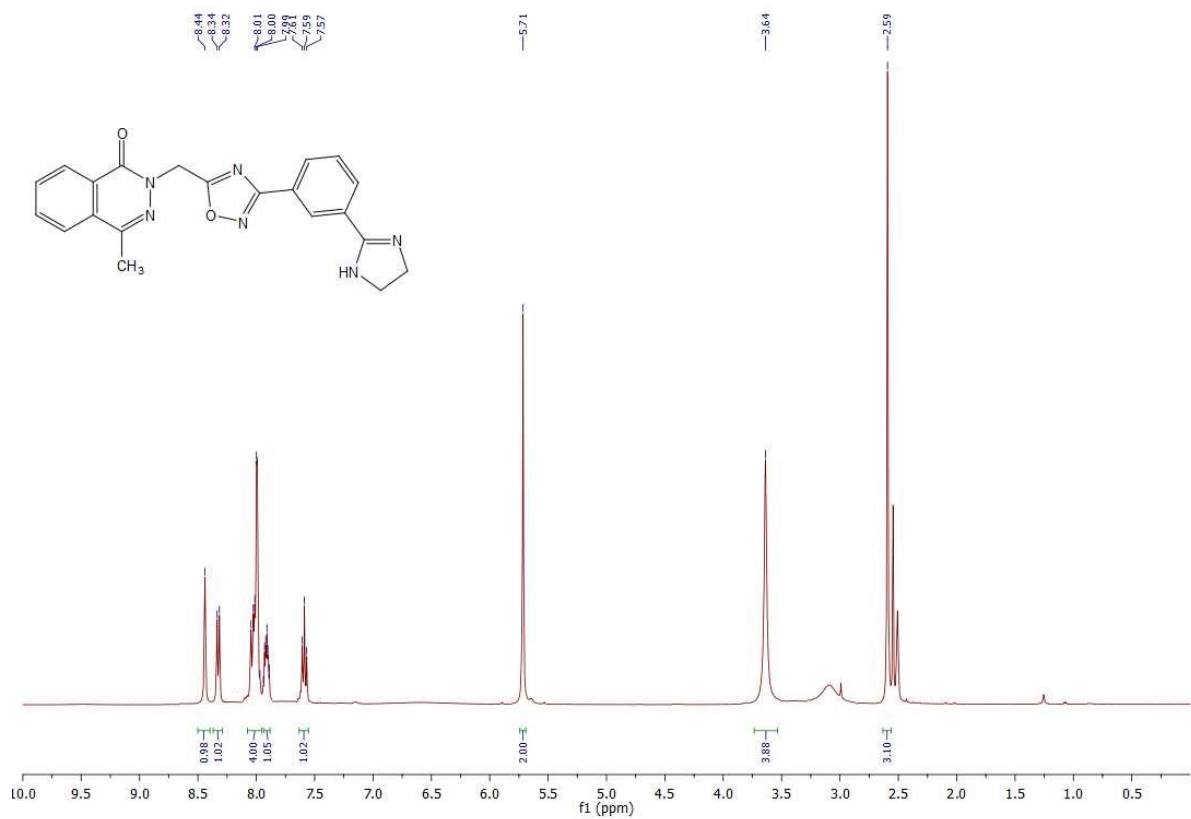
^1H and ^{13}C NMR spectra of 5-(3-chlorophenyl)-3-(3-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (**3e**)



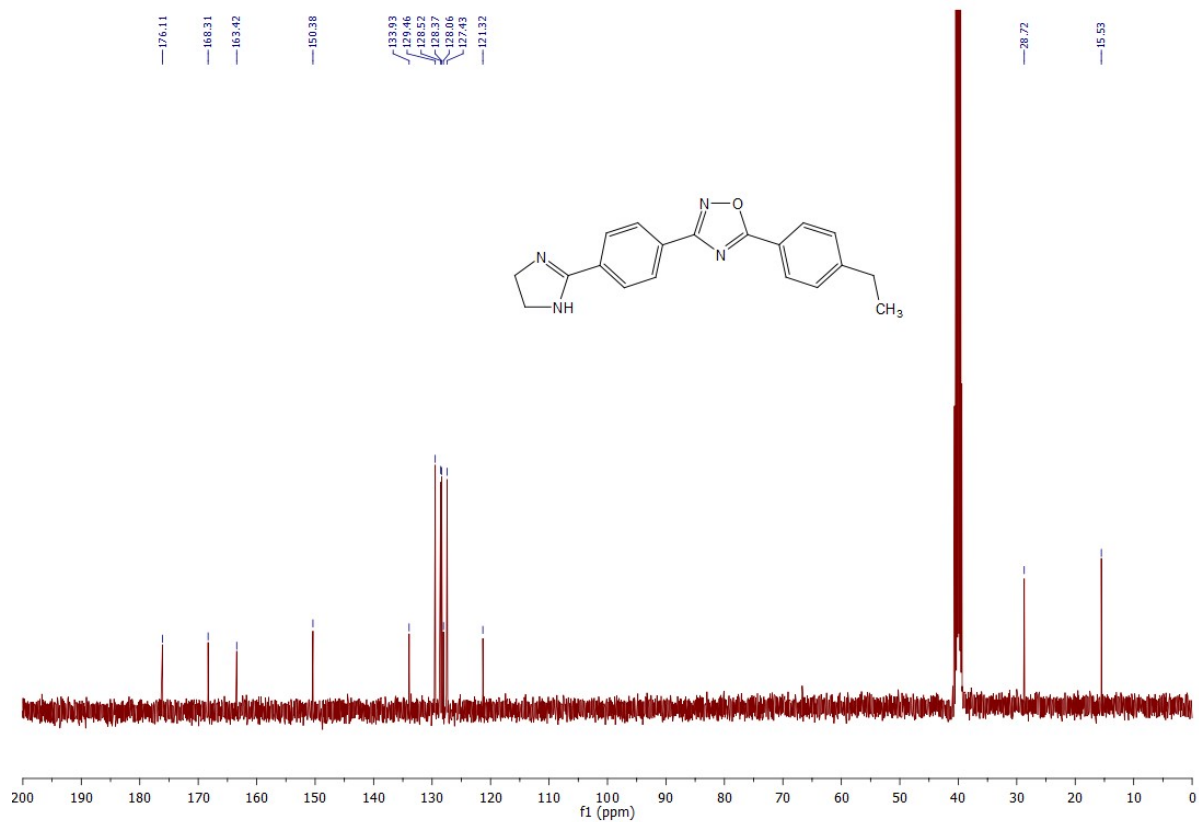
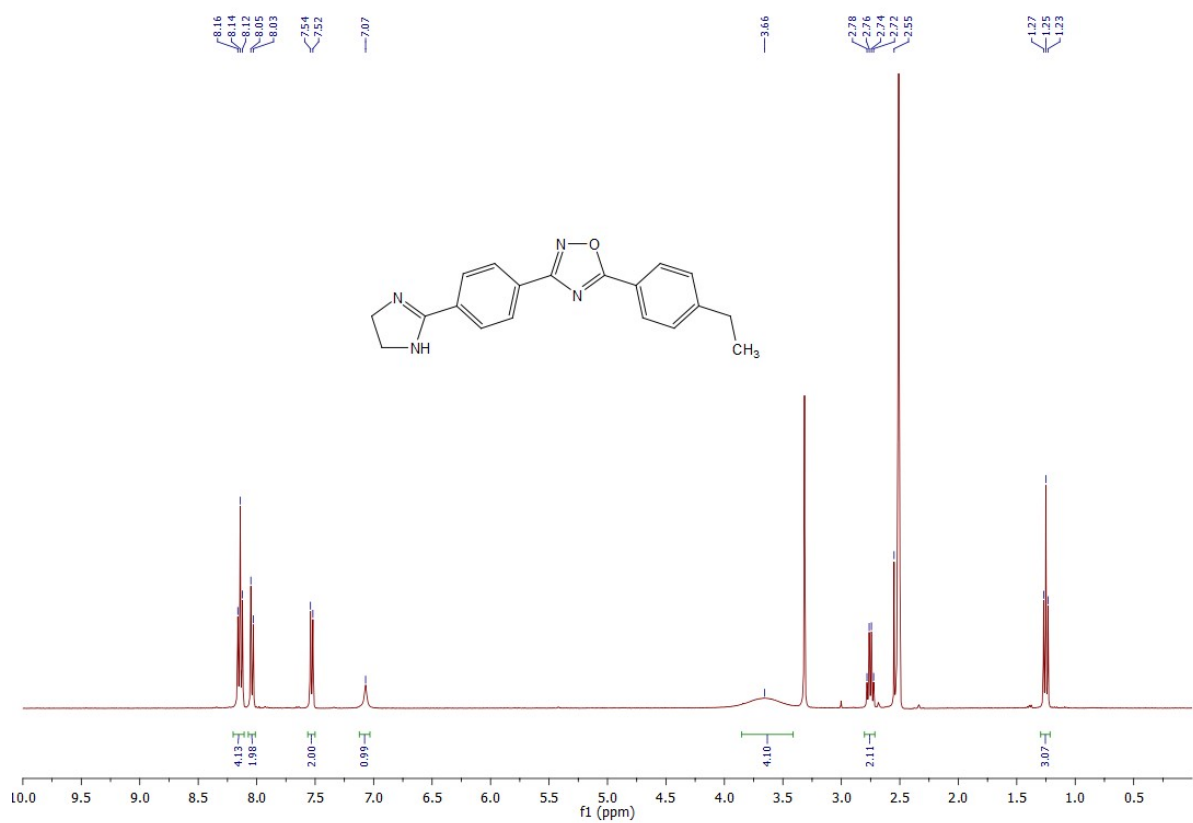
^1H and ^{13}C NMR spectra of 3-(3-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-5-(thiophen-2-yl)-1,2,4-oxadiazole (**3f**)



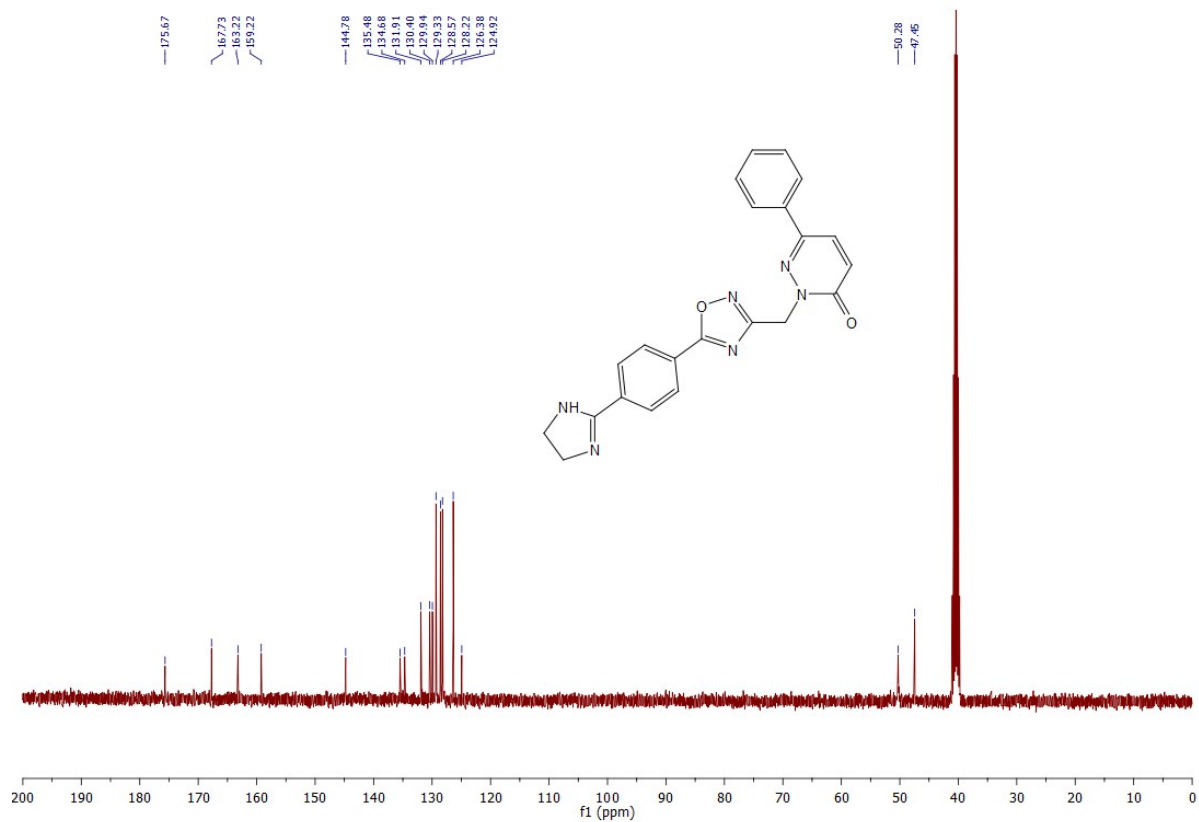
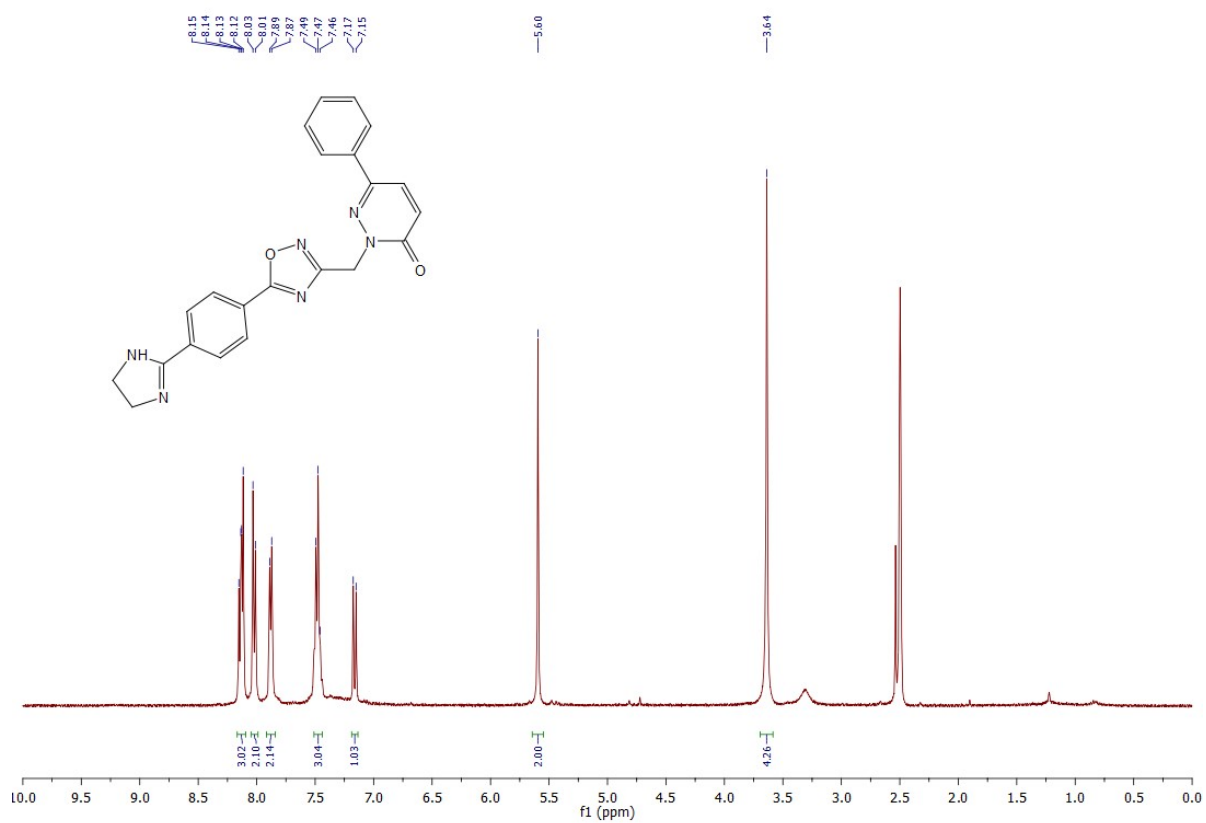
^1H and ^{13}C NMR spectra 2-((3-(3-(4, 5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-methylphthalazin-1(2*H*)-one (**3g**)



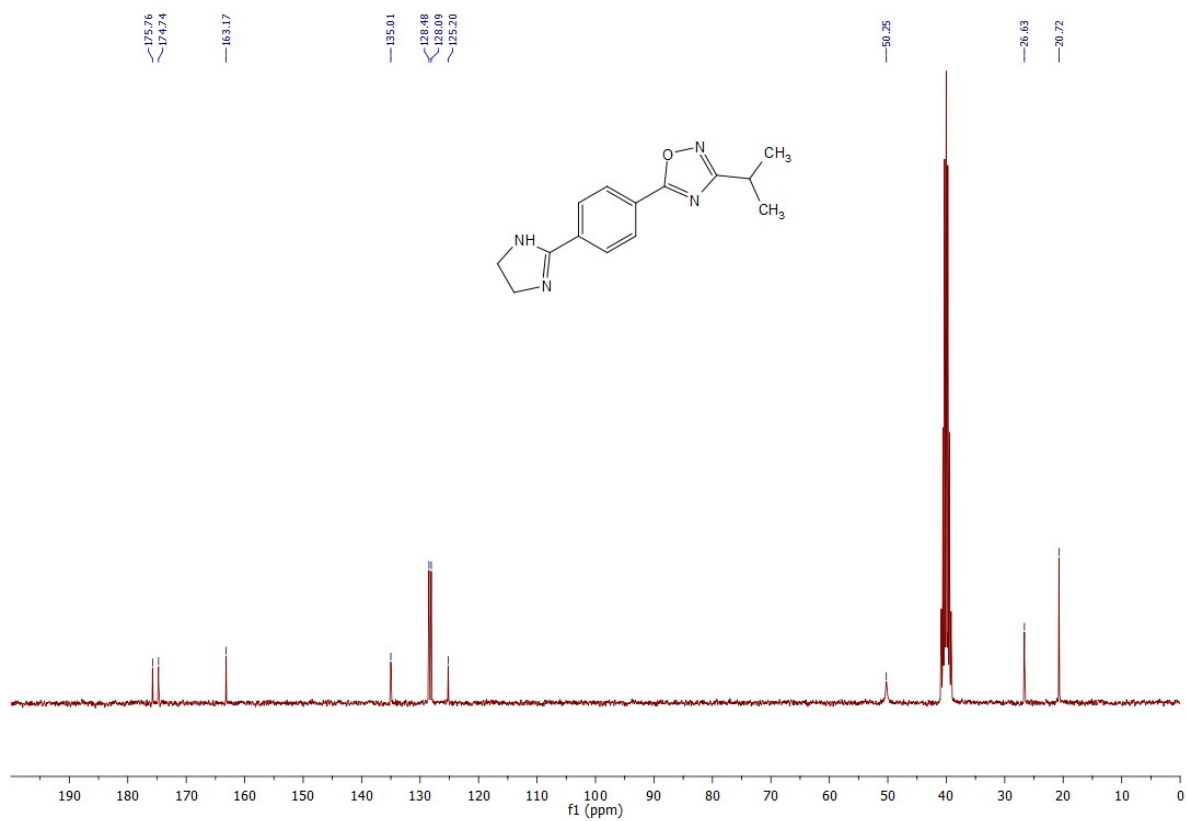
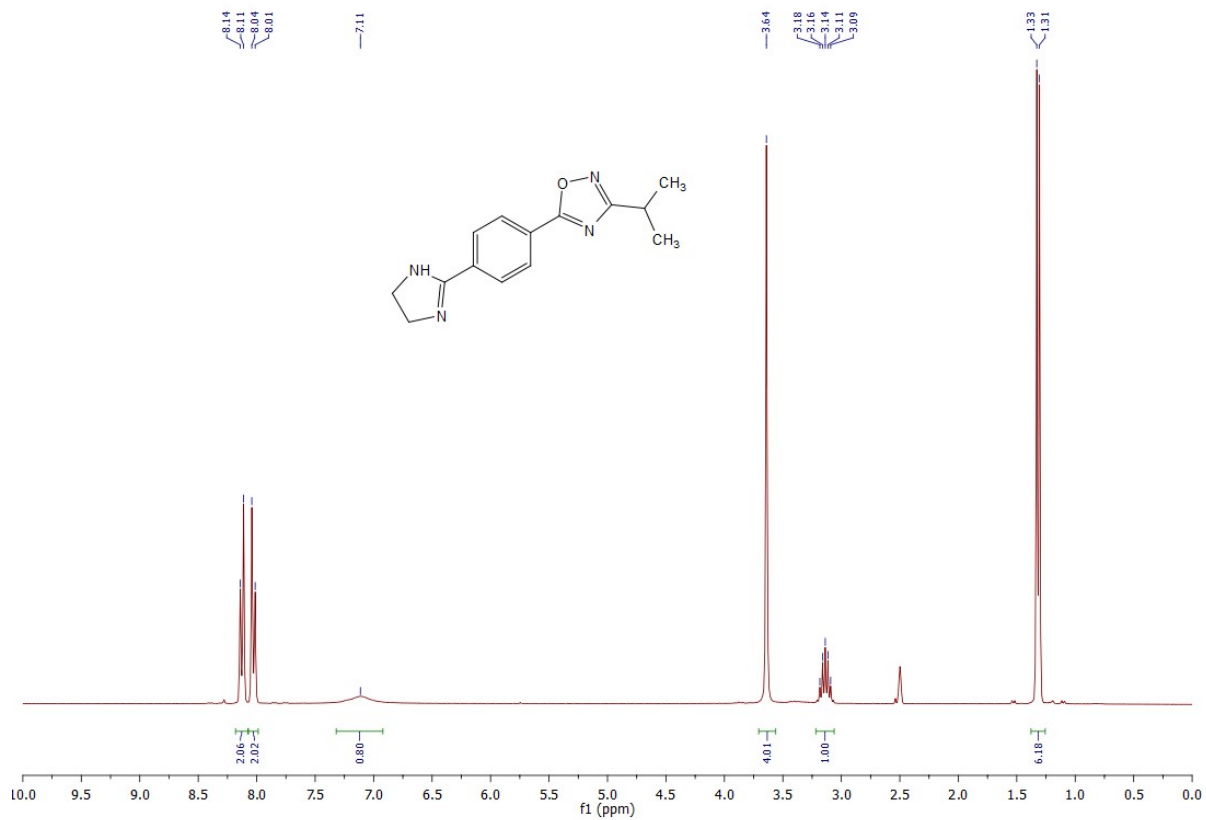
^1H and ^{13}C NMR spectra of 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(4-ethylphenyl)-1,2,4-oxadiazole (**3h**)



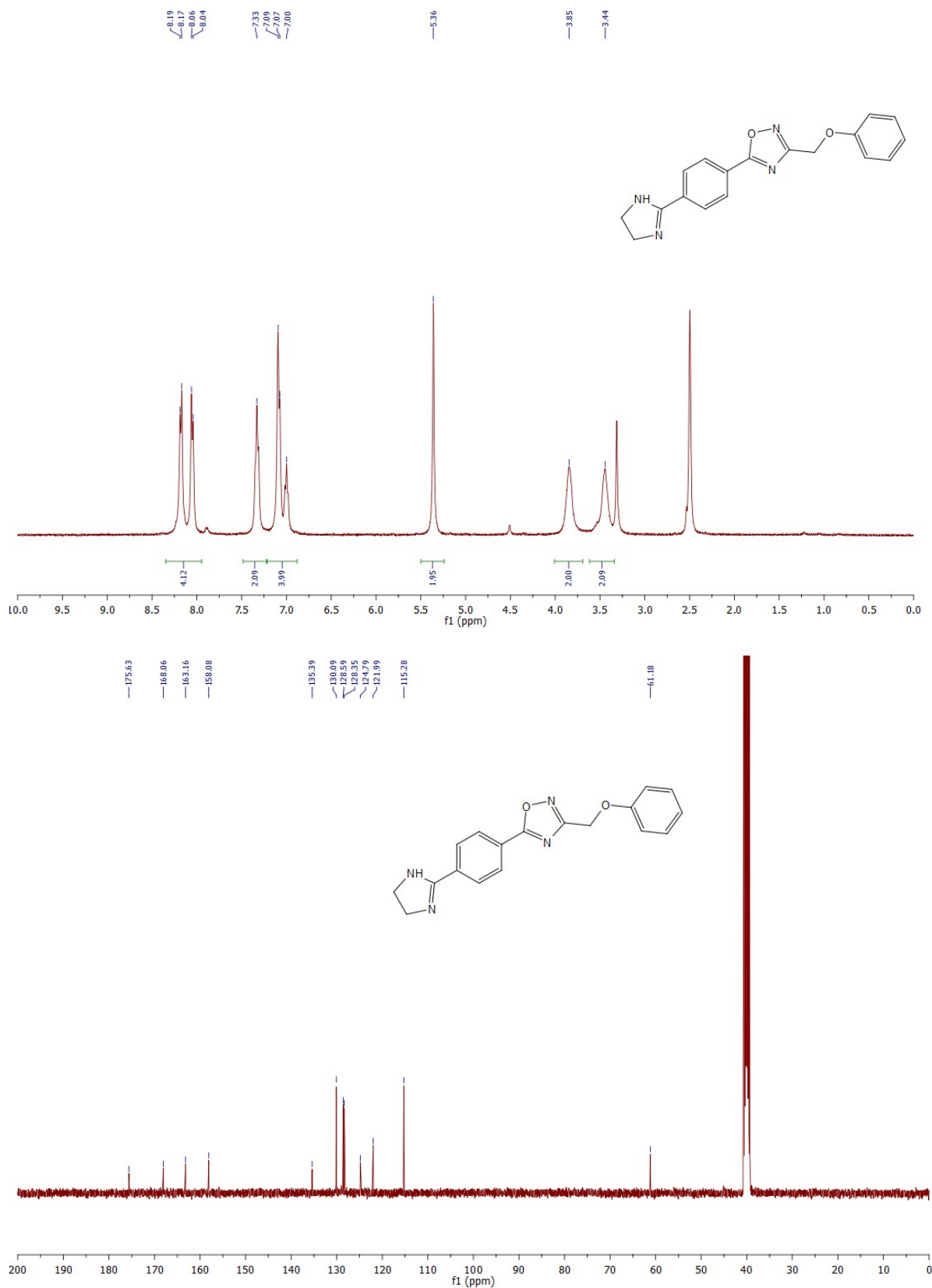
^1H and ^{13}C NMR spectra of 2-((5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazol-3-yl)methyl)-6-phenylpyridazin-3(2*H*)-one (**5a**)



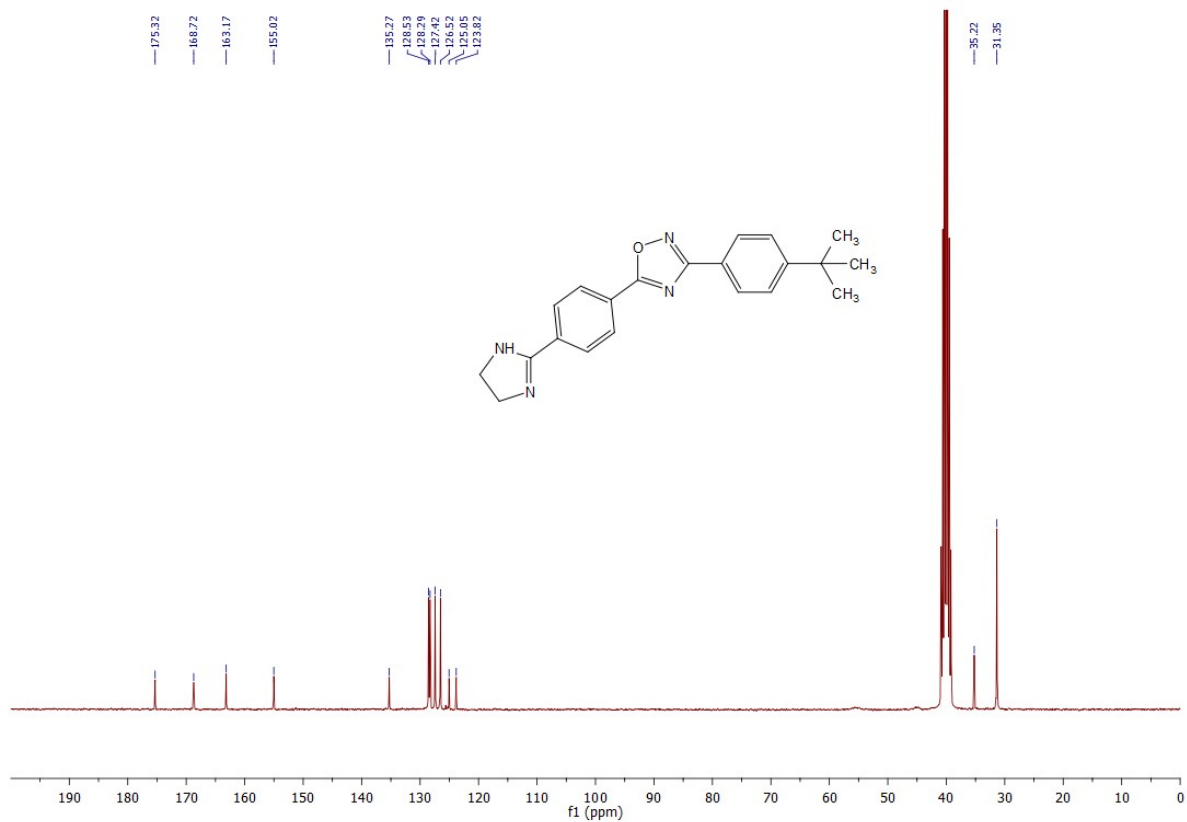
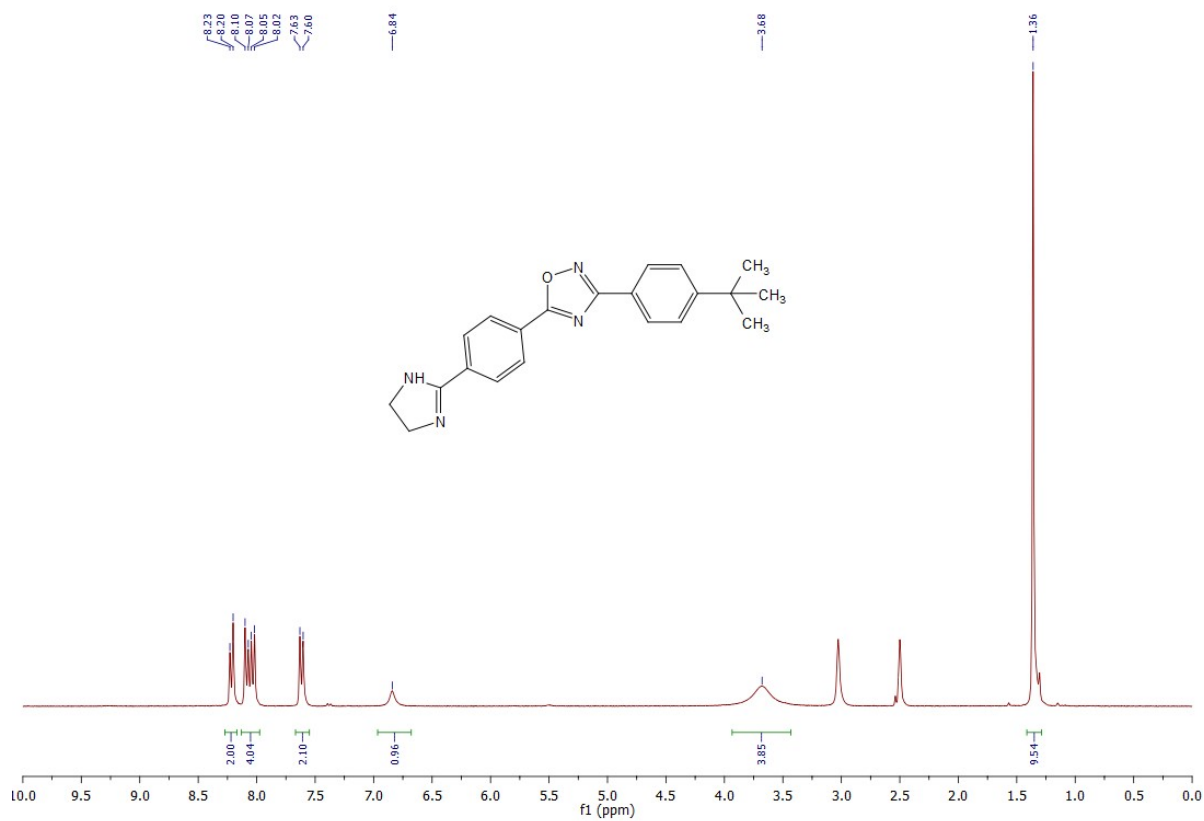
^1H and ^{13}C NMR spectra of 5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-3-isopropyl-1,2,4-oxadiazole (**5b**)



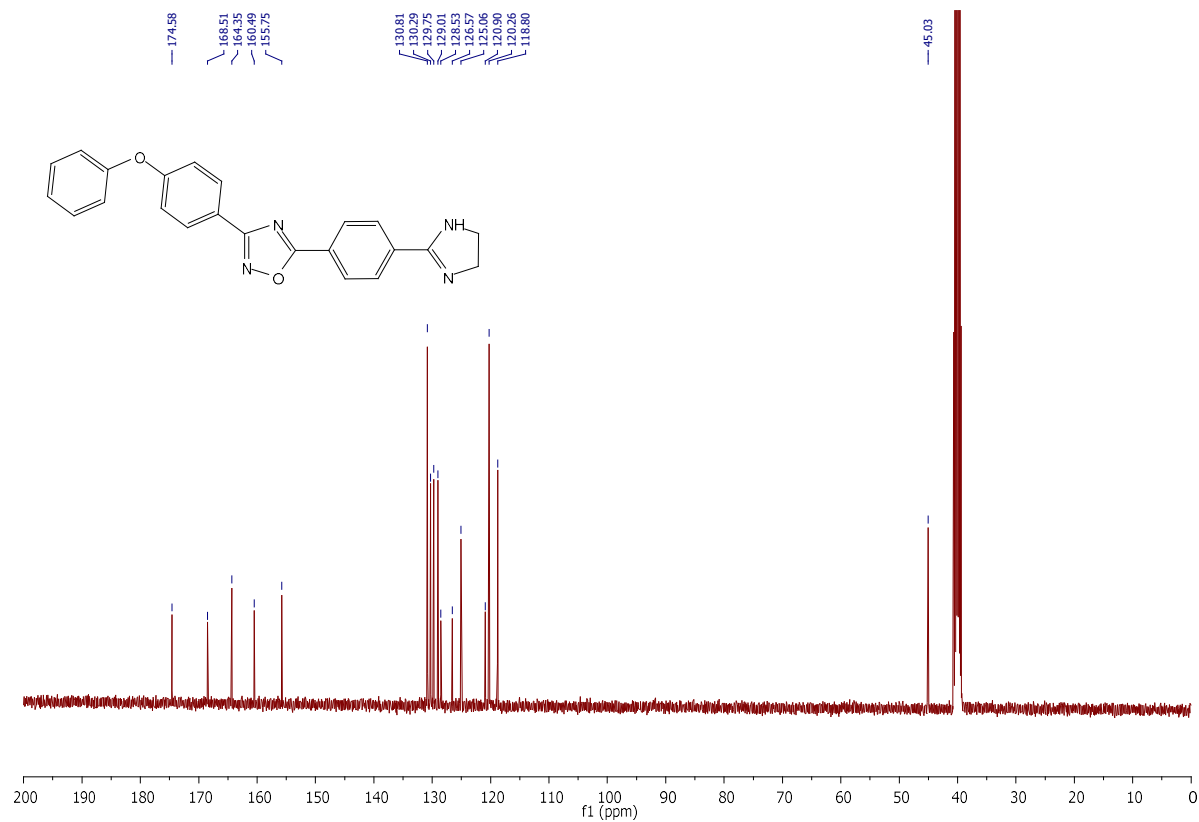
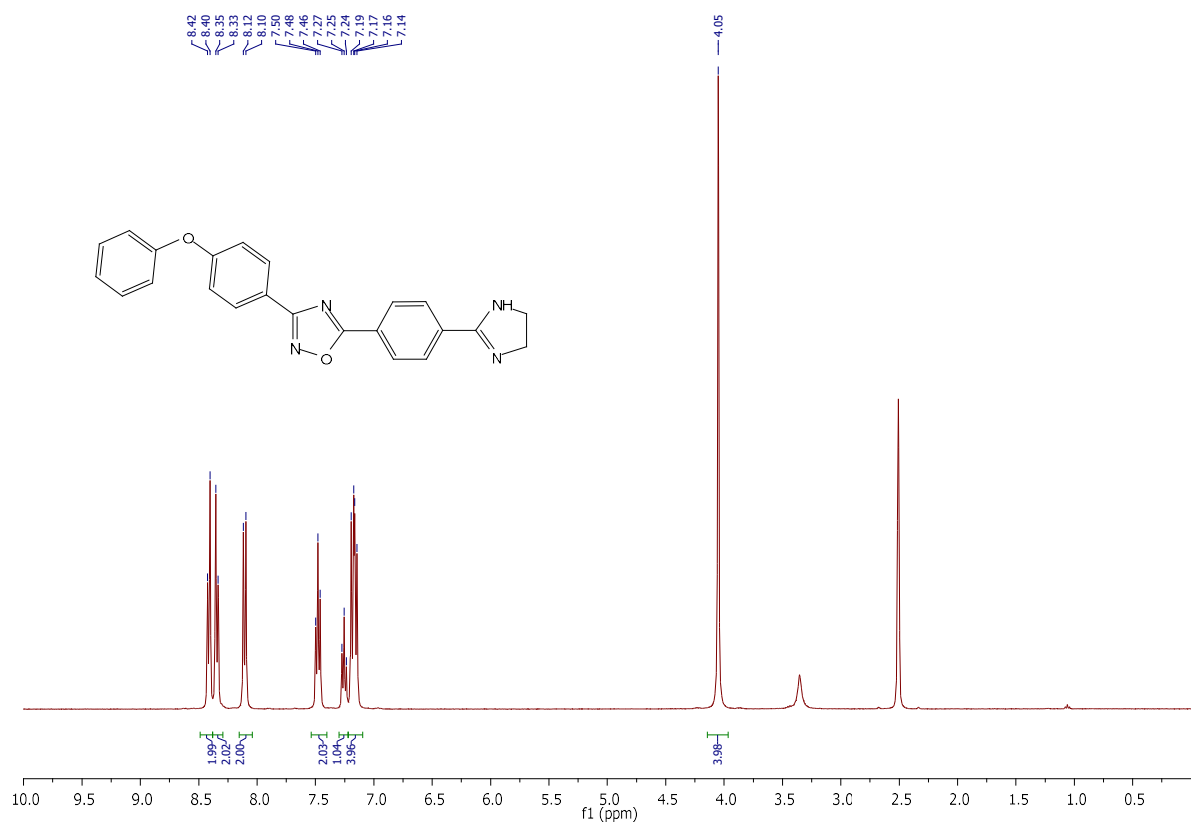
^1H and ^{13}C NMR spectra of 5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-3-(phenoxy)methyl-1,2,4-oxadiazole (**5c**)



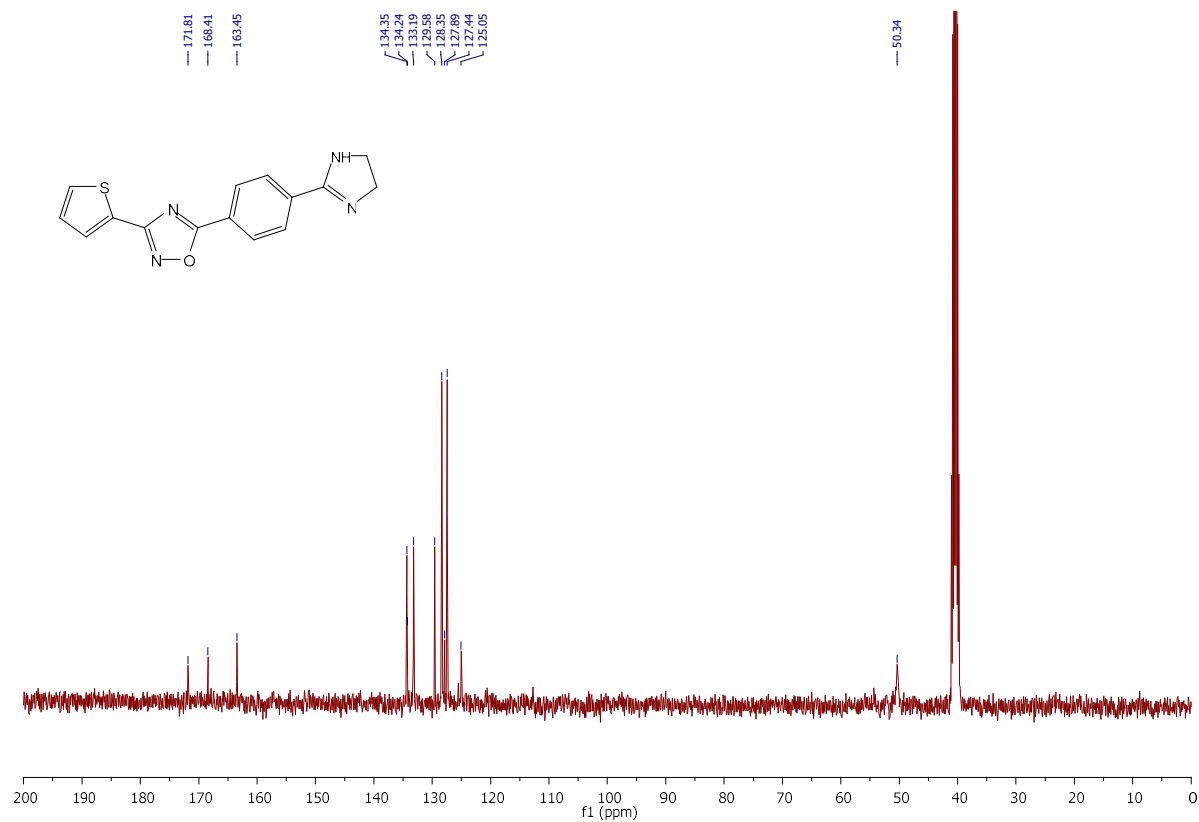
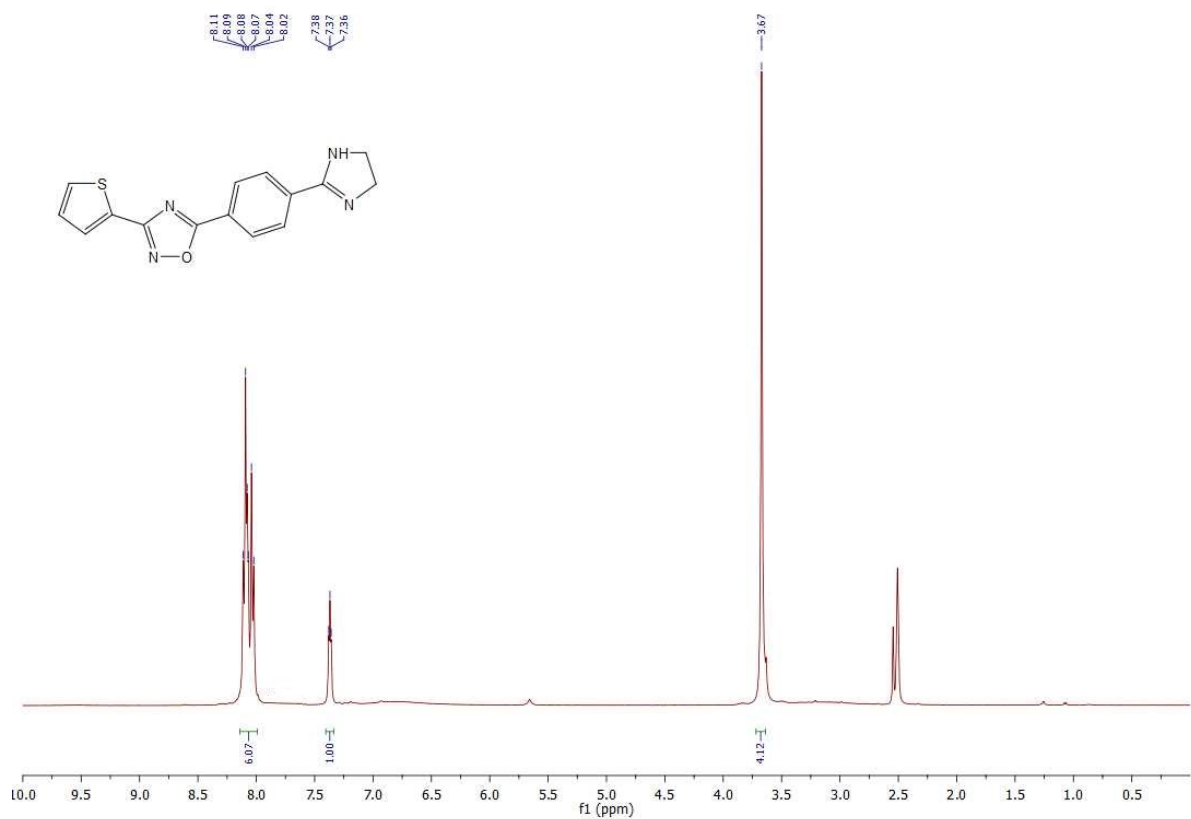
^1H and ^{13}C NMR spectra of 3-(4-*tert*-butylphenyl)-5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (**5d**)



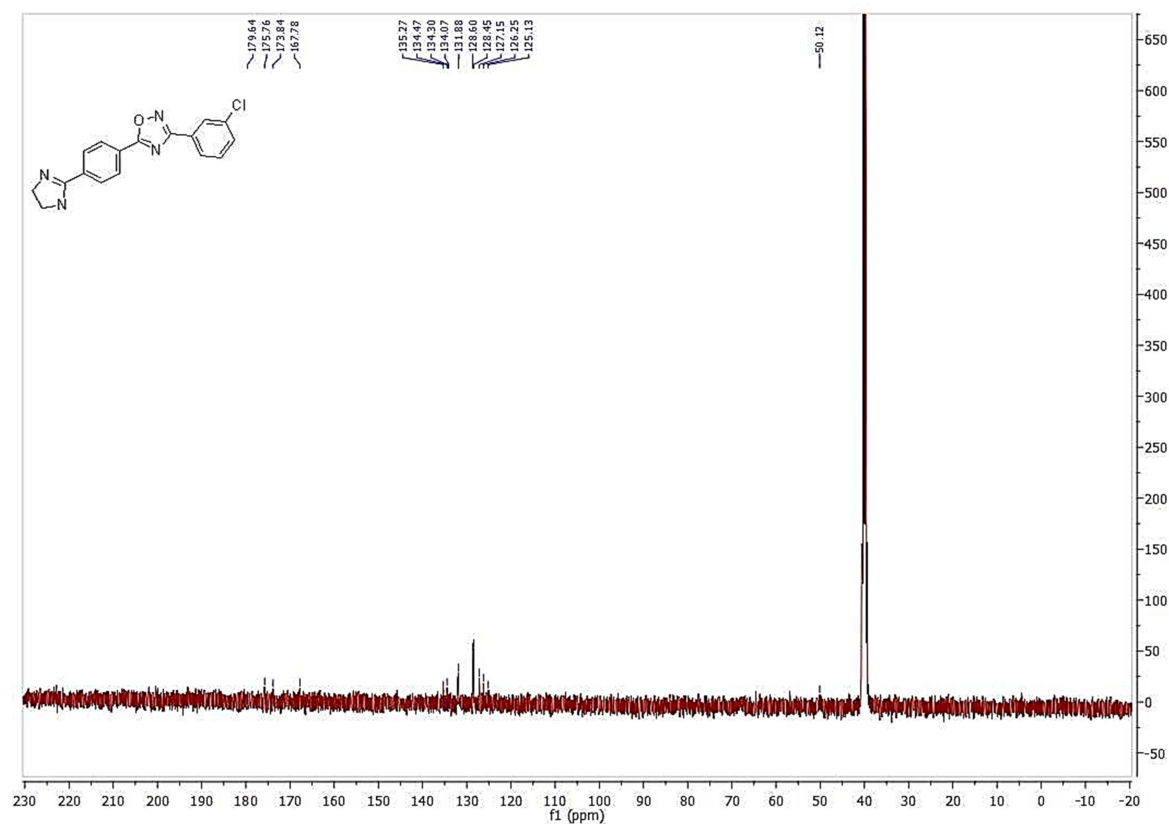
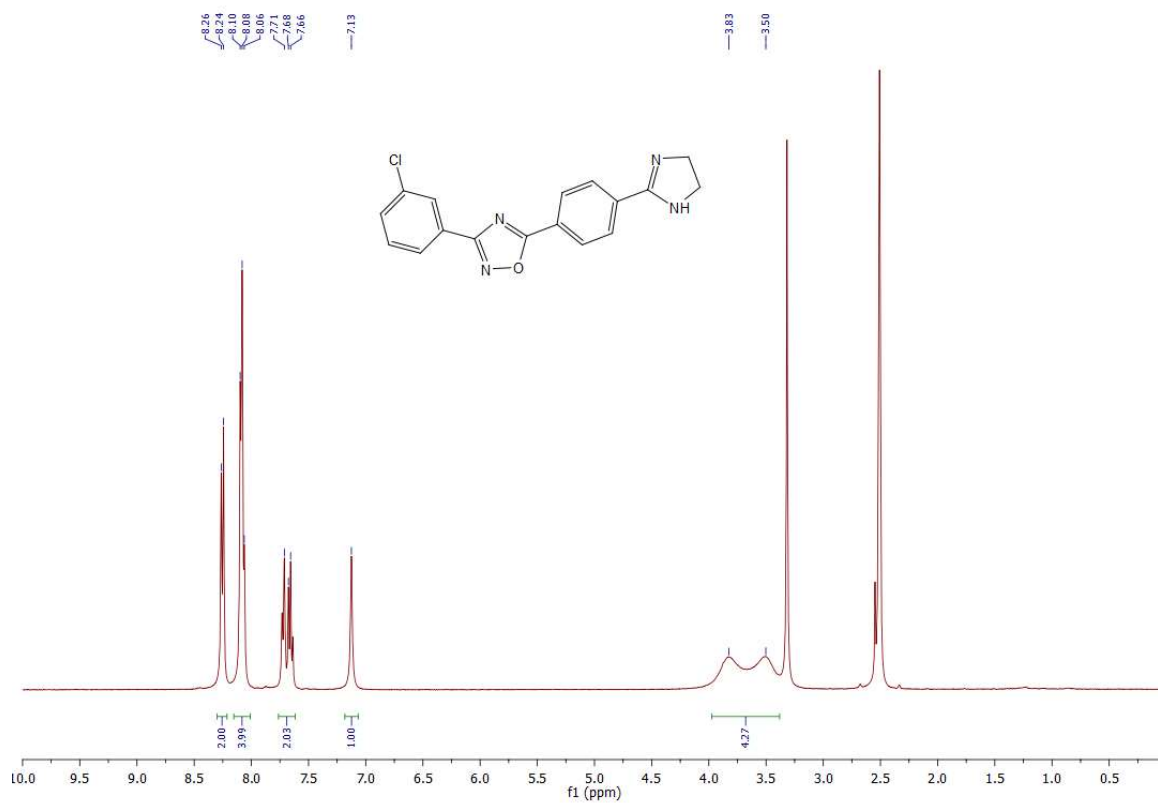
^1H and ^{13}C NMR spectra of 5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-3-(4-phenoxyphenyl)-1,2,4-oxadiazole (**5e**)



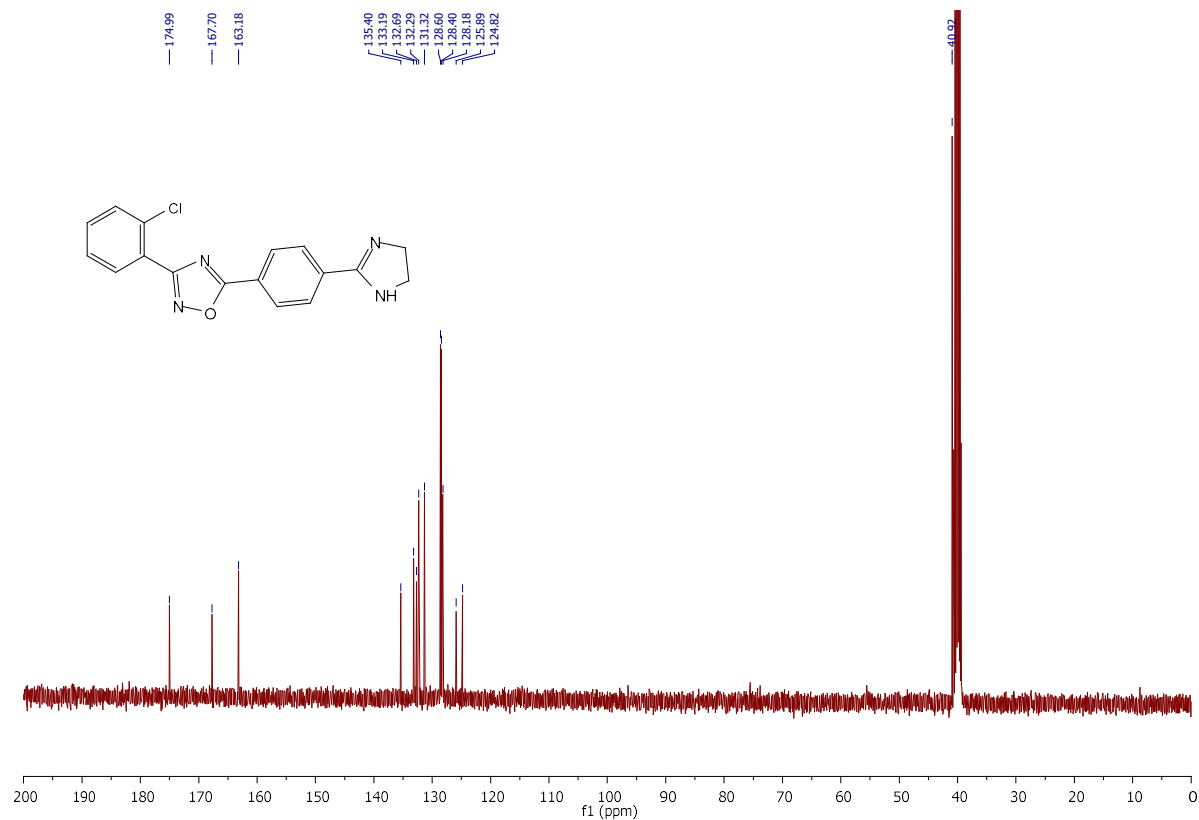
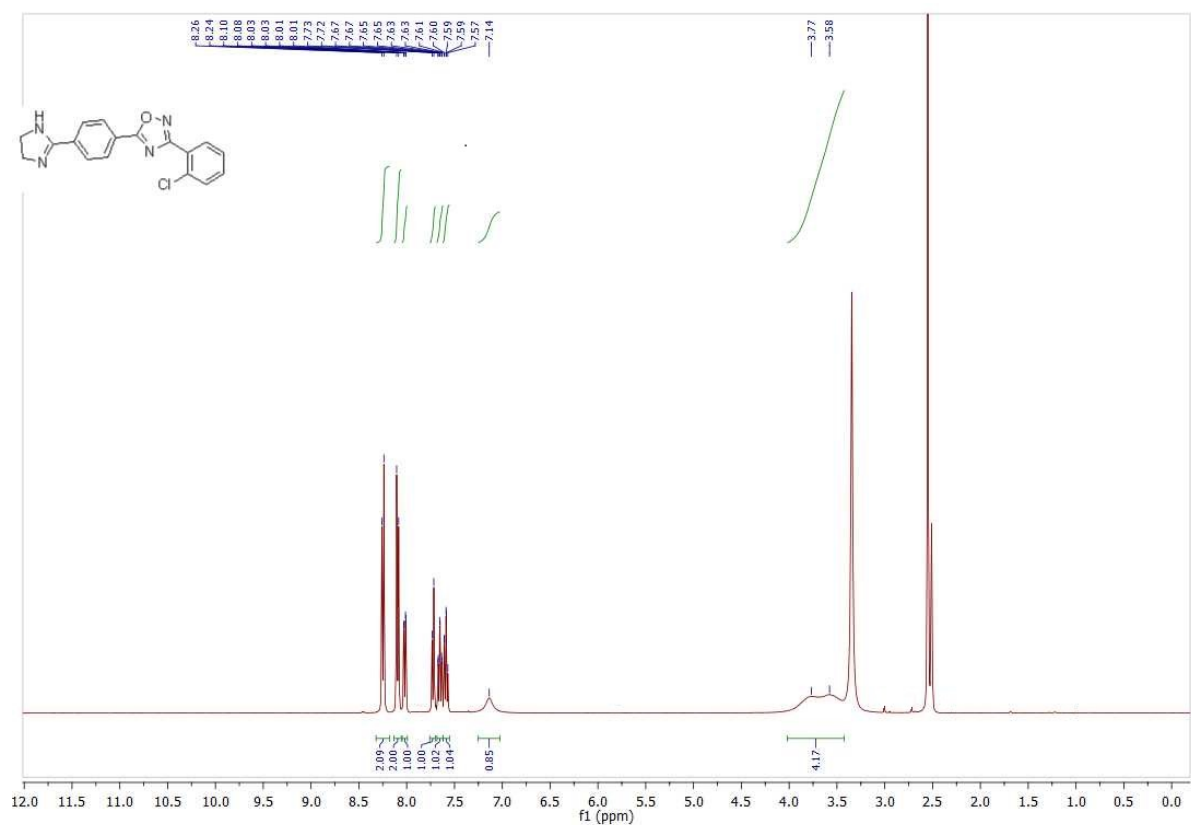
^1H and ^{13}C NMR spectra of 5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-3-(thiophen-2-yl)-1,2,4-oxadiazole (**5f**)



^1H and ^{13}C NMR spectra of 3-(3-chlorophenyl)-5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (**5g**)



^1H and ^{13}C NMR spectra of 3-(2-chlorophenyl)-5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (**5h**)



Chemical structure of compound 10: C1=CN(C1)c2ccc(cc2)-c3nc(Cn4cnc5ccccc45)c3

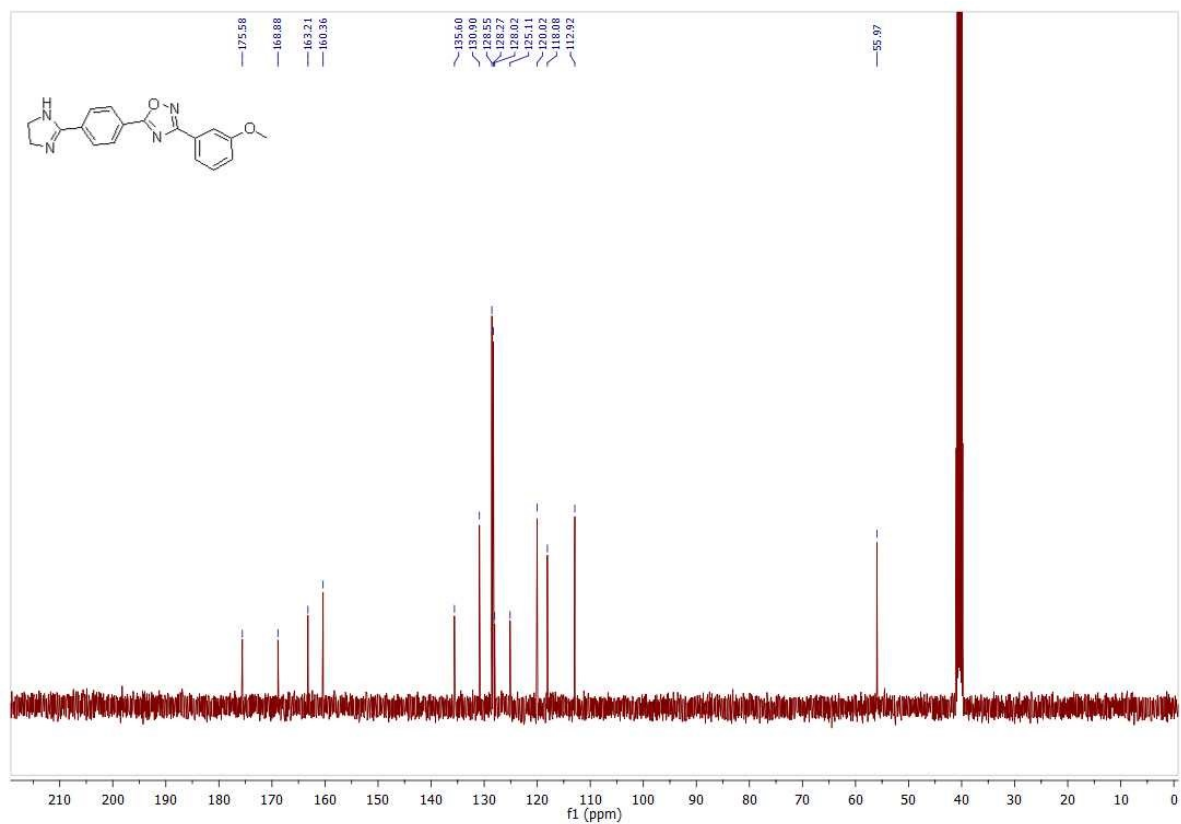
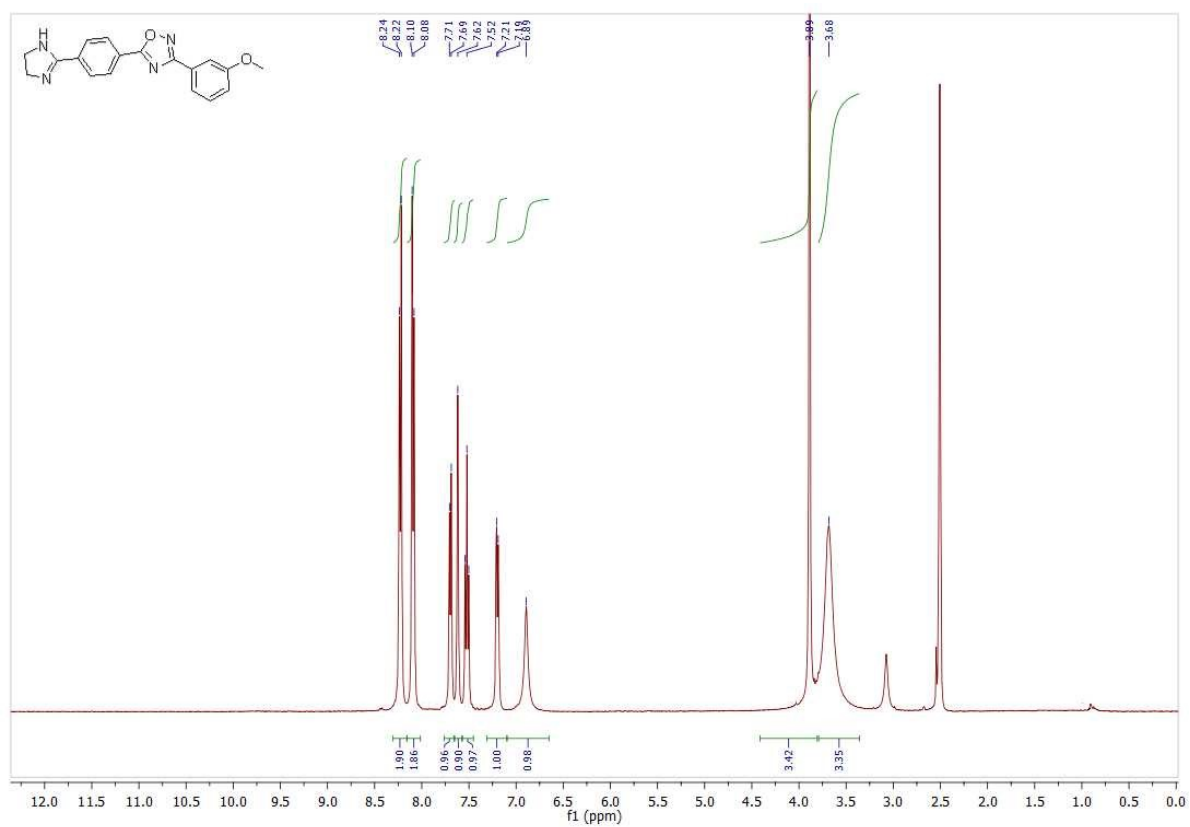
¹H NMR spectrum (CDCl₃) of compound 10. The x-axis represents the chemical shift in ppm (f1), ranging from 0.0 to 12.0. The spectrum shows several peaks, with integration values indicated below the baseline. Key peaks are labeled with their chemical shifts: 8.46, 8.22, 8.20, 8.11, 8.09, 8.04, 8.02, 7.97, 7.95, 7.93, 7.91, 7.90, 7.89, 6.86, 5.58, 3.65, and 3.59. Integration values are shown as green numbers below the baseline: 0.90, 0.92, 1.89, 1.89, 1.82, 1.00, 1.00, 1.98, and 3.99.



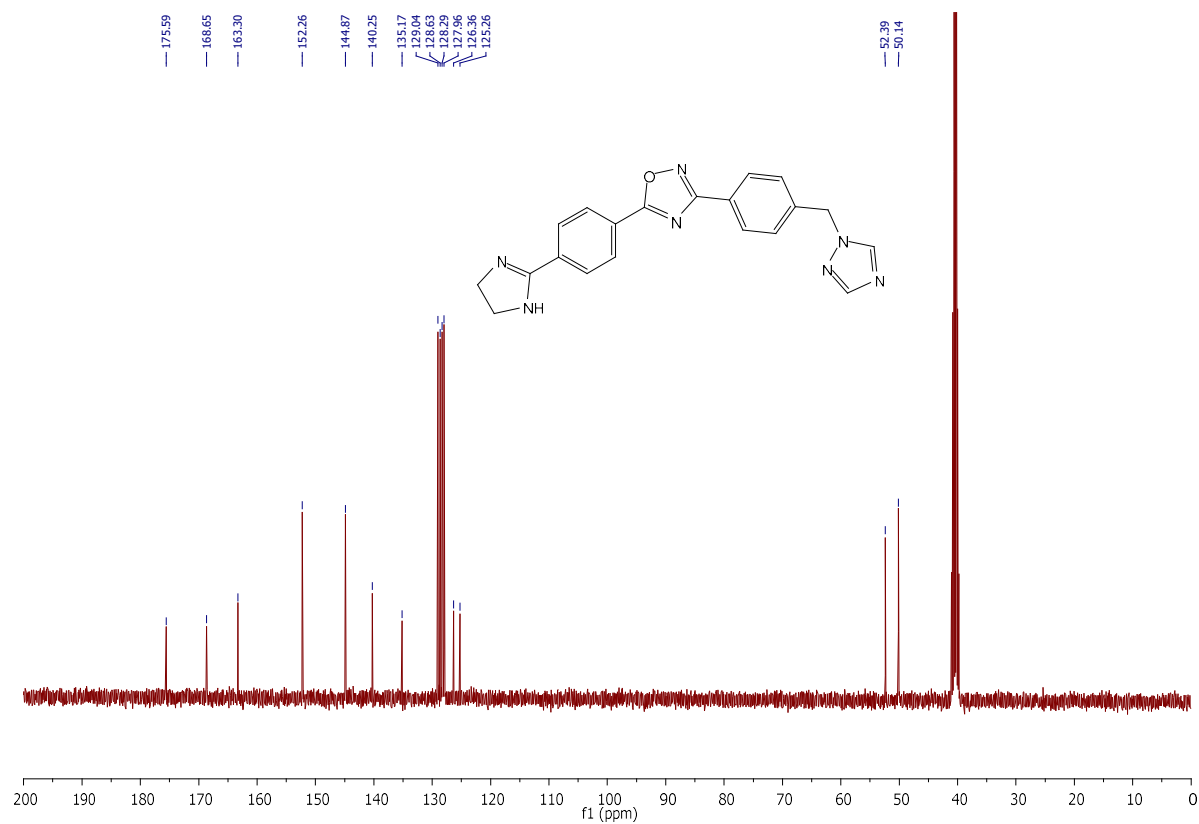
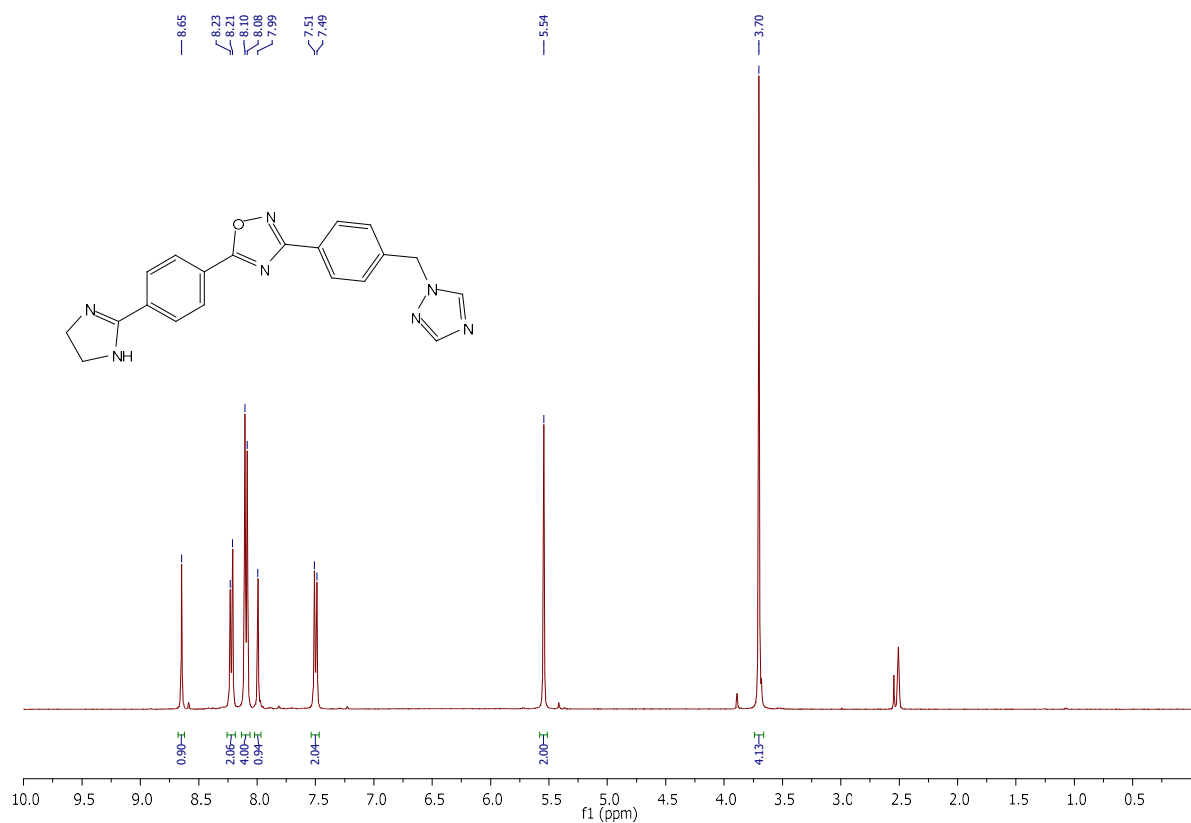
Chemical structure of 3,4-dimethoxy-1-(4-(1H-imidazol-2-yl)phenyl)-1H-imidazole-5-carboxamide is shown. The ^1H NMR spectrum (CDCl₃) displays peaks at 8.22, 8.20, 8.07, 8.05, 7.69, 7.67, 7.55, 7.15, 7.13, 3.87, 3.84, and 3.46 ppm. Integration values are indicated below the peaks: 2.07, 2.00, 1.05, 0.99, 2.01, 8.15, and 1.90.



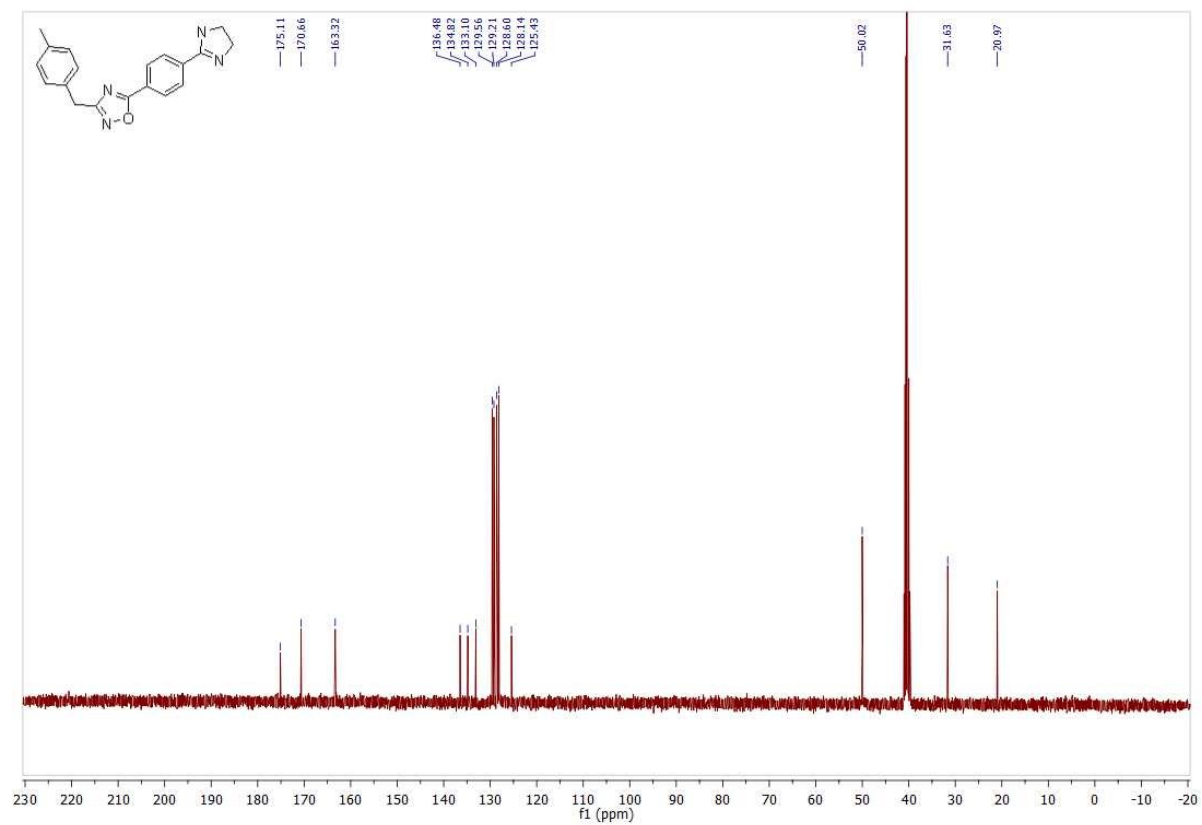
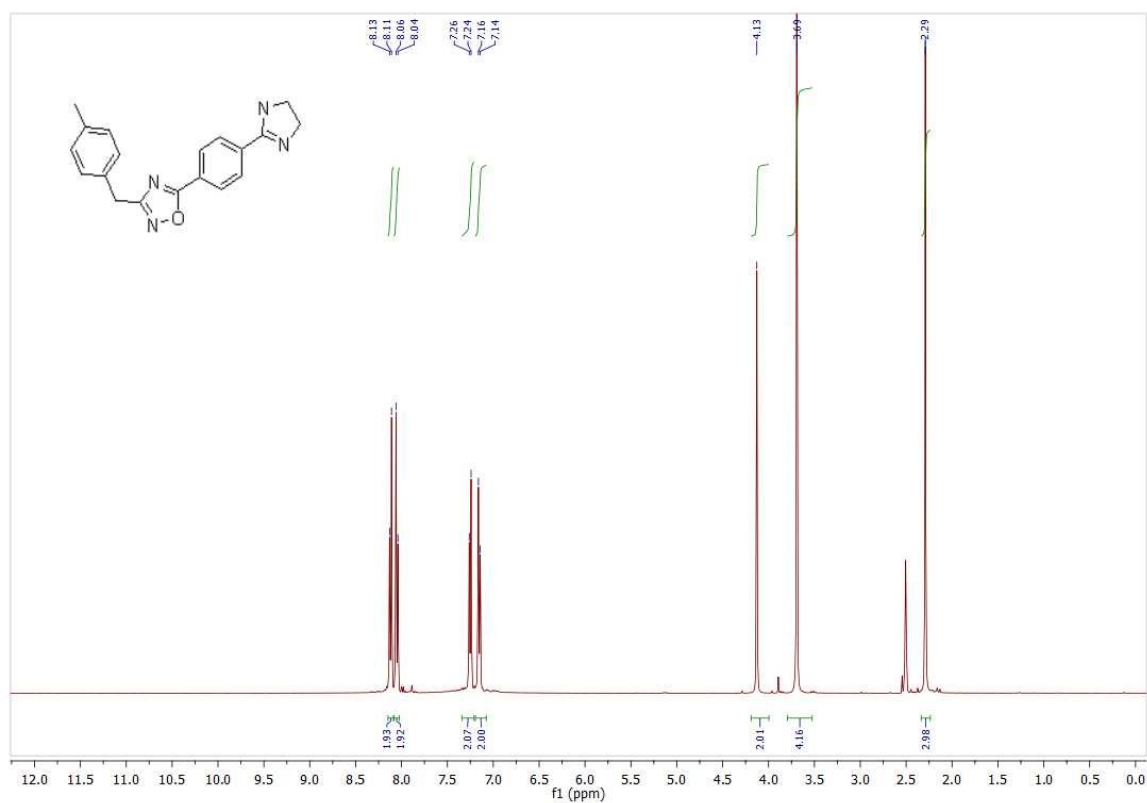
^1H and ^{13}C NMR spectra of 5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-3-(3-methoxyphenyl)-1,2,4-oxadiazole (**5k**)



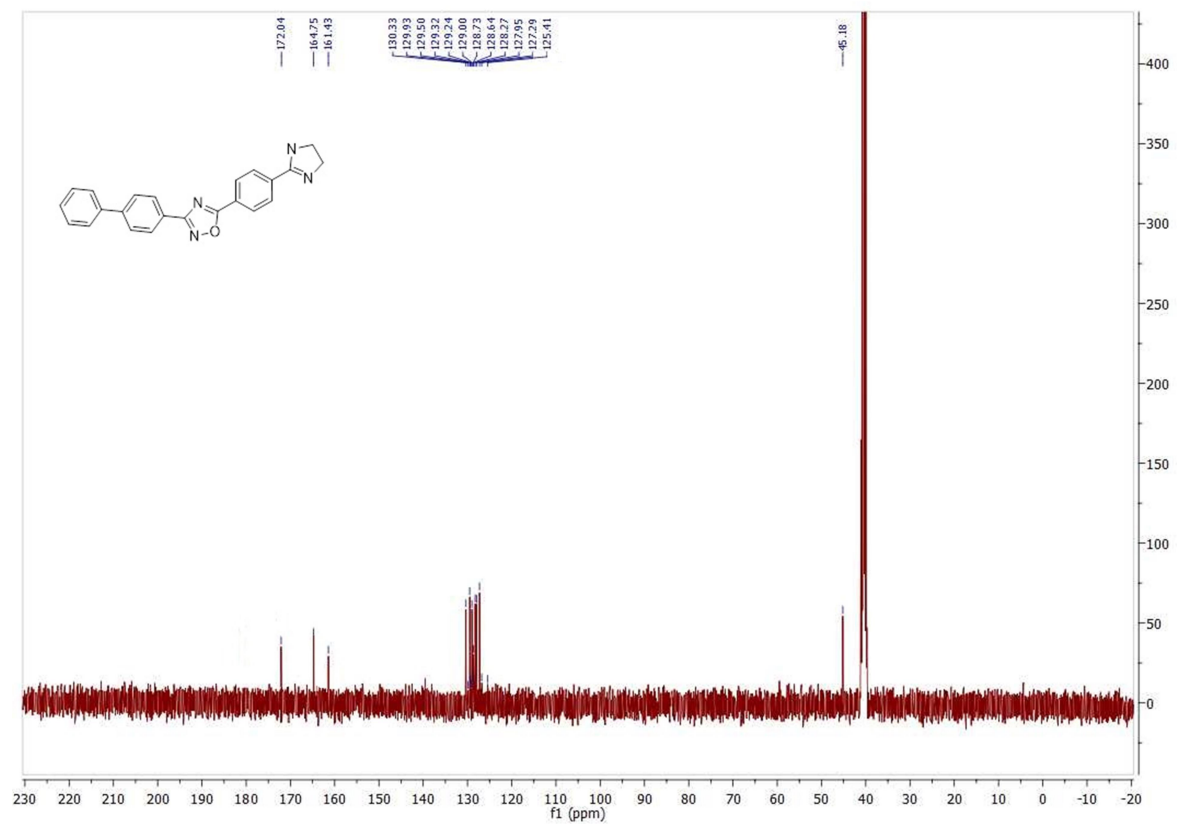
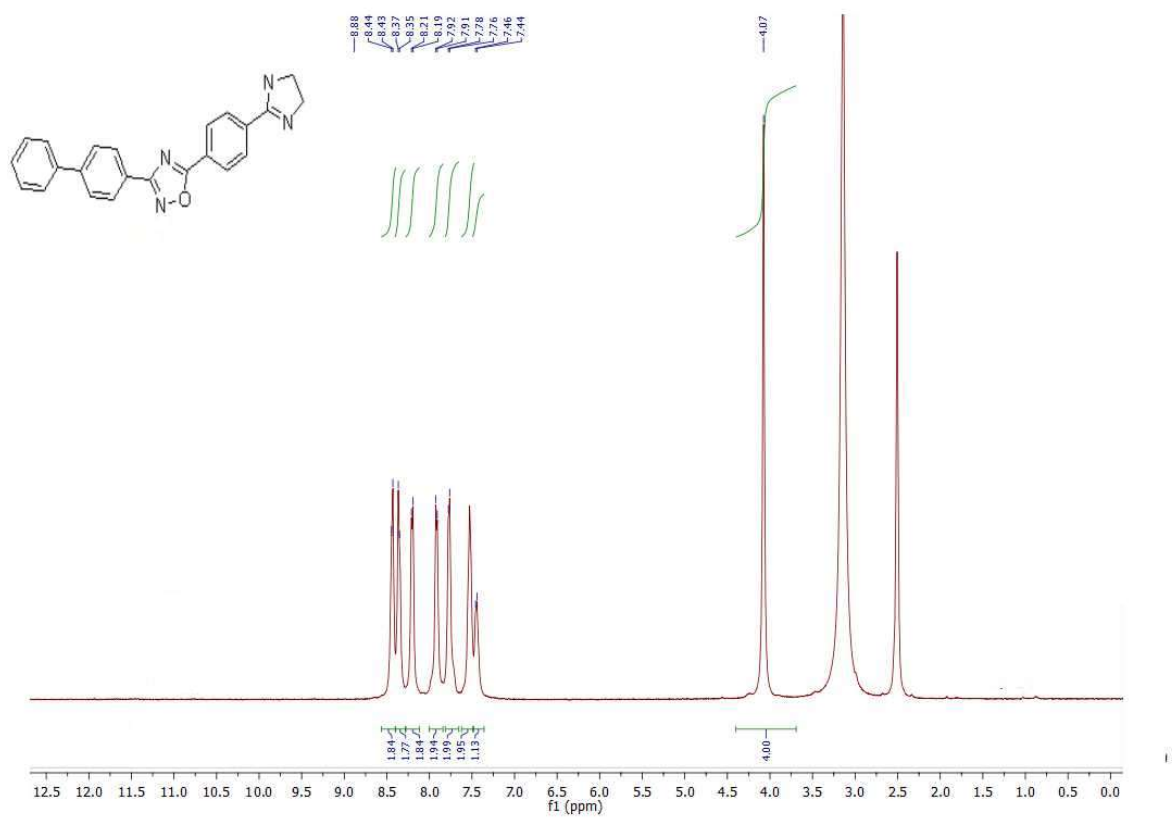
^1H and ^{13}C NMR spectra of 3-(4-((1*H*-1,2,4-triazol-1-yl)methyl)phenyl)-5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (**5l**)



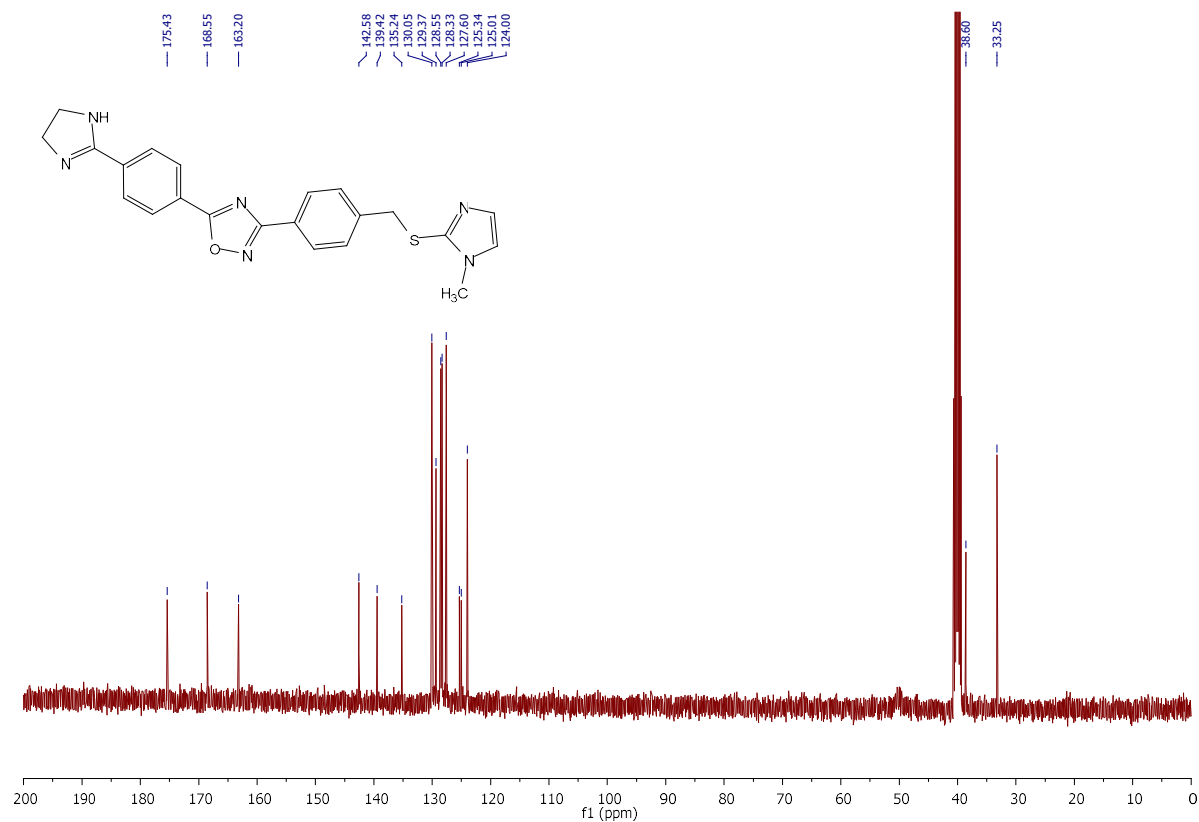
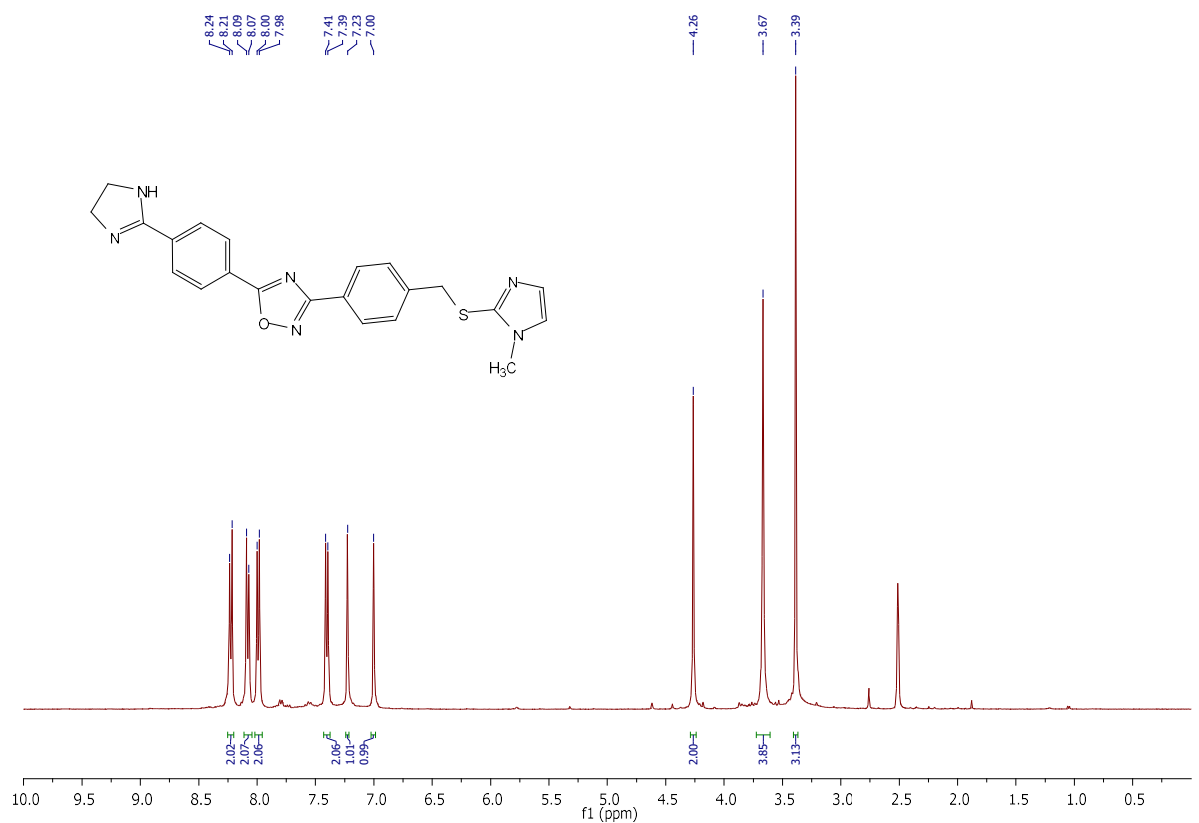
^1H and ^{13}C NMR spectra of 5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-3-(4-methylbenzyl)-1,2,4-oxadiazole (**5m**)



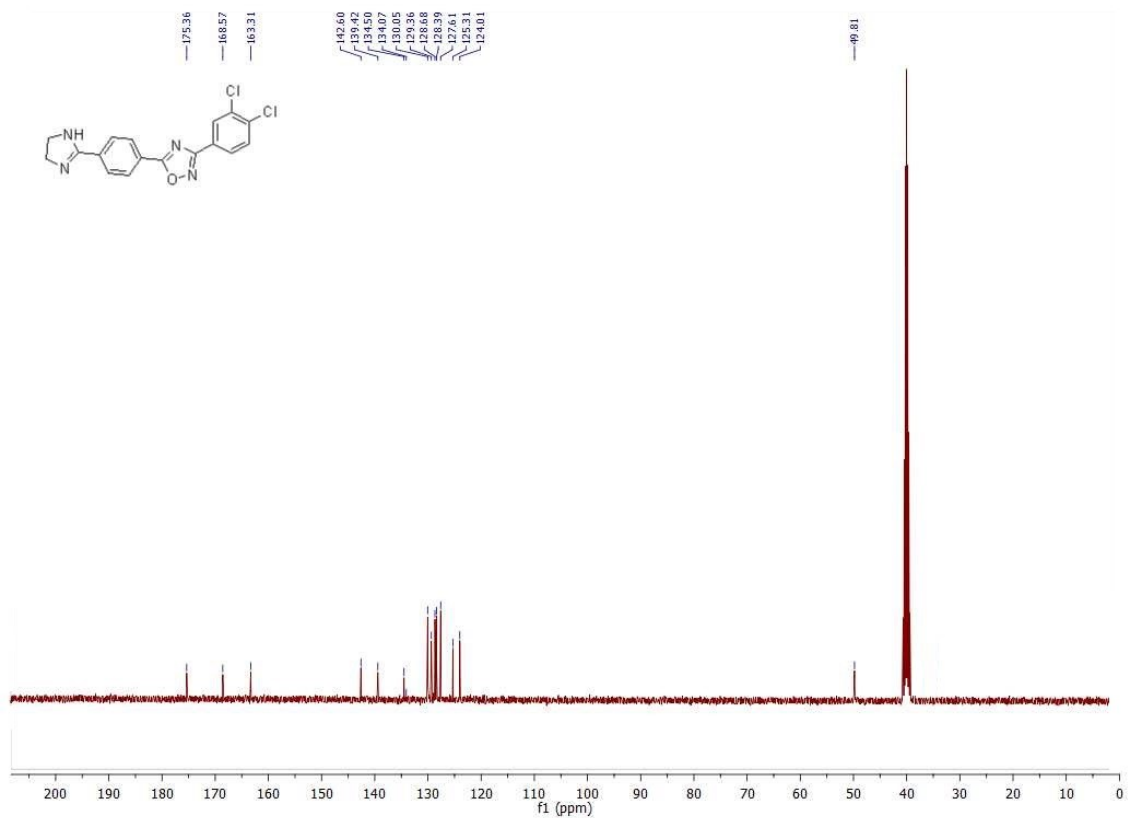
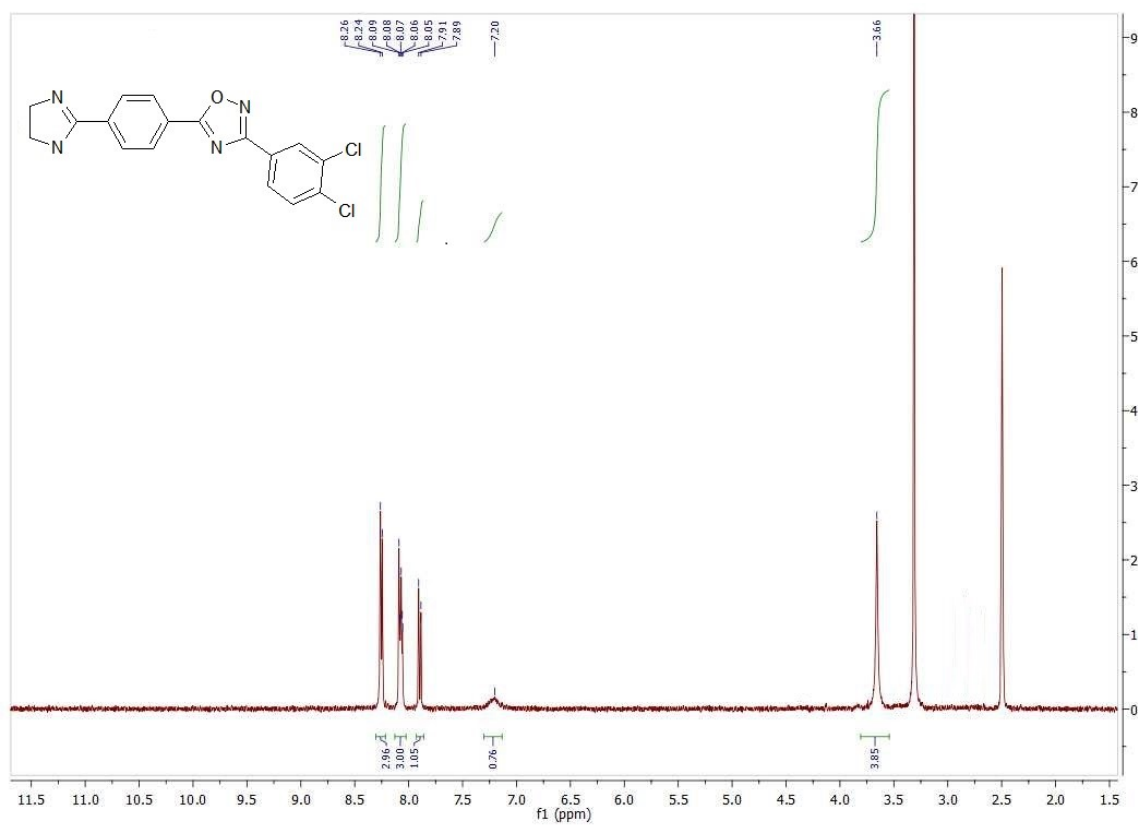
^1H and ^{13}C NMR spectra of 5-([1,1'-biphenyl]-4-yl)-3-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (**5n**)



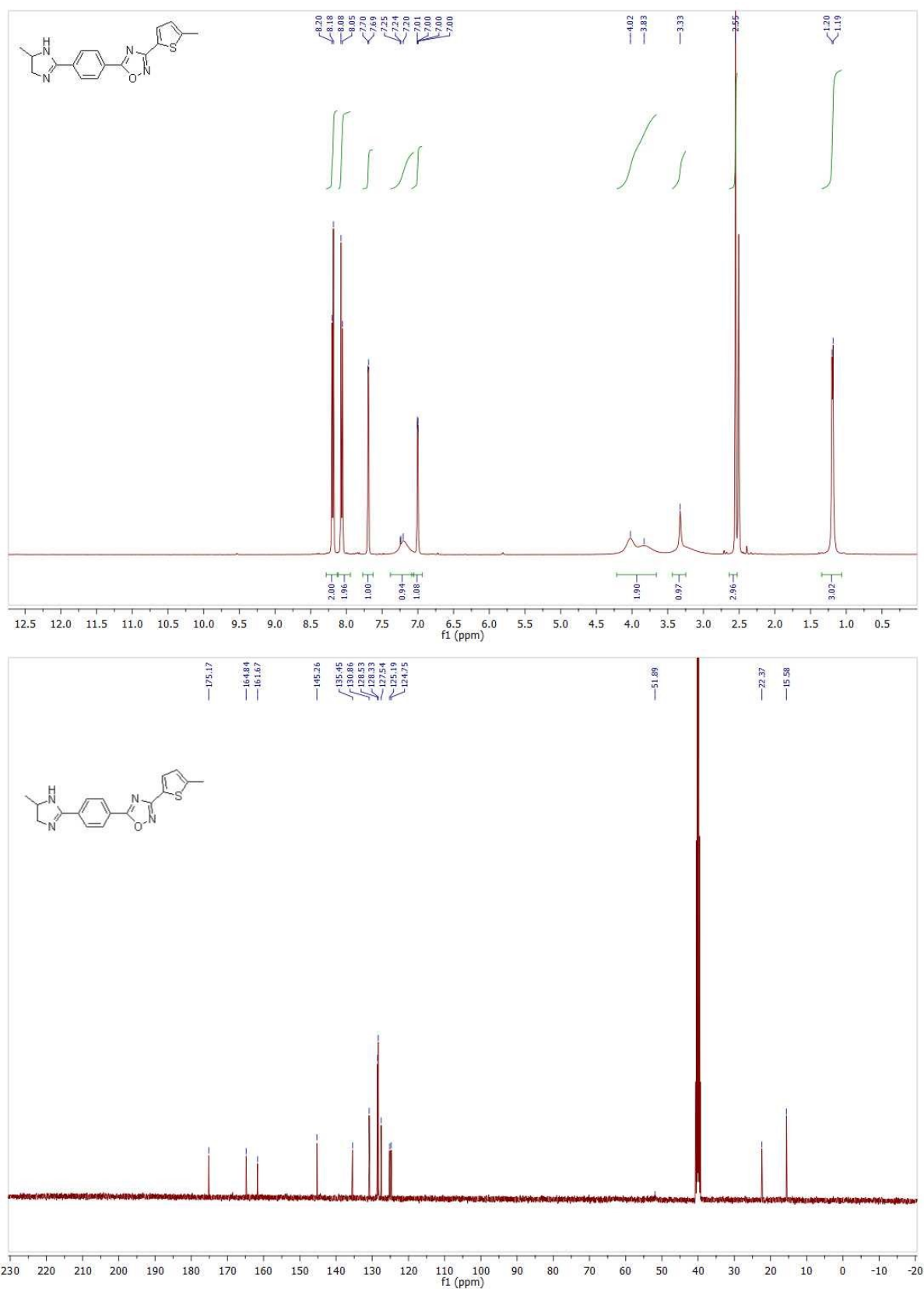
^1H and ^{13}C NMR spectra of 5-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-3-(4-(((1-methyl-1*H*-imidazol-2-yl)thio)methyl)phenyl)-1,2,4-oxadiazole (**5o**)



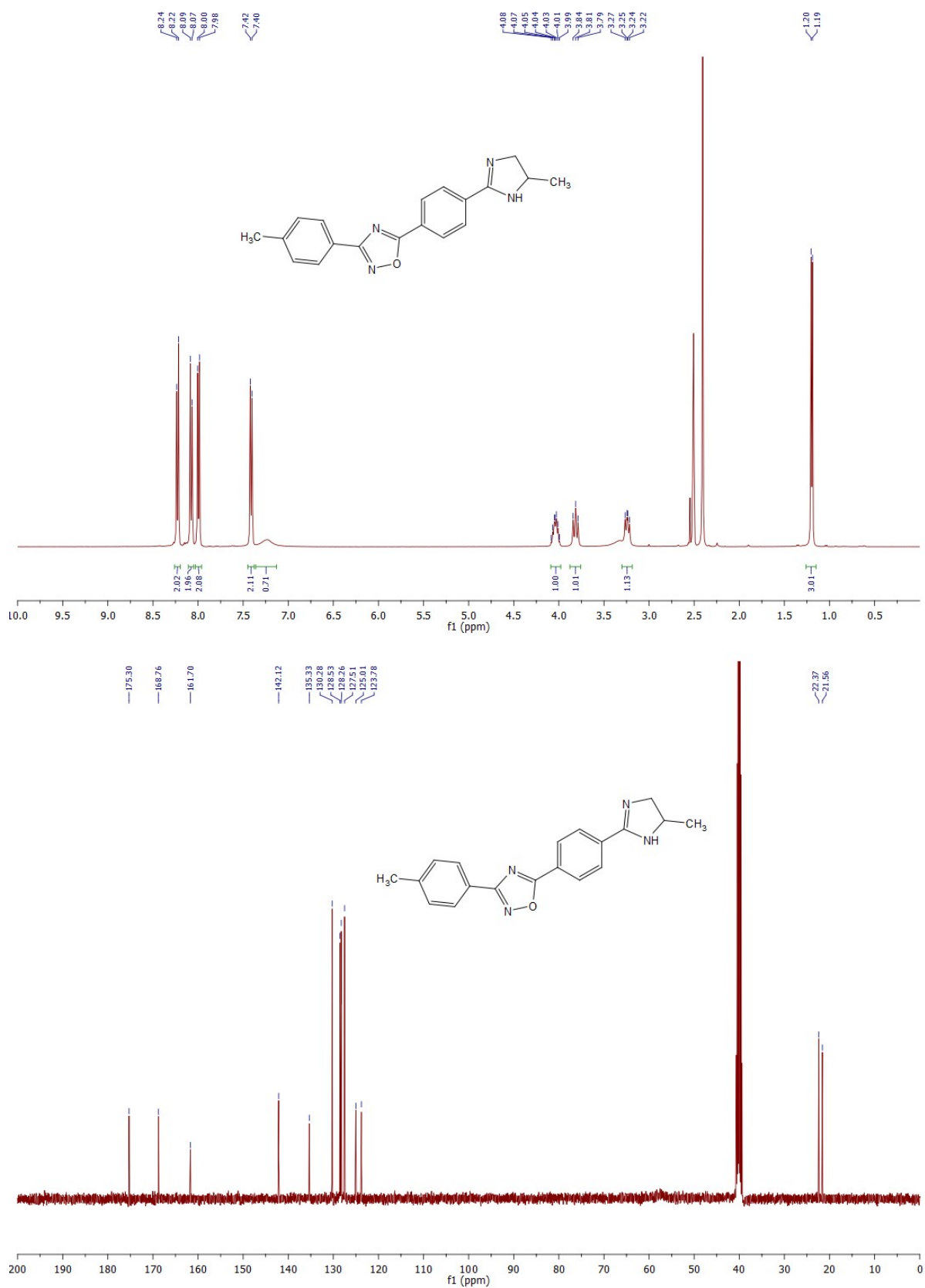
^1H and ^{13}C NMR spectra of 5-(3,4-dichlorophenyl)-3-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (**5p**)



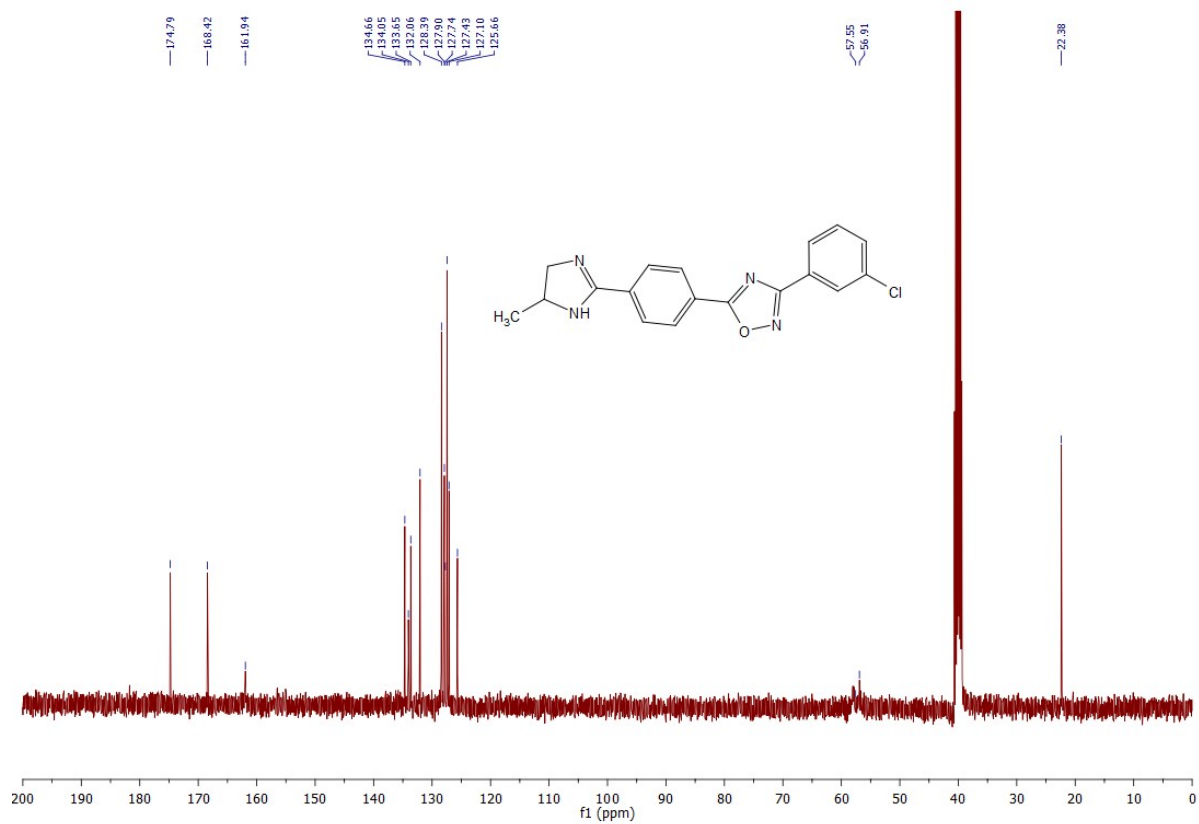
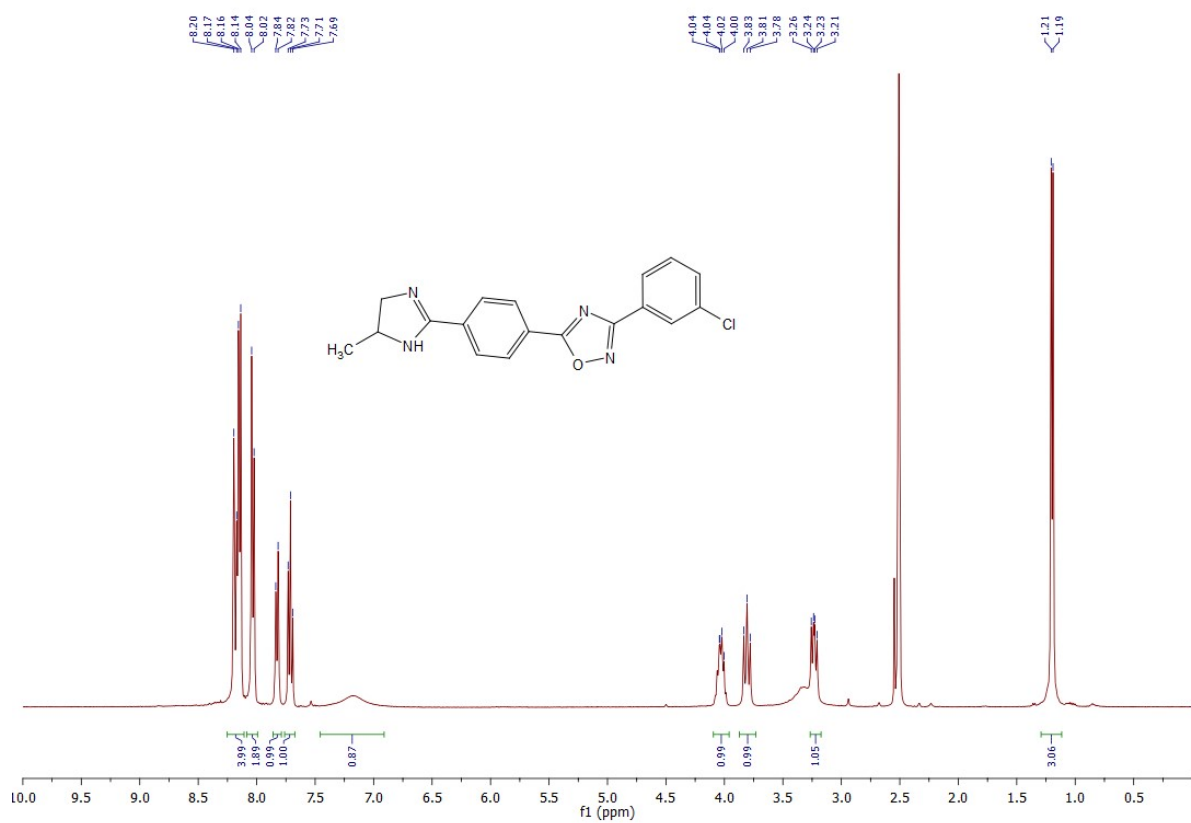
^1H and ^{13}C NMR spectra of 5-(4-(5-methyl-4,5-dihydro-1*H*-imidazol-2-yl)phenyl)-3-(5-methylthiophen-2-yl)-1,2,4-oxadiazole (**5q**)



^1H and ^{13}C NMR spectra of 5-(4-(5-Methyl-4,5-dihydro-1H-imidazol-2-yl)phenyl)-3-(p-tolyl)-1,2,4-oxadiazole (**5r**)



^1H and ^{13}C NMR spectra of 3-(3-chlorophenyl)-5-(4-(5-methyl-4,5-dihydro-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazole (**5s**)



^1H and ^{13}C NMR spectra of 5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-3-(p-tolyl)-1,2,4-oxadiazole (**5t**)

