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Nitrileimines as an alternative to azides in base-mediated click [3+2]cycloaddition with methylene active nitriles

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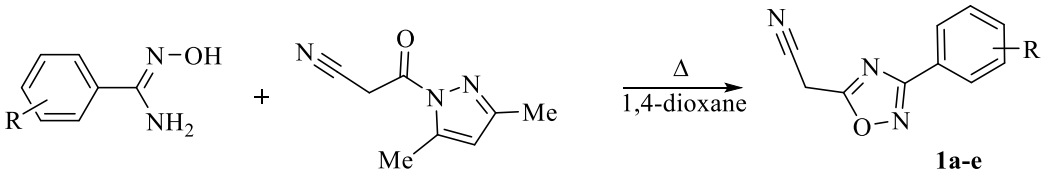
"Supporting Information"

General Methods: ^{1}H and ^{13}C NMR spectra were acquired on Varian Unity Plus 400 (400 and 101 MHz, respectively) and Bruker 170 Avance 500 (500 and 126 MHz, respectively) spectrometers in DMSO-d_6 solutions using TMS or the deuterated solvent as internal reference. HPLC-MS analysis was performed by using an Agilent 1100 Series high performance liquid chromatograph equipped with a diode array and mass selective Agilent LC/MSD SL detector. The method of ionization was chemical ionization at atmospheric pressure. Elemental analysis was performed on an analyzer Carlo Erba 1106. Melting points were measured on a Boetius apparatus.

General procedure for the synthesis of 2-(3-aryl-1,2,4-oxadiazol-5-yl)acetonitrile 1:



1a-e

A mixture of equimolar amidoxime (10 mmol) and 3-(3,5-dimethyl-*1H*-pyrazol-1-yl)-3-oxopropanenitrile (1.63 g, 10 mmol) in 25 ml of dioxane was refluxed for 24 hours. Then cooled and dioxane was evaporated in vacuum. The residue was washed with $NaHCO_3$ solution, filtered and dried yielding the target (1,2,4-oxadiazol-5-yl) acetonitrile **1**.

2-(3-Phenyl-1,2,4-oxadiazol-5-yl)acetonitrile (1a) was prepared as previously described by Pokhodylo N.T., Matiychuk V.S. in J. Heterocyclic Chem. 2010 47, 415.

2-(3-(o-Tolyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1b): Yield 1.65 g, 83%; yellow solid; m.p.: 77–78 ºC; ^{1}H NMR (500 MHz, DMSO-d_6): 7.92 (d, J = 7.6 Hz, 1H H^{Ar}-6), 7.49 (t, J = 7.4 Hz, 1H, H^{Ar}-5), 7.44 – 7.35 (m, 2H, H^{Ar}-3,4), 4.81 (s, 2H, CH_2), 2.55 (s, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): 171.12 ($C^{oxadiazole}$-5), 169.03 ($C^{oxadiazole}$-3), 138.10 (C^{Tol}-2), 131.99 (CH^{Tol}-3), 131.62 (CH^{Tol}-6), 130.21 (CH^{Tol}-4), 126.81 (CH^{Tol}-5), 125.41 (C^{Tol}-1), 114.92 (CN), 22.04 (Me), 17.50 (CH_2). MS (m/z): 200 (M^{+}+1). Anal. calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N 21.09; found: C 66.33; H 4.53; N 21.05

2-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1c): Yield 1.54 g, 76%; yellow solid; m.p.: 62–63 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 8.06 (dd, J = 8.5, 5.5 Hz, 2H, H^{Ar}-2,6), 7.41 (t, J = 8.8 Hz, 2H, H^{Ar}-3,5), 4.79 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d_6): 172.33 ($C^{oxadiazole}$-5), 167.67 ($C^{oxadiazole}$-3), 164.61 (d, $^{1}J_{C\text{-}F}$ = 249.8 Hz, C^{Ar}-4), 130.16 (d, $^{3}J_{C\text{-}F}$ = 9.1 Hz, 2xCH^{Ar}-2,6), 122.61 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz, C^{Ar}-1), 117.04 (d, $^{2}J_{C\text{-}F}$ = 22.3 Hz, 2xCH^{Ar}-3,5), 114.83 (CN), 17.63 (CH_2). MS (m/z): 204 (M^{+}+1). Anal. calcd. for $C_{10}H_6FN_3O$: C, 59.12; H, 2.98; N 20.68; found: C 59.13; H 2.95; N 20.69.

2-(3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1d): Yield 1.58 g, 72%; yellow solid; m.p.: 72–73 ºC; ^{1}H NMR (500 MHz, DMSO-d_6): 7.92 (d, J = 7.5 Hz, 1H, H^{Ar}-6), 7.70 (d, J = 7.9 Hz, 1H, H^{Ar}-3), 7.63 (t, J = 7.5 Hz, 1H, H^{Ar}-5), 7.56 (t, J = 7.3 Hz, 1H, H^{Ar}-4), 4.84 (s, 2H, CH_2). ^{13}C NMR (101

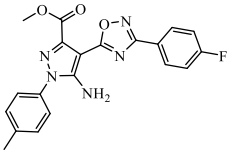
MHz, DMSO-d_6): 171.78 ($C^{oxadiazole}$-5), 167.24 ($C^{oxadiazole}$-3), 133.34 (CH^{Ar}-3), 132.61 (C^{Ar}-2), 132.25 (CH^{Ar}-6), 131.41 (CH^{Ar}-4), 128.26 (CH^{Ar}-5), 125.32 (C^{Ar}-1), 114.84 (CN), 17.59 (CH_2). MS (m/z): 220 (M^++1). Anal. calcd. for $C_{10}H_6ClN_3O$: C, 54.69; H, 2.75; N 19.13; found: C 54.67; H 2.76; N 19.11.

2-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1e): Yield 1.99 g, 91%; yellow solid; m.p.: 60–61 ºC; ^{1}H NMR (500 MHz, DMSO-d_6): 8.02 (d, J = 8.4 Hz, 2H, H^{Ar}-2,6), 7.65 (d, J = 8.5 Hz, 2H, H^{Ar}-3,5), 4.81 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d_6): 172.46 ($C^{oxadiazole}$-5), 167.68 ($C^{oxadiazole}$-3), 137.13 (C^{Ar}-4), 130.02 (2xCH^{Ar}-3,5), 129.35 (2xCH^{Ar}-2,6), 124.89 (C^{Ar}-1), 114.80 (CN), 17.66 (CH_2). MS (m/z): 220 (M^++1). Anal. calcd. for $C_{10}H_6ClN_3O$: C, 54.69; H, 2.75; N 19.13; found: C 54.70; H 2.74; N 19.12.

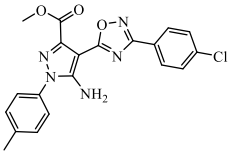
General procedure for the synthesis of 5-amino-*1H*-pyrazole-3-carboxylates 4a-d, 7a-h and *1,2,3-triazoles* 5a-e

A mixture of acetonitrile **1** (or oxopropanenitriles **6**) (2 mmol), chlorohydrazone **2** (2 mmol) [or azide 4 (2 mmol)], 5 mL MeOH, and sodium methoxide, that was prepared by dissolving 0.092 g (4 mmol) [or 0.046 g (2 mmol) in case of azides] sodium in 1 mL MeOH, was stirred at room temperature until the sediment was formed. The mixture monitoring by TLC. The resulting suspension was filtered and the solid product was washed with H_2O and MeOH to give target pyrazole **4, 7** [or triazoles **5**] as crystalline solid.

Methyl 5-amino-4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-(p-tolyl)-*1H*-pyrazole-3-carboxylate (4a): Yield 0.68 g, 87%; white solid; m.p.: 167–168 ºC; ^{1}H NMR (500 MHz, DMSO-d_6): 8.18 (s, 2H, H^{Ar}), 7.50 (d, J = 6.9 Hz, 2H, H^{Ar}), 7.45 – 7.32 (m, 4H, H^{Ar}), 6.86 (s, 2H, NH_2), 3.89 (s, 3H, MeO), 2.40 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d_6): 170.80 ($C^{oxadiazole}$-5), 166.44 ($C^{oxadiazole}$-3), 164.36 (d, $^1J_{C-F}$ = 249.2 Hz, C^{Ar}-4), 162.12 (O=C-O), 150.09 ($C^{pyrazole}$-5), 140.99 ($C^{pyrazole}$-3), 138.93 (C^{Tol}-4), 134.89 (C^{Tol}-1), 130.53 (2xCH^{Tol}-3,5), 130.21 (d, $^3J_{C-F}$ = 8.9 Hz, 2xCH^{Ar}-2,6), 125.06 (2xCH^{Tol}-2,6), 123.32 (d, ^4J = 2.7 Hz, C^{Ar}-1), 116.66 (d, $^2J_{C-F}$ = 22.1 Hz, 2xCH^{Ar}-3,5), 87.89 ($C^{pyrazole}$-4), 52.65 (OMe), 21.15 (Me). MS (m/z): 394 (M^++1). Anal. calcd. for $C_{20}H_{16}FN_5O_3$: C, 61.07; H, 4.10; N 17.80; found: C 61.09; H 4.05; N 17.85.

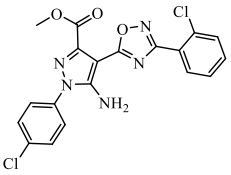


Methyl 5-amino-4-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(p-tolyl)-*1H*-pyrazole-3-carboxylate (4b): Yield 0.74 g, 91%; dark orange solid; m.p.: 145–146 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 8.11 (br.s, 2H, H^{Ar}), 7.60 (br.s, 2H, H^{Ar}), 7.48 (br.s, 2H, H^{Ar}), 7.39 (br.s, 2H, H^{Ar}), 6.87 (s, 2H, NH_2), 3.87 (s, 3H, MeO), 2.38 (s, 3H, Me). ^{13}C NMR (101 MHz, DMSO-d_6): 170.89 ($C^{oxadiazole}$-5), 166.46 ($C^{oxadiazole}$-3), 162.15 (O=C-O), 150.14 ($C^{pyrazole}$-5), 140.98 ($C^{pyrazole}$-3), 138.95 (C^{Tol}-4), 136.60 (C^{Ar}-4), 134.92 (C^{Tol}-1), 130.57 (2xCH^{Tol}-3,5), 129.72 (2xCH^{Ar}-3,5), 129.50 (2xCH^{Ar}-2,6), 125.64 (C^{Ar}-1), 125.07 (2xCH^{Tol}-2,6), 87.76 ($C^{pyrazole}$-4), 52.67 (OMe), 21.27 (Me). MS (m/z): 410 (M^++1). Anal. calcd. for $C_{20}H_{16}ClN_5O_3$: C, 58.61; H, 3.94; N 17.09; found: C 58.59; H 3.91; N 17.12.



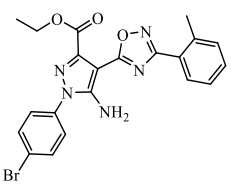
Methyl 5-amino-1-(4-chlorophenyl)-4-(3-phenyl-1,2,4-oxadiazol-5-yl)-*1H*-pyrazole-3-carboxylate (4c): Yield 0.65 g, 82%; yellow solid; m.p.: 138–139 ºC; ^{1}H NMR (500 MHz, DMSO-d_6): 8.12 (br.s, 2H, H^{Ar}), 7.67 (br.s, 4H, H^{Ar}), 7.58 (br.s, 3H, H^{Ar}), 7.01 (s, 2H, NH_2), 3.89 (s, 3H, MeO). ^{13}C NMR (126 MHz, DMSO-d_6): 170.64 ($C^{oxadiazole}$-5), 167.26 ($C^{oxadiazole}$-3), 162.04 (O=C-O), 150.30 ($C^{pyrazole}$-5), 141.47 ($C^{pyrazole}$-3), 136.26 (C^{Ar}-1), 133.67 (C^{Ar}-4), 131.88 (CH^{Ph}-4), 130.11 (2xCH^{Ar}-3,5), 129.55 (2xCH^{Ph}-3,5), 127.69 (2xCH^{Ph}-2,6), 127.08 (2xCH^{Ar}-2,6), 126.73 (C^{Ph}-1), 88.14 ($C^{pyrazole}$-4), 52.73 (OMe). MS (m/z): 396 (M^++1). Anal. calcd. for $C_{19}H_{14}ClN_5O_3$: C, 57.66; H, 3.57; N 17.69; found: C 57.68; H 3.55; N 17.70.

Methyl 5-amino-1-(4-chlorophenyl)-4-(3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl)-*1H*-pyrazole-3-carboxylate (4d): Yield 0.64 g, 75%; white solid; m.p.: 151–152 ºC; ^{1}H NMR (500 MHz, DMSO-d_6):



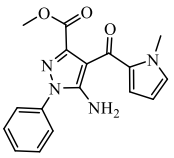
8.06 (d, J = 6.2 Hz, 1H, H^{Ar}), 7.77 – 7.58 (m, 6H, H_{Ar}), 7.55 (d, J = 6.5 Hz, 1H, H_{Ar}), 6.97 (s, 2H, NH_2), 3.90 (s,3H, MeO). ^{13}C NMR (126 MHz, DMSO-d_6): 170.21 ($C^{oxadiazole}$-5), 166.11 ($C^{oxadiazole}$-3), 162.00 (O=C-O), 150.48 ($C^{pyrazole}$-5), 141.41 ($C^{pyrazole}$-3), 136.23 (C^{Ar}-1), 133.67 (C^{Ar}-4), 132.92 (CH^{Ar}-3), 132.61 (C^{Ar}-2), 132.37 (CH^{Ar}-4), 131.26 (CH^{Ar}-6), 130.11 (2xCH^{Ar}-3,5), 128.09 (CH^{Ar}-5), 127.05 (2xCH^{Ar}-2,6), 125.97 (C^{Ar}-1), 87.90 ($C^{pyrazole}$-4), 52.76 (OMe). MS (m/z): 430 (M^++1). Anal. calcd. for $C_{19}H_{13}Cl_2N_5O_3$: C, 53.04; H, 3.05; N 16.28; found: C 53.01; H 3.03; N 16.30.

Ethyl 5-amino-1-(4-bromophenyl)-4-(3-(o-tolyl)-1,2,4-oxadiazol-5-yl)-*1H*-pyrazole-3-carboxylate (4d): Yield 0.88 g, 94%; yellow solid; m.p.: 163–164 ºC;^{1}H NMR (500 MHz, DMSO-d_6):



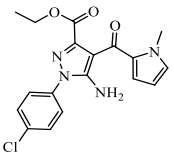
8.05 (d, J = 7.3 Hz, 1H, H^{Ar}), 7.79 (d, J = 7.1 Hz, 2H, H^{Ar}-2,6), 7.60 (d, J = 7.1 Hz, 2H, H^{Ar}-3,5), 7.51 – 7.44 (m, 1H, H^{Ar}), 7.39 (m, 2H, H^{Ar}-4,5), 6.95 (s, 2H, NH_2), 4.36 (q, J = 6.6 Hz, 2H, CH_2O), 2.58 (s, 3H, CH_3), 1.32 (t, J = 6.2 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): 169.75 ($C^{oxadiazole}$-5), 167.91 ($C^{oxadiazole}$-3), 161.69 (O=C-O), 150.17 ($C^{pyrazole}$-5), 141.92 ($C^{pyrazole}$-3), 137.96 (C^{Tol}-2), 136.71 (C^{Ar}-1), 133.09 (2xCH^{Ar}-3,5), 131.86 (CH^{Tol}-3), 131.25 (CH^{Tol}-6), 130.42 (CH^{Tol}-4), 127.40 (2xCH^{Ar}-2,6), 126.70 (C^{Tol}-1), 126.11 (C^{Tol}-5), 122.18 (C^{Ar}-4), 88.11 ($C^{pyrazole}$-4), 61.70 (CH_2O), 22.20 (Me), 14.51 (CH_3). MS (m/z): 468, 470 (M^++1). Anal. calcd. for $C_{21}H_{18}BrN_5O_3$: C, 53.86; H, 3.87; N 14.95; found: C 53.89; H 3.85; N 14.90.

Methyl 5-amino-4-[(1-methyl-*1H*-pyrrol-2-yl)carbonyl]-1-phenyl-*1H*-pyrazole-3-carboxylate (7a): Yield 0.54 g, 84 %; white solid; m.p.: 153–154 ºC; ^{1}H NMR (500 MHz, DMSO-d_6):



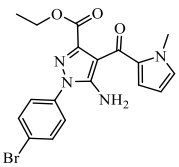
7.60–7.49 (m, 5H, Ph), 7.09 (s, 1H, H^{Pyr}-5), 6.45 (br. s, 3H, H^{Pyr}-3 + NH_2), 6.07 (br. s, 1H, H^{Pyr}-4), 3.87 (s, 3H, Me), 3.49 (s, 3H, Me). ^{13}C-NMR (126 MHz, DMSO-d_6): 179.55 (C=O), 163.50 (O=C-O), 150.28 ($C^{pyrazole}$-5), 144.08 ($C^{pyrazole}$-3), 137.66 (C^{Ph}-1), 132.56 (C^{pyr}-2), 130.59 (CH^{pyr}-5), 130.00 (2xCH^{Ph}-3,5), 128.73 (CH^{Ph}-4), 124.72 (2xCH^{Ph}-2,6), 117.81 (CH^{pyr}-3), 107.93 (CH^{pyr}-4), 104.25 ($C^{pyrazole}$-4), 52.35 (OMe), 36.29 (MeN); MS (m/z): 325 (M^++1). Anal. calcd. for $C_{17}H_{16}N_4O_3$: C 62.95; H 4.97; N 17.27; found: C 62.97; H 4.94; N 17.25.

Ethyl 5-amino-1-(4-chlorophenyl)-4-(1-methyl-*1H*-pyrrole-2-carbonyl)-*1H*-pyrazole-3-carboxylate (7b): Yield 0.64 g, 86 %; white solid; m.p.: 139–140 ºC; ^{1}H NMR (400 MHz, DMSO-d_6):



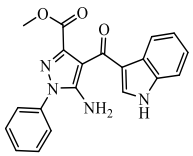
7.63 (br. s, 4H, H^{Ar}), 7.09 (s, 1H, H^{Pyr}-5), 6.50 (s, 2H, NH_2), 6.39 (s, 1H, H^{Pyr}-3), 6.05 (br. s, 1H, H^{Pyr}-4), 3.99 – 3.72 (m, 5H, OCH_2 + Me), 0.91 (br. s, 3H, EtO). ^{13}C NMR (101 MHz, DMSO-d_6): 179.62 (C=O), 162.92 (O=C-O), 150.57 ($C^{pyrazole}$-5), 144.55 ($C^{pyrazole}$-3), 136.57 (C^{Ar}-1), 133.13 (C^{Ar}-4), 132.77 (C^{pyr}-2), 130.54 (CH^{pyr}-5), 130.00 (2xCH^{Ar}-3,5), 126.67 (2xCH^{Ar}-2,6), 117.94 (CH^{pyr}-3), 108.00 (CH^{pyr}-4), 104.18 ($C^{pyrazole}$-4), 61.11 (CH_2O), 36.24 (MeN), 13.90 (CH_3); MS (m/z): 373 (M^++1). Anal. calcd. for $C_{18}H_{17}ClN_4O_3$: C, 57.99; H, 4.60; N, 15.03; found: C 57.95; H 4.62; N 15.05.

Ethyl 5-amino-1-(4-bromophenyl)-4-(1-methyl-*1H*-pyrrole-2-carbonyl)-*1H*-pyrazole-3-carboxylate (7c): Yield 0.74 g, 89%; white solid; m.p.: 135–136 ºC; ^{1}H NMR (500 MHz, DMSO-d_6):



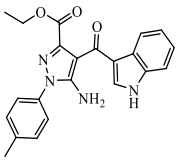
7.75 (d, J = 8.0 Hz, 2H, H^{Ar}-2,6), 7.58 (d, J = 8.0 Hz, 2H, H^{Ar}-3,5), 7.10 (br. s, 1H, H^{Py}-5), 6.53 (s, 2H, NH_2), 6.38 (br. s, 1H, H^{Py}-3), 6.05 (br. s, 1H, H^{Py}-4), 3.97 – 3.87 (m, 2H, CH_2O), 3.85 (s, 3H, MeN), 0.90 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6): 179.57 (C=O), 162.87 (O=C-O), 150.49 ($C^{pyrazole}$-5), 144.55 ($C^{pyrazole}$-3), 136.96 (C^{Ar}-1), 132.89 (2xCH^{Ar}-3,5), 132.72 (C^{pyr}-2), 130.53 (CH^{pyr}-5), 126.84 (2xCH^{Ar}-2,6), 121.49 (C^{Ar}-4), 117.91 (CH^{pyr}-3), 107.96 (CH^{pyr}-4), 104.19 ($C^{pyrazole}$-4), 61.09 (CH_2O), 36.22 (MeN), 13.88 (CH_3). MS (m/z): 417, 419 (M^++1). Anal. calcd. for $C_{18}H_{17}BrN_4O_3$: C, 51.81; H, 4.11; N, 13.43; found: C 51.85; H 4.07; N 13.45.

Methyl 5-amino-4-(*1H*-indol-3-ylcarbonyl)-1-phenyl-*1H*-pyrazole-3-carboxylate (7d): Yield



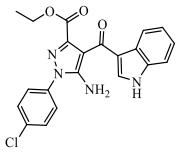
0.63 g, 87 %; white solid; m.p.: 143–144 ºC; ^{1}H NMR (500 MHz, DMSO-d_6): 11.85 (br. s, 1H, NH), 8.14 (d, J = 6.7 Hz, 1H, H^{Ind}-7), 7.73 (s, 1H, H^{Ind}-2), 7.66 (d, J = 6.9 Hz, 2H, H^{Ph}-2,6), 7.61 (t, J = 7.1 Hz, 2H, H^{Ph}-3,5), 7.53 – 7.47 (m, 2H, H^{Ph}-4+H^{Ind}-5), 7.26 – 7.18 (m, 2H, H^{Ind}-5,6), 6.34 (br. s, 2H, NH_2), 3.49 (s, 3H, MeO). ^{13}C NMR (126 MHz, DMSO-d_6): 184.08 (C=O), 163.61 (O=C-O), 149.83 ($C^{pyrazole}$-5), 143.26 ($C^{pyrazole}$-3), 137.93 (C^{Ar}-1), 137.03, 132.96, 130.02 (2xCH^{Ar}-3,5), 128.70 (CH^{Ar}-4), 126.30, 124.73 (2xCH^{Ar}-2,6), 123.13, 121.74, 121.52, 118.08, 112.57, 105.34 ($C^{pyrazole}$-4), 52.17 (OMe). MS (m/z): 361 (M^++1). Anal. calcd. for $C_{20}H_{16}N_4O_3$: C 66.66; H 4.48; N 15.55; found: C 66.43; H 4.37; N 15.63.

Ethyl 5-amino-4-(*1H*-indole-3-carbonyl)-1-(p-tolyl)-*1H*-pyrazole-3-carboxylate (7e): Yield 0.74



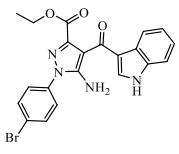
g, 96 %; white solid; m.p.: 227–228 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 11.80 (br. s, 1H, NH), 8.09 (d, J = 7.3 Hz, 1H, H^{Ind}-7), 7.68 (br. s, 1H, H^{Ind}-2), 7.51 (d, J = 7.8 Hz, 2H, H^{Ar}-2,6), 7.47 (d, J = 7.7 Hz, 1H, H^{Ind}-4), 7.38 (d, J = 7.7 Hz, 2H, H^{Ar}-3,5), 7.25 – 7.14 (m, 2H, H^{Ind}-5,6), 6.28 (s, 2H, NH_2), 3.87 (q, J = 6.8 Hz, 2H, CH_2O), 2.40 (s, 3H, Me), 0.76 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): 184.29 (C=O), 163.20 (O=C-O), 149.88 ($C^{pyrazole}$-5), 143.44 ($C^{pyrazole}$-3), 138.31 (C^{Tol}-4), 136.98, 135.39 (C^{Tol}-1), 132.67, 130.44 (2xCH^{Tol}-3,5), 126.25, 124.70 (2xCH^{Tol}-2,6), 123.14, 121.71, 121.40, 118.40, 112.52, 105.05 ($C^{pyrazole}$-4), 61.01 (CH_2O), 21.17 (CH_3), 13.77 (CH_3). MS (m/z): 389 (M^++1). Anal. calcd. for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42; found: C 68.05; H 5.17; N 14.43.

Ethyl 5-amino-1-(4-chlorophenyl)-4-(*1H*-indole-3-carbonyl)-*1H*-pyrazole-3-carboxylate (7f):



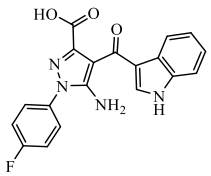
Yield 0.75 g, 92%; white solid; m.p.: 219–220 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 12.03 (br. s, 1H, NH), 8.09 (d, J = 7.4 Hz, 1H, H^{Ind}-7), 7.71 – 7.65 (m, 3H, H^{Ind}-2 + H^{Ar}-2,6), 7.63 (d, J = 8.6 Hz, 2H, H^{Ar}-3,5), 7.48 (d, J = 7.4 Hz, 1H, H^{Ind}-4), 7.27 – 7.12 (m, 2H, H^{Ind}-5,6), 6.40 (s, 2H, NH_2), 3.89 (q, J = 6.8 Hz, 2H, CH_2O), 0.77 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): 184.15 (C=O), 163.06 (O=C-O), 150.01 ($C^{pyrazole}$-5), 143.88 ($C^{pyrazole}$-3), 137.05, 136.80 (C^{Ar}-1), 133.00 (C^{Ar}-4), 132.84, 129.99 (2xCH^{Ar}-3,5), 126.60 (2xCH^{Ar}-2,6), 126.25, 123.13, 121.73, 121.39, 118.29, 112.62, 105.32 ($C^{pyrazole}$-4), 61.10 (CH_2O), 13.80 (CH_3). MS (m/z): 409 (M^++1). Anal. calcd. for $C_{21}H_{17}ClN_4O_3$: C, 61.69; H, 4.19; N, 13.70; found: C 61.67; H 4.20; N 13.71.

Ethyl 5-amino-1-(4-bromophenyl)-4-(*1H*-indole-3-carbonyl)-*1H*-pyrazole-3-carboxylate (7g):



Yield 0.89 g, 97 %; white solid; m.p.: 223–224 ºC; ^{1}H NMR (500 MHz, DMSO-d_6): 12.03 (br. s, 1H, NH), 8.10 (d, J = 7.3 Hz, 1H, H^{Ind}-7), 7.76 (d, J = 7.8 Hz, 2H, H^{Ar}-2,6), 7.68 (br. s, 1H, H^{Ind}-2), 7.62 (d, J = 7.8 Hz, 2H, H^{Ar}-3,5), 7.49 (d, J = 7.4 Hz, 1H, H^{Ind}-4), 7.27 – 7.10 (m, 2H, H^{Ind}-5,6), 6.41 (s, 2H, NH_2), 3.89 (q, J = 6.8 Hz, 2H, CH_2O), 0.77 (t, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): 184.11 (C=O), 163.01 (O=C-O), 149.94 ($C^{pyrazole}$-5), 143.89 ($C^{pyrazole}$-3), 137.19, 137.01 (C^{Ar}-1), 132.88 (2xCH^{Ar}-3,5), 132.78, 126.78 (2xCH^{Ar}-2,6), 126.21, 123.09, 121.69, 121.39 (C^{Ar}-4), 121.36, 118.27, 112.57, 105.33 ($C^{pyrazole}$-4), 61.07 (CH_2O), 13.77 (CH_3). MS (m/z): 453, 455 (M^++1). Anal. calcd. for $C_{21}H_{17}BrN_4O_3$: C, 55.64; H, 3.78; N, 12.36; found: C 55.65; H 3.76; N 12.35.

5-Amino-1-(4-fluorophenyl)-4-(*1H*-indole-3-carbonyl)-*1H*-pyrazole-3-carboxylic acid (7h):



Yield 0.57 g, 79%; white solid; m.p.: 259-260 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 12.71 (br. s, 1H, NH), 8.19 (d, J = 6.6 Hz, 1H, H^{Ind}-7), 8.07 (s, 1H, H^{Ind}-2), 7.77 – 7.60 (m, 2H, H^{Ar}-2,6), 7.44 – 7.26 (m, 3H, H^{Ind}-4,5,6), 7.07 (m, 2H, H^{Ar}-3,5), 6.31 (s, 2H, NH_2). ^{13}C NMR (101 MHz, DMSO-d_6): 185.54 (C=O), 168.48 (O=C-O), 161.08 (d, $^{1}J_{C\text{-}F}$ = 240.0 Hz), 153.81 ($C^{pyrazole}$-5), 149.81 ($C^{pyrazole}$-3), 136.92, 135.12, 134.16, 126.96, 126.34 (d, $^{3}J_{C\text{-}F}$ = 8.7 Hz, 2xCH^{Ar}-2,6), 122.27 (C^{Ar}-1), 121.78, 121.12, 117.33, 116.52 (d, $^{2}J_{C\text{-}F}$ = 23.0 Hz, 2xCH^{Ar}-2,6), 112.48, 103.66 ($C^{pyrazole}$-4). MS (m/z): 365 (M^++1). Anal. calcd. for $C_{19}H_{13}FN_4O_3$: C, 62.64; H, 3.60; N, 15.38; found: C 62.63; H 3.57; N 15.40.

4-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-phenyl-*1H*-1,2,3-triazol-5-amine (5a): Yield 0.56 g (87%), white solid; m.p.: 251–252°C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.26 (dd, J = 8.1, 5.7 Hz, 2H, H ^{Ar}-2,6), 7.69 – 7.57 (m, 5H, H^{Ph}), 7.41 (t, J = 8.7 Hz, 2H, H ^{Ar}-3,5), 6.96 (s, 2H, NH_2). ^{13}C NMR (126 MHz, DMSO-d_6): 169.57 (C^{oxadiazole}-5), 166.96 (C^{oxadiazole}-3), 164.46 (d, $^{1}J_{C\text{-}F}$ = 249.3 Hz, C^{Ar}-4), 145.20 (C^{triazole}-5), 134.82 (C^{Ph}-1), 130.43 (d, $^{3}J_{C\text{-}F}$ = 8.9 Hz, 2xCH^{Ar}-2,6), 130.33 (2xCH^{Ph}-3,5), 130.02 (CH^{Ph}-4), 125.20 (2xCH^{Ph}-2,6), 123.23 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, C^{Ar}-1), 116.68 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz, 2xCH^{Ar}-3,5), 115.13 (C^{triazole}-4). MS (m/z): 323 (M^++1). Anal. calcd. for $C_{16}H_{11}FN_6O$: C 59.63; H 3.44; N 26.08; found: C 59.72; H 3.49; N 26.01

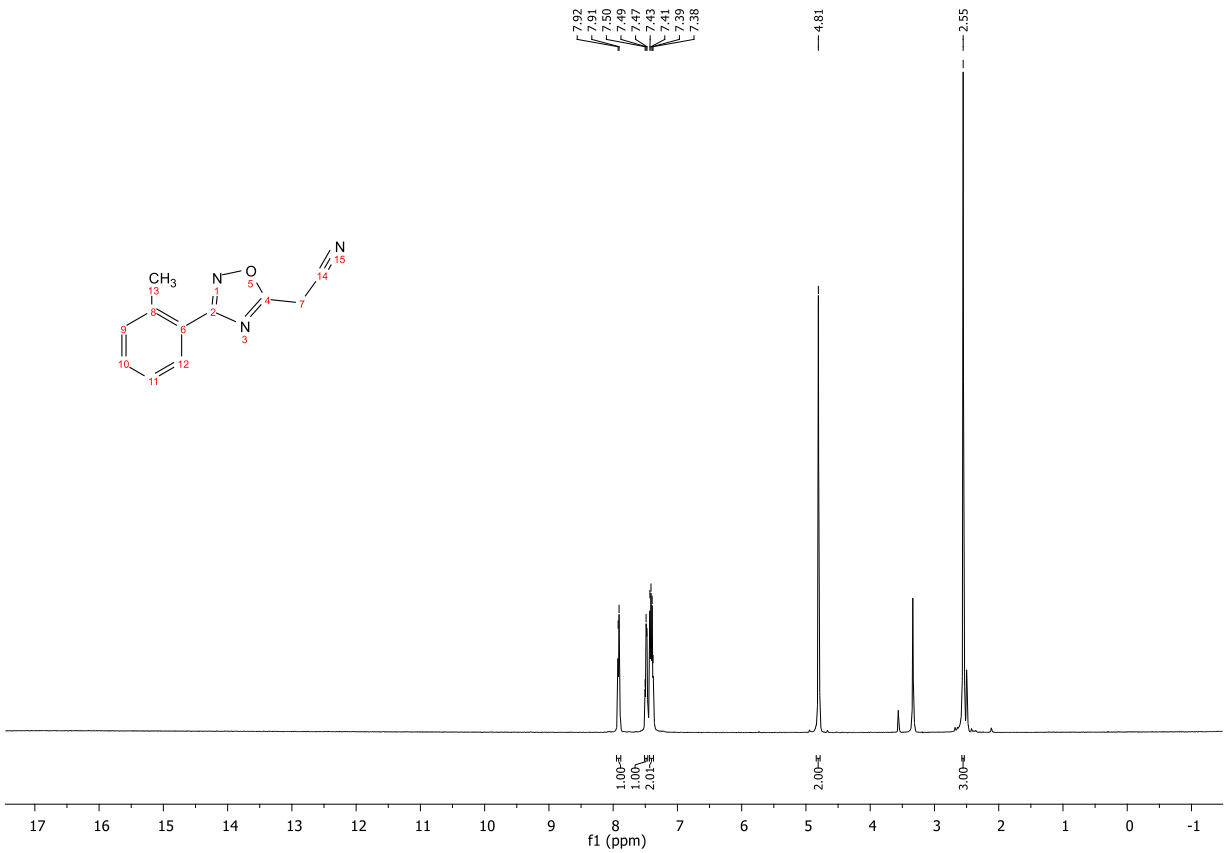
4-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-m-tolyl-*1H*-1,2,3-triazol-5-amine (5b): Yield 0.60 g (85%), white solid; m.p.: 252–253°C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.23 (d, 2H, J = 7.2 Hz, H^{Ar}-3,5), 7.66 (d, 2H, *J* = 7.2 Hz, H^{Ar}-2,6), 7.57 – 7.50 (m, 1H, H^{Ar}), 7.44-7.42 (m, 3H, H^{Ar}), 6.99 (s, 2H, NH_2), 2.43 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d_6): 169.74 (C^{oxadiazole}-5), 167.04 (C^{oxadiazole}-3), 145.21 (C^{triazole}-5), 140.13 (C^{Tol}-3), 136.81 (C^{Ar}-4), 134.71 (C^{Tol}-1), 130.69 (CH^{Tol}-5), 130.16 (CH^{Tol}-4), 129.77 (2xCH^{Ar}-3,5), 129.73 (2xCH^{Ar}-2,6), 125.67 (CH^{Tol}-2), 125.59 (C^{Ar}-1), 122.27 (CH^{Tol}-6), 115.06 (C^{triazole}-4), 21.36 (Me). MS (m/z): 353 (M^++1). Anal. calcd. for $C_{17}H_{13}ClN_6O$: C, 57.88; H, 3.71; N, 23.82; found: C 57.87; H 3.73; N 23.79

1-(4-Fluorophenyl)-4-(3-o-tolyl-1,2,4-oxadiazol-5-yl)-*1H*-1,2,3-triazol-5-amine (5c): Yield 0.61 g (91%), white solid; m.p.: 213–214°C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.17 (d, J = 7.5 Hz, 1H, H^{Ar}-6), 7.71 (dd, J = 8.6, 4.8 Hz, 2H, H^{Ar}-3,5), 7.55 – 7.45 (m, 3H, H^{Ar}), 7.40 (t, J = 7.2 Hz, 2H, H^{Ar}-2,6), 6.89 (s, 2H, NH_2), 2.61 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d_6): 168.56 (C^{oxadiazole}-5), 168.37 (C^{oxadiazole}-3), 162.77 (d, $^{1}J_{C\text{-}F}$ = 246.8 Hz, C^{Ar}-4), 145.47 (C^{triazole}-5), 138.07 (C^{Tol}-2), 131.79 (CH^{Tol}-3), 131.29 (CH^{Tol}-4), 131.18 (d, $^{4}J_{C\text{-}F}$ = 2.7 Hz, C^{Ar}-1), 130.69 (CH^{Tol}-6), 128.06 (d, $^{3}J_{C\text{-}F}$ = 9.3 Hz, 2xCH^{Ar}-2,6), 126.61(CH^{Tol}-5), 126.01 (C^{Tol}-1), 117.21 (d, $^{2}J_{C\text{-}F}$ = 23.3 Hz, 2xCH^{Ar}-3,5), 115.04 (C^{triazole}-4), 22.32 (Me). MS (m/z): 337 (M^++1). Anal. calcd. for $C_{17}H_{13}FN_6O$: C, 60.71; H, 3.90; N, 24.99; found: C 60.73; H 3.89; N 25.01

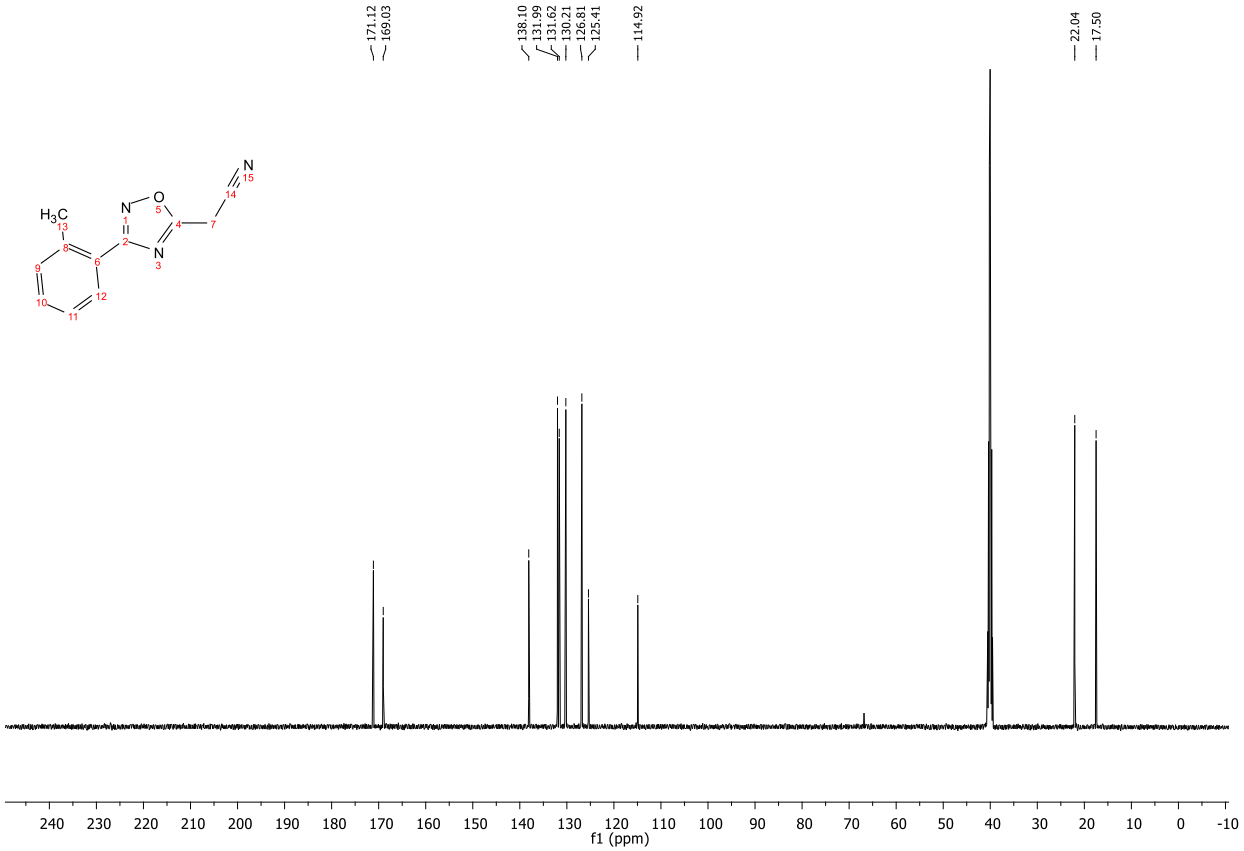
1-(4-Chlorophenyl)-4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-*1H*-1,2,3-triazol-5-amine (5d): Yield 0.56 g (78%), white solid; m.p.: 284–285°C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.26 (dd, J = 8.6, 5.2 Hz, 2H, H^{Ar}-2,6), 7.78 (d, J = 8.7 Hz, 2H, H^{Ar}-2,6), 7.69 (d, J = 8.7 Hz, 2H, H^{Ar}-3,5), 7.42 (t, J = 8.6 Hz, 2H, H^{Ar}-3,5), 6.98 (s, 2H, NH_2). ^{13}C NMR (101 MHz, DMSO-d_6): 169.73 (C^{oxadiazole}-5), 166.95 (C^{oxadiazole}-3), 164.63 (d, $^{1}J_{C\text{-}F}$ = 250.3 Hz, C^{Ar}-4), 146.63 (C^{triazole}-5), 134.19 (C^{Ar}-1), 133.93 (C^{Ar}-4), 130.45 (d, $^{3}J_{C\text{-}F}$ = 8.9 Hz, 2xCH^{Ar}-2,6), 130.22 (2xCH^{Ar}-3,5), 126.64 (2xCH^{Ar}-2,6), 123.42 (d, $^{4}J_{C\text{-}F}$ = 3.4 Hz, C^{Ar}-1), 116.74 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz, 2xCH^{Ar}-3,5), 114.93 (C^{triazole}-4). MS (m/z): 357 (M^++1). Anal. calcd. for $C_{16}H_{10}ClFN_6O$: C, 53.87; H, 2.83; N, 23.56; found: C 53.85; H 2.80; N 23.58

4-(3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(2,4-dichlorophenyl)-*1H*-1,2,3-triazol-5-amine (5e): Yield 0.67 g (82%), white solid; m.p.: 264–265°C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.19 (d, J = 7.2 Hz, 1H, H^{Ar}-6), 8.02 (s, 1H, H^{Ar}-3), 7.78 (d, J = 8.2 Hz, 1H, H^{Ar}-3), 7.74 – 7.66 (m, 2H, H^{Ar}), 7.62 (t, *J* = 7.2 Hz, 1H, H^{Ar}-4), 7.55 (t, J = 7.4 Hz, 1H, H^{Ar}-4), 7.08 (s, 2H, NH_2). ^{13}C NMR (126 MHz, DMSO-d_6): 168.99 (C^{oxadiazole}-5), 166.64 (C^{oxadiazole}-3), 146.52 (C^{triazole}-5), 136.92, 133.38, 133.02, 132.78, 132.71, 132.13, 131.25, 131.08, 130.72, 129.38, 128.04, 126.01, 113.91 (C^{triazole}-4). MS (m/z): 407, 409 (M^++1). Anal. calcd. for $C_{16}H_9Cl_3N_6O$: C, 47.14; H, 2.23; N, 20.62; found: C 47.16; H 2.21; N 20.61

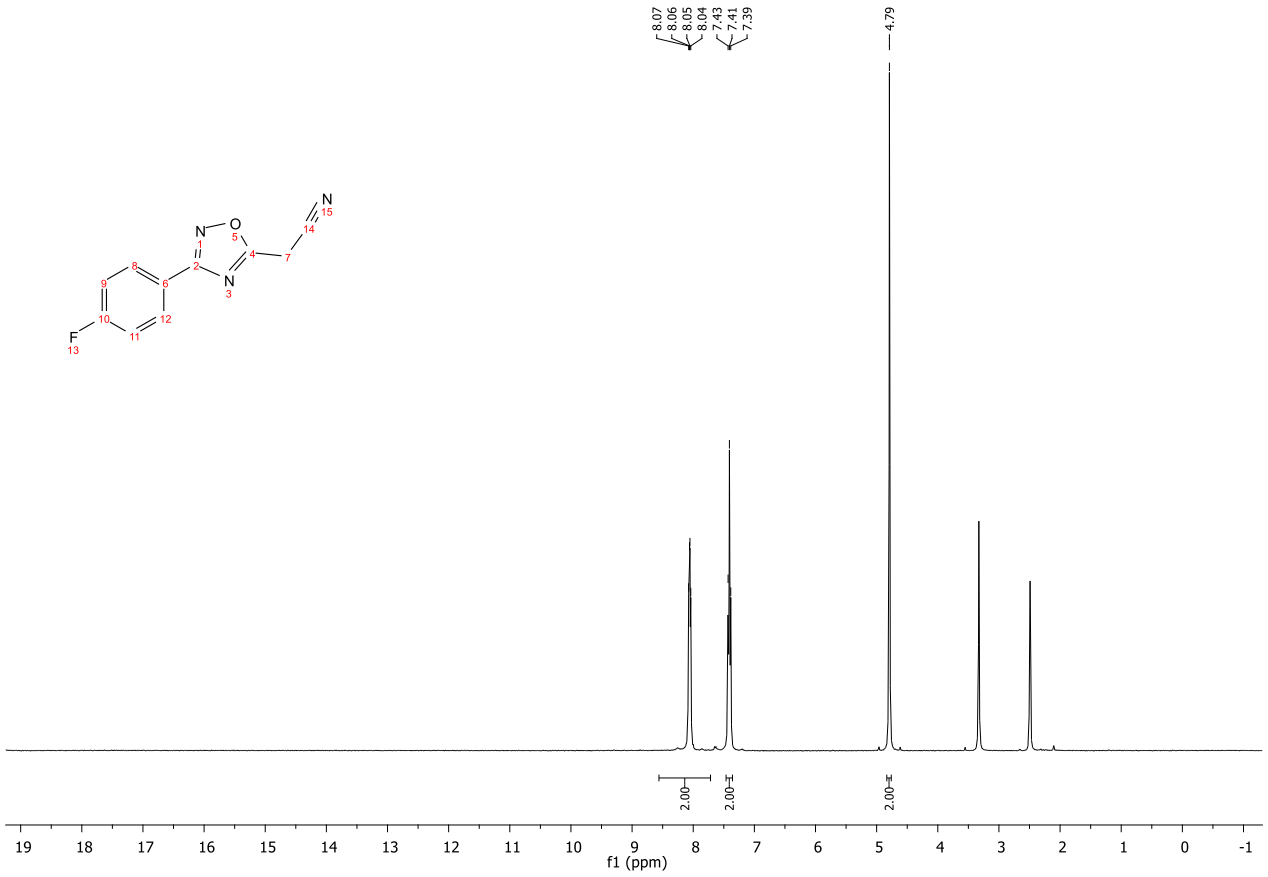
^{1}H NMR **2-(3-(o-Tolyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1b):**



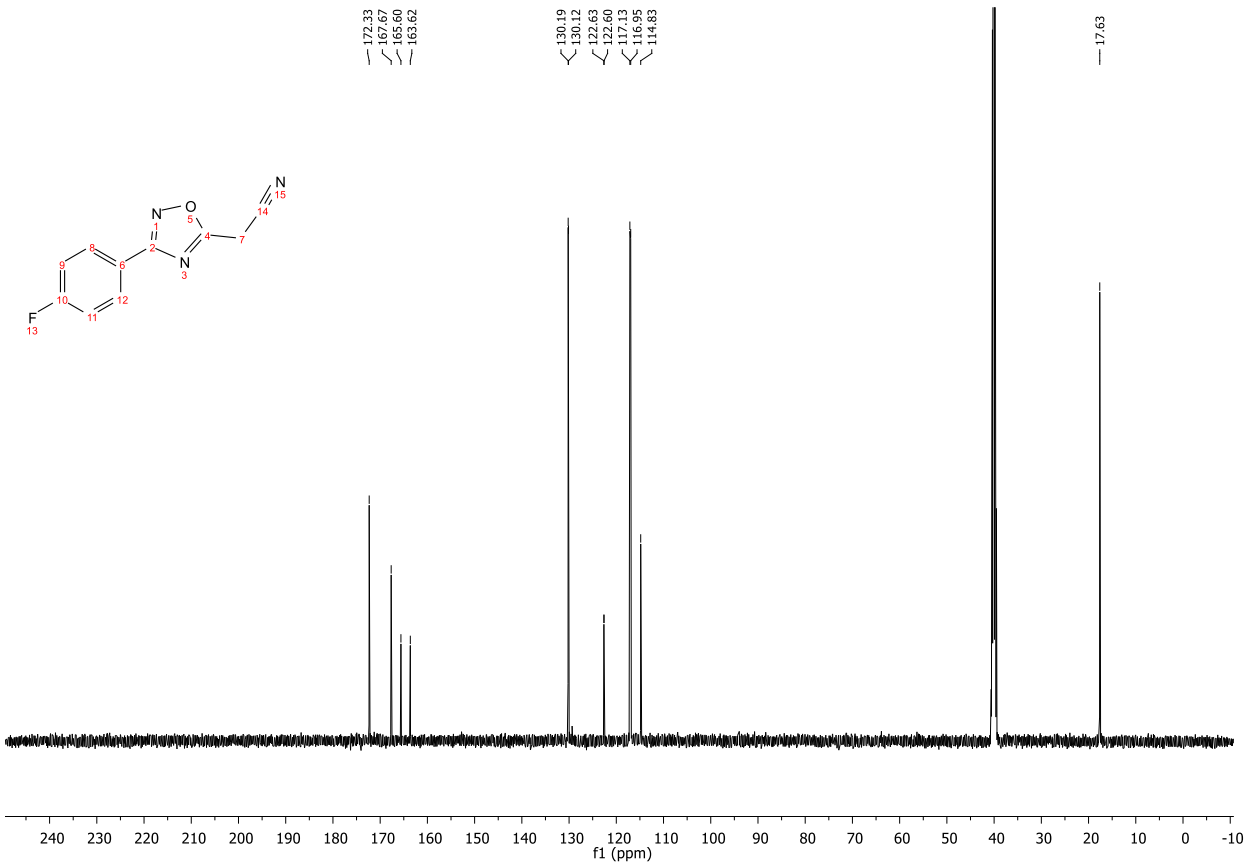
^{13}C NMR **2-(3-(o-Tolyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1b):**



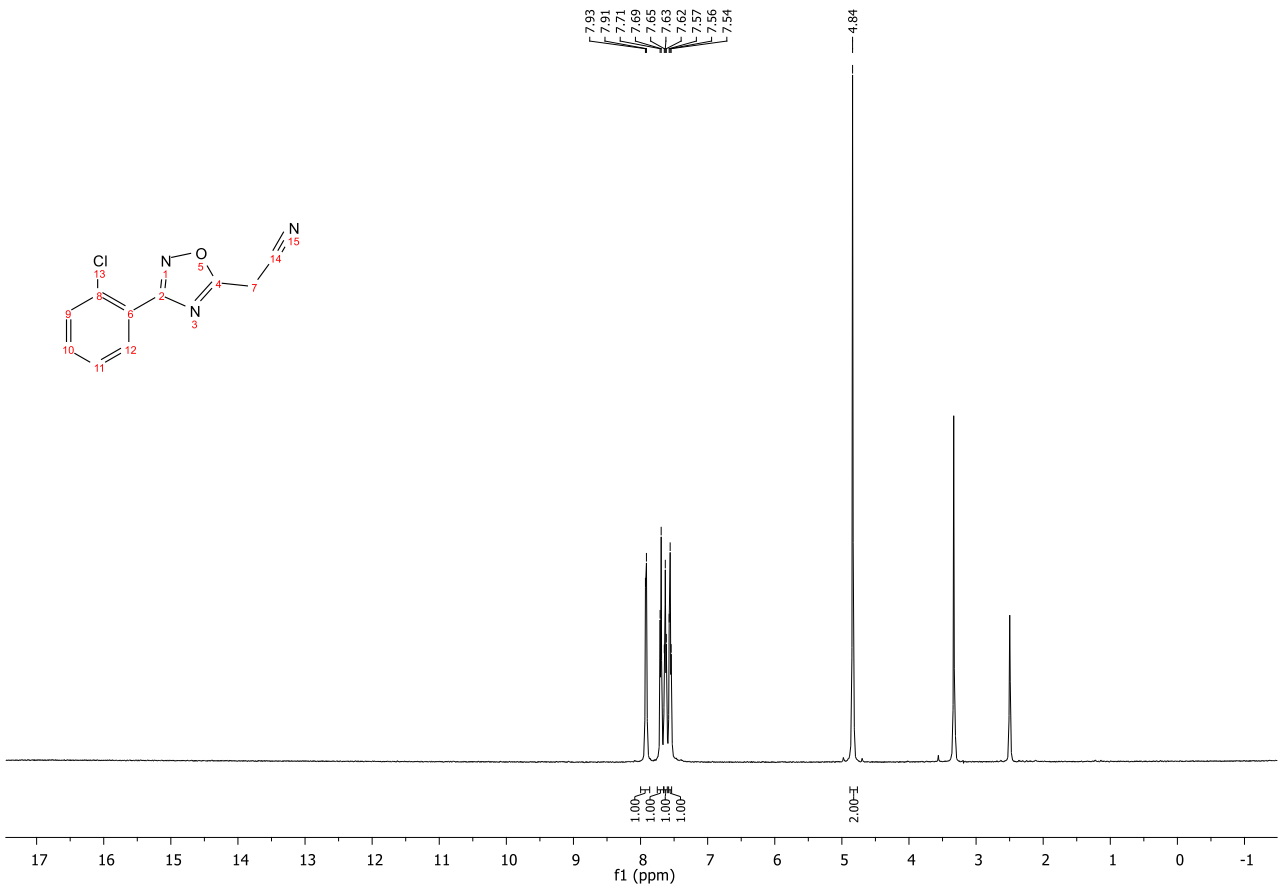
^{1}H NMR **2-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1c):**



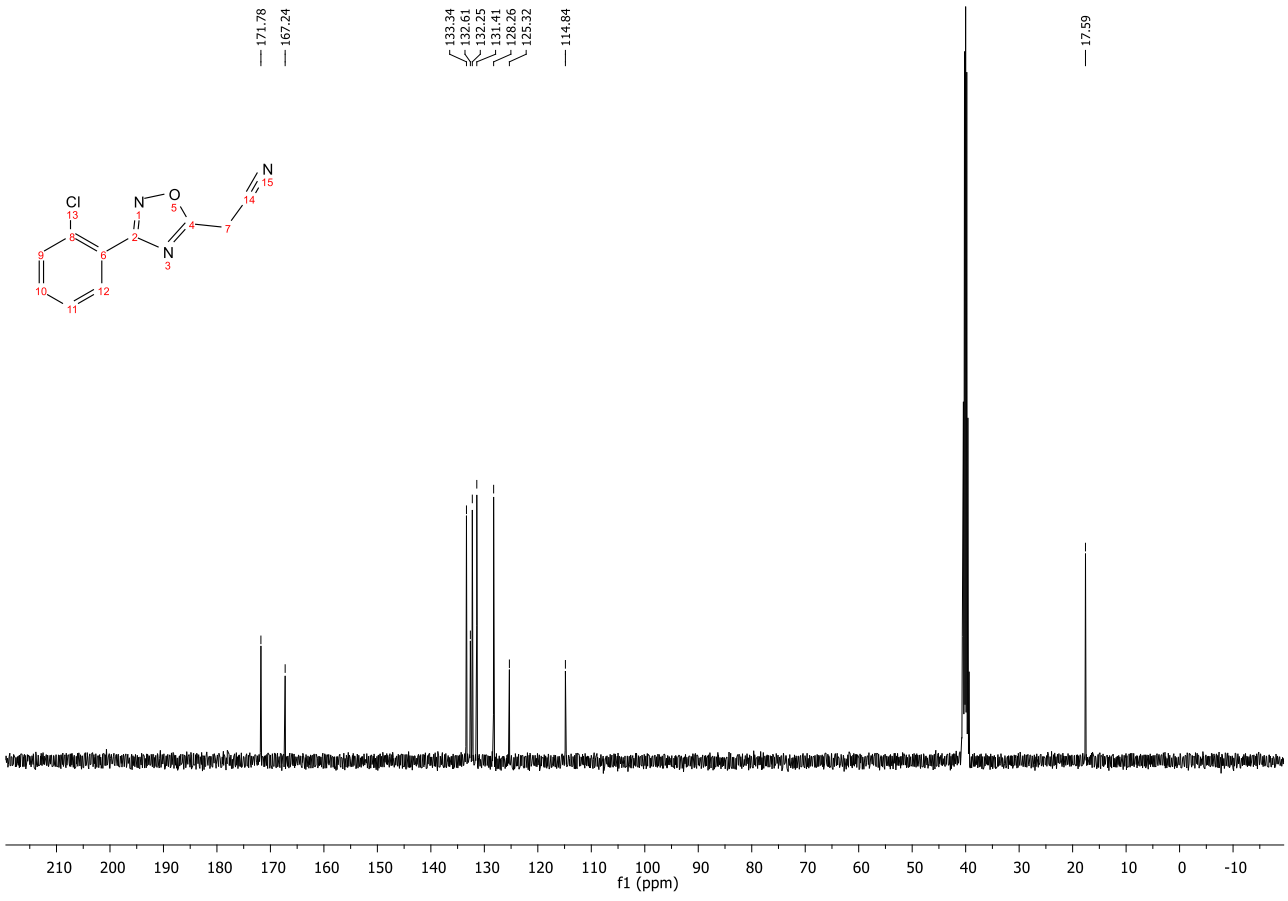
^{13}C NMR **2-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1c):**



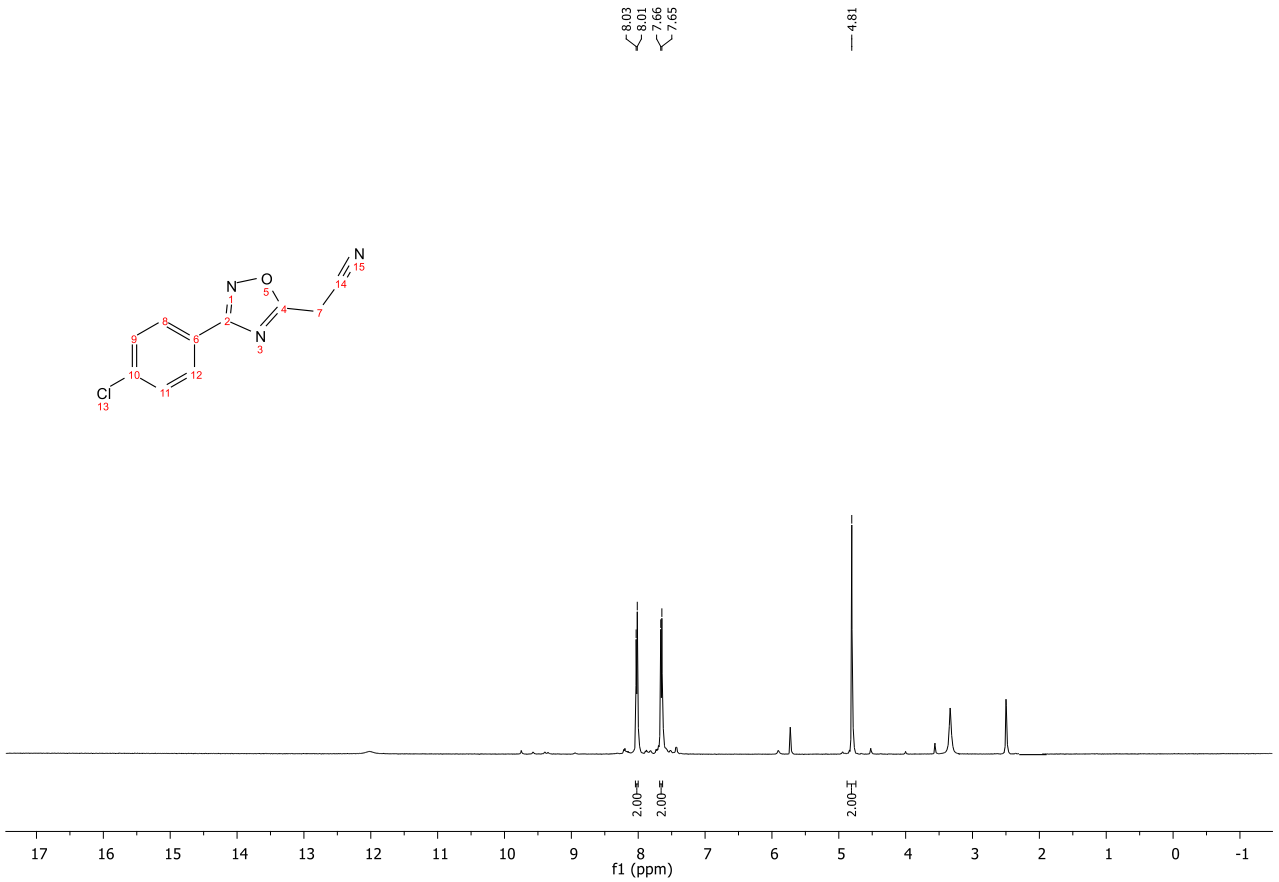
^{1}H NMR 2-(3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1d):



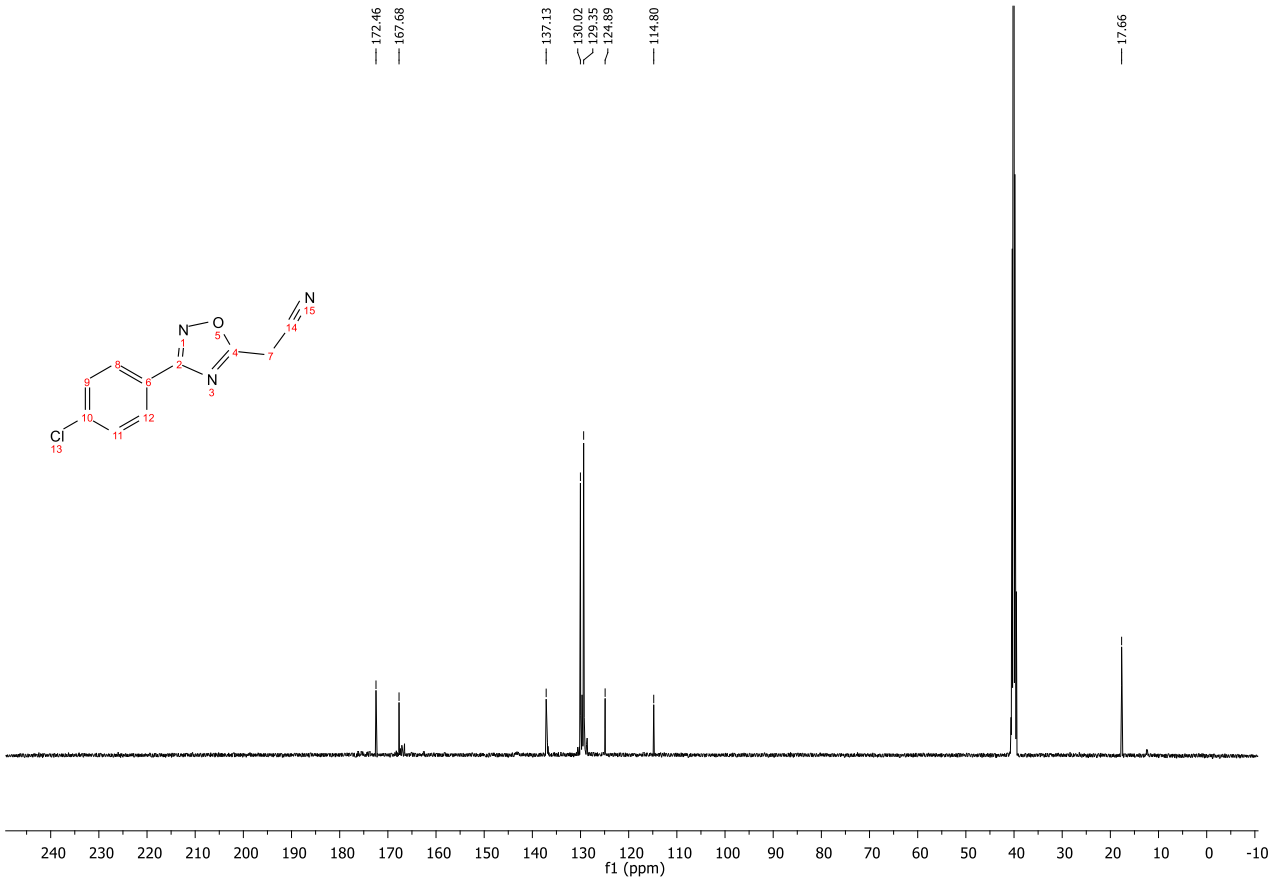
^{13}C NMR 2-(3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1d):



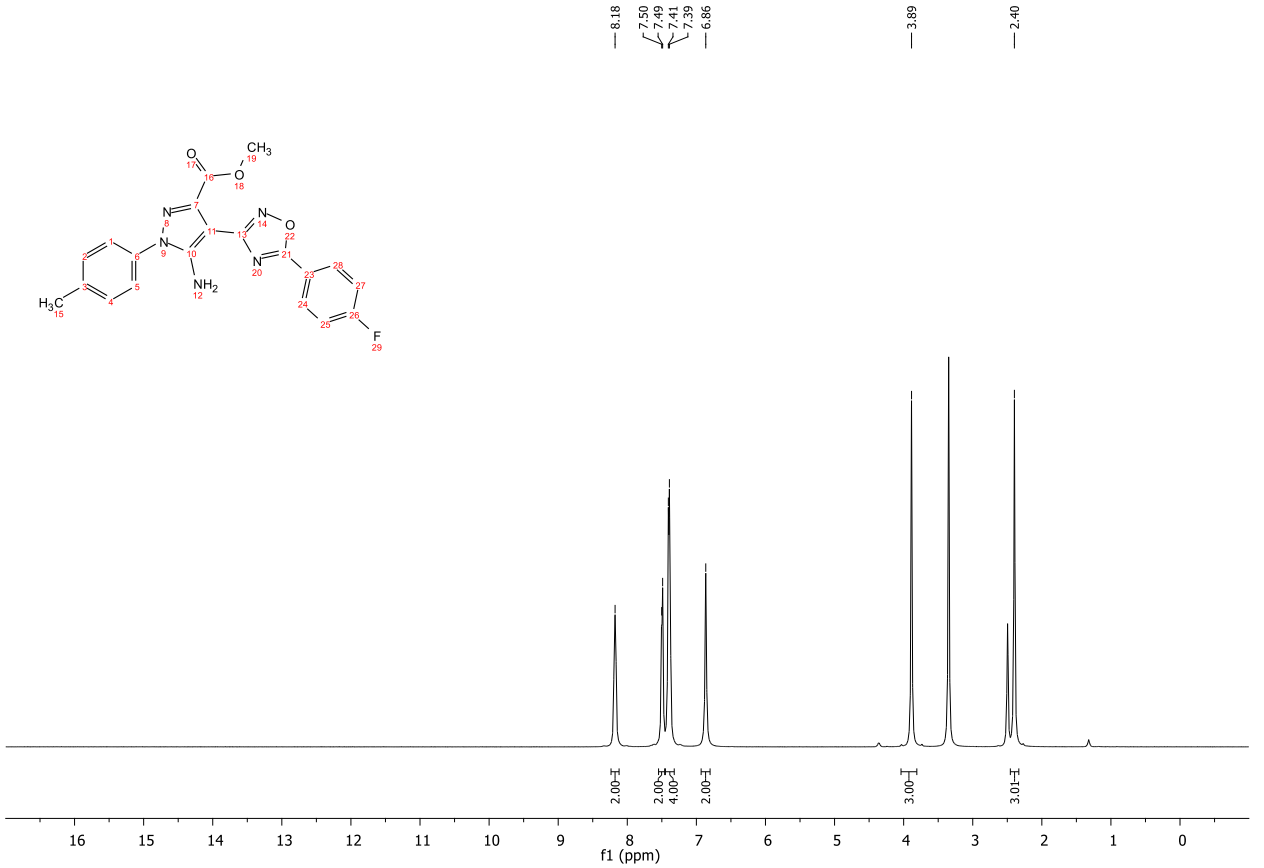
^{1}H NMR **2-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1e):**



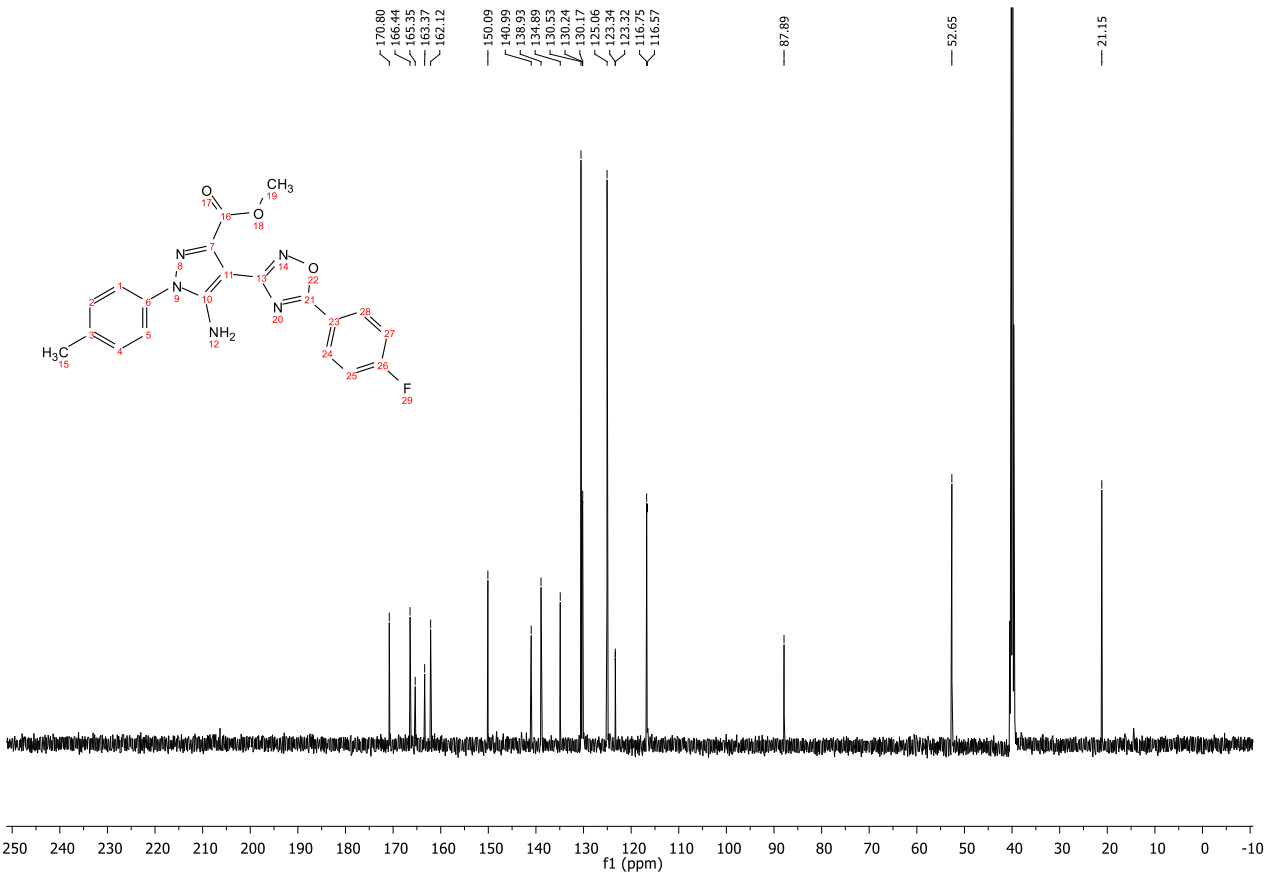
^{13}C NMR **2-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (1e):**



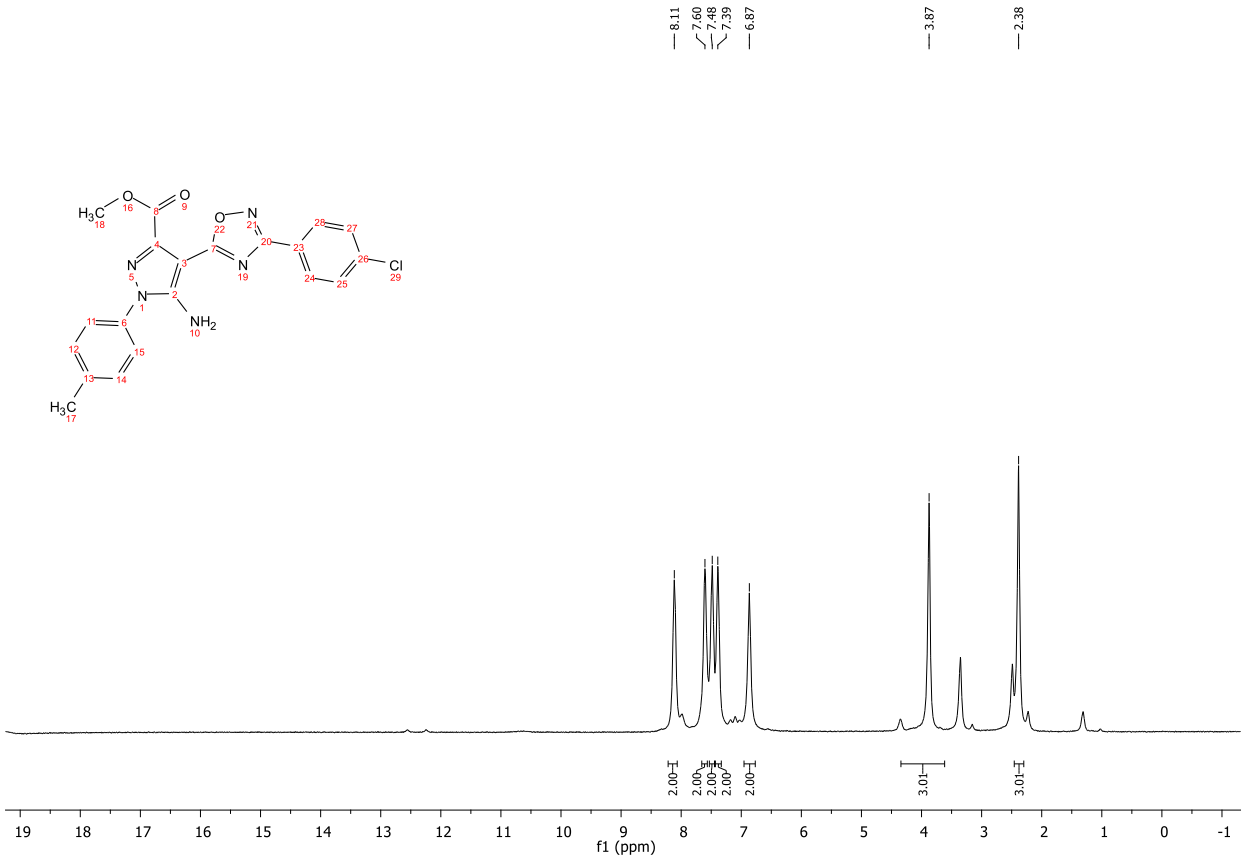
^{1}H NMR Methyl 5-amino-4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-(p-tolyl)-*1H*-pyrazole-3-carboxylate (4a):



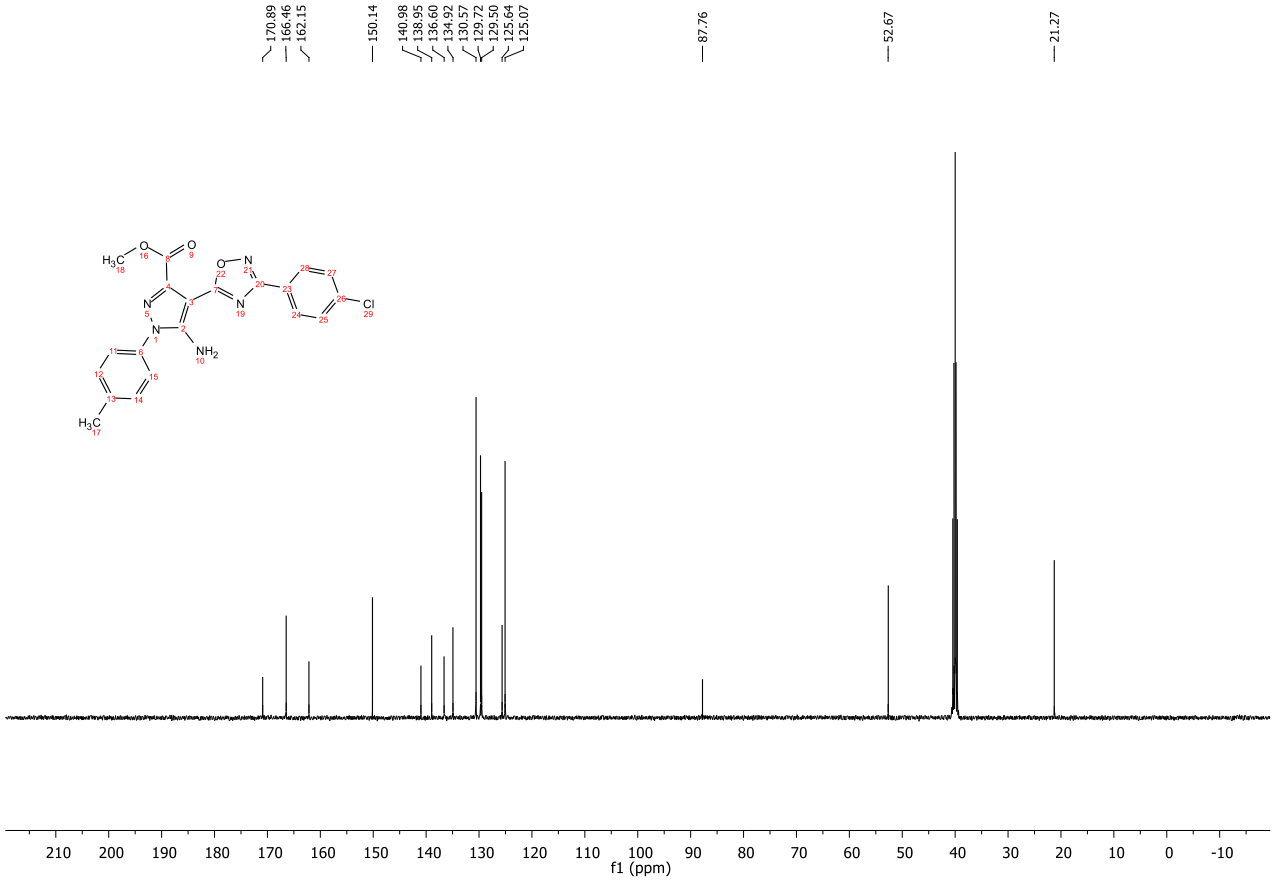
^{13}C NMR Methyl 5-amino-4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-(p-tolyl)-*1H*-pyrazole-3-carboxylate (4a):



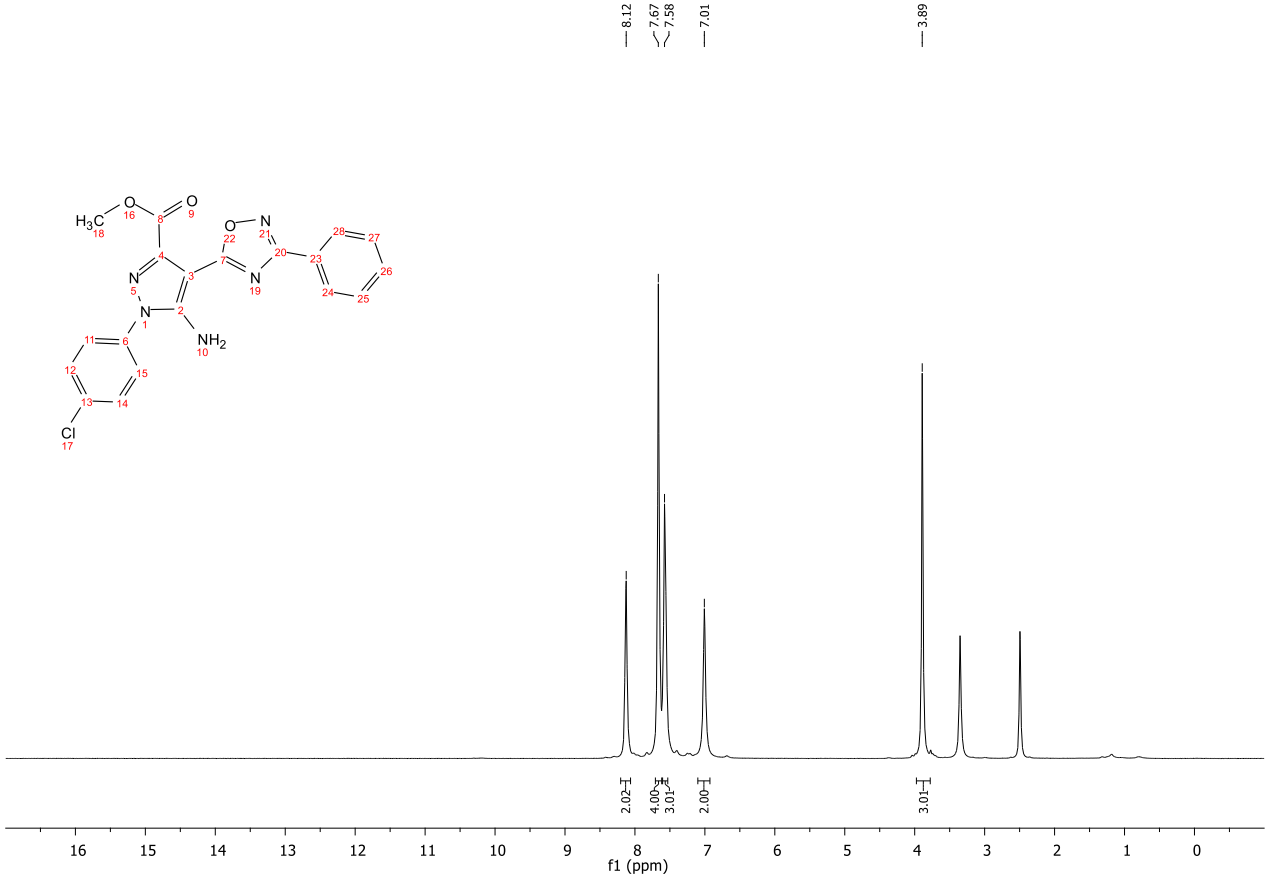
^{1}H NMR Methyl 5-amino-4-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(p-tolyl)-*1H*-pyrazole-3-carboxylate (4b):



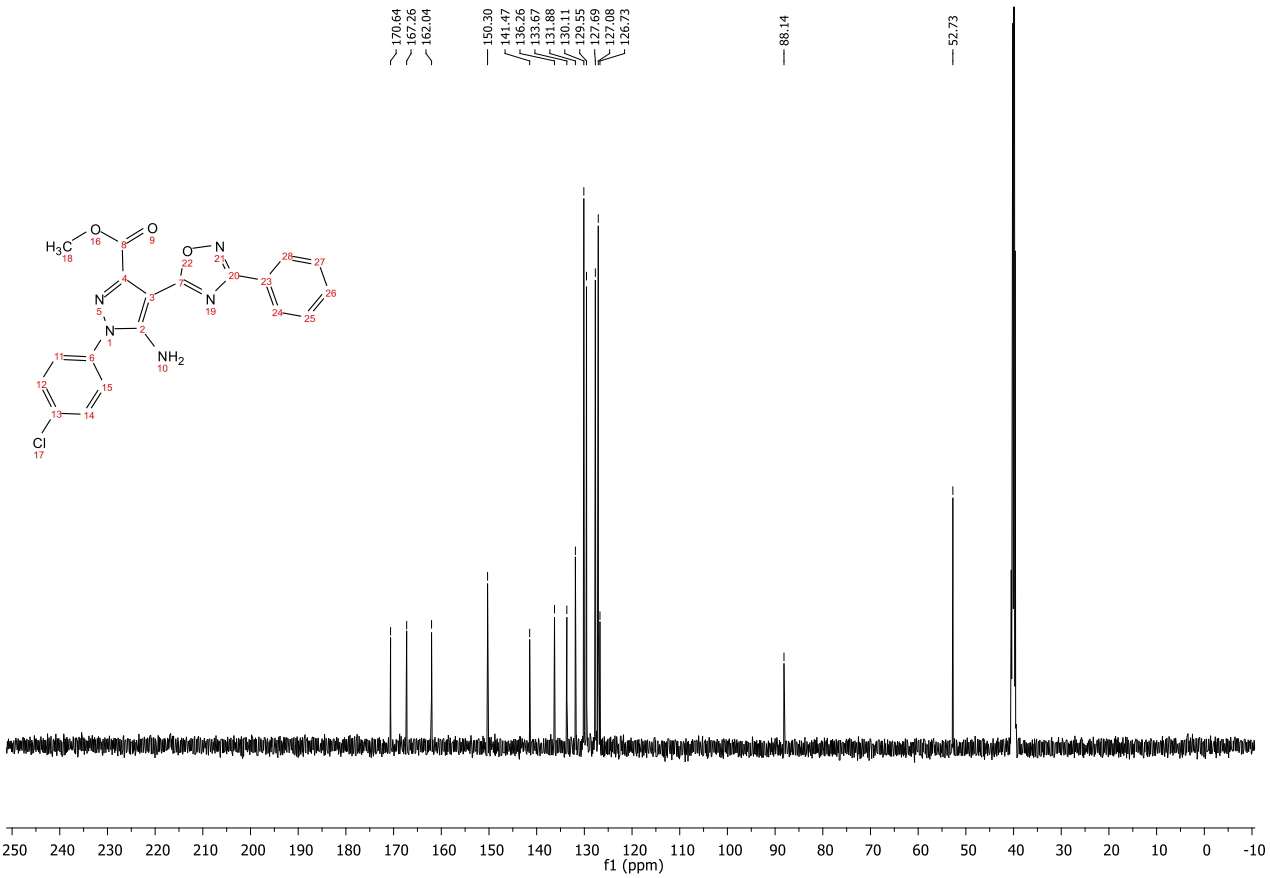
^{13}C NMR Methyl 5-amino-4-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(p-tolyl)-*1H*-pyrazole-3-carboxylate (4b):



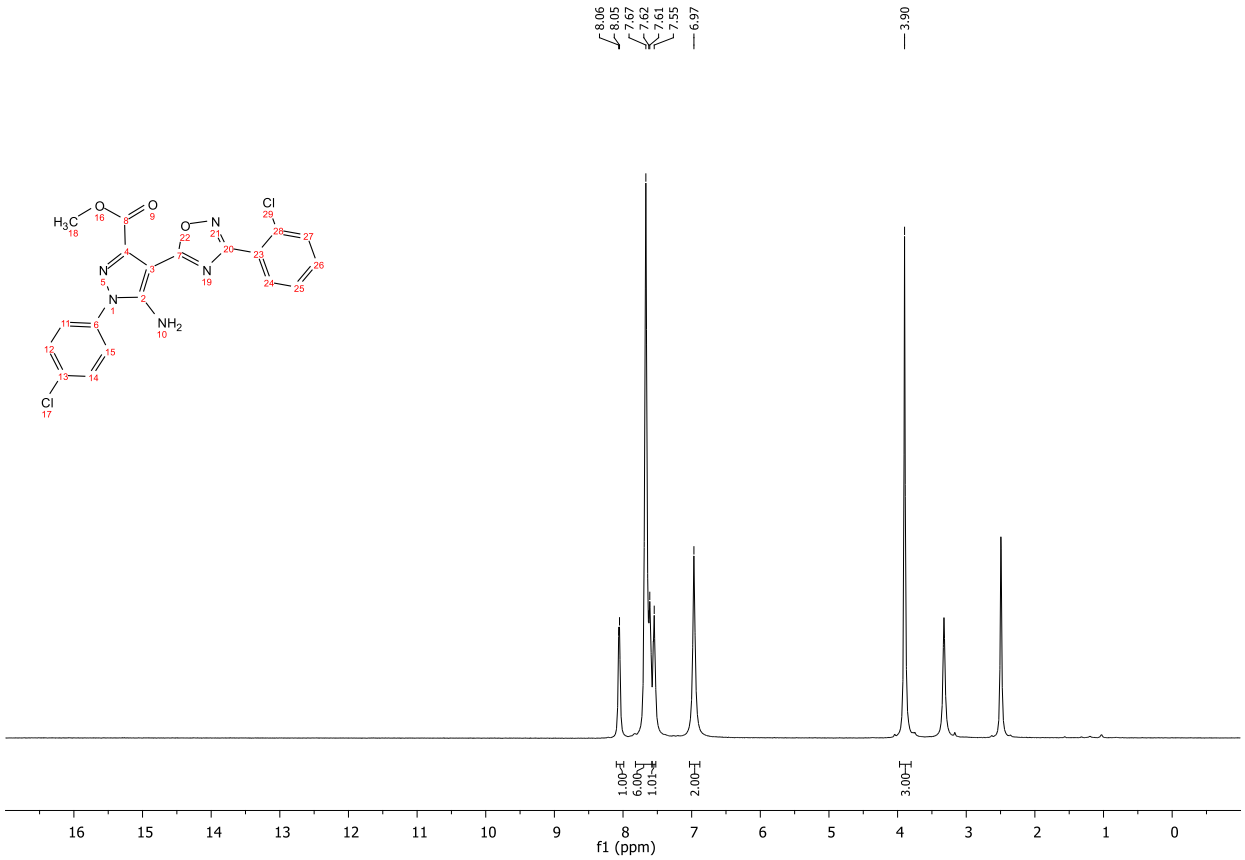
^{1}H NMR Methyl 5-amino-1-(4-chlorophenyl)-4-(3-phenyl-1,2,4-oxadiazol-5-yl)-*1H*-pyrazole-3-carboxylate (4c):



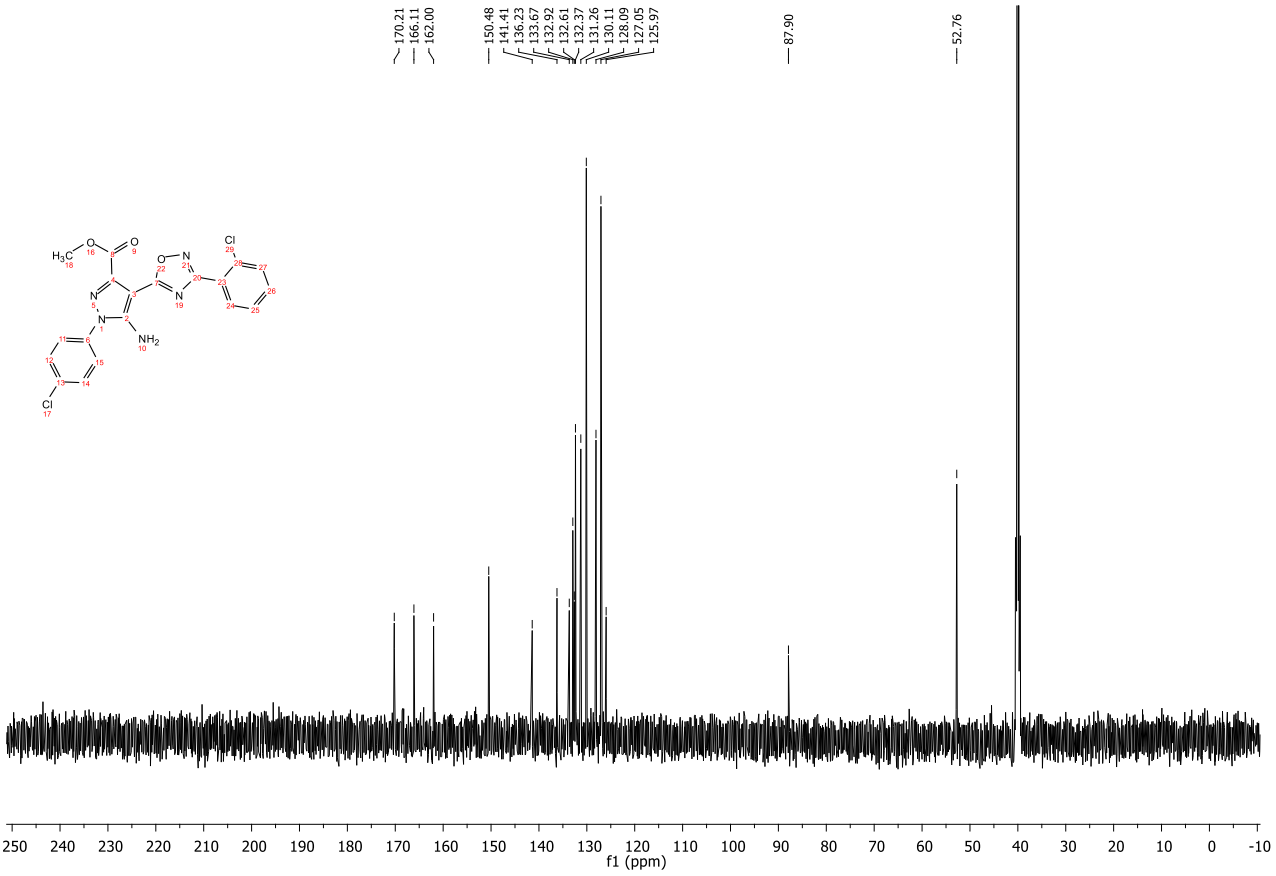
^{13}C NMR Methyl 5-amino-1-(4-chlorophenyl)-4-(3-phenyl-1,2,4-oxadiazol-5-yl)-*1H*-pyrazole-3-carboxylate (4c):



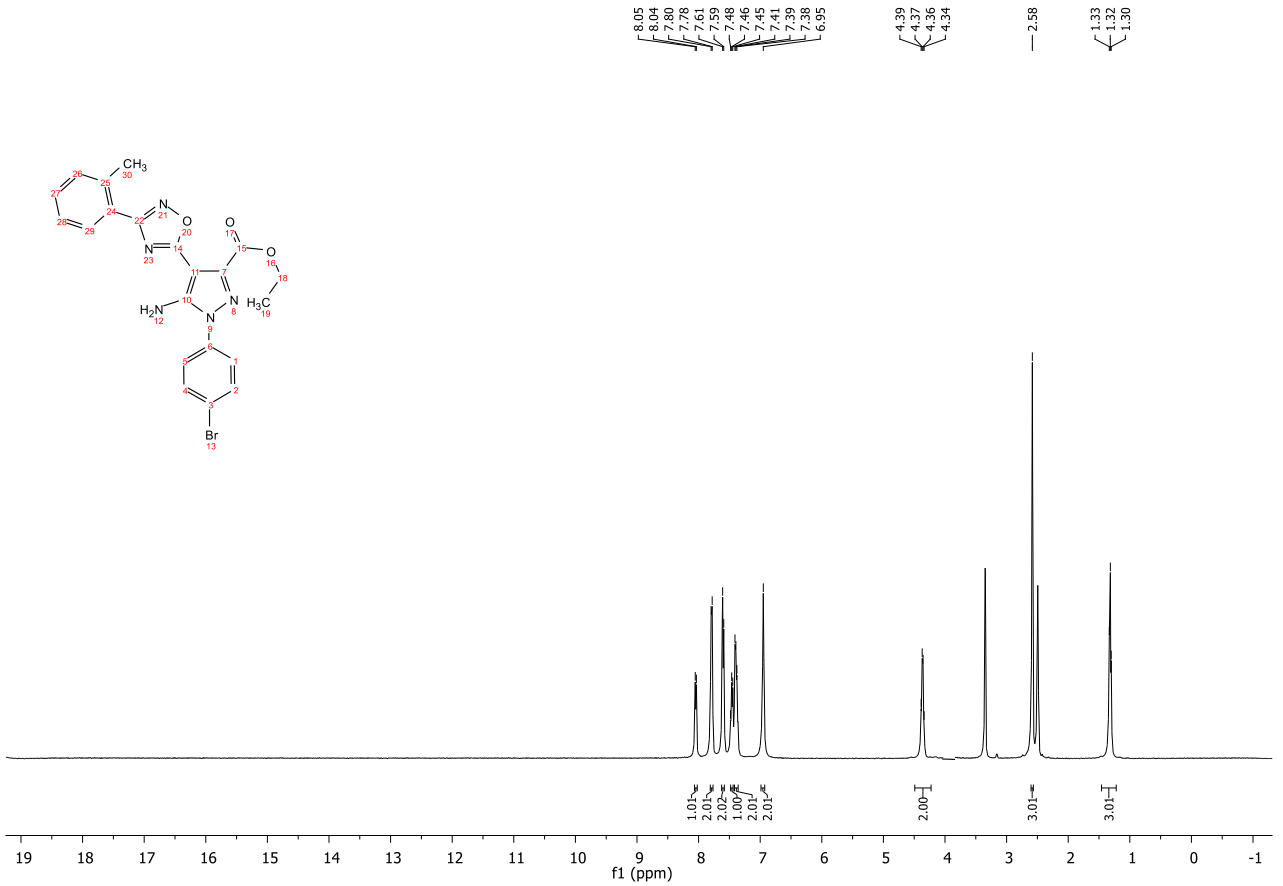
^{1}H NMR Methyl 5-amino-1-(4-chlorophenyl)-4-(3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl)-*1H*-pyrazole-3-carboxylate (4d):



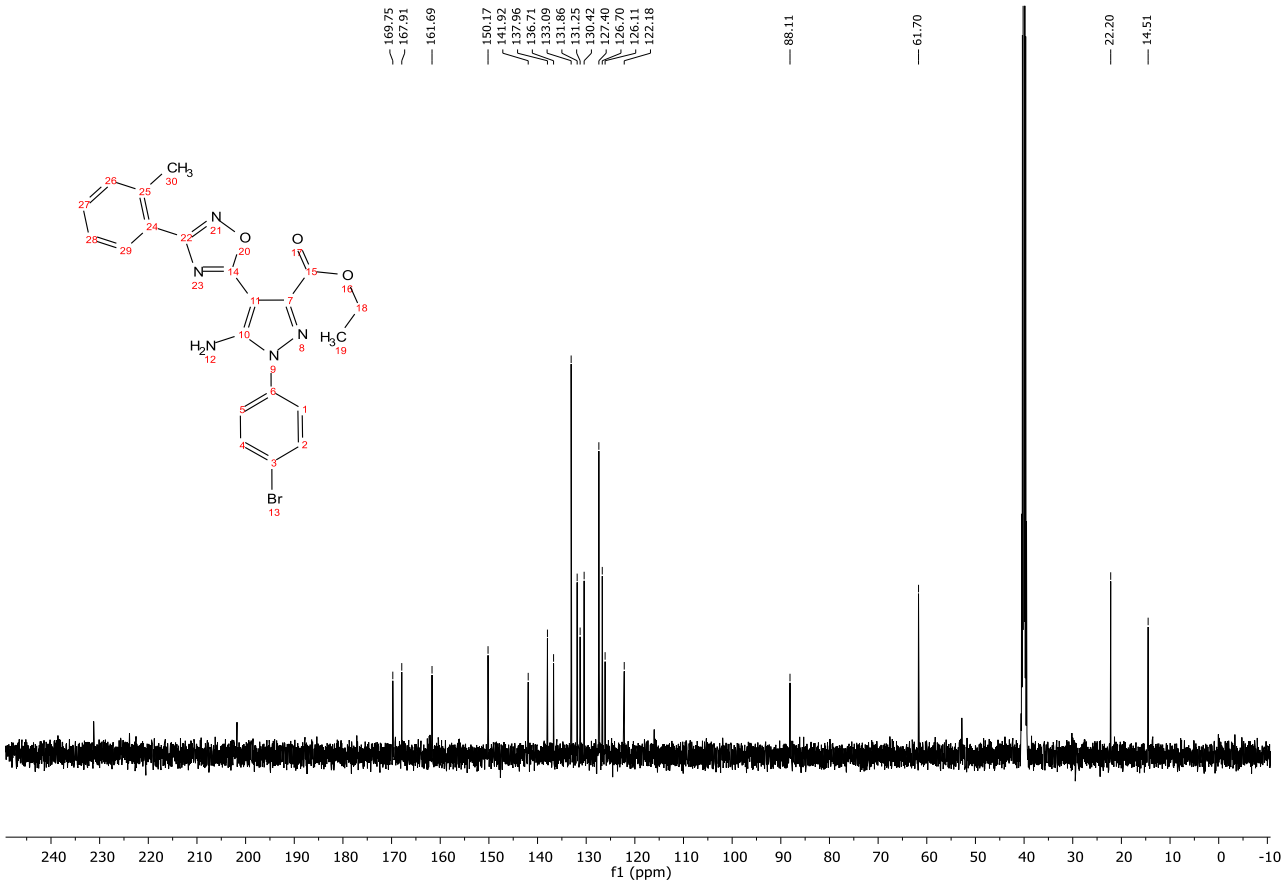
^{13}C NMR Methyl 5-amino-1-(4-chlorophenyl)-4-(3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl)-*1H*-pyrazole-3-carboxylate (4d):



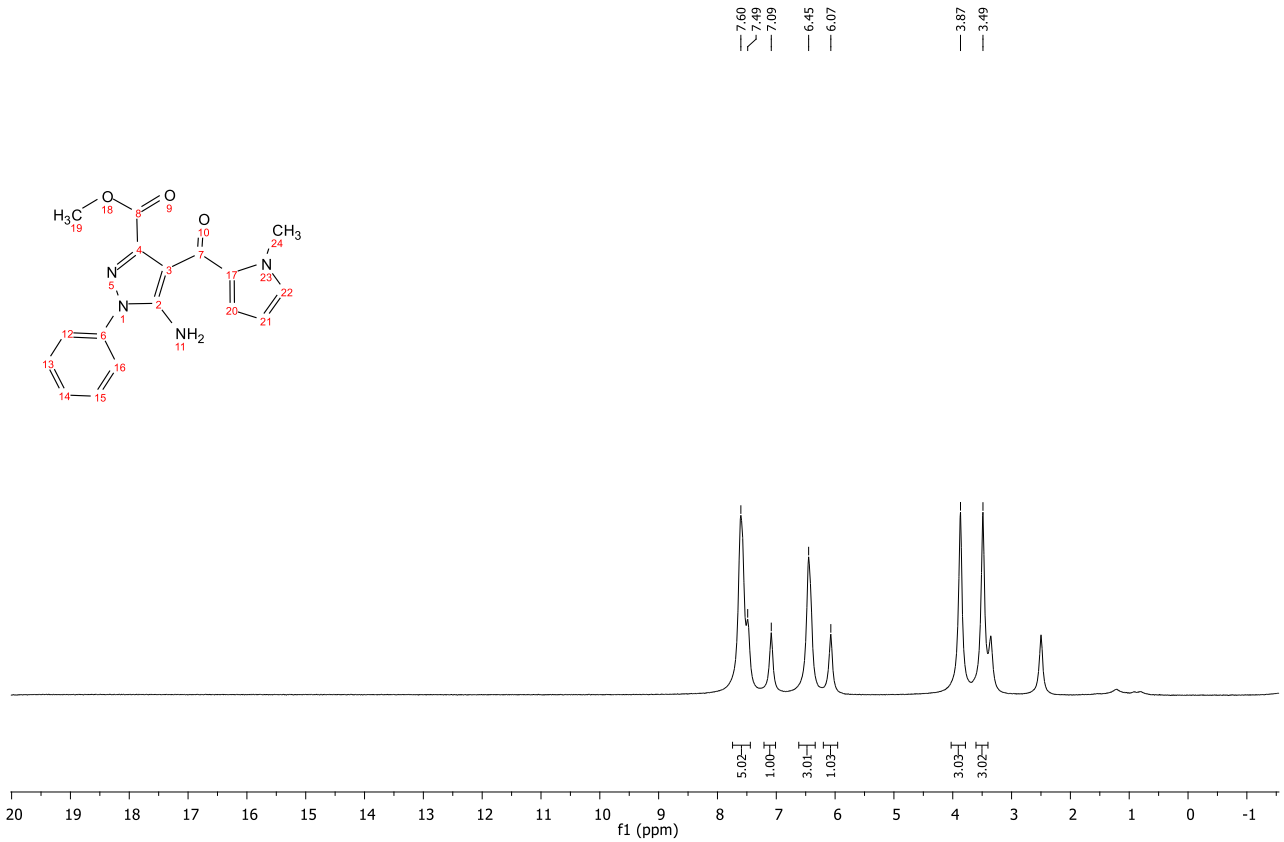
^{1}H NMR Ethyl 5-amino-1-(4-bromophenyl)-4-(3-(o-tolyl)-1,2,4-oxadiazol-5-yl)-*1H*-pyrazole-3-carboxylate (4e):



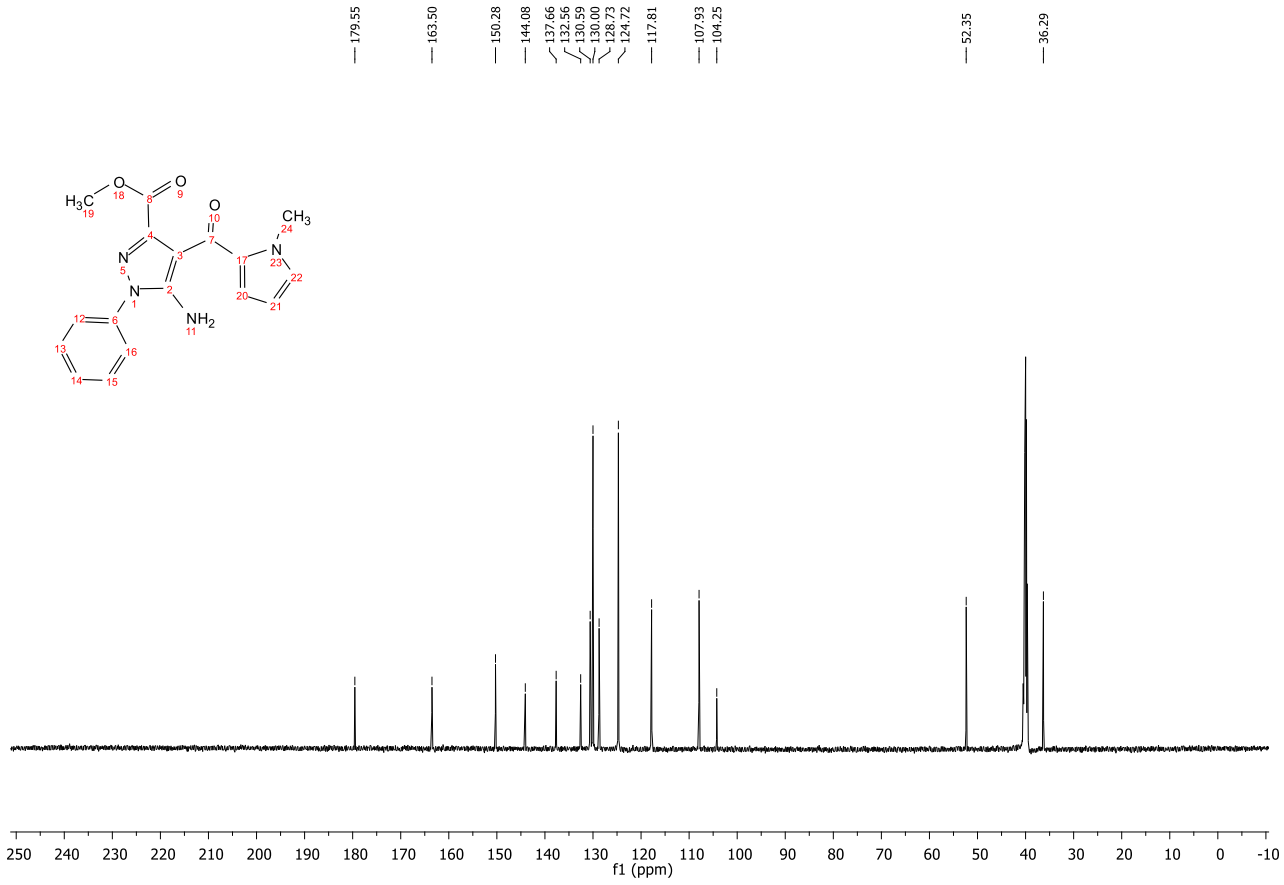
^{13}C NMR Ethyl 5-amino-1-(4-bromophenyl)-4-(3-(o-tolyl)-1,2,4-oxadiazol-5-yl)-*1H*-pyrazole-3-carboxylate (4e):



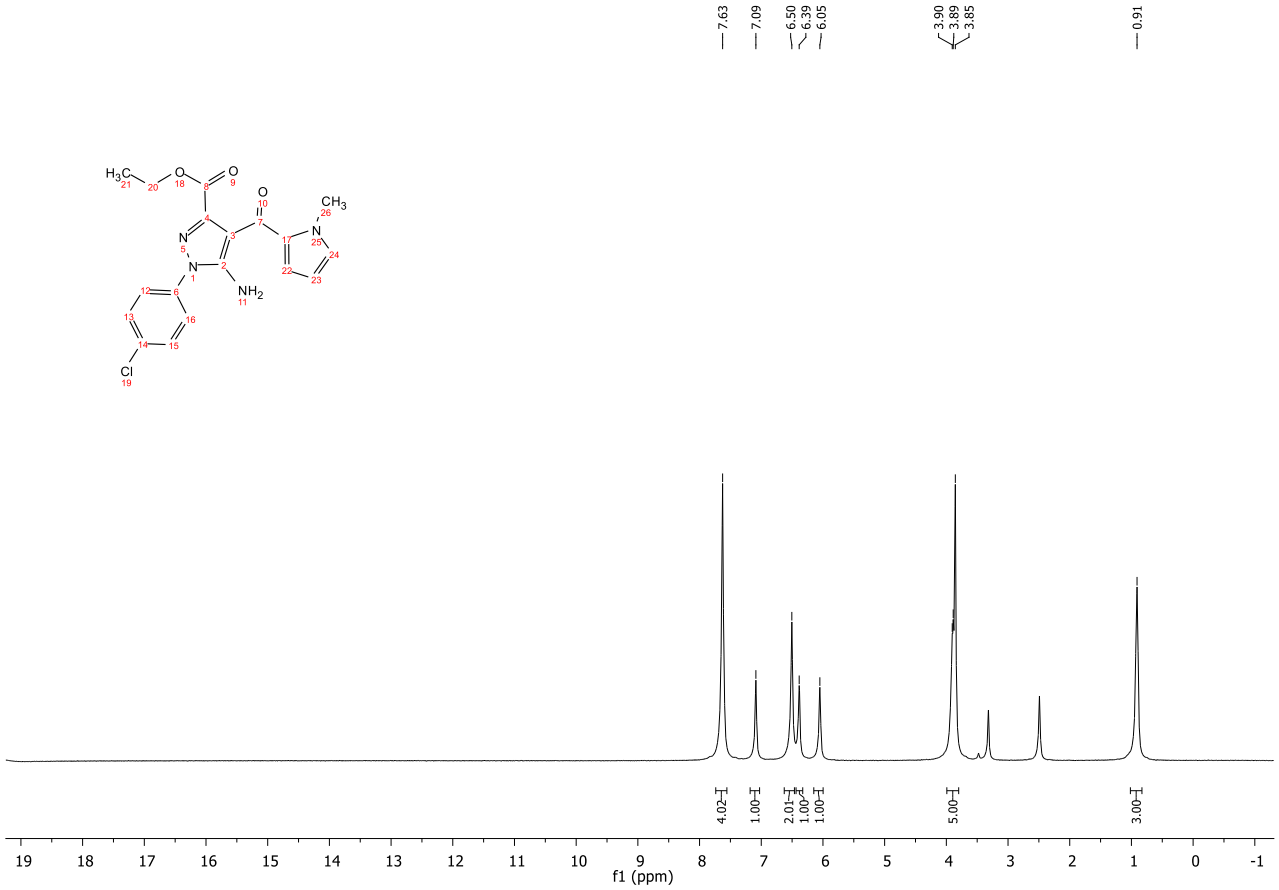
^{1}H NMR Methyl 5-amino-4-[(1-methyl-*1H*-pyrrol-2-yl)carbonyl]-1-phenyl-*1H*-pyrazole-3-carboxylate (7a):



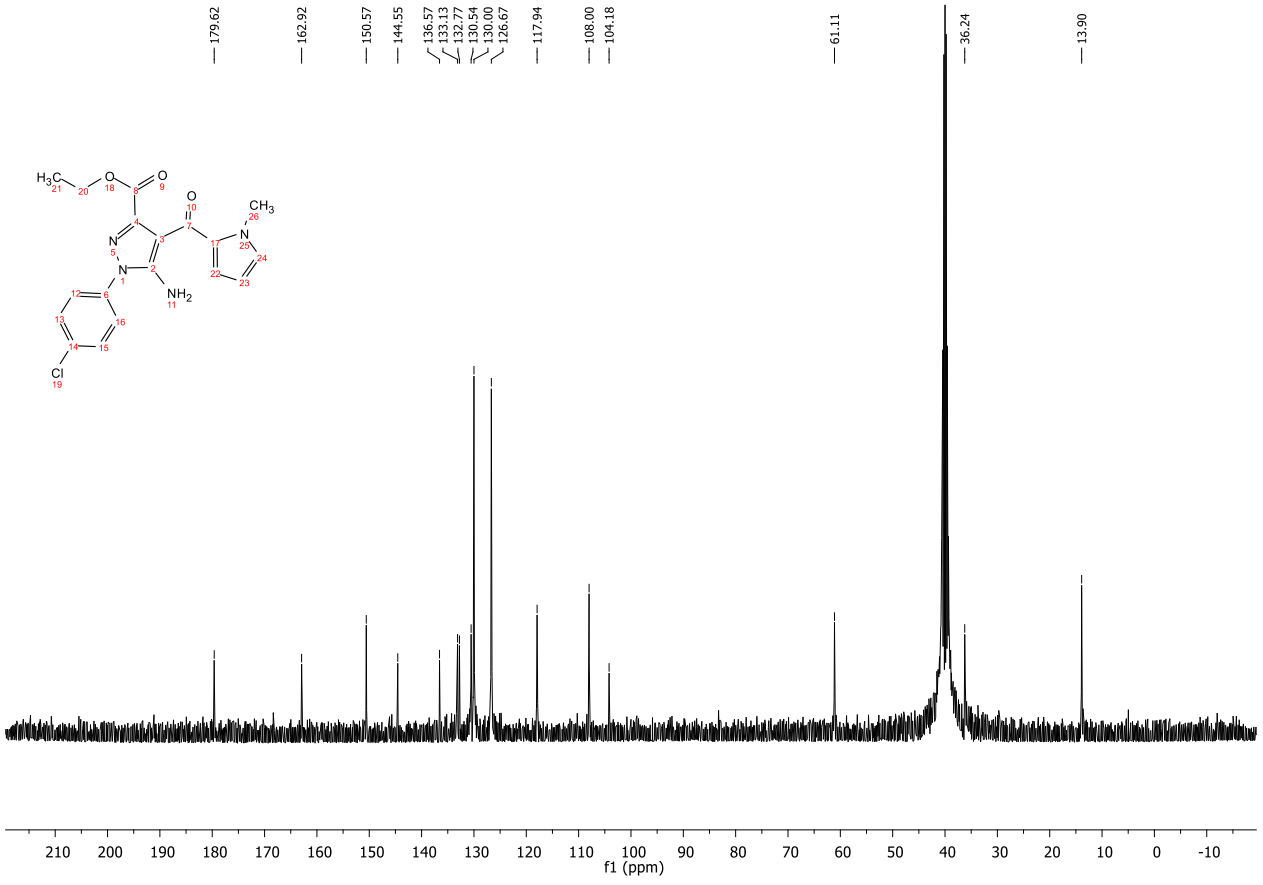
^{13}C NMR Methyl 5-amino-4-[(1-methyl-*1H*-pyrrol-2-yl)carbonyl]-1-phenyl-*1H*-pyrazole-3-carboxylate (7a):



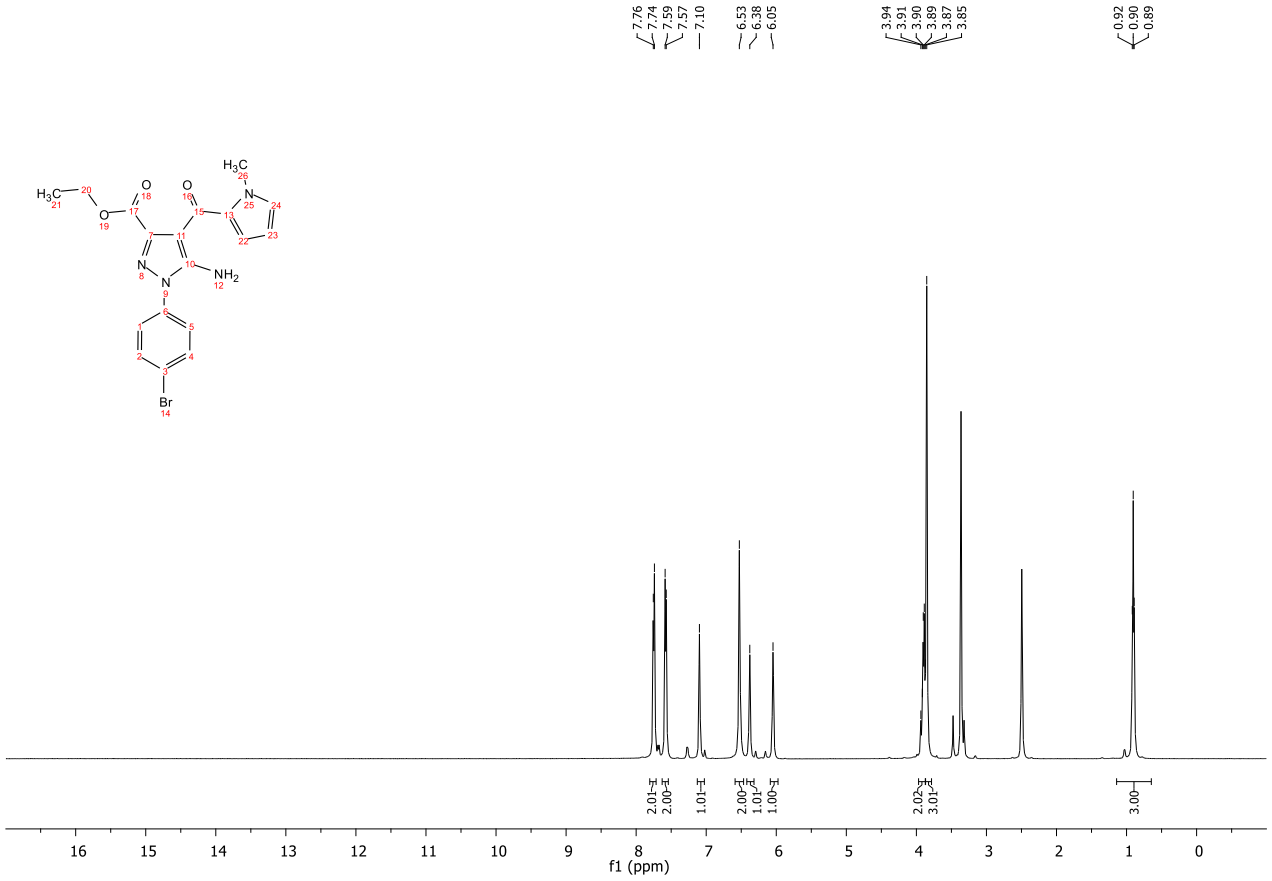
^{1}H NMR Ethyl 5-amino-1-(4-chlorophenyl)-4-(1-methyl-*1H*-pyrrole-2-carbonyl)-*1H*-pyrazole-3-carboxylate (7b):



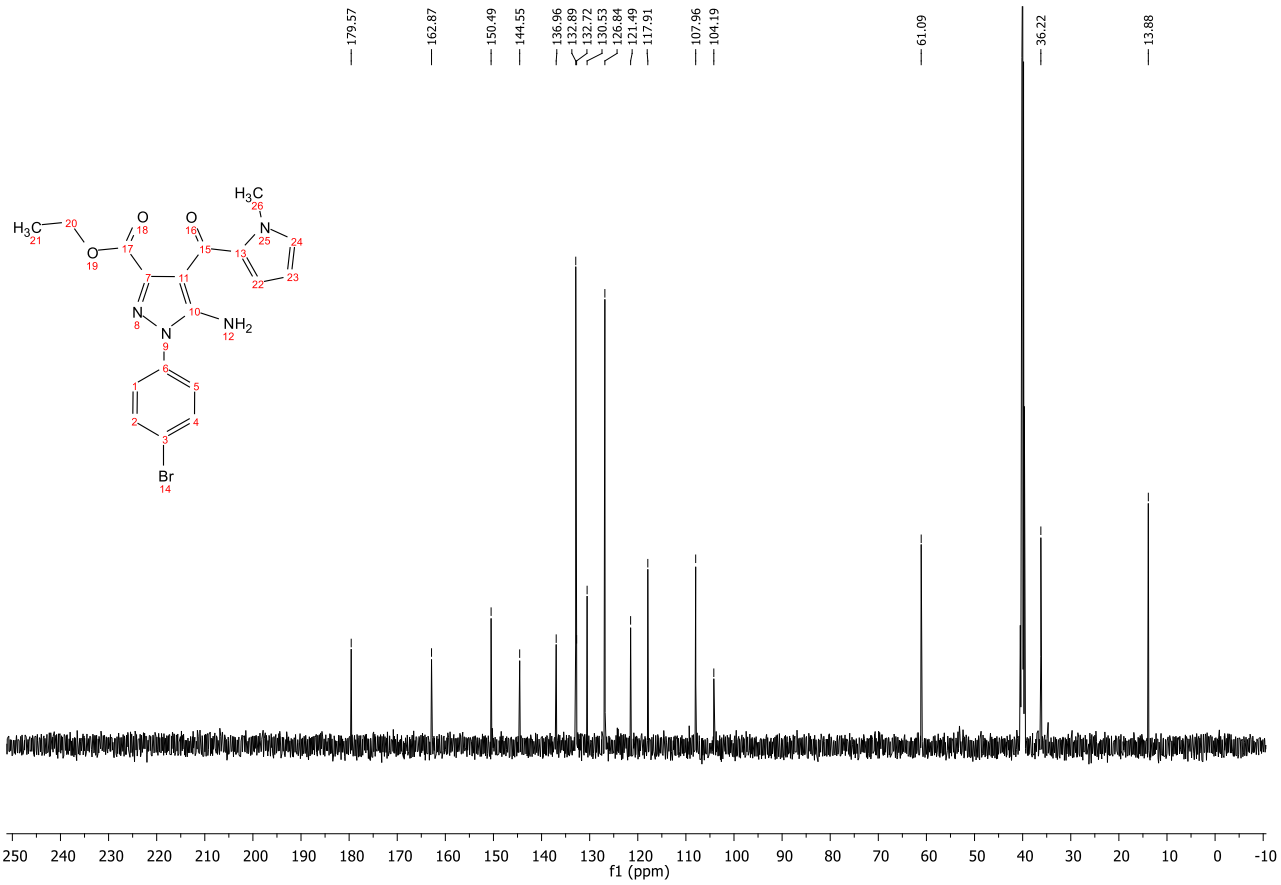
^{13}C NMR Ethyl 5-amino-1-(4-chlorophenyl)-4-(1-methyl-*1H*-pyrrole-2-carbonyl)-*1H*-pyrazole-3-carboxylate (7b):



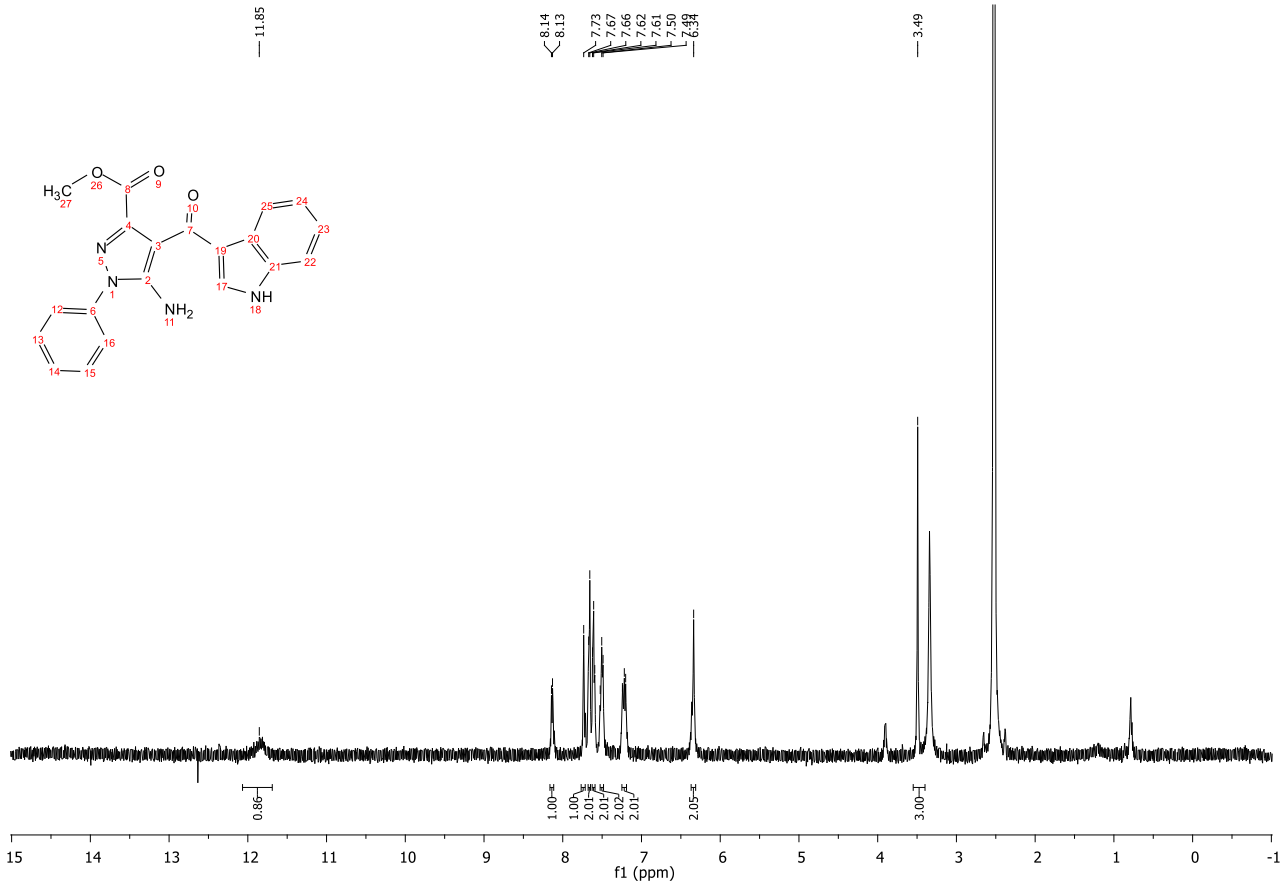
^{1}H NMR Ethyl 5-amino-1-(4-bromophenyl)-4-(1-methyl-*1H*-pyrrole-2-carbonyl)-*1H*-pyrazole-3-carboxylate (7c):



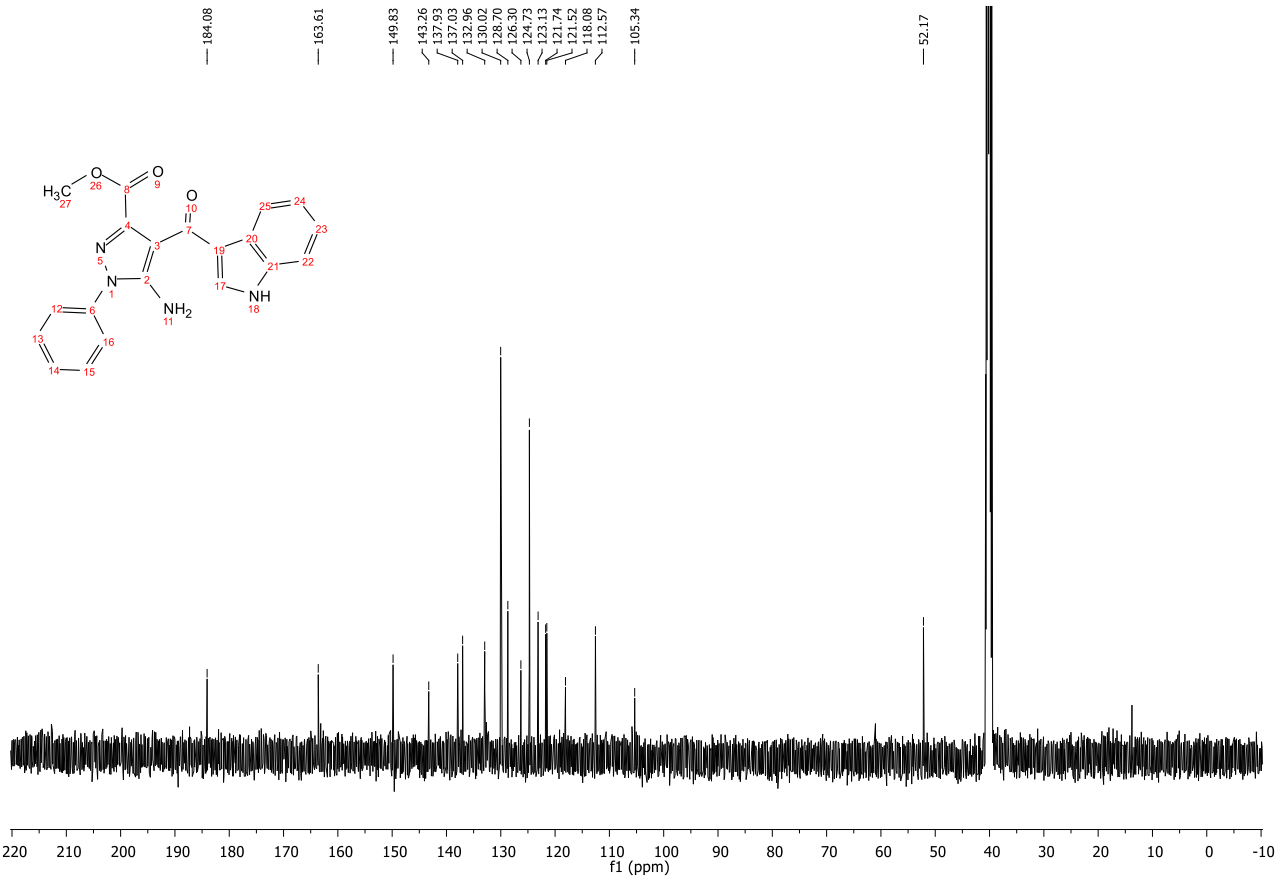
^{13}C NMR Ethyl 5-amino-1-(4-bromophenyl)-4-(1-methyl-*1H*-pyrrole-2-carbonyl)-*1H*-pyrazole-3-carboxylate (7c):



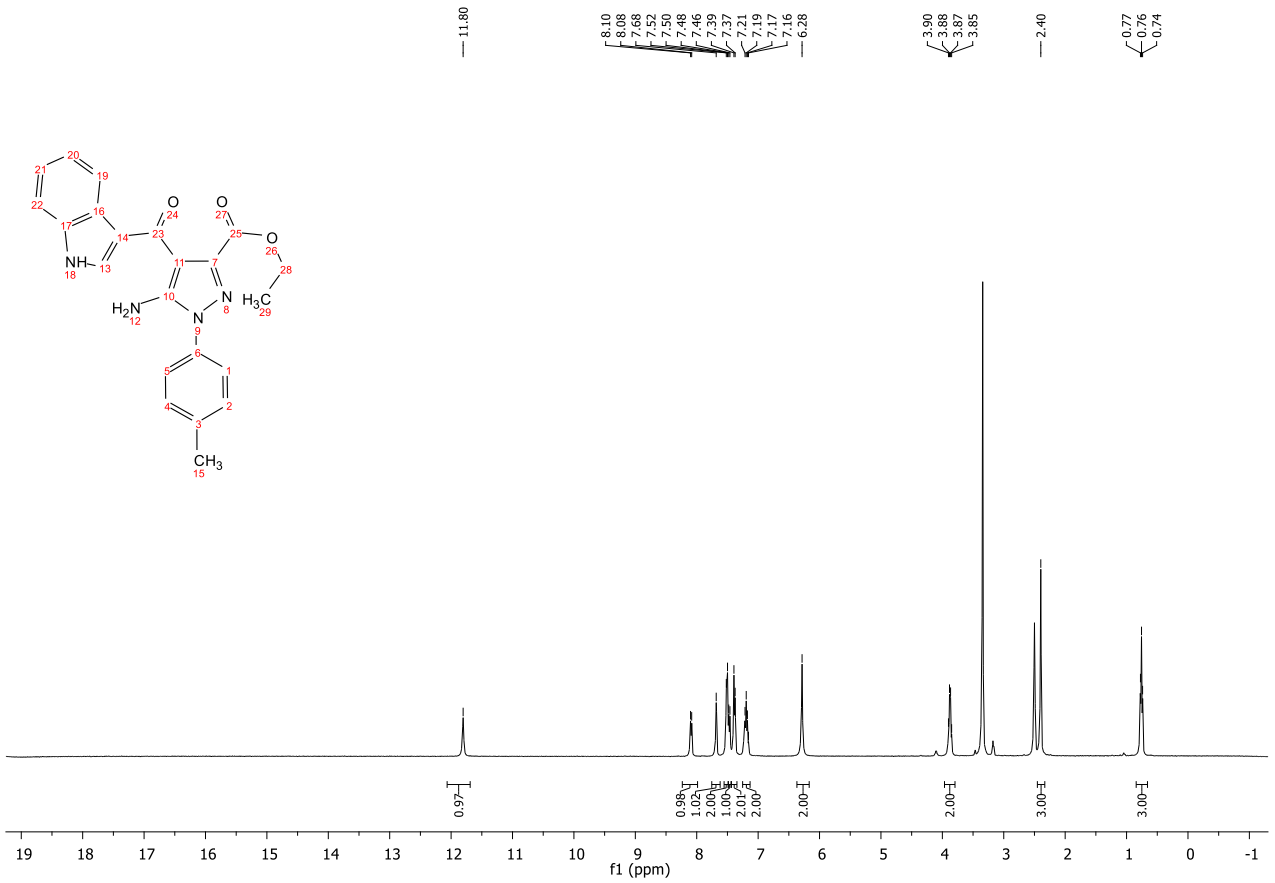
^{1}H NMR Methyl 5-amino-4-(*1H*-indol-3-ylcarbonyl)-1-phenyl-*1H*-pyrazole-3-carboxylate (7d):



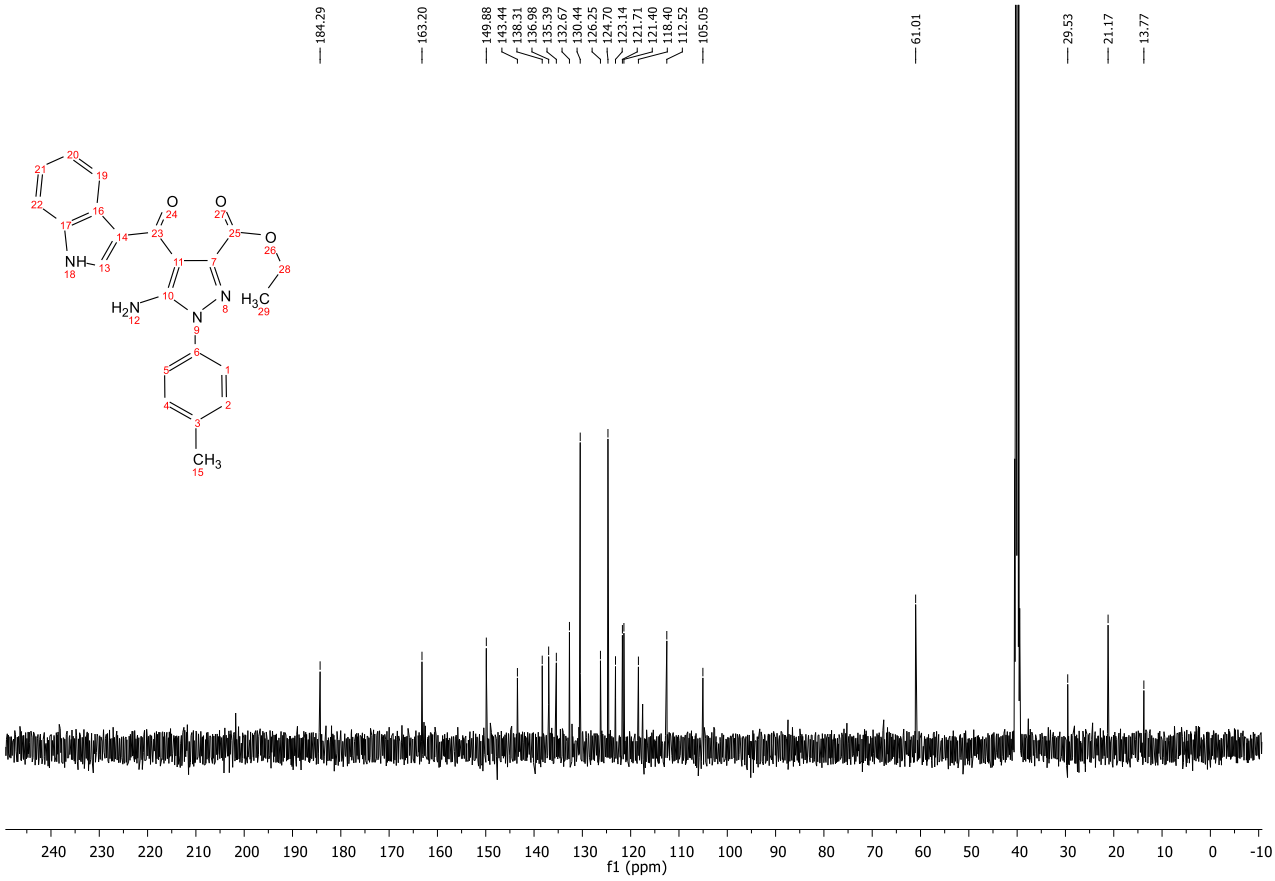
^{13}C NMR Methyl 5-amino-4-(*1H*-indol-3-ylcarbonyl)-1-phenyl-*1H*-pyrazole-3-carboxylate (7d):



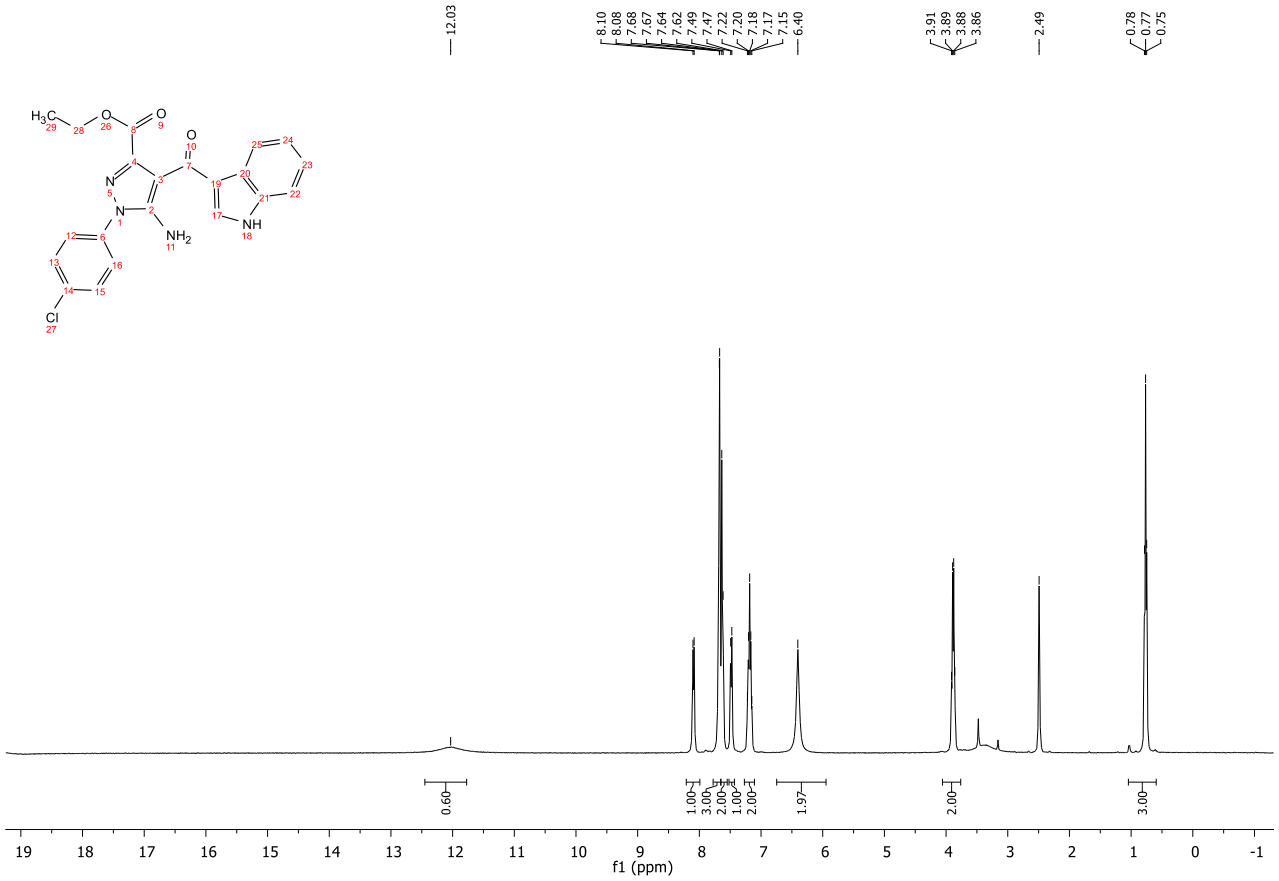
^{1}H NMR Ethyl 5-amino-4-(*1H*-indole-3-carbonyl)-1-(p-tolyl)-*1H*-pyrazole-3-carboxylate (7e):



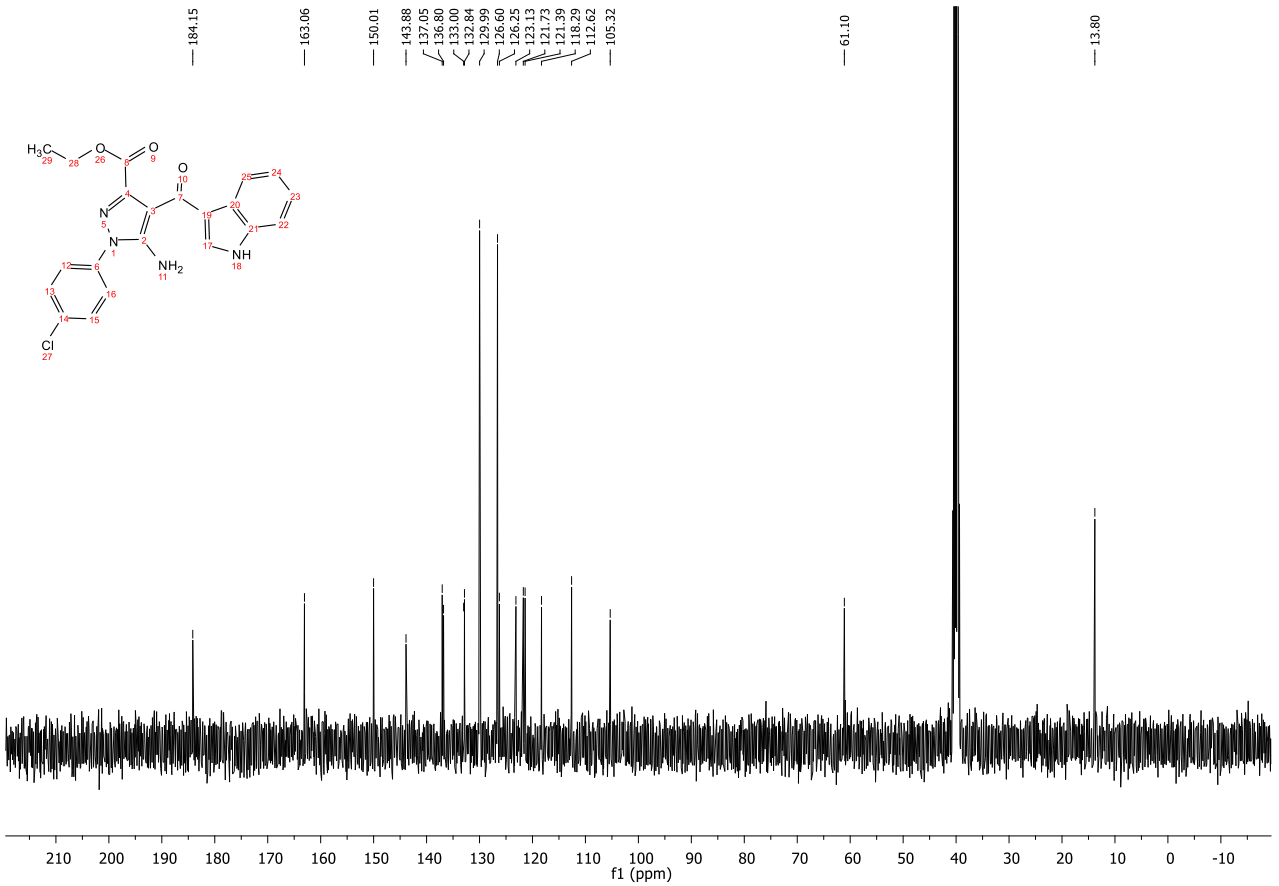
^{13}C NMR Ethyl 5-amino-4-(*1H*-indole-3-carbonyl)-1-(p-tolyl)-*1H*-pyrazole-3-carboxylate (7e):



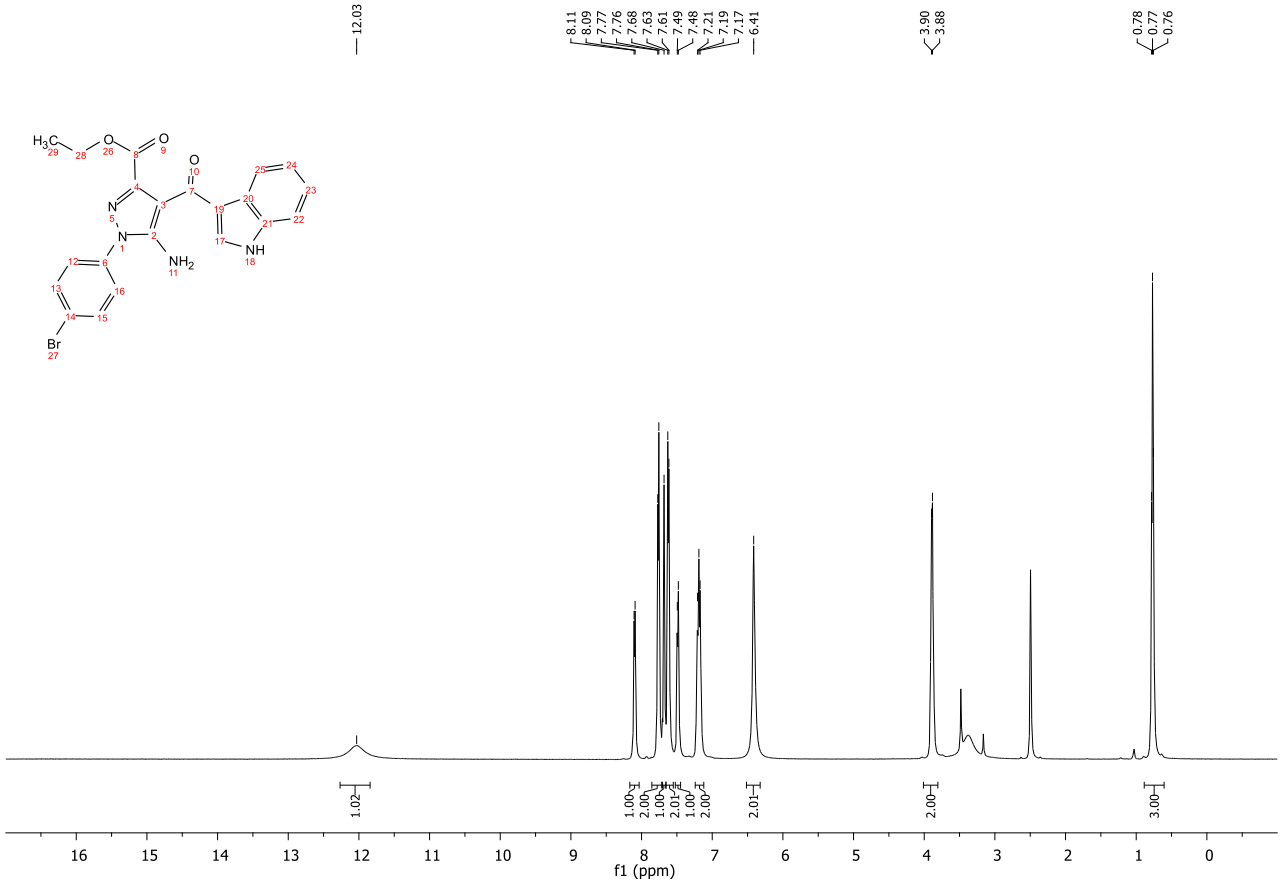
^{1}H NMR Ethyl 5-amino-1-(4-chlorophenyl)-4-(*1H*-indole-3-carbonyl)-*1H*-pyrazole-3-carboxylate (7f):



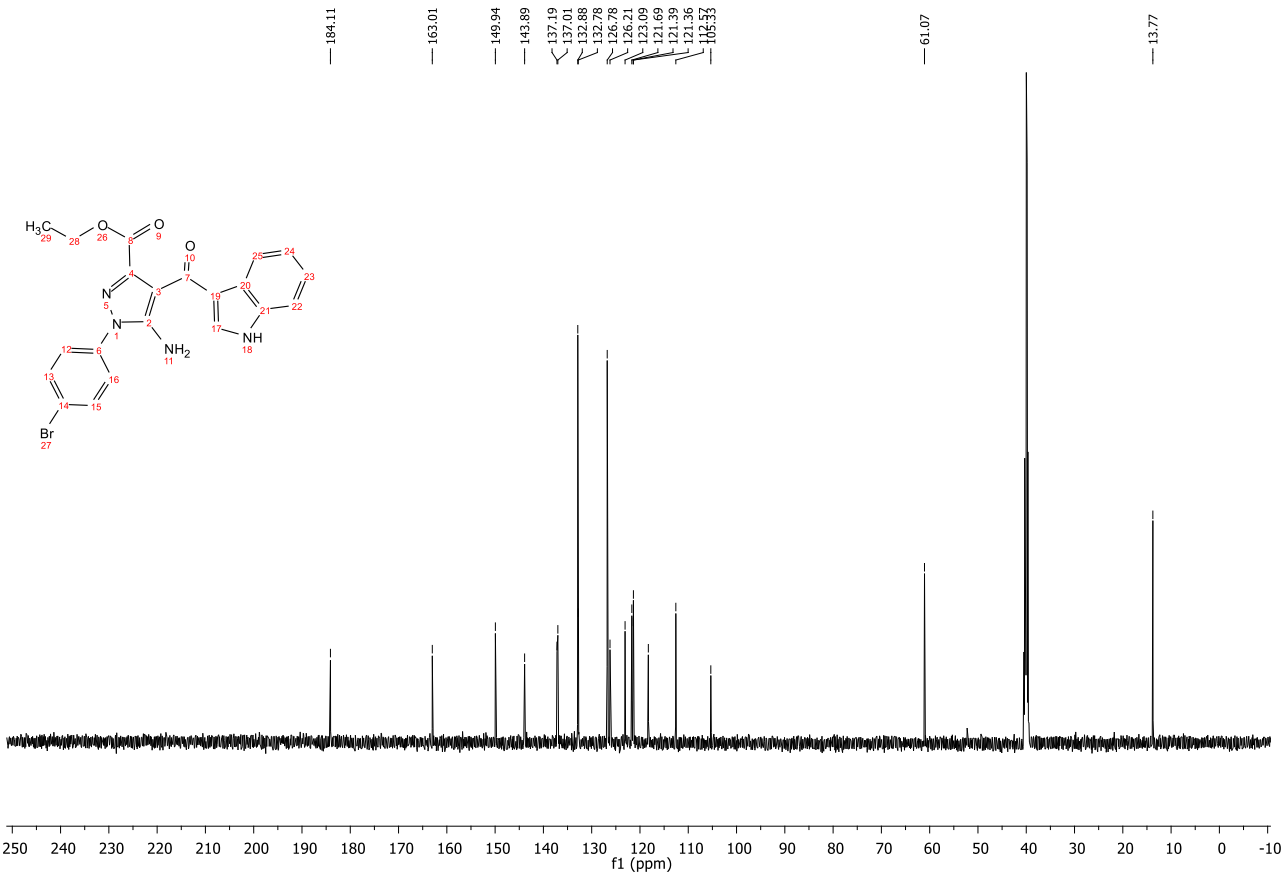
^{13}C NMR Ethyl 5-amino-1-(4-chlorophenyl)-4-(*1H*-indole-3-carbonyl)-*1H*-pyrazole-3-carboxylate (7f):



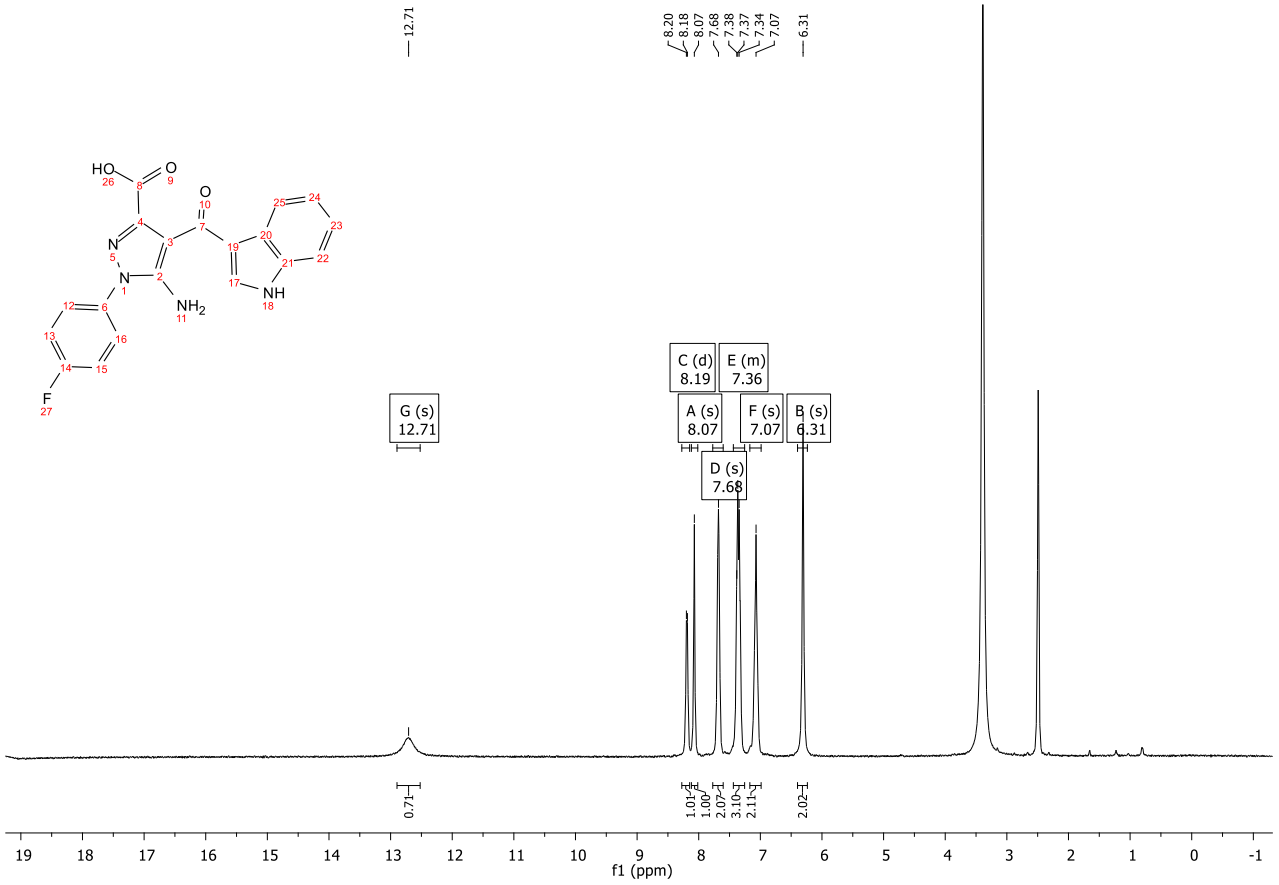
^{1}H NMR Ethyl 5-amino-1-(4-bromophenyl)-4-(*1H*-indole-3-carbonyl)-*1H*-pyrazole-3-carboxylate (7g):



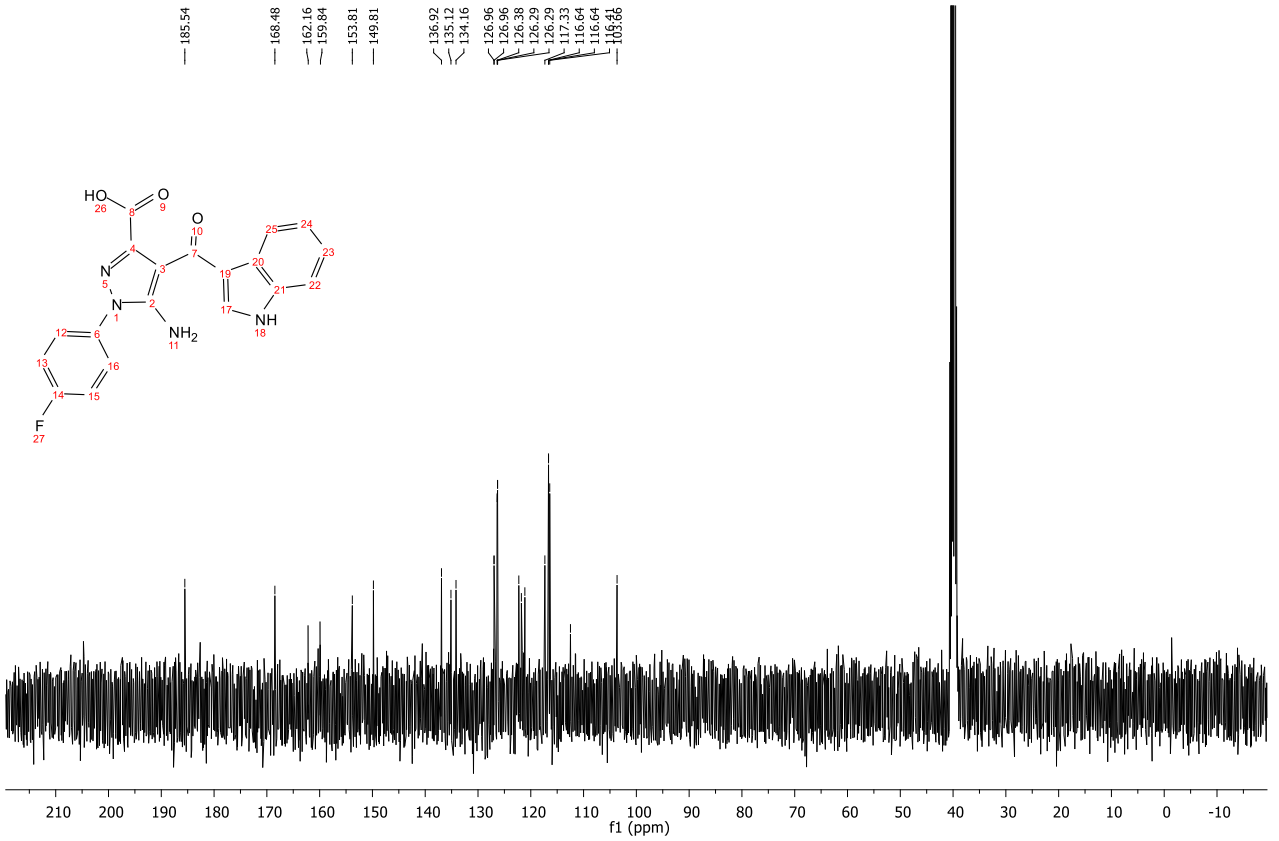
^{13}C NMR Ethyl 5-amino-1-(4-bromophenyl)-4-(*1H*-indole-3-carbonyl)-*1H*-pyrazole-3-carboxylate (7g):



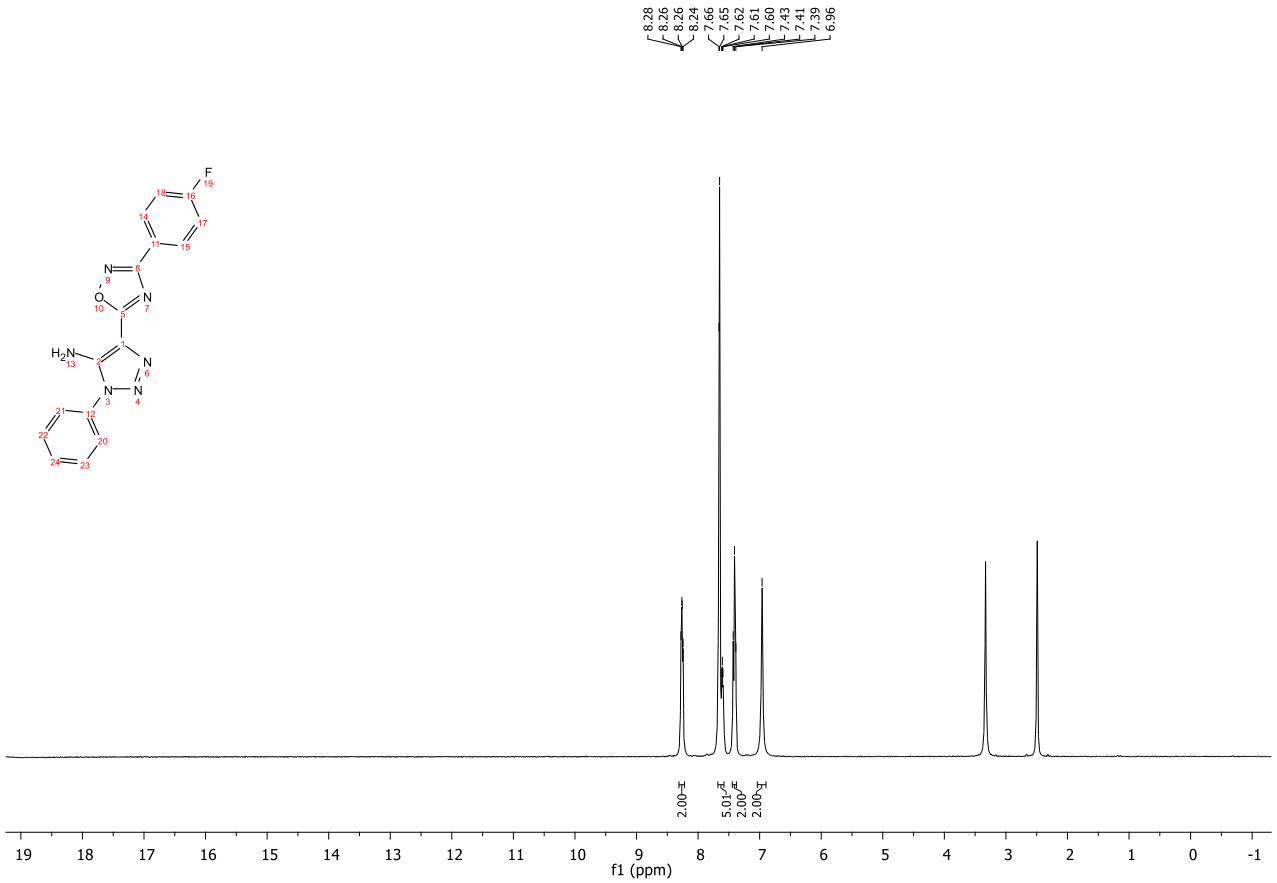
^{1}H NMR 5-Amino-1-(4-fluorophenyl)-4-(*1H*-indole-3-carbonyl)-*1H*-pyrazole-3-carboxylic acid (7h):



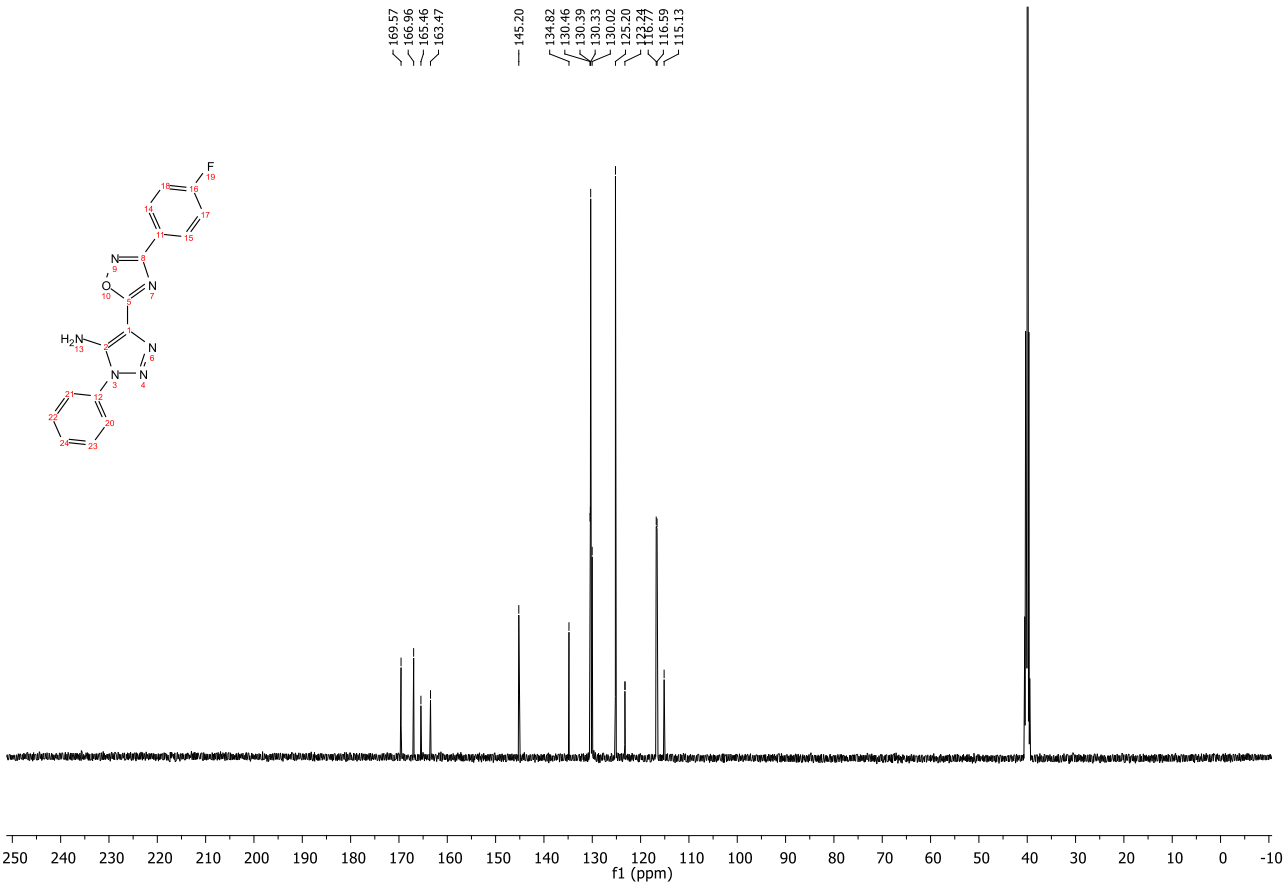
^{13}C NMR 5-Amino-1-(4-fluorophenyl)-4-(*1H*-indole-3-carbonyl)-*1H*-pyrazole-3-carboxylic acid (7h):



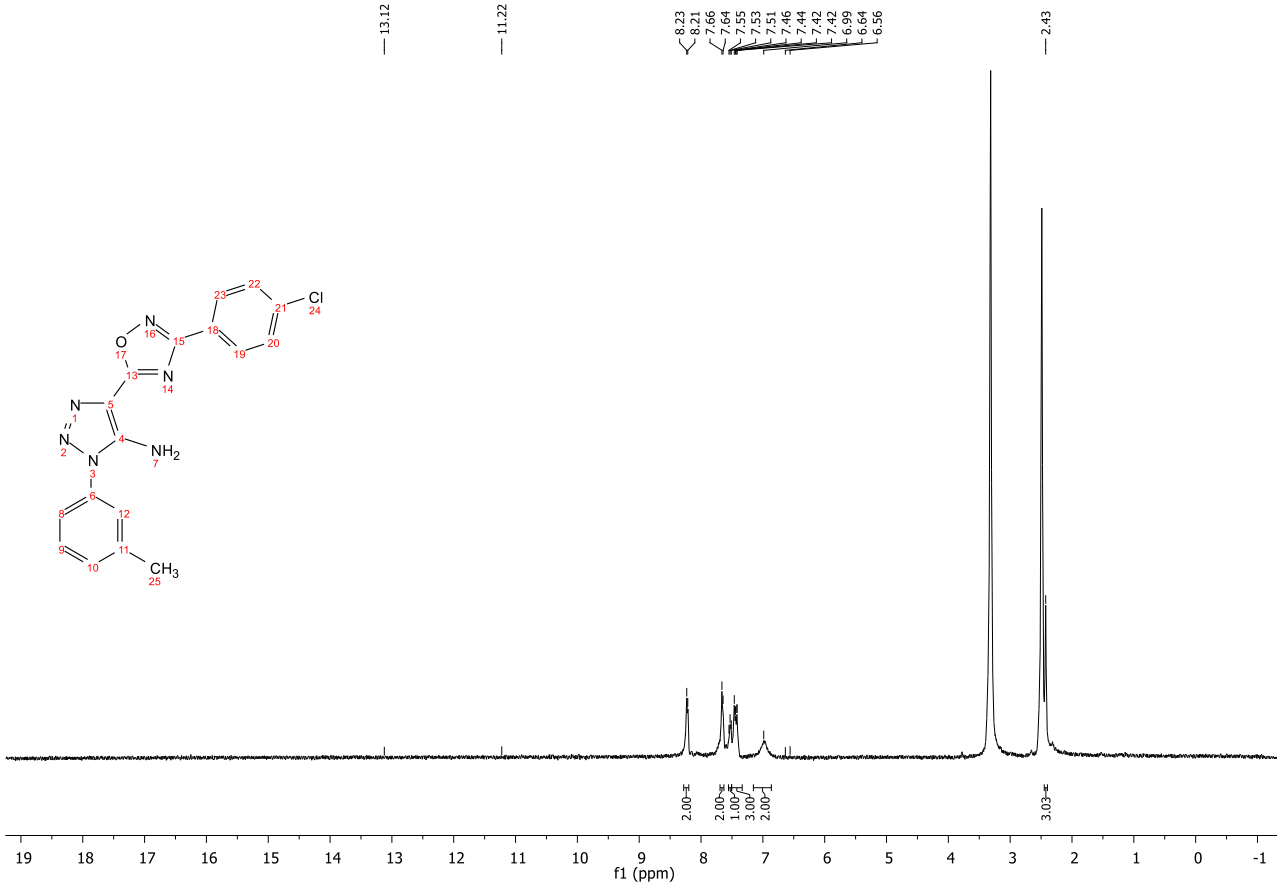
^{1}H NMR 4-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-phenyl-*1H*-1,2,3-triazol-5-amine (5a):



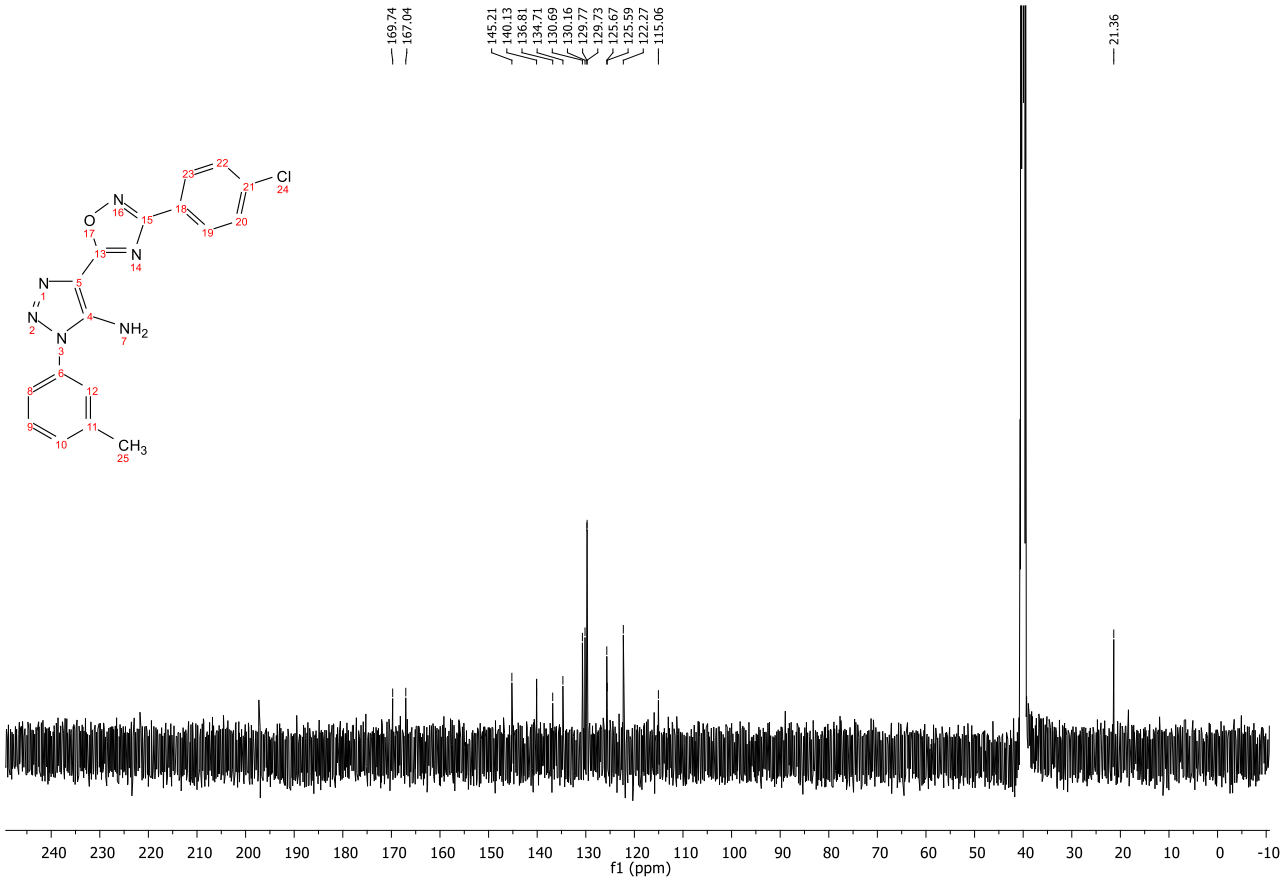
^{13}C NMR 4-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)-1-phenyl-*1H*-1,2,3-triazol-5-amine (5a):



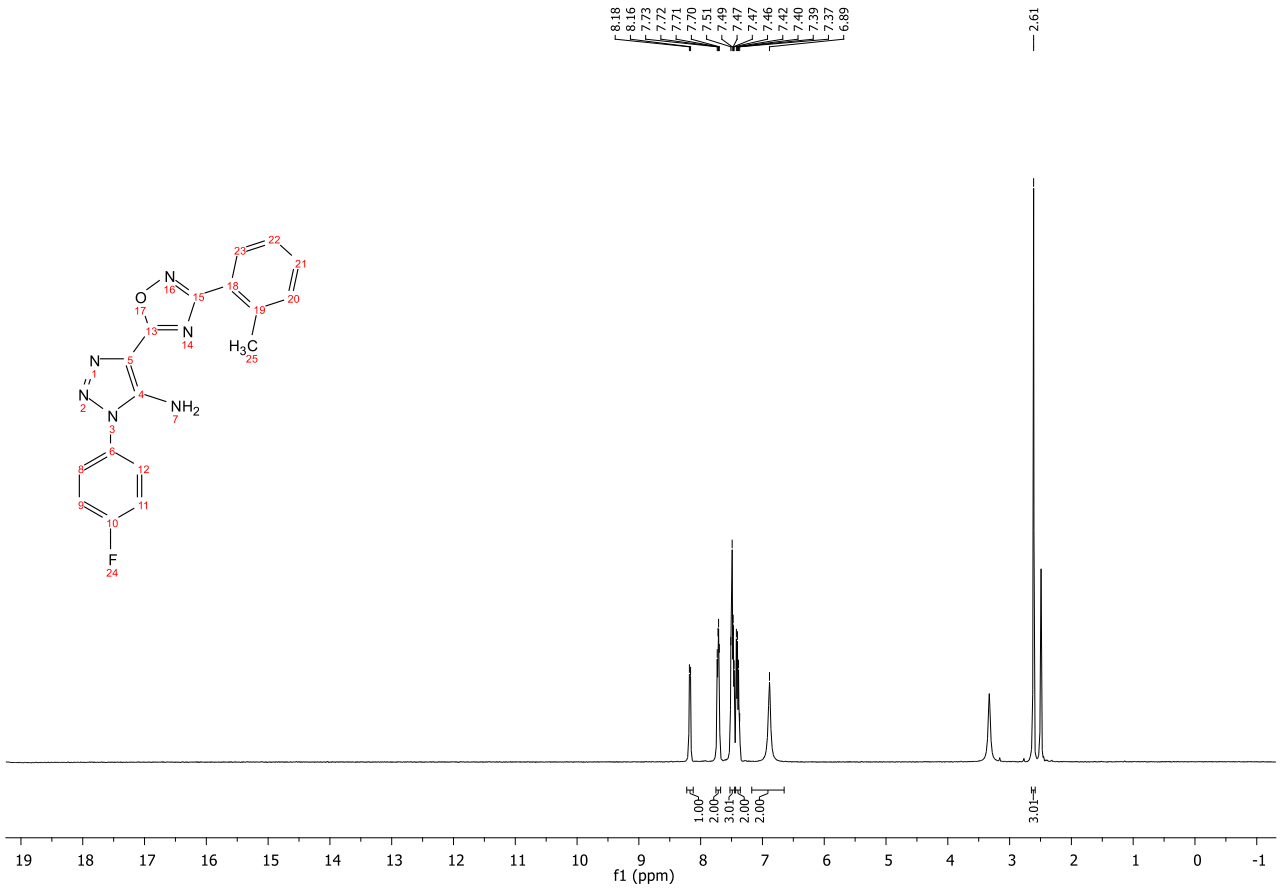
^{1}H NMR 4-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-m-tolyl-*1H*-1,2,3-triazol-5-amine (5b):



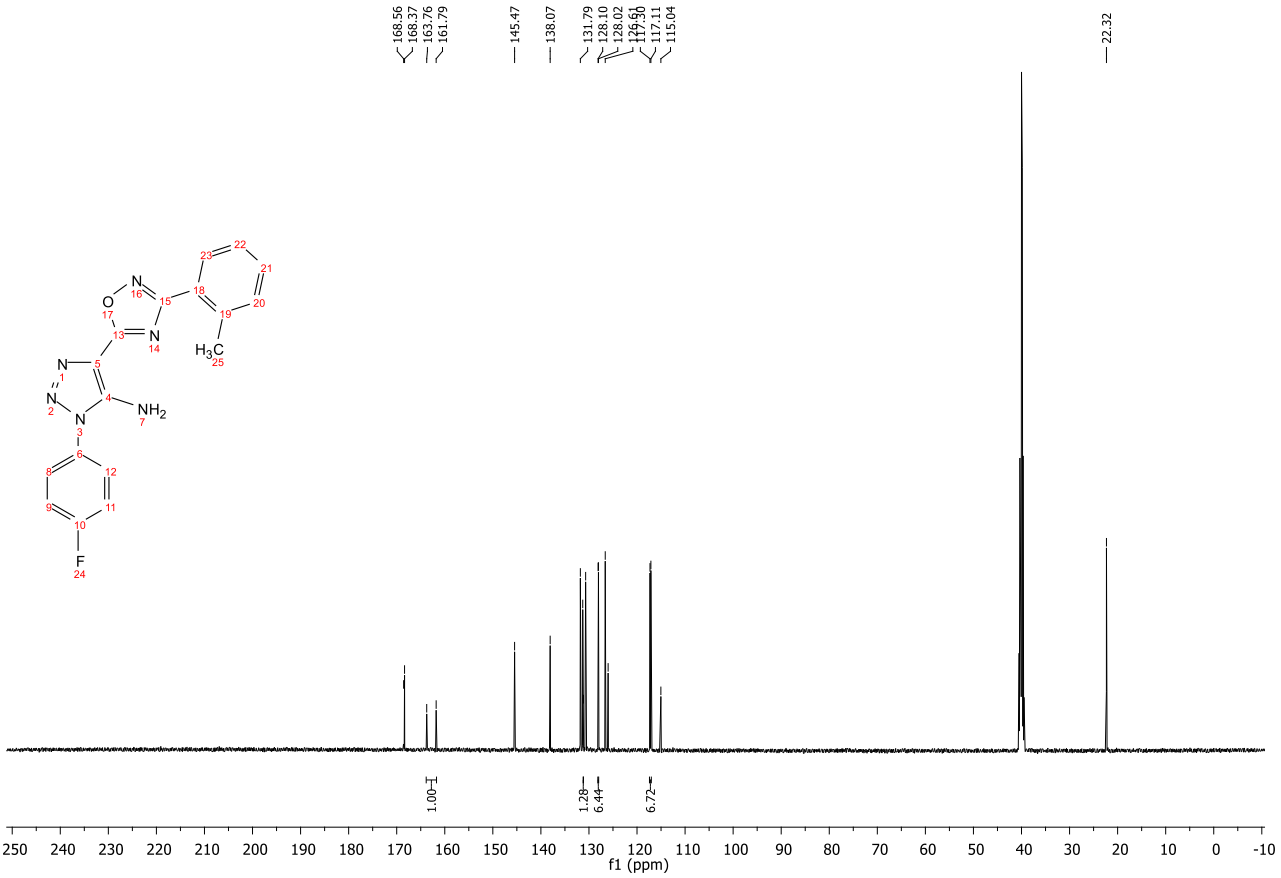
^{13}C NMR 4-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-m-tolyl-*1H*-1,2,3-triazol-5-amine (5b):



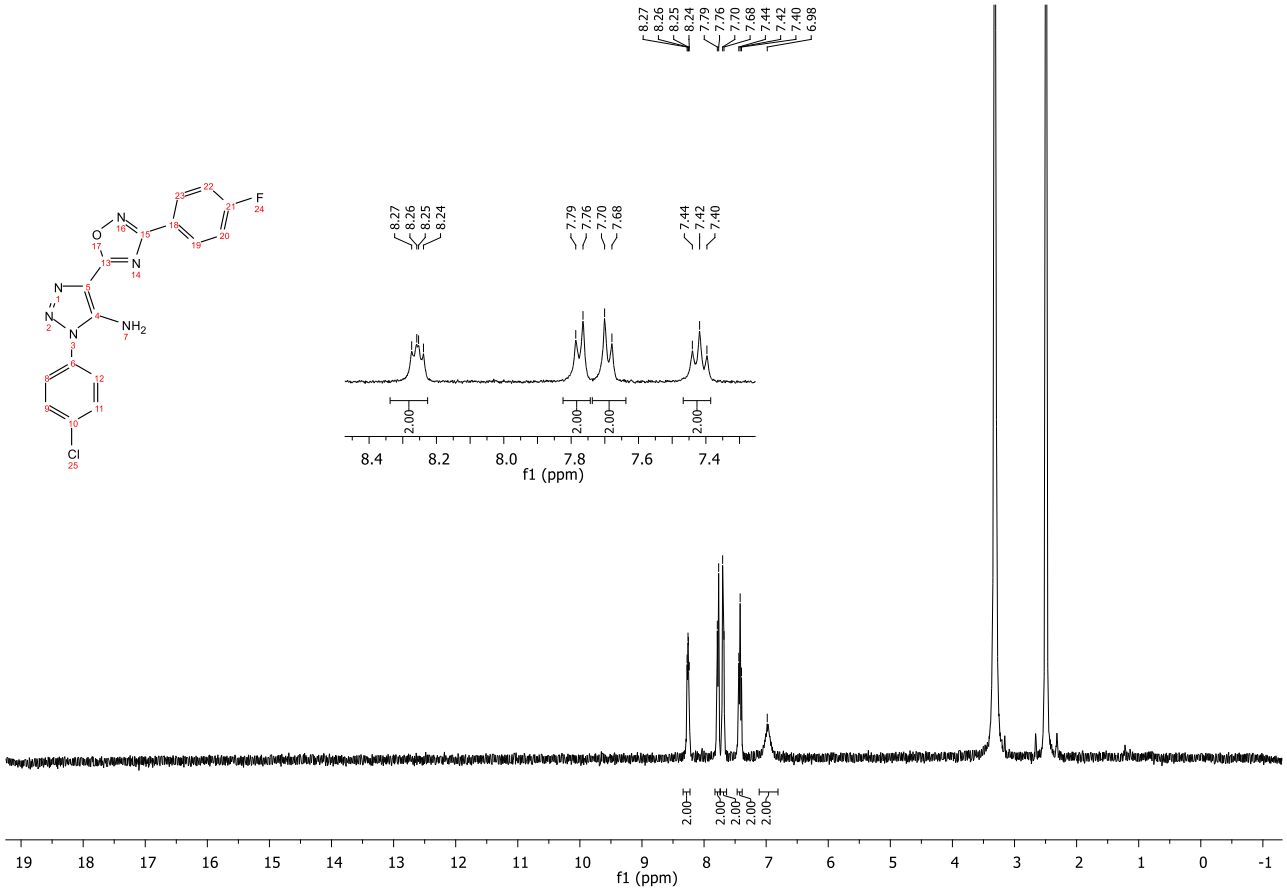
^{1}H NMR 1-(4-Fluorophenyl)-4-(3-o-tolyl-1,2,4-oxadiazol-5-yl)-*1H*-1,2,3-triazol-5-amine (5c):



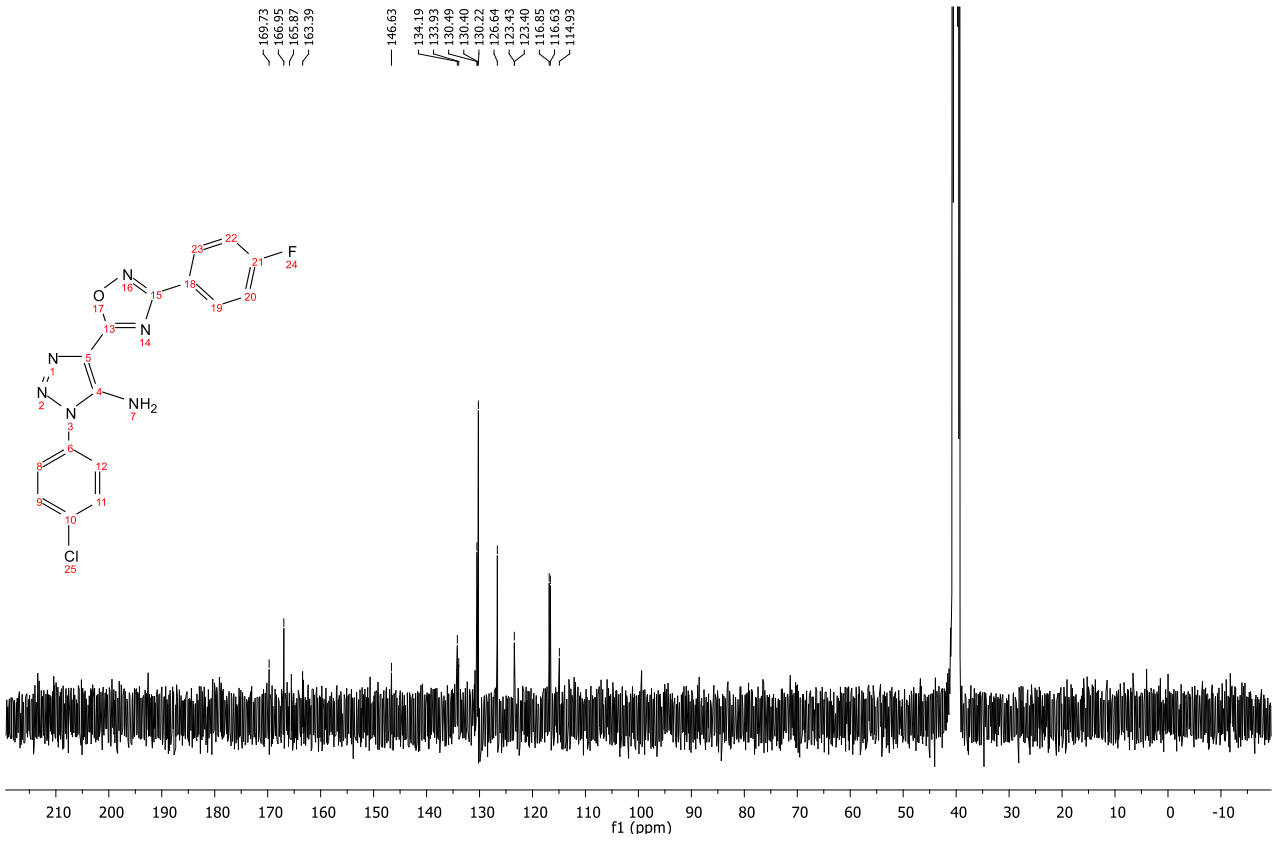
^{13}C NMR 1-(4-Fluorophenyl)-4-(3-o-tolyl-1,2,4-oxadiazol-5-yl)-*1H*-1,2,3-triazol-5-amine (5c):



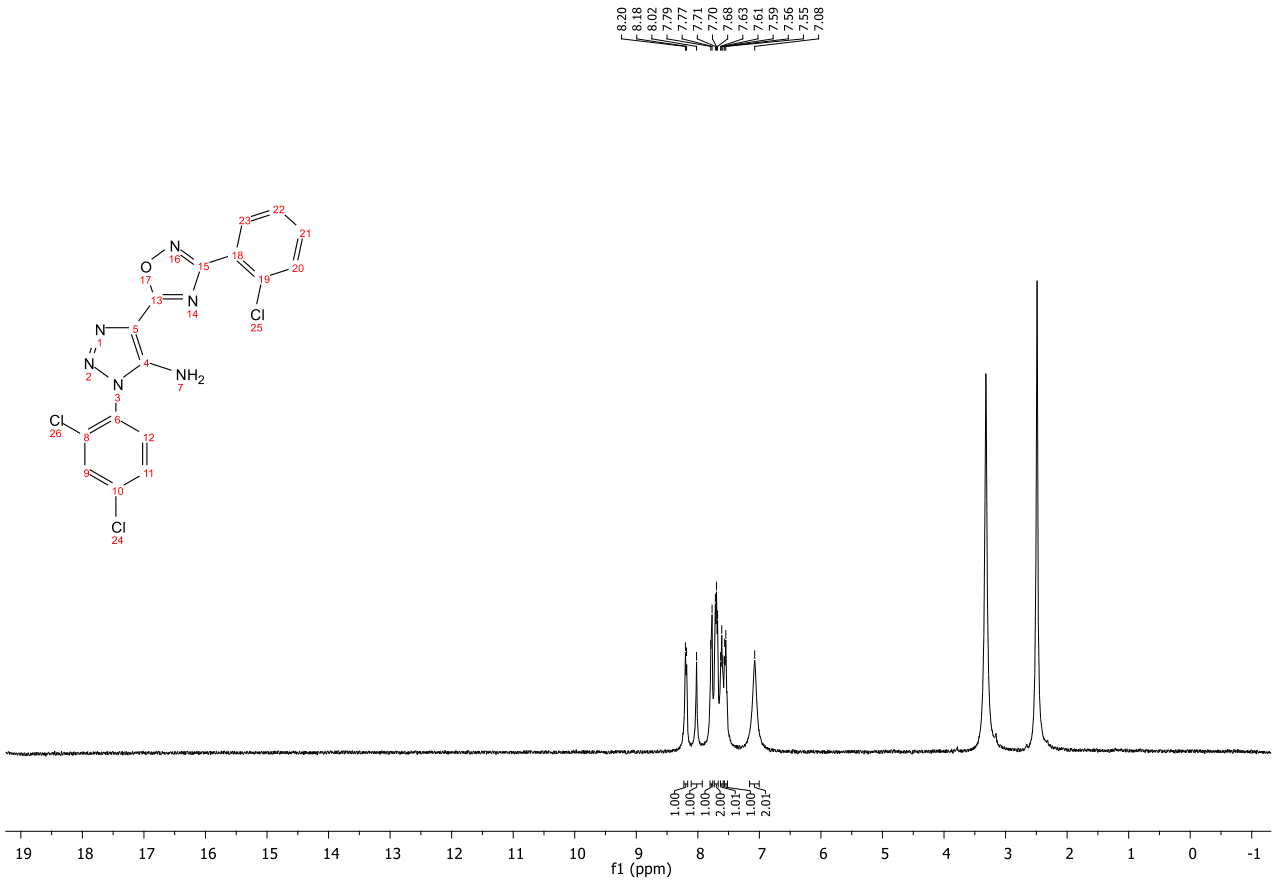
^{1}H NMR 1-(4-Chlorophenyl)-4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-*1H*-1,2,3-triazol-5-amine (5d):



^{13}C NMR 1-(4-Chlorophenyl)-4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-*1H*-1,2,3-triazol-5-amine (5d):



^{1}H NMR 4-(3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(2,4-dichlorophenyl)-*1H*-1,2,3-triazol-5-amine (5e):



^{13}C NMR 4-(3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-1-(2,4-dichlorophenyl)-*1H*-1,2,3-triazol-5-amine (5e):