Synthesis, molecular docking and QSAR study of thiazole clubbed pyrazole hybrid as α-amylase inhibitor

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Experimental

All the reagents including starting reactant were purchased from Sigma Aldrich and Merck. Melting points of compounds were determined in open capillaries and were uncorrected. IR spectra were recorded on Shimadzu IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR were recorded on Bruker (Advance-II) instrument at 400 and 500 MHz in DMSO (*d*$_6$) using tetramethylsilane (TMS) as an internal standard. The values of δ and coupling constant (*J*) are expressed in ppm and Hz. Mass spectra were recorded on Waters Micro mass Q-Tof Micro.

Synthesis of 1-((1-phenyl-3-aryl-1*H*-pyrazole-4-yl)methylene)-2-(4-arylthiazole-2-yl) hydrazine (4a-4r)

In 50 mL round bottom flask, a mixture of 1-aryl-3-phenyl-1*H*-pyrazole-4-carbaldehyde **(1a-1f)** (1.0 mmol), thiosemicarbazide **(2)** (1.1 mmol) and α-bromoacetophenone **(3a-3c)** (1.0 mmol) were refluxed for 5 min in 10 mL of ethanol. Progress of the reaction was monitored on TLC (petroleum ether: ethyl acetate (70:30, *v/v*)). A solid was separated out, which was filtered, dried and recrystallized from ethanol.

Spectral data

1-((3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4a)

Yield: 85%; **M.pt:** 220°C (Lit. M.pt(Alegaon et al. **2017**): 243-245°C); **IR (v_{max} cm^{-1}, KBr):** 3317 (NH Stretch), 1682 (C=N Stretch), 1574 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-*d*$_6$):** 11.92 (s, 1H, NH), 8.81 (s, 1H, -CH=N), 8.17 (s, 1H, pyrazole-H$_5$), 7.96 (d, *J* = 8.0 Hz, 2H, H$_7$/H$_{11}$), 7.83-7.77 (m, 4H, H$_{13}$/H$_{17}$, H$_{28}$/H$_{30}$), 7.68 (d, *J* = 8.5 Hz, 2H, H$_{14}$/H$_{16}$), 7.56-7.51 (m, 4H, H$_{27}$/H$_{31}$, H$_8$/H$_{10}$), 7.36 (t, *J* = 7.4 Hz, 1H, H$_9$), 7.26 (s, 1H, thiazole-H$_{23}$); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-*d*$_6$):** 168.05, 163.07, 149.36, 138.91, 134.44, 133.84, 131.55, 131.31, 131.25, 130.33, 129.40, 128.13, 127.38, 126.77, 121.76, 120.39, 118.60, 117.00**,** 103.96; **ESI-MS (m/z):** 578.02 (M+H), 580.01 (M+H+2), 582.01 (M+H+4); **Anal. Calc. For C$_{25}$H$_{17}$Br$_2$N$_5$S:** C, 51.83; H, 2.96; N, 12.09. **Found:** C, 51.78; H, 2.91; N, 12.01.

1-((3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl)thiazol -2-yl)hydrazine (4b)

Yield: 80%; **M.pt:** 235°C (Lit. M.pt(Alegaon et al. **2017**): 238-240°C); **IR (v_{max} cm^{-1}, KBr):** 3317 (NH Stretch), 1651 (C=N Stretch), 1574 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-*d*$_6$):** 12.01 (s, 1H, NH), 8.91 (s, 1H, -CH=N), 8.16 (s, 1H, pyrazole-H$_5$), 7.98 (d, *J* = 7.7 Hz, 2H, H$_7$/H$_{11}$), 7.87 (d, *J* = 8.6 Hz, 2H, H$_{13}$/H$_{17}$), 7.81 (d, *J* = 8.5 Hz, 2H, H$_{28}$/H$_{30}$), 7.73 (d, *J* = 8.5 Hz, 2H, H$_{27}$/H$_{31}$), 7.57-7.53 (m, 2H, H$_8$/H$_{10}$), 7.46 (d, *J* = 8.6 Hz, 2H, H$_{14}$/H$_{16}$), 7.43-7.33 (m, 2H, H$_9$, thiazole-H$_{23}$); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-*d*$_6$):** 168.03, 149.40, 149.20, 138.91, 134.53, 133.52, 131.84, 131.55, 131.41, 130.51, 129.59, 128.58, 127.17, 126.96, 121.81, 118.68, 116.96, 104.28; **Anal. Calc. For C$_{25}$H$_{17}$BrClN$_5$S:** C, 56.14; H, 3.20; N, 13.09. **Found:** C, 56.09; H, 3.17; N, 13.02.

1-((3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4c)

Yield: 88%; **M.pt:** 258°C (Lit. M.pt(Alegaon et al. **2017**): 248-250°C); **IR (v_{max} cm^{-1}, KBr):** 3326 (NH Stretch), 1598 (C=N Stretch), 1580 (C=C Stretch), 1505, 1340 (NO$_2$ Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-*d*$_6$):** 12.11 (s, 1H, NH), 8.93 (s, 1H, -CH=N), 8.27 (d, *J* = 8.9 Hz, 2H, H$_{28}$/H$_{30}$), 8.17 (s, 1H, pyrazole-H$_5$), 8.10 (d, *J* = 8.9 Hz, 2H, H$_{27}$/H$_{31}$), 7.98 (d, *J* = 7.8 Hz, 2H, H$_7$/H$_{11}$), 7.80 (d, *J* = 8.5 Hz, 2H, H$_{13}$/H$_{17}$), 7.73 (d, *J* = 8.5 Hz, 2H, H$_{14}$/H$_{16}$), 7.71(s, 1H, thiazole-H$_{23}$), 7.57-7.53 (m, 2H, H$_8$/H$_{10}$), 7.39 (t, *J* = 7.4 Hz, 1H, H$_9$); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-*d*$_6$):** 168.32, 149.44, 148.42, 146.14, 140.65, 138.89, 134.93, 131.54, 131.42, 130.52, 129.60, 128.66, 126.98, 126.28, 124.09, 121.84, 118.69, 116.87, 108.41; **Anal. Calc. For C$_{25}$H$_{17}$BrN$_6$O$_2$S:** C, 55.05; H, 3.14; N, 15.41. **Found:** C, 55.01; H, 3.08; N, 15.38.

1-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4d)

Yield: 82%; **M.pt:** 210°C (Lit. M.pt(Alegaon et al. **2017**): 223-225°C); **IR (v_{max} cm^{-1}, KBr):** 3310 (NH Stretch), 1612 (C=N Stretch), 1599 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-*d*$_6$):** 11.87 (s, 1H, NH), 8.74 (s, 1H, -CH=N), 8.16 (s, 1H, pyrazole-H$_5$), 7.95 (d, *J* = 7.7 Hz, 2H, H$_7$/H$_{11}$), 7.78 (d, *J* = 8.6 Hz, 2H, H$_{27}$/H$_{31}$), 7.74 (d, *J* = 8.8 Hz, 2H, H$_{13}$/H$_{17}$), 7.55-7.50 (m, 4H, H$_{28}$/H$_{30}$, H$_8$/H$_{10}$), 7.36-7.32 (m, 1H, H$_9$), 7.25 (s, 1H, thiazole-H$_{23}$), 7.06 (d, *J* = 8.8 Hz, 2H, H$_{14}$/H$_{16}$), 3.86 (s, 3H, -OCH$_3$); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-*d*$_6$):** 168.11, 159.41, 151.92, 150.63, 139.06, 134.87, 132.84, 131.27, 129.62, 129.33, 127.35, 127.04, 126.48, 124.67, 120.36, 118.49, 116.67, 113.78, 111.38, 55.0; **Anal. Calc. For C$_{26}$H$_{20}$BrN$_5$OS:** C, 58.87; H, 3.80; N, 13.20. **Found:** C, 58.85; H, 3.75; N, 13.11.

1-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (4e)

Yield: 83%; **M.pt:** 190°C (Lit. M.pt(Alegaon et al. **2017**): 236-238°C); **IR (v_{max} cm^{-1}, KBr):** 3310 (NH Stretch), 1612 (C=N Stretch), 1565 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-*d*$_6$):** 11.88 (s, 1H, NH), 8.74 (s, 1H, -CH=N), 8.15 (s, 1H, pyrazole-H$_5$), 7.95-7.92 (m, 2H, H$_7$/H$_{11}$), 7.84-7.82 (m, 2H, H$_{27}$/H$_{31}$), 7.73 (d, *J* = 8.4 Hz, 2H, H$_{13}$/H$_{17}$), 7.52-7.48 (m, 2H, H$_8$/H$_{10}$), 7.40-7.38 (m, 2H, H$_{28}$/H$_{30}$), 7.34-7.30 (m, 1H, H$_9$), 7.22 (s, 1H, thiazole-H$_{23}$), 7.05-7.03(m, 2H, H$_{14}$/H$_{16}$), 3.84 (s, 3H, OCH$_3$); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-*d*$_6$):** 55.07, 103.72, 113.77, 115.91, 116.68, 118.48, 124.68, 126.46, 127.03, 128.36, 129.32, 129.63, 131.91, 133.50, 134.86, 139.07, 149.23, 150.64, 159.41, 168.10; **ESI-MS (m/z):** 486.25 (M+H), 488.27 (M+H+2); **Anal. Calc. For C$_{26}$H$_{20}$ClN$_5$OS:** C, 64.26; H, 4.15; N, 14.41. **Found:** C, 64.17; H, 4.09; N, 14.35.

1-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl) thiazol-2-yl)hydrazine (4f)

Yield: 89%; **M.pt:** 230°C (Lit. M.pt(Alegaon et al. **2017**): 248-250°C); **IR (v_{max} cm^{-1}, KBr):** 3314 (NH Stretch), 1599 (C=N Stretch), 1509, 1343 (NO_2 Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 12.07 (s, 1H, NH), 8.87 (s, 1H, -CH=N), 8.28 (d, *J* = 8.9 Hz, 2H, H_{28}/H_{30}), 8.17 (s, 1H, pyrazole-H_5), 8.10 (d, 2H, *J* = 8.9 Hz, H_{27}/H_{31}), 7.98 (d, *J* = 7.6 Hz, 2H, H_7/H_{11}), 7.74 (d, *J* = 8.8 Hz, 2H, H_{13}/H_{17}), 7.71 (s, 1H, thiazole-H_{23}), 7.57-7.53 (m, 2H, H_8/H_{10}), 7.39-7.35 (m, 1H, H_9), 7.09 (d, *J* = 8.8 Hz, 2H, H_{14}/H_{16}), 3.85 (s, 3H, -OCH_3); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.38, 159.49, 150.71, 148.40, 146.14, 140.68, 139.03, 135.40, 129.78, 129.55, 127.63, 126.73, 126.28, 124.59, 124.09, 118.60, 116.53, 113.93, 108.33**,** 55.23; **Anal. Calc. For $C_{26}H_{20}N_6O_3S$:** C, 62.89; H, 4.06; N, 16.93. **Found:** C, 62.78; H, 3.95; N, 16.87.

1-((3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4g)

Yield: 85%; **M.pt:** 232.2-234.1°C; **IR (v_{max} cm^{-1}, KBr):** 3454 (NH Stretch), 1595 (C=N Stretch), 1500 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 11.96 (s, 1H, NH), 8.87 (s, 1H, -CH=N), 8.17 (s, 1H, pyrazole-H_5), 7.99 (d, *J* = 7.7 Hz, 2H, H_7/H_{11}), 7.81 (d, *J* = 8.5 Hz, 2H, H_{27}/H_{31}), 7.70 (d, *J* = 8.0 Hz, 2H, H_{13}/H_{17}), 7.60 (d, *J* = 8.6 Hz, 2H, H_{28}/H_{30}), 7.57-7.53 (m, 2H, H_8/H_{10}), 7.39-7.34 (m, 4H, H_{14}/H_{16}, H_9, thiazole-H_{23}), 2.41 (s, 3H, -CH_3); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.58, 151.34, 149.75, 139.55, 138.38, 137.85, 135.47, 134.41, 131.97, 130.04, 129.88, 129.61, 128.79, 127.99, 127.27, 120.91, 119.17, 117.31, 104.79, 21.39; **Anal. Calc. For $C_{26}H_{20}BrN_5S$:** C, 60.70; H, 3.92; N, 13.61. **Found:** C, 60.64; H, 3.87; N, 13.58.

1-((3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (4h)

Yield: 87%; **M.pt:** 200-203°C; **IR (v_{max} cm^{-1}, KBr):** 3456 (NH Stretch), 1579 (C=N Stretch), 1500 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 11.97 (s, 1H, NH), 8.87 (s, 1H, -CH=N), 8.17 (s, 1H, pyrazole-H_5), 7.99 (d, *J* = 7.9 Hz, 2H, H_7/H_{11}), 7.87 (d, *J* = 8.5 Hz, 2H, H_{27}/H_{31}), 7.70 (d, *J* = 8.0 Hz, 2H, H_{13}/H_{17}), 7.55 (t, *J* = 7.9 Hz, 2H, H_8/H_{10}), 7.47 (d, *J* = 8.6 Hz, 2H, H_{28}/H_{30}), 7.37 (m, 4H, H_{14}/H_{16}, H_9, thiazole-H_{23}), 2.40 (s, 3H, -CH_3); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.58, 151.34, 149.70, 139.55, 138.38, 135.45, 134.07, 132.33, 130.03, 129.88, 129.61, 129.06, 128.79, 127.96, 127.67, 127.26, 119.17, 117.32, 104.69, 21.38; **Anal. Calc. For $C_{26}H_{20}ClN_5S$:** C, 66.45; H, 4.29; N, 14.90. **Found:** C, 66.40; H, 4.25; N, 14.86.

1-((3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4i)

Yield: 83%; **M.pt:** 244-246°C; **IR (v_{max} cm^{-1}, KBr):** 3315 (NH Stretch), 1604 (C=N Stretch), 1500, 1344 (NO_2 Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 12.08 (s, 1H, NH), 8.89 (s, 1H, -CH=N), 8.28 (d, *J* = 8.9 Hz, 2H, H_{28}/H_{30}), 8.18 (s, 1H, pyrazole-H_5), 8.11 (d, *J* = 8.9 Hz, 2H, H_{27}/H_{31}), 8.00 (d, *J* = 7.7 Hz, 2H, H_7/H_{11}), 7.71-7.68 (m, 3H, H_{13}/H_{17}, thiazole-H_{23}), 7.55 (t, *J* = 7.9 Hz, 2H, H_8/H_{10}), 7.40-7.34 (m, 3H, H_{14}/H_{16}, H_9), 2.41 (s, 3H, CH_3); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.86, 151.39, 148.92, 146.65, 141.18, 139.53, 138.41, 135.83, 130.04, 129.85, 129.62, 128.80, 128.05, 127.29, 126.78, 124.57, 119.17, 117.22, 108.83, 21.39; **Anal. Calc. For $C_{26}H_{20}N_6O_2S$:** C, 64.99; H, 4.20; N, 17.49. **Found:** C, 64.96; H, 4.14; N, 17.43.

1-((3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol -2-yl)hydrazine (4j)

Yield: 79%; **M.pt:** 225.3-226.9°C; **IR (v_{max} cm^{-1}, KBr):** 3456 (NH Stretch), 1581 (C=N Stretch), 1502 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 11.97 (s, 1H, NH), 8.90 (s, 1H, -CH=N), 8.16 (s, 1H, pyrazole-H_5), 7.98 (d, *J* = 7.8 Hz, 2H, H_7/H_{11}), 7.89-7.8 (m, 2H, H_{13}/H_{17}), 7.80 (d, *J* = 8.5 Hz, 2H, H_{27}/H_{31}), 7.60 (d, *J* = 8.5 Hz, 2H, H_{28}/H_{30}), 7.56 (t, *J* = 7.9 Hz, 2H, H_8/H_{10}), 7.40-7.35 (m, 4H, H_{14}/H_{16}, H_9, thiazole-H_{23}); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.57, 163.94, 161.50, 158.26, 150.20, 139.47, 134.40, 131.98, 131.19, 131.11, 130.07, 129.34, 129.31, 128.79, 127.99, 127.36, 120.92, 119.16, 117.34, 115.97, 115.76, 104.82; **Anal. Calc. For $C_{25}H_{17}BrFN_5S$:** C, 57.92; H, 3.31; N, 13.51. **Found:** C, 57.87; H, 3.26; N, 13.44.

1-((3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl)thiazol -2-yl)hydrazine (4k)

Yield: 86%; **M.pt:** 215-218°C; **IR (v_{max} cm^{-1}, KBr):** 3454 (NH Stretch), 1560 (C=N Stretch), 1500 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 11.97 (s, 1H, NH), 8.90 (s, 1H, -CH=N), 8.16 (s, 1H, pyrazole-H_5), 7.99 (d, *J* = 7.7 Hz, 2H, H_7/H_{11}), 7.89-7.85 (m, 4H, H_{13}/H_{17}, H_{27}/H_{31}), 7.58-7.54 (m, 2H, H_8/H_{10}), 7.47 (d, *J* = 8.6 Hz, 2H, H_{28}/H_{30}), 7.40-7.35 (m, 4H, $H_{14}/H_{16,}$ H_9, thiazole-H_{23}); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.57, 161.50, 151.68, 150.20, 149.71, 139.47, 135.17, 134.06, 132.34, 131.20, 131.11, 130.07, 129.07, 128.79, 127.67, 127.37, 119.16, 117.34, 115.97, 115.76, 104.75; **Anal. Calc. For $C_{25}H_{17}ClFN_5S$:** C, 63.36; H, 3.62; N, 14.78. **Found:** C, 63.31; H, 3.57; N, 14.73.

1-((3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4l)

Yield: 78%; **M.pt:** 258.4-260°C; **IR (v_{max} cm^{-1}, KBr):** 3454 (NH Stretch), 1585 (C=N Stretch), 1510, 1344 (NO_2 Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 12.08 (s, 1H, NH), 8.92 (s, 1H, -CH=N), 8.28 (d, *J* = 8.9 Hz, 2H, H_{28}/H_{30}), 8.17 (s, 1H, pyrazole-H_5), 8.10 (d, *J* = 8.9 Hz, 2H, H_{27}/H_{31}), 7.98 (d, *J* = 7.8 Hz, 2H, H_7/H_{11}), 7.90-7.85 (m, 2H, H_{13}/H_{17}), 7.69 (s, 1H, thiazole-H_{23}), 7.56 (t, *J* = 7.9 Hz, 1H, H_8/H_{10}), 7.41-7.35 (m, 3H, H_{14}/H_{16}, H_9); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.87, 150.25, 148.92, 146.67, 141.18, 139.46, 135.94, 135.56, 131.21, 131.12, 130.07, 129.33, 128.90, 127.39, 126.79, 124.57, 119.17, 117.26, 115.98, 115.77, 108.86; **Anal. Calc. For $C_{25}H_{17}FN_6O_2S$:** C, 61.98; H, 3.54; N, 17.35. **Found:** C, 61.94; H, 3.48; N, 17.29.

1-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4m)

Yield: 71%; **M.pt:** 223-225°C (Lit. M.pt(Alegaon et al. **2017**): 248-250°C); **IR (ν_{max} cm^{-1}, KBr):** 3421 (NH Stretch), 1570 (C=N Stretch), 1500 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 12.01 (s, 1H, NH), 8.91 (s, 1H, -CH=N), 8.16 (s, 1H, pyrazole-H_5), 7.98 (d, J = 7.5 Hz, 2H, H_7/H_{11}), 7.87 (d, J = 8.5 Hz, 2H, H_{27}/H_{31}), 7.80 (d, J = 8.5 Hz, 2H, H_{28}/H_{30}), 7.61-7.53 (m, 6H, H_{13}/H_{17}, H_{14}/H_{16}, H_8/H_{10}), 7.40-7.36 (m, 2H, H_9, thiazole-H_{23}); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.02, 149.34, 138.89, 134.55, 133.85, 133.14, 131.48, 131.19, 130.23, 129.58, 129.14, 128.54, 128.48, 127.47, 126.94, 120.42, 118.66, 116.95, 104.35; **Anal. Calc. For $C_{25}H_{17}BrClN_5S$:** C, 56.14; H, 3.20; N, 13.09. **Found:** C, 56.09; H, 3.15; N, 13.03.

1-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (4n)

Yield: 82%; **M.pt:** 234-235°C (Lit. M.pt(Alegaon et al. **2017**): 183-185°C); **IR (ν_{max} cm^{-1}, KBr):** 3439 (NH Stretch), 1581 (C=N Stretch), 1494 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 12.01 (s, 1H, NH), 8.91 (s, 1H, -CH=N), 8.16 (s, 1H, pyrazole-H_5), 7.98 (d, J = 7.7 Hz, 2H, H_7/H_{11}), 7.88-7.85 (m, 4H, H_{13}/H_{17}, H_{27}/H_{31}), 7.60-7.53 (m, 4H, H_{28}/H_{30}, H_8/H_{10}), 7.46 (d, J = 8.6 Hz, 2H, H_{14}/H_{16}), 7.40-7.36 (m, 2H, H_9, thiazole-H_{23}); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.03, 149.33, 149.16, 138.89, 134.54, 133.51, 133.14, 131.83, 131.19, 130.23, 129.58, 128.57, 128.54, 128.48, 127.16, 126.93, 118.66, 116.96, 104.25; **Anal. Calc. For $C_{25}H_{17}Cl_2N_5S$:** C, 61.23; H, 3.49; N, 14.28; **Found:** C, 61.18; H, 3.43; N, 14.24.

1-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4o)

Yield: 83%; **M.pt:** 265.8-266.4°C (Lit. M.pt(Alegaon et al. **2017**): 249-251°C); **IR (ν_{max} cm^{-1}, KBr):** 3433 (NH Stretch), 1591 (C=N Stretch), 1504, 1342 (NO_2 Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 12.10 (s, 1H, NH), 8.93 (s, 1H, -CH=N), 8.28 (d, J = 9.0 Hz, 2H, H_{28}/H_{30}), 8.18 (s, 1H, pyrazole-H_5), 8.10 (d, J = 8.9 Hz, 2H, H_{27}/H_{31}), 7.98 (d, J = 7.7 Hz, 2H, H_7/H_{11}), 7.88 (d, J = 8.5 Hz, 2H, H_{13}/H_{17}), 7.70 (s, 1H, thiazole-H_{23}), 7.60 (d, J = 8.5 Hz, 2H, H_{14}/H_{16}), 7.58-7.54 (m, 2H, H_8/H_{10}), 7.41-7.37 (t, J = 7.4 Hz, 1H, H_9); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.83, 149.90, 148.93, 146.67, 141.17, 139.42, 135.46, 133.67, 131.71, 130.74, 130.09, 129.17, 128.99, 127.46, 126.78, 124.57, 119.20, 117.39, 108.89; **Anal. Calc. For $C_{25}H_{17}ClN_6O_2S$:** C, 59.94; H, 3.42; N, 16.78. **Found:** C, 59.88; H, 3.38; N, 16.71.

((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-2-(4-(4-bromophenyl)thiazol-2-yl)hydrazine (4p)

Yield: 81%; **M.pt:** 214.7-215.6°C; **IR (ν_{max} cm^{-1}, KBr):** 3300 (NH Stretch), 1566 (C=N Stretch), 1548 (C=C Stretch); **^{1}H-NMR (500 MHz, δ (ppm) DMSO-d_6):** 11.99 (s, 1H, NH), 8.90 (s, 1H, -CH=N), 8.18 (s, 1H, pyrazole-H_5), 8.00 (d, J = 7.7 Hz, 2H, H_7/H_{11}), 7.83-7.79 (m, 4H, H_{27}/H_{31}, H_{13}/H_{17}), 7.60 (d, J = 8.6 Hz, 2H, H_{28}/H_{30}), 7.57-7.53 (m, 4H, H_{14}/H_{16}, H_8/H_{10}), 7.50-7.46 (m, 1H, H_{15}), 7.39-7.36 (m, 2H, H_9, thiazole-H_{23}); **^{13}C-NMR (125 MHz, δ (ppm) DMSO-d_6):** 168.56, 151.45, 151.30, 149.74, 139.52, 135.28, 134.38, 132.74, 131.98, 130.06, 129.03, 128.95, 128.15, 127.98, 127.33, 120.92, 119.17, 117.40, 104.79; **Anal. Calc. For $C_{25}H_{18}BrN_5S$:** C, 60.00; H, 3.63; N, 14.00. **Found:** C, 59.95; H, 3.59; N, 13.93.

((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine (4q)

Yield: 82%; **M.pt:** 210-212°C; **IR (ν_{max} cm^{-1}, KBr):** 3307 (NH Stretch), 2920 (CH Stretch), 1597 (C=N Stretch), 1543 (C=C Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 11.97 (s, 1H, NH), 8.89 (s, 1H, -CH=N), 8.19 (s, 1H, pyrazole-H_5), 8.00 (d, J = 7.9 Hz, 2H, H_7/H_{11}), 7.87 (d, J = 8.5 Hz, 2H, H_{27}/H_{31}), 7.80 (d, J = 7.1 Hz, 2H, H_{13}/H_{17}), 7.58-7.53 (m, 4H, H_{28}/H_{30}, H_{14}/H_{16}), 7.50-7.45 (m, 3H, H_8/H_{10}, H_9), 7.41-7.37 (m, 2H, H_{15}, thiazole-H_{23}); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.57, 151.31, 149.70, 139.53, 135.30, 134.81 134.06, 132.76, 132.33, 130.05, 129.06, 129.02, 128.95, 128.15, 127.67, 127.33, 119.19, 117.42, 104.70. **Anal. Calc. For $C_{25}H_{18}ClN_5S$:** C, 65.85; H, 3.98; N, 15.36. **Found:** C, 65.79; H, 3.92; N, 15.32.

((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl) (4r)

Yield: 87%; **M.pt:** 239-241°C; **IR (ν_{max} cm^{-1}, KBr):** 3370 (NH Stretch), 2910 (C-H Stretch), 1611 (C=N Stretch), 1509, 1343 (NO_2 Stretch); **^{1}H-NMR (400 MHz, δ (ppm) DMSO-d_6):** 12.08 (s, 1H, NH), 8.91 (s, 1H, -CH=N), 8.28 (d, J = 8.9 Hz, 2H, H_{28}/H_{30}), 8.20 (s, 1H, pyrazole-H_5), 8.11 (d, J = 8.9 Hz, 2H, H_{27}/H_{31}), 8.00 (d, J = 7.8 Hz, 2H, H_7/H_{11}), 7.80 (d, J = 7.0 Hz, 2H, H_{13}/H_{17}), 7.71 (s, 1H, thiazole-H_{23}), 7.58-7.47 (m, 5H, H_{14}/H_{16}, H_8/H_{10}, H_9), 7.41-7.37 (m, 1H, H_{15}); **^{13}C-NMR (100 MHz, δ (ppm) DMSO-d_6):** 168.87, 167.94, 151.36, 148.93, 146.67, 141.19, 139.52, 135.69, 132.73, 130.07, 129.04, 128.97, 128.27, 127.37, 126.79, 124.58, 119.21, 117.33, 108.85; **Anal. Calc. For $C_{25}H_{18}N_6O_2S$:** C, 64.37; H, 3.89; N, 18.01. **Found:** C, 64.28; H, 3.82; N, 17.95.

Table S 1: Percentage of identity of splits 1–4.

Split	SET	Split 1(%)	Split 2(%)	Split 3(%)	Split 4(%)
Split 1	Total	100	0.0	0.0	0.0
	Training	100	0.0	0.0	0.0
	Invisible training	100	0.0	0.0	0.0
	Calibration	100	0.0	0.0	0.0
	Validation	100	0.0	0.0	0.0
Split 2	Total		100	0.0	0.0
	Training		100	0.0	0.0
	Invisible training		100	0.0	0.0
	Calibration		100	0.0	0.0
	Validation		100	0.0	0.0
Split 3	Total			100	3.7
	Training			100	7.4
	Invisible training			100	0.0
	Calibration			100	6.9
	Validation			100	0.0
Split 4	Total				100
	Training				100
	Invisible training				100
	Calibration				100
	Validation				100

Identity (%)= $[N_{ij}/0.5(N_i+N_j)]x100$
Where:
N_{ij} is the number of substances which are distributed into the same set for both i-th split and j-th split (set = training set, invisible training set, calibration set, validation set)
N_i is the number of substances which are distributed into the set for i-th split
N_j is the number of substances which are distributed into the set for j-th split

Table S 2: Details of statistical outcomes by using IIC.

Split				Compound	ID for different concentration	SMILES	Expt % inhibition	Calc % inhibition				Expt-Calc				Applicability			
1	2	3	4					Split 1	Split 2	Split 3	Split 4	Split 1	Split 2	Split 3	Split 4	Split 1	Split 2	Split 3	Split 4
+	-	#	*	4a	TCPH01	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1$	82.7200	80.3973	85.9843	87.4776	83.5057	2.3227	-3.2643	-4.7576	-0.7857	YES	YES	YES	YES
-	+	*	#	4b	TCPH02	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1$	80.3300	84.0411	81.5449	86.4629	81.9629	-3.7111	-1.2149	-6.1329	-1.6329	YES	YES	YES	YES
#	*	-	+	4c	TCPH03	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1$~	82.9000	82.8377	86.3826	83.1111	85.3661	0.0623	-3.4826	-0.2111	-2.4661	YES	YES	YES	YES
*	#	+	+	4d	TCPH04	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1$	79.0400	85.2571	84.8946	87.5607	82.9479	-6.2171	-5.8546	-8.5207	-3.9079	YES	YES	YES	YES
+	-	#	*	4e	TCPH05	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1$	82.1700	85.3417	86.7923	87.2476	82.9358	-3.1717	-4.6223	-5.0776	-0.7658	YES	YES	YES	YES
-	+	*	#	4f	TCPH06	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1$~	77.9400	74.8375	75.5110	81.2405	70.8667	3.1025	2.4290	-3.3005	7.0733	YES	YES	YES	YES
#	*	-	+	4g	TCPH07	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1$	89.1500	83.2757	86.7237	86.6281	80.4886	5.8743	2.4263	2.5219	8.6614	YES	YES	YES	YES
*	#	+	-	4h	TCPH08	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1$	88.4200	83.3602	88.6214	86.3150	80.4765	5.0598	-0.2014	2.1050	7.9435	YES	YES	YES	YES
+	-	#	*	4i	TCPH09	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1$	79.9600	74.6614	76.8717	81.2039	69.1598	5.2986	3.0883	-1.2439	10.8002	YES	YES	YES	YES
-	+	*	#	4j	TCPH10	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1$	81.2500	83.0308	81.3814	85.5845	78.1591	-1.7808	-0.1314	-4.3345	3.0909	YES	YES	YES	YES
#	*	-	+	4k	TCPH11	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1$	77.2100	82.9798	84.7686	86.2406	78.1285	-5.7698	-7.5586	-9.0306	-0.9185	YES	YES	YES	**NO**
*	#	+	-	4l	TCPH12	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(F)cc2)-c2ccccc2)n1$	86.0300	82.1081	86.2920	83.6930	78.2312	3.9219	-0.2620	2.3370	7.7988	YES	YES	YES	YES
+	-	#	*	4m	TCPH13	Clc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1$	83.8200	86.8886	85.2384	84.6894	82.0576	-3.0686	-1.4184	-0.8694	1.7624	YES	YES	YES	YES
-	+	*	#	4n	TCPH14	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1$	84.7400	80.4946	84.9270	87.1191	82.7089	4.2454	-0.1870	-2.3791	2.0311	YES	YES	YES	YES
#	*	-	+	4o	TCPH15	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1$	81.9900	82.9222	88.2803	82.7980	85.3540	-0.9322	-6.2903	-0.8080	-3.3640	YES	YES	YES	YES
*	#	+	-	4p	TCPH16	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1$	85.1800	75.6016	74.9436	82.2290	76.9287	9.5784	10.2364	2.9510	8.2513	YES	YES	YES	YES
+	-	#	*	4q	TCPH17	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1$	70.0400	75.7499	72.4322	81.2143	76.2013	-5.7099	-2.3922	-11.1743	-6.1613	YES	YES	YES	YES
-	+	*	#	4r	TCPH18	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1$	78.1300	78.0231	75.7951	76.8932	75.7489	0.1069	2.3349	1.2368	2.3811	YES	YES	YES	YES
#	*	-	+	4a	TCPH19	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1%	61.2100	65.9414	69.9739	69.6469	68.1737	-4.7314	-8.7639	-8.4369	-6.9637	YES	YES	YES	YES
*	#	+	-	4b	TCPH20	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1%	68.3800	69.5853	65.5345	68.6323	66.6309	-1.2053	2.8455	-0.2523	1.7491	YES	YES	YES	YES
+	-	#	*	4c	TCPH21	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1%	71.5100	68.3818	70.3722	65.2804	70.0342	3.1282	1.1378	6.2296	1.4758	YES	YES	YES	YES
-	+	*	#	4d	TCPH22	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-	67.4600	70.9963	69.3704	69.7300	71.4846	-3.5363	-1.9104	-2.2700	-4.0246	YES	YES	YES	YES

						c1ccc(Br)cc1)-c1ccccc1%												
#	*	-	+	4e	TCPH23	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1%	75.5500	71.0809	71.2680	69.4169	71.4725	4.4691	4.2820	6.1331	4.0775	YES	YES	YES	YES
*	#	+	-	4f	TCPH24	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1%	64.7100	60.5768	59.9867	63.4098	59.4034	4.1332	4.7233	1.3002	5.3066	YES	YES	YES	YES
+	-	#	*	4g	TCPH25	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1%	72.0600	69.0149	71.1995	68.7974	69.0253	3.0451	0.8605	3.2626	3.0347	YES	YES	YES	YES
-	+	*	#	4h	TCPH26	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1%	71.6900	69.0995	73.0971	68.4843	69.0132	2.5905	-1.4071	3.2057	2.6768	YES	YES	YES	YES
#	*	-	+	4i	TCPH27	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1%	52.2100	60.4006	61.3474	63.3733	57.6965	-8.1906	-9.1374	-11.1633	-5.4865	YES	YES	YES	YES
*	#	+	-	4j	TCPH28	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1%	70.5900	68.7700	65.8571	67.7538	66.6958	1.8200	4.7329	2.8362	3.8942	YES	YES	YES	YES
+	-	#	*	4k	TCPH29	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1%	64.7100	68.7190	69.2443	68.4100	66.6651	-4.0090	-4.5343	-3.7000	-1.9551	YES	YES	YES	**NO**
-	+	*	#	4l	TCPH30	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(F)cc2)-c2ccccc2)n1%	67.8300	67.6522	70.2815	65.8623	62.8993	0.1778	-2.4515	1.9677	4.9307	YES	YES	YES	YES
#	*	-	+	4m	TCPH31	Clc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1%	76.8400	72.6278	69.7141	66.8588	70.5943	4.2122	7.1259	9.9812	6.2457	YES	YES	YES	YES
*	#	+	-	4n	TCPH32	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1%	71.3200	66.0388	68.9166	69.2884	67.3769	5.2812	2.4034	2.0316	3.9431	YES	YES	YES	YES
+	-	#	*	4o	TCPH33	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1%	67.1000	68.4664	72.2698	64.9673	70.0220	-1.3664	-5.1698	2.1327	-2.9220	YES	YES	YES	YES
-	+	*	#	4p	TCPH34	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1%	61.4000	61.1457	58.9332	64.3983	61.5968	0.2543	2.4668	-2.9983	-0.1968	YES	YES	YES	YES
#	*	-	+	4q	TCPH35	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1%	58.8200	61.2941	56.4218	63.3836	60.8693	-2.4741	2.3982	-4.5636	-2.0493	YES	YES	YES	YES
*	#	+	-	4r	TCPH36	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1%	60.4800	63.5672	59.7847	59.0625	60.4169	-3.0872	0.6953	1.4175	0.0631	YES	YES	YES	YES
+	-	#	*	4a	TCPH37	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1&	56.8000	53.4687	64.6193	61.2471	59.6422	3.3313	-7.8193	-4.4471	-2.8422	YES	YES	YES	YES
-	+	*	#	4b	TCPH38	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1&	61.0300	57.1126	60.1798	60.2324	58.0994	3.9174	0.8502	0.7976	2.9306	YES	YES	YES	YES
#	*	-	+	4c	TCPH39	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1&~	68.5700	55.9091	65.0176	56.8806	61.5026	12.6609	3.5524	11.6894	7.0674	YES	YES	YES	YES
*	#	+	-	4d	TCPH40	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1&	58.8200	61.9894	64.9966	61.3302	64.4270	-3.1694	-6.1766	-2.5102	-5.6070	YES	YES	YES	YES
+	-	#	*	4e	TCPH41	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1&	69.4900	62.0739	66.8942	61.0171	64.4149	7.4161	2.5958	8.4729	5.0751	YES	YES	YES	YES
-	+	*	#	4f	TCPH42	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1&~	55.1500	51.5698	55.6130	55.0100	52.3458	3.5802	-0.4630	0.1400	2.8042	YES	YES	YES	YES
#	*	-	+	4g	TCPH43	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1&	65.8100	60.0080	66.8257	60.3976	61.9677	5.8020	-1.0157	5.4124	3.8423	YES	YES	YES	YES
*	#	+	-	4h	TCPH44	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1&	62.1300	60.0925	68.7233	60.0845	61.9556	2.0375	-6.5933	2.0455	0.1744	YES	YES	YES	YES
+	-	#	*	4i	TCPH45	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1&	48.3500	51.3937	56.9736	54.9734	50.6389	-3.0437	-8.6236	-6.6234	-2.2889	YES	YES	YES	YES
-	+	*	#	4j	TCPH46	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1&	57.3500	59.7630	61.4833	59.3540	59.6382	-2.4130	-4.1333	-2.0040	-2.2882	YES	YES	YES	YES
#	*	-	+	4k	TCPH47	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-	60.2900	59.7120	64.8705	60.0101	59.6076	0.5780	-4.5805	0.2799	0.6824	YES	YES	YES	**NO**

						c1ccc(Cl)cc1)-c1ccccc1&												
*	#	+	-	4l	TCPH48	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(F)cc2)-c2ccccc2)n1&	55.3300	55.1795	64.9269	57.4625	54.3677	0.1505	-9.5969	-2.1325	0.9623	YES	YES	YES	YES
+	-	#	*	4m	TCPH49	Clc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1&	67.2800	63.6209	65.3403	58.4589	63.5368	3.6591	1.9397	8.8211	3.7432	YES	YES	YES	YES
-	+	*	#	4n	TCPH50	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1&	68.8700	53.5660	63.5619	60.8886	58.8454	15.3040	5.3081	7.9814	10.0246	YES	YES	YES	YES
#	*	-	+	4o	TCPH51	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1&	56.0700	55.9937	66.9152	56.5675	61.4905	0.0763	-10.8452	-0.4975	-5.4205	YES	YES	YES	YES
*	#	+	-	4p	TCPH52	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1&	52.3900	48.6730	53.5785	55.9985	53.0652	3.7170	-1.1885	-3.6085	-0.6752	YES	YES	YES	YES
+	-	#	#	4q	TCPH53	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1&	40.9900	48.8213	51.0671	54.9838	52.3377	-7.8313	-10.0771	-13.9938	-11.3477	YES	YES	YES	YES
-	+	*	#	4r	TCPH54	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1&	52.9400	51.0945	54.4301	50.6627	51.8854	1.8455	-1.4901	2.2773	1.0546	YES	YES	YES	YES

Table S 3: Details of statistical outcomes without IIC

Split				Compound	ID for different concentration	SMILES	Expt % inhibition	Calc % inhibition				Expt-Calc				Applicability			
1	2	3	4					Split 1	Split 2	Split 3	Split 4	Split 1	Split 2	Split 3	Split 4	Split 1	Split 2	Split 3	Split 4
+	-	#	*	4a	TCPH01	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1$	82.7200	83.3162	86.9254	84.3608	84.9704	-0.5962	-4.2054	-1.6408	-2.2504	YES	YES	YES	YES
-	+	*	#	4b	TCPH02	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1$	80.3300	82.6811	83.5198	87.1583	90.6121	-2.3511	-3.1898	-6.8283	-10.2821	YES	YES	YES	YES
#	*	-	+	4c	TCPH03	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1$~	82.9000	85.6566	89.7685	87.6546	84.4887	-2.7566	-6.8685	-4.7546	-1.5887	YES	YES	YES	YES
*	#	+	+	4d	TCPH04	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1$	79.0400	85.7344	90.5941	87.8280	82.3092	-6.6944	-11.5541	-8.7880	-3.2692	YES	YES	YES	YES
+	-	#	*	4e	TCPH05	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1$	82.1700	87.5803	88.8403	85.5019	82.2821	-5.4103	-6.6703	-3.3319	-0.1121	YES	YES	YES	YES
-	+	*	#	4f	TCPH06	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1$~	77.9400	74.1167	75.8866	75.7363	70.6417	3.8233	2.0534	2.2037	7.2983	YES	YES	YES	YES
#	*	-	+	4g	TCPH07	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1$	89.1500	88.6285	92.4363	89.1927	84.7200	0.5215	-3.2863	-0.0427	4.4300	YES	YES	YES	YES
*	#	+	-	4h	TCPH08	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1$	88.4200	90.4745	90.6824	86.8666	84.6930	-2.0545	-2.2624	1.5534	3.7270	YES	YES	YES	YES
+	-	#	*	4i	TCPH09	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1$	79.9600	76.4410	81.1618	75.6813	70.6222	3.5190	-1.2018	4.2787	9.3378	YES	YES	YES	YES
-	+	*	#	4j	TCPH10	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1$	81.2500	77.6634	78.4969	86.3616	79.8238	3.5866	2.7531	-5.1116	1.4262	YES	YES	YES	YES
#	*	-	+	4k	TCPH11	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1$	77.2100	83.1784	87.1322	86.8243	78.1679	-5.9684	-9.9222	-9.6143	-0.9579	YES	YES	YES	**NO**
*	#	+	-	4l	TCPH12	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(F)cc2)-c2ccccc2)n1$	86.0300	83.0806	80.9623	80.4185	83.3255	2.9494	5.0677	5.6115	2.7045	YES	YES	YES	YES
+	-	#	*	4m	TCPH13	Clc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1$	83.8200	84.9385	87.3152	91.2716	83.9002	-1.1185	-3.4952	-7.4516	-0.0802	YES	YES	YES	YES
-	+	*	#	4n	TCPH14	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1$	84.7400	83.9362	85.1793	87.6210	84.0838	0.8038	-0.4393	-2.8810	0.6562	YES	YES	YES	YES
#	*	-	+	4o	TCPH15	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1$	81.9900	87.5025	88.0147	85.3285	84.4617	-5.5125	-6.0247	-3.3385	-2.4717	YES	YES	YES	YES
*	#	+	-	4p	TCPH16	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1$	85.1800	72.1797	76.9099	77.1675	78.0162	13.0003	8.2701	8.0125	7.1638	YES	YES	YES	YES
+	-	#	*	4q	TCPH17	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1$	70.0400	69.7579	73.5050	79.9650	78.7956	0.2821	-3.4650	-9.9250	-8.7556	YES	YES	YES	YES
-	+	*	#	4r	TCPH18	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1$	78.1300	73.3282	74.5167	77.6725	79.1911	4.8018	3.6133	0.4575	-1.0611	YES	YES	YES	YES
#	*	-	+	4a	TCPH19	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1%	61.2100	66.3301	72.5343	68.4292	65.6453	-5.1201	-11.3243	-7.2192	-4.4353	YES	YES	YES	YES
*	#	+	-	4b	TCPH20	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1%	68.3800	65.6950	69.1287	71.2267	71.2870	2.6850	-0.7487	-2.8467	-2.9070	YES	YES	YES	YES
+	-	#	*	4c	TCPH21	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1%	71.5100	68.6705	75.3774	71.7230	65.1637	2.8395	-3.8674	-0.2130	6.3463	YES	YES	YES	YES
-	+	*	#	4d	TCPH22	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1%	67.4600	66.9290	72.6547	71.8964	71.0791	0.5310	-5.1947	-4.4364	-3.6191	YES	YES	YES	YES

#	*	-	+	4e	TCPH23	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1%	75.5500	68.7749	70.9008	69.5703	71.0521	6.7751	4.6492	5.9797	4.4979	YES	YES	YES	YES
*	#	+	-	4f	TCPH24	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1%	64.7100	55.3113	57.9472	59.8047	59.4116	9.3987	6.7628	4.9053	5.2984	YES	YES	YES	YES
+	-	#	*	4g	TCPH25	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1%	72.0600	69.8231	74.4968	73.2611	73.4899	2.2369	-2.4368	-1.2011	-1.4299	YES	YES	YES	YES
-	+	*	#	4h	TCPH26	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1%	71.6900	71.6690	72.7430	70.9350	73.4629	0.0210	-1.0530	0.7550	-1.7729	YES	YES	YES	YES
#	*	-	+	4i	TCPH27	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1%	52.2100	57.6356	63.2224	59.7497	59.3921	-5.4256	-11.0124	-7.5397	-7.1821	YES	YES	YES	YES
*	#	+	-	4j	TCPH28	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1%	70.5900	58.8580	60.5575	70.4300	68.5938	11.7320	10.0325	0.1600	1.9962	YES	YES	YES	YES
+	-	#	*	4k	TCPH29	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1%	64.7100	64.3730	69.1928	70.8928	66.9378	0.3370	-4.4828	-6.1828	-2.2278	YES	YES	YES	**NO**
-	+	*	#	4l	TCPH30	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(F)cc2)-c2ccccc2)n1%	67.8300	66.0945	66.5711	64.4869	64.0005	1.7355	1.2589	3.3431	3.8295	YES	YES	YES	YES
#	*	-	+	4m	TCPH31	Clc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1%	76.8400	66.1331	69.3757	75.3400	72.6701	10.7069	7.4643	1.5000	4.1699	YES	YES	YES	YES
*	#	+	-	4n	TCPH32	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1%	71.3200	66.9501	70.7882	71.6894	64.7587	4.3699	0.5318	-0.3694	6.5613	YES	YES	YES	YES
+	-	#	*	4o	TCPH33	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1%	67.1000	70.5164	73.6235	69.3969	65.1367	-3.4164	-6.5235	-2.2969	1.9633	YES	YES	YES	YES
-	+	*	#	4p	TCPH34	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1%	61.4000	55.1936	62.5188	61.2359	58.6911	6.2064	-1.1188	0.1641	2.7089	YES	YES	YES	YES
#	*	-	+	4q	TCPH35	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1%	58.8200	52.7718	59.1138	64.0334	59.4705	6.0482	-0.2938	-5.2134	-0.6505	YES	YES	YES	YES
*	#	+	-	4r	TCPH36	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1%	60.4800	56.3422	60.1256	61.7409	59.8661	4.1378	0.3544	-1.2609	0.6139	YES	YES	YES	YES
+	-	#	*	4a	TCPH37	Brc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1&	56.8000	57.7383	65.4756	60.2027	60.0081	-0.9383	-8.6756	-3.4027	-3.2081	YES	YES	YES	YES
-	+	*	#	4b	TCPH38	Clc1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1&	61.0300	57.1032	62.0700	63.0002	65.6498	3.9268	-1.0400	-1.9702	-4.6198	YES	YES	YES	YES
#	*	-	+	4c	TCPH39	[O-][N+](=O)c1ccc(cc1)-c1csc(N\N=C\c2cn(nc2-c2ccc(Br)cc2)-c2ccccc2)n1&~	68.5700	60.0787	68.3187	63.4965	59.5264	8.4913	0.2513	5.0735	9.0436	YES	YES	YES	YES
*	#	+	-	4d	TCPH40	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1&	58.8200	62.6355	70.9803	63.6699	62.9936	-3.8155	-12.1603	-4.8499	-4.1736	YES	YES	YES	YES
+	-	#	*	4e	TCPH41	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1&	69.4900	64.4815	69.2264	61.3438	62.9666	5.0085	0.2636	8.1462	6.5234	YES	YES	YES	YES
-	+	*	#	4f	TCPH42	COc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1&~	55.1500	51.0178	56.2728	51.5782	51.3261	4.1322	-1.1228	3.5718	3.8239	YES	YES	YES	YES
#	*	-	+	4g	TCPH43	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1&	65.8100	65.5296	72.8224	65.0346	65.4044	0.2804	-7.0124	0.7754	0.4056	YES	YES	YES	YES
*	#	+	-	4h	TCPH44	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1&	62.1300	67.3756	71.0686	62.7084	65.3774	-5.2456	-8.9386	-0.5784	-3.2474	YES	YES	YES	YES
+	-	#	*	4i	TCPH45	Cc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(cc1)[N+]([O-])=O)-c1ccccc1&	48.3500	53.3421	61.5480	51.5231	51.3066	-4.9921	-13.1980	-3.1731	-2.9566	YES	YES	YES	YES
-	+	*	#	4j	TCPH46	Fc1ccc(cc1)-c1nn(cc1\C=N\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1&	57.3500	54.5645	58.8831	62.2035	60.5083	2.7855	-1.5331	-4.8535	-3.1583	YES	YES	YES	YES

#	*	-	+	4k	TCPH47	Fc1ccc(cc1)-c1nn(cc1\C=N\\Nc1nc(cs1)-c1ccc(Cl)cc1)-c1ccccc1&	60.2900	60.0795	67.5184	62.6662	58.8523	0.2105	-7.2284	-2.3762	1.4377	YES	YES	YES	**NO**
*	#	+	-	4l	TCPH48	[O-][N+](=O)c1ccc(cc1)-c1csc(N\\N=C\c2cn(nc2-c2ccc(F)cc2)-c2ccccc2)n1&	55.3300	57.5027	59.5125	56.2604	58.3632	-2.1727	-4.1825	-0.9304	-3.0332	YES	YES	YES	YES
+	-	#	*	4m	TCPH49	Clc1ccc(cc1)-c1nn(cc1\C=N\\Nc1nc(cs1)-c1ccc(Br)cc1)-c1ccccc1&	67.2800	61.8396	67.7013	67.1135	64.5846	5.4404	-0.4213	0.1665	2.6954	YES	YES	YES	YES
-	+	*	#	4n	TCPH50	Clc1ccc(cc1)-c1csc(N\\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1&	68.8700	58.3583	63.7295	63.4629	59.1214	10.5117	5.1405	5.4071	9.7486	YES	YES	YES	YES
#	*	-	+	4o	TCPH51	[O-][N+](=O)c1ccc(cc1)-c1csc(N\\N=C\c2cn(nc2-c2ccc(Cl)cc2)-c2ccccc2)n1&	56.0700	61.9246	66.5649	61.1704	59.4994	-5.8546	-10.4949	-5.1004	-3.4294	YES	YES	YES	YES
*	#	+	-	4p	TCPH52	Brc1ccc(cc1)-c1csc(N\\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1&	52.3900	46.6018	55.4601	53.0094	53.0539	5.7882	-3.0701	-0.6194	-0.6639	YES	YES	YES	YES
+	-	#	#	4q	TCPH53	Clc1ccc(cc1)-c1csc(N\\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1&	40.9900	44.1800	52.0552	55.8069	53.8333	-3.1900	-11.0652	-14.8169	-12.8433	YES	YES	YES	YES
-	+	*	#	4r	TCPH54	[O-][N+](=O)c1ccc(cc1)-c1csc(N\\N=C\c2cn(nc2-c2ccccc2)-c2ccccc2)n1&	52.9400	47.7504	53.0669	53.5144	54.2288	5.1896	-0.1269	-0.5744	-1.2888	YES	YES	YES	YES

Table S 4: External prediction criteria values for developed QSAR models of calibration and validation sets. Without IIC, using equation

Parameters	Calibration set				Validation set			
r2m(x,y):	Split 1	Split 2	Split 3	Split 4	Split 1	Split 2	Split 3	Split 4
r2	0.7683	0.6682	0.8008	0.7724	0.7629	0.7355	0.9088	0.7870
r20	0.7641	0.6232	0.7409	0.7454	0.7626	0.6633	0.9042	0.7716
rr20	0.7348	0.6461	0.8004	0.7666	0.7028	0.7348	0.8782	0.7772
(r2-r20)/r2	0.0054	0.0674	0.0749	0.0350	0.0004	0.0982	0.0051	0.0196
(r2-rr20)/r2	0.0435	0.0332	0.0005	0.0075	0.0787	0.0010	0.0337	0.0125
k	0.9956	1.0075	1.0358	1.0041	0.9617	1.0609	1.0128	0.9912
kk	0.9977	0.9831	0.9594	0.9887	1.0314	0.9363	0.9849	1.0045
R2m(test)	0.7189	0.5264	0.6047	0.6454	0.7498	0.5378	0.8469	0.6892
r2m(y, x):								
r2	0.7683	0.6682	0.8008	0.7724	0.7629	0.7355	0.9088	0.7870
r20	0.7348	0.6461	0.8004	0.7666	0.7028	0.7348	0.8782	0.7772
rr20	0.7641	0.6232	0.7409	0.7454	0.7626	0.6633	0.9042	0.7716
(r2-r20)/r2	0.0435	0.0332	0.0005	0.0075	0.0787	0.0010	0.0337	0.0125
(r2-rr20)/r2	0.0054	0.0674	0.0749	0.0350	0.0004	0.0982	0.0051	0.0196
K	0.9977	0.9831	0.9594	0.9887	1.0314	0.9363	0.9849	1.0045
Kk	0.9956	1.0075	1.0358	1.0041	0.9617	1.0609	1.0128	0.9912
R*2m(test)	0.6278	0.5687	0.7846	0.7136	0.5759	0.7155	0.7498	0.7089
R2m(av)	0.6733	0.5475	0.6947	0.6795	0.6629	0.6267	0.7984	0.6990
ΔR2m	0.0911	0.0423	0.1799	0.0682	0.1739	0.1777	0.0971	0.0197

$(r^2-r^2_0)/r^2$ should be <0.1; $(r^2-rr^2_0)/r^2$ should be <0.1; Should be 0.85 < k < 1.15; Should be 0.85 < kk < 1.15[65]; R^2_m(test) and R^{*2}_m(test) should be >0.5[66]; R^2_m (av) is average value of R^2_m and should be >0.5; ΔR^2_m should be < 0.2[67]

Table S 5: External prediction criteria values for developed QSAR models of calibration and validation sets. For SMILES with IIC using equation

Parameters	Calibration set				Validation set			
r2m(x,y):	Split 1	Split 2	Split 3	Split 4	Split 1	Split 2	Split 3	Split 4
r2	0.7681	0.7865	0.7162	0.8410	0.8728	0.7432	0.9198	0.8216
r20	0.7398	0.7376	0.6603	0.7945	0.8602	0.6732	0.9105	0.7944
rr20	0.7620	0.7863	0.7109	0.8397	0.8724	0.7427	0.8804	0.8210
(r2-r20)/r2	0.0368	0.0622	0.0780	0.0552	0.0144	0.0942	0.0101	0.0331
(r2-rr20)/r2	0.0080	0.0002	0.0075	0.0016	0.0004	0.0007	0.0428	0.0008
K	0.9831	0.9992	1.0170	0.9748	0.9727	1.0290	1.0084	0.9881
Kk	1.0111	0.9950	0.9745	1.0208	1.0245	0.9655	0.9893	1.0085
R2m(test)	0.6390	0.6126	0.5469	0.6598	0.7749	0.5465	0.8313	0.6861
r2m(y, x):								
r2	0.7681	0.7865	0.7162	0.8410	0.8728	0.7432	0.9198	0.8216
r20	0.7620	0.7863	0.7109	0.8397	0.8724	0.7427	0.8804	0.8210
rr20	0.7398	0.7376	0.6603	0.7945	0.8602	0.6732	0.9105	0.7944
(r2-r20)/r2	0.0080	0.0002	0.0075	0.0016	0.0004	0.0007	0.0428	0.0008
(r2-rr20)/r2	0.0368	0.0622	0.0780	0.0552	0.0144	0.0942	0.0101	0.0331
K	1.0111	0.9950	0.9745	1.0208	1.0245	0.9655	0.9893	1.0085
Kk	0.9831	0.9992	1.0170	0.9748	0.9727	1.0290	1.0084	0.9881
R*2m(test)	0.7080	0.7763	0.6638	0.8105	0.8555	0.7264	0.7372	0.8009
R2m(av)	0.6735	0.6944	0.6054	0.7351	0.8152	0.6365	0.7843	0.7435
ΔR2m	0.0691	0.1637	0.1169	0.1507	0.0807	0.1799	0.0941	0.1148

$(r^2\text{-}r^2_0)/r^2$ should be <0.1; $(r^2\text{-}rr^2_0)/r^2$ should be <0.1; Should be 0.85 < k < 1.15; Should be 0.85 < kk < 1.15[65]; R^2_m(test) and R^{*2}_m(test) should be >0.5[66]; R^2_m (av) is average value of R^2_m and should be >0.5; ΔR^2_m should be < 0.2[67]

Table S 6: Y-randomization results for four splits For Smiles Without IIC using equation

	Split 1			**Split 2**			**Split 3**			**Split4**		
	Train	InvTrain	Calib	Train	InvTrain	Calib	Train	InvTrain	Calib	Train	InvTrain	Calib
n	14	14	13	14	14	13	13	13	14	14	12	15
R^2	0.9243	0.9391	0.7683	0.9309	0.9256	0.6682	0.8653	0.8307	0.8008	0.8570	0.9076	0.7724
1	0.0768	0.0861	0.0974	0.0101	0.0797	0.0647	0.0188	0.0053	0.0000	0.0176	0.1338	0.0429
2	0.0397	0.0167	0.0178	0.0270	0.2223	0.2164	0.0301	0.1852	0.2827	0.0117	0.0009	0.0098
3	0.0043	0.0053	0.2240	0.0840	0.1464	0.0581	0.0300	0.0069	0.5824	0.1965	0.0047	0.0259
4	0.1800	0.0585	0.0001	0.0009	0.1123	0.1055	0.0477	0.0001	0.0289	0.1318	0.0325	0.0018
5	0.1118	0.0550	0.0129	0.0132	0.0337	0.0092	0.0590	0.0509	0.4836	0.0175	0.0983	0.0003
6	0.0942	0.0164	0.0909	0.0104	0.2889	0.0165	0.1196	0.0013	0.0323	0.1165	0.0058	0.0641
7	0.0694	0.0056	0.0126	0.1005	0.0008	0.0422	0.0067	0.0961	0.2894	0.0226	0.1426	0.0017
8	0.0249	0.1127	0.1619	0.0207	0.0145	0.0036	0.0008	0.0000	0.0113	0.0534	0.0092	0.0294
9	0.0697	0.0276	0.3001	0.0171	0.0016	0.0138	0.0550	0.0470	0.0039	0.0014	0.0007	0.3649
10	0.1926	0.1279	0.7496	0.1198	0.0453	0.2229	0.0051	0.0584	0.1778	0.0062	0.0524	0.0287
Rr^{2*}	0.0864	0.0512	0.1667	0.0404	0.0945	0.0753	0.0373	0.0451	0.1892	0.0575	0.0481	0.0569
$^{C}R^2_{p\ \#}$	0.8800	0.9132	0.6798	0.9105	0.8770	0.6295	0.8465	0.8079	0.6998	0.8277	0.8833	0.7434

* Average randomized R^2; # $^{C}R^2_p = R \times (R^2 - R^2_r)^{1/2}$ where $^{C}R^2_p$ should be greater than 0.5

Table S 7: Y-randomization results for four splits For Smiles With IIC using equation

	Split 1			Split 2			Split 3			Split4		
	Train	InvTrain	Calib	Train	InvTrain	Calib	Train	InvTrain	Calib	Train	InvTrain	Calib
N	14	14	13	14	14	13	13	13	14	14	12	15
R^2	0.8700	0.8355	0.7681	0.9438	0.9024	0.7865	0.9223	0.6517	0.7162	0.8006	0.9400	0.8410
1	0.3778	0.0877	0.0010	0.0722	0.2331	0.0104	0.0052	0.0042	0.1675	0.0101	0.0965	0.0618
2	0.0787	0.0228	0.0040	0.0356	0.0463	0.5848	0.2524	0.0615	0.2233	0.0272	0.0011	0.0284
3	0.0277	0.0459	0.0016	0.0081	0.0005	0.3146	0.0046	0.0015	0.0629	0.6171	0.0005	0.0022
4	0.0068	0.1821	0.0583	0.0088	0.0970	0.0395	0.1789	0.0100	0.0000	0.0103	0.0502	0.0084
5	0.0299	0.1091	0.0593	0.0002	0.3722	0.0000	0.0179	0.0236	0.0953	0.0007	0.0011	0.0116
6	0.0000	0.2061	0.0414	0.0028	0.0302	0.0001	0.0716	0.2725	0.0876	0.0910	0.2709	0.1318
7	0.0004	0.0003	0.3053	0.2071	0.0013	0.0829	0.0059	0.1093	0.0044	0.0199	0.0248	0.1867
8	0.1629	0.1710	0.0003	0.0396	0.0654	0.1639	0.0166	0.0100	0.1001	0.1294	0.0280	0.0529
9	0.0143	0.0009	0.0036	0.0107	0.0999	0.0381	0.0068	0.0000	0.0247	0.2251	0.0079	0.0001
10	0.1210	0.0939	0.1332	0.0142	0.0001	0.0071	0.1017	0.0003	0.1508	0.0030	0.0609	0.3965
Rr^{2*}	0.0819	0.0920	0.0608	0.0399	0.0946	0.1241	0.0661	0.0493	0.0917	0.1134	0.0542	0.0880
$^{C}R^2_{p}{}^{\#}$	0.8280	0.7881	0.7370	0.9237	0.8538	0.7218	0.8886	0.6266	0.6688	0.7417	0.9125	0.7958

* Average randomized R^2; # $^{C}R^2_p = R \times (R^2 - R^2_r)^{1/2}$ where $^{C}R^2_p$ should be greater than 0.5

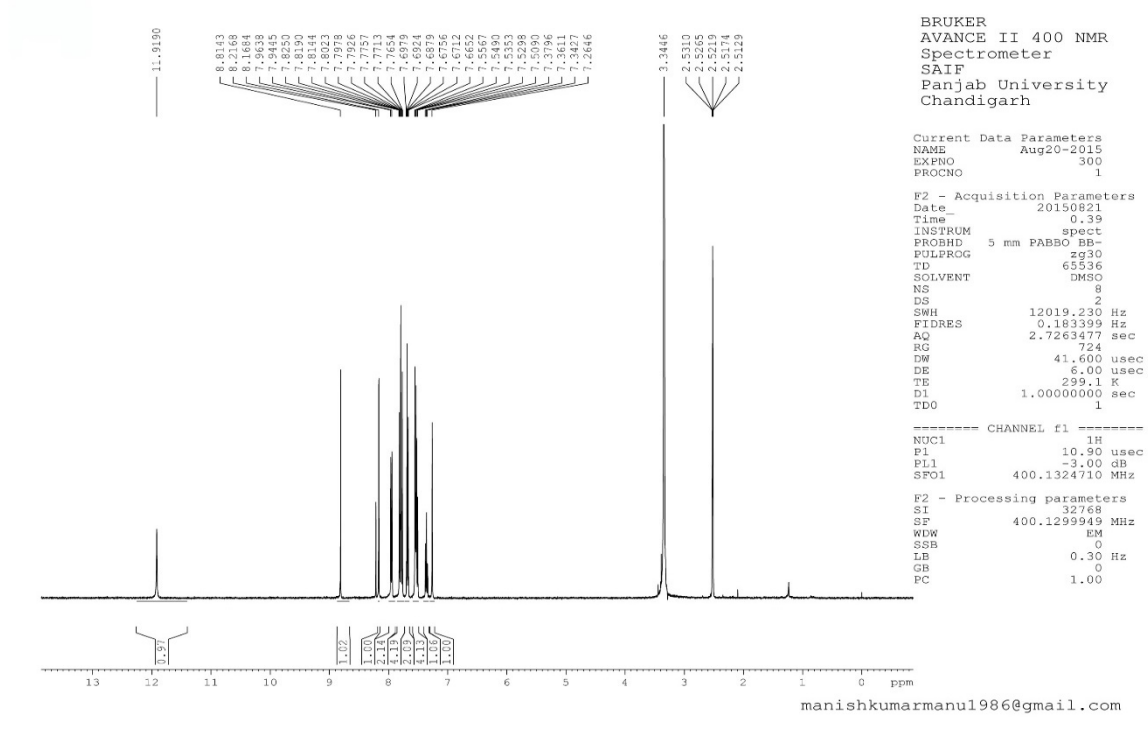


Figure 1: ^{1}H NMR of 1-((3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl)thiazol-2-yl)hydrazine (4a)

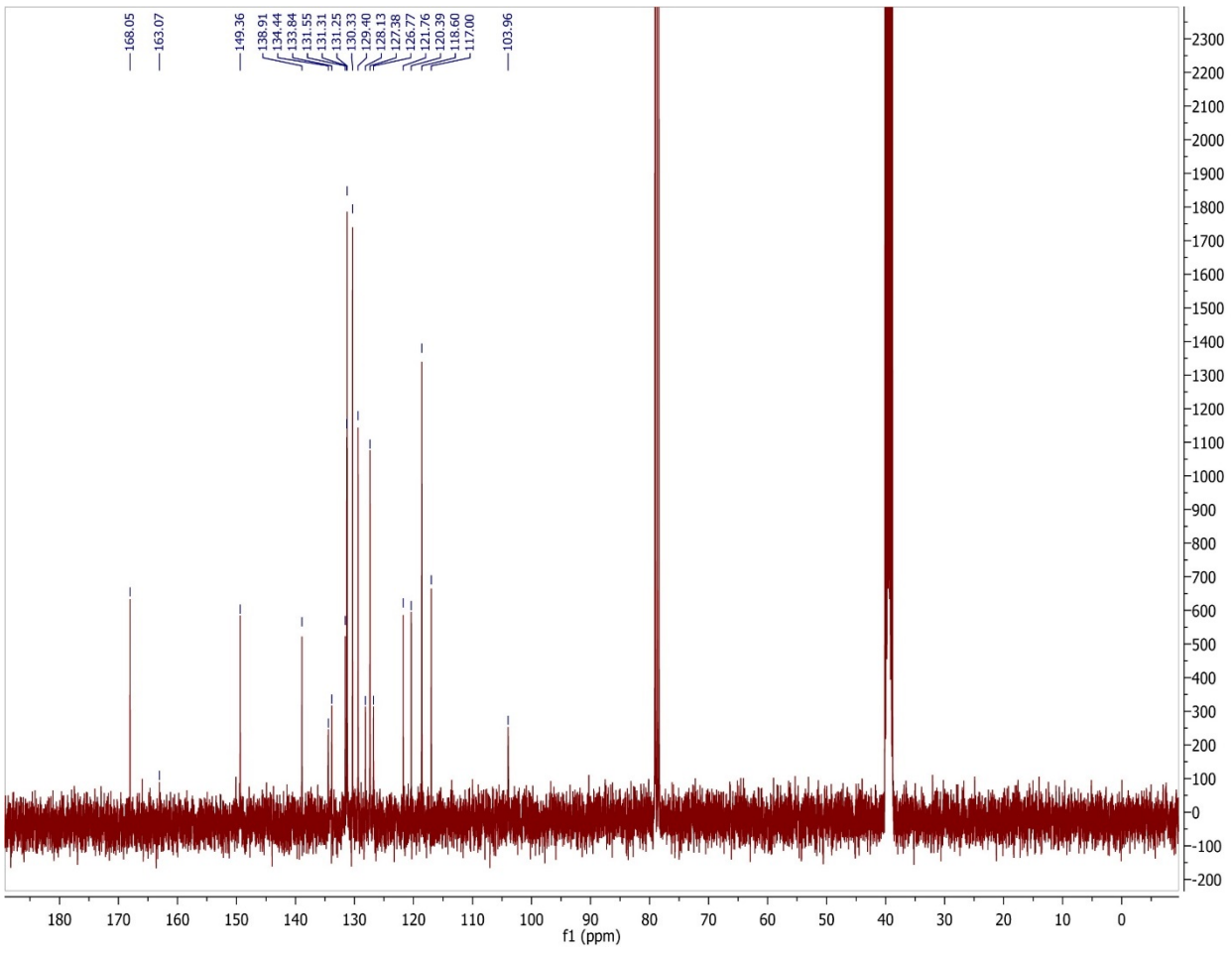


Figure 2: ^{13}C NMR of 1-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl)thiazol-2-yl)hydrazine (4a)

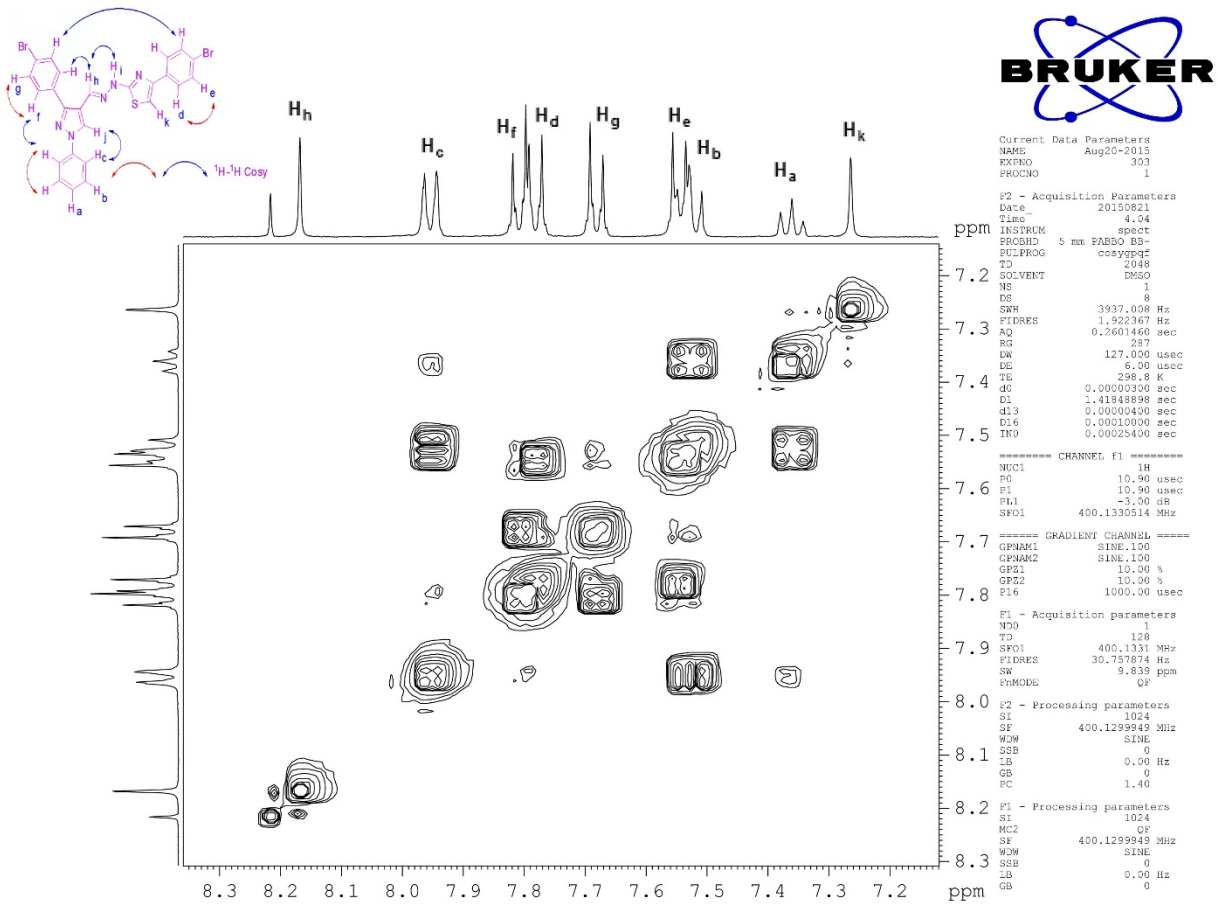


Figure 3: ^{1}H-^{1}H Cosy of 1-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl)thiazol-2-yl)hydrazine (4a)

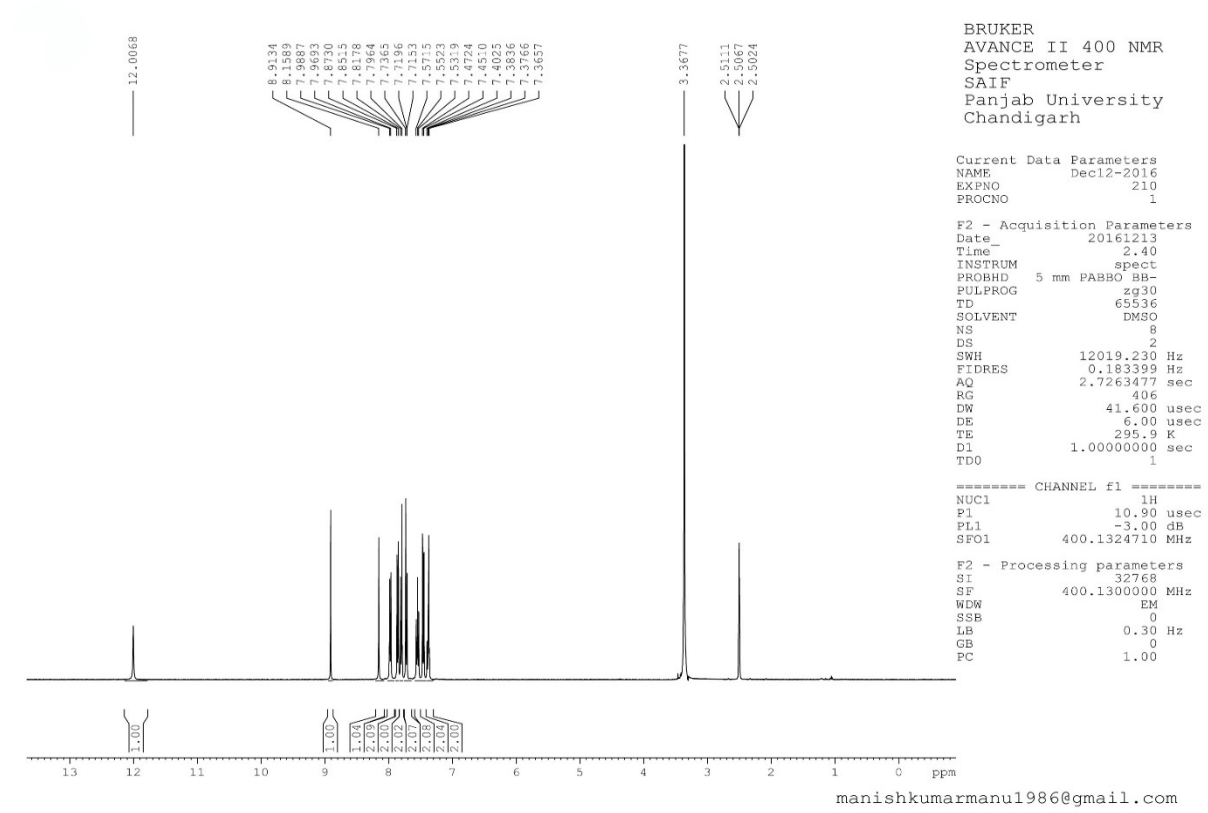


Figure 4: ^{1}H NMR 1-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl)thiazol -2-yl)hydrazine (4b)

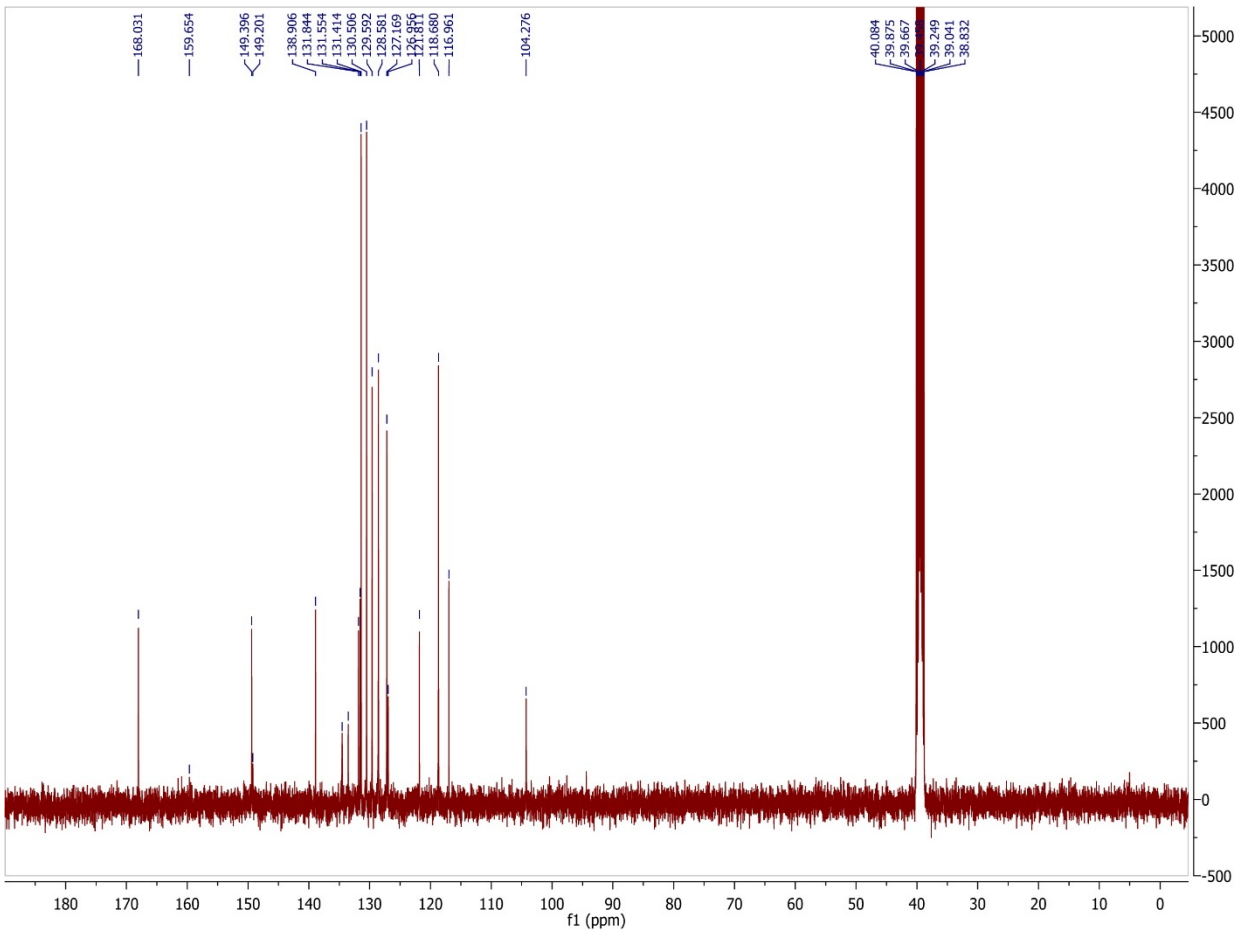
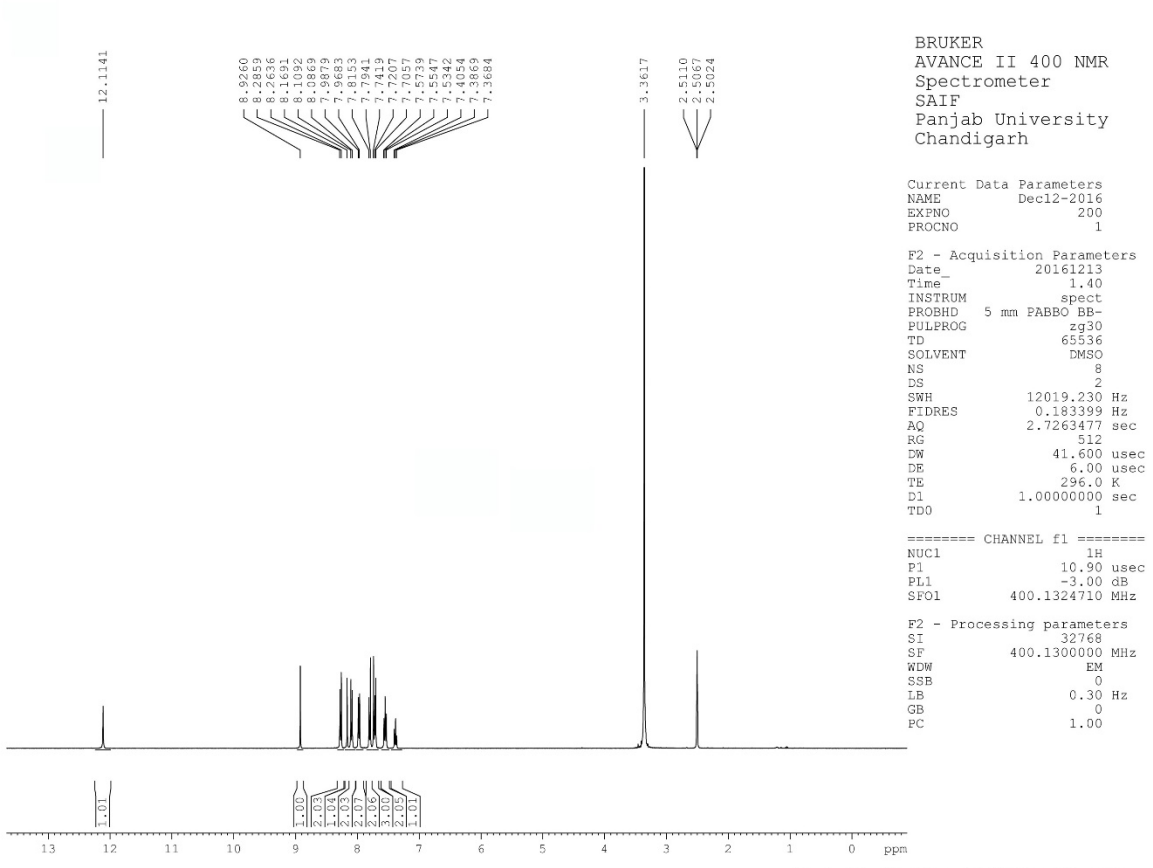


Figure 5: ^{13}C NMR of 1-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl)thiazol -2-yl)hydrazine (4b)



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AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
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PROCNO 1

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Figure 6: ^{1}H NMR of 1-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4c)

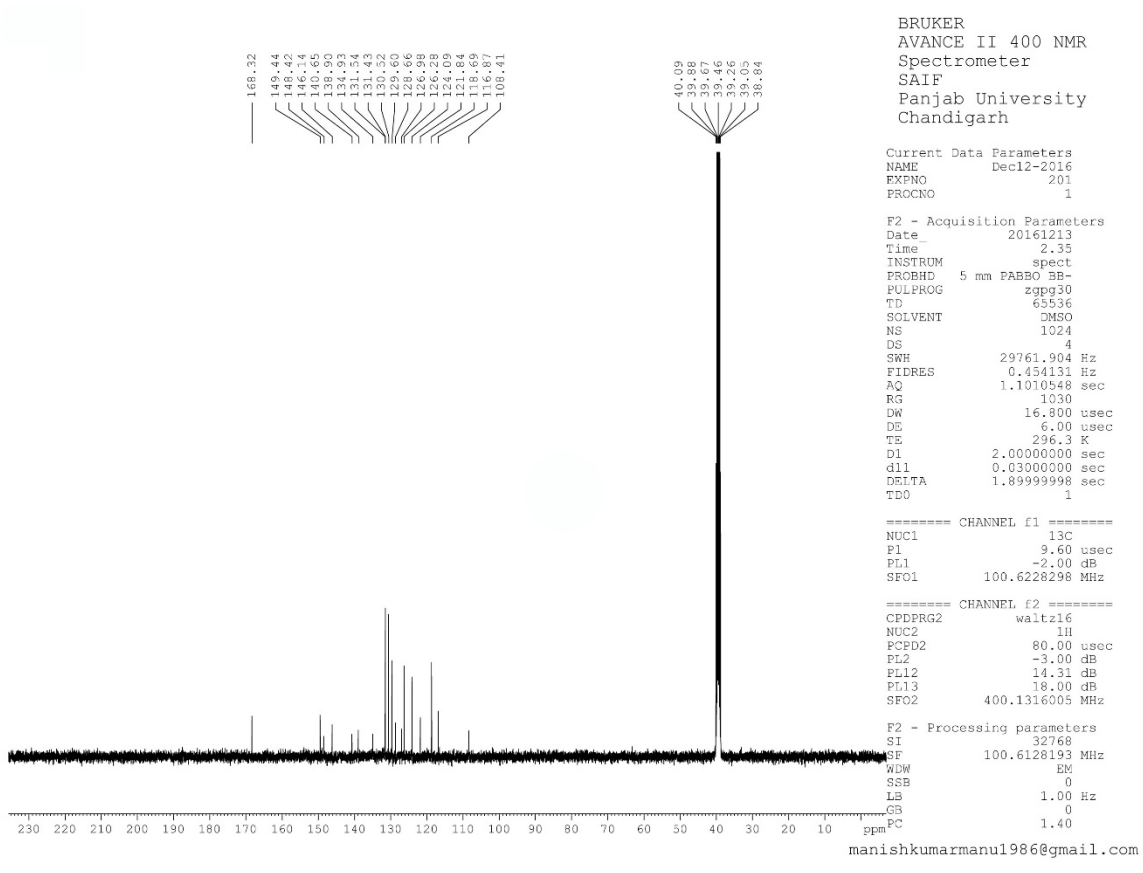

Figure 7: ^{13}C NMR of 1-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4c)

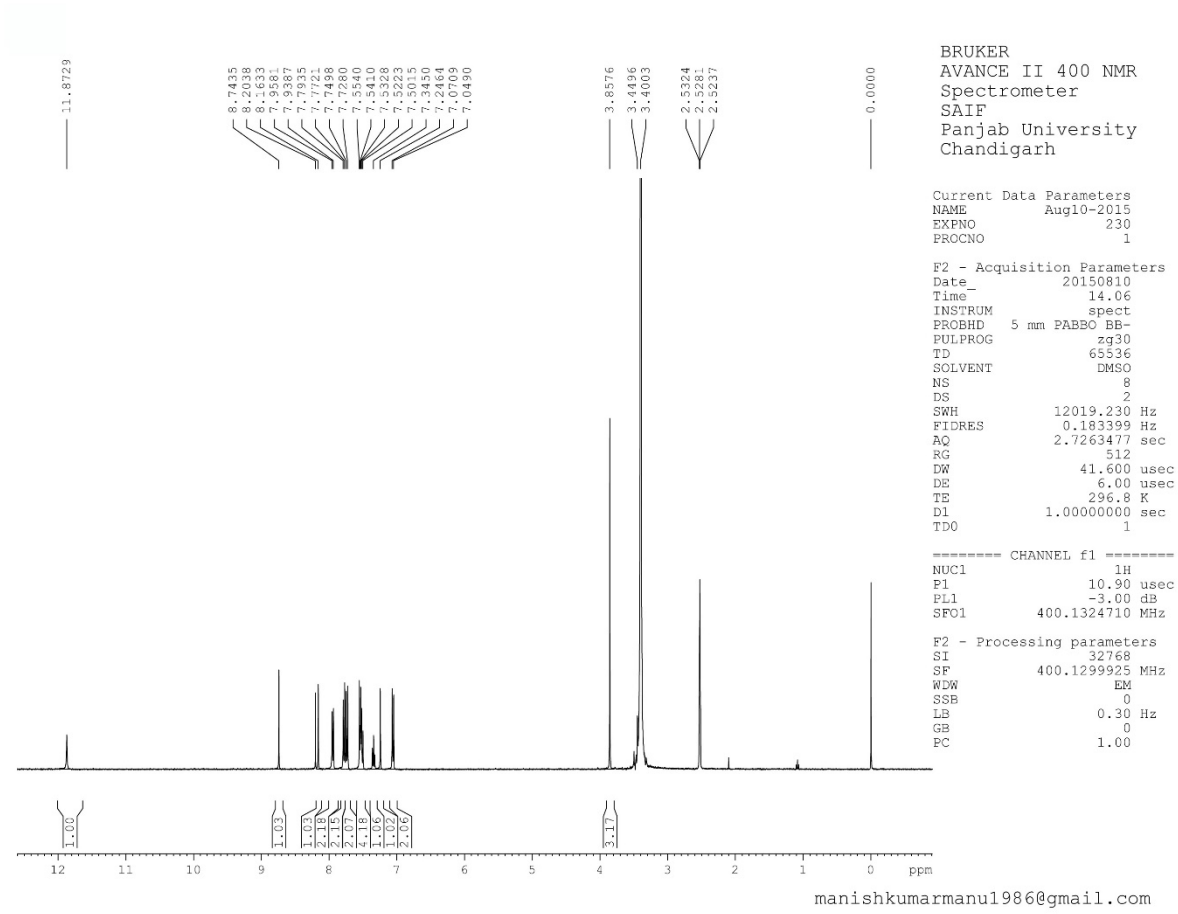

Figure 8: ^{1}H NMR of 1-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4d)

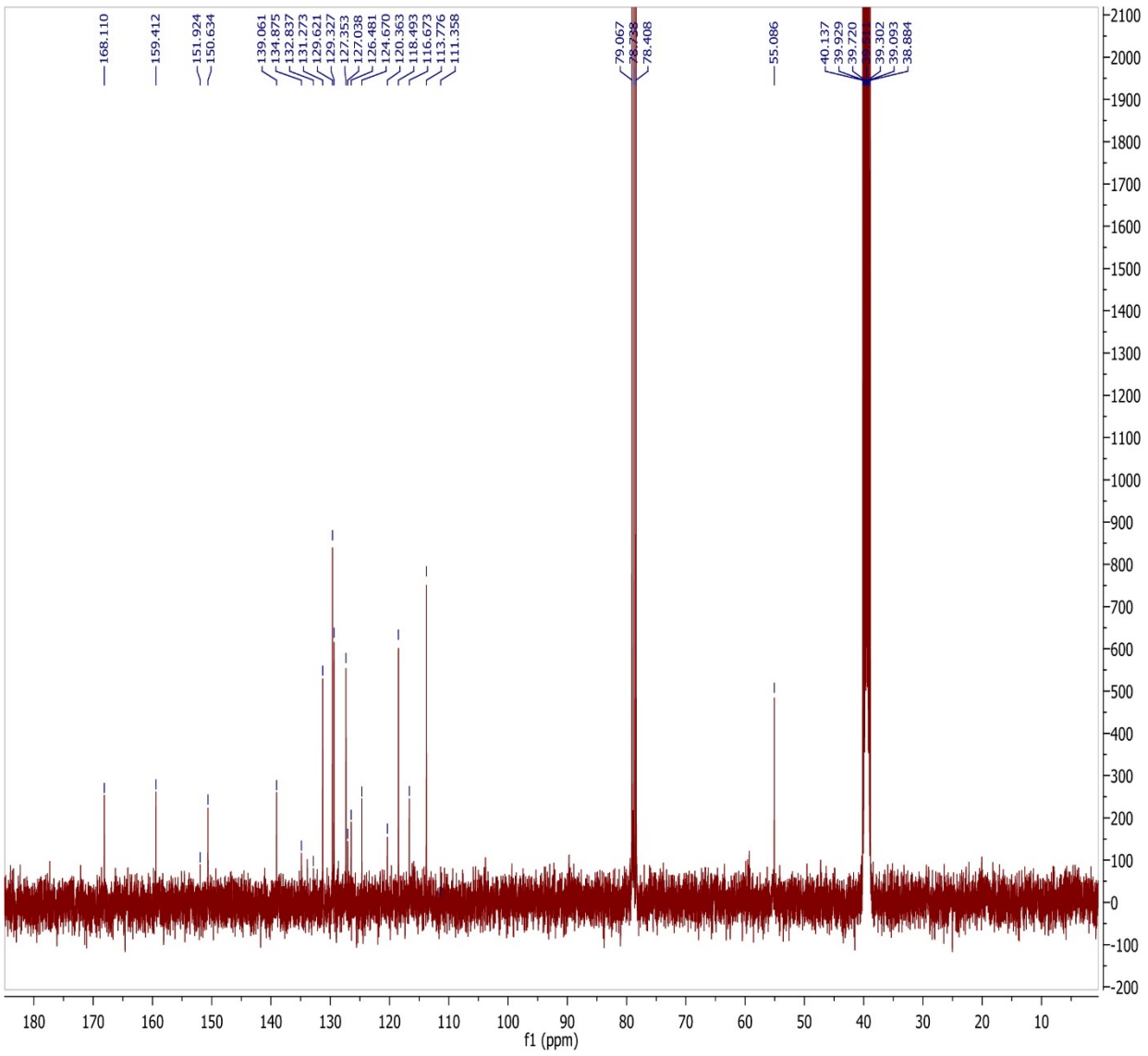

Figure 9: ^{13}C NMR of 1-((3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4d)

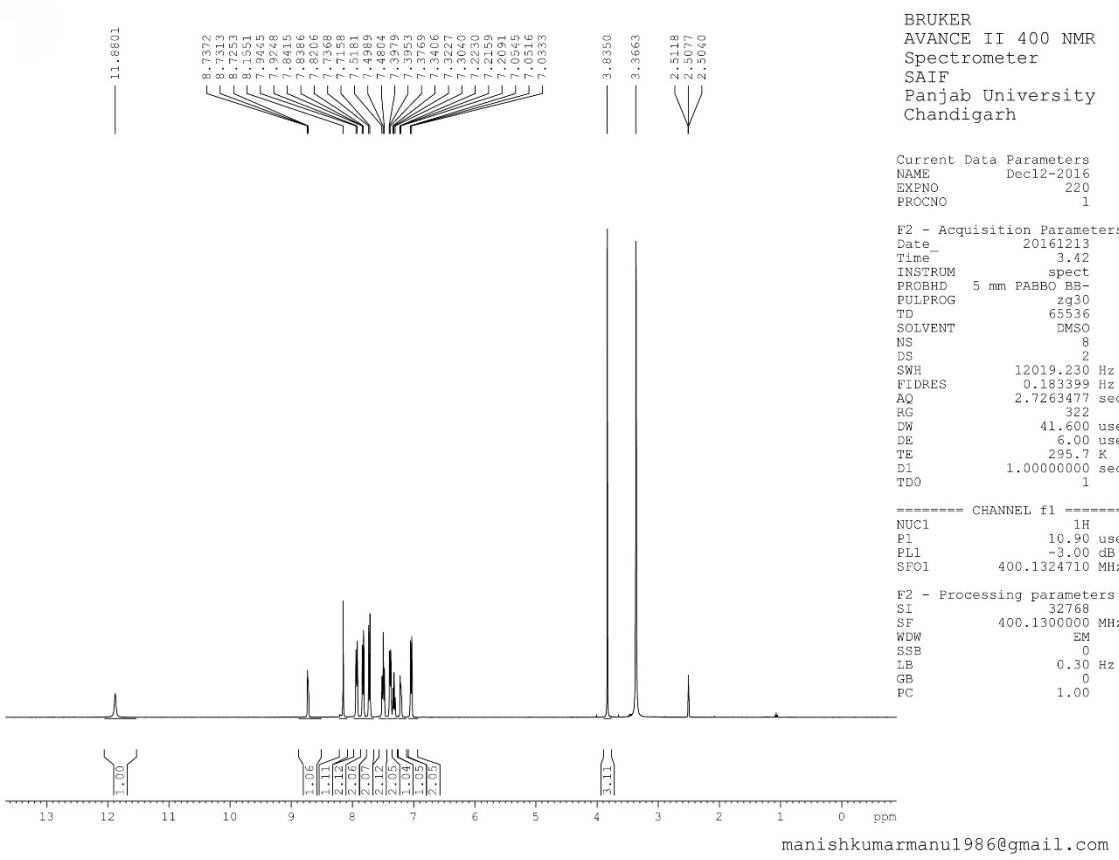

Figure 10: ^{1}H NMR of 1-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (4e)

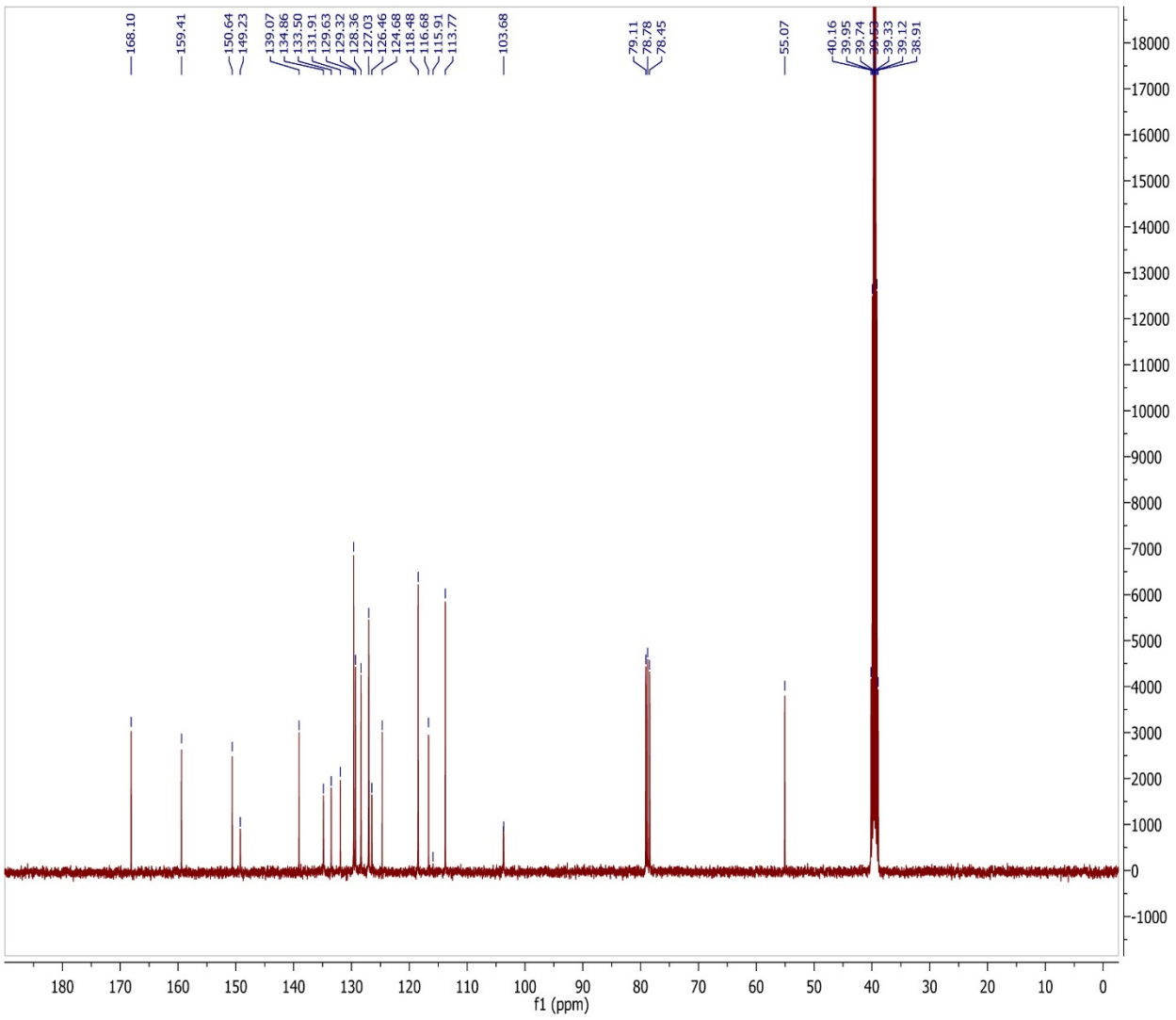

Figure 11: ^{13}C NMR of 1-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (4e)

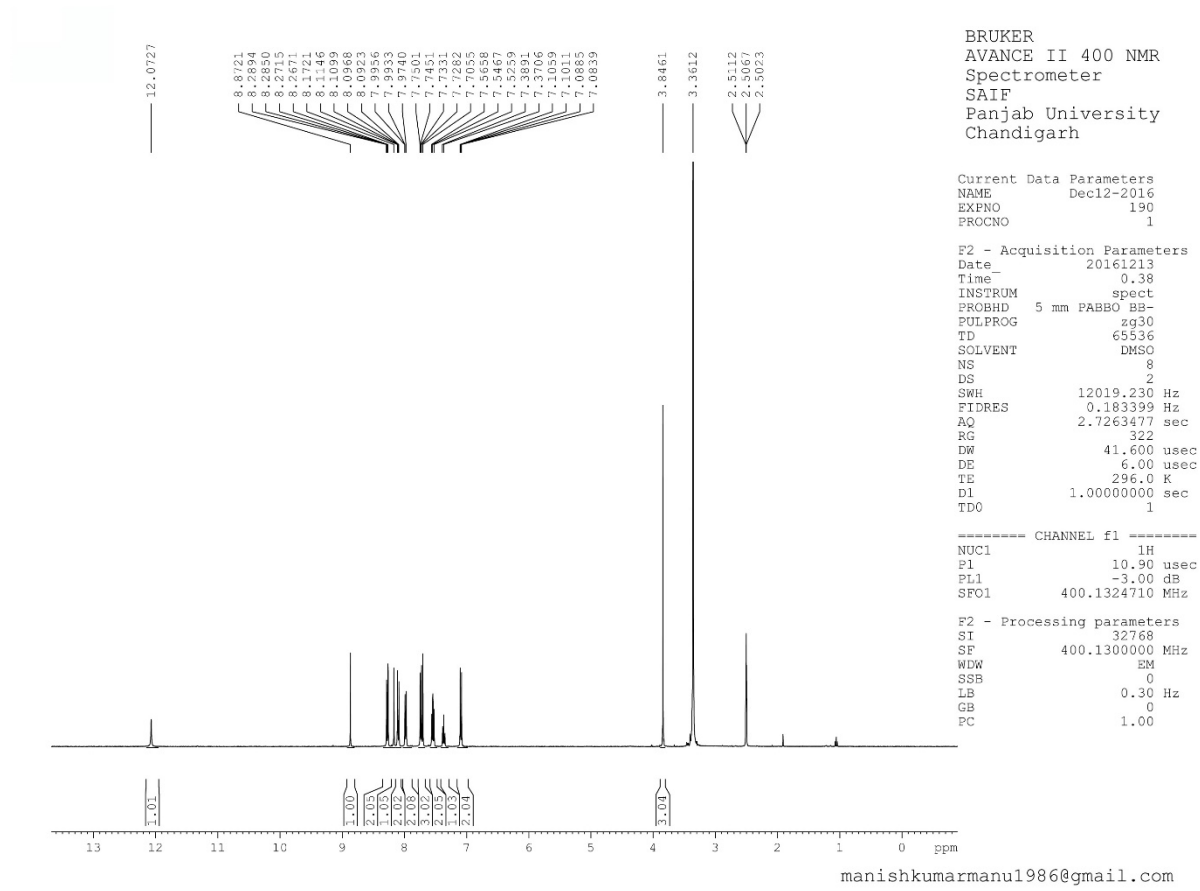

Figure 12: ^{1}H NMR of 1-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl) thiazol-2-yl)hydrazine (4f)

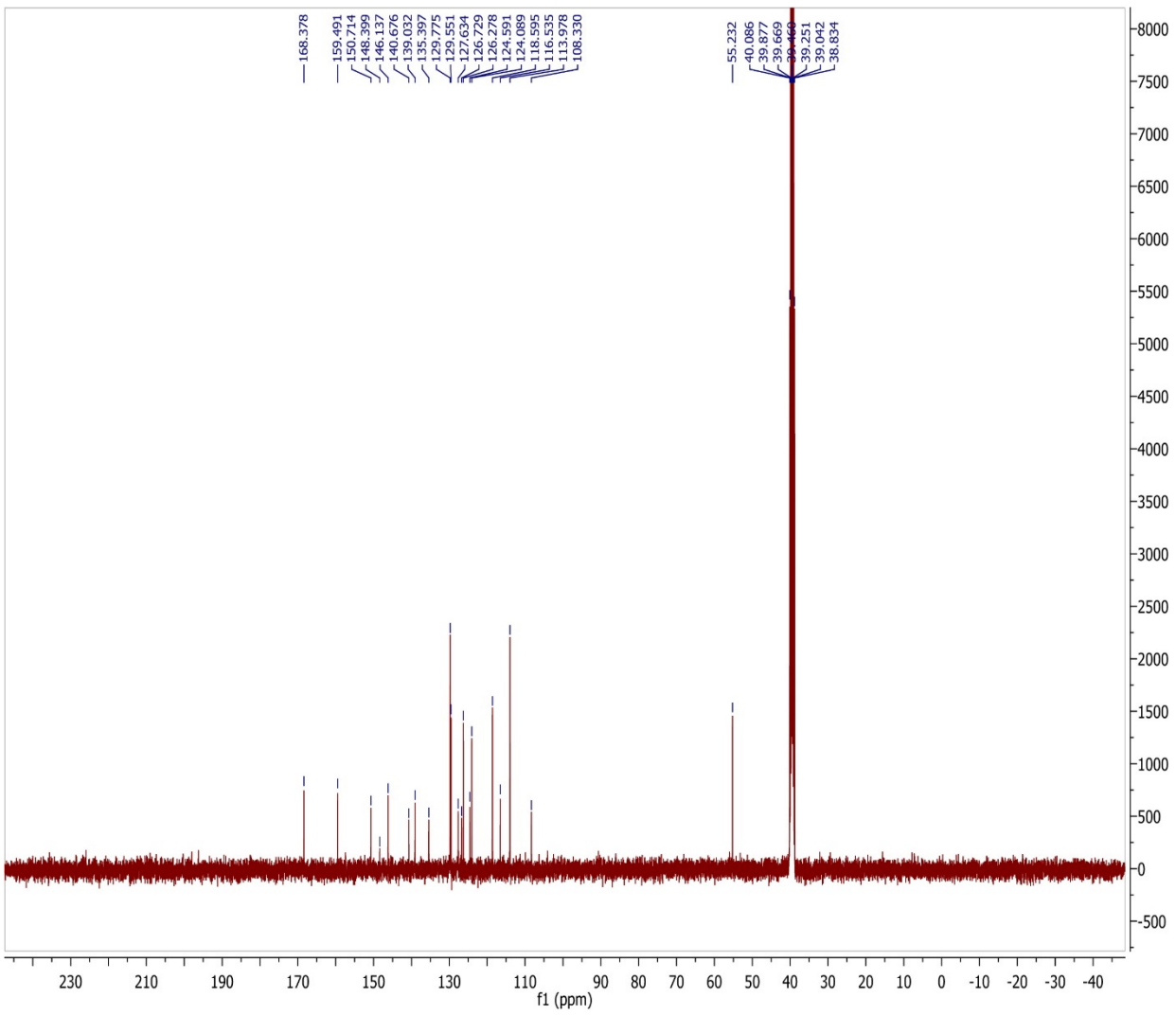

Figure 13: ^{13}C NMR of 1-((3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl) thiazol-2-yl)hydrazine (4f)

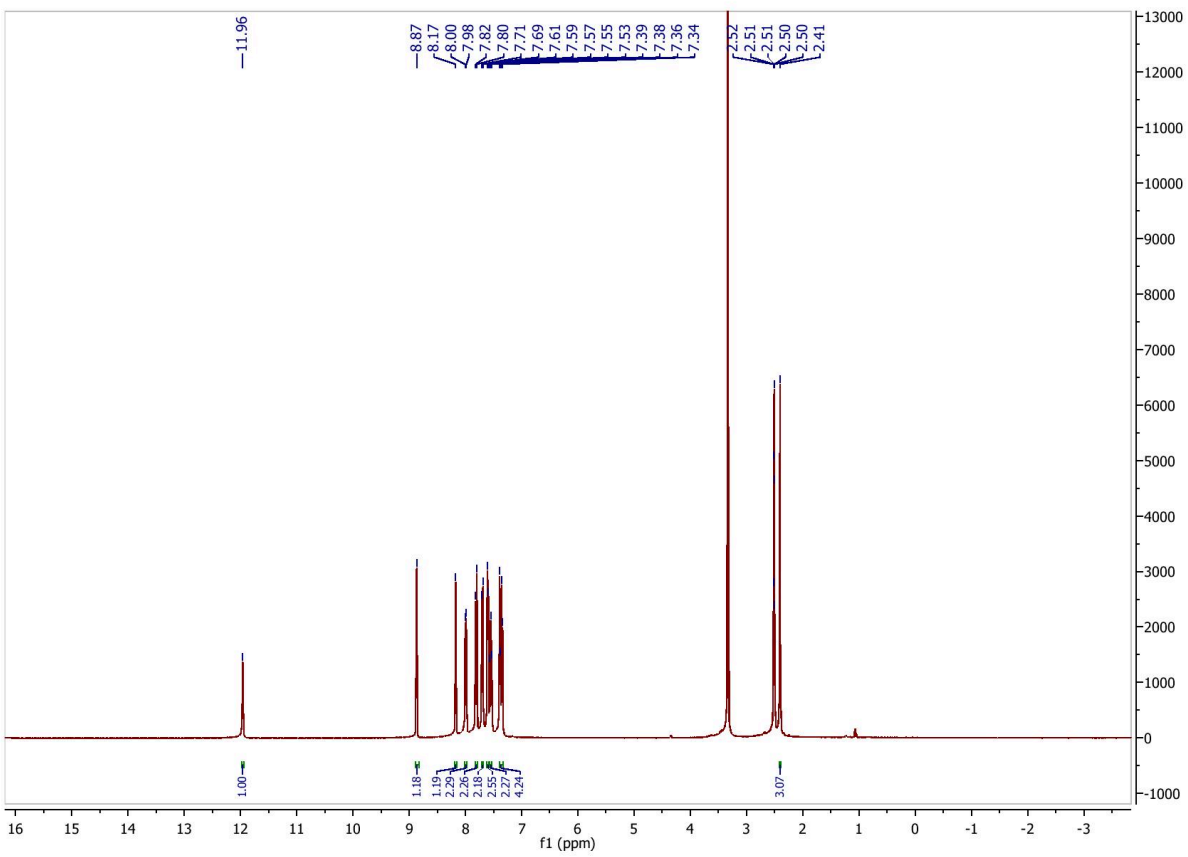

Figure 14: ^{1}H NMR of 1-((3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4g)

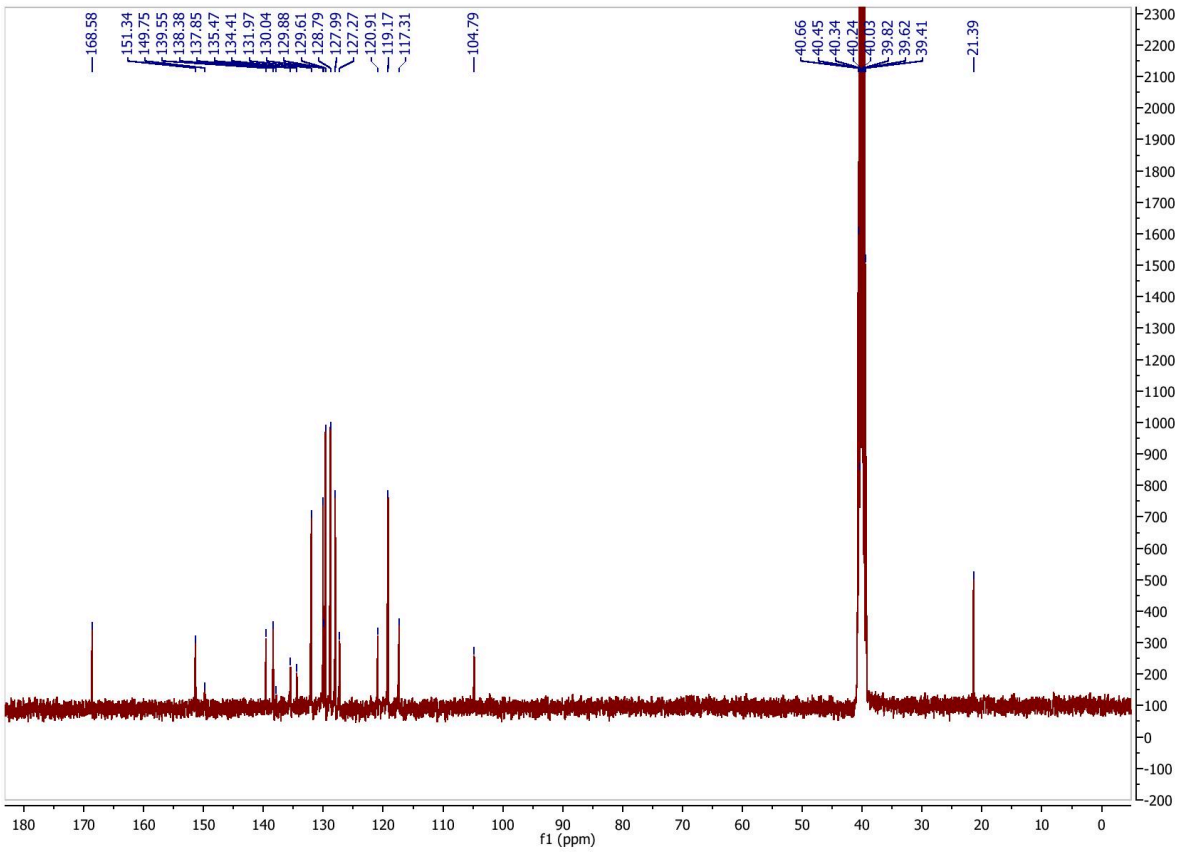

Figure 15: ^{13}C NMR of 1-((3-(4-Methylphenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4g)

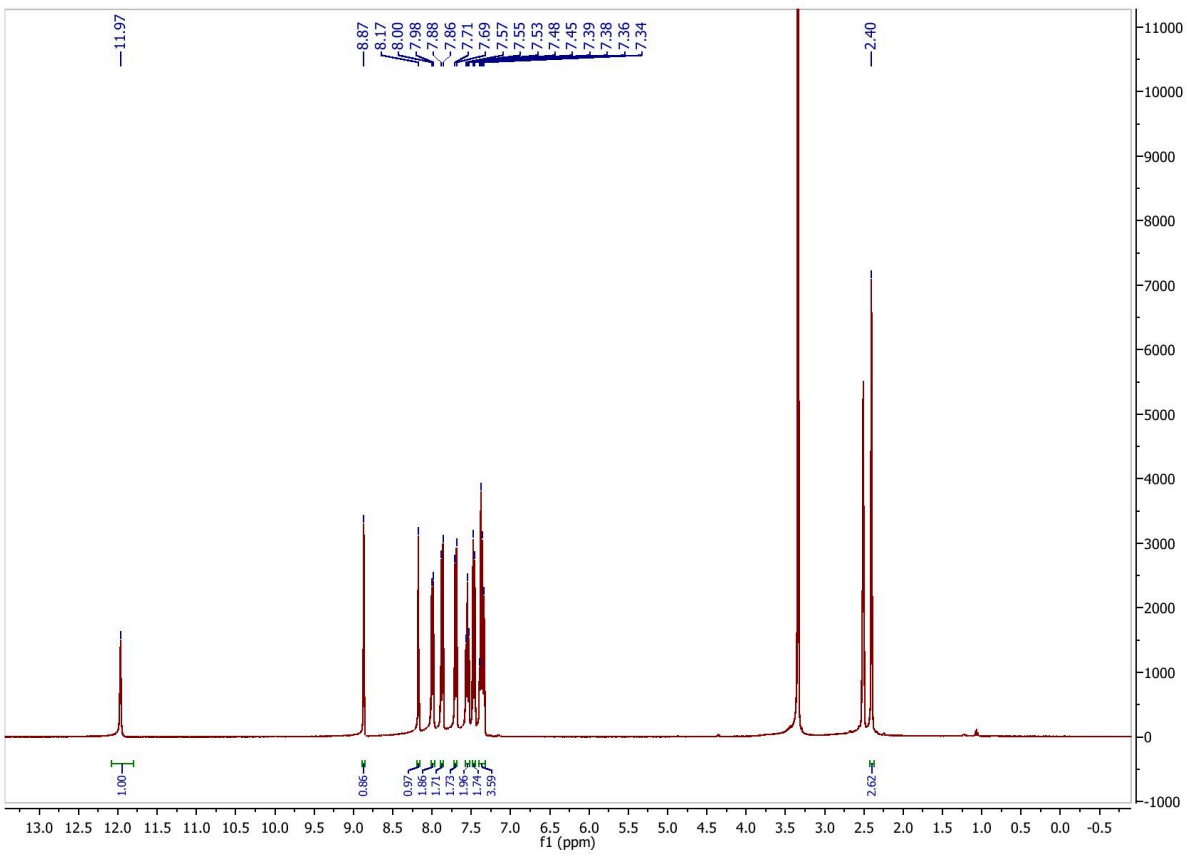

Figure 16: ^{1}H NMR of 1-((3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (4h)

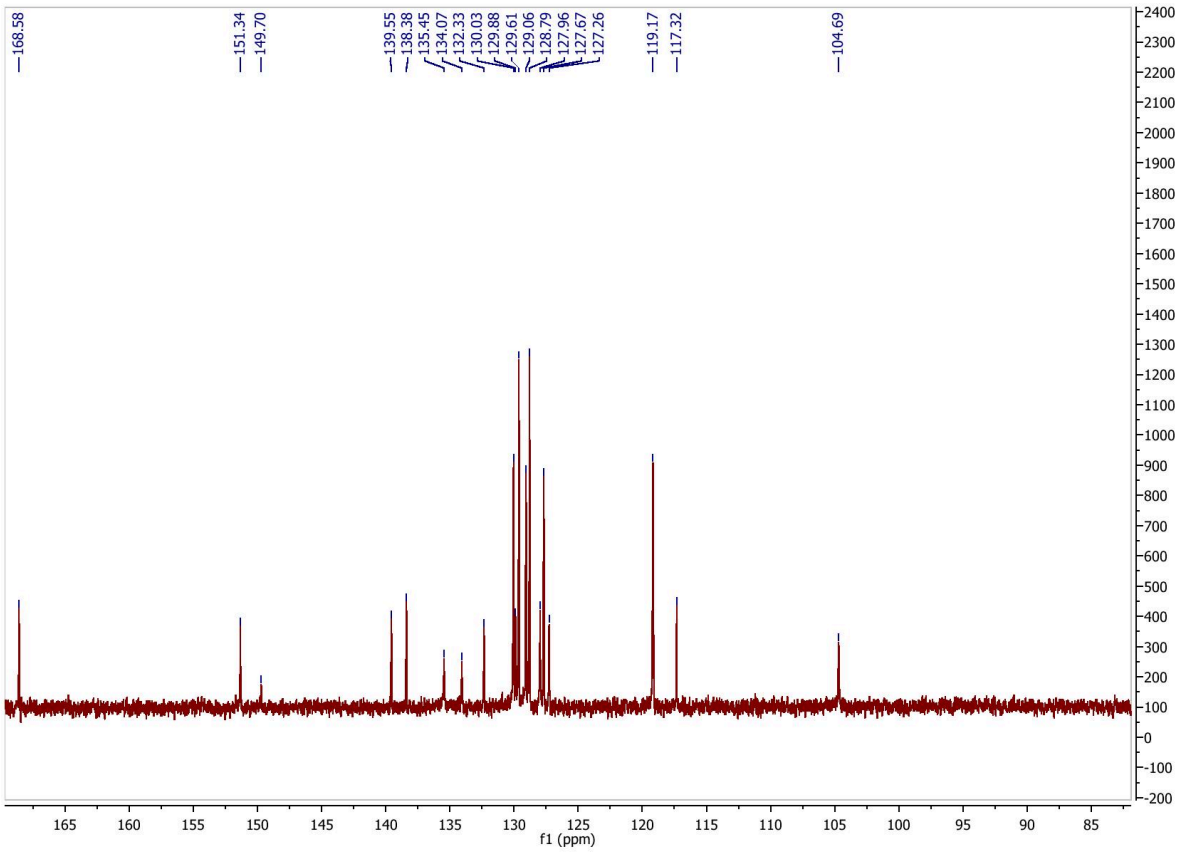

Figure 17: ^{13}C NMR of 1-((3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (4h)

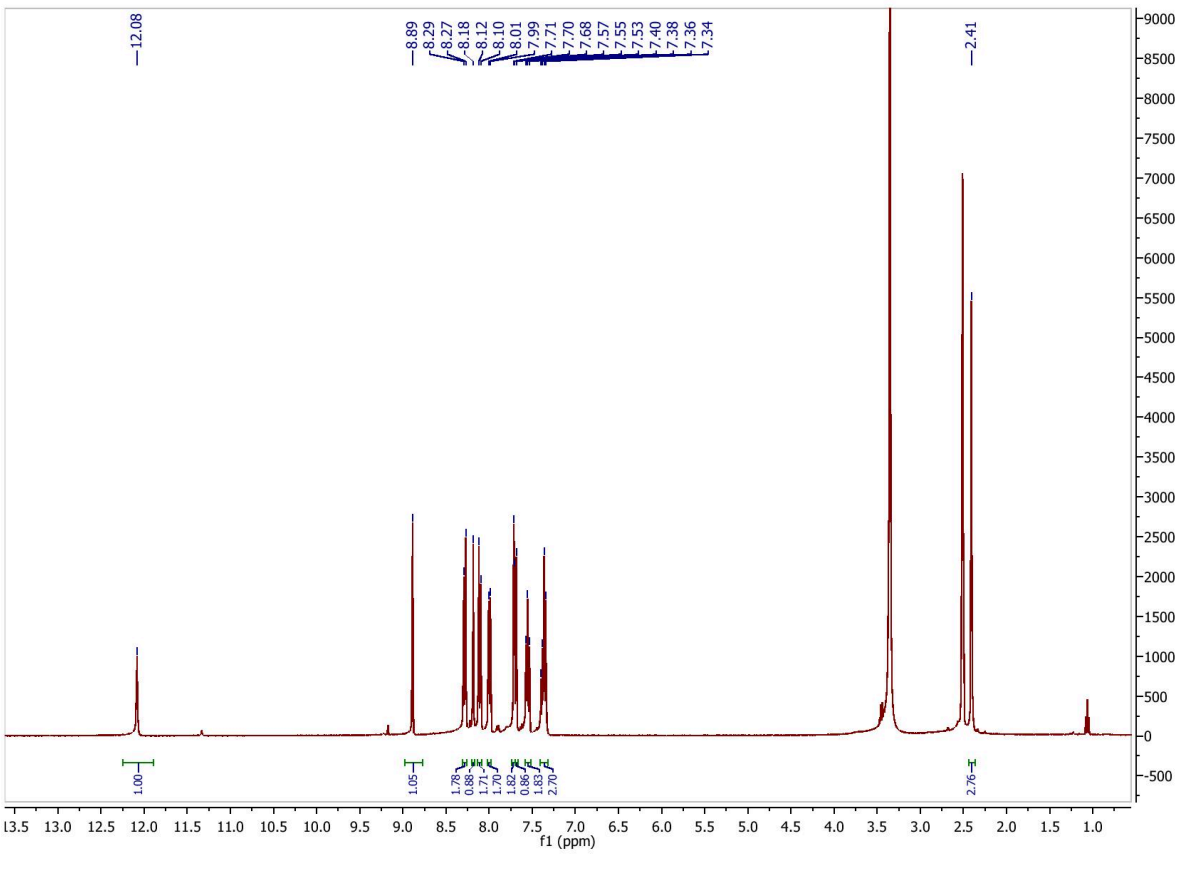

Figure 18: ^{1}H NMR of 1-((3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4i)

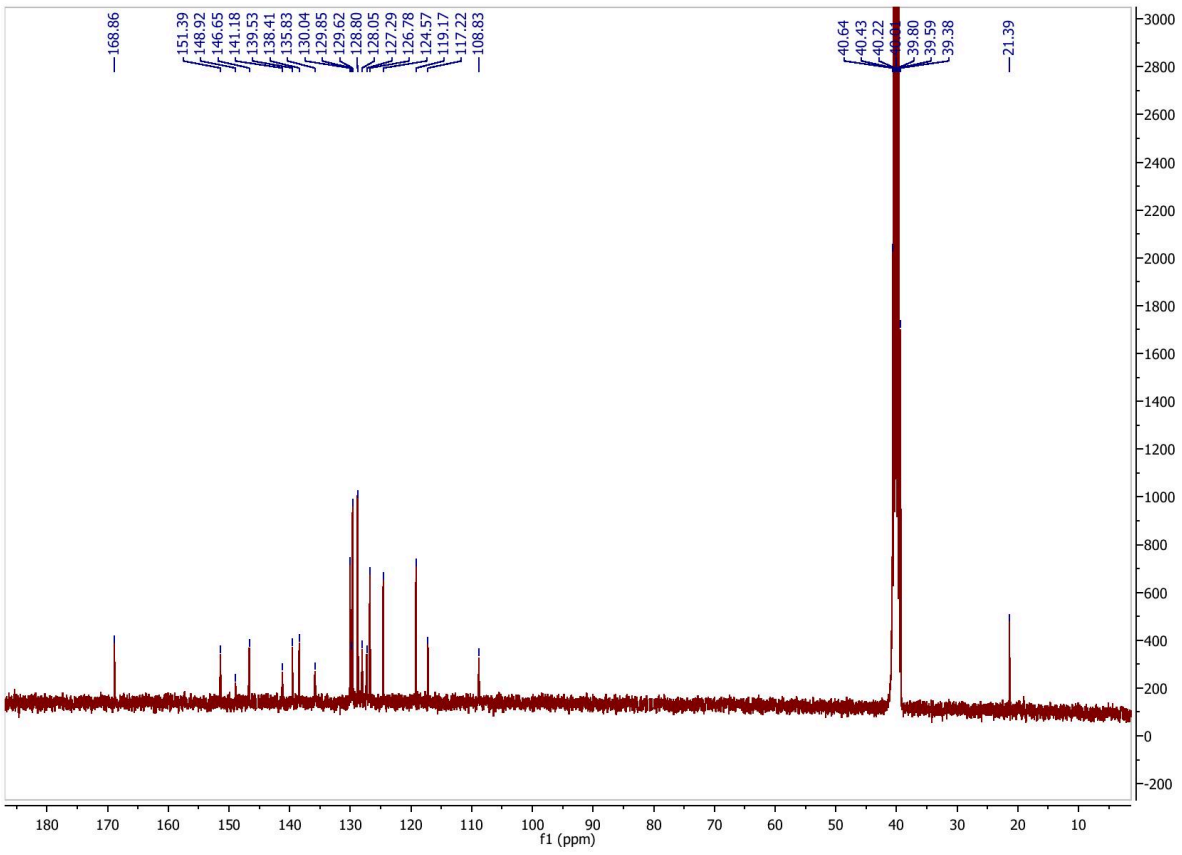

Figure 19: ^{13}C NMR of 1-((3-(4-Methylphenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4i)

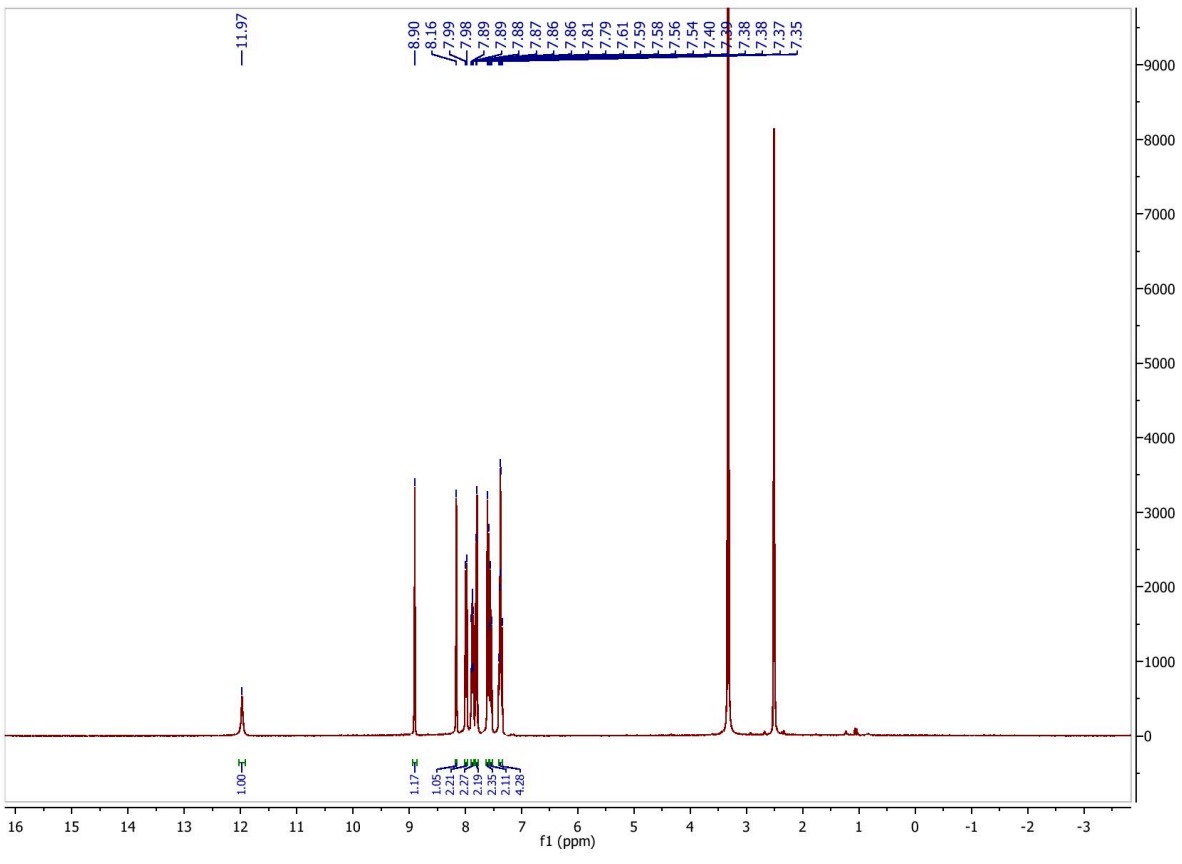

Figure 20: ^{1}H NMR of 1-((3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol -2-yl)hydrazine (4j)

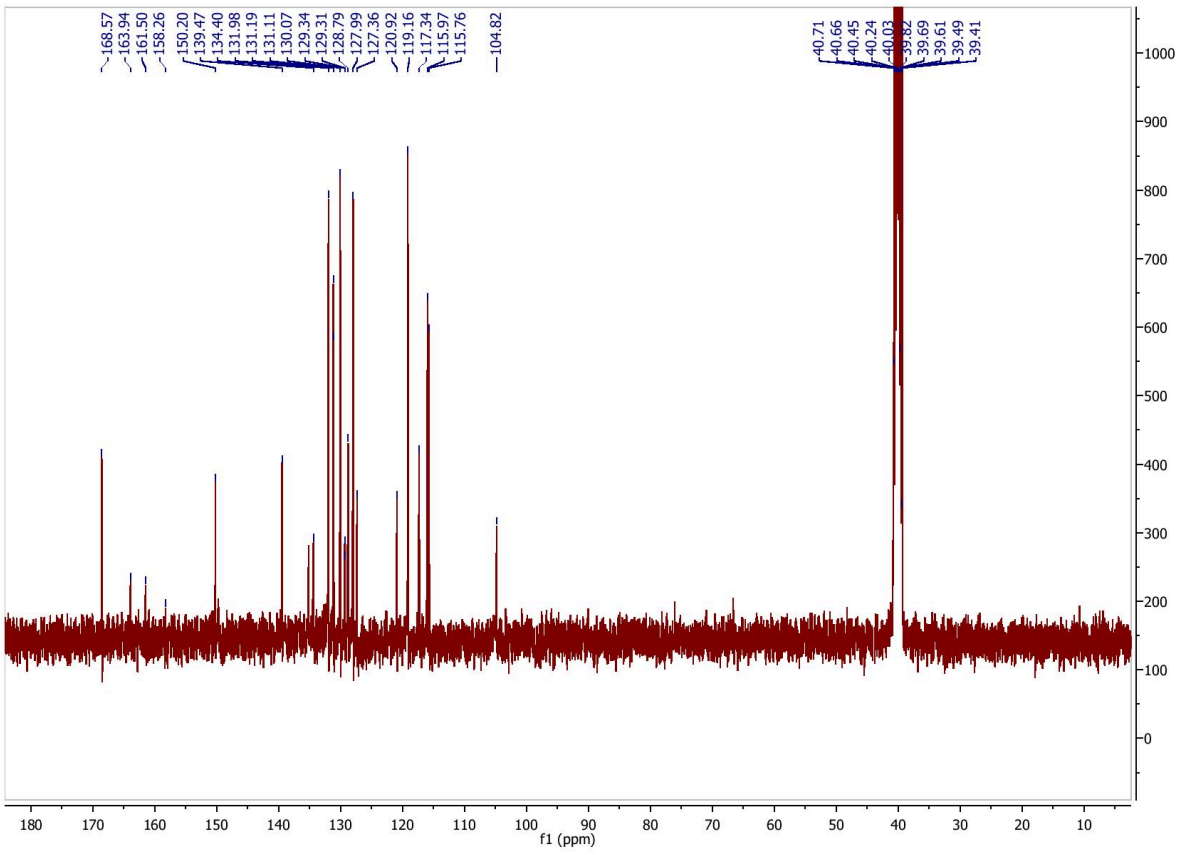

Figure 21: ^{13}C NMR of 1-((3-(4-Fluorophenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol -2-yl)hydrazine (4j)

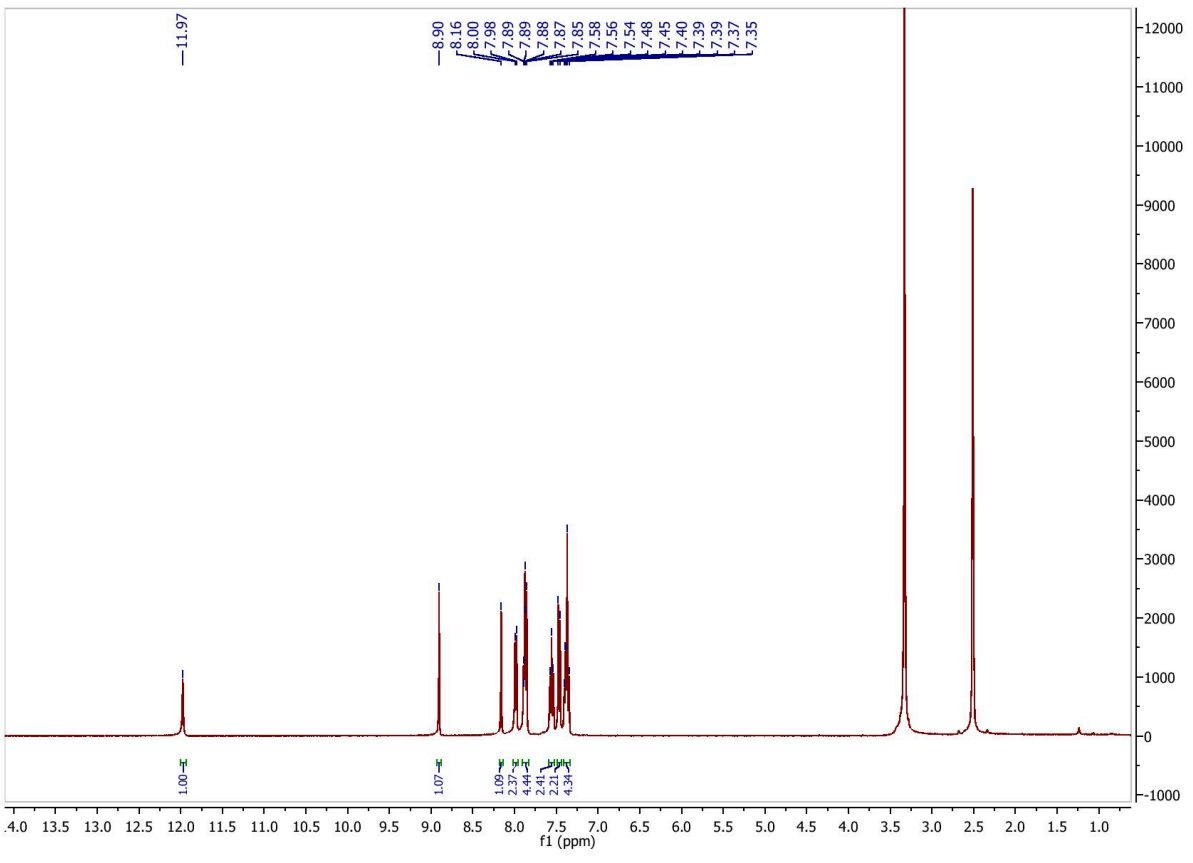

Figure 22: ^{1}H NMR of 1-((3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl)thiazol -2-yl)hydrazine (4k)

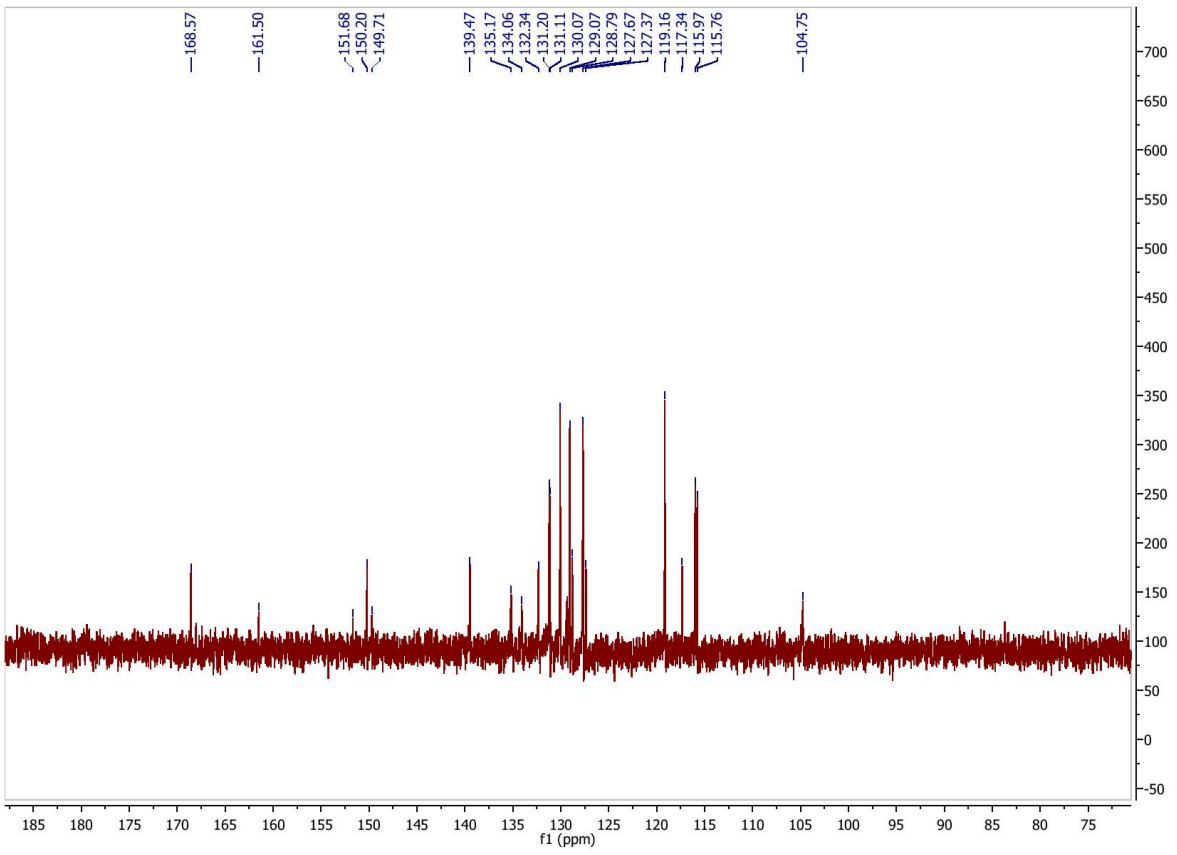

Figure 23: ^{13}C NMR of 1-((3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl)thiazol -2-yl)hydrazine (4k)

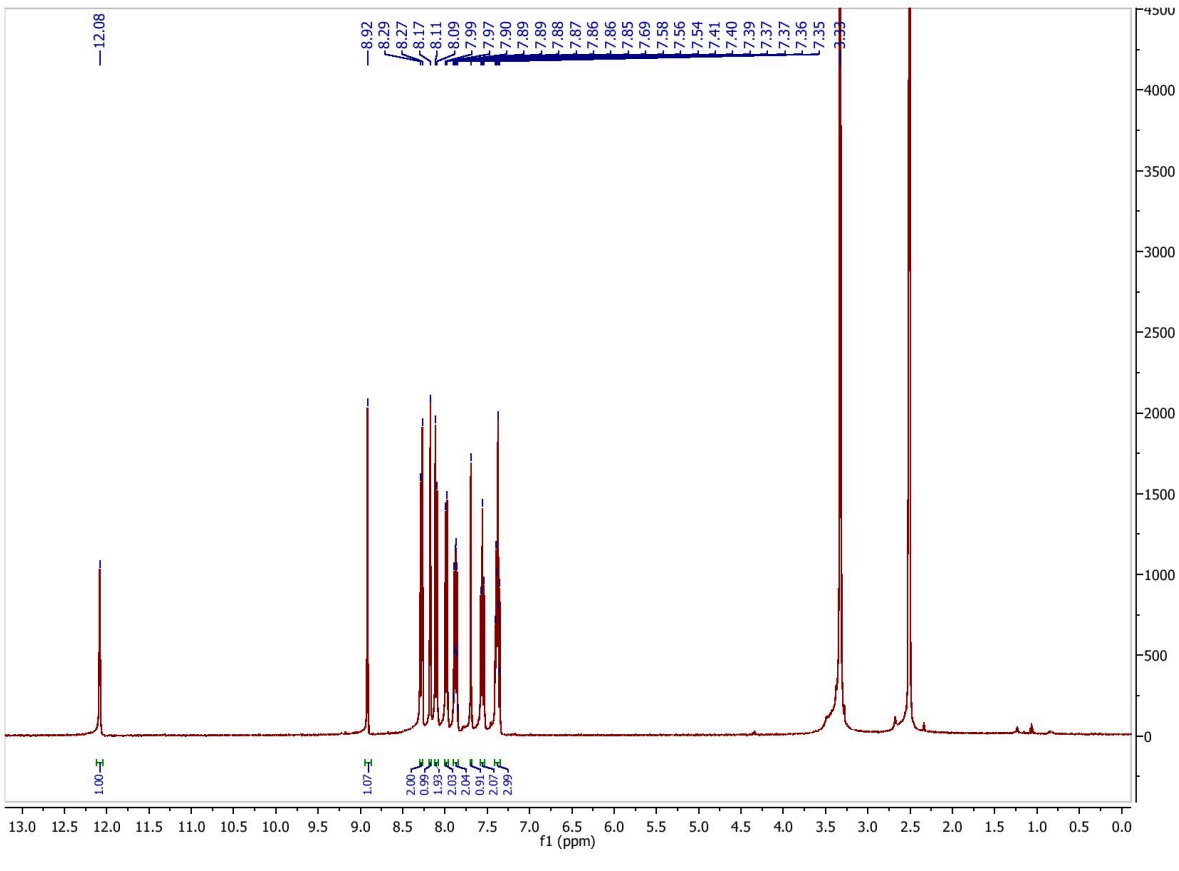

Figure 24: ^{1}H NMR of 1-((3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4l)

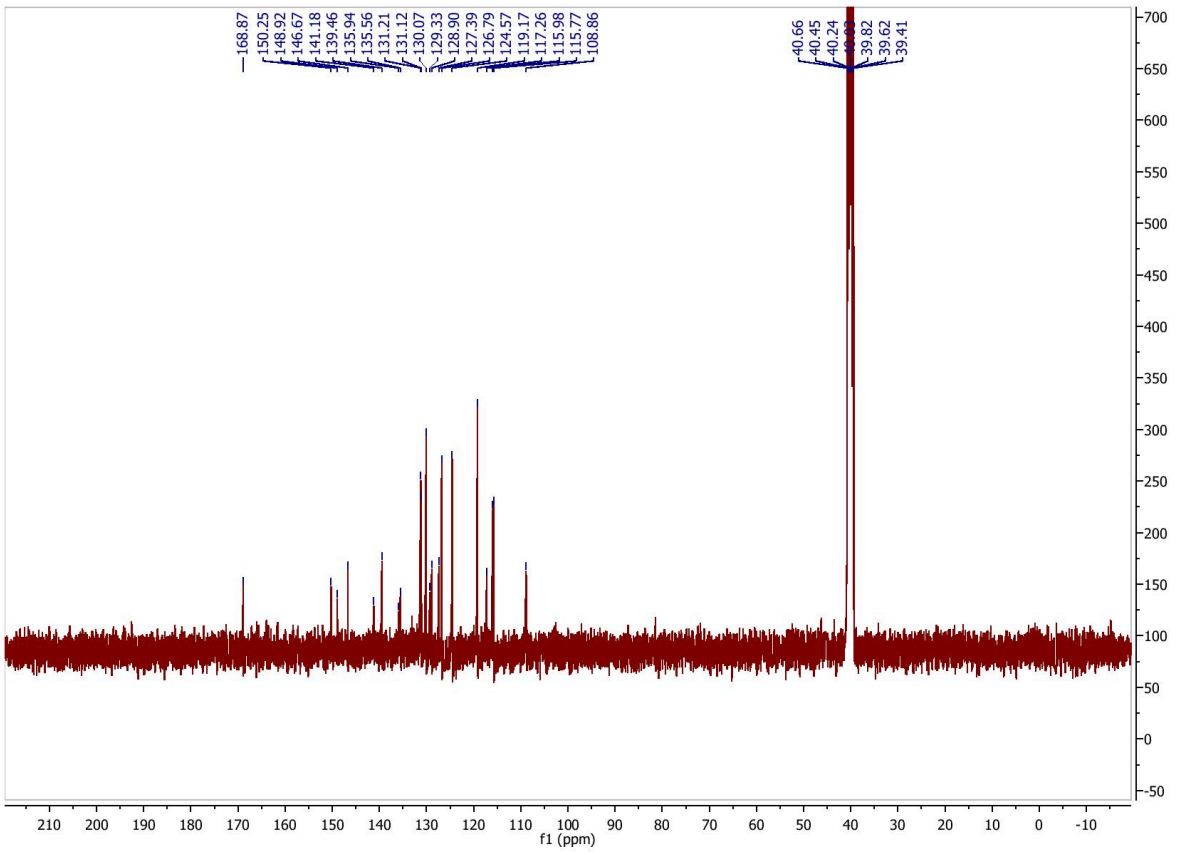

Figure 25: ^{13}C NMR of 1-((3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4l)

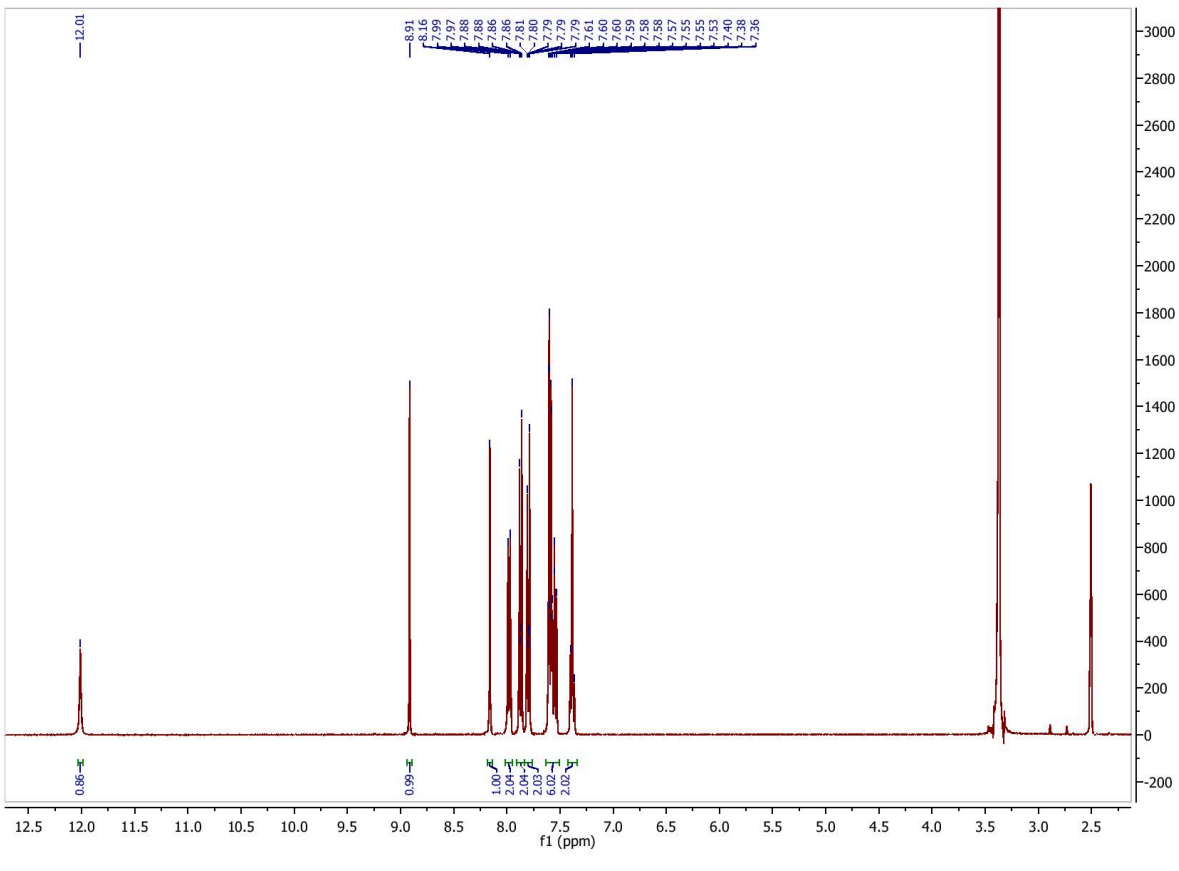

Figure 26: ^{1}H NMR of 1-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4m)

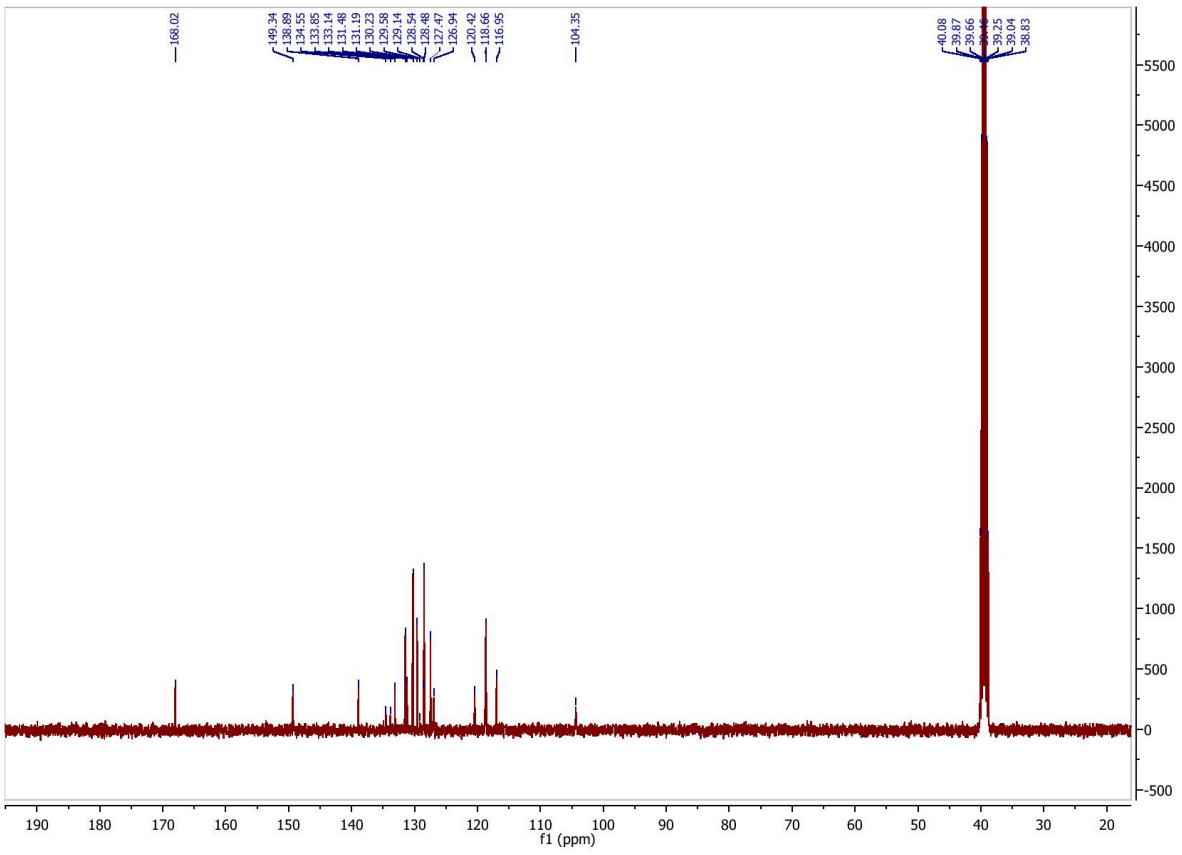

Figure 27: ^{13}C NMR of 1-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-bromophenyl) thiazol-2-yl)hydrazine (4m)

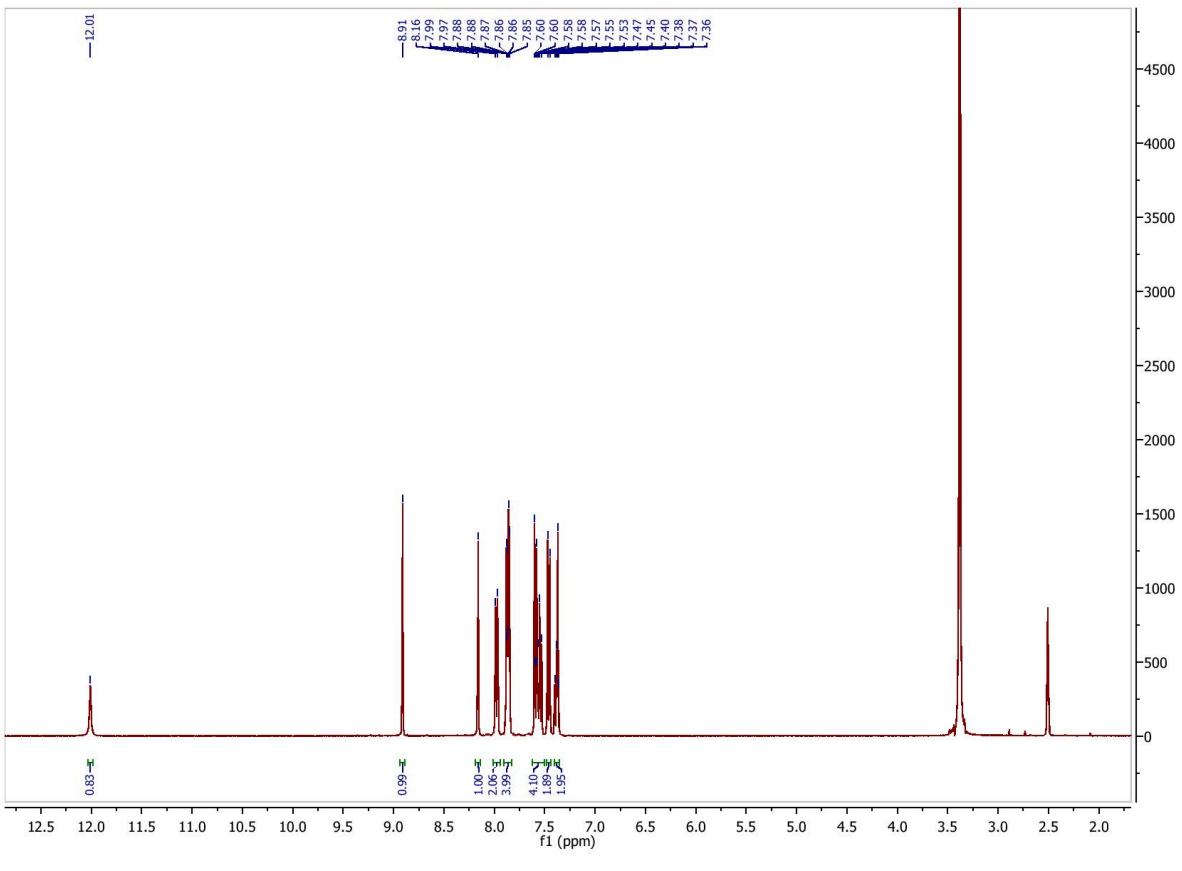

Figure 28: ^{1}H NMR of 1-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (4n)

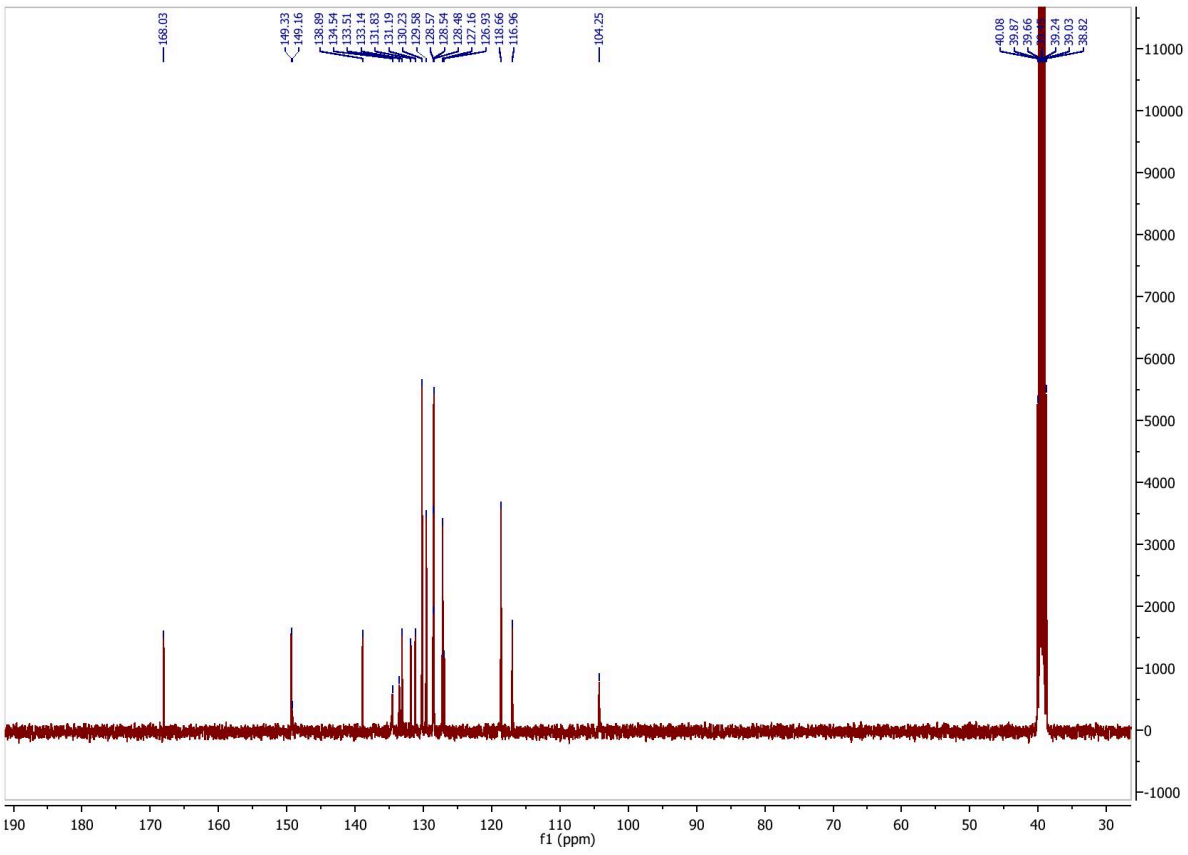

Figure 29: ^{13}C NMR of 1-((3-(4-Chlorophenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (4n)

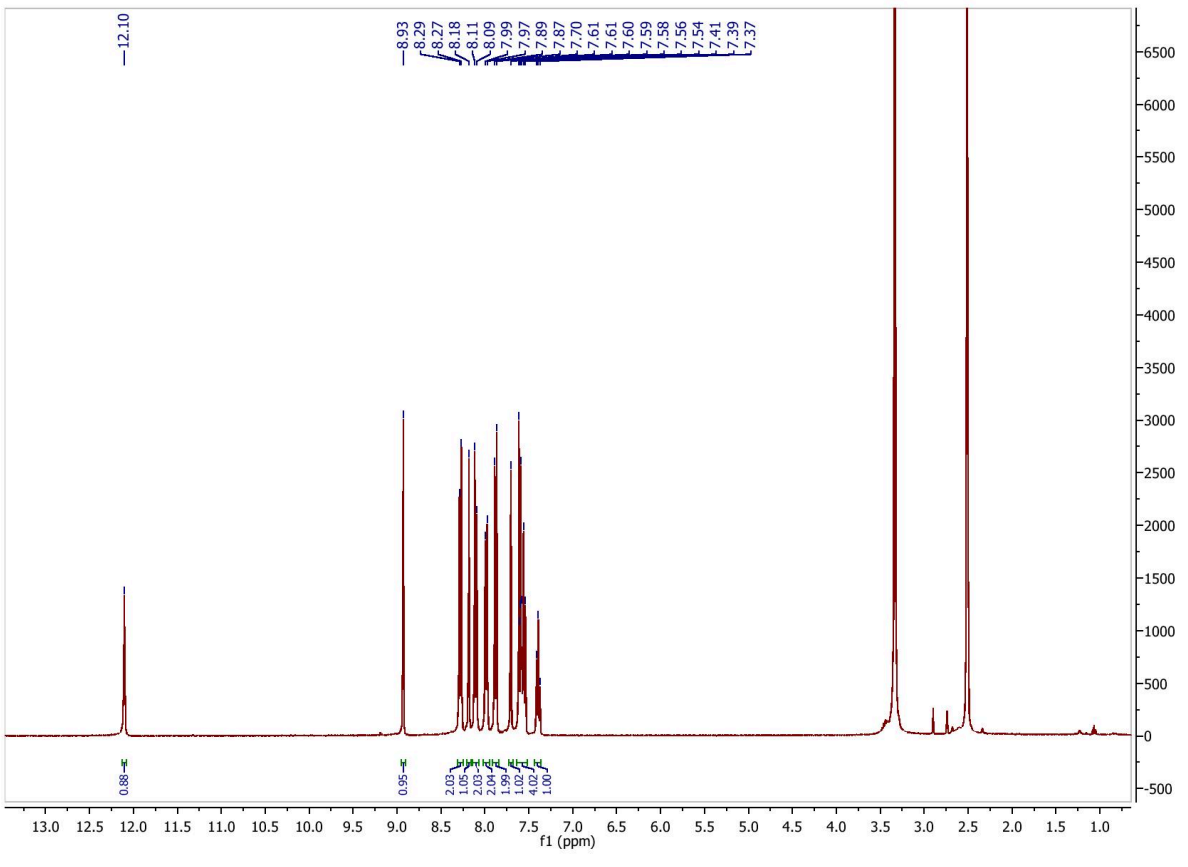

Figure 30: ^{1}H NMR of 1-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4o)

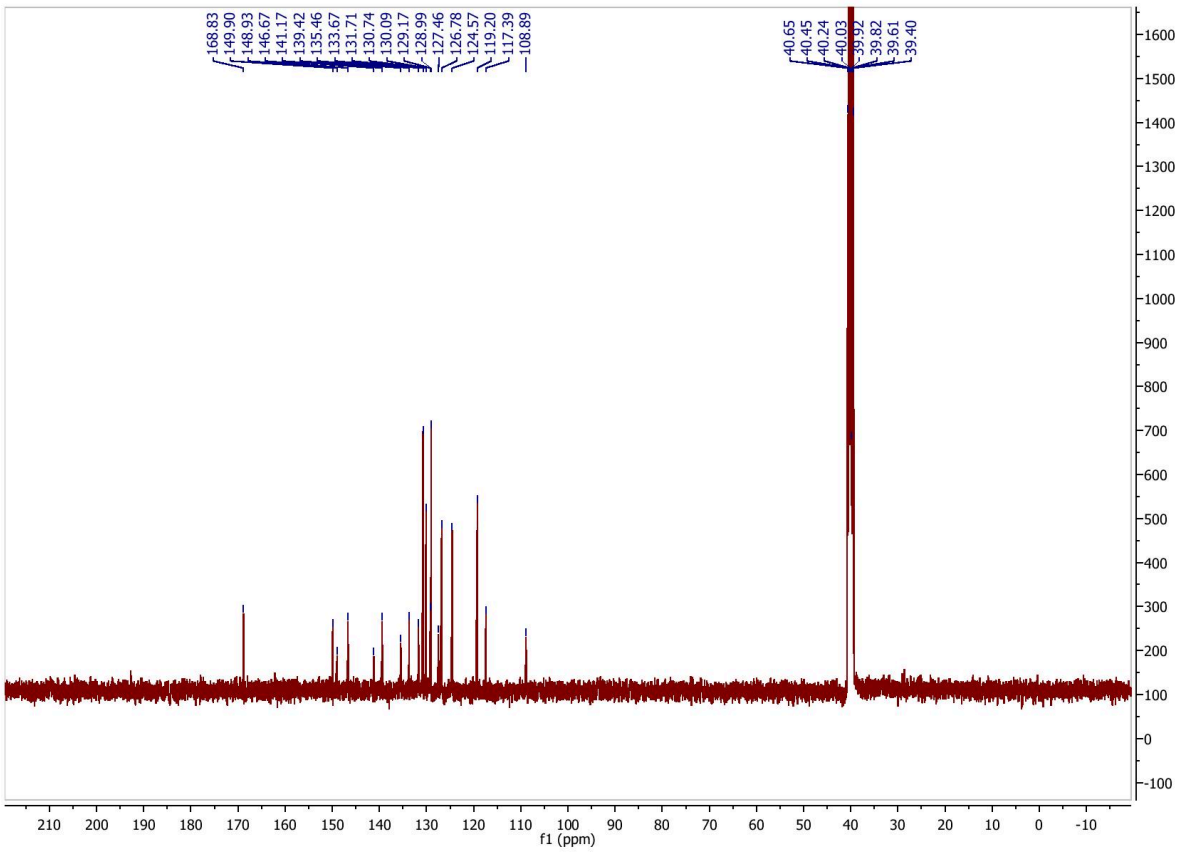

Figure 31: ^{13}C NMR of 1-((3-(4-Chlorophenyl)-1-phenyl-1H-pyrazole-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (4o)

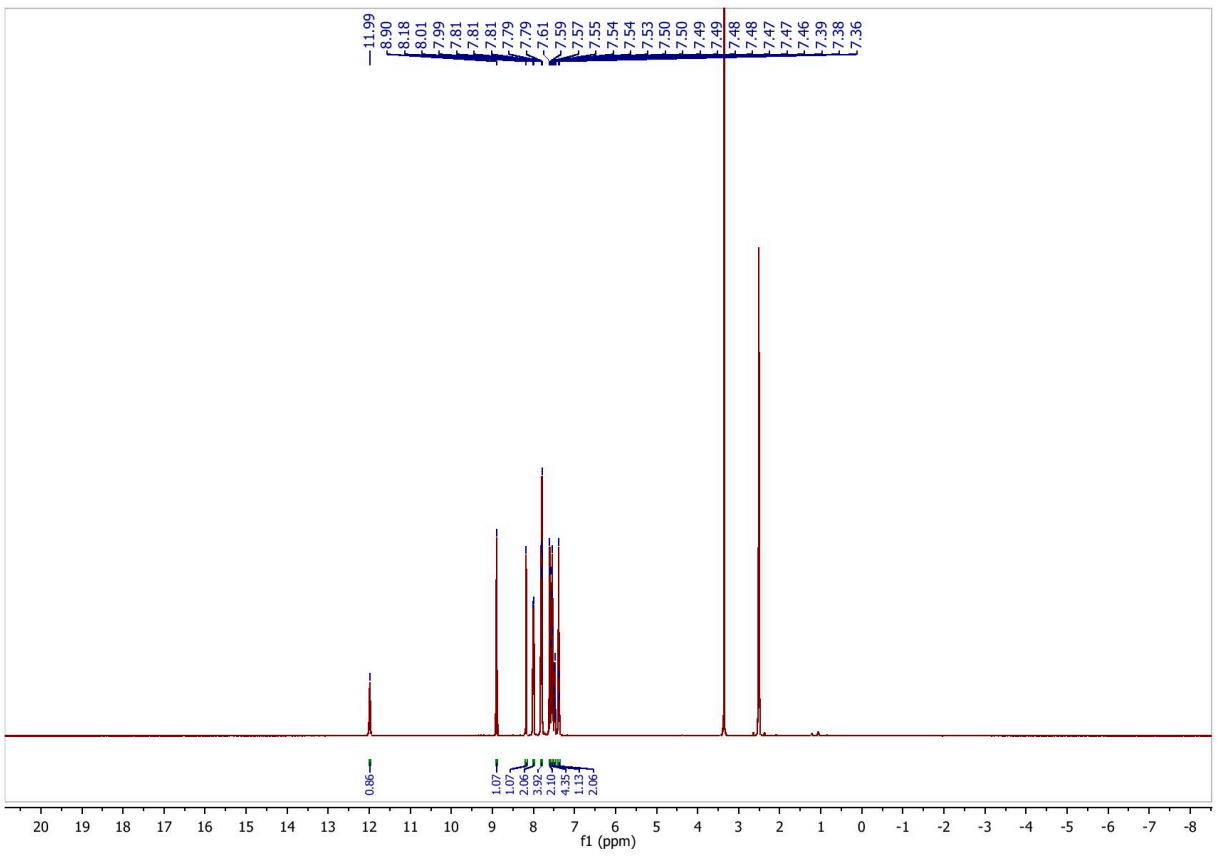

Figure 32: ^{1}H NMR of ((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-2-(4-(4-bromophenyl)thiazol-2-yl)hydrazine (4p)

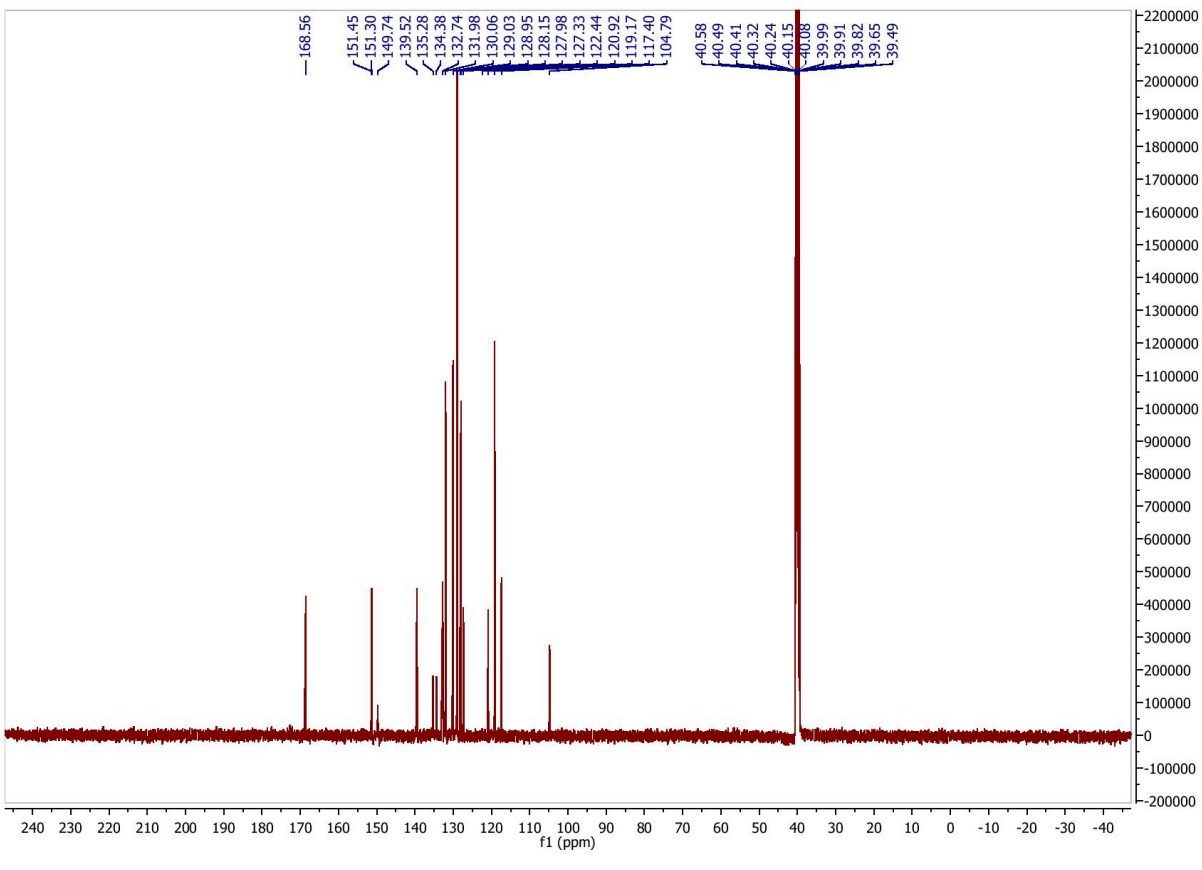

Figure 33: ^{13}C NMR of ((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-2-(4-(4-bromophenyl)thiazol-2-yl)hydrazine (4p)

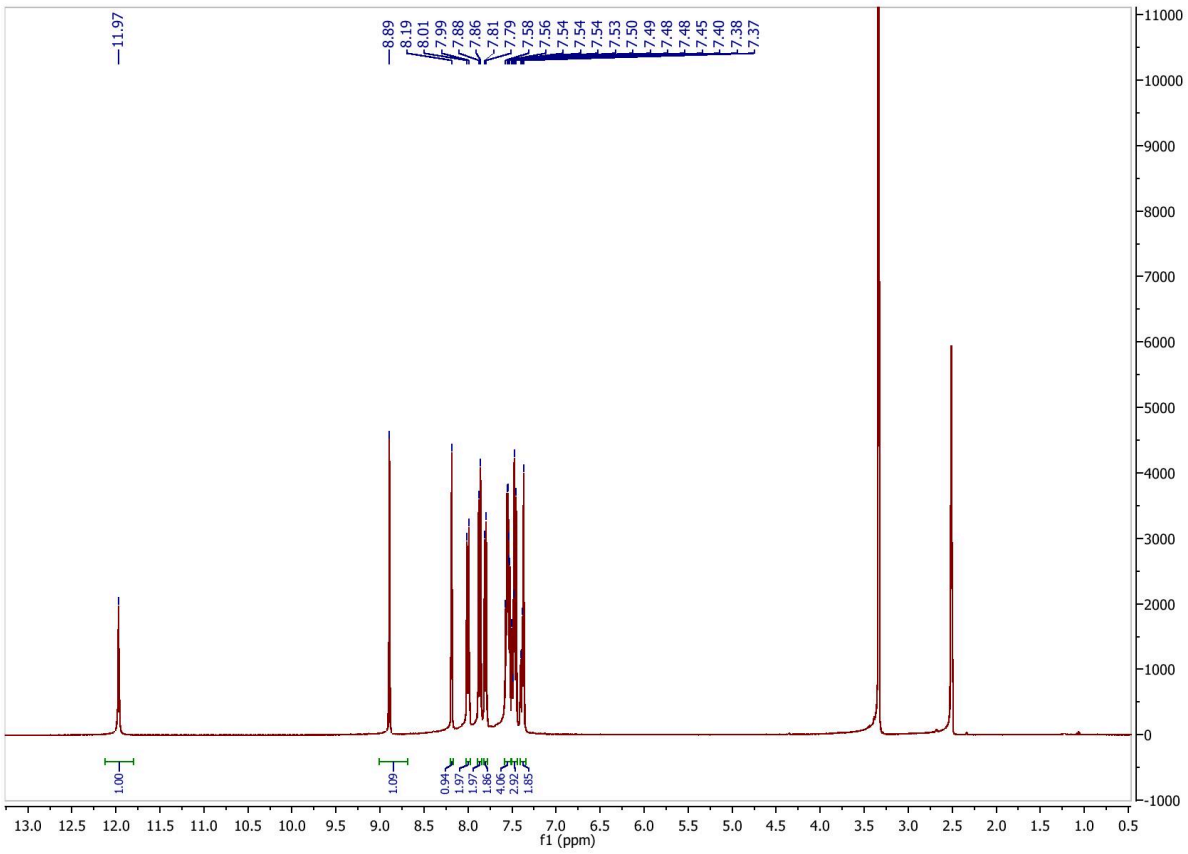

Figure 34: ^{1}H NMR of ((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine (4q)

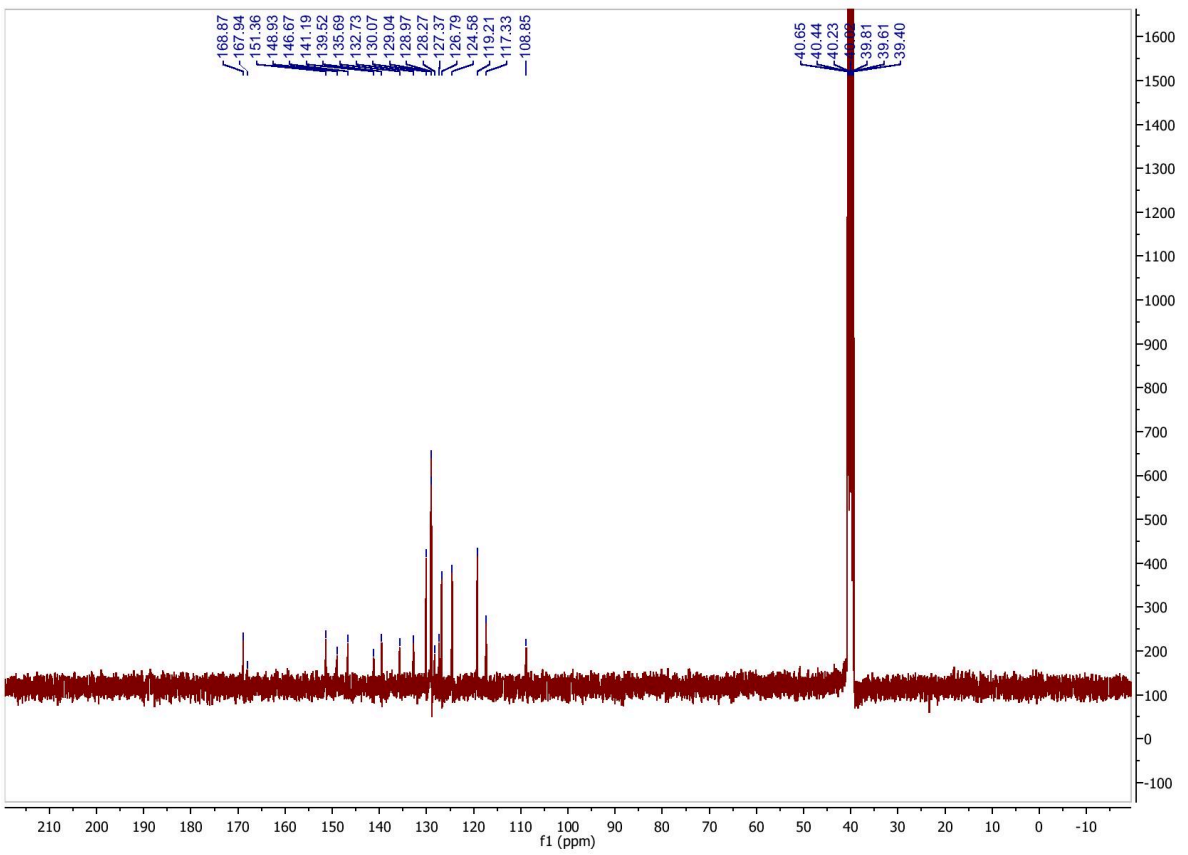

Figure 35: ^{13}C NMR of ((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine (4q)

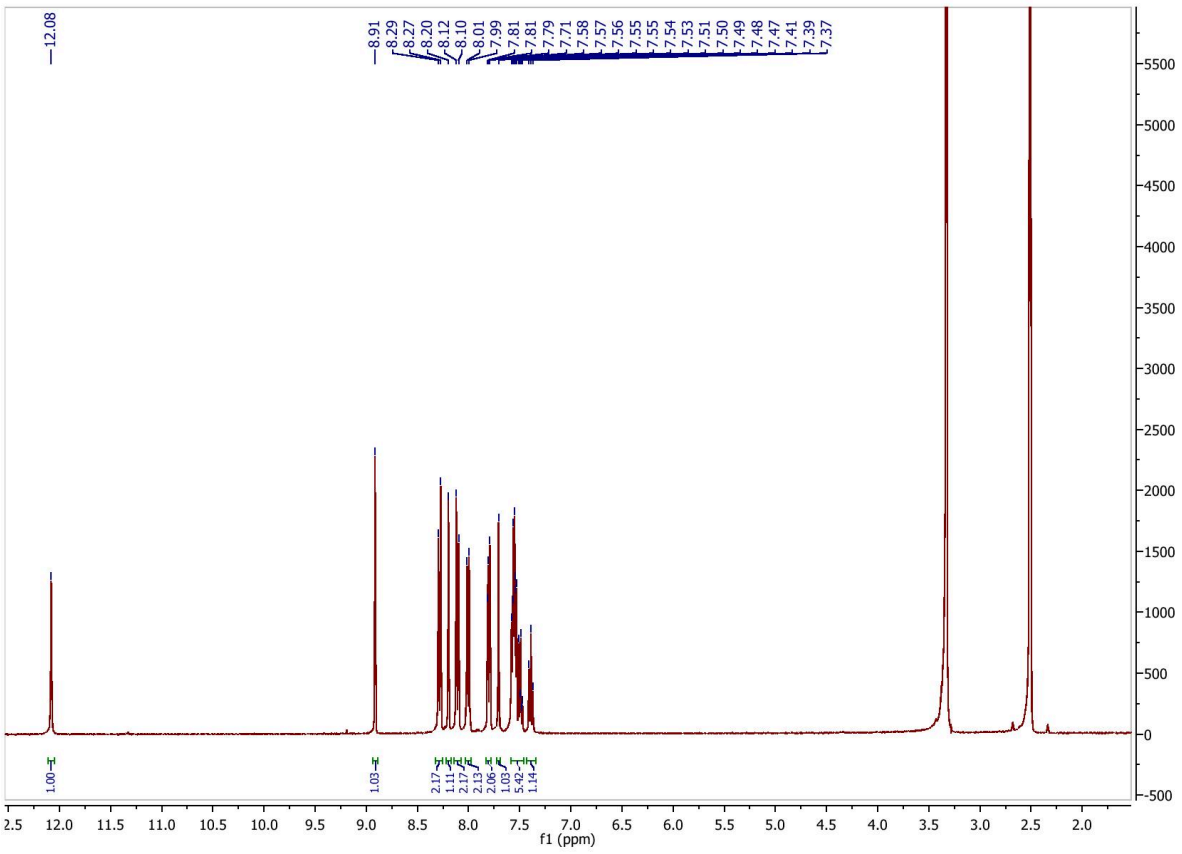

Figure 36: ^{1}H NMR of ((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl) (4r)

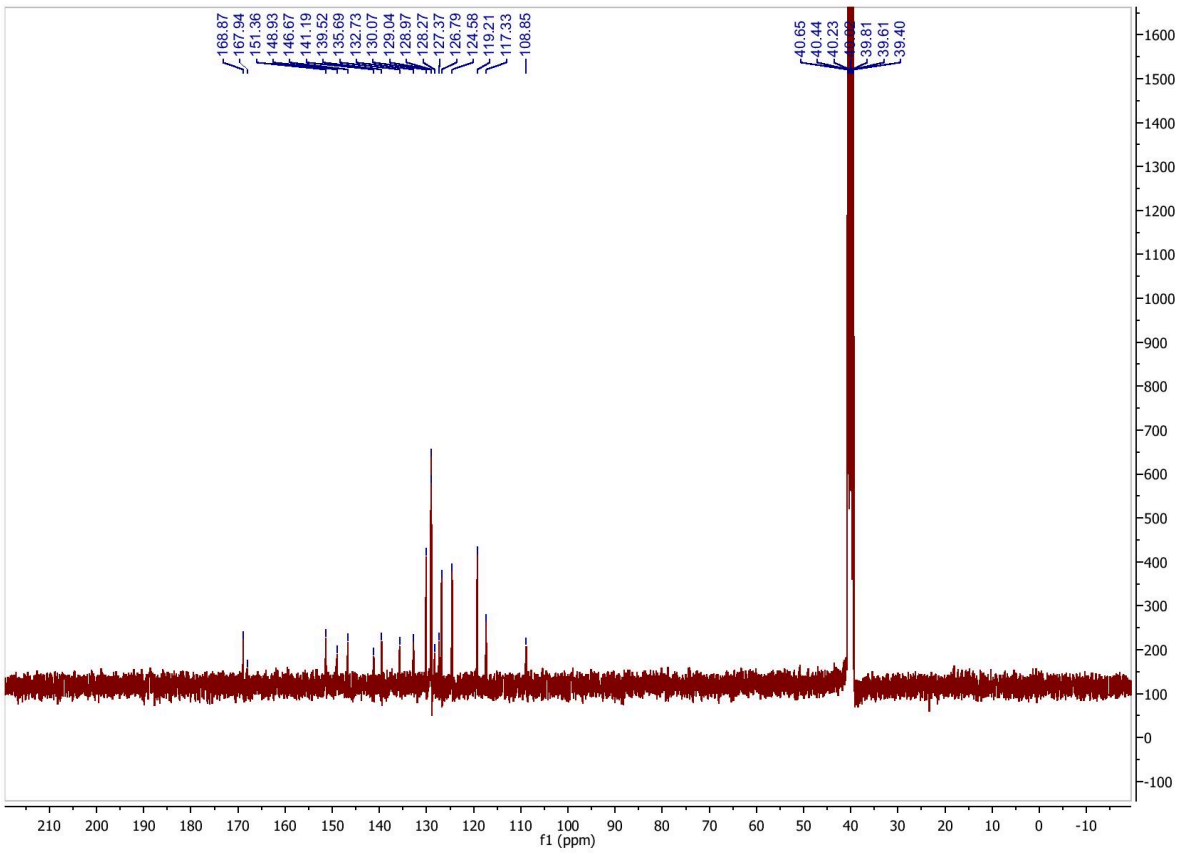

Figure 37: ^{13}C NMR of ((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl) (4r)

Alegaon, S. G., Hirpara, M. B., Alagawadi, K., Jalalpure, S., Rasal, V., Salve, P. S. & Kumbar, V. (**2017**). Synthesis and biological evaluation of 1, 3, 4-trisubstituted pyrazole analogues as anti-mycobacterial agents. *Med. Chem. Res. 26*: 1127-1138.