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Generation of Polar Semi-Saturated Bicyclic Pyrazoles for Fragment-Based Drug Discovery Campaigns.

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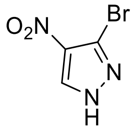
Contents

1. General experimental details

Chemicals and solvents were purchased from Aldrich Chemical Co., Acros, TCI, and Fluorochem. Room temperature (rt) refers to ambient temperature. Temperatures of 0 °C were maintained using an ice-water bath. Temperatures below 0 °C were maintained using an acetone-cardice bath. Yields refer to chromatographically and spectroscopically pure compounds. Analytical thin-layer chromatograph (TLC) was performed on precoated TLC plates (layer 0.20 mm silica gel 60 with fluorescent indicated UV254, from Merck). Developed plates were air-dried and analyzed under a UV lamp (UV 254/365 nm) or sprayed with a potassium permanganate solution to visualize oxidizable substances. Flash column chromatography was performed using prepacked silica gel catridge (230–400 mesh, 40– 63 µm, from SiliCycle) using a Teledyne ISCO Combiflash Companion or Combiflash Retrieve. Microwave-assisted chemistry was conducted using either a CEM or Biotage initiator microwave synthesizer. ^{1}H and ^{13}C NMR spectra were recorded either on a Bruker ARX-400 spectrometer (400 and 100 MHz for ^{1}H and ^{13}C NMR, respectively) or ARX-500 spectrometer (500 and 125 MHz for ^{1}H and ^{13}C NMR, respectively). Chemical shifts (δ) are reported in ppm relative to the residual solvent peak as internal reference and coupling constants (J) are reported in hertz (Hz). Data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, * = refers to peaks of the minor isomer of a regioisomeric/rotational isomeric mixture, ** = refers to overlapping peaks of regioisomers/rotamers), integration. LC–MS analyses were performed with either an Agilent HPLC 1100 series connected to a Bruker Daltonics MicrOTOF. LC–MS chromatographic separations were conducted with a Waters XBridge C18 column, 50 mm × 2.1 mm, 3.5 µm particle size; mobile phase, water–acetonitrile mixture with 0.1% formic acid, or water–acetonitrile mixture with 0.1% ammonia; linear gradient from 80:20 to 5:95 over 6.0 minutes; flow rate of 0.5 mL min–1. High resolution electrospray measurements were performed on a Bruker Daltonics MicrOTOF mass spectrometer. HPLC purification was conducted using Waters AutoPurification System with 3100 Mass Detector, with the column used either Waters XBridge C18 preparative OBD column, 19 mm × 100 mm, 5 µm particle size, or Waters XSelect CSH C18 preparative OBD column, 19 mm × 100 mm, 5 µm particle size.

2. Procedures and analytical data

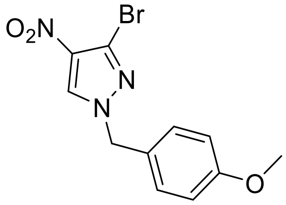
3-bromo-4-nitro-1H-pyrazole (**2a**)



To a solution of 3-bromo-1H-pyrazole **1** (2.8g, 19.7mmol) in H_2SO_4 (9.0ml, 177.5 mmol) was added HNO_3 (1.4ml, 33.5mmol) at rt. Then, the temperature was raised up to 50 °C and the final solution stirred overnight. Upon completion of the reaction, the mixture was poured into a cold saturated solution of $NaHCO_3$ and extracted with EtOAc (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo to afford **2a** as a white solid (3.6g, 18.7mmol, 95%).

^{1}H-NMR (500 MHz, DMSO-d_6): δ 14.30 (br, 1H) , 8.91 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d6): δ 133.17, 133.09, 121.85, 107.44; **LC-MS**, 6 min run, (ESI+) m/z 191.9400 ($[M+H]^+$, ^{79}Br), 193.9381 ($[M+H]^+$, ^{81}Br) Rt = 2.3 min.

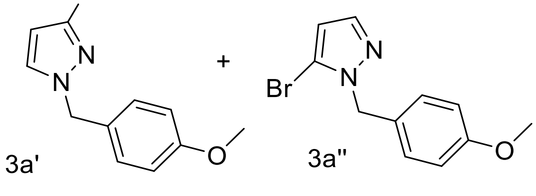
3-bromo-1-(4-methoxybenzyl)-4-nitro-1H-pyrazole (**2**)



To a solution of **2a** (3.6g, 18.7mmol) in MeCN (60ml) was added K_2CO_3 (3.1g, 22.44mmol) and the mixture was stirred at rt for 10 min. Then, 4-methoxybenzyl chloride (5.0ml, 37.4mmol) was added and the temperature raised up to 65 °C. After 48 h, the reaction was quenched with saturated solution of NH_4Cl, the layers separated and the aqueous phase extracted with EtOAc (2x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (EtOAc/Heptane, 15:85) to provide **2** as a white solid (4.7g, 15.06mmol, 79%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.27 (2H, m), 6.94-6.92 (2H, m), 5.22 (2H, s), 3.83 (3H, s); **^{13}C NMR** (125 MHz, $CDCl_3$) : δ 160.51, 133.58, 130.58, 130.42, 124.74, 122.22, 114.80, 57.47, 55.41; **LC-MS**, 6 min run, (ESI+) m/z 311.9985 ($[M+Na]^+$, ^{79}Br), 313.9942 ($[M+Na]^+$, ^{81}Br) Rt = 2.3 min.

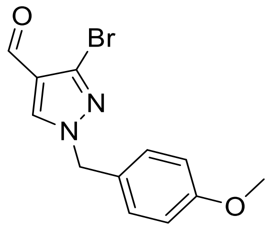
3-bromo-1-(4-methoxybenzyl)-1H-pyrazole (**3a'**), 5-bromo-1-(4-methoxybenzyl)-1H-pyrazole (**3a''**)



To a solution **1** (2.9g, 19.8mmol) in MeCN (60ml) was added K_2CO_3 (3.3g, 23.76mmol) and the mixture was stirred at rt for 10 min. Then, 4-methoxybenzyl chloride (4.0ml, 39.6mmol) was added and the temperature raised up to 65 °C. After 48 h, the reaction was quenched with saturated solution of NH_4Cl, the layers separated and the aqueous phase extracted with EtOAc (2x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (EtOAc/Heptane, 20:80) to provide a 1:0.25 regioisomeric mixture ((3-bromo-1-(4-methoxybenzyl)-1H-pyrazole: 5-bromo-1-(4-methoxybenzyl)-1H-pyrazole) 1:0.25 (**3a'**:**3a''**)) as a white solid (5.0g, 18.7mmol, 95%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.54 (s, 0.25H)*, 7.24-7.20 (m, 3.5H)**, 6.91 (m, 2H), 6.88 (m, 0.5H)*, 6.33 (s, 0.25H)*, 6.28 (s, 1H), 5.33 (s, 0.5H)*, 5.22 (s, 2H), 3.82 (s, 3H), 3.80 (s, 0.75H)*; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.68, 159.31, 140.46, 130.90, 129.56, 128.95, 128.26, 127.54, 125.44, 114.29, 114.09, 112.61, 108.83, 108.75, 56.09, 55.32, 55.27, 53.38; **LC-MS**, 6 min run, (ESI+) m/z 288.9955 ($[M+Na]^+$, ^{79}Br), 290.9956 ($[M+Na]^+$, ^{81}Br) Rt = 3.3 min.

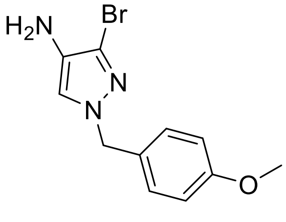
3-bromo-1-(4-methoxybenzyl)-1H-pyrazole-4-carbaldehyde (**3**)



To a solution of **3a'**+**3a''** (5.0g, 18.7mmol) in DMF (14.0 ml) was added $POCl_3$ (15 ml) at rt. Then, the temperature was raised up to 95 °C and the final mixture was stirred for 4 h. Subsequently, the solution was dropwise added to a cooled saturated solution of $NaHCO_3$ and, after the quenched mixture reached rt, extracted with EtOAc (2x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (EtOAc/Heptane, 20:80) to **3** as a yellow solid (3.6g, 12.1mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (1H, s), 7.72 (1H, s), 7.26 - 7.22 (2H, m), 6.94 - 6.89 (2H, m), 5.21 (2H, s), 3.82 (3H, s); **^{13}C NMR** (100MHz, DMSO-d6): δ 184.17, 160.53, 132.94, 130.17, 129.16, 125.55, 121.99, 114.72, 56.90, 55.32; **LC-MS**, 6 min run, (ESI+) m/z 295.0080 ($[M+H]^+$, ^{79}Br), 297.0089 ($[M+H]^+$, ^{81}Br) Rt = 3.2 min.

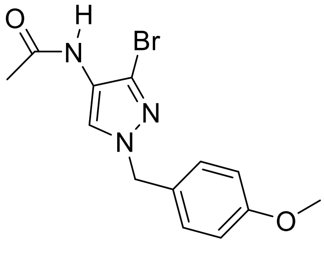
3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-amine (**20**)



To a suspension of **2** 1.42g, 4.53mmol) in EtOH (15mL), iron (2.03g, 36.24mmol) and $NHCl_4$ (970mg, 18.12mmol) in water (4.5 ml) were added. The reaction mixture was heated at 80° C for 2 h. Upon completion, the reaction mixture was allowed to reach r.t., it was basified with Na_2CO_3 and was filtered through a pad of celite eluting with DCM. Afterwards, volatiles were removed under vacuum, water was added and extracted with DCM (2x). The combine organics were then washed with brine, dried over $MgSO_4$ and evaporated under vacuum to afford **20** (1.2g, 4.26mmol, 94%) as a red oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.18 - 7.16 (m, 2H), 6.87 - 6.85 (m, 3H), 5.08 (s, 2H), 3.79 (s, 3H), 2.93 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.59, 129.41, 128.07, 127.97, 118.65, 117.92, 114.21, 56,38, 55.33; **LC-MS**, 6 min run, (ESI+) m/z 282.0248 ($[M+H]^+$, ^{79}Br), 284.0188 ($[M+H]^+$, ^{81}Br) Rt = 2.0 min.

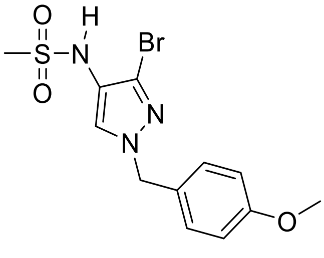
N-(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)acetamide (**21b**)



To a solution of **20** (368mg, 1.30mmol) and pyridine (0.12ml, 1.43mmol) in DCM (4mL) at 0 °C , acetyl chloride (1.0ml, 1.30mmol) was added and the reaction was left under stirring at 0 °C for 1 h. Then, a saturated solution of NH_4Cl was added and the two layers were separated. The aq. layer was further extracted with DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/Heptane, 45:55). The desired fractions were concentrated to dryness in vacuo to afford **21b** (392mg, 1.20mmol, 92%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.21 - 7.18 (m, 2H), 6.96 (s, 1H), 6.86 - 6.84 (m, 2H), 5.13 (s, 2H), 3.78 (s, 3H), 2.15 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.83, 159.70, 129.55, 127.51, 122.60, 120.14, 115.87, 114.30, 56.67, 55.31, 23.48; **LC-MS**, 6 min run, (ESI+) m/z 324.0375 ($[M+H]^+$, ^{79}Br), 326.0359 ($[M+H]^+$, ^{81}Br) Rt = 2.6 min.

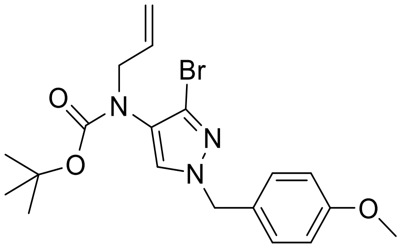
N-(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methanesulfonamide (**21c**)



To a mixture **20** (330mg, 1.17mmol) and pyridine (0.10ml, 1.28mmol) in DCM (3.8mL), methanesulfonyl chloride (0.09ml, 1.28mmol) was added at 0 °C. The mixture was stirred at 0 °C for 2 h. Then, a saturated solution of NH_4Cl was added and the two layers were separated. The aq. layer was further extracted with DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness to afford **21c** (410mg, 1.13mmol, 96%) as a pink solid. The solid was pure enough to be used in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.24-7.20 (m, 2H), 6.91-6.87 (m, 2H), 5.82 (s, 1H), 5.15 (s, 2H), 3.81 (s, 3H), 2.96 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.96, 129.86, 127.90, 126.53, 122.52, 117.73, 114.47, 57.07, 55.34, 39.65; **LC-MS**, 6 min run, (ESI+) m/z 360.0010 ([M+H]$^+$, ^{79}Br), 362.0011 ([M+H]$^+$, ^{81}Br) Rt = 2.8 min.

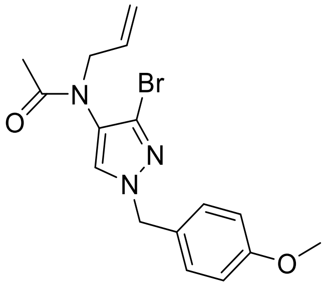
tert-butyl allyl(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)carbamate (**22a**)



To a solution of **20** (275mg, 0.97mmol) and Et$_3$N (0.16ml, 1.16mmol) in THF (2 mL) at rt under nitrogen was added Boc anhydride (255mg, 1.16mmol) solution in THF (1ml). The reaction mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure. The crude product (**21a**) was used in the next step without further purification. The crude (**21a**) was dissolved in THF (8ml) under nitrogen at 0 °C and NaH (60% dispersion in mineral oil, 58mg, 1.45mmol) was added portionwise. The reaction mixture was allowed to warm up to rt, then 3-bromoprop-1-ene (0.1ml, 1.16mmol) was added. The reaction mixture was stirred under reflux overnight. The reaction was cooled and EtOAc was added, then water was carefully added. The aq. layer was extracted with EtOAc (3x). The combined organics were then washed and dried over MgSO$_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ Heptane, 25:75). The desired fractions were concentrated to dryness in vacuo to afford **22a** (340mg, 0.80 mmol, 82%) as a white solid. Compound **22a** was isolated as a mixture 1:0.2 of two rotamers.

^{1}H-NMR (500 MHz, CDCl$_3$): δ 7.43 (s, 0.2H)*, 7.16 (br, 3.4H)**, 6.85-6.82 (m, 2H), 6.81-6.78 (m, 0.4H)*, 5.86 - 5.74 (m, 1.2H)**, 5.26 (s, 0.4H)*, 5.12 (s, 2H), 5.08 (m, 0.4H)*, 5.06 (t, J=1.4 Hz, 1H), 5.03 (qd, J=1.4, 7.5 Hz, 1H), 4.06 (br, 2.4H)**, 3.76 (s, 3H), 3.74 (s, 0.6H)*, 1.41 (s, 10.8H)**; **^{13}C NMR** (125 MHz, CDCl$_3$): δ 159.66, 159.28, 154.35, 137.77, 133.74, 129.14, 128.37, 127.99, 127.51, 125.17, 124.16, 117.42, 114.26, 114.05, 80.57, 56.55, 55.29, 55.24, 54.15, 52.32, 28.16; broadening of peaks is due to the slow rotation of the carbamate linkage; **LC-MS**, 6 min run, (ESI+) m/z 422.1087 ([M+H]$^+$, ^{79}Br), 424.1069 ([M+H]$^+$, ^{81}Br) Rt = 4.1 min

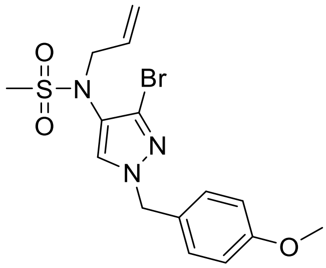
N-allyl-N-(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)acetamide (**22b**)



To a mixture of **21b** (392mg, 1.20mmol) and 3-bromoprop-1-ene (0.21ml, 2.40mmol) in DMF (5mL) , NaH (60% dispersion in mineral oil, 100mg, 2.40mmol) was added portionwise at 0 °C. The reaction was then left at rt for 2 h. Once the starting material was completely consumed, a saturated solution of NH$_4$Cl was added and extraction was performed with DCM (3x). The organics were then separated, washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ Heptane, 35:65). The desired fractions were concentrated to dryness in vacuo to provide **22b** (386mg, 1.05mmol, 87%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): d 7.22 - 7.19 (m, 3H), 6.93 - 6.91 (m, 2H), 5.83 - 5.74 (m, 1H), 5.20 (s, 2H), 5.11 (qd, J=1.2, 10.2 Hz, 1H), 5.05 (qd, J=1.2, 17.0 Hz, 1H), 4.19 (br, 2H), 3.84 (s, 3H), 1.91 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.07, 15.92, 132.99, 129.55, 128.41, 126.76, 125.60, 124.79, 118.25, 114.46, 56.90, 55.34, 51.32, 22.21; **LC-MS**, 6 min run, (ESI+) m/z 364.0675 ($[M+H]^+$, ^{79}Br), 366.0659 ($[M+H]^+$, ^{81}Br) Rt = 3.2 min

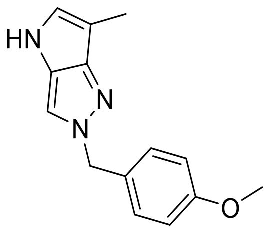
N-allyl-N-(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methanesulfonamide (**22c**)



To a mixture of **21c** (410mg, 1.13 mmol) and K_2CO_3 (236mg, 1.69mmol) in MeCN (7.5mL), 3-bromoprop-1-ene (0.15ml, 1.69mmol) was added. The final mixture was heated under reflux for 2h. Then, a saturated solution of NH_4Cl was added and extraction was carried out with EtOAc (3x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ Heptane, 30:70). The desired fractions were concentrated to dryness in vacuo to afford **22c** (406mg, 1.01mmol, 89%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (s, 1H), 7.21 - 7.17 (m, 2H), 6.90 - 6.87 (m, 2H), 5.83 - 5.74 (m, 1H), 5.14-5.10 (m, 3H), 4.15 (dt, J=1.2, 6.4 Hz, 2H), 3.80 (s, 3H), 2.98 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.90, 132.85, 131.93, 129.77, 126.49, 124.70, 119.83, 119.28, 114.44, 56.97, 55.34, 53.2, 39.97; **LC-MS**, 6 min run, (ESI+) m/z 400.0303($[M+H]^+$, ^{79}Br), 402.0427 ($[M+H]^+$, ^{81}Br) Rt = 3.4 min

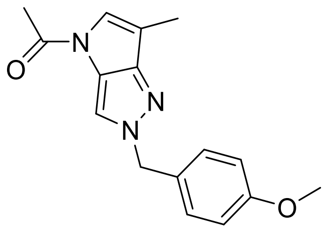
2-(4-methoxybenzyl)-6-methyl-2,4-dihydropyrrolo[3,2-c]pyrazole (**23a**)



A microwave vial was charged with **22a** (340mg, 0.80mmol) $Pd(dppf)Cl_2$ (58.7mg, 0.08mmol) Cs_2CO_3 (525mg, 1.60mmol) and DMF (3.5 mL). The vial was evacuated and backfilled three times with nitrogen and heated under microwave irradiation conditions at 140 °C and 200 W for 30min. Then, was were added and extraction was carried out with EtOAc (3x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ Heptane, 35:65). The desired fractions were concentrated to dryness in vacuo to afford **23a** (Boc protected) (170mg, 0.50mmol, 62%) as a white solid. A small amount of the latter was deprotected by using TFA in DCM, in order to get more comprehensible NMR spectra. LC-MS values of both the protected and deprotected version are reported.

^{1}H NMR (without Boc) (500 MHz, MeOD$_4$) δ 7.31 - 7.30 (m, 1H), 7.15 (m, 2H), 6.86 - 6.83 (m, 3H), 5.29 (s, 2H), 3.74 (s, 3H), 2.18 (t, 3H, J= 1.1 Hz); **^{13}C NMR** (without Boc) (125 MHz, CDCl$_3$): δ 159.35, 149.87, 129.68, 128.52, 128.38, 127.21, 113.53, 109.05, 101.27, 55.29, 54.2, 8.24; **LC-MS**, 6 min run, (ESI+) m/z 342.1222 [M+H]$^+$ (with Boc) Rt = 3.8 min; **LC-MS**, 6 min run, (ESI+) m/z 242.1298 [M+H]$^+$ (without Boc) Rt = 2.4 min.

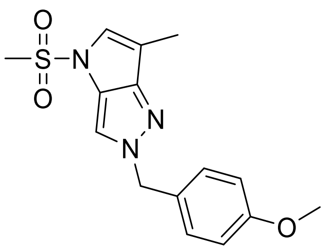
1-(2-(4-methoxybenzyl)-6-methylene-5,6-dihydropyrrolo[3,2-c]pyrazol-4(2H)-yl)ethan-1-one (**23b**)



A microwave vial was charged with **22b** (385mg, 1.05mmol), Pd(dppf)Cl$_2$ (78mg, 0.105mmol), Cs$_2$CO$_3$ (685mg, 2.10mmol) and DMF (4.0 mL). The vial was evacuated and backfilled three times with nitrogen and heated under microwave irradiation conditions at 140 °C and 200 W for 30min. Then, water was added and extraction was carried out with EtOAc (3x). The combined organics were washed with brine and dried over MgSO$_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ Heptane, 50:50). The desired fractions were concentrated to dryness in vacuo to afford **23b** (207mg, 0.73mmol, 69%) as a white solid. Compound **23b** was isolated as a mixture 1:0.5 of two rotamers.

^{1}H-NMR (500 MHz, CDCl$_3$): δ 7.58 (s, 1H), 7.43 (br, 0.5H)*, 7.24-7.19 (m, 3H)*, 7.13 (s, 0.5H)*, 6.94 (q, J=1.2 Hz, 1H) 6.90 - 6.83 (m, 3H), 5.35 (s, 1H)*, 5.34 (s, 2H), 3.80 (s, 1.5H)*, 3.79 (s, 3H), 2.43 (s, 3H), 2.42 (s, 1.5H)*, 2.25 (d, J=1.2 Hz, 3H), 2.24 (br, 1.5H)*; **^{13}C NMR** (125 MHz, CDCl$_3$): δ 165.80, 165.39, 159.50, 150.0, 129.31, 129.21, 128.60, 128.50, 125.66, 125.52, 124.31, 114.94, 114.3 114.2, 113.9, 112.31, 56.62, 56.56, 55.31, 23.24, 21.26, 9.90, 9.75; **LC-MS**, 6 min run, (ESI+) m/z 284.1419 [M+H]$^+$, Rt = 2.9 min.

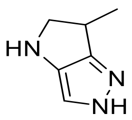
2-(4-methoxybenzyl)-6-methylene-4-(methylsulfonyl)-2,4,5,6-tetrahydropyrrolo[3,2-c]pyrazole (**23c**)



A microwave vial was charged with **22c** (406mg, 1.01mmol), Pd(dppf)Cl$_2$ (74mg, 0.101mmol) Cs$_2$CO$_3$ (660mg, 2.02mmol) and DMF (3.5mL) . The vial was evacuated and backfilled three times with nitrogen and heated under microwave irradiation conditions at 140 °C and 200 W for 30min. Then, water was added and extraction was carried out with EtOAc (3x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ Heptane, 40:60). The desired fractions were concentrated to dryness in vacuo to afford **23c** (256mg, 0.80mmol, 79%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.24-7.21 (m, 2H), 6.91 (q, J=1.4 Hz, 1H), 6.88-6.85 (m, 2H), 5.33 (s, 2H), 3.79 (s, 4H), 2.87 (s, 3H), 2.25 (d, J=1.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.68, 150.49, 129,51, 128.13, 127.12, 125.34, 115.28, 114.34, 113.09, 56.86, 55.30, 38.75, 9.76; **LC-MS**, 6 min run, (ESI+) m/z 320.1084 $[M+H]^+$, Rt = 3.1 min

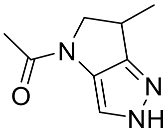
6-methyl-2,4,5,6-tetrahydropyrrolo[3,2-c]pyrazole (**4a**)



A 0.05 M solution of **23a** (170mg, 0.50mmol) in EtOH (10ml) was hydrogenated in H-cube Pro. Initially, the parameters (temperature: 50°C, pressure: 50bar, and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (4.5ml) and anisole (0.33ml, 3.0mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for12 h. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **4a** (30mg, 0.26mmol, 52%) as a colourless oil.

^{1}H-NMR (500 MHz, $MeOD_4$): δ 7.21 (s, 1H), 4.12 (dd, J=8.3, 10.5 Hz, 1H), 3.51 (dd, J=6.9, 10.5 Hz, 1H), 3.40 (qdd, J= 6.7, 6.9, 8.3 Hz, 1H), 1.33 (d, J=6.7 Hz, 3H); **^{13}C NMR** (125 MHz, $MeOD_4$): δ156.63, 131.97, 116.79, 63.09, 32.74, 18.57; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_6H_9N_3$: 124.0869, found: 124.0876.

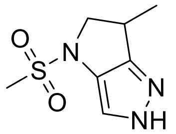
1-(6-methyl-5,6-dihydropyrrolo[3,2-c]pyrazol-4(2H)-yl)ethan-1-one (**4b**)



A 0.05 M solution of **23b** (207mg, 0.73mmol) in EtOH (15ml) was hydrogenated in H-cube. Initially, the parameters (temperature: 50°C, pressure: 50bar, and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA and anisole was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **4b** (73mg, 0.44mmol, 60%) as a white solid. Compound **4b** was isolated as a mixture 1:0.77 of two rotamers.

¹H-NMR (500 MHz, MeOD): δ 7.40 (s, 1H), 7.30 (s, 0.77H)*, 4.63 (dd, J=9.2, 10.7 Hz, 1H), 4.52 (dd, J=9.1, 12.1 Hz, 0.77H)*, 3.98 (dd, J=5.8, 10.7 Hz, 1H), 3.83 (dd, J=5.8, 12.1 Hz, 0.77H)*, 3.60 (qdd, J=5.8, 7.0, 9.2 Hz, 1H), 3.47 (qdd, J=5.8,6.8, 9.1 Hz, 0.77H)*, 2.21 (s, 2.3H)*, 2.13 (s, 3H), 1.36 (d, J=7.0 Hz, 3H), 1.33 (d, J=6.8 Hz, 2.3H)*; **^{13}C NMR** (125 MHz, , MeOD$_4$): δ 169.76, 168.76, 155.44, 154.61, 129.55, 129.34, 116.45, 115.26, 63.82, 62.53, 32.87, 31.31, 22.86, 21.39, 19.62, 19.60; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{11}N_3O$: 166.0975, found: 166.0980.

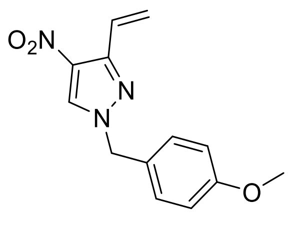
6-methyl-4-(methylsulfonyl)-2,4,5,6-tetrahydropyrrolo[3,2-c]pyrazole (**4c**)



A 0.05 M solution of **23c** (256mg, 0.80mmol) in EtOH (16 ml) was hydrogenated in H-cube. Initially, the parameters (temperature: 50°C, pressure: 50bar, and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA and anisole was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **4c** (90mg, 0.45mmol, 56%) as a white solid.

¹H-NMR (500 MHz, MeOD$_4$): δ 7.21 (s, 1H), 4.44 (dd, J=8.7, 11.1 Hz, 1H), 3.80 (dd, J=6.6, 11.1 Hz, 1H), 3.55 (qdd, J=6.6, 6.9, 8.7 Hz, 1H), 2.87 (s, 3H), 1.35 (d, J=6.9 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 154.79, 130.27, 116.22, 65.85, 33.25, 32.85, 19.05; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_{11}N_3O_2S$: 202.0645, found 202.0649: .

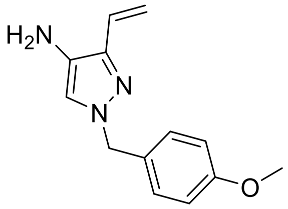
1-(4-methoxybenzyl)-4-nitro-3-vinyl-1H-pyrazole (**24**)



A flask was charged with **2** (1.22g, 3.90mmol), CsF (1250mg, 7.80mmol), Pd(t-Bu$_3$P)$_2$ (104mg, 0.19mmol) and THF (22 mL) under nitrogen atmosphere. Then, tributyl(vinyl)stannane (257.87mg, 4.68mmol) was added and the final mixture was stirred at rt for 24 h. Subsequently, the reaction was diluted with Et$_2$O and water was added. The two layers were separated and the aq. one was extracted further with Et$_2$O (2x). The combined organics were washed with brine and dried over MgSO$_4$ before concentration to dryness. The crude was then passed through celite eluting with DCM and purified by flash column chromatography (EtOAc/ Heptane, 20:80). The desired fractions were concentrated to dryness in vacuo to afford **24** (933mg, 3.32mmol, 85%) as a colourless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.28-7.25 (m, 2H), 7.21 (dd, J=11.2, 17.7 Hz, 1H), 6.94 - 6.92 (m, 2H), 6.22 (dd, J=1.8, 17.7 Hz, 1H), 5.54 (dd, J=1.8, 11.2 Hz, 1H), 5.21 (s, 2H), 3.83 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 160.27, 144.97, 130.21, 129.62, 125.48, 120.01, 120.56, 114.69, 56.93, 55.39; **LC-MS**, 6 min run, (ESI+) m/z 282.0852 $[M+H]^+$, Rt = 3.6 min

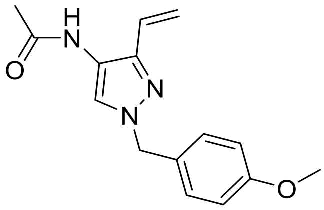
1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-amine (**25**)



To a suspension of **24** (933mg, 3.32mmol) in EtOH (10mL), iron (1.60g, 26.5mmol) and NH_4Cl (770mg, 13.28mmol) in water (1.7 ml) were added. The reaction mixture was heated at 80 °C for 2 h. Upon completion, the reaction mixture was allowed to reach rt, it was basified with Na_2CO_3 and was filtered through a pad of celite eluting with DCM. Afterwards, volatiles were removed under vacuum, water was added and extracted with DCM (2x). The combined organics were then washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The crude was then purified by flash column chromatography (MeOH/ DCM, 8:92). The desired fractions were concentrated to dryness in vacuo to afford **25** (650mg, 2.79mmol, 84%) as a reddish solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.18-7.15 (m, 2H), 6.87-6.84 (d, 2H), 6.86 (s, 1H), 6.71 (dd, J=11.7, 18.2 Hz, 1H), 5.69 (dd, J=1.4, 18.2 Hz, 1H), 5.29 (dd, J=1.4, 11.7 Hz, 1H), 5.09 (s, 2H), 3.79 (s, 3H), 2.54 (br, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.42, 139.75, 129.20, 128.60, 128.02, 127.71, 118.73. 114.14, 113.98, 55.77, 55.31; **LC-MS**, 6 min run, (ESI+) m/z 230.1292 $[M+H]^+$, Rt = 1.8 min

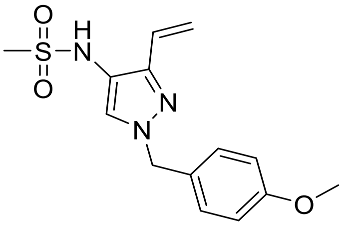
N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)acetamide (**26b**)



To a solution of **25** (155mg, 0.68mmol) and pyridine (0.083ml, 1.02mmol) in DCM 2mL) at 0 °C , acetyl chloride (0.081ml, 0.68mmol) was added and the reaction was left under stirring at 0 °C for 1 h. Then, a saturated solution of NH_4Cl was added and the two layers were separated. The aq. layer was further extracted with DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (MeOH/ DCM, 3:97). The desired fractions were concentrated to dryness in vacuo to afford **26b** (160mg, 0.58 mmol, 85%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.20-7.17 (m, 2H), 7.10 (br, 1H), 6.86-6.83 (d, 2H), 6.64 (dd, J=11.4, 18.0 Hz, 1H), 5.71 (dd, J=1.0, 18.0 Hz, 1H), 5.35 (dd, J=1.0, 11.4 Hz, 1H), 5.14 (s, 2H), 3.78 (s, 3H), 2.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.31, 159.51, 139.37, 129.38, 128.07, 126.87, 123.19, 118.47, 115.80, 114.21, 56.05, 55.30, 23.60; **LC-MS**, 6 min run, (ESI+) m/z 272.1415 $[M+H]^+$, Rt = 2.9 min

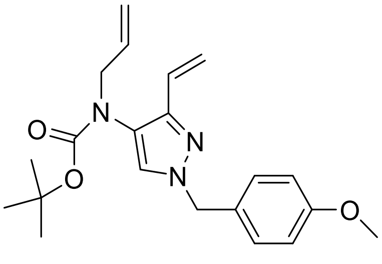
N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methanesulfonamide (**26c**)



To a mixture of **25** (130mg, 0.57mmol) and pyridine (0.069ml, 0.85mmol) in DCM (2mL), methanesulfonyl chloride (0.044ml, 0.57mmol) was added at 0 °C. The mixture was stirred at 0 °C for 2 h. Then, a saturated solution of NH_4Cl was added and the two layers were separated. The aq. layer was further extracted with DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness to afford **26c** (162mg, 0.52mmol, 91%) as a reddish solid. The latter was pure enough to be used in the next step without further purification.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.21 - 7.18 (m, 2H), 6.88 - 6.85 (m, 2H), 6.63 (dd, J=11.4, 17.9 Hz, 1H), 6.35 (s, 1H), 5.94 (dd, J=1.4, 17.9 Hz, 1H), 5.35 (dd, J=1.4, 11.4 Hz, 1H), 5.14 (s, 2H), 3.79 (s, 3H), 2.89 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.70, 144.65, 129.58, 128.04, 127.42, 125.82, 116.81, 115.46, 114.34, 56.31, 55.33, 39.17; **LC-MS**, 6 min run, (ESI+) m/z 308.1093 $[M+H]^+$, Rt = 2.7 min

tert-butyl allyl(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)carbamate (**27a**)

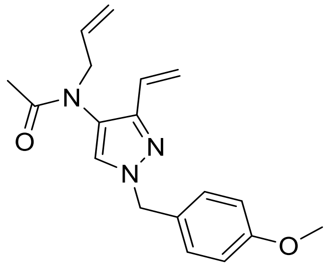


To a solution of **25** (200mg, 0.87mmol) and Et_3N (0.15ml, 1.05ml) in THF (3mL) at rt under nitrogen was added Boc anhydride (210mg, 0.95mmol) solution in THF (0.8ml). The reaction mixture was stirred at 25 °C for 12h. Then, volatiles were removed under reduced pressure and the crude product (**26a**) was used in the next step without further purification. The latter was dissolved in THF (4.7ml) under nitrogen at 0 °C and NaH (60% dispersion in mineral oil, 53mg, 1.3mmol) was added portionwise. The reaction mixture was allowed to warm up to rt, then 3-bromoprop-1-ene (0.09ml, 1.05mmol) was added. The reaction mixture was stirred under reflux overnight. The reaction was cooled and EtOAc was added, then water was carefully added. The aq. layer was extracted with EtOAc (3x). The organics were then separated, washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ heptane, 35:65). The desired fractions were concentrated to dryness in vacuo to afford **27a** (283mg, 0.76mmol, 87%) as a white solid. Compound **27a** was isolated as a mixture 1:0.18 of two rotamers.

^{1}H-NMR (400 MHz, $CDCl_3$): d 7.37 (br, 0.18H)*, 7.11 (br, 3H), 6.97 (br, 0.36H)*, 6.91 - 6.86 (m, 2H), 6.83 (d, J=8.4 Hz, 0.36H)*, 6.59 (dd, J=11.5, 17.9 Hz, 1H), 6.45 (dd, J=11.5, 17.9 Hz, 0.18H)*, 5.86 - 5.75

(m, 2.18H)**, 5.58 (dd, J=1.2, 17.9 Hz, 0.18H)*, 5.38 (d, J=12.4 Hz, 0.18H)**, 5.30 (dd, J=1.6, 11.5 Hz, 1.18H)**, 5.18 (s, 2H), 5.16 - 5.13 (m, 0.18H)*, 5.10 - 5.05 (m, 2.54H)**, 4.04 (br, 2.36H)**, 3.81 (s, 3H), 3.79 (s, 0.54H)*, 1.38 (br, 10.62H)**; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.43, 154.83, 145.24, 137.09, 133.77, 128.90, 127.50, 127.07, 122.63, 117.32, 115.56, 114.11, 80.26, 55.90, 55.39, 52.36, 28.18; broadening of peaks is due to the slow rotation of the carbamate linkage; **LC-MS**, 6 min run, (ESI+) m/z 370.2099 $[M+H]^+$, Rt = 4.1 min.

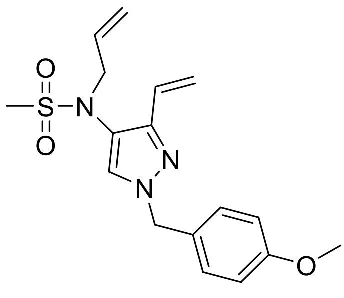
N-allyl-N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)acetamide (**27b**)



To a mixture of **26b** (160mg, 0.58mmol) and 3-bromoprop-1-ene (0.10ml, 1.16mmol) in DMF (3.5mL), NaH (60% dispersion in mineral oil, 45mg, 1.16mmol) was added portionwise at 0 °C. The reaction was then left at rt for 2 h. Once the starting material was completely consumed, water was added and extraction was performed with DCM (3x). The organics were then separated, washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ heptane, 50:50). The desired fractions were concentrated to dryness in vacuo to afford **27b** (165mg, 0.53mmol, 90%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.17 - 7.13 (m, 2H), 7.13 (s, 1H), 6.89 - 6.86 (m, 2H), 6.56 (dd, J=11.4, 18.0 Hz, 1H), 5.79 - 5.71 (m, 2H), 5.32 (dd, J=1.2, 11.4 Hz, 1H), 5.17 (s, 2H), 5.07 (dq, J=1.3, 10.0 Hz, 2H), 5.02 (dq, J=1.3, 17.0 Hz, 2H), 4.11 (br, 2H), 3.79 (s, 3H), 1.85 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.35, 159.68, 145.23, 132.94, 129.26, 127.97, 127.57, 126.53, 122.97, 118.23, 116.53, 114.34, 56.22, 55.33, 51.24, 22.24; **LC-MS**, 6 min run, (ESI+) m/z 312.1725 $[M+H]^+$, Rt = 3.4 min

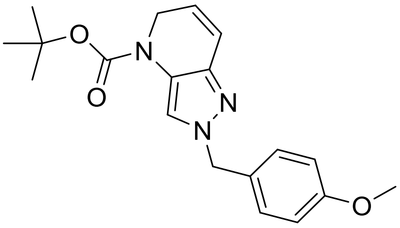
N-allyl-N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methanesulfonamide (**27c**)



To a mixture of **26c** (162mg, 0.52mmol) and K_2CO_3 (146mg, 1.04mmol) in MeCN (3.7mL), 3-bromoprop-1-ene (0.09ml, 1.04mmol) was added. The final mixture was heated under reflux for 2h. Then, a saturated solution of NH_4Cl was added and extraction was carried out with EtOAc (3x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ heptane, 40:60). The desired fractions were concentrated to dryness in vacuo to afford **27c** (170mg, 0.49mmol, 93%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 1H), 7.18 - 7.14 (m, 2H), 6.89-6.85 (m, 2H), 6.63 (dd, J=11.4, 17.9 Hz, 1H), 5.97 (dd, J=1.5, 17.9 Hz, 1H), 5.86 - 5.74 (m, 1H), 5.35 (dd, J=1.5, 11.4 Hz, 1H), 5.16 (s, 2H), 5.14 - 5.06 (m, 2H), 4.06 (d, J=6.6 Hz, 2H), 3.79 (s, 3H), 2.86 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.67, 146.51, 132.76, 129.89, 129.45, 127.39, 126.18, 119.55, 118.55, 116.74, 114.32, 56.33, 55.32, 54.12, 39.09; **LC-MS**, 6 min run, (ESI+) m/z 348.1417 $[M+H]^+$, Rt = 3.2 min.

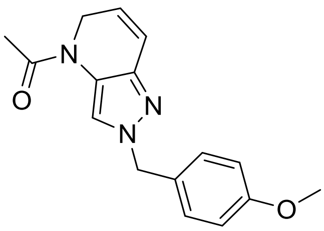
tert-butyl 2-(4-methoxybenzyl)-2,5-dihydro-4H-pyrazolo[4,3-b]pyridine-4-carboxylate (**28a**)



A flask with **27a** (283mg, 0.76mmol) **27a** in DCM (70mL) was degassed and backfilled with nitrogen three times. Then, Grubb's catalyst 2nd generation (32mg, 0.038mmol) was added and the final solution was heated at 40 °C for 2 h. Upon completion, DCM was removed and the crude was purified by flash column chromatography (EtOAc/ heptane, 45:55). The desired fractions were concentrated to dryness in vacuo to afford **28a** (193mg, 0.56mmol, 73%) as a colourless oil. Compound **28a** was isolated as a mixture 0.7:0.3 of two rotamers.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.55 (br, 0.3H)*, 7.25 (br, 0.7H), 7.20 - 7.13 (br, 2H)**, 6.89 (m, Hz, 2H)**, 6.75 - 6.64 (br, 1H)**, 5.81 (br, 1H)**, 5.20 (s, 2H)**, 4.41 (br, 1H)**, 4.34 (br, 1H)**, 3.72 (s, 3H)**, 1.48 (s, 9H)**; **^{13}C NMR** (125 MHz, DMSO-d6): δ 159.21, 152.13, 129.72, 129.44, 129.33, 129.19, 129.00, 129.38, 123.72, 121.07, 115.04, 114.77, 114.39, 81.28, 80.68, 55.54, 55.36, 52.28, 46.32, 45.20, 28.40, 27.88; broadening of peaks is due to the slow rotation of the carbamate linkage; **LC-MS**, 6 min run, (ESI+) m/z 342.1803 $[M+H]^+$, Rt = 4.2 min

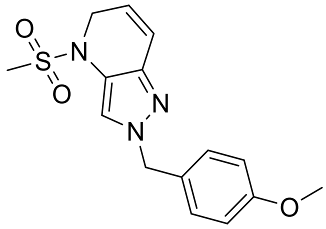
1-(2-(4-methoxybenzyl)-2,5-dihydro-4H-pyrazolo[4,3-b]pyridin-4-yl)ethan-1-one (**28b**)



A flask with **27b** (165mg, 0.53mmol) in DCM (48mL) was degassed and backfilled with nitrogen three times. Then, Grubb's catalyst 2nd generation (30mg, 0.035mmol) was added and the final solution was heated at 40 °C for 2 h. Upon completion, DCM was removed and the crude was purified by flash column chromatography (MeOH/ DCM, 2:98). The desired fractions were concentrated to dryness in vacuo to afford **28b** (105mg, 0.37mmol, 70%) as a colourless oil. Compound **28b** was isolated as a mixture 1:0.2 of two rotamers.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J=0.6 Hz, 1H), 7.21 - 7.17 (m, 2.4H)**, 6.99 (d, J=0.6 Hz, 0.2H)*, 6.89 - 6.83 (m, 2.4H)**, 6.61-6.59 (m, 0.2H)*, 6.57 (ddt, J=0.6, 2.4, 10.1 Hz 1H), 5.92 (td, J=3.9, 10.0 Hz, 0.2H)*, 5.74 (td, J=3.7, 10.0 Hz, 1H), 5.15 (s, 0.2H)*, 5.10 (s, 2H), 4.50 (dd, J=2.4, 3.7 Hz, 2.4H)**, 3.79 (s, 0.6H)*, 3.77 (s, 3H), 2.19 (s, 0.6H)*, 2.14 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.70, 167.96, 159.60, 159.39, 140.59, 138.62, 129.72, 129.16, 128.60, 128.12, 125.62, 122.38, 121.61, 120.20, 119.62, 119.05, 118.99, 114.41, 114.31, 114.17, 55.96, 55.64, 55.29, 47.43, 43.72, 22.98, 22.29; **LC-MS**, 6 min run, (ESI+) m/z 284.1417 $[M+H]^+$, Rt = 3.0 min

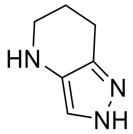
2-(4-methoxybenzyl)-4-(methylsulfonyl)-4,5-dihydro-2H-pyrazolo[4,3-b]pyridine (**28c**)



A flask with **27c** (170mg, 0.49mmol) in DCM (40mL) was degassed and backfilled with nitrogen three times. Then, Grubb's catalyst 2nd generation (25.5mg, 0.025mmol) was added and the final solution was heated at 40 °C for 2 h. Upon completion, DCM was removed and the crude was purified by flash column chromatography (EtOAc/ heptane, 50:50). The desired fractions were concentrated to dryness in vacuo to afford **28c** (120mg, 0.38mmol, 78%) as a colourless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J=0.6 Hz, 1H), 7.21 - 7.19 (m, 2H), 6.88 - 6.86 (m, 2H), 6.66 (dtd, J=0.6, 2.0, 10.0, 1H), 5.82 (td, J=4.0, 10.0 Hz, 1H), 5.13 (s, 2H), 4.38 (dd, J=2.0, 4.0 Hz, 2H), 3.79 (s, 3H), 2.72 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.64, 140.96, 129.39, 127.88, 122.89, 122.30, 120.45, 119.58, 114.33, 56.15, 55.32, 46.58, 35.85; **LC-MS**, 6 min run, (ESI+) m/z 320.1007 $[M+H]^+$, Rt = 3.2 min

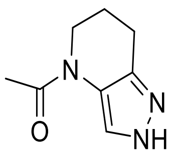
4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridine (**5a**)



A 0.05 M solution of **28a** (193mg, 0.56mmol) in EtOH (11ml) was hydrogenated in H-cube. Initially, the parameters (temperature: 25°C, pressure: 15bar and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (3.5ml) and anisole (0.23ml, 3.36mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **5a** (38mg, 0.30mmol, 53%) as a colourless oil.

^{1}H-NMR (500 MHz, MeOD$_4$): δ 7.09 (s, 1H), 3.10-3.07 (m, 2H), 2.70 (t, J=6.5 Hz, 2H), 1.95 - 1.90 (m, 2H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 135.96, 128.04, 122.83, 44.49, 24.00, 21.60; broadening of peaks is due to tautomerism; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_6H_9N_3$: 124.0869, found: 124.0878.

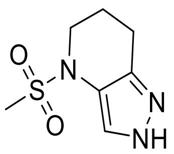
1-(2,5,6,7-tetrahydro-4H-pyrazolo[4,3-b]pyridin-4-yl)ethan-1-one (**5b**)



A 0.05 M solution of **28b** (105mg, 0.37mmol) in EtOH (7.5ml) was hydrogenated in H-cube. Initially, the parameters (temperature: 25°C, pressure: 15bar and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (3.2ml) and anisole (0.18ml, 2.22mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **5b** (40mg, 0.24mmol, 65%) as a white solid. Compound **5b** was isolated as a mixture 1:0.15 of two rotamers.

^{1}H-NMR (400 MHz, MeOD$_4$): δ 8.09 (s, 1H), 7.55 (s, 0.15H)*, 3.78 - 3.74 (m, 2.3H)**, 2.78 (t, J=6.0 Hz, 0.3H)*, 2.75 (t, J=6.3 Hz, 2H), 2.32 (s, 0.3H), 2.23 (s, 2H), 2.08 - 2.01 (m, 2H), 1.99 - 1.92 (m, 0.3 H)*; **^{13}C NMR** (100 MHz, MeOD$_4$): δ 168.58, 136.90, 123.14, 119.93, 45.76, 42.02, 22.24, 22.12, 21.90, 20.72, 20.40, 20.19; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{11}N_3O$: 166.0975, found: 166.0983.

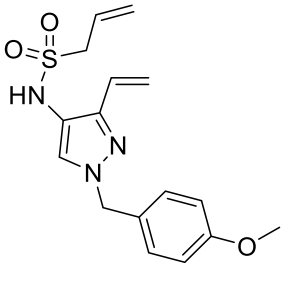
4-(methylsulfonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridine (**5c**)



A 0.05 M solution of **28c** (120mg, 0.38mmol) in EtOH (7.5ml) was hydrogenated in H-cube. Initially, the parameters (temperature: 25°C, pressure: 15bar and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (3.2ml) and anisole (0.18ml, 2.22mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **5c** (55mg, 0.27mmol, 71%) as a white solid.

^{1}H-NMR (500 MHz, MeOD$_4$): δ 7.55 (s, 1H), 3.65 - 3.62 (m, 2H), 2.85 (s, 3H), 2.75 (t, J=6.4 Hz, 2H), 2.05 - 1.99 (m, 2H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 137.64, 124.16, 121.49, 47.60, 35.45, 22.97, 21.30; **HRMS** (ESI): [M+H]$^+$ calcd. for $C_7H_{11}N_3O_2S$: 202.0645, found: 202.0660.

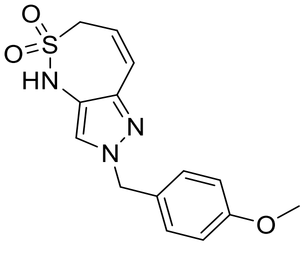
N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)prop-2-ene-1-sulfonamide (**29**)



To a solution of **25** (155mg, 0.67mmol) and pyridine (0.08ml, 1.0mmol) in DCM (2.5mL) at 0 °C , prop-2-ene-1-sulfonyl chloride (0.07ml, 0.67mmol) was added and the mixture was stirred for 1 h. Then, a saturated solution of NH_4Cl was added and the two layers were separated. The aq. layer was further extracted with DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ heptane, 30:70). The desired fractions were concentrated to dryness in vacuo to afford **29** (200mg, 0.60mmol, 89%) as a white solid.

^{1}H-NMR (500 MHz, CDCl$_3$): δ 7.41 (s, 1H), 7.20 - 7.17 (m, 2H), 6.88 - 6.85 (m, 2H), 6.61 (dd, J=11.4, 17.8 Hz, 1H), 6.27 (br, 1H), 5.90 (dd, J=1.4, 17.8 Hz, 1H), 5.87-5.79 (m, 1H), 5.39 (dq, J=10.2, 1.1 Hz, 1H), 5.34 (dd, J=1.4, 11.4 Hz, 1H), 5.32 (dq, J=17.0, 1.1 Hz), 5.14 (s, 2H), 3.79 (s, 3H), 3.70 (td, J=1.0, 7.3 Hz, 2H); **^{13}C NMR** (125 MHz, CDCl$_3$): δ 159.68, 143.92, 129.52, 127.53, 127.05, 125.72, 125.14, 124.42, 116.67, 115.76, 114.33, 56.30, 55.59, 55.33; **LC-MS**, 6 min run, (ESI+) m/z 334.1229 [M+H]$^+$, Rt = 3.0 min

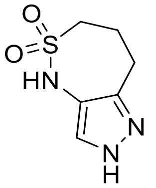
2-(4-methoxybenzyl)-2,6-dihydro-4H-pyrazolo[4,3-c][1,2]thiazepine 5,5-dioxide (**30**)



A flask with **29** (200mg, 0.60mmol) in DCM (60mL) was degassed and backfilled with nitrogen three times. Then, Grubb's catalyst 2nd (25mg, 0.03mmol) was added and the final solution was heated at 40 °C for 2 h. Upon completion, DCM was removed and the crude was purified by flash column chromatography (EtOAc/ heptane, 40:60). The desired fractions were concentrated to dryness in vacuo to afford **30** (153mg, 0.5mmol, 83%) as a colourless oil.

^{1}H-NMR (500 MHz, MeOD$_4$): δ 7.26 (d, J=0.7 Hz, 1H), 7.09 - 7.06 (m, 2H), 6.87 - 6.84 (m, 2H), 6.72 (dq, J=11.7, 0.8 Hz, 1H), 5.73 (td, J=5.8, 11.6 Hz, 1H), 5.32 (s, 2H), 4.11 (dd, J=1.3, 5.8 Hz, 2H), 3.75 (s, 3H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 160.93, 132.76, 132.57, 130.16, 129.25, 120.59, 120.43, 120.35, 115.24, 57.36, 55.79, 54.02; **LC-MS**, 6 min run, (ESI+) m/z 306.0545 [M+H]$^+$, Rt = 2.9 min.

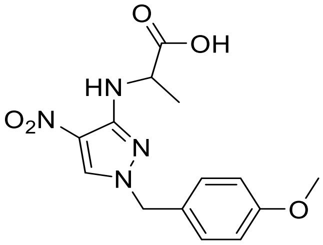
2,6,7,8-tetrahydro-4H-pyrazolo[4,3-c][1,2]thiazepine 5,5-dioxide (**6**)



A 0.05 M solution of **30** (153mg, 0.5mmol) in EtOH (13ml) was hydrogenated in H-cube. Initially, the parameters (temperature: 25°C, pressure: 15bar and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (4ml) and anisole (0.23ml, 3mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **6** (52mg, 0.28mmol, 56%) as a white solid.

^{1}H-NMR (500 MHz, MeOD$_4$): δ 8.49 (s, 1H), 7.45 (s, 1H), 3.47 - 3.43 (m, 2H), 2.93 - 2.90 (m, 2H), 2.19 - 2.14 (m, 2H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 146.50, 130.46, 116.10, 56.86, 25.34, 23.62; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_6H_9N_3O_2S$: 188.0488, found: 188.0490.

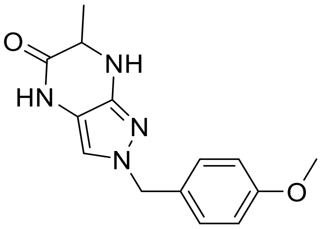
(1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)alanine (**31a**)



A microwave vial was charged with **2** (340mg, 1.14mmol), Cs_2CO_3 (710mg, 2.28mmol), CuI (20.4mg, 0.114mmol), alanine (291mg, 3.42mmol), water (0.58ml) and DMF (3ml). The vial was capped properly, and thereafter the mixture was heated under microwave irradiation conditions at 150 °C and 200 W for 4 h. Then, a saturated solution of NH_4Cl was added, and the aq. layer was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography eluting (EtOAc/Heptane 30:70). The desired fractions were concentrated to dryness in vacuo to afford **31b** (250mg, 0.78mmol, 69%) as a yellow solid.

^{1}H-NMR (500 MHz, CDCl$_3$): δ^{1}H 10.70 (s, 1H), 7.70 (s, 1H), 7.25 - 7.20 (m, 2H), 6.91 - 6.88 (m, 2H), 6.17 (d, J=6.1 Hz, 1H), 4.99 (s, 2H), 4.47 (dd, J=6.7, 6.7 Hz, 1H), 3.80 (s, 3H), 1.58 (d, J=7.2 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl$_3$): δ160.18, 150.23, 130.32, 128.50, 125.34, 125.29, 121.40, 114.58, 56.46, 56.43, 55.37, 18.31; **LC-MS**, 6 min run, (ESI+) m/z 321.1210 $[M+H]^+$, Rt = 2.7 min.

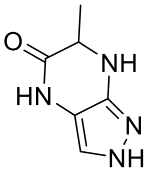
2-(4-methoxybenzyl)-6-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b]pyrazin-5-one (**32a**)



To a suspension of **31b** (250mg, 0.78mmol) in EtOH (3ml) was added iron (348mg, 6.24mmol) and NH_4Cl (166mg, 3.12mmol) in water (0.5ml). The final mixture was stirred at 80 °C for 48 h. After cooling, the mixture was neutralised with $NaHCO_3$ and filtered through celite eluting with DCM. Then, volatiles were removed in vacuo and water added to the solid residue followed by DCM. The two layers were separated and the aq. phase was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (MeOH+7N amonia/DCM 5:95). The desired fractions were concentrated to dryness in vacuo to afford **32b** (186mg, 0.68mmol, 87%) as a reddish solid.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 9.76 (s, 1H), 7.18-7.14 (m, 2H), 7.10 (s, 1H), 6.89-6.86 (m, 2H), 5.82 (d, J=2.1 Hz, 1H), 4.92 (s, 2H), 3.75-3.70 (m, 4H), 1.22 (d, J=6.7 Hz, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 167.80, 159.07, 145.34, 130.67, 129.46, 115.26, 114.19, 110.59, 55.54, 54.36, 52.99, 18.42; **LC-MS**, 6 min run, (ESI+) m/z 273.1385 $[M+H]^+$, Rt = 2.4 min.

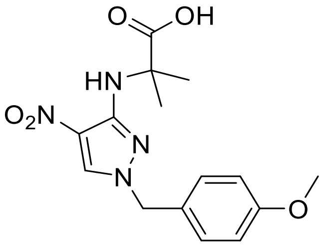
6-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b]pyrazin-5-one (**7a**)



32 (186mg, 0.68mmol) was dissolved in TFA (6ml) and anisole (0.44ml, 4.1mmol) was added. The final mixture was stirred for 12 h at 80 °C. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **7** (60mg, 0.39mmol, 57%) as a reddish solid.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 11.27 (1H, s), 9.77 (1H, s), 7.00 (1H, s), 5.74 (1H, s), 3.71 (1H, d, J=4.7 Hz), 1.22 (3H, d, J=6.1 Hz); **^{13}C NMR** (125 MHz DMSO-d_6): δ 168.09, 145.13, 114.00, 110.51, 53.09, 18.47; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_6H_8N_4O$: 153.0770, found: 153.0776.

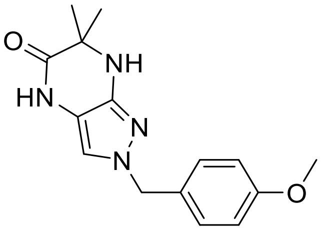
2-((1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)amino)-2-methylpropanoic acid (**31b**)



A microwave vial was charged with **2** (210mg, 0.67mmol), Cs_2CO_3 (420mg, 1.34mmol), CuI (24.4mg, 0.13mmol), 2-amino-2-methyl-propanoic acid (200mg, 2.01mmol), water (0.35ml) and DMF (2ml). The vial was capped properly, and thereafter the mixture was heated under microwave irradiation conditions at 150 °C and 200 W for 4 h. Then, a saturated solution of NH_4Cl was added, and the aq. layer was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography eluting (EtOAc/Heptane 30:70). The desired fractions were concentrated to dryness in vacuo to afford **31b** (153mg, 0.46mmol, 68%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.32 (br, 1H), 7.72 (s, 1H), 7.22-7.19 (m, 2H), 6.91 - 6.87 (m, 2H), 6.35 (s, 1H), 4.96 (s, 2H), 3.80 (s, 3H), 1.70 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 180.50, 160.09, 149.25, 130.35, 130.18, 127.97, 125.65, 121.90, 114.59, 114.52, 57.69, 56.48, 55.35, 25.26; **LC-MS**, 6 min run, (ESI+) m/z 335.1344 $[M+H]^+$, Rt = 3.3 min.

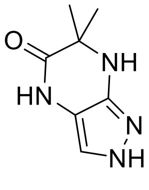
2-(4-methoxybenzyl)-6,6-dimethyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b]pyrazin-5-one (**32b**)



To a suspension of **31b** (153mg, 0.46mmol) in EtOH (1.4ml) was added iron (205mg, 3.68mmol) and NH_4Cl (98mg, 1.84mmol) in water (0.25ml). The final mixture was stirred at 80 °C for 48 h. After cooling, the mixture was neutralised with $NaHCO_3$ and filtered through celite eluting with DCM. Then, volatiles were removed in vacuo and water added to the solid residue followed by DCM. The two layers were separated and the aq. phase was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (MeOH+7N amonia/DCM 5:95). The desired fractions were concentrated to dryness in vacuo to afford **32b** (115mg, 0.4mmol, 89%) as a reddish solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.17 - 7.13 (m, 3H), 7.10 (s, 1H), 6.88 - 6.85 (m, 2H), 5.11 (s, 2H), 3.79 (s, 3H), 3.05 (s, 1H), 1.31 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.30, 159.44, 131.81, 128.73, 128.32, 124.58, 114.30, 111.79, 57.17, 55.32, 51.80, 25.22; **LC-MS**, 6 min run, (ESI+) m/z 287.1531 $[M+H]^+$, Rt = 2.5 min.

6,6-dimethyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b]pyrazin-5-one (**7b**)

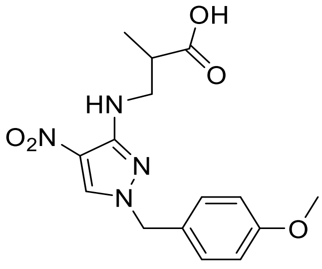


32 (115mg, 0.4mmol) was dissolved in TFA (3.5ml) and anisole (0.26ml, 2.4mmol) was added. The final mixture was stirred for 12 h at 80 °C. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an

AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **7** (37mg, 0.22mmol, 55%) as a reddish solid.

^{1}H-NMR (400 MHz, MeOD$_4$): δ 6.98 (s, 1H), 1.25 (s, 6H); **^{13}C NMR** (100 MHz, MeOD$_4$): δ 171.34, 144.58, 114.03, 109.64, 56.56, 24.50; **HRMS** (ESI): [M+H]$^+$ calcd. for $C_7H_{10}N_4O$: 167.0927, found: 167.0936.

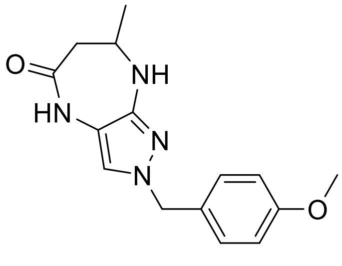
3-((1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)amino)-2-methylpropanoic acid (**33**)



A microwave vial was charged with **2** (610mg, 1.95mmol), Cs_2CO_3 (1280mg, 3.9mmol), CuI (73.2mg, 0.39mmol), 3-amino-2-methyl-propanoic acid (610mg, 5.85mmol), water (1ml) and DMF (6ml). The vial was capped properly, and thereafter the mixture was heated under microwave irradiation conditions at 150 °C and 200 W for 4 h. Then, saturated solution of NH_4Cl was added, and the aq. layer was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (EtOAc/Heptane 30:70). The desired fractions were concentrated to dryness in vacuo to afford **33** (460mg, 1.37mmol, 70%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.26-7.23 (m, 2H), 6.93-6.89 (m, 2H), 6.00 (d, J=7.9 Hz, 1H), 5.02 (s, 2H), 4.21 (ddq, J=5.0, 6.7, 7.1 Hz, 1H), 3.82 (s, 3H), 2.83 (dd, J=5.0, 15.8 Hz, 1H), 2.58 (dd, J=7.1, 15.8 Hz, 1H), 1.39 (d, J=6.7 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.66, 160.19, 150.42, 130.40, 128.30, 125.30, 121.34, 114.59, 56.48, 55.38, 45.46, 40.44, 20.54; **LC-MS**, 6 min run, (ESI+) m/z 335.1370 [M+H]$^+$, Rt = 3.0 min

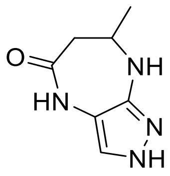
2-(4-methoxybenzyl)-7-methyl-2,6,7,8-tetrahydropyrazolo[3,4-b][1,4]diazepin-5(4H)-one (**34**)



To a suspension of **33** (460mg, 1.37mmol) in EtOH (7ml) was added iron (615mg, 10.9mmol) and NH_4Cl (297mg, 5.5mmol) in water (1.4ml). The final mixture was stirred at 80° C for 48 h. After cooling, the mixture was neutralised with $NaHCO_3$ and filtered through celite eluting with DCM. Then, volatiles were removed in vacuo and water added to the solid residue followed by DCM. The two layers were separated and the aq. phase was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (MeOH+7N amonia/DCM 5:95). The desired fractions were concentrated to dryness in vacuo to afford **34** (264mg, 0.92mmol, 67%) as a reddish solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H), 7.14-7.11 (m, 2H), 6.95 (s, 1H), 6.86 - 6.83 (m, 2H), 4.91 (s, 2H), 4.23 (br, 1H), 3.78-3.73 (m, 4H), 2.65 (d, J=5.2 Hz, 2H), 1.28 (d, J=6.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.67, 159.45, 146.44, 129.18, 128.34, 128.24, 120.01, 114.19, 107.85, 55.30, 47.35, 45.01, 23.24; **LC-MS**, 6 min run, (ESI+) m/z 287.1610 $[M+H]^+$, Rt = 2.3 min

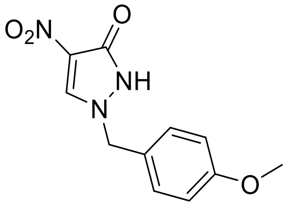
7-methyl-2,6,7,8-tetrahydropyrazolo[3,4-b][1,4]diazepin-5(4H)-one (**8**)



34 (264mg, 0.92mmol) was dissolved in TFA (8.4ml) and anisole (0.39ml, 5.52mmol) was added. The final mixture was stirred for 12 h at 80 °C. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **8** (80mg, 0.48mmol, 52%) as a reddish solid.

^{1}H-NMR (500 MHz, $MeOD_4$): δ 7.20 (s, 1H), 3.76 - 3.69 (m, 1H), 2.66 - 2.59 (m, 2H), 1.28 (d, J=6.6 Hz, 3H); **^{13}C NMR** (125 MHz, $MeOD_4$): δ 172.91, 144.62, 122.85, 106.28, 47.20, 44.38, 21.64; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_{10}N_4O$: 167.0927, found: 167.0930.

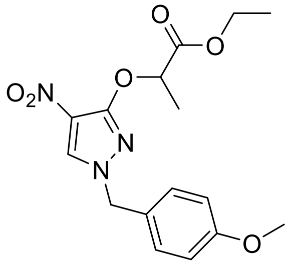
1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-ol (**35**)



A microwave vial was charged with **2** (575mg, 1.85mmol) Cs_2CO_3 (1800mg, 5.55mmol), $Pd_2(dba)_3$ (84.5mg, 0.092mmol), tBuBrettPhos (15.5mg, 0.18mmol), water (0.32ml) and DMF (8.5mL). The vial was capped properly, and thereafter the mixture was heated under microwave irradiation conditions at 130 °C and 200 W for 1 h. Then, saturated solution of NH_4Cl was added, and the aq. layer was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (EtOAc/Heptane 45:55). The desired fractions were concentrated to dryness in vacuo to afford **35** (260mg, 0.96mmol, 52%) as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.73 (s, 1H), 7.27—7.24 (m, 1H), 6.94-6.91 (m, 2H), 5.06 (s, 2H), 3.82 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 160.40, 156.25, 130.49, 129.79, 127.57, 124.74, 114.73, 57.01, 55.40; **LC-MS**, 6 min run, (ESI+) m/z 272.0662 $[M+Na]^+$, Rt = 2.5 min.

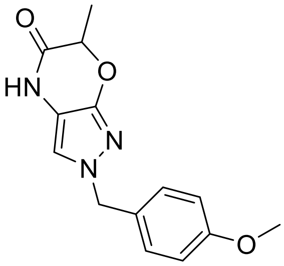
ethyl 2-((1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)oxy)propanoate (**36**)



To a mixture of **35** (104mg, 0.38mmol) and K_2CO_3 (66mg, 0.48mmol) in DMF (1.5mL), ethyl 2-bromopropanoate (0.062ml, 0.48mmol) was added at 0 °C. After 2h, water was added and extraction was carried out with DCM (3x). The organics were then washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ heptane, 30:70). The desired fractions were concentrated to dryness in vacuo to afford **36** (128mg, 0.36mmol, 93%) as an orange oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.20 - 7.18 (m, 2H), 6.91 - 6.88 (m, 2H), 5.11 (q, J=7.0 Hz, 1H), 4.98 (s, 2H), 4.17 (q, J=7.1 Hz, 2H), 3.81 (s, 3H), 1.67 (d, J=7.0 Hz, 3H), 1.20 (t, J=7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.92, 160.21, 154.83, 130.17, 129.86, 125.30, 121.18, 114.56, 61.24, 56.68, 55.38, 17.85, 14.09; **LC-MS**, 6 min run, (ESI+) m/z 350.1341 $[M+H]^+$, Rt = 4 min.

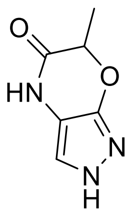
2-(4-methoxybenzyl)-6-methyl-2,4-dihydropyrazolo[3,4-b][1,4]oxazin-5(6H)-one (**37**)



To a suspension of **36** (128mg, 0.36mmol) in EtOH (2ml) was added iron (163.6mg, 2.88mmol) and NH_4Cl (78mg, 1.44mmol) in water (0.30ml). The final mixture was stirred at 80 °C for 24 h. After cooling, the mixture was neutralised with $NaHCO_3$ and filtered through celite eluting with DCM. Then, volatiles were removed in vacuo and water added to the solid residue followed by DCM. The two layers were separated and the aq. phase was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (EtOAc/Heptane 40:60). The desired fractions were concentrated to dryness in vacuo to afford **37** (82mg, 0.30mmol, 82%) as a reddish oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.77 (s, 1H), 7.18 (m, 2H), 6.87 (m, 2H), 6.84 (s, 1H), 4.99 (s, 2H), 4.77 (q, J=6.9 Hz, 1H), 3.79 (s, 3H), 1.58 (d, J=6.9 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.02, 159.60, 150.35, 129.52, 128.03, 115.02, 114.23, 107.94, 55.83, 55.32, 17.12; **LC-MS**, 6 min run, (ESI+) m/z 274.1202 $[M+H]^+$, Rt = 2.8 min.

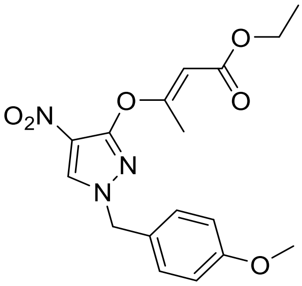
6-methyl-2,4-dihydropyrazolo[3,4-b][1,4]oxazin-5(6H)-one (**9**)



37 (82mg, 0.30mmol) was dissolved in TFA (2.6ml) and anisole (0.128ml, 1.80mmol) was added. The final mixture was stirred for 12 h at 80 °C. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **9** (32mg, 0.20mmol, 66%) as a pinkish solid.

^{1}H-NMR (400 MHz, $MeOD_4$): δ 7.15 (s, 1H), 4.76 (q, J=6.9 Hz, 1H), 1.51 (d, J=6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $MeOD_4$): δ 166.78, 114.55, 107.55, 75.58, 16.07; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_6H_7N_3O_2$: 154.0611, found: 154.0612.

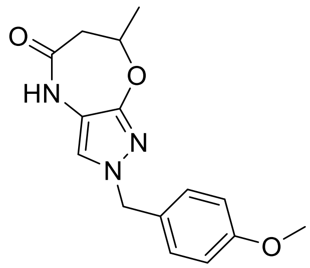
ethyl (E)-3-((1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)oxy)but-2-enoate (**38**)



To a flask was added DABCO (85mg, 0.76mmol) and **35** (206mg, 0.76mmol). The flask was evacuated then placed under a N_2 atmosphere. MeCN (1ml) was charged and the resulting solution heated to 70 °C. Ethyl but-2-ynoate (0.051ml, 0.76mmol) was added and the resulting mixture stirred at 70 °C for 1 h. The reaction mixture was diluted with EtOAc and then cooled to 0 °C in an ice bath. 1 M HCl aq. solution was added dropwise and the biphasic mixture allowed to warm to rt. The phases were separated and the organic layer was washed sequentially with 1 M NaOH aq. solution and water (2×). The crude was purified by flash column chromatography (EtOAc/Heptane 25:75). The desired fractions were concentrated to dryness in vacuo to afford **38** (254mg, 0.70mmol, 92%) as a yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.29-7.26 (m, 2H), 6.96-6.93 (m, 2H), 5.18 (q, J=0.7 Hz, 1H), 5.14 (s, 2H), 4.13 (q, J=7.1 Hz, 4H), 3.83 (s, 3H), 2.52 (d, J=0.7 Hz, 3H), 1.24 (t, J=7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.70, 166.49, 160.49, 150.34, 130.47, 129.97, 124.56, 123.85, 114.82, 98.89, 59.97, 57.29, 55.40, 17.66, 14.27; **LC-MS**, 6 min run, (ESI+) m/z 362.1358 $[M+H]^+$, Rt = 3.9 min.

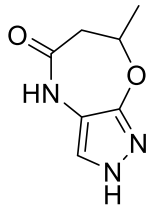
2-(4-methoxybenzyl)-7-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b][1,4]oxazepin-5-one (**39**)



A 0.05 M solution of **38** (254mg, 0.70mmol) in EtOH (12ml) and 1,4-dioxane (2ml) was hydrogenated in H-cube. Initially, the parameters (temperature: 80°C, pressure: 80bar, and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started (3 cycles). The reaction was monitored by LC-MS. Upon completion (complete reduction of the double bond and partial reduction of the nitro group), the reaction was concentrated up to 0.3M, iron (197mg, 3.5mmol) and NH_4Cl (113mg, 2.1mmol) in water (0.5ml) was added and the final mixture was heated at 80 °C for 24 h. After cooling, the mixture was neutralised with $NaHCO_3$ and filtered through celite eluting with DCM. Then, volatiles were removed in vacuo and water added to the solid residue followed by DCM. The two layers were separated and the aq. phase was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography eluting (EtOAc/Heptane 40:60). The desired fractions were concentrated to dryness in vacuo to afford **39** (131mg , 0.45mmol, 64%) as a reddish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.21-7.17 (m, 2H), 6.99 (s, 1H), 6.87 - 6.84 (m, 2H), 4.96 (s, 2H), 4.59-4.52 (m, 1H), 3.78 (s, 3H), 2.86 (dd, J=7.4, 16.2 Hz, 1H), 2.78 (d, J=16.2 Hz, 1H), 1.46 (d, J=6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.97, 159.60, 151.31, 129.58, 127.82, 119.42, 114.21, 106.50, 71.39, 55.85, 55.31, 45.05, 21.56; **LC-MS**, 6 min run, (ESI+) m/z 288.1369 $[M+H]^+$, Rt = 2.8 min.

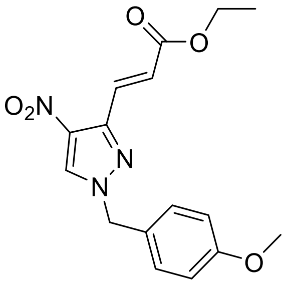
7-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b][1,4]oxazepin-5-one (**10**)



39 (131mg, 0.45mmol) was dissolved in TFA (4ml) and anisole (0.24ml, 2.7mmol) was added. The final mixture was stirred for12h at 80 °C. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **10** (42mg, 0.25mmol, 55%) as a pinkish solid.

^{1}H-NMR (500 MHz, $MeOD_4$): δ 7.27 (s, 1H), 4.60 (ddq, J=1.7, 6.4, 7.1 Hz, 1H), 2.85 (dd, J=7.1, 16.2 Hz, 1H), 2.79 (dd, J=1.7, 16.2 Hz, 1H), 1.43 (d, J=6.4 Hz, 3H); **^{13}C NMR** (125 MHz, $MeOD_4$): δ 173.32, 121.37, 107.21, 73.16, 21.56; broadening of peaks is due to tautomerism; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_9N_3O_2$: 168.0768, found: 168.0770.

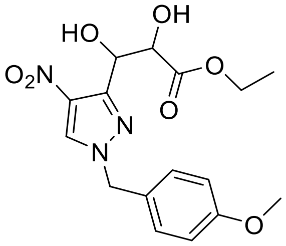
ethyl (E)-3-(1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)acrylate (**40**)



A mixture of **2** (470mg, 1.5mmol), Pd(dppf)Cl_2 (110 mg, 0.15 mmol), Cs_2CO_3 (970mg, 3mmol), and ethyl (2E)-3-(4,4,5,5-tetramethyl,3,2-dioxaborolan-2-yl)acrylate (500mg, 2.25 mmol) in DMF (4.7ml) were sealed in a vial and subjected to microwave irradiation at 145 °C and 200W for 45 min. The reaction mixture was diluted with water and EtOAc. The organic solution was separated and washed with brine, dried over $MgSO_4$ and concentrated. The crude was purified by flash column chromatography eluting (EtOAc/Heptane 20:80). The desired fractions were concentrated to dryness in vacuo to afford **40** (335mg, 1.07mmol, 71%) as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J=16.0 Hz, 1H), 8.00 (s, 1H), 7.29 - 7.26 (m, 2H), 6.95 - 6.92 (m, 2H), 6.86 (d, J=16.0 Hz, 1H), 5.22 (s, 2H), 4.28 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 1.34 (t, J=7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.16, 160.36, 142.31, 133.62, 131.25, 130.27, 130.01, 125.15, 124.27, 114.74, 60.84, 57.27, 55.40, 14.28; **LC-MS**, 6 min run, (ESI+) m/z 332.1259 $[M+H]^+$, Rt = 3.8 min.

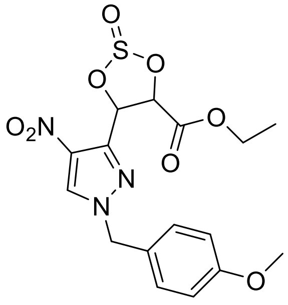
ethyl 2,3-dihydroxy-3-(1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)propanoate (**41**)



To a mixture of **40** (355mg, 1.07mmol) in acetone/water 9:1 (18ml/2ml) was added NMO (252mg, 2.14mmol) and the temperature was lowered up to 0 °C. OsO_4 (4% wt. solution in water, 0.24ml, 0.34mmol) was added and the reaction allowed to reach rt. After stirring for 24 h, the reaction was quenched by adding a saturated solution of Na_2SO_3 followed by EtOAc. The two layers were separated and the aq. phase was extracted with EtOAc (3x). The organics were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (EtOAc/Heptane 40:60) to afford **41** (370mg, 1.01 mmol, 94%) as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.26 - 7.24 (m, 2H), 6.95 - 6.92 (m, 2H), 5.61 (d, J=5.3 Hz, 1H), 5.24 (d, J=14.6 Hz, 1H), 5.24 (d, J=14.6 Hz, 1H), 4.62 (br, 1H), 4.36 (q, J=7.1 Hz, 2H), 3.83 (s, 3H), 3.67 (d, J=7.8 Hz, 1H), 3.30 (br, 1H), 1.36 (t, J=7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.22, 160.38, 147.27, 132.50, 130.38, 130.33, 125.02, 114.78, 72.29, 69.15, 62.52, 56.98, 55.40, 14.18; **LC-MS**, 6 min run, (ESI+) m/z 366.1301 $[M+H]^+$, Rt = 2.7 min.

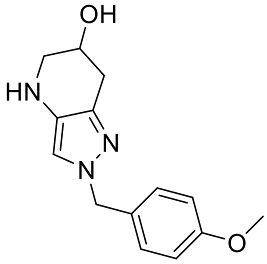
ethyl 5-(1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)-1,3,2-dioxathiolane-4-carboxylate 2-oxide (**42**)



To a stirred solution of **41** (370mg, 1.01 mmol) in pyridine (20mL), was added thionyl chloride (0.087mL, 1.21mmol) dropwise under nitrogen atmosphere at 0 °C and allowed to stir at 0 °C for 30 min. The reaction mixture was quenched by the addition of cold water and a saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with DCM (2 x). The organics were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (EtOAc/Heptane 20:80) to afford **42** (412mg, 0.96 mmol, 95%) as a pale yellow oil. **42** was isolated as two diastereomeric pairs of enantiomers.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.98 (s, 1H), 7.21-7.23 (m, 4H), 6.95 - 6.92 (m, 4H), 6.76 (d, J=6.4 Hz, 1H), 6.29 (d, J=6.4 Hz, 1H), 6.09 (d, J=6.4 Hz, 1H), 5.47 (d, J=6.4 Hz, 1H), 5.25 (s, 2H), 5.23 (s, 2H), 4.34 - 4.28 (m, 4H), 3.83 (s, 3H), 3.82 (s, 3H), 1.30 (t, J=7.1 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.77, 166.52, 160.49, 160.43, 141.63, 141.14, 133.76, 133.53, 130.48, 130.37, 130.33, 124.90, 124.74, 114.83, 114.79, 80.54, 78.64, 77.92, 76.36, 62.96, 62.88, 57.33, 57.28, 55.41, 55.40; **LC-MS**, 6 min run, (ESI+) m/z 429.1100 $[M+H+H_2O]^+$, Rt = 3.6 min.

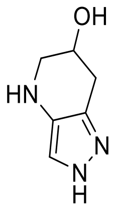
2-(4-methoxybenzyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-6-ol (**43**)



To the stirred solution of **42** (412mg, 0.96mmol) and $CoCl_2 \cdot 6H_2O$ (2.3mg, 0.009mmol) in EtOH (3mL), $NaBH_4$ (152mg, 3.84mmol) was added at 0 °C and allowed to stir for 12 h at 25 °C. After completion of reaction, it was poured into ice cold water. To the aqueous layer, ethyl acetate was added and combined mixture was passed through celite. The organic layer was separated and the aq. layer was extracted with ethyl acetate (2x). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **43** (63mg, 0.24mmol, 25%) as a yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ , 7.19 - 7.16 (m, 2H), 6.87 - 6.85 (m, 2H), 6.81 (s, 1H), 5.09 (s, 2H), 4.27 - 4.24 (m, 1H), 3.79 (s, 3H), 3.18 (ddd, J=1.2, 5.2, 11.7 Hz, 1H), 3.10 (d, J=11.0 Hz, 2H), 3.01 (dd, J=4.6, 16.4 Hz, 1H), 2.83 (ddd, J=0.8, 3.9, 16.4 Hz, 1H), 2.27 (d, J=7.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.44, 136.42, 129.25, 128.98, 127.46, 115.02, 114.20, 64.42, 55.66, 55.29, 48.67, 31.19; **LC-MS**, 6 min run, (ESI+) m/z 260.1391 $[M+H]^+$, Rt = 2.2 min.

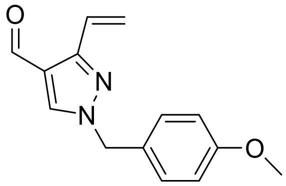
4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-6-ol (**11**)



43 (63mg, 0.24mmol) was dissolved in TFA (2.2mL) and anisole (0.025mL, 1.44mmol) was added. The final mixture was stirred for 12 h at 80 °C. After cooling, volatiles were evaporated and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were concentrated to dryness to provide **11** (18mg, 0.13mmol, 53%) as a pale yellow oil.

^{1}H-NMR (400 MHz, MeOD$_4$): δ 7.10 (d, J=1.2 Hz, 1H), 4.17 - 4.08 (m, 1H), 3.12 (d, J=11.7 Hz, 1H), 3.01 (d, J=5.1 Hz, 1H), 2.95-2.99 (m, 1H), 2.64 (dd, J=6.5, 16.0 Hz, 1H); **^{13}C NMR** (100 MHz, MeOD$_3$): δ 133.76, 125.82, 120.41, 64.28, 48.93, 29.44; broadening of peaks is due to tautomerism; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_6H_9N_3O$: 140.0818, found: 140.0825.

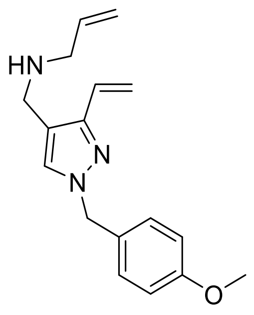
1-(4-methoxybenzyl)-3-vinyl-1H-pyrazole-4-carbaldehyde (**44**)



A flask was charged with **3** (640mg, 2.16mmol), CsF (660mg, 4.32mmol), Pd(t-Bu$_3$P)$_2$ (55.3mg, 0.11mmol) and THF (11.2mL) under nitrogen atmosphere. Then, tributyl(vinyl)stannane (0.77ml, 2.59mmol) was added and the final mixture was stirred at rt for 24h. Subsequently, the reaction was diluted with Et$_2$O and water was added. The two layers were separated and the aq. one was extracted further with Et$_2$O (2x). The combined organics were washed with brine and dried over MgSO$_4$ before concentration to dryness. The crude was passed through celite eluting with DCM and then purified by flash column chromatography eluting 30%EtOAc in heptane. The desired fractions were concentrated to dryness in vacuo to afford **44** (450mg, 1.69mmol, 78%) as a pale yellow oil.

^{1}H-NMR (500 MHz, CDCl$_3$): δ 9.87 (s, 1H), 7.73 (s, 1H), 7.26 - 7.22 (m, 2H), 7.00 (dd, J=11.3, 17.7 Hz, 1H), 6.91 - 6.89 (m, 2H), 6.18 (dd, J=1.7, 17.7 Hz, 1H), 5.49 (dd, J=1.7, 11.3 Hz, 1H), 5.21 (s, 2H), 3.80 - 3.80 (m, 3H); **^{13}C NMR** (125 MHz, CDCl$_3$): δ 159.98, 150.72, 134.55, 129.95, 126.67, 126.43, 121.30, 119.70, 114.51, 56.14, 55.34; **LC-MS**, 6 min run, (ESI+) m/z 265.0984 $[M+Na]^+$, Rt = 2.3 min.

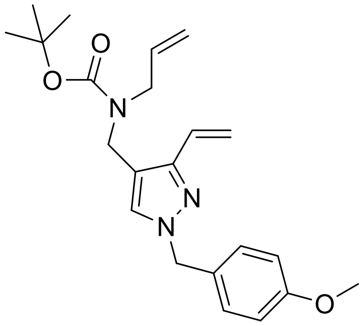
N-((1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methyl)prop-2-en-1-amine (**45**)



To a solution of **44** (450mg, 1.69mmol) in DCM (6ml) was added $MgSO_4$ (795mg, 6.76mmol) and propyilamine (0.2ml, 2.53mmol), and the reaction was stirred at rt for 24 h. Then, the mixture was filtered and volatiles were evaporated in vacuo. The solid residue was dissolved in MeOH (12ml) and $NaBH_4$ (23mg, 0.51mmol) was added at 0 °C. The reaction was stirred at 0 °C for 1h. Afterwards, water was added followed by EtOAc. The two layers were separated and the aq. phase was extracted with EtOAc (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (MeOH/DCM 4:96) to afford **45** (430mg, 1.5 mmol, 89%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26 - 7.21 (m, 3H), 6.91 - 6.89 (m, 2H), 6.78 (dd, J=11.4, 17.9 Hz, 1H), 5.99 - 5.90 (m, 1H), 5.85 (dd, J=1.6, 17.9 Hz, 1H), 5.34 (dd, J=1.6, 11.4 Hz, 1H), 5.24 - 5.20 (m, 3H), 5.14 (qd, J=1.4, 10.3 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 2H), 3.31 (td, J=1.4, 6.0 Hz, 2H), 1.38 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.45, 147.53, 136.70, 129.37, 129.14, 128.31, 128.15, 118.69, 116.09, 115.28, 114.16, 55.53, 55.25, 52.06, 43.01; **LC-MS**, 6 min run, (ESI+) m/z 284.1778 $[M+H]^+$, Rt = 2.1 min.

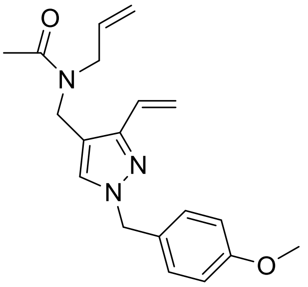
tert-butyl allyl((1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methyl)carbamate (**46a**)



To a solution of **45** (140mg, 0.5mmol) and Et_3N (0.083ml, 0.59mmol) in DCM (45mL) at 0 °C , Boc anhydride (139mg, 0.64mmol) was added and the reaction was left under stirring at 25 °C for 1 h. Then, a saturated solution of NH_4Cl was added and the two layers were separated. The aq. layer was further extracted with DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/ heptane, 35:65). The desired fractions were concentrated to dryness in vacuo to afford **46a** (180mg, 0.46mmol, 92%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ, 7.19 - 7.15 (m, 3H), 6.88-6.84 (m, 2H), 6.68 (dd, J=11.4, 17.8 Hz, 1H), 5.79 (d, J=17.8 Hz, 1H), 5.68 (br, 1H), 5.26 (dd, J=1.5, 11.4 Hz, 1H), 5.17 (s, 2H), 5.09 (br, 2H), 4.29 (s, 2H), 3.78 (s, 3H), 3.71 (s, 2H), 1.42 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.50, 155.22, 147.81, 133.84, 129.99, 129.37, 128.19, 127.45, 116.65, 115.47, 114.21, 79.79, 55.64, 55.30, 48.05, 39.19, 28.38; **LC-MS**, 6 min run, (ESI+) m/z 384.2264 $[M+H]^+$, Rt = 4.1 min.

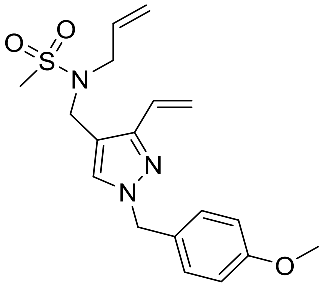
N-allyl-N-((1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methyl)acetamide (**46b**)



To a solution of **45** (180mg, 0.63mmol) and pyridine (0.28ml, 1.26mmol) in THF (2mL) at 0 °C , acetyl chloride (0.19ml, 0.95mmol) was added and the reaction was left under stirring at 0 °C for 1 h. Then, a saturated solution of NH_4Cl was added and the two layers were separated. The aq. layer was further extracted with DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (MeOH/ DCM, 2:98). The desired fractions were concentrated to dryness in vacuo to afford **46b** (177mg, 0.54mmol, 85%) as a yellow solid. **46b** was isolated as a mixture 1:0.4 of two rotamers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 1H), 7.18-7.14 (m, 2.8H)**, 7.07 (s, 0.4H)*, 6.88 - 6.84 (m, 2.8H)**, 6.71-6.60 (m, 1.4H)**, 5.82 (dd, J=1.6, 17.7 Hz, 1H), 5.77 - 5.62 (m, 1.8H)**, 5.32 (dd, J=0.9, 11.5 Hz, 0.4H)*, 5.26 (dd, J=1.6, 11.3 Hz, 1H), 5.19 - 5.04 (m, 5.6H)**, 4.45 (s, 2H), 4.37 (s, 0.8H)*, 3.95 (d, J=5.7 Hz, 0.8H)*, 3.79 (s, 1.2H)*, 3.78 (s, 3H), 3.77-3.74 (m, 2H), 2.10 (s, 1.2H)*, 2.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.61, 170.37, 159.58, 159.48, 147.95, 147.09, 133.03, 132.55, 130.39, 129.35, 129.30, 128.21, 128.18, 127.93, 127.72, 127.16, 117.47, 116.66, 116.16, 115.80, 115.67, 114.28, 114.19, 55.83, 55.67, 55.30, 49.40, 47.53, 42.75, 37.85, 21.48; **LC-MS**, 6 min run, (ESI+) m/z 326.1864 $[M+H]^+$, Rt = 3.6 min.

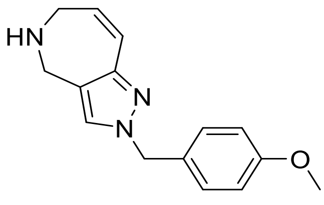
N-allyl-N-((1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methyl)methanesulfonamide (**46c**)



To a mixture of **45** (110mg, 0.38mmol) and pyridine (0.062ml, 0.76mmol) in DCM (1mL), methanesulfonyl chloride (0.044ml, 0.57mmol) was added at 0 °C. The mixture was stirred at 0 °C for 2 h. Then, a saturated solution of NH_4Cl was added and the two layers were separated. The aq. layer was further extracted with DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness to afford **46c** (132mg, 0.36mmol, 93%) as a yellow solid. The solid was pure enough to be used in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.19-7.16 (m, 2H), 6.8-6.85 (m, 2H), 6.70 (dd, J=11.3, 17.7 Hz, 1H), 5.87 (dd, J=1.6, 17.7 Hz, 1H), 5.82 - 5.70 (m, 1H), 5.32 (dd, J=1.6, 11.3 Hz, 1H), 5.24 - 5.17 (m, 4H), 4.29 (s, 2H), 3.79 (s, 3H), 3.74 (d, J=6.2 Hz, 2H), 2.77 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.57, 148.02, 132.41, 130.57, 129.33, 128.02, 126.81, 119.36, 116.22, 114.25, 114.21, 55.80, 55.31, 48.72, 39.94, 39.78; **LC-MS**, 6 min run, (ESI+) m/z 362.1528 $[M+H]^+$, Rt = 3.9 min.

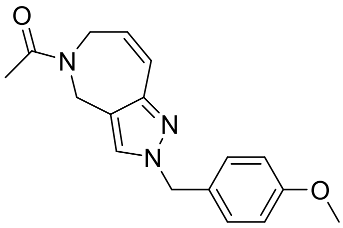
2-(4-methoxybenzyl)-2,4,5,6-tetrahydropyrazolo[4,3-c]azepine (**47a**)



A 0.05 M solution of **46a** (180mg, 0.46mmol) in DCM (46ml) was degassed and backfilled with nitrogen 3 times. Then, Grubbs' catalyst 2nd generation (19mg, 0.023mmol) was added to the reaction mixture and temperature was raised up to 40 °C. After 3 h, the reaction was cooled down and DCM was removed in vacuo. The solid residue was purified by flash column chromatography eluting (EtOAc/Heptane 45:65). The desired fractions were concentrated to dryness in vacuo to afford **47a** (with Boc) (130mg, 0.36mmol, 77%) as a white solid. A small amount of the latter was deprotected by using TFA in DCM, in order to get more comprehensible NMR spectra. LC-MS values of both the protected and deprotected version are reported.

^{1}H-NMR (without Boc) (500 MHz, $CDCl_3$): δ , 7.19 - 7.16 (m, 2H), 6.99 (s, 1H), 6.89 - 6.85 (m, 2H), 6.52 (dt, J=11.9, 1.7 Hz, 1H), 5.83 (dt, J=11.9, 4.0 Hz, 1H), 5.13 (s, 2H), 3.89 (s, 2H), 3.79 (s, 3H), 3.73 (dd, J=1.7, 4.0 Hz, 2H); **^{13}C NMR** (without Boc) (125 MHz, DMSO-d6): δ 159.49, 148.69, 132.77, 129.27, 128.50, 126.15, 123.33, 121.84, 114.21, 55.39, 55.30, 52.32, 45.42; **LC-MS**, 6 min run, (ESI+) m/z 356.2003 $[M+H]^+$ (with Boc), Rt = 3.5 min; 256.1460 $[M+H]^+$ (without Boc), Rt = 2.5 min.

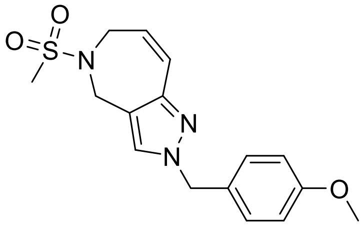
1-(2-(4-methoxybenzyl)-2,6-dihydropyrazolo[4,3-c]azepin-5(4H)-yl)ethan-1-one (**47b**)



A 0.05 M solution of **46b** (177mg, 0.54mmol) in DCM (54ml) was degassed and backfilled with nitrogen 3 times. Then, Grubbs' catalyst 2nd generation (14mg, 0.027mmol) was added to the reaction mixture and temperature was raised up to 40 °C. After 3 h, the reaction was cooled down and DCM was removed in vacuo. The solid residue was purified by flash column chromatography eluting (MeOH/DCM 3:97). The desired fractions were concentrated to dryness in vacuo to afford **47b** (123mg, 0.41mmol, 75%) as a white solid. **47b** was isolated as a mixture 1:0.8 of two rotamers.

^{1}H-NMR (500 MHz, $CDCl_3$): δ, 7.15-7.11 (m, 3.6H)**, 7.11 (s, 1H), 7.08 (s, 0.8H)*, 6.85-6.80 (m, 3.6H)**, 6.55 (td, J=1.7, 11.9 Hz, 1H), 6.45 (td, J=1.8, 11.8 Hz, 0.8H)*, 5.80-5.73 (m, 1.8H)**, 5.11 (s, 1.6H)*, 5.07 (s, 2H), 4.56 (s, 2H), 4.42 (s, 1.6H)*, 4.35 (d, J=3.9 Hz, 1.6H)*, 4.20 (d, J=4.0 Hz, 2H), 3.75 (s, 2.4H)*, 3.74 (s, 3H), 2.05 (s, 3H), 1.99 (s, 2.4H)*; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.08, 169.97, 159.54, 159.50, 148.38, 147.64, 129.42, 129.28, 128.49, 128.10, 128.04, 127.38, 126.09, 125.97, 124.38, 122.16, 118.55, 117.79, 114.25, 114.21, 55.50, 55.29, 51.13, 47.85, 45.83, 42.57, 21.17.21.13; **LC-MS**, 6 min run, (ESI+) m/z 298.1562 $[M+H]^+$, Rt = 2.7 min.

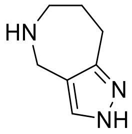
2-(4-methoxybenzyl)-5-(methylsulfonyl)-2,4,5,6-tetrahydropyrazolo[4,3-c]azepine (**47c**)



A 0.05 M solution of **46c** (132mg, 0.36mmol) in DCM was degassed and backfilled with nitrogen 3 times. Then, Grubbs' catalyst 2nd generation (9.2mg, 0.018mmol) was added to the reaction mixture and temperature was raised up to 40 °C. After 3 h, the reaction was cooled down and DCM was removed in vacuo. The solid residue was purified by flash column chromatography eluting (EtOAc/Heptane 50:50). The desired fractions were concentrated to dryness in vacuo to afford **47c** (97mg, 0.29mmol, 79%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ, 7.18 - 7.15 (m, 3H), 6.88 - 6.86 (m, 2H), 6.62 (ddt, J=0.7, 1.8, 12.0 Hz, 1H), 5.74 (dt, J=4.0, 12.0 Hz, 1H), 5.15 (s, 2H), 4.53 (d, J=0.6 Hz, 2H), 4.36-4.34 (m, 2H), 3.79 (s, 3H), 2.57 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.67, 147.92, 129.30, 127.83, 127.32, 126.86, 123.52, 117.85, 114.34, 55.70, 55.33, 50.59, 44.80, 40.10; **LC-MS**, 6 min run, (ESI+) m/z 334.1220 $[M+H]^+$, Rt = 3.0 min.

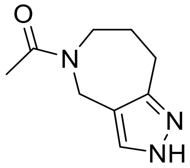
2,4,5,6,7,8-hexahydropyrazolo[4,3-c]azepine (**13a**)



A 0.05 M solution of **47a** (130mg, 0.36mmol) in EtOH (7ml) was hydrogenated in H-cube. Initially, the parameters (temperature: 25°C, pressure: 15bar and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (3.6ml) and anisole (0.24ml, 2.2mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was directly injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to provide **13a** (25mg, 0.18mmol, 49%) as a white solid.

^{1}H-NMR (500 MHz, $MeOD_4$): δ 7.38 (s, 1H), 3.82 (s, 2H), 3.19-3.16 (m, 2H), 2.88 - 2.84 (m, 2H), 1.84 - 1.78 (m, 2H); **^{13}C NMR** (125 MHz, $MeOD_4$): δ 150.33, 132.20, 120.00, 53.62, 45.30, 29.82, 28.16; broadening of peaks is due to tautomerism; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_{11}N_3$: 138.1026, found: 138.1039.

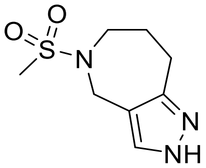
1-(2,6,7,8-tetrahydropyrazolo[4,3-c]azepin-5(4H)-yl)ethan-1-one (**13b**)



A 0.05 M solution of **47b** (123mg, 0.41mmol) in EtOH (41ml) was hydrogenated in an H-cubePro. Initially, the parameters (temperature: 25°C, pressure: 15bar and flowrate: 0.5ml/min) were selected and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (3.7ml) and anisole (0.27ml, 2.46mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to provide **13b** (40mg, 0.22mmol, 53%) as a white solid. Compound **13b** was isolated as a mixture 1:0.7 of two rotamers.

^{1}H-NMR (500 MHz, MeOD$_4$): δ 7.52 (s, 1H), 7.42 (s, 0.7H)*, 4.49 (s, 1.4H)*, 4.47 (s, 2H), 3.83-3.79 (m, 3.4H)**, 2.93-2.90 (m, 1.4H)*, 2.89-2.86 (m, 2H), 2.08 (s, 2.1H)*, 2.07 (s, 3H), 1.88-1.84 (m, 1.4H)*, 1.82 - 1.76 (m, 2H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 172.61, 172.12, 150.00, 149.91, 132.22, 131.84, 118.12, 117.85, 53.62, 50.53, 46.19, 42.30, 29.25, 27.67, 26.63, 27.59, 21.63, 21.52; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{13}N_3O$: 180.1131, found: 180.1137.

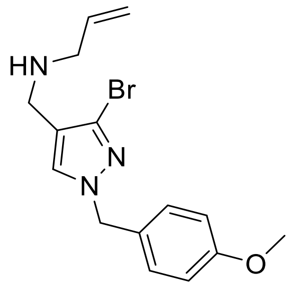
5-(methylsulfonyl)-2,4,5,6,7,8-hexahydropyrazolo[4,3-c]azepine (**13c**)



A 0.05 M solution of **47c** (97mg, 0.29mmol) in EtOH (29ml) was hydrogenated in an H-cubePro. Initially, the parameters (temperature: 25°C, pressure: 15bar and flowrate: 0.5ml/min) were selected and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (2.6ml) and anisole (0.19ml, 1.74mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to afford **13c** (36mg, 0.16mmol, 55%) as a white solid.

^{1}H-NMR (500 MHz, MeOD$_4$): δ 7.45 (s, 1H), 4.39 (s, 2H), 3.72 - 3.69 (m, 2H), 2.93 - 2.90 (m, 2H), 2.74 (s, 3H), 1.92 - 1.86 (m, 2H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 116.48, 51.45, 43.43, 37.84, 27.11, 26.05; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{13}N_3O_2S$: 216.0801, found: 216.0805.

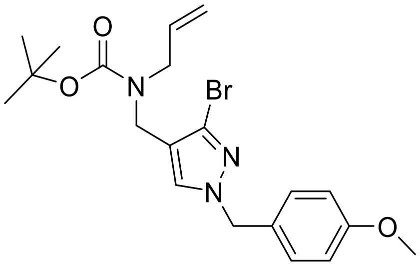
N-((3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)prop-2-en-1-amine (**48**)



To a solution of **3** (955mg, 3.24mmol) in DCM (10ml) was added $MgSO_4$ (1525mg, 12.96mmol) and propyilamine (0.35ml, 4.86mmol), and the reaction was stirred at rt for 24 h. Then, the mixture was filtered and volatiles were evaporated in vacuo. The solid residue was dissolved in MeOH (ml) and $NaBH_4$ (240mg, 6.48mmol) was added at 0 °C. The reaction was stirred at 0 °C for 1 h. Afterwards, water was added followed by EtOAc. The two layers were separated and the aq. phase was extracted with EtOAc (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (MeOH/DCM 3:97) to afford **48** (1.03 g, 3.05 mmol, 94%) as a yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.19 - 7.17 (m, 3H), 6.87 - 6.84 (m, 2H), 5.91 - 5.83 (m, 1H), 5.16 (qd, J=1.7, 17.1 Hz, 1H), 5.13 (s, 2H), 5.09 (qd, J=1.4, 10.2 Hz, 1H), 3.78 (s, 3H), 3.56 (s, 2H), 3.22 (td, J=1.4, 6.0 Hz, 2H), 1.35 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.69, 136.50, 129.66, 129.53, 127.48, 126.09, 120.06, 116.23, 114.29, 56.19, 55.31, 51.73, 42.84; **LC-MS**, 6 min run, (ESI+) m/z 336.0175 ($[M+H]^+$, ^{79}Br), 338.0602 ($[M+H]^+$, ^{81}Br) Rt = 2.3 min.

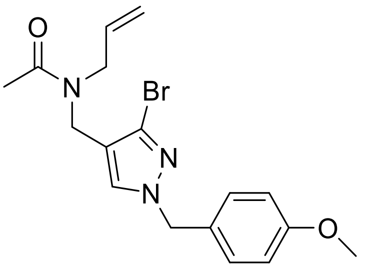
tert-butyl allyl((3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)carbamate (**49a**)



To a solution of **48** (375mg, 1.2mmol), DMAP (6.75mg, 0.06mmol) and Et_3N (0.23ml, 1.8mmol) in THF (mL), Boc anhydride (363mg, 1.8mmol) was added at 0 °C. After stirring at rt for 12 h, a saturated solution NH_4Cl was added. The two layers were separated and the aq. phase was further extracted with DCM (2x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (EtOAc/Heptane 30:70). The desired fractions were concentrated to dryness in vacuo to afford **49a** (452mg, 1.03mmol, 92%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34 (br, 0.6H), 7.18 (d, J=8.0 Hz, 2H), 7.11 (br, 0.4H)*, 6.86 (d, J=8.0 Hz, 2H), 5.71 (br, 1H), 5.13 (s, 2H), 5.09 (br, 2H), 4.12 (br, 2H), 3.78 (s, 3H), 3.76 (br, 2H), 1.42 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.74, 155.23, 133.72, 130.89, 129.68, 127.31, 126.25, 118.81, 116.60, 114.31, 79.77, 56.26, 55.40, 48.87, 40.06, 28.39; **LC-MS**, 6 min run, (ESI+) m/z 436.0800 ($[M+H]^+$, ^{79}Br), 438.0984 ($[M+H]^+$, ^{81}Br) Rt = 4.7 min.

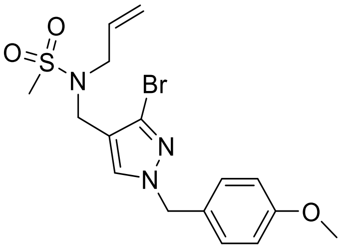
N-allyl-N-((3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)acetamide (**49b**)



To a solution of **48** (332mg, 0.98mmol) and pyridine (0.15ml, 1.47mmol) in DCM (3.2mL), acetyl chloride (0.11ml, 1.96mmol) was added at 0 °C. After stirring at 0 °C for 1 h, a saturated solution NH_4Cl was added. The two layers were separated and the aq. phase was further extracted with DCM (2x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (EtOAc/Heptane 60:40). The desired fractions were concentrated to dryness in vacuo to afford **49b** (335mg, 0.88mmol, 89%) as a white solid. **49b** was isolated as a mixture 1:0.3 of two rotamers.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.10 (s, 0.3H)*, 7.11 - 7.06 (m, 2.6H)**, 6.77-6.73 (m, 2.6H)**, 5.69 - 5.57 (m, 1.3H)**, 5.013 - 4.99 (m, 5.2H)**, 4.19 (s, 2H), 4.15 (s, 0.6H)*, 3.82 (d, J=5.8 Hz, 0.6H)*, 3.77 (m, 2H), 3.67 (s, 0.9H)*, 3.65 (s, 3H), 2.06 (s, 0.9H)*, 1.94 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.62, 170.02, 159.68, 159.56, 132.89, 132.51, 131.38, 129.48, 129.46, 129.32, 127.47, 127.23, 126.45, 125.30, 118.08, 117.39, 117.29, 116.72, 114.27, 114.17, 56.26, 56.14, 55.21, 55.20, 50.62, 47.25, 42.32, 39.03 21.71, 21.28; **LC-MS**, 6 min run, (ESI+) m/z 378.0826 ($[M+H]^+$, ^{79}Br), 380.0805 ($[M+H]^+$, ^{81}Br) Rt = 3.3 min.

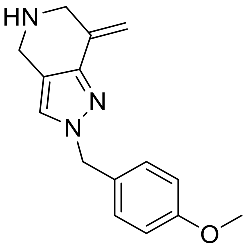
N-allyl-N-((3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)methanesulfonamide (**49c**)



To a solution of **48** (320mg, 0.95mmol) and pyridine (0.31ml, 3.80mmol) in DCM (3.2mL), methanesulfonyl chloride (0.22ml, 2.85mmol) was added at 0 °C. After stirring at 0 °C for 1 h, a saturated solution NH_4Cl was added. The two layers were separated and the aq. phase was further extracted with DCM (2x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo to afford **49c** (361mg, 0.87mmol, 92 %) as a yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.19 - 7.16 (m, 2H), 6.87 - 6.84 (m, 2H), 5.82 - 5.74 (m, 1H), 5.28 - 5.21 (m, 2H), 5.14 (s, 2H), 4.17 (s, 2H), 3.78-3.75 (m, 5H), 2.80 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.76, 132.30, 131.40, 129.55, 127.30, 126.55, 119.39, 116.82, 114.35, 56.42, 55.32, 49.38, 40.60, 40.09; **LC-MS**, 6 min run, (ESI+) m/z 414.0488 ($[M+H]^+$, ^{79}Br), 416.0467 ($[M+H]^+$, ^{81}Br) Rt = 2.3 min.

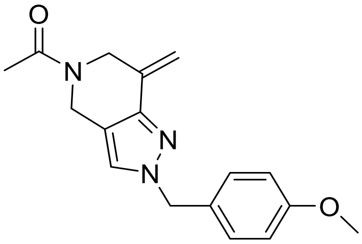
2-(4-methoxybenzyl)-7-methylene-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (**50a**)



A microwave vial was charged with **49a** (452mg, 1.03mmol), Cs_2CO_3 (670mg, 2.06mmol), $Pd(dppf)Cl_2$ (75mg, 0.103mmol) and DMF (3.5ml). The vial was evacuated and backfilled with nitrogen tree times. The vial was capped properly, and thereafter the mixture was heated under microwave irradiation conditions at 150 °C and 200 W for 100 min. Afterwards, water was added, and the aq. layer was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (EtOAc/heptane 40:60). The desired fractions were concentrated to dryness in vacuo to afford **50a** (with Boc) (204mg, 0.57mmol, 55%) as a white solid. A small amount of the latter was deprotected by using TFA in DCM, in order to get more comprehensible NMR spectra. LC-MS values of both the protected and deprotected version are reported.

^{1}H-NMR (without Boc) (500 MHz, $CDCl_3$): δ , 7.21 - 7.18 (m, 2H), 7.01 (s, 1H), 6.88 - 6.86 (m, 2H), 5.64 (d, J=1.1 Hz, 1H), 5.22 (s, 2H), 4.87 (d, J=1.2 Hz, 1H), 3.86 (s, 2H), 3.79 (s, 3H), 3.62 (t, J=1.0 2H), 1.70 (s, 1H); **^{13}C NMR** (without Boc) (125 MHz, $CDCl_3$): δ 159.50, 146.13, 136.25, 129.40, 128.40, 124.38, 117.71, 114.20, 104.96, 55.72, 55.31, 51.15, 42.13; **LC-MS**, 6 min run, (ESI+) m/z 356.2097 $[M+H]^+$ (with Boc), Rt = 3.8 min; **LC-MS**, 6 min run, (ESI+) m/z 256.1444 $[M+H]^+$ (without Boc), Rt = 3.2 min;

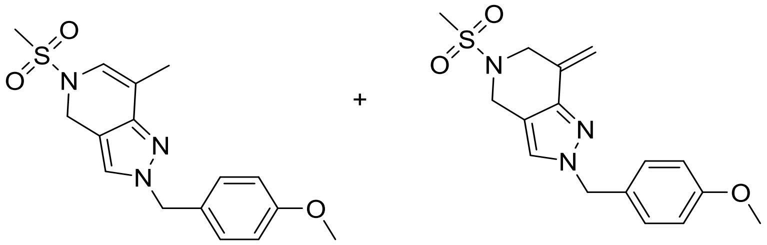
1-(2-(4-methoxybenzyl)-7-methylene-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)ethan-1-one (**50b**)



A microwave vial was charged with **49b** (335mg, 0.88mmol), Cs_2CO_3 (576mg, 1.76mmol), $Pd(dppf)Cl_2$ (65mg, 0.088mmol) and DMF (3ml). The vial was evacuated and backfilled with nitrogen tree times. The vial was capped properly, and thereafter the mixture was heated under microwave irradiation conditions at 150 °C and 200 W for 100 min. Afterwards, water was added and the aq. layer was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (MeOH/DCM 3:97). The desired fractions were concentrated to dryness in vacuo to afford **50b** (180mg, 0.60mmol, 68%) as a colourless oil. Compound **50b** was isolated as a mixture 1:0.45 of two rotamers.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.23 - 7.16 (m, 2.9H)**, 7.10 (s, 1H), 7.09 (s, 0.45H)*, 6.90 - 6.85 (m, 2.9H)**, 5.73 (s, 0.45H)*, 5.72 (s, 1H), 5.23 (s, 0.45H)*, 5.21 (s, 1H), 5.09 (br, 0.45H)*, 4.99 (br, 1H), 4.65 (s, 2H), 4.49 (s, 0.9H)*, br (4.41, 0.9H)*, 3.80 (s, 1.35H)*, 3.79 (s, 3H), 2.15 (s, 3H), 2.11 (s, 1.35H)*; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.59, 169.22, 159.63, 159.58, 146.01, 145.39, 133.02, 132.61, 129.50, 129.40, 128.02, 125.34, 124.64, 115.38, 114.26, 107.76, 106.69, 55.93, 55.90, 55.31, 53.44, 51.22, 45.91, 42.92, 38.70, 21.87, 21.30; broadening of peaks is due to the slow rotation of the amide linkage; **LC-MS**, 6 min run, (ESI+) m/z 298.1546 [M+H]$^+$, Rt = 2.7 min.

2-(4-methoxybenzyl)-7-methyl-5-(methylsulfonyl)-4,5-dihydro-2H-pyrazolo[4,3-c]pyridine (**50c'**); 2-(4-methoxybenzyl)-7-methylene-5-(methylsulfonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (**50c**'')

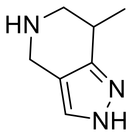


A MW vial was charged with **49c** (361mg, 0.87mmol), Cs_2CO_3 (565mg, 1.74mmol), Pd(dppf)Cl_2 (64mg, 0.087mmol) and DMF (3.5ml). The vial was evacuated and backfilled with nitrogen tree times. The vial was capped properly, and thereafter the mixture was heated under microwave irradiation conditions at 150 °C and 200 W for 100 min. Afterwards, water was added and extraction was carried out by using DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (EtOAc/Heptane 50:50). The desired fractions were concentrated to dryness in vacuo to afford **50c'** and **50c''** (180mg, 0.53mmol, 61%) as white solids. **50c'** and **50c''** were individually isolated in a 3.5:6.5 ratio.

50c': ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.18 - 7.16 (m, 2H), 7.02 (s, 1H), 6.87 - 6.85 (m, 2H), 6.37 (q, J=1.4 Hz, 1H), 5.17 (s, 2H), 4.70 (s, 2H), 3.77 (s, 3H), 2.81 (s, 3H), 2.04 (d, J=1.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.56, 145.93, 129.35, 128.22, 124.52, 122.00, 114.24, 113.97, 109.68, 55.62, 55.30, 42.21, 37.50, 14.36; **LC-MS**, 6 min run, (ESI+) m/z 334.1224 [M+H]$^+$, Rt = 3.1 min.

50c'': ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.20-7.17 (m, 2H), 7.12 (s, 1H), 6.89-6.86 (m, 2H), 5.82 (q, J=0.8 Hz, 1H), 5.22 (s, 2H), 5.09 (q, J=0.7 Hz, 1H), 4.51 (s, 2H), 4.23 (t, J=1.0 Hz, 2H), 3.80 (s, 3H), 2.65 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.70, 144.94, 131.62, 129.49, 127.72, 125.19, 114.33, 113.29, 108.54, 56.04, 55.33, 50.19, 42.58, 38.59; **LC-MS**, 6 min run, (ESI+) m/z 334.1231 [M+H]$^+$, Rt = 3.3 min.

7-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (**12a**)

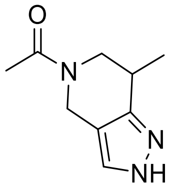


A 0.05 M solution of **50a** (204mg, 0.57mmol) in EtOH (11.5ml) was hydrogenated in an H-cubePro. Initially, the parameters (temperature: 50°C, pressure: 50bar, and flowrate: 0.5ml/min) were selected and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo, the solid residue was dissolved in TFA (7.3ml) and anisole (0.52ml, 3.42mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/MeCN 3:1:1.

The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to provide **12a** (37mg, 0.27mmol, 47%) as a white solid.

^{1}H-NMR (500 MHz, MeOD$_4$): δ 7.50 (s, 1H), 4.20 (d, J=14.6 Hz, 1H), 4.12 (d, J=14.6 Hz, 1H), 3.54 (dd, J=5.6, 12.4 Hz, 1H), 3.25 - 3.17 (m, 1H), 2.92 (dd, J=9.6, 12.4 Hz, 1H), 1.36 (d, J=6.9 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 148.01, 131.27, 110.04, 50.22, 41.90, 28.29, 17.33; broadening of peaks is due to tautomerism; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_{11}N_3$: 138.1026, found: 138.1030.

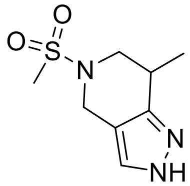
1-(7-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)ethan-1-one (**12b**)



A 0.05 M solution of **50b** (180mg, 0.60mmol) in EtOH (12ml) was hydrogenated in a H-cubePro. Initially, the parameters (temperature: 50°C, pressure: 50bar, and flowrate: 0.5ml/min) were selected and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo, the solid residue was dissolved in TFA (5.5ml) and anisole (0.4ml) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/ 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to provide **12b** (60mg, 0.33mmol, 55%) as a white solid. Compound **12b** was isolated as a mixture 1:0.8 of two rotamers.

^{1}H-NMR (500 MHz, CDCl$_3$): δ 9.94 (br, 1.8H)**, 7.34 (s, 0.8H)*, 7.31 (s, 1H), 4.81 (d, J=15.7 Hz, 1H), 4.55 (d, J=15.0 Hz, 0.8H)*, 4.45-4.42 (m, 1.8H)**, 4.26 (dd, J=4.8, 12.7 Hz, 0.8H)*, 3.77 (dd, J=4.8, 13.8 Hz, 1H), 3.27 (dd, J=7.8, 13.8 Hz, 1H), 3.11 (dd, J=8.4, 12.7 Hz, 0.8H)*, 3.08 - 2.97 (m, 1.8H)*, 2.18 (s, 3H), 2.16 (s, 2.4H)*, 1.30 (d, J=6.9 Hz, 3H), 1.26 (d, J=6.9 Hz, 2.4H)*; **^{13}C NMR** (125 MHz, MeOD$_4$): δ 170.07, 169.97, 147.58, 147.52, 128.95, 127.84, 111.76, 11.26, 51.14, 46.37, 42.97, 38.81, 29.55, 28.53, 21.99, 21.70, 17.29, 17.04; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{13}N_3O$: 180.1131, found: 180.1137.

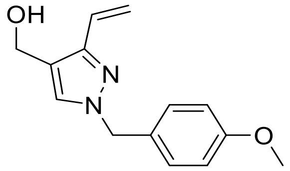
7-methyl-5-(methylsulfonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (**12c**)



A 0.05 M solution of **50c** (180mg, 0.53mmol) in EtOH (11ml) was hydrogenated in an H-cubePro. Initially, the parameters (temperature: 50°C, pressure: 50bar, and flowrate: 0.5ml/min) were selected and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (5.2ml) and anisole (0.37ml, 3.18mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to provide **12c** (65mg, 0.30mmol, 56%) as a white solid.

^{1}H-NMR (500 MHz, $MeOD_4$): δ 7.42 (s, 1H), 4.37 (d, J=14.0 Hz, 1H), 4.26 (d, J=14.0 Hz, 1H), 3.70 - 3.64 (m, 1H), 3.09 (m, 2H), 2.90 (s, 3H), 1.29 (d, J=6.6 Hz, 3H); **^{13}C NMR** (125 MHz, $MeOD_4$): δ 148.07, 130.00, 112.20, 51.72, 43.51, 35.92, 30.21, 17.85; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{13}N_3O_2S$: 216.0801, found: 216.0810.

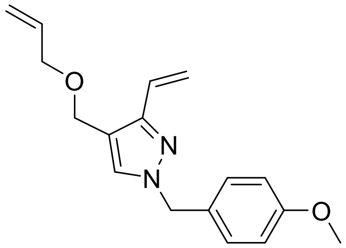
(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl) methanol (**51**)



To a solution of **44** (163mg, 0.67mmol) in MeOH (4ml) was added $NaBH_4$ (9.0mg, 0.22mmol) at 0 °C and the reaction was stirred for 1 h. Afterwards, the reaction was quenched with a saturated solution of NH_4Cl followed by DCM. The two layers were separated and the aq. phase was extracted with DCM (2x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo to **51** (156mg, 0.64 mmol, 95%) as a colourless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.21-7.18 (m, 2H), 6.88 - 6.86 (m, 2H), 6.75 (dd, J=11.4, 18.0 Hz, 1H), 5.83 (dd, J=1.5, 18.0 Hz, 1H), 5.34 (dd, J=1.5, 11.4 Hz, 1H), 5.17 (s, 2H), 4.60 (s, 2H), 3.80 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.57, 147.96, 129.50, 129.42, 128.04, 127.97, 119.43, 116.27, 114.25, 114.18, 55.78, 55.61, 55.32; **LC-MS**, 6 min run, (ESI+) m/z 245.1297 $[M+H]^+$, Rt = 2.4 min.

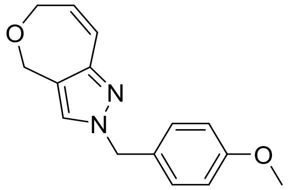
4-((allyloxy)methyl)-1-(4-methoxybenzyl)-3-vinyl-1H-pyrazole (**52**)



To a suspension of **51** (156mg, 0.64 mmol) in THF (2.7mL) was added portionwise NaH (60% dispersion in mineral oil, 38.2mg, 0.96mmol) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 30 min, then 3-bromoprop-1-ene (0.066ml, 0.77mmol) was added and the temperature was raised up to 50 °C. After 12 h, the reaction was cooled to 0 °C, diluted with EtOAc and water was added. The two layers were separated and the aq. phase was further extracted with EtOAc (2x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography eluting (EtOAc/Heptane 30:70). The desired fractions were concentrated to dryness in vacuo to afford **52** (172mg, 0.60mmol, 94%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (s, 1H), 7.20-7.17 (m, 2H), 6.87-6.84 (m, 2H), 6.73 (dd, J=11.3, 17.9 Hz, 1H), 5.96 - 5.88 (m, 1H), 5.81 (dd, J=1.5, 17.9 Hz, 1H), 5.32 (dd, J=1.5, 11.3 Hz, 1H), 5.27 (qd, J=1.5, 17.3 Hz, 1H), 5.19 - 5.16 (m, 3H), 4.40 (s, 2H), 3.98 (td, J=1.5, 5.8 Hz, 2H), 3.78 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.52, 148.52, 134.69, 130.04, 129.47, 128.14, 128.00, 117.27, 116.51, 116.22, 114.21, 70.91, 62.62, 55.57, 55.30; **LC-MS**, 6 min run, (ESI+) m/z 285.1623 $[M+H]^+$, Rt = 3.6 min.

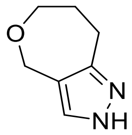
2-(4-methoxybenzyl)-2,6-dihydro-4H-oxepino[4,3-c]pyrazole (**53**)



A 0.01M solution of **52** (172mg, 0.60mmol) in DCM was degassed and backfilled with nitrogen 3 times. Then, Grubbs catalyst 2nd generation (25.6mg, 0.03mmol) was added to the reaction mixture and temperature was raised up to 40 °C. After 3h, the reaction was cooled down and DCM was removed in vacuo. The solid residue was purified by flash column chromatography eluting (EtOAc/Heptane 40:60). The desired fractions were concentrated to dryness in vacuo to afford **53** (120mg, 0.47mmol, 78%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.18 - 7.16 (m, 2H), 7.04 (d, J=0.7 Hz, 1H), 6.88 - 6.85 (m, 2H), 6.55 (ddt, J=0.7, 2.0, 11.9 Hz, 1H), 5.77 (td, J=3.6, 11.9 Hz, 1H), 5.15 (s, 2H), 4.65 (s, 2H), 4.54 (dd, J=2.0, 3.6 Hz, 2H), 3.79 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.50, 148.66, 130.65, 129.27, 128.34, 126.06, 121.60, 121.05, 114.22, 66.52, 55.44, 55.31; **LC-MS**, 6 min run, (ESI+) m/z 257.1305 $[M+H]^+$, Rt = 3.0 min.

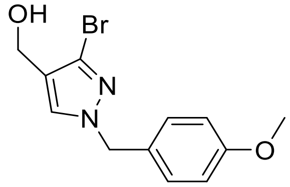
2,6,7,8-tetrahydro-4H-oxepino[4,3-c]pyrazole (**15**)



A 0.05 M solution of **53** (120mg, 0.47mmol) in EtOH (9.5ml) was hydrogenated in H-cube. Initially, the parameters (temperature: 25°C, pressure: 15bar and flowrate: 0.5ml/min) were selected on H-cube and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (4.3ml) and anisole (0.3ml, 2.8mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH. The latter sample was directly injected in autoprep and purified under basic conditions. The desired fractions were evaporated to provide **15** (32mg, 0.23mmol, 49%) as a white solid.

^{1}H-NMR (400 MHz, MeOD$_4$): δ 7.42 (s, 1H), 4.56 (s, 2H), 4.04-3.99 (m, 2H), 2.93-2.88 (m, 2H), 1.87 - 1.80 (m, 2H); **^{13}C NMR** (100 MHz, MeOD$_4$): δ 149.20, 130.25, 119.43, 74.93, 65.31, 29.26, 26.28; **HRMS** (ESI): [M+H]$^+$ calcd. for $C_7H_{10}N_2O$: 139.0866, found: 139.0870.

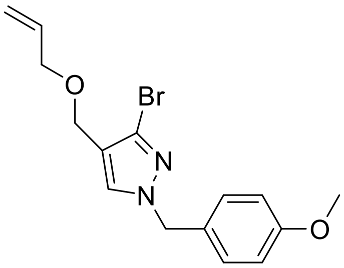
(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methanol (**54**)



To a solution of **3** (230mg, 0.78mmol) in MeOH (7ml) was added NaBH$_4$ (59mg, 1.56mmol) at 0 °C and the reaction was stirred for 1h. Afterwards, the reaction was quenched with saturated solution NH$_4$Cl followed by DCM. The aq. layer was then extracted with DCM (2x). The combined organic fractions were washed with brine, dried over MgSO$_4$ and evaporated in vacuo to afford **54** (223mg, 0.75 mmol, 96%).

^{1}H-NMR (500 MHz, CDCl$_3$): δ 7.12 (s, 1H), 7.03 - 7.00 (m, 2H), 6.71 - 6.68 (m, 2H), 4.93 (s, 2H), 4.27 (s, 2H), 3.61 (s, 3H), 3.53 (s, 1H); **^{13}C NMR** (125 MHz, CDCl$_3$): δ 159.60, 130.10, 129.62, 127.41, 125.60, 121.46, 114.26, 56.01, 55.30, 55.15; **LC-MS**, 6 min run, (ESI+) m/z 297.0200 ([M+H]$^+$, ^{79}Br), 299.0206 ([M+H]$^+$, ^{81}Br) Rt = 2.3 min.

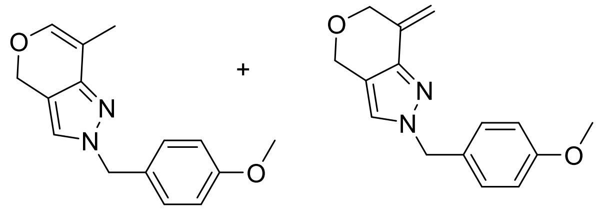
4-((allyloxy)methyl)-3-bromo-1-(4-methoxybenzyl)-1H-pyrazole (**55**)



To a suspension of **54** (223mg, 0.75mmol) in THF (4.3mL) was added portionwise NaH (60% dispersion in mineral oil, 44.8mg, 1.12mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, then 3-bromoprop-1-ene (0.081ml, 0.9mmol) was added and the temp was raised up to 50 °C. After 12 h, the reaction was cooled to 0° C and water was added followed by EtOAc. The two layers were separated and the aq. phase was extracted with EtOAc (3x). The organics were washed with brine, dried over MgSO$_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (EtOAc/Heptane 25:75) to afford **55** (235mg, 0.7mmol, 93%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.25 (s, 1H), 7.22-7.18 (m, 2H), 6.89 - 6.86 (m, 2H), 5.96 - 5.86 (m, 1H), 5.28 (qd, J=1.5, 17.2 Hz, 1H), 5.19 (qd, J=1.4, 10.3 Hz, 1H), 5.16 (s, 2H), 4.30 (s, 2H), 3.99 (td, J=1.4, 5.7 Hz, 2H), 3.80 (s, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 159.81, 134.50, 130.35, 129.76, 127.33, 126.62, 118.62, 117.49, 114.34, 71.17, 62.46, 56.30, 55.36; **LC-MS**, 6 min run, (ESI+) m/z 337.0464 ([M+H]$^+$, ^{79}Br), 339.0470 ([M+H]$^+$, ^{81}Br) Rt = 3.8 min.

2-(4-methoxybenzyl)-7-methyl-2,4-dihydropyrano[4,3-c]pyrazole (**56'**); 2-(4-methoxybenzyl)-7-methylene-2,4,6,7-tetrahydropyrano[4,3-c]pyrazole (**56''**)

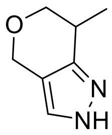


A microwave vial was charged with **55** (235mg, 0.7mmol), Cs_2CO_3 (456mg, 1.40mmol), Pd(dppf)Cl_2 (51mg, 0.07mmol) and DMF (2.5ml). The vial was capped properly, and thereafter the mixture was heated under microwave irradiation conditions at 150 °C and 200 W for 100 min. Afterwards, water was added, and the aq. layer was extracted with DCM (3x). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash column chromatography (EtOAc/Heptane 35:65). The desired fractions were concentrated to dryness in vacuo to afford **56'** and **56''** (116mg, 0.45mmol, 65%) as white solids. **56'** and **56''** were individually isolated in a 4:6 ratio.

56': ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.20 - 7.17 (m, 2H), 6.93 (s, 1H), 6.88 - 6.86 (m, 2H), 6.33 (q, J=1.5 Hz, 1H), 5.20 (s, 2H), 5.08 (s, 2H), 3.80 (s, 3H), 1.95 (d, J=1.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.49, 145.76, 141.62, 129.24, 128.71, 123.22, 114.20, 110.04, 107.03, 63.42, 55.31, 55.28; **LC-MS**, 6 min run, (ESI+) m/z 257.1312 $[M+H]^+$, Rt = 3.1 min.

56'': ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.21 - 7.16 (m, 2H), 7.03 (s, 1H), 6.87 - 6.84 (m, 2H), 5.69 (q, J=1.0 Hz, 1H), 5.22 (s, 2H), 4.91 (q, J=1.0 Hz, 1H), 4.67 (s, 2H), 4.35 (t, J=1.4 Hz, 2H), 3.77 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.52, 144.62, 134.51, 129.37, 128.25, 123.96, 116.31, 114.21, 105.29, 70.58, 63.54, 55.75, 55.29, 12.15; **LC-MS**, 6 min run, (ESI+) m/z 257.1312 $[M+H]^+$, Rt = 3.4 min.

7-methyl-2,4,6,7-tetrahydropyrano[4,3-c]pyrazole (**14**)

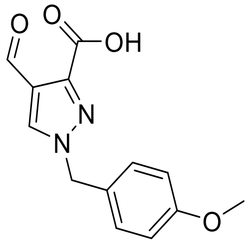


A 0.05 M solution **56** (116mg, 0.45mmol) in EtOH (9ml) was hydrogenated in an H-cubePro. Initially, the parameters (temperature: 50°C, pressure: 50bar, and flowrate: 0.5ml/min) were selected and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (4.1ml) and anisole (0.29ml, 2.70mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to provide **14** (32mg, 0.23mmol, 51%) as a white solid.

^{1}H-NMR (500 MHz, $MeOD_4$): δ 7.32 (s, 1H), 4.70 (d, J=13.3 Hz, 1H), 4.66 (d, J=13.3 Hz, 1H), 3.97 (dd, J=5.0, 11.2 Hz, 1H), 3.45 (dd, J=6.9, 11.2 Hz, 1H), 3.02 - 2.95 (m, 1H), 1.24 (d, J=6.9 Hz, 3H); **^{13}C NMR**

(125 MHz, MeOD$_4$): δ 135.46, 124.05, 114.21, 72.71, 64.69, 30.59, 16.82; broadening of peaks is due to tautomerism; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_{10}N_2O$: 139.0865, found: 139.0866.

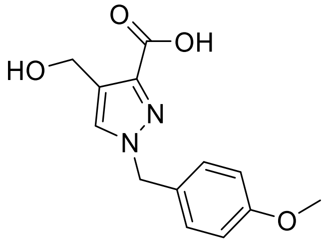
4-formyl-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylic acid (**57**)



To a microwave vial were added **3b** 945mg, 3.18mmol), 1,1,3-trioxo-1,2-benzothiazole-2-carbaldehyde (815mg, 3.81mmol), KF (560mg, 9.54mmol), Xantphos (558mg, 0.95mmol), Pd(OAc)$_2$ (3.8036mg, 0.318mmol) . Then, the microwave vial was capped, evacuated and backfilled three times with nitrogen. Afterwards, DMF (17mL) was added and the final mixture was stirred at 90 °C for 48h. Thereafter, water (0.087ml, 4.17mmol) and Et$_3$N (1.12ml, 7.95mmol) were added and the mixture was stirred for 30 more min at rt. The latter was finally filtered and DMF removed. The crude was then injected in an AutoPurification HPLC/MS system and purified under acidic conditions to afford **57** (400mg, 1.53mmol, 48%) as a white solid.

^{1}H-NMR (500 MHz, CDCl$_3$): δ 9.94 (s, 1H), 7.92 (s, 1H), 7.28 - 7.25 (m, 2H), 6.92-6.89 (m, 2H), 5.35 (s, 2H), 3.81 (s, 3H); **^{13}C NMR** (125 MHz, CDCl$_3$): δ 186.48, 160.38, 135.87, 130.34, 125.15, 122.88, 114.78, 57.14, 55.39; **LC-MS**, 6 min run, (ESI+) m/z 261.0889 $[M+H]^+$, Rt = 3.0 min.

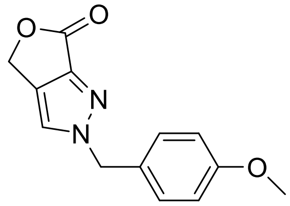
4-(hydroxymethyl)-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylic acid (**58**)



To a mixture of **57** (215mg, 0.82mmol) in Methanol (4.5mL) at 0 °C, NaBH$_4$ (19.3mg, 0.57mmol) was added and the reaction stirred for 30 min. Then, volatiles were removed under reduced pressure, a saturated solution of NH$_4$Cl was added and extraction was carried out with DCM (3 times). The organics were then washed with brine and dried over MgSO$_4$ before concentration to dryness. The crude was then injected in an AutoPurification HPLC/MS system and purified under acidic conditions to afford **58** (180mg, 0.68mmol, 83%) as a white solid.

^{1}H-NMR (500 MHz, MeOD$_4$): δ 7.62 (s, 1H), 7.26 - 7.24 (m, 2H), 6.90 - 6.88 (m, 2H), 5.27 (s, 2H), 4.71 (s, 2H), 3.76 (s, 3H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 165.78, 161.29, 141.22, 131.43, 130.63, 1299.46, 127.55, 115.29, 56.92, 56.61, 55.81; **LC-MS**, 6 min run, (ESI+) m/z 263.1165 $[M+H]^+$, Rt = 2.7 min.

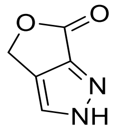
2-(4-methoxybenzyl)-2,4-dihydro-6H-furo[3,4-c]pyrazol-6-one (**59**)



To a solution of **58** (180mg, 0.68mmol) in DMF (7mL), HATU (113.3mg, 0.75mmol) and DIPEA (0.36ml, 2.04mmol) were added and the final mixture was stirred at rt for 2 h. Then, water was added and the mixture extracted with DCM (3x). The organics were washed with brine, separated and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/Heptane 35:65). The desired fractions were concentrated to dryness in vacuo to afford **59** (115mg, 0.46mmol, 68%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31 (t, J=0.9 Hz, 1H), 7.28 - 7.25 (m, 2H), 6.91 - 6.88 (m, 2H), 5.37 (s, 2H), 5.19 (d, J=0.9 Hz, 2H), 3.80 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 163.54, 159.96, 144.66, 131.76, 129.75, 126.99, 123.13, 114.45, 65.30, 57.30, 55.36; **LC-MS**, 6 min run, (ESI+) m/z 245.1199 $[M+H]^+$, Rt = 2.8 min.

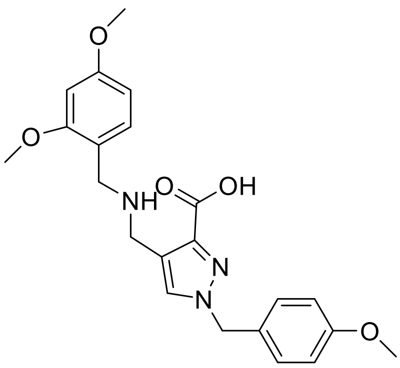
2,4-dihydro-6H-furo[3,4-c]pyrazol-6-one (**16**)



59 (115mg, 0.46mmol) was dissolved in TFA (4.3ml) and anisole (0.30ml, 2.76mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 2 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/MeCN/water 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to provide **16** (24mg, 0.19 mmol, 41%) as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.82 (br, 1H), 7.89 (s, 1H), 5.30 (s, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 164.27, 144.04, 132.28, 124.67, 66.21**;** **HRMS** (ESI): $[M+H]^+$ calcd. for $C_5H_4N_2O_2$: 125.0346, found: 125.0356.

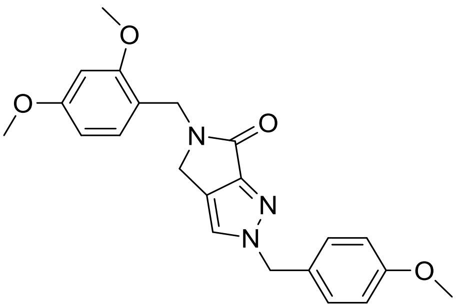
4-(((2,4-dimethoxybenzyl)amino)methyl)-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylic acid (**60**)



To a mixture of **57** (175mg, 0.67mmol) and $MgSO_4$ (384mg, 3.35mmol) in DCM (4mL) was added (2,4-dimethoxyphenyl)methanamine (0.11ml, 0.81mmol). The mixture was stirred at rt for 24 h. Then, the latter was filtered and volatiles were removed in vacuo. The crude was solubilized in MeOH (8mL) and $NaBH_4$ (24mg, 0.67mmol) was added. The reaction was stirred at 25 °C for 3 h. Subsequently, the mixture was quenched by adding $NaHCO_3$ and extraction was carried out with DCM (3x). The organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was purified by flash chromatography (EtOAc/Heptane 40:60). The desired fractions were concentrated to dryness in vacuo to afford **60** (256mg, 0.62mmol, 92%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.81 (br, 1H), 7.32 (br, 1H), 7.10 - 7.05 (m, 4H), 6.80 (d, J=8.5 Hz, 2H), 6.33 (s, 2H), 5.01 (s, 2H), 4.01 (s, 2H), 3.87 (s, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.88, 161.63, 159.45, 159.02, 147.62, 132.52, 130.18, 129.52, 127.91, 114.11, 113.65, 112.92, 104.28, 98.13, 55.46, 55.33, 55.26, 44.08, 41.02; **LC-MS**, 6 min run, (ESI+) m/z 412.1852 $[M+H]^+$, Rt = 2.6 min.

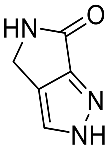
5-(2,4-dimethoxybenzyl)-2-(4-methoxybenzyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(2H)-one (**61**)



To a solution of **60** (256mg, 0.62mmol) in DMF (5mL), HATU (255mg, 0.68mmol) and DIPEA (0.317ml, 1.86mmol) were added and the final mixture was stirred at rt for 2 h. Then, water was added and the mixture extracted with DCM (3x). The organics were washed with brine, separated and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/Heptane 60:40). The desired fractions were concentrated to dryness in vacuo to afford **61** (200mg, 0.51mmol, 82%) as a white solid.

^{1}H-NMR (500 MHz, $MeOD_4$): δ 7.30 (s, 1H), 7.29-7.26 (m, 2H), 7.08 (d, J=8.2 Hz, 1H), 6.81 - 6.78 (m, 2H), 6.49 (d, J=2.3 Hz, 1H), 6.42 (dd, J=2.3, 8.2 Hz, 1H), 5.33 (s, 2H), 4.55 (s, 2H), 4.03 (s, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H); **^{13}C NMR** (125 MHz, $MeOD_4$): δ 162.54, 161.08, 160.67, 160.04, 140.59, 132.90, 131.88, 130.73, 130.69, 130.13, 118.31, 115.09, 105.74, 99.55, 56.01, 55.90,55.78, 54.25, 45.55, 42.78; **LC-MS**, 6 min run, (ESI+) m/z 394.1780 $[M+H]^+$, Rt = 3.5 min.

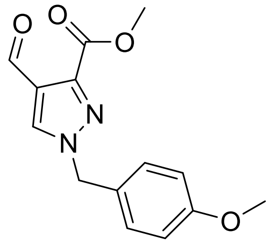
4,5-dihydropyrrolo[3,4-c]pyrazol-6(2H)-one (**17**)



61 (200mg, 0.51mmol) was dissolved in TFA (4.5ml) and anisole (0.33ml, 3.06mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 2 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to provide **17** (25mg, 0.2mmol, 40%) as a white solid.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 13.30 (br, 1H), 8.25 (br, 1H), 7.70 (br, 1H), 4.16 (d, 2H); **^{13}C NMR (**125 MHz, DMSO-d_6): δ 165.19, 150.83, 126.35, 123.12, 40.10; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_5H_5N_3O$: 124.0506, found: 124.0515.

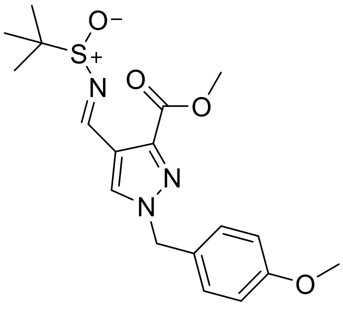
methyl 4-formyl-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylate (**62**)



To a microwave vial were added **3b** (770mg, 2.6mmol), 1,1,3-trioxo-1,2-benzothiazole-2-carbaldehyde (660mg, 3.12mmol), KF (455mg, 7.8mmol), Xantphos (452mg, 0.0508mmol), $Pd(OAc)_2$ (58.5mg, 0.26mmol). Then, the microwave vial was capped, evacuated and backfilled three times with nitrogen. Afterwards, DMF (14mL) was added and the final mixture was stirred at 90 °C for 48 h. Thereafter, MeOH (0.16ml, 3.9mmol) and Et_3N (0.9ml, 7.8mmol) were added and the mixture was stirred for 30 more min at rt. The latter was finally filtered and DMF removed in vacuo. The crude was then purified by flash column chromatography (EtOAc/Heptane 40:60). The desired fractions were concentrated to dryness in vacuo to afford **62** (358mg, 1.3mmol, 50%) as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 10.31 (s, 1H), 7.83 (s, 1H), 7.22-7.19 (m, 2H), 6.88 - 6.85 (m, 2H), 5.28 (s, 2H), 3.96 (s, 3H), 3.77 - 3.76 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.29, 161.84, 160.20, 142.95, 132.15, 130.07, 129.83, 125.69, 125.02, 114.63, 114.38, 56.90, 55.32, 52.48; **LC-MS**, 6 min run, (ESI+) m/z 275.1021 $[M+H]^+$, Rt = 3.5 min.

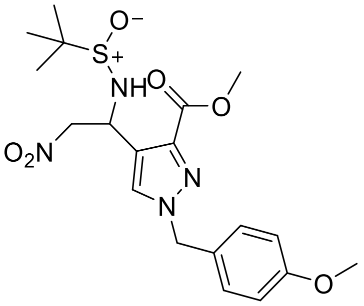
methyl (E)-4-(((tert-butylsulfinyl)imino)methyl)-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylate (**63**)



A solution of **62** (358mg, 1.3mmol) and $Ti(OEt)_4$ (1.36ml, 6.5mmol) in DCM (4.3mL) was stirred at 25 °C for 5 min. Then, 2-methylpropane-2-sulfinamide (173.5mg, 1.43mmol) was added and the final mixture was stirred at 25 °C for 3 h. Thereafter, water was added and the following suspension was filtered through celite, eluting with DCM. Solvent was removed in vacuo and the crude purified by flash column chromatography (EtOAc/Heptane 50:50). The desired fractions were concentrated to dryness in vacuo to afford **63** (462mg, 1.2mmol, 92%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.86 (s, 1H), 7.28-7.24 (m, 2H), 6.92-6.88 (m, 2H), 5.35 (d, J=14.6 Hz, 1H), 5.30 (d, J=14.6 Hz, 1H), 3.98 (s, 3H), 3.81 (s, 3H), 1.20 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 161.92, 160.05, 155.87, 141.86, 130.81, 129.90, 126.22, 121.31, 114.54, 57.55 56.92, 55.35, 52.47, 22.60; **LC-MS**, 6 min run, (ESI+) m/z 378.1466 $[M+H]^+$, Rt = 4.0 min.

methyl 4-(1-((tert-butylsulfinyl)amino)-2-nitroethyl)-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylate (**64**)

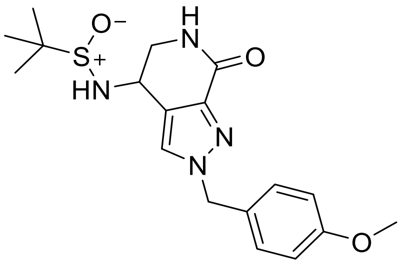


TBAF (1M solution in THF, 1.22ml, 1.2mmol) was added to a solution of **63** (462mg, 1.2mmol) in nitrometane/dioxane (4:1) (5.2ml). The final solution was stirred at rt for 30 min. Then, volatiles were removed under reduced pressure, water was added and extraction was carried out with DCM. The organics were washed with brine, separated and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (MeOH/DCM 3:97). The desired fractions were concentrated to dryness in vacuo to provide **64'** (R_sR/S_sS) and **64''** (R_sS/S_sR) (445mg, 1.1mmol, 90%) as pale yellow solids. **64'** and **64''** were individually isolated in a 2:8 ratio.

64': ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31 (s, 1H), 7.17-7.14 (m, 2H), 6.90 - 6.87 (m, 2H), 5.32 - 5.23 (m, 4H), 5.06 (dd, J=5.6, 12.9 Hz, 1H), 4.84 (dd, J=7.5, 13.0 Hz, 1H), 3.97 (s, 3H), 3.80 (s, 3H), 1.17 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 163.67, 159.97, 138.99, 129.62, 126.41, 122.35, 114.51, 56.70, 56.50, 55.32, 52.59, 50.62, 22.55; **LC-MS**, 6 min run, (ESI+) m/z 439.1662 $[M+H]^+$, Rt = 3.6 min.

64'': ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.19-7.16 (m, 2H), 6.89-7.86 (m, 2H), 5.32 (d, J=10.5 Hz, 1H), 5.27 (d, J=14.8 Hz, 1H), 5.23 (d, J=14.8 Hz, 1H), 5.19-5.14 (m, 1H), 4.80 (dd, J=9.5, 12.5 Hz, 1H), 4.48 (dd, J=5.1, 12.6 Hz, 1H), 3.96 (s, 3H), 3.79 (s, 3H), 1.15 (s, 9H); **^{13}C NMR** (125 MHz, DMSO-d6): δ 164.14, 159.99, 139.09, 130.07, 129.81, 126.27, 122.80, 114.55, 78.92, 56.74, 55.31, 52.63, 51.51, 22.48; **LC-MS**, 6 min run, (ESI+) m/z 439.1650 $[M+H]^+$, Rt = 3.7 min.

N-(2-(4-methoxybenzyl)-7-oxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-4-yl)-2-methylpropane-2-sulfinamide (**65**)

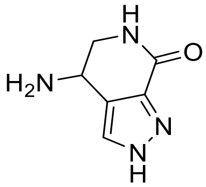


Separately, both diastereomeric pairs of enantiomers **64'** and **64''** (445mg, 1.1mmol) were dissolved in EtOH (11ml), Zn (1.33g, 22.0mmol) was subsequently added and the temperature raised up to 80 °C. Then, AcOH (11ml) was added and the final mixture was stirred at 80 °C for 30 min. Thereafter, the latter was filtered and solvents were removed under vacuum. To the crude was then added dioxane (10ml) and Et_3N (0.7ml, 5.5mmol), and the solution was stirred at rt. for 12 h. The solution was then diluted with DCM, followed by a saturated solution of NH_4Cl. The two layers were then separated and the aq. one was further extracted with DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (MeOH/DCM 5:95). The desired fractions were concentrated to dryness in vacuo to afford **65'** (R_sR/S_sS) and **65''** (R_sS/S_sR) (326mg, 0.86 mmol, 85%) as white solids.

65': ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.71 (d, J=8.4 Hz, 2H), 7.64 (s, 1H), 7.32 (d, J=8.4 Hz, 2H), 5.78 (d, J=14.6 Hz, 1H), 5.68 (d, J=14.6 Hz, 1H), 5.56 (d, J=8.7 Hz, 1H), 4.97 - 4.91 (m, 1H), 4.25 - 4.22 (m, 5H), 1.65 (s, 9H); **^{13}C NMR** (125 MHz, DMSO-d6): δ 162.52, 159.72, 141.98, 129.84, 128.78, 127.47, 126.63, 121.66, 114.28, 56.47, 56.35, 55.29, 48.91, 47.62, 22.72; **LC-MS**, 6 min run, (ESI+) m/z 377.1652 $[M+H]^+$, Rt = 3.0 min.

65'': ^{1}H-NMR (500 MHz, DMSO): δ 7.80 (s, 1H), 7.59 (t, J=2.7 Hz, 1H), 7.29-7.26 (m, 2H), 6.93-6.91 (m, 2H), 5.65 (d, J=7.8 Hz, 1H), 5.30 (s, 2H), 4.54 - 4.49 (m, 1H), 3.34 (td, J=2.7, 5.4 Hz, 2H), 3.32 (s, 3H), 1.12 (s, 9H); **^{13}C NMR** (125 MHz, DMSO-d6): δ 161.55, 159.48, 142.00, 130.08, 129.24, 128.74, 124.03, 114.43, 55.81, 55.61, 55.43, 48.25, 47.98, 23.09; **LC-MS**, 6 min run, (ESI+) m/z 377.1662 $[M+H]^+$, Rt = 3.1 min.

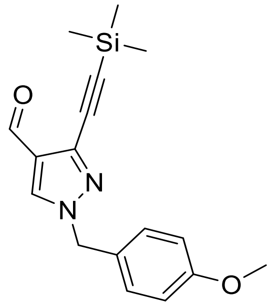
4-amino-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (**18**)



65' and **65''** (325mg, 0.86mmol) were dissolved in TFA (11ml) and anisole (0.77ml, 5.16mmol) was subsequently added to the reaction flask. The final mixture was heated at 80° C for 12 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to provide **18** (80mg, 0.52 mmol, 60%) as a reddish oil.

^{1}H-NMR (500 MHz, $MeOD_4$): δ 7.70 (s, 1H), 4.22 (dd, J=5.0, 6.7 Hz, 1H), 3.63 (dd, J=5.0, 12.7 Hz, 1H), 3.37 (dd, J=6.7, 12.7 Hz, 1H); **^{13}C NMR** (125 MHz, $MeOD_4$): δ 164.19, 140.43, 129.66, 125.82, 50.74, 44.05; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_6H_8N_4O$: 153.0771, found: 153.0774.

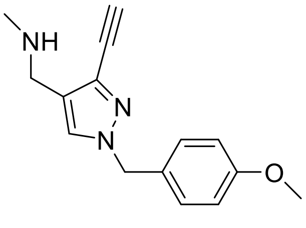
1-(4-methoxybenzyl)-3-((trimethylsilyl)ethynyl)-1H-pyrazole-4-carbaldehyde (**66**)



A flask was charged with **3b** (155mg, 0.52mmol), CsF (183.5mg, 1.19mmol), Pd(t-Bu$_3$P)$_2$ (10.7mg, 0.021mmol) and 1,4-dioxane (2ml) under nitrogen atmosphere. Then, trimethyl(2-tributylstannylethynyl)silane (0.20ml, 0.57mmol) was added and the final mixture was stirred at rt for 24h. Subsequently, the reaction was diluted with Et$_2$O and water was added. The two layers were separated and the aq. one was extracted further with Et$_2$O (2x). The combined organics were washed with brine and dried over MgSO$_4$ before concentration to dryness. The crude was passed through celite and then purified by flash column chromatography eluting 15% EtOAc in heptane. The desired fractions were concentrated to dryness in vacuo to afford **66** (138mg, 0.44mmol, 84%) as a white solid.

^{1}H-NMR (500 MHz, CDCl$_3$): δ 9.90 (s, 1H), 7.83 (s, 1H), 7.25-7.22 (m, 2H), 6.91 - 6.88 (m, 2H), 5.23 (s, 2H), 3.80 (s, 3H), 0.29 (s, 9H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 184.77, 160.45, 138.01, 130.37, 126.33, 125.45, 114.92, 101.07, 94.11, 57.01, 55.71, 0.00; **LC-MS**, 6 min run, (ESI+) m/z 313.1377 [M+H]$^+$, Rt = 4.2 min.

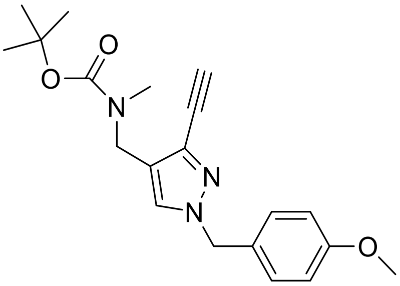
1-(3-ethynyl-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)-N-methylmethanamine (**67a**)



To a solution of **66** (138mg, 0.44mmol) in DCM 1.5(ml) was added MgSO$_4$ (213mg, 1.76mmol) and methylamine (2M in THF, 0.88ml, 1.76mmol), and the reaction was stirred at rt for 24h. Then, the mixture was filtered and volatiles were evaporated in vacuo. The solid residue was dissolved in MeOH (3ml) and NaBH$_4$ (33.5mg, 0.88mmol) was added at 0 °C. The reaction was stirred at rt temperature for 8h. Afterwards, a 3M NaOH aq. solution was added followed by EtOAc. The two layers were separated and the aq. phase was extracted with EtOAc (3x). The combined organic fractions were washed with brine, dried over MgSO$_4$ and evaporated in vacuo. The crude was then purified by flash column chromatography eluting (MeOH/DCM 6:94). The desired fractions were concentrated to dryness in vacuo to afford **67a** (89.2mg, 0.35mmol, 79%) as a reddish solid.

^{1}H-NMR (500 MHz, CDCl$_3$): δ, 7.22 (s, 1H), 7.18 (d, J=8.5 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 5.15 (s, 2H), 3.77 (s, 3H), 3.62 (s, 2H), 3.18 (s, 1H), 2.39 (s, 3H), 1.40 (br, 1H); **^{13}C NMR** (125 MHz, CDCl$_3$): δ 159.65, 132.97, 129.55, 128.18, 127.71, 124.27, 114.27, 80.23, 75.75, 56.08, 55.29, 45.22, 35.93; **LC-MS**, 6 min run, (ESI+) m/z 256.1461 [M+H]$^+$, Rt = 2.3 min.

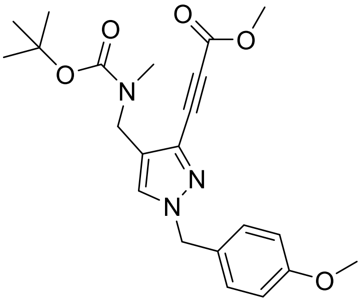
tert-butyl ((3-ethynyl-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)(methyl)carbamate (**67b**)



A solution of Boc anhydride (100mg, 0.45mmol) in THF (0.3ml) was added to a mixture of **67a** (89.2mg, 0.35mmol) and Et_3N (0.06ml, 0.42mmol) in THF (1.5ml) at 0 °C. Then, the temperature was allowed to reach rt and the reaction was stirred for 2 h. Afterwards, water was added, the two layers were separated and the aq. phase was extracted further with DCM (2x). The combined organic fractions were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (EtOAc/Heptane 20:80). The desired fractions were concentrated to dryness in vacuo to afford **67b** (123.8mg, 0.34mmol, 96%) as a yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.18 (d, J=8.4 Hz, 2H), 6.86 (d, J=8.4 Hz, 2H), 5.16 (s, 2H), 4.26 (s, 2H), 3.78 (s, 3H), 3.17 (s, 1H), 2.82 (s, 3H), 1.43 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.71, 155.74, 129.58, 129.37, 127.46, 122.28, 114.32, 80.15, 79.54, 75.61, 56.16, 55.30, 42.22, 34.12, 28.44; **LC-MS**, 6 min run, (ESI+) m/z 356.1982 $[M+H]^+$, Rt = 3.8 min.

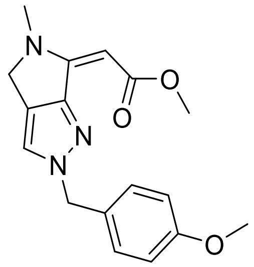
Methyl 3-(4-(((tert-butoxycarbonyl)(methyl)amino)methyl)-1-(4-methoxybenzyl)-1H-pyrazol-3-yl)propiolate (**68**)



67b (123.8mg, 0.34mmol) was dissolved in THF (1.8ml) at -78°C, followed by dropwise addition of *n*BuLi (2.5M in hexane, 0.182ml, 0.41mmol). The resulted solution stirred at -78°C for 30 min. Then, methyl chloroformate (0.035ml, 0.44mmol) was added and the solution was stirred for 30 more min. The mixture was allowed to reach r.t. and then was extracted with Et2O (2x) after addition of water. The organic layers were washed with brine and dried over $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography eluting 20%EtOAc in heptane. The desired fractions were concentrated to dryness in vacuo to afford **68** (124mg, 0.3mmol, 86%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31 (br, 1H), 7.15 (d, J=8.5 Hz, 2H), 6.82 (d, J=8.2 Hz, 2H), 5.14 (s, 2H), 4.23 (s, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 2.80 (s, 3H), 1.35 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.71, 155.74, 129.58, 129.37, 127.46, 122.28, 114.32, 80.15, 79.54, 75.61, 56.16, 55.30, 42.22, 34.12, 28.44; **LC-MS**, 6 min run, (ESI+) m/z 414.2038 $[M+H]^+$, Rt = 4.4 min.

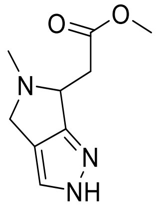
methyl (E)-2-(2-(4-methoxybenzyl)-5-methyl-4,5-dihydropyrrolo[3,4-c]pyrazol-6(2H)-ylidene)acetate (**69**)



68 (124mg, 0.3mmol) was solubilized in DCM (2ml) and hydrogen chloride (4M in 1,4-dioxane, 0.48ml, 0.12mmol) was added. The resulting mixture was stirred at rt for 4h. Then, volatiles were removed under reduced pressure and the solid crude was solubilized in dioxane (2ml). To this suspension, Et_3N (0.021ml, 0.15mmol) was added and the final suspension was stirred at rt for 1h. Afterwards, water was added followed by DCM. The two resulting layers were separated and the aq. phase was extracted further with DCM (2x). The organics were then combined, washed with brine and dried $MgSO_4$ before concentration to dryness. The crude was then purified by flash column chromatography (MeOH/DCM 4:96). The desired fractions were concentrated to dryness in vacuo to afford **69** (37.4mg, 0.12 mmol, 40%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.06 (s, 1H), 6.89 (m, 2H), 5.44 (s, 2H), 4.75 (s, 1H), 4.26 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.03 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.59, 169.22, 159.63, 159.58, 146.01, 145.39, 133.02, 132.61, 129.50, 129.40, 128.02, 125.34, 124.64, 115.38, 114.26, 107.76, 106.69, 55.93, 55.90, 55.31, 53.44, 51.22, 45.91, 42.92, 38.70, 21.87, 21.30; **LC-MS**, 6 min run, (ESI+) m/z 314.1487 $[M+H]^+$, Rt = 3.5 min.

methyl 2-(5-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-6-yl)acetate (**19**)

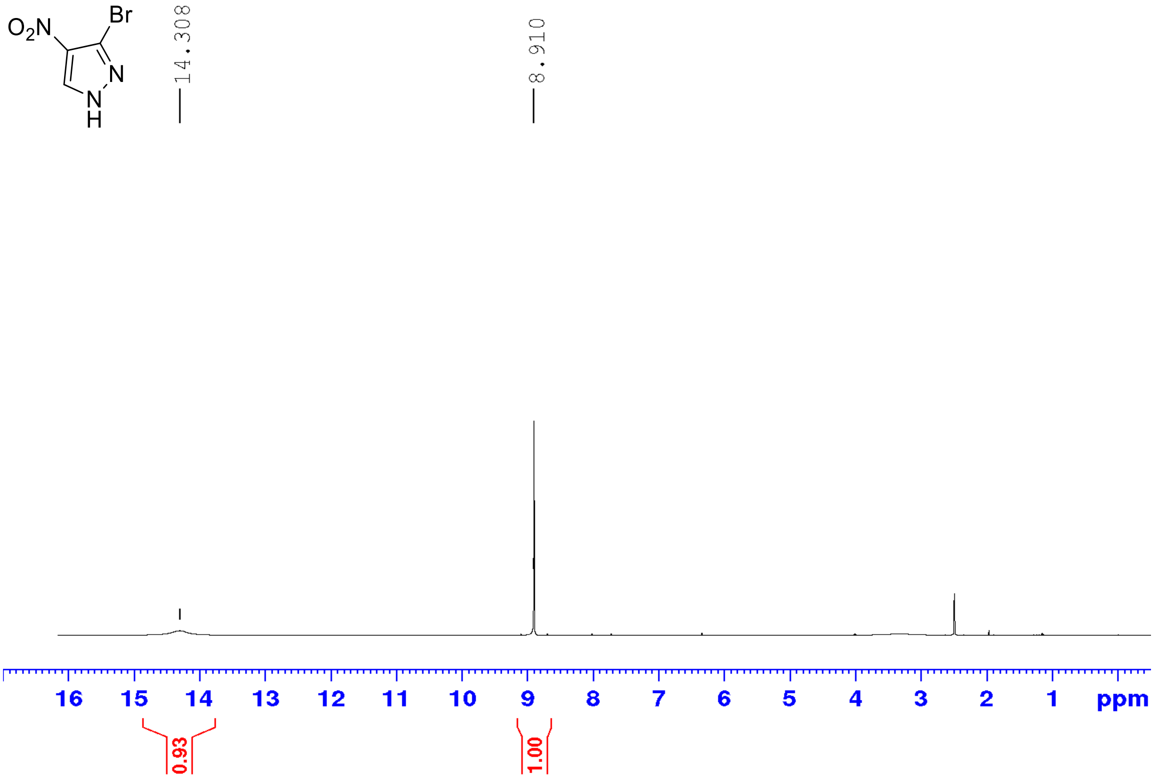


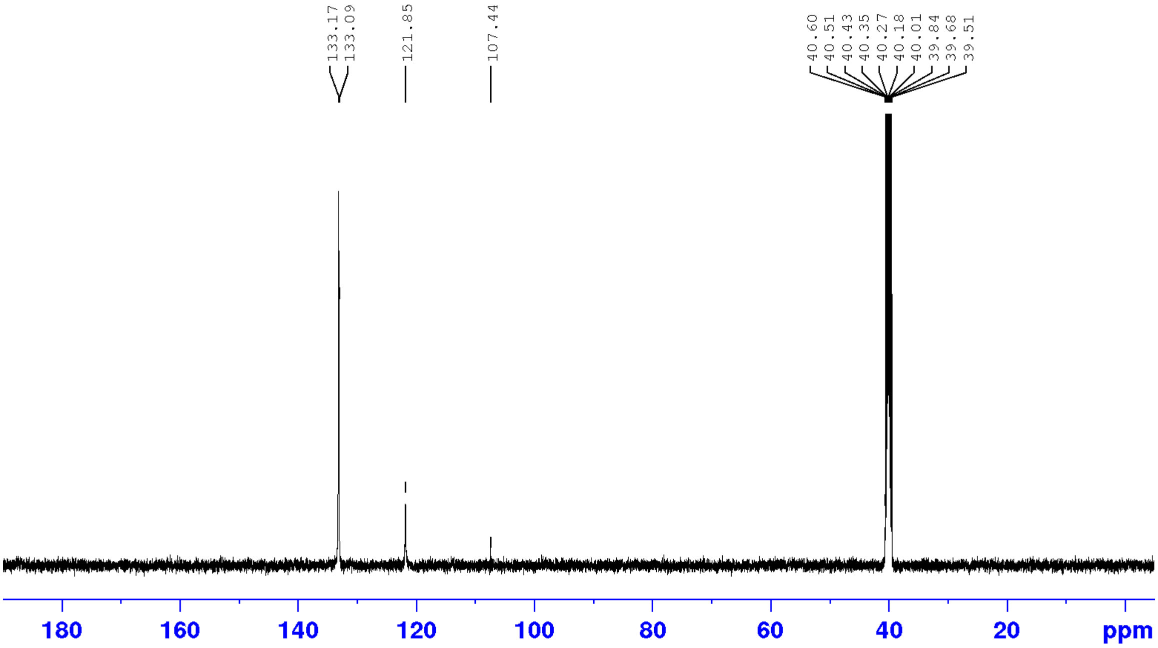
A 0.05 M solution of **69** (37.4mg, 0.12mmol) in EtOH (2.4ml) was hydrogenated in an H-cubePro. Initially, the parameters (temperature: 40°C, pressure: 30bar and flowrate: 0.5ml/min) were selected and a 10% Pd/C CatCart was fitted in the instrument. After pumping pure EtOH for 10 min, the injection line was moved into the flask containing the starting material solution and the hydrogenation process was started. The reaction was monitored by LC-MS. Upon completion, solvent was evaporated in vacuo and the solid residue was dissolved in TFA (0.35ml) and anisole (0.025ml, 0.72mmol) was subsequently added to the reaction flask. The final mixture was heated at 80 °C for 12 h. After cooling, the volatiles were removed in vacuo and the solid residue was dissolved in MeOH/water/MeCN 3:1:1. The latter sample was filtered and injected in an AutoPurification HPLC/MS system and purified under basic conditions. The desired fractions were evaporated to afford **19** (12mg, 0.061mmol, 51%) as a reddish solid

^{1}H-NMR (500 MHz, MeOD): δ 7.31 (s, 1H), 4.10-4.07 (m, 1H), 4.05 (dd, J=1.1, 11.9 Hz, 1H), 3.73 (s, 3H), 3.51 (ddd, J=1.0, 1.7, 11.9 Hz, 1H), 2.78 (dd, J=6.1, 16.0 Hz, 1H), 2.71 (dd, J=6.7, 16.0 Hz, 1H), 2.58 (s, 3H); **^{13}C NMR** (125 MHz, MeOD$_4$): δ 173.45, 122.95, 121.00, 61.85, 53.94, 52.34, 41.50, 39.12; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{14}N_3O_2$: 196.1081, found: 196.1082

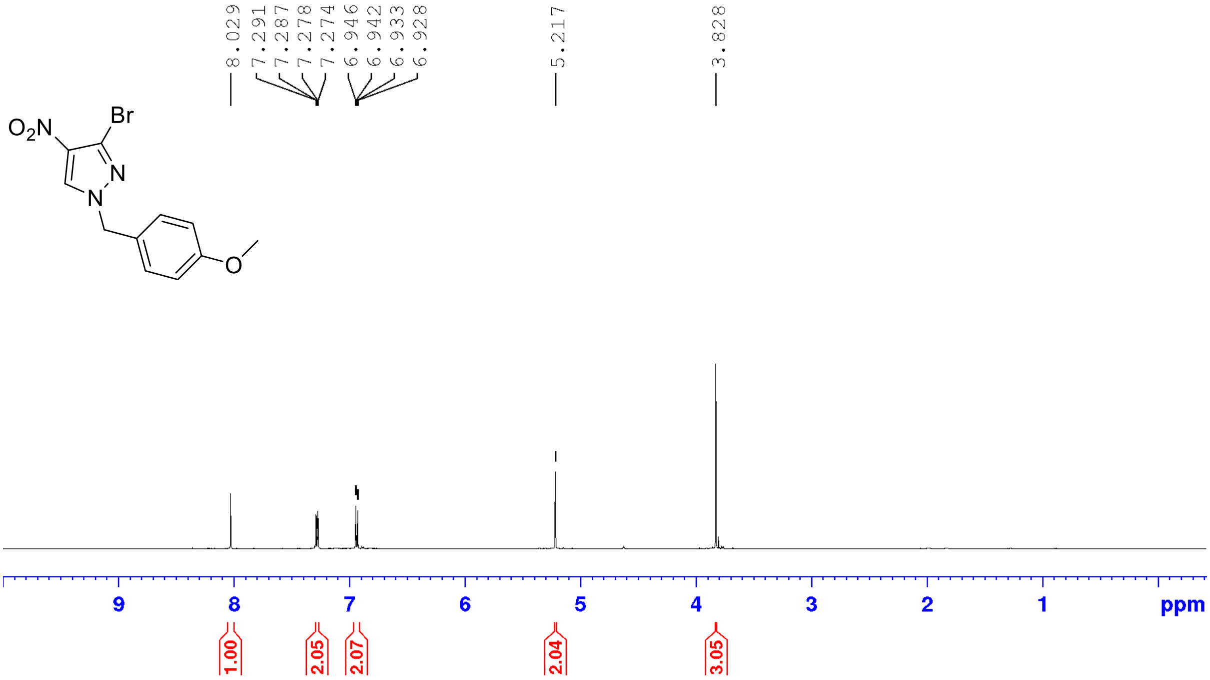
3. NMR spectra

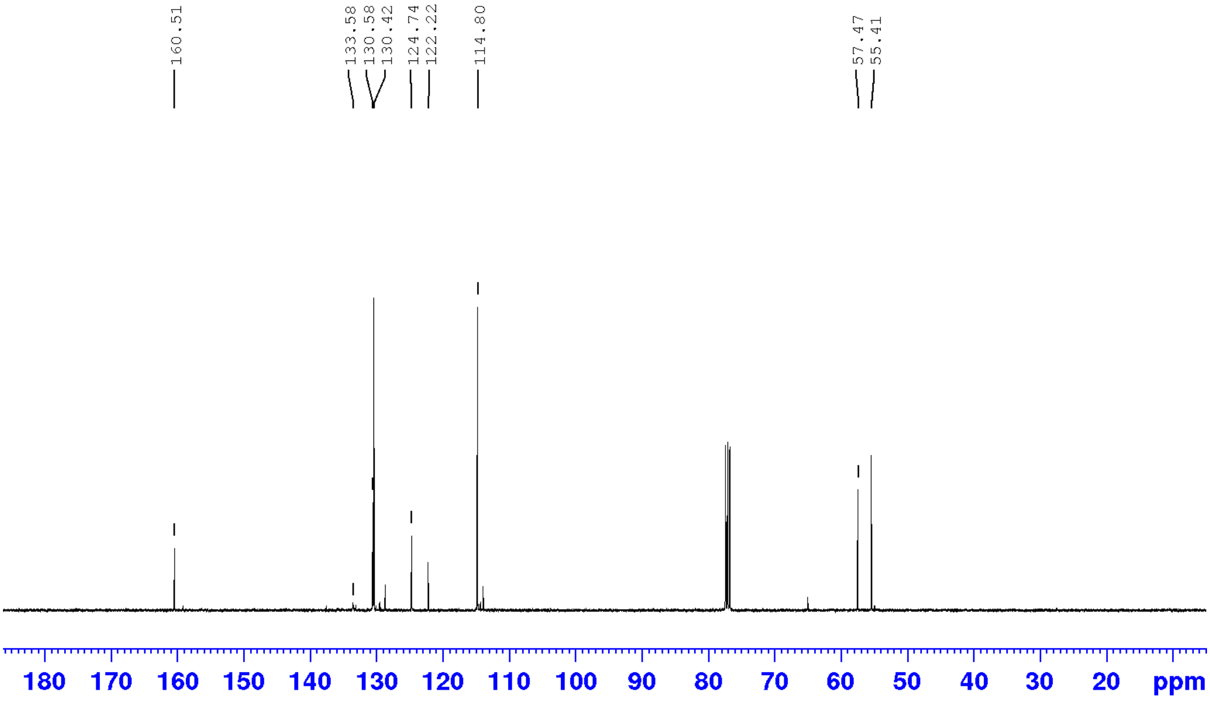
3-bromo-4-nitro-1H-pyrazole (**2a**)



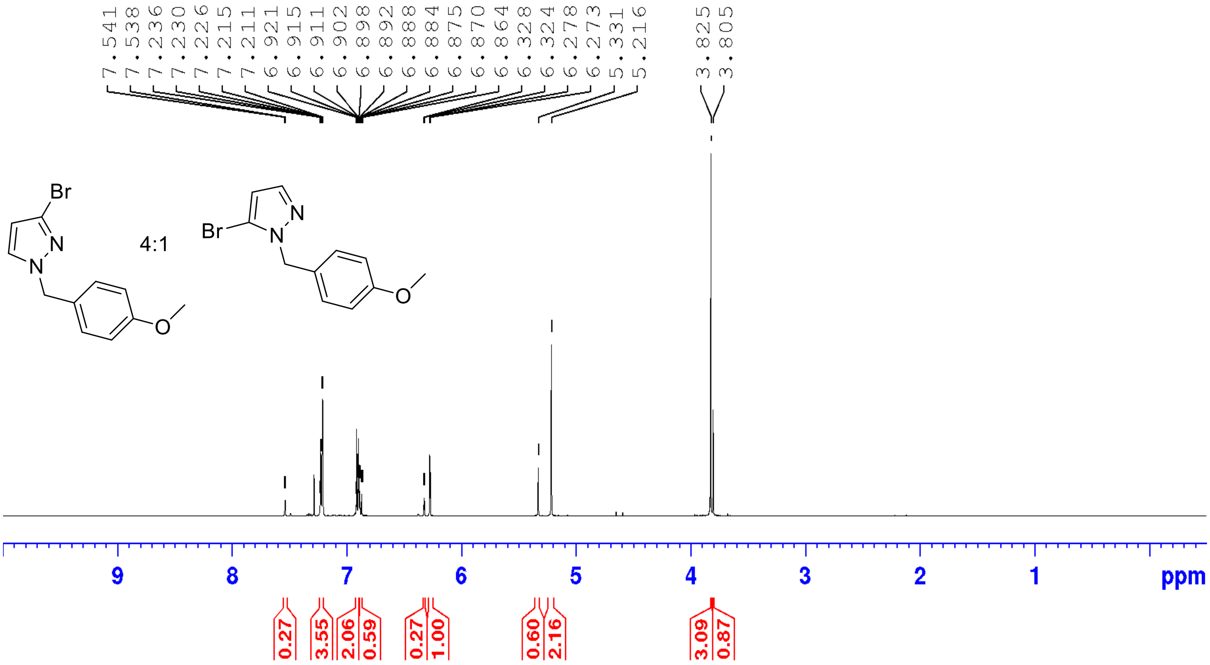


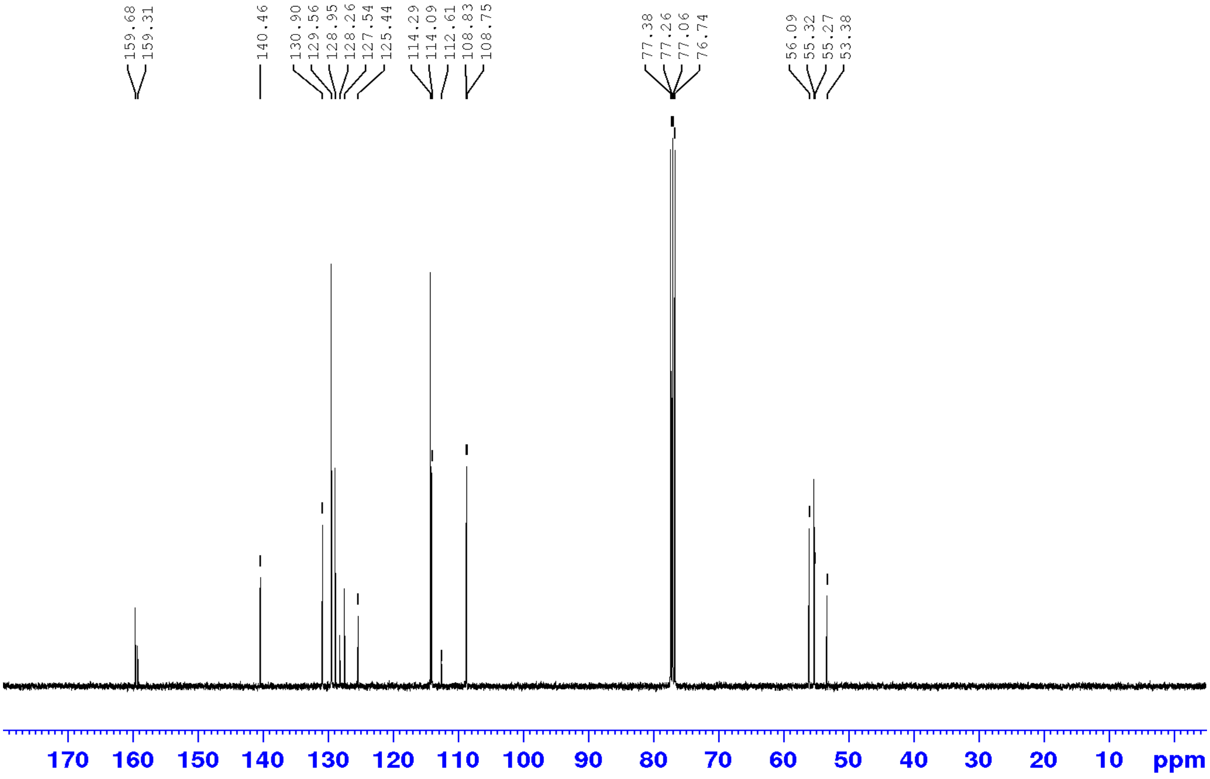
3-bromo-1-(4-methoxybenzyl)-4-nitro-1H-pyrazole (**2b**)



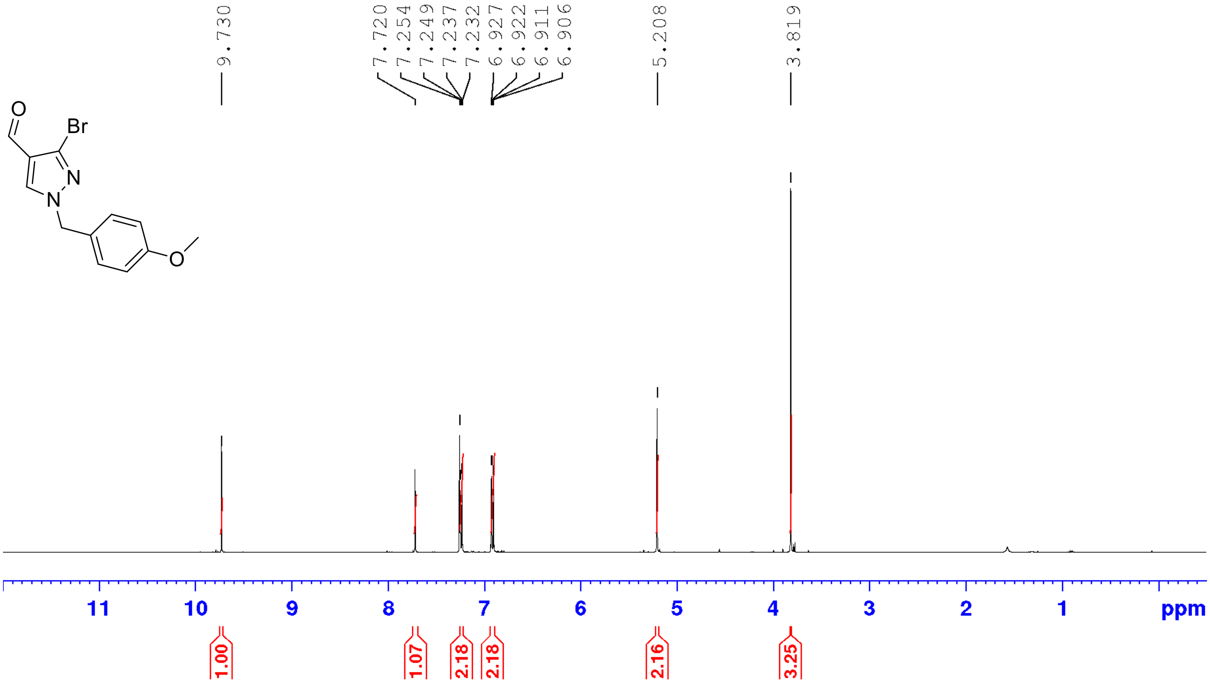


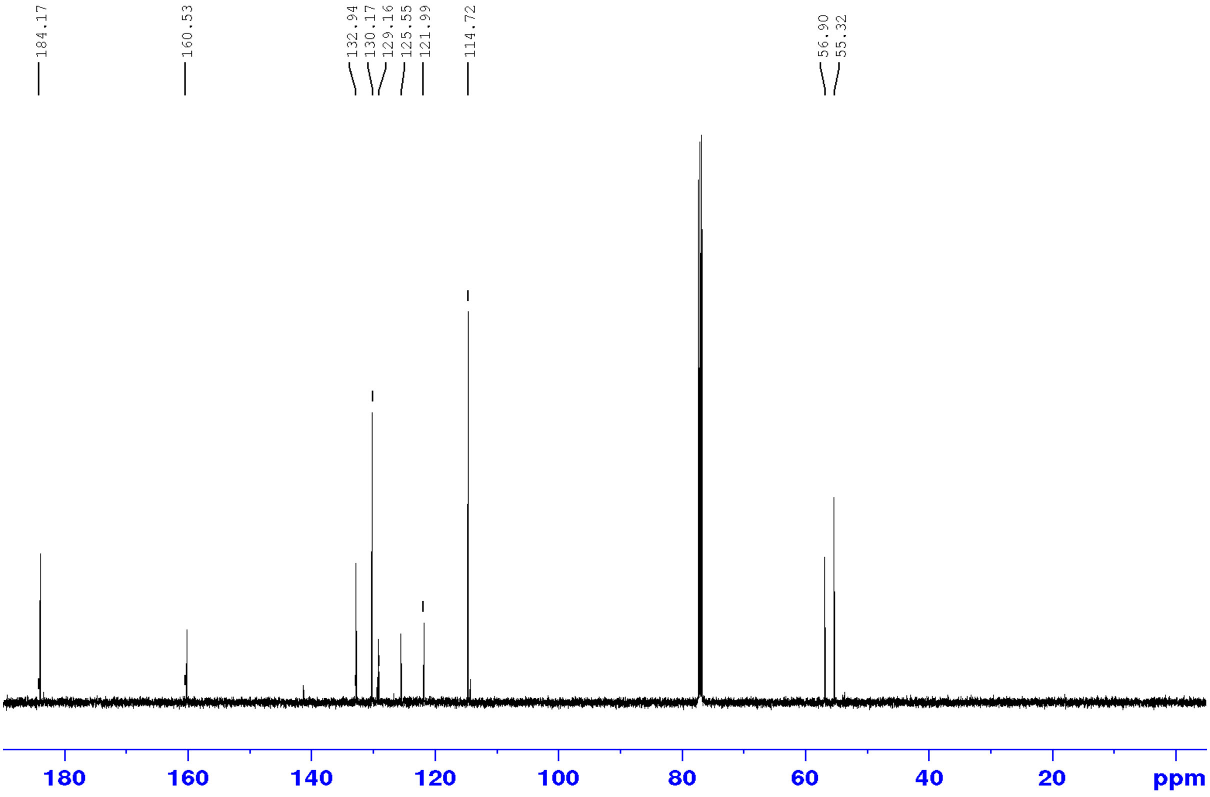
3-bromo-1-(4-methoxybenzyl)-1H-pyrazole (**3a**)



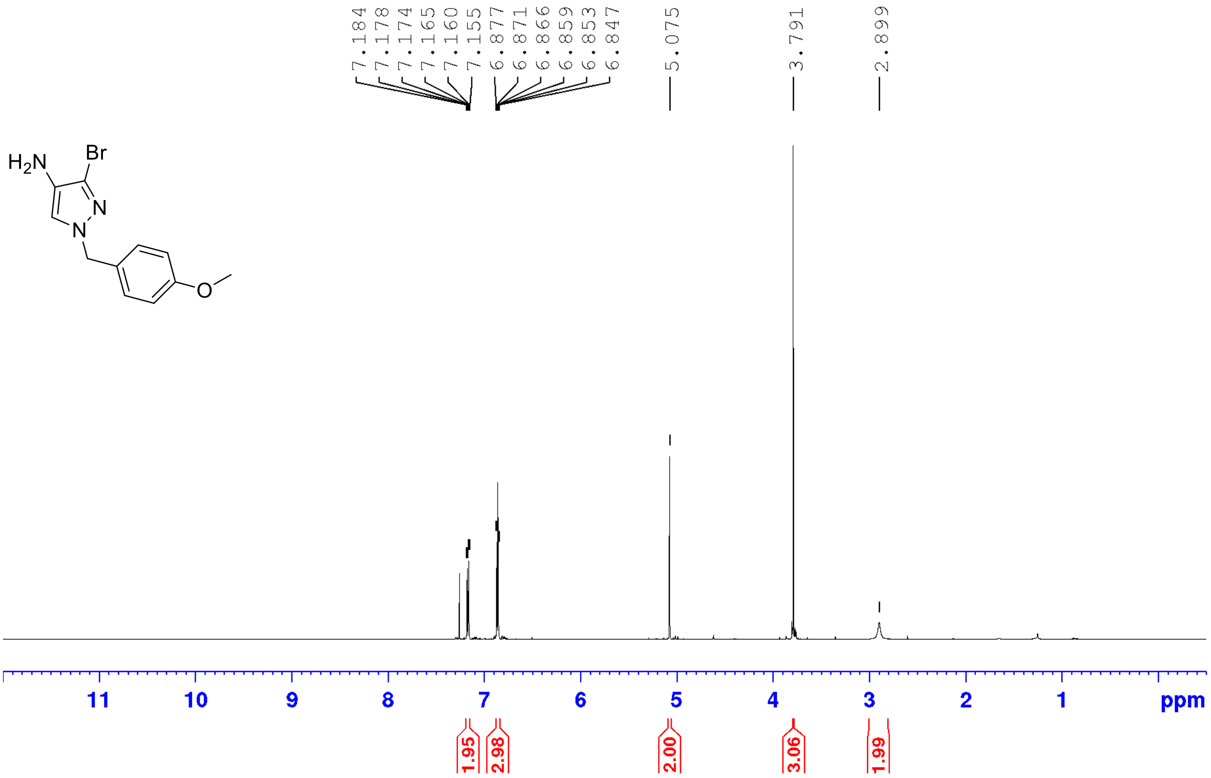


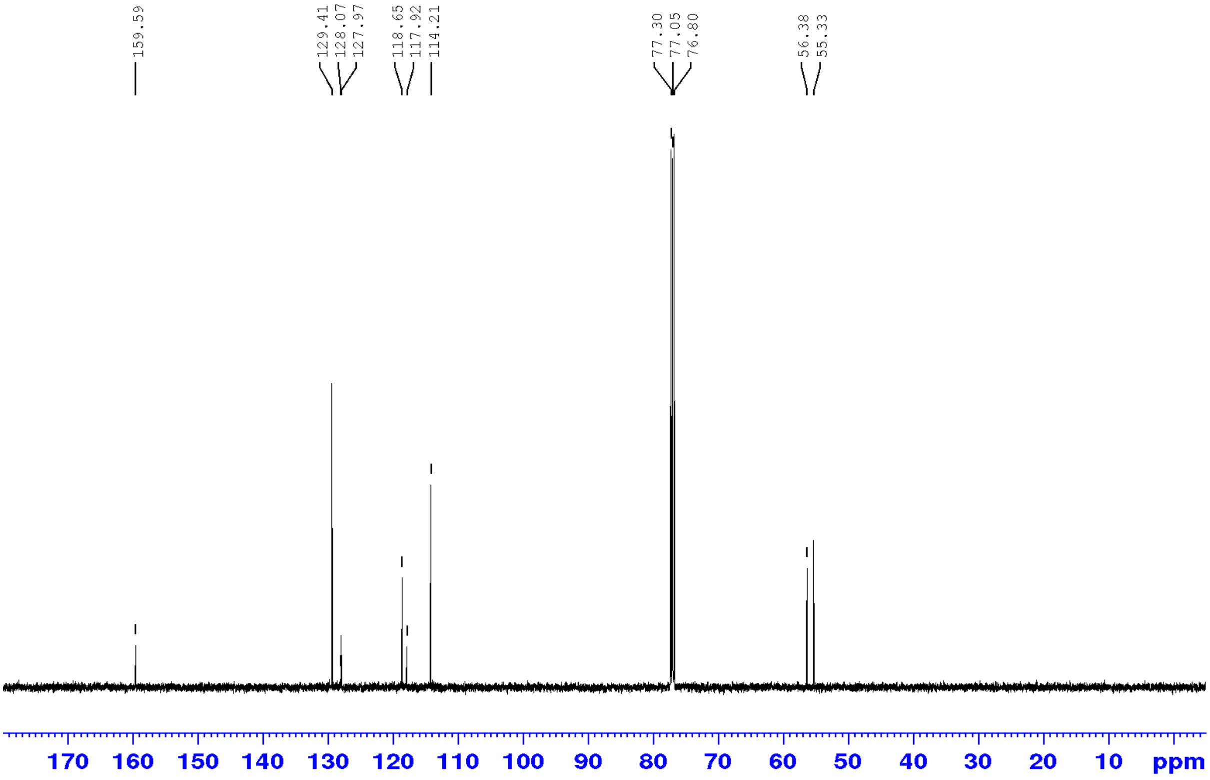
3-bromo-1-(4-methoxybenzyl)-1H-pyrazole-4-carbaldehyde (**3b**)



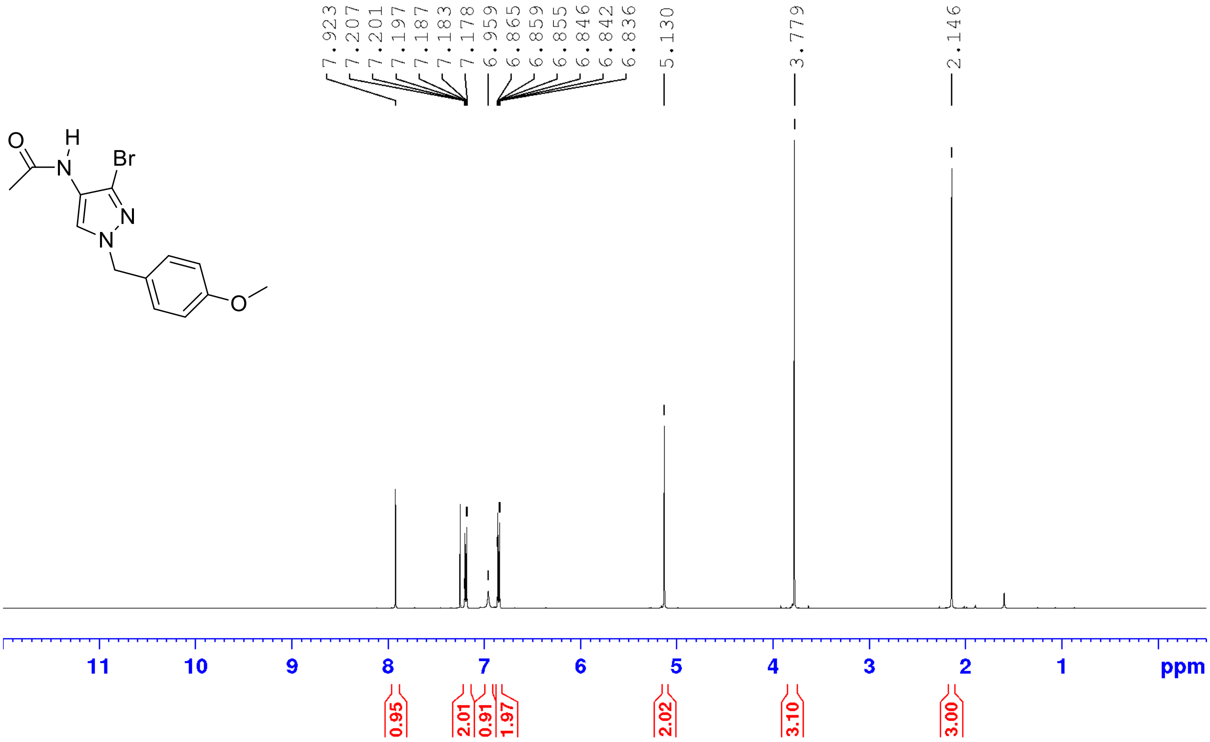


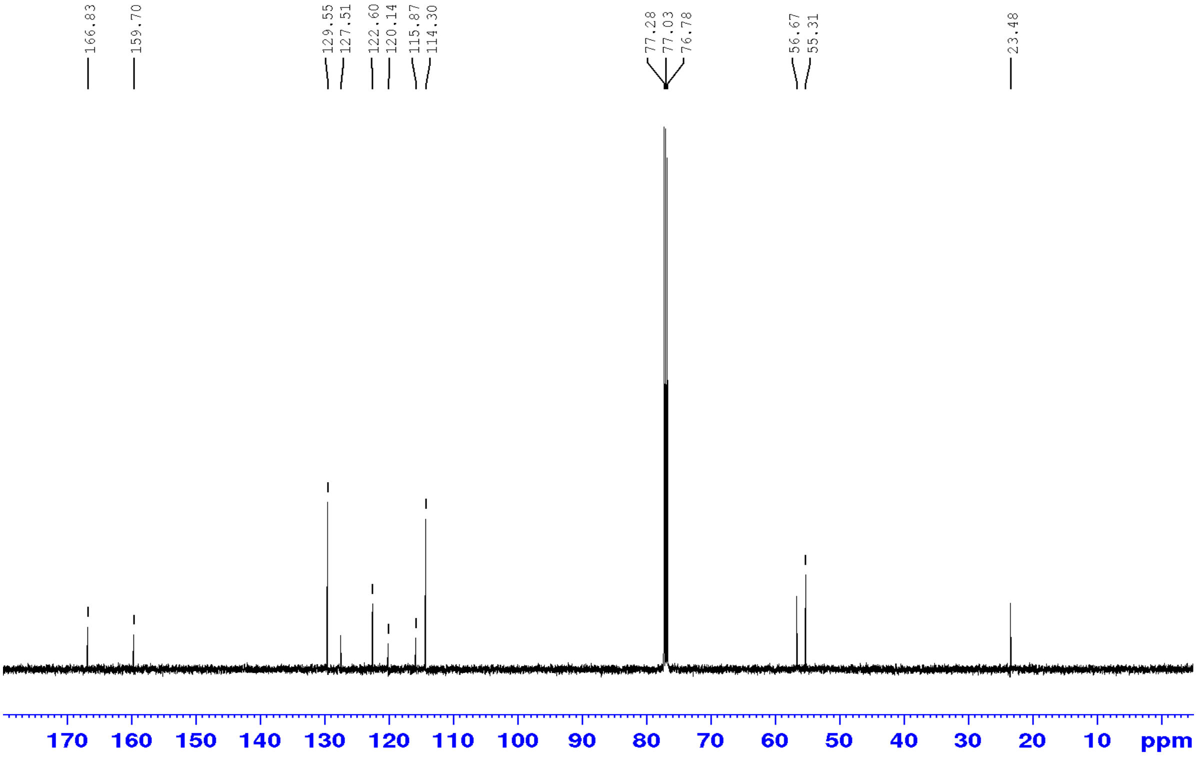
3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-amine (**20**)



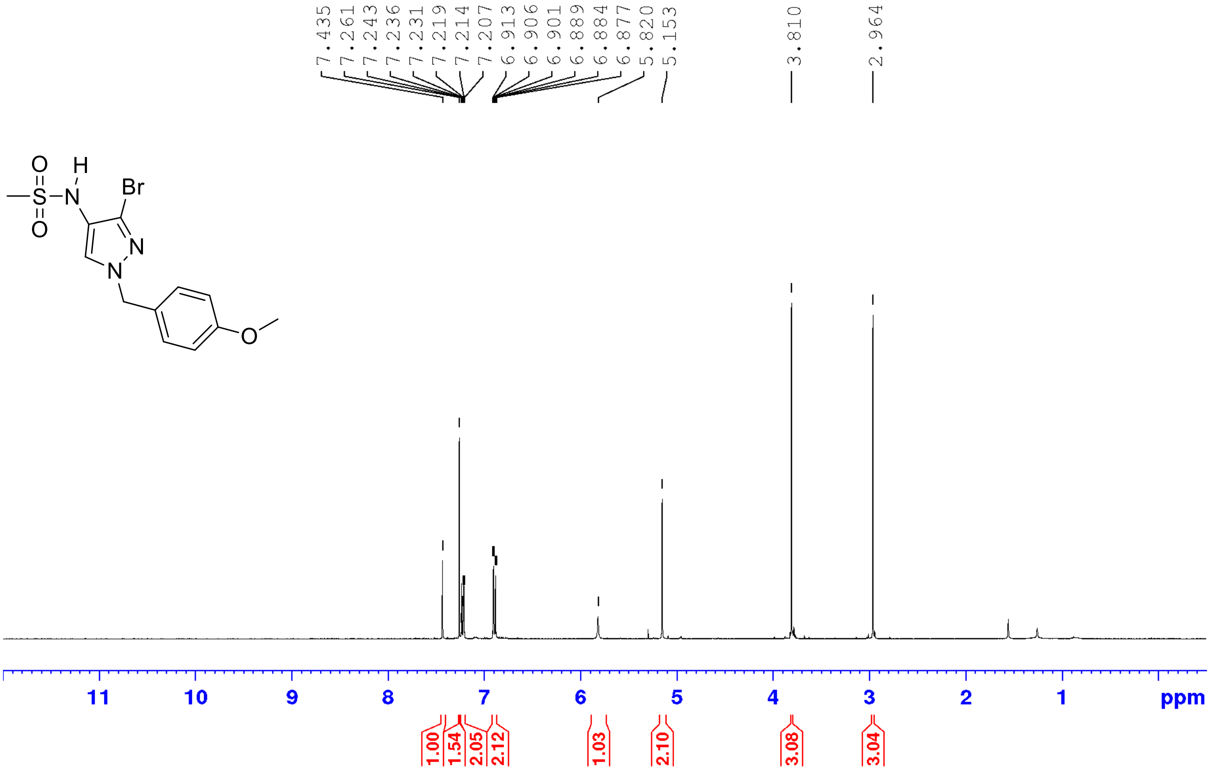


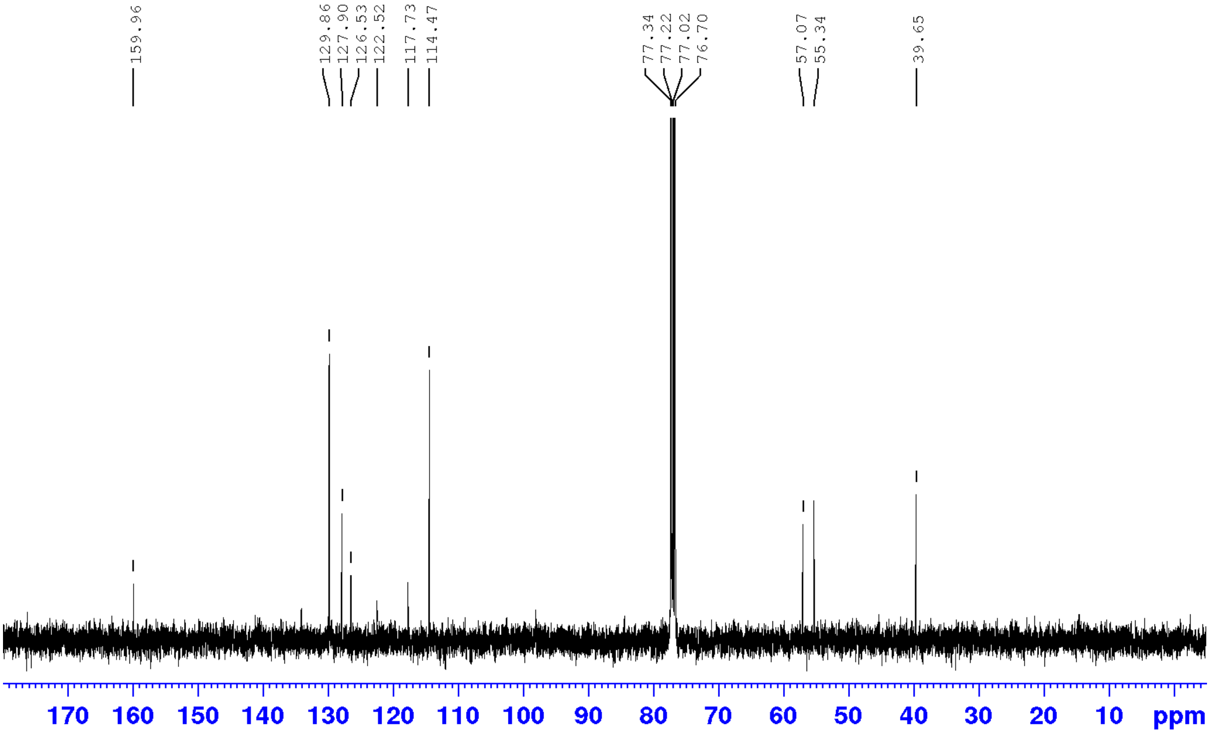
N-(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)acetamide (**21b**)



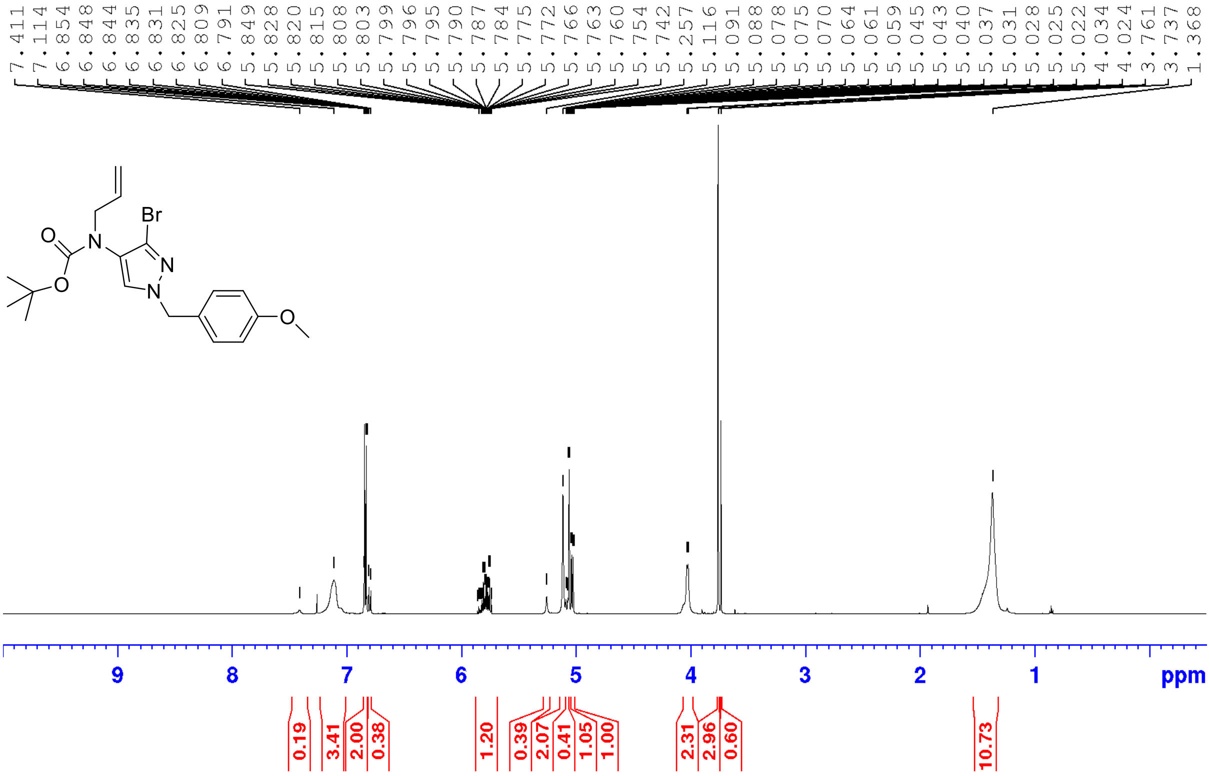


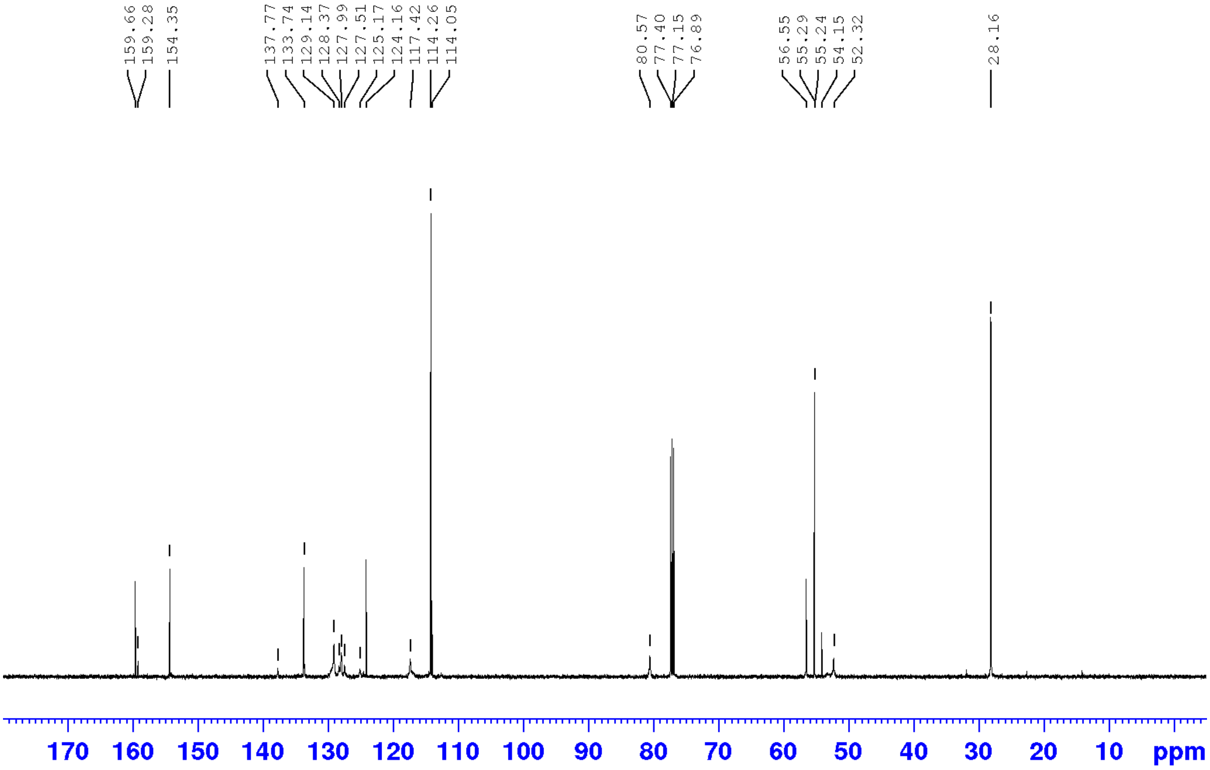
N-(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methanesulfonamide (**21c**)



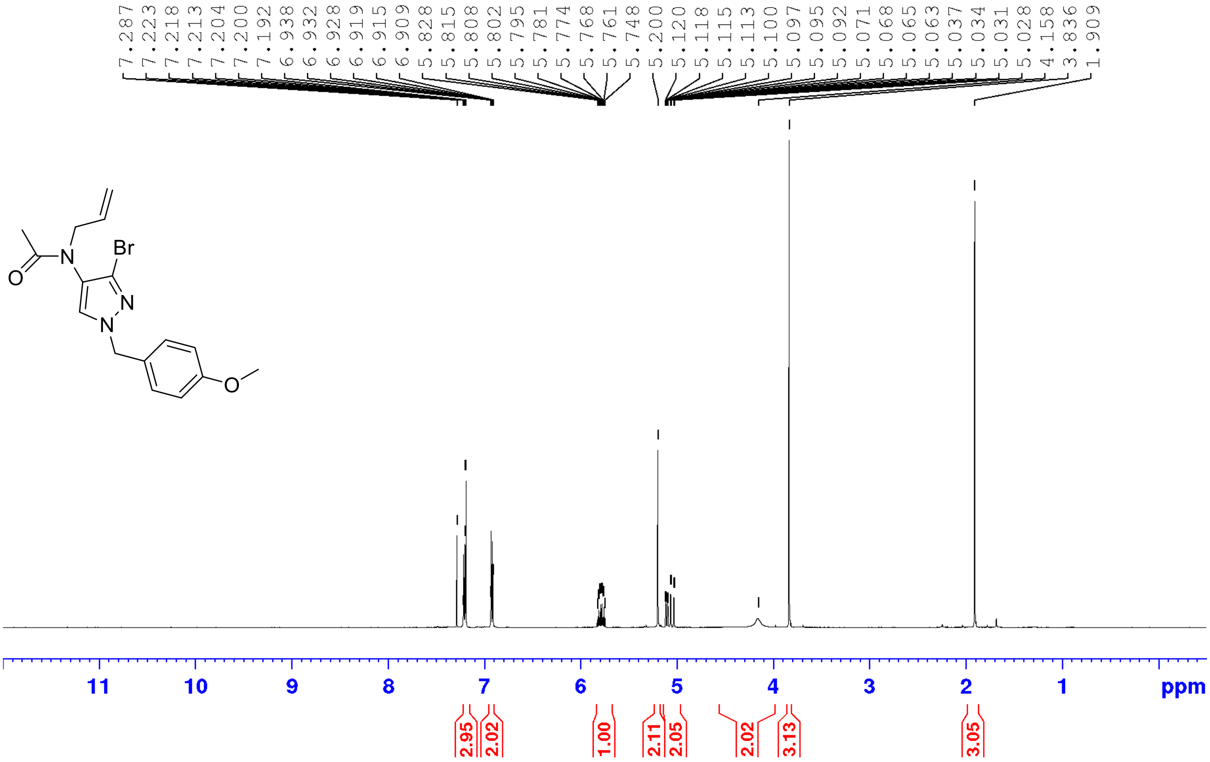


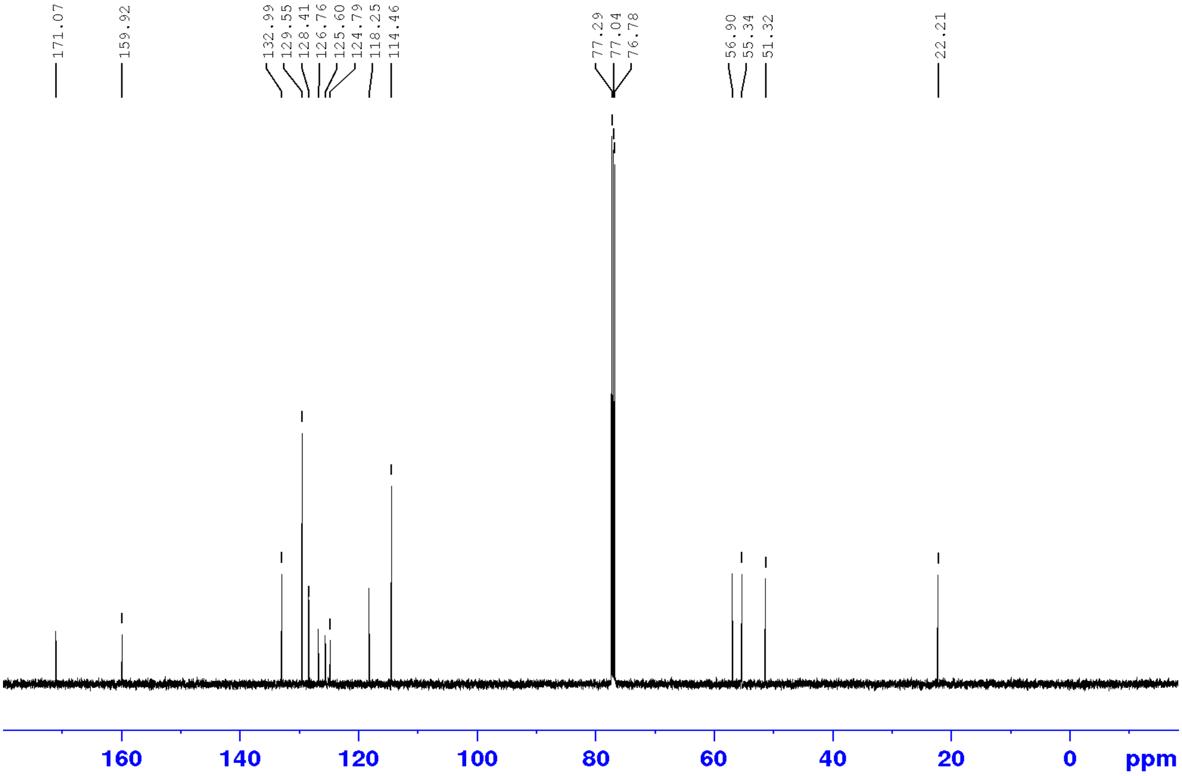
tert-butyl allyl(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)carbamate (**22a**)



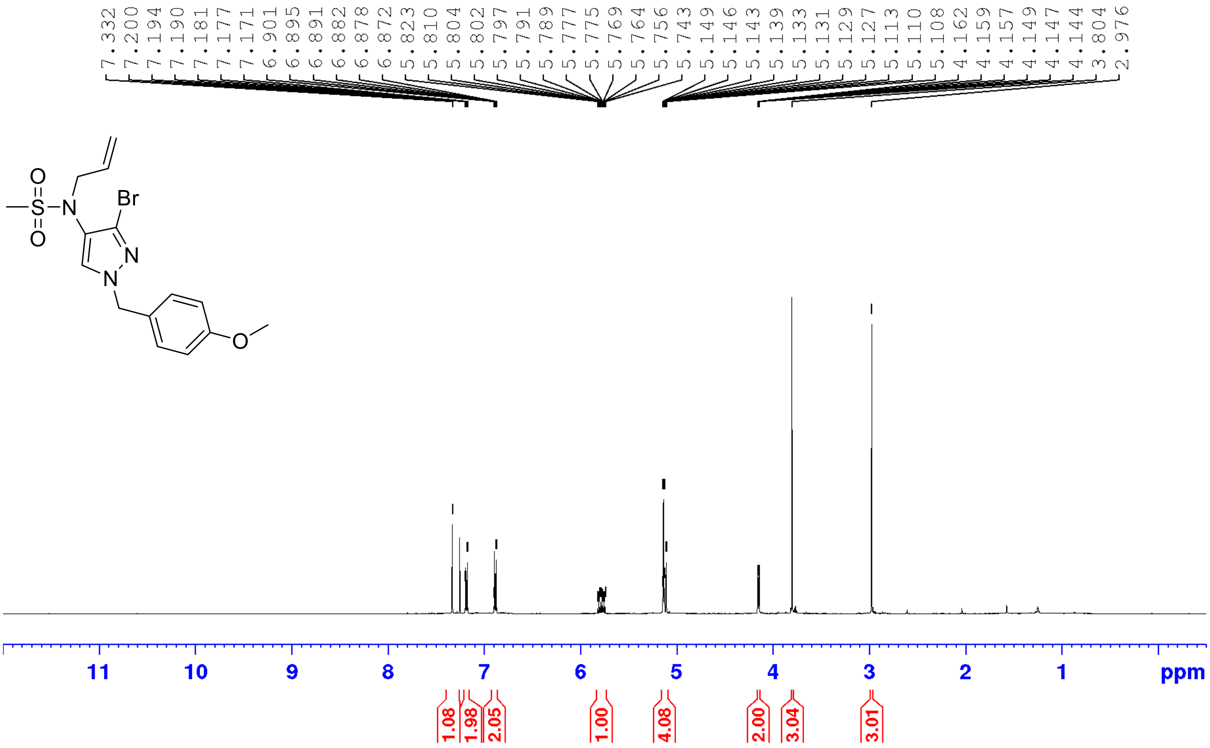


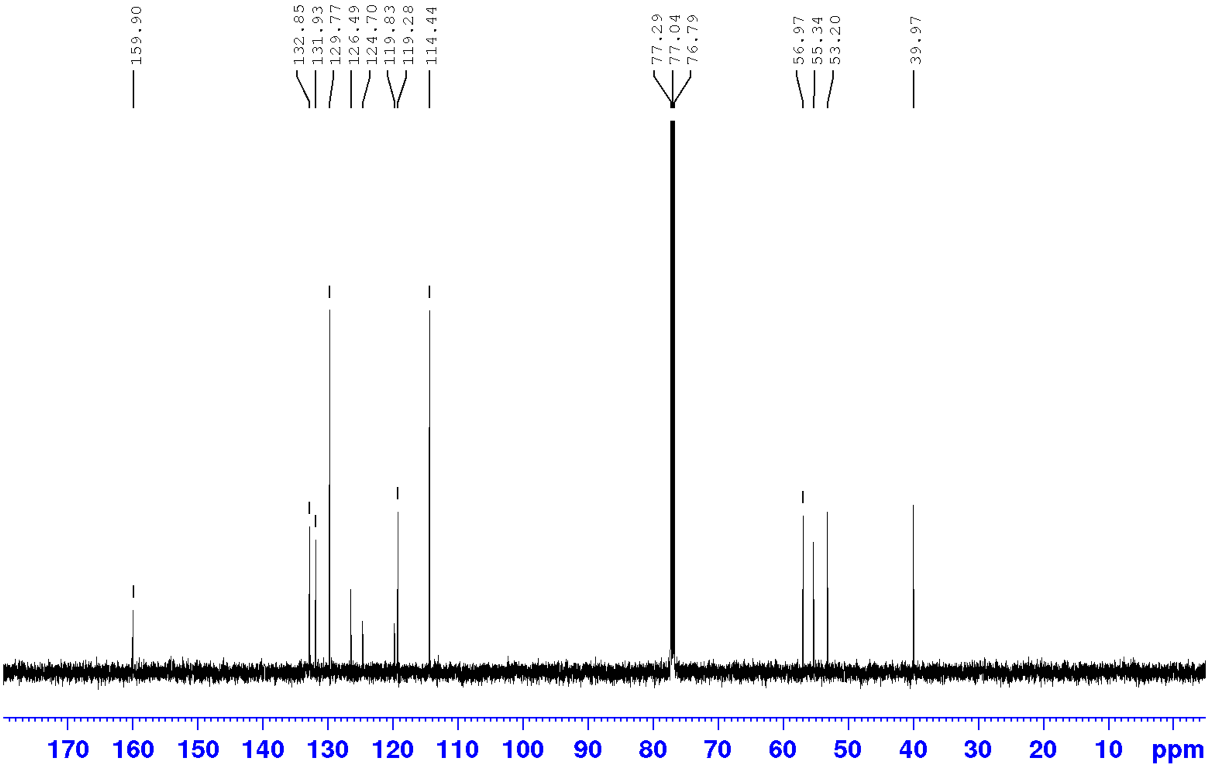
N-allyl-N-(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)acetamide (**22b**)



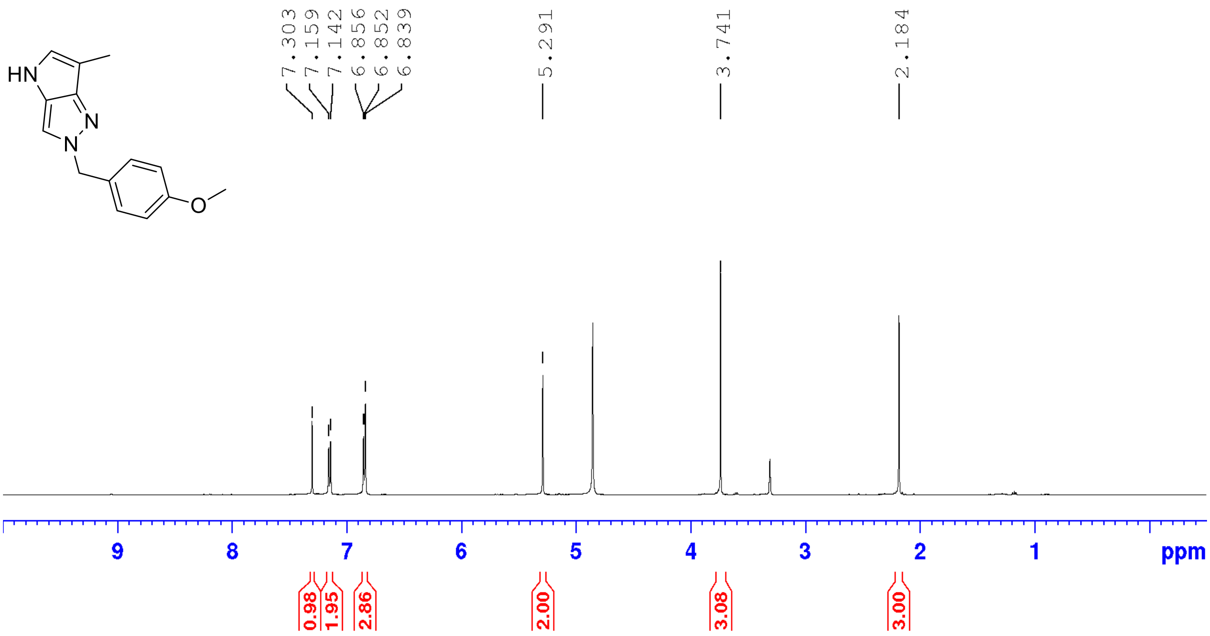


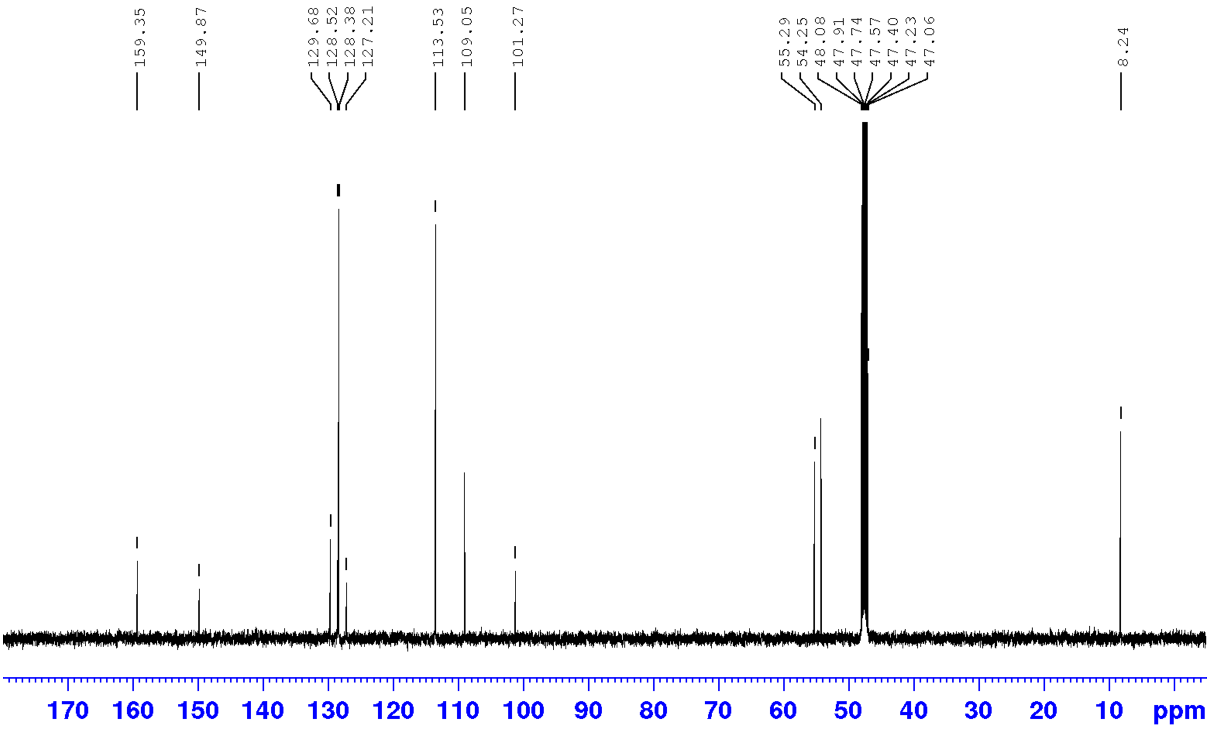
N-allyl-N-(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methanesulfonamide (**22c**)



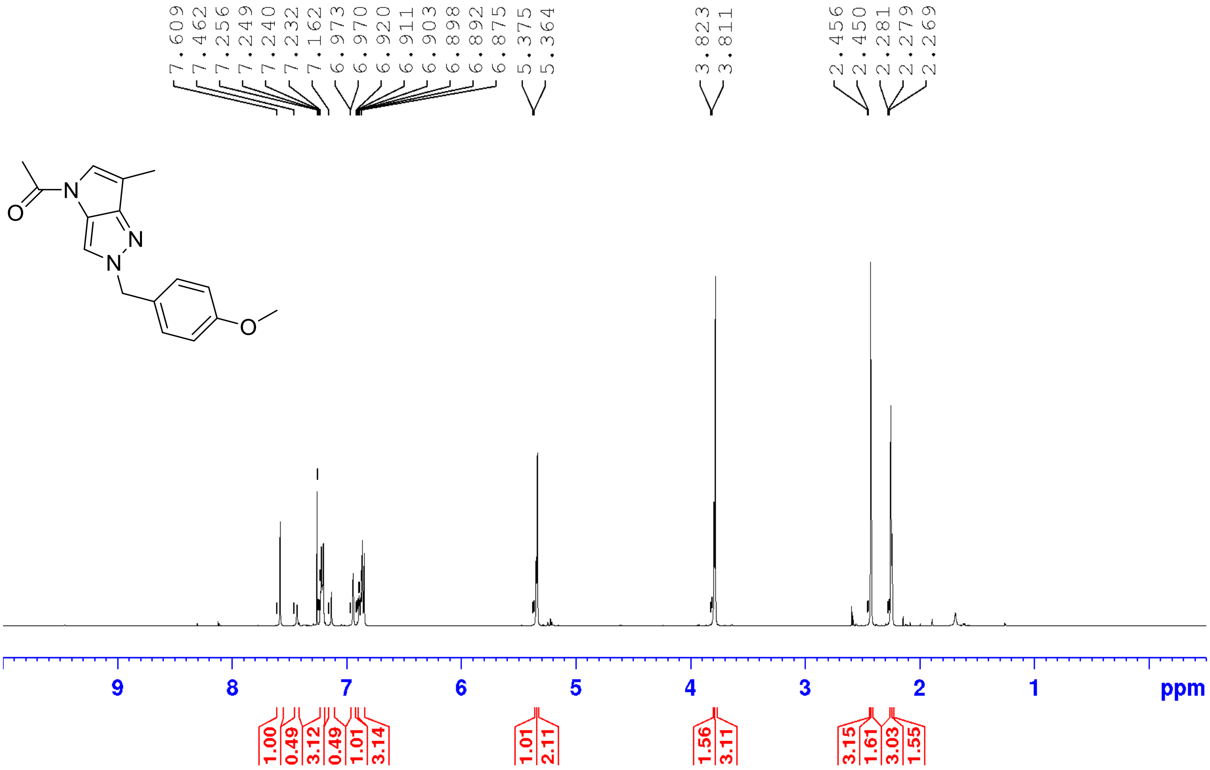


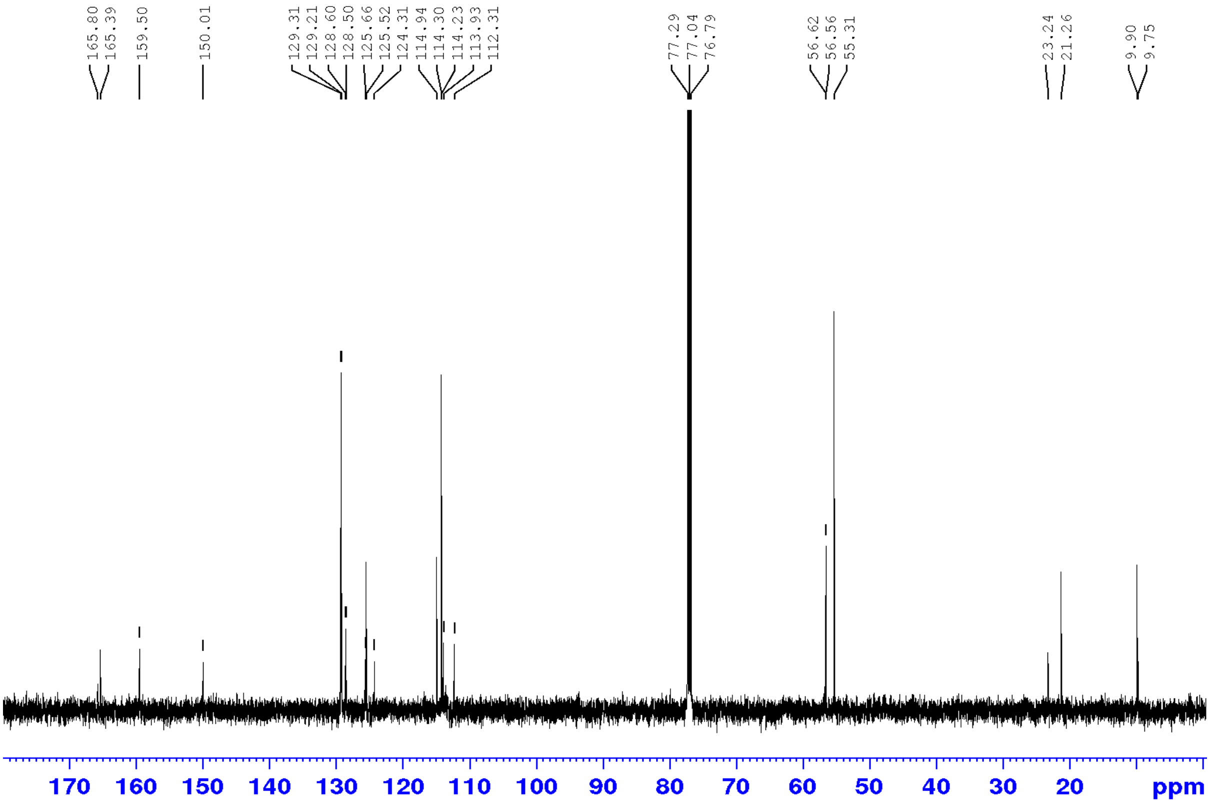
2-(4-methoxybenzyl)-6-methyl-2,4-dihydropyrrolo[3,2-c]pyrazole (**23a**)



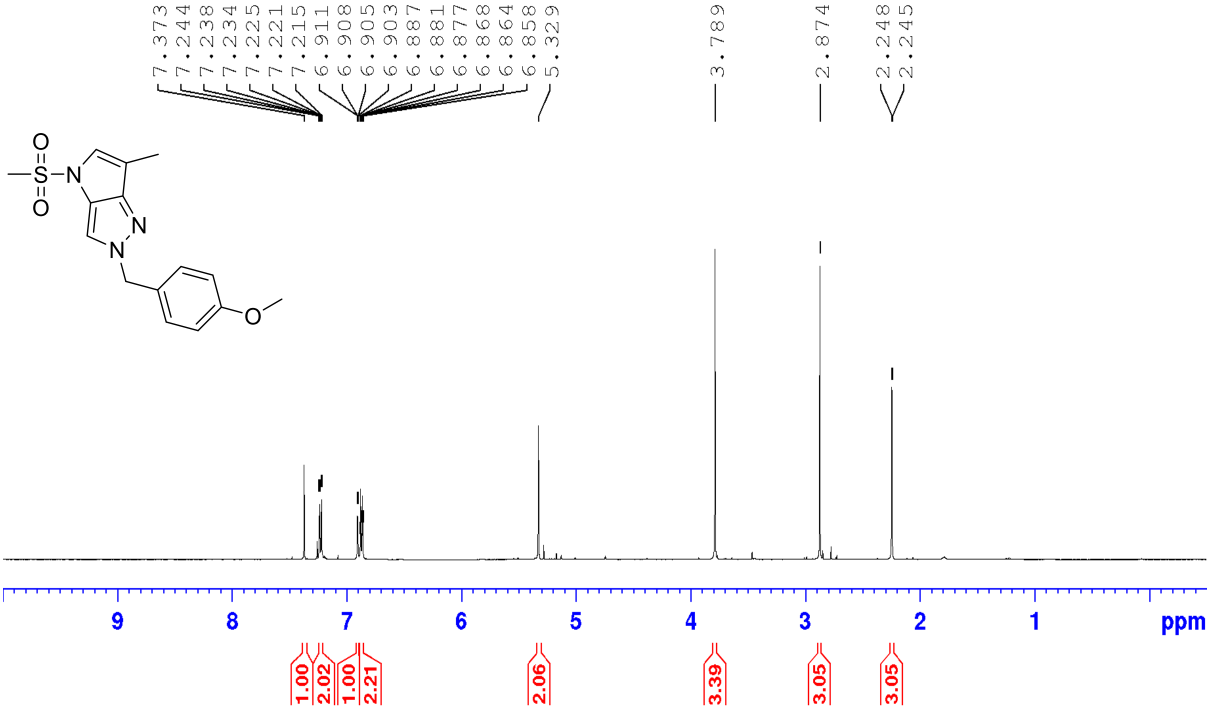


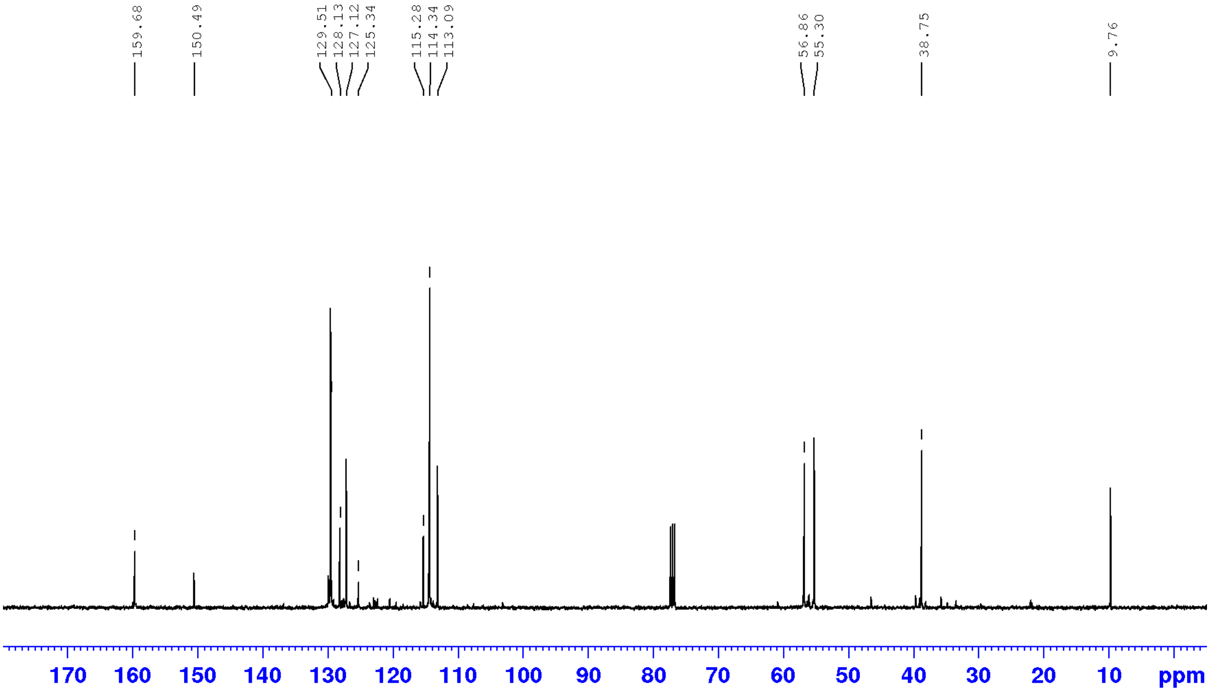
1-(2-(4-methoxybenzyl)-6-methylene-5,6-dihydropyrrolo[3,2-c]pyrazol-4(2H)-yl)ethan-1-one (**23b**)



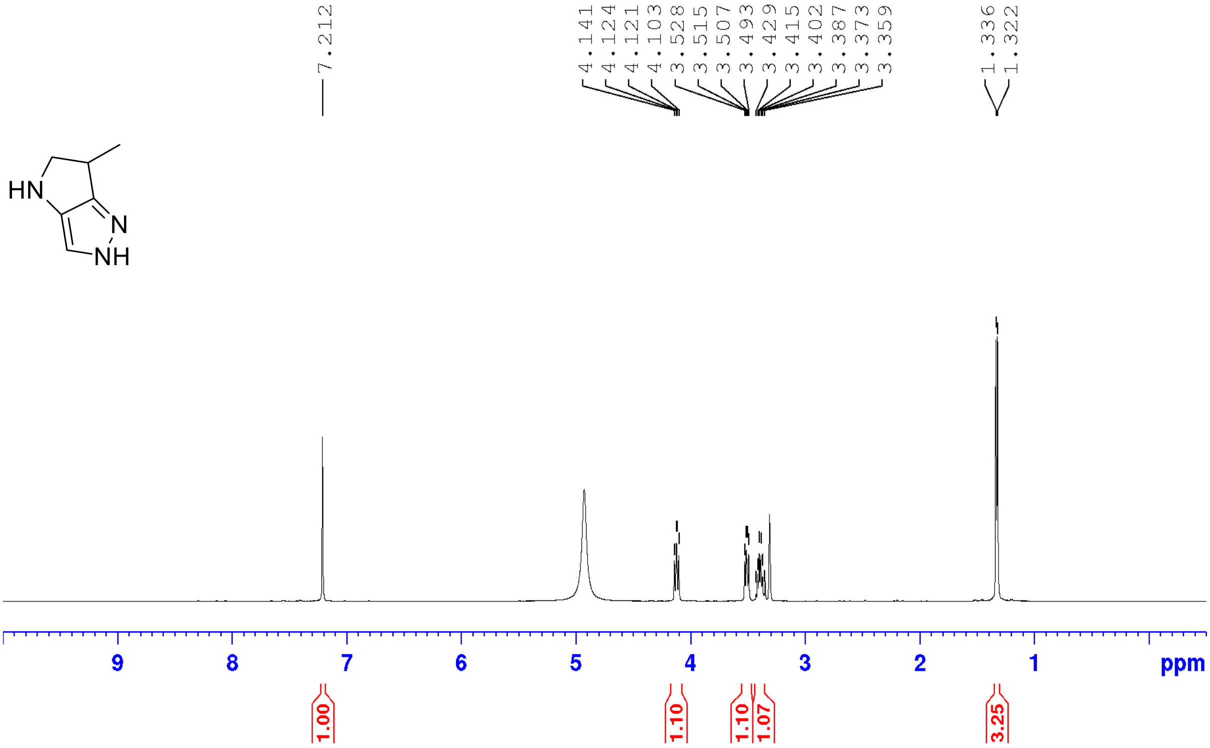


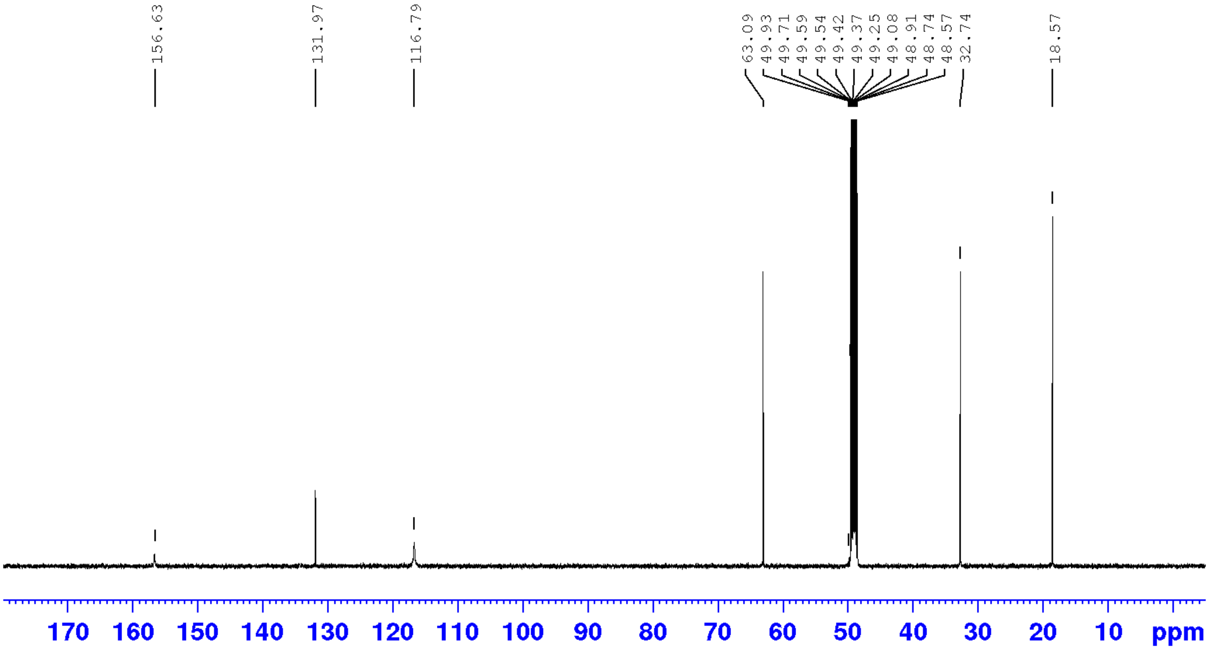
2-(4-methoxybenzyl)-6-methylene-4-(methylsulfonyl)-2,4,5,6-tetrahydropyrrolo[3,2-c]pyrazole (**23c**)



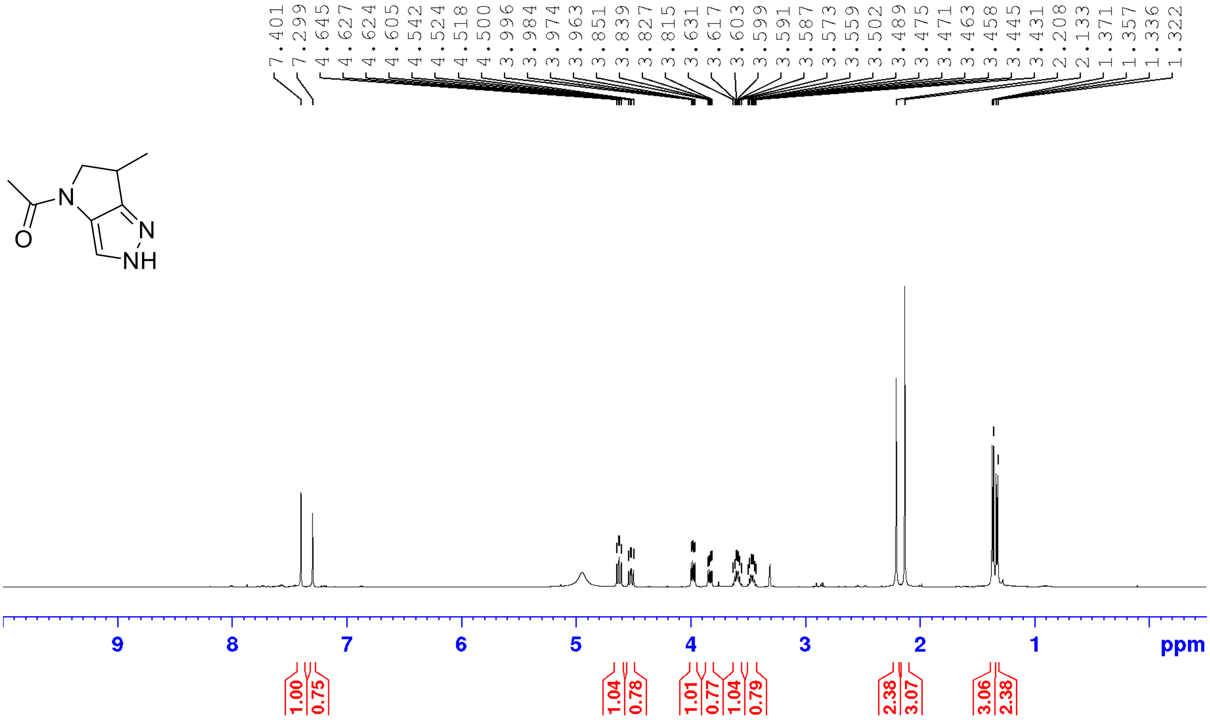


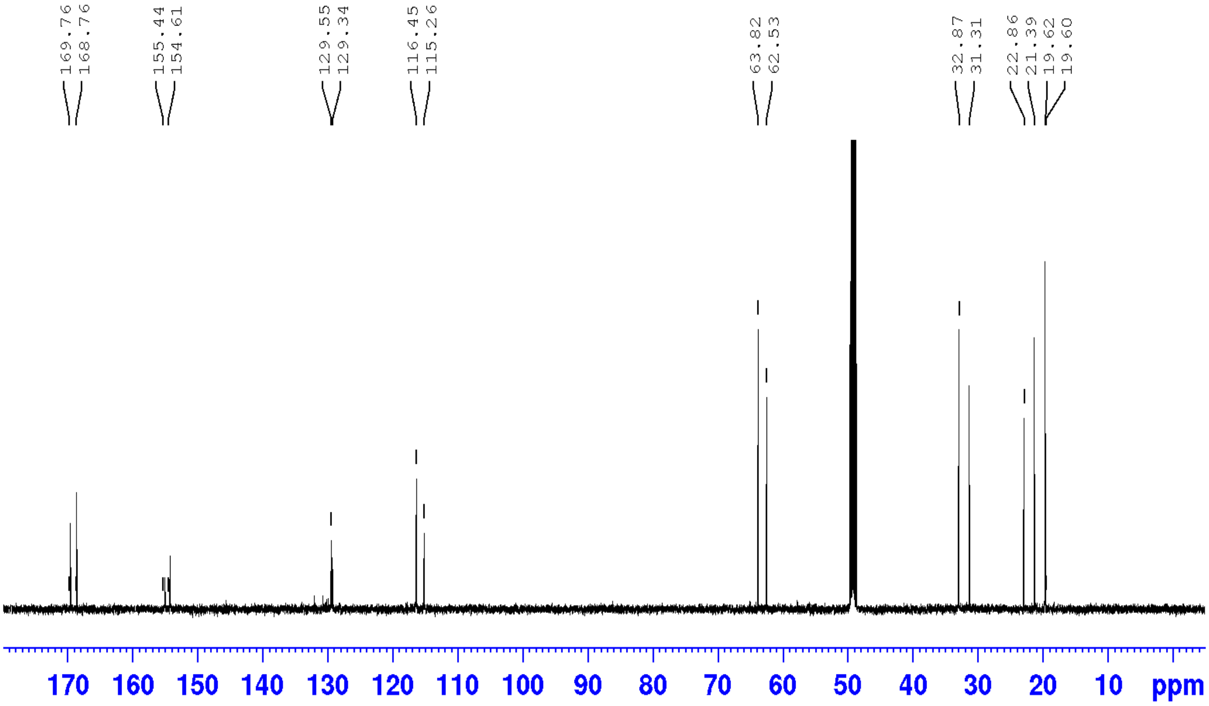
6-methyl-2,4,5,6-tetrahydropyrrolo[3,2-c]pyrazole (**4a**)



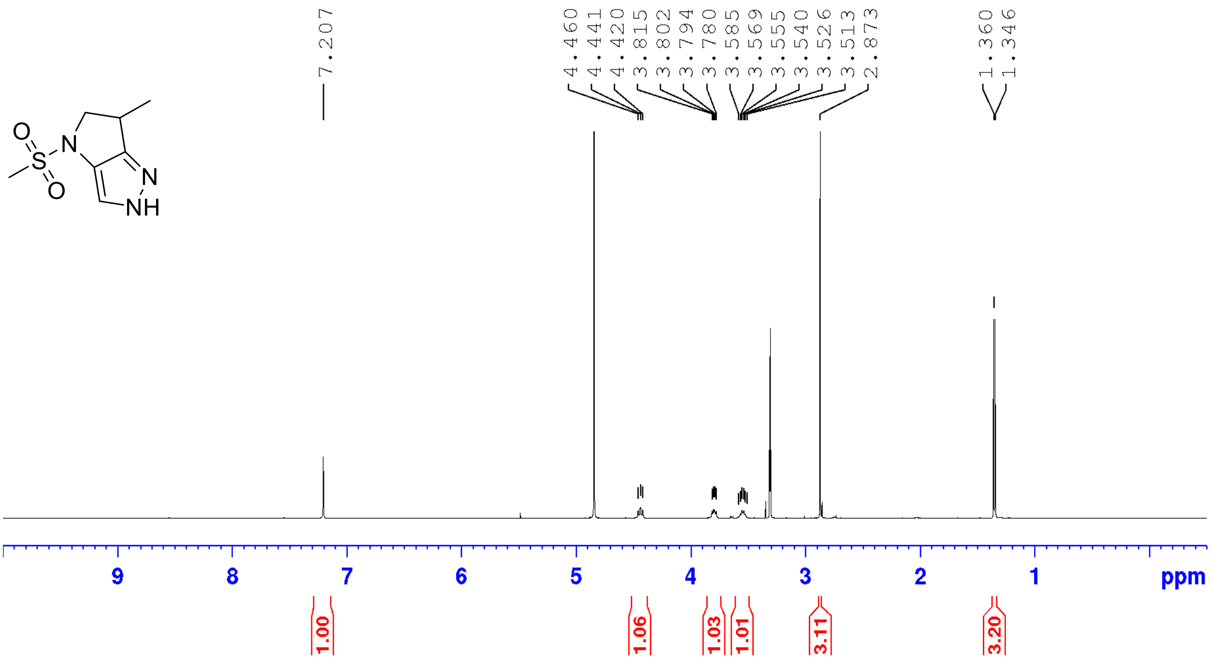


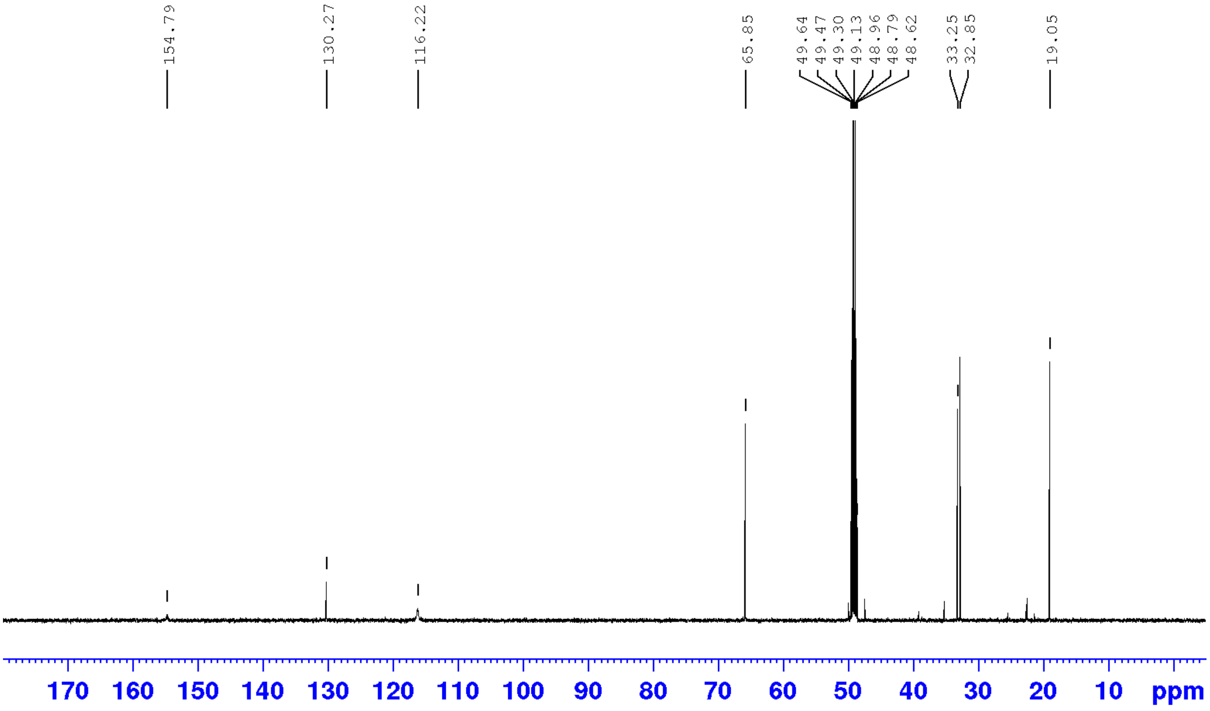
1-(6-methyl-5,6-dihydropyrrolo[3,2-c]pyrazol-4(2H)-yl)ethan-1-one (**4b**)



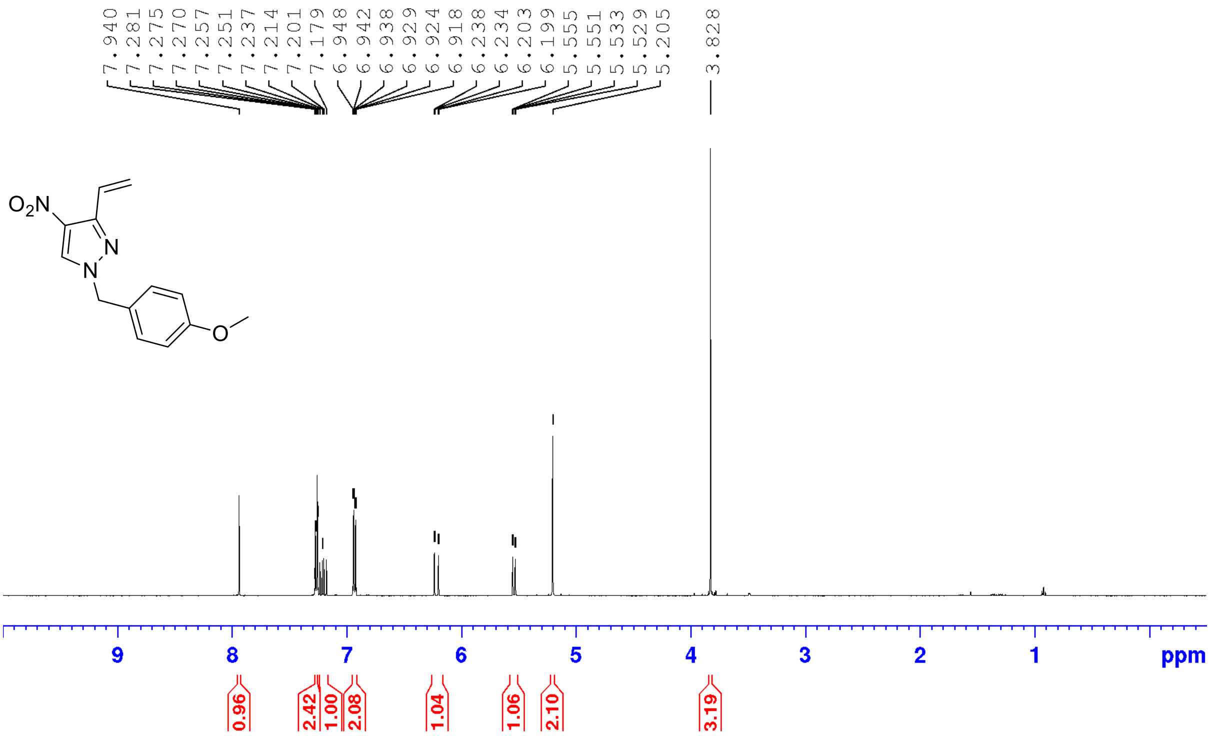


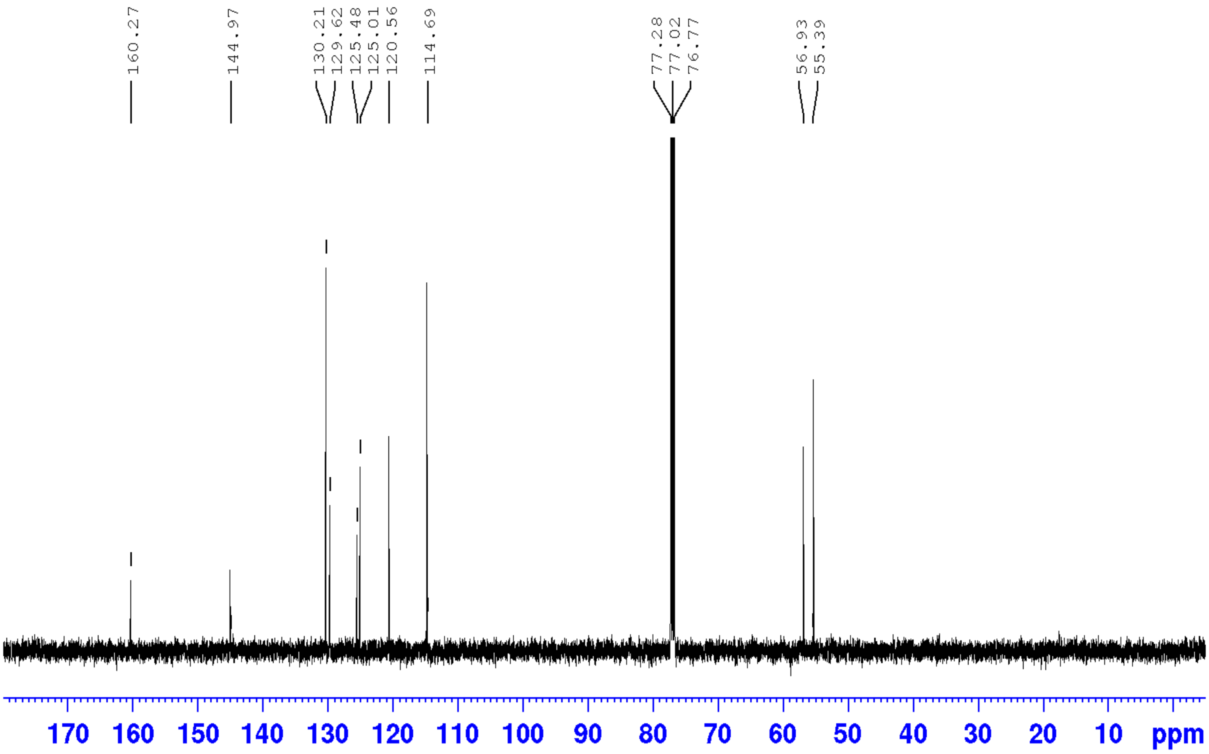
6-methyl-4-(methylsulfonyl)-2,4,5,6-tetrahydropyrrolo[3,2-c]pyrazole (**4c**)



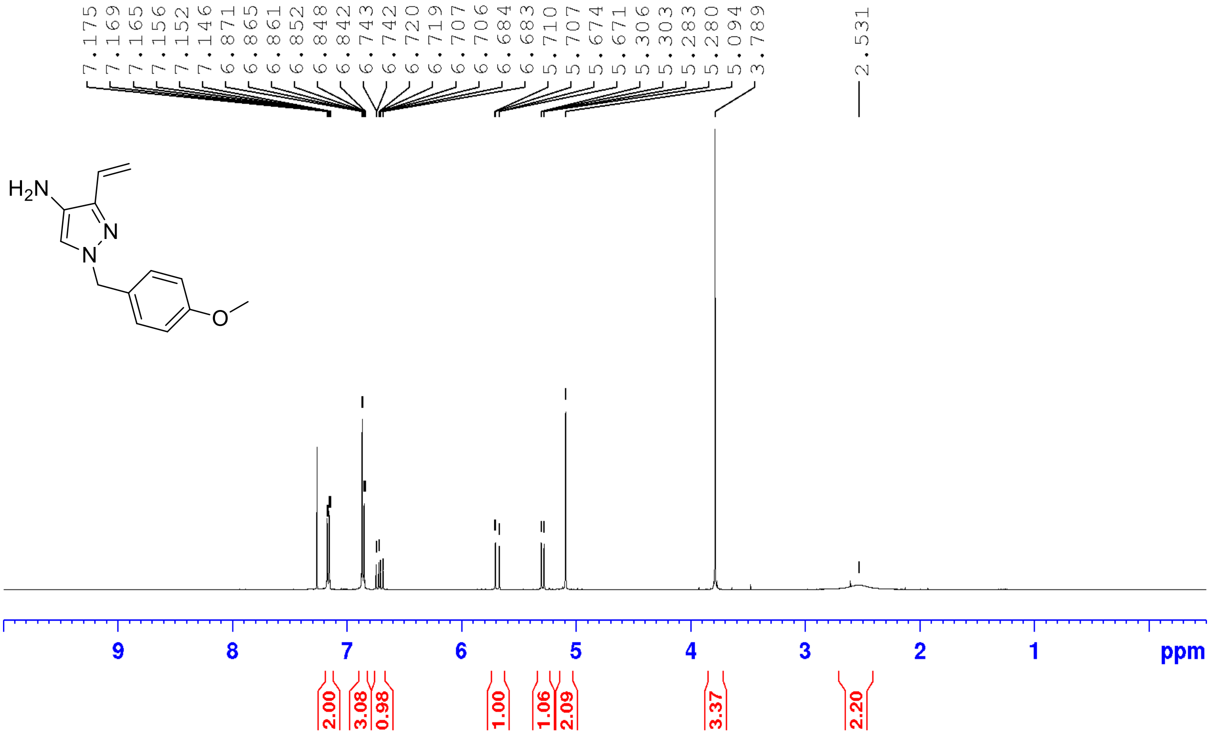


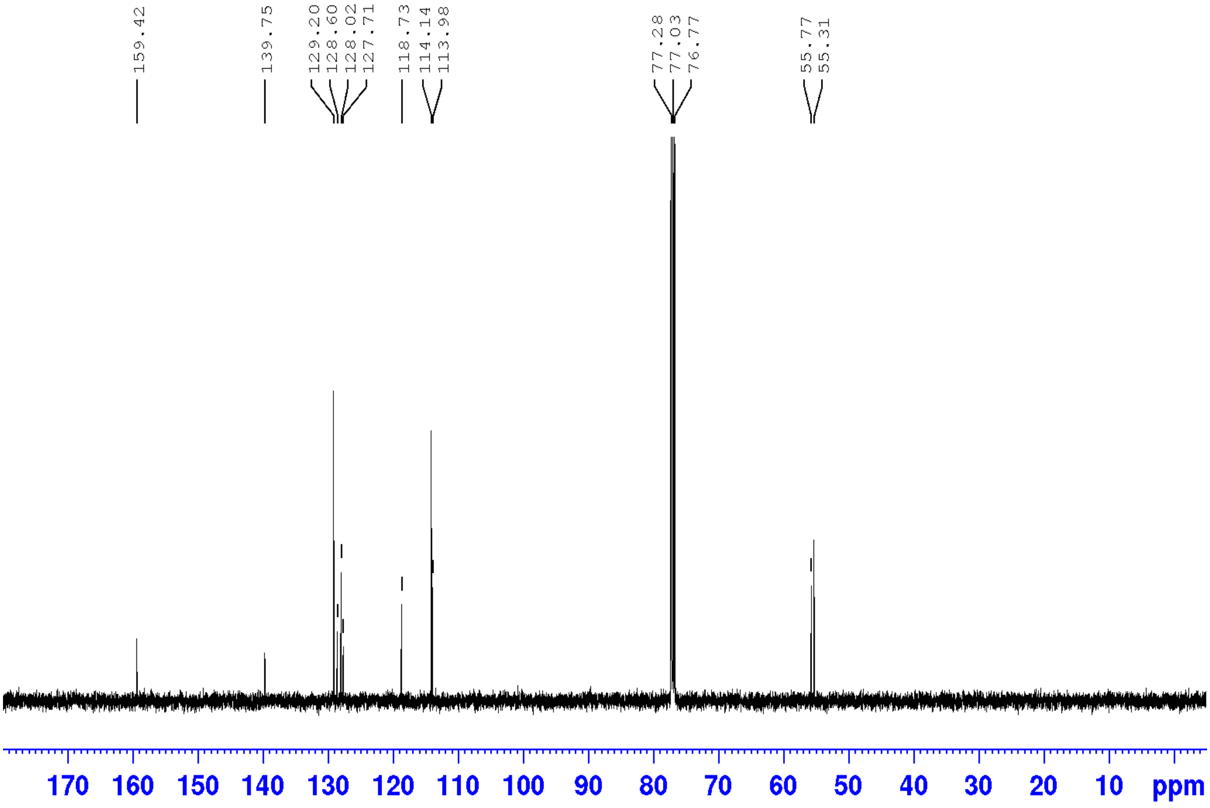
1-(4-methoxybenzyl)-4-nitro-3-vinyl-1H-pyrazole (**24**)



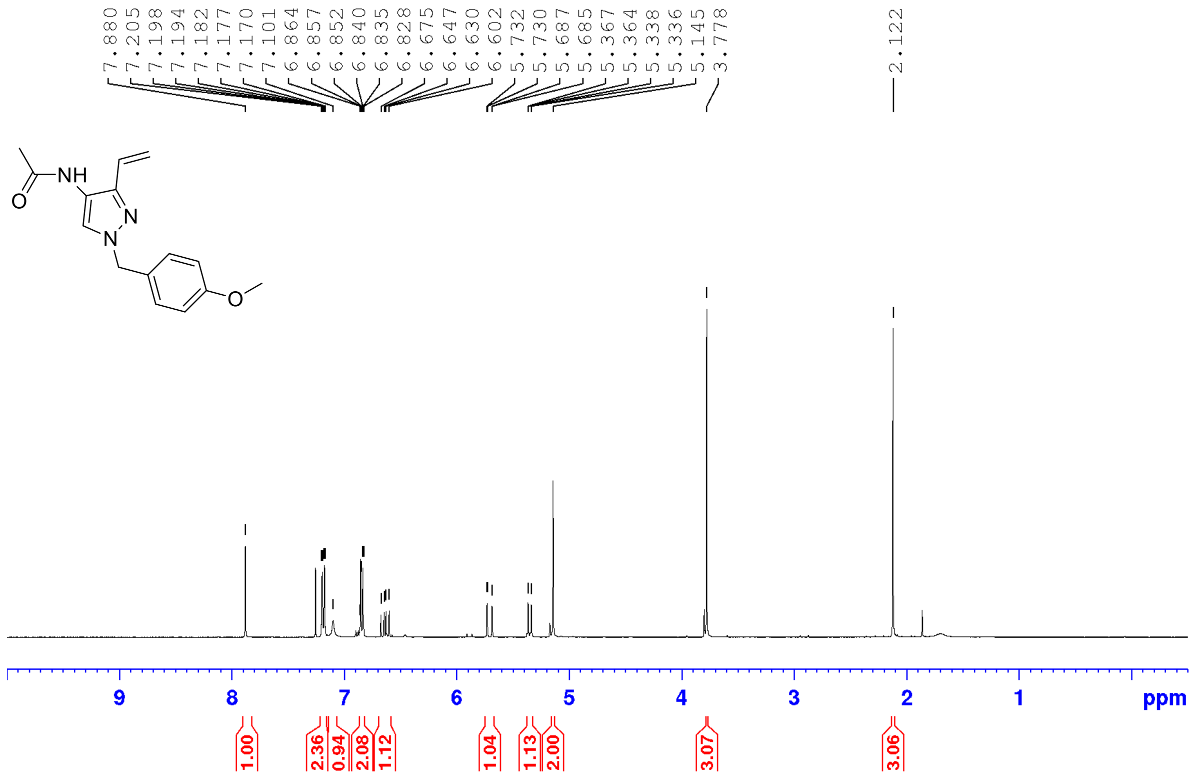


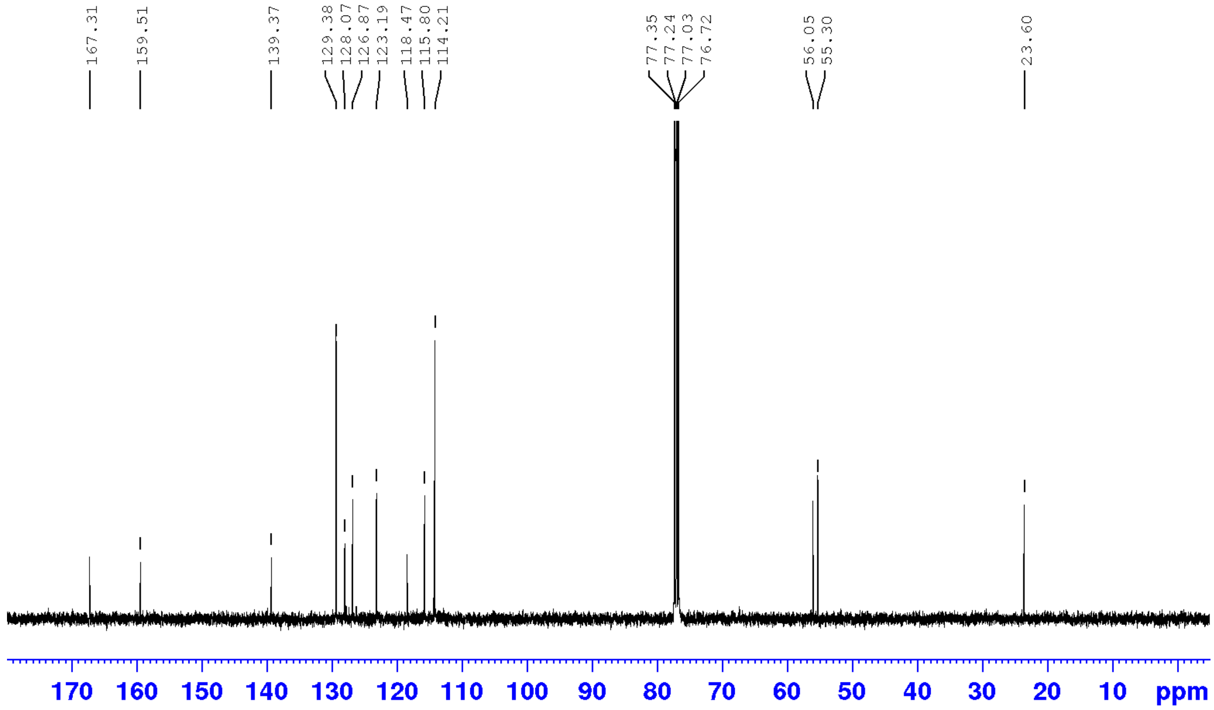
1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-amine (**25**)



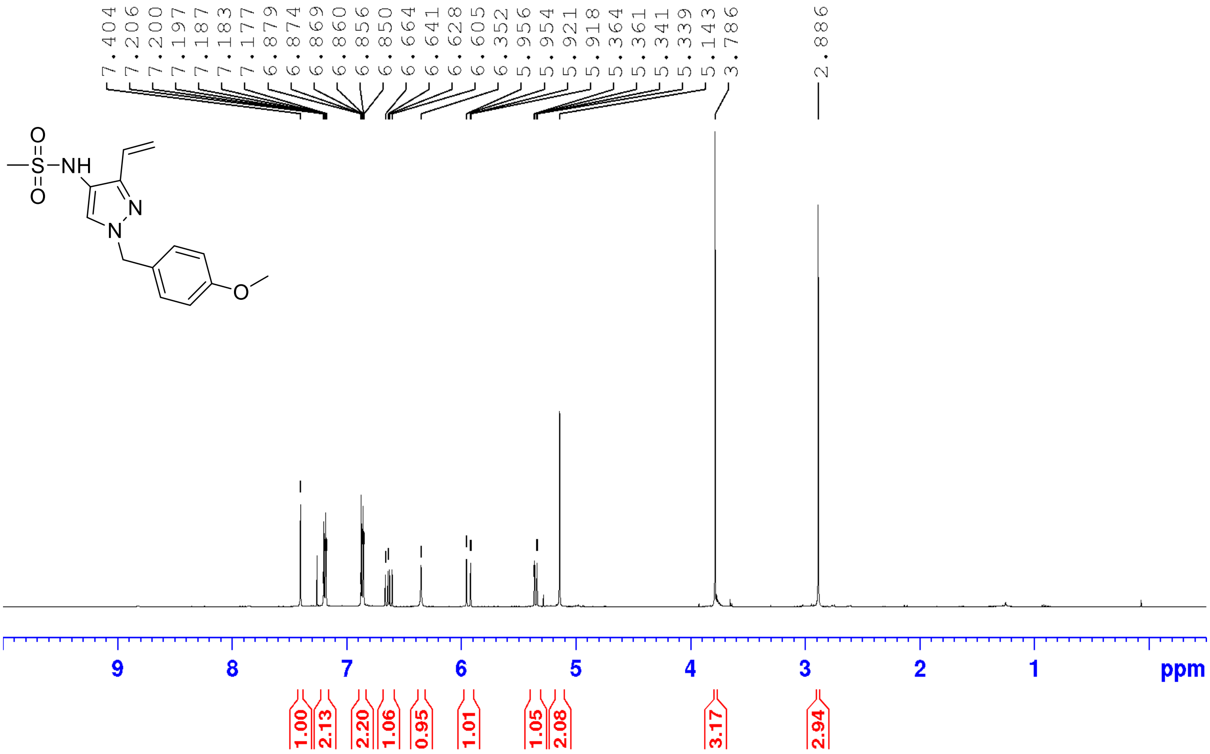


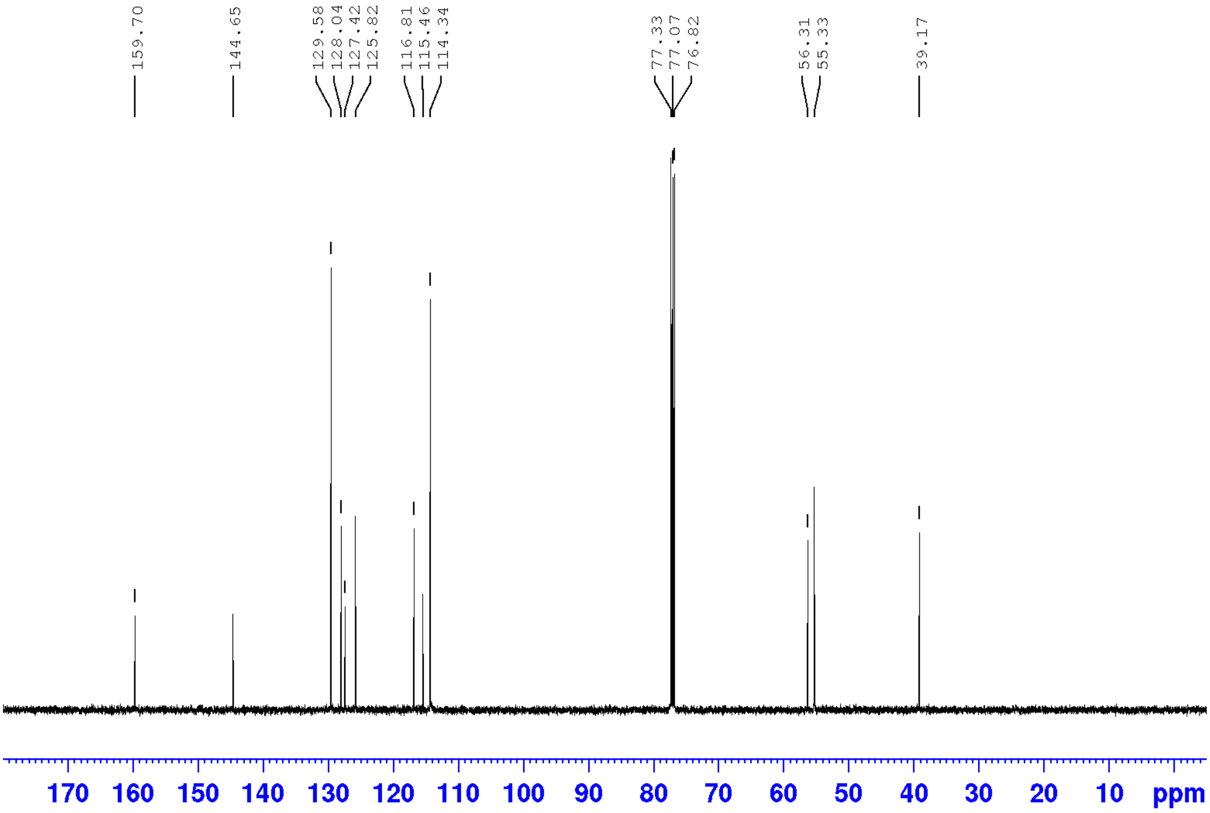
N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)acetamide (**26b**)



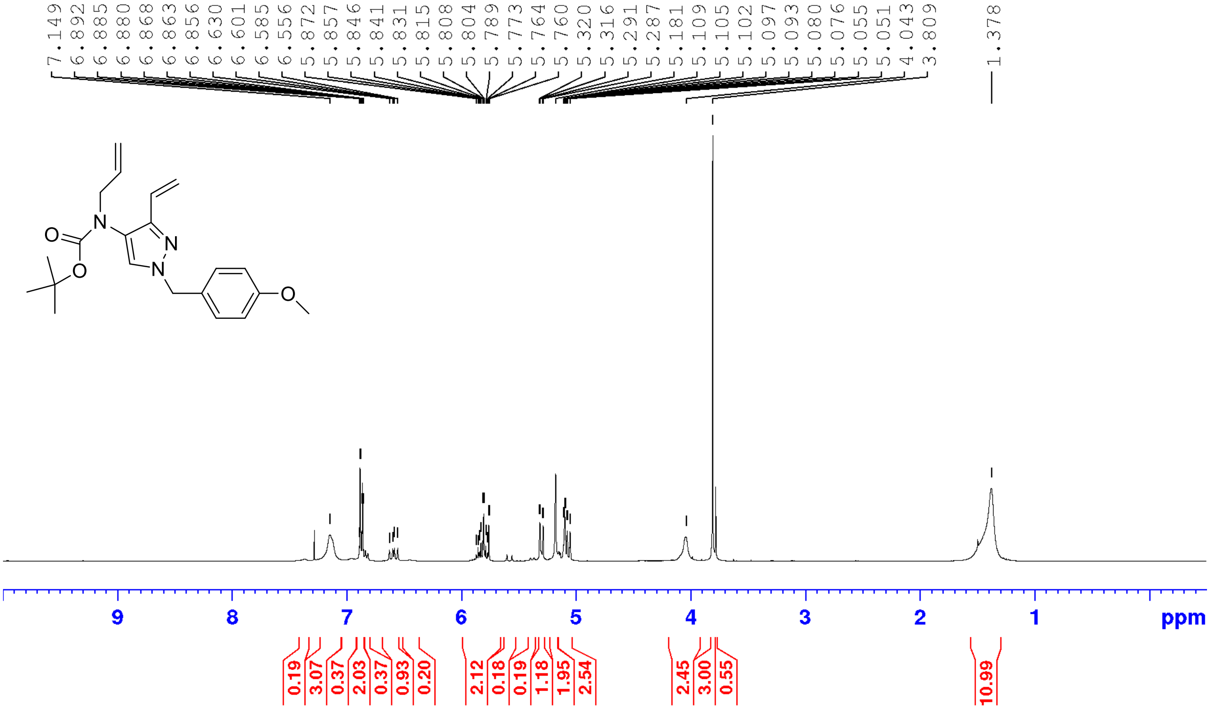


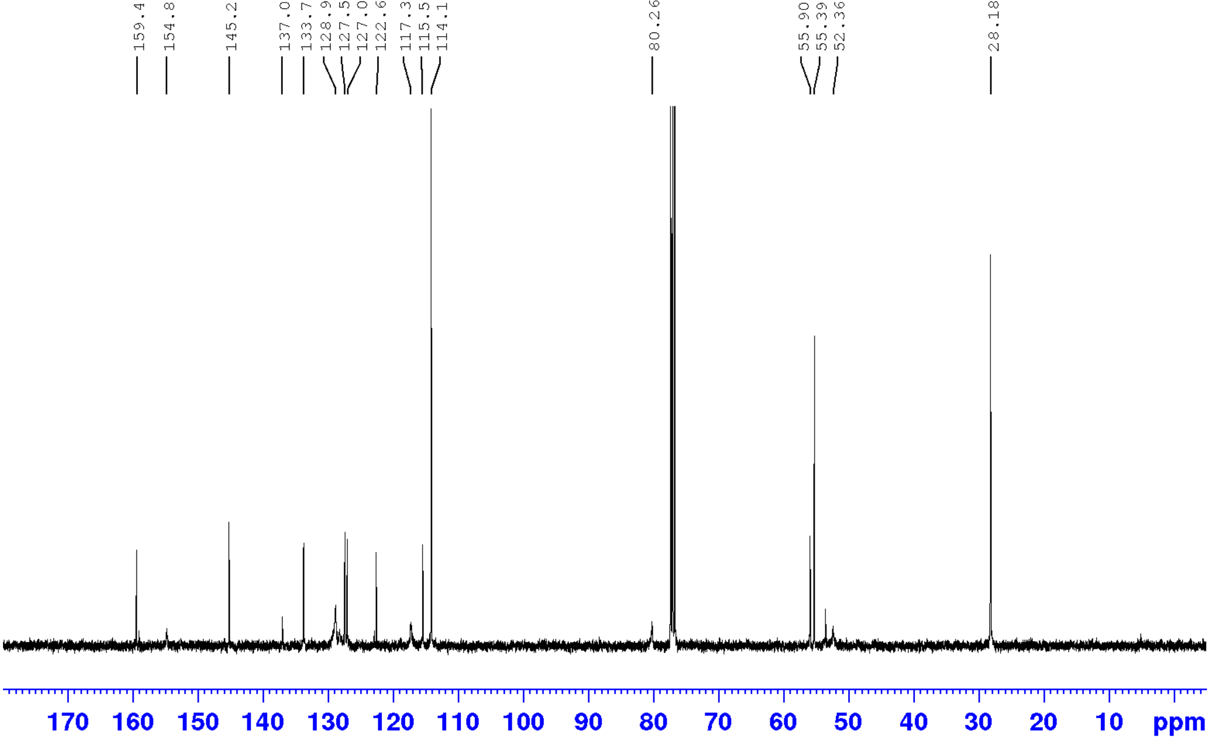
N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methanesulfonamide (**26c**)



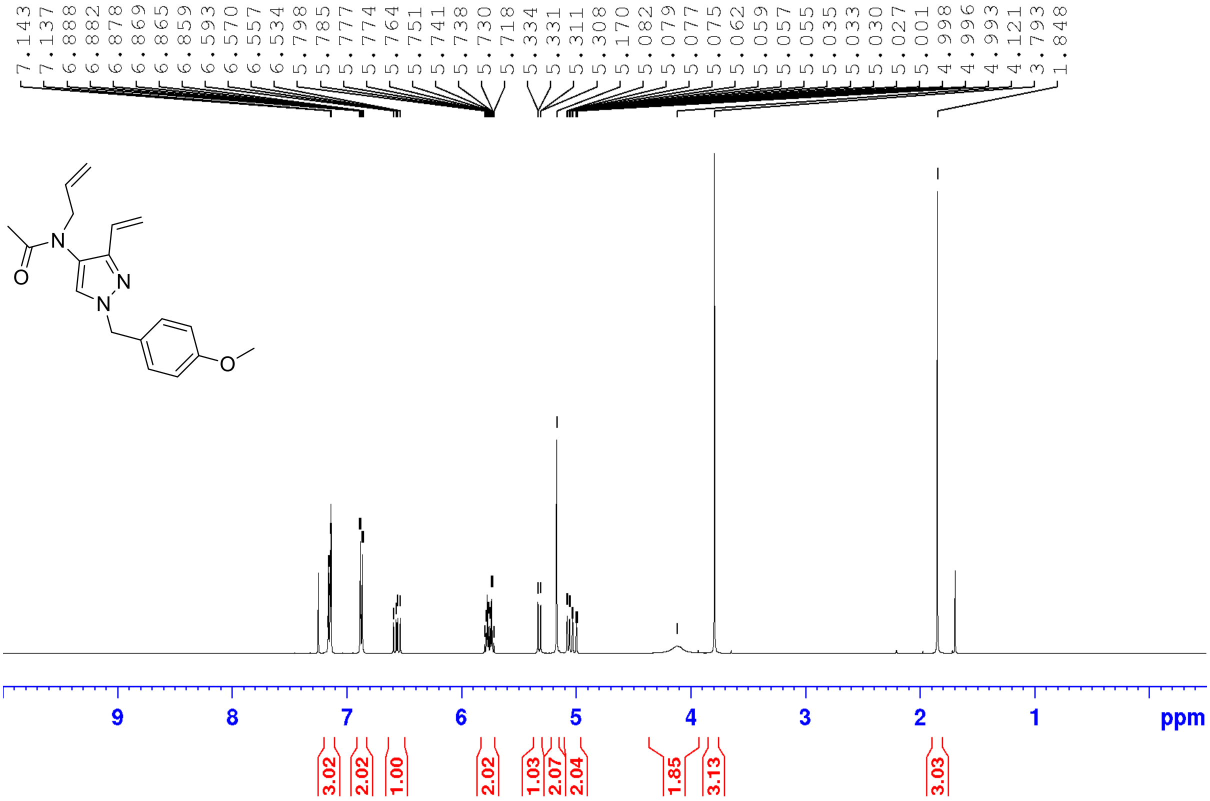


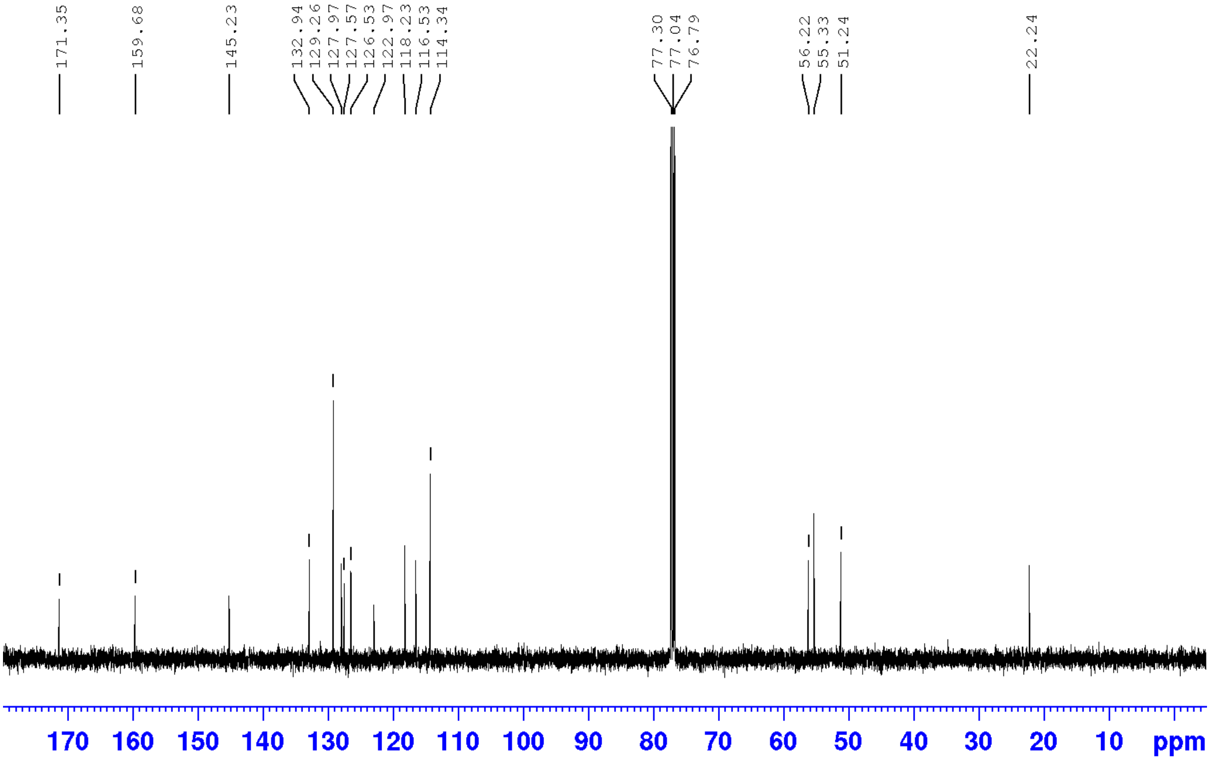
tert-butyl allyl(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)carbamate (**27a**)



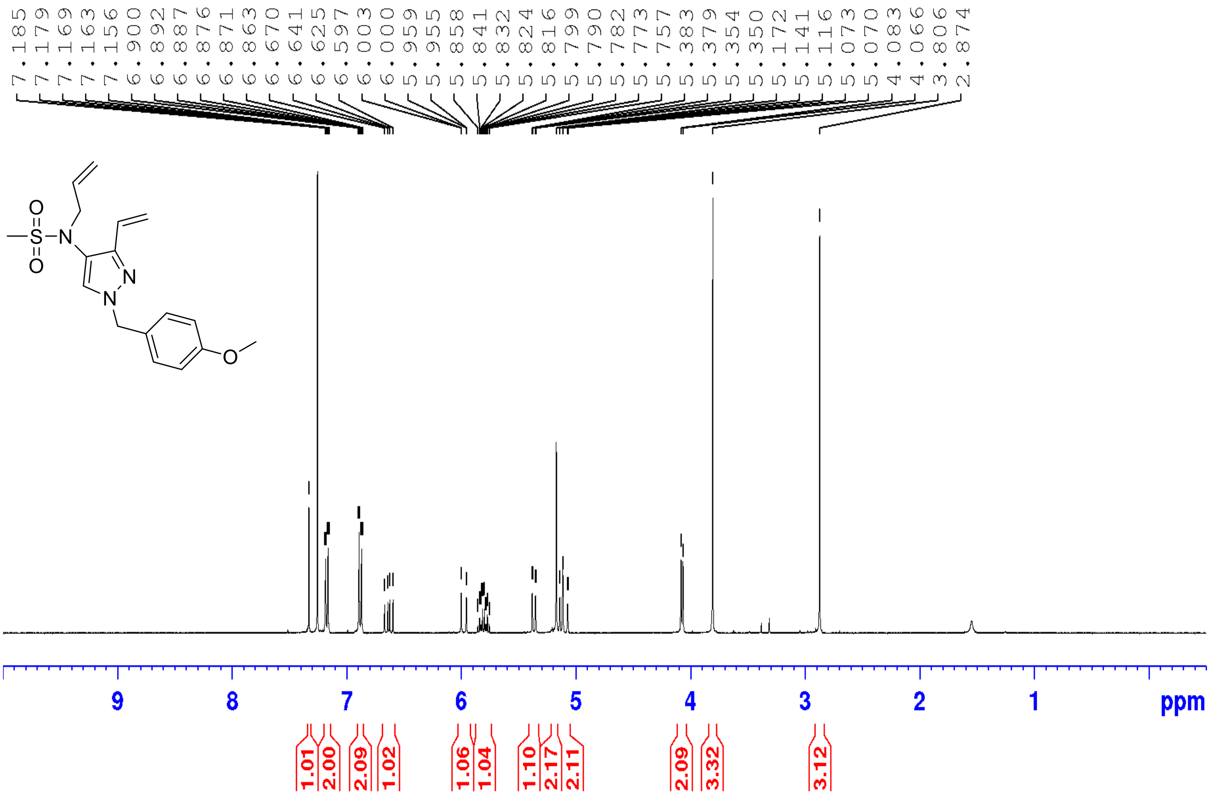


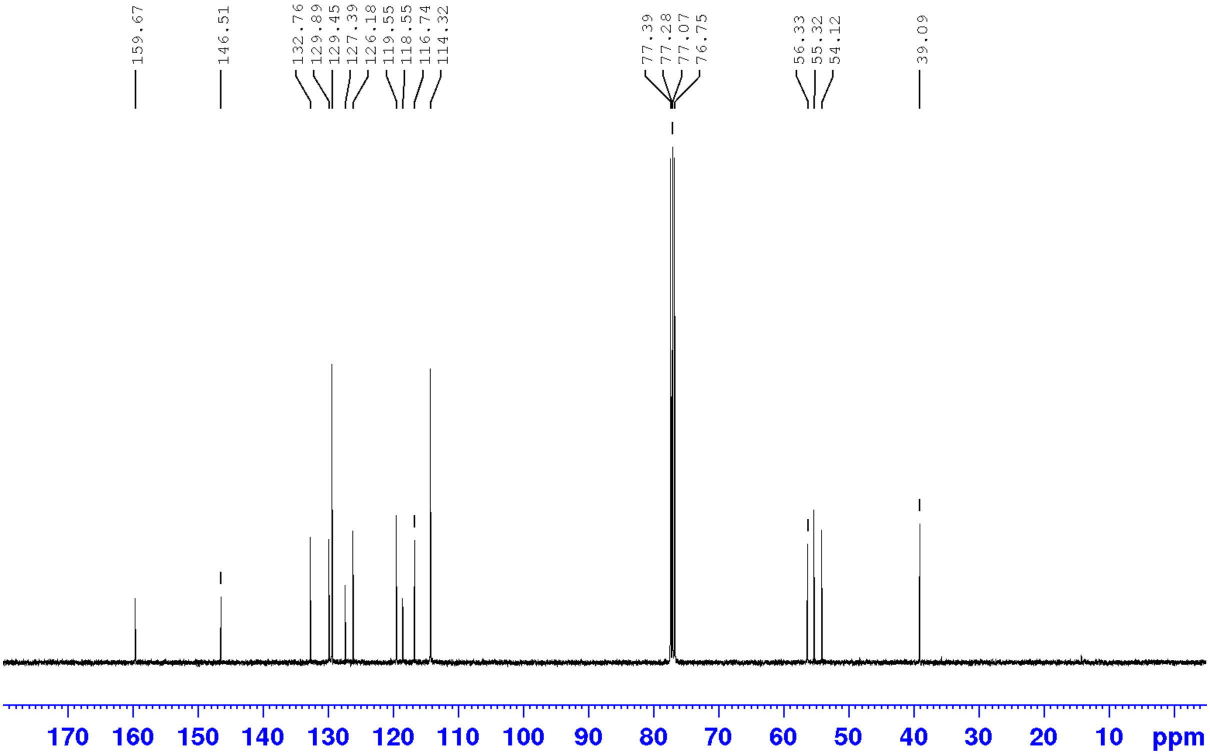
N-allyl-N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)acetamide (**27b**)



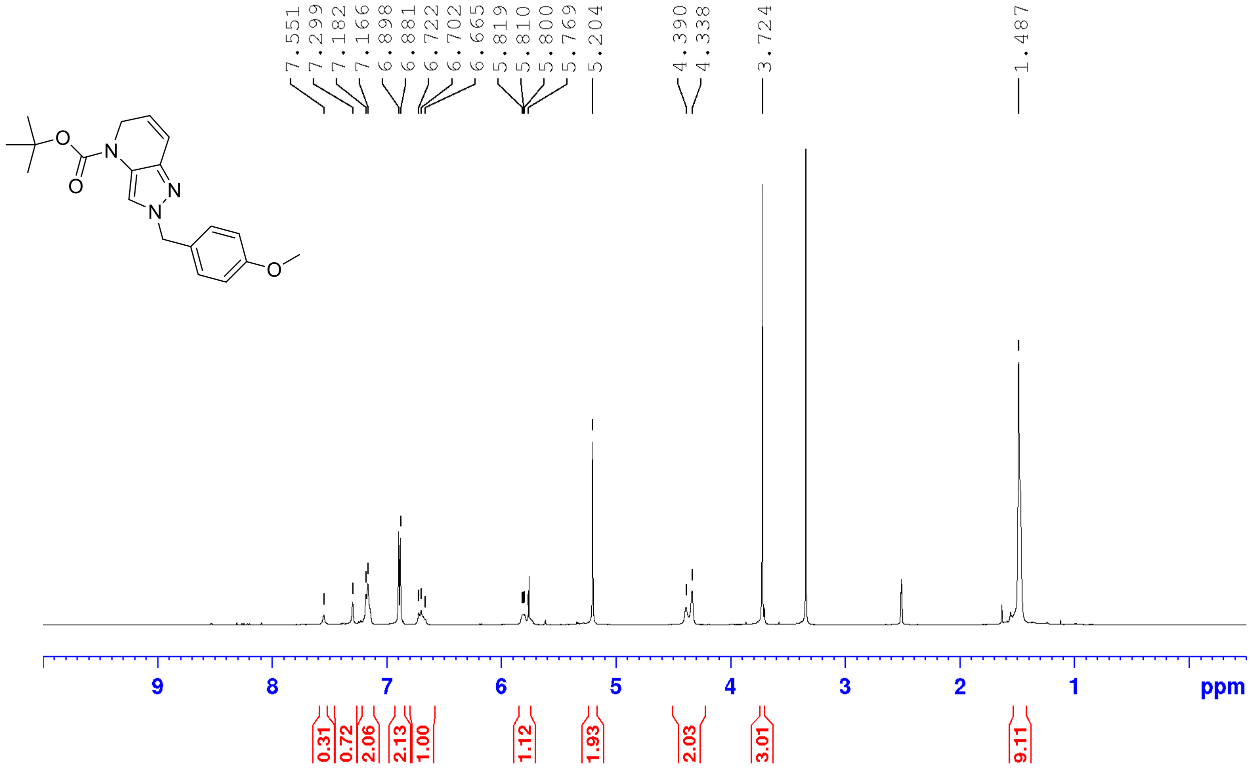


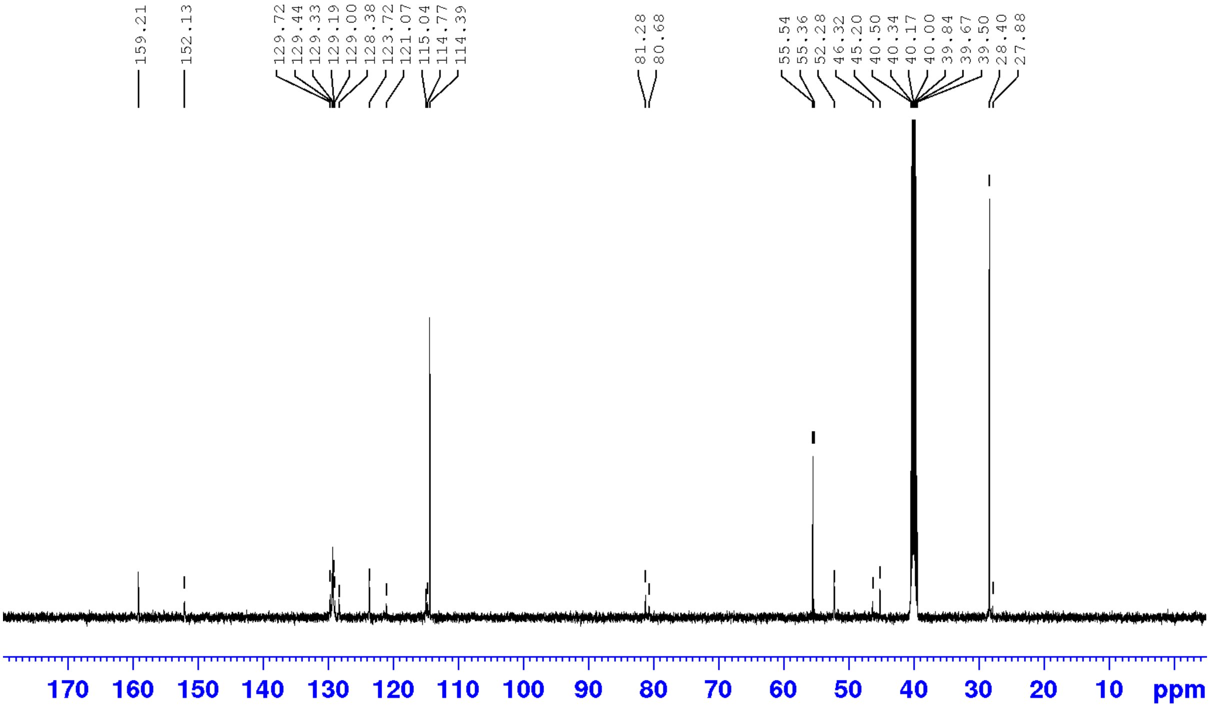
N-allyl-N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methanesulfonamide (**27c**)



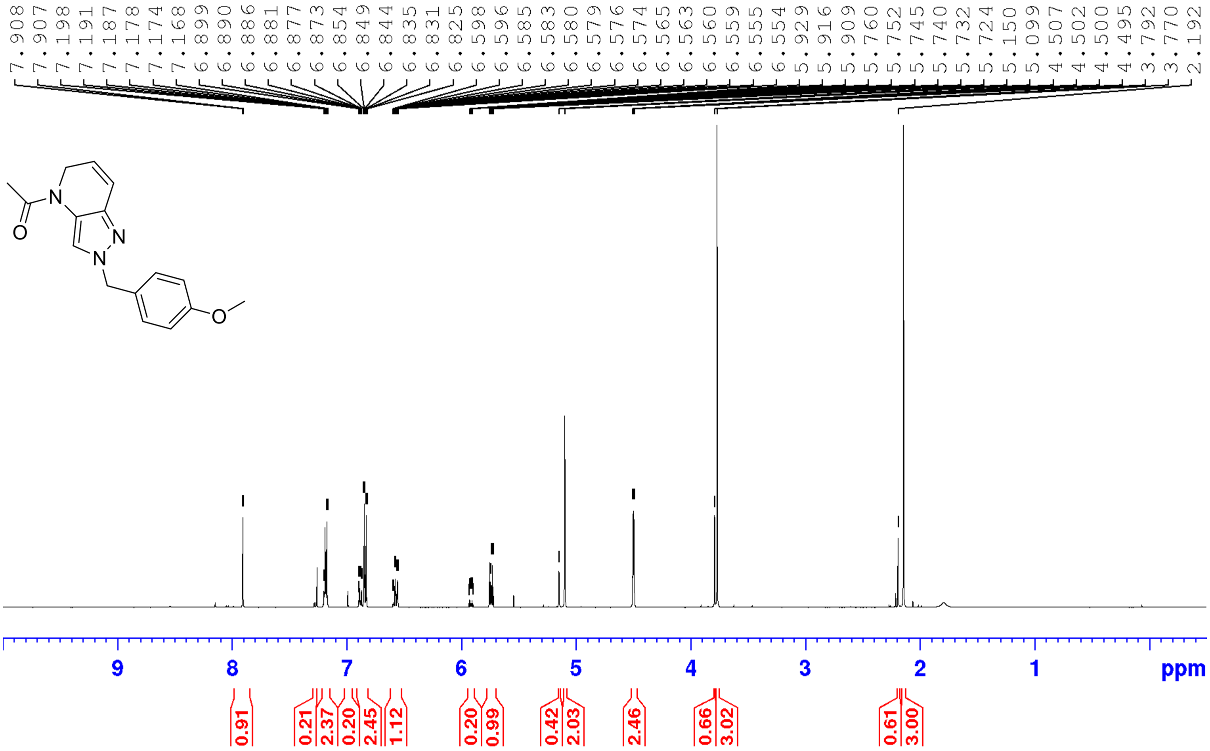


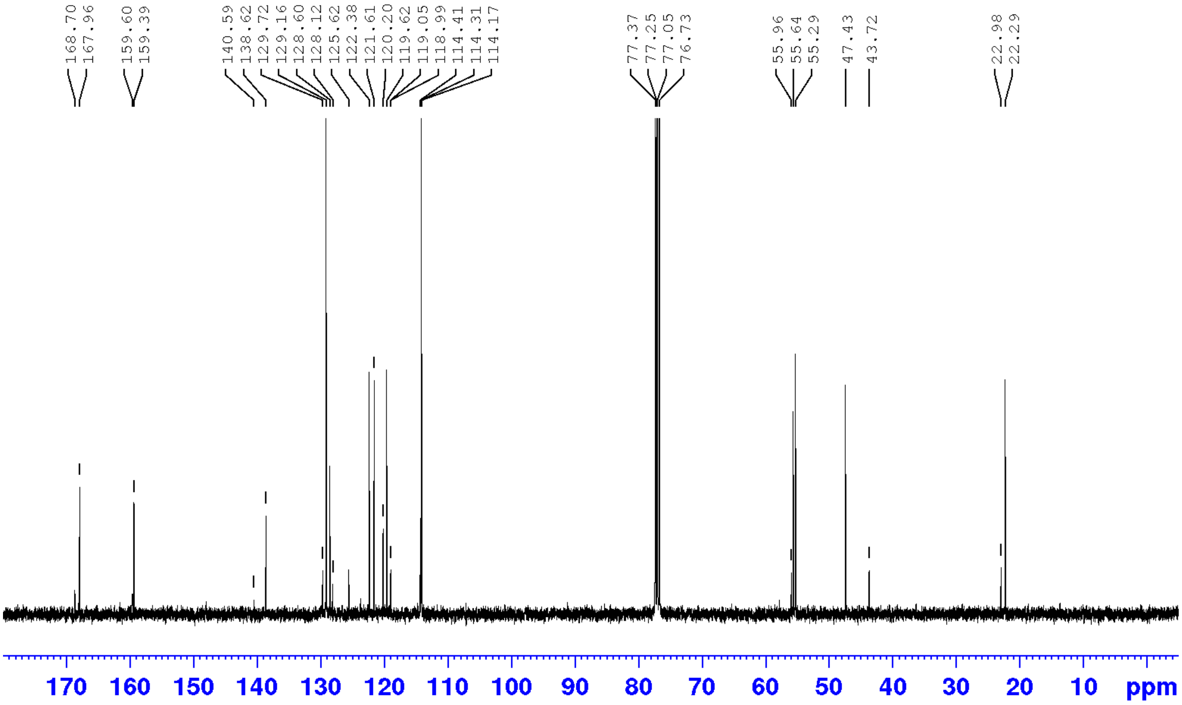
tert-butyl 2-(4-methoxybenzyl)-2,5-dihydro-4H-pyrazolo[4,3-b]pyridine-4-carboxylate (**28a**)



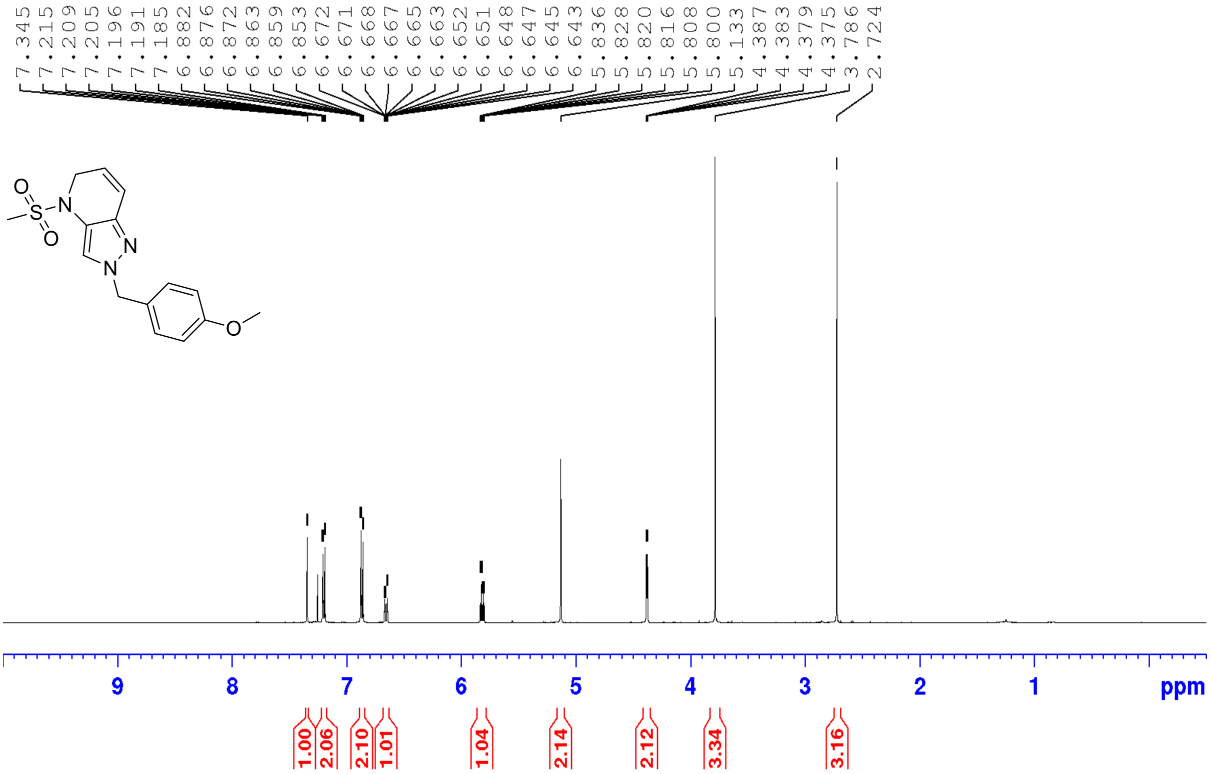


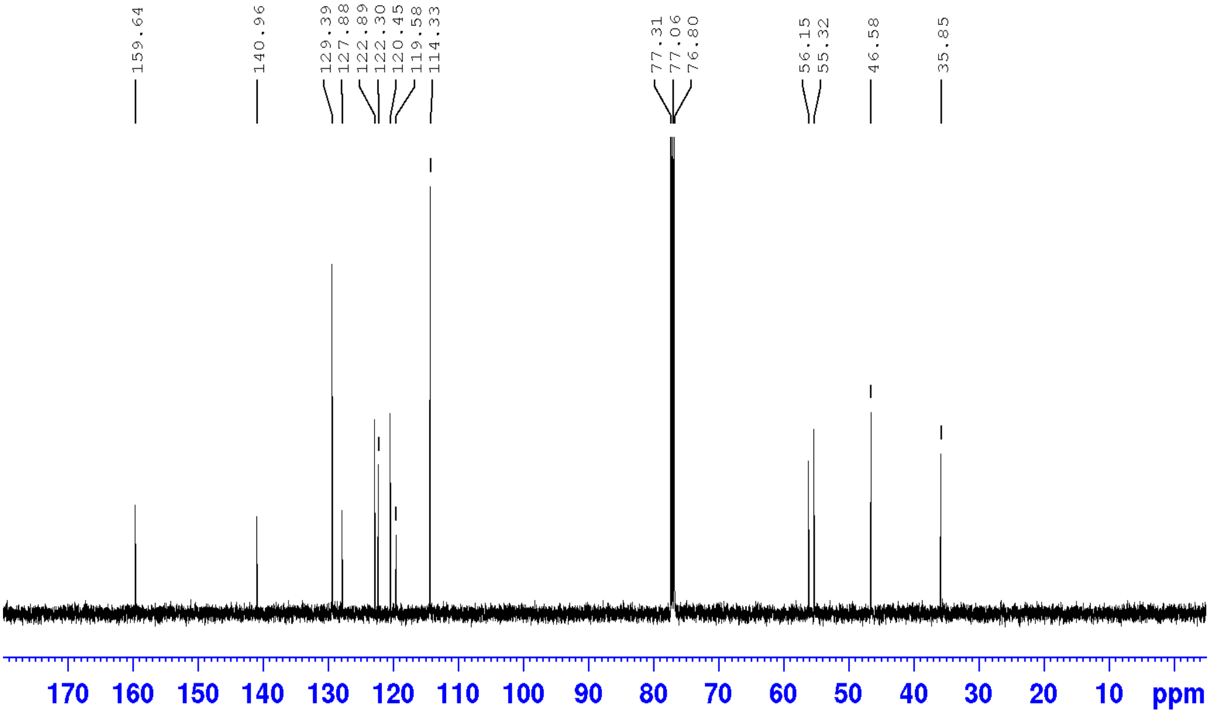
1-(2-(4-methoxybenzyl)-2,5-dihydro-4H-pyrazolo[4,3-b]pyridin-4-yl)ethan-1-one (**28b**)



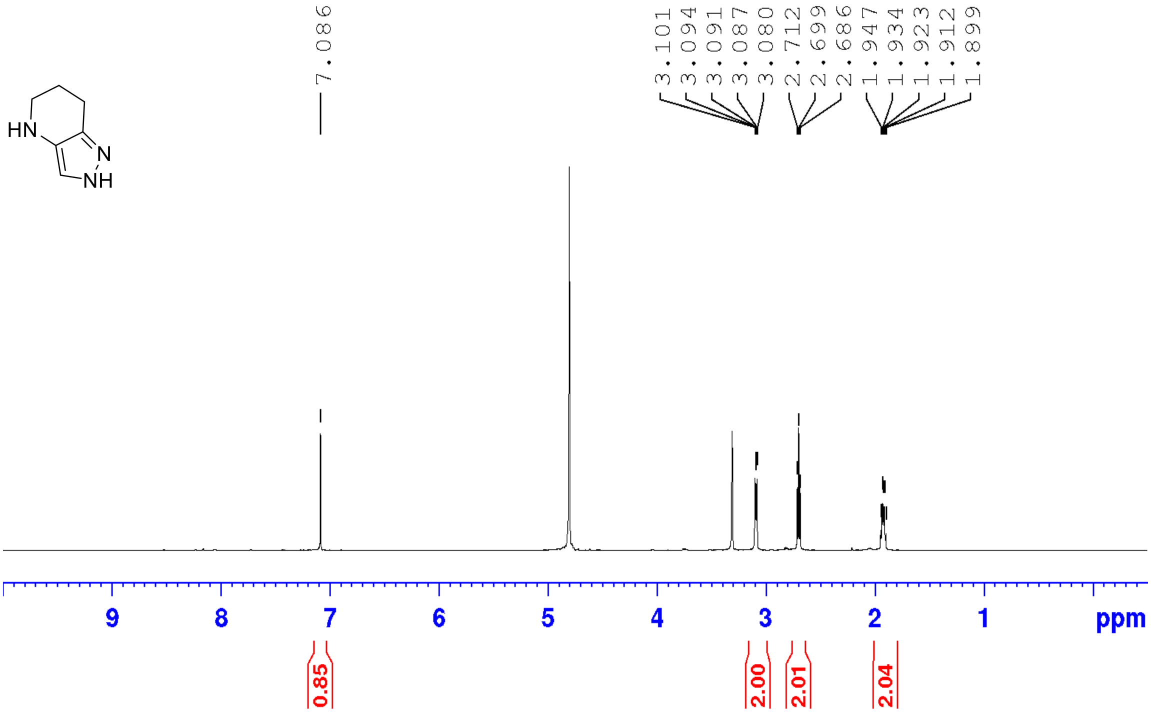


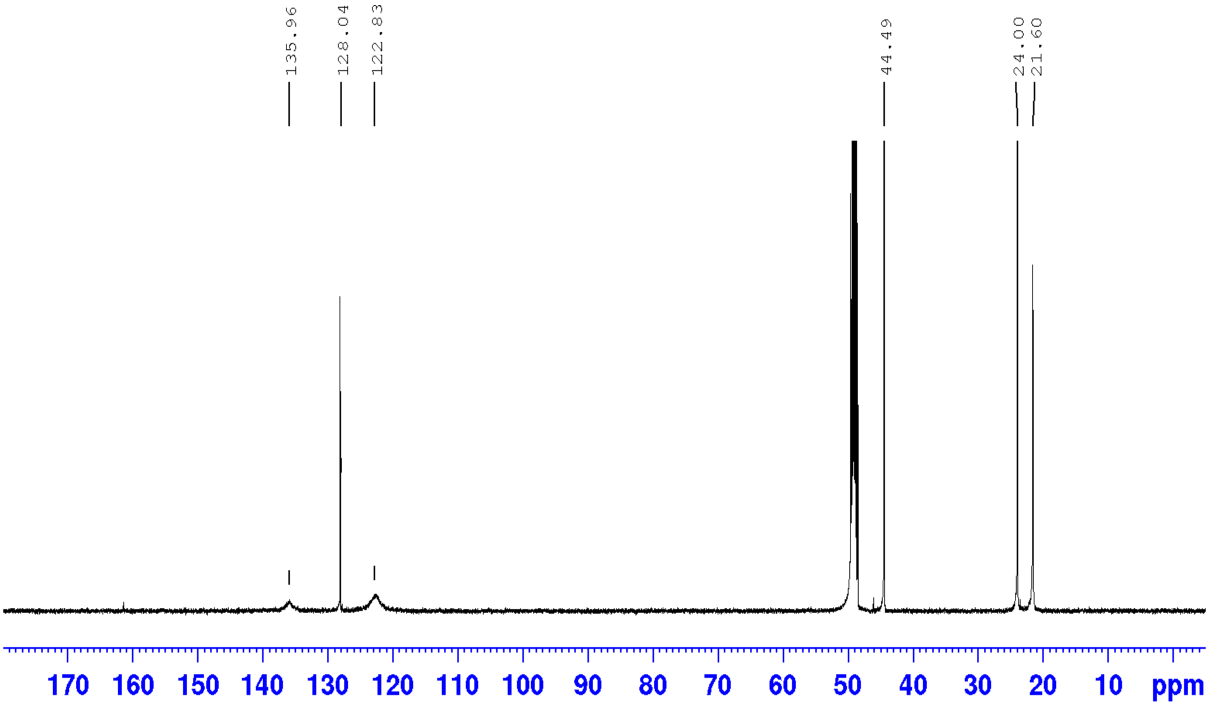
2-(4-methoxybenzyl)-4-(methylsulfonyl)-4,5-dihydro-2H-pyrazolo[4,3-b]pyridine (**28c**)



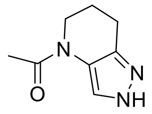


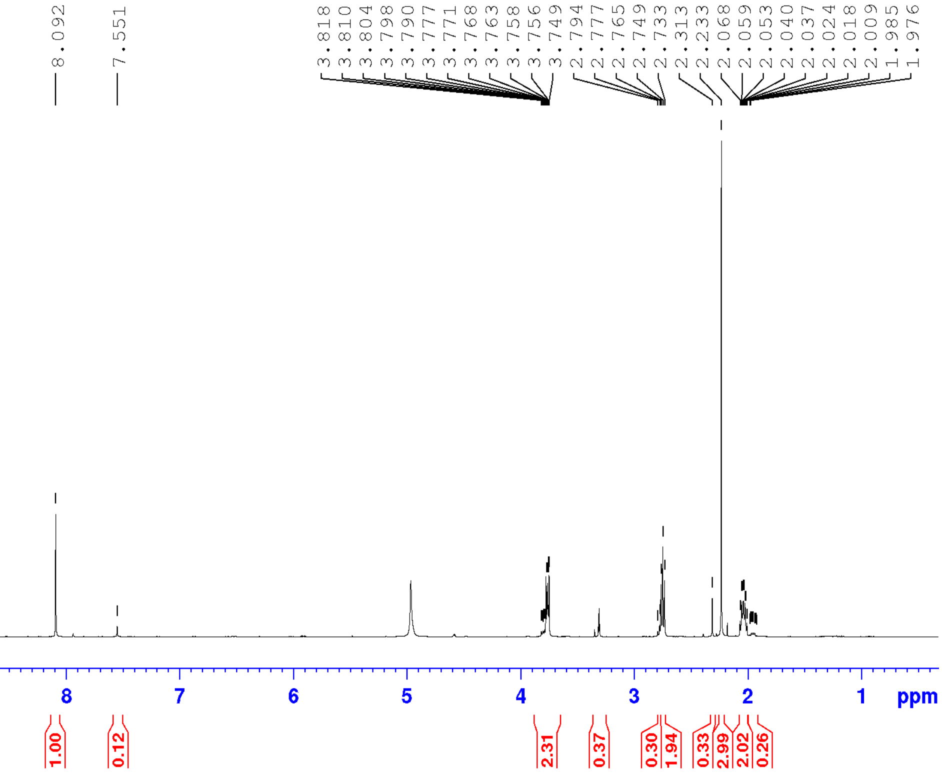
4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridine (**5a**)

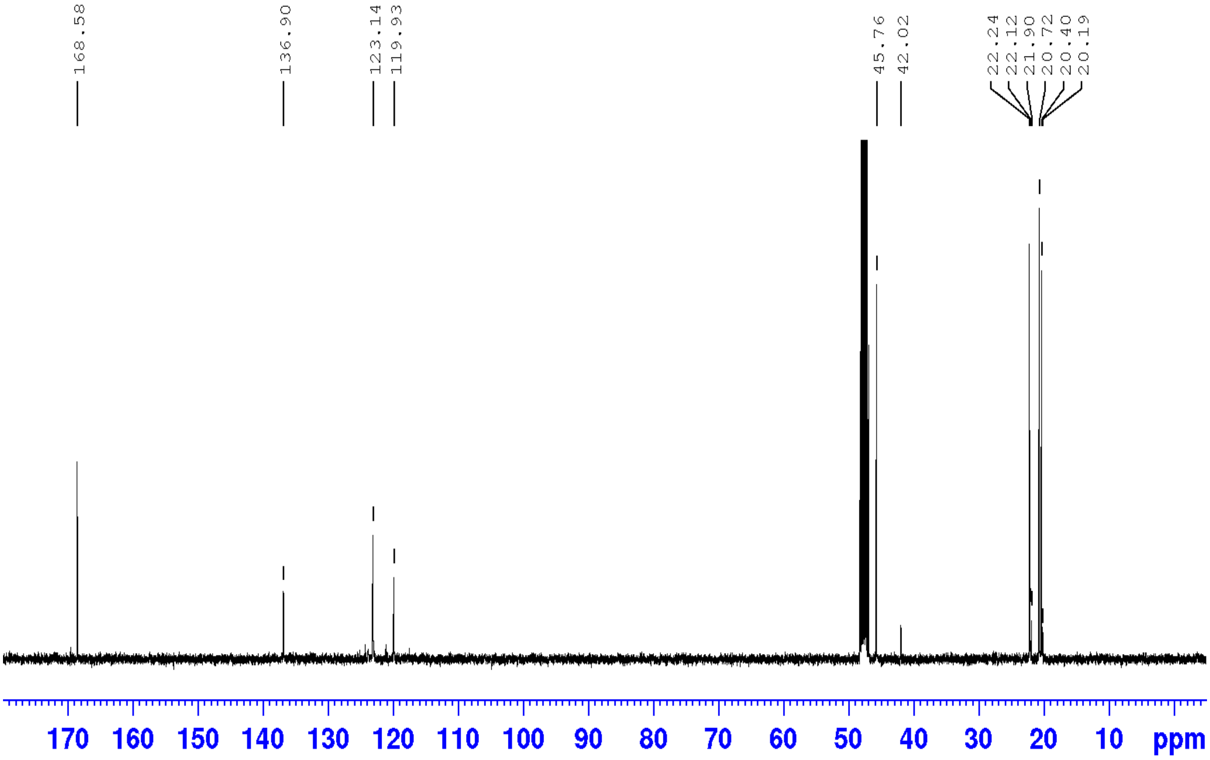




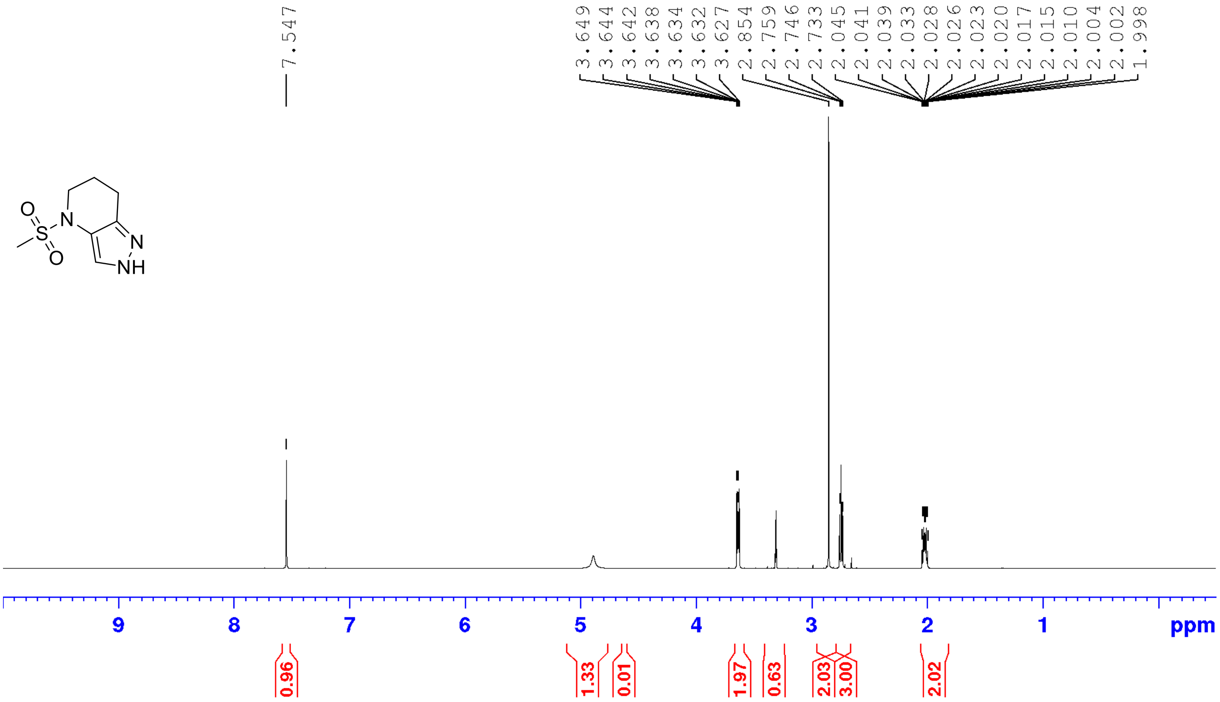
1-(2,5,6,7-tetrahydro-4H-pyrazolo[4,3-b]pyridin-4-yl)ethan-1-one (**5b**)

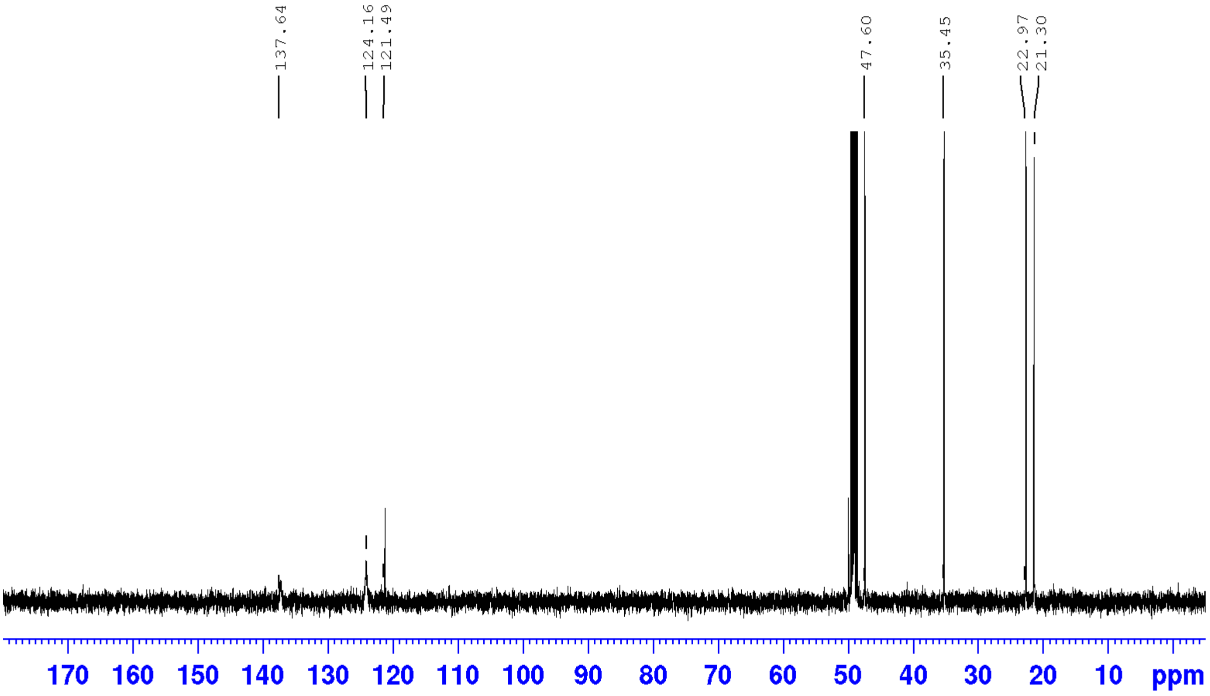




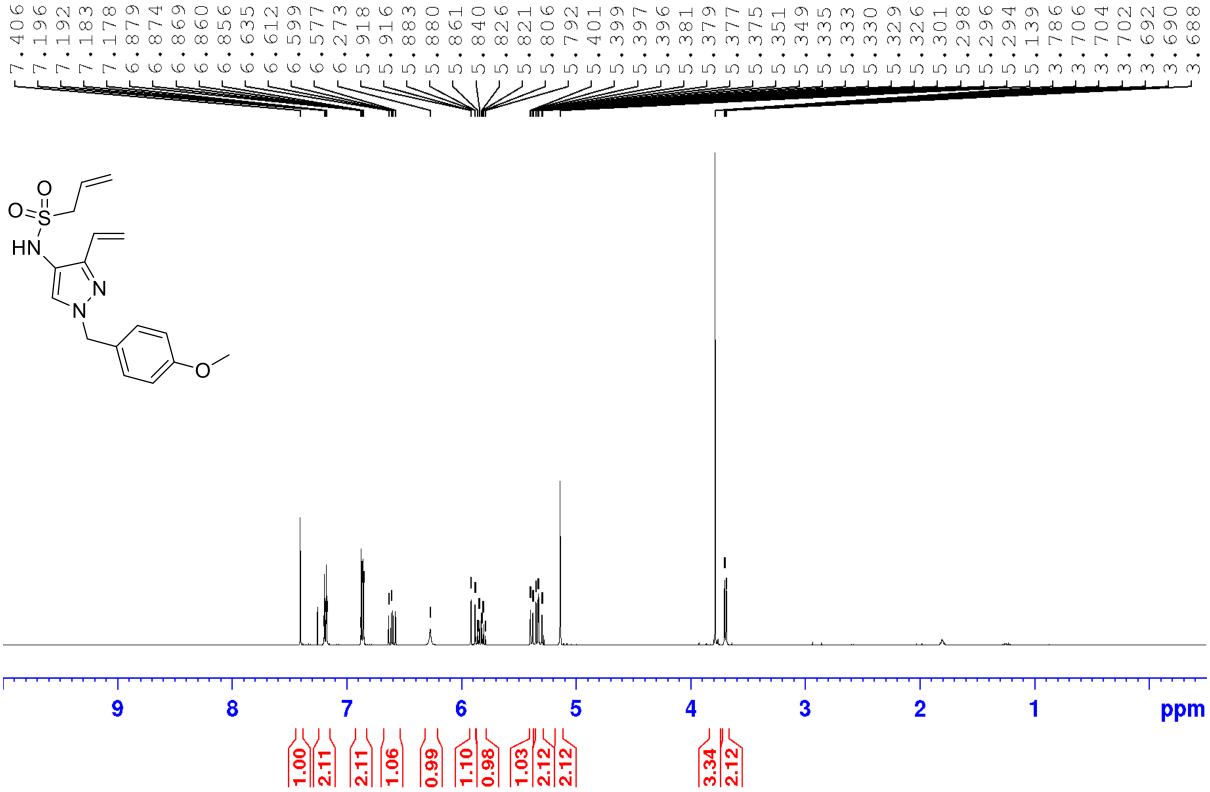


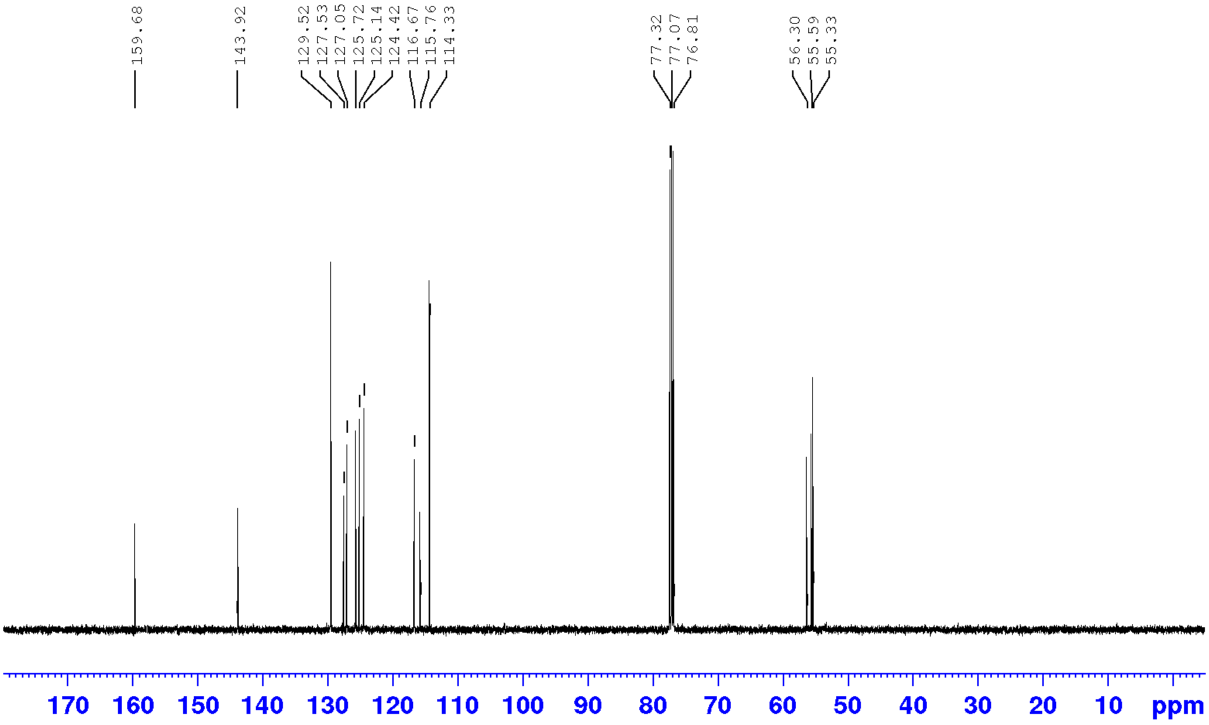
4-(methylsulfonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridine (**5c**)



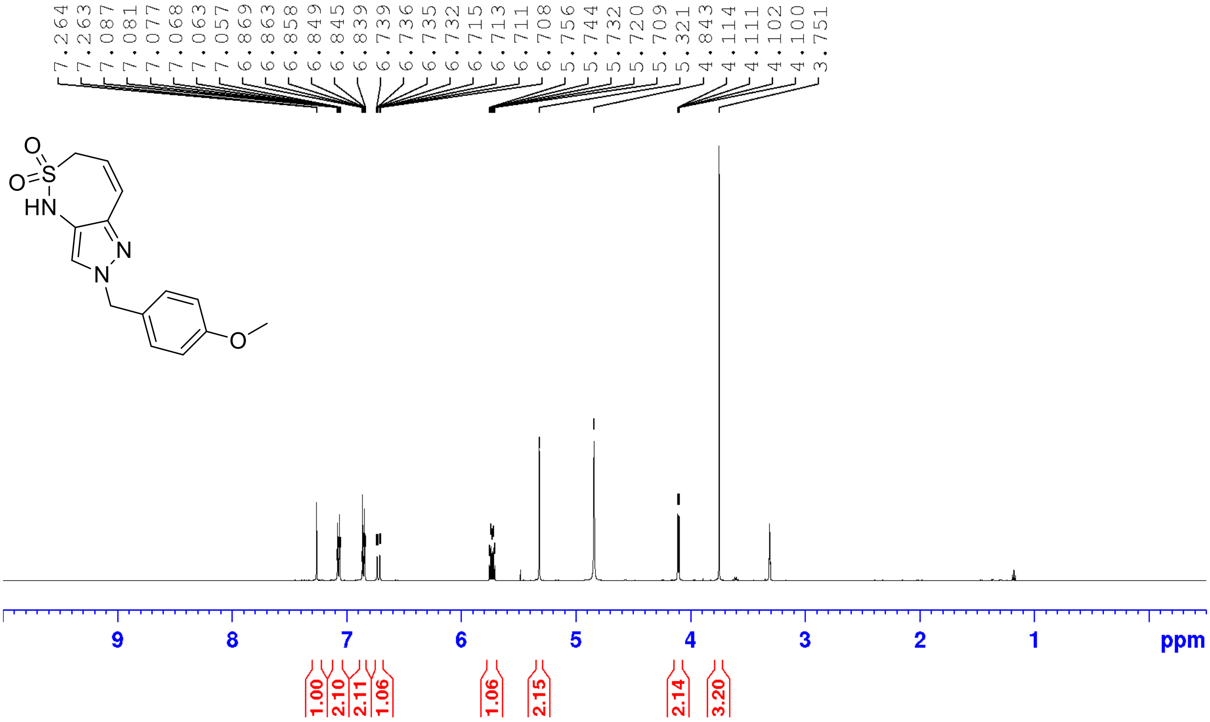


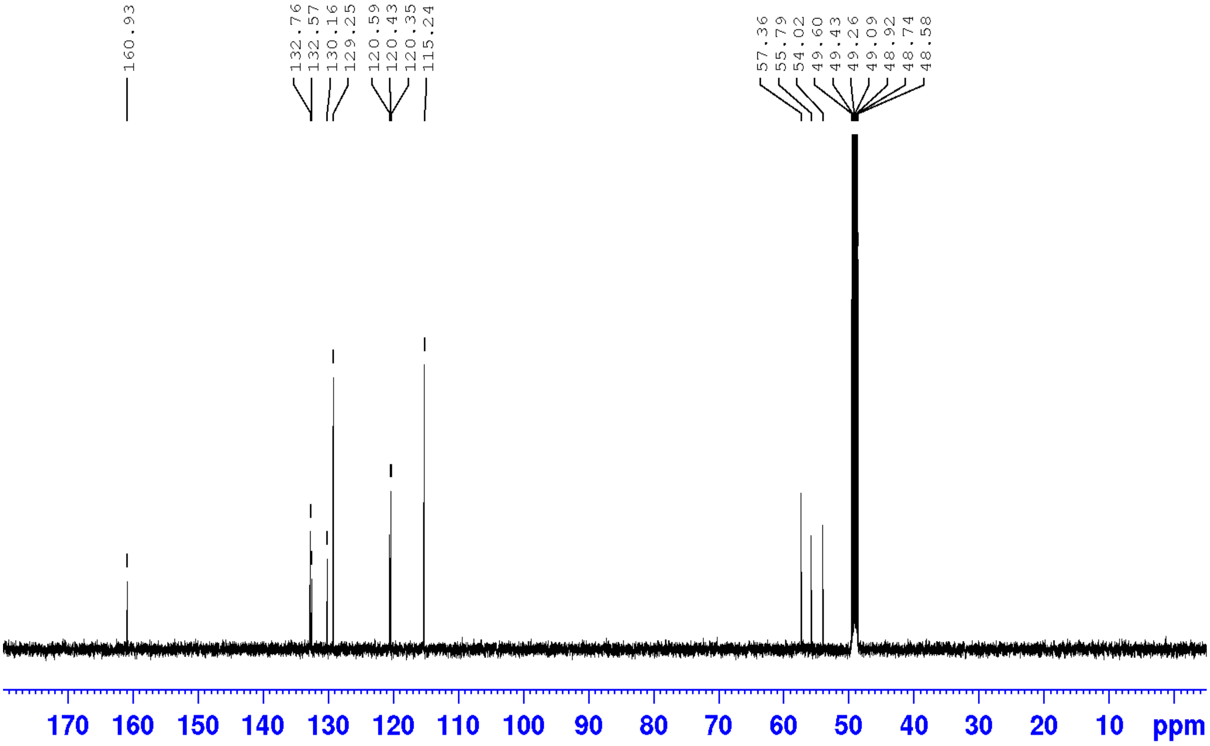
N-(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)prop-2-ene-1-sulfonamide (**29**)



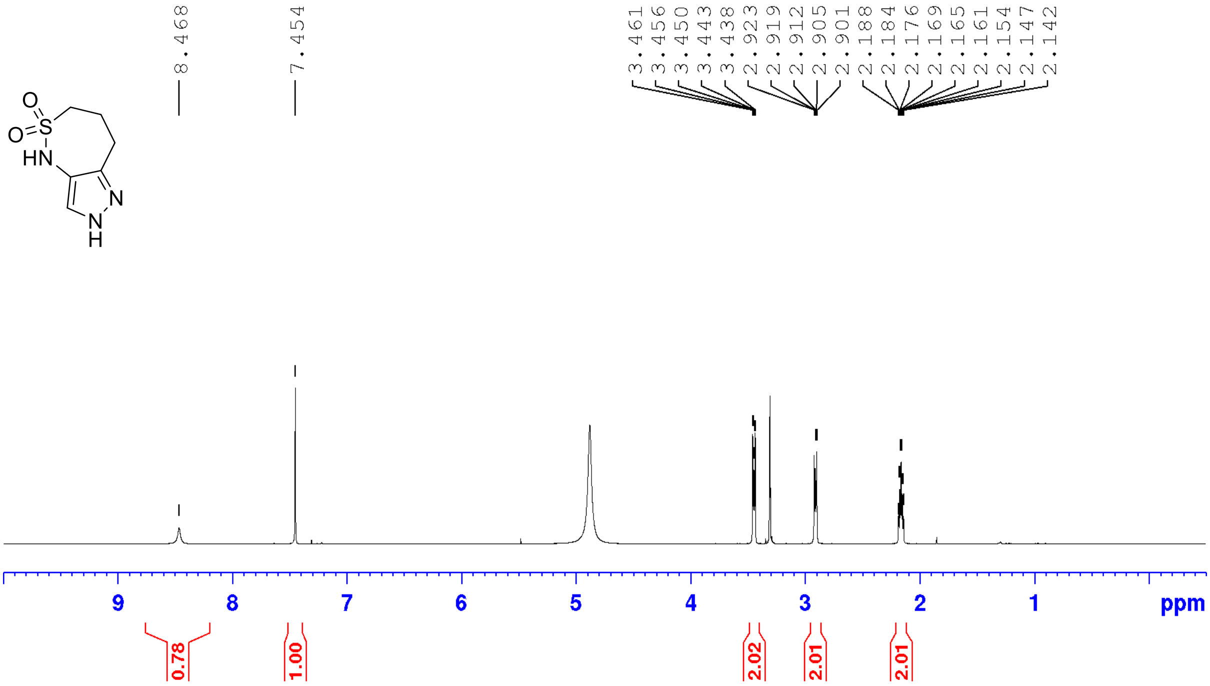


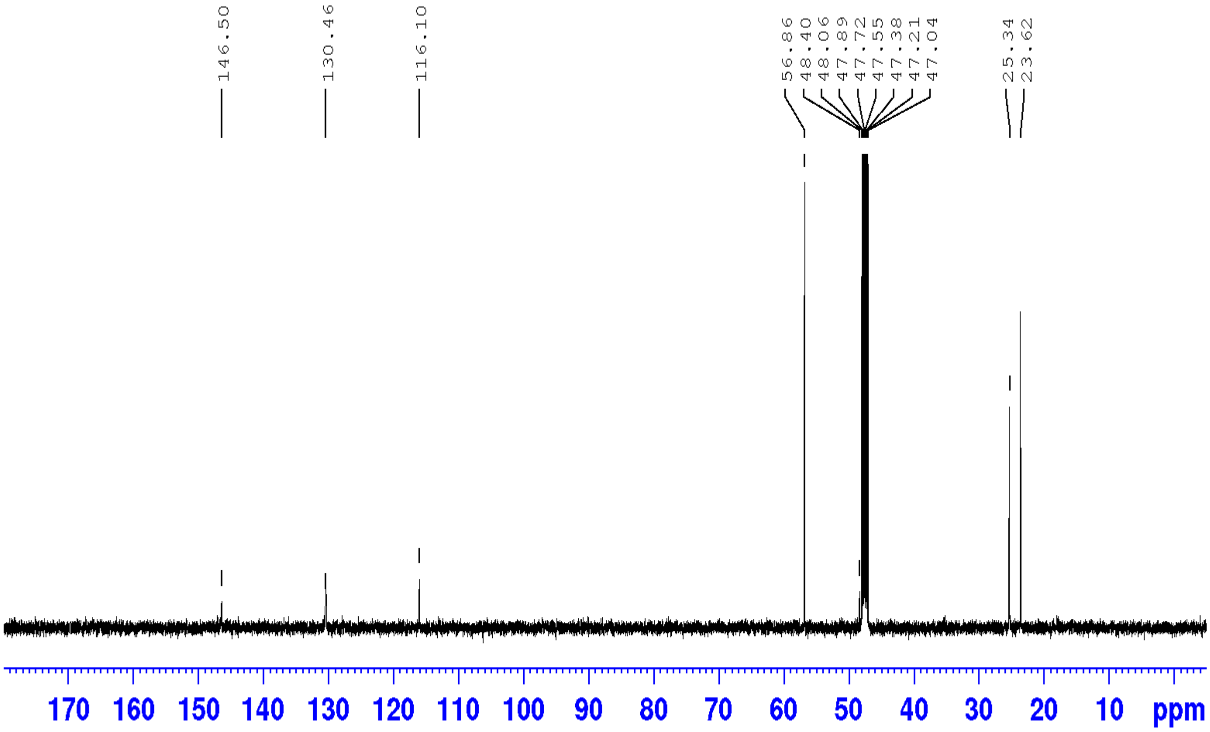
2-(4-methoxybenzyl)-2,6-dihydro-4H-pyrazolo[4,3-c][1,2]thiazepine 5,5-dioxide (**30**)



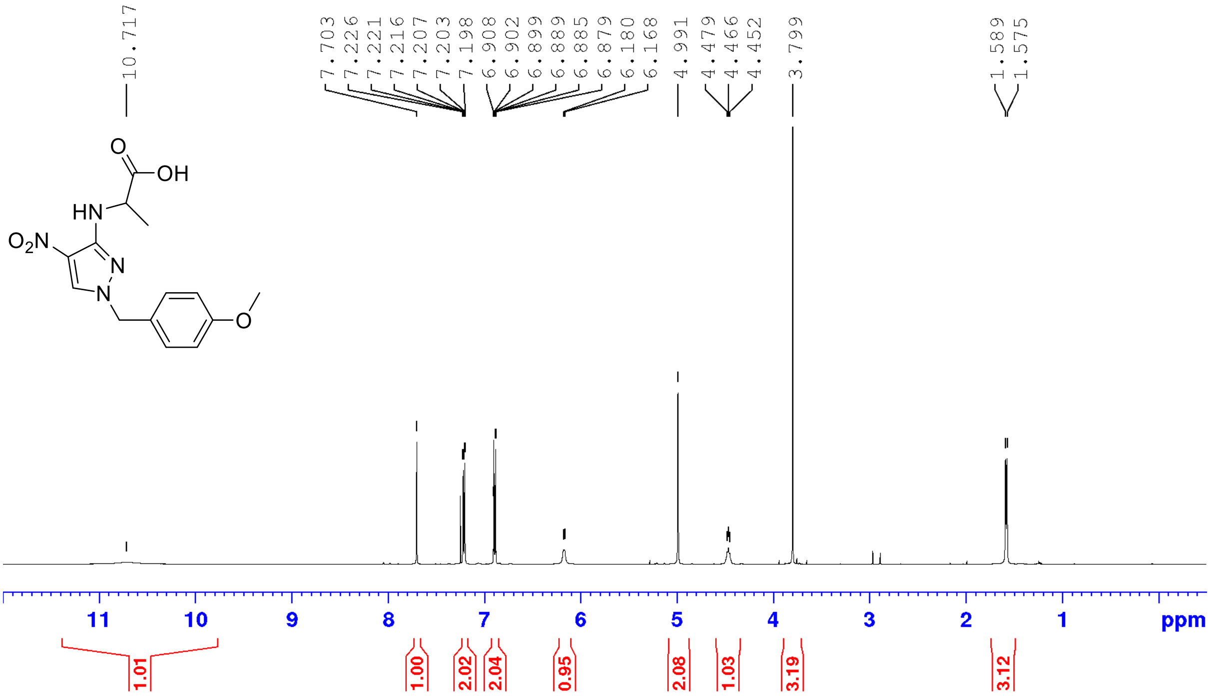


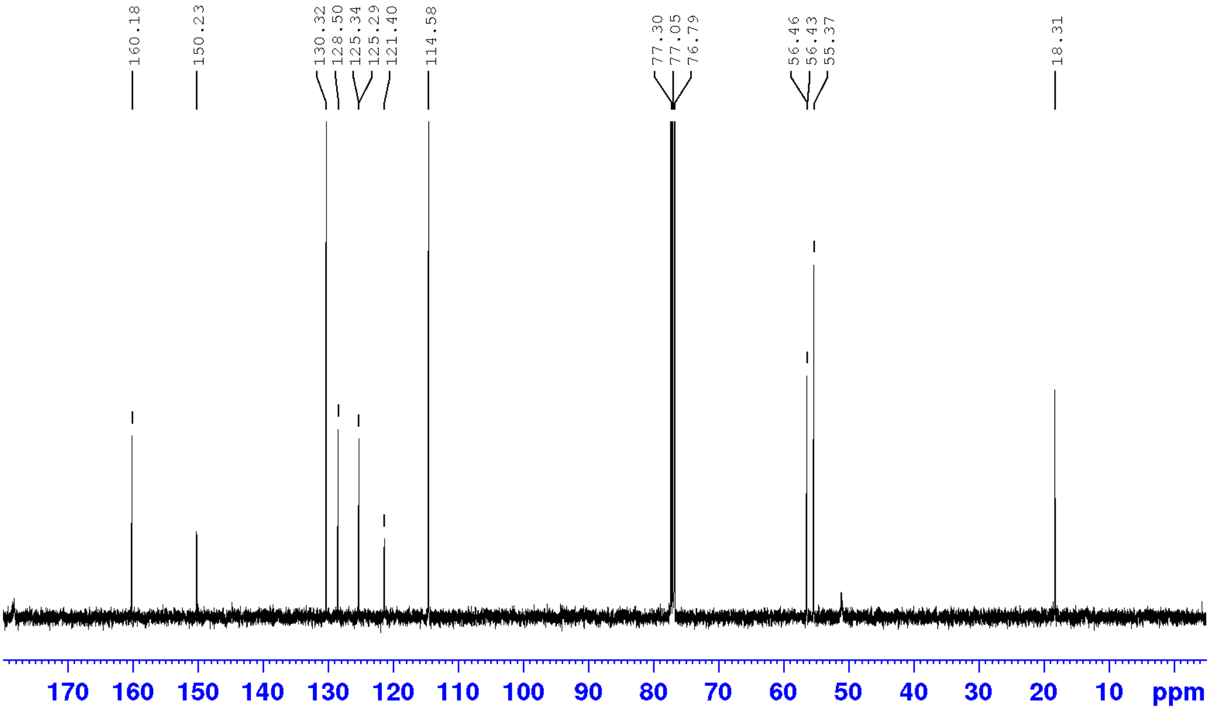
2,6,7,8-tetrahydro-4H-pyrazolo[4,3-c][1,2]thiazepine 5,5-dioxide (**6**)



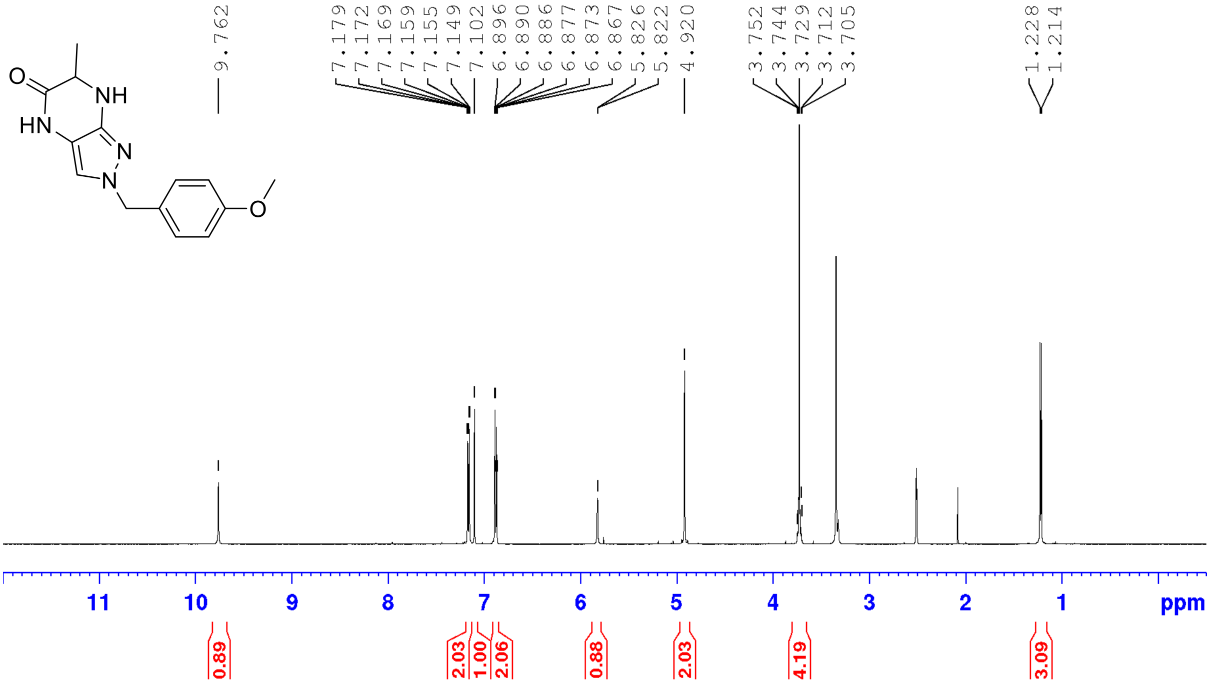


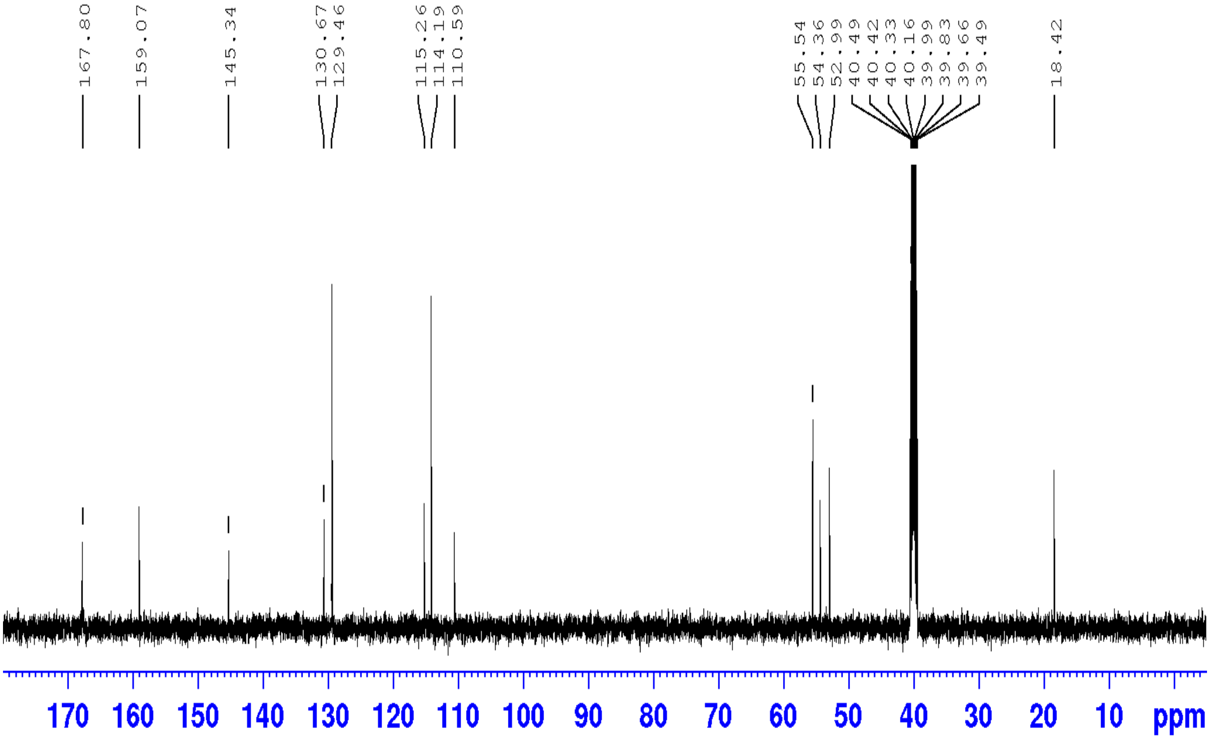
(1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)alanine (**31a**)



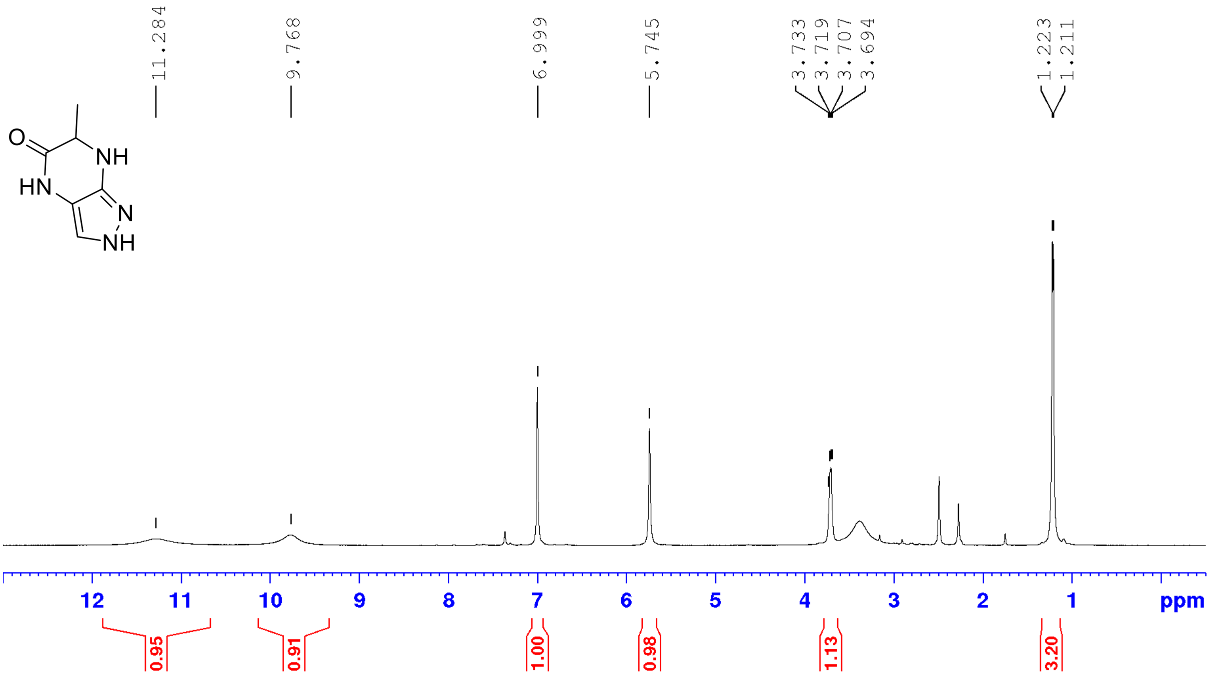


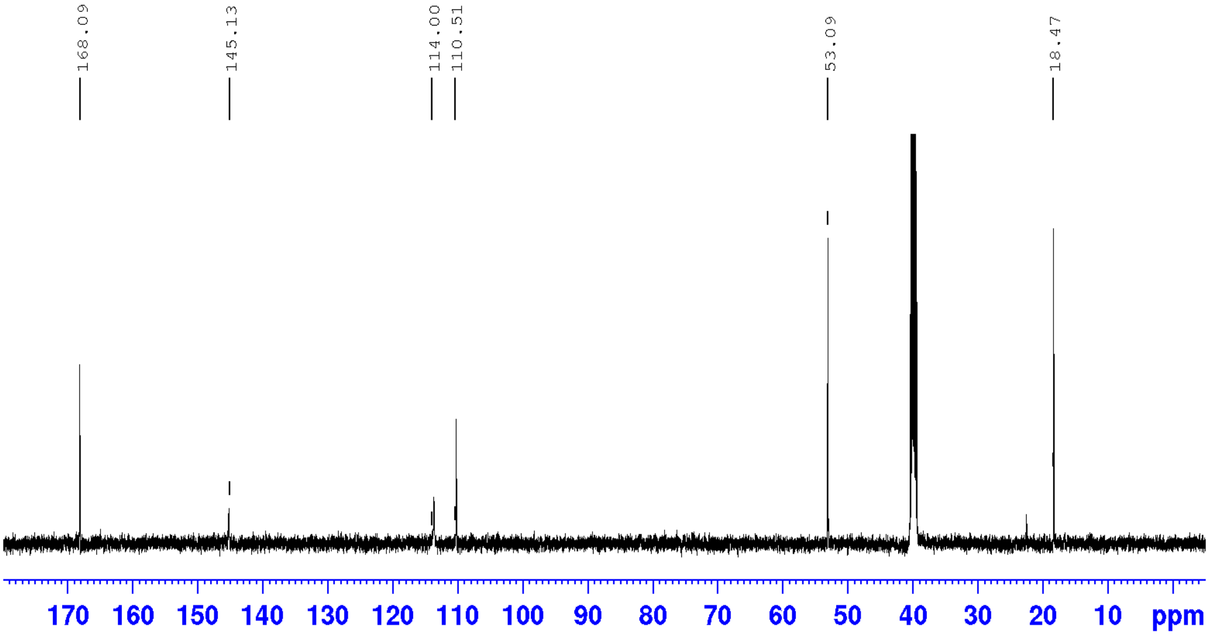
2-(4-methoxybenzyl)-6-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b]pyrazin-5-one (**32a**)



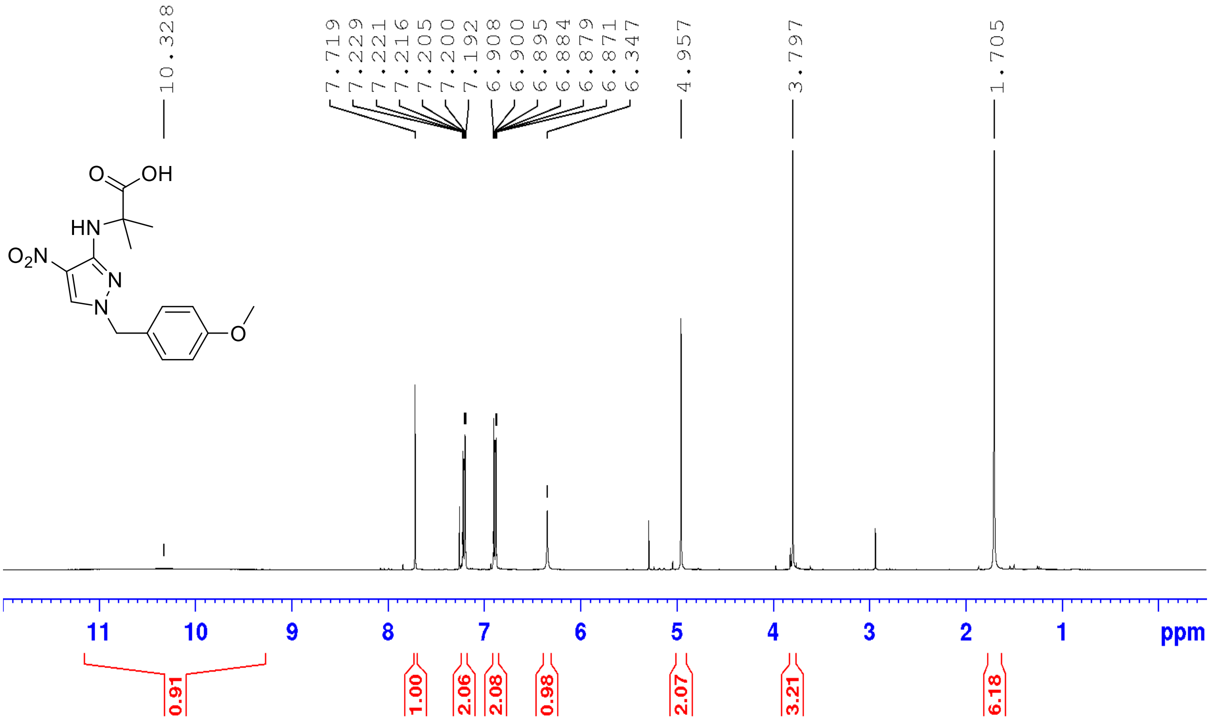


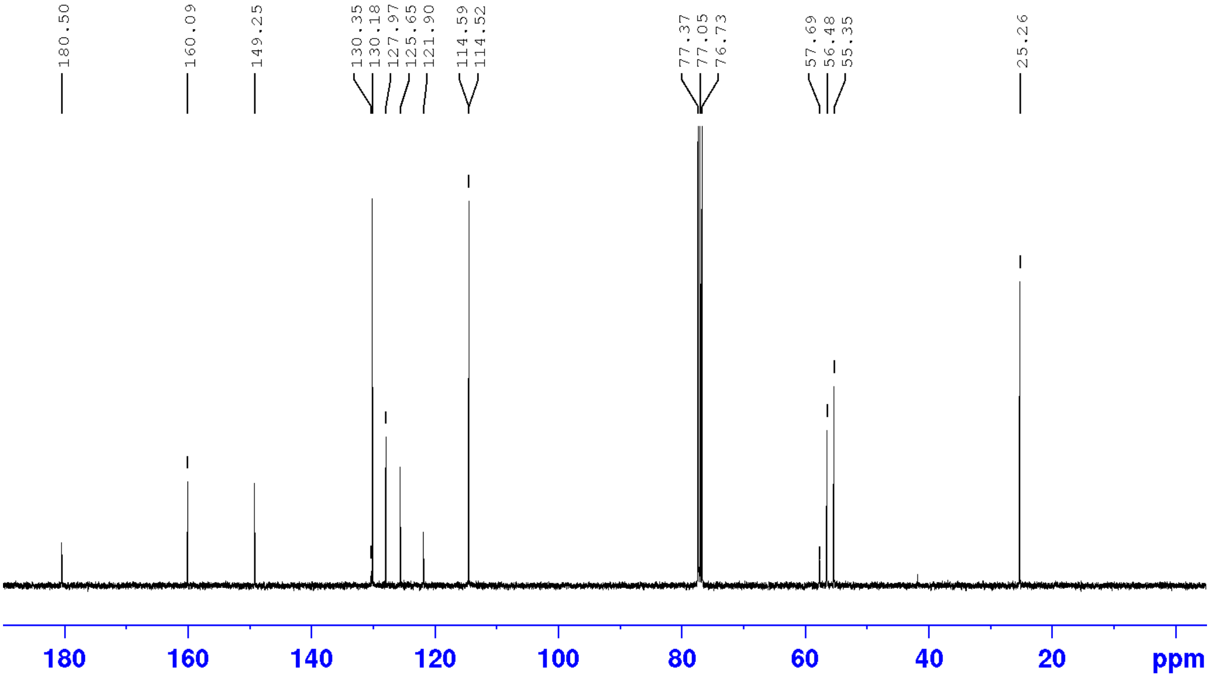
6-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b]pyrazin-5-one (**7a**)



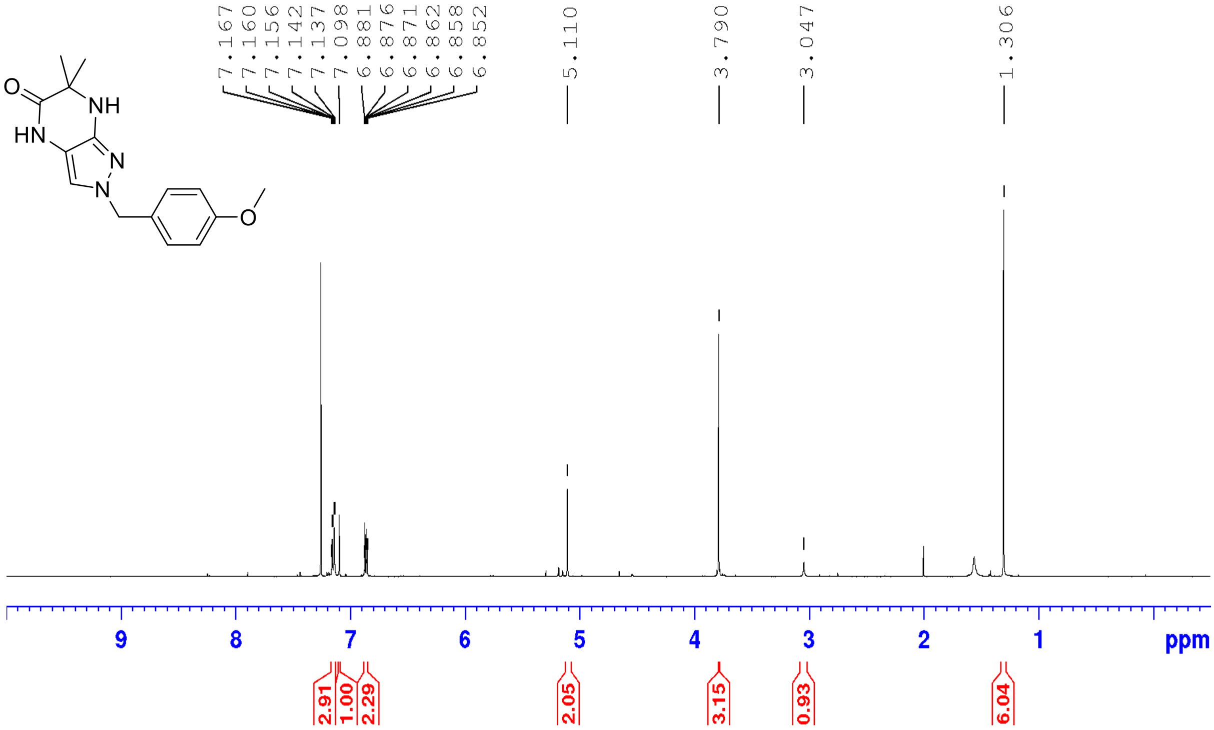


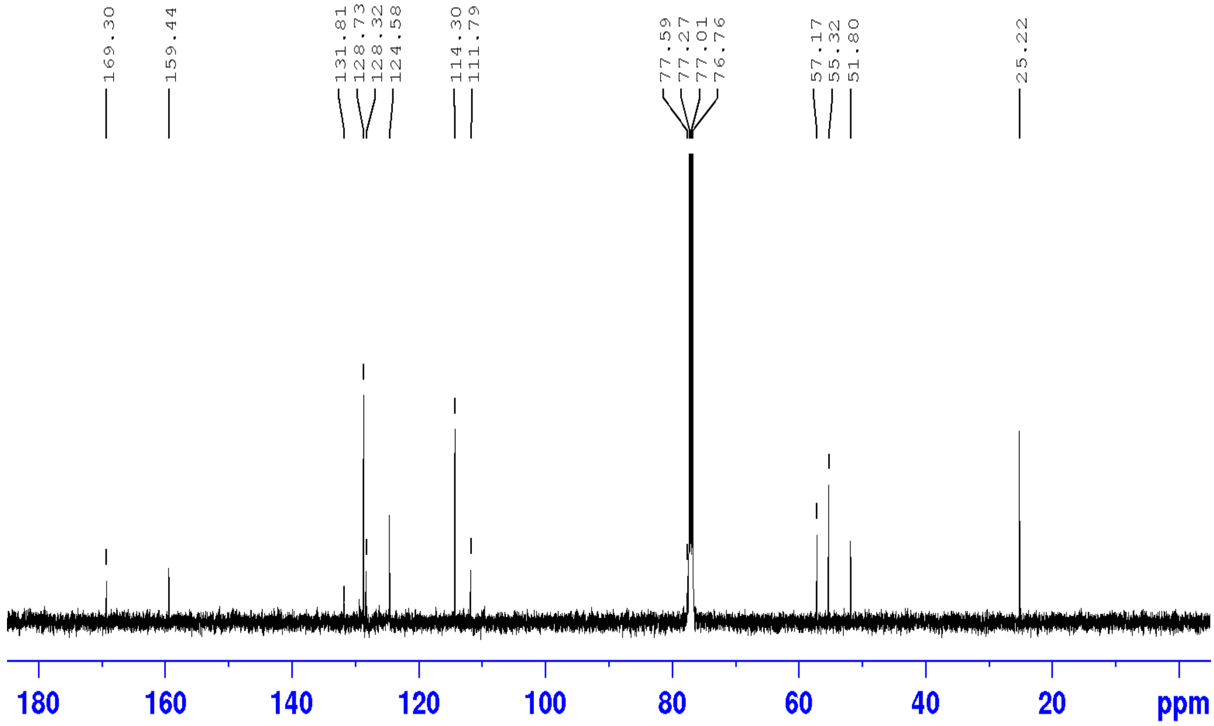
2-((1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)amino)-2-methylpropanoic acid (**31**)



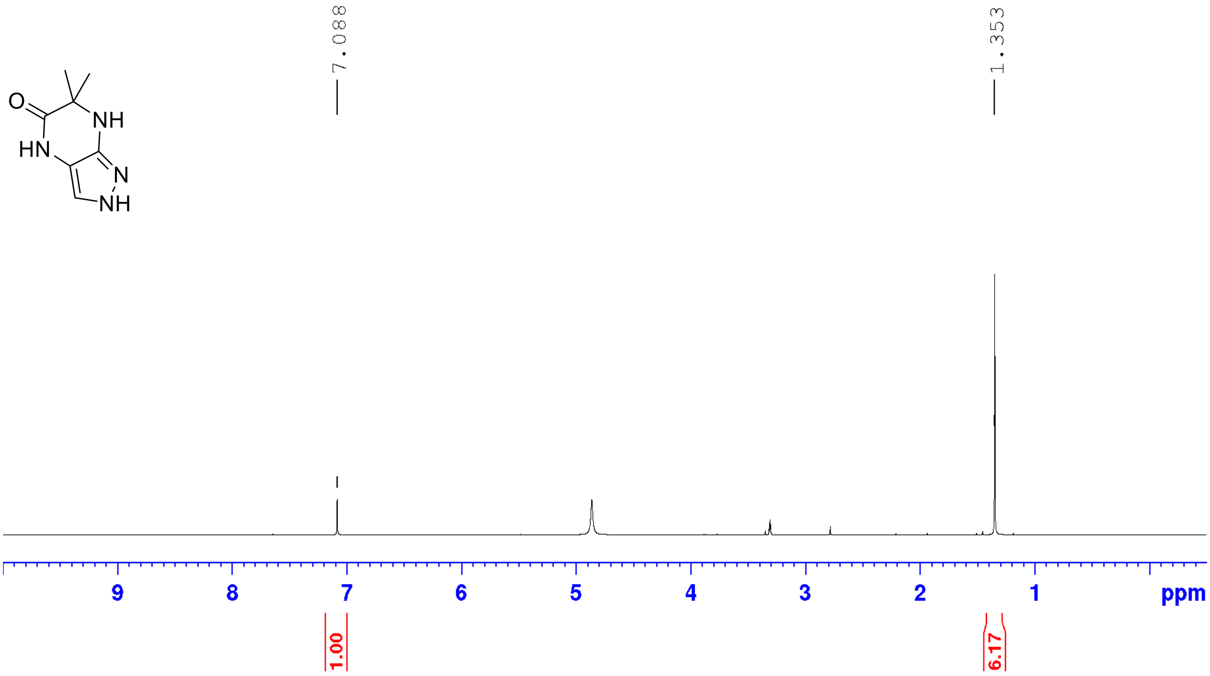


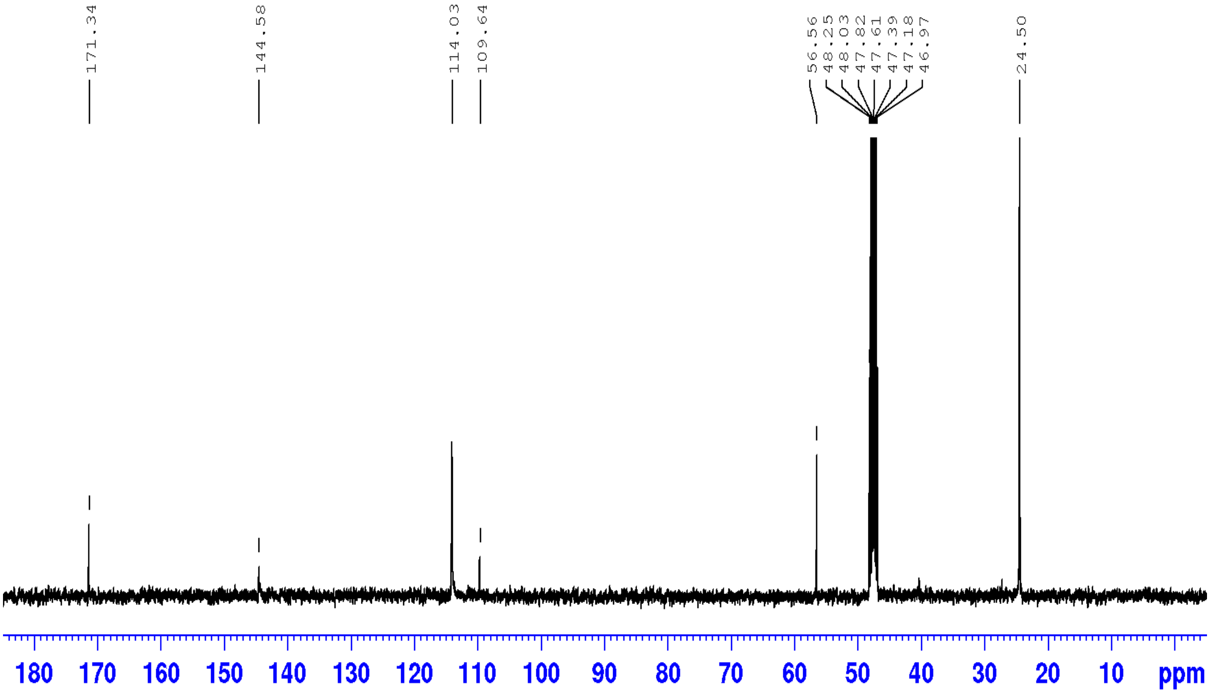
2-(4-methoxybenzyl)-6,6-dimethyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b]pyrazin-5-one (**32**)



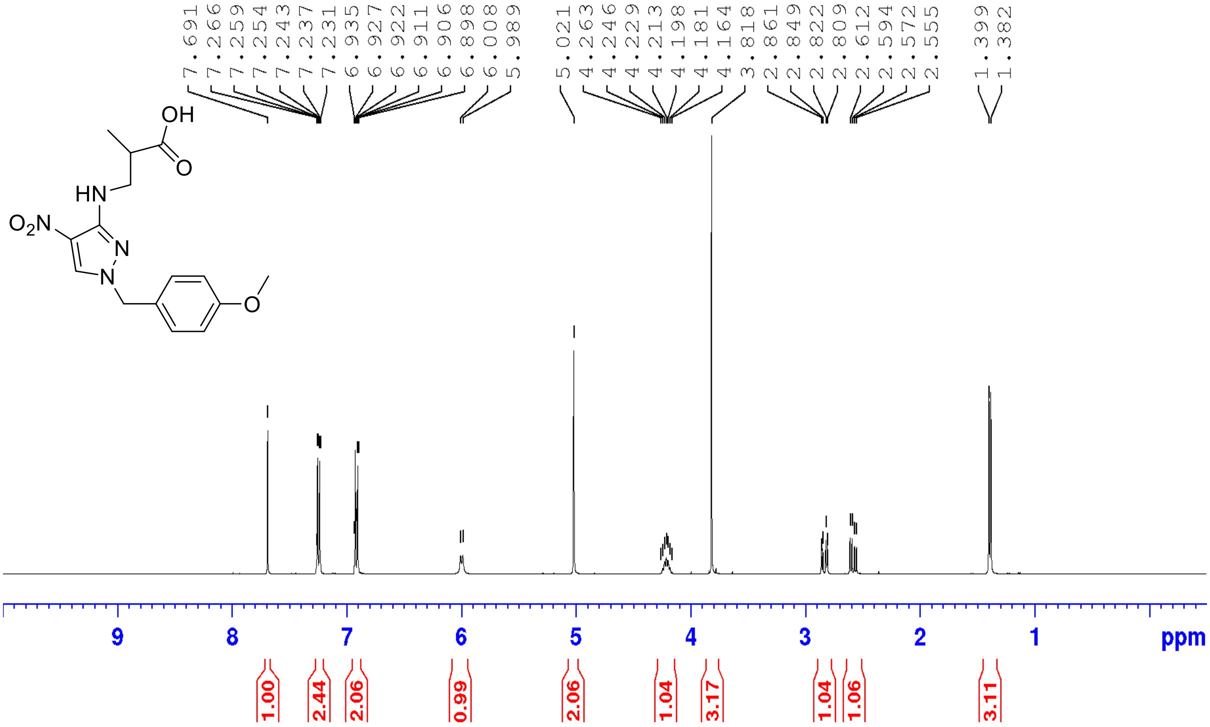


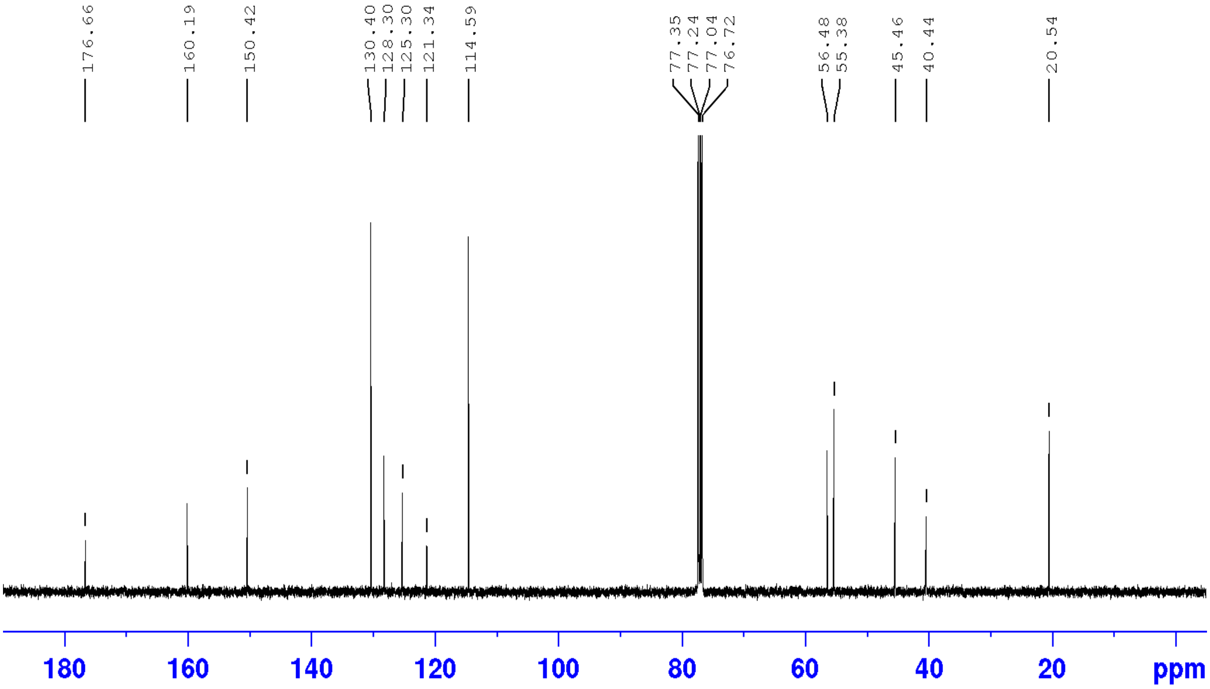
6,6-dimethyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b]pyrazin-5-one (**7**)



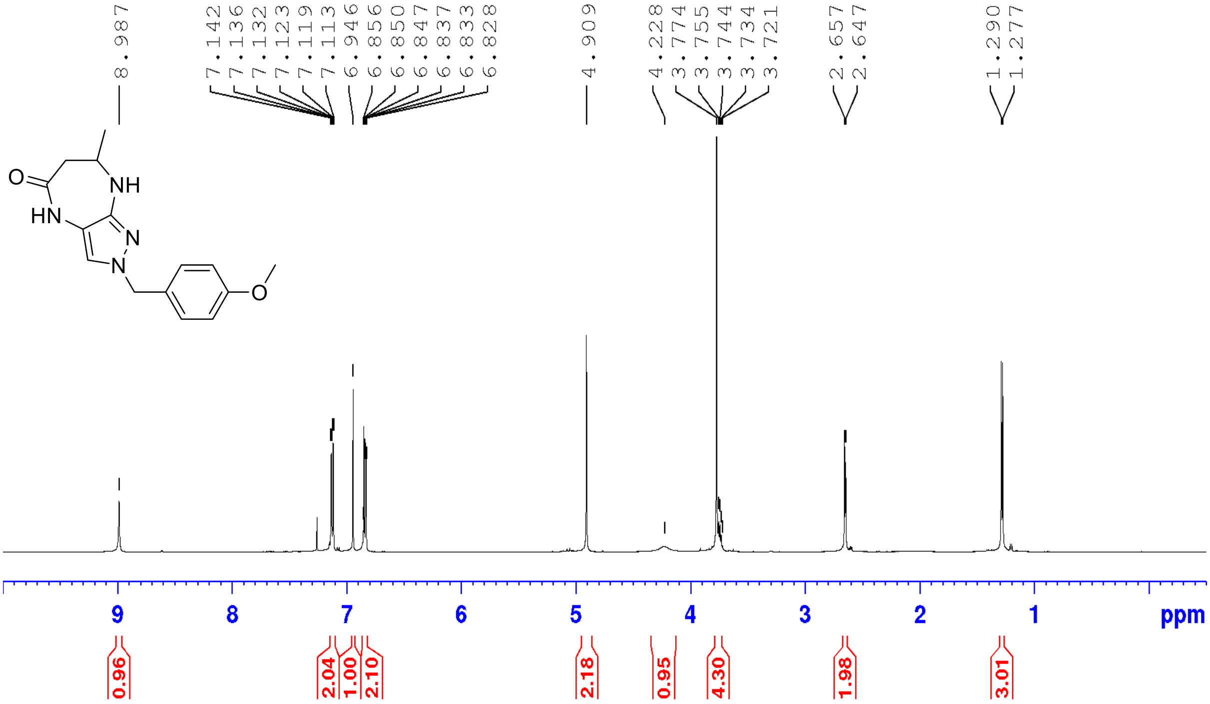


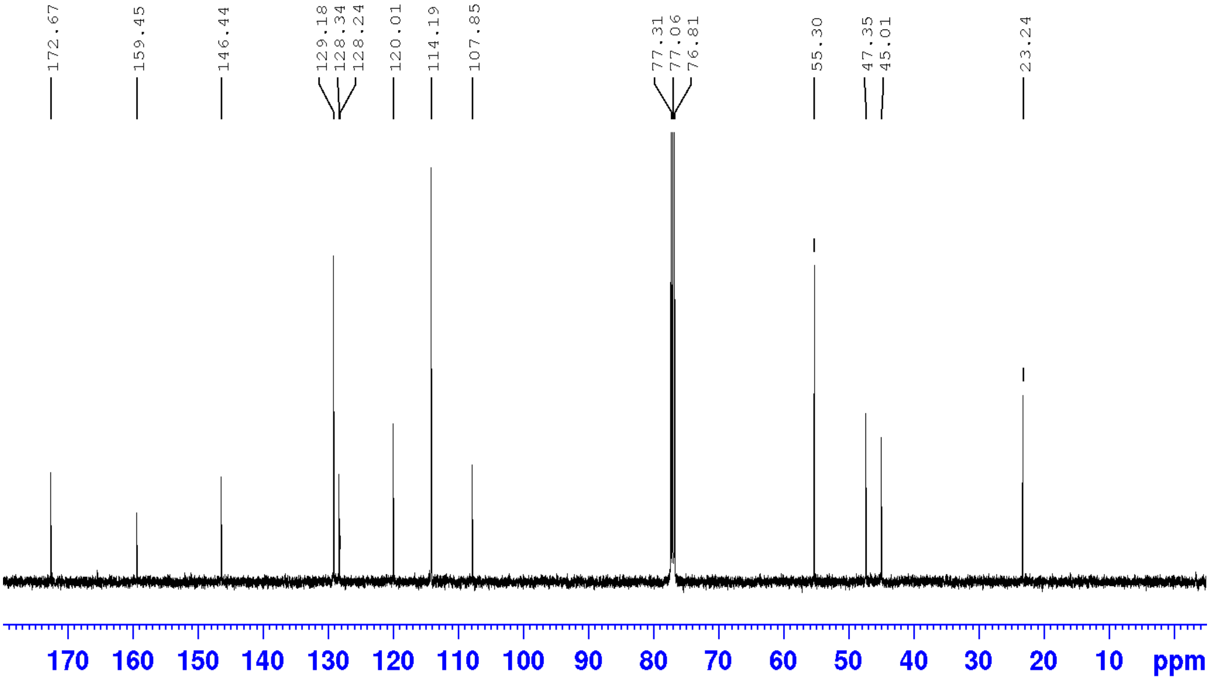
3-((1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)amino)-2-methylpropanoic acid (**33**)



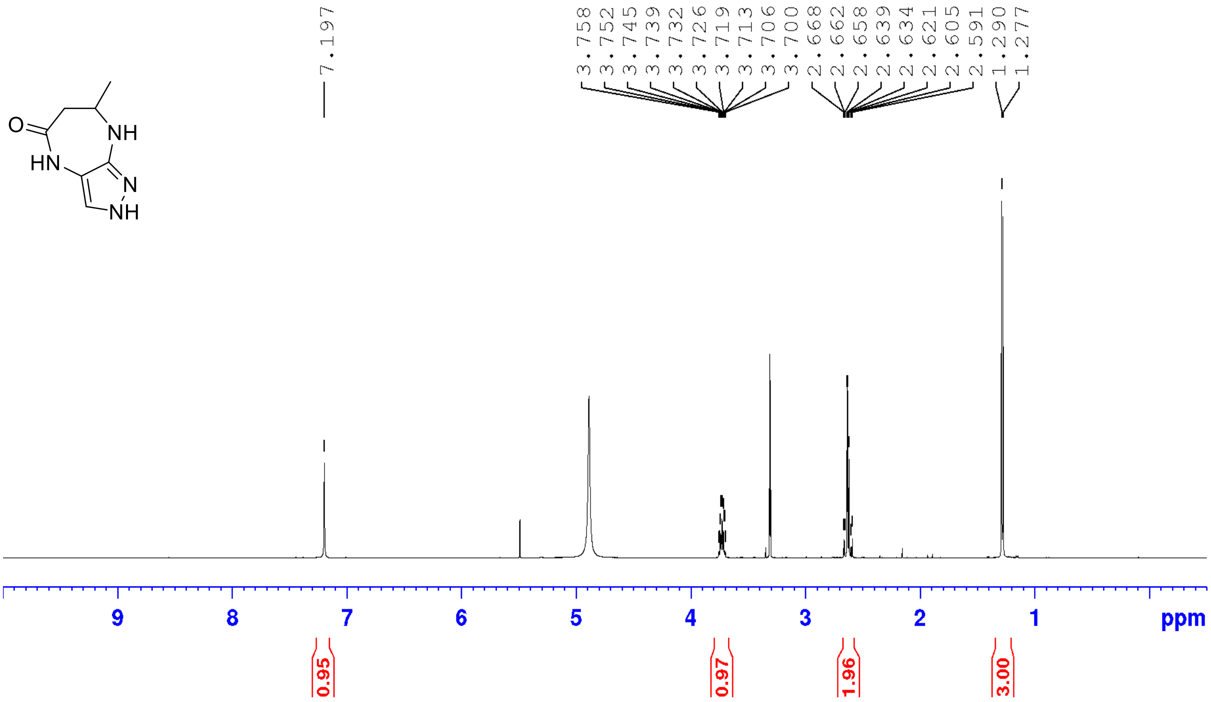


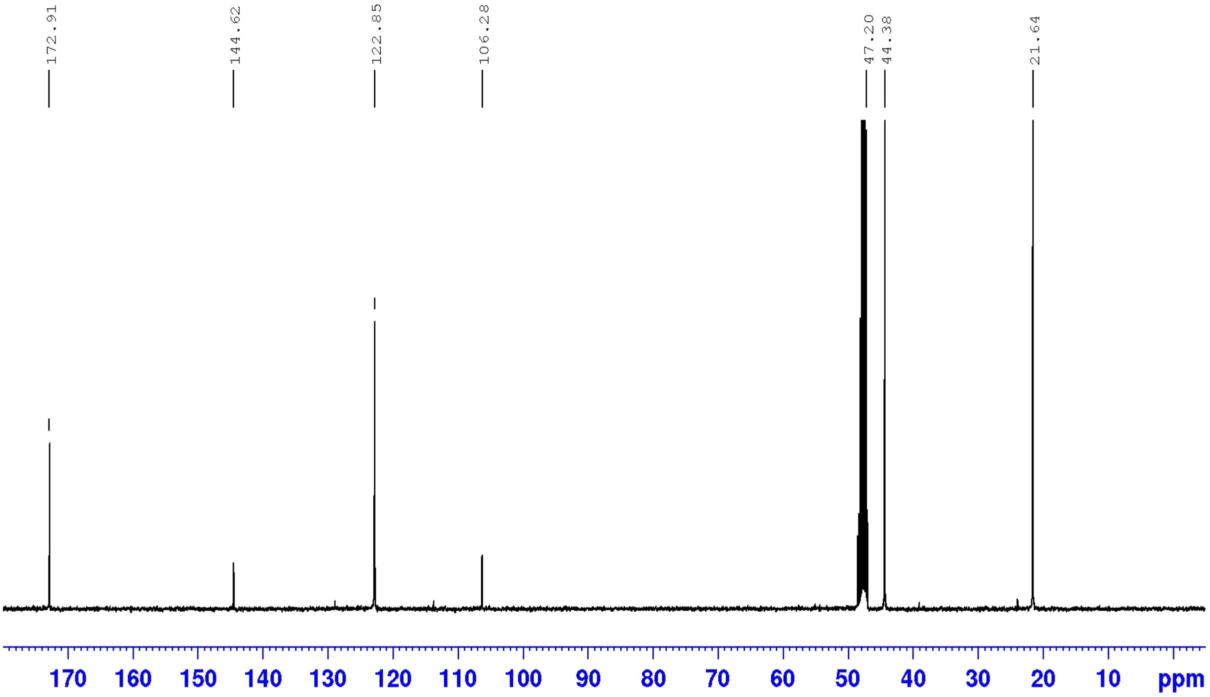
2-(4-methoxybenzyl)-7-methyl-2,6,7,8-tetrahydropyrazolo[3,4-b][1,4]diazepin-5(4H)-one (**34**)



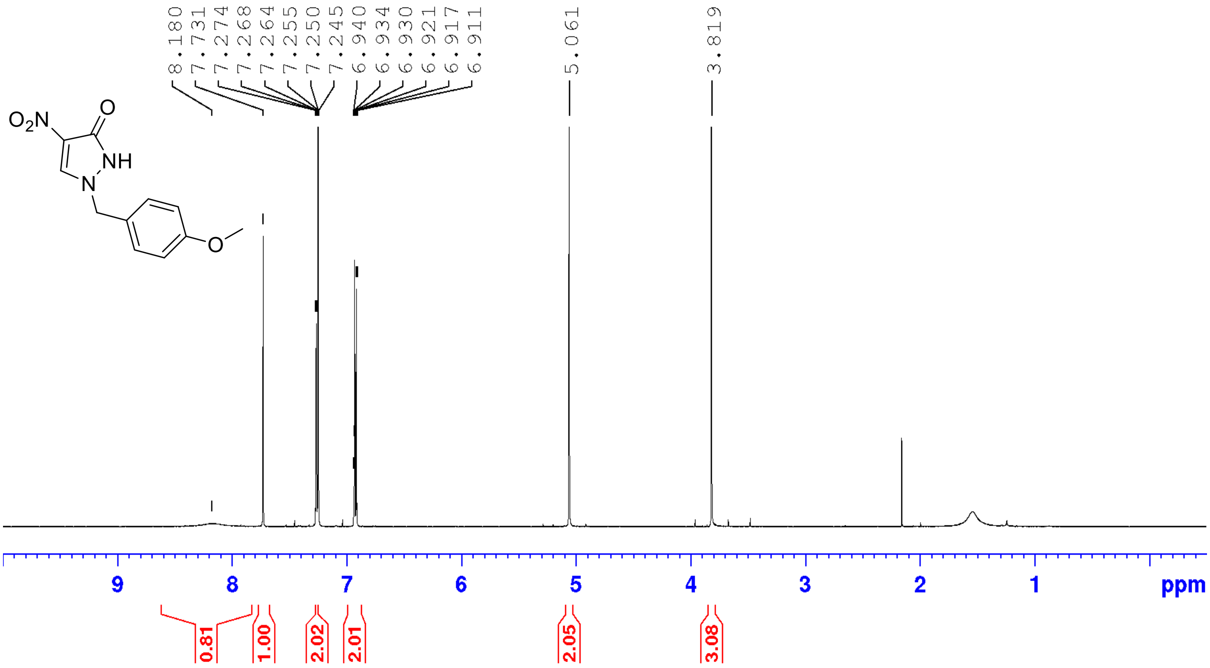


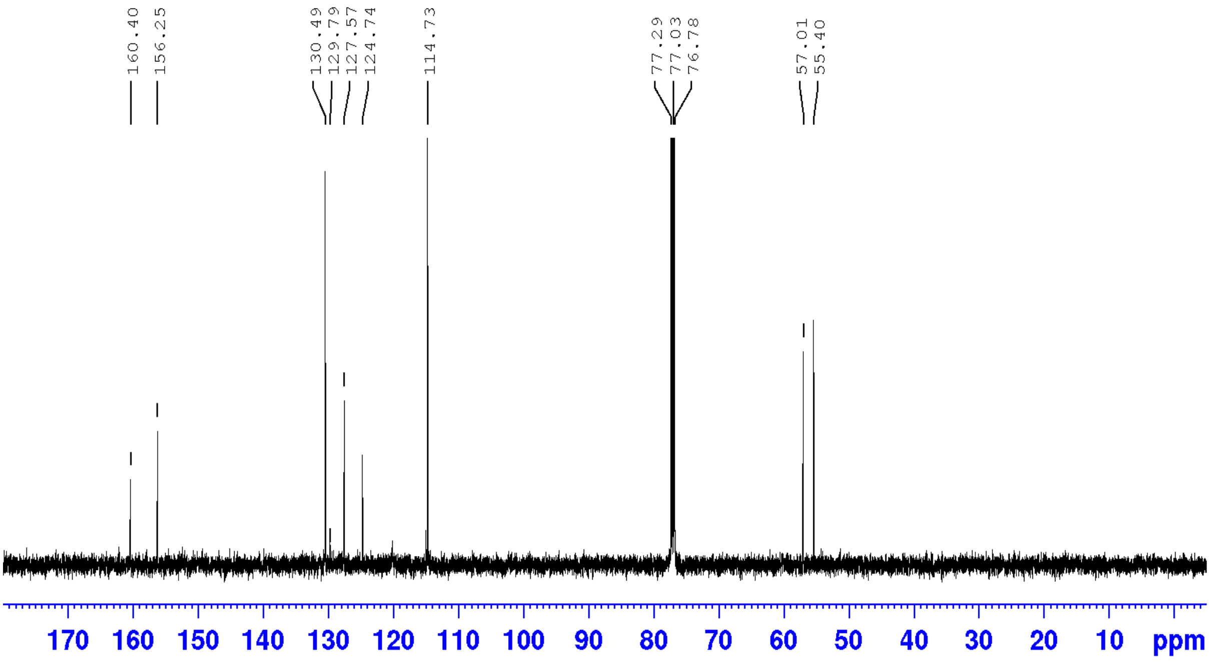
7-methyl-2,6,7,8-tetrahydropyrazolo[3,4-b][1,4]diazepin-5(4H)-one (**8**)



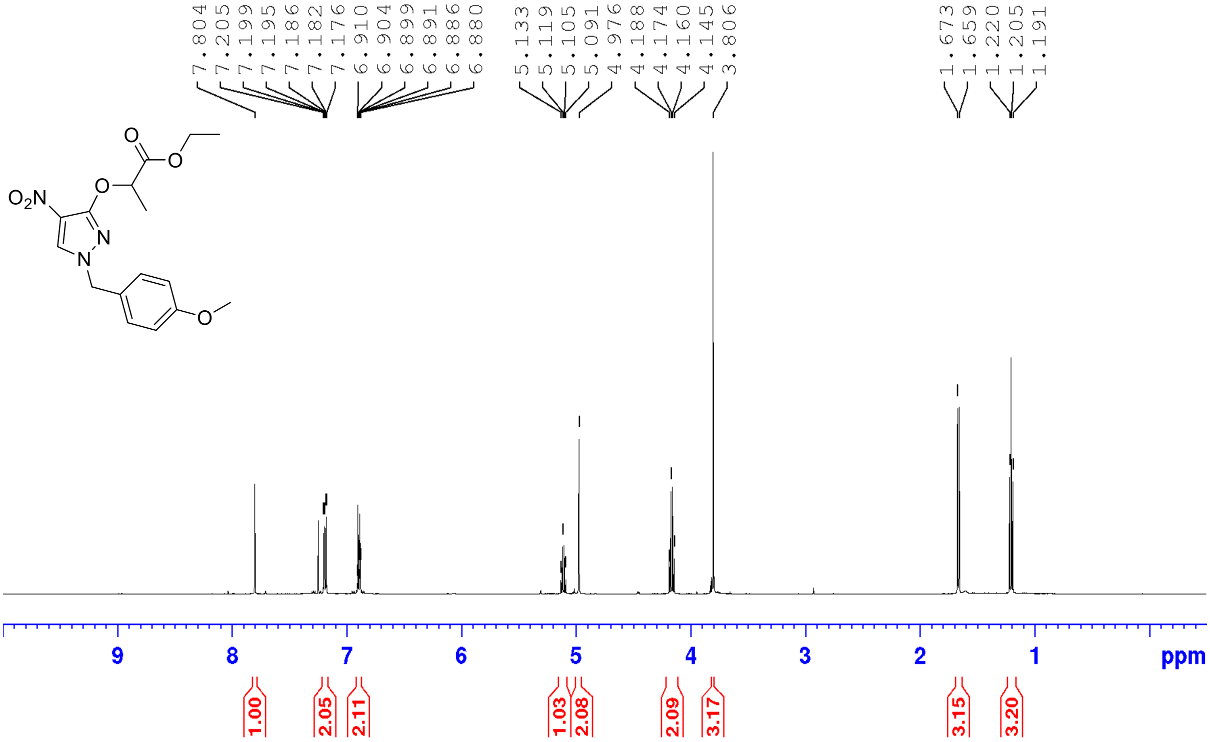


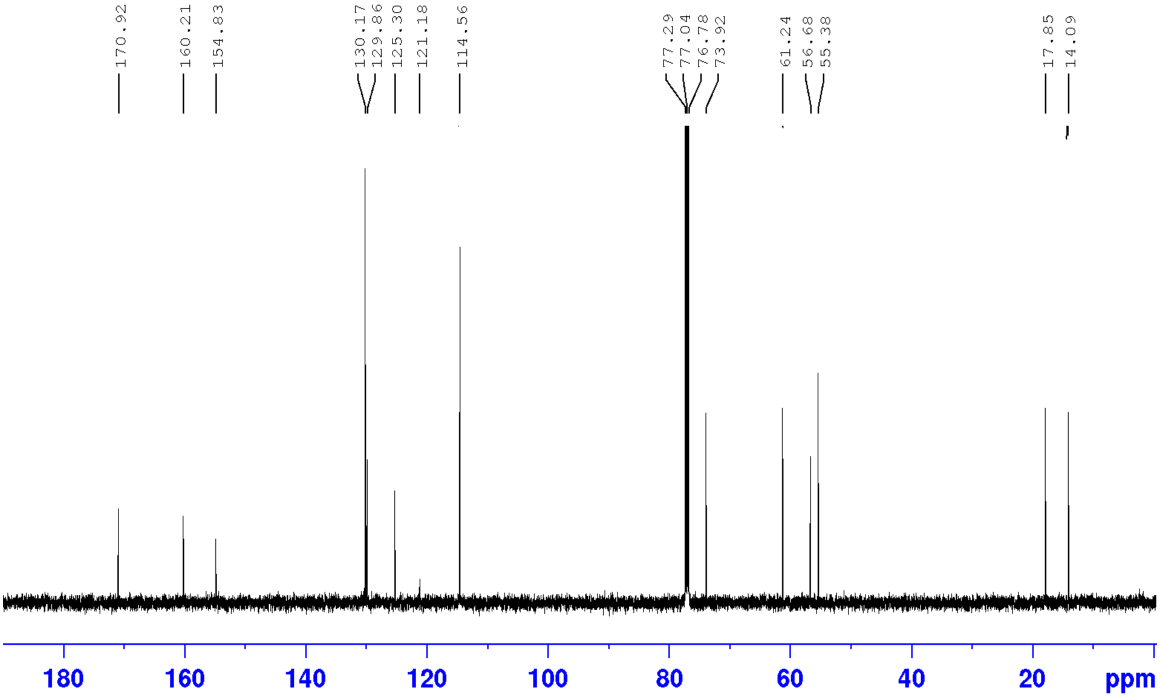
1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-ol (**35**)



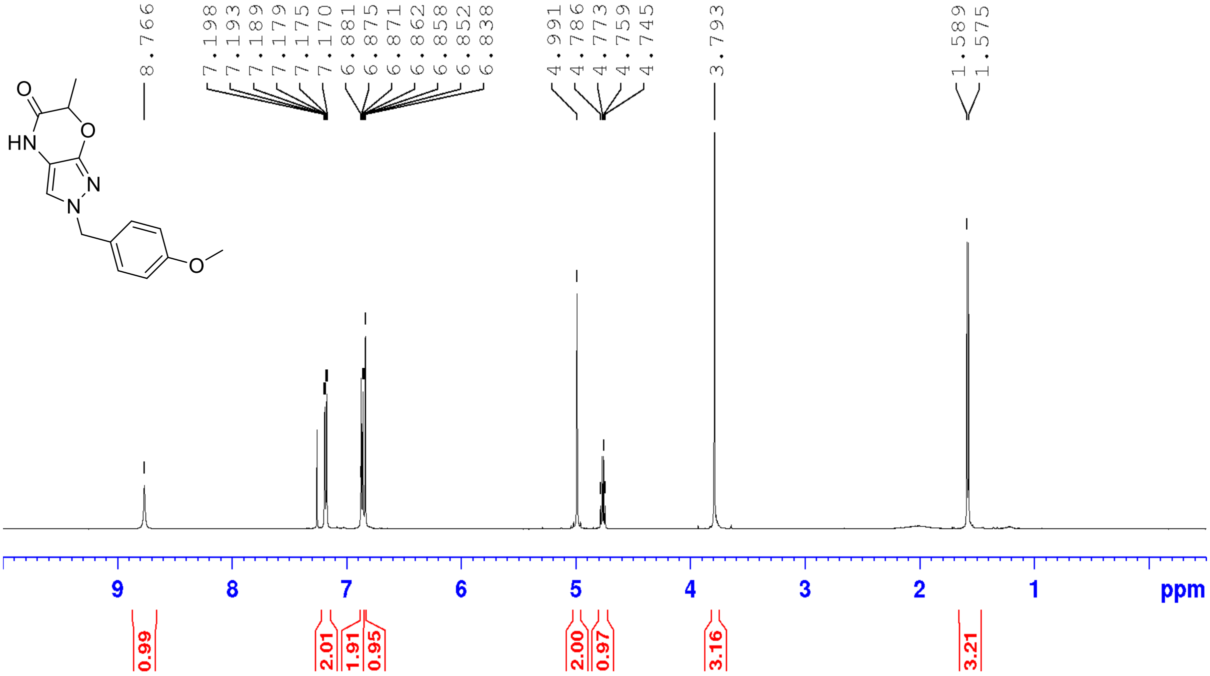


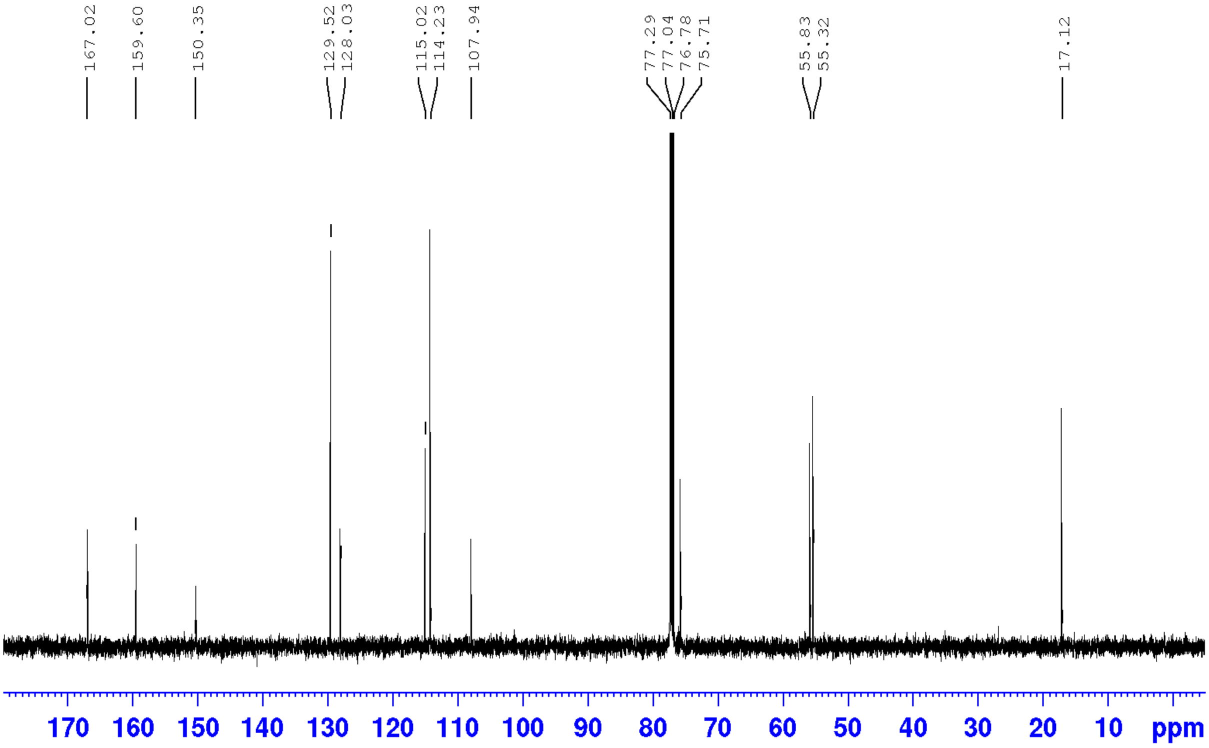
ethyl 2-((1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)oxy)propanoate (**36**)



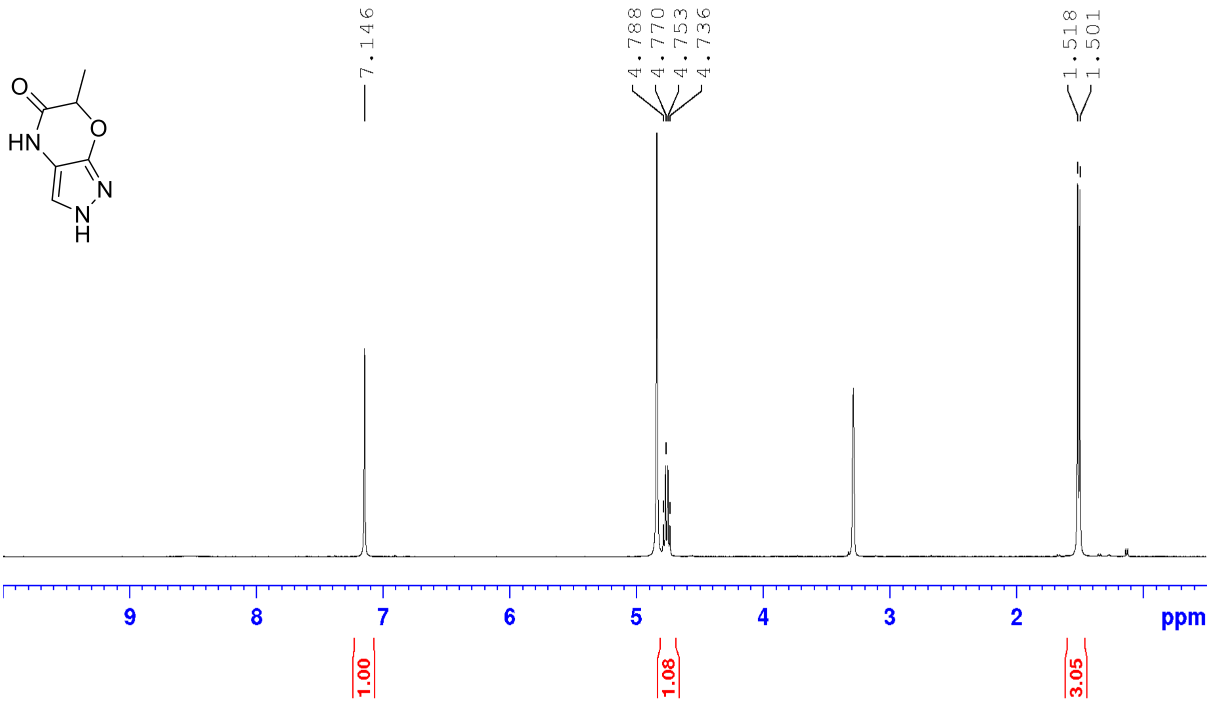


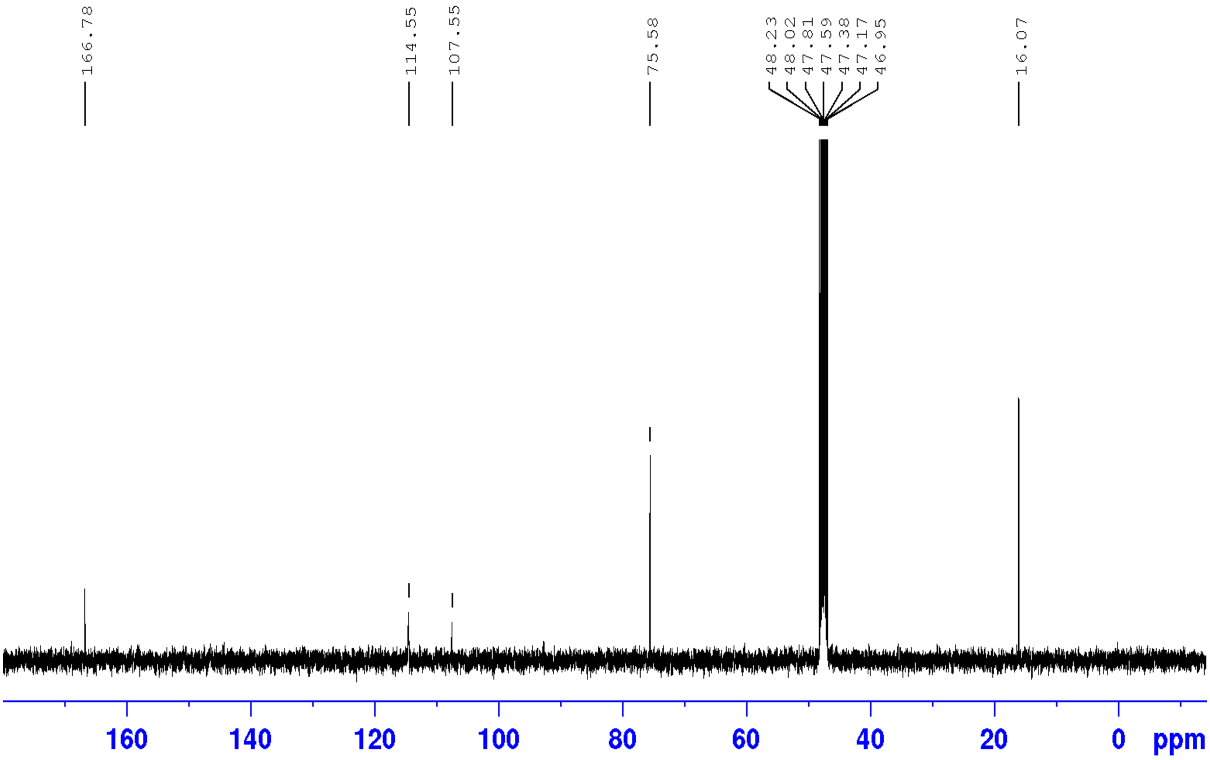
2-(4-methoxybenzyl)-6-methyl-2,4-dihydropyrazolo[3,4-b][1,4]oxazin-5(6H)-one (**37**)



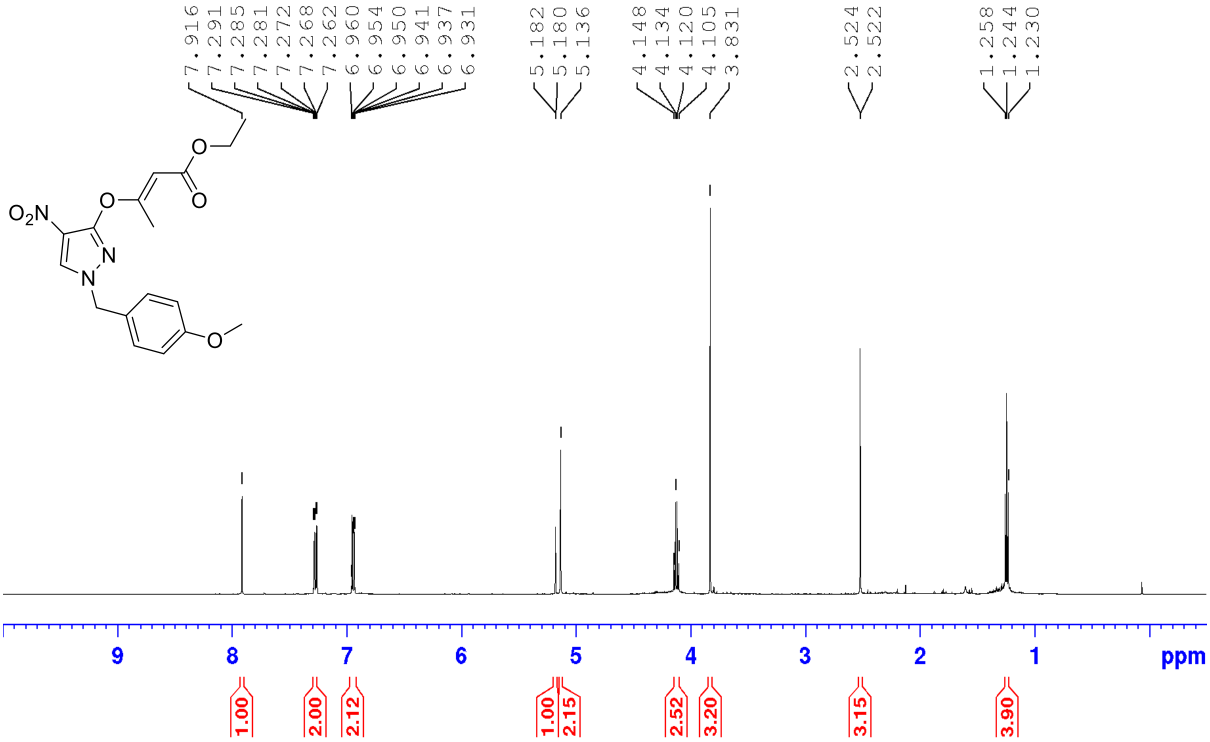


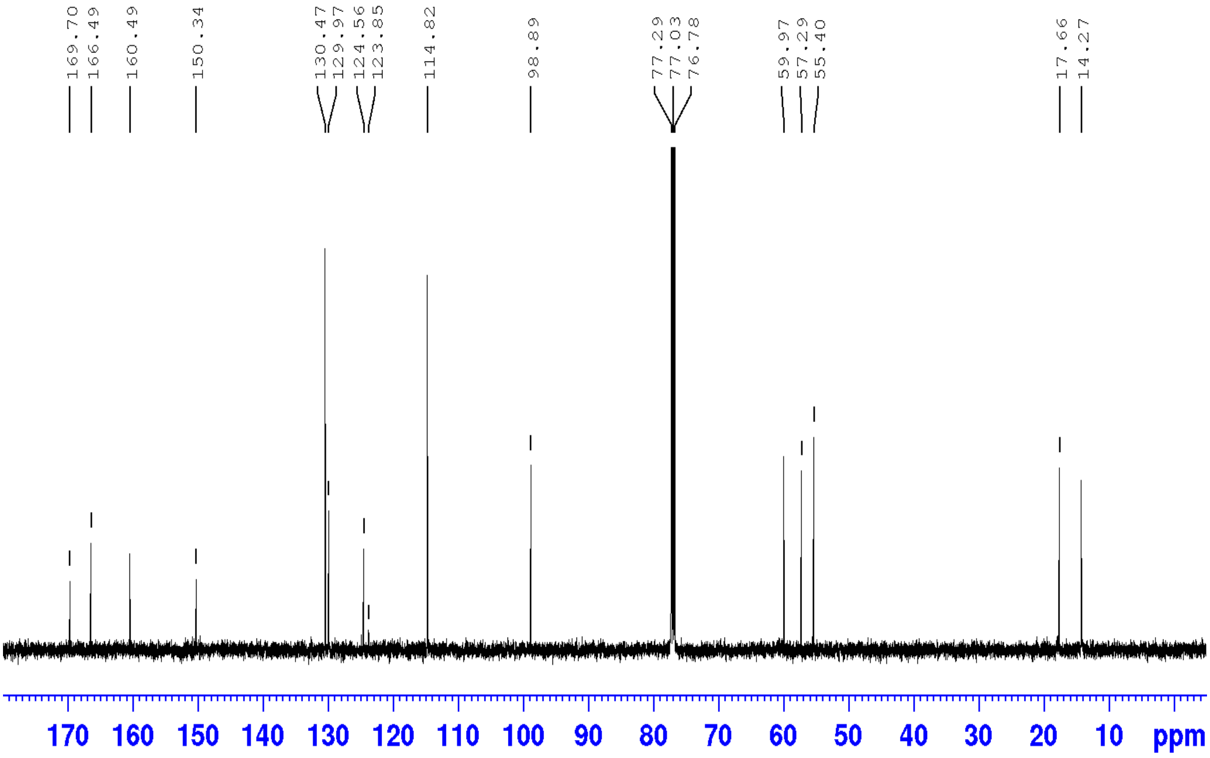
6-methyl-2,4-dihydropyrazolo[3,4-b][1,4]oxazin-5(6H)-one (**9**)



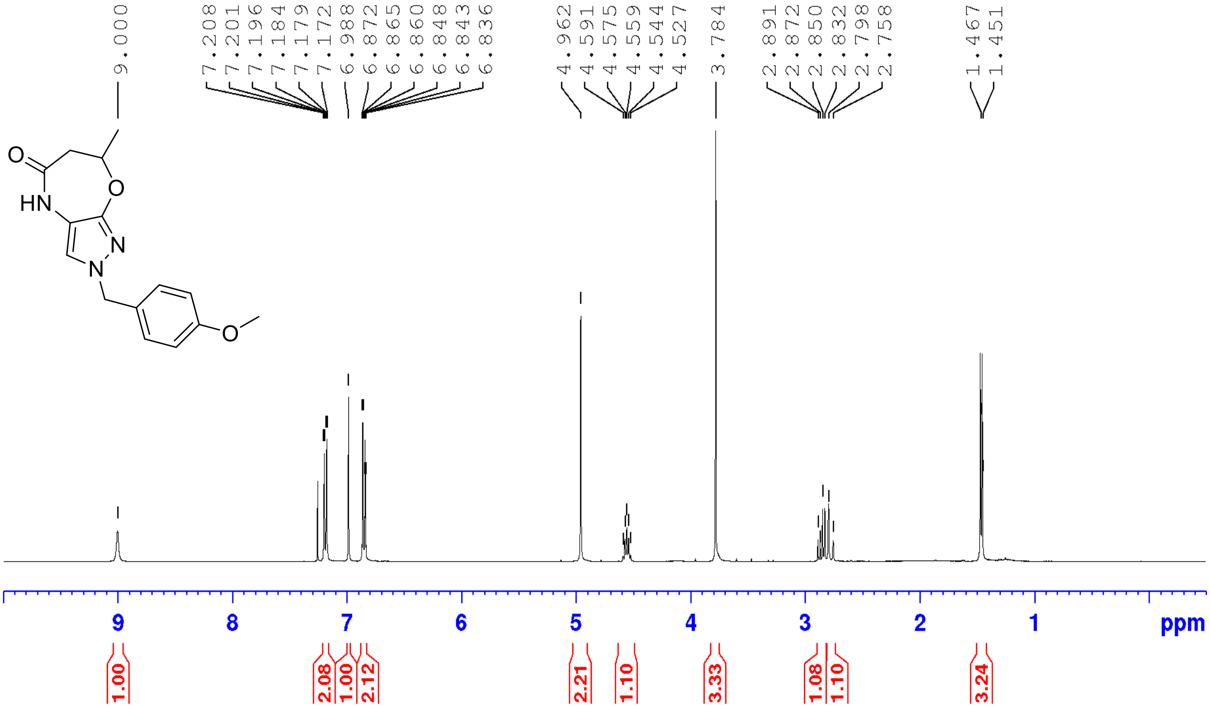


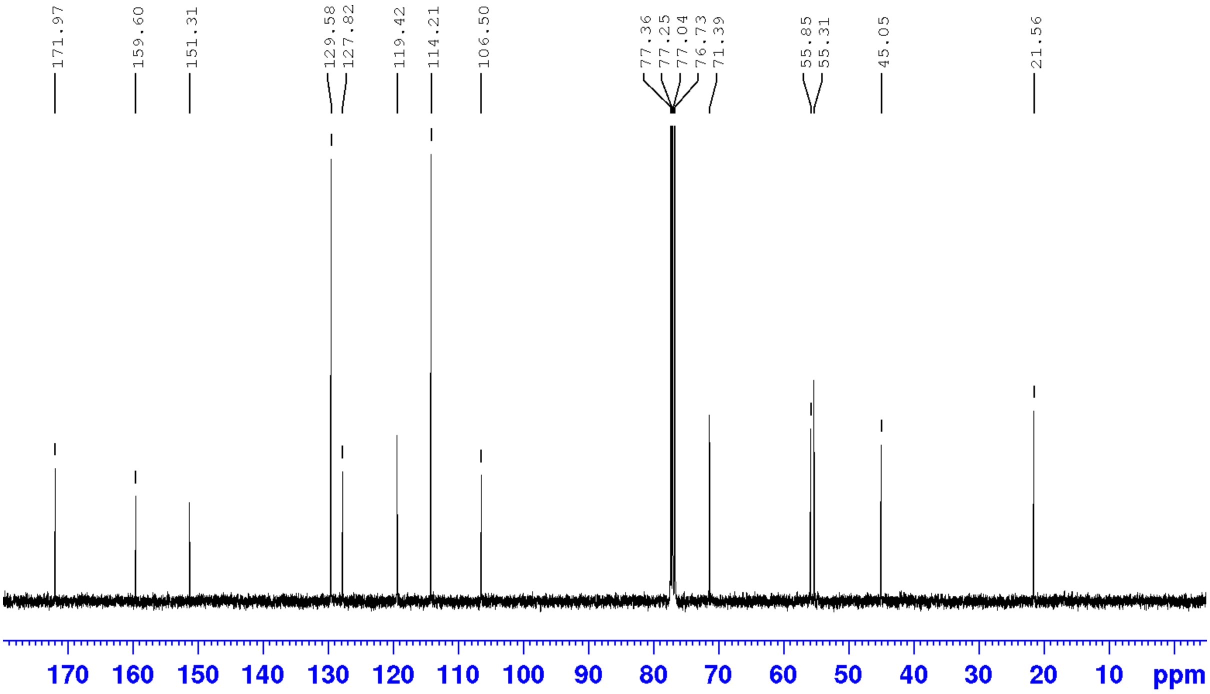
ethyl (E)-3-((1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)oxy)but-2-enoate (**38**)



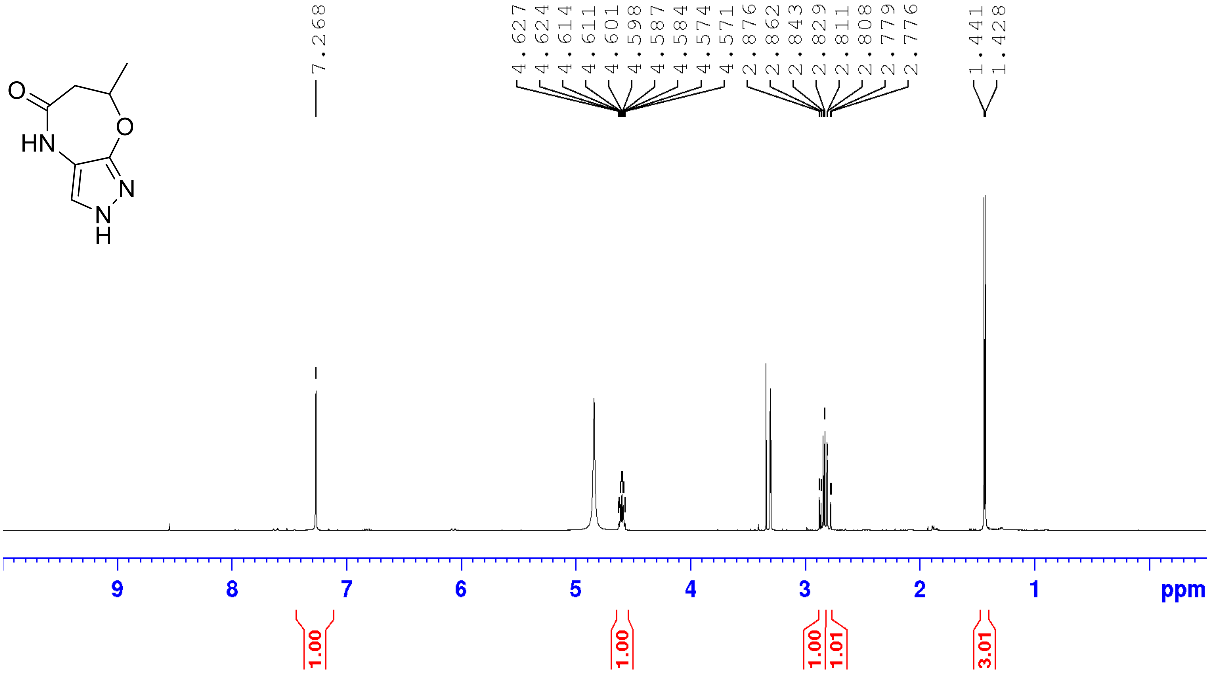


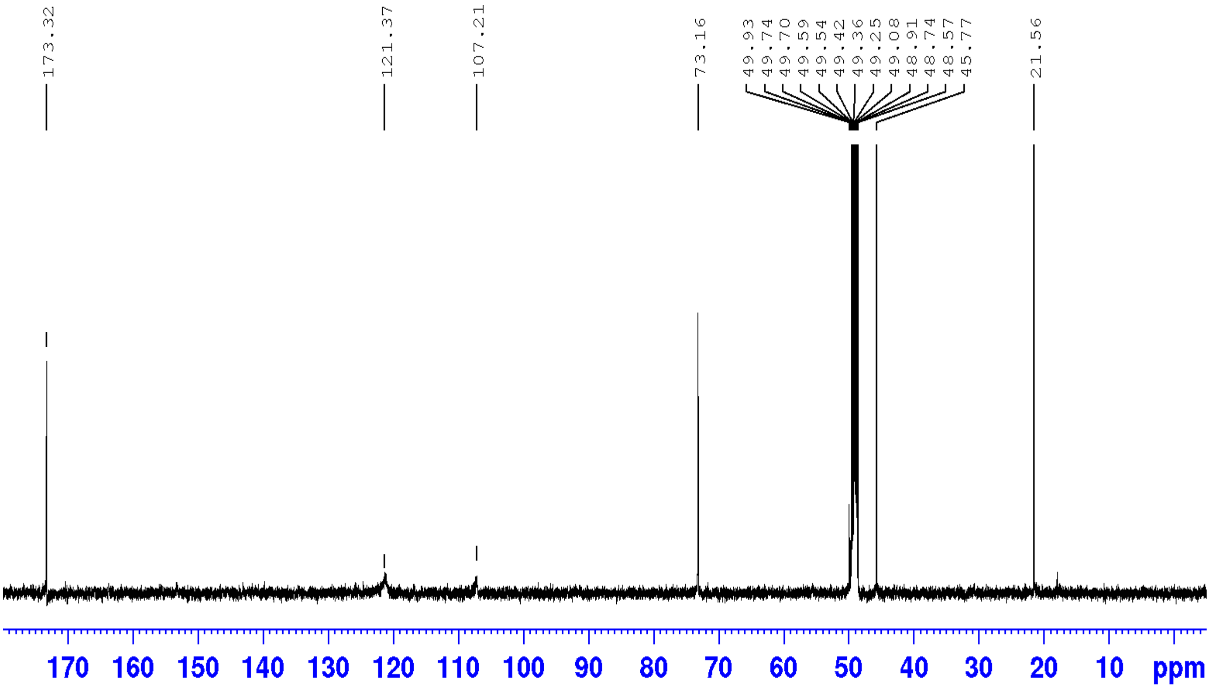
2-(4-methoxybenzyl)-7-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b][1,4]oxazepin-5-one (**39**)



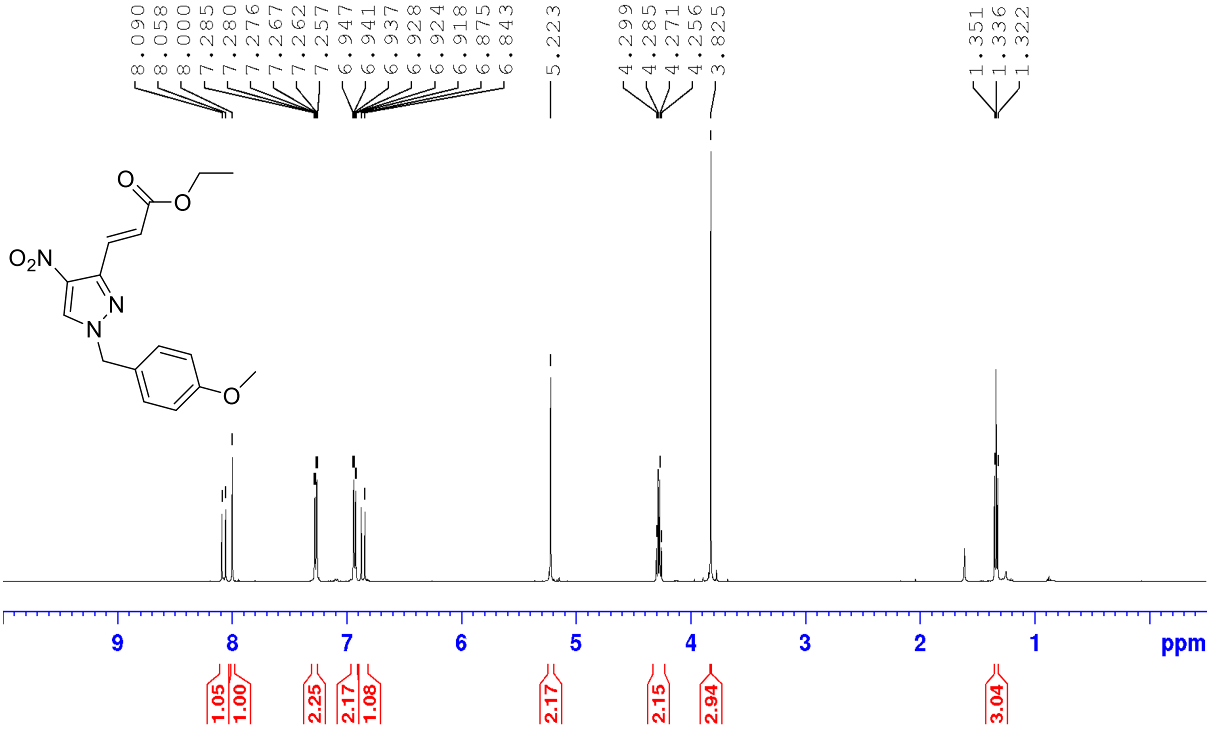


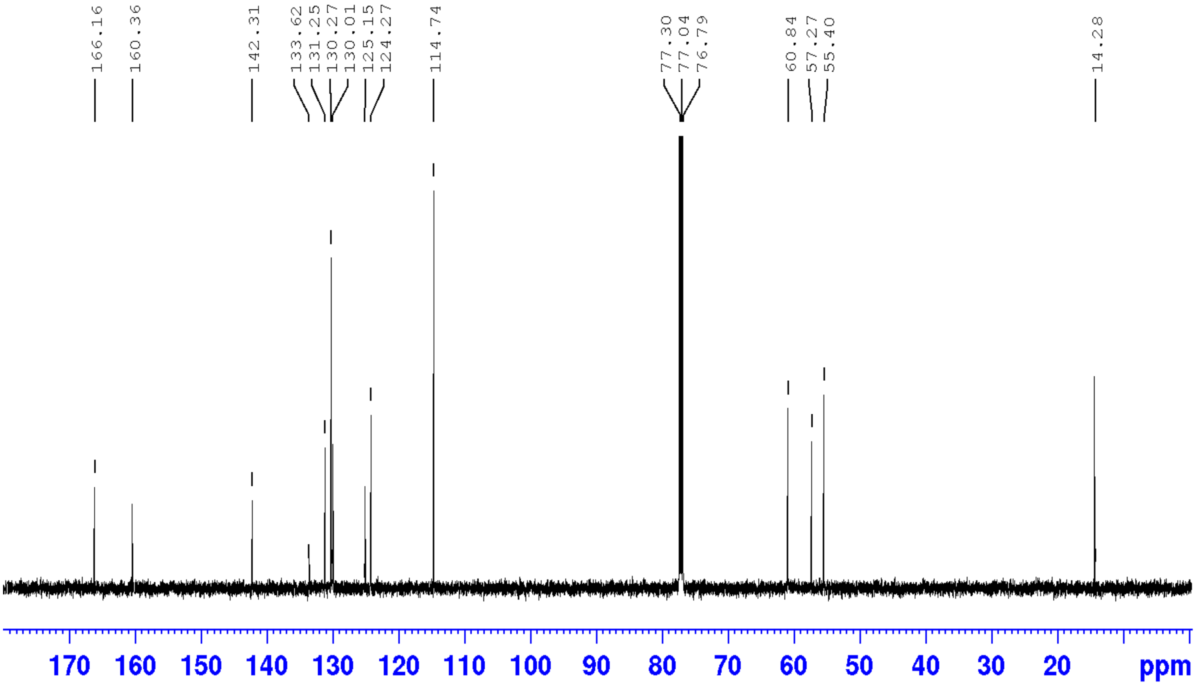
7-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-b][1,4]oxazepin-5-one (**10**)



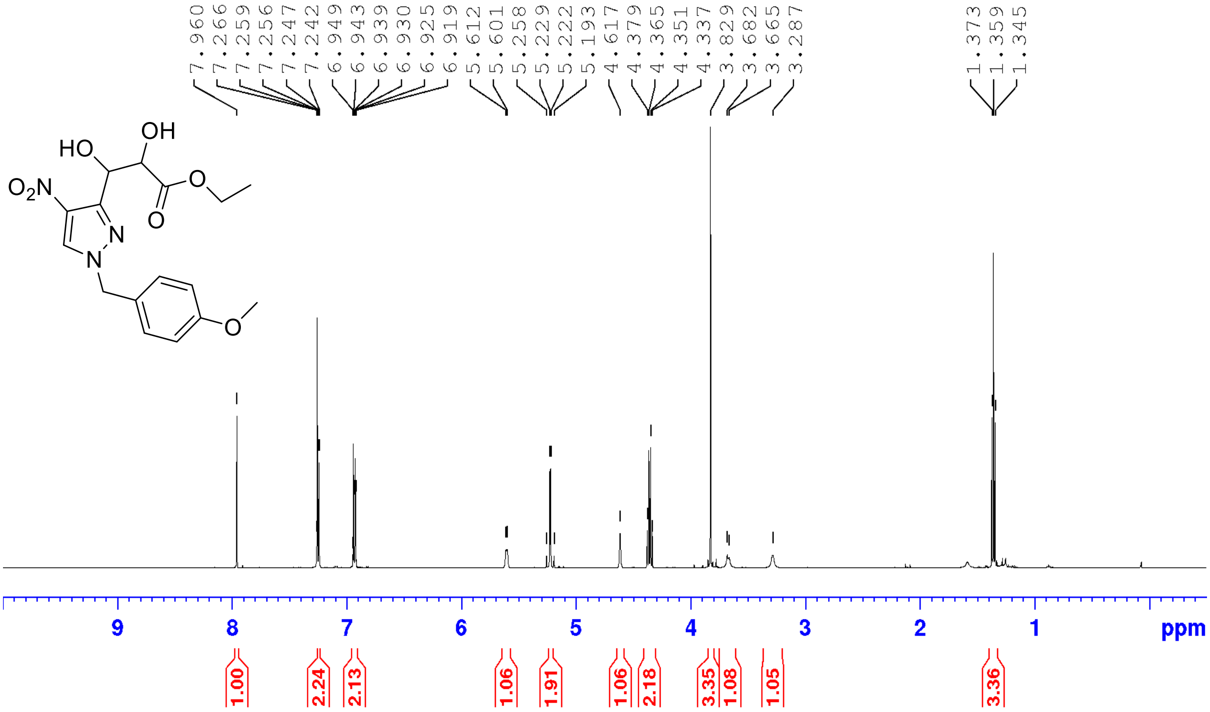


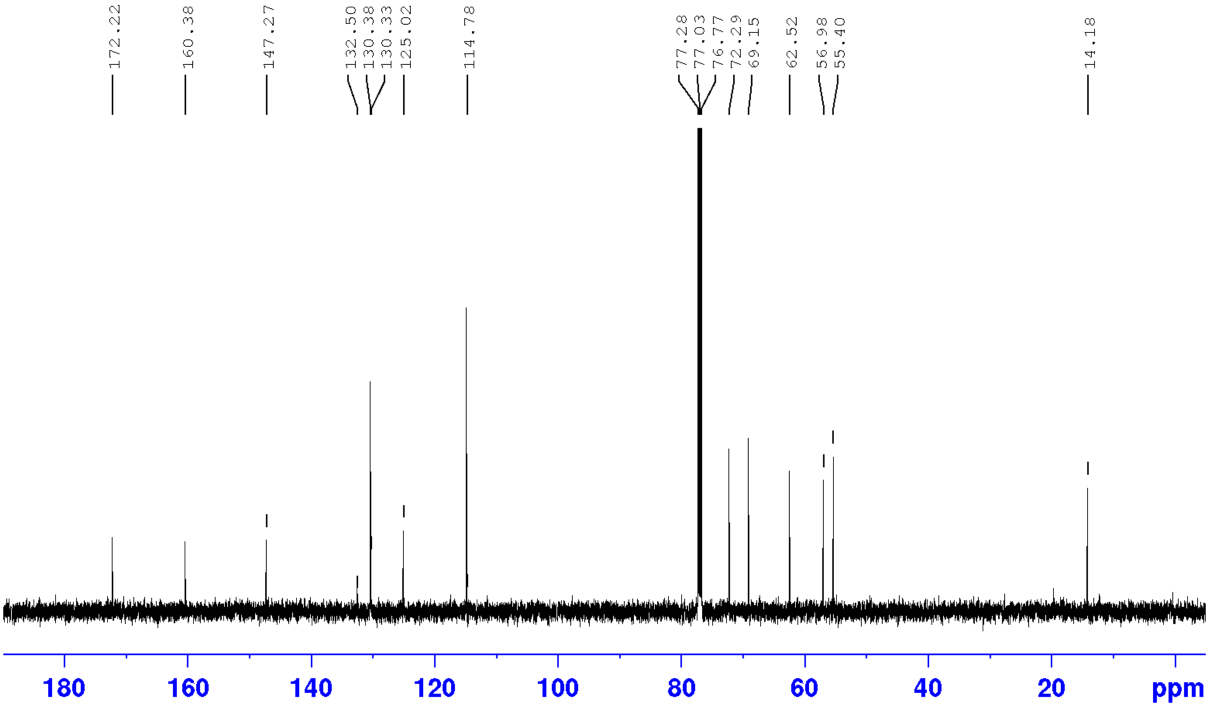
ethyl (E)-3-(1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)acrylate (**40**)



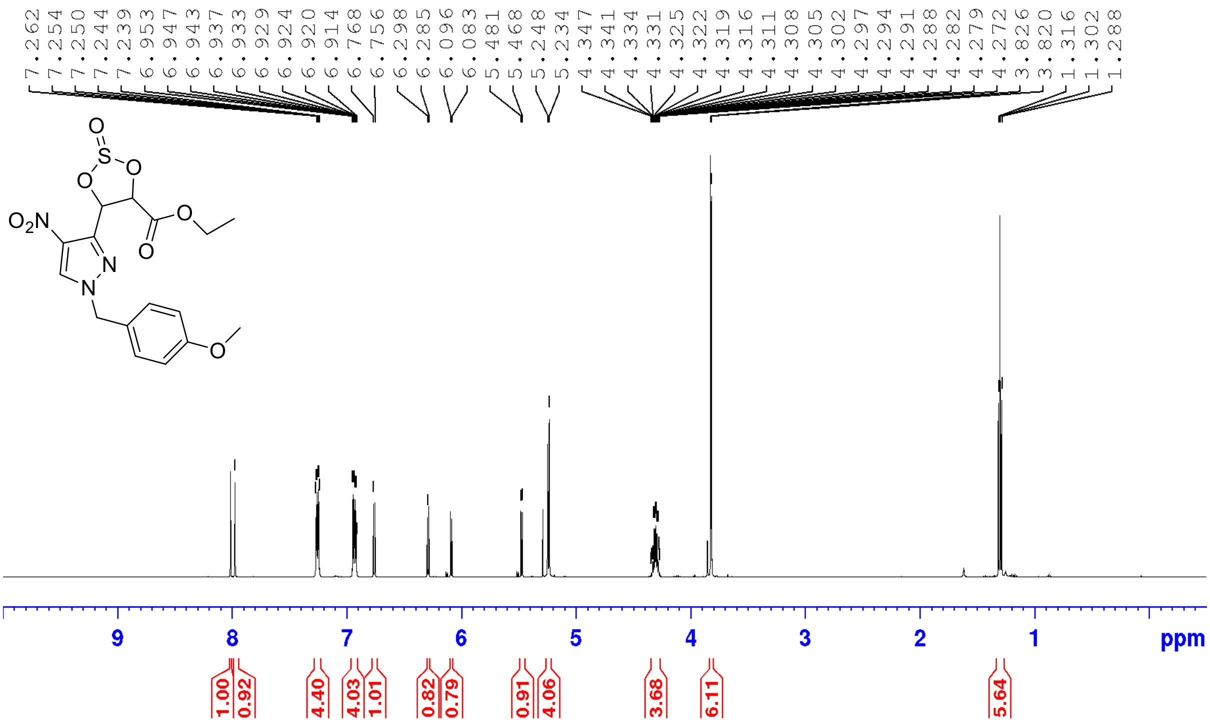


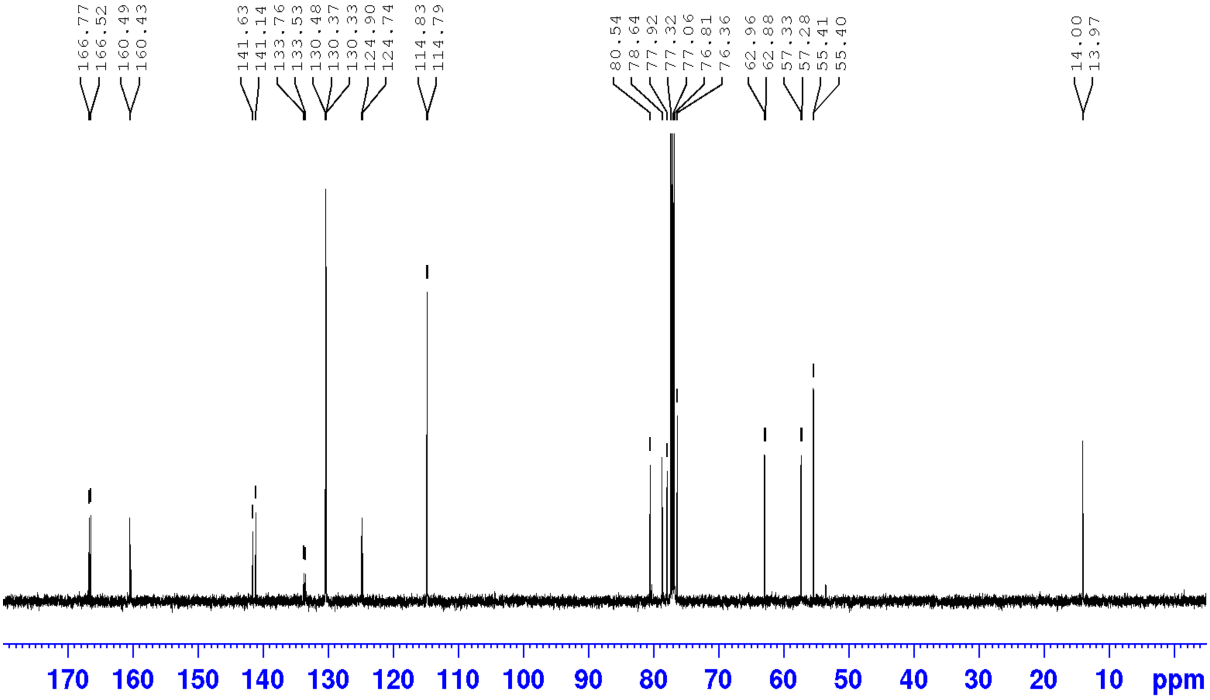
ethyl 2,3-dihydroxy-3-(1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)propanoate (**41**)



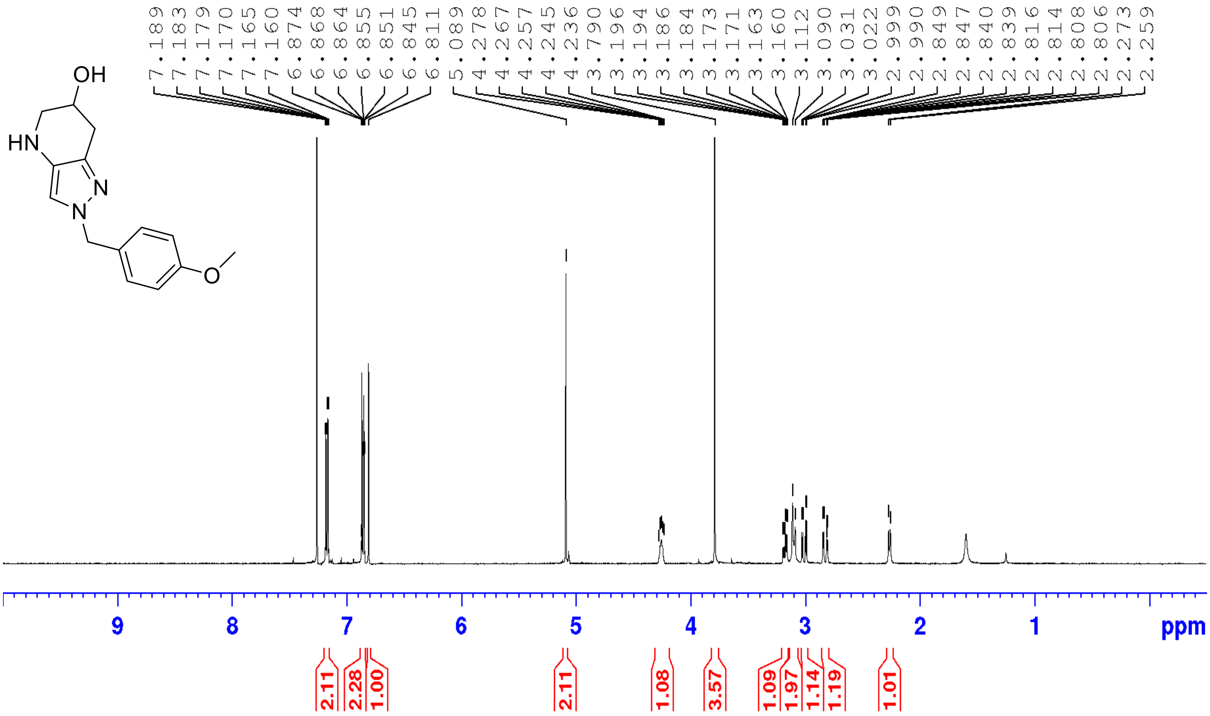


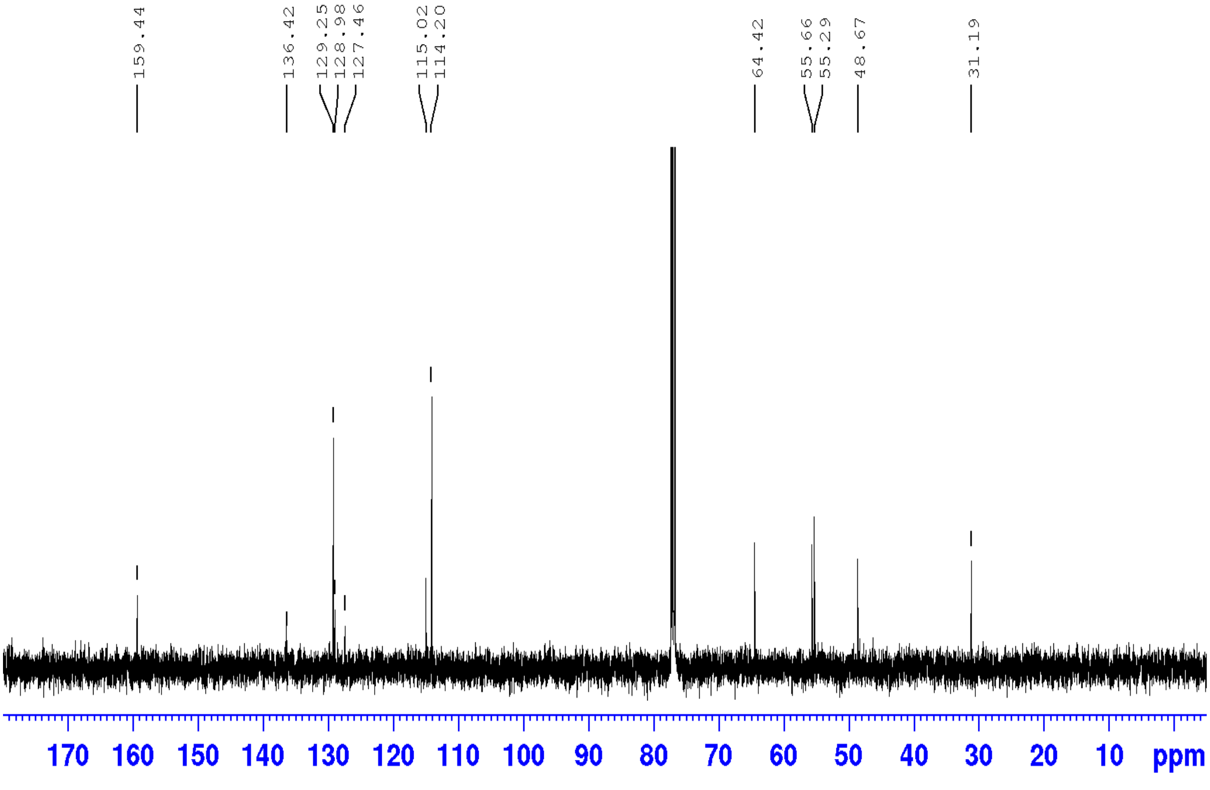
ethyl 5-(1-(4-methoxybenzyl)-4-nitro-1H-pyrazol-3-yl)-1,3,2-dioxathiolane-4-carboxylate 2-oxide (**42**)



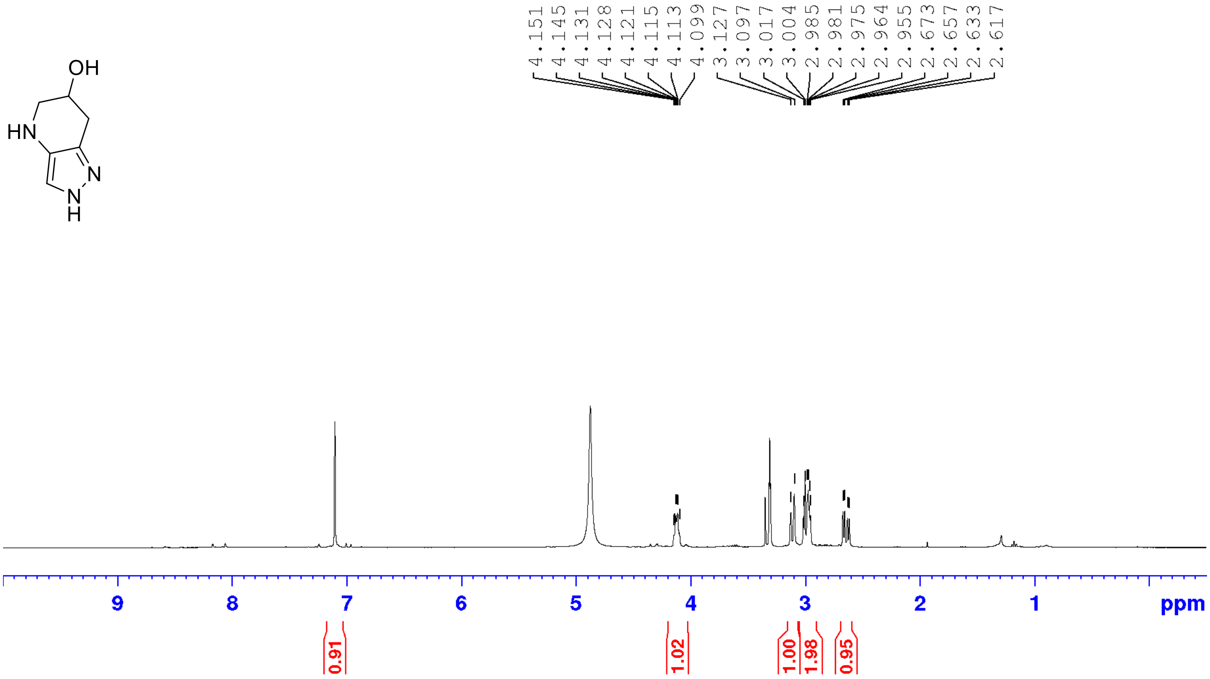


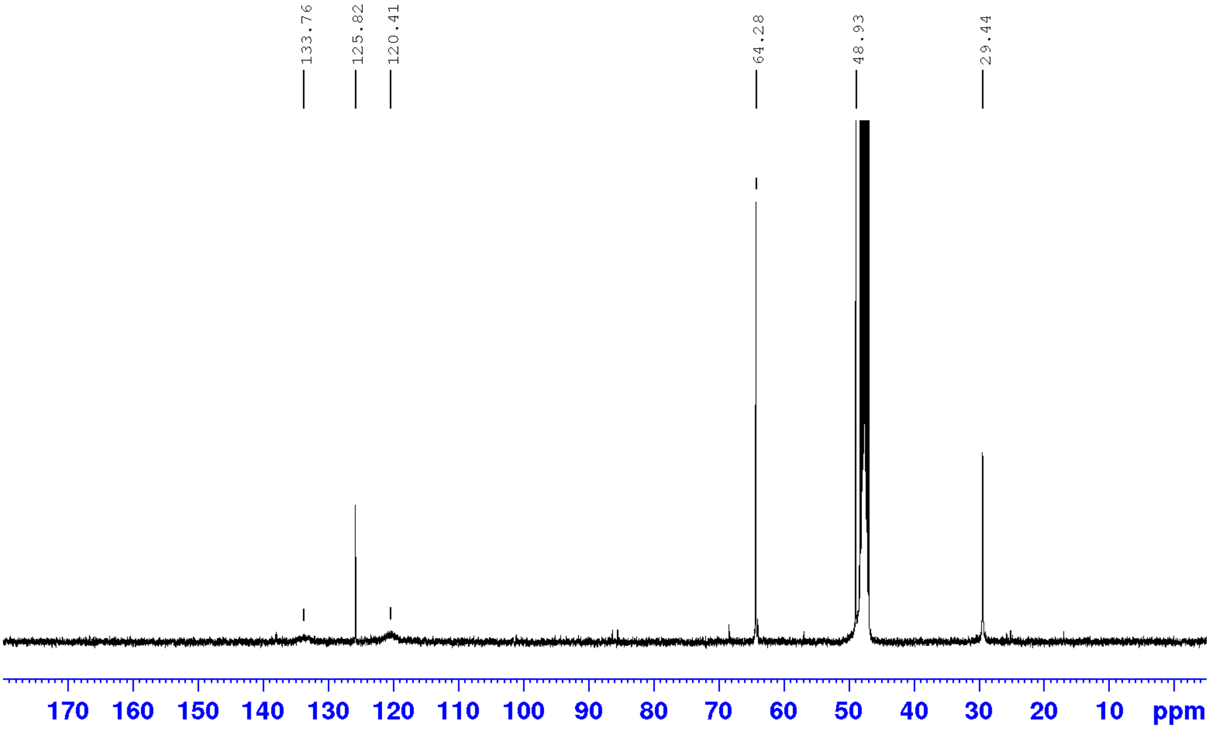
2-(4-methoxybenzyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-6-ol (**43**)



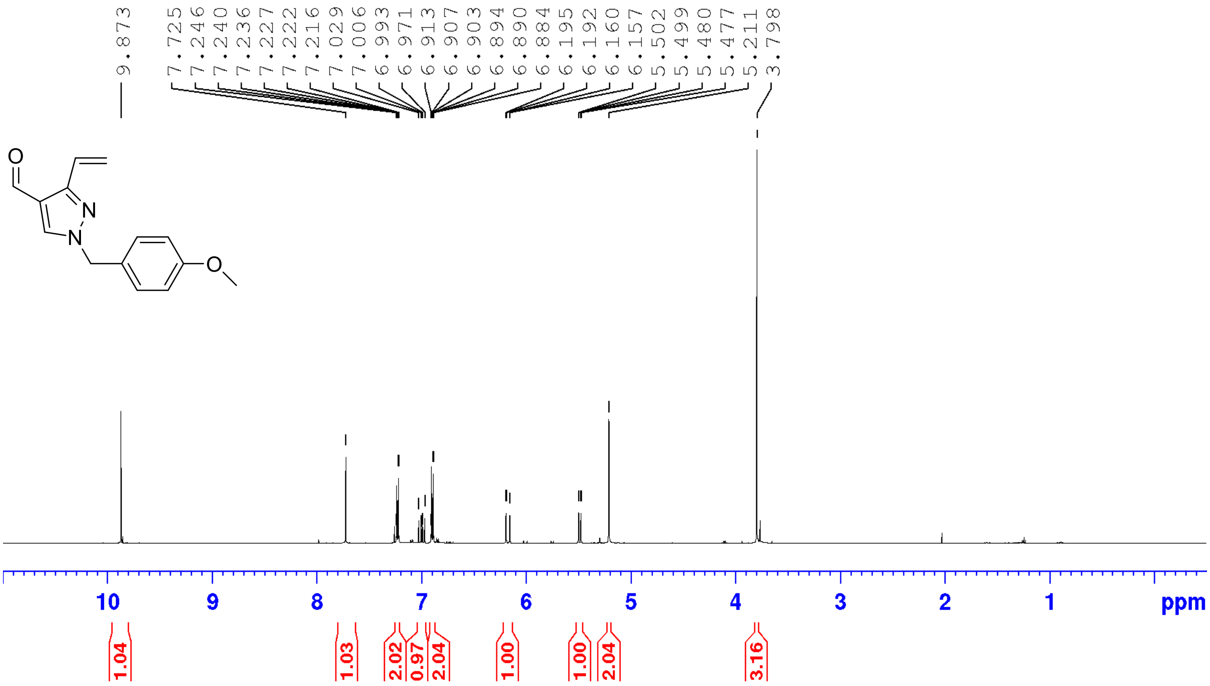


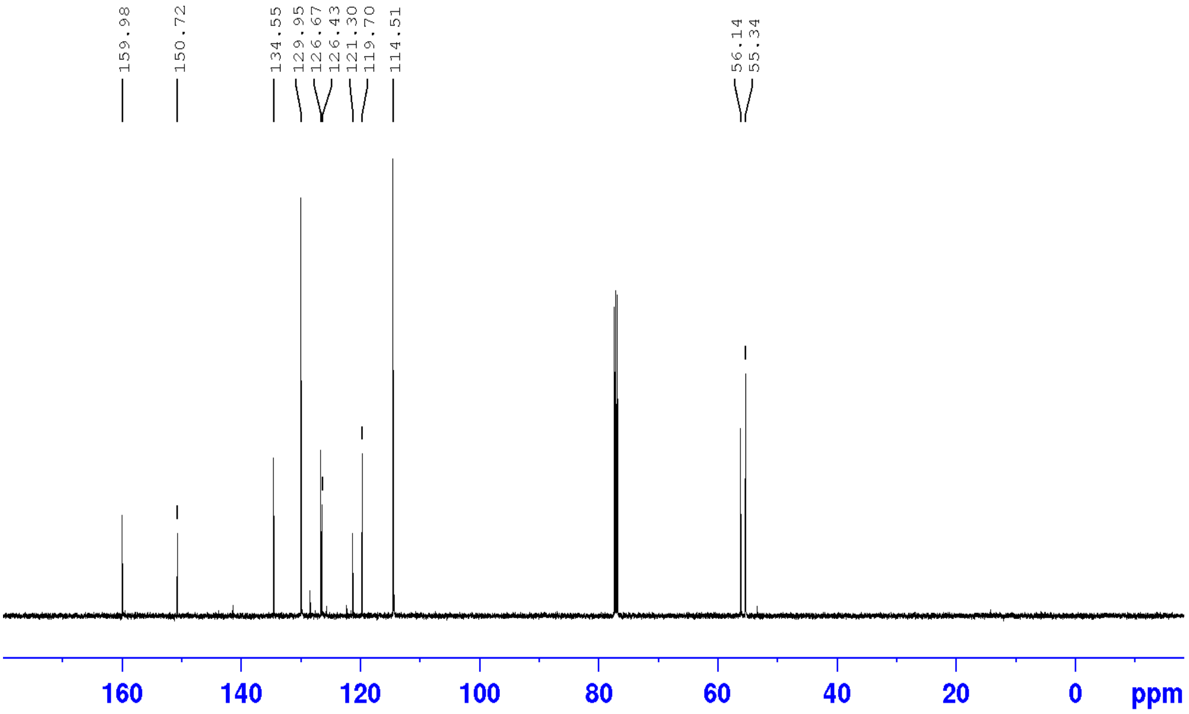
4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-6-ol (**11**)



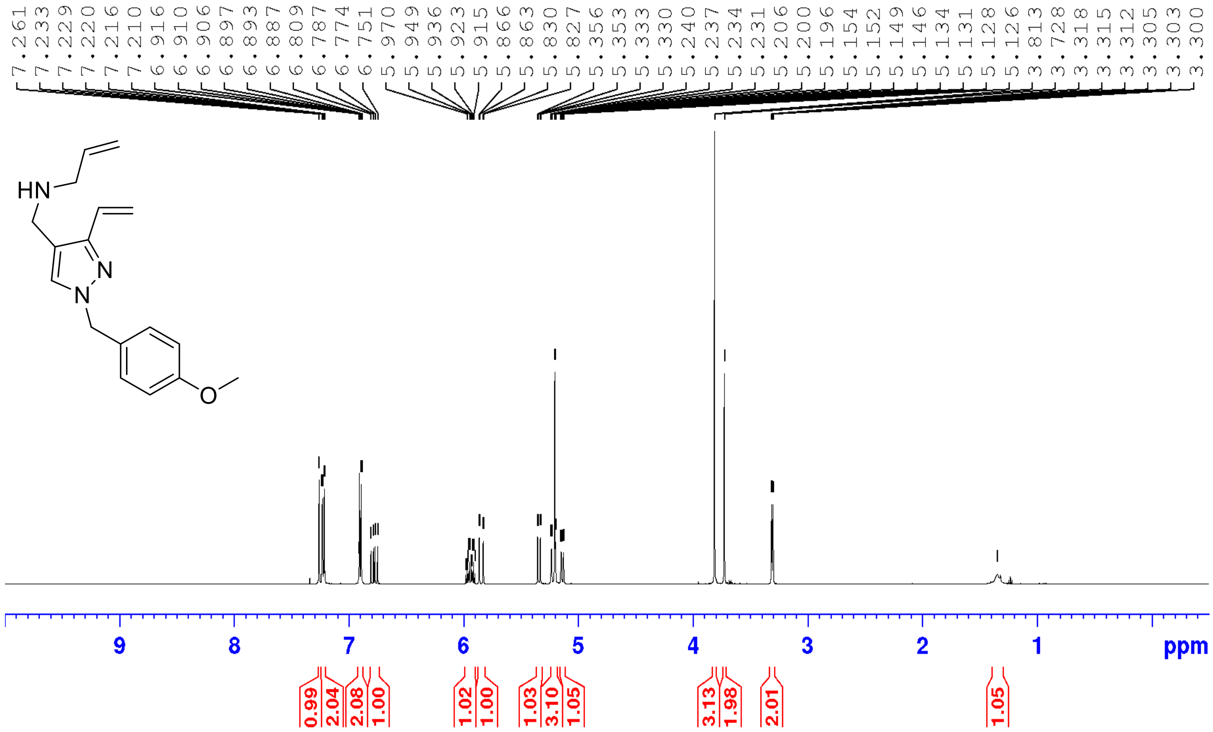


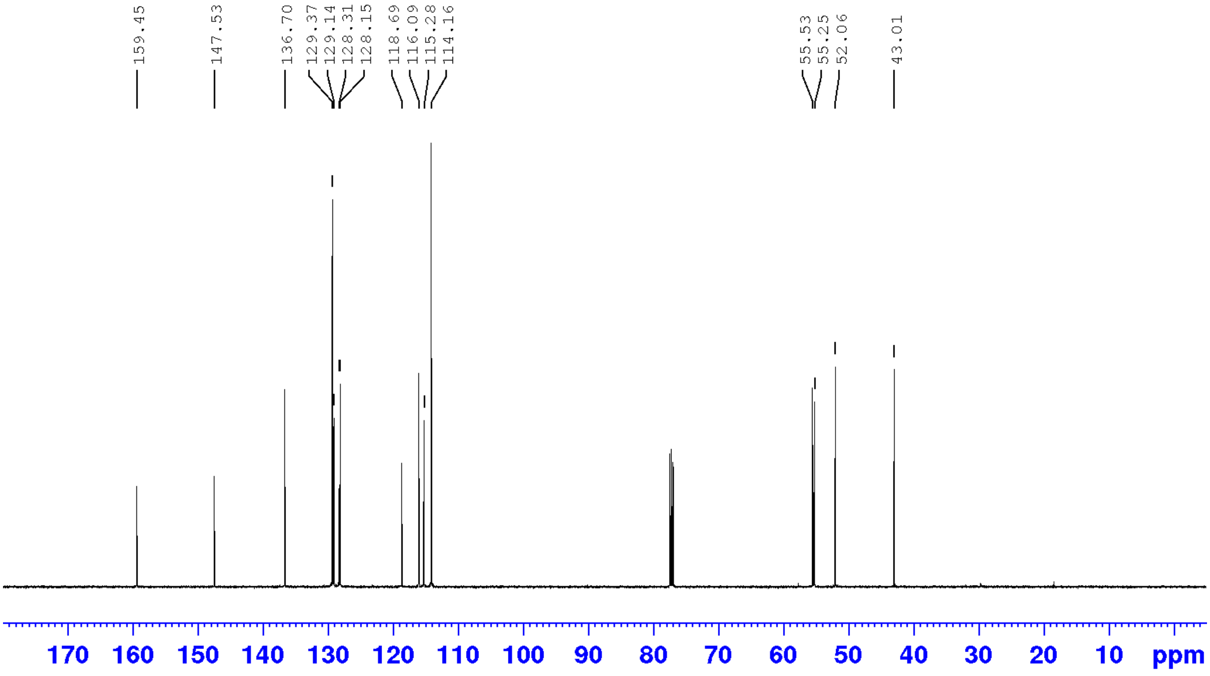
1-(4-methoxybenzyl)-3-vinyl-1H-pyrazole-4-carbaldehyde (**44**)



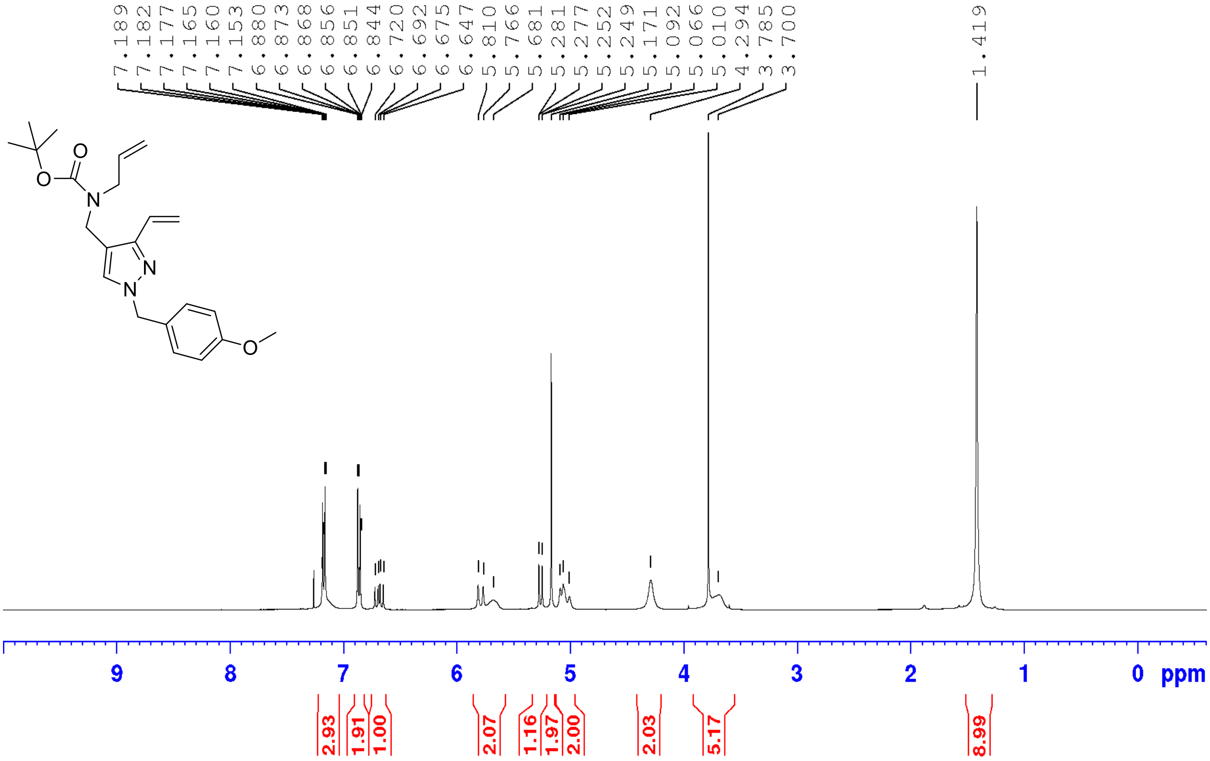


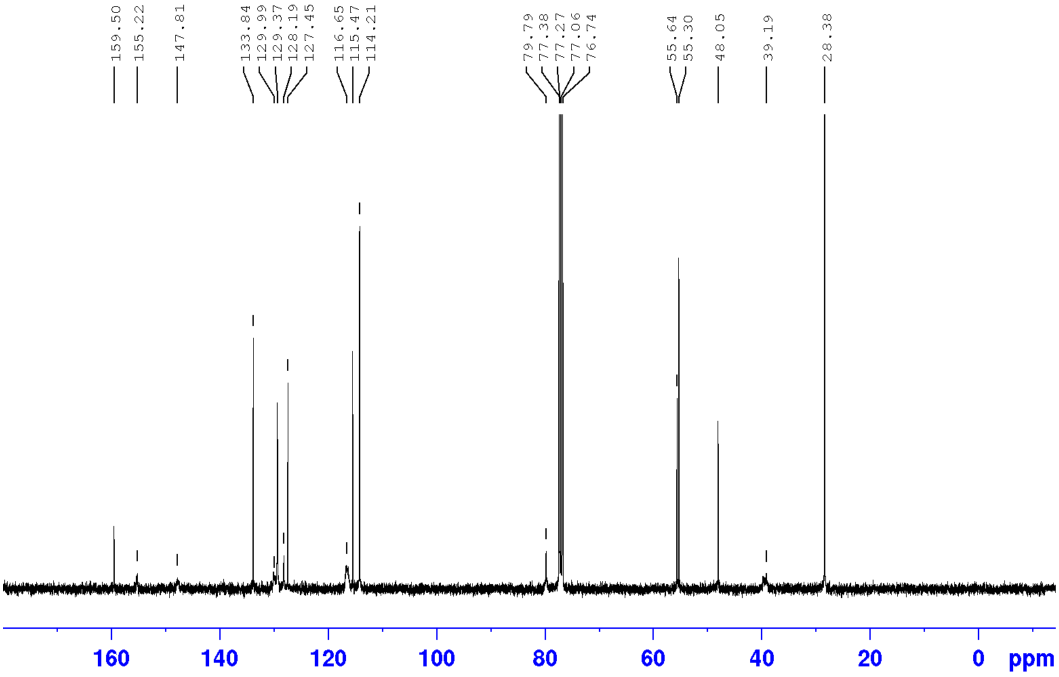
N-((1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methyl)prop-2-en-1-amine (**45**)



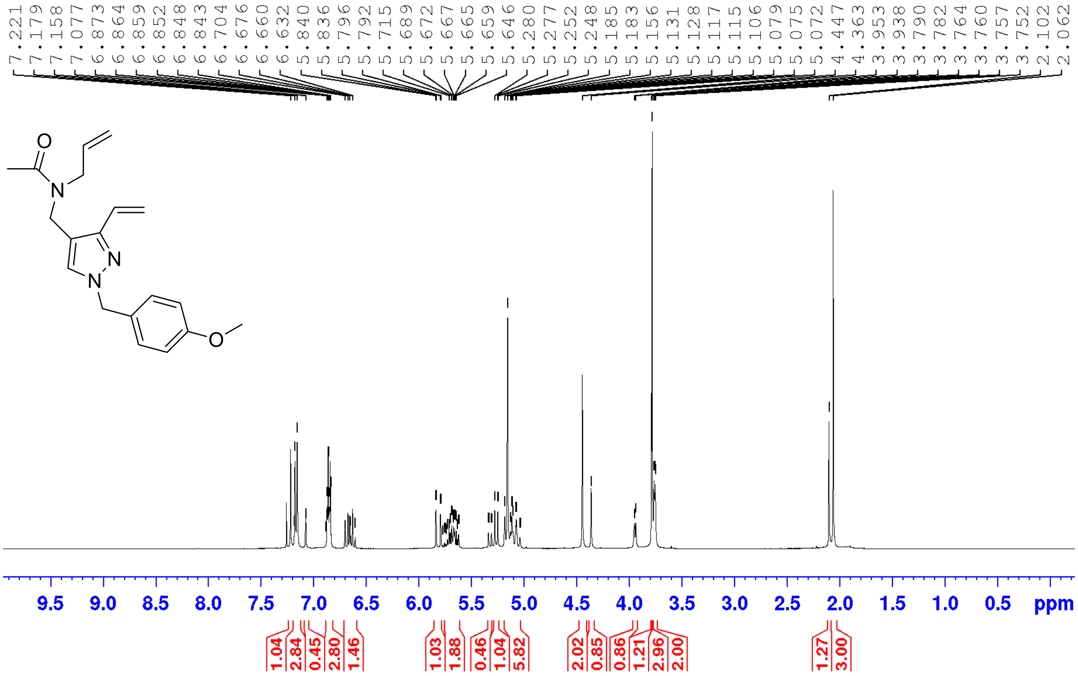


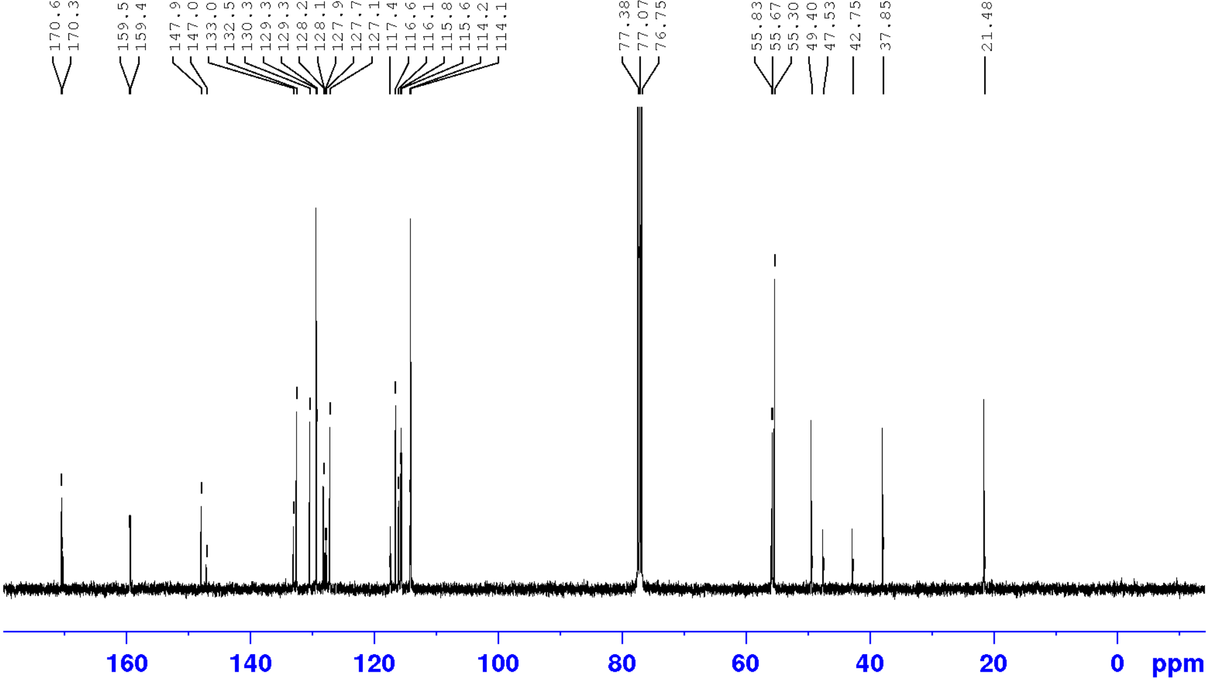
tert-butyl allyl((1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methyl)carbamate (**46a**)



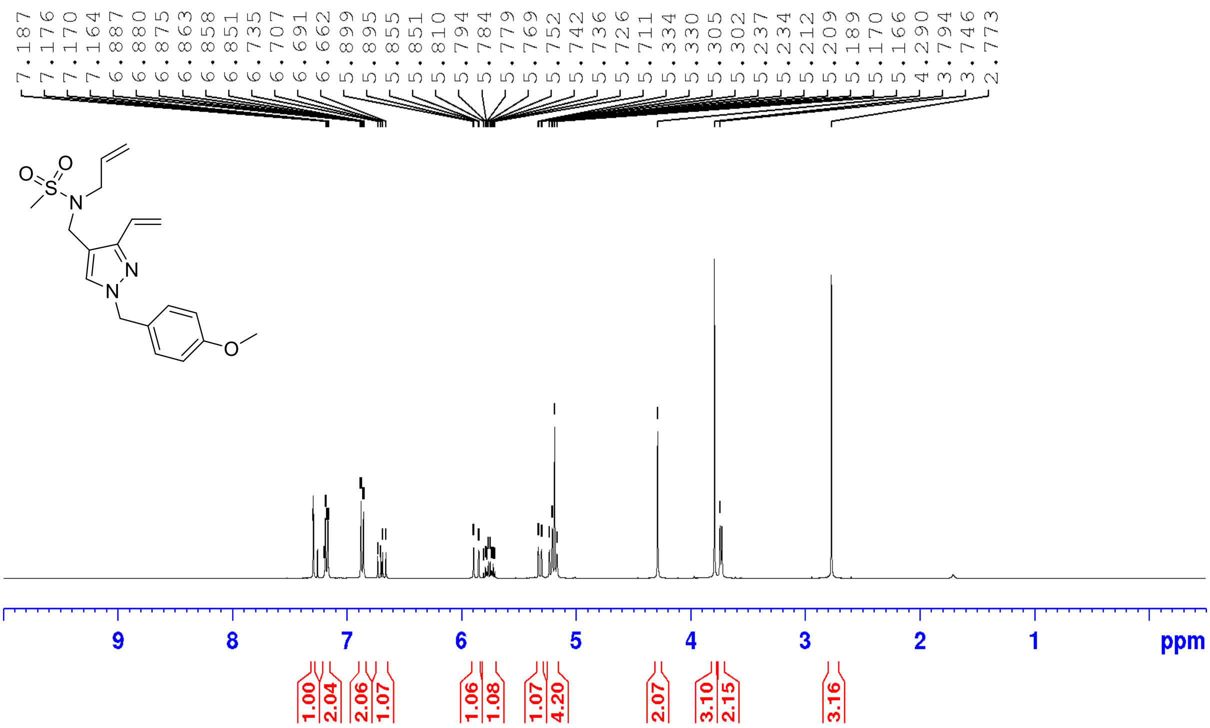


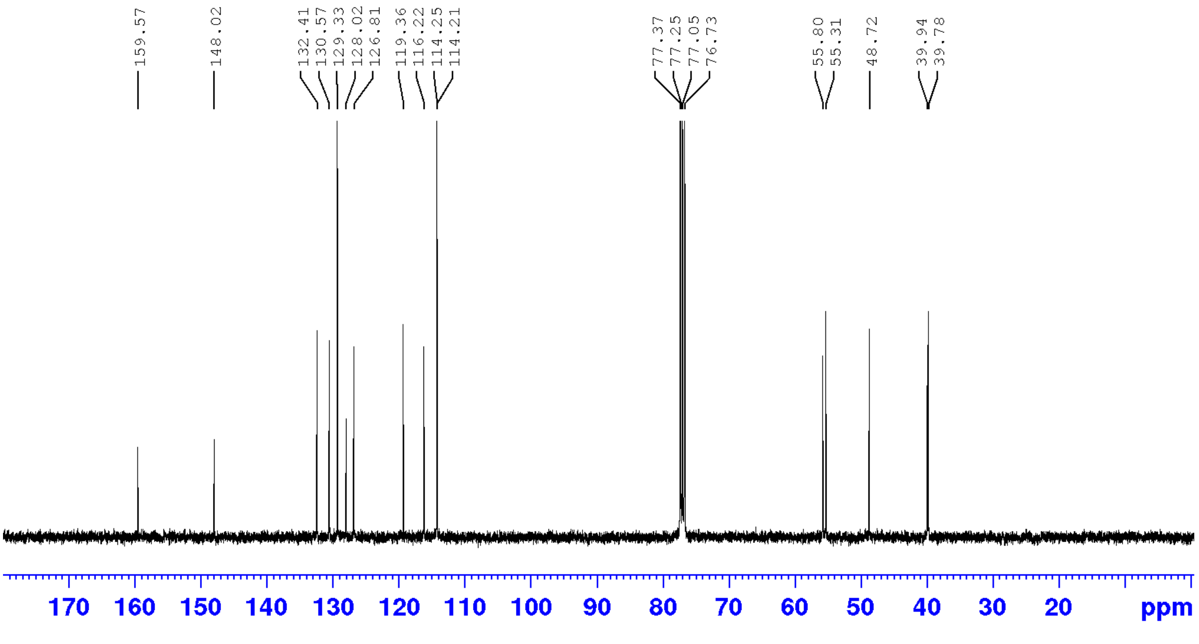
N-allyl-N-((1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methyl)acetamide (**46b**)



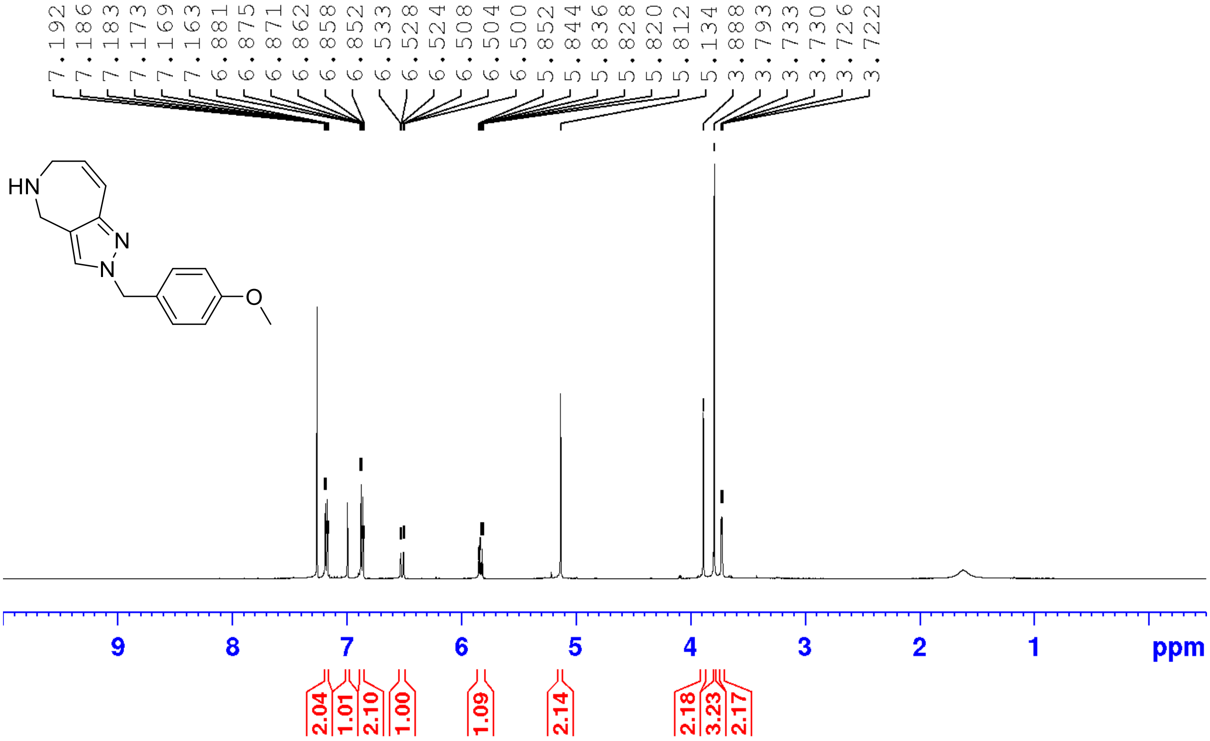


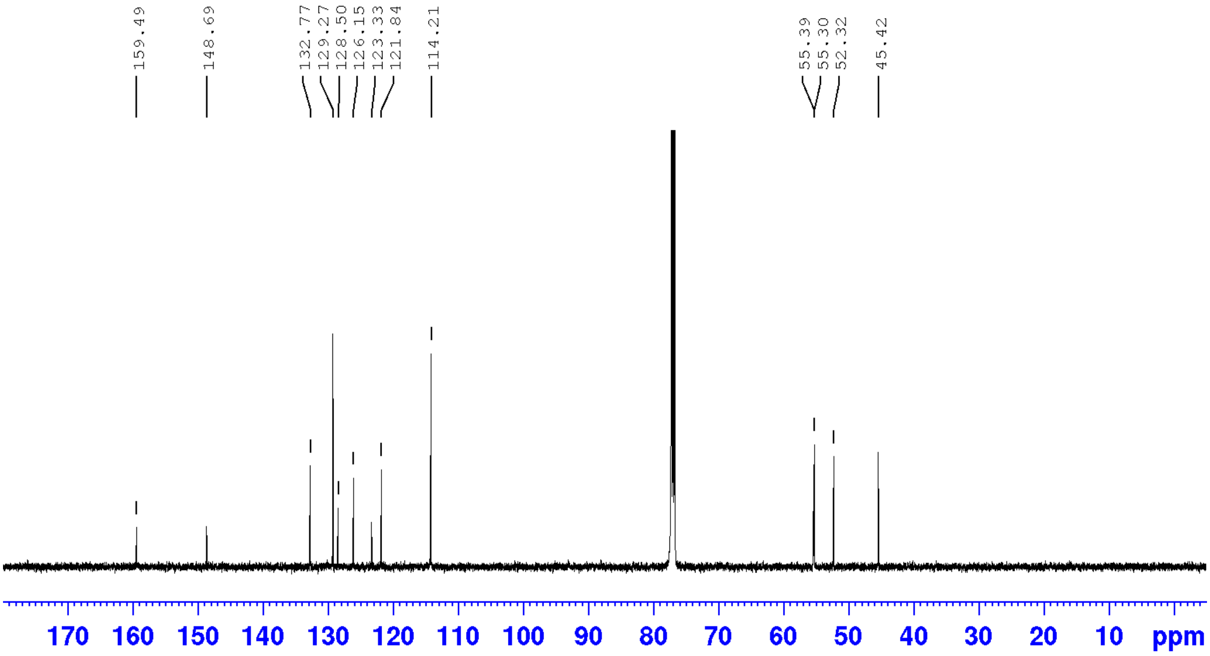
N-allyl-N-((1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl)methyl)methanesulfonamide (**46c**)



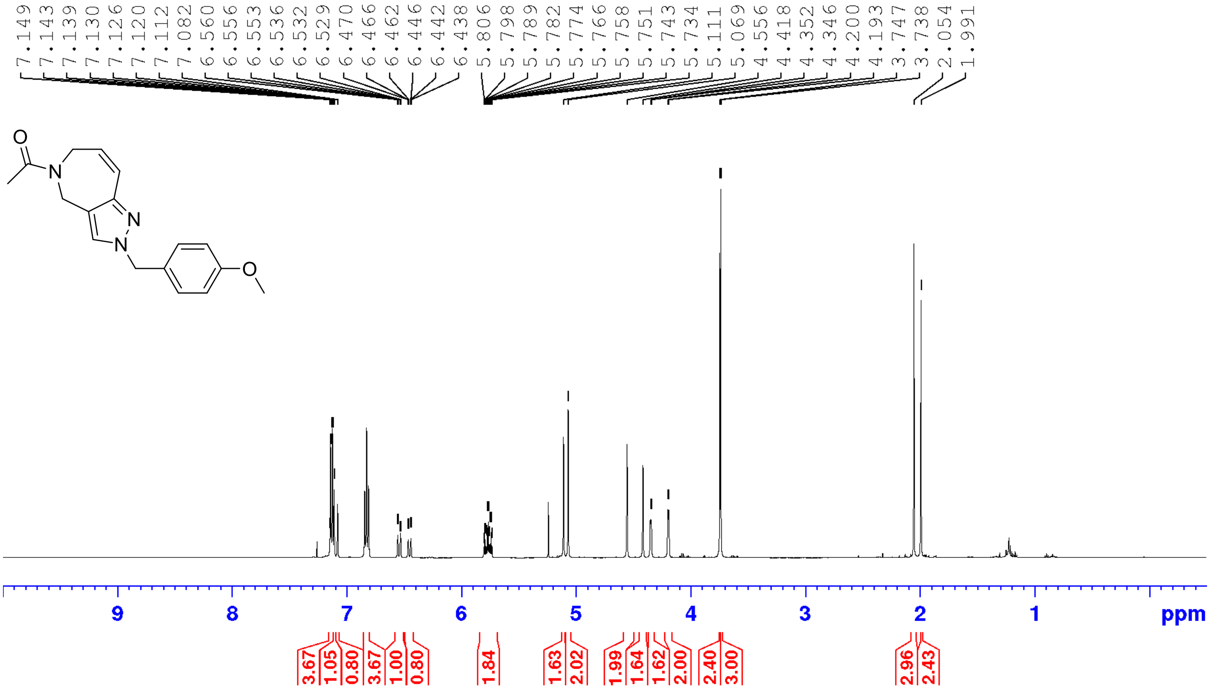


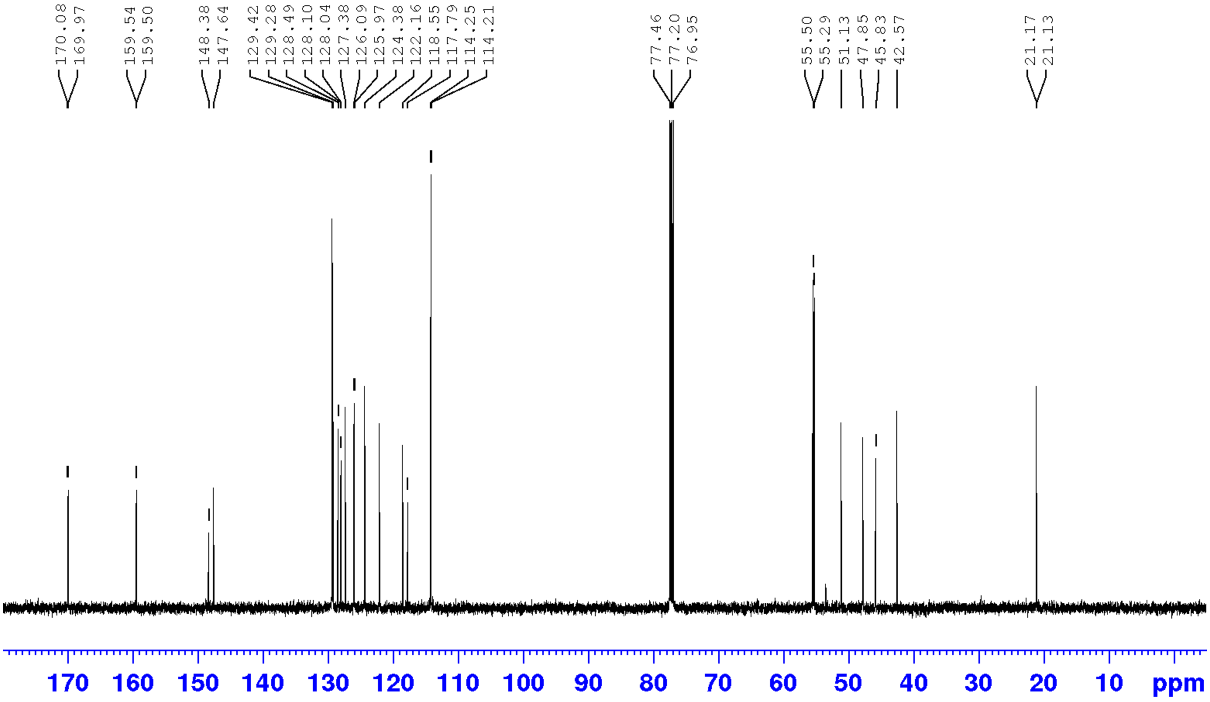
2-(4-methoxybenzyl)-2,4,5,6-tetrahydropyrazolo[4,3-c]azepine (**47a**)



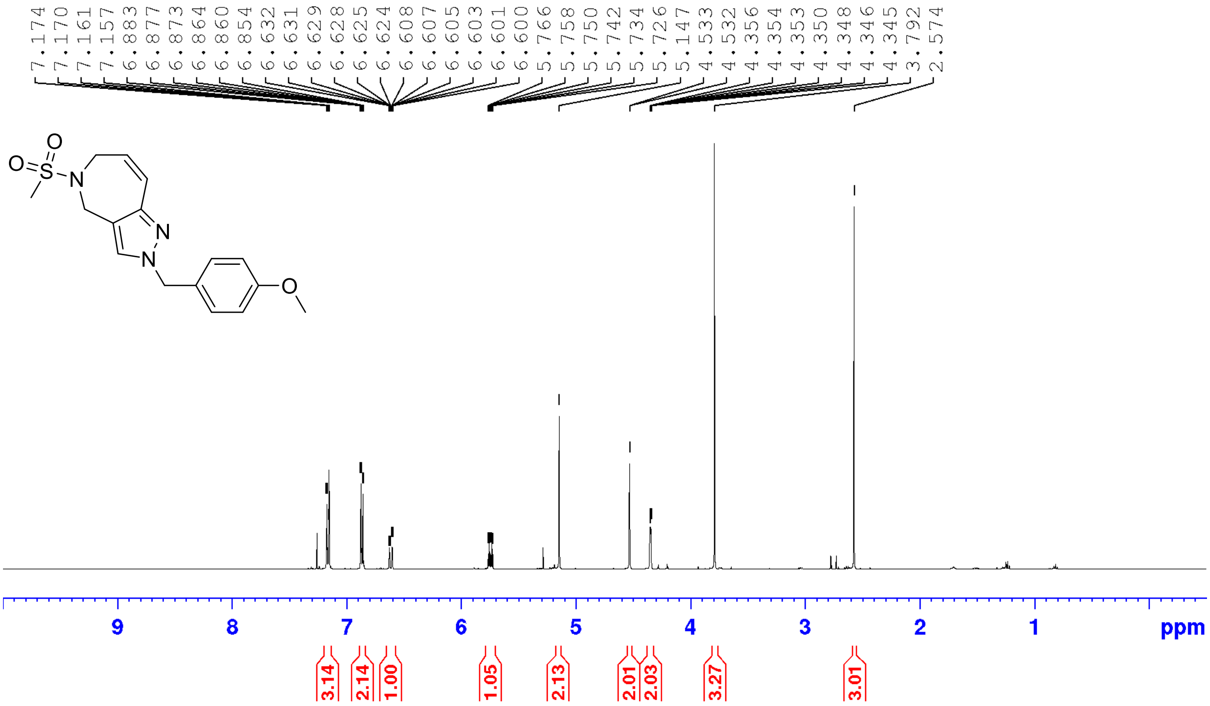


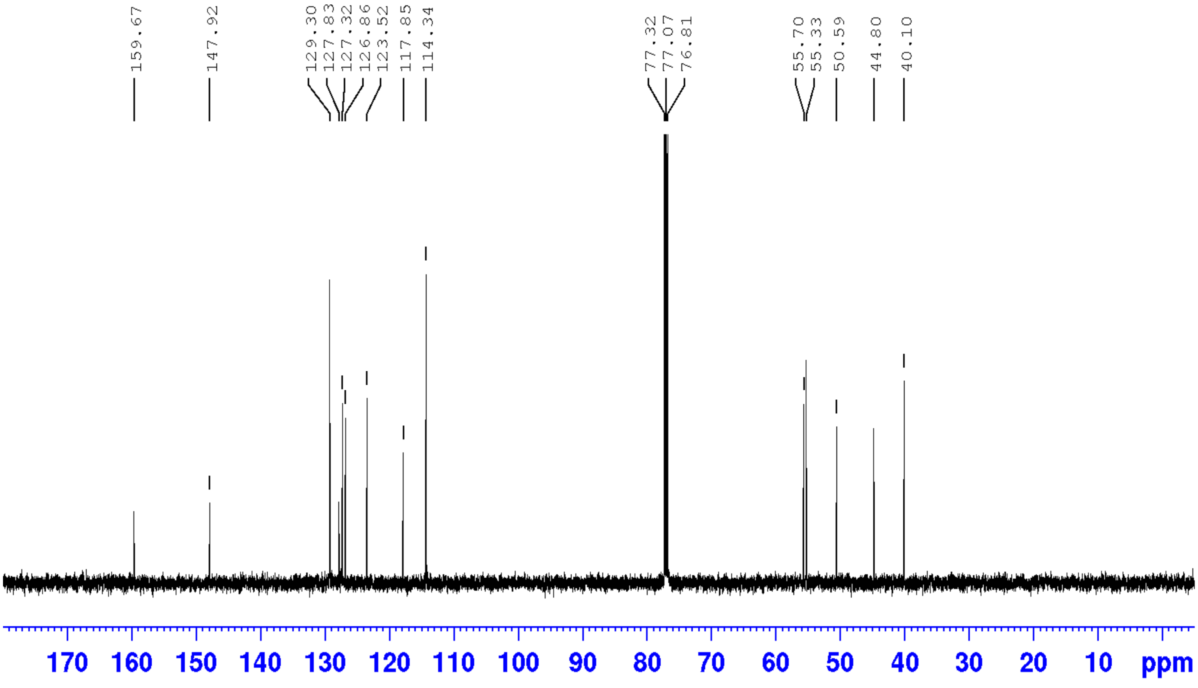
1-(2-(4-methoxybenzyl)-2,6-dihydropyrazolo[4,3-c]azepin-5(4H)-yl)ethan-1-one (**47b**)



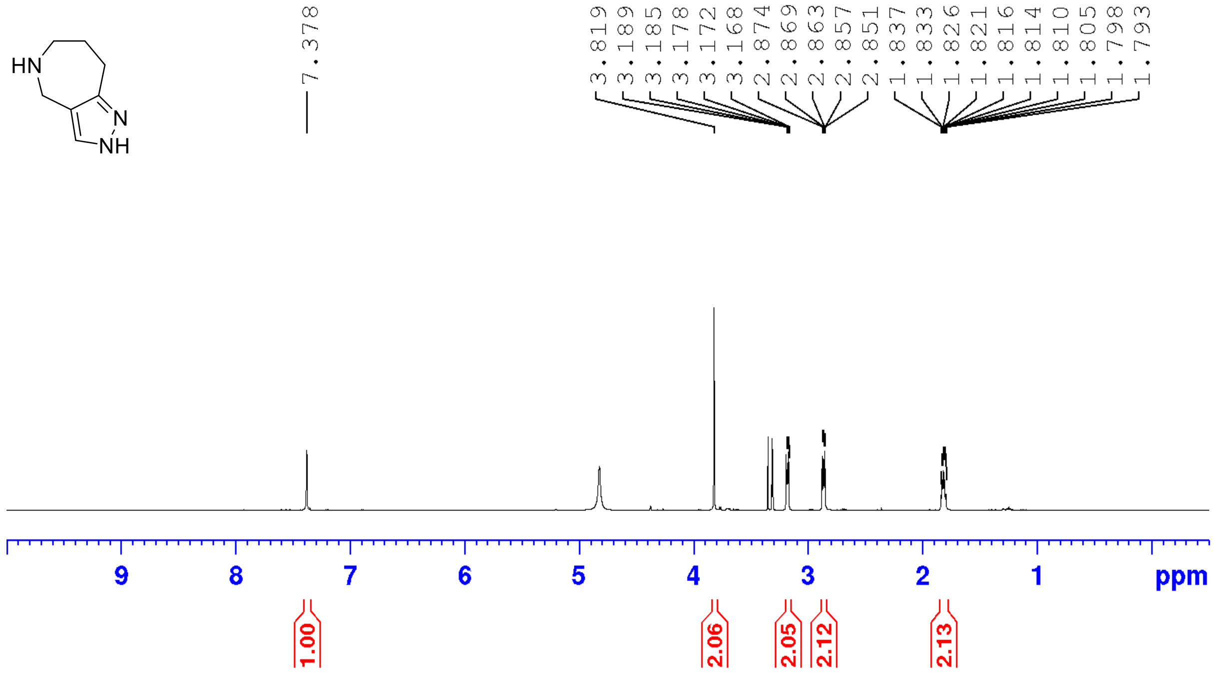


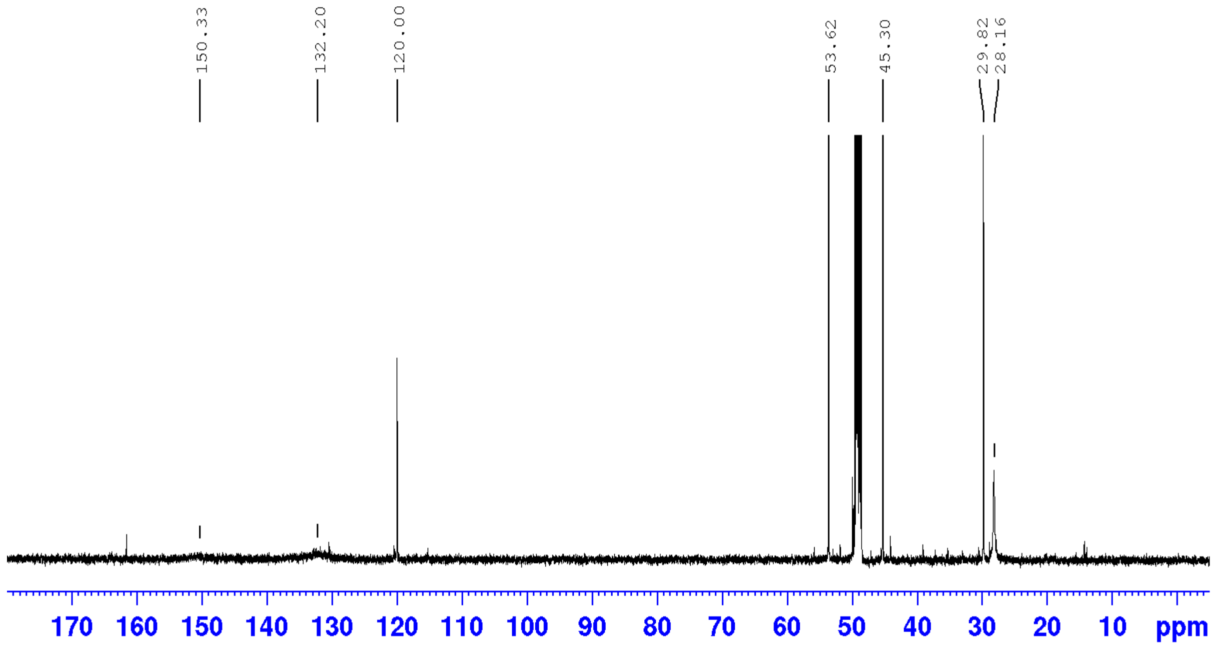
2-(4-methoxybenzyl)-5-(methylsulfonyl)-2,4,5,6-tetrahydropyrazolo[4,3-c]azepine (**47c**)



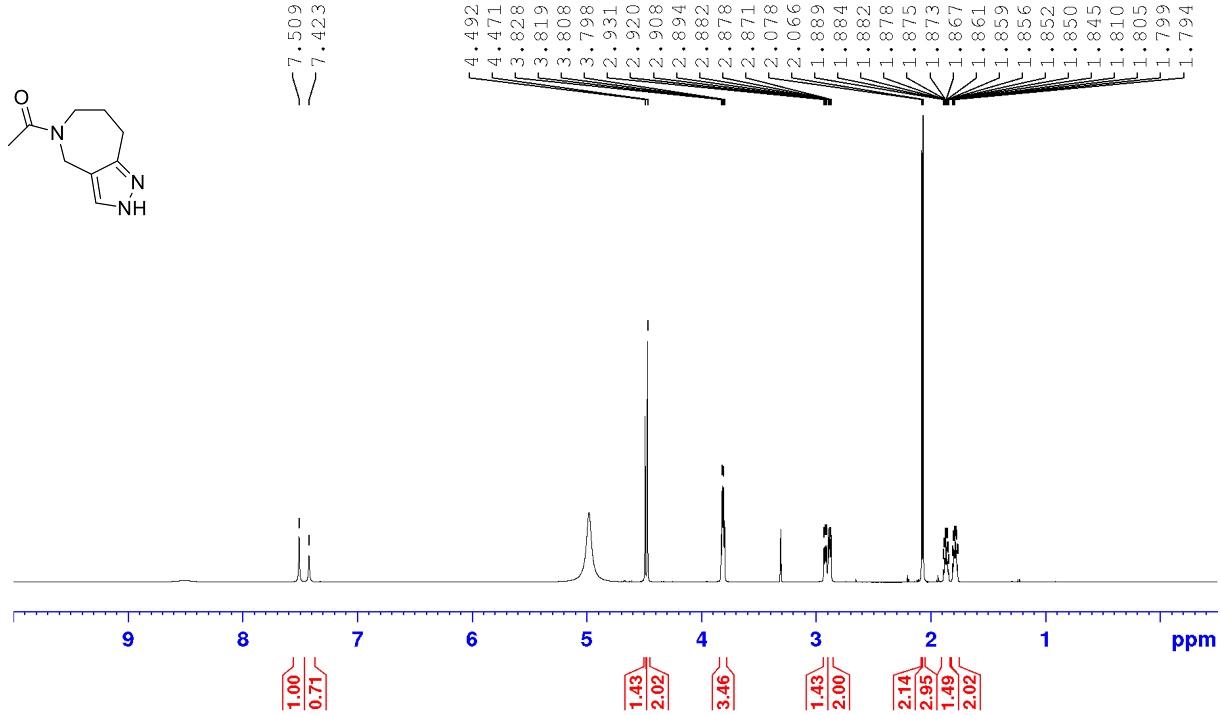


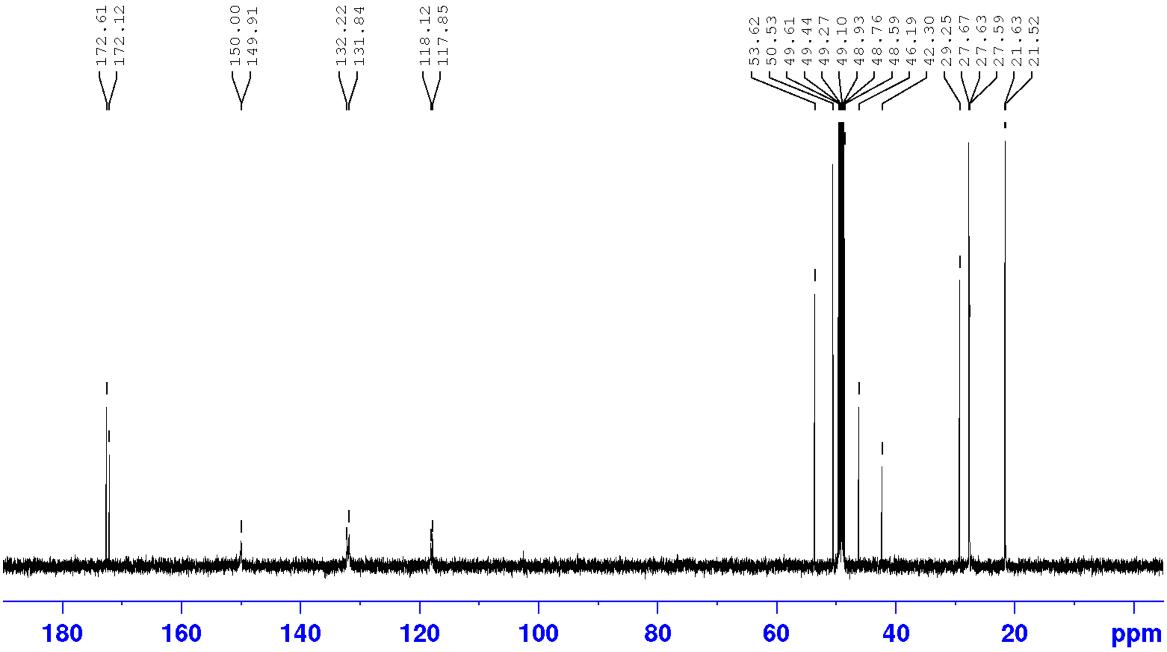
2,4,5,6,7,8-hexahydropyrazolo[4,3-c]azepine (**13a**)



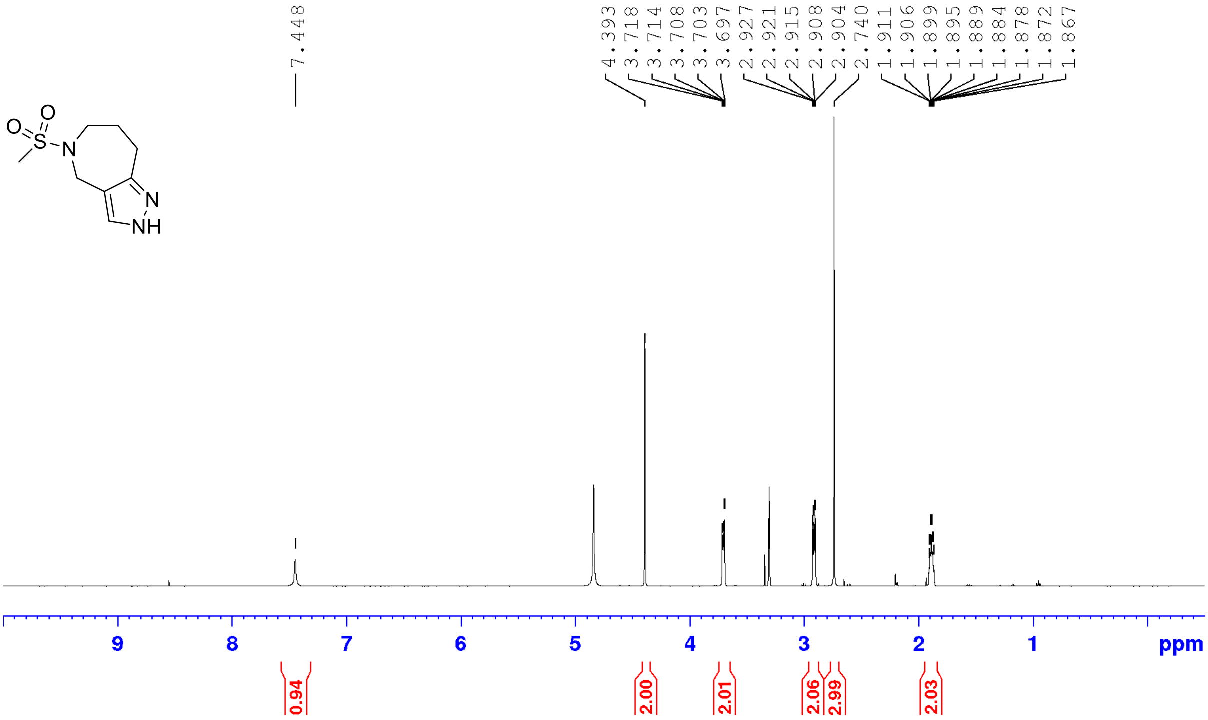


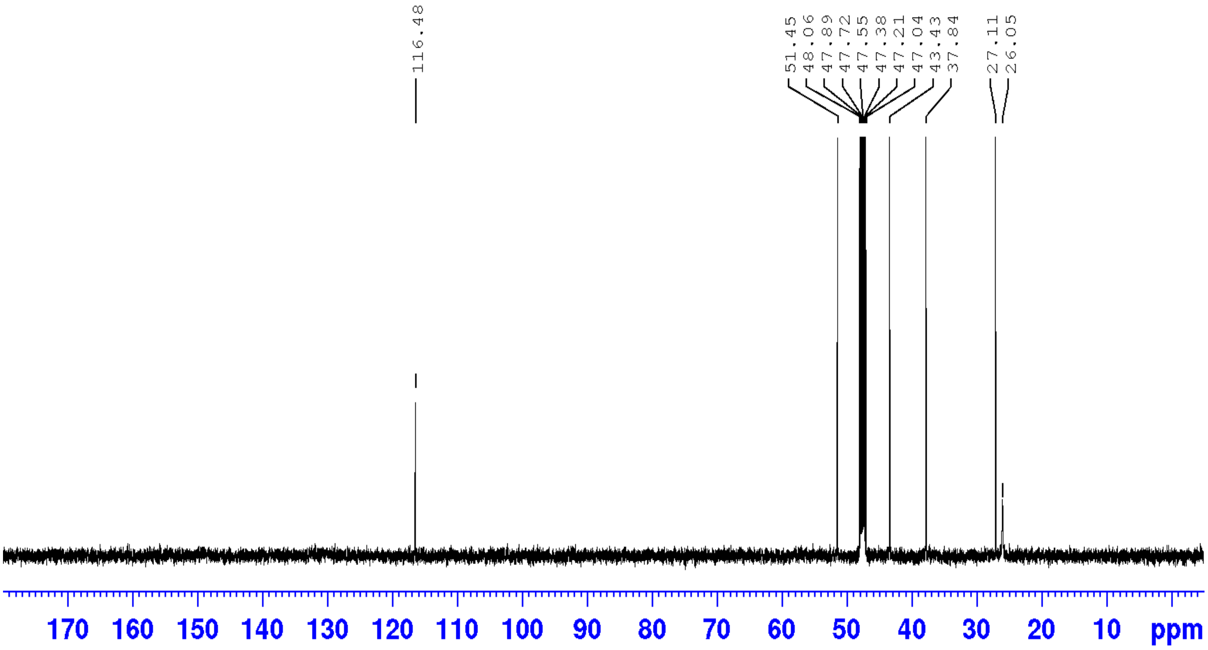
1-(2,6,7,8-tetrahydropyrazolo[4,3-c]azepin-5(4H)-yl)ethan-1-one (**13b**)



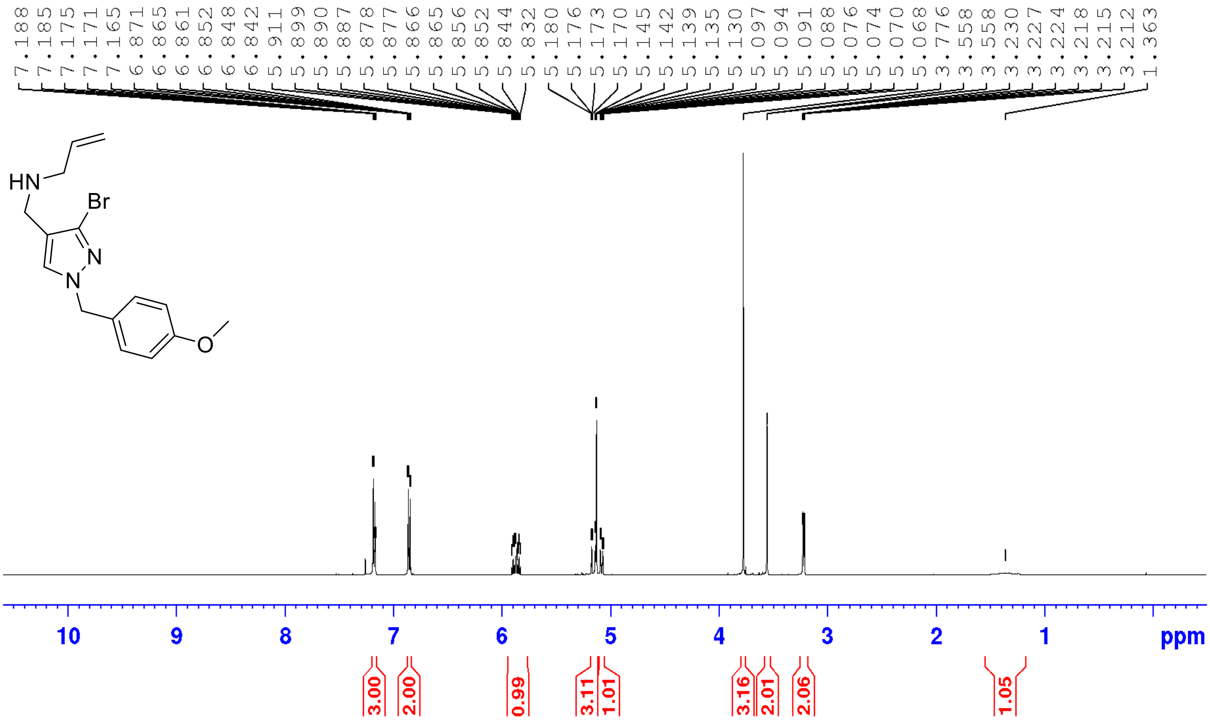


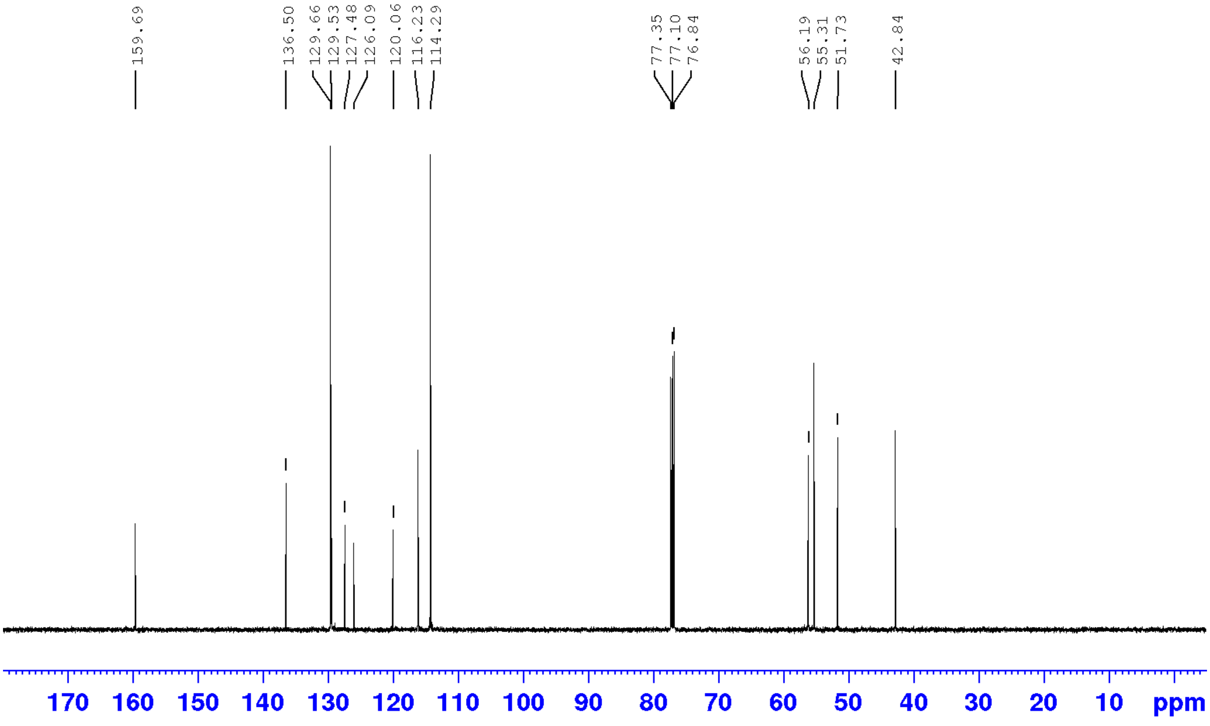
5-(methylsulfonyl)-2,4,5,6,7,8-hexahydropyrazolo[4,3-c]azepine (**13c**)



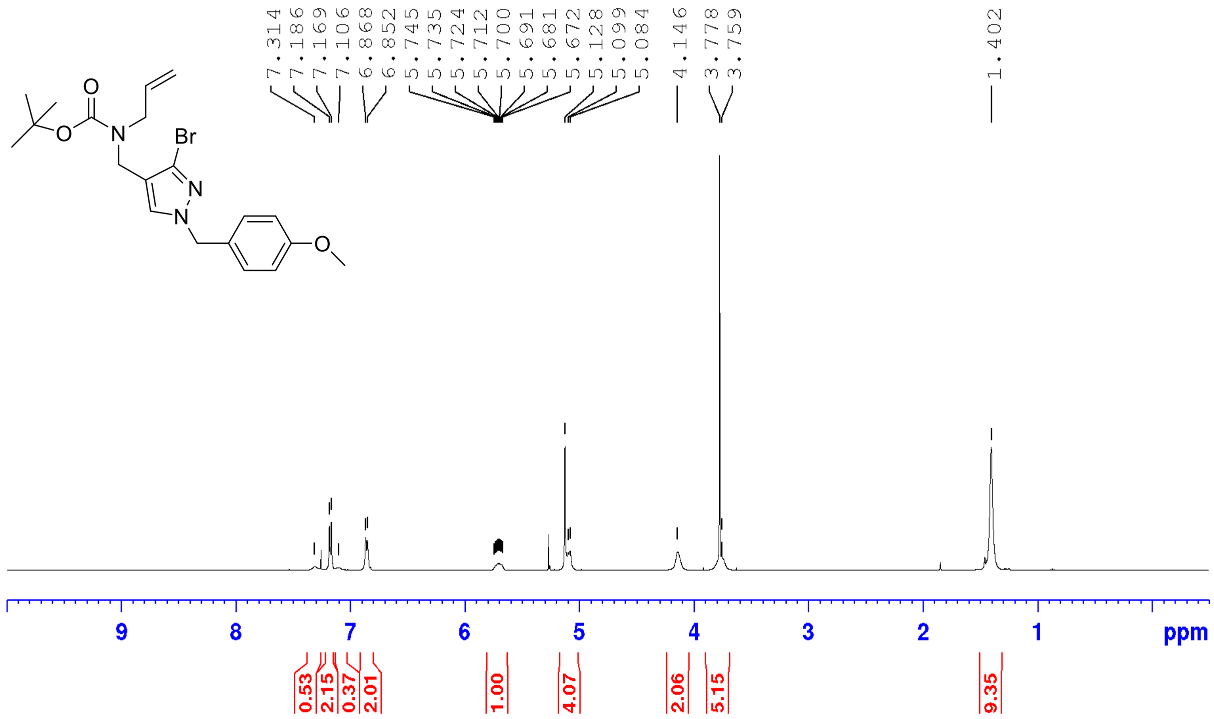


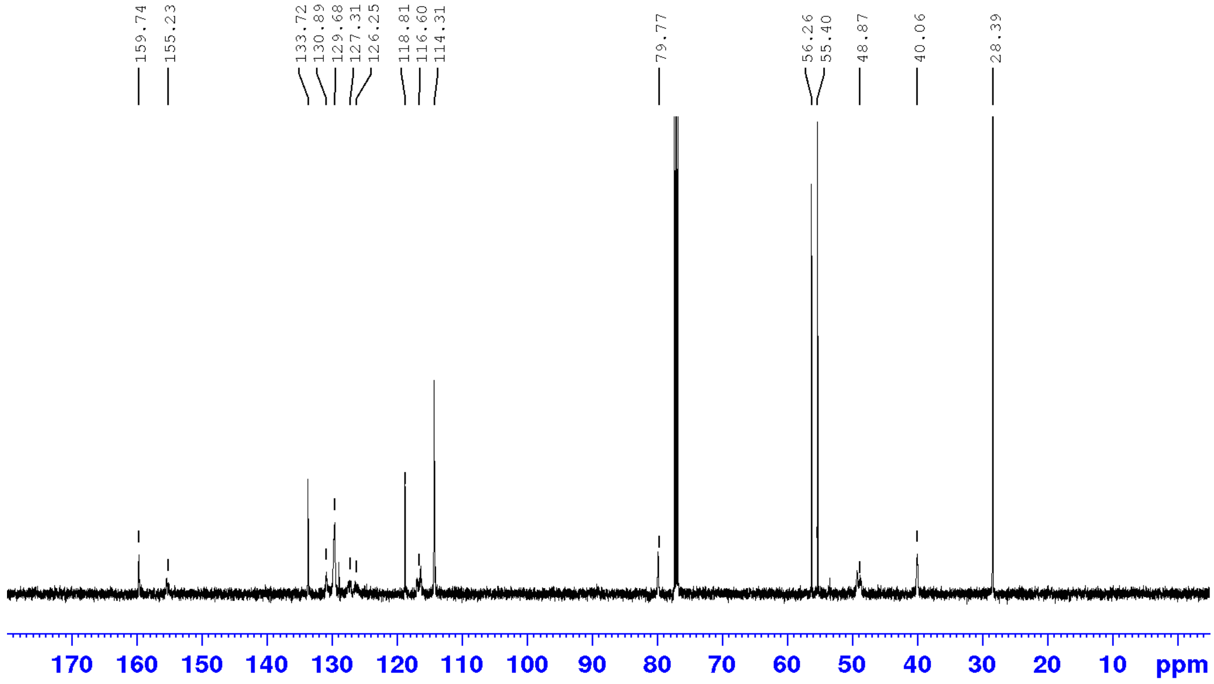
N-((3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)prop-2-en-1-amine (**48**)



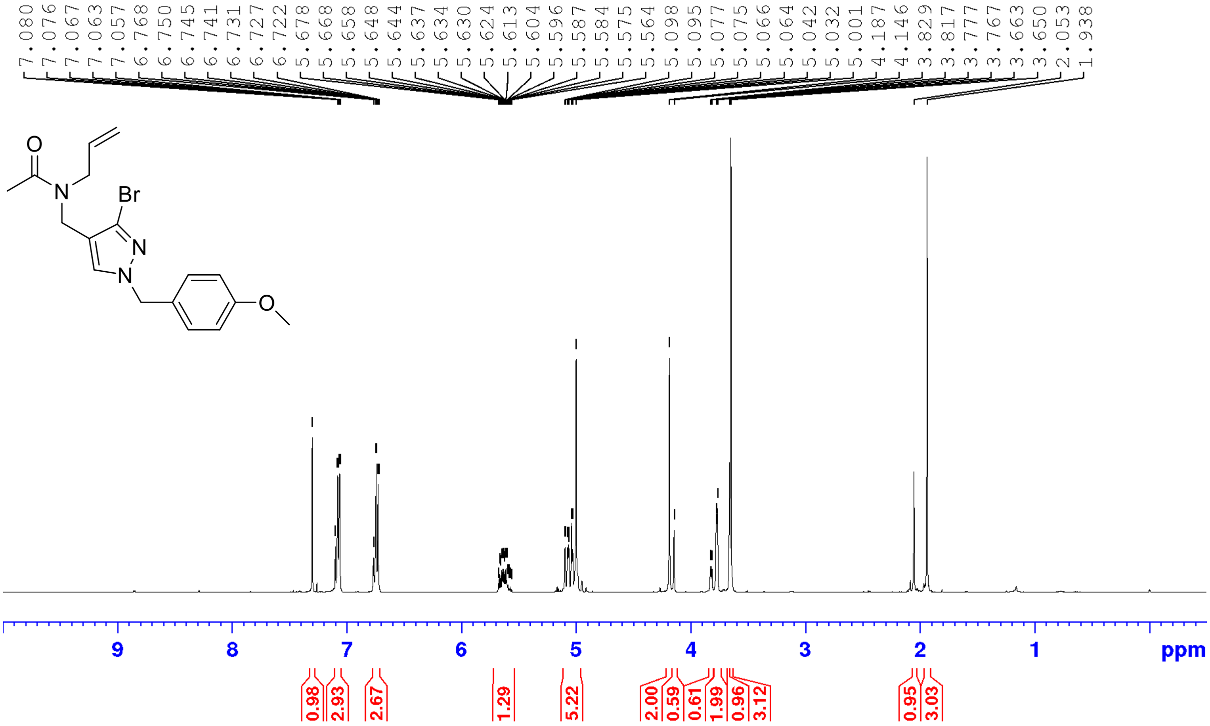


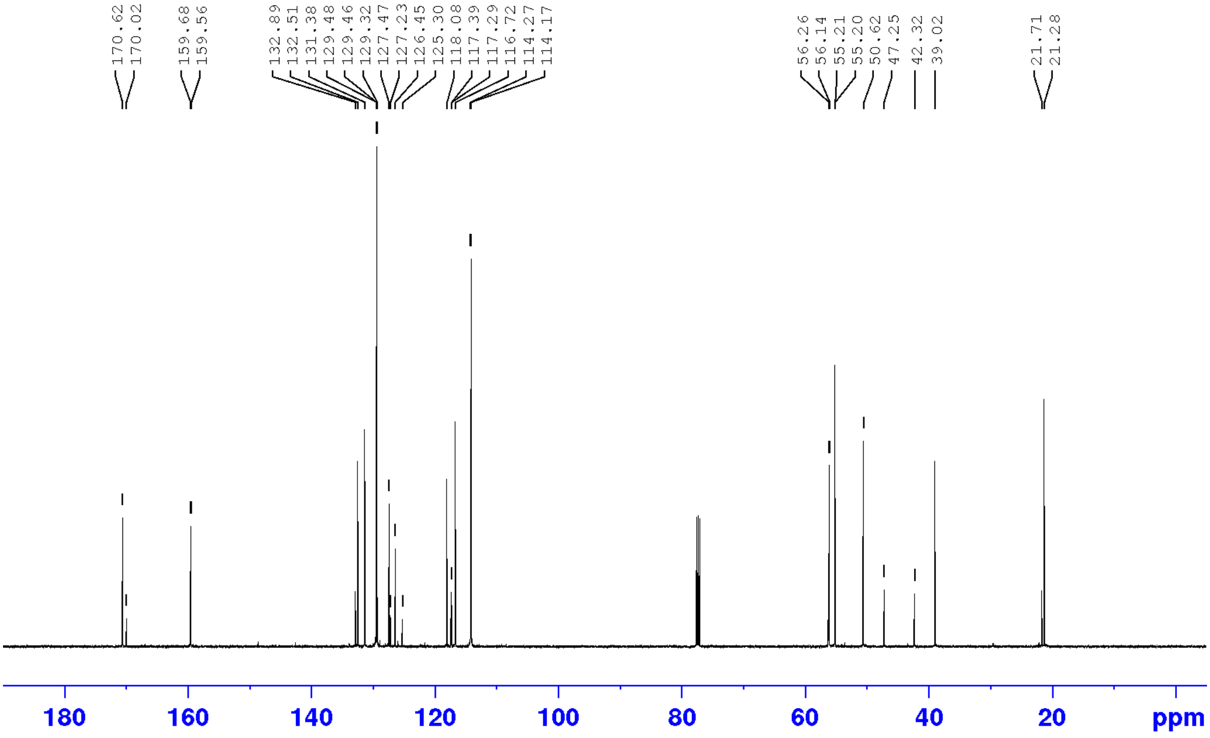
tert-butyl allyl((3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)carbamate (**49a**)



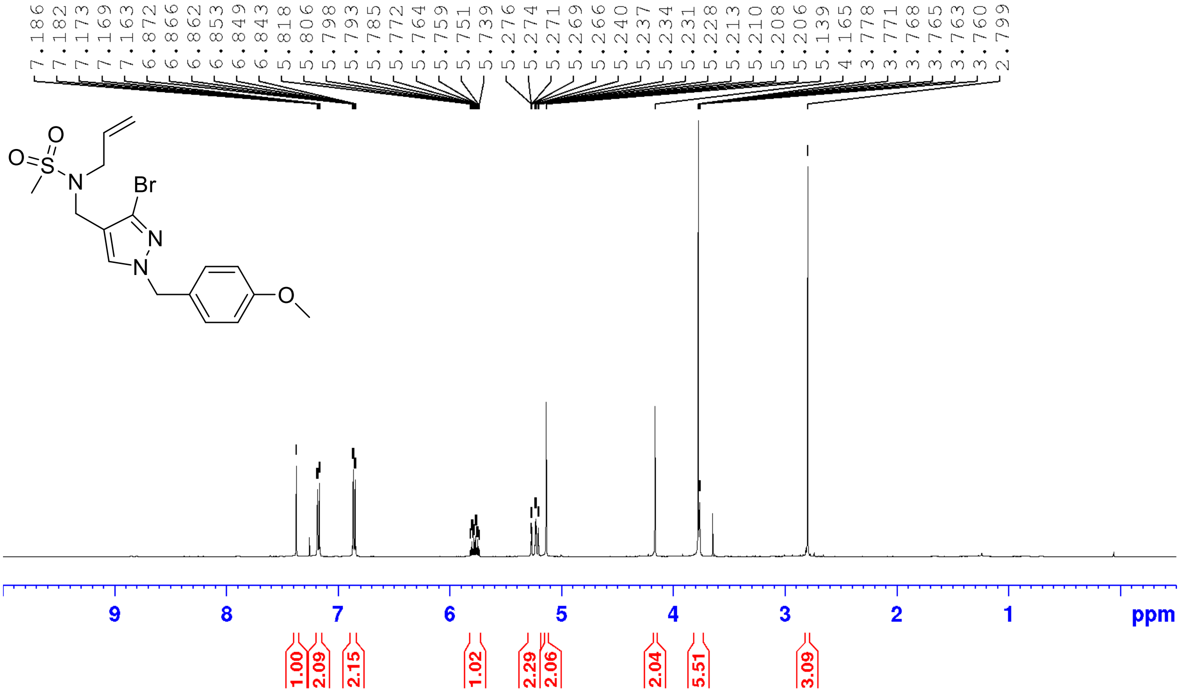


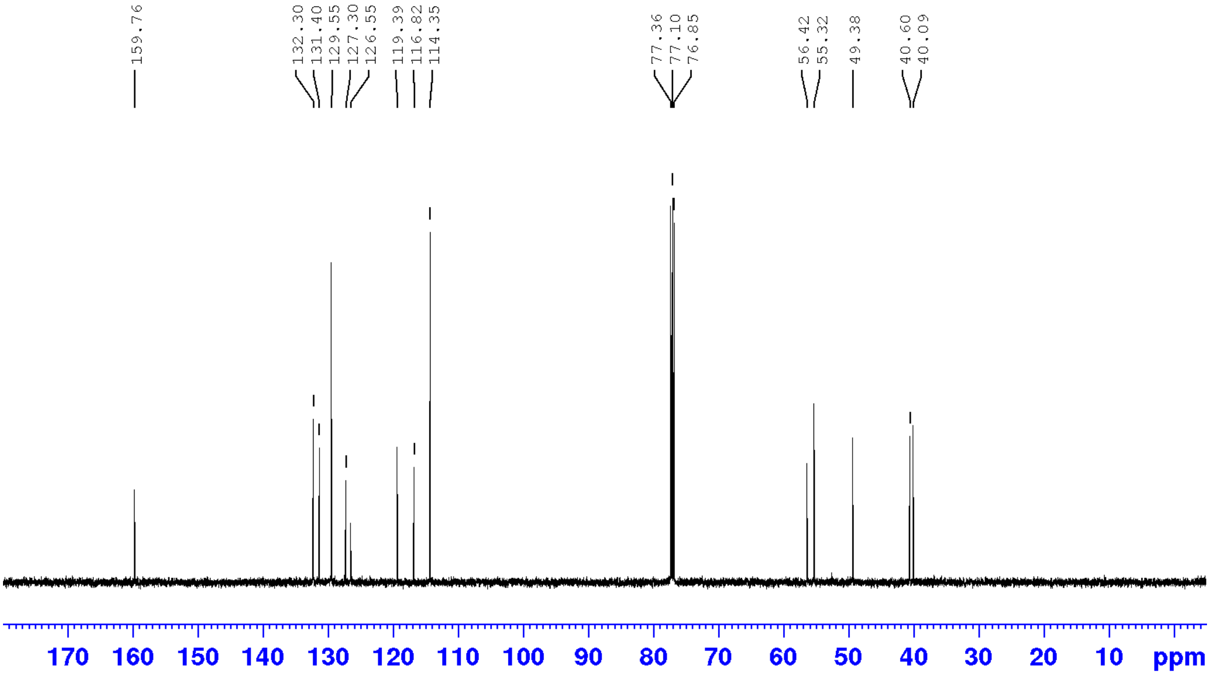
N-allyl-N-((3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)acetamide (**49b**)



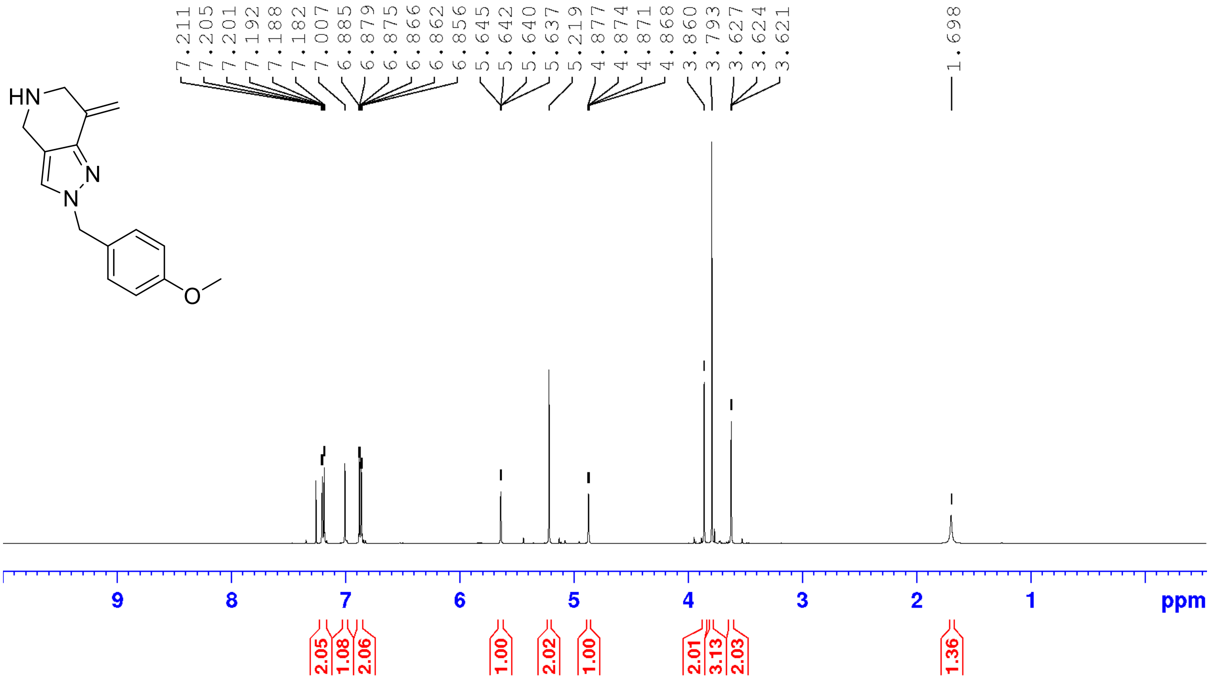


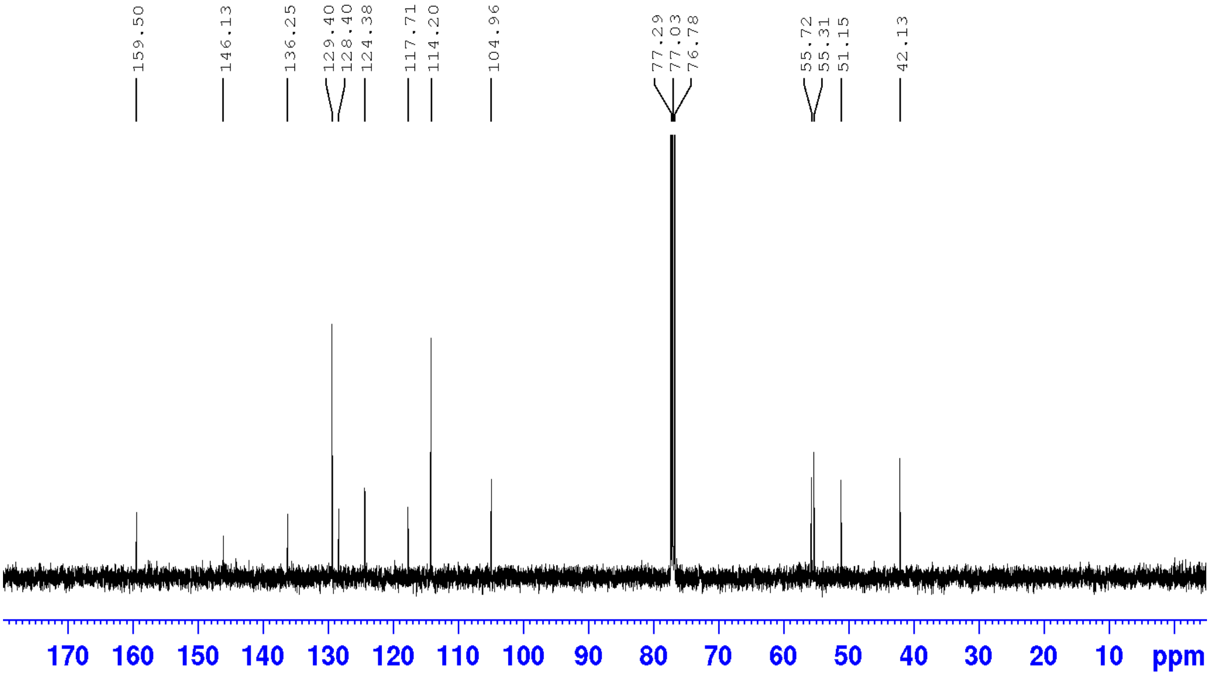
N-allyl-N-((3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)methanesulfonamide (**49c**)



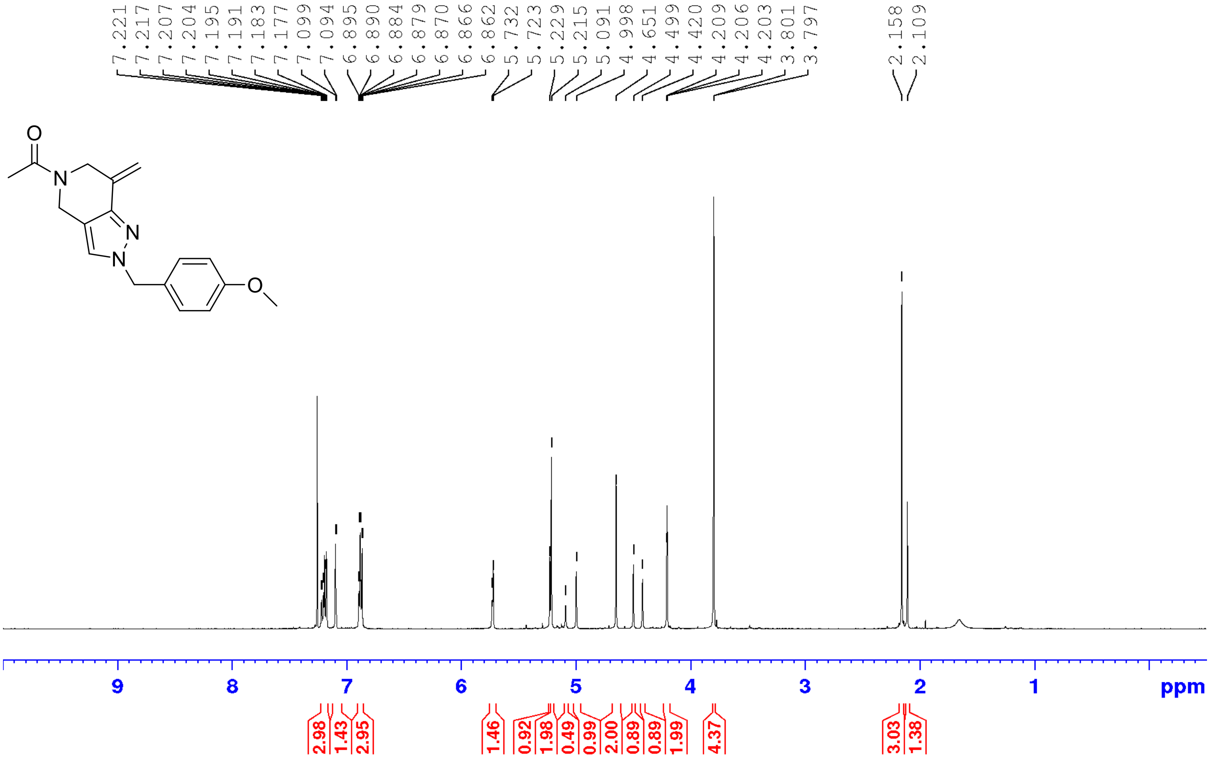


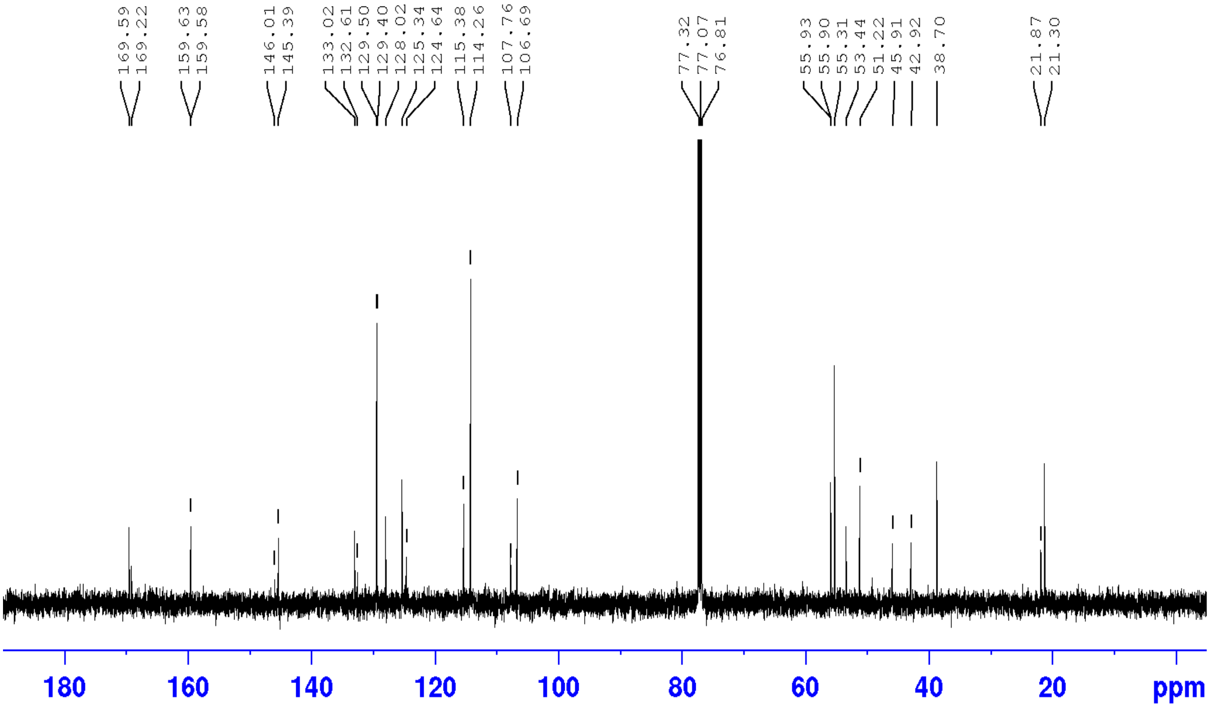
2-(4-methoxybenzyl)-7-methylene-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (**50a**)



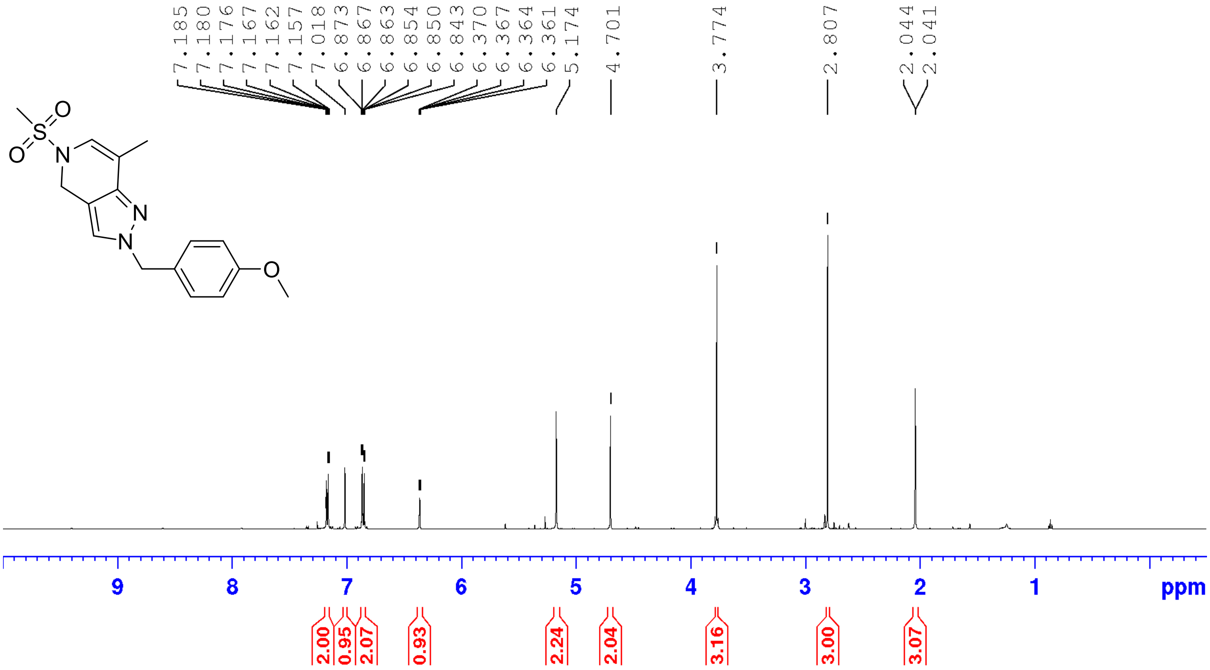


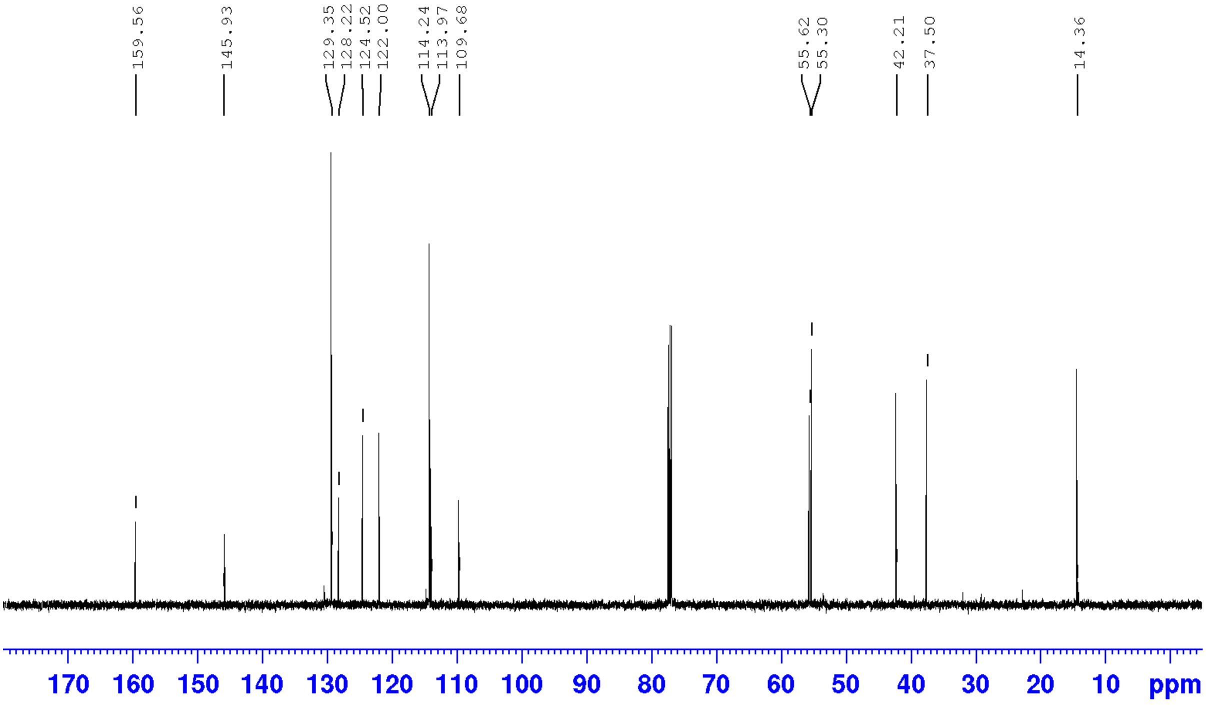
1-(2-(4-methoxybenzyl)-7-methylene-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)ethan-1-one (**50b**)



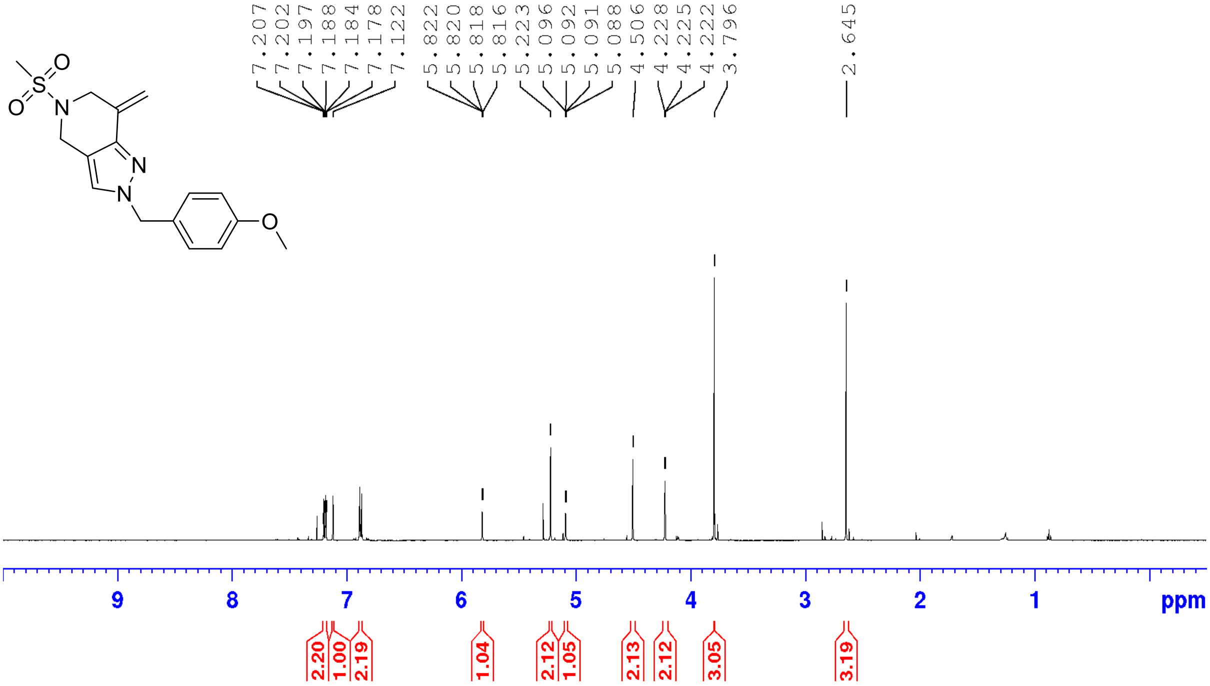


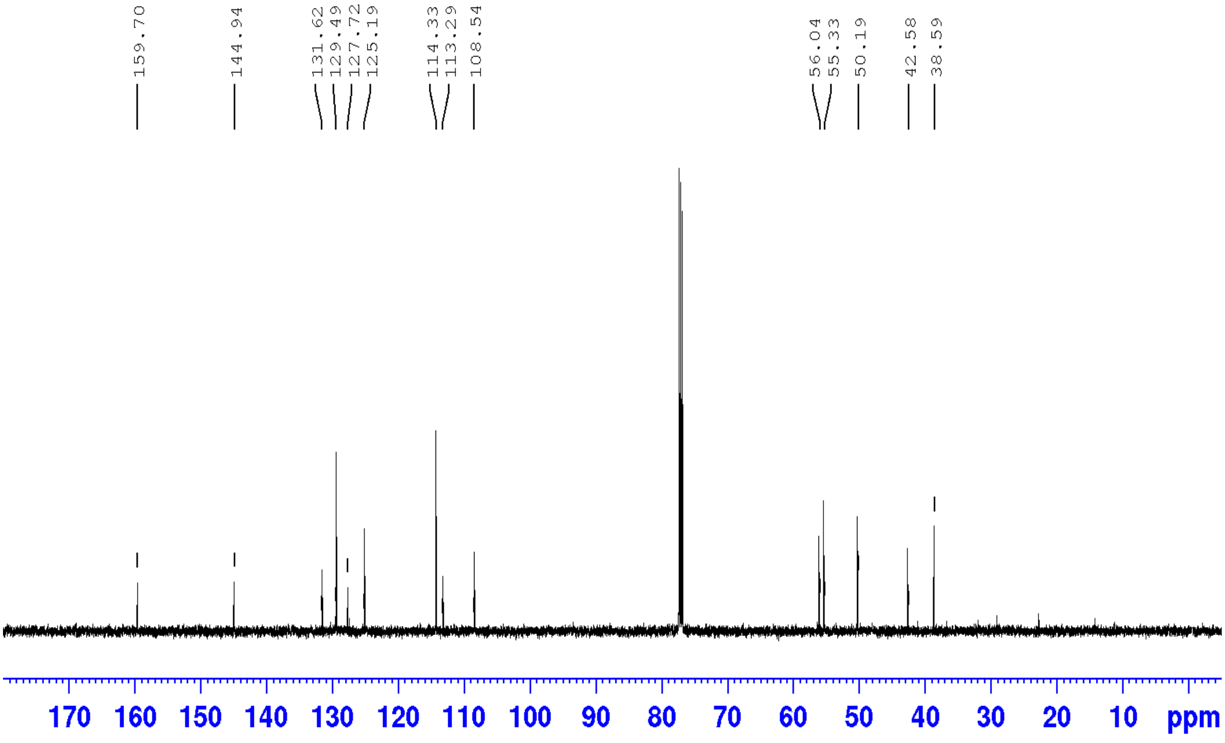
2-(4-methoxybenzyl)-7-methyl-5-(methylsulfonyl)-4,5-dihydro-2H-pyrazolo[4,3-c]pyridine (**50c'**)



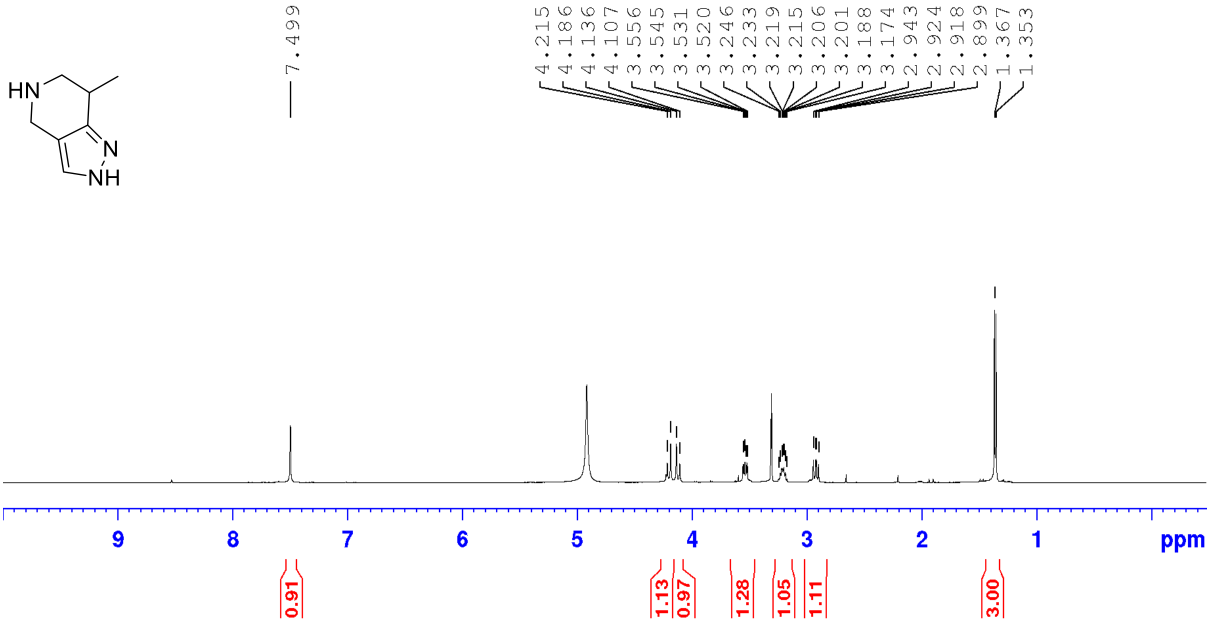


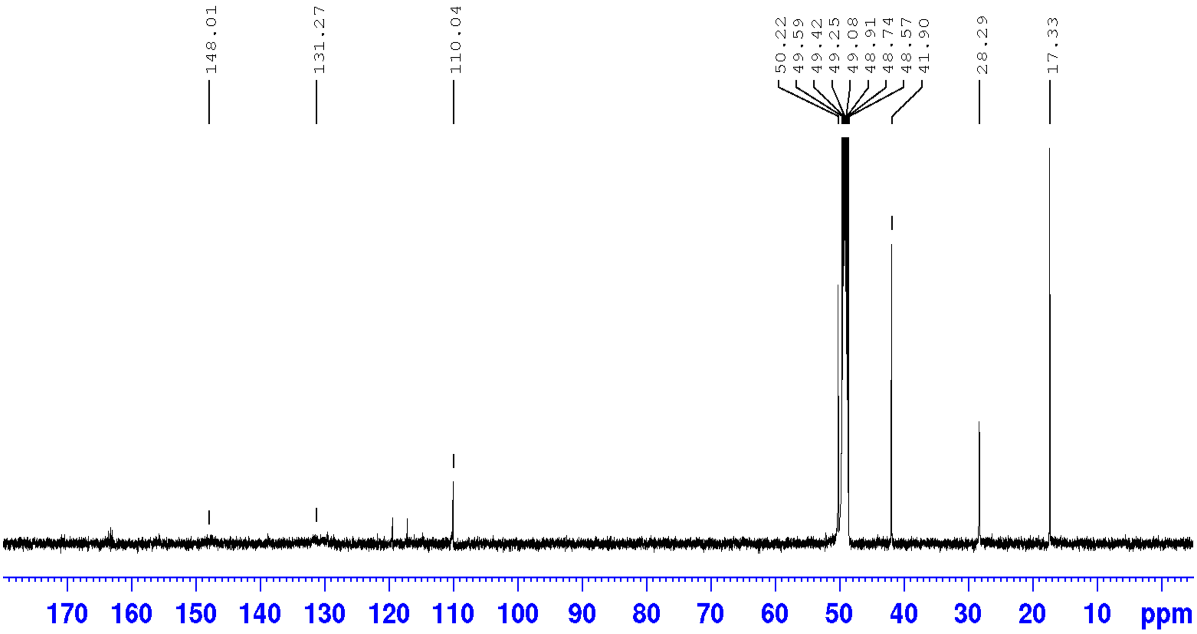
2-(4-methoxybenzyl)-7-methylene-5-(methylsulfonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (**50c''**)



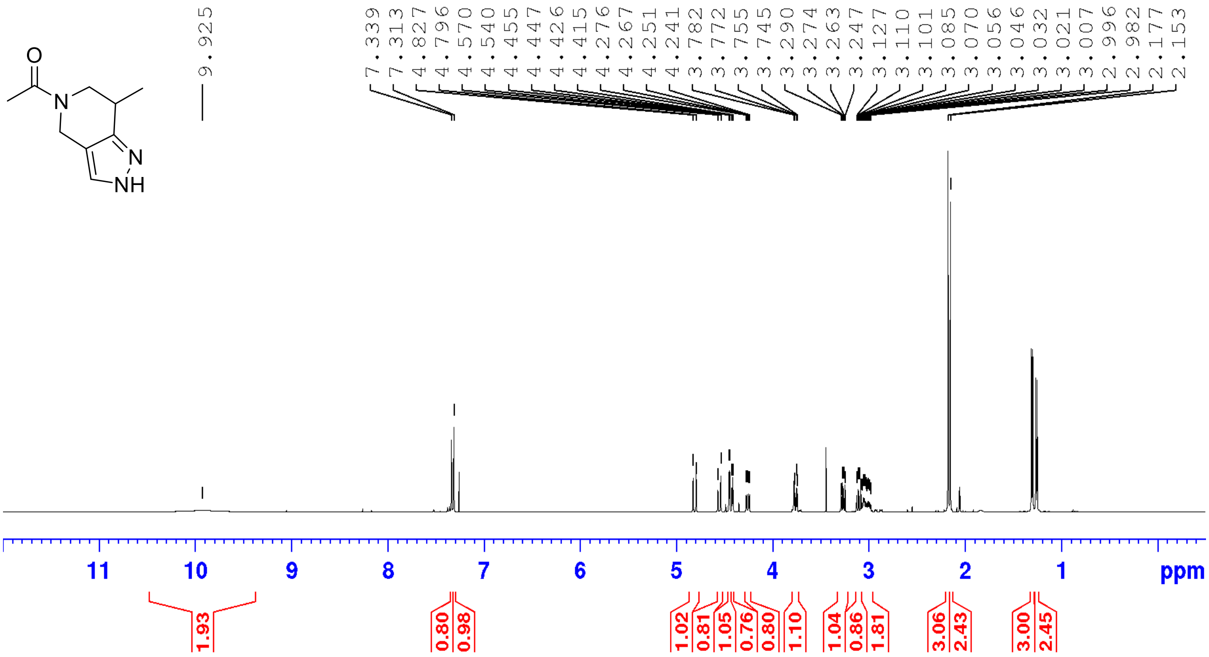


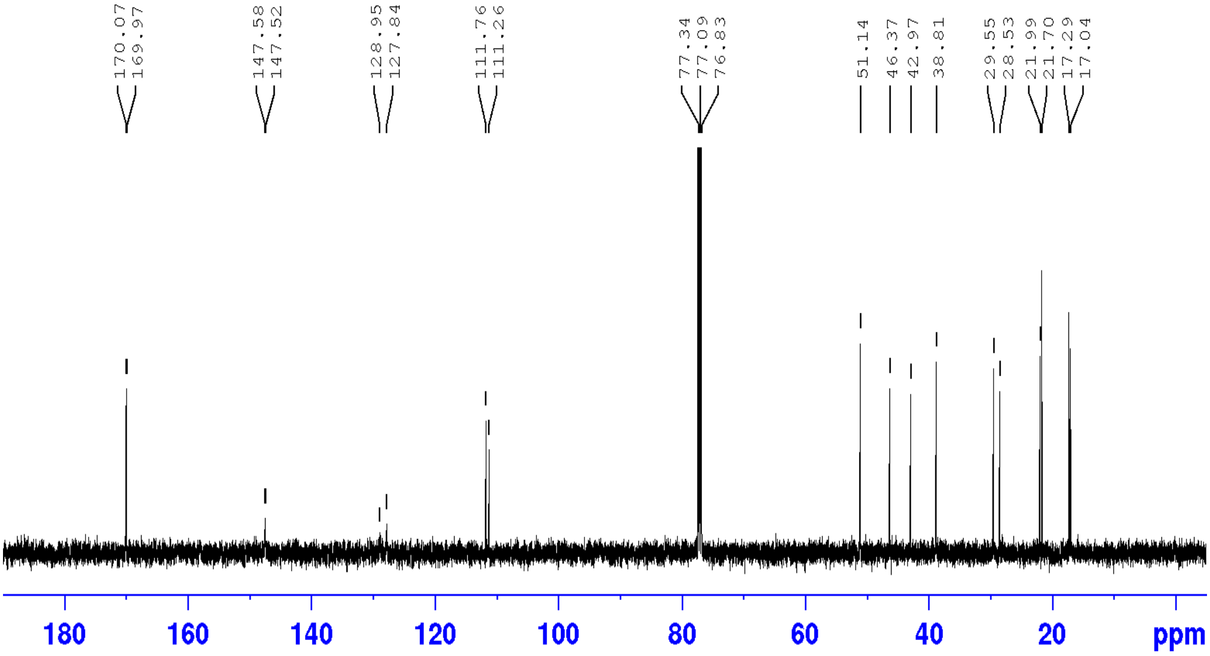
7-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (**12a**)



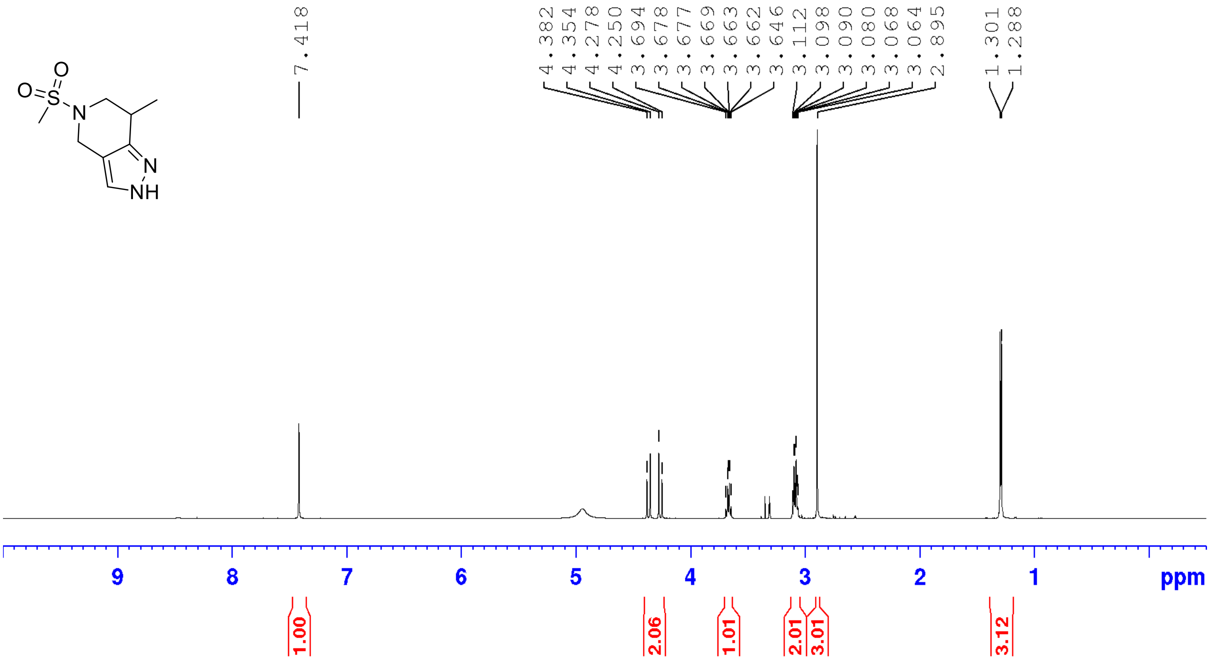


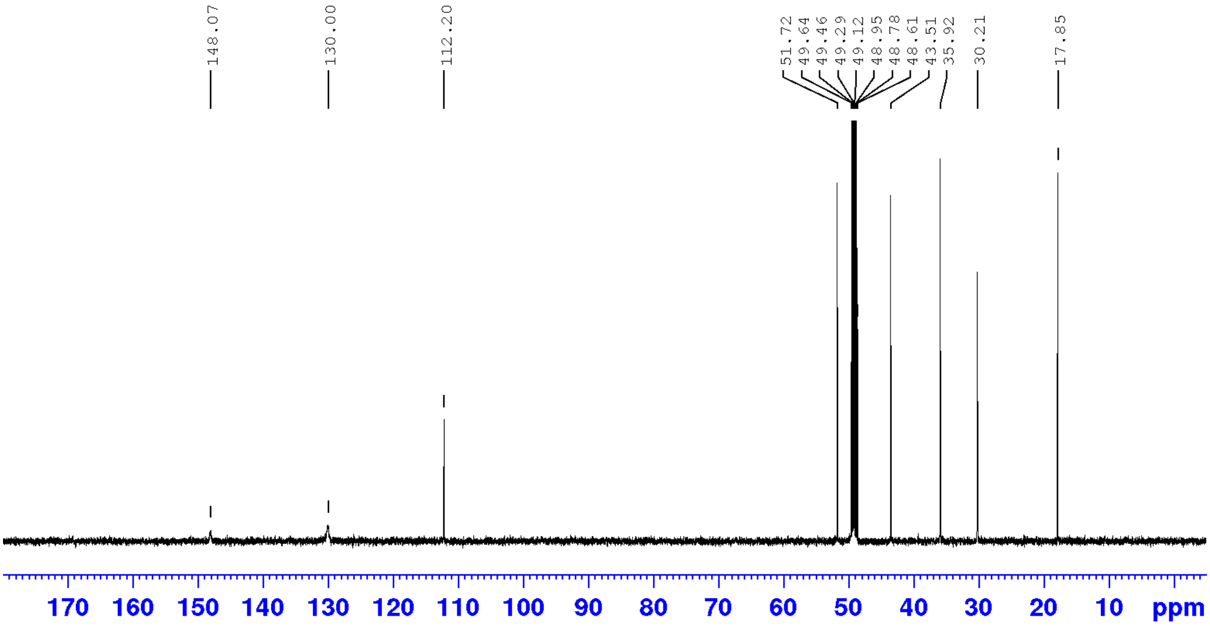
1-(7-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)ethan-1-one (**12b**)



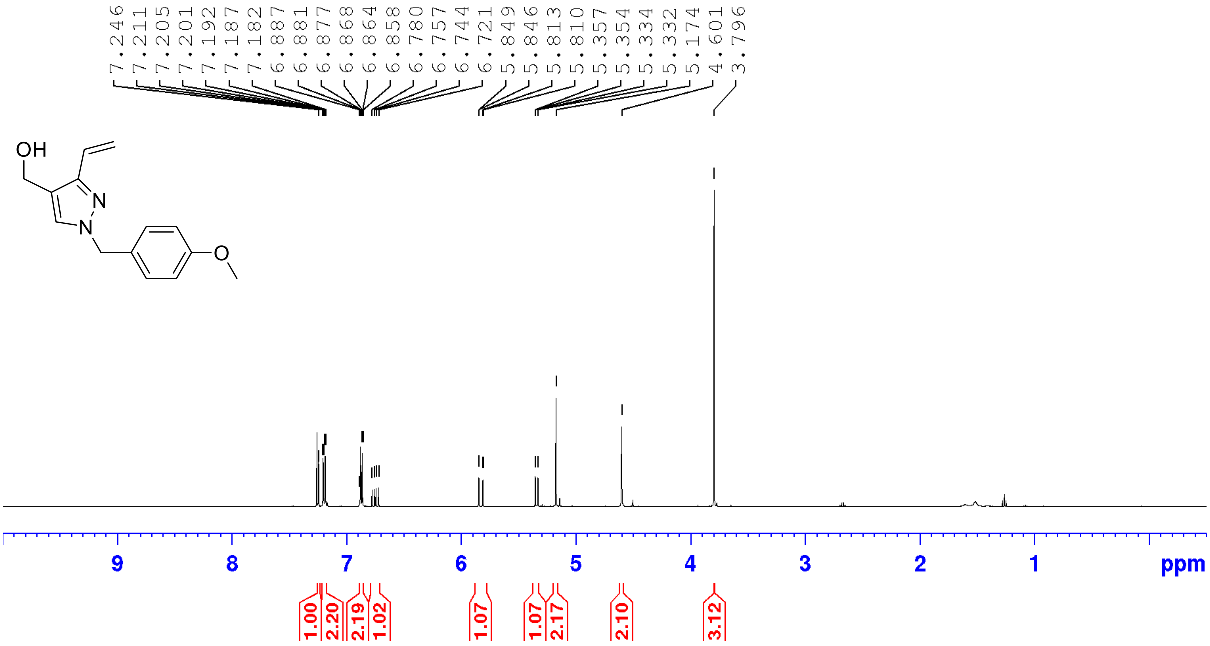


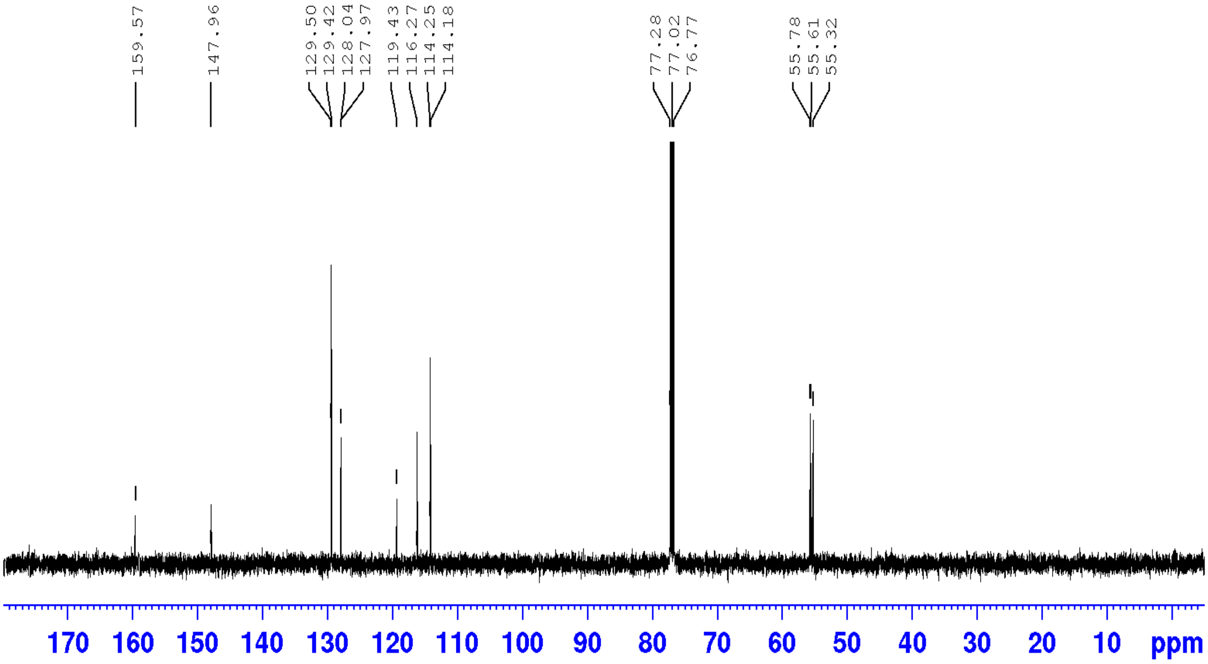
7-methyl-5-(methylsulfonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (**12c**)



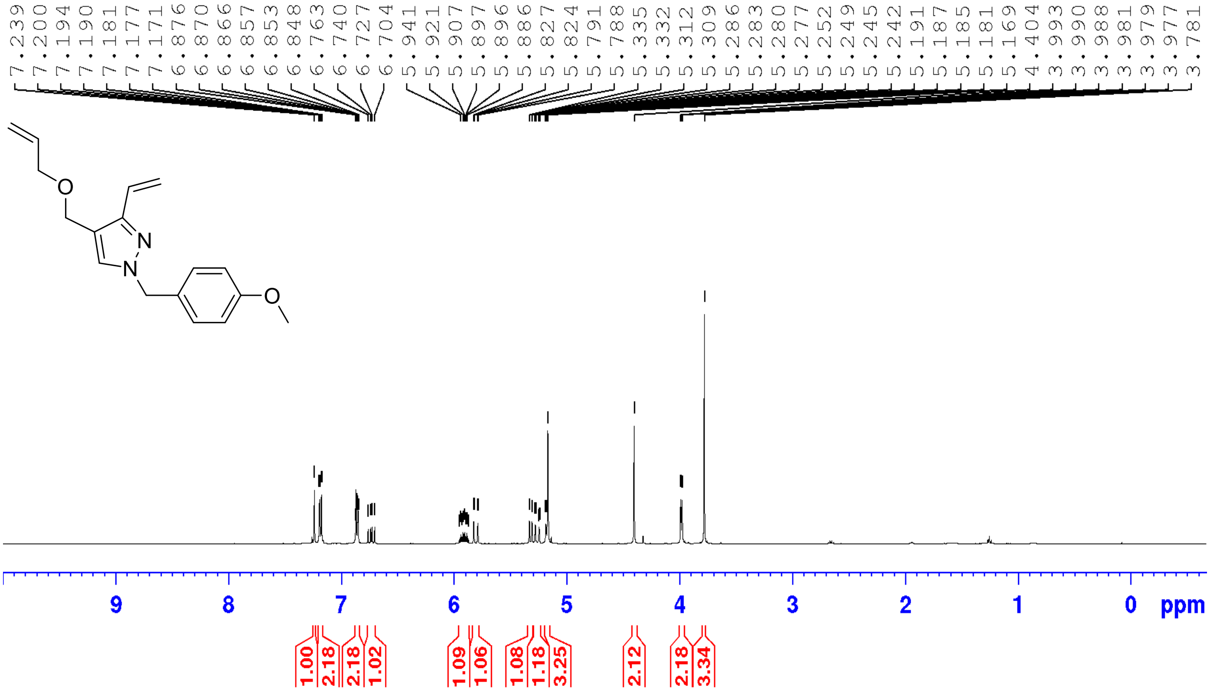


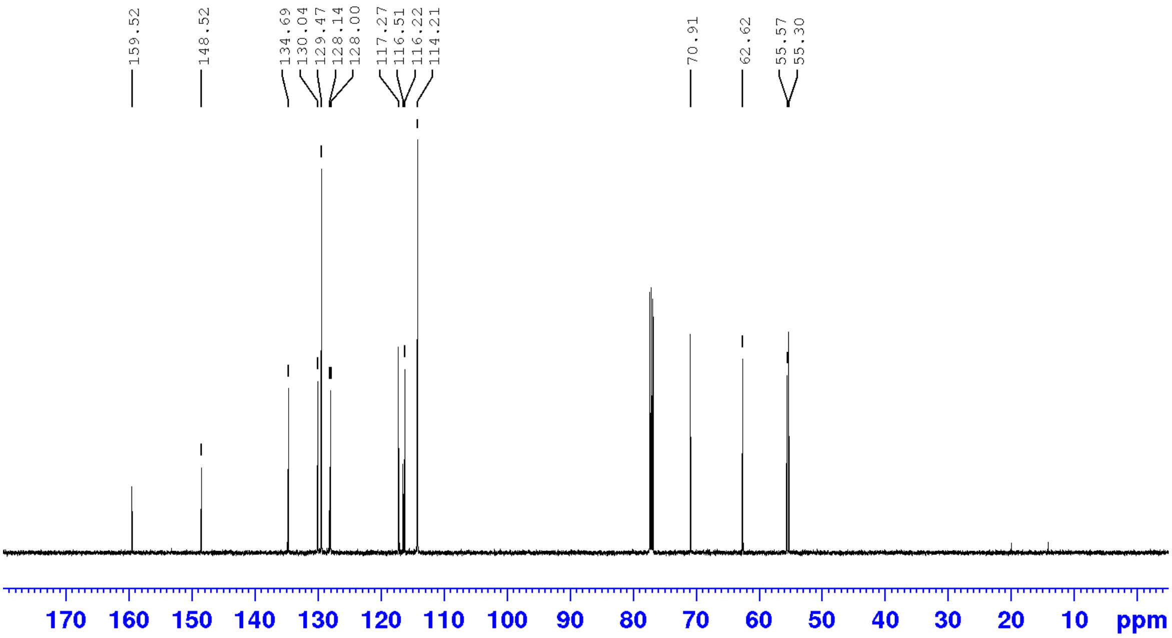
(1-(4-methoxybenzyl)-3-vinyl-1H-pyrazol-4-yl) methanol (**51**)



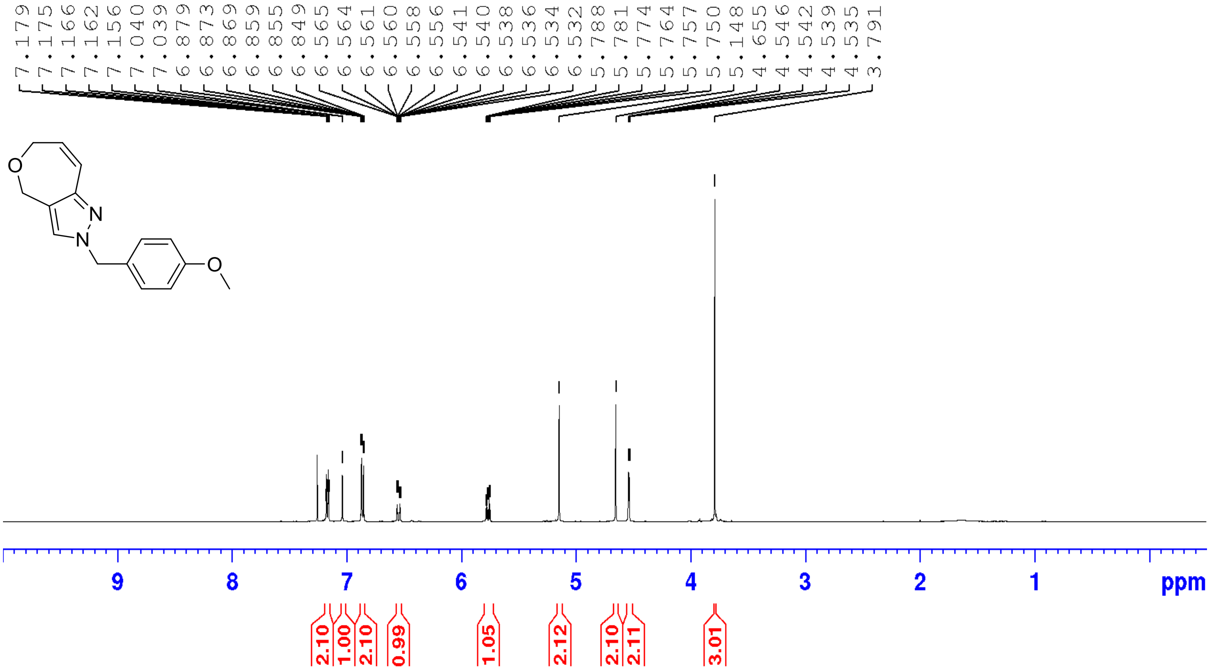


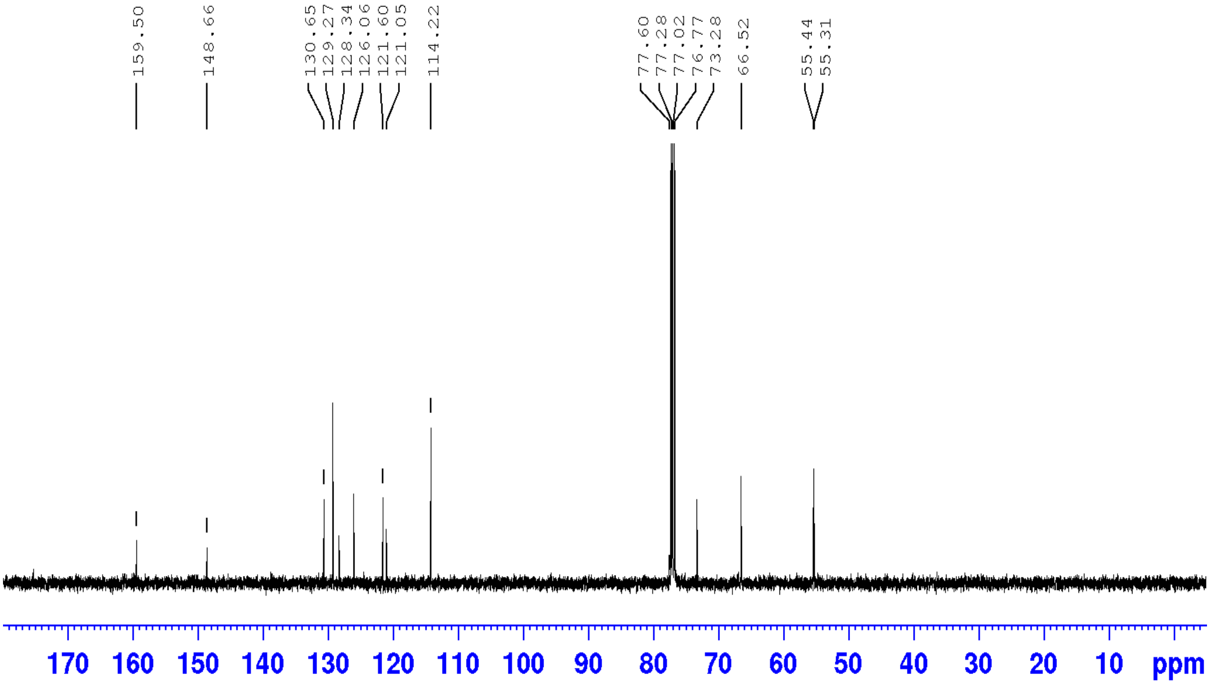
4-((allyloxy)methyl)-1-(4-methoxybenzyl)-3-vinyl-1H-pyrazole (**52**)



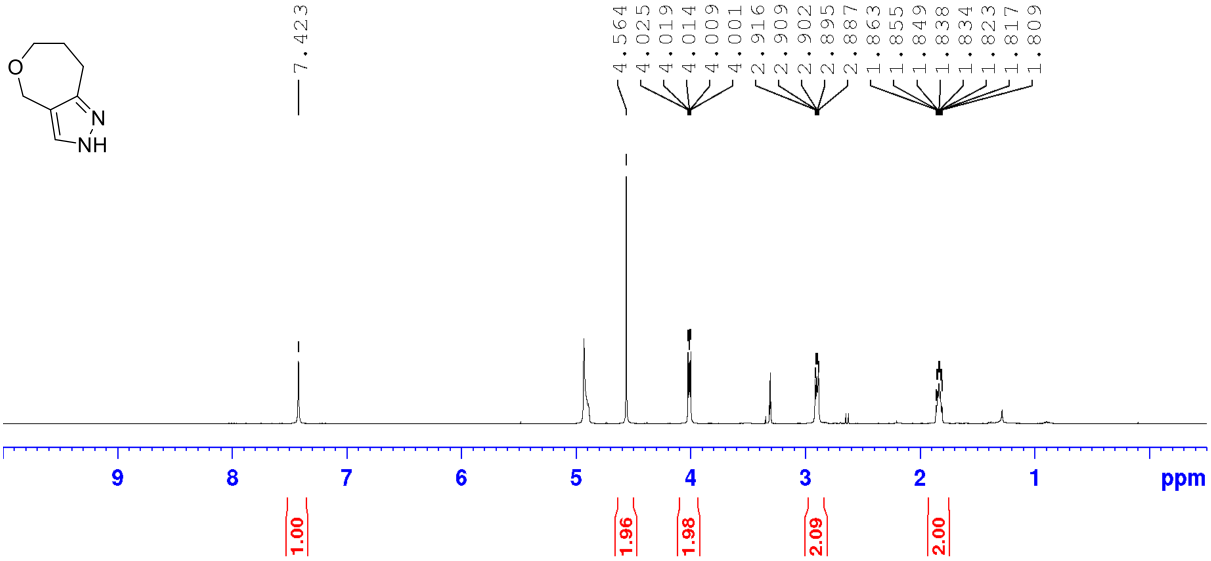


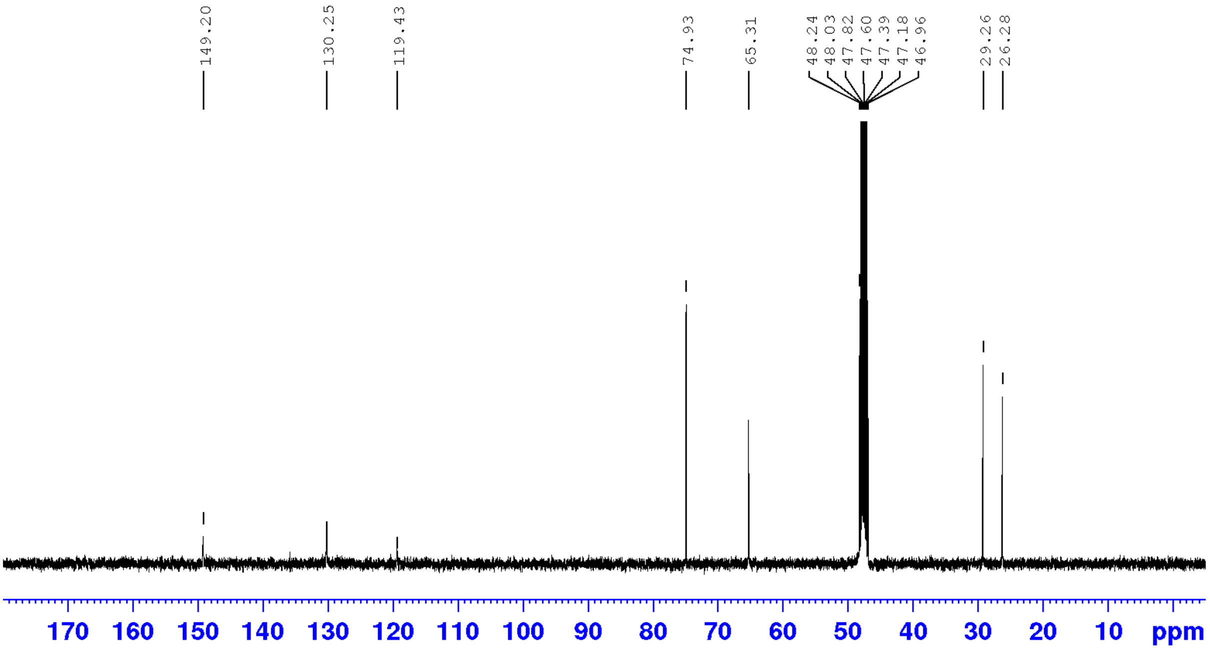
2-(4-methoxybenzyl)-2,6-dihydro-4H-oxepino[4,3-c]pyrazole (**53**)



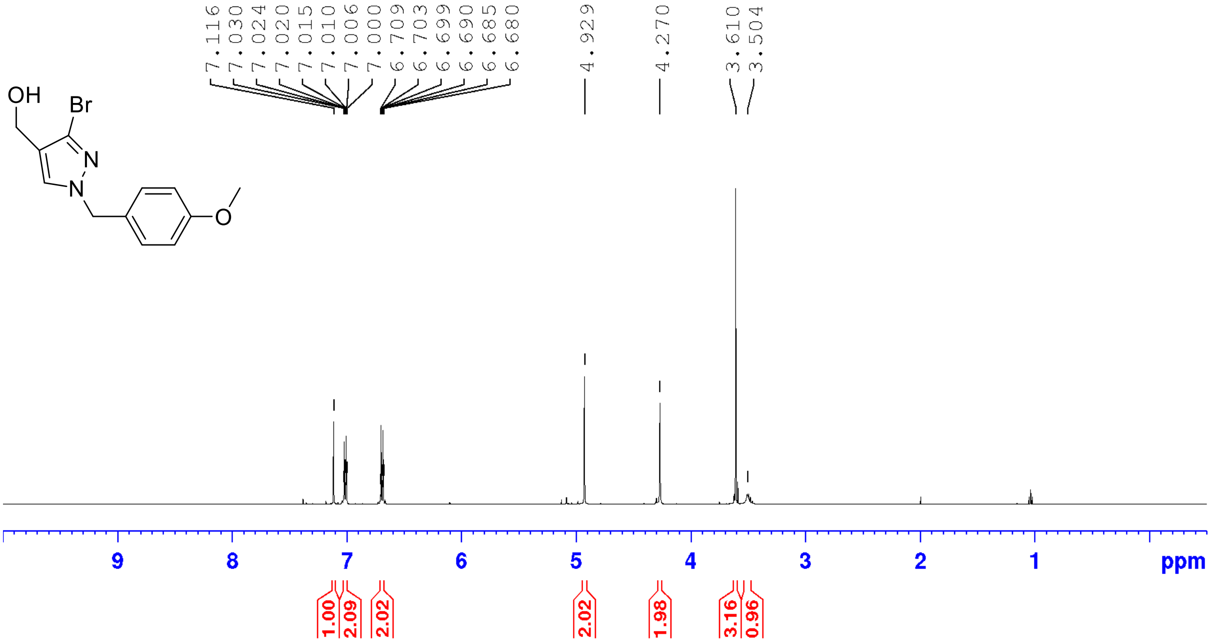


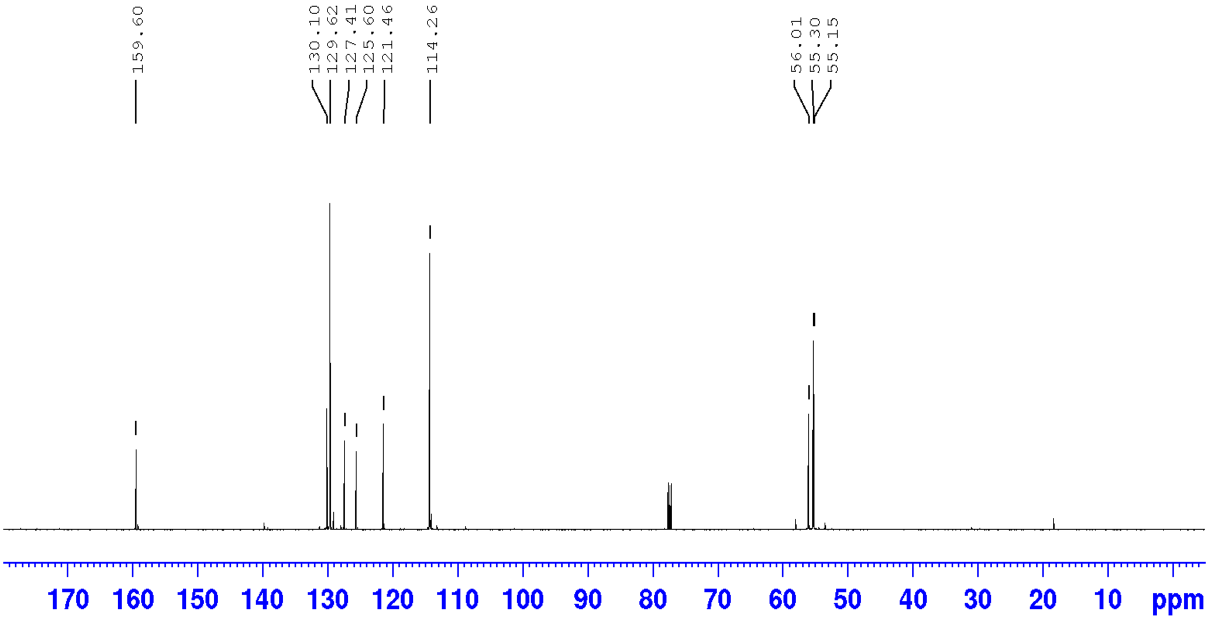
2,6,7,8-tetrahydro-4H-oxepino[4,3-c]pyrazole (**15**)



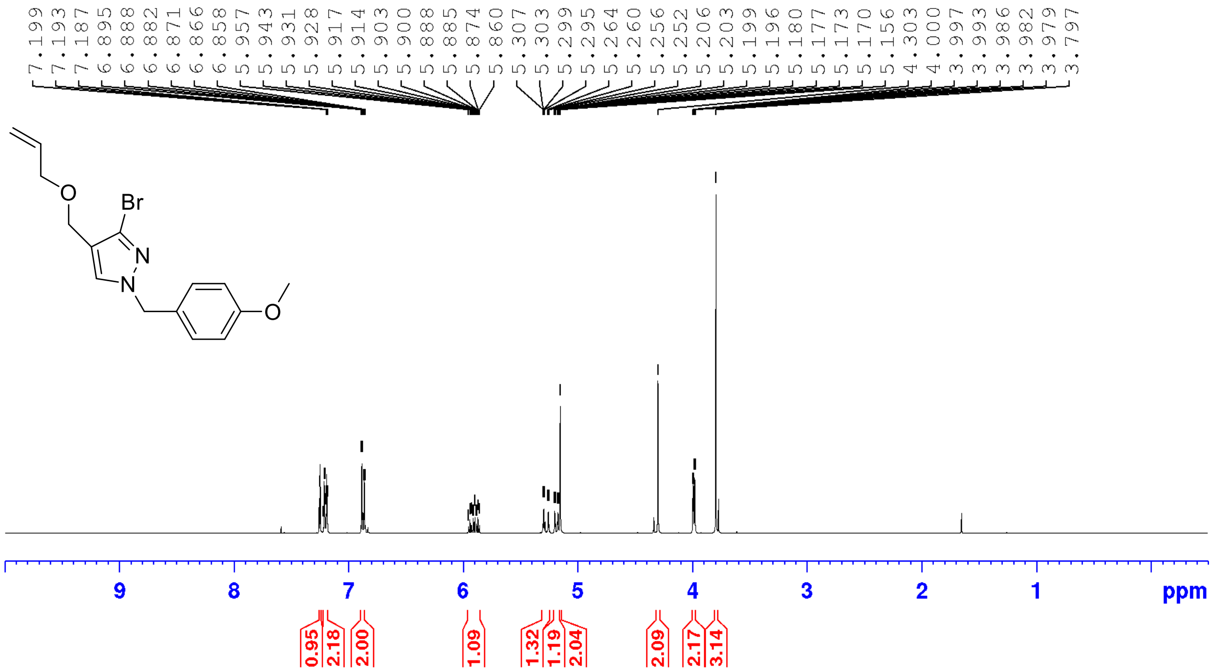


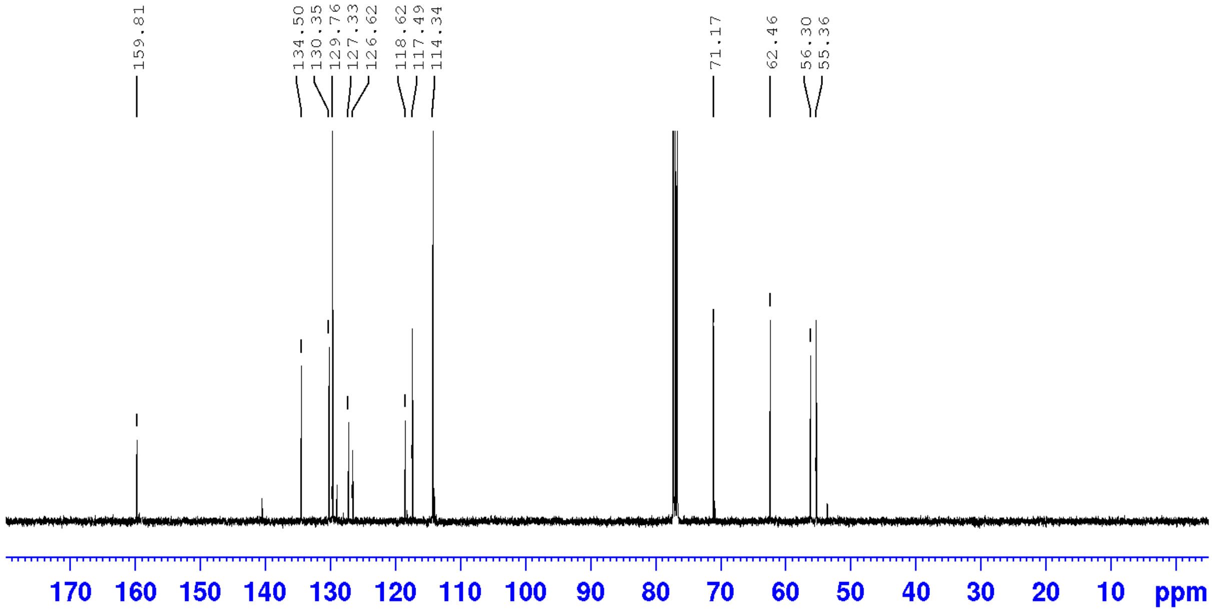
(3-bromo-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methanol (**54**)



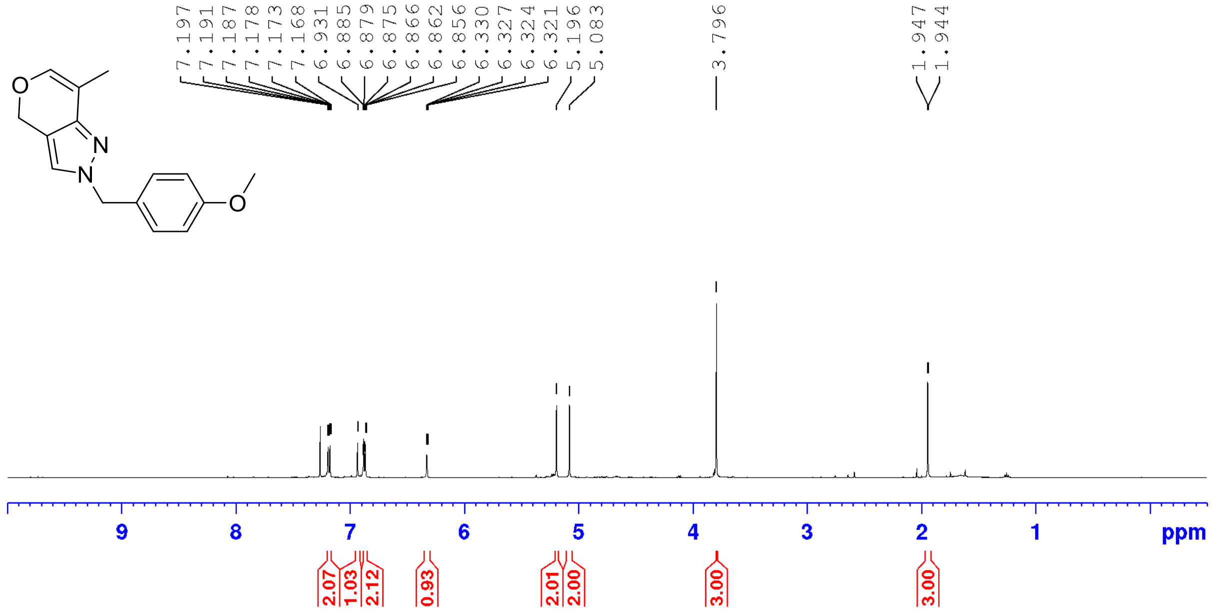


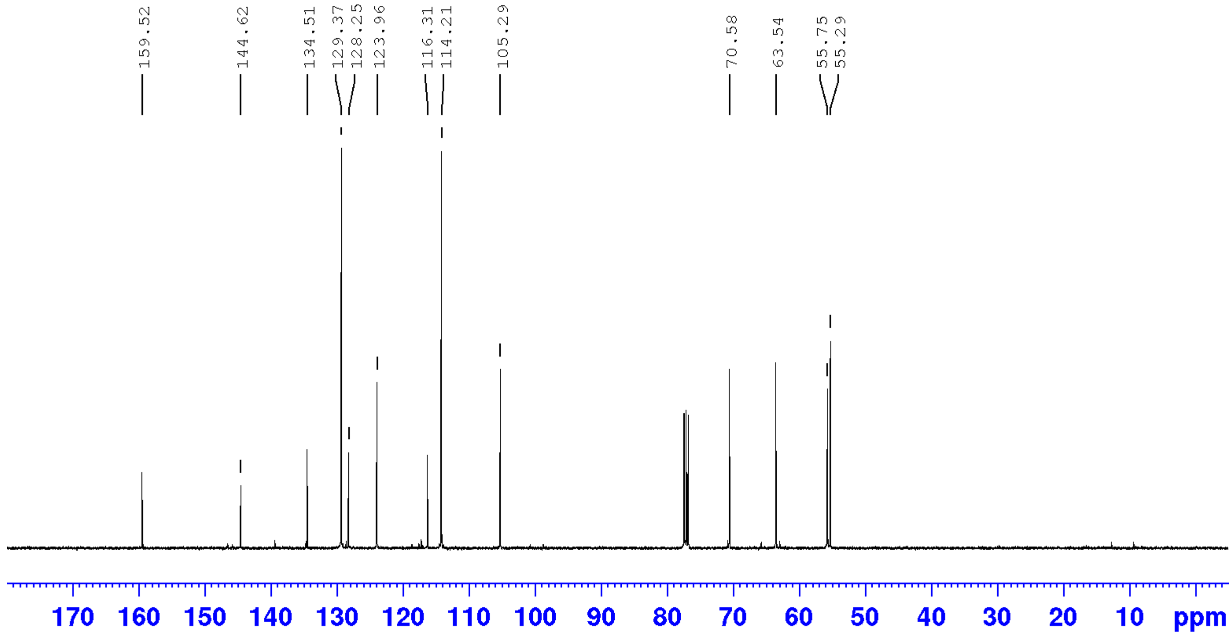
4-((allyloxy)methyl)-3-bromo-1-(4-methoxybenzyl)-1H-pyrazole (**55**)



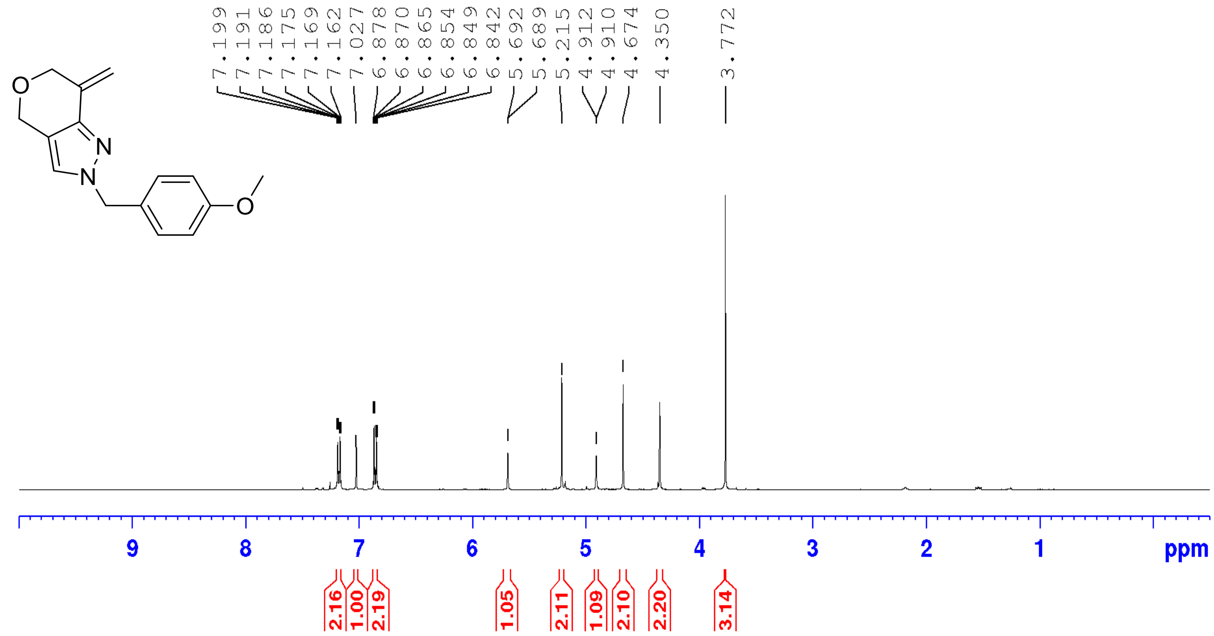


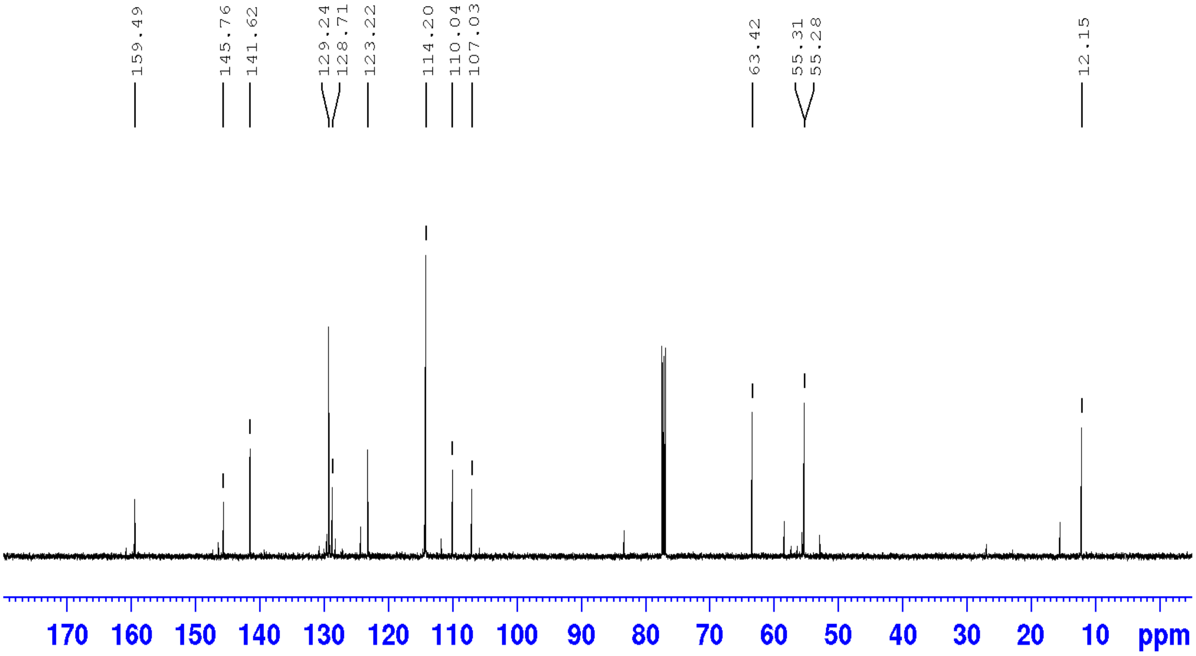
2-(4-methoxybenzyl)-7-methyl-2,4-dihydropyrano[4,3-c]pyrazole (**56’**)



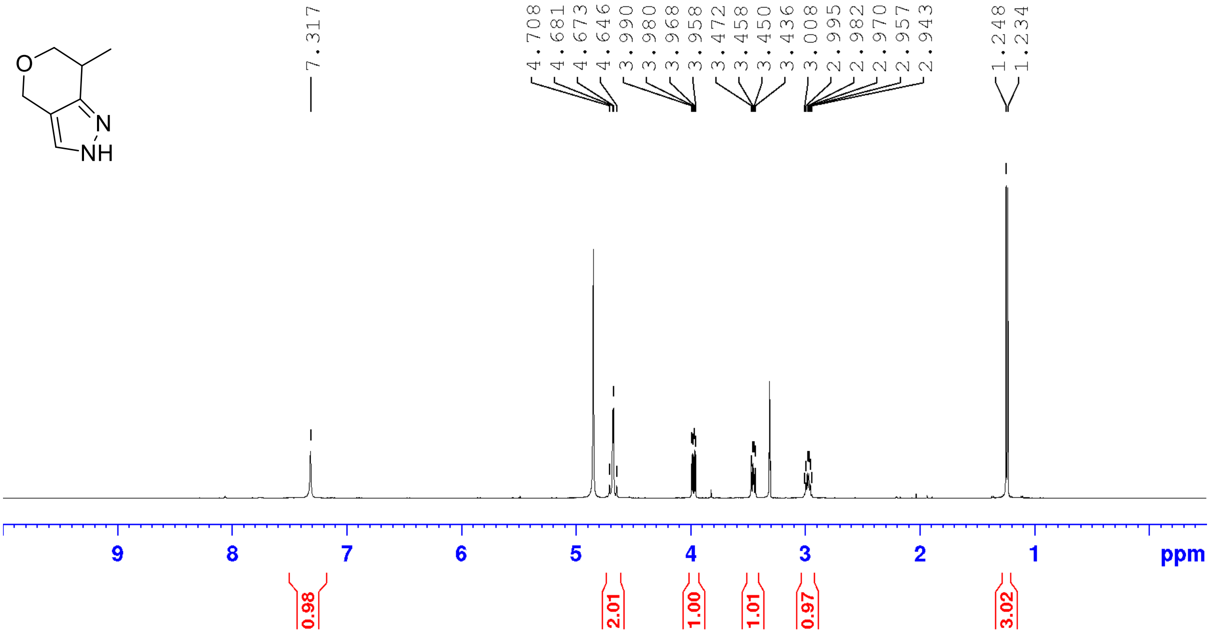


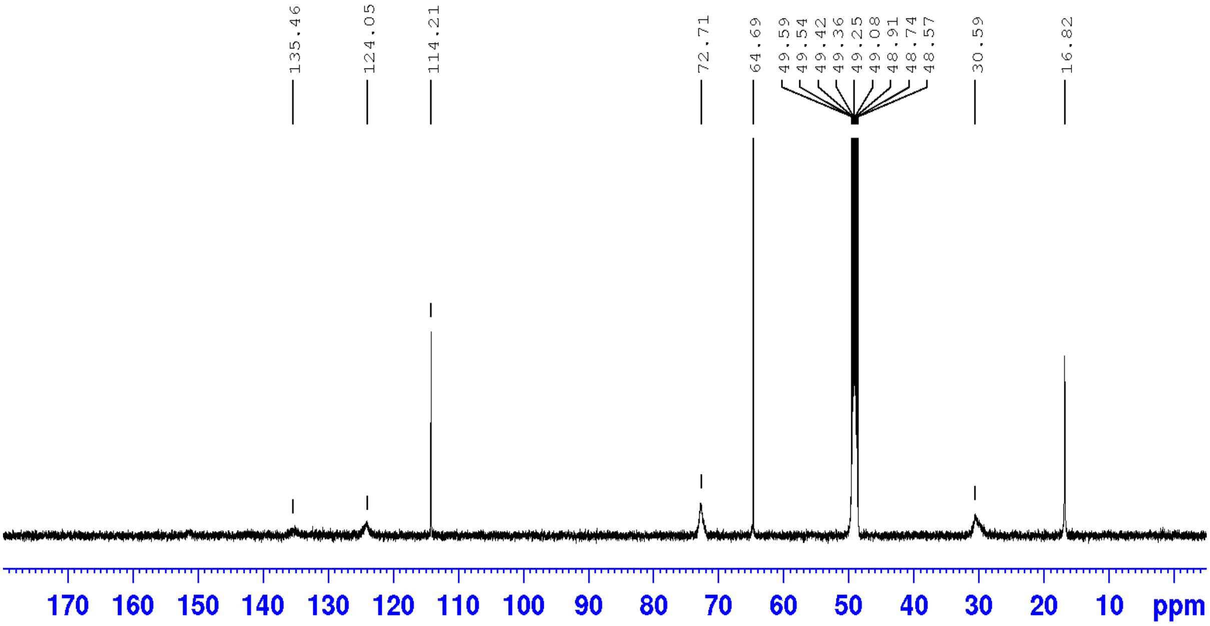
2-(4-methoxybenzyl)-7-methylene-2,4,6,7-tetrahydropyrano[4,3-c]pyrazole (**56’’**)



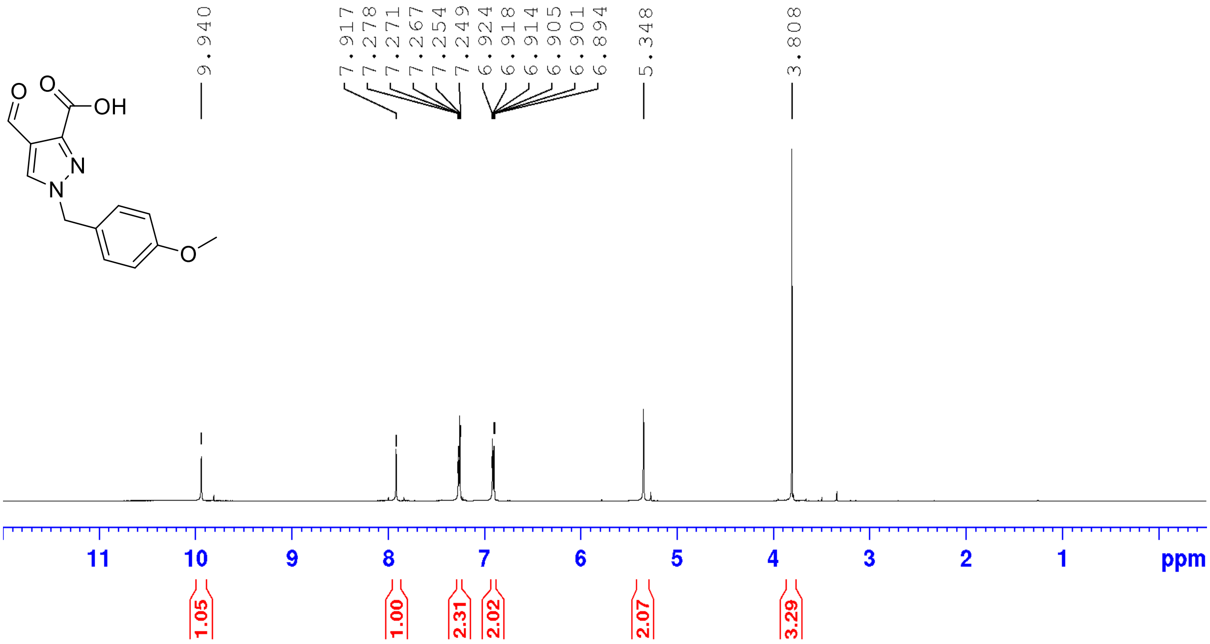


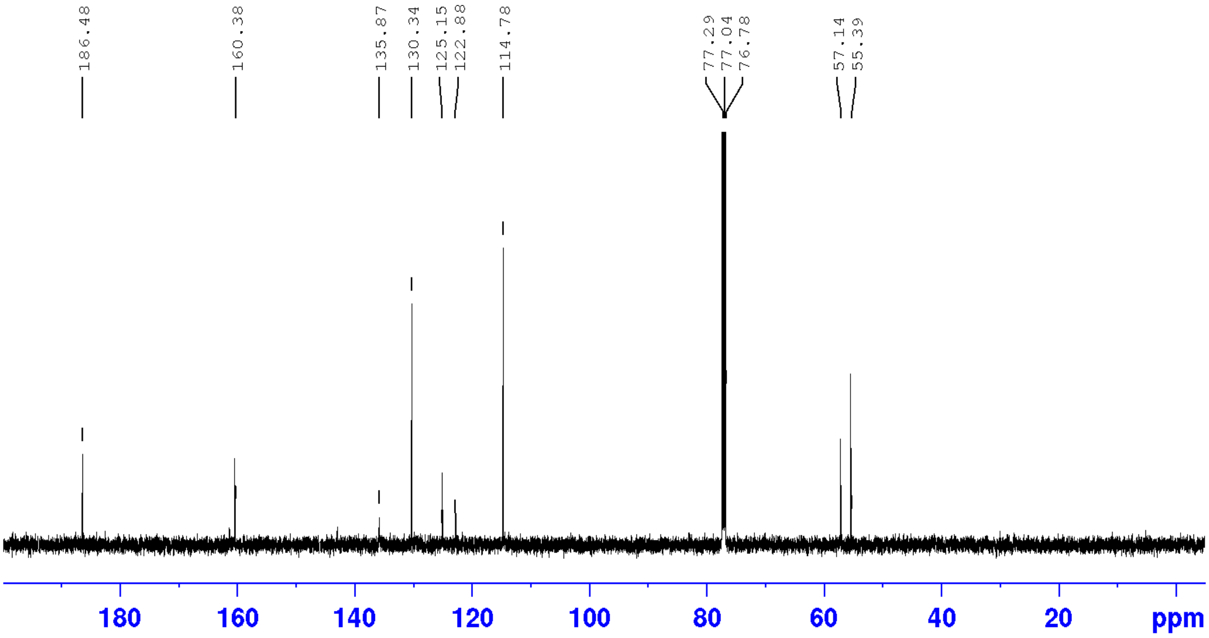
7-methyl-2,4,6,7-tetrahydropyrano[4,3-c]pyrazole (**14**)



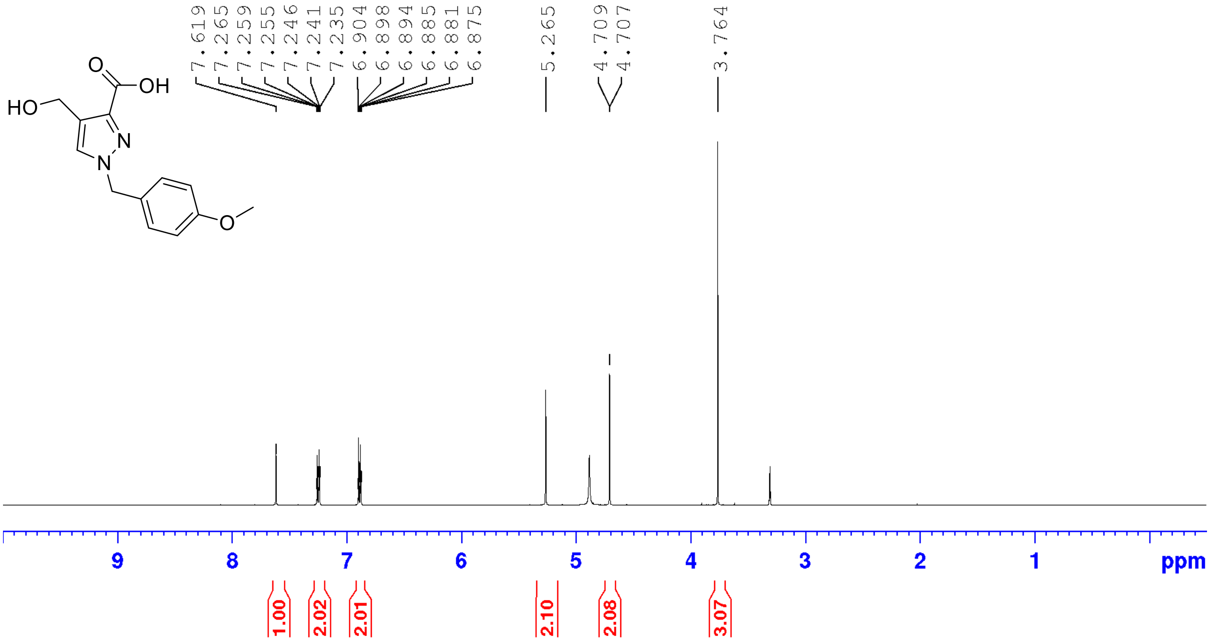


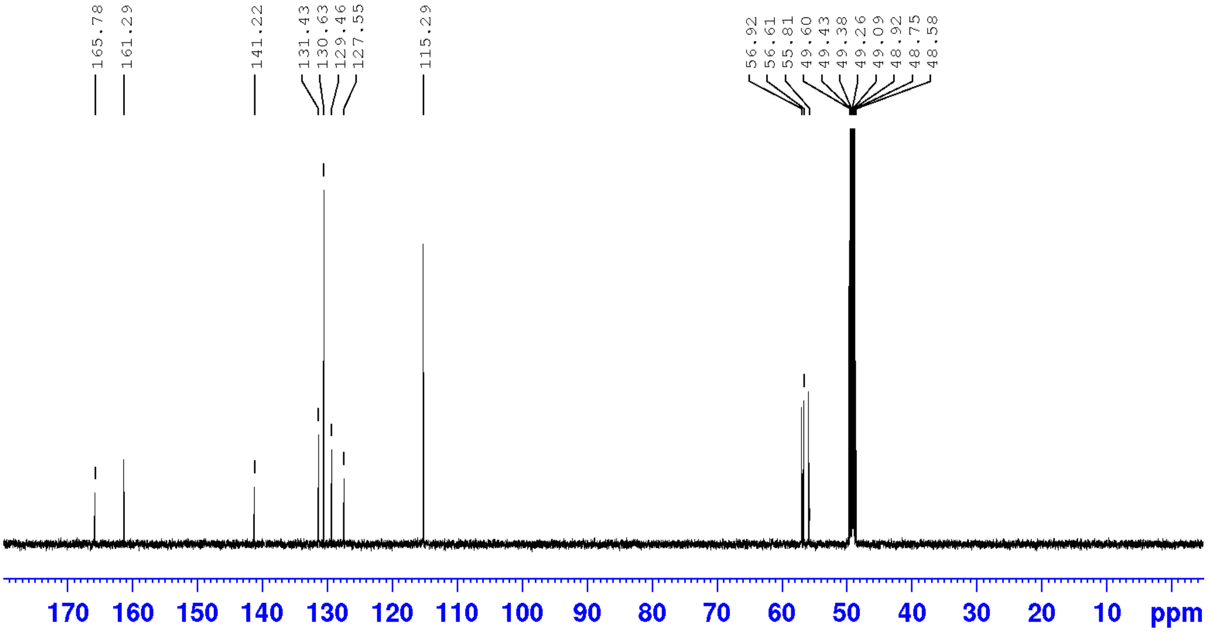
4-formyl-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylic acid (**57**)



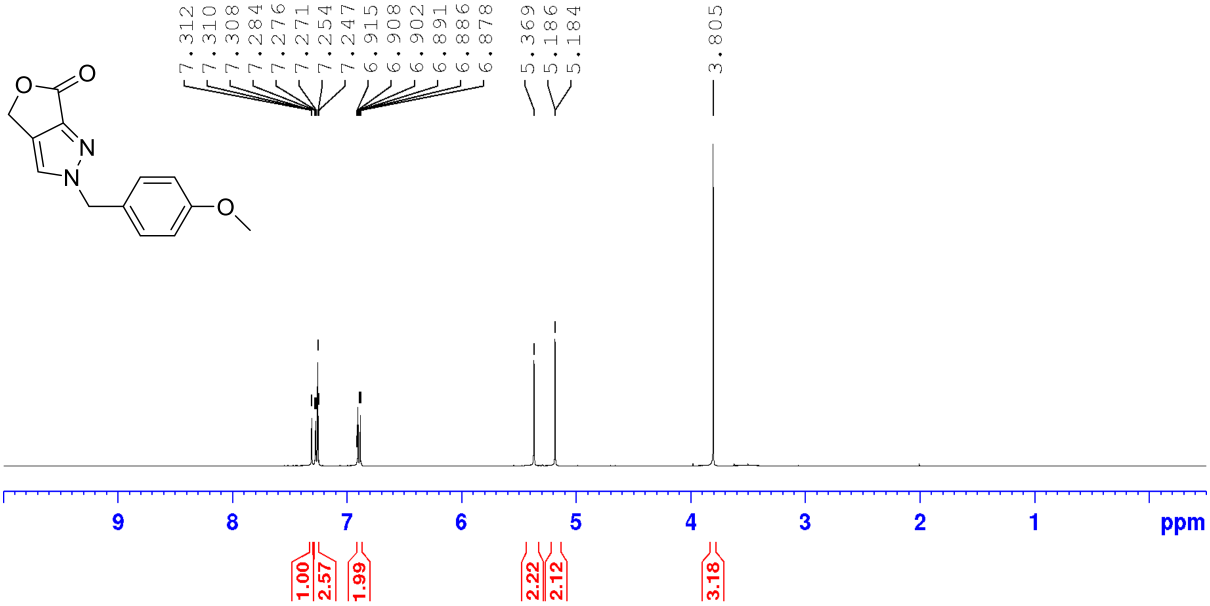


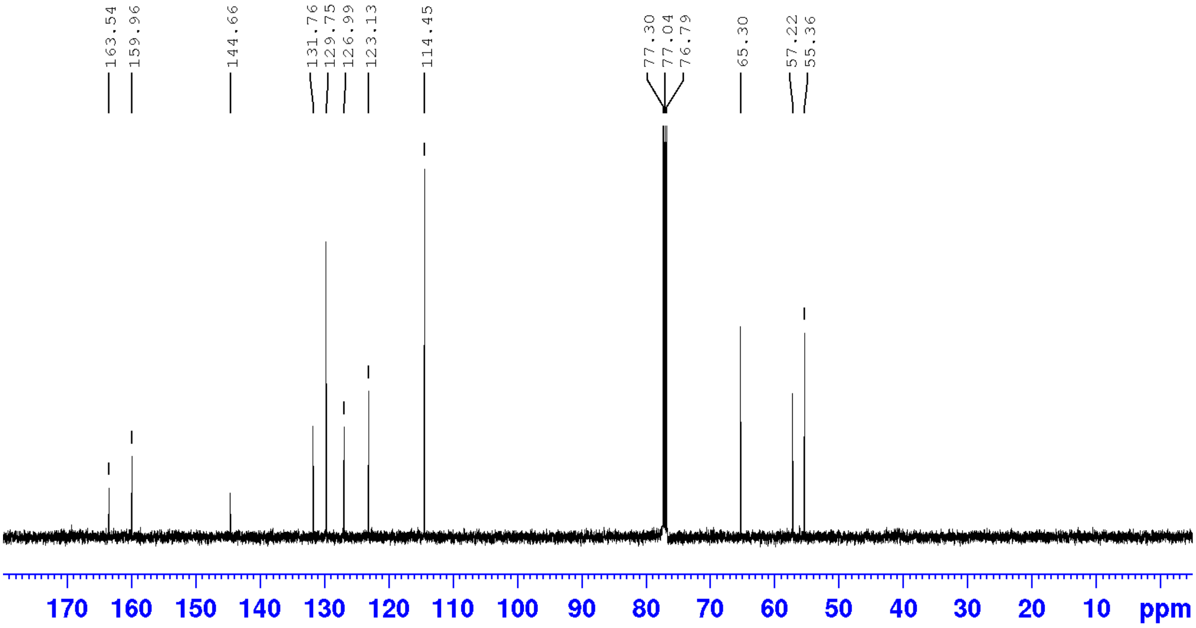
4-(hydroxymethyl)-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylic acid (**58**)



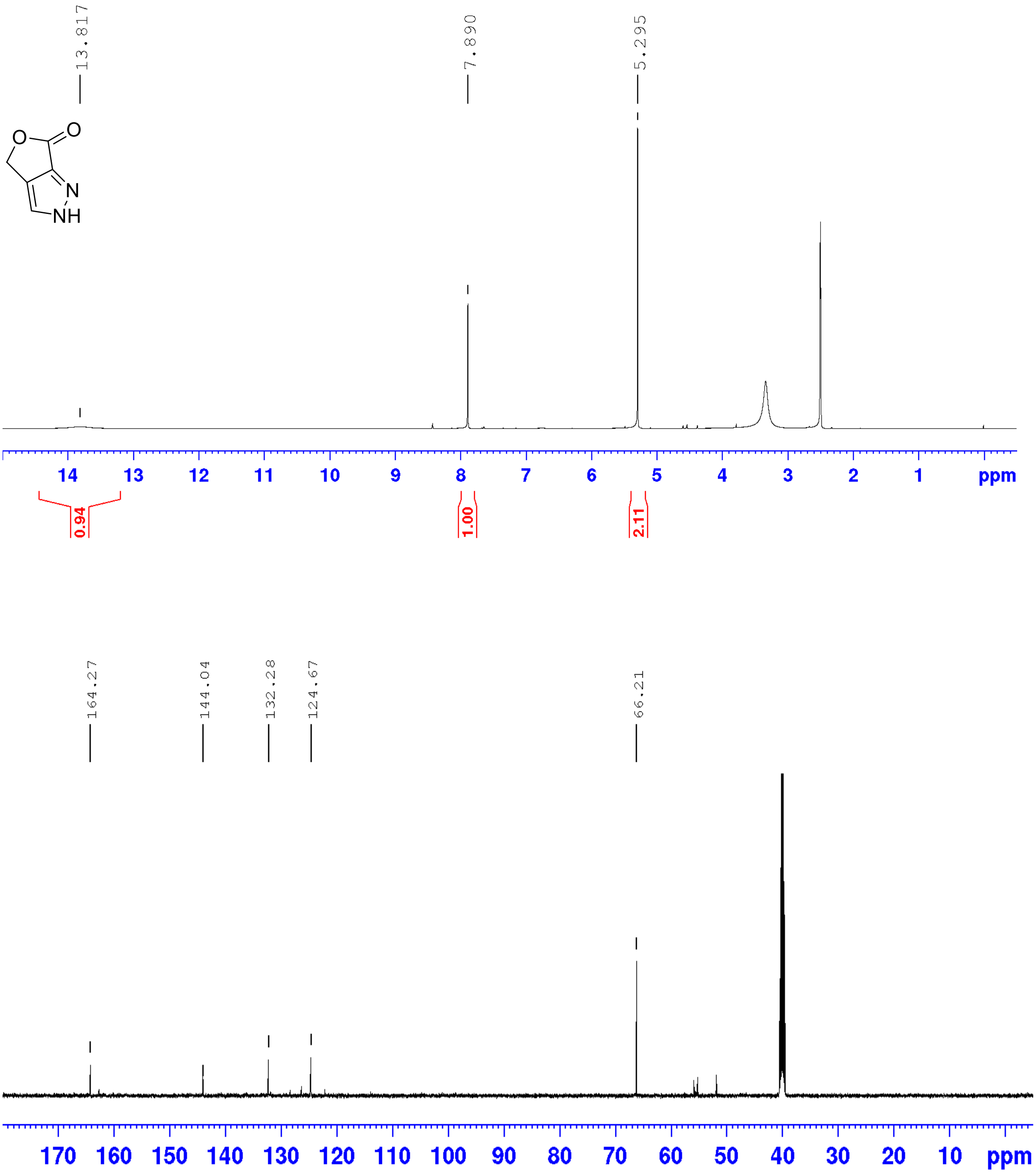


2-(4-methoxybenzyl)-2,4-dihydro-6H-furo[3,4-c]pyrazol-6-one (**59**)

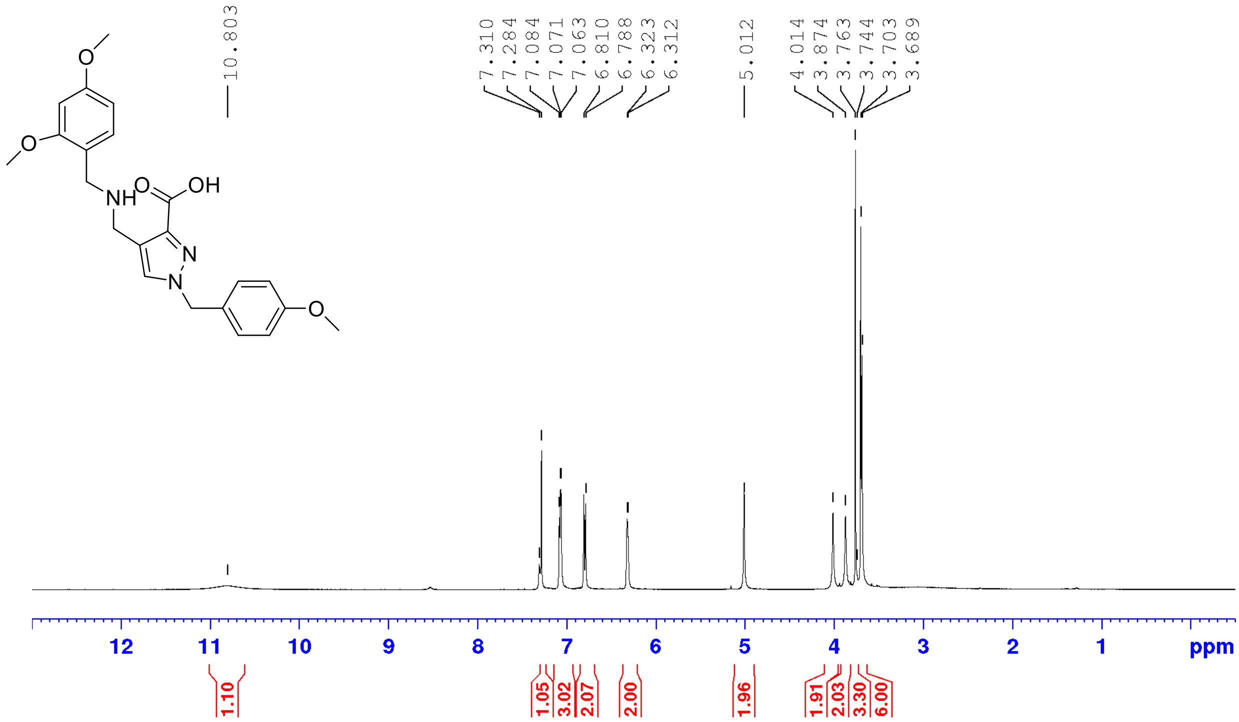


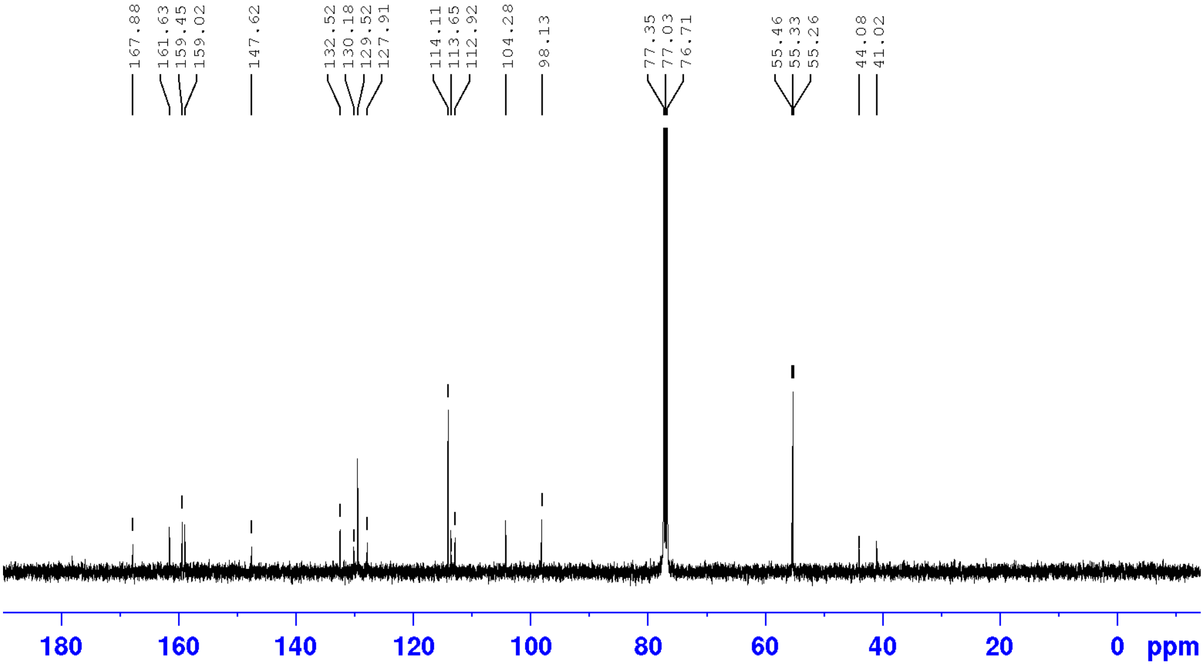


2,4-dihydro-6H-furo[3,4-c]pyrazol-6-one (**16**)

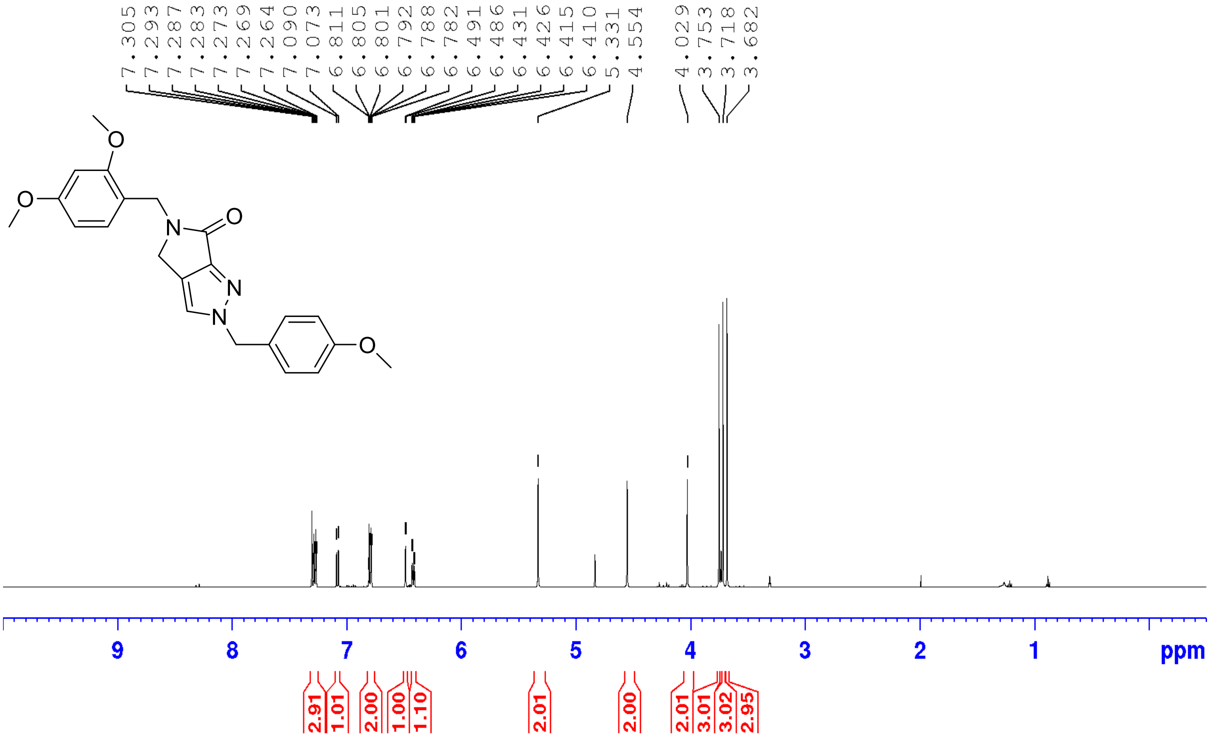


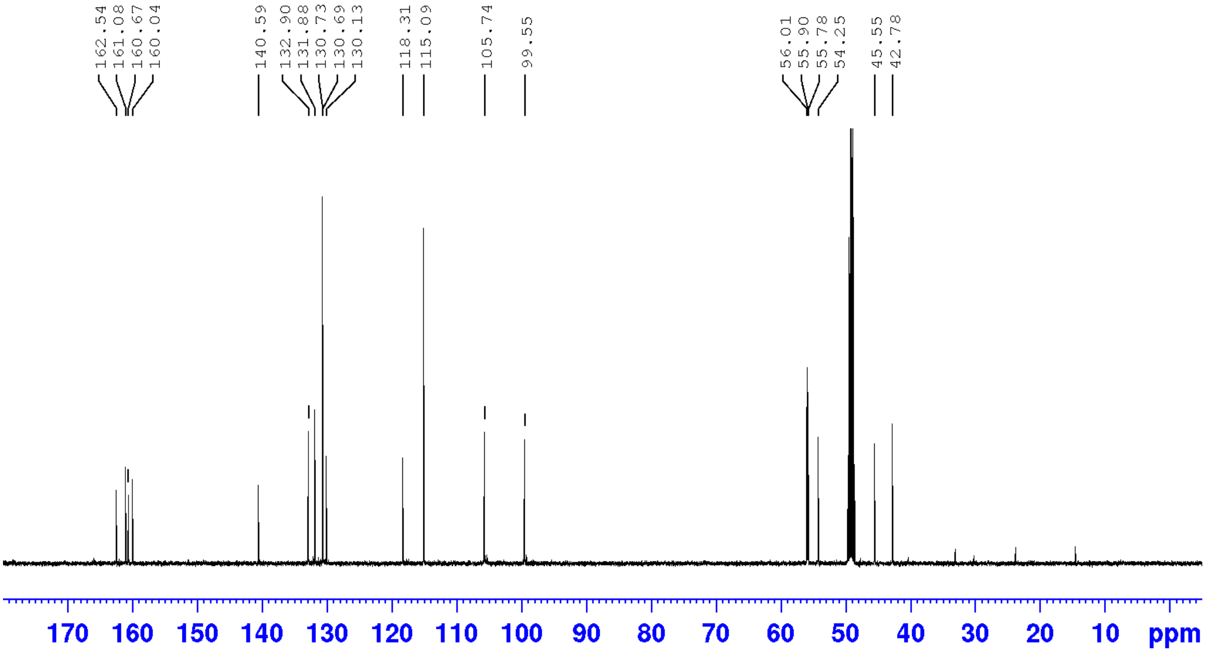
4-(((2,4-dimethoxybenzyl)amino)methyl)-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylic acid (**60**)



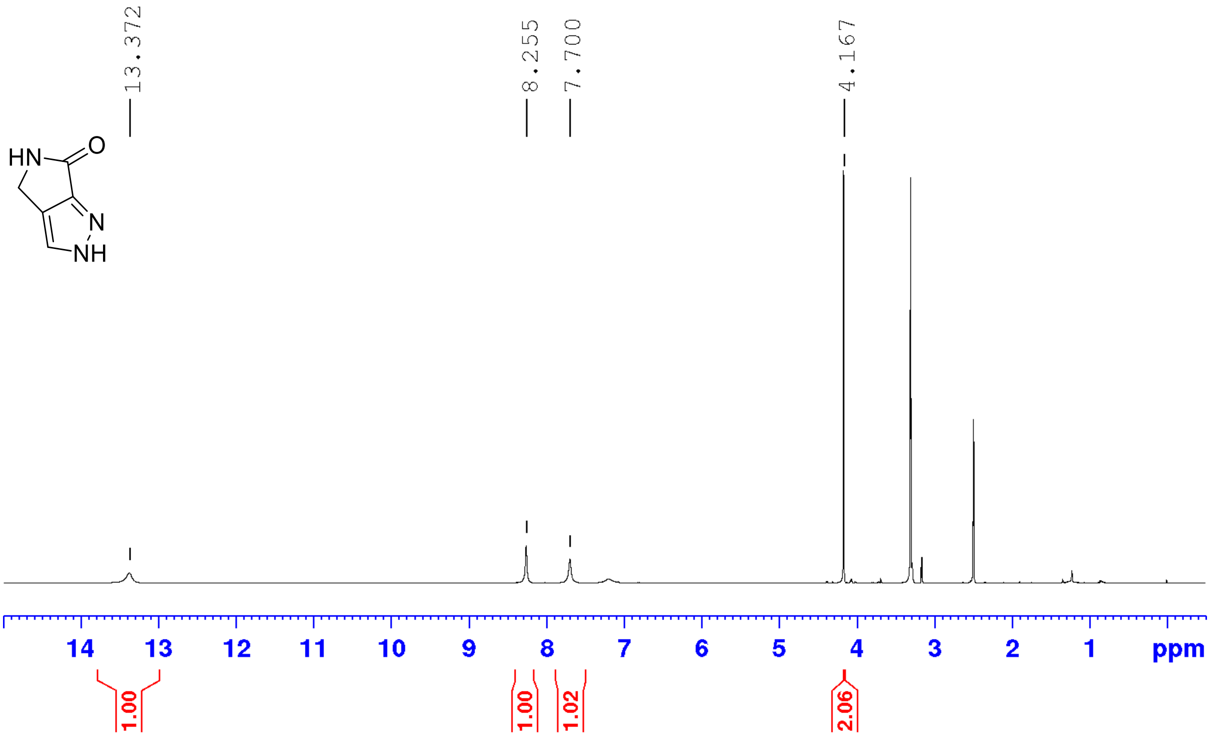


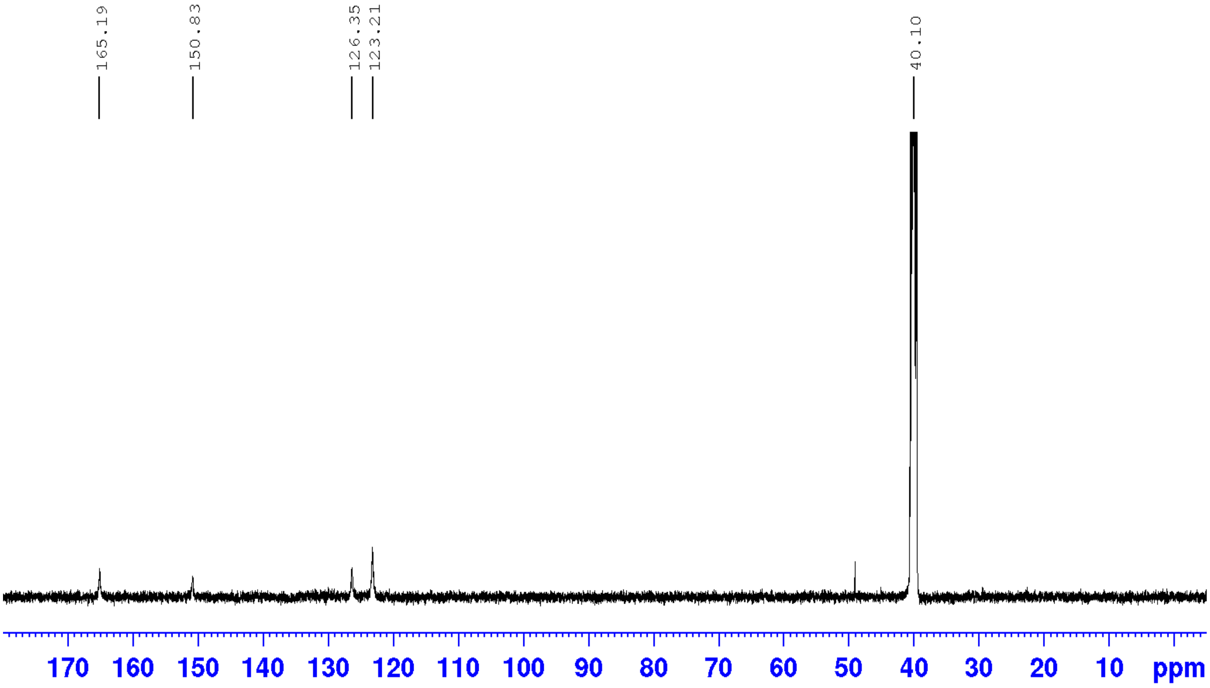
5-(2,4-dimethoxybenzyl)-2-(4-methoxybenzyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(2H)-one (**61**)



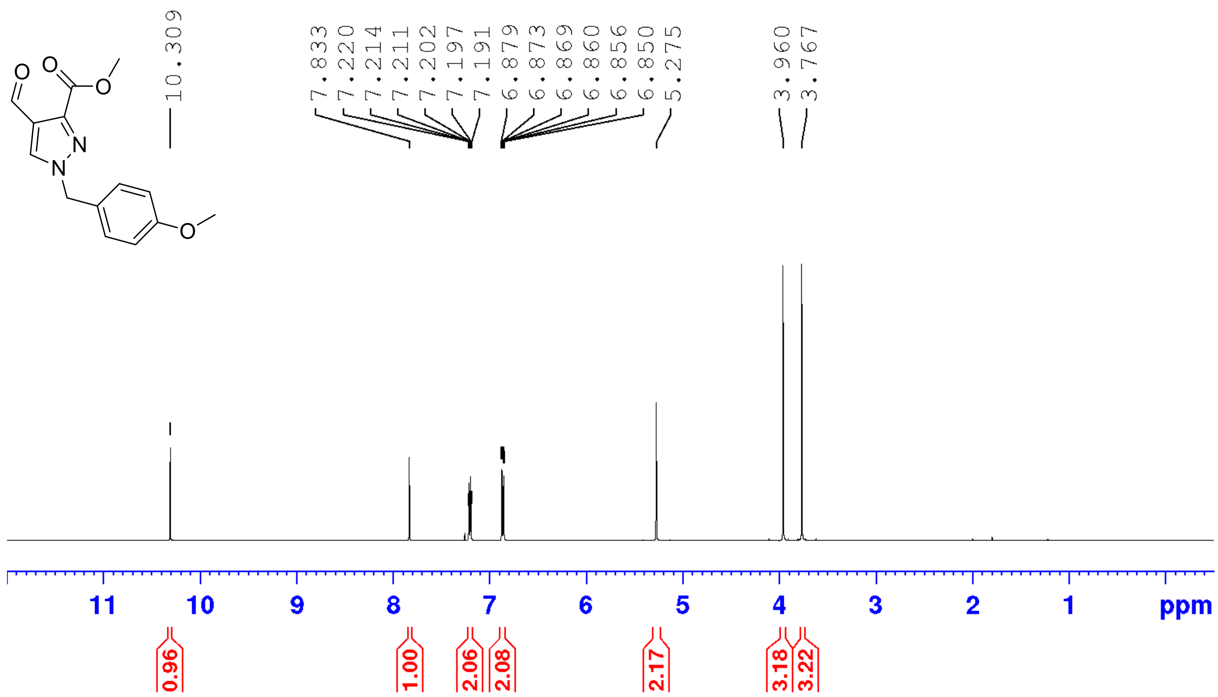


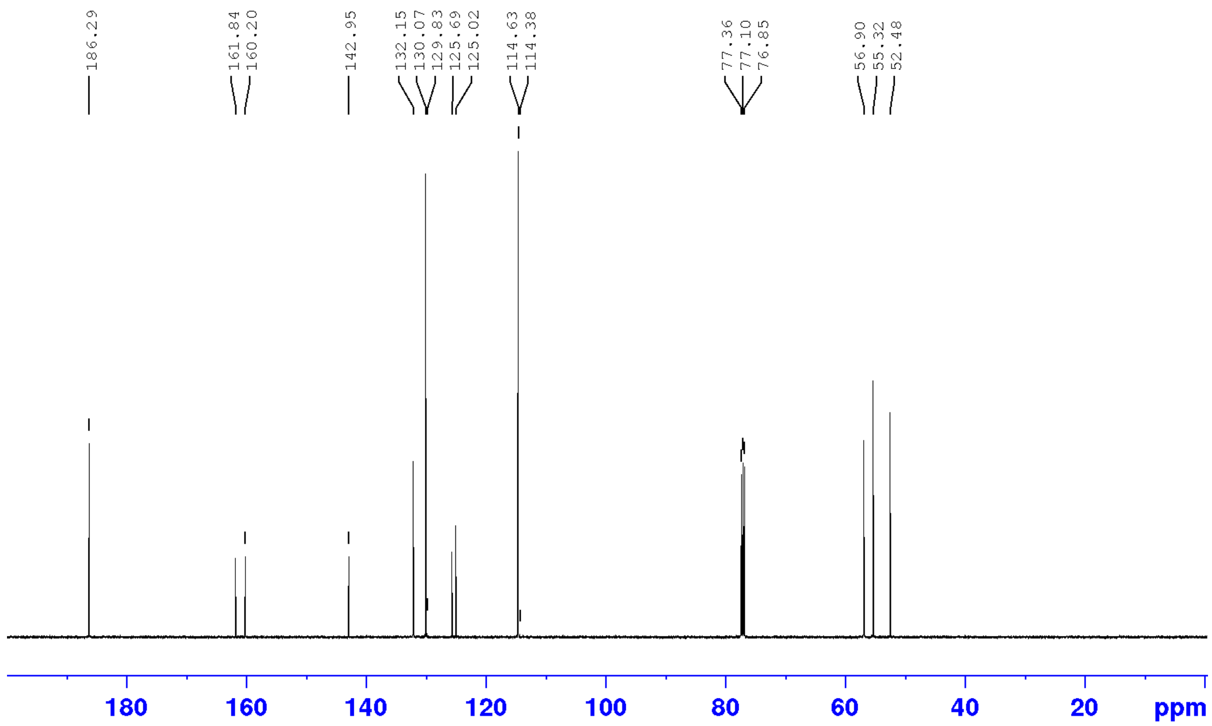
4,5-dihydropyrrolo[3,4-c]pyrazol-6(2H)-one (**17**)



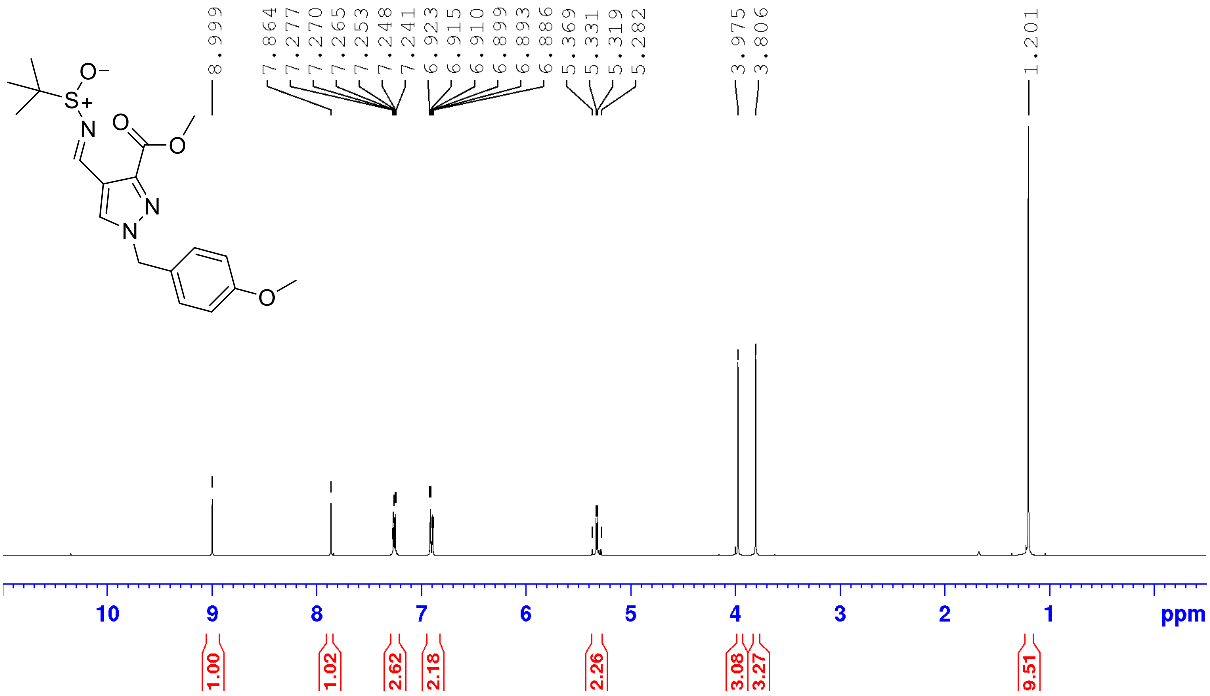


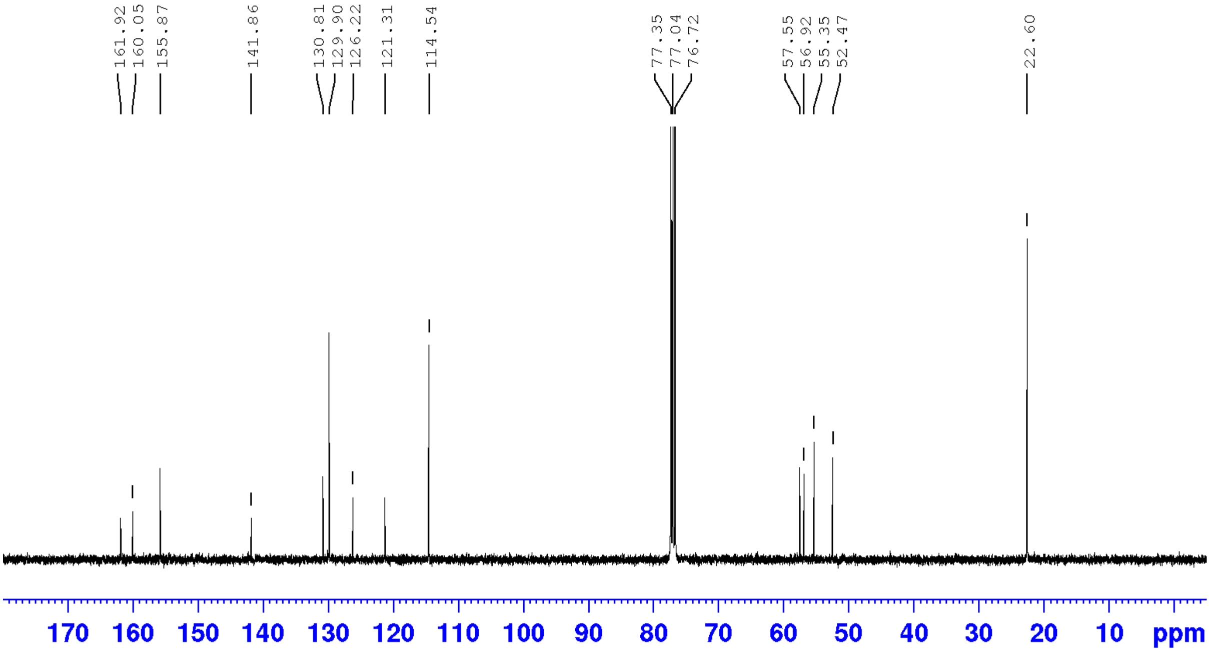
methyl 4-formyl-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylate (**62**)



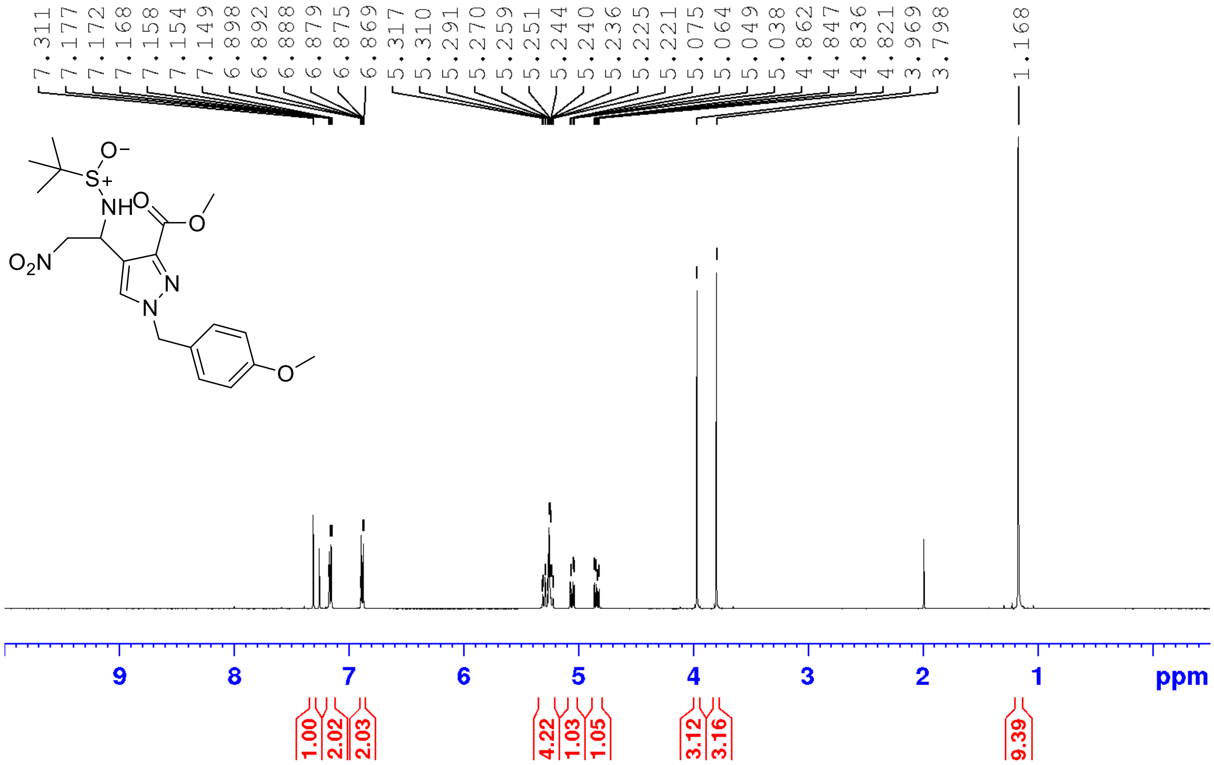


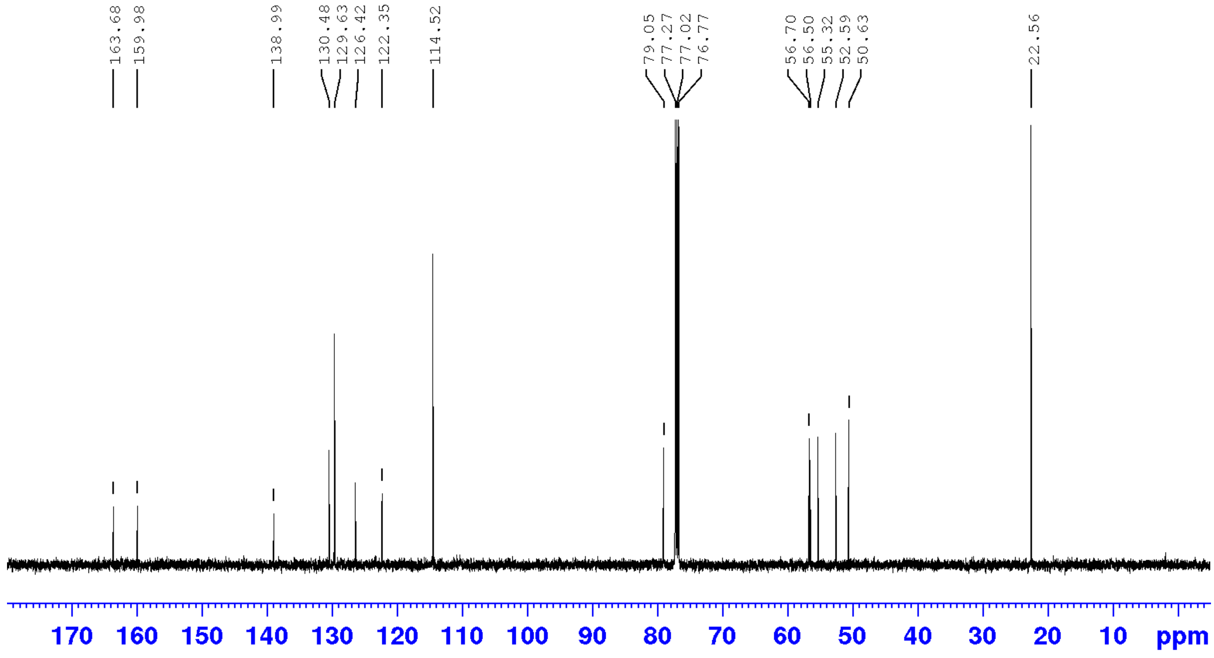
methyl (E)-4-(((tert-butylsulfinyl)imino)methyl)-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylate (**63**)



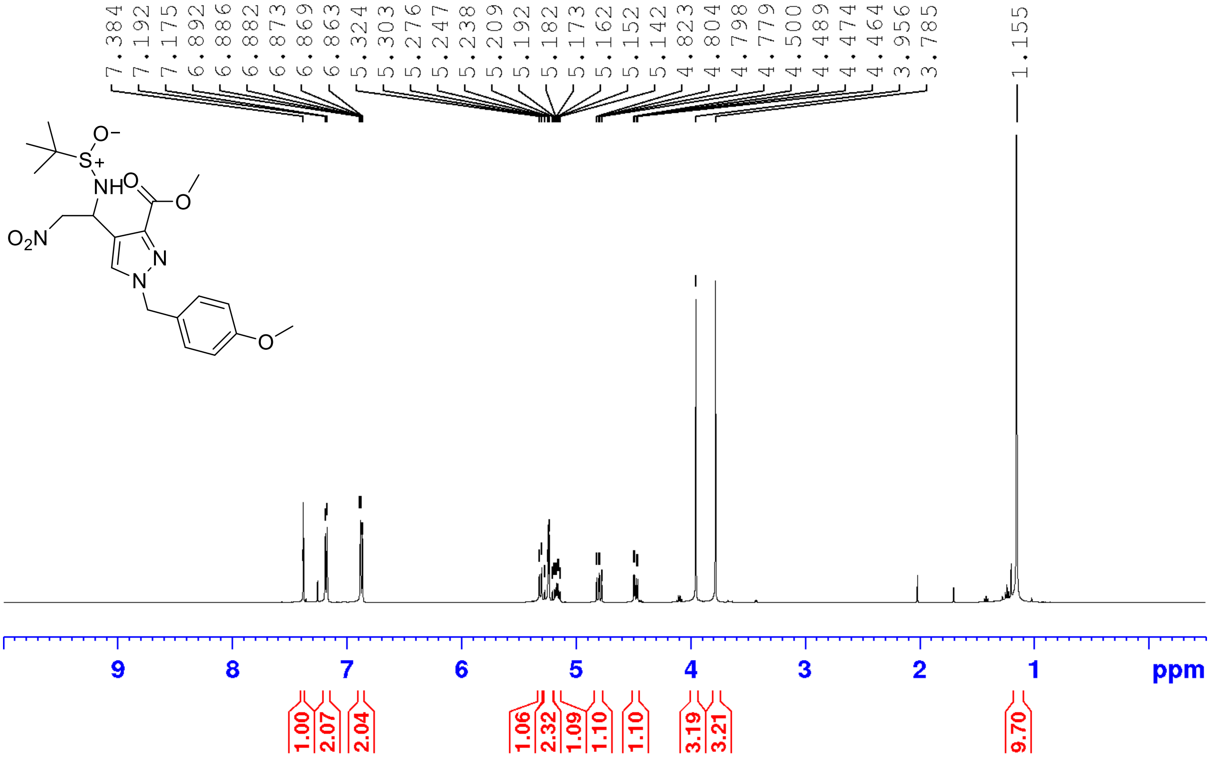


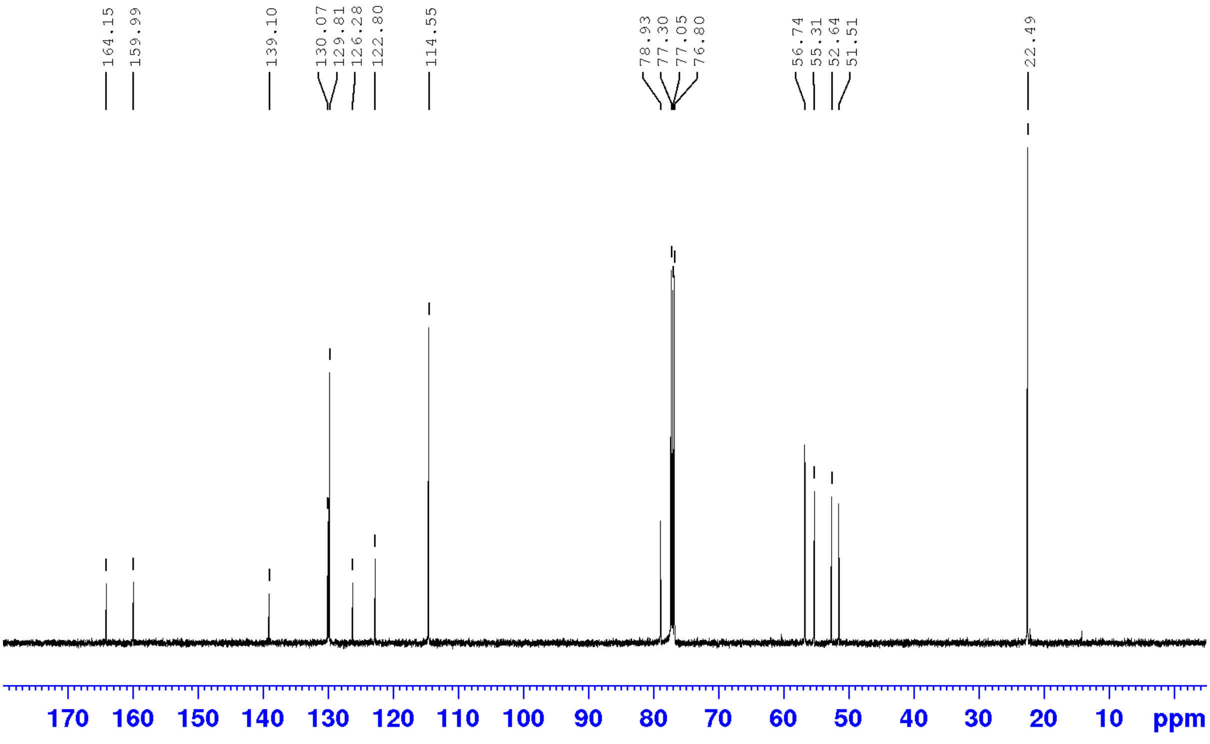
methyl 4-(1-((tert-butylsulfinyl)amino)-2-nitroethyl)-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylate (**64’**)



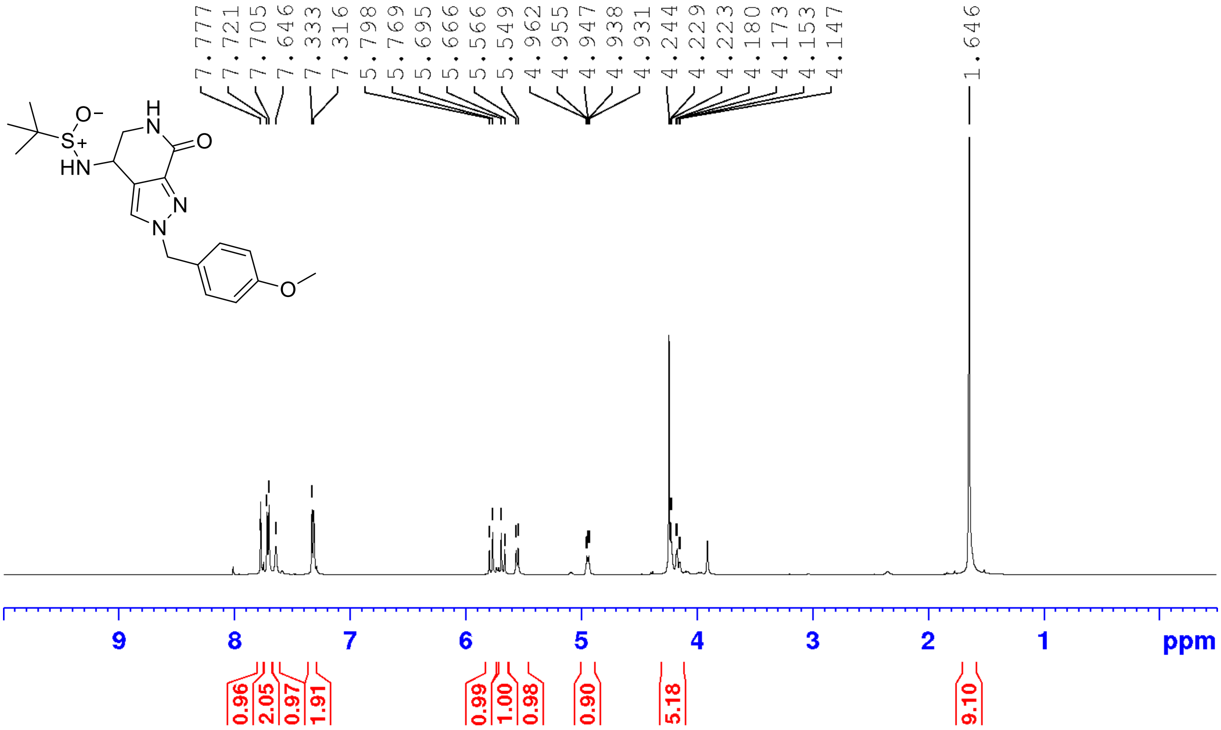


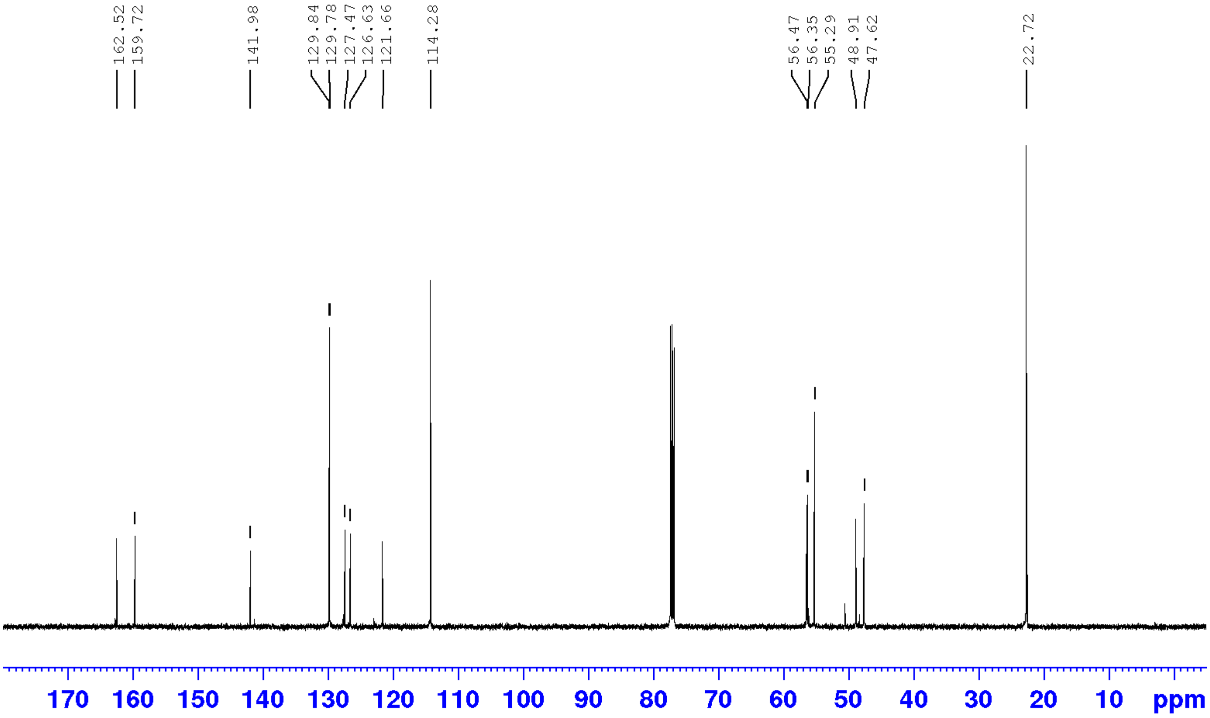
methyl 4-(1-((tert-butylsulfinyl)amino)-2-nitroethyl)-1-(4-methoxybenzyl)-1H-pyrazole-3-carboxylate (**64''**)



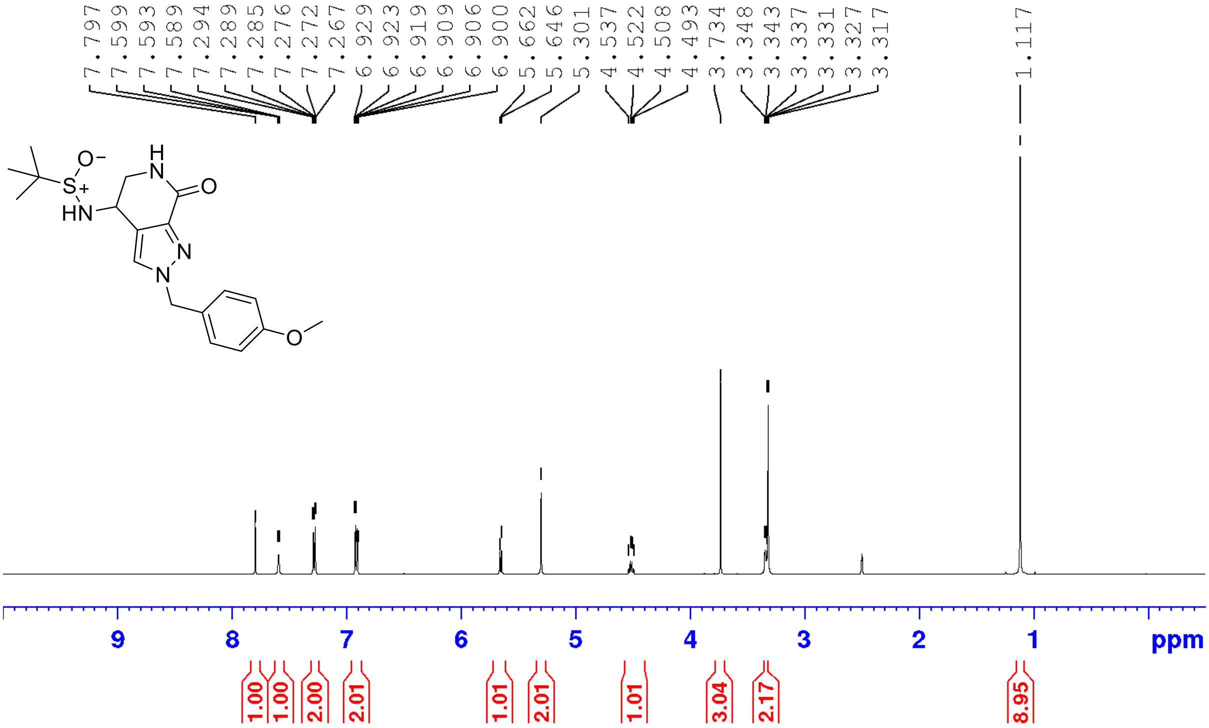


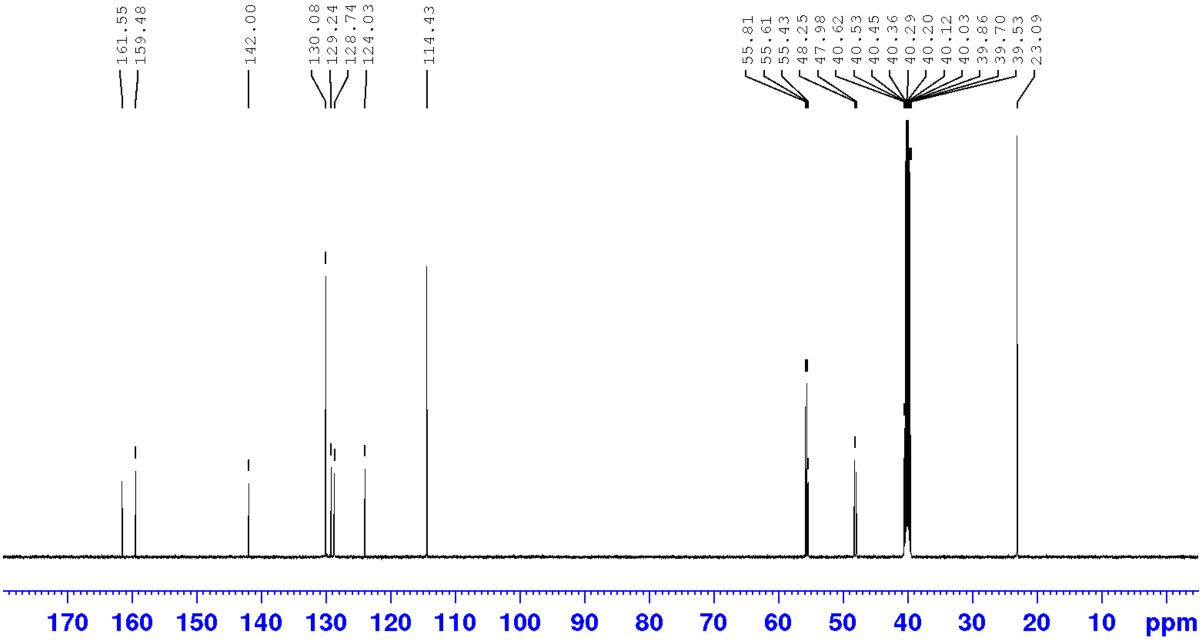
N-(2-(4-methoxybenzyl)-7-oxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-4-yl)-2-methylpropane-2-sulfinamide (**65’**)



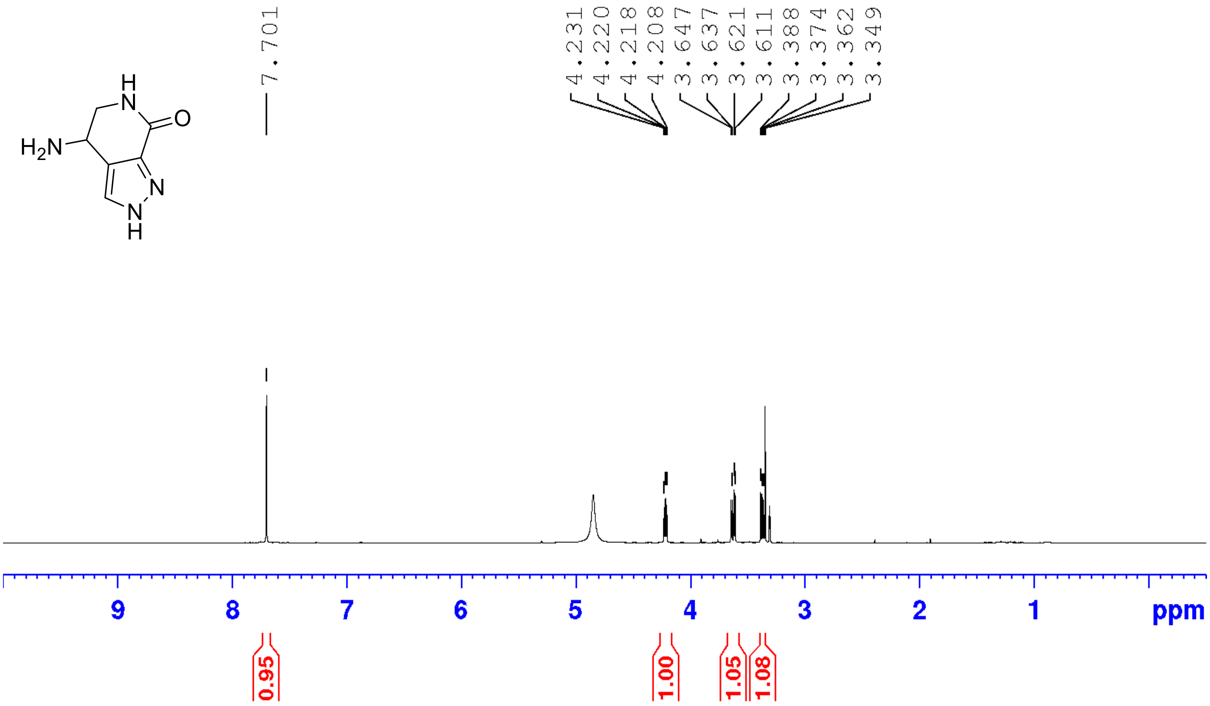


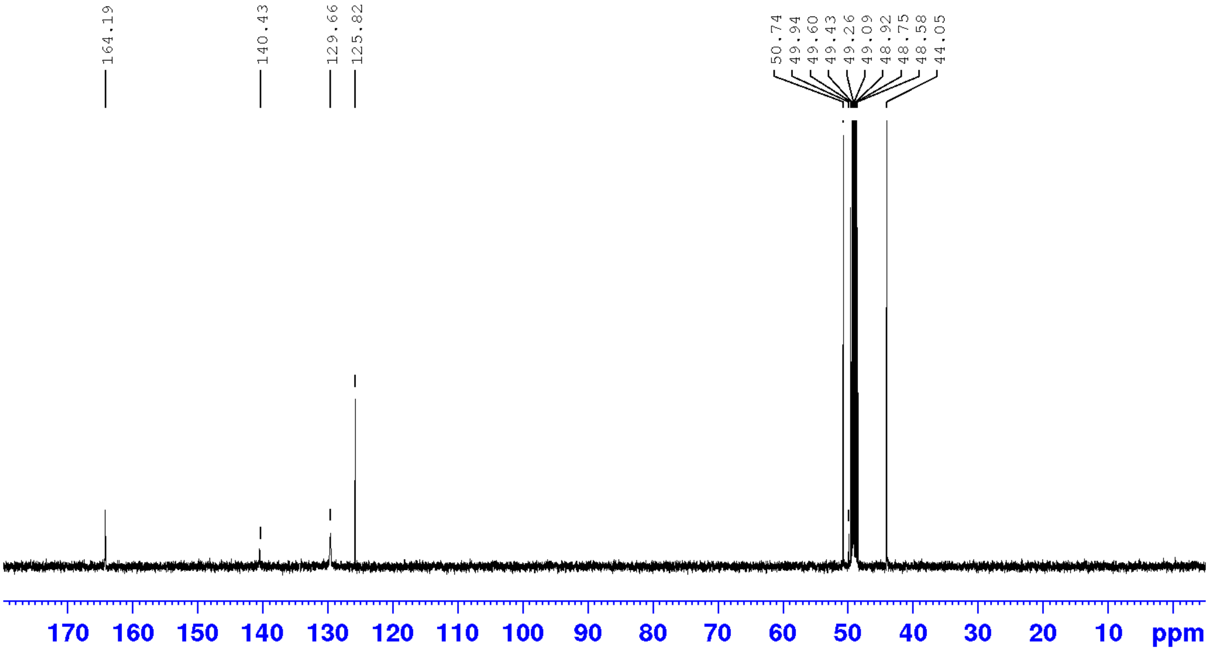
N-(2-(4-methoxybenzyl)-7-oxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-4-yl)-2-methylpropane-2-sulfinamide (**65’’**)



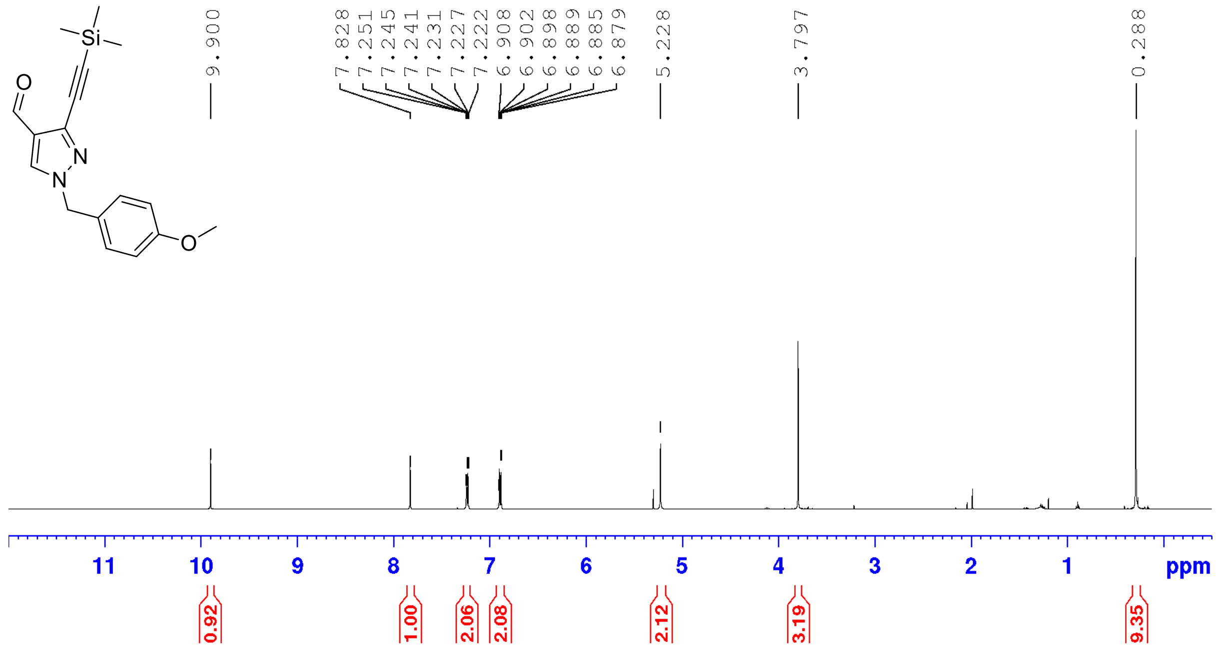


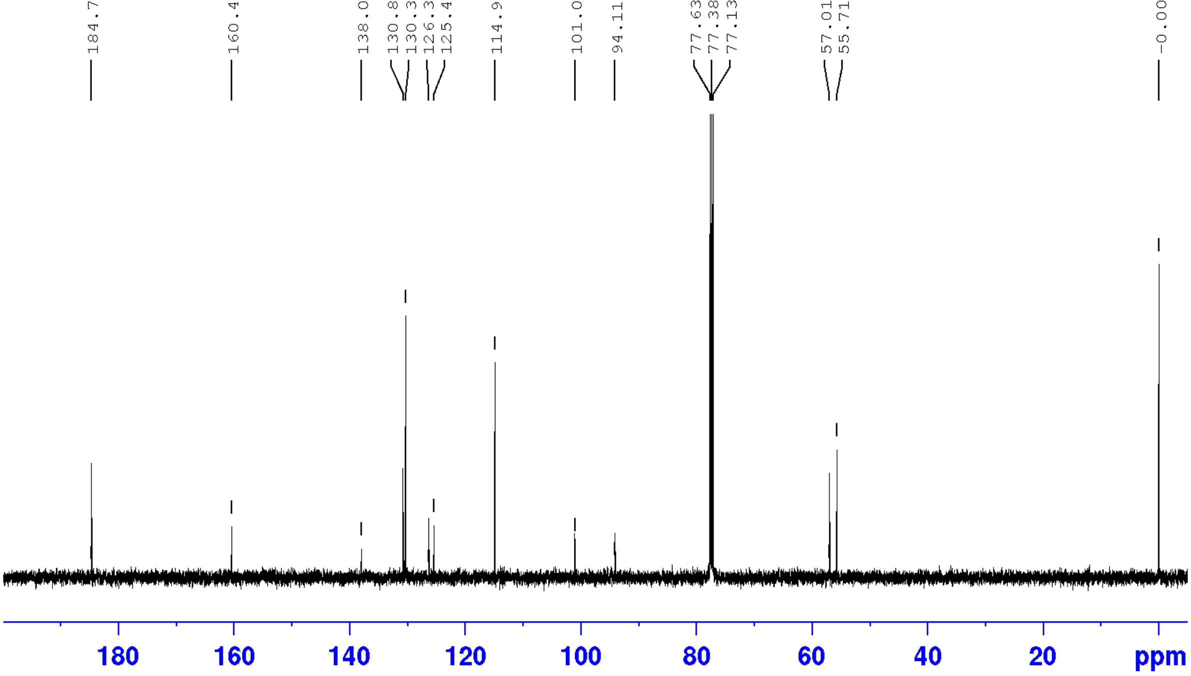
4-amino-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (**18**)



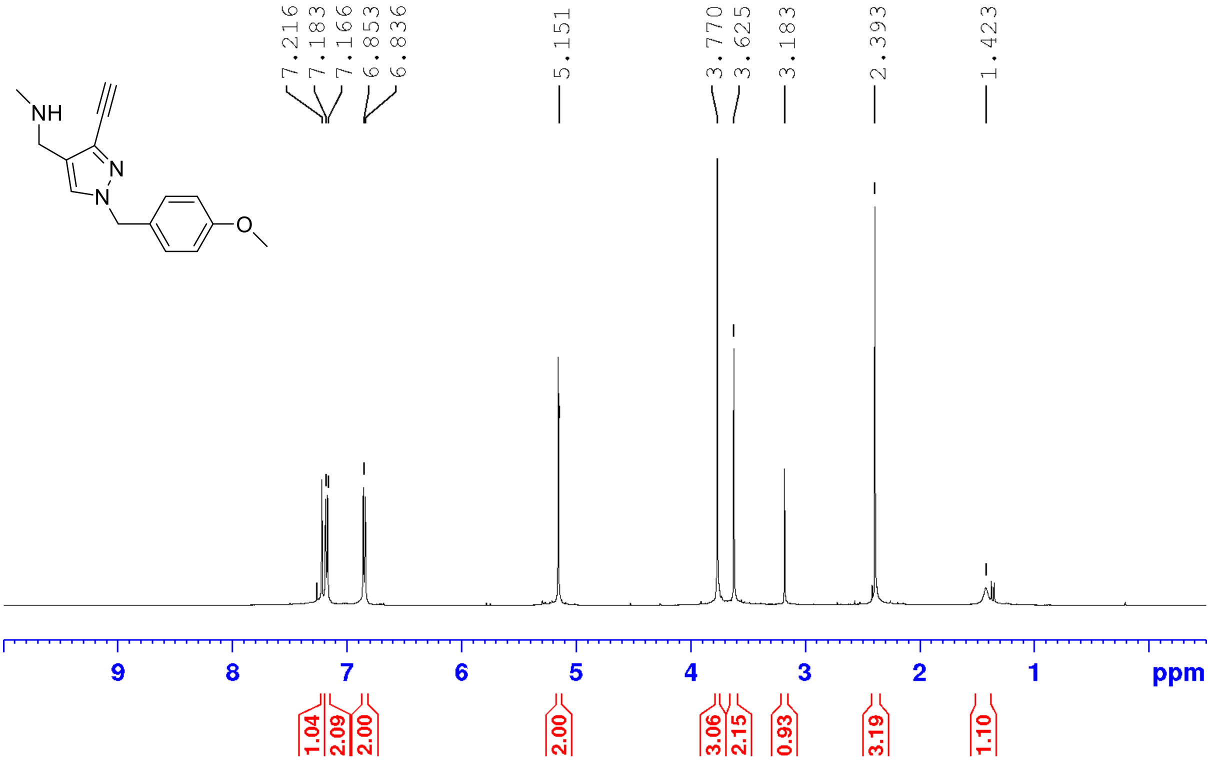


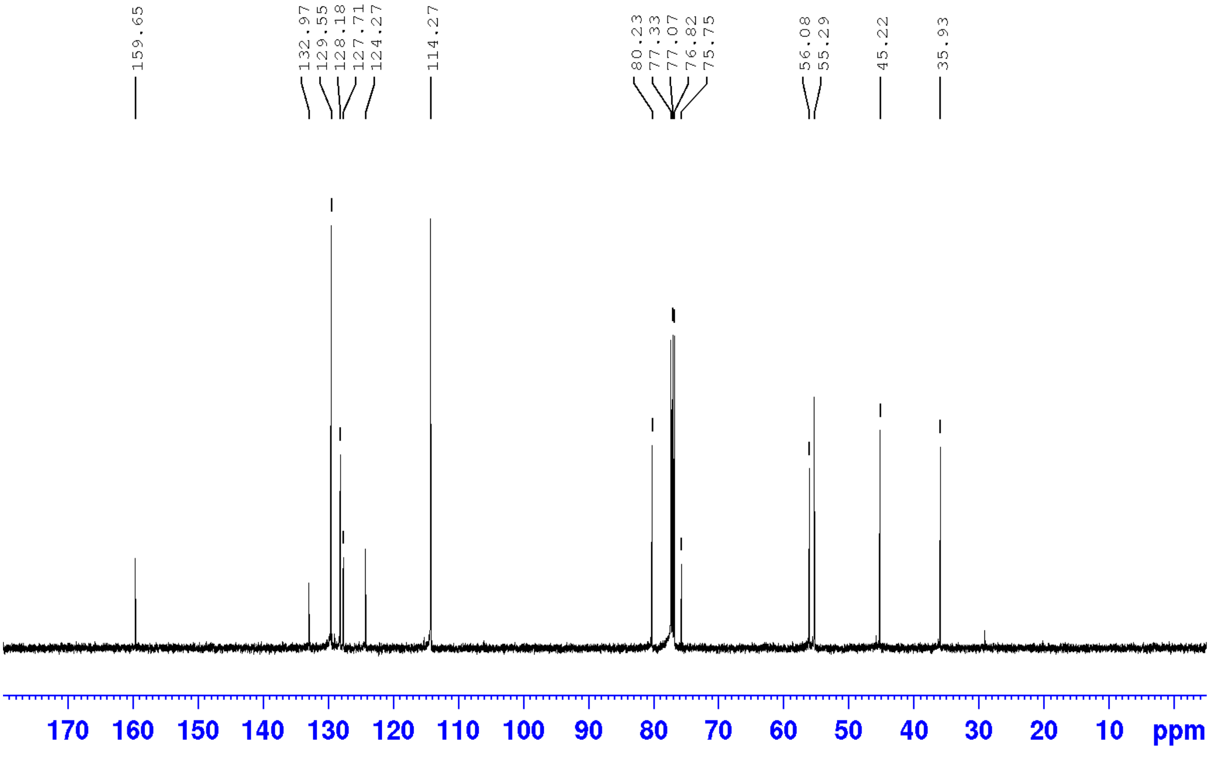
1-(4-methoxybenzyl)-3-((trimethylsilyl)ethynyl)-1H-pyrazole-4-carbaldehyde (**66**)



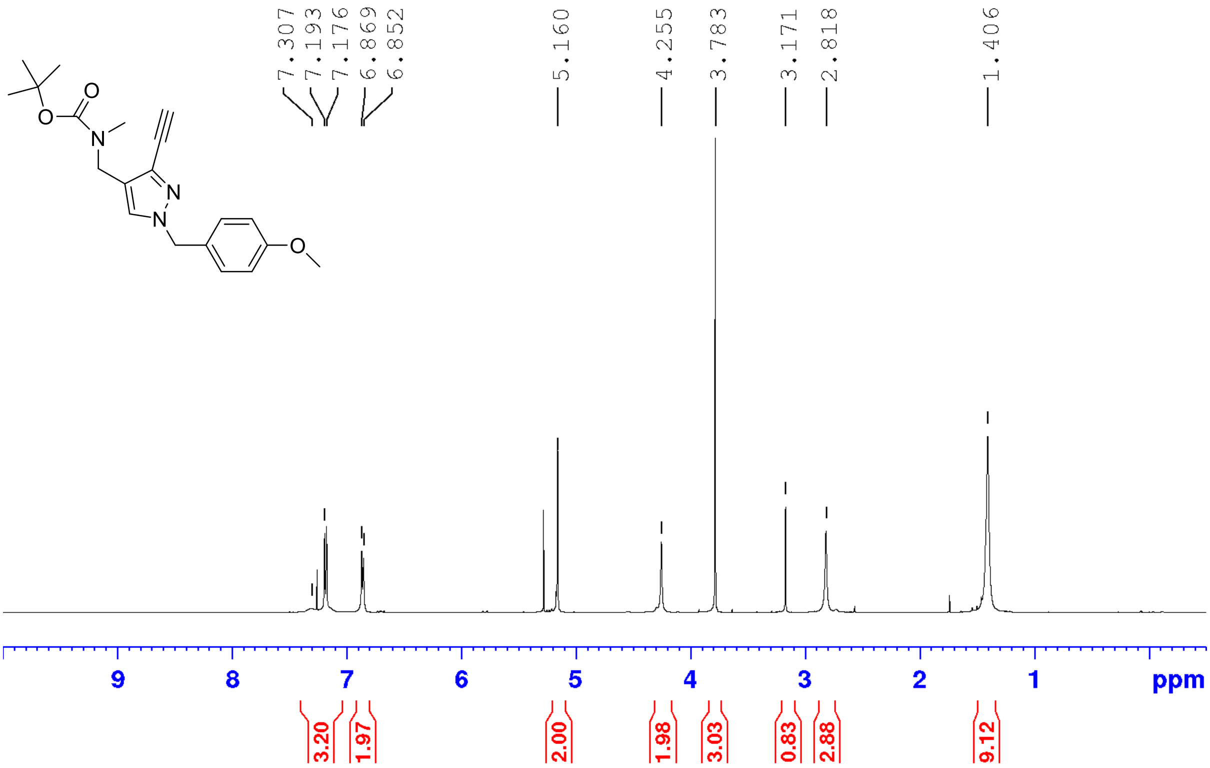


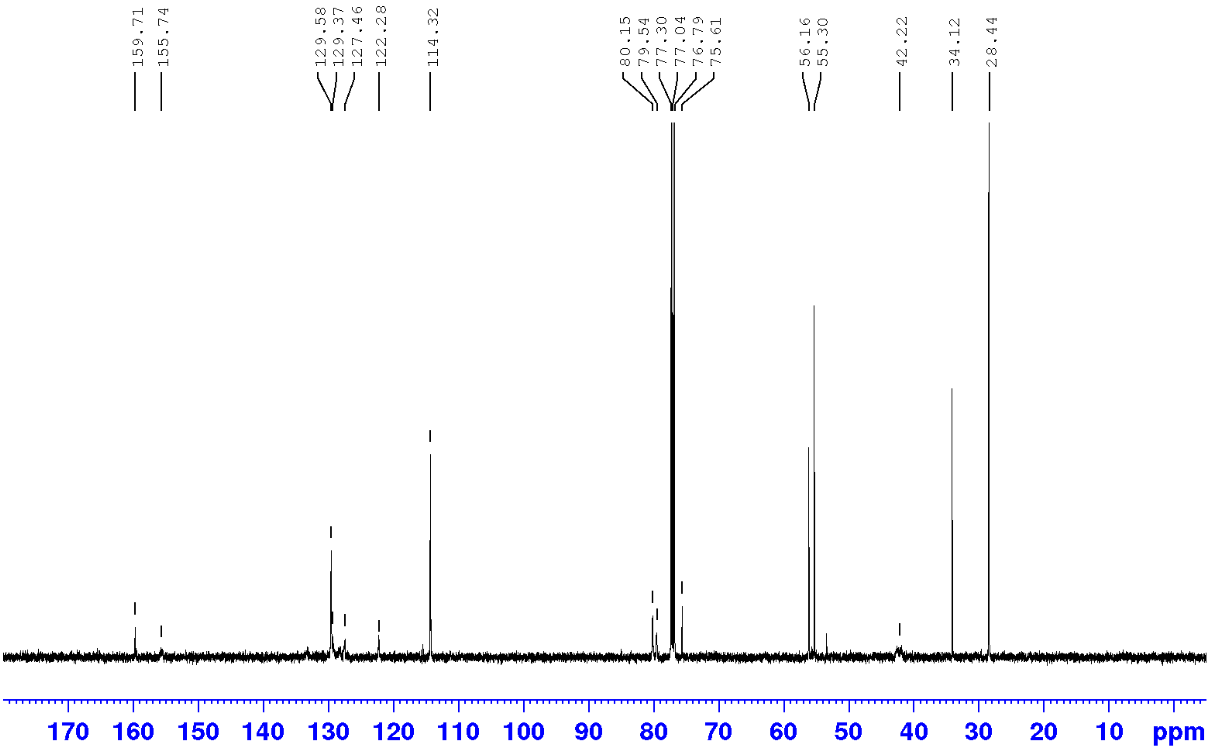
1-(3-ethynyl-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)-N-methylmethanamine (**67a**)



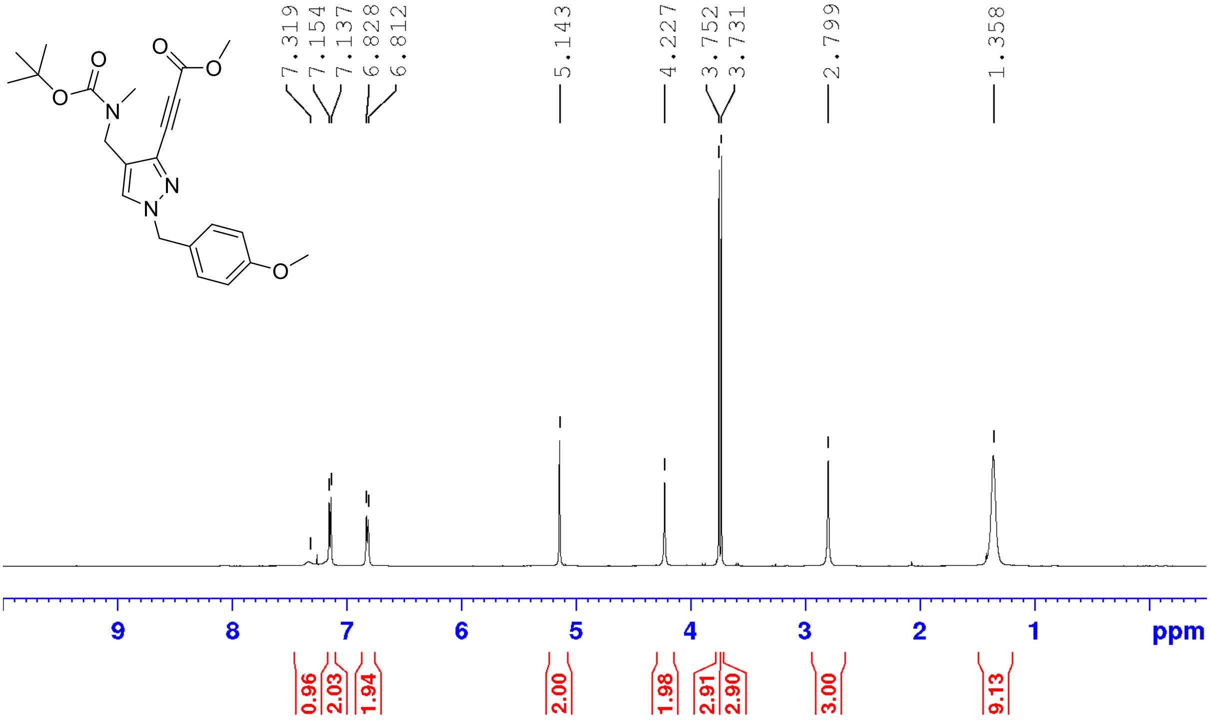


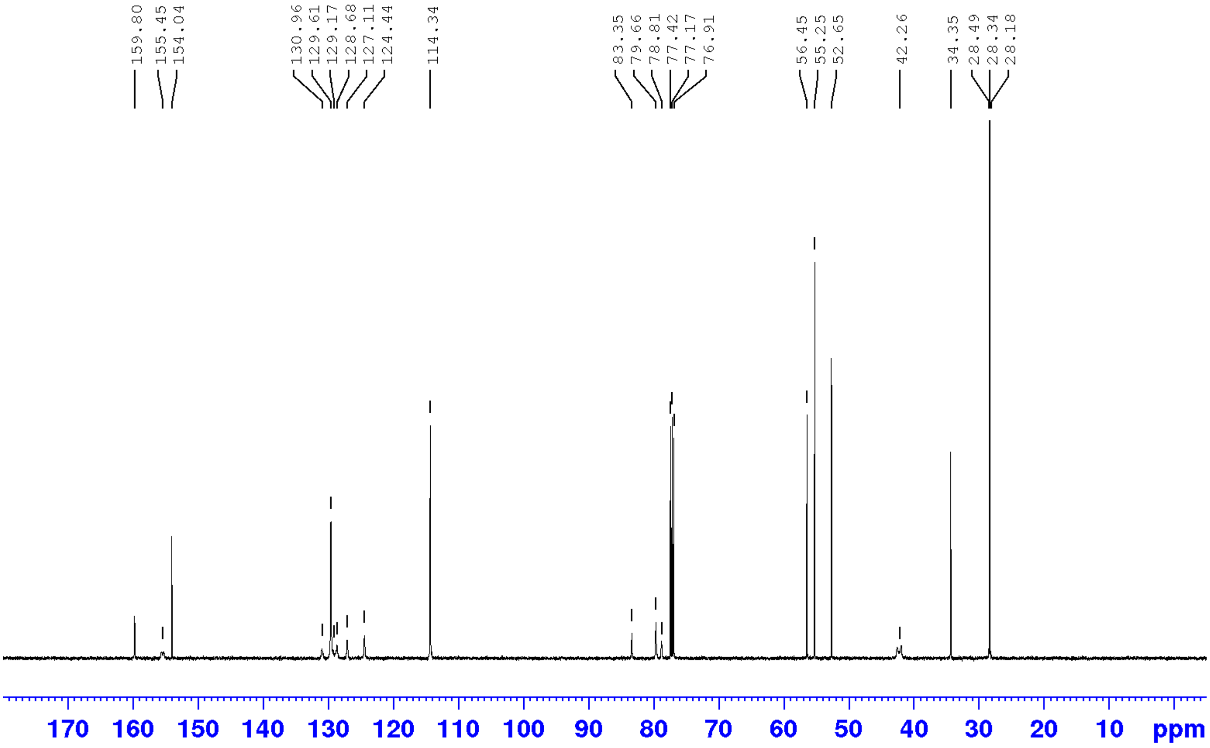
tert-butyl ((3-ethynyl-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)methyl)(methyl)carbamate (**67b**)



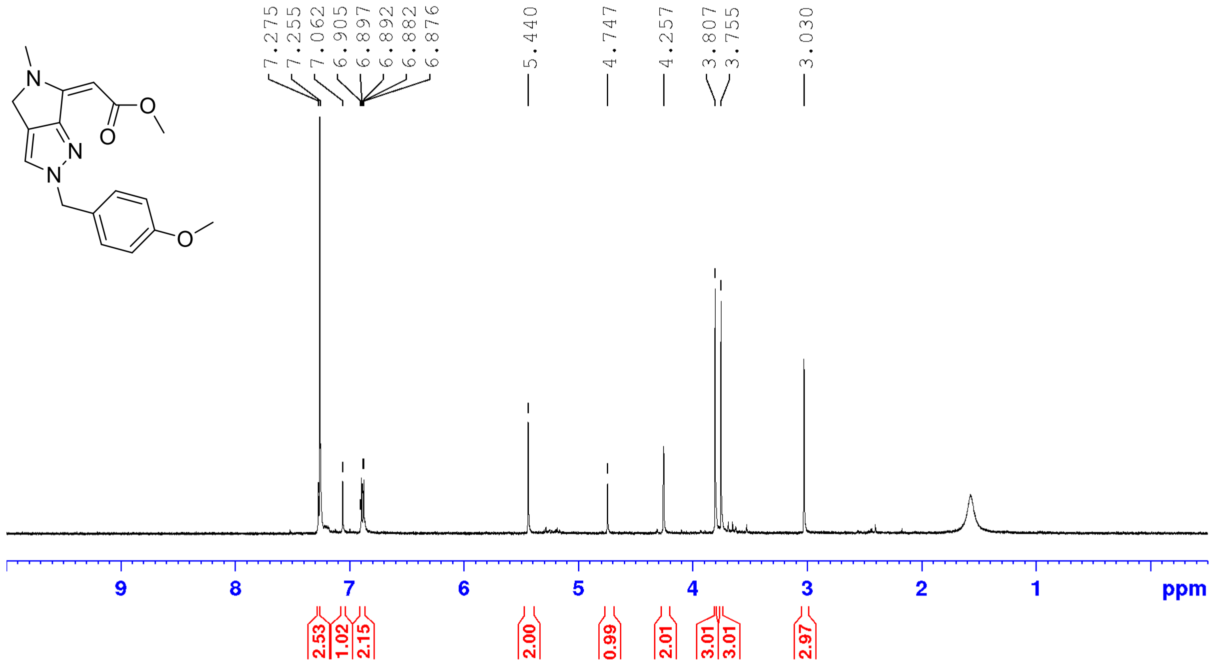


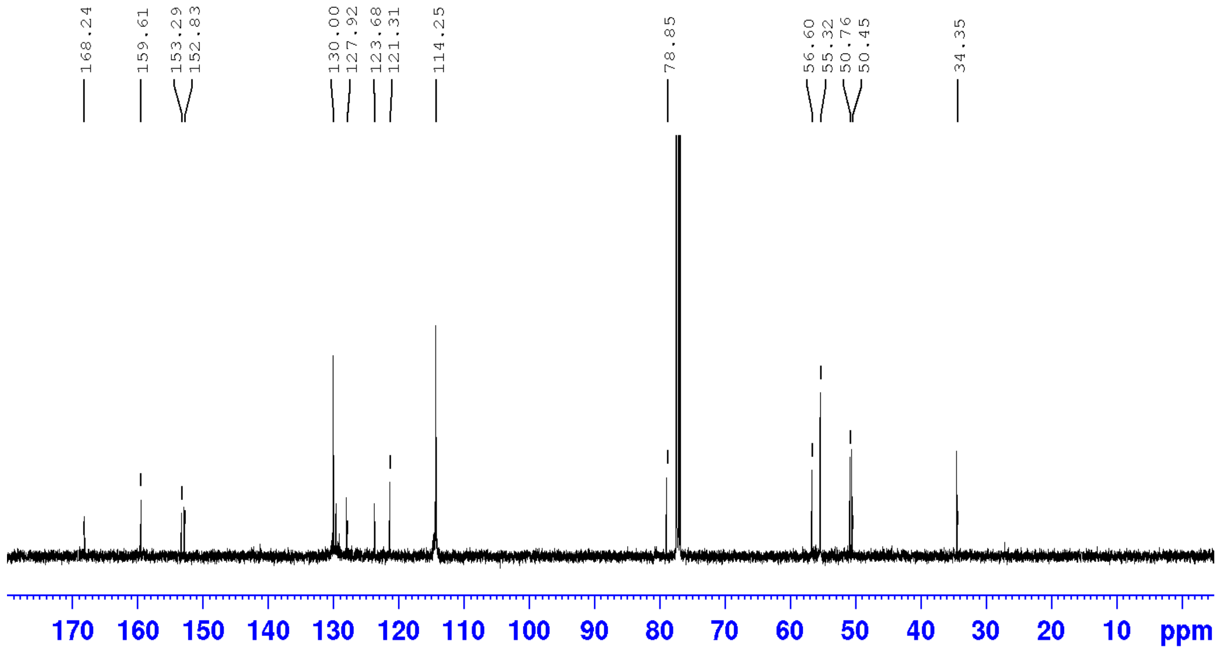
Methyl 3-(4-(((tert-butoxycarbonyl)(methyl)amino)methyl)-1-(4-methoxybenzyl)-1H-pyrazol-3-yl)propiolate (**68**)





methyl (E)-2-(2-(4-methoxybenzyl)-5-methyl-4,5-dihydropyrrolo[3,4-c]pyrazol-6(2H)-ylidene)acetate (**69**)





methyl 2-(5-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-6-yl)acetate (**19**)