Supplementary information pertaining to

Discovery of selective, metabolically stable pyrazole-based FLT3 inhibitors for the treatment of Acute Myeloid Leukemia

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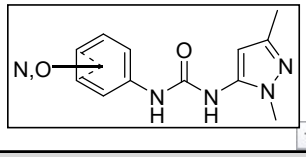
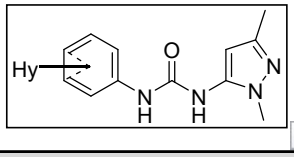
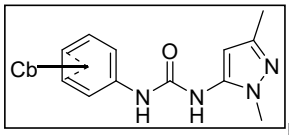
Table S1. Substructure search conducted on different pyrazolyl- urea scaffolds in Scifinder^n (Chemical Abstracts Services) – accessed November 2024

Search input			
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Patents	3077	409	14

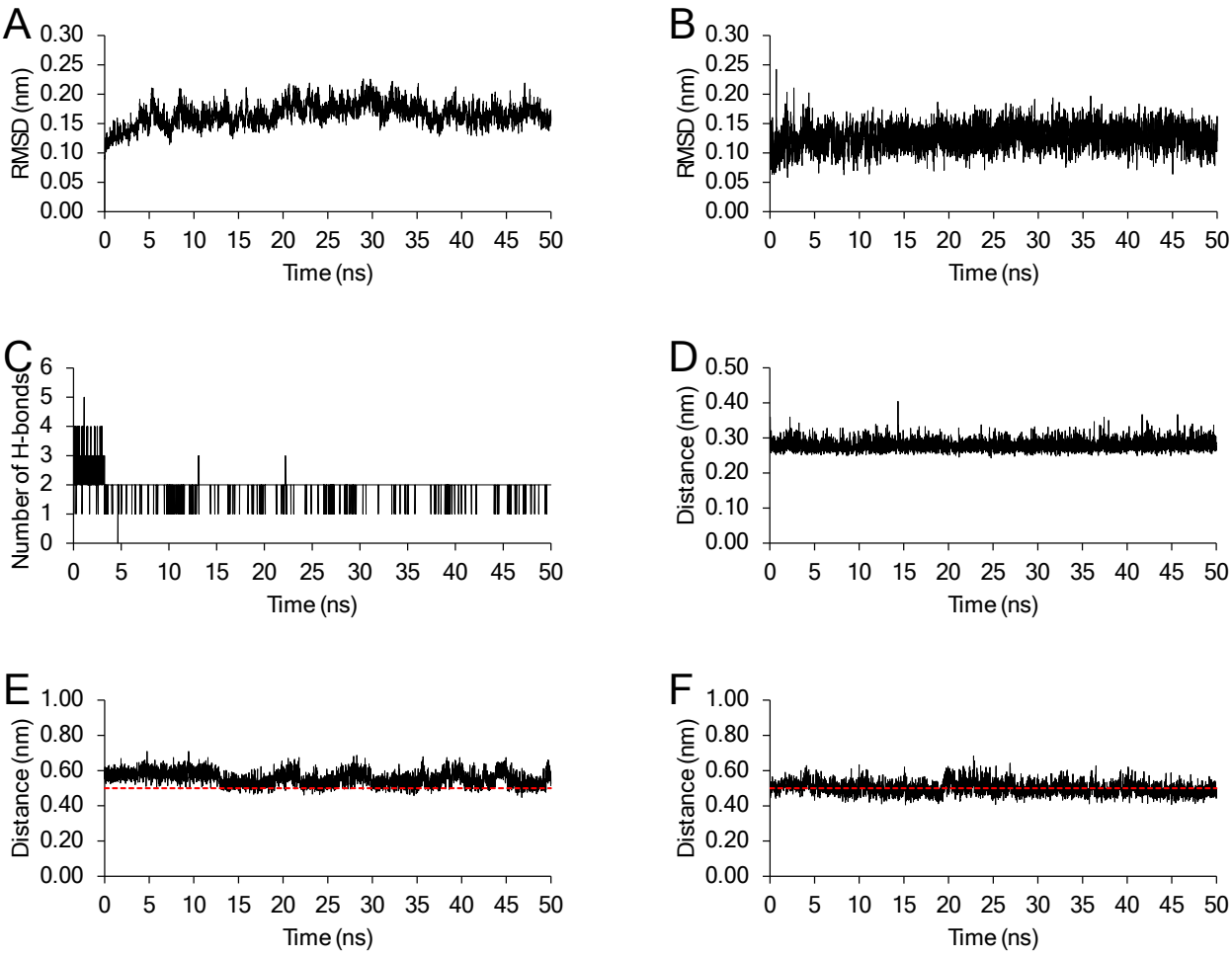


Figure S1. Summary of molecular dynamics simulation with WT-FLT3. A) Calpha-RMSD; B) **10q** heavy atoms RMSD; C) number of hydrogen bonds between FLT3 and **10q**; D) distance bewtween **10q** carbonyl oxygen and amide nitrogen of Cys694 (hinge region of FLT3); E) distance between the center of benzene ring of **10q** and the center of benzene ring of Phe830 (DFG motif); F) distance between the center of benzene ring of **10q** and the center of benzene ring of Phe691. The dashed red lines set at 0.5 nm in panel E-F indicate the common distance for a T-shaped arene-arene interaction

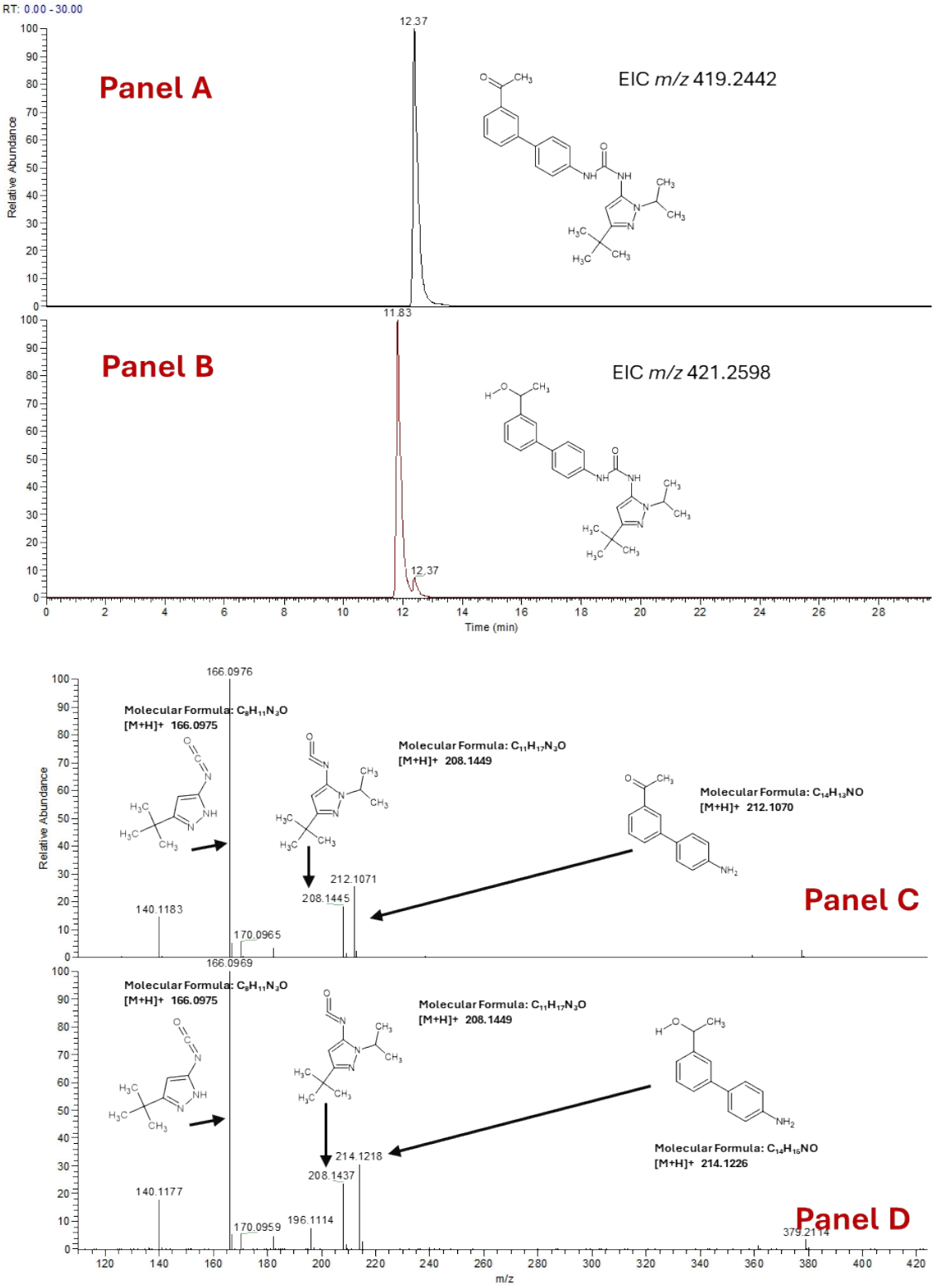


Figure S2: Panel A: Extracted Ion Chromatograms (EIC) for compound, m/z 419.2442; Panel B: EIC for m/z 421.2598 (hydrogenation) obtained after treating compound **10c** with human liver microsomes for 30 min (the treatment with mouse microsomes produced **10c** comparable results). Panel C: MS/MS spectrum acquired in HCD mode with a normalized collision energy (NCE) of 35 for compound **10c** and proposed structures for fragments; Panel D: MS/MS spectrum acquired in HCD mode with a normalized collision energy (NCE) of 35 for the species at m/z 421.2598 (rt 10.97 minutes) and proposed structures for fragments.

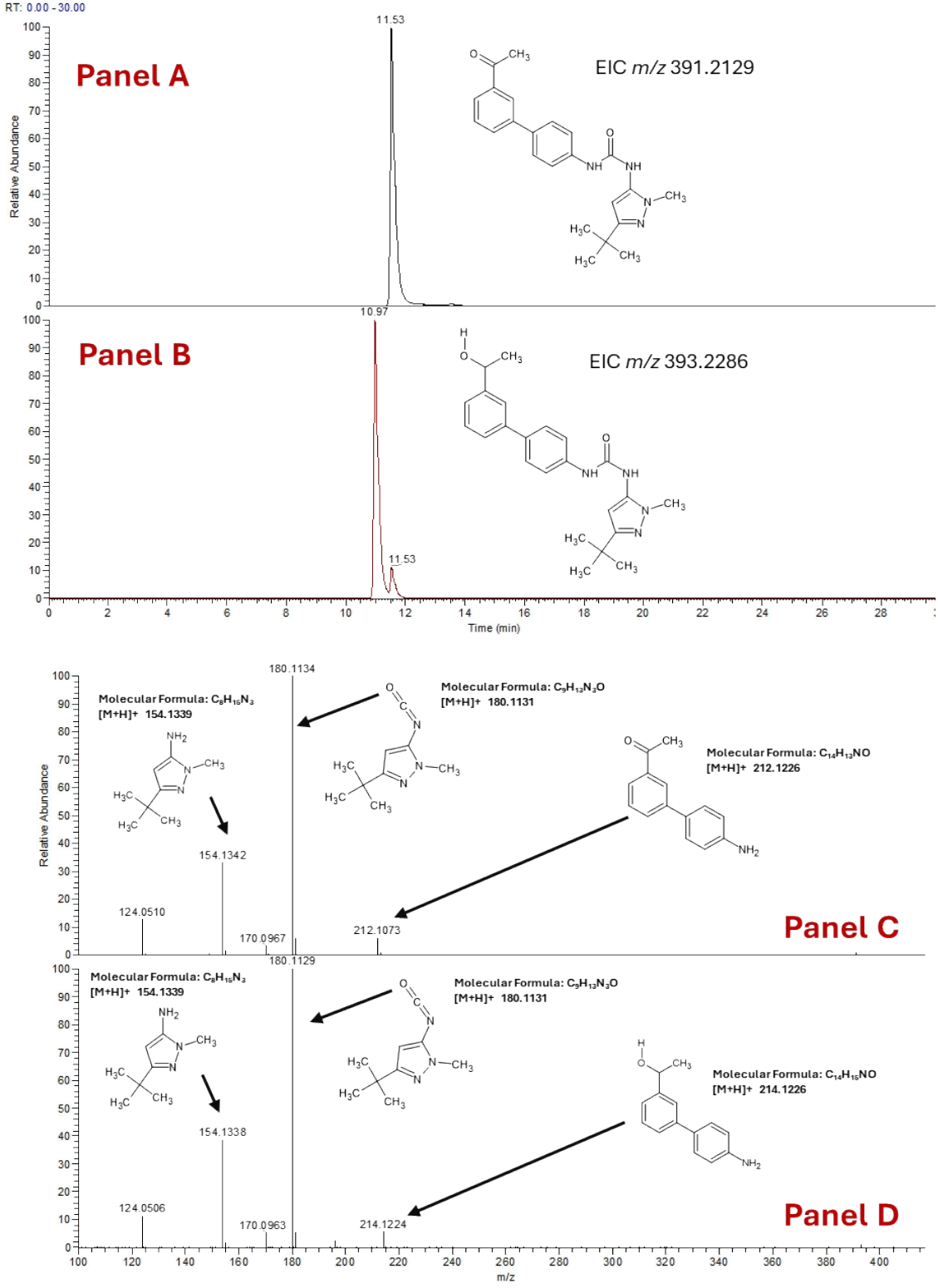


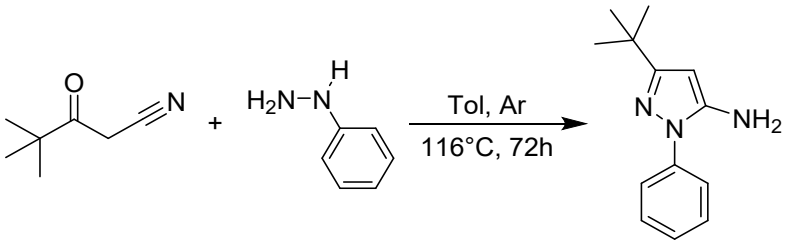
Figure S3: Panel A: Extracted Ion Chromatograms (EIC) for compound **10q**, m/z 391.2129; Panel B: EIC for m/z 393.2286 (hydrogenation) obtained after treating compound **10q** for 30 min with human liver microsomes (the treatment with mouse microsomes produced comparable results). Panel C: MS/MS spectrum acquired in HCD mode with a normalized collision energy (NCE) of 35 for compound **10q** and proposed structures for fragments; Panel D: MS/MS spectrum acquired in HCD mode with a normalized collision energy (NCE) of 35 for the species at m/z 393.2286 (rt 10.97 minutes) and proposed structures for fragments

Synthetic Procedures

General procedure A

Starting materials nitrile **1a-c** (4 mmol) and hydrazine **2a-c** (4.24 mmol) were dissolved under Argon atmosphere to a dried Schlenk flask in dry toluene (2 mL); when hydrochloride **1b** was used 1 additional eq. of Et_3N (4.24 mmol) was also added. The reaction mixture was stirred at 116 ºCfor 72h. The solvent was removed under vacuum and the crude purified by column chromatography as detailed.

3-(tert-butyl)-1-phenyl-1H-pyrazol-5-amine 3a



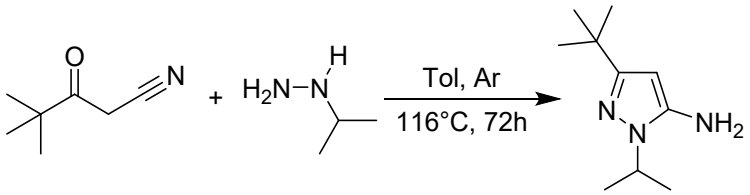
Following general procedure A compound **3a** was obtained starting from **1a** and **2a**. ~~4a~~ **3a** was purified by column chromatography (Silica, petroleum ether:EtOAc 7:3, R_f = 0.33). Concentration in vacuo of the product-rich fractions gave **3a** as a light orange solid (758 mg; yield 88%).

^{1}H-NMR (600 MHz, Chloroform-*d*) δ (ppm): 1.31 (s, 9H, $(CH_3)_3$), 5.52 (s, 1H, pyrazole), 7.27 – 7.32 (m, 1H, aromatic), 7.40 – 7.47 (m, 2H, aromatic), 7.54 – 7.57 (m, 2H, aromatic).

^{13}C-NMR (151 MHz, Chloroform-*d*) δ (ppm): 30.66, 60.75, 88.01, 124.36, 127.29, 129.73, 139.18, 145.12, 162.69.

ESI-MS (m/z): theoretical 216.15 $[C_{13}H_{17}N_3+H]^+$, experimental 216.27 $[C_{13}H_{17}N_3+H]^+$.

3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-amine 3b



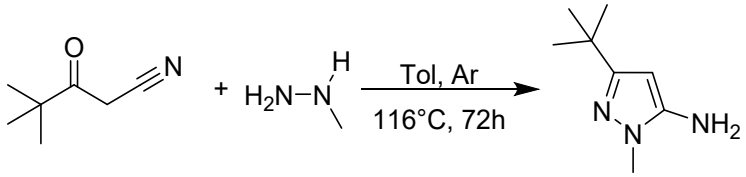
Following general procedure A compound **3b** was obtained starting from **1a** and **2b**. ~~4d~~ **3b** was purified by column chromatography (Silica, petroleum ether:EtOAc 7:3, R_f = 0.31). Concentration in vacuo of the product-rich fractions gave ~~4d~~ **3b** as light orange solid (522 mg; yield 72%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.17 (s, 9H, $(CH_3)_3$), 1.36 (d, 6H, $(CH_3)_2CH$), 3.30 (s broad, 2H, NH_2), 4.24 (hept, 1H, $CH(CH_3)_2$), 5.32 (s, 1H, pyrazole).

^{13}C-NMR (151 MHz, Chloroform-*d*) δ (ppm): 21.95, 30.61, 31.05, 48.66, 88.44, 91.61, 142.91, 159.84, 207.13.

ESI-MS (m/z): theoretical 182.16 $[C_{10}H_{19}N_3+H]^+$, experimental 182.26 $[C_{10}H_{19}N_3+H]^+$.

3-(tert-butyl)-1-methyl-1H-pyrazol-5-amine 3c



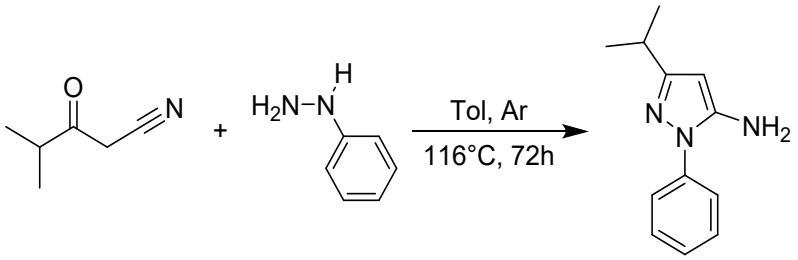
Following general procedure A compound **3c** was obtained starting from **1a** and **2c**. **3c** was purified by column chromatography (Silica, petroleum ether:EtOAc 7:3 → 0:1, R_f = 0.31). Concentration in vacuo of the product-rich fractions gave ~~**4c**~~ **3c** as pale-yellow solid (429 mg; yield 70%).

^{1}H-NMR (600 MHz, Chloroform-*d*) δ (ppm): 1.29 (s, 9H, $(CH_3)_3$), 2.15 (s, 2H, NH_2), 3.72 (s, 3H, NCH_3), 5.45 (s, 1H, pyrazole).

^{13}C-NMR (151 MHz, Chloroform-*d*) δ (ppm): 27.81, 30.57, 30.63, 34.29, 35.70, 88.64, 146.07, 160.65.

ESI-MS (m/z): theoretical 154.13 $[C_8H_{15}N_3+H]^+$, experimental 154.29 $[C_8H_{15}N_3+H]^+$.

3-isopropyl-1-phenyl-1H-pyrazol-5-amine 3d



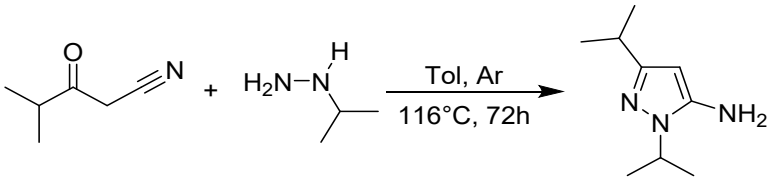
Following general procedure A compound **3d** was obtained starting from **1b** and ~~**3a**~~**2a**. ~~**4b**~~ **3d** was purified by column chromatography (Silica, petroleum ether:EtOAc 7:3, R_f = 0.28). Concentration in vacuo of the product-rich fractions gave ~~**4b**~~ **3d** as light orange solid (764 mg; yield 95%).

^{1}H-NMR (600 MHz, Chloroform-*d*) δ (ppm): 1.23 (d, *J* = 7.0 Hz, 6H, $(CH_3)_2CH$), 2.88 (hept, *J* = 7.0 Hz, 1H, $CH(CH_3)_2$), 3.83 (s broad, 2H, NH_2), 5.35 (s, 1H, pyrazole), 7.18 –7.50 (m, 5H, aromatic).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ (ppm): 22.86, 28.27, 87.84, 124.09, 127.21, 129.53, 138.66, 145.22, 159.91.

ESI-MS (m/z): theoretical 202.14 $[C_{12}H_{15}N_3+H]^+$, experimental 202.24 $[C_{12}H_{15}N_3+H]^+$.

1,3-diisopropyl-1H-pyrazol-5-amine 3e



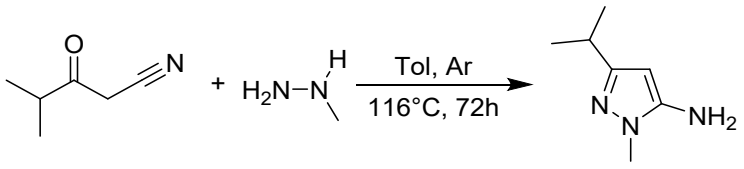
Following general procedure A compound **3e** was obtained starting from **1b** and **2b**. **3e** was purified by column chromatography (Silica, petroleum ether:EtOAc 7:3, R_f = 0.21). Concentration in vacuo of the product-rich fractions gave **3e** as pale-yellow solid (468 mg; yield 70%).

^{1}H-NMR (400 MHz, Chloroform-*d*) δ (ppm): 1.17 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2CH$),1.41 (d, *J* = 6.7 Hz, 6H, $(CH_3)_2CHN$), 2.85 (hept, *J* = 6.9, 1.8 Hz, 1H, $CH(CH_3)_2$), 3.44 (s, 3H, NH_2), 4.26 (hept, *J* = 6.7, 1.9 Hz, 1H, $NCH(CH_3)_2$), 5.34 (s, 1H, pyrazole).

^{13}C-NMR (151 MHz, Chloroform-*d*) δ (ppm): 22.01, 22.46, 23.26, 28.31, 48.33, 88.21, 143.50, 157.85.

ESI-MS (m/z): theoretical 168.15 $[C_9H_{17}N_3+H]^+$, experimental 168.09 $[C_9H_{17}N_3+H]^+$.

3-isopropyl-1-methyl-1H-pyrazol-5-amine 3f



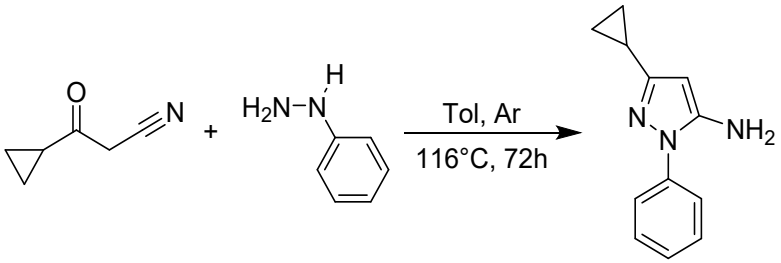
Following general procedure A compound ~~**4h**~~ **3f** was obtained starting from ~~**2b**~~ **1b** and ~~**3c**~~**2c**. ~~**4h**~~ **3f** was purified by column chromatography (Silica, petroleum ether:EtOAc 7:3 → 0:1, R_f = 0.38). Concentration in vacuo of the product-rich fractions gave ~~**4h**~~ **3f** as pale-yellow solid (390 mg; yield 70%).

^{1}H-NMR (600 MHz, Chloroform-*d*) δ (ppm): 1.22 (d, *J* = 6.9 Hz, 6H, (CH3)2CH), 2.74 – 2.94 (hept, *J* = 7.0 Hz, 1H, CH(CH3)2), 3.65 (s, 3H, CH3), 5.40 (s, 1H, pyrazole).

^{13}C-NMR (151 MHz, Chloroform-*d*) δ (ppm): 23.08, 28.28, 34.27, 88.58, 145.51, 158.13.

ESI-MS (m/z): theoretical 140.11 $[C_7H_{13}N_3+H]^+$, experimental 140.26 $[C_7H_{13}N_3+H]^+$.

3-cyclopropyl-1-phenyl-1H-pyrazol-5-amine 3g



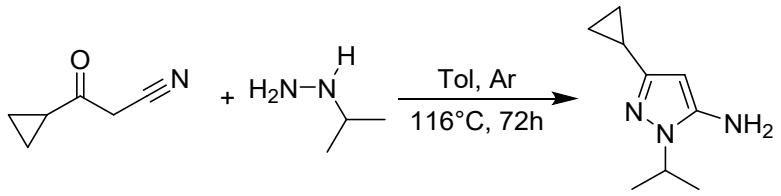
Following general procedure A compound **3g** was obtained starting from **1c** and **2a**. **3g** was purified by column chromatography (Silica, petroleum ether:EtOAc 7:3, R_f = 0.32). Concentration in vacuo of the product-rich fractions gave **3g** as light orange solid (542 mg; yield 68%).

^{1}H-NMR (600 MHz, Chloroform-*d*) δ (ppm): 0.80 (d, *J* = 5.0 Hz, 2H, CH_2), 0.99 (d, *J* = 8.3 Hz, 2H, CH_2), 1.83 – 2.17 (m, 1H, CH), 4.02 (s, 2H, NH_2), 5.32 (d, J = 1.2 Hz, 1H, pyrazole), 7.35 – 7.40 (m, 1H, aromatic), 7.49 (t, J = 7.5 Hz, 2H, aromatic), 7.53 – 7.57 (m, 2H, aromatic).

^{13}C-NMR (151 MHz, Chloroform-*d*) δ (ppm): 8.90 (d, *J* = 8.4 Hz), 9.82, 123.77, 127.70, 129.90 (d, *J* = 2.4 Hz), 156.29, 8.39, 9.39, 87.16, 124.65, 124.91, 130.07.

ESI-MS (m/z): theoretical 200.11 $[C_{12}H_{13}N_3+H]^+$, experimental 200.20 $[C_{12}H_{13}N_3+H]^+$.

3-cyclopropyl-1-isopropyl-1H-pyrazol-5-amine 3h



Following general procedure A compound **3h** was obtained starting from **1c** and **1b**. **3h** was purified by column chromatography (Silica, petroleum ether:EtOAc 7:3, R_f = 0.16). Concentration in vacuo of the product-rich fractions gave **3h** as light orange solid (436 mg; yield 66%).

^{1}H-NMR (600 MHz, Chloroform-*d*) δ (ppm): 0.55 – 0.64 (m, 2H, CH_2), 0.79 – 0.90 (m, 2H, CH_2), 1.44 (d, *J* = 6.7 Hz, 6H, $(CH_3)_2CH$), 1.88 (tt, *J* = 5.0, 8.4 Hz, 1H, $CH(CH_2)_2$), 4.27 (hept, *J* = 6.7 Hz, 1H, $CH(CH_3)_2$), 5.11 (s, 1H, pyrazole).

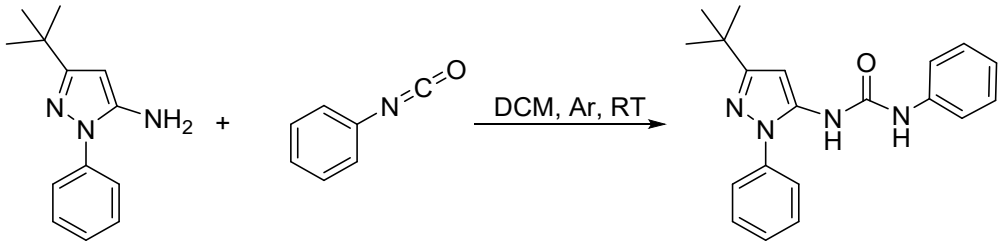
^{13}C-NMR (151 MHz, Chloroform-*d*) δ (ppm): 8.23, 9.95, 22.25, 48.46, 87.13, 144.03, 154.13.

ESI-MS (m/z): theoretical 166.12 $[C_9H_{15}N_3+H]^+$, experimental 166.28 $[C_9H_{15}N_3+H]^+$.

General procedure B

Pyrazoles **3a-f** (0.72 mmol where not otherwise stated) and bromophenyl isocyanates **4a-g** (0.88 mmol where not otherwise stated) were added to a died Schlenk flask under Argon atmosphere and dissolved in anhydrous DCM (4 mL). The reaction mixture was stirred overnight, after which the volatiles were removed in vacuo. The resulting crude was macerated overnight in diethyl ether (20 mL), after which the suspension was filtered and dried in vacuo to afford bromo urea **3a-x**.

1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-phenylurea 5a

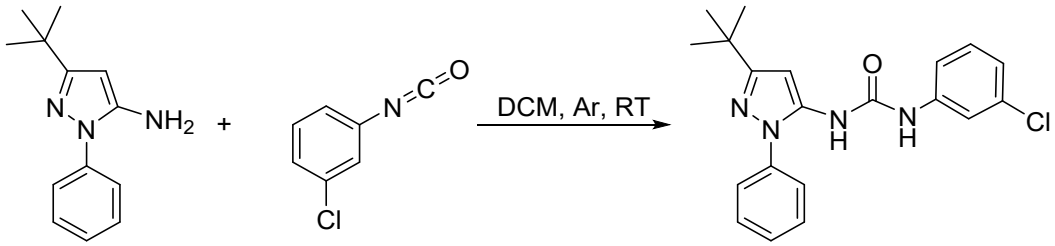


Following general procedure A compound **5a** was obtained from **3a** (60 mg, 0.24 mmol) and phenyl isocyanate **4a** (33 mg, 0.28 mmol). Yield: 18 mg, 22%;

^{1}H-NMR (600 MHz, DMSO) δ 9.00 (1 H, s, NH), 8.39 (1 H, s, NH), 7.54-7.53 (4 H, m, Ph), 7.42-7.40 (3 H, m, Ph), 7.28-7.25 (2 H, t, J=7.6 Hz, Ph), 6.99-6.96 (1 H, t, J=7.4 Hz, Ph), 6.38 (1 H, s, Pyrazole), 1.29 (9 H, s, tBu);

^{13}C-NMR (150 MHz, DMSO) δ 161.2, 152.0, 139.0, 137.7, 129.8, 129.3, 127.7, 124.8, 122.6, 118.6, 95.9, 32.5, 30

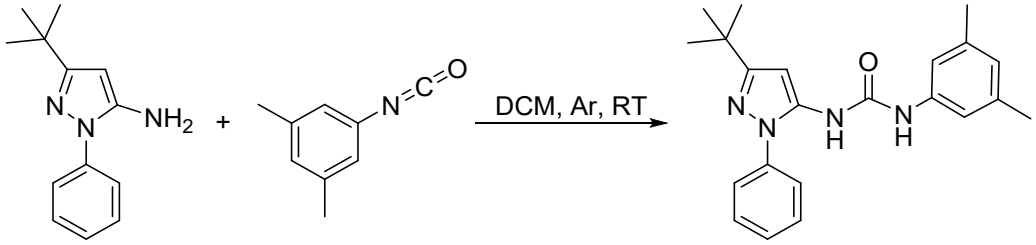
1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(3-chlorophenyl) urea 5b



Following general procedure A compound **5b** was obtained from **3b** (35.4 mg, 1.64 mmol) and 2-chlorophenyl isocyanate **4b** (24 mg, 1.52 mmol). Yield 465 mg, 82 %;

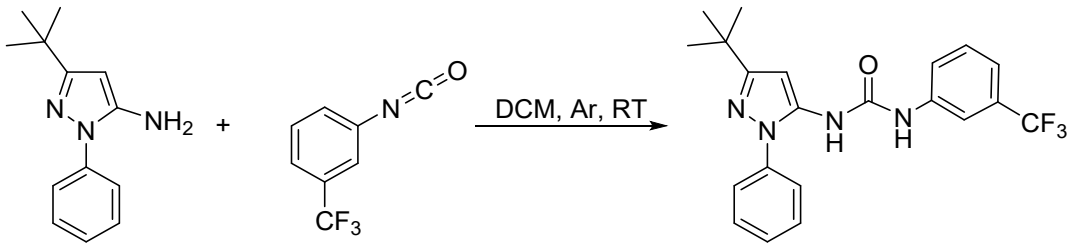
^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.36-7.32 (5 H, m, Ph), 7.26-7.23 (1 H, t, Ph-Cl), 7.11-7.08 (1 H, d, Ph-Cl, J=8.21 Hz), 7.07-7.04 (1 H, d, J=8.21 Hz, Ph-Cl), 6.98-6.96 (1 H, d, J=8.16 Hz, Ph-Cl), 6.33 (1 H, s, Pyrazole), 1.29 (9 H, s, *t*Bu);
^{13}C-NMR (150 MHz, $CDCl_3$) δ 162.7, 151.6, 138.9, 134.7, 130.0, 129.6, 128.4, 124.8, 124.0, 119.9, 117.9, 97.0, 32.5, 30.2

1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(3,5-dimethylphenyl) urea 5c



Following general procedure A compound **5c** was obtained from **3a** (168 mg, 0.78 mmol) and 3,5-dimethylphenyl isocyanate **4c** (313 mg, 2.13 mmol). Yield 13.1 mg, 14 %;
^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.37-7.31 (4H, m, Ph), 7.26-7.23 (1H, t, J=7.2 Hz, Ph), 6.85 (1H, s, 3,5-CH_3Ph), 6.80 (2H, s, 3,5-CH_3Ph), 6.67 (2H, s, NH), 6.36 (1H, s, Pyrazole), 2.17 (6H, s, CH_3), 1.29 (9H, s, *t*Bu);
^{13}C-NMR (150 MHz, $CDCl_3$) δ 162.5, 151.9, 139.1, 137.1, 129.6, 128.2, 126.5, 126.1, 124.8, 119.1, 118.9, 96.3, 32.5, 30.2, 21.3

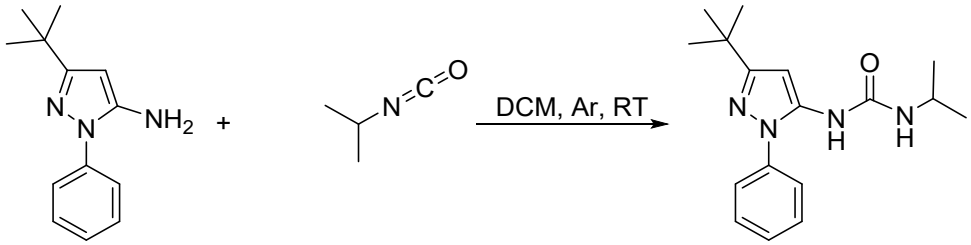
1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(3-(trifluoromethyl) phenyl) urea 5d



Following general procedure A compound **5d** was obtained from **3a** (359 mg, 1.58 mmol) and 3-trifluromethylphenyl isocyanate **4d** (273 mg, 1.46 mmol). Yield 206 mg, 36 %;

^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.02 (2 H, s, NH); 7.59 (1 H, s, CF_3-Ph); 7.37 (1 H, d, J=7.9 Hz, CF_3-Ph), 7.25-7.22 (5 H, m, Ph), 7.08-7.05 (2 H, m, CF_3-Ph), 6.94 (1 H, s, Pyrazole), 1.37 (9 H, s, *t*Bu);
^{13}C-NMR (150 MHz, $CDCl_3$) δ 160.9, 155.8, 150.0, 139.3, 138.5, 130.3, 129.6, 129.4, 128.6, 126.4, 123.0, 122.9, 122.3, 120.7, 94.7, 32.6, 29.2

1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-isopropylurea 5e

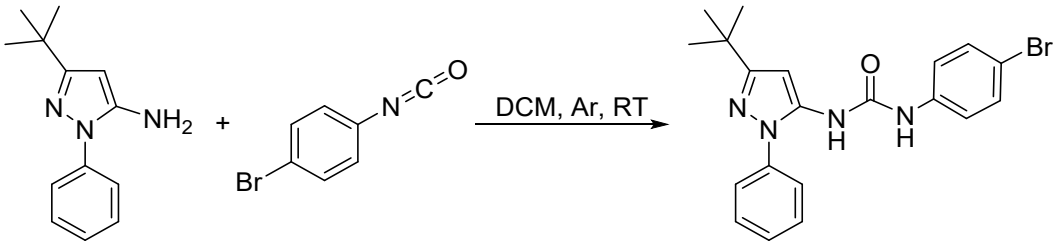


Following general procedure A compound **5e** was obtained from **3a** (99 mg, 0.46 mmol) and isopropyl isocyanate **4g** (126 mg, 1.48 mmol). The mixture was purified by flash column silica chromatography. Ethyl acetate and petroleum ether (1:3 – 1:1 – 3:1) were used as the eluent to give the title compound as a pale brown solid Yield 25.2 mg, 18 %;

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.50-7.45 (4 H, m, Ph); 7.36-7.34 (1H, t, J=7.25, 1.5, Ph); 6.22 (1 H, s, Pyrazole); 3.98-3.90 (1 H, septet, CH, J=6.6 Hz, 7.4 Hz) 1.35 (9 H, s, *t*Bu); 1.11-1.09 (6 H, d, J=6.5 Hz, CH_3);

^{13}C-NMR (150 MHz, $CDCl_3$) δ 162.5, 153.7, 138.3, 136.0, 129.5, 127.8, 124.3, 97.5, 42.6, 32.5, 30.3, 23.0

1-(4-bromophenyl)-3-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)urea 5f



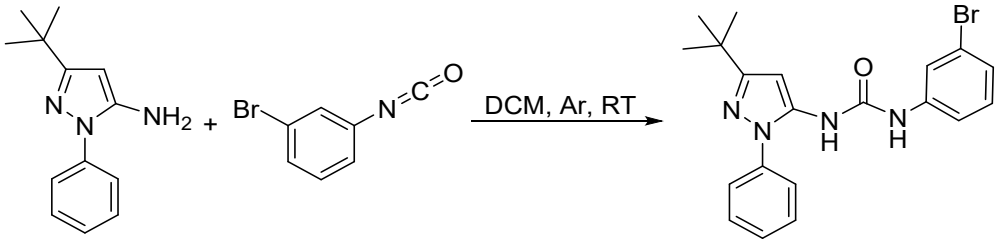
Following general procedure B compound **5f** was obtained from **3a** and isocyanate **4e** as a white solid (179 mg; yield 60%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.28 (s, 9H, $(CH_3)_3$), 6.37 (s, 1H), 7.44 – 7.35 (m, 5H, aromatic), 7.52 (d, *J* = 5.1 Hz, 4H, aromatic), 8.43 (s, 1H, urea), 9.15 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 32.05, 95.79, 113.49, 120.08, 124.26, 127.27, 129.29, 131.55, 136,98, 138.56, 138.84, 151.57, 160.79.

ESI-MS (m/z): theoretical 413.09 $[C_{20}H_{21}BrN_4O+H]^+$, experimental 413.28 $[C_{20}H_{21}BrN_4O+H]^+$.

1-(3-bromophenyl)-3-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)urea 5g



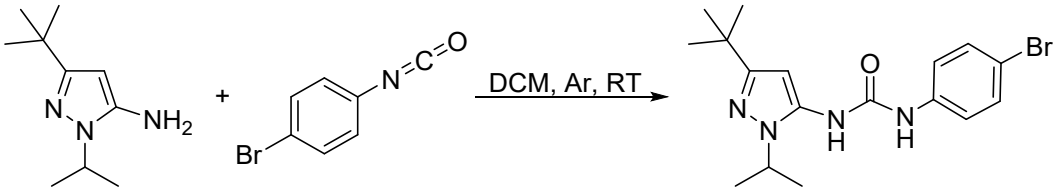
Following general procedure B compound **5g** was obtained starting from **3a** and isocyanate **4f.** After filtration **5g** was still impure. Therefore, the resultant residue was purified by chromatographic columns (Silica, DCM:EtOAc 98:2, R_f = 0.18). **5g** was obtained as a white solid (134 mg; yield 45%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28 (s, 9H, $(CH_3)_3C$), 6.38 (s, 1H, pyrazole), 7.15 (m, 1H, aromatic), 7.25 – 7.18 (m, 2H, aromatic), 7.41 (m, 1H, aromatic), 7.52 (m, 4H, aromatic), 7.83 (s, 1H, aromatic), 8.48 (s, 1H, urea), 9.21 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 87.04, 96.05, 112.76, 115.91, 117.04, 117.85, 120.44, 121.79, 122.50, 124.30, 124.71, 127.36, 129.02, 129.36, 130.78 (d, J = 8.5 Hz), 136.90, 138.58, 141.13, 151.66, 160.88.

ESI-MS (m/z): theoretical 413.09 $[C_{20}H_{21}BrN_4O+H]^+$, experimental 413.59 $[C_{20}H_{21}BrN_4O+H]^+$.

1-(4-bromophenyl)-3-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)urea 5h



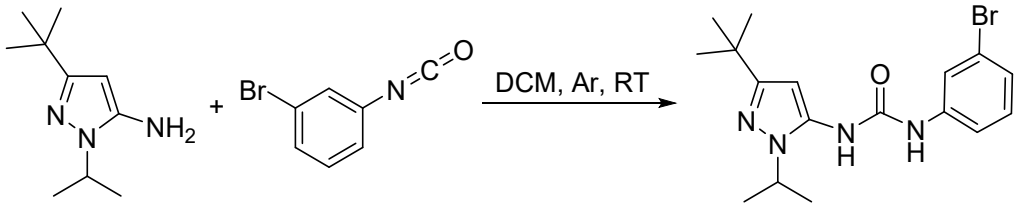
Following general procedure B compound **5h** was obtained starting from **3a** and isocyanate **4e** as white solid (137 mg; yield 50%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.21 (s, 9H. $(CH_3)_3$), 1.33 (d, J = 6.6 Hz, 6H, $(CH_3)_2CH$), 4.34 (hept, J = 6.7 Hz, 1H, $CH(CH_3)_2$), 6.00 (s, 1H, pyrazole), 7.35 – 7.50 (m, 4H, aromatic), 8.36 (s, 1H, urea), 8.99 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.25, 30.50, 31.98, 45.85, 47.80, 54.95, 94.84, 113.48, 115.85, 120.23, 120.35, 131.61, 135.19, 139.00, 139.06, 152.28, 158.59.

ESI-MS (m/z): theoretical 379.11 $[C_{17}H_{23}BrN_4O+H]^+$, experimental 379.54 $[C_{17}H_{23}BrN_4O+H]^+$.

1-(3-bromophenyl)-3-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)urea 5i



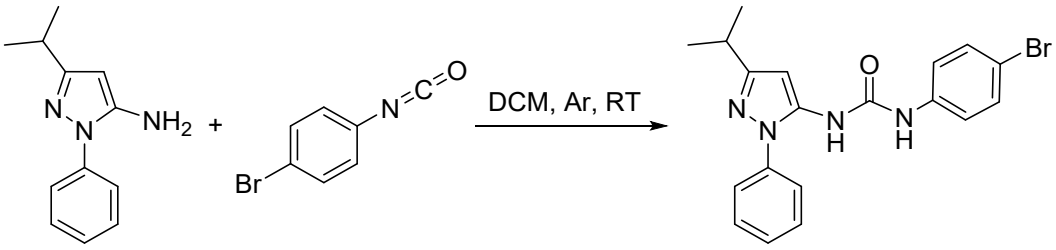
Following general procedure B compound **5i** was obtained starting from **3b** and isocyanate **4f** as white solid (251 mg; yield 92%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): δ 1.22 (s, 9H, $(CH_3)_3$), 1.34 (d, J = 6.6 Hz 6H, $(CH_3)_2CH$), 4.34 (hept, J = 6.6 Hz,1H, $CH(CH_3)_2$), 6.01 (s, 1H, pyrazole), 7.15 (m, 1H, aromatic), 7.23 (t, J = 8.0 Hz,1H, aromatic), 7.30 (m, 1H, aromatic), 7.85 (t, J = 2.0, 1H, aromatic), 8.43 (s, 1H, urea), 9.07 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.19, 30.56 (d, J = 39.4 Hz), 47.70, 94.79, 117.02, 120.41, 121.70, 124.49, 130.71, 135.04, 141.30, 152.18, 158.48, 206.49.

ESI-MS (m/z): theoretical 379.11 $[C_{17}H_{23}BrN_4O+H]^+$, experimental 379.76 $[C_{17}H_{23}BrN_4O+H]^+$.

1-(4-bromophenyl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea 5k



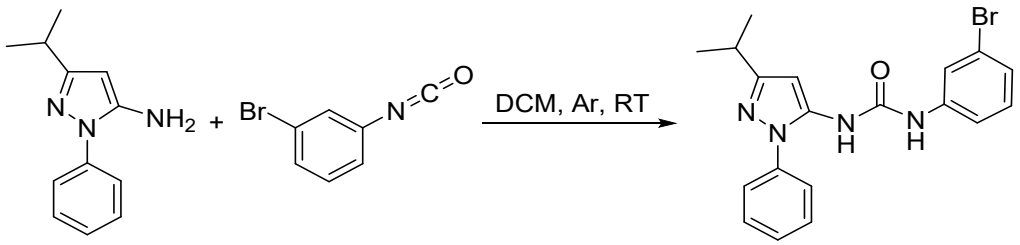
Following general procedure B compound **5k** was obtained starting from **3d** and isocyanate **4e** as a white solid (195 mg; yield 68%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.23 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.89 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 6.32 (s, 1H, pyrazole), 7.35 – 7.46 (m, 5H, aromatic), 7.52 (d, J = 4.4 Hz, 3H, aromatic), 8.46 (s, 1H, urea), 9.14 (s, 1H, urea).

^{13}C-NMR (151 MHz, Chloroform-d) δ (ppm): 159.68, 151.46, 136.85, 132.01, 129.73, 128.97, 124.99, 121.32, 116.57, 29.72, 27.88, 22.42, 1.03.

ESI-MS (m/z): theoretical 399.08 $[C_{19}H_{19}BrN_4O+H]^+$, experimental 399.46 $[C_{19}H_{19}BrN_4O+H]^+$.

1-(3-bromophenyl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea 5j



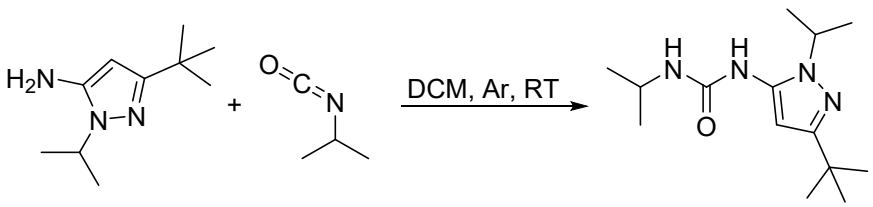
Following general procedure B compound **5j** was obtained starting from **3d** and isocyanate **4f** as a white solid (167 mg; yield 58%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.23 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.89 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 6.33 (s, 1H, pyrazole), 7.14 (dt, J = 1.8, 7.2 Hz, 1H, aromatic), 7.17 – 7.25 (m, 2H, aromatic), 7.38 – 7.43 (m, 1H, aromatic), 7.48 – 7.54 (m, 4H, aromatic), 7.82 (t, J = 1.9 Hz, 1H, aromatic), 8.50 (s, 1H, urea), 9.22 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.42, 27.64, 40.06, 54.89, 96.29, 116.95, 120.37, 121.72, 124.22, 124.61, 127.29, 129.28, 130.71, 136.95, 138.47, 141.07, 151.55, 158.04.

ESI-MS (m/z): theoretical 399.08 $[C_{19}H_{19}BrN_4O+H]^+$, experimental 399.72 $[C_{19}H_{19}BrN_4O+H]^+$.

1-(isopropyl)-3-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)urea 5l



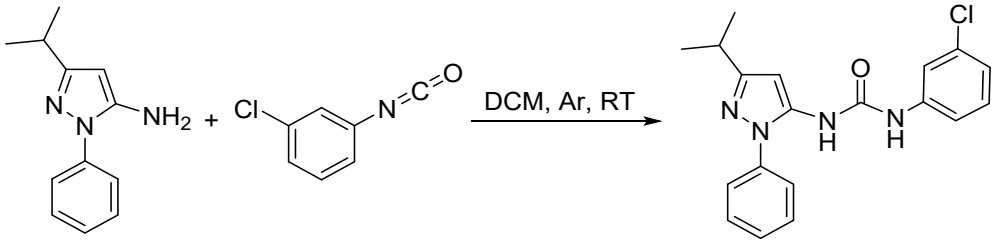
Following general procedure B compound **5l** was obtained starting from **3b** and isocyanate **4g** as a white solid (Yield 40%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (d, J = 6.5 Hz, 6H, $N(CH_3)_2CH$), 1.19 (s, 9H, $(CH_3)_{3)}$, 1.30 (d, J = 6.6 Hz, 6H, $(CH_3)_2CH$), 3.71 (hept, 1H, $NCH(CH_3)_2$), 4.27 (hept, J = 6.5 Hz, 1H, $CH(CH_3)_2$), 5.90 (s, 1H, pyrazole), 6.12 (d, J = 7.5 Hz, 1H, $NHCH(CH_3)_2$), 7.92 (s, 1H, urea).

^{13}C NMR (151 MHz, DMSO-d_6) δ 22.16, 22.94, 30.47, 41.24, 47.45, 79.19, 93.56, 136.29, 154.06, 158.32, 206.61.

ESI-MS (m/z): theoretical 267.21 $[C_{14}H_{26}N_4O+H]^+$, experimental 267.35 $[C_{14}H_{26}N_4O+H]^+$.

1-(3-chlorophenyl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea 5m



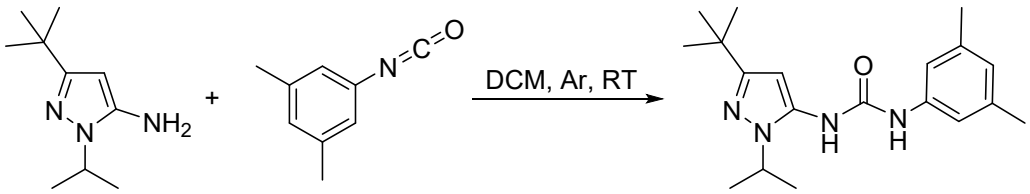
Following general procedure B compound **5m** was obtained starting from **3d** and isocyanate **4f** as a white solid (792 mg; yield 31%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (d, *J* = 6.6 Hz, 6H, (CH3)2CH), 2.89 (hept, *J* = 6.9 Hz, 1H, CH(CH3)2), 6.34 (s, *J* = 2.7 Hz, 1H, pyrazole), 7.02 (dp, *J* = 2.8, 8.1 Hz, 1H, aromatic), 7.14 – 7.23 (m, 1H), 7.28 (td, *J* = 3.4, 7.5, 8.4 Hz, 1H, aromatic), 7.34 – 7.49 (m, 1H, aromatic), 7.53 (q, *J* = 3.3, 3.7 Hz, 4H, aromatic), 7.67 (q, *J* = 2.6 Hz, 1H, aromatic), 8.49 (s, 1H, urea), 9.20 (s, 1H, urea).

^{13}C-NMR (101 MHz, DMSO-d_6) δ (ppm): 22.44, 27.65, 96.32, 116.62, 117.56, 121.76, 124.26, 127.33, 129.31, 130.44, 133.22, 136.98, 138.49, 140.94, 151.59, 158.08.

ESI-MS (m/z): theoretical 355.13 $[C_{19}H_{19}ClN_4O+H]^+$, experimental 355.525 $[C_{19}H_{19}ClN_4O+H]^+$.

1-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)-3-(3,5-dimethylphenyl)urea 5n



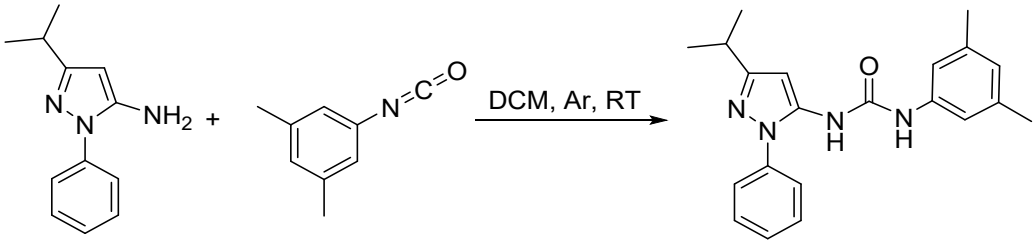
Following general procedure B compound **5n** was obtained starting from **3b** and isocyanate **4c** as a white solid (215 mg; yield 91%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.21 (s, 9H, $(CH_3)_3$), 1.34 (d, *J* = 6.5 Hz, 6H, $(CH_3)_2CH$), 2.22 (s, 6H, CH_3-aromatic), 4.33 (hept, *J* = 6.3 Hz, 1H, $CH(CH_3)_2$), 6.01 (s, 1H, pyrazole), 6.62 (s, 1H, aromatic), 7.05 (d, *J* = 1.6 Hz, 2H, aromatic), 8.30 (s, 1H, urea), 8.67 (s, 1H, urea).

^{13}C-NMR (101 MHz, DMSO-d_6) δ (ppm): 21.12, 22.18, 30.45, 30.70, 31.91, 47.66, 94.17, 115.93, 123.60, 135.48, 137.76, 139.38, 152.11, 158.46.

ESI-MS (m/z): theoretical 329.42 $[C_{19}H_{28}N_4O+H]^+$, experimental 329.42 $[C_{19}H_{28}N_4O+H]^+$,

1-(3,5-dimethylphenyl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea 5o



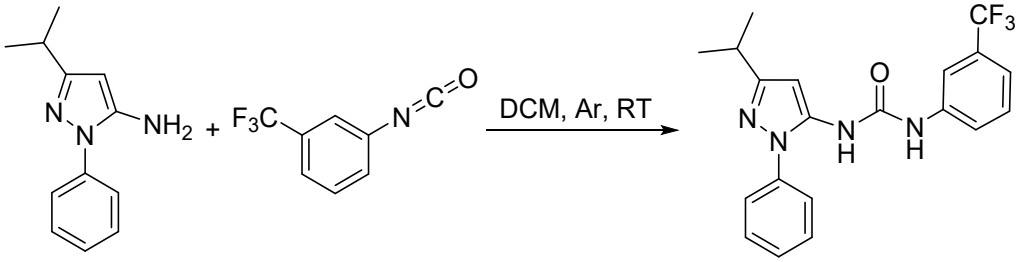
Following general procedure B compound **5o** was obtained starting from **3d** and isocyanate **4c** as a white solid (156 mg; yield 62%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.23 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.21 (s, 6H, CH_3-aromatic), 2.88 (p, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 6.33 (s, 1H, pyrazole), 6.61 (s, 1H, aromatic), 7.02 (d, *J* = 1.5 Hz, 2H, aromatic), 7.41 (ddd, *J* = 2.3, 5.6, 7.1 Hz, 1H, aromatic), 7.46 – 7.59 (m, 4H, aromatic), 8.36 (s, 1H, urea), 8.84 (s, 1H, urea).

^{13}C-NMR (101 MHz, DMSO-d_6) δ (ppm): 21.27, 22.65, 27.83, 96.03, 112.21, 116.17, 122.71, 124.02, 124.48, 127.59, 129.26, 129.56, 137.54, 137.81, 138.08, 138.62, 139.31, 151.81, 158.41.

ESI-MS (m/z): theoretical 349.20 $[C_{21}H_{24}N_4O+H]^+$, experimental 349.45 $[C_{21}H_{24}N_4O+H]^+$.

1-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(trifluoromethyl)phenyl)urea 5p



Following general procedure B compound **5p** was obtained starting from **3d** and isocyanate **4d** as a white solid (280 mg; yield 10%).

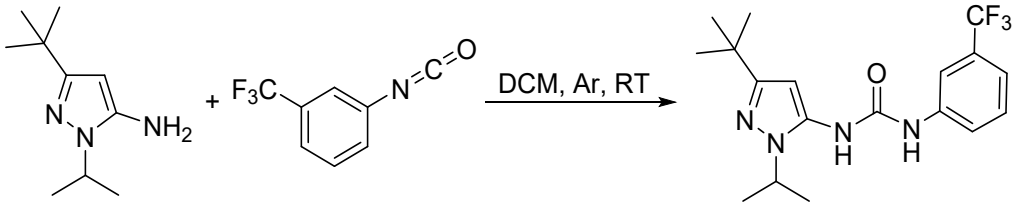
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (d, *J* = 6.6 Hz, 6H, (CH3)2CH), 2.89 (hept, *J* = 4.9, 7.4 Hz, 1H, CH(CH3)3), 6.35 (s, 1H, pyrazole), 7.31 (d, *J* = 6.4 Hz, 1H, aromatic), 7.41 (dd, *J* = 3.7, 7.4

Hz, 1H, aromatic), 7.47 – 7.57 (m, 6H, aromatic), 7.97 (d, *J* = 5.6 Hz, 1H, aromatic), 8.53 (s, 1H, urea), 9.37 (s, 1H, urea).

^{13}C-NMR (101 MHz, DMSO-d_6) δ (ppm): 22.45, 27.67, 30.71, 96.49, 121.79, 122.41, 124.25, 127.34, 128.98, 129.31, 129.99, 136.90, 138.49, 140.27, 151.75, 158.10.

ESI-MS (m/z): theoretical 389.15 $[C_{20}H_{19}F_3N_4O+H]^+$, experimental 389.44 $[C_{20}H_{19}F_3N_4O+H]^+$.

1-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)-3-(3-(trifluoromethyl)phenyl)urea 5q



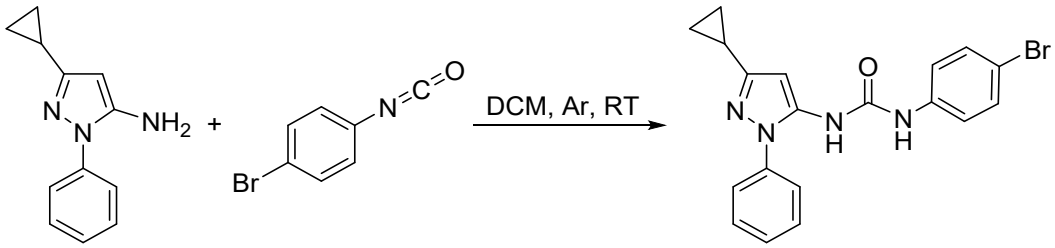
Following general procedure B compound **5q** was obtained starting from **3b** and isocyanate **4d** as a white solid (154 mg; yield 58%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.22 (s, 9H, $(CH_3)_3$), 1.34 (d, *J* = 6.6 Hz, 6H, $(CH_3)_2CH$), 4.36 (hept, *J* = 6.6 Hz, 1H, $CH(CH_3)_2$), 6.02 (s, 1H, pyrazole), 7.26 – 7.36 (m, 1H, aromatic), 7.51 (t, *J* = 7.9 Hz, 1H, aromatic), 7.54 – 7.62 (m, 1H, aromatic), 8.00 (d, *J* = 2.1 Hz, 1H, aromatic), 8.44 (s, 1H, urea), 9.22 (s, 1H, urea).

^{13}C-NMR (101 MHz, DMSO-d_6) δ (ppm): 22.14, 30.38, 31.88, 47.72, 95.01, 114.12, 118.21, 121.80, 129.32, 129.63, 129.92, 134.90, 140.39, 152.35, 158.53.

ESI-MS (m/z): theoretical 369.19 $[C_{18}H_{23}F_3N_4O+H]^+$, experimental 369.44 $[C_{18}H_{23}F_3N_4O+H]^+$.

1-(4-bromophenyl)-3-(3-cyclopropyl-1-phenyl-1H-pyrazol-5-yl)urea 5r



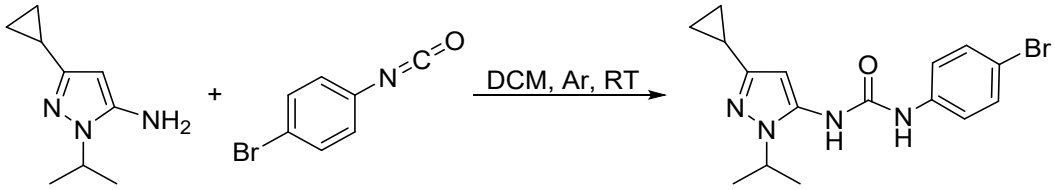
Following general procedure B compound **5r** was obtained starting from **3g** and isocyanate **4f** as a white solid (189 mg; yield 66%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 0.66 – 0.71 (m, 2H, $(CH_2)_2CH$), 0.85 – 0.91 (m, 2H, $(CH_2)_2CH$), 1.88 (tt, J = 5.0, 8.4 Hz, 1H, $CH(CH_2)_2$), 6.16 (s, 1H, pyrazole), 7.34 – 7.45 (m, 5H, aromatic), 7.48 – 7.54 (m, 4H, aromatic), 8.44 (s, 1H, urea), 9.12 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 7.70, 9.38, 95.60, 113.51, 120.11, 120.23, 124.20, 127.29, 129.29, 131.53, 137.19, 138.41, 138.79, 151.50, 152.27, 154.30.

ESI-MS (m/z): theoretical 397.06 $[C_{19}H_{17}BrN_4O+H]^+$, experimental 397.51 $[C_{19}H_{17}BrN_4O+H]^+$.

1-(4-bromophenyl)-3-(3-cyclopropyl-1-isopropyl-1H-pyrazol-5-yl)urea 5s



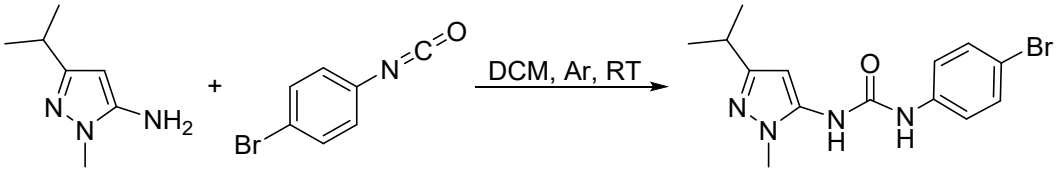
Following general procedure B compound **5s** was obtained starting from **3h** and isocyanate **4e** as a white solid (186 mg; yield 71%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 0.49 – 0.61 (m, 2H, $(CH_2)_2CH$), 0.77 – 0.84 (m, 2H, $(CH_2)_2CH$), 1.32 (d, J = 6.6 Hz, 6H, $(CH_3)_2CH$), 1.80 (tt, J = 5.0, 8.4 Hz, 1H, $CH(CH_2)_2$), 4.32 (hept, J = 6.6 Hz, 1H, $CH(CH_2)_3$), 5.77 (s, 1H, pyrazole), 7.23 – 7.72 (m, 4H, aromatic), 8.43 (s, 1H, urea), 8.97 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 7.56, 9.66, 14.08, 22.21, 47.59, 59.75, 94.05, 113.39, 120.15, 131.51, 135.51, 135.52, 138.96, 138.97, 152.00, 152.11.

ESI-MS (m/z): theoretical 365.08 $[C_{16}H_{19}BrN_4O+H]^+$, experimental 365.54 $[C_{16}H_{19}BrN_4O+H]^+$.

1-(4-bromophenyl)-3-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)urea 5t



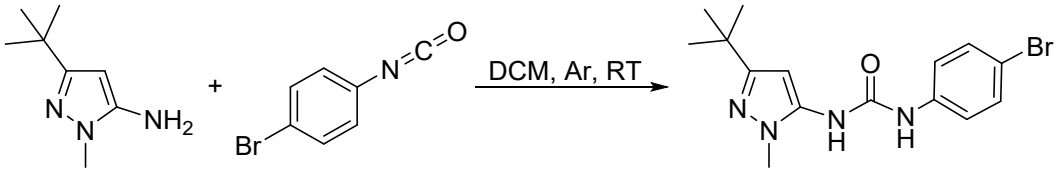
Following general procedure B compound **5t** was obtained starting from **3f** and isocyanate **4e** as a white solid (202 mg; yield 83%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.16 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.77 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.58 (s, 3H, NCH_3), 5.99 (s, 1H, pyrazole), 7.51 – 7.31 (m, 4H, aromatic), 8.53 (s, 1H, urea), 9.02 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.62, 27.51, 34.88, 40.06, 94.38, 113.43, 120.14, 131.53, 136.93, 138.94, 151.77, 155.72.

ESI-MS (m/z): theoretical 337.06 $[C_{14}H_{17}BrN_4O+H]^+$, experimental 337.43 $[C_{14}H_{17}BrN_4O+H]^+$.

1-(4-bromophenyl)-3-(3-(tert-butyl)-1-methyl-1H-pyrazol-5-yl)urea 5u



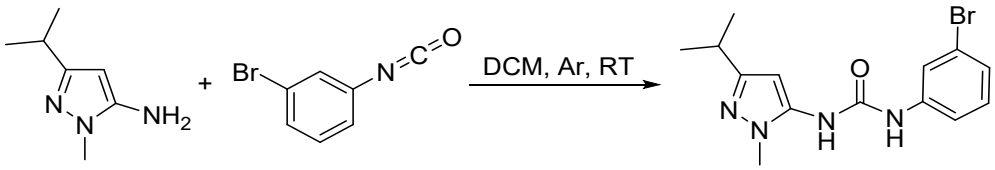
Following general procedure B compound **5u** was obtained starting from **3c** and isocyanate **4e** as a white solid (187 mg; yield 74%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.21 (s, 9H, $(CH_3)_3$), 3.59 (s, 3H, NCH_3), 6.04 (s, 1H, pyrazole), 7.55 – 7.36 (m, 5H, aromatic), 8.50 (s, 1H, urea), 9.02 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 30.37, 31.80, 34.93, 54.92, 93.96, 113.43, 115.74, 120.14, 131.54, 136.84, 138.95, 151.80, 152.27, 158.54.

ESI-MS (m/z): theoretical 353.07 $[C_{15}H_{19}BrN_4O+H]^+$, experimental 353.18 $[C_{15}H_{19}BrN_4O+H]^+$.

1-(3-bromophenyl)-3-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)urea 5v



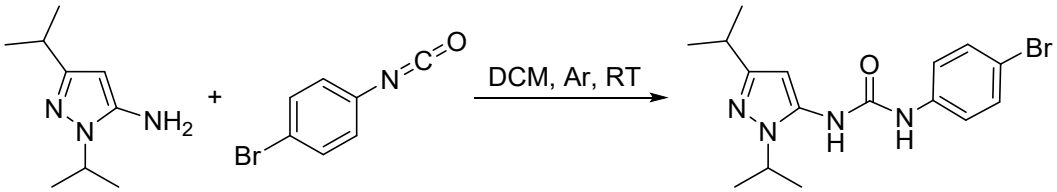
Following general procedure B compound **5v** was obtained starting from **3f** and isocyanate **4f** as a white solid (124 mg; yield 51%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.16 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.78 (hept, 1H, $CH(CH_3)_2$), 3.59 (s, 3H, CH_3), 6.01 (s, 1H, pyrazole), 7.16 (m, 1H, aromatic), 7.24 (m, 1H, aromatic), 7.34 – 7.28 (m, 1H, aromatic), 7.85 (m, 1H, aromatic), 8.62 (s, 1H, urea), 9.13 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.63, 27.52, 34.89, 94.48, 117.06, 117.23, 120.59, 121.72, 124.57, 130.74, 136.84, 141.21, 151.79, 155.76.

ESI-MS (m/z): theoretical 337.06 $[C_{14}H_{17}BrN_4O+H]^+$, experimental 337.49 $[C_{14}H_{17}BrN_4O+H]^+$.

1-(4-bromophenyl)-3-(1,3-diisopropyl-1H-pyrazol-5-yl)urea 5x



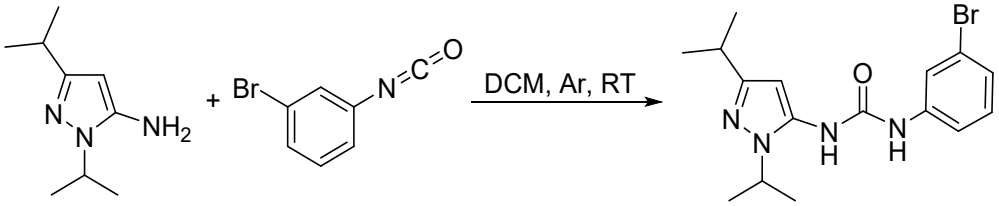
Following general procedure B compound **5x** was obtained starting from **3e** and isocyanate **4e** as a white solid (184 mg; yield 70%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.16 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 1.33 (d, J = 6.5 Hz, 6H, $(CH_3)_2CHN$), 2.80 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.35 (hept, 1H, $NCH(CH_3)_2$), 5.96 (s, 1H, pyrazole), 7.43 (s, 4H, aromatic), 8.52 (s, 1H, urea), 9.10 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.23, 22.75, 27.71, 47.59, 79.17, 94.84, 113.21, 120.08, 131.47, 135.49, 139.20, 152.29, 155.80.

ESI-MS (m/z): theoretical 367.09 $[C_{16}H_{21}BrN_4O+H]^+$, experimental 367.08 $[C_{16}H_{21}BrN_4O+H]^+$.

1-(32-~~aminophenyl~~bromophenyl)-3-(1,3-diisopropyl-1H-pyrazol-5-yl)urea 5y



Following general procedure B compound **5y** was obtained starting from **3e** and isocyanate **4f** as a white solid (132 mg; yield 50%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.16 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 1.33 (d, J = 6.5 Hz, 6H, $(CH_3)_2CHN$), 2.80 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.35 (hept, 1H, $NCH(CH_3)_2$), 5.98 (s, 1H, pyrazole), 7.15 (m, 1H, aromatic), 7.23 (m, 1H, aromatic), 7.30 (m, 1H, aromatic), 7.84 (m, 1H, aromatic), 8.43 (s, 1H, urea), 9.03 (s, 1H, urea).

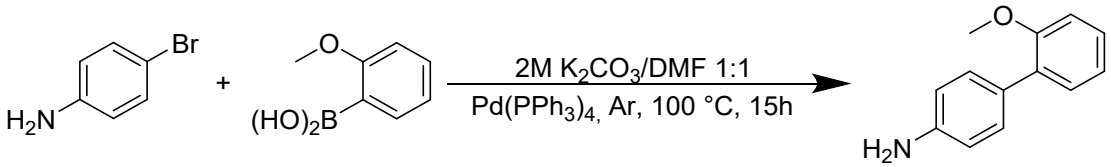
^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 14.10, 22.23, 22.75, 27.72, 47.66, 59.77, 79.18, 95.06, 117.06, 120.45, 121.71, 124.54, 130.74, 135.21, 141.26, 152.16, 155.88.

ESI-MS (m/z): theoretical 367.09 $[C_{16}H_{21}BrN_4O+H]^+$, experimental 367.08 $[C_{16}H_{21}BrN_4O+H]^+$.

General procedure C

Boronic acid **7a-d** (1.40 mmol), bromoaniline **6a-b** (1.16 mmol) and $Pd(PPh_3)_4$ (0.04 mmol) were dissolved in a degassed 1:1 solution of 2M $K_2CO_{3\,aq}$:DMF (4.4 mL). The reaction mixture was stirred at 100° for 15h under Argon atmosphere. After cooling, the reaction solution was extracted with EtOAc (100 mL) and washed with H_2O (2x100mL) and brine (100mL). The organic layer was dried with Na_2SO_4 and filtered. The solvent was removed under vacuum and the crude was purified by column chromatography.

2'-methoxy-[1,1'-biphenyl]-4-amine 8a



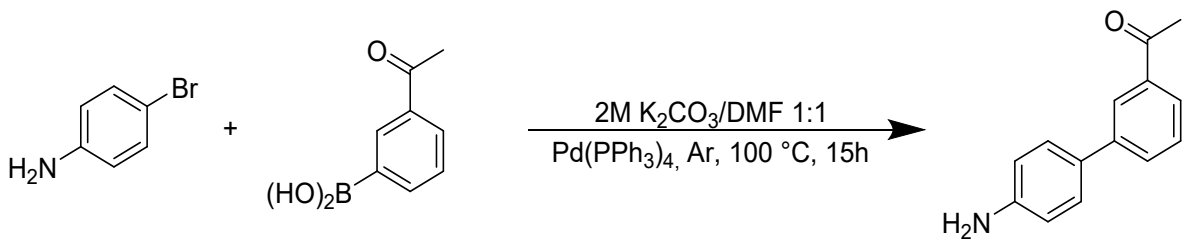
Following general procedure B compound **8a** was obtained starting from **7a** and **6a**. **7a** was purified by column chromatography (Silica, petroleum ether:EtOAc, 5:1 → 0:1, R_f = 0.41). Concentration in vacuo of the product-rich fractions gave **8a** as yellow oily liquid (141 mg; yield 61%).

^{1}H-NMR (400 MHz, Chloroform-*d*) δ (ppm): 3.81 (s, 3H, OCH_3), 6.80 – 6.72 (m, 2H, aromatic), 7.05 – 6.93 (m, 2H, aromatic), 7.33 – 7.23 (m, 2H, aromatic), 7.42 – 7.33 (m, 2H, aromatic).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ (ppm): 55.69, 111.35, 111.41, 114.95, 114.98, 120.95, 121.05, 127.93, 128.76, 128.95, 129.00, 130.60, 130.67, 130.89, 145.37, 145.44, 156.63.

ESI-MS (m/z): theoretical 200.25 $[C_{13}H_{13}NO+H]^+$, experimental 200.21 $[C_{13}H_{13}NO+H]^+$

1-(4'-amino-[1,1'-biphenyl]-3-yl)ethan-1-one 8b



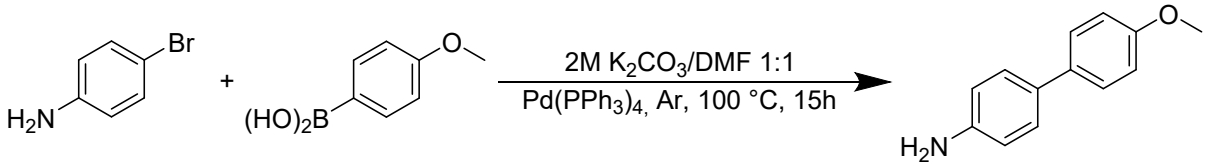
Following general procedure B compound **8b** was obtained starting from **6a** and **7c**. **8b** was purified by column chromatography (Silica, petroleum ether:EtOAc, 5:1 → 1:1, R_f = 0.28). Concentration in vacuo of the product-rich fractions gave **8b** as yellow oily liquid (157 mg; yield 64%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.63 (s, 3H, CH_3), 6.61 – 6.74 (m, 2H, aromatic), 7.38 – 7.47 (m, 2H, aromatic), 7.51 (t, *J* = 7.8 Hz, 1H, aromatic), 7.79 (dt, *J* = 1.7, 7.9 Hz, 2H, aromatic), 8.06 (t, *J* = 1.9 Hz, 1H, aromatic).

^{13}C-NMR (101 MHz, DMSO-d_6) δ (ppm): 55.47, 55.60, 66.36, 109.52, 112.31, 114.36, 117.39, 126.88, 127.91, 133.80, 147.28, 147.42, 148.98.

ESI-MS (m/z): theoretical 212.10 $[C_{14}H_{13}NO+H]^+$, experimental 212.19 $[C_{14}H_{13}NO+H]^+$.

4'-methoxy-[1,1'-biphenyl]-4-amine 8c



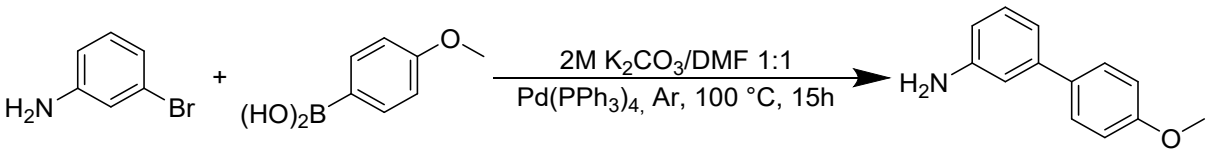
Following general procedure B compound **8c** was obtained starting from **6a** and **7d**. **8c** was purified by column chromatography (Silica, petroleum ether:EtOAc, 5:1 → 1:1, R_f = 0.32). Concentration in vacuo of the product-rich fractions gave **8c** as yellow oily liquid (118 mg, yield 51%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 3.75 (s, 3H, OCH_3), 5.10 (s, 2H, aromatic), 6.63 – 6.58 (m, 2H, aromatic), 6.96 – 6.90 (m, 2H, aromatic), 7.30 – 7.25 (m, 2H, aromatic), 7.47 – 7.41 (m, 2H, aromatic).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 55.08, 114.16, 114.26, 126.42, 126.69, 127.40, 133.35, 147.71, 157.64.

ESI-MS (m/z): theoretical 200.25 $[C_{13}H_{13}NO+H]^+$, experimental 200.19 $[C_{13}H_{13}NO+H]^+$.

4'-methoxy-[1,1'-biphenyl]-3-amine 8d



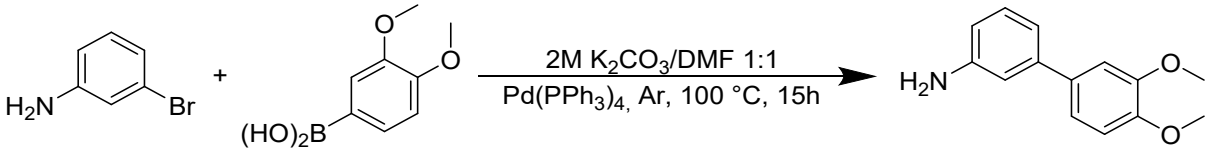
Following general procedure B compound **8d** was obtained starting from **6b** and **7a**. **8d** was purified by column chromatography (Silica, petroleum ether:EtOAc, 5:1 → 1:1, R_f = 0.41). Concentration in vacuo of the product-rich fractions gave **8d** as dark orang oily liquid (185 mg; yield 80%).

^{1}H-NMR (400 MHz, Chloroform-*d*) δ (ppm): 3.85 (s, 3H, OCH_3), 6.64 (ddd, J = 7.9, 2.4, 1.0 Hz, 1H, aromatic), 6.87 (t, J = 2.1 Hz, 1H, aromatic), 6.96 (m, 3H, aromatic), 7.20 (t, J = 7.8 Hz, 1H, aromatic), 7.50(m, 2H, aromatic).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ (ppm): 21.18, 55.48, 60.53, 113.67, 113.70, 114.22, 117.47, 128.23, 129.78, 134.09, 142.19, 146.84, 159.26.

ESI-MS (m/z): theoretical 200.25 $[C_{13}H_{13}NO+H]^+$, experimental 200.22 $[C_{13}H_{13}NO+H]^+$.

3',4'-dimethoxy-[1,1'-biphenyl]-3-amine 8e



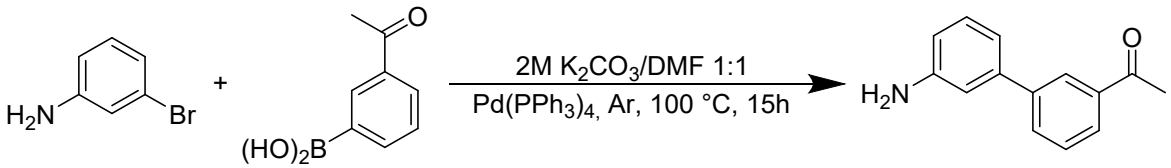
Following general procedure B compound **8e** was obtained starting from **6b** and **7b**. **8b** was purified by column chromatography (Silica, petroleum ether: EtOAc, 5:1 → 0:1, R_f = 0.41). Concentration in vacuo of the product-rich fractions gave **8e** as light-yellow solid (160 mg; yield 60%).

^{1}H-NMR (400 MHz, Chloroform-*d*) δ (ppm): 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.95 – 6.89 (m, 3H, aromatic), 7.10 – 7.04 (m, 2H, aromatic),7.44 – 7.39 (m, 2H, aromatic).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ (ppm): 56.10, 56.14, 110.65, 111.57, 114.54, 114.61, 118.55, 119.51, 129.87, 134.39, 142.55, 145.29, 148.80, 149.22.

ESI-MS (m/z): theoretical 230.28 $[C_{14}H_{15}NO_2+H]^+$, experimental 230.23 $[C_{14}H_{15}NO_2+H]^+$.

1-(3'-amino-[1,1'-biphenyl]-3-yl)ethan-1-one 8f



Following general procedure B compound **8f** was obtained starting from **6b and 7c**. **AG06** was purified by column chromatography (Silica, petroleum ether:EtOAc, 5:1 → 1:1, R_f = 0.50). Concentration in vacuo of the product-rich fractions gave **8f** as yellow oily liquid (184 mg; yield 75%).

^{1}H-NMR (400 MHz, Chloroform-*d*) δ (ppm): 2.65 (s, 3H, CH_3), 6.72 (ddd, J = 8.0, 2.4, 1.0 Hz, 1H, aromatic), 6.94 (t, J = 2.0 Hz, 1H, aromatic), 7.25 (t, J = 7.8 Hz, 1H, aromatic), 7.01 (ddd, J = 7.7, 1.7, 1.0 Hz, 1H, aromatic), 7.51 (t, J = 7.7 Hz, 1H, aromatic), 7.76 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H, aromatic), 7.92 (ddd, J = 7.8, 1.7, 1.1 Hz, 1H, aromatic), 8.15 (t, J = 1.9 Hz, 1H, aromatic).

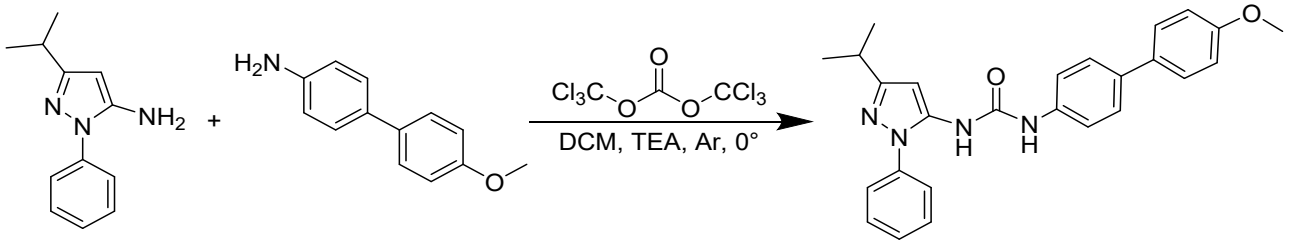
^{13}C-NMR (101 MHz, Chloroform-*d*) δ (ppm): 26.90, 113.95, 114.70, 117.73, 127.08, 127.28, 129.06, 130.01, 131.85, 137.68, 141.53, 142.04, 147.04, 198.31.

ESI-MS (m/z): theoretical 212.26 $[C_{14}H_{13}NO+H]^+$, experimental 212.19 $[C_{14}H_{13}NO+H]^+$.

General procedure D

Pyrazole **3a,b,d** (0.26 mmol) and Et_3N (0.6 mmol) dissolved in in anhydrous DCM (0.9 mL) was added dropwise to a solution of triphosgene (0.10 mmol) in anhydrous DCM (0.5 mL), at 0°C under Argon atmosphere and under magnetic stirring. After 30 min, aniline **8a-f** (0.26 mmol) and Et_3N (0.6 mmol) dissolved in anhydrous DCM (0.5 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight under Argon atmosphere. The crude was extracted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (2x50mL) and brine (50mL). The organic layer was dried with Na_2SO_4 and filtered. Removal of the volatiles in vacuo provided a residue, which was purified by column chromatography to afford ureas **9a-f** and **10 a-c.**

1-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)urea 10a



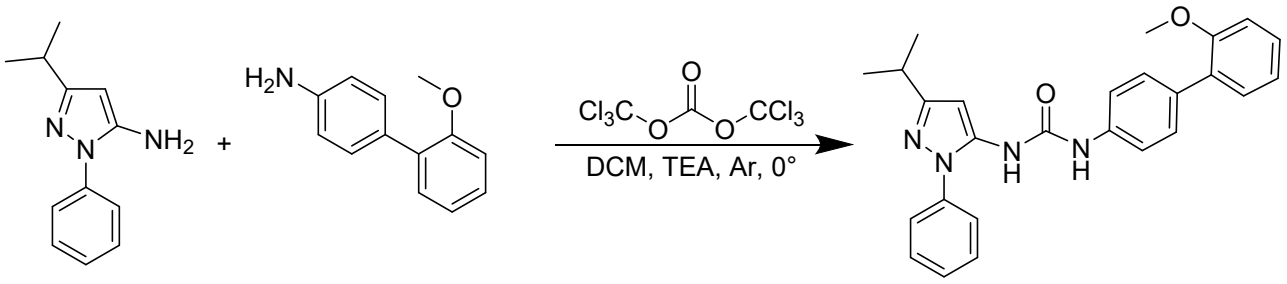
Following general procedure D compound **10a** was obtained starting from **8a** and **3d**. **10a** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.58). Concentration in vacuo of the product-rich fractions gave **10a** as white solid (33 mg; yield 30%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.89 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.78 (s, 3H, CH_3), 6.34 (s, 1H, pyrazole), 7.02 – 6.96 (m, 2H, aromatic), 7.48 – 7.38 (m, 3H, aromatic), 7.58 – 7.49 (m, 8H, aromatic), 8.45 (s, 1H, urea), 9.09 (s, 1H, urea).

^{13}C-NMR (101 MHz, DMSO-d_6) δ (ppm): 14.08, 20.76, 22.44, 27.65, 54.90, 55.14, 59.75, 95.91, 114.31, 118.54, 124.29, 126.47, 127.19, 127.29, 129.30, 132.23, 133.63, 137.31, 138.23, 138.53, 151.59, 158.05, 158.48, 170.35.

ESI-MS (m/z): theoretical 427.52 $[C_{26}H_{26}N_4O_2+H]^+$, experimental 427.48 $[C_{26}H_{26}N_4O_2+H]^+$.

1-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)-3-(2'-methoxy-[1,1'-biphenyl]-4-yl)urea 10b



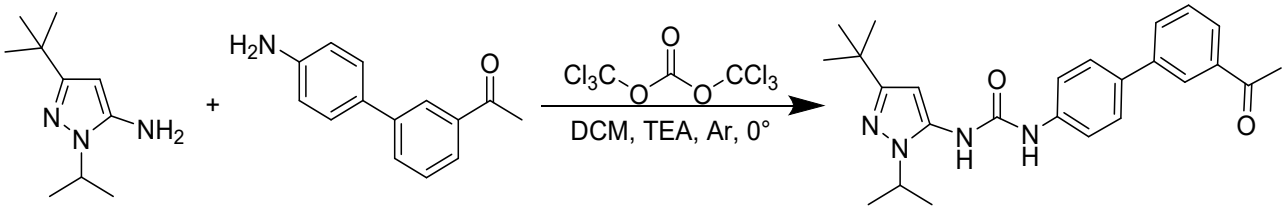
Following general procedure D compound **10b** was obtained starting from **3d** and **8c**. **10b** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.10). Concentration in vacuo of the product-rich fractions gave **10b** as white solid (52 mg; yield 47%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (d, *J* = 7.0 Hz, 6H, $(CH_3)_2CH$), 2.89 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.75 (s, 3H, CH_3), 6.35 (s, 1H, pyrazole), 7.00 (td, *J* = 1.1, 7.4 Hz, 1H, aromatic), 7.08 (d, *J* = 8.2 Hz, 1H, aromatic), 7.27 (ddd, J = 13.9, 7.1, 1.5 Hz, 2H, aromatic), 7.35 – 7.46 (m, 5H, aromatic), 7.54 (d, *J* = 3.8 Hz, 4H, aromatic), 8.44 (s, 1H, urea), 9.07 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.51, 27.70, 55.51, 59.83, 95.96, 111.77, 113.46, 117.82, 120.83, 122.46, 124.35, 125.64, 127.38, 128.50, 129.37, 129.49, 129.69, 130.16, 131.98, 137.36, 138.21, 138.56, 151.69, 156.15, 158.12.

ESI-MS (m/z): theoretical 427.52 $[C_{26}H_{26}N_4O_2+H]^+$, experimental 427.45 $[C_{26}H_{26}N_4O_2+H]^+$.

1-(3'-acetyl-[1,1'-biphenyl]-4-yl)-3-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)urea 10c



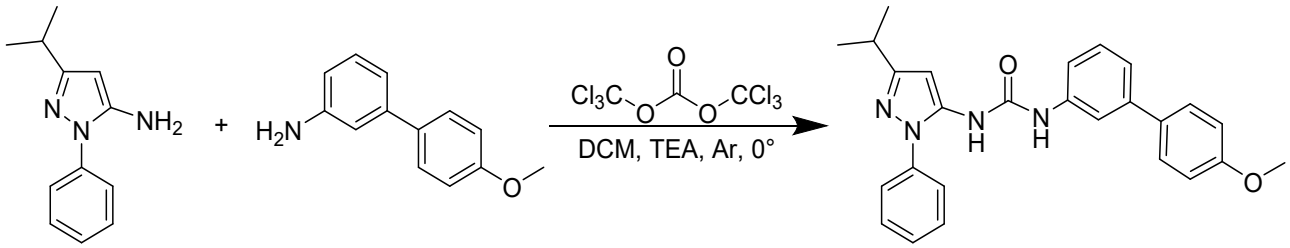
Following general procedure D compound **10c** was obtained starting from **3b** and **8b. 10r** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.24). Concentration in vacuo of the product-rich fractions gave the title compound as white solid (46 mg; yield 42%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.23 (s, 9H, $(CH_3)_3$), 1.35 (d, *J* = 6.5 Hz, 6H, $(CH)_2$ CH_3), 2.65 (s, 3H, OCH_3), 4.36 (hept, J = 6.5 Hz, 1H, $CH(CH_3)_2$), 6.03 (s, 1H, pyrazole), 7.51 – 7.64 (m, 3H, aromatic), 7.65 – 7.72 (m, 2H, aromatic), 7.86 – 7.94 (m, 2H, aromatuc), 8.16 (t, *J* = 1.8 Hz, 1H, aromatic), 8.37 (s, 1H, urea), 9.01 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.23, 26.96, 30.45, 30.48, 31.95, 47.75, 94.61, 118.59, 125.75, 126.56, 127.30, 129.38, 130.80, 132.76, 135.24, 135.31, 137.51, 139.58, 140.25, 152.23, 158.53, 198.16.

ESI-MS (m/z): theoretical 419.54 $[C_{25}H_{30}N_4O_2+H]^+$, experimental 419.46 $[C_{25}H_{30}N_4O_2+H]^+$.

1-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)-3-(4'-methoxy-[1,1'-biphenyl]-3-yl)urea 9a



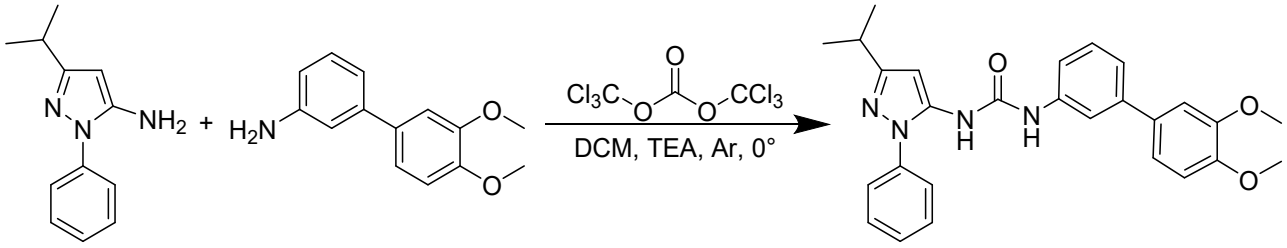
Following general procedure D compound **9a** was obtained starting from **3d** and **8d**. **9a** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.49). Concentration in vacuo of the product-rich fractions gave **9a** as white solid (29 mg; yield 26%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.88 (hept, J = 7.0 Hz, $CH(CH_3)_2$), 3.79 (s, 3H, OCH_3), 6.35 (s, 1H, pyrazole), 7.05 – 6.99 (m, 2H, aromatic), 7.21 (dt, J = 6.9, 1.9 Hz, 1H, aromatic), 7.35 – 7.27 (m, 2H, aromatic), 7.45 – 7.39 (m, 1H, aromatic), 7.57 – 7.51 (m, 6H, aromatic), 7.70 (m, 1H, aromatic), 8.44 (s, 1H, urea), 9.08 (s, 1H, urea).

^{13}C-NMR (101 MHz, DMSO-d_6) δ (ppm): 22.47, 27.67, 40.06, 55.19, 95.86, 114.38, 115.95, 116.59, 120.13, 124.35, 127.34, 127.70, 129.33, 129.36, 132.55, 137.31, 138.51, 139.91, 140.52, 151.67, 158.08, 158.97.

ESI-MS (m/z): theoretical 427.52 $[C_{26}H_{26}N_4O_2+H]^+$, experimental 427.45 $[C_{26}H_{26}N_4O_2+H]^+$.

1-(3',4'-dimethoxy-[1,1'-biphenyl]-3-yl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea 9b



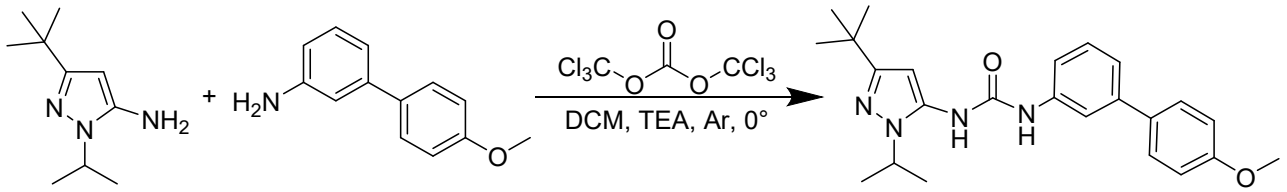
Following general procedure D compound **9b** was obtained starting from **3d** and **8e**. **9b** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.40). Concentration in vacuo of the product-rich fractions gave **9b** as white solid (50 mg; yield 42%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.89 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.79 (s, 3H, CH_3), 3.83 (s, 3H, CH_3),6.35 (s, 1H, pyrazole), 7.03 (d, J = 8.2 Hz, 1H, aromatic), 7.17 – 7.09 (m, 2H, aromatic), 7.24 (dt, J = 7.5, 1.5 Hz, 1H, aromatic), 7.32 (t, J = 7.8 Hz, 1H, aromatic), 7.38 (dt, J = 8.1, 1.5 Hz, 1H, aromatic), 7.50 – 7.38 (m, 1H, aromatic), 7.54 (m, 4H, aromatic), 7.62 (t, J = 1.9 Hz, 1H, aromatic), 8.45 (s, 1H, urea), 9.09 (s, 1H, urea).

^{13}C-NMR (101 MHz, DMSO-d_6) δ (ppm): 22.45, 27.65, 39.92, 40.06, 55.55, 55.57, 95.84, 110.35, 112.17, 116.12, 116.67, 118.80, 120.38, 124.34, 127.31, 129.26, 129.30, 132.95, 137.30, 138.50, 139.83, 140.81, 151.65, 158.04.

ESI-MS (m/z): theoretical 457.55 $[C_{27}H_{28}N_4O_3+H]^+$, experimental 457.48 $[C_{27}H_{28}N_4O_3+H]^+$.

1-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)-3-(4'-methoxy-[1,1'-biphenyl]-3-yl)urea 9c



Following general procedure D compound **9c** was obtained starting from **3b** and **8d**. **9c** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.45). Concentration in vacuo of the product-rich fractions gave **9c** as white solid (18 mg; yield 17%).

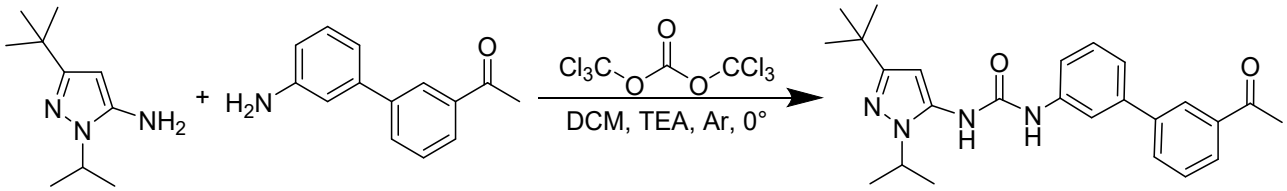
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.21 (s, 9H, CH_3), 1.33 (d, J = 6.6 Hz, 6H, $(CH_3)_2CH$),3.78 (s, 3H, CH_3), 4.35 (hept, J = 6.7 Hz, 1H, $CH(CH_3)_2$), 6.01 (s, 1H, pyrazole), 7.06 – 6.98 (m, 2H,

aromatic), 7.25 – 7.17 (m, 1H, aromatic), 7.37 – 7.28 (m, 2H, aromatic), 7.58 – 7.50 (m, 2H, aromatic), 7.72 (q, J = 1.5 Hz, 1H, aromatic), 8.35 (s, 1H, urea), 8.90 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.37, 30.66, 48.01, 55.42, 94.99, 114.61,116.25, 116.94, 120.33, 127.95, 129.63, 132.78, 135.51, 140.22, 159.18, 140.74, 152.64,158.88,

ESI-MS (m/z): theoretical 407.53 $[C_{24}H_{30}N_4O_2+H]^+$, experimental 407.24 $[C_{24}H_{30}N_4O_2+H]^+$.

1-(3'-acetyl-[1,1'-biphenyl]-3-yl)-3-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)urea 9d



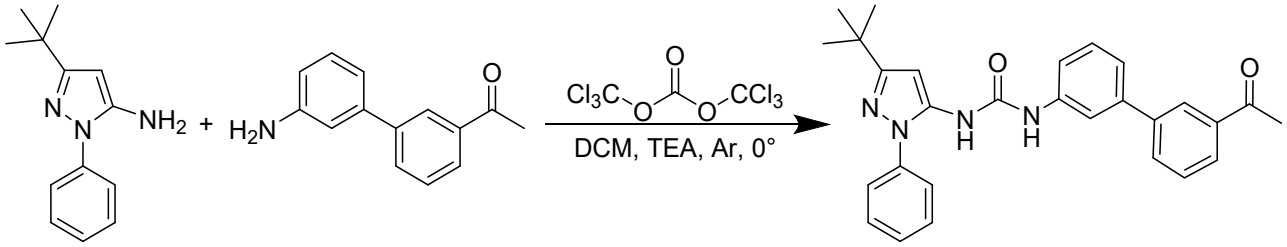
Following general procedure C compound **9d** was obtained starting from **3b** and **8f**. **9d** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.49). Concentration in vacuo of the product-rich fractions gave **9d** as white solid (25 mg; yield 23%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.22 (s, 9H, CH_3), 1.34 (d, *J* = 6.7 Hz, 6H, $(CH_3)_2CH$), 2.65 (s, 3H, CH_3), 4.38 (hept, J = 6.5 Hz, 1H, $CH(CH_3)_2$), 6.02 (s, 1H, pyrazole), 7.34 (dt, *J* = 1.5, 7.6 Hz, 1H, aromatic), 7.41 (t, *J* = 7.8 Hz, 1H, aromatic), 7.47 (d, J = 8.2 Hz, 1H, aromatic), 7.63 (t, *J* = 7.7 Hz, 1H, aromatic), 7.83 (t, *J* = 2.0 Hz, 1H), 7.89 (dt, *J* = 1.5, 7.8 Hz, 1H), 7.97 (dt, *J* = 1.4, 7.7 Hz, 1H, aromatic), 8.14 (d, J = 2.0 Hz, 1H, aromatic), 8.45 (s, 1H, urea), 9.06 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 20.82, 22.24, 26.95, 30.50, 47.76, 54.94, 59.83, 94.67, 116.59, 117.80, 120.65, 126.11, 127.45, 129.51, 129.63, 131.35, 135.36, 137.50, 140.00, 140.36, 140.71, 152.42, 158.56, 198.07.

ESI-MS (m/z): theoretical 419.54 $[C_{25}H_{30}N_4O_2+H]^+$, experimental 419.27 $[C_{25}H_{30}N_4O_2+H]^+$.

1-(3'-acetyl-[1,1'-biphenyl]-3-yl)-3-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)urea 9e



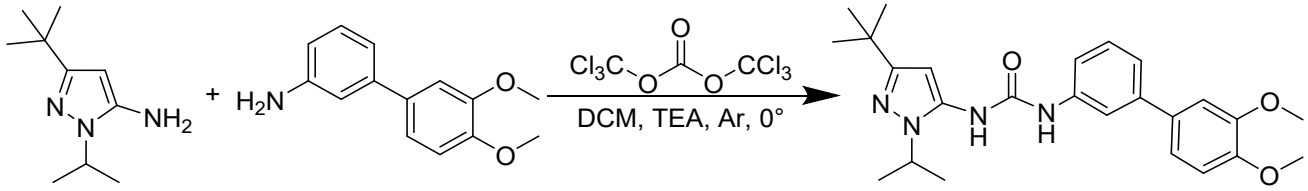
Following general procedure D compound **9e** was obtained starting from **3a** and **8f**. **9e** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.35). Concentration in vacuo of the product-rich fractions gave **9e** as white solid (12 mg; yield 10%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.29 (s, 9H, CH_3), 5.75 (s, 3H, OCH_3), 6.40 (s, 1H, pyrazole), 7.44 – 7.30 (m, 3H, aromatic), 7.52 – 7.41 (m, 1H, aromatic), 7.54 (d, J = 4.3 Hz, 4H, aromatic), 7.70 – 7.59 (m, 1H, aromatic), 7.80 (s, 1H, aromatic), 7.92 – 7.84 (m, 1H, aromatic), 7.97 (dt, J = 7.8, 1.3 Hz, 1H, aromatic), 8.13 (t, J = 1.8 Hz, 1H, aromatic), 8.46 (s, 1H, urea), 9.19 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 26.96, 30.26, 54.95, 95.75, 116.55, 117.75, 120.81, 122.52, 124.16, 124.39, 126.10, 127.38, 127.50, 129.32, 129.38, 129.53, 129.69, 131.38, 137.17, 137.51, 138.61, 140.04, 140.17, 140.67, 151.81, 160.91, 198.11.

ESI-MS (m/z): theoretical 453.56 $[C_{28}H_{28}N_4O_2+H]^+$, experimental 453.20 $[C_{28}H_{28}N_4O_2+H]^+$.

1-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)-3-(3',4'-dimethoxy-[1,1'-biphenyl]-3-yl)urea 9f



Following general procedure D compound **9f** was obtained starting from **8e** and **3b**. **9f** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.44). Concentration in vacuo of the product-rich fractions gave **9f** as white solid (68 mg; yield 60%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.34 (d, J = 6.5 Hz, 6H, $(CH_3)_2CH$), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.38 (hept, J = 6.6 Hz, 1H, $CH(CH_3)_2$), 6.02 (s, 1H, pyrazole), 7.04 (d, J = 8.4 Hz, 1H, aromatic), 7.18 – 7.12 (m, 2H, aromatic), 7.24 (ddd, J = 7.7, 1.8, 1.0 Hz, 1H, aromatic), 7.33 (t, J = 7.9 Hz, 1H, aromatic), 7.41 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H, aromatic), 7.69 (t, J = 2.0 Hz, 1H, aromatic), 1.22 (s, 9H, CH_3), 8.54 (s, 1H, urea), 9.08 (s, 1H, urea).

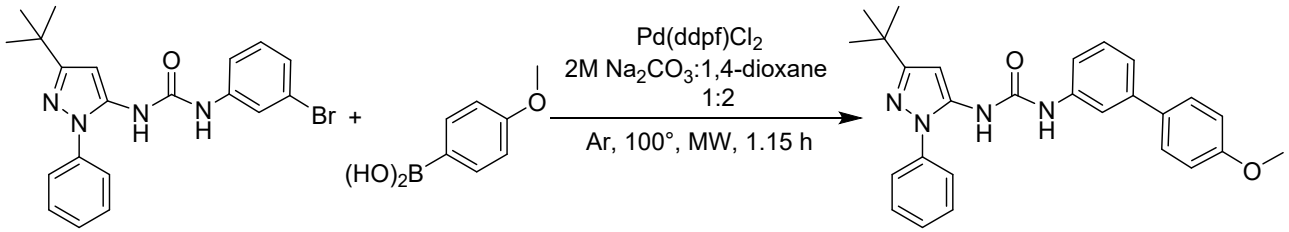
^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 14.09, 20.77, 22.20, 30.46, 31.91, 47.66, 59.75, 94.49, 110.37, 112.18, 116.16, 116.72, 118.79, 120.19, 129.22, 133.04, 135.44, 140.12, 140.78, 148.56, 149.01, 152.37, 158.43.

ESI-MS (m/z): theoretical 437.56 $[C_{25}H_{32}N_4O_3+H]^+$, experimental 437.28 $[C_{25}H_{32}N_4O_3+H]^+$.

General procedure E

Bromo urea **5f-k, 5r-x** (0.26 mmol), boronic acid **7a-d** (0.53 mmol) and $Pd(dppf)Cl_2$ (0.016 mmol) were dissolved in a degassed solution of 1:2 2M Na_2CO_3:1,4-dioxane (2 mL) and placed in a microwave reaction via under Argon atmosphere. The reaction mixture was heated for 1 hour at 100 ºC under MW irradiation and then left to cool for 10 minutes. After cooling, the reaction solution was extracted with EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x50 mL) and brine (1x 50 mL) and finally dried on Na_2SO_4. Volatiles were removed under vaccum and the resulting crude was purified by column chromatography to afford compounds **9g-i** and **10d-s**.

1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(4'-methoxy-[1,1'-biphenyl]-3-yl)urea 9g



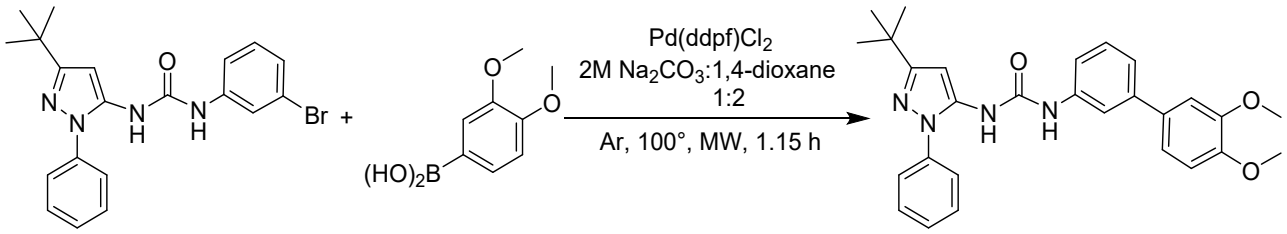
Following general procedure E compound **9g** was obtained starting from **5g**. **9g** was purified by column chromatography (Silica, DCM:EtOAc 95:5 → 1:1, R_f = 0.64) Concentration in vacuo of the product-rich fractions gave an impure white solid which was decanted in diethyl ether (10 mL) overnight. This was filtered and dried in vacuo, of which the solid phase gave the title product as a white powder (41 mg; yield 36%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.29 (s, 9H, $(CH_3)_3C$), 3.79 (s, 3H, OMe), 6.40 (s, 1H, pyrazole), 7.02 (m, 2H, aromatic), 7.21 (m, 1H, aromatic), 7.34 – 7.24 (m, 2H, aromatic), 7.46 – 7.38 (m, 1H, aromatic), 7.57 – 7.51 (m, 6H, aromatic), 7.71 (m, 1H, aromatic), 8.43 (s, 1H, urea), 9.10 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 14.15, 20.83, 30.26, 55.24, 59.85, 95.62, 114.43, 115.99, 124.40, 127.37, 127.76, 129.38, 137.23, 138.61, 151.77, 159.01, 160.89.

ESI-MS (m/z): theoretical 441.22 $[C_{27}H_{28}N_4O_2+H]^+$, experimental 441.50 $[C_{27}H_{28}N_4O_2+H]^+$.

1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(3',4'-dimethoxy-[1,1'-biphenyl]-3-yl)urea 9h



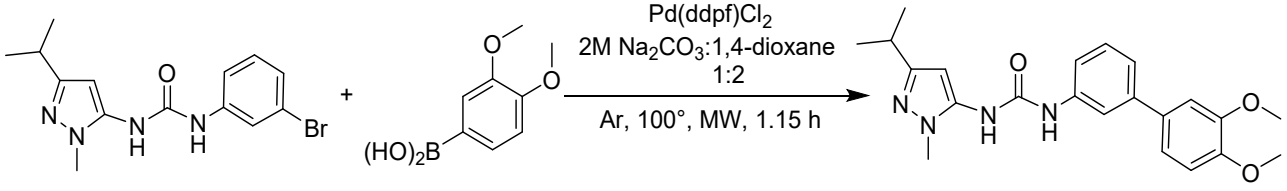
Following general procedure E compound **9h** was obtained starting from **5g**. **9h** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.39). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (56 mg; yield 46%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): δ 1.28 (s, 9H, $(CH_3)_3$), 3.79 (s, 3H, OMe), 3.82 (s, 3H, OMe), 6.39 (s, 1H, pyrazole), 7.03 (m, 1H, aromatic), 7.12 (m, 1H, aromatic), 7.14 (m, 1H, aromatic), 7.24 (m, 1H, aromatic), 7.32 (m, 1H, aromatic), 7.37 (m, 1H, aromatic), 7.42 (m, 1H, aromatic), 7.54 (m, 4H, aromatic), 7.62 (m, 1H, aromatic), 8.43 (s, 1H, urea), 9.10 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 30.23, 32.08, 40.43, 55.58, 55.60, 95.57, 112.20, 116.14, 116.69, 118.84, 120.42, 124.37, 127.32, 129.31, 129.33, 132.99, 137.21, 138.58, 139.87, 140.85, 148.60, 149.03, 151.72, 160.83.

ESI-MS (m/z): theoretical 471.57 $[C_{28}H_{30}N_4O_3+H]^+$, experimental 471.56 $[C_{28}H_{30}N_4O_3+H]^+$.

1-(3',4'-dimethoxy-[1,1'-biphenyl]-3-yl)-3-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)urea 9i



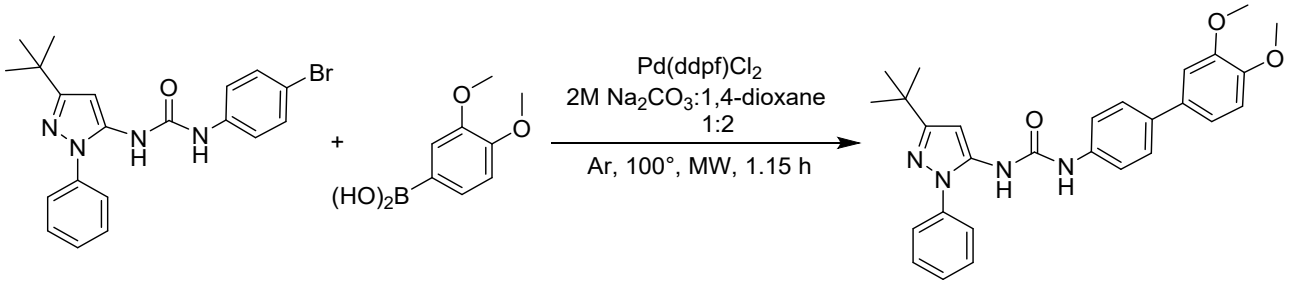
Following general procedure E compound **9i** was obtained starting from **5v**. **9i** was purified by column chromatography (Silica, DCM:EtOAc 9:1 → 1:1, R_f = 0.63). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (42 mg; yield 41%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.16 (d, 6H, J = 8 Hz, $(CH_3)_2CH$), 2.78 (m, 1H, $CH(CH_3)_2$), 3.60 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.02 (s, 1H, pyrazole), 7.04 (m, 1H, aromatic), 7.18 – 7.10 (m, 2H, aromatic), 7.26 (m, 1H, aromatic), 7.34 (t, *J* = 7.8 Hz, 1H, aromatic), 7.46 – 7.37 (m, 1H, aromatic), 7.68 (m, 1H , aromatic), 8.52 (s, 1H, urea), 8.93 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.64, 27.53, 34.87, 55.57 (d, J = 4.5. Hz), 94.17, 110.37, 112.19, 116.21, 116.77, 118.80, 120.33, 122.03, 128.81, 129.26, 132.99, 137.13, 139.92, 140.81, 148.57, 149.01, 151.89, 155.74.

ESI-MS (m/z): theoretical 395.20 $[C_{22}H_{26}N_4O_3+H]^+$, experimental 395.52 $[C_{22}H_{26}N_4O_3+H]^+$.

1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)urea 10d



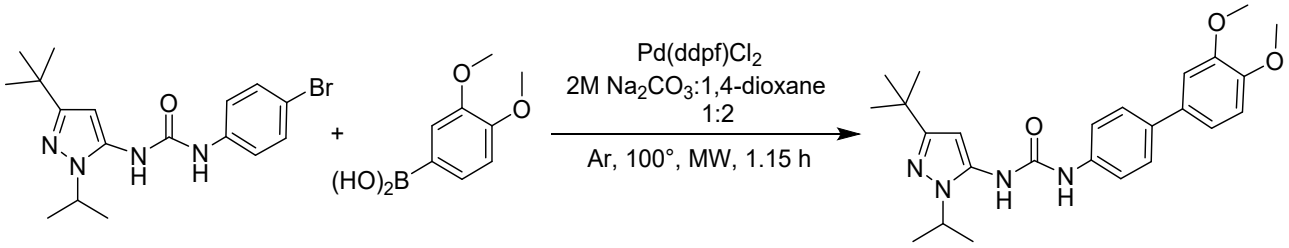
Following general procedure E compound **10d** was obtained starting from **5f**. **10d** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.32). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (43 mg; yield 35%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.28 (s, 9H, $(CH_3)_3$), 3.77 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.38 (s, 1H, pyrazole), 7.18 – 7.12 (m, 2H, aromatic), 7.41 (tt, *J* = 5.2, 3.4 Hz, 1H, aromatic), 7.46 (d, *J* = 8.7 Hz, 2H, aromatic), 7.57 – 7.52 (m, 5H, aromatic), 8.30 (s, 1H, aromatic), 8.43 (s, 1H urea), 9.11 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 30.67, 32.52, 40.47, 56.00, 56.04, 79.62, 96.03, 110.42, 112.69, 118.68, 118.89, 124.77, 127.14, 127.75, 129.77, 133.10, 134.35, 137.66, 138.78, 139.03, 148.55, 149.50, 152.09, 161.28.

ESI-MS (m/z): theoretical 471.24 $[C_{28}H_{30}N_4O_3+H]^+$, experimental 471.41 $[C_{28}H_{30}N_4O_3+H]^+$.

1-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)-3-(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)urea 10e



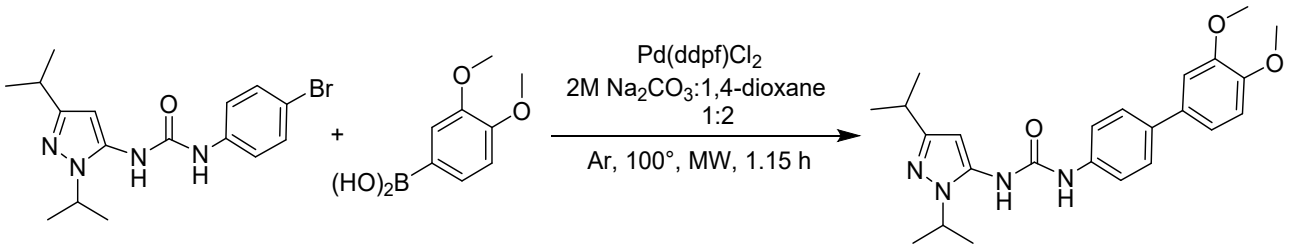
Following general procedure E compound **10e** was obtained starting from **5h**. **10e** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.55). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (28 mg; yield 25%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.35 (d, J = 6.6 Hz, 6H, $(CH_3)_2CH$), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.36 (hept, J = 6.6 Hz, 1H, $CH(CH_3)_2$), 6.02 (s, 1H, pyrazole), 7.00 (d, J = 8.4 Hz, 1H, aromatic), 7.15 (dd, J = 2.2, 8.3 Hz, 1H, aromatic), 7.18 (d, J = 2.2 Hz, 1H, aromatic), 7.48 – 7.53 (m, 2H, aromatic), 7.55 – 7.59 (m, 2H, aromatic), 8.35 (s, 1H, urea), 8.93 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.20, 30.45, 31.91, 47.67, 55.55 (d, J = 7.1 Hz), 94.42, 109.99, 112.23, 117.22, 118.19, 118.43, 120.59, 121.70, 124.60, 126.66, 130.72, 132.68, 133.76, 135.37, 138.49, 141.14, 148.07, 149.04, 152.17, 158.45.

ESI-MS (m/z): theoretical 437.25 $[C_{25}H_{32}N_4O_3]^+$, experimental 437.45 $[C_{25}H_{32}N_4O_3]^+$.

1-(1,3-diisopropyl-1H-pyrazol-5-yl)-3-(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)urea 10f



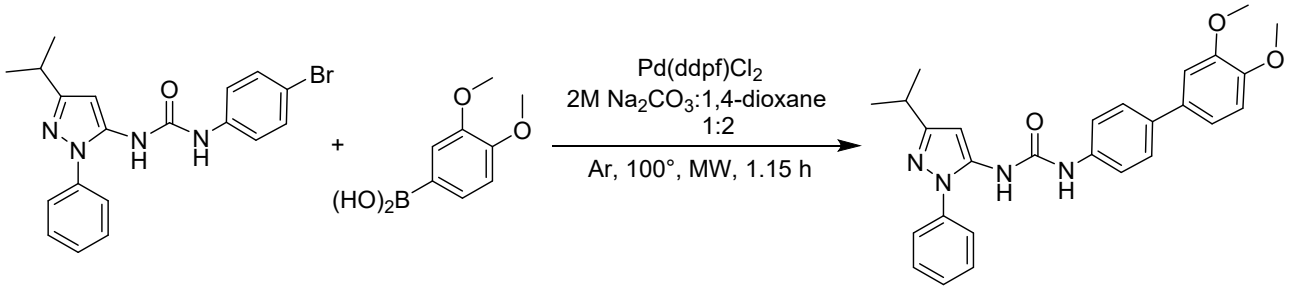
Following general procedure E compound **10f** was obtained starting from **5x**. **10f** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.13). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (51 mg; yield 46%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.17 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 1.34 (d, J = 6.6 Hz, 6H, $(CH_3)_2CHN$), 2.81 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.36 (hept, J = 6.7 Hz, 1H, $NCH(CH_3)_2$), 5.99 (s, 1H, pyrazole), 7.00 (d, J = 8.4 Hz, 1H, aromatic), 7.15 (dd, J = 2.2, 8.3 Hz, 1H, aromatic), 7.18 (d, J = 2.2 Hz, 1H, aromatic), 7.46 – 7.52 (m, 2H, aromatic), 7.55 – 7.59 (m, 2H, aromatic), 8.39 (s, 1H, urea), 8.92 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.22, 22.76, 27.72, 40.06, 47.60, 54.91, 55.55 (d, J = 7.2 Hz), 94.63, 109.99, 112.23, 118.19, 118.45, 126.66, 132.68, 133.78, 135.54, 138.47, 148.07, 149.04, 152.13, 155.82.

ESI-MS (m/z): theoretical 423.24 $[C_{24}H_{30}N_4O_3+H]^+$, experimental 423.51 $[C_{24}H_{30}N_4O_3+H]^+$.

1-(3',4'-dimethoxy-[1,1'-biphenyl]-4-yl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea 10g



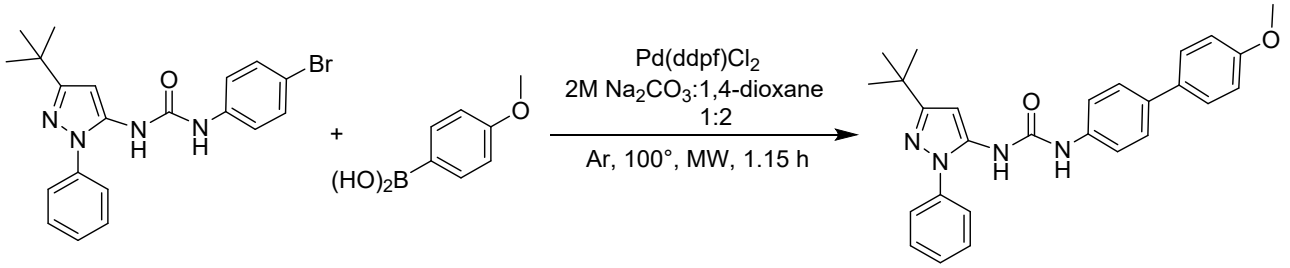
Following general procedure D compound **10g** was obtained starting from **5k**. **10g** was purified by column chromatography using (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.14). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (15 mg; yield 13%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.23 (d, *J* = 7.0 Hz, 6H, (CH3)2CH), 2.89 (hept, *J* = 6.9 Hz, 1H, CH(CH3)2), 3.76 (s, 3H, OCH3), 3.82 (s, 3H, OCH3), 6.34 (s, 1H, pyrazole), 6.99 (d, *J* = 8.4 Hz, 1H, aromatic), 7.10 – 7.20 (m, 2H, aromatic), 7.36 – 7.47 (m, 3H, aromatic), 7.48 – 7.60 (m, 6H), 8.41 (s, 1H, urea), 9.07 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 14.54, 22.92, 28.11, 56.01 (d, *J* = 6.4 Hz), 60.28, 96.41, 110.39, 112.68, 118.70, 118.96, 124.76, 127.14, 127.84, 129.80, 133.07, 134.40, 137.74, 138.69, 138.91, 148.54, 149.48, 152.07, 158.61.

ESI-MS (m/z): theoretical 457.22 $[C_{27}H_{28}N_4O_3+H]^+$, experimental 457.58 $[C_{27}H_{28}N_4O_3+H]^+$.

1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)urea 10h



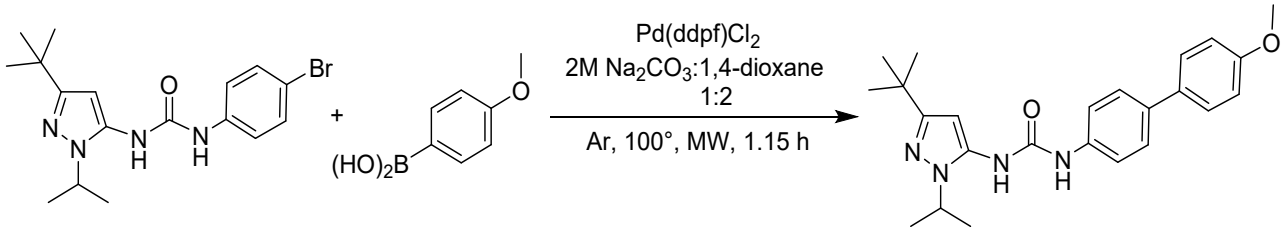
Following general procedure E compound **10h** was obtained starting from **5f**. **10h** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.37). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (49 mg; yield 43%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.29 (s, 9H, CH_3), 3.78 (s, 3H, OCH_3), 6.39 (s, 1H, pyrazole), 6.97 – 7.01 (m, 2H, aromatic), 7.41 (p, J = 4.3 Hz, 1H, aromatic), 7.45 – 7.47 (m, 2H, aromatic), 7.51 – 7.57 (m, 8H, aromatic), 8.45 (s, 1H, aromatic), 9.11 (s, 1H, aromatic).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 30.20, 30.69, 32.04, 54.91, 55.13, 59.75, 95.52, 114.30, 118.09, 118.49, 124.08, 124.29, 126.46, 127.18, 127.24, 128.80, 129.22, 129.28, 132.22, 133.58, 138.27, 138.59, 151.61, 158.47, 160.77, 206.49.

ESI-MS (m/z): theoretical 441.22 $[C_{27}H_{28}N_4O_2+H]^+$, experimental 441.56 $[C_{27}H_{28}N_4O_2+H]^+$.

1-(3-(tert-butyl)-1-isopropyl-1H-pyrazol-5-yl)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)urea 10i



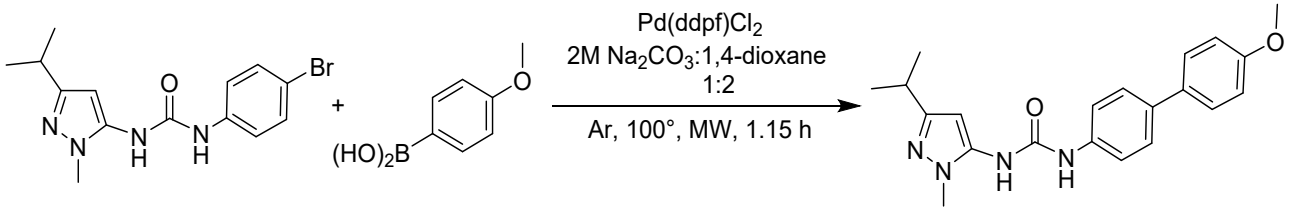
Following general procedure D compound **10i** was obtained starting from **5x**. **10i** was purified by column chromatography using (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.45). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (52 mg; yield 49%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.22 (s, 9H, $(CH_3)_3$), 1.35 (d, J = 6.6 Hz, 6H, $(CH_3)_2CH$), 3.79 (s, 3H, OCH_3), 4.36 (hept, 1H, $CH(CH_3)_2$), 6.02 (s, 1H, pyrazole), 6.92 – 7.03 (m, 2H, aromatic), 7.44 – 7.60 (m, 6H, aromatic), 8.35 (s, 1H, urea), 8.91 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 14.10, 20.78, 21.95, 22.21, 30.46, 31.93, 47.70, 55.15, 59.77, 94.46, 114.32, 118.15, 118.56, 126.48, 127.20, 132.28, 133.52, 135.38, 138.43, 152.21, 158.48.

ESI-MS (m/z): theoretical 407.24 $[C_{24}H_{30}N_4O_2+H]^+$, experimental 407.43 $[C_{24}H_{30}N_4O_2+H]^+$.

1-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)urea 10j



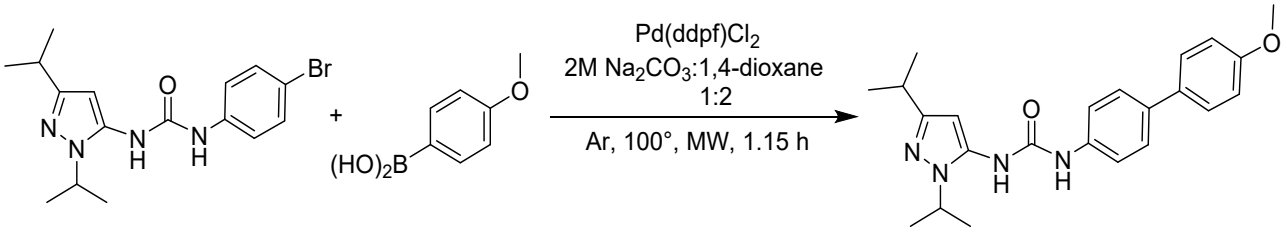
Following general procedure E compound **10j** was obtained starting from **5t**. **10j** was purified by column chromatography (Silica, DCM:EtOAc 9:1 → 1:1, R_f = 0.19). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (36 mg; yield 38%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.17 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.79 (hept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.61 (s, 3H, OCH_3), 3.79 (s, 3H, NCH_3), 6.02 (s, 1H, pyrazole), 6.91 – 7.09 (m, 2H, aromatic), 7.44 – 7.63 (m, 6H, aromatic), 8.52 (s, 1H, urea), 8.93 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 23.12, 28.01, 35.36, 55.62, 94.58, 114.79, 118.65, 119.05, 122.51, 126.96, 127.67, 129.29, 132.73, 134.05, 137.64, 138.80, 139.95, 152.27, 156.20, 158.95.

ESI-MS (m/z): theoretical 365.19 $[C_{21}H_{24}N_4O_2+H]^+$, experimental 365.45 $[C_{21}H_{24}N_4O_2+H]^+$.

1-(1,3-diisopropyl-1H-pyrazol-5-yl)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)urea 10k



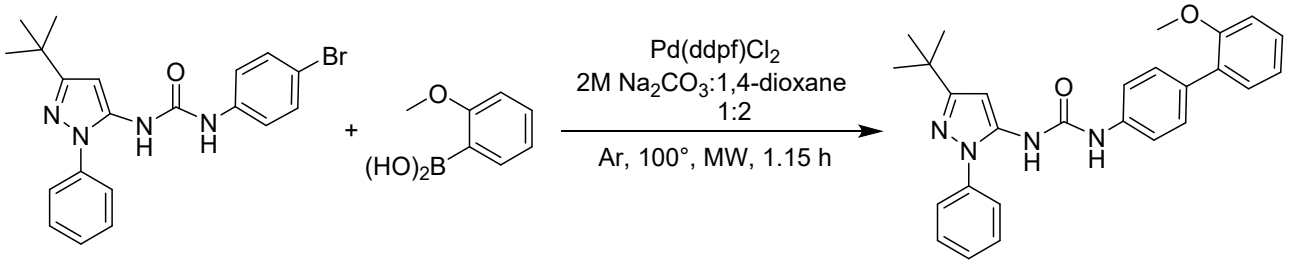
Following general procedure E compound **10k** was obtained starting from **5x**. Removal of the volatiles in vacuo provided a residue, which was purified by column chromatography (Silica, DCM:EtOAc 9:1 → 6:4, R_f = 0.09). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (49 mg; yield 48%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.17 (d, 6H, $(CH_3)_2CH$), 1.34 (d, 6H, $(CH_3)_2CHN$), 2.81 (hept, 1H, $CH(CH_3)_2$), 3.79 (s, 3H, OCH_3), 4.36 (hept, 1H, $NCH(CH_3)_2$), 5.99 (s, 1H, pyrazole), 7.00 (m, 2H, aromatic), 7.54 (m, 6H, aromatic), 8.36 (s, 1H, urea), 8.87 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 13C NMR (151 MHz, DMSO) δ 22.70, 23.24, 28.19, 48.09, 55.61, 95.14, 114.78, 119.05, 126.93, 127.66, 132.74, 133.96, 136.08, 138.91, 152.71, 156.34, 158.93.

ESI-MS (m/z): theoretical 393.22 $[C_{23}H_{28}N_4O_2+H]^+$, experimental 393.50 $[C_{23}H_{28}N_4O_2+H]^+$.

1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(2'-methoxy-[1,1'-biphenyl]-4-yl)urea 10l



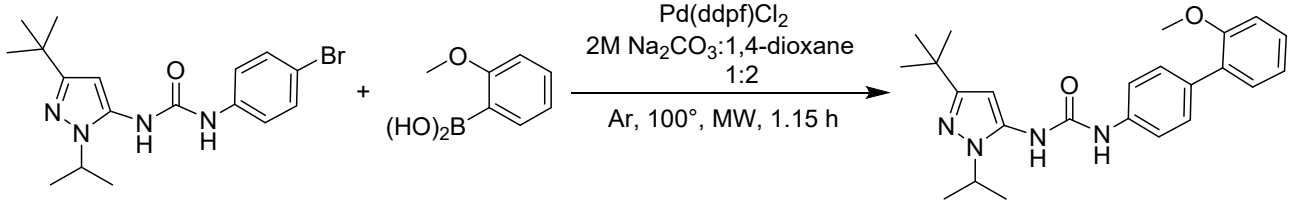
Following general procedure E compound **10l** was obtained starting from **5f**. **10l** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 92:8, R_f = 0.37). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (70 mg; yield 61%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.29 (s, 9H, $(CH_3)_3$), 3.75 (s, 3H, OCH_3), 6.39 (s, 1H, pyrazole), 7.00 (td, *J* = 1.1, 7.4 Hz, 1H, aromatic), 7.08 (dd, *J* = 1.1, 8.3 Hz, 1H, aromatic), 7.26 (dd, *J* = 1.8, 7.5 Hz, 1H, aromatic), 7.30 (ddd, *J* = 1.8, 7.3, 8.3 Hz, 1H, aromatic), 7.36 – 7.40 (m, 2H, aromatic), 7.40 – 7.45 (m, 3H, aromatic), 7.53 – 7.55 (m, 4H, aromatic), 8.42 (s, 1H, urea), 9.07 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 14.08, 20.76, 30.20, 32.04, 55.45, 59.75, 95.49, 111.71, 117.72, 120.75, 124.31, 127.26, 128.42, 129.29, 129.45, 129.63, 130.10, 131.88, 137.22, 138.20, 138.59, 151.62, 156.10, 160.77, 170.33.

ESI-MS (m/z): theoretical 441.22 $[C_{27}H_{28}N_4O_2+H]^+$, experimental 441.59 $[C_{27}H_{28}N_4O_2+H]^+$.

1-(3-(tert-butyl)-1-~~methyl~~isopropyl-1H-pyrazol-5-yl)-3-(2'-methoxy-[1,1'-biphenyl]-4-yl)urea 10m



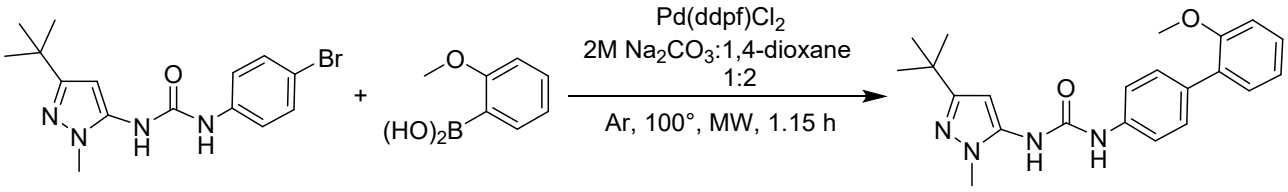
Following general procedure E compound **10m** was obtained starting from **5h**. **10m** was purified by column chromatography (Silica, DCM:EtOAc 9:1 → 1:1, R_f = 0.45). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (34 mg; yield 34%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.23 (s, 9H, $(CH_3)_3$), 3.36 (s, 3H, OCH_3), 6.06 (s, 1H, pyrazole), 7.36 – 7.24 (m, 42H), 7.51 – 7.36 (m, 2H), 7.55 (dd, J = 7.2, 1.9 Hz, 4H), 8.36 (s, 1H, urea), 8.99 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 21.94, 22.19, 30.19, 30.43, 30.45, 30.51, 55.21, 55.45, 110.29, 111.72, 113.34, 120.10, 120.25, 120.76, 131.51, 131.57, 131.77, 135,14, 135.30, 135.39, 138.37, 139.56, 152.21, 156.11, 158.44, 163.43

ESI-MS (m/z): theoretical 401.53 $[C_{24}H_{30}N_4O_2+H]^+$, experimental 401,21 $[C_{24}H_{30}N_4O_2+H]^+$.

1-(3-(tert-butyl)-1-methyl-1H-pyrazol-5-yl)-3-(2'-methoxy-[1,1'-biphenyl]-4-yl)urea 10n



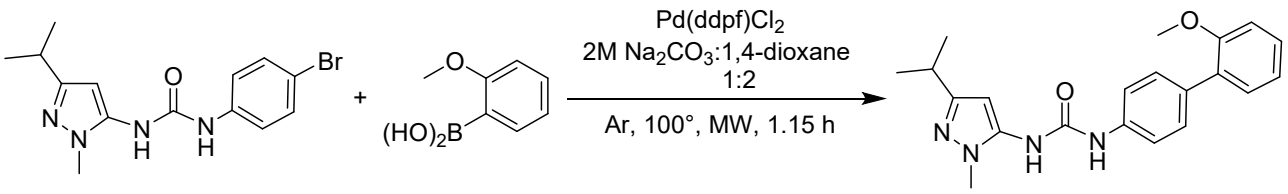
Following general procedure E compound **10n** was obtained starting from **5u**. **10n** was purified by column chromatography (Silica, DCM:EtOAc 9:1 → 1:1, R_f = 0.45). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (47 mg; yield 48%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.22 (s, 9H, $(CH_3)_3$), 3.61 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.06 (s, 1H, pyrazole), 7.01 (td, *J* = 7.4, 1.1 Hz, 1H, aromatic), 7.09 (dd, *J* = 8.3, 1.1 Hz, 1H, aromatic), 7.33 – 7.25 (m, 2H, aromatic), 7.40 (d, *J* = 8.6 Hz, 2H, aromatic), 7.48 (d, *J* = 8.7 Hz, 2H, aromatic), 8.53 (s, 1H, urea), 8.95 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 30.38, 31.81, 34.95, 55.46, 60.58, 65.86, 77.01, 93.53, 111.72, 117.76, 120.76, 128.41, 128.80, 129.49, 129.63, 130.11, 131.82, 137.11, 138.31, 151.82, 156.11, 158.52.

ESI-MS (m/z): theoretical 379.21 $[C_{22}H_{26}N_4O_2+H]^+$, experimental 379.06 $[C_{22}H_{26}N_4O_2+H]^+$.

1-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-3-(2'-methoxy-[1,1'-biphenyl]-4-yl)urea 10o



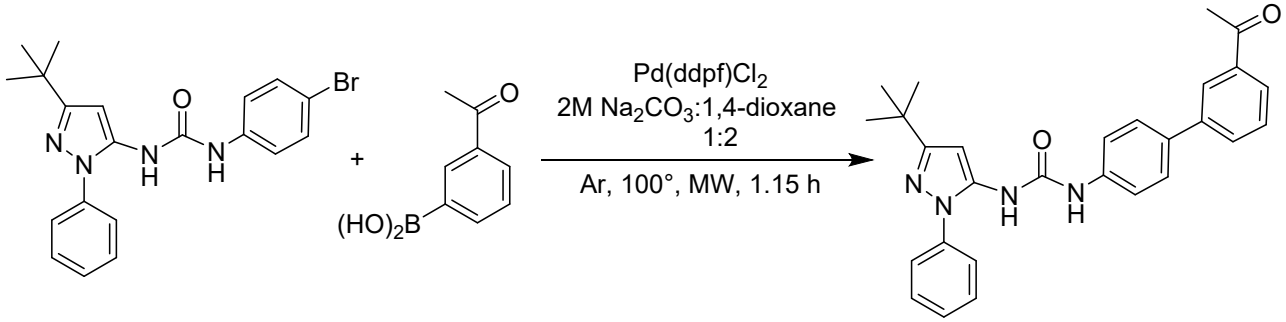
Following general procedure E compound **10o** was obtained starting from **5t**. **10o** was purified by column chromatography (Silica, DCM:EtOAc 9:1 → 1:1, R_f = 0.20). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (50 mg; yield 53%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.18 (d, *J* = 6.6 Hz, 6H, (CH3)2CH), 2.78 (hept, *J* = 6.9 Hz, 1H, CH(CH3)2), 3.60 (s, 3H, COCH3), 3.76 (s, 3H, NCH3), 6.02 (s, 1H, pyrazole), 7.01 (td, *J* = 1.1, 7.4 Hz, 1H, aromatic), 7.09 (dd, *J* = 1.2, 8.2 Hz, 1H, aromatic), 7.24 – 7.35 (m, 2H, aromatic), 7.33 – 7.57 (m, 4H, aromatic), 8.53 (s, 1H, urea), 8.92 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.81, 27.69, 35.02, 55.64, 94.40, 111.91, 113.67, 118.10, 121.00, 128.68, 129.62, 129.84, 129.92, 129.98, 130.31, 132.14, 137.38, 138.37, 152.09, 156.09, 156.29.

ESI-MS (m/z): theoretical 365.19 $[C_{21}H_{24}N_4O_2+H]^+$, experimental 365.41 $[C_{21}H_{24}N_4O_2+H]^+$.

1-(3'-acetyl-[1,1'-biphenyl]-4-yl)-3-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)urea 10p



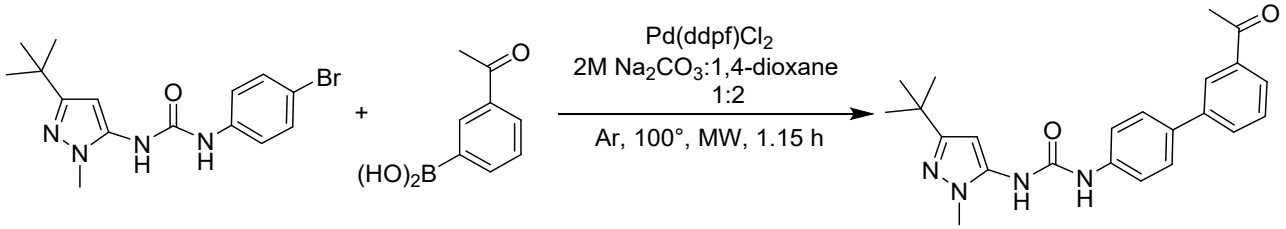
Following general procedure E compound **10p** was obtained starting from **5f**. **10p** was purified by column chromatography (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.64). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (42 mg; yield 36%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.29 (s, 9H, $(CH_3)_3$), 2.65 (s, 3H, $COCH_3$), 6.40 (s, 1H, pyrazole), 7.52 – 7.55 (m, 5H, aromatic), 7.57 – 7.60 (m, 1H, aromatic), 7.63 – 7.68 (m, 2H, aromatic), 7.90 (ddq, J = 1.1, 2.2, 7.9 Hz, 2H, aromatic), 8.15 (t, J = 1.8 Hz, 1H, aromatic), 8.31 (s, 2H, aromatic), 8.46 (s, 1H, urea), 9.20 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 14.10, 20.78, 26.94, 30.22, 32.07, 54.92, 59.78, 79.18, 95.64, 118.52, 124.32, 125.73, 126.56, 127.28, 129.32, 129.36, 130.77, 132.83, 137.14, 137.49, 138.59, 139.41, 140.19, 151.62, 160.82, 170.38, 198.12.

ESI-MS (m/z): theoretical 453.22 $[C_{28}H_{28}N_4O_2+H]^+$, experimental 453.36 $[C_{28}H_{28}N_4O_2+H]^+$.

1-(3'-acetyl-[1,1'-biphenyl]-4-yl)-3-(3-(tert-butyl)-1-methyl-1H-pyrazol-5-yl)urea 10q



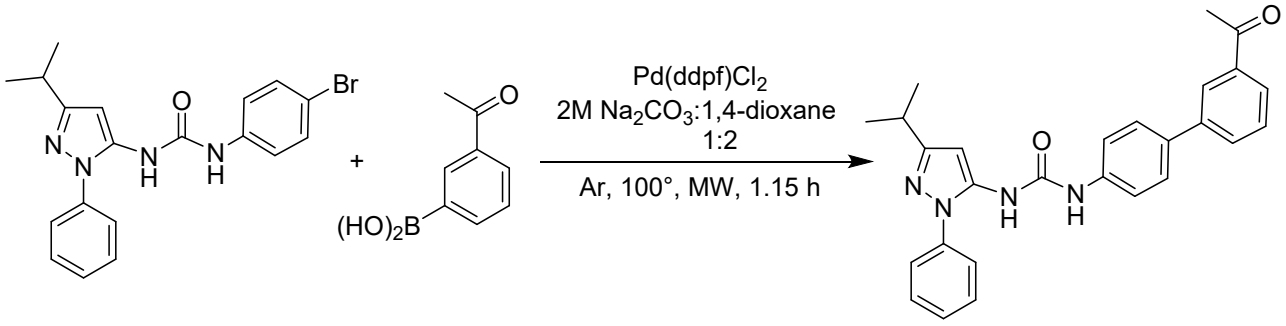
Following general procedure E compound **10q** was obtained starting from **5u**. **10q** was purified by column chromatography (Silica, DCM:EtOAc 9:1 → 1:1, R_f = 0.28). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (64 mg; 63%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.22 (s, 9H, $(CH_3)_3$), 2.65 (s, 3H, $COCH_3$), 3.61 (s, 3H, NCH_3), 6.07 (s, 1H, pyrazole), 7.59 (t, *J* = 7.9 Hz, 3H, aromatic), 7.65 – 7.71 (m, 2H, aromatic), 7.90 (ddt, *J* = 1.3, 6.2, 7.7 Hz, 2H, aromatic), 8.16 (t, *J* = 1.8 Hz, 1H, aromatic), 8.54 (s, 1H, urea), 9.06 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 26.93, 30.39, 34.95, 93.76, 118.56, 125.74, 126.53, 127.28, 129.34, 130.77, 132.78, 136.99, 137.48, 139.50, 140.21, 151.81, 158.55, 198.09.

ESI-MS (m/z): theoretical 391.21 $[C_{23}H_{26}N_4O_2+H]^+$, experimental 391.50 $[C_{23}H_{26}N_4O_2+H]^+$.

1-(3'-acetyl-[1,1'-biphenyl]-4-yl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea 10r



Following general procedure E compound **10r** was obtained starting from **5k**. **10r** was purified by column chromatography using (Silica, DCM:EtOAc 98:2 → 9:1, R_f = 0.39). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (41 mg; yield 36%).

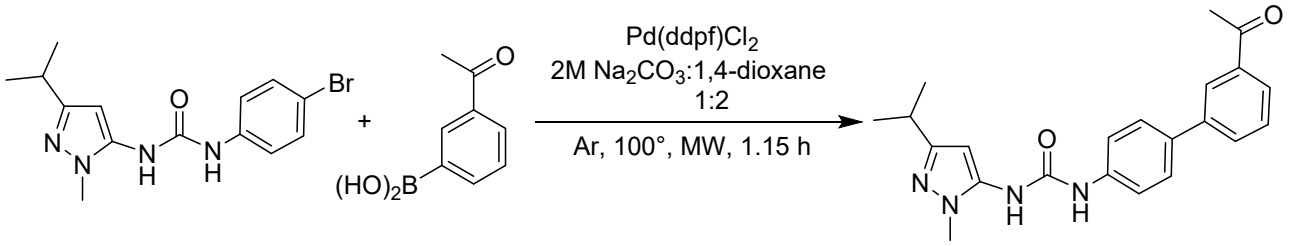
^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.24 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.65 (s, 3H, $COCH_3$), 2.90 (3.58 (s, 3H, NCH_3), *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 6.36 (s, 1H, pyrazole), 7.42 (p, *J* = 4.3 Hz, 1H, aromatic), 7.52 – 7.56 (m, 6H), 7.59 (t, *J* = 7.8 Hz, 1H, aromatic), 7.67 (d, *J* = 8.7 Hz, 2H, aromatic),

7.90 (ddd, *J* = 0.9, 2.0, 7.1 Hz, 2H, aromatic), 8.15 (t, *J* = 1.9 Hz, 1H, aromatic), 8.47 (s, 1H, urea), 9.18 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.44, 26.91, 27.65, 95.93, 118.50, 124.30, 125.72, 126.53, 127.26, 127.30, 129.30, 129.32, 130.74, 132.82, 137.23, 137.47, 138.51, 139.37, 140.16, 151.55, 158.04, 198.06.

ESI-MS (m/z): theoretical 438.21 $[C_{27}H_{26}N_4O_2]^+$, experimental 437.28 $[C_{27}H_{26}N_4O_2]^+$.

1-(3'-acetyl-[1,1'-biphenyl]-4-yl)-3-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)urea 10s



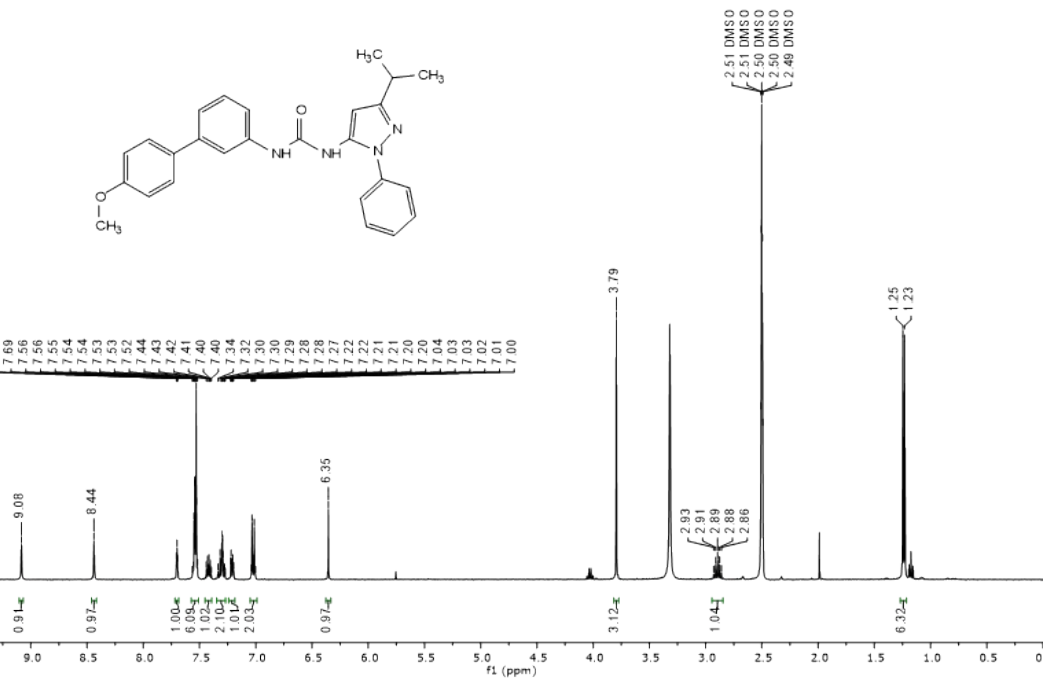
Following general procedure E compound **10s** was obtained starting from **5t**. **10s** was purified by column chromatography (Silica, DCM:EtOAc 9:1 → 1:1, R_f = 0.14 [as eluent 9:1]). Concentration in vacuo of the product-rich fractions gave the title product as a white powder (85 mg; yield 87%).

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 1.17 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.65 (s, 3H, CH_3), 2.78 (hept, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.61 (s, 3H, NCH_3), 6.02 (s, 1H, pyrazole), 7.53 – 7.63 (m, 3H, aromatic), 7.65 – 7.71 (m, 2H, aromatic), 7.80 – 7.95 (m, 2H, aromatic), 8.16 (t, *J* = 1.7 Hz, 1H, aromatic), 8.68 (s, 1H, urea), 9.15 (s, 1H, urea).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm): 22.65, 26.93, 27.54, 34.91, 94.16, 118.55, 125.74, 126.51, 127.26, 129.33, 130.76, 132.74, 137.15, 137.48, 139.54, 140.22, 151.83, 155.74, 198.09.

ESI-MS (m/z): theoretical 377.19 $[C_{22}H_{24}N_4O_2+H]^+$, experimental 377.42 $[C_{22}H_{24}N_4O_2+H]^+$.

9a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NH
N
N
O
CH3
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2.50 DMSO
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2.49 DMSO
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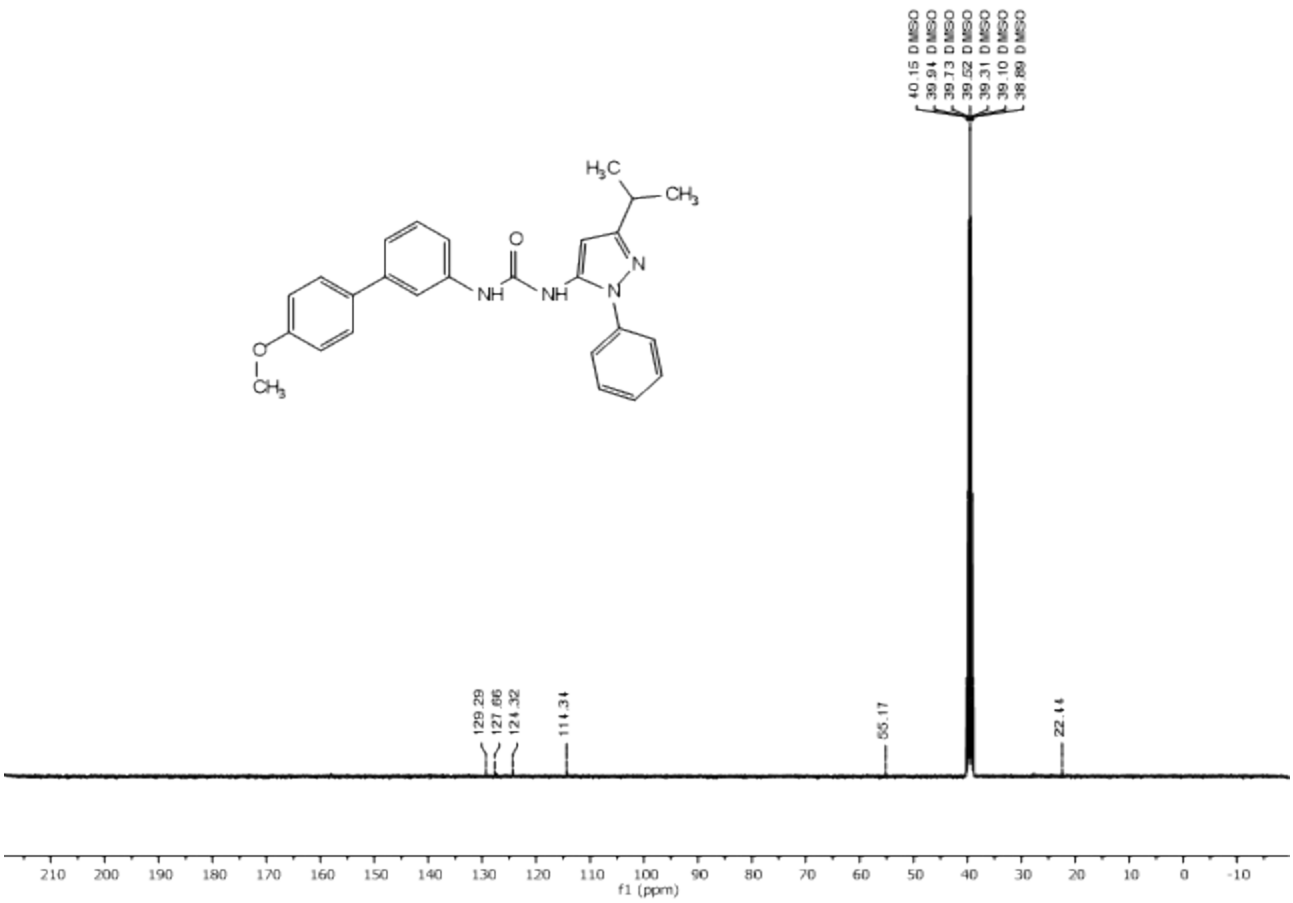
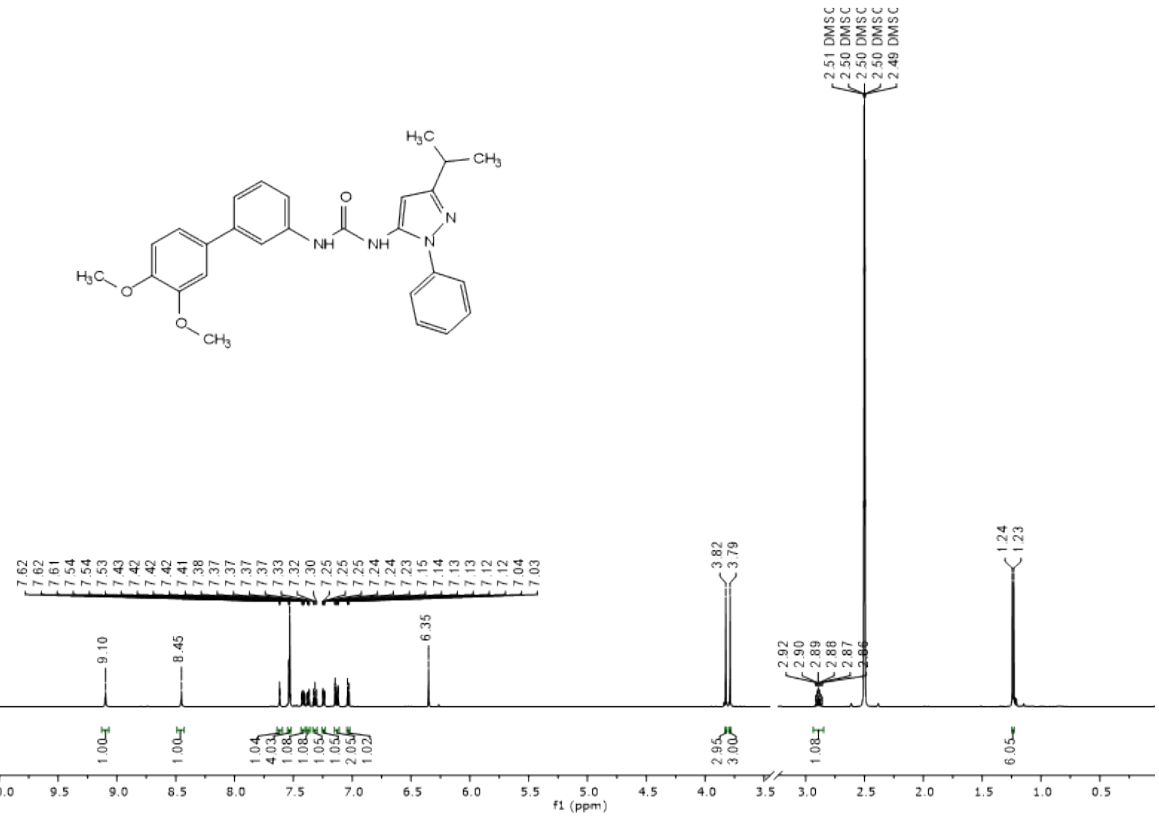
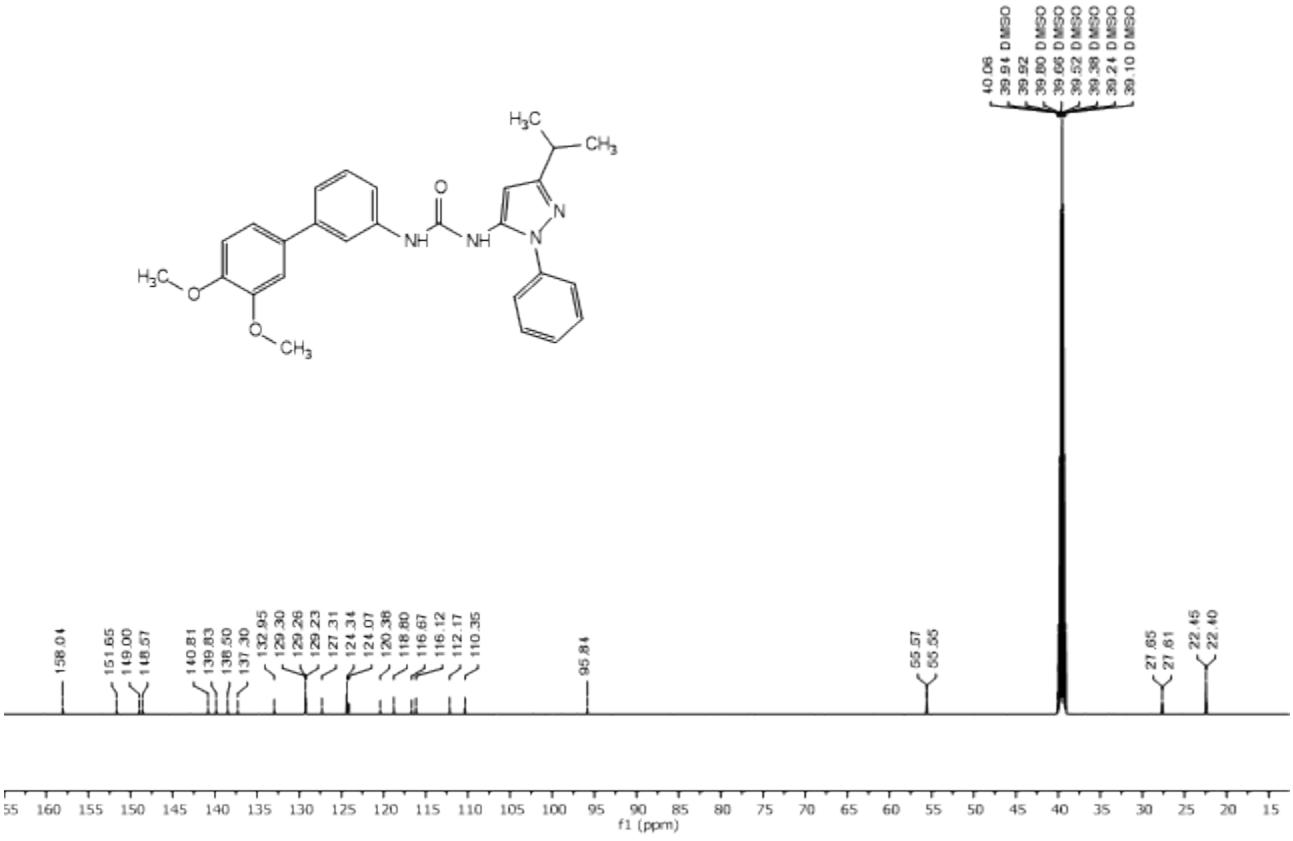
7.22
7.21
7.21
7.20
7.20
7.04
7.03
7.03
7.02
7.01
7.00
0.91
0.97
1.00
6.09
1.02
2.10
1.01
2.03
0.97
3.12
1.04
6.32
f1 (ppm)

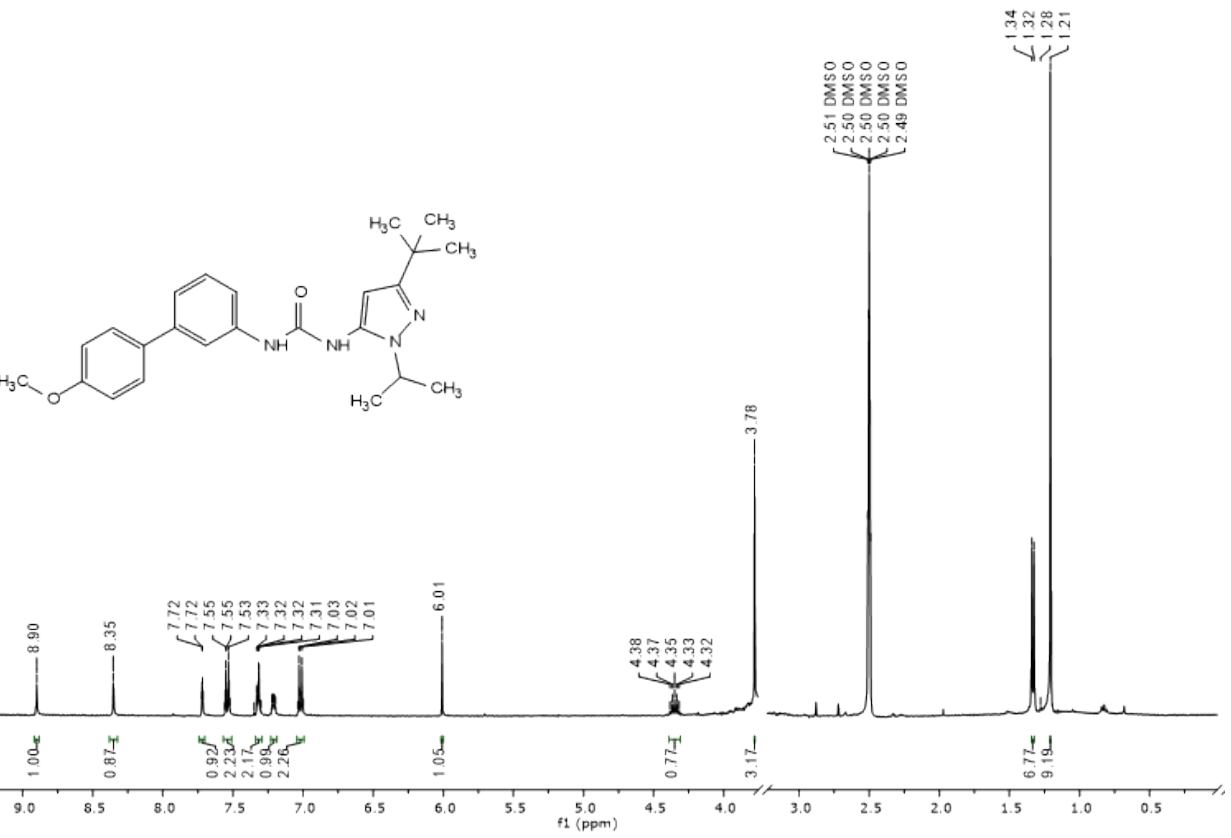

H3C
CH3
O
NH
NH
N
N
O
CH3
40.15 DMSO
39.94 DMSO
39.73 DMSO
39.52 DMSO
39.31 DMSO
39.10 DMSO
38.89 DMSO
129.29
127.66
124.32
114.34
55.17
22.44
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

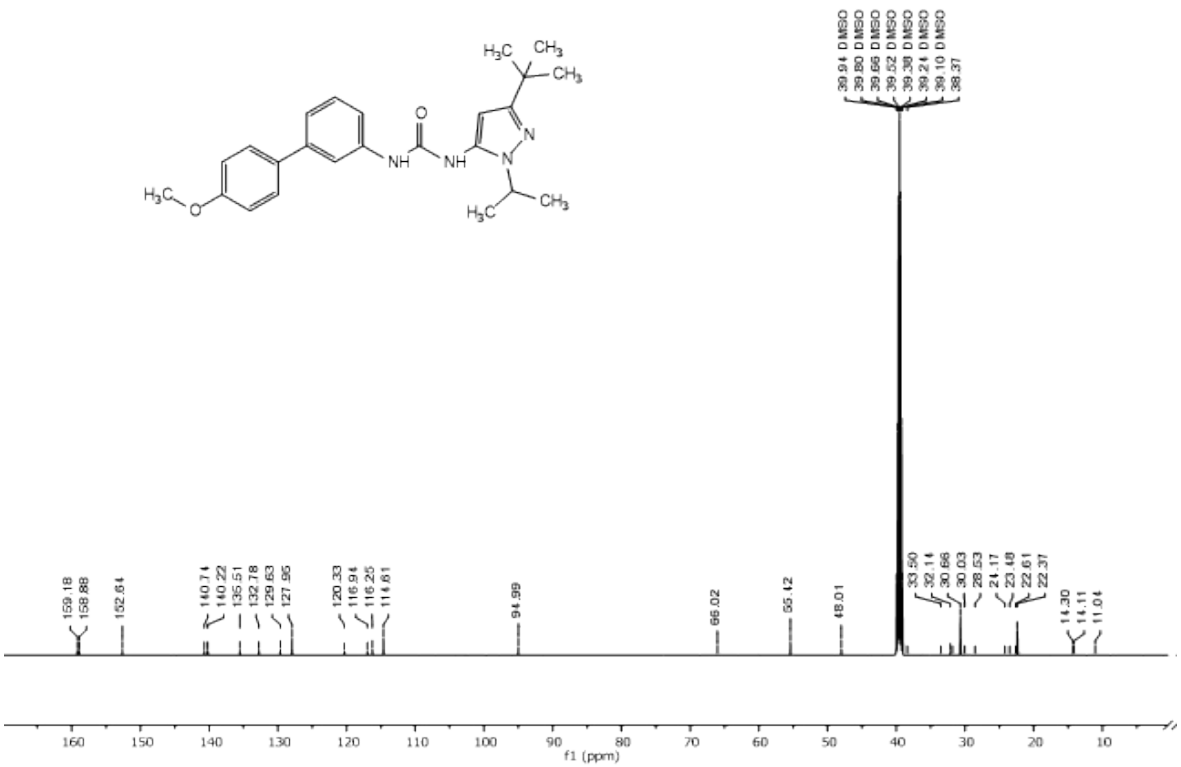
9b


H3C
CH3
O
NH
NH
N
N
H3C
O
O
CH3
7.62
7.62
7.61
7.54
7.54
7.53
7.43
7.42
7.42
7.42
7.41
7.38
7.37
7.37
7.37
7.37
7.33
7.32
7.30
7.25
7.25
7.25
7.24
7.24
7.23
7.15
7.14
7.13
7.13
7.12
7.12
7.04
7.03
9.10
8.45
6.35
3.82
3.79
2.92
2.90
2.89
2.88
2.87
2.86
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
1.24
1.23
1.00
1.00
1.04
4.03
1.08
1.08
1.05
1.05
2.05
1.02
2.95
3.00
1.08
6.05
f1 (ppm)

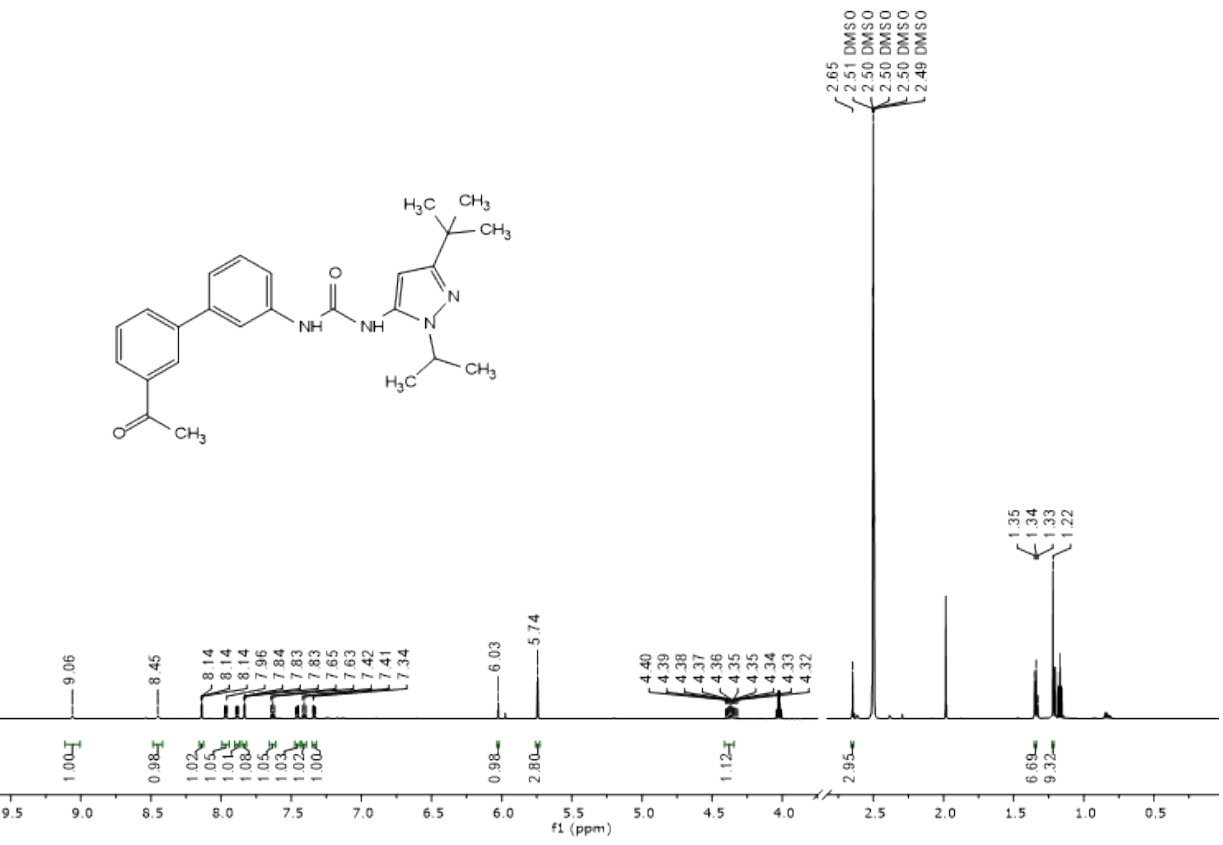

H3C
CH3
O
NH
NH
N
N
H3C
O
O
CH3
40.06 DMSO
39.94 DMSO
39.52
39.80 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
158.04
151.65
149.00
148.57
140.81
139.83
138.50
137.30
132.95
129.30
129.26
129.23
127.31
124.34
124.07
120.38
118.80
116.67
116.12
112.17
110.35
95.84
55.57
55.55
27.65
27.61
22.45
22.40
55 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
f1 (ppm)

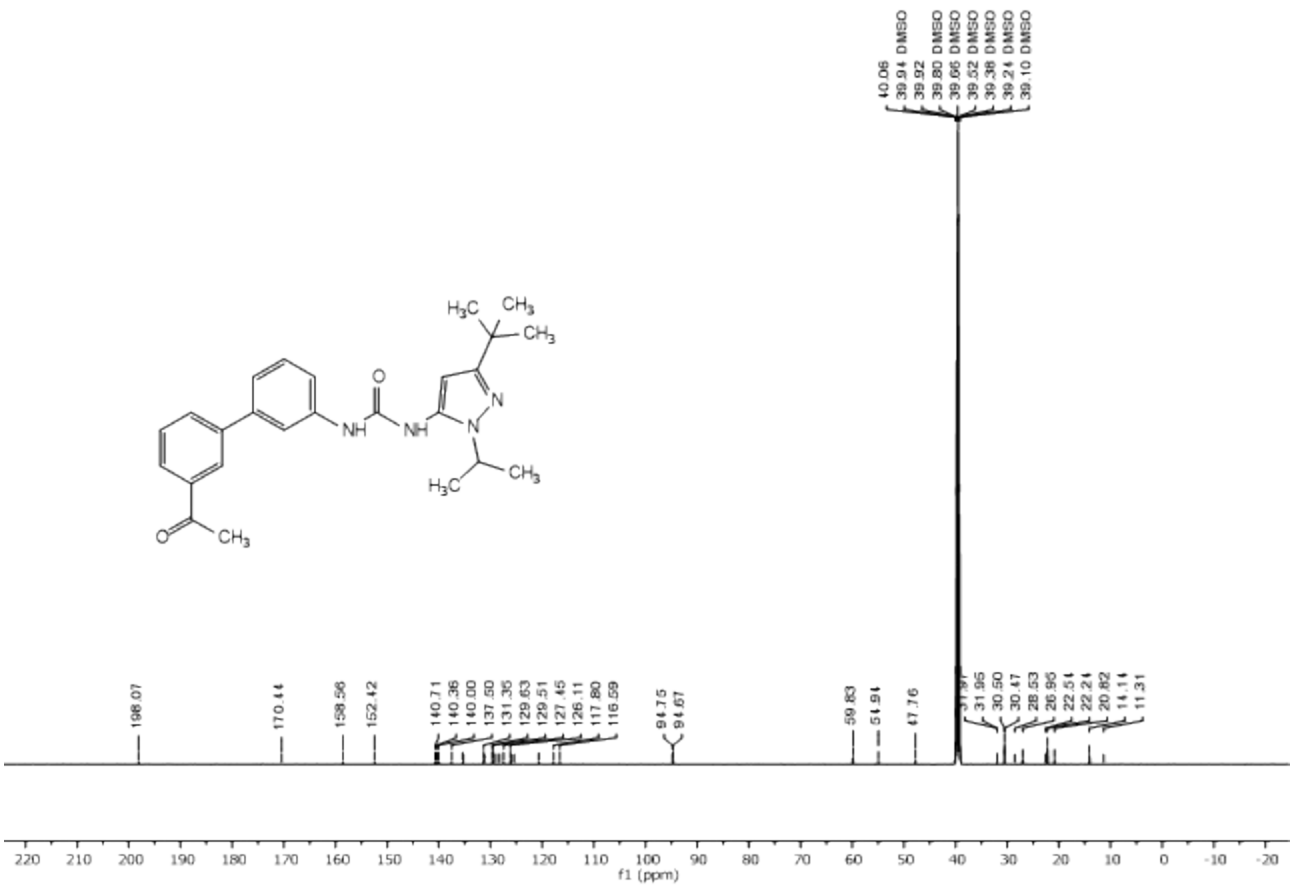
9c


H3C
CH3
CH3
O
NH
NH
N
N
H3C
CH3
H3C
O
8.90
8.35
7.72
7.72
7.55
7.53
7.33
7.32
7.32
7.31
7.03
7.02
7.01
6.01
4.38
4.37
4.35
4.33
4.32
3.78
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
1.34
1.32
1.28
1.21
1.00
0.87
0.92
2.23
2.17
0.99
2.26
1.05
0.77
3.17
6.77
9.19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

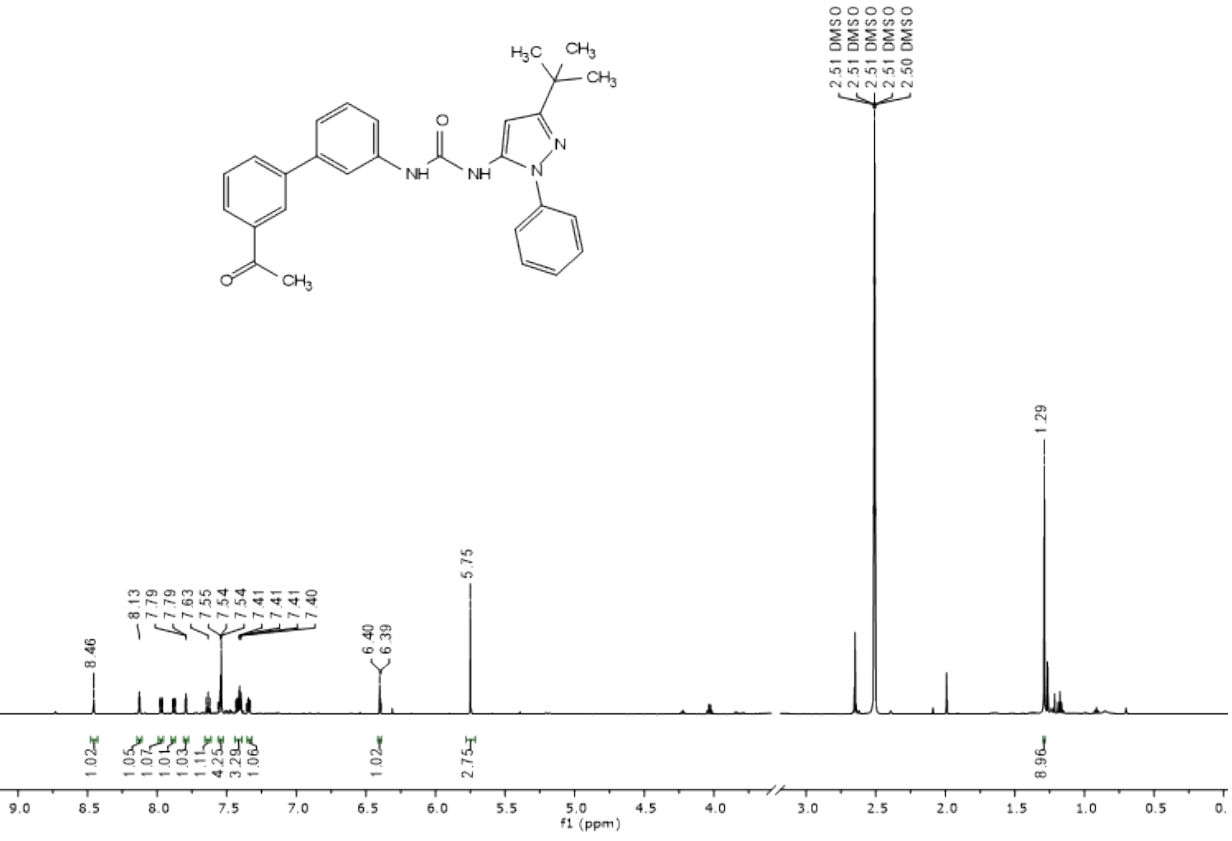

H3C
CH3
CH3
O
NH
NH
N
N
H3C
CH3
H3C
O
39.94 DMSO
39.80 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
38.37
159.18
158.88
152.64
140.74
140.22
135.51
132.78
129.63
127.95
120.33
116.94
116.25
114.61
94.99
66.02
55.42
48.01
33.50
32.14
30.66
30.03
28.53
24.17
23.48
22.61
22.37
14.30
14.11
11.04
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

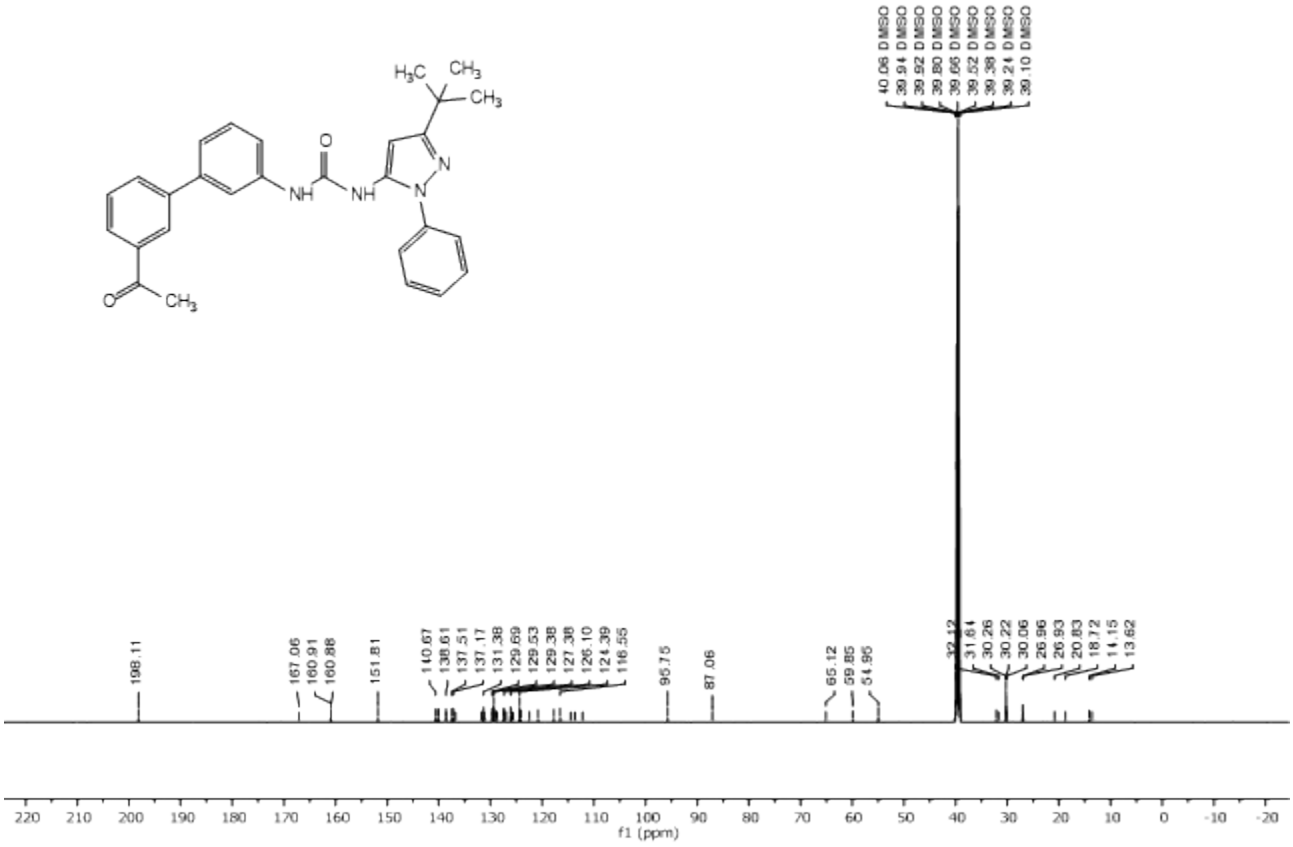
9d


H3C CH3
CH3
O
NH
NH
N
N
H3C CH3
O
CH3
2.65
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.50 DMSO
2.48 DMSO
1.35
1.34
1.33
1.22
9.06
8.45
8.14
8.14
8.14
7.96
7.84
7.83
7.83
7.65
7.63
7.42
7.41
7.34
6.03
5.74
4.40
4.39
4.38
4.37
4.36
4.35
4.35
4.34
4.33
4.32
1.00
0.98
1.02
1.05
1.01
1.08
1.05
1.03
1.02
1.00
0.98
2.80
1.12
2.95
6.69
9.32
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

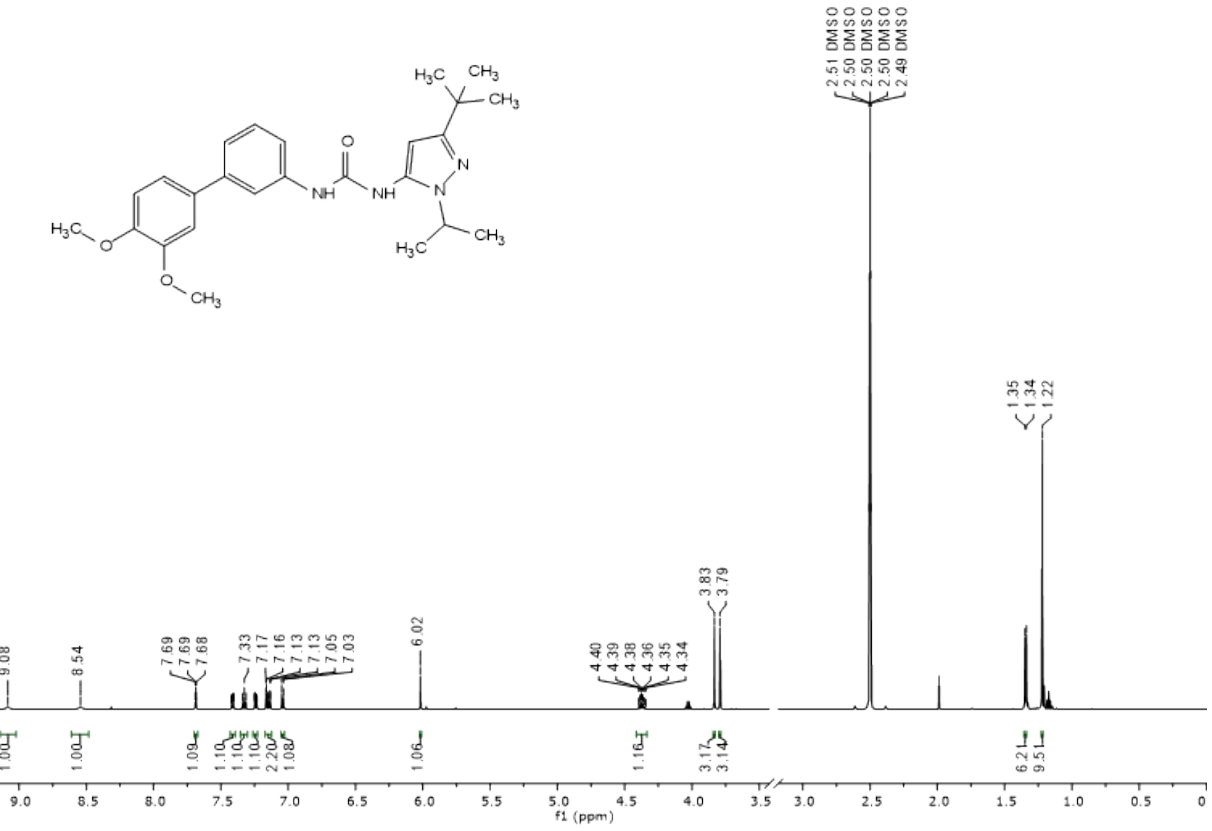

40.06
39.94 DMSO
39.92
39.80 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
198.07
170.44
158.56
152.42
140.71
140.36
140.00
137.50
131.35
129.63
129.51
127.45
126.11
117.80
116.59
94.75
94.67
59.83
51.94
47.76
31.95
30.50
30.47
28.53
26.95
22.54
22.24
20.82
14.14
11.31
f1 (ppm)

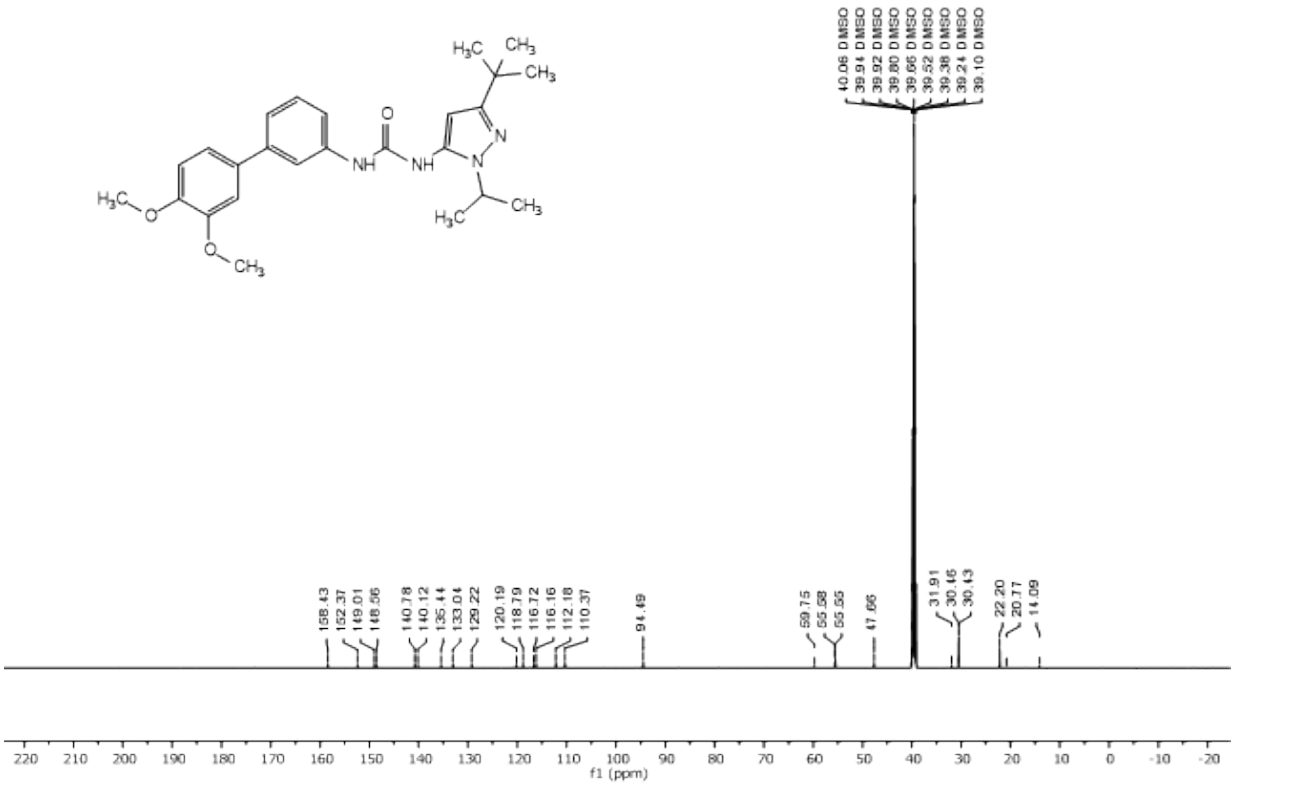
9e


H3C
CH3
CH3
O
NH
NH
N
N
O
CH3
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
1.29
8.46
8.13
7.79
7.79
7.79
7.63
7.55
7.54
7.54
7.41
7.41
7.41
7.40
6.40
6.39
5.75
1.02
1.05
1.07
1.01
1.03
1.11
4.25
3.29
1.06
1.02
2.75
8.96
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

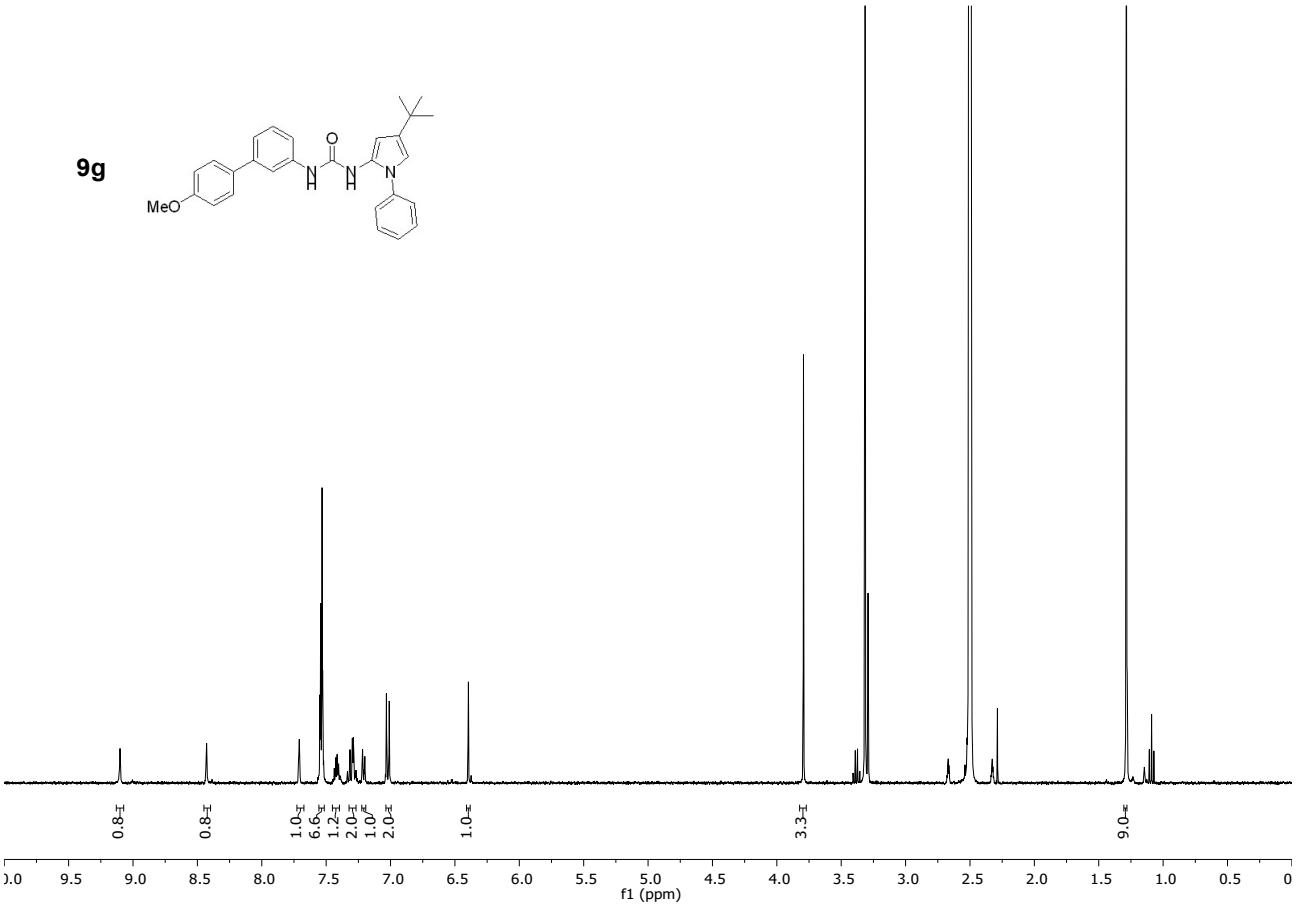

H3C
CH3
CH3
O
NH
NH
N
N
O
CH3
40.06 DMSO
39.94 DMSO
39.82 DMSO
39.80 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
198.11
167.06
160.91
160.88
151.81
140.67
138.61
137.51
137.17
131.38
129.69
129.53
129.38
127.38
126.10
124.39
116.55
95.75
87.06
65.12
59.85
54.96
32.12
31.64
30.26
30.22
30.06
26.96
26.93
20.83
18.72
14.15
13.62
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

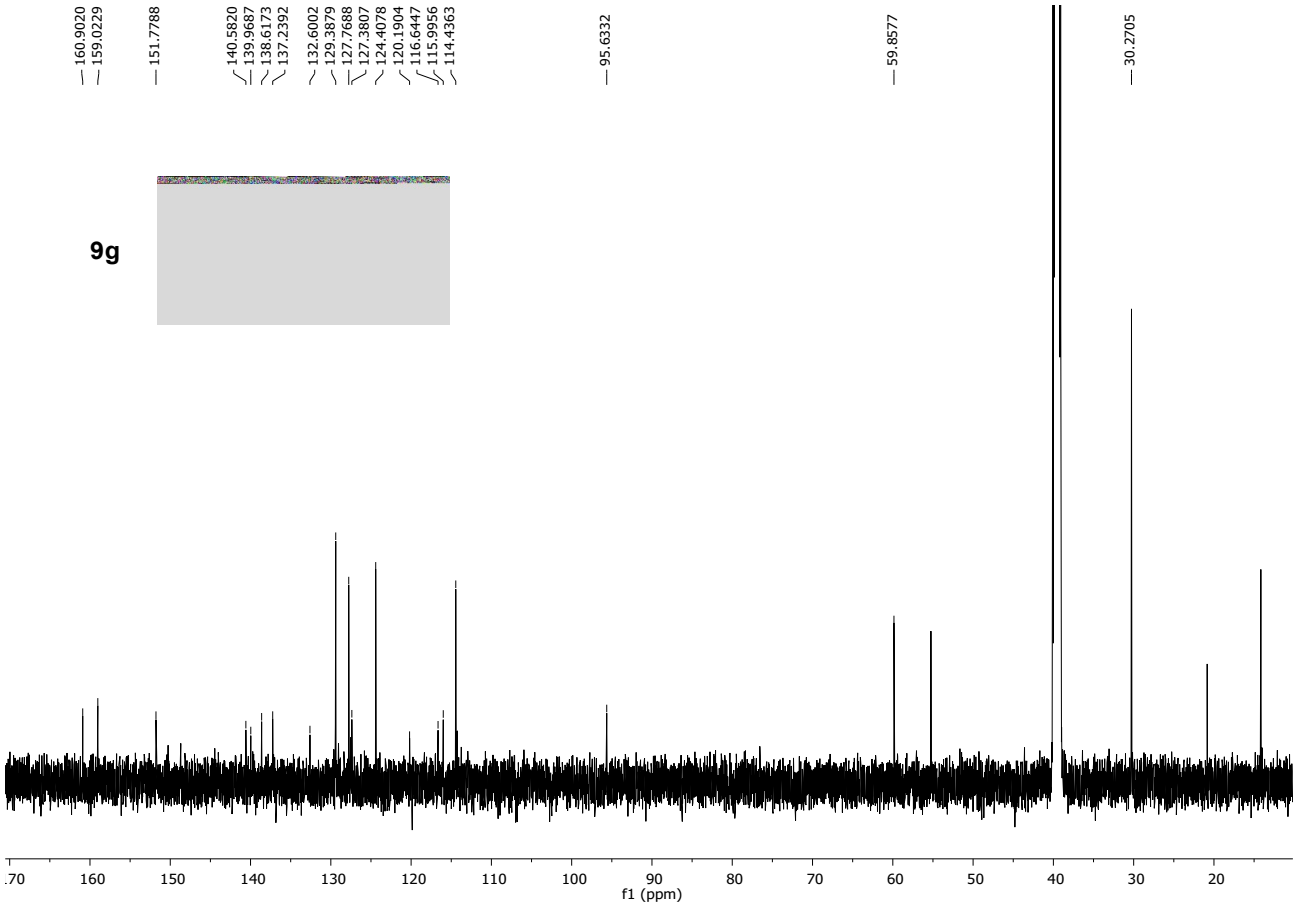
9f

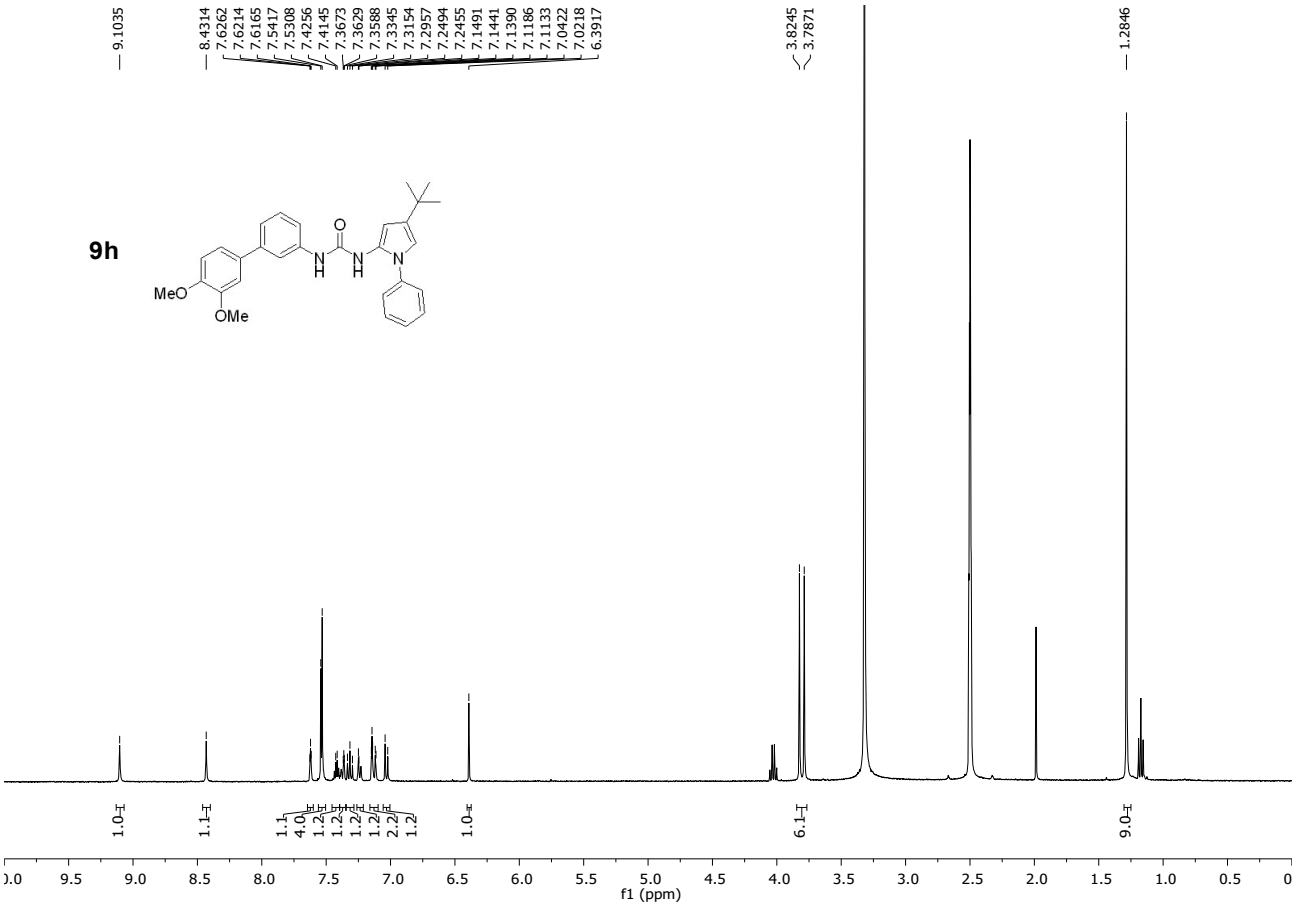

H3C
CH3
CH3
O
NH
NH
N
N
H3C
CH3
H3C
O
O
CH3
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
1.35
1.34
1.22
9.08
8.54
7.69
7.69
7.68
7.33
7.17
7.16
7.13
7.13
7.05
7.03
6.02
4.40
4.39
4.38
4.36
4.35
4.34
3.83
3.79
1.00
1.00
1.09
1.10
1.10
1.10
2.20
1.08
1.06
1.16
3.17
3.14
6.21
9.51
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

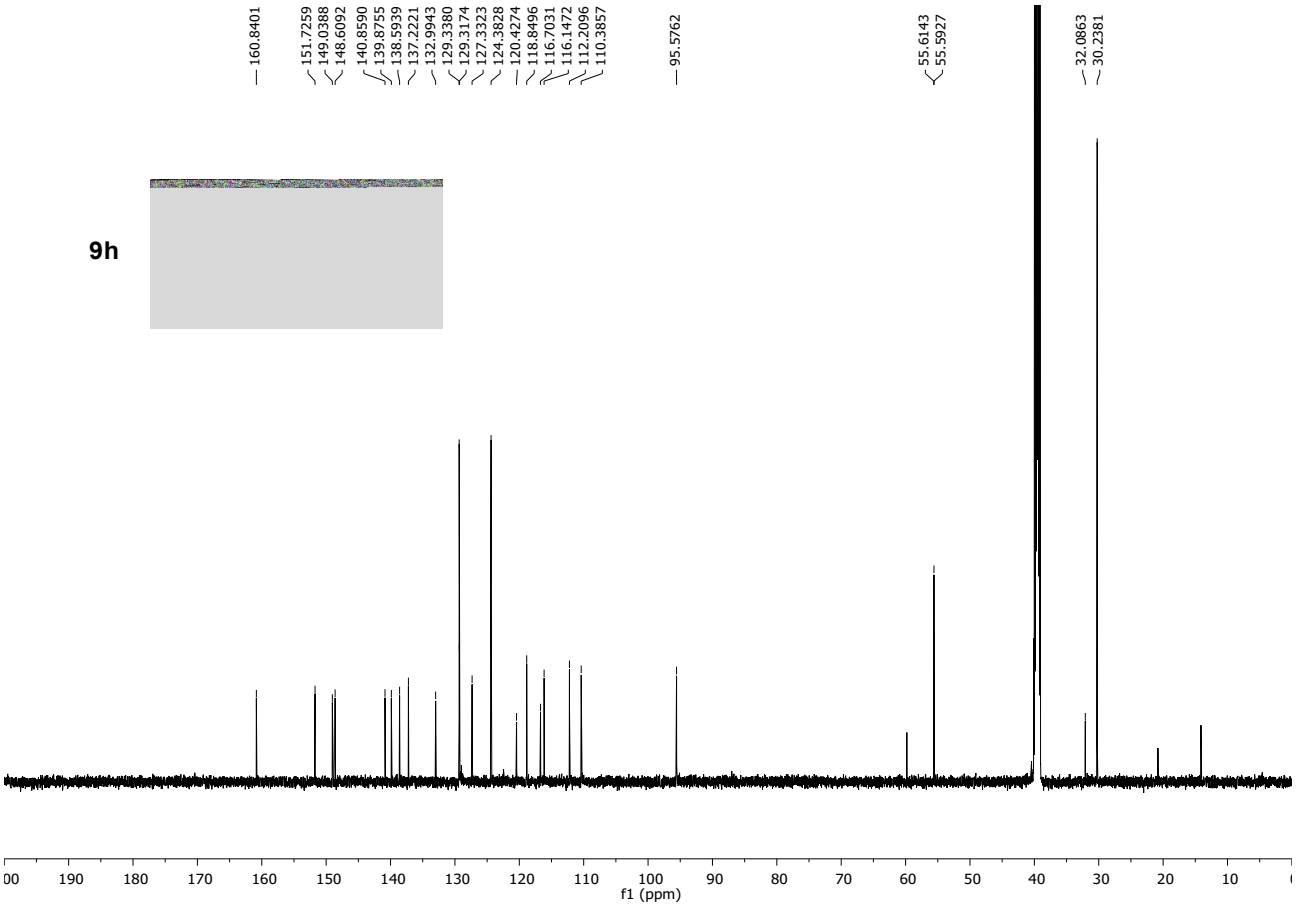

40.06 DMSO
39.94 DMSO
39.92 DMSO
39.80 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
158.43
152.37
149.01
148.56
140.78
140.12
135.44
133.04
129.22
120.19
118.79
116.72
116.16
112.18
110.37
94.49
59.75
55.58
55.55
47.66
31.91
30.46
30.43
22.20
20.77
14.09
f1 (ppm)

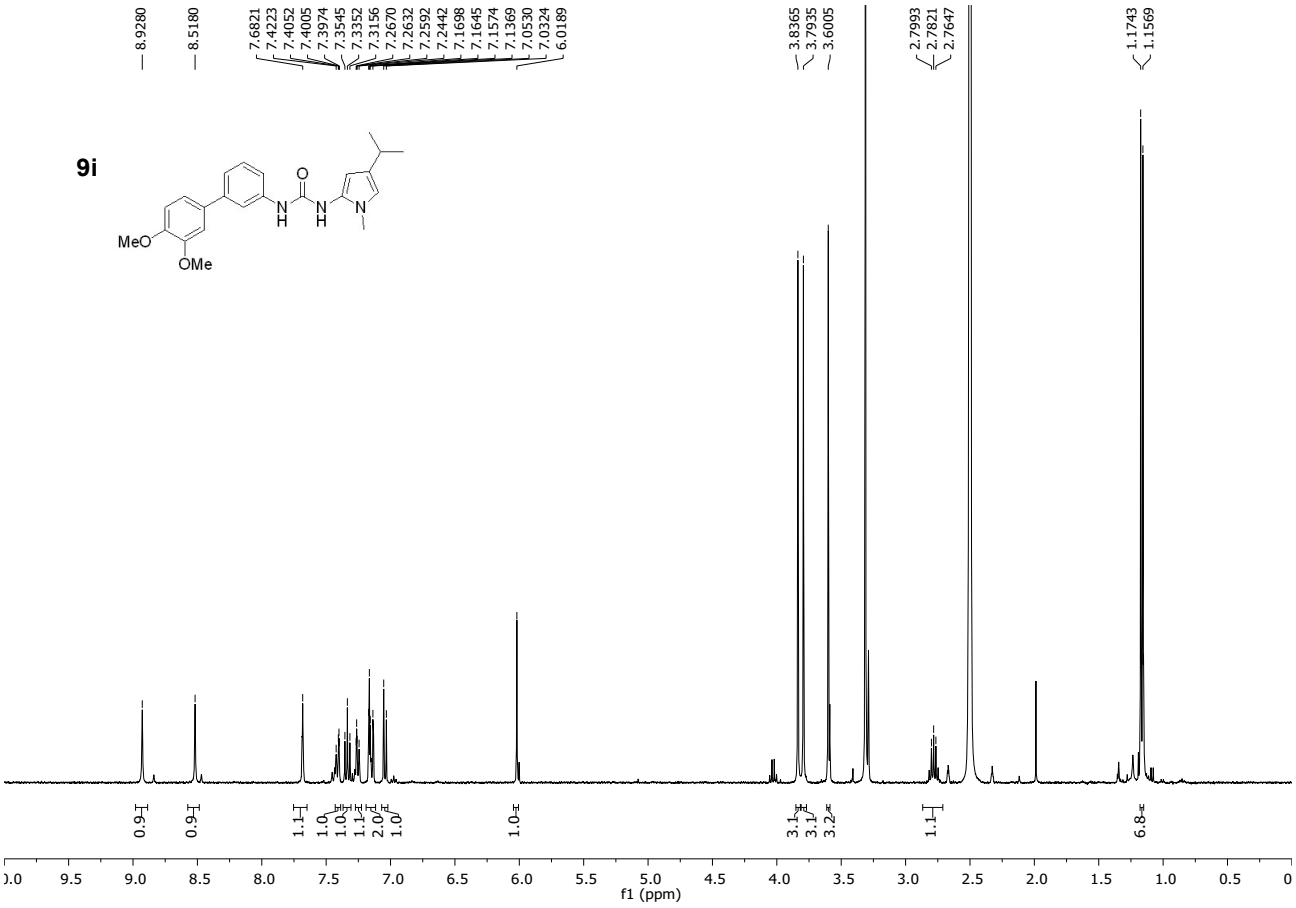
9g

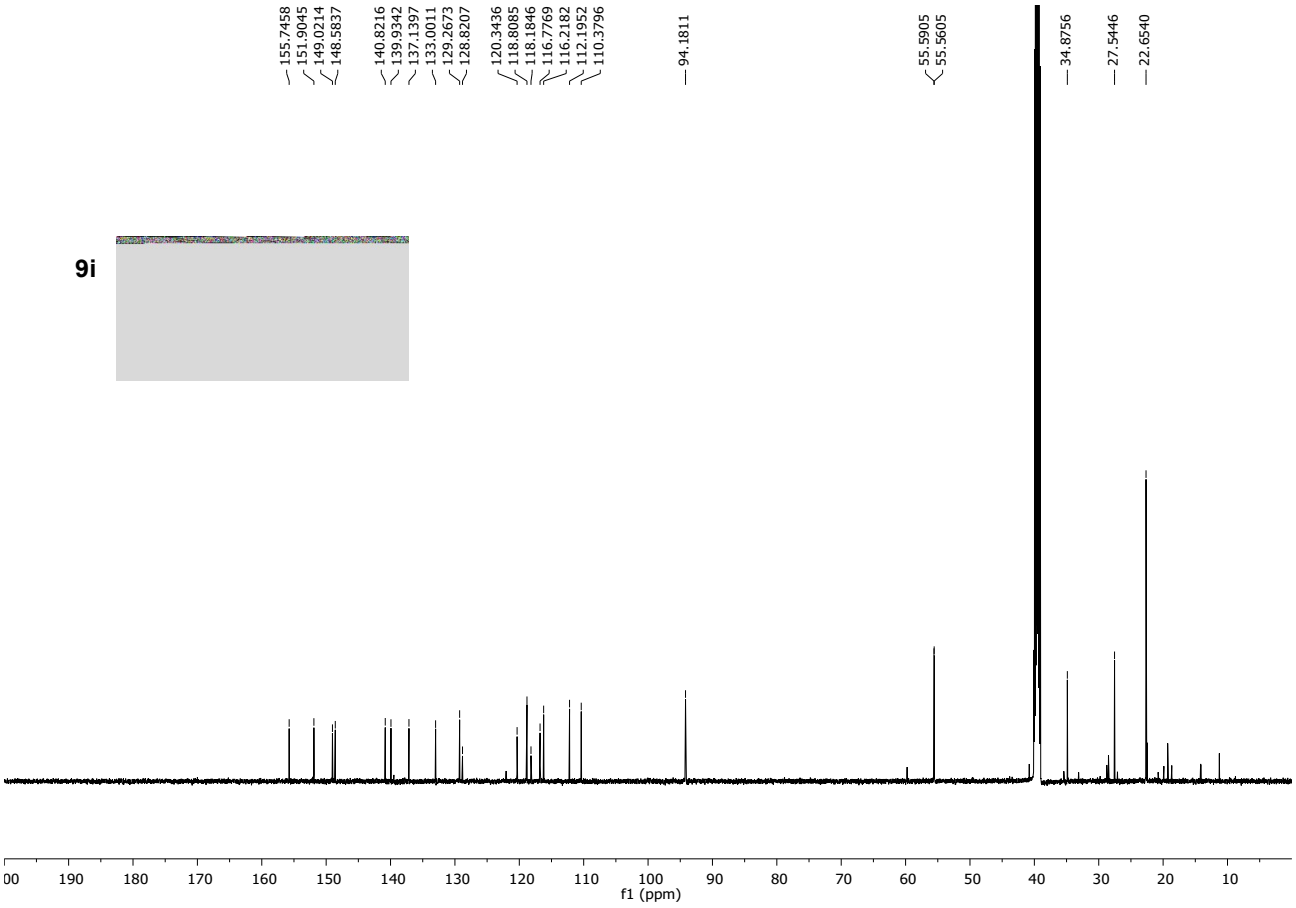

0.8
0.8
1.0
6.6
1.2
2.0
1.0
2.0
1.0
3.3
9.0
f1 (ppm)

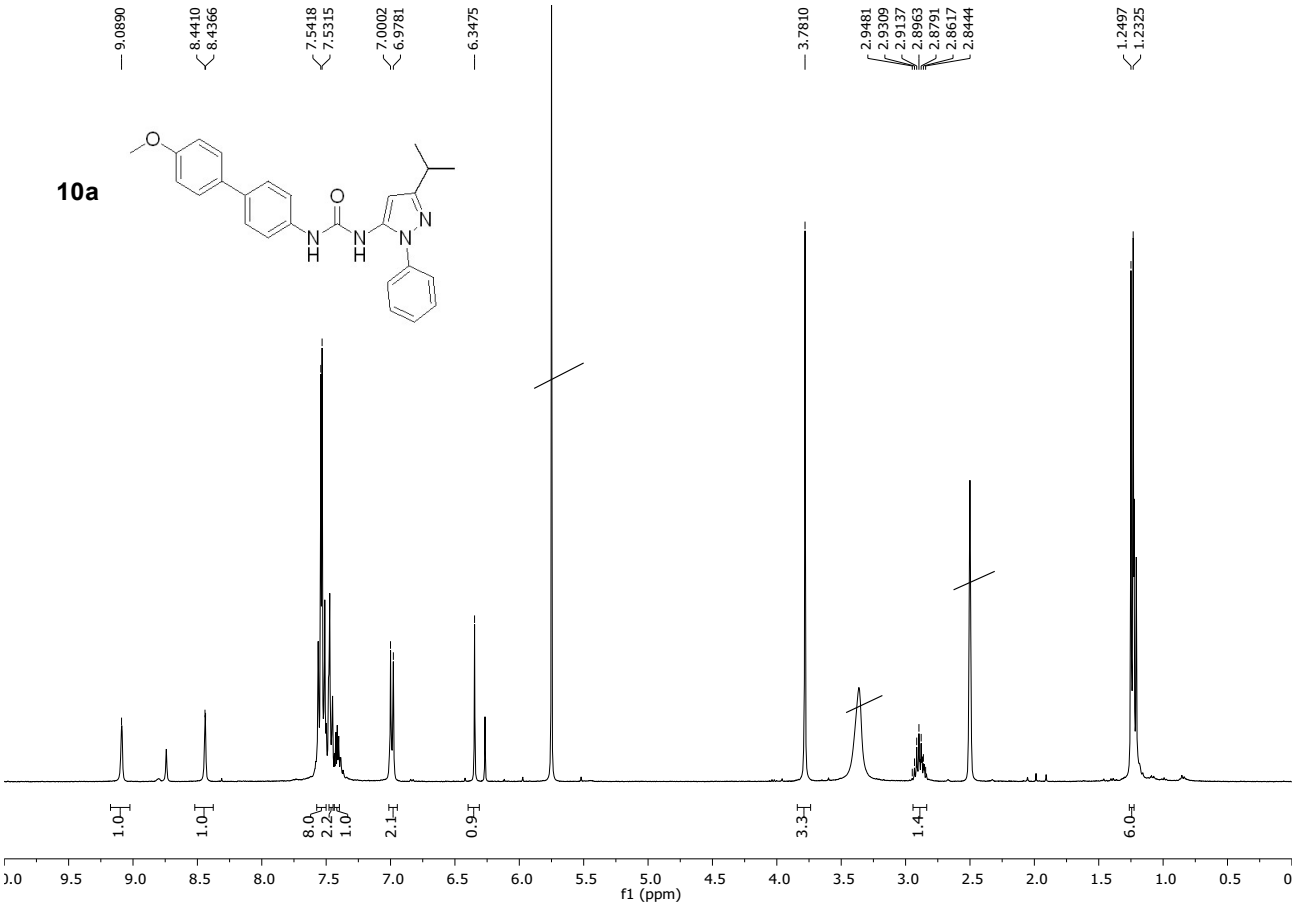

160.9020
159.0229
151.7788
140.5820
139.9687
138.6173
137.2392
132.6002
129.3879
127.7688
127.3807
124.4078
120.1904
116.6447
115.9956
114.4363
95.6332
59.8577
30.2705
9g
f1 (ppm)

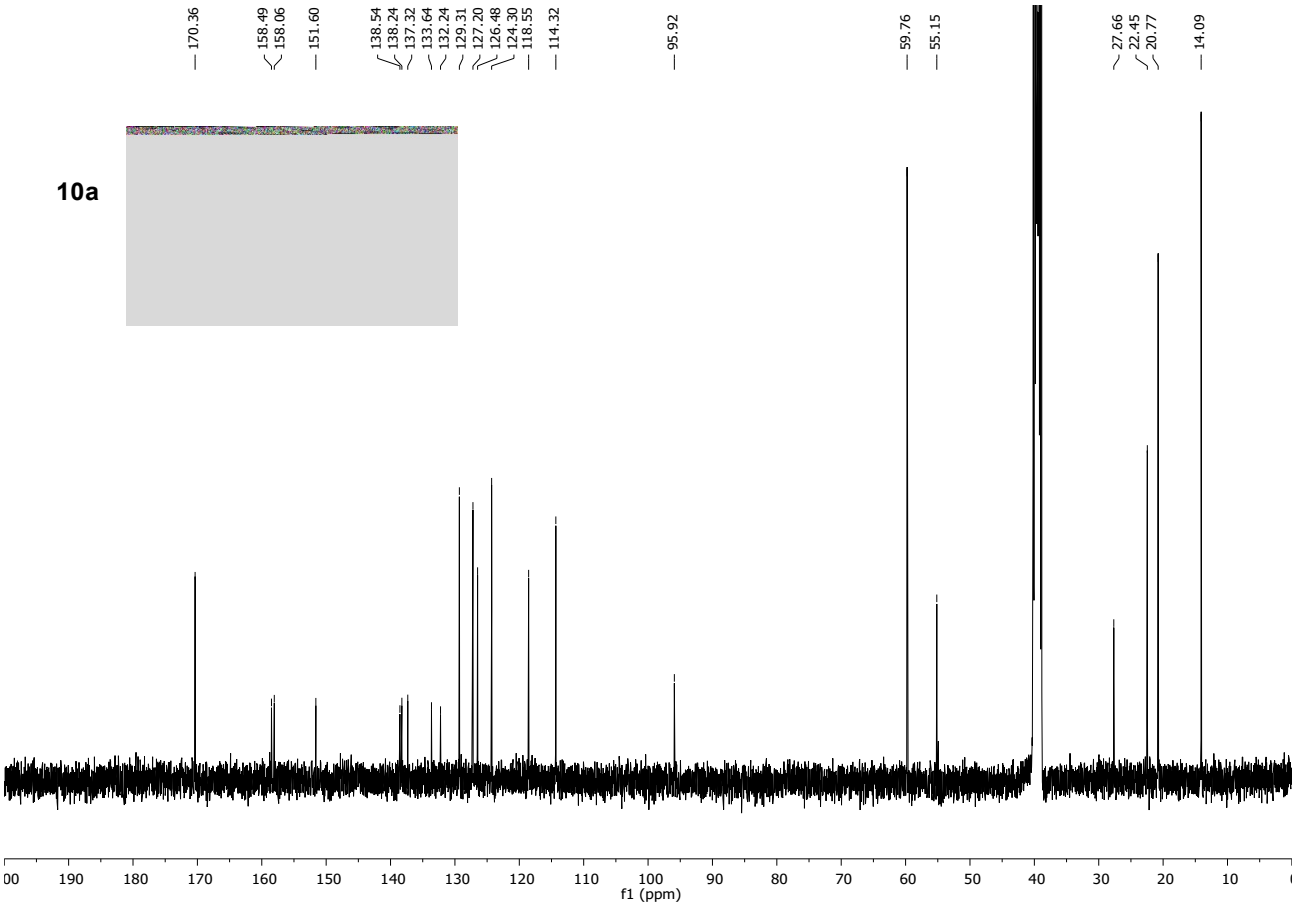

9.1035
8.4314
7.6262
7.6214
7.6165
7.5417
7.5308
7.4256
7.4145
7.3673
7.3629
7.3588
7.3345
7.3154
7.2957
7.2494
7.2455
7.1491
7.1441
7.1390
7.1186
7.1133
7.0422
7.0218
6.3917
3.8245
3.7871
1.2846
9h
MeO
OMe
O
N
H
N
H
N
1.0
1.1
1.1
4.0
1.2
1.2
1.2
1.2
2.2
1.2
1.0
6.1
9.0
f1 (ppm)

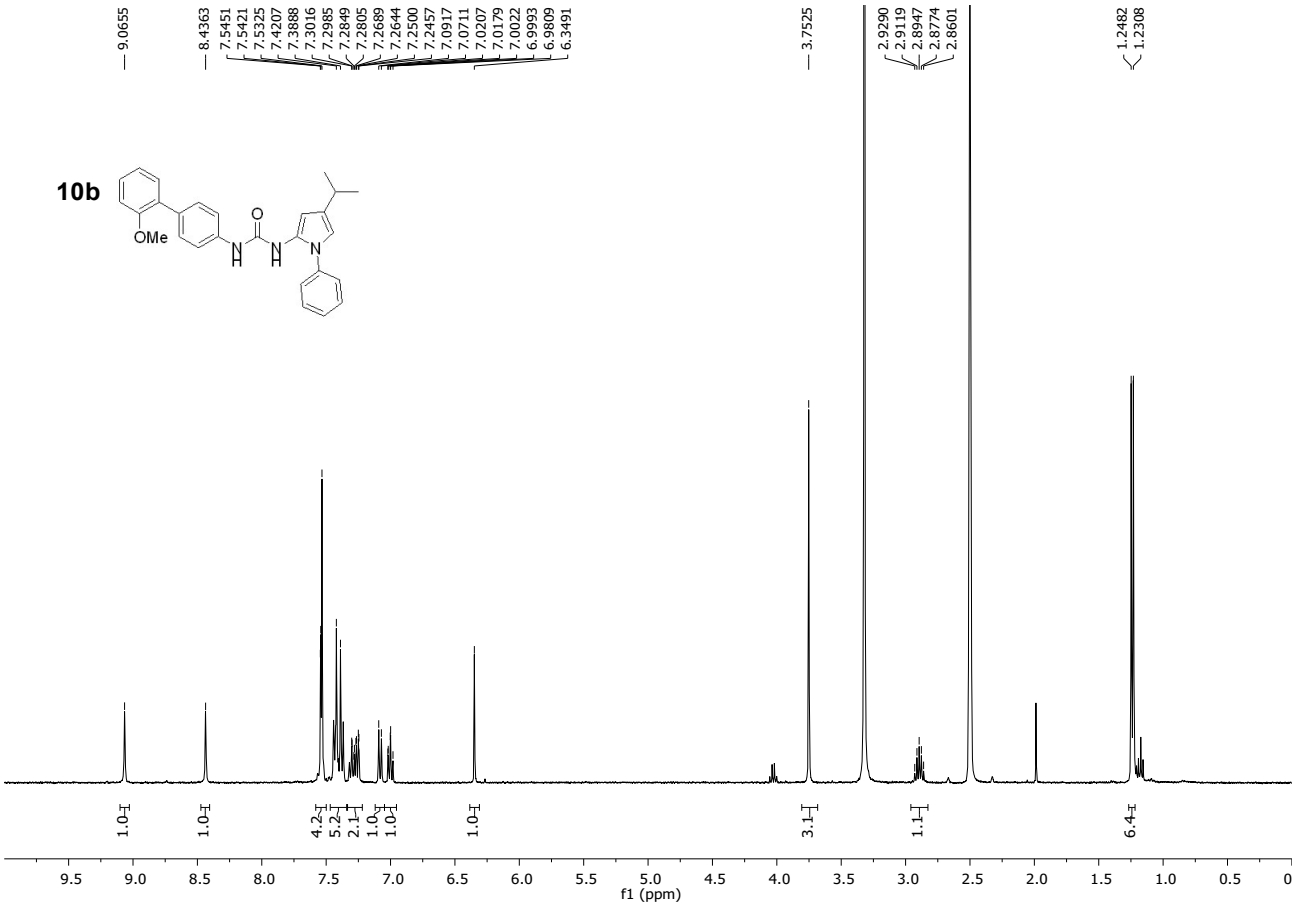

160.8401
151.7259
149.0388
148.6092
140.8590
139.8755
138.5939
137.2221
132.9943
129.3380
129.3174
127.3323
124.3828
120.4274
118.8496
116.7031
116.1472
112.2096
110.3857
95.5762
55.6143
55.5927
32.0863
30.2381
9h
f1 (ppm)

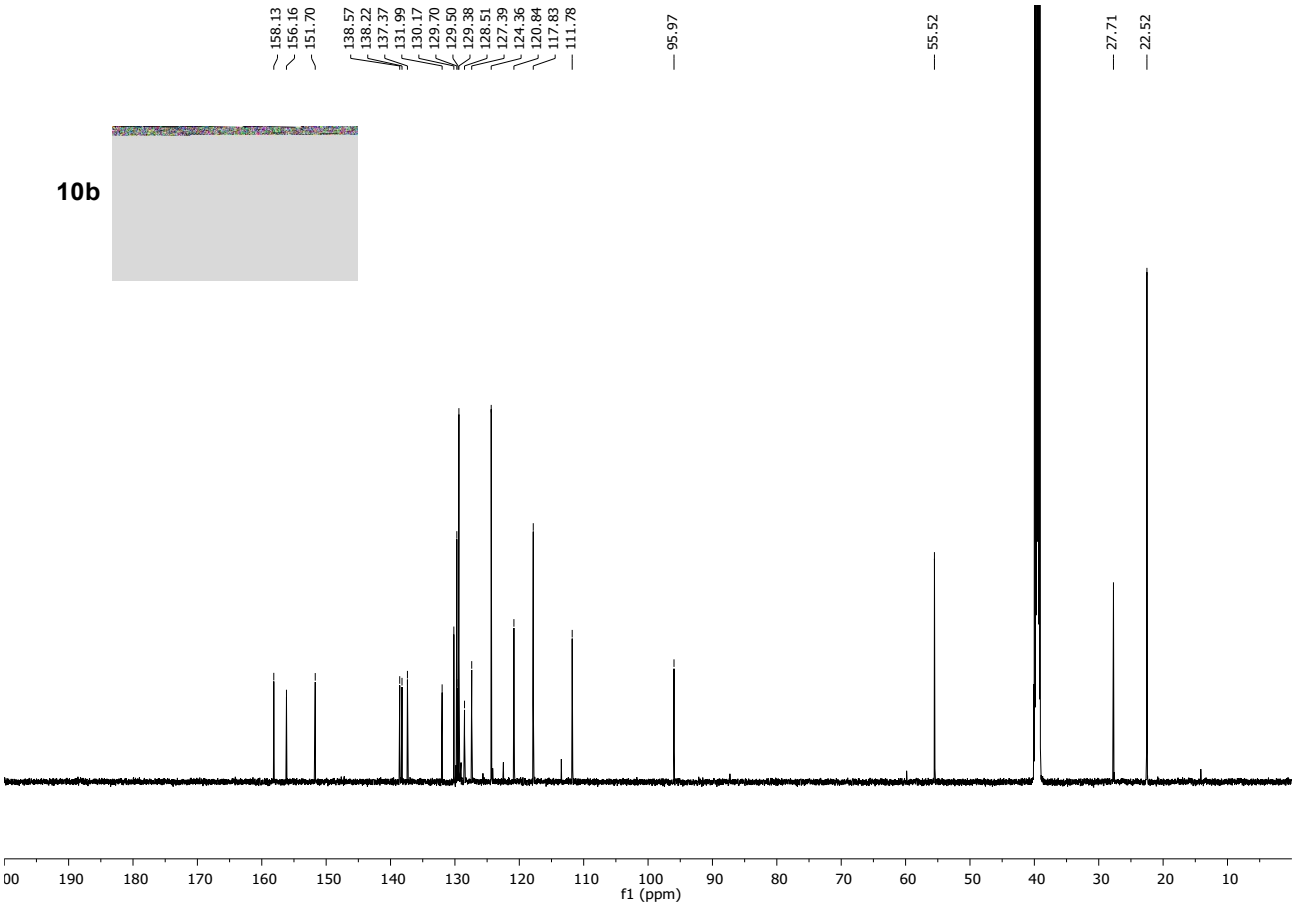

9i
MeO
OMe
8.9280
8.5180
7.6821
7.4223
7.4052
7.4005
7.3974
7.3545
7.3352
7.3156
7.2670
7.2632
7.2592
7.2442
7.1698
7.1645
7.1574
7.1369
7.0530
7.0324
6.0189
3.8365
3.7935
3.6005
2.7993
2.7821
2.7647
1.1743
1.1569
f1 (ppm)

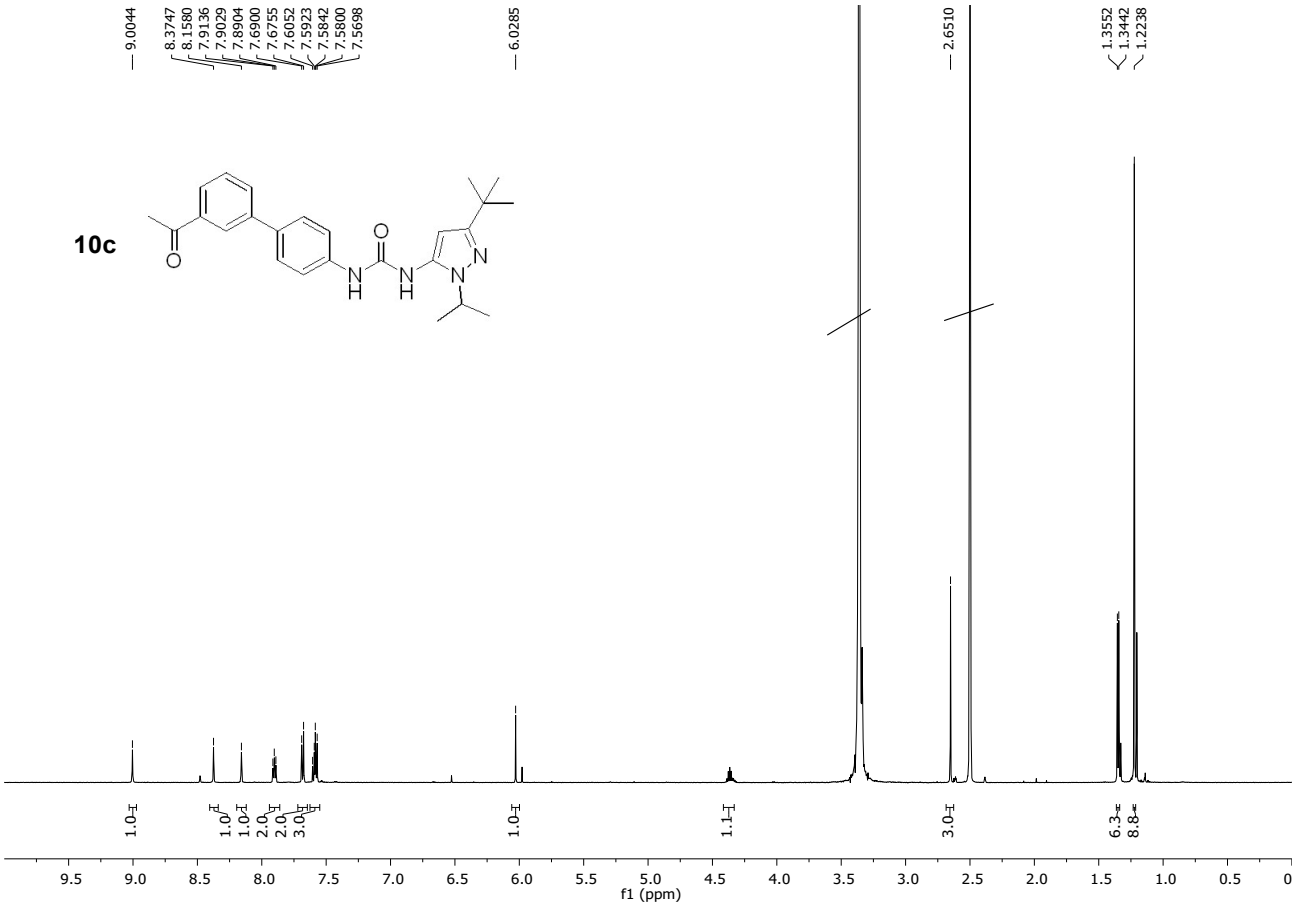

9i
155.7458
151.9045
149.0214
148.5837
140.8216
139.9342
137.1397
133.0011
129.2673
128.8207
120.3436
118.8085
118.1846
116.7769
116.2182
112.1952
110.3796
94.1811
55.5905
55.5605
34.8756
27.5446
22.6540
f1 (ppm)

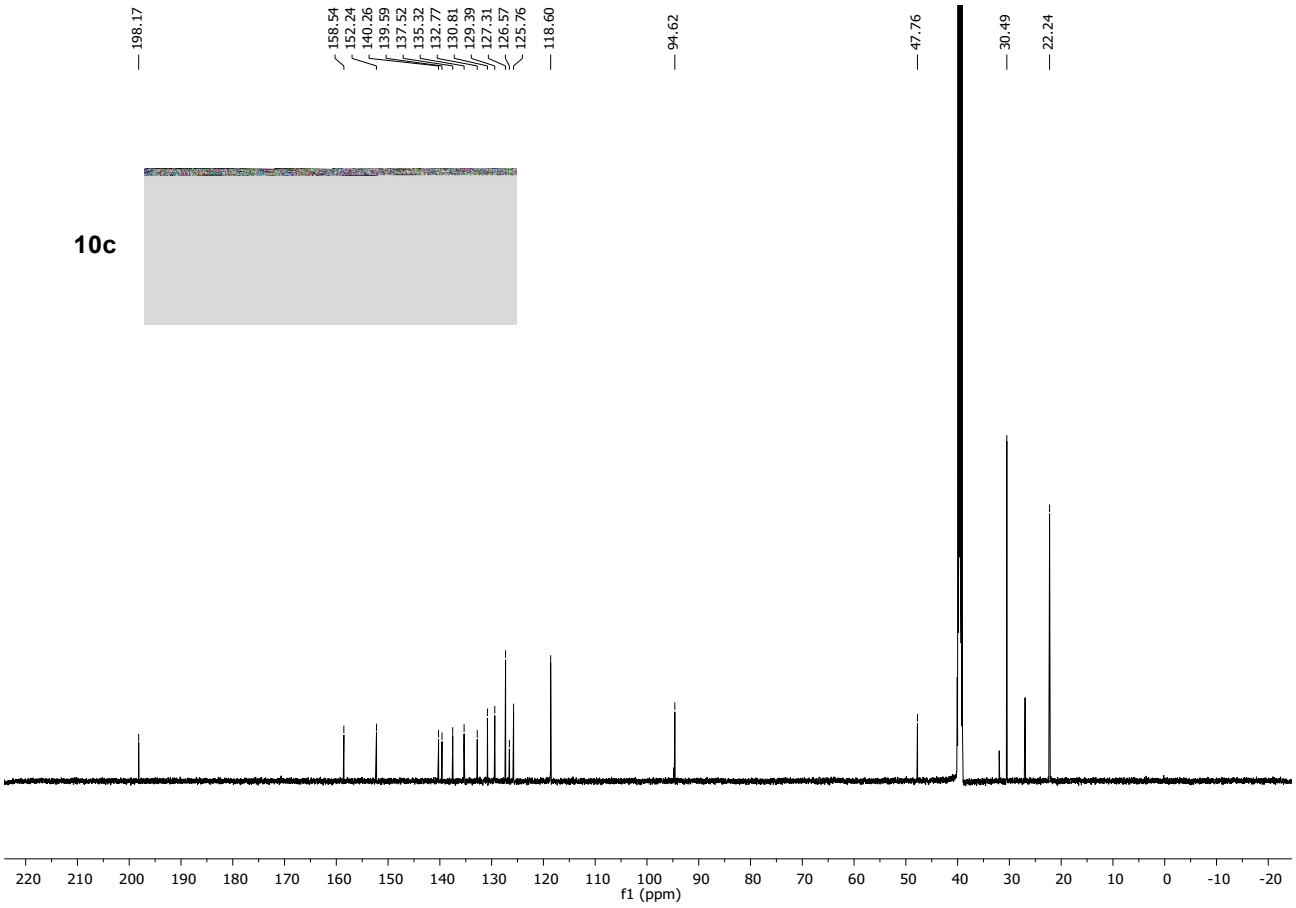

9.0890
8.4410
8.4366
7.5418
7.5315
7.0002
6.9781
6.3475
3.7810
2.9481
2.9309
2.9137
2.8963
2.8791
2.8617
2.8444
1.2497
1.2325
10a
1.0
1.0
8.0
2.2
1.0
2.1
0.9
3.3
1.4
6.0
f1 (ppm)


10a
170.36
158.49
158.06
151.60
138.54
138.24
137.32
133.64
132.24
129.31
127.20
126.48
124.30
118.55
114.32
95.92
59.76
55.15
27.66
22.45
20.77
14.09
f1 (ppm)


9.0655
8.4363
7.5451
7.5421
7.5325
7.4207
7.3888
7.3016
7.2985
7.2849
7.2805
7.2689
7.2644
7.2500
7.2457
7.0917
7.0711
7.0207
7.0179
7.0022
6.9993
6.9809
6.3491
3.7525
2.9290
2.9119
2.8947
2.8774
2.8601
1.2482
1.2308
10b
OMe
1.0
1.0
4.2
5.2
2.1
1.0
1.0
1.0
3.1
1.1
6.4
f1 (ppm)


158.13
156.16
151.70
138.57
138.22
137.37
131.99
130.17
129.70
129.50
129.38
128.51
127.39
124.36
120.84
117.83
111.78
95.97
55.52
27.71
22.52
10b
f1 (ppm)


9.0044
8.3747
8.1580
7.9136
7.9029
7.8904
7.6900
7.6755
7.6052
7.5923
7.5842
7.5800
7.5698
6.0285
2.6510
1.3552
1.3442
1.2238
10c
1.0
1.0
1.0
2.0
2.0
3.0
1.0
1.1
3.0
6.3
8.8
f1 (ppm)


198.17
158.54
152.24
140.26
139.59
137.52
135.32
132.77
130.81
129.39
127.31
126.57
125.76
118.60
94.62
47.76
30.49
22.24
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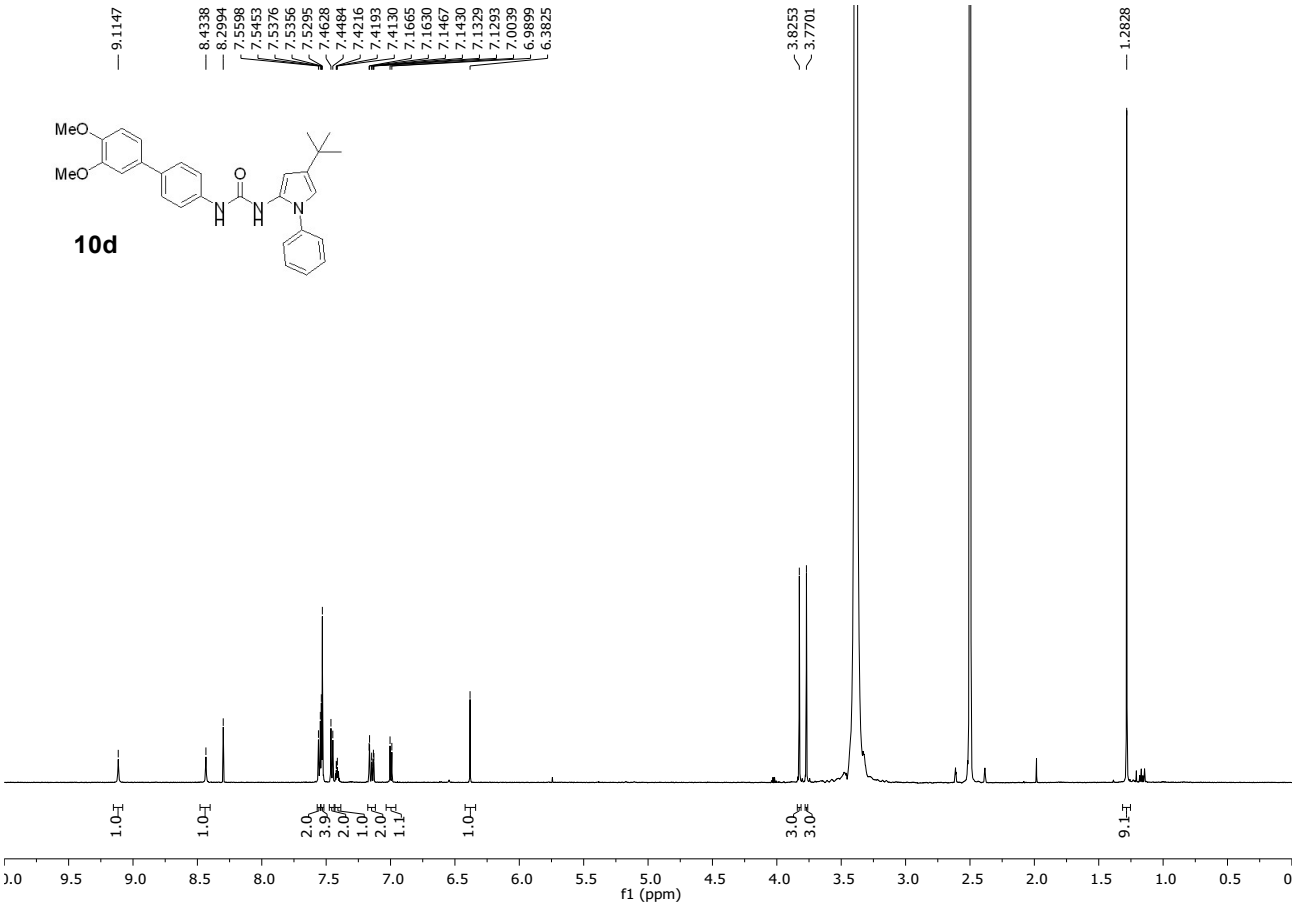
f1 (ppm)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7.5356
7.5295
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7.4216
7.4193
7.4130
7.1665
7.1630
7.1467
7.1430
7.1329
7.1293
7.0039
6.9899
6.3825
3.8253
3.7701
1.2828
MeO
MeO
O
N
H
H
N
10d
1.0
1.0
2.0
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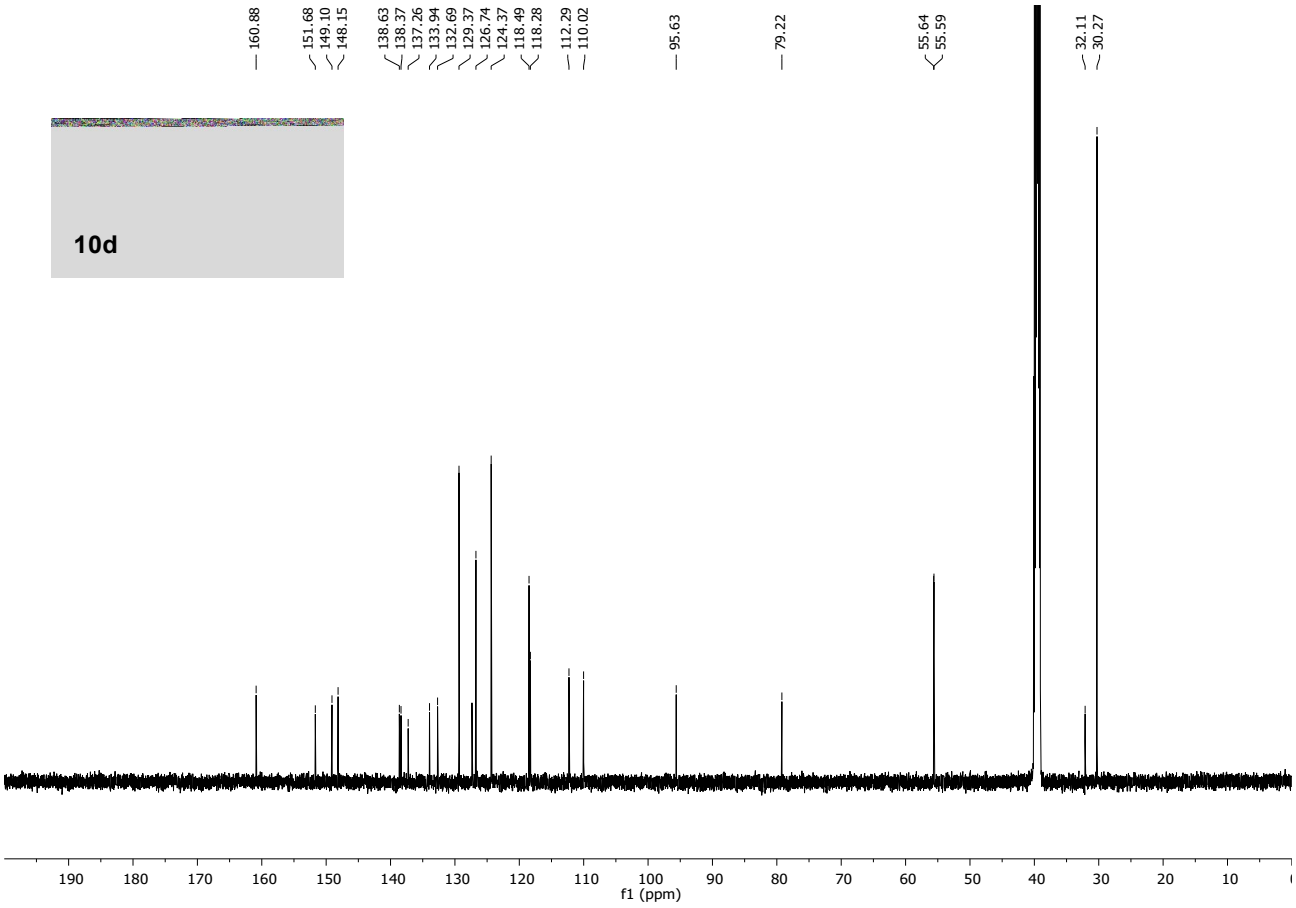
2.0
1.0
2.0
1.1
1.0
3.0
3.0
9.1
f1 (ppm)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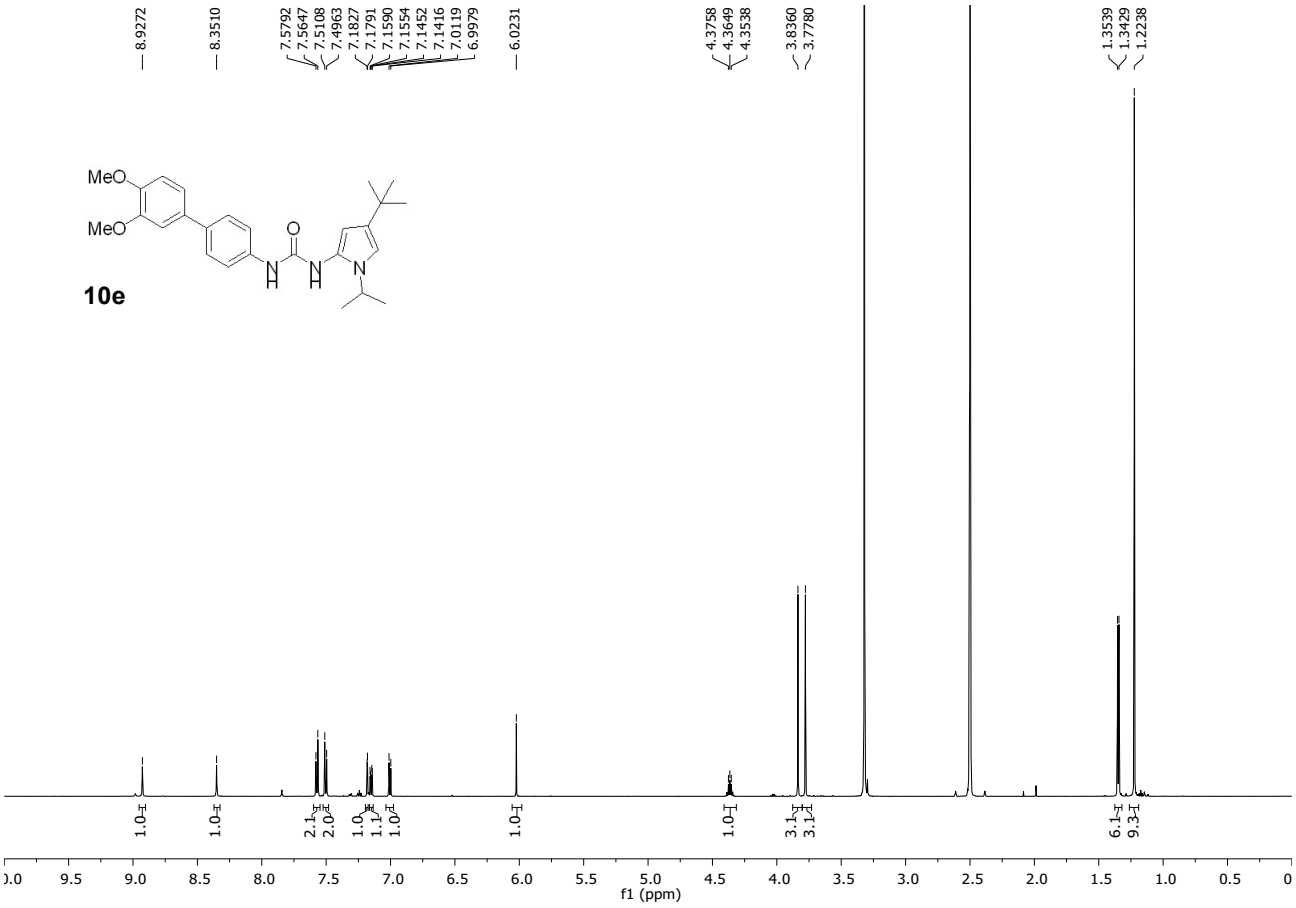
138.37
137.26
133.94
132.69
129.37
126.74
124.37
118.49
118.28
112.29
110.02
95.63
79.22
55.64
55.59
32.11
30.27
10d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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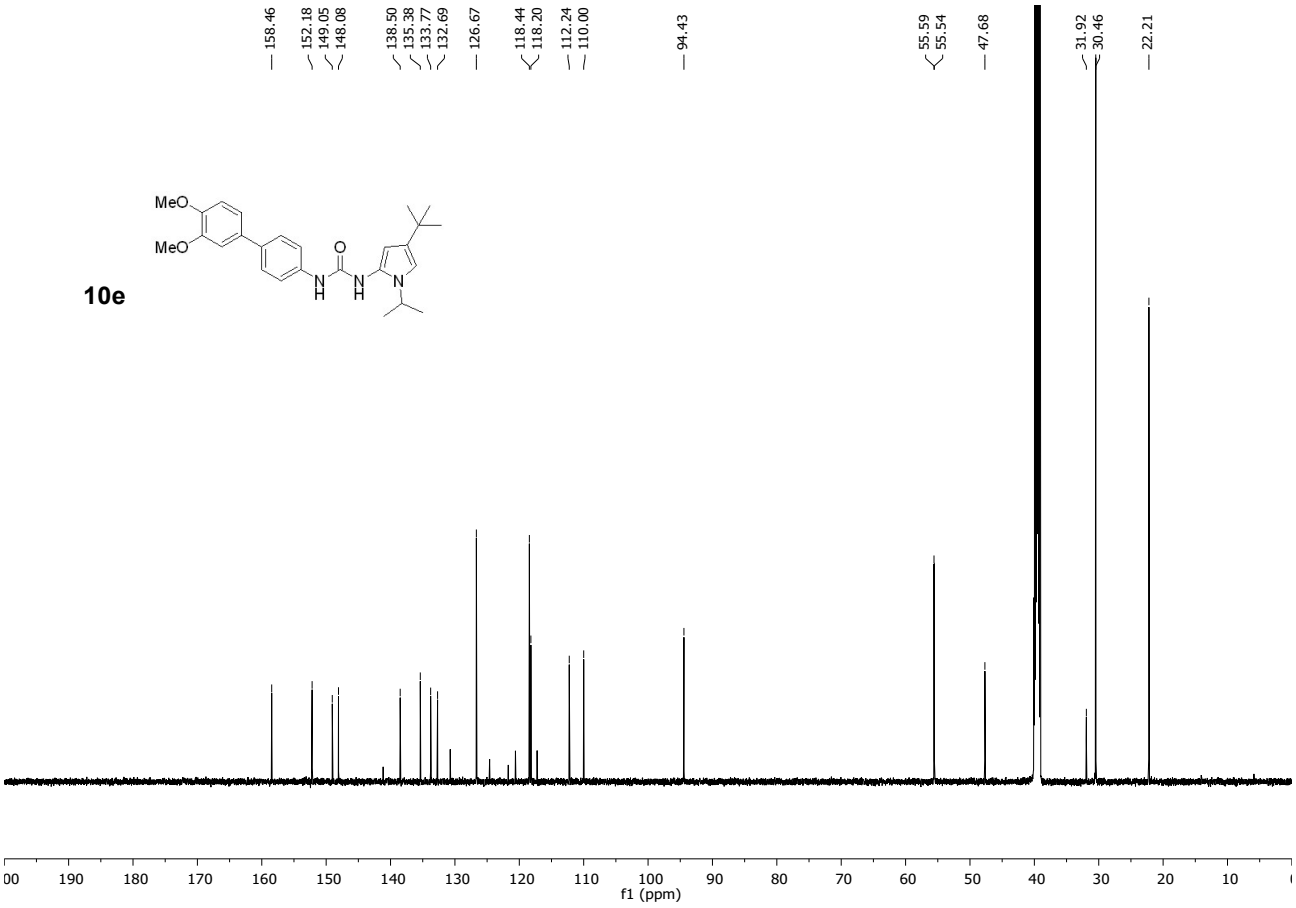
7.1590
7.1554
7.1452
7.1416
7.0119
6.9979
6.0231
4.3758
4.3649
4.3538
3.8360
3.7780
1.3539
1.3429
1.2238
MeO
MeO
O
N
H
N
H
N
10e
1.0
1.0
2.1
2.0
1.0
1.1
1.0
1.0
1.0
3.1
3.1
6.1
9.3
f1 (ppm)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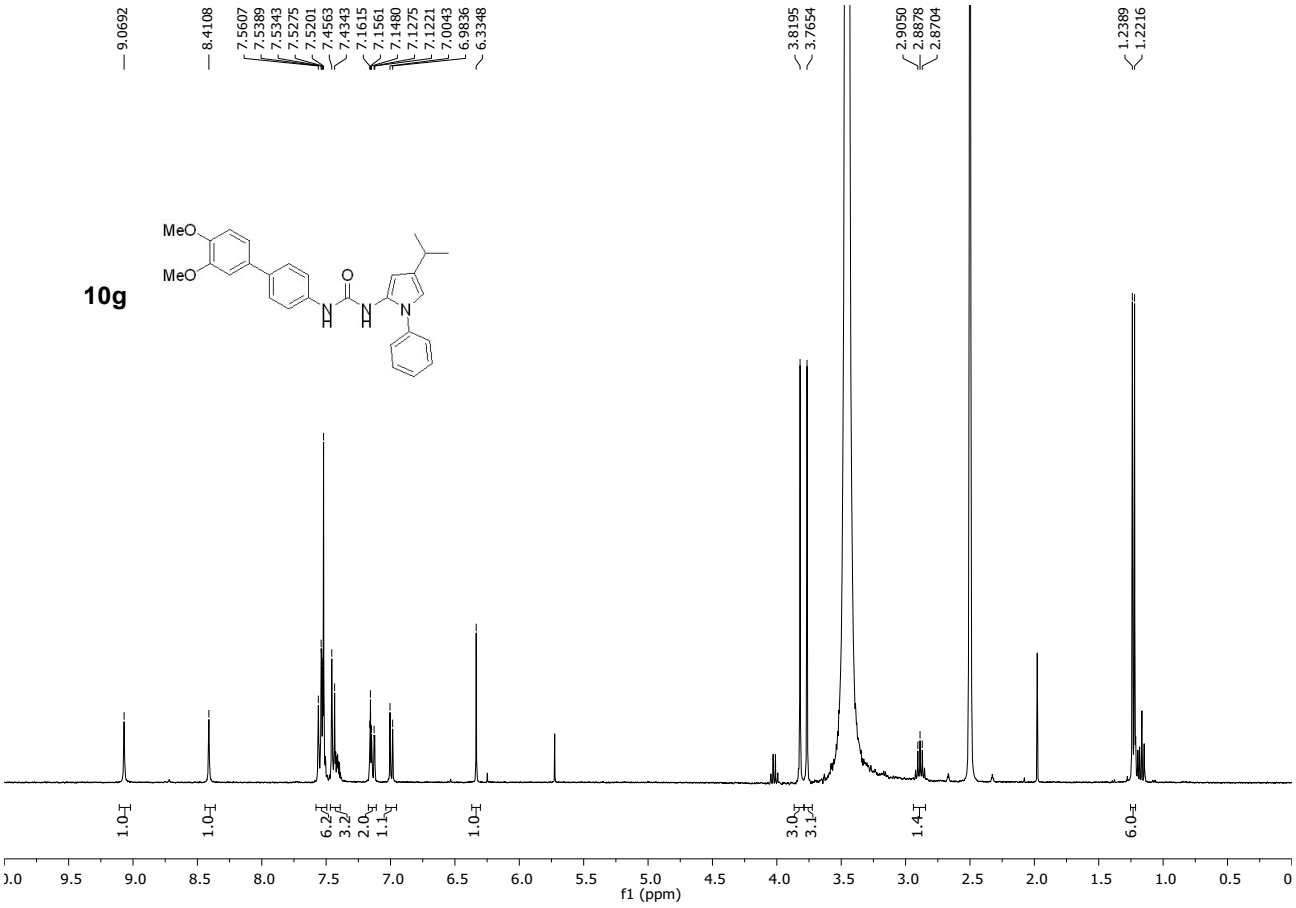
135.38
133.77
132.69
126.67
118.44
118.20
112.24
110.00
94.43
55.59
55.54
47.68
31.92
30.46
22.21
MeO
MeO
O
N
H
N
H
N
10e
f1 (ppm)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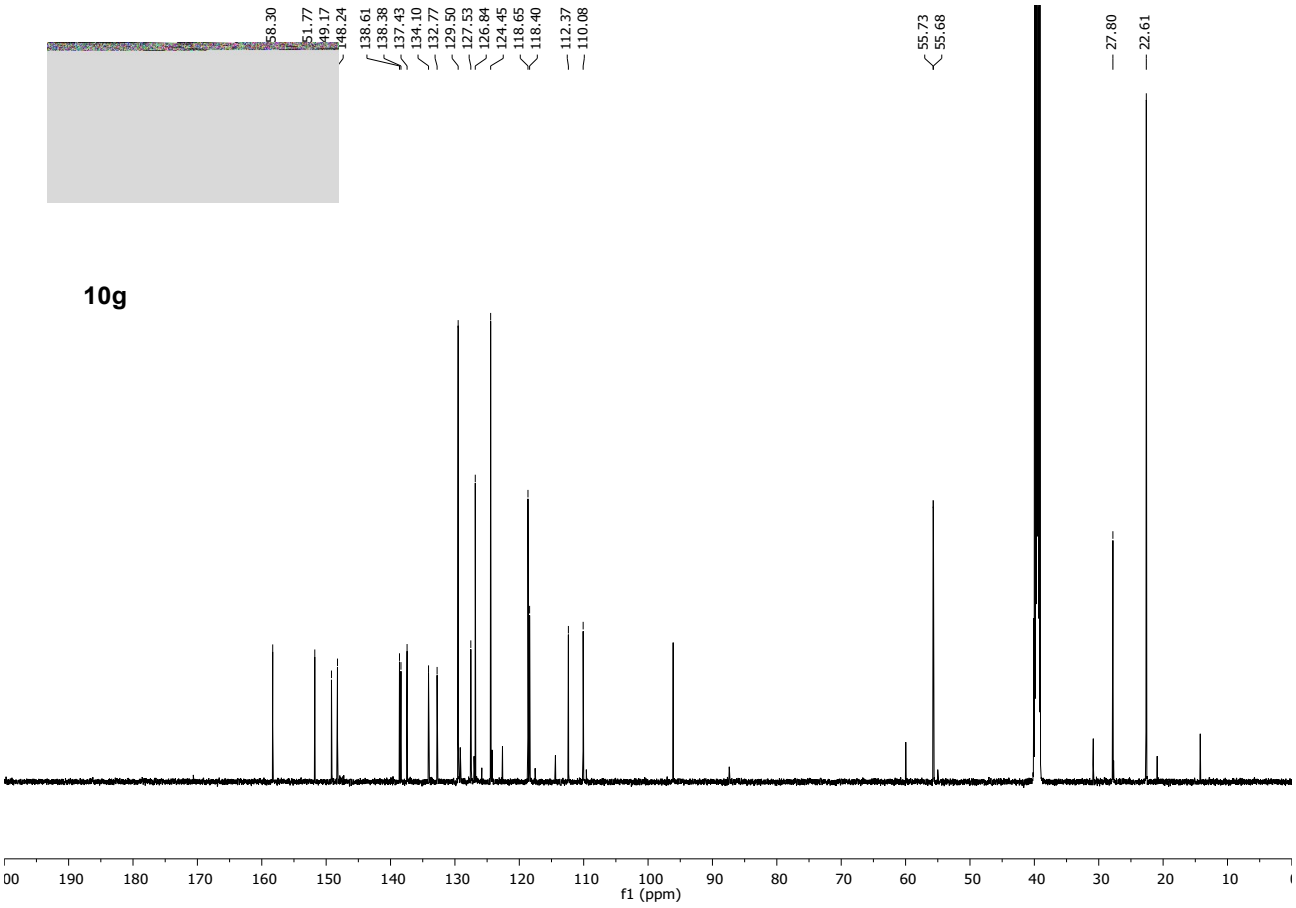
7.5389
7.5343
7.5275
7.5201
7.4563
7.4343
7.1615
7.1561
7.1480
7.1275
7.1221
7.0043
6.9836
6.3348
3.8195
3.7654
2.9050
2.8878
2.8704
1.2389
1.2216
10g
MeO
MeO
O
N
H
H
N
1.0
1.0
6.2
3.2
2.0
1.1
1.0
3.0
3.1
1.4
6.0
f1 (ppm)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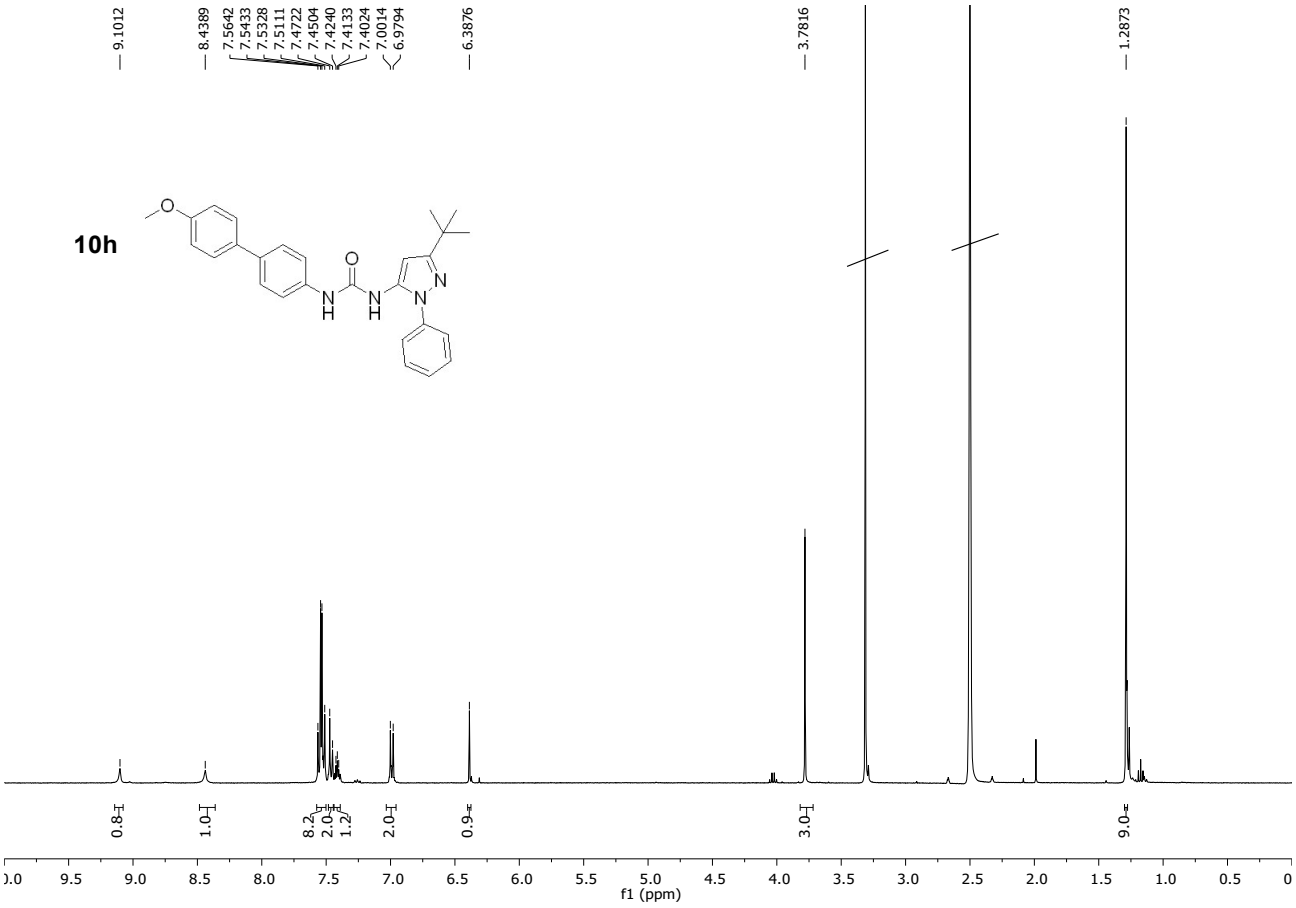
138.38
137.43
134.10
132.77
129.50
127.53
126.84
124.45
118.65
118.40
112.37
110.08
55.73
55.68
27.80
22.61
10g
f1 (ppm)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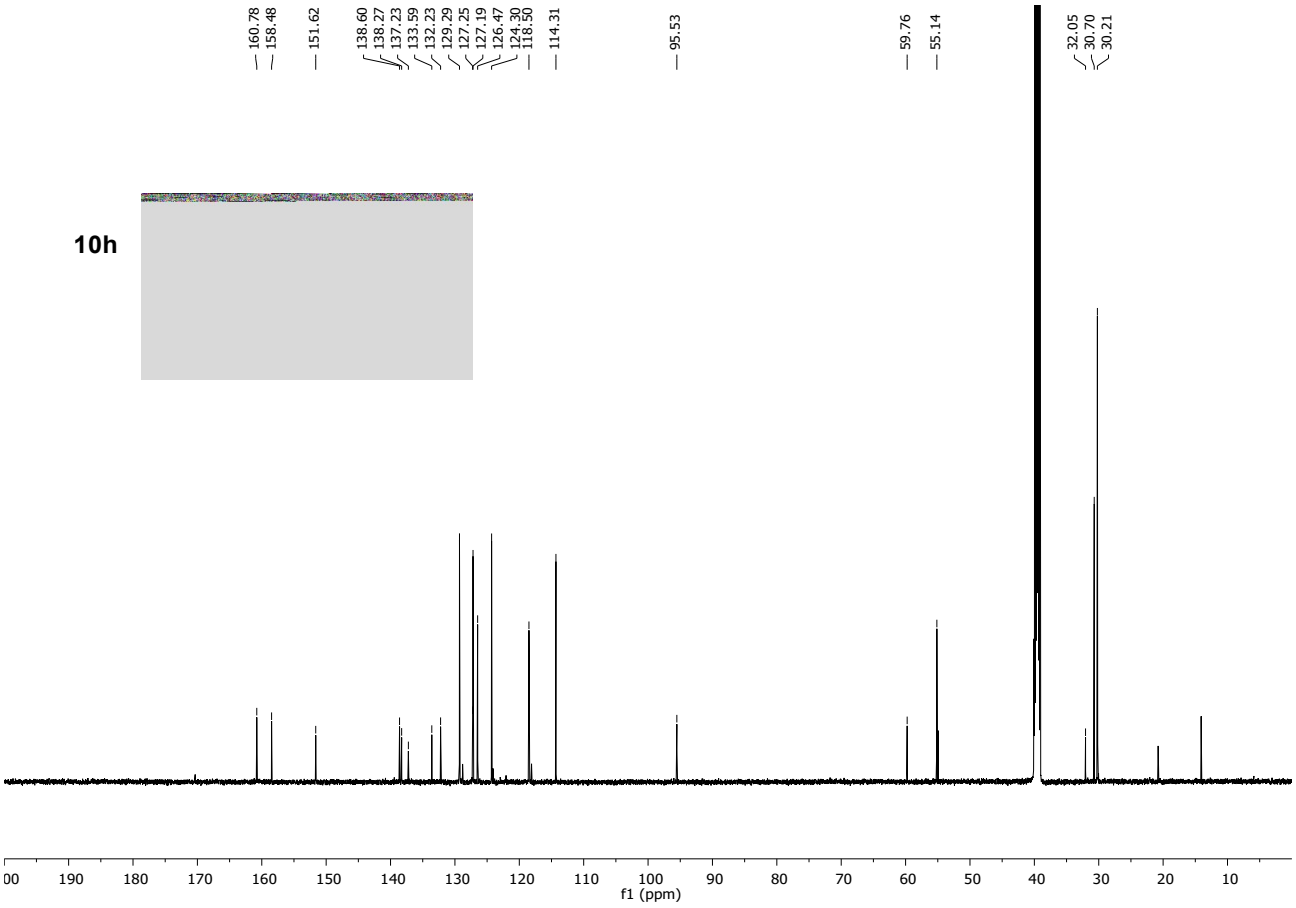
7.5642
7.5433
7.5328
7.5111
7.4722
7.4504
7.4240
7.4133
7.4024
7.0014
6.9794
6.3876
3.7816
1.2873
10h
O
N
H
O
N
H
N
N
0.8
1.0
8.2
2.0
1.2
2.0
0.9
3.0
9.0
f1 (ppm)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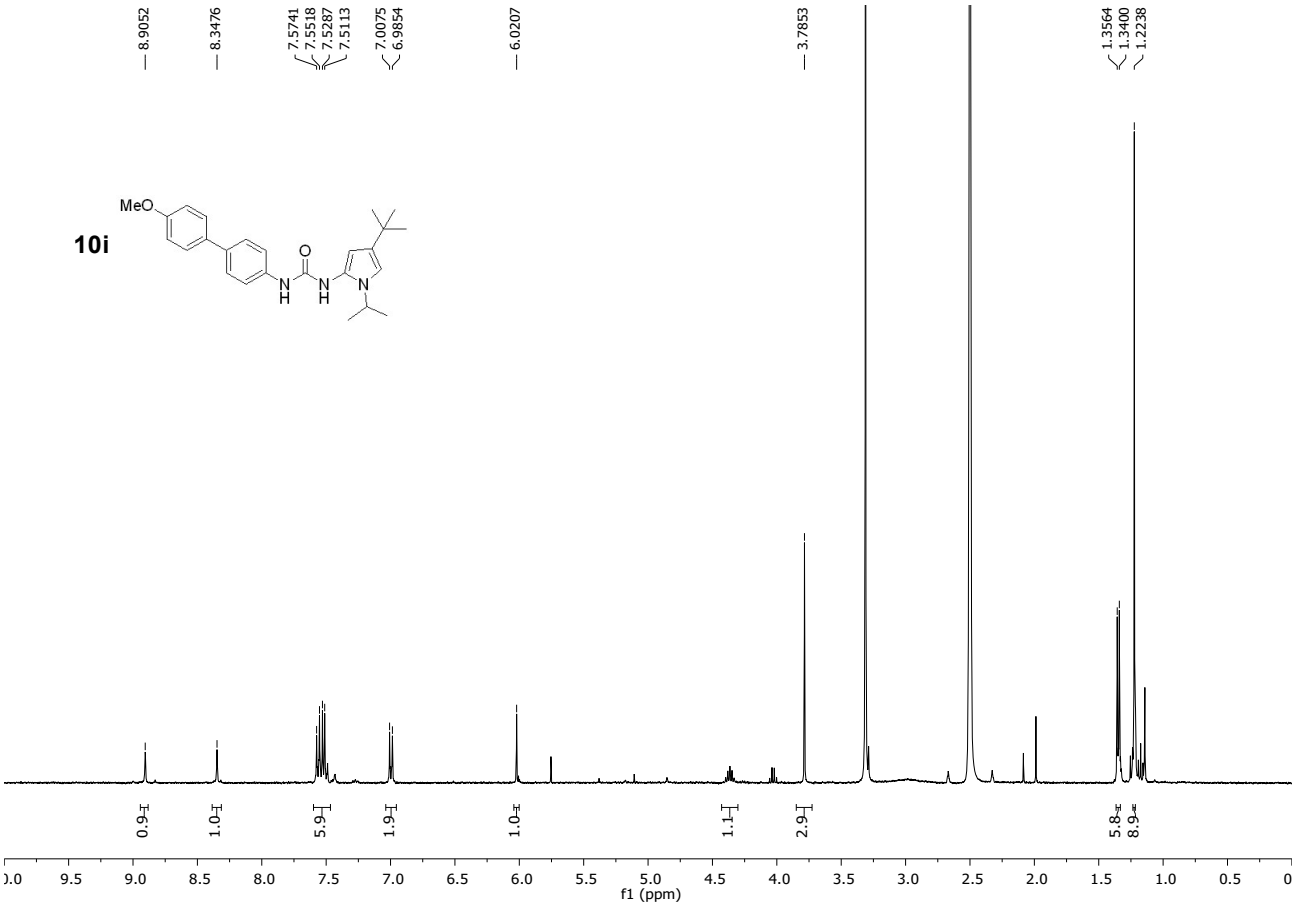
151.62
138.60
138.27
137.23
133.59
132.23
129.29
127.25
127.19
126.47
124.30
118.50
114.31
95.53
59.76
55.14
32.05
30.70
30.21
10h
f1 (ppm)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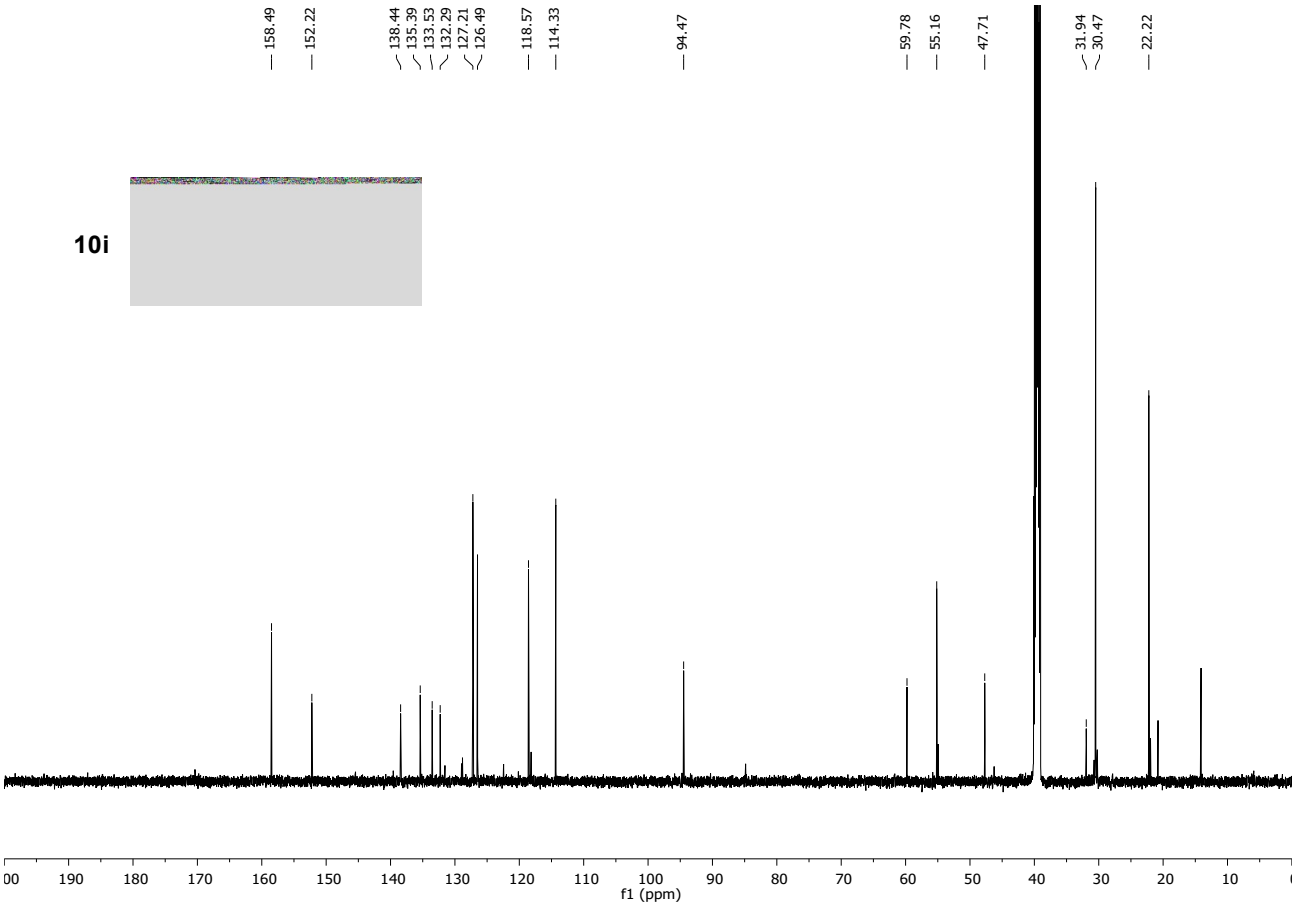
8.3476
7.5741
7.5518
7.5287
7.5113
7.0075
6.9854
6.0207
3.7853
1.3564
1.3400
1.2238
MeO
10i
O
N
H
N
H
N
0.9
1.0
5.9
1.9
1.0
1.1
2.9
5.8
8.9
f1 (ppm)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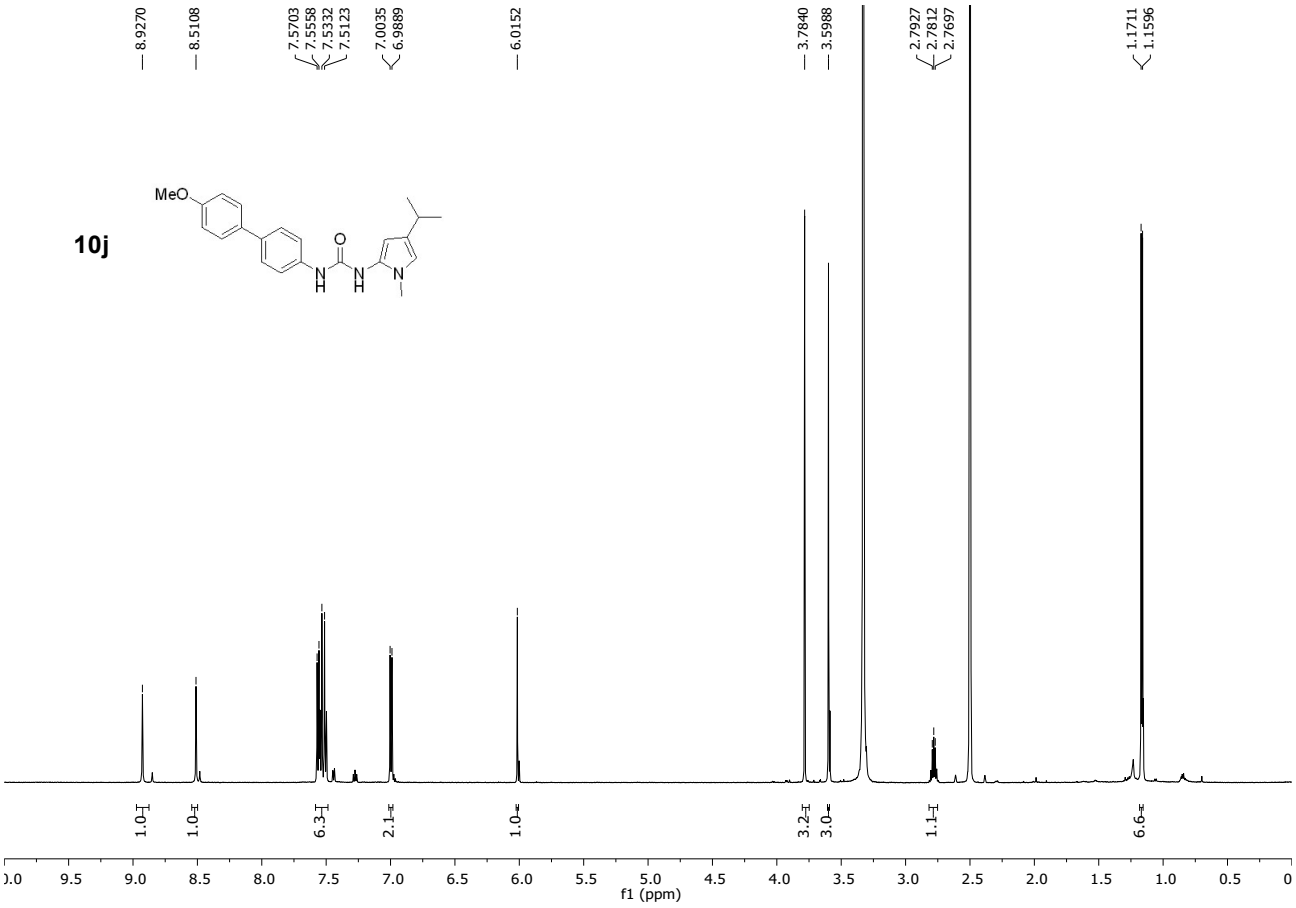
135.39
133.53
132.29
127.21
126.49
118.57
114.33
94.47
59.78
55.16
47.71
31.94
30.47
22.22
10i
f1 (ppm)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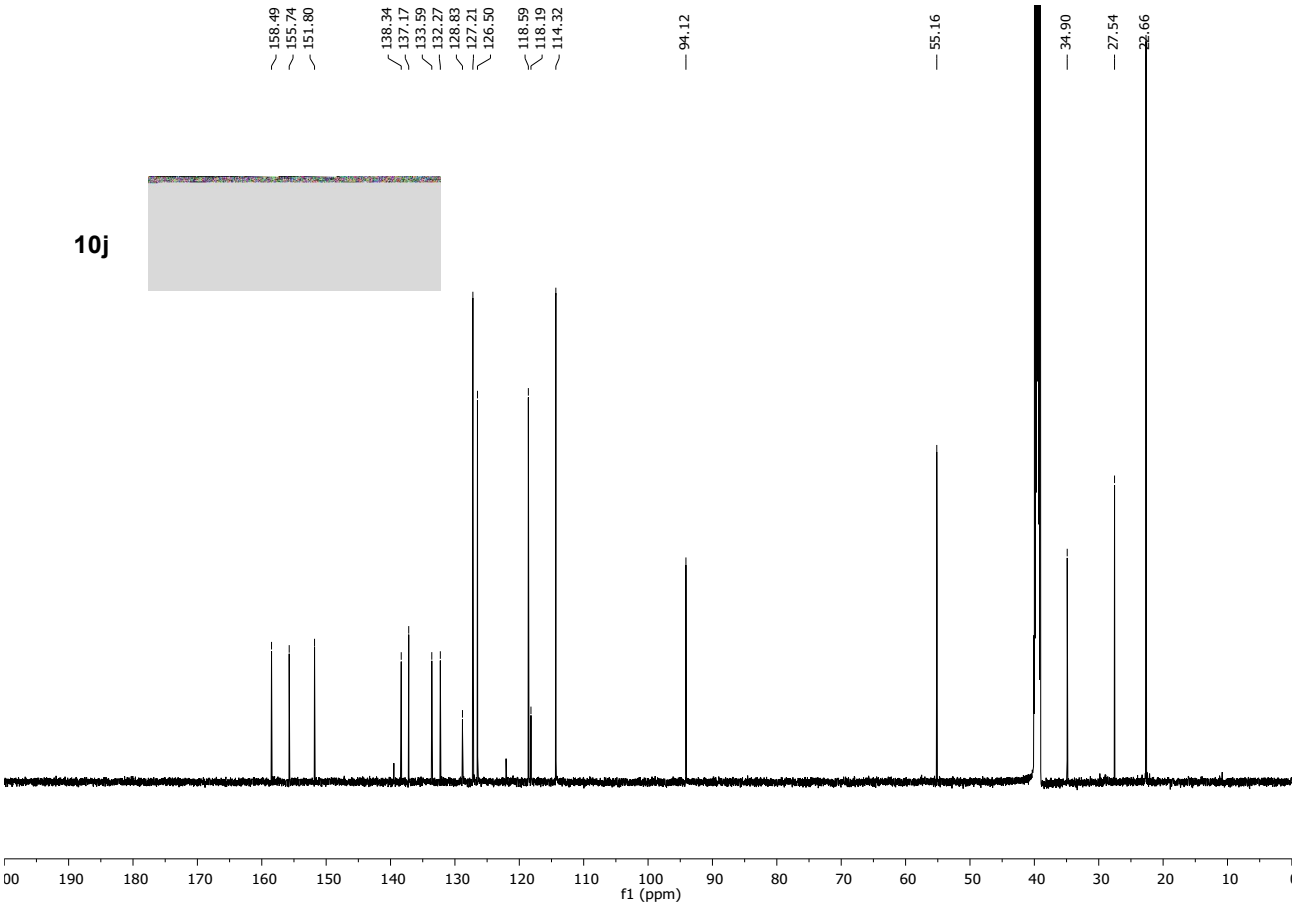
8.5108
7.5703
7.5558
7.5332
7.5123
7.0035
6.9889
6.0152
3.7840
3.5988
2.7927
2.7812
2.7697
1.1711
1.1596
10j
MeO
O
N
H
N
H
N
1.0
1.0
6.3
2.1
1.0
3.2
3.0
1.1
6.6
f1 (ppm)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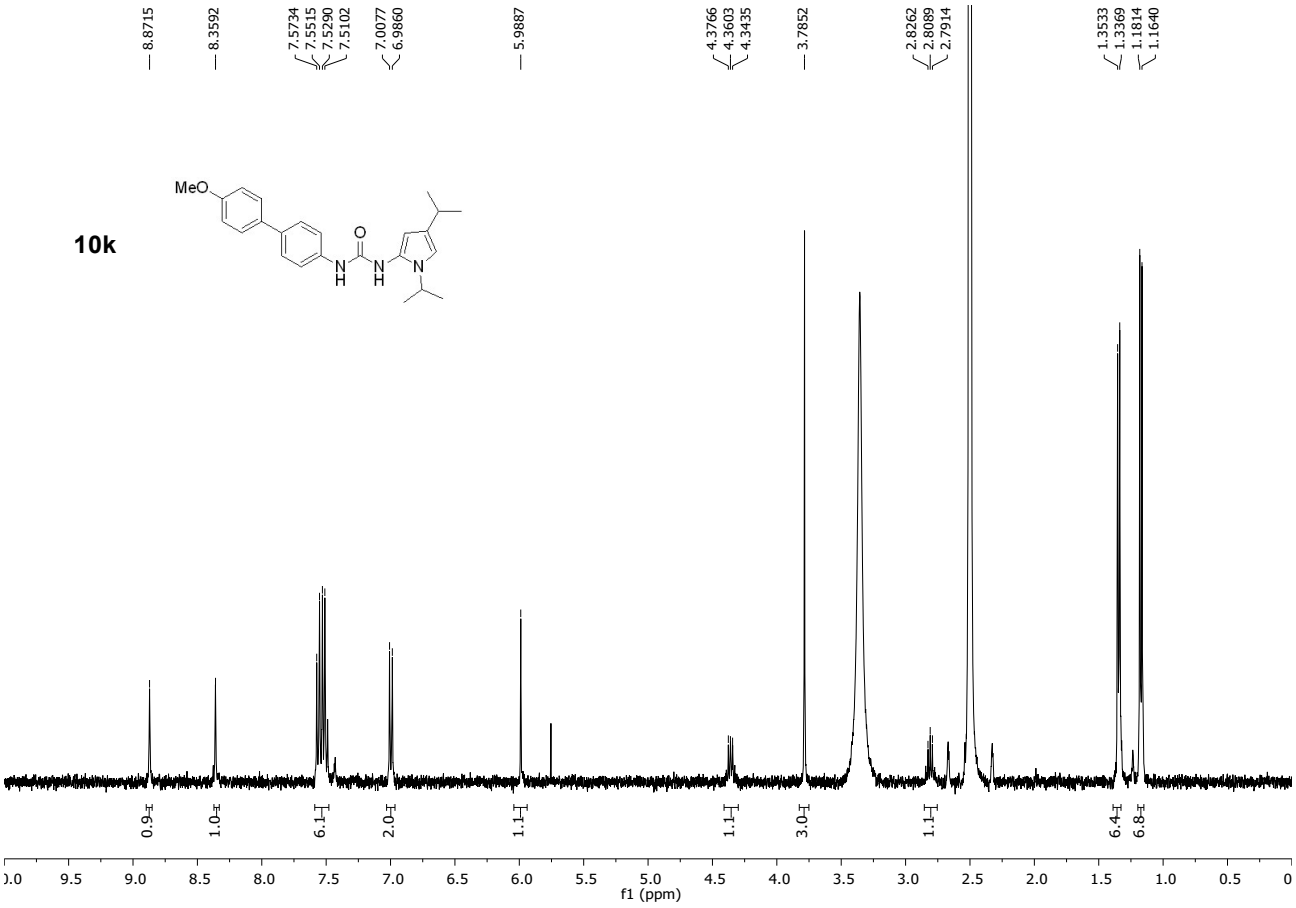
151.80
138.34
137.17
133.59
132.27
128.83
127.21
126.50
118.59
118.19
114.32
94.12
55.16
34.90
27.54
22.66
10j
f1 (ppm)


10k
MeO
O
N
H
N
H
N
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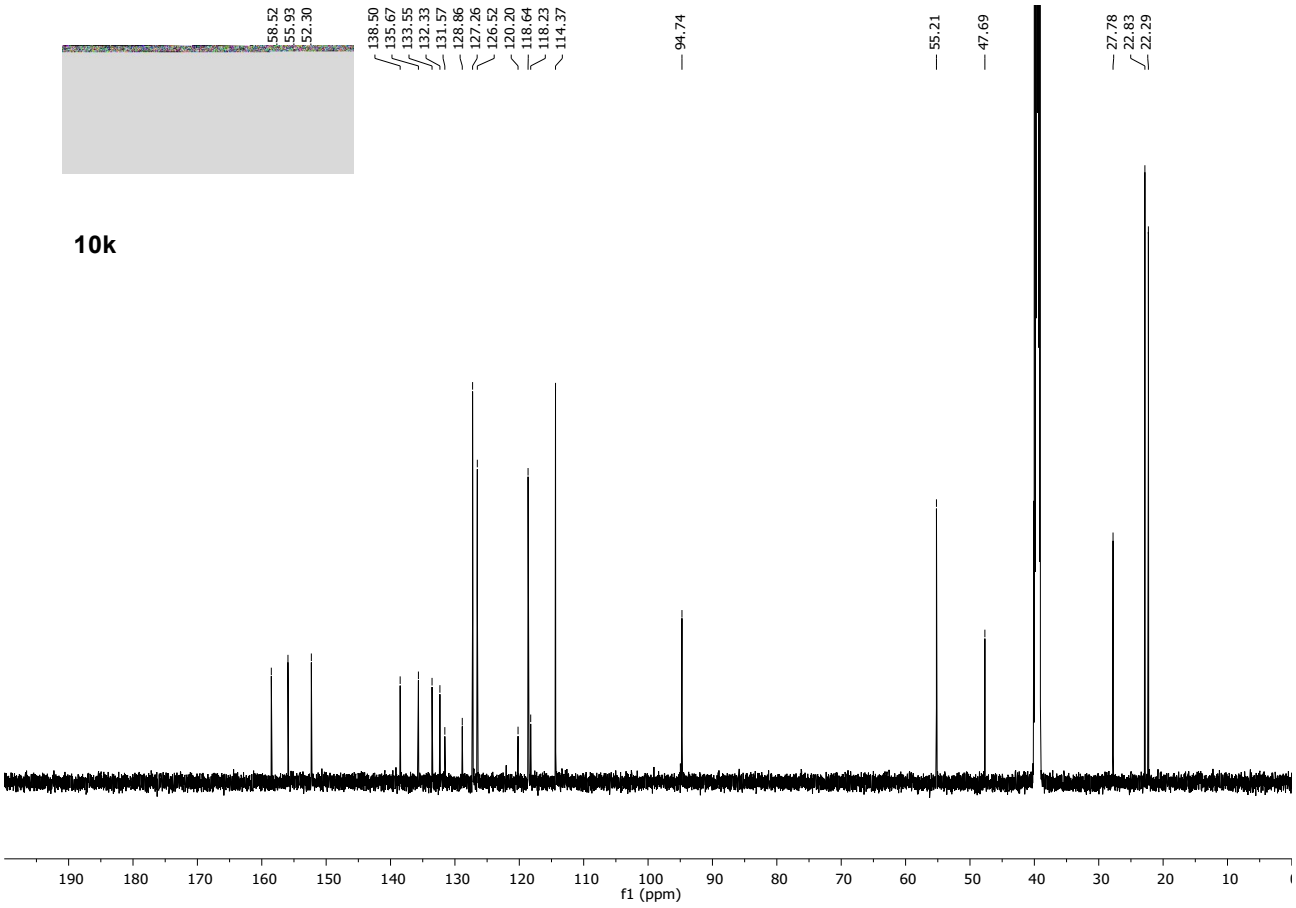
8.3592
7.5734
7.5515
7.5290
7.5102
7.0077
6.9860
5.9887
4.3766
4.3603
4.3435
3.7852
2.8262
2.8089
2.7914
1.3533
1.3369
1.1814
1.1640
0.9
1.0
6.1
2.0
1.1
1.1
3.0
1.1
6.4
6.8
f1 (ppm)


58.52
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132.33
131.57
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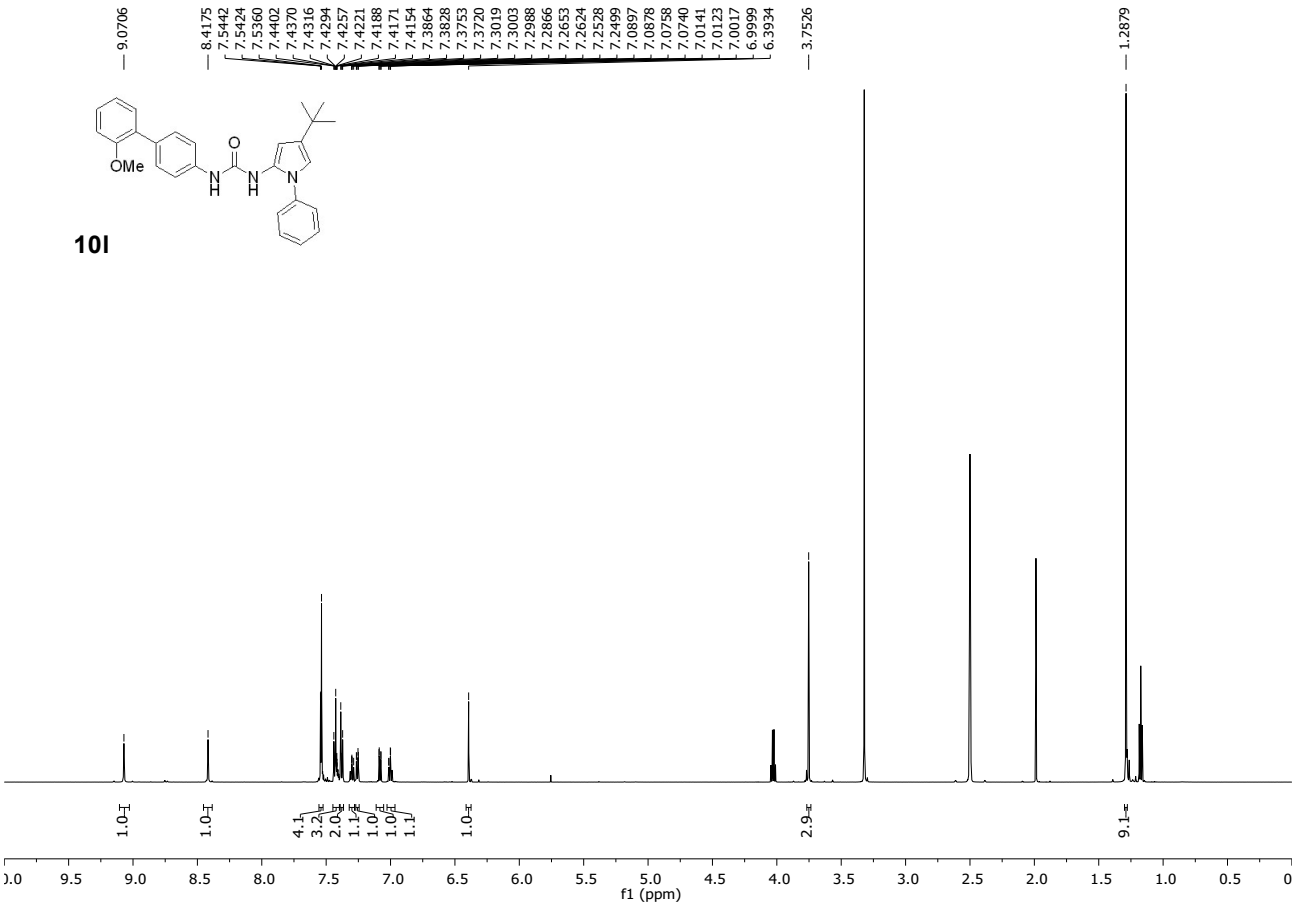
127.26
126.52
120.20
118.64
118.23
114.37
94.74
55.21
47.69
27.78
22.83
22.29
10k
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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7.4221
7.4188
7.4171
7.4154
7.3864
7.3828
7.3753
7.3720
7.3019
7.3003
7.2988
7.2866
7.2653
7.2624
7.2528
7.2499
7.0897
7.0878
7.0758
7.0740
7.0141
7.0123
7.0017
6.9999
6.3934
3.7526
1.2879
OMe
N
H
O
N
H
N
10l
1.0
1.0
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2.0
1.1
1.0
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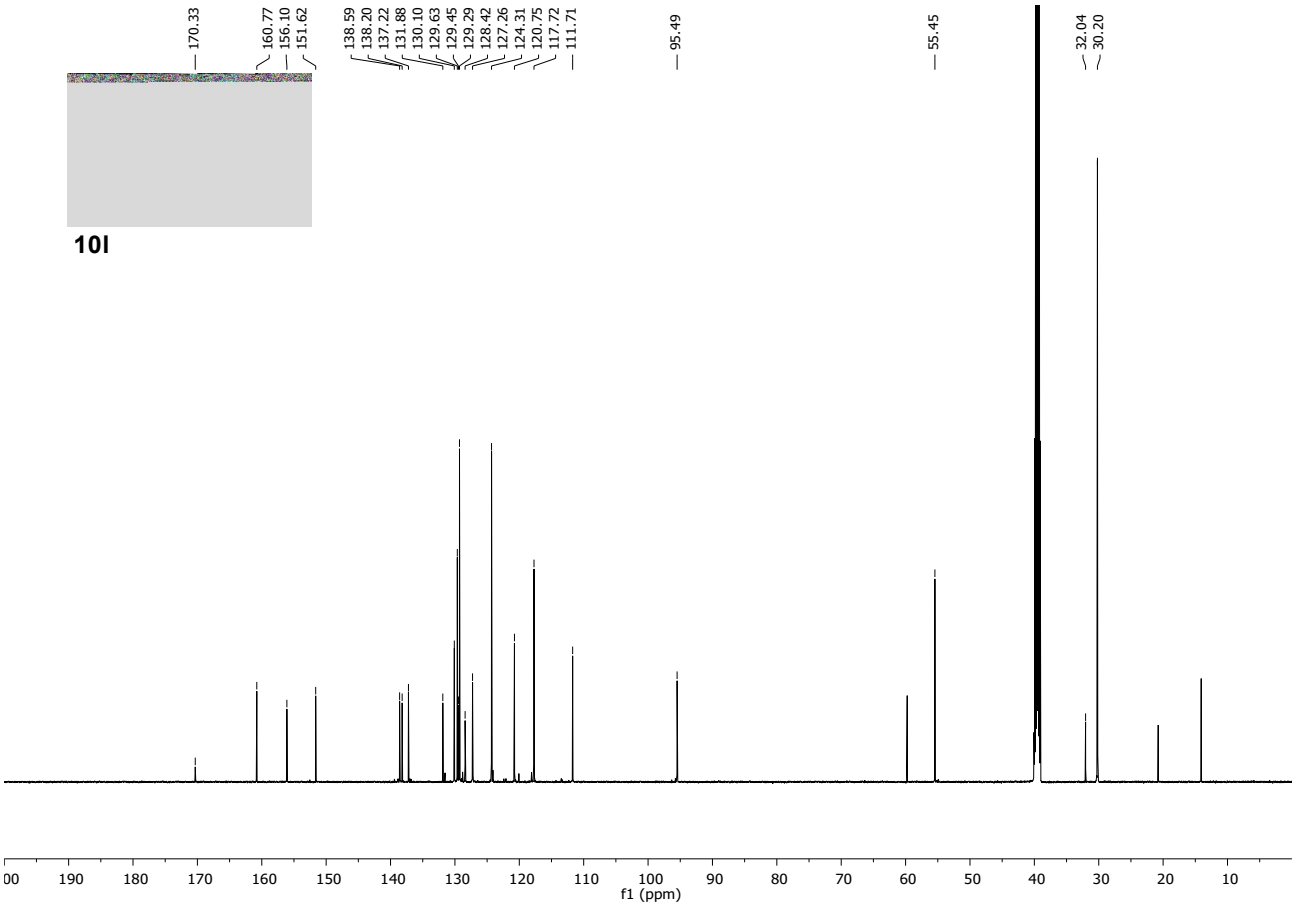
1.1
1.0
2.9
9.1
f1 (ppm)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138.20
137.22
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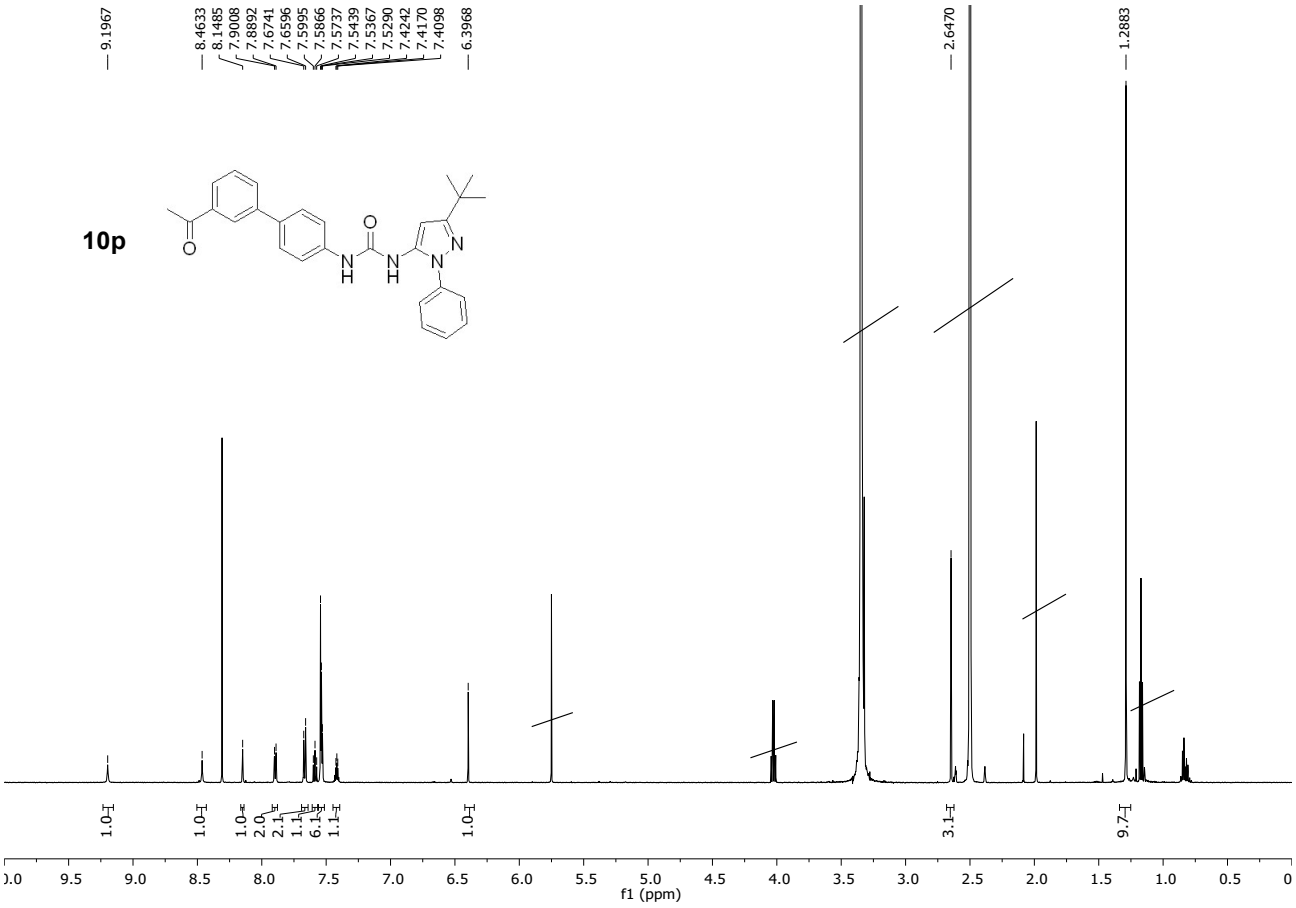
130.10
129.63
129.45
129.29
128.42
127.26
124.31
120.75
117.72
111.71
95.49
55.45
32.04
30.20
10l
f1 (ppm)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7.6741
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7.5995
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7.5737
7.5439
7.5367
7.5290
7.4242
7.4170
7.4098
6.3968
2.6470
1.2883
1.0
1.0
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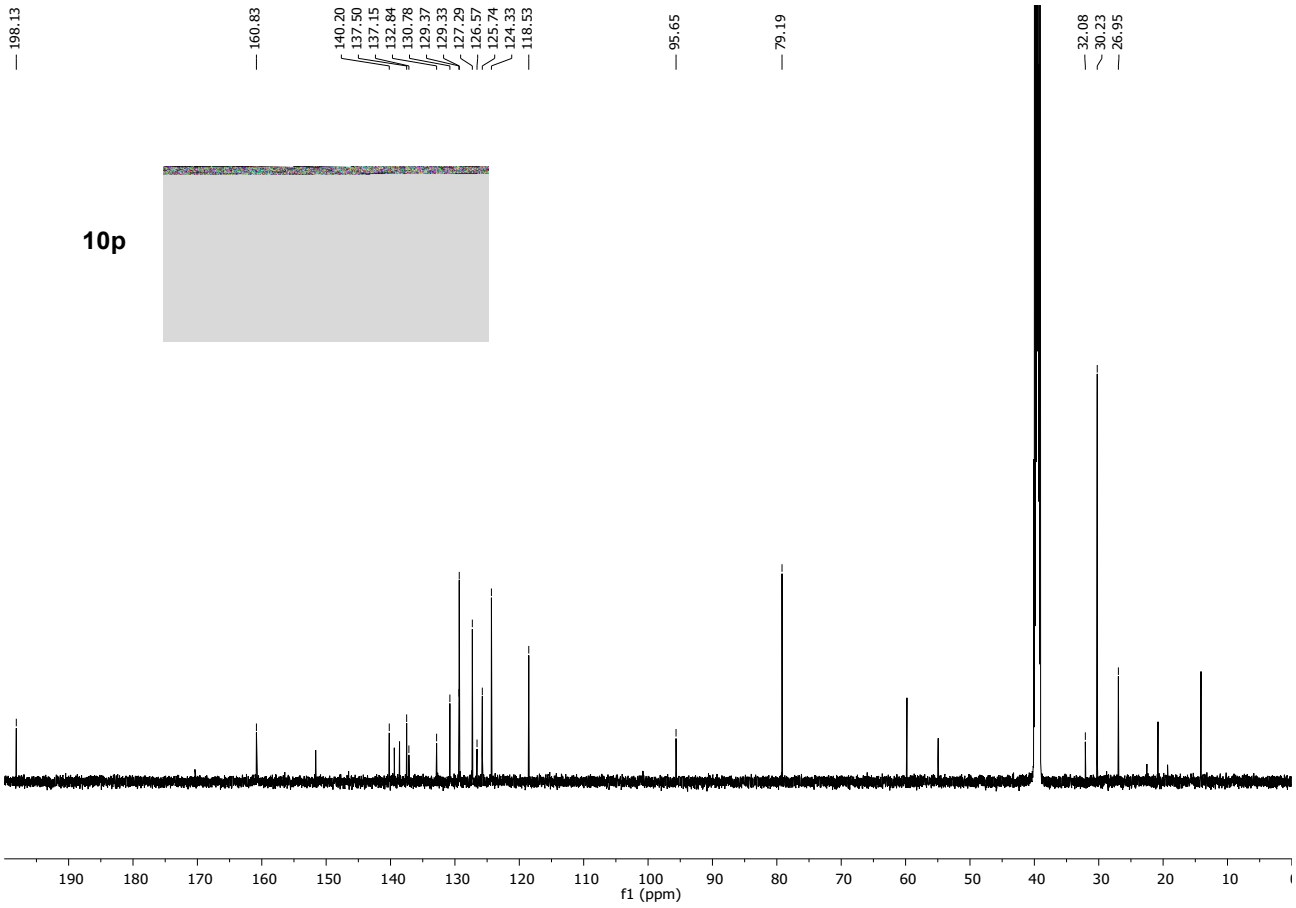
2.0
1.1
1.1
6.1
1.1
1.0
3.1
9.7
f1 (ppm)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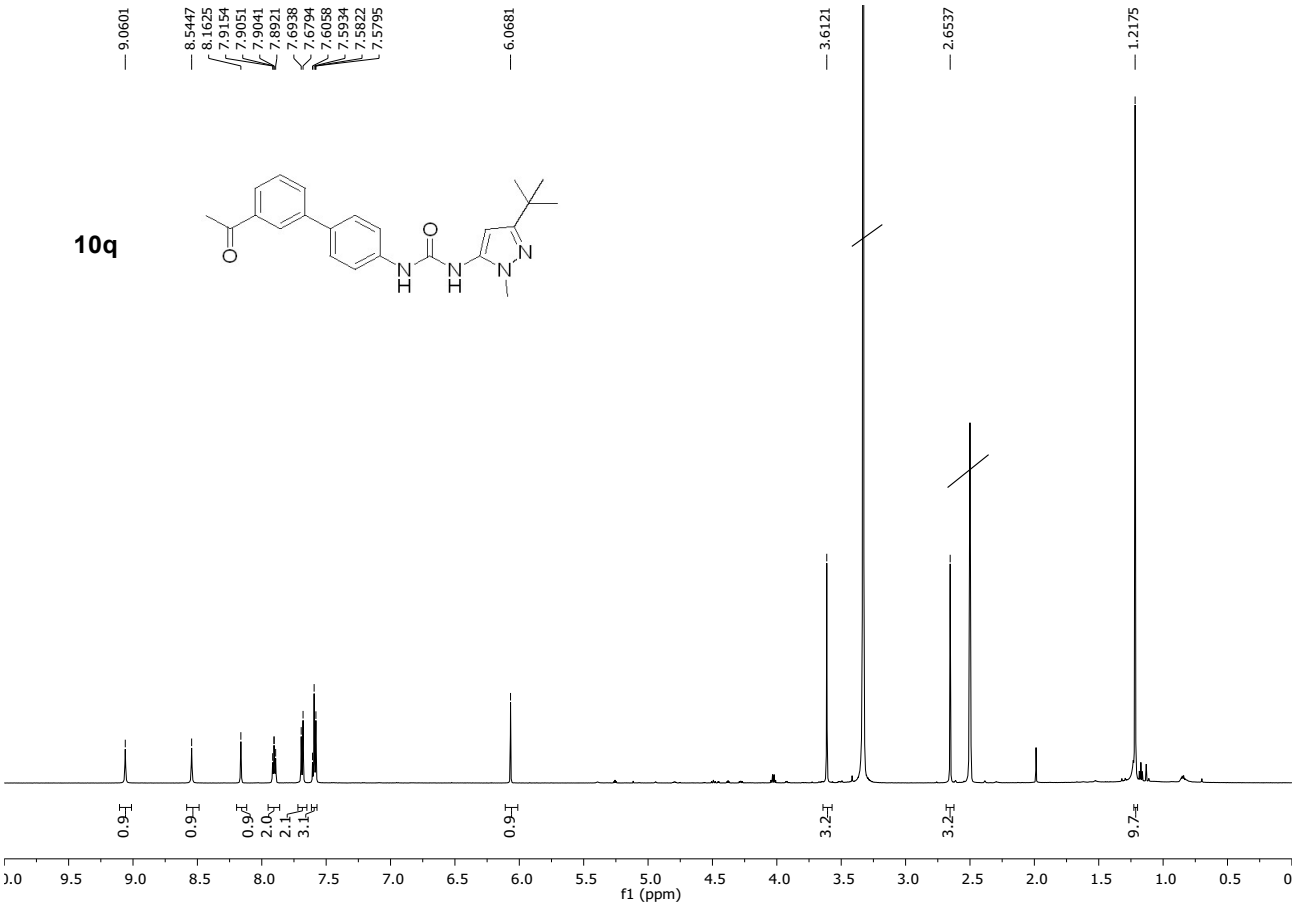
129.37
129.33
127.29
126.57
125.74
124.33
118.53
95.65
79.19
32.08
30.23
26.95
10p
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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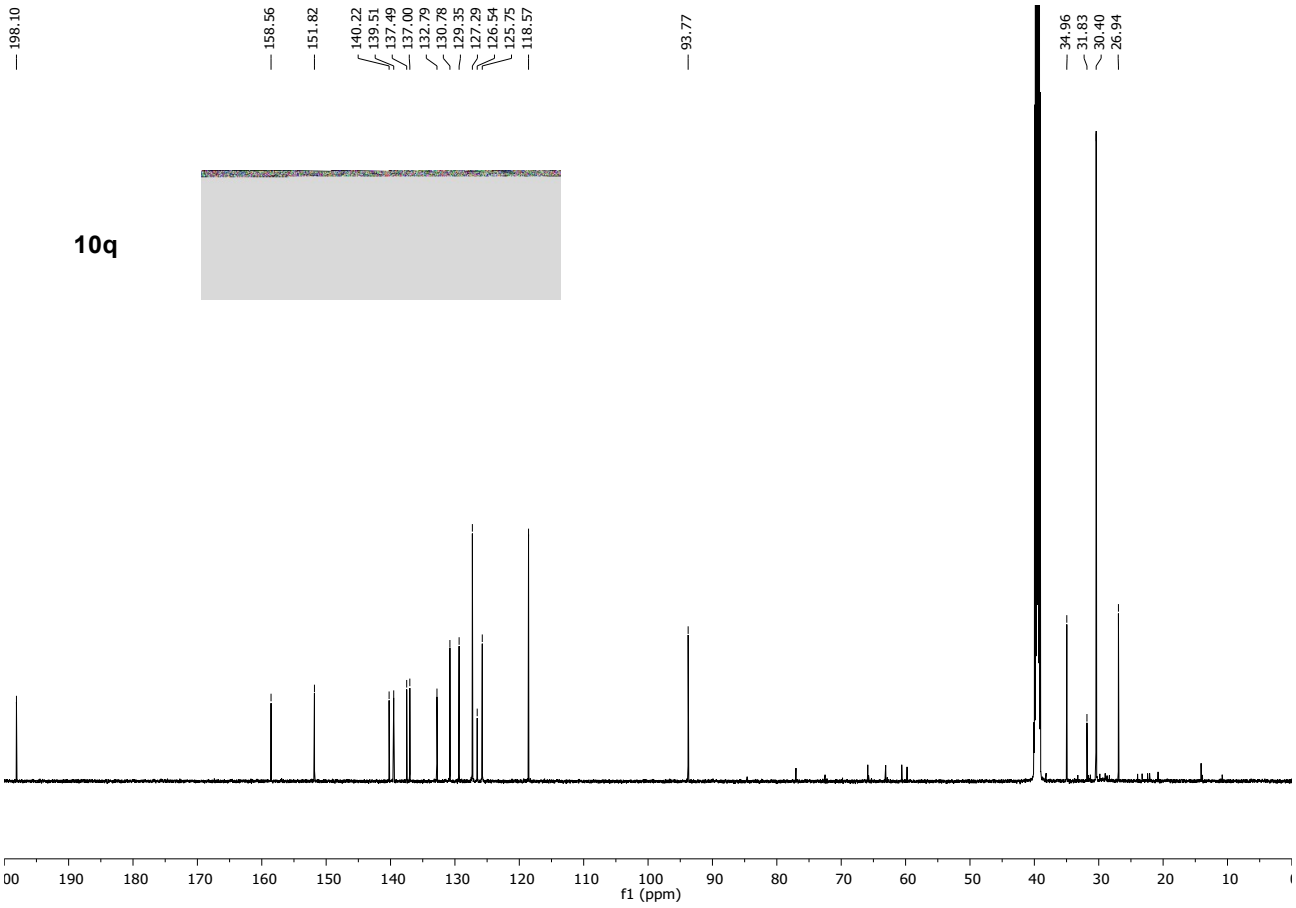
7.6938
7.6794
7.6058
7.5934
7.5822
7.5795
6.0681
3.6121
2.6537
1.2175
10q
0.9
0.9
0.9
2.0
2.1
3.1
0.9
3.2
3.2
9.7
f1 (ppm)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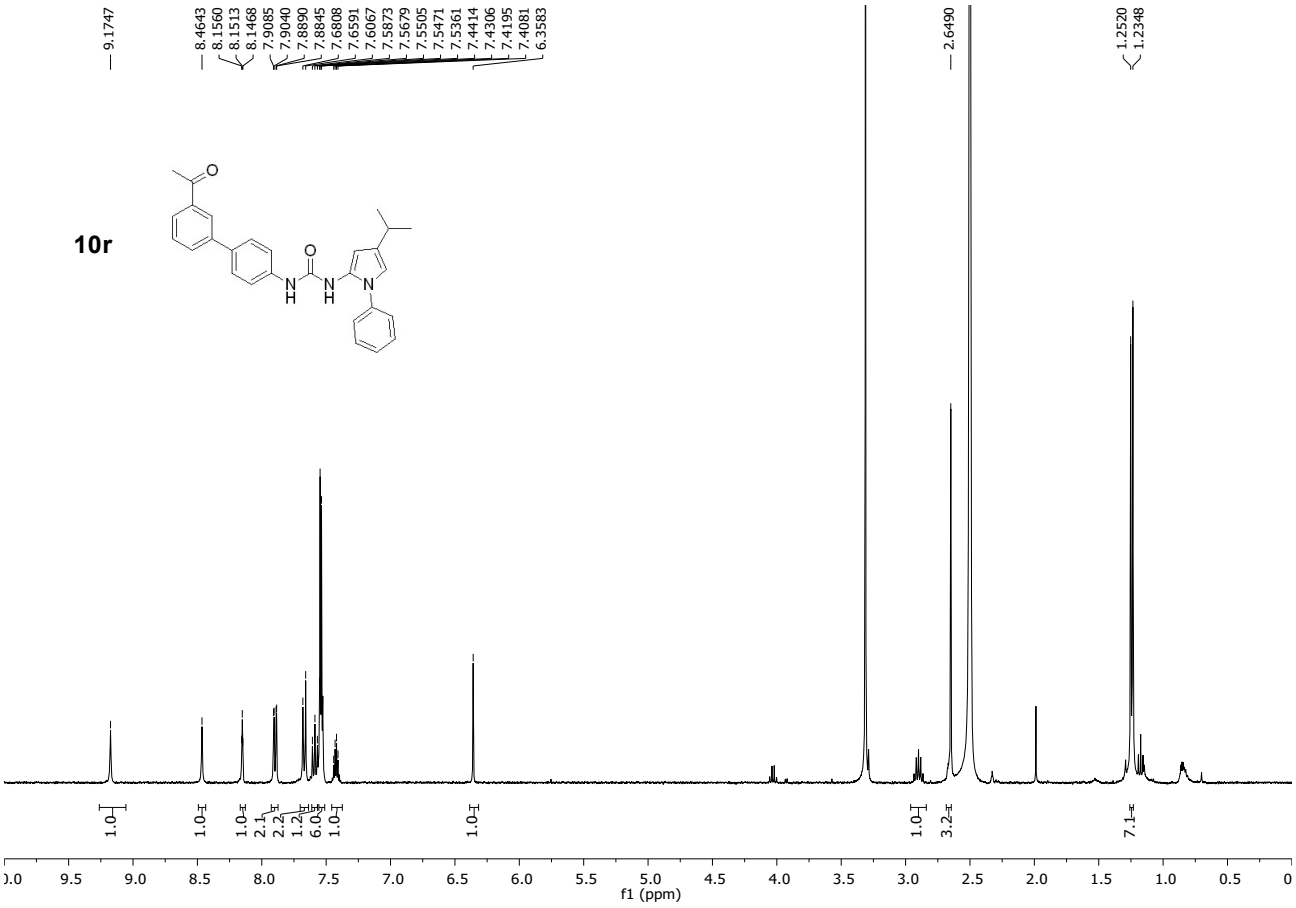
31.83
30.40
26.94
10q
f1 (ppm)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7.6067
7.5873
7.5679
7.5505
7.5471
7.5361
7.4414
7.4306
7.4195
7.4081
6.3583
2.6490
1.2520
1.2348
10r
O
O
N
H
N
H
N
1.0
1.0
1.0
2.1
2.2
1.2
6.0
1.0
1.0
1.0
3.2
7.1
9.5
9.0
8.5
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6.5
6.0
5.5
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
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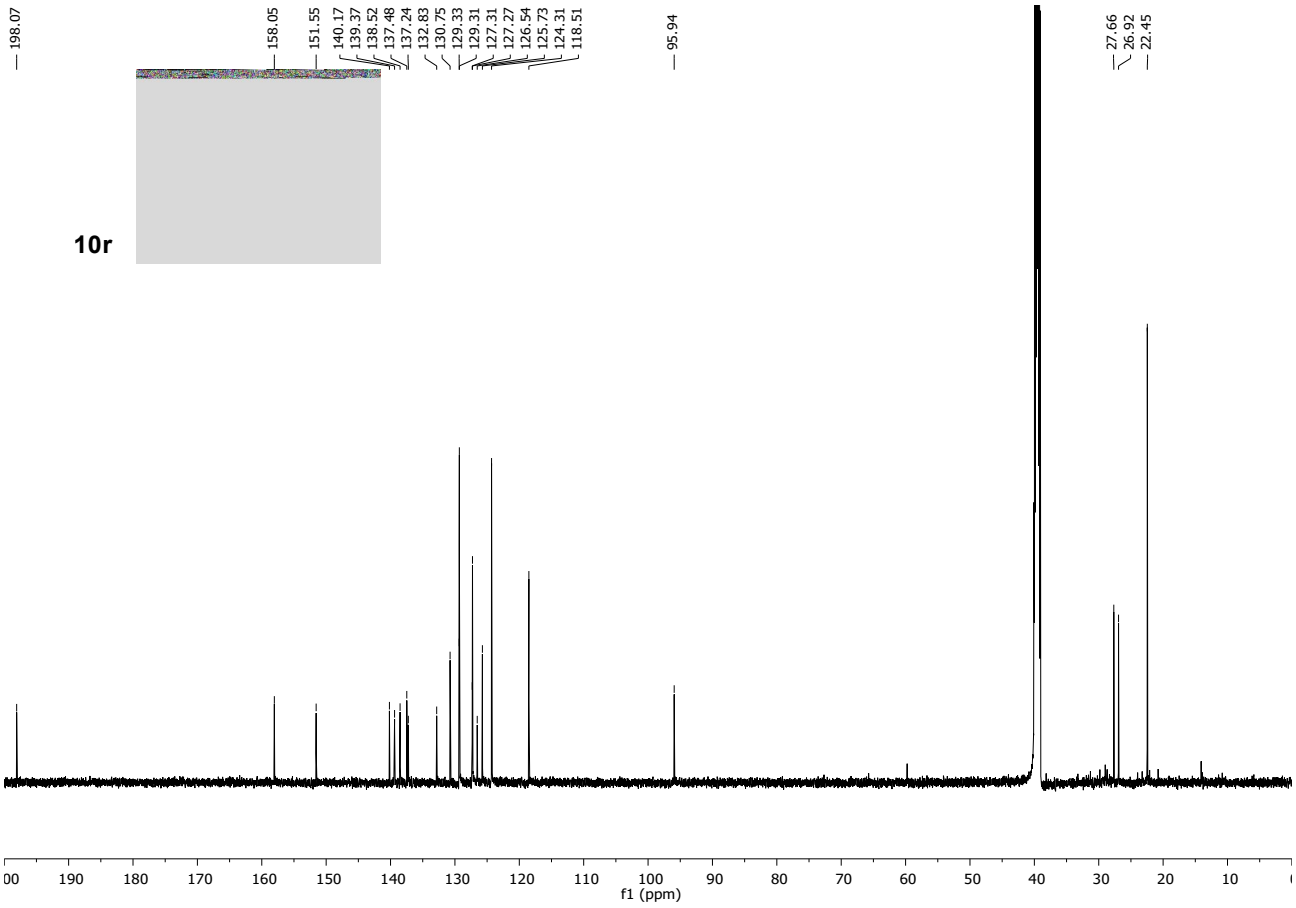
f1 (ppm)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137.24
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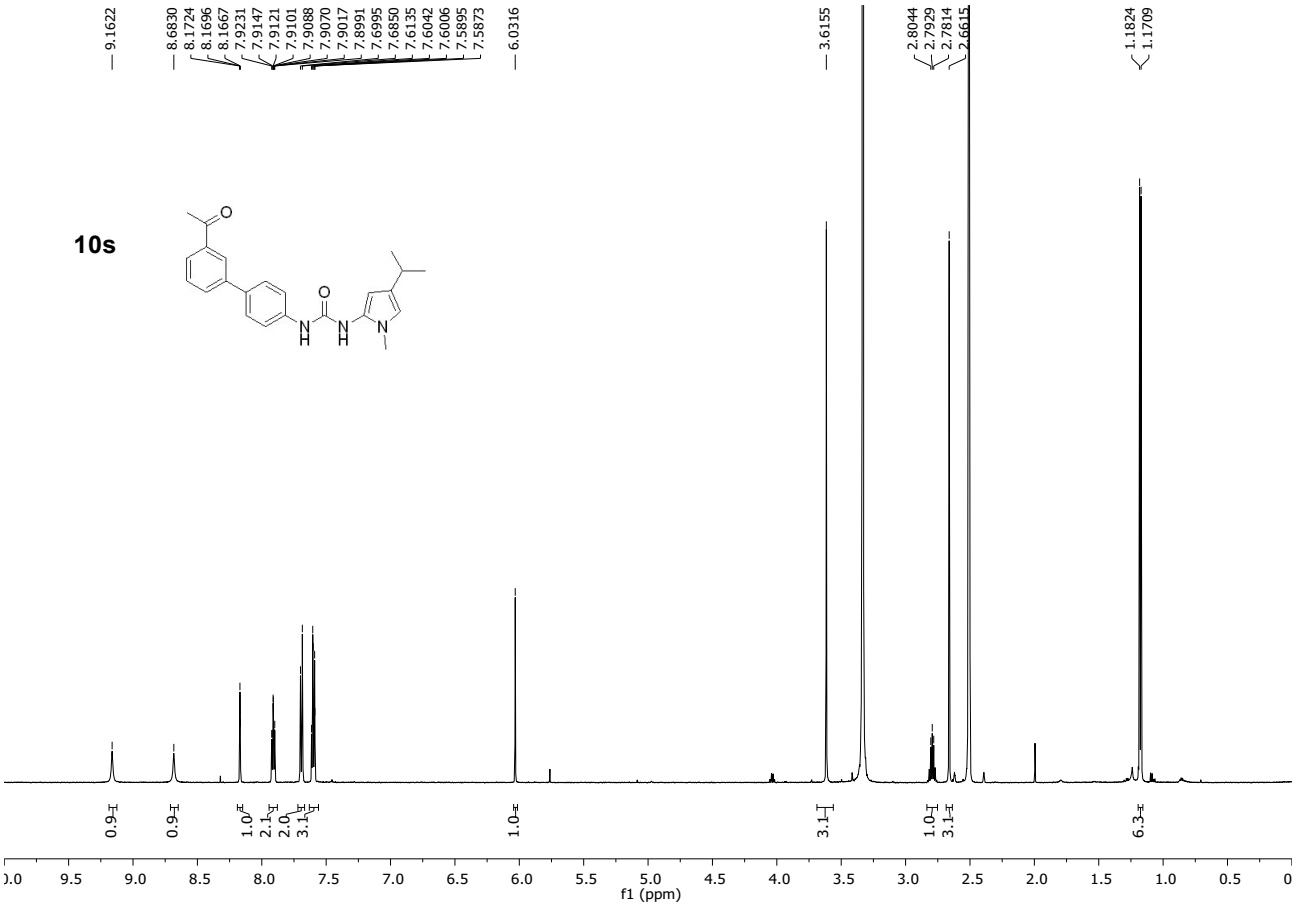
130.75
129.33
129.31
127.31
127.27
126.54
125.73
124.31
118.51
95.94
27.66
26.92
22.45
10r
f1 (ppm)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7.9070
7.9017
7.8991
7.6995
7.6850
7.6135
7.6042
7.6006
7.5895
7.5873
6.0316
3.6155
2.8044
2.7929
2.7814
2.6615
1.1824
1.1709
10s
0.9
0.9
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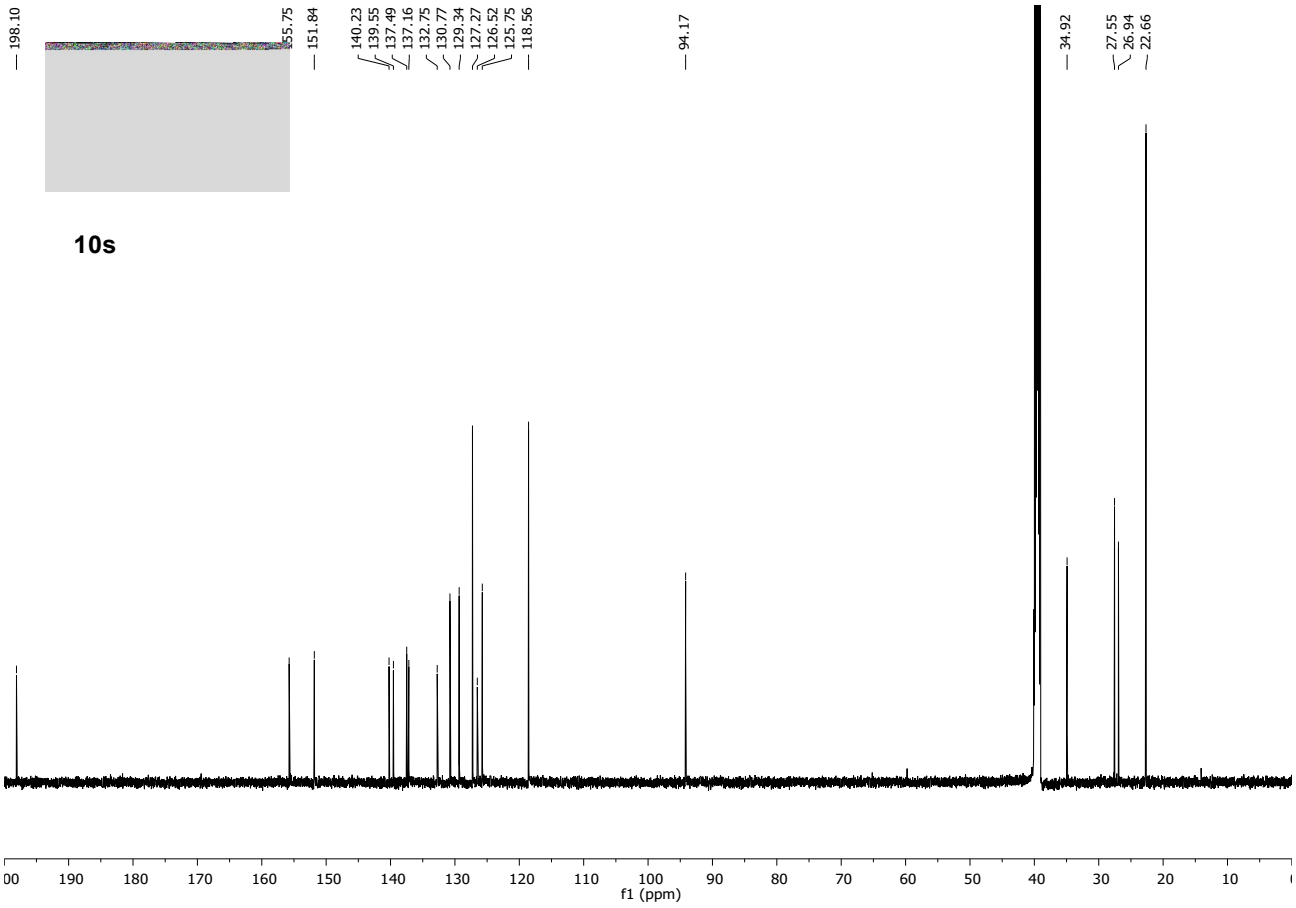
2.1
2.0
3.1
1.0
3.1
1.0
3.1
6.3
f1 (ppm)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127.27
126.52
125.75
118.56
94.17
34.92
27.55
26.94
22.66
10s
f1 (ppm)