**Supporting information for**

# Tri- and tetra-substituted pyrazole derivates: Regioisomerism switches activity from p38MAP kinase to important cancer kinases.

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**Contents of Supporting Information:**

**Computational Methods.** Crystal structures of B-Raf V600E (PDB: 3C4D, chain A), Src (PDB: 2BDF, chain A), and VEGFR-2 (PDB: 3B8R, chain A) were prepared for docking using Molecular Operating Environment (MOE). Hydrogens and protonation states were added using the Protonate3D procedure with default settings. The compounds were drawn in MOE and wash and minimization procedures were applied.

Docking was performed using GOLD v3.2 (CCDC).[1] Search efficiency was set to 200%. For all docking runs standard parameters were used. Water molecules were not included. The binding site was defined by the coordinates of the respective co-crystallized ligand. The GOLDScore fitness function was employed for all docking experiments. All docking poses were rescored using Chemscore.

**Biochemical Protein Kinase Assays.** A radiometric protein kinase assay ($^{33}$PanQinase® Activity Assay) was used for measuring the kinase activity of the protein kinases. All kinase assays were performed in 96-well FlashPlates™ (Perkin Elmer, Boston, MA, USA) in a 50 µl reaction volume. The assay for all enzymes contained 70 mM HEPES-NaOH, pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 µM Na-orthovanadate, 1.2 mM DTT, 1 µM ATP/[$\gamma$-$^{33}$P]-ATP (approx. 5 x $10^{05}$ cpm per well). The following amounts of enzyme and substrate were used per well: B-RAF wt/MEK1-KM(kinase-dead): 25 ng/500 ng; B-RAF V600E/MEK1-KM(kinase-dead): 20 ng/500 ng; EGF-R wt/poly(Glu,Tyr)$_{4:1}$: 10 ng/125 ng; EGF-R L858R/ poly(Glu,Tyr)$_{4:1}$: 5ng/250 ng; EGF-R T790M: 10 ng/125 ng: EGF-R L858R/T790M: 25 ng/125ng; SRC/poly(Glu,Tyr)$_{4:1}$:10 ng/125 ng; VEGF-R2/poly(Glu,Tyr)$_{4:1}$: 25 ng/ 125 ng. The reaction cocktails were incubated at 30° C for 60 minutes. The reactions were stopped with 50 µl of 2 % (v/v) $H_3PO_4$, plates were aspirated and washed two times with 200 µl 0.9 % (w/v) NaCl. Incorporation of $^{33}P_i$ was determined with a microplate scintillation counter (Microbeta, PerkinElmer, Boston, MA, USA). The residual kinase activities for each compound concentration and the compound $IC_{50}$ values were calculated using Quattro Workflow V3.1.0 (Quattro Research GmbH, Munich, Germany; www.quattro-research.com). The fitting model for the $IC_{50}$ determinations was "Sigmoidal response (variable slope)" with parameters "top" fixed at 100 % and "bottom" at 0 %. The fitting method used was a least-squares fit.

**General.** All commercially available reagents and solvents were used without further purification. Flash chromatography was performed using a LaFlash system (VWR) with Merck Silica gel (PharmPrep® 60 CC 25-40 µm). Melting points were determined with Büchi melting point B-545 apparatus and are thermodynamically corrected. NMR data were recorded on a Bruker Spectrospin AC200 or on a Bruker Avance 400 at room temperature. Chemical shifts are reported in ppm relative to the solvent resonance. IR-data were determined on a Perkin-Elmer Spectrum One spectrometer (ATR Technique). Low and

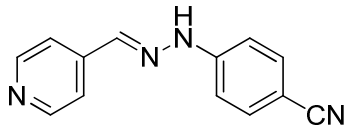
high resolution mass spectra data were obtained on a Thermo Finnigan TSQ70 instrument. The purity of the final compounds was determined by HPLC on a HPLC Hewlett-Packard HP 1090 Series II liquid chromatograph equipped with a UV diode array detector was used. The chromatographic separation was performed on a Betasil C8 column (150 x 4.6 mm I:D:, dp = 5 µm, Thermo Fisher Scientific, Waltham, MA, USA) at 35 °C oven temperature. The injection volume was 5 µL. HPLC Gradient (Flow: 1.5 mL/min): 0.01 M $KH_2PO_4$, pH 2.3 (Solvent A), Methanol (Solvent B): 40 % B to 85 % B in 8 min, 85 % B for 5 min, 85 % B to 40 % B in 1 min, 40 % B for 2 min, stop time 16 min. All tested compounds have a purity of >95%.

For preparation and analytical data of following compounds, see: 4-{[(2,4,6-trichlorophenyl)hydrazono]methyl}pyridine (**3a**),[2] 4-[(phenylhydrazono)methyl]pyridine (**3b**),[3] 4-{[(4-chlorophenyl)hydrazono]methyl}pyridine (**3c**),[3] 4-{[(4-methoxyphenyl)hydrazono]methyl}pyridine (**3d**),[4] 4-{[(4-nitrophenyl)hydrazono]methyl}pyridine (**3e**),[5] 4-[(*p*-tolylhydrazono)methyl]pyridine (**3f**),[4] *N*-(4-nitrophenyl)pyridine-4-carbohydrazonoyl chloride (**4e**).[6]

**General procedure for synthesis of hydrazones (3a-h):**

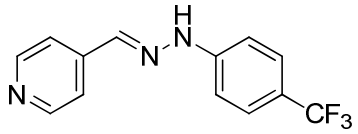
0.1 mol of isonicotinic aldehyde was added to a solution of 0.1 mol of the appropriate hydrazine or hydrazinum salt (hydrazinium salts were prior treated with an equivalent amount of $Et_3N$ to obtain free hydrazine) in ethanol (200 mL). The reaction mixture was heated to reflux until the reaction was finished (by TLC). The reaction was allowed to cool to room temperature and a pale yellow solid precipitated which was collected by filtration and recrystallized from hot ethanol.

**4-[2-(Pyridin-4-ylmethylene)hydrazine]benzonitrile (3g)**



Yield: 80%; mp. 245 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.23 (d, $J$ = 9 Hz, 2H), 7.64-7.68 (m, 4H), 7.93 (s, 1H, N=CH), 8.57 (d, $J$ = 6 Hz, 2H), 11.39 (s, 1H, NH); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 101.0, 113.1, 120.2, 120.7, 134.1, 137.3, 143.2, 148.4, 149.9; IR (ATR) 3220, 2989, 2938, 2810, 2212 (CN), 1604, 1578, 1542, 1501 (aromatic rings), 1417, 1361, 1278, 996, 907, 829, 813 cm$^{-1}$; MS-FAB: m/z = 223 $[M+H]^+$.

**4-{[(4-Trifluorophenyl)hydrazono]methyl}pyridine (3h)**

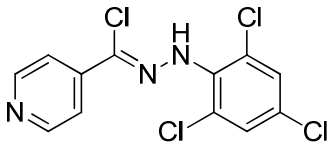


Yield: 73%; mp. 239 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.25 (d, $J$ = 8 Hz, 2H), 7.53-7.63 (m, 4H), 7.89 (s, 1H, N=CH), 8.56 (dd, $J_1$ = 6 Hz, $J_2$ = 1 Hz, 2H), 11.15 (s, 1H, NH); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 112.6, 120.4, 122.6, 126.8, 126.9, 136.4, 142.8, 148.0, 150.3; IR (ATR) 3229, 3184, 2997, 2947, 1617, 1602, 1578, 1555, 1541, 1510 (aromatic rings), 1420, 1325, 1277, 1158, 1101, 1061, 995, 900, 835 cm$^{-1}$; MS-FAB: m/z = 266 $[M+H]^+$.

**Genral procedure for synthesis of hydrazonyl chlorides (4a-h):**

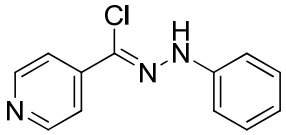
10 mmol of the appropriate hydrazone **3a**-**h** was dissolved in a minimum amount of dry DMF (20 mL) and 11 mmol of *N*-chlorosuccinimide (NCS) was added portionwise to the reaction mixture. The reaction became hot and then the product precipitated suddenly. The solid was collected by filtration and washed with petroleum ether.

***N*-(2,4,6-trichlorophenyl)pyridine-4-carbohydrazonoyl chloride (4a)**



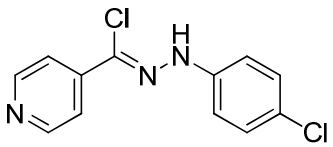
Yield: 62%; mp. 215 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 7.74-7.81 (m, 4H), 8.66 (d, $J$ = 6 Hz, 2H), 9.60 (s, 1H, NH); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 120.1, 128.6, 128.8, 129.4, 136.3, 136.9, 142.9, 150.4; IR (ATR) 3298, 3046, 1632, 1551, 1509, 1487 (aromatic rings), 971, 858, 815 cm$^{-1}$; MS-FAB: m/z = 336 $[M+H]^+$.

***N*-phenylpyridine-4-carbohydrazonoyl chloride (4b)**



Yield: 50%; mp. 106 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 6.92 (t, $J$ = 7 Hz, 1H), 7. 42-7.25 (m, 4H), 7.78 (d, $J$ = 6 Hz, 2H), 8.63 (d, $J$ = 6 Hz, 2H), 10.25 (s, 1H, NH); IR (ATR) 3182, 3057, 1602, 1562, 1541, 1520, 1495 (aromatic rings), 954, 822 cm$^{-1}$; MS-FAB: m/z = 232 $[M+H]^+$.

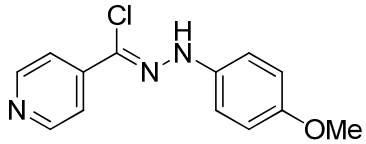
***N*-(4-chlorophenyl)pyridine-4-carbohydrazonoyl chloride (4c)**



Yield: 31%; mp. 263 °C (decomp.); $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.38 (d, $J$ = 9 Hz, 2H), 7.54 (d, $J$ = 9 Hz, 2H), 8.26 (d, $J$ = 7 Hz, 2H), 8.83 (d, $J$ = 7 Hz, 2H), 11.01 (s, 1H, NH); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 116.8, 118.9, 122.0, 126.6, 129.5, 142.1, 143.2, 148.4; IR (ATR) 3137, 3079, 3046, 2974,

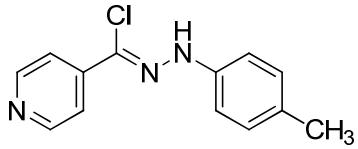
1636, 1605, 1600, 1533, 1483 (aromatic rings), 1402, 1374, 1237, 1202, 1162, 1086, 957, 833, 818 $cm^{-1}$; MS-FAB: m/z = 266 $[M+H]^+$.

**_N_-(4-methoxyphenyl)pyridine-4-carbohydrazonoyl chloride (4d)**



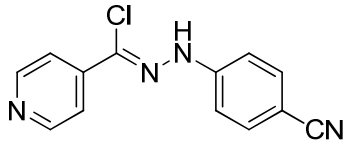

Yield: 52%; mp. 250 °C (decomp.); $^1$H NMR (400 MHz, DMSO-$d_6$) δ 3.73 (s, 3H), 6.94 (d, $J$ = 9 Hz, 2H), 7.47 (d, $J$ = 9 Hz, 2H), 8.20 (d, $J$ = 7 Hz, 2H), 8.78 (d, $J$ = 7 Hz, 2H), 10.87 (s, 1H, NH); $^{13}$C NMR δ (50 MHz, DMSO-$d_6$) 55.7, 115.0, 116.6, 116.7, 121.5, 136.7, 142.6, 149.0, 155.7; IR (ATR) 3152, 2975, 1711, 1635, 1598, 1534, 1488 (aromatic rings), 1233, 955, 850, 822, 805 $cm^{-1}$; MS-FAB: m/z = 262 $[M+H]^+$.

**_N_-(_p_-tolyl)pyridine-4-carbohydrazonoyl chloride (4f)**



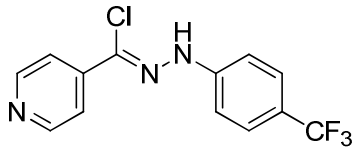

Yield: 80%; mp. 116 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 2.24 (s, 3H), 7.09 (d, $J$ = 8 Hz, 2H), 7.30 (d, $J$ = 8 Hz, 2H), 7.77 (d, $J$ = 6 Hz, 2H), 8.61 (d, $J$ = 6 Hz, 2H), 10.17 (s, 1H, NH); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 20.7, 114.4, 119.9, 124.0, 130.0, 130.5, 141.6, 150.4; IR (ATR) 3309, 3032, 2917, 1613, 1595, 1566, 1543, 1509 (aromatic rings), 1409, 1317, 1239, 1208, 1136, 996, 949, 816 $cm^{-1}$; MS-FAB: m/z = 246 $[M+H]^+$.

**_N_-(4-cyanophenyl)pyridine-4-carbohydrazonoyl chloride (4g)**




Yield: 64%; mp. 198 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.56 (d, $J$ = 8 Hz, 2H), 7.74 (d, $J$ = 9 Hz, 2H), 7.95 (d, $J$ = 6 Hz, 2H), 8.71 (d, $J$ = 6 Hz, 2H), 10.88 (s, 1H, NH); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 103.1, 114.9, 120.9, 122.8, 134.0, 143.0, 147.4, 149.0, 151.5; IR (ATR) 3236, 3068, 2219 (CN), 1645, 1606, 1542, 1519, 1487 (aromatic rings), 1451, 1236, 1164, 959, 833, 820 $cm^{-1}$; MS-FAB: m/z = 257 $[M+H]^+$.

***N*-(4-trifluoromethylphenyl)pyridine-4-carbohydrazonoyl chloride (4h)**

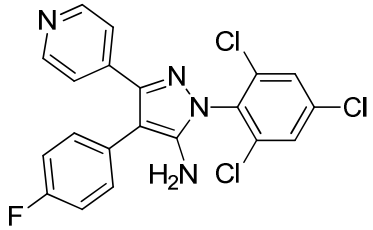


Yield: 74%; mp. 140 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.52-7.66 (m, 4H), 7.83 (d, $J$ = 5 Hz, 2H), 8.66 (d, $J$ = 5 Hz, 2H), 10.65 (s, 1H, NH); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 114.4, 120.3, 121.2, 122.3, 126.8, 126.9, 141.7, 147.1, 150.4; IR (ATR) 3310, 3080, 2911, 1615, 1570, 1528, 1492 (aromatic rings), 1413, 1318, 1061, 999, 953, 831, 818 cm$^{-1}$; MS-FAB: m/z = 300 $[M+H]^+$.

**General procedure for synthesis amino pyrazole derivatives (6a-h); Method A**

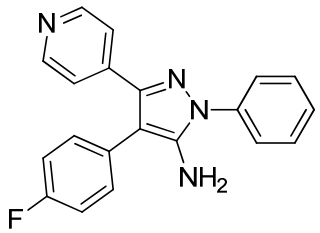
20 mmol of LDA was added to dry THF (30 mL) in a three neck flask and cooled to -78 °C. 14 mmol of 4-fluorophenyl acetonitrile (**5**) dissolved in THF (10 mL) was added dropwise and the reaction mixture was stirred for 45 min. 5 mmol of the appropriate hydrazonyl chloride **4a-h** (neat or dissolved in THF) was added slowly to the reaction. After about 1.0 h the reaction was finished and warmed to room temperature. Water (50 mL) followed by ethyl acetate (50 mL) was added to the reaction mixture and organic phase was separated. The aqueous phase was extracted with ethyl acetate (50 mL) and the combined organic layer was dried over $Na_2SO_4$. The solvent was removed under reduced pressure to about 5 mL, left overnight and the product precipitated from the solution. The respective product was filtered off, washed with diethyl ether and/or petroleum ether and dried. In case the product did not precipitate, the residue was purified by flash chromatography (petroleum ether/ ethyl acetate) to yield a pure solid.

**4-(4-Fluorophenyl)-3-(pyridin-4-yl)-1-(2,4,6-trichlorophenyl)-1*H*-pyrazol-5-amine (6a)**



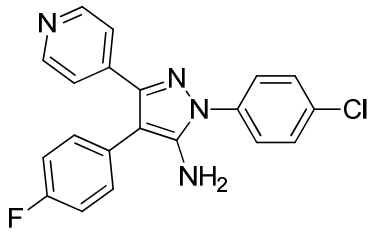
Yield: 35%; pale brown solid; mp. 215 °C; $^{1}$H NMR (200 MHz, DMSO-$d_6$) δ 5.53 (s, br, 2H, $NH_2$), 7.12-7.67 (m, 6H), 7.93 (s, 2H), 8.45 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 99.7, 116.1, 122.0, 129.2, 129.3, 132.0, 133.1, 135.9, 136.2, 141.2, 147.2, 147.5, 149.7, 161.5; IR (ATR) 3451, 3293, 3164 ($NH_2$), 1639 (C=N), 1604, 1573, 1552, 1519 (aromatic rings), 1466, 1212, 972,833 cm$^{-1}$; EI-HRMS: calcd. for $C_{20}H_{12}Cl_3FN_4$ 434.0112, obsd. 434.0058.

**4-(4-Fluorophenyl)-1-phenyl-3-(pyridin-4-yl)-1*H*-pyrazol-5-amine (6b)**



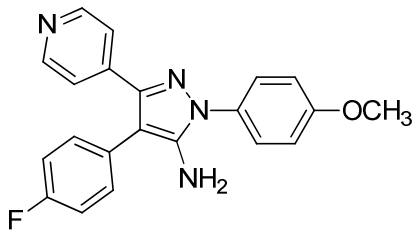
Yield: 30%; pale brown solid; mp. 244 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 5.22 (s, br, 2H, $NH_2$), 7.18-7.58 (m, 9H), 7.69 (d, $J$ = 6 Hz, 2H), 8.45 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 103.0, 116.1, 121.9, 124.0, 129.1, 129.2, 129.7, 132.3, 139.0, 141.3, 145.6, 146.5, 150.0, 161.5); IR (ATR) 3450, 3290, 3128 ($NH_2$), 1638 (C=N), 1596, 1570, 1547, 1514 (aromatic rings), 1487, 1454, 1388, 1218, 853, 763 cm$^{-1}$; EI-HRMS: calcd. for $C_{20}H_{15}FN_4$ 330.1281, obsd. 330.1296.

**1-(4-Chlorophenyl)-4-(4-fluorophenyl)-3-(pyridin-4-yl)-1*H*-pyrazol-5-amine (6c)**



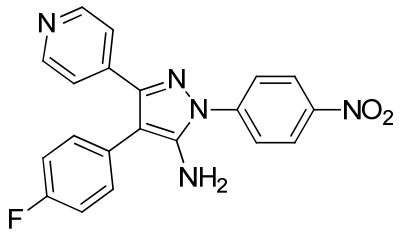
Yield: 40%; a pale yellow solid; mp. 209 °C; $^1$H NMR (200 MHz, DMSO-$d_6$): δ 5.33 (s, br, 2H, $NH_2$), 7.22-7.31 (m, 6H), 7.60 (d, $J$ = 7 Hz, 2H), 7.73 (d, $J$ = 7 Hz, 2H), 8.45 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 103.2, 116.0, 122.0, 125.6, 129.0, 129.6, 131.7, 132.3, 137.9, 141.1, 145.8, 146.4, 150.0, 161.4; IR (ATR) 3450, 3290, 3150 ($NH_2$), 1642 (C=N), 1604, 1573, 1549, 1514 (aromatic rings), 1484, 1216, 1088, 830, 675 cm$^{-1}$; MS: m/z (%) = 364/366 (100%) ($M^+$), 327, 224, 164, 43; EI-HRMS: calcd. for $C_{20}H_{14}ClFN_4$ 364.0891, obsd. 364.0913.

**4-(4-Fluorophenyl)-1-(4-methoxyphenyl)-3-(pyridin-4-yl)-1*H*-pyrazol-5-amine (6d)**



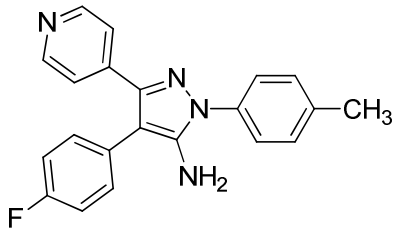
Yield: 60%; pale brown solid; mp. 200 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 3.82 (s, 3H), 5.10 (s, br, 2H, $NH_2$), 7.07-7.31 (m, 8H), 7.58 (d, $J$ = 9 Hz, 2H), 8.45 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 55.8 ($OCH_3$), 102.5, 114.8, 116.0, 121.9, 126.0, 129.4, 131.9, 132.2, 141.4, 145.4, 145.5, 149.9, 158.7, 161.5; IR (ATR) 3450, 3290, 3150 ($NH_2$), 1642 (C=N), 1604, 1573, 1549, 1514 (aromatic rings), 1484, 1216, 1088, 830, 675 cm$^{-1}$; EI-HRMS: calcd. for $C_{21}H_{17}N_4OF$ 360.1386, obsd. 360.1399.

**4-(4-Fluorophenyl)-1-(4-nitrophenyl)-3-(pyridin-4-yl)-1*H*-pyrazol-5-amine (6e)**



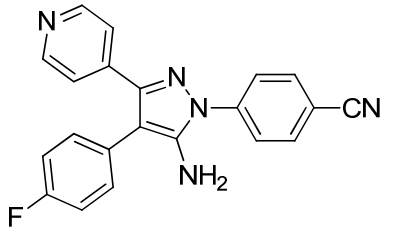
Yield: 36%; pale orange solid; mp. 259 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 5.58 (s, br, 2H, $NH_2$), 7.26-7.33 (m, 6H), 8.08 (d, $J$ = 8 Hz, 2H), 8.40 (d, $J$ = 8 Hz, 2H), 8.50 (d, $J$ = 8 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 104.0, 115.7, 119.0, 122.0, 123.1, 124.8, 128.6, 132.6, 140.7, 144.2, 146.4, 147.8, 150.2, 161.6; IR (ATR) 3385, 3190, 3106 ($NH_2$), 1643 (C=N), 1580,1573, 1514 (aromatic rings), (1546, 1333 $NO_2$), 1482, 1386, 1222, 970, 834, 752 cm$^{-1}$. EI-HRMS: calcd. for $C_{20}H_{14}FN_5O_2$ 375.1132, obsd. 375.1135.

**4-(4-Fluorophenyl)-3-(pyridin-4-yl)-1-*p*-tolyl-1*H*-pyrazol-5-amine (6f)**



Yield: 54%; pale brown solid; mp. 211 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 2.37 (s, 3H), 5.15 (s, br, 2H, $NH_2$), 7.21-7.36 (m, 8H), 7.56 (d, $J$ = 8 Hz, 2H), 8.45 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 21.3, 102.8, 116.0, 121.9, 124.0, 129.3, 130.1, 132.2, 136.5, 137.0, 141.5, 145.5, 145.7, 150.0, 161.4; IR (ATR) 3440, 3101 ($NH_2$), 1642 (C=N), 1601, 1573, 1550, 1520 (aromatic rings), 1424, 1391, 1209, 1152, 1089, 997, 810, 708 cm$^{-1}$; EI-HRMS: calcd. for $C_{21}H_{17}FN_4$ 344.1437, obsd. 344.1417.

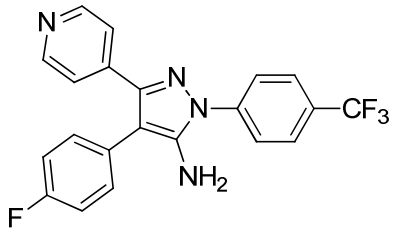
**4-[5-Amino-4-(4-fluorophenyl)-3-(pyridin-4-yl)-1*H*-pyrazol-1-yl]benzonitrile (6g)**



Yield: 62%; pale brown solid; mp. 266°C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 5.49 (s, br, 2H, $NH_2$), 7.23-7.32 (m, 6H), 7.96-8.01 (m, 4H), 8.47 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 104.0, 109.2, 116.2, 118.9, 122.0, 123.7, 128.6, 132.4, 133.9, 140.8, 142.8, 146.3, 147.4, 150.0, 161.5; IR (ATR) 3446, 3320, 3113 ($NH_2$), 2225 (CN), 1639 (C=N), 1600, 1561, 1544, 1512 (aromatic rings),

1485, 1382, 1337, 1221, 1160, 1138, 1095, 967, 834, 763 $cm^{-1}$; MS: m/z (%) = 356 $[M+H]^+$, 307, 289; EI-HRMS: calcd. for $C_{21}H_{14}FN_5$ 355.1233, obsd. 355.1214.

**4-(4-Fluorophenyl)-3-(pyridin-4-yl)-1-(4-trifluoromethyl)phenyl)-1*H*-pyrazol-5-amine (6h)**

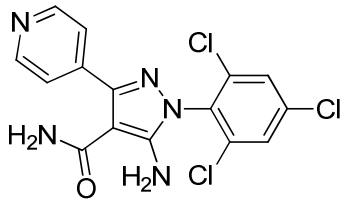


Yield: 25%; orange solid; mp. 186 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 5.46 (s, br, 2H, $NH_2$), 7.23-7.34 (m, 6H), 7.89 (d, $J$ = 6 Hz, 2H), 7.99 (d, $J$ = 6 Hz, 2H), 8.48 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 103.7, 116.1, 122.0, 123.9, 126.8, 127.2, 127.6, 128.8, 132.4, 141.1, 142.4, 146.2, 147.0, 149.9, 161.5; IR (ATR) 3380, 3177 ($NH_2$), 1604, 1572, 1547, 1510 (aromatic rings), 1425, 1389, 1324, 1218, 1165, 1107, 1066, 827, 675 $cm^{-1}$; EI-HRMS: calcd. for $C_{21}H_{14}F_4N_4$ 398.1155, obsd. 398.1157.

**General procedure for synthesis of amino pyrazole derivatives (7-9); Method B**

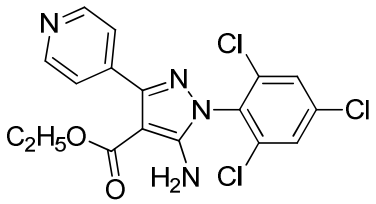
4.0 mmol of appropriate hydrazonyl chloride **4a**,**b** and 1.5 equiv. of the respective cyano derivative **5i**,**j** were dissolved in dry ethanol (20 mL) in cooled to 0 °C in an ice bath. 2.0 equiv. of sodium ethoxide solution (21%) was added dropwise to the reaction mixture and stirring was continued overnight. The precipitate was filtered from the reaction, washed with water to remove the salt and recrystallized from hot ethanol. In case the product did not precipitate, the residue was purified by flash chromatography (petroleum ether/ ethyl acetate) to yield a pure solid.

**5-Amino-3-(pyridin-4-yl)-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole-4-carboxamide (7)**



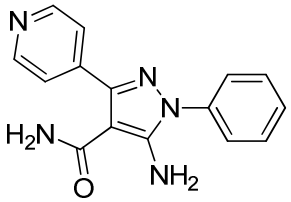
Yield: 45%; pale yellow solid; mp. 296 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 6.48 (s, 2H, $NH_2$), 6.61 (s, br, 2H, $CONH_2$), 7.58 (d, $J$ = 5 Hz, 2H), 7.97 (s, 2H), 8.63 (d, $J$ = 5 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 94.7, 123.4, 129.4, 132.2, 136.2, 140.9, 148.8, 150.0, 152.4, 165.9; IR (ATR) 3477, 3379, 3150 ($NH_2$), 3065, 1622 ($CONH_2$), 1600, 1552, 1520, 1506 (aromatic rings), 1408, 1417, 1381, 1195, 835, 747 $cm^{-1}$; EI-HRMS: calcd. for $C_{15}H_{10}Cl_3N_5O$ 380.9951, obsd. 380.9929.

**Ethyl 5-amino-3-(pyridin-4-yl)-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole-4-carboxylate (8)**



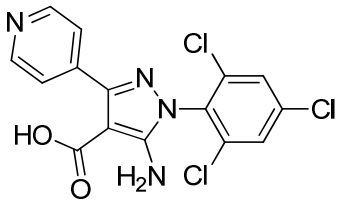
Yield: 56%; colorless solid; mp. 246 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 1.19 (t, $J$ = 7 Hz, 3H), 4.18 (q, $J$ = 7 Hz, 2H), 6.73 (s, 2H, $NH_2$), 7.63 (d, $J$ = 6 Hz, 2H), 7.99 (s, 2H), 8.60 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 14.1, 59.2, 90.7, 123.6, 129.1, 131.6, 135.7, 136.1, 140.9, 149.0, 150.2, 153.0, 163.0; IR (ATR) 3400, 3283 ($NH_2$), 1690 (COOEt), 1626 (C=N), 1608, 1552, 1510 (aromatic rings), 1467, 1414, 1381, 1262, 1125, 832, 786 cm$^{-1}$; EI-HRMS: calcd. for $C_{17}H_{13}Cl_3N_4O_2$ 412.0075, obsd. 412.0074.

**5-Amino-1-phenyl-3-(pyridin-4-yl)-1*H*-pyrazole-4-carboxamide (9)**



Yield: 40%; brown powder; mp. 227 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 6.35 (s, 2H, $NH_2$), 6.66 (s, br, 2H, $CONH_2$), 7.28-7.65 (m, 7H), 8.65 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 96.3, 123.1, 123.6, 127.6, 129.4, 137.8, 140.7, 147.2, 149.7, 150.3, 165.9; IR (ATR) 3352, 3270, 3181 ($NH_2$), 1648 ($CONH_2$), 1602, 1596, 1557, 1504 (aromatic rings), 1455, 1419, 1390, 1283, 1003, 829, 756 cm$^{-1}$; EI-HRMS: calcd. for $C_{15}H_{13}N_5O$ 279.1120, obsd. 279.1119.

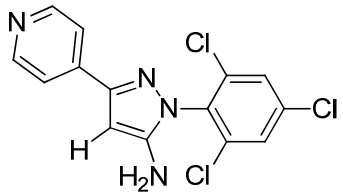
**5-Amino-3-(pyridin-4-yl)-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole-4-carboxylic acid (10)**



0.4 mmol of ethyl 5-amino-3-(pyridin-4-yl)-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole-4-carboxylate (**8**) was dissolved in (20 mL) and water (10 mL). 1.6 mmol of KOH was added and the reaction mixture was heated to reflux temperature for 4 h. The organic solvent was evaporated and the aqueous layer was neutralized in an ice bath by adding conc. HCl. The colorless precipitate was filtered and recrystalized from hot ethanol. Yield: 80%; colorless solid; mp. 208 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 6.69 (s, 2H, $NH_2$), 7.66 (d, $J$ = 5 Hz, 2H), 7.97 (s, 2H), 8.59 (d, $J$ = 5 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 91.2, 123.5, 129.0, 131.7, 135.7, 136.0, 140.5, 149.2, 150.3, 153.3, 164.7; IR (ATR) 3450-2500

(HOOC), 3409 ($NH_2$), 3062, 1635 (COOH), 1606, 1553, 1509 (aromatic rings), 1417, 1381, 1276, 1190, 1003, 991, 832 $cm^{-1}$; ESI-HRMS $[M+H]^+$: calcd. for $C_{15}H_9Cl_3N_4O_2$ 382.9864, obsd. 382.9865.

**3-(Pyridin-4-yl)-1-(2,4,6-trichlorophenyl)-1*H*-pyrazol-5-amine (11)**

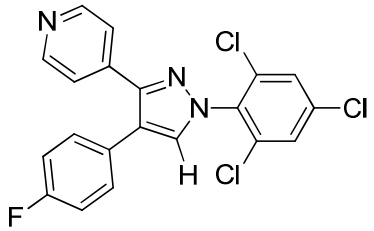


0.1 mmol of 5-amino-3-(pyridin-4-yl)-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole-4-carboxylic acid (**10**) was dissolved in MeOH-conc. HCl (10 mL, 1:1, V:V) and heated for 1 h to reflux temperature. The organic solvent was evaporated and the aqueous layer was neutralized in an ice bath by adding conc. KOH solution. The pure colorless precipitate was collected by filtration, washed with petroleum ether and dried. Yield: 90%; colorless solid; mp. 228 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 5.64 (s, 2H, $NH_2$), 5.96 (s, 1H), 7.67 (d, $J$ = 6 Hz, 2H), 7.93 (s, 2H), 8.55 (d, $J$ = 6 Hz, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 85.1, 120.0, 129.4, 133.4, 135.9, 136.2, 141.0, 149.7, 150.4, 150.7; IR (ATR) 3350, 3288, 3129 ($NH_2$), 3058, 1644(C=N), 1606, 1548, 1500 (aromatic rings), 1456,1417, 1377, 1148, 1098, 959, 833, 755 $cm^{-1}$ HRMS: calcd. for $C_{14}H_9Cl_3N_4$ 339.9863, obsd. 339.9863.

**General procedure for synthesis of pyrazole derivatives 13a and 13h**

Hydrazone derivate (**3a,h**) (4 mmol) was dissolved under $N_2$-atmosphere in dry THF (50 mL) at -78°C. *Tert*-BuOK solution in THF (2.7 mL, 4.0 mmol, 1.655 M) was added dropwise at -78°C and after 15 min trans-*p*-fluoro-ω-nitrostyrene (**12**) (0.51 g, 3 mmol) dissolved in THF (6 mL) was added dropwise via syringe to the reaction mixture. After 15 min TFA (1.0 mL, 10 mmol) was added, the reaction mixture was stirred at -78°C for 2 h and warmed to room temperature overnight. Ethyl acetate (50 mL) and water (50 mL) and water added to the reaction solution. The organic layer was separated, dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography and/or thick layer chromatography (ethyl acetate/ petroleum ether 1-4).

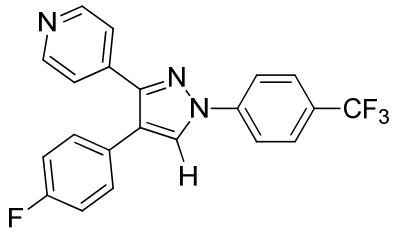
**4-(4-(4-Fluorophenyl)-1-(2,4,6-trichlorophenyl)-1*H*-pyrazol-3-yl)pyridine (13a)**



Yield: 32%; mp 124 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 7.22-7.44 (m, 4H), 7.66-7.71 (m, 2H), 8.04 (s, 2H), 8.45 (s, 1H), 8.68-8.72 (m, 2H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 116.1, 116.5, 122.1, 123.4,

123.5, 129.4, 131.1, 131.3, 134.4, 124.8, 136.2, 144.0, 146.3, 146.9; EI-HRMS: calcd. for $C_{20}H_{11}Cl_3FN_3$ 418.9973, obsd. 418.9980.

**4-(4-(4-Fluorophenyl)-1-(4-(trifluoromethyl)phenyl-1*H*-pyrazol-3-yl)pyridine (13h)**




Yield: 10%; orange yellowish solid; mp. 146 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 7.27-7.33 (m, 2H), 7.41-7.46 (m, 2H), 7.60 (d, *J* = 6 Hz, 2H), 7.96 (d, *J* = 8 Hz, 2H), 8.22 (d, *J* = 8 Hz, 2H), 8.66 (d, *J* = 6 Hz, 2H), 9.01 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 115.6, 118.8, 122.5, 122.8, 126.8, 126.9, 127.6, 129.5, 130.5, 130.6, 141.7, 147.1, 148.5, 161.6; IR (ATR) 3393, 3060, 1617, 1603, 1570, 1541, 1500 (aromatic rings), 1412, 1397, 1320, 1224, 1161, 1110, 1058, 956, 842, 830 cm$^{-1}$; EI-HRMS: calcd. for $C_{21}H_{13}F_4N_3$ 383.1046, obsd. 383.1047.

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