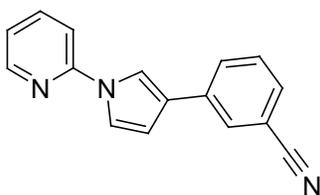


SUPPORTING INFORMATION¹⁻⁶

High Performance Liquid Chromatography (HPLC). HPLC was performed on compounds using a Zorbax SBC18 5 x 4.6 x 3.5 μm column eluting with the following solvents: A = $\text{H}_2\text{O}/\text{TFA}$ 100/0.1%, B = ACN/TFA 100/0.05%; 10% B to 95% B over 3 min, 1 mL/min, at 60°C. All target compounds were determined pure under these conditions.

Synthesis of 2-(3-bromo-1*H*-pyrrol-1-yl)pyridine (6)

Bromotrimethylsilane (10.9 mL, 84 mmol) was added to DMSO (5.7 mL, 84 mmol) in MeCN (200 mL) at 0°C. After stirring for 10min, 2-(1*H*-pyrrol-1-yl)pyridine **5** (10g, 70 mmol) in MeCN (50 mL) was added. The reaction mixture was stirred at 0°C and allowed to reach ambient temperature over 3h. H_2O (150 mL) and EtOAc (150 mL) were added and the reaction mixture was shaken, the EtOAc layer was separated and the aqueous layer shaken with EtOAc (3x150 mL). The combine organic layers were dried over Na_2SO_4 and concentrated to afford a brown oil. LCMS indicated good conversion to 2-(3-bromo-1*H*-pyrrol-1-yl)pyridine (**6**) and this was used in the next step without further purification. MS (ESI) 224 (M+H)⁺.

**Synthesis of 3-(1-pyridin-2-yl-1*H*-pyrrol-3-yl)benzonitrile (7)**

2-(3-Bromo-1*H*-pyrrol-1-yl)pyridine (1.34 g, 2 mmol), 3-cyanophenylboronic acid (0.59 g, 4 mmol), $\text{Pd}(\text{PPh}_3)_4$ (116 mg, 0.1 mmol) and potassium carbonate (560 mg,

4 mmol) were dissolved in a mixture of DME (18 mL) and H₂O (2 mL) and degassed for 15 min. with Ar (g). The reaction mixture was then heated at 84°C for 18 h. At this time, a further 0.25 eq. of 3-cyanophenylboronic acid (0.15 g, 1 mmol) was added and heating was continued. After a total of 42 h, the reaction mixture was cooled to ambient temperature, H₂O (40 mL) and EtOAc (40 mL) were added and the reaction mixture shaken, the EtOAc layer was separated and the aqueous layer shaken with EtOAc (2 x 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to a yellow oil. This was purified by liquid chromatography on silica gel eluting with EtOAc:hexane (3:7) to afford a white waxy solid that was further purified by liquid chromatography on silica gel eluting with dichloromethane to afford 3-(1-pyridin-2-yl-1*H*-pyrrol-3-yl)benzotrile (**7**) as a colorless oil (69 mg, 14% over two steps). ¹H NMR (CD₃Cl, 300 MHz) δ 8.49 – 8.52 (1H, m), 7.66 (1H, ddd, J = 6.8, 6.8, 1.7 Hz), 7.47 – 7.51 (2H, m), 7.33 – 7.39 (3H, m), 7.24 (1H, ddd, J = 6.8, 4.5, 0.8 Hz), 6.91 (1H, d, J = 7.3 Hz), 6.51 – 6.52 (1H, m), 6.43 (1H, dd, J = 5.9 Hz). MS (ESI) 246 (M+H)⁺; ¹³C NMR (CD₃OD, 500 MHz) δ 152.0, 148.6, 138.9, 136.7, 132.1, 131.2, 130.8, 129.5, 129.0, 124.6, 122.3, 120.0, 118.1, 113.0, 112.1, 110.0; HRMS Calcd. *m/e* 246.1031 (M+H)⁺; Found *m/e* 246.1020.

Synthesis of 3-iodo-1-(triisopropylsilyl)-1*H*-pyrrole (**8**)

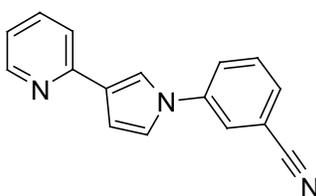
3-Iodo-1-(triisopropylsilyl)-1*H*-pyrrole (**8**) was prepared according to the method of Bray, B.L. *et al. J. Org. Chem.* **1990**, *55*, 6317-6328.

Synthesis of 2-(1*H*-pyrrol-3-yl)pyridine (9)

A solution of 3-iodo-1-(triisopropylsilyl)-1*H*-pyrrole **8** (1.0 g, 2.87 mmol), triphenylphosphine (27 mg, 0.103 mmol), and tetrakis(triphenylphosphine)palladium(0) (80 mg, 0.069 mmol) in THF (20 mL) was degassed with Ar (g) for 15 min., then 2-bromo(pyridin-2-yl)zinc (11.5 mL of 0.5M solution, 5.74 mmol) was added and degassing continued a further 15 min. The reaction was stirred at 70°C for 5 h and monitored by LC/MS. The reaction mixture was quenched with H₂O (40 mL) then extracted with EtOAc (3 x 25 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄, concentrated *in vacuo* and the crude residue was chromatographed on silica gel eluting with EtOAc:hexane (1:9) to afford 2-[1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]pyridine which was carried into the next step without further purification. Yield 9%; ¹H NMR (CDCl₃, 300 MHz) δ 8.56-8.54 (m, 1H), 7.65-7.59 (m, 1H), 7.53-7.49 (m, 1H), 7.45-7.44 (m, 1H), 7.05-7.04 (m, 1H), 6.84-6.79 (m, 2H), 1.57-1.47 (m, 3H), 1.17 (d, J=7.4 Hz, 12H); ¹³C NMR (CDCl₃, 75 MHz) δ 154.8, 149.4, 136.3, 127.1, 125.5, 123.4, 120.1, 119.3, 108.9, 17.8, 11.7.

To a solution of 2-[1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]pyridine (1 g, 3.2 mmol) in anhydrous THF (15 mL) was added TBAF (3.84 mL of a 1M solution in THF, 3.84 mmol). After stirring for 10 min. at ambient temperature the reaction was complete. The reaction mixture was quenched with H₂O (40 mL), extracted with EtOAc (3 x 25 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄, concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexane (1:1) to afford 2-(1*H*-pyrrol-3-yl)pyridine (**9**) as a clear oil which solidified upon standing at ambient temperature. Yield 80%; mp 129-130°C; ¹H NMR

(CD₃Cl, 300 MHz) δ 8.59 (br, 1H), 8.59-8.53 (m, 1H), 7.63-7.60 (dt, J=4.6 Hz, 1.0 Hz, 1H), 7.49-7.48 (dd, J=0.46 Hz, 4.8 Hz, 1H), 7.44 (d, J=1.0 Hz, 1H), 7.05-7.03 (m, 1H), 6.84 (dd, J=1.2 Hz, 2.7 Hz, 1H), 6.73 (d, J=1 Hz, 1H); MS (ESI) m/e 145.1 (M+1)⁺. See also N. D. Smith, D. Huang and N. D. P. Cosford *Org. Lett.* **2002**, 4(20), 3537 – 3539 for an alternate procedure.



Synthesis of 3-(3-pyridin-2-yl-1H-pyrrol-1-yl)benzonitrile (10)

2-(1H-Pyrrol-3-yl)pyridine (0.144 g, 1.0 mmol), 3-fluorobenzonitrile (1.21 g, 10 mmol), and potassium carbonate (0.276 g, 2 mmol) were heated at 145°C in DMF (0.5 mL) for 14 h. After this time, the reaction mixture was cooled to rt and quenched with H₂O (30 mL). The mixture was extracted with EtOAc (3x25 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄, concentrated *in vacuo* and the residue was chromatographed on silica gel eluting with EtOAc:hexane (2:3) to afford a white solid which was recrystallized from dichloromethane-hexane to give 3-(3-pyridin-2-yl-1H-pyrrol-1-yl)benzonitrile (**10**) as white crystals. Yield 37%; mp: 130-131°C; ¹H NMR (CD₃Cl, 300 MHz) δ 8.59 (m, 1H), 7.78~7.67 (m, 4H), 7.60-7.53 (m, 3H), 7.17~7.11 (m, 2H), 6.89 (dd, J=3 Hz, 1.6 Hz, 1H); ¹³C NMR (CD₃Cl, 75 MHz) δ 153.27, 149.33, 140.63, 136.36, 130.52, 128.99, 127.94, 123.97, 122.97, 120.83, 119.99, 119.09, 117.82, 117.64, 113.64, 109.98. MS (ESI) 246.1 (M⁺+H); HRMS Calcd. m/e 246.1026 (M+H)⁺; Found m/e 246.1040.

Synthesis of (2E)-3-ethoxy-N'-pyridin-2-ylprop-2-enohydrazide (12)

Ethyl vinyl ether (4.73 g, 65.6 mmol) was added dropwise to oxalyl chloride (12.5 g, 98.4 mmol) at 0°C, the resulting reaction mixture was first stirred at 0°C for 2 h, and then allowed to warm to ambient temperature. After 12h GC/MS analysis indicated formation of product and the reaction mixture was concentrated *in vacuo* and the crude (2E)-3-ethoxyprop-2-enoyl chloride used in the next step without further purification.

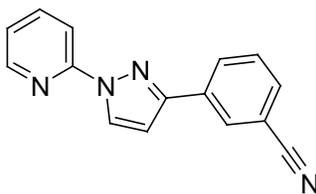
To a cold (0°C) solution of 2-hydrazinopyridine **11** (10.74 g, 98.4 mmol) and triethylamine (9.94 g, 98.4 mmol) in THF (100 mL) was added crude (2E)-3-ethoxyprop-2-enoyl chloride (based on 100% yield of previous step) dropwise. The resulting reaction mixture was allowed to warm to ambient temperature over 2 h and then heated at reflux for a further 5h. The reaction mixture was quenched with water (50 mL), extracted with EtOAc (3x50 mL) and washed with brine. The organic phase was dried over Na₂SO₄, concentrated *in vacuo*, purified using liquid chromatography on silica gel eluting with EtOAc to afford (2E)-3-ethoxy-N'-pyridin-2-ylprop-2-enohydrazide (**12**) as a brown oil (8.5 g, 62%). ¹H NMR (CD₃Cl, 300 MHz) δ 9.19 (br, 1H), 8.08 (m, 1H), 7.59~7.44 (m, 3H), 6.75~6.69 (m, 2H), 5.34 (d, J=15.9 Hz, 1H), 3.81 (q, J=6.9 Hz, 2H), 1.27 (t, J=7.1 Hz, 3H); MS (ESI) 208 (M⁺+H).

Synthesis of 1-pyridin-2-yl-1H-pyrazol-3-yl trifluoromethanesulfonate (13)

(2E)-3-Ethoxy-N'-pyridin-2-ylprop-2-enohydrazide (8.5 g, 41 mmol) was stirred with concentrated 37% HCl (20 mL) for 3h. The resulting reaction mixture was adjusted to pH 7 using 1N NaOH (aq) and a precipitate formed. The reaction mixture then

extracted with EtOAc (3x50 mL) and washed with brine. The combined organic phase was dried over Na₂SO₄, concentrated *in vacuo* purified using liquid chromatography on silica gel eluting with EtOAc (100%) to afford 1-pyridin-2-yl-1,2-dihydro-3*H*-pyrazol-3-one as a yellow solid. Yield 45%; ¹H NMR (CD₃Cl, 300 MHz) δ 12.00 (br, 1H), 8.43~8.39 (m, 2H), 7.85 (m, 1H), 7.64 (d, J=8.3 Hz, 1H), 7.16 (m, 1H), 5.99 (d, J=2.8 Hz, 1H); MS (ESI) 162 (M⁺+H).

To a solution of 1-pyridin-2-yl-1,2-dihydro-3*H*-pyrazol-3-one (0.161 g, 1.0 mmol) and triethylamine (0.112 g, 1.1 mmol) in THF (10 mL) at -78°C was added trifluoromethanesulfonic anhydride (0.253 g, 1 mmol) dropwise. The resulting reaction mixture was stirred and allowed to warm to ambient temperature over 4h. The reaction was quenched by the addition of H₂O (15 mL), then extracted with EtOAc (3x20 mL) and washed with brine. The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was chromatographed on silica gel eluting with EtOAc:hexane (1:9) to afford 1-pyridin-2-yl-1*H*-pyrazol-3-yl trifluoromethanesulfonate (**13**) as white crystals. Yield 80%; ¹H NMR (CD₃Cl, 300 MHz) δ 8.57 (d, J=2.7 Hz, 1H), 8.43 (d, J=4.5 Hz, 1H), 7.91~7.83 (m, 2H), 7.29~7.25 (m, 1H) 6.38 (d, J=2.7 Hz, 1H); MS (ESI) 294 (M⁺+H).

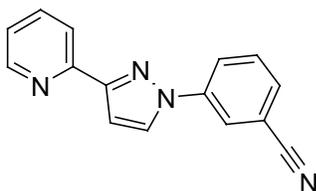


Synthesis of 3-(1-pyridin-2-yl-1H-pyrazol-3-yl)benzotrile (14)

1-Pyridin-2-yl-1H-pyrazol-3-yl trifluoromethanesulfonate (0.211g, 0.72mmol), 3-fluorobenzotrile (0.111g, 0.76mmol) and potassium carbonate (0.209g, 1.51mmol) in a mixture of ethyleneglycol dimethyl ether (20mL) and water (4mL) was degassed by argon bubbling for 15min., then tetrakis(triphenylphosphine)palladium(0) (20mg, 0.017mmol) was added the resulting solution degassed for a further 15min. The solution was stirred at 65°C for 12h. The reaction mixture was quenched with water (30mL), then extracted with EtOAc (3x30mL) and washed with brine. The combined organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was chromatographed on silica gel eluting with EtOAc:hexane (2:3) to afford a white solid which was recrystallized from EtOAc-hexane to give 3-(1-pyridin-2-yl-1H-pyrazol-3-yl)benzotrile (**14**) as a white solid. Yield 39%; mp 149-150°C; ¹H NMR (CD₃Cl, 300 MHz) δ 8.63 (d, J=1.6 Hz, 1H), 8.44 (d, J=2.3 Hz, 1H), 8.24 (s, 1H), 8.14-8.08 (m, 2H), 7.88-7.84 (m, 1H), 7.64-7.62 (m, 1H), 7.56-7.53 (m, 1H), 7.22 (dd, J=3.2 Hz, 4.3 Hz, 1H), 6.79 (d, J=1.6 Hz, 1H); ¹³C NMR (CD₃Cl, 75 MHz) δ 151.40, 151.31, 148.12, 138.82, 134.32, 131.82, 131.44, 130.06, 129.49, 128.75, 121.73, 118.81, 112.95, 112.52, 105.26; MS (ESI) 247 (M⁺+H); HRMS Calcd. *m/e* 269.0803 (M+Na)⁺; Found *m/e* 269.0806.

Synthesis of 2-(1*H*-pyrazol-3-yl)pyridine (15)

2-(1*H*-Pyrazol-3-yl)pyridine **15** (7.8g) was prepared according to the method of:
Wang, F.; Schwabacher, A.W. *Tetrahedron. Lett.* **1999**, *40*, 4779-4782.

**Synthesis of 3-(3-pyridin-2-yl-1*H*-pyrazol-1-yl)benzotrile (16)**

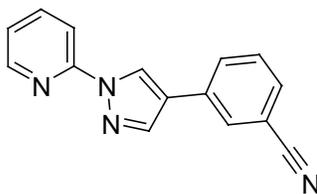
2-(1*H*-Pyrazol-3-yl)pyridine **15** (435mg, 3mmol), 3-fluorobenzotrile (0.32mL, 3mmol) and K₂CO₃ (830mg, 6mmol) were dissolved in DMF (10mL) under Ar (g) and heated at 145°C for 18h. After cooling to ambient temperature, H₂O (40mL) and EtOAc (40mL) were added and the reaction mixture shaken, the EtOAc layer was separated and the aqueous layer shaken with EtOAc (2x30mL). The combined organic layers were washed with brine (3x40mL), dried over Na₂SO₄ and concentrated onto silica gel. The crude material was purified by liquid chromatography on silica gel eluting with EtOAc:hexane (1:1) to afford a solid that was recrystallized from EtOAc-hexane to give 3-(3-pyridin-2-yl-1*H*-pyrazol-1-yl)benzotrile (**16**) as a solid (298 mg, 38%). mp 163-164°C. ¹H NMR (CD₃Cl, 300 MHz) δ 8.68 – 8.71 (1H, m), 8.18 (1H, m), 8.12 – 8.15 (1H, m), 8.02 – 8.06 (2H, m), 7.81 (1H, ddd, J = 7.0, 7.0, 1.5 Hz), 7.60 – 7.62 (2H, m), 7.30 (1H, m), 7.20 (1H, d, J = 2.3 Hz); ¹³C NMR ((CD₃C)₂SO, 500 MHz) δ 153.7, 151.2, 149.9, 140.3, 137.6, 131.5, 130.4, 130.4, 123.9, 123.4, 121.9, 120.5, 118.7, 113.0, 107.6; MS (ESI) 247 (M+H)⁺; HRMS Calcd. *m/e* 247.0984 (M+H)⁺. Found *m/e* 269.0979.

Synthesis of 2-(1*H*-pyrazol-1-yl)pyridine (17)

2-Hydrazinopyridine **11** (7.6g, 70 mmol), malondialdehyde-bis-(dimethylacetal) (11.5 mL, 70 mmol) and HCl (10M, 7 mL) in EtOH (100 mL) were heated at 75°C. After 2h, the resulting reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to give a brown solid. This was suspended in H₂O (100 mL) and EtOAc (100 mL), and NaHCO₃ added until there was no further effervescence. The EtOAc layer was then separated and the aqueous layer shaken with EtOAc (3x100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to afford 2-(1*H*-pyrazol-1-yl)pyridine (**17**) as a brown oil which was used in the next step without further purification. MS (ESI) 147 (M+H)⁺.

Synthesis of 2-(4-bromo-1*H*-pyrazol-1-yl)pyridine (18)

Bromine (10.8 mL, 210 mmol) in AcOH (50 mL) was added carefully to a solution of 2-(1*H*-pyrazol-1-yl)pyridine **17** (11 g, 70 mmol) in AcOH (100 mL) to give a brown precipitate. After stirring at ambient temperature for 3h, the resulting reaction mixture was poured into ice and saturated aqueous Na₂S₂O₅ was added until the liquid phase became clear. The precipitate was removed by filtration and recrystallized from EtOH:H₂O to give 2-(4-bromo-1*H*-pyrazol-1-yl)pyridine (**18**) as beige crystals (12.8 g, 82%). ¹H NMR (CD₃Cl, 300 MHz) δ 8.61 (1H, s), 8.42 (1H, br. s), 7.94 – 7.96 (1H, m), 7.84 (1H, m), 7.69 (1H, s), 7.21 – 7.28 (1H, m); MS (ESI) 225 (M+H)⁺.



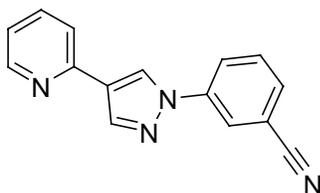
Synthesis of 3-(1-pyridin-2-yl-1H-pyrazol-4-yl)benzotrile (19)

A solution of 2-(4-bromo-1H-pyrazol-1-yl)pyridine **18** (0.446 g, 2.0 mmol), 3-cyanophenylboronic acid (0.302 g, 2.0 mmol), potassium carbonate (0.552 g, 4.0 mmol) in a mixture of ethylene glycol dimethyl ether (20 mL) and water (4 mL) was degassed by argon bubbling for 15 min., then tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.017 mmol) was added and degassing continued a further 15 min. The resulting solution was stirred at 70°C for 14h, whereupon H₂O (30 mL) was added, then extracted with EtOAc (3x30 mL) and the combined extracts washed with brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was chromatographed on silica gel eluting with EtOAc :hexane (2:3) to afford a white solid which was recrystallized from EtOAc/Hexane to give 3-(1-pyridin-2-yl-1H-pyrazol-4-yl)benzotrile (**19**) as a white solid. Yield 12%; mp = 160-161°C ¹H NMR (CD₃Cl, 300 MHz) δ 8.88 (s, 1H), 8.45 (d, J=3.8 Hz 1H), 8.03 (s, 1H), 8.01 (d, J=6.9 Hz 1H), 7.88-7.80 (m, 3H), 7.57~7.48 (m, 2H), 7.25 (m, 1H); MS (ESI) 247.1 (M⁺+H); HRMS Calcd. *m/e* 269.0803 (M+Na)⁺. Found *m/e* 269.0780.

Synthesis of 2-(1H-pyrazol-4-yl)pyridine (21)

2-(2-Pyridyl)malondialdehyde **20** (7.8 g, 52 mmol), purchased from Acros Organics, and hydrazine hydrate (3.7 mL) were heated at 75°C in ethanol (75 mL) for 18h. After cooling to ambient temperature and concentration *in vacuo*, recrystallization

from EtOAc/Hexane gave 2-(1*H*-pyrazol-4-yl)pyridine (**21**) as gold crystals (6.5g, 86%). MP = 136°C; ; ¹H NMR (CD₃Cl, 300 MHz) δ 6.48 – 8.51 (1H, m), 8.30 (1H, br. s), 8.07 (1H, br. s), 7.74 (1H, m), 7.68 (1H, m), 7.15 (1H, m); MS (ESI) 146 (M+H)⁺.

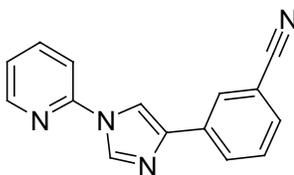


Synthesis of 3-(4-pyridin-2-yl-1*H*-pyrazol-1-yl)benzotrile (**22**)

To 2-(1*H*-pyrazol-4-yl)pyridine **21** (292 mg, 2 mmol), 3-cyanoboronic acid (590 mg, 4 mmol), Cu(OAc)₂ (547 mg, 3 mmol) and pyridine (0.32 mL, 4 mmol) in dichloromethane (4 mL) was added 0.5g of 4 Å molecular sieves. The resulting reaction mixture was stirred at ambient temperature under atmospheric conditions for 48h, whereupon it was filtered through Celite, washing with dichloromethane. The reaction mixture was concentrated onto silica gel *in vacuo* and purified by liquid chromatography on silica gel eluting with EtOAc:hexane (1:1 to 1:0) to afford a solid that was recrystallized from EtOH-H₂O to afford 3-(4-pyridin-2-yl-1*H*-pyrazol-1-yl)benzotrile (**22**) as a white solid (38 mg, 8%). mp 232-233 °C; ¹H NMR (CD₃Cl, 300 MHz) δ 8.63 – 8.64 (1H, m), 8.56 (1H, s), 8.23 (1H, s), 8.14 (1H, m), 8.00 – 8.05 (1H, m), 7.75 (1H, m), 7.57 – 7.66 (3H, m), 7.21 (1H, ddd, J = 6.8, 4.4, 0.9 Hz); ¹³C NMR ((CD₃C)₂SO, 500 MHz) δ 147.3, 144.9, 143.4, 141.1, 139.8, 131.7, 131.2, 129.2, 123.9, 123.8, 123.0, 122.3, 120.6, 118.5, 113.1; MS (ESI) 247 (M+H)⁺; HRMS Calcd. *m/e* 247.0978 (M+H)⁺; Found *m/e* 247.0998.

Synthesis of 2-(4-bromo-1*H*-imidazol-1-yl)pyridine (24)

2-Bromopyridine **23** (1.3 mL, 14 mmol) and 4-bromo-1*H*-imidazole (2 g, 14 mmol) were heated in dry NMP (15 mL) under an atmosphere of Ar (g) at 165°C for 18 h. After cooling to ambient temperature H₂O (40 mL) and EtOAc (40 mL) were added and the reaction mixture shaken, the EtOAc layer was separated, and the aqueous layer shaken with EtOAc (2 x 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to a brown oil. This was purified by liquid chromatography on silica gel eluting with EtOAc:hexane (4:6) to afford 2-(4-bromo-1*H*-imidazol-1-yl)pyridine (**24**) as a white solid (1.4g, 44%). mp 80-81°C ¹H NMR (CD₃Cl, 300 MHz) δ 8.50 – 8.52 (1H, m), 8.25 (1H, m), 7.87 (1H, m), 7.64 (1H, d), 7.28 – 7.36 (2H, m); MS (ESI) 224 (M+H)⁺.

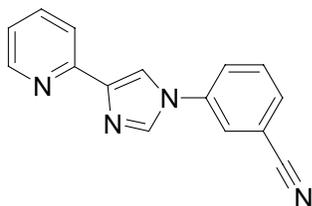
**Synthesis of 3-(1-pyridin-2-yl-1*H*-imidazol-4-yl)benzonitrile (25)**

2-(4-Bromo-1*H*-imidazol-1-yl)pyridine **24** (225 mg, 1 mmol), 3-cyanophenylboronic acid (162 mg, 1.1 mmol), Pd(PPh₃)₄ (58 mg, 0.05 mmol) and potassium carbonate (276 mg, 2 mmol) were dissolved in a mixture of DME (9 mL) and H₂O (1 mL) and degassed for 15 min. with Ar (g). The reaction mixture was then heated at 80°C for 18 h. After cooling to ambient temperature H₂O (40 mL) and EtOAc (40 mL) were added and the reaction mixture shaken, the EtOAc layer was separated, and the aqueous layer shaken with EtOAc (2 x 30 mL). The combined organic layers were dried over Na₂SO₄ and

concentrated to a yellow oil. This was purified by liquid chromatography on silica gel eluting with EtOAc:hexane (1:1) to afford 3-(1-pyridin-2-yl-1*H*-imidazol-4-yl)benzotrile (**25**) as a white solid (9 mg, 4%). ¹H NMR (CDCl₃, 300 MHz) δ 8.54 – 8.56 (1H, m), 8.41 (1H, s), 8.17 (1H, s), 8.09 – 8.11 (1H, m), 8.06 (1H, s), 7.87 – 7.93 (1H, m), 7.49 – 7.59 (2H, m), 7.46 (1H, m), 7.31 (1H, m). MS (ESI) 247 (M+H)⁺; ¹³C NMR (CD₃OD, 500 MHz) δ 148.8, 148.7, 140.5, 139.5, 135.9, 134.8, 130.3, 129.6, 129.0, 128.0, 122.6, 118.3, 113.6, 112.6, 112.6; HRMS Calcd. *m/e* 247.0978 (M+H)⁺; Found *m/e* 247.0997.

Synthesis of 3-(4-pyridin-2-yl-1*H*-imidazole (26)

3-(4-Pyridin-2-yl-1*H*-imidazole (**26**) was prepared according to the method of Wang, F.; Schwabacher, A. W. *Tetrahedron. Lett.* **1999**, *40*, 4779-4782.



Synthesis of 3-(4-pyridin-2-yl-1*H*-imidazol-1-yl)benzotrile (27)

2-(1*H*-Imidazol-4-yl)pyridine **26** (0.236 g, 1.6 mmol), 3-fluorobenzotrile (0.196 g, 1.6 mmol) and potassium carbonate (0.446 g, 3.2 mmol) were heated at 145°C in DMF (5 mL) for 12 h. The reaction mixture was quenched with H₂O (30 mL), then extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was chromatographed on silica gel eluting with EtOAc:hexane (3:2) to afford 3-(4-pyridin-2-

yl-1*H*-imidazol-1-yl)benzotrile (**27**) as a white solid (175 mg, 71%). mp: 160-161°C; ¹H NMR (CD₃Cl 300 MHz) δ 8.58 (m, 1H), 8.03-8.02 (m, 2H), 7.95 (d, J=1.4 Hz 1H), 7.80~7.62 (m, 5H), 7.20 (ddd, J=1.0 Hz, 4.8 Hz, 7.4 Hz 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 152.29, 149.37, 144.25, 137.82, 136.95, 135.41, 131.20, 131.10, 125.32, 124.33, 122.35, 119.52, 117.52, 116.16, 114.37; MS (ESI) 247.1 (M⁺+H); HRMS Calcd. *m/e* 247.0978 (M+H)⁺; Found *m/e* 247.1021.

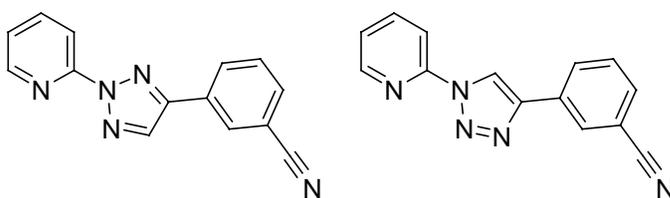
Synthesis of 3-(1*H*-1,2,3-triazol-4-yl)benzotrile (**29**)

3-Cyanobenzaldehyde **28** (3.0g, 22.9mmol), nitromethane (4.2 g, 68.7 mmol) and diethylamine (167 mg, 2.29 mmol) were stirred for 48 h in THF at 55°C in the presence of 4 Å molecular sieves. The resulting reaction mixture was filtered through celite and the resulting solution was concentrated *in vacuo*, then partitioned between EtOAc (200 mL) and H₂O (100 mL). The EtOAc layer was washed with H₂O (2x75mL) and brine (1x50 mL), then dried (MgSO₄), filtered, and concentrated *in vacuo*. The resulting residue was filtered through silica gel, eluting with hexanes:EtOAc (2:1) to obtain 3-(1-hydroxy-2-nitroethyl)benzotrile (3.37 g, 77% yield) as a pale yellow solid. MS (ESI) 193.1 (M⁺+H).

3-(1-Hydroxy-2-nitroethyl)benzotrile (3.32 g, 17.3 mmol) and triethylamine (4.37 g, 43.2 mmol) were stirred in anhydrous dichloromethane (100mL) at 0°C. To the resulting solution was added methanesulfonyl chloride (2.77 g, 24.2 mmol) dropwise *via* syringe, after which time the reaction was warmed to ambient temperature and stirred for 15 min. The resulting reaction mixture was diluted with additional dichloromethane (200 mL) and partitioned with H₂O (100 mL). The dichloromethane layer was dried (MgSO₄),

filtered and concentrated *in vacuo*. The resulting crude residue was filtered through silica gel eluting with hexane:EtOAc (4:1) to afford 3-[(*E*)-2-nitroethenyl]benzonitrile (2.79 g, 93% yield) as a yellow solid. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.99 (d, $J=13.8$ Hz, 1H), 7.86 (s, 1H), 7.78-7.82 (m, 2H), 7.65 (s, 1H), 7.62 (m, 1H).

3-[(*E*)-2-Nitroethenyl]benzonitrile (2.79 g, 16.0 mmol) and azidotrimethylsilane (2.76 g, 24.0 mmol) was stirred in anhydrous DMF (100 mL) at 50°C. To this was added tetrabutylammonium fluoride (17.6 mL of a 1.0 M solution in THF, 17.6 mmol) *via* syringe pump over 20 min. The resulting reaction was quenched with MeOH (25 mL) and concentrated *in vacuo* to a volume of *ca.* 30 mL. The resulting crude mixture was dissolved in EtOAc (300 mL) and washed with H_2O (2x100 mL). The product was then extracted from the EtOAc layer with 1M aqueous NaOH (4x75 mL). The combined basic aqueous portions were treated with 4M HCl to obtain an endpoint of pH = 4 and the product was extracted into EtOAc (4x100 mL). The combined EtOAc extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to obtain 3-(1*H*-1,2,3-triazol-4-yl)benzonitrile **29** (2.20 g, 81% yield) as a tan solid. MS (ESI) 171.1 ($\text{M}^+\text{+H}$).



Synthesis of 3-(2-pyridin-2-yl-2*H*-1,2,3-triazol-4-yl)benzonitrile (31) and 3-(1-pyridin-2-yl-1*H*-1,2,3-triazol-4-yl)benzonitrile (30)

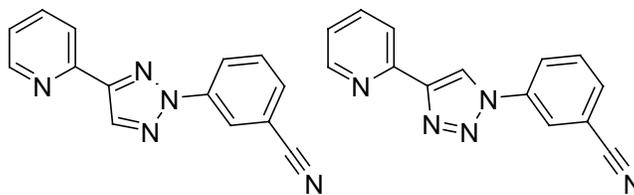
3-(1*H*-1,2,3-Triazol-4-yl)benzonitrile **29** (1.82 g, 10.69 mmol) was suspended in anhydrous MeOH (25 mL) under argon at ambient temperature. To this was added

NaOMe (21.4 mL of 0.5M solution in MeOH, 10.7 mmol), and the resulting reaction mixture was cooled to -78°C . A solution of *N*-fluoropyridinium triflate (2.95 g, 8.91 mmol) in anhydrous MeOH (5 mL) was then added dropwise *via* syringe. The reaction mixture was stirred at -78°C for 30 min, then warmed to ambient temperature and stirred for an additional 18 h. The reaction mixture was partitioned between EtOAc (300 mL) and 1N aqueous NaOH (100 mL). The EtOAc layer was washed with additional 1N aqueous NaOH (6x50 mL). The EtOAc layer was dried (MgSO_4), filtered and concentrated *in vacuo*. The resulting crude material was then chromatographed on silica gel eluting with hexanes:EtOAc (2:1) to afford 3-(2-pyridin-2-yl-2*H*-1,2,3-triazol-4-yl)benzotrile (**31**) as a tan solid (364 mg, 17% yield). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.65 (m, 1H), 8.27 (s, 1H), 8.14-8.21 (m, 3H), 7.92-7.98 (m, 1H), 7.70 (m, 1H), 7.59 (m, 1H), 7.37-7.41 (m, 1H); MS (ESI) 248.1 (M^+ +H). HRMS Calcd. *m/e* $\text{C}_{14}\text{H}_8\text{N}_5\text{Na}$ 270.0750; Found: 270.0761. The reaction also yielded 3-(1-pyridin-2-yl-1*H*-1,2,3-triazol-4-yl)benzotrile (**30**) as a tan solid (434 mg, 20% yield). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.90 (s, 1H), 8.54 (d, $J=4.8$ Hz, 1H), 8.16-8.27 (m, 3H), 7.97 (dd, $J=7.7$ Hz, $J=1.8$ Hz, 1H), 7.56-7.68 (m, 2H), 7.41 (m, 1H); MS (ESI) 248.1 (M^+ +H). HRMS Calcd. *m/e* $\text{C}_{14}\text{H}_8\text{N}_5\text{Na}$ 270.0750; Found: 270.0759.

Synthesis of 2-(2*H*-1,2,3-triazol-4-yl)pyridine (33)

2-Ethynylpyridine **32** (3.1 g, 30 mmol) and trimethylsilylazide (7.9 mL, 60 mmol) were combined under Ar (g) and heated at 95°C for 18 h. After cooling to ambient temperature, Et_2O (50 mL) and H_2O (2 mL) were added and the resulting reaction mixture was stirred for 2 h. The reaction mixture was then extracted with H_2O (3x50

mL) and the organic layer extracted with 1M KOH (3x30 mL). The two aqueous layers were combined and the pH adjusted to 7 with HCl (2M), extracted with EtOAc (3x50mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford 2-(2*H*-1,2,3-triazol-4-yl)pyridine **33** (1.1 g, 25%) as a brown solid that was used in the next step without further purification. ¹H NMR (CD₃Cl, 300 MHz) δ 8.59 – 8.60 (1H, m), 8.28 (1H, s), 8.06 (1H, d), 7.87 (1H, m), 7.34 (1H, m).



Synthesis of 3-(4-pyridin-2-yl-2*H*-1,2,3-triazol-2-yl)benzonitrile (35) and 3-(4-pyridin-2-yl-1*H*-1,2,3-triazol-1-yl)benzonitrile (34)

2-(2*H*-1,2,3-Triazol-4-yl)pyridine **33** (510 mg, 3.5 mmol), 3-fluorobenzonitrile (0.37 mL, 3.5 mmol) and K₂CO₃ (1 g, 7 mmol) were dissolved in DMF (10 mL) under Ar (g) and heated at 140°C for 18 h. After cooling to ambient temperature, H₂O (40 mL) and EtOAc (40 mL) were added and the resulting reaction mixture shaken. The EtOAc layer was separated and the aqueous layer shaken with EtOAc (2x30 mL). The combined organic layers were washed with brine (3x40 mL), dried over Na₂SO₄ and concentrated onto silica gel. This was purified by liquid chromatography on silica gel eluting with EtOAc:hexane (1:1) to afford: A) A white solid. This was dissolved in Et₂O/dichloromethane (20 mL/5 mL) and HCl (1M in Et₂O, 1.2 mL) was added. The resulting fine precipitate was filtered, and washed with dichloromethane to afford 3-(4-pyridin-2-yl-2*H*-1,2,3-triazol-2-yl)benzonitrile hydrochloride (**35**) (249 mg, 29%). Mp =

207-208 °C ^1H NMR (CD_3Cl , 300 MHz) δ 8.79 (1H, s), 8.75 – 8.78 (1H, m), 8.49 – 8.51 (1H, m), 8.38 – 8.43 (1H, m), 8.18 – 8.25 (1H, m), 8.11 (1H, ddd, $J = 7.0, 7.0, 1.5$ Hz), 7.91 – 7.95 (1H, m), 7.80 (1H, dd, $J = 7.1, 7.1$ Hz), 7.57 (1H, ddd, $J = 6.7, 4.4, 0.9$ Hz); ^{13}C NMR (CD_3OD , 500 MHz) δ 149.1, 148.8, 147.4, 139.6, 139.6, 136.2, 132.2, 131.8, 125.2, 123.6, 122.2, 122.1, 118.3, 113.2; MS (ESI) 248 ($\text{M}+\text{H}$) $^+$; HRMS Calcd. m/e 248.0931 ($\text{M}+\text{H}$) $^+$; Found m/e 248.0946. (B) A second white solid. This solid was recrystallized from EtOAc/Hexane to afford white crystals which were dissolved in Et₂O/dichloromethane (20 mL/5 mL). HCl (1M in Et₂O, 0.3 mL) was added. The resulting fine precipitate was filtered, washing with dichloromethane to afford 3-(4-pyridin-2-yl-1*H*-1,2,3-triazol-1-yl)benzotrile (**34**) (109 mg, 13%). Mp = 228-229 °C; ^1H NMR (CD_3Cl , 300 MHz) δ 9.64 (1H, s), 8.66 – 8.68 (1H, m), 8.51 (1H, m), 8.35 – 8.39 (1H, m), 8.16 – 8.24 (1H, m), 8.14 (1H, m), 7.94 – 8.00 (1H, m), 7.81 (1H, m), 7.54 (1H, m); ^{13}C NMR (CD_3OD , 500 MHz) δ 148.6, 148.0, 147.1, 140.0, 137.3, 133.1, 131.9, 125.5, 124.6, 124.2, 122.9, 121.3, 118.2, 113.3; MS (ESI) 248 ($\text{M}+\text{H}$) $^+$; HRMS Calcd. m/e 316.1193 ($\text{M}+\text{H}$) $^+$. Found m/e 316.1232. The structures of compounds **34** and **35** were assigned on the basis of data from nOe experiments.

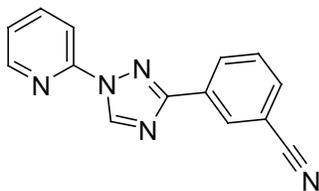
Synthesis of 3-bromo-1*H*-1,2,4-triazole (37)

3-Nitro-1,2,4 triazole **36** (2.0g, 17.5mmol) was heated at reflux for 8h in concentrated hydrobromic acid (40mL), after which time it was cooled to ambient temperature and poured slowly into water (100mL). The aqueous mixture was extracted with EtOAc (500mL), then the organic phase was washed with water (2x100mL) and brine (100mL). The organic phase was dried (MgSO_4), filtered, and concentrated *in*

vacuo. The resulting crude residue was washed with EtOAc (1mL), then with hexane (8mL) to afford 3-bromo-1H-1,2,4-triazole (**37**) as a yellow solid (2 g, 80%). ¹H NMR (CD₃OD, 300 MHz) δ 8.99 (s, 1H); MS (ESI) 147.95 (M⁺+2H).

Synthesis of 2-(3-bromo-1H-1,2,4-triazol-1-yl)pyridine (38)

3-Bromo-1H-1,2,4-triazole **37** (1.9 g, 12.8 mmol) was dissolved in anhydrous methanol (20 mL). NaOMe (51 mL of a 0.5M solution in methanol, 25.6 mmol) was then added to the stirred solution and the resulting reaction mixture was cooled to -78°C in an argon blanketed flask. 1-Fluoropyridinium triflate (4.9 g, 15 mmol) in anhydrous methanol (20 mL) was added dropwise to this stirred solution. The resulting yellow mixture was stirred at -78°C for 1h under argon atmosphere, then allowed to reach ambient temperature. The mixture was stirred for 16 h at ambient temperature, after which time it was concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (100 mL), the EtOAc solution washed with H₂O (100 mL), then brine (100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane:EtOAc (90:10) to afford 2-(3-bromo-1H-1,2,4-triazol-1-yl)pyridine **38** (0.5 g, 20%) as a white solid. ¹H NMR (CD₃OD, 300 MHz) δ 9.27 (s, 1H), 8.51 (d, 1H), 8.03 (dd, 1H), 7.88 (d, 1H), 7.45 (dd, 1H); MS (ESI) 224.9 (M⁺+2H).



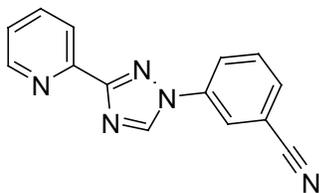
Synthesis of 3-(1-pyridin-2-yl-1H-1,2,4-triazol-3-yl)benzotrile (39)

2-(3-Bromo-1H-1,2,4-triazol-1-yl)pyridine **38** (0.25 g, 1.12 mmol) and 3-cyanophenylboronic acid (0.33 g , 2.23 mmol) were dissolved in toluene (20 mL) and methanol (2 mL), then deoxygenated *via* argon bubbling for 10 min. Potassium carbonate (0.23 g, 1.6 mmol) and tetrakis(triphenylphosphine)palladium (129 mg, 0.11 mmol) were then added to the stirred solution. The reaction flask was fitted with a reflux condenser and the mixture stirred at 90°C for 16 h, after which time it was cooled to ambient temperature and poured into a separatory funnel containing EtOAc (100 mL). The EtOAc solution was washed with H₂O (2x100 mL), then brine (100 mL) and the organic phase was dried (MgSO₄), filtered and concentrated *in vacuo*. The resulting crude residue was chromatographed on silica gel eluting with hexanes:EtOAc (40:60) to afford 3-(1-pyridin-2-yl-1H-1,2,4-triazol-3-yl)benzotrile (**39**) as a white solid (0.15 g , 54%) which was then dissolved in dichloromethane (10mL) and precipitated as the hydrochloride salt upon treatment with 1M HCl in diethyl ether (1mL). M.p.=185-188 °C; ¹H NMR (CD₃OD, 300 MHz) δ 9.42 (s, 1H), 8.49 (d, J=3.6 Hz, 1H), 8.37 (s, 1H), 8.34 (d, J=8.1 Hz 1H), 8.04 (dt, J=.1.8HZ J=8.2 Hz, 1H), 7.90 (t, J=8.7 Hz, 2H), 7.68 (t, 7.3 Hz, 1H), 7.44 (dt, J=1.6 Hz, J=6.5 Hz, 1H); ¹³C NMR (CD₃OD, 500 MHz) δ 160.5, 148.7, 148.6, 143.4, 140.1, 133.3, 131.1, 130.5, 130.3, 129.3, 123.8, 118.2, 113.0, 112.12; MS (ESI) 248.1 (M⁺+H); HRMS Calcd. *m/e* C₁₄H₉N₅ 248.0931; found *m/e* 248.0973.

Synthesis of 2-(1H-1,2,4-triazol 3-yl)pyridine (41)

2-Cyanopyridine **40** (5.2 g, 50 mmol) and hydrazine hydrate (2.95 g, 50 mmol) were mixed and a small amount of ethanol was added to obtain a clear solution. After standing overnight at ambient temperature, the resulting white crystals were collected by filtration. The resulting product was washed with diethyl ether and dried in the air to afford pyridine-2-carbohydrazonamide (3.9 g, 57%). ^1H NMR (DMSO, 300 MHz) δ 8.49 (d, J=6.3 Hz, 1H), 7.92 (d, J=9.0 Hz, 1H), 7.44 (t, J=9.0 Hz, 1H), 7.31 (t, J=5.7 Hz, 1H), 5.74 (s, 2H), 5.30 (s, 2H); ^{13}C NMR (CD_3OD , 500 MHz) δ 151.4, 149.7, 148.8, 137.3, 124.8, 120.6.

Pyridine-2-carbohydrazonamide (1.0 g, 7.3 mmol) was added in small amounts to an excess (15ml) of ice-cold formic acid. The resulting mixture was brought to, and maintained at, ambient temperature for about 30min, then heated at reflux for about 4h. Most of the excess acid was removed on a rotary evaporator, and the residual crude product was neutralized with 10% Na_2CO_3 solution and extracted with EtOAc (2x100 mL). The EtOAc solution was washed with H_2O (100 mL) and brine (100 mL), then dried (MgSO_4), filtered and concentrated *in vacuo*. The resulting crude product was crystallized from chloroform to afford 2-(1H-1,2,4-triazol 3-yl)pyridine **41** (0.38 g, 38%). M.P = 90-95°C; ^1H NMR (CD_3OD , 300 MHz) δ 8.67 (d,1H), 8.36 (s, 1H), 8.11 (d, 1H), 7.95 (t, 1H), 7.47 (m, 1H); MS (ESI) 146.9 ($\text{M}^+\text{+H}$).



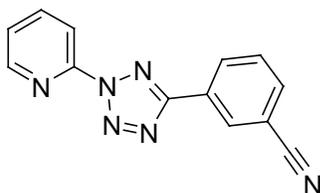
Synthesis of 3-(3-pyridin-2-yl-1H-1,2,4-triazol-1-yl)benzotrile (42)

2-(1H-1,2,4-Triazol-3-yl)pyridine **41** (0.24g, 1.6mmol), potassium carbonate (0.45 g, 3.2 mmol) and 3-fluorobenzotrile (0.20 g, 1.6 mmol) were stirred in DMF (20 mL) at ambient temperature. The resulting reaction mixture was heated at 145°C for 16h, after which time it was quenched with H₂O (30 mL) and diluted with EtOAc (200 mL). The EtOAc solution was washed with H₂O (3x100 mL), then brine (100 mL) and dried (MgSO₄), filtered, and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel eluting with hexane:EtOAc (40:60) to afford 3-(3-pyridin-2-yl-1H-1,2,4-triazol-1-yl)benzotrile (**42**) as a white solid (0.24, 60%). M.p.=194-195°C; ¹H NMR (CD₃OD, 300 MHz) δ 8.81 (d, J=3.0 Hz, 1H), 8.72 (s, 1H), 8.24 (t, J=7.8 Hz, 1H), 8.10 (d, J=1.2 Hz, 1H), 7.86 (t, J=1.8 Hz, 1H), 7.73-7.65 (m, 2H), 7.42-7.38 (m, 1H), 7.27 (s, 1H); ¹³C NMR (CD₃OD, 300 MHz) δ 163.2, 150.3, 148.2, 141.8, 137.5, 137.0, 131.6, 130.8, 124.6, 123.8, 123.3, 122.2, 117.5, 114.5; MS (ESI) 248.1 (M⁺+H). HRMS Calcd. *m/e* C₁₄H₉N₅ 248.0931; found 248.0963.

Synthesis of 3-(2H-tetrazol-5-yl)benzotrile (44)

1,3-Dicyanobenzene **43** (2.0 g, 15.6 mmol), azidotrimethylsilane (1.80 g, 15.6 mmol), and dibutyltin oxide (388 mg, 1.56 mmol) were combined in toluene (100 mL) at room temperature. The resulting mixture was then heated with stirring at 110°C. TLC analysis of the reaction at 1 hr showed consumption of starting material 1,3-dicyanobenzene. The

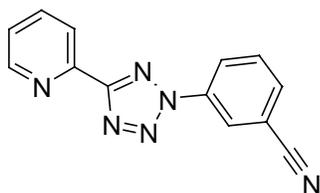
mixture was then cooled to room temperature and concentrated *in vacuo*. Contents were then resuspended via slow addition of MeOH (50 mL) and reconstituted *in vacuo*. The contents were then partitioned in a separatory funnel with EtOAc (200 mL) and 5% NaHCO₃ (100 mL). The EtOAc portion was washed with additional 5% NaHCO₃ (2x75 mL), and the combined aqueous layers back extracted with EtOAc (100 mL). The aqueous layer was then adjusted to pH 4 with 3N HCl. The resulting mixture was then extracted with EtOAc (3x100 mL). The combined EtOAc layers were dried over MgSO₄, filtered, and concentrated *in vacuo* to afford 3-(2*H*-tetrazol-5-yl)benzonitrile **44** (921 mg, 34%) as a white solid. MS (ESI) 172.1 (M⁺+H).



Synthesis of 3-(2-pyridin-2-yl-2*H*-tetrazol-5-yl)benzonitrile (**45**)

To a solution of 3-(2*H*-tetrazol-5-yl)benzonitrile (920 mg, 5.4 mmol) in anhydrous MeOH (30 mL) was added NaOMe (5.4 mmol, 10.8 mL of 0.5 M solution in MeOH) at room temperature under Ar (g). After 10 min of stirring at room temperature, the reaction flask was cooled to -78°C, and *N*-fluoropyridinium tetrafluoroborate (2.0 g, 10.8 mmol) was added as a solid through a septum inlet. Stirring at -78°C was continued for 1 h, then the cold bath was removed and the stirring was continued at room temperature for an additional 2 h, then quenched with H₂O (100 mL). The resulting aqueous mixture was partitioned with EtOAc (150 mL). The EtOAc layer was washed with 5% NaHCO₃ (2x50 mL). The combined aqueous layers were then back-extracted

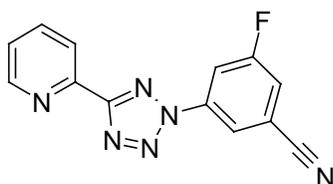
with EtOAc (100 mL). The EtOAc layers were combined, dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was then filtered through a short pad of SiO₂, eluting with 40% EtOAc in hexanes to afford 3-(2-pyridin-2-yl-2H-tetrazol-5-yl)benzonitrile **45** (418 mg, 31%) as a white solid. ¹H-NMR (CDCl₃, 300 MHz) δ 8.76 (d, J=4.83 Hz, 1H), 8.64 (s, 1H), 8.56 (d, J=7.92 Hz, 1H), 8.27 (d, J= 8.13 Hz, 1H), 8.07 (dd, J=7.8 Hz, J=1.8 Hz, 1H), 7.81 (m, 1H), 7.68 (dd, J=7.86 Hz, 1H), 7.56 (m, 1H); ¹³C-NMR (CDCl₃, 300 MHz) δ 164.2, 150.0, 148.9, 140.0, 134.4, 131.7, 131.2, 130.4, 128.5, 125.8, 118.4, 115.6, 113.8; MS (ESI) 249.1 (M⁺+H); HRMS Calcd. *m/e* C₁₃H₇N₆Na 271.0703; Found: 271.0717.



Synthesis of 3-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile (**47**)

To a solution of 2-pyridyl carboxaldehyde **46** (6.42 g, 60.0 mmol) stirred in EtOH (150 mL) at room temperature in a 1 L round bottom flask was added p-toluenesulfonyl hydrazide (11.2 g, 60.0 mmol). After 30 min. the reaction was determined to be complete by TLC analysis which showed the disappearance of starting aldehyde by 2,4-DNP stain. The condensation product 4-methyl-*N'*-[(1*E*)-pyridin-2-ylmethylene]benzenesulfonohydrazide was left in EtOH solution and treated at room temperature with NaOH pellets (12.0 g, 300.0 mmol). Upon full dissolution of the NaOH pellets, the reaction flask was cooled to -5°C (ice/salt bath) to await the next step in the procedure. Meanwhile, in a separate flask containing 3-aminobenzonitrile (7.0 g, 60.0

mmol) in 6M HCl (36 mL) at -5°C was added NaNO_2 (4.43 g, 64.2 mmol) dropwise as a solution in H_2O (10 mL). The resulting diazonium solution was left to stir for an additional 5 min. at -5°C , then transferred dropwise to the original flask containing the NaOH-treated solution of 4-methyl-*N'*-[(1*E*)-pyridin-2-ylmethylene]benzenesulfonohydrazide. After complete addition, the heterogeneous red reaction mixture was poured in to a separatory funnel and partitioned with EtOAc (400 mL) and H_2O (200 mL). The EtOAc layer was washed with additional H_2O (3x100 mL) and brine (100 mL). The combined aqueous extracts were back-extracted with EtOAc (150 mL). The organic layers were then combined, dried over MgSO_4 , filtered, and concentrated to dryness *in vacuo*. The crude material was purified by SiO_2 column chromatography, eluting with EtOAc:hexanes (1:1) to afford 3-(5-pyridin-2-yl-2*H*-tetrazol-2-yl)benzonitrile **47** (8.2 g, 55%) as an orange solid. MS (ESI) 249.1 ($\text{M}^+\text{+H}$); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.87 (d, $J=4.95$ Hz, 1H), 8.62 (s, 1H), 8.56 (m, 1H), 8.35 (d, $J=7.92$ Hz, 1H), 7.94 (dd, $J=7.74$ Hz, 1H), 7.73-7.85 (m, 2H), 7.49 (m, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 300 MHz) δ 165.6, 151.0, 146.3, 137.7, 137.4, 133.6, 131.3, 125.8, 124.3, 123.7, 123.4, 117.6, 114.5. HRMS Calcd. *m/e* $\text{C}_{13}\text{H}_7\text{N}_6\text{Na}$ 271.0703; Found: 271.0699.



Synthesis of 3-fluoro-5-(5-pyridin-2-yl-2*H*-tetrazol-2-yl)benzonitrile (**48**)

A high pressure flask (150 mL capacity) with a stirrer bar was charged with 3,5-difluorobenzonitrile (3.0 g, 21.6 mmol) then evacuated and filled with argon. The flask was cooled to -78°C and NH_3 gas (1.5 mL) was condensed into the cold flask. DMSO (20

mL) was added and the flask was sealed. The flask was warmed ambient temperature then heated to 90°C for 48 h. The flask was again cooled to -78°C and opened to liberate the NH₃ as it was allowed to reach ambient temperature. The reaction was quenched with H₂O (200 mL) and diluted with EtOAc (200 mL). The EtOAc solution was washed with H₂O (3x100 mL), then brine (100mL) and dried (MgSO₄), filtered, and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel eluting with hexane:EtOAc (1:1) to afford 3-amino5-fluorobenzonitrile (1.5 g, 70%). ¹H NMR (CD₃OD, 300 MHz) δ 6.69-6.71 (m, 2H), 6.65-6.58 (m, 1H), 4.07 (s, 2H).

3-Amino5-fluorobenzonitrile (1.5g, 11 mmol) was dissolved in a mixture of water (50 mL) and conc. HCl (3.5 ml). The solution was cooled to 0-5°C in an ice-salt bath and a solution of sodium nitrite(0.83 g, 12.1 mmol) in water (25 mL) was added dropwise, with stirring without allowing the temperature to exceed 5°C. In a separate flask 2-pyridylcarboxaldehyde (1.2 g, 11 mmol) was dissolved in EtOH (500 mL) and added benzylsulfonyl hydrazide (1.9g, 11 mmol) was added. After stirring for 20 min at ambient temperature the reaction mixture was concentrated *in vacuo* and the residue was dissolved in pyridine (20 mL). The solution was cooled to 0°C and to this solution was added the contents of the diazotization reaction dropwise over 15 min. After stirring at room temperature for 30 min. the precipitate was filtered. The resulting precipitate was chromatographed on silica gel eluting with hexane:EtOAc (1:1) to afford 3-fluoro-5-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile **48** (1.35, 80%) as a white solid. M.p.=135-137°C; ¹H NMR (CD₃OD, 300 MHz) δ 9.04-9.05 (d, J=3.0 Hz, 1H), 8.84-8.85 (d, J=3.0 Hz, 1H), 8.74-8.76 (dd, J= 6.0 Hz, 1H), 8.55(s, 1H), 8.44-8.47(m, 1H), 8.18-8.20(dd, J=6.0 HZ, 1H), 7.92-7.7.95(m, 1H); ¹³C NMR (CD₃OD, 300 MHz) δ 164.2, 162.2,

160.4, 146.4, 144.9, 140.6, 138.0 138.1, 128.6, 125.8, 121.7, 121.5, 120.2, 116.3, 116.2, 116.1, 113.07, 112.9.; MS (ESI) 267.1 ($M^+ + H$). HRMS Calcd. m/e $C_{13}H_6FN_6Na$ 289.0609; Found 289.0649.

References

1. Cosford, Nicholas David; Roppe, Jeffrey; Chen, Chixu; Smith, Nicholas; Reger, Thomas. **Heteroaryl Substituted Tetrazole Modulators of Metabotropic Glutamate Receptor 5**. PCT Int. Appl. (2003), WO 0329210 priority: Oct. 4, 2001.
2. Cosford, Nicholas David; Smith, Nicholas; Huang, Dehua. **Heteroaryl Substituted Imidazole Modulators of Metabotropic Glutamate Receptor 5**. PCT Int. Appl. (2003), WO 2003053922 priority Dec. 19, 2001.
3. Cosford, Nicholas David; Smith, Nicholas; Roppe, Jeffrey; Tehrani, Lida; Prasit, Peppi. **Heteroaryl Substituted Triazole Modulators of Metabotropic Glutamate Receptor 5**. PCT Int. Appl. (2003), WO 2003051315 priority Dec. 18, 2001.
4. Cosford, Nicholas David; Chen, Chixu; Munoz, Benito; Smith, Nicholas; Prasit, Peppi; Huang, Dehua; Eastman, Brian. **Heteroaryl Substituted Pyrazole Modulators of Metabotropic Glutamate Receptor 5**. PCT Int. Appl. (2003), WO 2003051833 priority Dec. 18, 2001.
5. Cosford, Nicholas David; Smith, Nicholas; Huang, Dehua. **Heteroaryl Substituted Pyrrole Modulators of Metabotropic Glutamate Receptor 5**. PCT Int. Appl. (2003), WO 2003059904 priority Dec. 21, 2001.
6. Smith, Nicholas; Cosford, Nicholas David; Reger, Thomas; Roppe, Jeffrey; Poon, Steven; Huang, Dehua; Chen, Chixu; Eastman, Brian. **Di-aryl Substituted Tetrazole Modulators of Metabotropic Glutamate Receptor 5**. PCT Int. Appl. (2003), WO 2003077918 priority Mar. 12, 2002.