Supplemental File 3. Synthesis of new inhibitors.

**Chemistry of new compounds from Paul O’Neill laboratory.**

**1,2-Bis (4-cyanophenoxy) ethane** (Ethamidine Precursor) **(1a)** 1



Sodium (0.16 g, 6.96 mmol) was added portionwise to anhydrous EtOH (4.0 mL) under an atmosphere of nitrogen. After dissolution of the sodium pieces, a solution of 4-cyanophenol (0.75 g, 6.38 mmol) dissolved in anhydrous EtOH (4.0 mL) was added followed by dropwise addition of 1,2-dibromoethane (0.28 mL, 3.19 mmol). The reaction mixture was allowed to stir at reﬂux under a nitrogen atmosphere for 3 days after which the mixture was cooled, ﬁltered, the solid washed with water and dried under vacuum. Puriﬁcation by column chromatography eluting with DCM: hexane (8:2) gave the desired dinitrile ethamidine precursor (**1a**) as a white solid (1.42 g, 84%). Mp 211-212°C; 1H NMR (CDCl3, 400MHz) δ 7.61 (d, 4H, *J* = 9.0 Hz, ArH), 7.01 (d, 4H, *J* = 9.0 Hz, ArH), 4.39 (s, 4H, CH2); 13C NMR (CDCl3, 100MHz) δ 161.6, 134.1, 118.9, 115.3, 104.7, 66.4; νmax (NujOI) /cm-1 3326 (C-O-C), 3033 (ArH), 2898 (OH), 2223 (CN), 1602 (Ar), 1509 (Ar), 1247 (C-O-C); *m/z* (CI) 282 ([M+NH4]+), found 282.12433, C16H16O2N3 requires 282.12424; anal. Found C 72.37, H 4.51, N 10.54, C16H12O2N2 requires C 72.71, H 4.57, N 10.60.

**4,4'-(ethane-1,2-diylbis(oxy))dibenzimidamide dihydrochloride dihydrate** (Ethamidine, Compound CHI/1/30/1) (**2**) 1



(0.51 g, 1.92 mmol) of **1a** was dissolved in a mixture of anhydrous benzene (54 mL) and EtOH (2.90 mL), cooled to 0 °C and saturated with HCl gas. The mixture was sealed and allowed to stir at room temperature for 3 days after which anhydrous Et2O (28 mL) was introduced and the mixture was allowed to stir for 10 minutes. The solids were ﬁltered under nitrogen and dissolved in a mixture of anhydrous EtOH (36 mL) and EtOH.NH3 (36 mL). The mixture was heated overnight (50 oC), cooled to room temperature and reduced by half *in vacuo*. Ether was added to precipitate the solid which was ﬁltered, washed and dried under vacuum. Puriﬁcation by recrystallisation (2N HCl) gave the desired compound **2** as ﬁne white needles (0.54 g, 70%). Mp 333°C; 1H NMR (MeOD, 400MHz) δ 7.85 (d, 4H, *J* = 9.0 Hz, ArH), 7.23 (d, 4H, *J* = 9.0 Hz, ArH), 4.52 (s, 4H, CH2); 13C NMR (MeOD, 100MHz) δ 167.9, 165.3, 131.5, 121.7, 116.7, 68.5; νmax (Nujol) /cm-1 3362 (NH), 3037 (ArH), 2940 (C-H), 1658 (C=N-H), 1606 (Ar), 1505 (Ar), 1245 (C-0-C); *m/z* (ESP) 299 ([M-H]-); anal. Found C 47.54 H 5.62 N 14.30, C16H24N4O4Cl2 requires C 47.18, H 5.94, N 13.76.

**4, 4’-(propane-1,3-diylbis(oxy))dibenzonitrile** (Propamidine Precursor) (**1b**)1



Sodium (0.16 g, 6.96 mmol) was added portionwise to anhydrous EtOH (4.0 mL) with stirring under an atmosphere of nitrogen. After dissolution of Na, a solution of 4-cyanophenol (0.75 g, 6.38 mmol) dissolved in dry ethanol (4.0 mL) was added followed by dropwise addition of 1,3-dibromopropane (0.32 mL, 3.19 mmol). The reaction mixture was allowed to stir at reﬂux under a nitrogen atmosphere for 3 days after which the mixture was cooled, ﬁltered, the solid washed with water and dried under vacuum. Puriﬁcation by column chromatography eluting with DCM: hexane (8:2) gave the desired compound **1b** as a white solid (1.40 g, 79%). Mp 190-191°C; 1H NMR (CDCl3, 400MHz) δ 7.59 (d, 4H, *J* = 8.5 Hz, ArH), 6.96 (d, 4H, *J* = 8.5 Hz, ArH), 4.20 (t, 4H, *J* = 6.0 Hz, CH2), 2.32 (m, 2H, CH2); 13C NMR (CDCl3, 100MHz) δ 161.9, 134.0, 119.1, 115.1, 104.2, 64.4, 28.8; νmax (Nujol) /cm-1 3104 (Ar-H), 2823 (C-H), 2221 (C≡N), 1604 (Ar), 1509 (Ar), 1253 (C-O); *m/z* (CI) 296 ([M+NH4]+), found 296.14037, C17H18N3O2 requires 296.13992; anal. Found C 73.22, H 5.13, N 10.03, C17H14N2O2 requires C 73.37, H 5.07, N 10.07.

**4,4’-(propane-1,3-diyl*bis*(oxy))dibenzimidamide dihydrochloride dihydrate** (Propamidine, Compound CHI/1/25/5) (**3**)1



(0.50 g, 1.79 mmol) of **1b** was dissolved in a mixture of anhydrous benzene (55 mL) and anhydrous ethanol (3.0 mL), cooled to 0 oC and saturated with HCl gas. The mixture was sealed and allowed to stir at room temperature for 3 days after which ether (30 mL) was added and the mixture was allowed to stir for 10 minutes. The solids were ﬁltered under nitrogen and dissolved in a mixture of anhydrous EtOH (36 ml) and EtOH.NH3 (36 mL). The mixture was heated overnight (50 °C), cooled to room temperature and reduced by half *in vacuo*. Et2O (15 mL) was added to precipitate the solid which was ﬁltered, washed and dried under vacuum. Puriﬁcation by recrystallisation (2N HCl) gave the desired compound **3** as ﬁne white needles (0.59 g, 78%). Mp 200°C; 1H NMR (MeOD, 400MHz) δ 7.82 (d, 4H, *J* = 9.0 Hz, ArH), 7.19 (d, 4H, *J* = 9.0 Hz, ArH), 4.34 (t, 4H, *J* = 6.0 Hz, CH2), 2.46 (m, 2H, CH2); 13C NMR (MeOD, 100MHz) δ 167.9, 165.5, 131.5, 121.5, 121.4, 116.6, 66.4, 30.3; νmax (Nujol) /cm-1 3280 (N-H), 3038 (Ar-H), 2929 (C-H), 1504 (Ar), 1606 (Ar), 1240 (C-O-C); *m/z* (ESP) 313 ([M-H]-); anal. Found C 48.60, H 6.10, N 13.25, C17H26N4O4Cl2 requires C 48.46, H 6.22, N 13.30.

**4,4’-(Butane-1,4-diylbis(oxy))dibenzonitrile** (Butamidine precursor) (**1c**)1



Sodium (0.10 g, 4.35 mmol) was added portionwise to dry EtOH (4.0 mL) stirring under an atmosphere of nitrogen. After dissolution of sodium, a solution of 4-cyanophenol (0.47 g, 3.95 mmol) dissolved in dry ethanol (4.0 mL) was added followed by dropwise addition of 1,4-dibromobutane (0.24 mL, 1.98 mmol). The reaction mixture was allowed to stir at reﬂux under a nitrogen atmosphere for 3 days after which the mixture was cooled, ﬁltered, the solid washed with water and dried under vacuum. Purification by column chromatography eluting with DCM: hexane (8:2) gave the desired compound **1c** as a white solid (1.03 g, 89%). Mp 174°C; 'H NMR (CDCI3, 400MHz) δ 7.59 (d, 4H, *J* = 8.9 Hz, ArH), 6.93 (d, 4H, *J* = 8.9 Hz, ArH), 4.08 (m, 4H, CH2), 2.01 (m, 4H, CH2); 13C NMR (CDCl3, 100MHz) δ 162,1, 134.0, 119.1, 115.1, 104.0, 67.7, 25.7; νmax (Nujol) /cm-1 3332 (C-O-C), 3033 (Ar-H). 2956 (C-H), 2219 (C≡N), 1604 (Ar). 1506 (Ar), 1251 (C-O-C); *m/z* (CI) 310 ([M+NH4]+) found 310.15532, C18H20N3O2 requires 310.15555; anal. Found C 74.03, H 5.55, N 9.55, C18H16N2O2 requires 73.95, H 5.52, N 9.58.

**4,4’-(Butane-l ,4-diylbis(oxy))dibenzimiamide dihydrochloride dihydrate** (Butamidine, Compound CHI/1/41/1) (**4**)1



Compound **1c** (0.42 g, 1.44 mmol) was dissolved in a mixture of anhydrous benzene (46 mL) and anhydrous ethanol (2.50 mL), cooled to 0 °C and saturated with HCl gas. The mixture was sealed and allowed to stir at room temperature for 3 days after which anhydrous Et2O (40 mL) was introduced and the mixture was allowed to stir for 10 minutes. The solids were ﬁltered under nitrogen and dissolved in a mixture of anhydrous EtOH (34 mL) and EtOH.NH3 (34 mL). The mixture was heated overnight (50 °C), cooled to room temperature and reduced by half *in vacuo*. Ether (15 mL) was added to precipitate the solid which was ﬁltered, washed and dried under vacuum. Puriﬁcation by recrystallisation (2N HCl) gave the desired compound **4** as ﬁne white needles (0.46 g, 73%). Mp 286-287°C', ‘H NMR (MeOD, 400MHz) δ, 7.80 (d, 4H, *J* = 9.0 Hz, ArH), 7.14 (d, 4H, *J* = 9.0Hz, ArH), 4.19 (m, 4H, CH2), 2.02 (m, 4H, CH2); 13 CNMR (MeOD, 100MHz) δ 165.7, 131.4, 121.2, 116.7, 69.7, 27.2; νmax (Nujol) /cm-1 3370 (N-H), 3129 (Ar-H), 2884 (C-H), 1650 (C≡N), 1606 (Ar), 1508 (Ar), 1257 (C-O); *m/z* (ESP) 327 ([M+H]+); anal. Found C 49.87, H 6.46, N 12.67, C18H28N4O4Cl2 requires C 49.66, H 6.48, N 12.87.

**4-(4-phenoxybutoxy) benzonitrile**



Sodium (0.16g, 6.96 mmol) was added dropwise to dry ethanol (5 mL) and dissolved under a nitrogen atmosphere. To this a solution of 4-cyanophenol (0.53g, 4.47 mmol) dissolved in anhydrous ethanol (5ml) was added followed by addition of 1,4-dibromobutane (0.53 mL, 4.47 mmol). The reaction mixture was allowed to stir at reflux and monitored by TLC. After consumption of 4-cyanophenol, the reaction mixture was allowed to cool to room temperature. In a separate ﬂask sodium (0 16 g, 6.96 mmol) was added portionwise to ethanol (5 mL) stirring under nitrogen. A solution of phenol (0.42 g, 4.47 mmol) in ethanol (5ml) was added and stirred for 10 minutes. This mixture was added dropwise to the cooled mixture and allowed to stir under reﬂux for 3 days after which the mixture was cooled, ﬁltered, the solid washed with water and dried under vacuum. Puriﬁcation by column chromatography eluting with DCM: hexane (8:2) gave the desired compound 4-(4-phenoxybutoxy) benzonitrileas a white solid (0.98 g, 82%). Mp 130°C; 1H NMR (CDCl3, 400MHZ) δ 7.57 (d, 2H, *J* = 8.9 Hz, ArH), 7.28 (d, 1H, *J* = 7.5 Hz, ArH), 7.26 (d, 1H, *J* = 8.1 Hz, ArH), 6.92 (m, 5H, ArH), 4.08 (t, 2H, *J* = 5.9 Hz, CH2), 4.03 (t, 2H, *J* = 5.9 Hz, CH2), 1.99 (m, 4H, CH2); 13C NMR (CDCl3, 100MHz) δ 162.6, 159.2, 134.3, 129.8, 121.1, 115.5, 114.8, 104.3, 68.3, 67.5, 26.2; νmax (Nujol) /cm-1 3043 (Ar-H), 2884 (C-H), 2219 (C≡N), 1602 (Ar), 1504 (Ar), 1247 (C-O); *m/z* (CI) 285 ([M+NH4]+), found 285.16020, C17H21N2O2 requires 285.16031; anal. Found C 76.40, H 6.46, N 5.44, C17H17NO2 requires C 76.38, H 6.40, N 5.24.

**4-(4-Phenoxybutoxy)benzimidamide hydrochloride hydrate** (Compound CHI/1/69/1)



4-(4-phenoxybutoxy) benzonitrile (0.27 g, 1.01 mmol) was dissolved in a mixture of anhydrous benzene (100 mL) and ethanol (1.60 mL), cooled to 0 °C and saturated with HCl gas. The mixture was sealed and allowed to stir at room temperature for 3 days after which anhydrous Et2O (16 mL) was introduced and the mixture was allowed to stir for an additional 10 minutes. The solids were ﬁltered under nitrogen and dissolved in a mixture of anhydrous EtOH (20 mL) and anhydrous EtOH.NH3 (20 mL). The mixture was heated overnight (50 oC), cooled to room temperature and reduced by half *in vacuo*. Ether (30 mL) was added to precipitate the solid which was ﬁltered, washed and dried under vacuum. Puriﬁcation by recrystallisation (2N HCl) gave the desired compound 4-(4**-**Phenoxybutoxy)benzimidamide hydrochloride hydrate as fine white needles (0.28 g, 82%). Mp 134-135°C; 1H NMR (DMSO, 400MHz) δ 9.28 (s, 2H, NH;), 9.08 (s, 2H, NHZ), 7.86 (d, 2H, *J* = 9.0 Hz, ArH), 7.29 (d, 1H, *J* = 7.0 HZ, ArH), 7.27 (d, 1H, *J* = 7.2 Hz, ArH), 7.16 (d, 2H, *J* = 9.0 Hz, ArH), 6.93 (d, 3H, *J* = 7.8 Hz, ArH), 4.16 (t, 2H, *J* = 5.9 Hz, CH2), 4.03 (t, 2H, *J* = 5.9 Hz, CH2), 1.89 (m, 4H, CH2); 13C NMR (DMSO, 100MHZ) δ 165.0, 163.3, 158.9, 130.5, 129.8, 120.7, 119.6, 115.1, 114.7, 68.1, 67.2, 25.6, 25.5; νmax (Nujol) /cm-1 3288 (N-H), 1656 (C=N-H), 1604 (Ar), 1506 (Ar), 1234 (C-O-C); *m/z* (ESP) 285 ([M+H]+), found 285.1603, C17H24N2O2 requires 285.1599; anal. Found C 59.50, H 6.75, N 8.33, C17H23N2O3Cl requires C 60.26, H 6.84, N 8.27.

**4-(5-(*p*-Tolyloxy)pentyloxy)benzonitrile**



Sodium (0.12 g, 5.22 mmol) was added portionwise to anhydrous ethanol (4.0 mL) and dissolved under a nitrogen atmosphere. To this a solution of 4-cyanophenol (0.57 g, 4.79 mmol) dissolved in anhydrous ethanol (4.0 mL) was added followed by dropwise addition of 1,5-dibromopentane (0.65 mL, 4.79 mmol). The reaction mixture was allowed to stir at reﬂux and monitored by TLC. After consumption of 4-cyanophenol the reaction mixture was cooled to room temperature. In a separate flask, sodium (0.57 g, 4,79 mmol) was added portionwise to anhydrous EtOH (4.0 ml) with stirring under nitrogen. To this, a solution of *p*-cresol (0.5 ml, 4.79 mmol) in anhydrous EtOH (4.0 ml) was added and stirred for 10 minutes. This mixture was added dropwise to the cooled mixture and stirred under reflux for 3 days after which the mixture was cooled, filtered and the solid washed with water and dried under vacuum. Purification by column chromatography eluting with DCM: hexane (8:2) gave the desired compound as a white solid(1.02 g, 72%). Mp 133°C; 1H NMR (CDCl3, 400MHz) δ 7.57 (d, 2H, *J* = 9 Hz, ArH), 7.07 (d, 2H, *J* = 8.6 Hz, ArH), 6.93 (d, 2H, *J =* 9.0 Hz, ArH), 6.79 (d, 2H, *J* = 8.6 Hz, ArH) 4.02 (t, 2H, *J* = 6.4 Hz, CH2) 3.96 (t, 2H, *J* = 6.4 Hz, CH2), 2.28 (s, 3H, CH3), 1.86 (m, 4H, CH2), 1.64 (m, 2H, CH2); 13C NMR (CDCl3, 100MHz) δ 162.7, 157.2, 134.3, 130.3, 130.2, 115.5, 114.7, 104.1, 68.5, 68.0, 29.4, 29.1, 23.0, 20.8; νmax (Nujol) /cm-1 3322 (C-O-C), 3031 (Ar-H), 2921 (C-H), 2223 (C≡N), 1602 (Ar), 1506 (Ar), 1234 (C-O-C); *m/z* (CI) 313 ([M+NH4]+), found 313.19092, C19H25N2O2 requires 313.19162; anal. Found C 77.19, H 7.13, N 5.02, C19H21NO2 requires C 77.26, H 7.17, N 4.74.

**4-(5-(*p*-tolyloxy)pentyyloxy)benzimidamide hydrochloride hydrate** (Compound CHI/1/72/1)



4-(5-(*p*-Tolyloxy)pentyloxy)benzonitrile (0.27 g, 0.91 mmol) was dissolved in a mixture of anhydrous benzene (100 mL) and anhydrous ethanol (1.60 mL), cooled to 0 oC and saturated with HCl gas. The mixture was sealed and allowed to stir at room temperature for 3 days after which anhydrous Et2O (20 mL) was introduced and the mixture was allowed to stir for 10 minutes. The solids were ﬁltered under nitrogen and dissolved in a mixture of anhydrous EtOH (20 mL) and EtOH.NH3 (20 mL). The mixture was heated overnight (50 °C), cooled to room temperature and reduced by half *in vacuo*. Ether (30 mL) was added to precipitate the solid which was ﬁltered, washed and dried under vacuum. Puriﬁcation by recrystallisation (2N HCl) gave the desired compound as ﬁne white needles (0.25 g, 75%). Mp 132°C; 1H NMR (DMSO, 400MHZ) δ 7.84 (d, 2H, *J* = 9.1 Hz, ArH), 7.15 (d, 2H, *J* = 9.1 Hz, ArH), 7.06 (d, 2H, *J* = 8.4 Hz, ArH), 6.80 (d, 2H, *J* = 8.4 Hz, ArH), 4.11 (t, 2H, *J* = 6.4 Hz, CH2), 3.93 (t, 2H, *J* = 6.4 Hz, CH2), 2.22 (s, 3H, CH3), 1.78 (m, 4H, CH2), 1.56 (m, 2H, CH2); 13C NMR (DMSO, 100MHz) δ 165.0, 163.3, 158.9, 130.5, 130.1, 115.1, 114.5, 79.5, 79.3, 79.0, 20.4; νmax (Nujol) /cm-1 3430 (NH), 3309 (C-O-C), 3093 (Ar-H), 1658 (C=N-H), 1606 (Ar), 1508 (Ar), 1245 (C-O-C); *m/z* (ESP) 313 ([M+H]+), found 313.1916, C19H25N2O2 requires 313.1907; anal. Found C 62.19, H 7.42, N 7.66, C19H27ClN2O3 requires C 62.20, H 7.42, N 7.66.

**Synthesis of ER 1004**

**4-bromobenzothioamide**



Triethylamine (3.8 mL) was added to a solution of 4-bromobenzonitrile (5 g, 27.5 mmol) in pyridine (17 mL). The solution was cooled to 10 oC and H2S (g) was bubbled through for 15 min. The resulting green solution was allowed to stir overnight (17 h). Nitrogen was bubbled through for 1 h to remove any excess H2S. Water (27 mL) was added and the mixture was stirred for 10 min, a further portion of water (62 mL) was added and the pale yellow suspension left stirring overnight. The precipitate was filtered and rinsed with water to afford the title compound as bright yellow crystals (5.52 g, 93%). 1H NMR (d6-acetone, 400MHz) 9.07 (bs, 1H, NH), 8.92 (s, 1H, NH), 7.94 (dd, 2H, *J* = 2.0, 6.5 Hz, ArH), 7.62 (dd, 2H, *J* = 2.0, 6.5 Hz, ArH); 13C NMR (d6-acetone, 100MHz) 201.9, 140.2, 132.3, 130.4, 126.5; *m/z* (CI) 216 (100%, [M+])

**2,4-bis(4-bromophenyl)thiazole**



2,4'-dibromoacetophenone (1 g, 3.60 mmol) was added to a solution of 4-bromobenzothioamide (777 mg, 3.60 mmol) in EtOH (15 mL) and warmed to 45 oC for 1 h. The mixture was cooled to room temperature and left for 30 min before filtering. The precipitate was washed with EtOH: water (3:1, 10 mL) and dried to afford the thiazole as a pale solid (1.33 g, 94%). 1H NMR (CDCl3, 250MHz) 7.89 (d, 2H, *J* = 8.5 Hz, ArH), 7.85 (d, 2H, *J* = 8.5 Hz, ArH), 7.59 (d, 2H, *J* = 5.5 Hz, ArH), 7.56 (d, 2H, *J* = 5.5 Hz, ArH), 7.47 (s, 1H, CH); *m/z* (CI) 396 (10%, [M+H]+).

**4,4'-(thiazole-2,4-diyl)dibenzonitrile**



A suspension of 2,4-bis(4-bromophenyl)thiazole (1 g, 2.53 mmol) and CuCN (906 mg, 10.12 mmol) in anhydrous DMF (15 mL) were heated to reflux for 21 h. On cooling, the reaction mixture was poured into aqueous NH4OH (10%, 50 mL) and extracted with CHCl3 (100 mL). Both layers were filtered to remove the dark precipitate. The organic layer was washed with water (2 x 50 mL), brine (50 mL) and dried MgSO4. Removal of solvent gave a dark oily solid. Purification by column chromatography eluting with CHCl3, afforded the title compound as a pale solid (361 mg, 50%). 1H NMR (CDCl3, 400MHz) 8.15 (d, 2H, *J* = 8.5 Hz, ArH), 8.11 (m, 2H, ArH), 7.77 (d, 2H, *J* = 8.5 Hz, ArH), 7.73 (t, 2H, *J* = 3.0 Hz, ArH), 7.26 (s, 1H, CH); 13C NMR (CDCl3, 100MHz) 166.5, 137.4, 133.2, 130.1, 127.3, 119.1, 117.1, 114.2, 112.4; *m/z* (CI) 288 (100 %, [M+H]+).

**4,4'-(thiazole-2,4-diyl)dibenzimidamide (ER1004)**



#### The Garigipati Reaction is a little known reaction which effects the conversion of hindered nitriles to unsubstituted amidines in a mild and effective manner 2, 3. This is an efficient one step transformation involving direct nucleophilic addition of an amine to a nitrile, affording the corresponding amidine (Scheme 1).



**Scheme 1.**

The alkylchloroaluminium amides are effectively generated from trimethyl aluminium and ammonium chloride and the intermediate aluminium complex is easily hydrolyzed by water adsorbed on silica gel (Scheme 2).

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**Scheme 2.**

The freshly prepared alkylchloroaluminum reagents (4 mL, 0.67 M, 2.7 mmol) were added to 4,4'-(thiazole-2,4-diyl)dibenzonitrile (78 mg, 0.27 mmol) in anhydrous toluene (1 mL) and heated to 80 oC overnight under nitrogen. On cooling, the aluminium complex was decomposed by pouring into a slurry of silica gel (2 g) in CHCl3. The mixture was stirred for 5 min before filtering, the filter cake was washed with MeOH (20 mL). Removal of solvent gave the crude amidine as a pale solid in quantitative yield. The crude product (100 mg) was purified by reverse phase HPLC using a YMC-pack ODS-A column (250 x 20 mm I.D, 5 µM) eluting with CH3CN: Water 0.1% TFA (20-80 % gradient over 20 min). Removal of solvent afforded the desired compound as an off-white solid (38 mg, 22%). Mp 271-272 oC; 1H NMR (DMSO, 400MHz) 9.32 (bs, 6H, NH & NH2), 8.54 (s, 1H, CH), 8.25 (d, 2H, *J* = 8.5 Hz, ArH), 8.22 (d, 2H, *J* = 8.5 Hz, ArH), 7.92 (d, 2H, *J* = 8.5 Hz, ArH), 7.90 (d, 2H, *J* = 8.5 Hz, ArH); 13C NMR (DMSO, 100MHz) 165.5, 165.4, 154.4, 138.7, 137.4, 129.6, 129.2, 127.9, 126.9, 126.8, 119.6; *m/z* (ES) 322 (88 % [M+H]+); Found (ES) 322.1121 C17H16N5S requires 322.1126; anal. Found C 46.05, H 3.10, N 12.44, S 5.77, C21H18N5O4F6S requires C 45.91, H 3.12, N 12.74, S 5.83.

References

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Chemistry of new compounds from David Boykin laboratory.

**General procedure for conversion of nitriles into amidine hydrochlorides (Method A).**

To a cold and stirred suspension of the nitrile or dinitrile (0.001 mol) in 15 ml dry THF was added 6.0 ml, (0.006 mol) LiN(TMS)2 (1 M in THF), stirred for 24 h, cooled, acidified carefully with saturated ethanolic-HCl, the precipitated white solid stirred for 2 h, solvent removed under reduced pressure, diluted with ether, filtered. The collected solid was added to 10 ml ice water, basified with 2M NaOH, the precipitate was filtered, washed with water and air dried. The solid was suspended in anhydrous ethanol (15 ml) and 5 ml saturated ethanolic-HCl and stirred for 6 h, ethanol was distilled off, triturated with dry ether and filtered. The solid was dried under reduced pressure at 800C for 12 h to yield (70-75%) amidine hydrochloride.

**General procedure for conversion of nitriles into amidine hydrochlorides (Method B).**

A suspension of the nitrile or dinitile (0.001 mole) in 20 ml saturated ethanol-HCl was stirred for 4 days in a closed stoppered flask, followed by precipitation with anhydrous ether. The precipitated light yellow solid imidate ester dihydrochloride was filtered and dried under reduced pressure for 3 h to yield (65% -70%) amidine hydrochloride. The imidate ester dihydrochloride (0.0005 mole) in 20 ml anhydrous ethanol was saturated with ammonia(g) or 0.03 equivalents of ethylene diamine stirred in ethanol (at reflux) for 12 h, solvent removed, 20 ml ice water added, basified to pH 10 with aqueous 2N NaOH, filtered, and washed with water. The precipitated solid was dried in air, suspended in 10 ml of saturated ethanolic-HCl, and stirred for 2 h. The solvent removed, dry ether 20 ml added, filtered, washed with ether and dried under reduced pressure for 12 h. The product amidine hydrochloride was obtained as yellow solid 60-66% yield.

**4-(5-(4-methoxyphenyl) furan-2-yl) benzimidamide hydrochloride (DB 607)**

A mixture of 5-(4-cyanophenyl)-2-bromo furan1 (1.23 g, 0.005 mole) and 4-methoxyphenyl boronic acid (0.93 g, 0.006 mole) in 75 ml dioxane under nitrogen was added K2CO3 (1.38 g, 0.01 mole, in 5 ml H2O), followed by Pd(PPh3)4 0.12 g (0.0001 mole) and the solution was heated under reflux for 12-24 h (tlc monitored). The solvent was removed under reduced pressure, solid filtered, washed with hexane and dried in air. The solid was suspended in DCM (100 ml), filtered through celite, concentrated under reduced pressure, triturated with ether: hexane (2:1), and filtered to yield 4-(5-(4-methoxyphenyl)furan-2-yl)benzonitrile as a yellow brown solid 0.76 g (74%) mp 250-2 °C dec ; 1H NMR (DMSO-d6): 7.94 (d, 2H, J= 10.4 Hz), 7.85 (d, 2H, J= 10.4 Hz), 7.78 (d, 2H, J= 10.8 Hz), 7.28 (d, 1H, J= 4.4 Hz), 7.02 (d, 2H, J= 10.8 Hz), 6.97 (d, 1H, J= 4.4 Hz), 3.81 (s, 3H); 13C NMR (DMSO-d6): 159.3, 154.5, 150.0, 134.1, 132.9, 125.4, 123.5, 122.5, 119.0, 114.4, 111.8, 108.8, 106.9, 55.2; MS: HRMS-ESI-POS: Calcd. for C18H14NO2 *m/z* 276.1024 (M++1), found *m/z* 276.1021.

The amidine hydrochloride was obtained as yellow solid (Method A) 0.24 g (74%) ; mp >318°C dec ; 1H NMR (DMSO-d6): 9.41 (brs, 2H), 9.1 (brs, 2H), 8.01 (d, 2H, J= 8.4 Hz), 7.92 (d, 2H, J= 8.4 Hz), 7.82 (d, 2H, J= 8.4 Hz), 7.324 (d, 1H, J= 3.6 Hz), 7.04 (d, 2H), 7.02 (d, 1H, J= 3.6 Hz), 3.82(s, #H); 13C NMR (DMSO-d6): 164.9, 159.2, 154.3, 150.2, 134.8, 128.8, 125.5, 125.4, 123.0, 122.5, 114.4, 111.4, 106.8, 55.2; ; MS: HRMS-ESI-POS.: Calcd. for C18H17N2O2 *m/z* 293.1289 (M++1), found *m/z* 293.1274; Anal. calcd. for C18H16N2O2-HCl: C, 65.75; H, 5.21; N, 8.52; Found: C, 65.78; H, 5.23; N, 8.44.

**4,4'-(thiophene-2,4-diyl) dibenzimidamide dihydrochloride (DB 1077)**

A mixture of 2, 4-dibromothiophene 1.21 g (0.005 mole), 4-cyanophenylboronic acid 1.75 g (0.012 mole) following procedure for DB 607, yielded 2,4-(4-cyanophenyl)thiophene as a yellow solid, 0.86 g (72%) mp >220°C dec ; 1H NMR (CDCl3): 7.75-7.21 (m, 8H), 7.71 (d, 1H, J= 1.2 Hz), 7.64 (d, 1H, J= 1.2 Hz); 13C NMR (CDCl3): 143.6, 141.6, 139.4, 138.0, 132.9, 132.8, 126.8, 126.1, 123.8, 123.7, 118.8, 118.6, 111.3, 111.1; MS: HRMS-ESI-POS: Calcd. for C14H11N2S *m/z* 239.0642 (M++1), found *m/z* 239.0639.

The diamidine hydrochloride was obtained as yellow solid (Method A) 0.32 g (74%) mp>300°C dec ; 1H NMR (DMSO-d6): 9.55 (brs, 2H), 9.54 (brs, 2H), 9.31 (brs, 4H), 8.42 (s, 1H), 8.32 (s, 1H), 8.09 (d, 2H, J= 8.4 Hz), 8.03-7.97 (m, 6H); 13C NMR (DMSO-d6): 164.9, 164.8, 142.5, 140.9, 139.5, 138.3, 129.1, 128.8, 126.6, 126.3, 126.2, 125.4, 125.0, 124.8; MS: HRMS-ESI-POS.: Calcd. for C18H18N4S *m/z* 161.0626 (M++2)/2, found *m/z* 161.0621; Anal. calcd. for C18H16N2S-2HCl-2H2O: C, 50.35; H, 5.16; N, 13.05; Found: C, 50.52; H, 5.23; N, 13.22.

**3,3'-(furan-2,5-diyl bis (4,1-phenylene)) dipropanimidamide dihydrochloride (DB 1061)**

To a mixture of 4-bromophenyl propionitrile 0.63 g (0.003 mole) and 2, 5-bis (tributylstannyl) furan in 30 ml anhydrous dioxane under nitrogen was added Pd(PPh3)4 0.14 g (0.00012 mole) and the solution was heated under reflux for 12 h (tlc monitored). The solvent was removed under reduced pressure, the solid was filtered, washed with hexane and dried in air. The solid was suspended in DCM (50 ml), stirred 2 h with 20 ml 10% KF (aqueous), the organic layer separated, filtered through celite dried over anhydrous MgSO4, filtered, concentrated, triturated with hexane and the solid filtered was filtered to yield 0.34 g (70%) of 3,3'-(furan-2,5-diylbis(4,1-phenylene))dipropanenitrile as a yellow solid mp 120-2°C dec; 1H NMR (CDCl3): 7.73 (d, 4H, J= 8.4 Hz), 7.30 (d, 4H, J= 8.4 Hz),7.28 (s, 2H), 3.0 (t, 4H, J= 7.6 Hz), 2.66 (t, 4H, J= 7.6 Hz); 13C NMR (CDCl3): 153.2, 137.2, 130.0, 128.9, 124.4, 119.2, 107.2, 31.5, 19.5; MS: HRMS-ESI-POS: Calcd. for C22H18N2ONa *m/z* 349.1317 (M++Na), found *m/z* 349.1332**.**

The diamidine dihydrochloride was obtained using Method B: 0.14 g (60%) mp>300°C dec ; 1H NMR (DMSO-d6): 9.13 (brs, 4H), 8.74 (brs, 4H), 7.64 (d, 4H, J= 8.4 Hz), 7.49 (s, 2H), 7.33 (d, 4H, J=8.4 Hz), 3.0 (t, 4H, J= 7.2 Hz), 2.74 (d, 4H, J= 7.2 Hz); 13C NMR (DMSO-d6): 170.6, 142.7, 139.4, 132.4, 129.6, 125.8, 125.2, 33.7, 32.03; MS: HRMS-ESI-POS: Calcd. for C22H26N4O *m/z* 181.1053 (M++2)/2, found *m/z* 181.1048; Anal. calc. for C22H24N4O-2HCl-2H2O: C, 56.29; H, 6.44; N, 11.93; Found: C, 56.35; H, 6.54; N, 11.86.

**2,5-bis(4-(2-(4,5-dihydro-1H-imidazol-2-yl) ethyl) phenyl) furan dihydrochloride (DB 1062)**

Similarly, 0.245 g (0.005 mole) of the above imidate ester in 20 ml of anhydrous ethanol was allowed to react under reflux (12 h) with 0.06 g (0.0015 mole) ethylene diamine. The solvent was removed under reduced pressure, diluted with water, solid was filtered, dried and converted to dihydrochloride using ethanolic-HCl to yield a yellow solid, 0.15 (62%), mp >325 oC, H NMR (DMSO-d6): 8.29 (br, 4H), 8.74 (brs, 4H), 7.77 (d, 4H, J= 8.4 Hz), 7.34 (s, 2H), 7.05 (d, 4H, J=8.4 Hz), 3.0 (t, 4H, J= 7.2 Hz), 2.74 (d, 4H, J= 7.2 Hz); 13C NMR (DMSO-d6): 170.2, 152.4, 138.5, 128.8, 128.6, 123.6, 108.0, 44.0, 30.5, 27.4; MS: HRMS-ESI-POS: Calcd. for C26H30N4O *m/z* 207.1209 (M++2)/2, found *m/z* 207.1203; Anal. calc. for C26H28N4O-2HCl-2.75H2O: C, 58.37; H, 6.68; N, 10.47; Found: C, 58.45; H, 6.54; N, 10.63.

**3,3'-(thiophene-2,5-diylbis(4,1-phenylene)) dipropanimidamide dihydrochloride (DB 1063)**

The dinitrile, 3,3'-(thiophene-2,5-diylbis(4,1-phenylene))dipropanenitrile, was prepared as described for DB1061 yielding a yellow solid 0.77 g (75%); mp 124-60C dec.;1H NMR (CDCl3): 7.62 (d, 4H, J= 8.0 Hz), 7.29 (d, 4H, J= 8.0 Hz),7.28 (s, 2H), 3.0 (t, 4H, J= 7.2 Hz), 2.66 (t, 4H, J= 7.2 Hz); 13C NMR (CDCl3): 143.3, 137.5, 133.5, 129.1, 126.2, 124.2, 119.2, 31.4, 19.4; MS: HRMS-ESI-POS: Calc. for C22H18N2SNa *m/z* 365.1088 (M++Na), found *m/z* 365.1089.

Similarly following the DB 1061 procedure the diamidine dihydrochloride was obtained as a yellow solid 0.16 g (66%), mp >2800C dec;  1H NMR (DMSO-d6): 9.19 (brs, 4H), 8.77 (brs, 4H), 7.64 (d, 4H, J= 8.0 Hz), 7.51 (s, 2H), 7.33 (d, 4H, J=804 Hz), 2.99 (t, 4H, J= 8.4 Hz), 2.73 (d, 4H, J= 8.4 Hz); 13C NMR (DMSO-d6):170.0, 142.2, 138.9, 131.9, 129.1, 125.3, 124.7, 33.2, 31.6;MS: HRMS-ESI-POS: Calcd. for C22H26N4S *m/z* 189.0939 (M++2)/2, found *m/z* 189.0931; Anal. calcd. for C22H24N4S-2HCl-1.5H2O: C, 55.45; H, 6.13; N, 11.76; Found: C, 55.52; H, 6.34; N, 11.63.

**2, 5-bis(4-(2-(4,5-dihydro-1H-imidazol-2-yl) ethyl) phenyl) thiophene dihydrochloride (DB 1064)**

Similarly following the procedure for DB1062 the diamidine dihydrochloride was obtained as a yellow solid, 0.17 g (62%); mp >225°C dec.; 1H NMR (DMSO-d6): 10.19 (s, 4H), 7.63 (d, 4H, J=7.6 Hz), 7.5 (s, 2H), 7.30 (d, 4H, J= 7.6 Hz), 3.78 (s, 8H),2.97 (t, 4H, J= 6.4 Hz), 2.81(t, 4H, J= 6.4 Hz); 13C NMR (DMSO-d6): 170.2, 140.2, 138.9, 131.9, 129.1, 125.4, 124.8, 44.1, 30.6, 27.4; MS: HRMS-ESI-POS: Calcd. for C26H29N4S *m/z* 429.2113 (M++1), found *m/z* 429.2109; Anal. calcd. for C26H28N4S-2HCl-3.0H2O: C, 56.21; H, 6.53; N, 10.08; Found: C, 56.34; H, 6.61; N, 10.24.

**4-(5-(1-methyl-1H-benzo[d]imidazol-2-yl) furan-2-yl) benzimidamide dihydrochloride (DB 960)**

To a stirred solution of 5-(4-cyanophenyl) furan-2-aldehyde2 1.23 g (0.005 mole), 1-amino-2-*N*-(methylamino) benzene 0.61 g (0.005 mol) in 20 ml dry DMF under N2 was added sodium metabisulfite 0.95 (0.005 mol) and the mixture was heated at 130°C for 12 h (tlc monitored). The solvent was removed, the residue was triturated with cold water, separated solid was filtered, washed with water and air dried. The solid was stirred with 1:1 mixture of DCM-ether, filtered and dried in vac at 70°C for 4 h to give the nitrile, 4-(5-(1-methyl-1H-benzo[d]imidazol-2-yl)furan-2-yl)benzonitrile, as a yellow brown solid, 1.1 g (72%), mp >290°C dec ; 1H NMR (DMSO-d6): 8.03 (d, 2H, J= 8.4 Hz), 7.92 (d, 2H, J= 8.4 Hz), 7.69-7.63 (m, 2H), 7.46 (d, 1H, J= 3.6 Hz), 7.40 (d, 1H, J= 3.6 Hz), 7.34-7.23 (m, 2H), 4.13 (s, 3H); 13C NMR (DMSO-d6): 152.4, 145.9, 143.2, 142.4, 136.0, 133.2, 132.9, 124.2, 122.7, 122.2, 118.9, 118.5, 114.7, 111.1, 110.2, 109.9, 31.4; MS: HRMS-ESI-POS: Calcd. for C19H14N3O *m/z* 300.1136 (M++1), found *m/z* 300.1132.

The amidine hydrochloride was obtained as yellow solid (Method B) 0.3 g (78%); mp >300°C dec; 1H NMR (DMSO-d6): 8.09 (d, 2H, J= 8.7 Hz), 7.90 (d, 2H, J= 8.7 Hz), 7.78-7.70 (m, 2H), 7.61 (d, 1H, J= 3.9 Hz), 7.48-7.42 (m, 2H), 7.45 (d, 1H, J= 3.9 Hz), 4.13 (s, 1H); 13C NMR (DMSO-d6): 165.5, 155.6, 141.5, 141.3, 135.3, 134.8, 133.9, 129.5, 128.0, 126.0, 125.8, 125.5, 119.6, 116.4, 112.4, 112.0, 32.9; MS: HRMS-ESI-POS: Calcd. for C19H18N4O *m/z* 159.0740 (M++2)/2, found *m/z* 159.0733; Anal. calcd. for C19H16N4O-2HCl-1H2O: C, 56.02; H, 4.94; N, 13.76; Found: C, 56.18; H, 4.91; N, 13.51.

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