Supporting Information

Design of Potent, Orally Available Antagonists of the Transient Receptor Potential Vanilloid 1 (TRPV1). Structure-Activity Relationships of 2-(Piperazin-1-yl)-1*H*-benzimidazoles

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Combustion Analysis Data

6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazol-4-amine (32a). Anal. Calcd for $C_{18}H_{16}F_6N_6$: C, 50.24; H, 3.75; N, 19.53. Found: C, 50.06; H, 3.57; N, 19.44.

***N*-(3,4,5-Trifluorobenzyl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-3*H*-benzo[*d*]imidazol-4-amine (32c).** Anal. Calcd for $C_{25}H_{19}F_9N_6$: C, 52.27; H, 3.33; N, 14.63. Found: C, 52.20; H, 3.41; N, 14.80.

1-(5-Chloro-6-(4-(5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)ethanone (37b). Anal. Calcd for $C_{19}H_{17}ClF_3N_5O \cdot H_2O$: C, 51.65; H, 4.33; N, 15.85; Found: C, 51.92; H, 4.01; N, 15.78.

6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (39). Anal. Calcd for $C_{18}H_{15}F_6N_5$: C, 52.05; H, 3.64; N, 16.86. Found: C, 51.77; H, 3.59; N, 16.64.

1-Benzyl-5-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (41). Anal. Calcd for $C_{25}H_{21}F_6N_5 \cdot 0.2$ EtOAc: C, 59.24; H, 4.35; N, 13.35. Found: C, 58.98; H, 4.24; N, 13.52.

6-Bromo-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (42). Anal. Calcd for $C_{17}H_{15}BrF_3N_5$: C, 47.90; H, 3.55; N, 16.43. Found: C, 47.94; H, 3.55; N, 16.33.

4-Bromo-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (44a). Anal. Calcd for $C_{18}H_{14}BrF_6N_5$: C, 43.74; H, 2.86; N, 14.17. Found: C, 43.78; H, 2.93; N, 14.11.

6-(Trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, trifluoroacetic acid salt (46b). Anal. Calcd for $C_{25}H_{18}F_9N_5 \cdot CF_3CO_2H$: C, 48.15; H, 2.84; N, 10.40. Found: C, 48.16; H, 2.61; N, 10.29.

(*R*)-5-Chloro-6-(4-(4-(4-fluorophenyl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-methylpiperazin-1-yl)pyridin-3-amine (46e). Anal. Calcd for $C_{24}H_{21}ClF_4N_6 \cdot 0.5$ EtOAc $\cdot$ 0.05 H_2O: C, 56.79; H, 4.60; N, 15.28; Found: C, 56.45; H, 4.37; N, 15.65.

6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazole (46m). Anal. Calcd for $C_{24}H_{16}F_9N_5$: C, 52.85; H, 2.94; N, 12.84. Found: C, 53.12; H, 3.04; N, 12.65.

4-(Thiazol-2-yl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, trifluoroacetic acid salt (46n). Anal. Calcd for $C_{21}H_{16}F_6N_6S \cdot 0.11\ CF_3CO_2H \cdot 0.22\ H_2O$: C, 49.49; H, 3.24; N, 16.32. Found: C, 49.85; H, 3.45; N, 16.01.

6-(Trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46q). Anal. Calcd for $C_{25}H_{18}F_9N_5$: C, 53.67; H, 3.24; N, 12.52. Found: C, 53.63; H, 3.23; N, 12.27.

4-Phenyl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46r). Anal. Calcd for $C_{24}H_{19}F_6N_5$: C, 58.66; H, 3.90; F, 23.20; N, 14.25. Found: C, 58.82; H, 3.86; N, 14.18.

4-(3-(Trifluoromethoxy)phenyl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, trifluoroacetic acid salt (46s). Anal. Calcd for $C_{25}H_{18}F_9N_5O \cdot 0.15\ CF_3CO_2H$: C, 51.28; H, 3.09; N, 11.82. Found: C, 51.62; H, 3.06; N, 11.48.

4-(4-*tert*-Butylphenyl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46t). Anal. Calcd for $C_{28}H_{27}F_6N_5$: C, 61.42; H, 4.97; N, 12.79. Found: C, 61.68; H, 4.94; N, 12.81.

4-(Thiophen-2-yl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, trifluoroacetic acid salt (46u). Anal. Calcd for $C_{22}H_{16}F_6N_5S \cdot 1.5\ CF_3CO_2H$: C, 44.92; H, 2.79; N, 10.48. Found: C, 44.63; H, 2.78; N, 10.52.

4-(Pyridin-4-yl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46v). Anal. Calcd for $C_{23}H_{18}F_5N_6$: C, 56.10; H, 3.68; N, 17.07. Found: C, 56.11; H, 3.65; N, 16.96.

4-(Pyrazin-2-yl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46w). Anal. Calcd for $C_{22}H_{17}F_6N_7$: C, 53.55; H, 3.47; N, 19.87. Found: C, 53.47; H, 3.51; N, 19.75.

4-(6-Methoxypyridin-3-yl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, trifluoroacetic acid salt (46x). Anal. Calcd for $C_{24}H_{20}F_6N_6O \cdot 0.95\ CF_3CO_2H \cdot 0.2\ H_2O$: C, 49.04; H, 3.39; N, 13.25. Found: C, 48.69; H, 3.30; N, 13.40.

4-(Benzo[*b*]thiophen-2-yl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46y). Anal. Calcd for $C_{26}H_{19}F_6N_5S$: C, 57.04; H, 3.50; N, 12.79. Found: C, 56.74; H, 3.38; N, 12.62.

4-(6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-3*H*-benzo[*d*]imidazol-4-yl)benzenamine (46z). Anal. Calcd for $C_{24}H_{20}F_6N_6 \cdot 0.12$ CF_3CO_2H: C, 55.98; H, 3.90; N, 16.16. Found: C, 56.24; H, 3.73; N, 16.02.

(*E*)-4-Styryl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46ab). Anal. Calcd for $C_{26}H_{21}F_6N_5 \cdot 0.1\ H_2O \cdot 0.3$ EtOAc: C, 60.40; H, 4.40; N, 12.95. Found: C, 60.79; H, 4.20; N, 13.27.

(*R*)-1-(5-Chloro-6-((*R*)-3-methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)ethane-1,2-diol and (*S*)-1-(5-chloro-6-((*R*)-3-methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)ethane-1,2-diol (46ad). Anal. Calcd for $C_{26}H_{22}ClN_5F_6O_2 \cdot 0.8\ H_2O$: C, 52.02; H, 3.96; N, 11.67; Found: C, 51.89; H, 3.79; N, 11.48.

6-Methyl-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole hydrochloride (47b). Anal. Calcd for $C_{18}H_{18}F_3N_5 \cdot HCl$: C, 54.34; H, 4.81; N, 17.60; Found: C, 54.24; H, 4.49; N, 17.44.

6-Fluoro-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, trifluoroacetic acid salt (47c). Anal. Calcd for $C_{17}H_{15}F_4N_5 \cdot 1.3$ CF_3COOH: C, 45.84; H, 3.20; N, 13.64. Found: C, 45.57; H, 3.54; N, 13.74.

6-Chloro-2-[4-(3-trifluoromethylpyridin-2-yl)piperazin-1-yl]-1*H*-benzo[*d*]imidazole (47d). Anal. Calcd for $C_{17}H_{15}ClF_3N_5$: C, 53.48; H, 3.96; N, 18.34. Found: C, 53.53; H, 3.94; N, 18.30.

2-(4-(3-(Trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile, trifluoroacetic acid salt (47e). Anal. Calcd for $C_{18}H_{15}F_3N_6 \cdot 1.4$ CF_3COOH: C, 46.96; H, 3.11; N, 15.80. Found: C, 46.71; H, 3.43; N, 16.15.

4,6-Bis(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (48). Anal. Calcd for $C_{18}H_{15}F_6N_5$: C, 47.21; H, 2.92; N, 14.49. Found: C, 47.21; H, 2.86; N, 14.45.

(*R*)-2-(4-(3-Bromopyridin-2-yl)-2-methylpiperazin-1-yl)-6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazole (51a). Anal. Calcd for $C_{24}H_{18}BrF_6N_5$: C, 50.54; H, 3.18; N, 12.28. Found: C, 50.58; H, 3.17; N, 11.97.

(*S*)-2-(4-(3-Bromopyridin-2-yl)-2-methylpiperazin-1-yl)-6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazole (51b). Anal. Calcd for $C_{24}H_{18}BrF_6N_5$: C, 50.54; H, 3.18; N, 12.28. Found: C, 50.44; H, 3.23; N, 12.19.

2-(4-(Pyridin-2-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (52a). Anal. Calcd for $C_{17}H_{16}F_3N_5$: C, 58.78; H, 4.64; N, 20.16. Found: C, 58.80; H, 4.64; N, 20.26.

6-(Trifluoromethyl)-2-(4-(4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (52b). Anal. Calcd for $C_{18}H_{15}F_6N_5$: C, 52.05; H, 3.64; N, 16.86. Found: C, 51.84; H, 3.46; N, 16.58.

6-(Trifluoromethyl)-2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (52c). Anal. Calcd for $C_{18}H_{15}F_6N_5$: C, 52.05; H, 3.64; N, 16.86. Found: C, 52.10; H, 3.60; N, 16.72.

6-(Trifluoromethyl)-2-(4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (52d). Anal. Calcd for $C_{18}H_{15}F_6N_5$: C, 52.05; H, 3.64; N, 16.86. Found: C, 51.77; H, 3.67; N, 16.65.

2-(4-(3-Chloropyridin-2-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (52e). Anal. Calcd for $C_{17}H_{15}ClF_3N_5 \cdot 0.25\ H_2O$: C, 52.86; H, 4.04; N, 18.13. Found: C, 52.88; H, 3.99; N, 17.99.

2-[4-(3-Iodopyridin-2-yl)piperazin-1-yl]-5-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (52f). Anal. Calcd for $C_{17}H_{15}F_3IN_5 \cdot 0.2\ H_2O$: C, 42.82; H, 3.26; N, 14.69. Found: C, 43.16; H, 3.26; N, 14.39.

2-(4-(3-Methylpyridin-2-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole, trifluoroacetic acid salt (52g). Anal. Calcd for $C_{18}H_{18}F_3N_5 \cdot 2.3\ CF_3CO_2H \cdot 0.25\ H_2O$: C, 41.84; H, 3.59; N, 10.79. Found: C, 41.81; H, 3.59; N, 10.74.

Ethyl 2-(4-(6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)nicotinate hydrochloride (52i). Anal. Calcd for $C_{20}H_{20}F_3N_5O_2 \cdot 1\ H_2O$: C, 50.69; H, 4.89; N, 14.78. Found: C, 50.31; H, 4.89; N, 14.58.

(5-Chloro-6-(4-(6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)methanol (52j). Anal. Calcd for $C_{18}H_{17}ClN_5F_3O$: C, 52.50; H, 4.16; N, 17.01; Found: C, 52.66; H, 4.31; N, 16.79.

5-Chloro-6-(4-(6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)nicotinamide (52k). Anal. Calcd for $C_{18}H_{16}ClN_6F_3O \cdot 0.4\ H_2O$: C, 50.04; H, 3.92; N, 19.45; Found: C, 50.36; H, 3.91; N, 19.13.

5-Chloro-*N*-methyl-6-(4-(6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)nicotinamide (52l). Anal. Calcd for $C_{19}H_{18}ClN_6F_3O \cdot 0.1$ EtOAc: C, 52.24; H, 4.25; N, 18.84. Found: C, 52.08; H, 4.29; N, 18.50.

6-(Trifluoromethyl)-2-(4-(2-(trifluoromethyl)phenyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (53a). Anal. Calcd for $C_{19}H_{16}N_4F_6$: C, 55.08; H, 3.89; N, 13.52; Found: C, 54.90; H, 3.72; N, 13.30.

6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-4-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (53b). Anal. Calcd for $C_{18}H_{15}F_6N_5$: C, 52.05; H, 3.64; N, 16.86. Found: C, 52.29; H, 3.73; N, 16.69.

2-(4-(5-Chloropyrimidin-4-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (53f). Anal. Calcd for $C_{16}H_{14}ClF_3N_6 \cdot 0.75\ H_2O$: C, 48.43; H, 3.97; N, 20.84. Found: C, 48.30; H, 3.86; N, 20.76.

Synthetic procedures for the intermediates, which were not included in the Experimental Section

(*R*)-2-Ethylpiperazine (7e). A mixture of 2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)butanoic acid (4.66 g, 15 mmol), methyl 2-aminoacetate hydrochloride (1.88 g, 15 mmol), 1-hydroxy-7-azabenzotriazole (2.04 g, 15 mmol), *N*,*N*-diisopropylethylamine (1.94 g, 15 mmol) and PS-carbodimide (10 g) in dichloromethane (50 mL) was stirred at room temperature for 16 h. The resin was filtered, washed with dichloromethane, and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (gradient: 25-50% EtOAc/hexane) to give 3.8 g (62%) of the amide **16a** as a white solid. MS (ESI, pos. ion) m/e: 397 (M+1).

A mixture of the amide **16a** from the previous step (3.6 g, 9.1 mmol) and piperidine (1.8 mL, 18 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 6 h. The reaction mixture was evaporated under reduced pressure and the solid residue was suspended in EtOAc. The suspension was filtered and the filter cake was washed with EtOAc, and dried in vacuo to give 1.15 g (89%) of the piperazine-2,5-dione **17a** as a white amorphous solid. ^{1}HNMR ($CDCl_3$): δ1.03 (t, J = 7.2 Hz, 3 H), 1.80-1.90 (m, 2 H), 4.00-4.10 (m, 3 H), 6.1 (br s, 1 H), 6.18 (br s, 1 H).

To a solution of the piperazine-2,5-dione **17a** from the previous step (0.7 g, 5 mmol) in tetrahydrofuran (40 mL) was added $LiAlH_4$ (20 mL, 1.0 M solution in tetrahydrofuran, 20

mmol) dropwise over a period of 10 min with stirring at 0 °C. After the addition, the reaction mixture was heated at 65 °C for 16 h, cooled to room temperature, and carefully quenched by the addition of sodium sulfate decahydrate (3 g). The reaction mixture was filtered through Celite®, and the filter cake was washed with ethyl acetate. The combined filtrate was evaporated under reduced pressure and the residue dried in vacuo to give 0.35 g (62%) of the title compound as a colorless oil. MS (ESI, pos. ion) m/e: 115 (M+1). ^{1}HNMR ($CDCl_3$): δ0.91 (t, J = 7.2 Hz, 3 H), 1.20-1.30 (m, 2 H), 2.30–3.30 (m, 7 H).

(*R*)-2-Propylpiperazine (7f). Following the procedure described for compound **16a**, (*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)pentanoic acid and methyl 2-aminoacetate hydrochloride provided the amide **16b** (58%) as a white amorphous solid. MS (ESI, pos. ion) *m/z*: 411 (M+1).

Following the procedure described for compound **17a**, the amide **16b** from the previous step and piperidine provided the piperazine-2,5-dione **17b** (53%) as a white amorphous solid. ^{1}HNMR (DMSO-d_6): δ0.87 (t, J = 7.2 Hz, 3 H), 1.30-140 (m, 2 H), 1.63-1.65 (m, 4 H), 3.00 (br s, 1 H), 3.32 (s, 3 H), 3.76 (br s, 3 H), 8.0 (br s, 1 H), 8.2 (br s, 1 H).

Following the procedure described for compound **7e**, the piperazine-2,5-dione **17b** from the previous step and $LiAlH_4$ provided the title compound (44%) as a colorless oil. MS (ESI, pos. ion) m/e: 129 (M+1).

***tert*-Butyl 4-(3-chloropyridin-2-yl)piperazine-1-carboxylate (8a)**. A mixture of 2-chloropyridine **6a** (10 g, 67.5 mmol), piperazine **7d** (12.58 g, 67.5 mmol), K_2CO_3 (9.33 g, 67.5 mmol) and copper powder (0.5 g) in DMF (100 mL) was stirred at 130 ^{o}C until TLC analysis confirmed the absence of starting materials. The mixture was left to reach room temperature, diluted with water (10 mL), and extracted with EtOAc (2 x 20 mL). The

combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel chromatography (15% EtOAc/hexane) to provide 18 g (90%) of the title compound as an orange oil. MS (ESI, pos. ion) *m/z*: 298 (M+1).

1-(3-Chloropyridin-2-yl)piperazine hydrochloride (8b). To a solution of compound **8a** (2.98 g, 10 mmol) in MeOH (5 mL) was added saturated solution of hydrogen chloride in EtOAc (50 mL) and the mixture stirred at room temperature for 4 h. The solvents were removed in vacuo and the residue was washed with EtOAc, and dried in the air to provide 2.02 g (66%) of the title compound as a light-yellow solid. MS (ESI, pos. ion) *m/z*: 198 (M+1).

1-(3-Iodopyridin-2-yl)piperazine (8c). A mixture of 2-chloropyridine **6c** (2.0 g, 9.0 mmol), piperazine **7a** (1.29 g, 15 mmol) and *N*,*N*-diisopropylethylamine (2 mL, 11.6 mmol) in dry *N*-methylpyrrolidone (2 mL) was heated in a microwave synthesizer at 240 ^oC for 60 min. The mixture was evaporated in vacuo and the residue was purified by silica gel chromatography (10% MeOH/CH_2Cl_2) to give 1.0 g (38%) of the title compound as a light-yellow amorphous solid. MS (ESI, pos. ion) *m/z*: 290 (M+1).

***tert*-Butyl 4-(3-(ethoxycarbonyl)pyridin-2-yl)piperazine-1-carboxylate (8d).** Following the procedure described for compound **8a**, ethyl 2-chloronicotinate (**6f**) and *tert*-butyl piperazine-1-carboxylate (**7d**) provided the title compound (99%) as yellow oil. MS (ESI, pos. ion) *m/z*: 336 (M+1).

Ethyl 2-(piperazin-1-yl)nicotinate hydrochloride (8e). Following the procedure described for compound **8b**, treatment of *tert*-butyl 4-(3-(ethoxycarbonyl)pyridin-2-yl)piperazine-1-carboxylate (**8d**) with saturated solution of hydrogen chloride in EtOAc

provided the title compound (98%) as light-yellow solid. MS (ESI, neg. ion) *m/z*: 306 (M-1).

1-(6-(Trifluoromethyl)pyridin-2-yl)piperazine (8f). A mixture of 2-chloro-6-trifluoromethyl-pyridine (0.84 g, 3 mmol), piperazine (0.52 g, 6 mmol) and *N*,*N*-diisopropylethylamine (1 mL) was heated in a microwave synthesizer at 200 ^{o}C for 40 min. The reaction mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (30% MeOH/DCM) to give 0.6 g (87%) of the title compound as a white amorphous solid. MS (ESI, pos. ion) *m/z*: 232 (M+1). ^{1}H NMR ($CDCl_3$): δ3.09-3.14 (m, 4 H), 3.65-3.78 (m, 4 H), 6.79 (d, *J* = 8.6 Hz, 1 H), 6.99 (d, *J* = 7.4 Hz, 1 H), 7.61 (t, *J* = 7.8 Hz, 1 H).

6-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-5-chloronicotinic acid (8g). Following the procedure described for compound **8a**, 5,6-dichloronicotinic acid (**6j**) and *tert*-butyl piperazine-1-carboxylate (**7d**) provided the title compound (77%) as yellow semi-solid. MS (ESI, neg. ion) *m/z*: 340 (M-1).

(5-Chloro-6-(piperazin-1-yl)pyridin-3-yl)methanol (8h). Following the procedure described for compound **8a**, (5,6-dichloropyridin-3-yl)methanol (**6g**) and piperazine (**7a**) provided the title compound (46%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 228 (M+1).

***tert*-Butyl 4-(3-chloro-5-(methoxy(methyl)carbamoyl)pyridin-2-yl)piperazine-1-carboxylate (8i).** A mixture of the acid **6j** (7.0 g, 0.036 mol), $(COCl)_2$ (50 mL) and DMF (2 drops) was stirred at room temperature for 4 h. The solution was evaporated in vacuo to give 7.66 g (100%) of the chloride as an orange solid.

A solution of the chloride from the previous step (3.24 g, 15.4 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a mixture of *O*,*N*-dimethyl-hydroxylamine hydrochloride (1.5 g, 15.4 mmol), 10% aqueous K_2CO_3 (20 mL) and CH_2Cl_2 (50 mL), and vigorously stirred at room temperature for 3 h. The organic phase was separated, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc) to give 3.2 g (88%) of the amide **6m** as a white solid. MS (ESI, pos. ion) *m/z*: 257 ($M+Na^+$).

Following the procedure described for compound **8a**, the amide **6m** from the previous step and *tert*-butyl piperazine-1-carboxylate (**7d**) provided the title compound (86%) as a white solid. MS (ESI, pos. ion) *m/z*: 385 (M+1).

***tert*-Butyl 4-(3-chloro-5-((perfluorophenoxy)carbonyl)pyridin-2-yl)piperazine-1-carboxylate (8j).** To a solution of compound **8g** (0.6 g, 1.7 mmol) and 2,3,4,5,6-pentafluorophenol (0.33 g, 1.76 mmol) in EtOAc (15 mL) was added 1,3-dicyclohexylcarbodiimide (0.351 g 1.7 mmol) at 0 ^oC. The reaction mixture was stirred for 16 h at room temperature, diluted with EtOAc (50 mL) and filtered through a Celite® pad. The filtrate was washed with saturated aqueous solution of $NaHCO_3$ (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered and evaporated in vacuo to give 0.9 g (100%) of the title compound as a yellow wax. MS (ESI, pos. ion) *m/z*: 508 (M+1).

***tert*-Butyl 4-(3-chloro-5-(methylcarbamoyl)pyridin-2-yl)piperazine-1-carboxylate (8k).** A mixture of compound **8j** (0.9 g, 1.77 mmol) and 2 M $MeNH_2$ in THF (9 mL, 18 mmol) was stirred at room temperature for 6 h. The solution was concentrated in vacuo and the residue was purified by silica gel column chromatography (gradient: 30-50%

EtOAc in hexane) to give 0.31 g (49%) of the title compound as colorless oil. MS (ESI, pos. ion) *m/z*: 355 (M+1).

5-Chloro-*N*-methyl-6-(piperazin-1-yl)nicotinamide hydrochloride (8l). Following the procedure described for compound **8b**, treatment of compound **8k** with saturated solution of hydrogen chloride in EtOAc provided the title compound (49%) as colorless oil. MS (ESI, pos. ion) *m/z*: 355 (M+1).

***tert*-Butyl 4-(5-acetyl-3-chloropyridin-2-yl)piperazine-1-carboxylate (8m).** To a solution of compound **8i** (1.0 g, 2.6 mmol) in anhydrous THF (20 mL) was added MeMgBr (2.6 mL, 3 M solution in Et_2O, 7.8 mmol) with stirring at 0 ^oC. The reaction mixture was stirred at room temperature for 4 h and poured into saturated aqueous solution of $NaHCO_3$ (20 mL). After the addition of EtOAc (50 mL), the mixture was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (70% EtOAc in hexane) to give 0.86 g (97%) of the title compound as a white solid. MS (ESI, pos. ion) *m/z*: 340 (M+1).

1-(5-Chloro-6-(piperazin-1-yl)pyridin-3-yl)ethanone hydrochloride (8n). Following the procedure described for compound **8b**, treatment of compound **8m** with saturated solution of hydrogen chloride in EtOAc provided the title compound (99%) as a white solid. MS (ESI, pos. ion) *m/z*: 240 (M+1).

***tert*-Butyl 4-(5-carbamoyl-3-chloropyridin-2-yl)piperazine-1-carboxylate (8o).** A mixture of 5,6-dichloro-nicotinic acid (7.0 g, 0.036 mol), $(COCl)_2$ (50 mL) and DMF (2 drops) was stirred at room temperature for 4 h. The solution was evaporated in vacuo to give 7.66 g (100%) of the chloride as an orange solid.

A solution of the chloride from the previous step (1.73 g, 8.22 mmol) in CH_2Cl_2 (50 mL) was added to a mixture of 28% aqueous solution of NH_4OH (20 mL), water (20 mL) and CH_2Cl_2 (50 mL), and the mixture was vigorously stirred at room temperature for 2 h. The organic phase was separated, washed with brine (50 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo to give 1.3 g (83%) of the amide **6l** as a white solid. MS (ESI, pos. ion) *m/z*: 191 (M+1).

Following the procedure described for compound **8a**, the amide **6l** from the previous step and *tert*-butyl piperazine-1-carboxylate (**7d**) provided the title compound (90%) as a light-yellow solid. MS (ESI, pos. ion) *m/z*: 341 (M+1).

5-Chloro-6-(piperazin-1-yl)nicotinamide, trifluoroacetic acid salt (8p). A mixture of compound **8o** (0.8 g, 2.35 mmol) and CF_3COOH (1.0 mL) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 2 h. The solvent was removed in vacuo to give 1.1 g (99%) of the title compound as an orange oil. MS (ESI, pos. ion) m/z: 241 (M+1).

(*R*)-1-(3-Bromopyridin-2-yl)-3-methylpiperazine (8q) and (*R*)-1-(3-Bromopyridin-2-yl)-2-methylpiperazine (9). Following the procedure described for compound **8c**, pyridine **6b** and (*R*)-(-)-2-methylpiperazine (**7b**) provided a mixture of the reaction products. The mixture was evaporated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 10% MeOH in dichloromethane to give the title compound **9** (22%) [MS (ESI, pos. ion) *m/z*: 256 (M+1)], and the title compound **8q** (33%) [MS (ESI, pos. ion) *m/z*: 256 (M+1)].

(*S*)-1-(3-Bromopyridin-2-yl)-3-methylpiperazine (8r). Following the procedure described for compound **8a**, pyridine **6b** and (*S*)-(+)-2-methylpiperazine (**7c**) provided the title compound (78%) as a light-brown solid. MS (ESI, pos. ion) *m/z*: 256 (M+ 1).

(*R*)-Methyl 5-chloro-6-(3-methylpiperazin-1-yl)nicotinate (8s). A solution of the acid **6j** (1.92 g, 10 mmol) and *p*-toluenesulfonic acid monohydrate (190 mg, 1.0 mmol) in methanol (5 mL) was heated at reflux for 25 h. The reaction mixture was cooled to room temperature, the solvent was removed in vacuo and the residue was dissolved in EtOAc (50 mL). The solution was washed with satd. $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 30% EtOAc/hexane to give 1.67 g (81%) of the ester **6k** as a white solid. MS ESI, pos. ion) m/e: 205 (M+1).

Following the procedure described for compound **8a**, the ester **6k** from the previous step and piperazine **7b** provided the title compound (57%) as a white solid. MS (ESI, pos. ion) *m/z*: 270 (M+1).

(*R*)-(5-Chloro-6-(3-methylpiperazin-1-yl)pyridin-3-yl)methanol (8t). Following the procedure described for compound **8a**, pyridine **6g** and piperazine **7b** provided the title compound (68%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 242 (M+1).

(*R*)-3-Methyl-1-(3-(trifluoromethyl)pyridin-2-yl)piperazine (8u). Following the procedure described for compound **8a**, pyridine **6d** and piperazine **7b** provided the title compound (86%) as an off-white solid. MS (ESI, pos. ion) *m/z*: 246 (M+1).

(*R*)-*tert*-Butyl 2-methyl-4-(3-(trifluoromethyl)pyridin-2-yl)piperazine-1-carboxylate (8v). To a mixture of compound **8u** (7.38 g, 30 mmol) and 1 N NaOH (60 mL) in THF (100 mL) was added di-*tert*-butyl dicarbonate (7.86 g, 36 mmol) portion-wise with stirring at room temperature. The mixture was stirred at room temperature for 30 min, diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The

filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 20% EtOAc/hexane to give 9.45 g (91%) of the title compound as a gum. MS (ESI, pos. ion) *m/z*: 346 (M+1). ^{1}H NMR ($CDCl_3$): δ1.28 (d, *J* = 6.6 Hz, 3 H), 1.49 (s, 9 H), 2.89-3.01 (m, 1 H), 3.15 (dd, *J* = 12.5, 3.5 Hz, 1 H), 3.24-3.38 (m, 3 H), 3.44 (d, *J* = 12.1 Hz, 1 H), 3.91 (d, *J* = 12.9 Hz, 1 H), 4.34 (s, 1 H), 7.05 (dd, *J* = 7.4, 4.7 Hz, 1 H), 7.90 (d, *J* = 7.8 Hz, 1 H), 8.46 (d, *J* = 4.3 Hz, 1 H).

(*R*)-*tert*-Butyl 4-(5-bromo-3-(trifluoromethyl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (8w). Bromine (1.52 mL, 29.7 mmol) was added dropwise over a period of 5 min to a solution of compound **8v** (9.34 g, 27 mmol) in dichloromethane (100 mL) with stirring at room temperature. The mixture was stirred at room temperature for 30 min, the solvent was removed in vacuo and the residue was dissolved in EtOAc (200 mL). The solution was washed with saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 10% EtOAc/hexane to give 8.72 g (76%) of the title compound as a gum. MS (ESI, pos. ion) m/e: 426 (M+1). ^{1}H NMR ($CDCl_3$): δ1.25 (d, *J* = 6.6 Hz, 3 H), 1.49 (s, 9 H), 2.88-2.98 (m, 1 H), 3.14 (dd, *J* = 12.5, 3.5 Hz, 1 H), 3.24-3.34 (m, 1 H), 3.35 (d, *J* = 12.5 Hz, 1 H), 3.43-3.52 (m, 1 H), 3.90 (d, *J* = 12.9 Hz, 1 H), 4.32 (s, 1 H), 7.98 (d, *J* = 2.0 Hz, 1 H), 8.47 (d, *J* = 2.3 Hz, 1 H).

(*R*,*E*)-*tert*-Butyl 4-(5-(3-methoxy-3-oxoprop-1-enyl)-3-(trifluoromethyl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (8x). A mixture of compound **8w** (8.48 g, 20 mmol), methyl acrylate (1.9 g, 22 mmol), palladium acetate (49 mg, 2.0 mmol) and benzyltriethyl ammonium chloride (456 mg, 2.0 mmol) in DMF (20 mL) was stirred at 40

^{o}C for 18 h. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with EtOAc (2 x 80 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 20% EtOAc/hexane to give 6.36 g (74%) of the title compound as a white solid. MS (ESI, pos. ion) m/e: 430 (M+1).

(*R*)-*tert*-Butyl 4-(5-formyl-3-(trifluoromethyl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (8y). A mixture of compound **8x** (6.02 g, 14 mmol), OsO_4 (4.43 mL, 0.7 mmol, 4% in H_2O) and *N*-methylmorpholine *N*-oxide (1.96 g, 16.8 mmol) in acetone (16 mL) was stirred at room temperature for 5 h. To the mixture was added saturated aqueous solution of $NaHSO_3$ (910 mL) and the mixture was extracted with EtOAc (2 x 40 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was dissolved in dichloromethane (20 mL). To the solution was added $Pb(OAc)_4$ (7.44 g, 16.8 mmol) in one portion and the mixture was stirred at 0 ^{o}C for 30 min. The mixture was diluted with hexane (10 mL), filtered through a Celite® pad, and the filter cake was washed with 50% EtOAc/hexane. The filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 30% EtOAc/hexane to give 1.74 g (81%) of the title compound as a gum. MS (ESI, pos. ion) m/e: 374 (M+1).

(*R*)-*tert*-Butyl 4-(5-(hydroxymethyl)-3-(trifluoromethyl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (8z). To a solution of compound **8y** (4.48 g, 12 mmol) in methanol (30 mL) was added $NaBH_4$ (542 mg, 14.4 mmol) portionwise with stirring at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 30 min and the solvent was removed in vacuo.

The residue was dissolved in EtOAc (60 mL), washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography, eluting with 50% EtOAc/hexane to give 4.01 g (89%) of the title compound as a gum. MS (ESI, pos. ion) m/e: 376 (M+1).

(*R*)-(6-(3-Methylpiperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)methanol (8aa). Following the procedure described for compound **8p**, the reaction of compound **8z** with CF_3CO_2H in CH_2Cl_2 provided the crude product as salt with trifluoroacetic acid. The salt was dissolved in EtOAc (100 mL), washed with saturated aqueous solution of $NaHCO_3$ (2 x 30 mL) and brine (20 mL), dried over Na_2SO_4, and filtered. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 90:10:1 mixture of MeOH/CH_2Cl_2/ammonium hydroxide to give 2.53 g (92%) of the title compound as a white solid. MS (ESI, pos. ion) m/e: 276 (M+1).

(*R*)-3-Ethyl-1-(3-(trifluoromethyl)pyridin-2-yl)piperazine (8ab). To a solution of 2-chloropyridine **6d** (0.18 g, 1.0 mmol) in 3-methyl-1-butanol (2 mL) was added the piperazine **7e** (0.115 g, 1.0 mmol) and Na_2CO_3 (0.085 g, 1.0 mmol). The reaction mixture was heated in a microwave synthesizer at 150 °C for 30 min. The reaction mixture was cooled to room temperature, filtered, and the filter cake was washed with methanol. The combined filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography (gradient: 2-10% MeOH/CH_2Cl_2) to give 0.10 g (38%) of the title compound as a film. MS (ESI, pos. ion) m/e: 260 (M+1). ^{1}HNMR ($CDCl_3$): δ0.96 (t, *J* = 7.6 Hz, 3 H), 1.32-1.52 (m, 2 H), 2.6 (dd, *J* = 12.0, 10.3 Hz, 1 H), 2.66-2.78 (m, 1 H), 2.85-3.05 (m, 2 H), 3.38-3.52 (m, 2 H), 7.12 (dd, *J* = 7.5, 4.9 Hz, 1 H), 7.98 (dd, *J* = 7.8, 1.6 Hz, 1 H), 8.44 (d, *J* = 3.7 Hz, 1 H).

(*R*)-3-Propyl-1-(3-(trifluoromethyl)pyridin-2-yl)piperazine (8ac). Following the procedure described for compound **8a,b**, 2-chloropyridine **6d** and piperazine **7f** provided the title compound (36%) as a colorless oil. MS (ESI, pos. ion) m/e: 274 (M+1). ^{1}HNMR ($CDCl_3$): δ0.93 (t, *J* = 7.2 Hz, 3 H), 1.36-1.46 (m, 4 H), 2.60 (t, *J* = 11.9 Hz, 1 H), 2.74-2.88 (m, 1 H), 2.90-3.04 (m, 3 H), 3.39 (d, *J* = 10.1 Hz, 1 H), 3.46 (d, *J* = 12.2 Hz, 1 H), 7.11 (dd, *J* = 7.5, 5.0 Hz, 1 H), 7.96 (d, *J* = 7.9 Hz, 1 H), 8.42 (d, *J* = 4.2 Hz, 1 H).

(*R*)-1-(3-Chloro-5-nitropyridin-2-yl)-3-methylpiperazine (8ad). Following the procedure described for compound **8c**, pyridine **6n** (prepared as described in Koch, V.; Schnatterer, S. *Synthesis*, **1990**, 499-501) and piperazine (**7b**) provided the title compound (99%) as yellow amorphous solid. ^{1}H NMR (CD_3OD): δ1.01 (d, *J* = 6.3 Hz, 3 H), 2.57-3.00 (m, 5 H), 4.07-4.15 (m, 2 H), 8.31 (s, 1 H), 8.84 (s, 1 H). MS (ESI, pos. ion) m/z: 257 (M+1).

(*R*)-1-(3-Chloropyridin-2-yl)-3-methylpiperazine (8ae). Following the procedure described for compound **8c**, pyridine **6a** and piperazine **7b** provided the title compound (90%) as off-white solid. MS (ESI, pos. ion) m/z: 212 (M+1).

(*R*)-1-(5-Bromo-3-chloropyridin-2-yl)-3-methylpiperazine (8af). Following the procedure described for compound **8w**, the reaction of pyridine **8ae** with bromine provided the title compound (71%) as a light-yellow solid. MS (ESI, pos. ion.) *m/z*: 292 (M+1). ^{1}H NMR (CD_3OD): δ1.25 (d, *J* = 6.6 Hz, 3 H), 2.80 (dd, *J* = 13.3, 10.2 Hz, 1 H), 2.99-3.10 (m, 1 H), 3.12-3.21 (m, 1 H), 3.22-3.27 (m, 1 H), 3.31-3.36 (m, 1 H), 3.75-3.86 (m, 2 H), 7.96 (d, *J* = 2.3 Hz, 1 H), 8.26 (d, *J* = 2.0 Hz, 1 H).

(1*S*)-1-[5-Chloro-6-[(3*R*)-3-methyl-piperazin-1-yl]-pyridin-3-yl]-ethanol and (1*R*)-1-[5-Chloro-6-[(3*R*)-3-methyl-piperazin-1-yl]-pyridin-3-yl]-ethanol (8ag). A mixture

of pyridine **6g** (1.78 g, 10 mmol) and MnO_2 (17.39 g, 200 mmol) in 1:1 CH_2Cl_2/hexane (10 mL) was stirred at room temperature for 1 h. The catalyst was filtered and washed with 50% EtOAc/hexane. The filtrate was evaporated and the residue dried in vacuo to give 1.07 g (61%) of aldehyde **6h**, which was used in the next step without additional purification. MS (ESI, pos. ion) *m/z*: 176 (M+1).

A solution of MeMgBr (2.5 mL, 7.5 mmol, 3.0 M in ether) was added dropwise to a solution of the aldehyde **6h** from the previous step (880 mg, 5.0 mmol) in THF (20 mL) with stirring at 0 ^oC. The mixture was stirred at 0 ^oC for 30 min, saturated aqueous solution of NH_4Cl (20 mL) was added, and the mixture was extracted with EtOAc (2 x 40 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography, eluting with 40% EtOAc/hexane to give 710 mg (74%)) of the alcohol **6i**. MS (ESI, pos. ion) *m/z*: 192 (M+1).

Following the procedure described for compound **8b**, the alcohol **6i** from the previous step and piperazine **7b** provided the title compound (45%) as a mixture of diastereisomers. MS (ESI, pos. ion) *m/z:* 256 (M+1).

***tert*-Butyl 4-(3-chloropyridin-4-yl)piperazine-1-carboxylate (11a).** Following the procedure described for compound **8a**, pyridine **10a** and piperazine **7d** provided the title compound (62%) as an orange oil. MS (ESI, pos. ion) *m/z*: 298 (M+1).

1-(3-Chloropyridin-4-yl)piperazine (11b). Following the procedure described for compound **8p**, the reaction of compound **11a** with CF_3CO_2H in CH_2Cl_2 provided the title compound (99%) as an orange oil. MS (ESI, pos. ion) *m/z*: 198 (M+1).

***tert*-Butyl 4-(3-(trifluoromethyl)pyridin-4-yl)piperazine-1-carboxylate (11c).** Following the procedure described for compound **8a**, pyridine **10b** and piperazine **7d** provided the title compound (68%) as a white solid. MS (ESI, pos. ion) *m/z*: 332 (M+1).

1-(3-(Trifluoromethyl)pyridin-4-yl)piperazine hydrochloride (11d). Following the procedure described for compound **8b**, treatment of compound **11c** with saturated solution of hydrogen chloride in EtOAc provided the title compound (90%) as a white solid. MS (ESI, pos. ion) *m/z*: 232 (M+1).

***tert*-Butyl 4-(5-chloropyrimidin-4-yl)piperazine-1-carboxylate (11e).** Following the procedure described for compound **8a**, pyridine **10c** and piperazine **7d** provided the title compound (52%) as an orange oil. MS (ESI, pos. ion) *m/z*: 299 (M+1).

5-Chloro-4-(piperazin-1-yl)pyrimidine, trifluoroacetic acid salt (11f). Following the procedure described for compound **8p,** the reaction of compound **11e** with CF_3CO_2H in CH_2Cl_2 provided the title compound (99%) as an orange oil. MS (ESI, pos. ion) *m/z*: 199 (M+1).

1-(2,6-Dichlorophenyl)piperazine (14). A mixture of 2,6-dichlorophenylaniline (810 mg, 5 mmol) and bis(2-chloroethyl)amine hydrochloride (823 mg, 5 mmol) was subjected to microwave irradiation at 200 ^{o}C for 10 min. The reaction mixture was allowed to cool to room temperature, treated with 5 N NaOH (5 mL), and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was purified by silica gel chromatography, eluting with 10% MeOH/CH_2Cl_2 + 1% ammonia (30% in water) to give 254 mg (22%) of the title compound. MS (ESI, pos. ion) *m/z*: 231 (M+1).

4-Bromo-5-(trifluoromethyl)benzene-1,2-diamine (18b). A mixture of 4-bromo-3-(trifluoromethyl)phenylamine (7.2 g, 30 mmol) and acetic anhydride (29 mL) was stirred at room temperature for 16 h. The reaction mixture was evaporated in vacuo to give 8.46 g (100 %) of the acetamide **22** as a white solid, which was used in the next step without additional purification. MS (ESI, pos. ion) *m/z*: 484 (M+1).

To a solution of the acetamide **22** from the previous step (8.46 g, 30 mmol) in concentrated sulfuric acid (32.5 mL) was added dropwise 90% HNO_3 (4.1 mL) with stirring at 0 ^oC. The resulting solution was stirred at room temperature for 3 h and poured into crushed ice (80 mL). The mixture was carefully neutralized with solid $NaHCO_3$ and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (25% EtOAc/hexane) to give 7.2 g (73%) of the nitro derivative **23** as a yellow solid. MS (ESI, neg. ion) *m/z*: 325 (M-1).

To a solution of the compound **23** from the previous step (4.5 g, 14 mmol) in MeOH (8 mL) was added aqueous 3 N NaOH (50 mL) at room temperature. The reaction mixture was stirred at 90 ^oC for 2 h, cooled to room temperature and extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with 1% aqueous HCl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (15% EtOAc/hexane) to give 3.5 g (88%) of the aniline **24** as a yellow solid. MS (ESI, neg. ion) *m/z*: 283 (M-1).

To a solution of the aniline **24** from the previous step (3.3 g, 10 mmol) in EtOAc (26 mL) and EtOH (13 mL) was added tin (II) chloride dihydrate (13.1 g, 45 mmol). The reaction mixture was stirred at 70 ^oC for 1 h. The light-yellow reaction solution was

poured to crushed ice (50 mL) and carefully neutralized using saturated aqueous solution of $NaHCO_3$. The resulting suspension was extracted with EtOAc (3 x 60 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the filtrate evaporated in vacuo to give 2.37 g (93%) of the title compound as a brown solid. MS (ESI, pos. ion) *m/z*: 257 (M+1).

3-Nitro-5-(trifluoromethyl)benzene-1,2-diamine (18c). 4-Amino-3, 5-dininitrobenzotrifluoride (25 g, 100 mmol) was added to a suspension of 10% Pd/C (4 g) in EtOH (150 mL) under a hydrogen atmosphere. The reaction mixture was stirred at room temperature for 4 h, filtered through a pad of Celite®, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with 45% EtOAc/hexane to give 18 g (81%) of the title compound as a yellow solid. MS (ESI, pos. ion) *m/z*: 222 (M+1).

5-Trifluoromethyl-pyridine-2,3-diamine (18d). To a 250-mL, round-bottomed flask was added 5-trifluoromethyl-pyridin-2-ylamine (8.3 g, 51.2 mmol) and H_2SO_4 (49 mL). The resulting mixture was cooled to 0 ^oC, and HNO_3 (8.2 mL) was added dropwise. The mixture was heated to 80 ^oC for 48 h, cooled to room temperature and added dropwise into a vigorously stirred ice-water (500 mL). After the addition, the mixture was basified to pH 9 with 10 N NaOH and extracted with EtOAc (2 x 500 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography, eluting with EtOAc/hexane (1:2) to give 1.2 g (11%) of the nitro derivative **27** as a yellow solid. MS (ESI, pos. ion) m/z: 208 (M+1).

A mixture of the nitro derivative **27** from the previous step (1.2 g, 5.59 mmol) and tin (II) chloride dihydrate (3.9 g, 17.3 mmol) in DMF (19 mL) was heated to 60 ^{o}C for 4 h. The reaction mixture was cooled to room temperature and $NaHCO_3$ (150 mL) was added. The mixture was stirred for 0.5 h, diluted with EtOAc (300 mL), stirred for 0.5 h, and filtered. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to give the title compound, which was used in the next step without additional purification. MS (ESI, pos. ion) m/z: 178 (M+1).

6-Trifluoromethyl-pyridine-2,3-diamine, trifluoroacetic acid salt (18e). A mixture of the 3-amino-2-chloro-6-(trifluoromethyl)pyridine (416 mg, 2.1 mmol), 4-methoxy-benzylamine (294 mg, 2.1 mmol) and sodium bicarbonate (265 mg, 3.2 mmol) in isoamyl alcohol (0.6 mL) was heated at 220 °C in a microwave synthesizer for 30 min. The reaction mixture was then cooled to room temperature, diluted with MeOH (5 mL), filtered and the filtrate was evaporated in vacuo. The residue was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give 100 mg (16%) of N^2-(4-methoxy-benzyl)-6-trifluoromethyl-pyridine-2,3-diamine (**29**) as a yellow oil. MS (ESI, pos. ion) *m/z*: 298 (M+1).

A solution of compound **29** from the previous step (220 mg, 0.7 mmol) in 1:1 TFA/DCM (4 mL) was stirred at room temperature for 90 min. The reaction mixture was evaporated under reduced pressure to yield a gummy residue, which was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give 120 mg (91%) of the title compound as an amorphous solid. MS (ESI, pos. ion) *m/z*: 178 (M+1).

6-*tert*-Butyl-2-chloro-1*H*-benzo[*d*]imidazole (20a). A mixture of benzene-1,2-diamine **18a** (5 g, 30.5 mmol) and 1,1'-carbonyldiimidazole (5.44 g, 33.5 mmol) in THF (30 mL) was stirred at room temperature for 16 h. The solvent was removed in vacuo and the resididue was purified by silica gel chromatography, eluting with EtOAc to give 5.4 g (93%) of 5-*tert*-butyl-1,3-dihydrobenzoimidazol-2-one (**19a**) as a white solid. MS (ESI, pos. ion) *m/z*: 191 (M+1).

A solution of compound **19a** from the previous step (5.4 g, 28 mmol) in $POCl_3$ (30 mL) was heated at 95 ^oC for 16 h. The reaction mixture was cooled to room temperature, the solvent was removed in vacuo and the resulting oily residue subjected to azeotropic distillation with toluene (3 x 50 mL) at 50 ^oC. The crude product was dissolved in EtOAc (50 mL), washed with brine (10 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue crystallized from EtOAc/hexane to give 5.2 g (89%) of the title compound as an off-white solid. MS (ESI, pos. ion) *m/z*: 209 (M+1).

5-Bromo-2-chloro-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (20b). Following the procedure described for compound **19a**, compound **18b** and 1,1'-carbonyldiimidazole provided the imidazolone **19b** (97%) as a light-yellow solid. MS (ESI, pos. ion) *m/z*: 283 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19b** from the previous step with $POCl_3$ provided the title compound (89%) as a white solid. MS (ESI, pos. ion) *m/z*: 301, 303 (M+1).

2-Chloro-4-nitro-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (20c). Following the procedure described for compound **19a**, compound **18c** and 1,1'-carbonyldiimidazole

provided the imidazolone **19c** (73%) as a yellow solid. MS (ESI, pos. ion) *m/z*: 248 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19c** from the previous step with $POCl_3$ provided the title compound (78%) as a yellow solid. MS (ESI, pos. ion) *m/z*: 266 (M+1).

2-Chloro-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole hydrochloride (20d). Following the procedure described for compound **19a**, compound **18d** and 1,1'-carbonyldiimidazole provided the crude product, which was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give the imidazolone **19d** (65%) as salt with trifluoroacetic acid. MS (ESI, pos. ion) *m/z*: 204 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19d** from the previous step with $POCl_3$ provided the title compound (26%) as an amorphous solid.

2-Chloro-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (20e). A mixture of compound **18e** (160 mg, 0.9 mmol) and *N*,*N*'-disuccinimidyl carbonate (250 mg, 0.9 mmol) in MeCN (5 mL) was stirred at room temperature for 13 h. Additional amount of *N*,*N*'-disuccinimidyl carbonate (125 mg, 0.5 mmol) was added, and the reaction mixture was heated at 75 °C for 90 min. The reaction mixture was cooled to room temperature and diluted with dichloromethane (20 mL). The precipitate was filtered and dried in vacuo to give the imidazolone **19e**, which was used in the next step without additional purification. MS (ESI, pos. ion) *m/z*: 204 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19e** from the previous step with $POCl_3$ provided the title compound (82%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 222 (M+1).

4-Bromo-2-chloro-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (20f). Following the procedure described for compound **19a**, compound **18f** and 1,1'-carbonyldiimidazole provided the imidazolone **19f** (68%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 281 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19f** from the previous step with $POCl_3$ provided the title compound (81%) as a white solid. MS (ESI, pos. ion) *m/z*: 299 (M+1).

2-Chloro-5-fluoro-1*H*-benzo[*d*]imidazole (20g). Following the procedure described for compound **19a**, compound **18g** and 1,1'-carbonyldiimidazole provided the imidazolone **19g** (79%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 153 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19g** from the previous step with $POCl_3$ provided the title compound (48 %) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 171 (M+1).

2-Chloro-1*H*-benzo[*d*]imidazole-5-carbonitrile (20h). Following the procedure described for compound **19a**, compound **18h** and 1,1'-carbonyldiimidazole provided the imidazolone **19h** (98%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 160 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19h** from the previous step with $POCl_3$ provided the title compound (32%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 178 (M+1).

2-Chloro-6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazole (20i). A mixture of imidazolone **19f** (1.12 g, 4 mmol), 3,4,5-trifluorophenylboronic acid (1.1 g, 6 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), Na_2CO_3 monohydrate (1 g, 8 mmol), dimethoxyethane (7 mL), H_2O (3 mL) and EtOH (2 mL) was heated in a microwave synthesizer at 120 ^oC for 10 min. Water (10 mL) was added and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel chromatography, eluting with 35% EtOAc/hexane to give 1.1 g (83%) of 6-trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1,3-dihydro-2*H*-benzimidazol-2-one **19i** as a light-brown solid. MS (ESI, pos. ion) *m/z*: 333 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19i** from the previous step with $POCl_3$ provided the title compound (61%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 178 (M+1).

2,6-Dichloro-1*H*-benzo[*d*]imidazole (20j). Following the procedure described for compound **19a**, compound **18i** and 1,1'-carbonyldiimidazole provided the imidazolone **19j** (68%) as a red amorphous solid. MS (ESI, pos. ion) *m/z*: 169 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19j** from the previous step with $POCl_3$ provided the title compound (69%) as a brown amorphous solid. MS (ESI, pos. ion) *m/z*: 187 (M+1).

2-Chloro-6-methyl-1*H*-benzo[*d*]imidazole (20k). Following the procedure described for compound **19a**, compound **18j** and 1,1'-carbonyldiimidazole provided the imidazolone **19k** (81%) as a off-white solid. MS (ESI, pos. ion) *m/z*: 149 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19k** from the previous step with $POCl_3$ provided the title compound (40%) as a pink amorphous solid. MS (ESI, pos. ion) *m/z*: 167 (M+1).

Methyl 2-chloro-1H-benzo[*d*]imidazole-5-carboxylate (20l). Following the procedure described for compound **19a**, compound **18k** and 1,1'-carbonyldiimidazole provided the imidazolone **19l** (86%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 193 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19l** from the previous step with $POCl_3$ provided the title compound (89%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 211 (M+1).

2-Chloro-4,6-bis(trifluoromethyl)-1*H*-benzo[*d*]imidazole (20m). Following the procedure described for compound **19a**, compound **18l** and 1,1'-carbonyldiimidazole provided the imidazolone **19m** (54%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 271 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19m** from the previous step with $POCl_3$ provided the title compound (78%) as an a white solid. MS (ESI, pos. ion) *m/z*: 289 (M+1).

2-Chloro-6-trifluoromethyl-1*H*-benzo[*d*]imidazole (20n). Following the procedure described for compound **19a**, compound **18m** and 1,1'-carbonyldiimidazole provided the imidazolone **19n** (65%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 203 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19n** from the previous step with $POCl_3$ provided the title compound (67%) as an amorphous solid. MS (ESI, pos. ion) *m/z*: 221 (M+1).

6-Bromo-2-chloro-1*H*-benzo[*d*]imidazole (20o). Following the procedure described for compound **19a**, compound **18n** and 1,1'-carbonyldiimidazole provided the imidazolone **19o** (85%) as a gray amorphous solid. MS (ESI, pos. ion) *m/z*: 214 (M+1).

Following the procedure described for compound **20a**, the reaction of the imidazolone **19o** from the previous step with $POCl_3$ provided the title compound (84%) as a gray amorphous solid. MS (ESI, pos. ion) *m/z*: 232 (M+1).

2-(Piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (30a). A mixture of piperazine **7a** (172 mg, 2 mmol) and benzoimidazole **20n** (221 mg, 1 mmol) in DMSO (2 mL) was stirred at 80 ^{o}C for 24 h. The mixture was cooled down to room temperature, diluted with water (10 mL), and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with water (2 x 5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was purified by silica gel chromatography, eluting with 10% MeOH/CH_2Cl_2 + 1% ammonia (30% in water) to give 235 mg (87%) of the desired product. MS (ESI, pos. ion) *m/z*: 271 (M+1).

(*S*)-2-(3-Methylpiperazin-1-yl)-5-(trifluoromethyl)-7-(3,4,5-trifluorophenyl)-1*H*-benzo[d]imidazole (30b). A mixture of piperazine **7c** (150 mg. 1.5 mmol), 2-chlorobenzoimidazole **20i** (350 mg, 1 mmol) and *N*,*N*-diisopropylethylamine (0.28 mL, 1.6 mmol) in MeCN (1 mL) was heated in a microwave synthesizer at 180 ^{o}C for 30 min. The mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 30% EtOAc/hexane, to give 200 mg (48%) of the title compound as a light-brown solid. MS (ESI, pos. ion) *m/z*: 415 (M+1).