Supporting information

Lerisetron Analogues with Antimalarial Properties: Synthesis, Structure-Activity Relationship Studies and Biological Assessment

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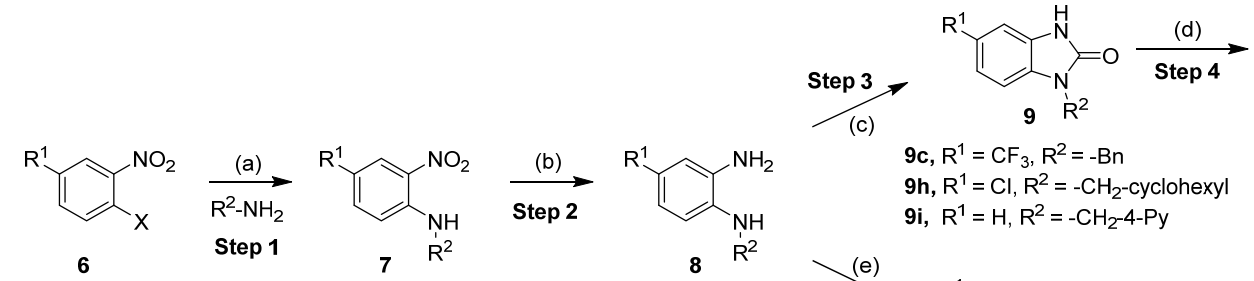
General procedure 1 (GP1) for the synthesis of 3, 14c, 14h-i, 15, 16a-b, 16f-g, 17-41, 42a & 42 k (Scheme S1);



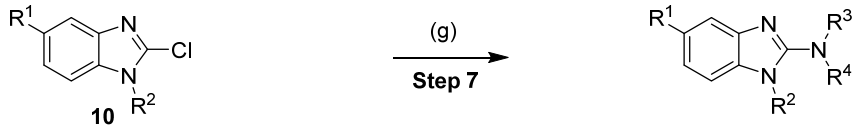
6a, X = Cl, R^1 = Cl
X = F: **6b**, R^1 = Br
6c, R^1 = CF_3
6d, R^1 = CO_2Me
6e, R^1 = SO_2Me

R^2 = Bn: **7a,** R^1 = Cl
7b, R^1 = Br
7c, R^1 = CF_3
7d, R^1 = CO_2Me
7e, R^1 = SO_2Me
R^1 = Cl: **7f,** R^2 = Ph
7g,R^2 = -CH_2CH_2-Ph
7h, R^2 = -CH_2-cyclohexyl

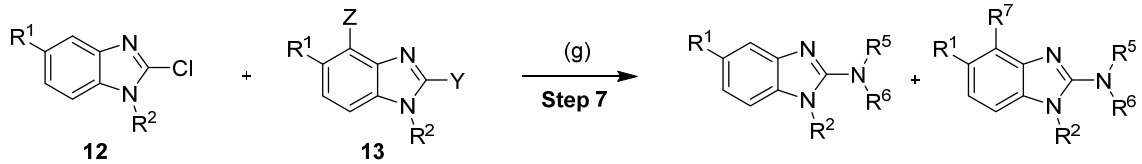
R^2 = Bn: **8a,** R^1 = Cl
8b, R^1 = Br
8c, R^1 = CF_3
8d, R^1 = CO_2Me
8e, R^1 = SO_2Me
R^1 = Cl: **8f**, R^2 = Ph
8g,R^2 = -CH_2CH_2-Ph
8h, R^2 = -CH_2-cyclohexyl
R^1 = H: **8i,** R^2 = -CH_2-4-Py

9c, R^1 = CF_3, R^2 = -Bn
9h, R^1 = Cl, R^2 = -CH_2-cyclohexyl
9i, R^1 = H, R^2 = -CH_2-4-Py

R^2 = Bn: **11a,** R^1 = Cl
11b, R^1 = Br
R^1 = Cl: **11f**, R^2 = Ph
11g, R^2 = -CH_2CH_2-Ph



10c, R^1 = CF_3, R^2 = -Bn
10h, R^1 = Cl, R^2 = -CH_2-cyclohexyl
10i, R^1 = H, R^2 = -CH_2-4-Py



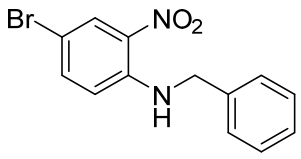
12a, R^1 = Cl, R^2 = Bn
12b, R^1 = Br, R^2 = Bn
12f, R^1 = Cl, R^2 = Ph
12g, R^1 = Cl, R^2 = -CH_2CH_2-Ph

13a, R^1 = Cl, R^2 = Bn, Y = Z = Cl
13b, Not observed
13f, R^1 = Cl, R^2 = Ph, Y = Z = Cl
13g, Not observed
13k, R^1 = Cl, R^2 = Bn, Y = Z = Br

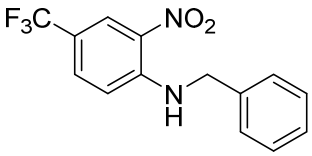
Step 1: General procedure for the synthesis of amino nitro derivatives

Method A: Synthesis of Compounds 7b, 7c, 7d & 7e:

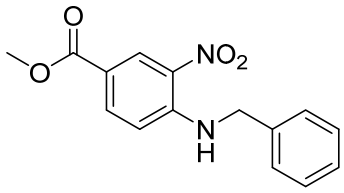
***N*-benzyl-4-bromo-2-nitroaniline (7b):**[1a] To a solution of 4-bromo-1-fluoro-2-nitrobenzene (10.0 g, 45.5 mmol) in acetonitrile (40 mL), benzylamine (7.31 g, 68.2 mmol) and triethylamine (12.51 mL, 91 mmol) were added slowly and the reaction mixture stirred at 50 °C for 16h, until TLC indicated that the reaction is completed. Added H_20 (100 mL) and EtOAc (100 mL) to the reaction mixture. Separated the organic phase, extracted the aqueous phase with additional EtOAc (2 x 50 mL). Combined the organic phases and washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to dryness to afford *N*-benzyl-4-bromo-2-nitroaniline (13.0 g, 93% yield) as an orange solid which was used directly for the next step without any further purification. TLC System R_f=0.41 [Hexane/EtOAc (9/1)]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.42 (br s, 1H), 8.36 (d, J = 2.4 Hz, 1H), 7.46 (dd, J = 9.1, 2.4 Hz, 1H), 7.42 – 7.32 (m, 5H), 6.75 (d, J = 9.2 Hz, 1H), 4.56 (d, J = 2.4 Hz, 2H).



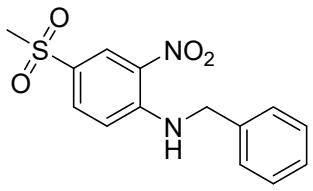
***N*-Benzyl-2-nitro-4-(trifluoromethyl)aniline (7c):**[1b] TLC System R_f= 0.41 [Hexane/EtOAc (9/1)]. (8.0 g, 56% yield), Orange solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.67 (brs, 1H), 8.52 (m, 1H), 7.64 – 7.58 (m, 1H), 7.47 – 7.31 (m, 5H), 6.94 (d, J = 9.0 Hz, 1H), 4.62 (d, J = 5.7 Hz, 2H).



Methyl 4-(benzylamino)-3-nitrobenzoate (7d):[2] TLC System R_f = 0.39 [Hexane/EtOAc (9/1)]. (7.0 g, 97% yield), Yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.93 (d, J = 2.1 Hz, 1H), 8.72 (brs, 1H), 8.04 (dd, J = 9.0, 2.1 Hz, 1H), 7.47 – 7.32 (m, 5H), 6.88 (d, J = 9.0 Hz, 1H), 4.62 (d, J = 5.6 Hz, 2H), 3.92 (s, 3H).

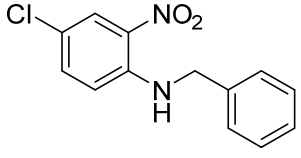


***N*-Benzyl-4-(methylsulfonyl)-2-nitroaniline (7e):**[3] TLC System R_f=0.40 [Hexane/EtOAc (8/2)]. (5.3 g, 76% yield), Yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.81 (d, J = 2.2 Hz, 1H), 7.87 (dd, J = 9.1, 2.2 Hz, 1H), 7.47 – 7.32 (m, 6H), 6.98 (d, J = 9.1 Hz, 1H), 4.64 (d, J = 5.6 Hz, 2H), 3.06 (s, 3H).



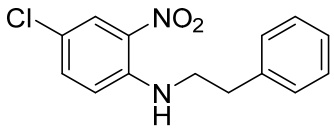
<u>Method B: Synthesis of Compounds 7a, 7f, 7g, 7h, 54a & 54b:</u>

N-benzyl-4-chloro-2-nitroaniline (7a): To a stirring solution of 1,4-chloro-2-nitrobenzene (2.5 g, 13.02 mmol) and benzylamine (1.4 g, 13.07 mmol) in DMF (10 mL) was added potassium carbonate (5.0 g, 36.2 mmol). The resulting reaction mixture was heated to 80 °C for 4 h. The reaction mixture was cooled to 25 °C and diluted with water (100 mL), acidified to pH 2 with conc. HCl then extracted with ethyl



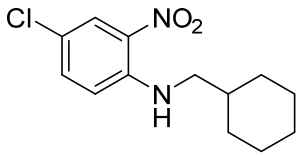
acetate (2 x 80 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified through flash chromatography using Hexane/DCM (90/10 to 80/20) and crystallized from isopropylether/hexane to get a pure *N*-benzyl-4-chloro-2-nitroaniline (1.38 g, 40% yield) as an orange crystals. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.43 (brs, 1H), 8.42 (d, *J*= 3.0 Hz, 1H), 7.43 – 7.28 (m, 6H), 6.80 (d, *J* = 9.0 Hz, 1H), 4.56 (d, *J* = 3.0 Hz, 2H).

4-Chloro-2-nitro-*N*-phenethylaniline (7g): Flash column chromatography using Hexane/EtOAc (0-20% gradient). (1.1 g, 25% yield), Orange solid.

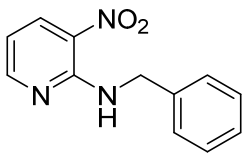


Note: No characterization was done, used as such in the next step.

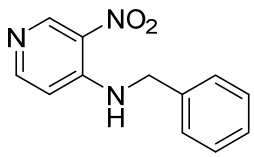
4-Chloro-*N*-(cyclohexylmethyl)-2-nitroaniline (7h): Crude yield (5.3 g, 95% yield). **1H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.25 – 8.08 (m, 2H), 7.47 – 7.23 (m, 1H), 6.83 (d, *J* = 9.2 Hz, 1H), 3.17 – 3.12 (m, 2H), 1.94 – 1.57 (m, 6H), 1.40 – 1.17 (m, 3H), 1.16 – 0.88 (m, 2H). Used as such in the next step.



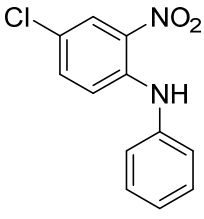
***N*-Benzyl-3-nitropyridin-2-amine (54a):**[4] Flash column chromatography using Hexane/DCM (70/30 to 50/50) yielded a (2.68 g) yellow oil. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.55 (brs, 1H), 8.49 – 8.45 (m, 2H), 7.40 – 7.28 (m, 5H), 6.73 – 6.69 (m, 1H), 4.90 (d, *J* = 6.0 Hz, 2H).



***N*-Benzyl-3-nitropyridin-4-amine (54b):**[5] (2.245 g, 98% yield), Orange oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.16 (s, 1H), 8.45 (brs, 1H), 8.20 (d, *J* = 6.0 Hz, 1H), 7.40 – 718 (m, 5H) 6.63 (d, *J* = 6.0 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 2H). The crude was used in the next step without further purification.



4-Chloro-2-nitro-*N*-phenylaniline (7f):[6] To a mixture of 1,4-dichloro-2-nitrobenzene (4.90 ml, 26.0 mmol) and aniline (7.28 g, 78 mmol) in DMSO (4.64 ml) was added potasium carbonate (3.60 g, 26.0 mmol) and the resulting mixture was heated to 120 ºC for 24 h. The reaction changes the colour slowly to dark brown from the initial orange colour. The reaction was cooled down to the room temperature and poured into a 50 mL water and extracted with DCM (2 x 75 mL). The seperated organic layer was washed two times with HCl (0.5 M, 100 mL) and then evaporated under reduced pressure. The residue was purified through silica gel column chromatography using Hexane/EtOAc (0-20%) gradient and obtained the 4-chloro-2-nitro-*N*-



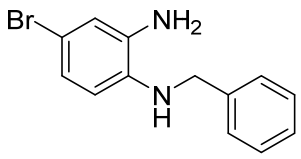
phenylaniline (6.05 g, 93% yield) as an orange solid. **1H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.46 (brs, 1H), 8.22 (d, J = 2.5 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.35 – 7.26 (m, 4H), 7.18 (d, J = 9.2 Hz, 1H).

Step 2: General procedures for the reduction of the nitro group

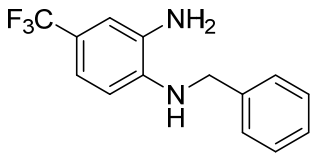
The reduction of the nitro group to the amine has been carried out in three ways

Method A: Synthesis of Compounds 8b, 8c & 8h:

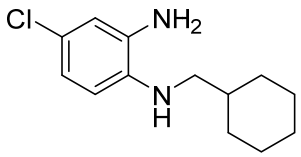
***N*1-benzyl-4-bromobenzene-1,2-diamine (8b):**[1a] To a solution of the crude *N*-benzyl-4-bromo-2-nitroaniline (**7b**) (10.00 g, 32.6 mmol) in MeOH (80 mL) was added Pt/C (0.635 g, 3.26 mmol) and the reaction mixture was stirred at 25ºC under a hydrogen atmosphere. After 2 days, TLC indicated that the reaction is completed. TLC System R_f=0.35 [Hexane/EtOAc (9/1)]. Filtered the reaction mixture through a bed of celite, concentrated *in vacuo* to dryness and purified by flash column chromatography using Hexane/EtOAc (0-50%) to afford *N*1-benzyl-4-bromobenzene-1,2-diamine (8.79 g, 88% yield) as a dark brown solid, which was used directly to the next step without any further purification. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.43 – 7.17 (m, 5H), 6.85 (d, J = 2.2 Hz, 1H), 6.68 (dd, J = 8.4, 2.3 Hz, 1H), 6.39 (d, J = 8.4 Hz, 1H), 4.33 (s, 2H).



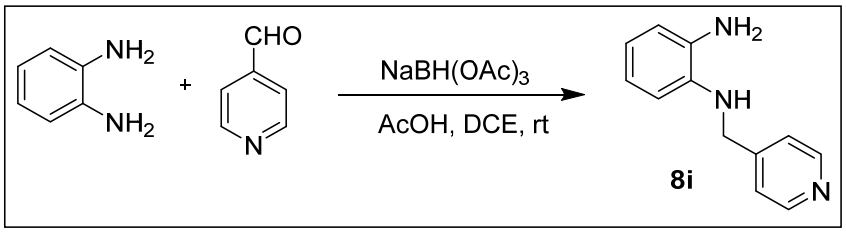
***N*1-Benzyl-4-(trifluoromethyl)benzene-1,2-diamine (8c)**:[1b] Reaction stirred for 3 days. TLC System R_f = 0.35 [Hexane/EtOAc (8/2)]. (7.0 g, 97% yield), Dark brown solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.42 – 7.18 (m, 5H), 6.96 (d, J = 2.1 Hz, 1H), 6.89 – 6.83 (m, 1H), 6.52 (d, J = 8.2 Hz, 1H), 4.42 (s, 2H).



4-Chloro-*N*1-(cyclohexylmethyl)benzene-1,2-diamine (8h): To 4-chloro-*N*-(cyclohexylmethyl) -2-nitroaniline (5 g, 18.61 mmol) in DCM (100 mL) was added Pt/C (300 mg, 1.538 mmol). The reaction was stirred under a hydrogen atmosphere overnight and after 18 h the starting material was completely consumed. The catalyst was filtered through a celite bed and solvent evaporated under reduced pressure to afford a dark oil (4.0 g, 90% yield). The material was used directly without further purification in the next step. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.78 (dd, J = 8.4, 2.3 Hz, 1H), 6.71 (d, J = 2.3 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 3.27 (brs, 3H), 3.00 – 2.87 (m, 2H), 1.93 – 0.98 (m, 11H).



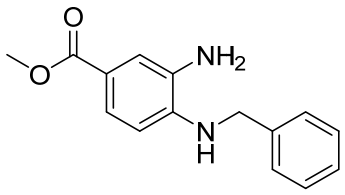
Synthesis of *N*1-(pyridin-4-ylmethyl)benzene-1,2-diamine (8i):



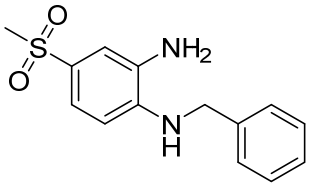
To a solution of the benzene-1,2-diamine (1.0 g, 9.25 mmol) in DCE (5 mL) was added isonicotinaldehyde (0.990 g, 9.25 mmol), Sodium triacetoxyborohydride (2.94 g, 13.87 mmol), AcOH (0.794 mL, 13.87 mmol) and powdered 3A^{o} molecular sieves. The reaction mixture was stirred at temperature of 25 ^{o}C. After 24 hrs, TLC indicated the disappearance of the starting material. Added H_20 (40 mL) and EtOAc (40 mL), separated the organic phase, extracted the aqueous phase with further portions of EtOAc (2 x 20 mL). Combined the organic phases, washed sequentially with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a crude brick red oily residue. Purification by column chromatography on SiO_2 gel using EtOAc (100%) to afford *N*1-(pyridin-4-ylmethyl)benzene-1,2-diamine, 870 mg (47% yield) as a brown solid which was used directly to the next step without any further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.62 – 8.53 (m, 2H), 7.39 – 7.33 (m, 2H), 6.80 – 6.70 (m, 3H), 6.60 – 6.50 (m, 1H), 4.41 (s, 2H), 3.98 (brs, 3H).

Method B: Synthesis of Compounds 8d, 8e & 8f:

Methyl 3-amino-4-(benzylamino)benzoate (8d):[2] To a suspension of methyl 4- (benzylamino)-3-nitrobenzoate (**7d**) (8.59 g, 30.0 mmol) in EtOH (200 mL), iron (8.04 g, 144 mmol) and saturated aqueous NH_4Cl (40 mL, 30.0 mmol) were added and the reaction mixture was heated to 80 ^{o}C. The solution changes from yellow to dark brown. After 6hrs, TLC indicated that the reaction is completed [TLC System: Hexane/EtOAc (9/1), R_f=0.39]. The reaction mixture was cooled to 25 ^{o}C, filtered through a bed of celite and extracted with EtOAc (2 x 100 mL). Combined the organic phases and washed with water (2 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to dryness to afford methyl 3-amino-4-(benzylamino)benzoate (5.31 g, 69% yield) as a yellow solid which was used directly to the next step without any further purification. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.44 – 7.12 (m, 7H), 6.49 (d, J = 8.3 Hz, 1H), 4.46 (s, 2H), 3.81 (s, 3H).

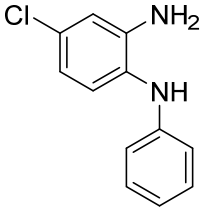


***N*1-Benzyl-4-(methylsulfonyl)benzene-1,2-diamine (8e):** TLC System R_f = 0.39 [Hexane/EtOAc (9/1)].



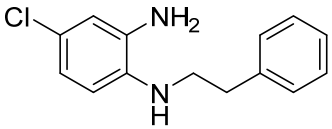
(4.2 g, 88% yield), Brown solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.42 – 7.23 (m, 5H), 7.20 (d, J = 2.2 Hz, 1H), 7.15 (dd, J = 8.4, 2.2 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 4.48 (s, 2H), 2.99 (s, 3H).

4-Chloro-*N*1-phenylbenzene-1,2-diamine (8f):[6] Reaction stirred for 18 h. Flash column chromatography



using Hexane/DCM (0-50% gradient). (5.254 g, 97% yield), White solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.27 – 7.20 (m, 2H), 7.05 (d, J = 8.3 Hz, 1H), 6.90 – 6.84 (m, 1H), 6.81 (d, J = 2.3 Hz, 1H), 6.77 – 6.71 (m, 3H).

Method C: Synthesis of 4-chloro-*N*1-phenethylbenzene-1,2-diamine (8g):

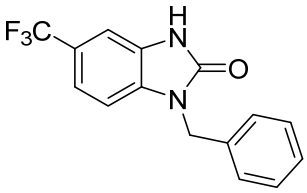


To a solution of the 4-chloro-2-nitro-*N*-phenethylaniline **(7g)** (1.10 g, 3.98 mmol) in MeOH (10 mL) was added hydrazine hydrate (1.877 ml, 39.8 mmol) and the reaction mixture was refluxed at a temperature of 80 ºC. After 2 hrs, TLC indicated that the reaction is completed. The solvent was evaporated under reduced pressure to afford a crude yellow oily residue. Added H_20 (20 mL) and EtOAc (40 mL), separated the organic phase, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a crude yellow oily residue. The crude was purified by column chromatography on SiO_2 gel and elution using Hexane/EtOAc (0-20% gradient) to afford a 4-chloro-*N*1-phenethylbenzene-1,2-diamine **(8g)** (600 mg, 61%) as a light-yellow oil.

Note: No characterization was done, used as such in the next step.

Step 3: General procedure for the cyclization (9c, 9h & 9i)

Synthesis of 1-benzyl-5-(trifluoromethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (9c): To a stirred



solution of *N*1-benzyl-4-(trifluoromethyl)benzene-1,2-diamine (**8c**) (5.0 g, 18.78 mmol) in DCM (25.0 mL) was slowly added a solution of triphosgene (2.229 g, 7.51 mmol) DCM (15.00 mL) and the reaction mixture stirred at a temperature at 25ºC. After 16 hrs, TLC and LCMS indicated that the reaction is completed. The orange suspension is poured into water (200 mL) and DCM (200 mL) and the resulting mixture stirred at room temperature of 25 ºC for 1 h. Separated the aqueous phase and the organic suspension is filtered off and dried to afford an off white solid 1-benzyl-5-(trifluoromethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (5.30 g, 94% yield) which was used directly in the next step without any further purification. TLC system R*f* = 0.48 [Hexane/EtOAc (6/4)]. **HPLC** purity

97%, Retention time (R_t) = 4.310 min; Method Used (General negative); LC-MS (APCI) *m/z* = found 291.1 $(M - H)^-$ on a negative mode [calcd for $C_{15}H_{10}F_3N_2O$ *m/z* = 291.07 $(M - H)^-$].

5-Chloro-1-(cyclohexylmethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (9h): (425 mg, 92% yield), Brick red solid. **1H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.86 (brs, 1H), 7.15 (d, *J* = 1.9 Hz, 1H), 7.07 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.70 (d, *J* = 7.4 Hz, 2H), 1.75 – 1.69 (m, 6H), 1.28 – 1.06 (m, 5H). **HPLC** purity 96%, Retention time (R_t) = 4.734 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 265.1 (M+) and 267.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{14}H_{18}ClN_2O$ *m/z* = 265.11 $(M + H)^+$].

1-(Pyridin-4-ylmethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (9i): TLC System R_f = 0.2 [EtOAc (100%)]. (1.15 g, 68% yield), Brick red residue. **HPLC** purity 76%, Retention time (R_t) = 2.686 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 226.1 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{13}H_{12}N_3O$ *m/z* = 226.01 $(M + H)^+$].

Step 4: General procedure for the chlorination (10c, 10h & 10i)

Synthesis of 1-benzyl-2-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole (10c):

To a suspension of 1-benzyl-5-(trifluoromethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (**9c**) (5.39 g, 18.44 mmol) in phosphorus oxychloride (39.5 ml, 424 mmol) was added slowly phosphorus pentachloride (6.68 g, 32.1 mmol) in one portion and the reaction mixture stirred at room temperature (25 °C) for 15 min, then heated to 110 °C for 1 h, until LCMS and TLC indicated the reaction is completed. Cooling of the yellow reaction mixture to room temperature at (25 °C), concentrated *in vacuo* to remove the excess $POCl_3$ to afford a yellow residue. Added EtOAc (40 mL) to the residue, then poured portion wise into a stirred ice cooled saturated sodium bicarbonate solution (100 mL) and stir for 20 min. Separated the organic phase, washed sequentially with H_2O (20 mL) and brine (20 mL). Dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a residue which was then triturated using Et_2O (20 mL), filtered and dried to afford 1-benzyl-2-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole (3.8 g, 45% yield) as an off-white solid, which was used directly in the next step without any further purification. **HPLC** purity 69%, Retention time (R_t) = 4.540 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 311.0 $(M + H)^+$ on a positive mode (calcd for $C_{15}H_{11}ClF_3N_2$ *m/z* = 311.056 $(M + H)^+$.

Synthesis of 2,5-dichloro-1-(cyclohexylmethyl)-1H-benzo[d]imidazole (10h): A mixture of 5-chloro-1-(cyclohexylmethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (**9h**) (450 mg, 1.700 mmol), phosphorus oxychloride (2376 µl, 25.5 mmol) and hydrochloric acid (5.16 µl, 0.170 mmol) was heated in a pressure tube at 150 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and then poured into ice cold water (50 mL), neutralized with 2N aqueous NaOH solution to a pH 6-7. Extracted with EtOAc (3 x 30 mL), combined the organic phases, washed with water (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by SiO_2 gel column chromatography using Hexane/EtOAc (0-20%) gradient to afford the desired product (230 mg, 44 % yield) as a white solid. **HPLC** purity 92%, Retention time (R_t) = 4.892 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 283.1 (M^+) and 285.1 $(M + 2)^+$ on a positive mode [calcd for $C_{14}H_{17}Cl_2N_2$ *m/z* = 283.08 $(M + H)^+$].

2-Chloro-1-(pyridin-4-ylmethyl)-1H-benzo[d]imidazole (10i): Following a above mentioned procedure (reaction stirred for 4 h, 700 mg, 51% yield), Brick red residue. **HPLC** purity 90%, Retention time (R_t) = 3.324 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 244.1 (M+) and 246.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{13}H_{11}ClN_3$ *m/z* = 244.06 $(M + H)^+$].

<u>Step 5: General procedure for cyclization (11a, 11b, 11f & 11g)</u>

Synthesis of 1-benzyl-5-bromo-1H-benzo[d]imidazole (11b):[1a] Heated a mix of *N*1-benzyl-4-bromobenzene-1,2-diamine (**8b**) (6.5 g, 23.45 mmol), formic acid (9.0 g, 196 mmol) and trimethoxymethane (12.0 g, 113 mmol) to 100 ºC for 1 h. After completion of the reaction, it was cooled to room temperature and all the volatiles were evaporated under reduced pressure. Diluted with a saturated solution of $NaHCO_3$ (100 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layer was washed with brine solution (30 mL) and dried over $MgSO_4$ and purified through SiO_2 gel flash chromatography using Hexane/EtOAc (60/40 to 40/60 to 20/80 to 0/100) to afford a 1-benzyl-5-bromo-1H-benzo[d]imidazole (4.66 g, 69% yield) as a beige solid. **1H NMR** (300 MHz, CD_3OD) δ (ppm) 8.28 (s, 1H), 8.02 (d, *J*= 1.8 Hz, 1H), 7.46 – 7.31 (m, 4H), 7.26 –7.16 (m, 3H), 5.42 (s, 2H).

Synthesis of 5-chloro-1-phenyl-1H-benzo[d]imidazole (11f):[7] To a mixture of 4-chloro-*N*1-phenylbenzene-1,2-diamine (**8f**) (500 mg, 2.286 mmol) and triethoxymethane (0.951 ml, 5.72 mmol) in THF (16 mL) was added 4-methylbenzenesulfonic acid (39.4 mg, 0.229 mmol) at room temperature and refluxed for 2 h. The reaction mixture was cooled to room temperature and evaporated the THF under reduced pressure. EtOAc (50 mL) was added to it and washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL) and dried over $MgSO_4$ and purified through SiO_2 gel chromatography using Hexane/EtOAc (0-40% gradient) to afford 5-chloro-1-phenyl-1H-benzo[d]imidazole (460 mg, 88% yield) as a light yellow solid. **1H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.22 (s, 1H), 7.90 (dd, J = 2.0, 0.6 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.56 – 7.49 (m, 3H), 7.47 (dd, J = 8.7, 0.6 Hz, 1H), 7.34 (dd, J = 8.7, 1.9 Hz, 1H). **HPLC** purity 99%, Retention time (R_t) = 1.486 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 229.1 (M^+) and 231.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{13}H_{10}ClN_2$ *m/z* = 229.05 $(M + H)^+$].

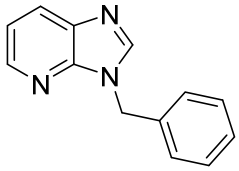
Synthesis of 5-chloro-1-phenethyl-1H-benzo[d]imidazole (11g): To 4-chloro-*N*1-phenethylbenzene-1,2-diamine (**8g**) (600 mg, 2.432 mmol) in a 35 mL microwave vial was added trimethoxymethane (258 mg, 2.432 mmol) and formic acid (112 mg, 2.432 mmol) and the reaction mixture was heated to 90 ºC. After 2 hrs, TLC indicated that the reaction was completed and LCMS indicated a mass ion peak m/z 257 $(M+H)^+$. Added H_20 (50 mL) and EtOAc (50 mL), separated the organic phase, extracted the aqueous phase with EtOAc (2 x 20 mL). Combined the organic phases and dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a crude yellow oily residue. Purified by column chromatography on SiO_2 gel and elution using Hexane/EtOAc (0-70% gradient) to afford 5-Chloro-1-phenethyl-1H-benzo[d]imidazole (550 mg, 85% yield) as a light-yellow oil. **HPLC** purity 97%, Retention time (R_t) = 4.656 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 257.1 (M^+) and 259.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{15}H_{14}ClN_2$ *m/z* = 257.08 $(M + H)^+$].

<u>One pot synthesis of 11a, 55a and 55b (reduction of nitro to amine followed by cyclization)</u>

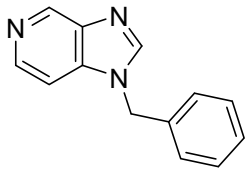
1-Benzyl-5-chloro-1H-benzo[d]imidazole (11a): A mixture of *N*-benzyl-4-chloro-2-nitroaniline (**7a**) (930 mg, 3.54 mmol) in 60 mL THF and 90 mg Pt/C in 4 mL MeOH were hydrogenated under hydrogen atmosphere (H_2 balloon) for 18 h at 25 ºC (in the case of **55a** and **55b**: 3 h). The catalyst was filtered off and the solvent evaporated to yield an oil. Then, formic acid (3.0 g, 65.2 mmol) and trimethoxymethane (4 g, 37.7 mmol) were added and the mixture was heated to 100 ºC for 1 h. After

evaporation of all volatiles, 80 mL $NaHCO_3$ solution were added and the mixture was extracted with EtOAc (2 x 80 mL) dried over Na_2SO_4 and evaporated. Flash SiO_2 gel chromatography using Hexane/EtOAc (60/40 to 40/60) yielded 1-Benzyl-5-chloro-1H-benzo[d]imidazole (680 mg, 79%) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.01 (s, 1H), 7.84 – 7.82 (m, 1H), 7.39 – 7.17 (m, 7H), 5.36 (s, 2H).

3-Benzyl-3H-imidazo[4,5-b]pyridine (55a):[8] Following the above mentioned procedure and flash chromatography [Hexane/EtOAc (50/50 to 80/20)]. (1.95 g, 82% yield), Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.45 (dd, J = 6.0, 3.0 Hz, 1H), 8.10 (dd, J = 9.0, 3.0 Hz, 1H) 8.06 (s, 1H) 7.40 – 7.24 (m, 6H) 5.50 (s, 2H).

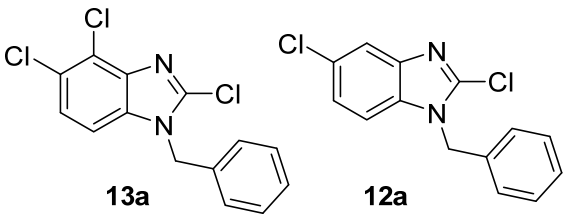


1-Benzyl-1H-imidazo[4,5-c]pyridine (55b):[8] Following the above mentioned procedure and Flash chromatography [EtOAc/THF/MeOH (75/20/0 to 50/50/0 to 48/48/4)]. (270 mg, 30% yield), Brownish oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.16 (s, 1H), 8.44 (d, J = 5.7 Hz, 1H), 8.07 (s, 1H), 7.40 – 7.36 (m, 3H), 7.31 (d, J = 5.7 Hz, 1H), 7.23 – 7.18 (m, 2H), 5.41 (s, 2H).



<u>Step 6: General procedure for the chlorination/bromination (12, 13, 56a-b)</u>

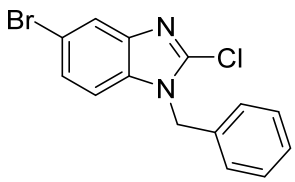
1-benzyl-2,4,5-trichloro-1H-benzo[d]imidazole & 1-Benzyl-2,5-dichloro-1H-benzo[d]imidazole (12a): A mixture of diisopropylamine (1.0 g, 9.88 mmol, 1.2 equiv) in dry tetrahydrofuran (25 mL) under nitrogen atmosphere was cooled to -78 °C (dry ice and MeOH) followed by the addition of 4.0 mL *n*-BuLi (1.2 equiv, 2.5 molar in Hexane, **(based on the concentration given by the vendor. If more than one equivalent was used some bis-chlorination was observed)** and stirred for 1 h at this temperature. Next, the solution of 1-benzyl-5-chloro-1H-benzo[d]imidazole **(11a)** (2.0 g, 8.24 mmol, 1 equiv) in 20 mL THF was added within 3 minutes and stirred for an additional 1 h at -78 °C. Perchloroethane (C_2Cl_6) (3.0 g, 12.67 mmol, 1.5 equiv) in 10 mL THF was added slowly to it at -78 °C and the stirring was continued for an additional 2-3 h at the same temperature and then warmed up to rt. LCMS and TLC of the reaction indicated the complete consumption of the starting material to the product. LCMS disclosed the formation of two isomers, major isomer 2,5-dichloro-1-benzyl-1H-benzo[d]imidazole (mono-Cl) along with a minor isomer 2,4,5-trichloro-1-benzyl-1H-benzo[d]imidazol (bis-Cl). Added a saturated solution of $NaHCO_3$ (80 mL) to the reaction mixture and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude was purified by ISCO Teledyne flash chromatography using Hexane/EtOAc (85/15 to 70/30) to yield pure 1-benzyl-2,5-dichloro-1H-benzo[d]imidazole (mono-Cl **12a**) (1.85 g, 81%) as an off-white solid.



We also collected the fractions which contain mixture of two isomers [mono-Cl (**12a**) & bis-Cl (**13a**)**]** (350 mg) and used in the next step without further purifications. **^{1}H NMR** for **12a** (300 MHz, $CDCl_3$) δ (ppm) 7.73 (d, J = 3.0 Hz, 1H), 7.40 – 7.13 (m, 7H), 5.40 (s, 2H).

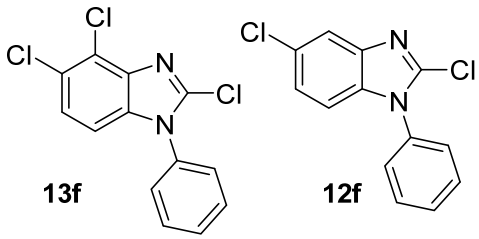
Note: We could not isolate the clean bis-Cl product (**13a**) as the separation was difficult.

1-Benzyl-5-bromo-2-chloro-1H-benzo[d]imidazole (12b): TLC system R*f* = 0.35 [Hexane/EtOAc (9/1)].



Crude yield (2.2 g, 96% yield), Brown solid. **1H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.87 (dd, J = 1.8, 0.5 Hz, 1H), 7.40 – 7.31 (m, 4H), 7.20 – 7.14 (m, 2H), 7.10 (dd, J = 8.6, 0.5 Hz, 1H), 5.38 (s, 2H). **HPLC** purity 98%, Retention time (R_t) = 5.040 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 321.0 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{14}H_{11}BrClN_2$ *m/z* = 321.0 $(M + H)^+$]. Crude product was used in the next step without further purifications.

2,4,5-trichloro-1-phenyl-1H-benzo[d]imidazole (bis-Cl:13f) & 2,5-Dichloro-1-phenyl-1H-benzo[d]imidazole (mono-Cl:12f):

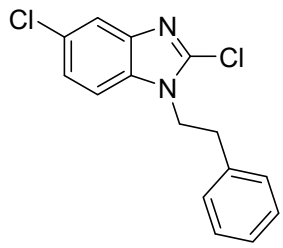


13f **12f**

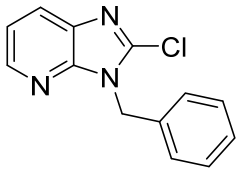
(bis-Cl:13f): Crude reaction HPLC purity 31%, Retention time (R_t) = 5.153 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 296.9 $(M + H)^+$ and on a positive mode M 280 nm [calcd for $C_{13}H_8Cl_3N_2$ *m/z* = 296.97 $(M + H)^+$]. **(mono-Cl:12f): Crude reaction HPLC** purity 66%, Retention time (R_t) = 5.053 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 263.0 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{13}H_9Cl_2N_2$ *m/z* = 263.0 $(M+H)^+$].

2,5-Dichloro-1-phenyl-1H-benzo[d]imidazole (mono-Cl:12f): Flash chromatography using Hexane/EtOAc (0-5% gradient). (150 mg, 33% yield), Off white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (dd, J = 2.0, 0.5 Hz, 1H), 7.68 – 7.56 (m, 3H), 7.47 – 7.42 (m, 2H), 7.27 (dd, J = 8.7, 2.0 Hz, 1H), 7.10 (dd, J = 8.7, 0.5 Hz, 1H).

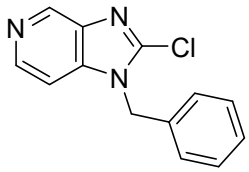
2,5-Dichloro-1-phenethyl-1H-benzo[d]imidazole (12g): Flash chromatography using Hexane/EtOAc (85/15 to 65/35). (280 mg, 56% yield), Off white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.69 (d, J = 3.0 Hz, 1H), 7.30 – 7.25 (m, 3H), 7.22 (dd, J = 9.0, 3.0 Hz, 1H), 7.09 – 7.04 (m, 3H), 4.41 (t, J = 6.0 Hz, 2H), 3.11 (t, J = 6.0 Hz, 2H).



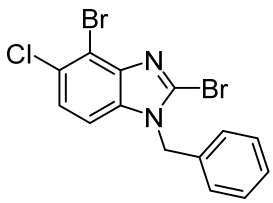
3-Benzyl-2-chloro-3H-imidazo[4,5-b]pyridine (56a):[9] Flash chromatography using Hexane/EtOAc (80/20 to 50/50). (1.59 g, 91% yield), Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.43 (dd, J =6.0, 3.0 Hz, 1H), 8.01 (dd, J = 9.0, 3.0 Hz, 1H,), 7.40 – 7.25 (m, 6H), 5.55 (s, 2H).



1-Benzyl-2-chloro-1H-imidazo[4,5-c]pyridine (56b): Flash chromatography using DCM/MeOH (95/5 to 93/7). (140 mg, 37% yield), Orange oil, which crystallized after a while. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.04 (s, 1H), 8.43 (d, J = 6.0 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.23 – 7.18 (m, 3H), 5.42 (s, 2H).



Synthesis of 1-benzyl-2,4-dibromo-5-chloro-1H-benzo[d]imidazole (Bis-bromination) (13k): A mixture of diisopropylamine (1.011 mL, 7.21 mmol, 3.5 equiv) in dry THF (10 ml) under a nitrogen atmosphere was cooled to -78 ºC and added *n*-butyl lithium (3.0 mL, 7.62 mmol, 3.7 equiv) dropwise and continued the stirring for 1 h. Then added 1-benzyl-5-chloro-1H-benzo[d]imidazole (**11a**) (500 mg, 2.060 mmol, 1 equiv) in 5 mL of THF and stirred for additional 1 h at -78 ºC. The solution of tetrabromomethane (2050 mg, 6.18 mmol, 3 equiv) in 5 mL of THF was added at -78 ºC and the stirring was continued for an additional 2 h at the same temperature. TLC and LCMS analysis of the reaction indicated the complete consumption of starting material. LCMS showed only bis-brominated product. The reaction mixture was warmed up to room temperature and added a saturated solution of $NaHCO_3$ (50 mL) to the reaction mixture and extracted with EtOAc (2x50 mL). The combined organic layer was dried over Na_2SO_4 and solvent was evaporated under reduced pressure which directly afforded pure 1-benzyl-2,4-dibromo-5-chloro-1H-benzo[d]imidazole (350 mg, 41% yield) as a brown solid. This compound was used in the next step without further purifications. **1H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.37 – 7.32 (m, 3H), 7.30 (d, J = 7.6 Hz, 1H), 7.18 – 7.13 (m, 2H), 7.1 (d, J = 8.6 Hz, 1H), 5.41 (s, 2H); **HPLC** purity 96%, Retention time (R_t) = 4.249 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 398.8 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{14}H_{10}Br_2ClN_2$ *m/z* = 398.89 $(M + H)^+$].

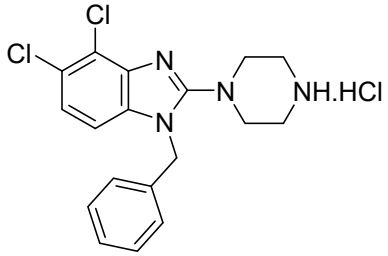


<u>Synthesis of 3, 14c, 14h-i, 15, 16f, 17-27, 29-40, 42a & 42k, (from Scheme S1); following a general procedure 1 (GP1); Step 7:</u>

1-benzyl-4,5-dichloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (42a) and 1-benzyl-5-chloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (3):

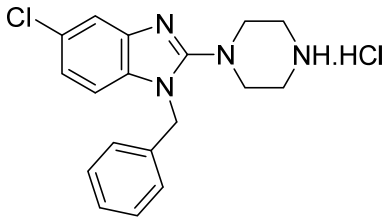
A (~2:1) mixture of (1.5 g, ~5.2 mmol), 1-benzyl-2,5-dichloro-1H-benzo[d]imidazole) (**12a**) (1.0 g, 3.61 mmol) and 1-benzyl-2,4,5-trichloro-1H-benzo[d]imidazole (**13a**) (0.5 g, 1.6 mmol), piperazine (3.0 g, 34.8 mmol) and triethylamine (2.0 g, 19.76 mmol) in 4 mL tBuOH was heated to 120 ºC in a pressure tube for 6 h. To the cooled solution was added 100 mL $NaHCO_3$ solution. The mixture was extracted with EtOAc (2 x 80 mL) dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography using DCM/MeOH/NEt_3 (94/4/2 to 88/8/4) yielded the corresponding free amines **42a** (515 mg) & **3** (705 mg) as an oil and 250 mg mixed material. These oily products were dissolved in EtOH and 2 M HCl in diethyl ether was added. The solvent was evaporated, and the material was crystallized from EtOAc/MeOH yielding the corresponding HCl salts **42a** (280 mg, 44%) and **3** (350 mg, 27%) as white solids.

1-benzyl-4,5-dichloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (42a):



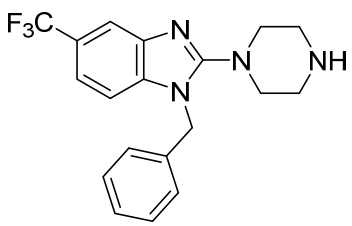
(280 mg, 44% yield), White solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.43 – 7.33 (m, 4H), 7.24 – 7.18 (m, 3H), 5.46 (s, 2H), 3.65 – 3.62 (m, 4H), 3.45 – 3.40 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 4.139 min; Method Used (General positive); LCMS (APCI) *m/z* = found *m/z* 361.1 (M+) and 363.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd $C_{18}H_{20}Cl_3N_4$ *m/z* =397.07 $(M + H)^+$].

1-benzyl-5-chloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (3):



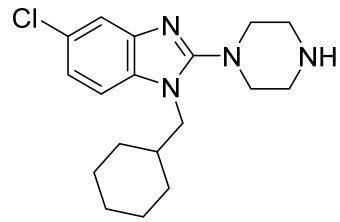
(350 mg, 27% yield), White solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.68 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.49 – 7.37 (m, 5H), 7.36 – 7.29 (m, 2H), 5.59 (s, 2H), 3.88 – 3.84 (m, 4H), 3.48 – 3.44 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 3.945 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 327.1 (M+) and 329.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{18}H_{21}Cl_2N_4$ *m/z* = 363.1 $(M + H)^+$].

1-Benzyl-2-(piperazin-1-yl)-5-(trifluoromethyl)-1H-benzo[d]imidazole (14c):



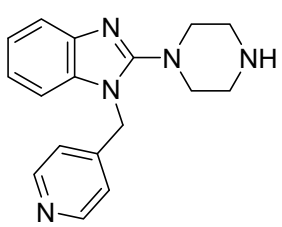
Flash column chromatography using DCM/MeOH (2% Et_3N) (0-30% gradient). (120 mg, 51% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.83 – 7.80 (m, 1H), 7.45 –7.42 (m, 1H), 7.40 – 7.29 (m, 4H), 7.20 – 7.16 (m, 2H), 5.44 (s, 2H), 3.43 – 3.39 (m, 4H), 3.18 – 3.15 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 0.456 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 361.1 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{19}H_{20}F_3N_4$ *m/z* = 361.16 $(M + H)^+$].

5-chloro-1-(cyclohexylmethyl)-2-(piperazin-1-yl)-1H-benzo[d]imidazole (14h):

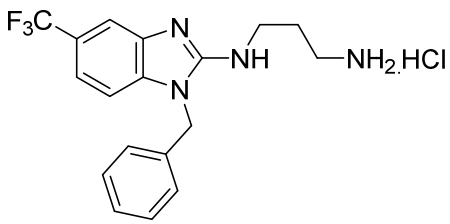


Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-10% gradient). (50 mg, 41% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.75 (dd, J = 8.8, 0.6 Hz, 1H), 7.66 (dd, J = 1.9, 0.5 Hz, 1H), 7.51 (dd, J = 8.8, 1.9 Hz, 1H), 4.20 (d, J = 7.5 Hz, 2H), 3.95 – 3.91 (m, 4H), 3.57 – 3.54 (m, 4H), 2.05-1.96 (m, 1H), 1.77 – 1.70 (m, 3H), 1.62-1.54 (m, 2H), 1.26 – 1.11 (m, 5H); **HPLC** purity 97%, Retention time (R_t) = 4.106 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 333.2 (M+) & 335.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{18}H_{26}ClN_4$ *m/z* = 333.18 $(M + H)^+$].

2-(piperazin-1-yl)-1-(pyridin-4-ylmethyl)-1H-benzo[d]imidazole (14i): Flash column chromatography using EtOAc/MeOH/Et_3N (92/6/2) afforded a clear pale-yellow oil. Added Et_2O (6 mL) and stirred at 25ºC for 1 h, the precipitate was filtered and dried to afford 2-(piperazin-1-yl)-1-(pyridin-4-ylmethyl)-1H-benzo[d]imidazole (260 mg, 71% yield) as a yellow solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.51 – 8.49 (m, 2H), 7.56 – 7.54 (m, 1H), 7.25 – 7.19 (m, 3H), 7.16 – 7.14 (m, 2H), 5.43 (s, 2H), 3.24 – 3.21 (m, 4H), 2.97 – 2.94 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 1.878 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 294.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{17}H_{20}N_5$ *m/z* = 294.17 $(M + H)^+$].

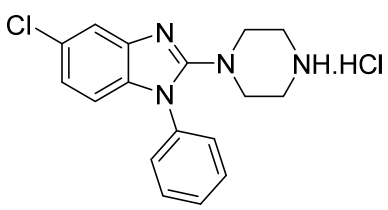


***N*1-(1-Benzyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)propane-1,3-diamine hydrochloride (15):**



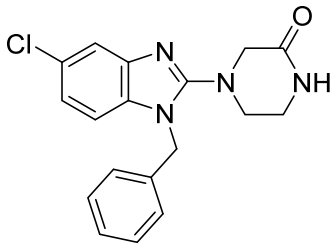
Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-25% gradient) yielded a pale yellow oil. The material was dissolved in MeOH (10 mL) and added 2.0 M solution HCl/Ether (4 mL) and concentrated *in vacuo* to dryness. Added Et_2O (6 mL) and stirred at room temperature of 25ºC for 1h, the precipitate was filtered and dried to afford *N*1-(1-benzyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)propane-1,3-diamine hydrochloride (140 mg, 55% yield) as an off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.82 (d, J = 1.5 Hz, 1H), 7.63 (dd, J = 8.6, 1.5 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.45–7.28 (m, 5H), 5.56 (s, 2H), 3.73 (t, J = 6.9 Hz, 2H), 3.13–3.06 (m, 2H), 2.17 (quin, J = 6.9 Hz, 2H); **HPLC** purity 99%, Retention time (R_t) = 0.367 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 349.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{18}H_{21}ClF_3N_4$ *m/z* = 385.14 $(M + H)^+$].

5-Chloro-1-phenyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (16f):



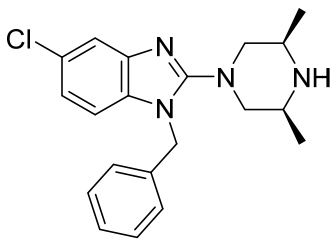
Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-15% gradient) yielded a yellow gummy residue. The material was dissolved in MeOH (1 mL) and added of 2 M HCl in diethyl ether (2 mL) and concentrated *in vacuo* to dryness. Added Et_2O (6 mL) and stirred at room temperature of 25 ºC for 1h, the precipitate was filtered and dried to afford 5-chloro-1-phenyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (55 mg, 27% yield) as an off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.80 – 7.73 (m, 5H), 7.66 (dd, J = 1.9, 0.5 Hz, 1H), 7.40 (dd, J = 8.7, 2.0 Hz, 1H), 7.18 (dd, J = 8.7, 0.5 Hz, 1H), 3.73 – 3.70 (m, 4H), 3.37 – 3.34 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 0.409 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 313.1 (M^+) & 315.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{17}H_{19}Cl_2N_4$ *m/z* = 349.1 $(M + H)^+$].

4-(1-Benzyl-5-chloro-1H benzo[d]imidazol-2-yl)piperazin-2-one (17):



Flash chromatography using EtOAc/THF/MeOH (89/10/1 to 88/10/2) followed by crystallization from EtOAc/DCM yielded the product **17**. (327 mg, 81% yield), White solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.65 (d, J = 1.9 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.15 – 7.09 (m, 3H), 6.98 (d, J = 8.5 Hz, 1H), 6.22 (brs, 1H), 5.26 (s, 2H), 3.99 (s, 2H), 3.50 (s, 4H); **HPLC** purity 98%, Retention time (R_t) = 4.476 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 341.1 (M^+) and 343.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{18}H_{18}ClN_4O$ *m/z* = 341.12 $(M + H)^+$].

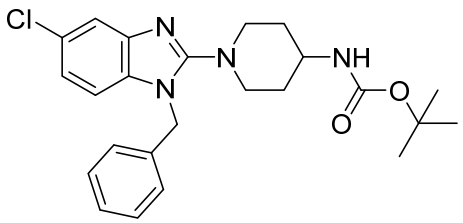
1-Benzyl-5-chloro-2-[(3S,5R)-3,5-dimethylpiperazin-1-yl]-1H-benzo[d]imidazole (27):



Flash column chromatography (EtOAc/MeOH/Et_3N) (94/4/2 to 925/3) followed by crystallization from EtOAc/iPropylether yielded 152 mg (58% yield), White solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.61 (d, J = 1.9 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.18 – 7.15 (m, 2H), 7.07 (dd, J = 8.5, 1.9 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 5.20 (s, 2H), 3.42 – 3.37 (m, 2H), 3.16 – 3.10 (m, 2H), 2.74-2.67 (m, 2H), 1.08 (d, J = 6.4 Hz, 6H); **HPLC** purity 97%, Retention time (R_t) = 4.123 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 355.2 (M^+) and 357.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{24}ClN_4$ *m/z* = 355.17 $(M + H)^+$].

<u>Synthesis of 1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperidin-4-amine hydrochloride (28):</u>

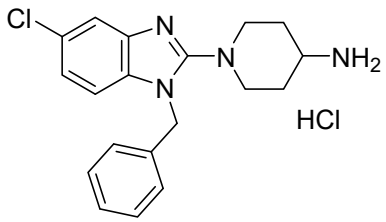
tert-butyl (1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperidin-4-yl)carbamate (61):



Flash chromatography using Hexane/EtOAc (80/20 to 70/30 to 60/40 to 50/50), (440 mg, 89% yield), Colorless foam. This crude was used in the next step without characterization.

Boc deprotection;

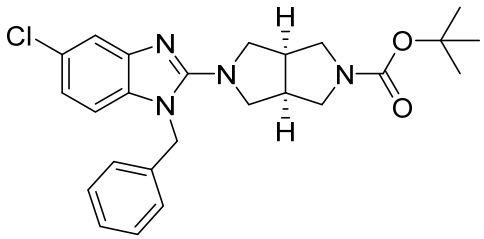
The *tert*-butyl (1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperidin-4-yl) carbamate (440 mg, 0.998 mmol) was dissolved in 6 mL Dioxane/HCl at RT. The solvent was evaporated after 24 h, and the residue crystallized from EtOAc/EtOH, which resulted in 400 mg white solid. **1H NMR** (300 MHz, CD_3OD) δ (ppm) 7.63 (d, J = 3.0 Hz, 1H), 7.49 – 7.30 (m, 7H), 5.53 (s, 2H), 3.99 – 3.93 (m, 2H), 3.53 – 3.43 (m, 3H), 2.20 – 2.14 (m, 2H), 1.95 – 1.82 (m, 2H); **HPLC** purity 99%, Retention time (R_t) = 4.050 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 341.2 (M^+) and 343.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{19}H_{23}Cl_2N_4$ *m/z* = 377.1300 $(M + H)^+$].



Note: EtOH solvent impurity was observed in NMR.

<u>Synthesis of 1-Benzyl-5-chloro-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1H-benzo[d]imidazole hydrochloride (29):</u>

tert-butyl (3aR,6aS)-5-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (62):



Flash column chromatography using Hexane/EtOAc (50/50 to 25/75 to 0/100), (160 mg, 75% yield), White solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (d, J = 3.0 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.19 (dd, J = 9.0, 3.0 Hz,1 H), 7.10 –7.08 (m, 2H), 6.99 (d, J = 9.0 Hz, 1H), 5.46 – 5.43 (m, 2H), 4.50 – 4.18 (m, 2H), 3.64 – 3.58 (m, 4H), 3.25 –3.20 (m, 4H), 1.47 (s, 9H). **Note:** NMR indicated rotamers.

Boc deprotection;

The tert-butyl (3aR,6aS)-5-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (160 mg, 0.353 mmol) was dissolved in 5 mL 1,4-dioxane/HCl at RT. The solvent was evaporated after 1 h, and the residue crystallized from EtOAc/MeOH, which resulted in 126 mg (91%) white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.56 – 7.54 (m, 1H), 7.47 – 7.27 (m, 7H), 5.71 (s, 2H), 4.08 – 4.02 (m, 2H), 3.98 – 3.93 (m, 2H), 3.63 – 3.57 (m, 2H), 3.40 – 3.25 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 3.856 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 353.2 (M^+) and 355.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{23}Cl_2N_4$ *m/z* = 389.13 $(M + H)^+$].

***N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)butane-1,4-diamine (30):**

Flash column chromatography (DCM/MeOH (0.5M NH_3 solution) (0-20% gradient). (83 mg, 68% yield), Yellow solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.35 – 7.27 (m, 4H), 7.16 – 7.12 (m, 2H), 6.99 (dd, *J* = 8.4, 0.5 Hz, 1H), 6.92 (dd, *J* = 8.4, 1.9 Hz, 1H), 5.25 (s, 2H), 3.47 (t, *J* = 7.0 Hz, 2H), 2.67 (t, *J* = 6.0 Hz, 2H), 1.72–1.65 (m, 2H), 1.57–1.49 (m, 2H); **HPLC** purity 98%, Retention time (R_t) = 2.689 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 329.1 (M^+) and 331.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{18}H_{22}ClN_4$ *m/z* = 329.15 $(M + H)^+$].

1-Amino-3-((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)propan-2-ol acetate (31):

The residue was purified through reverse preparative HPLC method. The column used was X Bridge prep C18 [5µm OBD, 19x250 mm column], Injection volume 500 µl, flow rate 15 mL/minute and column oven is set at 35 °C using gradient solvent A 10mM ammonium acetate (0.4% acetic acid) water and solvent B 10mM ammonium acetate (0.4% acetic acid) MeOH. Gradient: 30-100% B in 15 min (hold 4.5 min), 100-30% B in 0.5 min (hold 5 min) to afford an off white salt 1-amino-3-((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)propan-2-ol acetate (13 mg, 9% yield) as an off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.38 – 7.27 (m, 4H), 7.18 – 7.15 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 8.4, 1.9 Hz, 1H), 5.28 (s, 2H), 4.07-3.99 (m, 1H), 3.61 – 3.47 (m, 2H), 3.00 (dd, *J* = 12.9, 3.8 Hz, 1H), 2.83 (dd, *J* = 12.9, 7.6 Hz, 1H), 1.92 (s, 3H); **HPLC** purity 98%, Retention time (R_t) = 0.874 min; Method Used

(Gen in eral positive); LC-MS (APCI) *m/z* = found 331.1 (M^+) and 333.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{19}H_{24}ClN_4O_3$ *m/z* = 391.15 $(M + H)^+$].

Synthesis of *N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)propane-1,3-diamine hydrochloride (32):

tert-butyl (3-((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)propyl)carbamate (63): Flash chromatography using AcOEt/ Hexane (50/50 to 70/30 to 80/20), (0.216 g, 90% yield), Colourless foam. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 3.0 Hz, 1H), 7.38 – 7.20 (m, 5H), 7.15 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 1H), 5.37 – 5.24 (m, 2H), 3.80 – 3.74 (m, 2H), 3.21 – 3.14 (m, 2H), 1.92 – 1.84 (m, 2H), 1.45 (s, 9H). **Note:** NMR indicated rotamers

Boc deprotection;

The tert-butyl (3-((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)propyl)carbamate (0.216 g, 0.521 mmol) was dissolved in 1,4-dioxane/hydrogen chloride (4 mL, 4.00 mmol) at RT. Solvent evaporation after 18 h and crystallization from MeOH/EtOAc, yielded *N*1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)propane-1,3-diamine, Hydrochloride (120 mg, 65% yield) as a white solid. **^{1}H NMR** (300 MHz, CD_3OD) *δ* (ppm) 7.54 (d, *J* = 3.0 Hz, 1H), 7.48 – 7.26 (m, 7H); 5.49 (s, 2H), 3.68 (t, *J* = 9.0 Hz, 2H), 3.08 (t, *J* = 9.0 Hz, 2H), 2.12 (quin, *J* = 9.0 Hz, 2H); **HPLC** purity 99%, Retention time (R_t) = 3.649 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 315.2 (M^+) and 317.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{17}H_{21}Cl_2N_4$ *m/z* = 351.11 $(M + H)^+$].

***N*1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)ethane-1,2-diamine (33):**

Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-40% gradient). (140 mg, 83% yield), Off white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* (ppm) 7.43 (dd, *J* = 1.9, 0.5 Hz, 1H), 7.33 – 7.26 (m, 3H), 7.15 – 7.12 (m, 2H), 6.97 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.09 (s, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 3.00 (t, *J* = 5.7 Hz, 2H), 2.58 (brs, 3H); **HPLC** purity 97%, Retention time (R_t) = 0.335 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 301.2 (M+) and 303.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{16}H_{18}ClN_4$ *m/z* = 301.12 $(M + H)^+$].

Synthesis of *N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-*N*1-methylethane-1,2-diamine hydrochloride (34):

tert-butyl (2-((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)propyl)carbamate: Flash column chromatography **(64):** Reaction stirred for 7 days**.** Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-5% gradient), (105 mg 67% yield), Pale yellow gummy solid. **HPLC** purity 96%, Retention time (R_t) = 1.460 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 415.2 (M^+) and 417.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{22}H_{28}ClN_4O_2$ *m/z* = 415.2 $(M + H)^+$].

Boc deprotection;

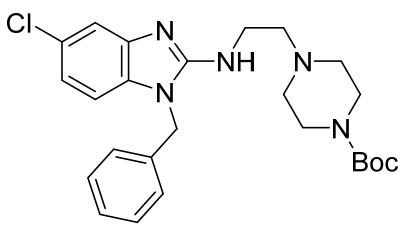
The tert-butyl (2-((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)(methyl)amino)ethyl)carbamate (105 mg, 0.253 mmol) was dissolved in 4 N HCl in 1,4-dioxane (1 ml) for 2 h at RT. LCMS shows complete consumption of the starting material. The solvent was then removed under reduced pressure and diethyl ether was added. The precipitate was filtered off to get pure *N*1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-*N*1-methylethane-1,2-diamine hydrochloride (**34**) (56 mg, 62% yield) as a pale brown solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.62 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.48 – 7.29 (m, 7H), 5.62 (s, 2H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.37 (t, *J* = 6.5 Hz, 2H), 3.28 (s, 3H); **HPLC** purity 98%, Retention time (R_t) = 1.136 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 315.2 (M^+) and 317.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{17}H_{21}Cl_2N_4$ *m/z* = 351.1 $(M + H)^+$].

***N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-*N*2,*N*2-dimethylethane-1,2-diamine hydrochloride (35):**

Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-25% gradient). The oily free amine was dissolve in MeOH (1 mL) and added 2 M HCl in diethyl ether, which immediately precipitated to afford pure *N*1-(1-benzyl-5-chloro-1H benzo[d] imidazol-2-yl)-*N*2,*N*2-dimethylethane-1,2-diamine hydrochloride (77 mg, 58% yield) as a light yellow solid. **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm) 9.79 (brs, 1H) 7.51 (d, *J* = 1.9 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.37 – 7.32 (m, 5H), 7.29 (dd, *J* = 8.6, 2.0 Hz, 1H), 5.61 (s, 2H), 4.02 – 3.96 (m, 2H), 3.49 – 3.40 (m, 2H), 2.86 (s, 6H); **HPLC** purity 99%, Retention time (R_t) = 0.385 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 329.2 (M^+) and 331.2 $(M + 2)^+$ on a positive mode M 280

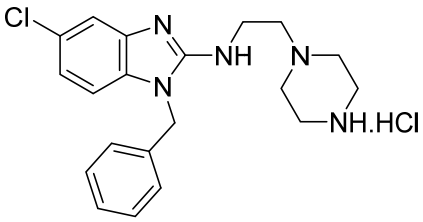
nm [calcd for $C_{18}H_{23}Cl_2N_4$ *m/z* = 365.13 $(M + H)^+$].

Synthesis of 1-Benzyl-5-chloro-*N*-(2-(piperazin-1-yl)ethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (36):

Synthesis of tert-butyl 4-(2-((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)ethyl)piperazine-1-carboxylate (65): 

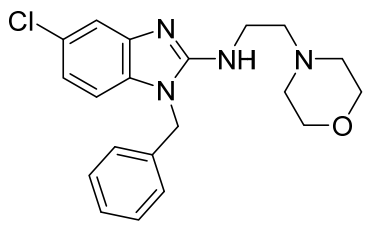
Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-10% gradient). (150 mg, 57% yield), Off white solid. **HPLC** purity 97%, Retention time (R_t) = 4.155 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 470.1 (M^+) and 472.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{25}H_{33}ClN_5O_2$ *m/z* = 470.2 $(M + H)^+$].

Boc deprotection;

The tert-butyl 4-(2-((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)ethyl)piperazine-1-carboxylate 

(150 mg, 0.319 mmol) was dissolved in 4N HCl in Dioxane (5.0 mL) at a temperature of 30 °C. After 16 h, TLC indicated the reaction is completed. Concentration of the reaction mixture *in vacuo* to afforded a brick red residue. Add DCM (10 mL) and concentrate *in vacuo* to dryness. Add Et_2O (5.0 mL) and stir at room temperature of 25°C for 1h, during this time a precipitate is formed. The solid was filtered off, washed with Et_2O (5.0 mL) and dried to afford 1-benzyl-5-chloro-*N*-(2-(piperazin-1-yl)ethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (41 mg, 0.100 mmol, 31% yield) as a brown solid. **^{1}H NMR** (300 MHz, CD_3OD) δ 7.55 (d, *J* = 2.4 Hz, 1H), 7.46 – 7.28 (m, 7H), 5.53 (s, 2H), 3.86 (t, *J* = 5.9 Hz, 2H), 3.46 – 3.39 (m, 4H), 3.28 – 3.14 (m, 6H); **HPLC** purity 99%, Retention time (R_t) = 2.592 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 370.1 (M^+) and 372.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{26}Cl_2N_5$ *m/z* = 406.16 $(M + H)^+$].

1-Benzyl-5-chloro-*N*-(2-morpholinoethyl)-1H-benzo[d]imidazol-2-amine (37):



Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-20% gradient). (95 mg, 69%), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) *δ* (ppm) 7.35 – 7.29 (m, 4H), 7.20 –7.14 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.0 Hz, 1H) 5.26 (s, 2H), 3.64 – 3.56 (m, 6H), 2.64 (t, *J* = 6.3 Hz, 2H), 2.49 – 2.46 (m, 4H); **HPLC** purity 99%,

Retention time (R_t) = 3.135 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 371.1 (M^+) and 373.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{24}ClN_4O$ *m/z* = 371.16 $(M + H)^+$].

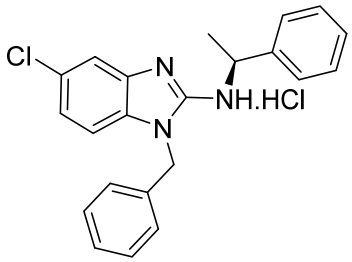
Synthesis of 1-benzyl-5-chloro-*N*-(pyrrolidin-2-ylmethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (38):

tert-butyl 2-(((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)methyl)pyrrolidine-1-carboxylate (66): Reaction stirred for 6 days. Flash column chromatography using DCM/MeOH (0-5% gradient). (135 mg, 76% yield), Pale brown gummy residue. **HPLC** purity 89%, Retention time (R_t) = 1.451 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 441.2 (M^+) and 443.0 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{24}H_{30}ClN_4O_2$ *m/z* = 441.2 $(M + H)^+$].

Boc deprotection;

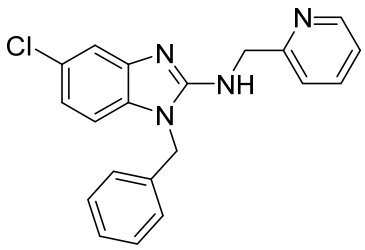
The tert-butyl 2-(((1- benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)methyl)pyrrolidine-1-carboxylate (135 mg, 0.306 mmol) was dissolved in 4 N HCl in 1,4 dioxane (1 mL) for 2 h at RT. The solvent was evaporated under reduced pressure and diethyl ether was added and evaporated. The residue was purified through reverse preparative HPLC method. The column used was X Bridge prep C18 [5□m, 19x250 mm column], Injection volume 500 µl, flow rate 15 mL/minute and column oven is set at 35 °C using solvent A 10 mM ammonium acetate (0.1% formic acid) water and solvent B 10 mM ammonium acetate (0.1% formic acid) ACN. Gradient: 10-100% B in 13 min (hold 8 min),100-10% B in 3 min (hold 1 min) to afford 1-benzyl-5-chloro-*N*-(pyrrolidin-2-ylmethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (17 mg, 14% yield) as an off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.58 – 7.55 (m, 1H), 7.45 – 7.31 (m, 7H), 5.54 (s, 2H), 4.08 – 3.97 (m, 1H), 3.92 (dd, *J* = 6.6, 2.3 Hz, 2H), 3.48 – 3.35 (m, 2H), 2.37 – 2.27 (m, 1H), 2.16 – 2.08 (m, 2H), 1.94 – 1.80 (m, 1H); **HPLC** purity 96%, Retention time (R_t) = 1.096 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 341.1 (M^+) and 343.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{19}H_{23}Cl_2N_4$ *m/z* = 377.13 $(M + H)^+$].

(S)-1-Benzyl-5-chloro-*N*-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (39):



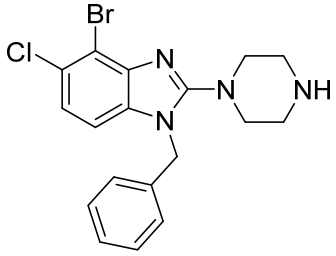
Reaction stirred for 18 days. Flash column chromatography using Hexane/EtOAc (0-50% gradient) yielded yellow gummy residue. The material was dissolved in MeOH (1 mL) and 2 M HCl (2 mL) in diethyl ether, which immediately afforded a ppt, which was filtered off and washed with excess of diethyl ether (5 mL) to yield pure (S)-1-benzyl-5-chloro-*N*-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (28 mg, 20% yield) as a light yellow solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.43 – 7.34 (m, 9H), 7.33 – 7.27 (m, 2H), 7.24 – 7.21 (m, 2H), 5.56 (d, J = 2.8 Hz, 2H), 5.04 (q, J = 6.8 Hz, 1H), 1.73 (d, J = 6.8 Hz, 3H); **HPLC** purity 99%, Retention time (R_t) = 1.376 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 362.2 (M^+) and 364.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{22}H_{22}Cl_2N_3$ *m/z* = 398.12 $(M + H)^+$].

1-Benzyl-5-chloro-*N*-(pyridin-2-ylmethyl)-1H-benzo[d]imidazol-2-amine (40):



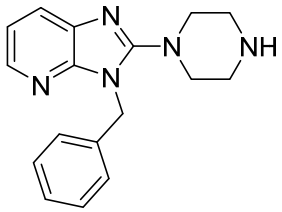
Reaction stirred for 3 days. Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-40% gradient). (67 mg, 53% yield), Light yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.49 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.69 (td, J = 7.7, 1.8 Hz, 1H), 7.54 (dd, J = 1.9, 0.5 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.29 – 7.20 (m, 3H), 7.06 (dd, J = 8.4, 1.9 Hz, 1H), 7.01 (dd, J = 8.4, 0.6 Hz, 1H), 5.25 (s, 2H), 4.86 (s, 2H); **HPLC** purity 99%, Retention time (R_t) = 4.237 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 349.0 (M^+) and 351.0 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{18}ClN_4$ *m/z* = 349.12 $(M + H)^+$].

1-Benzyl-4-bromo-5-chloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole (42k):



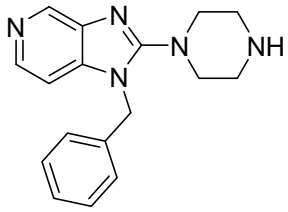
Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-25% gradient). (51 mg, 50% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.39 – 7.29 (m, 3H), 7.24 (d, J = 8.5 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.11 (d, J = 8.5 Hz, 1H), 5.35 (s, 2H), 3.32 – 3.30 (m, 4H), 3.01 – 2.95 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 1.125 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 405.0 (M^+) & 407.0 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{18}H_{19}BrClN4$ *m/z* = 405.05 $(M + H)^+$].

3-Benzyl-2-(piperazin-1-yl)-3H-imidazo[4,5-b]pyridine (57a):



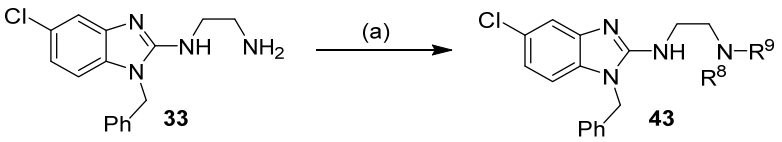
Flash column chromatography using DCM/MeOH/Et_3N (88/10/2) followed by crystallization in iPropylether/hexane. (780 mg, 80% yield), White solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.16 (dd, J = 6.0, 3.0 Hz, 1H), 7.84 (dd, J = 9.0, 3.0 Hz, 1H), 7.37 – 7.19 (m, 6H), 5.44 (s, 2H), 3.30 – 3.27 (m, 4H), 2.91 – 2.88 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 2.488 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 294.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{17}H_{20}N_5$ *m/z* = 294.17 $(M + H)^+$].

1-Benzyl-2-(piperazin-1-yl)-1H-imidazo[4,5-c]pyridine (57b):



Flash column chromatography using DCM/MeOH/Et_3N (93/5/2 to 88/10/2 to 83/15/2) followed by crystallization in EtOAc/MeOH. (40 mg, 25% yield), Brown solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.75 (s, 1H), 8.24 (d, J = 6.0 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.22 – 7.18 (m, 2H), 5.46 (s, 2H), 3.55 – 3.52 (m, 4H), 3.34 – 3.31 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 0.688 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 294.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{17}H_{20}N_5$ *m/z* = 294.17 $(M + H)^+$].

<u>Synthesis of compounds 43a & 43d, (Scheme S2); following a general procedure 2 (GP2):</u>



43a-d

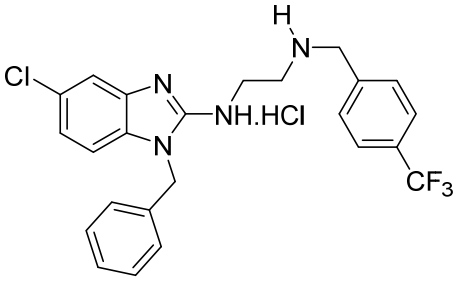
43a; $R^8 = R^9 = -CH_2Ph$

R^8= H: **43b;** $R^9 = -CH_2$-Ph

43c; $R^9 = -CH_2$-4-Py

43d; $R^9 = -CH_2$-Ph-4-CF_3

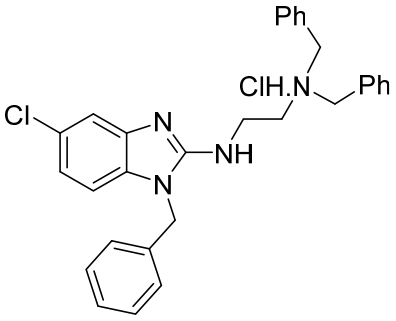
***N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-*N*2-(4-(trifluoromethyl)benzyl)ethane-1,2-diamine hydrochloride (43d):**



Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-5% gradient). (16 mg, 16% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.84 – 7.78 (m, 4H), 7.55 – 7.54 (m, 1H), 7.42 – 7.30 (m, 7H), 5.53 (s, 2H), 4.43 (s, 2H), 3.99 (t, J = 6.0 Hz, 2H), 3.54 (t, J = 6.1 Hz, 2H); **HPLC** purity 98%,

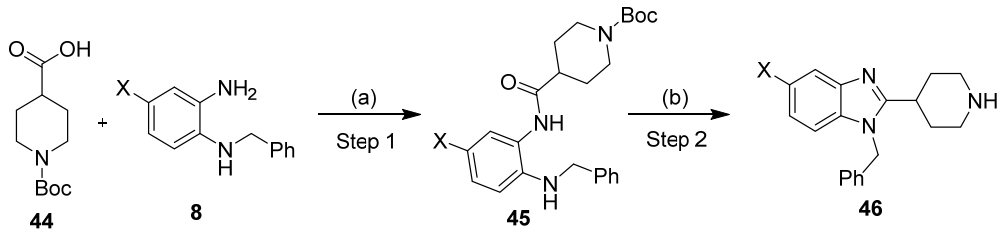
Retention time (R_t) = 1.361 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 459.2 (M^+) and 361.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{24}H_{24}Cl_2F_3N_4$ *m/z* = 495.13 $(M + H)^+$].
Note: Dibenzylated product (minor) (5 mg, 4% yield) was also obtained.

***N*1,*N*1-Dibenzyl-*N*2-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)ethane-1,2-diamine hydrochloride (43a)**:



Sodium triacetoxyborohydride (148 mg, 0.698 mmol) was added to a mixture of *N*1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)ethane-1,2-diamine (70 mg, 0.233 mmol), benzaldehyde (0.059 ml, 0.582 mmol), and acetic acid (0.040 mL, 0.698 mmol) in DCE (7 mL) and stirring was continued for 24 h at room temperature. TLC and LCMS showed complete consumption of starting material and observed both monobenzylated (minor) and dibenzylated (major) products. Then, the reaction was quenched by the addition of NaOH (1N) solution (30 ml) and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over Na_2SO_4 and the residue was purified by flash chromatography using ISCO Teledyne on a 12g RediSep Rf column, using a DCM/MeOH (0.5M NH_3 solution) (0-10%) gradient to afford gummy compounds separately. Then the dibenzylated product was dissolved in MeOH (1 mL) and added 2 M HCl (2 mL) in diethyl ether, which immediately afforded an off white precipitation, which was filtered off and washed with excess of diethyl ether (5 mL) to get a pure *N*1,*N*1-dibenzyl-*N*2-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)ethane-1,2-diamine hydrochloride (46 mg, 37% yield) as a white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.66 (d, *J* = 7.2 Hz, 4H), 7.45 – 7.31 (m, 12H), 7.25 (d, *J* = 7.4 Hz, 2H), 5.43 (s, 2H), 4.51 (s, 4H), 3.84 (t, *J* = 5.8 Hz, 2H), 3.55 (t, *J* = 5.7 Hz, 2H); **HPLC** purity 99%, Retention time (R_t) = 5.329 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 481.1 (M^+) and 483.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{30}H_{31}Cl_2N_4$ *m/z* = 517.19 $(M + H)^+$].
Note: Mono-benzylated (minor) product 3 mg (3% yield) was also obtained.

Synthesis of compounds 46b-46e, (Scheme S3); following a general procedure 3 (GP3);

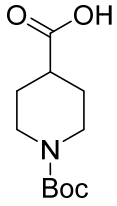


8a, X = Cl
8b, X = Br
8c, X = CF_3
8d. X = CO_2Me
8e, X = SO_2Me

45a, X = Cl
45b, X = Br
45c, X = CF_3
45d. X = CO_2Me
45e, X = SO_2Me

46a, X = Cl
46b, X = Br
46c, X = CF_3
46d. X = CO_2Me
46e, X = SO_2Me

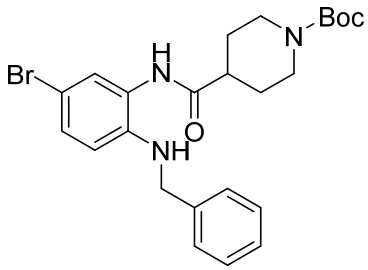
Synthesis of compound 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (44): To a solution of



piperidine-4-carboxylic acid (3.0 g, 23.23 mmol) in a mixture of 1,4-dioxane:water (46:23 mL) (2:1) and 1N NaOH (23 mL), was added Boc-anhydride (5.66 mL, 24.39 mmol) at 0 °C, the reaction mixture was then warmed up to room temperature. After complete disappearance of the starting material (TLC), the solvent was reduced to about 10-15 mL under reduced pressure. The reaction mixture was then acidified to pH 3-4 using 1N HCl. The mixture was then extracted with ethyl acetate (3 x 30 mL), the combined organic layer was then washed with 50 mL of water and 50 mL of brine. The organic layer was then dried over anhydrous sodium sulphate and concentrated under reduced pressure. The white solid was then recrystallised from ethyl acetate/hexane mixture to afford 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (3.2 g, 60% yield) as a white solid. **1H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.07 – 4.01 (m, 2H), 2.89 (t, J = 12.3 Hz, 2H), 2.57 – 2.47 (m, 1H), 1.96 – 1.90 (m, 2H), 1.75 – 1.61 (m, 2H), 1.48 (s, 9H).

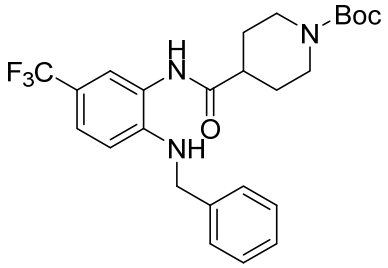
Step 1: Synthesis of compounds 45b-45e:

tert-Butyl 4-((2-(benzylamino)-5-bromophenyl)carbamoyl)piperidine-1-carboxylate (45b): TLC



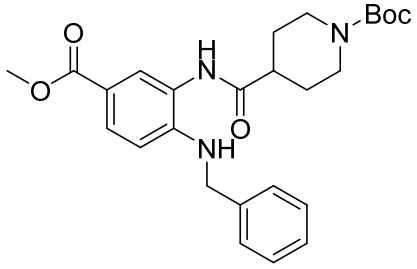
System R_f= 0.25 [Hexane/EtOAc (4/6)]. (680 mg, 94% yield), Brown oil. **HPLC** purity 97%, Retention time (R_t) = 4.761 min; Method Used (General negative); LC-MS (APCI) *m/z* = found 486.1 $(M - H)^-$ on a negative mode M 280 nm [calcd for $C_{24}H_{29}ClN_3O_3$ *m/z* = 486.14 $(M - H)^-$].

tert-Butyl 4-((2-(benzylamino)-5-(trifluoromethyl)phenyl)carbamoyl)piperidine-1-carboxylate (45c):



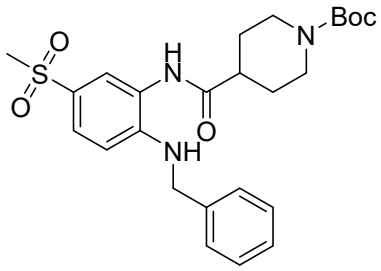
TLC System R_f = 0.25 [Hexane/ EtOAc (4/6)]. (600 mg, 47% yield). Orange oil. **HPLC** purity 71%, Retention time (R_t) = 0.782 min; Method Used (General negative); LC-MS (APCI) *m/z* = found 476.2 $(M - H)^-$ on a negative mode M 280 nm [calcd for $C_{25}H_{29}F_3N_3O_3$ *m/z* = 476.2161 $(M - H)^-$].

tert-Butyl 4-((2-(benzylamino)-5-(methoxycarbonyl)phenyl)carbamoyl)piperidine-1-carboxylate (45d):



TLC System R*f* = 0.35 [Hexane/EtOAc (4/6)]. (640 mg, 45% yield), Dark reddish oil. **HPLC** purity 65%, Retention time (R_t) = 0.718 min; Method Used (General negative); LC-MS (APCI) *m/z* = found 466.2 $(M - H)^-$ on a negative mode M 280 nm [calcd for $C_{26}H_{32}N_3O_5$ *m/z* = 466.2342 $(M - H)^-$].

tert-Butyl 4-((2-(benzylamino)-5-(methylsulfonyl)phenyl)carbamoyl)piperidine-1-carboxylate (45e):

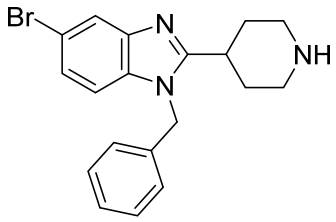


TLC System R*f* = 0.30 [Hexane/EtOAc (4/6)]. (530 mg, 59% yield), Brown oil. **HPLC** purity 78%, Retention time (R_t) = 0.654 min; Method Used (General negative); LC-MS (APCI) *m/z* = found 486.2 $(M - H)^-$ on a negative mode M 280 nm [calcd for $C_{25}H_{32}N_3O_5S$ *m/z* = 486.2063 $(M - H)^-$].

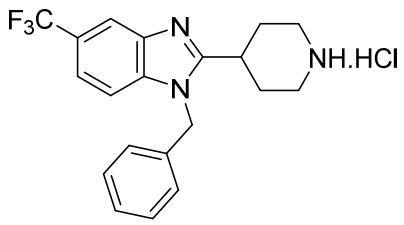
<u>Step 2: Synthesis of compounds 46b-46e:</u>

1-Benzyl-5-bromo-2-(piperidin-4-yl)-1H-benzo[d]imidazole (46b):

Flash column chromatography DCM/MeOH (2% Et_3N) (0-30% gradient). (214 mg, 41% yield), Brown solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.80 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.36 – 7.31 (m, 5H), 7.11 – 7.07 (m, 2H), 5.55 (s, 2H), 3.14 – 3.09 (m, 3H), 2.68 (td, *J* = 12.6, 3.0 Hz, 2H), 1.95 – 1.74 (m, 4H); **HPLC** purity 98%, Retention time (R_t) = 3.653 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 370.1 (M^+) & 372.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{19}H_{21}BrN_3$ *m/z* = 370.09 $(M + H)^+$].



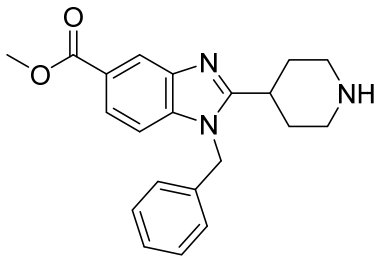
1-Benzyl-2-(piperidin-4-yl)-5-(trifluoromethyl)-1H-benzo[d]imidazole hydrochloride (46c):



Flash column chromatography DCM/MeOH (0.5M NH_3 solution) (0-25% gradient). The purified pale yellow oil was dissolved in MeOH (5 mL) and added 2.0 M solution HCl/Ether (4 mL) and concentrated *in vacuo* to dryness, add Et_2O (6 mL) and stirred for 1 h at RT (25°C), the precipitate filtered and dried to afford 1-benzyl-2-(piperidin-4-yl)-5-(trifluoromethyl)-1H-benzo[d]imidazole hydrochloride (180 mg, 71 % yield) as an off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.20 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.43 – 7.32 (m, 5H), 5.95 (s, 2H), 4.06 – 3.83 (m, 1H), 3.61 – 3.57 (m, 2H), 3.27 – 3.26 (m, 2H), 2.31 – 2.18 (m, 4H); **HPLC** purity 98%, Retention time (R_t) = 0.448 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 360.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{22}ClF_3N_3$ *m/z* = 396.15 $(M + H)^+$].

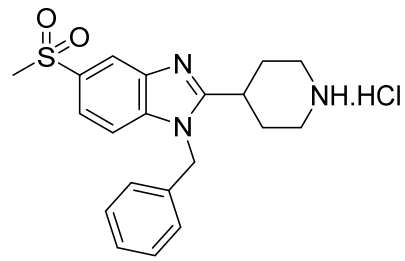
Methyl 1-benzyl-2-(piperidin-4-yl)-1H-benzo[d]imidazole-5-carboxylate (46d):

Flash column chromatography DCM/MeOH (0.5M NH_3 solution) (0-25% gradient). (130 mg, 55% yield),



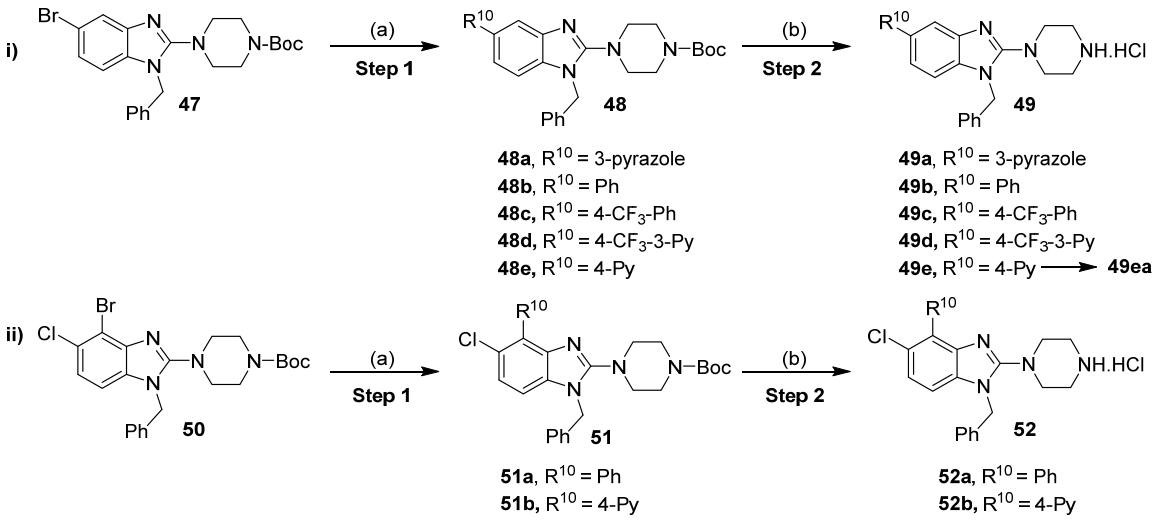
Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.37 (dd, J = 1.6, 0.6 Hz, 1H), 7.97 (dd, J = 8.5, 1.6 Hz, 1H), 7.51 (dd, J = 8.6, 0.7 Hz, 1H), 7.35 – 7.30 (m, 3H), 7.13 – 7.10 (m, 2H), 5.61 (s, 2H), 3.95 (s, 3H), 3.22 – 3.14 (m, 3H), 2.78 – 2.69 (m, 2H), 1.95 – 1.78 (m, 4H); **HPLC** purity 95%, Retention time (R_t) = 0.407 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 350.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{21}H_{24}N_3O_2$ *m/z* = 350.2 $(M + H)^+$].

1-Benzyl-5-(methylsulfonyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride (46e):



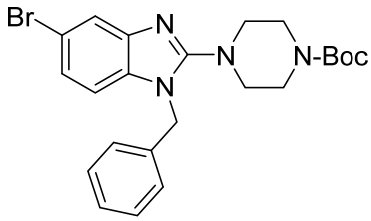
Flash column chromatography DCM/MeOH (0.5M NH_3 solution) (0-25% gradient) yielded pale yellow oil. The material was dissolved in MeOH (5 mL) and added 2.0 M solution HCl/Ether (4 mL) and concentrated *in* vacuo to dryness. Added Et_2O (6 mL) and stirred for 1 h at RT (25°C), the precipitate filtered and dried to afford 1-benzyl-5-(methylsulfonyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride (100 mg, 39% yield) as a yellow solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 8.36 (s, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.53 – 7.19 (m, 5H), 5.85 (s, 2H), 3.86 – 3.76 (m, 1H), 3.58 – 3.50 (m, 2H), 3.26 – 3.17 (m, 2H), 3.18 (s, 3H), 2.25 – 2.10 (m, 4H); **HPLC** purity 98%, Retention time (R_t) = 0.349 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 370.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{25}ClN_3O_2S$ *m/z* = 406.14 $(M + H)^+$].

Synthesis of compounds 49b-e and **52a-b, (Scheme S4); following a general procedure 4 (GP4):**



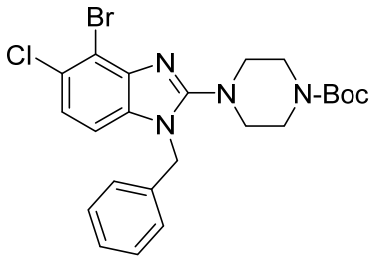
Synthesis of compounds 47 and 50

tert-butyl 4-(1-benzyl-5-bromo-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (47):



A pressure vial was charged with 1-benzyl-5-bromo-2-chloro-1H-benzo[d]imidazole (**12b**) (1.2 g, 3.73 mmol), tert-butyl piperazine-1-carboxylate (6.95 g, 37.3 mmol) and triethylamine (5.20 mL, 37.3 mmol) in tert-butanol (30 mL) and heated to 120 ºC for 110 h. The reaction mixture was cooled to RT and added saturated solution of $NaHCO_3$ (80 mL) and extracted with EtOAc (2x100 mL). The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue was purified by flash SiO_2 gel column chromatography using Hexane/EtOAc as an eluent (0-30%) gradient afforded a desired tert-butyl 4-(1-benzyl-5-bromo-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (1.3 g, 73% yield) as a light yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 1.9, 0.4 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.22 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.17 – 7.11 (m, 2H), 6.90 (dd, *J* = 8.4, 0.5 Hz, 1H), 5.23 (d, *J* = 1.0 Hz, 2H), 3.61 – 3.50 (m, 4H), 3.29 – 3.18 (m, 4H), 1.49 (s, 9H). **HPLC** purity 99%, Retention time (R_t) = 1.922 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 471.1 (M^+) & 473.0 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{23}H_{28}BrN_4O_2$ *m/z* = 471.12 $(M + H)^+$].

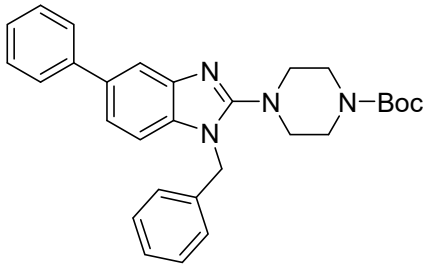
tert-butyl 4-(1-benzyl-4-bromo-5-chloro-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (50):



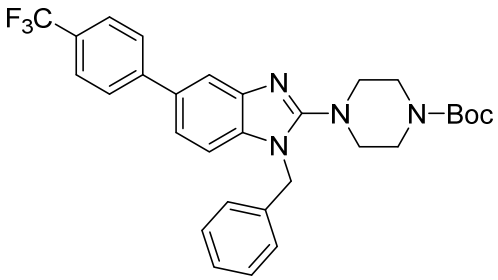
To a stirred solution of 1-benzyl-4-bromo-5-chloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole (**13K**) (202 mg, 0.498 mmol) and di-tert-butyl dicarbonate (217 mg, 0.996 mmol) in a Ethyl acetate (4 mL) was added saturated solution of sodium bicarbonate (4 mL). The resulting reaction mixture was stirred for an hour. LCMS shows complete consumption of a starting material. The organic layer was separated and dried over sodium sulphate. The residue was purified by flash SiO_2 gel column chromatography using Hexane/EtOAc (0-50% gradient) to afford a tert-butyl 4-(1-benzyl-4-bromo-5-chloro-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (224 mg, 79% yield) as a light yellow solid. **^{1}H NMR** (300 MHz, CD_3OD) δ 7.39 – 7.30 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.18 – 7.15 (m, 2H), 7.13 (d, *J* = 8.5 Hz, 1H), 5.37 (s, 2H), 3.58– 3.55 (m, 4H), 3.29 – 3.25 (m, 4H), 1.49 (s, 9H); **HPLC** purity 89%, Retention time (R_t) = 4.997 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 505.1 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{23}H_{27}BrClN_4O_2$ *m/z* = 505.1 $(M + H)^+$].

<u>Step 1: Synthesis of compounds 48b-48e and 51a-51b</u>

tert-Butyl 4-(1-benzyl-5-phenyl-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (48b): Flash column chromatography using Hexane/EtOAc (0-40% gradient). (145 mg, 97% yield), Off white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* (ppm) 7.94 (d, *J* = 1.7 Hz, 1H), 7.66 – 7.63 (m, 2H), 7.48 – 7.34 (m, 7H), 7.24 –7.20 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 1H), 5.30 (s, 2H), 3.60 – 3.57 (m, 4H), 3.32 – 3.28 (m, 4H), 1.50 (s, 9H); **HPLC** purity 96%, Retention time (R_t) = 1.706 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 469.3 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{29}H_{33}N_4O_2$ *m/z* = 469.26 $(M + H)^+$].



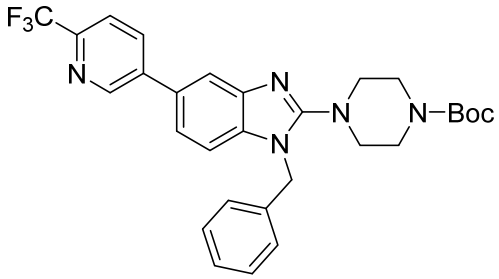
tert-Butyl 4-(1-benzyl-5-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (48c):



Flash column chromatography using Hexane/EtOAc (0-40% gradient)]. (124 mg, 60% yield), Off white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* (ppm) 7.96 (d, *J* = 1.5 Hz, 1H), 7.76 – 7.68 (m, 4H), 7.44 – 7.36 (m, 4H), 7.23 – 7.18 (m, 2H), 7.15 (d, *J* = 8.3 Hz, 1H), 5.31 (s, 2H), 3.61 – 3.58 (m, 4H), 3.35 – 3.33 (m, 4H), 1.49 (s, 9H); **HPLC** purity 83%, Retention time

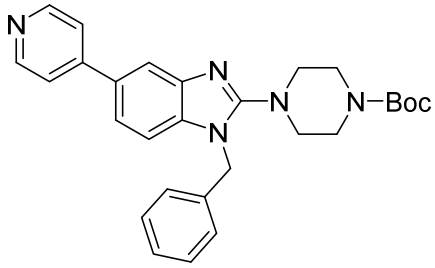
(R_t) = 5.191 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 537.1 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{30}H_{32}F_3N_4O_2$ *m/z* = 537.25 $(M + H)^+$].

tert-Butyl 4-(1-benzyl-5-(6-(trifluoromethyl)pyridin-3-yl)-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (48d):



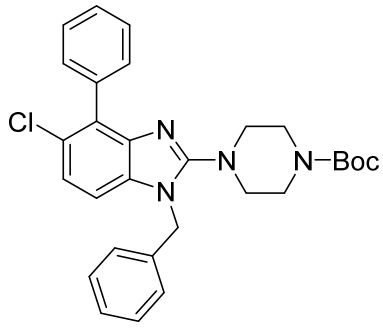
Flash column chromatography using Hexane/EtOAc (0-40% gradient). (110 mg, 64% yield), Off white solid. **HPLC** purity 99%, Retention time (R_t) = 1.893 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 538.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{29}H_{31}F_3N_5O_2$ *m/z* = 538.24 $(M + H)^+$], which was used directly to the next step.

tert-Butyl 4-(1-benzyl-5-(pyridin-4-yl)-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (48e):



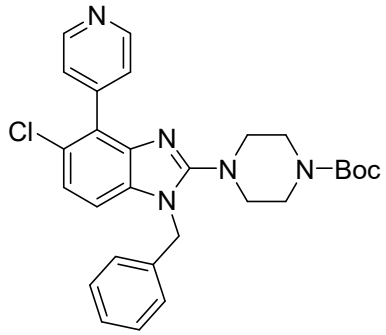
Flash column chromatography using DCM/MeOH (0.5M NH_3 in MeOH) (0-10% gradient)]. (100 mg, 58% yield), Brown solid. **HPLC** purity 87%, Retention time (R_t) = 1.105 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 470.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{28}H_{32}N_5O_2$ *m/z* = 470.26 $(M + H)^+$], which was used directly to the next step.

tert-butyl 4-(1-benzyl-5-chloro-4-phenyl-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (51a):



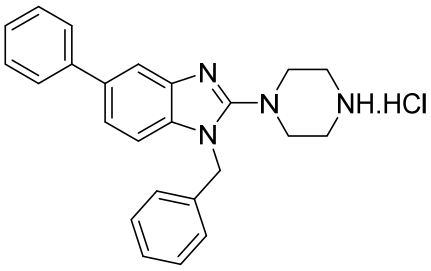
Flash column chromatography using Hexane/EtOAc (0-25% gradient). (70 mg, 57% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.52 – 7.31 (m, 8H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.15 (d, *J* = 8.6 Hz, 1H), 5.39 (s, 2H), 3.53 – 3.50 (m, 4H), 3.17 – 3.13 (m, 4H), 1.46 (s, 9H); **HPLC** purity 97%, Retention time (R_t) = 2.199 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 503.2 (M+) and 505.2 (M+ 2)$^+$ on a positive mode M 280 nm [calcd for $C_{29}H_{32}ClN_4O_2$ *m/z* = 503.22 $(M + H)^+$].

tert-butyl 4-(1-benzyl-5-chloro-4-(pyridin-4-yl)-1H-benzo[d]imidazol-2-yl)piperazine-1-carboxylate (51b): Flash column chromatography using Hexane/EtOAc (0-70% gradient). (83 mg, 66% yield), Light yellow solid. **HPLC** purity 95%, Retention time (R_t) = 1.635 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 504.2 (M+) and 506.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{28}H_{31}ClN_5O_2$ *m/z* = 504.22 $(M + H)^+$], which was used directly to the next step.



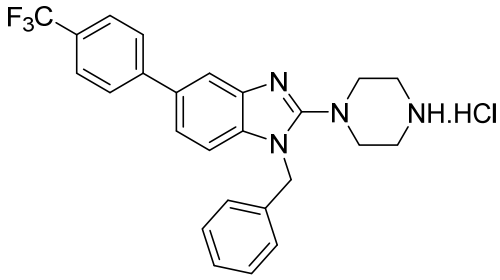
<u>Step 2: Synthesis of compounds 49b-49e and 52a-52b:</u>

1-benzyl-5-phenyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (49b):



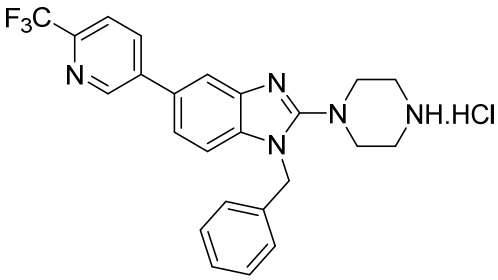
(20 mg, 16% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.84 (dd, *J* = 1.6, 0.6 Hz, 1H) 7.71 – 7.65 (m, 3H), 7.53 – 7.34 (m, 9H), 5.63 (s, 2H), 3.87 – 3.84 (m, 4H), 3.50 – 3.46 (m, 4H); **HPLC** purity 98%, Retention time (R_t) = 0.996 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 369.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{24}H_{26}ClN_4$ *m/z* = 405.19 $(M + H)^+$].

1-benzyl-2-(piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazole hydrochloride (49c):



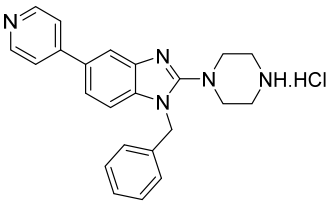
(15 mg, 15% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.92 – 7.79 (m, 5H), 7.74 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.53 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.36 – 7.34 (m, 2H), 5.63 (s, 2H), 3.87 – 3.84 (m, 4H), 3.50 – 3.46 (m, 4H); **HPLC** purity 98%, Retention time (R_t) = 1.224 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 437.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{25}H_{25}ClF_3N_4$ *m/z* = 473.17 $(M + H)^+$].

1-benzyl-2-(piperazin-1-yl)-5-(6-(trifluoromethyl)pyridin-3-yl)-1H-benzo[d]imidazole hydrochloride (49d):



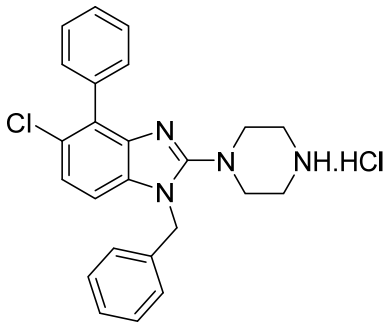
(49 mg, 53% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 9.04 (d, J = 2.2 Hz, 1H), 8.34 (dd, J = 8.1, 2.2 Hz, 1H), 7.98 – 7.97 (m, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.77 (dd, J = 8.5, 1.7 Hz, 1H), 7.57 (dd, J = 8.6, 0.6 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.36 – 7.33 (m, 2H), 5.63 (s, 2H), 3.86 – 3.83 (m, 4H), 3.49 – 3.46 (m, 4H); **HPLC** purity 96%, Retention time (R_t) = 1.076 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 438.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{24}H_{24}ClF_3N_5$ *m/z* = 474.16 $(M + H)^+$].

1-Benzyl-2-(piperazin-1-yl)-5-(pyridin-4-yl)-1H-benzo[d]imidazole hydrochloride (49e): (50 mg, 61% yield), Brown solid. **HPLC** purity 88%, Retention time (R_t) = 2.431 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 370.1 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{23}H_{24}ClN_5$ *m/z* = 405.17 $(M + H)^+$]. **Note: purity was <95%.**



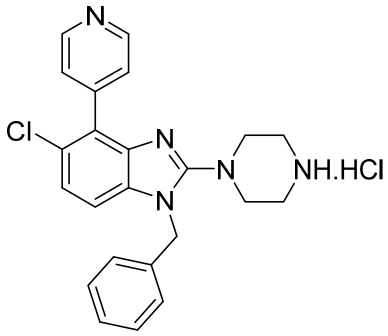
1-Benzyl-2-(piperazin-1-yl)-5-(pyridin-4-yl)-1H-benzo[d]imidazole (49ea): To a stirred solution of 1-benzyl-2-(piperazin-1-yl)-5-(pyridin-4-yl)-1H-benzo[d]imidazole hydrochloride (**49e**) (purity 88%) (50 mg, 0.123 mmol) in EtOAc (3 mL) was added a saturated solution of $NaHCO_3$ (3 mL) and stirring was continued for 3 h. The organic layer was then separated and dried over sodium sulphate and concentrated *in vaccuo*. The residue was purified by the flash chromatography using ISCO Teledyne on 12g RediSep Rf column and elution using DCM/MeOH (0.5M NH_3 solution) (0-10%) gradient to afford a desired 1-benzyl-2-(piperazin-1-yl)-5-(pyridin-4-yl)-1H-benzo[d]imidazole (23 mg, 50% yield) product as a grey solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 8.59 – 8.58 (m, 2H), 7.91 (d, J = 1.7 Hz, 1H), 7.71– 7.70 (m, 2H), 7.50 (dd, J = 8.3, 1.8 Hz, 1H), 7.37 – 7.26 (m, 4H), 7.20 – 7.18 (m, 2H), 5.36 (s, 2H), 3.20 – 3.19 (m, 4H), 2.92 – 2.90 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 2.472 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 370.1 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{23}H_{24}N_5$ *m/z* = 370.2 $(M + H)^+$].

1-Benzyl-5-chloro-4-phenyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (52a):



(37 mg, 62% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.61 – 7.39 (m, 10H), 7.38 – 7.35 (m, 2H), 5.60 (s, 2H), 3.77 – 3.73 (m, 4H), 3.41 – 3.38 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 1.335 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 403.1 (M^+) & 405.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{24}H_{25}Cl_2N_4$ *m/z* = 439.15 $(M + H)^+$].

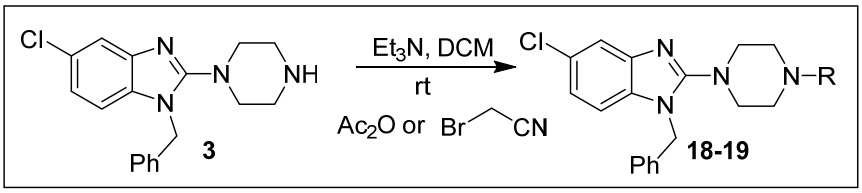
1-Benzyl-5-chloro-2-(piperazin-1-yl)-4-(pyridin-4-yl)-1H-benzo[d]imidazole hydrochloride (52b):



(55 mg, 76% yield), Yellow solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 9.05 (d, *J* = 5.7 Hz, 2H), 8.44 (d, *J* = 5.9 Hz, 2H), 7.54 –7.37 (m, 5H), 7.32 – 7.28 (m, 2H), 5.56 (s, 2H), 3.72 – 7.68 (m, 4H), 3.42 – 3.39 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 1.087 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 404.2 (M^+) & 406.2 $(M + 2)^+$ on a positive mode M 280 nm (calcd for $C_{23}H_{24}Cl_2N_5$ *m/z* = 440.14 $(M + H)^+$].

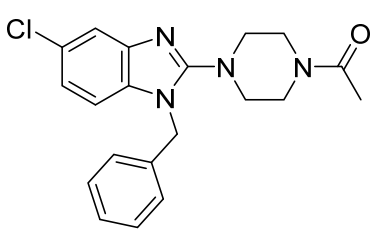
General procedure 5 (GP5) for acylation/alkylation/benzoylation/sulfonylation: Synthesis of compounds 18, 19, 20, 23 and 25

Method A) Acylation /alkylation



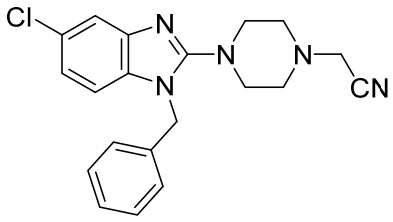
1-benzyl-5-chloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole **(3)** 250 mg (0.765mmol, 1 equiv) was dissolved in 5 mL THF, 1.0 g triethylamine (13 equiv) and 1.0 g acetic anhydride (13 equiv) **or** 1.0 g 2-bromoacetonitrile (11 equiv) were added and stirred at RT for 2 h. 80 mL $NaHCO_3$ solution was added and extracted with EtOAc (2 x 80 mL), dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography and crystallized in an appropriate solvent yielded corresponding products.

1-(4-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)ethan-1-one (18):



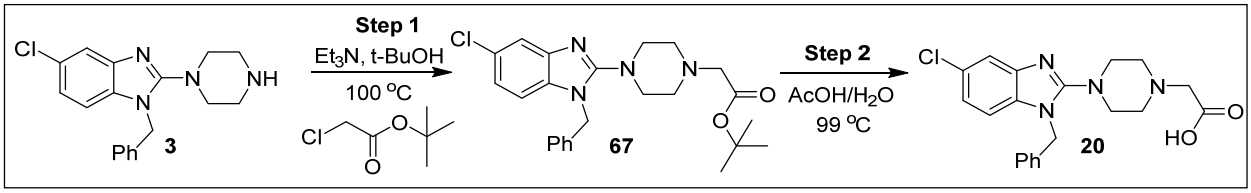
Flash column chromatography using EtOAc/MeOH (98/2 to 96/4 to 94/6), (190 mg, 65% yield), White crystal. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.66 (d, J = 6.0 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.16 – 7.11 (m, 3H), 6.98 (d, J = 9.0 Hz, 1H), 5.25 (s, 2H), 3.74 – 3.61 (m, 4H), 3.40 – 3.22 (m, 4H), 2.14 (s, 3H); **HPLC** purity 97%, Retention time (R_t) = 4.674 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 369.1 (M^+) and 371.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{22}Cl_2N_4O$ *m/z* = 369.15 $(M + H)^+$].

2-(4-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)acetonitrile (19):



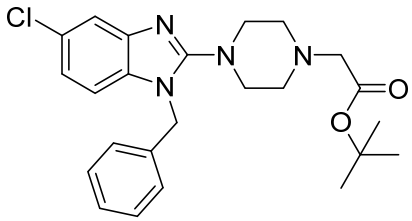
Flash column chromatography using Hexane/EtOAc (30/70 to 20/80 to 10/90 to 0/100%), (146 mg, 51% yield), White solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.66 (d, J = 3.0 Hz, 1H,), 7.41 – 7.31 (m, 3H), 7.18 – 7.14 (m, 2H), 7.11 (dd, J = 9.0, 3.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.25 (s, 2H), 3.60 (s, 2H), 3.38 – 3.35 (m, 4H), 2.76 – 2.73 (m, 4H); **HPLC** purity 97%, Retention time (R_t) = 4.785 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 366.2 (M^+) and 368.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{21}ClN_5$ *m/z* = 366.15 $(M + H)^+$].

Synthesis of 2-(4-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)acetic acid (20)



Step 1: *N*-Alkylation of 3

Synthesis of tert-butyl 2-(4-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)acetate (67).



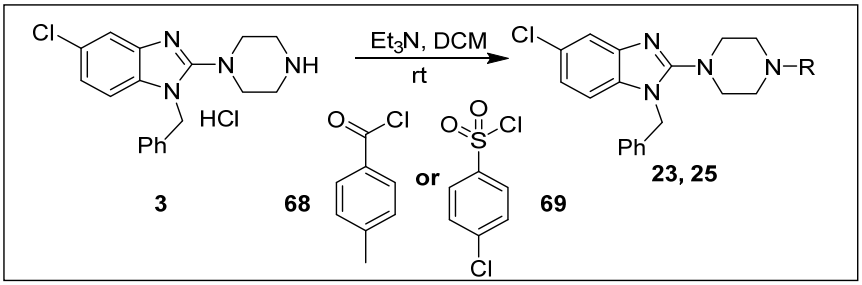
A mixture of 1-benzyl-5-chloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole **(3)** (0.115 g, 0.352 mmol), triethylamine (0.50 g, 4.94 mmol) and tert-butyl 2-chloroacetate (0.50 g, 3.32 mmol) in 3 mL tBuOH in a pressure tube was heated to 100 °C for 50 min, cooled and the solvent evaporated. The crude mix was purified by flash chromatography using EtOAc/Hexane/NEt_3 50/49/1 to yield tert-butyl 2-(4-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)acetate after recrystallization from Hexane/EtOAc (67 mg, 60%) as white solid. **1H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.64 (s, 1H), 7.33 – 7.29 (m, 3H), 7.08 – 7.02 (m, 3H),

6.88 (d, J = 9.0 Hz, 1H), 5.16 – 5.08 (m, 2H), 3.60 – 3.47 (m, 4H), 3.30 – 3.27 (m, 2H), 3.00 – 2.94 (m, 4H), 1.40 (s, 9H) **Note: We observed rotamers; HPLC** purity 99%, Retention time (R_t) = 0.564 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 441.3 (M^+) and 445.3 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{24}H_{30}ClN_4O_2$ *m/z* = 441.21 $(M + H)^+$].

Step 2: Hydrolysis of ester to acid (20):

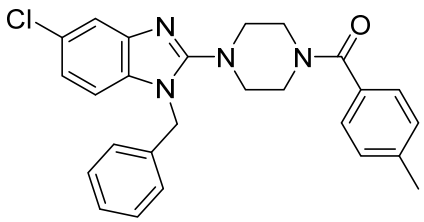
Tert-butyl 2-(4-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)acetate (0.067 g, 0.152 mmol) in 2 mL AcOH/2 mL water was heated to 99 ºC for 4 h. Cooled the solution and evaporated the solvent completely. Redissolve in MeOH and iPrOH and evaporate to ~1 mL and let the product crystallize. Removed the mother liquor and dry under high vacuum to yield 2-(4-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)acetic acid (**20)** (55 mg, 91% yield) as a white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.53 (d, J = 3.0 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.19 – 7.12 (m, 4H), 5.39 (s, 2H), 3.63 (s, 2H), 3.55 – 3.52 (m, 4H), 3.41 – 3.33 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 0.467 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 385.2 (M^+) and 387.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{20}H_{22}ClN_4O_2$ *m/z* = 385.14 $(M + H)^+$].

Method B) Benzoylation/Sulfonylation



To a solution of 1-benzyl-5-chloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride salt (73 mg, 0.201 mmol) and triethylamine (25 equiv) in 10 mL CH_2Cl_2 was added a solution of 4-methylbenzoyl chloride **(68)** (31 mg, 0.201 mmol) **or** 4-chlorobenzenesulfonyl chloride **(69)** (43 mg, 0.201 mmol) in 3 mL CH_2Cl_2 at RT. This mixture was stirred for 1 h and then evaporated onto silica gel. The crude was purified by Flash chromatography using Hexane/EtOAc and evaporation of the product fractions to~1 mL yielded the desired products.

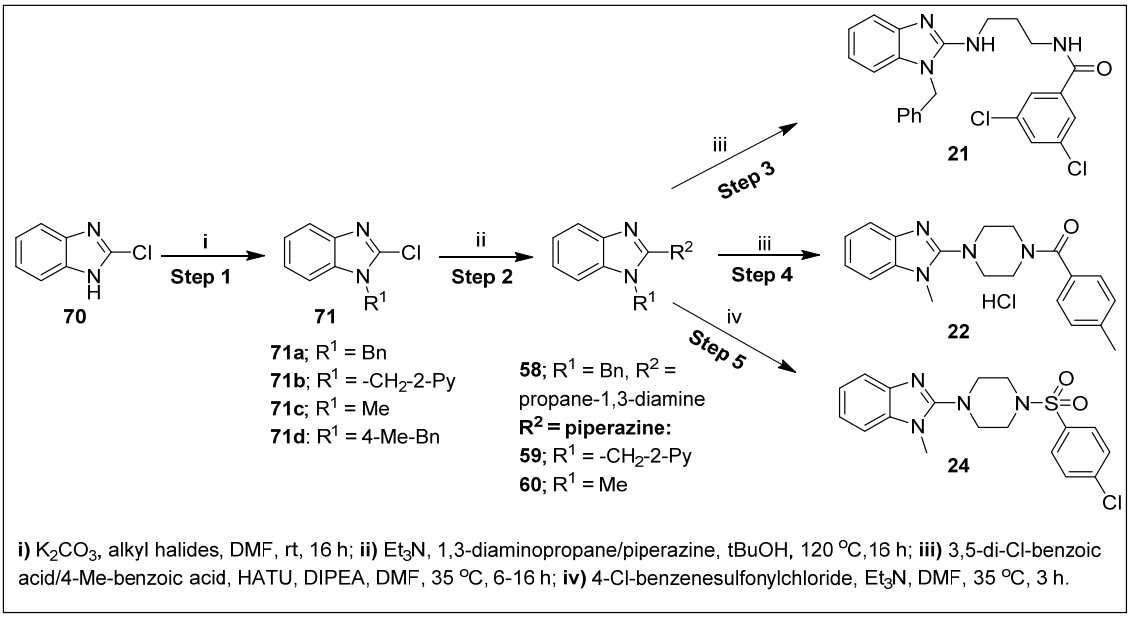
(4-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)(p-tolyl)methanone (23):



Flash column chromatography using Hexane/EtOAc (60/40 to 50/50 to 30/70), (70 mg, 78% yield), White crystal. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.75 – 7.73 (m, 1H), 7.43 – 7.33 (m, 3H), 7.33 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.19 – 7.10 (m, 3H), 6.99 (d, J = 8.6 Hz, 1H), 5.29 – 5.22 (m, 2H), 3.76 – 3.30 (m, 8H), 2.40 (s, 3H); **Note: We observed rotamers**. **HPLC** purity 99%, Retention time (R_t) = 5.175 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 445.2 (M^+) and 447.2 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{26}H_{26}ClN_4O$ *m/z* = 445.18 $(M + H)^+$].

1-Benzyl-5-chloro-2-(4-((4-chlorophenyl)sulfonyl)piperazin-1-yl)-1H-benzo[d]imidazole (25): Flash column chromatography using Hexane/EtOAc (70/30 to 50/50), (62 mg, 61% yield), White crystals. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.71 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 1.9 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.40 – 7.32 (m, 3H), 7.13 – 7.04 (m, 3H), 6.92 (d, J = 8.5 Hz, 1H), 5.17 (m, 2H), 3.48 – 3.38 (m, 4H), 3.20 – 3.15 (m, 4H); **Note: We observed rotamers. HPLC** purity 99%, Retention time (R_t) = 5.269 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 501.1 (M^+) and 503.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{24}H_{23}Cl_2N_4O_2S$ *m/z* = 501.09 $(M + H)^+$].

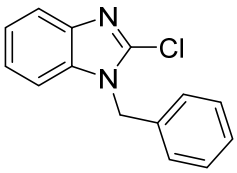
Synthesis of 21, 22, 24, 58, 59 and 60:



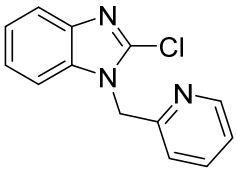
Step 1: *N*-alkylation of benzimidazole

To a solution of the 2-chloro-1H-benzo[d]imidazole **(70)** (1.0 equiv.) in DMF (0.4 M) was added benzyl bromide **or** methyl iodide **or** 2-(bromomethyl)pyridine hydrobromide (1.5 equiv) and potassium carbonate (2.0 equiv) and the reaction mixture stirred at 25ºC. After 16 hrs, TLC indicated the reaction is completed. Added H_2O (50 mL) and EtOAc (70 mL). Separated the organic phase and extracted the aqueous phase with a further portion of EtOAc (2 x 30 mL). Combined the organic phases, washed sequentially with saturated $NaHCO_3$ (30 mL) and brine (30 mL) and dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford crude 1-alkyl/benzyl-2-chloro-1H-benzo[d]imidazole in good to moderate yields which was used directly to the next step without any further purification.

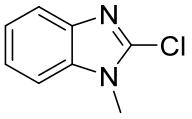
1-Benzyl-2-chloro-1H-benzo[d]imidazole (71a):[10a] (2.0 g, 58% yield). Pale yellow solid. **HPLC** purity 94%, Retention time (R_t) = 4.046 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 243.1 (M^+) and 245.0 $(M + 2)^+$ on a positive mode [calcd for $C_{14}H_{12}ClN_2$ *m/z* = 243.07 $(M + H)^+$].



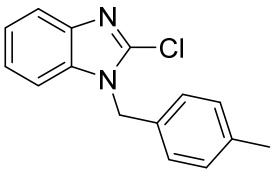
2-Chloro-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazole (71b):[10b] (300 mg, 68% yield), Green oil. **HPLC** purity 73%, Retention time (R_t) = 3.688 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 244.1 (M^+) and 246.1 $(M + 2)^+$ on a positive mode [calcd for $C_{13}H_{11}ClN_3$ *m/z* = 244.06 $(M + H)^+$].



2-Chloro-1-methyl-1H-benzo[d]imidazole (71c):[10c] (600 mg, 92% yield), Yellow residue. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.73 – 7.70 (m, 1H), 7.34 – 7.30 (m, 3H), 3.81 (s, 3H).

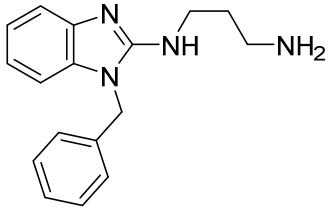


2-Chloro-1-(4-methylbenzyl)-1H-benzo[d]imidazole (71d):[10d] (600 mg, 71%), **HPLC** purity 82%, Retention time (R_t) = 3.965 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 257.1 (M^+) and 259.0 $(M + 2)^+$ on a positive mode (calcd for $C_{15}H_{14}ClN_2$ *m/z* = 257.09 $(M + H)^+$).



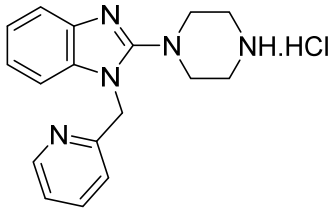
Step 2: Following GP 1: Step 7

***N*1-(1-benzyl-1H-benzo[d]imidazol-2-yl)propane-1,3-diamine (58):**



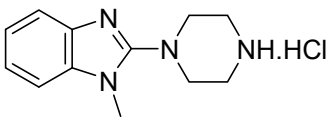
Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-25% gradient). (750 mg, 64% yield), Off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.36 – 7.25 (m, 4H), 7.16 – 7.13 (m, 2H), 7.08 – 7.02 (m, 2H), 6.98 – 6.95 (m, 1H), 5.25 (s, 2H), 3.53 (t, J = 6.8 Hz, 2H), 2.70 (t, J = 7.0 Hz, 2H), 1.82 (quin, J = 6.9 Hz, 2H); **HPLC** purity 99%, Retention time (R_t) = 2.017 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 281.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{17}H_{21}N_4$ *m/z* = 281.18 $(M + H)^+$].

2-(piperazin-1-yl)-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazole hydrochloride (59):



Flash column chromatography using EtOAc/MeOH/Et_3N (92/6/2) yielded a clear pale-yellow oil. The material was dissolved in MeOH/EtOAc (5 mL), added 2.0 M solution HCl/Ether (3 mL) and concentrated *in vacuo* to dryness. Added Et_2O (6 mL) and stirred for 1 h at RT (25°C), the precipitate filtered and dried to afford 2-(piperazin-1-yl)-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazole hydrochloride (170 mg, 40% yield) as a brown solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm); 8.75 – 8.72 (m, 1H), 8.32 ('t', J = 7.6 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.81 – 7.77 (m, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.55 – 7.45 (m, 1H), 7.43 – 7.35 (m, 2H), 5.89 (s, 2H), 3.99 – 3.96 (m, 4H), 3.58 – 3.54 (m, 4H); **HPLC** purity 95%, Retention time (R_t) = 2.544 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 294.2 $(M + H)^+$ on a positive mode M 280 nm (calcd for $C_{17}H_{21}ClN_5$ *m/z* = 330.15 $(M + H)^+$].

1-methyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (60):[11]

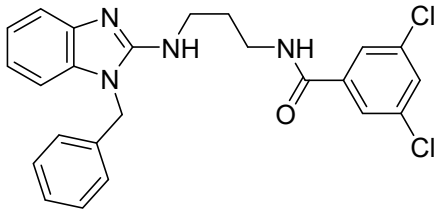


Flash column chromatography using EtOAc/MeOH/Et_3N (92/6/2) afforded clear pale-yellow oil. The material was dissolved in EtOAc/MeOH (10 mL) and added 2.0 M solution HCl/Ether (3 mL) and concentrated in vacuo to dryness, added Et_2O (6 mL) and stirred at room temperature of 25°C for 1h, the precipitate filtered and dried to afford a pure 1-methyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (600 mg, 65%) as an off white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.71 – 7.66 (m, 1H), 7.64 – 7.60 (m, 1H), 7.56 – 7.49 (m, 2H), 3.97 – 3.94 (m, 4H), 3.91 (s, 3H), 3.60 – 3.56 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 0.940 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 217.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{12}H_{18}ClN_4$ *m/z* = 253.12 $(M + H)^+$].

Step 3 and 4: Amide formation

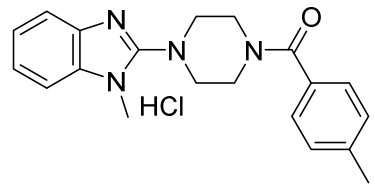
To a solution of the amine **(58)/(60)** (1 equiv) in DMF (0.11 M) was added 3,5-dichlorobenzoic acid (1.0 equiv) **or** 4-methylbenzoic acid (1.2 equiv), HATU (1.2 equiv) and DIEA (2.5 equiv). The reaction mixture was stirred at 35 ^{o}C. After 16 and 6 hrs respectively, TLC and LCMS indicated that the reaction is completed. Added H_20 (30 mL) and EtOAc (60 mL). Separated the organic phase, extracted the aqueous phase with a further portion of EtOAc (2 x 30 mL). Combined the organic phases and washed sequentially with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a crude residue. Purification was done by flash chromatography using ISCO Teledyne on 12g RediSep Rf column and elution using DCM/MeOH or Hexane/EtOAc to afford **21** and **22** in low yields.

***N*-(3-((1-benzyl-1H-benzo[d]imidazol-2-yl)amino)propyl)-3,5-dichlorobenzamide (21):**



Flash column chromatography using DCM/MeOH (0.5M NH_3 solution) (0-15% gradient). (60 mg, 24% yield), Brown solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.83 (d, J = 1.9 Hz, 2H), 7.64 ('t', J = 1.9 Hz, 1H), 7.35 – 7.26 (m, 4H), 7.19 – 7.17 (m, 2H), 7.08 – 7.03 (m, 2H), 6.99 – 6.94 (m, 1H), 5.27 (s, 2H), 3.56 (t, J = 6.7 Hz, 2H), 3.45 (t, J = 6.6 Hz, 2H), 1.95 (quin, J = 6.7 Hz, 2H); **HPLC** purity 99%, Retention time (R_t) = 0.531 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 453.2 (M^+) & 455.2 $(M + H)^+$ on a positive mode M 280 nm [calcd for $C_{24}H_{23}Cl_2N_4O$ *m/z* = 453.13 $(M + H)^+$].

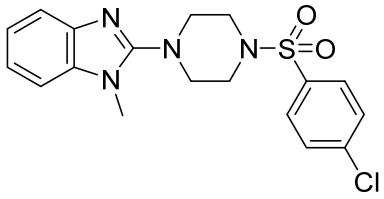
(4-(1-methyl-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)(p-tolyl)methanone hydrochloride (22):



Flash column chromatography using Hexane/EtOAc (0-100% gradient) afforded clear pale-yellow oil. The material was dissolved in EtOAc:MeOH (5 mL) and added 2.0 M solution HCl/Ether (2 mL) and concentrated in vacuo to dryness, added Et_2O (6 mL) and stirred for 1 h at RT (25^{o}C), the precipitate filtered and dried to afford a pure (4-(1-methyl-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)(p-tolyl)methanone (60 mg, 44% yield) as a pale yellow solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.67 – 7.64 (m, 1H), 7.59 – 7.56 (m, 1H), 7.51 – 7.48 (m, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 3.94 – 3.89 (m, 4H), 3.88 (s, 3H), 3.76 – 3.74 (m, 4H), 2.44 (s, 3H); **HPLC** purity 99%, Retention time (R_t) = 4.044 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 335.2 $(M + H)^+$ on a positive mode M 280 nm (calcd for $C_{20}H_{24}ClN_4O$ *m/z* = 371.16 $(M + H)^+$].

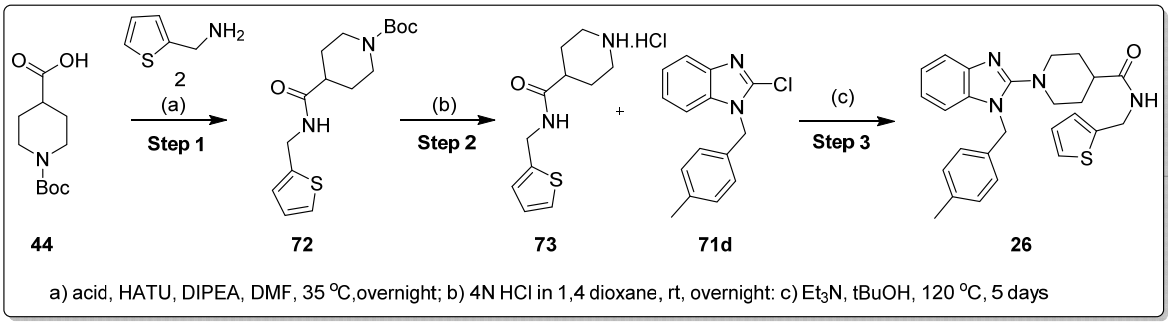
Step 5: Sulphonamide formation

Synthesis of 2-(4-((4-chlorophenyl)sulfonyl)piperazin-1-yl)-1-methyl-1H-benzo[d]imidazole (24):

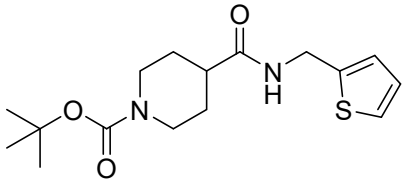


To a mixture of 1-methyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (**60**) (100 mg, 0.396 mmol) in DMF (4.0 mL) was added 4-chlorobenzenesulfonyl chloride (100 mg, 0.475 mmol) and triethylamine (0.136 mL, 0.989 mmol). The reaction mixture stirred at 35ºC. After 3 hrs, LCMS indicated a mass ion peak m/z 391 $(M+H)^+$ and TLC indicated that the reaction is completed. Added saturated aqueous $NaHCO_3$ (30 mL) and EtOAc (60 mL). Separated the organic phase and extracted the aqueous phase with a further portion of EtOAc (2 x 30 mL). Combined the organic phases and dried over anhydrous Na_2SO_4. Concentrated *in vacuo* to afford a crude residue. The crude residue was purified by flash chromatography using ISCO Teledyne on 12g RediSep Rf column and elution using Hexane/EtOAc (0-70% gradient) to afford **24** (97 mg, 61% yield) as an off-white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.90 – 7.86 (m, 2H), 7.75 – 7.72 (m, 2H), 7.50 – 7.47 (m, 1H), 7.38 – 7.35 (m, 1H), 7.23 – 7.19 (m, 2H), 3.63 (s, 3H), 3.44 – 3.40 (m, 4H), 3.31 – 3.27 (m, 4H); **HPLC** purity 98%, Retention time (R_t) = 4.436 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 391.1 (M^+) and 393.1 $(M + 2)^+$ on a positive mode M 280 nm [calcd for $C_{18}H_{20}ClN_4O_2S$ *m/z* = 391.1 $(M + H)^+$].

Synthesis of 1-(1-(4-methylbenzyl)-1H-benzo[d]imidazol-2-yl)-*N*-(thiophen-2-ylmethyl)piperidine-4-carboxamide (26)



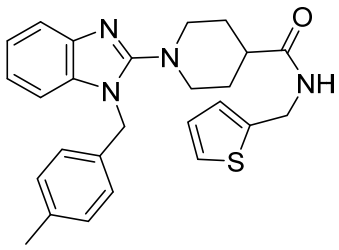
Step 1: Synthesis of tert-butyl 4-((thiophen-2-ylmethyl)carbamoyl)piperidine-1-carboxylate (72):



1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid **(44)** (1.0 g, 4.36 mmol) and HATU (V) (1.990 g, 5.23 mmol) were dissolved in DMF (10 mL) and DIPEA (3.05 ml, 17.45 mmol) was then added and the mixture was left to stir for 15 minutes at RT. Thiophen-2-ylmethanamine (0.494 g, 4.36 mmol) was added at last and the reaction left to stir overnight. After complete

consumption of the starting material (TLC) 20 ml of water was added to the reaction mixture and extracted with ethyl acetate (3x30 mL). The combined organic layer was dried over anhydrous sodium sulphate and solvent evaporated under reduced pressure. The crude product was then purified using Hexane/EtOAc (0/100%) to afford 1.2 g (85%) as pale red solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.26 – 7.23 (m, 1H), 6.99 – 6.95 (m, 2H), 5.87 (brs, 1H), 4.64 (d, J = 5.0 Hz, 2H), 4.20 – 4.11 (m, 2H), 2.82 – 2.72 (m, 2H), 2.34 – 2.23 (m, 1H), 1.88 – 1.81 (m, 2H), 1.75 – 1.56 (m, 2H), 1.47 (s, 9H). This pale red solid was dissolved in 2 mL of DCM and 2 mL of Hydrogen chloride solution. The reaction was left for overnight. After TLC has shown complete consumption of the starting material the solvent was decanted, and the precipitate was washed with DCM several times and dried under reduced pressure afforded *N*-(thiophen-2-ylmethyl)piperidine-4-carboxamide hydrochloride (**73**) in a quantitative yield. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.30 – 7.25 (m, 1H), 6.99 – 6.93 (m, 2H), 4.55 (s, 2H), 3.24 – 2.88 (m, 2H), 2.74 – 2.34 (m, 2H), 2.23 – 2.15 (m, 1H), 1.87 – 1.67 (m, 4H).

Step 3: Synthesis of 1-(1-(4-methylbenzyl)-1H-benzo[d]imidazol-2-yl)-*N*-(thiophen-2-ylmethyl)piperidine-4-carboxamide (26)[12]



A mixture of 2-chloro-1-(4-methylbenzyl)-1H-benzo[d]imidazole (**71d**) (115 mg, 0.517 mmol), N-(thiophen-2-ylmethyl)piperidine-4-carboxamide HCl salt (**73**) (1161 mg, 5.17 mmol) and triethylamine (0.721 ml, 5.17 mmol) in tBuOH (5 mL) were heated at 120 °C with continuous monitoring. The starting material was consumed after 5 days. The reaction was cooled to room temperature and 20 mL of saturated sodium bicarbonate was added to it and extracted with ethyl acetate (3 x 20 mL), the combined organic layer was dried over anhydrous sodium sulphate and solvent evaporated under reduced pressure. The residue was purified using ethyl acetate as eluent and was crystallized from Hexane/DCM mixture to afford pure product (17 mg, 7% yield) as a white solid. **^{1}H NMR** (300 MHz, CD_3OD) δ (ppm) 7.52 – 7.50 (m, 1H), 7.28 (dd, J = 5.0, 1.3 Hz, 1H), 7.18 – 7.06 (m, 7H), 7.01 – 6.89 (m, 2H), 5.27 (s, 2H), 4.56 (d, J = 0.9 Hz, 2H), 3.57 – 3.51 (m, 2H), 3.04 – 2.94 (m, 2H), 2.48 – 2.37 (m, 1H), 2.31 (s, 3H), 2.00 – 1.83 (m, 4H); **HPLC** purity 99%, Retention time (R_t) = 4.111 min; Method Used (General positive); LC-MS (APCI) *m/z* = found 445.1 $(M + H)^+$ on a positive mode [calcd for $C_{26}H_{29}N_4OS$ *m/z* = 445.2 $(M + H)^+$].

Figure S1: 1-benzyl-5-chloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (3)

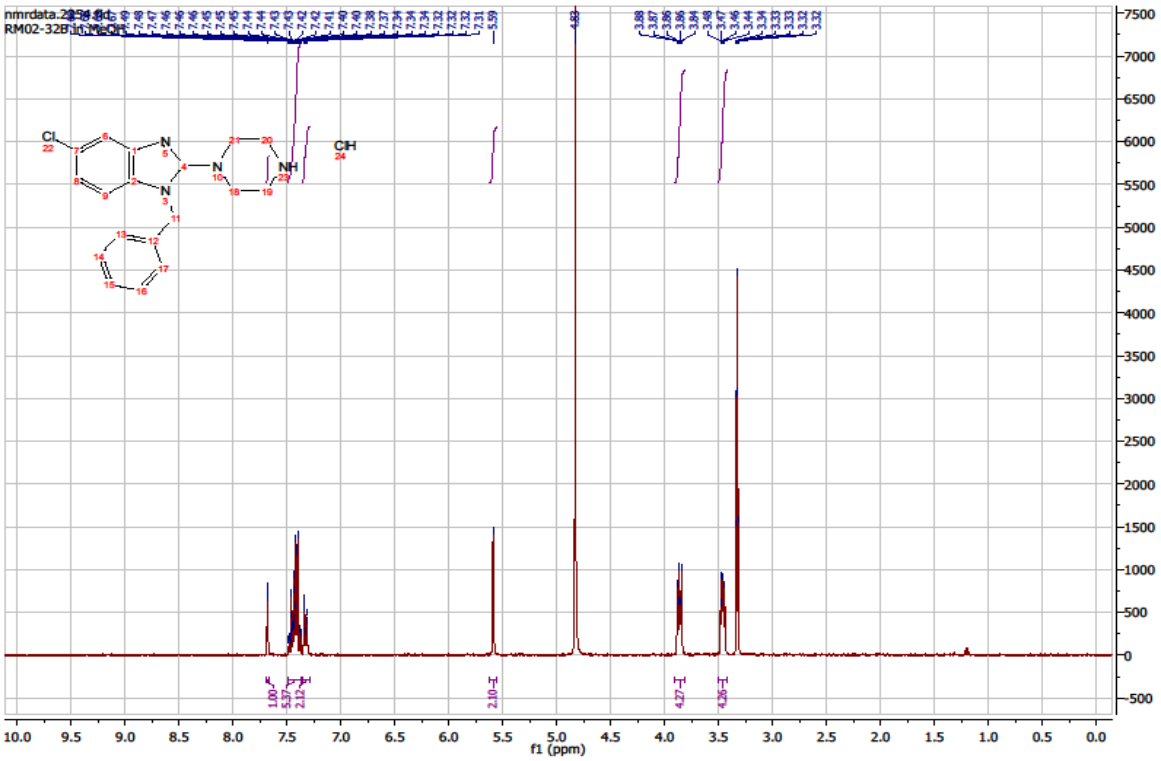


Figure S2: 1-Benzyl-2-(piperazin-1-yl)-5-(trifluoromethyl)-1H-benzo[d]imidazole (14c)

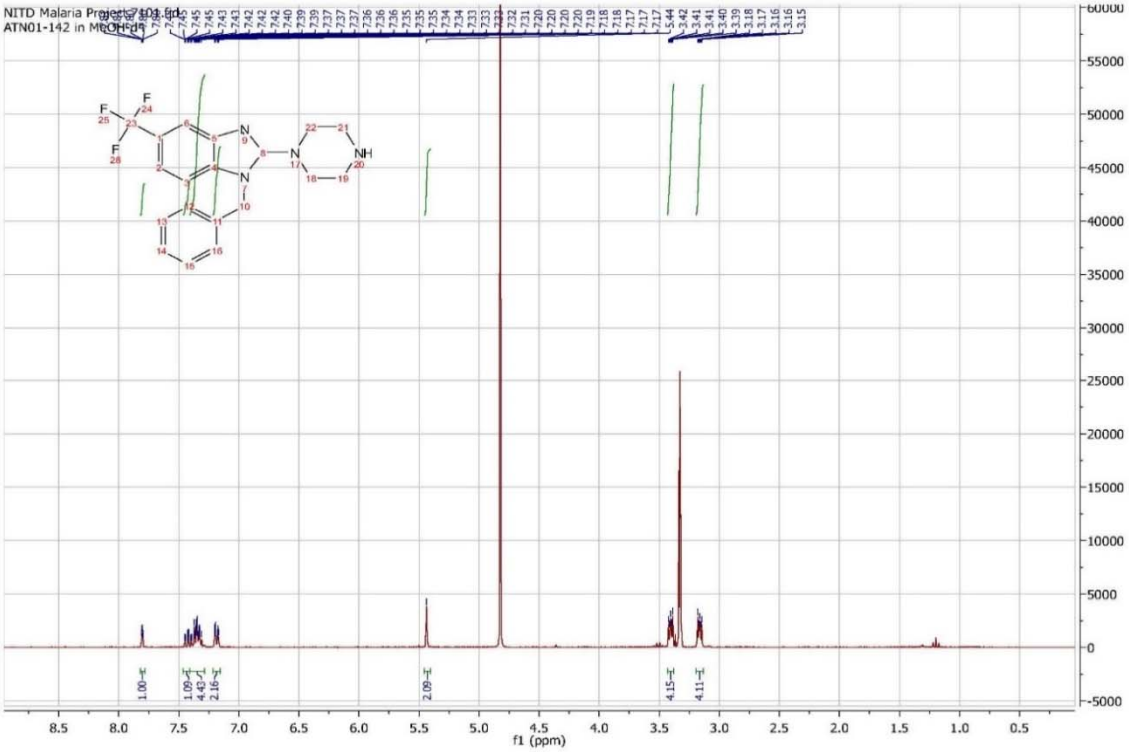


Figure S3: 5-chloro-1-(cyclohexylmethyl)-2-(piperazin-1-yl)-1H-benzo[d]imidazole (14h)

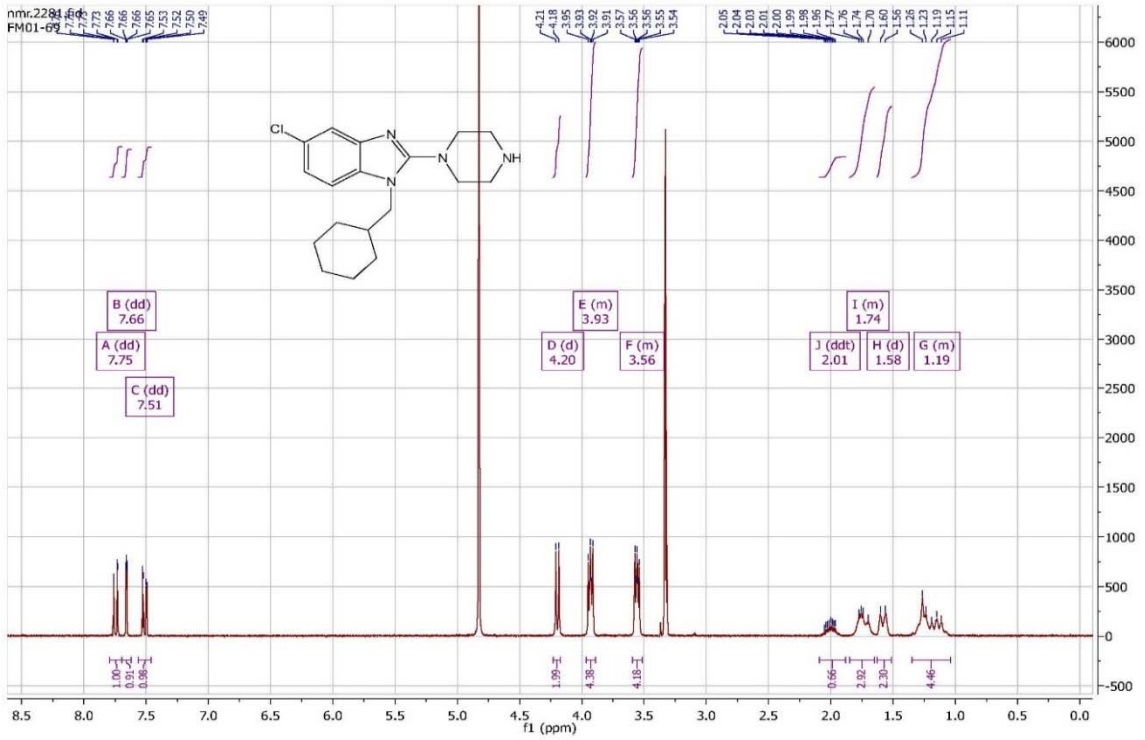


Figure S4: 2-(piperazin-1-yl)-1-(pyridin-4-ylmethyl)-1H-benzo[d]imidazole (14i)

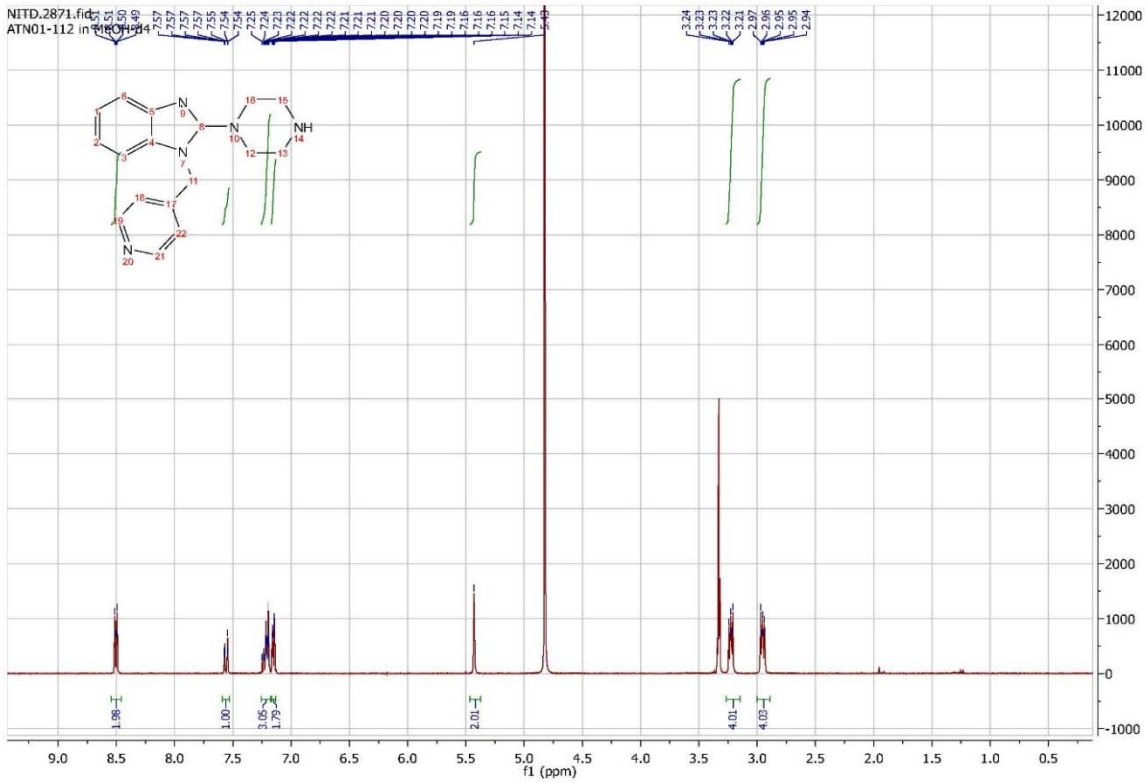


Figure S5: *N*1-(1-Benzyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)propane-1,3-diamine hydrochloride (15)

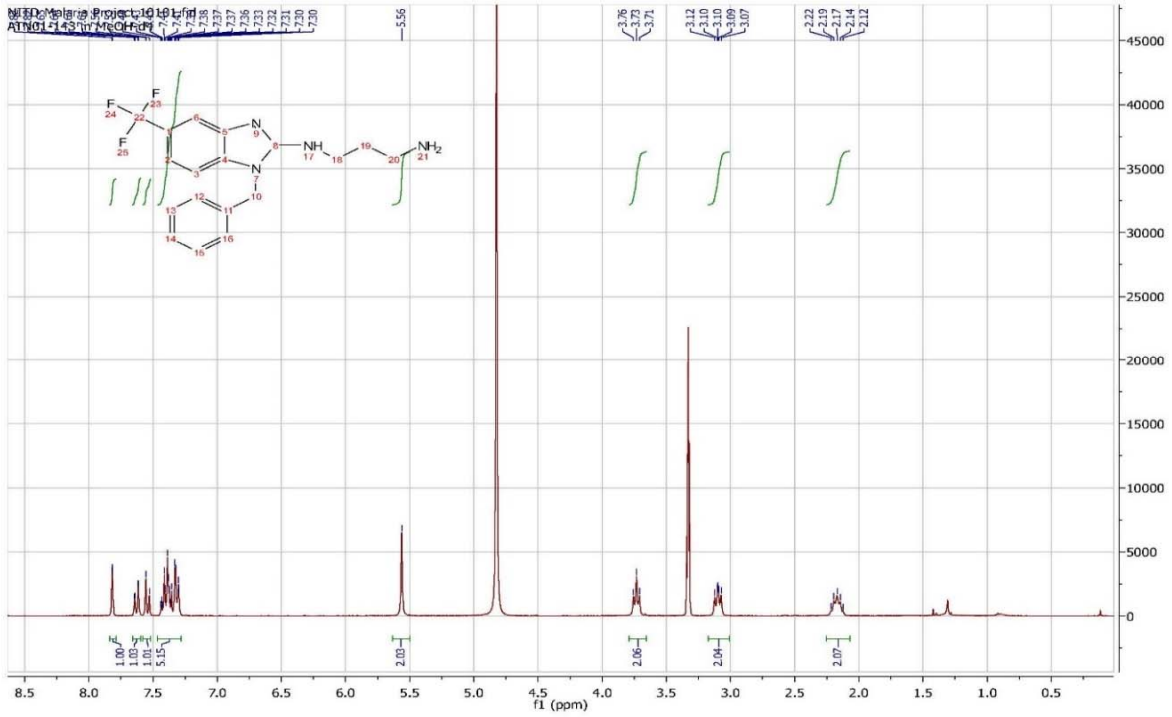


Figure S6: 4-(1-Benzyl-5-chloro-1H benzo[d]imidazol-2-yl)morpholine (16a)

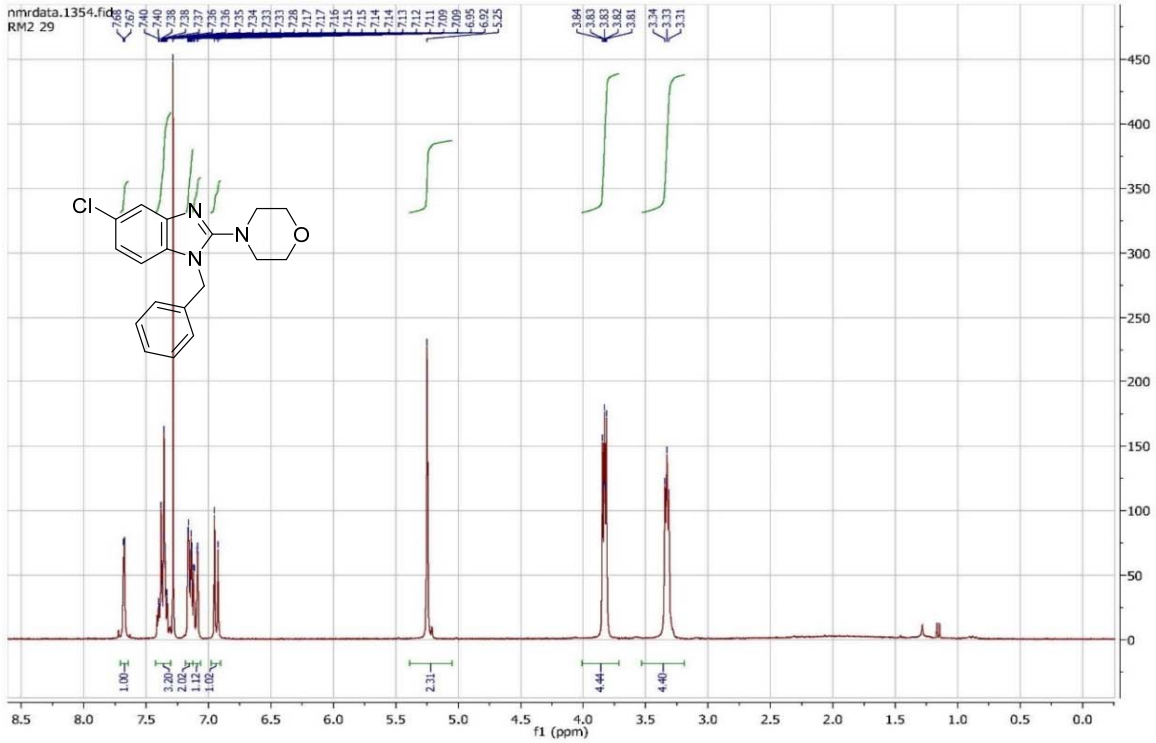


Figure S7: 1-Benzyl-5-bromo-2-(piperazin-1-yl)-1H-benzo[d]imidazole (16b)

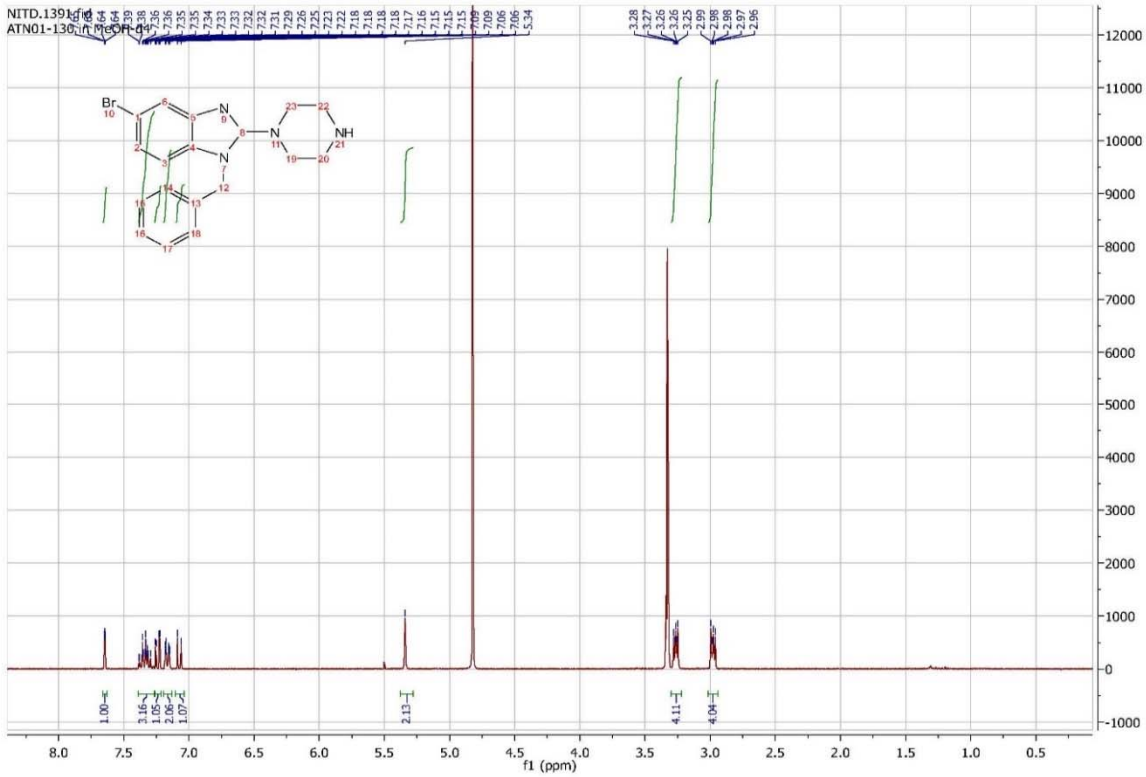


Figure S8: 5-Chloro-1-phenyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (16f)

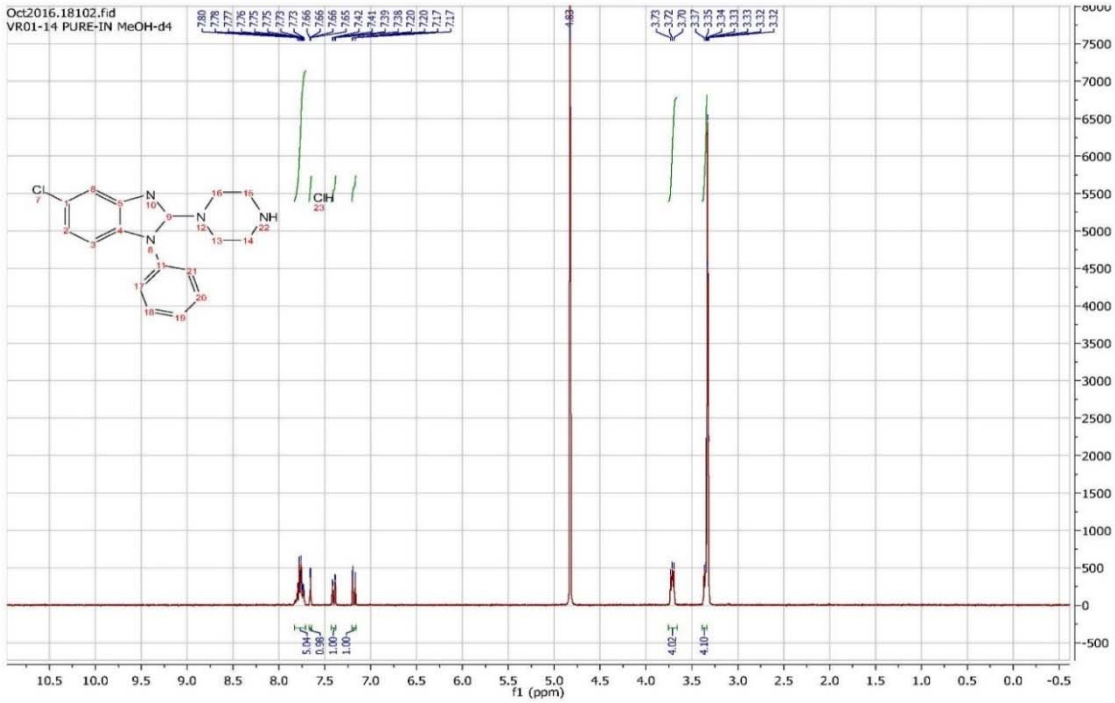


Figure S9: 5-Chloro-1-phenethyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (16g)

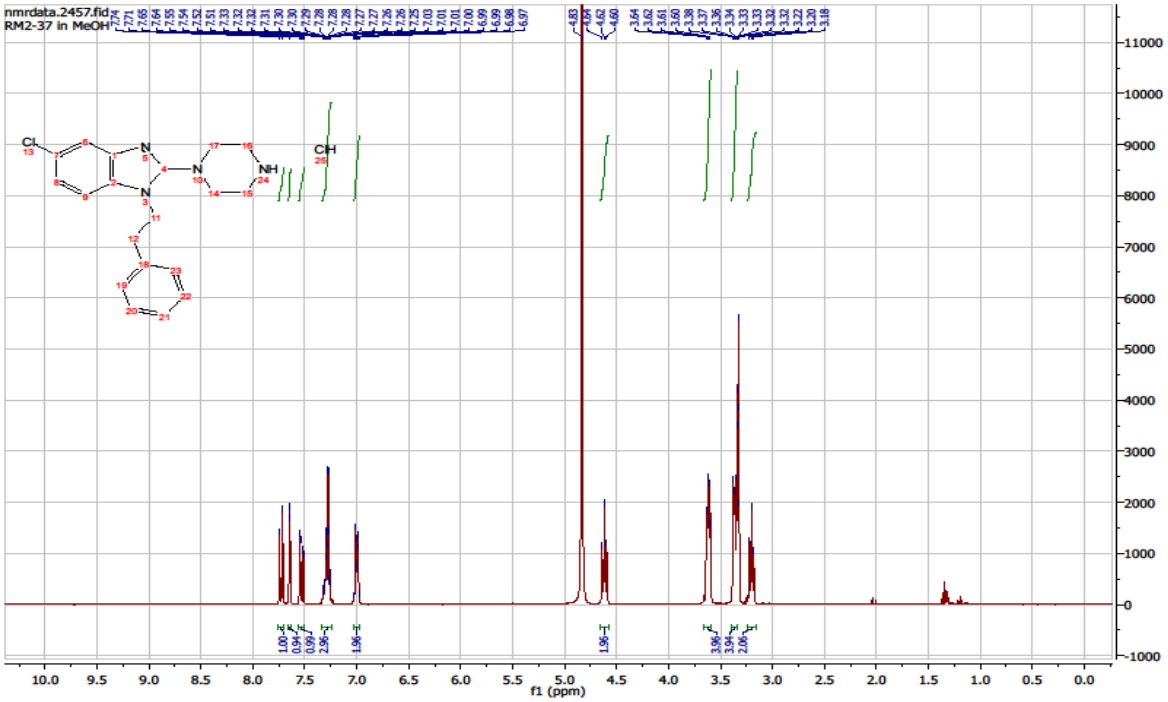


Figure S10: 4-(1-Benzyl-5-chloro-1H benzo[d]imidazol-2-yl)piperazin-2-one (17)

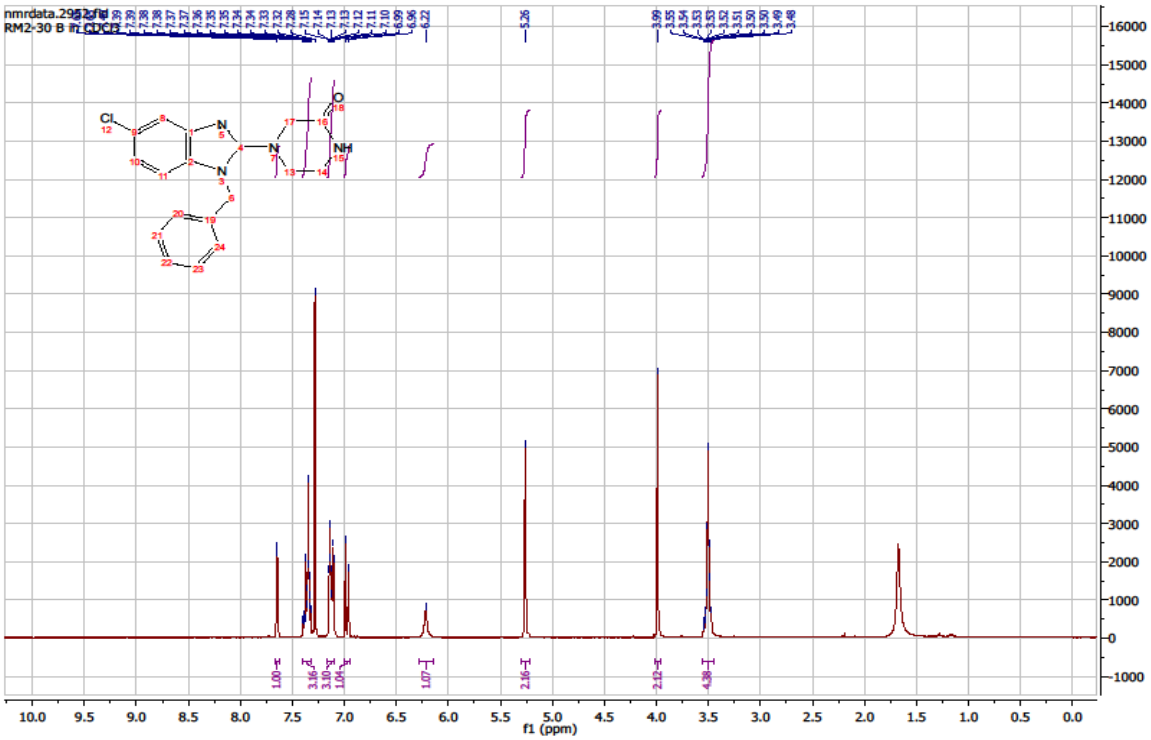


Figure S11: 1-(4-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)ethan-1-one (18)

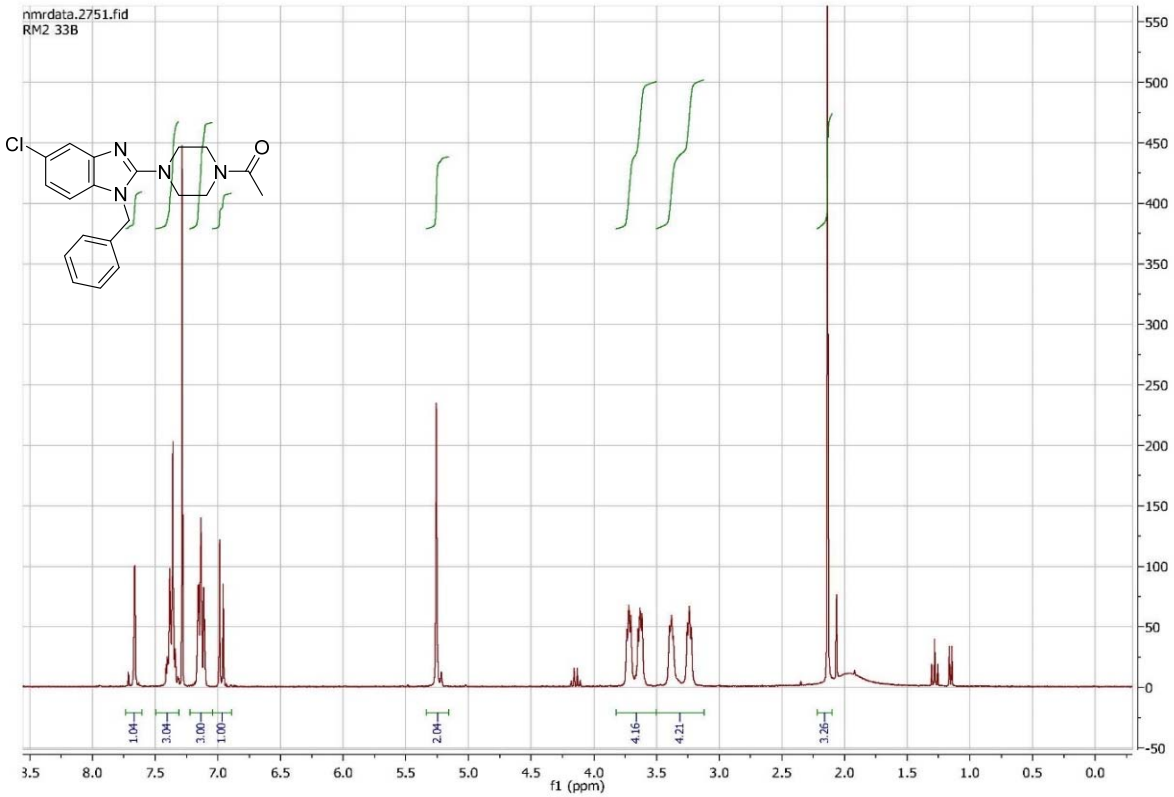


Figure S12: 2-(4-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)acetonitrile (19)

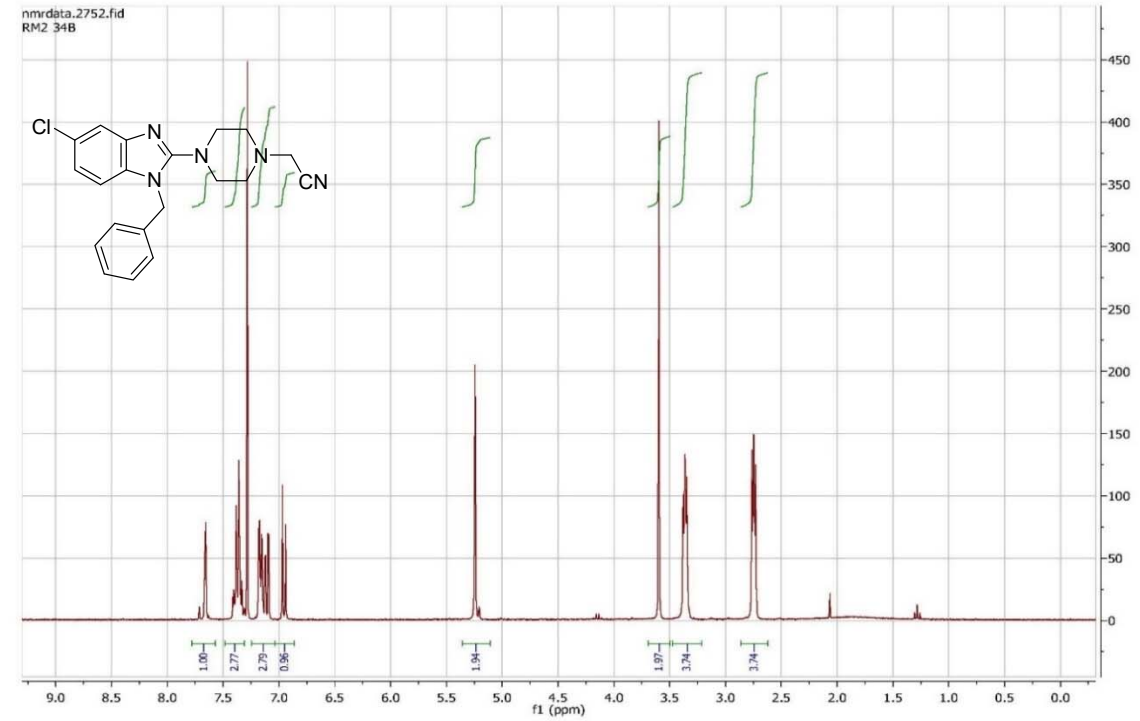


Figure S13: 2-(4-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)acetic acid (20)

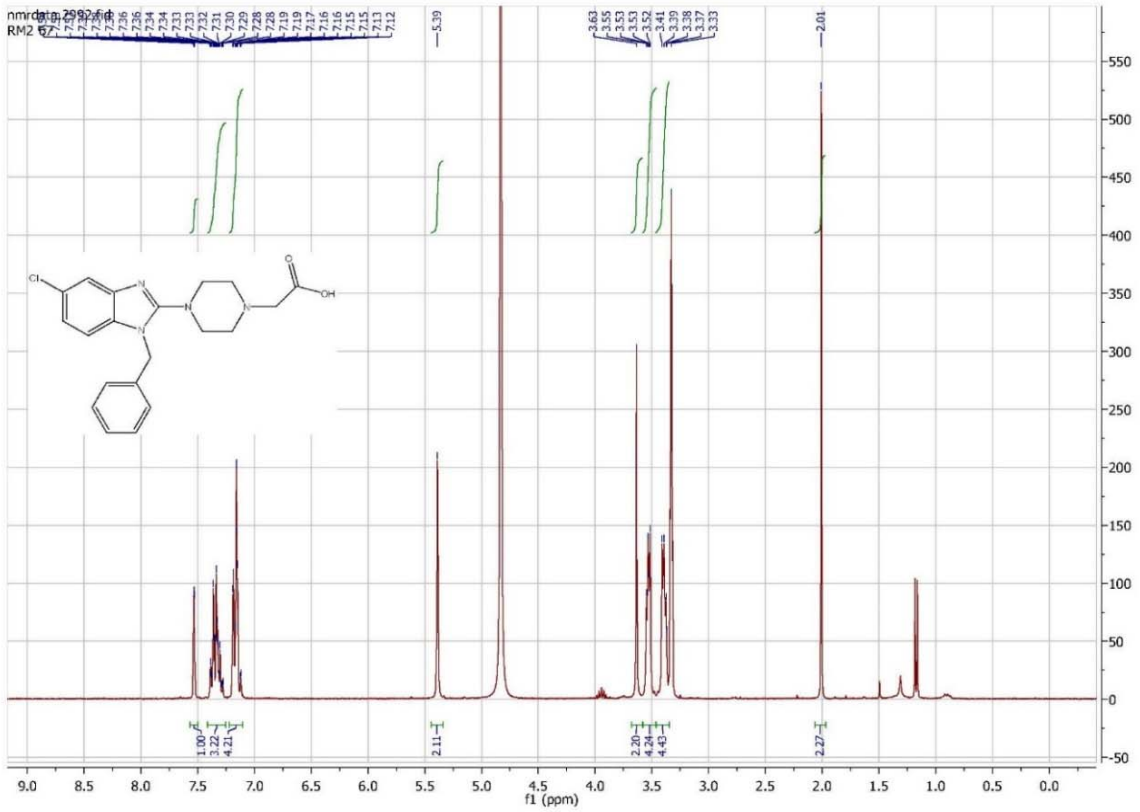


Figure S14: *N*-(3-((1-benzyl-1H-benzo[d]imidazol-2-yl)amino)propyl)-3,5-dichlorobenzamide (21)

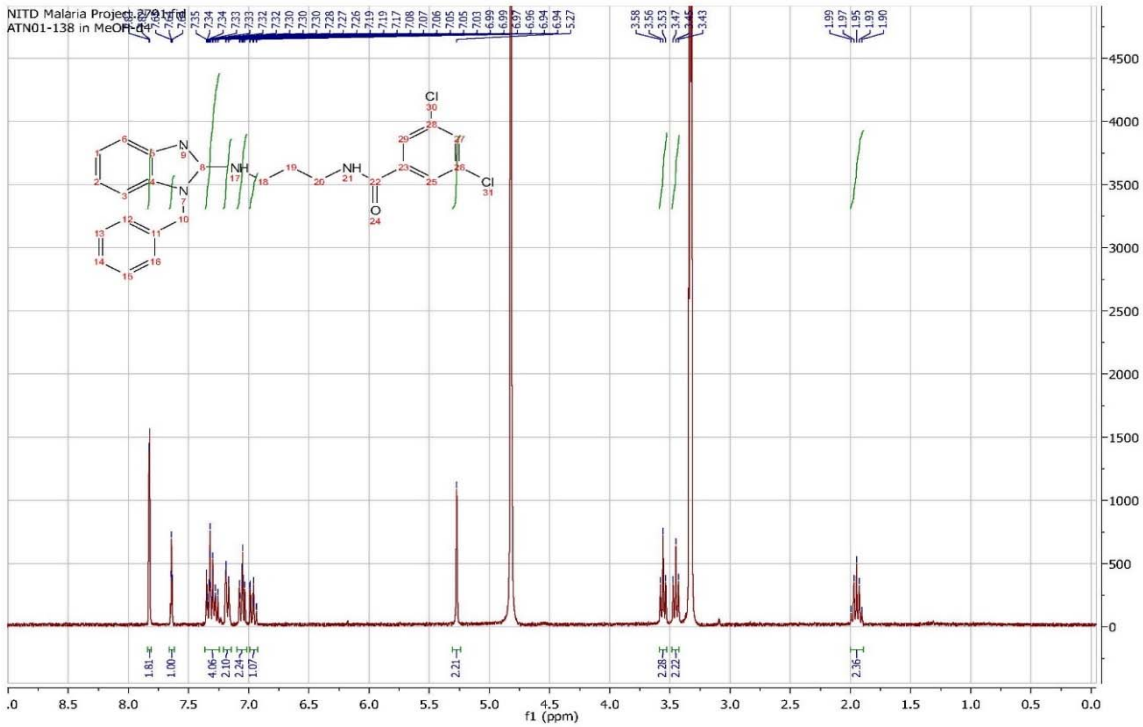


Figure S15: (4-(1-methyl-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)(p-tolyl)methanone hydrochloride (22)

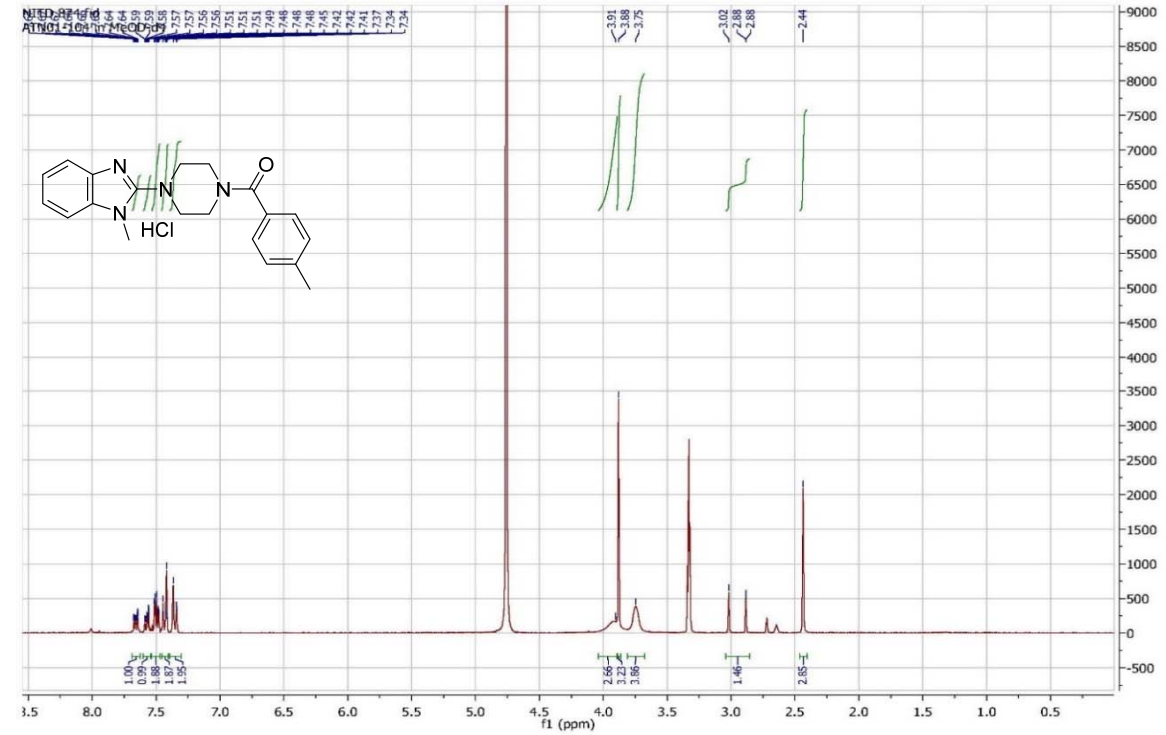


Figure S16: (4-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperazin-1-yl)(p-tolyl)methanone (23)

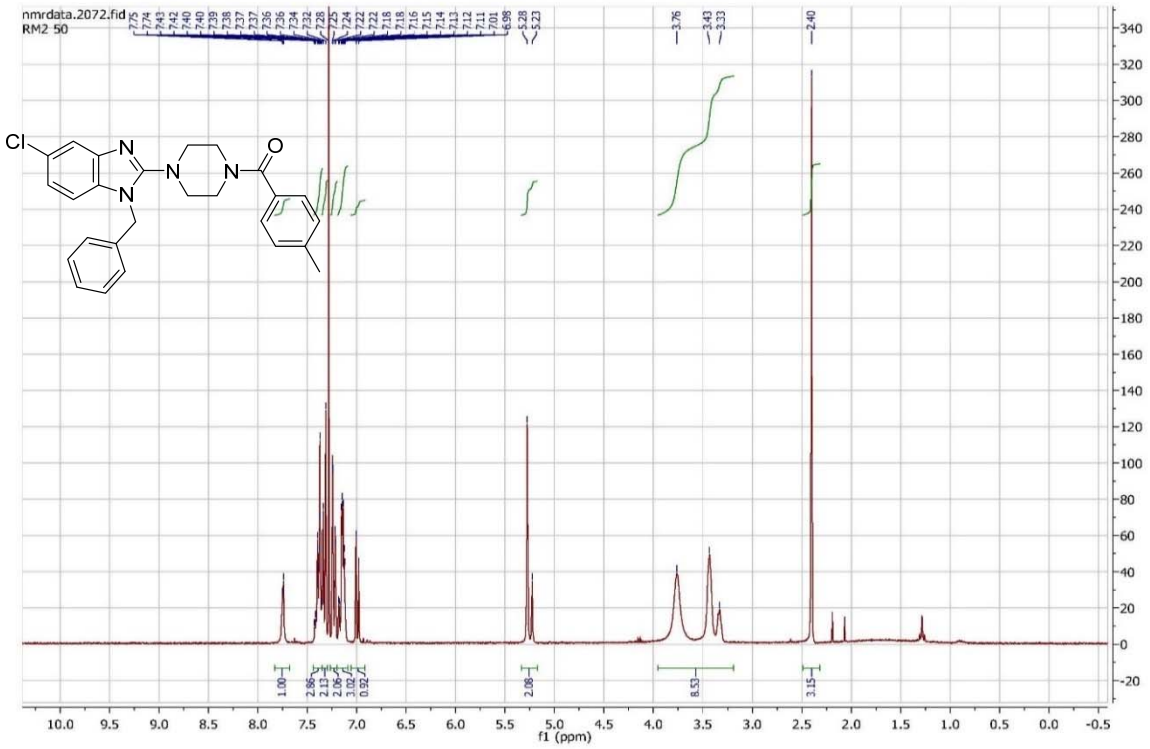


Figure S17: 2-(4-((4-chlorophenyl)sulfonyl)piperazin-1-yl)-1-methyl-1H-benzo[d]imidazole (24)

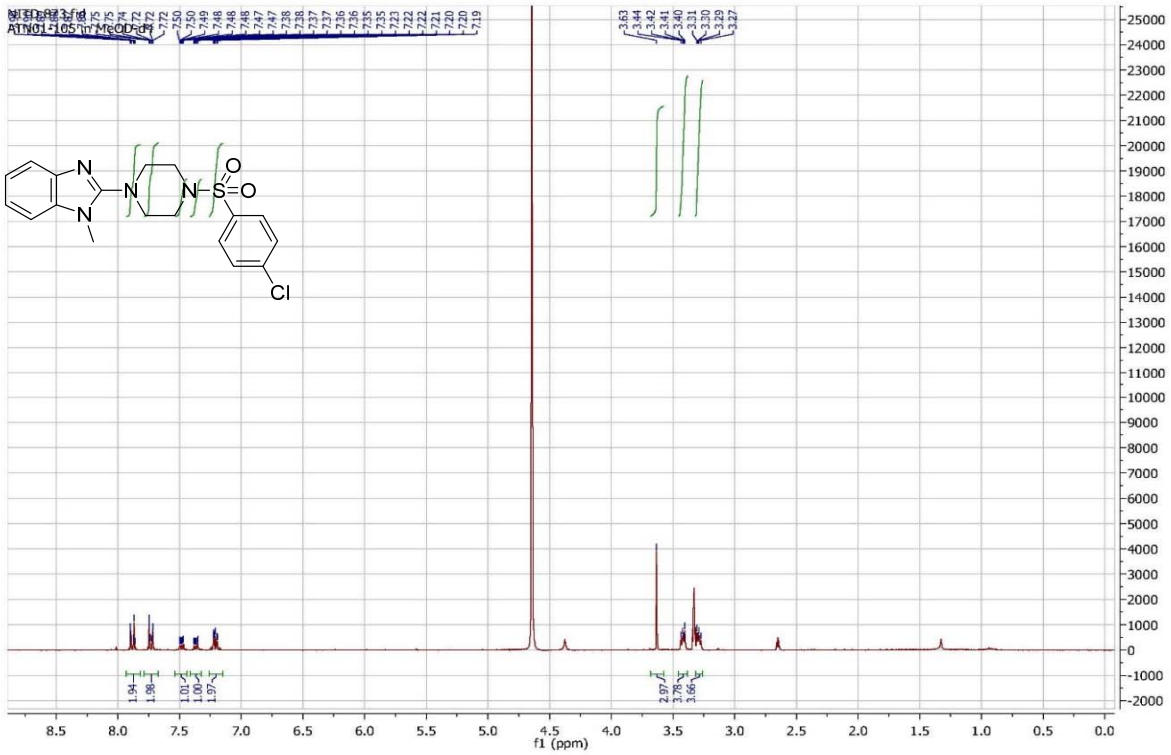


Figure S18: 1-Benzyl-5-chloro-2-(4-((4-chlorophenyl)sulfonyl)piperazin-1-yl)-1H-benzo[d]imidazole (25)

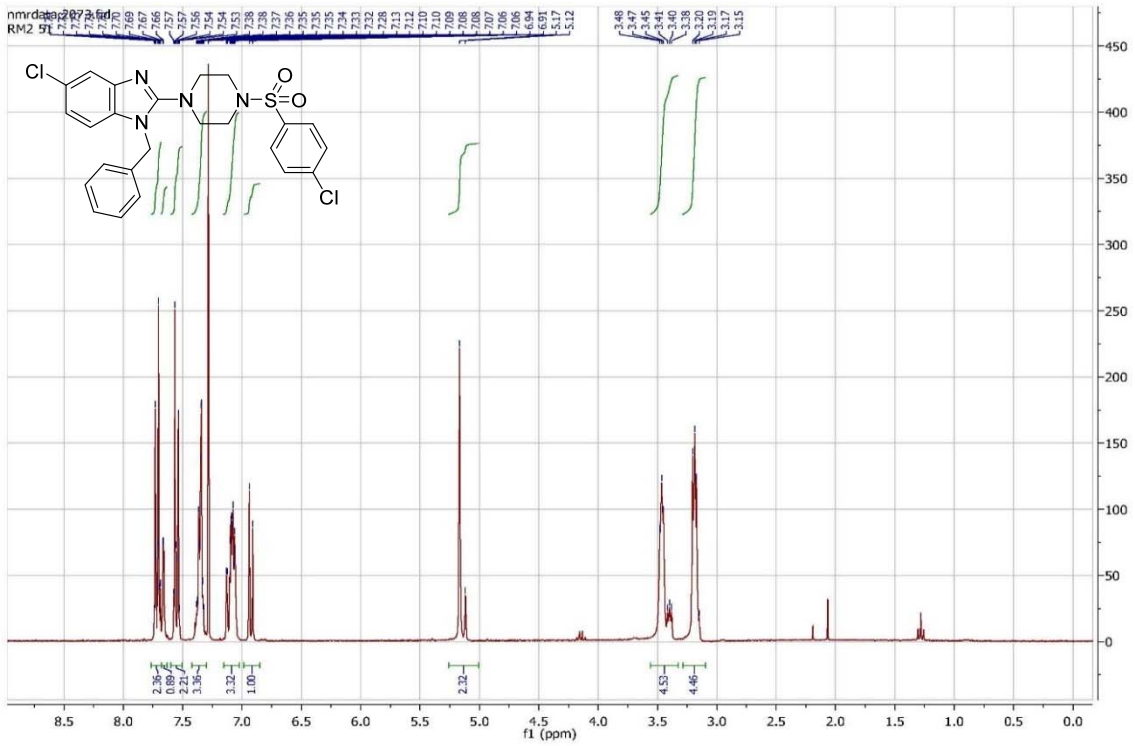


Figure S19: 1-(1-(4-methylbenzyl)-1H-benzo[d]imidazol-2-yl)-*N*-(thiophen-2-ylmethyl)piperidine-4-carboxamide (26)

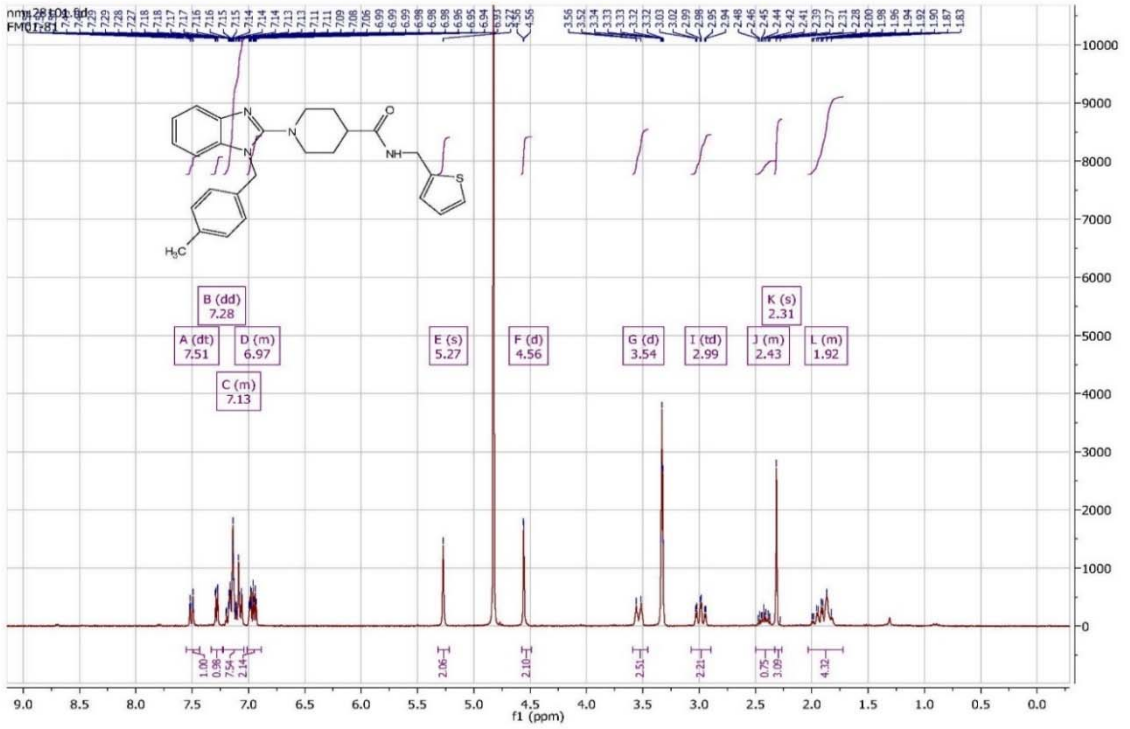


Figure S20: 1-Benzyl-5-chloro-2-[(3S,5R)-3,5-dimethylpiperazin-1-yl]-1H-benzo[d]imidazole (27)

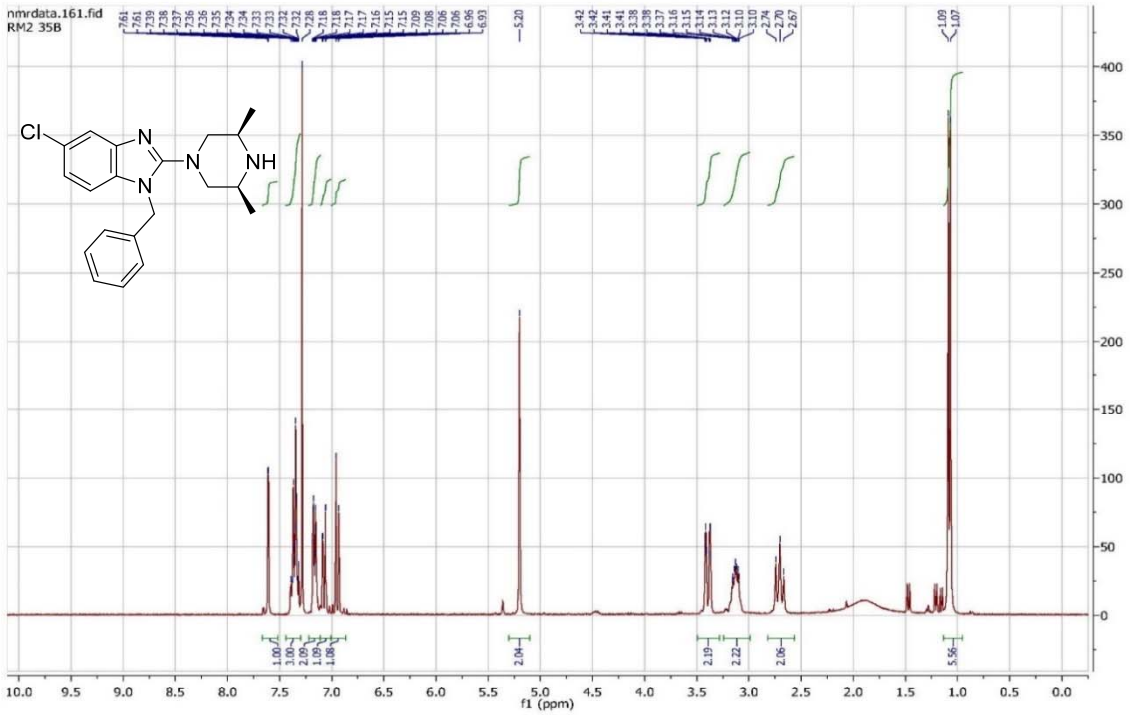


Figure S21: 1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)piperidin-4-amine hydrochloride (28)

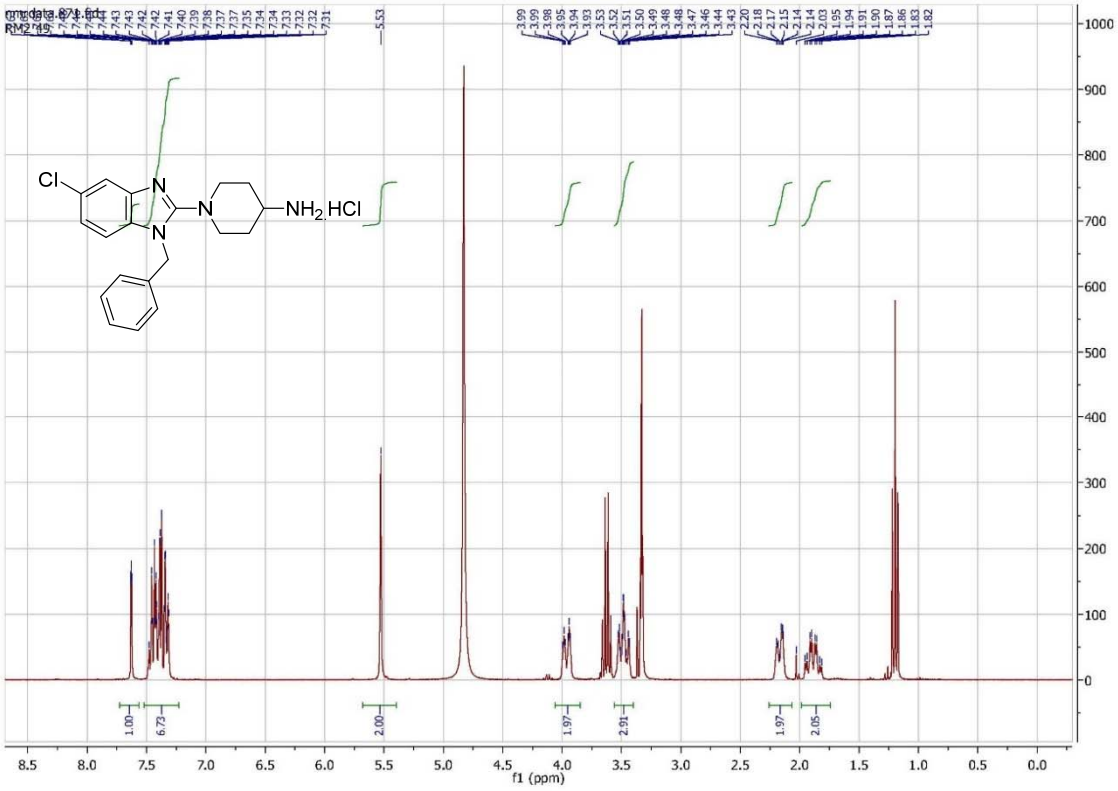


Figure S22: 1-Benzyl-5-chloro-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1H-benzo[d]imidazole hydrochloride (29)

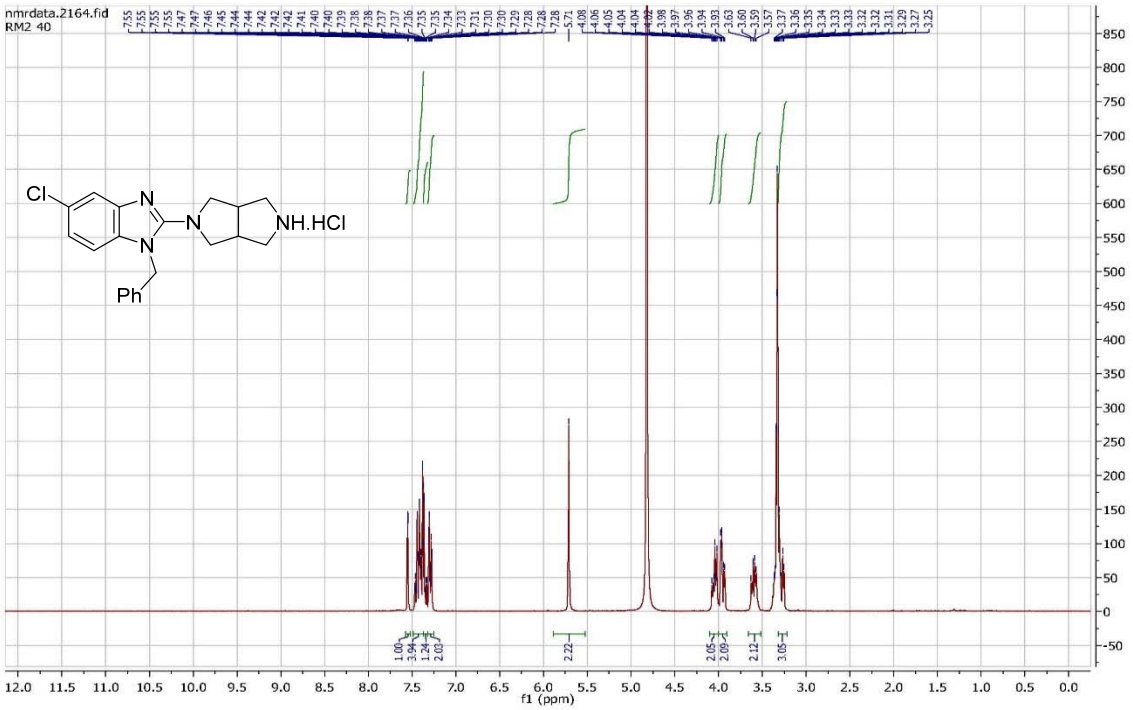


Figure S23: *N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)butane-1,4-diamine (30)

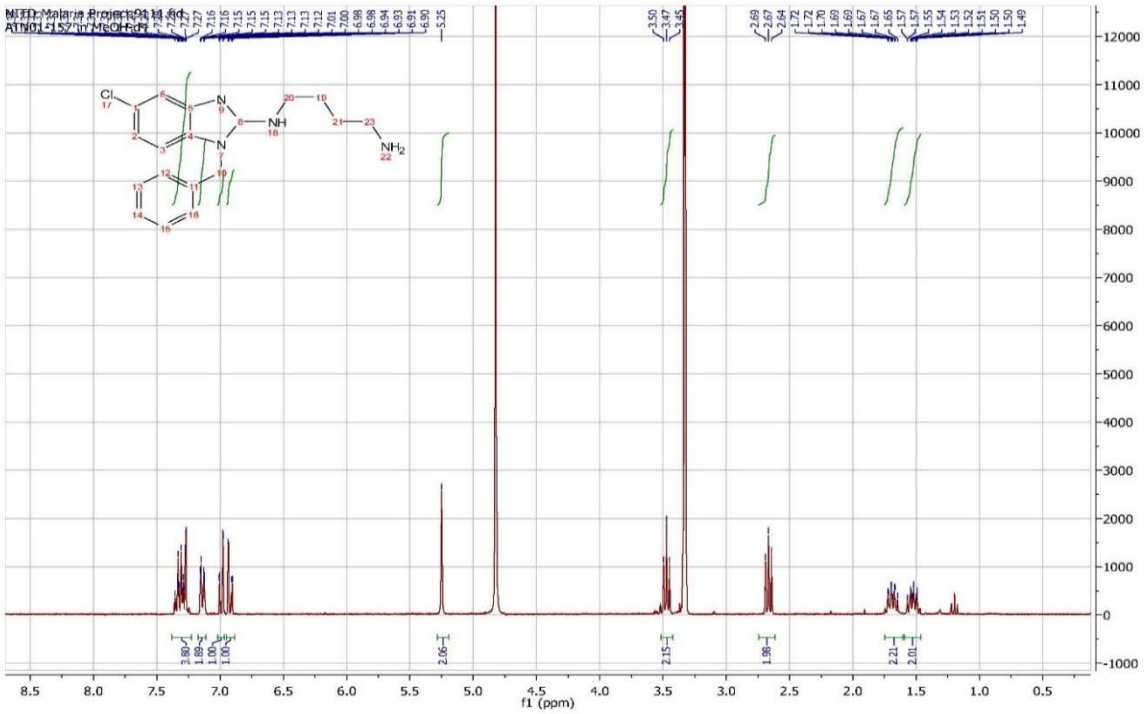


Figure S24: 1-Amino-3-((1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)amino)propan-2-ol acetate (31)

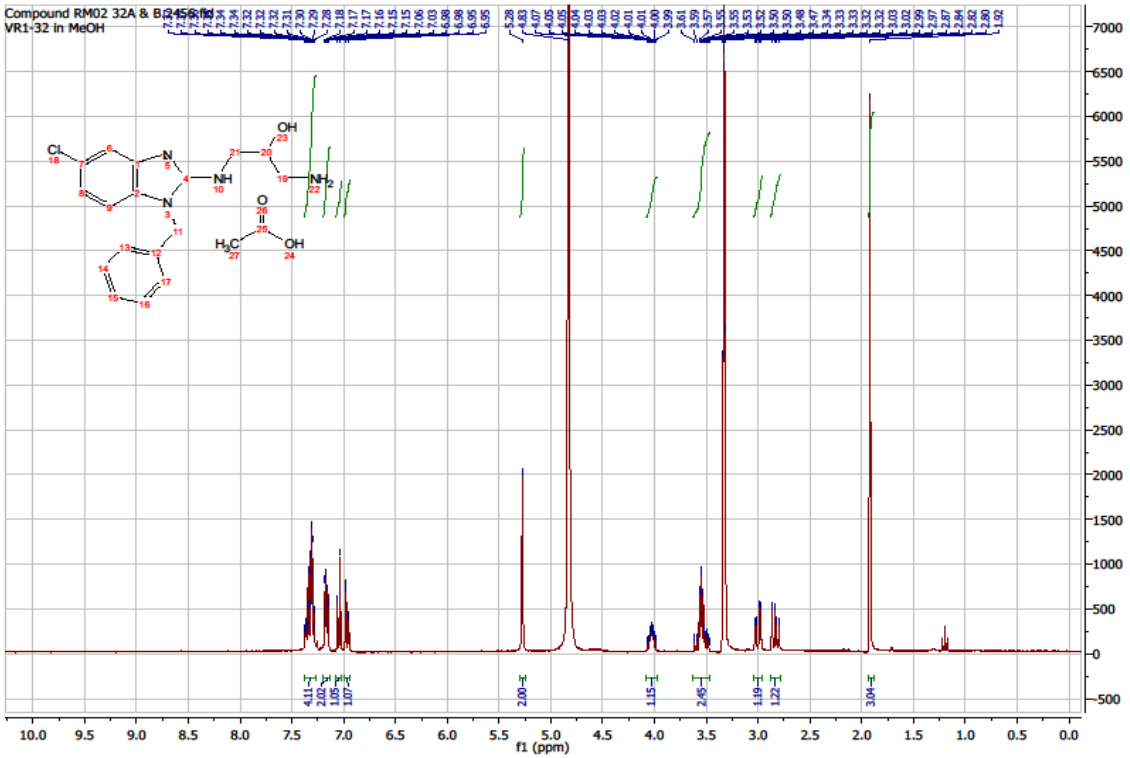


Figure S25: *N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)propane-1,3-diamine hydrochloride (32)

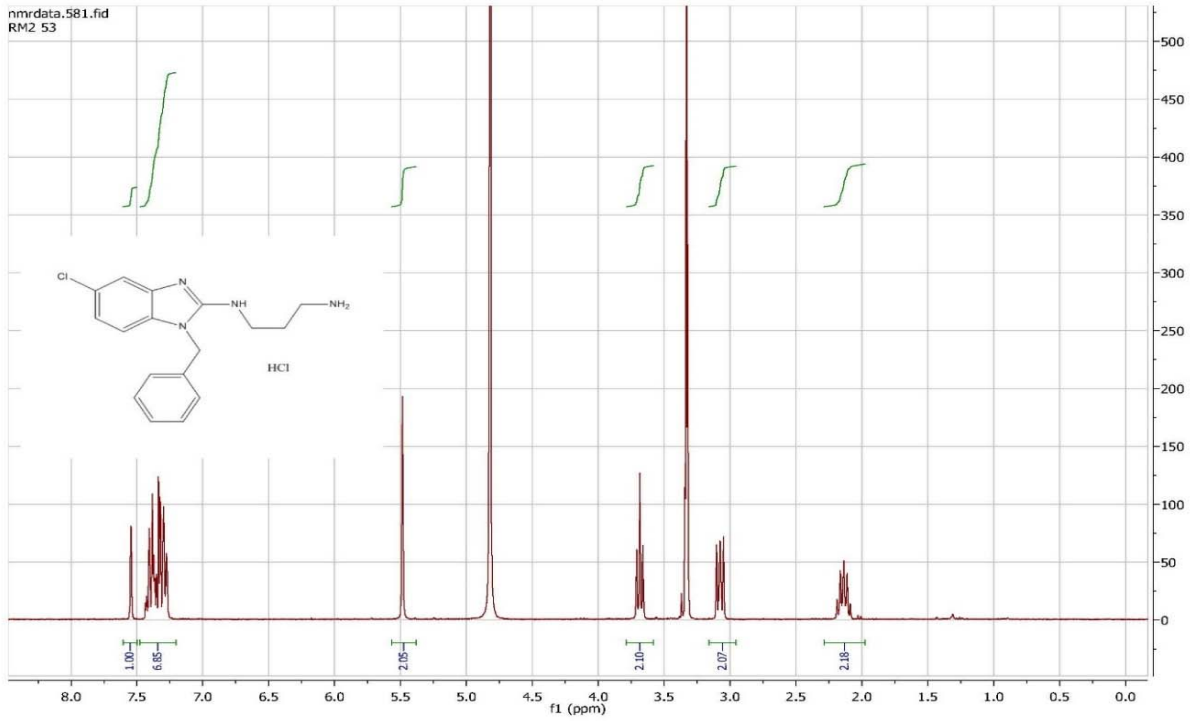


Figure S26: *N*1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)ethane-1,2-diamine (33)

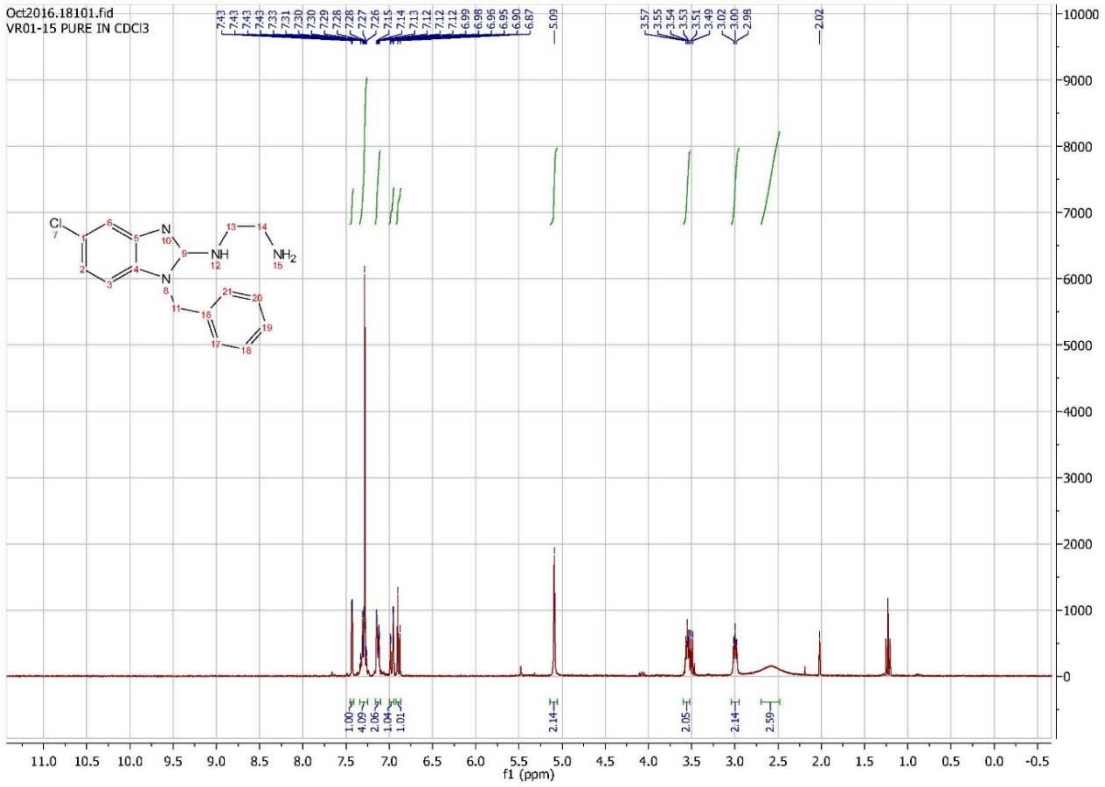


Figure S27: *N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-*N*1-methylethane-1,2-diamine hydrochloride (34)

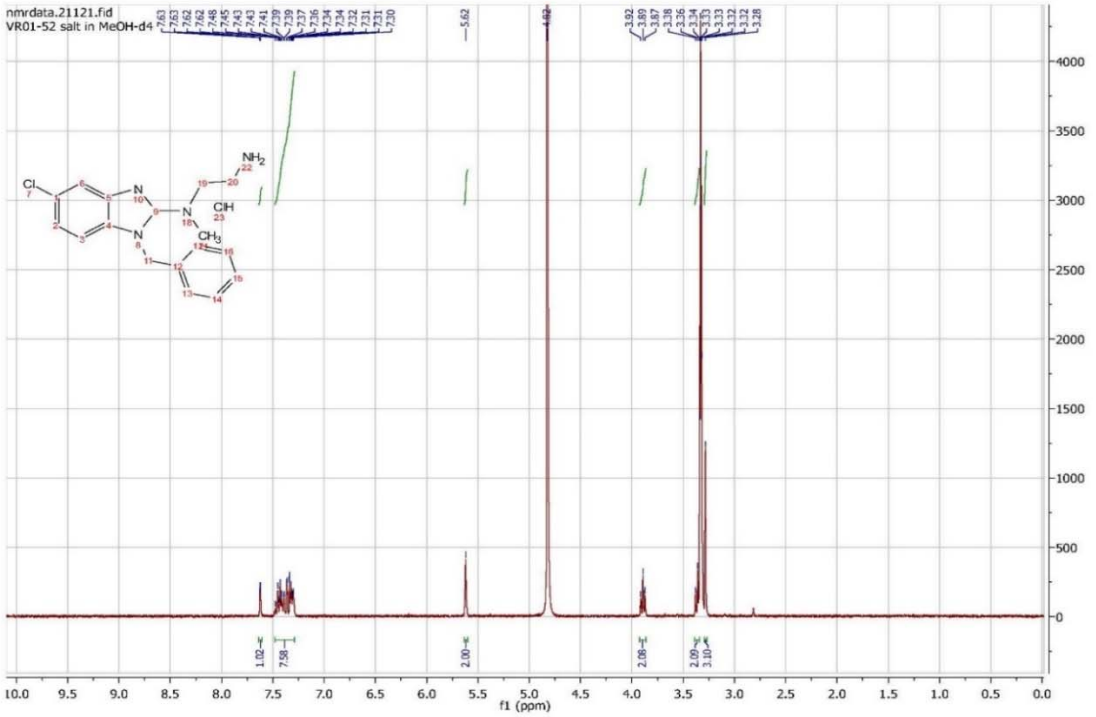


Figure S28: *N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-*N*2,*N*2-dimethylethane-1,2-diamine hydrochloride (35)

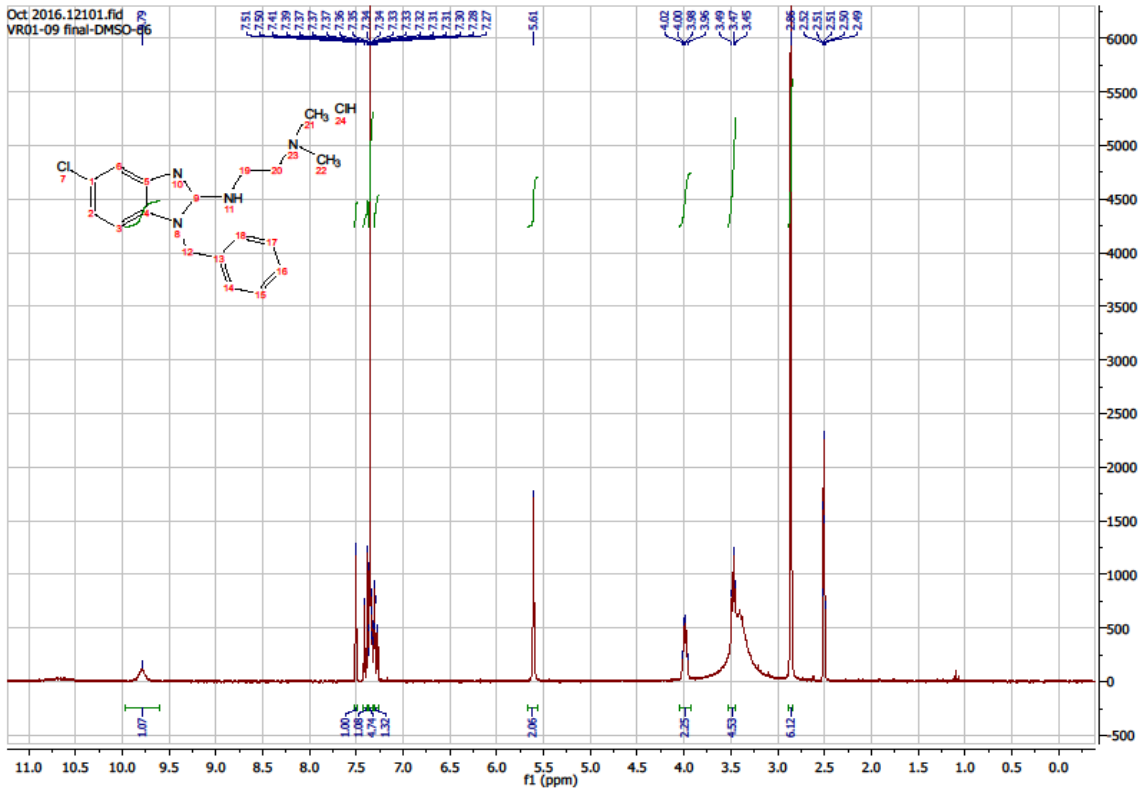


Figure S29: 1-Benzyl-5-chloro-*N*-(2-(piperazin-1-yl)ethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (36)

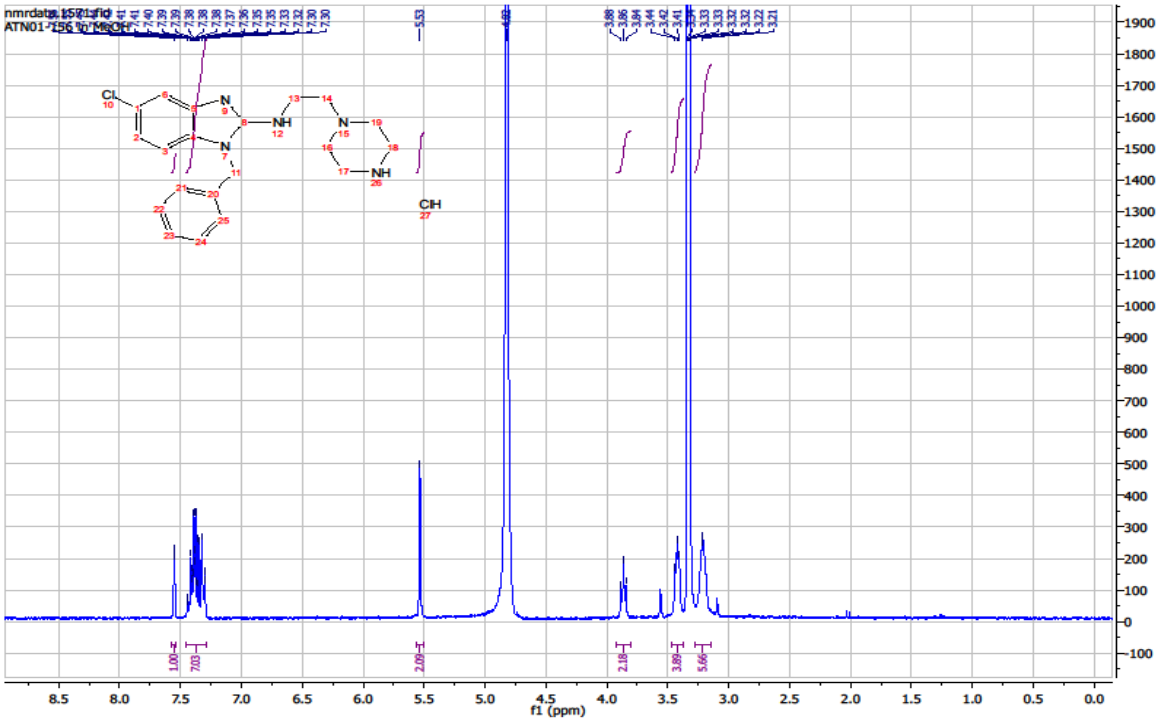


Figure S30: 1-Benzyl-5-chloro-*N*-(2-morpholinoethyl)-1H-benzo[d]imidazol-2-amine (37)

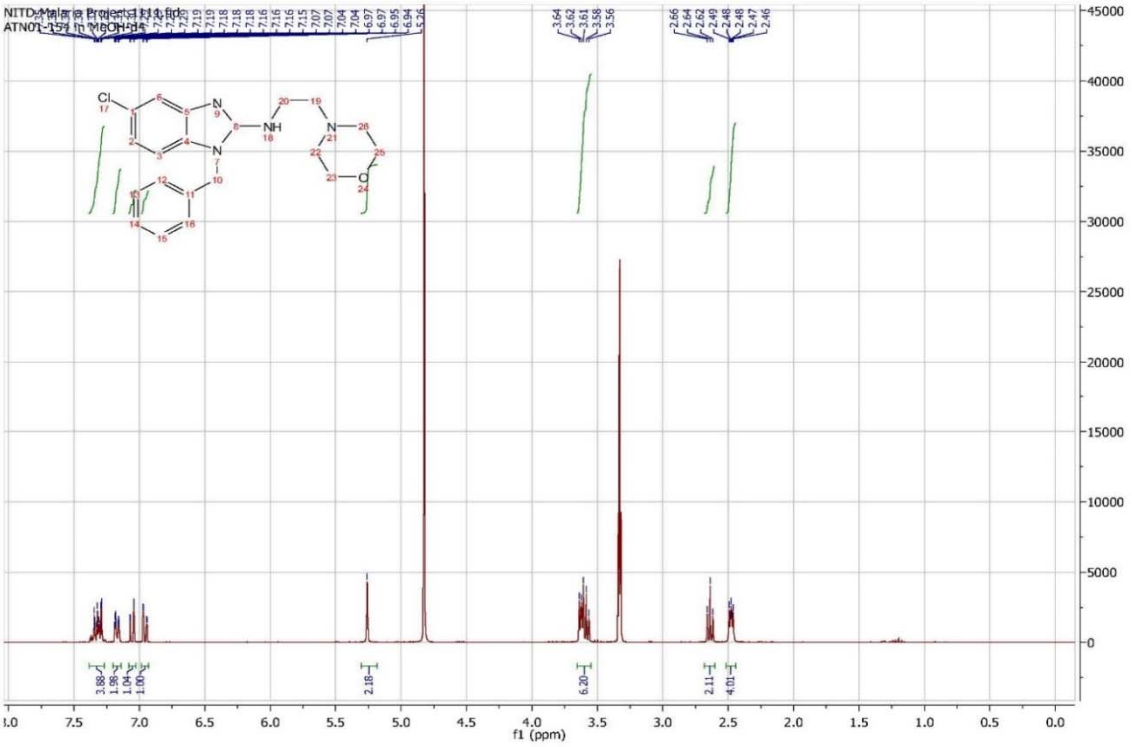


Figure S31: 1-benzyl-5-chloro-*N*-(pyrrolidin-2-ylmethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (38):

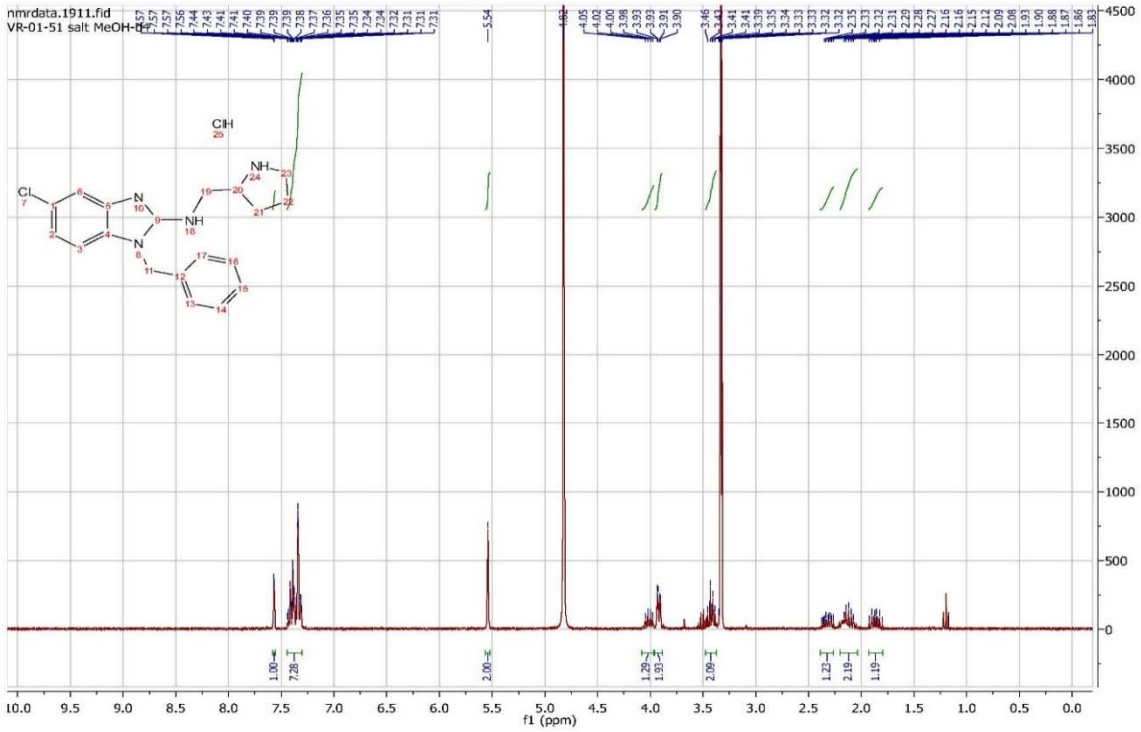


Figure S32: (S)-1-Benzyl-5-chloro-*N*-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (39)

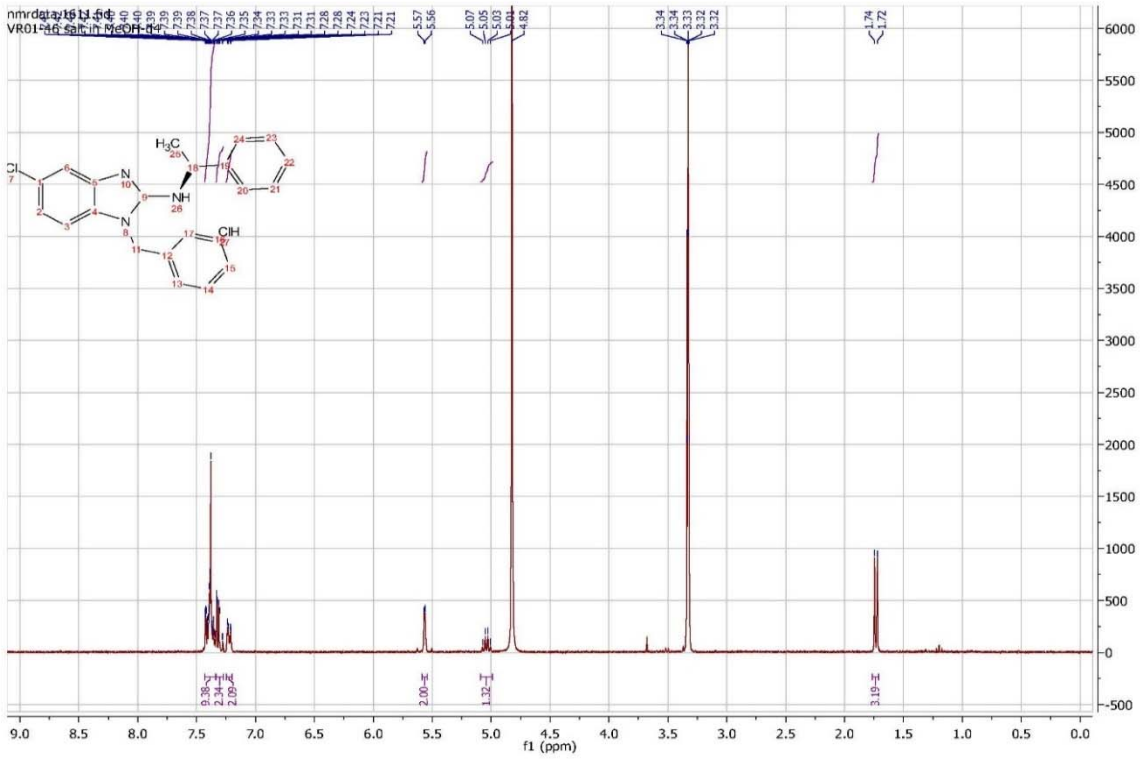


Figure S33: 1-Benzyl-5-chloro-*N*-(pyridin-2-ylmethyl)-1H-benzo[d]imidazol-2-amine (40)

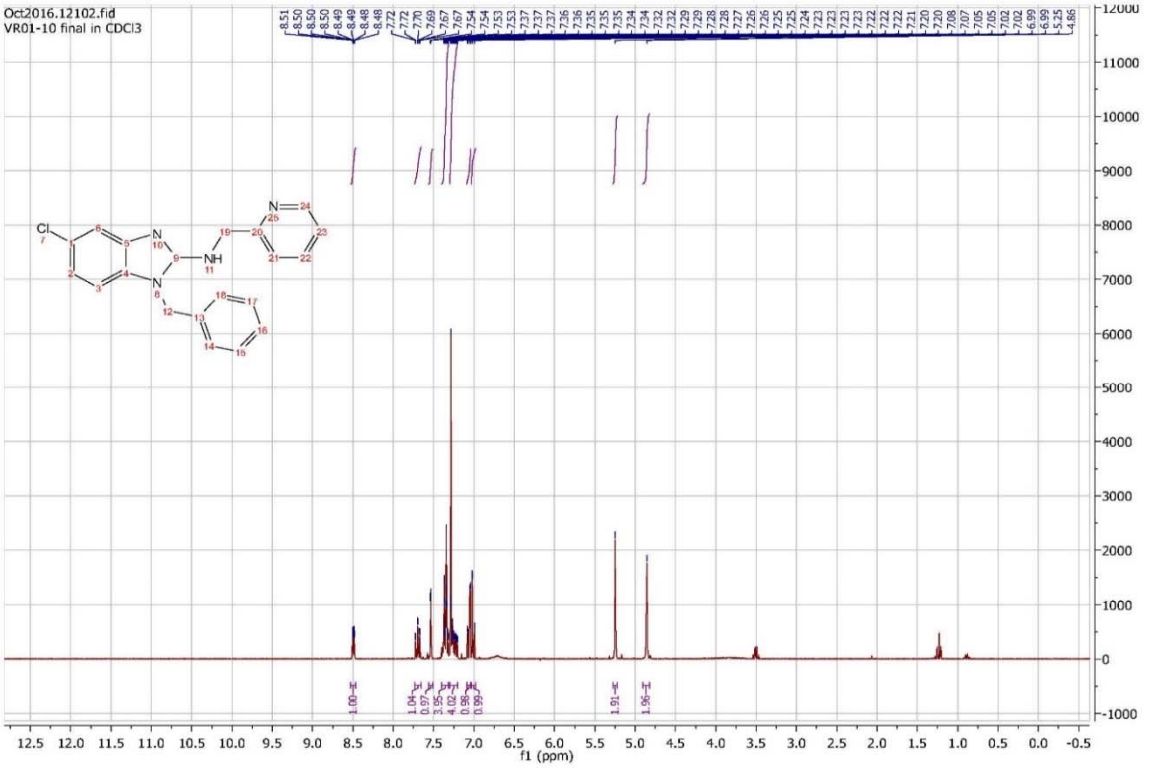


Figure S34: *N*1-(1-benzyl-5-bromo-1H-benzo[d]imidazol-2-yl)propane-1,3-diamine (41)

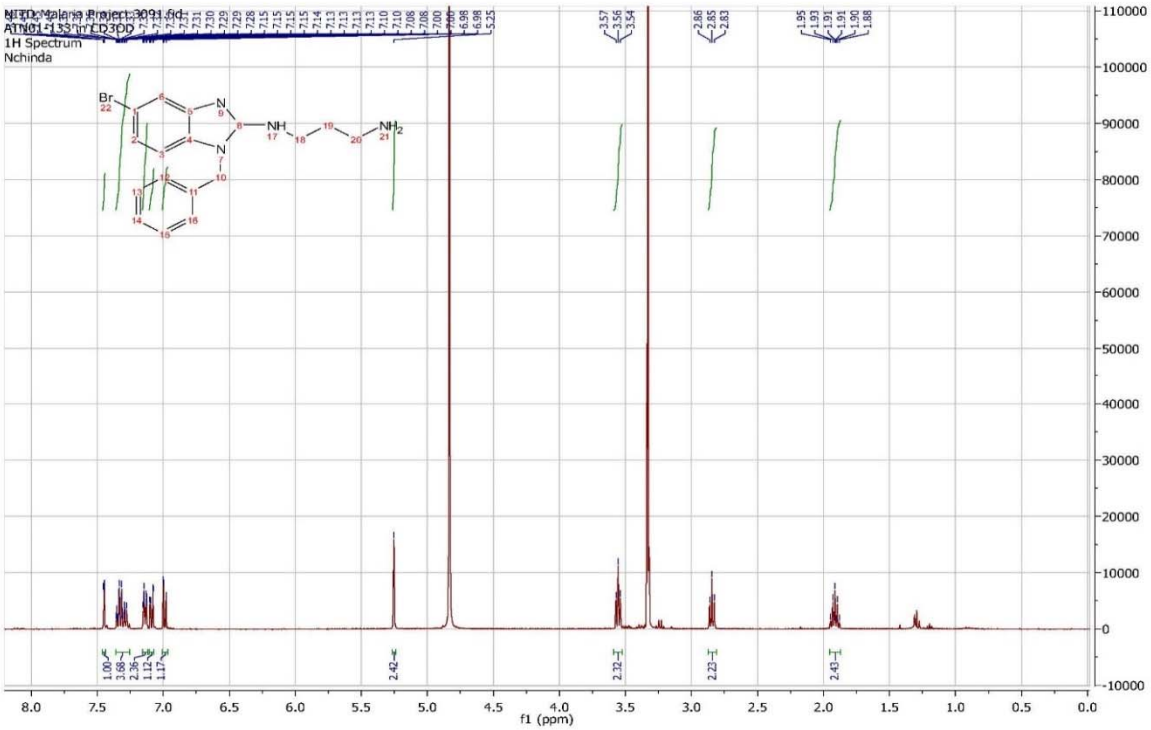


Figure S35: 1-benzyl-4,5-dichloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (42a)

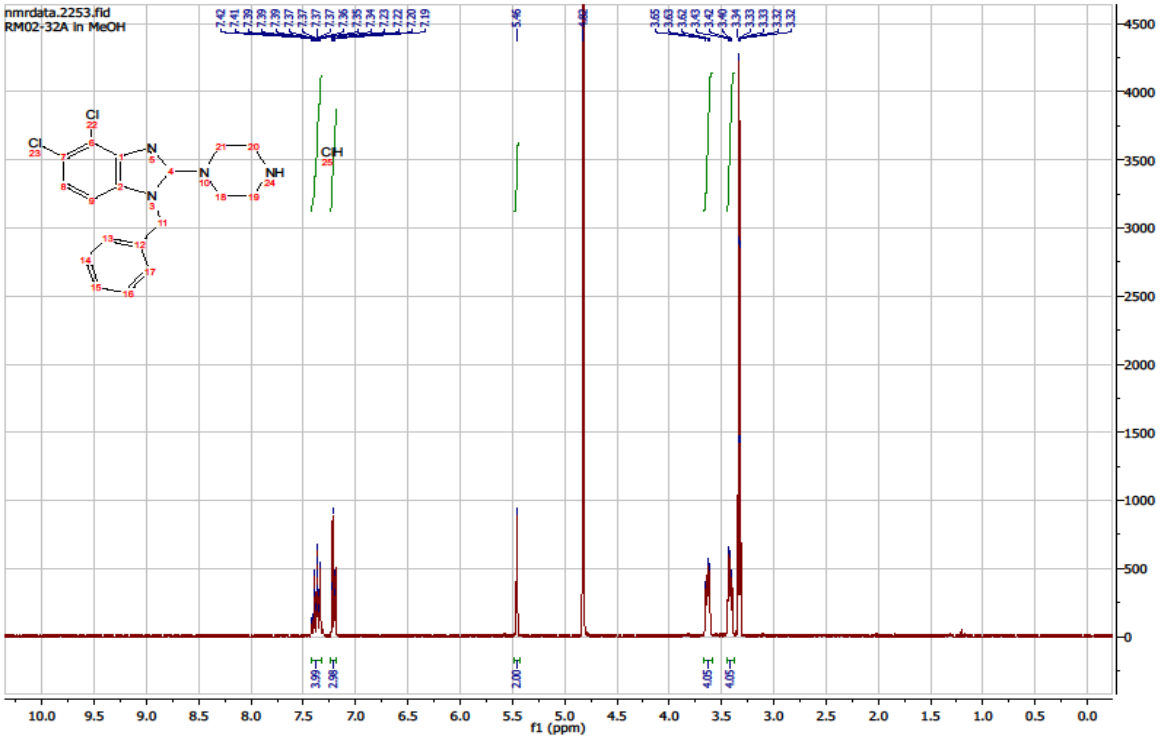


Figure S36: 1-Benzyl-4-bromo-5-chloro-2-(piperazin-1-yl)-1H-benzo[d]imidazole (42k)

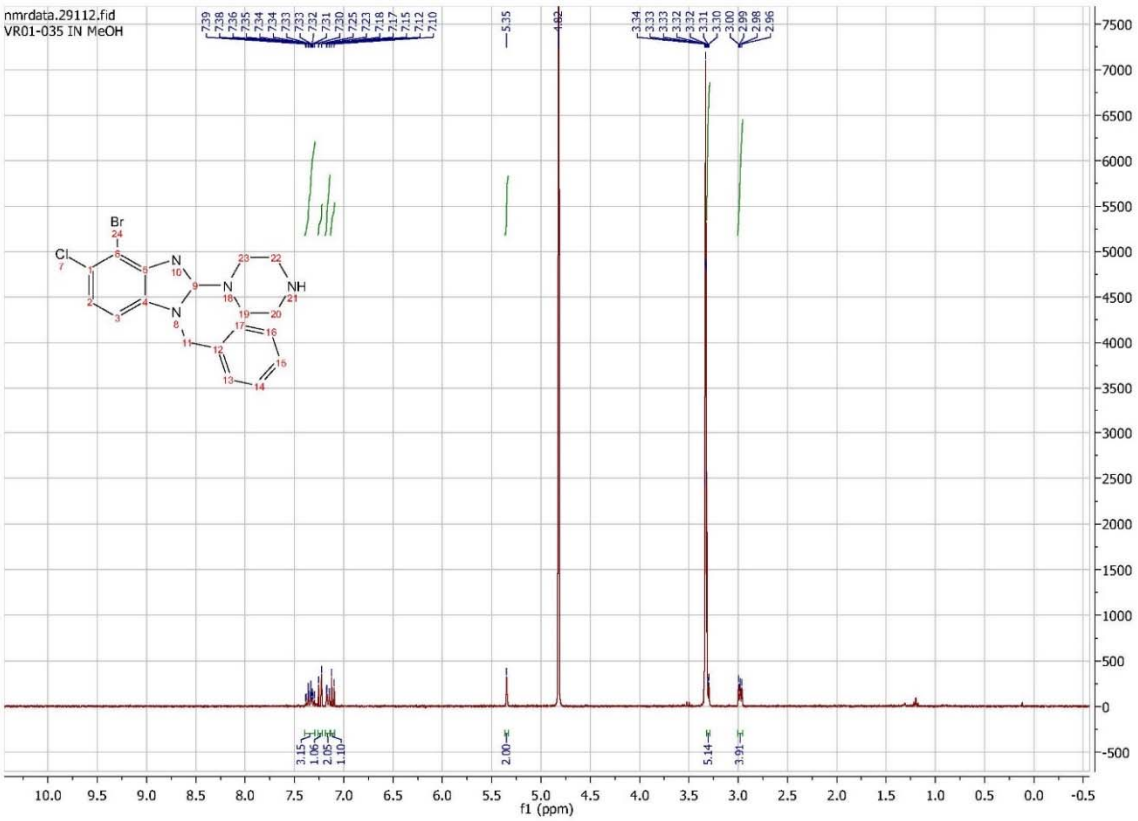


Figure S37: *N*1,*N*1-Dibenzyl-*N*2-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)ethane-1,2-diamine hydrochloride (43a)

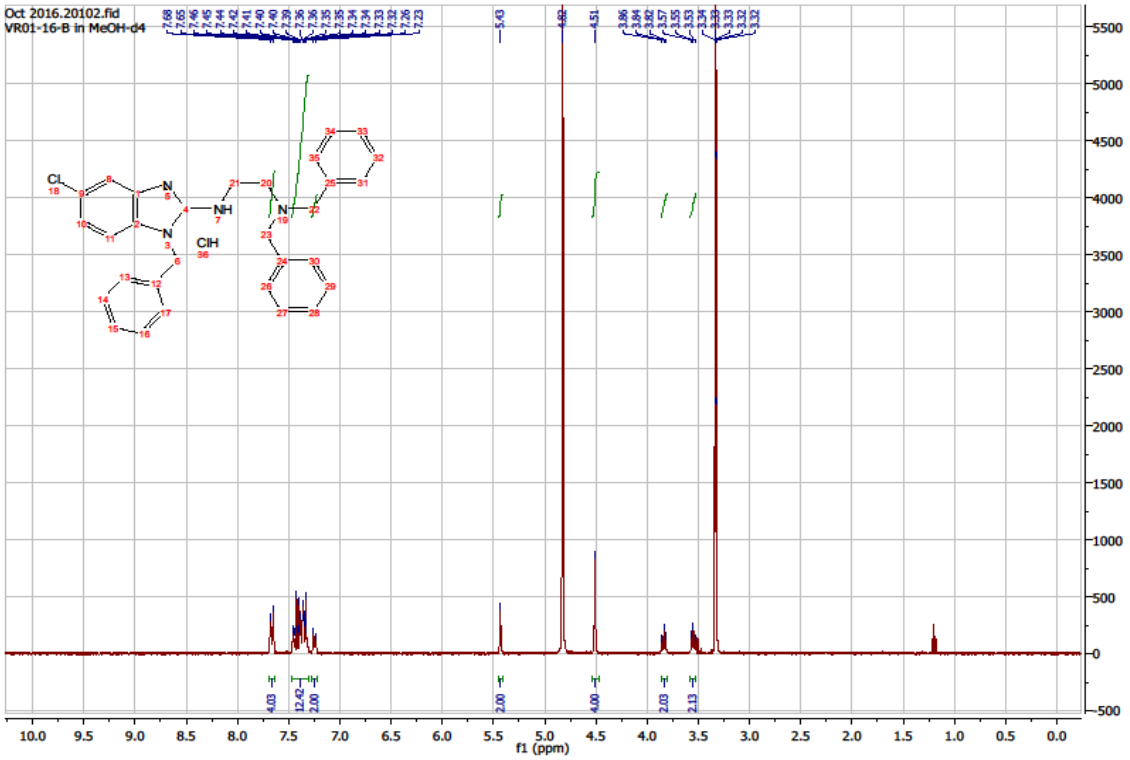


Figure S38: *N*1-benzyl-*N*2-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)ethane-1,2-diamine hydrochloride (43b)

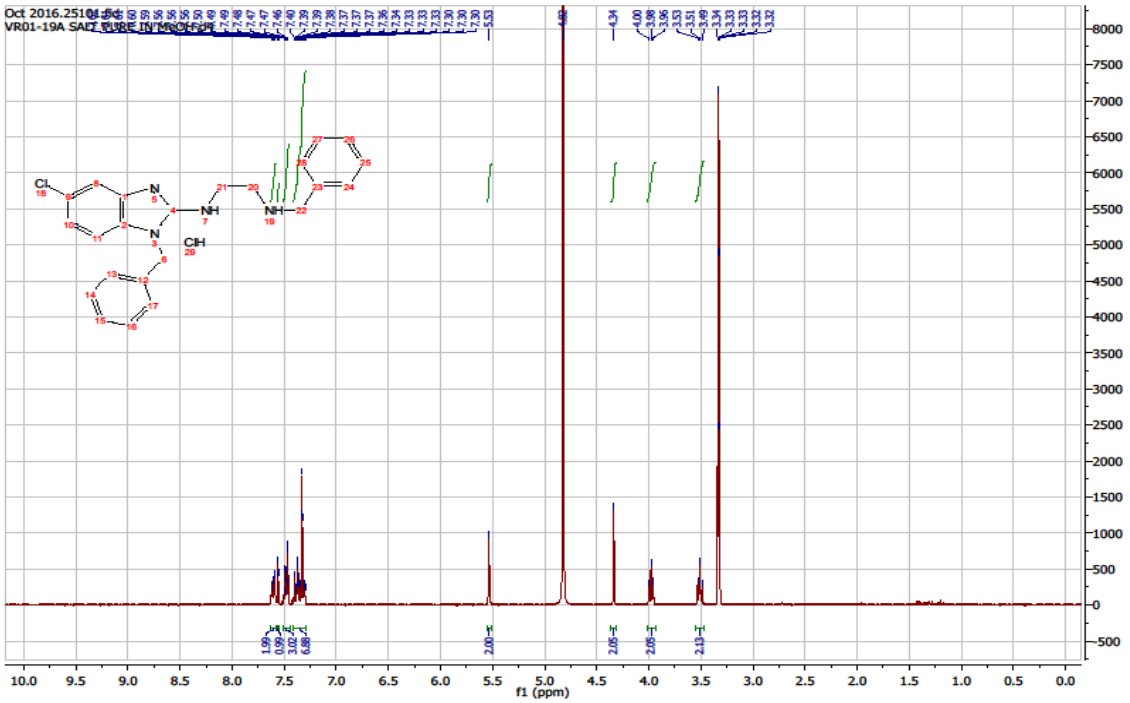


Figure S39: *N*1-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-*N*2-(pyridin-4-ylmethyl)ethane-1,2-diamine hydrochloride (43c)

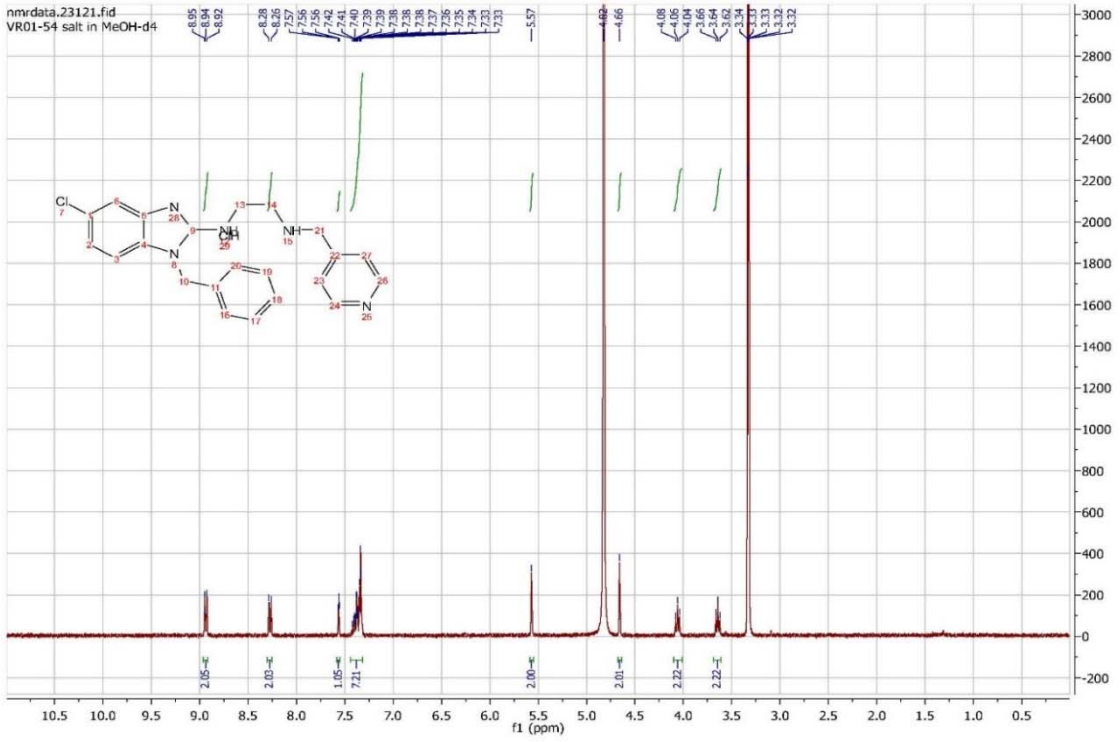


Figure S40: *N*1-(1-Benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-*N*2-(4-(trifluoromethyl)benzyl)ethane-1,2-diamine hydrochloride (43d)

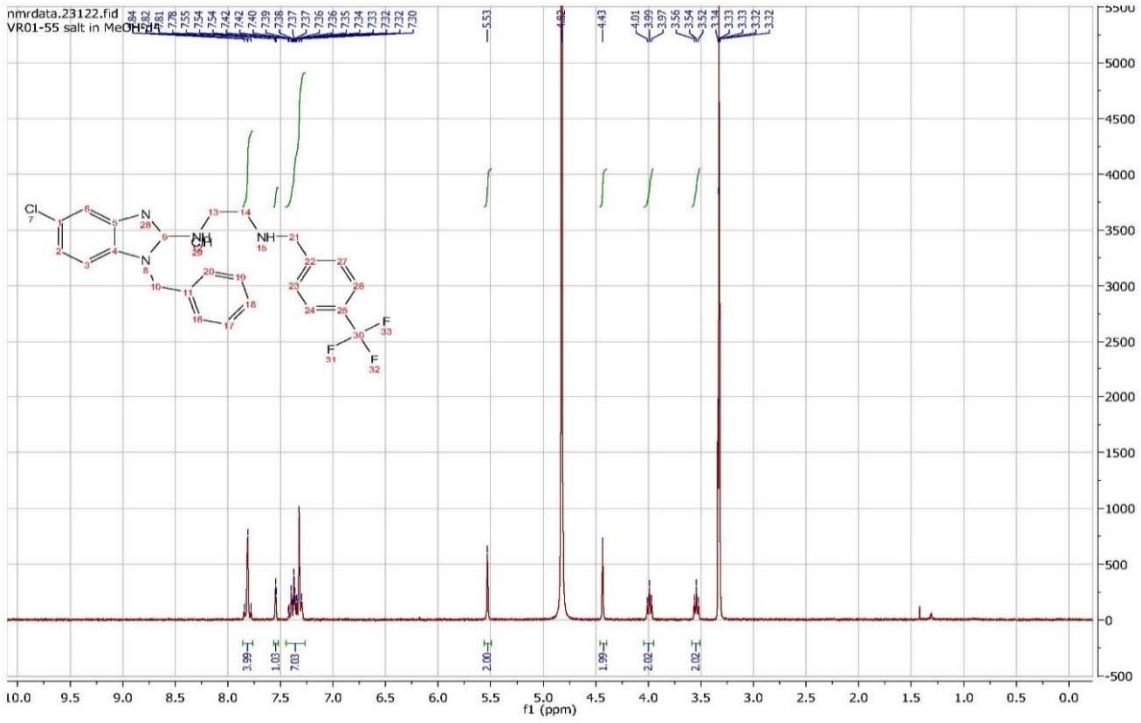


Figure S41: 1-benzyl-5-chloro-2-(piperidin-4-yl)-1H-benzo[d]imidazole (46a)

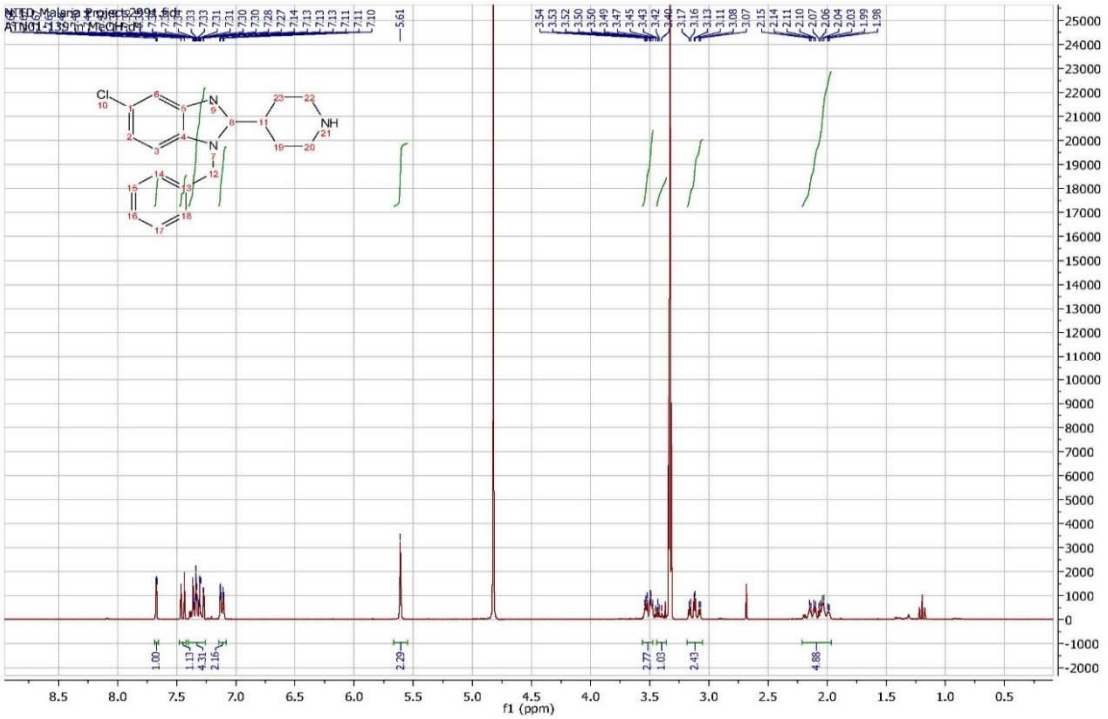


Figure S42: 1-Benzyl-5-bromo-2-(piperidin-4-yl)-1H-benzo[d]imidazole (46b)

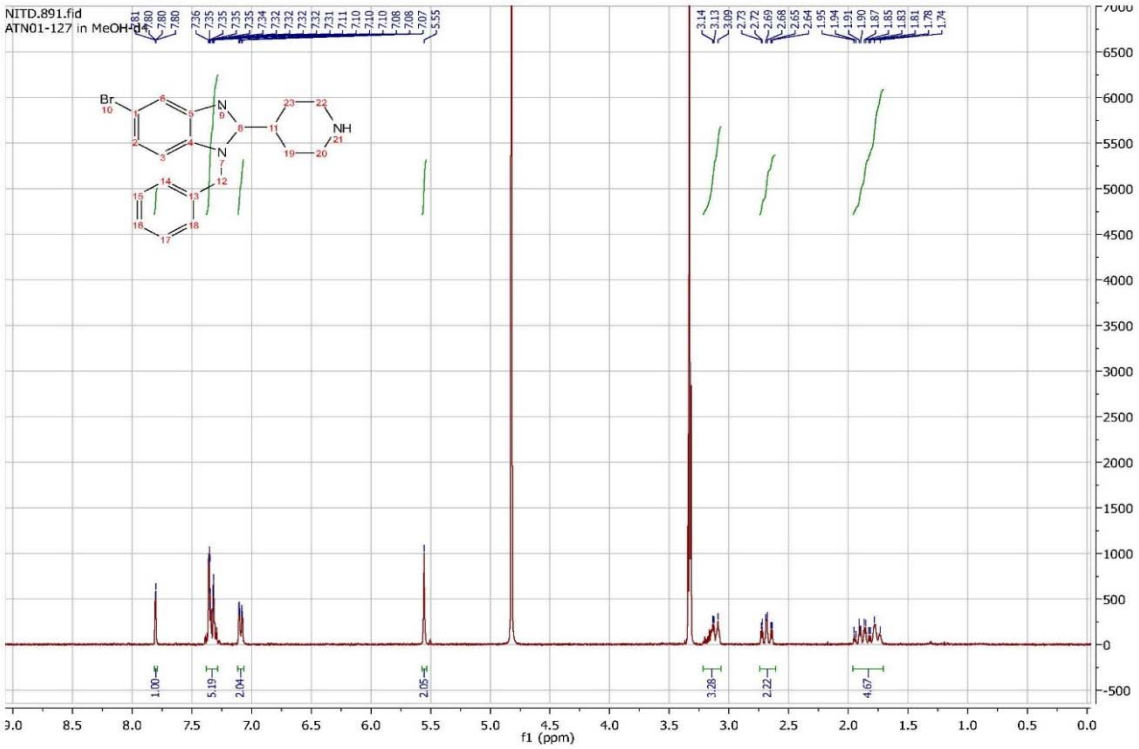


Figure S43: 1-Benzyl-2-(piperidin-4-yl)-5-(trifluoromethyl)-1H-benzo[d]imidazole hydrochloride (46c)

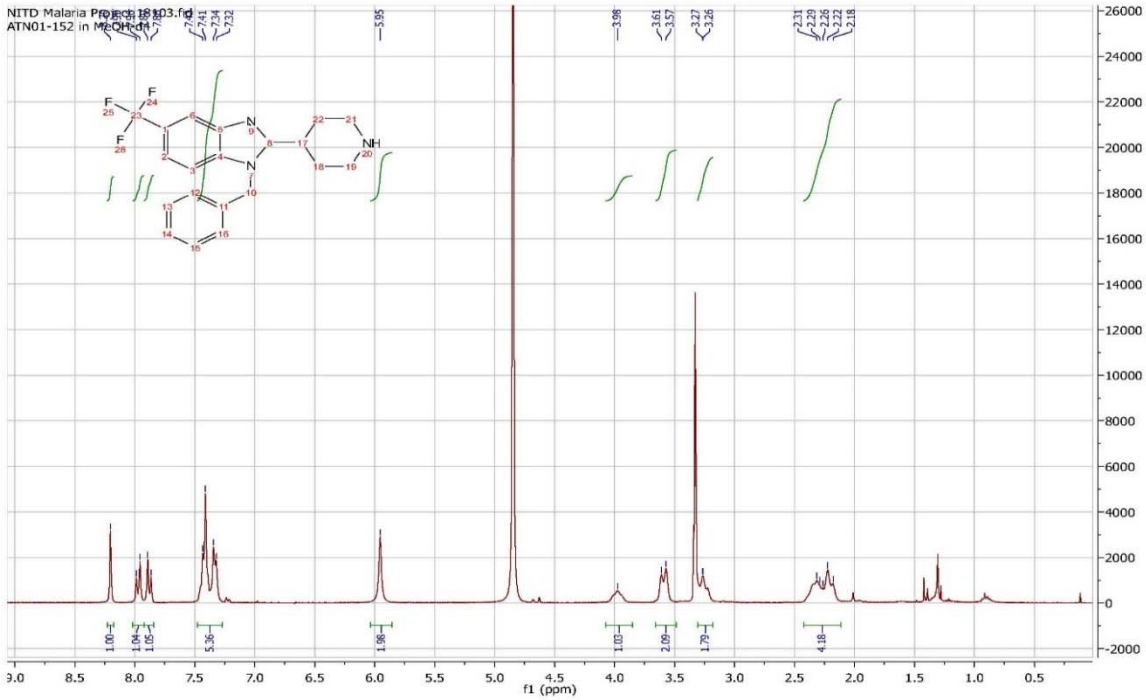


Figure S44: Methyl 1-benzyl-2-(piperidin-4-yl)-1H-benzo[d]imidazole-5-carboxylate (46d)

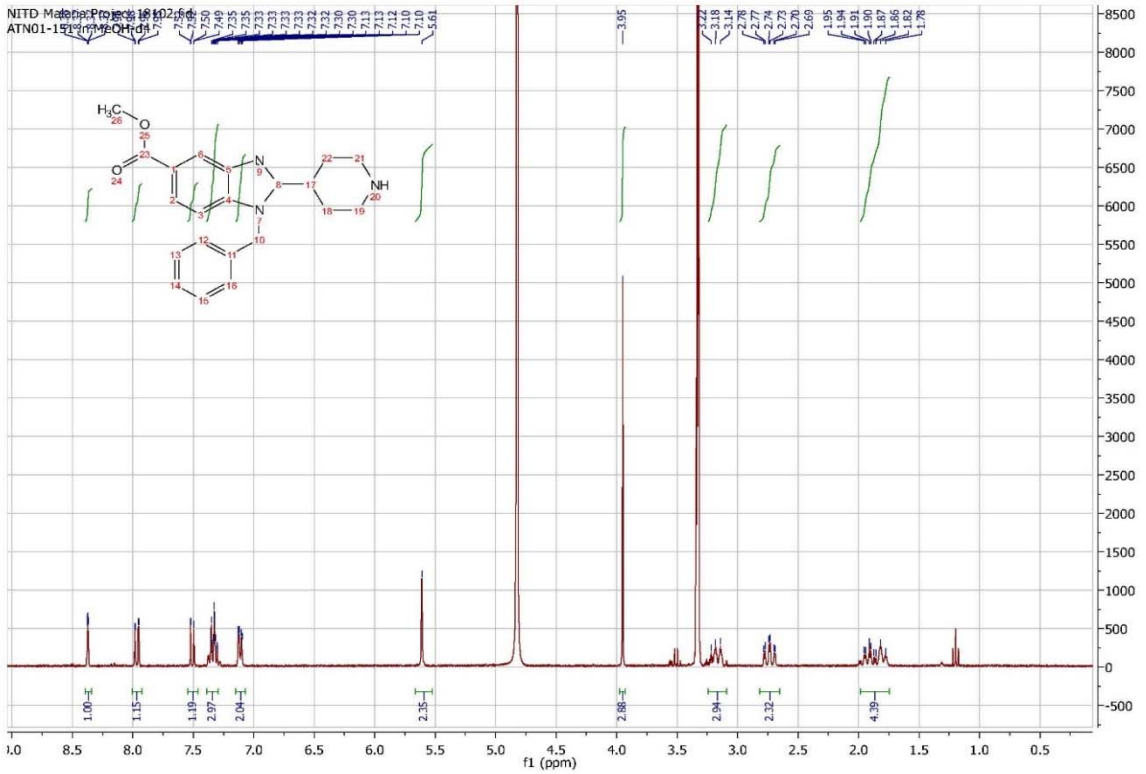


Figure S45: 1-Benzyl-5-(methylsulfonyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride (46e)

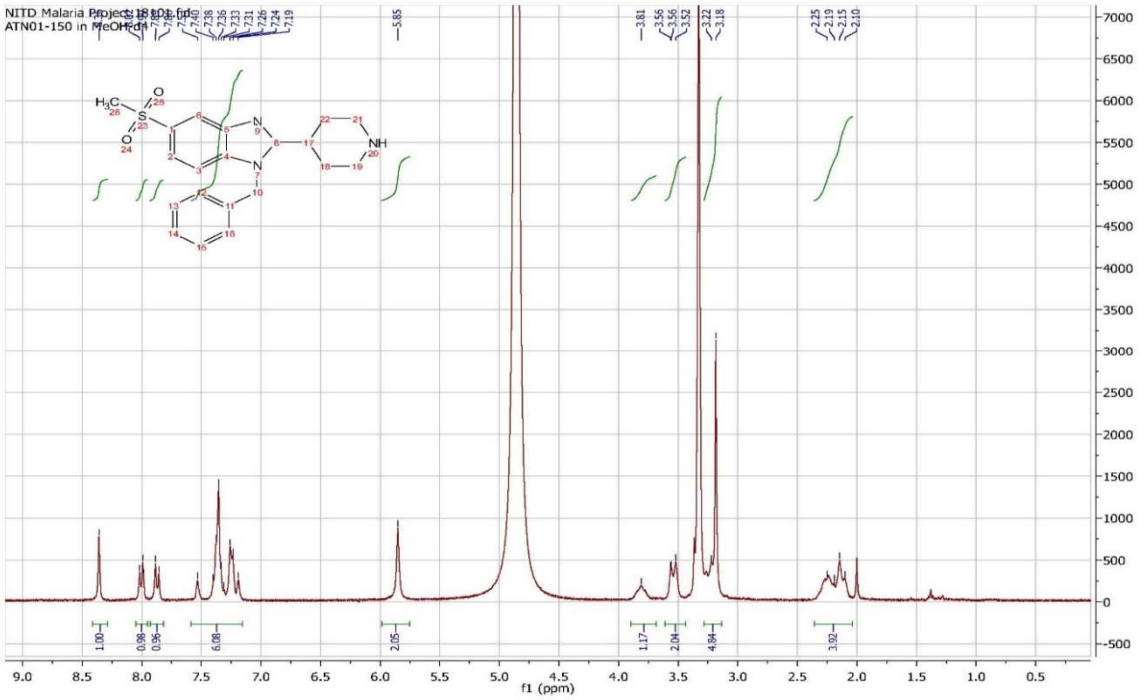


Figure S46: 1-Benzyl-2-(piperazin-1-yl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazole hydrochloride (49a)

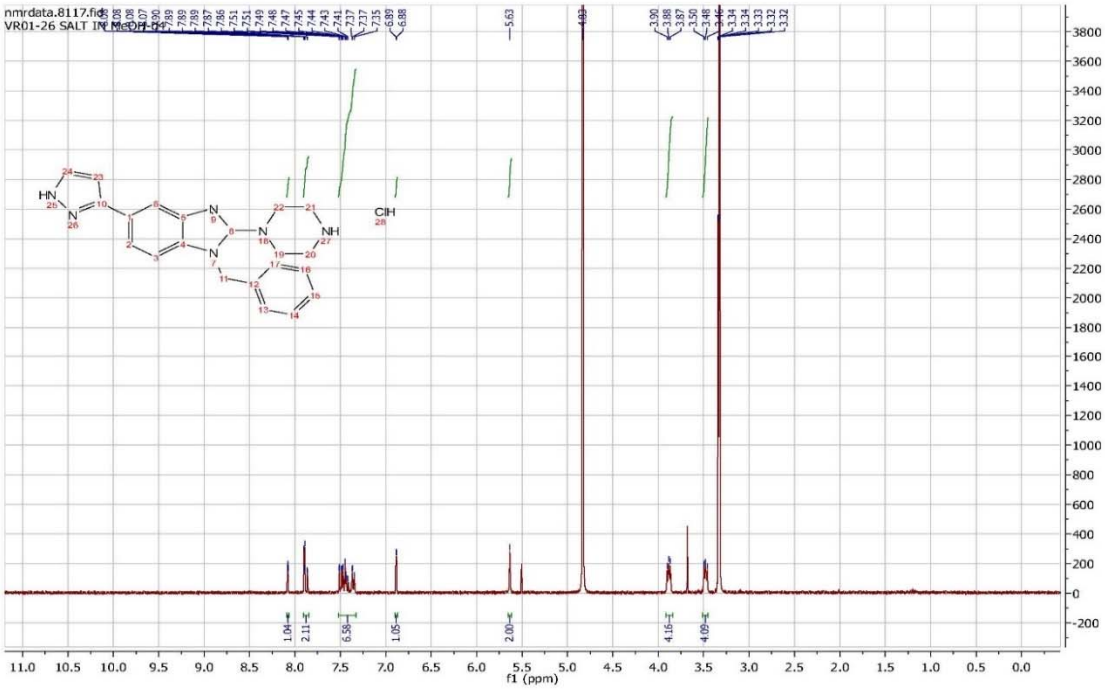


Figure S47: 1-benzyl-5-phenyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (49b)

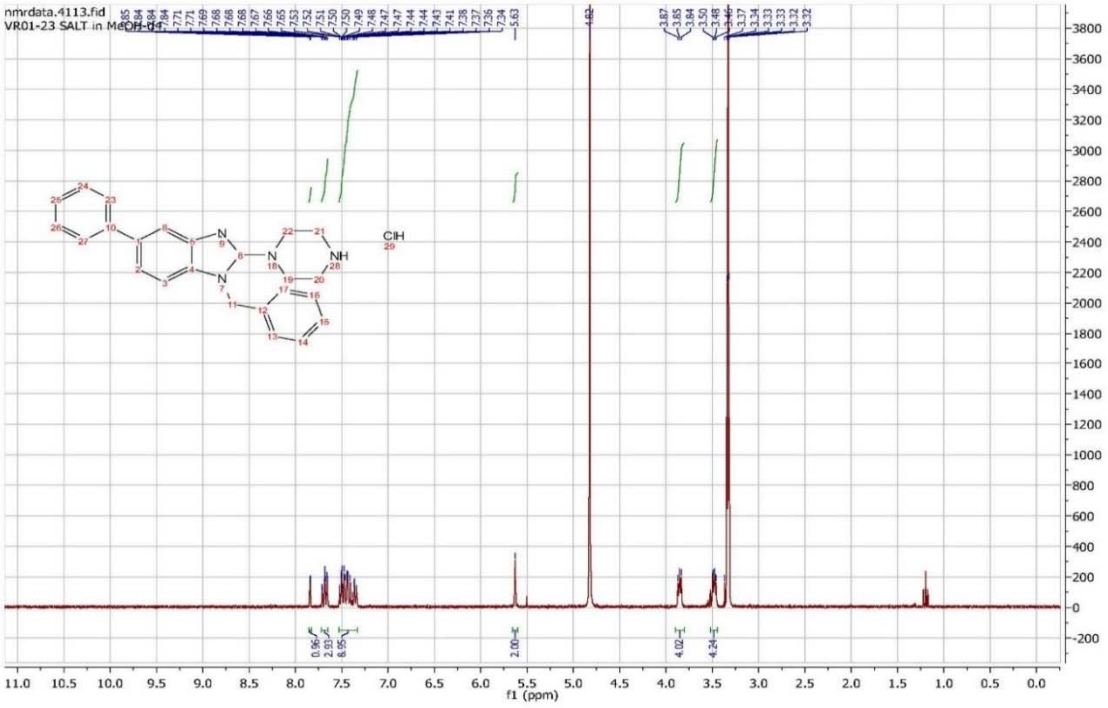


Figure S48: 1-benzyl-2-(piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazole hydrochloride (49c)

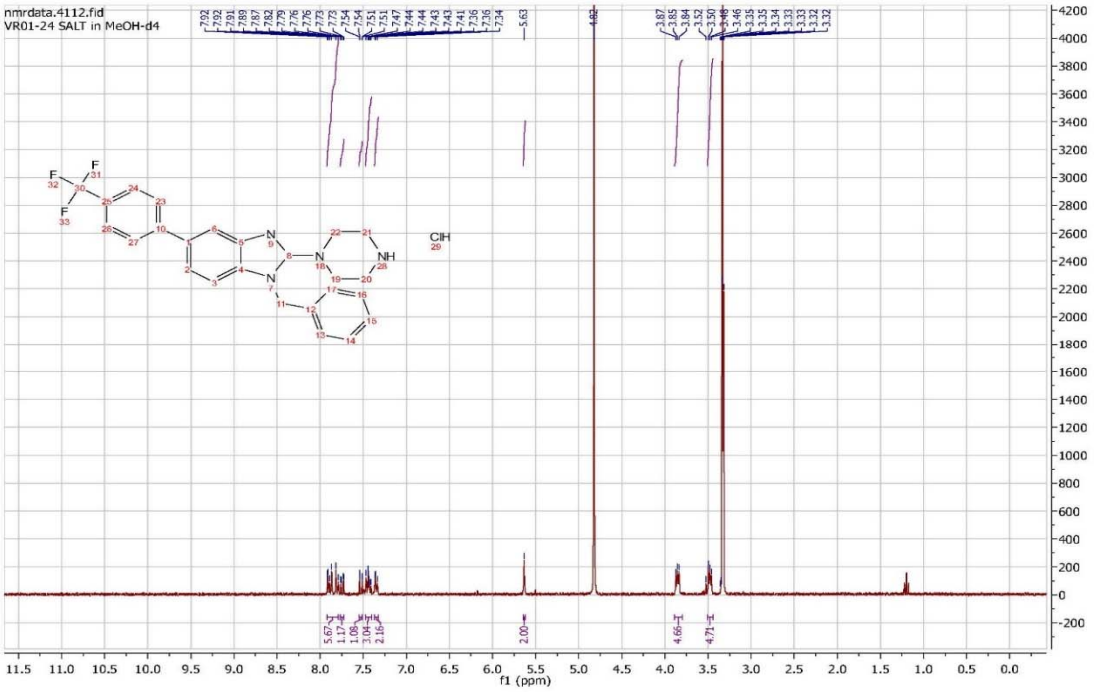


Figure S49: 1-benzyl-2-(piperazin-1-yl)-5-(6-(trifluoromethyl)pyridin-3-yl)-1H-benzo[d]imidazole hydrochloride (49d)

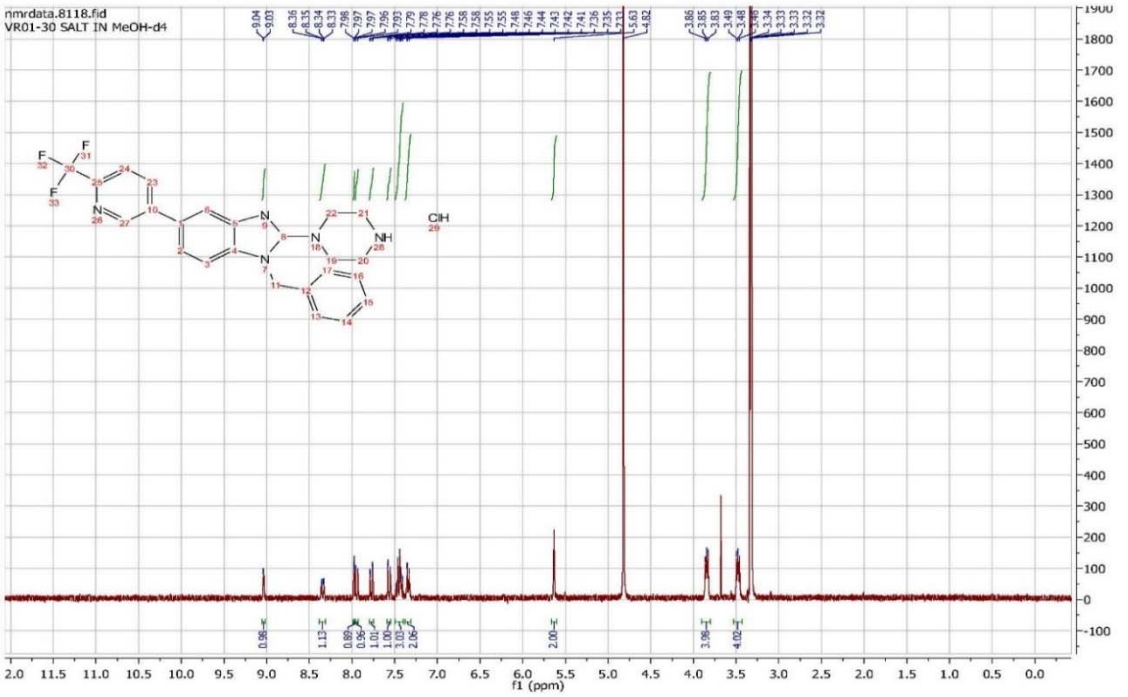


Figure S50: 1-Benzyl-2-(piperazin-1-yl)-5-(pyridin-4-yl)-1H-benzo[d]imidazole (49ea)

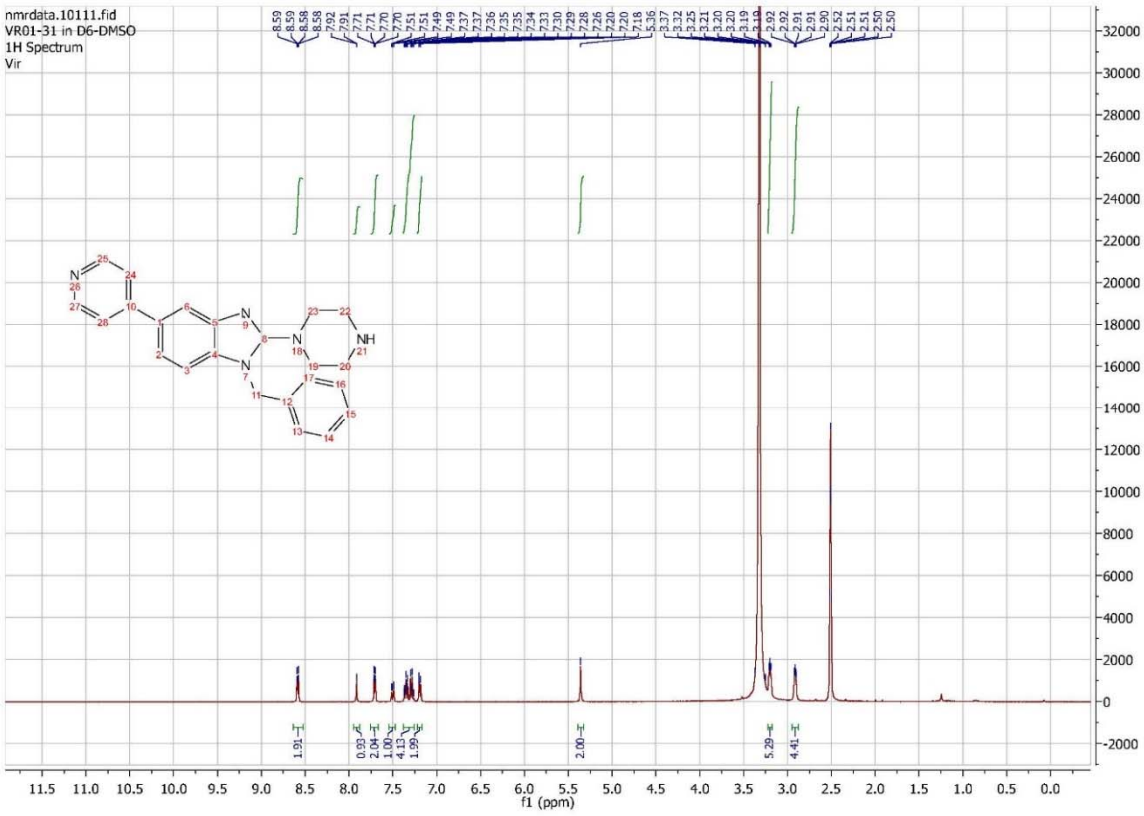


Figure S51: 1-Benzyl-5-chloro-4-phenyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (52a)

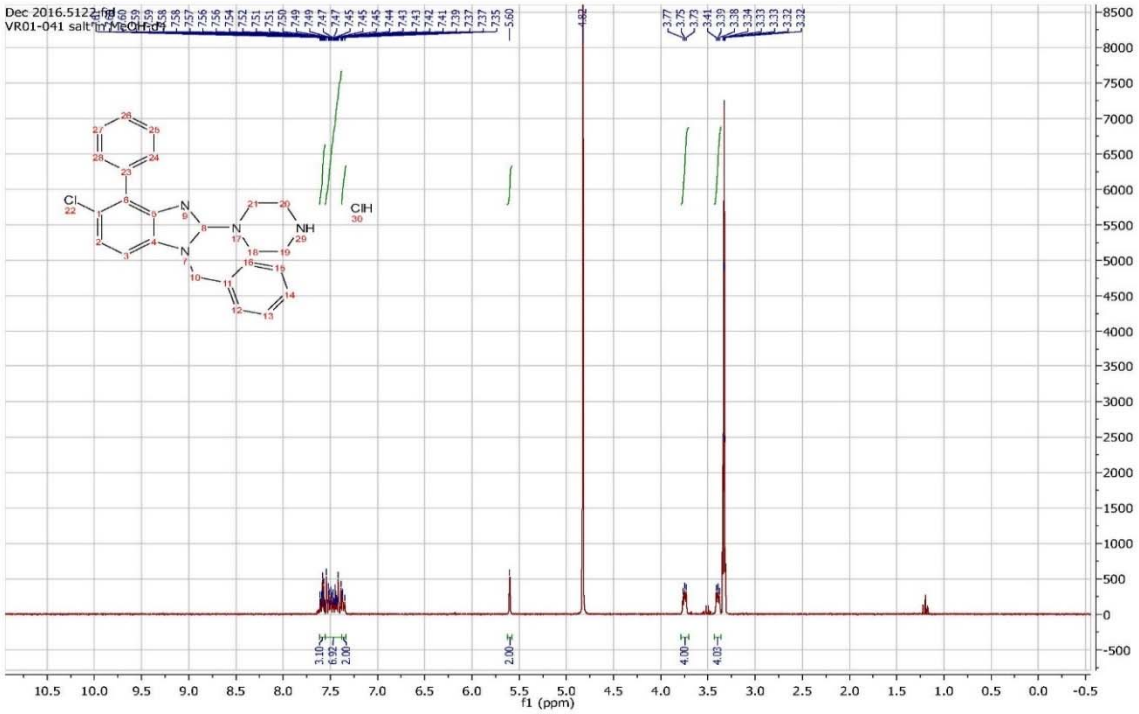


Figure S52: 1-Benzyl-5-chloro-2-(piperazin-1-yl)-4-(pyridin-4-yl)-1H-benzo[d]imidazole hydrochloride (52b)

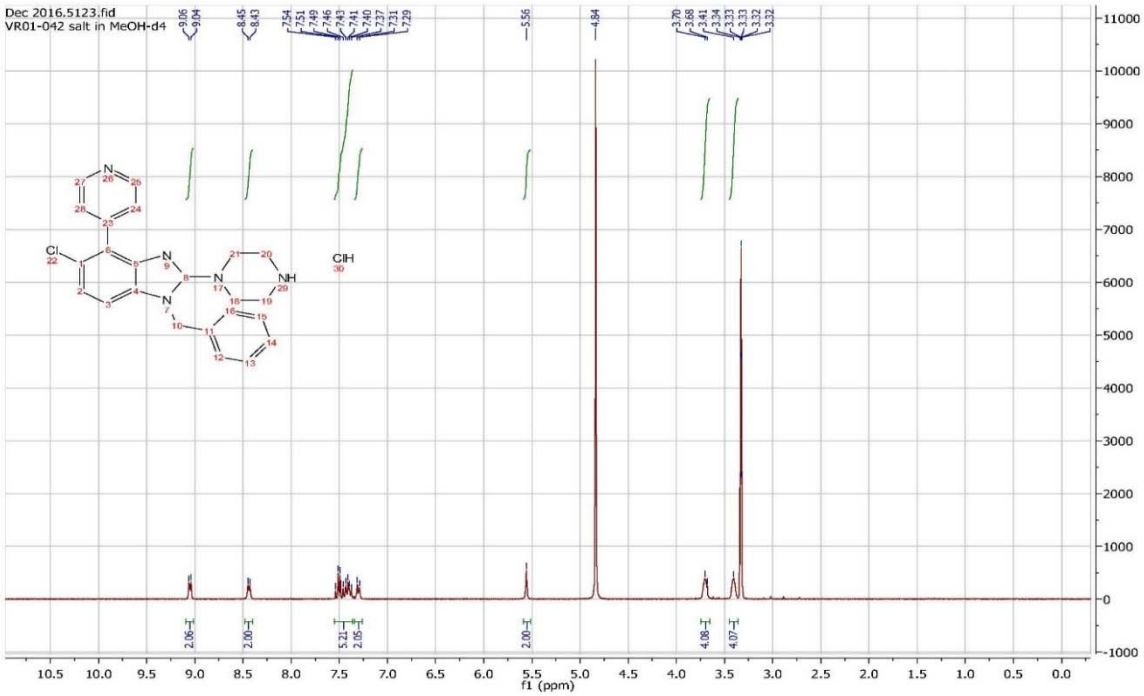


Figure S53: 3-Benzyl-2-(piperazin-1-yl)-3H-imidazo[4,5-b]pyridine (57a)

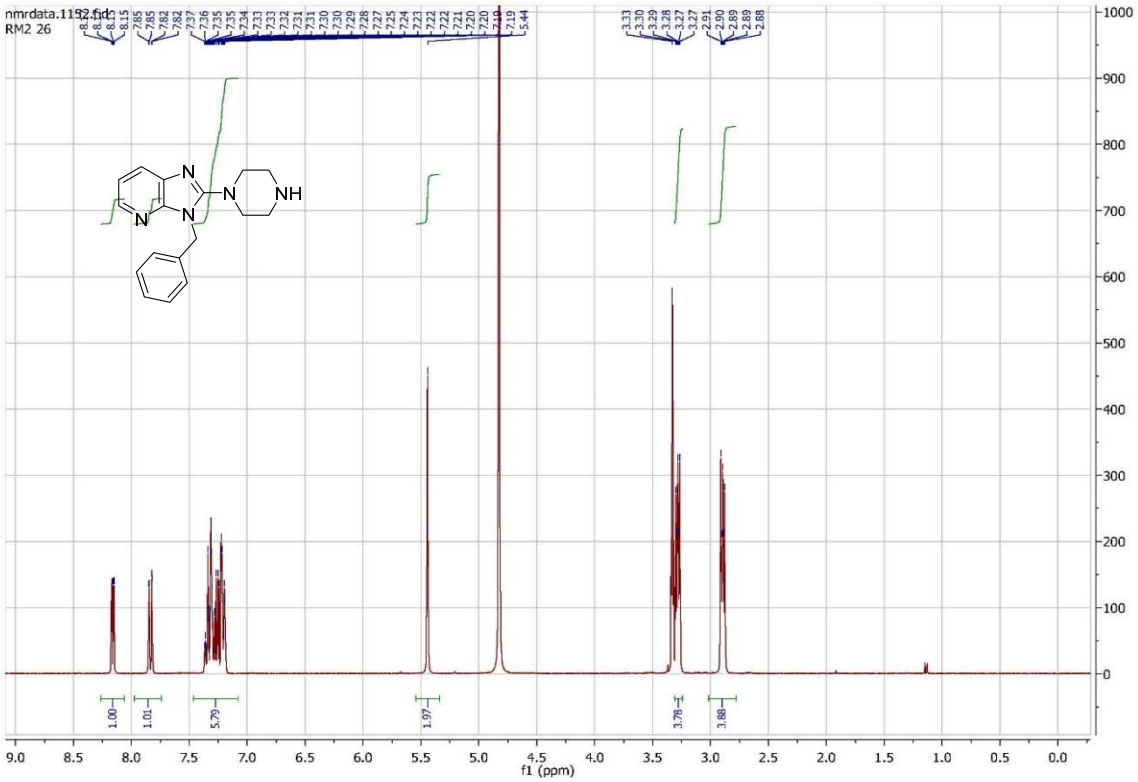


Figure S54: 1-Benzyl-2-(piperazin-1-yl)-1H-imidazo[4,5-c]pyridine (57b)

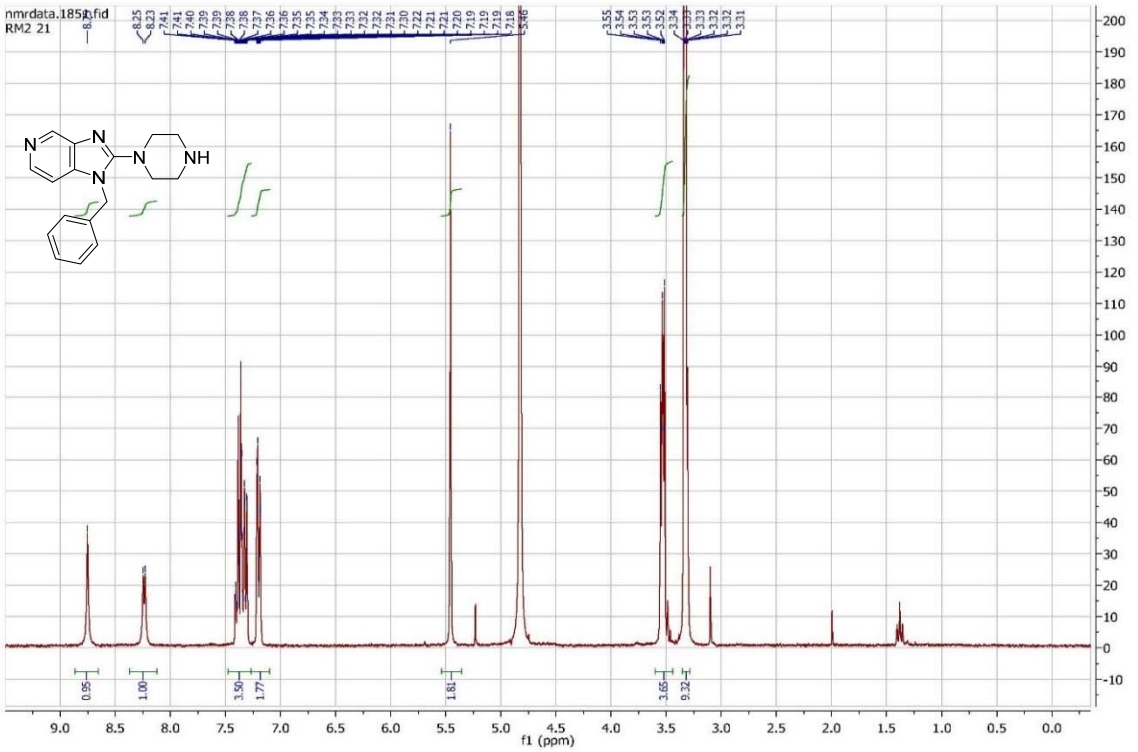


Figure S55: *N*1-(1-benzyl-1H-benzo[d]imidazol-2-yl)propane-1,3-diamine (58)

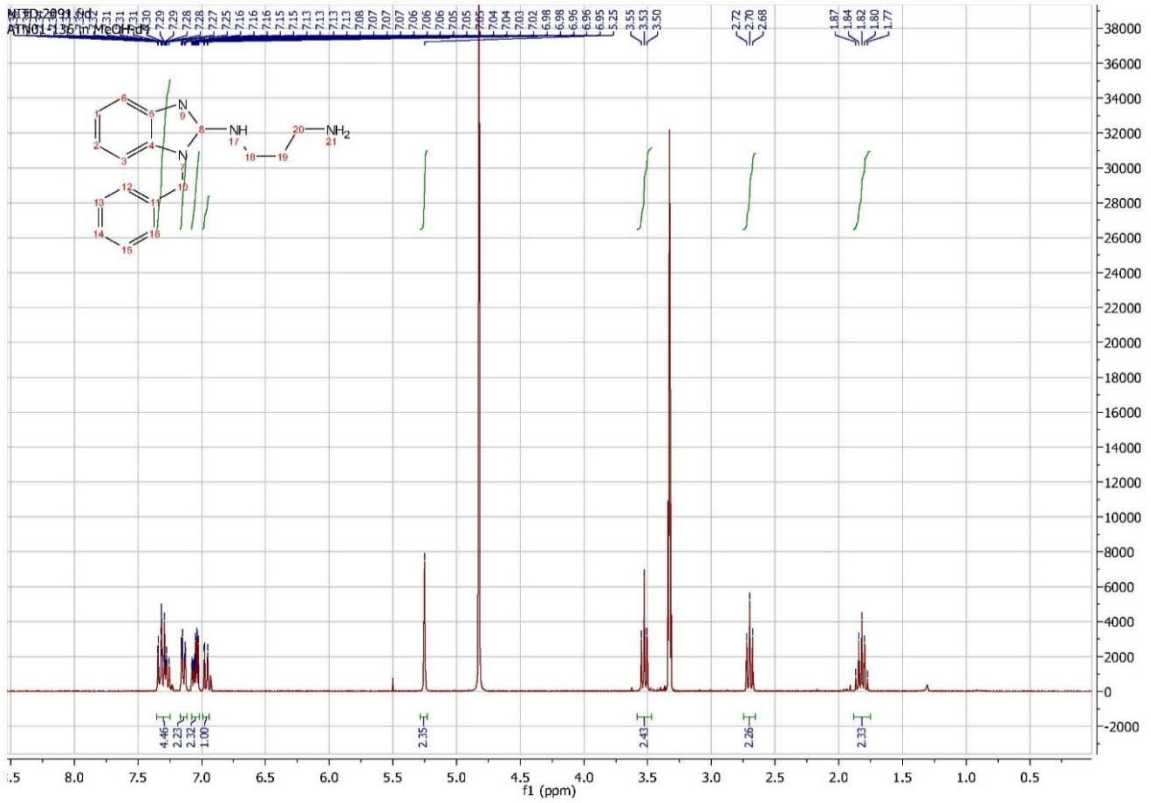


Figure S56: 2-(piperazin-1-yl)-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazole hydrochloride (59)

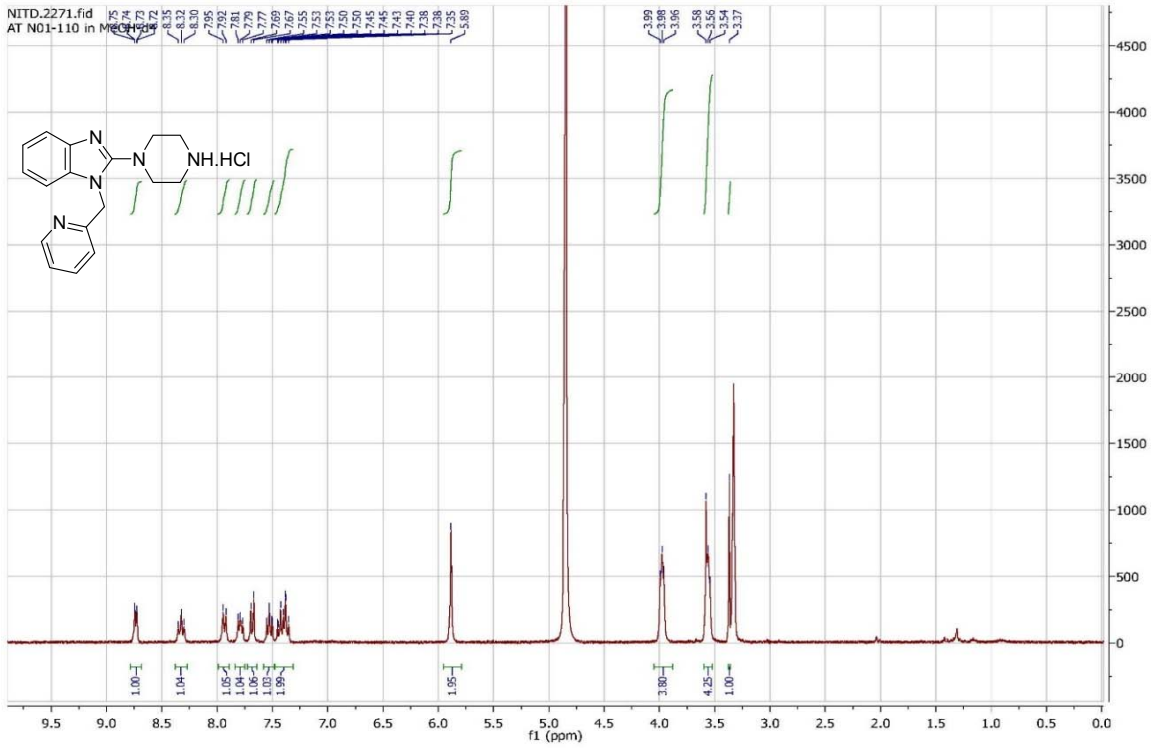
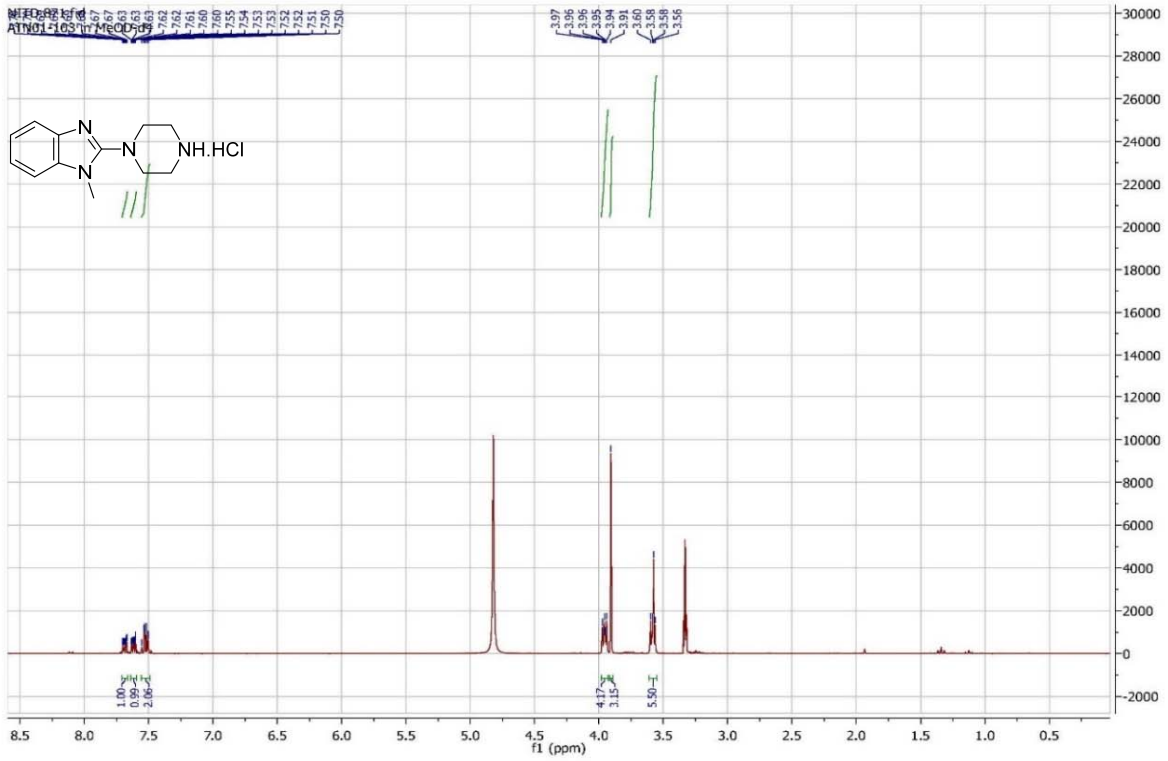


Figure S57: 1-methyl-2-(piperazin-1-yl)-1H-benzo[d]imidazole hydrochloride (60):



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