DESIGN AND SYNTHESIS OF NOVEL DERIVATIVES OF CHIRAL BENZIMIDAZOLE

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ABSTRACT

Benzimidazole nucleus is a constituent of many bioactive heterocyclic compounds that are of wide interest because of their biological and clinical applications. This created interest to synthesized benzimidazole containing derivatives. Eleven new derivatives were synthesized under mild conditions by the reaction of (1S)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1H-benzimidazol-2-yl} ethanamine with different carboxylic acids in good yields. (1S)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1H-benzimidazol-2-yl} ethanamine was characterized by IR, ^{1}H and ^{13}C NMR and LCMS. The derivatives of (1S)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1H-benzimidazol-2-yl} ethanamine were characterized by ^{1}H NMR and LCMS.

KEYWORDS: Synthesis, benzimidazole, (1*S*)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1*H*-benzimidazol-2-yl} ethanamine, carboxylic acids

INTRODUCTION

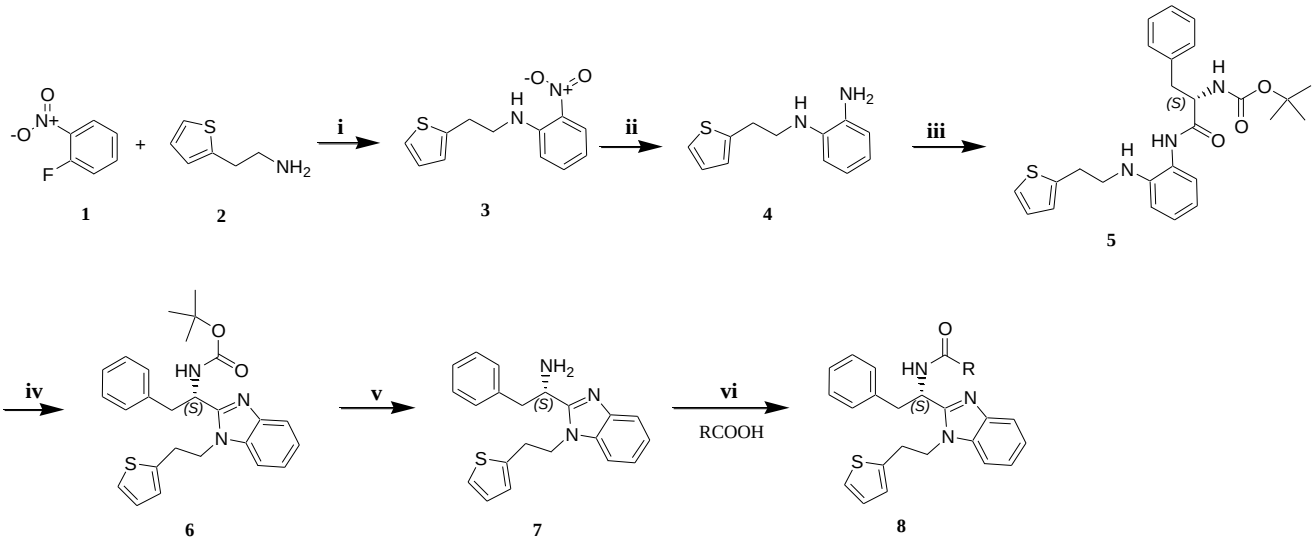
For a long time heterocyclic compounds have one of the largest areas of research in organic chemistry. Heterocyclic compounds have particular importance as they are associated with a wide variety of biological activities with wide variety of heterocyclic systems. The incorporation on benzimidazole nucleus, a biologically accepted pharmacophore in medicinal compounds, has made it a versatile heterocyclic moiety possessing wide range of biological activities [1]. Benzimidazoles are extensively investigated compounds and have fascinated organic chemists to look for their synthesis. Some benzimidazole derivatives with different

pharmacological effects including antifungal[2,3,4], antihelmintic[5], antiHIV[6], anticancer[7,8], antiviral[9], antihypertensive[10], antitumor[11], and antimicrobial[12] are in chemical use.

In connection with these studies, a series of new benzimidazole nucleus containing (1*S*)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1*H*-benzimidazol-2-yl} ethanamine derivatives was prepared by the reaction of (1*S*)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1*H*-benzimidazol-2-yl} ethanamine with different carboxylic acids for the evolution of their biological activities.

RESULTS AND DISCUSSION

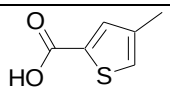
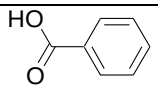
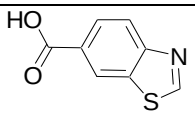
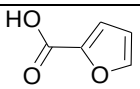
The synthesis of new benzimidazole nucleus containing amides **8a-k** were performed by the coupling of (1*S*)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1*H*-benzimidazol-2-yl} ethanamine **7** with different carboxylic acids using mukaiyama reagent and triethylamine in DMF within 0.5 hour (Scheme 1). **3** was prepared by coupling of **1** and **2** in dry THF within 4 hours. Reduction of **3** using iron powder gave **4** after 1 h. **5** was obtained in the course of a reaction with **4** and boc-L-phenylalanine using dicyclohexylcarbodiimide (DCC) as a dehydrating agent in dry DCM within 12 hours. Several dehydrating agents were used in the synthesis of **5**. Because of good yield and easy purification, **5** was synthesized using DCC as the byproduct was easily removed by filtration. By heating in acetic acid at 80 ^{o}C for 1 hour **5** was converted into **6**. Finally removal of boc group in **6** with 4M hydrochloric acid in 1, 4 dioxane solution afforded hydrochloride of **7** after 4 hours which on basification gave **7**.

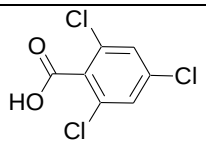
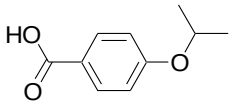
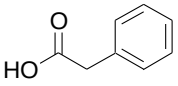
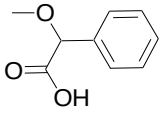
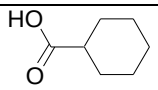
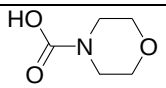
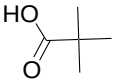


Scheme 1: Reagents and conditions: **i**. THF, r.t., 4 h. **ii**. Fe, CH_3COOH, 100 ^oC, 1 h. **iii**. DCC, Boc-L-phenylalanine, DCM, r.t. 12 h. **iv**. CH_3COOH, 80 ^oC, 1 h. **v**. 4M HCl in 1, 4-Dioxane, DCM, r.t. 4 h. **vi**. Mukaiyama reagent, TEA, DMF, 0 ^oC. 0.5 - 2 h.

After completion of cyclisation of compound **5** in acetic acid at 80 ^oC, and removal of solvent the corresponding crude material **6** was obtained, this was subsequently treated with 4M hydrogen chloride in dioxane solution to remove the boc group. Evaporation of reaction mixture to dryness gave the crude amine **7** which was crystallized with diethyl ether. Finally the reaction of **7** with different carboxylic acid using mukaiyama reagent and triethylamine in DMF at 0 ^oC afforded (1*S*)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1*H*-benzimidazol-2-yl} ethanamine derivatives **8a-k** in good yields (Table 1). The (1S)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1H-benzimidazol-2-yl} ethanamine was characterized ^1H and ^{13}C NMR, IR and LCMS. The final products **8a-k** were fully characterized by ^1H NMR and LCMS.

Table 1: Synthesis of (1S)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1H-benzimidazol-2-yl} ethanamine derivatives 8a-k

Entry	Compound	Carboxylic Acid (RCOOH)	Time (h)	Yield[a] (%)
1	**8a**		**1.0**	**91**
2	**8b**		**0.5**	**96**
3	**8c**		**1.5**	**93**
4	**8d**		**0.5**	**95**

5	**8e**		**0.5**	**88**
6	**8f**		**1.5**	**91**
7	**8g**		**1.5**	**92**
8	**8h**		**1.5**	**80**
9	**8i**		**2.0**	**86**
10	**8j**		**2.0**	**75**
11	**8k**		**1.5**	**79**

[a] Yields of pure and isolated products.

CONCLUSIONS

The aforementioned literature revealed that benzimidazole is versatile heterocyclic nucleus having high potential for the development of new chemical entities for the treatment of infectious diseases, cancer, metabolic and inflammatory conditions. Eleven new benzimidazoles including chiral center were prepared facilely and efficiently. There is no purification required by column chromatography in a single step. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. The biological profiles of these new generations of benzimidazole would represent a fruitful matrix for further development of better medicinal agents.

Experimental Section

General.

All reagents were purchased from commercial suppliers and used without further purification. . Analytical thin layer chromatography was carried out on silica pre-coated glass plates (Silica gel 60 F254, 0.25 mm thickness) and visualized with UV light at 254 nm. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400-MHz Ultrashield Advance II 400 model (400 and 100 MHz, respectively) at ambient temperature with $CDCl_3$ or DMSO-*d6* as solvents with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. The chemical shifts (δ) are reported in ppm and the coupling constant (J) in hertz. An infrared (IR) spectrum was recorded on an FT-IR Perkin-Elmer spectrometer. The specifications of the LCMS instrument are the following: Electrospray (+) ionization, mass range of 100-1000 Da, 20V cone voltage, Acquity BEH C-18 column (2.1 x 100mm, 1.7 μm), and gradient mobile phase consisting of 5 mM ammonium acetate in water and acetonitrile, and a flow rate of 0.5 mL/min.

General procedures.

(2-Nitro-phenyl)- (2-thiophen-2-yl-ethyl) amine (3).

To a stirred solution of 1-fluoro-2-nitrobenzene **1** (5 g, 35.4 mmol) in THF (50 mL) was added 2-(thiophen-2-yl) ethanamine **2** (9 g, 70.8 mmol) at r.t. The reaction mixture was stirred for 4h at r.t. After completion, the reaction mixture was concentrated and the resulting solid was filtered off, washed with diethyl ether and dried giving yellow solid **3** (8.5 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.16 (t, J = 6.8 Hz, 2H), 3.60-3.65 (m, 2H), 6.69 (t, J = 8 Hz, 1H), 6.97 (s, 1H), 6.98 (s, 1H), 7.05 (d, J = 8.8 Hz, 1H), 7.35-7.37 (m, 1H), 7.54 (t, J = 7.6 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.16 (s, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{12}H_{12}N_2O_2S$: 249.06. Found: 249.26.

***N*-(2-(Thiophen-2-yl-ethyl)-benzene-1, 2-diamine (4).**

To a stirred solution of (2-Nitro-phenyl)-(2-thiophen-2-yl-ethyl) amine **3** (8.5 g, 34.2 mmol) in acetic acid (100 mL) was added iron powder (9.5 g, 171.1 mmol) at r.t. The reaction mixture was heated at 100 ^{o}C until the disappearance of starting **3** (1h, monitored by TLC). The reaction mixture was filtered through cilite and washed with acetic acid. The filtrate was poured into ice water and the resulting solid was filter off, washed with water, diethyl ether and dried giving brown liquid **4** (5.5 g).

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.08 (t, J = 7.6 Hz, 2H), 3.26-3.33 (m, 2H), 4.46 (s, 2H), 4.55 (t, J = 5.2 Hz, 1H), 6.41-6.56 (m, 4H), 6.95 (s, 1H), 6.96 (s, 1H), 7.32-7.34 (m, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{12}H_{14}N_2S$: 219.09. Found: 219.05.

{(S)-2-Phenyl-1-[2-(2-thiophene-2-yl-ethylamino)-phenylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester (5).

To a stirred solution of *N*-(2-(Thiophen-2-yl-ethyl)-benzene-1, 2-diamine **4** (5.5 g, 25.1 mmol) in THF (50 mL) and (2*S*)-2-[(*tert*-butoxycarbonyl) amino]-3-phenylpropanoic acid (7.3 g, 27.7 mmol) was added DCC (6.2 g, 30.2 mmol) at 0 ^{o}C. The reaction mixture was warmed to r.t. until the disappearance of starting **4** (12 h, monitored by TLC). The DCU by-product precipitated, which was removed by filtration. The filtrate was concentrated under reduced pressure to dryness and the residue was taken up in ethyl acetate. The ethyl acetate layer was washed with 2 M sodium hydroxide solution, with brine before drying over sodium sulphate. The filtrate was concentrated under reduced pressure to dryness to give white solid **5** (6.5 g).

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.36 (s, 9H), 2.84-3.09 (m, 4H), 3.28-3.32 (m, 2H), 4.30 (t, J = 6.4 Hz, 1H), 4.85 (d, J = 5.2 Hz, 1H), 6.56 (t, J = 7.2 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.93-6.95 (m, 2H), 7.04-7.08 (m, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.22-7.32 (m, 6H), 9.27 (s, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{26}H_{31}N_3O_3S$: 466.21. Found: 466.20.

{(S)-2-Phenyl-1-[1-(2-thiophene-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-carbamic acid tert-butyl ester (6).

A stirred solution of {(S)-2-Phenyl-1-[2-(2-thiophene-2-yl-ethylamino)-phenylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester **5** (6.5 g, 13.9 mmol) in acetic acid (60 mL) was heated to 80 ^{o}C until the disappearance of starting **5** (1h, monitored by TLC). After completion, the reaction mixture was concentrated and the resulting solid was filtered off, washed with diethyl ether and dried giving white solid **6** (6.0 g).

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.24 (s, 9H), 3.02-3.13 (m, 3H), 3.22-3.31 (m, 1H), 4.33-4.51 (m, 2H), 4.93-4.99 (m, 1H), 6.77 (s, 1H), 6.91-6.63 (m, 1H), 7.19-7.22 (m, 7H), 7.32-7.34 (m, 1H), 7.45-7.48 (m, 1H), 7.53-7.55 (m, 1H), 7.62-7.64 (m, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{26}H_{29}N_3O_2S$: 448.20. Found: 448.21.

(1*S*)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1*H*-benzimidazol-2-yl} ethanamine (7).

A stirred solution of {(S)-2-Phenyl-1-[1-(2-thiophene-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-carbamic acid tert butyl ester **6** (6.0 g, 13.4 mmol) in DCM (50 mL) was added 4M HCL in 1, 4-dioxane (13.4 mL, 53.6 mmol) at 0 ^{o}C. The reaction mixture was stirred to r.t. until the disappearance of starting **6** (1h, monitored by TLC). After completion, the reaction mixture was concentrated and the resulting residue was diluted with water, basified using saturated sodium bicarbonate and washed with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to dryness giving white solid **7** (4.5 g).

IR (KBR, ν_{max}, cm^{-1}): 3367 (m, *v*N-H), 3057 (m), 2924 (m), 1598 (s), 1458 (s) 1340 (s), 1282 (m), 847 (s), 747 (s); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H 1.88 (br s, 2H), 2.96-3.19 (m, 4H), 4.04 (s, 1H), 4.27-4.41 (m, 2H), 6.72 (s, 1H), 6.90 (s, 1H), 7.13-7.24 (m, 7H), 7.32 (s, 1H), 7.49 (s, 1H), 7.60 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d$_6$): δ_C 29.08, 43.23, 44.39, 49.60, 118.77, 121.35, 121.84, 124.63, 125.96, 126.10, 127.12, 128.11, 129.34, 128.83, 139.81; LCMS (EI): *m/z* [M+H] calcd. For $C_{21}H_{21}N_3S$: 348.15. Found: 348.11.

Typical procedure for the preparation of (1S)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1H-benzimidazol-2-yl} ethanamine derivatives (8a-k).

To a stirred solution of **7 (**1 mmol) and carboxylic acid **a-k** (1.1 mmol) in DMF were added mukaiyama reagent (2 mmol) and triethylamine (2 mmol) at 0 ^{o}C. The reaction mixture was stirred until the disappearance of the starting **7** (0.5 h – 2 h, monitored by TLC). The mixture was poured into ice water and the resulting solid was filtered off, washed with distilled water and dried. The solid was again washed with diethyl ether giving solid product **8a-k**.

4-Methyl-thiophene-2-carboxylic acid {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-amide (8a).

White solid; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H 2.16 (s, 3H), 2.73-3.21 (m, 3H), 3.40-3.45 (m, 1H), 4.38-4.42 (m, 1H), 4.53-4.60 (m, 1H), 5.38-5.44 (m, 1H), 6.77 (s, 1H), 6.91 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.14-7.23 (m, 6H), 7.29 (s, 1H), 7.34 (s, 1H), 7.51 (d, J = 6.4 Hz, 1H), 7.68 (s, 2H), 9.11 (d, J = 8.4 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{27}H_{25}N_3OS_2$: 472.14. Found: 472.20.

N-{(S)-2-Phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-benzamide (8b).

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.06-3.13 (m, 2H), 3.18-3.23 (m, 1H), 3.44-3.50 (m, 1H), 4.40-4.47 (m, 1H), 4.59-4.63 (m, 1H), 5.47-5.54 (m, 1H), 6.75 (s, 1H), 6.93 (s, 1H), 7.11-7.15 (m, 1H), 7.19-7.23 (m, 4H), 7.24-7.28 (m, 2H), 7.33-7.41 (m, 3H), 7.45-7.52 (m, 2H), 7.64 (s, 1H), 7.79 (d, J = 7.2 Hz, 1H), 9.14 (d, J = 8.8 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{28}H_{25}N_3OS$: 452.17. Found: 452.07.

Benzothiazole-6-carboxylic acid {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-amide (8c).

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.05-3.14 (m, 2H), 3.22-3.27 (m, 1H), 3.48-3.52 (m, 1H), 4.43-4.48 (m, 1H), 4.58-4.63 (m, 1H), 5.52-5.58 (m, 1H), 6.76 (s, 1H), 6.91 (s, 1H), 7.11-7.15 (m, 1H), 7.21-7.34 (m, 7H), 7.52 (d, J = 6.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.60 (s, 1H), 9.31 (d, J = 8.0 Hz, 1H), 9.50 (s, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{29}H_{24}N_4OS_2$: 509.14. Found: 509.22.

Furan-2-carboxylic acid {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-amide (8d).

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.78-2.83 (m, 1H), 2.95-3.05 (m, 1H), 3.25-3.30 (m, 1H), 3.43-3.48 (m, 1H), 4.01-4.07 (m, 1H), 4.35-4.40 (m, 1H), 5.45-5.51 (m, 1H), 6.45 (s, 1H), 6.53 (s, 1H), 6.81 (s, 1H), 7.06-7.09 (m, 4H), 7.16-7.26 (m, 5H), 7.27-7.31 (m, 2H), 7.41 (s, 1H), 7.79 (d, J = 7.2 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{26}H_{23}N_3O_2S$: 442.15. Found: 442.29.

2, 4, 6-Trichlorophenyl-carboxylic acid {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-amide (8e).

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.81-2.88 (m, 1H), 3.05-3.25 (m, 2H), 3.55-3.60 (m, 1H), 3.96-3.40 (m, 1H), 4.27-4.34 (m, 1H), 5.51-5.56 (m, 1H), 6.56 (s, 1H), 6.73 (s, 1H), 6.84-6.88 (m, 1H), 7.06-7.12 (m, 3H), 7.18-7.22 (m, 5H), 7.28-7.40 (m, 3H), 7.74 (d, J = 7.6 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{28}H_{22}Cl_3N_3OS$: 554.05. Found: 553.93.

4-Isopropoxy-N- {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-benzamide (8f).

Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.29 (d, J = 7.6 Hz, 6H), 2.78-2.80 (m, 1H), 3.01-3.03 (m, 1H), 3.45-3.50 (m, 2H), 4.02-4.03 (m, 2H), 4.35-4.37 (m, 1H), 5.52-5.54 (m , 1H), 6.54 (s, 1H), 6.80-6.86 (m, 3H), 6.97-7.26 (m, 8H), 7.27-7.31 (m, 2H), 7.67 (d, J = 8.8

Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{31}H_{31}N_3O_2S$: 510.21. Found: 510.15.

2-Phenyl-N- {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-acetamide (8g).

Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.97-3.10 (m, 3H), 3.24-3.30 (m, 2H), 3.38 (s, 1H), 4.31-4.37 (m, 1H), 4.46-4.52 (m, 1H), 5.19-5.25 (m, 1H), 6.67 (s, 1H), 6.88 (s, 1H), 6.90-6.99 (m, 2H), 7.11-7.22 (m, 10H), 7.31-7.39 (m, 2H), 7.62-7.67 (m, 1H), 8.86 (d, J = 8.8 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{29}H_{27}N_3OS$: 466.19. Found: 466.18.

2-Methoxy-2-phenyl-N- {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-acetamide (8h).

Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.90-3.10 (m, 2H), 3.11 (s, 1H), 3.16 (s, 3H), 3.26-3.41 (m, 2H), 4.28-4.34 (m, 1H), 4.43-4.49 (m, 1H), 5.16-5.27 (m, 1H), 6.65 (s, 1H), 6.87 (s, 1H), 7.10-7.21 (m, 12H), 7.28-7.36 (m, 1H), 7.56-7.67 (m, 2H), 8.80 (d, J = 8.4 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{30}H_{29}N_3O_2S$: 496.20. Found: 496.39.

Cyclohexanecarboxylic acid {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-amide (8i).

Off White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.08-1.25 (m, 6H), 1.36-1.56 (m, 4H), 2.00-2.09 (m, 1H), 3.04-3.26 (m, 4H), 4.34-4.39 (m, 1H), 4.46-4.52 (m, 1H), 5.22-5.26 (m, 1H), 6.75 (s, 1H), 6.91 (s, 1H), 7.15-7.21 (m, 7H), 7.33 (s, 1H), 7.48 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 8.38 (d, J = 8.8 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{28}H_{31}N_3OS$: 458.22. Found: 458.15.

Morpholine-4-carboxylic acid {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-amide (8j).

Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.97-3.07 (m, 4H), 3.30 (t, J = 2.6 Hz, 4H), 3.40 (t, J = 4.4 Hz, 4H), 4.31-4.36 (m, 1H), 4.56-4.60 (m, 1H), 5.15-5.21 (m, 1H), 6.77 (s, 1H), 6.92 (s, 1H), 7.15-7.22 (m, 8H), 7.34 (s, 1H), 7.47-7.49 (m, 1H), 7.63 (d, J = 8.8 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{26}H_{28}N_4O_2S$: 461.19. Found: 461.21.

2, 2-Dimethyl-N- {(S)-2-phenyl-1-[1-(2-thiophen-2-yl-ethyl)-1H-benzimidazol-2-yl]-ethyl}-propionamide (8k).

Brown solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.90 (s, 9H), 3.06-3.12 (m, 3H), 3.32-3.40 (m, 1H), 4.37-4.45 (m, 1H), 4.48-4.56 (m, 1H), 5.27-5.31 (m, 1H), 6.77 (s, 1H), 6.93 (s, 1H), 7.12-7.17 (m, 1H), 7.18-7.24 (m, 6H), 7.34-7.38 (m, 1H), 7.50-7.56 (m, 1H), 7.63-7.69 (m, 1H), 7.98 (d, J = 8.8 Hz, 1H); LCMS (EI): *m/z* [M+H] calcd. For $C_{26}H_{29}N_3OS$: 432.20. Found: 432.13.

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