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Synthesis, characterization and evaluation of antimicrobial activity of novel chiral benzimidazoles

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Abstract: Benzimidazole derivatives play important role in medicinal field with many pharmacological activities. This created interest to synthesized benzimidazole containing derivatives. In the present scheme we have an attempt to synthesize some novel chiral benzimidazole derivatives. Ten new derivatives were synthesized under mild conditions by the reaction of (1*S*)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1*H*-benzimidazol-2-yl} ethanamine with different aldehydes 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: Benzimidazole, aldehyde, antibacterial and antifungal activity, MIC.

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[2-4], antihelmintic[5], antiHIV[6], anticancer[7,8], antiviral[9], antihypertensive[10], antitumor[11], and antimicrobial[12] are in chemical use. Some benzimidazole drugs used in both human and veterinary medicine such as anti-inflammatory[13], anticancer[14], protein

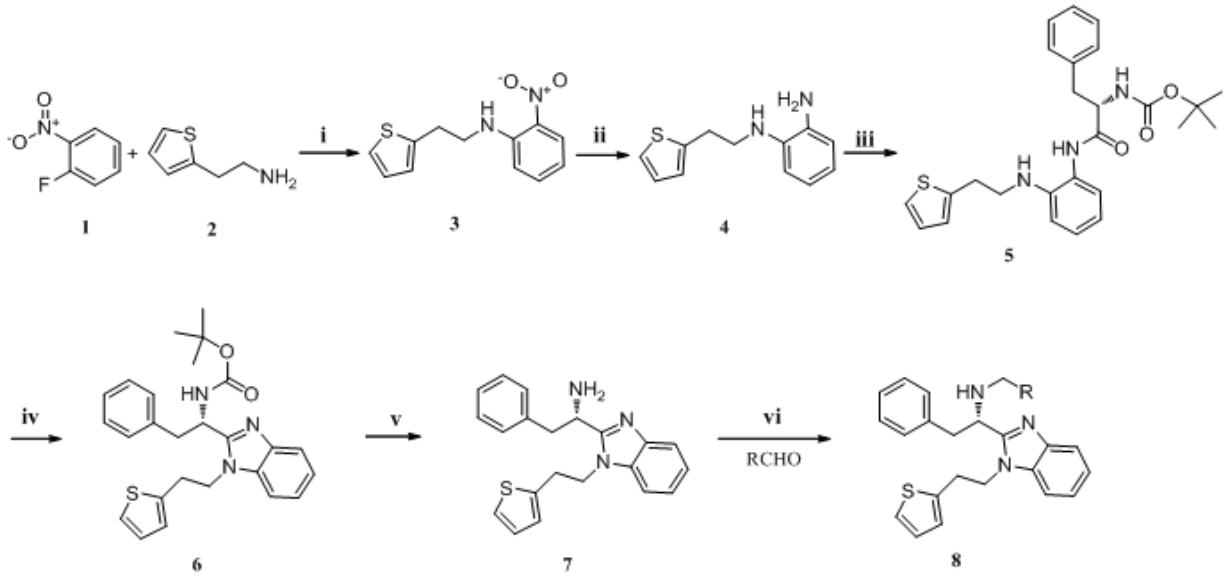
kinase inhibitory[15], lipase inhibition[16] and anti urease[17]. Because of these biological activities, nowadays there has been an increasing interest in the chemistry of imidazole fused benzimidazole.

Heterocyclic systems are one of the most important classes of organic compounds present in nature or synthesized in laboratory. These compound posses several interesting biological activity. Indeed, one of the richest sources of diversity for the medicinal chemist are heterocyclic rings, which, in addition to often exhibiting biological activity, may serve as rigid scaffolds for further display of functionalities. In continuation of interest on the synthesis of benzimidazoles herein an easy, practical and cost effective procedure for the synthesis of new series of benzimidazoles was prepared by reductive amination of (S)-2-phenyl-1-(1-(2-(thiophen-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)ethanamine with different aldehydes. We, in this article, are reporting the use of simple methodology for the exclusive synthesis of benzimidazoles. The present work comprises of synthesis of new agent, in which 1-fluoro-2-nitrobenzene and 2-(thiophen-2-yl)ethanamine are used as a starting materials. Novel ten benzimidazole derivatives were synthesized as mentioned in scheme.

Results and Discussion

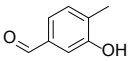
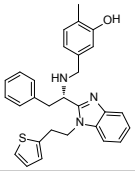
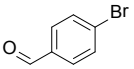
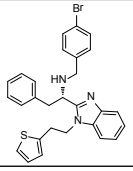
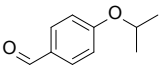
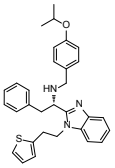
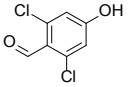
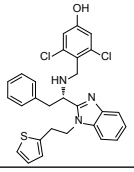
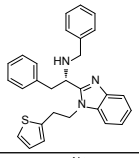
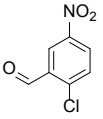
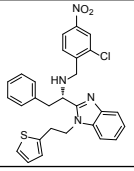
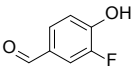
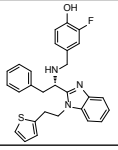
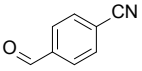
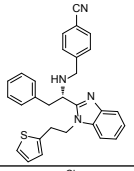
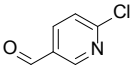
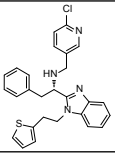
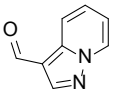
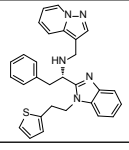
Chemistry

In the present research work ten new benzimidazole derivatives(Table 1) were synthesised by reductive amination of (S)-2-phenyl-1-(1-(2-(thiophen-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)ethanamine **7** with different aldehydes in DCM using sodium triacetoxyborohydride (Scheme 1). **3** was prepared by coupling of **1** and **2** in methanol within 4 hours. Without any work up, ammonium chloride and zinc were added to reaction mixture at room temperature for the purpose of reduction of **3** and to give **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



Scheme 1. General scheme and reaction conditions for the synthesis of title compound: **i**. methanol, RT, 4 h. **ii**. Zn, NH_4Cl, methanol, RT, 1 h. **iii**. DCC, Boc-L-phenylalanine, DCM, RT, 12 h. **iv**. CH_3COOH, 80 ^oC, 1 h. **v**. 4M HCl in 1, 4-Dioxane, DCM, RT, 4 h. **vi**. $Na(OAc)_3BH$, DCM, CH_3COOH, RT, 1 - 4 h.

Table 1. Synthesis of benzimidazole derivatives

S.N.	Entry	Aldehyde	Product	Mol. Formula	M. P. (°C)	Yield (%)
1	**8a**			$C_{29}H_{29}N_3OS$	175	89
2	**8b**			$C_{28}H_{26}BrN_3S$	179	81
3	**8c**			$C_{31}H_{33}N_3OS$	160	83
4	**8d**			$C_{28}H_{25}C_{l2}N_3OS$	183	91
5	**8e**			$C_{28}H_{27}N_3S$	156	93
6	**8f**			$C_{28}H_{25}ClN_4O_2S$	179	85
7	**8g**			$C_{28}H_{26}FN_3OS$	181	79
8	**8h**			$C_{29}H_{26}N_4S$	163	81
9	**8i**			$C_{27}H_{25}ClN_4S$	195	78
10	**8j**			$C_{29}H_{27}N_5S$	201	75

yield and easy purification, **5** was synthesized using DCC as the by-product was easily removed by filtration. By heating in acetic acid at 80 °C for 1 hour **5** was converted into **6**. Finally removal of boc group in **6** by using 4M hydrochloric acid in 1, 4 dioxane solution afforded hydrochloride of **7** after 4 hours. After basification of salt using saturated solution of sodium bicarbonate gave **7**. After completion of cyclisation of compound **5** in acetic acid at 80 °C, 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 aldehydes using sodium triacetoxyborohydride and acetic acid in DCM at ambient temperature afforded (S)-2-phenyl-1-(1-(2-(thiophen-2-yl) ethyl)-1H-benzo[d]imidazol-2-yl)ethanamine **8a-j** in good yields (Table 1). (1S)-2-phenyl-1-{1-[2-(thiophen-2-yl) ethyl]-1H-benzimidazol-2-yl} ethanamine was characterized ^{1}H and ^{13}C NMR, IR and LCMS. The final compounds of reductive amination (S)-N-substituted-2-phenyl-1-(1-(2-(thiophen-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl) ethanamine were characterized ^{1}H and LCMS.

Biology

All the novel synthesized compounds **(8a-j)** have been screened for their in vitro antibacterial activity against two gram positive strains i.e. *Bacillus subtilis* (NCIM 2439) and *Staphylococcus aureus* (NCIM 2079) and two gram negative strains i.e. *Escherichia coli* (NCIM 2064) and *Pseudomonas aeruginisa* (NCIB 8650) by using Mueller Hinton Agar and antifungal activity against fungus *Aspergillus niger* ((NCIM 501) using Sabouraud Dextrose agar using cup plate agar diffusion method by measuring the inhibition zone in mm. The

Table 2. Inhibition zone (in mm) of the compounds **8a-j**.

Compounds	Antibacterial			Antifungal	
	B. subtilis (NCIM 2439)	S. aureus (NCIM 2079)	E. coli (NCIM 2064)	P. aeruginosa (NCIB 8650)	A. niger (NCIM 501)
8a	13	18	-	11	17
8b	15	13	09	-	20
8c	17	15	09	13	18
8d	-	-	13	17	19
8e	10	14	16	-	18
8f	18	13	18	16	16
8g	18	-	10	18	16
8h	13	12	-	-	21
8i	10	17	18	15	22
8j	12	19	16	17	19
Ampicillin	20	22	20	20	-
Clotrimazole	-	-	-	-	25
DMSO	-	-	-	-	-

compounds were taken at a concentration of 1mg/mL using DMSO as negative control. Ampicillin was used as a slandered for antibacterial and Clotrimazole for antifungal activity. 10 mL of this sterilized agar media were poured into petridishes and allowed to solidify. On the surface of media microbial suspension were spread with the help of sterilized triangular loop. A stainless steel cylinder of 10 mm diameter was used to bore the cavity. Into these wells were added 0.1 mL portion of the test compound in the solvent. The drug solution was allowed to diffuse for about an hour into the medium. The plates were incubated at 37°C for 24 hours for bacteria and 28°C for 72-96 hours for fungus. Zone of inhibition observed around cup after respective incubation was measured in four directions with the help of Vernier Calipers. The results of antibacterial and antifungal activities are given in Table 2.

Material and methods:

Chemistry

Melting points of all the compounds were determined in open capillary tubes and are uncorrected. Thin layer chromatography was performed using silica gel coated on glass plate and sposts were visualized by exposure to UV light. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker NMR (400 MHZ) spectrophotometer in using TMS as internal standard chemical shifts recorded ppm). Liquid chromatography/mass spectrometry (LC/MS) data was obtained to verify molecular mass and analyze purity of products. The specifications of the LC/MS 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 procedure for compounds 8a-j:

To the solution of (S)-N-substituted-2-phenyl-1-(1-(2-(thiophen-2-yl) ethyl)-1H-benzo[d] imidazol-2-yl) ethanamine (1.0 mmol) in DCM was added appropriate aldehyde (1.1 mmol) followed by addition of drops of acetic acid at room temperature. After 30 min sodium triacetoxyborohydride (1.5mmol) was added to the reaction mixture at 0°C and the reaction mixture stirred for an additional time to complete at room temperature. After completion of reaction, reaction mass was diluted with water and extracted with DCM. DCM layer was dried over sodium sulphate and concentrate to dryness under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate as eluent. Analytical data of some of the final compounds are as follows.

(S)-2-methyl-5-(((2-phenyl-1-(1-(2-(thiophen-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl) ethyl)amino)methyl)phenol (8a):
Analysis calcd. for $C_{29}H_{29}N_3OS$: C, 74.48; H, 6.25; N, 8.99; O, 3.42; S, 6.86. Found: C, 74.51; H, 6.24; N, 8.98; O, 3.43; S, 6.87; ^{1}H NMR (400 MHz, DMSO-d6, TMS δ ppm): 2.043 (3H, s, CH_3), 2.499-2.713 (1H, m, CH_2), 2.912-2.950 (1H, m, CH_2), 3.052-3.104 (1H, m, CH_2), 3.203-3.250 (1H, m, CH_2), 3.316 (1H, s, CH), 3.484-3.517 (1H, m, CH_2), 4.073-4.142 (3H, m, CH_2), 6.519 (1H, d, *J 7.2 Hz*, CH), 6.648-6.681 (2H, m, CH), 6.876-6.909 (2H, m, CH), 7.066-7.177 (7H, m, CH), 7.287-7.299 (1H, s, CH), 7.416-7.428 (1H, m, CH), 7.625-7.643 (1H, m, CH), 9.091 (1H, s, OH).

(S)-N-(4-bromobenzyl)-2-phenyl-1-(1-(2-(thiophen-2-yl)ethyl)-1H-benzo[d]imidazol-2-yl)ethanamine (8b):
Analysis calcd. for $C_{28}H_{26}BrN_3S$: C, 65.11; H, 5.07; Br, 15.47; N, 8.14; S, 6.21. Found: C, 65.12; H, 6.25; Br, 15.49; N, 8.97; S, 6.88; ^{1}H NMR (400 MHz, DMSO-d6, TMS δ ppm): 2.668-2.797 (3H, m, CH_2), 2.994-3.086 (2H, m, CH_2), 3.179-3.226 (1H, m, CH_2), 3.388-3.424 (1H, m, CH_2), 3.599-3.634 (1H, m, CH_2), 4.051

(1H, s, NH), 4.150-4.187 (2H, m, CH_2), 6.654-6.651 (1H, m, CH), 6.817-6.891 (1H, m, CH), 7.094-7.212 (10H, m, CH), 7.291-7.303 (1H, m, CH), 7.388-7.450 (3H, m, CH), 7.619-7.641 (1H, m, CH).

Conclusion

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. Ten new benzimidazoles including chiral center were prepared facilely and efficiently. There is no purification required by column chromatography in an initial single step. Chromatographic purification required only in the final step of reductive amination. 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.

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