

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL BENZIMIDAZOLE BASED THIAZOLYL AMINES

N .Vasu¹, B. Bharath Kumar Goud^{1,*}, Y. Bharathi Kumari² and B. Rajitha³

¹Suven Life Sciences Ltd, Jeedimetla, Hyderabad-500055, (AP), India

²Department of Chemistry, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad 500072, (AP), India

*E-mail: vasunamani@gmail.com

ABSTRACT

A series of various novel phenyl-(6*H*-thiazolo[4,5-*e*] benzoimidazole-2-yl)-amines (**5a-f**) have been synthesized by involving 4-nitro-1*H*-benzoimidazole (**1**) as starting material and 4-amino-1*H*-benzoimidazole (**2**), (1*H*-benzoimidazole-4-yl)-dithiocarbamic acid methyl ester (**3**), 1-(1*H*-benzoimidazole-4-yl)-3-(substituted-phenyl)-thiourea (**4a-f**) as intermediates. The title compounds were screened for their antibacterial and antifungal activity against various microorganisms and some of these compounds were found as potential antimicrobial agents.

Keywords: Benzimidazole, thiazolyl amines, antimicrobial activity.

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INTRUDUCTION

Thiazole derivatives are an important class of heterocyclic compounds. They occupy an important position in medicinal chemistry, presenting a wide range of bioactivities. As medicines, many of them display wide range of biological activities including antibacterial and antifungal,¹⁻³ anti-HIV^{4,5} hypertension,⁶ anti-inflammatory,⁷ anticancer,⁸ anti-convulsant,⁹ antiinflammation¹⁰ and antidepressant activities.¹¹ Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities. Thiazoles have been incorporated into a wide variety of therapeutically interesting candidates.

Benzimidazoles are among the important heterocyclic compounds found in several natural and non-natural products such as Vitamin B₁₂,¹² marine alkaloid kealiquinone,¹³ benzimidazole nucleosides.¹⁴ Some of their derivatives are marketed as anti-fungal agents such as Carbendazim,¹⁵ anti-helmintic agents such as Mebendazole, thiabendazole¹⁶ and anti-psychotic drug such as Pimozide¹⁷. Resistance to number of antimicrobial agents among a variety of clinically significant species of bacteria is becoming increasingly important global problem. Benzimidazole ring displays an important heterocyclic pharmacophore in drug discovery. Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications. The compounds carrying different substituents in the benzimidazole structure are associated with a wide range of interesting biological activities such as anti-tubercular,¹⁸ anticancer¹⁹ and anticoagulant properties.²⁰

EXPERIMENTAL

Research chemicals were purchased from either Aldrich Company or Fluka and used without further purification, or were prepared according to the procedure described in the literature. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F₂₅₄; Merck) visualizing with ultraviolet light or iodine vapors. The yields of the products reported here are unoptimized. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 5000 spectrometer, using KBr pellets. ¹H NMR spectra were recorded on a Varian Gemini spectrometer, operating at 300 MHz. Chemical shifts (δ) are reported in parts per million down field from tetramethylsilane. Mass spectra were obtained on a VG micro mass 7070H spectrometer operating at 70 eV.

Synthesis of 4-amino-1H-benzimidazole (2)

A solution of 4-nitro-1H-benzimidazole (**1**) (0.01 mol) in ethyl alcohol (20 ml) containing $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (10 mmol) was refluxed on steam-bath for 30 min. A usual work-up, followed by crystallisation of the product from dichloro methane furnished pure **2**.

Synthesis of (1H-benzimidazole-4-yl)-dithiocarbamic acid methyl ester (3)

A solution of 4-amino-1H-benzimidazole (**2**) (0.01 mol) in pyridine (2 ml) was cooled in freezing mixture 0 °C. Then CS_2 (0.03 mol) was added to it, and the solution was stirred for 1 h maintaining the temperature at 0 °C. Then CH_3 (0.03 mol) was added to the reaction mixture and stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was poured into crushed ice. The solid separated was filtered, dried and purified by recrystallization with hot ethanol to give pure **3**.

Synthesis of 1-(1H-benzimidazole-4-yl)-3-(substituted-phenyl)-thiourea (4a-f)

A solution of (1H-benzimidazole-4-yl)-dithiocarbamic acid methyl ester (**3**) (0.01 mol) and PhNH_2 or substituted PhNH_2 (0.15 mol) in methanol (15 ml) was refluxed for 6-8 h. After completion of the reaction (monitored by TLC), the solvent was removed by distillation and the residue purified by crystallization from methanol, which yielded the corresponding **4a-f** in pure form.

Synthesis of phenyl-(6H-thiazolo-[4,5-e]-benzimidazole-2-yl)-amines (5a-f)

A solution of 1-(1H-benzimidazole-4-yl)-3-(substituted-phenyl)-thiourea (**4**) was cyclized by bromine (0.01 mol) in acetic acid (2 ml) under constant stirring at room temperature for 4-5 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into crushed ice. The solid separated was filtered, dried and purified by recrystallization with ethanol to give pure **5a-f**.

(1H-Benzimidazole-4-yl)-dithiocarbamic acid methyl ester (3): Yellow solid, yield: 73%, mp: 136-138 °C; IR (KBr): 3124 (N-H), 3032 (C-H, Ar), 1574 (C=C, Ar), 1465 (C=S), 1416 (C=N), 1225 (C-S), cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 13.16 (bs, 1H, NH), 11.88 (s, 1H, NH), 8.10 (s, 1H, CH), 7.74-7.32 (m, 3H, Ar-H), 2.58 (s, 3H, CH_3); MS: 223 m/z (M^+).

1-(1H-Benzimidazole-4-yl)-3-phenyl-thiourea (4a): Pale yellow solid, yield: 72%, mp: 131-133 °C; IR (KBr): 3145 (N-H), 3028 (C-H, Ar), 1565 (C=C, Ar), 1458 (C=S), 1420 (C=N) cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 10.52 (bs, 1H, NH), 9.98 (s, 1H, NH), 9.30 (s, 1H, NH), 8.12 (s, 1H, CH), 7.75-7.12 (m, 8H, Ar-H); MS: 268 m/z (M^+).

1-(1H-Benzimidazole-4-yl)-3-(3-nitro-phenyl)-thiourea (4b): Brown solid, yield: 70%, mp: 145-147 °C; IR (KBr): 3184 (N-H), 3025 (C-H, Ar), 1555 (C=C, Ar), 1462 (C=S), 1416 (C=N), 1375 (N=O) cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 10.65 (bs, 1H, NH), 9.84 (s, 1H, NH), 9.36 (s, 1H, NH), 8.17 (s, 1H, CH), 7.74-7.32 (m, 6H, Ar-H), 7.15 (s, 1H, Ar-H); MS: 313 m/z (M^+).

1-(1H-Benzimidazole-4-yl)-3-(4-nitro-phenyl)-thiourea (4c): Orange solid, yield: 72%, mp: 120-122 °C; IR (KBr): 3162 (N-H), 3024 (C-H, Ar), 1568 (C=C, Ar), 1455 (C=S), 1423 (C=N), 1368 (N=O) cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 10.62 (bs, 1H, NH), 9.89 (s, 1H, NH), 9.27 (s, 1H, NH), 8.14 (s, 1H, CH), 7.73-7.28 (m, 3H, Ar-H), 7.62 (d, 2H, $J = 7.5$ Hz, Ar-H), 7.25 (d, 2H, $J = 7.5$ Hz, Ar-H); MS: 313 m/z (M^+).

1-(1H-Benzimidazole-4-yl)-3-(4-chloro-phenyl)-thiourea (4d): Pale yellow solid, yield: 73%, mp: 150-152 °C; IR (KBr): 3140 (N-H), 3028 (C-H, Ar), 1585 (C=C, Ar), 1462 (C=S), 1418 (C=N) cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 10.28 (bs, 1H, NH), 9.92 (s, 1H, NH), 9.28 (s, 1H, NH), 8.08 (s, 1H, CH), 7.84-7.21 (m, 3H, Ar-H), 7.54 (d, 2H, $J = 7.7$ Hz, Ar-H), 7.29 (d, 2H, $J = 7.7$ Hz, Ar-H); MS: 302 m/z (M^+).

1-(1H-Benzimidazole-4-yl)-3-(4-bromo-phenyl)-thiourea (4e): Pink solid, yield: 75%, mp: 127-129 °C; IR (KBr): 3184 (N-H), 3012 (C-H, Ar), 1570 (C=C, Ar), 1448 (C=S), 1423 (C=N) cm^{-1} ; ^1H NMR (300 MHz,

DMSO- d_6): δ 10.39 (bs, 1H, NH), 9.82 (s, 1H, NH), 9.32 (s, 1H, NH), 8.18 (s, 1H, CH), 7.81-7.19 (m, 3H, Ar-H), 7.59 (d, 2H, J = 7.2 Hz, Ar-H), 7.32 (d, 2H, J = 7.2 Hz, Ar-H); MS: 347 m/z (M^+).

1-(1H-Benzimidazole-4-yl)-3-(4-methyl-phenyl)-thiourea (4f): Yellow solid, yield: 77%, mp: 160-162 °C; IR (KBr): 3162 (N-H), 3040 (C-H, Ar), 2965 (C-H, CH₃), 1585 (C=C, Ar), 1455 (C=S), 1428 (C=N) cm^{-1} ; ¹H NMR (300 MHz, DMSO- d_6): δ 10.74 (bs, 1H, NH), 9.89 (s, 1H, NH), 9.36 (s, 1H, NH), 8.14 (s, 1H, CH), 7.84-7.26 (m, 3H, Ar-H), 7.68 (d, 2H, J = 7.4 Hz, Ar-H), 7.37 (d, 2H, J = 7.4 Hz, Ar-H), 2.36 (s, 3H, CH₃); MS: 282 m/z (M^+).

Phenyl-(6H-thiazolo[4,5-e]benzimidazole-2-yl)-amine (5a): Pale yellow solid, yield: 74%, mp: 141-143 °C; IR (KBr): 3170 (N-H), 3025 (C-H, Ar), 1568 (C=C, Ar), 1436 (C=N), 1225 (C-S) cm^{-1} ; ¹H NMR (300 MHz, DMSO- d_6): δ 10.62 (s, 1H, NH), 9.75 (s, 1H, NH), 7.84 (s, 1H, CH), 7.54 (d, 1H, J = 6.7 Hz, CH), 7.45-7.18 (m, 5H, Ar-H), 7.21 (d, 1H, J = 6.7 Hz, Ar-H); MS: 265 (M^+).

(3-Nitro-Phenyl)-(6H-thiazolo[4,5-e]benzimidazole-2-yl)-amine (5b): Orange solid, yield: 72%, mp: 122-124 °C; IR (KBr): 3154 (N-H), 3016 (C-H, Ar), 1570 (C=C, Ar), 1426 (C=N), 1385 (N=O), 1218 (C-S) cm^{-1} ; ¹H NMR (300 MHz, DMSO- d_6): δ 10.54 (s, 1H, NH), 9.74 (s, 1H, NH), 7.85 (s, 1H, CH), 7.48 (d, 1H, J = 7.2 Hz, Ar-H), 7.47-7.26 (m, 3H, Ar-H), 7.23 (d, 1H, J = 7.2 Hz, Ar-H), 7.21 (s, 1H, Ar-H); MS: 311 m/z (M^+).

(4-Nitro-Phenyl)-(6H-thiazolo[4,5-e]benzimidazole-2-yl)-amine (5c): Brown solid, yield: 71%, mp: 144-146 °C; IR (KBr): 3162 (N-H), 3028 (C-H, Ar), 1572 (C=C, Ar), 1444 (C=N), 1375 (N=O), 1236 (C-S) cm^{-1} ; ¹H NMR (300 MHz, DMSO- d_6): δ 10.59 (s, 1H, NH), 9.84 (s, 1H, NH), 7.92 (s, 1H, CH), 7.52 (d, 2H, J = 7.5 Hz, Ar-H), 7.46 (d, 1H, J = 7.2 Hz, Ar-H), 7.32 (d, 2H, J = 7.5 Hz, Ar-H), 7.26 (d, 1H, J = 7.2 Hz, Ar-H); MS: 311 m/z (M^+).

(4-Chloro-Phenyl)-(6H-thiazolo[4,5-e]benzimidazole-2-yl)-amine (5d): Yellow solid, yield: 73%, mp: 119-121 °C; IR (KBr): 3162 (N-H), 3025 (C-H, Ar), 1568 (C=C, Ar), 1442 (C=N), 1222 (C-S) cm^{-1} ; ¹H NMR (300 MHz, DMSO- d_6): δ 10.61 (s, 1H, NH), 9.62 (s, 1H, NH), 7.89 (s, 1H, CH), 7.59 (d, 2H, J = 7.5 Hz, Ar-H), 7.48 (d, 1H, J = 7.3 Hz, Ar-H), 7.38 (d, 2H, J = 7.5 Hz, Ar-H), 7.26 (d, 1H, J = 7.3 Hz, Ar-H); MS: 300 m/z (M^+).

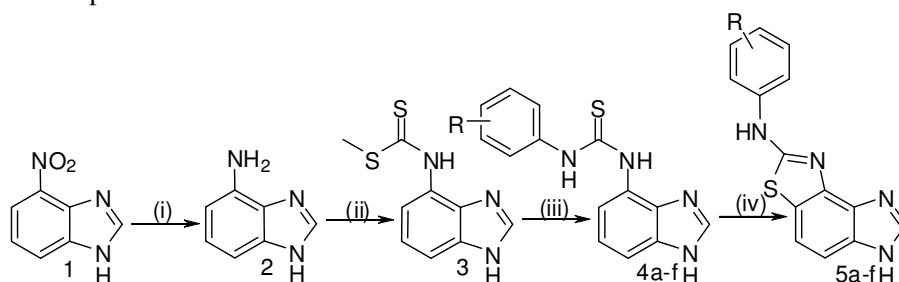
(4-Bromo-Phenyl)-(6H-thiazolo[4,5-e]benzimidazole-2-yl)-amine (5e): Greenish gray solid, yield: 74%, mp: 155-157 °C; IR (KBr): 3154 (N-H), 3026 (C-H, Ar), 1565 (C=C, Ar), 1438 (C=N), 1226 (C-S) cm^{-1} ; ¹H NMR (300 MHz, DMSO- d_6): δ 10.65 (s, 1H, NH), 9.72 (s, 1H, NH), 8.06 (s, 1H, CH), 7.62 (d, 2H, J = 7.2 Hz, Ar-H), 7.54 (d, 1H, J = 7.0 Hz, Ar-H), 7.42 (d, 2H, J = 7.2 Hz, Ar-H), 7.39 (d, 1H, J = 7.0 Hz, Ar-H); MS: 345 m/z (M^+).

(4-Methyl-Phenyl)-(6H-thiazolo[4,5-e]benzimidazole-2-yl)-amine (5f): Brown solid, yield: 71%, mp: 130-132 °C; IR (KBr): 3165 (N-H), 3027 (C-H, Ar), 2965 (C-H, CH₃), 1563 (C=C, Ar), 1428 (C=N), 1232 (C-S) cm^{-1} ; ¹H NMR (300 MHz, DMSO- d_6): δ 10.48 (s, 1H, NH), 9.68 (s, 1H, NH), 8.08 (s, 1H, CH), 7.58 (d, 2H, J = 7.2 Hz, Ar-H), 7.49 (d, 1H, J = 7.5 Hz, Ar-H), 7.42 (d, 2H, J = 7.2 Hz, Ar-H), 7.36 (d, 1H, J = 7.5 Hz, Ar-H), 2.32 (s, 3H, CH₃); MS: 280 m/z (M^+).

Antimicrobial Activity

The disc diffusion method²¹ was used for the screening of anti microbial activity. The *in vitro* antibacterial activity of the synthesized compounds **5a-f** was tested against three gram-positive bacteria *i.e.* *Staphylococcus aureus*, *Staphylococcus albus*, *Streptococcus faecalis* and three gram-negative bacteria *i.e.*, *Escherichia coli*, *Proteus mirabilis*, *Salmonella typhi* using a nutrient agar medium. The antifungal activity of the compounds was screened against two representative fungal organisms namely *Candida albicans* and *Aspergillus fumigatus* using Sabouraded dextrose agar medium. The sterilized medium (autoclaved at

121°C for 15 min.) was inoculated with the suspension of the micro organisms and poured into a Petri dish to give a depth of 3-4 mm. The paper impregnated with the synthesized compounds **5a-f** (300 µg/ml in DMF) was placed on the solidified medium. The plates were pre incubated for 1 h at room temperature and incubated at 37° for 24 h and 48 h for antibacterial and antifungal activity respectively. Amicacin (300 µg/ml) was used in antibacterial activity studies, whereas Fluconazole (300 µg/ml) was used in antifungal activity studies as reference compounds. After incubation, the relative susceptibility of the micro organisms to the potential antimicrobial agent is demonstrated by a clear zone of growth inhibition around the disc. The lowest concentration (highest dilution) of the compounds at which, there was no visually detectable bacterial growth was taken as minimum inhibitory concentration (MIC) and it was determined for the compounds **5a-f**. The zone of inhibition caused by the various compounds on the micro organisms was measured and the activity rated on the basis of the size of the inhibition zone. The observed zone of inhibition in mm is presented in Table-1.



Scheme-1: (i) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, reflux, 30 mins; (ii) CS_2 , pyridine, CH_3I , 0 °C, 1h; (iii) PhNH_2 , MeOH, reflux, 6-8h; (iv) Br_2 , AcOH, 4-5h; 4/5 R (a) = H; (b) = 3- NO_2 ; (c) = 4- NO_2 ; (d) = 4-Cl; (e) = 4-Br; (f) = 4- CH_3 .

Table-1: Antimicrobial activity of compounds 5a-f Zone of inhibition in mm (activity index)*

Compound	Antibacterial activity					Antifungal activity		
	<i>S. aureus</i>	<i>S. albus</i>	<i>S. faecalis</i>	<i>E. coli</i>	<i>P. mirabilis</i>	<i>S. Typhi</i>	<i>C. albicans</i>	<i>A. fumigatus</i>
5a	20 (0.83)	18 (0.81)	19 (0.73)	15 (0.75)	16 (0.76)	16 (0.88)	16 (0.69)	20 (0.80)
5b	21 (0.87)	19 (0.86)	18 (0.69)	16 (0.80)	17 (0.81)	15 (0.83)	21 (0.91)	22 (0.88)
5c	18 (0.75)	19 (0.86)	20 (0.77)	14 (0.70)	15 (0.71)	15 (0.83)	21 (0.91)	23 (0.92)
5d	20 (0.83)	17 (0.77)	22 (0.84)	17 (0.85)	18 (0.85)	17 (0.94)	16 (0.69)	21 (0.84)
5e	22 (0.91)	20 (0.90)	24 (0.92)	14 (0.70)	14 (0.66)	15 (0.83)	21 (0.91)	23 (0.92)
5f	19 (0.79)	19 (0.86)	21 (0.80)	15 (0.75)	16 (0.76)	14 (0.77)	22 (0.95)	16 (0.64)
Amicacin	24	22	26	20	21	18	—	—
Fluconazole	—	—	—	—	—	—	23	25

* Activity index = Inhibition area of the sample/inhibition area of the standard; Diameter of disc is 5 mm

The results of the antimicrobial screening of the tested compounds revealed that, all the tested compounds exhibited antimicrobial activity comparable with that of reference compounds. Most of the compounds showed significant and high activity against both bacteria and fungi. Both compounds **5b** and **5c** with same substituents at different positions exhibited highest antifungal activity against *C. albicans* and *A. fumigatus* as compared to the standard drug used. Highest antimicrobial activity was observed in the product **5e** against *S. aureus*, *S. albus* and *S. faecalis*, as compared to the standard, but shows only

moderate activity against *E. coli* and *P. mirabilis*. This compound also performed high activity against two fungal organisms with marked activity index. In antimicrobial activity studies, it is clear that, an introduction of bromo group reflected better activity against different organisms in compound **5e**. The remaining compounds exhibit moderate to good activity against all organisms employed.

RESULTS AND DISCUSSION

Based on these observations and inspired by the biological profile of thiazoles and benzimidazoles, we introduced thiazole moiety into the benzimidazole ring which leads to the synthesis of the title compounds with the both active pharmacophores in a single molecular frame work for the intensified biological activities. Thus we have designed and synthesized a series of novel phenyl-(6*H*-thiazolo-[4,5-*e*]-benzoimidazole-2-yl)-amines (**5a-f**). The synthetic route leading to the title compounds is summarized in scheme 1. The initial intermediate, 4-amino-1*H*-benzoimidazole (**2**) was prepared on reduction of 4-nitro-1*H*-benzoimidazole (**1**) with SnCl₂ under reflux for 30 minutes. Compound **2** on reaction with CS₂ and CH₃I in pyridine on constant stirring at 0 °C for 1h afforded the subsequent intermediate (1*H*-benzoimidazole-4-yl)-dithiocarbamic acid methyl ester (**3**). The intermediate, 1-(1*H*-benzoimidazole-4-yl)-3-(substituted-phenyl)-thiourea (**4a-f**) used for the preparation of target compounds have been synthesized in good yields from the reaction between compound **3** and phenyl hydrazine in methanol under reflux for 6-8 h. Further compounds **4a-f** are converted into the target compounds, phenyl-(6*H*-thiazolo-[4,5-*e*]-benzoimidazole-2-yl)-amines (**5a-f**) through a cyclization reaction with molecular bromine in acetic acid at room temperature for 4-5 h. The chemical structures of all the newly synthesized compounds were confirmed by their IR, ¹H NMR and Mass spectral data and further the compounds **5a-f** have been used to evaluate their antimicrobial activity.

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