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Synthesis and Antimicrobial Evaluation of Some New Thiazolo Imidazole Analogs

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Thiazole and imidazole derivatives have attracted medicinal chemists owing to their extensive biological activities. Present paper describes the synthesis of some new thiazolo imidazole derivatives. 4-Substituted phenacyl bromides were prepared from substituted acetophenones. The products were condensed with thiourea to obtain 2-amino-4-(4-substituted phenyl)thiazoles which on further reaction with 4-substituted phenacyl bromides resulted in 3,6-di(substituted phenyl)imidazo[2,1-b] thiazoles (**3a-3i**). The formation of all the compounds was established by spectral techniques like IR, ^{1}H NMR and Mass spectral data. The title compounds were screened for their antimicrobial activity against Gram-positive bacteria *S. aureus* and *B. subtilis*, Gram-negative bacteria *E. coli* and *K. pneumoniae* and the fungal strains like *A. niger*, *C. albicans* and *C. neoformans.* The results indicated that the compounds coded **3a**, **3c**, **3g** and **3i** showed significant activity than the remaining compounds.

Keywords: Thiazole, Imidazoles, Synthesis, Antibacterial, Antifungal.

INTRODUCTION

Over the past few decades considerable advances have been achieved in the introduction of new structural prototypes as effective antimicrobials. Many antimicrobial agents still suffer from major limitations like lack of selectivity, their unwanted side effects, non-economical and time-consuming synthetic processes, emergence of drug resistance by the micro-organisms, *etc*. Therefore attention is focussed in the design and synthesis of new antimicrobial agents to overcome these limitations.

Among the various types of heterocyclic compounds, thiazole and imidazole derivatives have received considerable attention towards synthetic medicinal chemists as they are endowed with wide range of therapeutic properties and applications. Compounds containing thiazole nucleus are unique molecules reported to possess an array of biological activities such as antibacterial [1], antifungal [2], antitumor [3,4], anti-inflammatory [5,6], anticonvulsant [7], anthelmintic activity [8], *etc*. Imidazoles are more vital in many biological processes since they are present in many natural compounds. Many synthetic pyrimidine analogs are also known to exhibit a variety of therapeutic uses including antiviral [9], anti-mycobacterial [10], antitumor [11], anti-inflammatory [12], antidepressant [13], branchodilatory [14], antifungal activity [15], *etc*.

Thiazolo imidazoles are the fused ring systems involving thiazole and imidazole with a common brige-head nitrogen at position-4. Substituted thiazolo imidazoles are also of great importance because of their remarkable biological activities including antimicrobial [16], anticancerous [17], antiproliferative [18], antitubercular [19], lipoxygenase inhibiting [20], anti-infective activity [16], *etc*. Still their antimicrobial activities have shown only handful of results so far. In continuation to these efforts and with an objective to develop novel and potent therapeutic agents of synthetic origin, we have studied and reported the synthesis, characterization and antimicrobial activity of some novel thaizolo imidazole analogs.

EXPERIMENTAL

All the chemicals and solvents were of analytical grade and procured from commercial suppliers and used without purification or drying unless otherwise noted. The melting points of the intermediates and products were determined in open capillary tubes and uncorrected. The purity of the compounds was routinely checked by TLC using silica gel-G with solvents as *n*-hexane and ethyl acetate (7:3). The physical data of the compounds is shown separately (Table-1). UV- absorption data of the intermediates and target compounds was collected by using UV-visible spectrophotometer SL-159, Elico India Ltd. reported in λ_{max} values. ^{1}H NMR spectra were recorded in DMSO at 400 MHz on Bruker AMX using tetramethylsilane

TABLE-1
PHYSICAL DATA OF THE TITLE COMPOUNDS

Code	m.f.	m.w.	Yield (%)	m.p. (°C)	R_f value
3a	$C_{17}H_{10}N_2SCl_2$	344	78.2	188-190	0.58
3b	$C_{18}H_{13}ON_2SCl$	340	74.5	202-204	0.76
3c	$C_{17}H_{10}O_2N_3SCl$	355	62.2	156-158	0.52
3d	$C_{18}H_{13}ON_2SCl$	340	70.5	170-172	0.61
3e	$C_{19}H_{16}O_2N_2S$	336	67.4	139-141	0.48
3f	$C_{18}H_{13}O_3N_3S$	351	70.5	208-210	0.72
3g	$C_{17}H_{10}O_2N_3SCl$	355	66.6	150-152	0.69
3h	$C_{18}H_{13}O_3N_3S$	351	68.8	218-220	0.55
3i	$C_{17}H_{10}O_4N_4S$	366	71.6	146-148	0.66

(TMS) as internal standard and the data was reported ppm. IR spectra of the compounds were collected using KBr pellet on Shimadzu FTIR-8700 spectrophotometer and frequencies were recorded in wave numbers. Mass spectra were recorded in Shimadzu LC MS-2010A at Quest Research Training Institute Ltd. Bangalore, India.

General procedure for the synthesis of 4-substituted phenacyl bromides (1a-c): To a solution of 4-substituted acetophenone (0.3 mol) and acetic acid (75 mL), added drop-wise bromine (20 mL) in acetic acid (75 mL). The contents were stirred for 1 h at 0-10 °C and further for 1 h at room temperature. Then the reaction mixture was poured into crushed ice, the solid separated was filtered and washed with water [21,22]. The product was recrystallized from methanol. R_f was determined in a solvent mixture of *n*-hexane and ethyl acetate (7:3).

Compound 1a (R = Cl): Pale yellow solid; Yield 80.70 %; m.p. 89 °C; R_f 0.72.

Compound 1b (R = OCH_3): Pale yellow solid; Yield 82.40 %; m.p. 80 °C; R_f 0.63.

Compound 1c (R = NO_2): yellow solid; Yield 79.60 %; m.p. 82 °C; R_f 0.69.

General procedure for the synthesis of 2-amino-4-(4-substituted phenyl)thiazoles (2a-c): Substituted phenacyl bromide (0.01 mol) and thiourea (0.76 g, 0.01 mol) were taken in a reaction vessel and added water (10 mL). The reaction mixture was irradiated under micro wave (40 W) for 10-15 min. The solid separated was filtered, washed with water and recrystallized from absolute alcohol [17,23].

Compound 2a (R = Cl): White solid; Yield 78.70 %; m.p. 188 °C; R_f 0.80; λ_{max} 238 nm; IR (KBr, ν_{max}, cm^{-1}): 3360.20 ($1^{\circ}NH_2$, str.), 3063.22 (Ar-CH, str), 1686.10 (Ar C=C), 1602.45 (NH_2 bend), 1534.30 (CN str.), 770.60 (C-S), 687.10 (C-Cl).

Compound 2b (R = OCH_3): White solid; Yield 84.40 %; m.p. 176 °C; R_f 0.68; λ_{max} 244 nm; IR (KBr, ν_{max}, cm^{-1}): 3362.40 ($1^{\circ}NH_2$, str.), 3068.28 (Ar-CH, str), 1684.16 (Ar C=C), 1605.15 (NH_2 bend), 1535.35 (CN str.), 1245.45 (Ar-O-C, str), 773.65 (C-S).

Compound 2c (R = NO_2): White solid; Yield 81.60 %; m.p. 232 °C; R_f 0.76; λ_{max} 242 nm; IR (KBr, ν_{max}, cm^{-1}): 3363.45 ($1^{\circ}NH_2$, str.), 3065.20 (Ar-CH, str), 1684.30 (Ar C=C), 1604.25 (NH_2 bend), 1535.35 (CN str.), 1350.40 (N-O of NO_2), 773.65 (C-S).

General protocol for the synthesis of 3,6-di(substituted phenyl)imidazo[2,1b]thiazoles (3a-i): 2-Amino-4-(4-substituted phenyl)thiazole (0.01 mol) was dissolved in acetone (25 mL) and treated with the substituted 2-phenacyl bromide (0.01 mol). The mixture was refluxed for 8 h and then concentrated to 10 mL. To make the resulting solution alkaline, 15 % NH_4OH was added drop-wise to get pH 8-9. The mixture was then poured into CH_2Cl_2, washed and concentrated [17,23]. The product was filtered and recrystallized from absolute alcohol (**Scheme-I**). The spectral data of the products **(3a-3i)** is given below:

3,6-Di(4-chloro phenyl)imidazo[2,1-b]thiazole (3a): λ_{max} 265 nm, IR (KBr, ν_{max}, cm^{-1}): 3056.50 (Ar-CH, str.), 2912.80 (Aliph.CH, str), 1687.20 (Ar C=C-), 1537.15 (C=N str), 762.33 (C-S), 692.05 (C-Cl); ^{1}H NMR (DMSO) δ ppm: 8.52 (s, 1H, imid N-H), 7.92 (d, 2H, 22 & 62-H, phenyl ring on imid), 7.50 (d, 2H, 22 & 62-H, phenyl ring on thiaz.), 7.30 (d, 2H, 32 & 52-H, phenyl ring on thiaz.), 6.92 (d, 2H, 32 & 52-H, phenyl ring on imid.), 6.46 (s, 22-H, thiaz.); MS: *m/z*: 344.12 $[M]^+$.

3-(4-Chloro phenyl)-6-(4-methoxy phenyl)imidazo[2,1-b]thiazole (3b): λ_{max} 268 nm; IR (KBr, ν_{max}, cm^{-1}): 3052.30 (Ar-CH, str.), 2910.80 (Aliph.CH, str), 1686.10 (Ar C=C-), 1537.25 (C=N str), 1245.45 (Ar-O-C, str), 762.33 (C-S), 692.05 (C-Cl); ^{1}H NMR (DMSO) δ ppm: 8.54 (s, 1H, imid N-H), 7.95 (d, 2H, 22 & 62-H, phenyl ring on imid), 7.55 (d, 2H, 22 & 62-H, phenyl ring on thiaz.), 7.38 (d, 2H, 32 & 52-H, phenyl ring on thiaz.), 6.90 (d, 2H, 32 & 52-H, phenyl ring on imid.), 6.46 (s, 22-H, thiaz.), 3.86 (s, 3H, -OCH_3); MS: *m/z*: 340.08 $[M]^+$.

3-(4-Chloro phenyl)-6-(4-nitro phenyl)imidazo[2,1b]-thiazole (3c): λ_{max} 268 nm; IR (KBr, ν_{max}, cm^{-1}): 3055.30 (Ar-CH, str.), 1685.10 (Ar C=C-), 1536.15 (C=N str), 1350.40 (N-O of NO_2), 1295.60 (Ar.C-N-, str), 763.22 (C-S), 690.15 (C-Cl); ^{1}H NMR (DMSO) δ ppm: 8.55 (s, 1H, imid N-H), 7.95 (d, 2H, 22 & 62-H, phenyl ring on imid), 7.52 (d, 2H, 22 & 62-H, phenyl ring on thiaz.), 7.40 (d, 2H, 32 & 52-H, phenyl ring on thiaz.), 6.86 (d, 2H, 32 & 52-H, phenyl ring on imid.), 6.40 (s, 22-H, thiaz.); MS: *m/z*: 355.10 $[M]^+$.

3-(4-Methoxy phenyl)-6-(4-chloro phenyl)imidazo[2,1-b]thiazole (3d): λ_{max} 270 nm; IR (KBr, ν_{max}, cm^{-1}): 3052.60 (Ar-CH, str.), 2911.80 (Aliph.CH, str), 1688.10 (Ar C=C-), 1536.20 (C=N str), 1247.30 (Ar-O-C, str), 764.50 (C-S), 692.70 (C-Cl); ^{1}H NMR (DMSO) δ ppm: 8.58 (s, 1H, imid N-H), 7.92 (d, 2H, 22 & 62-H, phenyl ring on imid), 7.54 (d, 2H, 22 & 62-H, phenyl ring on thiaz.), 7.40 (d, 2H, 32 & 52-H, phenyl ring on thiaz.), 6.88 (d, 2H, 32 & 52-H, phenyl ring on imid.), 6.43 (s, 22-H, thiaz.), 3.88 (s, 3H, -OCH_3); MS: *m/z*: 340.14 $[M]^+$.

3,6-Di(4-methoxy phenyl)imidazo[2,1-b]thiazole (3e): λ_{max} 280 nm; IR (KBr, ν_{max}, cm^{-1}): 3054.30 (Ar-CH, str.), 2911.80 (Aliph.CH, str), 1687.10 (Ar C=C-), 1539.45 (C=N str), 1244.65 (Ar-O-C, str), 764.60 (C-S); ^{1}H NMR (DMSO) δ ppm: 8.60 (s, 1H, imid N-H), 7.85 (d, 2H, 22 & 62-H, phenyl ring on imid), 7.52 (d, 2H, 22 & 62-H, phenyl ring on thiaz.), 7.40 (d, 2H, 32 & 52-H, phenyl ring on thiaz.), 6.80 (d, 2H, 32 & 52-H, phenyl ring on imid.), 6.40 (s, 22-H, thiaz.), 3.82 (s, 3H, -OCH_3); MS: *m/z*: 336.05 $[M]^+$.

3-(4-Methoxy phenyl)-6-(4-nitro phenyl)imidazo[2,1-b]thiazole (3f): λ_{max} 268 nm; IR (KBr, ν_{max}, cm^{-1}): 3052.30 (Ar-CH, str.), 2914.80 (Aliph.CH, str), 1685.80 (Ar C=C-), 1538.55 (C=N str), 1352.50 (N-O of NO_2), 1288.60 (Ar.C-N-

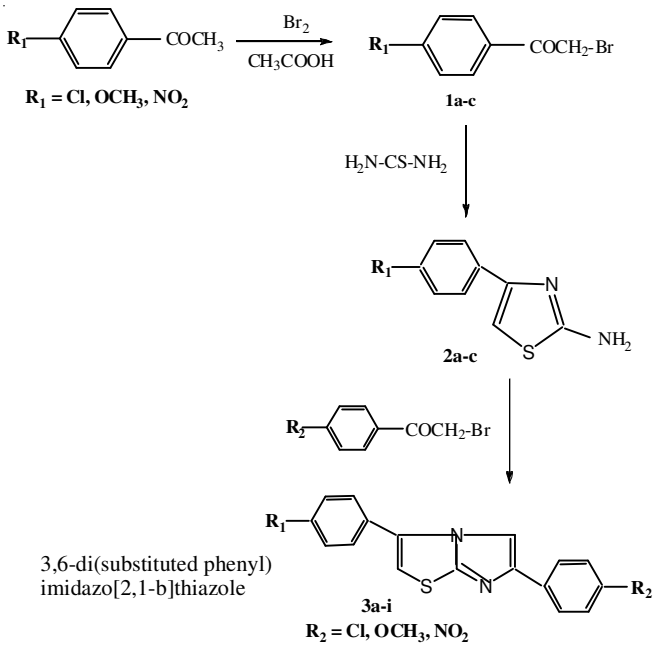
, str) 1245.45 (Ar-O-C, str), 760.33 (C-S); ^{1}H NMR (DMSO) δ ppm: 8.58 (s, 1H, imid N-H), 7.90 (d, 2H, 22 & 62-H, phenyl ring on imid), 7.55 (d, 2H, 22 & 62-H, phenyl ring on thiaz.), 7.42 (d, 2H, 32 & 52-H, phenyl ring on thiaz.), 6.92 (d, 2H, 32 & 52-H, phenyl ring on imid.), 6.48 (s, 22-H, thiaz.), 3.85 (s, 3H, -OCH_3); MS: *m/z*: 351.14 $[M]^+$.

3-(4-Nitro phenyl)-6-(4-chloro phenyl)imidazo[2,1b]-thiazole (3g): λ_{max} 278 nm; IR (KBr, ν_{max}, cm^{-1}): 3056.40 (Ar-CH, str.), 1688.10 (Ar C=C-), 1535.35 (C=N str), 1353.40 (N-O of NO_2), 1294.60 (Ar.C-N-, str), 762.82 (C-S), 690.55 (C-Cl); ^{1}H NMR (DMSO) δ ppm: 8.53 (s, 1H, imid N-H), 7.93 (d, 2H, 22 & 62-H, phenyl ring on imid), 7.54 (d, 2H, 22 & 62-H, phenyl ring on thiaz.), 7.40 (d, 2H, 32 & 52-H, phenyl ring on thiaz.), 6.85 (d, 2H, 32 & 52-H, phenyl ring on imid.), 6.42 (s, 22-H, thiaz.); MS: *m/z*: 355.05 $[M]^+$.

3-(4-Nitro phenyl)-6-(4-methoxy phenyl)imidazo[2,1b]-thiazole (3h): λ_{max} 284 nm; IR (KBr, ν_{max}, cm^{-1}): 3050.50 (Ar-CH, str.), 2916.70 (Aliph.CH, str), 1687.30 (Ar C=C-), 1540.55 (C=N str), 1353.80 (N-O of NO_2), 1295.60 (Ar.C-N-, str), 1246.45 (Ar-O-C, str), 764.33 (C-S), ^{1}H NMR (DMSO) δ ppm: 8.55 (s, 1H, imid N-H), 7.95 (d, 2H, 22 & 62-H, phenyl ring on imid), 7.52 (d, 2H, 22 & 62-H, phenyl ring on thiaz.), 7.40 (d, 2H, 32 & 52-H, phenyl ring on thiaz.), 6.88 (d, 2H, 32 & 52-H, phenyl ring on imid.), 6.44 (s, 22-H, thiaz.), 3.85 (s, 3H, -OCH_3); MS: *m/z*: 351.00 $[M]^+$.

3,6-Di(4-nitro phenyl)imidazo[2,1-b]thiazole (3i): λ_{max} 268 nm; IR (KBr, ν_{max}, cm^{-1}): 3052.30 (Ar-CH, str.), 1685.80 (Ar C=C-), 1538.55 (C=N str), 1354.50 (N-O of NO_2), 1296.60 (Ar.C-N-, str), 762.33 (C-S); ^{1}H NMR (DMSO) δ ppm: 8.57 (s, 1H, imid N-H), 7.94 (d, 2H, 22 & 62-H, phenyl ring on imid), 7.54 (d, 2H, 22 & 62-H, phenyl ring on thiaz.), 7.32 (d, 2H, 32 & 52-H, phenyl ring on thiaz.), 6.90 (d, 2H, 32 & 52-H, phenyl ring on imid.), 6.45 (s, 22-H, thiaz.); MS: *m/z*: 366.16 $[M]^+$.

Antibacterial and antifungal activity: The antimicrobial activity of the new compounds was determined *in vitro* by cup-plate agar diffusion method using DMSO as solvent [24-26]. Antibacterial activity was determined against Gram-positive bacteria *Staphylococcus aureus* (ATCC 11632) and *Bacillus subtilis* (ATCC 60711) and Gram-negative bacteria *Escherichia coli* (ATCC 10536) and *Klebsiella pneumoniae* (ATCC 13883), while antifungal activity against *Aspergilus niger* (ATCC 1781), *Candida albicans* (ATCC 2501) and *Cryptococcus neoformans*



Scheme-I: Synthesis of 3,6-di(substituted phenyl)imidazo[2,1-b]thiazole derivatives (**3a-3i**)

(ATCC 32042) at 50 µg/0.1 mL concentration. After 24 h of incubation at 37 ± 1 °C and 48 h at 28 ± 1 °C, the antibacterial and antifungal activity respectively was determined by measuring zones of inhibitions in mm. Standard antibacterial ampicillin and antifungal miconazole nitrate were used respectively under similar conditions for comparison. Control test with solvents were performed for every assay but showed no inhibition of microbial growth. The responses of organisms to the synthesized compounds were measured as mean of three values and compared with standards. Standard deviation was also calculated (Table-2).

RESULTS AND DISCUSSION

The formation of intermediates, 2-amino thiazole derivatives (**2a-c**) is confirmed by specific IR absorption band for primary amine at 3360 cm^{-1} (stretching vibrations) and 1602 cm^{-1} (bending vibrations). There is also absorption bands for C=N stretching at 1534 cm^{-1} and for C-S-C str. at 770 cm^{-1}. From UV-visible absorption data, it is observed that the intermediates 2-amino thiazoles and the title compounds exhibited λ_{max} at 238-244

TABLE-2
MICROBIAL ACTIVITY DATA OF SOME THIAZOLO IMIDAZOLE DERIVATIVES

Compd. No.	R_1	R_2	Zone of inhibition (mm)						
			Antibacterial activity				Antifungal activity		
			S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*	*A. niger*	*C. albicans*	*C. neoformans*
3a	Cl	Cl	21.66 ± 0.57	19.33 ± 1.00	21.00 ± 1.52	17.00 ± 1.73	18.33 ± 1.15	16.66 ± 1.52	15.00 ± 1.73
3b	Cl	OCH_3	NA	NA	NA	NA	NA	NA	NA
3c	Cl	NO_2	19.00 ± 1.00	18.00 ± 1.73	20.66 ± 1.52	17. 33 ± 0.57	17.66 ± 1.15	16.33 ± 0.57	14.66 ± 1.52
3d	OCH_3	Cl	14.66 ± 0.57	12.00 ± 1.73	10. 66 ± 0.57	NA	10.99 ± 0.57	NA	NA
3e	OCH_3	OCH_3	NA	NA	NA	NA	NA	NA	NA
3f	OCH_3	NO_2	16. 33 ± 1.15	14. 00 ± 1.73	13.66 ± 1.52	11.66 ± 0.57	08. 66 ± 1.52	NA	NA
3g	NO_2	Cl	20.66 ± 0.57	17.66 ± 0.57	21.33 ± 1.52	18.00 ± 1.73	14.00 ± 1.00	15.00 ± 1.73	13.00 ± 1.73
3h	NO_2	OCH_3	NA	NA	NA	NA	NA	NA	NA
3i	NO_2	NO_2	20.66 ± 1.15	17.33 ± 1.15	21.33 ± 0.57	17.66 ± 1.52	18.66 ± 1.52	15.33 ± 1.52	13. 33 ± 0.57
Ampicillin			23.33 ± 0.57	19.66 ± 1.15	24.00 ± 1.73	18.66 ± 1.52	–	–	–
Miconazole nitrate			–	–	–	–	27.66 ± 1.73	24.33 ± 0.57	23.66 ± 1.52

nm and 265-284 nm, respectively. This indicates batho-chromic shift in the formation of these compounds.

The structures of the title compounds (**3a-3i**) are characterized by specific IR absorption bands for C=N stretching at 1540-1535 cm^{-1}, Ar-C-N stretching at 1295-1288 cm^{-1} and C-S-C stretching at 765-759 cm^{-1}, *etc*. The presence of other special functional groups like Cl, OCH_3 and NO_2 are indicated by their specific bands (692-690, 1247-1244, 1354-1350 cm^{-1}, respectively). The structural characteristics were further supported by ^1H NMR and mass-spectral data.

From antibacterial screening study it was observed that the compounds containing electron withdrawing substituents on both the rings such as **3a** (R_1 = Cl, R_2 = Cl), **3c** (R_1 = Cl, R_2 = NO_2), **3g** (R_1 = NO_2, R_2 = Cl) and **3i** (R_1 = NO_2, R_2 = NO_2) exhibited significant activity. The compounds containing electron donating group at R_1 and electron withdrawing group at R_2 showed moderate activity, **3d** (OCH_3, Cl) and **3f** (OCH_3, NO_2).The remaining compounds showed no activity. Of the nine compounds screened for antifungal activity, only the compounds coded **3a, 3c, 3g** and **3i** displayed significant fungicidal activity than the remaining compounds, indicates the significance of electron withdrawing groups.

Conclusion

Owing to the pronounced biological importance associated with the drugs containing thiazole and imidazole rings, we have hereby studied and reported the synthesis and structural characterization of some thiazolo imidazole derivatives. The compounds containing electron withdrawing groups on either ring showed significant antibacerial and antifungal activity. The insight obtained in this work will be useful for the study of other structurally modified thiazolo imidazoles.

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