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Synthesis and antimicrobial activities of some ethyl 2-arylthio-6-arylimidazo[2,1-*b*]thiazole-3-carboxylates and their sulfones

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A series of new 2-arylthio-3-ethoxycarbonyl-6-arylimidazo[2,1-*b*]thiazoles **(4a–4h)** and 2-arenesulfonyl-3-ethoxycarbonyl-6-arylimidazo[2,1-*b*]thiazoles **(5a–5h)** have been prepared and characterized by analytical and spectral methods. The title compounds **4a–4h** and **5a–5h** were obtained by the reaction of 2-amino-4-ethoxycarbonyl-5-arylthiothiazoles **(2a** and **2b)**/2-amino-4-ethoxycarbonyl-5-arenesulphonylthiazoles **(3a** and **3b)** with various phenacyl bromides in anhydrous ethanol. These newly synthesized compounds (**4a–4h** and **5a–5h**) were screened for their antibacterial activity against Gram-negative bacterium *Escherichia coli*, Gram-positive bacterium *Staphylococcus aureus,* and antifungal properties against *Aspergillus niger* and *Candida albicans.*

Keywords: imidazo[2,1-*b*]thiazole; sulfides; sulfones; antimicrobial activity; ethyl 2-amino-5-bromothiazole-4-carboxylate

1. Introduction

Bis-(4-aminophenyl)sulfone, a well-known antitubercular and antileprotic drug, was first evaluated by Buttle et al. (*1*) as an antibacterial which was 100 times as active as sulfanilamide in streptococcus infections. In order to increase the antibacterial activity and to reduce the toxicity, usually one or both phenyl rings are substituted by heterocyclic rings such as thiazole. Thiazole sulfides and sulfones have been shown to display potent antibacterial, analgesic, and anti-inflammatory activities. A lot of work on the synthesis and biological activities of the condensed imidazo[2,1-*b*]thiazoles has been reported since the discovery of the novel broad-spectrum anthelmintic, tetramisole (*2*). But not a single drug better than tetramisole has been evaluated till now among the derivatives containing imidazo[2,1-*b*]thiazole basic moiety. Imidazothiazole derivatives have been shown to display potent antitumor and fungistatic activities (*3–6*). In continuation of our work on nitrogen containing bridgehead heterocycles (*7, 8*), we thought it worthwhile to prepare sulfides and sulfones of thiazoloimidazoles expecting them to exhibit better antimicrobial properties.

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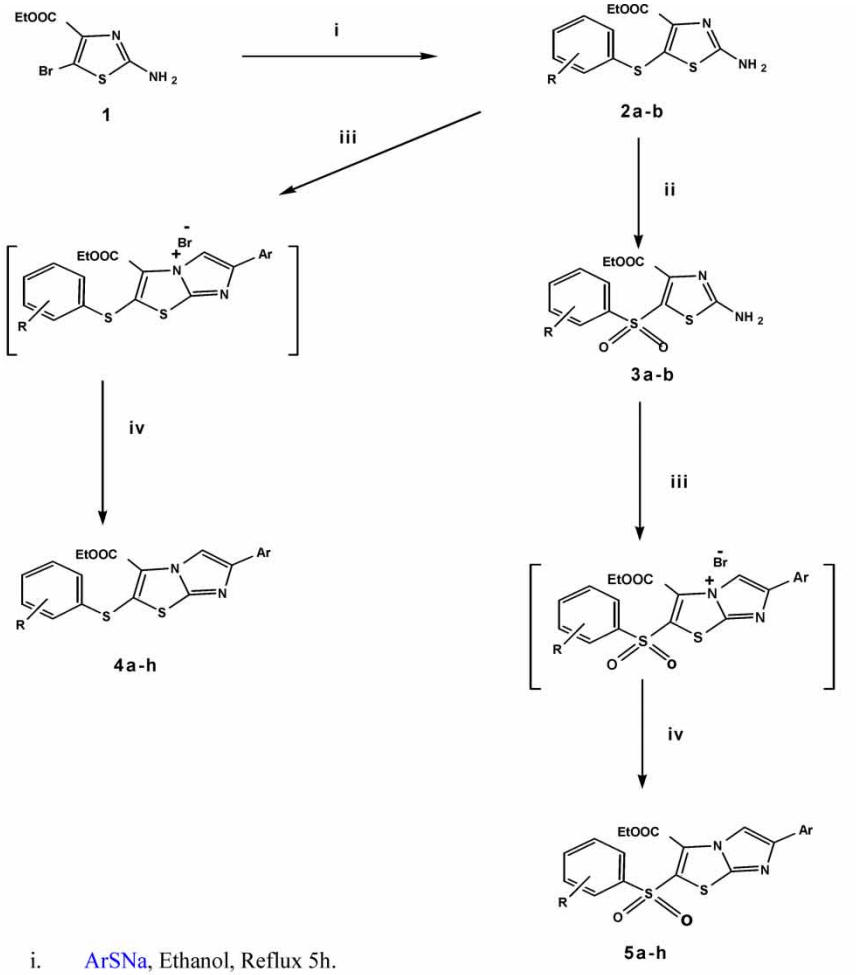
2. Chemistry

The synthetic pathway for the preparation of the title compounds is depicted in Scheme 1. The starting compound 2-amino-4-ethoxycarbonyl-5-arylthiothiazoles **(2a** and **2b)** were obtained by the nucleophilic displacement reaction of 2-amino-4-ethoxycarbonyl-5-bromothiazole (*9*) using an appropriate thiophenoxide anion. These initially prepared sulfides **(2a** and **2b)** on oxidation with hydrogen peroxide gave the respective sulfones **(3a** and **3b)**. The imidazothiazole ring was



i. ArSNa, Ethanol, Reflux 5h.

ii. H_2O_2, AcOH, rt 48h.

iii. $ArCOCH_2Br$, Ethanol, Reflux 12h.

iv. Aq. Na_2CO_3

a, R=Cl, Ar=p-tolyl; **b,** R=Cl , Ar=p-NO_2 Ph; **c,** R=Cl, Ar=p-Cl Ph; **d,** R=Cl, Ar=p-Br Ph;

e, R=CH_3, Ar=p-tolyl; **f,** R=CH_3, Ar=p-NO_2 Ph; **g,** R=CH_3, Ar=p-Cl Ph; **h,** R=CH_3, Ar=p-Br Ph.

Scheme 1.

synthesized by adopting the 3 + 2 approach wherein the nucleophilic sites from the thiazole nucleus and electrophilic sites from α-haloketones were utilized. Thus, condensation of 2-amino-4-ethoxycarbonyl-5-arylthiothiazoles **(2a** and **2b)** and their sulfones **(3a** and **3b)** with various phenacyl bromides yielded the hydrobromide salts of imidazothiazole derivatives, which on neutralization with aqueous sodium carbonate gave the required free bases **(4a**–**4h** and **5a**–**5h)**. The structures of all these newly synthesized 2-arylthio-3-ethoxycarbonyl-6-arylimidazo[2,1-*b*]thiazoles **(4a**–**4h)** and 2-arenesulfonyl-3-ethoxycarbonyl-6-arylimidazo[2,1-*b*]thiazoles **(5a**–**5h)** were established by analytical and spectroscopic methods. UV spectral data of **5a**–**5h** reveal the presence of two absorption bands, one in the region of 274–283 nm and other at 304–319 nm. These bands are due to n–π^* transition pertaining to S=O group which appears near at 220 nm and undergoes hypsochromic shift with increase in solvent polarity. IR spectra of **5a**–**5h** shows bands at 1724 (C=O of ester), 1535 (C=N), 1329 (asym), and 1180 (sym) (S=O of sulfone) cm^{-1}.

The alternative approach for the synthesis of title compounds starting from the preconstructed imidazothiazole is not feasible as any electrophilic substitution carried out on the imidazothiazole would takes place at the 5-position (Imidazole ring) rather than the 2-position (thiazole ring).

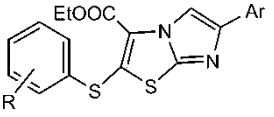
3. Biological activity

Antibacterial activity of **4a**–**4h** and **5a**–**5h** in dimethylformamide (DMF) was performed by cup plate method (*10*) using nutrient agar. Each test compound (5 mg) was dissolved in DMF (5 ml) to give a solution of 1000 μg/ml and 0.1 ml of this solution (100 μg/ml) was used. Norfloxacin (CAS 70458-96-7) was used as a reference drug. One day prior to the screening, inoculation of *E. coli* and *S. aureus* was made in the nutrient agar solution (2%) and pH adjusted to 7.2. It was autoclaved for 30 min and incubated at 37°C for 22–24 h. Base layer medium was used as seed layer medium of pH 7.2 and sterilized by autoclaving. Then it was mixed with overnight grown subculture (2%). About 10–15 ml of this medium was poured over base layer taken in a Petridish and allowed to attain room temperature. The cups were made by scooping out nutrient agar with sterilized cork borer. To these cups, 0.1 ml of the test solution was added and incubated at 37°C for 48 h. Zone of inhibition was then measured in each case (in mm) and compared with that of the reference drug. DMF was used as control. Results are given in Tables 1 and 2.

Antifungal activity of **4a**–**4h** and **5a**–**5h** in DMF was also performed by cup plate method by using Grieseofulvin as the standard. One-and-half day prior to the experiment, the fungal cultures of *Aspergillus niger* and *Candida albicans* were prepared in the inoculation medium and were incubated at 37°C for 36 h, and the pH adjusted to 7.2. It was autoclaved for 20 min at 15 psi. Fungal medium was used at pH 7.2 and sterilized by autoclaving. It was then mixed with one-and-half -day grown subculture. The cups were made by scooping out nutrient agar with sterilized cork borer. To these cups, 0.1 ml of the test solution was added and incubated at 37°C for 48 h. Zone of inhibition was then measured in each case (in mm) and compared with that of the reference drug. DMF was used as control.

The results of antimicrobial screening (Tables 1 and 2) reveals that both arylthio-and arenesulfonylimidazo(2,1-*b*)thiazole carboxylates (**4** and **5**) displayed better antibacterial activity compared with their antifungal activities. It is observed that generally 2-arenesulfonyl derivatives (**5**) exhibited better antibacterial activities compared with their arylthio counterparts (**4**). These compounds are found to be more effective against *E. coli.* Among the arylthio derivatives tested, the compound with 4-chloro substituent in the phenyl ring and 4-nitrophenyl substitution at C-5 (**4b**) exhibited maximum activity against *E. coli* followed by **4c**(R=4-Cl and Ar=4-Cl Ph) and **4g** (R=4-CH_3 and Ar=4-Cl Ph). Compound **4e** (R=4-CH_3, Ar=4-CH_3 Ph) was found to be more active against *S. aureus*. The activity trends in arenesulfonyl compounds (**5a**–**5h**) reveal that

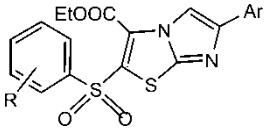
Table 1. Antimicrobial activity.



Ethyl 2-arylthio-6-arylimidazo[2,1-*b*]thiazole-3-carboxylates (**4a**–**4h**)

		Antibacterial		Antifungal	
R	Ar	E. coli (mm)	S. aureus (mm)	C. albicans (mm)	A. niger (mm)
4-Cl	4-CH_3Ph	14	13	13	12
4-Cl	4-NO_2Ph	17	15	9	10
4-Cl	4-ClPh	16	13	13	12
4-Cl	4-BrPh	15	12	12	17
4-CH_3	4-CH_3Ph	14	17	12	14
4-CH_3	4-NO_2Ph	15	13	9	12
4-CH_3	4-ClPh	16	12	11	10
4-CH_3	4-BrPh	13	12	8	13
Norfloxacin		23	22	–	–
Griseofulvin		–	–	22	21

Table 2. Antimicrobial activity.



Ethyl 2-arenesulfonyl-6-arylimidazo[2,1-*b*]thiazole-3-carboxylates (**5a**–**5h**)

		Antibacterial		Antifungal	
R	Ar	E. coli (mm)	S. aureus (mm)	C. albicans (mm)	A. niger (mm)
4-Cl	4-CH_3Ph	16	15	14	13
4-Cl	4-NO_2Ph	18	16	10	10
4-Cl	4-ClPh	17	14	14	13
4-Cl	4-BrPh	19	14	12	19
4-CH_3	4-CH_3Ph	16	12	13	15
4-CH_3	4-NO_2Ph	17	11	10	13
4-CH_3	4-ClPh	20	14	12	11
4-CH_3	4-BrPh	18	13	9	14
Norfloxacin		23	22	–	–
Griseofulvin		–	–	22	21

compound **5g** (R=4-CH_3 and Ar=4-Cl Ph) displayed maximum activity against *E. coli* which is comparable to the standard. But compound **5d** (R=4-Cl and Ar=4-Br Ph) displayed comparable antifungal activity against *A. niger* as well as antibacterial activity against *E. coli*. Hence, among all the compounds tested, compounds **5d** and **5g** displayed better antibacterial activity against *E. coli* comparable to the standard norfloxacin.

4. Experimental

Melting points were determined in open capillaries and are uncorrected. The IR spectra of samples such as KBr pellets were recorded on a Nicolet FT IR Spectrometer (model-410, USA). NMR spectra of the samples in DMSO-d_6 were recorded on a Bruker 300 MHz Spectrometer (Model

RX-300, Switzerland) using TMS as an internal standard. C, H, and N analyses were carried out on a Thermoquest CHN analyzer (Thermpoquest, Italy). These data were obtained from the instruments at University Scientific Instruments Centre, Karnatak University, Dharwad.

Ethyl 2-amino-5-bromothiazole-4-carboxylate was prepared according to methods given in literature (*11*).

4.1. *Ethyl-2-amino-5-(p-chlorophenyl)thiothiazole-4-carboxylate (2a)*

To an alcoholic solution of freshly cut sodium metal (0.23 g, 0.01 mol), in an alcoholic solution of chlorothiophenol (1.1 g, 0.01 mol) was added with stirring a solution of ethyl 2-amino-5-bromothiazole-4-carboxylate (**1**) (2.5 g, 0.01 mol) in alcohol. The mixture was then refluxed on a steam bath for 5 h. The solvent was removed and the residue added to crushed ice. The obtrained solid was collected by filtration and purified by crystallization from ethanol followed by column chromatography over neutral alumina using a mixture of ethyl acetate–hexane (EA:Hex) (20:80 v/v) as eluent. Evaporation of the first six fractions gave a pure product. Yield 68%, m.p. 118–119°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (d, 2H, ArH), 7.30 (d, 2H, ArH), 5.16 (br s, 2H, NH_2 exchangeable with D_2O), 4.40 (q, 2H, CH_2 of ester), and 1.25 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{12}H_{11}ClN_2O_2S_2$: C, 45.78; H, 3.52; N, 8.90. Found: C, 45.86; H, 3.59; N, 8.84%.

4.2. *Ethyl-2-amino-5-(p-methylphenyl)thiothiazole-4-carboxylate (2b)*

Yield 65%, m.p. 140–141°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, 2H, ArH), 7.32 (d, 2H, ArH), 5.16 (br s, 2H, NH_2 exchangeable with D_2O), 4.34 (q, 2H, CH_2 of ester), 2.12 (s, 3H, CH_3), and 1.20 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52. Found: C, 53.17; H, 4.86; N, 9.47%.

4.3. *Ethyl 2-amino-5-(p-chlorophenyl)sulfonylthiazole-4-carboxylate (3a)*

To a solution of ethyl-2-amino-5-(*p*-chlorophenyl)thiothiazole-4-carboxylate (0.1 mol) in a minimum quantity of glacial acetic acid was added hydrogen peroxide (6 ml, 30%), and the mixture was stirred at room temperature for 48 h with the intermittent addition of hydrogen peroxide (1 ml) at every 12 h. The solid detained was collected by filtration and purified by crystallization from alcohol. Yield 70%, m.p. 165–166°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.24 (br, 2H, NH_2, exchangeable with D_2O), 7.66 (d, 2H, ArH), 7.35 (d, 2H, ArH), 4.32 (q, 2H, CH_2 of ester), and 1.34 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{12}H_{11}ClN_2O_4S_2$: C, 41.56; H, 3.20; N, 8.08. Found: C, 41.68; H, 3.31; N, 7.98%.

4.4. *Ethyl 2-amino-5-(p-methylphenyl)sulfonylthiazole-4-carboxylate (3b)*

Yield 70%, m.p. 181–182°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.35 (br, 2H, NH_2, exchangeable with D_2O), 7.72 (d, 2H, ArH), 7.40 (d, 2H, ArH), 4.25 (q, 2H, CH_2 of ester), 2.14 (s, 3H, CH_3), and 1.28 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{13}H_{14}N_2O_4S_2$: C, 47.84; H, 4.32; N, 8.58. Found: C, 47.95; H, 4.44; N, 8.44%.

4.5. *Ethyl 2-(p-chlorophenyl)thio-6-(p-methylphenyl)imidazo[2,1-b]-thiazole-3-carboxylate (4a)*

A mixture of ethyl 2-amino-5-(*p*-chlorophenyl)thiothiazole-4-carboxylate (0.01 mol) and phenacyl bromide (0.01 mol) in anhydrous ethanol (60 ml) was heated to reflux on a steam

bath for 12 h. Excess of solvent was distilled off and the residue poured into ice-cold water (200 ml) to get crude 2-(*p*-chlorophenyl)thio-3-ethoxycarbonyl-6-(*p*-methylphenyl)imidazo[2,1-*b*]thiazolium bromide.

Neutralization of the above hydrobromides with aqueous sodium carbonate solution afforded the corresponding free bases, ethyl 2-(*p*-chlorophenyl)thio-6-(*p*-methylphenyl)imidazo[2,1-*b*]-thiazole-3-carboxylate (**5a**). They were purified by column chromatography over neutral alumina using ethyl acetate–hexane (EA:Hex) mixture (20:80 v/v) as eluent. Yield 50%, m.p. 170–172°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.31 (s, 1H, C-5H), 7.80 (d, $J = 7.8$ hz, 2H, ArH), 7.68 (d, $J = 7.8$ hz, 2H, ArH), 7.61 (d, $J = 8.0$ hz, 2H, ArH), 7.45 (d, $J = 8.0$ hz, 2H, ArH), 4.30 (q, 2H, CH_2 of ester), 2.20 (s, 3H, CH_3), and 1.35 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{21}H_{17}ClN_2O_2S_2$: C, 58.80; H, 3.99; N, 6.53. Found: C, 58.70; H, 4.05; N, 6.43%.

4.6. *Ethyl 2-(p-chlorophenyl)thio-6-(p-nitrophenyl)imidazo[2,1-b] thiazole-3-carboxylate (4b)*

Yield 54%, m.p. 210–212°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.35 (s, 1H, C-5H), 8.10 (d, $J = 8.5$ hz, 2H, ArH), 8.00 (d, $J = 8.5$ hz, 2H, ArH), 7.86 (d, $J = 8.3$ hz, 2H, ArH), 7.45 (d, $J = 8.3$ Hz, 2H, ArH), 4.30 (q, 2H, CH_2 of ester), and 1.45 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{20}H_{14}ClN_3O_4S_2$: C, 52.23; H, 3.07; N, 9.14. Found: C, 52.36; H, 3.18; N, 9.03%.

4.7. *Ethyl 2-(p-chlorophenyl)thio-6-(p-chlorophenyl)imidazo[2,1-b]-thiazole-3-carboxylate (4c)*

Yield 56%, m.p. 169–171°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.33 (s, 1H, C-5H), 7.84 (d, $J = 7.9$ hz, 2H, ArH), 7.66 (d, $J = 8.0$ hz, 2H, ArH), 7.56 (d, $J = 8.2$ hz, 2H, ArH), 7.43 (d, $J = 8.2$ hz, 2H, ArH), 4.30 (q, 2H, CH_2 of ester), and 1.30 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{20}H_{14}Cl_2N_2O_2S_2$: C, 53.46; H, 3.14; N, 6.23. Found: C, 53.53; H, 3.25; N, 6.12%.

4.8. *Ethyl 2-(p-chlorophenyl)thio-6-(p-bromophenyl)imidazo[2,1-b]-thiazole-3-carboxylate (4d)*

Yield 55%, m.p. 180–182°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.26 (s, 1H, C-5H), 7.75 (d, $J = 8.2$ hz, 2H, ArH), 7.59 (d, $J = 8.2$ hz, 2H, ArH), 7.50 (d, $J = 8.0$ hz, 2H, ArH), 7.38 (d, $J = 8.0$ hz, 2H, ArH), 4.25 (q, 2H, CH_2 of ester), and 1.35 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{20}H_{14}BrClN_2O_2S_2$: C, 48.64; H, 2.86; N, 5.67. Found: C, 48.72; H, 2.99; N, 5.60%.

4.9. *Ethyl 2-(p-methylphenyl)thio-6-(p-methylphenyl)imidazo[2,1-b]-thiazole-3-carboxylate (4e)*

Yield 55%, m.p. 172–174°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (d, $J = 8.1$ hz, 2H, ArH), 7.85 (d, $J = 8.1$ hz, 2H, ArH), 7.68 (d, $J = 8.0$ hz, 2H, ArH), 7.50 (d, $J = 8.0$ hz, 2H, ArH), 4.15 (q, 2H, CH_2 of ester), 2.15 (s, 6H, CH_3), and 1.35 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{22}H_{20}N_2O_2S_2$: C, 64.68; H, 4.93; N, 6.86. Found: C, 64.77; H, 5.05; N, 6.78%.

4.10. *Ethyl 2-(p-methylphenyl)thio-6-(p-nitrophenyl)imidazo[2,1-b]thiazole-3-carboxylate (4f)*

Yield 54%, m.p. 166–168°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.47 (s, 1H, C-5H), 8.27 (d, $J = 8.7$ hz, 2H, ArH), 7.97 (d, $J = 8.7$ hz, 2H, ArH), 7.65 (d, $J = 8.3$ hz, 2H, ArH), 7.51

(d, $J = 8.3$ hz, 2H, ArH), 4.58 (q, 2H, CH_2 of ester), 2.19 (s, 3H, CH_3), and 1.54 (t, 3H, CH_3 of ester); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.0 (C=O of ester), 148.6 (C-1″), 147.3 (C-4″) 140.4 (C-2), 138.5 (C -6), 137.1 (C-8), 134.4 (C-2″ andC-6″), 133.5 (C-2″ and C-6″), 132.6 (C-1″), 131.3 (C-4″), 130.7 (C-3″ andC-5″), 126.1(C-5), 125.5 (C-3″ and C-5″), 113.1 (C-3), 62.2 (CH_2 of ester), 31.3 (CH_3), and 15.1 (CH_3 of ester). Anal. Calcd. for $C_{21}H_{17}N_3O_4S_2$: C, 57.39; H, 3.90; N, 9.56. Found: C, 57.47; H, 4.02; N, 9.43%.

4.11. *Ethyl 2-(p-methylphenyl)thio-6-(p-chlorophenyl)imidazo[2,1-b]-thiazole-3-carboxylate (4g)*

Yield 52%, m.p. 181–183°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.35 (s, 1H, C-5H), 8.20 (d, $J =$ 8.4 hz, 2H, ArH), 7.86 (d, $J = 8.4$ hz, 2H, ArH), 7.71 (d, $J = 8.2$ hz, 2H, ArH), 7.53 (d, $J =$ 8.2 hz, 2H, ArH), 4.30 (q, 2H, CH_2 of ester), 2.30 (s, 3H, CH_3), and 1.20 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{21}H_{17}ClN_2O_2S_2$: C, 58.80; H, 3.99; N, 6.53. Found: C, 58.92; H, 4.09; N, 6.46%.

4.12. *Ethyl 2-(p-methylphenyl)thio-6-(p-bromophenyl)imidazo[2,1-b] thiazole-3-carboxylate (4h)*

Yield 56%; m.p. 177–179°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.36 (s, 1H, C-5H), 8.24 (d, $J =$ 8.6 hz, 2H, ArH), 7.94 (d, $J = 8.6$ hz, 2H, ArH), 7.62 (d, $J = 8.3$ hz, 2H, ArH), 7.49 (d, $J =$ 8.3 hz, 2H, ArH), 4.56 (q, 2H, CH_2 of ester), 2.19 (s, 3H, CH_3), and 1.54 (t, 3H, CH_3 of ester); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.0 (C=O of ester), 147.4 (C-1″), 146.5 (C-4″), 145.1 (C-2), 144.4 (C-6), 140.2 (C-8), 137.4 (C-2′ andC-6′), 136.6 (C-2″ and C-6″), 131.8 (C-1′), 130.7 (C-4′), 129.7 (C-3′ and C-5′), 126.2(C-5), 125.3 (C-3″ and C-5″), 112.1 (C-3), 62.5 (CH_2 of ester), 31.7 (CH_3), and 15.5 (CH_3 of ester). Anal. Calcd. for $C_{21}H_{17}BrN_2O_2S_2$: C, 53.28; H, 3.62; N, 5.92. Found: C, 53.36; H, 3.69; N, 5.85%.

4.13. *Ethyl 2-(p-chlorophenyl)sulfonyl -6-(p-methylphenyl)imidazo[2,1-b] thiazole-3-carboxylate (5a)*

A mixture of ethyl 2-amino-5-(*p*-chlorophenyl)sulfonyl thiazole-4-carboxylate (0.01 mol) and phenacyl bromide (0.01 mol) in anhydro us ethanol (60 ml) was heated to reflux on a steam bath for 12 h. Excess of solvent was distilled off and the residue poured into ice cold water (200 ml) to get crude 2-(*p*-chlorophenyl)thio-3-ethoxycarbonyl-6-(*p*-methylphenyl) imidazo[2,1-*b*]thiazolium bromide. Freebase **5a** was obtained by the neutralization of the corresponding hydrobromides using sodium carbonate solution (pH 7). These free bases were recrystallized from ethanol and further purified by column chromatography on neutral alumina using chloroform and methanol as eluent (90%:10% v/v). Yield 51%, m.p. 176–178°C; ^{1}H NMR (300 MHz, CDCl3) δ: 8.25 (s, 1H, C-5H), 8.10 (d, $J = 8.0$ hz, 2H, ArH), 7.81 (d, $J = 8.0$ hz, 2H, ArH), 7.88 (d, $J = 8.1$ hz, 2H, ArH), 7.53 (d, $J = 8.1$ hz, 2H, ArH), 4.25 (q, 2H, CH_2 of ester), 2.25 (s, 3H, CH_3), and 1.35 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{21}H_{17}ClN_2O_4S_2$: C, 54.72; H, 3.72; N, 6.08. Found: C, 54.84; H, 3.80; N, 6.01%.

4.14. *Ethyl 2-(p-chlorophenyl)sulfonyl-6-(p-nitrophenyl)imidazo[2,1-b] thiazole-3- carboxylate (5b)*

Yield 51%, m.p. 150–152°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (s, 1H, C-5H), 8.00 (d, $J = 8.2$ hz, 2H, ArH), 7.72(d, $J = 8.4$ hz, 2H, ArH), 7.92 (d, $J = 8.0$ hz, 2H, ArH), 7.00

(d, $J = 8.0$ hz, 2H, ArH), 4.30 (q, 2H, CH_2 of ester), and 1.20 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{20}H_{14}ClN_3O_6S_2$: C, 48.83; H, 2.87; N, 8.54. Found: C, 48.90; H, 2.95; N, 8.44%.

4.15. *Ethyl 2-(p-chlorophenyl)sulfonyl-6-(p-chlorophenyl)imidazo[2,1-b] thiazole-3-carboxylate (5c)*

Yield 50%, m.p. 170–172°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.35 (s, 1H, C-5H), 8.22 (d, $J = 8.4$ hz, 2H, ArH), 7.85 (d, $J = 8.4$ hz, 2H, ArH), 7.80 (d, $J = 8.2$ hz, 2H, ArH), 7.40 (d, $J = 8.2$ hz, 2H, ArH), 4.35 (q, 2H, CH_2 of ester), and 1.25 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{20}H_{14}Cl_2N_2O_4S_2$: C, 49.90; H, 2.93; N, 5.82. Found: C, 49.98; H, 3.02; N, 5.79%.

4.16. *Ethyl 2-(p-chlorophenyl)sulfonyl-6-(p-bromophenyl)imidazo[2,1-b] thiazole-3-carboxylate (5d)*

Yield 50%, m.p. 170–172°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25 (s, 1H, C-5H), 8.14 (d, $J = 8.1$ hz, 2H, ArH), 7.86 (d, $J = 8.1$ Hz, 2H, ArH), 7.78 (d, $J = 7.9$ Hz, 2H, ArH), 7.55 (d, $J = 7.9$ hz, 2H, ArH), 4.20 (q, 2H, CH_2 of ester), and 1.30 (t, 3H, CH_3 of ester); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.8 (C=O of ester), 163.3 (C-1″), 149.4 (C-1′), 146.3 (C-8), 143.8 (C-4″), 140.4 (C-4′), 137.2 (C-3′ and C-5′), 136.5 (C-2″ and C-6″), 135.6 (C-2′ and C-6′), 134.8 (C-3″ and C-5″), 133.4 (C-2), 130.1 (C-6), 129.0 (C-5), 127.0 (C-3), 65.4 (CH_2 of ester), and 16.5 (CH_3 of ester). Anal. Calcd. for $C_{20}H_{14}BrClN_2O_4S_2$: C, 45.68; H, 2.68; N, 5.33. Found: C, 45.76; H, 2.79; N, 5.25%.

4.17. *Ethyl 2-(p-methylphenyl)sulfonyl-6-(p-methylphenyl)imidazo[2,1-b]-thiazole-3-carboxylate (5e)*

Yield 50%, m.p. 182–184°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25 (s, 1H, C-5H), 8.09 (d, $J = 8.2$ hz, 2H, ArH), 7.90 (d, $J = 8.2$ hz, 2H, ArH), 7.76 (d, $J = 8.0$ hz, 2H, ArH), 7.62 (d, $J = 8.0$ hz, 2H, ArH), 4.35 (q, 2H, CH_2 of ester), 2.20 (s, 3H, CH_3), and 1.20 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{22}H_{20}N_2O_4S_2$: C, 59.98; H, 4.58; N, 6.36. Found: C, 60.07; H, 4.67; N, 6.24%.

4.18. *Ethyl 2-(p-methylphenyl)sulfonyl-6-(p-nitrophenyl)imidazo[2,1-b] thiazole-3-carboxylate (5f)*

Yield 52%, m.p. 190°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (s, 1H, C-5H), 8.22 (d, $J = 8.6$ hz, 2H, ArH), 7.96 (d, $J = 8.6$ hz, 2H, ArH), 7.85 (d, $J = 8.0$ hz, 2H, ArH), 7.74 (d, $J = 8.2$ hz, 2H, ArH), 4.35 (q, 2H, CH_2 of ester), 2.30 (s, 3H, CH_3), and 1.25 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{21}H_{17}N_3O_6S_2$: C, 53.49; H, 3.63; N, 8.91. Found: C, 53.55; H, 3.70; N, 8.84%.

4.19. *Ethyl 2-(p-methylphenyl)sulfonyl-6-(p-chlorophenyl)imidazo[2,1-b] thiazole-3-carboxylate (5g)*

Yield 51%, m.p. 176–178°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (s, 1H, C-5H), 8.12 (d, $J = 8.3$ hz, 2H, ArH), 7.81 (d, $J = 8.3$ hz, 2H, ArH), 7.70 (d, $J = 7.8$ hz, 2H, ArH), 7.63 (d, $J = 7.9$ hz, 2H, ArH), 4.30 (q, 2H, CH_2 of ester), 2.25 (s, 3H, CH_3), and 1.40 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{21}H_{17}ClN_2O_4S_2$: C, 54.72; H, 3.72; N, 6.08. Found: C, 54.84; H, 3.81; N, 5.98%.

4.20. *Ethyl 2-(p-methylphenyl)sulfonyl-6-(p-bromophenyl)imidazo[2,1-b]-thiazole-3-carboxylate (5h)*

Yield 56%, m.p. 166–168°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20 (s, 1H, C-5H), 8.07 (d, J = 8.4 hz, 2H, ArH), 7.84 (d, J = 8.4 hz, 2H, ArH), 7.76 (d, J = 8.0 Hz, 2H, ArH), 7.58 (d, J = 8.0 hz, 2H, ArH), 4.25 (q, 2H, CH_2 of ester), 2.15 (s, 3H, CH_3), and 1.45 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{21}H_{17}BrN_2O_4S_2$: C, 49.91; H, 3.39; N, 5.54. Found: C, 50.02; H, 3.45; N, 5.50%.

References

(1) Buttle, G.A.H.; Stephenson, D.; Smith, S.; Dewing, T.; Foster, G.E. *Lancet* **1937,** *1*, 1331–1333; *Chem. Abstr.* **1937,** *31,* 7118.
(2) Thienopont, D.C.; Vanparijs, O.F.J.; Raeymaekers, A.H.M.; Vandenberk, J.; Demoen, P.J.A.; Allewijn, F.T.N.; Marsboom, R.P.H.; Niemegeers, C.J.E.; Shellekens, K.H.L.; Janssen, P.A.J. *Nature* **1966,** *209,* 1084–1087.
(3) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Lenaz, G.; Fato, R.; Bergamini, C.; Farruggia. G. *J. Med. Chem.* **2005,** *48,* 3085–3089.
(4) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Garaliene, V.; Welsh, W.; Arora, S.; Farruggia, G. et al. *J. Med. Chem.* **2005,** *48,* 5604–5607.
(5) Robert, J.F.; Boukraa, S.; Panouse, J.J.; Loppinet, V.; Chaumont, J.P. *Eur. J. Med. Chem.* **1990,** *25,* 731–736.
(6) Andreani, A.; Rambaldi, M.; Leoni, A.; Morigi, M.; Locatelli, A.; Georgi, G.; Lenaz, G.; Ghelli, A.; Esposti, M.D. *Eur. J. Med. Chem.* **1999,** *34,* 888–895.
(7) Khazi, I.M.; Mahajanshetti, C.S.; Gadad, A.K. *Arzneim Forsch.* Drug re. **1996,** *46,* 949–952.
(8) Khazi, I.M.; Koti, R.S.; Chadha, M.V.; Mahajanshetti, C.S. *Arzneim Forsch*. Drug re. **2005,** *55,* 107–113.
(9) Mahajanshetti, C.S.; Basanagoudar, L.D. *Can. J. Chem.* **1967,** *45,* 1807–1811.
(10) Seely, H.W.; Van Demark, D.J. *"Microbes in Action" – A Laboratory Manual of Microbiology*; D.B. Taraporovala and Sons. Pvt. Ltd.: Bombay, 1975, pp. 73–75.
(11) Blank, B.; DiTullio, N.W.; Owings, F.F. *J. Med. Chem.* **1977,** *20,* 572–576.