IJPSR (2011), Vol. 2, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 March, 2011; received in revised form 03 May, 2011; accepted 28 May, 2011

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL 3, 6- DISUBSTITUTED IMIDAZO [2, 1-*B*] [1, 3] THIAZOLES

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Keywords:

Antifungal,
Antimicrobial,
3, 6-disubstituted imidazo[2, 1-b][1, 3]thiazole

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ABSTRACT

Cyclocondensation of α-bromo ketones with thiourea afforded 4-substituted 1, 3-thiazole-2-amines. These compounds on further treatment with α-bromo ketones afforded 3, 6-disubstituted imidazo[2, 1-*b*][1, 3]thiazole **(1a-1j).** All the synthesized compounds were confirmed for their structure by FTIR, ^{1}H NMR and GSMS spectra and tested in vitro for their anti-microbial activity by cup plate method against Gram-positive bacterial strains (*Bacillus subtillis, Staphylococcus aureus)* Gram-negative bacterial strains (*Pseudomonas aerugenosa, Kleibsella pneumonia)* and fungal strains (*Aspergillus niger, Candida albicans).* The analogues **1b, 1h** and **1i** showed promising antimicrobial activity against gram-negative *Kleibsella pneumonia;* where as analogues **1b, 1e, 1g** and **1h** showed promising antifungal activity against *Candida albicans*.

INTRODUCTION: Emergence of multi-drug resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci and also resistant fungi is reported worldwide. Antibiotic resistance is currently the greatest challenge to the effective treatment of infections globally [1, 2]. Antimicrobial drug resistance is a natural phenomena and it is exacerbated by under use and over use of antimicrobials [2]. Further the frequent use of therapeutic drugs and increased number of nosocomial infections especially in immuno-compromised patients; have led to increasing incidence of Candida infections [3].

Therefore, novel antibacterial and antifungal therapies are urgently required. This is the reason why it appears essential to investigate new antimicrobial compounds with new mechanisms of action, to overcome antimicrobial resistance and to develop effective therapies [4]. An imidazothiazole derivative, Levamisole (the levo isomer of tetramisole) is a broad spectrum anthelmintic, belonging to a general class of agents called biologic response modifiers and has been originally designed for anthelmintic properties and also possess immuno-modulating and immuno-stimulating properties [5]. Many novel β-lactams with anti-MRSA activity had been reported recently [6, 7].

A novel anti-MRSA β-lactam, CP50686, which had an imidazo [5, 1-b] thiazolium side chain on carbapenem skeleton has been reported [8]. Closely analogous imidazo [2, 1-b] thiazoles possess diverse pharmacological activities viz. anticoccidial [9], anticancer [10-17], anti-alzheimer's, anti-parkinsonian,

antistroke [18], antibacterial [19-22], antifungal [23], antihelmentic [24, 25], antitubercular [26], acetyl cholinesterase inhibitors [27], positive ionotropic agent [28-29], Neuromuscular blocking agent [30].

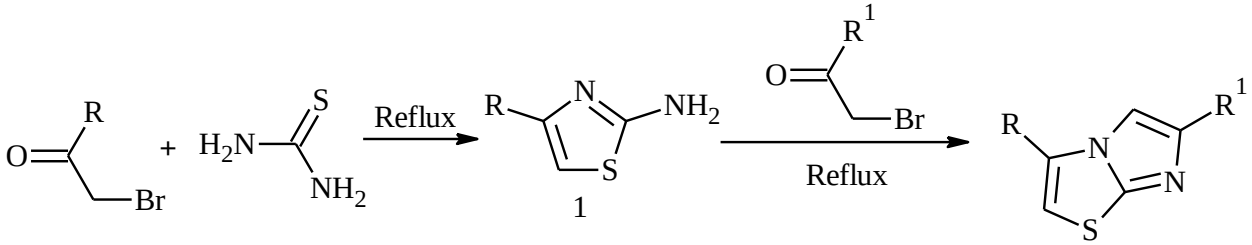
In the present work 3, 6-disubstituted imidazo[2, 1-*b*][1, 3]thiazoles **(1a-10j)** were synthesized. The structures of the synthesized compounds were supported by spectral data. All the synthesized compounds were evaluated for antimicrobial activity by cup plate method against two Gram-positive bacterial strains (*Bacillus subtillis, Staphylococcus aureus),* two Gram-negative bacterial strains (*Pseudomonas aerugenosa, Kleibsella pneumonia)* and two fungal strains (*Aspergillus niger, Candida albicans).*

MATERIALS AND METHODS: Melting points of the compounds were determined in open capillaries and are uncorrected. Purity of the compounds was checked by preparative TLC using silica gel G precoated plates using benzene-methanol (9:1, v/v) as mobile phase. The IR spectra were recorded on FTIR 8400 F-Schimadzu Spectrometer using KBr disc pellet method. ^{1}H NMR spectra were recorded on AVANCE II 400 and Verian Mercury ^{1}H 300 and Jeol FT NMR AL-300 using DMSO and $CDCl_3$ as solvent and TMS as internal standard and the chemical shift values are expressed in δ ppm (parts per million). GC Mass spectra were recorded on GC-MS-QP-5050 Schimadzu. All the solvents and chemicals used were purified according to literature procedures and supplied by Loba Chemie.

General procedure for the synthesis of 4-substituted-1, 3-thiazol-2-amines (1) [31]: Appropriate of α-bromo ketone (0.0043 mole) was dissolved in absolute ethanol (25ml) and treated with thiourea (0.0043 mole). The reaction mixture was refluxed for 4 hrs. On the completion of reaction the solvent was distilled under reduced pressure. The resulting semisolid residue was poured over crushed ice with stirring. The resulting solution is made just alkaline with ammonia solution. The separated product was filtered and washed with water. The product was recrystallized from alcohol. The physical data is shown in **Table 1**.

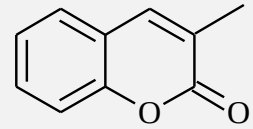
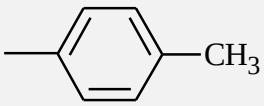
General procedure for the synthesis of 3, 6-disubstituted imidazo[2, 1-b][1, 3]thiazoles (1a-1j)

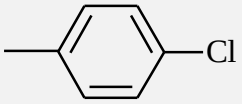
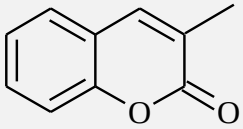
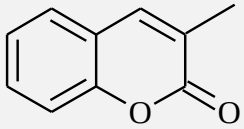
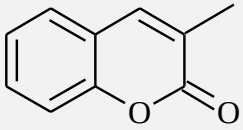
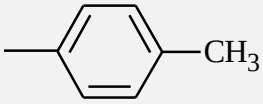
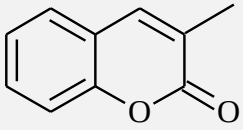
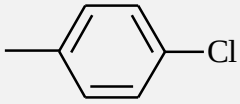
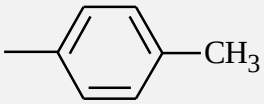
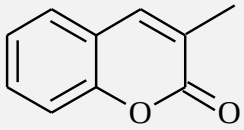
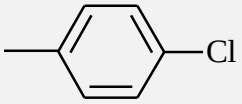
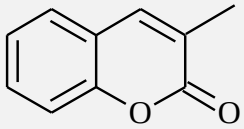
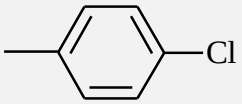
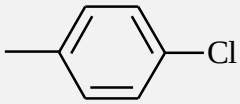
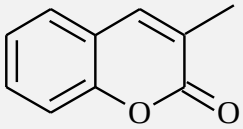
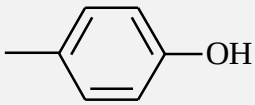
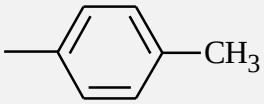
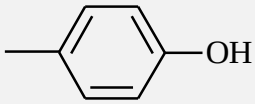
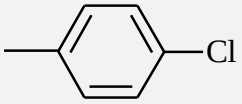
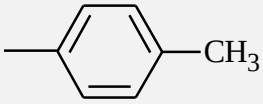
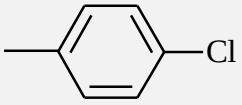
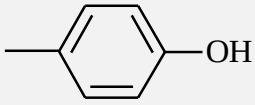
A mixture of 4-substituted-1, 3-thiazol-2-amine (0.03 mole) and appropriate α-bromo ketones (0.03 mole) in ethanol (150 ml) was refluxed for 12 hours. On the completion of reaction the excess solvent was removed under reduce pressure to obtain the solid hydrobromide. The solid hydrobromide salts was treated with cold aqueous solution of sodium carbonate (pH 7.0) which yielded the corresponding free bases. All free bases were recrystallized from ethanol. Yield and mp (Table 1).



Scheme 1

TABLE 1: PHYSICAL DATA OF 3, 6-DISUBSTITUTED IMIDAZO[2, 1-*B*][1, 3]THIAZOLES (1A-1J)

Compound	R	R^1	Formula	MW	m. pt. (^{o}C)	Yield (%)
1		-	$C_{15}H_{10}N_2O_2S$	282.3	237	80
1		-	$C_{12}H_{10}N_2S$	214.2	123- 124	84

1		-	$C_{11}H_7ClN_2S$	234.7	163- 164	82
1a			$C_{24}H_{14}N_2O_4S$	426.4	105	50
1b			$C_{22}H_{16}N_2O_2S$	372.4	102-104	54
1c			$C_{21}H_{13}ClN_2O_2S$	392.8	112-113	60
1d			$C_{21}H_{14}N_2O_2S$	358.4	108	57
1e			$C_{20}H_{11}ClN_2O_2S$	378.3	120-123	58
1f			$C_{17}H_{10}Cl_2N_2S$	345.2	154-158	62
1g			$C_{21}H_{14}N_2O_3S$	374.4	118-120	60
1h			$C_{18}H_{14}N_2OS$	306.3	62-64	62
1i			$C_{18}H_{13}ClN_2S$	324.8	160-161	59
1j			$C_{17}H_{11}ClN_2OS$	326.8	67-70	54

Antimicrobial activity: The antimicrobial and antifungal activity was carried out by using cup-plate method [33-34] by using microbial strains as *Bacillus subtillis, Staphylococcus aureus, Pseudomonas aerugenosa* and *Kleibsella pneumonia* with incubation period of 24 hours at temperature 37^{o}C. The standard drug used was Norfloxacin (50 µg/0.1 mL) and the test compounds at concentrations of 200 and 400 µg/0.1 mL. For antifungal activity fungal strains *Aspergillus niger, Candida albicans* were used and were incubated at 28 ^{o}C for 48 hours. The standard drug used was Griseofulvin (50 µg/0.1 mL) and the test compounds at concentrations of 200 and 400 µg/0.1 mL (**Table 2**).

TABLE 2: ANTIMICROBIAL ACTIVITY OF 3, 6-DISUBSTITUTED IMIDAZO[2, 1-*B*][1, 3]THIAZOLE

Comp.	Zone Of Inhibition (In mm)											
	B.subtillis (NCIM 2711)		*S.aureus* (NCIM2079)		*K.pneumoniae* (ATCC27853)		*P.aeruginosa* (ATCC 4352)		*C.albicans* (ATCC 60193)		*A.niger* (NCIM 515)	
Conc.	A	B	A	B	A	B	A	B	A	B	A	B
1a	4	5	5	8	3	5	4	5	4	9	3	7
1b	2	4	6	10	4	11	5	7	6	10	5	9
1c	4	9	5	7	6	6	5	8	4	6	3	7
1d	5	7	3	5	5	9	4	9	4	5	3	8
1e	2	5	4	7	6	8	4	6	5	12	3	8
1f	5	8	6	9	3	5	4	6	4	9	5	9
1g	3	6	5	5	5	9	6	7	8	11	10	11
1h	4	8	5	9	6	13	5	9	8	13	9	12
1i	5	8	7	9	6	11	7	10	3	7	5	8
1j	6	9	8	13	4	7	3	9	4	6	6	11
N	14		15		15		15		--		--	
G	--		--		--		--		13		14	

A = 200 µg/0.1 mL; B = 400 µg/0.1 mL. All tests were performed in triplicate. N : Norfloxacin 50 µg/0.1ml G: Griseofulvin50 µg/0.1ml

RESULTS AND DISUSSION: We had planned for synthesis of for 3, 6-disubstituted imidazo[2, 1-*b*][1, 3] thiazole and were confirmed by spectral data (**Table 3**). Compounds synthesized in this series were tested for anti-microbial activity using Norfloxacin and Griseofulvin as standards.

TABLE 3: SOPHISTICATED ANALYTICAL DATA FOR 3, 6-DISUBSTITUTED IMIDAZO[2, 1-*B*][1, 3]THIAZOLE

Comp.	IR, 1H NMR and GC-MS spectra
1a	**IR:** 3060-3030 (aryl C-H),1725-1750 (keto -CO), 1600(-CH=CH-), 600(-C-S-) **^{1}H NMR:** δ 3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole, 7.6 singlet from coumarin ,multiplet at 7.4-7.8 (aromatic hydrogens), **GC-MS:** M^{+1} 244,118.04,123,137.02,145.03,159.04,64.03,27.99
1b	**IR:** 3060-3030 (aryl C-H), 1600(-CH=CH-), 600(-C-S-) **^{1}H NMR:** δ3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole, 7.7-8.4 for disubstituted imidazo[2,1-*b*][1,3]thiazole hydrogen atom (C=CH), multiplet at 7.4-7.8 (aromatic hydrogens), 2.3-2.4 singlet for aromatic *p*-CH_3 **GC-MS:**M^{+1} 214.2,123,199.03,91.05,42.03,15.02
1c	**IR:** 3060-3030 (aryl C-H),1725-1750, 1600(-CH=CH-), 600(-C-S-) **^{1}H NMR:** δ3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole,7.7-8.4 for disubstituted imidazo[2,1-*b*][1,3]thiazole hydrogen atom (C=CH), multiplet at 7.4-7.8 (aromatic hydrogens **GC-MS:**M^{+1} 234,199.03,123,111,34.9,52.02
1d	**IR:** 3060-3030 (aryl C-H),1725-1750 (keto -CO), 1600(-CH=CH-), 600(-C-S-) **^{1}H NMR:** δ3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole, 7.6 singlet from coumarin H Cis for methylene, 7.7-8.4 for disubstituted imidazo[2,1-*b*][1,3]thiazole hydrogen atom (C=CH), multiplet at 7.4-7.8 (aromatic hydrogens) **GC-MS:**M^{+1} 426,286.04,267.02,145.03,159.04,76.03
1e	**IR:** 3060-3030 (aryl C-H),1725-1750 (keto -CO), 1600(-CH=CH-), 600(-C-S-) **^{1}H NMR:** δ3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole, 7.6 singlet from coumarin H Cis for methylene, 7.7-8.4 for disubstituted imidazo[2,1-*b*][1,3]thiazole hydrogen atom (C=CH), multiplet at 7.4-7.8

	(aromatic hydrogens), 2.3-2.4 singlet for aromatic *p*-CH_3 **GC-MS:**M^{+1} 372,213.05,281.04,159.04,91.05,53.04
1f	**IR:** 3060-3030 (aryl C-H),1725-1750 (keto -CO), 1600(-CH=CH-), 600(-C-S-) **^{1}H NMR:** δ3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole, 7.6 singlet from coumarin H Cis for methylene, 7.7-8.4 for disubstituted imidazo[2,1-*b*][1,3]thiazole hydrogen atom (C=CH), multiplet at 7.4-7.8 (aromatic hydrogens) **GC-MS:**M^{+1} 393,319.05,281.04,232.9,159.04,111,72.9
1g	**IR:** 3060-3030 (aryl C-H),1725-1750 (keto -CO), 1600(-CH=CH-), 600(-C-S-), 3400(-OH) **^{1}H NMR:** δ3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole, 7.6 singlet from coumarin H Cis for methylene, 7.7-8.4 for disubstituted imidazo[2,1-*b*][1,3]thiazole hydrogen atom (C=CH), multiplet at 7.4-7.8 (aromatic hydrogens), 5.36 aromatic *p*-OH **GC-MS:**M^{+1} 374,281.04,203.03,172.05,93.03,17
1h	**IR:** 3060-3030 (aryl C-H), 1600(-CH=CH-), 600(-C-S-), 3400(-OH) **^{1}H NMR:** δ3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole, 7.7-8.4 for disubstituted imidazo[2,1-*b*][1,3]thiazole hydrogen atom (C=CH), multiplet at 7.4-7.8 (aromatic hydrogens), 2.3-2.4 singlet for aromatic *p*-CH_3, 5.36 aromatic *p*-OH **GC-MS:**M^{+1}306,289.08,215.03,213.05,91.05,93.03,17
1i	**IR:** 3060-3030 (aryl C-H), 1600(-CH=CH-), 600(-C-S-), 3400(-OH) **^{1}H NMR:** δ3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole, 7.7-8.4 for disubstituted imidazo[2,1-*b*][1,3]thiazole hydrogen atom (C=CH), multiplet at 7.4-7.8 (aromatic hydrogens), 2.3-2.4 singlet for aromatic *p*-CH_3 **GC-MS:**M^{+1} 309.03,213.05,232.99,111,91.05,15.02
1j	**IR:** 3060-3030 (aryl C-H), 1600(-CH=CH-), 600(-C-S-), 3400(-OH) **^{1}H NMR:** δ3.1- 3.2 doublet for methylene C-CH & C=CH, 7.13 singlet for imidazole, 7.33 singlet for thiazole, 7.7-8.4 for disubstituted imidazo[2,1-*b*][1,3]thiazole hydrogen atom (C=CH), multiplet at 7.4-7.8 (aromatic hydrogens, 5.36 aromatic *p*-OH **GC-MS:**M^{+1}326,271.01 ,232.99,193.98,134.06,55.02,93.03

CONCLUSION: In summery, the present study revealed that out of the synthesized 3, 6-disubstituted imidazo[2, 1-*b*][1, 3]thiazoles, the compounds 1h and 1j were shown to possess highest antimicrobial activity against *S. aureus, K. pneumonia,* and *C. albicans* at the concentration 400 µg/0.1 mL. All other compounds were shown mild to moderate antimicrobial activity.

ACKNOWLEDGEMENT: Authors are thankful to President, GMSPM'S, Otur and Principal, Sharad Chandra Pawar College of Pharmacy, Dumberwadi, Otur, Tal: Junnar, Dist.-Pune-412409, Maharashtra, India, for cooperation and providing facilities for completion of this research work.

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