ISSN 0975-6299 Vol.1/Issue-4/Oct-Dec.2010

International Journal of Pharma and Bio Sciences

ANTI-MYCOBACTERIAL ACTIVITY OF SOME SYNTHESIZED 2[2[1]- PHENYL -4[1]- BENZIDINYL- 5[1]- OXO- IMIDAZOLINE- 1YL- AMINO] -6 FLUORO- 7- SUBSTITUTED (1,3) BENZOTHIAZOLES.

B.S. SATHE*[1], E. JAYCHANDRAN[2], V. A. JAGTAP[1] AND G.M SREENIVASA[2]

[1]Department of Pharmaceutical Analysis, Smt. S. S. Patil College of Pharmacy, Chopda – 425 107
[2] P. G. Department of Pharmaceutical Chemistry, S. C. S. College of Pharmacy, Harapanahalli – 583 131

Corresponding Author drbss1978@rediffmail.com

ABSTRACT

2[2'- Phenylidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- substituted (1,3) benzothiazoles have been synthesized and screened for antitubercular activity. Literature revealed that vast majority of benzothiazoles and imidazole compounds are known to possess pharmacologically proven therapeutic potentials. Though extensive research work is reported on benzothiazoles, reactively very little is known so for about fluorobenzothiazole incorporated imidazolines with fluorine at 6th position. The reaction of 6- fluro-7-chloroaniline[1] with potassium thiocynate (KSCN) in presence of bromine and glacial acetic acid and ammonia to get 2-amino 6- fluro-7-chloro(1,3) benzothiazoles[2-5] (1) which was further treated with hydrazine hydrate in presence of ethylene glycol and sulphuric acid to yield 2-hydrazino-6-fluoro-7-chloro(1,3) benzothiazoles(2). It was reacted with prepared Oxazolone i.e.2-phenyl-4-benzylidine-5-oxazolone (3) to yield 2[2'- Phenylidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro(1,3) benzothiazole(4), which was treated with variety of aromatic anilines in presence of DMF to yield different derivatives (5a-5i).

KEYWORDS

Flourine, Benzothiazole, Oxazalinone, Imidazoline, Antimycobacterial activity.

INTRODUCTION

Fluorobenzothiazoles and Imidazoles exhibit the broad range of biological activities. In the recent years, the chemistry of oxazolones has received much attention due to their use as intermediates for synthesis of some heterocyclic systems. In the present study we made an attempt to link fluorobenzothiazoles with imidazoles for generating various derivatives having antimycobacterial activity. Benzylidine derivatives were found to possess MAO Inhibitory activity, therefore in the present work we have treated oxazolones benzothiazole ring to get biological and pharmacological active leads.

MATERIALS AND METHODS

Purity of compounds was checked by TLC. Melting points were determined by open capillaries method and uncorrected. IR spectra (NaCl) are recorded on FTIR (Schimadzu-84005) spectrophotometer using nujol mull technique. [1]HNMR spectra are recorded on a

spectrophotometer (Bruker AMX) at 500MHz, using TMS as internal reference. For anti mycobacterial activity *in vitro* by tube dilution technique using the human virulent $H_{37}RV$ strain of M. tuberculosis. The tubes were incubated at 37^0C for 21 days. Rifampicin and Isoniazide were used as standard for the antimycobacterial activity. All the results related to above data are given as MIC values in Table No. 2.

Table No. 2
Antimycobacterial activity

Comp. No.	Activity Data Codes	H37RV strain of M. tuberculosis 21 days
01	5a	23
02	5b	25
03	5c	24
04	5d	15
05	5e	13
06	5f	17
07	5g	21
08	5h	18
09	5i	14

Standard 1 – Rifampicin 0.25, Standard 2 – Isoniazide 0.007

EXPERIMENTAL

First Step
Synthesis of 2-amino-6-fluoro-7-chloro-(1,3)benzothiazole [2-5](1):
To the glacial acetic acid (20ml) which is cooled below room temperature,8gm (0.08mol) of potassium thiocynate and 1.45g (0.01 mol) of fluorochloroaniline was added. The mixture was placed in freezing mixture of ice and salt, mechanically stirred while 1.6ml of bromine in 6ml of glacial acetic acid was added, from a dropping funnel at such a rate that the temperature never rose beyond room temperature. After all the bromine was added (105min), the solution was stirred for 2 hours below room temperature and at room temperature for 10 hours, it was then allowed to stand over night, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and slurry was heated at 85^0c on a steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85^0c and filtered hot. The combined filtrate was cooled and neutralized with concentrated ammonia solution to p^H 6. A dark yellow precipitate was collected. Recrystalised from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow plates of 2-amino-6-fluoro-7-chloro-(1,3) benzothiazole. After drying in a oven at 80^0c, the dry material (1gm 51.02%) melted at $210\text{-}212^0c$. UV 307.4, 269nm, IR $1542cm^{-1}$(aromatic C=C) and $3475cm^{-1}$ (NH_2); 1456 cm^{-1}(thiazole), 1215 cm^{-1}(aromatic-F), 712 cm^{-1}(aromatic-Cl).

Second Step
Synthesis of 2-Hydrazino-6-fluoro-7-chloro (1, 3) benzothiazole [4-5](2):
Concentrated HCl (10ml) was added drop wise with stirring to hydrazine hydrate (12ml, 0.2mol) at $5\text{-}10^0c$ followed by ethylene glycol (40ml). To the above solution 2-amino-6-fluoro-7-chloro (1,3) benzothiazole (0.01mol) was added in portion and the resulting mixture was refluxed for 2 hrs, cooled, poured in crushed ice. The solid separated, was filtered,

dried and recrystalised from ethanol (Yield 76%). The dry material melted at 182^{0}c. IR (NaCl) 3476 cm^{-1}(Ar-NH_2 stretching), 3094 cm^{-1}(Ar-NH bending), 1632 cm^{-1} (C=N stretching), 1348 cm^{-1} (Ar-NH bending), 1194 cm^{-1}(C-F stretching), 688 cm^{-1}(C-Cl stretching).

Third Step

Synthesis of 2-Phenyl- 4-benzylidine-5-oxazol-5-one (oxazolone)[6] (3):

Redistilled benzaldehyde was treated with benzoyl glyciene (Hippuric acid) in presence of acetic anhydride (dry acetic acid) and anhydrous sodium acetate to get 4-benzylidene-2-phenyl-oxazol-5-one(oxazolone).Upon washing with ice cold alcohol and then with boiling water (Yield 80%),melted at 165-166^{0}C, IR (NaCl) 1790 cm^{-1}(Lactone carbonyl) and another bond at 1650 cm^{-1}(C=N stretching).

Synthesis of 2[2'- Phenyl -4'- benzidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro (1,3) benzothiazoles[2,5,7,8](4):

A mixture of 0.01 mol. of 2-hydrazino-6-fluoro-7-chloro benzothiazole and 2-phenyl-4-benzylidene-5-oxazolinone (2.49g. 0.01mol) was refluxed in pyridine for 6-8 hours. excess of pyridine was distilled off and resulting mass was poured on to crushed ice and neutralized with dil HCl, filtered and product was recrystalised from ethanol. The dry material melted at 110-112^{0}c (72%).IR(NaCl) 3452 cm^{-1}(-NH stretching), 121 cm^{-1}(C-F), 677 cm^{-1}(C-Cl stretching),3091 cm^{-1}(C=C stretching),1601 cm^{-1}(C=O stretching).

Preparation of various derivatives [2,5,9](5a-5i):

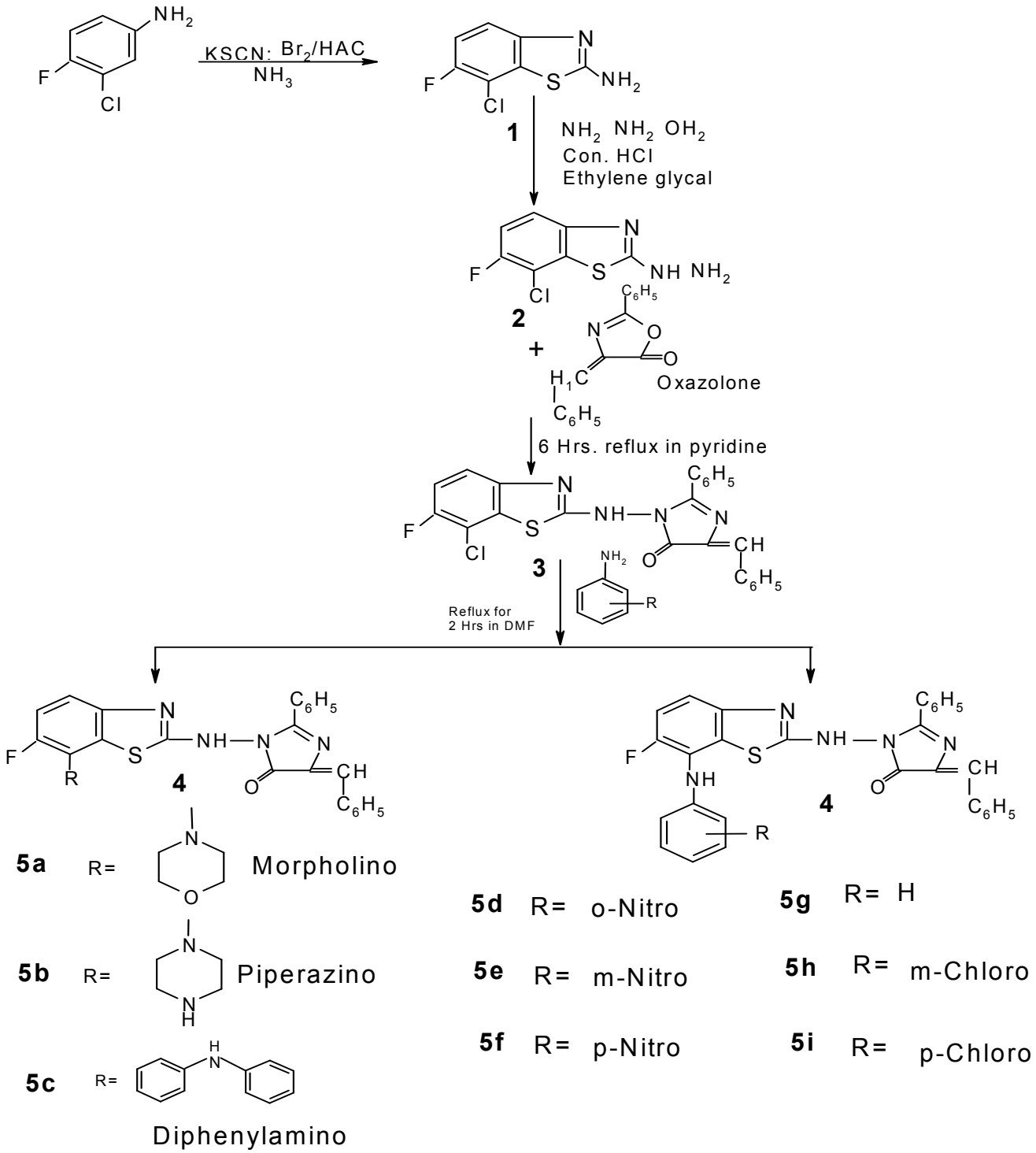
2[2'- Phenyl -4'- benzidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro (1,3) benzothiazole (4) was treated with various aromatic amines Refluxed for 2 hrs. in presence of DMF (dimethyl formamide) yields various 2[2'- Phenyl -4'- benzidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro (1,3) benzothiazole derivatives(5a-5i).

IR (NaCl) spectrum of 2[2'- Phenyl -4'- benzidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro (1,3) benzothiazole 3440 cm^{-1}(-NH stretching), 1640 cm^{-1}(imidazoline ring carbonyl), 1490 cm^{-1}(C=C stretching), 714 cm^{-1}(C-Cl), 1196 cm^{-1}(C-F stretching). Similarly the remaining 5b-5i compounds showed appropriate IR spectra confirming their structures. Similarly ^{1}HNMR spectra's of compounds 5g 6.8-8.5 δ (13 H), 5-5 δ (-NH group), 2.7-4.0 δ (8 H) multiplet. The analytical data of the synthesized derivatives is given in Table No. 1.

Table No. 1

Analytical Data of the Compounds (5a-5i)

Sr. No.	Comp. Code	% Yield	MP/BP (^{0}c)	Molecular Formula	Mol. Weight	Calculated (%)			Rf Value
						C	H	N	
01	5a	50%	117-118	$C_{27}H_{18}N_5O_2SF$	495	65.45	3.63	14.14	0.89
02	5b	72%	114-115	$C_{27}H_{19}N_6OSF$	494	65.58	3.84	17.00	0.63
03	5c	64%	126-127	$C_{35}H_{24}N_5OSF$	581	72.28	4.13	12.04	0.72
04	5d	60%	120-121	$C_{29}H_{19}N_6O_3SF$	550	63.27	3.45	15.72	0.62
05	5e	60%	143-144	$C_{29}H_{19}N_6O_3SF$	550	63.30	3.45	15.3	0.82
06	5f	68%	146-147	$C_{29}H_{19}N_6O_3SF$	550	63.30	3.45	15.3	0.73
07	5g	62%	140-142	$C_{29}H_{20}N_5OSF$	505	68.91	3.96	13.86	0.97
08	5h	67%	121-122	$C_{29}H_{19}N_6OSFCl$	540	64.44	3.51	12.96	0.94
09	5i	70%	105-106	$C_{29}H_{19}N_5OSFCl$	540	64.44	3.51	12.96	0.76



SCHEME

ACKNOWLEDGEMENT

The authors express thanks to Dr. A.S. Bobde, Haffkine Institute, Mumbai for providing testing facilities for Anti-tubercular activity
.

REFERENCES

1. Sangal S. K., Rastivona P. K., Chem. Abstr., 1986, 104, 34029.
2. Gurupadiaiah, B. M., Jaychandran E., Nargund L. V. G., Shivkumar B., Indian J. Heterocycl., 1998, 7. 213-216.
3. Labendeno N. Yu., Chem. Abstr., 1980, 92, 922882.
4. Areas J., J. Chem. Abst., 1991, 14, 71453d.
5. Jaychandran E., Nargund L. V. G., Oriental J. Chem., 2003, 19(1), 139-142.
6. A. I. Vogel's Textbook of Practical Org. Chem., ELBS, 1978, 4, 884-885.
7. Merja, B. C., Joshi A.M., Parikh K. A., Oriental J. Chem., 2003, 13(1), 157-160.
8. Verma V. M., Chturvedi A. K., Pamar S. S., J. Pharm. Sci., 1974, 463, 1740.
9. Bhusari K. P., Khedkar P. B., Umathe, S. N., Raghuramrao A., Indian J. Heterocycl. Chem., 2000, 13, 798-800.
10. Vashi B.S, Mehta D.S.& Shah V. H., Indian J. of Chemistry ,1995,34B,802-808