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Antimycobacterial Activity of Some Synthesized Fluorinated Benzothiazolo Imidazole Compounds

B.S. SATHE[*], E. JAYCHANDRAN[§],
G.M SREENIVASA[§] and V. A. JAGTAP

Department of Pharmaceutical Analysis
Smt. S. S. Patil College of Pharmacy, Chopda - 425 107, India
[§]P. G. Department of Pharmaceutical Chemistry
S. C. S. College of Pharmacy, Harapanahalli - 583 131, India
drbss1978@rediffmail.com

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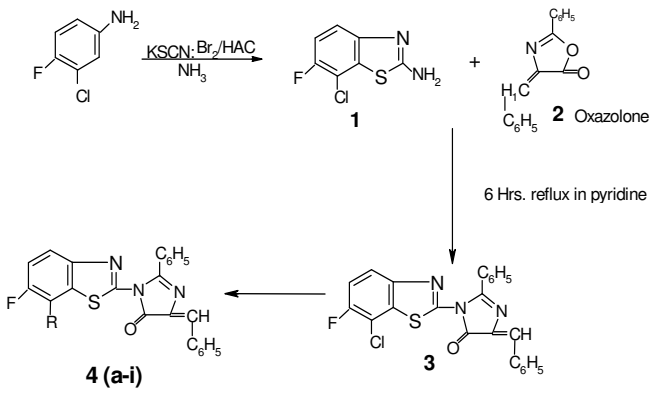
Abstract: 4-Fluoro-3-chloroanilline treated with potassium thiocyanate in presence of glacial acetic acid and bromine was converted into 2-amino-6-fluoro-7-chlorobenzothiazole, resulting into 2-amino benzothiazole. The synthesized compound in presence of 2-phenyl-4-benzylidine-5-oxazolinone refluxed in pyridine to obtain 2-(2-phenyl-4-benzylidenyl-5-oxo-imidazolin -1-yl amino)-6-fluoro-7-substituted(1,3)benzothiazoles. The above said compound was treated with *ortho, meta* and *para* nitroanillines, *ortho*, *meta*, *para* chloroanillines, morpholino, piperazine, diphenylamine in the presence of DMF to obtain different derivatives. Some compounds showed promising anti-microbial activity.

Keywords: Flourine, Benzothiazole, Oxazalinone, Imidazoline, Antimycobacterial activity.

Introduction

Fluorobenzothiazoles and imidazoles exhibit the broad range of antibacterial[1], antifungal[2], anthelmintic[3], anti-inflammatory[4] and antitubercular[5] activity. In the recent years, the chemistry of oxazolones[6] 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[7-8] fluorobenzothiazoles with imidazoles for generating various derivatives, screened for antimycobacterial activity by using *in-vitro* models[10]. Benzylidine derivatives were found to possess MAO Inhibitory activity[9], therefore in the present work we have treated oxazolones benzothiazole ring to get potent antimycobacterial leads.



Experimental

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-8300) spectrophotometer using nujol mull technique. For antimycobacterial activity *in vitro* by tube dilution technique using the human virulent $H_{37}RV$ strains of M. tuberculosis.

General Procedure

2-Amino-6-fluoro-7-chloro-(1,3)benzothiazole (**1**)

To the glacial acetic acid (20 mL) which is cooled below room temperature, 8 g (0.08 mol) of potassium thiocyanate and 1.45 g (0.01 mol) of fluorochloroaniline was added. The mixture was placed in freezing mixture of ice and salt, mechanically stirred while 1.6 mL of bromine in 6 mL 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 (105 min), the solution was stirred for 2 h below room temperature and at room temperature for 10 h, it was then allowed to stand over night, during which period an orange precipitate settle at the bottom, water (6 mL) was added quickly and slurry was heated at 85 ^{0}C on a steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10 mL of glacial acetic acid heated again to 85 ^{0}C and filtered hot. The combined filtrate was cooled and neutralized with concentrated ammonia solution to pH 6. A dark yellow precipitate was collected. Recrystallised from benzene-ethanol mixture (1:1) after treatment with animal charcoal gave yellow plates of 2-amino-6-fluoro-7-chloro-(1,3) benzothiazole. After drying in an oven at 80 ^{0}C, the dry material (1 g 51.02%) melted at 210-212 ^{0}C. UV 307.4, 269 nm, IR 1542 cm^{-1} (aromatic C=C) and 3475 cm^{-1} (NH_2); 1456 cm^{-1} (thiazole), 1215 cm^{-1} (aromatic-F), 712 cm^{-1} (aromatic-Cl).

2-Phenyl- 4-benzylidine-5-oxazol-5-one (oxazolone) (**2**)

Redistilled benzaldehyde was treated with benzoyl glycine (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).

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

A mixture of 0.01 mol. of 2-amino-6-fluoro-7-chloro-(1,3)benzothiazole (**1**) with 2-phenyl-4-benzylidine-5-oxazol-5-one (oxazolone)(**2**) 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 recrystallised 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 (**4a-i**)

2[2'- Phenyl -4'- benzidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro (1,3) benzothiazole (**3**) was treated with various aromatic amines. Refluxed for 2 h. 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 (**4a-i**). The solid separated was cooled and poured on to crushed ice. The solid separated was filtered off, dried and recrystallised from benzene and super dry alcohol (1;1).

Table 1. Analytical data of the synthesized compounds (**4a-i**)

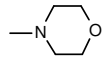
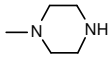
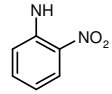
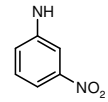
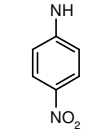
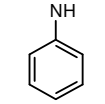
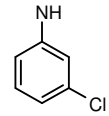
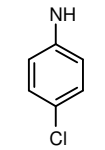
Comp No	R	M.P. ºC	Yield %	M. F.	Elemental Analysis %			
						C	H	N
4a		117	80	$C_{27}H_{17}N_4O_2SF$	Found	68.00	3.56	12.00
					Calc.	67.50	3.54	11.66
4b		128	79	$C_{27}H_{18}N_4OSF$	Found	70.01	3.90	12.13
					Calc.	69.67	3.87	12.04
4c	-N-$(C_6H_5)_2$	117	74	$C_{35}H_{23}N_4OSF$	Found	74.90	4.15	10.09
					Calc.	74.20	4.06	9.89
4d		116	66	$C_{29}H_{18}N_5O_3SF$	Found	65.09	3.56	13.89
					Calc.	65.04	3.36	13.08
4e		126	68	$C_{29}H_{18}N_5O_3SF$	Found	66.00	3.89	14.02
					Calc.	65.04	3.36	13.08
4f		122	70	$C_{29}H_{18}N_5O_3SF$	Found	66.09	3.45	12.80
					Calc.	65.04	3.36	13.08
4g		111	72	$C_{29}H_{19}N_4OSF$	Found	71.09	3.90	12.56
					Calc.	71.02	3.87	11.42
4h		85	77	$C_{29}H_{18}N_4OSFCl$	Found	67.77	3.89	10.89
					Calc.	66.28	3.42	10.66
4i		115	70	$C_{29}H_{18}N_4OSFCl$	Found	67.05	3.67	11.09
					Calc.	66.28	3.42	10.66

Table 2. IR spectral data of the synthesized compounds (**4a-i**)

Comp. Code	NH cm^{-1}	Imidazoline ring carbonyl cm^{-1}	C=N stretching cm^{-1}	C=C stretching cm^{-1}	NO_2 cm^{-1}	C-F cm^{-1}	C-Cl cm^{-1}
4a	3353	1640	1612	1485	---	1167	---
4b	3200	1640	1673	1460	---	1161	---
4c	3200	1630	1600	1490	---	1163	---
4d	3300	1640	1600	1490	802	1167	---
4e	3350	1639	1613	1487	799	1163	---
4f	3400	1630	1640	1400	890	1167	---
4g	3351	1641	1610	1460	---	1164	---
4h	3350	1643	1600	1462	---	1169	714
4i	3349	1637	1653	1493	---	1160	714

Screening for antimycobacterial activity (in vitro models)

Sterile Kirchner's medium was dispensed in each borosilicate test tube (150 x 20 mm) and to this sterile horse serum (0.5 mL) was added. The stock solution was sterile by passing through a 0.2 mm polycarbonate sterile membrane (Nuclepore) filters. Further the serial dilution of test compounds were carried out. Test compounds at various concentrations (250, 125, 62, 32, 16, 8, 4 and 1 µg/mL) were added to culture medium in a sterilized borosilicate test tube and strain of *M.tuberculosis* was inoculated at concentration (106 bacilli/mL). The tubes were incubated at 37^0 for 21 days and then examined for the presence or absence of growth of the test organisms. All experiments were performed in triplicate. The lowest concentration, which showed no visible growth, was taken as the end point *i.e*. minimum inhibitory concentration (MIC). Rifampin and isoniazid (INH) were used as standard for antimycobacterial activity.

Table 3. Antimycobacterial activity of synthesized compounds (**4a-i**)

Comp. No.	Activity Data Codes	H37RV strain of *M. tuberculosis* 21 days
01	**4a**	20
02	**4b**	26
03	**4c**	25
04	**4d**	13
05	**4e**	15
06	**4f**	21
07	**4g**	17
08	**4h**	20
09	**4i**	17
Standard 1	Rifampicin	0.25
Standard 2	Isoniazide	0.007

Conclusion

All the synthesized fluorinated benzothiazole imidazole compounds have given appreciable yield with satisfactory elemental analysis. It is inferred from the Table 3 that synthesized compounds (**4a-i**), have shown significant antimycobacterial activity. However, animal study and other studies are necessary for its activity and also there is a need to elucidate its mechanism of antimycobacterial action.

Acknowledgment

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References

1. Sangal S K and Rastivona P K, *Chem Abstr*., 1986, **104**, 34029
2. Gurupadiaiah B M, Jaychandran E, Nargund L V G and Shivkumar B, *Indian J Heterocycl.,* 1998, **7,** 213-216
3. Labendeno N Yu, *Chem Abstr*., 1980, **92**, 922882
4. Areas J J, *Chem Abstr.,* 1991, **14**, 71453
5. Jaychandran E, Nargund L V G, Shivkumar B and Kamal Bhatia, *Oriental J Chem.*, 2003, **19(1)**, 139-142
6. Vogel A I, Vogel's Textbook of Practical Organic Chemistry; ELBS, 1978, **4**, 884-885.
7. Merja B C, Joshi A M and Parikh K A, Oriental J Chem., 2003, **13(1)**, 157-160
8. Verma V M, Chturvedi A K and Pamar S S, *J Pharm Sci*., 1974, **463**, 1740.
9. Bhusari K P, Khedkar P B, Umathe S N and Raghuramrao A, *Indian J Heterocycl Chem.,* 2000, **13**, 798-800
10. Shieke V G and Bodade A S, *Chem Abstr*., 1991, 11423845r