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ANTI-TUBERCULAR ACTIVITY OF FLUORO BENZOTHIAZOLE COMPRISING POTENT THAIZOLIDINONE.

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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. The synthesized compound in presence of m-nitro benzaldehyde refluxed in ethanol to obtained 3-[6'-fluoro-7'-chloro(1',3') benzo thiazol-2'-yl]-m-nitrophenyl(1,3) thiazolidine-4-one. 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-mycobacterial activity.

KEYWORDS

Antitubercular activity, Fluorobenzothiazole, Thiazolidinone.

INTRODUCTION

Fluorobenzothiazoles 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 thiazolidinones[6-8] 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 thiazolidinone for generating various derivatives, screened for antitubercular activity by using in-vitro models[9]. Benzylidine derivatives were found to possess MAO Inhibitory activity[10], therefore in the present work we have treated thiazolidinones benzothiazole ring to get potent antitubercular 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. For anti-tubercular 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. 3.

EXPERIMENTAL

First Step

Synthesis of 2-amino-6-fluoro-7-chloro-(1,3)benzothiazole (1):

To the glacial acetic acid (20ml) which is cooled below room temperature,8gm (0.08mol) of potassium thiocyanate 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 neutrilised 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 210-212^0c. 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-[m-nitrobenzylidine]-6-fluoro-7-chloro (1, 3) benzothiazole (2):

0.01 mol of 2-[m-nitrobenzylidine]-6-fluoro-7-chloro (1, 3) benzothiazole with 0.015 mol solution of m-nitro benzaldehyde, added 20 ml ethanol and 3-4 drops of HCl and refluxed for 2-3 Hrs. Solution cooled and poured into crushed ice. Recrystalised with benzene and ethanol.

Third Step

Synthesis of 3-[6'-fluoro-7'-chloro(1',3') benzo thiazol-2'-yl]m-nitrophenyl(1,3) thiazolidine-4-one (3):

A mixture of Schiff's base (0.01 mol) and 0.025 mol of 2-thioglycolic acid heated on oil-bath at 115º-120 º c for 12 Hrs. After reflux cool and triturated with 10% sodium bicarbonate solution. Crystallized from water.

Preparation of various derivatives (BT_1-BT_9):

3-[6'-fluoro-7'-chloro(1',3') benzo thiazol-2'-yl]m-nitrophenyl(1,3) thiazolidine-4-one were treated with equimolar quantities of various aromatic amines, refluxed for 2 hours in presence of DMF, recrystalised from alcohol and benzene.

Table No. 1
Analytical Data of the Compounds (BT_1-BT_9)

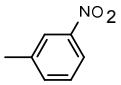
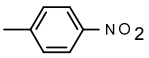
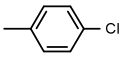
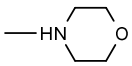
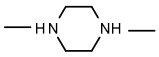
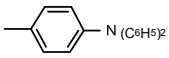
Compds	R	M.P (ºC)	Yield (%)	Molecular Formula	Molecular Wt.	Elemental Analysis Data (Calculated in %)		
						C	H	N
BT_1		115	65.00	$C_{22}H_{13}N_5O_5S_2F$	478	55.23	2.71	14.64
BT_2		119	76.00	$C_{22}H_{13}N_5O_5S_2F$	478	55.23	2.71	14.64
BT_3		101	72.00	$C_{22}H_{13}N_5O_5S_2F$	478	55.23	2.71	14.64
BT_4		182	69.00	$C_{21}H_{13}N_4O_3S_2FCl$	698	66.18	1.86	8.02
BT_5		202	52.00	$C_{21}H_{13}N_4O_3S_2FCl$	698	66.18	1.86	8.02
BT_6		152	63.00	$C_{21}H_{13}N_4O_3S_2FCl$	698	66.18	1.86	8.02
BT_7		174	58.00	$C_{20}H_{12}N_4O_4S_2F$	423	56.73	2.83	13.23
BT_8		187	56.00	$C_{20}H_{13}N_5O_3S_2F$	454	52.86	2.86	15.41
BT_9		118	63.00	$C_{27}H_{17}N_4O_3S_2F$	528	61.36	3.21	10.60

Table2
IR spectral assignments of synthesized compounds (BT_1-BT_9)

Compounds	*Characteristic absorption bonds (in cm^{-1})*									
	Ar-NH_2 Str.	C=O Str.	Aro.C=C Str.	C-F Str.	C-Cl Str.	NO_2	C=C	3º-Nitrogen	C-H	*C-S-C*
BT_1	3385	1770	1597	1260	---	1370	1597	3020	3460	*1301*
BT_2	3400	1870	1625	1249	---	1309	1625	3090	3433	*1392*
BT_3	3390	1820	1697	1249	---	1303	1525	3050	3300	*1392*
BT_4	3128	1790	1595	1195	1170	---	1670	3080	3380	*1352*
BT_5	3228	1820	1670	1219	1166	---	1525	3093	3352	*1307*
BT_6	3201	1825	1690	1249	1197	---	1525	3095	3435	*1360*
BT_7	3200	1800	1550	1295	---	---	1380	3360	3240	*1336*
BT_8	3370	1825	1600	1250	---	---	1590	3100	3460	*1300*
BT_9	*3350*	*1835*	*1597*	*1290*	---	---	*1395*	*3020*	*3400*	*1330*

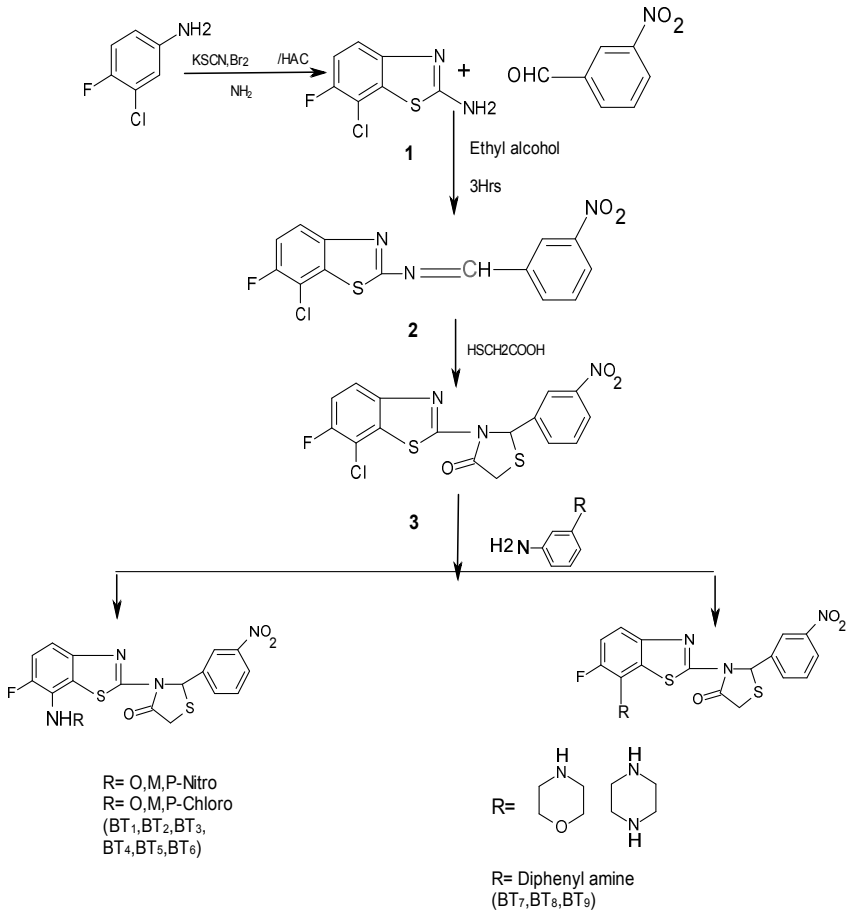
Antitubercular Screening Procedure

Sterile Kirchner's medium was dispensed in each borosilicate test tube (150 x20mm) 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 Isoniazide (INH) were used as standard for antimycobacterial activity.

Table No. 3
Antitubercular activity (BT_1-BT_9)

Comp. No.	Activity Data Codes	H37RV strain of M. tuberculosis 21 days
Standard 1	**Rifampicin**	0.25
Standard 2	**Isoniazide**	0.007
01	**BT_1**	21
02	**BT_2**	24
03	**BT_3**	26
04	**BT_4**	18
05	**BT_5**	15
06	**BT_6**	22
07	**BT_7**	19
08	**BT_8**	24
09	**BT_9**	21

SCHEME



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