ANTI – MYCOBACTERIAL ACTIVITY FLUORO SUBSTITUTED SULPHONAMIDE BENZOTHIAZOLE COMPRISING HETEROCYCLIC MOIETIES

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ABSTRACT

Few 3-[6'Fluoro-7'-substituted-(1',3')benzothiazol-2'-yl]p-benzene sulphonamido-2-o-nitrobenzene (1,3) thiazoline-4-one were synthesized using appropriate synthetic route. The structure of these compounds was characterized by means of physical constants, elemental analysis, solubility tests, TLC and by UV, IR spectral studies. All the compounds were evaluated for *in-vitro* anti-mycobacterial activity. Compounds showed significant activity.

KEY WORDS: Fluorobenzothiazole, Sulphonamido, Thiazolidinone, Anti-mycobacterial activity.

1.INTRODUCTION

We report herein the new synthesis of fluoro benzothiazoles (Feller, 1995) comprising thiazolidinone derivatives. The sulfonamide drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and cure of bacterial infection in human beings (Bahar and Siddiqui, 1998). The chemistry and pharmacology of thiazole have been of great interest because of its various biological activities (Jatav, 2006), so that the biological and pharmacological activity of thiazolidinone with fluoro sulphonamidobenzothiazoles may be taken into account for synergism. It is well known that the introduction of fluorine atom into an organic molecule (Conte, 1995) causes dramatic changes in its biological profile, mainly due to high electro negativity of fluorine, the strong carbon-fluorine bond and increased solubility in lipids. In search for new bioactive potent molecule, it was thought worth while to incorporate some additional heterocyclic moieties in the thiazolidinone nucleus and study their biological and pharmacological activity, the review of literature reveal prompted us to synthesis of substituted fluoro sulphonamidobenzothiazolyl thiazolidinone compounds and those will be screened for anti-mycobacterial activity by *in-vitro* method (Shieke and Bobade, 1991) to get potent bioactive molecule.

2.EXPERIMENTAL

The sample compounds were tested *in vitro* by the tube dilution technique using the human virulent $H_{37}Rv$ strain of *M. tuberculosis*. The tubes were incubated at 37°c for 21 days. Rifampicin and Isoniazide were used as standard for antimycobacterial activity.

Condensation of 2-amino-6-fluoro-7-chloro-(1,3)benzothiazole and p-acetamido benzene sulphonyl chloride (2)

2-amino-6-fluoro-7-chloro (1,3) benzothiazole (0.013 mol) was taken in pyridine (4 ml) and acetic anhydride (20 ml), to this p-acetamido benzene sulphonyl chloride (0.01 mol) were added and the mixture was kept in water bath for 2 hrs. The reaction mixture then poured in to 20 ml of ice cold water. The solid obtained was filtered and recrystalised from dil.ethanol (80%) to get pure compound 6-fluoro-7-chloro-2-(p-acetamido benzene sulphonamido) (1,3)-benzothiazole.

Synthesis of 6-fluoro-7-chloro-2-(p-amino benzene sulphonamido) (1,3) benzothiazole (3)

The derivatives obtained were then hydrolyzed by boiling them in 50 ml of 80% acetic acid for 4 to 5 hrs and the contents were poured onto crushed ice. The obtained hydrolyzed derivatives were filtered at suction and dried.

Synthesis of 6-fluoro-7-chloro-2-[p-(m-nitro benzylidine) amino benzene sulphonamido] (1,3) benzothiazole (4)

0.01 mol of 6-fluoro-7-chloro-2-(p-amino benzene sulphonamido) (1,3) benzothiazoles with 0.015 mol solution of p-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.

Synthesis of 3-[6'Fluoro-7'-Chloro-(1',3')benzothiazol-2'-yl]p-benzene sulphonamido-2-m-nitrobenzene (1,3) thiazolidin-4-one (5)

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

Synthesis of 3-[6'Fluoro-7'-substituted-(1',3')benzothiazol-2'-yl]p-benzene sulphonamido-2-m-nitrobenzene (1,3) thiazolidin-4-one (B_1-B_{12})

3-[6'Fluoro-7'-Chloro-(1',3')benzothiazol-2'-yl]p-benzene sulphonamido-2-m-nitrobenzene (1,3) 3-chloro-azetidin-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 (B_1-B_{12})

Compds	R	M.P (°C)	Yield (%)	Molecular Formula	Molecular Wt.	Elemental Analysis Data (Calculated in %)		
						C	H	N
B_1		110	78	$C_{28}H_{19}N_6O_7S_3F$	666	50.45	2.85	12.61
B_2		156	89	$C_{28}H_{19}N_6O_7S_3F$	666	50.45	2.85	12.61
B_3		125	76	$C_{28}H_{19}N_6O_7S_3F$	666	50.45	2.85	12.61
B_4		90	75	$C_{28}H_{19}N_5O_5S_3FCl$	656	51.21	2.89	10.67
B_5		115	82	$C_{28}H_{19}N_5O_5S_3FCl$	656	51.21	2.89	10.67
B_6		142	89	$C_{28}H_{19}N_5O_5S_3FCl$	656	51.21	2.89	10.67
B_7		92	79	$C_{29}H_{20}N_5O_7S_3F$	665	52.23	3.00	10.52
B_8		120	62	$C_{28}H_{20}N_5O_5S_3F$	621	54.10	3.22	11.27
B_9		165	87	$C_{26}H_{22}N_5O_6S_3F$	615	50.73	3.57	11.38
B_{10}		188	82	$C_{26}H_{23}N_6O_5S_3F$	614	50.81	3.74	13.68
B_{11}	$-N(C_6H_5)_2$	210	56	$C_{34}H_{24}N_5O_5S_3F$	697	58.53	3.44	10.04
B_{12}	$-N(CH_3)_2$	156	76	$C_{24}H_{20}N_5O_5S_3F$	573	50.26	3.49	12.21

Table2. IR spectral assignments of synthesized compounds (B_1-B_{12})

Compounds	Characteristic absorption bonds (in cm^{-1})									
	Ar-NH_2 Str.	S=O Str.	Aro.C=C Str.	C-F Str.	C-Cl Str.	NO_2	SO_2-NH Str.	3°-Nitrogen	CH_3 Str.	C-S-C
B_1	3300	1822	1456	1200	---	725	1334	3100	1334	1200
B_2	3423	1856	1434	1232	---	778	1390	3200	1297	1290
B_3	3345	1876	1456	1231	---	789	1400	3100	1287	1200
B_4	3200	1825	1708	1278	1190	---	1359	3372	1295	1200
B_5	3220	1823	1578,1700	1300	1187	---	1398	3318	1300	1286
B_6	3301	1825	1562,1698	1399	1183	---	1385	3400	1309	1289
B_7	3208	1827	1600	1200	---	---	1380	3200	1329	1198
B_8	3380	1825	1640	1323	---	---	1390	3298	1289	1170
B_9	3370	1840	1597	1309	---	---	1345	3100	1345	1300
B_{10}	3390	1890	1560	1209	---	---	1395	3100	1300	1150
B_{11}	3120	1867	1623	1250	---	---	1395	3306	1289	1200
B_{12}	3397	1820	1455	1240	---	---	1395	3100	1356	1287

Anti – mycobacterial Screening

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). Rifampicin and Isoniazide (INH) were used as standard for antimycobacterial activity.

Compounds	$H_{37}RV$ strain of *M. tuberculosis* 21 days
Rifampicin (Standard 1)	0.25
Isoniazide (Standard 2)	0.007
B_1	20
B_2	22
B_3	27
B_4	23
B_5	22
B_6	18
B_7	20
B_8	21
B_9	20
B_{10}	17
B_{11}	16
B_{12}	23

3.RESULTS AND DISCUSSION

In present investigation synthesis of several novel 3-[6'Fluoro-7'-substituted-(1',3')benzothiazol-2'-yl]p-benzene sulphonamido-2-substituted (1,3) thiazolidin-4-one (B_1-B_{12}) is reported. All the synthesized compounds exhibited significant anti-mycobacterial activity. In conclusion a new class of different aromatic primary and secondary amines encompassing sulfonamidothiazolidinone to get targeted molecules were synthesized and evaluated for anti-mycobacterial activity.

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