SYNTHESIS AND ANTHELMINTIC ACTIVITY OF FLUORO BENZOTHIAZOLE LINKED THIAZOLIDINONE

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

ABSTRACT

Fluorobenzothiazole linked Thiazolidinones using 3-nitro benzaldehyde, various novel derivatives were synthesized and evaluated for anti-microbial, anti-tubercular,anthelmintic activity.Structures of these compounds has been established by melting point, elemental analysis,UV and IR data. Compounds showed significant anthelmintic activity.

KEY WORDS: Anthelmintic activity, Fluorobenzothiazole, Thiazolidinones.

1.INTRODUCTION

Benzothiazoles incorporated with fluorine (Feller, 1995) to get promising molecule for clinical use.Fluorobenzothiazole (Trivedi and Shah, 1992) are biologically versatile as they have been found to be anticancer agent anti-tubercular agent (Litvinchuk and Farmakol, 1963), fungicidal (Rao, 1996), cardiovascular agent, local anaesthetic activity.The above said nucleus is modified by linking thiazolidinones, the derivatives of thiazolidine which belong to the important group of heterocyclic compounds (Satizinger and Liebijs,1963). In recent years several new methods for the preparation of thiazolidinone derivatives and reactions have been reported in literature. This attempt is made to link fluorobenzothiazole with potent thiazolidinone in present work by using 3nitrobenzaldehyde in hope to get promising clinically useful biodynamic compounds.

2.MATERIALS AND METHODS

Purity of compounds was checked by TLC. Melting points were determined by open capillaries method and are uncorrect. IR spectra (NaCl) are recorded on FTIR (Schimadzu-84005) spectrophotometer using nujol mull technique. For anthelmintic activity *in vitro* technique by using earthworms species *Perituma posthuma*, (Jayachandran, 2003). Compounds showed significant anthelmintic activity.

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 raised 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 (1:1), after treatment with animal charcoal gave yellow plates of 2-amino-6-fluoro-7chloro-(1,3) benzothiazole. After drying in a oven at 80^0c, the dry material (1gm, 51.02%) melted at 210212^0c. 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-7chloro (1, 3) benzothiazole (2)

0.01 mol of 2-amino-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]mnitrophenyl(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.

SCHEME

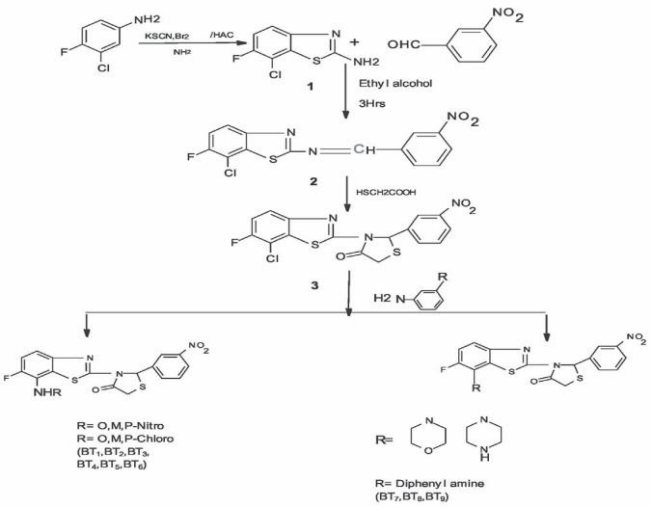

Table No. 1 Analytical Data of the Compounds (BT_1-BT_9)

Compds	R	M.P (°C)	Yield (%)	Molecular Formula	Molecular Wt.	Elemental Analysis Data (Calculated in %)		
						C	H	N
BT_1		115	65.00	$C_{22}H_{14}N_5O_5S_2F$	511	51.66	2.73	13.69
BT_2		119	76.00	$C_{22}H_{14}N_5O_5S_2F$	511	51.66	2.73	13.69
BT_3		101	72.00	$C_{22}H_{14}N_5O_5S_2F$	511	51.66	2.73	13.69
BT_4		182	69.00	$C_{22}H_{14}N_4O_3S_2FCl$	501	52.69	2.79	11.17
BT_5		202	52.00	$C_{22}H_{14}N_4O_3S_2FCl$	501	52.69	2.79	11.17
BT_6		152	63.00	$C_{22}H_{14}N_4O_3S_2FCl$	501	52.69	2.79	11.17
BT_7		174	58.00	$C_{20}H_{17}N_4O_4S_2F$	406	52.17	3.69	12.17
BT_8		187	56.00	$C_{20}H_{18}N_5O_3S_2F$	459	52.28	3.92	15.25
BT_9	$-N(C_6H_5)_2$	118	63.00	$C_{28}H_{19}N_4O_3S_2F$	542	61.25	3.50	10.33

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	3°-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

Procedure for Anthelmintic activity (Jayachandran, 2003)

The synthesized compounds are screened for anthelmintic activity by using earthworms. Six earthworms of nearly equal size were placed in standard drug solution and test compounds solutions at room temperature. Normal saline was used as control. The standard drug and test compounds were dissolved in minimum quantity of DMF and the volume was adjusted upto 15 ml. with normal saline solution to get the concentration of 0.1%, 0.2% and 0.5%. Albendazole was used as a standard drug. The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. The time taken by worms to become motionless was noted as paralysis time. To ascertain the death of the motionless worms, these were frequently applied the external stimuli, which stimulates and induces movement in the worms, if alive.

The mean lethal time and paralysis time of earthworms for different test compounds and standard drug are tabulated in Table 3.

Table No. 3 Anthelmintic activity (BT_1-BT_9)

Compounds	Concentration (%)					
	Time for paralysis (min.)			Time for death (min.)		
	0.1	0.2	0.5	0.1	0.2	0.5
Control	--	--	--	--	--	--
Albendazole	50	45	40	70	63	55
BT_1	48	33	30	130	125	110
BT_2	39	45	47	97	102	98
BT_3	23	25	20	130	129	118
BT_4	26	20	19	110	94	85
BT_5	48	35	30	192	168	128
BT_6	49	38	38	174	168	120
BT_7	32	30	26	125	118	110
BT_8	45	34	28	130	125	101
BT_9	60	42	32	179	157	122

3.RESULTS AND DISCUSSION

Some novel analogs of the fluorobenzothiazole schiffs base using m-nitro benzaldehyde and screened for anthelmintic activity using *Perituma posthuma* earthworms. Some of the compounds showed significant activity.

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