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SYNTHESIS, CHARACTERIZATION AND ANTHELMINTIC ACTIVITY (PERITUMA- POSTHUMA) OF FLUORO SUBSTITUTED BENZOTHIAZOLE FOR BIOLOGICAL AND PHARMACOLOGICAL SCREENING.

VIJAYA JAVALI, JAYACHANDRAN E.*, RAVI SHAH, KALPESH PATEL, SREENIVASA G.M.

*P.G. Department of Pharmaceutical Chemistry, S.C.S. College of Pharmacy Harapanahalli.-583131, Karnataka, India.

Corresponding Author drjc_2006@rediffmail.com, vijayakumarjavali@yahoo.in

ABSTRACT

Various substituted 7-chloro-6-fluoro-N-(1,3-thiazol-2-yl)-1,3 benzothiazol-2-amine 1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl) thiaourea containing different functional groups have been synthesized by condensing Chloroacetyl chloride with 2-aminobenzothiazole in Ammonium thiocyanate/Hcl The synthesized compounds was identify were confirmed on the basis of their spectral (UV-VIS, IR, ^{1}HNMR and MASS) data. All the compounds have been screened for their antibacterial activity.

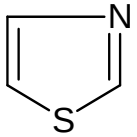
KEY WORDS

Fluorine, Benzothiazole, Thiazole.

INTRODUCTION

The 2-Substituted Benzothiazoles found to possess broad spectrum of pharmacological activity. of clinical importance. Local anaesthetics[1], Hypoglycemic agents[2], Carbonic anhydrase inhibitors[3], Antitubercular activity[4], Anticancer[5], Cardiovascular drugs[6], Antimicrobial[7], Enzyme inhibitors[8],choleratic agent[9], Central dopaminergic agents[10].

Thiazole are the important class of heterocyclic compounds which contains one Sulphur and Nitrogen in 1,3 position of five membered ring is known as thiazole. Benzothiazole with thiazole group etc. were reported to posses various pharmacological activity of clinical importance.



This class of compounds is present in many natural and synthetic products with a wide range of pharmacological activities such as anticancer[11], anti-inflammatory[12], antibacterial[13], antimicrobial[14], anticonvulsant[15], anthelmintic[16-19] and diuretic[20] activities.

MATERIAL AND METHODS

Melting point was determined by open capillary tube method and are uncorrected. T.L.C. was run on silica gel G plates using petroleum ether and ethyl acetate (2:1) as developing solvent for the purity of the compounds. I.R. spectra were recorded on SHIMADZU FTIR-8400S spectrophotometer by using KBr pellets technique.

SCHEME

1st Step :
Synthesis of 6-fluoro-7-chloro-(1,3)-benzothiazole-2-amine.

To glacial acetic acid (20ml) cooled below room temperature were added 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of fluoro chloro aniline. The mixture was placed in a water bath and stirred with magnetic stirrer 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 rise 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^{0}C and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85^{0}C and filtered hot. The combined filtrate was cooled and neutralised with ammonia solution to the pH range 6.0 A dark yellow precipitate was collected. Recrystalised from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow crystals of 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole. After drying in a oven at 80^{0}C, the dry material(1gm 51.02%) melted at 210-212^{0}C.

2nd Step :
Synthesis of 1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl) thiourea.

Benzoyl chloride (14.0 g, 0.1 mol) was added dropwise to ammonium thiocyanate (7.6 g, 0.1 mol) in dry acetone 50ml with stirring.After the intial reaction had subsided, the mixture was heated for 5 min and then a hot solution of 2-amino benzothiazole (15 g, 0.1 mol) in dry acetone (50ml) was added with constant stirring.After refluxing and 1 hrs, the mixture was poured into water. A crystalline solid precipitated out slowly. After filtration the soild was heated with 10% NaOH solution (300) and filtered again. The filtrate was acidified with conc. HCl and then made alkaline by addition of a little ammonia. The solid so obtained was filtered, washed with water and dried. The product was recrystallized using ethanol.

3rd Step :
Synthesis of 7-chloro-6-fluoro-N-(1,3-thiazol-2-yl)-1,3-benzothiazol-2-amine.

0.01 mol of 1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl) thiourea in 30ml ethanol was taken with 0.01 mol solution Chloroacetyl chloride in 40ml ethanol refluxed for 4 hrs on a water bath. On cooling, the crystalline solid obtained was filtered, washed with water and dried. The product was recrystallized using ethanol.

4th Step :
Synthesis of Thiazole derivatives

Thiazole was treated with equimolar quantities of various substituted primary and secondary

amines refluxed for 2 hours in oil bath in the presence of N-N', dimethyl formamide(DMF). The mixture was cooled and poured into crushed ice. The solid separated was filtered off, dried and recrystallized from alcohol.

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 compound's solutions at room temperature. Normal saline used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl formamide (DMF) and adjusted the volume up to 10 ml with normal saline solution to get the concentration of 0.075 % w/v, 0.150 % w/v and 0.225% w/v. 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 were frequently applied with external stimuli, which stimulates and induces movement in the worms, if alive.
The mean lethal time and paralysis time of the earthworms for different test compounds and standard drug are tabulated in Table No. 4.

Table No. 4
Anthelmintic activity

Sl. No.	Name	Time in Minutes					
		For Paralysis			For Death		
		% of Concentration			% of Concentration		
		0.1	0.2	0.5	0.1	0.2	0.5
01	Control (0.9 % Concentration)	--	--	--	--	--	--
02	Albendazole	17.0	13.0	7.0	67.0	52.0	37.0
03	V_1	21.0	14.0	6.0	70.0	54.0	28.0
04	V_2	19.0	14.0	7.0	69.0	52.0	25.0
05	V_3	21.0	13.0	7.0	67.0	52.0	29.0
06	V_4	22.0	14.0	7.0	66.0	55.0	32.0
07	V_5	17.0	13.0	8.0	68.0	51.0	28.0
08	V_6	18.0	14.0	6.0	58.0	48.0	27.0
09	V_7	22.0	12.0	8.0	59.0	48.0	34.0
10	V_8	19.0	12.0	8.0	58.0	47.0	25.0
11	V_9	18.0	12.0	7.0	66.0	53.0	32.0
12	V_{10}	19.0	13.0	8.0	64.0	52.0	28.0
13	V_{11}	21.0	14.0	7.0	57.0	47.0	24.0

RESULTS AND DISCUSSION

Anthelmintic Activity

The above screened compounds were tested for anthelmintic activity.

Among the compounds tested V_1, V_2, V_3, V_4, V_7, V_{11}, showed significant paralytic time of earthworms compared to standard drug albendazole of 0.1 %, 0.2 %, 0.5 % concentrations and test compounds showed comparatively better death time of earthworms with that of standard drug. After all, the synthesized compounds in overall estimation confirms the better activity against peritum posthuma.

TABLE NO. 1
ANALYTICAL DATA

Sl. No	Compound Code	M.P °C	% Yield	MOL. FORM	M. Wt	Calculated %		
						C	H	N
1	V_1	230	78%	$C_{17}H_{13}FN_4OS_2$	372	54.83	3.49	15.05
2	V_2	218	82%	$C_{17}H_{13}FN_4OS_2$	372	54.83	3.49	15.05
3	V_3	182	75%	$C_{17}H_{13}FN_4OS_2$	372	54.83	3.49	15.05
4	V_4	221	72%	$C_{16}H_{10}ClFN_4S_2$	376	51.06	2.65	14.89
5	V_5	216	74%	$C_{16}H_{10}ClFN_4S_2$	376	51.06	2.65	14.89
6	V_6	226	73%	$C_{16}H_{10}ClFN_4S_2$	376	51.06	2.65	14.89
7	V_7	222	76%	$C_{16}H_{10}FN_5O_2S_2$	387	49.61	2.58	18.08
8	V_8	224	65%	$C_{16}H_{10}FN_5O_2S_2$	387	49.61	2.58	18.08
9	V_9	230	69%	$C_{16}H_{10}FN_5O_2S_2$	387	49.61	2.58	18.08
10	V_{10}	205	83%	$C_{14}H_{13}FN_4O_2S_2$	336	50	3.86	16.66
11	V_{11}	197	77%	$C_{17}H_{11}FN_4O_2S_2$	386	52.84	2.84	14.50

Characteristics IR absorption bands of different synthesised compounds are tabulated below :

TABLE NO. 2

Compound	Ar-NH (in cm^{-1})	C=N Stretching (in cm^{-1})	C=C Stretching (in cm^{-1})	NO_2 (in cm^{-1})	C-F (in cm^{-1})	Sec.Ar. Amine (in cm^{-1})	C – Cl Stretching (in cm^{-1})	C-S-C Stretching (in cm^{-1})
V_1	3479	1534	1671	-	1195	1293	-	700
V_2	3475	1541	1670	-	1196	1289	-	702
V_3	3476	1537	1670	-	1197	1292	-	701
V_4	3476	1558	1670	-	1196	1288	876	702
V_5	3476	1536	1670	-	1122	1287	877	703
V_6	3475	1537	1670	-	1196	1289	876	701
V_7	3475	1537	1669	1457	1197	1291	-	705
V_8	3476	1535	1671	1457	1122	1287	-	703
V_9	3476	1537	1669	1457	1195	1288	-	702
V_{10}	3348	1539	1670	-	1196	1293	-	704
V_{11}	3476	1537	1671	-	1196	1291	-	701

TABLE NO. 3
NMR Spectral Data

Sl no	Compound Code	Hydrogen H	δ(ppm)	Multiplity	Solvent
1	V_1	-Ar-H- -NH-	7.59 - 8.17 4.87	Multiplet Singlet	DMSO
2	V_4	-Ar-H- -NH-	7.59 - 8.17 4.87	Multiplet Singlet	DMSO
3	V_7	-Ar-H- -NH-	7.59 - 8.17 3.37	Multiplet Singlet	DMSO
4	V_{11}	-Ar-H- -NH-	7.6 - 8.18 3.36	Multiplet Singlet	DMSO

CONCLUSION

Scheme

In present work, fluorochloroaniline was treated with KSCN in presence of bromine in glacial acetic acid and ammonia to get 2- amino–6-fluoro-7-chloro (1,3)- benzothiozole, which was treated with Ammonium thiocyanate/Hcl to get 1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl) thiourea. treated with Chloroacetyl chloride reflexed for 4hrs to get 7-chloro-6-fluoro-*N*-(1,3-thiazol-2-yl)-1,3-benzothiazol-2-amine. Thiazole was treated with equimolar quantities of various substituted anisidine, aniline, morpholine, piperazine and paba refluxed for 2 hours in presence of N,N-dimethyl formamide (DMF). were treated to get newly targeted compound through replacing at 7th position chlorine.

The lead compounds of scheme were characterized by melting point, TLC, calculated elemental analysis, UV, IR and ^{1}HNMR spectral studies.

The anthelmintic studies of synthesized compounds V_1, V_2, V_3, V_4, V_7, V_{11}, showed significant activity at low and high concentration compared to standard; still further studies are requested.

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