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Research Article

N-Substituted Fluoro Benzothiazolo Schiff's Bases: Synthesis and Characterisation of New Novel Anthelmintic Agents

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ABSTRACT

Various substituted N-[6-fluoro-7-substituted benzothiazol-2-yl]-2-(furan-2-yl methylene) hydrazine carbothioamide containing different functional groups have been synthesized by treating fluoro chloro aniline with KSCN in presence of bromine in glacial acetic acid and ammonia to get 2-amino-6-fluoro-7-chloro-(1,3)- benzothiazole, which was treated with hydrazine hydrate, carbondisulphide and sodium chloro acetate in the presence of ethanol to get N-(7-chloro-6-fluoro benzothiazol-2-yl) hydrazine carbothioamide, which will refluxed with furfuraldehyde in the presence of ethanol to get newly N-(6-fluoro-7-chloro benzothiazol-2-yl)-2-(furan-2-yl methylene) hydrazine carbothioamide or schiff' base. To the above schiff's base different substitutents in presence of Dimethyl formamide (DMF) were treated to get newly targeted compounds through replacing at 7th position of chlorine. The lead compounds were characterized by Melting point, TLC, calculated elemental analysis, UV, IR, and H^1 NMR spectral studies. The synthesized compounds were treated for anthelmintic activity against Earthworms (perituma posthuma) nearly equal size had shown significant activity at different concentrations compared to standard; still further studies are requested.

Keywords: Fluoro benzothiazoles, Schiff's bases, Anthelmintic activity.

INTRODUCTION

The substituted benzothiazoles found to possess a broad spectrum of pharmacological and biological activity of clinical importance. These derivatives find a variety of applications ranging from Anti-inflammatory[1-2], Anti-microbial[3-5], Anti-convulsant[6-7], Anti-diabetic[8], Anthelmintic[9], Anti-mycobacterial[10], Anti-oxidant[11-12], Anti-tubercular[13], agents activity.

Schiff's bases are the important class of compounds which is a functional group that contain a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group –but not hydrogen. General formula of schiff's bases are $R_1R_2C=N-R_3$, where R_3 is an aryl or alkyl group that makes the Schiff base a stable imine. It is mainly characterized by the –N=H- group which imparts in elucidating the mechanism of transamination and rasemination reaction in biological system. There were reported to posses various pharmacological activity of clinical importance.

RNH_2 + R-CH ————› R-N=CHR + H_2

This class of compounds is present in many natural and synthetic products with a wide range of pharmacological activities such as Anti-microbial[14], Anti-oxidant[15], Anthelmintic[16], Anti-inflammatory[17], activities.

MATERIALS AND METHODS

Chemicals and Reagents: 4-fluoro-3-chloro aniline, KSCN, Glacial acetic acid, Bromine, Carbondisulphide, Ammonia, Alcohol, Hydrazine hydrate, Sodium chloroacetate, Furfuraldehyde, DMF, various substituted anilines, Morpholine, Piperazine, Amino phenols, Diethyl amine, O-toluidine and m-Anisidine.

Experimental section: Step 1: 4-Fluoro-3-chloro aniline was treated with KSCN in presence of glacial acetic acid and bromine to get corresponding 2-amino benzothiazoles.

Step 2: The above 2-amino benzothiazole was treated with hydrazine hydrate, carbon di sulphide and sodium chloro acetate in presence of ethanol to get thiosemicarbazide.

Step 3: These thiosemicarbazide was refluxed with furfuraldehyde in presence of ethanol to get N-(6-fluoro-7-chloro benzothiazol-2-yl)-2-(furan-2-yl methylene) hydrazine carbothioamide or schiff's base.

Step 4: The schiff's base was treated with equimolar quantities of various substituents like substituted anilines, morpholine, piperazine, amino phenols, diethyl amine, o-toluidine, and m-anisidine, refluxed for 2 hours in presence of Dimethyl formamide (DMF) to get newly targeted compounds through replacing at 7th position of chlorine. The mixture was cooled and poured in to crushed ice. The solid separated was filtered off, dried and crystallized from alcohol and benzene.

General procedures: Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using a Perkin-Elmer spectrophotometer (table no. 2). H^1 NMR spectra were recorded using tetra methyl saline (TMS) as an internal standard and DMSO-d6 as a

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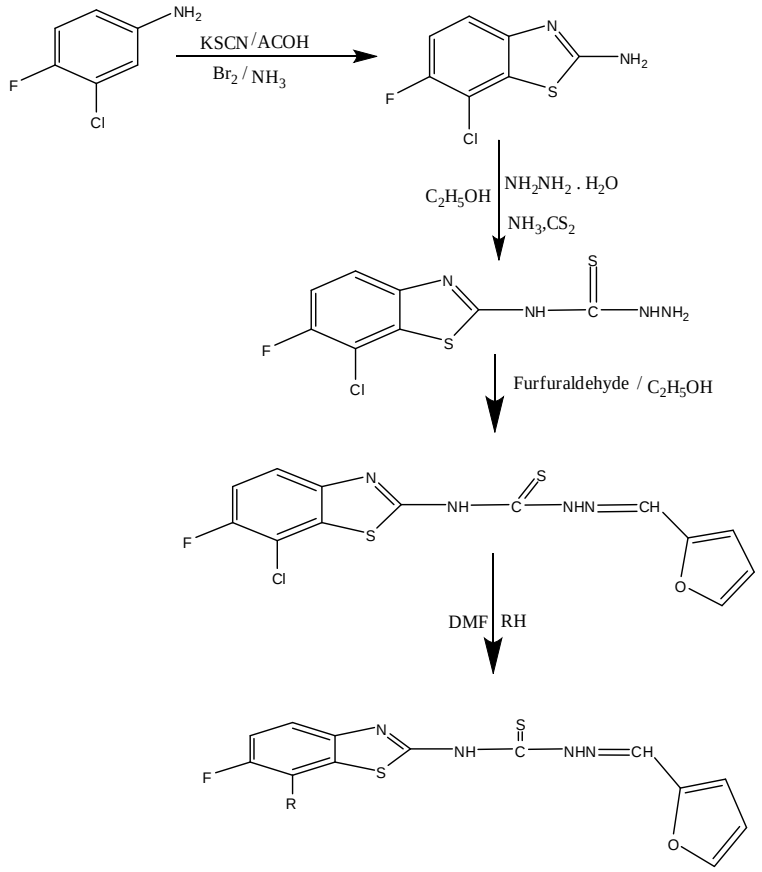
SCHEME



R=Aniline, m-anisidine, PABA, Diethylamine, Dimethylamine, 2,3,4-amino phenol, morpholine, o,m-toluidine,piperazine.

Table 1: Analytical Data

S. No	Compound Code	Mol. Formula	Mol.Wt	M.P/B.P °C	% Yield	Calculated %		
						C	H	N
1	BZT 1	$C_{19}H_{14}FN_5OS_2$	411.5	106-108	22	55.46	3.43	17.02
2	BZT 2	$C_{20}H_{16}FN_5O_2S_2$	441.5	125-127	37	54.41	3.65	15.86
3	BZT 3	$C_{19}H_{14}FN_5O_2S_2$	427.5	168-170	41	53.38	3.30	16.38
4	BZT 4	$C_{19}H_{14}FN_5O_2S_2$	427.5	177-179	37.2	53.38	3.30	16.38
5	BZT 5	$C_{19}H_{14}FN_5O_2S_2$	427.5	172-174	39	53.38	3.30	16.38
6	BZT 6	$C_{20}H_{14}FN_5O_3S_2$	455.5	97-99	31.6	52.74	3.10	15.38
7	BZT 7	$C_{17}H_{17}FN_6OS_2$	404.5	118-120	30.6	50.48	4.24	20.78
8	BZT 8	$C_{17}H_{18}FN_5OS_2$	391.5	121-123	27.4	52.16	4.63	17.89
9	BZT 9	$C_{15}H_{14}FN_5OS_2$	363.4	133-135	29.9	49.57	3.88	19.27
10	BZT 10	$C_{20}H_{16}FN_5OS_2$	425.5	112-114	30.7	56.45	3.79	16.46
11	BZT 11	$C_{20}H_{16}FN_5OS_2$	425.5	95-97	28.7	56.45	3.79	16.46
12	BZT 12	$C_{17}H_{16}FN_5O_2S_2$	405.5	132-134	35.5	50.36	3.98	17.27

solvent. Chemical shifts are given in parts per million (PPM). Splitting patterns are designated as follows: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet (table no. 3).

All the synthesized compounds were purified by recrystallization, the reaction were followed up and the purity of compounds was monitored on precoated TLC plates and visualizing the spots with iodine chamber.

Anthelmintic activity (*in vitro*): The synthesized compounds are screened for their anthelmintic activity by using earthworms (perituma posthuma). Test samples of the drugs were prepared at the concentrations 50,100 and 150 µg/ml in DMSO and six earthworms of approximately equal size (same type) were placed in each 9cm petridish containing 25ml of above test solutions of prepared compounds. Albendazole was used as reference standard and DMSO as control. All the test and standard drug solutions were prepared freshly before starting the experiments. Observations were made for the time taken for paralysis was noted when no movement of any sort

Table 2: Characteristics Ir Absorption Bands Of Similar Compounds

S. No.	Compound Code	ArC=C cm^{-1}	Acyclic C=N cm^{-1}	C-F cm^{-1}	C-N cm^{-1}	Ar-C-O cm^{-1}	C=S cm^{-1}
1	BZT-1	1541	1632	1068	1192	1215	1452
2	BZT-2	1541	1644	1067	1191	1214	1447
3	BZT-3	1543	1606	1068	1188	1231	1501
4	BZT-4	1539	1642	1015	1191	1215	1449
5	BZT-5	1542	1642	1067	1191	1215	1448
6	BZT-6	1539	1605	1066	1152	1227	1455
7	BZT-7	1547	1606	1067	1187	1230	1390
8	BZT-8	1537	1602	1070	1164	1242	1571
9	BZT-9	1535	1604	1072	1165	1242	1570
10	BZT-10	1537	1603	1072	1165	1242	1571
11	BZT-11	1580	1607	1004	1150	1227	1537
12	BZT-12	1540	1606	1065	1152	1224	1579

Table 3: Nmr Spectral Data

S. No.	Compound Code	No. of Protons	Hydrogen	δ (ppm)	Multiplity	Solvent
			-Ar-H	6.14-7.09	Multiplet	
1	BZT-4	14	-OH	9.21	Singlet	DMSO
			-NH-	3.78	Singlet	
			-Ar-H	6.29-7-19	Multiplet	
2	BZT-8	18	$-CH_2-$	3.49	Quintet	DMSO
			-NH-	3.91	Singlet	
			$-CH_3-$	1.42	Triplet	
			-Ar-H	6.25-7.05	Multiplet	
3	BZT-9	14	$-CH_3$	2.85	Doublet	DMSO
			-NH-	3.81	Singlet	
			-Ar-H	6.42-7.09	Multiplet	
4	BZT-10	16	$-CH_3$	2.19	Singlet	DMSO
			-NH-	3.79	Singlet	
			-Ar-H	6.23-7.06	Multiplet	
5	BZT-12	16	$-CH_2-$	3.09	Quintet	DMSO
			-NH-	3.96	Singlet	

Table no. 4: Anthelmintic Activity (*In Vitro* Method)

S. No	Name	Time in seconds					
		For paralysis concentration			For death concentration		
		50µg/ml	100µg/ml	150µg/ml	50µg/ml	100µg/ml	150µg/ml
1	Control		6			8	
2	Albendazole(1mg/ml)		5			7	
3	BZT 1	10	9	7	13	10	9
4	BZT 2	12	11	9	13	12	10
5	BZT 3	12	10	9	14	13	11
6	BZT 4	13	11	10	15	13	12
7	BZT5	14	13	11	16	14	13
8	BZT 6	9	8	6	11	10	8
9	BZT 7	13	11	10	15	13	12
10	BZT 8	10	8	7	12	10	9
11	BZT 9	9	7	6	11	9	8
12	BZT 10	13	12	11	14	13	12
13	BZT 11	11	10	9	13	11	10
14	BZT 12	8	9	13	15	12	9

could be observed except when the worms were shaken vigorously. Time for death of worms were recorded after ascertaining that worms neither moved when shaken vigorously nor when dipped in warm water(50^0c). All the results were shown in table no 4.

RESULTS AND DISCUSSION

Synthesis and pharmacological screening of N-(6-fluoro-7-substituted benzothiazol-2-yl)-2-(furan-2-yl methylene) hydrazine carbothioamide were tested for the Anthelmintic activity by using earthworms (perituma posthuma), mean lethal time was compared to standard Albendazole showed significant anthelmintic activity.

Among the synthesized compounds tested BZT-6 and BZT-8 had showed significant anthelmintic activity compared to standard Albendazole.

CONCLUSION

From the above results, It is concluded that Synthesized N-(6-fluoro-7-substituted benzothiazol-2-yl)-2-(furan-2-yl methylene) hydrazine carbothioamide or schiff's bases have a potent anthelmintic activity when compared with standard drug. In this present study anthelmintic assay was performed on the adult Indian earthworm *Perituma posthuma* due to its anatomical and physiological resemblance with the intestinal roundworm parasite of human beings. Further studies are needed to establish the mechanism of action and synthesis of future investigations responsible for the anthelmintic activity.

Melting point, TLC, calculated elemental analysis, UV, IR and H^1 NMR spectral studies are performed for lead compounds of the scheme (Synthesized compounds).

The anthelmintic studies of synthesized compounds BZT-6 and BZT-8 showed significant activity at low and high concentrations compared to standard Albendazole and hence the study would deserve for future investigation and derivatisation; still further studies are requested.

REFERENCES

1. M.Vedhavathi, Aleti rajareddy G.M. Sreenivasa, E. Jayachandran; "The in vitro anti denaturation effects induced by synthetic assay for products in Bovine serum albumin in proposed as a screening assay for the detection of anti- inflammatory compounds without the use of animals". *Int. jou .of pharm. Sci.* Jan-April 2010; 2(1): 404-410.
2. Vijaykumar,M.M.J, suchalatha, yogananda.R, snehalatha, nagaraja T.S; "N-substituted–thiazolidin-4-ones, synthesis and characterisation of new novel anti-inflamatory agents". *Int.J.ph.sci* may–august 2009; 1(1): 42 -54.
3. Sonia George, R. Sabitha, V. Govind hammal & T.K Ravi; "Synthesis and antimicrobial activity studies of certain pyramidinyl oxadiazolo azetidinones". *Indian journal of chemistry* November-2011; vol 51B: 1637-1641.
4. Navin B patel , Sarvil D patel , Arvind L patel ,Jaymin C patel & Jignesh N patel., "synthesis and antimicrobial studies of Schiff bases of fluroquinolone". *Indian journal of chemistry* November 2011; vol 51B: 1645-1657.
5. Vinay Mahyavanshi, Sunil I.marjadi; "Design and synthesis of 1-(2-amino-1-(meteoxy phenyl)eteyl) cyclohexanoi analogs as potential microbial agents". *Int.j. of drug design and discovery* april-june-2011; vol-2, Issue-2: 474-482.
6. Mohd amir, Mohd J Ahsan&Israr Ali; "synthesis of N'-(3-chloro-4-flourophenyl)-N substituted semicarbazones as novel anticonvulsant agents". *Indian journal of chemistry* November-2010; vol.49B: 1509-1514.
7. Hozaifa Hasan, Maymoona Akhter, Masim Akhter, Israr Ali, Mohd. Zaheer, Iftikhar Ahsan and Danish Mahamood; "Design and synthesis of novel N-substituted-3-chloro-2-azetidinone derivatives as potential anticonvulsant agents". *Medicinal Chemistry Research* 2011; 20: 1357-1363.
8. S.R.Pattan, Ch.Suresh, V.D.Pujar, V.V.K.Reddy, V.P.Rasal and B.C.Koti; "synthesis and antidiabetic activity of 2-amino[5'(4-sulphonyl benzylindine)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzthiazole". *Indian Journal of Chemistry* Nov 2005; vol-44B: 2404-2408.
9. Vijaya Javali, Jayachandran.E, Ravi shah, Kalpesh Patel, and sreenivasa.G.M; "Synthesis characterization and anthelmintic activity of fluoro substituted benzthiazole for biological and pharmacological screening". *Int.j.of Pharma and Biosciences*. july-sep 2010; Vol-1; Issue-3: 1-8.
10. Jagtap V.A, Jayachandran E, Sreenivasa G.M and sathe B.S; "Synthesis and screening of some fluoro substituted sulphonamide benzthiazole comprising azetidinones for anti-mycobacterial activity". *Journal of Pharmacy Research* 2011; 4(5): 1359-1360.
11. Ch.Suresh, J.Venkateshwar rao, K.N Jayaveera and G.Jayapal reddy; "Synthesis of 2-hydrazino benzthiazoles-2-amino-(4-substituted)-acetanilides for anti-oxidant activity". *Int. J. of Pharmacy and Biological Sciences* Oct-Dec 2011; Vol-1;Issue-4: 409-413.
12. Shivaji B Bole; "Synthesis of substituted fluoro pyrazoles for antibacterial and anti-oxidant activity". *Int. J. of Ph. Research and Development* Aug 2011; Vol-3(6): 161-166.
13. A.V Shindikar and C.L viswanathan; "Synthesis and *invitro* anti-tubercular activity of 7-substituted fluoroquinolones". *Indian Journal of Pharmaceutical Sciences* Mar-Apr 2007; 69(2): 316-318.
14. N.C Desai, Niraj Shihory, Kiran Rajpara and Amit Dodiya; "Synthesis characterization and antimicrobial screening of novel quinoline-thiazole derivatives". *Indian Journal of Chemistry* March 2012; Vol-51B: 508-513.
15. Mohan kumar K.M, Thorat Dattatraya B, Shiva kumar Hugar, Nagendra rao R, Jayakumar swamy B.H.M and Shivakumar B; "Microwave assisted synthesis of some 2-(N^2-arylidene hydrazine)-7-chloro-6-fluoro (1,3) benzothiazoles as potent antibacterial and antioxidant agents". *Research and*
16. *Reviews in Biomedicine and Biotechnology* 2010; Vol-1; Issue-1: 45-54.
17. M.M.J vijaykumar, L.Shankarappa, H.Shameer, E.Jayachandran and G.M Sreenivasa; "N-substituted-3-chloro-2-azetidinones: synthesis and

characterization of novel anthelmintic agents". *Research Journal of Pharmaceutical, Biological and Chemical Sciences* Apr-Jun 2010; Vol-1(2): 52-58.

18. Vijay kumar M.M.J, Nagaraja T.S, Shameer.H, Jayachandran.E and Sreenivasa G.M; "N-substituted-3-chloro-2-azetidinones: synthesis and characterization of new novel anti-inflammatory agents". *J. of Pharma. Sci. and Research* 2009; Vol-1(2): 83-92.