SYNTHESIS, CHARACTERIZATION AND ANTHELMINTIC ACTIVITY OF NOVEL *N*-SUBSTITUTED- THIAZOLIDIN–4–ONES.

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ABSTRACT

Various substituted 2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'- substituted (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one containing different functional groups have been synthesized by treating fluorochloroaniline 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 anthranillic acid in presence of dry pyridine to get 2 (o-amino phenyl amido) 6–fluoro -7-chloro (1,3) benzothiazole. To the above, refluxed with vanillin and alcohol in presence of Conc.HCl to get 2 (3-hydroxy-4-methoxy benzylidene amino phenyl amido) 6-fluoro-7-chloro- (1,3) benzothiazole (or) Schiff's base. A mixture of Schiff's base (0.01 mol) and Thioglycollic acid was heated on oil bath using 1,4 dioxone as solvent to get thiazolidine. To the above product different aromatic primary and secondary amines, in presence of DMF were treated to get newly targeted compound through replacing at 7th position chlorine.

The lead compounds were characterized by melting point, TLC, calculated elemental analysis, UV, IR and ^{1}HNMR spectral studies. The compounds were tested for anthelmintic activity against earthworms, *Perituma posthuma* and some compounds showed significant activity at low and high concentrations compared to standard; still further studies are required.

KEYWORDS: Fluorine, Benzothiazole, Thiazolidinone, Anthelmintic activity.

1. Introduction

We report here in the new and unreported yet the synthesis of fluoro benzothiazoles (Filler R, 1986) comprising thiazolidinone derivatives. The chemistry and pharmacology of thiazolidinone have been of great interest because, of its various biological activities in the areas of antimicrobial (Sutoris, 1984), anti-tuburcular (Ares Jaffrey, 1991), carbonic anhydrase inhibitors (Wollesdrof, 1989), local anaesthatics (Costakes, 1979), anti-inflammatory (Sreenivasa Rao, 2005), anthelmintic (Sreenivasa, 2006), anticonvulsant (Turner,1965), hypoglycemic agents (Chernykh , 1983) etc, so that the biological and pharmacological activity of thiazolidinone with fluoro benzothiazoles may be taken into account for synergism (Conte, 1995).

It is well known that the introduction of fluorine atom (Desbois Michel, 1987) into an organic molecule 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. Therefore it was thought worthwhile to synthesize better kinds of drugs by incorporating thiazolidinone in benzothiazole moiety.

In search for new biodynamic potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in the thiazolidinone nucleus and study their biological and pharmacological activity (Indian Pharmacopoeia, 1996), the review of literature reveal prompted us to synthesize substituted fluorobenzothiazole, thiazolidinone targeted compounds and those will be screened for anthelmintic activity against earthworms, *Perituma posthuma*.

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2. Materials and Methods

2.1. Chemicals and Reagents

4-fluoro-3-chloro aniline, Potassium thiocyanate, Glacial acetic acid, Bromine, Anthranillic acid, Pyridine, Vanillin, Ethanol, Conc.Hydrochloric acid, Thioglycollic acid, 1,4 Dioxane, Sodium bicarbonate, N,Np-dimethyl formamide (DMF), various substituted aniline, morpholine, piperazine and diphenylamine.

2.2. Experimental Section

Step I: 4-fluoro-3-chloro aniline was treated with potassium thiocyanate (KSCN) in presence of glacial acetic acid and bromine to get 2-amino-6-fluoro-7-chloro-benzothiazole.

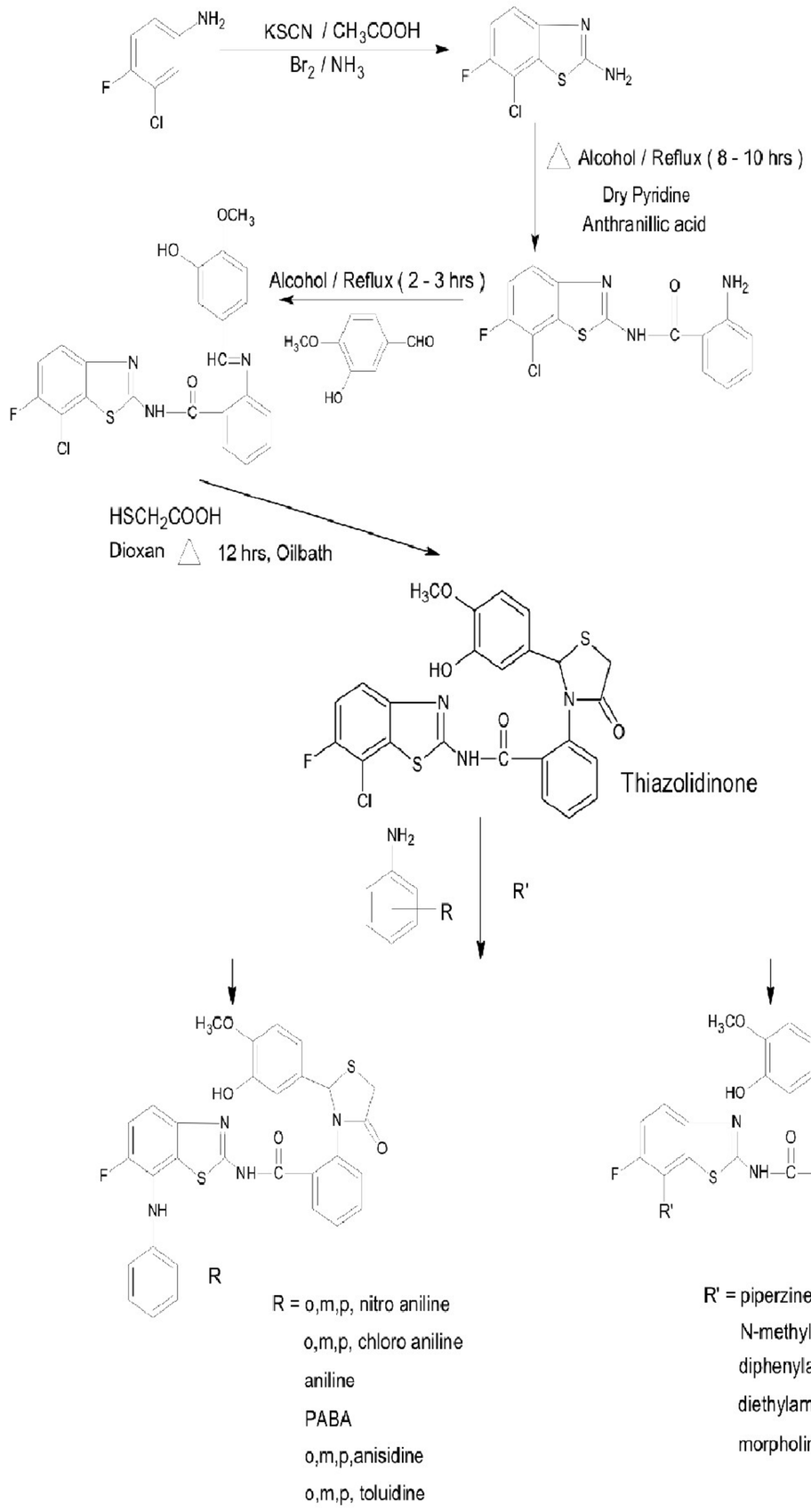
Step II: 2-amino-6-fluoro-7-chloro-benzothiazole treated with Anthranillic acid in presence of Pyridine to get 2 (o-amino phenyl amido) 6–fluoro -7-chloro (1,3) benzothiazole.

Step III: 2 (o-amino phenyl amido) 6–fluoro -7-chloro (1,3) benzothiazole reflexed with vanillin and alcohol in presence of Conc.HCl to get 2 (3-hydroxy-4-methoxy benzylidene amino phenyl amido) 6-fluoro-7-chloro-(1,3) benzothiazole (or) Schiff's base.

Step IV: A mixture of Schiff's base (0.01 mol) and Thioglycollic acid was refluxed on oilbath at 115° – 120° C for 12 hrs using 1,4 dioxane as solvent. The reaction mixture was cooled and triturated with 10% Sodium bicarbonate solution. The separated solid was filtered and washed with excess of water and then recrystalised from water.

Step V: Thiazolidinone was treated with equimolar quantities of various substituted aromatic aniline, PABA, piperzino, diphenylamine, N- methyl piperzino and o- toludine refluxed for 2 hours in presence of N,Np-dimethyl formamide (DMF) were treated to get newly targeted compound through replacing at 7th position chlorine. The mixture was cooled and poured in to crushed ice. The solid separated was filtered off, dried and crystallized from alcohol and benzene.

Scheme



2.3. General Procedures

Melting points were determined in open capillaries and are uncorrected. IR spectra (Nujol mull technique) were recorded using a Perkin-Elmer 237 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker AM 400 instrument (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO-*d6* as a solvent. Chemical shifts are given in parts per million (ppm). Splitting patterns are designated as follows: s- singlet, d- doublet, t- triplet, q- quartet and m-multiplet. Mass spectra (MS) were recorded on Schimadzu GC-MS operating at 70eV. All the synthesized compounds were purified by recrystallization the reactions were followed up and the purity of compounds was monitored on pre-coated TLC plates and visualizing the spots in ultraviolet light.

2.4. In vitro anthelmintic study

The synthesized compounds are screened for anthelmintic activity by using earthworms, *Perituma posthuma* (Jayachandran, 2003). 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 15 ml with normal saline solution to get the concentration of 0.1 % w/v, 0.2 % w/v and 0.5% w/v. Albendazole was used as a standard drug (Bushan Kumar S Sathe, 2006). 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 stimulate and induce 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.

Table No. 1 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	9.0	9.0	4.0	10.0	10.0	8.0
03	T_1	2.0	2.0	1.0	6.0	4.0	3.0
04	T_2	3.0	2.0	1.0	3.0	3.0	2.0
05	T_3	2.0	2.0	1.0	3.0	2.0	2.0
06	T_4	2.0	2.0	1.0	6.0	5.0	3.0
07	T_5	4.0	2.0	1.0	6.0	4.0	3.0
08	T_6	3.0	3.0	2.0	8.0	8.0	7.0
09	T_7	2.0	3.0	5.0	14.0	12.0	8.0
10	T_8	7.0	2.0	1.0	8.0	7.0	5.0
11	T_9	2.0	2.0	1.0	6.0	3.0	2.0
12	T_{10}	3.0	3.0	2.0	6.0	6.0	5.0
13	T_{11}	5.0	4.0	4.0	7.0	7.0	4.0
14	T_{12}	4.0	3.0	1.0	6.0	5.0	5.0
15	T_{13}	4.0	4.0	2.0	6.0	6.0	5.0
16	T_{14}	3.0	3.0	2.0	10.0	8.0	4.0
17	T_{15}	3.0	3.0	2.0	10.0	6.0	5.0
18	T_{16}	2.0	2.0	1.0	6.0	5.0	3.0
19	T_{17}	2.0	2.0	1.0	5.0	5.0	4.0
20	T_{18}	4.0	3.0	2.0	8.0	6.0	4.0
21	T_{19}	3.0	2.0	1.0	9.0	5.0	4.0

Table No. 2 ANALYTICAL DATA

Sl. No	Compound Code	M.P/ B.P°C	% Yield	MOL. FORM	M.Wt.	Calculated %		
						C	H	N
1	T_1	210	78	$C_{30}H_{22}O_6S_2N_5F$	631	57.04	3.51	11.09
2	T_2	205	82	$C_{30}H_{22}O_6S_2N_5F$	631	57.04	3.51	11.09
3	T_3	212	75	$C_{30}H_{22}O_6S_2N_5F$	631	57.04	3.51	11.09
4	T_4	238	72	$C_{30}H_{22}O_4S_2N_4FCl$	621	58.01	3.57	9.02
5	T_5	208	74	$C_{30}H_{22}O_4S_2N_4FCl$	621	58.01	3.57	9.02
6	T_6	215	73	$C_{30}H_{22}O_4S_2N_4FCl$	621	58.01	3.57	9.02
7	T_7	219	76	$C_{30}H_{23}O_4S_2N_4F$	586	61.42	3.95	9.55
8	T_8	217	65	$C_{31}H_{25}O_5S_2N_4F$	616	60.38	4.09	9.09
9	T_9	213	69	$C_{31}H_{25}O_5S_2N_4F$	616	60.38	4.09	9.09
10	T_{10}	210	83	$C_{31}H_{25}O_5S_2N_4F$	616	60.38	4.09	9.09
11	T_{11}	208	77	$C_{31}H_{25}O_4S_2N_4F$	600	61.98	4.19	9.33
12	T_{12}	218	85	$C_{31}H_{25}O_4S_2N_4F$	600	61.98	4.19	9.33
13	T_{13}	228	86	$C_{28}H_{25}O_5S_2N_4F$	580	57.92	4.34	9.65
14	T_{14}	220	78	$C_{28}H_{26}O_4S_2N_5F$	579	58.02	4.52	12.08
15	T_{15}	232	80	$C_{29}H_{28}O_4S_2N_5F$	593	58.67	4.75	11.80
16	T_{16}	210	78	$C_{31}H_{23}O_6S_2N_4F$	630	59.04	3.68	8.88
17	T_{17}	202	76	$C_{36}H_{27}O_4S_2N_4F$	662	65.24	4.11	8.45
18	T_{18}	218	72	$C_{26}H_{23}O_4S_2N_4F$	538	57.98	4.30	10.40
19	T_{19}	220	82	$C_{28}H_{27}O_4S_2N_4F$	566	59.35	4.80	9.89

Table No. 3 Characteristics IR absorption bands

Compound	Ar-NH (in cm^{-1})	C=O Stretching (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})	C S Stretching (in cm^{-1})	Sec.Ar. Amine (in cm^{-1})	C Cl Stretching (in cm^{-1})	C-O-C Stretching (in cm^{-1})	Ar-OH Stretching (in cm^{-1})
T_1	3310	1685	1550	1635	1460	1120	720	1310	-	1220	1360
T_2	3300	1685	1555	1640	1450	1130	720	1310	-	1220	1390
T_3	3310	1690	1555	1635	1450	1110	720	1340	-	1225	1380
T_4	3400	1680	1550	1645	-	1115	725	1310	845	1215	1370
T_5	3380	1685	1550	1650	-	1155	720	1330	845	1220	1370
T_6	3380	1690	1555	1630	-	1130	725	1315	840	1215	1390
T_7	3380	1685	1555	1650	-	1105	730	1320	-	1220	1385
T_8	3380	1685	1555	1645	-	1110	725	1320	-	1220	1390
T_9	3370	1680	1550	1645	-	1120	730	1310	-	1230	1385
T_{10}	3370	1700	1555	1630	-	1125	725	1310	-	1210	1390
T_{11}	3370	1690	1555	1630	-	1125	725	1305	-	1220	1390
T_{12}	3370	1685	1555	1640	-	1155	730	1315	-	1215	1385
T_{13}	3290	1690	1550	1650	-	1115	730	-	-	1230	1390
T_{14}	3290	1690	1550	1645	-	1110	720	-	-	1220	1390
T_{15}	3290	1685	1555	1645	-	1110	720	-	-	1210	1385
T_{16}	3370	1690	1555	1635	-	1165	720	1300	-	1210	1390
T_{17}	3370	1690	1580	1640	-	1155	725	1310*	-	1220	1390
T_{18}	3380	1690	1555	1650	-	1110	720	1355*	-	1215	1390
T_{19}	3370	1680	1550	1650	-	1160	725	1310*	-	1210	1380

* = Tertiary Aromatic Amine

Table No. 4 ^{1}HNMR Spectral Data

Sl no	Compound Code	Hydrogen	δ(ppm)	Multiplity	Solvent
1	T_{14}	-Ar-H- -NH-	6.9 - 8.0 5.3	Multiplet Singlet	$CDCl_3$
2	T_{16}	-Ar-H- - NH -	7.0 – 8.0 5.4	Multiplet Singlet	$CDCl_3$

Table No. 5 MASS Spectral Data

Sl no	Compound Code	Calc. Mol. weight	Mol Formula	Fragmentation	m/z
1	T_{14}	579.66	$C_{28}H_{26}O_4S_2N_5F$	M^{+1}(CH_3O-C_6H_3-) M^{+2} ($C_4H_9N_2$) M^{+3} (C_9H_6OSN)	473.4 386.1 201.2
2	T_{16}	630.66	$C_{31}H_{23}O_6S_2N_4F$	M^{+1}(CH_3O, OH, COOH, O) M^{+2} (C_6H_3) M^{+3} (C_6H_4.NH, C_3H_3SN) M^{+4} (C_5H_9)	519.1 445.8 269.7 201.5

3. Results and Discussion

Synthesized compounds of 2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'- substituted (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one were tested for anthelmintic activity against earthworms, *Perituma posthuma* compared to standard Albendazole.

T_1, T_2, T_3, T_4, T_5,T_6,T_7, T_9,T_{10}, T_{12}, T_{13},T_{16}, T_{17} and T_{19} showed significant activity compared to standard Albendazole.

4. Conclusion

Result of present study demonstrate that, a new class of different aromatic primary and secondary amines encompassing thiazolidinone to get targeted molecules were synthesized and evaluated for anthelmintic activity. The newly synthesized heterocyclics exhibited promising anthelmintic activity against earthworms, *Perituma posthuma* at low and high concentration compared to standard Albendazole. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

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