SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF THIAZOLIDIN -4- ONE DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS

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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 dioxane as solvent to get thiazolidinone. To the above product different aromatic aniline, PABA, piperzino, diphenylamine, N- methyl piperzino, o- toludine 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 antimicrobial studies and showed significant activity at low and high concentration compared to standard; still further studies are requested.

Keywords: Fluorine, Benzothiazole, Thiazolidinone, Anti-microbial activity

1. INTRODUCTION

We report here in the new and unreported yet the synthesis of fluoro benzothiazoles (Filler R, 1986) comprising thiazolidinone derivatives of pharmacological activity of clinical importance in the areas of antibacterial (Chalreck P, 1988), antifungal (Lipathay T, 1981), anti-tuburcular (Shirke VG, 1991), carbonic anhydrase inhibitors (Wollesdrof OW Jr, 1989), local anaesthetics (Costakes E, 1979), anti-inflammatory (Sreenivasa Rao D, 2005), anthelmintic (Sreenivasa GM, 2006), anticonvulsant (Turner RA, 1965), hypoglycemic agents (Chernykh VP, 1983). The chemistry and pharmacology of thiazolidinone have been of great interest because, of its various biological activities, so that the biological and pharmacological activity of thiazolidinone with fluoro benzothiazoles may be taken into account for synergism (Conte L et al., 1995).

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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 compounds and those will be screened for antimicrobial activity.

2. MATERIALS AND METHODS

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.

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.

General Procedures

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr pellet 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.

In vitro antimicrobial study

Synthesised compounds were screened for antibacterial and antifungal activities at two different conc (50㎎/ml, 100㎎/ml) against Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa, Candida albicans and Aspergillus flavus by cup plate method (diffusion technique) using Procaine penicillin, Streptomycin, Cefazolin Sodium, Sporafloxin and Griseofulvin respectively as standards (Sreenivasa GM, 2004). The results are the mean value of zone of inhibition measured in millimeter of two sets. The results are tabulated.

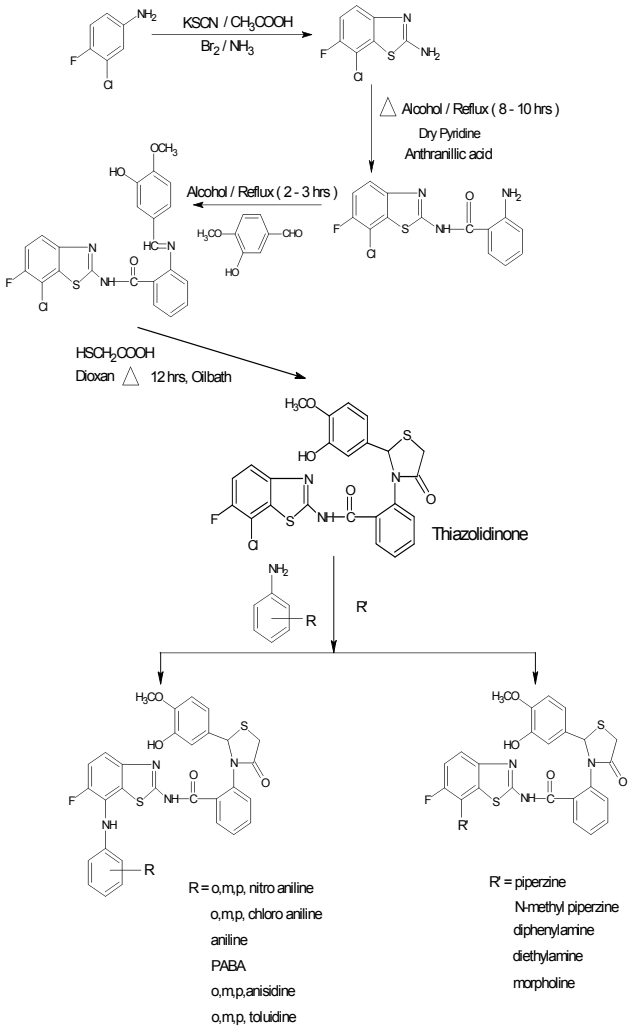

Table No. 1 Antibacterial activity

Sl. No	Name of the compounds	Mean zone of inhibition (in mm*)							
		S. aureus		*E. coli*		*B. Subtilis*		*P. aeruginosa*	
		50µg	100µg	50µg	100µg	50µg	100µg	50µg	100µg
01	Procaine penicillin	19	22	-	-	-	-	-	-
02	Streptomycin	-	-	19	24	-	-	-	-
03	Cefazolin Sod	-	-	-	-	20	25	-	-
04	Sporafloxin	-	-	-	-	-	-	20	27
05	T_1	12(0.63)	15(0.68)	13(0.68)	16(0.66)	12(0.60)	14(0.56)	12(0.60)	15(0.55)
06	T_2	12(0.63)	15(0.68)	12(0.63)	15(0.63)	13(0.65)	15(0.60)	12(0.60)	17(0.63)
07	T_3	13(0.68)	17(0.77)	12(0.63)	15(0.63)	12(0.60)	14(0.56)	13(0.65)	16(0.59)
08	T_4	12(0.63)	14(0.64)	12(0.63)	14(0.58)	11(0.55)	14(0.56)	14(0.70)	16(0.59)
09	T_5	12(0.63)	15(0.68)	13(0.68)	17(0.71)	12(0.60)	15(0.60)	12(0.60)	15(0.55)
10	T_6	11(0.58)	14(0.64)	13(0.68)	17(0.71)	12(0.60)	15(0.60)	11(0.55)	14(0.52)
11	T_7	10(0.52)	13(0.59)	13(0.68)	16(0.66)	11(0.55)	14(0.56)	14(0.70)	17(0.63)
12	T_8	12(0.63)	17(0.77)	13(0.68)	15(0.63)	12(0.60)	15(0.60)	14(0.70)	18(0.66)
13	T_9	12(0.63)	14(0.64)	13(0.68)	15(0.63)	11(0.55)	14(0.56)	12(0.60)	14(0.52)
14	T_{10}	12(0.63)	14(0.64)	12(0.63)	14(0.58)	12(0.60)	15(0.60)	11(0.55)	14(0.52)
15	T_{11}	14(0.74)	18(0.82)	10(0.53)	13(0.54)	11(0.55)	14(0.56)	13(0.65)	19(0.70)
16	T_{12}	11(0.58)	14(0.64)	13(0.68)	16(0.66)	12(0.60)	15(0.60)	11(0.55)	14(0.52)
17	T_{13}	12(0.63)	15(0.68)	13(0.68)	16(0.66)	12(0.60)	16(0.64)	10(0.50)	12(0.44)
18	T_{14}	11(0.58)	14(0.64)	14(0.74)	18(0.75)	13(0.65)	17(0.68)	11(0.55)	13(0.48)
19	T_{15}	11(0.58)	13(0.59)	14(0.74)	17(0.71)	14(0.70)	17(0.68)	11(0.55)	13(0.48)
20	T_{16}	10(0.52)	12(0.55)	13(0.68)	15(0.63)	10(0.50)	14(0.56)	11(0.55)	14(0.52)
21	T_{17}	12(0.63)	14(0.64)	13(0.68)	17(0.71)	13(0.65)	15(0.60)	12(0.60)	16(0.59)
22	T_{18}	12(0.63)	14(0.64)	13(0.68)	16(0.66)	12(0.60)	16(0.64)	11(0.55)	13(0.48)
23	T_{19}	10(0.52)	13(0.59)	14(0.74)	17(0.71)	13(0.65)	17(0.68)	11(0.55)	14(0.52)

Activity Index = Test Compound / Standard compound

Table No. 2 Antifungal activity

Sl. No	Name of the compounds	Mean zone of inhibition (in mm*)			
		C. albicans		*A. flavus*	
		50µg	100µg	50µg	100µg
01	Griseofulvin	18	23	19	24
02	T_1	15(0.83)	18(0.78)	16(0.84)	19(0.79)
03	T_2	14(0.77)	17(0.74)	15(0.79)	19(0.79)
04	T_3	16(0.89)	20(0.87)	16(0.84)	19(0.79)
05	T_4	15(0.83)	19(0.83)	14(0.74)	17(0.71)
06	T_5	14(0.77)	17(0.74)	13(0.68)	15(0.63)
07	T_6	13(0.72)	17(0.74)	12(0.63)	14(0.58)
08	T_7	12(0.67)	18(0.78)	12(0.63)	14(0.58)
09	T_8	16(0.89)	19(0.83)	13(0.68)	16(0.66)
10	T_9	15(0.83)	19(0.74)	14(0.74)	19(0.79)
11	T_{10}	14(0.77)	17(0.74)	15(0.79)	19(0.79)
12	T_{11}	12(0.67)	15(0.65)	11(0.58)	14(0.58)
13	T_{12}	13(0.72)	20(0.87)	12(0.63)	16(0.66)
14	T_{13}	11(0.61)	14(0.61)	16(0.84)	19(0.79)
15	T_{14}	15(0.83)	20(0.87)	17(0.89)	21(0.88)
16	T_{15}	16(0.89)	20(0.87)	15(0.79)	20(0.83)
17	T_{16}	15(0.83)	19(0.83)	14(0.74)	16(0.66)
18	T_{17}	16(0.89)	20(0.87)	13(0.68)	15(0.63)
19	T_{18}	15(0.83)	19(0.83)	12(0.63)	18(0.75)
20	T_{19}	14(0.77)	20(0.87)	14(0.74)	23(0.96)

Activity Index = Test Compound / Standard compound

Table No. 3 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	$C_{33}H_{25}O_5S_2N_4F$	616	60.38	4.09	9.09
9	T_9	213	69	$C_{33}H_{25}O_5S_2N_4F$	616	60.38	4.09	9.09
10	T_{10}	210	83	$C_{33}H_{25}O_5S_2N_4F$	616	60.38	4.09	9.09
11	T_{11}	208	77	$C_{33}H_{25}O_4S_2N_4F$	600	61.98	4.19	9.33
12	T_{12}	218	85	$C_{33}H_{25}O_4S_2N_4F$	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	$C_{33}H_{33}O_6S_2N_4F$	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	$C_{26}H_{25}O_4S_2N_4F$	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

3. RESULTS AND DISCUSSION

Anti-bacterial activity

Synthesis and pharmacological screening 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 the antibacterial activity against following bacteria.
a)1] *S.aureus*, ii] *B.subtilis* (gram +ve) and
b)iii] *E.coli,* iv] *Pseudomonas* (gram –ve).

The test compounds T_1, T_2, T_3, T_8, T_{11} and T_{14} showed moderate antibacterial activity against *S.aureus* (gram +ve) compare to standard drug procaine penicillin.

Compounds T_1, T_5, T_6, T_{14}, T_{15} and T_{17} showed promising antibacterial activity against, *E.coli* (gram – ve) compared to standard drugs and streptomycin.

Compounds T_2, T_8, T_{13}, T_{14} and T_{19} showed antibacterial activity against, gram +ve (*B.subtillis*) at lower concentration (50 ìg/ml).

Compounds T_3, T_7, T_8, T_{11} and T_{17} showed moderate activity against gm –ve (*pseudomonas*) at both lower and higher concentration compare to standard drug streptomycin.

Anti-fungal activity

Synthesized compounds were tested for antifungal activity against *Candida albicans* and *Aspergillus niger*. Among the compounds tested; T_1, T_3, T_8, T_9, T_{14}, T_{15} and T_{16} showed good activity against *Candida albicans* at both concentration compare to standard Griseofulvin.

T_1, T_3, T_{10}, T_{14} and T_{19} showed significant activity against *Aspergillus niger* compared to standard Griseofulvin.

4. CONCLUSION

Result of present study demonstrate that, a new class of different aromatic aniline, PABA, piperzine, diphenylamine, N-methyl piperzine, o- toludine encompassing thiazolidinone derivatives were synthesized and evaluated as antibacterial agents. The newly synthesized heterocyclics exhibited promising antimicrobial activity against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa* and *Escherichia coli*. The antifungal studies against *Candida albicans* and *Asperagillus niger* showed significant activity at low and high concentration compared to standard. 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.

ACKNOWLEDGEMENT

The authors are thankful to Shri. Sha. Bra. Chandramouleshwara Shivacharya Swamiji, President, Sri. T. M. Chandrashekhariah, Secretary, T.M.A.E. Society, Harapanahalli, for providing necessary facilities through the Principal, S.C.S. College of Pharmacy, Harapanahalli to carryout this work.

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