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Research Article
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N-Substituted-Thiazolidin-4-Ones: Synthesis and Characterization of New Novel Potential Anticonvulsant Agents

Vijay Kumar, M.M.J., [I] Snehalatha., [II] Shameer, H., [III] Jayachandran, E., [III] Sreenivasa, G.M. *[III]

[I] P.G. Dept of Pharm. Chemistry, [II] Dept of Pharm. Ceutics, S.J.M. College of Pharmacy, Chitradurga-577502, Karnataka, INDIA.
[III] P.G. Dept. of Pharm. Chemistry, S.C.S. College of Pharmacy, Harapanahalli–583131, Karnataka, INDIA.

This paper describes the synthesis of 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 primary and secondary aromatic functional groups through replacing at seventh position chlorine. The products, characterized on the basis of satisfactory analytical and spectral (IR, ^{1}H NMR, Mass) data, have shown moderate to good Anticonvulsant activity by PTZ induced method. Among the nineteen compounds in the series T_7, T_9, T_{12}, T_{14} and T_{16} exhibited equipotent anticonvulsant activity with reference to the standard, Diazepam; still further studies are requested.

KEYWORDS: Anticonvulsant activity, Benzothiazole, Fluorine, Thiazolidinone.

INTRODUCTION

4-Thiazolidinones are one of the most intensively investigated classes of aromatic five membered heterocycles.[1] These derivatives find a variety of applications ranging from antimicrobial, [2] anti-tubercular, [3] carbonic anhydrase inhibitors, [4] local anaesthatics, [5] anti-inflammatory, [6] anthelmintic, [7] anticonvulsant, [8] hypoglycemic agents activity.[9] Due to this, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists.

It is well known that the introduction of fluorine atom 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.[10] In search for new biodynamic potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in the 4-Thiazolidinone nucleus and study their biological and pharmacological activity.[11] The review of literature reveal prompted us to synthesize substituted fluorobenzothiazole, 4-Thiazolidinone targeted compounds and those will be screened for anticonvulsant activity.

Corresponding Author

Vijay Kumar M.M.J.

E-mail : gms_2006@rediffmail.com

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,N-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^{o} – 120^{o} C for 12 hrs using 1,4 dioxone 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,N-dimethyl formamide (DMF) were treated to get newly targeted compound through replacing at 7^{th} position chlorine. The mixture was cooled and poured in to crushed ice. The solid separated was filtered off, dried and crystallised from alcohol and benzene (Table no. 1).

General Procedures

Melting points were determined in open capillaries and are uncorrected (Table No.2). IR spectra (KBr pellet technique) were recorded using a Perkin-Elmer 237 spectrophotometer (Table No. 3). ^{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 (Table No. 4). 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 Shimadzu GC-MS operating at 70eV (Table No. 5). 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 Anticonvulsant Study

In the present study the mice of either sex, weighing between 18-25 g were selected and divided into control, test and standard.

Before experiment the animal were fasted for 24 hrs with only water *ad-libitum*. Control group received only 0.5 ml DMF as vehicle. Standard group animals were received diazepam (4 mg/kg b.w.) oral test group animals were received the synthesized derivatives at 4 mg/kg b.w. oral in DMF.

Now for the animals of control group pentylene tetrazole (PTZ) 1 ml / 100 g b.w. was administered and actions like straubs tail, jerky movements of whole body and conclusions were observed.

For animals of standard test group PTZ was injected (1 ml/100 g b.w.). After 30 mins animals of standard and test received diazepam and synthesized derivatives respectively.[12] Observations were made and results were tabulated (Table No. 6).

RESULTS AND DISCUSSION

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 anticonvulsant activity by PTZ induced method compared to standard Diazepam; showed significant anticonvulsant activity.

Among compounds tested T_7, T_9, T_{12}, T_{14} and T_{16} showed significant anticonvulsant activity.

SCHEME:

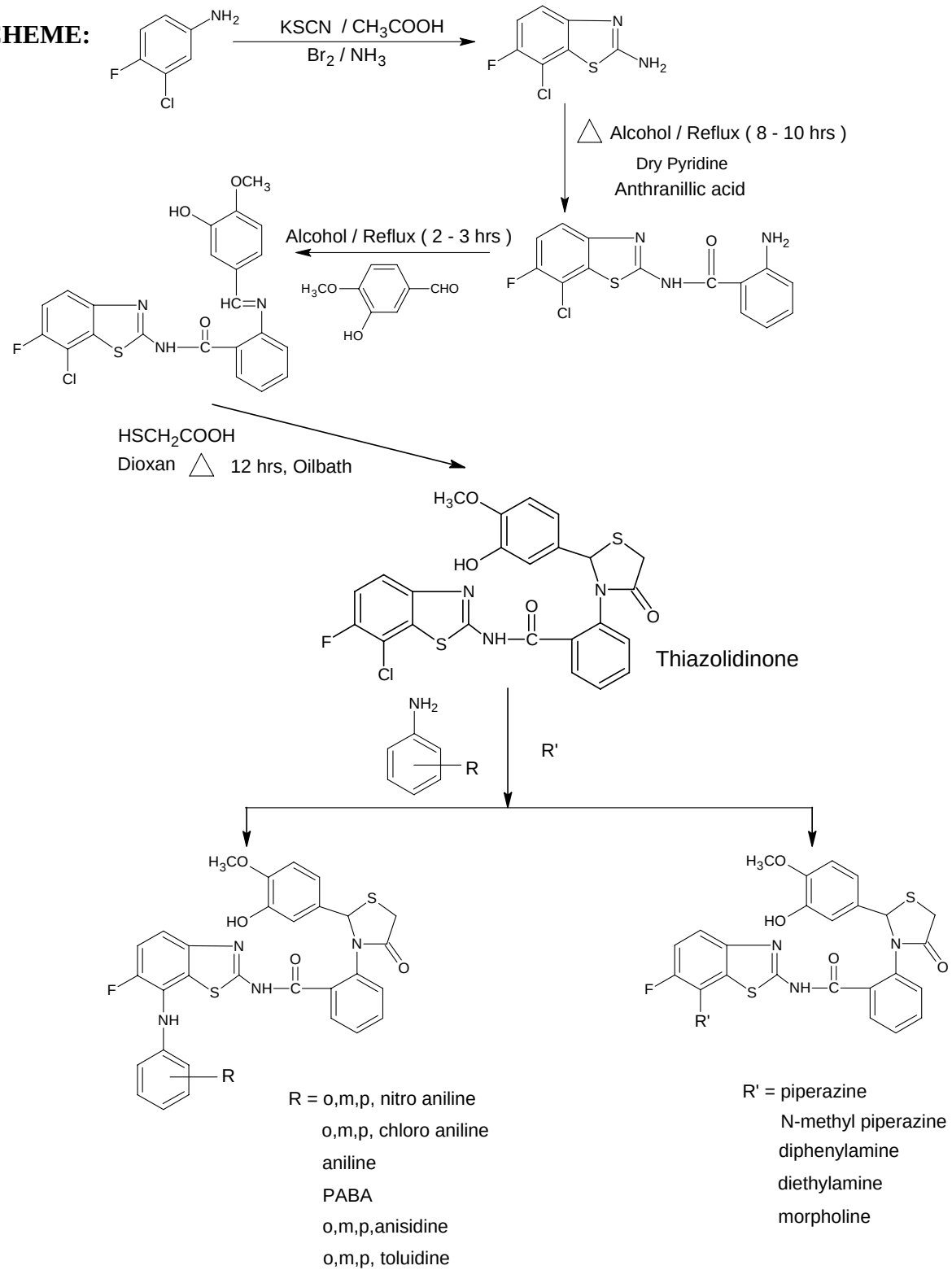
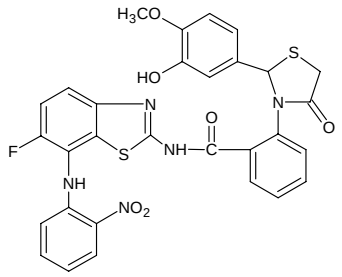
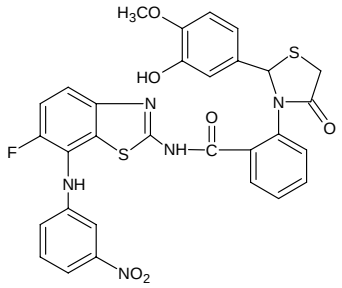
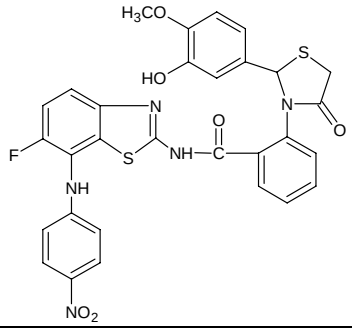
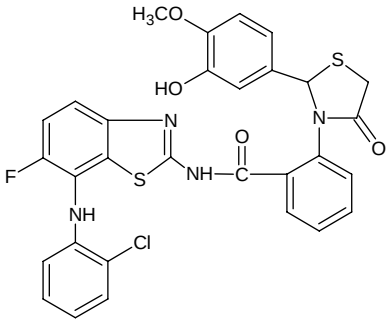
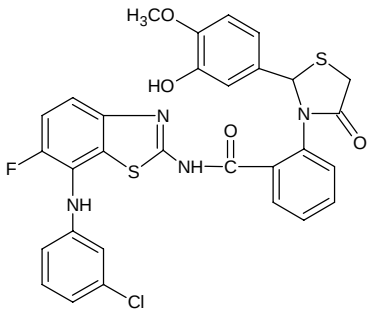
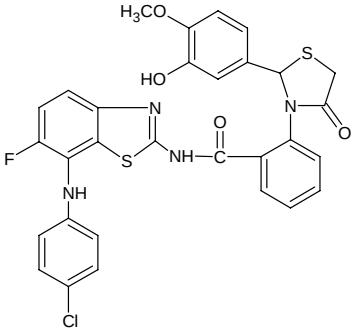
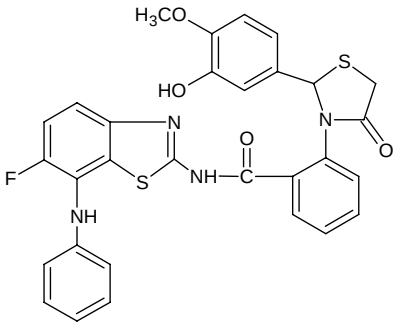
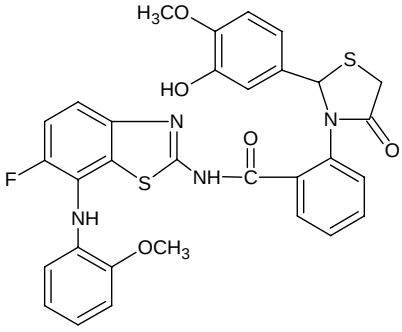
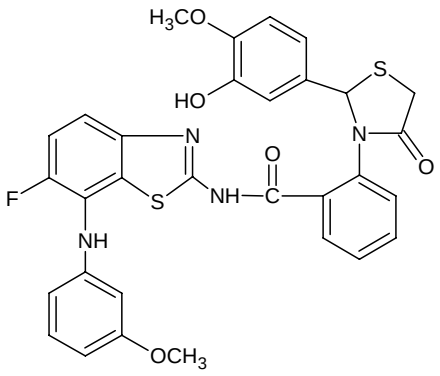
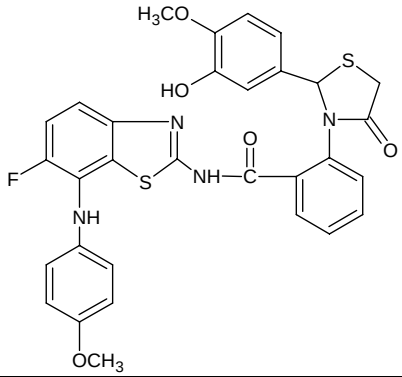
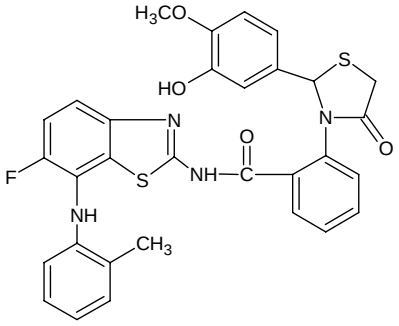
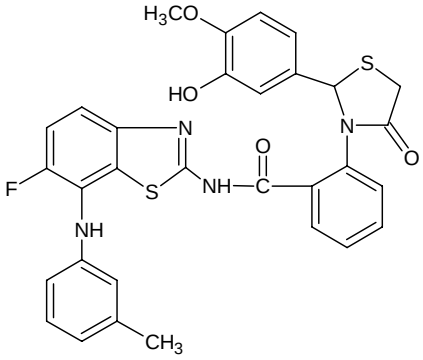
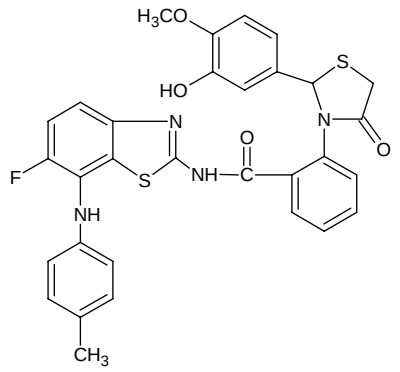
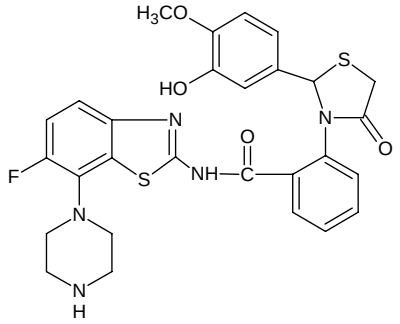
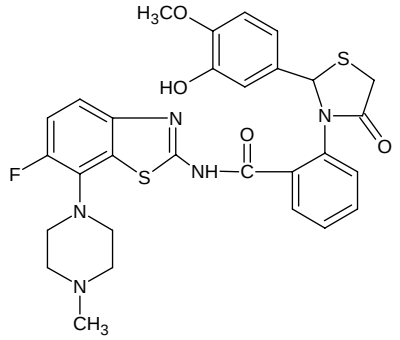
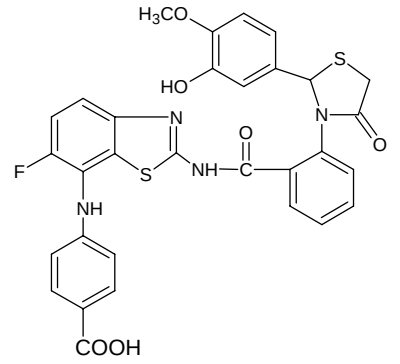


Table No. 1 List of compounds synthesized

Sl. No.	Compound Code	Structure	Chemical Name
1.	T_1		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-o-nitroanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
2.	T_2		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-m-nitroanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
3.	T_3		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-p-nitroanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
4.	T_4		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-o-chloroanilino(1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one

5.	T_5		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-m-chloroanilino (1, 3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
6.	T_6		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-p-chloroanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
7.	T_7		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-anilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
8.	T_8		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-o-methoxyanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one

9.	T_9		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-m-methoxyanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
10.	T_{10}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-p-methoxyanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
11	T_{11}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-o-methylanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
12.	T_{12}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-m-methylanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one

13.	T_{13}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-p-methylanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
14.	T_{14}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-piperzino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
15.	T_{15}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'- N -methylpiperzino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
16	T_{16}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'- p – carboxyanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one

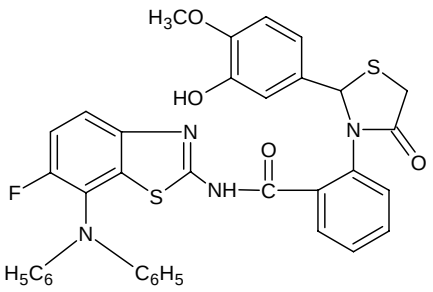
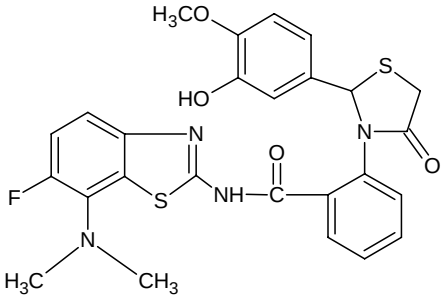
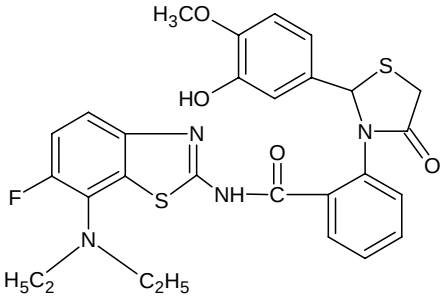
17.	T_{17}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-diphenylamino(1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
18.	T_{18}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-dimethylamino(1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one
19	T_{19}		2(m-hydroxy-p-methoxy phenyl)-3[(6'-fluoro-7'-diethylamino (1,3)-benzothiazol-2'-yl) amido-2-phenyl](1,3) thiazolidin–4–one

Table No. 4 ^{1}H NMR 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	$C_{35}H_{29}O_4S_2N_4F$	M^{+1} (CH_3O-C_2H_2-) M^{+2} ($C_6H_5N_2$) M^{+3} (C_6H_6OSN)	473.4 386.1 201.2
2	T_{16}	630.66	$C_{31}H_{23}O_4S_2N_4F$	M^{+1} (CH_3O, OH, COOH, O) M^{+2} (C_6H_5) M^{+3} (C_6H_5NH, C_3H_3SN) M^{+4} (C_3H_3)	519.1 445.8 269.7 201.5

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. 6 Anti Convulsant Activity (PTZ – Induced)

Stock Solution. Test Drugs 5 mg/ml
Mice (Body weight- 18-25gm)
Dose: PTZ – 80 mg/kg I.P.

Animal – Albino
PTZ – 8 mg/ml
Test Drugs – 50 mg / kg orally

SL. No.	Treatment	Dose (mg/kg)	Convulsion			Death / Recovery
			Onset (Sec)	Nature of Severity	Clonic time in Sec	
1	Water + PTZ	5 ml / kg + 80	43	Jerky Movement	55	5/5
2			75		103	
3			63		95	
4			55		75	
5			45		55	

1	T_1 + PTZ	5 ml / kg + 80	43	Jerky Movement	85	4/5
2			75		80	
3			63		88	
4			55		76	
5			45		68	
1	T_2 + PTZ	5 ml / kg + 80	43	Jerky Movement	95	5/5
2			75		83	
3			63		95	
4			55		75	
5			45		95	
1	T_3 + PTZ	5 ml / kg + 80	43	Jerky Movement	105	4/5
2			75		93	
3			63		95	
4			55		75	
5			45		85	
1	T_4 + PTZ	5 ml / kg + 80	43	Jerky Movement	95	5/5
2			75		93	
3			63		95	
4			55		75	
5			45		95	
1	T_5 + PTZ	5 ml / kg + 80	43	Jerky Movement	95	5/5
2			75		93	
3			63		95	
4			55		75	
5			45		95	
1	T_6 + PTZ	5 ml / kg + 80	43	Jerky Movement	85	5/5
2			75		93	
3			63		95	
4			55		105	
5			45		105	
1	T_7 + PTZ	5 ml / kg + 80	43	Straub's Tail	350	1/5
2			75		351	
3			63		420	
4			55		595	
5			45		423	
1	T_8 + PTZ	5 ml / kg + 80	43	Jerky Movement	85	5/5
2			75		93	
3			63		95	
4			55		75	
5			45		95	
1	T_9 + PTZ	5 ml / kg + 80	43	Straub's Tail	450	5/5
2			75		451	
3			63		320	
4			55		395	
5			45		423	
1	T_{10} + PTZ	5 ml / kg + 80	43	Jerky Movement	105	5/5
2			75		93	
3			63		95	
4			55		75	
5			45		105	
1	T_{11}	5 ml / kg + 80	43	Jerky	95	5/5

2	PTZ		75	Movement	93	
3			63		95	
4			55		75	
5			45		95	
1	T_{12} + PTZ	5 ml / kg + 80	43	Straub's Tail	350	0/5
2			75		551	
3			63		320	
4			55		395	
5			45		323	
1	T_{13} + PTZ	5 ml / kg + 80	43	Jerky Movement	105	4/5
2			75		93	
3			63		95	
4			55		75	
5			45		105	
1	T_{14} + PTZ	5 ml / kg + 80	43	Straub's Tail	350	1/5
2			75		351	
3			63		320	
4			55		495	
5			45		323	
1	T_{15} + PTZ	5 ml / kg + 80	43	Jerky Movement	85	5/5
2			75		93	
3			63		95	
4			55		75	
5			45		95	
1	T_{16} + PTZ	5 ml / kg + 80	43	Straub's Tail	430	0/5
2			75		451	
3			63		320	
4			55		495	
5			45		323	
1	T_{17} + PTZ	5 ml / kg + 80	43	Jerky Movement	95	5/5
2			75		83	
3			63		95	
4			55		75	
5			45		85	
1	T_{18} + PTZ	5 ml / kg + 80	43	Jerky Movement	105	5/5
2			75		103	
3			63		95	
4			55		75	
5			45		95	
1	T_{19} + PTZ	5 ml / kg + 80	43	Jerky Movement	55	5/5
2			75		103	
3			63		125	
4			55		115	
5			45		105	
1	Diazapam + PTZ	50 + 80	97	Straub's Tail	445	0/5
2			105		455	
3			110		210	
4			85		385	
5			93		415	

Table No. 3 Characteristics IR absorption bands

Compound	Ar-NH (cm^{-1})	C=O Stretching (cm^{-1})	C=N Stretching (cm^{-1})	C=C Stretching (cm^{-1})	NO_2 (cm^{-1})	C-F (cm^{-1})	C – S Stretching (cm^{-1})	Sec Ar. Amine (cm^{-1})	C – Cl Stretching (cm^{-1})	C-O-C Stretching (cm^{-1})	Ar-OH Stretching (cm^{-1})
T_1	3310	1685	1550	1635	1480	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

CONCLUSION

Result of present study demonstrate that, a new class of different aromatic aniline, anisidine, PABA, piperzine, encompassing thaizolidinone derivatives were synthesized and evaluated as antibacterial agents. The newly synthesized heterocyclics exhibited promising anticonvulsant activity using PTZ induced method. The anticonvulsant studies 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.

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