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Synthesis and Pharmacological Evaluation of Newer Substituted 2-oxo/thiobarbiturinylbenzoxa/thiazepine Derivatives as Potent Anticonvulsant Agents

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ABSTRACT

A new series of 4-(2'-Oxo/thiobarbiturinyl)-2-(substitutedphenyl)-3-[(substituted aminomethylene)]-2,3-dihydro-1,5-benzothiazepines (5a-5l) and 4-(2'-oxo/thiobarbiturinyl)-2-(substituted-phenyl)-3-(substitutedaminomethylene)]-2,3-dihydro-1, 5- benzoxazepines (6a-6l) were synthesized. All the newly synthesized compounds were screened in vivo, for their acute toxicity and anticonvulsant activity in MES and PTZ models and were compared with standard drugs phenytoin sodium and sodium valporate. Out of the compounds studied, the most active compound of this series was 5h, showed activity (90%) more potent than the standard drug.

Key words: Anticonvulsant Agents, in vivo, standard drugs.

INTRODUCTION

The barbiturates comprise an important and valuable class of central nervous system depressants. Barbituric acid (2,4,6–trioxohexahydrophrimidine) derivative, phenobarbital and mephobarbital are used for clinical treatment of epilepsy. Further substitution pattern at 5th position of barbituric acid[3-8] by different alkyl, aryl or heteroaryl moieties plays a pivotal role in modulation of anticonvulsant activity. Moreover, compounds containing a fused seven, membered heterocyclic ring i.e. bengzothiazepine/ benzoxazepine nucleus make up a broad class that attracted attention in the past few years owing to its wide range of biological activities especially anticonvulsant and CNS depressant activities [9-14]. However, these compounds have not been in clinical use as they possess either less activity or more side effects.

Incorporating these moieties in 5th position of 2-oxo/thiobarbituric acid nucleus might be thought to yield more potent anticonvulsant compounds as substituted moieties are themselves anticonvulsant and substituting at 5thposition further results in protecting against convulsions. Thus, the substitution by these moieties may be synergistic. The present project is therefore, aimed at synthesizing such compounds.

Chemistry

The synthetic routes of compounds are outlined in scheme 1. 5-Acetyl-2-oxo/thiobarbituric acid 1a-1b weresynthesized by the reaction of 2-oxo/thiobarbituric acid and acetyl chloride. Compounds 1a-1b on reaction with different aromatic aldehydes yielded 1-(2'-oxo/thiobarbiturinyl)-3-chalcones i.e. compounds 2a-2fwhich on cyclization with 2-thio/aminophenol in presence of glacial acetic acid yielded compounds 3a-3f and 4a-4f respectively. compounds 3a-3f and 4a-4f further undergoes Mannichreaction with different substituted anilines to afford compounds 5a-5l and 6a-6l.

RESULTS AND DISCUSSION

Anticonvulsant activity and acute toxicity of these new substituted 2-oxo/thiobarbiturinylenzoxa/thiazepine derivatives 2a-2f, 3a-3f, 4a-4f, 5a-5l and 6a-6l are represented in Table-1.

Anticonvulsant activity (maximum electroshock induced seizures and pentylenetetrazol induced seizure pattern test)

The characteristic feature of the compounds of this series is the incorporation of two heterocyclic moieties, that is 2-oxo/thiobarbituric acid and benzoxazepine/benzothiazepine into a single molecular framework with the aim to develop more potent anticonvulsant agents withminimum or no side effects.

5-Acetyl-2-oxo/thiobarbituric acids 1a-1b showed 10-20% anticonvulsant activity at a dose of 50mg/kg i.p. in maximal electroshock and pentylenetetrazole induced seizures, respectively. Screening of step-2 compounds 1-(2'-oxo/thiobarbiturinyl)-3-arylidenylchalcones 2a-2f revealed that these compoundsshowed somewhat increase in anticonvulsant activity in both the models (ranging from 20 to 50% and 10 to 50% in MES and PTZ models, respectively) in comparison to step-1 compounds when tested at same dose.

Compounds 4-(2'-oxo/thiobarbiturinyl)-2-substitutedphenyl)-2,3,-dihydro-1,5-benzothiazepines 3a-3f showed high percentage protection ranging from 40 to 80% and 30 to 80% in MES and PTZ models, respectively. The most active compound among 3a-3f is compound 3d. This compound was found to be equipotent (80% protection) to phenytoin sodium (standard drug for MES model) and sodium valproate (standard drug for PTZ model) and hence due to its potent nature it was studied in detail at three graded doses (17.5, 25 and 50mg/kg i.p.) for its anticonvulsant activity and was found to possess 20, 40, 80% and 20, 30, 80% protection of seizures in MES and PTZ models, respectively. It was also observed that compound 3c (having 3-methoxyphenyl group) showed least activity 40% while compound 3d (having 2-chlorophenyl group) exhibited maximum response 80% in comparison to other substituted compounds. Further compounds having thiobarbituric acid possess more potent activity than the compounds having oxobarbituricacid ring.

Further, the next step compounds(5a-5l) was characterized by presence of different arylaminomethylene substitutions at the third position of benzothiazepine ring.They exhibited potent anticonvulsant activity ranging from 60 to 90% and 50 to 90% inbothmodels, that is MES and PTZ respectively.Out of the twelve compounds 5a-5l the most active compound is 5h. (having 4-methoxyphenyl aminomethylen substitution at third position of benzothiazepine ring and 2-chlorophenyl substitution at second position of benzodiazepine ring) was found to be most potent compound of this series exhibiting 90% inhibition in both MES and PTZ models. This compound was found to be more potent (90% protection) to phenytoin sodium (standard drug for MES model) and sodium valproate (standard drug for PTZ model). This compound was studied in details at three graded doses(17.5, 25 and 50mg/kg i.p.) for its anticonvulsant activity and was found to possess 20, 50, 90% and 20, 40, 90% protection of seizures in MES and PTZ models, respectively. On the other hand compounds 4a-4f possessed benzoxazepine ring with 2-oxo/thiobarbituric acid, substituted by different moieties at second position exhibited aniconvulsnat activity ranging from 40 to 70% and 30 to 60% in both MES and PTZ models respectively. So the compounds 4a-4f showed a decrease in anticonvulsant activity in comparison to compounds 3a-3f i.e. benzothiazepine compounds.Further the compounds of next step i.e. 6a-6l were characterized

by different arylaminomethylene substitutions at the third position of benzoxazepine ring. All the twelve compounds 6a-6l of this step exhibited anticonvulsant activity ranging from 50 to 70% and 40 to 60% protection of seizures in MES and PTZ models, respectively.

ALD_{50} Studies

The toxicity study of these compounds indicate their good safety margin.

EXPERIMENTAL

Chemistry

Melting points were determined in open capillaries with the help of thermonic melting point apparatus and are uncorrected. 1R spectra (KBr) are recorded on Backmann Acculab-10-spectrophotometer. ^{1}H NMR spectra were recorded by Bruker WM 400 FT instrument using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference standard. All chemical shift (d)are in ppm. The purities of the compounds were checked by thin layer chromatography (TLC) on silicagel-G plates of 0.5mm thickness. The elemental analysis of the compounds were performed on HeracusCarlo Erba 1108 analyser.

5-Acetyl-2-oxobarbituric acid 1a. Acetyl chloride (50ml) was added to 2-oxobarbituric acid (20g) drop by drop with stirring at 0-5^{0}C. The reaction mixture was further stirred for 10h using a magnetic stirrer and kept overnight. The excess of acetyl chloride was distilled off with the help of a distillation assembly and the residue thus obtained was washed with petroleum ether 40-60^{0}C, a number of times and then poured onto ice. The solid thus obtained was filtered with the help of a filteration pump and recrystallised from methanol/water to give compounds 1a (75%), mp 180°C; 1R (KBr) 3100 (NH), 1750, 1720, 1700, 1690, (C=O) cm^{-1}; ^{1}HNMR ($CDCl_3$) of 9.25 (ss, 2H, 2NHCO), 5.79 (s, 1H, $CHCOCH_3$), 2.47 (s, 3H, $COCH_3$) (ppm); MS : M^+ 170. Anal.calcd. for $C_6H_6N_2O_4$; C, 42.35; H,3.52; N, 16.47. Found : C, 42.33; H, 3.50; N, 16.51.

-Acetyl-2-thiobarbituric acid (1b). 77%,m.p. 250°C (methanol/water); 1R (KBr) 3140 (NH), 1133 (C=S) cm^{-1};^{1}H NMR ($CDCl_3$) d 9.28 (ss, 2H, 2NHCO), 5.71 (s,1H, $CHCOCH_3$), 2.50 (s, 3H,$COCH_3$) (ppm); MS : M^+ 178. Anal. calcd. for $C_6H_6N_2O_3S$; C, 38.70; H, 3.22; N,15.05. Found :C, 38.71; H, 3.20; N, 15.07.

1-(2^1-Oxobarbiturinyl)-3-(2-chlorophenyl) chalcone (2a). A mixture of 5-acetyl-2-barbituric acid (0.01 mole) and 2-chloroaldehyde (0.01 mole) in absolute methanol (50ml) in presence of 2% NaOH were refluxed for 12h. The resulting mixture was concentrated, cooled and poured onto ice. The solid thus obtained was filtered, washed with petroleum ether (40-60°C) and recrystallised from methanol/water to give compound 2a (90%), mp 240°C; IR (KBr) 3320 (NH), 1620 (CH=CH), 1730, 1720, 1715, 1680 (amidic (C=O),1580 (C…C of aromatic ring), 710 (C-Cl) cm^{-1}; ^{1}H NMR ($CDCl_3$) d 5.80 (m, 1H, CHCO), 6.65 (d, 1H, -COCH=), 7.80-7.27 (m, 4H,Ar-H), 8.30 (d, 1H, = CH-Ar), 9.30 (ss, 2H, 2NHCO) (ppm); MS : M^+292.5. Anal.calcdfor $C_{13}H_9N_2O_4Cl$; C,53.33; H,3.07; N,9.57. Found C,53.30; H, 3.02; N, 9.59.

1-(2'-Oxobarbituriyl)-3-(p-hydroxyphenyl)-chalcone (2b). 85%, mp 250ºC (DMF); 1R (KBr) 3320 (NH), 1620 (CH=CH), 1690, 1710, 1715 (amidic C=O), 1530 (C…C) of aromatic ring cm^{-1}; ^{1}H NMR ($CDCl_3$) d 9.10 (3, 1H, Ar-OH) 5.80 (m, 1H, CHCO), 6.65 (d, 1H,- COCH=), 7.10 -8.10 (m, 4H, Ar-H), 8.48 (d,1H, =CH-Ar), 9.25 (ss, 2H, 2NHCO) (ppm); MS : M^+ 258. Anal.Calcd.for $C_{13}H_{10}N_2O_5$; C, 60.46; H, 3.93 ; N, 10.85. Found : C. 60.40 ; H, 3.85; N, 10.88

1-(2'-Oxobarbiturinyl) -3-(m-methoxyphenyl)-chalcone (2c). 80%, mp 280ºC (methanol/water) ; IR (KBr) 3345 (NH), 1600 (CH=CH), 1680, 1700, 1710 (amidic C=O), 1550 (C…C) of aromatic ring cm^{-1} ; ^{1}H NMR ($CDCl_3$) d 3.47 (s, 3H, Ar-OCH_3), 5.75 (m, 1H, CHCO), 6.69 (d, 1 H, -COCH=), 7.50-8.45 (m, 4H, Ar- H), 8.30 (d, 1H, = CH-Ar), 9.28 (ss, 2H, 2NHCO) (ppm) ; MS : M^+ 288. Anal.Calcd.for $C_{14}H_{12}N_2O_5$; C, 58.33 ; H, 4.16 ; N, 9.72. Found : C, 58.32; H, 4.15 ; N, 9.76.

1-(2^1-Thiobarbiturinyl) -3- (o-chlorophenyl) chalcone (2d). 86%, mp 275°C (ethanol/water); IR (KBr) 3343 (NH), 1610 (CH=CH), 1690, 1715 (amidic (C=O), 730 (C-Cl), 1510 (C…C) of aromatic ring, 1031 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$) d 5.83 (m 1H, CHCO), 6.73 (d. 1H,-COCH=), 7.15-8.00 (m, 4H, Ar-H), 8.45 (d, 1H, = CH-Ar), 9.29 (ss,

Table 1: Anticonvulsant activity and toxicity data of compounds 1a-6l (Scheme 1)

Compd.	X	R	R^1	Dose (mg/kg i.p)	Anticonvulsant Activity		ALD50 (mg/kgi.p.)
					MES	PTZ	
1a	O	-	-	50	20	10	>1000
1b	S	-	-	50	20	20	>1000
2a	O	2-Cl	-	50	40	40	>1000
2b	O	4-OH	-	50	30	20	>1000
2c	O	3-OCH-$_3$	-	50	20	10	>1000
2d	S	2-Cl	-	50	50	50	>1000
2e	S	4-OH	-	50	30	20	>1000
2f	S	3-OCH_3	-	50	40	30	>1000
3a	O	2-Cl	-	50	60	60	>1000
3b	O	4-OH	-	50	60	40	>1000
3c	O	3-OCH_3	-	50	40	40	>1000
3d	S	2-Cl	-	50	80	80	
				2	40	30	>2000
				17.5	20	20	
3e	S	4-OH	-	50	60	60	>1000
3f	S	3-OCH_3	-	50	70	60	>1000
4a	O	2-Cl	-	50	50	50	>1000
4b	O	4-OH	-	50	40	30	>1000
4c	O	3-OCH_3	-	50	40	40	>1000
4d	S	2-Cl	-	50	70	60	>1000
4e	S	4-OH	-	50	60	50	>1000
4f	S	3-OCH_3	-	50	60	60	>1000
5a	O	2-Cl	4-Cl	50	60	60	>1000
5b	O	2-Cl	4-OCH_3	50	70	70	>1000
5c	O	4-OH	4-Cl	50	60	50	>1000
5d	O	4-OH	4-OCH_3	50	60	50	>1000
5e	O	3-OCH_3	4-Cl	50	70	70	>1000
5f	O	3-OCH_3	4-OCH_3	50	70	60	>1000
5g	S	2-Cl	4-Cl	50	60	60	>1000
5h	S	2-Cl	4-OCH_3	50	90	90	
				25	50	40	>2000
				17.5	20	20	
5i	S	4-OH	4-Cl	50	80	80	>1000
5j	S	4-OH	4-OCH_3	50	80	70	>1000
5k	S	3-OCH_3	4-Cl	50	70	60	>1000
5l	S	3-OCH_3	4-OCH_3	50	80	80	>1000
6a	O	2-Cl	4-Cl	50	50	40	>1000
6b	O	2-Cl	4-OCH_3	50	50	50	>1000
6c	O	4-OH	4-Cl	50	60	50	>1000
6d	O	4-OH	4-OCH_3	50	60	60	>1000
6e	O	3-OCH_3	4-Cl	50	60	50	>1000
6f	O	3-OCH_3	4-OCH_3	50	60	60	>1000
6g	S	2-Cl	4-Cl	50	70	50	>1000

6h	S	2-Cl	4-OCH_3	50	60	60	>1000
6i	S	4-OH	4-Cl	50	70	60	>1000
6j	S	4-OH	4-OCH_3	50	60	60	>1000
6k	S	3-OCH_3	4-Cl	50	70	60	>1000
6l	S	3-OCH_3	4-OCH_3	50	60	50	>1000
Phenytoin sodium				30	80		
Sodium valproate				80		80	
Propylene glycol				50	0	0	

*p < 0.05, **p<0.01, ***p <0.001.

2H, 2NHCO) (ppm); MS: M^+ 308.5. Anal.Calcd.for $C_{13}H_9N_2O_3ClS$; C, 50.56; H, 2.91 ; N, 9.07; Found : C, 50.50; H, 2.95; N, 9.01.

1-(2'-Thiobarbiturinyl)-3-(p-hydroxyphenyl) chalcone (2e). 82%, mp 205°C (DMF); IR (KBr) 3345 (NH), 1620 (CH=CH), 1705, 1715 (amidic C=O), 1500 (C...C) of aromaticring, 1060 (C=S) cm^{-1} ;^{1}H NMR ($CDCl_3$) d 9.15 (s, 1H. Ar-OH),, 5.65 (m, 1H, CHCO), 6.80 (d, 1H, -COCH=), 7.00-8.15 (m, 4H, Ar-H), 8.40 (d, 1H, = CH-Ar), 9.26 (ss, 2H, 2NHCO) (ppm); MS: M^+290. Anal.Calcd.for $C_{13}H_{10}N_2O_4S$; C,53.79; H,3.44; N,9.65; Found : C,53.81; H,3.47; N,9.68.

1-(2'-Thiobarbiturinyl)-3-(m-methoxyphenyl) chalcone (2f). 80%, mp 220°C (benzene/petroleum ether); IR (KBr) 3330 (NH), 1630 (CH =CH), 1685, 1690 (amidic C =O), 1560 (C...C) of aromatic ring, 1030 (C=S) cm^{-1} ; ^{1}H NMR ($CDCl_3$) d 3.43 (s, 3H, Ar-OCH_3), 5.60 (m, 1HCHCO), 6.75 (d, 1H, -COCH=), 7.30-8.60 (m, 4H, Ar-H), 8.30 (d, 1H, = CH-Ar), 9.20 (ss, 2H, 2NHCO) (ppm) ; MS : M^+ 304. Anal.Calcd.for $C_{14}H_{12}N_2O_4S$; C, 53.79 ; H, 3.44; N, 9.65. Found : C,. 53.81; H, 3.47; N, 9.68.

4-(2^1-Oxobarbiturinyl)-2-(o-chlorophenyl)-2, 3 – dihydro-1, 5-benzothiazepines (3a). The methanolic solution (50mL) of 1-(2^1-oxobarbiturinyl)- 3- (m-chlorophenyl)- chalcone (2a) (0.01 mol) was added 2-aminothiophenol (0.01 mol) with few drops of glacial acetic acid and refluxed for 3-5h. After refluxing solvent was distilled off under reduced pressure and the solid thus obtained was recrystallized from ethanol to give 3a (85%), mp 148°C; IR (KBr) 3345 (NH), 1690, 1710, 1715 (amidic C = O), 1629 (C=C), 1460 (C=N), 690 (C-Cl), 671 (C-S-C) cm^{-1}; ^{1}H NMR ($CDCl_3$) d 9.25 (ss, 2H,) 2NHCO), 3.60 (t, 1H, -CH), 7.65 (d, 2H, C_3-H of thiazepine ring), 7.70-6.65 (m, 8H, Ar-H), 6.49 (t, 1H, C_2-H of thiazepine ring) (ppm); MS : M^+ 399.5 .Anal. Calcd.for $C_{19}H_{14}N_3O_3SCl$; C, 57.07; H, 3.50; N, 10.51. Found : C, 57.10; H, 3.48; N, 10.55.

4 - (2^1-Oxobarbiturinyl) - 2- (p-hydroxyphenyl) -2,3 – dihydro - 1,5 - benzothiazepines (3b). 78%, mp 158°C (Ethanol); IR (KBr) 3320 (NH), 1700, 1710, 1715 (amidic C=O), 3438 (OH), 1638 (C=C), 1469 (C=N), 680 (C-S-C) cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 9.23 (ss, 2H, 2NHCO), 3.91 (t,1H, -CH), 9.11(s, 1H, Ar-OH), 7.68 (d, 2H, C_3-H of thiazepine ring). 7.72-6.69 (m, 8H, Ar-H), 6.48 (t, 1H, C-$_2$-H of thiazepine ring) (ppm). MS : M^+ 381. Anal.Calcd for $C_{19}H_{15}N_3O_4S$; C, 59.8; H, 3.93; N, 11.02.Found : C,59.02; H,3.95; N, 11.05.

4-(2^1-Oxobarbiturinyl) – 2 - (m - methoxyphenyl) - 2,3 – dihydro - 1,5 - benzothiazepines (3c). 78%, mp 146°C (methanol) ; IR (KBr) 3343 (NH), 1690, 1700, 1725 (amidic C=O), 1625 (C=C), 1462 (C=N), 1225 (OCH_3), 675 (C-S-C) cm^{-1} ; ^{1}H NMR ($CDCl_3$) d 9.21 (ss, 2H, 2NHCO), 3.62 (t, 1H,-CH), 7.75-6.71 (m, 8H, Ar-H), 7.65 (d, 2H, C_3H of thiazepine ring), 6.45 (t, 1H, C_2-H of thiazepine ring), 3.42 (s, 3H, OCH_3) (ppm) ; MS : M^+ 411. Anal.Calcd.for $C_{20}H_{17}N_3O_5S$; C, 58.39 ; H, 4.13 ; N, 10.21. Found : C, 58.35; H, 4.15; N, 10.25.

4 - (2^1-Thiobarbiturinyl) – 2 - (o-chlorophenyl) - 2, 3- dihydro - 1,5 -benzothiazepine (3d). 80%, mp 155°C (ethanol); IR (KBr) 3330 (NH), 1700, 1710 (amidic C=O), 1050 (C=S), 1625 (C=C), 1455 (C=N), 680 (C-Cl) cm^{-1}; ^{1}H NMR ($CDCl_3$) 9.30 (ss, 2H, 2 NHCO), 3.57 (t, 1H,-CH), 7.71-6.74 (m, 8H, Ar-H), 7.68 (d, 2H, C_3-H of thiazepine ring),

6.40 (t, 1H, C-$_2$-H of thiazepine ring) (ppm); MS : M^+ 415.5 Anal Calcd. for $C_{19}H_{14}N_3O_2S_2Cl$; C, 54.87; H, 3.36 ; N, 10.10. Found : C, 54.82 ; H, 3.31; N, 10.13.

4 - (2^1-Thiobarbiturinyl) – 2 - (p-hydroxyphenyl) - 2,3 – dihydro - 1,5 - benzothiazepine (3e). 78%, mp 170°C (ethanol); IR (KBr) 3415(NH), 1690, 1705 (amidic C=O), 1060 (C=S), 3440 (OH), 1640 (C=C), 1470 (C=N), 688 (C-S-C) cm^{-1} ; ^{1}H NMR CCDCl$_3$) δ 9.20 (ss, 2H, 2NHCO), 3.62 (t, 1H,-CH), 7.70-6.65 (m, 8H, Ar-H), 9.15 (s, 1H, Ar-OH) 7.63 (d, 2H, C_3-H of thiazepine ring), 6.42 (t, 1H, C-$_2$-H of thiazepine ring) (ppm); MS : M^+ 397. Anal.Calcd.for $C_{19}H_{15}N_3O_3S_2$; C,57.43; H,3.77; N, 10.57. Found : C,57.40; H,3.79; N, 10.60.

4 - (2^1-Thiobarbiturinyl) – 2 - (m-methoxyphenyl) - 2,3 – dihydro - 1,5 - benzothiazepine (3f). 75%, mp 164°C (methanol); IR (KBr) 3410 (NH), 1700, 1710 (amidic C=O), 1055 (C=S), 1629 (C=O), 1460 (C=N), 1230 (OCH_3), 680 (C-S-C) cm^{-1} ; ^{1}H NMR CDCl$_3$) d 9.23 (ss, 2H, 2NHCO), 3.59 (t, 1H,-CH), 7.71-6.68 (m, 8H, Ar-H), 7.60 (d, 2H, C_3-H of thiazepine ring), 6.48 (t, 1H, C-$_2$-H of thiazepine ring) (ppm); MS : M^+427. Anal.Calcd.for $C_{20}H_{17}N_3O_4S_2$; C,56.20 ; H,3.98; N,9.83. Found : C,56.22 ; H, 3.94; N,9.80.

4 - (2^1-Oxobarbiturinyl) – 2 - (o-chlorophenyl) - 2,3 – dihydro - 1,5 -benzoxazepines (4a). The methanolic solution (50mL) of 1-(2^1-oxobarbiturinyl)-3-(m-chlorophenyl)-chalcone (2a) (0.01 mol) was added 2-aminophenol (0.01mol) with few drops of glacial acetic acid and refluxed for 3-5h. After refluxing solvent was distilled off under reduced pressure and the solid thus obtained was recrystallized from ethanol to give 4a (85%), mp 150°C ; IR (KBr) 3340 (NH), 1680, 1700, 1710 (amidic C=O), 1633 (C=C), 1470 (C=N), 660 (C-Cl), 1075 (C-O-C) cm^{-1} ; ^{1}H NMR (CDCl$_3$) d 9.26 (ss, 2H, 2NHCO), 3.91 (t, 1H,-CH), 7.72 (d, 2H, C_3-H of oxazepine ring), 6.52 (t, 1H, C_2-H of oxazepine ring), 7.72-6.74 (m, 8H, Ar-H) (ppm) ; MS : M^+383.5. Anal.Calcd.for $C_{19}H_{14}N_3O_4Cl$; C,59.45; H,3.65 ; N, 10.95. Found : C,59.48; H,3.62; N,10.91.

4 - (2^1-Oxobarbiturinyl) – 2 - (p-hydroxyphenyl) - 2,3 – dihydro - 1,5 - benzoxazepines (4b). 76%, mp 160°C (ethanol) ; IR (KBr) 3347 (NH), 1690, 1710, 1715 (amidic C=O), 3444 (OH), 1624 (C=C), 1474 (C=N), 685 (C-O-C) cm^{-1} ; ^{1}H NMR (CDCl$_3$) d 9.30 (ss, 2H, 2NHCO), 3.85 (t, 1H,-CH), 7.70 (d, 2H, C_3-H of oxazepine ring), 6.50 (t, 1H, C_2-H of oxazepine ring), 7.70-6.74 (m, 8H, Ar-H) 9.10 (s, 1H, Ar-OH) (ppm) ; MS : M^+ 365. Anal.Calcd.for $C_{19}H_{15}N_3O_5$; C,62.46; H,4.10; N,11.50. Found : C,62.41; H,4.13; N,11.48.

4 - (2^1-Oxobarbiturinyl) – 2 - (m-methoxy phenyl) - 2,3 – dihydro - 1,5 -benzoxazepines (4c). 80%, mp 156°C (benzene) ; IR (KBr) 3330 (NH), 1700, 1710, 1715 (amidic C=O), 1628 (C=C), 1465 (C=N), 1230 (OCH_3), 1070(C-O-C) cm^{-1} ; ^{1}H NMR (CDCl$_3$) d 9.28 (ss, 2H, 2NHCO), 3.57 (t, 1H,-CH), 7.64.6.68 (m, 8H, Ar-H) 7.68 (d, 2H, C_3 –H of oxazepinering), 6.48 (t, 1H, C_2-H of oxazepine ring), 3.48 (s, 3H, OCH_3) (ppm) ; MS : M^+ 395. Anal.Calcd.for $C_{20}H_{17}N_3O_6$; C, 60.75; H,4.30; N,10.63. Found : C,60.72; H,4.33; N,10.67.

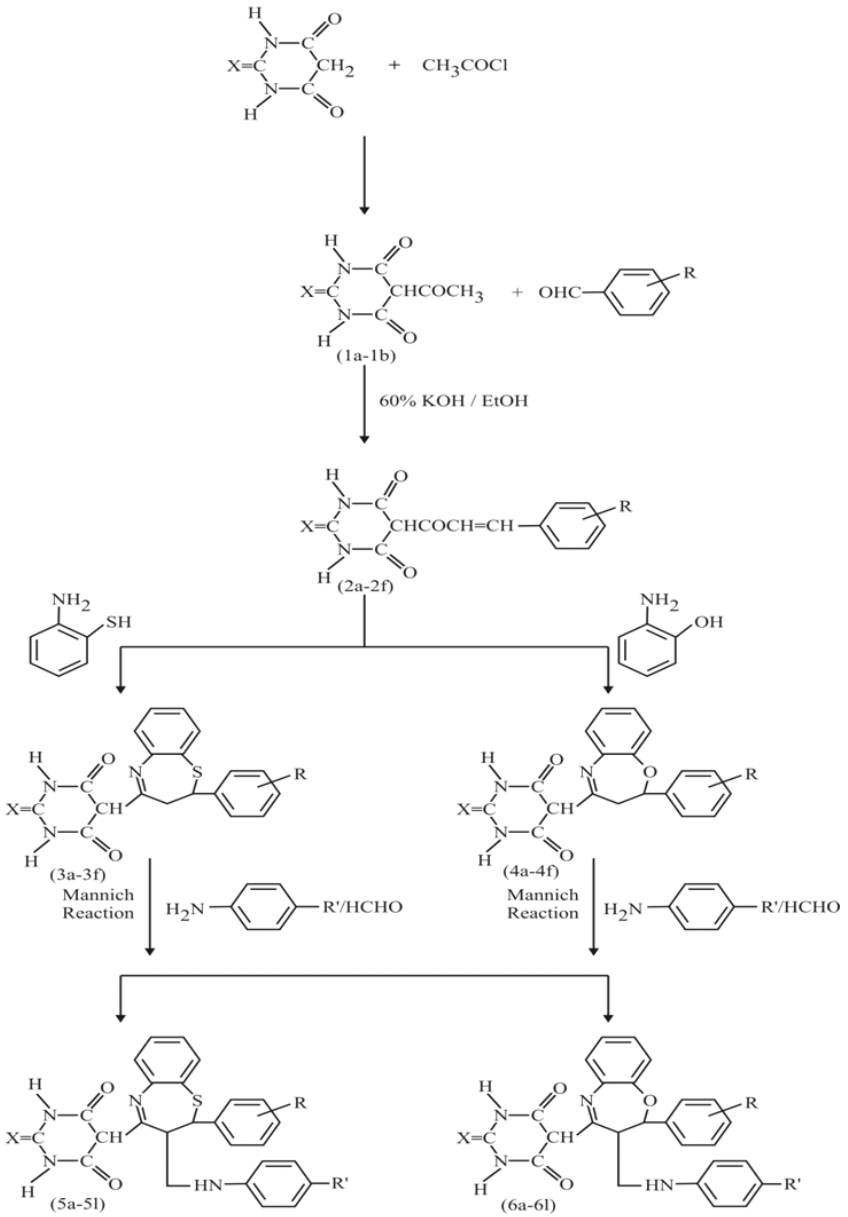
4 - (2^1-Thiobarbiturinyl) – 2 - (o-chlorophenyl) - 2,3 – dihydro - 1,5 - benzoxazepine (4d). 85%, mp 166°C (ethanol); IR (KBr) 3320 (NH), 1690, 1720 (amidic C=O), 1070(C=S), 1633(C=C), 1470 (C=N), 660 (C-Cl) 1075 (C-O-C) cm^{-1} ; ^{1}H NMR (CDCl$_3$) d 9.26 (ss, 2H, 2NHCO), 3.59 (t, 1H,-CH), 7.72-6.62 (m, 8H, Ar-H), 7.70 (d, 2H, C_3-H of oxazepine ring), 6.52 (t, 1H, C-$_2$-H of oxazepine ring) (ppm); MS : M^+ 332. Anal.Calcd.for $C_{19}H_{14}N_3O_3SCl$; C, 68.67 H,4.21; N, 12.65. Found : C,68.64 ; H,4.24; N,12.67.

4 - (2^1-Thiobarbiturinyl) – 2 - (p-hydroxyphenyl) - 2,3 – dihydro - 1,5 -benzoxazepine (4e). 80%, mp 173°C (ethanol); IR (KBr) 3345 (NH), 1700, 1715 (amidic C=O), 1080 (C=S), 3438 (OH), 1628 (C=C), 1465 (C=N), 1072 (C-O-C) cm^{-1} ; ^{1}H NMR (CDCl$_3$) d 9.23 (ss, 2H, 2NHCO), 3.62 (t, 1H,-CH), 7.72 (d, 2H, C_3-H of oxazepine ring), 6.50 (t, 1H, C-$_2$-H of oxazepine ring), 9.15 (s, 1H, Ar-OH), 7.70-6.74 (m, 8H, Ar-H), (ppm); MS : M^+ 381. Anal Calcd.for $C_{19}H_{15}N_3O_4S$; C, 73.75; H,3.93; N, 11.02 Found : C,73.70 ; H,3.95 ; N,11.08.

4 - (2^1-Thiobarbiturinyl) – 2 - (m-methoxyphenyl) - 2,3 – dihydro - 1,5 - benzoxazepine (4f). 75%, mp 178°C (benzene); IR (KBr) 3347 (NH), 1690, 1720 (amidic C=O), 1060 (C=S), 1630 (C=C), 1470 (C=N), 1233 (OCH_3), 1080 (C-O-C) cm^{-1} ; ^{1}H NMR (CDCl$_3$) d 9.33 (ss, 2H,

2NHCO), 3.65 (t, 1H,-CH), 6.48 (t, 1H, C_2-H of oxazepine ring), 7.68 (d, 2H, C_3-H of oxazepine ring), 3.48 (ss, 3H, OCH_3), 7.65-6.71 (m, 8H, Ar-H), (ppm); MS : M^+ 395. Anal.Calcd.for $C_{20}H_{17}N_3O_4S$; C,60.75; H,4.30; N, 10.63. Found : C,60.78; H,4.26 ; N,10.65.

4 - (2^1-Oxobarbiturinyl) – 2 - (o-chlorophenyl) – 3 [(p-chlorophenylamino methylene)] -2,3 – dihydro - 1,5 - benzothiazepines (5a). 62%, mp 185°C; IR (KBr) 3320 (NH), 1690, 1710, 1715 (amidic C=O), 1625 (C=C), 1465 (C=N), 715 (C-Cl), 678 (C-S-C) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.25 (ss, 2H, 2NHCO), 3.60 (t, 1H,-CH), 7.62 -6.74 (m, 12H, Ar-H) 3.70 (d, 1H, C_3-H of thiazepine ring), 6.45 (t, 1H, C_2-H of thiazepine ring), 3.04 (hump, 1H, CH_2NH exchangeable with D_2O), 1.62 (t, 2H, $NHCH_2CH=$) (ppm) ; MS : M^+ 467. Anal.Calcd.for $C_{26}H_{19}N_4O_3SCl_2$; C,66.80; H,4.06; N,11.99. Found : C,66.84; H,4.10; N,11.94.



Scheme 1:

4 - (2^1-Oxobarbiturinyl) – 2 - (o-chlorophenyl) – 3 -[(p-methoxyphenylamino methylene)] - 2,3-dihydro-1,5-benzothiazepines (5b). 70%, mp 172°C (ethanol) ; IR (KBr) 3342 (NH), 1710, 1715, 1720 (amidic C=O), 1630 (C=C), 1462 (C=N), 720 (C-Cl), 671, (C-S-C), 1229 (OCH_3) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.26 (ss, 2H, 2NHCO), 3.62 (t, 1H,-CH), 7.66 -6.64 (m, 12H, Ar-H) 3.72 (d, 1H, C_3-H of thiazepine ring), 7.66-6.64 (m,12H, Ar-H), 3.72 (d, 1H, C_3-H of thiazepine ring), 6.43 (t, 1H, C_2-H of thiazepine ring), 3.06 (hump, 1H, CH_2NH exchangeable with D_2O), 1.65 (t, 2H, $NHCH_2CH$=), 3.45 (s.3H, OCH_3) (ppm) ; MS : M^+ 534.5. Anal.Calcd.for $C_{27}H_{23}N_4O_4SCl$; C,60.61; H,4.30; N,10.47. Found : C,60.65; H,4.32; N,10.42.

4 - (2^1-Oxobarbiturinyl) – 2 - (p-hydroxyphenyl) – 3 - [(p-chlorophenylaminomethylene)]- 2,3 – dihydro - 1,5-benzothiazepines (5c). 68%, mp 167°C (methanol) ; IR (KBr) 3345 (NH), 1700, 1715, 1725 (amidic C=O), 1638 (C=C), 1465 (C=N), 710 (C-Cl), 678 (C-S-C), 3457 (OH) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.23 (ss, 2H, 2NHCO), 3.68 (t, 1H,-CH),7.64-6.60 (m, 12H, Ar-H), 3.70 (d, 1H, C_3-H of thiazepine ring), 6.58 (t, 1H, C_2-H of thiazepine ring), 3.12 (hump, 1H, CH_2NH exchangeable with D_2O), 1.62 (t, 2H, $NHCH_2CH$=) 9.15 (s, 1H, Ar-OH) (ppm) ; MS : M^+ 456.5 Anal. Calcd.for $C_{26}H_{21}N_4O_4SCl$; C,68.34; H,4.60; N,12.26. Found : C,68.30; H,4.62; N,12.22.

4 - (2^1-Oxobarbiturinyl) – 2 - (p-hydroxyphenyl) – 3 - [(p-methoxyphenylamino methylene)] - 2,3 – dihydro - 1,5 - benzothiazepines (5d). 54%, mp 184°C (DMF/Water) ; IR (KBr) 3330 (NH), 3460 (OH), 1680, 1700, 1715 (amidic C=O), 1645 (C=C), 1480 (C=N), 682 (C-S-C), cm^{-1} ; ^1H NMR ($CDCl_3$) d 7.64-6.62 (m, 12H, Ar-H), 9.27 (ss, 2H, 2NHCO), 3.57 (t, 1H. CH-), 3.75, (d, 1H, C_3-H of thiazepine ring), 6.41 (t, 1H, C_2-H of thiazepine ring), 3.44 (s, 3H, OCH_3), (,1H, Ar-OH), 3.10 (hump, 1H, CH_2NH exchangeable with D_2O), 1.60 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 516 Anal. Calcd.for $C_{27}H_{24}N_4O_5S$; C,62.79; H,4.65 ; N,10.85. Found : C,62.76; H,4.63; N,10.88.

4 - (2^1-Oxobarbiturinyl) – 2 - (m-methoxyphenyl) – 3 - [(p-chlorophenylamino methylene)]- 2,3-dihydro-1,5-benzothiazepines (5e). 52%, mp 173°C (benzene); IR (KBr) 3360 (NH), 1670, 1700, 1720 (amidic C=O), 1650 (C=C), 1465 (C=N), 710 (C-Cl), 688 (C-S-C), cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.30 (ss, 2H, 2NHCO), 3.55 (t, 1H, CH-), 7.65-6.78 (m, 12H, Ar-H) 3.72 (d, 1H, C_3-H of thiazepine ring), 6.55 (t, 1H, C_2-H of thiazepine ring), 3.35 (s, 3H, OCH_3), 3.10 (hump, 1H, CH_2NH exchangeable with D_2O), 1.68 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 534.5 Anal. Calcd.for $C_{27}H_{23}N_4O_4SCl$; C,60.61; H,4.30; N,10.47. Found : C,60.63; H,4.28; N,10.43.

4 - (2^1-Oxobarbiturinyl) – 2 - (m-methoxyphenyl) – 3 - [(p-methoxyphenylamino methylene)]- 2,3 – dihydro - 1,5 - benzothiazepines (5f). 67%, mp 168°C (DMF/Water); IR (KBr) 3347 (NH), 1700, 1710, 1720 (amidic C=O), 3432 (OH), 1618 (C=C), 1458 (C=N), 1221 (OCH_3), 665 (C-S-C), cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.29 (ss, 2H, 2NHCO), 3.59 (t, 1H, CH-), 7.68-6.80 (m, 12H, Ar-H) 3.70 (d, 1H, C_3-H of thiazepine ring), 6.40 (t, 1H, C_2-H of thiazepine ring), 6.40 (t, 1H, C_2-H of thiazepine ring), 3.41 (s, 6H, 2xOCH_3). 3.00 (hump, 1H, CH_2NH exchangeable with D_2O), 1.59 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 530 Anal. Calcd.for $C_{28}H_{26}N_4O_5S$; C,63.39 ; H,4.90 ; N, 10.56. Found : C,63.41; H,4.88 ; N, 10.58.

4 - (2^1-Thiobarbiturinyl) – 2 - (o-chlorophenyl) – 3 - [(p-chlorophenylamino methylene)]- 2,3 – dihydro - 1,5 - benzothiazepines (5g). 53%, mp 177°C (ethanol); IR (KBr) 3328 (NH), 1680, 1710, (amidic C=O), 1620 (C=C), 1440 (C=C), 720 (C=Cl), 690 (C-S-C), 1130 (C=S) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.27 (ss, 2H, 2NHCO), 3.65 (t, 1H, CH-), 7.65- 6.74 (m, 12H, Ar-H) 3.72 (d, 1H, C_3-H of thiazepine ring), 6.55 (t, 1H, C_2-H of thiazepine ring), 3.10 (hump, 1H, CH_2NH exchangeable with D_2O), 1.65 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 554 Anal. Calcd.for $C_{26}H_{19}N_4O_2S_2Cl_2$; C,56.31 ; H,3.42; N,10.10. Found : C,56.33; H,3.45; N,10.14.

4 - (2^1-Thiobarbiturinyl) – 2 - (o-chlorophenyl) – 3 - [(p-chlorophenylamino methylene)]- 2,3 – dihydro - 1,5 - benzothiazepines (5h). 44%, mp 183°C (ethanol); IR (KBr) 3347 (NH), 1700, 1710, (amidic C=O), 1628(C=C), 1490 (C=N), 730 (C=Cl), 675 (C-S-C), 1235 (OCH_3) 1127 (C=S) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.30 (ss, 2H, 2NHCO), 3.68 (t, 1H, CH-), 7.68- 6.64 (m, 12H, Ar-H) 3.70 (d, 1H, C_3-H of thiazepine ring), 6.58 (t, 1H, C_2-H of

thiazepine ring), 3.08 (hump, 1H, CH_2NH exchangeable with D_2O), 1.70 (t, 2H, $NHCH_2CH$=), 3.52 (s, 3H, OCH_3), ppm) ; MS : M^+ 550.5 Anal. Calcd.for $C_{27}H_{23}N_4O_3S_2Cl$; C,58.85 ; H,4.17 ; N,10.17. Found : C, 58.82 ; H, 4.19 ; N,10.20.

4 - (2^1-Thiobarbiturinyl) – 2 - (p-hydroxyphenyl) - 3- [(p-chlorophenylamino methylene)]- 2,3-dihydro-1,5-benzothiazepines (5i). 55%, mp 163°C (methanol); IR (KBr) 3348 (NH), 1690, 1700, (amidic C=O), 1133 (C=S), 1648 (C=C), 1478 (C=N), 760 (C-Cl), 680 (C-S-C), 3460 (OH) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.26 (ss, 2H, 2NHCO), 3.75 (t, 1H, CH), 7.65-6.74 (m, 12H, Ar-H), 3.70 (d, 1H, C_3-H of thiazepine ring), 6.65 (t, 1H, C_2-H of thiazepine ring), 3.15 (hump, 1H, CH_2NH exchangeable with D_2O), 1.68 (t, 2H, $NHCH_2CH$=), 9.10 (s, 1H, Ar-OH) (ppm) ; MS : M^+ 536.5 Anal. Calcd.for $C_{26}H_{21}N_4O_3S_2Cl$; C, 58.15 ; H,3.91 ; N,10.43. Found : C,58.11; H,3.94; N, 10.45.

4 - (2^1-Thiobarbiturinyl) – 2 - (p-hydroxyphenyl) – 3 - [(p-methoxyphenylamino methylene)]- 2,3-dihydro-1,5-benzothiazepines (5j). 68%, mp 185°C (DMF/Water); IR (KBr) 3328 (NH), 3465 (OH), 1680, 1700 (amidic C=O), 1650 (C=C), 1470 (C=N), 1128 (C=S), 680 (C-S-C), cm^{-1} ; ^1H NMR ($CDCl_3$) d 7.60-6.75 (m, 2H, Ar-H), 9.30 (ss, 2H, 2NHCO), 3.52 (t, 1H, CH-), 3.75 (d, 1H, C_3-H of thiazepine ring), 6.45 (t, 1H, C_2-H of thiazepine ring), 3.48 (S, 3H, OCH_3) 9.11 (s, 1H, Ar - OH), 3.13 (hump, 1H, CH_2NH exchangeable with D_2O), 1.65 (t, 2H, $NHCH_2CH$=), (ppm) ; MS : M^+ 532 Anal. Calcd.for $C_{27}H_{24}N_4O_4S_2$; C,60.90 ; H, 4.51 ; N,10.52 . Found : C,60.92 ; H,4.48 ; N,10.54.

4 - (2^1-Thiobarbiturinyl) – 2 - (m-methoxyphenyl) – 3 - [(p-chlorophenylamino methylene)]- 2,3 – dihydro -1,5-benzothiazepines (5k). 60%, mp 162°C (benzene); IR (KBr) 3350 (NH), 1700, 1720 (amidic C=O), 1145 (C=S), 1653 (C=C), 1470 (C=N), 730 (C-Cl), 690 (C-S-C), cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.36 (ss, 2H, 2NHCO), 3.48 (t, 1H, CH-), 7.68-6.60 (m, 12H, Ar-H), 3.70 (d, 1H, C_3-H of thiazepine ring), 3.38 (s, 3H, OCH_3) 3.08 (hump, 1H, CH_2NH exchangeable with D_2O), 1.64 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 550.5. Anal.Calcd.for $C_{27}H_{23}N_4O_3S_2Cl$; C, 58.85; H,4.17; N,10.17. Found : C,58.88; H, 4.12; N,10.14.

4 - (2^1-Thiobarbiturinyl) – 2 - (m-methoxyphenyl) – 3 - [(p-methoxyphenylamino methylene)]- 2,3-dihydro-1,5-benzothiazepines (5l). 70%, mp 182°C (DMF/Water); IR (KBr) 3350 (NH), 1710, 1715 (amidic C=O), 1150 (C=S), 3435 (OH), 1620 (C=C), 1470 (C=N), 1220 (OCH_3), 670 (C-S-C), cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.23 (ss, 2H, 2NHCO), 3.63 (t, 1H, CH-), 7.62-6.60 (m, 12H, Ar-H), 3.71 (d, 1H, C_3-H of thiazepine ring), 6.43 (t, 1H, C_2-H of thiazepine ring), 3.44 (s, 6H, 2xOCH_3), 3.04 (hump, 1H, CH_2NH exchangeable with D_2O), 1.62 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 546. Anal.Calcd.for $C_{28}H_{26}N_4O_4S_2$; C,61.53 ; H,4.76; N,10.25. Found : C,61.55 ; H,4.79; N,10.21.

4 - (2^1-Oxobarbiturinyl) – 2 - (o-chlorophenyl) – 3 - [(p-Chlorophenylamino methylene)]- 2,3 – dihydro - 1,5 - benzoxazepines (6a). 65%, mp 189°C (ethanol); IR (KBr) 3343 (NH), 1690, 1710, 1720 (amidic C=O), 1630 (C=C), 1469 (C=N), 1040 (C-O-C), 715 (C=Cl), cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.29 (ss, 2H, 2NHCO), 3.58 (t, 1H, -CH), 7.60-6.68(m, 12H, Ar-H), 3.72 (d, 1H, C_3-H of thiazepine ring), 6.50 (t, 1H, C_2-H of thiazepine ring), 3.08 (hump, 1H, CH_2NH exchangeable with D_2O), 1.65 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 522. Anal.Calcd.for $C_{26}H_{19}N_4O_4Cl_2$; C,59.77 ; H, 3.63 ; N,10.72 . Found : C,59.74 ; H, 3.65 ; N,10.70.

4 - (2^1-Oxobarbiturinyl) – 2 - (o-chlorophenyl) – 3 - [(p-methoxyphenylamino methylene)]- 2,3-dihydro-1,5-benzoxazepines (6b). 55%, mp 195°C (benzene); IR (KBr) 3350 (NH), 1700, 1710, 1715 (amidic C=O), 1637 (C-C), 1469 (C=N), 715 (C-Cl), 1035 (C-O-C), 1221 (OCH_3) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.24 (ss, 2H, 2NHCO), 3.60 (t, 1H, -CH), 7.65-6.74 (m, 12H, Ar-H), 3.70 (d, 1H, C_3-H of oxazepine ring), 6.59 (t, 1H, C_2-H of oxazepine ring), 3.12 (hump, 1H, CH_2NH exchangeable with D_2O), 1.62 (t, 2H, $NHCH_2CH$=), 3.39 (s. 3H, OCH_3) (ppm) ; MS : M^+ 518.5 Anal. Calcd.for $C_{27}H_{23}N_4O_5Cl$; C, 62.48 ; H,4.43; N,10.80. Found : C,62.46; H,4.47; N,10.78.

4 - (2^1-Oxobarbiturinyl) – 2 - (p-hydroxyphenyl) – 3 - [(p-chlorophenylamino methylene)]- 2,3-dihydro-1,5-benzoxazepines (6c). 61%, mp 200°C (methanol); IR (KBr) 3353 (NH), 1700, 1712, 1717 (amidic C=O), 1634 (C=C), 1470

(C=N), 720 (C-Cl), 1045 (C-O-C), 3468 (OH) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.30 (ss, 2H, 2NHCO), 3.57 (t, 1H, -CH), 7.78 – 6.60 (m,12J. Ar-H), 3.75 (d, 1H, C_3-H of oxazepine ring), 6.61 (t, 1H, C_2-H of oxazepine ring), 3.16 (hump, 1H, CH_2NH exchangeable with D_2O), 1.70 (t, 2H, $NHCH_2CH$=), 9.15 (s, 1H, OH-Ar), (ppm) ; MS : M^+ 504.5. Anal.Calcd.for $C_{26}H_{21}N_4O_5Cl$; C, 61.84 ; H,4.16 ; N,11.10. Found : C,61.80; H, 4.18 ; N,11.13.

4 - (2^1-Oxobarbiturinyl) – 2 - (p-hydroxyphenyl) – 3 - [(p-methoxyphenylamino methylene)]- 2,3-dihydro-1,5-benzoxazepines (6d). 48%, mp 207°C (methanol); IR (KBr) 3347 (NH), 3458 (OH), 1690, 1700, 1710 (amidic C=O), 1630 (C=C), 1490 (C=N), 1035 (C-O-C), cm^{-1} ; ^1H NMR ($CDCl_3$) d 7.80-6.85 (m, 12H, Ar-H), 9.35 (ss, 2H, 2NHCO), 3.60 (t, 1H, CH-), 3.75 (d, 1H, C_3-H of oxazepine ring), 6.61 (t, 1H, C_2-H of oxazepine ring), 3.31 (s, 3H, OCH_3), 9.10 (s, 1H, Ar-OH), 3.12 (hump, 1H, CH_2NH exchangeable with D_2O), 1.62 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 500. Anal.Calcd.for $C_{27}H_{24}N_4O_6$; C,62.4; H, 4.8; N, 11.2. Found : C, 62.8; H,4.4 ; N, 11.4.

4 - (2^1-Oxobarbiturinyl) – 2 - (m-methoxyphenyl) – 3 - [(p-chlorophenylamino methylene)]- 2,3-dihydro-1,5-benzoxazepines (6e). 58%, mp 192°C (DMF/Water); IR (KBr) 3350 (NH), 1670, 1700, 1720 (amidic C=O), 1647 (C=C), 1460 (C=N), 715 (C-Cl), 1025 (C-O-C), cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.36 (ss, 2H, 2NHCO),3.50. (t, 1H, CH-) 7.85-6.70 (m, 12H, Ar-H) 3.77 (d, 1H, C_3-H of oxazepine ring), 6.40 (t, 1H, C_2-H of oxazepine ring), 3.02 (hump, 1H, CH_2NH exchangeable with D_2O), 1.60 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 518.5 Anal. Calcd.for $C_{27}H_{23}N_4O_5Cl$; C,62.48; H, 4.43 ; N, 10.80. Found : C, 62.44 ; H,4.45 ; N,10.77.

4 - (2^1-Oxobarbiturinyl) – 2 - (m-methoxyphenyl) – 3 - [(p-methoxyphenylamino methylene)]- 2,3-dihydro-1,5-benzoxazepines (6f). 61%, mp 198°C (ethanol); IR (KBr) 3350 (NH), 1700, 1710, 1720 (amidic C=O), 3434 (OH), 1618 (C=C), 1458 (C=N), 1221 (OCH_3), 1030 (C-O-C), cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.40 (ss, 2H, 2NHCO), 3.56 (t, 1H, CH-), 7.80-6.74 (m, 12H, Ar-H). 3.70 (d, 1H, C_3-H of oxazepine ring), 6.40 (t, 1H, C_2-H of oxazepine ring), 3.41 (s, 6H, 2xOCH_3), 3.00 (hump, 1H, CH_2NH exchangeable with D_2O), 1.59 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 514. Anal.Calcd.for $C_{28}H_{26}N_4O_6$; C, 65.36 ; H, 5.05 ; N,10.89. Found : C,65.33; H,5.07 ; N,10.84.

4 - (2^1-Thiobarbiturinyl) – 2 - (o-chlorophenyl) – 3 - [(p- chlorophenylamino methylene)]- 2,3-dihydro-1,5-benzoxazepines (6g). 52%, mp 200°C (ethanol); IR (KBr) 3329 (NH), 1690,, 1710 (amidic C=O), 1630 (C-O-C), 1140 (C=S), cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.36 (ss, 2H, 2NHCO), 3.62 (t, 1H, CH-), 7.70-6.68 (m, 12H, Ar-H) 3.75 (d, 1H, C_3-H of thiazepine ring), 6.45 (t, 1H, C_2-H of thiazepine ring), 3.05 (hump, 1H, CH_2NH exchangeable with D_2O), 1.58 (t, 2H, $NHCH_2CH$=) (ppm) ; MS : M^+ 538. Anal.Calcd.for $C_{26}H_{19}N_4O_3SCl_2$; C, 57.99; H,3.53 ; N,10.40. Found : C,57.97; H,3.56 ; N, 10.38.

4 - (2^1-Thiobarbiturinyl) – 2 - (o-chlorophenyl) – 3 - [(p-methoxyphenylamino methylene)]- 2,3-dihydrobenzoxazepines (6h). 69%, mp 171°C (benzene); IR (KBr) 3345 (NH), 1700, 1710 (amidic C=O), 1625 (C=C), 1440 (C=N), 760 (C-Cl), 1028 (C-O-C), 1148 (C=S), 1230 (OCH_3) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.30 (ss, 2H, 2NHCO), 3.68 (t, 1H, CH-) 7.88-6.78 (m, 12H, Ar-H) 3.72 (d, 1H, C_3-H of oxazepine ring), 6.59 (t, 1H, C_2-H of oxazepine ring), 3.12 (hump, 1H, CH_2NH exchangeable with D_2O), 1.62 (t, 2H, $NHCH_2CH$=), 3.39 (s, 3H, OCH_3) (ppm) ; MS : M^+ 534.5. Anal.Calcd.for $C_{27}H_{23}N_4O_4SCl$; C,60.61 ; H,4.30 ; N, 10.47. Found : C, 60.63; H,4.34 ; N, 10.41.

4 - (2^1-Thiobarbiturinyl) – 2 - (p-hydroxyphenyl) – 3 - [(p-chlorophenylamino methylene)]- 2,3-dihydro-1,5- benzoxazepines (6i). 48%, mp 175°C (methanol); IR (KBr) 3347 (NH), 1700, 1715, (amidic C=O), 1630 (C=C), 1460 (C=N), 730 (C-Cl), 1030 (C-O-C), 1145 (C=S), 3455 (OH) cm^{-1} ; ^1H NMR ($CDCl_3$) d 9.28 (ss, 2H, 2NHCO), 3.60 (t, 1H, CH-), 7.85-6.80 (m, 12H, Ar-H), 3.77 (d, 1H, C_3-H of oxazepine ring), 6.62 (t, 1H, C_2-H of oxazepine ring), 3.15 (hump, 1H, CH_2NH exchangeable with D_2O), 1.58 (t, 2H, $NHCH_2CH$=), 9.20 (s, 1H, Ar- OH) (ppm) ; MS : M^+ 520.5 Anal. Calcd.for $C_{26}H_{21}N_4O_4SCl$; C,59.94; H,4.03 ; N,10.75. Found : C,59.90 ; H, 4.05 ; N,10.71.

4 - (2^1-Thiobarbiturinyl) – 2 - (p-hydroxyphenyl) – 3 - [(p-methoxyphenylamino methylene] – 2,3- dihydro-1,5- benzoxazepines (6j).

65% ,mp 166C^0 (methanal); IR(KBr) 3337 (NH), 3460 (OH), 1680, 1700 (midic C=O), 1640 (C=C), 1455 (C=N), 1150 (C=S), 1040(C-O-C) Cm^1; ^{1}H NMR ($CDCl_3$), 7.80-6.68(m, 12H,Ar-H), 9.32 (ss,2H 2NHO), 3.59 (t,1H,CH-), 3.75 (d,1H, C_3-H of oxazepine ring), 3.45 (s,3H,OCH_3), 9.15 (s, 1H, Ar-OH) 3.02 (hump,) 1H, CH_2NH exchangeable with D_2O), 1.60 (t,2H $NHCH_2CH$=), 6.40 (t,1H, C_2-H of oxazepine ring) (ppm); MS:$^+$ M 516, Anal. calcd. fer $C_{27}H_{24}N_4O_5S$; C,62.79; H,4.65; N,10.85. Found: C, 62.74; H,4.62; N,10.87.

4 - (2^1-Thiobarbiturinyl) – 2 - (m-methoxyphenyl) – 3 - [(p-chlorophenylamino methylne)] - 2,3 - dihydro- 1-5 - benzoxazepines (6K). 50%, mp 174^{0}C (DMF/Water); IR (KBr) 3345 (NH), 1710, 1715 (amidic C=O), 1133 (C=S), 1615 (C=C), 1455 (C=N), 720 (C-Cl), 1040 (C-O-C) cm-^{1}; ^{1}H NMR ($CDCl_3$) δ 9.33 (ss, 2H, 2NHCO), 3.58 (t,1H, CH-), 7.90-6.85 (m,12H,Ar-H), 3.73 (d,1H, C_3-H of oxazepine ring,), 6.65 (t,1H C_2–H of oxazepine ring), 3.34 (s,3H, OCH_3), 3.20 (hump, 1H CH_2NH exchangeable with D_2O), 1.60 (t, 2H, NH CH_2CH=) (ppm;) MS; M$^+$ 534.5.Anal Calcd.for $C_{27}H_{23}N_4O_4SCl$; C, 60.61; H, 4.30; N,1O.47. Found: C, 60.63; H, 4.27; N, 10.49.

4-(2^1-Thiobarbiturinyl)-2- (m-methoxyphenyl)-3[(p-methoxyphenylamino methylene)] -2,3-dihydro-1,5-benzoxazepines (6l). 45%, mp 210^{0}C (ethanol);IR (KBr) 3348 (NH), 1700, 1710 (amidic C=O), 1127 (C=S), 1620 (C=C), 1452 (C=N), t210 (OCH_3), 1048 (C-O-C) cm-^{1}; ^{1}H NMR ($CDCl_3$) δ 9.38 (ss,2H, 2NHCO), 3.60 (t,1H,CH-), 7.88-6.74 (m,12H,Ar-H), 3.77 (d,1H,C_3-H of oxazepine ring), 6.60 (t,1H, C_2-H of oxazepine ring), 3.40 (S,6H, 2×OCH_3), 3.28 (hump,1H, CH_2NH exchangealele with D_2O), 1.62 (t,2H, $NHCH_2CH$=) (ppm); MS: M$^+$ 530 Anal. Calcd.for $C_{28}H_{26}N_4O_5S$; C, 63.39; H,4.90; N,1056. Found: C, 63.37; H, 4.43; N, 10.58.

Pharmacological evaluation

Anticonvulsant activity. Maximum electroshock seizure (MES) test

This test was performed according to the method of Tomen et.al[15]. The group of ten rats was treated with test drugs (50mg/kg i.p.) phenytoin sodium (30mg/kg i.p.). After 1h, they were subjected to the shock of 150mA by convulsiometer through ear electrodes for 0.2s and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats.

Pentylenetetrazole (PTZ) induced seizures test. This test was performed by following the method of Fischer[16]. The rats were injected with pentylenetetrazol in dose of 70 mg/kg subcutaneously in scruff of neck. After 2-4 min of PTZ injection animals developed sequence of excitement, myoclonic jerks, clonic seizures, one or more maximum tonic seizures. Animals exhibiting these seizures patterns were selected standard drug used in this model was sodium valproate (80 mg/kg i.p) and was injected 60 min prior to PTZ challenge.

Approximate lethal dose (ALD_{50})

Approximate 50% lethal dose (ALD_{50}) of the compounds were determined in albino mice. The mice of either sex 20-25g were used. The test compounds were injected intraperitoneally at different dose levels in groups of 10 animals. After 24h of drug administration, percent mortality in each group was observed from the data obtained. ALD_{50} was calculated by the method of Smith[17].

CONCLUSION

While considering all the newly synthesized compounds of this series together, we may conclude that:

1. 2-Thiobarbituric acid, containing compounds were found to possess potent anticonvulsant activity in comparison to 2-oxobarbituric acid, containing compounds.
2. Presence of benzothiazepine moiety has shown better anticonvulsant activity than the compounds having benzoxazepine moiety.
3. Compounds having benzothiazepine moiety with thiobarbituric acid showed better anticonvulsant activity than the compounds having benzoxazepine moiety with oxobarbituric acid.
4. 2-Chlorophenyl substitution at second position of benzothiazepines ring showed more potent activity than other substituted benzothiazepines.
5. Presence of electronegative atom (chlorine)

plays a pivotal role to increase the anticonvulsant activity. Regarding acute toxicity studies it may be concluded that all the compounds showed high value of ALD_{50} thus indicating a good safety margin.

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