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Synthesis of Novel Indolylbenzothiazepines/ Indolylbenzoxaziepines Substituted 2-Oxo/Thiobarbituric acids as Potential Anticonvulsant Agents

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ABSTRACT

4-(2'-Oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)-2,3-dihydro--1,5-benzothiazepines (7-10) and 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)-2,3-dihydro--1,5-benzoxazepines (11-14) undergoes Mannich reaction to afford compounds 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)–3-(substitutedphenyl aminomethylene)-2,3-dihydro-1,5-benzothiazepines (15-22) and 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)–3-(substitutedphenyl aminomethylene)-2,3-dihydro-1,5-benzoxazepines (23-30) correspondingly. All the chemical framework of these newer drugs were elucidated by using elemental and IR and NMR spectroscopy. All these newly synthesized compounds were tested for antiepileptic effect against SMES experimental models and the results were collated with phenytoin sodium-standard drug. Results of antiepileptic profile showed promising effect in most of the derivatives synthesized. Activity equal to standard drug was shown by compounds 9 and 28. The most promising and active compound of this project was found to be 4-(2'- thiobarbiturinyl acid)–2-(2"-chloro-1"H-indolyl)–3-(chlorophenyl aminomethylene)-2,3-dihydro-1,5-benzothiazepines, which elicited activity greater than the standard drug. All the antiepileptic drugs of the produced in this projects were also tested for ALD_{50}.

Keywords: Benzothiazepines, Benzoxazepines, indoles, oxo/thiobarbituric acid, synthesis, antiepileptic activity, ALD50.

INTRODUCTION

Epilepsy is a disorder related to the nervous system affecting the brain and its activity by causing frequent seizures and sometimes, loss of awareness. In simple words, epilepsy is a disorder or disease of the brain with a potential of making a human unconscious. A group of medicative agents that are used for the treatment of epilepsy are referred to as anticonvulsant agents. Although a large number of anticonvulsant drugs are present and are being used for the treatment of epileptic seizures, yet their long exposure can lead to drug resistance. In addition, the presently available drugs are also associated with severe side effects such as hypnosis, sedation, etc. thereby retarding everyday performance. As

per epidemiological studies[1-3], currently the disease affects more than 60 million people worldwide. Thus, a novel and a safer anticonvulsant drug is the most needed scientific discovery of today.

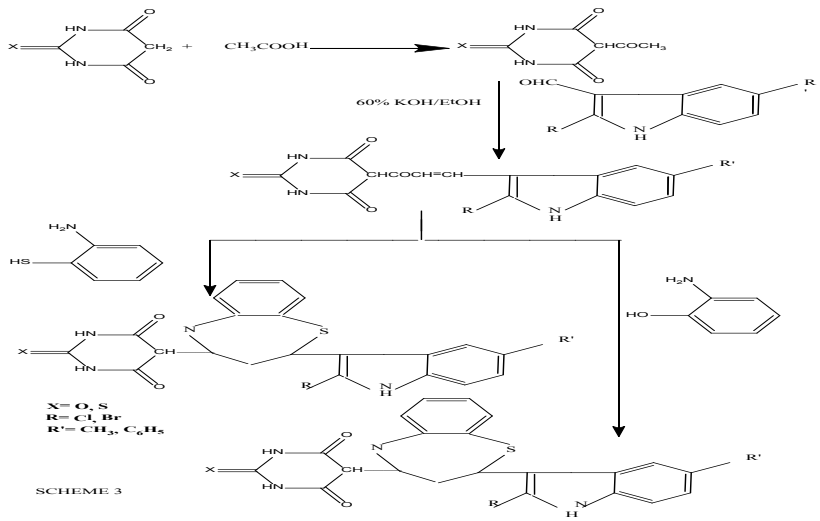
Mephobarbital[4] and phenobarbital[5], which are derivatives of 2,4,6-tri-oxo-hexahydropyrimidine (barbituric acid) are medically being used for the treatment of epilepsy. The substitution with various alkyl, aryl or heteroaryl moieties at fifth position of barbituric acid[6-9] and thiobarbituric acid[9-12] was found to plays an essential role in modulating the antiepileptic effect. Indoles[13-17] have been found to possess antiepileptic activity in maximal electroshock seizure model experiment. Literature survey reveals that derivatives of benzo-thiazepines as well as benzo-oxazepines were used in the synthesis and design of new and different antiepileptic drugs. The chemistry and pharmacology of benzothiazepine and benzoxazepine derivatives have been of substantial attraction to health professionals for the reason that their by-products were found to possess various biotic activities such as antiinflammatory[18], antimicrobial[18-19], antioxidant[20], antitumor[21], antipsychotic[22-23], anticonvulsant[23-26], etc. In view of above discussion the motive of this study is to synthesize newer antiepileptic drugs by embodying benzothiazepine and benzoxazepine segments on 2-oxo/thiobarbituric acids (at fifth position) which was already incorporated with indole moiety. The introduction of these components on 2-oxo/thiobarbituric acids (at fifth position), may be innovative as the substituted groups themselves possess anticonvulsant effect and their introduction on 2-oxo/thiobarbituric acids (at fifth position) was further expected to enhance the antiepileptic activity.

MATERIAL AND METHODS

Chemistry

Melting points were recorded with the help of thermonic melting point apparatus. The open capillary tubes were used for taking the melting points which were faulty (not correct). The homogeneousness and pureness of the drugs produced were examined using TLC (thin layer chromatography) utilizing plates of silica gel-G. Methanol-benzene mixture in the ratio of 2:8 was used as an eluent. The spots of TLC were located with the help of iodine. Carlo Erba 1108 analyzer was used to perform elemental analysis (C, H, N) and were found within the range of ±0.04% of the conceptual values. Perkin Elmer 881 FT-IR spectrophotometer (ν_{max} in cm^{-1}) was used to record IR spectra. Bruker DRX-300-FTNMR instrument was used to record ^{1}H-NMR spectra in $CDCl_3$.

Compounds (1-14) were synthesized according to the routes depicted in Fig. 1. The physical data (melting points, recrystallization solvents, yields, molecular weights, elemental analysis) of derivatives (1-14) is stated in Table 1. These synthesized drugs (1-14) were also evaluated for their antiepileptic activeness and also for their ALD_{50} (acute toxicity). The standard drug used for antiepileptic activity was phenytoin sodium. The results of biological activity that is antiepileptic acitivty and acute toxicity is depicted in (Table 2).



SCHEME 3

Synthesis

General procedure to synthesize 5-methoxy-2-thio/ oxo barbituric acids (1-2)

To 2-thio/oxobarbituric acid (20 g), acetyl chloride (50 mL) was add on little by little with regularly moving the liquid round and round and maintaining the temperature between 0-5^{0}C. Magnetic stirrer was used to stir the reaction mixture for another 10 hours. After stirring the mixture was kept overnight. Distillation assembly was used to distill off excess of acetic acid. The solid residue obtained after distillation was washed with water again and again and was then poured into ice. Filtration pump was used to filter the solid residue. The solid residue thus obtained was filtered which was again solidified using suitable solvents. The analytical as well as physical details of compounds 1-2 is stated in Table 1. Compound 1: ^{1}H-NMR $CDCl_3$ δ: 5.80 (s, 1H, $CHCOCH_3$), 2.55 (s, 3H, $COCH_3$), 9.20 (s, 2H, 2N-HC=O). IR (cm^{-1}, KBr): 1740, 1720, 1690, 1700 (C=O), 3180 (-N-H).

General procedure to synthesize 1-(2'-oxo/ thiobarbiturinyl acid)-3-(2"-halo-1"H-indolyl)-prop-2-en-1-ones (3-6)

Compounds 1-2 (0.01 mole) were fused in pure ethanol (50 mL). To this mixture obtained, 3-formyl-2-halo-1H-indoles (0.01 mol) were put on. Refluxing of reaction mixture was done for about 12 h in the presence of 60% KOH. These reaction mixtures obtained after refluxing were evaporated, chilled and finally gushed onto ice. Filtration pump was used to produce solids. The solids produced were filtered. The solids obtained after filtration were further cleaned with petroleum ether (40-60^{0}C), after which they were crystallized again using suitable solvents. The analytical as well as physical details of compounds 3-6 are specified in Table 1. Compound 3: ^{1}H-NMR $CDCl_3$ δ: 8.99 (s, 2H, 2NHCO), 9.80 (brs, 1H, N-H of indole), 5.65 (m, 1H, CHCO), 6.95-7.25 (m, 4H, Ar-H), 8.45 (d, 1H, =CH-), 6.55 (d, 1H, -COCH=),. IR (cm^{-1}, KBr): 3180 (N-H of indole), 1585 (C-C of aromatic ring), 1750, 1710, 1700,1730 (C=O), 710 (C-Cl), 1625 (CH=CH).

Table 1: Physical and analytical details of compounds 1-30

Compound No	X	R	R'	m.p.(^{0}C)	Recryst. Solvent	Yield(%)	Molecular Formula	Calcd. (Found)% C	H	N
1	O	-	-	180	methanol	46	$C_6H_6O_4N_2$	42.35(42.30)	3.52(3.50)	16.47(16.50)
2	S	-	-	250	ethanol	66	$C_6H_6O_3N_2S$	38.70(38.68)	3.22(3.19)	15.05(15.08)
3	O	Cl	-	240	DMF	62	$C_{15}H_{10}O_4N_2Cl$	56.69(56.72)	3.14(3.17)	8.81(8.79)
4	O	Br	-	280	acetone	55	$C_{15}H_{10}O_4N_2Br$	49.72(49.68)	2.76(2.78)	7.73(7.69)
5	S	Cl	-	275	ethanol	58	$C_{15}H_{10}O_3N_2ClS$	53.97(54.00)	2.99(3.01)	8.39(8.42)
6	S	Br	-	250	methanol	48	$C_{15}H_{10}O_3N_2BrS$	47.61(47.57)	2.64(2.67)	7.40(7.36)
7	O	Cl	-	150	ethanol	42	$C_{21}H_{16}O_3N_4ClS$	57.33(57.35)	3.64(3.66)	12.74(12.77)
8	O	Br	-	230	pet.ether	55	$C_{21}H_{16}O_3N_4BrS$	52.06(52.09)	3.30(3.27)	11.57(11.61)
9	S	Cl	-	210	ethanol/water	44	$C_{21}H_{16}O_2N_4ClS_2$	55.32(55.29)	3.51(3.48)	12.29(12.32)
10	S	Br	-	200	toluene	46	$C_{21}H_{16}O_2N_4BrS_2$	50.40(50.37)	3.20(3.17)	11.20(11.18)
11	O	Cl	-	225	acetone	42	$C_{21}H_{16}O_4N_4Cl$	59.50(59.59)	3.77(3.80)	13.22(13.19)
12	O	Br	-	260	ethanol	40	$C_{21}H_{16}O_4N_4Br$	53.84(53.86)	3.41(3.39)	11.96(12.00)
13	S	Cl	-	235	DMF	58	$C_{21}H_{16}O_3N_4ClS$	57.33(57.36)	3.64(3.67)	12.74(12.71)
14	S	Br	-	225	methanol	48	$C_{21}H_{16}O_3N_4BrS$	52.06(52.09)	3.30(3.26)	11.57(11.69)
15	O	Cl	4-OCH_3	180	ethanol	46	$C_{29}H_{25}O_4N_5ClS$	60.57(60.60)	4.35(4.38)	12.18(12.21)
16	O	Cl	4-Cl	160	methanol	40	$C_{28}H_{22}O_3N_5Cl_2S$	58.13(58.09)	3.80(3.77)	12.11(12.08)
17	O	Br	4-OCH_3	155	ethanol	62	$C_{29}H_{25}O_4N_5BrS$	56.21(56.18)	4.03(4.06)	11.30(11.27)
18	O	Br	4-Cl	225	ethanol	40	$C_{28}H_{22}O_3N_5BrClS$	53.88(53.91)	3.52(3.49)	11.22(11.19)
19	S	Cl	4-OCH_3	200	DMF	46	$C_{29}H_{25}O_3N_5ClS_2$	58.98(59.00)	4.23(4.19)	11.86(11.89)
20	S	Cl	4-Cl	230	methanol	38	$C_{28}H_{22}O_2N_5Cl_2S2$	56.56(56.52)	3.70(3.67)	11.78(11.80)
21	S	Br	4-OCH_3	205	acetone	42	$C_{29}H_{25}O_3N_5BrS_2$	54.80(54.77)	3.93(3.89)	11.02(11.05)
22	S	Br	4-Cl	245	methanol	40	$C_{28}H_{22}O_2N_5BrClS_2$	52.54(52.57)	3.44(3.47)	10.94(10.97)
23	O	Cl	4-OCH_3	260	pet.ether	36	$C_{29}H_{25}O_5N_5Cl$	62.30(62.27)	4.47(4.50)	12.53(12.49)
24	O	Cl	4-Cl	240	ethanol	46	$C_{28}H_{22}O_4N_5Cl_2$	59.78(59.91)	3.91(3.89)	12.45(12.48)
25	O	Br	4-OCH_3	235	ethanol	48	$C_{29}H_{25}O_5N_5Br$	57.71(57.68)	4.14(4.17)	11.60(11.57)
26	O	Br	4-Cl	195	ethanol	50	$C_{28}H_{22}O_4N_5BrCl$	55.30(55.27)	3.62(3.59)	11.52(11.49)
27	S	Cl	4-OCH_3	215	ethanol	45	$C_{29}H_{25}O_3N_5ClS$	62.30(62.27)	4.47(4.50)	12.53(12.50)
28	S	Cl	4-Cl	205	acetone	42	$C_{28}H_{22}O_3N_5Cl_2S$	58.13(58.15)	3.80(3.78)	12.11(12.09)
29	S	Br	4-OCH_3	250	methanol	44	$C_{29}H_{25}O_4N_5BrS$	56.21(56.18)	4.03(4.00)	11.30(11.26)
30	S	Br	4-Cl	200	methanol	44	$C_{28}H_{22}O_3N_5BrClS$	53.88(53.91)	3.52(3.49)	11.22(11.19)

C, H, N were found within ±0.04%

Table 2: Pharmacological details of compounds (1-30)

Compound number	Acute toxicity ALD_{50} (mg/kg i.p.)	Anticonvulsant activity	
		Dose (mg/kg i.p.)	Percentage inhibition of seizures
1	>1000	30	40*
2	>1000	30	40*
3	>1000	30	50*
4	>1000	30	40*
5	>1000	30	60**
6	>1000	30	50**
7	>1000	30	60*
8	>1000	30	50**
9	>1000	7.5	30*
		15	60**
		30	80***
10	>1000	30	60**
11	>1000	30	50*
12	>1000	30	50**
13	>1000	30	70**
14	>1000	30	60**
15	>1000	30	70***
16	>1000	30	80**
17	>1000	30	60**
18	>1000	30	70***
19	>1000	30	70**
20	>1000	7.5	50*
		15	60**
		30	90***
21	>1000	30	60**
22	>1000	30	70*
23	>1000	30	70**
24	>1000	30	70**
25	>1000	30	60*
26	>1000	30	70**
27	>1000	30	70**
28	>1000	7.5	40**
		15	60**
		30	80***
29	>1000	30	70**
30	>1000	30	70***
Phenytoin Sodium		30	80***
Propylene Glycol		2.0	0

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

General procedure to synthesize 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)-2,3-dihydro- -1,5-benzo-thiazepines (7-10)

1-(2'-Oxo/thiobarbiturinyl acid)-3-(2"-halo-1"H-indolyl)-prop-2-en-1-ones (3-6) (0.01 mole) were added to methanol (50 mL) to form various solutions. 2-amino-thiophenol (0.01 mole) having some drops of extremely cold acetic acid (1 mL) was also added to the solutions formed. These solutions were refluxed for 4-5 hours. The execution of reactions were noticed by TLC. Then after, extra solvents were distilled off using distillation assembly under lesser pressure to get solid remnant. The solids which were produced after distillation were resolidified by using appropriate solvents to afford compounds 7-10. The analytical as well as physical details of compounds 7-10 are stated in Table 1. Compound 7: ^{1}H-NMR $CDCl_3$ δ: 5.60 (m, 1H, CH of barbituric acid), 9.12 (ss, 2H, 2NHCO), 9.88 (brs, 1H, N-H of indole), 6.90-7.68 (m, 8H, Ar-H), 6.59 (s, 1H, C_2-H of thiazepine ring), 7.25 (d, 2H, C_3-H of thiazepine ring), 4.25 (t, 1H, C_4-H of thiazepine ring). IR (cm^{-1}, KBr): 3188 (N-H of indole), 1740, 1710, 1720 (C=O), 717 (C-Cl), 1616 (C=C), 690 (C-S-C), 3045 (aromatic C-H), 1585 (C-C of aromatic ring), 690 (C-S-C), 1485 (C-N).

General procedure to synthesize 4-(2'-oxo/ thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)-2,3-dihydro- -1,5-benzoxazepines (11-14)

Methanol about 50 mL and 1-(2'-Oxo/ thiobarbiturinyl acid)-3-(2"-halo-1"H-indolyl)-prop-2-en-1-ones (3-6) (0.01 mol) were mixed together and a clear solution was formed. 2-Aminophenol containing some drops of glacial acetic acid (1 mL) were put in together to this methanolic solutions of compounds (3-6) and were refluxed for about 4-5 hours. The progression of the reactions were determined by TLC. The extra solvents were distilled off using distillation assembly with the reduced pressure. The solid yields which were produced were crystallized again by using suitable and appropriate solvents to yield compounds 11-14. The analytical as well as physical details of compounds (11-14) are mentioned in Table 1. Compound 14: ^{1}H-NMR $CDCl_3$ δ: 5.66 (m, 1H, CH of barbituric acid), 9.15 (ss, 2H, 2NHCO), 7.10-7.88 (m, 8H, Ar-H), 6.50 (s, 1H, C_2-H of oxazepine ring), 9.85 (brs, 1H, NH of indole),7.68 (d, 2H, C_3-H of oxazepine ring), 4.20 (t, 1H, C4-H of oxazepine ring). IR (cm^{-1}, KBr): 3040 (aromatic CH), 3192 (NH of indole), 1735, 1720, 1715 (C=O), 720 (C-Cl), 1620 (C=C), 1488 (C-N), 1588 (C-C of aromatic ring), 1666 (C=N), 1070 (C-O-C).

General procedure to synthesize 4-(2'-oxo/ thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)–3-(substitutedphenyl aminomethylene)-2,3-dihydro-1,5-benzothiazepines (15-22)

4-(2'-Oxo/thiobarbiturinyl acid) – 2 - (2"-halo-1"H-indolyl)-2,3-dihydro-1,5-benzothiazepines (7-10) (0.001 mole), formaldehyde (0.01 mole) and anilines having different substitutions (0.001 mole) in methanol (50 mL) are mixed together to form clear solutions. The solutions formed were refluxed for nearly 5-6 hours. On accomplishment of refluxing, the mixtures produced were first evaporated, then chilled and finally put onto ice. After doing so semi-solid products were separated. The semi solids which separated out were kept in petroleum ether (40-60^{0}C) and were left ovenight. The next day solid products were produced, which were crystallized again with suitable solvents. The analytical as well as physical details of the compounds (15-22) are stated in Table 1. Compound 15: 1H-NMR $CDCl_3$: 5.60 (m, 1H, CH of barbituric acid), 9.12 (ss, 2H, 2NHCO), 9.88 (brs, 1H, N-H of indole), 7.68-6.80 (m, 12H, Ar-H), 3.45 (s, 3H, OCH_3),6.59 (s, 1H, C_2-H of thiazepine ring), 7.25 (d, 2H, C3-H of thiazepine ring), 4.25 (t, 1H, C4-H of thiazepine ring), 1.60 (t, 2H, $NHCH_2CH$), 3.05 (hump, 1H, CH_2NH exchangeable with D2O). IR (cm^{-1}, KBr): 1668 (C=N),3188 (NH of indole), 1740, 1720, 1710 (C=O), 717 (C-Cl), 1616 (C=C), 3045 (aromatic CH), 1585 (C-C of aromatic ring), 1485 (C-N), 1228 (OCH_3), 690 (C-S-C).

General procedure to synthesize 4-(2'-oxo/ thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)–3-(substitutedphenyl aminomethylene)-2,3-dihydro-1,5-benzoxazepines (23-30)

4-(2'-Oxo / thiobarbiturinyl acid) – 2 - (2"-halo-1"H-indolyl)-2,3-dihydro - -1,5-benzoxazepines (11-14) (0.001 mole), formaldehyde (0.01 mole) and anilines having different substitutions (0.001 mole) were dissolved in methanol (50 mL) to obtain clear solutions. The solution thus obtained were refluxed for about 5-6 hours. The reaction mixtures formed after refluxing were first evaporated, then chilled and finally put onto ice. After pouring onto ice semisolid products separated out. These semisolids were kept in petroleum ether (40-60^{0}C) and were left overnight. The solid products were obtained the next day which were recrystallized using suitable solvents. The analytical as well as physical details of the compounds (23-30) are mentioned in Table 1. Compound 23: ^{1}H-NMR $CDCl_3$ δ : 5.66 (m, 1H, CH of barbituric acid), 9.16 (ss, 2H, 2NHCO), 9.85 (brs, 1H, N-H of indole), 7.62-6.82 (m, 12H, Ar-H), 3.48 (s, 3H, OCH_3), 6.62 (s, 1H, C_2-H of oxazepine ring), 7.48 (d, 2H, C_3-H of oxazepine ring), 4.25 (t, 1H, C_4-H of oxazepine ring), 1.62 (t, 2H, $NHCH_2CH$), 3.10 (hump, 1H, CH_2NH exchangeable with D_2O). IR (cm^{-1}, KBr): 1730, 1725, 1720 (C=O), 720 (C-Cl), 1618 (C=C), 1582 (C-C of aromatic ring), 3184 (N-H of indole), 3048 (aromatic C-H), 1666 (C=N), 1482 (C-N), 1232 (OCH_3), 1035 (C-O-C).

Pharmacology

Anticonvulsant activity

Supra maximal electroshock seizure pattern test (SMES) model was used for screening antiepileptic activity. Method of Tomen *et al.,*[27] was utilized for this model. Albino rats having weight ranging between 90-120 g of either sex were put to use for test. The rats were splited into groups. Groups were made in such a way that each group of rats contains ten animals. Test drugs as well as the standard drug-phenytoin sodium were injected intraperitoneally (i.p.) in rats. After 1 h of drug administration, the rats were put through a shock of

150 milliampere via ear electrodes for 0.2 seconds. The absence or presence of extensor response in the rats was duly observed. Rats (animals) in which extensor reciprocation was put to end were taken as secured rats.

Acute Toxicity (ALD_{50})

The acute toxicity studies were carried out in mice. All the compounds which were prepared were scrutinized for acute toxicity (ALD_{50}) in mice. This test was done by using the plan opf action given by Smith[28].

RESULTS

Anticonvulsant activity in rats

All the compounds (1-30) synthesized were studied for their antiepileptic activity. The novel compounds were synthesized according the routes depicted in Fig. 1. The compounds were tested for their biological activity i.e. antiepileptic test at a dose of 30 mg/kg i.p. against SMES experimental model (supra maximal electroshock induced seizures). The compounds 1-30 showed substantive activity varying between 40% to 90%. Out of thirty compounds evaluated, compounds 9, 20 and 28 exhibit excellent protection against convulsions thereby providing 80%, 90% and 80% protection against convulsions, correspondingly. The outcome of antiepileptic test are stated in Table 2.

The peculiarity of the compounds synthesized in this series is the presence of benzothiazepione/benzoxazepine nuclei on 2-thio/oxobarbituric acids (at the fifth position) containing indolyl moiety into a single molecular skeleton. The first step compounds i.e. 5-methoxy-2-oxo/thiobarbituric acids (1-2) showed mild (40%) antiepileptic effect. Going to the second step compounds i.e. 1-(2'-oxo/thiobarbiturinyl acid)-3-(2"-halo-1"H-indolyl)-prop-2-en-1-ones (3-6) a small increase in percentage protection was observed which was found ranging between 40% to 60%.

The next step of the series i.e. compounds 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)-2,3-dihydro- -1,5-benzothiazepines (7-10) and 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)-2,3-dihydro- -1,5-benzoxazepines (11-14) were prepared following path-1 and path-2 depicted in Fig. 1. These compounds i.e. compounds (7-10) and (11-14) were found to possess good protection varying from 50% to 80% and 50% to 90% respectively in SMES model. The most potent compound of (7-14) is compound 9, which showed activity as good as reported by phenytoin sodium (which was used as standard drug) i.e. possessing similar protection of 80% as. Due to its potential character, it was further considered thoroughly at three graded and different doses of 7.5, 15 and 30 mg/kg i.p. for its antiepileptic profile and was found to have 30%, 60% and 80% protection. The compounds 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)-2,3- dihydro- -1,5-benzothiazepines (7-10) and 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)-2,3– di-hydro- -1,5-benzo-thiazepines (7-10) were further incorporated with various substituted anilines via Mannich reaction to yield compounds 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)–3- (substitutedphenyl aminomethylene)-2,3-dihydro-1,5-benzothiazepines (15-22) and 4-(2'-oxo/thiobarbiturinyl acid)–2-(2"-halo-1"H-indolyl)–3-(substitutedphenyl aminomethylene)-2,3-dihydro-1,5-benzoxazepines (23-30) respectively, which elicited good percentage protection against convulsion. Compounds (15-22), which were final compounds prepared via route-1 showed remarkable anticonvulsant activity differing from 60% to 90% whereas compounds (23-30) which which were final compounds synthesized via route-2 also showed unusual activity varying between 60% to 80%. Compound 20 was found to be the most potent compound among all the final stage compounds (15-30). This compound 20, as well as other potent compound 28 were also considered in details at three different and graded doses of 7.5 mg/kg i.p., 15 mg/kg i.p. and 30 mg/kg i.p. The results elicited that both of these compounds (20 and 28) showed same percentage protection of 40% and 60% at lesser doses of 7.5 and 15 mg/kg i.p. respectively. But a different percentage of protection against seizures was observed at a higher dose of 30 mg/kg i.p. (90% and 80% by compounds 20 and 28 respectively).

CONCLUSION

If we consider the anticonvulsant activity observed in all the newly synthesized compounds, it may concluded that:

1. Compounds containing thiobarbituric acid were proved to be better antiepileptic agents

than the compounds having barbituric acid.

2. Benzothiazepine containing compounds were found to be more potent anticonvulsant agents than the benzoxazepine containing compounds.
3. Existence of electronegative atoms (chlorine and bromine) were found to increase the anticonvulsant effect in the compounds.
4. Presence of 2-chloro phenyl moiety at second position of benzothiazepine / benzoxazepine moiety elicited more promising effect than the 2-bromophenyl containing benzothiazepines/ benzoxazepines.

Acute toxicity (Studied in mice)

All the compounds (1-30) synthesized were also evaluated for ALD_{50} (approximate lethal dose). They all were found to possesss excessive and good value of ALD_{50} greater than 1000 mg/kg i.p. Compound 20 showed exceptionally higher ALD_{50} greater than 2000 mg/kg i.p. Such higher ALD_{50} suggests the safer nature of these compounds. Table 2, contains the data of acute toxicity studies of these compounds.

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Conflict of interest

The co-authors of this work declare and agree with the contents and there is no financial or ant other conflict of interest among them to report.

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