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Synthesis of Thiazolidinonyl/Azetidinonyl Substituted 1,5-Benzothia/Oxaze-pines as Potent Anticonvulsant Agents

Abstract

Various new 2-(4'-oxo-2'-substitutedaryl thiazolidinonyl) iminomethyl-1,5-benzothia / oxazepines (17-26) and 2-(4'-oxo-3'-chloro-2'-substitutedaryl azetidinonyl)-iminomethyl-1,5-benzothia/oxazepines (27-36) have been synthesized by cyclisation of 2-substituted benzylidene hydrazine methyl-1,5-benzothia/oxazepines (7-16) by treating compounds (7-16) with thioglycolic acid and trimethylamine with monochloroacetyl chloride respectively. The structures of the synthesized compounds were confirmed by elemental anaylsis, IR and ^{1}H-NMR spectroscopy. Out of the compounds tested most active compound of this series was found to be compound 18 i.e. 2-(4'-oxo-2'-p-methoxyphenyl thiazolidinonyl) iminomethyl-1,5-benzothiazepines.

Keywords: Thiazolidinonyl Benzothia/Oxazepines, Azetiodinonyl Benzothia/Oxazepines, Anticonvulsant Activity, Maximal Electroshock, Acute Toxicity.

Archana
Assistant Professor
Medicinal Chemistry Laboratory,
Department of Chemistry,
Meerut College,
Meerut, U.P.

Sachin Saini
Research Scholar
Department of Chemistry,
Mewar University,
Chittorgarh, Rajasthan

Introduction

Epilepsy is one of the most disturbing disorder of nervous system and is usually characterized by a specific type of psychic dysfunction and localized and widespread convulsive movements which may be accompanied with episodes of unconsciousness. Occurrence of seizure is a common symptom of epilepsy. The term epilepsy is a collective term that includes disorders of the brain function characterized by the periodic and unpredictable occurrence of seizures . The usage of most anticonvulsant agents is limited, not only by rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of epilepsy and drug side-effects.

Aim of the Study

Although number of antiepileptic drugs have been developed but none meet the ideal criteria as currently available drugs have low margin of safety, strong sedation hampering day time work, tremendous abuse liability and enzyme induction property with other agents. The objective of this study is to synthesize some potential antiepileptic compounds devoid of any side-effects.

Review of Literature

1,5-Benzothiazepine/benzoxazepine comprise an important and valuable class of central nervous system depressants. And hence, benzothiazepine/benzoxazepine nucleus make up a broad class that attracted attention in the past few years owing to its wide range of pharmacological applications like antimicrobial [1], CNS depressant [2], antipsychotic[3-4] and anticonvulsant [5-10] activities. Moreover, thiazolidinones [11-15] and azetidinones [16-] have also been reported to possess anticonvulsant activity. Although there are a number of drugs being used but still need of more safe antiepileptic drug with minimum side effects exists. So in the on going quest to develop potent anticonvulsant agents for controlling epilepsy, we therefore, propose to synthesize some promising anticonvulsant agents by incorporating thiazolidinonyl and azetidinonyl moieties at 2nd position of benzothiazepine/ benzoxazepine nucleus. These compounds were evaluated for anticonvulsant activity and were found to possess highly remarkable protection against convulsions produced by maximal electroshock.

Materials and Methods

Chemistry

All the melting points were determined in open capillary tubes with electro thermal melting point apparatus and are uncorrected. The purity of the compounds was monitored by ascending thin layer chromatography (TLC), on silica gel-G coated plates visualized by iodine vapours. IR spectra were recorded on Beckman-Acculab-10-Spectrophotometer (V_{max} in cm^{-1}) using KBr pellets. ^{1}H-NMR spectra were recorded on a Bruker 300-FT instrument.

The compounds 7-36 (see table 2) were tested both for their anticonvulsant activity and acute toxicity. Phenytoin sodium was used as reference drug for anticonvulsant activity.

Synthesis

Synthesis of methyl-1,5-benzothiazepine (1)

This compound was prepared by the reported method of Pant and Gupta [21]. To the solution of 2-aminobenzenethiol (0.01 mole, 1.25g/1.0913g) in dry xylene (50ml) was added ethyl acetoacetate (0.01 mole, 1.3014g) in dry xylene (10ml) dropwise during 30 min. The reaction mixture was refluxed for 4 hours and the solvent was distilled off. The residue thus obtained was left overnight at room temperature and products obtained were recrystallized with dry xylene. Physical and analytical data of compounds 1 and 2 are given in Table-1. M.p. 160^{0}C ; yield 80%. IR (KBr; cm^{-1}) : 3320 (NH), 1620 (CO), 700 (C-S-C). ^{1}H-NMR ($COCl_3$) : 9.68 (ss, 1H, NH), 2.50 (s, 3H, CH_3), 6.63-7.55 (m, 5H, Ar-H) (ppm) (Scheme-1).

Compound 2 was prepared by following the method of preparation of compound 1.

Synthesis of 1-Bromomethyl-1,5-benzothiazepine (3)

To a solution of compound 1 (0.01 mole) in glacial acetic acid (50ml) was added the solution of bromine (0.02 mole) in glacial acetic acid (10ml), dropwise during 3 hours with continuous stirring by mechanical stirrer. The reaction mixture was poured onto crushed ice. The solid thus obtained was filtered, dried and recrystallized from methanol to give compound 3. Physical and analytical data of compounds 3 and 4 are given in Table-1. M.p. 198^{0}C ; yield 75%. IR (KBr; cm^{-1}) : 3315 (NH), 1600 (CO), 700 (C-S-C). ^{1}H-NMR ($COCl_3$) : 9.70 (ss, 1H, NH), 3.73 (s, 2H, CH_2Br), 6.43-7.15 (m, 5H, Ar-H) (ppm) (Scheme-1).

Compound 4 was prepared by following the method of preparation of compound 3.

Synthesis of 2-hydrazinomethyl-1,5-benzothiazepine (5)

The solution of compound 3 (0.02 mole) in dry chloroform (50ml) was refluxed for 6 hours with hydrazine hydrate (98%) (0.02 mole). The solvent was distilled off and solid thus separates out was filtered and recrystallised from ethanol to give compound 5. Physical and analytical data of compounds 5 and 6 are given in Table-1.M.p. 160^{0}C, yield 70%. IR (KBr; cm^{-1}) : 3326 (NH, NH_2), 1620 (CO), 700 (C-S-C). ^{1}H-NMR ($COCl_3$) : 9.77 (ss, 1H, NH of thiazepine ring), 3.09 (d, J=10.65 Hz, 2H, CH_2NH), 8.80 (bs, 2H, NH_2), 6.63-7.00 (m, 5H, Ar-H) (ppm) (Scheme-1).

Compound 6 was prepared by following the method of preparation of compound 5.

Synthesis of 2-(benzylidene hydrazinomethyl)-1,5-benzothiazepine (7)

An equimolar mixture of compound 5 (0.01 mole) in ethanol (50ml) in the presence of a few drops of glacial acetic acid (2ml) and benzaldehyde (0.01 mole) was refluxed for 10 hours. The reaction mixtures were concentrated, cooled and poured onto ice. The separated solid was filtered and recrystallised from methanol/water to afford compound 7. Physical and analytical data of compounds 7 to 16 are given in Table-1.M.p. 228^{0}C, yield 70%. IR (KBr; cm^{-1}) : 3468 (NH), 1628 (C=O), 700 (C-S-C), 1660 (C=N), 1250 (N-N), 1510 (C=C of aromatic ring). ^{1}H-NMR ($COCl_3$) : 9.78 (ss, 1H, NH of thiazepine ring), 8.50 (ss, 1H, N=CH), 2.50 (bs, 1H, NH), 6.60-7.70 (m, 10H, Ar-H) (ppm) (Scheme-1).

Compounds 8-16 were prepared by following the method of preparation of compound 7.

Synthesis of 2-(4'-oxo-2'-benzylidenyl thiazolidinonyl)-iminomethyl-1,5-benzothiazepine 17

To the solution of compound 7 (0.01 mole) in methanol (50ml) containing a pinch of $ZnCl_2$ was added thioglycolic acid (0.01 mole) dropwise with constant stirring and refluxed for 10 hours, filtered, concentrated and poured onto ice. The resulting solid was recrystallized with ethanol/water to afford compound 15. Physical and analytical data of compounds 17 to 26 are given in Table-1.M.p. 150^{0}C, yield 70%. IR (KBr; cm^{-1}) : 3340 (NH), 1600 (C=O), 690 (C-S-C), 1510 (C-N of N-CH-Ar group). ^{1}H-NMR ($COCl_3$) : 9.88 (ss, 1H, NH of thiazepine ring), 5.30 (bs, 1H, CH_2NH), 5.83 (s, 1H, CH-Ar), 6.70-7.78 (m, 10H, Ar-H), 2.80 (s, 2H,CH_2S) (ppm) (Scheme-1).

Compounds 18-26 were prepared by following the method of preparation of compound 17.

Synthesis of 2-(4'-oxo-3'chloro-2'-benzylidenyl azetidinonyl)-iminomethyl-1,5-benzothiazepine 27

To the stirred solution of compound 17 (0.01 mole) and trimethylamine (few drops) in DMF (50 ml, dry), was added monochloroacetyl chloride (0.01 mole) at 0-5^{0}C. The reaction mixture was stirred for 30 minutes at room temperature and refluxed for 3 hours. The solid thus obtained after removal of DMF was recrystallized with benzene/petroleum ether to give compound 27. Physical and analytical data of compounds 27 to 36 are given in Table-1.M.p. 185^{0}C, yield 50%. IR (KBr; cm^{-1}) : 3300 (NH), 1610 (C=O), 700 (C-S-C), 1295 (C-N), 680 (C-Cl). ^{1}H-NMR ($COCl_3$) : 9.63 (ss, 1H, NH of thiazepine ring), 5.20 (bs, 1H, CH_2NH), 6.20 (d, J=9Hz,1H, N-CH-Ar), 4.60 (d, J=9Hz,1H, CH-Cl), 6.70-7.76 (m, 10H, Ar-H), 3.20 (d, J=10.65Hz,2H,CH_2NH) (ppm) (Scheme-1).

Compounds 28-36 were prepared by following the method of preparation of compound 27.

Pharmacology

Anti-convulsant activity

Supra maximal electroshock seizure pattern test (SMES)

It was performed according to the method of Toman et al. [22], on albino rats of Charles Foster strain of either sex weighing between 80 and 120 g.

Rats were divided into groups of 10 animals each. Pregnancy was excluded in female rats. The rats were treated with different doses of test drugs or phenytoin sodium 30mg/kg i.p. After 1 hour they were subjected to a shock of 150 M.A. by convulsiometer through ear electrodes for 0.2s and the absence or presence of extensor response was noted. Animals in which extensor response was abolished were taken as abolished were taken as protected rats.

Acute toxicity

The compounds were investigated for their acute toxicity (ALD_{50}) in mice by following the method of Smith [23].The test compounds were given orally at different dose levels in separate groups of animals. After 24 hours of drug administration, percent mortality in each group was observed. ALD_{50} was calculated from the data obtained.

Results

Anti-convulsant activity

In MES test, out of 30 compounds, compounds 18, 23, 26 and 28 were found to be most active with 90%, 80%, 80% and 80% inhibition of seizures respectively. The results are shown in Table 2.

Acute toxicity in mice

All the compounds of this series showed ALD_{50} > 1000 mg/kg i.p. thus suggesting a good safety margin. However, compound 18 exhibited an ALD_{50} > 2000 mg/kg i.p.

Discussion

Anticonvulsant data of the compounds of this series are depicted in Table 2. Out of the compounds tested, compound 18 was found to possess most potential anti-convulsant activity of 90% i.e. more potent than the standard drug phenytoin sodium. Compound 23, 26 and 28 werefound to possess activity equipotent to reference drug. Compounds 18 and 28 were studied in detail at three graded doses of 7.5, 15 and 30 mg/kg i.p. Results are depicted in Table 2. However, almost all the compounds have shown promising anti-convulsant activity, compounds having a phenyl group as substituent i.e. 7, 12, 17, 22, 27 and 32 revealed the least percentage inhibition (ranging between 40% to 50%) of seizures in rats, while compounds having phenyl ring with methoxy group at 4^{th} position 8, 13, 18, 28 and 33 as substituent exhibited maximum activity (ranging between 70% to 90%). Furthermore, compounds having phenyl ring with 3-methoxy, 4-hydroxy group i.e. compounds 9, 14, 19, 24 with 4-N,N-dimethyl group i.e. compounds 10, 15, 20, 25, 30, 35 and with 4-hydroxy group i.e. compounds 11, 16, 21, 26, 31, 36 as substituent showed protection varying between 50% to 80% against MES induced seizures. Thiazolidinones showed an increase in activity as compared to their corresponding azetidinones. It was also noted that benzothiazepines derivatives showed more potent activity as compared to their corresponding benzoxazepine derivatives.

Hence, it can be concluded that:

1. Thiazolidinones 17-26 possess more potent activity than their corresponding azetidinones 27-36.
2. Benzothiazepine containing compounds 7-11, 17-21 and 27-31 showed more potent activity than their corresponding benzoxazepine 12-16, 22-26 and 32-36 containing compounds.
3. Compounds having 4-methoxyphenyl group as substituent elicited the most potent anticonvulsant activity.

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Table 1 : Physical and Analytical Data of Compounds 1-36

Compd. No	X	R	M.P. (^{0}C)	Yield (%)	Recryst. Solvent	Molecular Formula	Elemental Analysis % Calcd. (Found) %		
							C	H	N
1.	S	-	44	80	xylene	$C_{10}H_9NSO$	62.80 (62.78)	4.71 (4.34)	7.32 (6.72)
2.	O	-	75	75	methanol	$C_{10}H_9NO_2$	57.97 (57.95	4.34 (4.30)	6.76 (6.72)
3.	S	-	198	75	xylene	$C_{10}H_8NOBr$	47.24 (47.22)	3.14 (3.16)	5.51 (5.49)
4.	O	-	175	70	DMF	$C_{10}H_8NO_2Br$	47.24 (47.22)	3.14 (3.16)	5.51 (5.49)
5.	S	-	160	70	ethanol	$C_{10}H_{11}N_3SO$	54.29 (54.26)	4.97 (4.94)	19.00 (19.04)
6.	O	-	160	70	ethanol	$C_{10}H_{11}N_3O_2$	58.53 (58.50)	5.36 (5.38)	20.48 (20.50)
7.	S	H	228	70	methanol	$C_{17}H_{15}N_3SO$	66.01 (66.04)	4.85 (4.82)	13.59 (13.55)
8.	S	4-OCH_3	220	60	methanol	$C_{18}H_{17}N_3SO_2$	63.71 (63.68)	5.01 (5.00)	12.38 (12.36)
9.	S	4-OCH_3, 4-OH	235	65	ethanol	$C_{18}H_{17}N_3SO_3$	60.84 (64.54)	4.78 (4.81)	11.83 (11.85)
10.	S	4-$N(CH_3)_2$	250	56	ethanol	$C_{19}H_{21}N_4SO$	64.58 (64.54)	5.94 (5.97)	15.86 (15.87)
11.	S	4-OH	240	65	ethanol	$C_{17}H_{15}N_3SO_2$	62.76 (62.72)	4.61 (4.59)	12.92 (12.90)
12.	O	H	220	60	acetone	$C_{17}H_{15}N_3O_2$	69.62 (69.60)	5.11 (5.09)	14.33 (14.32)
13.	O	4-OCH_3	240	70	benzene	$C_{18}H_{17}N_3O_3$	66.87 (66.90)	5.26 (5.29)	13.00 (13.03)
14.	O	4-OCH_3, 4-OH	250	65	acetone	$C_{18}H_{17}N_3O_4$	63.71 (63.69)	5.01 (5.00)	12.38 (12.40)
15.	O	4-$N(CH_3)_2$	220	68	benzene	$C_{19}H_{21}N_4O_2$	67.65 (67.61)	6.23 (6.25)	16.61 (16.59)
16.	O	4-OH	245	64	acetone	$C_{17}H_{15}N_3O_3$	66.01 (66.00)	4.85 (4.83)	13.59 (13.61)
17.	S	H	150	70	ethanol	$C_{20}H_{19}N_3O_2S$	65.67 (65.70)	5.20 (5.18)	51.10 (51.08)

18.	S	4-OCH_3	190	60	ethanol	$C_{21}H_{21}N_3O_3S$	82.95 (82.93)	5.31 (5.29)	10.63 (10.60)
19.	S	4-OCH_3, 4-OH	180	75	acetone	$C_{21}H_{21}N_3O_4S$	61.31 (61.29)	5.10 (5.08)	10.21 (10.19)
20.	S	4-$N(CH_3)_2$	115	73	ethanol	$C_{22}H_{24}N_4O_2S$	64.70 (64.68)	5.88 (5.90)	57.12 (57.09)
21.	S	4-OH	190	68	ethanol	$C_{20}H_{19}N_3O_3S$	62.99 (63.00)	4.98 (5.00)	11.02 (11.00)
22.	O	H	205	50	methanol	$C_{20}H_{19}N_3O_3$	68.76 (68.74)	5.44 (5.42)	12.03 (12.00)
23.	O	4-OCH_3	200	55	Ethanol	$C_{21}H_{21}N_3O_4$	66.14 (66.12)	5.51 (5.49)	11.02 (11.00)
24.	O	4-OCH_3, 4-OH	225	60	Acetone	$C_{21}H_{21}N_3O_5$	63.79 (63.81)	5.31 (5.29)	10.63 (10.60)
25.	O	4-$N(CH_3)_2$	250	65	Ethanol	$C_{22}H_{24}N_4O_3$	67.34 (67.31)	6.12 (6.09)	14.28 (14.31)
26.	O	4-OH	210	56	acetone	$C_{20}H_{19}N_3O_4$	65.75 (65.78)	5.20 (5.18)	11.50 (11.48)
27.	S	H	185	50	benzene	$C_{19}H_{16}N_3O_2SCl$	59.14 (59.11)	4.15 (4.13)	10.89 (10.91)
28.	S	4-OCH_3	175	45	methanol	$C_{20}H_{18}N_3O_3SCl$	56.14 (56.12	4.21 (4.19)	9.82 (9.79)
29.	S	4-OCH_3, 4-OH	160	52	benzene	$C_{20}H_{18}N_3O_4SCl$	55.61 (55.59)	4.17 (4.20)	9.73 (9.69)
30.	S	4-$N(CH_3)_2$	120	55	DMF	$C_{21}H_{21}N_4O_2SCl$	58.80 (58.78	4.90 (4.87)	13.06 (13.08)
31.	S	4-OH	140	48	acetone	$C_{19}H_{16}N_3O_3SCl$	56.78 (56.60)	3.98 (4.00)	10.46 (10.48)
32.	O	H	120	56	ethanol	$C_{19}H_{16}N_3O_3Cl$	57.57 (57.60)	4.79 (4.81)	12.59 (12.61)
33.	O	4-OCH_3	150	55	methanol	$C_{20}H_{18}N_3O_4Cl$	60.07 (60.05)	4.50 (4.49)	10.51 (10.48)
34.	O	4-OCH_3, 4-OH	135	48	benzene	$C_{20}H_{18}N_3O_5Cl$	60.64 (60.62)	4.33 (4.35)	10.10 (10.09)
35.	O	4-$N(CH_3)_2$	140	45	acetone	$C_{21}H_{21}N_4O_3Cl$	61.09 (61.11)	5.09 (5.11)	13.57 (13.60)
36.	O	4-OH	155	52	methanol	$C_{19}H_{16}N_3O_4Cl$	59.11 (59.11)	4.15 (4.16)	14.52 (14.49)

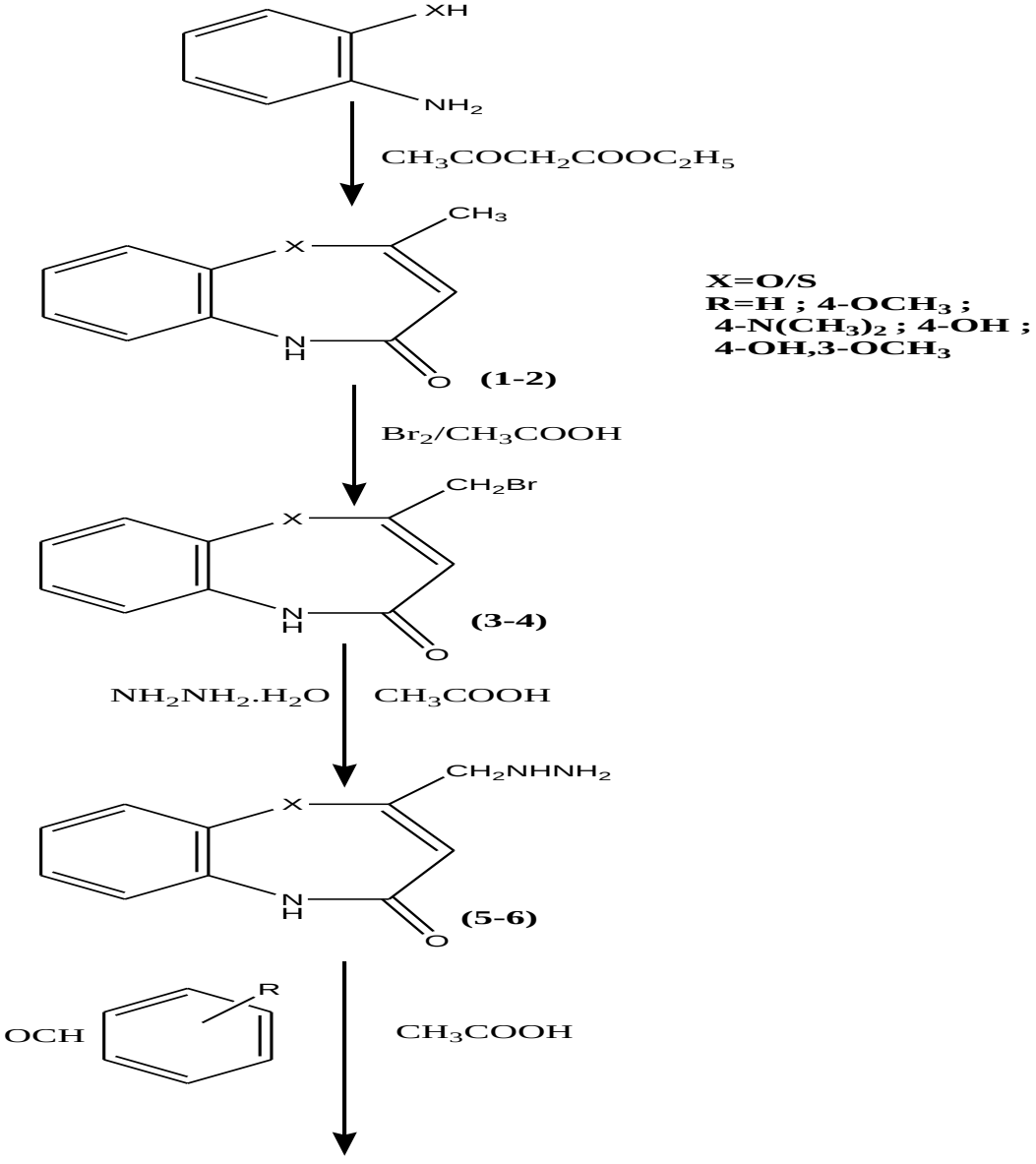
C , H , N were found within ±0.4%

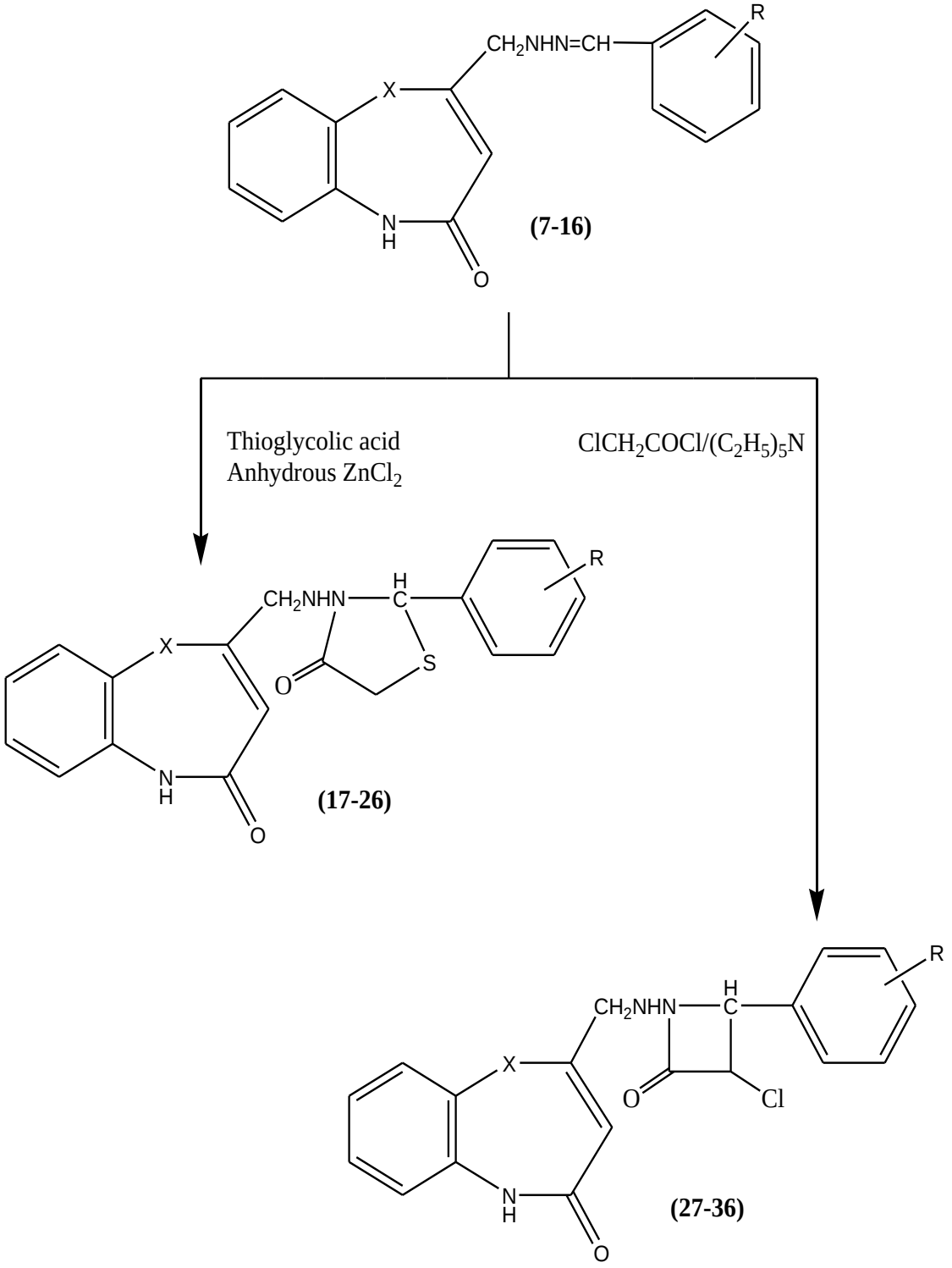
Table 2 : Pharmacological Data of Compound 7-36

Compound No.	Acute Toxicity ALD_{50} (mg/kg i.p.)	Anticonvulsant Activity	
		Dose (mg/kg i.p.)	% inhibition of seizures
7.	>1000	30	40**
8.	>1000	30	70**
9.	>1000	30	50**
10.	>1000	30	60**
11.	>1000	30	50**
12.	>1000	30	40**
13.	>1000	30	70**
14.	>1000	30	40**
15.	>1000	30	50**
16.	>1000	30	60**
17.	>1000	30	50**
18.	>2000	7.5 15 30	20 60** 90***
19.	>1000	30	70**
20.	>1000	30	60**
21.	>1000	30	70**
22.	>1000	30	50**
23.	>1000	30	80***
24.	>1000	30	60**

25.	>1000	30	60**
26.	>1000	30	80***
27.	>1000	30	50**
28.	>2000	7.5 15 30	0 60** 80***
29.	>1000	30	70**
30.	>1000	30	70**
31.	>1000	30	70**
32.	>1000	30	50**
33.	>1000	30	70**
34.	>1000	30	70**
35.	>1000	30	60**
36.	>1000	30	60**
Phenytoin Sodium		30	80***
Propylene Glycol		2ml	0

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




R
CH2NHN=CH
X
N
H
O
(7-16)
Thioglycolic acid
Anhydrous ZnCl2
ClCH2COCl/(C2H5)5N
R
H
CH2NHN
C
X
O
S
N
H
O
(17-26)
R
H
CH2NHN
C
X
O
Cl
N
H
O
(27-36)

SCHEME-1