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Synthesis and evaluation of some newerthiazolidinonyl substituted quinazolinones as potent anticonvulsant agents

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Abstract : A new series of 3-(Aminoacetylthiosemicarbazido)-2-methyl mono substituted quinazolin-4(3H)-ones(3-4),3-(Aminoacetyl thiosemicarbazido substituted arylidene)-2-methyl monosubstituted-quinazolin-4(3H)-ones (5-14) and 3-[3'-(Amino acetyl thiosemicardazido)-4'-oxo-2'-(substitutedaryl)-1'-thiazolidinonyl]-2-methyl mono substitute dquinazolinones (15-24) were synthesised and evaluated for anticonvulsant activity. All these compounds were screened in vivo, for their anticonvulsant activity and acute toxicity. Compound **22**,3-[3'-(Amino acetyl thiosemicardazido)-4'-oxo-2'-(3-methoxy-4hydroxy arylidene)-1'-thiazolidinonyl]-2-methyl-6-bromoquinazolinones, was found to be most potent compound of this series, more potent (exhibiting 90%protection) than standard drug phenytoin sodium (having 80% protection). The homogeneity of all the compounds have been established by elemental analysis, IR and ^{1}H-NMR spectroscopy.
Keywords : Thiazolidinones, quinazolinones, anticonvulsant activity, acute toxicity.

Introduction

Epilepsy is all-prevailing disease characterized by intermittent seizures and inflicts more than 60 million people worldwide according to epidemiological studies[1-3]. Every year approximately 250000 new cases are added to this figure. It is roughly estimated that 28-30% of patients are resistant to the available medical therapies. Despite the development of several new anticonvulsants[4-5], the treatment of epilepsy remain still inadequate, and the patients suffer from a lot of specific problems like neurotoxicity, depression and other CNS related diseases. Although several new anticonvulsants are already in clinical use, some types of seizures are still not adequately treated with current therapy and have limitations along with intolerable side effects. In response to these limitations, the development of new drugs to optimally manage seizures has been advocated. Thus, the search for new anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry[6].

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Methaqualone[7] [2-methyl-3(o-tolyl)-4-(3H)-quinazolinone], a sedative and hypnotic drug has been reported to possess anticonvulsant activity. Significane is that this compound possessed the potent pharmacodynamic nucleus i.e. quinazolinone. In addition the chemistry and pharmacology of quinazolinone have been of great interest to medicinal chemists because quinazolinone derivatives possessed various biological activities, such as anticonvulsant[8-16], antibacterial[17], CNS[18-19] and anti-inflammatory[20-23]. Moreover, literature survey reveals that compounds containing thiazolidinone[24-29] nucleus make up a broad class that attracted attention in the past few years owing to its wide range of activities especially anticonvulsant and CNS depressant activities. These findings prompted our interest to incorporate quinazolinone and thiazolidinone in a single molecular frame with the hope to get better anticonvulsant agent as both these pharmachore possess anticonvulsant activity.

Materials and Methods

The melting points are uncorrected. Carbon, hydrogen and nitrogen analysis were performed on CHN, Carlo Erba 1108, Heracus, at Central Drug Research Institute (Lucknow). Analysis (C,H, N) were within ± 0.04% of the theoretical values. The spectra were recorded on Beckman Acculab-10 spectrophotometer (υ_{max} in cm^{-1}). The ^{1}H-NMR spectra were recorded in $CDCL_3$ ON ABrucker 400-FT instrument. The homogeneity of all the compounds was checked by using silica gel- G plates.

Synthesis of 3-(Chloroacetyl amino)-2-methyl-quinazolin-4(3H)-one (1) :

Chloroacetyl chloride (0.02 mole) was added to a well stirred solution of 3- amino-2-methyl quinazolin-4(3H)-one (0.01 mole) in chloroform (dry 50ml), drop by drop at 0-5^{0}C during 1 hour. Reaction mixture was then stirred for 2 hours at room temperature and then refluxed for 4 hours, concentrated, cooled and poured onto ice. The solid thus separated out was filtered and recrystallised from ethanol/ water to obtain compound 1.M.P. 208-210^{0}C, Yield 80%. IR (KBr, cm^{-1}): 3250 (NH), 2960 (CH_2), 2920 (methyl C-H stretch), 1668 (C=O of quinazolinone ring), 680 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 8.80 (brs, 1H, NHCO), 7.20-6.10 (m, 4H, Ar-H), 3.40 (s, 2H, -CH_2Cl), 2.15 (s, 3H, CH_3) (ppm). MS: $[M]^+$ m/z 251.(Scheme 1).

Other compounds of this step were also prepared similarly. Their physical and analytical data are given in Table 1.

Table 1: Physical and analytical data of compounds 1-24

Compd. No.	X	R	M.P. (^{0}C)	Yield (%)	Recrystallis -ation Solvent	Molecular Formula	Elemental Analysis					
							C Calcd .Found		H Calcd.Found		N Calcd.Found	
1	H	-	210	80	ethanol	$C_{11}H_{10}O_2N_3Cl$	52.48	52.52	3.97	3.95	16.69	16.72
2	6-Br	-	225	70	ethanol	$C_{11}H_9O_2N_3BrCl$	39.93	39.95	2.72	2.75	12.70	12.74
3	H	-	120	75	ethanol	$C_{12}H_{14}O_2N_6S$	47.05	47.03	4.57	4.60	27.45	27.43
4	6-Br	-	210	68	ethanol	$C_{12}H_{13}O_2N_6SBr$	37.40	37.44	3.37	3.35	21.81	21.83
5	H	H	140	60	DMF	$C_{19}H_{18}O_2N_6S$	57.86	57.88	4.56	4.52	21.31	21.35
6	H	4-OCH_3	130	55	DMF	$C_{20}H_{20}O_3N_6S$	56.60	56.64	4.71	4.74	19.81	19.84
7	H	3-OCH_3, 4-OH	150	62	benzene	$C_{20}H_{20}O_4N_6S$	54.54	54.56	4.54	4.58	19.09	19.12
8	H	4-$N(CH_3)_2$	100	52	methanol	$C_{21}H_{23}O_2N_7S$	57.66	57.62	5.26	5.30	22.42	22.40
9	H	4-OH	110	55	methanol	$C_{19}H_{18}O_3N_6S$	55.60	55.64	4.39	4.35	20.48	20.52
10	6-Br	H	170	50	pet.ether	$C_{19}H_{17}O_2N_6SBr$	48.2048.23		3.59	3.57	17.75	17.78
11	6-Br	4-OCH_3	180	50	benzene	$C_{20}H_{19}O_3N_6SBr$	47.71	47.74	3.77	3.74	16.69	16.72
12	6-Br	3-OCH_3, 4-OH	160	52	benzene	$C_{20}H_{19}O_4N_6SBr$	46.24	46.20	3.66	3.62	16.18	16.20
13	6-Br	4-$N(CH_3)_2$	200	55	ethanol	$C_{21}H_{22}O_2N_7SBr$	48.83	48.80	4.26	4.30	18.99	18.95
14	6-Br	4-OH	120	55	ethanol	$C_{19}H_{17}O_3N_6SBr$	46.62	46.60	3.47	3.43	17.17	17.20
15	H	H	180	50	DMF	$C_{21}H_{20}O_3N_6S_2$	53.84	53.88	4.27	4.25	17.94	17.97
16	H	4-OCH_3	150	50	methanol	$C_{22}H_{22}O_4N_6S_2$	53.01	53.05	4.41	4.45	16.86	16.90
17	H	3-OCH_3, 4-OH	170	58	methanol	$C_{22}H_{22}O_5N_6S_2$	51.36	51.40	4.28	4.30	16.34	16.38
18	H	4-$N(CH_3)_2$	120	48	benzene	$C_{23}H_{25}O_3N_7S_2$	54.01	54.04	4.89	4.93	19.17	19.21
19	H	4-OH	130	50	DMF	$C_{21}H_{20}O_4N_6S_2$	52.06	52.09	4.13	4.16	17.35	17.32
20	6-Br	H	162	48	methanol	$C_{21}H_{19}O_3N_6S_2Br$	46.06	46.02	3.47	3.51	15.35	15.38
21	6-Br	4-OCH_3	198	45	DMF	$C_{22}H_{21}O_4N_6S_2Br$	45.75	45.78	3.63	3.67	14.55	14.58

22	6-Br	3-OCH_3, 4-OH	178	50	acetone	$C_{22}H_{21}O_5N_6S_2Br$	44.51	44.53	3.54	3.57	14.16	14.20
23	6-Br	4-$N(CH_3)_2$	165	50	benzene	$C_{23}H_{24}O_3N_7S_2Br$	46.77	46.73	4.06	4.04	16.61	16.65
24	6-Br	4-OH	185	52	DMF	$C_{21}H_{19}O_4N_6S_2Br$	44.76	44.72	3.37	3.40	14.92	14.90

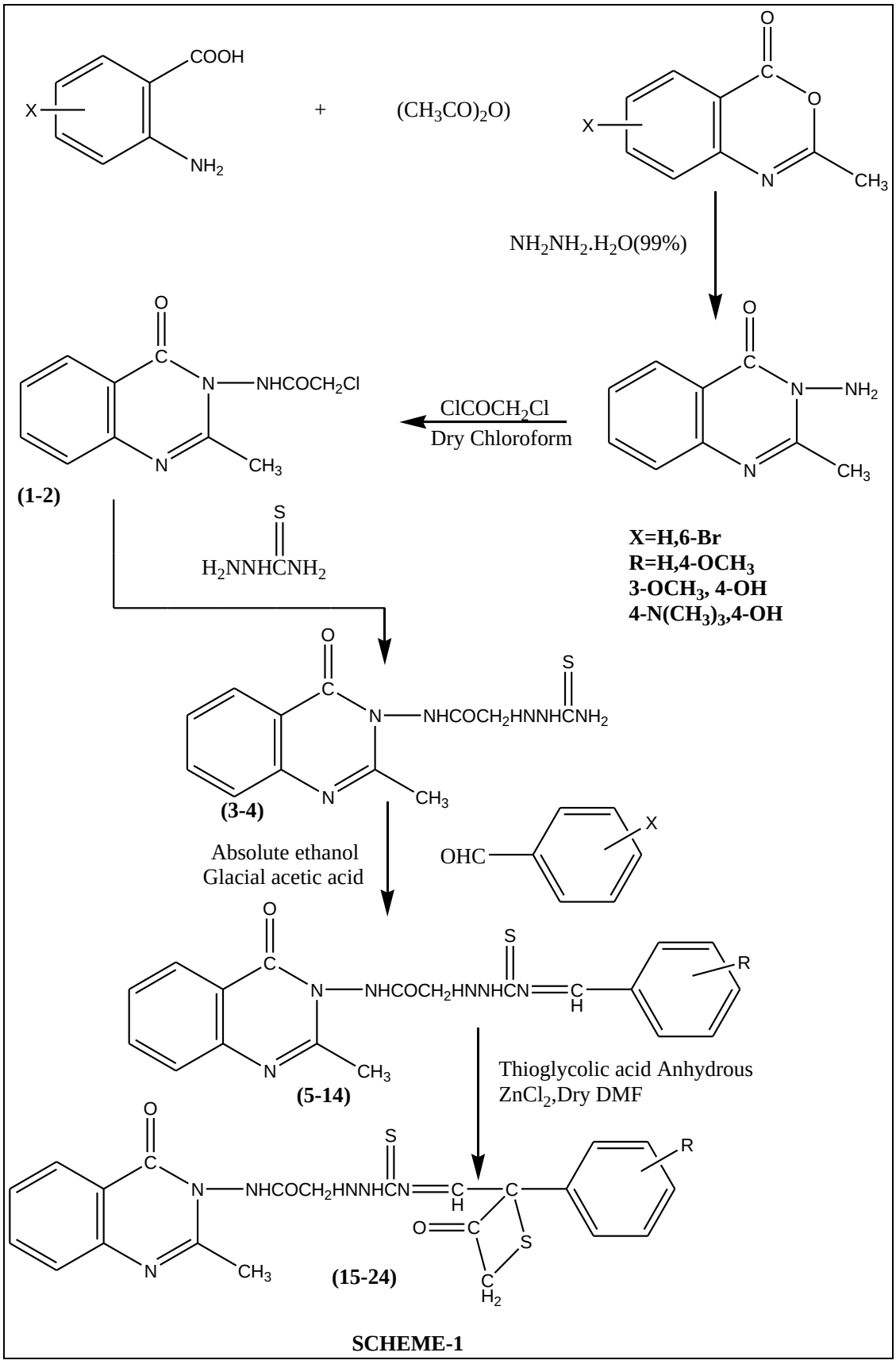
Synthesis of 3- (Aminoacetylthiosemicarbazido)-2-methyl quinazolin-4(3H)-ones (3) :

Thiosemicarbazide (0.01 mole) and compound 1, 3-(Chloroacetyl amino)-2-methyl-quinazolin-4(3H)-one (0.01 mole) in methanol (80 ml) were refluxed on a steam bath for 6 hours. The excess of the solvent was distilled off and the viscous mass is poured onto ice cold water, filtered and recrystallised from ethanol/ water to afford compound 3. M. P. 120^0C, Yield 75%. IR (KBr, cm^{-1}): 3340 (NH_2), 3050 (aromatic C-H), 2962 (CH_2), 1660 (C=O), 1565 (C-C of aromatic ring), 1190 (C=S). ^{1}H-NMR ($CDCl_3$) δ: 8.90 (brs, 1H, NHCO), 8.32 (complex m, 4H, $NHNHCSNH_2$), 7.50-6.60 (m, 4H, Ar-H), 4.75 (s, 2H, $COCH_2$), 2.25 (s, 3H, CH_3) (ppm). MS: $[M]^+$ m/z 306.(Scheme 1).

Other compounds of this step were also prepared similarly. Their physical and analytical data are given in Table 1.

Synthesis of 3- (Amino acetyl thiosemicarbazidoarylidene)-2-methyl quinazolin-4(3H)-ones (5) :

A mixture of compound 3, 3- (Aminoacetylthiosemicarbazido)-2-methyl quinazolin-4(3H)-ones (0.01 mole) in absolute ethanol, few drops of glacial acetic acid and benzaldehyde (0.01 mole) were refluxed for 6-8 hours. The excess of the solvent was distilled off and the reaction mixture was poured onto ice cold water, filtered and recrystallised from DMR/ water to obtain compound 5. M.P. 140^0C , Yield 60%. IR (KBr, cm^{-1}): 3283 (NH), 3050 (aromatic C-H), 2918 (methyl C-H stretch), 2845 (CH_2), 1650 (C=O of NHCO), 1600 (C=N), 1560 (C-C of aromatic ring), 1180 (C=S). ^{1}H-NMR ($CDCl_3$) δ: 8.90 (brs, 1H, NHCO), 8.60 (s, 1H, -N=CH), 7.90-7.40 (complex m, 8H, Ar-H), 6.90 (brs, 2H, 2 X NH), 4.70 (s, 2H, $COCH_2$), 2.30 (s, 3H, CH_3) (ppm). MS: $[M]^+$ m/z 394.(Scheme 1).



SCHEME-1

Other compounds of this step were also prepared similarly. Their physical and analytical data are given in Table 1.

Synthesis of 3-[3'-(Amino acetyl thiosemicardazido)-4'-oxo-2'-(aryl)-1'-thiazolidinonyl]-2-methyl quinazolinone (15) :

A stirred solution of compound 5, 3- (Amino acetyl thiosemicarbazidoarylidene)-2-methyl quinazolin-4(3H)-ones (5)(0.01mole) in dry DMF, containing a pinch of anhydrous $ZnCl_2$ and thioglycolic acid (0.02 mole) were refluxed for 8 hours. Excess of solvent was distilled off, then the reaction mixture was cooled and poured into ice cold water. The separated solid was filtered , washed and recrystallised from DMF/water to give compound 15. M. P. 180^0 C, Yield 50%. IR (KBr, cm^{-1}): 3200 (NH), 3040 (aromatic C-H), 2850 (CH_2 of thiazolidinone ring), 1760 (C=O of β- thialactam ring), 1670 (C=O of NHCO), 1590 (C-N), 1563 (C-C of aromatic ring), 1170 (C=S), 1140 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.50 brs, 1H, NHCO), 8.10- 7.35 (m, 8H, Ar-H), 6.70 (brs, 2H, 2 X NH), 5.54 (s, 1H, -CH-Ar), 4.72 (d, 2H, $COCH_2$), 3.65 (s, 2H, CH_2 of thiazolidinone ring), 2.15 (s, 3H, CH_3) (ppm). MS: $[M]^+$ m/z 468.(Scheme 1).

Other compounds of this step were also prepared similarly. Their physical and analytical data are given in Table 1.

Pharmacology

Anticonvulsant activity- Maximal Electroshock Seizure Test:

In MES test, rats receive an electrical stimulus of sufficient intensity to induce maximal seizures of their hind limbs (a stimulus about 5-10 times higher than the individual electrical seizures threshold of animals, in order to avoid bias in the induction of tonic seizures due to daily fluctuations in seizure threshold). MES stimulation can be applied through ear electrode using convulsiometer. The test will be considered positive if the animal exhibits tonic extensor seizure for more than 3s following 10 s after stimulation. Only animals that exhibit MES, while unmedicated , should be used.

The anticonvulsant activity was performed according to the method of Toman[30]et al on Charles Foster rats of either sex weighing , between 80-120 g. Rats were divided into groups of ten animals each. Pregnancy was excluded in female rats. The rats were treated with different doses of test drugs or phenytoin sodium 30 mg/kg i.p. After 1h they were subjected to a shock of 150 mA 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. The results are depicted in Table 2.

Table 2: Anticonvulsant activity of compounds 1-24

Compd. No.	X	R	Dose(mg/kg i.p.) In MES model	Anticonvulsant activity: No.of animals exhibiting convulsions in MES model	Anticonvulsant activity: % seizure protection in MES model	ALD_{50} (mg/kg i.p.)
P.G.[a]			2.0 ml	10	0	
Phenyt-oin sodium[b]			7.5	9	10	
			15	6	40*	
			30	2	80***	
1	H	-	30	8	20	>1000
2	6-Br	-	30	6	40	>1000
3	H	-	30	5	50*	>1000
4	6-Br	-	30	6	40	>1000
5	H	H	30	5	50*	>1000
6	H	4-OCH_3	30	3	70**	>1000
7	H	3-OCH_3, 4-OH	30	3	70**	>1000
8	H	4-$N(CH_3)_2$	30	4	60*	>1000
9	H	4-OH	30	4	60**	>1000
10	6-Br	H	30	4	60**	>1000

11	6-Br	4-OCH_3	30	3	70^{**}	>1000
12	6-Br	3-OCH_3,	7.5	9	10	
		4-OH	15	6	40	>1000
			30	2	80^{**}	
13	6-Br	4-$N(CH_3)_2$	30	3	70^{**}	>1000
14	6-Br	4-OH	30	3	70^{**}	>1000
15	H	H	30	4	60^{**}	>1000
16	H	4-OCH_3	30	3	70^{**}	>1000
17	H	3-OCH_3,	30	2	80^{**}	>1000
		4-OH				
18	H	4-$N(CH_3)_2$	30	2	80^{***}	>1000
19	H	4-OH	30	3	70^{**}	
20	6-Br	H	30	3	70^{**}	>1000
21	6-Br	4-OCH_3	30	2	80^{***}	>1000
22	6-Br	3-OCH_3 ,	7.5	8	20	
		4-OH	15	5	50^{*}	>2000
			30	1	90^{***}	
23	6-Br	4-$N(CH_3)_2$	30	2	80^{***}	>1000
24	6-Br	4-0H	30	2	80^{***}	>1000

$^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

[a]P.G. = Propylene Glycol standard for control group

[b]Phenytoin Sodium = reference standard for control group for anticonvulsant activity (MES model)

Acute toxicity

The compounds were also investigated for their acute toxicity (ALD_{50}) in mice by following the method of Smith[31] and the results are depicted in Table 2.

Results and Discussion

All the newly synthesized compounds were tested in vivo in order to screen them for their anticonvulsant activity . The pharmacological data of all the compounds of this series have been reported in table 1. Newly synthesized compounds were evaluated for anticonvulsant activity at a dose of 30 mg/kg i.p. and were found to exhibit substantive anticonvulsant activity ranging from 20% to 90% and were found statistically significant. All these compounds were compared with standard drug phenytoin sodium.

Compounds (1-2) (Table 2) exhibited lower degree of anticonvulsant activity varying from 20% to 40%. The next stage compounds i.e. compounds (3 and 4) afforded mild anticonvulsant activity of 40% and 50% respectively. As we proceed further i.e. compounds (5-14) (table 1) an increase in anticonvulsant activity(varying between 50% to 80%) was noticed. While evaluating the anticonvulsant activity, it as observed that compounds having 3-amino-2-methyl-6-bromoquinazolin-4(3H)-onyl moiety showed more protection in comparison to compounds having 3-amino-2-methylquinazolin-4(3H)-onyl moiety. All the compounds (5-14) (table 2) exhibited promising anticonvulsant activity. It was observed that compounds having phenyl group compound (5 and 10) as substituent showed least activity (50% and 60% respectively) while compounds (7 and 12) substituted with 3-methoxy-4-hydroxy phenyl ring exhibited maximum percent protection (70% and 80% respectively) against seizures induced by maximal electroshock (MES). Compounds substituted with 4-methoxy phenyl group (6 and 11) exhibited 70% inhibition of seizures. Compounds having 4-hydroxy phenyl group also elicited remarkable anticonvulsant activity of 60% (compound 9) and 70% (compound 14). Similarly compounds having 4-N,N-dimethyl phenyl group also showed same percentage protection of seizures i.e. 60% (compound 8) and 70% (compound 13).Taking into consideration the newly synthesized compounds of this step, it may be concluded that substitution with 3-methoxy-4-hydroxyphenyl group is beneficial for anticonvulsant activity.

Further, the next step of the series was characterized by the presence of a thiazolidinone(β-thialactam) ring in addition. All compounds (15-24)(table 2) showed potent anticonvulsant activity, however, compound (17 and 22) substituted with 3-methoxy-4-hydroxyphenyl group have shown most potent activity of 80% and 90% respectively i.e. equipotent and more potent than standard drug phenytoin sodium. Compounds (15 and 20) having phenyl ring showed 60% and 70% protection respectively whereas compounds (16 and 21) having 4-methoxy phenyl group exhibited 70% and 80% protection respectively. Compounds with 4-hydroxyphenyl group (19 and 24) have also shown remarkable percentage protection of 70% and 80% respectively. 80% protection was exhibited by the compounds substituted with 4-N,N-dimethylphenyl group against seizures induced by maximal electroshock (MES).

Therefore, considering the compounds of this step, it may be concluded that when the β-thialactam ring is substituted with 3-methoxy-4-hydroxyphenyl group, then it showed promising anticonvulsant activity. Table 2 shows the anticonvulsant activity of compounds 12, 22 and standard drug phenytoin sodium at three graded doses of 7.5, 15 and 30 mg/kg i.p. in MES models. Interestingly, at all the three doses compound 12 exhibited activity equipotent to standard drug phenytoin sodium. Compound 22 was found to exhibitmore potent activity than phenytoin sodium at all the three dose levels.

The compounds of this series were also evaluated for acute toxicity . All the compounds (1-24) tested showed ALD_{50} greater than 1000 mg/kg i.p. except the most potent compound of this series i. e. compound 22, which elicited ALD_{50} greater than 2000 mg/kg i.p. thereby suggesting a good safety margin.

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