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Original article

Synthesis of newer thiadiazolyl and thiazolidinonyl quinazolin-4(3*H*)-ones as potential anticonvulsant agents

Archana [1], V.K. Srivastava, Ashok Kumar *

Medicinal Chemistry Division, Department of Pharmacology, L.L.R.M. Medical College, Meerut, UP 250004, India

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Abstract

A series of 3-{[5-(alkylbenzylideneamino)-1,3,4-thiadiazol-2-yl]methylamino}-2-methyl-6-monosubstitutedquinazolin-4(3*H*)-one (**4a**–**4l**) have been synthesized via condensation of 3-[(5-amino-1,3,4-thiadiazol-2-yl)methylamino]-2-methyl-6-monosubstitutedquinazolin-4(3*H*)-one (**3a**–**3b**) with various aromatic aldehydes. Cycloaddition of thioglycolic acid with **4a**–**4l** yielded 3-({4-[2-(alkylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-monosubstitutedquinazolin-4(3*H*)-one (**5a**–**5l**). The compounds were screened for their anticonvulsant activity and were compared with the standard drugs, phenytoin sodium, lamotrigine and sodium valproate. Out of the 30 compounds the most active compound was 3-({4-[2-(m-methoxy-*p*-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-bromo-quinazolin-4(3*H*)-one (**5l**).

Keywords: Thiadiazolyl quinazolin-4(3*H*)-ones; Thiadiazolyl thiazolidinonyl quinazo-lin-4(3*H*)-ones; Anticonvulsant activity; Acute toxicity

1. Introduction

Quinazolinone derivatives [1–4] substituted by different heterocyclic moieties at 3rd position of this heterocyclic system have been reported to exhibit anticonvulsant property. Several of these three-heterocyclic substituted quinazolinones show a high level of protection against maximal electroshock (MES) induced convulsions in animal models. Thiadiazoles [5–8] have been observed to exhibit anticonvulsant properties in experimentally MES convulsions. Similarly, substituted thiazolidinones [9–12] have been found to show anticonvulsant effect in various experimental models. However, these compounds have not been in clinical use as they possess either less activity or more side effects.

Incorporating these moieties in 3rd position of quinazolinone nucleus might be thought to yield more potent anticonvulsant compound as substituted moieties are themselves anticonvulsant and substitution at 3rd position further results in protection against convulsions. Thus, the substitution by these moieties may be synergistic. The present project is therefore, aimed at synthesizing such compounds.

2. Chemistry

The synthetic routes of compounds are outlined in Fig. 1. Reaction of ethyl chloroacetate with 3-amino-2-methyl-6-mono-substitutedquinazolin-4(3*H*)-ones yielded *N*-(3,4-dihydro-2-methyl-4-oxo-6-monosubstitutedquinazolin-3-yl)glycynate d'ethyle i.e. compound **1a**–**1b**, which on reaction with thiosemicarbazide resulted in the formation of 1-[*N*-3,4-dihydro-2-methyl-4-oxo-6-monosubstitutedquinazolin-3-yl) glycyl]-thiosemicarbazide **2a**–**2b**. Compounds **2a**–**2b** on dehydrative cyclisation by conc. H_2SO_4 furnished the thiadiazole **3a**–**3b**, which on condensation with various aromatic aldehydes afforded compounds **4a**–**4l**. Addition of thioglycolic acid followed by cyclisation in compounds **4a**–**4l** introduced the thiazolidinone moiety in these compounds to 3-({4-[2-(alkylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-monosubstitutedquinazolin-4(3*H*)-one (**5a**–**5l**).

* Correspondence and reprints
E-mail address: rajput_ak@indiatimes.com (A. Kumar).
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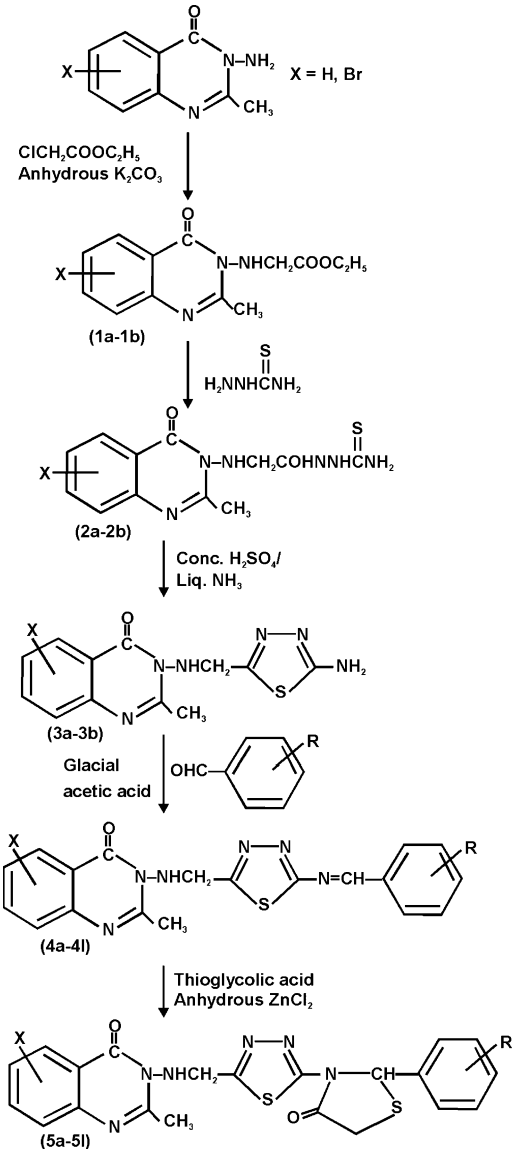

Fig. 1. Route for the synthesis of compounds.

Appearance of a sharp singlet between 9.60 and 9.61 for one-proton of NHCH_2, a doublet between 4.28 and 4.30 for two-protons of NHCH_2, a triplet between 1.20 and 1.27 for three-protons of $COOCH_2CH_3$ and a quartet between 4.10 and 4.12 for two-protons of $COOCH_2CH_3$ in the ^{1}H-NMR of **1a**–**1b** confirmed their formation. Appearance of a band between 1130 and 1135 cm^{-1} (>C=S) in the IR spectrum of compounds **2a**–**2b** and disappearance of a triplet between 1.20 and 1.27 for three-protons of $COOCH_2CH_3$ and a quartet between 4.10 and 4.12 for two-protons of $COOCH_2CH_3$ with the appearance of a multiplet between 8.50 and 8.65 for four-protons of NHNHCSNH_2 in the ^{1}H-NMR spectrum supported their formation. Cyclisation of compounds **2a**–**2b** resulted into compounds **3a**–**3b** which was confirmed by the presence of a band between 680 and 690 cm^{-1} (C–S–C) in the IR spectrum. Further, their formation was supported by the absence of a multiplet between 8.50 and 8.65 (4H, NHNHCSNH_2) and by the presence of a singlet between 8.45 and 8.60 (2H, NH_2) in the ^{1}H-NMR spectrum. Appearance of a singlet between 8.20 and 8.45 and disappearance between 8.50 and 8.60 for one-proton of N=CH–Ar and two-protons of NH_2 in the ^{1}H-NMR spectrum of compounds **4a**–**4l** confirmed the synthesis of these compounds. Compounds **5a**–**5l** exhibited a band between 1738 and 1766 cm^{-1} (C=O of β-thialactam moiety) in the IR spectrum and a singlet between 3.60 and 3.70 dueto two-protons of CH_2 of β-thialactam ring in the ^{1}H-NMR spectrum which confirmed their synthesis.

3. Pharmacological results and discussion

All new compounds were tested in vivo in order to evaluate their anticonvulsant activity at a dose of 30 mg kg^{-1} i.p. The anticonvulsant effects of all the compounds of this series have been reported in Tables 1–3.

The characteristic feature of this series is the presence of a five-membered thiadiazole ring at the 3rd position of 3-amino-2-methyl-6-monosubstitutedquinazolin-4(3H)-onyl moieties which were further substituted with alkyl benzylidenyl groups at the 2nd position of five-membered thiadiazole ring. While evaluating the anticonvulsant activity, it was 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 **4a**–**4l** exhibited promising anticonvulsant activity. It was observed that compounds having phenyl group (compounds **4a** and **4g**) as substituent showed least activity (50 and 60%, respectively) while compounds (**4f** and **4l**) substituted with 3-methoxy-4-hydroxy phenyl ring exhibited the maximum percent protection (70 and 80%, respectively) against seizures induced by MES. Compounds substituted with 4-methoxyphenyl group (**4b** and **4h**) and 3-methoxyphenyl group (**4c** and **4i**) exhibited 60 and 70% inhibition of seizures, respectively. Compounds having 4-hydroxy phenyl group also elicited remarkable anticonvulsant activity of 60 (**4d**) and 70% (**4j**). Similarly compounds having 4-*N*,*N*-dimethylphenyl group also showed same percentage protection of seizures i.e. 60 (**4e**) and 70% (**4k**).

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 characterised by the presence of a thiazolidinone (β-thialactam) ring in addition to thiadiazole ring. All compounds showed potent anticonvulsant activity, however, compounds **5f**

Table 1
Characterisation data and anticonvulsant activity of compounds **1a**–**1b**, **2a**–**2b** and **3a**–**3b**

Compound	X	M.p. (°C)	Yield (%)	Recrystallisation solvent	Molecular formula	Molecular weight [a]	Anti-convulsant activity (% inhibition)	ALD_{50} (mg kg^{-1} i.p. maximum dose tested)
1a	H	120–121	60	Methanol–water	$C_{13}H_{15}N_3O_3$	261	20	> 1000
1b	6-Br	160–162	65	Methanol–water	$C_{13}H_{14}BrN_3O_3$	340	30	> 1000
2a	H	118–120	70	Benzene–petroleum ether	$C_{12}H_{14}N_6O_2S$	306	30	> 1000
2b	6-Br	95–96	68	Benzene–petroleum ether	$C_{12}H_{13}BrN_6O_2S$	385	50	> 1000
3a	H	169–170	65	Methanol–water	$C_{12}H_{12}N_6OS$	288	40	> 1000
3b	6-Br	140–142	68	Methanol–water	$C_{12}H_{11}N_6BrOS$	367	50	> 1000
	P.G. [c]						0	
	Phenytoin sodium [d]						80 [b]	
	Lamotrigine [d]						90 [b]	

[a] C, H, N were found within ±0.4% except compound **1a** in which C was found +0.5%.
[b] $P < 0.001$.
[c] Propylene glycol standard for control group.
[d] Standard drug for supra maximal electroshock seizure pattern test.

Table 2
Characterisation data and anticonvulsant activity of compounds **4a–4l**

Compound	X	R	M.p. (°C)	Yield (%)	Recrystallisation solvent	Molecular formula	Molecular weight [a]	Gross CNS behaviour	Pentobarbitone sodium induced sleeping time in minutes ±SEM		Dose (mg kg^{-1} i.p.)		Anti-convulsant activity (% inhibition)		ALD_{50} (mg kg^{-1} i.p. maximum dose tested)
									Before drug treatment	After drug treatment	For MES model	For PTZ model	For MES model	For PTZ model	
4a	H	H	178–180	62	Methanol–water	$C_{19}H_{16}N_6OS$	376	–	–	–	30	–	50	–	> 1000
4b	H	*p*-OCH_3	125–127	70	Benzene	$C_{20}H_{18}N_6O_2S$	406	–	–	–	30	–	70	–	> 1000
4c	H	*m*-OCH_3	130–131	68	Benzene–petroleum ether	$C_{20}H_{18}N_6O_2S$	406	–	–	–	30	–	60	–	> 1000
4d	H	*p*-OH	155–156	74	DMF	$C_{19}H_{16}N_6O_2S$	392	–	–	–	30	–	60	–	> 1000
4e	H	*p*-$N(CH_3)_2$	139–140	58	Benzene–petroleum ether	$C_{21}H_{21}N_7OS$	419	–	–	–	30	–	60	–	> 1000
4f	H	*m*-OCH_3, *p*-OH	110–111	65	Ethanol–water	$C_{20}H_{18}N_6O_3S$	422	–	–	–	30	–	70	–	> 1000
4g	6-Br	H	63–65	65	Methanol–petroleum ether	$C_{19}H_{15}BrN_6OS$	455	–	–	–	30	–	60	–	> 1000
4h	6-Br	*p*-OCH_3	109–110	70	Acetone–water	$C_{20}H_{17}BrN_6O_2S$	485	–	–	–	30	–	70	–	> 1000
4i	6-Br	*m*-OCH_3	90–92	64	DMF	$C_{20}H_{17}BrN_6O_2S$	485	–	–	–	30	–	60	–	> 1000
4j	6-Br	*p*-OH	69–70	70	Acetone	$C_{19}H_{15}BrN_6O_2S$	471	–	–	–	30	–	70	–	> 1000
4k	6-Br	*p*-$N(CH_3)_2$	45–47	60	DMF	$C_{21}H_{20}BrN_7OS$	498	–	–	–	30	–	70	–	> 1000
4l	6-Br	*m*-OCH_3, *p*-OH	65–66	62	Acetone–petroleum ether	$C_{20}H_{17}BrN_6O_3S$	501	No effect	24.0±2.32	24.5±2.28	7.5, 15, 30	18.5, 37, 74	10, 40, 80 [b]	30, 50, 70	> 1000
		P.G. [c]						No effect	23.0±22.14	23.5±2.32	2.0 mL		0		
		Phenytoin sodium [d]									7.5, 15, 30	–	10, 40, 80 [b]	–	
		Lamotrigine									7.5, 15, 30	–	20, 50, 90 [b]	–	
		Sodium valporate [e]										18.5, 37, 74	–	20, 40, 80 [b]	

No effect implies no loss of sound reflex, pinna reflex, righting reflex and spontaneous activity.
[a] C, H, N were found within ±0.4% except compound **4d** in which C was found +0.9%.
[b] $P < 0.001$.
[c] Propylene glycol standard for control group.
[d] Standard drug for supra maximal electroshock seizure pattern test.
[e] Standard drug for pentylene tetrazol seizure pattern test.

Table 3
Characterisation data and anticonvulsant activity of compounds **5a–5l**

Compound	X	R	M.p. (°C)	Yield (%)	Recrystallisation solvent	Molecular formula	Molecular weight [a]	Gross CNS behaviour	Pentobarbitone sodium induced sleeping time in minutes ±SEM		Dose (mg kg^{-1} i.p.)		Anti-convulsant activity (% inhibition)		ALD_{50} (mg kg^{-1} i.p. maximum dose tested)
									Before drug treatment	After drug treatment	For MES model	For PTZ model	For MES model	For PTZ model	
5a	H	H	219–220	58	Ethanol–water	$C_{21}H_{18}N_6O_2S_2$	450	–	–	–	30	–	60	–	> 1000
5b	H	*p*-OCH_3	150–151	52	Methanol	$C_{22}H_{20}N_6O_3S_2$	480	–	–	–	30	–	70	–	> 1000
5c	H	*m*-OCH_3	163–165	50	Acetone	$C_{22}H_{20}N_6O_3S_2$	480	–	–	–	30	–	70	–	> 1000
5d	H	*p*-OH	120–121	55	DMF	$C_{21}H_{18}N_6O_3S_2$	466	–	–	–	30	–	80 [b]	–	> 1000
5e	H	*p*-$N(CH_3)_2$	180–182	60	Benzene–petroleum ether	$C_{23}H_{23}N_7O_2S_2$	493	–	–	–	30	–	70	–	> 1000
5f	H	*m*-OCH_3, *p*-OH	129–130	62	Ethanol–water	$C_{22}H_{20}N_6O_4S_2$	496	–	–	–	30	–	80 [c,b]	–	> 1000
5g	6-Br	H	93–95	62	Methanol	$C_{21}H_{17}BrN_6O_2S_2$	529	–	–	–	30	–	70	–	> 1000
5h	6-Br	*p*-OCH_3	140–141	50	Methanol–water	$C_{22}H_{19}BrN_6O_3S_2$	559	–	–	–	30	–	70	–	> 1000
5i	6-Br	*m*-OCH_3	135–136	52	DMF	$C_{22}H_{19}BrN_6O_3S_2$	559	–	–	–	30	–	80 [b]	–	> 1000
5j	6-Br	*p*-OH	144–145	56	Ethanol	$C_{21}H_{17}BrN_6O_3S_2$	545	–	–	–	30	–	80 [b]	–	> 1000
5k	6-Br	*p*-$N(CH_3)_2$	85–86	50	Hexane	$C_{23}H_{22}BrN_7O_2S_2$	572	–	–	–	30	–	80 [b]	–	> 1000
5l	6-Br	*m*-OCH_3, *p*-OH	99–100	58	Methanol	$C_{22}H_{19}BrN_6O_4S_2$	575	No effect	26.0±2.88	25.5±2.65	7.5, 15, 30	18.5, 37, 74	20, 50, 90 [b]	30, 50, 90 [b]	> 1000
		P.G. [c]						No effect	23.0±22.14	23.5±2.32	2.0 mL		0		
		Phenytoin sodium [d]									7.5, 15, 30	–	10, 40, 80 [b]	–	
		Lamotrigine									7.5, 15, 30	–	20, 50, 90 [b]	–	
		Sodium valporate [e]										18.5, 37, 74	–	20, 40, 80 [b]	

No effect implies no loss of sound reflex, pinna reflex, righting reflex and spontaneous activity.
[a] C, H, N were found within ±0.4%.
[b] $P < 0.001$.
[c] Propylene glycol standard for control group.
[d] Standard drug for supra maximal electroshock seizure pattern test.
[e] Standard drug for pentylene tetrazol seizure pattern test.

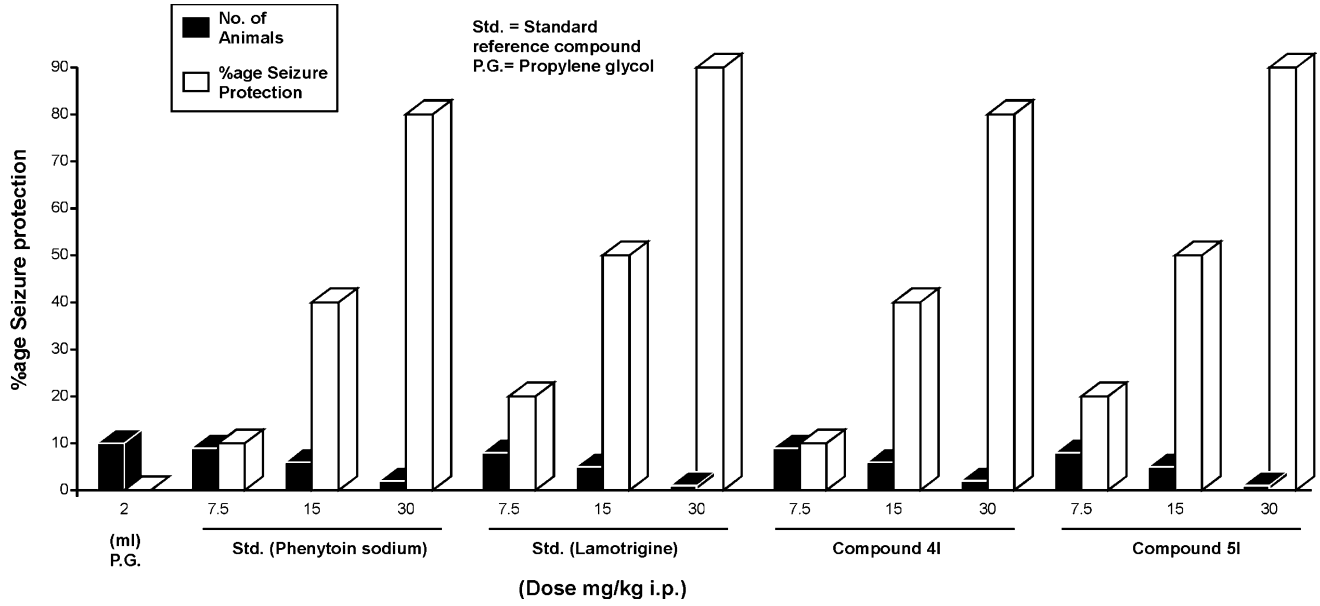

Fig. 2. The bar diagram showing anticonvulsant activity (% age seizure protection) of compounds **4l** and **5l** their comparison with phenytoin sodium and lamotrigine in supra maximal electroshock seizure pattern test.

and **5l** substituted with 3-methoxy, 4-hydroxy phenyl group have shown most potent activity of 80 and 90%, respectively i.e. equipotent and less potent, more potent and equipotent than standard drugs phenytoin sodium and lamotrigine, respectively. Compounds **5a** and **5g** having phenyl ring showed 60 and 70% protection, respectively whereas compounds (**5b** and **5h**) having 4-methoxy phenyl group and those with 3-methoxyphenyl group (**5c** and **5i**) exhibited 70 and 80% protection, respectively. Compounds with 4-hydroxyphenyl group **5d** and **5j** have also shown remarkable percentage protection of 70 and 80%, respectively. Eighty percent protection was exhibited by the compounds substituted with 4-*N*,*N*-dimethyl phenyl group against seizures induced by MES.

Therefore, considering the compounds of this step, it may be concluded that when the β-thialactam ring is substituted with 3-methoxy- 4-hydroxy phenyl group, then it showed promising anticonvulsant activity. Fig. 2 shows the anticonvulsant activity of compound **4l**, **5l** and standard drugs phenytoin sodium and lamotrigine at three graded doses of 7.5, 15 and 30 mg kg^{-1} i.p. in MES models. Interestingly, at all the three doses compound **4l** exhibited activity equipotent to standard

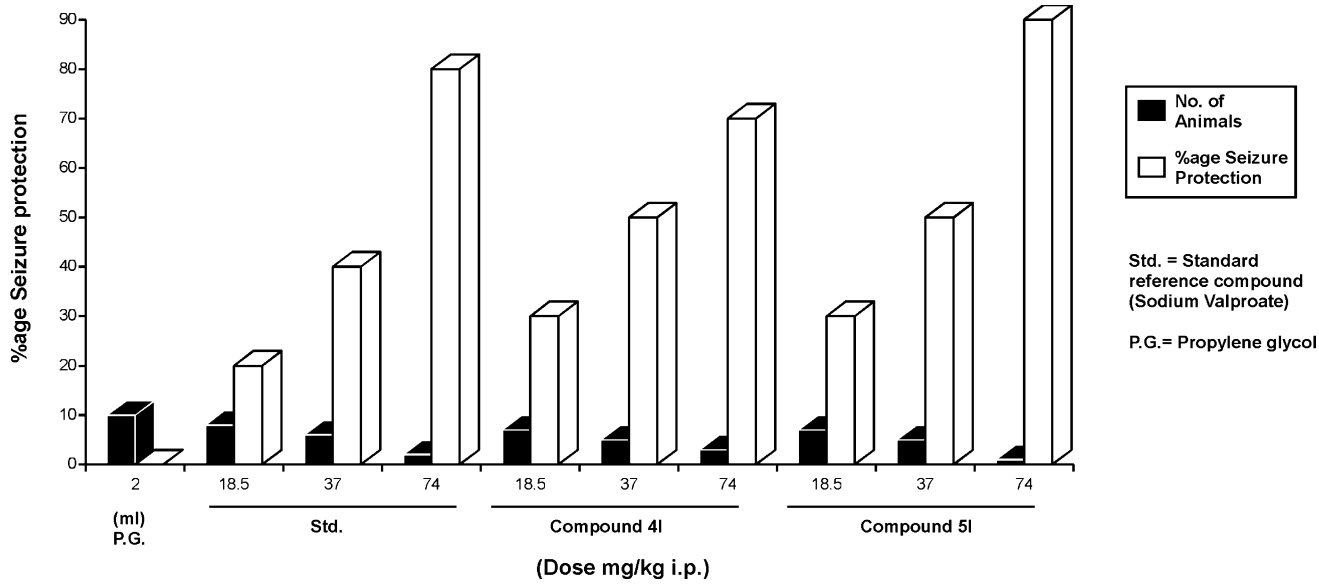

Fig. 3. The bar diagram showing anticonvulsant activity (% age seizure protection) of compounds **4l** and **5l** their comparison with sodium valproate in pentylene tetrazol seizure pattern test.

drug phenytoin sodium and less potent than standard drug lamtrigine. Compound **5l** was found to exhibit more potent activity then phenytoin sodium and equipotent activity to lamotrigine at all the three dose levels.

Being the potent nature of these compounds (**4l** and **5l**) it was thought worthwhile to evaluate these compounds in PTZ model also. Compounds **4l** and **5l** were evaluated at three graded doses in PTZ model and were compared with standard drug sodium valproate. However, compound **4l** was found to be more potent at lower doses (18.5 and 37 mg kg^{-1} i.p.) and less potent at a higher dose (74 mg kg^{-1} i.p.) than standard drug sodium valproate. Moreover, compound **5l** exhibited more potent anticonvulsant activity than sodium valproate at all the three tested doses (18.5, 37 and 74 mg kg^{-1} i.p.). Fig. 3 shows the bar diagram of compounds **4l** and **5l** and their comparison with standard drug sodium valproate in PTZ model.

Interestingly these two compounds (**4l** and **5l**) were devoid of hypnotic and sedative activities.

4. Conclusion

While considering all the newly synthesized compounds of this series together, we may conclude that the compounds having 3-amino-2-methyl-6-bromoquinazolin-4(3*H*)-onyl moiety showed more protection than the compounds having 3-amino-2-methyl-quinazolin-4(3*H*)-onyl moiety. Further, thiazolidinones showed more potent anticonvulsant activity in comparison to their corresponding thiadiazoles. Furthermore, we also conclude that substitution with 3-methoxy-4-hydroxyphenyl group was found to increase the anticonvulsant activity.

5. Experimental

5.1. Chemistry

M.p.s were taken in open capillary tubes and are uncorrected. The homogeniety of all the compounds was checked by using silica gel-G plates. Carbon, hydrogen and nitrogen analyses were performed on CHN analyses, Carlo Erba 1108, Heracus, at the Central Drug Research Institute (Lucknow). Analyses (C, H, N) were within $\pm 0.4\%$ of the theoretical values. The IR spectra were recorded on Backman Acculab-10 spectrophotometer (ν_{max} in cm^{-1}; KBr). The ^{1}H-NMR spectra were recorded in $CDCl_3$ on Brucker 400-FT instrument. The starting compounds i.e. 3-amino-2-methyl-6-monosubstitutedquinazolin-4(3*H*)-ones have been synthesized according to the method [13] given in literature.

5.1.1. *N-(3,4-dihydro-2-methyl-4-oxo-6-monosubstitutedquinazolin-3-yl)glycynate d'ethyle (**1a–1b**)*

A solution of 3-amino-2-methyl-6-monosubstituted-quinazolin-4(3*H*)-ones (0.01 mol), ethyl chloroacetate (0.01 mol), anhydrous C_3H_6O (90 mL), anhydrous K_2CO_3 (8.0 g) were refluxed for 24 h. After refluxing, the excess of solvent was distilled off. The reaction mixture was cooled, filtered and washed with water and recrystallised from appropriate solvents. Physical, analytical and spectroscopic data of compounds **1a**–**1b** are given in Tables 1 and 4, respectively.

5.1.2. *-[N-3,4-Dihydro-2-methyl-4-oxo-6-monosubstitutedquinazolin-3-yl)glycyl]thiosemicarbazide (**2a–2b**)*

A solution of compound **1a**–**1b** (0.075 mol) and thiosemicarbazide (0.075 mol) in MeOH (dry 50 mL) was refluxed on a steam bath for about 15 h. The excess of the solvent was distilled off and the viscous mass poured into ice-cold water, filtered and recrystallised from appropriate solvents. Physical, analytical and spectroscopic data of compound **2a**–**2b** given in Tables 1 and 4, respectively.

5.1.3. *-[(5-Amino-1,3,4-thiadiazol-2-yl)methylamino]-2-methyl-6-monosubstitutedquinazolin-4(3H)-one (**3a–3b**)*

Concentrated H_2SO_4 (15 mL) was added to compounds **2a**–**2b** (0.05 mol) and the reaction mixture was kept overnight at room temperature (r.t.), poured into ice-cold water, neutrallised with liq. NH_3 and filtered. The product obtained was washed with water, dried and triturated with petroleum ether (40–60°) and recrystallised from appropriate solvents. Physical, analytical and spectroscopic data of compound **3a**–**3b** are given in Tables 1 and 2, respectively.

5.1.4. *-{[5-(Alkylbenzylideneamino)-1,3,4-thiadiazol-2-yl]methyl- amino}-2-methyl-6-monosubstitutedquinazolin-4(3H)-one (**4a–4l**)*

A mixture of compounds **3a–3b** (2.5 mol) was condensed with various aromatic aldehydes (2.5 mol) in presence of a few drops of glacial CH_3COOH in MeOH for 8 h. The excess of solvent was distilled off and the residue thus obtained were recrystallised from appropriate solvents. Physical, analytical and spectroscopic data of compounds **4a**–**4l** are given in Tables 2 and 4, respectively.

5.1.5. *-({4-[2-(Alkylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-monosubstitutedquinazolin-4(3H)-one (**5a–5l**)*

To a cooled mixture of compound **4a**–**4l** (0.01 mol) and anhydrous $ZnCl_2$ (0.02 mol) in DMF (50 mL), thioglycolic acid (0.02 mol) was added dropwise with

Table 4
Spectral data of compounds (**1a**–**1b**), (**2a**–**2b**), (**3a**–**3b**), (**4a**–**4l**) and (**5a**–**5l**)

Compound	^{1}H-NMR ($CDCl_3$) δ (ppm)	IR (KBr) (cm^{-1})
1a	9.60 (ss, 1H, N*H*CH_2), 7.90–7.25 (m, 4H, Ar–H), 4.38 (d, 2H, NHC*H*$_2$), 4.10 (q, 2H, $J = 7$ Hz, COOC*H*$_2$CH$_3$), 2.30 (s, 3H, C*H*$_3$), 1.20 (t, 3H, $J = 7$ Hz, COOCH$_2$C*H*$_3$)	3250 (NH), 2840 (CH_2), 1740 (C=O of ester), 1550 (C=C of aromatic ring)
1b	9.61 (ss, 1H, N*H*CH_2), 7.80–7.40 (m, 3H, Ar–H), 4.28 (d, 2H, NHC*H*$_2$), 4.12 (q, 2H, $J = 7$ Hz, COOC*H*$_2$CH$_3$), 2.23 (s, 3H, C*H*$_3$), 1.27 (t, 3H, $J = 7$ Hz, COOCH$_2$C*H*$_3$)	3300 (NH), 2835 (CH_2), 1740 (C=O of ester), 1560 (C=C of aromatic ring)
2a	9.40 (brs, 1H, N*H*CH_2), 8.65 (m, 4H, N*H*N*H*CS–N*H*$_2$), 8.15–7.10 (m, 4H, Ar–*H*), 4.40 (d, 2H, NHC*H*$_2$), 2.30 (s, 3H, C*H*$_3$)	3400 (NH, NH_2), 2853 (CH_2), 1710 (C=O of amides), 1130 (>C=S)
2b	9.48 (brs, 1H, N*H*CH_2), 8.50 (m, 4H, N*H*N*H*CS–N*H*$_2$), 7.80–7.20 (m, 3H, Ar–*H*), 4.45 (d, 2H, NHC*H*$_2$), 2.25 (s, 3H, C*H*$_3$)	3380 (NH, NH_2), 2845 (CH_2), 1738 (C=O of amides), 1135 (>C=S)
3a	9.50 (brs, 1H, N*H*CH_2), 8.60 (s, 2H, N*H*$_2$), 8.10–7.10 (m, 4H, Ar–*H*), 4.20 (d, 2H, NHC*H*$_2$), 2.20 (s, 3H, C*H*$_3$)	3420 (NH, NH_2), 2845 (CH_2), 1720 (C=O of quinazolon ring), 1610 (C=N), 680 (C–S–C)
3b	9.46 (brs, 1H, N*H*CH_2), 8.45 (s, 2H, N*H*$_2$), 7.60–7.20 (m, 3H, Ar–*H*), 4.50 (d, 2H, NHC*H*$_2$), 2.30 (s, 3H, C*H*$_3$)	3400 (NH, NH_2), 2863 (CH_2), 1750 (C=O of quinazolon ring), 1635 (C=N), 690 (C–S–C)
4a	9.45 (brs, 1H, N*H*CH_2), 8.45 (s, 1H, N=C*H*–Ar), 8.00–7.10 (m, 9H, Ar–*H*), 4.22 (d, 2H, NHC*H*$_2$), 2.26 (s, 3H, C*H*$_3$)	3410 (NH), 2915 (CH_2), 1720 (C=O of quinazolon ring), 1620 (C=N), 688 (C–S–C)
4b	9.45 (brs, 1H, N*H*CH_2), 8.40 (s, 1H, N=C*H*–Ar), 8.20–7.00 (m, 8H, Ar–*H*), 4.25 (d, 2H, NHC*H*$_2$), 3.40 (s, 3H, Ar–OC*H*$_3$), 2.40 (s, 3H, C*H*$_3$)	3400 (NH), 2910 (CH_2), 1700 (C=O of quinazolon ring), 1620 (C=N), 683 (C–S–C)
4c	9.42 (brs, 1H, N*H*CH_2), 8.45 (s, 1H, N=C*H*–Ar), 8.20–7.10 (m, 8H, Ar–*H*), 4.28 (d, 2H, NHC*H*$_2$), 3.37 (s, 3H, Ar–OC*H*$_3$), 2.36 (s, 3H, C*H*$_3$)	3400 (NH), 2912 (CH_2), 1712 (C=O of quinazolon ring), 1624 (C=N), 682 (C–S–C)
4d	9.43 (brs, 1H, N*H*CH_2), 9.30 (s, 1H, Ar–O*H*), 8.46 (s, 1H, N=C*H*–Ar), 8.40–7.15 (m, 8H, Ar–*H*), 4.25 (d, 2H, NHC*H*$_2$), 2.32 (s, 3H, C*H*$_3$)	3380 (NH), 2913 (CH_2), 1720 (C=O of quinazolon ring), 1619 (C=N), 686 (C–S–C)
4e	9.46 (brs, 1H, N*H*CH_2), 8.43 (s, 1H, N=C*H*–Ar), 8.35–7.20 (m, 8H, Ar–*H*), 4.22 (d, 2H, NHC*H*$_2$), 2.30 (s, 3H, C*H*$_3$), 1.45 (s, 6H, Ar–N(C*H*$_3$)$_2$)	3395 (NH), 2916 (CH_2), 1718 (C=O of quinazolon ring), 1617 (C=N), 685 (C–S–C)
4f	9.40 (brs, 1H, N*H*CH_2), 9.25 (s, 1H, Ar–O*H*), 8.42 (s, 1H, N=C*H*–Ar), 8.20–7.00 (m, 7H, Ar–*H*), 4.20 (d, 2H, NHC*H*$_2$), 3.38 (s, 3H, Ar–OC*H*$_3$), 2.36 (s, 3H, C*H*$_3$)	3380 (NH), 2920 (CH_2), 1720 (C=O of quinazolon ring), 1615 (C=N), 682 (C–S–C)
4g	9.56 (brs, 1H, N*H*CH_2), 8.40 (s, 1H, N=C*H*–Ar), 8.30–7.10 (m, 8H, Ar–*H*), 4.18 (d, 2H, NHC*H*$_2$), 2.30 (s, 3H, C*H*$_3$)	3400 (NH), 2910 (CH_2), 1750 (C=O of quinazolon ring), 1580 (C=N), 680 (C–S–C)
4h	9.53 (brs, 1H, N*H*CH_2), 8.32 (s, 1H, N=C*H*–Ar), 8.35–7.15 (m, 7H, Ar–*H*), 4.15 (d, 2H, NHC*H*$_2$), 3.39 (s, 3H, Ar–OC*H*$_3$), 2.35 (s, 3H, C*H*$_3$)	3420 (NH), 2912 (CH_2), 1740 (C=O of quinazolon ring), 1560 (C=N), 682 (C–S–C)
4I	9.60 (brs, 1H, N*H*CH_2), 8.35 (s, 1H, N=C*H*–Ar), 8.30–7.10 (m, 7H, Ar–*H*), 4.12 (d, 2H, NHC*H*$_2$), 3.45 (s, 3H, Ar–OC*H*$_3$), 2.36 (s, 3H, C*H*$_3$)	3420 (NH), 2914 (CH_2), 1742 (C=O of quinazolon ring), 1565 (C=N), 682 (C–S–C)
4j	9.55 (brs, 1H, N*H*CH_2), 9.10 (s, 1H, Ar–O*H*), 8.30 (s, 1H, N=C*H*–Ar), 7.45–7.20 (m, 7H, Ar–*H*), 4.15 (d, 2H, NHC*H*$_2$), 2.30 (s, 3H, C*H*$_3$)	3410 (NH), 2920 (CH_2), 1750 (C=O of quinazolon ring), 1572 (C=N), 690 (C–S–C)
4k	9.58 (brs, 1H, N*H*CH_2), 8.25 (s, 1H, N=C*H*–Ar), 7.45–7.15 (m, 7H, Ar–*H*), 4.20 (d, 2H, NHC*H*$_2$), 2.28 (s, 3H, C*H*$_3$), 1.25 (s, 6H, Ar–N(C*H*$_3$)$_2$)	3430 (NH), 2915 (CH_2), 1758 (C=O of quinazolon ring), 1560 (C=N), 688 (C–S–C)
4l	9.48 (brs, 1H, N*H*CH_2), 9.25 (s, 1H, Ar–O*H*), 8.20 (s, 1H, N=C*H*–Ar), 7.50–7.10 (m, 6H, Ar–*H*), 4.22 (d, 2H, NHC*H*$_2$), 3.40 (s, 3H, Ar–OC*H*$_3$), 2.25 (s, 3H, C*H*$_3$)	3425 (NH), 2910 (CH_2), 1760 (C=O of quinazolon ring), 1568 (C=N), 685 (C–S–C)
5a	9.50 (brs, 1H, N*H*CH_2), 8.30–7.15 (m, 9H, Ar–*H*), 6.14 (s, 1H, C*H*–Ar), 4.25 (d, 2H, NHC*H*$_2$), 3.68 (s, 2H, C*H*$_2$ of β-thialactam ring), 2.30 (s, 3H, C*H*$_3$)	3410 (NH), 2920 (CH_2), 1745 (C=O of β-thialactam moiety), 1718 (C=O of quinazolon ring), 1632 (C=N), 688 (C–S–C)
5b	9.40 (brs, 1H, N*H*CH_2), 8.25–7.15 (m, 8H, Ar–*H*), 6.10 (s, 1H, C*H*–Ar), 4.20 (d, 2H, NHC*H*$_2$), 3.65 (s, 2H, C*H*$_2$ of β-thialactam ring), 3.60 (s, 3H, Ar–OC*H*$_3$), 2.39 (s, 3H, C*H*$_3$)	3400 (NH), 2900 (CH_2), 1750 (C=O of β-thialactam moiety), 1720 (C=O of quinazolon ring), 1635 (C=N), 690 (C–S–C)
5c	9.45 (brs, 1H, N*H*CH_2), 8.20–7.10 (m, 8H, Ar–*H*), 6.15 (s, 1H, C*H*–Ar), 4.25 (d, 2H, NHC*H*$_2$), 3.62 (s, 2H, C*H*$_2$ of β-thialactam ring), 3.40 (s, 3H, Ar–OC*H*$_3$), 2.32 (s, 3H, C*H*$_3$)	3400 (NH), 2910 (CH_2), 1745 (C=O of β-thialactam moiety), 1718 (C=O of quinazolon ring), 1639 (C=N), 689 (C–S–C)
5d	9.55 (brs, 1H, N*H*CH_2), 9.10 (s, 1H, Ar–O*H*), 8.10–7.12 (m, 8H, Ar–*H*), 6.20 (s, 1H, C*H*–Ar), 4.30 (d, 2H, NHC*H*$_2$), 3.60 (s, 2H, C*H*$_2$ of β-thialactam ring), 2.30 (s, 3H, C*H*$_3$)	3420 (NH), 2918 (CH_2), 1760 (C=O of β-thialactam moiety), 1720 (C=O of quinazolon ring), 1645 (C=N), 685 (C–S–C)
5e	9.60 (brs, 1H, N*H*CH_2), 8.10–7.00 (m, 8H, Ar–*H*), 6.10 (s, 1H, C*H*–Ar), 4.20 (d, 2H, NHC*H*$_2$), 3.60 (s, 2H, C*H*$_2$ of β-thialactam ring), 2.25 (s, 3H, C*H*$_3$), 1.55 (s, 6H, Ar–N (C*H*$_3$)$_2$)	3410 (NH), 2920 (CH_2), 1750 (C=O of β-thialactam moiety), 1725 (C=O of quinazolon ring), 1640 (C=N), 688 (C–S–C)
5f	9.50 (brs, 1H, N*H*CH_2), 9.15 (s, 1H, Ar–O*H*), 8.20–7.00 (m, 7H, Ar–*H*), 6.25 (s, 1H, C*H*–Ar), 4.35 (d, 2H, NHC*H*$_2$), 3.65 (s, 2H, C*H*$_2$ of β-thialactam ring), 3.45 (s, 3H, Ar–OC*H*$_3$), 2.28 (s, 3H, C*H*$_3$)	3400 (NH), 2915 (CH_2), 1740 (C=O of β-thialactam moiety), 1728 (C=O of quinazolon ring), 1648 (C=N), 682 (C–S–C)

Table 4 (*Continued*)

Compound	^{1}H-NMR ($CDCl_3$) δ (ppm)	IR (KBr) (cm^{-1})
5g	9.45 (brs, 1H, N*H*CH_2), 8.22–7.10 (m, 8H, Ar–*H*), 6.14 (s, 1H, C*H*–Ar), 4.22 (d, 2H, NHC*H*$_2$), 3.70 (s, 2H, C*H*$_2$ of β-thialactam ring), 2.45 (s, 3H, C*H*$_3$)	3410 (NH), 2915 (CH_2), 1738 (C=O of β-thialactam moiety), 1720 (C=O of quinazolon ring), 1630 (C=N), 687 (C–S–C)
5h	9.50 (brs, 1H, N*H*CH_2), 8.05–7.00 (m, 7H, Ar–*H*), 6.15 (s, 1H, C*H*–Ar), 4.30 (d, 2H, NHC*H*$_2$), 3.68 (s, 2H, C*H*$_2$ of β-thialactam ring), 3.45 (s, 3H, Ar–OC*H*$_3$), 2.40 (s, 3H, C*H*$_3$)	3410 (NH), 2910 (CH_2), 1760 (C=O of β-thialactam moiety), 1728 (C=O of quinazolon ring), 1638 (C=N), 687 (C–S–C)
5i	9.46 (brs, 1H, N*H*CH_2), 8.15–7.10 (m, 7H, Ar–*H*), 6.20 (s, 1H, C*H*–Ar), 4.35 (d, 2H, NHC*H*$_2$), 3.68 (s, 2H, C*H*$_2$ of β-thialactam ring), 3.46 (s, 3H, Ar–OC*H*$_3$), 2.40 (s, 3H, C*H*$_3$)	3400 (NH), 2920 (CH_2), 1766 (C=O of β-thialactam moiety), 1730 (C=O of quinazolon ring), 1640 (C=N), 685 (C–S–C)
5j	9.50 (brs, 1H, N*H*CH_2), 9.00 (s, 1H, Ar–O*H*), 8.00–7.00 (m, 7H, Ar–*H*), 6.10 (s, 1H, C*H*–Ar), 4.22 (d, 2H, NHC*H*$_2$), 3.63 (s, 2H, C*H*$_2$ of β-thialactam ring), 2.35 (s, 3H, C*H*$_3$)	3430 (NH), 2922 (CH_2), 1765 (C=O of β-thialactam moiety), 1724 (C=O of quinazolon ring), 1650 (C=N), 684 (C–S–C)
5k	9.60 (brs, 1H, N*H*CH_2), 8.15–7.10 (m, 7H, Ar–*H*), 6.20 (s, 1H, C*H*–Ar), 4.25 (d, 2H, NHC*H*$_2$), 3.65 (s, 2H, C*H*$_2$ of β-thialactam ring), 2.25 (s, 3H, C*H*$_3$), 1.50 (s, 6H, Ar–N (CH_3)$_2$)	3420 (NH), 2910 (CH_2), 1745 (C=O of β-thialactam moiety), 1730 (C=O of quinazolon ring), 1650 (C=N), 685 (C–S–C)
5l	9.55 (brs, 1H, N*H*CH_2), 9.30 (s, 1H, Ar–O*H*), 8.30–7.20 (m, 6H, Ar–*H*), 6.20 (s, 1H, C*H*–Ar), 4.30 (d, 2H, NHC*H*$_2$), 3.68 (s, 2H, C*H*$_2$ of β-thialactam ring), 3.39 (s, 3H, Ar–OC*H*$_3$), 2.28 (s, 3H, C*H*$_3$)	3410 (NH), 2920 (CH_2), 1735 (C=O of β-thialactam moiety), 1730 (C=O of quinazolon ring), 1645 (C=N), 683 (C–S–C)

stirring at ambient temperature and the mixture was kept for 2 days at r.t. and refluxed for 12 h. The reaction mixture was filtered, washed with water and poured into cooled water. The resulting products were recrystallised from appropriate solvents. Physical, analytical and spectroscopic data of compounds **5a**–**5l** are given in Tables 3 and 4, respectively.

5.2. Pharmacology

5.2.1. Anti-convulsant activity

5.2.1.1. Supra maximal electroshock seizure pattern test (SMES). It was performed according to the method of Toman et al. [14] on albino rats of the 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 30 mg kg^{-1} i.p. After 1 h they were subjected to a shock of 150 M.A. by convulsiometer through ear electrodes for 0.2 s and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats.

5.2.1.2. Pentylenetetrazole seizure pattern test (PTZ). It was performed according to the method of Fisher [15]. Albino rats weighing 100–200 g were injected with pentylenetetrazol in dose of 70 mg kg^{-1} subcutaneously in scruff of neck. The dose of PTZ was selected by preliminary screening. Lower dose failed to produce typical seizure pattern while higher dose only increased the mortality. After 2–4 min of PTZ injection the animals develop sequence of excitement, myoclonic jerks, clonic seizures, one or more maximal tonic seizures/death. Animals exhibiting these seizures were selected and divided into eight groups. Standard drug used in this model was sodium valproate (74 mg kg^{-1} i.p.) and was injected 60 min prior to PTZ challenge.

5.2.2. Sedative and hypnotic activity

5.2.2.1. Spontaneous behaviour activity loss of sound reflex and pinna reflex. They were studied according to the method of Borsy et al. [16].

5.2.2.2. Loss of righting reflex. It was done as per the method of Janscen et al. [17].

5.2.2.3. Potentiation of pentobarbitone sodium induced sleeping time. It was done according to the procedure of Swinyard and Castelion [18]

5.2.3. Acute toxicity

The compounds were investigated for their acute toxicity (ALD_{50}) in mice by following the method of Smith [19].

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