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Laboratory note

Synthesis and anticonvulsant activity of some potential thiazolidinonyl 2-oxo/thiobarbituric acids

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Abstract

A series of 5-[(*N*-substituted benzylidenylimino)amino]-2-oxo/thiobarbituric acids **(3a–3h)** have been synthesized by the condensation of 5-hydrazino-2-oxo/thiobarbituric acids **(2a–2b)** with various aromatic aldehydes. Cycloaddition of thioglycolic acid to **3a–3h**, yielded 5-[(2′-substituted phenyl-4′-oxothiazolidin-3′-yl)amino]-2-oxo/thiobarbituric acids **(4a–4h)**. All these compounds were screened, in vivo, for their anticonvulsant activity and acute toxicity studies. Compounds **4f** and **4g** were found to be most potent compounds of this series and were compared with the reference drugs, phenytoin sodium, lamotrigine and sodium valproate. The structures of these compounds have been established by IR, ^{1}H NMR and mass spectroscopic data.

Keywords: Iminoamino-2-oxo/thiobarbituric acid; Thiazolidinonylamino-2-oxo/thiobarbituric acid; Anticonvulsant activity; Acute toxicity

1. Introduction

Barbituric acid derivatives i.e. phenobarbital [1], mephobarbital [2], are well known drugs which are used for the treatment of epilepsy. Although these drugs are very effective in controlling the seizures, they have major side effects like sedation, hypnosis, etc. Substituted heterocyclic/substituted aryl systematic variation at the 5 position of barbituric [3–5]/thiobarbituric [6–8] acids nucleus remarkably increase the antiepileptic activity. Furthermore thiazolidinone derivatives [9–11] are also well known for their pronounced anticonvulsant activity. In view of these observations, it was thought worthwhile to synthesize some newer more potent derivatives of barbituric/thiobarbituric acids by incorporating thiazolidinone moieties at 5 position, with a hope to get better anticonvulsant drugs without side effects.

2. Chemistry

The synthetic routes of compounds are outlined in Scheme 1. As shown in Scheme 1, the bromination of oxo/thiobarbituric acids yielded 5-bromo-2-oxo/thiobarbituric acids i.e. compounds **1a–1b**. Compounds **1a–1b** on reaction with hydrazine hydrate gave 5-hydrazino-2-oxo/thiobarbituric acids i.e. compounds **2a–2b**, which on further reaction with different substituted aromatic aldehydes yielded their corresponding 5-[(*N*-Substituted benzylidenylimino) amino]-2-oxo/thiobarbituric acids i.e. compounds **3a–3h**. Compounds **3a–3h**, further undergoes cycloaddition with thioglycolic acid in presence of anhydrous $ZnCl_2$ to afford 5-[(2′-substituted phenyl-4′-oxothiazolidin-3′-yl)amino]-2-oxo/thiobarb-5-ituric acids i.e. compounds **4a–4h**.

The formation of compounds **1a–1b** were confirmed by the appearance of a singlet at δ 5.6 and δ 5.8 for 1 proton of > CH-Br and a sharp singlet at δ 9.25 and δ 9.26 for 2 protons of > NHCO group in oxo and thiobarbituric acids, respectively, in the ^{1}H NMR spectra. Appearance of a band at 610 cm^{-1} (C-Br in oxobarbituric acid) and 612 cm^{-1} (C-Br in thiobarbituric acid) in IR spectra also confirmed their structures. Appearance of a band at 1275 cm^{-1} (N-N in barbituric acid) and 1270 cm^{-1} (N-N in thiobarbituric acid) in the IR spectra of compounds **2a–2b** and presence of a broad singlet at δ 4.85 and δ 4.83 for 3 protons of $NH.NH_2$ in oxo/thiobarbituric acids, respectively, in the ^{1}H NMR spectra, supported their formation. Appearance of a band between 1670 and 1685 cm^{-1} (N=CH) in the IR spectrum of compounds **3a–3h** and appearance of a

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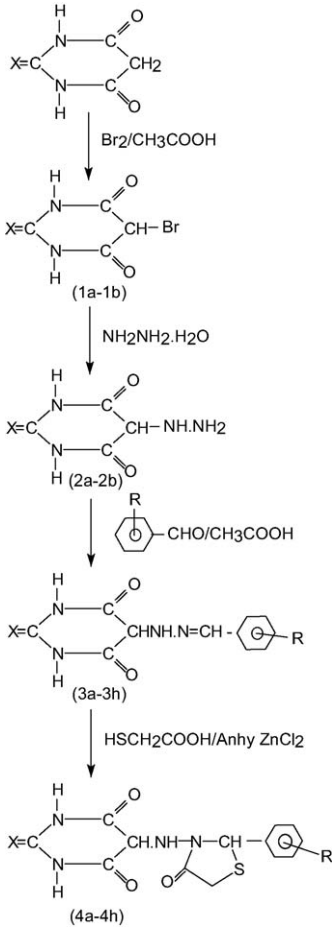

Scheme 1.

singlet in between δ 8.48 and δ 8.65 for one proton of =CH–Ar and a multiplet between δ 8.10 and δ 7.75 for aromatic protons in the ^{1}H NMR spectra also supported their structures. Cycloaddition of thioglycolic acid to **3a–3h** resulted into compounds **4a–4h** which was confirmed by the presence of a band between 1755 and 1777 cm^{-1} (C=O of β-thialactum ring) in the IR spectra and appearance of a singlet of two protons of CH_2 of thiazolidinone ring in the ^{1}H NMR spectra.

3. Pharmacological results and discussion

All the newly synthesized compounds were tested in vivo in order to evaluate their anticonvulsant activity. The pharmacological data of all the compounds of this series have been reported in Table 3. These compounds when screened for their anticonvulsant activity against maximal electroshock induced seizures tested at 30 mg kg^{-1} i.p., exhibited substantive anticonvulsant activity. The characteristic feature of this series is the substitution by the substituted phenyl thiazolidinonylamino group at fifth position of barbituric/thiobarbituric acids. While evaluating the anticonvulsant activity, it was observed that compounds **1a–1b** exhibited a lower degree of anticonvulsant activity i.e. 20%. The next stage compounds i.e. **2a–2b** afforded mild anticonvulsant activity varying between 30% and 40%. Further the next step of this series was characterized by the incorporation of *N*-substituted benzylidenyliminoamino group at the fifth position of-2-oxo/thiobarbituric acids. All compounds showed potent anticonvulsant activity, however, compound **3b, 3f, 3g** and **3h**, showed better response against MES model i.e. 70% each, in comparison to the other substituted derivatives. Moreover, compounds **4a–4h**, substituted with different thiazolidinonylamino moieties at fifth position of oxo/thiobarbituric acids, have shown varying degree (50–90%) of anticonvulsant activity, however compound **4f** and **4g** having [2′-(*p*-methoxy)phenyl-4′-oxothiazolidin-3′-yl)amino] and [2′-(*m*-methoxy-*p*-hydroxy) phenyl-4′-oxothiazolidin-3′-yl)amino]substitution at fifth position of thiobarbituric acid) have shown most potent response against MES test i.e. 90% and 80% protection. Compound **4f** has been found to be more potent and equipotent than both the standard drugs phenytoin sodium and lamotrigine while compound **4g** has shown equipotency and less potency than both the standard drugs phenytoin sodium and lamotrigine.

Therefore, considering the results of compounds of this series, it may be concluded that substitution by substituted thiazolidinone moieties in oxo/thiobarbituric acid derivatives showed promising anticonvulsant activity. Further, *p*-methoxyphenyl-substituted and *m*-methoxy-*p*-hydroxyphenyl-substituted derivatives have shown more potent response in comparison to other substituted derivatives i.e. compounds **4f** and **4g**, respectively. These compounds were tested at three graded doses i.e. 7.5, 15 and 30 mg kg^{-1} i.p.

In the MES model, compound **4f** showed more potent anticonvulsant activity as compared to standard drug phenytoin sodium at all the tested doses whereas in comparison to standard drug lamotrigine **4f** showed higher activity at the dose of 7.5 and 15 mg kg^{-1} i.p. but equipotent response at the dose of 30 mg kg^{-1} i.p.

Compound **4g** showed equipotent anticonvulsant activity at the dose of 7.5 mg kg^{-1} (20% inhibition) than the standard drugs phenytoin sodium and lamotrigine while less potent activity (40% inhibition) at 15 mg kg^{-1} i.p. than both the standard drugs whereas at the dose of 30 mg kg^{-1}, **4g** has shown equipotent and less potent response than the reference drug phenytoin sodium and lamotrigine, respectively (Table 3 and Fig. 1).

Being the most potent compounds of this series, compounds **4f** and **4g** were also tested for PTZ model and compared with reference drug sodium valproate. Compound **4g** has shown equipotent response at the dose of 20 and 40 mg kg^{-1} (i.e. 30% and 50% inhibition) and higher degree of protection (i.e. 90% inhibition) at the dose of 80 mg kg^{-1} than the reference drug sodium valproate while compound **4f** has been found to exhibit less potent response at the dose of 20 and 40 mg kg^{-1} (i.e. 20% and 30% inhibition, respectively) and equipotent effect (i.e. 80% inhibition) at the dose of 80 mg kg^{-1} (Table 3 and Fig. 2) in the PTZ model.

4. Conclusion

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

Table 1
Physical and analytical data of compounds **1a–1b, 2a–2b, 3a–3h** and **4a–4h**

Compound number	X	R	m.p. (°C)	Yield (%)	Recrystallization solvent	Molecular formula	% Elemental analysis		
							C calculated (found)	H calculated (found)	N calculated (found)
1a	O	–	196	51	Methanol	$C_4H_3N_2O_3Br$	23.19 (23.05)	1.45 (1.59)	13.53 (13.74)
1b	S	–	256	55	Ethanol	$C_4H_3N_2O_2SBr$	21.52 (21.70)	1.34 (1.22)	12.56 (12.74)
2a	O	–	210	56	Methanol	$C_4H_6N_4O_3$	30.38 (30.48)	3.80 (3.77)	35.44 (35.12)
2b	S	–	225	58	Acetone	$C_4H_6N_4O_2S$	27.59 (27.44)	3.45 (3.54)	32.18 (32.28)
3a	O	-H	230	70	Methanol	$C_{11}H_{10}N_4O_3$	53.66 (53.75)	4.07 (4.02)	22.76 (22.94)
3b	O	*p*-OCH_3	185	72	Ethanol	$C_{12}H_{12}N_4O_4$	52.17 (52.47)	4.35 (4.12)	20.29 (20.01)
3c	O	*m*-OCH_3, *p*-OH	246	74	Acetone	$C_{12}H_{12}N_4O_5$	49.32 (49.70)	4.11 (4.44)	19.18 (19.04)
3d	O	*p*-$N(CH_3)_2$	175	75	Methanol	$C_{13}H_{15}N_5O_3$	53.98 (53.57)	5.19 (5.34)	24.22 (24.05)
3e	S	-H	204	71	Methanol	$C_{11}H_{10}N_4O_2S$	50.38 (50.22)	3.82 (3.68)	21.37 (21.50)
3f	S	*p*-OCH_3	190	68	Ethanol	$C_{12}H_{12}N_4O_3S$	49.32 (49.64)	4.11 (4.05)	19.18 (19.26)
3g	S	*m*-OCH_3, *p*-OH	210	72	Benzene	$C_{12}H_{12}N_4O_4S$	46.75 (46.62)	3.90 (3.78)	18.18 (18.26)
3h	S	*p*-$N(CH_3)_2$	180	75	Acetone	$C_{13}H_{15}N_5O_2S$	51.15 (51.24)	4.92 (4.72)	2.30 (2.45)
4a	O	-H	210	58	Methanol	$C_{13}H_{12}N_4O_4S$	48.75 (48.94)	3.75 (3.58)	17.50 (17.32)
4b	O	*p*-OCH_3	192	60	Methanol	$C_{14}H_{14}N_4O_5S$	48.00 (47.73)	4.00 (4.38)	16.00 (16.25)
4c	O	*m*-OCH_3, *p*-OH	228	72	Ethanol	$C_{14}H_{14}N_4O_6S$	45.90 (45.74)	3.82 (3.72)	15.30 (15.55)
4d	O	*p*-$N(CH_3)_2$	148	70	Acetone	$C_{15}H_{17}N_5O_4S$	49.59 (49.44)	4.68 (4.92)	19.28 (19.47)
4e	S	-H	175	68	Methanol	$C_{13}H_{12}N_4O_3S_2$	46.43 (46.48)	3.57 (3.68)	16.67 (16.82)
4f	S	*p*-OCH_3	206	65	Benzene	$C_{14}H_{14}N_4O_4S_2$	45.90 (45.78)	3.82 (3.94)	15.30 (15.16)
4g	S	*m*-OCH_3, *p*-OH	182	62	Acetone	$C_{14}H_{14}N_4O_5S_2$	43.98 (43.84)	3.66 (3.49)	14.66 (14.35)
4h	S	*p*-$N(CH_3)_2$	158	72	Ethanol	$C_{15}H_{17}N_5O_3S_2$	47.49 (47.58)	4.48 (4.32)	18.47 (18.58)

- Compounds having thiazolidinone substitution at position fifth of oxo/thiobarbituric acids showed better protection against MES test;
- Substituted thiazolidinonylthiobarbituric acids showed better response than substituted thiazolidinonyl oxobarbituric acids;
- *m*-Methoxy-*p*-hydroxyphenyl substituted and *p*-methoxyphenyl substituted thiazolidinonylthiobarbituric acids showed more promising results than the other substituted ones;
- Compound substituted with two electron repelling group (*m*-methoxy-*p*-hydroxyphenyl-substituted)i.e. compound **4g** showed better response towards pentylene tetrazole (PTZ) model than substituted with one electron repelling group (*p*-methoxy-substituted phenyl) i.e. compound **4f**.

5. Experimental

5.1. Chemistry

The melting points of the compounds were determined in open capillaries with the help of Thermonic melting point apparatus and were uncorrected. The homogeneity of all the newly synthesized compounds was routinely checked by thin layer chromatography on Silica gel G plates of 0.5 mm thickness, eluent was the mixture of different polar and nonpolar solvent in varying proportions and spots were located by using iodine chamber. Elemental analysis (C, H, N) of all the compounds were determined through Carlo-Erba 1108 elemental analyzer and results were found within ± 0.4% of theoretical values. Infra red (IR) spectra were recorded in KBr on Bruker IFS-66V FI-IR instrument and ν_{max} was recorded in cm^{-1}. ^1H NMR spectra were recorded by Brucker DRX-400 FTNMR instrument using $CDCl_3$ and DMSO d_6 as solvent and tetramethyl silane (TMS) as internal reference standard. Chemical shift value was recorded as δ (ppm). Mass spectra were determined on mass spectrum El instrument.

5.1.1. 5-Bromo-2-oxo/thiobarbituric acid (*1a–1b*)

Barbituric acid/thiobarbituric acid (0.1 mol) was suspended in excess of glacial acetic acid and to this was added bromine (0.2 mol) drop-5-wise. After complete addition of bromine, the reaction mixture was stirred for 10 hours and poured into ice-cold water then left overnight at room temperature. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from suitable solvents to afford compounds **1a–1b**. Physical, analytical and spectral data are given in Tables 1 and 2, respectively.

5.1.2. 5-Hydrazino-2-oxo/thiobarbituric acid (*2a–2b*)

The mixture of compounds **1a–1b** (0.1 mol) and hydrazine hydrate (0.2 mol) in methanol was refluxed for 8 hours. The excess of solvent was distilled off and poured into ice. The solid thus obtained was filtered, washed with water and recrystallized from suitable solvents to give compounds **2a–2b**. Physical, analytical and spectral data are given in Tables 1 and 2, respectively.

5.1.3. 5-[N-substituted benzylidenylimino)amino]-2-oxo/thiobarbituric acid (*3a–3h*)

The equimolar mixture (0.1 mol) of methanolic solution of compounds **2a–2b** and different aromatic aldehydes with few drops of acetic acid, was refluxed for 8 hours and poured into ice cold water. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from suitable solvents to yield compounds **3a–3h**. Physical, analytical and spec-

Table 2
Spectral data of compounds **1a–1b, 2a–2b, 3a–3h** and **4a–4h**

Compounds	$[M]^+$ *m/z*	^{1}H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm)	IR (KBr) ν_{max} (cm^{-1})
1a	207	9.25 (ss, 2H, 2x N*H*CO of barbituric acid, 5.6 (s, 1H, C*H*-Br).	610 (C-Br), 1300 (C-N), 1710, 1720, 1740 (C=O of barbituric acid), 3300 (N-H of amide)
1b	223	9.26 (ss, 2H, 2x N*H*CO of thiobarbituric acid), 5.8 (s, 1H, C*H*-Br)	612 (C-Br), 1305 (C-N), 1710, 1720 (C=O of thiobarbituric acid), 1260 (C=S), 3305 (N-H of amide)
2a	158	9.24 (ss, 2H, 2x N*H*CO of barbituric acid), 5.2 (d, 1H, C*H*.NH.NH_2), 4.85 (brs, 3H, N*H*.NH_2 exchangeable)	1275 (N-N), 1310 (C-N), 1715, 1720, 1735 (C=O of barbituric acid), 3210 (NH.NH_2) 3290 (N-H of amide)
2b	174	9.25 (ss, 2H, N*H*CO of thiobarbituric acid), 5.4 (d, 1H, C*H*.NH.NH_2), 4.83 (brs, 3H, N*H*.NH_2 exchangeable)	1270 (N-N), 1310 (C-N), 1715, 1725 (C=O of thiobarbituric acid) 1265 (C=S), 3220 (NH,NH_2), 3300 (N-H of amide)
3a	246	9.25 (ss, 2H, 2x N*H*CO of barbituric acid), 8.60 (s, 1H, =C*H*-Ar), 8.20–7.80 (m, 5H, Ar-*H*), 5.2 (d, 1H, >C*H*-NH), 4.5 (brs, 1H, >CH.N*H*)	1285 (N-N), 1305 (C-N) 1610 (C···C of aromatic ring), 1680 (C=N), 1710, 1715, 1735 (C=O of barbituric acid), 3142 (C-H aromatic), 3292 (N-H of amide)
3b	276	9.27 (ss, 2H, 2x N*H*CO of barbituric acid), 8.59 (s, 1H, =C*H*-Ar), 8.18–7.78 (m, 4H, Ar-*H*), 5.4 (d, 1H, > C*H*-NH), 4.5 (brs, 1H, > CH-N*H*) 3.39 (s, 3H, OCH_3)	1060 (C-O-C), 1290 (N-N), 1300 (C-N), 1600 (C···C of aromatic ring), 1675 (C=N), 1715, 1720, 1730 (C=O of barbituric acid), 3150 (C-H aromatic), 3295 (N-H of amide)
3c	292	11.19 (s, 1H, OH exchangeable) 9.26 (ss, 2H, 2× N*H*CO of barbituric acid), 8.58 (s, 1H, =C*H*-Ar), 8.15–7.85 (m, 3H, Ar-*H*), 5.5 (d, 1H, >C*H*-NH), 4.3 (brs, 1H, >CH-N*H*), 3.48 (s, 3H, OCH_3)	1065 (C-O-C), 1295 (N-N) 1305 (C-N), 1605 (C···C of aromatic ring), 1680 (C=N), 1710, 1720, 1730 (C=O of barbituric acid), 3145 (C-H aromatic), 3290 (N-H of amide) 3420 (O-H)
3d	289	9.25 (ss, 2H, 2x N*H*CO of barbituric acid), 8.53 (s, 1H, =C*H*-Ar), 8.20–7.80 (m, 4H, Ar-*H*), 5.4 (d, 1H, >C*H*-NH), 4.5 (brs, 1H, >CH-N*H*), 1.5 (ss, 6H, N(CH_3)$_2$)	1290 (N-N), 1310 (C-N), 1610 (C···C of aromatic ring), 1675 (C=N), 1715, 1725, 1730 (C=O of barbituric acid), 3140 (C-H aromatic), 3295 (N-H of amide)
3e	262	9.26 (ss, 2H, 2x N*H*CO of thiobarbituric acid), 8.65 (s, 1H, = C*H*-Ar), 8.18–7.79 (m, 5H, Ar-*H*), 5.5 (d, 1H, >C*H*-NH), 4.6 (brs, 1H, >CH.N*H*)	1260 (C=S), 1295 (N-N), 1305 (C-N), 1610 (C···C of aromatic ring), 1680 (C=N), 1710, 1725 (C=O of thiobarbituric acid), 3145 (C-H aromatic), 3295 (N-H of amide)
3f	292	9.25 (ss, 2H, 2x N*H*CO of thiobarbituric acid), 8.61 (s, 1H, =C*H*-Ar), 8.15–7.75 (m, 4H, Ar-*H*), 5.3 (d, 1H, >C*H*-NH), 4.8 (brs, 1H, >CH.N*H*), 3.40 (s, 3H, OCH_3)	1065 (C-O-C), 1255 (C=S) 1292 (N-N), 1302 (C-N), 1605 (C···C of aromatic ring), 1670 (C=N), 1712, 1720 (C=O of thiobarbituric acid), 3145 (C-H aromatic), 3290 (N-H of amide)
3g	308	11.20 (s, 1H, O*H* exchangeable) 9.28 (ss, 2H, 2x N*H*CO of thiobarbituric acid), 8.57 (s, 1H, =C*H*-Ar), 8.17–7.86 (m, 3H, Ar-*H*), 5.4 (d, 1H, >C*H*=NH), 4.2 (brs, 1H, >CH.N*H*), 3.47 (s, 3H, OCH_3)	1060 (C-O-C), 1262 (C=S), 1290 (N-N), 1304 (C-N), 1608 (C···C of aromatic ring), 1685 (C=N), 1715, 1725 (C=O of thiobarbituric acid), 3147 (C-H aromatic), 3288 (C-H of amide), 3415 (O-H)
3h	305	9.27 (ss, 2H, 2x N*H*CO of thiobarbituric acid), 8.48 (s, 1H, =CH-Ar), 8.10–7.75 (m, 4H, Ar-*H*), 5.5 (d, 1H, >C*H*-NH), 4.4 (brs, 1H, >CH.N*H*), 1.6 (s, 6H, N(CH_3)$_2$	1260 (C=S), 1285 (N-N), 1315 (C-N), 1615 (C···C of aroma-s-tic ring), 1680 (C=N), 1715, 1730 (C=O of thiobarbituric acid), 3140 (C-H aromatic), 3290 (N-H of amide)
4a	320	9.22 (ss, 2H, 2x N*H*CO of barbituric acid), 8.25–7.79 (m, 5H, Ar-*H*), 5.95 (s, 1H, C*H*-Ar), 5.3 (d, 1H, > C*H*.NH), 4.49 (brs, 1H, > CH.N*H*), 3.75 (s, 2H, CH_2 of thiozolidinone ring)	675 (C-S-C), 1280 (N-N), 1306 (C-N), 1605 (C···C of aromatic ring), 1715, 1720,1730 (C=O of barbituric acid), 1770 (C=O of β-thialactum ring), 3145 (C-H aromatic), 3290 (N-H of amide)
4b	350	9.23 (ss, 2H, 2x N*H*CO of barbituric acid), 8.20–7.70 (m, 4H, Ar-*H*) 5.90 (s, 1H, C*H*-Ar), 5.2 (d, 1H, >C*H*.NH), 4.45 (brs, 1H, >CH.N*H*), 3.70 (s, 2H, CH_2 of thiazolidinone ring), 3.42 (s, 3H, OCH_3)	680 (C-S-C), 1065 (C-O-C), 1305 (C-N), 1610 (C···C of aromatic ring), 1710, 1720, 1735 (C=O of barbituric acid), 1775 (C=O of β-thialactum ring), 3142 (C-H aromatic), 3295 (N-H of amide)
4c	366	11.22 (s, 1H, O*H* exchangeable), 9.22 (ss, 2H, 2x N*H*CO of barbituric acid), 8.15–7.65 (m, 3H, Ar-*H*), 5.80 (s, 1H, C*H*-Ar), 5.25 (d, 1H, >C*H*-NH), 4.42 (brs, 1H, >CH-N*H*), 3.76 (s, 2H, CH_2 of thiazolidinone ring), 3.48 (s, 3H, OCH_3)	685 (C-S-C), 1060 (C-O-C), 1310 (C-N), 1605 (C···C of aromatic ring), 1705, 1715, 1730 (C=O of barbituric acid), 1765 (C=O of β-thialactum ring), 3145 (C-H aromatic), 3292 (N-H of amide), 3430 (O-H)
4d	363	9.24 (ss, 2H, 2x N*H*CO of barbituric acid), 8.20–7.71 (m, 4H, Ar-*H*), 5.79 (s, 1H, C*H*-Ar), 5.23 (d, 1H, >C*H*-NH), 4.43 (brs, 1H, >CH-N*H*), 3.70 (s, 2H, CH_2 of thiazolidinone ring), 1.5 (s, 6H, N(CH_3)$_2$	682 (C-S-C), 1308 (C-N), 1608 (C···C of aromatic ring), 1708, 1715, 1725 (C=O of barbituric acid), 1755 (C=O of β-thialactum ring), 3140 (C-H aromatic), 3295 (N-H of amide)
4e	336	9.23 (ss, 2H, 2xN*H*CO of thiobarbituric acid), 8.21–7.75 (m, 5H, Ar-*H*), 5.88 (s, 1H, C*H*-Ar), 5.4 (d, 1H, >C*H*-NH), 4.42 (brs, 1H, >CH-N*H*), 3.62 (s, 2H, CH_2 of thiazolidinone ring)	670 (C-S-C), 1255 (C=S), 1275 (N-N), 1310 (C-N), 1610 (C···C of aromatic ring), 1715, 1725 (C=O of thiobarbituric acid), 1772 (C=O of β-thialactum ring), 3145 (C-H aromatic), 3285 (N-H of amide)
4f	366	9.24 (ss, 2H, 2x N*H*CO of thiobarbituric acid), 8.25–7.78 (m, 4H, Ar-*H*), 5.85 (s, 1H, C*H*-Ar), 5.4 (d, 1H, > C*H*-NH), 4.5 (brs, 1H, > CH-N*H*), 3.75 (s, 2H, CH_2 of thiazolidinone ring), 3.45 (s, 3H, OCH_3)	682 (C-S-C), 1068 (C-O-C), 1265 (C=S), 1305 (C-N), 1608 (C···C of aromatic ring), 1705, 1715 (C=O of thiobarbituric acid), 1775 (C=O of β-thialactum ring), 3142 (C-H aromatic), 3280 (N-H of amide)
4g	382	11.20 (s, 1H, O*H* exchangeable) 9.25 (ss, 2H, 2x N*H*CO of barbituric acid), 8.05–7.55 (m, 3H, Ar-*H*), 5.73 (s, 1H, C*H*-Ar), 5.24 (d, 1H, > C*H*-NH), 4.45 (brs, 1H, > CH-N*H*), 3.73 (s, 2H, CH_2 of thiazolidinone ring), 3.47 (s, 3H, OCH_3)	685 (C-S-C), 1065 (C-O-C), 1266 (C=S), 1310 (C-N), 1610 (C···C of aromatic ring), 1708, 1717, (C=O of thiobarbituric acid), 1777 (C=O of β-thialactum ring), 3145 (C-H aromatic), 3275 (N-H of amide)
4h	379	9.22 (ss, 2H, 2x N*H*CO of barbituric acid), 8.15–7.65 (m, 4H, Ar-*H*), 5.76 (s, 1H, C*H*-Ar), 5.25 (d, 1H, > C*H*-NH), 4.45 (brs, 1H, > CH-N*H*), 3.75 (s, 2H, CH_2 of thiazolidinone ring), 1.8 (s, 6H, N(CH_3)$_2$	682 (C-S-C), 1255 (C=S), 1310 (C-N), 1605 (C···C of aromatic ring), 1710, 1715 (C=O of thiobarbituric acid), 1775 (C=O of β-thialactum ring), 3140 (C-H aromatic), 3280 (N-H of amide)

Table 3
Pharmacological data of compounds **1a–1b, 2a–2b, 3a–3h** and **4a–4h**

Compounds	Acute toxicity ALD_{50} (mg kg^{-1} p.o.)	Dose (mg kg^{-1} i.p.)		Anticonvulsant activity (% inhibition)	
		For MES model	For PTZ model	For MES model	For PTZ model
1a	> 1000	30	–	20	–
1b	> 1000	30	–	20	–
2a	> 1000	30	–	30	–
2b	> 1000	30	–	40*	–
3a	> 1000	30	–	40*	–
3b	> 1000	30	–	70**	–
3c	> 1000	30	–	60**	–
3d	> 1000	30	–	60**	–
3e	> 1000	30	–	50**	–
3f	> 1000	30	–	70**	–
3g	> 1000	30	–	70**	–
3h	> 1000	30	–	70**	–
4a	> 1000	30	–	50**	–
4b	> 1000	30	–	60**	–
4c	> 1000	30	–	60**	–
4d	> 1000	30	–	50**	–
4e	> 1000	30	–	70**	–
4f	> 2000	7.5	20	30	20
		15	40	60**	30
		30	80	90***	80***
4g	> 2000	7.5	20	20	30
		15	40	40*	50**
		30	80	80***	90***
4h	> 1000	30	–	60**	–
P.G.[a]		0.5 ml	0.5 ml	0	0
Phenytoin sodium[b]		7.5	–	20	–
		15	–	50**	–
		30	–	80***	–
Lamotrigine[b]		7.5	–	20	–
		15	–	50**	–
		30	–	90***	–
Sodium valproate[c]		–	20	–	30
		–	40	–	50**
		–	80	–	80***

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
[a] Propylene glycol standard for control group.
[b] Standard drug for SMES pattern test.
[c] Standard drug for PTZ seizure pattern test.

tral data of compounds of this step **(3a–3h)** are given in Tables 1 and 2, respectively.

5.1.4. 5-[(2′-Substituted phenyl-4′-oxothiazolidin-3′-yl)amino]-2-oxo/thiobarbituric acid (*4a–4h*)

The mixture of compounds **(3a–3h)** (0.01 mol) and thioglycolic acid (0.01 mol) in presence of a pinch of anhydrous $ZnCl_2$ in methanol, was refluxed at water bath for 10 hours. The reaction mixture was poured in ice-cold water and filtered. The product was recrystallized from suitable solvents to give compounds **(4a–4h)**. Physical, analytical and spectral data of compounds of this step **(4a–4h)** are mentioned in Tables 1 and 2, respectively.

5.2. Pharmacology

5.2.1. Acute toxicity

The compounds were investigated for their acute toxicity (ALD_{50}) in albino mice by following the method of Smith [12].

5.2.2. Anticonvulsant activity

5.2.2.1. Supra-maximal electroshock seizure (SMES) pattern test. This activity was performed according to the method of Tomon et al. [13] on albino rats of the Charles foster strain of either sex, weighing, between 80 and 120 g. Rats were divided into the groups of 10 animals and pregnancy was excluded in female rats. The rats were treated with the different doses of test drugs or phenytoin sodium 30 mg kg^{-1} i.p. or lamotrigine 30 mg kg^{-1} i.p. After 1 how they were subjected to the shock of 150 mA 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.

5.2.2.2. Pentylene tetrazole (PTZ) induced seizures test. It was performed according to the method of Fisher [14]. Albino rats, weighing 100–120 g, were injected with PTZ in a dose of 70 mg kg^{-1} subcutaneously in scruff of neck. After 2–4 min of PTZ injection animals developed the sequence of excite-

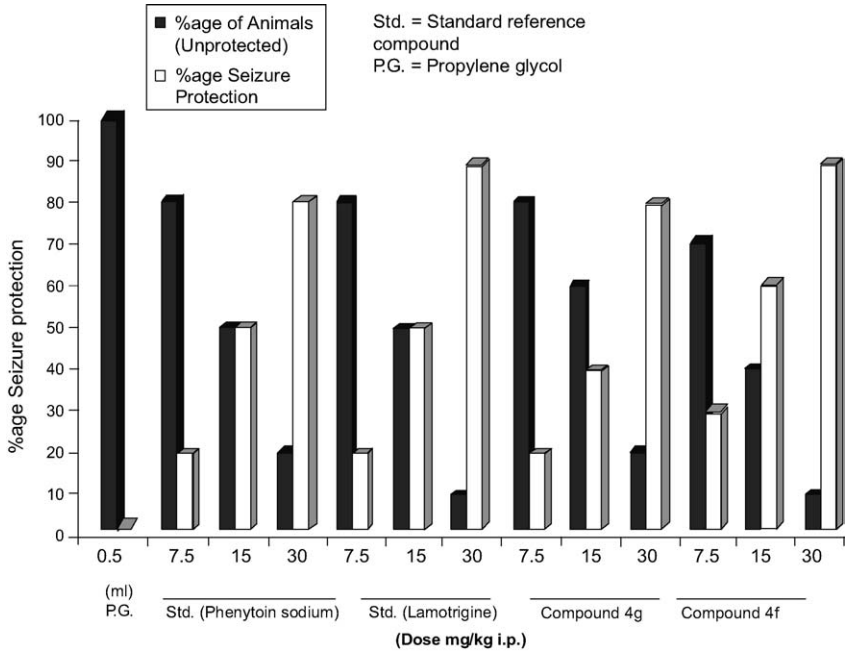

Fig. 1. The bar diagram showing anticonvulsant activity (% age seizure protection) of compounds **4f** and **4g** their comparison with phenytoin sodium and lamotrigine in supra-maximal electroshock pattern test.

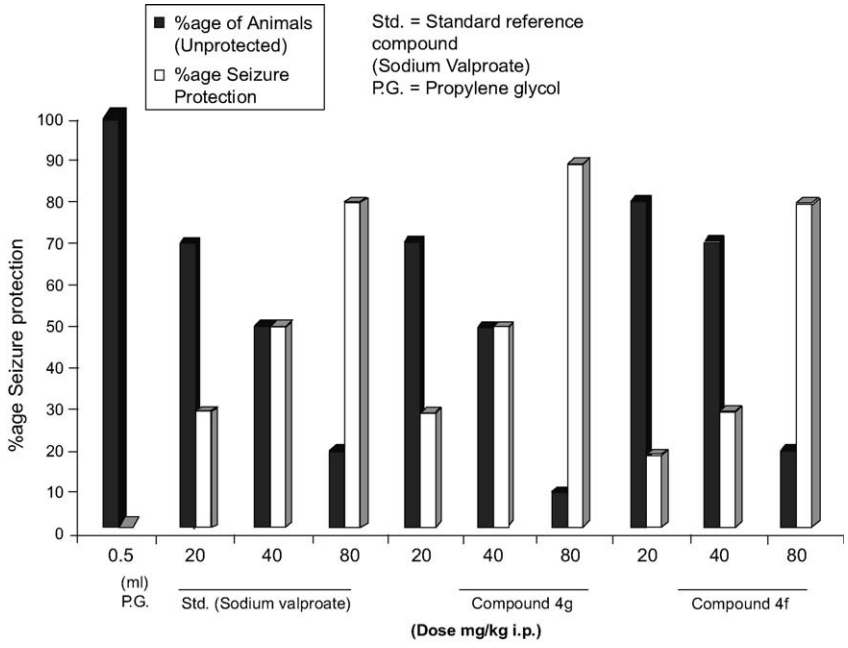

Fig. 2. The bar diagram showing anticonvulsant activity (% age seizure protection) of compounds **4f** and **4g** their comparison with sodium valproate in pentylene tetrazol seizure pattern test.

ment, myoclonic jerks, clonic seizures, one or more maximal tonic seizures. Animals exhibiting these seizure patterns were selected and divided into the groups of 10 animals each. Standard drug in this model was sodium valproate (80 mg kg^{-1} i.p.) and was injected 60 min prior to PTZ challenge.

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