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Original article

Synthesis of some novel N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazides as potential anticonvulsants

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Abstract

A series of N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazides were designed and synthesized to meet the structural requirements essential for anticonvulsant activity. Anticonvulsant activity was determined after intraperitoneal (i.p.) administration to mice by maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ)-induced seizure tests and minimal motor impairment was determined by rotorod test. A majority of the compounds exhibited significant anticonvulsant activity after intraperitoneal administration. Some of the selected compounds were evaluated orally in rats for activity in scPTZ test at several time points (50 mg/kg). The most active compounds carry bromo, fluoro and nitro substituents at 4-position in the phenyl ring. The biochemical estimations of malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) from brain homogenate not only clearly implicated the role of free radicals in PTZ-induced convulsion but also explained the possible mechanism of protective effect of semicarbazides, through the reduced formation of MDA and increased formation of SOD and GSH-Px.

Keywords: Anticonvulsant activity; Naphtha[1,2-*d*]thiazol-2-amine; Semicarbazides; Neuroprotection

1. Introduction

Epilepsy is a neurological disorder of varied etiology, affecting about 1% of the world's population and characterized by recurrent seizure attacks [1]. In fact, epilepsy is the third most frequent neurological disorder encountered in the elderly after cerebrovascular disease and dementia [2]. There is continuing demand for new anticonvulsant agents as several of the currently available antiepileptic drugs (AEDs) have been associated with severe side effects and fail to control seizures in about 30% of epileptic patients [1,3,4].

The prolonged excitation of neurons during seizures can lead to injury and death resulting from underlying biochemical mechanisms that are not well understood. Recent data concerning this problem show the efficacy of some substances with antioxidant properties in the therapy of convulsive disorders and support the hypothesis that experimental epilepsy is mediated by oxidative stress, leading to abnormal structural alterations of cellular proteins, membrane lipids, DNA and RNA [5–9].

The oxidative stress, defined by the excessive production of free radicals, can alter dramatically the cell function and an overproduction of these compounds has been related to seizure-induced neuronal death [10]. Superoxide (O_2^-), a free radical can be generated in the brain by several mechanisms such as inefficiency of the electron-carrying components of the mitochondrial transport chain, monoamines degradation, xanthine oxidase reaction and by the metabolism of arachidonic acid. Nevertheless, the produced O_2^- could be metabolized by superoxide dismutases (SOD), which are present in both cytosol (copper–zinc-associated isoform) and mitochondria (manganese-associated isoform) [11]. The hydrogen peroxide (H_2O_2) is not a free radical per se but in high concentration

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can react with superoxide (Haber–Weiss reaction) or iron (Fenton reaction) producing highly reactive hydroxyl radical ($OH^{\bullet}$). The detoxification of H_2O_2 to H_2O is made by glutathione peroxidase (GSH-Px) [12,13] and involves the glutathione (a thiol-containing tripeptide) which is a cofactor of this enzyme [14,15]. The oxidant–antioxidant system is in equilibrium in normal conditions. However, an imbalance in this system causes tissue injury by oxidant injury. Reactive oxygen species attack membrane lipids and result in LPO. Malondialdehyde (MDA) is the end-product of lipid peroxidation (LPO) and thus serves as an index of LPO. It was also shown that pretreatment with melatonin, an endogenous hormone with antioxidant properties, suppressed PTZ-induced seizures and decreased the concentration of LPO products in the brain [9].

Therefore, one of the main trends of current investigations is the search for novel antiepileptic drugs with neuroprotective properties [16]. Several anticonvulsant drugs such as zonisamide [17], allopurinol [18] and drugs such as MK-801, which is an *N*-methyl-D-aspartate receptor antagonist, protect the brain against iron-induced oxidative stress in rats [19]. A variety of Na^+ channel blockers, such as Phenytoin [20] and lamotrigine [21,22] have been demonstrated to protect neurons against focal as well as global cerebral ischemia in rats.

Thiazoles are important nitrogen and sulfur-containing five-membered heterocyclic compounds. Several thiazole derivatives possess important pharmacological activities and therefore they are useful materials in drug research. They are of interest as potential neuroprotective agents [23–25]. Furthermore, various 2-benzothiazolamine derivatives including riluzole [6-(trifluoromethoxy) 2-benzothiazolamine] exhibited potent anticonvulsant activity [26–28].

In recent years, aryl and heteroaryl semicarbazones have documented increasing advances in AED drug design and were found to act by blocking the voltage-gated Na^+ channels [29–34]. Their role for the treatment of neuronal damage following global and focal ischemia has been documented [35]. Others [31,36] have suggested the identifiable features for anticonvulsant activity like (i) hydrophobic aryl ring, (ii) a hydrogen bonding domain, (iii) an electron-donor group, and (iv) another distal hydrophobic site.

The aryl group can be replaced by other hydrophobic moieties with retention of anticonvulsant activity [37]. In addition, the potency of 2-benzothiazolamine derivatives as sodium flux inhibitors increases with increasing lipophilicity [26]. Moreover, naphthalene ring serves as the lipophilic aryl portion in nafimidone derivatives which have been recognized as potential anticonvulsants [38–41]. Furthermore, tricyclic molecules (e.g. dibenzazepines, dibenzocycloheptadienes, phenothiazines) exhibit widespread pharmaceutical application in the chemical neurosciences, being used as drugs for such varied indications as epilepsy, migraine, chronic pain, depression and psychosis.

In view of these general requirements of activity (Fig. 1) and in continuation of our work on biologically active nitrogen and sulfur-containing heterocycles [42–44], we have designed N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazides in which distal hydrophobic aryl moiety has been varied to include hydrophobic naphthalene ring in conjugation with thiazole ring as tricyclic molecule, naphtha[1,2-*d*]thiazol-2-amine for enhanced lipophilicity and membrane permeability. The compounds were evaluated for their antiepileptic and neurotoxic properties. The extent of oxidative stress has been evaluated by measuring LPO, SOD and GSH-Px activities in selected compounds.

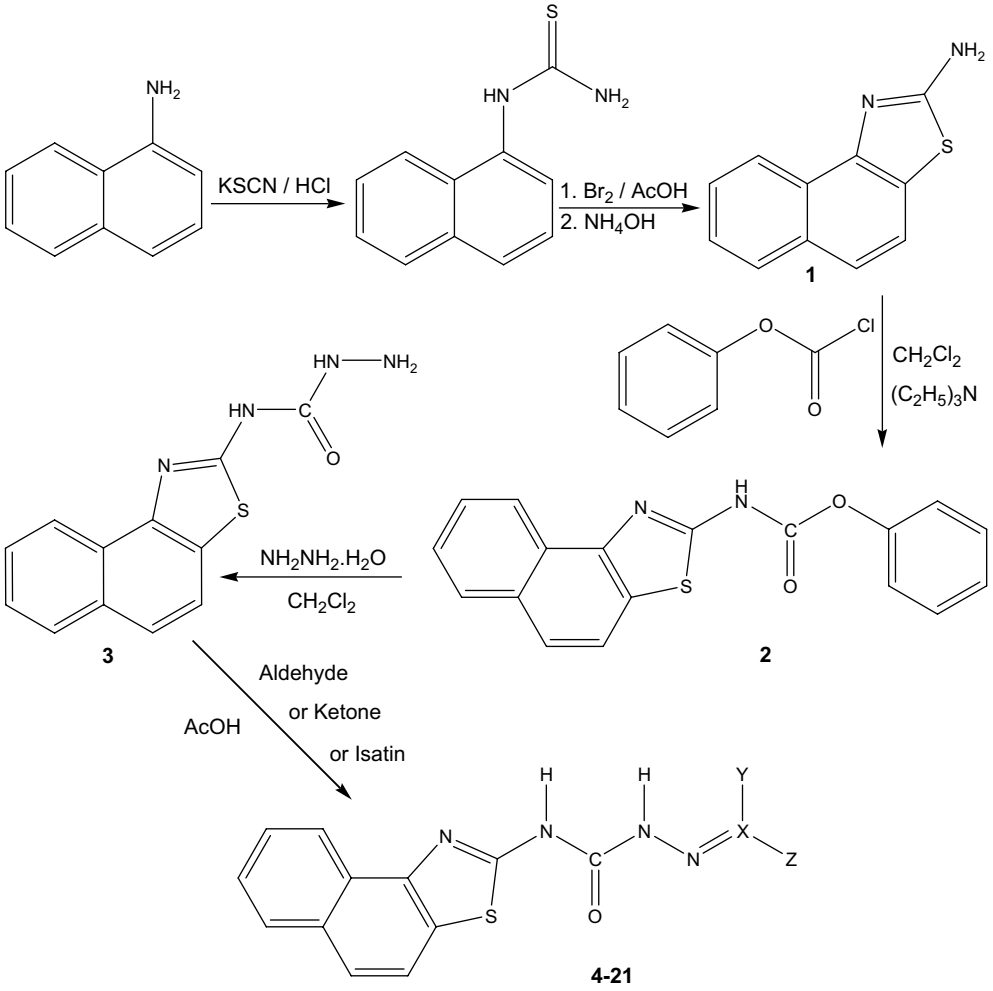
2. Synthesis

In the present study N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazides were synthesized as presented in Scheme 1. Naphtha[1,2-*d*]thiazol-2-amine (**1**) was prepared using a literature protocol [45] with minor modifications. Naphtha[1,2-*d*]thiazol-2-amine (**1**) was treated with phenylchloroformate in dichloromethane at room temperature to yield phenyl-*N*-(naphtha[1,2-*d*]thiazol-2-yl)carbamate (**2**). The carbamate on condensation with hydrazine hydrate in methylene chloride gave N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazide (**3**). The semicarbazone derivatives (**4–21**) were prepared by reaction of the appropriate aryl aldehyde or ketone or isatin with N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazide (**3**). All compounds showed a single spot on TLC and had IR, ^1H NMR and mass spectra in accord with their anticipated structures. The physical characterization data of the compounds are given in Table 1.

3. Results and discussion

Initial anticonvulsant activity and neurotoxicity (NT) data for the semicarbazones are given in Table 2 along with the literature data on phenytoin, carbamazepine, sodium valproate, phenobarbital and ethosuximide [31,46,47]. The maximal electroshock (MES) model has served to identify AEDs that are functionally similar to phenytoin, and most of these compounds display in common the ability to inactivate voltage-dependent Na^+ channels in a use-dependent fashion. Activity in this model seems highly predictive of the ability of those AEDs to protect against partial and secondarily generalized tonic–clonic seizures. Carbamazepine, as well as several newer agents such as felbamate, gabapentin, lamotrigine, and topiramate, fit this model of AED activity [48,49]. The subcutaneous pentylenetetrazole (scPTZ) model has proven to be a good predictor of clinical efficacy against generalized spike-wave epilepsies of the absence type. Thus, the MES and scPTZ screens have become the most widely employed seizure models for early identification of candidate anticonvulsants.

Preliminary anticonvulsant evaluation of all the synthesized compounds was obtained by testing procedures described in National Institute of Neurological Disorders and Stroke, NIH, Bethesada, MD, USA, for Anticonvulsant Screening Project (ASP). Each compound was administered as an i.p. injection at three dose levels (30, 100 and 300 mg/kg) and the anticonvulsant activity was assessed after 30 min and 4 h intervals of administration. The anticonvulsant efficacy was evaluated by the MES-induced seizure and scPTZ-induced seizure threshold tests. NT in mice was measured by the rotorod test.



Scheme 1. Synthetic route to **4**–**21**.

All the compounds, except **5**, **7** and **14** exhibited anticonvulsant activity. Majority of the compounds, except **6**, **16**, **19** and **20**, were active in both MES and scPTZ tests making them useful for broad spectrum of seizure types. Compounds **9**, **11** and **13** with chloro, bromo and fluoro substituents, respectively, showed activity at 100 mg/kg after 0.5 h in MES test. Compounds **9** and **11** were found to be active at the same dose after 4 h. The activity of compounds **9** and **11** having

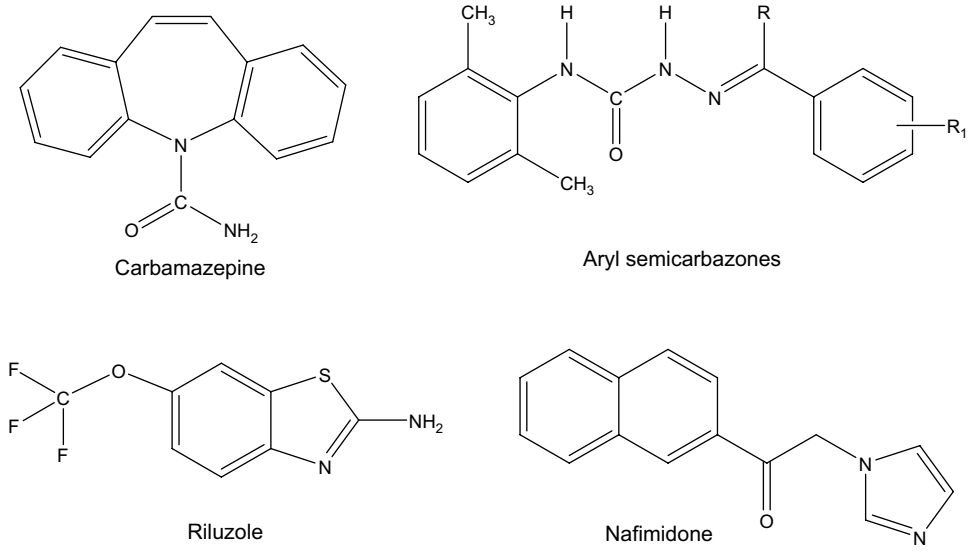
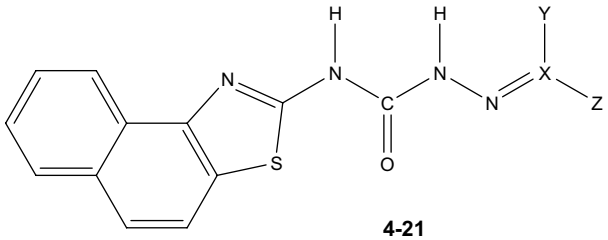


Fig. 1. Structures of some well-known anticonvulsants.

Table 1
Physical characterization of compounds **4–21**



4-21

Compound	X	Y	Z	Yield (%)	M.p. (°C)	Mol. formula[a]	Mol. weight	R_f [b]
4	C	H	H	58	190	$C_{19}H_{14}N_4OS$	346.41	0.67
5	C	H	4-$OMeC_6H_4$	76	238	$C_{20}H_{16}N_4O_2S$	376.43	0.58
6	C	H	2,5-$OMeC_6H_3$	72	250	$C_{21}H_{18}N_4O_3S$	406.46	0.72
7	C	H	3,5-$OMeC_6H_3$	68	268	$C_{21}H_{18}N_4O_3S$	406.46	0.57
8	C	H	3,4,5-$OMeC_6H_2$	76	216	$C_{22}H_{20}N_4O_4S$	436.48	0.69
9	C	H	4-BrC_6H_4	81	252	$C_{19}H_{13}BrN_4OS$	425.3	0.78
10	C	H	2-ClC_6H_4	79	260	$C_{19}H_{13}ClN_4OS$	380.85	0.71
11	C	H	4-ClC_6H_4	72	246	$C_{19}H_{13}ClN_4OS$	380.85	0.73
12	C	H	4-FC_6H_4	83	242	$C_{19}H_{13}FN_4OS$	364.4	0.76
13	C	H	2-OHC_6H_4	61	262	$C_{19}H_{14}N_4O_2S$	362.41	0.89
14	C	H	4–OHC_6H_4	68	238	$C_{19}H_{14}N_4O_2S$	362.41	0.92
15	C	H	4-OH, 3-$OMeC_6H_3$	73	228	$C_{20}H_{16}N_4O_3S$	392.43	0.71
16	C	H	2-$NO_2C_6H_4$	65	242	$C_{19}H_{13}N_5O_3S$	391.4	0.61
17	C	H	4-$NO_2C_6H_4$	73	246	$C_{19}H_{13}N_5O_3S$	391.4	0.65
18	C	Me	4-MeC_6H_4	78	264	$C_{21}H_{18}N_4OS$	360.43	0.59
19	C	Me	C_6H_5	73	218	$C_{20}H_{16}N_4OS$	374.46	0.57
20	C	H	4-$NMe_2C_6H_4$	71	226	$C_{21}H_{19}N_5OS$	389.47	0.64
21	2-Oxoindolin-3-ylidene	–	–	57	292	$C_{20}H_{13}N_5O_2S$	387.41	0.61

[a] Elemental analyses for C, H, and N were within ±0.4% of the theoretical values.
[b] Solvent system: chloroform/methanol (95:5).

4-bromo and 4-chloro substituents, respectively, at the phenyl ring in MES test is comparable to standard drug phenobarbital (100 mg/kg) after 0.5 h, indicating that they have rapid onset and shorter duration of action. Compounds **4**, **6**, **8**, **12**, **15**, **17** and **18** were less active and inhibited the seizures at a dose of 300 mg/kg in the MES screen after 0.5 h. Some compounds like **8**, **12**, **15** and **17** were also active after 4.0 h extended period of activity. Compound **10** with chloro substituent at 2-position of the phenyl ring was active at 300 mg/kg after 4 h in the MES screen. Majority of the compounds also showed activity in scPTZ screen. Compounds **9** and **12** showed activity both at 0.5 h and 4 h periods (100 mg/kg). However, compound **17** showed activity at 100 mg/kg after 0.5 h and at 300 mg/kg after 4 h time period which is comparable to the standard drug carbamazepine. Introduction of the fluoro or trifluoromethyl substituents into the aryl moiety enhanced the anticonvulsant efficacy in comparison to respective chloro, methoxy or methyl analogues [50]. Furthermore, introduction of *p*-nitrophenyl substituent exhibited best activity in scPTZ test [51]. The importance of the 4-bromophenyl substituent for the anticonvulsant activity is documented in the literature [34]. Our results are in accordance with these findings.

On the other hand, compounds **8** and **10** showed activity at 300 mg/kg after 4 h. Compounds showing activity at 300 mg/kg after 0.5 h included **11** and **21**. Compounds that showed moderate protection at a dose of 300 mg/kg both at 0.5 h and 4 h include **4**, **13**, **15**, **16**, **18**, **19** and **20**. In a neurological toxicity screening test, compounds **4**, **9**, **11**, **12**, **17**, **18**, **20** and **21** were found to be toxic at the maximum administrated dose (300 mg/kg). Compounds **8**, **13**, **15**, and **16** were toxic at 100 mg/kg dose.

Some of the selected compounds **9**, **12** and **17** were evaluated orally in rats for activity in scPTZ test at several time points (Table 3). The compounds were tested at 50 mg/kg and compared with standard drug ethosuximide. Compounds **9** and **12** exhibited bioactivity throughout the time period up to 2 h similar to ethosuximide. These compounds did not exhibit NT at the tested dose of 50 mg/kg.

Some active compounds (**9**, **12** and **17**), were selected for the measurement of antioxidant enzyme activities from the brain homogenate to investigate their role in the pathophysiology of epilepsy. The antioxidant effects of the compounds were compared with valproate, which is one of the major antiepileptic drugs, biochemically and clinically. Oxidative stress in the central nervous system has been shown in several rodent models of experimental epilepsy such as the PTZ kindling model [6]. PTZ trigger a variety of biochemical processes including the activation of membrane phospholipases, proteases, and nucleases [52]. Marked alterations in membrane phospholipid metabolism result in the liberation of free fatty acids, diacylglycerols, eicosanoids, lipid peroxides and free radicals [52]. PTZ-induced seizure activity coincides with an

Table 2
Anticonvulsant and NT screening of synthesized compounds **4**–**21**

Compound	Intraperitoneal injection in mice[a] (h)					
	MES screen		scPTZ screen		NT screen	
	0.5	4	0.5	4	0.5	4
4	300	–	300	300	100	300
5	–	–	–[b]	–	–	–
6	300	–	–	–[b]	300	–
7	–	–	–[b]	–	–	–
8	300	300	–	300	100	100
9	100	100	100	100	100	300
10	–	300	–	300	300	–
11	100	100	300	–[b]	100	300
12	300	300	100	100	300	300
13	100	–	300	300	100	100
14	–	–	–[b]	–	–	–
15	300	300	300	300	300	100
16	–	–	300	300	–	100
17	300	300	100	300	300	300
18	300	–	300[c]	300	–	300
19	–	–	300	300	100	–
20	–	–	300	300	300	300
21	–	300	300	–	100	300
Ethosuximide[d]	–	–	300	–	–	–
Phenobarbital[d]	100	30	30	30	100	300
Phenytoin[d]	30	30	–	–	100	100
Carbamazepine[d]	30	100	100	300	100	300
Valproic acid[d]	–	–	300	–	–	–

[a] Doses of 30, 100 and 300 mg/kg were administered. The figures in the table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 h after administration. The dash (–) indicates an absence of activity at maximum dose administered (300 mg/kg).
[b] Death following tonic extension.
[c] Myoclonic jerks.
[d] Data from Refs. [31,46,47].

enhanced oxidative stress in brain tissue. When PTZ was administered, the content of dihydroxy butyric acid reflected the $OH^{\bullet}$ generation during the development of the convulsions, or after fully developed seizures [6], this demonstration of early seizure-induced $OH^{\bullet}$ formation fulfils the critical requirement in establishing the role of reactive oxygen species in the pathophysiology of epilepsy.

The elevated level of MDA, a marker of lipid peroxidation, indicates increased free radical generation in the PTZ treated mice. PTZ-induced increment in MDA content of the tissue was significantly prevented by the treatment of valproate as well as compounds **9**, **12** and **17**. There was a simultaneous significant decrease in the SOD and GSH-Px activities in PTZ treated mice. GSH-Px is an endogenous antioxidant enzyme and it reacts with the free radicals and prevents the generation of hydroxyl radicals, the most toxic form of free radicals. During this defensive process, GSH-Px converts reduced glutathione to its oxidized form. The decreased GSH-Px activity in PTZ treated mice seen in our study indicates that there was an increased generation of free radicals and the decreased GSH-Px was depleted during the process of combating oxidative stress. There was a marked increase in the SOD and GSH-Px activities in the group treated with compounds **9**, **12** and **17**. The results are summarized in Table 4. These findings made us consider the possibility that the decrease in MDA levels and increase in the SOD and GSH-Px activities in compounds **9**, **12**, **17** and valproate treated groups may be due to the antioxidant property associated with the semicarbazides and valproate.

Table 3
Evaluation of some compounds in the scPTZ test after oral administration (50 mg/kg) to rats

Compound	Oral administration to rats[a] (h)			
	0.25	0.5	1.0	2.0
9	3	3	2	1
12	3	2	2	1
17	2	2	1	0
Ethosuximide	0	2	1	1

[a] The figures indicate the number of rats out of four which were protected.

4. Conclusions

In conclusion, we have identified a new series of N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazides that are active against tonic convulsions induced by electrical and chemical stimuli in mice and rats. Biochemical investigations showed that preventing oxidative injury by semicarbazides produces important neuroprotective and anticonvulsive effects against PTZ-induced NT. Some of the most potent compounds appear worthy of a further investigation aimed at assessing their anticonvulsant activity in other models and at elucidating the underlying mechanism of action.

5. Experimental protocols

5.1. Chemistry

Synthetic starting material, reagents and solvents were of analytical reagent grade or of the highest quality commercially available and were purchased from Aldrich Chemical Co., Merck Chemical Co. and were dried when necessary. The progress of the reactions was monitored by thin layer chromatography with F_{254} silica-gel precoated sheets (Merck) using chloroform/methanol 95/5 as eluent; UV light and iodine

Table 4
Biochemical estimation from brain homogenate

Compound	Lipid peroxidation (pmol MDA/mg protein)	GSH-Px (nM NADPH oxidized/mg protein)	SOD (Units/mg protein)
9[a]	292 ± 15*	13.23 ± 2.14*	60 ± 15*
12[a]	278 ± 13*	12.38 ± 1.93*	57 ± 17*
17[a]	309 ± 12	14.37 ± 1.14*	58 ± 13*
Valproic acid	216 ± 11*	17.81 ± 2.31*	65 ± 16
PTZ	418 ± 17*	8.21 ± 1.09*	42 ± 11*
Control	209 ± 14	18.41 ± 2.40	68 ± 12

Each value represents the mean ± SEM from 6 animals in each group; *$P < 0.05$ significant as compared to control and the remaining values are not significant at $P < 0.05$ (Student's *t*-test).
[a] Tested at 100 mg/kg i.p.

vapours were used for detection. IR spectra were recorded, as KBr pellets, on a Schimadzu 8201 PC FT-IR spectrophotometer and wave numbers are given in cm^{-1}. The mass spectra were recorded on Jeol SX-102 (FAB). ^1H NMR spectra, in DMSO-d_6 and $CDCl_3$ solution, were recorded on a Bruker DRX-300 instrument at 298 K. Chemical shifts are reported as ppm relative to TMS as internal standard. Melting points (°C) were determined with an open glass capillary tube and are uncorrected. Elemental analyses were performed on Elementar Vario EL III instrument.

*5.1.1. Synthesis of naphtha[1,2-d]thiazol-2-amine (**1**)*

To *N*-naphthylthiourea (0.05 mol) in 100 ml glacial acetic acid was added bromine (0.05 mol) in 10 ml glacial acetic acid at 10 °C during 1 h. After being stirred at room temperature for 4 h, the reaction mixture was diluted with hot water, the solid impurities were filtered off and the filtrate was basified with NH_4OH when a soft base crystallizeable from acetonitrile (5.8 g, 58%), m.p. 191 °C, was obtained. Lit. [46] m.p. 190 °C.

*5.1.2. Synthesis of phenyl-N-(naphtha[1,2-d] thiazol-2-yl)carbamate (**2**)*

To a solution of phenylchloroformate (0.1 mol) in dichloromethane (40 ml) was added 0.1 mol of naphtha[1,2-*d*]thiazol-2-amine (**1**) and triethylamine (0.1 mol) dropwise and stirred at the room temperature for 6 h. The reaction mixture was concentrated to one-third volume and, after cooling, 100 ml of petroleum ether (40–60) was added to the reaction mixture. The precipitate appeared immediately, which was filtered, washed with a large quantity of water and dried. Yield 89%; m.p. 286 °C; IR (KBr) ν_{max} 3148, 3043, 2867, 1739, 1536, 1483, 1218 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04–7.95 (m, 10 H, ArH), 8.66–8.68 (d, 1H, $J = 7.3$ Hz), 10.68 (s, 1H, CONH, D_2O exchangeable); MS (FAB) *m/z* 321 $(M + 1)^+$.

*5.1.3. Synthesis of N^4-(naphtha[1,2-d] thiazol-2-yl)semicarbazide (**3**)*

To a solution of 0.1 mol of phenyl-*N*-(naphtha[1,2-*d*]thiazol-2-yl)carbamate (**2**) in dichloromethane (100 ml), 9.7 ml of hydrazine hydrate (0.2 mol) was added dropwise and the mixture was stirred at room temperature for 24 h. The precipitate of 4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazide was separated out, filtered, washed with dichloromethane, and dried. Yield 89%; m.p. 198 °C; IR (KBr) ν_{max} 3340, 3267, 3222, 3103, 2923, 1701, 1600, 1537, 1367, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.76 (s, 2H, NH_2, D_2O exchangeable), 7.49–8.23 (m, 5H, ArH), 8.50–8.52 (d, 1H, $J = 7.4$ Hz), 10.78 (s, 1H, CONH, D_2O exchangeable), 11.21 (s, 1H, $NHNH_2$, D_2O exchangeable); MS (FAB) *m/z* 259 $(M + 1)^+$.

*5.1.4. General method for the synthesis of N^4-(naphtha[1,2-d]thiazol-2-yl)semicarbazides (**4–21**)*

To a solution of 0.002 mol of N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazide (**3**) in ethanol (25 ml), an equimolar quantity of appropriate aldehyde or ketone or isatin in ethanol (5 ml) and glacial acetic acid (1 ml) were added. The mixture was refluxed with stirring for 1–6 h until the completion of the reaction and the resultant precipitate was filtered and dried. The product was recrystallized from 95% ethanol. The physical data of the compounds are presented in Table 1. The spectral data of the compounds are the following.

*5.1.4.1. 1-Benzylidene-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**4**).* IR (KBr) ν_{max} 3399, 3182, 3039, 2928, 1703, 1608, 1548, 1363, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29–8.27 (m, 10H, ArH), 8.38 (d, 1H, $J = 7.9$ Hz), 9.66 (s, 1H, imine H), 10.01 (s, 1H, CONH, D_2O exchangeable), 10.89 (s, 1H, $NHNH_2$, D_2O exchangeable); MS (FAB) *m/z* 347 $(M + 1)^+$.

*5.1.4.2. 1-(4-Methoxybenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**5**).* IR (KBr) ν_{max} 3379, 3205, 3093, 2956, 1705, 1608, 1539, 1502, 1369, 1253, 1107, 790 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.89 (s, 3H, OCH_3), 6.96–7.99 (m, 9H, ArH), 8.63 (d, 1H, $J = 7.5$ Hz), 8.92 (s, 1H, imine H), 9.87 (s, 1H, CONH, D_2O exchangeable), 10.96 (s, 1H,=NNH, D_2O exchangeable); MS (FAB) *m/z* 377 $(M + 1)^+$.

*5.1.4.3. 1-(2,5-Dimethoxybenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**6**).* IR (KBr) ν_{max} 3379, 3205, 3093, 2960, 1695, 1583, 1541, 1498, 1365, 1263, 1222, 1109, 1018, 804, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H, $ArOCH_3$), 3.91 (s, 3H, $ArOCH_3$), 6.87–7.95 (m, 8H, ArH), 8.26 (s, 1H, H_6-phenyl), 8.65 (s, 1H, imine H), 9.32 (s, 1H, CONH, D_2O exchangeable), 10.57 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 407 $(M + 1)^+$.

*5.1.4.4. 1-(3,5-Dimethoxybenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**7**).* IR (KBr) ν_{max} 3379, 3205, 3093, 3001, 2937, 1701, 1541, 1514, 1377, 1267, 1137, 1024, 800, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.51 (s, 3H, $ArOCH_3$), 3.61 (s, 3H, $ArOCH_3$), 6.99 (d, 1H, $J = 8.2$ Hz), 6.78 (d, 1H, $J = 8.1$ Hz), 7.01–7.54 (m, 6H, ArH), 8.19 (d, 1H, $J = 7.9$ Hz), 8.51 (s, 1H, imine H), 9.52 (br s, 1H, CONH, D_2O exchangeable), 10.61 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 407 $(M + 1)^+$.

*5.1.4.5. 1-(3,4,5-Trimethoxybenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**8**).* IR (KBr) ν_{max} 3388, 3215, 3093, 3001, 1701, 1577, 1541, 1375, 1332, 1134, 999, 796 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H, 4-OCH_3), 3.97 (s, 6H, 3,5-OCH_3), 6.94–6.99 (m, 7H, ArH), 8.61 (d, 1H, $J = 7.7$ Hz), 8.96 (s, 1H, imine H), 9.91 (br s, 1H, CONH, D_2O exchangeable), 11.10 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 437 $(M + 1)^+$.

*5.1.4.6. 1-(4-Bromobenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**9**).* IR (KBr) ν_{max} 3390, 3205, 3093, 2960, 1701, 1542, 1375, 1323, 1070, 798 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52–7.95 (m, 9H, ArH), 8.01 (s, 1H, imine H), 8.62 (d, 1H, $J = 8.0$ Hz), 10.18 (s, 1H, CONH, D_2O exchangeable), 11.32 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 426 $(M + 1)^+$.

*5.1.4.7. 1-(2-Chlorobenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**10**).* IR (KBr) ν_{max} 3388, 3195, 3082,

2962, 1705, 1583, 1542, 1375, 1323, 792, 748, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.96 (m, 7H, ArH), 8.33 (s, 1H, H_3-phenyl), 8.49 (s, 1H, H_6-phenyl), 8.62 (d, 1H, $J = 7.6$ Hz), 9.61 (s, 1H, imine H), 10.38 (br s, 1H, CONH, D_2O exchangeable), 11.47 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 382 $(M + 1)^+$.

*5.1.4.8. 1-(4-Chlorobenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**11**).* IR (KBr) ν_{max} 3384, 3205, 3093, 2964, 1701, 1585, 1541, 1373, 1323, 1149, 1085, 798 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–8.01 (m, 9H, ArH), 8.62 (d, 1H, $J = 7.9$ Hz), 9.38 (s, 1H, imine H), 10.14 (s, 1H, CONH, D_2O exchangeable), 11.30 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 382 $(M + 1)^+$.

*5.1.4.9. 1-(4-Fluorobenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**12**).* IR (KBr) ν_{max} 3379, 3195, 3093, 2960, 1701, 1602, 1541, 1375, 1234, 1016 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.92–8.44 (m, 10H, ArH), 9.16 (s, 1H, imine H), 9.85 (s, 1H, CONH, D_2O exchangeable), 11.05 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 365 $(M + 1)^+$.

*5.1.4.10. 1-(2-Hydroxybenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**13**).* IR (KBr) ν_{max} 3413, 3226, 3082, 1691, 1580, 1488, 1365, 1274, 1211, 952, 819 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88–7.96 (m, 9H, ArH), 8.32 (s, 1H, imine H), 8.58 (d, 1H, $J = 7.8$ Hz), 9.93 (s, 1H, CONH, D_2O exchangeable), 11.01 (s, 1H, =NNH, D_2O exchangeable), 12.32 (s, 1H, OH); MS (FAB) *m/z* 363 $(M + 1)^+$.

*5.1.4.11. 1-(4-Hydroxybenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**14**).* IR (KBr) ν_{max} 3467, 3328, 3195, 2945, 1708, 1608, 1541, 1506, 1377, 1267, 1166, 833, 796 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.7 (d, 2H, $J = 8.5$ Hz), 7.32–7.76 (m, 6H, ArH), 8.43 (d, 1H, $J = 7.8$ Hz), 9.35 (s, 1H, imine H), 9.78 (s, 1H, CONH, D_2O exchangeable), 10.84 (s, 1H, =NNH, D_2O exchangeable), 12.21 (s, 1H, OH); MS (FAB) *m/z* 363 $(M + 1)^+$.

*5.1.4.12. 1-(4-Hydroxy-3-methoxybenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**15**).* IR (KBr) ν_{max} 3350, 3205, 3093, 2941, 1695, 1585, 1541, 1371, 1265, 1012, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3H, $ArOCH_3$), 6.82 (d, 1H, $J = 8.0$ Hz), 7.03 (d, 1H, $J = 7.9$ Hz), 7.42–7.55 (m, 2H, ArH), 7.62 (d, 1H, $J = 8.6$ Hz), 7.75 (d, 1H, $J = 8.6$ Hz), 7.84 (d, 2H, $J = 6.4$ Hz), 8.52 (d, 1H, $J = 7.9$ Hz), 8.69 (s, 1H, imine H), 8.74 (s, 1H, CONH, D_2O exchangeable), 9.93 (s, 1H, =NNH, D_2O exchangeable), 10.95 (s, 1H, OH); MS (FAB) *m/z* 393 $(M + 1)^+$.

*5.1.4.13. 1-(2-Nitrobenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**16**).* IR (KBr) ν_{max} 3467, 3388, 3195, 3072, 2960, 1685, 1587–1477, 1375, 1334, 1157, 1018, 800, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–8.62 (m, 10H, ArH), 9.78 (s, 1H, imine H), 10.22 (br s, 1H, CONH, D_2O exchangeable), 11.58 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 392 $(M + 1)^+$.

*5.1.4.14. 1-(4-Nitrobenzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**17**).* IR (KBr) ν_{max} 3338, 3201, 2960, 1701, 1587, 1550, 1517, 1344, 1161, 1107, 800, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–7.90 (m, 10H, ArH), 9.80 (s, 1H, imine H), 10.10 (br s, 1H, CONH, D_2O exchangeable), 11.53 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 392 $(M + 1)^+$.

*5.1.4.15. 4-(Naphtha[1,2-d]thiazol-2-yl)-1-(1-p-tolylethylidene)semicarbazide (**18**).* IR (KBr) ν_{max} 3390, 3192, 3082, 2920, 1697, 1533, 1485, 1369, 1272, 1137, 794 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (s, 3H, N=CH–CH_3), 2.40 (s, 3H, Ar–CH_3), 7.24 (d, 2H, $J = 7.6$ Hz), 7.51–7.95 (m, 7H, ArH), 8.59 (d, 1H, $J = 7.9$ Hz), 10.32 (s, 1H, CONH, D_2O exchangeable), 10.99 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 375 $(M + 1)^+$.

*5.1.4.16. 4-(Naphtha[1,2-d]thiazol-2-yl)-1-(1-phenylethylidene)semicarbazide (**19**).* IR (KBr) ν_{max} 3390, 3192, 3082, 2920, 1697, 1533, 1485, 1369, 1272, 1137, 794 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (s, 3H, N=CH–CH_3), 7.27–7.93 (m, 10H, ArH), 8.58 (d, 1H, $J = 7.9$ Hz), 9.34 (s, 1H, CONH, D_2O exchangeable), 10.17 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 361 $(M + 1)^+$.

*5.1.4.17. 1-(4-(Dimethylamino)benzylidene)-4-(naphtha[1,2-d]thiazol-2-yl)semicarbazide (**20**).* IR (KBr) ν_{max} 3390, 3196, 3093, 2939, 1705, 1610, 1537, 1504, 1363, 1182 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.05 [s, 6H, $N(CH_3)_2$], 6.72–7.95 (m, 9H, ArH), 8.64 (d, 1H, *J* 7.9 Hz), 8.70 (s, 1H, imine H), 9.37 (s, 1H, CONH, D_2O exchangeable), 10.56 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 390 $(M + 1)^+$.

*5.1.4.18. 4-(Naphtha[1,2-d]thiazol-2-yl)-1-(2-oxoindolin-3-ylidene)semicarbazide (**21**).* IR (KBr) ν_{max} 3159, 3047, 2898, 1726, 1691, 1606, 1548, 1467, 1296, 1190, 1053 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.75–7.76 (m, 9H, ArH), 7.95 (d, 1H, $J = 6.9$ Hz), 8.26 (s, 1H, CONH-indolin, D_2O exchangeable), 9.67 (s, 1H, CONH, D_2O exchangeable), 10.44 (s, 1H, =NNH, D_2O exchangeable); MS (FAB) *m/z* 388 $(M + 1)^+$.

5.2. Pharmacological evaluation

All the compounds were screened for anticonvulsant activity in MES-induced seizure test and scPTZ-induced seizure threshold test. The NT was measured by the rotorod test. The results are summarized in Table 2.

5.2.1. Anticonvulsant screening

Anticonvulsant evaluation of semicarbazones was undertaken by following the National Institute of Health (NIH) Anticonvulsant Drug Development (ADD) Program protocol [53,54]. Male Swiss albino mice (18–25 g) and male albino rats (Wistar, 100–125 g) were used as experimental animals.

The semicarbazones were suspended in 5% gum acacia/water mixture. All the compounds were administered i.p. in doses of 30, 100 and 300 mg/kg to 1–4 animals. Some selected compounds were examined for oral activity in rats. All the tests have been performed in accordance with the guidelines laid out by the Institutional Animal Ethics Committee.

5.2.1.1. MES test. MES seizures were elicited (Techno Convulsiometer Model No. C-2, Techno Electronics, Lucknow, India) with a 60 cycle altering current of 50 mA intensity (5–7 times that necessary to elicit minimal electroshock seizures) delivered for 0.25 s via corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of the electrodes in order to prevent the death of the animal. Abolition of the hind limb tonic extensor component of the seizure is defined as protection, and results are expressed as number of animals protected/number of animals tested.

5.2.1.2. scPTZ test. Thirty minutes after the administration of the test compounds, mice were injected with PTZ dose of 85 mg/kg intraperitoneally to cause seizures in more than 97% of the animals. This is called the convulsive dose (CD_{97}). A dose of 70 mg/kg scPTZ was used for rats. The animals were observed during the following 4 h for the occurrence of seizures. A threshold convulsion is defined as one episode of clonic spasms which persists for at least 5 s. Absence of even a threshold convulsion during the period of observation is taken as the endpoint in this test.

5.2.1.3. NT screening. The rotorod test was used to evaluate NT. The mice were trained to stand on an accelerating rotarod rotating at 10 revs./min. The rod diameter was 3.2 cm (Techno Rotarod system, Techno Electronics, Lucknow, India). The mice were placed on the rotarod to measure the effect of the drug on their motor performance [55]. The dose at which animals fell off the rotarod was determined. Before the beginning of all experiments, the riding ability of the animals in the rotarod was checked. Thus, the mice were initially put on a rotating rod, and mice that immediately dropped off (within 30 s) were removed from the experiment.

5.2.2. Biochemical estimations

5.2.2.1. Animals. A total of 36 male Swiss albino mice (18–25 g) were used in this study. The animals were housed in a temperature controlled room (22–25 °C) with a 12:12 light–dark cycle; water and food were given ad libitum. The experimental animals were grouped as follows: Group 1: 0.9% NaCl, ($n = 6$); Group 2: 0.9% NaCl 30 min prior to PTZ ($n = 6$); Group 3: valproic acid, 100 mg/kg i.p., 30 min prior to PTZ ($n = 6$); Group 4: compound 9, 100 mg/kg i.p., 30 min prior to PTZ ($n = 6$); Group 5: compound 12, 100 mg/kg i.p., 30 min prior to PTZ ($n = 6$); Group 6: compound 17, 100 mg/kg i.p., 30 min prior to PTZ ($n = 6$). PTZ dissolved in 0.9% NaCl was injected at a dose of 85 mg/kg.

5.2.2.2. Sample preparation and biochemical evaluation. Mice were sacrificed by decapitation 4 h after the last injection. The brains were quickly removed and were washed twice with cold saline solution, placed into glass bottles, labeled, and stored in a deep freeze (−30 °C) until processing (maximum 10 h). Tissues were homogenized in four volumes of ice-cold Tris–HCl buffer (50 mM, pH 7.4) using a glass Teflon homogenizer (Ultra Turrax IKA T18 Basic, USA) after cutting up the brains into small pieces with scissors (for 2 min at 5000 rpm). MDA and protein levels activities were carried out at this stage. The homogenate was then centrifuged at 5000g for 60 min to remove debris. Clear upper supernatant fluid was taken and GSH-Px activity was carried out at this stage. The supernatant solution was extracted with an equal volume of an ethanol/chloroform mixture (5:3, v/v). After centrifugation at 5000g for 30 min, the clear upper layer (the ethanol phase) was taken and used in the SOD activity. All preparation procedures were performed at +4 °C.

5.2.2.2.1. Lipid peroxidation assay. The extent of lipid peroxidation in brain homogenates was determined by measuring the release of thiobarbituric acid reactive substance (TBARS) in terms of MDA equivalent using a molar extinction coefficient of 1.56×10^5/min/cm as described by Ohkawa et al. [56]. Briefly, the homogenate was centrifuged at 3000g for 15 min and supernatant was used for assay. Samples of 0.1 ml homogenate were mixed with 0.2 ml of 8.1% SDS, 1.5 ml 20% glacial acetic acid and 1.5 ml of 0.8% thiobarbituric acid. Following these additions, tubes were mixed and heated at 95 °C for 1 h on a water bath and cooled under tap water before mixing 1 ml of distilled water and 5 ml mixture of *n*-butanol and pyridine (15:1). The mixture was centrifuged at 2200g for 10 min. The amount of MDA formed was measured by the absorbance of upper organic layer at a wavelength of 532 nm in Perkin Elmer spectrophotometer using appropriate controls. The results are expressed as pmol MDA/mg protein.

5.2.2.2.2. Superoxide dismutase (SOD) activity determination. Total (Cu–Zn and Mn) SOD activity was determined according to the method of Sun et al. [57]. The principle of the method is based on the inhibition of nitroblue tetrazolium (NBT) reduction by the xanthine–xanthine oxidase system as a superoxide generator. Activity was assessed in the ethanol phase of the brain homogenate after 1.0 ml ethanol/chloroform mixture (5/3, v/v) was added to the same volume of sample and centrifuged. One unit of SOD was defined as the enzyme amount causing 50% inhibition in the NBT reduction rate. SOD activity was expressed as units per mg protein.

5.2.2.2.3. Glutathione peroxidase (GSH-Px) activity determination. GSH-Px activity was measured spectrophotometrically by a coupled enzyme procedure at 27 °C monitoring loss of NADPH at 340 nm as described by Lawrence and Burk [58]. The homogenate was centrifuged at 4 °C at 500g for 15 min and the resulting supernatant at 10 000g for 20 min. The enzymatic reaction was conducted in 3 ml quartz cuvettes of 1 cm path length in a Perkin–Elmer spectrophotometer. The reaction mixture contained 50 mM phosphate buffer (pH 7.4), 4 mM NADPH, 1 unit glutathione reductase, 0.1 ml of supernatant sample and 0.7 mM H_2O_2 as substrate. Reactions were initiated by the addition of H_2O_2. Direct proportionality was seen with GSH-Px enzyme activity over time

and with sample concentration. GSH-Px activity was estimated from the decrease of optical density at 340 nm due to NADPH oxidation between 2 and 4 min after the start of the reaction. The results are expressed as nmol NADPH oxidized/mg protein. One unit of the GSH-Px activity is defined as the amount of enzyme necessary to catalyze 1 nmol NADPH/min g wet weight at 27 °C.

5.2.2.2.4. Total protein determinations. Total protein concentration of brain homogenates was determined by folin–phenol reaction as described by Lowry et al. [59]. The bovine serum albumin was used as a standard.

5.3. Statistical analysis

All data are expressed as mean ± SD. Statistical comparison was made relative to the appropriate control group by student's *t*-test and analysis of variance. The 0.05 level was selected as the point of minimal statistical significance in every comparison.

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