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Design, synthesis and biological evaluation of novel thiosemicarbazide analogues as potent anticonvulsant agents

Reshma J. Nevagi *, Avinash S. Dhake, Harsha I. Narkhede, Prabhjeet Kaur

Department of Pharmaceutical Chemistry, SMBT College of Pharmacy, Nandi Hills, Dhamangaon, Igatpuri, Nashik 422403, Maharashtra, India

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ABSTRACT

Novel thiosemicarbazide derivatives were synthesised and evaluated for their anticonvulsant activity and neurotoxicity. Anticonvulsant activity was done for grand mal and petit mal types of epilepsies by maximal electroshock (MES) and pentylenetetrazol (PTZ) induced convulsions methods respectively. Rotarod test was done to determine neurotoxicity. Amongst synthesised compounds, N-(4-bromophenyl)2-[(2-phenylhydrazinyl) carbonothioyl] hydrazinecarbothioamide (**5e**) is a broad-spectrum anticonvulsant agent since it was active in both (MES) and (PTZ) induced seizure models with no neurotoxicity and N,N-(bis(chlorophenyl)hydrazine-1,2-dicarbothoamide (**5g**) acts as a selective agent for grand mal epilepsy.

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1. Introduction

Epilepsy is a collective term that includes over 40 different types of human seizure disorders. Approximately 1% of the world population (50 million people worldwide) is afflicted with this serious neurological disorder [1]. Epilepsy is a major neurological disorder, characterised by periodic and unpredictable occurrence of seizures, which take various forms depending on the part of the brain affected [2]. Thiosemicarbazides have aroused considerable interest in chemistry and biology due to their antibacterial [3], anti-malarial [4], anti-cancer [5], anti-HIV [6], anti-tubercular [7], anti-viral [8], anti-tumor [9] and anti-protozoal [10] properties. Along with these activities, recent reports suggested that this moiety also possess good anticonvulsant properties [11–13].

There have been several attempts to postulate a general pharmacophore for the different anticonvulsant classes [14–17]. A 3 point pharmacophore model was proposed for anticonvulsants acting through blocking of voltage-gated sodium Channel by superimposing carbamazepine (CBZ), phenytoin (DPH), lamotrigine (LAM), zonisamide (ZON), and rufinamide (CGP). The common structural features essential for the activity were at least one aryl ring, one electron donor atom and a second donor atom in proximity to the N—H group, forming a hydrogen bond acceptor or donor [18]. Later on, a new generalised 4-point pharmacophoric model was proposed by studying structurally different compounds with anticonvulsant activity with different mechanisms of action [19,20]. A simple pictorial representation of pharmacophoric model is as below [21]:

According to pharmacophoric model, there are four structural requirements for the anticonvulsant activity.

A. An aryl hydrophobic binding site with halo substituent preferably in the para position.
B. A system containing 2 electron donor systems.
C. Hydrogen bonding domain exemplified by the presence of —NHCO/—NHCS grouping.
D. Another hydrophilic–hydrophobic site controlling the pharmacokinetic properties of the anticonvulsant.

1.1. Designed strategy for the molecules

According to published model (Fig. 1), we synthesised new thiosemicarbazide analogues to explore their anticonvulsant properties. The target compounds (**5a–h**) possessed all the required pharmacophoric elements (Fig. 2). The aryl ring substituted with halo group can be referred to the aryl hydrophobic binding site (A), the sulphur of thiosemicarbazide moiety can act as a two electron donor system (B), —C(S)NH— grouping constitutes the hydrogen bonding domain (C) and R^1 represents hydrophilic–hydrophobic site.

2. Materials and methods

Melting points were taken by open cup capillary method and are uncorrected. IR spectra were taken on FTIR JASCO-4100 type

* Corresponding author. Fax: +91 02553 202000.
E-mail address: rjnevagi@gmail.com (R.J. Nevagi).

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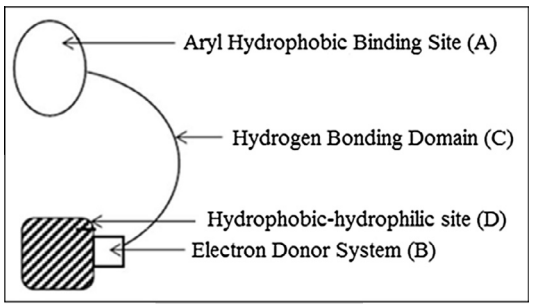


Fig. 1. Structural requirements for displaying Anticonvulsant activity.

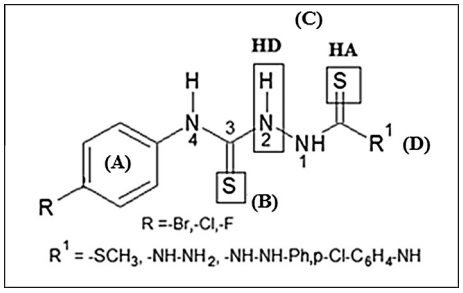


Fig. 2. Target molecules. Where, A = Aryl hydrophobic binding site, D = electron donor system, HD and HA = Hydrogen bonding domains, R^1 = Hydrophilic–hydrophobic site.

A spectrophotometer using KBr pellet. Proton and Carbon nuclear magnetic resonance (NMR) spectra were recorded using DMSO as a solvent at ambient temperature using tetramethylsilane as an internal standard on BRUKER AVANCE II 400 Spectrometer. Mass spectra were recorded on Varian 410 Prostar Binary LC 500 instrument using THF as solvent. The chemicals used were of LR grade and used without further purification. Thin layer chromatography was performed on silica gel G and spots were visualised under ultraviolet (UV) lamp.

3. Experimental procedure

*3.1. Synthesis of aryl thiosemicarbazides (**4a–c**)*

Aryl thiosemicarbazides were prepared from the respective anilines by 2 routes (Route A and B).

Route A was employed according to the procedure reported earlier [22]. p-Chloro aniline on treatment with carbon disulphide in the presence of sodium hydroxide and dimethyl sulphate gave corresponding dithiocarbamate (**3a**), which was then isolated and reacted with hydrazine hydrate to yield p-chlorophenyl thiosemicarbazide (**4a**).

Route B was employed according to the procedure reported earlier [23]. Anilines on treatment with carbon disulphide in the presence of ammonia, water and sodium chloroacetate gave sodium acetate salt of the corresponding dithiocarbamate (**3b**, **3c**), which on reaction with hydrazine hydrate yielded the respective thiosemicarbazide (**4b**, **4c**).

*3.2. General method for the synthesis of hydrazinecarbodithioates (**5a**, **5b**)*

Substituted thiosemicarbazide (**4b–c**) (0.05 mole) was dissolved in 20 ml DMSO. To this reaction mixture, CS_2 (0.05 mole) and the aqueous solution of 2.0 M NaOH (6 ml) was added over 30 min. with stirring at room temperature (27–30 °C). The reaction mixture was stirred for 8 h. To the reaction mixture, dimethyl sulphate (0.05 mole) was added dropwise with stirring at 0–5 °C and stirred further for 5 h. After completion of the reaction confirmed by TLC, ice-cold water was added to obtain the hydrazinecarbodithioate product. The solid obtained was filtered through suction pump, washed with water, dried and recrystallised from DMSO to obtain the pure hydrazinecarbodithioate. The traces of DMSO were removed by giving the ethyl acetate slurry wash to the recrystallised compounds.

*3.2.1. Methyl 2-[(4-bromophenyl) carbamothioyl hydrazinecarbodithioate (**5a**)*

IR (KBr) γ_{max} cm^{-1} 3433, 3255 (—NH stretch), 1593 (—NH bend), 1534 (C=C stretch), 1073 (C=S), 502 (C—Br); ^{1}H NMR (DMSO-d6, 400 MHz) δ 2.65 (s, 3H, $-CH_3$), 3.67 (s, 1H, —NH), 7.55 (d, J = 8.32 Hz, 2H, Ar—H), 7.37 (d, J = 8.20 Hz, 2H, Ar—H), 10.30 (s, 1H, Ar—NH); ^{13}C NMR (DMSO-d6, 100 MHz) δ 18.52, 126.59, 127.63, 128.39, 137.96, 178.35, 202.56; MS (EI): $[M]^+$ 336.2.

*3.2.2. Methyl 2-[(4-fluorophenyl) carbamothioyl hydrazinecarbodithioate (**5b**)*

IR (KBr) γ_{max} cm^{-1} 3459, 3260 (NH stretch), 1551 (NH bend), 1506 (C=C stretch), 1405 (C—F), 1207 (C=S); ^{1}H NMR (DMSO-d6, 400 MHz) δ 2.68 (s, 3H, $-CH_3$), 3.75 (s, 1H, —NH), 7.56 (d, J = 8.32 Hz, 2H, Ar—H), 7.39 (d, J = 8.23 Hz, 2H, Ar—H), 10.28 (s, 1H, Ar—NH); ^{13}C NMR (DMSO-d6, 100 MHz) δ 18.52, 113.75, 127.91, 133.46, 161.28, 178.35, 202.5; MS (EI): $[M]^+$ 275.6.

*3.3. General method for synthesis of hydrazinedithioamides (**5c–5f**)*

To the solution of substituted thiosemicarbazide (**4b**, **4c**) (0.01 mole) in DMSO (20 ml), CS_2 (0.01 mole) and the aqueous solution of 2.0 M KOH (0.01 mole) were added and the reaction mixture was stirred at 0–5 °C for 2 h to form corresponding potassium salt of dithiocarbamate. To a stirred mixture, hydrazine hydrate or phenylhydrazine (0.01 mole) was added, and stirring was continued at 80 °C for several hours. After the completion of the reaction was confirmed by TLC, crushed ice was added to obtain the corresponding hydrazinedithioamide. The obtained solid was then filtered, washed with cold water, dried and recrystallised using DMSO. The traces of DMSO were removed by giving the ethyl acetate slurry wash to the recrystallised compounds.

*3.3.1. N-(4-bromophenyl)-2-(hydrazinylcarbonothioyl) hydrazinecarbothioamide (**5c**)*

IR (KBr) γ_{max} cm^{-1} 3443, 3293 (NH stretch), 1619, 1549 (NH Bend), 1483 (C=C stretch), 1058 (C=S), 727 (C—Br); ^{1}H NMR (DMSO-d6, 400 MHz) δ 2.54–3.41 (s, 4H, 4X—NH), 3.75 (s, 1H, —NH), 7.52 (d, J = 8.76 Hz, 2H, Ar—H), 7.30 (d, J = 8.76 Hz, 2H, Ar—H), 7.64 (s, 2H, NH_2), 9.76 (s, 1H, Ar—NH); ^{13}C NMR (DMSO-d6, 100 MHz) δ 126.59, 127.63, 128.39, 137.96, 178.35, 179.33; MS (EI): $[M]^+$ 320.2.

*3.3.2. N-(4-fluorophenyl)-2-(hydrazinylcarbonothioyl) hydrazinecarbothioamide (**5d**)*

IR (KBr) γ_{max} cm^{-1} 3423, 3236 (NH stretch), 1613, 1572 (NH bend), 1506 (C=C stretch), 1327 (C—F), 1057 (C=S); ^{1}H NMR (DMSO-d6, 400 MHz) δ 2.51–3.40 (s, 4H, 4X—NH), 3.74 (s, 1H, —NH), 7.52 (d, J = 8.76 Hz, 2H, Ar—H), 7. 30 (d, J = 8.76 Hz, 2H, Ar—H), 7.63 (s, 2H, NH_2), 9.78 (s, 1H, Ar—NH); ^{13}C NMR (DMSO-d6, 100 MHz) δ 113.75, 127.91, 133.46, 161.28, 178.35, 179.33; MS (EI): $[M]^+$ 259.4.

*3.3.3. N-(4-bromophenyl)2-[(2-phenylhydrazinyl) carbonothioyl] hydrazine carbothioamide (**5e**)*

IR (KBr) γ_{max} cm^{-1} 3243, 3180 (NH stretch), 1602, 1546 (NH bend), 1496 (C=C stretch), 1076 (C=S), 617 (C—Br); ^1H NMR (DMSO-d6, 400 MHz) δ 7.33–7.46 (5H, m, Ar—H), 7.51–7.59 (m, 4H, Ar—H), 10.58, 10.04 (s, 3H, 3X—NH), 10.65 (s, 2H, Ar—NH), ^{13}C NMR (DMSO-d6, 100 MHz) δ 112.88, 120.51, 126.59, 127.63, 128.39, 128.84, 137.96, 145.7, 178.35, 179.33; MS (EI): $[M]^+$ 396.3.

*3.3.4. N-(4-fluorophenyl)2-[(2-phenylhydrazinyl) carbonothioyl] hydrazinecarbothioamide (**5f**)*

IR (KBr) γ_{max} cm^{-1} 3315, 3162 (NH stretch), 1637, 1528 (NH bend, 1506 (C=C stretch), 1283 (C—F), 1071 (C=S); ^1H NMR (DMSO-d6, 400 MHz) δ 7.34–7.48 (5H, m, Ar—H), 7.53–7.60 (m, 4H, Ar—H), 10.60, 10.06 (s, 3H, 3X—NH), 10.67 (s, 2H, Ar—NH); ^{13}C NMR (DMSO-d6, 100 MHz) δ 113.75, 120.51, 127.91, 128.39, 128.8, 133.46, 145.17, 161.28, 178.35, 179.33; MS (EI): $[M]^+$ 335.2.

*3.4. General method for the synthesis of hydrazine-1,2-dicarbothioamides (**5g**, **5h**)*

In round bottom flask (RBF), methyl 4-chloro phenyl carbodithioate **3a** (0.01 mole) was dissolved in DMF. To this solution, 4-chlorothiosemicarbazide **4a** (0.01 mole) was added. The flask was then attached to reflux condenser, and the temperature was maintained between 125–130 °C. After the completion of the reaction, the flask was cooled in ice bath and ice-cold water was added to the reaction mixture to obtain the product. The solid was filtered, dried and recrystallised using DMF. The traces of DMF were removed by giving the ethyl acetate slurry wash to the recrystallised compound.

*3.4.1. N,N-bis (4-chlorophenyl)hydrazine-1,2-dicarbothioamide (**5g**)*

IR (KBr) γ_{max} cm^{-1} 3209, 3175 (NH stretch), 1590 (NH bend), 1533 (C=C stretch), 1012 (C=S), 575 (C—Cl); ^1H NMR (DMSO-d6, 400 MHz) δ 2.79, 2.93 (s, 2H, 2X—NH), 7.31–7.62 (8H, m, Ar—H), 10.11–10.60 (s, 2H, Ar—NH); ^{13}C NMR (DMSO-d6, 100 MHz) δ 128.51, 130.23, 134.64, 136.82, 178.35; MS (EI): $[M]^+$ 371.3.

*3.4.2. N-(4-chlorophenyl)-N-(4-fluorophenyl) hydrazine-1,2-dicarbothioamide (**5h**)*

IR (KBr) γ_{max} cm^{-1} 3311, 3175 (—NH stretch), 1638 (—NH bend), 1533 (C=C stretch), 1089 (C=S), 1397 (C—F), 728 (C—Cl). ^1H NMR (DMSO-d6, 400 MHz) δ 2.80, 2.94 (s, 2H, 2X—NH), 7.33–7.64 (8H, m, Ar—H), 10.13–10.63 (s, 2H, Ar—NH), ^1H NMR (DMSO-d6, 400 MHz) δ 113.75, 127.91, 128.51, 130.23, 133.46, 133.51, 134.64, 136.82, 161.28, 178.35; MS (EI): $[M]^+$ 354.8.

The physical data of all the synthesised compounds (**5a**–**5h**) is represented in Table 1.

Table 1
Physical constants of titled compounds.

Compound	Molecular formula[a]	Melting point (°C)	Rf[b]	Yield (%)
5a	C9H10N3S3Br	180	0.87	89
5b	C9H10N3S3F	187	0.77	85
5c	C8H10N5S2Br	238(d)	0.85	50
5d	C8H10N5S2F	175	0.82	45
5e	C14H14N5S2Br	227	0.96	47.5
5f	C14H14N5S2F	239	0.93	50
5g	C14H12N4S2Cl2	208	0.94	60
5h	C14H12N4S2ClF	233	0.92	58

[a] Elemental analyses for C, H, N were within ±0.4% of the theoretical values.
[b] Eluent used for TLC was benzene:ethyl acetate (8:2).

3.5. Biological assay

The preliminary anticonvulsant evaluation was carried out by MES and scPTZ methods using reported procedures [24]. Male Swiss Albino mice weighing 20–40 g were used as the experimental animals. The animals were maintained at ambient temperature, in a group of 5 per cage under the standard laboratory conditions, receiving standard laboratory chow and water ad libitum. A 12 h light and dark cycle was maintained throughout the experimental studies. All the tests have been performed in accordance with the guidelines laid by the Institutional Animal Ethics Committee (Ref. No. 1329/AC/10/CPCSEA). The electroconvulsometer and rotarod equipments used were of Omega scientific industries. Pentylenetetrazole (PTZ) was obtained by Sigma–Aldrich. The test compounds were suspended in a mixture of 0.3% carboxymethylcellulose and 0.2% dimethyl sulfoxide [25]. Phenytoin and Carbamazepine were used as reference drugs. The animals were divided into three groups (control, standard and test) and each group comprised of five mice ($n = 5$). The control group received only mixture of 0.3% carboxymethylcellulose and 0.2% dimethyl sulfoxide suspension.

3.5.1. Anticonvulsant screening

Some selected derivatives (**5a**–**5e**, **5g**) were examined for anticonvulsant activity. In the preliminary screening, each compound was administered as an i.p. injection at three dose levels (30, 100 and 300 mg/kg) and the anticonvulsant activity assessed after 30 min and 4 h intervals of administration. The anticonvulsant efficacy was evaluated by the maximal electroshock-induced seizure (MES) [26], and pentylenetetrazole (PTZ) induced convulsions methods [27].

3.5.2. Neurotoxicity screen

Minimal motor impairment was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod that rotates at 10 rpm. Doses used were 100 and 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least one min in each of the three trials.

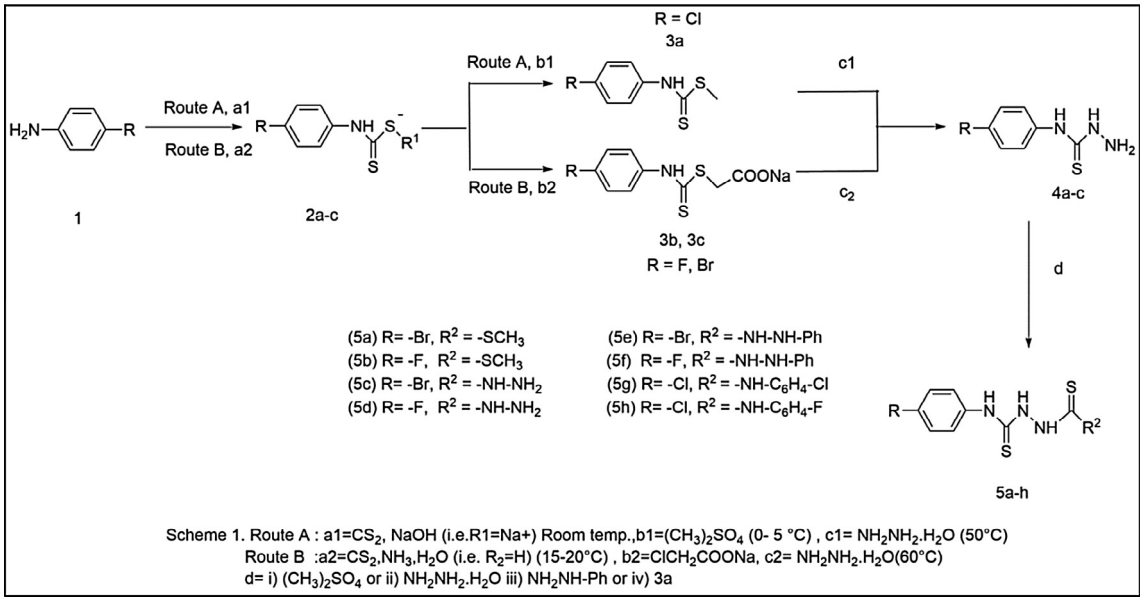
4. Results and discussion

4.1. Chemistry

General route for the synthesis of the substituted thiosemicarbazide is shown in Scheme 1. Two similar methods were used to synthesise the required thiosemicarbazides. In the first route (A), p-chloro aniline treated with carbon disulphide in the presence of sodium hydroxide and dimethyl sulphate gave corresponding dithiocarbamate (**3a**), which was isolated and reacted with hydrazine hydrate to yield p-chlorophenyl thiosemicarbazide (**4a**). In the second route (B), anilines on treatment with carbon disulphide in the presence of ammonia water and sodium chloroacetate gave sodium acetate salt of the corresponding dithiocarbamate (**3b**, **3c**), which on treatment with hydrazine hydrate yielded the respective thiosemicarbazide (**4b**, **4c**).

Route B proved to be efficient in terms of time and yield compared to Route A. The compounds were obtained in pure form with the general yield of 50–80%. The time required was comparatively less as it was one pot synthesis. Route A required isolation of dithiocarbamate intermediate whereas, in route B, direct hydrazinolysis of the salt formed therein was carried out.

The target compounds were synthesised by the reaction of aryl thiosemicarbazide, carbon disulphide under basic condition with hydrazine hydrate, phenyl hydrazine and phenyl carbodithioate



Scheme 1. Synthetic protocol for the titled compounds.

Table 2
Anticonvulsant and neurotoxicity screening results of the titled compounds.

Compound	MES screen		PTZ screen		Neurotoxicity screen		Log *P*[a]
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	
5a	–	–	–	300	–	300	2.849
5b	–	–	–	–	–	100	2.204
5c	–	–	–	–	–	–	0.660
5d	100	–	–	–	300	300	0.015
5e	–	100	–	100	–	–	3.566
5g	100	100	–	–	–	–	3.716
Phenytoin	30	30	–	–	100	100	–
Carbamazepine	30	100	100	300	100	300	–

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 animal. 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).

[a] Log *P* values were calculated by using molinspiration online services (http://www.molinspiration.com/cgi-bin/properties).

(according to the requirement of the final compound) [as shown in the Scheme 1].

The spectroscopic data (IR, ^{1}HNMR) and mass spectra were consistent with the assigned structures. All the compounds showed characteristic NH stretching and peak for C=S in IR spectroscopy. The ^{1}HNMR spectrum revealed that the —SCH_3 showed a singlet at $\delta = 2.68$ ppm. The different compounds showed a singlet for the aromatic —NH proton (Ar—NH) in the range of 9.76–10.65 ppm and the multiplet was observed in an aromatic region 7.31–7.62 ppm. In ^{13}C NMR spectrum, aromatic carbons were observed in the region of 112.88–161.28 ppm. The characteristics carbon for C=S was observed at 178.33 and 178.33 ppm. In mass spectrometry, compounds showed characteristics molecular ion peak. All this data supported the synthesis of the molecules.

4.2. Pharmacology

Preliminary anticonvulsant evaluation of the synthesised novel compounds was established by electrical and chemical tests. The electrical test employed was maximal electroshock seizure (MES) pattern test and chemical test was PTZ seizure threshold test. Rotarod test was used to determine the acute neurotoxicity. Male Albino mice were divided into three groups (control, standard and test) and each group comprised of five mice. The results of MES and PTZ screening are reported in Table 2.

Three compounds **5d**, **5e** and **5g** exhibited activity in the preliminary MES screen, indicative of their ability to prevent seizure spread. At the dose of 100 mg/kg, compounds **5d**, **5g** and **5e** showed protection in half or more of the tested mice. Compounds **5d** and **5g** showed rapid onset (0.5 h) with a shorter duration of action. Compound **5g** was found to be active even after four hours indicative of its longer duration of action. Compound **5e** showed activity at 100 mg/kg as well as 300 mg/kg but only after four hours indicating its slow onset of action.

In the PTZ test, a test used to identify compounds that elevate seizures threshold, compounds **5a** and **5e** showed protection with slow onset of action (4 h). Compound **5e** has broad-spectrum anticonvulsant activity as it is active in both MES and PTZ screens. Therefore, we can say that, clinically, it is effective in both grand mal and petit mal types of epilepsy. Compound **5d** and **5g** are showed activity only in MES model. Therefore, they are selective agents for the treatment of only grand mal epilepsy.

In the acute neurotoxicity screen, compounds **5e** and **5g** were found to be devoid of any neurotoxicity at the highest dose administered (300 mg/kg). There was no distinction between anticonvulsant dose and neurotoxicity dose for the compound **5a**. Rest of the compounds **5b**, **5c**, **5d** showed neurotoxicity at dose of 300 mg/kg. Results are given in Table 2.

The data reveals that 66% of the compounds were active in the MES screen as compared to 34% in the PTZ screen. Compound **5b** and **5c** showed no activity in all the screenings.

The 100% protection was observed for the compounds **5e** and **5g**, and 0% mice showed neurotoxicity. The compounds **5a** showed activity at the neurotoxic dose and compound **5d** was active at 100 mg/kg, but it was found to be neurotoxic at higher dose 300 mg/kg.

From this study, it was observed that the hydrophobic binding site (A) and hydrophilic–hydrophobic site (R^1) when incorporated in the structure shows the different activity depending on their structural properties (Fig. 2). The compounds having p-bromo substitution on the aryl ring (**5a**, **5e**) were observed to have good anticonvulsant activity because of their bulkier bromine group which increases lipophilicity of the molecule and also helps to cross blood-brain barrier.

At R^1 position (Fig. 2), compound with —SCH_3 group (**5a**) was found to be active but at higher dose. Replacement of —SCH_3 group with —NH—NH—Ph (**5e**) shows activity at comparatively low dose and with —p—Cl—C_6H_4—NH— substitution (**5g**) shows moderate activity though —p—Cl—C_6H_4—NH— analogue has highest log*P* value amongst all others. The function —p—Cl—C_6H_4—NH— may bring the rigidity to the system, and this may be the reason for not controlling the proper pharmacokinetic properties of the system.

5. Conclusion

Hydrazine-thioate and hydrazine-(carbo)-thioamide molecules were synthesised. The present study identified compounds **5e** and **5g** as lead molecules. Study demonstrated that the compound 5e possesses broad-spectrum anticonvulsant activity as indicated by its effect in both PTZ and MES models with no neurotoxicity. Compound **5g** is active in MES model at 30 min and 4 h, has a fast-moderate onset and long duration with no sign of neurotoxicity. The R^1 substitution with the phenylhydrazine or aniline was found to be beneficial for the anticonvulsant activity. Our study validated that the presence of a second aryl or phenyl ring increases the anticonvulsant potential by attachment to the binding site using van der waals forces. The further modification at R^1 with other substituted anilines would open up new horizons for thiosemicarbazide analogues. It is interesting to note that long chain enriched with —C(S) NH— functions as in compound **5g** functionality can serve as peptidomimetics in drug–receptor binding and further development in this area will be clinically rewarding.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bioorg.2014.04.002.

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