Med Chem Res (2012) 21:2661–2670
DOI 10.1007/s00044-011-9791-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Synthesis of benzothiazole derivatives having acetamido and carbothioamido pharmacophore as anticonvulsant agents

**Mohd. Amir · S. Asif · Israr Ali · Mohd. Zaheen Hassan**

Received: 1 March 2011 / Accepted: 2 September 2011 / Published online: 18 September 2011


**Abstract** A new series of *N*-(6-chlorobenzothiazol-2-yl)-2-substituted-acetamides (**3a–h**) and *N*-(6-chlorobenzothiazol-2-yl)-2-(substituted-benzylidene)hydrazinecarbothioamides (**5a–h**) were synthesized and characterized by IR, $^{1}$H NMR, mass and elemental analysis. In vivo anticonvulsant and acute toxicity screening of all the synthesized compounds showed morpholino (**3f**) and imidazolyl (**3g**) derivatives as promising anticonvulsant lead. Furthermore, *In silico* drug-likeness parameters have also been investigated for filtering out the likelihood of poor drug absorption or brain penetration. 3D four-point pharmacophore measurements of compounds were also carried out to match these with established anticonvulsants agents.

**Keywords** Benzothiazole · Acetamide · Carbothioamide · Drug-likeness · Anticonvulsant activity

## Introduction

Epilepsy is the recurrent, serious neuropathological syndrome affecting about 1–2% of the world's population, covering over 40 different types of human seizures (Yogeeswari *et al.*, 2005a, b). Despite the availability of around 20 permitted AEDs, there is an importunate demand for newer broad spectrum antiepileptic agents to improve the drug safety profile and to cope with uncontrolled and/or resistant seizure patients (Lin and Kadaba 1997). Furthermore, therapeutic regimen for epilepsy often involves a change of first line drug or polytherapy, putting an enormous economic trouble to patients. Therefore, development of safer and effective antiepileptic drugs would have an enormous socioeconomic impact (Rosaria *et al.*, 2006; Hong *et al.*, 2009).

Many investigations indicated that the presence of hydrogen bonding domain as amide (–CONH–) and their bioisoester carbothioamide (–CSNH–) seems to be valuable in the structure of anticonvulsants (Siddiqui *et al.*, 2007; Amnekar and Bhusari 2010; Siddiqui *et al.*, 2009). Moreover, hydrophobic benzothiazoles have also an immense interest in medicinal chemistry as these structural moieties exist in large number of natural products (Bondock *et al.*, 2009) as well as in pharmaceutically active compounds showing diverse biological properties like anticonvulsant (Chopade *et al.*, 2002), anticancer (Brantley *et al.*, 2006), anti-inflammatory (Naik *et al.*, 1996) and antimicrobials (Bondock *et al.*, 2010). Riluzole (2-aminobenzothiazole derivative) is a clinically available AED with neuroprotective effect acting on sodium channels and *N*-methyl-D-aspartate (NMDA) receptors (Zarate and Manji 2008). Encouraged by these observations and in continuation of our interest in the synthesis of heterocyclic compounds (Amir *et al.*, 2008, 2010), we thought it worthwhile to synthesize a new series of compounds having acetamide or carbothioamide moieties along with benzothiazole pharmacophore with the hope that hybridization of these bioactive moieties will have synergistic anticonvulsant effect due to increased lipophilicity.

A pharmacophore model along with physicochemical determination provides a useful tool for designing prototypic molecules and explanation of plausible interactions (Malawska 2003). In term of interaction at binding site, the titled compounds have common structural features such as an aromatic hydrophobic domain (A), = N– as an electron donor atom (D), C=O or C=S as hydrogen bond acceptor

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(HA), and N–H as hydrogen bond donor (HD) (Yogeeswari *et al.*, 2005b). This work also outlines the four point pharmacophore models for the development of prototype compound using structurally different classes of anticonvulsants.

Furthermore, an *In silico* investigation of drug-likeness parameters has always been a critical filter for drugs with poor intestinal permeability or poor aqueous solubility and hence ensuring the development of orally active drugs (Walters *et al.*, 1999). In present investigation all the synthesized compounds were subjected to prediction of molecular properties and drug-likeness parameters so as to avoid costly late-stage preclinical and clinical failures.

## Results and discussion

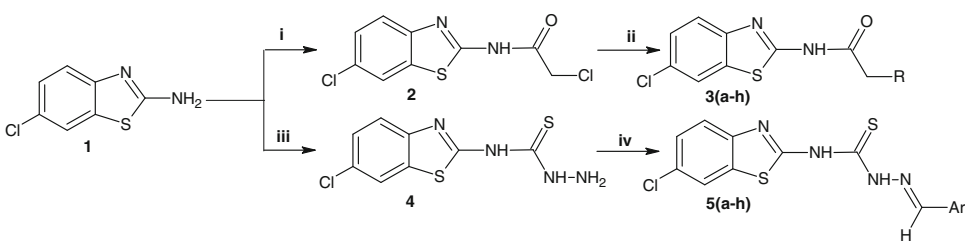
### Chemistry

The synthesis of *N*-(6-chlorobenzothiazol-2-yl)-2-substituted acetamides (**3a**–**h**) and *N*-(6-chlorobenzothiazol-2-yl)-2-(substitutedbenzylidene)hydrazinecarbothioamides (**5a**–**h**) was carried out as presented in Scheme 1. Synthesis of 6-chloro-2-aminobenzothiazole (**1**) involves the cyclization of 4-chloroaniline with potassium thiocyanate and bromine in presence of glacial acetic acid. Compound **1** on acylation followed by treatment with various amine afforded acetamide derivatives (**3a**–**h**). Furthermore, reaction of compound **1** with $CS_2$ and $NH_3$ followed by treatment with hydrazine hydrate resulted in the formation of hydrazinecarbothioamide derivative (**4**). Compound **4** on condensation with various aromatic aldehyde afforded substituted benzylidene hydrazinecarbothioamides (**5a**–**h**).

The $^1$H NMR spectrum of 6-chlorobenzothiazol-2-amine (**1**) showed a doublet at $\delta$ 7.11–7.14 for aromatic proton at 5th position. The signals for aromatic protons at 4th and 7th position were observed as a doublet at $\delta$ 7.22 and 7.66, respectively, whereas a signal for two protons of amino group was observed at $\delta$ 7.57. The formation of compound (**2**) was confirmed by appearance of a singlet at $\delta$ 9.73 and $\delta$ 4.32 for –CONH and –$COCH_2$ protons, respectively, in the $^1$H NMR spectrum. The $^1$H NMR spectrum of compound **3a**, showed a singlet indicating the presence of three $CH_3$ groups at $\delta$ 1.31 and –$COCH_2$ at $\delta$ 3.42. Moreover, the presence of additional peak due to –NH proton at $\delta$ 2.99 beside a signal of –CONH proton at $\delta$ 7.18 confirmed the formation of amino-acetamide linkage. The $^1$H NMR spectrum of compound **4** showed a broad singlet at $\delta$ 8.64 corresponding to –NHCSNH– group; whereas, a signal for $NH_2$ proton was observed at $\delta$ 4.48. The formation of compound **5a** was confirmed by appearance of a singlet at $\delta$ 5.99 due to N=CH proton. The singlets were also observed at $\delta$ 9.41 and $\delta$ 6.67 due to –CSNH– and –NH protons, respectively. The elemental analysis results were within ±0.4% of the theoretical values. The physicochemical properties of the titled compounds are presented in Table 1.

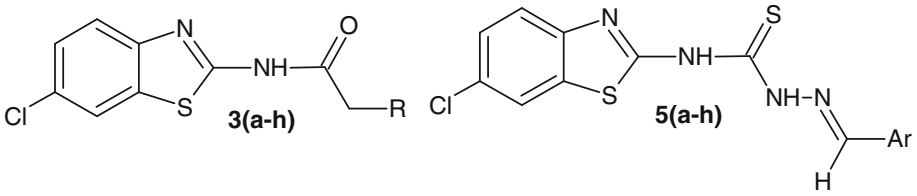
### Pharmacology

The introduction of diverse bioactive groups at benzothiazolamine and their subsequent screening led to an understanding of electronic property, size and lipophilicity influence at benzothiazole nucleus. The amide linkage –NHCO– with delocalized electrons is a key determinant of anticonvulsant activity, which would be greatly influenced by the nature of adjoining substituent. Therefore, compounds **3**(**a**–**h**) were synthesized to explore the effects of adding substituents to acetamide linkage at benzothiazole ring. In MES screening, all the synthesized compounds having acetamide linkage were shown to have rapid onset and long duration of action except compound **3b** and **3d**. The potency order for protection of hind limb tonic extension was observed as morpholino (**3f**), imidazolyl (**3g**) > tert-butylamino (**3a**), pipredinyl (**3e**) > *p*-fluorophenylamino (**3c**) > indolyl substituted derivative (**3h**). Out of these, compound **3f** and **3g** having log *P* 2.32 and 2.14, respectively, showed excellent anti-generalized tonic-clonic activity after 0.5 h and 4 h at 30 mg/kg. In the scPTZ screen, compounds **3a**, **3c**, **3e**, **3f**, and **3g** elevated seizure threshold at dose of 100 mg/kg after 0.5 h out of which, compound **3f** and **3g** were again shown to have longer duration of action at same dose. To further evaluate the potential of 2-aminobenzothiazole, we synthesized hybrid compounds having hydrazinecarbothioamide pharmacophore. In hydrazinecarbothioamide series, compound having *p*-flourobenzylidene group (**5d**) (log *P* 5.22) were shown to have rapid onset and long duration of action at




**Scheme 1** Reagents and conditions: (i) $ClCH_2COCl$, dry benzene, (ii) 1°/2° amine, dry benzene, TEA (iii) $CS_2$, $NH_3$, $ClCH_2COONa/NH_2{\cdot}NH_2$ $2H_2O$ (iv) ArCHO, EtOH, $CH_3COOH$

**Table 1** Physicochemical parameters of synthesized compounds **3a–h** and **5a–h**




| Compound | R/Ar | Mol. formula (Mol. Wt.) | log *P* (C log *P*)[a] | m.p (°C) | Yield (%) | $R_f$[b] |
|---|---|---|---|---|---|---|
| **3a** | Tert-butylamino | $C_{13}H_{16}ClN_3OS$ (297.80) | 3.02 (3.22) | 182 | 80 | 0.55 |
| **3b** | 4-Chlorophenylamino | $C_{15}H_{11}Cl_2N_3OS$ (352.24) | 4.24 (4.57) | 156 | 70 | 0.62 |
| **3c** | 4-Fluorophenylamino | $C_{15}H_{11}FClN_3OS$ (335.78) | 3.88 (4.02) | 170 | 55 | 0.60 |
| **3d** | Diphenylamino | $C_{21}H_{16}ClN_3OS$ (393.89) | 6.12 (5.88) | 230 | 62 | 0.65 |
| **3e** | Piperidin-1yl | $C_{14}H_{16}ClN_3OS$ (309.81) | 3.16 (3.75) | 80 | 58 | 0.45 |
| **3f** | Morpholino | $C_{13}H_{14}ClN_3O_2S$ (311.79) | 2.32 (2.43) | 140 | 70 | 0.50 |
| **3g** | 1*H*-imidazol-1-yl | $C_{12}H_9ClN_4OS$ (292.74) | 2.14 (2.21) | 152 | 73 | 0.55 |
| **3h** | 1*H*-indol-1yl | $C_{17}H_{12}ClN_3OS$ (341.81) | 4.62 (4.74) | 196 | 66 | 0.75 |
| **5a** | Phenyl | $C_{15}H_{11}ClN_4S_2$ (346.86) | 4.86 (4.95) | 148 | 74 | 0.70 |
| **5b** | 4-Chlorophenyl | $C_{15}H_{10}Cl_2N_4S_2$ (381.30) | 5.52 (5.71) | 132 | 72 | 0.80 |
| **5c** | 2-Chlorophenyl | $C_{15}H_{10}Cl_2N_4S_2$ (381.30) | 5.46 (5.64) | 130 | 51 | 0.75 |
| **5d** | 4-Fluorophenyl | $C_{15}H_{10}ClFN_4S_2$ (364.85) | 5.22 (5.16) | 116 | 62 | 0.76 |
| **5e** | 4-Nitrophenyl | $C_{15}H_{10}ClN_5O_2S_2$ (391.86) | 4.68 (4.87) | 158 | 70 | 0.64 |
| **5f** | 4-Hydroxyphenyl | $C_{15}H_{11}ClN_4OS_2$ (362.86) | 4.78 (4.70) | 222 | 63 | 0.62 |
| **5g** | 4-Methoxyphenyl | $C_{16}H_{13}ClN_4O_2$ (376.88) | 5.16 (5.08) | 110 | 60 | 0.76 |
| **5h** | 4-Dimethylamino phenyl | $C_{17}H_{16}ClN_5S_2$ (389.93) | 5.24 (5.12) | 144 | 54 | 0.80 |

[a] Log *P* was determined by octanol:phosphate buffer method; C log *P*, in parentheses was calculated using software ACD/log *P* 1.0

[b] Solvent system: toluene/ethyl acetate/formic acid (5:4:1)

30 mg/kg (phenytoin 30 mg/kg). Also compound with *p*-nitrobenzylidene (**5e**) and *p*-hydroxybenzylidene groups (**5f**) showed protection at 100 mg/kg in MES test. In scPTZ test compounds **5d** and **5e** showed rapid onset and long duration of action at dose 100 and 300 mg/kg, respectively.

Results from the rotarod motor impairment test demonstrated that compounds **3f**, **3g**, and **3c** did not show neurotoxicity at the maximum dose administered (300 mg/kg). Rest of the compounds showed neurotoxicity at 100 or 300 doses mg/kg. All the compounds were evaluated for the CNS depressant effect using Porsolt's swimming pool test and their immobility times were compared with respect to reference drug carbamazepine (Table 3). Compounds **3a**, **3e**, **3f**, and **3g** were found to have no significant CNS depressant effect with respect to control. All other compounds were found having CNS depressant effect as they increased the immobility time significantly.

## *In silico* studies and Partition coefficient

Choosing "drug-like" molecule from non-drug-like molecules at the preliminary stage and to avoid drug with poor oral bioavailability is the main aim of current study. Good intestinal absorption, reduced molecular flexibility (measured by the number of rotatable bonds), low polar surface area or total hydrogen bond count (sum of donors and acceptors), are important predictors of good oral bioavailability (Bakht *et al.*, 2010). Moreover, Lipinski's "rule of five" is a heuristic approach for predicting drug-likeness stating that molecules having molecular weight >500, log *P* >5, hydrogen bond donors >5 and hydrogen bond acceptors >10 have poor absorption or permeation (Lipinski *et al.*, 1997). Therefore, all the compounds were investigated for absorption (% ABS), molecular polar surface area (PSA) and Lipinski's parameters (Table 2). In this rule, any oxygen (O) and nitrogen (N) atoms are defined as hydrogen bond acceptors and N–H or O–H groups are considered as hydrogen bond donors. Results of this analysis indicate that the number of hydrogen bond donors (2–3) and hydrogen bond acceptors (3–6) are in good agreement with "rule of five". Number of rotatable bonds (NROTB) indicates the conformational flexibility of molecule for receptors or channels binding and should be ≤10 (Veber *et al.*, 2002). All the synthesized compounds have number of rotatable bonds in the range of 3–6 exhibiting restrained conformational flexibility. PSA (polar surface area) is also an important

predictor of absorption, defined as part of the molecular surface that arises from oxygen or nitrogen atoms, or hydrogen atoms attached to nitrogen or oxygen atoms. Several studies have identified that M. Wt. of CNS active drugs should be <450 and PSA <90 $Å^2$ are to be recommended for the penetration of BBB (van de Waterbeemd *et al.* 1998). The predicted PSA value of all the synthesized compounds were found in the range of 35.58–75.14 $Å^2$ with M. Wt. maximum of 395.57 indicating their excellent brain penetration which is a criterion for anticonvulsant effect.

Partition coefficient (log *P*) is an imperative physicochemical marker of drug permeability across the blood brain barrier (BBB) for inadequate drug concentration in crucial brain areas (Kwan and Brodie 2005). Therefore, partition coefficients of all the compounds were determined to establish the correlation between log *P* and anticonvulsant activity. The log *P* values of some of the active compounds indicated in parentheses, viz. **3f** (2.32), **3g** (2.14) and **5d** (5.22). This clearly indicates that moderate log *P* value (2.14–2.32) is prerequisite for showing anticonvulsant activity without neurotoxicity.

Drug-likeness model score (a collective effect of physicochemical properties, pharmacokinetics and pharmacodynamics) of all the compounds were positive with maximum of 1.15 therefore, the synthesized compounds are adequate to be treated like candidate drugs. The most active compounds **3f** and **3g** have also good drug-likeness score 0.44 and 0.75 (Fig. 1).

There have been several attempts to provide insight into pharmacophore modeling of the putative MES receptor showing several common structural features essential for activity at sodium ion channel. Although, the chemical diversity and various mechanisms of action of anticonvulsants make it difficult to identify a common pharmacophore, the essential structural elements in the four-point pharmacophore model were assumed as lipophilic aryl ring center (A), =O or =N– as an electron donor atom (D), C=O or C=S as hydrogen bond acceptor (HA), and N–H as hydrogen bond donor (HD) (Fig. 2) (Unverferth *et al.*, 1998). All the molecules are 3D optimized and were conformers which bring the above-mentioned groups closely together. Table 4 shows the distances between the various groups postulated as essential for anticonvulsant action. Comparison of average distance requirements showed that the compounds **3f** and **3g** were in good conformity with the sodium channel blockers.

## Conclusion

Some newer acetamide and carbothiomide derivatives having benzothiazole nucleus were synthesized with good drug-likeness score and evaluated for anticonvulsant, neurotoxicity, and CNS depressant activities. Structure–activity relationship study led to presume the possible interactions of compound with specific binding site. Benzothiazole possessing acetamide derivatives showed better protection indices than carbothiomide linkage in MES and ScPTZ screen without any CNS depressant effect or neurotoxicity. Comparing the structures of acetamide series it was

**Table 2** Calculated absorption (%ABS), polar surface area (PSA), Lipinski parameters and drug-likeness model score of the benzothiazole derivatives

| Compd. | % ABS | Mol.Vol. ($A^3$) | PSA ($A^2$) | NROTB | HBA | HBD | Drug-likeness model score |
|---|---|---|---|---|---|---|---|
| **3a** | 93.31 | 290.44 | 45.45 | 4 | 4 | 2 | 0.94 |
| **3b** | 93.66 | 294.45 | 44.46 | 4 | 3 | 2 | 0.24 |
| **3c** | 93.66 | 283.17 | 44.46 | 4 | 3 | 2 | 0.42 |
| **3d** | 96.72 | 357.95 | 35.58 | 5 | 3 | 1 | 0.60 |
| **3e** | 95.74 | 296.80 | 38.41 | 3 | 4 | 1 | 0.62 |
| **3f** | 93.01 | 287.04 | 46.32 | 3 | 5 | 1 | 0.44 |
| **3g** | 93.01 | 251.80 | 46.33 | 3 | 4 | 1 | 0.75 |
| **3h** | 95.97 | 306.19 | 37.76 | 3 | 3 | 1 | 0.16 |
| **5a** | 94.60 | 305.44 | 41.73 | 5 | 4 | 2 | 0.89 |
| **5b** | 94.60 | 322.64 | 41.73 | 5 | 4 | 2 | 0.87 |
| **5c** | 94.60 | 320.11 | 41.73 | 5 | 4 | 2 | 1.09 |
| **5d** | 94.60 | 311.36 | 41.73 | 5 | 4 | 2 | 0.99 |
| **5e** | 83.07 | 330.43 | 75.14 | 6 | 6 | 2 | 0.20 |
| **5f** | 88.64 | 315.99 | 59.00 | 5 | 5 | 3 | 0.97 |
| **5g** | 91.70 | 337.29 | 50.12 | 6 | 5 | 2 | 1.15 |
| **5h** | 93.57 | 354.95 | 44.70 | 6 | 4 | 2 | 0.76 |

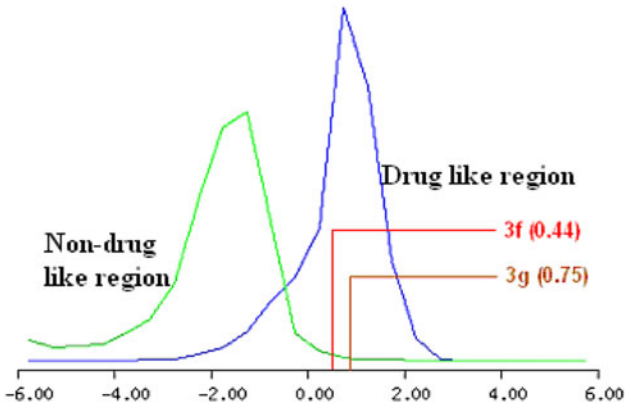



**Fig. 1** Drug-likeness model score plot for compounds **3f** and **3g** using Molsoft

found that substitution with morpholine (**3f**) and imidazolyl (**3g**) group is favored over lipophilic distal phenyl ring.

Partition coefficient determinations (log *P*), clearly indicate that in general the optimal hydrophobicity (log $P \approx 2$) of the molecules is essential for anticonvulsant activity without any neurotoxicity. These new aspects of benzothiazolyl-acetamide molecules might be useful for designing potential anticonvulsants.

## Experimental

### General chemistry

The entire chemicals used in the synthesis were supplied by E. Merck and S.D. Fine Chemicals. Melting point is determined by open capillary tube method and is uncorrected. Purity of the compound was checked on thin layer chromatography using iodine vapors as visualizing agents. IR spectra were obtained on a Perkin-Elmer 1720 FTIR spectrometer (KBr pellets). $^1$H-NMR spectra were obtained on a Bruker 300 MHz NMR spectrometer using Tetramethysilane (TMS) as the internal reference (chemical shifts in $\delta$ ppm). Mass spectra were recorded at Jeol SX-102 spectrometer.

### Procedure for the preparation of 2-chloro-*N*-(6-chlorobenzothiazol-2-yl)acetamide (**2**)

6-Chloro-2-aminobenzothiazole (0.05 mol, 9.22 g) and chloroacetylchloride (0.05 mol, 3.98 ml) in dry benzene was refluxed for 1 h. The solution was filtered and residue was washed with benzene and then with sodium bicarbonate solution. Finally, it was washed with distilled water and recrystallized from ethanol. Yield 85%; m.p. 140°C; IR (KBr, cm$^{-1}$): 3316 (NH), 2842 (CH), 1673 (C=O), 1585 (C=N). $^1$HNMR ($CDCl_3$-300 MHz) $\delta$: 4.32 (s, 2H, $COCH_2$), 7.43 (d, 1H, 5th Ar–H, $J = 8.8$ Hz), 7.73 (d, 1H, 4th Ar–H, $J = 8.8$ Hz), 7.81 (s, 1H, 7th Ar–H), 9.73 (s, 1H, CONH). Mass (*m*/*z*): 260 (M + 1). Anal. calcd for $C_9H_6Cl_2N_2OS$: C, 41.40; H, 2.32; N, 10.73%; Found: C, 41.36; H, 2.29; N, 10.69%.

### General procedure for the preparation of *N*-(6-chlorobenzothiazol-2-yl)-2-substituted-acetamides (**3a–h**)

To substituted amine (0.0019 mol) dissolved in dry benzene (30 ml) was added triethylamine (0.0019 mol, 0.274 ml) and refluxed for 10 min. To this 2-chloro-*N*-(6-chlorobenzothiazol-2-yl)acetamide (0.0019 mol, 500 mg) was added slowly and refluxed for 6 h. The solid thus obtained was filtered and washed with benzene and then with distilled water and recrystallized from ethanol.

### 2-(Tert-butylamino)-*N*-(6-chlorobenzothiazol-2-yl) acetamide (**3a**)

IR (KBr, cm$^{-1}$): 3440 (NH), 3330 (CH aromatic), 2641 ($CH_2$), 1685 (C=O), 1592 (C=N). $^1$HNMR ($CDCl_3$-300 MHz) $\delta$: 1.31 (s, 9H, $3CH_3$), 2.99 (s, 1H, NH), 3.24 (s, 2H, $COCH_2$), 7.18 (s, 1H, CONH), 7.40 (d, 1H, 5th ArH-benzo., $J = 8.7$ Hz), 7.72 (d, 1H, 4th ArH-benzo., $J = 8.7$ Hz), 7.74 (s, 1H, 7th ArH-benzo.). MS (*m*/*z*): 298 (M + 1). Anal. Calcd for $C_{13}H_{16}ClN_3OS$: C, 52.43; H, 5.42; N, 14.11%; found: C, 52.47; H, 5.46; N,14.15%.

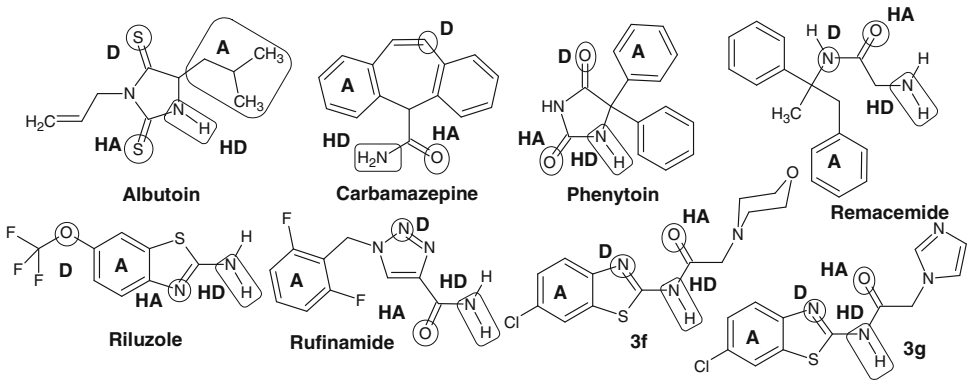



**Fig. 2** Established anticonvulsant drugs along with synthesized compounds showing essential pharmacophoric elements: aryl unit/hydrophobic domain (A), electron donor atom (D), and coupled hydrogen donor (HD)–hydrogen acceptor (HA) group

*N*-(6-chlorobenzothiazol-2-yl)-2-(4-chlorophenylamino)acetamide (**3b**)

IR (KBr, $cm^{-1}$): 3353 (NH), 3173 (CH aromatic), 2652 ($CH_2$), 1670 (C=O), 1598 (C=N). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 3.97 (d, 2H, $COCH_2$, $J = 5.2$ Hz), 5.46 (s, 1H, NH), 6.51 (d, 2H, 3&5 ArH, $J = 8.0$ Hz), 7.00 (d, 2H, 2&6 ArH, $J = 7.6$ Hz), 7.26 (1H, d, 5th Ar–H-benzo., $J = 8.4$ Hz), 7.56 (d, 1H, 4th ArH-benzo., $J = 8.0$ Hz), 7.69 (s, 1H, 7th Ar–H-benzo.), 11.96 (s, 1H, CONH). MS *m/z*: 352 (M + 1). Anal. Calcd for $C_{15}H_{11}Cl_2N_3OS$: C, 51.15; H, 3.15; N, 11.93%; found: C, 51.19; H, 3.20; N, 11.97%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(4-fluorophenylamino) acetamide (**3c**)

IR (KBr, $cm^{-1}$): 3436 (NH), 3333 (CH aromatic), 2664 ($CH_2$), 1655 (C=O), 1584 (C=N). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 3.97 (d, 2H, $COCH_2$, $J = 5.2$ Hz), 5.42 (s, 1H, NH), 6.44–7.01 (m, 4H, ArH), 7.29 (d, 1H, 5th ArH-benzo., $J = 8.4$ Hz), 7.57 (d, 1H, 4th ArH-benzo., $J = 8.0$ Hz), 7.68 (1H, s, 7th Ar-H-benzo.), 11.97 (1H, s, CONH). MS (*m/z*): 335 ($M^+$). Anal. calcd for $C_{15}H_{11}ClFN_3OS$: C, 53.65; H, 3.30; N, 12.51%; found: C, 53.61; H, 3.32; N, 12.49%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(diphenylamino)acetamide (**3d**)

IR (KBr, $cm^{-1}$): 3421 (NH), 3070 (CH aromatic), 2693 ($CH_2$), 1672 (C=O), 1594 (C=N). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 5.10 (2H, s, $COCH_2$), 6.76-8.11 (13H, m, ArH), 10.27 (1H, s, CONH). MS (*m/z*): 394 (M + 1). Anal. calcd for $C_{21}H_{16}ClN_3OS$: C, 64.03; H, 4.09; N, 10.67%; found: C, 64.08; H, 4.13; N, 10.71%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(piperidin-1yl) acetamide (**3e**)

IR (KBr, $cm^{-1}$): 3414 (NH), 3286 (CH aromatic), 2672 ($CH_2$), 1688 (C=O), 1594 (C=N). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 1.69-1.49 (6H, m, $(CH_2)_3$), 2.57 (4H, t, $(CH_2)_2$,), 3.21 (2H, s, $COCH_2$), 6.34 (1H, s, CONH), $J = 4.8$ Hz), 7.40 (1H, d, 5th ArH-benzo., $J = 8.7$ Hz), 7.71 (1H, d, 4th ArH-benzo., $J = 8.7$ Hz), 7.78 (1H, s, 7th ArH-benzo.). MS (*m/z*): 310 (M + 1). Anal. calcd for $C_{14}H_{16}ClN_3OS$: C, 54.27; H, 5.21; N, 13.56%; found: C, 54.30; H, 5.25; N, 13.60%.

*N*-(6-chlorobenzothiazol-2-yl)-2-morpholinoacetamide (**3f**)

IR (KBr, $cm^{-1}$): 3320 (NH), 3075 (CH aromatic), 2655 ($CH_2$), 1678 (C=O), 1576 (C=N). $^1$HNMR ($CDCl_3$-300 MHz) $\delta$: 2.66 (t, 4H, $CH_2$–N–$CH_2$, $J = 4.5$ Hz), 3.28 (s, 2H, $COCH_2$), 3.81 (t, 4H, $CH_2$–O–$CH_2$, $J = 4.5$ Hz), 7.41 (d, 1H, 5th ArH-benzo., $J = 8.7$ Hz), 7.70 (d, 1H, 4th ArH-benzo., $J = 8.7$ Hz), 7.78 (d,1H, 7th ArH-benzo., $J = 8.0$ Hz), 10.34 (s, 1H, CONH). MS (*m/z*): 311 ($M^+$). Anal. Calcd for $C_{13}H_{14}ClN_3O_2S$: C, 50.08; H,4.53; N,13.48%; found: C, 50.12; H,4.58; N, 13.52%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(1H-imidazol-1-yl) acetamide (**3g**)

IR (KBr, $cm^{-1}$): 3342 (NH), 3034 (CH aromatic), 2609 ($CH_2$), 1647 (C=O), 1566 (C=N). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 5.11 (s, 2H, $COCH_2$), 6.90–8.02 (m, 6H, Ar–H), 8.07 (s, 1H, CONH). MS (*m/z*): 293 (M + 1). Anal. Calcd for $C_{12}H_9ClN_4OS$: C, 49.23; H, 3.10; N, 19.14%; found: C, 49.27; H, 3.18; N, 19.10%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(1H-indol-1yl) acetamide (**3h**)

Appearance—pale yellow color solid; IR (KBr, $cm^{-1}$): 3442 (NH), 3217 (CH aromatic), 2606 ($CH_2$), 1684 (C=O), 1594 (C=N). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 5.21 (s, 2H, $COCH_2$), 6.40–8.12 (m, 9H, ArH), 10.17 (s, 1H, CONH). MS (*m/z*): 342 (M + 1). Anal. calcd for $C_{17}H_{12}ClN_3OS$: C, 59.73; H, 3.54; N, 12.29%; found: C, 59.78; H, 3.58; N, 12.83%.

Procedure for the preparation of *N*-(6-chlorobenzothiazol-2-yl)-hydrazinecarbothioamide (**4**)

6-Chloro-2-aminobenzothiazole (13.7 g, 0.1 mol) was dissolved in ethanol (95%, 50 ml) and ammonia solution 20 ml was added slowly within 15 min with shaking and then $CS_2$ was added slowly. After complete addition of $CS_2$, the solution was allowed to stand for 1 h; sodium chloroacetate (9.4 g, 0.1 mol) was added to it. The reaction was exothermic with change in color from red to yellowish green. To it 50% hydrazine hydrate (20 ml) was added. The mixture was warmed gently filtered and boiled to half of its volume and kept overnight. Next day, the product thiosemicarbazide was filtered, recrystallized from ethanol. Appearance—pale yellow color solid; Yield: 75%; m.p. 175°C. IR (KBr, $cm^{-1}$): 3359 ($NH_2$), 3079 (CH), 1585 (C=N), 1175 (C=S). $^1$H NMR (DMSO-$d_6$-300 MHz) $\delta$: $\delta$ 4.48 (s, 2H, $NH_2$), 7.19 (d, 1H, 4th ArH-benzo.), 7.29 (d, 1H, 5th ArH-benzo.), 7.70 (s, 1H, 7th ArH-benzo.), 8.64 (bs, 2H, NH–CS–NH). MS (*m/z*): 259. Anal. calcd for $C_8H_7ClN_4S_2$: C, 37.13; H, 2.73; N, 21.65%; found: C, 37.17; H, 2.77; N, 21.69%.

General procedure for the preparation of *N*-(6-chlorobenzo[d]thiazol-2-yl)-2-substituted-hydrazinecarbothioamides (**5a–h**)

To a solution of 6-chloro-1,3-benzothiazole-2yl-thiosemicarbazide (0.0019 mol) in ethanol (25 ml) an equimolar quantity of substituted benzaldehyde in ethanol and acetic acid (2 drops) were added. The mixture was refluxed with stirring for 8 h and the resultant precipitate was filtered and dried. The product was recrystallized from 95% ethanol.

2-benzylidene-*N*-(6-chlorobenzothiazol-2-yl) hydrazinecarbothioamide (**5a**)

IR (KBr, $cm^{-1}$): 3458 (NH), 3001 (CH aromatic), 1587 (C=N), 1178 (C=S). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 5.99 (s, 1H, N=CH), 6.67 (s, 1H, NH), 6.94 (d, 1H, 5th ArH-benzo., $J = 5.0$ Hz), 7.27–7.49 (m, 5H, ArH), 7.63 (s, 1H, 7th ArH-benzo.), 8.03 (d, 1H, 4th ArH-benzo., $J = 5.7$ Hz), 9.41 (s, 1H, CSNH). MS (*m/z*): 346 ($M^+$). Anal. calcd for $C_{15}H_{11}ClN_4S_2$: C, 51.94; H, 3.20; N, 16.15%; found: C, 51.97; H, 3.22; N, 16.19%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(4-chlorobenzylidene)hydrazinecarbothioamide (**5b**)

IR (KBr, $cm^{-1}$): 3384 (NH), 3029 (CH aromatic), 1613 (C=N), 1197 (C=S). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 5.97 (s, 1H, N=CH), 6.79 (d, 2H, 3′&5′ Ar–H, $J = 5.4$ Hz), 7.12 (d, 2H, 2'&6' ArH, $J = 5.4$ Hz), 7.41 (1H, d, 5th ArH-benzo., $J = 8.4$ Hz), 7.70 (1H, d, 4th ArH-benzo., $J = 8.7$ Hz), 7.72 (s, 1H, 7th ArH-benzo.), 8.34 (s, 1H, NH), 10.12 (s, 1H, CSNH). MS (*m/z*): 380 ($M^+$). Anal. calcd for $C_{15}H_{10}Cl_2N_4S_2$: C, 47.25; H, 2.64; N, 14.69%; found: C, 47.29; H, 2.70; N, 14.75%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(2-chlorobenzylidene)hydrazinecarbothioamide (**5c**)

IR (KBr, $cm^{-1}$): 3453 (NH), 3068 (CH aromatic), 1597 (C=N), 1155 (C=S). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 5.98 (s, 1H, N=CH), 6.68 (s, 1H, NH), 6.94 (d, 1H, 5th ArH-benzo., $J = 5.0$ Hz), 7.26–7.46 (m, 4H, ArH), 7.63 (s, 1H, 7th ArH-benzo.), 8.02 (d, 1H, 4th ArH-benzo., $J = 5.7$ Hz), 9.40 (s, 1H, CSNH). MS (*m/z*): 380 ($M^+$). Anal. calcd for $C_{15}H_{10}Cl_2N_4S_2$: C, 47.25; H, 2.64; N, 14.69%; found: C, 47.31; H, 2.68; N, 14.76%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(4-fluorobenzylidene)hydrazinecarbothioamide (**5d**)

IR (KBr, $cm^{-1}$): 3394 (NH), 3000 (CH aromatic), 1560 (C=N), 1188 (C=S). $^1$HNMR (DMSO-$d_6$-300 MHz) $\delta$: 6.02 (s, 1H, N=CH), 6.64 (s, 1H, NH), 6.91 (d, 1H, 5th ArH-benzo., $J = 5.0$ Hz), 6.99-7.56 (m, 4H, ArH), 7.61 (s, 1H, 7th ArH-benzo.), 8.03 (d, 1H, 4th ArH-benzo., $J = 5.7$ Hz), 9.44 (s, 1H, CSNH). MS (m/z): 364 ($M^+$). Anal. Calcd for $C_{15}H_{10}ClFN_4S_2$: C, 49.38; H, 2.76; N, 15.36%; found: C, 49.43; H, 2.80; N, 15.41%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(4-nitrobenzylidene) hydrazinecarbothioamide (**5e**)

IR (KBr, $cm^{-1}$): 3394 (NH), 3021 (CH aromatic), 1576 (C=N), 1158 (C=S) $cm^{-1}$. $^1$HNMR ($CDCl_3$-300 MHz) $\delta$ ppm: 10.34 (s, 1H, CSNH), 8.35 (s, 1H, NH), 7.74 (s, 1H, 7th ArH-benzo.), 7.80 (d, 1H, 4th ArH-benzo., $J = 8.7$ Hz), 7.51 (d, 1H, 5$^{th}$ ArH-benzo., $J = 8.4$ Hz), 7.22 (d, 2H, 2′&6′ ArH, $J = 5.4$ Hz), 6.69 (d, 2H, 3′&5′ Ar–H, $J = 5.4$ Hz), 5.87 (s, 1H, N=CH). MS (*m/z*): 391 ($M^+$). Anal. Calcd for $C_{15}H_{10}ClN_5O_2S_2$; C, 45.98; H, 2.57; N, 17.86%; found: C, 46.02; H, 2.62; N, 17.91%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(4-hydroxybenzylidene)hydrazinecarbothioamide (**5f**)

IR (KBr, $cm^{-1}$) $v_{max}$: 3557 (OH), 3315 (NH), 3012 (CH aromatic), 1590 (C=N), 1175 (C=S). $^1$HNMR ($CDCl_3$-300 MHz) $\delta$ ppm: 5.87 (s, 1H, N=CH), 6.77 (d, 2H, 3′&5′ Ar–H, $J = 5.4$ Hz), 7.11 (d, 2H, 2′&6′ ArH, $J = 5.4$ Hz), 7.40 (d, 1H, 5th ArH-benzo., $J = 8.4$ Hz), 7.72 (d, 1H, 4th ArH-benzo., $J = 8.7$ Hz), 7.78 (s, 1H, 7th ArH-benzo.), 8.24 (s, 1H, NH), 10.00 (s, 1H, CSNH), 12.18 (s, 1H, OH). MS (m/z): 362 ($M^+$). Anal. Calcd for $C_{15}H_{11}ClN_4OS_2$; C, 49.65; H, 3.06; N, 15.44%; found; C, 49.69; H, 3.10; N, 15.49%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(4-methoxy benzylidene)hydrazinecarbothioamide (**5g**)

IR (KBr, $cm^{-1}$): 3420, (NH), 3004 (CH aromatic), 1586 (C=N), 1127 (C=S). $^1$HNMR ($CDCl_3$-300 MHz) $\delta$: 3.88 (s, 3H, $OCH_3$), 6.64 (s, 1H, N=CH), 6.90-7.80 (m, 7H, ArH), 7.83 (s, 1H, NH), 9.19 (s, 1H, CSNH). MS (m/z): 376 ($M^+$). Anal. calcd for $C_{16}H_{13}ClN_4OS_2$: C, 50.99; H, 3.48; N, 14.87%; found: C, 51.02; H, 3.52; N, 14.91%.

*N*-(6-chlorobenzothiazol-2-yl)-2-(4-(dimethyl-aminobenzylidene)hydrazinecarbothioamide (**5h**)

IR (KBr, $cm^{-1}$): 3353 (NH), 2906 (CH aromatic), 2477 ($CH_3$), 1598 (C=N), 1217 (C=S). $^1$HNMR ($CDCl_3$-300 MHz) $\delta$ ppm: 3.28 (s, 6H, $(CH_3)_2$), 5.86 (s, 1H, N=CH), 6.75 (d, 2H, 3′&5′ ArH, $J = 5.4$ Hz), 7.12 (d, 2H, 2′&6′ ArH, $J = 5.4$ Hz), 7.41 (d, 1H, 5th Ar–H-benzo.,

$J = 8.4$ Hz), 7.73 (d, 1H, 4th ArH-benzo., $J = 8.7$ Hz), 8.26 (s, 1H, NH), 7.78 (s, 1H, 7th ArH-benzo.), 10.34 (s, 1H, CSNH). MS (*m/z*): 389 ($M^+$). Anal. calcd for $C_{17}H_{16}ClN_5S_2$: C, 52.36; H, 4.14; N, 17.96%; found: C, 52.40; H, 4.18; N, 18.01%.

## Pharmacology

The anticonvulsant screening of all the newly synthesized compounds were performed according to the standard protocol provided by epilepsy branch of the National Institute of Neurological Disorders and Stroke (NINDS) following the protocol adopted by Antiepiletic Drug Development (ADD) program.

The preliminary anticonvulsant screening were carried out by maximal electroshock test (MES) (Krall *et al.*, 1978) and subcutaneous pentylenetetrazole (ScPTZ) (Swinyard *et al.*, 1989). Minimal motor impairment was assessed by rotorod method (Dunham and Miya 1957). Compounds were administered intra peritoneal as a solution in polyethyleneglycol (PEG) and tested using three graded doses of 30, 100, and 300 mg/kg at two different time intervals. CNS depressant activity was carried out by Porsolt's swim test (1978). The results are presented in Table 3.

### Maximum electroshock (MES) test

The anticonvulsant activity in MES test was indicated by the lower dose which protected the hind limb tonic extension in more than half of the animals ($n = 4$). Each animal received i.p. injection of the test compounds (30/100/300 mg/kg) followed by electroshock with 60 cycle altering current of 50 mA for 0.25 s via ear clip electrode through electroconvulsometer as per the reported procedure and activity was assessed at 0.5 h and 4 h after administration (Anticonvulsant Screening Project, 1978; Krall *et al.*, 1978).

### Subcutaneous pentylenetetrazole (scPTZ) seizure threshold test

For anticonvulsant screening test compounds were administered 0.5 h before the scPTZ treatment and protection was detected in terms of failure to observe an episode of clonic spasms for 5 s duration. The control group received subcutaneous PTZ solution (in 0.9% sodium chloride) in the

**Table 3** Anticonvulsant Activity, Neurotoxicity and CNS depressant effect of synthesized compounds

| Compound | Intraperitoneal injection in mice[a] | | | | | | Mean average immobility time[b](s) | |
|---|---|---|---|---|---|---|---|---|
| | MES screen | | Sc PTZ screen | | Neurotoxicity screen | | Mean ± SEM | |
| | 0.5 h | 4.0 h | 0.5 h | 4.0 h | 0.5 h | 4.0 h | Control (24 h before) | Post-treatment (60 min after) |
| **3a** | 30 | 100 | 100 | 300 | – | 300 | 118 ± 7.57 | 129 ± 9.59$^{NS}$ |
| **3b** | 100 | – | – | – | – | 100 | 113 ± 4.22 | 161 ± 8.16 |
| **3c** | 100 | 100 | 100 | 300 | – | – | 116 ± 5.98 | 169 ± 9.79 |
| **3d** | 300 | – | – | – | 300 | – | 109 ± 6.13 | 196 ± 8.16 |
| **3e** | 30 | 100 | 100 | – | – | 300 | 119 ± 9.70 | 145 ± 4.16$^{NS}$ |
| **3f** | 30 | 30 | 100 | 100 | – | – | 122 ± 5.49 | 140 ± 8.05$^{NS}$ |
| **3g** | 30 | 30 | 100 | 100 | – | – | 126 ± 7.62 | 137 ± 4.49$^{NS}$ |
| **3h** | 100 | 300 | – | 300 | 100 | 300 | 120 ± 9.12 | 152 ± 7.30 |
| **5a** | – | 300 | – | – | 300 | 300 | 108 ± 5.70 | 162 ± 8.18 |
| **5b** | 300 | – | – | – | 300 | – | 116 ± 7.87 | 191 ± 4.02 |
| **5c** | 300 | – | – | – | – | 100 | 110 ± 6.91 | 177 ± 5.39 |
| **5d** | 30 | 30 | 100 | 100 | 100 | 100 | 143 ± 8.35 | 188 ± 7.08 |
| **5e** | 100 | – | 300 | 300 | 300 | 300 | 111 ± 7.43 | 157 ± 8.05 |
| **5f** | 100 | – | 100 | – | – | 100 | 110 ± 8.00 | 169 ± 9.79 |
| **5g** | – | 300 | – | – | 100 | 300 | 120 ± 6.09 | 181 ± 8.70 |
| **5h** | – | – | – | – | 100 | 100 | 112 ± 6.83 | 172 ± 7.97 |
| Phenytoin | 30 | 30 | – | – | 100 | 100 | NT | NT |
| Carbamezepine | 30 | 100 | 100 | 100 | 100 | 300 | 111 ± 6.51 | 179 ± 8.62 |

[a] Doses of 30, 100, and 300 mg/kg were administered. The data indicate the minimum dose whereby protection was demonstrated in more than half of the mice (four in each group). The animals were examined at 0.5 and 4.0 h. A dash indicates the absence of anticonvulsant activity and neurotoxicity at the maximum dose administered (300 mg/kg)

[b] Each value represents the mean ± SEM of six mice, significantly different from the control at $P < 0.05$, and NS denotes not significant at $P < 0.05$ (Student's *t* test)

posterior midline of the mice and the onset and severity of convulsion was noted (Swinyard *et al.*, 1989).

Neurotoxicity screening

The neurotoxicity of all the test compounds was evaluated using rotarod test. Mice were trained to balance on the rotating rod (3.2 cm diameter) that rotates at 6 rpm. Trained animals were treated with test compounds at a dose of 20–1000 mmol/kg administered intraperitoneally. Neurotoxicity was determined by the inability of the animal to remain on the rod for 1 min (Dunham and Miya 1957).

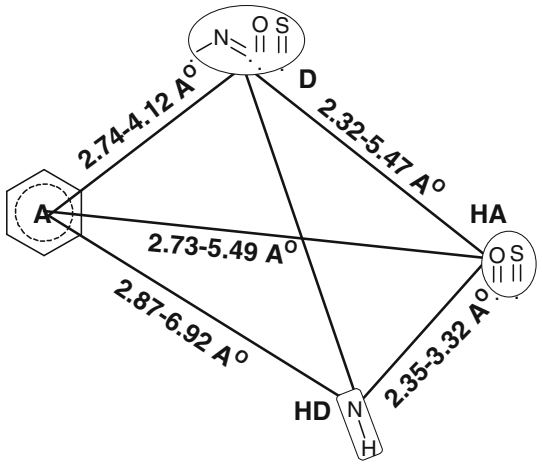
Porsolt's swim test

Behavioral depression was measured by evaluating the immobility time of the mice during swimming phase. Before starting test the animals were trained for swimming (24 h before). Then the trained animals were given an i.p. injection (100 mg/kg) of the test compounds 60 min before the test session. The duration of passive floating without struggling was recorded during the last 4 min of the 6 min testing period as the immobility time (Porsolt *et al.*, 1978).

*In silico* studies

The partition coefficient (log *P*) between octanol and phosphate buffer was determined by the procedure described in literature (Farrar *et al.*, 1993). The calculated log *P* (C log *P*) values were taken from the software ACD/log *P* 1.0 and the results are shown in Table 1. The experimental data were in agreement with the calculated log *P* values. Christopher Lipinski's rule-of-five analysis provides a useful tool for filtering out molecules likely to have poor oral absorption. Therefore, for the confirmation whether molecules are more or less drug-like, synthesized compounds were subjected to molecular properties and drug-likeness prediction using Molinspiration and Molsoft molecular processing programs. The analysis was done considering pharmacokinetic (ADME) related descriptors like molecular weight, log *P*, number of H-bond donors, and number of H-bond acceptors while pharmacodynamic related descriptors employed total polar surface area, and number of rotatable bonds. Results clearly showed that compounds **3f** and **3g** passed the rule of five status (Table 2). The 4-point pharmacophore group's distance estimations were done on 3D optimized structures using ACD/Chemsketch/3-D viewer 2.0 version program (Brooks *et al.*, 1983). Our analyses of the distance relationship showed that the synthesized compounds **3f** and **3g** did fulfill the essential demands of the pharmacophore when compared to the average distance requirement (Table 4).

**Table 4** Calculated distance ranges between the pharmacophoric elements




| Compound | A–HA | A–HD | A–D | HA–HD | HD–D | HA–D |
|---|---|---|---|---|---|---|
| Albutoin | 5.02 | 2.87 | 3.34 | 3.08 | 4.84 | 5.35 |
| Carbamazepine | 3.77 | 3.99 | 3.79 | 2.35 | 5.27 | 4.21 |
| Phenytoin | 4.56 | 3.76 | 4.12 | 2.39 | 3.66 | 4.69 |
| Remacemide | 5.49 | 6.92 | 3.96 | 3.32 | 3.26 | 2.32 |
| Riluzole | 2.73 | 3.77 | 2.74 | 2.44 | 7.37 | 5.47 |
| Rufinamide | 5.34 | 6.51 | 3.91 | 2.37 | 4.52 | 4.58 |
| Av. distance | 4.48 | 4.63 | 3.64 | 2.65 | 4.82 | 4.43 |
| **3g** | 5.05 | 3.91 | 2.36 | 2.33 | 2.54 | 2.79 |
| **3f** | 4.67 | 3.89 | 2.36 | 2.30 | 2.51 | 2.37 |

**Acknowledgments** The author Asif S. deeply acknowledges the University Grants Commission, India, for providing the Junior Research Fellowship. The authors also wish to express their thanks to Hamdard University, New Delhi, India for providing animal research facilities.

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