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Design, synthesis and anticonvulsant evaluation of *N*-(benzo[*d*]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4*H*)-carbothioamide derivatives: A hybrid pharmacophore approach

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ABSTRACT

Novel *N*-(benzo[*d*]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4*H*)-carbothioamide derivatives were synthesized and evaluation of their anticonvulsant effects was done using various models of experimental epilepsy. Initial anticonvulsant activities of the compounds were investigated using intraperitoneal (i.p.) maximal electroshock shock (MES), subcutaneous pentylenetetrazole (*sc*PTZ) seizure models in mice. The quantitative assessment after oral administration in rats showed that the most active was 2-methyl-4-oxo-*N*-(6-(trifluoromethoxy)benzo[*d*]thiazol-2-ylcarbamoyl)quinazoline-3(4*H*)-carbothioamide (**SA 24**) with ED_{50} values of 82.5 μmol/kg (MES) and 510.5 μmol/kg (*sc*PTZ). This molecule was more potent than phenytoin and ethosuximide which were used as reference antiepileptic drugs. To explain the possible mechanism for anticonvulsant action, some of the selected active compounds were subjected to GABA (γ-amino butyric acid) assay and AMPA ((*S*)-2-amino-3-(3-hydroxyl-5-methyl-4-isoxazolyl) propionic acid) induced seizure test.

1. Introduction

Epilepsy is a heterogeneous group of disorders characterized by neuronal hyperexcitability and hypersynchronous neuronal firing presented with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness [1]. Epilepsy is one of the most common disorders of the brain, affecting more than 50 million individuals worldwide [2,3]. Lamotrigine, tiagabine, felbamate, pregabalin, stiripentol and topiramate are recent antiepileptic drugs (AEDs) which are effective toward only 60–80% of patients companioned with undesirable side effects, such as headache, nausea, anorexia, ataxia, hepatotoxicity, drowsiness, gastrointestinal disturbance, gingival hyperplasia, and hirsutism [4–8]. In many cases the clinical use of AEDs is restricted by their side effect. Therefore, a substantial need remains to discover novel chemical entities for the development of new effective and safer AEDs. Quinazolin-4(3*H*)-one **1** and their derivatives constitute a significant class of heterocyclic compounds and are shown to have potent central nervous system (CNS) activities such as anticonvulsant and CNS depressant [9–14]. 2-Aminobenzothiazoles and derivatives like 2-benzothiazolamines, benzothiazoles containing sulphonamide and guanidines emerged as new classes of anticonvulsant agents and one of its derivatives, riluzole (2-amino-6-trifluoromethoxy benzothiazole) **4** is clinically available drug reported to diminish sensitivity of one of the sub types from the family of ionotropic glutamate receptors (iGluRs) (*S*)-2-amino-3-(3-hydroxyl-5-methyl-4-isoxazolyl)propionic acid (AMPA) and also reported to show no effect on pentylenetetrazole (PTZ) induced convulsions in moderate doses [15–17]. Over activities of iGluRs are linked to mediate excitatory synaptic transmission. In particular AMPA antagonists have shown anticonvulsant and neuroprotective activity in various animal models [18]. They also offer therapeutic innervations without side effects associated with inhibition of *N*-methyl-D-aspartate (NMDA) receptors [19].

A literature survey revealed that the presence of a substituted aromatic ring at position 3 and a methyl group at position 2 on quinazolin-4(3*H*)-one nucleus is a necessary requirement for CNS depression and anticonvulsant activities [20]. Methaqualone **2a** (2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone) is a well known anticonvulsant and sedative-hypnotic containing quinazolin-4(3*H*)-one nucleus responsible for its activity and its 3-(2-chlorophenyl)-2-methyl-4(3*H*)-quinazolinone analog (Mecloqualone) **2c** was found to be 1.5 times more potent than phenytoin in maximal electroshock (MES) induced convulsions and 10 times more potent than

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troxidone against PTZ induced seizure [21–23]. It has been reported that convulsant induced seizure by inhibiting γ-amino butyric acid (GABA) neurotransmission (such as PTZ) and $GABA_A$ antagonist [24]. $GABA_A$ agonist shows therapeutic effects by increasing chloride influx via brain chloride channel or directly antagonizes the inhibitory spinal reflex of glycine. Quinazolin-4(3*H*)-one derivatives reported to control seizure induced by MES and PTZ *i.e.* exhibited broad spectrum of activity in animal models possibly via GABA activation [25–27].

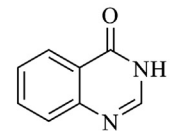
In view of the above mentioned knowledge based facts of different pharmacophores and in continuation of our research program we have synthesized benzothiazole moiety, quinazolinone nucleus along with incorporated urea and electronic environment to get single molecular framework in the form of titled compounds **5** comprising the four pharmacophoric elements that are necessary for good anticonvulsant activity as suggested by Pandeya et al. (Fig. 1) [28]. These elements are present in many currently used antiepileptic drugs. These are hydrophobic domain (A), hydrogen bonding domain (HBD), electron donor moiety (D), and distal hydrophobic domain (R). The attachment of a second aryl ring designated as the distal ring to the proximal aryl ring to increase the van der waal's bonding at the binding site and to increase potency have also been reported [28,29].

Intrigued by the above observations, and in an attempt to design and develop new potential anticonvulsant agents, a hybrid pharmacophoric approach was adopted in which the quinazolin-4(3*H*)-one and benzothiazole nuclei were hybridized in one structure hoping to synergize the anticonvulsant potential of both groups. The validity of this design was assessed through anticonvulsant screening of the target compounds.

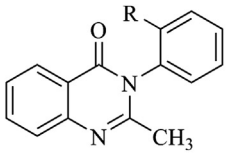
2. Result and discussion

2.1. Chemistry

The titled compounds (**SA 1**–**30**) described in this study were prepared as outlined in Scheme 1. Synthesis of substituted-benzothiazol-2yl-amines (**1a**–**j**) and substituted benzothiazol-2yl-



Quinazol-4(3H)-one
(1)



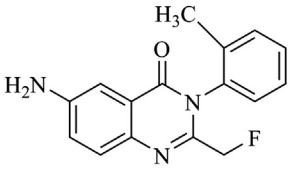
(2)

R - CH_3 = Methaqualone (2a)

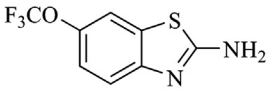
R - C_2H_5 = Etaqualone (2b)

R - Cl = Mecloqualone (2c)

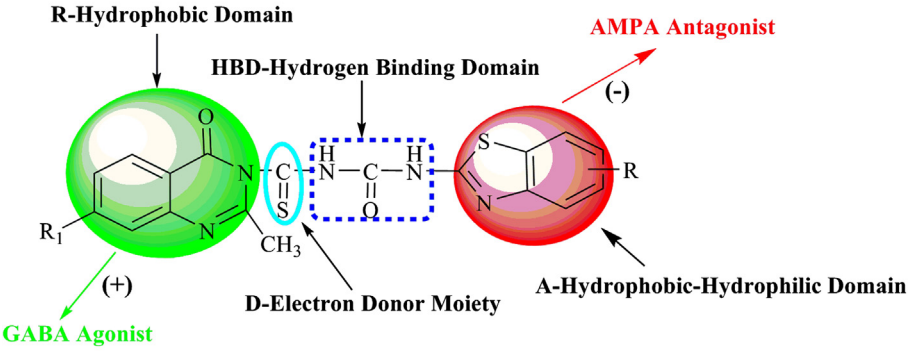
R - Br = Mebroqualone (2d)



Afloqualone
(3)

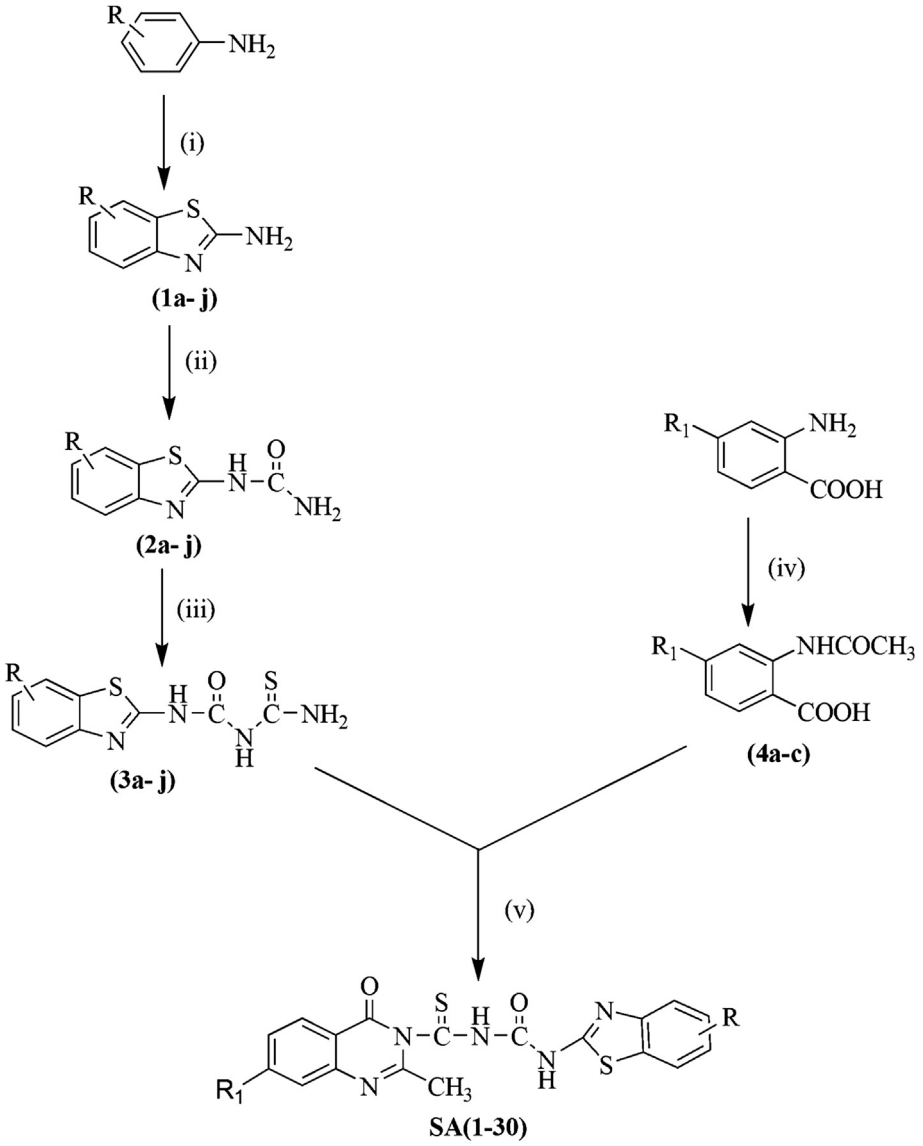


Riluzole
(4)



Overlay of pharmacophores and biological targets in titled compounds SA(1-30)
(5)

Fig. 1. Chemical structure of (1) quinazol-4(3*H*)-one, (2) reported quinazolinones as anticonvulsants, (3) afloqualone, (4) riluzole, (5) titled compounds **SA** (**1**–**30**).

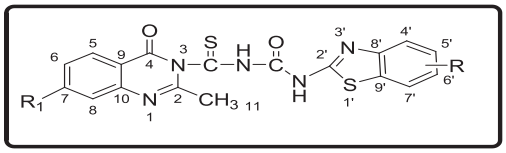


Scheme 1. Synthetic protocol of the target compounds SA (1–30). Reagents and conditions: (i) Br_2, glacial acetic acid, potassium thiocyanate (KSCN), (ii) glacial acetic acid, NaOCN, (iii) NH_4SCN, HCl, CH_3COCl, toluene, (v) toluene (dry), PCl_3, reflux.

urea-(**2a**–**j**) was carried out according to procedure mentioned in literature [30,31] except *o*-benzothiazol-2yl-amines that were synthesized using *o*-substituted aniline in dry methanol and purified over silica gel using chloroform ($CHCl_3$):ethyl acetate (EtOAc) (7:3) as eluent. The resulting thiourea was dissolved in bromine and $CHCl_3$ (Br_2:$CHCl_3$; 1:9) mixture and isolated by column chromatography using $CHCl_3$:EtOAc (7:3). Benzothiazol-2yl-dicarbonimidothioic diamide (**3a**–**j**) were accomplished by reaction of hydrochloric acid and ammonium thiocyanate in equimolar quantities followed by re-crystallization from ethanol (C_2H_5OH). 4-Substituted-2-acetamidobenzoic acid (**4a**–**c**) were synthesized from 4-substituted anthranilic acid (0.1 mol) in toluene via acylation by acetyl chloride through nucleophilic addition–elimination and allowed to stand for 2 h. It was further re-crystallized from $CHCl_3$:C_2H_5OH (9:1) to furnish the desired product in moderate to good yield. Titled compounds optimize the Grimmel's condition for generation of C(2)N(3)-disubstituted 4-quinazolinones. Using Grimmel's methodology 4-substituted carbonyl amino benzoic acid (4-substituted carbonyl anthranilic acid) were heated with free amino groups as in case of benzothiazole in toluene or xylene in presence of dehydrating agent such as PCl_3, $POCl_3$ and $SOCl_2$ to furnish the targeted compounds [32,33]. In addition, it is possible to carry out the reaction using phosphorus oxychloride in place of the trichloride although the yields and purity of products suffer moderately. The quinazolinone ring built up was performed from equimolar quantities of 4-substituted-2-acetamidobenzoic acid (**4a**–**c**) and substituted benzothiazol-2yl dicarbonimidothioic diamide (**3a**–**j**) with PCl_3 (1:3 with **4a**–**c**) in dry toluene refluxed, stirred for 3 h followed by washing with Na_2CO_3 and re-crystallization to afford titled compounds (**SA 1**–**30**).

The structure of novel compounds was elucidated by spectroscopic measurements (IR, Mass, ^1H NMR and ^{13}C NMR). Thin layer chromatography (TLC) was used throughout to optimize the reaction for purity and completion along with physical and elemental analyses data for titled compounds are summarized in Table 1. The formation of substituted benzothiazol-2yl-amines (**1a**–**j**) from substituted aniline was confirmed by IR, ^1H NMR. The IR spectra displayed broad band of 3240 cm^{-1} attributed to $-NH_2$ stretching vibration and

Table 1
Physicochemical data of synthesized compounds **SA** (**1**–**30**).



Compd. no.	R	R_1	Mol. formula (Mol. weight)	R_f value[a]	Yield[b] (%)	M.p. (°C)	Elemental analyses[c] calculated/found (%)		
							C	H	N
SA 1	6-F	F	$C_{18}H_{11}F_2N_5O_2S_2$ (431.44)	0.74	48.2	>300	50.11	2.57	16.23
							50.05	2.50	16.20
SA 2	6-Cl	F	$C_{18}H_{11}ClFN_5O_2S_2$ (447.89)	0.70	55.5	>300	48.27	2.48	15.64
							48.25	2.44	15.60
SA 3	6-Br	F	$C_{18}H_{11}BrFN_5O_2S_2$ (492.34)	0.68	54.8	>300	43.91	2.25	14.22
							43.88	2.27	14.24
SA 4	6-OCF_3	F	$C_{19}H_{11}F_4N_5O_3S_2$ (497.45)	0.72	43.7	>300	45.87	2.23	14.08
							45.89	2.20	14.11
SA 5	6-OH	F	$C_{18}H_{12}FN_5O_3S_2$ (429.45)	0.67	62.2	254–256	50.34	2.82	16.31
							50.31	2.81	16.28
SA 6	6-OCH_3	F	$C_{19}H_{14}FN_5O_3S_2$ (443.47)	0.54	68.7	263–266	51.46	3.18	15.79
							51.44	3.21	15.82
SA 7	4-Cl	F	$C_{18}H_{11}ClFN_5O_2S_2$ (447.89)	0.65	38.8	274–278	48.27	2.48	15.64
							48.23	2.45	15.65
SA 8	5-Cl	F	$C_{18}H_{11}ClFN_5O_2S_2$ (447.89)	0.69	42.6	276–275	48.27	2.48	15.64
							48.29	2.44	15.68
SA 9	6-CH_3	F	$C_{19}H_{14}FN_5O_2S_2$ (427.48)	0.58	64.6	258–260	53.38	3.30	16.38
							53.41	3.32	16.39
SA 10	4-Br	F	$C_{18}H_{11}BrFN_5O_2S_2$ (492.34)	0.78	36.4	284–285	43.91	2.25	14.22
							43.88	2.27	14.25
SA 11	6-F	Cl	$C_{18}H_{11}ClFN_5O_2S_2$ (447.89)	0.72	50.8	>300	48.27	2.48	15.64
							48.29	2.45	15.67
SA 12	6-Cl	Cl	$C_{18}H_{11}Cl_2N_5O_2S_2$ (464.35)	0.70	64.8	>300	46.56	2.39	15.08
							46.58	2.36	15.11
SA 13	6-Br	Cl	$C_{18}H_{11}BrClN_5O_2S_2$ (508.80)	0.74	68.0	280–285	42.49	2.18	13.76
							42.45	2.21	13.79
SA 14	6-OCF_3	Cl	$C_{19}H_{11}ClF_3N_5O_3S_2$ (513.90)	0.77	44.5	>300	44.41	2.16	13.63
							44.43	2.17	13.67
SA 15	6-OH	Cl	$C_{18}H_{12}ClN_5O_3S_2$ (445.90)	0.68	55.4	267–270	48.48	2.71	15.71
							48.45	2.75	15.73
SA 16	6-OCH_3	Cl	$C_{19}H_{14}ClN_5O_3S_2$ (459.93)	0.63	68.8	276–278	49.62	3.07	15.23
							49.59	3.11	15.26
SA 17	4-Cl	Cl	$C_{18}H_{11}Cl_2N_5O_2S_2$ (464.35)	0.70	45.5	258–261	46.56	2.39	15.08
							46.60	2.41	15.11
SA 18	5-Cl	Cl	$C_{18}H_{11}Cl_2N_5O_2S_2$ (464.35)	0.68	43.3	261–264	46.56	2.39	15.08
							46.58	2.41	15.11
SA 19	6-CH_3	Cl	$C_{19}H_{14}ClN_5O_2S_2$ (443.93)	0.62	74.3	250–255	51.41	3.18	15.78
							51.44	3.21	15.81
SA 20	4-Br	Cl	$C_{18}H_{11}BrClN_5O_2S_2$ (508.80)	0.66	36.5	259–262	42.49	2.18	13.76
							42.52	2.21	13.78
SA 21	6-F	H	$C_{18}H_{12}FN_5O_2S$ (413.45)	0.60	67.8	240–245	52.29	2.93	16.94
							52.25	2.95	16.97
SA 22	6-Cl	H	$C_{18}H_{12}ClN_5O_2S_2$ (429.90)	0.64	74.8	236–238	50.29	2.81	16.29
							50.27	2.84	16.27
SA 23	6-Br	H	$C_{18}H_{12}BrN_5O_2S_2$ (472.96)	0.73	53.9	230–235	45.58	2.55	14.76
							45.57	2.53	14.80
SA 24	6-OCF_3	H	$C_{19}H_{12}F_3N_5O_3S_2$ (479.46)	0.62	50.8	290–292	47.60	2.52	14.61
							47.58	2.54	14.63
SA 25	6-OH	H	$C_{18}H_{13}N_5O_3S_2$ (411.46)	0.64	65.8	225–230	52.54	3.18	17.02
							52.51	3.21	17.05
SA 26	6-OCH_3	H	$C_{19}H_{15}N_5O_3S_2$ (425.48)	0.64	70.8	233–235	53.63	3.55	16.46
							53.66	3.51	16.42
SA 27	4-Cl	H	$C_{18}H_{12}ClN_5O_2S_2$ (429.90)	0.73	48.8	220–223	50.29	2.81	16.29
							50.25	2.83	16.25
SA 28	5-Cl	H	$C_{18}H_{12}ClN_5O_2S_2$ (429.90)	0.73	42.8	215–217	50.29	2.81	16.29
							50.27	2.84	16.27
SA 29	6-CH_3	H	$C_{19}H_{15}N_5O_2S_2$ (409.48)	0.64	72.6	210–212	55.73	3.69	17.10
							55.71	3.65	17.08
SA 30	4-Br	H	$C_{18}H_{12}BrN_5O_2S_2$ (472.96)	0.70	36.6	244–246	45.58	2.55	14.76
							45.54	2.53	14.79

[a] Solvent for TLC – benzene:ethanol (8:2).
[b] Solvent for re-crystallization – ethanol:water (9:1).
[c] Elemental analyses for C, H, and N were within ±0.4% of the theoretical values.

moderate intensity absorption at 1565 cm^{-1} corresponding to CH═N stretching vibration. In ^1H NMR showed singlet corresponding to $-NH_2$ protons at δ 9.70 ppm exchangeable with D_2O. Aromatic proton appeared as set of multiplet in the region δ 7.89–8.16 ppm thereby confirms the formation. The formation of substituted benzothiazol-2yl-urea (**2a**–**j**) from substituted benzothiazol-2yl-amines (**1a**–**j**) was confirmed from IR and ^1H NMR spectral studies. In its IR spectra appearance of two bands at 3220 cm^{-1} (NH) and 3167 cm^{-1} (NH_2) along with strong band at 1678 cm^{-1} indicates the presence of C═O stretching thereby confirming the formation of urea linkage. In its ^1H NMR spectra one singlet of NH_2 and one singlet of NH appears at δ 9.24 and 9.96 exchangeable with D_2O. The formation of 4-substituted-2-acetamidobenzoic acid (**4a**–**c**) from 4-substituted anthranilic acid was confirmed by IR and ^1H NMR spectral studies. In IR spectra appearance of strong absorption band of C═O stretching confirms the formation of NH–CO linkage at 1650 cm^{-1}. A band at 815 cm^{-1} confirms 1,4-disubstituted benzene (aromatic substitution) and weak multiple bands of C–H stretching at 1478 cm^{-1}. In ^1H NMR spectra displayed a singlet at δ 13.62–13.98 ppm reassert to COOH group and δ 11.65 ppm confirms to NH (D_2O exchangeable) with a set of multiplet between 7.20 and 8.65 ppm supports to aromatic protons.

The structural assignments to new compound **SA 24** were based on elemental and spectral (FT-IR, ^1H NMR, ^{13}C NMR and Mass Spectra) analysis. The IR spectra of titled compounds **SA 24** showed absorption bands of N–H stretching vibration (secondary amine) at 3430 cm^{-1} along with multiple weak absorption bands of quinazoline–H and aromatic–H at 2800–3100 cm^{-1}. Skelton vibrations appear for fused and heterocyclic rings appear in between 1445 and 1525 cm^{-1}. The characteristic strong bands appears for C═O stretching in quinazoline at 1655 cm^{-1} and urea at 1640 cm^{-1} respectively along with moderate band of C═N stretching at 1530 cm^{-1} and weak band of C–S–C at 670 cm^{-1}. In ^1H NMR spectra –NH– protons resonated as two broad singlets at δ 8.90 ppm corresponding to NHC═O other at 11.88 ppm tallying to NHC═S, that was D_2O exchangeable, also revealed a set of signals of 4 protons of quinazoline–H, 3 protons of benzothiazole–H within δ 6.75–8.35 ppm, and three methyl protons (quinazoline–CH_3) appear at δ 2.34 ppm. The mass spectra show $M^+ + 1$ (m/z) peaks respectively confirming their purity and molecular weight. The ^{13}C NMR depicted the peaks of quinazoline nucleus corresponding to δ 166.5 (quinazoline–C═O), 160.5, 148.6, 128.9, 126.6, 122.5 ppm. The characteristic C═S peak appear at δ 185.6 ppm, and urea peak (–NH–CO–NH) at δ 155.3 ppm. In benzothiazole nucleus aromatic carbons appear at δ 156.5 (C–OCF_3), 146.5, 131.6, 120.5, 118.8, 116.6, 108.5 and thiazole carbon (N═C–S) comes out at δ 161.5 ppm along with aliphatic carbons (quinazoline–CH_3) at δ 22.5 ppm thereby confirming the formation of the titled compounds in full agreement with the proposed structures.

2.2. Pharmacology

The anticonvulsant activity and neurotoxicity of the titled compounds were evaluated following the standard procedures proposed by the NIH anticonvulsant drug development (ADD) program, via the anticonvulsant screening project (ASP). The initial evaluation (Phase I) comprises of the MES, *sc*PTZ and neurotoxicity. The MES test is linked with the electrical induction of the seizure, whereas PTZ test involves a chemical induction to generate the convulsion. Neurotoxicity is primarily determined by the rotorod screen. The test compounds were administered intraperitoneally (i.p.) into the mice at the doses of 30, 100 and 300 mg/kg in the MES screen whereas 100 and 300 mg/kg in the *sc*PTZ screen. Phenytoin and carbamazepine were selected as standard drugs in the MES and minimal motor impairment test whereas ethosuximide was preferred for the *sc*PTZ screening. The generalized tonic–clonic seizure evaluation using the MES tests identified some clinical candidates that prevented seizure spread. In this test, the synthesized compounds **SA 21**, **SA 22** and **SA 24** were found to be active at 30 mg/kg at 0.5 h duration. Interestingly, **SA 24** continued to provide protection from the seizures at a dose of 30 mg/kg at 4.0 h also, indicating rapid onset and longer duration of action at a lower dose equalizing the effect of standard drug phenytoin. Compounds **SA 21** and **SA 22** were also active at 4.0 h but at a higher dose of 100 mg/kg suggesting rapid onset and shorter duration of action at a lower dose thereby jibing the effect of carbamazepine. The compounds **SA 12**, **SA 13**, **SA 14**, **SA 23** and **SA 28** had shown activity at the dose level of 100 mg/kg at both the time intervals 0.5 h and 4.0 h respectively except **SA 23** and **SA 28** that exhibited activity at 300 mg/kg after 4.0 h. **SA 13** did not show any activity at the maximum dose at 4.0 h indicating rapid absorption but ceasing of activity at longer duration. **SA 2**, **SA 3**, **SA 7**, **SA 8**, **SA 10**, **SA 11**, **SA 17**, **SA 18** and **SA 29** depicted protection at the maximum dose of 300 mg/kg at 0.5 h except **SA 11** that continued to show activity at both the time interval at the same dose (Table 2).

In the *sc*PTZ screen **SA 12**, **SA 22** and **SA 24** showed anti-*sc*PTZ activity at the minimum dose of 100 mg/kg except **SA 22** and **SA 24** that showed activity at 300 mg/kg at 4.0 h, thereby indicating comparable activity to the standard drug ethosuximide. Compound

Table 2
Anticonvulsant screening project (ASP): phase I results for compounds **SA** (**1**–**30**).

Compd.	Intraperitoneal injection in mice[a]					
	MES[b]		*sc*PTZ[c]		NT[d]	
	0.5 h	4 h	0.5 h	4 h	0.5	4 h
SA 1	–	–	–	–	×	×
SA 2	300	–	–	300	100	–
SA 3	300	–	–	–	300	–
SA 4	–	300	300	–	100	300
SA 5	–	–	–	–	×	×
SA 6	–	–	–	–	×	×
SA 7	300	–	–	–	300	–
SA 8	300	–	–	300	100	300
SA 9	–	–	–	–	×	×
SA 10	300	–	–	–	300	–
SA 11	300	300	–	300	×	×
SA 12	100	100	100	–	300	×
SA 13	100	–	–	–	300	300
SA 14	100	100	300	–	300	–
SA 15	–	–	–	–	×	×
SA 16	–	–	–	–	×	×
SA 17	300	–	–	–	–	300
SA 18	300	–	–	–	×	×
SA 19	–	–	–	–	×	×
SA 20	–	–	–	–	×	×
SA 21	30	100	–	300	300	–
SA 22	30	100	100	300	300	300
SA 23	100	300	–	300	300	–
SA 24	30	30	100	300	300	–
SA 25	–	–	–	–	×	×
SA 26	–	–	–	–	×	×
SA 27	–	–	–	300	300	–
SA 28	100	300	300	–	100	–
SA 29	300	–	–	–	300	–
SA 30	–	–	–	–	×	×
Phenytoin[e]	30	30	–	–	100	100
Ethosuximide[e]	–	–	100	300	–	–
Carbamazepine[f]	30	100	–	–	100	300

(×) Activity not performed.
[a] Number of animal used = 4, doses of 30, 100, and 300 mg/kg were administered. The figure in the table indicates the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined at 0.5 and 4 h. Dash (–) indicates the absence of anticonvulsant activity and neurotoxicity at the maximum dose administered (300 mg/kg).
[b] Maximal electroshock test.
[c] Subcutaneous pentylenetetrazole test.
[d] Neurotoxicity screening-rotorod test.
[e] Reference drugs, data for phenytoin and ethosuximide data from Ref. [44].
[f] Reference drug, carbamazepine data from Ref. [34].

SA 4, **SA 14** and **SA 28** rendered protection at 300 mg/kg at 0.5 h indicating quick onset of action at a higher dose. Whereas compound **SA 2**, **SA 8**, **SA 11**, **SA 21**, **SA 23** and **SA 27** also gave protection at the same dose but at 4.0 h duration suggesting delayed onset and longer duration of action. Rest of the compounds did not display any activity at the selected criterion. The synthesized compounds that exhibited protection against MES and *sc*PTZ induced convulsions were further evaluated for minimal motor impairment using rotorod test. Compound **SA 3**, **SA 7**, **SA 10**, **SA 12**, **SA 13**, **SA 14**, **SA 21**–**24**, **SA 27** and **SA 29** were less neurotoxic than phenytoin and exhibited motor impairment at the dose of 300 mg/kg at 0.5 h except **SA 13** and **SA 22** that showed prolonged neurotoxicity level at this dose at 4.0 h time interval. **SA 2**, **SA 4**, **SA 8** and **SA 28** exhibited neurotoxicity at 100 mg/kg at 0.5 h out of which **SA 4** and **SA 8** had neurotoxicity equivalent to carbamazepine. Compound **SA 17** showed minimal motor impairment at 300 mg/kg at 4.0 h exhibiting delayed onset but sustained neurotoxicity. The overall results suggest the fact that compound **SA 22** and **SA 24** were found to be the most potent compounds having significant anticonvulsant potential and minimal toxicity compared to the standard drugs. Likewise **SA 21** was active against generalized tonic–clonic seizures as depicted through MES test and **SA 12** showed protection against absence seizures induced by pentylenetetrazole with minimal toxicity. The preliminary outcomes of the anticonvulsant screening in mice and in accordance with the anticonvulsant screening project (ASP) disposition, **SA 22** and **SA 24** were selected for probing their anticonvulsant potential (MES and *sc*PTZ screen) after oral administration into rats at a dose of 30 mg/kg and 50 mg/kg respectively. A valuable property of a candidate anticonvulsant is its ability to inhibit convulsions when given by the oral route. This screen discloses the time of onset, the approximate time of peak effect (TPE) and the duration of anticonvulsant activity or neurotoxicity. The data exemplified one peak of 100% protection at 2 h and 4 h and 75% at 0.5 h and 1 h for **SA 24** suggesting it to be the most active of the series in MES screen. **SA 22** like phenytoin attained 75% protection at 2 h and 4 h respectively besides retaining merely 50% protection at 0.5 h and 1 h and 25% after quarterly administration. Likewise the *sc*PTZ study of **SA 24** canvassed a peak of 50% protection at 4 h compared to 25% at 0.5 h, 1 h and 2 h respectively. It remarked **SA 24** to have retained anti-*sc*PTZ potential after 4 h of oral administration compared to ethosuximide used as reference anticonvulsant. **SA 22** was less active demonstrating a peak of 25% protection after 2 h and 4 h of oral administration in rats.

The increased protection graph of the compounds **SA 22** and **SA 24** after oral administration in both MES and *sc*PTZ screen is suggestive of slow but sustained absorption of these compounds besides having prolonged duration of action.

The quantitative evaluation of the pharmacological parameters (ED_{50} and TD_{50}) for the compounds **SA 22** and **SA 24** in the MES and *sc*PTZ screen was performed at the previously estimated time of peak effect (TPE). An instill into the quantification data of MES screen provided us with **SA 24** more potent than phenytoin but less than carbamazepine with low neurotoxicity as evidenced from its protective indices (TD_{50}/ED_{50}) of >26. Furthermore, **SA 22** exhibited a protective window lesser than that of phenytoin and carbamazepine chosen as reference drugs. In the *sc*PTZ attainments **SA 24** displayed a remarkable decrease in the ED_{50} to 510.5 μmol/kg and TD_{50} > 2150 μmol/kg ensuing in very promising protection index of >4.2 compared to the >3.0 for the standard drug ethosuximide. **SA 22** afforded corresponding protection to ethosuximide (Table 3).

Concurrent with the above screens and with the prospective exploration of anticonvulsant molecules among the chemically diversified compounds prosecuted in NIH/NINDS, recent anti 6-Hz screen formalized as a model of therapy-resistant epilepsy was further executed. **SA 22** and **SA 24** were administrated intraperitoneally at a dose of 100 mg/kg. The psychomotor seizure test data inculcated a 100% protection in **SA 22** at 0.5 h followed by 75% (**SA 22** at 1 h and 2 h, **SA 24** at 0.5 h) and 50% (**SA 22** at 2 h, **SA 24** at 1 h, 2 h and 4 h). **SA 22** was inferred as more active compound than **SA 24** in the anti 6-Hz screen. The maximum protection was exhibited by both the compounds after 0.5 h of administration.

The quantification study of the active compound **SA 22** in the psychomotor seizure test at the TPE displayed a greater median effective dose (ED_{50}) 1227.9 μmol/kg than the standard drug ethosuximide thereby ceasing its further evaluation (Table 4).

Hepatotoxicity is the major adverse reactions contributing to the ruling out of many marketed drugs. The destitute from this drug-induced unpredictable and idiosyncratic toxicity consternation was provided through the estimation of serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) after chronic administration of **SA 22** and **SA 24** to rats for two weeks. The compounds did not depict any significant increase or malfunctioning of these enzymes compared to the control as well as the standard drug phenytoin (Table 5).

To deduce the effect on GABA receptor, **SA 22** and **SA 24** were subjected to neurochemical investigation for the determination of GABA in different regions of whole rat brain. Both the tested compounds statistically increased the GABA concentration compared to the control with **SA 22** ($P < 0.001$) level of significance and **SA 24** ($P < 0.004$) significant after 2 h of i.p. administration. After seven days of chronic oral administration a non-significant result was obtained for **SA 22** compared to **SA 24** ($P < 0.01$) significant. Both the compounds demonstrated lesser or nearly equal concentration of GABA to the standard anticonvulsant drug clobazam (Table 6).

In order to correlate the anticonvulsant activity of novel compounds **SA 22** and **SA 24** with affinity for AMPA receptor, an additional test against AMPA-induced seizures in mice was performed. As shown in Fig. 2(a) and (b), the clonic and tonic phases of the seizures induced by intracerebroventricular (i.c.v.) administration of AMPA were significantly reduced 30 min after i.p. administration of **SA 22** and **SA 24**; the measured ED_{50} values are reported in Table 7. **SA 24** was found to be active showing potency comparable to GYKI 52446.

The findings of the anticonvulsant study conducted on *N*-(benzo[*d*]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4*H*)-carbothioamide analogs manifested us to draw the following structural correlation:

- Unsubstituted quinazoline ring (**SA 22** and **SA 24**) favored the compounds to hold back the anticonvulsant potential.
- The presence of electron withdrawing groups like trifluoromethoxy and chloro group on the benzothiazole ring necessitated significant anticonvulsant activity and minimal toxicity compared to reference drugs.
- The trifluoromethoxy substitution in benzothiazole ring of **SA 24** played a vital role antagonizing AMPA mediated excitatory neurotransmission as envisaged from its structural analogy to the well known marketed anticonvulsant drug riluzole.
- The para chloro substituted benzothiazole ring in **SA 22** increased the effectuality of the compound at the GABA receptor thereby increasing its concentration in the rat brain assay

3. Conclusion

The series of 30 new *N*-(benzo[*d*]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4*H*)-carbothioamide derivatives were designed, synthesized and their anticonvulsant activity were evaluated in three seizure models namely MES, *sc*PTZ and 6-Hz model. The compounds (6-chlorobenzo[*d*]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4*H*)-carbothioamide (SA 22: PI = >3.4; *sc*PTZ) and

Table 3
Quantification studies of selected compounds **SA 22** and **SA 24** in rats after oral administration.

Compd.	TPE (h)[a]	MES ED_{50}[b] (μmol/kg)	*sc*PTZ ED_{50}[b] (μmol/kg)	NT TD_{50}[c] (μmol/kg)	PI[d]
SA 22	4	142 (88.9–217)	722.5 (568.1–782.7)	>2500	>17 (MES) >3.4 (*sc*PTZ)
SA 24	0.5	82.5 (50.3–122)	510.5 (484.4–648.5)	>2150	>26 (MES) >4.2 (*sc*PTZ)
Phenytoin[e]	2	92 (84.8–101)	>3540	>1980	>22 (MES)
Carbamazepine[e]	1	15.1 (10.2–20)	>1060	1528 (1350–1700)	101 (MES)
Ethosuximide[f]	2	>3540	1182 (821.7–1678.8)	>3540	>3.0 (*sc*PTZ)

[a] Time to peak effect.
[b] ED_{50} – median effective dose required to assure anticonvulsant protection in 50% animals.
[c] TD_{50} – median toxic dose eliciting minimal neurological toxicity in 50% animals.
[d] PI – protective index (TD_{50}/ED_{50}).
[e] Reference drugs, phenytoin and carbamazepine, data from Ref. [36] converted to μmol/kg.
[f] Reference drug, ethosuximide, data from Ref. [37] converted to μmol/kg.

Table 4
Quantification studies of **SA 22** in psychomotor seizure test (6-Hz, current 32 mA).

Compd.[a]	TPE (h)[b]	ED_{50}[c] (μmol/kg)	TD_{50}[d] (μmol/kg)	PI[e]
SA 22	2	1227.9(1157.3–1235.0)	ND	ND
Ethosuximide[f]	1	1178.5(804.5–1573.9)	2406.4(2046.5–2709)	2.0

ND – not determined.
[a] Intraperitoneal injection into mice.
[b] Time to peak effect.
[c] ED_{50} – median effective dose required to assure anticonvulsant protection in 50% animals.
[d] TD_{50} -median toxic dose eliciting minimal neurological toxicity in 50% animals.
[e] PI – protective index (TD_{50}/ED_{50}).
[f] Reference drug, ethosuximide data from Ref. [37].

2-methyl-4-oxo-(6-(trifluoromethoxy)benzo[*d*]thiazol-2ylcarbamoyl)quinazoline-3(4*H*)-carbothioamide (SA 24: PI = >26; MES, >4.2; *sc*PTZ) depicted comparable to higher activity than that of the reference compound phenytoin (PI = >22; MES) and ethosuximide (PI = >3.0; *sc*PTZ). Interestingly, they also exhibited anticonvulsant activity against AMPA and GABA induced seizures in accord of an involvement of these receptors in inducing seizures. In light of these findings we conclude that the compounds **SA 22** and **SA 24** can be anticipated to have activity at multiple receptors thereby acquitting as templates for future design, modification and investigation to produce more active analogs. However, studies need to be carried out for precise mechanism and study of pharmacokinetic parameters.

4. Experimental protocols

4.1. Chemistry

All reagents were used as purchased from commercial suppliers like Merck India Ltd., S.D Fine Chemicals, Sigma Aldrich and Qualigens and were used without purification. The purity and homogeneity of the compounds were assessed by the TLC performed on Merck silica gel 60 F_{254} aluminum sheets using toluene:methanol (8:2) as eluents. Iodine chamber and Schimadzu (UV-160) spectrometer were used for visualization of TLC spots. Ashless Whatmann No. 1 filter paper was used for vacuum filtration. Melting points were determined in one end open capillary tubes on Buchi 530 melting point apparatus and are uncorrected. Elemental data of C, H, and N were within ±0.4% of the theoretical value as determined by Perkin Elmer Model 240 analyzer. The Infrared Spectra of compounds were recorded on Perkin Elmer Spectrum BX-II Spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra of DMSO-d_6/$CDCl_3$ solutions were respectively recorded at 400 and 100 MHz with Bruker model DRX 400 NMR Spectrometer using TMS [$(CH_3)_4Si$] as internal standard. Signal multiplicities are represented by the following abbreviations: s (singlet), br s (broad singlet), d (doublet), t (triplet), and m (multiplet). Chemical shifts are reported in δ values (ppm) relative to TMS $\delta = 0$. The Mass Spectra was recorded on a Waters Micro-mass ZQ 2000 Spectrophotometer. The structures were confirmed by both spectral (IR, ^{1}H NMR, ^{13}C NMR, MS) and elemental analysis. The syntheses of starting material [**1a–j** (4.1.1.), 2a-j (4.1.2.), 3a-j (4.1.3.) and 4a-c (4.1.4.)] along with spectral characterization are given as Supplementary material.

4.1.1. General procedure for the synthesis of compounds (*SA 1–30*)

A solution of compound 4-substituted-2-acetamidobenzoic acid (**4a–c**) (0.1 mol) and (substituted-benzthiazol-2yl)-dicarbonimidothioic diamide (**3a–j**) (0.1 mol) in dry toluene (40 mL) was taken in a dropper and was added drop-wise with constant stirring to a mixture of PCl_3 (6 g) in dry toluene (20 mL) placed in a round bottomed flask. The reaction mixture was stirred at reflux temperature for 3 h. After the completion of the reaction (TLC monitoring), the solvent was removed in vacuum under pressure and the residue obtained was treated with a 5% solution of Na_2CO_3 (100 mL), the obtained solid was filtered, washed with water, dried

Table 5
Effect on serum levels of liver transaminases of selected compounds **SA 22** and **SA 24** in six rats.

Compd.[a]	SGPT[b,f] (units/mL)	SGOT[c,f] (units/mL)
Control[d]	46.1 ± 5.25	74.2 ± 5.95
SA 22	48.5 ± 3.25	71.2 ± 4.68
SA 24	44.7 ± 4.35	72.4 ± 4.05
Phenytoin[e]	52.6 ± 3.48	84.1 ± 6.50

[a] The compounds were tested at a dose of 30 mg/kg oral for 14 days.
[b] Denotes serum glutamate oxaloacetate transaminase.
[c] Denotes serum glutamate pyruvate transaminase.
[d] Control animals (six rats) were treated with 0.5% methylcellulose for 14 days.
[e] Reference drug, phenytoin (tested at 25 mg/kg oral for 14 days) data from Ref. [35].
[f] Each value represents the mean ± SEM of six rats, not significant from the control value at $p < 0.05$ (Student's *t* test).

Table 6
Effect of selected compounds **SA 22** and **SA 24** in GABA system.

Compd.[b]	GABA level in rat whole brain concentration[a] (μg/100 mg of tissue)	
	2 h post-treatment[c]	7 days post-treatment[d]
Control	46.4 ± 5.50	51.5 ± 2.60
SA 22	92.1 ± 8.75*	111 ± 2.75
SA 24	75.5 ± 6.17**	68.2 ± 4.75***
Clobazam[e]	101 ± 6.77	110 ± 4.83

[a] The data indicate the minimum concentration whereby at least 50% inhibition was demonstrated in one or more time points.
[b] The compounds were tested at a dose of 100 mg/kg (i.p.) except clobazam (30 mg/kg).
[c] Each value represents the mean ± SEM of six rats, significantly different from the control at $p < 0.001$;*, $p < 0.004$;**, $p < 0.01$;*** (Student's *t* test).
[d] The compounds were tested at a dose of 30 mg/kg oral for 7 days.
[e] Reference drug, clobazam data from Ref. [35].

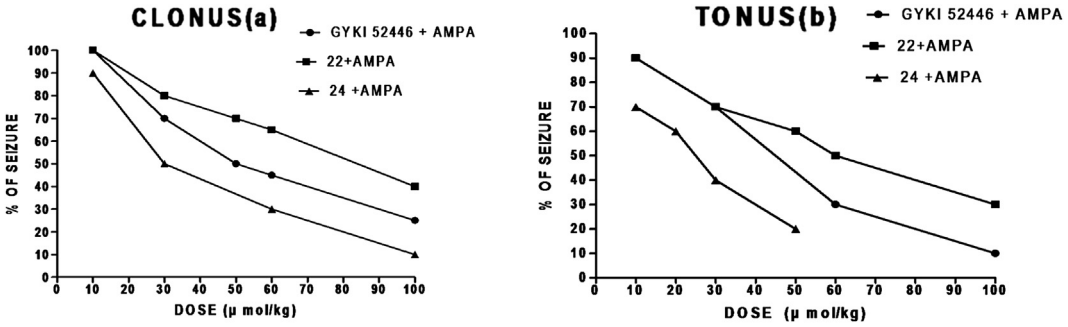


Fig. 2. Anticonvulsant effects of **SA 22**, **SA 24** and GYKI 52446 against seizures induced by AMPA in mice. The ordinate shows % of response of clonic (a) or tonic (b) seizures, abscissa shows the dose in μmol/kg i.p. For the determination of each point ten animals were used.

and re-crystallized with suitable solvent to get the desired compounds (**SA 1**–**30**).

*4.1.1.1. 7-Fluoro-(6-fluorobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 1**).* IR (KBr) ν_{max} (cm^{-1}): 3423 (Secondary amide NH), 3041 (Ar—CH), 2928 (Aliphatic CH), 1654 (C═O of quinazoline), 1634 (C═O of urea), 1523 (C═N), 1320 (C—F), 1055 (C═S), 678 (C—S—C); ^{1}H NMR (δ) DMSO-d_6: 2.62 (s, 3H, quinazoline—CH_3), 6.89 (d, 1H, Ar—H of benzothiazole), 7.20 (d, 1H, Ar—H of benzothiazole), 7.60 (d, 1H, Ar—H at C_5—H quinazoline), 7.80 (s, 1H, Ar—H of benzothiazole), 8.30 (br s, 1H of NHC═O, D_2O exchangeable), 8.40 (d, 1H, Ar—H at C_6—H quinazoline), 8.50 (s, 1H, Ar—H at C_8—H quinazoline), 13.07 (br s, 1H of NHC═S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 26.5 (C-11), 107.7 (C-7′), 110.1 (C-5′), 120.6 (C-4′), 122.2 (C-6), 126.4 (C-8), 128.8 (C-10), 130.2 (C-5), 131.1 (C-9′), 145.3 (C-8′), 147.6 (C-9), 154.7 (C═O), 156.5 (C-6′), 158.7 (C-2), 161.1 (C-2′), 166.6 (C-7), 168.4 (C-4), 186.5 (C═S); MS (*m*/*z*, %): 432.22 ($M^+ + 1$, 98.30).

*4.1.1.2. (6-Chlorobenzo[d]thiazol-2-ylcarbamoyl)-7-fluoro-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 2**).* IR (KBr) ν_{max} (cm^{-1}): 3426 (Secondary amide NH), 3070 (Ar—CH), 2950 (Aliphatic CH), 1650 (C═O of quinazoline), 1631 (C═O of urea), 1520 (C═N), 1325 (C—F), 1050 (C═S), 820 (C—Cl), 679 (C—S—C); ^{1}H NMR (δ) DMSO-d_6: 2.42 (s, 3H, quinazoline—CH_3), 6.80 (d, 1H, Ar—H of benzothiazole), 7.10 (d, 1H, Ar—H of benzothiazole), 7.65 (d, 1H, Ar—H at C_5—H quinazoline), 7.75 (s, 1H, Ar—H of benzothiazole), 8.17 (br s, 1H of NHC═O, D_2O exchangeable), 8.40 (d, 1H, Ar—H at C_6—H quinazoline), 8.55 (s, 1H, Ar—H at C_8—H quinazoline), 12.98 (br s, 1H of NHC═S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 24.2 (C-11), 118.7 (C-7′), 120.1 (C-4′), 120.6 (C-5′), 123.2 (C-6), 124.7 (C-8), 127.4 (C-6′), 127.8 (C-10), 130.2 (C-5), 131.5 (C-9′), 144.4 (C-8′), 148.6 (C-9), 156.5 (C═O), 158.7 (C-2), 160.2 (C-2′), 165.6 (C-7), 169.5 (C-4), 184.5 (C═S); MS (*m*/*z*, %): 448.20 ($M^+ + 1$ for ^{35}Cl, 96.20), 450.32 ($M^+ + 1$ for ^{37}Cl, 30.33).

*4.1.1.3. (6-Bromobenzo[d]thiazol-2-ylcarbamoyl)-7-fluoro-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 3**).* IR (KBr) ν_{max} (cm^{-1}): 3428 (Secondary amide NH), 3075 (Ar—CH), 2970 (Aliphatic CH), 1655 (C═O of quinazoline), 1637 (C═O of urea), 1525 (C═N), 1328 (C—F), 1055 (C═S), 675 (C—S—C), 570 (C—Br); ^{1}H NMR (δ) DMSO-d_6: 2.45 (s, 3H, quinazoline—CH_3), 6.75 (d, 1H, Ar—H of benzothiazole), 7.11 (d, 1H, Ar—H of benzothiazole), 7.65 (s, 1H, Ar—H of benzothiazole), 7.75 (d, 1H, Ar—H at C_5—H quinazoline), 8.30 (d, 1H, Ar—H at C_6—H quinazoline), 8.45 (s, 1H, Ar—H at C_8—H quinazoline), 9.17 (br s, 1H of NHC═O, D_2O exchangeable), 11.78 (br s, 1H of NHC═S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 24.4 (C-11), 112.3 (C-7′), 119.6 (C-6′), 120.5 (C-6), 121.5 (C-4′), 124.2 (C-8), 126.4 (C-5′), 129.8 (C-10), 130.1 (C-5), 130.5 (C-9′), 145.4 (C-8′), 150.6 (C-9), 154.3 (C═O), 159.7 (C-2), 161.2 (C-2′), 167.6 (C-7), 168.5 (C-4), 188.2 (C═S); MS (*m*/*z*, %): 492.10 ($M^+ + 1$ for ^{79}Br, 90.43), 494.20 ($M^+ + 1$ for ^{81}Br, 43.13).

*4.1.1.4. 7-Fluoro-2-methyl-4-oxo-(6-(trifluoromethoxy)benzo[d]thiazol-2-ylcarbamoyl) quinazoline-3(4H)-carbothioamide (**SA 4**).* IR (KBr) ν_{max} (cm^{-1}): 3424 (Secondary amide NH), 3084 (Ar—CH), 2978 (Aliphatic CH), 1665 (C═O of quinazoline), 1631 (C═O of urea), 1520 (C═N), 1324 (C—F), 1175 (C—OCF_3), 1052 (C═S), 672 (C—S—C); ^{1}H NMR (δ) DMSO-d_6: 2.62 (s, 3H, quinazoline—CH_3), 6.95 (d, 1H, Ar—H of benzothiazole), 7.40 (d, 1H, Ar—H of benzothiazole), 7.55 (d, 1H, Ar—H at C_5—H quinazoline), 7.95 (s, 1H, Ar—H of benzothiazole), 8.35 (d, 1H, Ar—H at C_6—H quinazoline), 8.45 (s, 1H, Ar—H at C_8—H quinazoline), 8.73 (br s, 1H of NHC═O, D_2O exchangeable), 12.61 (br s, 1H of NHC═S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 26.4 (C-11), 105.5 (C-7′), 116.4 (C-5′), 118.5 (C-4′), 120.7 (—OCF_3), 122.2 (C-6), 125.4 (C-8), 127.8 (C-10), 130.5 (C-5), 131.1 (C-9′), 145.4 (C-8′), 147.7 (C-9), 152.6 (C═O), 156.4 (C-6′), 158.7 (C-2), 161.2 (C-2′), 164.6 (C-7), 168.6 (C-4), 186.6 (C═S); MS (*m*/*z*, %): 498.40 ($M^+ + 1$, 98.20).

*4.1.1.5. 7-Fluoro-(6-hydroxybenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 5**).* IR (KBr) ν_{max} (cm^{-1}): 3434 (Secondary amide NH), 3085 (Ar—CH), 2983 (Aliphatic CH), 1668 (C═O of quinazoline), 1631 (C═O of urea), 1530 (C═N), 1321 (C—F), 1190 (C—O), 1050 (C═S), 678 (C—S—C); ^{1}H NMR (δ) DMSO-d_6: 2.38 (s, 3H, quinazoline—CH_3), 6.85 (d, 1H, Ar—H of benzothiazole), 7.20 (d, 1H, Ar—H of benzothiazole), 7.45 (d, 1H, Ar—H at C_5—H quinazoline), 7.68 (s, 1H, Ar—H of benzothiazole), 8.48 (d, 1H, Ar—H at C_6—H quinazoline), 8.65 (s, 1H, Ar—H at C_8—H quinazoline), 8.86 (br s, 1H of NHC═O, D_2O exchangeable), 10.62 (s, 1H Ar—OH of benzothiazole), 13.07 (br s, 1H of NHC═S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 27.4 (C-11), 117.6 (C-7′), 120.5 (C-5′), 121.5 (C-6), 122.2 (C-4′), 126.4 (C-8), 129.8 (C-10), 132.2 (C-5), 133.5 (C-9′), 145.4 (C-8′), 148.6 (C-9), 150.5 (C-6′), 153.6 (C═

Table 7
Anticonvulsant activity of selected compounds **SA 22** and **SA 24** against the AMPA-induced seizures.

Compd[a]	Dose range	ED_{50} AMPA[b] (μmol/kg)	
		Clonic phase[c]	Tonic phase[c]
SA 22	10–100	70.3(57.7–84.2)	56.9(40.8–79.1)
SA 24	10–100	37.9(28.3–51.8)	28.5(20.5–28.5)
GYKI 52446[d]	10–100	57.5(43.5–76.0)	40.5(26.3–60.8)

[a] Intraperitoneal injection into mice.
[b] AMPA was administered i.c.v. at the CD_{97} for either clonus (9.7 nmol) or forelimb tonic extension (11.7 nmol) 30 min after injection of each compound.
[c] ED_{50} values with 95% confidence limits were calculated according to the method of Litchfield and Wilcoxon Ref. [38].
[d] 1-(4′-Aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466) has been identified as a potent and selective non-competitive AMPA-receptor antagonist. Reference, GYKI 52466 data from Ref. [39].

O), 160.8 (C-2), 161.2 (C-2′), 164.6 (C-7), 167.4 (C-4), 188.2 (C=S); MS (*m*/*z*, %): 430.50 ($M^+ + 1$, 100).

*4.1.1.6. 7-Fluoro-(6-methoxybenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 6**).* IR (KBr) ν_{max} (cm^{-1}): 3454 (Secondary amide NH), 3094 (Ar–CH), 2983 (Aliphatic CH), 1665 (C=O of quinazoline), 1625 (C=O of urea), 1537 (C=N), 1311 (C–F), 1185 (C–OCH_3), 1055 (C=S), 673 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.56 (s, 3H, quinazoline–CH_3), 3.84 (s, 3H Ar–OCH_3 of benzothiazole), 6.93 (d, 1H, Ar–H of benzothiazole), 7.15 (d, 1H, Ar–H of benzothiazole), 7.55 (d, 1H, Ar–H at C_5–H quinazoline), 7.65 (s, 1H, Ar–H of benzothiazole), 8.13 (br s, 1H of NHC=O, D_2O exchangeable), 8.44 (d, 1H, Ar–H at C_6–H quinazoline), 8.62 (s, 1H, Ar–H at C_8–H quinazoline), 12.81 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 24.8 (C-11), 52.2 (OCH_3), 108.8 (C-7′), 118.4 (C-5′), 121.6 (C-6), 124.2 (C-4′), 125.4 (C-8), 126.5 (C-10), 130.5 (C-5), 132.5 (C-9′), 142.4 (C-8′), 145.5 (C-9), 152.6 (C=O), 154.5 (C-6′), 160.6 (C-2), 161.2 (C-2′), 164.6 (C-7), 168.5 (C-4), 185.6 (C=S); MS (*m*/*z*, %): 444.34 ($M^+ + 1$, 99.80).

*4.1.1.7. (4-Chlorobenzo[d]thiazol-2-ylcarbamoyl)-7-fluoro-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 7**).* IR (KBr) ν_{max} (cm^{-1}): 3423 (Secondary amide NH), 3055 (Ar–CH), 2960 (Aliphatic CH), 1655 (C=O of quinazoline), 1621 (C=O of urea), 1520 (C=N), 1325 (C–F), 1045 (C=S), 834 (C–Cl), 673 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.40 (s, 3H, quinazoline–CH_3), 6.95 (d, 1H, Ar–H of benzothiazole), 7.30 (t, 1H, Ar–H of benzothiazole), 7.65 (d, 1H, Ar–H at C_5–H quinazoline), 7.85 (d, 1H, Ar–H of benzothiazole), 8.23 (br s, 1H of NHC=O, D_2O exchangeable), 8.50 (d, 1H, Ar–H at C_6–H quinazoline), 8.68 (s, 1H, Ar–H at C_8–H quinazoline), 13.02 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 27.5 (C-11), 116.4 (C-5′), 118.7 (C-6′), 120.5 (C-7′), 121.6 (C-4′), 122.2 (C-6), 126.4 (C-8), 128.8 (C-10), 130.2 (C-5), 131.5 (C-9′), 145.4 (C-8′), 148.6 (C-9), 154.5 (C=O), 160.7 (C-2), 161.2 (C-2′), 164.6 (C-7), 168.5 (C-4), 185.5 (C=S); MS (*m*/*z*, %): 448.10 ($M^+ + 1$ for ^{35}Cl, 100), 450.22 ($M^+ + 1$ for ^{37}Cl, 28.33).

*4.1.1.8. (5-Chlorobenzo[d]thiazol-2-ylcarbamoyl)-7-fluoro-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 8**).* IR (KBr) ν_{max} (cm^{-1}): 3428 (Secondary amide NH), 3045 (Ar–CH), 2965 (Aliphatic CH), 1649 (C=O of quinazoline), 1620 (C=O of urea), 1510 (C=N), 1330 (C–F), 1055 (C=S), 830, 780 (C–Cl), 678 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.45 (s, 3H, quinazoline–CH_3), 7.15 (d, 1H, Ar–H of benzothiazole), 7.30 (d, 1H, Ar–H of benzothiazole), 7.50 (d, 1H, Ar–H at C_5–H quinazoline), 7.68 (s, 1H, Ar–H of benzothiazole), 7.98 (br s, 1H of NHC=O, D_2O exchangeable), 8.53 (d, 1H, Ar–H at C_6–H quinazoline), 8.68 (s, 1H, Ar–H at C_8–H quinazoline), 12.71 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 25.5 (C-11), 118.7 (C-7′), 120.2 (C-4′), 120.6 (C-6′), 123.2 (C-6), 127.4 (C-5′), 128.5 (C-8), 129.5 (C-10), 131.2 (C-5), 132.5 (C-9′), 145.4 (C-8′), 150.6 (C-9), 155.5 (C=O), 158.7 (C-2), 160.2 (C-2′), 165.6 (C-7), 168.5 (C-4), 188.5 (C=S); MS (*m*/*z*, %): 448.13 ($M^+ + 1$ for ^{35}Cl, 99.26), 450.32 ($M^+ + 1$ for ^{37}Cl, 35.33).

*4.1.1.9. 7-Fluoro-2-methyl-(5-methylbenzo[d]thiazol-2-ylcarbamoyl)-4-oxoquinazoline-3(4H)-carbothioamide (**SA 9**).* IR (KBr) ν_{max} (cm^{-1}): 3440 (Secondary amide NH), 3045 (Ar–CH), 2928 (Aliphatic CH), 1658 (C=O of quinazoline), 1635 (C=O of urea), 1525 (C=N), 1328 (C–F), 1058 (C=S), 670 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.42 (s, 3H, quinazoline–CH_3), 2.60 (s, 3H, Ar–CH_3 of benzothiazole), 7.10 (d, 1H, Ar–H of benzothiazole), 7.37 (d, 1H, Ar–H of benzothiazole), 7.70 (d, 1H, Ar–H at C_5–H quinazoline), 7.85 (s, 1H, Ar–H of benzothiazole), 8.36 (br s, 1H of NHC=O, D_2O exchangeable), 8.40 (d, 1H, Ar–H at C_6–H quinazoline), 8.60 (s, 1H, Ar–H at C_8–H quinazoline), 12.81 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 20.5 (–CH_3), 22.5 (C-11), 108.5 (C-7′), 118.7 (C-5′), 120.5 (C-4′), 122.2 (C-6), 127.4 (C-8), 127.8 (C-10), 129.2 (C-5), 130.8 (C-6′), 131.5 (C-9′), 145.4 (C-8′), 147.6 (C-9), 156.5 (C=O), 160.1 (C-2), 161.2 (C-2′), 166.6 (C-7), 169.5 (C-4), 185.8 (C=S); MS (*m*/*z*, %): 428.35 ($M^+ + 1$, 95.80).

*4.1.1.10. (4-Bromobenzo[d]thiazol-2-ylcarbamoyl)-7-fluoro-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 10**).* IR (KBr) ν_{max} (cm^{-1}): 3425 (Secondary amide NH), 3060 (Ar–CH), 2976 (Aliphatic CH), 1650 (C=O of quinazoline), 1632 (C=O of urea), 1528 (C=N), 1322 (C–F), 1054 (C=S), 678 (C–S–C), 595 (C–Br); ^{1}H NMR (δ) DMSO-d_6: 2.35 (s, 3H, quinazoline–CH_3), 6.87 (d, 1H, Ar–H of benzothiazole), 7.22 (t, 1H, Ar–H of benzothiazole), 7.87 (d, 1H, Ar–H of benzothiazole), 7.95 (d, 1H, Ar–H at C_5–H quinazoline), 8.45 (d, 1H, Ar–H at C_6–H quinazoline), 8.75 (s, 1H, Ar–H at C_8–H quinazoline), 9.20 (br s, 1H of NHC=O, D_2O exchangeable), 11.58 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 26.4 (C-11), 114.6 (C-4′), 119.6 (C-7′), 120.2 (C-6′), 121.5 (C-6), 122.2 (C-5′), 126.5 (C-8), 128.8 (C-10), 130.5 (C-5), 131.5 (C-9′), 144.4 (C-8′), 148.6 (C-9), 154.3 (C=O), 159.4 (C-2), 162.5 (C-2′), 166.6 (C-7), 168.5 (C-4), 186.2 (C=S); MS (*m*/*z*, %): 492.20 ($M^+ + 1$ for ^{79}Br, 95.45), 494.08 ($M^+ + 1$ for ^{81}Br, 48.33).

*4.1.1.11. 7-Chloro-(6-fluorobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 11**).* IR (KBr) ν_{max} (cm^{-1}): 3445 (Secondary amide NH), 3020 (Ar–CH), 2980 (Aliphatic CH), 1650 (C=O of quinazoline), 1625 (C=O of urea), 1520 (C=N), 1322 (C–F), 1058 (C=S), 825 (C–Cl), 680 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.44 (s, 3H, quinazoline–CH_3), 6.95 (d, 1H, Ar–H of benzothiazole), 7.28 (d, 1H, Ar–H of benzothiazole), 7.40 (d, 1H, Ar–H at C_5–H quinazoline), 7.88 (s, 1H, Ar–H of benzothiazole), 8.28 (d, 1H, Ar–H at C_6–H quinazoline), 8.41 (s, 1H, Ar–H at C_8–H quinazoline), 8.97 (br s, 1H of NHC=O, D_2O exchangeable), 12.73 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 23.8 (C-11), 108.6 (C-7′), 119.7 (C-5′), 122.2 (C-8), 125.4 (C-4′), 127.8 (C-6), 128.6 (C-10), 130.2 (C-5), 136.4 (C-7), 131.5 (C-9′), 145.4 (C-8′), 147.6 (C-9), 151.6 (C=O), 154.5 (C-6′), 161.2 (C-2), 164.6 (C-2′), 168.5 (C-4), 189.5 (C=S); MS (*m*/*z*, %): 448.11 ($M^+ + 1$ for ^{35}Cl, 99.80), 450.32 ($M^+ + 1$ for ^{37}Cl, 32.45).

*4.1.1.12. 7-Chloro-(6-chlorobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 12**).* IR (KBr) ν_{max} (cm^{-1}): 3440 (Secondary amide NH), 3030 (Ar–CH), 2980 (Aliphatic CH), 1655 (C=O of quinazoline), 1635 (C=O of urea), 1520 (C=N), 1055 (C=S), 840, 825 (C–Cl), 688 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.51 (s, 3H, quinazoline–CH_3), 6.90 (d, 1H, Ar–H of benzothiazole), 7.30 (d, 1H, Ar–H of benzothiazole), 7.45 (d, 1H, Ar–H at C_5–H quinazoline), 7.90 (s, 1H, Ar–H of benzothiazole), 8.18 (d, 1H, Ar–H at C_6–H quinazoline), 8.21 (s, 1H, Ar–H at C_8–H quinazoline), 8.38 (br s, 1H of NHC=O, D_2O exchangeable), 12.61 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 23.6 (C-11), 118.7 (C-7′), 119.4 (C-5′), 122.4 (C-4′), 123.5 (C-8), 125.4 (C-6), 127.4 (C-6′), 128.8 (C-10), 130.2 (C-5), 131.5 (C-9′), 135.5 (C-7), 141.5 (C-8′), 145.4 (C-9), 155.5 (C=O), 160.2 (C-2), 165.6 (C-2′), 169.5 (C-4), 184.5 (C=S); MS (*m*/*z*, %): 465.30 ($M^+ + 1$ for ^{35,35}Cl, 100), 466.25 ($M^+ + 1$ for ^{35,37}Cl, 77.33), 470.37 ($M^+ + 1$ for ^{37,37}Cl, 16.33).

*4.1.1.13. (6-Bromobenzo[d]thiazol-2-ylcarbamoyl)-7-chloro-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 13**).* IR (KBr) ν_{max} (cm^{-1}): 3430 (Secondary amide NH), 3045 (Ar–CH), 2880 (Aliphatic CH), 1645 (C=O of quinazoline), 1625 (C=O of urea), 1530 (C=N), 1045 (C=S), 675 (C–S–C), 585 (C–Br); ^{1}H NMR (δ) DMSO-d_6: 2.66 (s, 3H, quinazoline–CH_3), 6.99 (d, 1H, Ar–H of benzothiazole), 7.20 (d, 1H, Ar–H at C_5–H quinazoline), 7.30 (d, 1H, Ar–H of benzothiazole), 7.88 (s, 1H, Ar–H of benzothiazole), 8.10 (d, 1H, Ar–H at C_6–H quinazoline), 8.31 (s, 1H, Ar–H at C_8–H quinazoline), 8.91 (br s, 1H of NHC=O, D_2O exchangeable), 12.63 (br s, 1H of NHC=S, D_2O

exchangeable); ^{13}C NMR (δ) DMSO-d_6: 25.9 (C-11), 112.5 (C-7′), 118.7 (C-6′), 120.3 (C-4′), 123.5 (C-8), 125.8 (C-6), 127.7 (C-5′), 128.5 (C-10), 130.6 (C-5), 134.5 (C-7), 131.5 (C-9′), 143.4 (C-8′), 145.4 (C-9), 152.5 (C=O), 162.2 (C-2), 164.6 (C-2′), 168.5 (C-4), 186.6 (C=S); MS (*m*/*z*, %): 509.70 ($M^+ + 1$ for ^{35,37}Cl and ^{79,81}Br, 100), 508.25 ($M^+ + 1$ for ^{35}Cl and ^{79}Br, 72.23), 511.92 ($M^+ + 1$ for ^{37}Cl and ^{81}Br, 70.13).

*4.1.1.14. 7-Chloro-2-methyl-4-oxo-(6-(trifluoromethoxy)benzo[d] thiazol-2-ylcarbamoyl) quinazoline-3(4H)-carbothioamide (**SA 14**).* IR (KBr) ν_{max} (cm^{-1}): 3440 (Secondary amide NH), 3055 (Ar–CH), 2899 (Aliphatic CH), 1640 (C=O of quinazoline), 1615 (C=O of urea), 1520 (C=N), 1322 (C–F), 1170 (C–OCF_3), 1055 (C=S), 670 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.47 (s, 3H, quinazoline–CH_3), 6.99 (d, 1H, Ar–H of benzothiazole), 7.10 (d, 1H, Ar–H at C_5–H quinazoline), 7.45 (d, 1H, Ar–H of benzothiazole), 7.85 (s, 1H, Ar–H of benzothiazole), 8.25 (d, 1H, Ar–H at C_6–H quinazoline), 8.30 (s, 1H, Ar–H at C_8–H quinazoline), 8.99 (br s, 1H of NHC=O, D_2O exchangeable), 11.44 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 26.1 (C-11), 106.5 (C-7′), 116.8 (C-5′), 119.7 (C-4′), 120.2 (–OCF_3), 122.5 (C-8), 126.4 (C-6), 127.8 (C-10), 130.5 (C-5), 132.1 (C-9′), 135.5 (C-7), 145.4 (C-8′), 146.7 (C-9), 152.8 (C=O), 156.4 (C-6′), 162.5 (C-2), 165.6 (C-2′), 167.6 (C-4), 186.6 (C=S); MS (*m*/*z*, %): 514.91 ($M^+ + 1$ for ^{35}Cl, 100), 516.52 ($M^+ + 1$ for ^{37}Cl, 32.45).

*4.1.1.15. 7-Chloro-(6-hydroxybenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 15**).* IR (KBr) ν_{max} (cm^{-1}): 3445 (Secondary amide NH), 3095 (Ar–CH), 2985 (Aliphatic CH), 1665 (C=O of quinazoline), 1635 (C=O of urea), 1535 (C=N), 1220 (C–O), 1055 (C=S), 670 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.48 (s, 3H, quinazoline–CH_3), 6.95 (d, 1H, Ar–H of benzothiazole), 7.05 (d, 1H, Ar–H at C_5–H quinazoline), 7.20 (d, 1H, Ar–H of benzothiazole), 7.88 (s, 1H, Ar–H of benzothiazole), 8.28 (d, 1H, Ar–H at C_6–H quinazoline), 8.35 (s, 1H, Ar–H at C_8–H quinazoline), 8.98 (br s, 1H of NHC=O, D_2O exchangeable), 10.48 (s, 1H Ar–OH of benzothiazole), 12.98 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 24.4 (C-11), 117.6 (C-7′), 120.5 (C-5′), 122.8 (C-8), 125.2 (C-4′), 126.4 (C-6), 129.8 (C-10), 132.2 (C-5), 133.5 (C-9′), 136.2 (C-7), 145.4 (C-8′), 148.6 (C-9), 150.5 (C-6′), 154.4 (C=O), 158.8 (C-2), 161.2 (C-2′), 165.4 (C-4), 188.6 (C=S); MS (*m*/*z*, %): 446.95 ($M^+ + 1$ for ^{35}Cl, 99.70), 548.52 ($M^+ + 1$ for ^{37}Cl, 38.40).

*4.1.1.16. 7-Chloro-(6-methoxybenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 16**).* IR (KBr) ν_{max} (cm^{-1}): 3450 (Secondary amide NH), 3010 (Ar–CH), 2985 (Aliphatic CH), 1675 (C=O of quinazoline), 1635 (C=O of urea), 1535 (C=N), 1185 (Ar–OCH_3), 1045 (C=S), 825 (C–Cl), 670 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.40 (s, 3H, quinazoline–CH_3), 3.65 (s, 3H Ar–OCH_3 of benzothiazole), 6.95 (d, 1H, Ar–H of benzothiazole), 7.15 (d, 1H, Ar–H at C_5–H quinazoline), 7.35 (d, 1H, Ar–H of benzothiazole), 7.85 (s, 1H, Ar–H of benzothiazole), 8.34 (d, 1H, Ar–H at C_6–H quinazoline), 8.52 (s, 1H, Ar–H at C_8–H quinazoline), 8.73 (br s, 1H of NHC=O, D_2O exchangeable), 12.08 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 26.2 (C-11), 50.2 (–OCH_3), 108.5 (C-7′), 118.4 (C-5′), 121.6 (C-4′), 124.2 (C-8), 126.5 (C-6), 127.9 (C-10), 131.5 (C-5), 132.5 (C-9′), 135.4 (C-7), 145.5 (C-8′), 148.6 (C-9), 152.5 (C=O), 154.4 (C-6′), 161.5 (C-2), 164.6 (C-2′), 168.5 (C-4), 185.6 (C=S); MS (*m*/*z*, %): 460.95 ($M^+ + 1$ for ^{35}Cl, 100), 462.52 ($M^+ + 1$ for ^{37}Cl, 35.60).

*4.1.1.17. 7-Chloro-(4-chlorobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 17**).* IR (KBr) ν_{max} (cm^{-1}): 3433 (Secondary amide NH), 3055 (Ar–CH), 2970 (Aliphatic CH), 1665 (C=O of quinazoline), 1625 (C=O of urea), 1550 (C=N), 1060 (C=S), 834, 820 (C–Cl), 680 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.40 (s, 3H, quinazoline–CH_3), 6.91 (d, 1H, Ar–H of benzothiazole), 7.10 (d, 1H, Ar–H at C_5–H quinazoline), 7.40 (t, 1H, Ar–H of benzothiazole), 7.85 (d, 1H, Ar–H of benzothiazole), 8.30 (d, 1H, Ar–H at C_6–H quinazoline), 8.64 (s, 1H, Ar–H at C_8–H quinazoline), 8.80 (br s, 1H of NHC=O, D_2O exchangeable), 12.72 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 24.6 (C-11), 116.4 (C-7′), 118.7 (C-6′), 120.5 (C-4′), 122.6 (C-8), 126.5 (C-5′), 127.5 (C-6), 128.8 (C-10), 130.2 (C-5), 131.5 (C-9′), 135.7 (C-7), 146.4 (C-8′), 148.6 (C-9), 155.5 (C=O), 162.2 (C-2), 164.6 (C-2′), 168.5 (C-4), 186.2 (C=S); MS (*m*/*z*, %): 465.20 ($M^+ + 1$ for ^{35,35}Cl, 100), 466.34 ($M^+ + 1$ for ^{35,37}Cl, 75.43), 470.41 ($M^+ + 1$ for ^{37,37}Cl, 18.38).

*4.1.1.18. 7-Chloro-(5-chlorobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 18**).* IR (KBr) ν_{max} (cm^{-1}): 3435 (Secondary amide NH), 3065 (Ar–CH), 2975 (Aliphatic CH), 1675 (C=O of quinazoline), 1625 (C=O of urea), 1555 (C=N), 1060 (C=S), 834, 810 (C–Cl), 685 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.43 (s, 3H, quinazoline–CH_3), 7.15 (d, 1H, Ar–H of benzothiazole), 7.30 (d, 1H, Ar–H of benzothiazole), 7.50 (d, 1H, Ar–H at C_5–H quinazoline), 7.86 (s, 1H, Ar–H of benzothiazole), 7.99 (br s, 1H of NHC=O, D_2O exchangeable), 8.23 (d, 1H, Ar–H at C_6–H quinazoline), 8.48 (s, 1H, Ar–H at C_8–H quinazoline), 11.51 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 27.1 (C-11), 118.7 (C-7′), 120.2 (C-4′), 122.2 (C-6′), 122.8 (C-8), 126.5 (C-6), 127.4 (C-5′), 128.5 (C-10), 131.5 (C-5), 132.5 (C-9′), 134.9 (C-7), 145.5 (C-8′), 149.6 (C-9), 155.5 (C=O), 161.2 (C-2), 164.6 (C-2′), 168.5 (C-4), 186.2 (C=S); MS (*m*/*z*, %): 465.11 ($M^+ + 1$ for ^{35,35}Cl, 100), 466.28 ($M^+ + 1$ for ^{35,37}Cl, 80.11), 470.46 ($M^+ + 1$ for ^{37,37}Cl, 19.35).

*4.1.1.19. 7-Chloro-2-methyl-(6-methylbenzo[d]thiazol-2-ylcarbamoyl)-4-oxoquinazoline-3(4H)-carbothioamide (**SA 19**).* IR (KBr) ν_{max} (cm^{-1}): 3445 (Secondary amide NH), 3055 (Ar–CH), 2950 (Aliphatic CH), 1660 (C=O of quinazoline), 1625 (C=O of urea), 1535 (C=N), 1055 (C=S), 834 (C–Cl), 675 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.40 (s, 3H, quinazoline–CH_3), 2.65 (s, 3H, Ar–CH_3 of benzothiazole), 7.10 (d, 1H, Ar–H of benzothiazole), 7.37 (d, 1H, Ar–H of benzothiazole), 7.60 (d, 1H, Ar–H at C_5–H quinazoline), 7.85 (s, 1H, Ar–H of benzothiazole), 8.20 (d, 1H, Ar–H at C_6–H quinazoline), 8.25 (s, 1H, Ar–H at C_8–H quinazoline), 8.36 (br s, 1H of NHC=O, D_2O exchangeable), 12.31 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 20.5 (–CH_3), 26.5 (C-11), 109.5 (C-7′), 118.7 (C-5′), 121.6 (C-4′), 122.2 (C-8), 126.5 (C-6), 128.5 (C-10), 129.9 (C-6′), 130.8 (C-5), 131.5 (C-9′), 136.1 (C-7), 145.4 (C-8′), 147.6 (C-9), 152.5 (C=O), 160.2 (C-2), 162.2 (C-2′), 169.5 (C-4), 185.8 (C=S); MS (*m*/*z*, %): 444.95 ($M^+ + 1$ for ^{35}Cl, 100), 446.52 ($M^+ + 1$ for ^{37}Cl, 38.60).

*4.1.1.20. (4-Bromobenzo[d]thiazol-2-ylcarbamoyl)-7-chloro-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 20**).* IR (KBr) ν_{max} (cm^{-1}): 3435 (Secondary amide NH), 3070 (Ar–CH), 2986 (Aliphatic CH), 1655 (C=O of quinazoline), 1635 (C=O of urea), 1525 (C=N), 1055 (C=S), 670 (C–S–C), 590 (C–Br); ^{1}H NMR (δ) DMSO-d_6: 2.45 (s, 3H, quinazoline–CH_3), 6.95 (d, 1H, Ar–H of benzothiazole), 7.22 (t, 1H, Ar–H of benzothiazole), 7.45 (d, 1H, Ar–H at C_5–H quinazoline), 7.95 (d, 1H, Ar–H of benzothiazole), 8.23 (d, 1H, Ar–H at C_6–H quinazoline), 8.55 (s, 1H, Ar–H at C_8–H quinazoline), 9.15 (br s, 1H of NHC=O, D_2O exchangeable), 11.30 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 26.1 (C-11), 114.4 (C-4′), 119.2 (C-7′), 122.5 (C-8), 126.2 (C-6′), 128.2 (C-5′), 127.5 (C-6), 128.8 (C-10), 130.5 (C-5), 136.3 (C-7), 131.5 (C-9′), 144.4 (C-8′), 148.6 (C-9), 154.3 (C=O), 158.4 (C-2), 162.5 (C-2′), 168.5 (C-4), 186.2 (C=S); MS (*m*/*z*, %): 509.66 ($M^+ + 1$ for ^{35,37}Cl and ^{79,81}Br, 100), 508.15 ($M^+ + 1$ for ^{35}Cl and ^{79}Br, 74.28), 511.82 ($M^+ + 1$ for ^{37}Cl and ^{81}Br, 72.53).

*4.1.1.21. (6-Fluorobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 21**).* IR (KBr) ν_{max} (cm^{-1}): 3425 (Secondary amide NH), 3060, 3040 (Ar–CH), 2925 (Aliphatic CH), 1654 (C=O of quinazoline), 1640 (C=O of urea), 1525 (C=N),

1325 (C–F), 1049 (C=S), 675 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.40 (s, 3H, quinazoline–CH_3), 6.82–8.20 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 8.70 (br s, 1H of NHC=O, D_2O exchangeable), 13.27 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 26.5 (C-11), 105.5 (C-7′), 108.8 (C-5′), 122.8 (C-5 and C-8), 125.5 (C-4′), 126.6 (C-6 and C-7), 131.2 (C-10), 131.5 (C-9′), 147.5 (C-8′), 148.6 (C-9), 155.3 (C=O), 157.5 (C-6′), 160.4 (C-2), 161.5 (C-2′), 168.5 (C-4), 186.6 (C=S); MS (*m*/*z*, %): 414.12 ($M^+ + 1$, 66.30).

*4.1.1.22. (6-Chlorobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 22**).* IR (KBr) ν_{max} (cm^{-1}): 3430 (Secondary amide NH), 3050, 3045 (Ar–CH), 2930 (Aliphatic CH), 1649 (C=O of quinazoline), 1638 (C=O of urea), 1530 (C=N), 1055 (C=S), 825 (C–Cl), 672 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.36 (s, 3H, quinazoline–CH_3), 6.83–8.17 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 8.20 (br s, 1H of NHC=O, D_2O exchangeable), 12.61 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 23.8 (C-11), 118.8 (C-7′), 120.5 (C-5′), 121.3 (C-5 and C-8), 122.2 (C-4′), 126.6 (C-6 and C-7), 127.5 (C-6′), 130.5 (C-10), 131.2 (C-9′), 146.5 (C-8′), 148.8 (C-9), 155.5 (C=O), 158.4 (C-2), 160.5 (C-2′), 166.6 (C-4), 188.6 (C=S); MS (*m*/*z*, %): 430.20 ($M^+ + 1$ for ^{35}Cl, 65.25), 432.12 ($M^+ + 1$ for ^{37}Cl, 22.33).

*4.1.1.23. (6-Bromobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 23**).* IR (KBr) ν_{max} (cm^{-1}): 3420 (Secondary amide NH), 3045, 3030 (Ar–CH), 2920 (Aliphatic CH), 1658 (C=O of quinazoline), 1648 (C=O of urea), 1520 (C=N), 1050 (C=S), 675 (C–S–C), 615 (C–Br); ^{1}H NMR (δ) DMSO-d_6: 2.43 (s, 3H, quinazoline–CH_3), 6.82–8.27 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 9.19 (br s, 1H of NHC=O, D_2O exchangeable), 12.81 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 26.8 (C-11), 112.3 (C-7′), 119.8 (C-6′), 120.2 (C-4′), 122.2 (C-5 and C-8), 126.6 (C-5′), 127.7 (C-6 and C-7), 131.2 (C-10), 133.5 (C-9′), 146.5 (C-8′), 148.6 (C-9), 155.3 (C=O), 159.4 (C-2), 161.6 (C-2′), 165.5 (C-4), 184.6 (C=S); MS (*m*/*z*, %): 472.50 ($M^+ + 1$ for ^{79}Br, 41.45), 474.20 ($M^+ + 1$ for ^{81}Br, 48.23).

*4.1.1.24. 2-Methyl-4-oxo-(6-(trifluoromethoxy)benzo[d]thiazol-2-ylcarbamoyl)quinazoline-3(4H)-carbothioamide (**SA 24**).* IR (KBr) ν_{max} (cm^{-1}): 3430 (Secondary amide NH), 3055, 3030 (Ar–CH), 2950 (Aliphatic CH), 1655 (C=O of quinazoline), 1640 (C=O of urea), 1530 (C=N), 1320 (C–F), 1180 (C–OCF_3), 1058 (C=S), 670 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.41 (s, 3H, quinazoline–CH_3), 6.75–8.37 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 8.90 (br s, 1H of NHC=O, D_2O exchangeable), 11.88 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 22.5 (C-11), 108.5 (C-7′), 116.8 (C-5′), 118.8 (C-4′), 120.5 (–OCF_3), 122.5 (C-5 and C-8), 126.6 (C-6 and C-7), 128.9 (C-10), 131.6 (C-9′), 146.5 (C-8′), 148.6 (C-9), 155.3 (C=O), 156.5 (C-6′), 160.5 (C-2), 161.5 (C-2′), 166.5 (C-4), 185.6 (C=S); MS (*m*/*z*, %): 480.52 ($M^+ + 1$, 60.35).

*4.1.1.25. (6-Hydroxybenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 25**).* IR (KBr) ν_{max} (cm^{-1}): 3436 (Secondary amide NH), 3255 (Ar–OH), 3085, 3050 (Ar–CH), 2985 (Aliphatic CH), 1670 (C=O of quinazoline), 1635 (C=O of urea), 1525 (C=N), 1055 (C=S), 670 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.34 (s, 3H, quinazoline–CH_3), 6.63–8.20 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 9.74 (br s, 1H of NHC=O, D_2O exchangeable), 10.55 (s, 1H Ar–OH of benzothiazole), 12.85 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 24.8 (C-11), 118.8 (C-7′), 120.5 (C-5′), 124.5 (C-5 and C-8), 125.6 (C-4′), 127.7 (C-6 and C-7), 131.5 (C-10), 133.2 (C-9′), 147.5 (C-8′), 148.6 (C-9), 150.5 (C-6′), 154.3 (C=O), 160.4 (C-2), 161.5 (C-2′), 168.5 (C-4), 186.6 (C=S); MS (*m*/*z*, %): 412.55 ($M^+ + 1$, 60.88).

*4.1.1.26. (6-Methoxybenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 26**).* IR (KBr) ν_{max} (cm^{-1}): 3340 (Secondary amide NH), 3090, 3065 (Ar–CH), 2980 (Aliphatic CH), 1665 (C=O of quinazoline), 1630 (C=O of urea), 1520 (C=N), 1185 (C–OCH_3), 1060 (C=S), 675 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.30 (s, 3H, quinazoline–CH_3), 3.52 (s, 3H Ar–OCH_3 of benzothiazole), 6.84–8.29 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 8.43 (br s, 1H of NHC=O, D_2O exchangeable), 12.41 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 24.5 (C-11), 48.5 (–OCH_3), 108.8 (C-7′), 118.5 (C-5′), 122.5 (C-5 and C-8), 122.8 (C-4′), 126.6 (C-6 and C-7), 131.5 (C-10), 133.2 (C-9′), 146.5 (C-8′), 148.6 (C-9), 154.5 (C=O), 155.3 (C-6′), 161.4 (C-2), 162.5 (C-2′), 168.5 (C-4), 185.6 (C=S); MS (*m*/*z*, %): 426.77 ($M^+ + 1$, 58.28).

*4.1.1.27. (4-Chlorobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 27**).* IR (KBr) ν_{max} (cm^{-1}): 3440 (Secondary amide NH), 3055, 3020 (Ar–CH), 2970 (Aliphatic CH), 1665 (C=O of quinazoline), 1630 (C=O of urea), 1525 (C=N), 1060 (C=S), 834 (C–Cl), 678 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.44 (s, 3H, quinazoline–CH_3), 6.77–8.35 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 8.97 (br s, 1H of NHC=O, D_2O exchangeable), 13.02 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 24.6 (C-11), 116.6 (C-7′), 118.8 (C-6′), 121.5 (C-4′), 123.2 (C-5 and C-8), 125.5 (C-5′), 126.6 (C-6 and C-7), 130.5 (C-10), 134.2 (C-9′), 144.5 (C-8′), 149.8 (C-9), 154.5 (C=O), 158.4 (C-2), 160.6 (C-2′), 166.8 (C-4), 184.5 (C=S); MS (*m*/*z*, %): 430.11 ($M^+ + 1$ for ^{35}Cl, 61.23), 432.32 ($M^+ + 1$ for ^{37}Cl, 20.44).

*4.1.1.28. (5-Chlorobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 28**).* IR (KBr) ν_{max} (cm^{-1}): 3445 (Secondary amide NH), 3055, 3040 (Ar–CH), 2960 (Aliphatic CH), 1662 (C=O of quinazoline), 1630 (C=O of urea), 1520 (C=N), 1060 (C=S), 845, 790 (C–Cl), 670 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.52 (s, 3H, quinazoline–CH_3), 6.85–8.15 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 8.80 (br s, 1H of NHC=O, D_2O exchangeable), 11.92 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 25.5 (C-11), 119.5 (C-7′), 121.3 (C-4′), 122.8 (C-5 and C-8), 123.2 (C-6′), 126.2 (C-6 and C-7), 127.5 (C-5′), 130.8 (C-10), 131.2 (C-9′), 144.5 (C-8′), 146.8 (C-9), 154.5 (C=O), 158.4 (C-2), 163.5 (C-2′), 165.6 (C-4), 185.6 (C=S); MS (*m*/*z*, %): 430.21 ($M^+ + 1$ for ^{35}Cl, 60.22), 432.21 ($M^+ + 1$ for ^{37}Cl, 22.82).

*4.1.1.29. 2-Methyl-(6-methylbenzo[d]thiazol-2-ylcarbamoyl)-4-oxoquinazoline-3(4H)-carbothioamide (**SA 29**).* IR (KBr) ν_{max} (cm^{-1}): 3440 (Secondary amide NH), 3065, 3030 (Ar–CH), 2960 (Aliphatic CH), 1665 (C=O of quinazoline), 1635 (C=O of urea), 1510 (C=N), 1065 (C=S), 670 (C–S–C); ^{1}H NMR (δ) DMSO-d_6: 2.44 (s, 3H, quinazoline–CH_3), 2.66 (s, 3H, Ar–CH_3 of benzothiazole), 6.94–8.38 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 8.78 (br s, 1H of NHC=O, D_2O exchangeable), 11.70 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 20.5 (–OCH_3), 24.5 (C-11), 114.4 (C-7′), 118.8 (C-5′), 120.5 (C-4′), 121.3 (C-5 and C-8), 126.6 (C-6 and C-7), 129.8 (C-10), 130.5 (C-9′), 132.2 (C-6′), 145.5 (C-8′), 146.8 (C-9), 155.5 (C=O), 157.4 (C-2), 161.5 (C-2′), 165.6 (C-4), 188.6 (C=S); MS (*m*/*z*, %): 410.57 ($M^+ + 1$, 68.58).

*4.1.1.30. (4-Bromobenzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide (**SA 30**).* IR (KBr) ν_{max} (cm^{-1}): 3445 (Secondary amide NH), 3065, 3050 (Ar–CH), 2940 (Aliphatic CH), 1660 (C=O of quinazoline), 1630 (C=O of urea), 1520 (C=N), 1055 (C=S), 675 (C–S–C), 580 (C–Br); ^{1}H NMR (δ) DMSO-d_6: 2.66 (s, 3H, quinazoline–CH_3), 6.90–8.57 (a set of signals, 4H, quinazoline–H and 3H, benzothiazole–H), 9.37 (br s, 1H of NHC=O, D_2O exchangeable), 11.71 (br s, 1H of NHC=S, D_2O exchangeable); ^{13}C NMR (δ) DMSO-d_6: 26.8 (C-11), 112.3 (C-4′), 119.8 (C-7′), 121.5 (C-5

and C-8), 125.6 (C-6′), 127.7 (C-6 and C-7), 128.5 (C-5′), 129.7 (C-10), 130.5 (C-9′), 146.5 (C-8′), 148.6 (C-9), 155.3 (C=O), 158.4 (C-2), 161.6 (C-2′), 164.5 (C-4), 185.6 (C=S); MS (*m*/*z*, %): 472.62 ($M^+ + 1$ for ^{79}Br, 45.70), 474.36 ($M^+ + 1$ for ^{81}Br, 43.23).

4.2. Pharmacology

Albino Rat (Wistar, 150–200 g), albino mice (Swiss, 25–30 g) were used in groups as experimental animals. The test compounds and standard drug were suspended in tween 80 (1%) or in a 0.5% methyl cellulose–water mixture and administered intraperitoneally. Animals were housed in wire-mesh cages under the laboratory conditions (26 ± 2 °C), 12–12 h light/dark. Animals were allowed to acclimatize with free access to food and water for a 24 h period before testing. All the experimental protocols were carried out with the permission of the Institutional Animal Ethics Committee (IAEC). Animals were obtained from the Central Animal House Facility (173/CPCSEA, 28 Jan., 2000), Jamia Hamdard, New Delhi, India.

4.2.1. Maximal electroshock test (MES)

In the MES screen, an electrical stimulus of 0.2 s in duration (50 mA in mice and 150 mA in rat at 60 Hz) is delivered via corneal electrodes primed with an electrolyte solution containing an anesthetic agent.

4.2.2. Subcutaneous pentylenetetrazole seizure test (scPTZ)

This screen utilizes a dose of pentylenetetrazole (85 mg/kg in mice and 70 mg/kg in rats) that produces clonic seizures lasting for a period of at least 5 s in 97% (CD_{97}) of animals tested. At the anticipated time of testing the convulsant is administered subcutaneously. All the compounds were injected intraperitoneally into mice at the dose levels of 30, 100 and 300 mg/kg with anticonvulsant activity and neurotoxicity assessment at 0.5 and 4 h after administration.

Selected derivatives were administrated orally into rats using four animals at a fixed dose of 30 mg/kg (MES test) and 50 mg/kg (*sc*PTZ test). This screen discloses the time of onset, the approximate time of peak effect (TPE) and the duration of anticonvulsant activity. For both doses the motor impairment was studied in parallel. Rats were tested at five time periods ranging from one quarter to 4 h post substance administration.

4.2.3. Neurological toxicity (NT)

Neurological toxicity induced by a compound was detected in mice using standardized rotorod test [40]. Untreated control mice or rats, when placed on the rod, can maintain their equilibrium for a prolonged time period. The acute motor impairment can be demonstrated by the inability of the animal to maintain equilibrium for a given time (1 min).

4.2.4. Quantification studies

The quantitative determination of ED_{50} and TD_{50} values was performed at previously estimated time of peak effect after oral administration into rats. Groups of eight rats received various doses of the compound until at least three points were established in the range of 10–90% seizure protection or minimal neurotoxicity. From the plot of the data obtained, the respective ED_{50} and TD_{50} values, 95% confidence intervals, slope of the regression line, and standard error of the slope were calculated by means of a computer program.

4.2.5. The 6-Hz model

This screen was carried out according to the protocol originally described by Brown et al. [41] and more recently by Barton et al. [42] and Kaminski et al. [43]. It is an alternative electroshock paradigm that uses low-frequency (6-Hz), long-duration (3 s) electrical stimulation. Corneal stimulation (0.2 ms-duration monopolar rectangular pulses at 6-Hz for 3 s) was delivered by a constant-current (32 mA) device. During the stimulation, mice were manually restrained and released into the observation cage immediately after the current application. The seizures manifest in 'stunned' posture associated with rearing, forelimb, automatic movements and clonus, twitching of the vibrissae and Straub-tail. The duration of the seizure activity ranges from 60 to 120 s in untreated animals. At the end of the seizure, animals resume their normal exploratory behavior. The experimental end point is protection against the seizure. The animal is considered to be protected if it resumes its normal exploratory behavior within 10 s from the stimulation [44].

4.2.6. Hepatotoxicity studies

The animals were divided into groups of six, and the control group received a basal diet and vehicle. Other groups were administered the test drug in a dose of 30 mg/kg/day oral (in PEG 400 or 2% methylcellulose) for 14 days. After the stipulated period, each animal was anesthetized by anesthetic ether, and blood was collected by cardiac puncture to assess the transaminase activity. The *in vitro* determination of transaminase activity was carried out according to the 2,4-dinitrophenyl hydrazine method using SPAN diagnostic reagent kits [45,46].

4.2.7. Isolation of rat brain regions and GABA assay

The GABA assay was performed in brain tissue extracts enzymatically. Adult Wistar rats were divided into three groups of six animals each. After 2 h of drug administration (100 mg/kg, i.p.), the animals were decapitated and the brains were dropped into separate vials containing 4–6 mL of ice-cold 80% ethanol and processed further as described previously [47]. A chronic study was also carried out after oral administration of the test compounds (30 mg/kg) for 7 days.

4.2.8. AMPA-induced seizures in mice

Seizures were also induced by i.c.v. injection of AMPA. The CD_{50} of AMPA for clonus was 1.76 (1.06–3.07) whilst that for tonus was 2.90 (1.83–4.58) nmol. The CD_{97} (the dose which induced convulsions in 97% of the mice) values of 9.7 nmol for all-limb clonic seizures (latency 1.3 ± 0.3 min) and 11.7 nmol for forelimb tonic seizures (latency 1.9 ± 0.4 min), respectively were used to assess the effects of selected compounds on the convulsant properties of AMPA. For i.c.v. injection, mice were anaesthetized with diethyl ether and injections were made in the left or right lateral ventricle (coordinates: 1 mm posterior and 1 mm lateral to the bregma; depth 2.4 mm) using a 10 mL Hamilton microsyringe (type 701N) fitted with a nylon cuff on the needle as previously described [48]. Injections of drugs by this procedure led to a uniform distribution throughout the ventricular system within 10 min. The animals were placed singly in a 30 × 30 × 30 cm box and the observation time was 30 min after the administration of AMPA.

1-(4′-Aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466) has been identified as a potent and selective non-competitive AMPA-receptor antagonist that appears to act via a novel allosteric site on the receptor complex [49,50]. It shows anticonvulsant properties and behaves as a neuroprotective agent in focal and global ischemia. In spite of its chemical similarity to 1,4-benzodiazepines, does not bind to the benzodiazepine receptor (BZR) complex and therefore, it is devoid of any sedative-hypnotic effect [51].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2013.06.026. These data include MOL files and InChiKeys of the most important compounds described in this article.

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