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Full Paper

Synthesis and Anticonvulsant Activity Evaluation of 4-Phenyl-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one and Its Derivatives

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A series of 4-(substituted-phenyl)-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones (**6a–x**) with triazole and other heterocyclic substituents (**7–14**) were synthesized and the compounds were evaluated for their anticonvulsant activity and neurotoxicity by maximal electroshock (MES) and rotarod neurotoxicity tests. Among the compounds studied, **6o** and **6q** showed wide margins of safety with protective indices (PIs) that were much higher than those of currently used drugs ($PI_{6o} > 25.5$, $PI_{6q} > 26.0$). Compounds **6o** and **6q** showed significant oral activity against MES-induced seizures in mice, with ED_{50} values of 88.02 and 94.6 mg/kg, respectively. The two compounds were also found to have potent activity against seizures that were induced by pentylenetetrazole and bicuculline.

Keywords: Anticonvulsant / BIC / Maximal electroshock / sc-PTZ / Synthesis / Triazole

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Introduction

Epilepsy is the most common neurological disorder in the world, and affects about 45–100 million people [1]. Antiepileptic drugs (AEDs) can control seizures to some extent; however, about 30% of epilepsy patients are thought to be undertreated [2]. Many currently available AEDs also have serious side effects [3–7], and in general, patients require lifelong medication. This has resulted in a continuous challenge for us to find new antiepileptic agents with more selectivity and lower toxicity. In this article, we describe the synthesis and evaluation of several molecules with potential anticonvulsant activity (only compounds **6d**, **6f**, **6h**, **6i**, **6u**, **6v**, **6w**, and **11–13** are new).

Heterocyclic compounds are widely studied as potential new bioactive scaffolds in both the agrochemical and pharmaceutical industries [8]. Quinazoline was first prepared in 1903, but breakthroughs in the late 20th century have increased its medicinal value [9, 10]. The pharmacology of quinazoline and quinazolinone derivatives is broad and they have been shown to possess anti-inflammatory, antimicrobial, anticonvulsant, antiparasitic, and anticancer properties [11–17]. The quinazoline motif has previously been referred to as the "master key" to antiepileptic therapy [18–20]. Therefore, the potency and selectivity of quinazolines have recently aroused the interest of many researchers in the field of anticonvulsant design. In a previous study in our laboratory, we synthesized several 5-substituted-[1,2,4]triazolo[4,3-*a*]-quinazolines (**I**) and tested their anticonvulsant activities. Among them, 5-(heptyloxy)-[1,2,4]triazolo[4,3-*a*]quinazoline (**II**) ($ED_{50} = 39.4$ mg/kg, PI = 8.3) was found to be especially potent [21]. Among clinically active anticonvulsants such as

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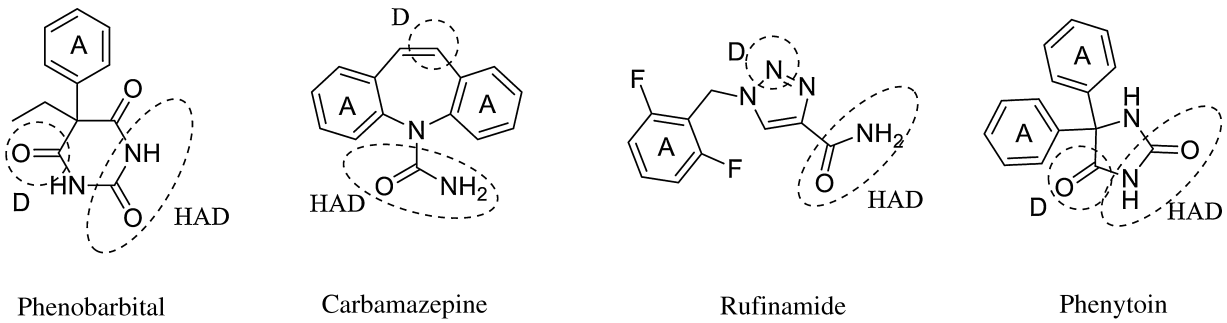

Figure 1. Clinically available antiepileptic drugs which have the major characteristics.

phenobarbital, carbamazepine, rufinamide, and phenytoin (Fig. 1), we can see that a commonly reoccurring motif in their structures is the presence of hydrophobic binding sites (A), a hydrogen bonding domain (HBD), and an electron–donor group (D).

Based on the observations above, we decided to attach a phenyl group onto the NH group of quinazolin-4(3*H*)-one (**III**) to serve as the hydrophobic binding site, and then combine 3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one with triazole (as the HBD) in order to reach our target compound (**6a**), and the products (**6b–x**) after the chemical modification were obtained. We also synthesized its derivatives (**7–14**) by using bioisosterism, among other strategies. Here, we describe our most recent work on the design, synthesis, and preliminary evaluation of a series of 4-(substituted-phenyl)-[1,2,4]-triazolo[4,3-*a*]quinazolin-5(4*H*)-ones and their derivatives (Fig. 2). In phase II, with quantitative anticonvulsant evaluation of compounds (**6j**, **6m**, **6o**, and **6q**) in mice after i.p. injection, the most active compounds **6o** and **6q** after p.o. injection were determined by evaluating time to peak. In order to establish a structure–activity relationship, we compared the activity of compounds with different substituted phenyl groups and compounds where triazole had been replaced. Following this, compounds **6o** and **6q** were used in PTZ- and BIC-induced seizure tests and the potency of compounds **6o** and **6q** against PTZ- and BIC-induced seizures was also established in this study.

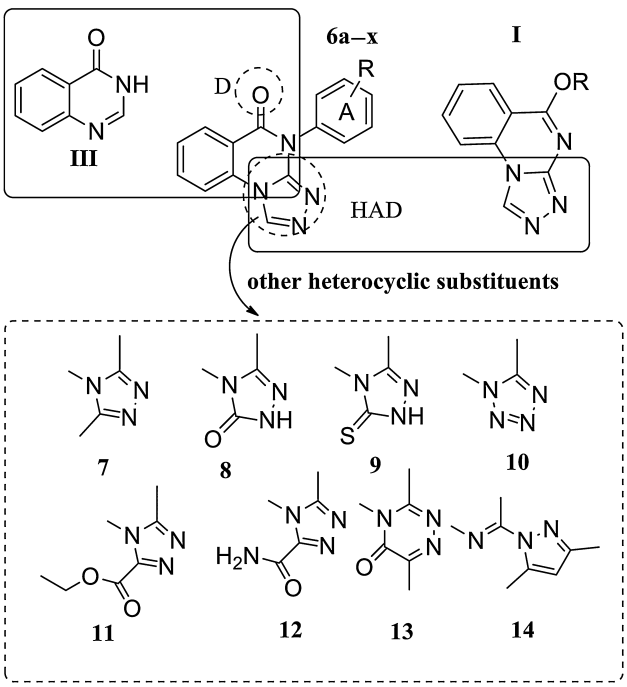

Figure 2. Design of compounds **6a–x** and **7–14**.

Results and discussion

Chemistry

All the compounds were synthesized by slightly modifying a previously reported method as depicted in Scheme 1. To begin with, the substituted aniline was dissolved in DMSO and reacted with carbon disulfide and aqueous sodium hydroxide to give the sodium salt of a 4-substituted phenylcarbamodithioate (**1a–x**). This was then reacted with dimethyl sulfate to afford a methyl 4-substituted phenylcarbamodithioate (**2a–x**). Next, a solution of **(2a–x)** in ethanol was treated with methyl anthranilate in the presence of anhydrous potassium carbonate to obtain methyl 2-(3-substituted-phenyl-thiourеido)benzoate as an intermediate (**3a–x**), which upon basic hydrolysis yielded the compounds **4a–x**. Then, **4a–x** was reacted with hydrazine hydrate in ethanol to furnish a 2-hydrazono-3-substituted-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**5a–x**). This was treated with formic acid and refluxed overnight to acquire the compounds **6a–x**, which were recrystallized from ethanol as colorless crystals. To obtain the target compounds (**7–14**), **5a** was reacted with acetic acid, urea, carbon disulfide, sodium nitrite, diethyl oxalate, ammonia, pyruvic acid, and acetyl acetone, respectively [22–29].

Pharmacology

Anticonvulsant activity was screened using the MES test and neurotoxicity was measured by rotarod test. The MES test and rotarod test were carried out according to the standard

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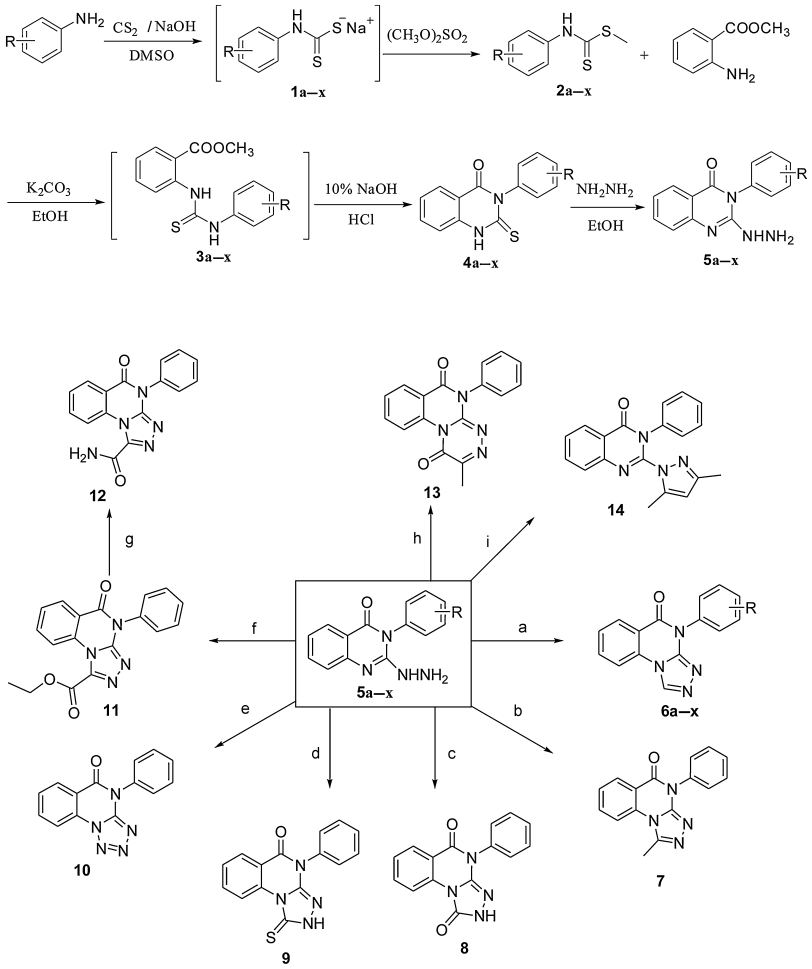

Scheme 1. Synthesis of compounds **6a–x**, and **7–14**. (a) HCOOH, reflux, 12 h; (b) CH_3COOH, reflux, 12–16 h; (c) NH_2CONH_2, 200°C, 1.5 h; (d) CS_2, KOH, ethanol, reflux, 8–12 h; (e) $NaNO_2$, 10% HCl, 0–3°C, 6 h; (f) diethyl oxalate, reflux, 1 h; (g) $NH_3 \cdot H_2O$, ethanol, rt, 3 h; (h) CH_3CO-COOH, ethanol, ref, 10 h; (i) $(CH_3CO)_2CH_2$, 1, 4-dioxane, ref, 3 h.

procedure described in the Antiepileptic Drug Development Program of the National Institutes of Health (USA) [30, 31]. The described pharmacological evaluation was accepted by Ethics Commission of China. All the compounds were dissolved in DMSO, and Kunming mice (provided by the Laboratory of Animal Research, College of Pharmacy, Yanbian University) in the 18–22 g weight range were used. We decided to determine the time–activity curve by administering compounds orally because of their lower neurotoxicities, and after that, we determined their median effective dose (ED_{50}) and median toxic dose (TD_{50}). The quantitative studies were performed at estimated time of peak effect (TPE) for MES test. (Fig. 3) Finally, we chose the two best compounds (**6o** and **6q**), which had similar ED_{50} values, and used them in PTZ- and BIC-induced seizure tests.

In this text, to target grand-mal epilepsy, so phase I studies only involved two tests: MES to detect agents that prevent the spread of seizures and rotarod test used for evaluation of neurotoxicity. This preliminary screening covered all of the compounds that we synthesized and the results are summarized in Table 1. Eleven compounds possessed anticonvulsant activity against MES-induced seizures at a dose of 100 mg/kg, and five of these (**6m**, **6n**, **6o**, **6q**, and **6x**) were found to remain active at a dose of 30 mg/kg. As shown in Table 1, it is noteworthy that in the derivatives with triazole (**6a**) and other heterocyclic substituents (**7–14**), four (**6a**, **11**, **13**, and **14**) were found to be active at a dose of 100 mg/kg. In these four

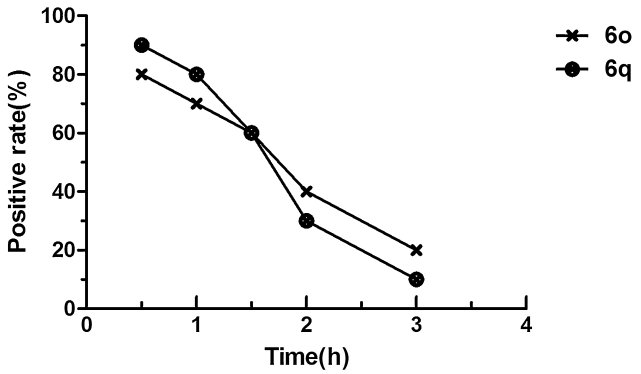

Figure 3. Time-course of **6o** and **6q** in the MES test (i.p., 50 mg/kg, the number of animals was 10).

Table 1. Phase I evaluation of anticonvulsant activity in mice (i.p.).

Compounds	R	MES[a)]		TOX	
		100	30	100	30
6a	–H	1/3	–[b)]	0/3	–
6b	*o*-OCH_3	0/3	–	0/3	–
6c	*p*-OCH_3	0/3	–	0/3	–
6d	*p*-OC_3H_7	0/3	–	0/3	–
6e	*p*-OC_4H_9	0/3	–	0/3	–
6f	*p*-OC_5H_{11}	0/3	–	0/3	–
6g	*p*-O(isoC_5H_{11})	0/3	–	0/3	–
6h	*p*-OC_6H_{13}	0/3	–	0/3	–
6i	*p*-OC_8H_{17}	0/3	–	0/3	–
6j	*o*-F	3/3	0/3	1/3	–
6k	*m*-F	0/3	–	0/3	–
6l	*p*-F	0/3	–	0/3	–
6m	*o*-Cl	3/3	1/3	2/3	0/3
6n	*m*-Cl	2/3	1/3	1/3	0/3
6o	*p*-Cl	3/3	1/3	0/3	0/3
6p	*m*-Br	0/3	–	0/3	–
6q	*p*-Br	3/3	1/3	0/3	0/3
6r	*o*-CH_3	1/3	–	0/3	–
6s	*m*-CH_3	0/3	–	0/3	–
6t	*p*-CH_3	0/3	–	0/3	–
6u	*p*-CF_3	0/3	–	0/3	–
6v	3,4-Cl_2	0/3	–	0/3	–
6w	2,6-$(CH_3)_2$	0/3	–	0/3	–
6x	3,4-$(CH_3)_2$	3/3	1/3	3/3	0/3
7	–H	0/3	–	0/3	–
8	–H	0/3	–	0/3	–
9	–H	0/3	–	0/3	–
10	–H	0/3	–	0/3	–
11	–H	1/3	–	2/3	–
12	–H	0/3	–	2/3	–
13	–H	1/3	–	2/3	–
14	–H	1/3	–	2/3	–

[a)] Maximal electroshock test (number of animals protected/number of animals tested), the number of mice is three; the dose measured in mg/kg.
[b)] Not tested.

compounds, only compound **6a** did not show toxicity at a dose of 100 mg/kg. Naturally, triazole-containing compound **6a** was verified to be better than the compounds with other heterocycle substituents, so we try to investigate the derivants of **6a** through structural modification. We hypothesize that the inclusion of a triazole group is necessary for our compounds to show antiepileptic activity. Although the compounds that contained other heterocyclic substituents were not suitable for our intended purpose, it is a great achievement to have synthesized such a series of 4-(substituted-phenyl)-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones. Among compounds **6b** to **6i**, none showed anticonvulsant activity at a dose of 100 mg/kg. We can infer that the length of the alkyl chain has a small effect on the anticonvulsant activity of the 4-(4-phenyl)-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives. Among compounds **6j** to **6q** and **6v**, most of the compounds that contained a halogen atom at the 2- and 4-position on the phenyl ring showed anticonvulsant activity against MES-induced seizures. It can also be seen that singly substituted phenyls are better than doubly substituted and that *meta*-substitution is not as good as *ortho*- and *para*-substitution. However, some of the compounds showed different degrees of neurotoxicity (**6j**, 1/3, **6m**, 2/3, **6n**, 1/3) at the dose of 100 mg/kg.

On the basis of the results obtained in phase I testing, four compounds (**6j**, **6m**, **6o**, and **6q**) were subjected to trials with a view to quantifying their anticonvulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) in mice when administered by intraperitoneal injection. The ED_{50} of their anti-MES activity was not any better than that of the currently used antiepileptic drug carbamazepine, phenytoin, and phenobarbital. However, the neurotoxicity of two compounds (**6o** and **6q**) was minimal ($TD_{50} > 700$ mg/kg) and was markedly lower than carbamazepine and valproate.

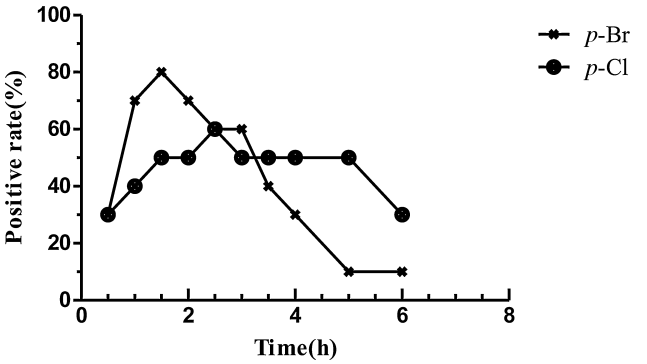

Figure 4. Time-course of **6o** (*p*-Cl, 100 mg/kg) and **6q** (*p*-Br, 120 mg/kg) in the MES test (p.o., the number of animals was 10).

Obviously, compounds **6o** and **6q** also had a higher protective index than the positive control. According to the results of phase II (i.p.), we conducted a time-course test of compounds **6o** and **6q** in the maximal electroshock seizure test (Fig. 4), in which compound **6o** reached the TPE at 2.5 h and **6q** reached the TPE at 1.5 h after administered orally, and then their anti-MES activities decreased over time. Therefore, we choose 2.5 h as the testing time of the compound **6o** in phase II quantitative anticonvulsant evaluation in mice (p.o.). To our surprise, they did not show neurotoxicity even at a dose of 2000 mg/kg. All the data from phase II are shown in Table 2.

Overall, bioevaluation demonstrated that the compounds that possessed a triazole displayed the best anticonvulsant activity in the MES test. The compounds that contained halogen-substituted phenyl rings expressed significant anticonvulsant activity. The trend in activity was *p*-Br > *p*-Cl > *o*-F > *o*-Cl, and compounds **6o** and **6q** showed marked lower neurotoxicity compared to carbamazepine and therefore a higher protective index. What we really need now is to accept that an electron donating group introduced to the phenyl rings is not conducive to increase the antiepileptic activity, but a strong electron-withdrawing group can do it, especially the group at the 2- or 4-position on the phenyl ring.

Finally, compounds **6o** and **6q** were tested against seizures induced by PTZ and BIC in order to prove they displayed wide spectrum activity in several models. Compounds **6o**, **6q**, and the reference drug carbamazepine were administered (i.p.) into mice at 50 mg/kg.

Compounds **6o**, **6q**, and carbamazepine did not inhibit the clonic seizures induced by sc-PTZ, but they did inhibit the tonic seizures and, to some extent, reduce lethality. Carbamazepine inhibited clonic seizures, tonic seizures, and death induced by sc-PTZ with success rates of 0, 100, and 100%, respectively. For comparison, the values for compounds **6o** and **6q** were 0, 90, 20% and 0, 100, 60%, respectively (Table 3). In the BIC-induced seizure model, both carbamazepine and **6o** inhibited tonic seizures and death, but did not inhibit clonic seizures. Carbamazepine and **6o** showed inhibition of clonic seizures, tonic seizures, and death with success rates of 0, 100, 90% and 0, 80, 100%, respectively. Compound **6q** showed inhibition of clonic and tonic seizures and death with success rates of 0, 60, and 10%, respectively (Table 3). Thus, compounds **6o** and **6q** can protect the mice from tonic seizures in the sc-PTZ and BIC model

Conclusion

In the present study, 32 derivatives of 4-phenyl-[1,2,4]-triazolo[4,3-*a*]quinazolin-5(4*H*)-ones have been designed, synthesized, and evaluated for their anticonvulsant activity. In the derivatives **6a–x**, variation in the substituents on the phenyl group affected activity. An electron-withdrawing group was a more profitable structural feature than an electron-donating group.

Compounds **6o** and **6q** displayed a wide margin of safety with a protective index (PI) much higher than that of existing

Table 2. Quantitative anticonvulsant data in mice.

Compounds	ED_{50} (MES)[a)]	TD_{50} (NT)[b)]	PI[c)]
6j (i.p.)	63.10 (53.83–73.96)[d)]	62.24 (46.34–82.04)	0.99
6m (i.p.)	40.64 (30.41–54.32)	31.04 (24.72–38.99)	0.76
6o (i.p.)	27.39 (17.20–43.61)	>700	>25.56
6q (i.p.)	26.89 (20.20–35.79)	>700	>26.03
Carbamazepine (i.p.)[e)]	8.8 (5.5–14.1)	71.6 (45.9–135)	8.1
Phenytoin (i.p.)[e)]	9.5 (8.1–10.4)	65.5 (52.5–72.9)	6.9
Phenobarbital (i.p.)[e)]	21.8 (21.8–25.5)	69.0 (62.8–72.9)	3.2
Valproate (i.p.)[e)]	272 (247–338)	426 (369–450)	1.6
6o (p.o.)	88.02 (60.92–127.17)	>2000	>22.72
6q (p.o.)	94.60 (81.88–109.30)	>2000	>21.14
Carbamazepine (p.o.)	30.4	235.7	7.7

[a)] ED_{50}: Median effective dose affording anticonvulsant protection in 50% of animals, the dose is measured in mg/kg.
[b)] TD_{50}: Median toxic dose eliciting minimal neurological toxicity in 50% of animals, the dose is measured in mg/kg.
[c)] PI: Protective index (TD_{50}/ED_{50}).
[d)] 95% confidence intervals given in parentheses.
[e)] Data from Krall et al. [30].

Table 3. Effects of compounds 6o and 6q on chemical-induced seizures in mice (i.p.).

Chemical substances	Compounds	Doses (mg/kg)	Test time (h)[a)]	Clonic seizures (%)[b)]	Tonic seizures (%)	Lethality (%)
Pentylenetetrazol	DMSO	–	0.5	100	100	90
	Carbamazepine	50	0.5	100	0	0
	6o	50	0.5	100	10	80
	6q	50	0.5	100	0	40
Bicuculline	DMSO	–	0.5	100	100	100
	Carbamazepine	50	0.5	100	0	10
	6o	50	0.5	100	20	0
	6q	50	0.5	100	40	90

[a)] At 0.5 h after the administration of the test compound, chemical substances were administered in mice.
[b)] The number of mice with clonic seizures, tonic seizures, and deaths/the number of animals tested × 100%.

drugs ($PI_{6o} > 25.5$, $PI_{6q} > 26.0$), and also showed significant oral activity against MES-induced seizures in mice, with an ED_{50} of 88.02 and 94.60 mg/kg, respectively. Moreover compounds **6o** and **6q** could protect the mice from tonic seizures and reduce the mortality rate in the sc-PTZ and BIC model to a certain extent. Hence, the compounds **6o** and **6q** displayed wide spectrum activity in several models.

Experimental

Chemistry

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on IR Prestige-21 (PerkineElmer, Waltham, MA, USA). ^{1}H NMR and ^{13}C NMR spectra were measured on an AV-300 (Bruker, Switzerland), and all chemical shifts were given in ppm relative to TMS. Mass spectra were measured on a HP1100LC (Agilent Technologies, USA). High resolution mass spectra were measured on an MALDI-TOF/TOF mass spectrometer (Bruker Daltonik, Germany). The chemicals were purchased from Aldrich Chemical Corporation.

*Synthesis of methyl phenylcarbamodithioate derivatives (**2a–x**) [32]*

To a solution of substituted aniline (0.03 mol) in DMSO (20 mL), carbon disulfide (2.74 g, 0.036 mol) and an aqueous solution of sodium hydroxide (1.5 mL, 20 M) were added simultaneously with stirring at room temperature to afford salt (**1a–x**) as an intermediate. After 2–4 h, dimethyl sulfate (0.03 mol) was added dropwise while the reaction mixture was kept stirring in a freezing mixture for 5 h. After completion, the reaction mixture was poured into ice water. The solid obtained was filtered, washed, and re-crystallized from ethanol to obtain methyl-substituted phenylcarbamodithioate (**2a–x**).

*Synthesis of 3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one derivatives (**4a–x**) [33]*

A solution of **2a–x** (0.02 mol), methyl anthranilate (0.02 mol), anhydrous potassium carbonate (200 mg), and ethanol (40 mL) was refluxed for 25–33 h. The reaction mixture was poured into cold water. The solid methyl 2-(3-phenylthiouroeido)benzoate derivative (**3a–x**) that was obtained was filtered and refluxed in 10% alcoholic sodium hydroxide solution for 2 h. After cooling to room temperature, it was re-precipitated by treatment with dilute hydrochloric acid. The solid obtained was washed with water and recrystallized from ethanol to afford (**4a–x**).

*Synthesis of 2-hydrazono-3-phenyl-2,3-dihydroquinazolin-4(1H)-one derivatives (**5a–x**) [34]*

3-Phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one derivative (**4a–x**) (0.01 mol) was dissolved in ethanol (25 mL). Hydrazine hydrate (60%, 0.12 mol) was added and refluxed for 4 h under nitrogen. The reaction mixture was then poured into cold water. The solid (**5a–x**) obtained was filtered, washed with water, dried, and purified by silica gel column chromatography using CH_2Cl_2/CH_3OH (80:1) as the eluent.

*Synthesis of 4-(4-phenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one derivatives (**6a–x**) [22]*

Compounds **5a–x** (0.01 mol) and formic acid (25 mL) were added to a round-bottomed flask, refluxed overnight, and then poured into ice water. The target compound (**6a–x**) obtained was filtered, washed with water, dried, and purified by silica gel column chromatography using CH_2Cl_2/CH_3OH (100:1) as the eluent.

*4-Phenyl-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6a**)*

Yield: 30%, mp: 303–305°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.48–8.48 (m, 9H, Ar-H), 8.81(s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.5, 148.9, 135.5, 134.2, 134.1, 132.5, 130.8, 129.8, 129.6, 128.1, 127.5, 117.3, 114.7. IR (KBr, cm^{-1}): 1688 (C=O), 1614, 1599, 1300, 1148. ESI-HRMS calcd. for $C_{15}H_{11}N_4O^+$ ($[M+H]^+$): 263.0927; found: 263.0934.

*4-(2-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6b**)*

Yield: 35%, mp: 206–208°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.78 (s, 3H, $-CH_3$), 7.11–8.48 (m, 8H, Ar-H), 8.85 (s, 1H, –N=CH–).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 162.8, 158.4, 154.9, 148.6, 135.3, 134.2, 132.7, 131.5, 130.8, 129.7, 127.4, 122.6, 121.4, 114.9, 112.6, 55.8. IR (KBr, cm^{-1}): 1684 (C=O), 1614, 1594, 1296, 1147, 1176, 1255. ESI-HRMS calcd. for $C_{16}H_{13}N_4O_2^+$ ($[M+H]^+$): 293.1033; found: 293.1036.

*4-(4-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6c**)*
Yield: 39%, mp: 276–278°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.88 (s, 3H, $-CH_3$), 7.07–8.48 (m, 8H, Ar-H), 8.80 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 160.2, 158.8, 149.2, 135.4, 134.2, 132.5, 130.8, 129.1, 127.5, 126.7, 117.3, 115.1, 114.7, 55.6. IR (KBr, cm^{-1}): 1684 (C=O), 1614, 1595, 1296, 1148, 1177, 1256. ESI-HRMS calcd. for $C_{16}H_{13}N_4O_2^+$ ($[M+H]^+$): 293.1033; found: 293.1034.

*4-(4-Propoxyphenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6d**)*
Yield: 41%, mp: 252–254°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (t, 3H, $J = 7.50$ Hz, $-CH_3$), 1.81–1.90 (m, 2H, $-CH_2-$), 3.98 (t, 2H, $J = 6.00$ Hz, $-OCH_2-$), 7.06–8.47 (m, 8H, Ar-H), 8.80 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.8, 158.8, 149.2, 135.4, 134.3, 132.5, 130.7, 129.1, 127.4, 126.4, 127.3, 115.6, 114.8, 69.8, 22.5, 10.5. IR (KBr, cm^{-1}): 1690 (C=O), 1614, 1599, 1290, 1142, 1175, 1252. ESI-HRMS calcd. for $C_{18}H_{17}N_4O_2^+$ ($[M+H]^+$): 321.1346; found: 321.1349.

*4-(4-Butoxyphenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6e**)*
Yield: 38%, mp: 231–233°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.99 (t, 3H, $J = 7.50$ Hz, $-CH_3$), 1.48–1.83 (m, 4H, $-CH_2-$), 4.02 (t, 2H, $J = 7.50$ Hz, $-OCH_2-$), 7.02–8.44 (m, 8H, Ar-H), 8.95 (s, 1H, –N=CH–). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 159.6, 158.8, 135.4, 134.7, 132.5, 130.4, 129.4, 129.1, 127.3, 126.5, 117.1, 115.4, 115.1, 67.9, 31.1, 19.1, 13.8. IR (KBr, cm^{-1}): 1690 (C=O), 1614, 1598, 1290, 1141, 1176, 1251. ESI-HRMS calcd. for $C_{19}H_{19}N_4O_2^+$ ($[M+H]^+$): 335.1503; found: 335.1502.

*4-(4-(Pentyloxy)phenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6f**)*
Yield: 50%, mp: 213–215°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.95 (t, 3H, $J = 7.50$ Hz, $-CH_3$), 1.39–1.85 (m, 6H, $-CH_2-$), 4.01 (t, 2H, $J = 6.00$ Hz, $-OCH_2-$), 7.05–8.47 (m, 8H, Ar-H), 8.80 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.8, 149.2, 135.4, 134.2, 132.5, 130.8, 129.1, 127.5, 126.4, 118.5, 117.3, 115.6, 114.7, 68.3, 28.9, 28.2, 22.5, 14.0. IR (KBr, cm^{-1}): 1690 (C=O), 1614, 1597, 1290, 1140, 1177, 1250. ESI-HRMS calcd. for $C_{20}H_{21}N_4O_2^+$ ($[M+H]^+$): 349.1659; found: 349.1662.

*4-(4-(Isopentyloxy)phenyl)-[1,2,4]triazolo[4,3-a]-quinazolin-5(4H)-one (**6g**)*
Yield: 48%, mp: 216–218°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.99 (t, 6H, $J = 9.00$ Hz, $-CH_3$), 1.63–1.74 (m, 2H, $-CH_2-$), 1.80–1.93 (m, 1H, –CH), 4.04 (t, 2H, $J = 7.50$ Hz, $-OCH_2-$), 7.05–8.48 (m, 8H, Ar-H), 8.81 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.8, 158.8, 149.2, 135.4, 134.2, 132.5, 130.8, 129.1, 127.5, 126.4, 117.3, 115.6, 114.8, 66.6, 37.9, 25.0, 22.6. IR (KBr, cm^{-1}): 1690 (C=O), 1614, 1596, 1290, 1141, 1178, 1252. ESI-HRMS calcd. for $C_{20}H_{21}N_4O_2^+$ ($[M+H]^+$): 349.1659; found: 349.1660.

*4-(4-(Hexyloxy)phenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6h**)*
Yield: 38%, mp: 223–225°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (t, 3H, $J = 16.50$ Hz, $-CH_3$), 1.35–1.84 (m, 8H, $-CH_2-$), 4.01 (t, 2H, $J = 7.50$ Hz, $-OCH_2-$), 7.05–8.48 (m, 8H, Ar-H), 8.80 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.8, 158.9, 149.2, 135.4, 134.2, 132.5, 130.8, 129.1, 127.5, 126.4, 117.3, 115.6, 114.8, 68.3, 31.6, 29.1, 25.7, 22.6, 11.1. IR (KBr, cm^{-1}): 1690 (C=O), 1614, 1597, 1290, 1138, 1179, 1248. ESI-HRMS calcd. for $C_{21}H_{23}N_4O_2^+$ ($[M+H]^+$): 363.1816; found: 363.1820.

*4-(4-(Octyloxy)phenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6i**)*
Yield: 41%, mp: 221–223°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.90 (t, 3H, $J = 4.50$ Hz, $-CH_3$), 1.31–1.83 (m, 12H, $-CH_2-$), 4.01 (t, 2H, $J = 7.50$ Hz, $-OCH_2-$), 7.06–8.47 (m, 8H, Ar-H), 8.80 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.8, 158.8, 149.9, 149.2, 135.4, 134.1, 132.5, 130.8, 129.1, 127.5, 126.4, 117.3, 115.6, 114.7, 68.3, 31.8, 29.3, 29.3, 29.2, 26.0, 22.7, 14.1. IR (KBr, cm^{-1}): 1690 (C=O), 1614, 1595, 1290, 1138, 1179, 1249. ESI-HRMS calcd. for $C_{23}H_{27}N_4O_2^+$ ($[M+H]^+$): 391.2129; found:391.2134.

*4-(2-Fluorophenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6j**)*
Yield: 54%, mp: 220–222°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35–8.49 (m, 8H, Ar-H), 8.30 (s, 1H, –N=CH–). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 151.9, 148.9, 142.0, 142.0, 134.5, 131.3, 131.2, 127.6, 127.2, 126.3, 125.4, 125.4, 124.0, 123.8, 122.3, 120.1, 117.6, 117.3, 117.0. IR (KBr, cm^{-1}): 1697 (C=O), 1612, 1601, 1298, 1147. ESI-HRMS calcd. for $C_{15}H_{10}FN_4O^+$ ($[M+H]^+$): 281.0833; found: 281.0838.

*4-(3-Fluorophenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6k**)*
Yield: 44%, mp: 273–275°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.23–8.48 (m, 8H, Ar-H), 8.82 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 164.7, 161.4, 158.4, 148.5, 135.7, 134.3, 132.5, 131.1, 131.0, 130.9, 130.8, 127.7, 124.1, 117.0, 116.8, 116.2, 115.9, 114.8. IR (KBr, cm^{-1}): 1697 (C=O), 1612, 1601, 1298, 1146. ESI-HRMS calcd. for $C_{15}H_{10}FN_4O^+$ ($[M+H]^+$): 281.0833; found: 281.0827.

*4-(4-Fluorophenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6l**)*
Yield: 39%, mp: 300–302°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.25–8.48 (m, 8H, Ar-H), 8.81 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 161.2, 158.6, 148.8, 146.7, 139.2, 135.6, 134.3, 132.5, 130.8, 130.1, 130.0, 127.6, 117.1, 117.1, 116.8, 114.8. IR (KBr, cm^{-1}): 1697 (C=O), 1612, 1601, 1298, 1145. ESI-HRMS calcd. for $C_{15}H_{10}FN_4O^+$ ($[M+H]^+$): 281.0833; found: 281.0837.

*4-(2-Chlorophenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6m**)*
Yield: 51%, mp: 240–242°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.51–8.49 (m, 8H, Ar-H), 8.81 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 157.9, 153.5, 149.0,135.7, 134.3, 132.8, 132.7, 132.0, 131.3, 130.9, 130.4, 128.4, 127.6, 116.9, 114.9. IR (KBr, cm^{-1}): 1699 (C=O), 1614, 1599, 1294, 1144. ESI-HRMS calcd. for $C_{15}H_{10}ClN_4O^+$ ($[M+H]^+$): 297.0538; found: 297.0541.

*4-(3-Chlorophenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6n**)*
Yield: 33%, mp: 275–277°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.44–8.38 (m, 8H, Ar-H), 9.29 (s, 1H, –N=CH–). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 163.3, 153.1, 146.0, 140.6, 140.4, 139.4, 137.5, 135.8, 135.4, 134.8, 134.3, 133.5, 133.2, 132.2, 131.7. IR (KBr, cm^{-1}): 1699 (C=O), 1614, 1599, 1294, 1144. ESI-HRMS calcd. for $C_{15}H_{10}ClN_4O^+$ ($[M+H]^+$): 297.0538; found: 297.0543.

*4-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6o**)*
Yield: 37%, mp: 291–293°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.44–8.47 (m, 8H, Ar-H), 8.81 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.4, 148.6, 135.7, 135.6, 134.4, 132.6, 130.8, 130.1, 129.5, 127.6, 124.4, 117.1, 114.9. IR (KBr, cm^{-1}): 1699 (C=O), 1614, 1599, 1294, 1143. ESI-HRMS calcd. for $C_{15}H_{10}ClN_4O^+$ ($[M+H]^+$): 297.0538; found: 297.0537.

*4-(3-Bromophenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6p**)*
Yield: 42%, mp: 287–289°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.46–8.47 (m, 8H, Ar-H), 8.82 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.4, 147.6, 135.7, 135.2, 132.9, 132.5, 131.5, 131.0, 130.8, 127.7, 127.0, 123.0, 118.3, 117.0, 114.9. IR (KBr, cm^{-1}): 1695 (C=O), 1616, 1597, 1292, 1143. ESI-HRMS calcd. for $C_{15}H_{10}BrN_4O^+$ ($[M+H]^+$): 341.0032; found: 341.0040.

*4-(4-Bromophenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6q**)*
Yield: 41%, mp: 289–291°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.37–8.47 (m, 8H, Ar-H), 8.82 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.4, 148.5, 135.7, 134.4, 133.3, 133.0, 132.5, 130.8, 129.8, 127.6, 123.7, 117.0, 114.9. IR (KBr, cm^{-1}): 1695 (C=O), 1616, 1597, 1292, 1142. ESI-HRMS calcd. for $C_{15}H_{10}BrN_4O^+$ ($[M+H]^+$): 341.0032; found: 341.0038.

*4-(o-Tolyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6r**)*
Yield: 29%, mp: 245–247°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.30 (s, 3H, Ar–CH_3), 7.38–8.50 (m, 8H, Ar-H), 8.11 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 156.7, 149.2, 145.6, 142.0, 135.7, 134.5, 132.0, 130.7, 127.7, 127.6, 127.4, 126.3, 123.9, 117.4, 113.0, 18.1. IR (KBr, cm^{-1}): 1703 (C=O), 1618, 1549, 1273, 1130. ESI-HRMS calcd. for $C_{16}H_{13}N_4O^+$ ($[M+H]^+$): 277.1084; found: 277.1087.

*4-(m-Tolyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6s**)*
Yield: 46%, mp: 240–242°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.44 (s, 3H, Ar–CH_3), 7.29–8.48 (m, 8H, Ar-H), 8.80 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.6, 149.0, 140.0, 135.4, 134.2, 134.0, 132.5, 130.8, 130.6, 129.7, 128.6, 127.5, 125.0, 117.3, 114.8, 21.4. IR (KBr, cm^{-1}): 1692 (C=O), 1612, 1597, 1300, 1142. ESI-HRMS calcd. for $C_{16}H_{13}N_4O^+$ ($[M+H]^+$): 277.1084; found: 277.1088.

*4-(p-Tolyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6t**)*
Yield: 41%, mp: 274–276°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.45 (t, 3H, Ar–CH_3), 7.38–8.48 (m, 8H, Ar-H), 8.80 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.7, 149.0, 139.8, 135.4, 134.2, 132.5, 131.5, 130.8, 130.5, 127.7, 127.5, 117.3, 114.7, 21.3. IR (KBr, cm^{-1}): 1692 (C=O), 1612, 1597, 1300, 1141. ESI-HRMS calcd. for $C_{16}H_{13}N_4O^+$ ($[M+H]^+$): 277.1084; found: 277.1076.

*4-(4-(Trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-a]-quinazolin-5(4H)-one (**6u**)*
Yield: 35%, mp: 274–276°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.61–8.48 (m, 8H, Ar-H), 8.83 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.3, 148.4, 137.2, 135.8, 134.4, 132.5, 131.9, 131.4, 130.9, 128.9, 127.7, 127.0, 126.9, 116.9, 114.9. IR (KBr, cm^{-1}): 1695 (C=O), 1614, 1600, 1294, 1134. ESI-HRMS calcd. for $C_{16}H_{10}F_3N_4O^+$ ($[M+H]^+$): 331.0801; found: 331.0809.

*4-(3,4-Dichlorophenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6v**)*
Yield: 28%, mp: 298–300°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.37–8.47 (m, 7H, Ar-H), 8.82 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 148.3, 147.0, 135.9, 134.4, 134.2, 133.8, 133.1, 131.7, 131.4, 130.9, 130.5, 127.7, 127.7, 116.9, 114.9. IR (KBr, cm^{-1}): 1694 (C=O), 1614, 1597, 1290, 1138. ESI-HRMS calcd. for $C_{15}H_{10}Cl_2N_4O^+$ ($[M+H]^+$): 331.0148; found: 331.0154.

*4-(3,4-Dimethylphenyl)-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**6w**)*
Yield: 47%, mp: 204–206°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.15 (s, 3H, –CH_3), 2.40 (s, 3H, –CH_3), 7.21–8.48 (m, 7H, Ar-H), 8.81 (s, 1H, –N=CH–). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.3, 148.5, 145.8, 140.1, 135.5, 135.4, 134.4, 132.7, 132.4, 130.7, 128.3, 128.0, 127.4, 117.1, 114.9, 21.3, 17.6. IR (KBr, cm^{-1}): 1692 (C=O), 1614, 1599, 1292, 1148. ESI-HRMS calcd. for $C_{17}H_{15}N_4O^+$ ($[M+H]^+$): 291.1240; found: 291.1244.

*Synthesis of 1-methyl-4-phenyl[1,2,4]triazolo[4,3-a]-quinazolin-5(4H)-one (**7**) [32]*
Compound **5a** (0.01 mol) was dissolved in acetic acid (25 mL), refluxed overnight, and then poured into ice water. The resultant solid (**7**) was filtered, washed with water, dried, and purified by silica gel column chromatography using CH_2Cl_2/CH_3OH (100:1) as the eluent. Yield: 31%, mp: 303–305°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.46 (s, 3H, –CH_3), 7.34–8.47 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.6, 149.5, 145.8, 135.1, 134.4, 134.2, 131.0, 129.8, 129.5, 128.2, 126.9, 117.8, 115.0, 15.7. IR (KBr, cm^{-1}): 1682 (C=O), 1610, 1597, 1317, 1180. ESI-HRMS calcd. for $C_{16}H_{13}N_4O^+$ ($[M+H]^+$): 277.1084; found: 277.1089.

*Synthesis of 4-phenyl-[1,2,4]triazolo[4,3-a]quinazoline-1,5(2H,4H)-dione (**8**) [23]*
Compound **5a** (0.01 mol) and carbamide (4.8 g, 0.08 mol) were added to a round-bottomed flask and heating up to 200°C to melt them. The reaction was followed using TLC and, upon completion, the mixture was cooled and then washed with enough hot water to wash off the excess urea. The target compound (**8**) obtained was filtered, dried, and purified by silica gel column chromatography using CH_2Cl_2/CH_3OH (60:1) as the eluent. Yield: 36%, mp: >300°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.47–8.70 (m, 9H, Ar-H), 11.83 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 159.1, 152.7, 151.1, 142.1, 135.3, 135.3, 134.4, 129.6, 129.5, 129.4, 128.9, 126.0, 117.3, 114.9. IR (KBr, cm^{-1}): 3177 (N–H), 1748 (C=O), 1709 (C=O), 1614, 1491, 1352, 1287, 1128, 1031. ESI-HRMS calcd. for $C_{15}H_{11}N_4O_2^+$ ($[M+H]^+$): 279.0877; found: 279.0873.

*Synthesis of 4-phenyl-1-thioxo-1,2-dihydro-[1,2,4]-triazolo[4,3-a]quinazolin-5(4H)-one (**9**) [24]*
To an ice-cooled solution of **5a** (0.01 mol) in absolute ethanol (10 mL) was added potassium hydroxide (0.56 g, 0.01 mol) followed by the dropwise addition of carbon disulfide (1.52 g, 0.02 mol) with stirring. The mixture was diluted with absolute ethanol (5 mL), filtered, concentrated, diluted with water, and neutralized with acetic acid. The solvent was evaporated and the material was purified by silica gel column chromatography using CH_2Cl_2/CH_3OH (60:1) as the eluent to receive the product **9**. Yield: 30%, mp: 187–189°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.45–10.39 (m, 9H, Ar-H), 13.85 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 162.2, 158.8, 147.0, 136.0, 134.9, 129.7, 129.6, 129.2, 129.0, 127.4, 118.5, 116.1. IR (KBr, cm^{-1}): 1703 (C=O), 1618, 1549, 1273, 1130. ESI-HRMS calcd. for $C_{15}H_{11}N_4OS^+$ ($[M+H]^+$): 295.0648; found: 295.0653.

*Synthesis of 4-phenyltetrazolo[1,5-a]quinazolin-5(4H)-one (**10**) [25]*
Compound **5a** (0.01 mol) was dissolved in 20 mL dilute hydrochloric acid and 10% $NaNO_2$ (0.69 g, 0.01 mol) solution was added dropwise to the mixture in an ice bath such that the reaction temperature remained below 5°C. The mixture was then stirred at room temperature and monitored by TLC. At the end of the reaction, the mixture was extracted with dichloromethane (20 mL × 3), dried over anhydrous $MgSO_4$, evaporated to dryness and purified by silica gel column chromatography using CH_2Cl_2 as the eluent to give the product **10**. Yield: 34%, mp: 187–189°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.49–8.51 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.7, 150.7, 136.1, 133.9, 132.8, 130.3, 130.0, 129.9, 128.9, 127.7, 116.7, 116.0. IR (KBr, cm^{-1}): 1703 (C=O), 1618, 1549, 1273, 1130. ESI-HRMS calcd. for $C_{14}H_{10}N_5O^+$ ($[M+H]^+$): 264.0880; found: 264.0884.

*Synthesis of ethyl 5-oxo-4-phenyl-4,5-dihydro-[1,2,4]-triazolo[4,3-a]quinazoline-1-carboxylate (**11**) [26]*
Compound **5a** (0.02 mol) was added to diethyl oxalate (30 mL) and the mixture was stirred and refluxed for 1 h. After the reaction mixture was cooled, the white precipitate was collected through filtration and washed with ethanol to give pure compound **11**. Yield: 38%, mp: 187–189°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.40 (t, 3H, J = 7.50 Hz, –CH_3), 4.54 (m, 2H, J = 7.00 Hz, –CH_2–), 7.53–8.42 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 159.0, 158.8, 151.3, 141.3, 135.5, 135.2, 133.5, 129.8, 129.6, 129.4, 129.2, 128.1, 119.1, 118.6, 63.3, 14.4. IR (KBr, cm^{-1}): 1724 (C=O), 1692 (C=O), 1611, 1541, 1481, 1273, 1192. ESI-HRMS calcd. for $C_{18}H_{15}N_4O_3^+$ ($[M+H]^+$): 335.1139; found: 335.1135.

*Synthesis of 5-oxo-4-phenyl-4,5-dihydro-[1,2,4]-triazolo[4,3-a]quinazoline-1-carboxamide (**12**) [27]*
Compound **11** (0.01 mol) was dissolved in methanol (10 mL), ammonia (10 mL) was added and the mixture was stirred for 3 h at room temperature. After this time, the precipitate was collected through filtration, washed with water, dried, and purified by silica gel column chromatography using CH_2Cl_2/CH_3OH (40:1) as the eluent to obtain the product **12**. Yield: 30%, mp: 266–268°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.53–8.62 (m, 9H, Ar-H), 8.24 (s, 1H, NH), 8.66 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 160.4, 158.8, 150.8, 144.2, 135.7, 135.3, 133.8, 129.7, 129.5, 129.4, 129.2, 127.8, 118.9, 118.4. IR (KBr, cm^{-1}): 3468 (N–H), 3349 (N–H), 1701 (C=O), 1678 (C=O), 1612, 1584, 1440, 1288. ESI-HRMS calcd. for $C_{18}H_{12}N_5O_2^+$ ($[M+H]^+$): 306.0986; found: 306.0977.

*Synthesis of 2-methyl-5-phenyl-1H-[1,2,4]triazino[4,3-a]quinazoline-1,6(5H)-dione (**13**) [28]*
A mixture of **5a** (0.02 mol) and pyruvic acid (0.03 mol) in absolute ethanol (10 mL) and glacial acetic acid (10 mL) was refluxed for 10 h. After cooling, the precipitate was collected. A mixture of the precipitate and acetic acid (20 mL) was refluxed for 46 h. The crystal formed on cooling was collected by filtration, washed with water, dried, and purified by silica gel column chromatography using CH_2Cl_2/CH_3OH (80:1) as the eluent to give the product **13**. Yield: 28%, mp: 187–189°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.88 (s, 3H, –CH_3), 7.48–8.30 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 158.9, 152.1, 149.6, 146.0, 135.7, 135.7, 134.5, 129.8, 129.7, 129.3, 129.2, 127.0, 118.0, 116.5, 15.4. IR (KBr, cm^{-1}): 1712 (C=O), 1686 (C=O), 1612, 1597, 1568, 1487, 1439, 1315. ESI-HRMS calcd. for $C_{17}H_{13}N_4O_2^+$ ($[M+H]^+$): 305.1033; found: 305.1040.

*Synthesis of 2-(3,5-dimethyl-1H-pyrazol-1-yl)-3-phenylquinazolin-4(3H)-one (**14**) [29]*
A mixture of the hydrazine **5a** (0.01 mol) and acetylacetone (0.012 mmol) in absolute 1,4-dioxane (20 mL) was heated under reflux for 3 h. The reaction mixture was cooled and the resultant precipitate was filtered, washed with ethanol, dried, and purified by silica gel column chromatography using CH_2Cl_2 as the eluent. Yield: 34%, mp: 178–179°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.00 (s, 3H, N=C–CH_3), 2.31 (s, 3H, C=C–CH_3), 5.71 (s, 1H, C=CH–C), 7.17–8.38 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 162.5, 150.6, 146.2, 144.1, 141.4, 135.5, 135.0, 128.6, 128.0, 127.9, 127.9, 127.6, 121.3, 114.9, 106.8, 13.2, 11.5. IR (KBr, cm^{-1}): 1692 (C=O), 1611, 1595, 1287,

1273, 1153. ESI-HRMS calcd. for $C_{19}H_{17}N_4O^+$ ($[M+H]^+$): 317.1397; found: 317.1402.

Pharmacology

Maximal electroshock seizure

Seizures were elicited in mice using a 60 Hz alternating current of 50 mA. The current was applied via corneal electrodes for 0.2 s. Protection against the spread of MES-induced seizures was defined as the abolition of tonic hind leg extension. At 0.5 h after the administration of the compounds, the activities were evaluated using the MES test. In phase I screening, each compound was administered at the dose levels of 30 and 100 mg/kg as a preliminary investigation of anticonvulsant activity. In phase II screening, groups of 10 mice were given a range of intraperitoneal and peroral doses of the tested compound until at least three points were established in the range of 10–90% seizure prevention or minimal neurotoxicity was observed. From the plot of these data, the respective ED_{50} and TD_{50} values, 95% confidence intervals, were calculated by a computer program based on the methods described by Finney [35].

Neurotoxicity (NT) screening

The mice were given i.p. or p.o. injections of the test compounds. Animals were trained to stay on an accelerating rotarod of 1-inch diameter that rotates at 6 rpm for 1 min after the specific time, respectively. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of three trials.

sc-PTZ-induced seizures

At 0.5 h after the administration of the test compound, 85 mg/kg PTZ dissolved in saline (0.9% NaCl) was administered s.c. The animals (10 mice in one group) were placed in isolation cages and observed for 0.5 h. The numbers of clonic seizure, tonic seizure, and deaths were noted.

Bicuculline-induced seizure test

At 0.5 h after the administration of the compounds, the animals (10 mice in one group) were given an s.c. dose of 5.4 mg/kg bicuculline. Individual mice were then placed in isolation cages and observed for at least 0.5 h for the presence or absence of clonic seizures, and tonic seizures, and lethality was also recorded.

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