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Original article

# Synthesis and anticonvulsant activity of 7-phenyl-6,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones and their derivatives

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ABSTRACT

Herein, we described the syntheses and anticonvulsant activities of 7-(substituted-phenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones (**1a**–**1o**) and their derivatives. Most of the synthesized compounds exhibited potent anticonvulsant activities in the maximal electroshock test (MES). The most promising compound **1i** showed significant anticonvulsant activity in MES test with $ED_{50}$ value of 19.7 mg/kg. It displayed a wide margin of safety with protective index much higher than the standard drugs. In addition, the potence of compound **1i** against seizures induced by Pentylenetetrazole, Isoniazid, Thiosemicarbazide, 3-Mercaptopropionic acid, and Bicuculline in the chemical-induced seizure tests suggested that compound **1i** displayed broad spectrum activity in several models, and it is likely to have several mechanisms of action including inhibiting voltage-gated ion channels and modulating GABAergic activity.



## 1. Introduction

Epilepsy, one of the most frequent neurological afflictions in men characterized by excessive temporary neuronal discharges resulting in uncontrolled convulsion, inflicts more than 60 million people worldwide [1,2]. Although the current drugs provide adequate seizure control in many patients, it is roughly estimated that up to 28–30% of patients are poorly treated with the available antiepileptic drugs (AEDs) [3,4]. Moreover, many AEDs have serious side effects [5–10], and lifelong medication may be required. Toxicity, intolerance, and lack of efficacy are the limitations of the current AEDs. All of these have stimulated intensive research on novel AEDs.

We previously described the synthesis and anticonvulsant activity evaluation of some compounds containing triazole, the majority of which exhibited potent activity in maximal electroshock test (MES) and several chemical models such as Pentylenetetrazole- and Isoniazid-induced seizure tests (Fig. 1) [11–16]. From the currently used AEDs, the major characteristics important in newly synthesized compounds are the inclusion of a hydrophobic site and H-bond donors/acceptors. With respect to the compounds mentioned above, obviously the hydrophobic site is the phenyl group and the substituents on it, and the H-bond acceptor is the triazole.

As part of our continuous efforts to find better anticonvulsant agents in this area, a series of 7-(substituted-phenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones (**1a**–**1o**) were designed and synthesized in this study, which also possessing the H-bond acceptor – triazole and the hydrophobic site – phenyl group. Compounds **2a**–**2c** were synthesized by substituting the hydrogen of the NH group in the compound **1a** to identify whether the amide group is of necessity for the anticonvulsant activity of this frame. For further structure–activity relationship (SAR) establishment, other three series of compounds: 5-(substituted-phenyl)-5,6-dihydroimidazo[1,2-*a*]pyrimidin-7(8*H*)-ones (**3a**–**3d**), 7-(substituted-phenyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-ones (**4a**–**4d**), and 7-(substituted-phenyl)-7,8-dihydrophenyl[*d*]imidazo[1,2-*a*]pyrimidin-9(10*H*)-ones (**5a**–**5d**) were also prepared by replacing the triazole in the compound **1** with imidazole, pyrazole, and phenyl [*d*]imidazole. The structures of all target compounds were characterized. Anticonvulsant activity and neurotoxicity were also evaluated. For explaining the possible mechanism of action, the most active compound **1i** was tested in Pentylenetetrazole (PTZ), Isoniazid (ISO), Thiosemicarbazide (TSC), 3-Mercaptopropionic acid (3-MP), and Bicuculline (BIC) induced seizure tests.

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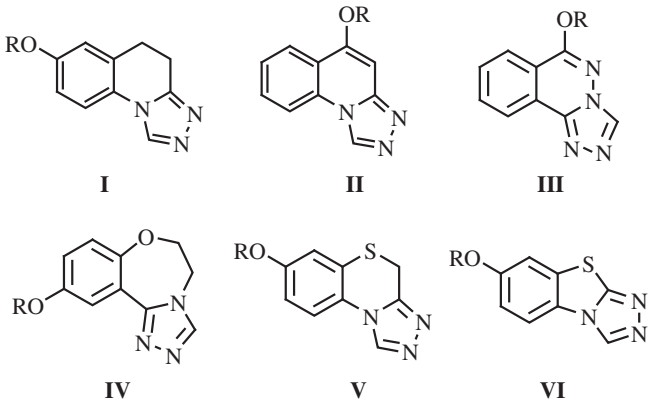
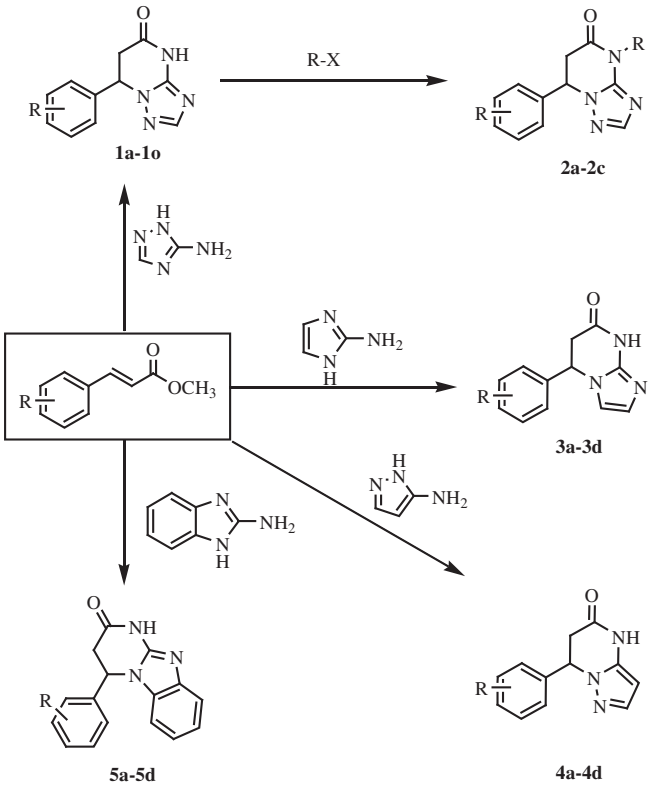



**Fig. 1.** Structures of some compounds in containing triazole.

## 2. Chemistry

For the preparation of all compounds described in this paper, appropriate substituted methyl cinnamates were used as starting materials. All the compounds were prepared as outlined in Scheme 1. Cyclization of methyl cinnamates with 1,2,4-triazol-3-amine gave [1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones **1a**–**1o** under high temperature conditions [17]. The syntheses of compounds **2a**–**2c**, which bear substituents in the N atom, were performed by treating **1a** with $(CH_3)_2SO_4$, bromohexane, and benzyl chloride, respectively. Cyclization of methyl cinnamates with 2-aminoimidazole hemisulfate and $K_2CO_3$ in DMF led to 5-(substituted-phenyl)-5,6-dihydroimidazo [1,2-*a*]pyrimidin-7(8*H*)-ones **3a**–**3d**. Similarly, cyclization of methyl cinnamates with 1*H*-pyrazol-5-amine or 1*H*-benzo[*d*]imidazol-2-amine led to 7-(substituted-phenyl)-6,7-dihydropyrazolo[1,5-*a*] pyrimidin-5(4*H*)-ones **4a**–**4d** or 7-(substituted-phenyl)-7,8-dihydrophenyl[*d*]imidazo[1,2-*a*]pyrimidin-9(10*H*)-ones **5a**–**5d**, respectively. Their chemical structures were characterized using $^1$H NMR, $^{13}$C NMR, MS and elemental analysis techniques. The detailed physical and analytical data are listed in Section 6.




**Scheme 1.** Synthetic route of target compounds.

## 3. Pharmacology

All the target compounds were screened for their anticonvulsant activity using the most adopted seizure model – the maximal electroshock seizure (MES) test. Neurotoxicity was assessed by rotarod test. The MES test and rotarod test were carried out by the methods described in the Antiepileptic Drug Development Program (ADD) of the National Institutes of Health following previously described testing procedures (USA) [18,19]. All the compounds, dissolved in DMSO, were evaluated for anticonvulsant activities with KunMing mice in the 18–22 g weight range, which were purchased from the Laboratory of Animal Research, College of Pharmacy, Yanbian University. Some compounds possessed better activity were quantified their anticonvulsant activity, and the best one was tested in Pentylenetetrazole (PTZ), Isoniazid (ISO), Thiosemicarbazide (TSC), 3-Mercaptopropionic acid (3-MP), and Bicuculline (BIC)-induced seizure tests.

## 4. Results and discussion

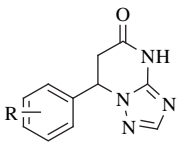
### 4.1. Phase I evaluation of anticonvulsant activity

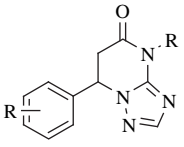
As with any other class of drugs, the preclinical discovery and development of a new chemical entity for the treatment of epilepsy rely heavily on the use of predictable animal models. At present, there are three models in vivo – the maximal electroshock seizure (MES), the subcutaneous pentylenetetrazol (sc-PTZ), and the kindling model – which are routinely used by most AED discovery programs. Of these, the MES and sc-PTZ seizure models represent the two animal seizure models most widely used in the search for new AEDs [20,21]. In the present study we used the MES seizure model for screening the anticonvulsant activity of target compounds. Compounds **1a**–**1o** were prepared to evaluate the influence of the phenyl ring on anticonvulsant activity. Their preliminary anticonvulsant activity were obtained and listed in Table 1. After i.p. injection in mice using doses of 30, 100, and 300 mg/kg, the following observations can be made. All of the compounds except **1h** were active in the MES test indicating their anticonvulsant properties. At the dose of 100 mg/kg, compounds **1a**, **1b**, **1e**, **1f**, **1i**, **1j**, and **1l** showed complete protection, while **1g**, **1m** showed protection in 1/3 of the tested mice. Compounds **1b**, **1e**, and **1i** exhibited protection at 30 mg/kg in 1/3, 3/3, and 3/3, respectively. None of the compounds showed protection in the 4 h period.

Compounds **2a**–**2c**, which have substitutes in the N atom of the amide, were also evaluated for their anticonvulsant activity. All of them showed protection in 1/3 of the tested mice at 100 mg/kg. Decrease of their anticonvulsant activity was observed when compared to **1a**, which showed complete protection at 100 mg/kg.

These pharmacology data indicated that compounds containing halogen in the ortho position (**1b**, **1e**, **1i**) possessed better anticonvulsant activity than the others. What is more the amide in the middle ring was also essential. Thus, with three substituents (*o*-F, *o*-Cl, *o*-Br) and non-substituent reserved in the phenyl ring, compounds **3a**–**3d**, **4a**–**4d**, and **5a**–**5d** were prepared for structure–activity relationships (SAR) studies. The anticonvulsant activities of these compounds were shown in Table 1. For the 5-(substituted-phenyl)-5,6-dihydroimidazo[1,2-*a*]pyrimidin-7(8*H*)-ones (**3a**–**3d**), all the four compounds were active in the MES test.

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


**1a-1o**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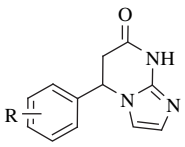
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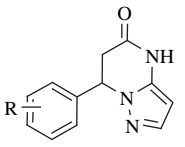
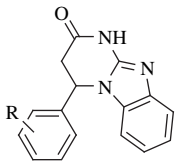

**4a-4d**


**5a-5d**

| Compds. | R | MES[a] (mg/kg) | | | | | | Toxicity (mg/kg) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.5 h | | | 4 h | | | 0.5 h | | | 4 h | | |
| | | 30 | 100 | 300 | 30 | 100 | 300 | 30 | 100 | 300 | 30 | 100 | 300 |
| **1a** | H | 0/3 | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | –[b] | 0/3 | ***1/3*** | – | 0/3 | 0/3 |
| **1b** | 2-F | ***1/3*** | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | 0/3 | ***1/3*** | – | 0/3 | 0/3 |
| **1c** | 3-F | 0/3 | 0/3 | ***2/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **1d** | 4-F | 0/3 | 0/3 | ***2/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **1e** | 2-Cl | ***3/3*** | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | 0/3 | ***1/3*** | – | 0/3 | 0/3 |
| **1f** | 3-Cl | 0/3 | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | 0/3 | ***1/3*** | – | 0/3 | 0/3 |
| **1g** | 4-Cl | 0/3 | ***1/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **1h** | 2,4Cl | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **1i** | 2-Br | ***3/3*** | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | 0/3 | 0/3 | – | 0/3 | 0/3 |
| **1j** | 3-Br | 0/3 | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | 0/3 | 0/3 | – | 0/3 | 0/3 |
| **1k** | 4-Br | 0/3 | 0/3 | ***2/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **1l** | 3-$CF_3$ | 0/3 | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | ***1/3*** | ***3/3*** | – | 0/3 | 0/3 |
| **1m** | 4-$CH_3$ | 0/3 | ***1/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **1n** | 2-$OCH_3$ | 0/3 | 0/3 | ***1/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **1o** | 4-$OCH_3$ | 0/3 | 0/3 | ***1/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **2a** | $CH_3$ | 0/3 | ***1/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **2b** | $C_6H_{13}$ | 0/3 | ***1/3*** | ***2/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **2c** | $CH_2C_6H_5$ | 0/3 | ***1/3*** | ***2/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **3a** | H | 0/3 | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | 0/3 | 0/3 | – | 0/3 | 0/3 |
| **3b** | 2-F | 0/3 | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | 0/3 | ***1/3*** | – | 0/3 | 0/3 |
| **3c** | 2-Cl | 0/3 | ***1/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **3d** | 2-Br | 0/3 | ***2/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **4a** | H | ***1/3*** | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | ***2/3*** | ***3/3*** | – | 0/3 | 0/3 |
| **4b** | 2-F | ***1/3*** | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | ***1/3*** | ***3/3*** | – | 0/3 | 0/3 |
| **4c** | 2-Cl | 0/3 | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | ***2/3*** | ***3/3*** | – | 0/3 | 0/3 |
| **4d** | 2-Br | 0/3 | ***3/3*** | ***3/3*** | 0/3 | 0/3 | 0/3 | – | ***1/3*** | ***3/3*** | – | 0/3 | 0/3 |
| **5a** | H | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **5b** | 2-F | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **5c** | 2-Cl | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |
| **5d** | 2-Br | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | – | – | – | – | – | – |

All positive reaction numbers are in bold italic.
[a] Maximal electroshock test (number of animals protected/number of animals tested), the number of mice is three.
[b] Not tested.

Compounds **3a** and **3b** showed complete protection at 100 mg/kg, while **3c**, **3d** showed protection in 1/3 and 2/3 of the tested mice, respectively. No neurotoxicity was found except **3b**. Compounds **4a**–**4d**, which contained a pyrazole, showed complete protection at the dose of 100 mg/kg, and compounds **4a** and **4b** exhibited protection in 1/3 of the tested mice at 30 mg/kg. However, there was no separation between the anticonvulsant dose and the neurotoxic dose (100 mg/kg for both). When the triazole was replaced by benzo[*d*]imidazole, all four compounds **5a**–**5d** showed no protection at 300 mg/kg.

### 4.2. Phase II evaluation of anticonvulsant activity

On the basis of the considerable anticonvulsant activity suggested in phase I testing, compounds **1a**, **1b**, **1e**, **1f**, **1i**, **1j**, **1l**, **3a**, **3b**, and **4a**–**4d** were subjected to phase II trials for quantification of their anticonvulsant activity (indicated by $ED_{50}$) and neurotoxicity (indicated by $TD_{50}$) in mice. Results of the quantitative test for selected compounds, along with the data on the current antiepileptic drugs, are shown in Table 2. Among the tested compounds, 7-(2-bromophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-one (**1i**) was the most active and promising compound in this work. It possessed strong anti-MES activity with $ED_{50}$ of 19.7 mg/kg, which was close to currently used antiepileptic drugs phenytoin and carbamazepine and better than that of phenobarbital and valproate. The neurotoxicity caused by it was minimal and was markedly lower than all the drugs compared. It showed a protective index of 34.8, which was many folds higher than the current antiepileptic drugs having the PI values in the range of 1.6–6.9. Furthermore, compounds **1a**, **1b**, **1e**, and **1f** also showed higher protective index than these current antiepileptic drugs.

### 4.3. Structure–activity relationships discussions

Analyzing the activities of the synthesized compounds, the following structure–activity relationships (SAR) were obtained.

In the first group compounds (**1a**–**1o**), effects of different substitutions at phenyl were observed. Introduction of halogen on the phenyl ring changed (reduced or increased) the anticonvulsant activity at different levels (compared with **1a**). The bioevaluation led to an understanding of the importance of the position of the halogen at the phenyl. Compounds **1b**, **1e**, **1i**, contained halogen in

**Table 2**
Quantitative anticonvulsant data in mice (i.p.).

| Compds. | R | $ED_{50}$ (mg/kg) (MES) | $TD_{50}$ (mg/kg) | PI[a] |
|---|---|---|---|---|
| **1a** | H | 51.9(48.5–55.3) | 547.5(497.7–602.2) | 10.5 |
| **1b** | 2-F | 31.7 (28.8–34.9)[b] | 456.4 (410.3–507.7) | 14.4 |
| **1e** | 2-Cl | 25.5 (23.6–27.5) | 464.8 (417.8–517.1) | 18.2 |
| **1f** | 3-Cl | 47.3 (43.0–52.0) | 528.1 (474.7–587.5) | 11.2 |
| **1i** | **2-Br** | **19.7 (17.9–21.7)** | **684.7 (615.5–761.6)** | **34.8** |
| **1j** | 3-Br | 84.9 (77.2–93.4) | 591.7 (537.9–650.9) | 7.0 |
| **1l** | 3-$CF_3$ | 54.8 (49.8–60.3) | 158.4 (144.0–174.2) | 2.9 |
| **3a** | H | 68.2 (62.0–75.0) | 458.3 (416.6–504.1) | 6.7 |
| **3b** | 2-F | 88.0 (80.0–96.8) | 387.2 (320.0–468.5) | 4.4 |
| **4a** | H | 47.3 (43.0–52.0) | 118.3 (107.5–127.2) | 2.5 |
| **4b** | 2-F | 47.3 (43.0–52.0) | 118.3 (107.5–127.2) | 2.5 |
| **4c** | 2-Cl | 63.4 (57.6–69.7) | 94.7 (88.1–101.8) | 1.5 |
| **4d** | 2-Br | 39.4 (35.8–43.4) | 132.0 (120.0–145.2) | 3.4 |
| Carbamazepine | – | 11.8 (9.7–14.1) | 76.1(69.1–83.7) | 6.4 |
| Phenytoin | – | 9.5 (8.1–10.4) | 65.5 (52.5–72.9) | 6.9 |
| Phenobarbital | – | 21.8 (21.8–25.5) | 69 (62.8–72.9) | 3.2 |
| Valproate | – | 272 (247–338) | 426 (369–450) | 1.6 |

[a] PI = Protective ($TD_{50}/ED_{50}$).
[b] The 95% confidence limits.

the ortho position, displayed better potency than **1a**, while introduction of halogen on the other position of the phenyl ring led to weaker activity. Introduction of the strong electron-withdrawing and lipophilic group $-CF_3$ resulted in a similar activity to that of **1a**, while its large neurotoxicity made it impossible to be a candidate. Three electron-donor derivatives containing *p*-$CH_3$, *o*-$OCH_3$, and *p*-$OCH_3$ were also prepared. However, these compounds exhibited reduced anticonvulsant activities than the corresponding halogen substituted derivatives. Introduction of the $-CH_3$ was found to show better activity than substitution with the -$OCH_3$ group.

Compounds **2a**–**2c**, prepared by replacing the hydrogen atom of the amide in compound **1a** with different substituents, exhibited decreased activity when compared to the unsubstituted compound **1a**. Thus, it is concluded that the amide group in this frame was important for its anticonvulsant activity. The sizes of the substituents had no significant effects on their activity.

When the triazole ring was replaced by other heterocycles: imidazole, pyrazole, and phenyl[*d*]imidazole, the anticonvulsant activity was altered. The compounds containing the imidazole ring (**3a**–**3d**) decreased the activity slightly compared to the compounds **1a**–**1o** bearing the triazole ring. Compounds containing the pyrazole ring (**4a**–**4d**) showed anticonvulsant activity similar to compounds with the triazole. However, they showed higher neurotoxicity, which led to a lower protective index (PI) compared to the compounds with the triazole. Replacement of the triazole ring by phenyl[*d*]imidazole (**5a**–**5d**) led to a sharp descending in activity, which might be due to steric hindrance to binding by the additional phenyl group on the imidazole. Thus, these data indicate that the frame with the triazole displayed the best anticonvulsant activity and favorable PI, and this site may be one of the active centers.

### 4.4. Speculation of mechanism

In this study, the majority of synthesized compounds were highly potent in the MES test, and the MES test is known to be sensitive to sodium channel inhibitors (e.g. phenytoin, carbamazepine), which suggested that the tested compounds may inhibit voltage-gated ion channels (particularly sodium channels). To further investigate the effects of the anticonvulsant activity in several different models and speculate about the possible mechanism of anticonvulsant action, compound **1i** was tested against convulsions induced by chemical substances, including PTZ, ISO, 3-MP, TSC and BIC. Compound **1i** was administered to mice at 50 mg/kg i.p., which was higher than its $ED_{50}$ value and far below its $TD_{50}$ value. The reference drug carbamazepine was also administered at 50 mg/kg i.p.

In the sc-PTZ model, carbamazepine inhibited the clonic seizures, tonic seizures and death at the rates of 0%, 100%, and 100%, respectively. While compound **1i** inhibited the clonic seizures, tonic seizures and lethality completely induced by sc-PTZ (Table 3), which revealed that compound **1i** possessed excellent activity against sc-PTZ. Compound **1i**, exhibiting high anticonvulsant activity in the MES and sc-PTZ models which are most widely used in the search for new AEDs, suggested that it really possesses a good anticonvulsant profile. In the ISO model, carbamazepine inhibited the clonic seizures, tonic seizures and death induced by ISO at the rates of 50%, 100% and 100%, respectively. Compound **1i** showed inhibition of the clonic seizure, tonic seizures induced by ISO at the rates of 0%, 100%, respectively and also showed partial inhibition of the death compared to the control (Table 3). PTZ and ISO have been reported to produce seizures by inhibiting γ-aminobutyric acid (GABA) neurotransmission [22,23]. GABA is the main inhibitory neurotransmitter in the brain, and is widely implicated in epilepsy. Inhibition of GABAergic neurotransmission or activity has been shown to promote and facilitate seizures [24], while enhancement of GABAergic neurotransmission is known to inhibit or attenuate seizures. The findings of the present study suggest that the newly synthesized compound **1i** might inhibit or attenuate PTZ-induced

**Table 3**
Effects of compound **1i** on chemical-induced seizures in mice.

| Chemical substances | Compound | Doses (mg/kg) | Test time (h) | Clonic seizures (%) | Tonic seizures (%) | Lethality (%) |
|---|---|---|---|---|---|---|
| Pentylenetetrazol | DMSO | – | 0.5 | 100 | 60 | 60 |
| | Carbamazepine | 50 | 0.5 | 100 | 0 | 0 |
| | **1i** | 50 | 0.5 | 0 | 0 | 0 |
| Isoniazid | DMSO | – | 1 | 100 | 100 | 60 |
| | Carbamazepine | 50 | 1 | 50 | 0 | 0 |
| | **1i** | 50 | 1 | 100 | 0 | 30 |
| 3-Mercaptopropionic acid | DMSO | – | 0.5 | 100 | 100 | 100 |
| | Carbamazepine | 30 | 0.5 | 100 | 0 | 0 |
| | **1i** | 30 | 0.5 | 100 | 0 | 10 |
| Thiosemicarbazide | DMSO | – | 2.5 | 100 | 100 | 100 |
| | Carbamazepine | 30 | 2.5 | 100 | 0 | 0 |
| | **1i** | 30 | 2.5 | 100 | 0 | 100 |
| Bicuculline | DMSO | – | 0.5 | 100 | 100 | 100 |
| | Carbamazepine | 30 | 0.5 | 100 | 0 | 20 |
| | **1i** | 30 | 0.5 | 100 | 10 | 50 |

seizures and ISO-induced seizures in mice by enhancing GABAergic neurotransmission.

In the 3-MP induced seizure model, carbamazepine inhibited the clonic seizures, tonic seizures and death at the rates of 0%, 100%, and 100%, respectively. In comparison, compound **1i** showed the anticonvulsant effect similar to that of carbamazepine in inhibiting the clonic and tonic seizures, and inhibited the death largely induced by 3-MP with the inhibition rate of 90% (Table 3). In the TSC-induced seizure model, the anticonvulsant effect is similar to that of the 3-MP induced seizure model. Compared with the control group, carbamazepine showed inhibition of clonic and tonic seizures and death at rates of 0%, 100%, and 100%, respectively. Compound **1i** showed inhibition of clonic and tonic seizures at rates of 0% and 100%; however, there was no effect on death rates induced by TSC (Table 3). 3-MP and TSC are competitive inhibitors of the GABA synthesis enzyme glutamate decarboxylase (GAD), and they inhibit the synthesis of GABA resulting in decrease of GABA levels in the brain [25]. Compound **1i** showed moderate antagonism to both 3-MP induced seizures and TSC-induced seizures, suggesting that it might activate GAD or inhibit aminotransferase (GABA-T) in the brain.

In the BIC induced seizure model, both carbamazepine and **1i** inhibited tonic seizures and death, but did not inhibit clonic seizures. Carbamazepine showed inhibition of clonic and tonic seizures and death at rates of 0%, 100%, and 80%, respectively. Compound **1i** showed inhibition of clonic and tonic seizures and death at rates of 0%, 90%, and 50%, respectively (Table 3). BIC is a competitive antagonist of $GABA_A$ receptor. BIC produces convulsions through its antagonism of the $GABA_A$ receptor [26]. As compound **1i** inhibited the seizures induced by BIC, it likely exerts anticonvulsant activity at least partially through $GABA_A$-mediated mechanisms.

## 5. Conclusion

In the present study we described the syntheses and anticonvulsant activity evaluation of 7-(substituted-phenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones (**1a**–**1o**). In addition, several series of derivatives were also synthesized and evaluated for their anticonvulsant activity for SAR studies, which included 7-(substituted-phenyl)-4-substituted-6,7-dihydro-[1,2,4]triazolo [1,5-*a*]pyrimidin-5(4*H*)-ones (**2a**–**2c**), 5-(substituted-phenyl)-5,6-dihydroimidazo[1,2-*a*]pyrimidin-7(8*H*)-ones (**3a**–**3d**), 7-(substituted-phenyl)-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-5(4*H*)-ones (**4a**–**4d**), and 7-(substituted-phenyl)-7,8-dihydrophenyl[*d*] imidazo[1,2-*a*]pyrimidin-9(10*H*)-ones (**5a**–**5d**). Bioevaluation demonstrated that the compounds possessing a triazole (**1a**–**1o**) displayed the best anticonvulsant activity and favorable PI. Compound **1i** showed better anticonvulsant activity as compared to the standard drugs in MES test. It also showed marked lower neurotoxicity and therefore a higher protective index. In addition, the potency of compound **1i** against seizures induced by PTZ, ISO, 3-MP, TSC, and BIC in the chemical-induced seizure tests suggested its broad spectrum activity in several models. It is likely to have several mechanisms of action including inhibition of voltage-gated ion channels and modulation of GABAergic activity.

## 6. Experimental protocols

### 6.1. Chemistry

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on IRPrestige-21. $^1$H NMR and $^{13}$C NMR spectra were measured on an AV-300 (Bruker, Switzerland), and all chemical shifts were given in parts per million relative to tetramethysilane. Mass spectra were measured on a HP1100LC (Agilent Technologies, USA). Elemental analyses were performed on a 204Q CHN (Perkin Elmer, USA). The chemicals were purchased from Aldrich Chemical Corporation.

#### 6.1.1. Synthesis of 7-(substituted-phenyl)-6,7-dihydro-[1,2,4] triazolo[1,5-a]pyrimidin-5(4H)-one derivatives (*1a*–*1o*)

A mixture of appropriate substituted methyl cinnamates (6.2 mmol) and 1,2,4-triazol-3-amine (12.4 mmol, 1.04 g) was stirred for 16 h at 200 °C. After cooling down, a yellow solid was obtained, which was isolated and purified by silica gel column chromatography with dichloromethane and methanol (50:1) to give a white solid (**1a**–**1o**).

#### 6.1.2. Synthesis of 7-(substituted-phenyl)-4-substituted-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one derivatives (*2a*–*2c*)

KOH (6.4 mmol, 0.36 g) and 7-phenyl-6,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-one (2.3 mmol, 0.5 g) were dissolved in acetonitrile (40 mL). The reaction mixture was refluxed for 0.5 h, then $(CH_3)_2SO_4$ (for **2a**) or bromohexane (for **2b**) or benzyl chloride (for **2c**) (2.4 mmol) were added into the mixture accompanied with some of benzyltriethylamine chloride (TEBA). The reaction mixture was heated for 4–24 h at reflux temperature. Then the mixture was poured into 100 mL of water. Aqueous layer was extracted with dichloromethane (30 mL × 3). The combined layer of dichloromethane was dried by anhydrous $MgSO_4$. The evaporation of the solvent gave a crude product, which was purified by silica gel column chromatography with dichloromethane and methanol (80:1) to give a white solid.

#### 6.1.3. Synthesis of 5-(substituted-phenyl)-5,6-dihydroimidazo[1,2-a]pyrimidin-7(8H)-one derivatives (*3a*–*3d*)

To a solution of the appropriate substituted methyl cinnamates (6.2 mmol) in DMF (20 mL) were added 2-aminoimidazole hemisulfate (3.1 mmol, 0.82 g) and $K_2CO_3$ (0.86 g 6.2 mmol). The mixture was refluxed for 6 h. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography with dichloromethane and methanol (50:1) to give a white solid (**3a**–**3d**).

#### 6.1.4. Synthesis of 7-(substituted-phenyl)-6,7-dihydropyrazolo[1,5-a]pyrimidin-5(4H)-one derivatives (*4a*–*4d*)

A mixture of appropriate substituted methyl cinnamates (3.1 mmol) and 1*H*-pyrazol-5-amine (6.2 mmol, 0.51 g) was stirred for 16 h at 200 °C. After cooling down, the mixture was isolated and purified by silica gel column chromatography with dichloromethane and methanol (50:1) to give a white solid (**4a**–**4d**).

#### 6.1.5. Synthesis of 7-(substituted-phenyl)-7,8-dihydrophenyl[d] imidazo[1,2-a]pyrimidin-9(10H)-one derivatives (*5a*–*5d*)

To a solution of the appropriate substituted methyl cinnamates (6.2 mmol) in DMF (5 mL) was added 1*H*-benzo[*d*]imidazol-2-amine (6.2 mmol, 0.82 g). The reaction mixture was refluxed for 12 h. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography with dichloromethane and methanol (50:1) to give a white solid (**5a**–**5d**).

*6.1.5.1. 7-Phenyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1a**).* M.p. 214–216 °C, yield = 60%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.14 (dd, 1H, $J_1 = 4.9$ Hz, $J_2 = 16.8$ Hz, H-6), 3.39 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 16.8$ Hz, H-6), 5.63 (dd, 1H, $J_1 = 4.9$ Hz, $J_2 = 7.2$ Hz, H-7),

7.15–7.41 (m, 5H, Ar–H), 7.82 (s, 1H, H-2), 11.40 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 39.0, 56.0, 126.4, 128.7, 129.4, 139.3, 150.5, 150.7, 167.6. IR (KBr, cm$^{-1}$): 1699 (C=O), 3191 (NH). MS *m/z* 215 (M + 1). *Anal*. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.78; H, 4.79; N, 26.03.

*6.1.5.2. 7-(2-Fluorophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1b**).* M.p. 200–201 °C, yield = 70%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.15 (dd, 1H, $J_1$ = 4.1 Hz, $J_2$ = 16.9 Hz, H-6), 3.40 (dd, 1H, $J_1$ = 7.3 Hz, $J_2$ = 16.9 Hz, H-6), 5.90 (dd, 1H, $J_1$ = 4.1 Hz, $J_2$ = 7.3 Hz, H-7), 7.11–7.36 (m, 4H, Ar–H), 7.82 (s, 1H, H-2), 10.73 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 37.4, 51.3, 116.5 (d, $J_{C-F}$ = 84.0 Hz), 125.4 (d, $J_{C-F}$ = 12.0 Hz), 126.0 (d, $J_{C-F}$ = 51.0 Hz), 128.5 (d, $J_{C-F}$ = 12.0 Hz), 131.2 (d, $J_{C-F}$ = 33.0 Hz), 150.7 (d, $J_{C-F}$ = 45.0 Hz), 158.4, 161.6, 167.2. IR (KBr, cm$^{-1}$): 1705 (C=O), 3190 (NH). MS *m/z* 233 (M + 1). *Anal*. Calcd. for $C_{11}H_9FN_4O$: C, 56.89; H, 3.91; N, 24.13. Found: C, 56.97; H, 3.95; N, 24.05.

*6.1.5.3. 7-(3-Fluorophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1c**).* M.p. 196–197 °C, yield = 68%. $^1$H NMR ($CDCl_3$ 300 MHz) δ 3.11 (dd, 1H, $J_1$ = 4.6 Hz, $J_2$ = 16.8 Hz, H-6), 3.40 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 16.8 Hz, H-6), 5.63 (dd, 1H, $J_1$ = 4.6 Hz, $J_2$ = 7.2 Hz, H-7), 6.95–7.41 (m, 4H, Ar -H), 7.82 (s, 1H, H-2), 10.79 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 38.3, 55.1, 113.5 (d, $J_{C-F}$ = 90.0 Hz), 115.3 (d, $J_{C-F}$ = 84.0 Hz), 122.2, 131.1 (d, $J_{C-F}$ = 33.0 Hz), 141.5 (d, $J_{C-F}$ = 21.0 Hz), 150.3 (d, $J_{C-F}$ = 54.0 Hz), 160.7, 163.9, 167.0. IR (KBr, cm$^{-1}$): 1708 (C=O), 3194 (NH). MS *m/z* 233 (M + 1). *Anal*. Calcd. for $C_{11}H_9FN_4O$: C, 56.89; H, 3.91; N, 24.13. Found: C, 57.03; H, 3.98; N, 24.07.

*6.1.5.4. 7-(4-Fluorophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1d**).* M.p. 210–212 °C, yield = 71%. $^1$H NMR ($CDCl_3$ 300 MHz) δ 3.10 (dd, 1H, $J_1$ = 5.0 Hz, $J_2$ = 16.8 Hz, H-6), 3.40 (dd, 1H, $J_1$ = 7.0 Hz, $J_2$ = 16.8 Hz, H-6), 5.61 (dd, 1H, $J_1$ = 5.0 Hz, $J_2$ = 7.0 Hz, H-7), 7.06–7.16 (m, 4H, Ar–H), 7.79 (s, 1H, H-2), 11.07 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 38.9, 55.4, 116.2 (d, $J_{C-F}$ = 87.0 Hz), 128.9 (d, $J_{C-F}$ = 36.0 Hz), 135.3, 150.6 (d, $J_{C-F}$ = 63.0 Hz), 160.7, 163.9, 167.5. IR (KBr, cm$^{-1}$): 1703 (C=O), 3192 (NH). MS *m/z* 233 (M + 1). *Anal*. Calcd. for $C_{11}H_9FN_4O$: C, 56.89; H, 3.91; N, 24.13. Found: C, 57.09; H, 4.02; N, 24.00.

*6.1.5.5. 7-(2-Chlorophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1e**).* M.p. 225–226 °C, yield = 62%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.16 (dd 1H, $J_1$ = 4.1 Hz, $J_2$ = 17.0 Hz, H-6), 3.43 (dd, 1H, $J_1$ = 7.7 Hz, $J_2$ = 17.0 Hz, H-6), 5.63 (dd, 1H, $J_1$ = 4.1 Hz, $J_2$ = 7.7 Hz, H-7), 7.15–7.41 (m, 4H, Ar–H), 7.85 (s, 1H, H-2). $^{13}$C NMR (DMSO-$d_6$) δ 37.3, 53.7, 127.6, 128.4, 130.5, 130.7, 131.8, 136.2, 151.0, 151.1, 167.0. IR (KBr, cm$^{-1}$): 1703 (C=O), 3188 (NH). MS *m/z* 249 (M + 1), 251 (M + 3). *Anal*. Calcd. for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; N, 22.53. Found: C, 53.27; H, 3.72; N, 22.46.

*6.1.5.6. 7-(3-Chlorophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1f**).* M.p. 225–226 °C, yield = 69%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.11 (dd 1H, $J_1$ = 5.0 Hz, $J_2$ = 16.9 Hz, H-6), 3.39 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 16.9 Hz, H-6), 5.60 (dd, 1H, $J_1$ = 5.0 Hz, $J_2$ = 7.2 Hz, H-7), 7.03–7.36 (m, 4H, Ar–H), 7.66 (s, 1H, H-2), 10.47 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 38.7, 55.5, 125.4, 126.8, 128.8, 131.0, 131.3, 133.9, 141.5, 150.8, 167.4. IR (KBr, cm$^{-1}$): 1700 (C=O), 3186 (NH). MS *m/z* 249 (M + 1), 251 (M + 3). *Anal*. Calcd. for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; N, 22.53. Found: C, 53.21; H, 3.76; N, 22.41.

*6.1.5.7. 7-(4-Chlorophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1g**).* M.p. 227–228 °C, yield = 71%. $^1$H NMR ($CDCl_3$ 300 MHz) δ 3.14 (dd, 1H, $J_1$ = 4.5 Hz, $J_2$ = 16.8 Hz, H-6), 3.40 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 16.8 Hz, H-6), 5.60 (dd, 1H, $J_1$ = 4.5 Hz, $J_2$ = 7.2 Hz, H-7), 7.10 (d, 2H, $J$ = 8.4 Hz, Ar–H), 7.38 (d, 2H, $J$ = 8.4 Hz, Ar–H), 7.77 (s, 1H, H-2), 9.83 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 38.8, 55.4, 128.6, 129.3, 133.4, 138.1, 150.2, 150.7, 167.4. IR (KBr, cm$^{-1}$): 1701 (C=O), 3191 (NH). MS *m/z* 249 (M + 1), 251 (M + 3). *Anal*. Calcd. for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; N, 22.53. Found: C, 53.19; H, 3.60; N, 22.46.

*6.1.5.8. 7-(2,4-Dichlorophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1h**).* M.p. 267–268 °C, yield = 78%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.15 (dd, 1H, $J_1$ = 4.6 Hz, $J_2$ = 16.8 Hz, H-6), 3.40 (dd, 1H, $J_1$ = 7.1 Hz, $J_2$ = 16.8 Hz, H-6), 6.00 (dd, 1H, $J_1$ = 4.6 Hz, $J_2$ = 7.1 Hz, H-7), 6.55–7.80 (m, 3H, Ar–H), 8.75 (s, 1H, H-2). $^{13}$C NMR (DMSO-$d_6$) δ 37.1, 53.4, 128.6, 129.4, 130.1, 133.0, 134.4, 135.3, 151.0, 151.3, 166.9. IR (KBr, cm$^{-1}$): 1703 (C=O), 3189 (NH). MS *m/z* 283 (M + 1), 285 (M + 3). *Anal*. Calcd. for $C_{11}H_8Cl_2N_4O$: C, 46.67; H, 2.85; N, 19.79. Found: C, 46.83; H, 2.93; N, 19.70.

*6.1.5.9. 7-(2-Bromophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1i**).* M.p. 239–240 °C, yield = 66%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.15 (dd, 1H, $J_1$ = 4.3 Hz, $J_2$ = 17.1 Hz, H-6), 4.43 (dd, 1H, $J_1$ = 7.7 Hz, $J_2$ = 17.1 Hz, H-6), 6.04 (dd, 1H, $J_1$ = 4.3 Hz, $J_2$ = 7.7 Hz, H-7), 6.59 (d, 1H, $J$ = 7.4 Hz, Ar–H), 7.21–7.32 (m, 2H, Ar–H), 7.65 (d, 1H, $J$ = 7.6 Hz, Ar–H), 7.85 (s, 1H, H-2), 10.59 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 37.5, 55.9, 121.9, 127.6, 129.0, 130.9, 134.0, 137.7, 151.0, 151.4, 166.9. IR (KBr, cm$^{-1}$): 1699 (C=O), 3192 (NH). MS *m/z* 293 (M + 1). *Anal*. Calcd. for $C_{11}H_9BrN_4O$: C, 45.07; H, 3.09; N, 19.11. Found: C, 45.22; H, 3.16; N, 19.04.

*6.1.5.10. 7-(3-Bromophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1j**).* M.p. 245–246 °C, yield = 70%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.08 (dd, 1H, $J_1$ = 5.1 Hz, $J_2$ = 16.8 Hz, H-6), 3.39 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 16.8 Hz, H-6), 5.59 (dd, 1H, $J_1$ = 5.1 Hz, $J_2$ = 7.2 Hz, H-7), 7.06–7.52 (m, 4H, Ar–H), 7.78 (s, 1H, H-2), 10.22 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 38.7, 55.4, 122.2, 125.8, 127.6, 129.7, 131.2, 131.6, 135.5, 150.8, 167.4. IR (KBr, cm$^{-1}$): 1704 (C=O), 3187 (NH). MS *m/z* 293 (M + 1). *Anal*. Calcd. for $C_{11}H_9BrN_4O$: C, 45.07; H, 3.09; N, 19.11. Found: C, 45.21; H, 3.17; N, 19.02.

*6.1.5.11. 7-(4-Bromophenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1k**).* M.p. 235–236 °C, yield = 72%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.09 (dd, 1H, $J_1$ = 4.9 Hz, $J_2$ = 17.0 Hz, H-6), 3.36 (dd, 1H, $J_1$ = 7.5 Hz, $J_2$ = 17.0 Hz, H-6), 5.58 (dd, 1H, $J_1$ = 4.9 Hz, $J_2$ = 7.7 Hz, H-7), 7.04 (d, 2H, $J$ = 8.0 Hz, Ar–H), 7.53 (d, 2H, $J$ = 8.0 Hz, Ar–H), 7.76 (s, 1H, H-2), 9.58 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 38.7, 55.5, 122.0, 128.9, 132.3, 138.5, 150.5, 150.7, 167.4. IR (KBr, cm$^{-1}$): 1696 (C=O), 3194 (NH). MS *m/z* 293 (M + 1). *Anal*. Calcd. for $C_{11}H_9BrN_4O$: C, 45.07; H, 3.09; N, 19.11. Found: C, 45.16; H, 3.12; N, 19.08.

*6.1.5.12. 7-(3-(Trifluoromethyl)phenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1l**).* M.p. 176–178 °C, yield = 80%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.10 (dd, 1H, $J_1$ = 4.9 Hz, $J_2$ = 17.0 Hz, H-6), 3.41 (dd, 1H, $J_1$ = 7.5 Hz, $J_2$ = 17.0 Hz, H-6), 5.68 (dd, 1H, $J_1$ = 4.9 Hz, $J_2$ = 7.7 Hz, H-7), 7.31–7.66 (m, 4H, Ar–H), 7.83 (s, 1H, H-2), 11.37 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ 38.7, 55.7, 123.8, 125.6, 129.4, 130.5, 131.0, 140.4, 150.7, 150.8, 167.4. IR (KBr, cm$^{-1}$): 1701 (C=O), 3190 (NH). MS *m/z* 283 (M + 1). *Anal*. Calcd. for $C_{12}H_9F_3N_4O$: C, 51.07; H, 3.21; N, 19.85. Found: C, 51.22; H, 3.34; N, 19.77.

*6.1.5.13. 7-(4-Methylphenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1m**).* M.p. 206–207 °C, yield = 63%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H, $-CH_3$), 3.11 (dd, 1H, $J_1$ = 5.3 Hz, $J_2$ = 16.8 Hz, H-6), 3.34 (dd, 1H, $J_1$ = 7.0 Hz, $J_2$ = 16.8 Hz, H-6), 5.57 (dd, 1H, $J_1$ = 5.3 Hz, $J_2$ = 7.0 Hz, H-7), 7.06 (d, 2H, $J$ = 8.0 Hz, Ar–H),

7.20 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.79 (s, 1H, H-2), 11.28 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.1, 39.0, 55.8, 126.3, 129.9, 136.3, 138.1, 150.4, 150.6, 167.6. IR (KBr, cm$^{-1}$): 1707 (C=O), 3194 (NH). MS $m/z$ 229 (M + 1). *Anal.* Calcd. for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.31; H, 5.37; N, 24.43.

*6.1.5.14. 7-(2-Methoxyphenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1n**).* M.p. 199–200 °C, yield = 65%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.09 (dd, 1H, $J_1$ =3.4 Hz, $J_2 = 17.0$ Hz, H-6), 3.35 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 17.0$ Hz, H-6), 3.83 (s, 3H, –$OCH_3$), 5.85 (dd, 1H, $J_1 = 3.4$ Hz, $J_2 = 8.2$ Hz, H-7), 6.68–7.35(m, 4H, Ar–H), 7.80 (s, 1H, H-2), 10.93 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 37.1, 52.7, 55.9, 112.1, 121.0, 126.9, 127.1, 130.3, 150.7, 150.8, 156.4, 167.6. IR (KBr, cm$^{-1}$): 1688 (C=O), 3185 (NH). MS $m/z$ 245 (M + 1). *Anal.* Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.17; H, 4.84; N, 22.85.

*6.1.5.15. 7-(4-Methoxyphenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**1o**).* M.p. 182–183 °C, yield = 65%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.11 (dd, 1H, $J_1 = 5.5$ Hz, $J_2 = 16.8$ Hz, H-6), 3.33 (dd, 1H, $J_1 = 6.9$ Hz, $J_2 = 16.8$ Hz, H-6), 3.80 (s, 3H, –$OCH_3$), 5.55 (dd, 1H, $J_1 = 5.5$ Hz, $J_2 = 6.9$ Hz, H-7), 6.89 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.13 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.79 (s, 1H, H-2), 11.35 (s, 1H, H-4). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 39.0, 55.5, 55.6, 114.7, 127.8, 131.1, 150.3, 150.5, 159.6, 167.7. IR (KBr, cm$^{-1}$): 1696 (C=O), 3192 (NH). MS $m/z$ 245 (M + 1). *Anal.* Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.23; H, 4.99; N, 22.81.

*6.1.5.16. 4-Methyl-7-phenyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one(**2a**).* M.p. 87–88 °C, yield =86%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.17 (dd, 1H, $J_1 = 5.2$ Hz, $J_2 = 16.7$ Hz, H-6), 3.38 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 16.7$ Hz, H-6), 3.46 (s, 3H, $NCH_3$), 5.57 (dd, 1H, $J_1$ =5.2 Hz, $J_2 = 7.0$ Hz, H-7), 7.08–7.38 (m, 5H, Ar–H), 7.73 (s, 1H, H-2). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 29.4, 39.0, 55.8, 126.6, 128.8, 129.4, 139.0, 150.5, 151.9, 166.2. IR (KBr, cm$^{-1}$): 1683 (C=O). MS $m/z$ 229 (M + 1). *Anal.* Calcd. for C12H12N4O: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.29; H, 5.26; N, 24.41.

*6.1.5.17. 4-Hexyl-7-phenyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**2b**).* M.p. 92–94 °C, yield = 81%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.90 (t, 3H, $J = 6.8$ Hz, $CH_3$), 1.28–1.69 (m, 8H, $(CH_2)_4$), 3.15 (dd, 1H, $J_1 = 4.4$ Hz, $J_2 = 16.9$ Hz, H-6), 3.38 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 16.9$ Hz, H-6), 3.99 (t, 2H, $J = 7.0$ Hz, $NCH_3$), 5.58 (dd, 1H, $J_1 = 4.4$ Hz, $J_2 = 7.1$ Hz, H-7), 7.08–7.36 (m, 5H, Ar–H), 7.74 (s, 1H, H-2). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 14.3, 22.4, 26.2, 27.6, 31.3, 39.1, 42.5, 55.6, 126.3, 128.7, 129.3, 138.9, 150.7, 151.4, 166.0. IR (KBr, cm$^{-1}$): 1678 (C=O). MS $m/z$ 299 (M + 1). *Anal.* Calcd. for $C_{17}H_{22}N_4O$: C, 68.43; H, 7.43; N, 18.78. Found: C, 68.57; H, 7.49; N, 18.74.

*6.1.5.18. 4-Benzyl-7-phenyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (**2c**).* M.p. 79–80 °C, yield = 84%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.17 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 16.6$ Hz, H-6), 3.41 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 16.6$ Hz, H-6), 5.18 (s, 2H, $NCH_2$), 5.56 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 7.0$ Hz, H-7), 6.94–7.45 (m, 10H, Ar–H), 7.74 (s, 1H, H-2). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 39.1, 45.8, 55.7, 126.5, 127.1, 127.9, 128.1, 128.8, 129.3, 136.9, 138.7, 150.6, 151.5, 166.2. IR (KBr, cm$^{-1}$): 1699 (C=O), 3191 (NH). MS $m/z$ 305 (M + 1). *Anal.* Calcd. for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.16; H, 5.41; N, 18.32.

*6.1.5.19. 5-Phenyl-5,6-dihydroimidazo[1,2-a]pyrimidin-7(8H)-one (**3a**).* M.p. 210–211 °C, yield = 31%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.91 (dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 16.4$ Hz, H-6), 3.12 (dd, 1H, $J_1 = 6.1$ Hz, $J_2 = 16.4$ Hz, H-6), 5.38 (dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 6.1$ Hz, H-7), 6.49 (s, 1H, imidazole–H), 6.76 (s, 1H, imidazole–H), 7.14–7.39 (m, 5H, Ar–H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 39.1, 54.1, 115.4, 126.1, 126.4, 128.6, 129.4, 140.0, 143.0, 167.3. IR (KBr, cm$^{-1}$): 1681 (C=O), 3194 (NH). MS $m/z$ 214 (M + 1). *Anal.* Calcd. for C12H11N3O: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.73; H, 5.26; N, 19.77.

*6.1.5.20. 5-(2-Fluorophenyl)-5,6-dihydroimidazo[1,2-a]pyrimidin-7(8H)-one (**3b**).* M.p. 205–207 °C, yield = 31%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.02 (dd, 1H, $J_1 = 5.7$ Hz, $J_2 = 16.8$ Hz, H-6), 3.21 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 16.8$ Hz, H-6), 5.66 (dd, 1H, $J_1 = 5.7$ Hz, $J_2 = 6.6$ Hz, H-7), 6.53 (s, 1H, imidazole–H), 6.84–7.16 (m, 3H, Ar–H), 7.26 (s, 1H, imidazole–H), 7.32–7.37 (m, 1H, Ar–H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 37.5, 49.1, 115.4, 116.5 (d, $J_{C-F} = 84.0$ Hz), 125.5, 126.4, 127.1 (d, $J_{C-F} = 54.0$ Hz), 131.0 (d, $J_{C-F} = 33.0$ Hz), 143.2, 158.0, 161.2, 166.9. IR (KBr, cm$^{-1}$): 1688 (C=O), 3197 (NH). MS $m/z$ 232 (M + 1). *Anal.* Calcd. for $C_{12}H_{10}FN_3O$: C, 62.33; H, 4.36; N, 18.17. Found: C, 62.51; H, 4.43; N, 18.08.

*6.1.5.21. 5-(2-Chlorophenyl)-5,6-dihydroimidazo[1,2-a]pyrimidin-7(8H)-one (**3c**).* M.p. 233–234 °C, yield = 28%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.01 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 16.7$ Hz, H-6), 3.26 (dd, 1H, $J_1 = 6.9$ Hz, $J_2 = 16.7$ Hz, H-6), 5.80 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 6.9$ Hz, H-7), 6.55 (s, 1H, imidazole–H), 6.75 (d, 1H, $J = 7.5$ Hz, Ar–H), 6.96 (s, 1H, imidazole-H), 7.23–7.47 (m, 3H, Ar–H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 37.1, 51.8, 115.6, 126.5, 126.7, 128.5, 130.5, 130.7, 131.5, 137.1, 143.2, 166.6. IR (KBr, cm$^{-1}$): 1688 (C=O), 3197 (NH). MS $m/z$ 248 (M + 1). *Anal.* Calcd. for $C_{12}H_{10}FN_3O$: C, 62.33; H, 4.36; N, 18.17. Found: C, 62.51; H, 4.43; N, 18.08.

*6.1.5.22. 5-(2-Bromophenyl)-5,6-dihydroimidazo[1,2-a]pyrimidin-7(8H)-one (**3d**).* M.p. 238–239 °C, yield = 35%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.02 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 16.7$ Hz, H-6), 3.26 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 16.7$ Hz, H-6), 5.80 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 7.0$ Hz, H-7), 6.54 (s, 1H, imidazole–H), 6.76 (d, 1H, $J = 7.6$ Hz, Ar–H), 6.95 (s, 1H, imidazole–H), 7.20–7.33 (m, 2H, Ar–H), 7.64 (d, 1H, $J = 7.6$ Hz, Ar–H), 11.31 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 37.3, 54.0, 115.6, 121.8, 126.6, 126.8, 129.0, 130.8, 134.0, 138.6, 143.3, 166.5. IR (KBr, cm$^{-1}$): 1684 (C=O), 3187 (NH). MS $m/z$ 292 (M + 1). *Anal.* Calcd. for $C_{12}H_{10}BrN_3O$: C, 49.34; H, 3.45; N, 14.38. Found: C, 49.52; H, 3.53; N, 14.44.

*6.1.5.23. 7-Phenyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-5(4H)-one (**4a**).* M.p. 187–189 °C, yield = 37%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.05 (dd, 1H, $J_1 = 3.8$ Hz, $J_2 = 16.5$ Hz, H-6), 3.35 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 16.5$ Hz, H-6), 5.67 (dd, 1H, $J_1 = 3.8$ Hz, $J_2 = 7.0$ Hz, H-7), 5.76 (d, 1H, $J = 1.6$ Hz, pyrazole–H), 7.45 (d, 1H, $J = 1.6$ Hz, pyrazole–H), 7.01–7.34 (m, 5H, Ar–H), 9.35 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 40.8, 57.2, 89.8, 126.0, 128.3, 129.2, 139.9, 140.1, 140.6, 166.2. IR (KBr, cm$^{-1}$): 1695 (C=O), 3182 (NH). MS $m/z$ 214 (M + 1). *Anal.* Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.76; H, 5.25; N, 19.85.

*6.1.5.24. 7-(2-Fluorophenyl)-6,7-dihydropyrazolo[1,5-a]pyrimidin-5(4H)-one (**4b**).* M.p. 157–159 °C, yield = 39%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.07 (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 16.8$ Hz, H-6), 3.35 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 16.8$ Hz, H-6), 5.79 (d, 1H, $J = 1.5$ Hz, pyrazole–H), 5.95 (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 7.2$ Hz, H-7), 6.46–7.30 (m, 4H, Ar–H), 7.46 (d, 1H, $J = 1.5$ Hz, pyrazole–H), 9.10 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 37.6, 52.5, 89.8, 116.4 (d, $J_{C-F} = 84.0$ Hz), 125.3, 127.2, 127.5, 131.7 (d, $J_{C-F} = 33.0$ Hz), 140.4 (d, $J_{C-F} = 51.0$ Hz), 157.9, 161.1, 165.8. IR (KBr, cm$^{-1}$): 1690 (C=O), 3201 (NH). MS $m/z$ 232 (M + 1). *Anal.* Calcd. for $C_{12}H_{10}FN_3O$: C, 62.33; H, 4.36; N, 18.17. Found: C, 62.51; H, 4.42; N, 18.07.

*6.1.5.25. 7-(2-Chlorophenyl)-6,7-dihydropyrazolo[1,5-a]pyrimidin-5(4H)-one (**4c**).* M.p. 188–189 °C, yield = 34%. $^1$H NMR ($CDCl_3$,

300 MHz) δ 3.09 (dd, 1H, $J_1 = 2.7$ Hz, $J_2 = 16.8$ Hz, H-6), 3.38 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 16.8$ Hz, H-6), 5.80 (d, 1H, $J = 1.8$ Hz, pyrazole–H), 6.06 (dd, 1H, $J_1 = 2.7$ Hz, $J_2 = 7.5$ Hz, H-7), 6.36–7.43 (m, 4H, Ar–H), 7.47 (d, 1H, $J = 1.8$ Hz, pyrazole–H), 9.17 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$) δ 37.2, 55.2, 89.9, 126.8, 128.3, 130.4, 130.6, 131.2, 137.4, 140.6, 140.8, 165.5. IR (KBr, cm$^{-1}$): 1694 (C=O), 3209 (NH). MS *m*/*z* 248 (M + 1). *Anal*. Calcd. for $C_{12}H_{10}ClN_3O$: C, 58.19; H, 4.07; N, 16.97. Found: C, 58.31; H, 4.01; N, 16.85.

*6.1.5.26. 7-(2-Bromophenyl)-6,7-dihydropyrazolo[1,5-a]pyrimidin-5(4H)-one (**4d**).* M.p. 197–198 °C, yield = 33%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.12 (dd, 1H, $J_1 = 2.2$ Hz, $J_2 = 16.8$ Hz, H-6), 3.38 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 16.8$ Hz, H-6), 5.81 (d, 1H, $J = 1.8$ Hz, pyrazole–H), 6.04 (dd, 1H, $J_1 = 2.2$ Hz, $J_2 = 7.7$ Hz, H-7), 6.37 (d, 1H, $J = 5.5$ Hz, Ar–H), 7.16–7.26 (m, 2H, Ar–H), 7.48 (d, 1H, $J = 1.8$ Hz, pyrazole–H), 7.60 (d, 1H, $J = 7.1$ Hz, Ar–H), 9.65 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$) δ 37.4, 57.4, 89.9, 121.4, 126.8, 128.9, 130.6, 133.9, 138.9, 140.6, 140.8, 165.5. IR (KBr, cm$^{-1}$): 1698 (C=O), 3205 (NH). MS *m*/*z* 292 (M + 1). *Anal*. Calcd. for $C_{12}H_{10}BrN_3O$: C, 49.34; H, 3.45; N, 14.38. Found: C, 49.52; H, 3.56; N, 14.27.

*6.1.5.27. 7-Phenyl-7,8-dihydrophenyl[d]imidazo[1,2-a]pyrimidin-9(10H)-one (**5a**).* M.p. 282–283 °C, yield = 47%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.01 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 16.4$ Hz, H-6), 3.42 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 16.4$ Hz, H-6), 5.80 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 7.1$ Hz, H-7), 5.76 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 7.1$ Hz, H-7), 6.88–7.53 (m, 9H, Ar–H). $^{13}$C NMR (DMSO-$d_6$) δ 39.0, 52.4, 109.9, 118.0, 121.4, 122.2, 126.1, 128.7, 129.5, 132.8, 139.7, 142.4, 148.5, 167.7. IR (KBr, cm$^{-1}$): 1680 (C=O), 3190 (NH). MS *m*/*z* 264 (M + 1). *Anal*. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.15; H, 4.89; N, 15.87.

*6.1.5.28. 7-(2-Fluorophenyl)-7,8-dihydroimidazo[1,2-a]pyrimidin-9(10H)-one (**5b**).* M.p. 269–270 °C, yield = 45%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.17 (dd, 1H, $J_1 = 2.8$ Hz, $J_2 = 16.9$ Hz, H-6), 3.42 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 16.9$ Hz, H-6), 5.80 (dd, 1H, $J_1 = 2.8$ Hz, $J_2 = 7.6$ Hz, H-7), 6.00 (dd, 1H, $J_1 = 2.8$ Hz, $J_2 = 7.6$ Hz, H-7), 6.70–7.79 (m, 8H, Ar–H). $^{13}$C NMR (DMSO-$d_6$) δ 37.3, 55.4, 109.7, 116.7 (d, $J_{C-F} = 84.0$ Hz), 118.0, 121.5, 122.3, 125.6, 126.4 (d, $J_{C-F} = 54.0$ Hz), 127.4, 131.1 (d, $J_{C-F} = 33.0$ Hz), 132.5, 142.4, 158.2, 161.5, 167.3. IR (KBr, cm$^{-1}$): 1681 (C=O), 3194 (NH). MS *m*/*z* 282 (M + 1). *Anal*. Calcd. for $C_{16}H_{12}FN_3O$: C, 68.32; H, 4.30; N, 14.94. Found: C, 68.48; H, 4.41; N, 14.83.

*6.1.5.29. 7-(2-Chlorophenyl)-7,8-dihydroimidazo[1,2-a]pyrimidin-9(10H)-one (**5c**).* M.p. 272–273 °C, yield = 44%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.17 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 16.8$ Hz, H-6), 3.42 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 16.8$ Hz, H-6), 5.80 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 3.0$ Hz, H-7), 6.11 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 3.0$ Hz, H-7), 6.64–7.87 (m, 8H, Ar–H). $^{13}$C NMR (DMSO-$d_6$) δ 37.0, 50.2, 109.6, 118.1, 121.6, 122.4, 126.6, 128.6, 130.7, 130.9, 131.7, 132.4, 136.4, 142.4, 148.7, 167.0. IR (KBr, cm$^{-1}$): 1682 (C=O), 3193 (NH). MS *m*/*z* 298 (M + 1). *Anal*. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; N, 14.11. Found: C, 64.61; H, 4.13; N, 14.21.

*6.1.5.30. 7-(2-Bromophenyl)-7,8-dihydroimidazo[1,2-a]pyrimidin-9(10H)-one (**5d**).* M.p. 280–281 °C, yield = 41%. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.17 (dd, 1H, $J_1 = 2.7$ Hz, $J_2 = 16.8$ Hz, H-6), 3.47 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 16.8$ Hz, H-6), 5.80 (dd, 1H, $J_1 = 2.7$ Hz, $J_2 = 7.9$ Hz, H-7), 6.09 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 3.0$ Hz, H-7), 6.68–7.85 (m, 8H, Ar–H), 13.27 (s, 1H, N–H). $^{13}$C NMR (DMSO-$d_6$) δ 37.1, 52.4, 109.6, 118.1, 121.7, 121.9, 122.5, 126.7, 129.2, 131.0, 132.3, 134.2, 137.9, 142.4, 148.7, 167.0. IR (KBr, cm$^{-1}$): 1688 (C=O), 3195 (NH). MS *m*/*z* 342 (M + 1). *Anal*. Calcd. for $C_{16}H_{12}BrN_3O$: C, 56.16; H, 3.53; N, 12.28. Found: C, 56.28; H, 3.44; N, 12.17.

### 6.2. Pharmacology

#### 6.2.1. Anticonvulsant effects in the maximal electroshock seizure (MES) test [27,28]

The MES test was carried out by the methods described in the ADD of the National Institutes of Health (USA) [18,19]. Seizures were elicited with a 60 Hz alternating current of 50 mA intensity in mice. 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 the tonic maximal extension of the hind leg. At 0.5 h and 4 h after the administration of the compounds, the activities were evaluated in MES test. In phase-I screening, each compound was administered at the dose levels of 30, 100, and 300 mg/kg for evaluating the preliminary anticonvulsant activity. For determination of the median effective dose ($ED_{50}$) the median toxic dose ($TD_{50}$), the phase-II screening was prepared. Groups of 10 mice were given a range of intraperitoneal doses of the tested compound until at least three points were established in the range of 10–90% seizure protection or minimal observed neurotoxicity. From the plot of this data, the respective $ED_{50}$ and $TD_{50}$ values, 95% confidence intervals, slope of the regression line, and the standard error of the slope were calculated by means of a computer program written at National Institute of Neurological Disorders and Stroke [18,19].

#### 6.2.2. Neurotoxicity (NT) screening [18,19]

The neurotoxicity of the compounds was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod of diameter 3.2 cm that rotates at 10 rpm. Trained animals were given i.p. injection of the test compounds. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the trials.

#### 6.2.3. sc-PTZ-induced seizures [18,19]

At 0.5 h after the administration of the test compound, 85 mg/kg PTZ dissolved in saline was administered sc. The animals (10 mice in one group) placed in individual cages and observed for 0.5 h. The numbers of clonic seizure (range from exaggerated twitches of the limbs to violent shaking or vibrating of the stiffened extremities) and tonic seizure (the extremities pull towards the body or rigidly push away from it, usually maximal extension of the hind leg) as well as the number of deaths were noted.

#### 6.2.4. Isoniazid-induced seizures test [29]

At 0.5 h after the administration of the test compound, the animals (10 mice in one group) were given in i.p. at dose of ISO (250 mg/kg), a dose at which 100% of the animals showed convulsive reactions. The mice were placed in individual cages and observed for 1 h. The numbers of clonic and tonic seizures as well as the number of deaths were noted.

#### 6.2.5. 3-MP induced seizures test [30]

At 0.5 h after the administration of the test compound, 60 mg/kg of 3-MP in saline solution was injected sc to mice (10 mice in one group). The mice were placed in individual cages and observed for 0.5 h. The numbers of clonic and tonic seizures as well as the number of deaths were noted.

#### 6.2.6. Thiosemicarbazide-induced seizures test [31]

At 0.5 h after the administration of the test compound, the animals (10 mice in one group) were given an i.p. dose of TSC (50 mg/kg). The mice were placed in individual cages and observed for 2.5 h. The number of clonic seizures, tonic seizures, and the lethality were recorded.

*6.2.7. Bicuculline-induced seizures test [29]*

At 0.5 h after the administration of compounds, the animals (10 mice in one group) were given a subcutaneous dose of 5.4 mg/kg for Bicuculline (within 15–45 min after preparation due to instability). 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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