Molecular Diversity
https://doi.org/10.1007/s11030-019-09940-9

ORIGINAL ARTICLE

Novel fused 1,2,3-triazolo-benzodiazepine derivatives as potent anticonvulsant agents: design, synthesis, in vivo, and in silico evaluations

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Received: 29 January 2019 / Accepted: 13 March 2019

Abstract

A novel series of 1,2,3-triazolo-benzodiazepine derivatives **6a–o** has been synthesized and evaluated in vivo for their anticonvulsant activities using by pentylenetetrazole (PTZ)- and maximal electroshock (MES)-induced seizures in mice. The synthetic approach started with diazotizing 2-aminobenzoic acids **1** to produce 2-azidobenzoic acids **2**. Next, reaction of the latter compounds with propargylamine **3**, benzaldehyde **4**, and isocyanides **5** led to the formation of the title compounds **6a–o,** in good yields. All the synthesized compounds exhibited high anticonvulsant activity in the PTZ test, comparable to or better than the standard drug diazepam. Among the tested compounds, *N*-(tert-butyl)-2-(9-chloro-6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(3-bromophenyl)acetamide **6h** was the most potent compound in this assay. Moreover, compounds **6i** and **6k** showed excellent activity in MES test. Loss of the anticonvulsant effect of compound **6h** in the presence of flumazenil in the PTZ test and appropriate interaction of this compound in the active site of benzodiazepine (BZD)-binding site of $GABA_A$ receptor confirm involvement of BZD receptors in the anticonvulsant activity of compound **6h**.

Graphical abstract

A novel series of 1,2,3-triazolo-benzodiazepine derivatives **6a–o** have been synthesized and evaluated in vivo for their anticonvulsant activities using by pentylenetetrazole (PTZ)- and maximal electroshock (MES)-induced seizures in mice. All the synthesized compounds exhibited high anticonvulsant activity, comparable to or better than the standard drug diazepam in

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11030-019-09940-9) contains supplementary material, which is available to authorized users.

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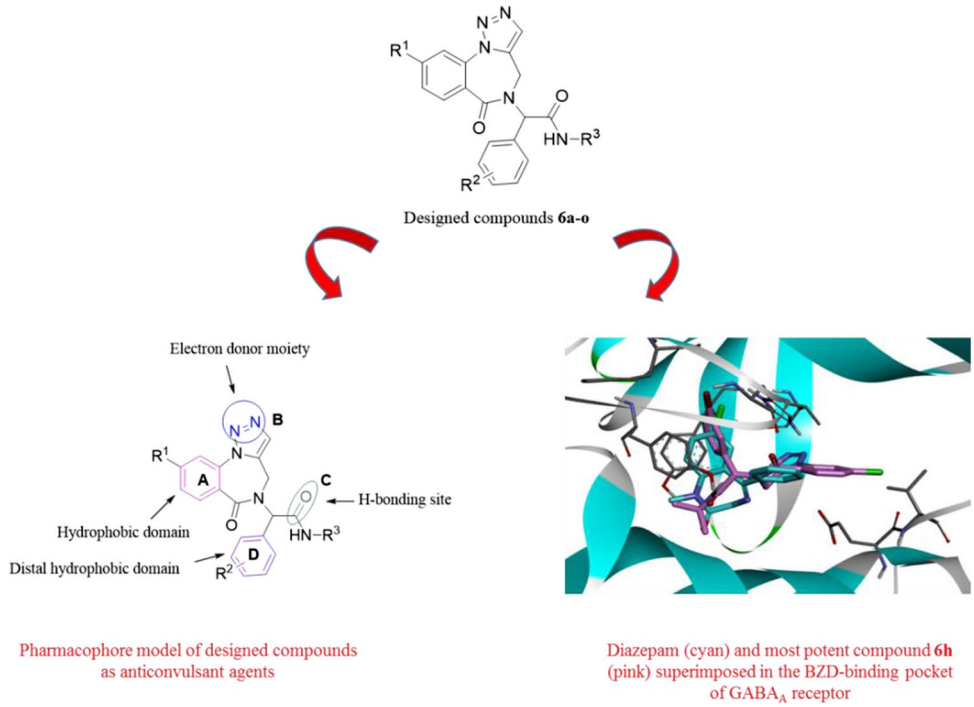
Published online: 20 March 2019

the PTZ test and compounds **6i** and **6k** showed excellent activity in MES test. Flumazenil test and in silico docking study confirm involvement of benzodiazepine receptors in the anticonvulsant activity of these compounds.



Keywords Anticonvulsant · Seizure · 1,2,3-Triazolo-benzodiazepine · Docking study

Introduction

After cerebrovascular disease and dementia, epilepsy is the third most frequent neurological disorder affecting approximately 50 million people worldwide [1]. This disease is caused by the abnormal discharge of cerebral neurons and is associated with the periodic and unpredictable occurrence of seizures. Several antiepileptic drugs such as phenobarbital, sodium valproate, carbamazepine, phenytoin, and diazepam are available but they fail to control seizures in about 30% of epileptic patients [2]. In addition, some of these drugs display several severe side effects [3]. Thus, there is continuing demand to discover and develop new effective and safe anticonvulsant agents.

Benzodiazepines (BZDs) such as diazepam (Valium), lorazepam (Ativan), clonazepam (Klonopin) and alprazolam (Xanax) are a popular class of drugs that are used to treat anxiety, insomnia, agitation, and seizures [4]. BZDs enhance the effect of the neurotransmitter GABA through agonist binding to a specific domain of $GABA_A$ receptor known as BZD pocket [5]. With minor changes in structures of BZDs, agents with the mentioned therapeutic effects and or different biologically active compounds with novel applications can be achieved. For example, alprazolam and estazolam are two effective derivatives of BZDs with 1,2,4-triazole-benzodiazepine scaffold [6]. Biagia et al. in 1996 reported that derivatives of 1,2,3-triazole fused to benzodiazepine acted as potent agonists for BZD receptor (Fig. 1, **A**) [7]. Fused 1,2,3-triazolo-benzodiazepine derivatives such as compounds **B** and **C** were also introduced that acted as antitumor and serine protease inhibitor agents, respectively (Fig. 1) [8, 9]. Due to the importance of BZD derivatives, diverse routes have been reported for the synthesis of these compounds [10–13].

In this work, taking into account the anticonvulsant structures **D** and **E**, a novel series of fused 1,2,3-triazolo-benzodiazepine derivatives **6a–o** were designed using a hybrid approach to achieve new scaffolds as potent anticonvulsant drugs (Fig. 1) [14]. Figure 2 shows the pharmacophore model of designed compounds for anticonvulsant activity [15]. Fused 1,2,3-triazolo-benzodiazepines **6a–o** were tested for their in vivo anticonvulsant activity. Furthermore, to evaluate the mechanism action of these compounds as BZD receptor agonists, flumazenil test and in silico molecular docking studies were also performed.

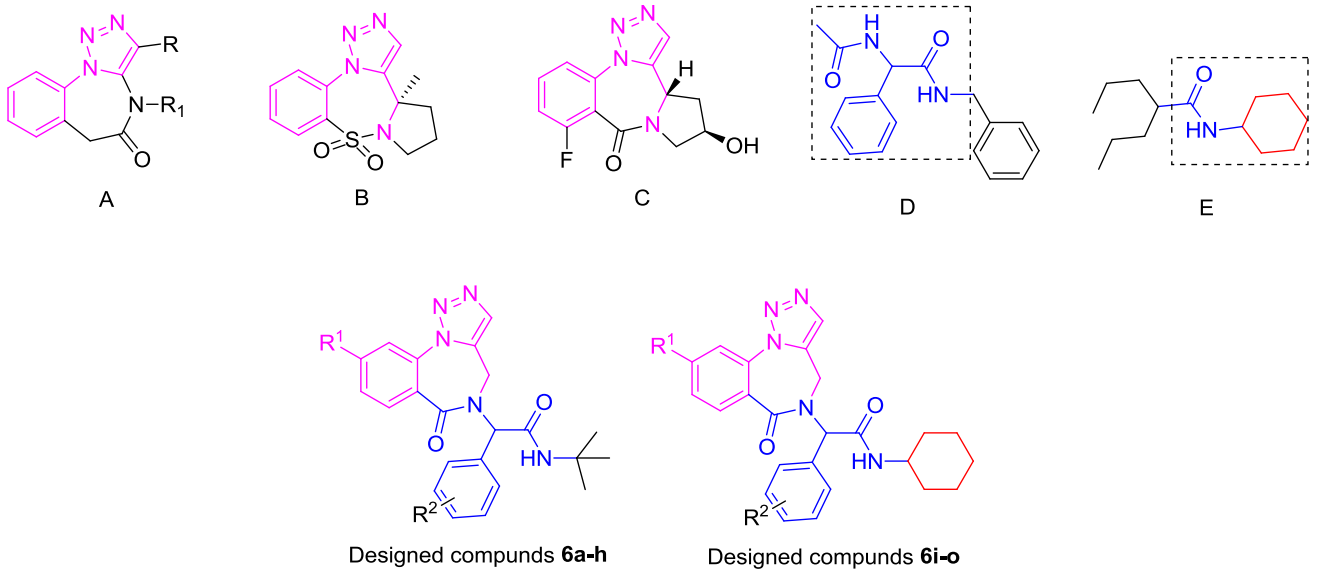
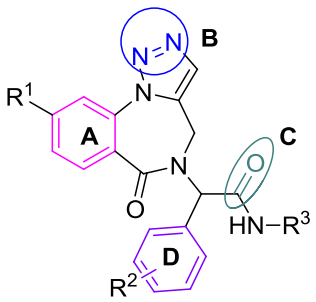


Fig. 1 Chemical structures of biological active compounds with 1,2,3-triazolo-benzodiazepine scaffold **A**, **B**, and **C**, anticonvulsant compounds **D** and **B**, and designed compounds **6a–o** as new anticonvulsant agents

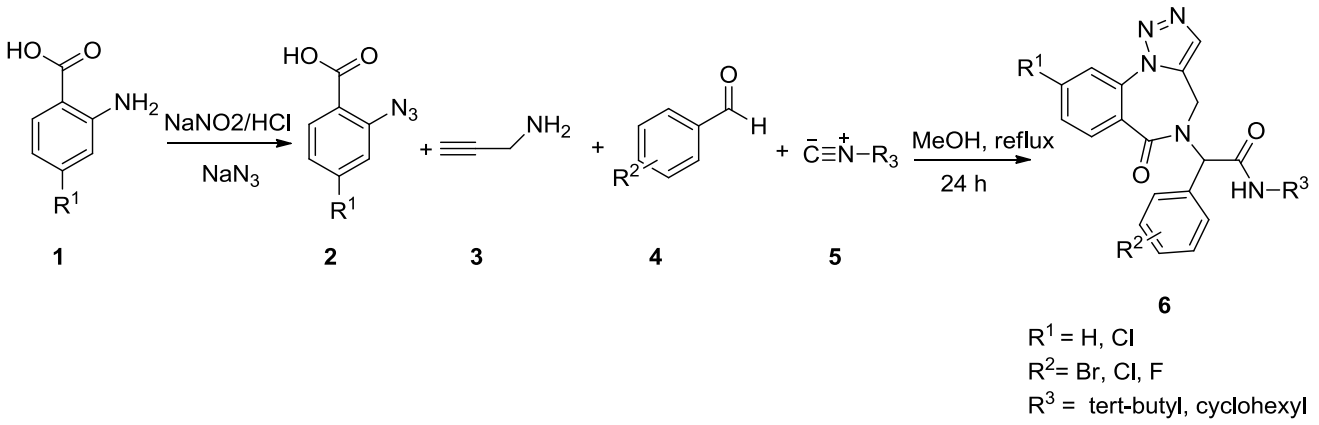


Designed compounds **6a-o**

Fig. 2 Pharmacophore model of designed compounds **6a–o** for anticonvulsant activity. **A** hydrophobic domain, **B** electron donor moiety, **C** H-bonding site, **D** distal hydrophobic domain

Chemistry

Scheme 1 shows the synthetic route for the synthesis of fused triazolo-benzodiazepines. In the first step, 2-azidobenzoic acids **2** were obtained from azidation of 2-aminobenzoic acids **1** in the presence of $NaNO_2$, HCl, and NaN_3. Next, 2-Azidobenzoic acids **2** reacted with propargylamine **3**, benzaldehyde **4**, and isocyanide **5** in methanol at reflux to give desired triazolo-benzodiazepines **6a–o** in good yields (65–79%).



Scheme 1 Synthesis of 1,2,3-triazolo-benzodiazepine derivatives **6a–o**

Pharmacology

Anticonvulsant activity

Anticonvulsant activity against PTZ-induced seizures

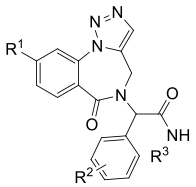
Percentage of clonic seizure threshold in the PTZ test of target compounds revealed that all of these compounds had excellent anticonvulsant activity, comparable or more than the standard drug diazepam (Table 1). Among 1,2,3-triazolo-benzodiazepines **6a**–**o**, compounds **6g**, **6h**, **6n**, and **6o** were the most potent compounds with activity more than diazepam.

Synthesized derivatives **6a**–**o**, structurally, can be divided to two series: tert-butyl derivatives **6a**–**h** and cyclohexyl derivatives **6i**–**o**.

Compound **6a** with 4-fluoro substituent on pendant phenyl group is the weakest derivative among synthesized compounds. The presence of a chlorine atom on pendant phenyl ring, especially in 2-position, led to a significant increase in activity as observed in compounds **6b** and **6c**. On the other hand, adding a second chlorine atom to 3-position of pendant phenyl group in 2-chloro derivative **6b**, as in compound **6d**, decreased anticonvulsant activity. Moreover, 3 or 4-bromo derivatives **6e** and **6f** showed activity similar to 4-chloro derivative **6c.** Introduction of 9-chloro substituent on benzodiazepine moiety improve anticonvulsant potency in tert-butyl derivatives. In this regard, the comparison of percentage of clonic seizure threshold of 9-chloro derivatives **6g** and **6h** with their analogs **6a** and **6e** revealed that the chlorine atom had an important role in the anticonvulsant activities obtained.

In the cyclohexyl series, the 9-unsubstituented derivatives **6i**–**m** showed approximately the same anticonvulsant activity (Table 1). In this series, similar to tert-butyl series, the most potent compounds were derivatives with 9-chloro substituent on benzodiazepine moiety (**6n** and **6o**). A comparison of anticonvulsant activity of tert-butyl derivatives with their corresponding cyclohexyl analogs revealed that cyclohexyl analogs except **6i** and **6l** were as active as their tert-butyl analogs. In the case of compounds **6i** and **6l**, the anticonvulsant activity of these cyclohexyl derivatives was more than their tert-butyl analogs **6a** and **6d**, respectively.

Table 1 Anticonvulsant activities of compounds **6a**–**o** in PTZ test



Compound	R^1	R^2	R^3	Dose[a] (mg/kg)	Clonic seizure threshold (%)
6a	H	4-F	Tert-butyl	0.145	44.32
6b	H	2-Cl	Tert-butyl	0.148	51.68
6c	H	4-Cl	Tert-butyl	0.148	49.37
6d	H	2,3-Dichloro	Tert-butyl	0.161	45.27
6e	H	3-Br	Tert-butyl	0.165	48.19
6f	H	4-Br	Tert-butyl	0.165	48.11
6g	Cl	4-F	Tert-butyl	0.155	54.60*
6h	Cl	3-Br	Tert-butyl	0.175	56.94**
6i	H	4-F	Cyclohexyl	0.152	48.23
6j	H	2-Cl	Cyclohexyl	0.158	51.68*
6k	H	4-Cl	Cyclohexyl	0.158	50.43
6l	H	2,3-Dichloro	Cyclohexyl	0.170	49.15
6m	H	3-Br	Cyclohexyl	0.175	48.64
6n	Cl	4-F	Cyclohexyl	0.165	54.60
6o	Cl	4-Br	Cyclohexyl	0.185	55.02**
Diazepam	–	–	–	0.1	53.87

*$P < 0.05$; **$P < 0.01$ compared to vehicle group

[a]Synthesized compounds and standard drug diazepam were used in an equimolar dose

Table 2 Anticonvulsant activities of compounds **6a–o** in MES test

Compound	Dose (mg/kg)[a]	Tonic seizure protection (%)
Vehicle	–	12.5
6a	0.725	75*
6b	0.74	75*
6c	0.74	62.5*
6d	0.805	75*
6e	0.805	25
6f	0.825	25
6g	0.775	62.5*
6h	0.875	62.5*
6i	0.76	87.5**
6j	0.79	50
6k	0.79	100***
6l	0.85	25
6m	0.875	75*
6n	0.825	75*
6o	0.925	75*
Diazepam	0.5	87.5**

[a]Synthesized compounds and standard drug diazepam were used in an equimolar dose

*$P<0.05$; **$P<0.01$; ***$P<0.001$ compared to vehicle group

Anticonvulsant activity against MES-induced seizures

The target compounds **6a–o** were also screened for their anticonvulsant activities against maximal electroshock (MES)-induced seizure in mice [17]. Among the synthesized compounds, cyclohexyl derivative **6k** showed 100% protection against MES-induced seizure while diazepam (standard drug) showed 87.5% protection in this assay (Table 2). Moreover, compound **6i** showed protection equal with diazepam. Other synthesized compounds exhibited less protective percentage of diazepam in the MES-induced seizure assay.

Table 3 Neurotoxicity evaluation of promising compounds **6h** and **6k**

Compound	Dose (mg/kg)[a]	Rotarod test	
		No. of animals fall/ no. of animals tested	Muscle incoordination (%)
6h	0.875	2/4	50
6k	0.79	3/4	75
Diazepam	0.5	4/4	100

[a]Synthesized compounds and diazepam were used in an equimolar dose

In vivo neurotoxicity

Compounds **6h** and **6k** as most potent compounds, respectively, in PTZ and maximal electroshock (MES) tests were screened for their neurotoxicity in mice by using rotarod test [18]. Rotarod test is used widely to evaluate neurotoxicity of new anticonvulsant agents in mice. As shown in Table 3, these compounds showed neurological deficits less than diazepam.

Study on mechanism of action

To study the mechanism of action, effect of flumazenil as an antagonist of BZD receptor on anticonvulsant activity of compound **6h** was evaluated. In this assay, flumazenil antagonized anticonvulsant activity of the most potent compound **6h** in the PTZ test. This finding confirms that title compounds can act as agonists for BZD receptors.

Docking study

To study the interaction mode of the title compounds in the BZD-binding pocket of $GABA_A$ receptor (α1β2 γ2), a docking study was performed using Auto Dock Tools (version 1.5.6) [19]. The superposed structure of diazepam and the most potent compound **6h** in the binding pocket is shown in Fig. 3. The detailed binding mode of diazepam showed that benzodiazepine moiety interacted with α1 Tyr159 (π–π) and α1 Tyr 209 (π–π), and α1 Thr206 (hydrogen bond) (Fig. 4a). Pendant phenyl group of this compound formed a π–π and a π–anion interactions with γ2 Phe77 and α1 His101. Furthermore, a weak hydrophobic interaction between chlorine atom and α1 Val211 was also observed.

The most active compound **6h** established π interactions with γ2Glu189 and α1 His101 through benzodiazepine and

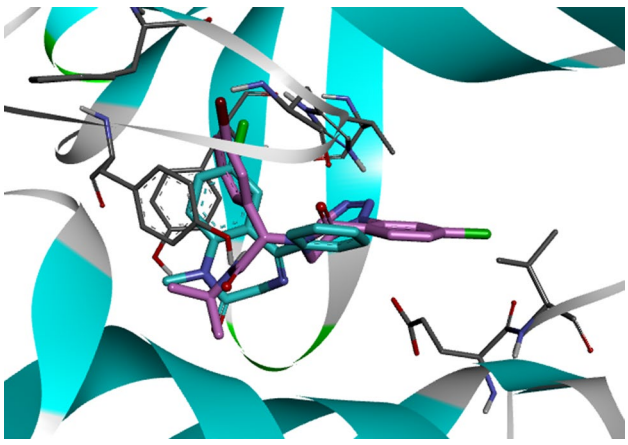


Fig. 3 Diazepam (cyan) and most potent compound **6h** (pink) superimposed in the BZD-binding pocket of $GABA_A$ receptor (α1β2 γ2)

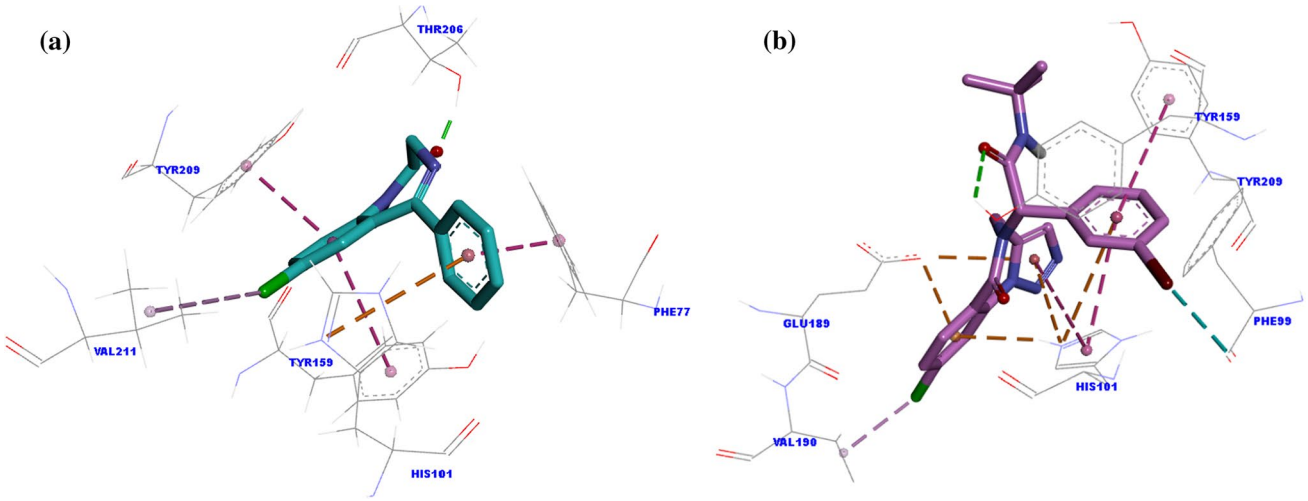


Fig. 4 **a** The binding modes of diazepam and **b** compound **6h** in the BZD-binding pocket of $GABA_A$ receptor (α1β2 γ2)

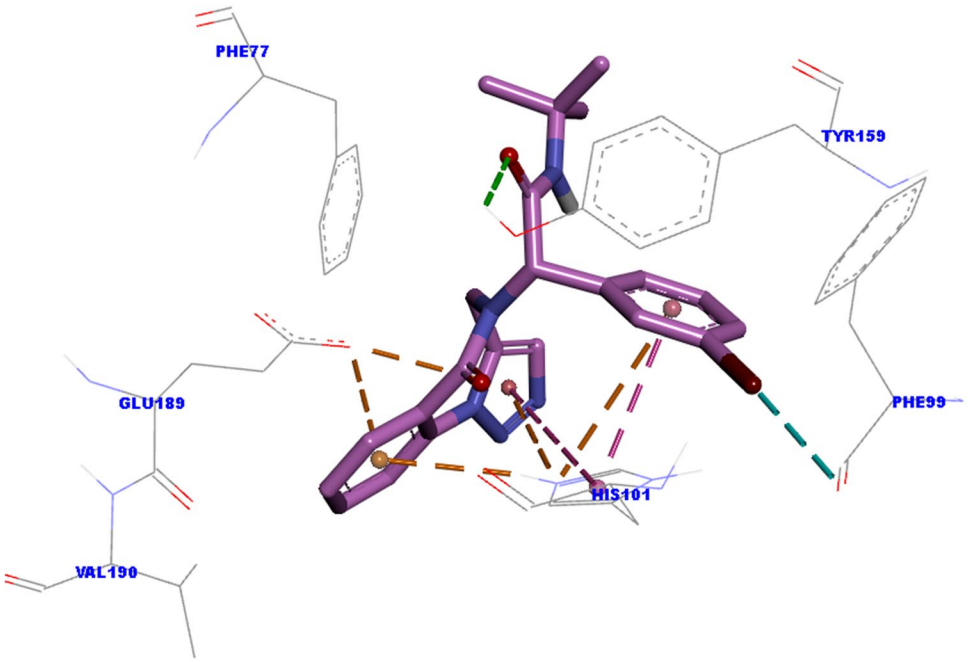


Fig. 5 The binding mode of compound **6e** in the BZD-binding pocket of $GABA_A$ receptor (α1β2 γ2)

1,2,3-triazole moieties (Fig. 4b). A hydrogen bond between carbonyl unit attached to *N*-tert-butyl moiety and α1 Tyr159 was formed. Several π interactions were also observed between pendant phenyl ring of compound **6h** and BZD-binding pocket residues α1 His101 and α1 Tyr 209. 3-Bromo of pendant phenyl group and 9-chloro of benzodiazepine moiety of this compound, interacted with α1 Phe99 and γ2 Val190, respectively.

The comparison of interaction modes of the most potent compound **6h** (Fig. 4b) with it 9-unsubstituented analog **6e** (Fig. 5) showed that compound **6h** interacted with six residues—γ2Glu189, α1 His101, α1 Tyr159, α1 Tyr 209, α1 Phe99, and γ2 Val190—while compound **6e** displayed interactions with four residues—γ2Glu189, α1 His101, α1 Tyr159, and α1 Phe99—in the BZD-binding pocket. It appears that the difference in the anticonvulsant activity of these two compounds can be reasonably explained by two additional interactions of compound **6h** with BZD-binding pocket (α1 Tyr 209 and γ2 Val190) in comparison with compound **6e**.

Conclusion

In conclusion, we presented design, synthesis, in vivo anticonvulsant activity of a novel series of 1,2,3-triazolo-benzodiazepine derivatives **6a**–**n**. All synthesized compounds **6a**–**o** showed high anticonvulsant activity in the PTZ test, comparable to or more than diazepam as the standard drug. Among synthesized compounds, the 9-chloro-benzodiazepin derivatives **6g**, **6h**, **6n**, and **6o** displayed more potent activity than diazepam in the PTZ test. Among the synthesized compounds, compounds **6k** and **6i** were most potent compounds in MES test. The promising compounds **6h** and **6k** showed neurological deficits less than diazepam in the rotarod test. The experimental investigation of action of mechanism compound **6h** by flumazenil and docking study of this compound showed this compound can act as BZD receptor agonist.

Experimental

Chemistry

Melting points of target compounds **6a**–**o** were measured by a Kofler hot stage apparatus and are uncorrected. A Bruker FT-500 spectrometer was used to record ^{1}H and ^{13}C NMR spectra, using CDCl3 as a solvent and TMS as an internal standard. The IR spectra were obtained by a Nicolet Magna FTIR 550 spectrometer (in KBr disks). High-resolution mass spectra were determined with an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. All reagents and solvents used in this study were purchased from Aldrich or Merck Company without the requirement of any purification.

General procedure for the synthesis of 2-azidobenzoic acids **2**

A suspension of 2-aminobenzoic acids **1** (21.78 mmol) in water (15 mL) and concentrated hydrochloric acid (5.55 mL) was cooled to − 5 °C. Then, a solution of sodium nitrite (22.8 mmol) dissolved in water (4.5 mL) was prepared and added dropwise to the suspension and the resulting mixture was stirred for 30 min at − 5 °C. The reaction mixture (without diazonium salt isolation) was poured into a solution of sodium azide (24.5 mmol) in water (4.5 mL) and ice (20 g), and a pale yellow precipitate formed immediately. The reaction mixture was set aside overnight. Next, the precipitate was isolated by filtration, washed with water and dried under reduced pressure to provide compounds **2** (yield 93%).

*General procedure for the synthesis of N-(alkyl)-2-(9-chloro-6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(substituted phenyl)acetamide (**6a–o**)* 2-azidobenzoic acids **2** (1 mmol), propargylamine **3** (1 mmol), substituted benzaldehydes **4** (1 mmol), and isocyanides **5** (1 mmol) were refluxed in MeOH (10 mL) for 24 h. Then, the reaction mixture was poured into crushed ice, and the precipitated products were filtered and dried at 60 °C to obtain pure compounds **6a**–**o** (64–79%).

N-(tert-butyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(4-fluorophenyl)acetamide (6a) White solid; yield: 79%, mp 232–235 °C. IR (KBr) (ν_{max}/cm^{-1}): 3302, 3061, 2965, 1673, 1611, 1546.^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.33$ (9H, s), 4.43 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 4.67 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 6.27 (1H, s, CH_{Chiral}), 6.80 (1H, s, $CH_{triazole}$), 7.04 (2H, t, $J = 8.5$ Hz), 7.19–7.32 (2H, m), 7.54 (1H, td, $J = 7.7$, 1.2 Hz), 7.67 (1H, td, $J = 7.8$, 1.6 Hz), 7.94 (1H, d, $J = 8.1$ Hz), 8.08 (1H, dd, $J = 7.9$, 1.5 Hz), 8.13 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 28.58$, 36.53, 28.58, 36.53, 52.11, 59.98, 116.00, 116.17, 122.57, 126.51, 128.84, 130.59, 130.86, 132.74, 133.15, 135.28, 138.05, 161.86, 163.84, 166.87, 167.22 ppm. Anal. Calcd for $C_{22}H_{22}FN_5O_2$ (407.44): C, 64.85; H, 5.44; N, 17.19. Found: C, 64.71; H, 5.63; N, 17.25.

N-(tert-butyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(2-chlorophenyl)acetamide (6b) White solid; yield: 78%, mp 273–275 °C. IR (KBr) (ν_{max}/cm^{-1}): 3305, 3066, 2961, 1675, 1615, 1549. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.36$ (9H, s), 4.42 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 4.64 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 6.40 (1H, s, CH_{Chiral}), 6.91 (1H, s, $CH_{triazole}$), 7.30–7.34 (1H, m), 7.38–7.44 (2H, m), 7.55 (1H, t, $J = 7$ Hz), 7.63–7.71 (2H, m), 7.95(1H, d, $J = 8$ Hz), 8.13 (1H, d, $J = 8$ Hz), 8.24 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 28.58$, 36.89, 52.10, 59.15, 122.59, 126.41, 127.13, 128.73, 130.32, 130.43, 130.56, 132.27, 132.91, 132.97, 133.04, 134.83, 166.09, 166.34 ppm. Anal. Calcd for $C_{22}H_{22}ClN_5O_2$ (423.9): C, 62.34; H, 5.23; N, 16.52. Found: C, 62.51; H, 5.48; N, 16.39.

N-(tert-butyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(4-chlorophenyl)acetamide (6c) White solid; yield: 76%, mp 242–243 °C. IR (KBr) (ν_{max}/cm^{-1}): 3301, 3065, 2959, 1678, 1613, 1544. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.35$ (9H, s), 4.46 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 4.82 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 6.30 (1H, s, CH_{Chiral}), 6.77 (1H, s, $CH_{triazole}$), 7.17–7.30 (2H, m), 7.35 (2H, d, $J = 8.0$ Hz), 7.56 (1H, t, $J = 7.7$ Hz), 7.69 (1H, t, $J = 7.5$, Hz), 7.96(1H, d, $J = 8.1$ Hz), 8.09 (1H, d, $J = 7.9$ Hz), 8.24 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 28.57$, 29.65, 36.59, 47.32, 62.12, 122.59, 126.44, 128.86, 129.24, 130.30, 132.72, 133.20, 135.01, 139.49,

165.78, 166.92 ppm. Anal. Calcd for $C_{22}H_{22}ClN_5O_2$ (423.9): C, 62.34; H, 5.23; N, 16.52. Found: C, 62.47; H, 5.11; N, 16.65.

N-(tert-butyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(2,3-dichlorophenyl)acetamide (6d) White solid; yield: 69%, mp 270–272 °C. IR (KBr) (ν_{max}/cm^{-1}): 3302, 3064, 2959, 1676, 1614, 1547. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.34 (9H, s), 4.42 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 4.78 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 6.45 (1H, s, CH_{Chiral}), 6.97 (1H, s, $CH_{triazole}$), 7.37 (1H, t, J = 7.9 Hz), 7.49–7.63 (3H, m), 7.69 (1H, td, J = 7.8, 1.6 Hz), 7.96 (1H, d, J = 7.5 Hz), 8.11 (1H, d, J = 7.5 Hz), 8.20 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.54, 36.87, 49.20, 59.26, 118.56, 119.07, 121.74, 123.13, 126.40, 128.41, 128.79, 131.28, 132.74, 132.80, 133.18, 136.99, 166.84, 167.59 ppm. Anal. Calcd for $C_{22}H_{21}Cl_2N_5O_2$ (458.34): C, 57.65; H, 4.62; N, 15.28. Found: C, 57.46; H, 4.39; N, 15.09.

N-(tert-butyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(3-bromophenyl)acetamide (6e) White solid; yield: 68%, mp 207–209 °C. IR (KBr) (ν_{max}/cm^{-1}): 3300, 3064, 2967, 1674, 1612, 1544 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.37 (9H, s), 4.27 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 4.78 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 6.30 (1H, s), 6.89 (1H, s), 7.15–7.27 (2H, m), 7.48 (1H, s), 7.54 (1H, d, J = 8 Hz), 7.58 (1H, t, J = 7.7 Hz), 7.71(1H, t, J = 7.5 Hz), 7.99 (1H, d, J = 8.0 Hz), 8.05 (1H, s), 8.12 (1H, d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.59, 36.68, 48.22, 60.06, 118.78, 120.13, 122.61, 123.07, 126.40, 128.86, 130.56, 132.11, 132.74, 132.80, 133.21, 137.03, 166.97, 167.90. EIMS, *m/z* (%): 470 (M^+ ^{81}Br, 9), 468 (M^+ ^{79}Br, 9), 368 (100), 339 (54), 261 (20), 185 (28), 171 (62), 155 (67), 130 (72), 115 (39), 57 (82), 41 (25). Anal. Calcd for $C_{22}H_{22}BrN_5O_2$ (468.35): C, 56.42; H, 4.73; N, 14.95. Found: C, 56.27; H, 4.91; N, 15.12.

N-(tert-butyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(4-bromophenyl)acetamide (6f) White solid; yield: 77%, mp 208–210 °C. IR (KBr) (ν_{max}/cm^{-1}): 3275, 3089, 1683, 2966, 1644, 1564. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.37 (9H, s), 4.14 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 4.73 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 6.26 (1H, s, CH_{Chiral}), 6.75 (1H, s, $CH_{triazole}$), 7.09–7.25 (2H, m), 7.49–7.55 (2H, m), 7.58 (1H, t, J = 7.7 Hz), 7.72(1H, t, J = 7.7 Hz), 7.98 (1H, d, J = 8.1 Hz), 8.12 (1H, d, J = 7.9 Hz), 8.18 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.59, 36.61, 52.18, 60.16, 116.91, 118.02, 122.61, 126.41, 128.90, 130.62, 132.25, 132.75, 133.24, 139.39, 161.32, 166.93 ppm. EIMS, *m/z* (%): 470 (M^+ ^{81}Br, 7), 468 (M^+ ^{79}Br, 7), 368 (100), 339 (51), 260 (11), 186 (22), 171 (69), 155 (41), 130 (53), 115 (27), 89 (18), 57 (53), 41 (19). Anal. Calcd for $C_{22}H_{22}BrN_5O_2$ (468.35): C, 56.42; H, 4.73; N, 14.95. Found: C, 56.22; H, 4.87; N, 15.06.

N-(tert-butyl)-2-(9-chloro-6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(4-fluorophenyl)acetamide (6g) White solid; yield: 67%, mp 298–300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3279, 3085, 1681, 2968, 1647, 1562. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.35 (9H, s), 4.46 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 4.68 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 6.25 (1H, s, CH_{Chiral}), 6.83 (1H, s, $CH_{triazole}$), 7.06 (2H, t, J = 8.5 Hz), 7.22–7.31 (2H, m), 7.51 (1H, dd, J = 8.5, 2.1 Hz), 7.99 (1H, d, J = 2.1 Hz), 8.04 (1H, d, J = 8.5 Hz), 8.20 (1H, s) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.60, 36.44, 52.18, 60.43, 116.07, 116.24, 119.12 122.57, 124.71, 129.08, 133.49, 134.20, 135.08, 139.36, 161.19, 163.16, 166.07, 166.57 ppm. Anal. Calcd for $C_{22}H_{21}ClFN_5O_2$ (441.89): C, 59.80; H, 4.79; N, 15.85. Found: C, 59.69; H, 4.57; N, 16.01.

N-(tert-butyl)-2-(9-chloro-6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(3-bromophenyl)acetamide (6h) White solid; yield: 66%, mp 209–211 °C. IR (KBr) (ν_{max}/cm^{-1}): 3278, 3083, 1682, 2969, 1645, 1564. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.37 (9H, s), 4.45 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 4.73 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 6.25 (1H, s, CH_{Chiral}), 6.90 (1H, s, $CH_{triazole}$), 7.16–7.27 (2H, m), 7.46 (1H, s), 7.51–7.56 (2H, m), 8.01 (1H, d, J = 2.1 Hz), 8.07 (1H, d, J = 8.5 Hz), 8.20 (1H, s)ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.59, 36.60, 52.26, 60.30, 118.96, 122.60, 123.13, 124.61, 127.50, 129.09, 130.60, 131.82, 132.22, 133.52, 134.20, 136.84, 139.43, 166.16, 166.84 ppm. Anal. Calcd for $C_{22}H_{21}BrClN_5O_2$ (502.79): C, 52.55; H, 4.21; N, 13.93. Found: C, 52.61; H, 4.35; N, 14.07.

N-(cyclohexyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(4-fluorophenyl)acetamide (6i) White solid; yield: 76%, mp 249–251 °C. IR (KBr) (ν_{max}/cm^{-1}): 3235, 3073, 2934, 2858, 1637, 1569. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.00–1.99 (10H, m), 3.80 (1H, m), 4.36 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 4.82 (1H, d, J = 15 Hz, $CH_{diastrotopic}$), 6.41 (1H, s, CH_{Chiral}), 6.76 (1H, s, CH_{Chiral}), 6.87 (1H, d, J = 8.0 Hz), 7.05 (2H, t, J = 8.3 Hz), 7.16–7.34 (2H, m), 7.54 (1H, t, J = 7.7 Hz), 7.69(1H, t, J = 7.7 Hz), 7.97(1H, d, J = 8.1 Hz), 8.05(1H, d, J = 7.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.64, 24.66, 25.33, 32.61, 32.77, 36.57, 48.71, 59.65, 115.91, 116.08, 122.57, 126.44, 128.77, 130.56, 132.61, 132.76, 133.14, 135.06, 161.83, 163.77, 166.92, 167.27 ppm. EIMS, *m/z* (%):434 (M^+, 11), 334 (5), 308 (100), 279 (71), 235 (17), 206 (21), 155 (32), 130 (41), 109 (50), 83 (19), 55 (24), 41 (10). Anal. Calcd for $C_{24}H_{24}FN_5O_2$ (433.48): C, 66.50; H, 5.58; N, 16.16. Found: C, 66.31; H, 5.62; N, 16.26.

N-(cyclohexyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(2-chlorophenyl)acetamide (6j) White solid; yield: 75%, mp 240–242 °C. IR (KBr) (ν_{max}/cm^{-1}): 3233, 3075, 2937, 2861, 1636, 1565. ^{1}H NMR ($CDCl_3$,

500 MHz): $\delta = 1.00–2.02$ (10H, m), 3.83 (1H, m), 4.32–4.75 (2H, m, $CH_{2diastrotopic}$), 6.45 (1H, s, CH_{Chiral}), 6.83 (1H, s, $CH_{triazole}$), 7.03 (1H, d, $J = 8$ Hz), 7.29–7.36 (1H, m), 7.37–7.44 (2H, m), 7.56 (1H, td, $J = 7.7$, 1.2 Hz), 7.64 (1H, dd, $J = 7.5$, 2.6 Hz), 7.70(1H, td, $J = 7.8$, 1.6 Hz), 7.96(1H, d, $J = 8$ Hz), 8.12(1H, d, $J = 7.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.62$, 24.67, 25.36, 32.63, 32.70, 48.05, 59.79, 119.55, 121.06, 122.61, 126.43, 127.13, 128.77, 130.41, 130.56, 132.08, 132.91, 133.07, 165.81, 166.33 ppm. Anal. Calcd for $C_{24}H_{24}ClN_5O_2$ (449.93): C, 64.07; H, 5.38; N, 15.57. Found: C, 63.91; H, 5.22; N, 15.73.

N-(cyclohexyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(4-chlorophenyl)acetamide (6k) White solid; yield: 79%, mp 248–250 °C. IR (KBr) (ν_{max}/cm^{-1}): 3234, 3086, 2930, 2857, 1638, 1569. ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.01–2.02$ (10H, m), 3.82 (1H, m), 4.42 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 4.88 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 6.36 (1H, s, CH_{Chiral}), 6.83 (1H, s, $CH_{triazole}$), 7.11 (1H, d, $J = 7.9$ Hz), 7.19–7.30 (2H, m), 7.32–7.43 (2H, m), 7.57 (1H, t, $J = 7.7$ Hz), 7.71(1H, t, $J = 7.7$ Hz), 7.99(1H, d, $J = 8$ Hz), 8.10(1H, d, $J = 8$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.66$, 25.33, 32.63, 32.81, 36.64, 48.76, 59.73, 119.06, 122.62, 126.37, 128.84, 129.23, 130.27, 132.66, 132.78, 133.23, 134.98, 164.64, 166.98 ppm. EIMS, *m/z* (%): 452 ($M^{+\ 37}Cl$, 7), 450 ($M^{+\ 35}Cl$, 25), 350 (9), 324 (100), 295 (67), 155 (43), 125 (59), 98 (12), 83 (18), 55 (21), 41 (16). Anal. Calcd for C24H24ClN5O2 (449.93): C, 64.07; H, 5.38; N, 15.57. Found: C, 64.26; H, 5.45; N, 15.73.

N-(cyclohexyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(2,3-dichlorophenyl)acetamide (6l) White solid; yield: 70%, mp 241–243 °C. IR (KBr) (ν_{max}/cm^{-1}): 3233, 3084, 2931, 2859, 1635, 1566. ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.01–1.94$ (10H, m), 3.80 (1H, m), 4.46 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 4.62 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 6.29 (1H, d, $J = 3$ Hz, CH_{Chiral}), 6.81(1H, s, $CH_{triazole}$), 7.15 (1H, d, $J = 7.9$ Hz) 7.35(1H, t, $J = 7.9$ Hz), 7.50–7.61 (3H, m), 7.70 (1H, t, $J = 7.5$ Hz), 7.97 (1H, d, $J = 8.1$ Hz), 8.08(1H, d, $J = 7.9$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.60$, 24.65, 25.33, 32.53, 32.64, 36.87, 48.89, 59.46, 118.34, 122.68, 126.27, 127.50, 128.50, 128.79, 131.18, 132.77, 132.88, 133.18, 134.45, 134.69, 137.28, 166.47, 167.39 ppm. Anal. Calcd for $C_{24}H_{23}Cl_2N_5O_2$ (484.38): C, 59.51; H, 4.79; N, 14.46. Found: C, 59.33; H, 4.48; N, 14.57.

N-(cyclohexyl)-2-(6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(3-bromophenyl)acetamide (6m) White solid; yield: 67%, mp 211–213 °C. IR (KBr) (ν_{max}/cm^{-1}): 3231, 3084, 2933, 2862, 1632, 1563.^1H NMR ($CDCl_3$, 500 MHz): $\delta = 0.92–2.03$ (10H, m), 3.79 (1H, m), 4.47 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 4.78 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 6.43 (1H, s, CH_{Chiral}), 6.78(1H, s, $CH_{triazole}$), 7.10–7.24 (3H, m),7.45 (1H, s), 7.50 (1H, d, $J = 7.7$ Hz), 7.53(1H, t, $J = 7.7$ Hz), 7.69(1H, t, $J = 7.7$ Hz), 7.96 (1H, d, $J = 8.1$ Hz), 8.02 (1H, d, $J = 7.9$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.65$, 25.34, 32.60, 32.75, 36.74, 48.75, 59.76, 119.95, 122.61, 123.03, 126.34, 127.47, 128.80, 130.52, 131.67, 132.06, 132.65, 132.80, 133.22, 136.99, 162.29, 167.04 ppm. Anal. Calcd for $C_{24}H_{24}BrN_5O_2$ (494.38): C, 58.31; H, 4.89; N, 14.17. Found: C, 58.52; H, 4.78; N, 14.05.

N-(cyclohexyl)-2-(9-chloro-6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(4-fluorophenyl)acetamide (6n) White solid; yield: 69%, mp 239–241 °C. IR (KBr) (ν_{max}/cm^{-1}): 3234, 3085, 2931, 2865, 1633, 1567. ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.02–1.99$ (10H, m), 3.68–3.92 (1H, m), 4.32–4.70 (2H, m, $CH_{2diastrotopic}$), 6.27 (1H, s, CH_{Chiral}), 6.86 (1H, s, $CH_{triazole}$), 7.06 (2H, t, $J = 8.4$ Hz), 7.20–7.25 (2H, m), 7.52 (1H, dd, $J = 8.8$, 2.0 Hz), 7.97–8.02 (1H, m), 8.06 (1H, d, $J = 8.5$ Hz), 8.23 (1H, d, $J = 2.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.67$, 25.34, 32.69, 32.84, 36.56, 48.83, 62.20, 116.05, 116.22, 122.59, 124.66, 129.08, 133.51, 134.08, 134.19, 135.05, 139.40, 160.33, 162.34, 166.10, 167.14 ppm. Anal. Calcd for $C_{24}H_{23}ClFN_5O_2$ (467.92): C, 61.60; H, 4.95; N, 14.97. Found: C, 61.56; H, 4.81; N, 15.06.

N-(cyclohexyl)-2-(9-chloro-6-oxo-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepin-5(6H)-yl)-2-(4-bromophenyl)acetamide (6o) White solid; yield: 65%, mp 277–279 °C. IR (KBr) (ν_{max}/cm^{-1}): 3233, 3081, 2932, 2866, 1637, 1564. ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.00–2.03$ (10H, m), 3.81 (1H, m), 4.25 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 4.90 (1H, d, $J = 15$ Hz, $CH_{diastrotopic}$), 6.29 (1H, s, CH_{Chiral}), 6.76 (1H, d, $J = 3$ Hz), 6.94 (1H, s, $CH_{triazole}$), 7.17 (2H, d, $J = 8.1$ Hz), 7.51–7.54 (3H, m), 8.03–8.06 (2H, m) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.98$, 25.33, 32.68, 32.86, 50.29, 61.08, 122.84, 126.37, 128.62, 128.96, 129.99, 132.32, 132.66, 133.23, 135.08, 139.49, 162.12, 166.69 ppm. Anal. Calcd for $C_{24}H_{23}BrClN_5O_2$ (528.83): C, 54.51; H, 4.38; N, 13.24. Found: C, 54.69; H, 4.55; N, 13.12.

Anticonvulsant activity

Animals and drugs Male mice (Pasteur Institute of Iran) weighing 24–30 g were used as experimental animals. The animals were housed in a temperature-controlled room (22 ± 1 °C) on a 12-h light/dark cycle with free access to water and food for a 24-h period before testing, except during the experiment. Mice were assigned to experimental groups randomly, and each animal was used only once for the experiments. Diazepam (Sigma) was used as a reference drug, and pentylenetetrazole (PTZ, Sigma) was applied to

induce convulsions in mice. PTZ was dissolved in physiological saline solution, and diazepam and synthesized compounds **6a**–**o** were dispersed in carboxymethyl cellulose (CMC, 0.5%) [16].

All procedures were carried out in accordance with the institutional guidelines for animal care and use that are in compliance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978). Ethical approval ID from ethics committee for involving animals in this work is IR.NIMAD.REC.1397.111.

Determination of seizure threshold

The threshold of PTZ-induced seizure was evaluated by infusing PTZ into the tail vein of the animal using 30-gauge butterfly needle, at a constant rate of 1 mL/min. Infusion was stopped when forelimb clonus followed by full clonus was observed in the body. The minimal dose of PTZ (80 mg/kg of animal weight) needed to induce clonic seizure was determined as an index of seizure threshold.

In addition, flumazenil (0.5 mg/kg) was administered 15 min prior to injection of the vehicle, diazepam (0.1 mg/kg) or most potent compound **6h** (0.175 mg/kg). After induction of seizure by PTZ, clonic seizure threshold in mice was evaluated.

Maximal electroshock (MES) induced seizures test

The MES-induced seizure is an electrical test for evaluating anticonvulsant activity [15]. In this assay, MES that induced 100% maximal seizures was found to be 50 mA alternating current of 50 Hz frequency for 1 s, using ECT UNIT (model number 7801, UGO Basile, Varese, Italy) [20]. Equimolar dose of synthesized compounds and standard drug diazepam were injected i.p. 5 min later, mice were restrained by hand and subjected to electric shock (through their ears), and released immediately following electrical stimulation, to permit observation of the maximal seizure [20]. The results were recorded as number of animals protected/number of animals tested.

Rotarod (acute neurotoxicity) test

Male NMRI mice with a weight 20–30 g were used for rotarod test. The selected compounds, diazepam and vehicle were administered i.p ($n=4$); and 30 min after administration, the animals were placed for 30 s on the rotating rod (5 rpm) and the numbers of mice falling during this time were recorded [18].

Docking study

Docking study of the compounds **6h** and **6e** in the BZD-binding pocket of $GABA_A$ receptor (α1β2 γ2) was performed by Auto dock Tools (version 1.5.6), using previously described method [19].

Acknowledgements This work was supported by Grants from the National Institute for Medical Research Development (NIMAD) (Grant Number: 971149).

Compliance with ethical standards

Conflict of interest The authors have declared no conflict of interest.

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