Bioorganic Chemistry 89 (2019) 102989

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Design, synthesis, *in vivo*, and *in silico* evaluation of new coumarin-1,2,4-oxadiazole hybrids as anticonvulsant agents

Maryam Mohammadi-Khanaposhtani[a], Nematollah Ahangar[b], Sepideh Sobhani[c], Patrick Honarchian Masihi[d], Aidin Shakiba[d], Mina Saeedi[e,f], Tahmineh Akbarzadeh[c,f,*]

[a] Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[b] Department of Pharmacology, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[c] Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[d] Student Researches Committee, Ramsar Campus, Mazandaran University of Medical Sciences, Ramsar, Iran
[e] Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[f] Persian Medicine and Pharmacy Research Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Coumarin
1,2,4-Oxadiazole
Molecular hybridization
In silico
In vivo
Coumarin-1 2 4-oxadiazole

ABSTRACT

A novel series of coumarin-1,2,4-oxadiazole hybrids were designed, synthesized, and evaluated as anticonvulsant agents. The title compounds were easily synthesized from reaction of appropriate coumarins and 3-aryl-5-(chloromethyl)-1,2,4-oxadiazole derivatives. *In vivo* anticonvulsant activity of the synthesized compounds were determined using pentylenetetrazole (PTZ)- and maximal electroshock (MES)-induced seizures confirming that they were more effective against MES test than PTZ test. It should be noted that compounds **3b**, **3c**, and **3e** showed the best activity in MES model which possessed drug-like properties with no neurotoxicity. Anticonvulsant activity of the most potent compound **3b** was remarkably reduced after treatment with flumazenil which confirmed the participation of a benzodiazepine mechanism in the anticonvulsant activity. Also, docking study of compound **3b** in the BZD-binding site of $GABA_A$ receptor confirmed possible binding of **3b** to the BZD receptors.

1. Introduction

Epilepsy is the third most frequent neurological disorder after cerebrovascular disease and dementia. It has affected approximately 50 million people of all ages worldwide [1] along with imposing a large economic burden on the societies [2]. The disease can be caused by the abnormal discharge of cerebral neurons [3] and is associated with the periodic and unpredictable occurrence of seizures. Although there are several epileptic drugs such as diazepam, carbamazepine, phenobarbital, sodium valproate, and phenytoin for the treatment of epilepsy, they have failed to control seizures in about 30% of patients [4]. Also, some of anticonvulsant agents have major side effects like somnolence, nausea, gastrointestinal complaints, dizziness, etc. [5]. In this respect, there is a continuing demand to develop new, effective, and safe agents for the treatment of epilepsy.

Coumarins are the privileged scaffolds which have been reported to possess a wide range of biological activities such as antidyslipidemic, antibacterial, antitumor, and anticoagulant [6–9]. Moreover, various coumarin derivatives have exhibited potent anticonvulsant activity (**A-C**) (Fig. 1) [10–12]. On the other hand, numerous derivatives of 5-membered heterocycles such as oxadiazoles (compound **D**), triazoles, and thiadiazoles have been reported for their good to excellent anticonvulsant activity [13–15]. In this regard, we have previously designed 1,2,4-oxadiazole-acridone hybrids **E** possessing anticonvulsant activity through benzodiazepine (BZD) receptors [16]. Herein, in continuation of our study on design and synthesis of new anticonvulsant agents [16], novel coumarin-1,2,4-oxadiazole hybrids were prepared.

The rationale behind the synthesis of the target compounds **3a-m** refers to the anticonvulsant activities of coumarin derivatives **A-C** and 1,2,4-oxadiazole derivatives **D** and **E**. For this purpose, required moieties for binding to BZD receptors have been considered (Fig. 2): (A) an aromatic ring, (B) a coplanar proton-accepting group in a suitable distance, and (C) second out-of-plane aromatic ring that potentiates binding of agonists to the receptor [17]. We hypothesize that the synthesized compounds will show anticonvulsant activity by binding to BZD receptor.

* Corresponding author at: Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
E-mail address: akbarzad@tums.ac.ir (T. Akbarzadeh).

https://doi.org/10.1016/j.bioorg.2019.102989
Received 6 March 2019; Received in revised form 14 May 2019; Accepted 17 May 2019
Available online 18 May 2019
0045-2068/

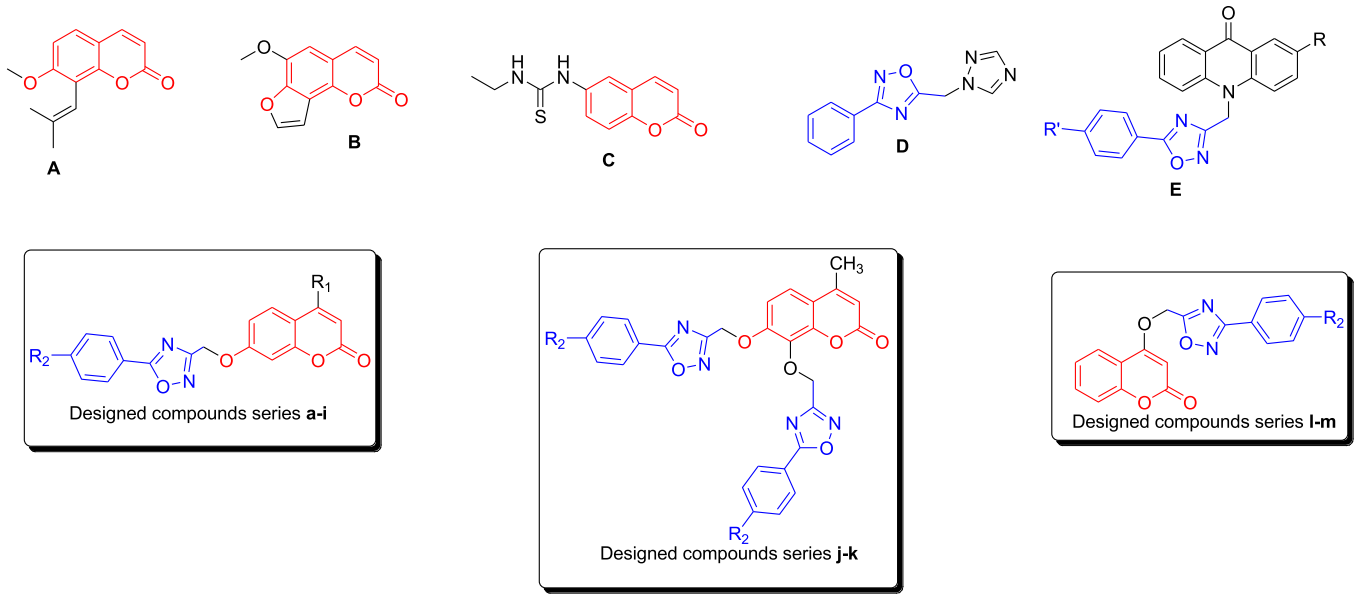


Fig. 1. The structure of potent anticonvulsant agents: coumarin derivatives **A-C**, 1,2,4-oxadiazole derivatives **D** and **E**, and designed compounds.

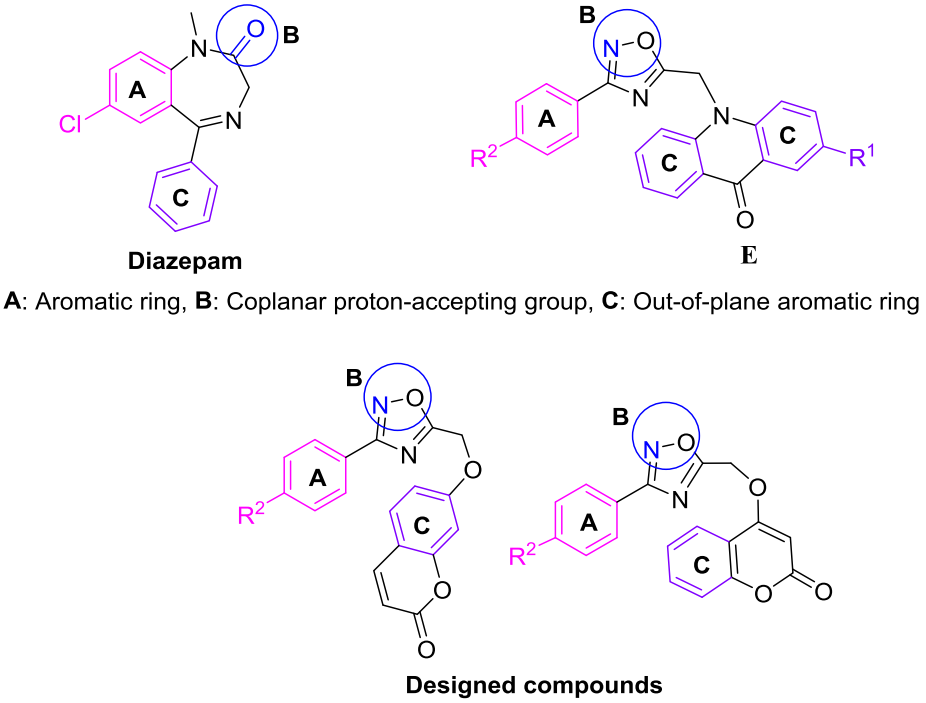


Fig. 2. Pharmacophoric features of diazepam as standard benzodiazepine agonists, compounds **E**, and the designed compounds.

2. Results and discussion

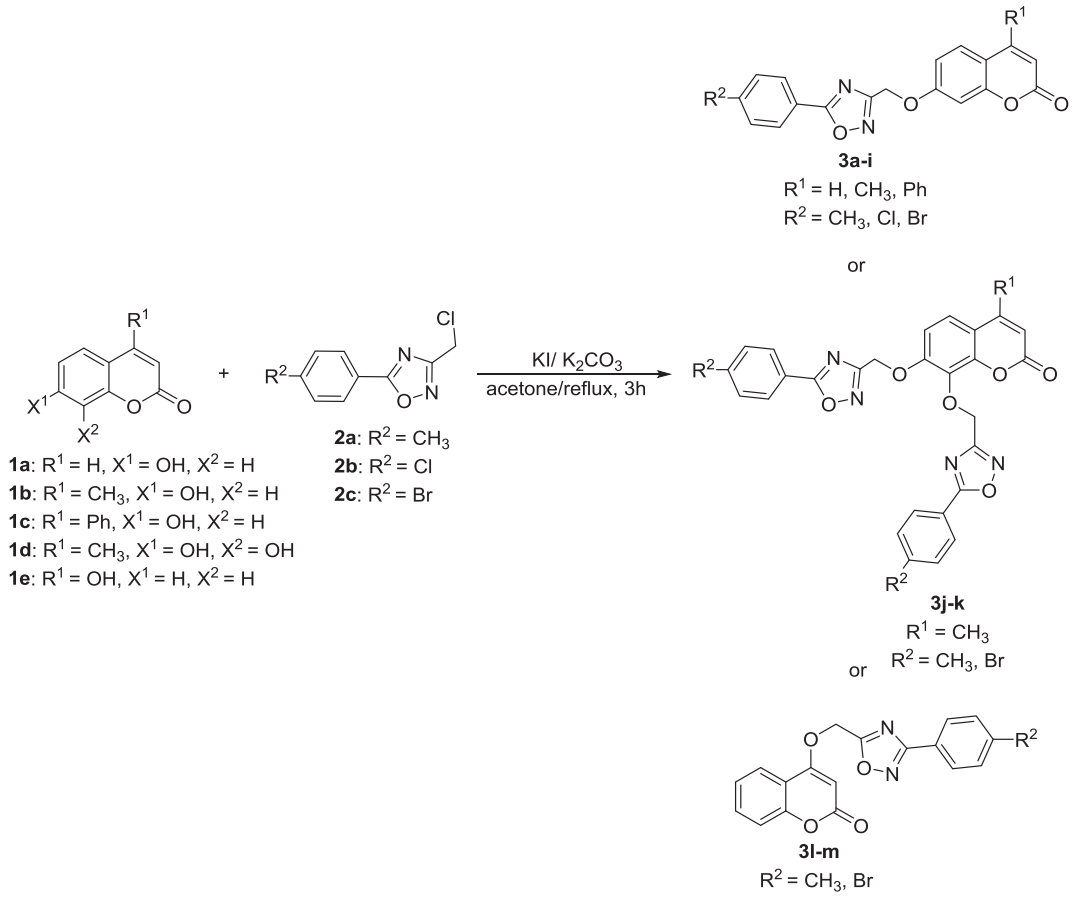
2.1. Chemistry

Synthetic route for the preparation of the coumarin-1,2,4-oxadiazole hybrids **3a-3m** is shown in Scheme 1. Coumarins **1a-1e** reacted with 3-aryl-5-(chloromethyl)-1,2,4-oxadiazole derivatives **2a-2c** using KI and K_2CO_3 in acetone at reflux to give the target compounds **3a-m** in good yields (70–80%). The structure of all compounds and their molecular weights, melting points, and yields are shown in Table 1.

2.2. Anticonvulsant activity

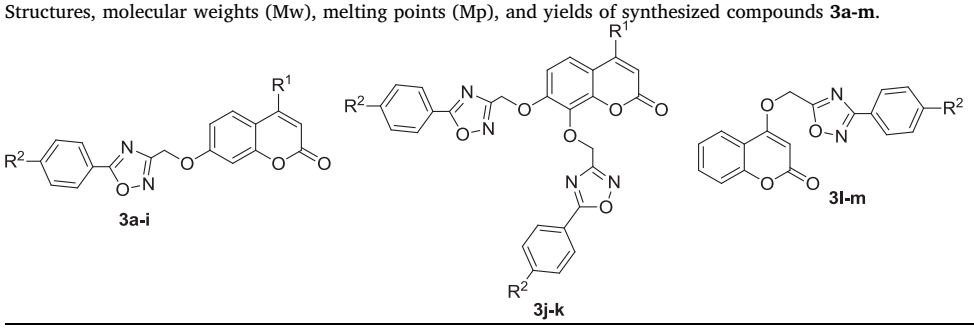
To develop anticonvulsant activity and delineation of structure activity relationship (SAR), a wide range of coumarin moieties such as 7-hydroxycoumarine **1a**, 7-hydroxy-4-methylcoumarine **1b**, 7-hydroxy-4-phenylcoumarine **1c**, 7,8-dihydroxy-4-methylcoumarin **1d**, and 4-hydroxycoumarine **1e** as well as different 3-aryl-5-(chloromethyl)-1,2,4-oxadiazole derivatives **2a-c** (Scheme 1) were used for the synthesis of compounds **3a-m**. All of them were evaluated for their anticonvulsant activity using pentylenetetrazole (PTZ) and maximal electroshock (MES)-induced seizures in mice.

The obtained results were compared with diazepam as the standard drug (Table 2). The synthesized compounds were found to be more



Scheme 1. Synthesis of compounds **3a-m**.

Table 1
Structures, molecular weights (Mw), melting points (Mp), and yields of synthesized compounds **3a-m**.



Compound	R^1	R^2	Mw (g/mol)	Mp (°C)	Yield (%)
3a	H	CH_3	334.33	181–183	75
3b	H	Cl	354.74	190–192	77
3c	H	Br	399.19	174–175	78
3d	CH_3	CH_3	348.11	162–164	70
3e	CH_3	Cl	368.06	171–174	73
3f	CH_3	Br	413.22	141–143	73
3g	Ph	CH_3	410.42	135–136	75
3h	Ph	Cl	430.84	176–178	77
3i	Ph	Br	475.29	177–179	70
3j	CH_3	CH_3	522.51	142–144	73
3k	CH_3	Br	652.25	196–198	72
3l	–	CH_3	334.33	171–173	77
3m	–	Br	399.19	168–170	72

Table 2
Anticonvulsant activities of compounds **3a-m** in PTZ and MES tests.

Compound	Dose (mg/kg)	PTZ[a]		MES[b]	
		No. of animals protected/ No. of animals tested	% Protection	No. of animals protected/ No. of animals tested	% Protection
3a	2.5	–	–	0/5	0
	5	–	–	1/5	20
	10	–	–	3/5	60
	20	1/5	20	3/5	60
3b	2.5	–	–	0/5	0
	5	0/6	0	2/5	40
	7	0/4	0	4/4	100
	10	–	–	4/4	100
	20	0/4	0	–	–
3b[c]	10	–	–	0/5	0
3c	2.5	–	–	1/5	20
	5	–	–	2/5	40
	10	–	–	3/5	60
	20	0/5	0	4/5	80
	40	–	–	5/5	100
3d	5	–	–	0/5	0
	10	–	–	1/5	20
	20	0/5	0	–	–
3e	2.5	–	–	2/5	40
	5	0/3	0	3/5	60
	10	0/4	0	4/5	80
	20	0/4	0	5/5	100
3f	5	–	–	0/5	0
	10	–	–	0/5	0
	20	0/5	0	1/5	20
3g	2.5	–	–	0/5	0
	5	–	–	0/5	0
	10	1/4	25	0/5	0
3h	5	–	–	1/5	20
	10	–	–	2/5	40
	20	0/5	0	–	–
3i	2.5	–	–	0/5	0
	5	–	–	0/5	0
	10	0/5	0	0/5	0
	20	0/5	0	0/5	0
3j	5	–	–	1/5	20
	10	–	–	2/5	40
	20	0/5	0	3/5	60
3k	5	–	–	0/5	0
	10	0/5	0	0/5	0
	20	1/5	20	0/5	0
3l	2.5	–	–	0/5	0
	5	–	–	2/5	40
	10	–	–	3/5	60
	20	0/5	0	–	–
3m	2.5	–	–	2/5	40
	5	–	–	4/5	80
	10	–	–	4/5	80
	20	0/5	0	2/5	40
Diazepam	2	6/6	100	4/4	100
Diazepam[c]	2	0/5	0	0/5	0

[a] Pentylentetrazole (100 mg/kg, ip) induced lethal convulsion.
[b] Maximal electroshock seizure test: 50 mA, 60 Hz, ac, 0.2 s.
[c] Flumazenil as a selective benzodiazepine receptor antagonist (1 mg/kg, ip) was administered 15 min before seizure induction.

effective against MES test than against PTZ test. According to our results from MES test, all compounds except **3g**, **3i**, and **3k** demonstrated good to moderate anticonvulsant effects while compounds **3a**, **3g**, and **3k** showed moderate activity in the PTZ test.

To get a better insight into the SAR of synthesized compounds, they were divided into three categories: (i) compounds **3a-i**, (ii) compounds **3j-k**, and (iii) compounds **3l-m** depending on the hydroxycoumarin derivative used for their synthesis, 7-hydroxycoumarin, 7,8-dihydroxycoumarin, and 4-hydroxycoumarin, respectively.

2.2.1. Anticonvulsant activity against PTZ-induced seizures

As can be seen in Table 2, most of synthesized compounds were not active against PTZ-induced seizures and three compounds **3a**, **3g**, and **3k** were found to be active. Our results revealed that compound **3g** possessing phenyl at 4-position of coumarin moiety and 4-methylaryl connected to 1,2,4-oxadiazole ring showed the most potent anticonvulsant activity in such a manner that it demonstrated 25% protection at the dose of 10 mg/kg. However, it depicted no protection at lower doses (2.5 and 5 mg/kg). Removal of the phenyl group from 4-position of coumarin moiety (compound **3a**) led to lower activity with 20% protection at the dose of 20 mg/kg. Also, introduction of methyl into the corresponding position (compound **3d**) abolished the anticonvulsant activity. It seems that 4-methylaryl moiety connected to 1,2,4-oxadiazole ring played important role in the activity of the first category of compounds since compounds lacking this moiety showed no activity, while it was not significant in the case of compounds series **j-m**. Results related to compound **3k** (Table 2) showed that the presence of 7,8-bis-aryl moiety could be beneficial for inducing the anticonvulsant activity depending on the substituents on the aryl group. The presence of 4-bromoaryl group connected to 1,2,4-oxadiazole ring (compound **3k**) led to good activity at dose of 20 mg/kg and replacement of that by 4-methylaryl group (compound **3j**) afforded no activity.

2.2.2. Anticonvulsant activity against MES-induced seizures

As reported in Table 2, compounds **3b**, **3c**, and **3e** from the first series of compounds induced 100% protection against MES-induced seizures at the doses of 7, 40, and 20 mg/kg, respectively. Compound **3b** possessing 4-chloroaryl group connected to 1,2,4-oxadiazole ring and lacking substituent at 4-position of coumarin showed the best activity with 100% protection at the dose of 7 mg/kg. Introduction of methyl group into 4-position of coumarin (compound **3e**) led to 100% protection at higher dose (20 mg/kg). It should be noted that introduction of phenyl group into 4-position of coumarin (compound **3h**) reduced anticonvulsant activity with 40% protection at the dose of 40 mg/kg. However, the presence of 4-chlorophenyl moiety seemed to be an important factor against MES-induced seizures since the replacement of Cl by Me group (compounds **3a**, **3d**, and **3g**) led to a significant decrease in the anticonvulsant activity. Compounds **3a** and **3d** showed 60 and 20% protection at the dose of 10 mg/kg, respectively and compound **3g** showed no activity. Also, replacement of Cl by Br (compounds **3c**, **3f**, and **3i**) resulted in lower activity, depending on the substituents at 4-position of coumarin moiety. Compound **3c** as the analogue of **3a** showed 100% protection at the dose of 40 mg/kg. Changing the substituents to methyl (compound **3f**) and phenyl (compound **3i**) led to the reduction of activity. Compound **3f** demonstrated 20% protection at the dose of 20 mg/kg and compound **3i** showed no activity. It is clear that the substituent at 4-position of coumarin in the first series of compounds **3a-i** was significant in the order of H > CH_3 > Ph. The presence of phenyl group at 4-position of coumarin generally deteriorated activity in the first category of compounds since compounds **3g** and **3i** showed no activity and compound **3h** showed lower activity comparing with its analogues **3b** and **3e**.

The anticonvulsant activity of the second category of compounds having 4-methyl group at 4-position of coumarin moiety (compounds **3j** and **3k**) depended on aryl group connected to 1,2,4-oxadiazole ring. Compound **3j** having 4-methylaryl group showed moderate activity with 60% protection at the dose of 20 mg/kg and compound **3k** having 4-bromoaryl group showed no activity.

In the case of third series of compounds (compounds **3l** and **3m**) containing 1,2,4-oxadiazole moiety at 4-position of coumarin moiety, they were found to be more potent than the second category. In this series, compounds **3l** and **3m** showed 60 and 80% protection at the doses of 10 and 5 mg/kg, respectively. It seems that 4-bromoaryl group in this class of compounds played a remarkable role to induce anticonvulsant activity.

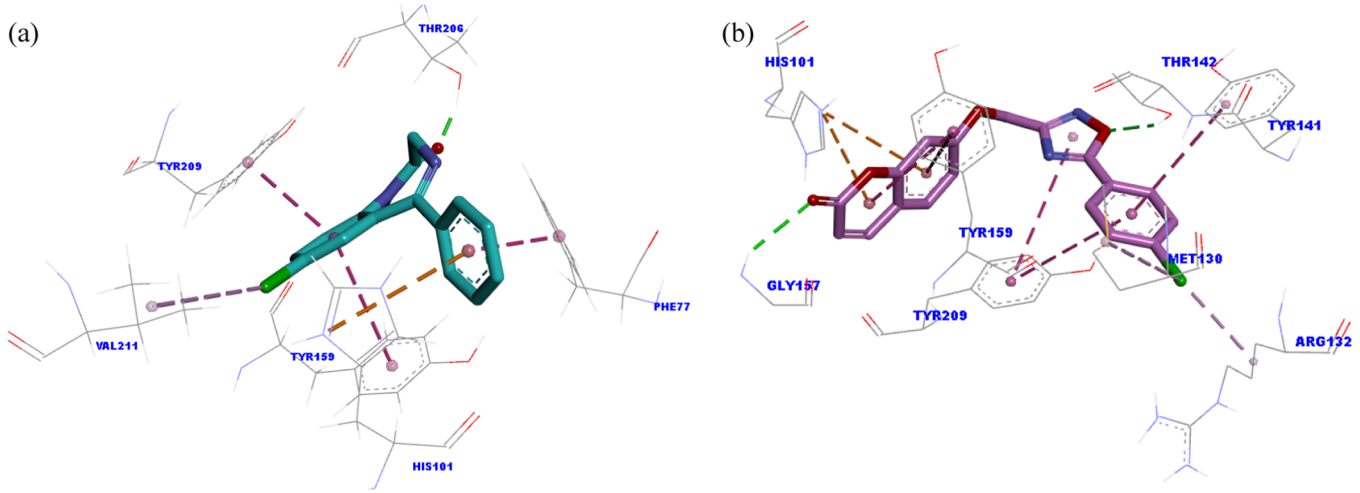


Fig. 3. (a) The binding modes of diazepam and (b) compound **3b** in the BZD-binding pocket of $GABA_A$ receptor.

2.3. Studying the mechanism of action

2.3.1. Evaluation of flumazenil effect on anticonvulsant activity of compounds *3b* and *3c*

The most potent compounds in MES test (compounds **3b** and **3c**) were selected to study the mechanism of action of the synthesized compounds comparing with diazepam as the standard BZD receptor agonist. In this regard, effect of flumazenil as a BZD receptor antagonist on the anticonvulsant activity of selected compounds was investigated. As can be seen in Table 2, comparing our results with diazepam; flumazenil antagonized anticonvulsant activity of the compounds **3b** and **3c**. This finding confirmed that the title compounds can act as agonists for BZD receptors.

2.3.2. Docking study

In order to confirm the involvement of BZD receptors in the anticonvulsant activity of the title compounds, a docking study was also performed by Autodock Tools (1.5.6). Docking poses of the diazepam (standard agonist of BZD receptor) and selected synthesized compounds **3b**, **3e**, and **3h** in the BZD binding pocket of $GABA_A$ receptor are shown in Figs. 3 and 4 [15].

Benzodiazepine moiety of diazepam interacted with α1 Tyr159 (π-π), α1 Tyr 209 (π-π), and α 1 Thr206 (hydrogen bond) (Fig. 3a). Pendant phenyl group of this drug formed π-π and π-anion interactions with α1 His101 and γ2 Phe77. Furthermore, a hydrophobic interaction was also observed between chlorine atom and α1 Val211.

Coumarin ring of the most active compound **3b** (in the MES assay) established two π-cation and two π-π interactions with α1 His101 and α1 Tyr159, respectively (Fig. 3b). Furthermore, a hydrogen bond between carbonyl of coumarin ring and α1 Gly157 was also observed. 1,2,4-Oxadiazole ring formed a π-π interaction with α1 Tyr209 and oxygen of this ring established a hydrogen bond with α1 Thr142. Aryl ring attached to 1,2,4-oxadiazole interacted with α1 Tyr141 and α1 Tyr209 *via* π-π interactions. As can be seen in the Fig. 3b, chlorine substituent formed hydrophobic interactions with α1 Met130 and α1 Arg132.

Introduction of a methyl group into 4-position of coumarin ring in compound **3e** led to a decrease of anticonvulsant activity (Fig. 4a).

Table 3
The muscle relaxtant activity (Rota-rod Test) of compounds 3b and 3c.

Compound	Dose (mg/kg)	Time to stay on bar (s)	
		0.5 h after injection	4 h after injection
DMSO	5 ml/kg	43.5 ± 7.07	60
3b	5	25.6 ± 2.84	44.8 ± 1-.13
	10	7.6 ± 1.89	29.6 ± 1-.23
3c	10	7.2 ± 0.63	22 ± 0.9-4
	20	5.78 ± 1.89	22.2 ± 0-.74
Diazepam	2	0	18.5 ± 2-.12

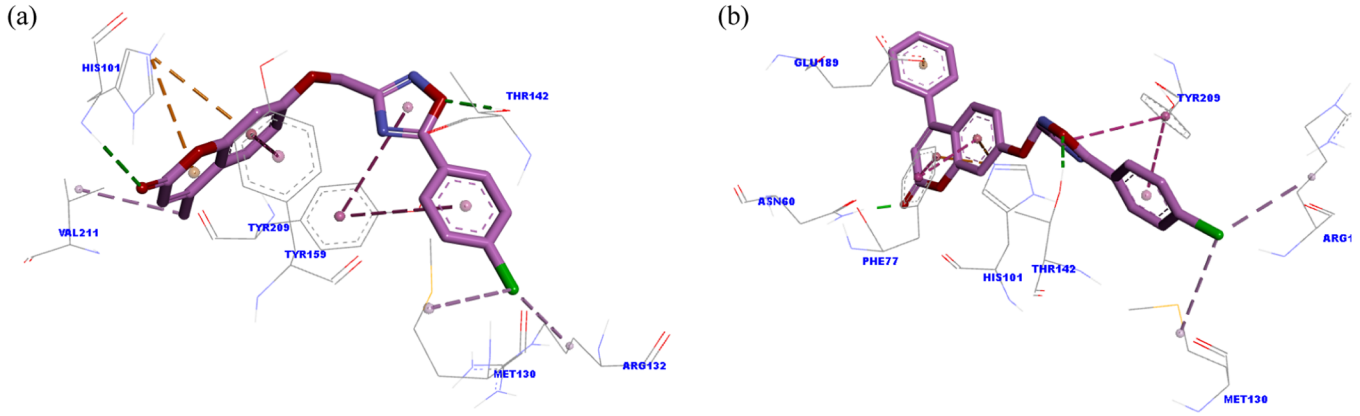


Fig. 4. (a) The binding modes of compound **3e** and (b) compound **3h** in the BZD-binding pocket of $GABA_A$ receptor.

Table 4
Drug likeliness parameters of the synthesized compounds **3a-m**.

Entry	M_W	Clog P	HBD	HBA	RBC	Lipiniski's violations	tPSA	BBB score[a]
Rule	< 500	< 5	< 5	< 10	< 10	< 1	–	–
3a	334.33	3.46	0	4	4	0	69.48	+0.067
3b	354.74	3.68	0	4	4	0	69.48	+0.034
3c	399.19	3.83	0	4	4	0	69.48	+0.035
3d	348.11	3.96	0	4	4	0	69.48	+0.034
3e	368.06	4.17	0	4	4	0	69.48	+0.021
3f	413.22	4.33	0	4	4	0	69.48	+0.023
3g	410.42	5.35	0	4	4	1	69.48	+0.046
3h	430.84	5.56	0	4	4	1	69.48	+0.034
3i	475.29	5.71	0	4	4	1	69.48	+0.034
3j	522.51	5.35	0	7	8	2	112.66	−0.030
3k	652.25	6.092	0	7	8	2	112.66	−0.031
3l	334.33	3.60	0	4	4	0	69.48	+0.063
3m	399.19	3.96	0	4	4	0	69.48	+0.052

[a] SVM_MACCSFP BBB Score.

Interestingly, replacement of the methyl group with a phenyl group in compound **3h** caused more decrease in anticonvulsant activity (Fig. 4b). As can be seen in Fig. 3b and 4, all three compounds formed two π-cation interactions with α1 His101. Compound **3b** showed two π-π interactions with α1 Tyr159 while compound **3e** established a π-π interaction with the same residue. On the other hand, compound **3h** formed two π-π interactions with γ2 Phe77 (instead of α1 Tyr159). Carbonyl group of compounds **3b**, **3e**, and **3h** formed a hydrogen bond with α1 Gly157, α1 His101, and Asn60, respectively. Moreover, 4-methy group of compound **3e** formed a hydrophobic interaction with α1 Val211 and 4-phenyl group of compound **3h** formed a π-anion interaction with α1 Glu189. 1,2,4-Oxadiazole ring and attached 4-chloroaryl group in compounds **3b**, **3e**, and **3h** showed similar interactions with BZD binding pocket of $GABA_A$ receptor. In the case of compound **3b**, there was an additional π-π interaction between aryl group attached to 1,2,4-oxadiazole ring and α1 Tyr209.

2.4. In vivo neurotoxicity

Rotarod assay is applied widely to evaluate neurotoxic effects of new anticonvulsant agents in mice. In this respect, neurotoxicity is indicated by the measurement of ability to maintain balance on a rotating rod in each trial [18]. Accordingly, the neurological toxicity of the compounds **3b** and **3c** as the most potent compounds in the MES test, was evaluated and compared with negative and positive controls (DMSO and diazepam, respectively). As shown in Table 3, the test compounds showed neurological deficits less than diazepam at the effective doses.

2.5. Drug likeliness parameters

An effective anticonvulsant agent should have drug-like properties and must be able to cross the BBB [19]. Some physicochemical and topological properties of designed compounds including molecular weight (M_W), octanol/water partition coefficients (Clog P), a number of H-bond donors (HBD), a number of H-bond acceptors (HBA), a number of rotatable bonds (RBC), and the polar surface area (tPSA) were calculated and shown in Table 4. For BBB penetration, online BBB predictor (www.cbligand.org) was used. This software predicted that compounds with SVM_MACCSFP BBB score greater than 0.02 were able to cross the BBB (Table 4). According to Lipinski rule of 5, most compounds possessed good pharmacokinetic properties (MW < 500, Clog P < 5, HBD < 5, HBA < 10, and RBC < 10) [19]. Also, these compounds possessed tPSA between 69.48 and 112.66 (Veber rule: tPSA ≤ 140 $Å^2$) [20]. According to our results, all the synthesized compounds except compounds **3j** and **3k** were suitable to cross the BBB.

3. Conclusion

In conclusion, we designed and synthesized a novel series of coumarin-1,2,4-oxadiazole hybrids **3a-m** as new anticonvulsant agents. Anticonvulsant evaluation of the synthesized compounds using MES and PTZ tests in mice revealed that they are more effective against MES test than against PTZ model. All synthesized compounds except **3g**, **3k**, and **3i** showed good to moderate activity in the MES test. Involvement of BZD receptors in the anticonvulsant activity of synthesized compounds was confirmed by the results obtained from flumazenil test and docking study of prototype compound **3b**. Moreover, the most potent compounds **3b** and **3c** showed neurological deficits less than diazepam in the rotarod test. The *in silico* drug-likeliness parameters indicated that most of compounds violate Lipinski's rule of five and that were able to cross the BBB.

4. Experimental

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker FT-500, using TMS as an internal standard. IR spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (KBr disks). Elemental analysis was performed with an Elementar Analysensystem GmbH VarioEL CHNS mode. 3-Aryl-5-(chloromethyl)-1,2,4-oxadiazole derivatives **2** were prepared according to our previous study [16].

4.1. General procedure for the synthesis of coumarin based-1,2,4 oxadiazole derivatives *3a-m*

A suspension of coumarin derivative **1** (1 mmol) and K_2CO_3 (2 mmol) in acetone (5 ml) was stirred at room temperature for 15 min. Then, it was added to a suspension of 3-aryl-5-(chloromethyl)-1,2,4-oxadiazole derivative **2** (1 mmol for compounds **3a-i** and **3l-m** or 2 mmol for compounds **3j-k**) and KI (1 mmol) in acetone (5 ml) and the reaction mixture was stirred at reflux for 5 h. After that, the solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate. Then, the organic phase was washed with water (3 × 20 ml) and brine (1 × 10 ml), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was recrystallized from ethyl acetate to obtain pure coumarin-1,2,4 oxadiazole hybrids (70–80%).

4.1.1. 7-((3-(p-Tolyl)-1,2,4-oxadiazol-5-yl)methoxy)-2H-chromen-2-one (*3a*)

White solid, isolated yield: 75%, mp: 181–183 °C. IR (KBr): 1444, 1483, 1511, 1580, 1618, 1726, 2913, 3026, 3090 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.39 (s, 3H, CH_3), 5.73 (s, 2H, CH_2), 6.349 (d, J = 9.5 Hz, 1H, H_3), 7.12 (dd, J = 9.0, 2.0 Hz, 1H, H_6), 7.22 (d, J = 2.0 Hz, 1H, H_8), 7.39 (d, J = 7.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.70 (d, J = 9.0 Hz, 1H, H_5), 7.9 (d, J = 7.5 Hz, 2H, $H_{2'}$, $H_{6'}$), 8.02 (d, J = 9.5 Hz, 1H, H_4). ^{13}C NMR (125 MHz, DMSO-d_6): 21.1, 61.29, 101.8, 112.7, 113.1, 113.3, 123.3, 127.1, 129.7, 129.9, 130.9, 142.3, 144.2, 155.0, 160.0, 168.1, 175.1. Anal. Calcd for $C_{19}H_{14}N_2O_4$: C, 68.26; H, 4.22; N, 8.38. Found: C, 68.51; H, 4.49; N, 8.21.

4.1.2. 7-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-2H-chromen-2-one (*3b*)

White solid, isolated yield: 77%, mp: 190–192 °C. IR (KBr): 1474, 1511, 1573, 1616, 1745, 2925, 3071 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 5.75 (s, 2H, CH_2), 6.35 (d, J = 9.5 Hz, 1H, H_3), 7.12 (dd, J = 8.5, 2.0 Hz, 1H, H_6), 7.22 (d, J = 2.0 Hz, 1H, H_8), 7.66 (d, J = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.7 (d, J = 8.5 Hz, 1H, H_5), 8.01–8.04 (m, 3H, H_4, $H_{2'}$, $H_{6'}$). ^{13}C NMR (125 MHz, DMSO-d_6): 61.3, 101.9, 112.7, 113.3, 124.6, 128.9, 129.5, 129.7, 130.1, 136.6, 137.1, 144.1, 155.1, 160.1, 167.0, 175.5. Anal. Calcd for $C_{18}H_{11}ClN_2O_4$: C, 60.94; H, 3.13; N, 7.90. Found: C, 61.18; H, 3.40; N, 7.78.

*4.1.3. 7-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-2H chromen-2-one (**3c**)*

White solid, isolated yield: 78%, mp: 174–175 °C. IR (KBr): 1468, 1509, 1563, 1617, 1731, 2944, 3084 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 5.75 (s, 2H, CH_2), 6.35 (d, J = 9.5 Hz, 1H, H_3), 7.12 (dd, J = 8.5, 2.5 Hz, 1H, H_6), 7.22 (d, J = 2.5 Hz, 1H, H_8), 7.70 (d, J = 8.5 Hz, 1H, H_5), 7.8 (d, J = 7.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.95 (d, J = 7.0 Hz, 2H, $H_{2'}$, $H_{6'}$), 8.02 (d, J = 9.5 Hz, 1H, H_4). ^{13}C NMR (125 MHz, DMSO-d_6): 61.29, 101.8, 112.7, 113.4, 113.5, 125.0, 125.4, 129.0, 129.7, 130.1, 132.5, 144.1, 155.0, 160.1, 167.5, 175.1. Anal. Calcd for $C_{18}H_{11}BrN_2O_4$: C, 54.16; H, 2.78; N, 7.02. Found: C, 54.37; H, 2.58; N, 6.83.

*4.1.4. 4-Methyl-7-((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methoxy)-2H-chromen-2-one (**3d**)*

White solid, isolated yield: 70%, mp: 162–164 °C. IR (KBr): 1480, 1570, 1609, 1733, 2910, 3070 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.38 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.73 (s, 2H, CH_2), 6.26 (s, 1H, H_3), 7.13 (dd, J = 9.0, 2.0 Hz, 1H, H_6), 7.19 (d, J = 2.0 Hz, 1H, H_8), 7.38 (d, J = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.75 (d, J = 9.0 Hz, 1H, H_5), 7.90 (d, J = 8.0 Hz, 2H, $H_{2'}$, $H_{6'}$). ^{13}C NMR (125 MHz, DMSO-d_6): 18.1, 21.1, 61.2, 101.9, 111.8, 112.4, 114.3, 117.4, 123.3, 125.9, 126.8, 127.1, 129.9, 143.1, 154.3, 160.0, 168.1, 175.2. Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 69.21; H, 4.48; N, 8.25.

*4.1.5. 7-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-4-methyl-2H-chromen-2-one (**3e**)*

White solid, isolated yield: 73%, mp:171–174 °C. IR (KBr): 1472, 1568, 1609, 1733, 2928, 3080 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.41 (s, 3H, CH_3), 5.76 (s, 2H, CH_2), 6.27 (s, 1H, H_3), 7.13 (dd, J = 9.0, 2.0 Hz, 1H, H_6), 7.21 (d, J = 2.0 Hz, 1H, H_8), 7.66 (d, J = 8.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.75 (d, J = 9.0 Hz, 1H, H_5), 8.02 (d, J = 8.5 Hz, 2H, $H_{2'}$, $H_{6'}$). ^{13}C NMR (125 MHz, DMSO-d_6): 18.2, 61.2, 101.9, 111.8, 112.4, 114.2, 116.2, 124.8, 126.8, 128.9, 129.6, 136.9, 154.1, 155.0, 161.2, 166.9, 176.1. Anal. Calcd for $C_{19}H_{13}ClN_2O_4$: C, 61.88; H, 3.55; N, 7.60. Found: C, 61.70; H, 3.28; N, 7.81.

*4.1.6. 7-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-4-methyl-2H-chromen-2-one (**3f**)*

White solid, isolated yield: 73%, mp:141–143 °C. IR (KBr): 1450, 1509, 1568, 1619, 1724, 2919, 3080 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.41 (s, 3H, CH_3), 5.76 (s, 2H, CH_2), 6.13 (s, 1H, H_3), 7.13 (dd, J = 9.0, 2.0 Hz, 1H, H_6), 7.21 (d, J = 2.0 Hz, 1H, H_8), 7.61 (d, J = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.75 (d, J = 9.0 Hz, 1H, H_5), 7.95 (d, J = 8.0 Hz, 2H, $H_{2'}$, $H_{6'}$). ^{13}C NMR (125 MHz, DMSO-d_6): 18.1, 61.2, 101.9, 102.1, 110.2, 111.8, 112.4, 112.8, 126.6, 126.8, 129.1, 132.5, 153.6, 154.8, 160.3, 167.9, 176.1. Anal. Calcd for $C_{19}H_{13}BrN_2O_4$: C, 55.23; H, 3.17; N, 6.78. Found: C, 55.50; H, 3.31; N, 6.57.

*4.1.7. 4-Phenyl-7-((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methoxy)-2H-chromen-2-one (**3g**)*

White solid, isolated yield: 75%, mp: 135–136 °C. IR (KBr): 1418, 1607, 1722, 2921, 3071 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.39 (s, 3H, CH_3), 5.75 (s, 2H, CH_2), 6.3 (s, 1H, H_3), 7.1 (dd, J = 9.5, 2.5 Hz, 1H, H_6), 7.32 (d, J = 2.0 Hz, 1H, H_8), 7.38–7.42 (m, 3H, H_5, $H_{3'}$, $H_{5'}$), 7.53–7.58 (m, 5H, Ph), 7.91 (d, J = 8.0 Hz, 2H, $H_{2'}$, $H_{6'}$). ^{13}C NMR (125 MHz, DMSO-d_6): 21.1, 61.3, 102.3, 112.8, 112.9, 124.5, 127.1, 128.1, 128.5, 128.9, 129.7, 129.9, 134.8, 141.8, 155.1, 155.2, 160.0, 160.9, 168.1, 175.1. Anal. Calcd for $C_{25}H_{18}N_2O_4$: C, 73.16; H, 4.42; N, 6.83. Found: C, 73.34; H, 4.21; N, 6.58.

*4.1.8. 7-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-4-phenyl-2H-chromen-2-one (**3h**)*

White solid, isolated yield: 77%, mp: 176–178 °C. IR (KBr): 1447, 1473, 1570, 1603, 1718, 3071 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 5.77 (s, 2H, CH_2), 6.30 (s, 1H, H_3), 7.11 (dd, J = 9.0, 2.0 Hz, 1H, H_6), 7.32 (d, J = 2.0 Hz, 1H, H_8), 7.41 (d, J = 9.0 Hz, 1H, H_5), 7.53–7.58 (m, 5H, Ph), 7.66 (d, J = 8.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 8 (d, J = 8.5 Hz, 2H, $H_{2'}$, $H_{6'}$). ^{13}C NMR (125 MHz, DMSO-d_6): 61.3, 102.3, 112.1, 112.8, 112.9, 124.5, 126.8, 128.1, 128.5, 128.9, 129.5, 129.7, 134.8, 136.6, 155.1, 155.2, 160.2, 160.9, 168.2, 175.1. Anal. Calcd for $C_{24}H_{15}ClN_2O_4$: C, 66.91; H, 3.51; N, 6.50. Found: C, 67.11; H, 3.72; N, 6.32.

*4.1.9. 7-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-4-phenyl-2H-chromen-2-one (**3i**)*

White solid, isolated yield: 70%, mp:177–179 °C. IR (KBr): 1469, 1568, 1609, 1713, 3079 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 5.77 (s, 2H, CH_2), 6.31 (s, 1H, H_3), 7.1 (dd, J = 9.0, 2.5 Hz, 1H, H_6), 7.32 (d, J = 2.5 Hz, 1H, H_8), 7.41 (d, J = 9.0 Hz, 1H, H_5), 7.53–7.58 (m, 5H, Ph), 7.79 (d, J = 8.5 Hz, 2H, H_2, $H_{6'}$), 7.96 (d, J = 8.5 Hz, 2H, $H_{2'}$, $H_{6'}$). ^{13}C NMR (125 MHz, DMSO-d_6): 61.3, 102.3, 112.1, 112.8, 112.9, 124.9, 125.4, 128.1, 128.5, 128.9, 129.1, 129.7, 132.5, 134.5, 155.0, 155.3, 160.0, 160.2, 168.1, 175.9. Anal. Calcd for $C_{24}H_{15}BrN_2O_4$: C, 60.65; H, 3.18; N, 5.89. Found: C, 60.37; H, 3.34; N, 5.58.

*4.1.10. 4-Methyl-7,8-bis((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methoxy)-2H-chromen-2-one (**3j**)*

White solid, isolated yield: 73%, mp: 142–144 °C. IR (KBr): 1506, 1568, 1604, 1728, 2925, 2962 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 5.74 (s, 2H, CH_2), 6.30 (s, 1H, H_3), 7.28–7.33 (m, 5H, H_6, $H_{3'}$, $H_{5'}$, $H_{3''}$, $H_{5''}$) 7.60 (d, J = 9.0 Hz, 1H, H_5), 7.79–7.83 (m, 4H, $H_{2'}$, $H_{6'}$, $H_{2''}$, $H_{6''}$). ^{13}C NMR (125 MHz, DMSO-d_6): 18.2, 21.1, 61.8, 64.9, 109.9, 112.2, 115.2, 121.6, 122.9, 123.1, 126.1, 126.9, 127.0, 129.7, 129.8, 134.1, 142.5, 142.7, 148.1, 152.7, 153.4, 159.1, 167.6, 174.8, 175.1. Anal. Calcd for $C_{30}H_{24}N_4O_6$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.31; H, 4.77; N, 10.24.

*4.1.11. 7,8-bis((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-4-methyl-2H-chromen-2-one (**3k**)*

White solid, isolated yield: 72%, mp: 196–198 °C. IR (KBr): 1506, 1566, 1602, 1729, 2922, 3071 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.41 (s, 3H, CH_3), 5.2 (s, 2H, CH_2), 5.71 (s, 2H, CH_2), 6.30 (s, 1H, H_3), 7.31 (d, J = 9.0 Hz, 1H, H_6), 7.61 (d, J = 9.0 Hz, 1H, H_5), 7.65 (d, J = 8.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.72 (d, J = 8.5 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.80 (d, J = 8.5 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.82 (d, J = 8.5 Hz, 2H, $H_{2''}$, $H_{6''}$). ^{13}C NMR (125 MHz, DMSO-d_6): 175.5, 175.1, 166.9, 159.1, 153.3, 152.6, 148.2, 144.6, 133.2, 132.3, 132.2, 128.9, 128.82, 125.3, 125.1, 124.9, 124.7, 121.6, 115.3, 112.2, 109.8, 65.0, 61.7, 18.2. Anal. Calcd for $C_{28}H_{18}Br_2N_4O_6$: C, 50.47; H, 2.72; N, 8.41. Found: C, 50.61; H, 2.57; N, 8.19.

*4.1.12. 4-((3-(p-Tolyl)-1,2,4-oxadiazol-5-yl)methoxy)-2H-chromen-2-one (**3l**)*

White solid, isolated yield: 77%, m.p:171–173 °C. IR (KBr): 1487, 1567, 1603, 1613, 1730, 2855, 2919, 3075 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.40 (s, 3H, CH_3), 5.88 (s, 2H, CH_2), 6.19 (s, 1H, H_3), 7.40 (d, J = 8.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.42–7.46 (m, 2H, H_6, H_8), 7.12 (t, J = 7.5 Hz, 1H, H_7), 7.89 (d, J = 7.5 Hz, 1H, H_5), 7.93 (d, J = 8.5 Hz, 2H, $H_{2'}$, $H_{6'}$). ^{13}C NMR (125 MHz, DMSO-d_6): 21.1, 62.1, 92.1, 114.6, 116.6, 122.8, 124.5, 127.1, 129.9, 130.2, 133.1, 141.9, 152.7, 161.3, 163.8, 167.8, 174.0. Anal. Calcd for $C_{19}H_{14}N_2O_4$: C, 68.26; H, 4.22; N, 8.38. Found: C, 68.54; H, 4.50; N, 8.52.

*4.1.13. 4-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-2H-chromen-2-one (**3m**)*

White solid, isolated yield: 72%, m.p:168–170 °C. IR (KBr): 1451, 1526, 1564, 1603, 1628, 1731, 2861, 2922, 2980, 3093 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 5.89 (s, 2H, CH_2), 6.19 (s, 1H, H_3), 7.41–7.46 (m, 2H, H_6, H_8), 7.69–7.73 (m, 1H, H_7), 7.81 (d, J = 7.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.89 (d, J = 7.5 Hz, 1H, H_5), 7.98 (d, J = 7.5 Hz, 2H, $H_{2'}$, $H_{6'}$). ^{13}C NMR (125 MHz, DMSO-d_6): 62, 92.1, 114.6, 116.5, 122.8, 124.5, 124.8,

127.0, 129.1, 132.5, 133.1, 141.9, 152.7, 161.3, 163.8, 167.8, 174.0. Anal. Calcd for $C_{18}H_{11}BrN_2O_4$: C, 54.16; H, 2.78; N, 7.02. Found: C, 54.32; H, 2.57; N, 6.83.

4.2. Anticonvulsant activity

All *in vivo* experiments were achieved according to ethical principles approved by Animal Ethics Committee of Tehran University of Medical Sciences with ID IR.TUMS.UCR.REC.1397.1100. NMRI mice (Male) with 20–30 g weight and 3 months old were used for the evaluation of anticonvulsant activity of synthesized compounds. The mice housed in the standard Plexiglas cages at 25 ± 2 °C with free access to food and water. Each animal was transferred to the laboratory at least 1 h before the treatment. All synthesized compounds **3a-m**, diazepam (standard drug), and pentylenetetrazole (PTZ) were dissolved in dimethylsulfoxide (DMSO) in normal saline 0.9% and administered i.p. at the required doses. DMSO was used as negative control group.

4.2.1. PTZ-induced seizure test

PTZ was injected i.p. at the dose of 100 mg/kg, 30 min after treatment of the mice with test compounds. After that, the treated animals were placed in individual cages and monitored for 0.5 h. The number of death of mice following tonic-clonic convulsions was recorded and the results were reported as number of animal protected/number of animals tested [21].

4.2.2. MES-induced seizure test

The synthesized compounds **3a-m** were administrated i.p. to the animals and 30 min later, animals were manually restrained for screening hind limb tonic extension (HLTE). The occurrence of HLTE in animals following applying MES (60 Hz, 50 mA and 0.2 s) was assessed. The electrical current was applied *via* ear electrodes and mice were monitored for 30 s for incidence of HLTE. The number of mice with abolition of the HLTE component of the epilepsy was recorded as protected mice. The results were presented as number of animal protected/number of animals tested [22].

To evaluate the mechanism of action of synthesized compounds, selected compounds **3b** and **3c**, vehicle, or diazepam as BZD agonist (positive control) were administered i.p. and seizure was induced 30 min later. Flumazenil as an antagonist of BZD receptors was also administered 15 min before seizure induction. Mice were under observation for 30 min after the induction of epilepsy and the results were presented as number of animal protected/number of animals tested.

4.3. Docking study

Docking study of compounds **3b**, **3e**, and **3h** in the BZD-binding pocket of $GABA_A$ receptor ($\alpha1\beta2\gamma2$) was performed by Auto dock Tools (version 1.5.6) according to previously described method [16,23].

4.4. Rotarod test (acute neurotoxicity)

The most potent compound **3b**, diazepam and vehicle were administered i.p and 30 min after administration, the animals were placed on the rotating rod (5 rpm) for 60 s and the time to stay on bar 30 min or 4 h after injection was recorded [22].

4.5. In silico molecular properties prediction

The Clog P values and tPSA of the designed compounds were calculated using the ChemDraw Ultra 12.0. HBD and HBA of these compounds were calculated by the means of MarvineSketch 5.8.3 and RBCs were calculated using Autodock Tools (ver.1.5.6). BBB penetration of title compounds was predicted by online BBB predictor (www.cbligand.org). This BBB predictor was built by applying the support vector machine (SVM) and LiCABEDS17 algorithms on fingerprints of 1593 reported compounds [24].

Acknowledgment

This work was supported by Research Council of Tehran University of Medical Sciences with project No. 97-03-33-39706.

References

[1] W. Löscher, New visions in the pharmacology of anticonvulsion, Eur. J. Med. Chem. 342 (1998) 1–13.
[2] I. Megiddo, A. Colson, D. Chisholm, T. Dua, A. Nandi, R. Laxminarayan, Health and economic benefits of public financing of epilepsy treatment in India: an agent-based simulation model, Epilepsia 57 (2016) 464–474.
[3] O.T. Jones, Ca^{2+} channels and epilepsy, Eur. J. Pharmacol. 447 (2002) 211–225.
[4] K.J. Meador, Newer anticonvulsants: dosing strategies and cognition in treating patients with mood disorders and epilepsy, J. Clin. Psychiatry 64 (2003) 30–34.
[5] J.A. Cramer, S. Mintzer, J. Wheless, R.H. Mattson, Adverse effects of antiepileptic drugs: a brief overview of important issues, Expert Rev. Neurother. 10 (2010) 885–891.
[6] K.V. Sashidhara, M. Kumar, R.K. Modukuri, A. Srivastava, A. Puri, Discovery and synthesis of novel substituted benzocoumarins as orally active lipid modulating agents, Bioorg. Med. Chem. Lett. 21 (2011) 6709–6713.
[7] Y. Shi, C.H. Zhou, Synthesis and evaluation of a class of new coumarin triazole derivatives as potential antimicrobial agents, Bioorg. Med. Chem. Lett. 21 (2011) 956–960.
[8] F. Belluti, G. Fontana, L. Dal Bo, N. Carenini, C. Giommarelli, F. Zunino, Design, synthesis and anticancer activities of stilbene-coumarin hybrid compounds: identification of novel proapoptotic agents, Bioorg. Med. Chem. 18 (2010) 3543–3550.
[9] G. Cravotto, G.M. Nano, G. Palmisano, S. Tagliapietra, An asymmetric approach to coumarin anticoagulants via hetero-Diels–Alder cycloaddition, Tetrahedron Asymmetry 12 (2001) 707–709.
[10] J.J. Luszczki, M. Andres-Mach, W. Cisowski, I. Mazol, K. Glowniak, S.J. Czuczwar, Osthole suppresses seizures in the mouse maximal electroshock seizure model, Eur. J. Med. Chem. 607 (2009) 107–109.
[11] F. Tosun, Ç.A. Kızılay, K. Erol, F.S. Kılıç, M. Kürkçüoğlu, K.H.C. Başer, Anticonvulsant activity of furanocoumarins and the essential oil obtained from the fruits of Heracleum crenatifolium, Food Chem. 107 (2008) 990–993.
[12] K.M. Amin, D.E.A. Rahman, Y.A. Al-Eryani, Synthesis and preliminary evaluation of some substituted coumarins as anticonvulsant agents, Bioorg. Med. Chem. 16 (2008) 5377–5388.
[13] N. Ahangar, A. Ayati, E. Alipour, A. Pashapour, A. Foroumadi, S. Emami, 1-[(2-Arylthiazol-4-yl) methyl] azoles as a new class of anticonvulsants: design, synthesis, in vivo screening, and in silico drug-like properties, Chem. Biol. Drug Des. 78 (2011) 844–852.
[14] M. Faizi, M. Sheikhha, N. Ahangar, H.T. Ghomi, B. Shafaghi, A. Shafiee, S.A. Tabatabai, Design synthesis and pharmacological evaluation of novel 2-[2-(2-chlorophenoxy) phenyl]-1, 3, 4-oxadiazole derivatives as benzodiazepine receptor agonists, Iranian J. Pharm. Res.: IJPR 11 (2012) 83.
[15] H.J. Lankau, K. Unverferth, C. Grunwald, H. Hartenhauer, K. Heinecke, K. Bernöster, R. Dost, U. Egerland, C. Rundfeldt, New GABA-modulating 1, 2, 4-oxadiazole derivatives and their anticonvulsant activity, Eur. J. Med. Chem. 42 (2007) 873–879.
[16] M. Mohammadi-Khanaposhtani, M. Shabani, M. Faizi, I. Aghaei, R. Jahani, Z. Sharafi, N.S. Zafarghandi, M. Mahdavi, T. Akbarzadeh, S. Emami, A. Shafiee, Design, synthesis, pharmacological evaluation, and docking study of new acridone-based 1,2,4-oxadiazoles as potential anticonvulsant agents, Eur. J. Med. Chem. 112 (2016) 91–98.
[17] M. Faizi, S. Dabirian, H. Tajali, F. Ahmadi, E.R. Zavareh, S. Shahhosseini, S.A. Tabatabai, Novel agonists of benzodiazepine receptors: design, synthesis, binding assay and pharmacological evaluation of 1,2,4-triazolo [1,5-a] pyrimidinone and 3-amino-1,2,4-triazole derivatives, Bioorg. Med. Chem. 23 (2015) 480–487.
[18] L. Dehestani, N. Ahangar, S.M. Hashemi, H. Irannejad, P.H. Masihi, A. Shakiba, S. Emami, Design, synthesis, in vivo and in silico evaluation of phenacyl triazole hydrazones as new anticonvulsant agents, Bioorg. Chem. 78 (2018) 119–129.
[19] C.A. Lipinski, Drug-like properties and the causes of poor solubility and poor permeability, J. Pharmacol. Toxicol. Methods 44 (2000) 235–249.
[20] D.F. Veber, S.R. Johnson, H.Y. Cheng, B.R. Smith, K.W. Ward, K.D. Kopple, Molecular properties that influence the oral bioavailability of drug candidates, J. Med. Chem. 45 (2002) 2615–2623.
[21] A.K. Chaturvedi, J.P. Barthwal, S.S. Parmar, V.I. Stenberg, Anticonvulsant activity of N, N′-bis [3-(3-substituted urea) propyl] piperazines, J. Pharm. Sci. 64 (1975) 454–456.
[22] R.L. Krall, J.K. Penry, B.G. White, H.J. Kupferberg, E.A. Swinyard, Antiepileptic drug development: II. Anticonvulsant drug screening, Epilepsia 19 (1978) 409–428.
[23] L. Richter, C. de Graaf, W. Sieghart, Z. Varagic, M. M€orzinger, I.J. de Esch, G.F. Ecker, M. Ernst, Diazepam-bound GABAA receptor models identify new benzodiazepine binding-site ligands, Nat. Chem. Biol. 8 (2012) 455–464.
[24] H. Liu, L. Wang, M. Lv, R. Pei, P. Li, Z. Pei, Y. Wang, W. Su, X.Q. Xie, AlzPlatform: an Alzheimer's disease domain-specific chemogenomics knowledgebase for polypharmacology and target identification research, J. Chem. Inf. Model. 54 (2014) 1050–1060.