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Synthesis and anticonvulsant activity of 8-alkoxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one derivatives

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ABSTRACT

A series of novel 8-alkoxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one derivatives were synthesized and screened for their anticonvulsant activities by the maximal electroshock (MES) test, subcutaneous pentylenetetrazol (scPTZ) test, and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). The results of these tests demonstrated that 8-heptyloxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one (**3f**) and 8-hexyloxy -5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one (**3e**) were the most promising compounds, with median effective dose (ED_{50}) of 17.6 and 17.9 mg/kg, and protective index (PI) of greater than 63.4 and 62.4 in the MES test, respectively. These PI values were higher than the PI value of the prototype antiepileptic drug carbamazepine. The scPTZ test showed that 8-pentyloxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one (**3d**) was the most potent with ED_{50} value of 38.0 mg/kg and PI value of greater than 29.4, which is much safer than marketed drug carbamazepine. The possible structure–activity relationship was discussed.

1. Introduction

According to literature reports, currently available antiepileptic drugs (AEDs) provide adequate seizure control in many patients, still about 28–30% of patients are estimated to be poorly treated [1,2]. Therefore, continued search for safer and more effective AEDs is urgently necessary. Much efforts devoted in the recent years for the development of novel compounds as potential anticonvulsant agents [3–11].

Benzazepine derivatives exhibit a broad spectrum of pharmacological activity [12–15]. Triazole compounds have wide variety of biological activities, the introduction of triazole ring to some active molecules may significantly improve the biological activity of the parent molecule due to the superposition of biological activity [16–20]. In our search for new compounds with anticonvulsant activity, 1,3,4,5-tetrahydro-7- alkoxy-2*H*-1-benzazepin-2-one derivatives showed a moderate anticonvulsant activity, among which 1,3,4,5-tetrahydro-7-butyloxy-2*H*-1-benzazepin-2-one (**1b**), revealed as the best anticonvulsant activity with an effective dose of 52.8 mg/kg in the anti-MES test. In order to obtain compounds with better anticonvulsant activity, the target compounds were synthesized through a convenient synthetic sequence. The new compounds were evaluated as anticonvulsant agents in experimental epilepsy models, i.e., the maximal electroshock (MES) test, subcutaneous pentylenetetrazol (scPTZ) test, and neurotoxicity were evaluated by using the rotarod test.

2. Results and discussion

2.1. Chemistry

Target compounds were prepared according to Scheme 1. The starting material 1,3,4,5-tetrahydro-7-hydroxy -2*H*-1-benzazepin-2-one was synthesized using the method described in a former paper of our group [12], which reacted with appropriate alkyl halide to produce the compounds **1a**–**p** [12]. Compounds **1a**–**p** then reacted with phosphorus pentasulfide in acetonitrile in the presence of triethylamine under protection of nitrogen, and the resulting compounds **2a**–**p** reacted further with methyl hydrazine carboxylate in *n*-butanol to produce the target compounds **3a**–**p**. The structures of all the new compounds were confirmed by IR, ^{1}H NMR, MS and elemental analyses and their anticonvulsant activities have been initially screened.

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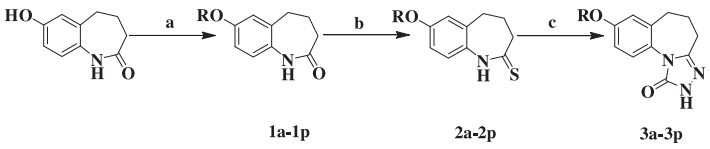

1a-1p 2a-2p 3a-3p

R:

3a = n- C_3H_7 3e = n-C_7H_{15} 3i = $CH_2C_6H_4$(*m*-Cl) 3m = $CH_2C_6H_4$(*p*-F)

3b = n-C_4H_9 3f =n-C_8H_{17} 3j = $CH_2C_6H_4$(*p*-Cl) 3o= $CH_2C_6H_4$(*p*-CH_3)

3c = n-C_5H_{11} 3g = $CH_2C_6H_5$ 3k = $CH_2C_6H_4$(*o*-F) 3p= $CH_2C_6H_4$(*p*-Br)

3d= n-C_6H_{13} 3h = $CH_2C_6H_4$(*o*-Cl) 3l = $CH_2C_6H_4$(*m*-F)

Reagents: (**a**) RX/C_2H_5OH, 80-92℃; (**b**) P_2S_5, $(C_2H_5)_3N$ /CH_3CN, 86-92℃, 5-7 h; (**d**) $H_2NNHCOOCH_3$/$(CH_3)(CH_2)_3OH$, 140-150℃, 40-48 h

Scheme 1. The synthesis route of compounds **3a**–**p**.

2.2. Pharmacology

Based on previous reports [21–23], we knew that trazoles have activity against both major and minor seizures. The MES test is regarded as the pharmacologic model of grand mal, and the scPTz test as the pharmacologic model of petit mal seizures. Therefore we carried out those two tests to evaluate the anticonvulsant activity of the synthesized compounds.

The results of preliminary (phase I) screening of compounds **3a**–**p** are summarized in Table 1. In the anti-MES test, all the synthesized compounds exhibited anticonvulsant activity, among which eight compounds (**3d**–**g**, **3j**, and **3l**–**n**) possessed anticonvulsant activity against MES-induced seizure at the dose of 30 mg/kg, and seven compounds (**3b**–**c**, **3h**–**i**, **3k** and **3o**–**p**) were active at the dose of 100 mg/kg. The remaining one compound **3a** exhibited anti-MES effect only under the high dose of 300 mg/kg. As a result of preliminary screening, compounds **3b**–**p** were subjected to phase II trials for quantification of their anticonvulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) in mice (Table 2). Among these derivatives, the most potent compounds **3f** and **3m** exhibited similar activity with ED_{50} value of 17.6 mg/kg, furthermore, they had significantly lower neurotoxicity (TD_{50} > 1117.4 mg/kg, TD_{50} > 931.2 mg/kg, respectively) than the marked antiepileptic drug carbamazepine. And their PI value (PI > 63.4, PI > 52.6, respectively) was superior to that of carbamazepine (TD_{50} = 71.6 mg/kg, PI = 8.1) in the MES test.

Analyzing the activities of the synthesized compounds the following structure–activity relationships (SAR) were obtained. Generally, the anticonvulsant activity of an organic compound might be increased remarkably after the introduction of a halogen atom. So, some halogen substituted derivatives were designed and synthesized in this paper. Comparison of the halogen substituted derivatives indicated that different halogen atoms contributed to the anticonvulsant activity in the order of F > Cl > Br; the introduction of F atom on the benzyl ring led to stronger activity. Comparing the derivatives with different F-substitution positions on the benzyl ring, their activity order was *m*-F > *o*-F > *p*-F, and activity order of the Cl- and Br-atom substituted derivatives was *m*-Cl > *o*-Cl > *p*-Cl > *p*-Br. One electron donor derivative (**3o**) was also designed and prepared, and its activity was slightly low. The anticonvulsant activity of compounds containing substituted benzyloxy (*m*-F, *o*-F, *p*-F, *m*-Cl) was stronger than that of the compound with non-substituted benzyloxy (**3h**). The anticonvulsant activity of another four substituted-benzyloxy derivatives **3i**, **3k**, **3o** and **3p** was lower than that of the compound **3h**. The *m*-F-substituted derivative **3m** exhibited the strongest anticonvulsant activity.

Length of the alkyl chain appeared to have a direct impact on anticonvulsant activity of the 7-alkoxyl derivatives. From compound **3a** to **3g**, as alkyl chain length increased, ED_{50} gradually increased with the compound **3f** being the most active. However, the anticonvulsant activity decreased when alkyl chain number lengthened to 8.

In the anti-scPTz test, the synthesized compounds exhibited a less- to moderate-degree of anticonvulsant activity. As a result of preliminary screening, eight compounds (**3c**–**j**) were quantitatively evaluated for their anticonvulsant activity. They showed less effective against scPTZ-induced seizures but exhibited a high degree of protection against scPTz-induced seizures. 8-Pentyloxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one (**3d**) was among the most active but also has the lowest toxicity. It showed the ED_{50} value of 38.0 mg/kg, and the PI of greater than 29.4, which is also much greater than the PI of the marked antiepileptic drug carbamazepine.

Pentylenetetrazole has been reported to produce seizures by inhibiting γ-aminobutyric acid (GABA) neurotransmission [24,25]. GABA is the main inhibitory neurotransmitter substance in the brain, and is widely implicated in epilepsy. Inhibition of GABAergic neurotransmission has been shown to promote and facilitate seizures [26], while enhancement of GABAergic neurotransmission is known to inhibit or attenuate seizures. The compound **3d** might enhance GABAergic neurotransmission.

Table 1
Phase I anticonvulsant data in mice of compounds **3a**–**p** (i.p.).[a]

Comp.	R	MES[b]			scPTZ[b]		
		30[c]	100	300	30[c]	100	300
3a	$-CH_3$	1/5	1/5	5/5	0/5	0/5	0/5
3b	$-C_3H_7$	1/5	4/5	–[d]	0/5	1/5	1/5
3c	$-C_4H_9$	2/5	5/5	–[d]	1/5	5/5	–[d]
3d	$-C_5H_{11}$	5/5	–[d]	–[d]	1/5	5/5	–[d]
3e	$-C_6H_{13}$	5/5	–[d]	–[d]	1/5	5/5	–[d]
3f	$-C_7H_{15}$	5/5	–[d]	–[d]	1/5	5/5	–[d]
3g	$-C_8H_{17}$	4/5	–[d]	–[d]	1/5	5/5	–[d]
3h	$-PhCH_2$	3/5	5/5	–[d]	1/5	1/5	1/5
3i	$-CH_2C_6H_4$(*o*-Cl)	3/5	5/5	–[d]	1/5	0/5	1/5
3j	$CH_2C_6H_4$(*m*-Cl)	4/5	–[d]	–[d]	1/5	1/5	1/5
3k	$-CH_2C_6H_4$(*p*-Cl)	2/5	5/5	–[d]	1/5	1/5	0/5
3l	$-CH_2C_6H_4$(*o*-F)	5/5	–[d]	–[d]	0/5	1/5	0/5
3m	$-CH_2C_6H_4$(*m*-F)	5/5	–[d]	–[d]	0/5	0/5	1/5
3n	$-CH_2C_6H_4$(*p*-F)	4/5	–[d]	–[d]	0/5	1/5	1/5
3o	$-CH_2C_6H_4$(*p*-CH_3)	3/5	4/5	–[d]	0/5	0/5	1/5
3p	$-CH_2C_6H_4$(*p*-Br)	1/5	5/5	–[d]	1/5	1/5	1/5

[a] All of tested compounds were dissolved in DMSO.
[b] The maximal electroshock test was induced after 30 min past administration of the tested compounds.
[c] Doses are denoted in milligrams per kilogram.
[d] Not tested.