European Journal of Medicinal Chemistry 84 (2014) 574–583

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and anticonvulsant activity of novel purine derivatives

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ARTICLE INFO

Article history:
Received 10 January 2014
Received in revised form
19 July 2014
Accepted 21 July 2014
Available online 22 July 2014

Keywords:
Synthesis
Purine
Triazole
Maximal electroshock
Neurotoxicity
Pentylenetetrazole

ABSTRACT

A series of new purines containing triazole and other heterocycle substituents was synthesized and evaluated for their preliminary anticonvulsant activity and neurotoxicity by using the maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and rotarod neurotoxicity (TOX) tests. Among the compounds studied, 9-decyl-6-(1*H*-1,2,4-triazol-1-yl)-9*H*-purine (**5e**) was the most potent compound, with a median effective dose of 23.4 mg/kg and a high protective index of more than 25.6 after intraperitoneal administration in mice. Compound **5e** showed significant oral activity against MES-induced seizures in mice, with an ED_{50} of 39.4 mg/kg and a PI above 31.6. These results demonstrate that compound **5e** possesses better anticonvulsant activity and is safer than the commercially available drugs carbamazepine and valproate in MES, scPTZ and TOX models.

1. Introduction

Epilepsy is a heterogeneous neurological disorder characterized by the onset of spontaneous convulsive and non-convulsive seizures. This disorder affects over 50 million people worldwide, and it is estimated that only 50% of patients are adequately treated for their symptoms with currently available antiepileptic drugs (AEDs). Of the remaining patients, approximately 20% are either inadequately treated or treated at the expense of severe side effects, leaving approximately 30% of patients with refractory epilepsy [1,2]. Conventional antiepileptic agents (phenytoin and carbamazepine) and recent antiepileptic drugs (gabapentin, vigabatrin, remacemide, and loreclezole) are clinically effective against different types of seizures. However, many AEDs have serious side effects [3–7]. Therefore, the continued search for safer and more effective AEDs is necessary.

The purine nucleus is one of the most important and widely exploited heterocyclic ring for the development of bioactive molecules. The literature contains many examples of purine derivative synthesis, and these compounds exhibiting a range of biological properties, including anticonvulsant [8,9], antibacterial [10,11], antifungal [12], antimalarial [13], anticancer [14–16], and anti-inflammatory [17] activities.

Previously, we reported the synthesis of several triazole-containing heterocycles, including triazoloquinolines, triazolophthalazines, triazolobenzothiazines, and triazolobenzooxazepines, and evaluated their anticonvulsant activity. The majority of these heterocycles exhibited potent anticonvulsant activity [18–21] (Fig. 1). Here, a series of 7-alkyl-7*H*-[1,2,4]triazolo[4,3-*g*]purine derivatives (**4a**–**o**) was designed to combine both purine and triazole moieties. Based on the anticonvulsant activities of compounds **4a**–**o**, another series of 9-alkyl-6-(1*H*-1,2,4-triazol-1-yl)-9*H*-purine derivatives (**5a**–**p**) was designed and synthesized through the ring-opening of compounds **4a**–**o**. For the sake of having a structure–activity relationship, the triazole ring in compounds **5a**–**p** was replaced by other heterocycles such as imidazole, methylimidazole, or pyrazole rings to give compounds **6**–**8** and **9**, and their structures were characterized using IR, ^{1}H NMR, MS, and ^{13}C NMR techniques. The anticonvulsant activity of the titled compounds was evaluated using the maximal electroshock test in mice, and their neurotoxicity was evaluated using the rotarod test. The activity of compound **5e** against pentylenetetrazole-induced seizures was also established.

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http://dx.doi.org/10.1016/j.ejmech.2014.07.074
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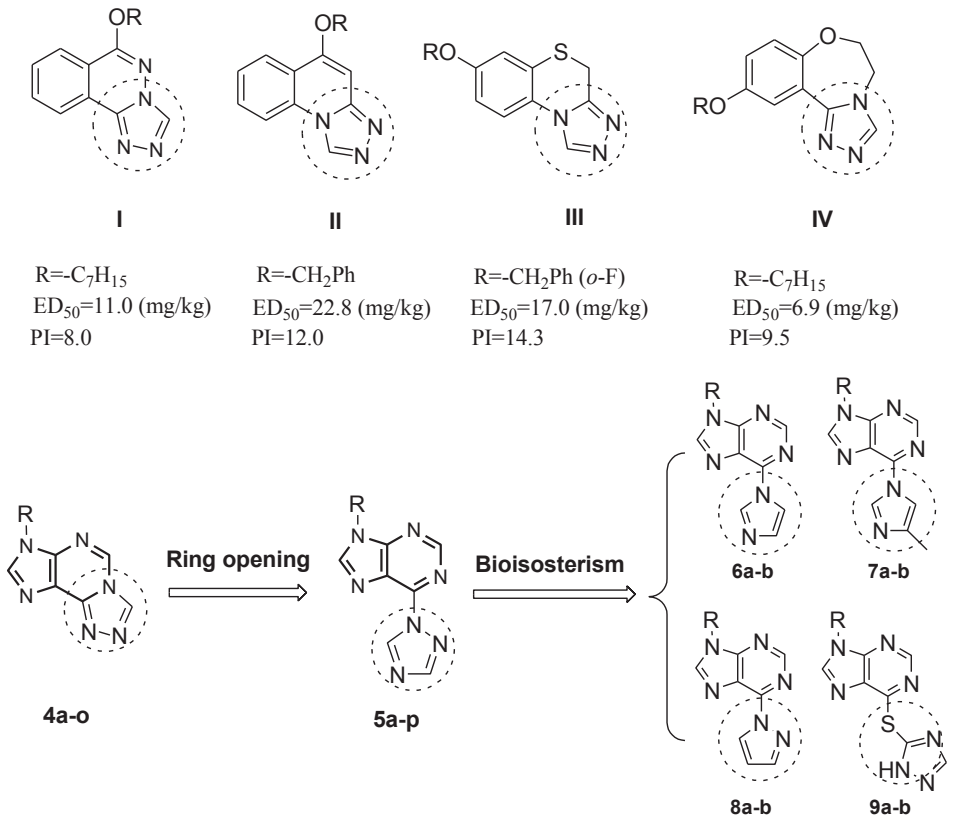

Fig. 1. Structures of some compounds containing triazole and target compounds.

2. Results and discussion

2.1. Chemistry

6-Chloro-9-alkyl-9*H*-purines (**2a**–**p**) were prepared by alkylating 6-chloro-9*H*-purine (**1**) using alkyl bromide or benzyl chloride derivatives (Scheme 1) [22]. Treatment of **2a**–**p** with hydrazine hydrate in methanol afforded 1-(9-alkyl-9*H*-purin-6-yl) hydrazines (**3a**–**o)** in a high yield [23]. Cyclization of compounds **3a**–**o** with triethyl orthoformate yielded 7-alkyl-7*H*-[1,2,4]triazolo [4,3-*g*]purines (**4a**–**o)**. When 6-chloro-9-alkyl-9*H*-purines (**2a**–**p**) were allowed to react with different azoles such as triazole, imidazole, methylimidazole and pyrazole in refluxing dimethylformamide (DMF) in the presence of K_2CO_3 [24,25], the 9-chlorine atom of 2 was easily substituted by these heterocylces, producing the corresponding purines: 9-alkyl-6-(1*H*-1,2,4-triazol-1-yl)-9*H*-purine (**5a**–**p)**, 9-alkyl-6-(1*H*-imidazol-1-yl)-9*H*-purine (**6a**–**b)**, 9-alkyl-6-(4-methyl-1*H*-imidazol-1-yl)-9*H*-purine (**7a**–**b)**, and 9-alkyl-6-(1*H*-pyrazol-1-yl)-9*H*-purine (**8a**–**b)**. 9-Alkyl-6-(3*H*-1,2,4-triazol-3-ylthio)-9*H*-purines (**9a**–**b)** were synthesized by reacting compounds **2a**–**p** with 1*H* (2*H*), (4*H*)-1,2,4-triazole-3-thiol in acetonitrile in the presence of sodium methylate. The structures of the targeted compounds were characterized using spectral methods, and all spectral data corroborated the assumed structures.

2.2. Pharmacology

The obtained compounds were submitted for *in vivo* evaluation using the methods described in the Antiepileptic Drug Development Program (ADD) of the National Institutes of Health according to previously described testing procedures (USA) [26,27]. The described pharmacological evaluation was accepted by Ethics Commission of China. Primary studies of anticonvulsants in mice involved two tests: MES and neurotoxicity tests. The most promising derivatives were subjected to quantitative determination of their ED_{50} and TD_{50}. Experiments were performed in KunMing mice (weighing 18–22 g) purchased from the Laboratory of Animal Research, College of Pharmacy, Yanbian University, Yanji, Jilin Province, China. The animals had free access to food and water, except during the testing period. The test compounds were dissolved in DMSO.

The MES seizure model was used for preliminary screening of purine derivatives. All the compounds were administered by intraperitoneal injection in triplicate at doses of 30 and 100 mg/kg. The findings were recorded at 0.5 h, and the results are presented in Table 1 and Table 2 (phase I).

The MES test showed that some derivatives of the series **4a**–**o** were active at a dose of 100 mg/kg (Table 1), indicating their ability to prevent the seizer spread. Four derivatives (**4b**–**e**) out of the six alkyltriazolopurines (**4a**–**f**) showed anticonvulsant activity. The length of the alkyl chain appeared to affect the anticonvulsant activity of the alkyl-substituted derivatives (**4a**–**f**). We observed a correlation between the length of the alkyl chain of compounds (**4a**–**f**) and the corresponding anticonvulsant activity. An increase in the length of the alkyl chain gradually increased the anticonvulsant activity, with the maximum anticonvulsant activity being shown by compound **4c** ($R = C_6H_{13}$), after which a gradual decrease in activity was observed. In this study, the activity curve of the alkyl chain substituted derivatives was bell-shaped with a maximum activity peak. Compound **4c** showed the maximum activity peak, which may reflect the optimal partition coefficient associated with the easiest crossing of biological membranes. Among the benzyl group-substituted derivatives (**4g**–**o**), compounds **4g**, **4j** and **4o**