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Original article

Design and synthesis of new of 3-(benzo[d]isoxazol-3-yl)-1-substituted pyrrolidine-2, 5-dione derivatives as anticonvulsants

Sachin Malik, Priya Ahuja, Kapendra Sahu, Suroor Ahmad Khan*

Department of Pharmaceutical Chemistry, Faculty of Pharmacy Jamia Hamdard (Hamdard University), New Delhi 110062, India

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ABSTRACT

A series of 3-(benzo[d]isoxazol-3-yl)-N-substituted pyrrolidine-2, 5-dione (**7a**–**7d**, **8a**–**8d**, **9a**–**9c**) have been prepared and evaluated for their anticonvulsant activities. Preliminary anticonvulsant activity was performed using maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) tests after intraperitoneal (ip) injection into mice, which are the most widely employed models for early identification of anticonvulsant candidate. The acute neurological toxicity (NT) was determined applying rotorod test. The quantitative evaluation after oral administration in rats showed that the most active was 3-(benzo[d]isoxazol-3-yl)-1-(4-fluorophenyl) pyrrolidine-2, 5-dione (**8a**) with ED_{50} values of 14.90 mg/kg. Similarly the most potent in scPTZ was 3-(benzo[d]isoxazol-3-yl)-1-cyclohexylpyrrolidine-2, 5-dione (**7d**) with ED_{50} values of 42.30 mg/kg. These molecules were more potent and less neurotoxic than phenytoin and ethosuximide which were used as reference antiepileptic drugs.

1. Introduction

Epilepsy is the most common neurologic disorder affecting people of all ages. Up to 3% of the population will suffer epilepsy at some point in their lives, and approximately 50 million people are affected worldwide. The prevalence of epilepsy is highest in the first decade of life and after the age of 60 years, with rates in men usually higher [1,2]. The currently available anti epileptic drugs (AEDs) are effective in reducing the severity and number of seizures in less than 70% of patients. However, all currently approved anticonvulsant agents have specific problems of neurotoxicity, symptoms of depression, CNS related ailments, cosmetic (gingival hyperplasia) to life threatening (hepatotoxicity, megaloblastic anemia) [3–7]. The need of marketing new drugs was refractory epilepsy and severe side-effects of classical AEDs. The ideal antiepileptic should prevent different types of seizures without producing side effects that affect adversely patients' quality of life. Taking into consideration the above continued search for safer, more effective and possibly antiepileptogenic drugs is urgently necessary.

Rational methodologies find it difficult to discover new antiepileptic drugs due to incomplete information regarding molecular pathway of human epilepsy (no clear histopathological abnormalities are identified) and complex mechanism of action of for majority of AEDs [8]. So the most important strategy to develop new anticonvulsants is the ligand-based approach that utilizes existing biological data from old and new drugs, other historical compounds or different pharmacophore models that were established through the analysis of structural characteristics of clinically effective AEDs, as well as other anticonvulsant active compounds in clinical or preclinical development. This method is applied mainly for structural modifications of currently available AEDs in aim to obtain more efficacious drugs that will suppress seizures and/or drugs with minimal or no adverse effects compared to parental compound. The past decades have endorsed many approaches to identify the structural features of compounds essential for anticonvulsant activity. As a result, it is well established that the crucial core fragment of anticonvulsants is defined by nitrogen heteroatomic system, usually a cyclic imide, at least of one carbonyl group and phenyl or alkyl groups connected to the heterocyclic system [9,10]. This common template is present in the structures of first generation of AEDs such as phenytoin (**2**) or primidone (**3**) (Fig. 1), to molecules in preclinical development (1-(4-phenylpiperazin-1-yl)-3-(2-(trifluoromethyl) phenyl) pyrrolidine-2, 5-dione) (**8**) which are known to be active against maximal electroshock (MES) seizure test, the experimental animal model for generalized tonic-clonic epilepsy. The extensive structure activity relationship (SAR) studies of AEDs revealed, however, that the phenyl substituents attached at the heteroatomic imide or cyclic amide ring are not necessary to retain the anticonvulsant activity. An example of such molecules is ethosuximide (Ist generation) (**4**),

* Corresponding author.
E-mail address: sakhanpchem@gmail.com (S.A. Khan).

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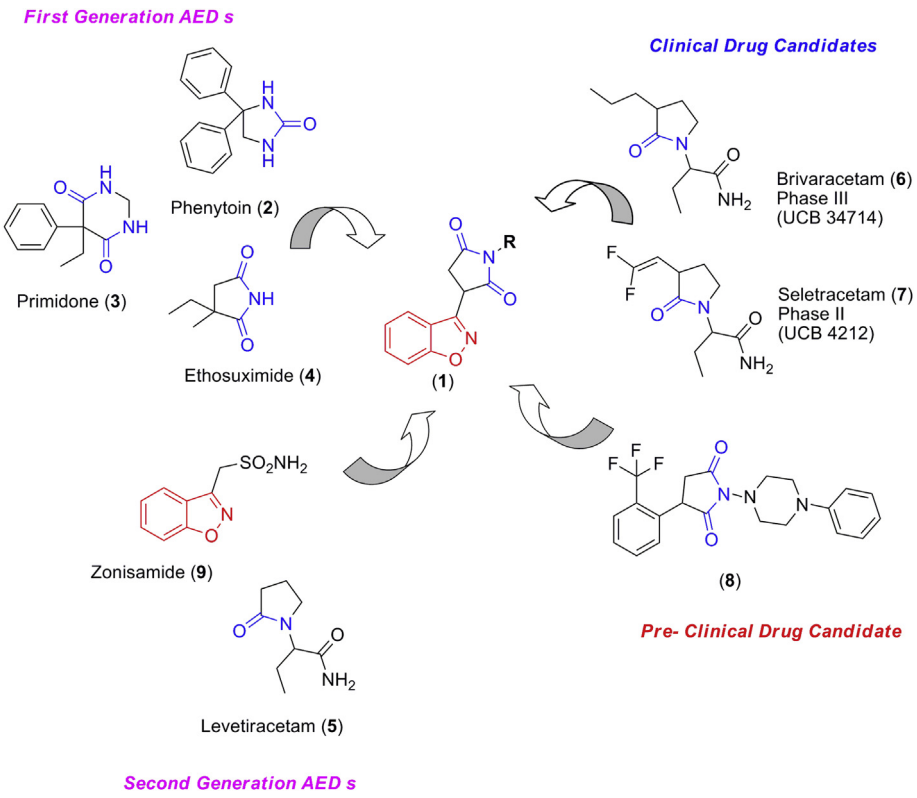

Fig. 1. Structural similarities between different generation known AEDs, compounds in clinical or pre-clinical development and the 3-(benzo[d]isoxazol-3-yl)-1-substituted pyrrolidine-2, 5-dione.

recently marked AED levetiracetam(II generation) (**5**) or compounds being currently under the clinical trials, namely brivaracetam (UCB 34714, Phase III) (**6**)and seletracetam (UCB 4212, Phase II) (**7**)(Fig. 1) [11–14]. In contrast to the drugs described above these molecules were inactive in the MES screen. They revealed protection in the subcutaneous pentylenetetrazole seizure test (scPTZ), the animal model of absence epilepsy, or in secondarily generalized motor seizures screen in corneally kindled mice, which is claimed to detect compounds that can act to prevent the development of seizures. Such substances could be termed 'anti-epileptogenetic' [15].

Taking into consideration the above our investigations have been focused on different structural modifications on 1 and 3 position of pyrrolidine-2, 5-diones which have been reported as targets for new antiepileptic drugs [16–23]. Furthermore, using the benzisoxazole template after development of Zonisamide (ZNS, 1, 2-benzisoxazole-3-methanesulfonamide; Zonegran; Excegran) (**9**) as one of the structurally novel AEDs with a broad spectrum of antiepileptic activity [20]. It appears to inhibit the spread of seizure discharges and suppress epileptogenic focus. Clinical experience documented its efficacy in treatment of medically refractory simplex and complex partial seizures, generalized convulsions including tonic-clonic, absence, myoclonic seizures, as well as secondary generalized or combined seizures. Significant effectiveness was also demonstrated in lennox-gastaut, west syndrome and infantile spasms [24–28]. Currently, ZNS is believed to use different mechanisms of action as it blocks both the neuronal voltage-gated sodium channels and the low-voltage (T-type) calcium channels and inhibits carbonic anhydrase. Some studies have also displayed the effects of ZNS on synthesis, release, and degradation of different neurotransmitters (i.e., glutamate, δ-amino butyric acid (GABA), dopamine and serotonin) suggesting its possible role in modulating synaptic inhibition [29,30]. It is demonstrated to have phenytoin like profile by protecting animals against MES [31]. Additionally risperidone atypical antipsychotic, containing 1, 2 benzisoxazole nuclei can also be used in combination therapies of epilepsy [32].

The main goal was to obtain compounds active both in maximal electroshock (MES) seizure and the subcutaneous pentylenetetrazole (scPTZ) screens. Following these findings, as part of our efforts to design new anticonvulsant agents in the present studies we have synthesized a new series of 3-(benzo[d]isoxazol-3-yl)-1-substituted pyrrolidine-2, 5-dione. These molecules have been designed as analogs of compounds (**1**) (Fig. 1) in which amine functions have been modified with different alkyl, cycloalkyl, aromatic and heteroaromatic groups and evaluate against anticonvulsant activity.

2. Result and discussion

2.1. Chemistry

The synthesis of compounds **7a**–**7d**, **8a**–**8d**, **9a**–**9c** was accomplished as shown in Scheme 1. Initially, 2-hydroxyacetophenone war reacted with hydroxylamine that yielded oxime intermediate (**1**) which was subsequently acetylated and then refluxed with pyridine to obtained cyclized product 3-methylbenzo[d]isoxazole (**3**). Oximes are formed by nucleophilic attack of hydroxylamine at the carbonyl carbon (C=O) of an aldehyde or ketone to give an unstable tetrahedral intermediate to form a new C=N bond with elimination of water. Further oxidation of reactive methyl group to aldehyde group by selenium dioxide works well for condensed analogs and led to the formation of benzo[d]isoxazole-3-carbaldehyde (**4**) in good yield. Then the condensation of aldehyde with cyanoacetic esters was accomplished with subsequent addition of potassium