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Design, synthesis, biological evaluation, homology modeling and docking studies of (*E*)-3-(benzo[*d*][1,3]dioxol-5-ylmethylene) pyrrolidin-2-one derivatives as potent anticonvulsant agents

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ABSTRACT

A series of (*E*)-3-(benzo[*d*][1,3]dioxol-5-ylmethylene)pyrrolidin-2-one derivatives were designed, synthesized, and evaluated for their anticonvulsant activities. In the preliminary screening, compounds **5**, **6a**–**6f** and **6h**–**6i** showed promising anticonvulsant activities in MES model, while **6f** and **6g** represented protection against seizures at doses of 100 mg/kg and 0.5 h in scPTZ model. The most active compound **6d** had a high-degree protection against the MES-induced seizures with ED_{50} value of 4.3 mg/kg and TD_{50} value of 160.9 mg/kg after intraperitoneal (*i.p.*) injection in mice, which provided **6d** in a high protective index (TD_{50}/ED_{50}) of 37.4 comparable to the reference drugs. Beyond that, **6d** has been selected and evaluated *in vitro* experiment to estimate the activation impact. Apparently, **6d** clearly inhibits the $Na_v1.1$ channel. Our preliminary results provide new insights for the development of small-molecule activators targeting specifically $Na_v1.1$ channels to design potential drugs for treating epilepsy. The computational parameters, such as homology modeling, docking study, and ADME prediction, were made to exploit the results.

Nowadays, it is urgent to discover new chemical entities as antiepileptic drugs (AEDs), since about one-third of patients undergoing epilepsy is still insufficiently treated.[1] Besides, currently available AEDs tend to cause multiple serious side-effects, such as drowsiness, ataxia, gastrointestinal disturbances, gingival hyperplasia, hirsutism, and megaloblastic anaemia.[2–4]

Due to incomplete information on the pathogenesis of human epilepsy and the complex mechanisms of actions of AEDs, it is challenging to use rational methodologies to discover new AEDs.[5] Therefore, the ligand-based pharmacophore approach is an important strategy for designing novel anticonvulsant agents.[6–8] For example, Malik S. et al. reported a series of 3-(benzo[*d*]isoxazol-3-yl)-*N*-substituted pyrrolidine-2,5-diones, which were designed dependent upon the existing biological data from old drugs, new drugs, and some other anticonvulsant active components. In this regard, we examined the structural characteristics of typical anticonvulsant agents, such as ethosuximide,[9] levetiracetam,[10] brivaracetam,[11] and seletracetam[12] (Fig. 1). The inspection showed that these drugs shared a common pyrrolidinone moiety in their molecules. Inspired by this observation, we assumed that the compound containing pyrrolidinone moiety in a single molecule could be favorable to anticonvulsant activity.

An earlier structure-activity relationship studies of stiripentol[13] revealed the remarkable anticonvulsant activity for the skeleton of benzo[*d*][1,3]dioxole. Aboul-enein et al.[13] attached semicarbazone moiety to the backbone of stiripentol (strategy **a**) and cyclization of the semicarbazone (strategy **b**) to afford the semicarbazone $\mathbf{S_1}$ and racemic pyrazoline $\mathbf{S_2}$ (Fig. 2), respectively. $\mathbf{S_1}$ showed an excellent ED_{50} value of 87 mg/kg in the MES model, while $\mathbf{S_2}$ had a good activity against scPTZ-induced seizures (ED_{50} = 110 mg/kg).

In this study, we implemented the strategy **c**. To be specific, a five-membered pyrrolidinone ring was used to modify neopentyl

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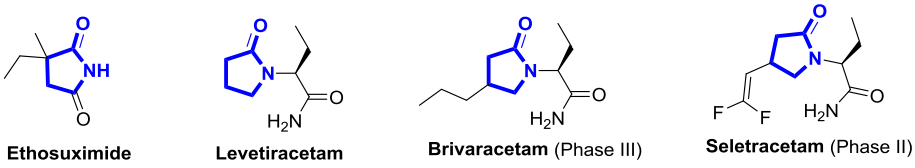


Fig. 1. Anticonvulsant agents bearing pyrrolidinone fragments.

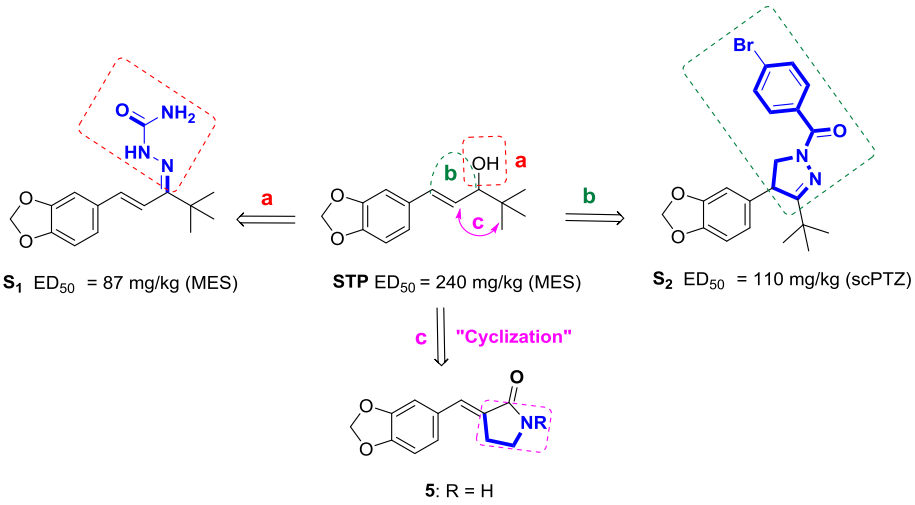
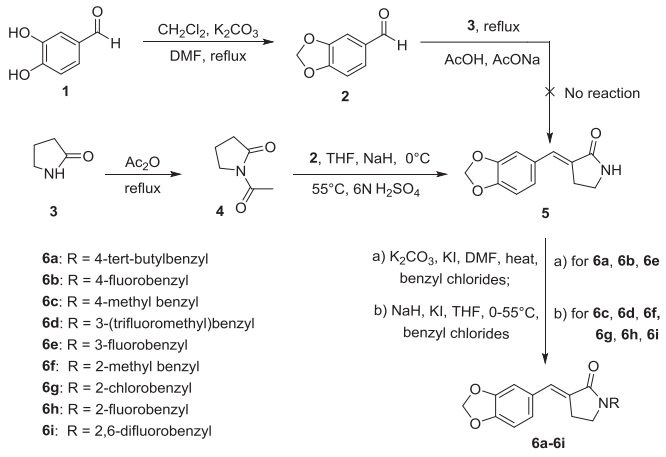


Fig. 2. Stiripentol and designed anticonvulsant agents.

alcohol, which aimed to generate a synergetic effect in the treatment of epilepsy. The structures of designed targeting compounds along with stiripentol were presented in Fig. 2.

Generally speaking, the benzyl-based derivatives were beneficial and important for anticonvulsant activity, which had been depicted in numerous studies[14–16] including the marketed drugs Lacosamide, Rufinamide, Safinamide, and Retigabine. Herein, the influences of *N*-terminal benzyl substitutions on the anticonvulsant profiles of **5** were further explored *via* synthesis and pharmacological evaluation of **6a–6i**.

The synthetic route of targeting compounds was illustrated in Scheme 1. 3,4-Dihydroxy benzaldehyde **1** was firstly reacted with CH_2Cl_2 in presence of DMF according to the published method.[17] Besides, the resulting **2** was used as an active scaffold for the synthesis of *E*-configuration **5** carrying Knoevenagel condensation reaction. However, due to the weak acidity of pyrrolidone **3** α-hydrogens, benzo[*d*][1,3]dioxole-5-carbaldehyde **2** could not be directly condensed with **3**. Instead, compound **3** was initially reacted with acetic anhydride to produce **4**. Herein, the *N*-acetyl group is an electron-withdrawing group which facilitates the condensation reaction through enhancing the acidity of the α-hydrogens.[18] Then, an excess of base was used during the condensation and the activating group was easily removed from the product **5**. Furthermore, the resulting **5** was modified with different substituted benzyl chlorides and **6a-6i** was obtained.



Scheme 1. The synthesis route of targeting compounds **6a–6i**.

Compound **5** did not form crystals suitable for X-ray diffraction (XRD) analysis. As a result, the further structural elucidations were limited to the ^{1}H NMR experiments. From the two hypothetical conformations of **5** (Fig. 4), the *E*-configuration was proposed as the more feasible one. Besides, a long-range spin-spin coupling of H-4, H′-4 and H-Me was observed in the NMR spectrum of **5**. Additionally, the signal of protons H-4 and H′-4 appeared as a triplet of doublets with two vicinal coupling constants of $J_{H4,\ H'4\text{-}H5,\ H'5}$ = 6.6 and $J_{H4,\ H'4\text{-}HMe}$ = 3.0 (in Hz). It is worth mentioning that the NOE experiment showed no correlations between the H-Me and H-4, H′-4 signals, suggesting that H-Me and H-4H′-4 were on the opposite sides of the double bond, which was only possible for the *E*-configuration **5** (See Supplementary Fig. S2 ^{1}H NMR and NOE spectrums in Supplementary data).

The preclinical discovery and development of novel chemical entities to treat epilepsy heavily rely on using animal models of seizures. The maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screening are two important and routine animal models for the anticonvulsant studies.[19,20] Almost all AEDs are protective in at least one of these two models.[21] Therefore, these two kinds of anticonvulsant tests are significant for the clinical prediction of the anticonvulsant drug candidates. Besides, the acute neurological toxicity (NT) was required and determined by the rotarod test.[22] The screening results had been summarized in Table 1.