European Journal of Medicinal Chemistry 73 (2014) 217–224

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Design, synthesis and evaluation of the antidepressant and anticonvulsant activities of triazole-containing quinolinones

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ARTICLE INFO

Article history:
Received 12 July 2013
Received in revised form
11 December 2013
Accepted 12 December 2013
Available online 25 December 2013

Keywords:
Antidepressant
Anticonvulsant
Quinolinone
Triazole
Forced swimming test
Maximal electroshock seizure

ABSTRACT

A series of 1-substituted-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1*H*)-ones were designed, synthesized, and screened for their antidepressant and anticonvulsant activities. Interestingly, compounds **5i**, **5j**, **5m**, and **5n** led to significant reductions in the immobility time in the forced swimming test at a dose of 50 mg/kg, and exhibited higher levels of efficacy than the reference standard fluoxetine. In addition, compound **5i** exhibited greater efficacy than fluoxetine in the tail suspension test. The results of an open field test further confirmed that compound **5i** provided a good antidepressant effect. In the maximal electroshock seizure screen, compounds **5c** and **5d** showed moderate levels of anticonvulsant activity and protected 100% of the animals at a dose of 100 mg/kg. None of the synthesized compounds showed any neurotoxicity in the rotarod test at a dose of 100 mg/kg.

1. Introduction

Depression and epilepsy are two of the most commonly encountered neurological disorders [1,2], and several reports have recently appeared in the literature concerning the connection between these two disorders [3–6]. It is now effectively well recognized that depression is common among people suffering with epilepsy, and in a community-based study of people with epilepsy, the rate of depression was found to be 37% [7]. In patients typically referred to epilepsy centers (representing a group of people with seizures that are particularly refractory to medication), the rate of depression was found to be 50 percent (Fig. 1) [7]. A large number of patients with epilepsy require some form of antidepressant medication, and this has recently led many experts in the field to question whether the prescribing of antidepressants to this special group could exacerbate the occurrence of seizures. Ojemann et al. [8] performed a retrospective study of the use of the tricyclic antidepressant doxepin in epilepsy patients, and found that whilst the depressive symptoms of the patients had been reduced by 89%, the frequency of their seizures had increased by 79%. These results therefore suggested the existence of a negative relationship between these two effects. In contrast, favale et al. [9] used fluoxetine (20 mg/day) to treat 17 epilepsy patients with symptoms of depression, and reported the complete remission of seizures in six patients. Furthermore, the other patients also experienced a 30% reduction in the frequency of their seizures. The two antidepressants described in these cases clearly have different effects (i.e., positive and negative) on patients with epilepsy. Research on antidepressants for the treatment of depressive symptoms in patients with epilepsy is currently an area of considerable activity, and the search for novel and increasingly effective drugs with anticonvulsant and antidepressant activities (the same type as fluoxetine) represent an important and challenging area of medicinal chemistry.

There is a growing body of evidence in the literature that suggests that quinolinone derivatives possess a broad range of biologically interesting properties, including anticonvulsant [10–12], anti-cancer [13,14], antifungal and anti-inflammatory [15], antibacterial [16,17], and antidepressant activities [18–20]. Earlier studies by Oshiro et al. [21] have demonstrated that 3,4-dihydro-2(1*H*)-quinolinones (Fig. 2, **I**) have promising antidepressant activities [21]. Several studies in this area have recently confirmed

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http://dx.doi.org/10.1016/j.ejmech.2013.12.014

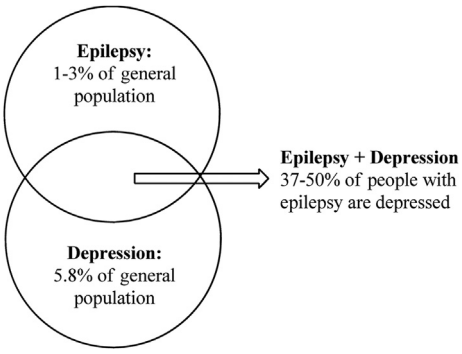


Fig. 1. Epilepsy and depression: estimates of their occurrence.

the antidepressant properties of aripiprazole, which is a 3,4-dihydro-2(1*H*)-quinolinone-containing compound (Fig. 2) that was initially marketed as an antipsychotic agent [22–27]. Triazole is the core structural motif in a variety of different compounds in medicinal chemistry and has been reported to exhibit a broad range of biological properties, including antimicrobial [28,29], enzyme inhibition [30,31], antinociceptive [32], anti-inflammatory [33], antidepressant [34,35], and anticonvulsant activities [36,37]. Our previous work towards the synthesis and evaluation of a series of triazole-containing compounds showed that the addition of a triazole ring to other heterocycles effectively strengthened their anticonvulsant activities (Fig. 2, **II** and **III**) [38–41]. Based on these results, we recently embarked on a program to combine the antidepressant and anticonvulsant activities of 3,4-dihydro-2(1*H*)-quinolinone and triazole through the preparation of a hybrid molecule composed on the two individual units (Fig. 2). Herein, we describe our most recent work towards the design, synthesis, and evaluated of 19 new triazole-containing quinolinones (**5a**–**5s**) for their antidepressant and anticonvulsant activities.

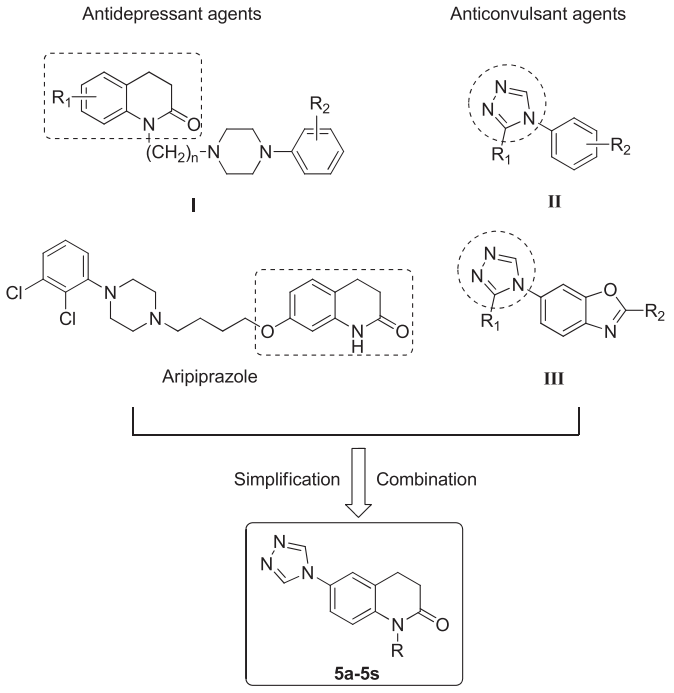


Fig. 2. Design of compounds **5a**–**5s**.

2. Chemistry

All of the target compounds were synthesized according to the route depicted in Scheme 1. Compound **3** was synthesized via the sequential nitration and catalytic hydrogenation of the commercially available 3,4-dihydro-2(1*H*)-quinolinone according to methods previously described in the literature [42]. Compound **3** was then treated with dimethoxy-*N*,*N*-dimethylmethanamine (DMF-DMA) and formylhydrazine in acetonitrile to provide compound **4** [43]. The subsequent alkylation of compound **4** with a variety of different alkylating agents gave the target compounds (**5a**–**s**). The chemical structures of these compounds were characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy. The physical and analytical data are listed in Section 6.

3. Pharmacology

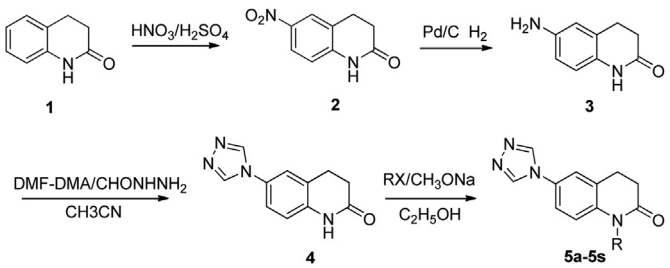
All of the compounds synthesized in the current study were screened for their antidepressant activities using Porsolt's behavioral despair (forced swimming) test [44]. The anticonvulsant activities and neurotoxicities of the compounds were also evaluated. We followed the protocols issued for the phase I tests by the Epilepsy Branch of the Antiepileptic Drug Development (ADD) program at the National Institutes of Health [45,46] with two exceptions. We used a different strain of mice and seizures were elicited in mice with ear stimulation. Compound **5i** was also evaluated using the tail suspension test (TST) [47,48] and the open field test [49] to further confirm its antidepressant activity.

All of the compounds tested in the pharmacology experiments were dissolved in dimethylsulfoxide and administrated intraperitoneally (i.p.) to KunMing mice (22 ± 2 g). The mice were housed collectively in polycarbonate cages in groups of ten, where they were maintained on a 12 h light/dark cycle in a temperature controlled (25 ± 2 °C) laboratory with free access to food and water. Each animal was used only once. All efforts were made to minimize both the suffering of the animals and the number of animals used in the experiments.

4. Results and discussion

4.1. Antidepressant activities

The antidepressant activities of the compounds were investigated in mice using the forced swimming test (FST). The FST was designed by Porsolt et al. [44] as a primary screening test for antidepressants and remains one of the best models of depression because it provides a low-cost, fast and reliable platform for testing potential antidepressants with a strong predictive validity. This animal model is therefore still one of the most widely used tools for the preclinical screening of putative antidepressant agents [50–53]. In the FST, the mice are forced to swim under inescapable conditions, and consequently adopt an immobility behavior



Scheme 1. The synthesis route of compounds **5a**–**5s**.