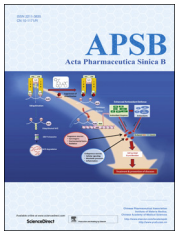
Acta Pharmaceutica Sinica B 2015;5(4):343–349

HOSTED BY

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



ORIGINAL ARTICLE

Synthesis, potential anticonvulsant and antidepressant effects of 2-(5-methyl-2, 3-dioxoindolin-1-yl)acetamide derivatives

Xinghua Zhen[a,†], Zhou Peng[a,†], Shuilian Zhao[a], Yan Han[a], Qinghao Jin[b,*], Liping Guan[a,]**

[a]*Food and Pharmacy College, Zhejiang Ocean University and Zhejiang Provincial Engineering Technology Research Center of Marine Biomedical Products, Zhoushan 316022, China*
[b]*Hailisheng Pharmaceutical Co., Lid., Zhoushan 316021, China*

Received 11 September 2014; received in revised form 30 December 2014; accepted 4 January 2015

KEY WORDS

2,3-Dioxoindolin-1-acetamide;
Synthesis;
Anticonvulsant activity;
Antidepressant activity;
Pentylenetetrazole

Abstract A new series of 2-(5-methyl-2,3-dioxoindolin-1-yl)acetamide derivatives were synthesized and evaluated for their anticonvulsive activity in a pentylenetetrazole (PTZ)-evoked convulsion model and antidepressant activity in the forced swimming test (FST) model. Eleven synthesized compounds were found to be protective against PTZ-induced seizure and showed the anticonvulsant activity. In addition, four of the synthesized compounds (**4l**, **4m**, **4p** and **4q**) showed potent antidepressant-like activity. Among these compounds, compound **4l** was found to have the most potent antidepressant-like activity, and significantly reduced the duration of immobility time at 100 mg/kg dose level when compared to the vehicle control, which is similar to the reference drug fluoxetine.

*Corresponding author. Tel./fax: +86 580 2085559.
**Corresponding author. Tel.: +86 580 2550005; fax: +86 580 2554781.
E-mail addresses: 13957204963@163.com (Qinghao Jin); glp730@163.com (Liping Guan).
†These authors contributed equally to this work.

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

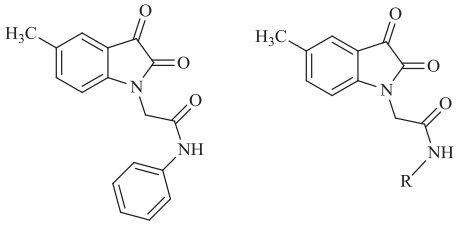
http://dx.doi.org/10.1016/j.apsb.2015.01.008

1. Introduction

Isatin (2,3-dioxindole) is an endogenous compound identified in humans and its effect has been studied in a variety of systems. Biological properties of isatin include a range of actions in the brain, protection against certain types of bacterial infections, antiproliferative, anti-inflammatory, antiprotozoal, proconvulsive and anticonvulsive activities[1–3].

In addition, Sridhar et al.[4] reported the anticonvulsant activity of hydrazones, the Schiff and Mannich bases of isatin, by the maximal electroshock method (MES) and metrazol-induced convulsions (MET). Li et al.[5] studied the inhibitory effect of isatin on amygdaloid kindling in rats, seizure-inducing and anticonvulsant effect in convulsion models. Pajouhesh et al.[6] synthesized a series of cyclohexane and other cyclic ketone derivatives of isatin and screened them for anticonvulsant activity. These results suggest that the researchers explored isatin as a new chemical entity with potential anticonvulsant activity. Furthermore, several researchers reported that isatin can not only evidently improve internal monoamine neurotransmitter to antagonize electric[7] and metrazol-induced seizure in mice effectively, but also decrease the epilepsy probability of audiogenic seizure in rats and enhance the anticonvulsant effect of propranolol[8–10]. In addition, in our studies[11], we synthesized a series of isatin-1-*N*-phenylacetamide derivatives and tested their anticonvulsant activity. Among these analogs, the compound **I** (Fig. 1) showed the highest anticonvulsant activity in the anti-MES and anti-PTZ tests.

As a result of our continuous effort in this area, a series of new 2-(5-methyl-2,3-dioxoindolin-1-yl)acetamide derivatives were synthesized (Scheme 1). The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and high resolution mass spectra, and evaluated for their anticonvulsant activity against convulsions evoked by chemical substance pentylenetetrazole (PTZ) and antidepressant activity by the forced swimming test (FST), respectively.



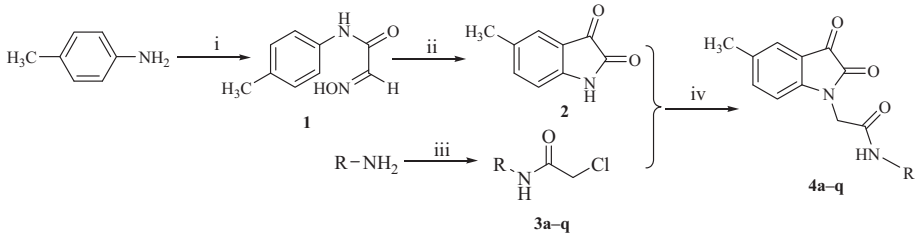
I 4a–q

Figure 1 The structures of compounds **I**, **4a–q**

2. Results and discussion

The targeted compounds **4a–q** were synthesized according to the sequence shown in Scheme 1[12]. Briefly compound **1** was prepared by the condensation of *p*-methlyphenylamine with chloral hydrate and hydroxylamine hydrochloride in 89% yield. Then, the subsequent cyclization of compound **1** in the presence of concentrated sulfuric acid at 80 °C afforded compound **2**. Compounds **3a–q** were obtained by an acylation reaction of substituted anilines using 2-chloroacetyl chloride in 80%-92% yields. Finally, compounds **4a–q** were obtained by an alkylation reaction of compounds **3a–q** with compound **2**.

The anticonvulsant activity of the synthesized compounds **4a-q** was investigated in PTZ-induced model against convulsions and the results from these experiments are shown in Table 1. To explore the structure-activity relationships of 2-(5-methyl-2,3-dioxoindolin-1-yl)acetamide derivatives, we varied the substituents on the phenyl group in the phenylacetamide ring, which contained both electron-withdrawing and electron-donating substituents. Compounds **4a–q** and the reference drug carbamazepine were administered *i.p.* into mice at a dose of 100 mg/kg. Among the synthesized compounds, eleven compounds were found to be protective against PTZ-induced seizure and showed the anticonvulsant activity. Analyzing the activity of eleven compounds (**4a**, **4d**, **4f**, **4h**, **4k–q**) led to the following structure-activity relationship. The electron-donating groups showed the following trend in anticonvulsant activity: -2-CH_3-C_6H_4 > -4-OCH_3-C_6H_4 > $CH_2C_6H_5$ ≈ compound **I**, in which the methyl group at the 3-position and 4-position on the phenyl ring did not exhibit the anticonvulsant activity against PTZ-induced seizures. The structure-activity relationships of compounds **4e–p** were analyzed. Freqently, the activity is markedly changed upon the introduction of a halogen atom. Therefore, in this paper some halogen-substituted derivatives were designed and synthesized. All halogenated compounds (**4e–p**) except **4e**, **4g**, **4i**, and **4j** displayed the anticonvulsant activity against PTZ-induced seizure, The Br analog showed higher anticonvulsant activity than F and Cl analogs and the rank of the activity order of halogen-substituted derivatives was Br > F > Cl. Bis-halogenated compounds **4n** (2,4-Cl_2) and **4o** (2,4-Br_2) also showed the anticonvulsant activity against PTZ-induced seizure. In addition, compound **4p** with an electron-



R:

4a = 2-CH_3-C_6H_4	**4b** = 3-CH_3-C_6H_4	**4c** = 4-CH_3-C_6H_4	**4d** = 4-OCH_3-C_6H_4	**4e** = 2-F-C_6H_4
4f = 3-F-C_6H_4	**4g** = 4-F-C_6H_4	**4h** = 2-Cl -C_6H_4	**4i** = 3-Cl -C_6H_4	**4j** = 4-Cl -C_6H_4
4k = 2-Br-C_6H_4	**4l** = 3-Br-C_6H_4	**4m** = 4-Br-C_6H_4	**4n** = 2,6-Cl_2-C_6H_3	**4o** = 2,4-Br_2-C_6H_3
4p = 3-CF_3-C_6H_4	**4q** = -$CH_2C_6H_5$			

Scheme 1 The synthetic pathway of titled compounds **4a–q** Reaction and condition: (i) $CCl_3CH(OH)_2$, $NH_2OH \cdot HCl$, Na_2SO_4, HCl; (ii) concentrated H_2SO_4; (iii) $ClCH_2COCl$, HOAc; (iv) DMF, KI, K_2CO_3.