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# Synthesis and structure–activity relationship of novel cinnamamide derivatives as antidepressant agents

Min Han [a], Xiaohui Ma [a,b,*], Yuanpeng Jin [a], Wangyi Zhou [a], Jing Cao [a], Yahu Wang [a], Shuiping Zhou [a], Guocheng Wang [a], Yonghong Zhu [a]

[a] Tianjin Tasly Academy, Tasly Holding Group Co., Ltd, Tianjin 300410, China
[b] School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China

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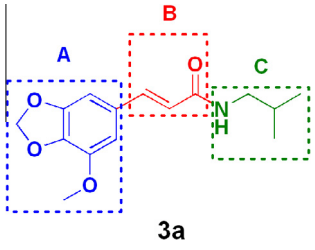
ABSTRACT

Cinnamamide **3a**, a leading compound with antidepressant-like activity, and its derivatives were synthesized and their antidepressant activity and structure–activity relationship were investigated. Most of the compounds with trifluoromethyl group in methylenedioxyphenyl moiety (**3f**, **4b**–**c** and **6a**–**b**) exhibited significant antidepressant activity, measured in terms of percentage decrease in immobility duration by tail suspension test. In addition, the dose-dependent antidepressant effect of the most potent compound **3f** was subsequently confirmed in tail suspension test and forced swim test. The test results showed that **3f** was equal to or more effective than the standard drug fluoxetine at a concentration of 10 mg/kg. Furthermore, compound **3f** did not show any central nervous system stimulant properties in the open-field test and the preliminary results were promising enough to warrant further detailed antidepressant research around this scaffold.



Depression is a serious and burdensome psychiatric illness with estimates reaching as high as 21% of the world people.[1] It is characterized by anhedonia or the loss of interest or pleasure in normal daily activities and feelings of sadness.[2] The World Health Organization predicts that it will be the second leading cause of death by the year 2020 due to complications arising from stress and the cardiovascular system.[3] To date, several classes of monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitors, selective noradrenaline reuptake inhibitors, serotonin modulators and norepinephrine serotonin modulators are being used in the clinical treatment.[4] However, a significant proportion of these patients will not respond to treatment, or will show adverse effects such as sedation, apathy and fatigue, cognitive impairment, and sexual dysfunction. There is a need for faster, more effective and safer therapeutic treatments, in order to limit the impact of depression on patient's lives.[5,6]

Natural products are always special sources for the discovery of potential drugs with novel structures and varying biological activity. The species of the *Piper* genus family have shown high efficacy and safety in the treatment of depression, such as *Hypericum perforatum* L. (St. John's wort)[7] and *Piper methysticum* Forst.[8] Some natural piperamides like piperine,[9] laetispicine,[10] piplartine,[11] were reported as potential antidepressant and anticonvulsant agents. Several researchers have reported MAO inhibitory activity for various piperamide derivatives.[12]




3a

**Figure 1.** The structure of **3a** divided into three key regions.

Our group had previously isolated and identified (*E*)-*N*-isobuty-3′,4′-methylendioxy-5′-methoxy-cinnamamide (**3a**, Fig. 1) from the *Piper laetispicum* C. DC, which shown moderate antidepressant-like activity in forced swim test (FST) and tail suspension test (TST) and excellent inhibition capability in the serotonin reuptake inhibition test in vitro.[13] Additionally, with the methylenedioxy and methoxy substituent in benzene ring function **3a** owning poor solubility in lipophilic environment, so most probably that only small amount of **3a** can pass through blood–brain barrier (BBB). Thus, the optimization for leading compound **3a** may be proved

* Corresponding author. Tel.: +86 22 26732626; fax: +86 22 26736376.
*E-mail address:* maxiaohui@tasly.com (X. Ma).

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**Table 1**
The serial numbers and evaluation of the derivatives of **3a** at a dose of 10 mg/kg (*i.g*) in tail suspension test and the open-field test in mice

| Compound | Exploratory activity in the open-field test (counts) | Duration of immobility (s)[a] (mean ± SEM) | Percentage decrease in immobility duration (% DID) |
|---|---|---|---|
| **3a** | 100.92 ± 4.11 | 180.10 ± 6.08[#] | 11.7 |
| **3b** | 89.24 ± 6.88 | 177.07 ± 8.30[#] | 13.2 |
| **3c** | 98.00 ± 4.96 | 190.69 ± 11.00[#] | 6.4 |
| **3d** | 94.42 ± 6.92 | 173.14 ± 9.35[*#] | 15.1 |
| **3e** | 94.75 ± 8.24 | 155.29 ± 9.18[**#] | 29.1 |
| **3f** | 99.40 ± 6.22 | 117.34 ± 9.46[**] | 42.5 |
| **4a** | 84.00 ± 6.90 | 178.32 ± 8.13[#] | 12.6 |
| **4b** | 95.30 ± 4.76 | 121.91 ± 6.57[**] | 40.2 |
| **4c** | 83.60 ± 7.17 | 139.70 ± 15.37[**] | 31.5 |
| **4d** | 91.54 ± 5.06 | 158.43 ± 10.33[*#] | 21.8 |
| **4e** | 86.20 ± 3.33 | 154.99 ± 11.68[**#] | 24.0 |
| **6a** | 93.20 ± 6.18 | 136.44 ± 12.49[**] | 33.1 |
| **6b** | 87.40 ± 7.08 | 128.76 ± 11.36[**] | 37.1 |
| **7** | 86.60 ± 7.30 | 145.32 ± 11.26[**] | 28.8 |
| Fluoxetine (10 mg/kg) | 102.00 ± 4.71 | 123.58 ± 8.79[**] | 39.4 |
| Control[b] | 94.50 ± 6.18 | 204.05 ± 10.71[#] | — |

[*] Significantly compared with control ($p < 0.05$).
[**] Very significantly compared with control ($p < 0.01$).
[#] Very significantly compared with **3f** ($p < 0.01$).
[a] Values represent the mean ± SEM ($n = 10$).
[b] The vehicle group.

useful in the development of selective antidepressant agent. The aim of this study is to design and synthesize its analogues with better antidepressant activity and BBB permeability, and to discuss structure–activity relationships.

Compound **3a** consists of three important components, a methylenedioxyphenyl moiety (Fig. 1, part A), a side chain with conjugated double bond (Fig. 1, part B) and an amide moiety attached to side chain (Fig. 1, part C). Each of these moieties might influence the antidepressant activity and the stability. In the present study, a series of cinnamamide derivatives were designed and synthesized (Table 1) to find a novel class of antidepressant agents with better activity. The methylenedioxyphenyl moieties of these compounds were designed to bear various electron withdrawing groups or donating groups. Since the length of the carbon linker and the steric hindrance of the amide moiety can play an important role in antidepressant activity, derivatives with different lengths of the carbon linker and different amide groups were chosen as the prototype for our investigation. Herein, we report the detail of our investigation.

Compound **3a** and its derivatives were prepared as outlined in Schemes 1 and 2. According to the methods described previously,[14] cinnamic acid derivatives **2a–f** were synthesized from aldehyde **1a–f** bearing different substituents and malonic acid, which were then coupled with isobutylamine in the presence of EDC·HCl, afforded the corresponding cinnamamide derivatives **3a–f** in excellent yield. The resulting compounds **4a–e** were synthesized by the same methods as **3a–f**, from cinnamic acid **2f** and different amines. The synthesis route of the derivatives of **3a** with different lengths and saturation of the conjugated double bond were shown in Scheme 2. Oxidation of 5-trifluoromethyl-piperonal **1f** with $KMnO_4$ proceeded smoothly to afford acid **5**, which was then further transformed into amide **6a–b**. Compound **3f** was hydrogenated with $H_2$ in the presence of Pd/C to give saturated amide derivative **7** in a 90% yield.[15] The structures of the synthesized compounds were conformed from chemical identification data obtained by $^1H$, $^{19}F$, $^{13}C$ NMR and mass spectra. The chemical shift and multiplicity patterns were correlated well with the proposed structures.

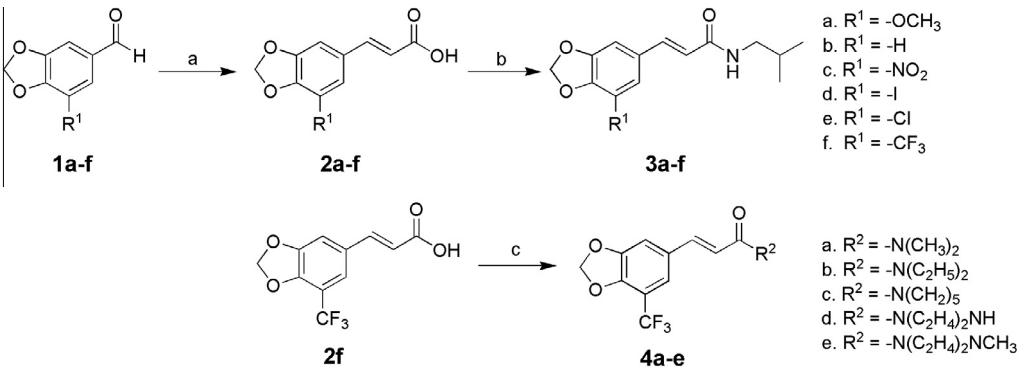
In this study, all of the synthesized compounds **3a–f**, **4a–e**, **6a–b** and **7** were assayed for antidepressant activities at dose of 10 mg/kg (*i.g*) in TST model in mice and the results were shown in Table 1. TST model could effectively predict the activities of a wide variety of antidepressants such as MAO inhibitors and typical antidepressants.[16] The ability of a compound to decrease immobility duration in TST was taken as a measure of its antidepressant activity. Percentage decrease in immobility duration (% DID) for test and standard drugs was calculated using following formula:[17]

$$\%\ \mathrm{DID} = (A - B)/A \times 100,$$

where $A$ is the duration of immobility (s) in control group and $B$ is the duration of immobility (s) in test group.

As shown in Table 1, among the derivatives **3a–f** with different substituents in methylenedioxyphenyl moieties, **3e** and **3f** significantly reduced the immobility times compared with the control ($p < 0.01$). The most active compound was **3f** and its antidepressant activity was equal to that of fluoxetine. This is because the lipophilic nature of the trifluoromethyl group can increase lipid solubility of **3f**, thus enhancing penetration of the molecule through the blood–brain barrier in sufficient concentration to create the desired level of biological activity.[18] Contrary to **3f**, methoxy group and nitro group could increase the hydrophilic property of **3a** and **3b**, and reduce the antidepressant activity. Comparing derivatives with different substituents on the benzene ring, their activity order was —$CF_3$ > —Cl > —I > —H > —OMe > —$NO_2$.

On the basis of the replacement of methoxy group in methylenedioxyphenyl moiety with trifluoromethyl group, the influence of modification in the amide moiety was investigated. From the immobility times of TST treated with compounds **3f** and **4a–e**, we predict that the steric effect of amide moiety could increase




**Scheme 1.** The synthesis routes of compounds **3** and **4**. Reagents and conditions: (a) pyridine, piperidine, 90 °C, 12 h; (b) isobutylamine, TEA, EDCI, DCM, 0–20 °C, 5 h; and (c) EDCI, TEA, DCM, 0–20 °C, 5 h.