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Original article

Design, synthesis and biological evaluation of novel dicarbonylalkyl piperazine derivatives as neuroprotective agents

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ABSTRACT

In the search of novel neuroprotective agents with higher potency than our previously identified anti-ischemic stroke drug candidate **1**, a series of novel dicarbonyl piperazine derivatives were synthesized and evaluated on their neuroprotective activity *via* oxygen–glucose deprivation test in the neuron-like PC12 cells, hypoxia tolerance model in mice and focal cerebral ischemia model in rats. The result obtained indicated that compounds **7f**, **7k** and **7o**, exhibited neuroprotective activity. Particularly, compound **7o** containing 2,5-dimethylpiperazin moiety, showed prolonged life time of mice and reduced cerebral infarction of rats, which provided a potential candidate for the development of neuroprotective agents.

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1. Introduction

Stroke has been the second-leading cause of death and a main cause of neurological disability in the world over the past decade [1]. In particular, ischemic stroke, which accounts for more than 80% of all strokes, carries a high morbidity and mortality. Furthermore, strokes are likely to significantly increase in prevalence given its associated risk factors, such as obesity, diabetes, and hypertension [2,3]. However, available drugs are very limited, and some of them suffer from poor efficacy and high toxicity. Clinically, intravenous thrombolysis and mechanical thrombectomy are current strategies for treating acute ischemic stroke [4], and tissue plasminogen activator (rt-PA) is the only FDA-approved drug for thrombolysis treatment. Unfortunately, it is used in less than 5% of patients due to its narrow therapeutic window and complexity of administration [5]. Edaravone [6–9] and Butylphthalide [10–14] (Fig. 1) were approved by CFDA for acute treatment as neurointervention therapy and cerebral microcirculation improvement drug in ischemic stroke patients in 2005 and 2002, respectively. They exhibited neuroprotective effects and antithrombotic activity in cerebral infarction and acute stroke, but the potency is limited unless administered with other antistroke drugs. Most critically, the penumbra (a peripheral zone of focal cerebral ischemia that is damaged but potentially reversible) transfers to irreversible damage within a few hours [15,16]. Hence, there is an emergent need for development of novel effective neuroprotective agents.

Previous studies have showed that aralkyl dicarbonyl piperazine compound **1** (Fenazinel, Fig. 1) exhibited potent anti-ischemic stroke activity as neuroprotective therapy, and was developed into clinical trials [17–21]. In order to investigate the structure–activity relationships (SARs), a series of novel dicarbonyl piperazine derivatives (Fig. 2) were synthesized and evaluated on their neuroprotective activity *via* oxygen–glucose deprivation test in neuron-like PC12 cells, a hypoxia tolerance model in mice, and a focal cerebral ischemia model in rats.

2. Experimental

All the starting materials were obtained from commercial sources and used directly without further purification. All the reactions were monitored by TLC analysis, carried out on silica gel

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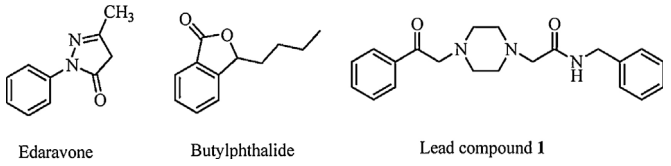


Fig. 1. Chemical structures of representative anti-ischemic stroke agents and the lead compound **1**.

plates HSGF254 (Yantai Jiangyou Chemical, China). Melting points (uncorrected) were determined on a Shanghai Jingmi WRR apparatus. ^{1}H NMR spectra were recorded on a Varian INOVA-400 NMR spectrometer, using TMS as an internal standard and DMSO as solvents. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. ESI mass spectra were performed on a Finning-MAT 212 spectrometer. Silica gel column chromatography was performed with Silica gel 60G (Qingdao Haiyang Chemical, China).

The general synthetic routes of compounds **7a–t** are outlined in Schemes 1 and 2. Compounds **2a–c** were acylated by chloro-substituted acyl chloride in $CHCl_3$ to give compounds **3a–f**. Intermediates **5a-i** were obtained by alkylation of **4a** or **b** with **3a–f** in EtOH *via* refluxing, which was subsequently alkylated with **6a–e** in acetone at presence of K_2CO_3 to afford the targeted compounds **7a–r** in 79%–87% yield. Compounds **7s** and **t** were synthesized *via* two alkylation steps. 2,5-Dimethylpiperazine (**8**) was alkylated with **6d-e** in presence of KOH and CTBA with molar ratio of 3.5:1:1:0.01, and then alkylated with **3a** and **b** in MeOH at presence of K_2CO_3 to afford **7s** and **t** in 80%–85% yield. Structures of targeted compounds **7a–t** are illustrated in Table 1.

All the compounds **7a–t** were evaluated on their neuroprotective activity *via in vitro* (oxygen–glucose deprivation test in PC12 cells) and *in vivo* assays (hypoxia tolerance model in mice and focal cerebral ischemia model in rats).

The detailed synthetic procedure, *in vitro* and *in vivo* biological evaluations, and identification data of target compounds **7a–t**, characterized by ^{1}H NMR and mass spectrometry techniques are shown in the Supporting information.

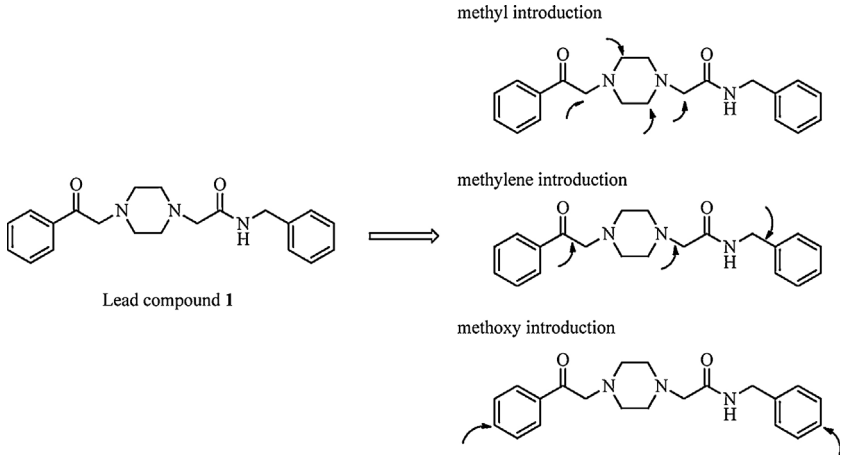
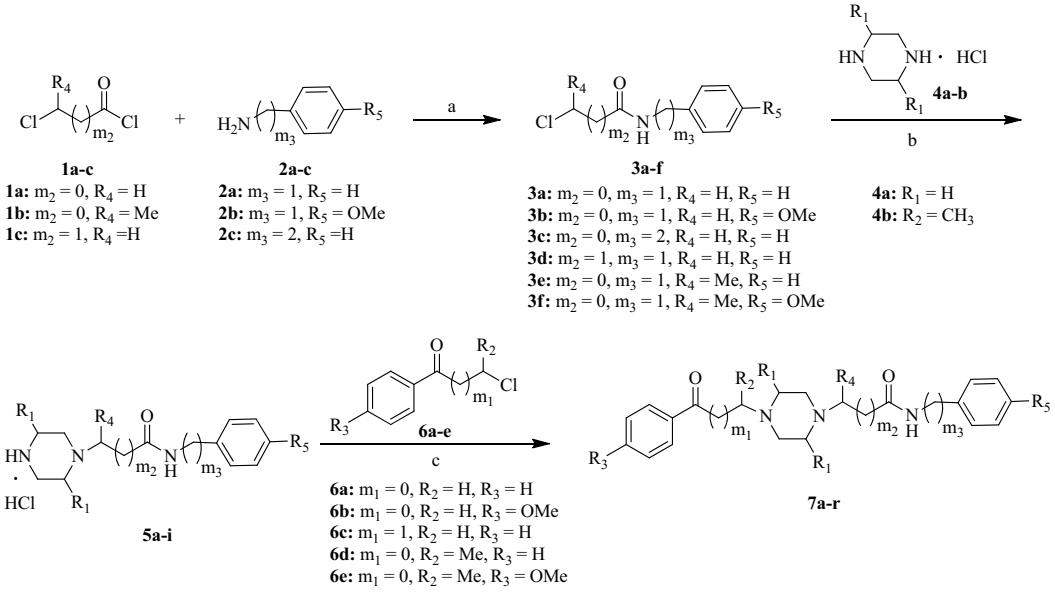


Fig. 2. Design rational of the targeted compounds **7a–t**.



Scheme 1. Synthetic route of compounds **7a–r**. Reagents and conditions: (a) $CHCl_3$, 0 °C, 2 h, 60%–75%; (b) EtOH, reflux, 1.5 h, 75%–85%; (c) K_2CO_3, acetone, reflux, 12 h, 79%–87%.

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