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Synthesis and biological evaluation of novel naphthalene compounds as potential antidepressant agents

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ABSTRACT

In this study, a series of novel naphthalene compounds were synthesized and screened for their antidepressant-like activities *in vitro* and *in vivo*. Their values for two descriptors (ClogP, tPSA) of the blood–brain barrier (BBB) were calculated for early assessment of the central nervous system (CNS) drug-likeness. Seven of them (**6d**, **6i**, **6k**, **6o**, **6p**, **6s** and **6t**) demonstrated potential protective effects on corticosterone-induced lesion of PC12 cells although they cannot repair the irreversible oxidant injury to PC12 cells by hydrogen peroxide. Compounds with promising neurorestorative activities (**6k**, **6o** and **6p**) were further evaluated for their *in vivo* effects by forced swim test (FST) and open field test (OFT) in C57 mice models. The FST results showed that compounds **6k**, **6o** and **6p** remarkably reduced the immobility time of the tested mice. Among them, compound **6k** was the most potent one, much more effective than Agomelatine and comparable to Fluoxetine. The OFT results showed that mice treated with compound **6k** traveled a longer distance than those treated with Agomelatine or Fluoxetine, indicating a better general locomotor activity. The paper also proposed a possible binding mode of compound **6k** with glucocorticoid receptor by docking study. The *in vitro* cytotoxicity data on HEK293 and L02 cells suggested compound **6k** to be a promising antidepressant candidate for subsequent investigation.

1. Introduction

Major depression is a mental disorder characterized by a pervasive and persistent low mood which is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities [1]. The World Health Organization (WHO) report has predicted that major depression will become a key contributor to illness-induced disability by the year 2020, second only to ischemic heart diseases [2,3]. Moreover, new research indicated that patients with major depression have an increased onset risk of aging-related somatic diseases such as heart disease, diabetes, obesity and cancer [4].

Despite of a large number of antidepressant drugs commercially available, there are still many issues leading to risks of depression therapy. It was reported in clinic that part of patients do not respond fully to the antidepressant drugs, even the present blockbuster drugs like Imipramine, Fluoxetine, Citalopram and Venlafaxine [4]. Besides, the long-lasting therapy period gives rise to poor patient compliance, along with several adverse effects as well as the drug–drug interactions. Consequently there is a desirable need to find new chemical entities as potential antidepressant candidates with novel action mechanism, which may lead to a more advantageous benefit-risk balance.

Neuroscientists have put great efforts on the investigation of neurobiological and structural changes of the treated or non-treated patients with mental disorders, and found that neuronal plasticity, neurogenesis and their regulation may play important role in the treatment of major depression [5]. For example, several studies showed that hippocampal volume is reduced in patients with major depression compared with healthy controls [6–9]. On

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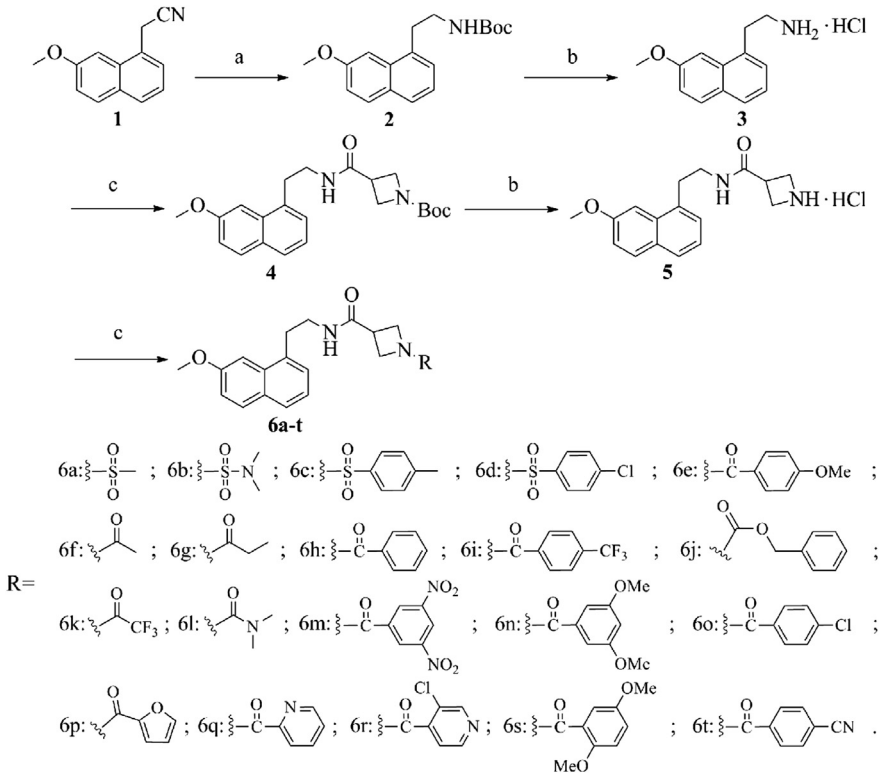
the other hand, the recently marketed antidepressant drug, Agomelatine, was shown to induce cell proliferation and neurogenesis in the ventral part of dentate gyrus, a region implicated in the response to emotion and anxiety, which gave the basis for the neuroplasticity hypothesis of major depression. Fluoxetine also shared above neurogenetic effects [10–15]. Meanwhile, many studies indicated that antidepressant drugs are able to prevent neuronal damage and cell loss that may occur in the brain of patients with mood disorders [16–19]. As a result, neurorestorative or neuroprotective effect of antidepressants has been proposed as a highly possible mechanism to treat mental disorders [20].

On the other hand, it was widely reported that compounds containing naphthalene scaffold displayed antidepressant activities [21–25]. Thus researchers made great efforts on structural modification of compounds with naphthalene scaffold and get some excellent antidepressant candidates and the most successful example is the discovery of Agomelatine, which was approved for the treatment of major depression by European Medicines Agency last 2009 [26]. Most naphthalene derivatives exhibited activities on neurological or neuropsychiatric disorders contained a core structure of 2-(naphthalen-1-yl)ethanamine [23,24]. Inspired by the mentioned findings, we designed and synthesized a series of novel 2-(naphthalen-1-yl) ethanamine compounds by introduction of various side chains with different properties, looking forward to discovery of potential antidepressant agents with neurorestorative or neuroprotective mechanism.

It is well known that one of the bottlenecks to rapidly develop effective drugs for treatment of mental disorders including depression is poorly predictive capability of *in vitro* and *in vivo* screening models. PC12 is a cell lineage derived from a pheochromocytoma of rat adrenal medulla and has been widely used to investigate the mechanisms involved in neurotoxicity, neuroprotection and neurorestoration [27,28]. Glucocorticoids at high concentration lead to PC12 neuronal damage under depressive disorder, and this feature makes PC12 cells very useful as a model system for *in vitro* screening [20]. Oxidant injury of PC12 cells is more destructive and sometimes the damage is irreversible. Nevertheless, a few antidepressant drugs showed protective effects in this model [27,29,30]. Besides, oxygen glucose deprivation, glutamate, Aβ2535, and even physical methods can also lead into PC12 cells lesion *in vitro* models, which have also been used in studies of mental disorders. Herein, H_2O_2 and corticosterone were employed as stimulants to induce traumatic lesion of PC12 cells, which were further used as two typical *in vitro* models to investigate the neurorestorative and neuroprotective activities of our novel naphthalene compounds. In addition, all of the target compounds were also tested for their *in vitro* cytotoxicities on human normal liver L02 cells and human embryonic kidney 293 cells by MTT method. Two descriptors of their penetrating abilities of blood–brain barrier (BBB) such as lipophilicity (logP) and molecular topological polar surface area (tPSA) were also employed calculated for early assessment of their central nervous system drug-likeness. Based on *in vitro* and *in silicon* results, four compounds (**6d**, **6k**, **6o** and **6p**) were selected to *in vivo* forced swim test in C57 m*ice*. The general locomotor activity of compound **6k** was further measured by an open field test, which confirmed its antidepressant potential. Docking study was conducted to illustrate the binding mode of **6k** with glucocorticoid receptor, a possible molecule target of neuroprotective agents.

2. Chemistry

To achieve the synthesis of the target compounds **6a-t**, the steps outlined in Scheme 1 were adopted. The intermediate **3** was synthesized from commercially available 2-(7-methoxynaphthalen-1-yl)acetonitrile (**1**) according to literature with appropriate



Scheme 1. General synthetic route of compounds **6a–t**.