European Journal of Medicinal Chemistry 82 (2014) 263–273

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

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

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ARTICLE INFO

Article history:
Received 27 January 2014
Received in revised form
6 May 2014
Accepted 25 May 2014
Available online 27 May 2014

Keywords:
Depression
PC12 cells
Corticosterone-induced
Forced swim test
Open field test
Glucocorticoid receptor

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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http://dx.doi.org/10.1016/j.ejmech.2014.05.061
0223-5234/

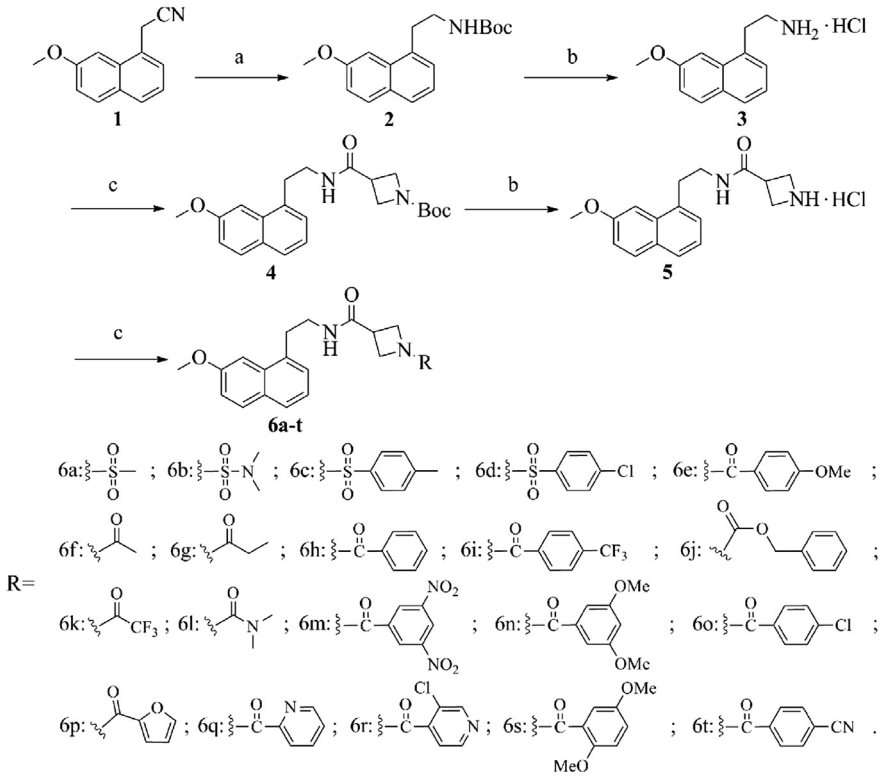
the other hand, the recently marketed antidepressant drug, Agomelatine, was shown to induce cell proliferation and neurogenesis in the ventral part of dentate gyrus, a region implicated in the response to emotion and anxiety, which gave the basis for the neuroplasticity hypothesis of major depression. 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**.

revision [31–33]. The reported method directly used sodium borohydride/nickel chloride system to reduce the start material **1**, resulting in oily material difficult to solidify. As a result, we improved the process by taking advantage of an *in situ N*-Boc protection to obtain high purity of intermediate **2** in a single step. Our modification avoided the contamination of impurities such as oxime, secondary amine and acyl amine and the white solid **3** was readily obtained in high purity after de-protection of *N*-Boc under acidic condition. The common key intermediate **4** was prepared by a condensation reaction with 1-(tert-butoxycarbonyl) azetidine-3-carboxylic acid according to a reported method [34]. The final compounds (**6a**–**t**) were prepared by acylation of the key intermediate **5** with various carboxyl acids according to literature [35,36].

3. Result and discussion

3.1. BBB penetration ability of the designed compounds

As we know, the ability to penetrate the blood–brain barrier (BBB) is a significant parameter for CNS drugs. Lipophilicity (logP) and molecular topological polar surface area (tPSA) were widely used to describe CNS penetration ability [37,38]. For marketed CNS drugs, the value range of CLogP is 0.16–6.59 and that of tPSA is 4.63–108. In order to predict the BBB penetration ability of the designed naphthalene compounds in advance, we calculated the values of these two descriptors for them by the trial version of ChemBioOffice ® Ultra 13.0 and the data were listed in Table 1, where we can see that the ClogP values of the synthesized naphthalene compounds are quite similar to the marketed antidepressant Fluoxetine or Agomelatine, and the tPSA values of them are in the range of the marketed CNS drugs. With these calculated values in hand, we started to synthesize the planned compounds since there seemed no designed molecules went beyond the established drug-like space.

3.2. Restorative effects on H_2O_2-injured PC12 cells

Commercially there are three types of PC12 cells, i.e. undifferentiated, low-differentiated and high-differentiated PC12 cells. Undifferentiated PC12 cells were far different from neurons. However, the high-differentiated PC12 cells were not able to proliferate in culture condition, thus not convenient and ready for *in vitro* screening. Low-differentiated PC12 cells share properties similar to neurons and are able to proliferate in culture conditions. Consequently, low-differentiated PC12 cells were selected in our *in vitro* model for primary screen of antidepressant. In order to determine whether the final compounds have the restorative effects on the oxidant injury of PC12 cells by hydrogen peroxide, we took advantage of MTT method to measure the viability of PC12 cells 48 h after drug treatment of the H_2O_2-injured cell culture at three different drug concentrations of 10 μM, 20 μM and 40 μM. As shown in Table 2, only thirteen compounds displayed weak repair activities in certain concentration. Even Fluoxetine and Agomelatine displayed weak repair activities at 10 μM and 20 μM respectively. For compounds **6d**, **6h** and **6j**, showed weak restoration activity in 10 μM, 20 μM and 30 μM, however, their restoration rates did not exhibited linear correlation with drug concentration. For example, **6d** exhibited almost similar restoration rates at drug concentration of 10 μM and 20 μM. For compound **6h**, the restoration rates decreased when the drug concentration was doubled to 40 μM. Seven compounds did not possess restorative effects on the oxidant injury of PC12 cells in all tested drug concentration, this may contributed to their cytotoxicity on PC12 cells. Which may suggest the oxidant injury of PC12 cells by hydrogen peroxide is too destructive to restore and not a suitable *in vitro* model for preliminary screening of potential naphthalene antidepressant hits.

Table 1
Calculated logP (ClogP) and topological polar surface area (tPSA) values of the target compounds.

Compd	ClogP	tPSA	Compd	ClogP	tPSA
6a	2.9	75.7	**6l**	3.5	61.9
6b	3.1	79.0	**6m**	3.7	162.3
6c	4.9	75.7	**6n**	4.3	77.1
6d	5.1	75.7	**6o**	4.8	58.6
6e	4.2	67.9	**6p**	3.2	67.9
6f	2.6	58.6	**6q**	2.9	71.0
6g	3.1	58.6	**6r**	3.7	71.0
6h	4.0	58.6	**6s**	4.3	77.1
6i	5.0	58.6	**6t**	3.6	82.4
6j	5.5	67.9	**Flu**	4.6	21.3
6k	3.7	58.6	**Ago**	2.1	38.3

3.3. Protective effects on corticosterone-injured PC12 cells

All the target compounds were tested for their protection activities on PC12 cells from corticosterone-induced lesion at drug concentration of 1.25 μM and the data were shown in Table 3. From the mean values listed in Table 3, 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 as stated in Section 3.2. Three amide compounds (**6k**, **6o** and **6p**) showed pronounced efficacy with protection rates of 43.5 ± 4.3%, 39.2 ± 1.7% and 38.8 ± 4.6% respectively. Although it is not easy to get clear structure–activity relationship from the present data, some deduction, requiring further confirmation by more studies on medicinal chemistry, can be reasonably expected. Among the synthesized compounds, the active ones likely fell in the category with another aromatic group introduced to the side chain of 2-(naphthalen-1-yl)ethanamine scaffold although the most active compound **6k** are substituted with a trifluoroacetyl group at the same position. Herein, the pi–pi interaction of compounds **6d**, **6i**, **6o**, **6p**, **6s** and **6t**, or hydrogen-bonding interaction of compound **6k** with potential biological target may play a part. Compared compound **6d** and **6o**, the conclusion can be drawn that the acyl linker (**6o**: 39.2 ± 1.7%) is superior to its sulfonyl counterpart (**6d**: 25.3 ± 0.9) for the introduction of another aromatic group.

From above results, it seemed that corticosterone-injured PC12 cells is a fruitful *in vitro* model for preliminary screening of antidepressant drugs and we would like to pick out the active hits (**6k**, **6o** and **6p**) with better protective effects than the positive controls (Fluoxetine: 19.7 ± 0.7%; Agomelatine: 26.2 ± 2.4%) to further evaluation.

To visually observe the protective effect of the active compounds in corticosterone-induced PC12 cells, we assessed the morphological changes of PC12 cells using inverted microscopy before and after treated with **6k** and **6o** respectively (Fig. 1). PC12 cells treated 0.2 mM of corticosterone (Fig. 1B) turned into cycloid compared with cells treated normal saline (Fig. 1A), while much less morphological changes of PC12 cells were observed when treated with test drugs (Fig. 1C–G). The photos illustrated in Fig. 1 indicated that **6k** (Fig. 1F) and **6o** (Fig. 1G) possess protective effects on corticosterone-induced injury of PC12 cells.

To give a precise description of the morphological changes of PC12 cells, we counted the morphologically changed cells and normal neuron-like cells carefully in three random microscopic vision fields by simple computer-assisted image analysis. The PC12 cells with shrunk axons and cycloid shape were regarded as

Table 2
The restoration rates of the target compounds on H_2O_2-injured PC12 cells.

Compd	RR[a] (%)			Compd	RR[a] (%)		
	10 μM	20 μM	40 μM		10 μM	20 μM	40 μM
6a	0.9 ± 0.1	–	3.7 ± 0.3	**6k**	–	–	–
6b	–	2.1 ± 0.2	–	**6l**	–	1.2 ± 0.1	4.3 ± 0.4
6c	–	–	–	**6m**	–	1.7 ± 0.1	–
6d	4.6 ± 0.4	4.5 ± 0.3	6.8 ± 0.4	**6n**	–	2.1 ± 0.1	–
6e	–	–	–	**6o**	0.3 ± 0.1	–	4.7 ± 0.4
6f	–	0.6 ± 0.2	1.0 ± 0.1	**6p**	–	–	–
6g	–	–	7.5 ± 0.3	**6q**	0.7 ± 0.1	–	–
6h	2.9 ± 0.1	6.6 ± 0.3	4.6 ± 0.3	**6r**	–	–	2.1 ± 0.6
6i	–	–	–	**6s**	–	–	–
6j	3.2 ± 0.1	6.6 ± 0.5	7.3 ± 0.8	**6t**	–	–	–
Flu	2.8 ± 0.2	–	–	**Ago**	–	2.7 ± 0.2	–

[a] RR represents the restoration rate of the tested compound calculated from six independent experiments measured at 48 h after treatment with the test compound at three different concentrations (10 μM, 20 μM and 40 μM). RR = $(A_d - A_c)/A_c$*100% ± S.D., where, A_c represents the mean absorbance value of six independent experiments of control group merely treated with corticosterone, A_d means the mean absorbance value of six independent experiments of test group treated with corticosterone and test drug and S.D. means the standard deviation. Data are presented as mean ± S.D. '–' represents compounds did not shown restoration effects on H_2O_2-injured PC12 cells.

Table 3
The protection rates of the target compounds on corticosterone-injured PC12 cells.

Compd	PR[a] (%)	Compd	PR[a] (%)
6a	1.4 ± 1.8	**6k**	43.5 ± 4.3
6b	–	**6l**	–
6c	–	**6m**	–
6d	25.3 ± 0.9	**6n**	–
6e	–	**6o**	39.2 ± 1.7
6f	–	**6p**	38.8 ± 4.6
6g	–	**6q**	–
6h	–	**6r**	–
6i	14.6 ± 2.0	**6s**	22.3 ± 2.6
6j	–	**6t**	25.8 ± 2.4
Flu	19.7 ± 0.7	**Ago**	26.2 ± 2.4
Mif	31.1 ± 1.2		

[a] PR represents the protection rate of the tested compound calculated from six independent experiments measured at 24 h after treatment with the test compound at the concentration of 1.25 μM. PR = $(A_d - A_c)/A_c$*100% ± S.D., where, A_c represents the mean absorbance value of six independent experiments of control group merely treated with corticosterone, A_d means the mean absorbance value of six independent experiments of test group treated with corticosterone and test drug and S.D. means the standard deviation. Data are presented as mean ± S.D. '–' represents compounds did not shown protection effects on corticosterone-injured PC12 cells.

morphologically changed ones injured by stimulant and the result was shown in Fig. 2. Compound **6k** exhibited better protective effect than the positive controls. Compound **6o** displayed comparable protective effect to Agomelatine, but worse than Mifepristone.

3.4. Cytotoxicity

All of the target compounds (**6a**–**t**) were evaluated *in vitro* on human normal liver L02 cells and human embryonic kidney 293 cells. As shown in Table 4, most of the naphthalene compounds did not show apparent inhibitory effects on the test cell lines at concentration of 80 μM compared. The most promising compounds **6k**, **6o** and **6p** demonstrated lower cytotoxicity on both cell lines, superior to Fluoxetine and Agomelatine.

3.5. Forced swim test

As shown in Fig. 2, compounds **6k**, **6o** and **6p** displayed remarkable activities compared with control group. Treatment with compound **6k**, **6o** or **6p** remarkably reduced the immobility time of C57 mice with a percentage of 58.4%, 49.1% and 36.2% respectively. Compound **6k** exhibited better antidepressant-like

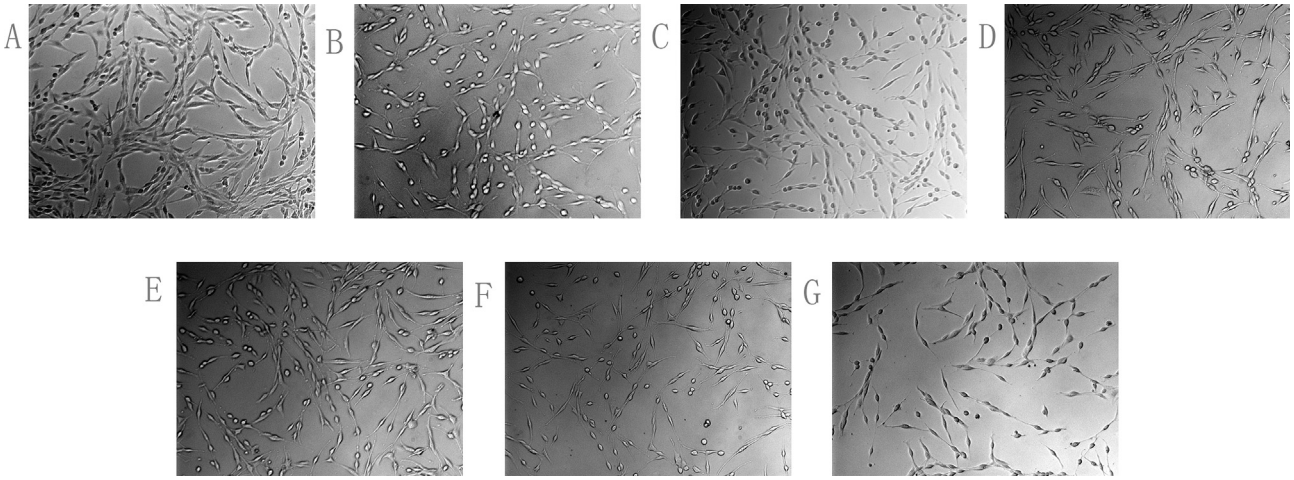


Fig. 1. Morphological changes in PC12 cells treated with **6k** and **6o** (100×). PC12 cells were seeded in 6-well plates at a density of 1×10^6 cells/mL in the growth medium for 1 d, and then the cells were treated with indicating drugs respectively. (A) cells treated with normal saline; (B) cells exposed to corticosterone 0.2 mM; (C) cells treated with corticosterone 0.2 mM and Fluoxetine 1.25 μM; (D) cells treated with corticosterone 0.2 mM and Agomelatine 1.25 μM; (E) cells treated with corticosterone 0.2 mM and Mifepristone 1.25 μM; (F) cells treated with corticosterone 0.2 mM and **6k** 1.25 μM; (G) cells treated with corticosterone 0.2 mM and **6o** 1.25 μM.

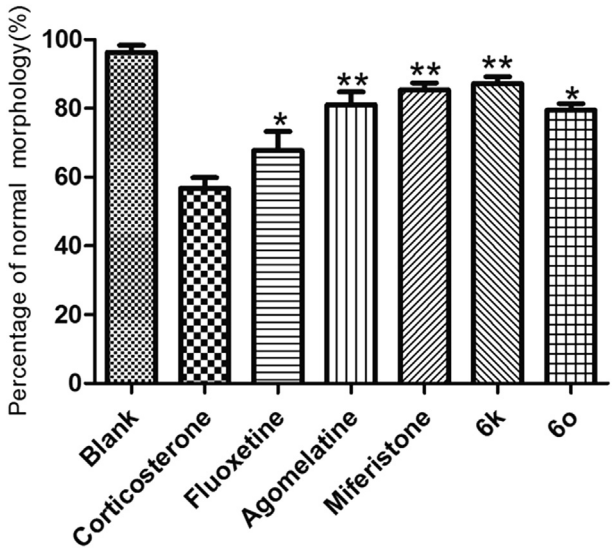


Fig. 2. The percentage of normal morphological cells. $^{*}P < 0.01$, $^{**}P < 0.05$.

potency than Fluoxetine (50.7%) and Agomelatine (8.4%). Compound **6o** and **6p** also displayed *in vivo* antidepressant-like effects, which is well correlated with the *in vitro* corticosterone-induced PC12 model. However, sulfonyl compound **6d** with good neuroprotective *in vitro* was shown to be ineffective in FST test, largely different from its acyl counterpart **6o**. The completely opposite results may be owed to the difference of tPSA value of compound **6d** (75.7) from that of compound **6o** (58.6) as listed in Table 1. Compound **6o** with a lower tPSA value was more liable to cross the blood–brain barrier than compound **6d.**

3.6. Open field locomotor activity

To exclude the nonspecific motor activities in the forced swim test, the most effective compound **6k** was selected to further test its spontaneous locomotor activity in an open field apparatus (Fig. 3). Mice administrated with compound **6k** traveled a longer total distance by 88.5% than the model ones, while Fluoxetine and Agomelatine showed that percentage of 66.4% and 85.3%. These results well confirmed the antidepressant-like activity of **6k**.

Table 4
Cytotoxicities of the final compounds on human normal liver L02 cells and human embryonic kidney cell line 293.

Compd	IR[a] (%)		Compd	IR[a] (%)	
	L02	293		L02	293
6a	4.4 ± 0.5	8.5 ± 5.4	**6k**	2.6 ± 2.2	–
6b	7.4 ± 3.1	4.6 ± 2.8	**6l**	–	2.5 ± 1.6
6c	2.7 ± 0.9	3.6 ± 0.6	**6m**	15.8 ± 0.5	11.1 ± 2.4
6d	33.6 ± 7.7	21.5 ± 0.4	**6n**	13.1 ± 1.6	13.1 ± 3.5
6e	7.8 ± 2.9	8.9 ± 5.5	**6o**	5.9 ± 0.7	11.8 ± 2.4
6f	2.3 ± 1.3	6.2 ± 0.7	**6p**	3.2 ± 0.5	26.4 ± 2.6
6g	2.9 ± 1.4	11.2 ± 1.7	**6q**	11.2 ± 0.4	31.8 ± 1.4
6h	3.8 ± 0.4	11.9 ± 1.2	**6r**	4.8 ± 0.8	17.3 ± 1.4
6i	7.9 ± 4.2	24.6 ± 7.2	**6s**	1.3 ± 0.8	33.4 ± 2.7
6j	12.1 ± 2.1	1.0 ± 0.9	**6t**	1.0 ± 0.2	17.5 ± 4.8
Flu	28.5 ± 6.9	55.8 ± 2.9	**Ago**	20.2 ± 7.6	26.6 ± 1.6

[a] IR is the mean inhibitory rate calculated from three independent experiments measured at 24 h after treatment with the test compound at the concentration of 80 μM. The viability of the untreated cells was regarded as 100%. Data are expressed as the mean ± S.D. '–' represents compounds did not shown cytotoxicity on tested cells.

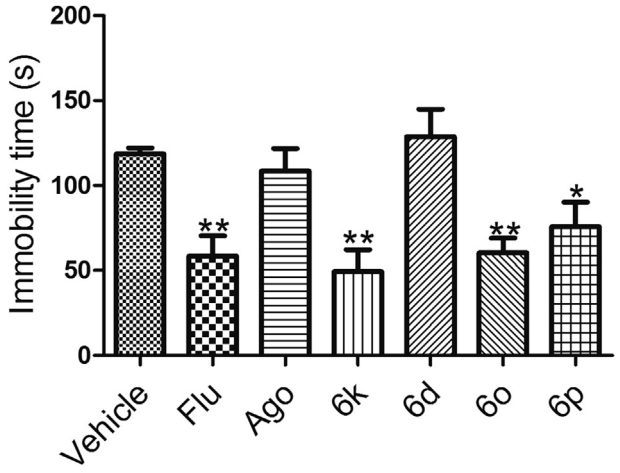


Fig. 3. Effects of compounds **6d**, **6k**, **6o**, **6p** and positive controls in forced swim test. Mice were treated on days 2–15 with compound (i.p.32 mg/kg/day). Data represent the mean ± S.D. of 10 mice per group. Values are significant at $^{*}P < 0.01$ when compared with vehicle group.

3.7. Docking study

In order to gain better understanding of the molecular mechanism of the most active compound **6k**, a docking study was performed by docking compound **6k** or **6d** or Agomelatine into the active site of glucocorticoid receptor (PDB code: 1NHZ). As shown in Fig. 4, compound **6k** formed two hydrogen bonds with GLN570 and ASN564, exhibited best protective effects on corticosterone-injured PC12 cells and antidepressant-like activity *in vivo*. With only one hydrogen bond observed in binding model with glucocorticoid receptor, Agomelatine displayed less activity than **6k** *in vitro* and *in vivo*.

With a purpose of a clear understanding of binding mode of **6k**, some more detail docking study was shown in Fig. 5. The appropriate length of the side chain in compound **6k** made it capable of the occupation of the inner cavity (Fig. 5b) and forming another hydrogen bond with GLN570 in the receptor, which is quite different from that of Agomelatine (Fig. 6).

4. Conclusions

In this paper, we synthesized twenty novel *N*-(2-(7-methoxynaphthalen-1-yl) ethyl) amide derivatives and tested

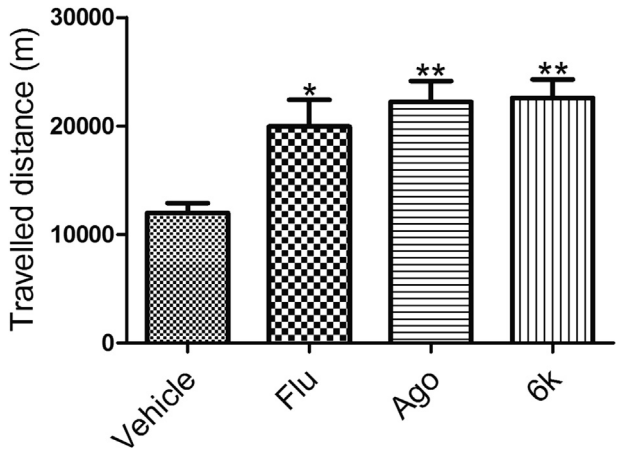


Fig. 4. Antidepressant-like effects of compound **6k** and positive controls in the open field test. Mice were treated on days 2–15 with test compounds (i.p. 32 mg/kg/day). Data represent the mean ± S.D. of 10 mice per group. $^{*}P < 0.01$, $^{**}P < 0.05$.

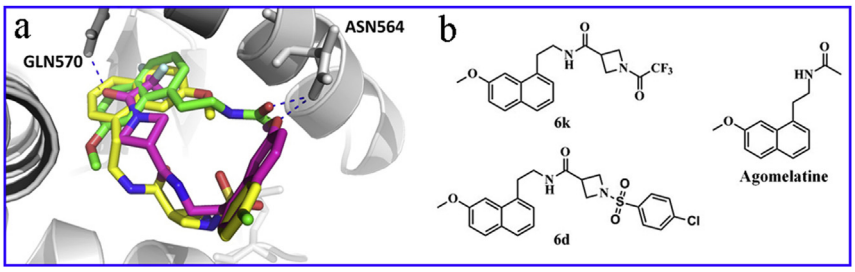


Fig. 5. (a) The binding modes of compounds **6k**, **6d** and Agomelatine with glucocorticoid receptor. **6k** colored in pink, **6d** in yellow and Agomelatine in green, respectively. (b) Chemical structures of compound **6k**, **6d** and Agomelatine. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

their neuroprotective or neurorestorative activities on injured PC12 cells induced by corticosterone or H_2O_2 respectively. The results from these two *in vitro* models showed that corticosterone-injured PC12 cells model is a fruitful *in vitro* model for preliminary screening of antidepressant candidates. Four compounds **6k**, **6o**, **6d** and **6p** with better protection rates than positive controls (Agomelatine and Fluoxetine) were further evaluated on forced swim test model. Among them, compound **6k** exhibited better anti-immobility activity than Fluoxetine and Agomelatine. In open field test, mice treated with **6k** traveled longer distance than Fluoxetine and Agomelatine, displaying a better general locomotor activity. Docking study of compound **6k** with glucocorticoid receptor proposed a possible binding mode with hydrogen-bonding interactions with residues of ASN564 and GLN570 in glucocorticoid receptor, which was different from that of Agomelatine, where no hydrogen-bonding interaction with residue of GLN570 was involved. The cytotoxicity data suggested a good safety profile of compound **6k**, providing a promising antidepressant candidate with neuroprotective mechanism.

5. Experiment section

5.1. Materials

Corticosterone was obtained from Aladdin Reagents (Shanghai) Company. Methyl thiazolyltetrazolium (MTT) were bought from Sigma Company. Fluoxetine and Agomelatine were purchased from Dalian Meilun Biotech Company.

Male C57 mice (20–24 g) were purchased from Beijing HFK Bio-Technology Co. ltd. They were kept on a 12 h/12 h light/dark cycle and were given access to food and water ad libitum. All the procedures in this study were performed followed the protocols approved by the Institutional Animal Care and Treatment Committee of Sichuan University. All mice in this study were treated humanely throughout the experimental period.

All solvents and reagents were analytical reagents and used directly without further purification.

All melting points were determined on a SGW X-4 Micro Melting Point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance (Varian Unity Inova) 400 MHz spectrometer using TMS as internal reference chemical shift in δ, ppm. High-resolution mass (HRMS) spectrometry was carried out on a Waters Q-TOF Premier mass spectrometer.

All compounds used for biological assays were at least of 98% purity based on HPLC analytical results monitored with full wavelengths.

5.2. Chemistry

5.2.1. Tert-butyl (2-(7-methoxynaphthalen-1-yl)ethyl)carbamate (**2**)

A mixture of 2-(7-methoxynaphthalen-1-yl)acetonitrile (compound **1**, 1.99 g, 10.0 mmol), $NiCl_2$ (475 mg, 5.0 mmol) and $(Boc)_2O$ (0.2 mL) in 20 mL MeOH were stirred in an ice-bath, then $NaBH_4$ (417 mg, 11.0 mmol) was added in batches under N_2 atmosphere. The ice-bath was removed and the mixture was stirred at room temperature for 12 h. After the completion of reaction (as evidenced by TLC), 20 mL H_2O was added and the resulting mixture was concentrated under reduced pressure. Then 20 mL H_2O was added, extracted with ethyl acetate (20 mL × 3), the combined organic layer were concentrated under reduced pressure to obtained brown solid (2.41 g, yield: 80%). mp: 98.6–100.5 °C, ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J = 8 Hz, 1H), 7.68 (dd, J = 8 Hz, J = 4 Hz, 1H), 7.45 (s, 1H), 7.30–7.25 (m, 2H), 7.17 (dd, J = 8 Hz, J = 4 Hz, 1H), 4.75 (s, 1H), 3.97 (s, 3H), 3.54 (dd, J = 16 Hz, J = 8 Hz, 2H), 3.24 (t, J = 8 Hz, 2H), 1.46 (s, 9H); MS (TOF) m/z calcd. for $C_{18}H_{23}NO_3$ [M + H$^+$] 302.2, found: 302.4.

5.2.2. 2-(7-methoxynaphthalen-1-yl)ethanamine hydrochloride (**3**)

Compound **2** (2.41 g, 8.00 mmol) was dissolved in 10 mL CH_2Cl_2 and 10 mL TFA, after stirred at room temperature for 3 h. The completion of reaction was monitored by TLC. Then adjust to pH = 10 with 10% NaOH solution, then washed with H_2O (20 mL × 3) and brine (20 mL × 1), dry over Na_2SO_4, filtered and treated with a saturated solution of hydrogen chloride in Et_2O,

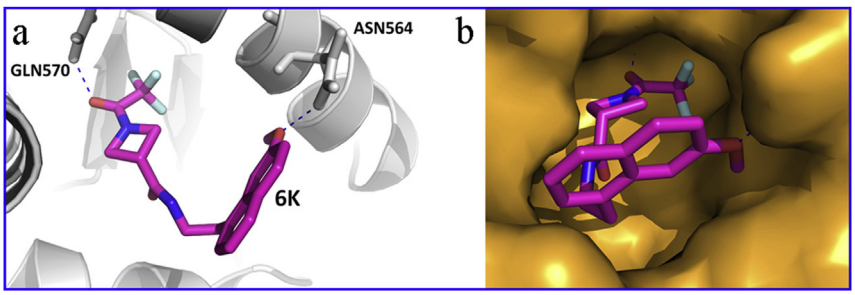


Fig. 6. (a) The binding mode of compound **6k** with glucocorticoid receptor. **6k** colored in pink, hydrogen bond colored in blue. (b) Binding cavity of **6k** and glucocorticoid receptor. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

compound **3** was obtained after concentrated under reduced pressure as gray solid (963 mg, yield: 64%). mp: 242.7–245.5 °C; ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 3H), 7.88 (d, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 1H), 7.41–7.38 (m,1H), 7.33–7.29 (m, 2H), 7.22 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 3.95 (s, 3H), 3.36–3.31 (m, 2H), 3.11–3.08 (m, 2H), MS (TOF) m/z calcd. for $C_{12}H_{13}NO$ [M + H$^+$] 188.1, found: 188.2.

*5.2.3. Tert-butyl 3-((2-(7-methoxynaphthalen-1-yl)ethyl) carbamoyl)azetidine-1-carboxylate (**4**)*

Compound **3** (1.00 g, 4.21 mmol) and DIEA (2.20 ml, 12.63 mmol) were dissolved in CH_2Cl_2 (30 mL) and DMF (3 mL). 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (940 mg, 4.63 mmol), EDC (970 mg, 5.05 mmol), HOBt (682 mg, 5.05 mmol), DMAP (154 mg, 1.26 mmol) were added. After stirring at room temperature for 24 h, the reaction mixture was diluted with 100 mL CH_2Cl_2 and washed with H_2O (30 mL × 3), 1 N HCl (30 mL × 3), $NaHCO_3$ (30 mL × 3) and brine (30 mL × 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give pink solid (1.49 g, yield: 92%). mp: 56.5–58.8 °C; ^{1}H NMR ($CDCl_3$): δ 7.75 (d, J = 12 Hz, 1H), 7.68–7.65 (m, 1H), 7.42 (d, J = 4 Hz, 1H), 7.27–7.24(m 2H), 7.16 (dd, J = 8 Hz, J = 4 Hz, 1H), 6.06 (s, 1H), 4.11–3.98 (m, 4H), 3.96 (s, 3H), 3.64 (dd, J = 12 Hz, J = 4 Hz, 2H), 3.24 (t, J = 8 Hz, 2H), 3.12–3.09 (m, 1H), 1.43 (s, 9H); MS (TOF) m/z calcd. for $C_{22}H_{28}N_2O_4$ [M + H$^+$] 385.2, found: 385.4.

*5.2.4. N-(2-(7-methoxynaphthalen-1-yl)ethyl)azetidine-3-carboxamide hydrochloride (**5**)*

Compound **4** (823 mg, 2.14 mmol) was dissolved in 1 mL CH_2Cl_2. Then TFA (1.8 mL, 15.16 mmol) was added dropwise. After stirring at room temperature for 3 h, adjust to pH = 10 with 10% NaOH solution under ice-bath condition. Then the reaction mixture was diluted with 100 mL CH_2Cl_2 and washed with H_2O (30 mL × 1) and brine (30 mL × 1). The organic layer was dried over Na_2SO_4 and filtered. Then treated with saturated solution of hydrogen chloride in Et_2O to pH = 1 and concentrated under reduced pressure to afford white solid (515 mg, yield: 75%). mp: 175–176.5 °C; ^{1}H NMR (DMSO-d_6): δ 9.54 (s, 1H), 8.99 (s, 1H), 8.56 (t, J = 8 Hz, 1H), 7.85 (d, J = 12 Hz, 1H), 7.72 (d, J = 8 Hz, 1H), 7.56 (d, J = 4 Hz, 1H), 7.34–7.25 (m, 2H), 7.18 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 3.99–3.94 (m, 7H), 3.61–3.52 (m, 1H), 3.44–3.39 (m, 2H), 3.16 (t, J = 8 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 169.76, 157.44, 133.84, 132.74, 130.13, 128.77, 127.09, 126.58, 123.11, 117.88, 102.58, 55.33, 46.97, 34.88, 32.72; HRMS (TOF) m/z calcd. for $C_{17}H_{20}N_2O_2$ [M + H$^+$] 285.1603, found: 285.1597.

*5.2.5. General procedure for the synthesis of N-substituted analogues **6a–l***

N-(2-(7-methoxynaphthalen-1-yl)ethyl)azetidine-3-carboxamide hydrochloride (500 mg, 1.56 mmol) and DIPEA (0.8 mL, 4.84 mmol) was dissolved in CH_2Cl_2 (10 mL), then different substituted acyl chloride or sulfonyl chloride or anhydride (3.12 mmol) was added dropwise under ice bath. After stirring at room temperature for 24 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), then washed with H_2O (20 mL), $NaHCO_3$ saturated solution (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure and the residue was purified by chromatography on silica gel to afford respective compounds **6a-l**.

*5.2.5.1. N-(2-(7-methoxynaphthalen-1-yl)ethyl)-1-(methylsulfonyl) azetidine-3-carbox-amide (**6a**).* Following general procedure to obtain pure product as white solid 452 mg (yield: 80%). mp: 148.5–149.7 °C; ^{1}H NMR ($CDCl_3$): δ 7.78 (d, J = 8 Hz, 1H), 7.71–7.69 (m, 1H), 7.39 (d, J = 4 Hz, 1H), 7.27 (d, J = 4 Hz, 1H), 7.18 (dd, J_1 = 12 Hz, J_2 = 8 Hz, 1H), 5.62 (s, 1H), 4.04 (d, J = 8 Hz, 4H), 3.97 (s, 3H), 3.68 (q, J = 8 Hz, 2H), 3.27 (t, J = 4 Hz, 2H), 3.15–3.07 (m, 1H), 2.94 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.83, 158.00, 133.15, 133.10, 130.42, 129.33, 127.26, 127.17, 123.18, 118.08, 102.60, 55.51, 52.97, 40.10, 34.44, 32.81, 32.74; HRMS (TOF) m/z calcd. for $C_{18}H_{22}N_2O_4S$ [M + H$^+$] 363.1379, found: 363.1381.

*5.2.5.2. 1-(N′,N′-dimethylsulfamoyl)-N-(2-(7-methoxynaphthalen-1-yl)ethyl)azetidine-3-carboxamide (**6b**).* Following general procedure to obtain pure product as white solid 440 mg (yield: 72%). mp: 99.4–101.1 °C; ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J = 8 Hz, 1H), 7.69 (t, J = 4 Hz, 1H), 7.41 (d, J = 4 Hz, 1H), 7.28–7.27 (m, 2H), 7.18 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.65 (s, 1H), 4.04–3.96 (m, 7H), 3.69 (q, J = 8 Hz, 2H), 3.28 (t, J = 8 Hz, 2H), 3.18–3.11 (m, 1H), 2.81 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 170.97, 158.01, 133.30, 133.13, 130.35, 129.32, 127.1, 123.17, 118.20, 102.51, 55.53, 53.50, 40.05, 38.18, 33.66, 32.90; HRMS (TOF) m/z calcd. for $C_{19}H_{25}N_3O_4S$ [M + Na$^+$] 414.1463, found: 414.1460.

*5.2.5.3. N-(2-(7-methoxynaphthalen-1-yl)ethyl)-1-tosylazetidine-3-carboxamide (**6c**).* Following general procedure to obtain pure product as white solid 568 mg (yield: 83%). mp: 143.3–144.7 °C; ^{1}H NMR (CDCl3): δ 7.38–7.35 (m, 3H), 7.23–7.15 (m, 3H), 5.56 (s, 1H), 3.93 (s, 3H), 3.90–3.82 (m, 4H), 3.57 (q, J = 8 Hz, 2H), 3.17 (t, J = 4 Hz, 2H), 3.04–2.97 (m, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.21, 157.98, 144.43, 133.19, 133.07, 130.97, 130.35, 129.92, 129.30, 128.46, 127.19, 127.11, 118.18, 102.47, 55.50, 53.14, 39.95, 33.21, 32.88, 21.67; HRMS (TOF) m/z calcd. for $C_{24}H_{26}N_2O_4S$ [M + H$^+$] 439.1692, found: 439.1692.

*5.2.5.4. 1-((4-chlorophenyl)sulfonyl)-N-(2-(7-methoxynaphthalen-1-yl)ethyl) azetidine-3-carboxamide (**6d**).* Following general procedure to obtain pure product as white solid 516 mg (yield: 72%). mp: 152.5–154.6 °C, ^{1}H NMR ($CDCl_3$): δ 7.79–7.76 (m, 3H), 7.68 (d, J = 8 Hz, 1H), 7.55 (d, J = 8 Hz, 2H), 7.33 (d, J = 4 Hz, 1H), 7.27–7.16 (m, 2H), 5.48 (s, 1H), 3.94 (s, 3H), 3.93–3.84 (m, 4H), 3.59 (q, J = 4 Hz, 2H), 3.19 (t, J = 8 Hz, 2H), 3.01–2.98 (m,1H); ^{13}C NMR ($CDCl_3$): δ 169.90, 157.41, 138.55, 133.79, 132.73, 132.42, 130.10, 130.07, 129.58, 128.74, 126.99, 126.55, 123.04, 117.92, 102.52, 55.20, 53.01, 32.71, 31.64; HRMS (TOF) m/z calcd. for $C_{23}H_{23}ClN_2O_4S$ [M + Na$^+$] 481.0965, found: 481.0969.

*5.2.5.5. 1-(4-methoxybenzoyl)-N-(2-(7-methoxynaphthalen-1-yl) ethyl)azetidine-3-carboxamide (**6e**).* Following general procedure to obtain pure product as white solid 554 mg (yield: 85%). mp: 65.3–67.1 °C; ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J = 8 Hz, 1H), 7.70–7.67 (m, 1H), 7.60 (dt, J = 8 Hz, J = 4 Hz, 2H), 7.41 (d, J = 4 Hz, 1H), 7.27 (s, 1H), 7.17 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 6.90 (dt, J_1 = 8 Hz, J_2 = 4 Hz, 2H), 5.67 (s, 1H), 4.53 (brs, 1H), 4.30 (t, J = 8 Hz, 2H), 4.23 (brs, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 3.69 (q, J = 8 Hz, 2H), 3.27 (t, J = 8 Hz, 2H), 3.24–3.17 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 171.48, 169.94, 161.87, 157.98, 133.40, 133.15, 130.33, 129.80, 129.29, 127.13, 124.97, 123.16,118.20,113.66, 102.52, 55.54, 55.38, 51.55, 40.10, 32.92, 32.98; HRMS (TOF) m/z calcd. for $C_{25}H_{26}N_2O_4$ [M + H$^+$] 419.1968, found: 419.1971.

*5.2.5.6. 1-Acetyl-N-(2-(7-methoxynaphthalen-1-yl)ethyl)azetidine-3-carboxamide (**6f**).* Following general procedure to obtain pure product as yellow oil 372 mg (yield: 73%). ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J = 8 Hz, 1H), 7.69 (t, J = 4 Hz, 1H), 7.41 (d, J = 4 Hz, 1H), 7.18 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.80 (brs, 1H), 4.32 (t, J = 8 Hz, 1H), 4.14 (t, J = 8 Hz, 1H), 4.05 (d, J = 8 Hz, 2H), 3.97 (s, 3H), 3.68–3.67 (m, 2H), 3.28–3.25 (m, 2H), 3.15–3.08 (m, 1H), 1.84 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.36, 170.64, 157.97, 133.39, 133.14, 130.34, 129.30, 127.13, 123.16, 118.14, 102.57, 55.53, 52.51, 50.64, 40.09, 32.91, 32.55,

18.52; HRMS (TOF) *m/z* calcd. for $C_{19}H_{22}N_2O_3$ [M + H^+] 326.1709, found: 326.1709.

*5.2.5.7. N-(2-(7-methoxynaphthalen-1-yl)ethyl)-1-propionylazetidine-3-carboxamide (**6g**).* Following general procedure to obtain pure product as yellow oil 370 mg (yield: 70%). ^{1}H NMR ($CDCl_3$): δ 7.78 (d, *J* = 12 Hz, 1H), 7.69 (t, *J* = 4 Hz, 1H), 7.41 (d, *J* = 4 Hz, 1H), 7.28 (d, *J* = 4 Hz, 1H), 7.18 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.56 (s, 1H), 4.31 (t, *J* = 8 Hz, 1H), 4.16–4.06 (m, 3H), 3.98 (s, 3H), 3.72–3.66 (m, 2H), 3.29–3.25 (m, 2H), 3.17–3.09 (m, 1H), 2.12–2.05 (m, 2H), 1.60–1.59 (m, 2H), 1.12 (t, *J* = 4 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 172.73, 171.48, 157.41, 133.99, 132.81, 130.10, 128.77, 127.02, 126.53, 123.09, 117.85, 102.63, 55.25, 51.95, 49.94, 32.71, 31.84, 23.50, 8.62; HRMS (TOF) *m/z* calcd. for $C_{20}H_{24}N_2O_3$ [M + H^+] 341.1865, found: 341.1865.

*5.2.5.8. 1-Benzoyl-N-(2-(7-methoxynaphthalen-1-yl)ethyl)azetidine-3-carboxamide (**6h**).* Following general procedure to obtain pure product as white solid 424 mg (yield: 70%). mp: 55.5–57.3 °C; ^{1}H NMR ($CDCl_3$): δ 7.77 (d, *J* = 8 Hz, 1H), 7.70–7.67 (m, 1H), 7.62 (dt, J_1 = 8 Hz, J_2 = 4 Hz, 2H), 7.49–7.39 (m, 4H), 7.27 (s, 1H), 7.16 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.65 (s, 1H), 4.51 (t, *J* = 4 Hz, 1H), 4.30–4.27 (m, 3H), 3.97 (s, 3H), 3.69 (q, *J* = 8 Hz, 2H), 3.29–3.25 (m, 2H), 3.24–3.17 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 171.41, 168.85, 157.41, 134.00, 132.82, 130.98, 130.09, 128.78, 128.41, 127.64, 127.03, 126.53, 123.08, 117.84, 102.65, 55.22, 54.88, 51.01, 32.76, 32.68; HRMS (TOF) *m/z* calcd. for $C_{24}H_{24}N_2O_3$ [M + Na^+] 411.1685, found: 411.1681.

*5.2.5.9. N-(2-(7-methoxynaphthalen-1-yl)ethyl)-1-(4-(trifluoromethyl)benzoyl) azetidine-3-carboxamide (**6i**).* Following general procedure to obtain pure product as white solid 520 mg (yield: 73%). mp: 76.3–78 °C; ^{1}H NMR ($CDCl_3$): δ 7.78–7.67 (m, 6H), 7.40 (d, *J* = 4 Hz, 1H), 7.27 (s, 1H), 7.18 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 5.57 (s, 1H), 4.50 (t, *J* = 8 Hz, 1H), 4.34–4.23 (m, 3H), 3.97 (s, 3H), 3.70 (q, *J* = 8 Hz, 2H), 3.27 (td, J_1 = 8 Hz, J_2 = 4 Hz, 2H), 3.25–3.17 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 171.07, 168.75, 158.00, 136.11, 133.24, 133.12, 133.02, 132.70, 130.40, 129.32, 128.22, 127.22, 127.15, 125.50, 125.44, 125.00, 123.16, 122.29, 55.51, 55.16, 51.62, 40.11, 33.80, 32.85; HRMS (TOF) *m/z* calcd. for $C_{25}H_{23}F_3N_2O_3$ [M + H^+] 457.1739, found: 457.1738.

*5.2.5.10. Benzyl 3-((2-(7-methoxynaphthalen-1-yl)ethyl)carbamoyl) azetidine-1-carboxylate (**6j**).* Following general procedure to obtain pure product as white solid 464 mg (yield: 71%). ^{1}H NMR ($CDCl_3$): δ 7.77 (d, *J* = 12 Hz, 1H), 7.70–7.67 (m, 1H), 7.40 (d, *J* = 4 Hz, 1H), 7.38 (s, 1H), 7.33–7.28 (m, 2H), 7.25 (d, *J* = 4 Hz, 3H), 7.17 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.52 (s, 1H), 4.16–4.14 (m, 2H), 4.07 (t, *J* = 8 Hz, 2H), 3.97 (s, 3H), 3.68 (q, *J* = 8 Hz, 2H), 3.26 (t, *J* = 8 Hz, 2H), 3.15–3.08 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 171.36, 157.42, 155.64, 136.84, 133.98, 132.82, 130.09, 128.78, 128.38, 127.85, 127.60, 127.02, 126.54, 123.08, 117.85, 102.64, 65.62, 55.21, 51.89, 51.32, 32.70, 32.50; HRMS (TOF) *m/z* calcd. for $C_{25}H_{26}N_2O_4$ [M + Na^+] 441.1790, found: 441.1790.

*5.2.5.11. N-(2-(7-methoxynaphthalen-1-yl)ethyl)-1-(2,2,2-trifluoroacetyl)azetidine-3-carboxamide (**6k**).* Following general procedure to obtain pure product as colorless oil 433 mg (yield: 73%). ^{1}H NMR ($CDCl_3$): δ 7.78 (d, *J* = 8 Hz, 1H), 7.71 (d, *J* = 4 Hz, 1H), 7.39 (s, 1H), 7.19 (d, *J* = 8 Hz, 1H), 5.59 (s, 1H), 4.59 (brs, 1H), 4.43 (t, *J* = 8 Hz, 1H), 4.22–4.17 (m, 2H), 3.97 (s, 3H), 3.70 (d, *J* = 8 Hz, 2H), 3.28–3.22 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 170.65, 169.84, 157.42, 133.96, 133.80, 132.78, 128.77, 127.07, 126.55, 123.09, 117.85, 102.61, 55.25, 54.28, 51.34, 47.28, 34.91, 32.60; HRMS (TOF) *m/z* calcd. for $C_{19}H_{19}F_3N_2O_3$ [M + Na^+] 403.1245, found: 403.1262.

*5.2.5.12. N-(2-(7-methoxynaphthalen-1-yl)ethyl)-N′,N′-dimethylazetidine-1,3-dicarboxamide (**6l**).* Following general procedure to obtain pure product as yellow oil 382 mg (yield: 69%). ^{1}H NMR ($CDCl_3$): δ 7.77 (d, *J* = 8 Hz, 1H), 7.70–7.67 (m, 1H), 7.42 (d, *J* = 4 Hz, 1H), 7.28 (s, 1H), 7.17 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.66 (s, 1H), 4.09–4.03 (m, 4H), 3.98 (s, 3H), 3.68 (q, *J* = 8 Hz, 2H), 3.27 (t, *J* = 8 Hz, 2H), 3.16–3.08 (m,1H); ^{13}C NMR (DMSO-d_6): δ 171.67, 162.22, 157.42, 134.02, 132.83, 130.08, 128.78, 127.01, 126.52, 123.08, 117.85, 102.64, 55.22, 54.88, 52.93, 36.43, 32.76; HRMS (TOF) *m/z* calcd. for $C_{20}H_{25}N_3O_3$ [M + Na^+] 378.1794, found: 378.1788.

*5.2.6. General procedure for the synthesis of N-substituted analogues **6m–t***

N-(2-(7-methoxynaphthalen-1-yl)ethyl)azetidine-3-carboxamide hydrochloride (800 mg, 2.50 mmol) and DIPEA (1.5 mL, 9.08 mmol) was dissolved in CH_2Cl_2 (20 mL) and DMF (3 mL), then different substituted carboxylic acid (2.74 mmol), EDC (574 mg, 2.99 mmol), HOBt (404 mg, 2.99 mmol) and DMAP (91 mg, 0.748 mmol) was added. After stirring at room temperature for 24 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), then washed with H_2O (20 mL), 10% HCl (20 mL), $NaHCO_3$ saturated solution (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure and the residue was purified by chromatography on silica gel to afford respective compounds **6m–t**.

*5.2.6.1. 1-(3,5-dinitrobenzoyl)-N-(2-(7-methoxynaphthalen-1-yl) ethyl)azetidine-3-carboxamide (**6m**).* Following general procedure to obtain pure product as white solid 897 mg (yield: 75%). mp: 147.8–149.9 °C; ^{1}H NMR (DMSO-d_6): 8.91 (s, 1H), 8.67 (d, *J* = 4 Hz, 2H), 8.28–8.25 (m, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.68 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 4 Hz, 1H), 7.30–7.22 (m, 2H), 7.64 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.73 (s, 1H), 4.48 (t, *J* = 8 Hz, 1H), 4.31 (t, *J* = 8 Hz, 1H), 4.20 (t, *J* = 8 Hz, 1H), 4.12–4.08 (m, 1H), 3.91 (s, 3H), 3.41–3.36 (m, 3H), 3.14 (t, *J* = 8 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.06, 164.31, 157.38, 148.07, 135.68, 133.95, 132.79, 130.07, 128.74, 127.68, 127.04, 126.53, 123.08, 120.40, 117.80, 115.47, 102.60, 55.20, 51.46, 40.08, 32.77, 32.63; HRMS (TOF) *m/z* calcd. for $C_{24}H_{22}N_4O_7$ [M + Na^+] 501.1386, found: 501.1388.

*5.2.6.2. 1-(3,5-dimethoxybenzoyl)-N-(2-(7-methoxynaphthalen-1-yl)ethyl)azetidine-3-carboxamide (**6n**).* Following general procedure to obtain pure product as white solid 695 mg (yield: 62%). mp: 55.1–57 °C; ^{1}H NMR ($CDCl_3$): δ 7.77 (d, *J* = 8 Hz, 1H), 7.69 (t, *J* = 4 Hz, 1H), 7.41 (d, *J* = 4 Hz, 1H), 7.27 (s, 1H), 7.17 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 6.75 (d, *J* = 4 Hz, 2H), 6.55–6.54 (m, 1H), 5.59 (s, 1H), 4.50 (brs, 1H), 4.28 (t, *J* = 8 Hz, 3H), 3.97(s, 3H), 3.84–3.78 (m, 6H), 3.69–3.67 (m, 2H), 3.27 (t, *J* = 8 Hz, 2H), 3.21–3.19 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 171.45, 168.64, 157.98, 153.59, 150.13, 133.40, 133.12, 130.30, 129.29, 127.09, 123.90, 123.14, 118.19, 117.01, 114.04, 112.75, 102.50, 56.29, 55.82, 55.52, 53.07, 51.13, 40.05, 33.49, 33.03; HRMS (TOF) *m/z* calcd. for $C_{26}H_{28}N_2O_5$ [M + Na^+] 471.1896, found: 471.1897.

*5.2.6.3. 1-(4-chlorobenzoyl)-N-(2-(7-methoxynaphthalen-1-yl)ethyl) azetidine-3-carboxamide (**6o**).* Following general procedure to obtain pure product as white solid 761 mg (yield: 72%). mp: 47.9–51.3 °C; ^{1}H NMR ($CDCl_3$): δ 7.77 (d, *J* = 8 Hz, 1H), 7.69 (t, *J* = 4 Hz, 1H), 7.56 (d, *J* = 8 Hz, 2H), 7.40–7.38 (m, 3H), 7.27 (s, 1H), 7.18 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.58 (s, 1H), 4.50 (brs, 1H), 4.26 (s, 3H), 3.97 (s, 3H), 3.70 (q, *J* = 8 Hz, 2H), 3.29–3.26 (m, 2H), 3.23–3.16 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 171.19, 169.08, 158.00, 137.40, 133.28, 133.14, 131.10, 130.37, 129.32, 129.28, 128.74, 127.19, 127.14, 123.16, 118.16, 102.55, 55.53, 55.30, 51.58, 40.11, 33.83, 32.89; HRMS (TOF) *m/z* calcd. for $C_{24}H_{23}ClN_2O_3$ [M + H^+] 423.1475, found: 423.1475.

*5.2.6.4. 1-(Furan-2-carbonyl)-N-(2-(7-methoxynaphthalen-1-yl) ethyl)azetidine-3-carboxamide (**6p**).* Following general procedure to obtain pure product as white solid 681 mg (yield: 72%). mp: 140.1–142.4 °C; ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J = 12 Hz, 1H), 7.70–7.66 (m, 1H), 7.48 (d, J = 0.8 Hz, 1H), 7.42 (d, J = 4 Hz, 1H), 7.27 (s, 1H), 7.17 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 7.04 (d, J = 4 Hz, 1H), 6.47 (m, 1H), 5.71 (s, 1H), 4.70 (brs, 1H), 4.57 (t, J = 8 Hz, 1H), 4.25 (d, J = 8 Hz, 2H), 3.97 (s, 3H), 3.69 (q, J = 8 Hz, 2H), 3.30–3.21 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 171.45, 158.70, 157.98, 147.64, 144.68, 133.43, 133.16, 130.30, 129.29, 127.11, 123.14, 118.18, 115.47, 111.57, 102.50, 55.51, 54.71, 51.12, 40.14, 34.20, 32.97; HRMS (TOF) m/z calcd. for $C_{22}H_{22}N_2O_4$ [M + Na^+] 401.1477, found: 401.1475.

*5.2.6.5. N-(2-(7-methoxynaphthalen-1-yl)ethyl)-1-picolinoylazetidine-3-carboxamide (**6q**).* Following general procedure to obtain pure product as white solid 486 mg (yield: 50%). mp: 168–169 °C; ^{1}H NMR ($CDCl_3$): δ 8.56 (d, J = 4 Hz, 1H), 8.09 (d, J = 4 Hz, 1H), 7.82–7.67 (m, 3H), 7.43 (d, J = 4 Hz, 1H), 7.38–7.27 (m, 2H), 7.16 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.67 (s, 1H), 4.87–4.79 (m, 2H), 4.37–4.28 (m, 2H), 3.97 (s, 1H), 3.71–3.66 (m, 2H), 3.29–3.21 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 171.73, 164.96, 158.00, 151.64, 148.10, 136.79, 133.39, 133.14, 130.30, 129.30, 127.13, 125.40, 123.65, 123.14, 118.25, 102.45, 57.27, 55.53, 51.35, 40.01, 34.04, 33.04; HRMS(TOF) m/z calcd. For $C_{23}H_{23}N_3O_3$ [M + Na^+] 412.1637, found: 412.1637.

*5.2.6.6. 1-(3-chloroisonicotinoyl)-N-(2-(7-methoxynaphthalen-1-yl) ethyl)azetidine-3-carboxamide (**6r**).* Following general procedure to obtain pure product as white solid 530 mg (yield: 50%). mp: 65.8–67.8 °C; ^{1}H NMR ($CDCl_3$): 7.77 (d, J = 8 Hz, 1H), 7.71–7.68 (m,1H), 7.50 (s, 1H), 7.39–7.38 (m, 2H), 7.29–7.27 (m, 1H), 7.18 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 5.57 (s, 1H), 4.49 (t, J = 4 Hz, 1H), 4.31–4.23 (m, 3H), 3.97 (s, 3H), 3.70 (q, J = 4 Hz, 2H), 3.28 (td, J_1 = 8 Hz, J_2 = 4 Hz, 2H), 3.24–3.17 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 170.76, 166.07, 157.99, 152.20, 150.33, 143.10, 133.20, 133.13, 130.41, 129.31, 127.24, 127.16, 123.16, 122.65, 120.43, 118.21, 102.58, 55.53, 54.99, 51.74, 40.15, 33.79, 32.77; HRMS (TOF) m/z calcd. for $C_{23}H_{22}ClN_3O_3$ [M + H^+] 424.1428, found: 424.1429.

*5.2.6.7. 1-(2,5-dimethoxybenzoyl)-N-(2-(7-methoxynaphthalen-1-yl)ethyl)azetidine-3-carboxamide (**6s**).* Following general procedure to obtain pure product as white solid 807 mg (yield: 72%). mp: 58.9–61.8 °C; ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J = 8 Hz, 1H), 7.68 (t, J = 4 Hz, 1H), 7.41 (d, J = 4 Hz, 1H), 7.25 (s, 1H), 7.17 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 6.94–6.89 (m, 2H), 6.84 (d, J = 12 Hz, 1H), 5.69 (s, 1H), 4.30–4.18 (m, 3H), 4.03 (t, J = 8 Hz, 1H), 3.96 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.70–3.64 (m, 2H), 3.25 (t, J = 8 Hz, 2H), 3.21–3.14 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 171.45, 168.64, 157.98, 153.59, 150.13, 133.40, 133.12, 130.30, 129.29, 127.09, 123.90, 123.14, 118.19, 117.01, 114.04, 112.75, 102.50, 56.29, 55.82, 55.52, 53.07, 51.13, 40.05, 33.49, 33.03; HRMS (TOF) m/z calcd. for $C_{26}H_{28}N_2O_5$ [M + Na^+] 471.1896, found: 471.1896.

*5.2.6.8. 1-(4-cyanobenzoyl)-N-(2-(7-methoxynaphthalen-1-yl)ethyl) azetidine-3-carboxamide (**6t**).* Following general procedure to obtain pure product as white solid 765 mg (yield: 74%). mp: 75.6–77.5 °C; ^{1}H NMR ($CDCl_3$): δ 7.80 (d, J = 8 Hz, 1H), 7.74 (s, 4H), 7.41 (s, 1H), 7.28 (s, 3H), 7.20 (d, J = 8 Hz, 1H), 5.58 (s, 1H), 4.52 (brs, 1H), 4.33–4.29 (m, 3H), 3.99 (s, 3H), 3.72 (d, J = 8 Hz, 2H), 3.30 (brs, 2H), 3.24–3.23 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 170.96, 168.12, 158.00, 136.86, 133.20, 133.12, 132.31, 130.41, 129.33, 128.46, 127.25, 127.14, 123.16, 118.12, 118.03, 114.70, 102.57, 55.53, 55.11, 51.73, 40.11, 33.80, 32.82; HRMS (TOF) m/z calcd. for $C_{25}H_{23}N_3O_3$ [M + Na^+] 436.1637, found: 436.1624.

5.3. Biological assay

5.3.1. Cytotoxicity measurement

L02 cells purchased from the cell Bank of the Chinese Academy of Science and human embryonic kidney cell line 293 cells purchased from the American Type Culture Collection were respectively seeded in 96-well plates at a density of 5 × 10^3 cells per well and cultured in the medium consisted of 90% 1640 or DMEM, 10% fetal calf serum, penicillin 200 kU/L, and streptomycin 100 mg/L in a humidified incubator with 5% CO_2 for 24 h. At this point, Cells were exposed to different concentrations of compounds for another day. The viability of cells was evaluated using MTT assay. Briefly, the cells were incubated with MTT (final concentration, 0.5 mg/ml) for another 4 h at 37 °C. After incubation, the medium were removed and 150 μL of DMSO was added to each well for 15 min at room temperature and absorbance measured at 570 nm using a microplate reader.

5.3.2. Corticosterone-induced PC12 cells lesion and detection of cell viability with MTT assay [39,40]

PC12 cells were plated at a density of 1 × 10^4 cells per well in 96-well plates and cultured in the medium consisting of 90% Dulbecco's Modified Eagle's Medium (DMEM), 5% heat-inactivated horse serum, 10% fetal calf serum (FBS) for 24 h. Later, the PC12 cells were treated with 200 μM corticosterone and Fluoxetine, Agomelatine or other compounds at different concentrations for 1 day. After incubation, cells were treated with the MTT solution (final concentration 0.5 mg/ml) for 4 h. The dark blue formazan crystals formed in intact cells were solubilized with DMSO and absorbance at 570 nm was measured with a microplate reader.

5.3.3. Morphological observation

PC12 cells were seeded in 6-well plates at a density of 1 × 10^6 cells/mL in the growth medium for 1 d, and then the cells were classified into following groups: control, corticosterone 0.2 mM, corticosterone 0.2 mM + Agomelatine 1.25 μM, corticosterone 0.2 mM + Fluoxetine 1.25 μM, corticosterone 0.2 mM + **6k** 1.25 μM and corticosterone 0.2 mM + **6o** 1.25 μM. After incubated with for another 24 h, the cells were photographed by a digital camera attached to an inverted microscope. Images from three fields were randomly taken in each group.

5.3.4. H_2O_2-induced PC12 cells lesion and detection of cell viability with MTT assay [27,41,42]

PC12 cells were plated onto 96-well plates at a density of 1 × 10^4 cells/well and were cultured in DMEM with 10% FBS, 5% horse serum for 24 h. Then, after removing the original medium, the cells were cultured for another 1 h in the presence of 200 μM H_2O_2. Later, the cells were washed with phosphate-buffered saline (PBS) twice and cultured with or tested compounds at three different concentrations (10 μM, 20 μM and 40 μM) in DMEM for 48 h, Fluoxetine and Agomelatine were used as positive control. After incubation, cell viability was determined by MTT assay. Briefly, cells were cocultured with MTT (final concentration 0.5 mg/ml) for 4 h. The dark blue formazan crystals formed in intact cells were solubilized with DMSO and measured with a microplate reader at a wavelength of 570 nm.

5.3.5. Forced swim test

C57 mice were assigned into 7 groups (n = 10): Fluoxetine group (32 mg/kg), Agomelatine group (32 mg/kg), vehicle group (32 mg/kg), **6d** group (32 mg/kg), **6k** group (32 mg/kg), **6o** group (32 mg/kg) and **6p** group (32 mg/kg). Every group had 10 mice.

Forced Swim Test (FST) was conducted as described previously, with some modifications [43]. Each mouse was plunged

individually into a Plexiglass cylinder (diameter 20 cm, height 50 cm) filled with 15 cm height of water at 22–25 °C. On the 1st day, the animal was forced to swim for 15 min. On days 2–15, indicating drugs (Fluoxetine, Agomelatine, vehicle, **6d**, **6k**, **6o**, **6p**) were dissolved in 30% β-Cyclodextrin and given mice by the way of intraperitoneal injection at a density of 32 mg/kg. On the 2nd day and 15th day, after 30 min of administration, each mouse was placed again into the water and forced to swim for 6 min. The session was videotaped and the duration of immobility during the last 4 min was measured using the Xeye Animal behavior analysis system (Xeye Aba V3.2) obtained from Beijing MacroAmbition S & T Development Co. Ltd. The mouse was considered as in immobile state when its speed was less than 20 mm/s.

5.3.6. *Open field locomotor activity [44]*

C57 mice were assigned into 4 groups ($n = 10$): Fluoxetine group, Agomelatine group, vehicle group, **4k** group. Mice obtained administrations by the way of intraperitoneal injection at a density of 32 mg/kg for 14 days. Then they were placed individually in the center of open field (50 × 50 × 50 cm) which had a video camera positioned directly above. The traveled distance during the six minutes were recorded and analyzed using the Xeye Animal behavior analysis system obtained from Beijing MacroAmbition S & T Development Co. Ltd. Every time, feces were cleared in order to avoid interference.

5.3.7. *Docking study*

The crystal structures of the proteins complex were retrieved from the RCSB Protein Data Band (http://www.rcsb.org/pdb/home/home.do). Docking calculations were conducted with GOLD, version 5.0. Default parameters were used and 10 docked conformations were generated for each compound, docking was repeated several times until no change in position of the ligand and a constant value of binding energy was observed. H-bonds between the respective compound and enzyme were explored.

5.3.8. *Statistical analysis*

Data are expressed as mean ± S.D. Dunnett's test was used to exam the differences between the different treatment groups. The GraphPad Prism 5.0 software was used to perform the statistics. $P < 0.05$ was considered to be statistically significant ($^{*}P < 0.05$, $^{**}P < 0.01$).

Acknowledgements

This work was supported by New Century Talent Fund by Ministry of Education (NCET-13-0388) of China.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.05.061.

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