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Synthesis and evaluation of amide side-chain modified Agomelatine analogues as potential antidepressant-like agents

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ABSTRACT

In this work, nineteen analogues of Agomelatine were readily synthesized through structural modification of the acetamide side-chain starting from the key common intermediate 2-(7-methoxynaphthalen-1-yl) ethanamine (**3**), which was prepared from commercially available compound 2-(7-methoxynaphthalen-1-yl) acetonitrile (**2**) in two steps. Corticosterone-induced PC12 pheochromocytoma cells phenotypic *in vitro* model was utilized to evaluate their potential antidepression activities. Imide compound **4a** and acylamino carboxylic acid analogue **5b** showed good protective effects on traumatic PC12 cells with protection rates of 34.2% and 23.2%, respectively. Further *in vivo* assessments in C57 mice FST (forced swim test) model demonstrated that compound **4a** significantly reduced the immobility time of the tested subjects, indicating antidepressant-like activity. Preliminary toxicity assays conducted on human normal liver L02 cells and embryonic kidney 293 cells suggested a relatively low safety risk for compound **4a** compared with the marketed drugs Agomelatine and Fluoxetine. The promising antidepressant-like efficacy of compound **4a**, together with the relatively low toxicity to the normal tested cells and high liability of diffusion through the blood–brain barrier (BBB), presents us insights of exploration of me-better drug candidates of Agomelatine.

Depression, with high prevalence worldwide, is a mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration.[1] By 2020, according to the WHO report, depression will be the second disease next to ischemic heart disease and become one of the major contributors to the global disease burden.[2]

The current antidepressant drugs in clinic can generally be classified into several categories, which include selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors (NRIs), tricyclic antidepressants (TCAs) and dopamine–noradrenaline reuptake inhibitors (DNRIs) (Fig. 1).[3,4] Although these antidepressants are often helpful, their full efficacy is only apparent after several weeks of administration and many patients only partially respond, and some remain refractory and severe side effects.[5] Thus to search for new candidate agents with novel action mechanism is strongly desirable.

Agomelatine was approved for the treatment of major depression disorders by European Medicines Agency in 2009.[6] However, cases of liver injury, including hepatic failure,[7,8] elevations of liver enzymes exceeding 10 times the upper limit of normal, hepatitis and jaundice have been reported in patients treated with Agomelatine during the first months of the treatment. Although the serum transaminases usually returned to normal when discontinued use of Agomelatine, there is still a need for structural modification of Agomelatine in order to enhance its efficacy and decrease its toxicity.

In our continuing efforts to develop novel antidepression agents with improved pharmacological profiles than the marketed ones, we started a structural modification program of Agomelatine on its amide side-chain. Two structural classes of Agomelatine bioisomers, imides (Scheme 1) and asymmetrical ureas (Scheme 3), were synthesized and investigated for its potential effects on in vitro and in vivo depression models. The synthesis and biological assessment of the acylamino carboxylic acids (Scheme 2) were also undertook herein in consideration that they are ring-opening

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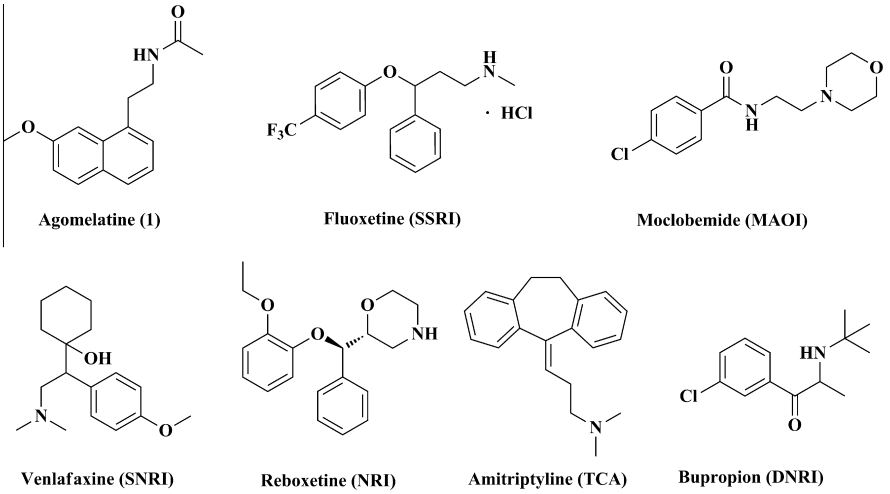
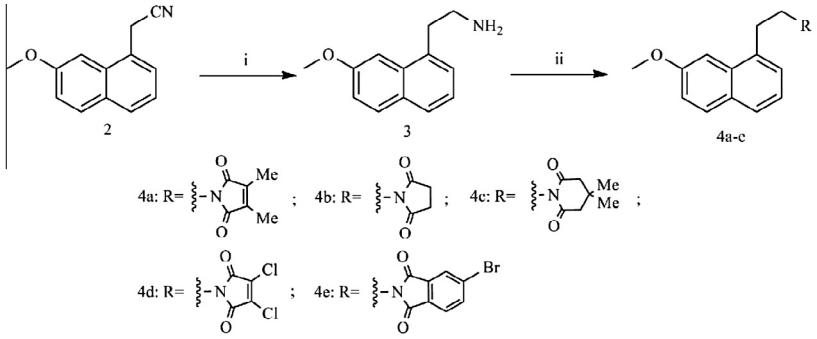
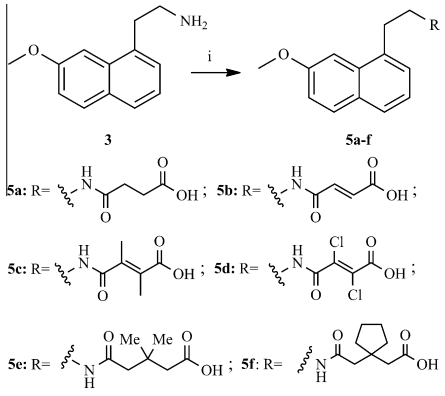


Figure 1. Chemical structures of representative antidepressants.



Scheme 1. Synthetic route of imide analogues **4a**–**e**. Reagents and conditions: (i) $NaBH_4$, $(Boc)_2O$, $NiCl_2$, MeOH; TFA, DCM; (ii) appropriate cyclic anhydride, NaOAc, HOAc, reflux, 3 h.



Scheme 2. Synthetic route of and acylamino carboxylic acid analogues **5a**–**f**. Reagents and conditions: (i) appropriate cyclic anhydride, CH_2Cl_2, rt, 6 h.

forms of the corresponding imides and easily prepared in similar reaction conditions, which can bring us insights when compared their effects with those of imides although acylamino carboxylic acid may not be a good candidate for passing the BBB for the high polarity of carboxylic acid group, which can be readily modified to its ester or carbamate form if needed.

To achieve the synthesis of the target compounds **4a**–**e**, the steps outlined in Scheme 1 were adopted. The key common intermediate **3** was synthesized starting from commercially available 2-(7-methoxynaphthalen-1-yl) acetonitrile in two steps according to literature[9] with minor revision. Firstly 2-(7-methoxynaphthalen-1-yl) acetonitrile was reduced to the corresponding amine with sodium borohydride/nickel chloride system followed by in situ N-Boc protection with dibutyldicarbonate in methanol. After N-Boc deprotection of compound **2** with trifluoroacetic acid in dichloromethane, the common key intermediate **3** was obtained. It is worthwhile to point out that the in situ N-Boc protection procedure is quite necessary, otherwise the direct reduction product would be contaminated with a mixture of side products such as oxime, secondary amine and acyl amine, which would turn into dark green when exposed to the atmosphere and was difficult to purify. Compounds **4**–**6** were prepared according to reported procedure.[10–13] The key intermediate **3** was reacted with the appropriate cyclic anhydride in the presence of sodium acetate and acetic acid under reflux for 3 h to obtained **4**.

The compounds **5a**–**f** can be prepared conveniently by stirring 2-(7-methoxynaphthalen-1-yl) ethanamine (**3**) with the appropriate cyclic anhydride in the presence of sodium acetate and acetic acid at room temperature for 6 h. For compounds **5a**–**e**, the amino group of compound **3** nucleophilic attack the carbon atom of carbonyl group in room temperature, formed target amide compounds. When heated to reflux, the secondary amino group of compounds **5a**–**f** further nucleophilic attack another carbon atom of carbonyl group, obtained **4a**–**e**.

The asymmetrical urea compounds (**6a**–**h**) were synthesized from the activated intermediate **3a** and appropriate secondary amine in the presence of triethyl amine at ambient condition. The non-isolated intermediate **3a** was made in situ by stirring