Bioorganic & Medicinal Chemistry Letters 20 (2010) 1705–1711

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Arylpiperazine-containing pyrrole 3-carboxamide derivatives targeting serotonin 5-HT$_{2A}$, 5-HT$_{2C}$, and the serotonin transporter as a potential antidepressant

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ARTICLE INFO

Article history:
Received 8 December 2009
Revised 7 January 2010
Accepted 8 January 2010
Available online 21 January 2010

Keywords:
Depression
Antidepressant
Serotonin
Piperazine
Pyrrole

ABSTRACT

Arylpiperzine-containing pyrrole 3-carboxamide derivatives were synthesized and evaluated as novel antidepressant compounds. The various analogues were efficiently prepared and bio-assayed for binding to 5-HT$_{2A}$, 5-HT$_{2C}$ receptor, and 5-HT transporter. Based on their in vitro and in vivo activities as well as selectivity over other neurotransmitter receptors and PK profiles, **33** and **34** were identified as lead compounds. Consequently, this pyrrole series of compounds appears to be promising enough to warrant further investigation.

Depression, especially major depression is among the serious psychiatric disorders.[1,2] Symptoms of depression include sadness, loss of interest or pleasure in activities that were once enjoyed, change in appetite or weight, difficulty sleeping or oversleeping, physical slowing or agitation, energy loss, feeling of worthlessness or inappropriate quilt, difficulty thinking or concentrating, and recurrent thoughts of death or suicide. And depression is estimated to affect 7–8% of the world population.[3] Since the synaptic actions of monoamine neurotransmitters such as norepinephrine (NE) and serotonin (SER, 5-HT) were known as important drug target of psychiatric diseases, an increasing number of treatment options have become more available over the past two decades for individuals with major depression disorder.[4,5] Tricyclic antidepressants (TCAs) and nonselective monoamine oxidase inhibitors (MAOIs) were developed as first generation of antidepressant. Although they are highly effective in treating depression, they also have side effects, for example dry mouth, blurred vision, urinary retention, postural hypotension, and insomnia.[6,7] The first class of psychotropic drugs to be rationally designed, selective serotonin reuptake inhibitors (SSRIs) have been the most widely prescribed antidepressants since 1980s.[8] Although SSRIs such as fluoxetine, sertraline, paroxetine, and citalopram have achieved great success in treating depression, they also have some troublesome effects including sedation, anxiety, headache, tremor, and sexual dysfunction (especially anorgasmia) and generally effective only less than two-third patients. Additionally, delayed onset of action (2–6 weeks) is less than desirable in the treatment of depression.[9]

In recent years, the novel antidepressant model was studied to prepare compounds with dual or multiple activities.[10] Because numerous side effects are associated with non-selective binding at post-synaptic 5-HT receptors, it has been proposed that addition of a 5-HT receptor antagonist component could increase synaptic 5-HT levels, eventually achieve rapid onset time.[11–13] With those approaches, various compounds have been proposed and developed as potential antidepressants, with dual activity at SERT while binding antagonistically to the 5-HT$_{2A}$ receptor. For example, Eli Lilly's LY367265, **1** exhibits excellent binding affinities (K_i = 2.3 nM for SERT; K_i = 0.81 nM for 5-HT$_{2A}$).[14] Yamanouchi has also discovered YM-35992, **2** as an antidepressant with moderate affinities for SERT/5-HT$_{2A}$ (K_i = 21 nM and 86 nM, respectively).[15] Bristol–Myers Squibb's Nefazodone, **3** has been described as having a similar mode of action with an improved side effect profile.[16] This compound had advantages over other antidepressants including reduced possibility to disturbed sleep or sexual dysfunction, and ability to treat some patients who did not respond to other antidepressant drugs.

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doi:10.1016/j.bmcl.2010.01.093

However, Bristol–Myers Squibb discontinued the sale on 2004 with adverse hepatic events including liver failure.[17] More recently, aripiprazole, **4**, which was approved for the treatment of atypical antipsychotics, was also used together with other medications to treat major depressive disorder in adults. Unlike other FDA-approved atypical antipsychotics targeting D_2 receptor, aripiprazole appears a 5-HT_{1A} partial agonist, 5-HT_{2A} antagonist, and 5-HT_{2C} partial agonist. In addition, it has moderate affinity for the serotonin transporter. However, it has numerous side effects including headache, nausea, constipation, anxiety, restlessness, insomnia, nervousness, and so on. In this regard, there are still urgent medical needs on the development of novel drugs with better developability characteristics: improved pharmacologic properties and reduced side effects. Herein, we wish to describe the design, synthesis, and biological evaluation of novel arylpiperazine-containing pyrrole 3-carboxamide derivatives targeting serotonin 5-HT_{2A}, 5-HT_{2C}, and the serotonin transporter as a potential antidepressant (see Fig. 1).

From the literature, common structure of antidepressants having dual activities appeared to exhibit combination of two distinct structural motifs. Aryl piperazine elements and heterocyclic motifs were connected to each other using a linker frequently to serve as SERT and 5-HT receptor inhibitors. With this in mind, the general structure of our target compounds is shown in Figure 2. We envisioned that novel target compounds **A** can be readily prepared by typical amide coupling with acid and amine at the final stage. Pyrrole 3-carboxylic acid **B** and arylpiperazinyl alkyl amine **C** can be used as acid and amine partners, respectively.

Preparation of pyrrole derivatives, particularly consisting of 5-phenyl and 3-carboxylic acid, started from alkylation of ethyl acetoacetate (**5**) with 2-bromo-1-phenylethanone (**6**) using sodium hydride to produce alkylated acetoacetate **7** (Scheme 1).[18] Cyclization of **7** to ethyl 2-methyl-5-phenyl-1H-pyrrole-3-carboxylate (**8**) was accomplished by heating ammonium acetate in acetic acid at 80 °C. Various alkyl groups were substituted at NH of pyr-

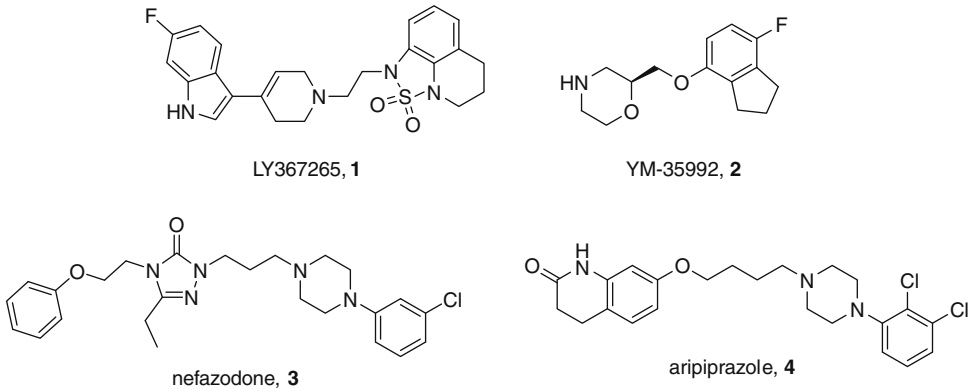


Figure 1. Chemical structures of representative antidepressant compounds.

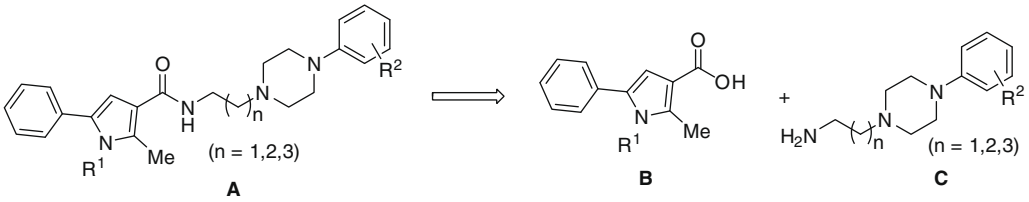
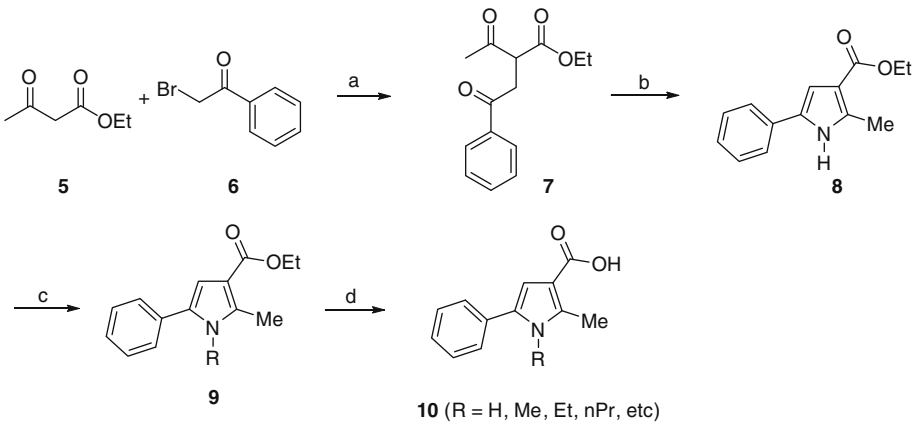


Figure 2. Preparation of target compounds using peptide bond formation.



Scheme 1. Reagents and conditions: (a) NaH, THF; (b) NH_4OAc, AcOH, 80 °C; (c) NaH, RI, DMF; and (d) NaOH, EtOH, reflux.