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Arylpiperazine derivatives of diphenylsulfide: Synthesis and evaluation for dual 5-HT_{1A}/SSRI activities

Xue Dan Wu [a], Dong Zhi Liu [a], Ai Jun Li [a,b,*], Xue Qin Zhou [a]

[a] School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China
[b] College of Chemical and Pharmaceutical Engineering, Hebei University of Science and Technology, Shijiazhuang 050018, China

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Abstract

The design, synthesis and biological evaluation of a novel series of arylpiperazine derivatives of diphenylsulfide with dual 5-HT_{1A}/SSRI activities are reported. The target compounds exhibit low to moderate 5-HT transporter affinity and moderate to high 5-HT_{1A} affinity. Compound **13a** shows moderate dual activities and is a promising lead compound for further structure–activity relationships studies.

Keywords: Antidepressants; 5-HT_{1A}/SSRI; Arylpiperazines; 5-HT_{1A} receptor; Diphenylsulfide

Selective serotonin (5-HT) reuptake inhibitors (SSRIs) are the most widely used antidepressants and have numerous advantages over other therapies. But they are not without problems such as side effects and a delayed onset of action of 2–6 weeks [1]. Recent design strategy incorporating both a 5-HT_{1A} antagonist pharmacophore and a SSRI pharmacophore within a single molecule could provide a rapid onset antidepressant (5-HT_{1A}/SSRI). This drug could form the basis of the next generation of antidepressants and has received much attention [2–15]. In the reported design strategies the long chain arylpiperazine has been successfully utilized as a 5-HT_{1A} antagonist pharmacophore to produce potent activities. Their general chemical structure consists of an alkyl chain (2–4 methylene units) attached to the N4 atom of the piperazine moiety, and a terminal amide or an imide fragment. The length of the spacer between the arylpiperazine and the amide moiety is of great importance for 5-HT_{1A} affinity and selectivity [16].

Diphenylsulfide derivatives are a new class of potent SSRIs. Several substituted diphenylsulfide derivatives have been reported to display high affinity to 5-HT transporter (5-HTT) [17,18]. However, diphenylsulfide derivatives have not been used as a SSRI pharmacophore in the reported 5-HT_{1A}/SSRI strategies. With above-mentioned knowledge, we hypothesized that diphenylsulfide derivatives attached to long chain arylpiperazine could represent a new class of compounds with dual 5-HT_{1A}/SSRI activities. In this letter, we disclose our initial investigation of a new series of arylpiperazine derivatives of diphenylsulfide. The new derivatives consisted diphenylsulfide as the SSRI pharmacophore and long chain arylpiperazines as the 5-HT_{1A} pharmacophore (Fig. 1). We expected these

* Corresponding author at: College of Chemical and Pharmaceutical Engineering, Hebei University of Science and Technology, Shijiazhuang 050018, China.
E-mail address: lajd@tju.edu.cn (A.J. Li).

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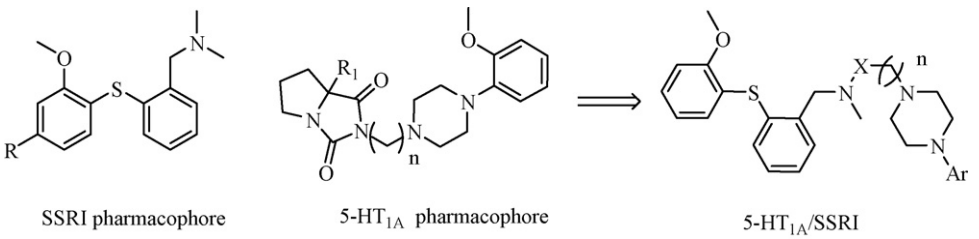


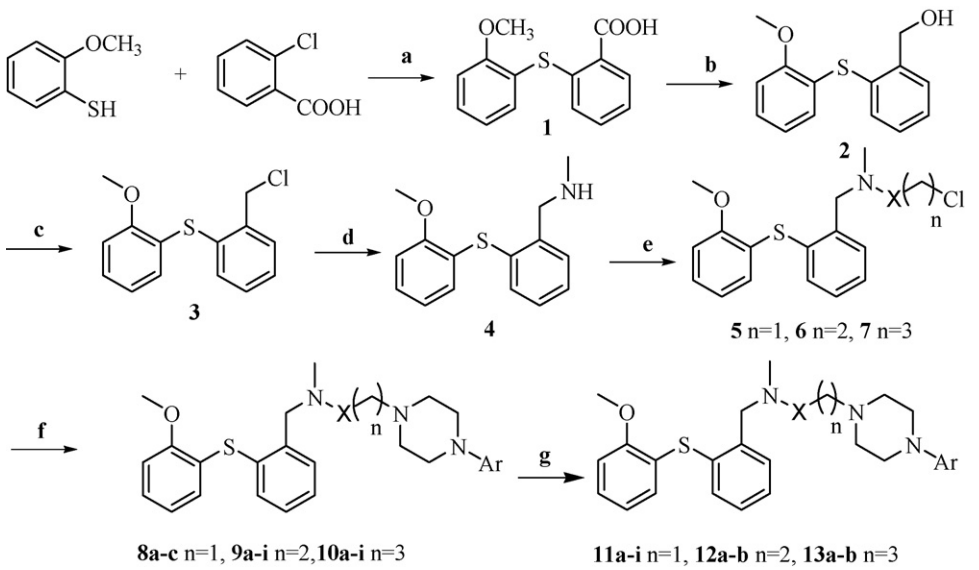
Fig. 1. Designed arylpiperazines derivatives of diphenylsulfide.

compounds could have an improvement in the affinity for both the 5-HTT and the 5-HT_{1A} receptor, and be a new class of antidepressants with faster onset of action. The synthesis and SAR for this new class of arylpiperazine derivatives of diphenylsulfide that exhibit dual activity for the 5-HTT and the 5-HT_{1A} receptor are reported herein.

Scheme 1 shows the synthesis of the target molecules. The condensation of 2-methoxythiophenol and 2-chlorobenzoic acid gave 2-(2-methoxyphenylthio) benzoic acid **1** in high yield (75.5%). Reduction of 1 with $LiAlH_4$ led to [2-(2-methoxyphenylthio) phenyl] methanol **2** (91.8%), which was then treated with thionyl chloride to give 2-(2-methoxyphenylthio) benzyl chloride **3** (82.8%). Compound **3** was then converted to amine **4** using CH_3NH_2 and then treated with $ClCO(CH_2)_nCl$ to give compounds **5–7**. The amide series of target compounds **8a–c**, **9a–i** and **10a–i** were prepared by nucleophylic substitution of arylpiperazine with **5–7**. Finally **8a–i**, **9a–i** and **10a–i** were reduced with $LiAlH_4$ to obtain another series of target compounds **11a–i**, **12a–b** and **13a–b**, all of which were novel compounds and have been characterized (selected spectral and analytical data for **12b** and **13a** are given in Ref. [19]).

Target compounds were evaluated for their affinity to 5-HTT and 5-HT_{1A} receptor using a protocol similar to that of Orús et al. [3]. Fluoxetine and 8-OH-DPAT were used as reference compounds. The biological results for the target compounds are summarized in Table 1.

All of the target compounds exhibited low to moderate affinity to 5-HTT and moderate to high affinity to 5-HT_{1A} receptor. Compound **13a** showed moderate dual 5-HT_{1A}/SSRI activities (5-HTT 74% inhib. and 5-HT_{1A} 90% inhib.) and is a promising lead compound for further SAR studies. Attaching arylpiperazines moiety to diphenylsulfide results in a reduced binding affinity to 5-HTT compared to that of diphenylsulfide itself according to Ref. [17,18]. Changes of either the groups or the spacer length in the arylpiperazine component has little effect on the binding affinity for 5-HTT



Scheme 1. Reagents and conditions: (a) K_2CO_3, cat. Cu, DMF, 100 °C, 24 h; (b) $LiAlH_4$, THF, reflux, 5 h; (c) $SOCl_2$, $CHCl_3$, Et_3N, rt, 4 h; (d) CH_3NH_3, CH_3OH, rt, 49.8%; (e) $ClCO(CH_2)_nCl$, Et_3N, $CHCl_3$, rt, 89.6–91.2%; (f) Et_3N, CH_3CN, arylpiperazines, reflux, 37.9–65.6%; (g) $LiAlH_4$, THF, reflux, 5 h, 41.5–59.3%.