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ORIGINAL PAPER

Synthesis of new aryl(hetaryl)-substituted tandospirone analogues with potential anxiolytic activity via reductive Heck type hydroarylations

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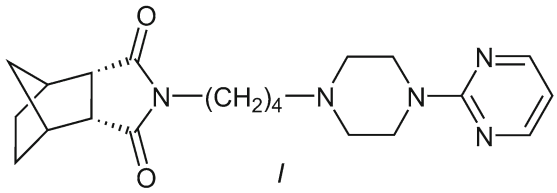
Tandospirone (*I*), developed as an anxiolytic drug, is an aryl-piperazine compound that binds to both 5-HT_{1A} and dopamine D4 receptors. Palladium-catalysed hydroarylation reactions of tandospirone analogues containing an oxygen bridge and 3-(trifluoromethyl)phenyl or 2,3-dichlorophenyl groups were studied in order to find a new stereoselective access to a series of new *exo*-aryl(hetaryl)-substituted derivatives with potential biological activity.

Keywords: tandospirone, arylpiperazines, C–C coupling, hydroarylation, heterocycles

Introduction

N-Arylpiperazines are heterocyclic compounds important as intermediates in organic synthesis. They are commonly found as fragments in natural products, receptor ligands, and in many pharmacologically active molecules. A series of aryl-piperazine compounds are effective pharmaceuticals for the treatment of conditions related to or affected by the serotonin 1_A receptor; as they are particularly effective antagonists to this receptor and are particularly useful for alleviating the symptoms of nicotine and tobacco withdrawal (Godfrey et al., 2006; Kulig et al., 2009; Sarswat et al., 2011). Tandospirone (*I*) (Fig. 1), developed as an anxiolytic drug marketed in Japan, is an aryl-piperazine compound that binds to both 5-HT_{1A} and dopamine D4 receptors (Kishimoto et al., 2000; Amano et al., 2001; Nishikawa et al., 2007; Takahashi et al., 2008).

There are a few reports in the literature on the synthesis of tandospirone analogues with changes in the bicyclic system or the pyrimidin-2-yl group (Kossakowski & Jarocka, 2001; Kossakowski et al., 2008; Makan et al., 2009). Therefore, the synthesis of more bioactive aryl- and heteroaryl substituted tandospirones by reductive Heck reactions and isoxazoline derivatives via 1,3-dipolar cycloadditions came into attention (Kulu, 2012). In this work, the pyrimidine group in the tandospirone molecule was replaced with 3-(trifluoromethyl)phenyl or the 2,3-dichlorophenyl group, which are structurally similar to 1-(3-(trifluoromethyl)phenyl)piperazine (TFMPP) and 1-(2,3-dichlorophenyl)piperazine analogues, respectively. TFMPP is a recreational drug of the piperazine class. It shows affinity to the 5-HT_{1A}, 5-HT_{1B},



I

Fig. 1. Structure of tandospirone (*I*).

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