



Synthesis and 5-HT_{1A}/5-HT_{2A} receptor activity of N-(4-arylpiperazin-1-yl)alkyl derivatives of 2-azaspiro[4.4]nonane and [4.5]decane-1,3-dione

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Abstract:

Two series of N-(4-arylpiperazin-1-yl)-alkyl-2-azaspiro[4.4]nonane (**5–10**) and [4.5]decane-1,3-dione (**11–16**) derivatives were synthesized and their serotonin 5-HT_{1A} and 5-HT_{2A} receptor affinities were determined. Compounds with the methylene spacer (**5–7** and **11–13**) exhibited low 5-HT_{1A}/5-HT_{2A} receptor affinity, in contrast to their ethylene analogues regarded as potent 5-HT_{1A} ligands, especially those containing a cyclohexane moiety (**14–16**; *K_i* = 5.1, 2.7 and 4.3 nM, respectively) in the 3-position of the pyrrolidine-2,5-dione ring. Moreover, derivatives with 3-chloro substituent (**10** and **14**) showed distinct affinity for 5-HT_{2A} receptors. The functional activity of compounds **10**, **14**, **15** and **16** was tested *in vivo* in the commonly used animal models. In those experiments, the tested compounds showed features of agonists of pre- and postsynaptic (**14**), agonists of presynaptic and antagonists of postsynaptic (**10**, **15**), or agonists of postsynaptic (**16**) 5-HT_{1A} receptors. Additionally, **10** and **16** exhibited properties of potential 5-HT_{2A} receptor antagonists. The above results suggested a crucial role of the spacer between the amide fragment and 4-arylpiperazine moiety, as well as of the size of the cycloalkyl ring at the 3-position of pyrrolidine-2,5-dione ring in functional 5-HT_{1A}/5-HT_{2A} properties.

Key words:

5-HT_{1A}/5-HT_{2A} receptor ligands, 2-azaspiro[4.4]nonane- and [4.5]decane-1,3-dione, arylpiperazine, structure-activity relationship
