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Role of the aromatic substituent at position 5 for D_2/ α_1-adrenoceptor action of novel ester-hydantoin derivatives of arylpiperazines

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The dopaminergic receptors D_2 as well as α_1--adrenoceptors are important GPCRs biological targets involving in various diseases of central- or peripheral nervous systems. The dopamine D_2 receptors play an important role in neurodegenerative diseases, e.g. schizophrenia and Parkinson's disease as well as they influence on mood, mindfulness and sleep [1]. The α_1-adrenergic receptors play a role in cardiac hypertrophy, effects on heart contractile function, cardiac rhythm and protection from ischemic injury [2]. Thus, their antagonists can have therapeutic usage as antiarrhythmic drugs. Our previous studies focused on hydantoin phenylpiperazine dervatives allowed to find the 3-ester compound **JH-38** that dispalyed significant and comparable affinity to both of the GPCRs. The compound has been selected as lead structure for further chemical modifications. This work is concentrated on the lead modifications to obtain a series of new compounds with conserved ester moiety at position 3, various substituent at phenylpiperzine phenyl ring and 5-methyl-5-aryl substitution at position 5 of hydantoin (Fig.1).

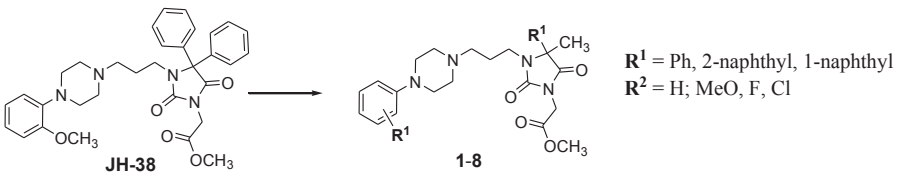

Fig. 1

The 4-step synthesis was carried to give the 8 final products (1-8, Fig. 1). The compounds were investigated on their affinity for the dopamine D_2R and α_1-AR in the radioligand binding assays. All of the tested compounds displayed higher activity for α_1-AR than that for D_2R. The 5-naphthyl substituents were more profitable than the 5-phenyl ones.

[1] Missale C., Nash S. R., Robinson S.W. et al. *Physiological Reviews.* 78 (1998) 189.
[2] Handzlik J., Bajda M., Zygmunt M. et al. *Bioorg. Med. Chem.* 20 (2012) 2290.

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