8-ALKOXY-7-PHENYLPIPERAZINYLALKYL-PURINE-2,6-DIONES AS 5-HT_{1A}/5-HT_{2A} RECEPTOR LIGANDS

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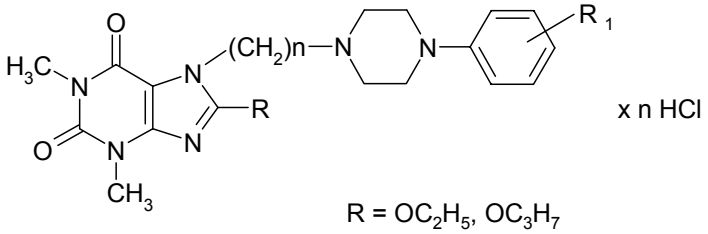
Our chemical and pharmacological studies on a group of the 1,3-dimethyl-8-[3-(4-phenyl-1-piperazinyl)-propylamino]-purine-2,6-dione derivatives with n-alkyl, arylalkyl or ester substituent in the 7-position showed that some compounds with arylalkyl group are selective 5-HT_{1A} ligands (K_i = 8 – 50 nM), with moderate affinity for 5-HT_{2A} receptors (K_i = 300-500 nM) [1, 2]. Several behavioral models demonstrated that these active compounds may be classified as 5-HT_{1A} postsynaptic antagonists [2]. As a continuation of our research on the structure-activity relationship we designed and synthesized a set of new 8-alkoxy-1,3-dimethyl-7-(4-phenyl-1-piperazinyl)-alkyl-purine-2,6-dione derivatives by multi step procedure. The earlier obtained 1,3-dimethyl-7-(3-chloroalkyl)-8-alkoxy-purine-2,6-dione derivatives in the reaction with the appropriate piperazine derivatives yielded final products. The structures of the new compounds were confirmed by examination of their ^{1}H-NMR, MS and UV spectra as well as by elemental analyses. For binding studies the free bases were converted into water soluble hydrochloride salts.



R = OC_2H_5, OC_3H_7
R_1 = H, 2-OCH_3, 3-Cl
n = 3, 4

The new series is under evaluation for their affinities for 5-HT_{1A} and 5-HT_{2A} receptors by determining their ability to displace [^{3}H]-8-OH-DPAT from the rat hippocampus or [^{3}H]-ketanserin from rat cortex membrane, respectively, according to previously described methods [1, 2].

[1] M. Pawłowski, G. Chłoń, J Obniska, A. Zejc, S. Charakchieva-Minol, M. J. Mokrosz: Il Farmaco, 2000, 55, 461-468.

[2] G. Chłoń, M. Pawłowski, B. Duszyńska, A. Szaro, E. Tatarczyńska, A. Kłodzińska, E. Chojnacka-Wójcik: Pol. J. Pharmacol., 2001, 53, 359-368.