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Synthesis, in vitro and in vivo Pharmacological Evaluation of new Arylpiperazines Containing a Pyrimido[2,1-*f*]purine Fragment

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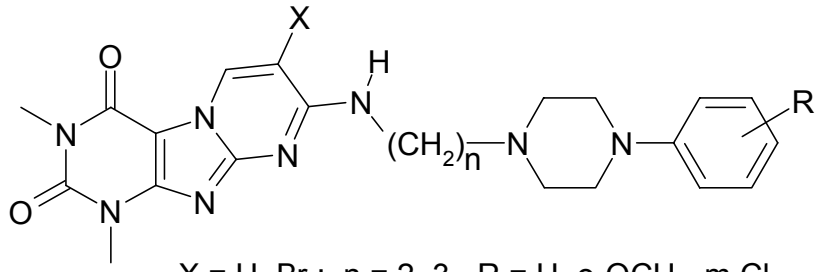
New 1H,3H-pyrimido[2,1-*f*]purine-2,4-dione derivatives of arylpiperazine were prepared and evaluated in vitro for their affinity at 5-HT_{1A}, 5-HT_{2A}, α_1 and D_2 receptors.

The synthesis route was started from derivatives of 1,3-dimethyl-8-chloro-1H,3H-pirymido[2,1-*f*]purine-2,4-dione, which were converted into target compounds by the coupling with appropriate phenylpiperazinealkylamine derivatives. Obtained compounds were purified by column chromatography and transformed into hydrochloride salts.

The tested compounds showed high affinity for 5-HT_{1A} and α_1 receptors (K_i = 1.1–87 and 10–62 nM, respectively), and moderate to low for D_2 (K_i = 94–1245 nM) and 5-HT_{2A} ones (K_i = 56–881 nM).



X = H, Br ; n = 2, 3 R = H, o-OCH_3, m-Cl

On the basis of in vivo functional tests a few compounds, mostly 3'-chlorophenylpiperazine derivatives, can be classified as mixed 5-HT_{1A}/5-HT_{2A}/α_1 ligands. 8-Phenylpiperazinoethylamino, 8-(2'-methoxyphenylpiperazino)ethyl-amino and 8-phenylpiperazinopropylamino derivatives of 1,3-dimethyl-1H,3H-pyrimido[2,1-*f*]purine-2,4-dione were identified as potential pre- and postsynaptic 5-HT_{1A} receptor antagonists. 1,3-Dimethyl-7-brom-8-(phenylpiperazino-propylamino)-1H,3H-pyrimido[2,1-f]purine-2,4-dione (**I**) behaved like an agonist of presynaptic and a partial agonist of postsynaptic 5-HT_{1A} receptors. In terms of that functional intrinsic activity compound **I** resembles ipsapirone, reveales marked anxiolytic-like activity in the Vogel test in rats, comparable to that of the reference drug diazepam, and exhibited antidepresant-like activity in the Porsolt test in mice. A sedative effect of the compound **I**, evaluated in open field test in rats, appeared at doses twice as high as those which induced a minimal anxiolytic-like effect, and was similar to that of diazepam.