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DESIGN AND SYNTHESIS OF NEW 7-PHENYLPIPERAZINYLALKYL AND 7-TETRAHYDROISOQUINOLINYLALKYL DERIVATIVES OF PURINE-2,6,8-TRIONE AS POTENTIAL SEROTONIN RECEPTOR AGENTS

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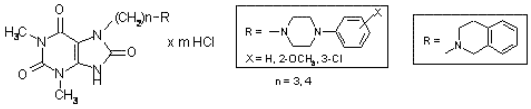
It is known that pharmacophoric arylpiperazine fragment is well recognized by 5-HT$_{1A}$, 5-HT$_{2A}$, as well as 5-HT$_7$ receptors. Although the terminal amide fragment significantly affects binding of 1-arylpiperazine derivatives with serotonin receptors, its role is not clear yet. In our earlier attempt to find new 5-HT$_{1A}$ / 5-HT$_{2A}$ receptor ligands several series of arylpiperazinylalkyl theophylline derivatives have been synthesized and their affinities for 5-HT$_{1A}$ and 5-HT$_{2A}$ were determined [1-3]. The selected compounds were potent 5-HT$_{1A}$ receptor ligands [2]. In order to explain the influence of theophylline (purine-2,6-dione) moiety on serotonin receptors affinity, purine-2,6,8-trione analogues were obtained. Additionally the arylpiperazine fragment was modified by introduction of 1,2,3,4-tetrahydroisoquinoline.



Previously obtained 1,3-dimethyl-7-(3-chloroalkyl)-8-methoxy-purine-2,6-dione in the reaction with appropriate piperazine derivatives and 1,2,3,4-tetrahydroisoquinoline yielded final products, which were isolated as a hydrochloride salts. The purity of the compounds were controlled by TLC, the structures were confirmed by spectral (^{1}H-NMR, MS, UV), and C, H, N analyses.

The 7-{4-[4-(3-chlorophenyl)-piperazin-1-yl]-butyl}-1,3-dimethyl-7,9-dihydro-3H-purine-2,6,8-trione was preliminary evaluated for its affinity to 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_7$ receptors. It was found that this compound was 5-HT$_{2A}$ receptor ligand (K_i = 63 nM) with moderate 5-HT$_{1A}$ (K_i = 263 nM), and low 5-HT$_7$ (K_i = 1820 nM) receptor affinity.

References:

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ROPINIROL - GENERIC DRUG FOR PARKINSON'S DISEASE

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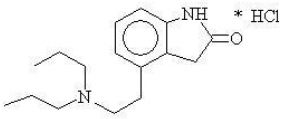
Multistep synthesis of 4-[2-(dipropylamino)-etyhl]-1,3-dihydro-2*H*-indol-2-one hydrochloride (ropinirole hydrochloride) was elaborated in Pharmaceutical Research Institute. From ten steps of synthesis - reduction of starting 2-methyl-3-nitrobenzoic acid to the corresponding alcohol, reaction of chain extension and reductive cyclization to indolone ring play significant role in the process of the formation find product.



Development of synthetic steps one to four was based on the literature data [1] and steps five to ten were carried out according to the patent procedure [2].

References

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2. Patent EP 113964 (1982).

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SYNTHESIS OF NEW 4,5-DIHYDRO-3aH-IMIDAZO[1,5-a]QUINOLINE DERIVATIVES AS 5-HT$_{1A}$ SEROTONIN RECEPTOR LIGANDS.

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Long-chain arylpiperazines (LCAPs) with an amide or imide moiety represent one of the most important classes of 5-HT$_{1A}$ receptor ligands (e.g. buspirone, tandospirone, WAY 100135, WAY 100635, NAN-190, flesinoxan). Buspirone, an