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ARYLPIPERAZINE DERIVATIVES OF 3-ALKYL-B-TETRALONOHYDANTOIN AS NEW 5-HT1A AND 5-HT2A RECEPTOR LIGANDS

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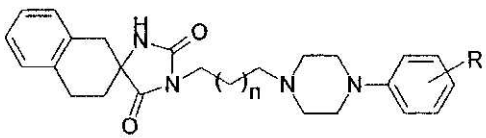
5,5-Disubstituted hydantoins and their N3-modified derivatives showed a wide spectrum of activity on the central nervous system mediated by 5-HT1A, 5-HT2A, α_1-adrenergic, dopaminergic D2, and other receptors. In previous studies we have demonstrated that in 3-(ω-aminoalkyl)-5,5-dialkyl (or 1',5-spirocycloalkyl)-hydantoins containing 1-phenylpiperazine or 1-(o-methoxyphenyl)-piperazine fragment in 3 position, the terminal hydantoin moiety plays an important role in the stabilization of the 5-HT1A and 5-HT2A receptor- ligand complexes [1, 2, 3]. Two compounds: 1',5-cyclopentanespiro-[3-(4-phenyl-1-piperazinyl)-propyl]-hydantoin and its 1',5-cyclohexanespiro analogue were found to exhibit high 5-HT2A receptor affinity (Ki = 34 and 37 nM, respectively), but unfortunately they had low affinity for 5-HT1A receptors. Furthermore 1',5-cyclohexanespiro-3-[4-[4-(o-methoxyphenyl)-1-piperazinyl]-butyl]-hydantoin is a new highly potent 5-HT1A ligand (K_i = 0,51 nM) with a moderate affinity for 5-HT2A receptors (Ki = 213 nM). These results prompted us to continue our search for mixed 5-HT1A/5-HT2A receptor ligands within arylpiperazine derivatives of spirohydantoin.

A series of new analogues of 3-[ω-(4-arylpiperazinyl)-propyl(or butyl)]-cyclohexane-1',5-spirohydantoin, with aromatic ring fused in amide moiety were synthesized and evaluated for affinity at 5-HT1A and 5-HT2A receptors.



R = H, o-CH_3, m-Cl, o-F, p-F, m-CF

n = 1, 2

The structure of compounds was confirmed by ^{1}H-NMR, MS, UV spectral data as well as by C, H, N analysis. The purity of products was checked by TLC. The influence of the substitution mode in the phenyl ring of phenylpiperazine moiety on the affinity for both receptors has been discussed. The most potent 5-HT1A (K_i = 15-53 nM) and 5-HT2A (K_i = 14-76 nM) ligands were evaluated in *in vivo* tests.

The obtained results indicate that all *in vivo* tested compounds containing propylene group alkylen spacer showed pharmacological profile as a 5-HT2A antagonist and may offer a new lead for the development of potential psychotropic agents. The compounds linked butylene spacer can be a new class of agents possesing potential anxiolytic/antidepressant activity.

References:

1. H. Byrtus, M. Pawłowski, S. Charakchieva-Minol, B. Duszyńska, M.J. Mokrosz J.L. Mokrosz, A. Zejc: Arch. Pharm. (Weinheim), 6, 283, 1996.

2. I. Wolska, H. Byrtus, A. Zejc: Pol. J. Chem. 71, 1005, 1997.

3. H. Byrtus, M. Pawłowski, B. Duszyńska, A. Wesołowska, E. Chojnacka-Wójcik, A.J. Bojarski: Pol. J. Pharmacol. 53, 395, 2001.

This study was supported by KBN (Grant No. 4 P05F 03517, 1999-2002).