Synthesis and Biological Evaluation of *cis*- and *trans*-2-Butene Arylpiprerazine Derivatives Investigated AS 5-HT$_{1A}$ Receptor Ligands

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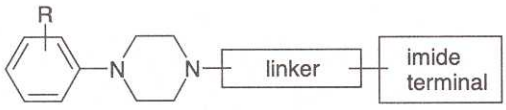
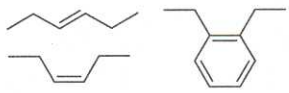
It is well known, that even a small changes in the structure of long chain arylpiperazines (LCAPs) can significantly influence both their affinity and functional profile at 5-HT$_{1A}$ receptors. The significance of the respective parts of LCAPs for 5-HT$_{1A}$ receptor affinity and intrinsic activity has been the subject of many SAR studies. With regard to arylpiperazine moiety, the influence of substituents in the phenyl ring as well as other aromatic and heteroaromatic groups is relatively well established. A majority of structural modifications in LCAPs concerned terminal fragment (containing imide, amide, aryl, heteroaryl etc.). The role of aliphatic spacer, linking both pharmacophore termini – the structural feature characteristic for all LCAPs – has also been investigated, generally focusing on its length. Other groups than methylene, i.e. heteroatoms (O, NH, S), carbonyl, or the amide fragment, and multiple bonds have seldom been introduced to the spacer.

Starting from the structures of highly potent 5-HT$_{1A}$ agents: MM77 and PK13 obtained in our laboratories, as well as NAN-190 – a well known 5-HT$_{1A}$ antagonist, we obtained their *cis* and *trans*-2-butene and 1,2-bis-methylbenzene analogues.

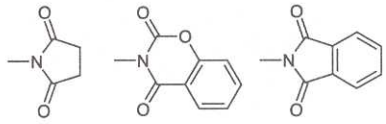


R: *o*-OCH_3, *m*-Cl

linker:



imide:



The influence of double bond configuration and the presence of aromatic ring in the linker on 5-HT$_{1A}$ affinity and *in vivo* functional profile was analyzed. It was observed that *trans*-2-butene derivatives always displayed higher *in vitro* activity than the respective *cis* isomers. Introduction of additional aromatic ring, conserving *cis* arrangement, was found unfavorable.

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