CONFORMATIONALLY RESTRICTED ANALOGS OF MP-3022 AS 5-HT$_{1A}$ RECEPTOR LIGANDS

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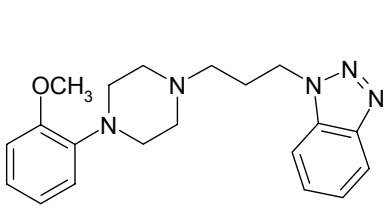
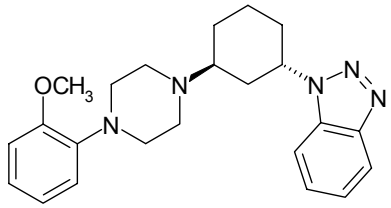
Long chain arylpiperazines (LCAPs) with an amide or imide moiety represent one of the most important classes of the 5-HT$_{1A}$ receptor ligands. Due to their high conformational freedom, it is difficult to predict spatial arrangement of arylpiperazine fragment and a second pharmacophoric group within the 5-HT$_{1A}$ receptor binding pocket. Thus our research group has been focussed on the design, synthesis and pharmacological evaluation of rigid analogs of LCAPs. Recently we described compound MP-272[1], a rigid analog of MP-3022 (a well known full 5-HT$_{1A}$ receptor antagonist, frequently used as pharmacological tool).



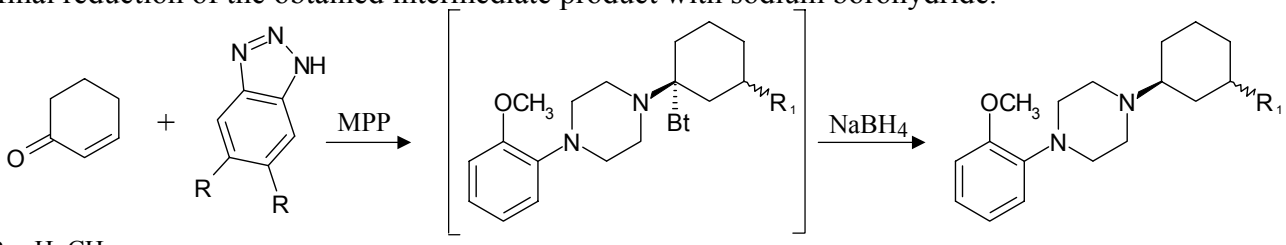
MP-3022



MP-272

Replacement of an aliphatic linker with a 1e,3e-disubstituted cyclohexane ring caused change of *in vivo* activity in comparison with the parent compound; MP-272 showed properties of partial agonist at postsynaptic 5-HT$_{1A}$ receptors. Several new constrained analogs of MP-3022 were synthesized to investigate a bioactive conformation of those 5-HT$_{1A}$ ligands.

Target compounds were received by 1,4-addition of respective benzotriazole to 2-cyclohexen-1-one and direct reaction with 1-(2-methoxyphenyl)-piperazine (MPP) followed by final reduction of the obtained intermediate product with sodium borohydride.



R = H, CH_3
R_1 = 1-Bt, 2-Bt, 1-(5,6-dimethyl-Bt), 2-(5,6-dimethyl-Bt)

Preliminary binding studies revealed differences in 5-HT$_{1A}$ affinity between structural isomers: a higher activity was observed for 1e,3e-cyclohexane derivatives, whereas those containing 1e,3a-cyclohexane fragment were less potent.

Due to their unique and defined arrangement such agents can be used to study a real structure-affinity and structure-functional profile relationships as well as in *in silico* modeling of ligand–5-HT$_{1A}$ receptor interactions.

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1. M. H. Paluchowska, M. J. Mokrosz, A. Bojarski, A. Wesołowska, J. Borycz, S. Charakchieva-Minol, E. Chojnacka-Wójcik, *J. Med. Chem.*, **1999**, *42*, 4952