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Functional in vivo profile of the conformationally restricted arylpiperazine analogues MP349 and MP401 at serotonin 5-HT_{1A} receptors

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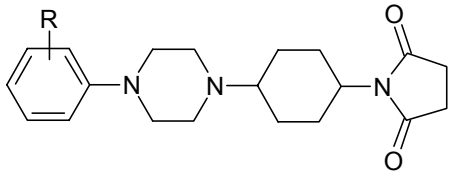
Arylpiperazines are of great importance to many different biological targets, particularly central nervous system receptors. The most thoroughly studied group, called long chain arylpiperazines (LCAPs), can be found as serotonin receptor ligands, especially 5-HT_{1A} and 5-HT_{2A} ones. The majority of them (to list only the most common: buspirone – used in the treatment of anxiety; gepirone, ipsapirone, tandospirone, flesinoxan – in various phases of clinical studies; NAN-190, WAY 100635 or MP 3022 – frequently used as pharmacological tools) contain a flexible aliphatic chain of different length, which connects an arylpiperazine fragment with a second terminal pharmacophoric group. Due to a high conformational freedom of these agents, it is difficult to draw their reliable structure-activity relationships and to predict their conformation within the receptor pocket.



MP349 - R = o-OMe
MP401 - R = H

In our earlier studies we showed that 5-HT_{1A} receptor affinities of rigid compounds (obtained by replacing an aliphatic linker with a 1,4-di-substituted cyclohexane ring) were only slightly lower than their chain analogues (e.g. NAN-190, MP3022) (1, 2). Interestingly, all the constrained derivatives in functional *in vivo* tests acted as antagonists of postynaptic 5-HT_{1A} receptors. Moreover, compound **MP349** behaved like an antagonist also at presynaptic 5-HT_{1A} receptors (3), becoming the first full antagonist from the arylpiperazine group with a precisely defined 3-D structure. Since all the previously tested constrained derivatives contained a 4-(2-methoxyphenyl)-1-piperazinyl fragment, we wondered whether the methoxy substituent or frozen extended linear conformation determined the full antagonistic profile of **MP349**. To answer this question, a new analogue (**MP401**) devoid of 2-methoxy substituent was designed and synthesized. It displayed pre- and postsynaptic agonistic activity in a hypothermia model in mice and in a lower lip retraction test in rats, respectively. Thus it seems that the substitution mode of the phenyl ring may be a determining factor influencing the ligand function at 5-HT_{1A} receptor.

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(1) Paluchowska, M.H.; Mokrosz, M.J.; Bojarski, A.J.; Wesołowska, A.; Borycz, J.; Charakchieva-Minol, S.; Chojnacka-Wójcik, E. *J. Med. Chem.* **1999**, *42*, 4952-4960.
(2) Paluchowska, M.H.; Bojarski, A.J.; Charakchieva-Minol, S.; Wesołowska, A. *Eur. J. Med. Chem.* **2002**, *37*, 273-283.
(3) Wesołowska A.; Paluchowska M.H.; Gołembiowska K.; Chojnacka-Wójcik E. *J. Pharm. Pharmacol.*, **2003**, 55 533-543.