# Functional *in vivo* Profile of New Analogs of MM77 and MP349 with Modified Imide Fragment at Postsynaptic 5-$HT_{1A}$ Receptors

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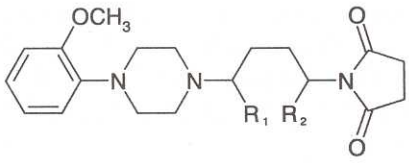
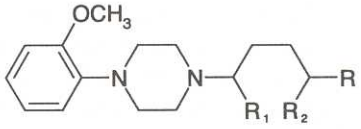
Systematic structure-activity relationship studies in arylpiperazine group of 5-$HT_{1A}$ ligands have allowed our research group to obtained highly potent compound MM77, a postsynaptic 5-$HT_{1A}$ antagonist,[1] for which anxiolytic–like activity has been described.[2] Quite recently we published synthesis and pharmacological characteristic of conformationally restricted analog of MM77 – compound MP349 – which was characterized as a full 5-$HT_{1A}$ receptor antagonist also with an anxiolytic–like profile in animal anxiety models.[3,4] Moreover, MP349 became the first antagonist from arylpiperazine group with a precisely defined 3-D structure.

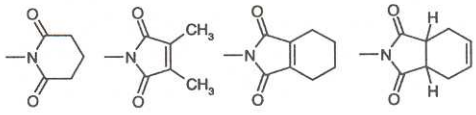


**1a** (MM77): $R_1 = R_2 = H$
**1b** (MP349): $R_1, R_2 = -(CH_2)_2-$



**2-5**
series **a**: $R_1 = R_2 = H$
series **b**: $R_1, R_2 = -(CH_2)_2-$

R =



In present work we synthesized series of MM77 and MP349 analogs with modified imide fragments. We wondered if such structural changes will influence on *in vitro* and *in vivo* activity of new derivatives at 5-$HT_{1A}$ receptor sites. Compounds of both series were obtained in the reaction of 4-[4-(*o*-methoxyphenyl)piperazine]cyclohexylamine with appropriate anhydride in boiling xylene. The structure of new derivatives was confirmed by $^1H$ NMR spectra and elemental analyses of their hydrochlorides The affinity at 5-$HT_{1A}$ receptors for all synthesized compounds was determined by standard competitive displacement assays using [$^3H$]-8-OH-DPAT as a competitive ligand.
Derivatives of both series demonstrated very high affinity for 5-$HT_{1A}$ receptors ($K_i$ ranged from 3 to 33 nM). To determine their postsynaptic 5-$HT_{1A}$ receptor activity the rat lower lip retraction model was used. In series **a** (MM77 analogs) the changes in the imide structure did not affect the functional profile of the tested compounds in comparison with MM77, they behaved like 5-$HT_{1A}$ receptor antagonists; only **5a** showed features of a partial agonist of these receptors. The limitation of conformational freedom of the ligands of series **b** only in the case of **4b** caused an alternation of functional profile at postsynaptic 5-$HT_{1A}$ receptors, this compound can be classified as a partial agonist of these sites.

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