Flexible and corresponding conformationally constrained arylpiperazines: synthesis, binding to serotonin 5-HT_{1A}, 5-HT_{2A}, α_1-adrenergic and dopaminergic D_2 receptors, and in vivo 5-HT_{1A} functional characteristics

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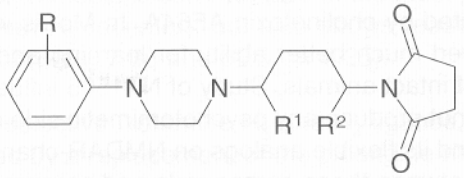
Starting with the structure of potent 5-HT_{1A} ligands, i.e. MM77 (1-(2-methoxyphenyl)-4-(4-succinimido)butyl)piperazine) and its constrained version (MP349) [1], previously obtained in our laboratory, a series of their direct analogues with differently substituted phenyl ring (R = H, *m*-Cl, *m*-CF_3, *m*-OCH_3, *p*-OCH_3) were synthesized.



R = H, *o*-OCH_3, *m*-Cl, *m*-CF_3, *m*-OCH_3, *p*-OCH_3
R^1, R^2 = H or $-(CH_2)_2-$

The flexible and the corresponding 1e,4e-disubstituted cyclohexane derivatives were designed in order to investigate the influence of rigidification on 5-HT_{1A} affinity, selectivity for 5-HT_{2A}, α_1 and D_2 binding sites and functional profile at pre- and postsynaptic 5-HT_{1A} receptors. The new compounds were found to be highly active 5-HT_{1A} receptor ligands (K_i = 4–44 nM) and their affinity for α_1 receptors was controlled by phenyl substituents. Regarding 5-HT_{2A} receptors both, the R groups and spacer rigidification influenced compounds activity in vitro, whereas very low affinity values were obtained for D_2 receptors (K_i = 5.3–31 μM).

A several in vivo models were used to asses functional activity at pre- (hypothermia in mice) and postsynaptic 5-HT_{1A} receptors (lower lip retraction in rats and serotonin syndrome in reserpinized rats). Unlike the parent antagonists MM77 and MP349, all the new derivatives tested were classified as partial agonists with different potency, however, similar effects were observed within pairs (flexible and rigid) of the analogues. The obtained results indicated that substitution in the phenyl ring, but not spacer rigidification, controls the 5-HT_{1A} functional activity of the investigated compounds. Moreover, an *o*-methoxy substituent in the structure of MP349 seems to be necessary for its full antagonistic properties. Of all the new compounds studied, *trans*-4-(4-succinimidocyclohexyl)-1-(3-trifluoromethylphenyl)piperazine was the most potent 5-HT_{1A} receptor ligand in vitro (K_i = 4 nM) and in vivo, with at least 100-fold selectivity for the other receptors tested.

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[1] Paluchowska MH, Bojarski AJ, Charakchieva-Minol S, Wesołowska A, Active Conformation of Some Arylpiperazine Postsynaptic 5-HT_{1A} Receptor Antagonists. Eur J Med Chem 2002;37:273-83.