IMIDES VERSUS AMIDES – NEW ANALOGS OF NAN-190 AND MM-77 – 5-HT_{1A} RECEPTOR LIGANDS

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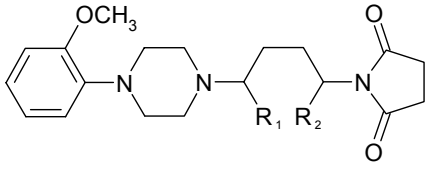
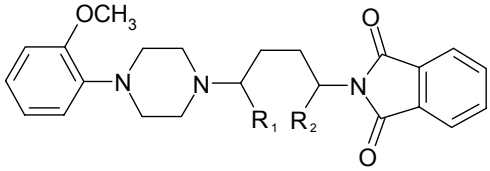
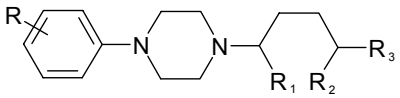
In the last years we focused our study on the determination of bioactive conformation of 5-HT_{1A} receptor ligands imposing conformational restriction on flexible 5-HT_{1A} receptor agents. Among others we synthesized rigid analogues of postsynaptic antagonist: NAN-190 and MM-77, i.e. MP-245 (intrinsic activity like parent compound) and MP-349 (full antagonist exhibiting anxiolytic-like activity in some animal models) respectively.[1] These findings prompted as to conduct further studies on determination of structural features important to the ligand-receptor complex formation and their *in vivo* functional activity. We designed and synthesized two new series of NAN-190 and MM-77 analogues devoid of one of the carbonyl groups: **a** – containing tetrametylene chain, and **b** – with 1e,4e-cyclohexylene ring. Structural modifications concerned phenyl substitution patterns.



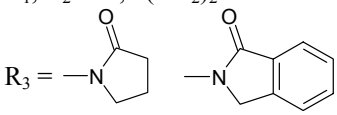
MM-77 ($R_1 = R_2 = H$)
MP-349 ($R_1, R_2 = –(CH_2)_2–$)



NAN-190 ($R_1 = R_2 = H$)
MP-245 ($R_1, R_2 = –(CH_2)_2–$)



R = H, *o*-OCH_3, *m*-Cl, *m*-CF_3
R_1, R_2 = H, $–(CH_2)_2–$



Analogues of NAN-190 were readily obtained from the appropriate anhydrides and amines by refluxing in xylene. Phthalimidies were received by reduction with zinc and acetic acid. Five-membered lactams were prepared by coupling amines to 4-chlorobutyryl chloride to gave intermediates that were subsequently cyclized to lactams by treatment with NaH.

All the new compounds were evaluated for affinity at 5-HT_{1A} receptor. The flexible derivatives (series **a**) and their constrained counterparts (series **b**) showed high *in vitro* activity. Research of their *in vivo* functional profile are in the course.

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1. Paluchowska, M.H. et al.; Eur. J. Med. Chem. 2002, 37, 273