A HYDROGEN BOND INFLUENCES THE 5-HT1A/D4 SELECTIVITY OF WAY-100635 ANALOGUES: AN IN SILICO APPROACH

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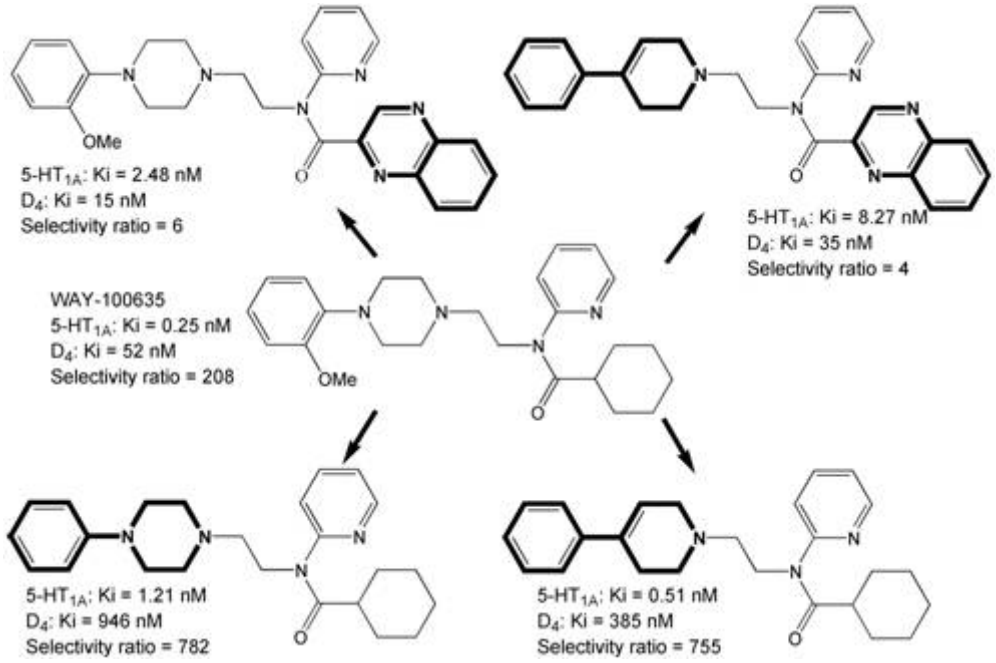
WAY-100635 is widely used *in vitro* and *in vivo* as an antagonist of 5-HT_{1A} receptors [1]. In terms of pharmacological tools and pharmacological investigations, the ideal reference molecule would be highly selective for its target over other related and non-related targets. However WAY-100635 displays affinity for and activity at D_4 dopamine receptors, and that "off-target" activity confounds its use in pharmacological studies, particularly when both receptors are present [2]. In this context, we carried out various chemical modifications of the WAY-100635 structure in order to improve its 5-HT_{1A} *versus* D_4 selectivity. An important increase of selectivity was obtained when the basic side chain of WAY-100635 was replaced by a 4-phenylpiperazine or a 4-phenyl-1,2,3,6-tetrahydropyridine moiety [3]. In contrast, the introduction of nitrogen atoms in the acyl group decreased the selectivity by reducing the affinity for 5-HT_{1A} receptors, on the one hand, and enhancing the affinity for D_4 receptors on the other hand [3].



In order to explain the reduced 5-HT_{1A}/D_4 selectivity of aza-derivatives, the binding modes of the compounds were explored by docking analysis on homology models of the two receptors. It appears that the formation of an additional hydrogen bond within D_4 receptors could be the key of the decreased selectivity. These results will be very helpful for developing molecules with an improved 5-HT_{1A}/D_4 selectivity.

Acknowledgments and funding:

S.D. and J.-F.L. are Postdoctoral Fellow and Research Director of the "Fonds National de la Recherche Scientifique" (F.R.S-FNRS) of Belgium, respectively. This study is supported in part by grants of the Fonds de la Recherche Scientifique-FNRS (F.R.S.-FNRS) and the Fonds Spéciaux pour la Recherche of the University of Liège (Belgium).

References

1) Forster, E. et al. A pharmacological profile of the selective silent 5-HT1A receptor antagonist, WAY-100635. Eur J Pharmacol 1995, 281, 81-8.
2) Chemel, B. et al. WAY-100635 is a potent dopamine D4 receptor agonist. Psychopharmacology (Berl) 2006, 188, 244-51.
3) Mangin, F. et al. Moderate chemical modifications of WAY-100635 improve the selectivity for 5-HT1A versus D4 receptors. Bioorg Med Chem Lett, 2012, 22, 4550-4554.