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ATTI DEL CONGRESSO

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Towards metabolically stable serotonin 5-HT_7 receptor ligands: structural modification of LP-211 and *in silico* prediction model

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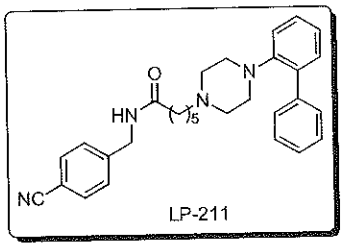
Serotonin 5-HT_7 receptors (5-HT_7Rs) are expressed in functionally relevant regions of the brain suggesting a role in many pathophysiological processes, such as depression, mood disorders, modulation of learning and memory [1]. During last years, our research group has been involved in the development of selective 5-HT_7 receptor ligands and the most relevant outcome is represented by LP-211, a brain penetrant selective 5-HT_7R agonist. However, LP-211 is transformed *in vivo* into the main metabolite 1-(2-biphenyl)piperazine that retains affinity for the 5-HT_7R [2]. Since the pharmacology of this metabolite has been poorly explored, it is unknown if its presence can revert or attenuate the action of the LP-211 *in vivo*. On such basis, the availability of novel 5-HT7R agonists with improved pharmacokinetic properties is desirable. Following this aim, we manipulated the chemical structure of LP-211 to improve overall pharmakocinetic properties, leaving unchanged the structural features that are responsible for affinity, selectivity and agonistic properties towards the 5-HT_7R. In parallel, machine learning methods have been applied to build an *in silico* model for the prediction of metabolic stability of the newly designed compounds.



LP-211

[1] Leopoldo et al. Pharmacol. Ther., 2011, 129, 120-148.
[2] Hedlund et al Neurosci. Lett. 2010, 481, 12-16.