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## NOVEL POTENT SEROTONIN 5-HT$_7$ RECEPTOR LIGANDS: STRUCTURAL MODIFICATION TO IMPROVE PHARMACOKINETIC PROPERTIES AND IN SILICO PREDICTION MODEL

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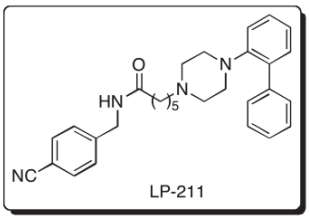
Serotonin 5-HT7 receptors (5-HT7Rs) are expressed in functionally relevant regions of the brain suggesting a role in many pathophysiological processes, such as depression, mood disorders, modulation of learning and memory [1]. During last years, our research group has been involved in the development of selective 5-HT7 receptor ligands and the most relevant outcome is represented by LP-211, a brain penetrant selective 5-HT7R agonist.

However, when LP-211 is administered *in vivo*, it is transformed into the main metabolite 1-(2-biphenyl)piperazine that retains affinity for the 5-HT7R [2].



LP-211

Since the pharmacology of this metabolite has been poorly explored, it is not known if its presence revert or attenuate the action of LP-211 *in vivo*. On such basis, the availability of novel 5-HT7R agonists with improved pharmacokinetic properties is desirable. Therefore, the scaffold of LP-211 has been manipulated to improve pharmakocinetic properties, leaving unchanged the structural features that are responsible for affinity, selectivity and agonistic properties towards the 5-HT7R. In silico model based on different molecular descriptors for the prediction of metabolic stability of the newly designed compounds has been developed using various machine learning techniques.

References:

1.) Leopoldo et al. Pharmacol. Ther., **2011**, *129*, 120-148.

2.) Hedlund et al Neurosci. Lett. **2010**, *481*, 12-16.