POSTER COMMUNICATION – ABSTRACT

Molecular Modeling for Rational Design and Virtual Screening

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WLB-73502 is an internally developed dual σ1 receptor (σ1R) and μ-opioid receptor (MOR) ligand that has been shown in preclinical models to have full antinociceptive efficacy, better neuropathic pain relief and a better safety profile than opioid monotherapy, and it is currently ready for Phase II clinical trials.

At Welab we routinely apply computational methods to help and efficiently accelerate the drug discovery process. We describe here the 3D pharmacophore models that we have developed for σ1R and MOR and how both pharmacophores were merged to integrate the required features for binding in a unique central core, giving rise to the dual active family of 4-alkyl-1-oxa-4,9-diazaspiro[5.5]undecane derivatives to which WLB-73502 belongs.

Additionally, to pharmacophore techniques, which we use to efficiently virtually screen large chemical libraries and collections of chemical proposals, we have as well studied the most interesting structures by docking to the available crystal structures of the receptors followed by molecular dynamic simulations of each complex. We show here the binding pose adopted by WLB-73502 both in the σ1R and MOR and the key ligand binding interactions that explain its affinity.