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Beyond pharma R&D services, scientific solutions

Molecular Modeling for Rational Design and Virtual Screening

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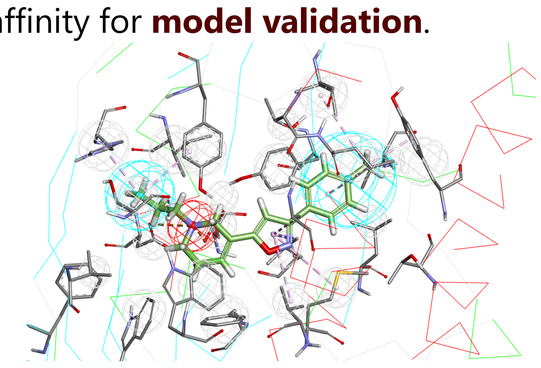
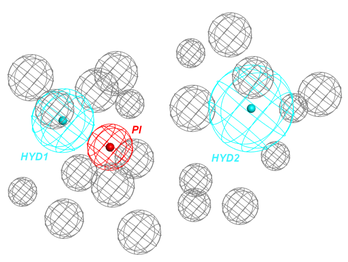
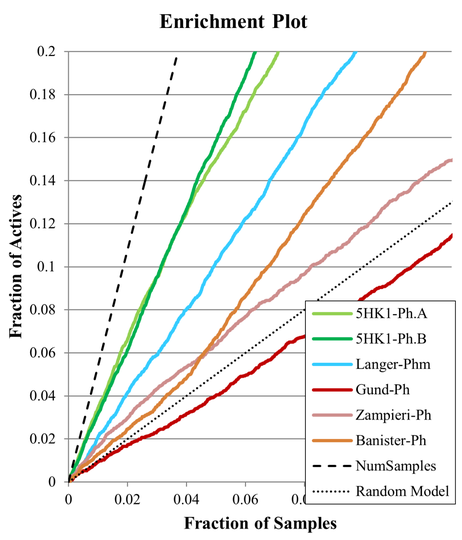
PHARMACOPHORE MODELING

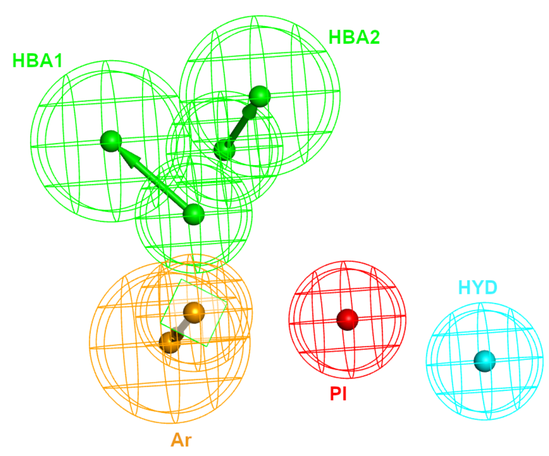
σ1-pharmacophore model was **developed** based on receptor-ligand interactions found in the 5HK1 crystal structure and the chemical knowledge on σ1 ligands[1].
Virtual Screening was performed on more than **25,000 structures** from our internal database with experimentally determined σ1R affinity for **model validation**.

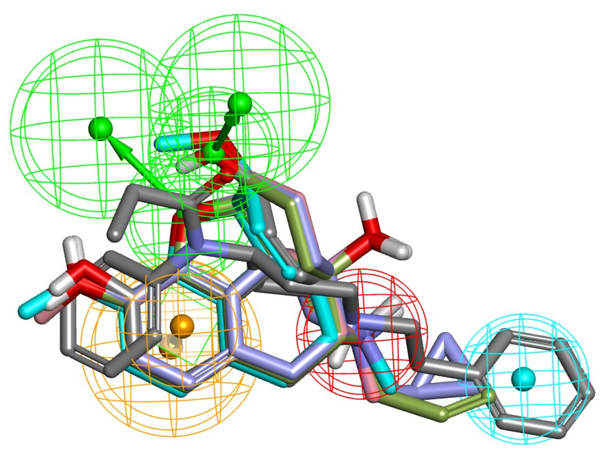






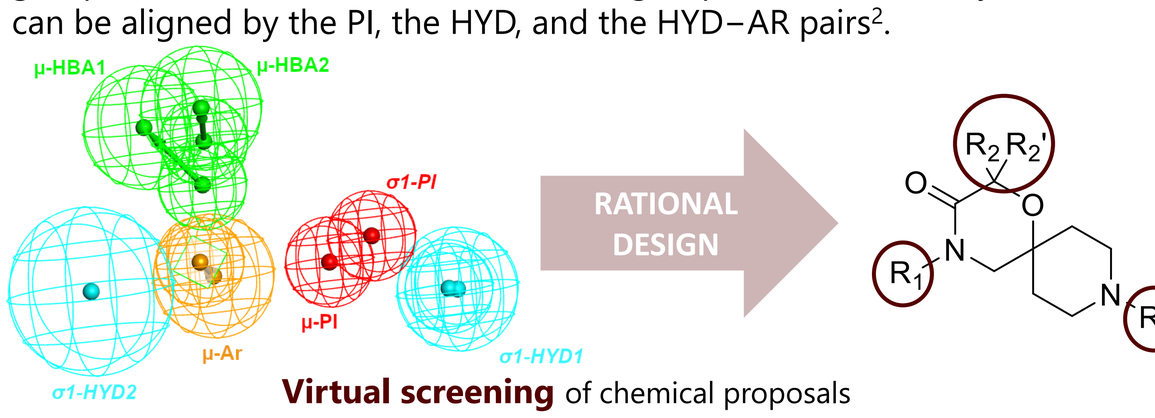
μ-pharmacophore model development based on the structurally rigid morphine and other morphinan analogs, but also taking into account the additional hydrophobic feature at the other site of the basic amine present in fentanyl-like ligands.





Pharmacophore Merging approach for dual μ-opioid/σ1 receptor rational ligand design

The goal of the **pharmacophore merging approach** is to combine the two target pharmacophores in the same central core. In the project aiming to discover multimodal compounds targeting the σ1R and the MOR, it turned out feasible as both pharmacophores require a basic amine, (PI), a hydrophobic group (HYD) next to it, and the aromatic group (AR) of MOR may as well match a HYD present in the σ1R pharmacophore. Thus, both σ1R and MOR models can be aligned by the PI, the HYD, and the HYD−AR pairs[2].

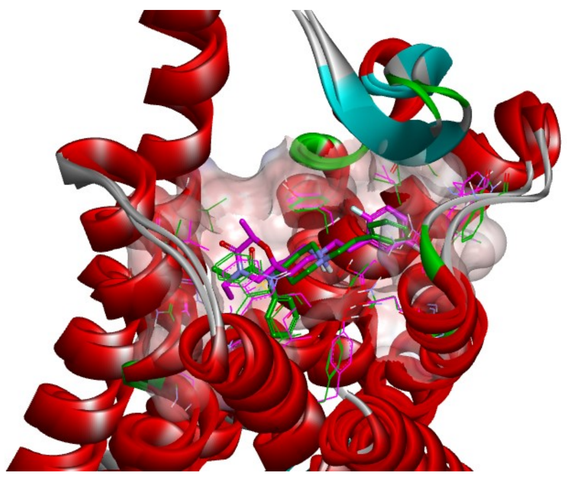


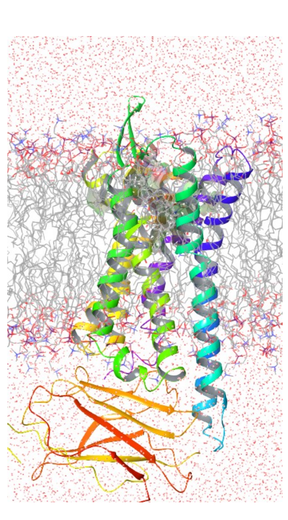
Virtual screening of chemical proposals

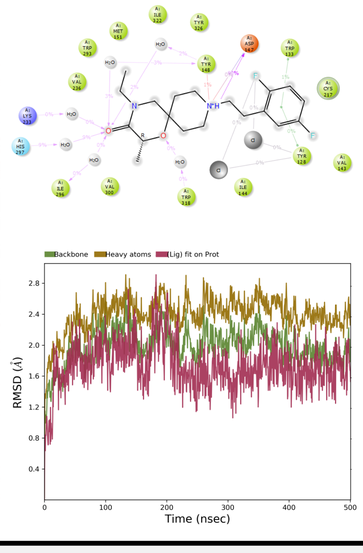
DOCKING and MOLECULAR DYNAMICS

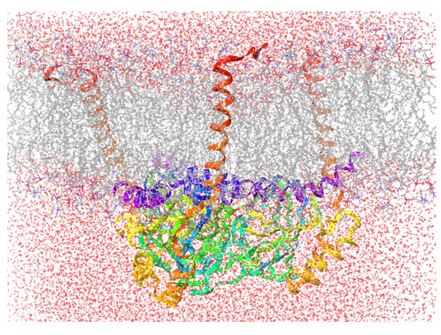
Docking of the dual **clinical candidate WLB-735023**[3] in the active form of MOR (5C1M) and **molecular dynamic simulation** of the docked pose shows good stability and allows the identification of the **key ligand-receptor interactions**.
MOR protein based structural superposition of our published binding pose of WLB-73502[4] and the later published fentanyl-bound MOR crystal structure[5] show a nice similarity.

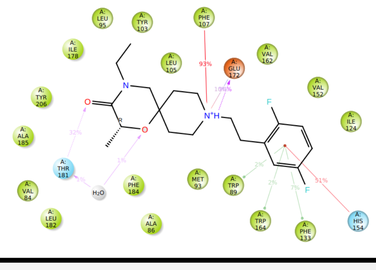
Docking of WLB-73502 in the σ1R[6] and molecular dynamic simulations confirm the anchoring ionic interaction of the basic nitrogen with Glu172 and show a relevant pi-cation interaction of the difluorophenyl group with His154 and an important H-bond role of the carbonyl with Thr181 additionally to the characteristic hydrophobic interactions of the σ1R binding site.

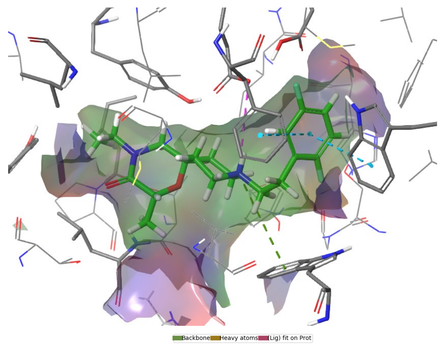


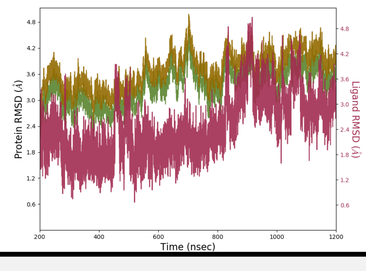












References

(1) Pascual, R. et all. *Front. Pharmacol.* **2019**, doi.org/10.3389/fphar.2019.00519. (2) García, M. et al. *J. Med. Chem.* **2020,** *63*, 2434-2454. (3) García, M. et al. *J. Med. Chem.* **2020**, *63*, 15508-15526. (4) Vidal-Torres, A. et al. *Acta Pharmaceutica Sinica B* **2022**, doi.org/10.1016/j.apsb.2022.09.018. (5) Zhuang, Y. et al. *Cell* **2022**, 185, 4361-4375. (6) Schmidt, H.R. et al. *Nature* **2016**, *532*, 527-530.