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Welab BARCELONA

Beyond pharma R&D services, scientific solutions

MedChem approaches to Multimodal Therapy

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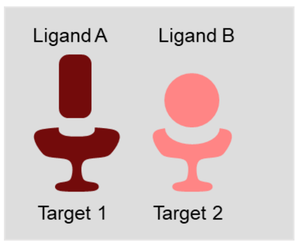
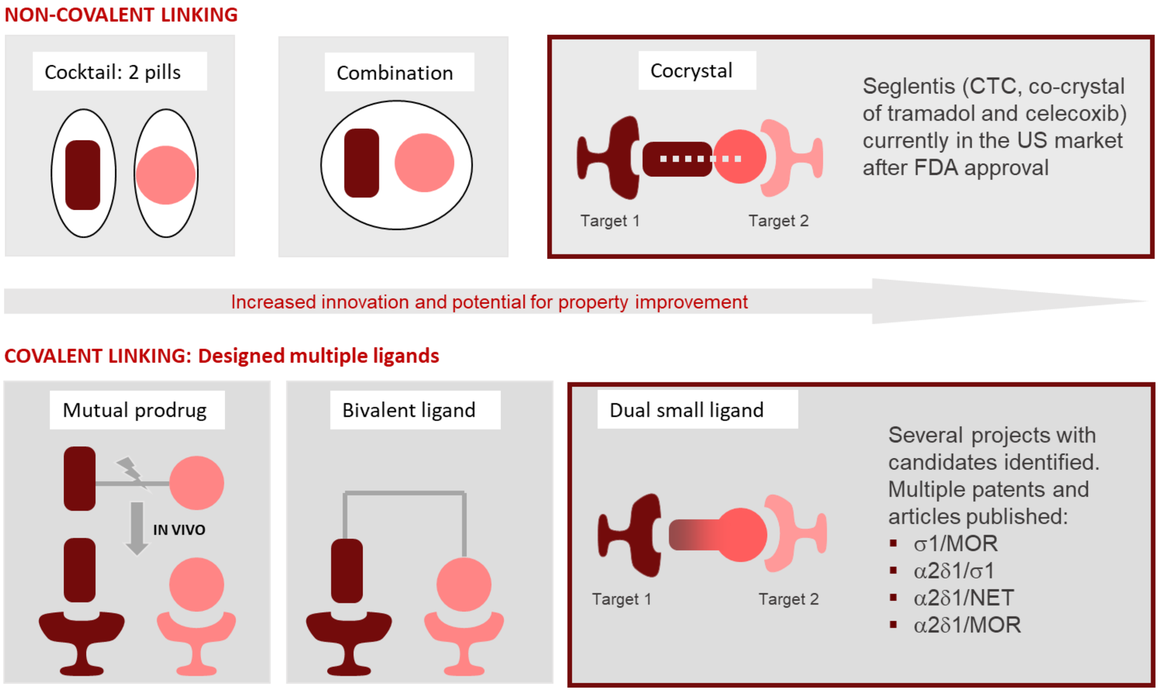
MULTIMODAL THERAPY

Multimodal Therapy may be a way of improving the R&D output obtained using the "one drug-one target" approach,[1] as many pathological states are multimodal in nature and require multiple mediators. **Welab MedChem team is highly experienced in achieving drug-like multimodal compounds.**

Dual small ligands are the best approach to Multimodal Therapy offering the potential, *vs* cocktails or fixed-dose combinations, of:

- improving the efficacy and safety ratio
- decreasing the risk of drug-drug interactions
- providing simpler pharmacokinetics
- being associated to less variability among patients
- addressing more complex etiologies





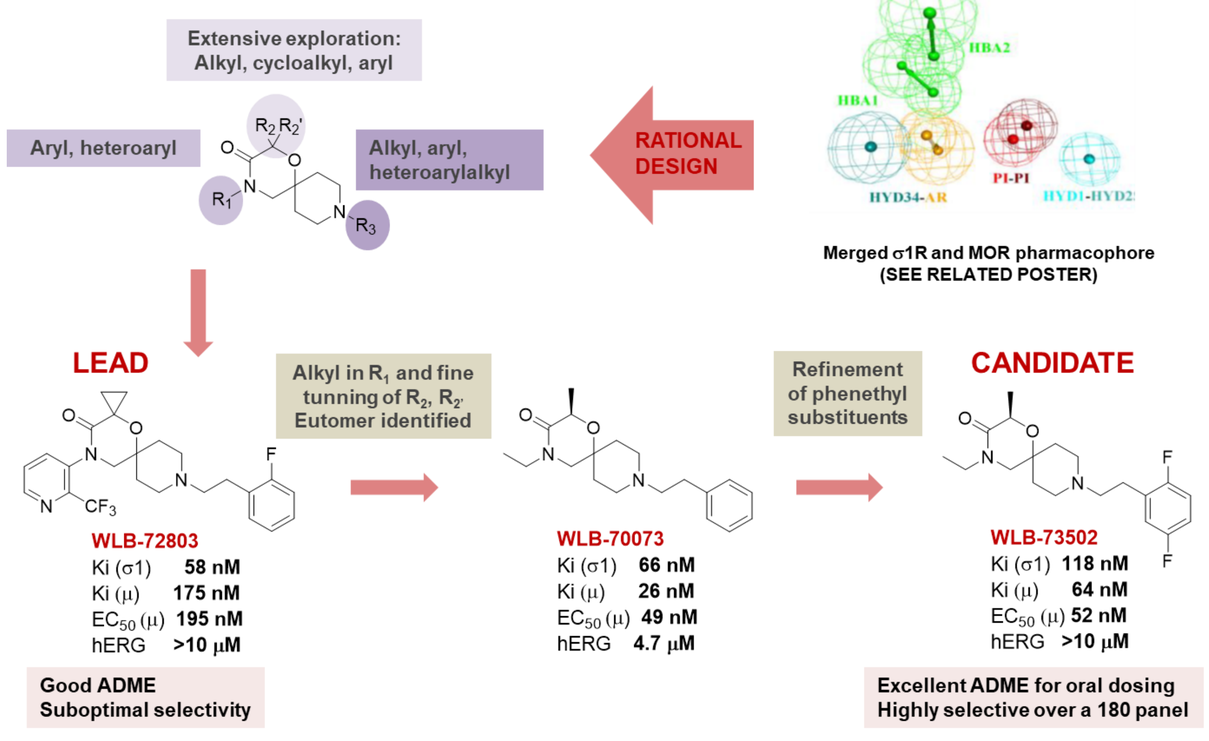
CASE STUDIES

Dual μ-opioid/σ_1 receptor ligand WLB-73502

As a new approach for the treatment of chronic pain, we undertook a program to discover **multimodal compounds** targeting the σ_1 receptor (σ_1R) and the μ-opioid receptor (MOR), based on the potentiation of opioid analgesia with σ_1R antagonists and the efficacy of the later in neuropathic pain, where opioids are poorly effective.

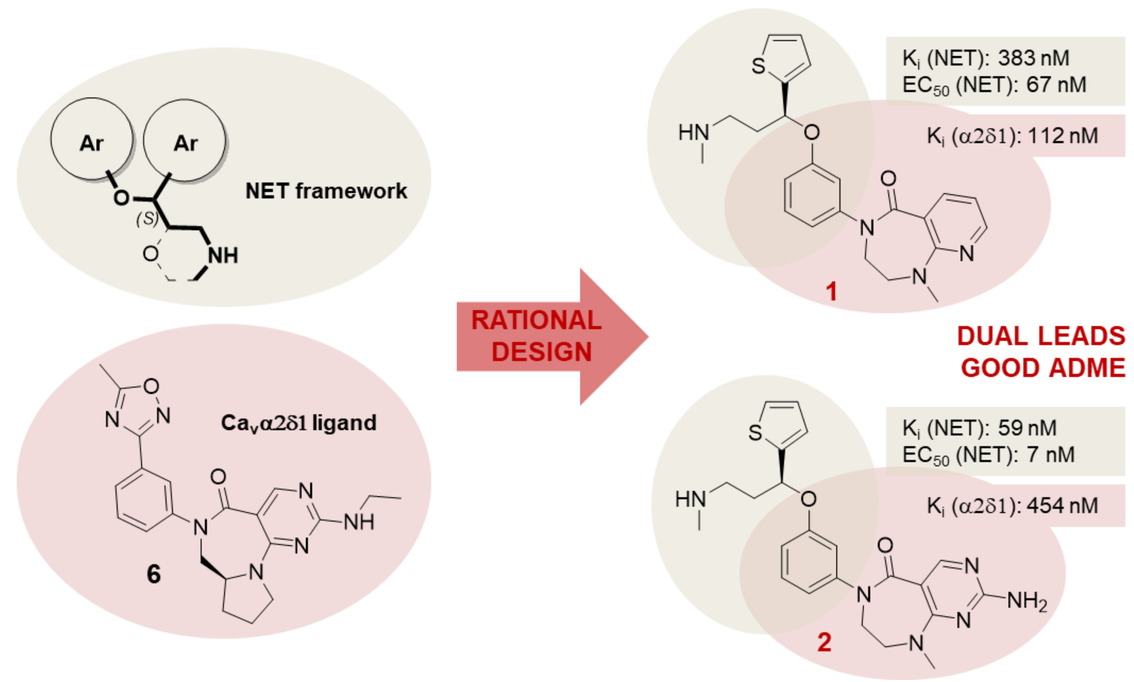
Following a merging approach of MOR and σ_1R pharmacophores, we designed a new series of dually active spirocycles. Applying a **Multiparametric Optimization Approach** to deal with hERG blockade and suboptimal selectivity for α_{1A}R in the hit-to-lead phase of the project, we identified the lead compound WLB-72803.[2]

A Lead Optimization program[3] led to the **clinical candidate WLB-73502,[4] currently ready for Phase II clinical trials**. In preclinical models it displays similar nociceptive pain relief, **better neuropathic pain relief, improved tolerability, less respiratory depression and less abuse potential than strong opioids**, confirming the potential of the dual approach for improving the standard of care in the treatment of pain.



Bicyclic diazepinones as dual ligands of $Ca_v\alpha2\delta$-1 and NET

Another approach to improving the existing analgesic armamentarium aimed at the finding of dual ligands of the α2δ-1 subunit of voltage-gated calcium channels ($Ca_v\alpha2\delta$-1) and the norepinephrine transporter (NET, SLC6A2), two mechanisms with clear rationale in the treatment of pain. We focused on non-aminoacidic $Ca_v\alpha2\delta$-1 ligands, since the space around the marketed aminoacidic drugs (gabapentin and pregabalin) was very restricted. The pyrimidodiazepinone scaffold of compound **6**,[5] was selected for merging with the NET pharmacophore, common to all marketed drugs of this class (ie, fluoxetine, reboxetine or duloxetine).



Achieving an adequate dual and drug-like profile was not obvious, as both target pharmacophores do not have much in common. Among the NET patterns explored, 3-methylamino-1-thiophenylpropoxy moieties in the meta position of the phenyl ring of **6**, provided **balanced dual compounds, such as 1 and 2,**[6] that showed:

- Good physicochemical profile (complying Lipinski; kinetic solubility > 10 μM)
- Good stability in human and rodent liver microsomes (Cl_{int} < 5 μL/min/mg protein)
- No potential for drug-drug interactions based on the low inhibition (< 50% at 1 μM) of rhCYP isoforms (1A2, 2C9, 2C19, 2D6, and 3A4)
- IC_{50} above 10 μM in the hERG patch clamp assay

Both **lead compounds showed an excellent NET functionality despite being substantially larger than prototypic NET inhibitors.** The existence of a cavity located near the NET primary binding site, which might allow the accommodation of larger derivatives, can explain this fact.

A Lead Optimization program based on **1** and **2** allowed the identification of candidates with interesting analgesic profiles that will be reported in due curse.

REFERENCES

(1) Bornot, A. et al *J. Med. Chem*, **2013**, *56*, 1197-1210. (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) Pyrimidodiazepinone Derivatives. US20,100,190,775, 2010. (6) Díaz, J. L. et al. *J. Med. Chem*, **2021,** *64*, 2167-2185.