Advanced pharmacophores for accurate virtual screening and identification of opioid lead compounds

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Virtual screening has gained considerable impact for the efficient discovery of novel bioactive compounds in modern pharmaceutical research. In addition, pharmacophore modeling has evolved to be an important and successful method for early lead discovery during the last several decades. The concept of chemical feature-based pharmacophore models has been established as a state-of-the-art technique for describing the interactions between small molecules and proteins or nucleic acids.

At Inte:Ligand GmbH, LigandScout, a pharmacophore modeling and virtual screening platform, has been developed to rapidly and efficiently interpret protein-ligand interactions and subsequently transform this information into 3D-chemical feature based pharmacophore models that can be used for rapid and efficient virtual screening or for transparently deriving key features for lead optimization of compounds by medicinal chemists. In addition, ligand-based pharmacophore models can be derived based on a set of bioactive molecules when target information is not available.

In this study we utilized LigandScout to derive ligand-based pharmacophore models for virtual screening in an effort to validate our Dmt-Tic opioid pharmacophore hypothesis as well as identify new lead opioid compounds. Opioid therapeutics function not only to control severe pain, but also are effective in the treatment of immunosuppression, narcotic addiction, autism and Tourette's syndrome. Therapeutic opportunities that span beyond pain control and aim to reduce or modulate the negative effects associated with opioid drugs have led to the development of compounds specifically targeted for opioid receptors.

One intriguing opioid design motif involves 2′,6′-dimethyltyrosine (Dmt), 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) and 1H-benzimidazole-2-yl (Bid). The incorporation of Dmt into the sequence of opioid peptides resulted in dramatic effects, exemplified by as much as 8500-fold increases in δ-opioid receptor affinity and changes in bioactivity profiles. Furthermore, δ-opioid receptor agonism appeared consistently after incorporation of Bid into the sequence Dmt-Tic peptides. In several publications, we proposed a 3D-model of the 'Dmt-Tic' pharmacophore that represented the bioactive conformation of opioid peptides containing the Dmt-Tic motif. We utilized this pharmacophore model along with x-ray structural information involving three Dmt-Tic derivatives to create 3D ligand-based pharmacophore models using LigandScout that were used to screen several virtual chemical libraries.

The hit compounds tested thus far exhibited μ-opioid receptor affinities ranging from 0.080 nM to 6.030 μM. The most potent compound minimally demonstrated antinociception via intracerebroventricular administration. Another hit, SC-39566 retrieved from the Derwent World Drug Index (WDI), is a μ-opioid receptor antinociceptive tripeptide that contains the Dmt-Tic motif.

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