In silico SAR rationalization and evaluation of pharmacokinetic properties of σ_1 receptor ligands

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The σ_1 receptor is implicated in numerous studies, concerning both its function and mechanism of action and possible ligands. This receptor is very interesting from the pharmacological point of view, as it is involved in several diseases, e.g. Alzheimer's and addiction to drugs and alcohol. Since a crystal structure of the σ_1 receptor is not available, we conducted ligand-based studies.

We analyzed 72 congeneric compounds with a propyl-aminic sub-structure, but having different K_is in the range from nanomolar to millimolar, partially published [1]. In order to assess the potential of novel ligands, we divided this work in two parts: affinity rationalization and evaluation of pharmacokinetic properties. First, we generated a shape-based alignment with ROCS [2,3], using only 45 compounds, with a K_i<100 nM, excluding the other 27 less affine compounds. We refined the alignment of the compounds giving more importance to the positive charge on the residual nitrogen. Based on this alignment [4] we generated a 3D-pharmacophore model with LigandScout [5]. A shared-feature model finally had 3 important features: 2 hydrophobic regions, one of them containing an aromatic ring, and a H-bond donor, that usually is a protonated nitrogen. The pharmacophore model was used to compare the ligands with active ligands from literature and the similarity suggests similar binding modes. We complementary created a QSAR model using 2D and 3D descriptors [6], to quantitatively rationalize activity. Our model shows the activity to be linearly correlated with logS, logP, molecular refractivity and related descriptors, as evaluated with Pearson's correlation coefficient.

In the second part of this work, we evaluated aspects of ADME and pharmacokinetic properties for our set. We verified that the compounds obey the 'rule of 5' of Lipinski [7], suggesting potential oral bioavailability. Then we analyzed which cytochrome P450 enzymes (CYPs) are potentially involved in the metabolism, using a 2D-descriptor based decision tree model [8]. With this in-house CYP isoform assignment tool, all compounds are predicted to be metabolized by the isoforms CYP 3A4 or 2D6, which have respectively a large and basic binding pocket. These characteristics fit perfectly with the characteristics of our compounds, that have a molecular weight in the range 216 Da through 403 Da and have at least one basic nitrogen. With this study we are able to explain how the features of our σ_1 ligands are directly related to the activity, and our insights will further be exploited in lead optimization of this set of σ_1 receptor ligands.

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