

effect locally by light. This study focuses on the pharmacological characterization of a novel designed series of photoswitchable ligands for the H<sub>3</sub>R. Significant shifts in binding affinity were observed when converting the photoswitchable ligands from one to the other isomer.

## P35

### SEQUENTIAL DOCKING SUPPORTING THE FRAGMENT LINKING STRATEGY FOR G PROTEIN-COUPLED RECEPTORS

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Fragment-based drug discovery employs growing and linking strategies for optimization. In this work we carried out binding mode prediction of multiple fragments bound to a single target using a sequential docking methodology employing Glide to support the identification and linking of fragment hits. Sampling and scoring accuracy for the first and second site binders in self- and cross-docking situations was found suitable for prospective use.<sup>1</sup> This sequential docking methodology was then applied to computationally predict starting points for fragment linking using the human dopamine D3 receptor crystal structure and a human dopamine D2 receptor homology model. Two focused fragment libraries were docked in the primary and secondary binding sites, and best fragment combinations were enumerated. Similar top scoring fragments were found for the primary site, while secondary site fragments were predicted to convey selectivity. The three synthesized linked compounds showed selectivity in favor of D3 and the subtype selectivity of the compounds was assessed on a structural basis.<sup>2</sup> Further work will be directed towards multi-model protein selectivity predictions and design of ligands with desired polypharmacological profiles.

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## P36

### BECAUSE TWO IS ALWAYS BETTER THAN ONE – TOWARDS THE SEARCH OF DUAL 5-HT<sub>x</sub>-SERT LIGANDS

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Serotonin (5-Hydroxytryptamine, 5-HT) is an important tryptophan-derived neurotransmitter, playing profoundly important functions in the majority of physiological and behavioral processes such as sleep, appetite, memory and mood control, cardiovascular function, digestion, and muscle contraction. [1] After its release from the nerve cells, serotonin is picked up by receptors from serotonergic system and after the completion of the signaling task it is fed back into the neurons by serotonin transporter (SERT) or undergoes degradation by monoamine oxidase. It has been established that abnormalities in the

serotonergic system function are responsible for various mental disorders, such as depression, schizophrenia, anxiety and bipolar disorder [2].

The aim of the study was to develop a virtual screening protocol oriented at finding new ligands with dual activity towards selected serotonin receptor subtypes (5-HT<sub>1A</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub>) and SERT. Due to the limited number of compounds with dual activity reported in the ChEMBL database, the retrospective screening strategy was applied in order to determine the activity threshold for the division between active/inactive classes providing the most efficient discrimination between these groups of compounds. Then, the Enamine database (containing over 2.5 million of compounds) was screened with the use of the SVM algorithm and with the application of the consensus-fingerprint approach. [3] The selection of compounds for purchasing was supported by docking to homology models of 5-HT<sub>x</sub>R and SERT and their biological activity will be evaluated in the *in vitro* experiments.

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## P37

### STRUCTURE-BASED DESIGN OF CXCR4 CHEMOKINE RECEPTOR LIGANDS

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The chemokine receptor 4 (CXCR4) belongs to class A of G-protein coupled receptors (GPCRs) and plays an important role in inflammation. The release of new crystal structures (Fig. 1A-B) [1,2] of chemokine receptors open up new possibilities for the structure-based design of small molecule ligands that can modulate the function of CXCR4. GPCR DOCK 2010 has

demonstrated the challenges of predicting the structure of chemokine receptor-ligand complexes (Fig 1B-C).[3] We are currently combining the new structural insights in CXCR4-ligand binding with systematic mining of ligand SAR and receptor mutation data (Fig. 1E)[4] and protein-ligand interaction fingerprint (IFP) analyses (Fig. 1D) construct structural models of CXCR4-ligand complexes. In particular ligand-dependent effects of mutations[5] provide useful information to: i) select and rank molecular docking poses for protein-ligand binding mode prediction, ii) develop customized structure-based virtual screening for new biologically active ligands[6], and iii) guide ligand design and optimization.

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