P68

Development of selective GPCR ligands – 5-HT$_{1B/2B}$ case study

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Compounds targeting multiple receptors, have both beneficial and harmful properties. The promiscuity of such compounds results in activating or blocking multiple therapeutic targets, facilitating a more complex response. However, this also means that multiple off-target receptors may be activated, causing undesirable side effects.
Finding new, selective drugs, that target only one type of receptor while not interacting with other receptors, especially with closely related ones, is proving to be quite complicated. In this study, new compounds selective for 5-HT$_{1B}$ and 5-HT$_{2B}$ receptors were designed (with both 1B/2B and 2B/1B selectivity). The study focused on the selectivity of compounds defined by their interactions with the secondary (allosteric) binding pockets of target proteins while retaining standard interactions with the orthosteric binding pockets.
During the study a new type of fingerprint – the Substructural Connectivity Fingerprint (SCFP), a two-dimensional fingerprint containing information on connectivity of substructural features of a compound, was utilized. This novel methodology was used to create multiple machine learning-based classifiers, which were further used in a multi-step compound selection protocol, consisting additionally of docking protocols and multiple scoring methods. In the last step, the compounds were visually inspected and selected for *in vitro* testing. This complex process helped to ensure, that the compounds selected in virtual screening campaign would have the highest probability of being 1B/2B selective. Within the study, a database containing 4.9 million compounds (MCule) was searched for 1B/2B and 2B/1B selective ligands, and 10 structures (5 for each selectivity type) have been highlighted for *in vitro* testing.

Acknowledgements:
This study was partially funded by the PRELUDIUM grant no. 2015/17/N/ST6/03578, funded by the National Science Center and Hungarian Brain Research Program (KTIA-NAP-13-1-2014-0009).