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

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Promiscuous drugs, that is compounds binding to more than one target receptor, have both beneficial and harmful properties. On one hand, they can act on multiple therapeutic targets, facilitating a more complex response. On the other hand, since they will also bind to non-therapeutic targets, they are the cause of most of the undesirable side effects.

Development of selective drugs, targeting one type of receptor without binding to other selected types is challenging, especially in cases when the receptors in question are extremely similar. In this study, new compounds selective for 5-HT_{1B} and 5-HT_{2B} receptors in both manners (1B-selective and 2B-selective) were designed. 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 methodology, combined with extensive selection protocols employing various machine learning methods, docking protocols, and multiple scoring methods, ensures a proper recognition of selectivity features within the tested compounds.

The main indicators of compounds' selectivity were their different interactions with the secondary (allosteric) binding pockets of both target proteins, while standard binding modes within the orthosteric binding pocket were preserved.

During the study the MCule database containing 4.9 million compounds was screened in search for 1B/2B selective ligands, and 10 structures (5 for each selectivity type) have been highlighted for *in vitro* testing.

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