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Bioisosteric substitution of sulphonyl group in 5-HT$_6$R ligands - A study on ligand-receptor interactions

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Bioisosterism is a method extensively used by medicinal chemists to design new molecules by structural modifications of known biologically active compounds, to obtain substances with improved pharmacokinetic and/or pharmocodynamic profile.[1]Additionally, bioisosterism can be used for analysis of ligand-receptor interactions.

Most (86%) of known 5-HT$_6$R ligands can be described by a pharmacophore containing four elements: hydrophobic/aromatic group (e.g. phenyl), double hydrogen bond acceptor (e.g. sulphonyl group), hydrophobic core (e.g. indole, naphthalene) and basic nitrogen atom.[2,3,4,5] The remaining 14% of ligands does not possess either sulphonyl group or basic nitrogen but still are very active towards 5-HT$_6$R. In order to investigate the influence of sulphonyl group for interactions with receptor binding pocket, a series of ligands with bioisosteric substitution of sulphonyl group with carbonyl or methylene group were designed and synthesized. These groups either conserve hydrogen bond acceptor or spatial properties of sulphonyl group.

With the use of molecular modelling techniques and crystal structure analysis, a detailed analysis of binding mode was performed. A new model of interactions between ligand and amino acid residues in receptor binding pocket was proposed.

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