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P-4: Comprehensive analysis of bioisosteric replacement in ligands of a serotonin receptors family

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A bioisosteric replacement transforms an active compound into another one by exchanging a group of atoms with broadly similar (in physicochemical properties) groups. Implementations of this technique are aimed on increase of affinity, improvement of pharmacokinetic properties or exploration of new, unknown scaffolds.

For compounds with determined affinity for any serotonin receptor stored in the ChEMBL [1] database (version 16 May 2013) all possible bioisosteres were generated in Pipeline Pilot [2]. Analysis of this collection, consisting of more than 1 million structures, showed that in average 31% of known ligands of a particular target are mutual bioisosteres. Further data exploration revealed the most frequent and the most efficient replacements in modulating ligands activity for different subtypes of serotonin receptors.

As regards, for example, 5-HT_6 receptor ligands, the most frequently explored modifications were halogen substitution and ring modification (contracting, expanding, changing linear fragments to rings, etc). Analysis showed that the most appropriate fragments for increasing ligands affinity for 5-HT_6R are phenyl and sulfonamide. Moreover, it was found that ring modifications in ligands of other targets may result in more potent compounds acting on 5-HT_6 receptor. On the other hand, substitution to nitrile group or introduction of any pyridines instead of other aromatic ring, caused decrease of ligands activity.

Similar observations and selectivity analysis, are presented and discussed for each of serotonin receptor subtype.

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