Bioisosteric replacement in search for novel 5-HT$_6$R ligands

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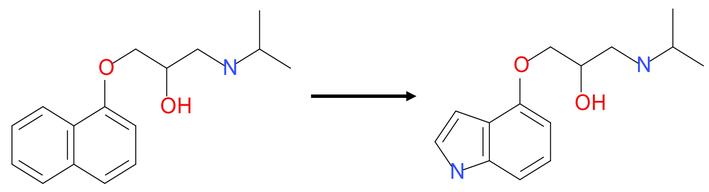
Bioisosteric replacement

A bioisosteric replacement transforms an active compound into another one by exchanging a group of atoms with broadly similar (in terms of physicochemical properties) groups. Implementations of this technique are aimed on increase of affinity, improvement of pharmacokinetic properties or exploration of new, unknown scaffolds. One of the most spectacular examples is discovery of pindolol (a non-selective beta blocker), by replacing naphtalene system from propranolol, with indole moiety. As comes out from the analysis of the in-house database of known 5-HT$_6$ receptor ligands (~4300 compounds) 31% are bioisosteres of themselves. Here we applied bioisosteric approach to search for new 5-HT$_6$R ligands in commercial databases.



Propranolol
β_2-adrenergic
K_i=1.35 nM

Pindolol
β_2-adrenergic
K_i=1.00 nM

Input structures

4 298 compounds acting on 5-HT$_6$ receptor with K_i (or equivalent) less than 1000 nM extracted from ChEMBL database, other papers and patents

Bioisoster generation

Bioizosteres database

142 183 bioisosteres of known ligands

Inputs and duplicates removal

Screening input

137 951 unique compounds

Commercial databases

ChemBridge	ChemDiv	Enamine	UORSY	VIT
831 708 cmpds	543 312 cmpds	1 531 671 cmpds	1 403 954 cmpds	1 088 399 cmpds

Available chemical space: 5.4 M compounds

Similarity search

The search for compounds from commercial databases with Tanimoto similarity coefficient higher or equal to 0.9 against any structure from screening input

1718 compounds

Physicochemistry filter

The search for compounds that pass Lipinski Rule of five, Veber filter and have appropriate pKa

854

ADME/Tox filter

The search for compounds with appriopriate values of ADME/Tox parameters, like logP, blood-brain barrier permeability, number of reactive groups, etc.

664

Pharmacophore mapping

The search for compounds mapping on at least one of 4 different 5-HT$_6$ pharmacophore models

129

Final selection

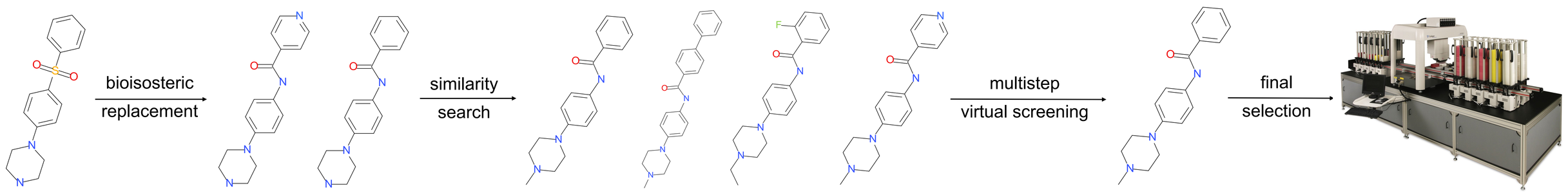
Clustering, patentability checking, visual inspection, availability checking and purchasing

11

Final results

Among 11 ordered and in vitro tested compounds, one was found to be a potent 5-HT$_6$R ligand (K_i = 128 nM), whereas two other showed affinity at micromolar level. Interestingly, their scaffolds have never been reported in aminergic GCPR research, thus they could serve as leads for new classes of 5-HT$_6$ receptor ligands.

Example path for single compound



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