Hybridization of ligands as a way of generating combinatorial libraries of drug candidates

S. Smusz[1,2], R. Kurczab[2], D. Warszycki[2], T. Kościółek[2], S. Mordalski[2], A. J. Bojarski[2]

[1]Faculty of Chemistry, Jagiellonian University, R. Ingardena 3, 30-060 Kraków
[2]Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, 31-343 Kraków

Introduction

Computational techniques have become an indispensable tool in the process of drug design. Thanks to virtual screening (VS), that is one of methodologies used in chemoinformatics tasks, we can select drug candidates out of large libraries of chemical compounds. This strategy may be applied not only to commercially available databases but also to combinatorial set of structures generated by various methods. [1,2]

5-HT$_6$ receptors

The 5-hydroxytryptamine-6 (5-HT$_6$) receptors are seven-transmembrane receptors coupled to the G protein (GPCRs) located in the central nervous system. Studies have shown that its blockade leads to cognitive enhancement and therefore they have been suggested as a target for treating neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, schizophrenia and depression.

BREED

BREED is a computational implementation of a method for generation of novel active ligands by joining fragments of already known ones. It uses a bond-matching and fragment-swapping algorithm in order to generate all structurally reasonable „products" of pairing ligand fragments. As there is a possibility to obtain two generations of new structures, BREED may lead to very large sets of potentially active compounds. [4] (Figure 2.)
As a set of initial ligands we used our internal (IF PAS, Department of Medicinal Chemistry) database of 5-HT$_6$ antagonists. A hybridization was performed with the use of BREED implemented in Maestro from Schrodinger Suite 2010, which resulted in obtaining a combinatorial library of over 400 000 different structures.

Virtual screening

A multi-step virtual screening protocol was applied for the set of new compounds. [5] (Figure 1.) We used tools of ChemAxon software (InstantJChem) - Lipinski's Rule of Five, Veber Filter, Physicochemical Property Filter (Figure 3.), QikProp - ADMET Filter and Discovery Studio - Pharmacophore Filter. Due to the fact that all structures that passed through the Pharmacophore Filter were neither present in the commercial databases offered by Asinex nor by Life Chemicals company, the Similarity Search was performed and the VS protocol was re-applied from the beginning. Then, the structures were docked into four different receptor models (Maestro; Figure 4.) and those with the highest scores underwent visual inspection. Finally, 30 compounds were ordered to determine their affinity towards 5-HT$_6$ receptor.

Acknowledgements

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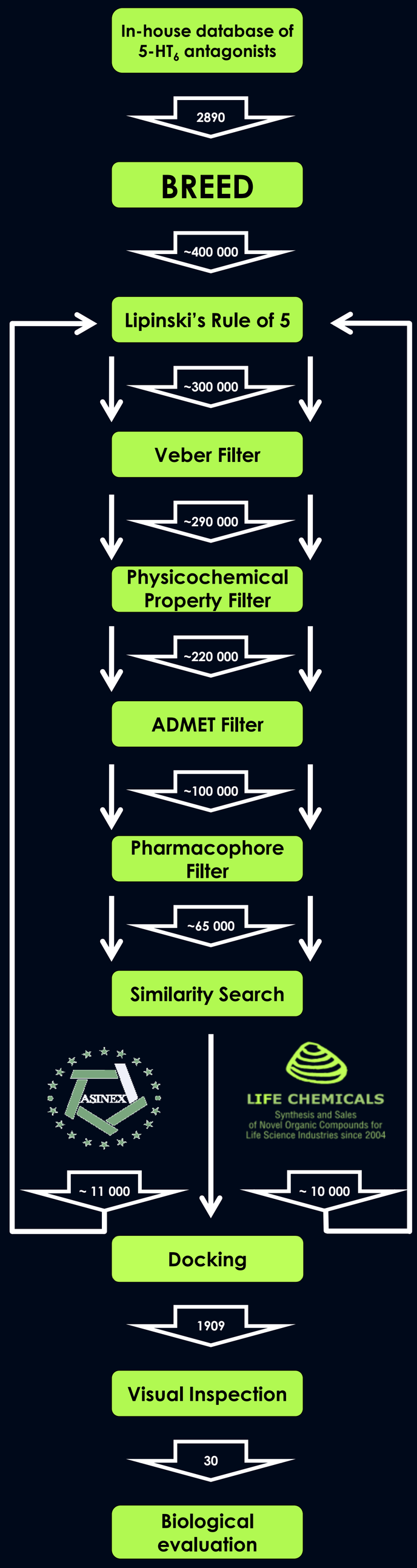

Figure 1. A scheme of the multi-step virtual screening protocol.

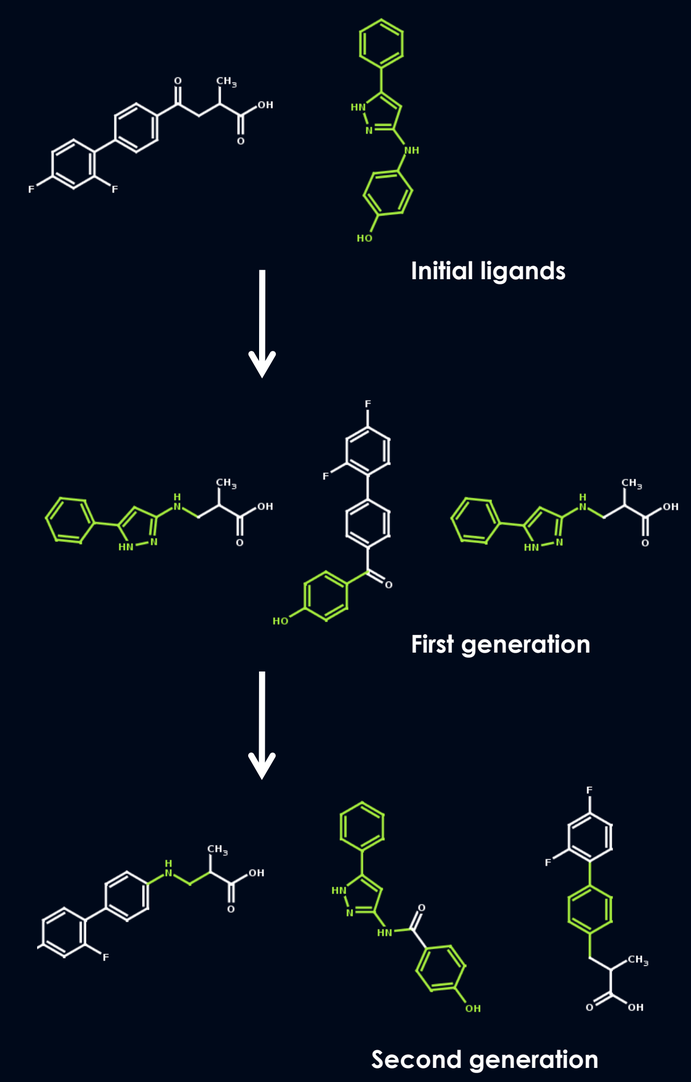

Figure 2. Illustration of generation of new ligands by BREED technique.

	CdId	Structure	Mol Weight	Formula	Breed score	Lipinski rule of 5	Veber filter	Strongest basic pKa
1	1		405,51	C23H23N3O2S	0,00	☑	☑	9,22
2	2		549,66	C27H27N5O4S2	1,43	☑	☑	9,26
3	3		563,69	C28H29N5O4S2	1,43	☑	☑	9,26
4	4		604,53	C26H23Cl2N5O4S2	1,43	☑	☑	9,26

Figure 3. Filtering of structures with the use of InstantJChem.

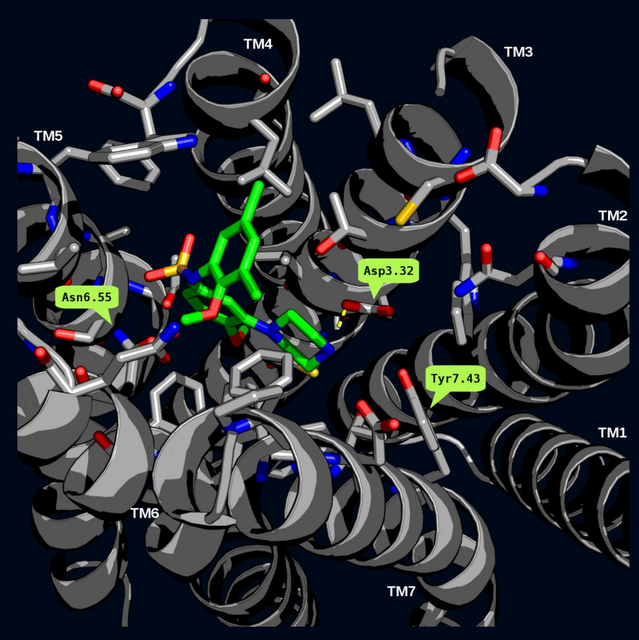

Figure 4. Visualisation of an exemplary ligand docked into the 5-HT$_6$ receptor binding site.

References

[1] Schwaighofer, A.; Schroeter, T.; Mika, S.; Blanchard, G. Comb. Chem. *High Throughput Screen.*, **12**, 453, (2009).

[2] Geppert, H.; Vogt, M.; Bajorath, J. *J. Chem. Inf. Model.*, **50**, 205, (2010).

[3] Bhatt, S.; Chaudhary, S.; Mahesh, R.; Gautam, B.; Jindal, A. *Int. J .Pharm. Pharm. Sci*.**1**, 7, (2010).

[4] Pierce, A.; Rao, G.; Bemis, G. *J. Med. Chem*. **47**, 2768, (2004).

[5] Kurczab, R.; Nowak, M.; Chilmonczyk, Z.; Sylte, I.; Bojarski, A. J. *Bioorg Med. Chem. Lett*., **8**, 2465, (2010)