Application of interaction patterns to discriminate ligand preference to target/antitarget protein

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Introduction

SIFts (Structural Interaction Fingerprints) are precise and rapid tool for binding site description. In this research, SIFt describing physical ligand-protein interactions consists of 9-bit fragments providing information with residues and type of interaction. A collection of such fingerprints is then merged into an averaged string showing frequencies of occurrence of each interaction.

In this project, interaction patterns are generated for active (Ki < 10 nM) and inactive (Ki > 1000 nM) ligands docked into our target (5-HT6R) and antitarget (H1R) receptor structure. Each set of compounds consisted of 250 structures.
Having those interaction profiles, we compare them with SIFt fingerprints produced for our test set. Basing on complementarity between those two we can search compounds collections for potential high-affinity ligands of our target and low affinity for antitarget.

Fingerprint preparation

The fist step of our study, was generating fingerprints for our target and antitarget structures. Two homology models of 5-HT6 receptor, based on different tamplates (A2A - PDB ID:3QAK, and CXCR4 - PDB ID: 3OE0), and crystal structure of H1 receptor (PDB ID: 3RZE), were used for modeling target and antitarget, respectively (Fig. 2). Next, known active ligands were docked to virtual receptors structures.
Moreover, 8 known selective 5-HT_6R/H1R compounds, retrieved from ChemBL database, were docked to all receptor structures. Six of the ligands did not return docking poses.

SIFts enabled recognition of residues involved in ligand binding and furthermore, types of interactions between specific residues. In this research nine bits were used to describe those associations: any contact, backbone, side chain, polar, hydrophobic, hydrogen bond donor/acceptor, aromatic and charged (Fig. 3). The fingerprints were produced for every ligand-receptor complex retrieved.

SIFt analysis

Crucial stage in interaction analysis was constructing SIFt profiles. For each receptor structure used an averaged SIFts were generated for ligand docking poses. Structural interaction fingerprints of selective ligands were then compared to such prepared profiles. Implemented workflow is focused on finding inconsistencies between profiles and investigated ligand poses. A home made tool allowed us to make such comparison in the automated manner, pointing out residues not fitting the SIFt profile

Results and conclusions

Comparing the single SIFts with consensual profiles of target and antitarget allowed us to reflect receptor preference of selective ligands. The compounds were highly compatible with 5-HT_6R binding mode, besides two peripheral residues forming the binding pocket. On the other hand, differences between antitarget interaction profile and test compounds were much more significant: increased number of mismatching amino acids (present in SIFt but not in profile) and its location (Fig 4).

Presented method may be useful in discriminating ligand preference to receptor in easy and automated way. However, further evaluation of method, would allow to investigate its capabilities and limitations.

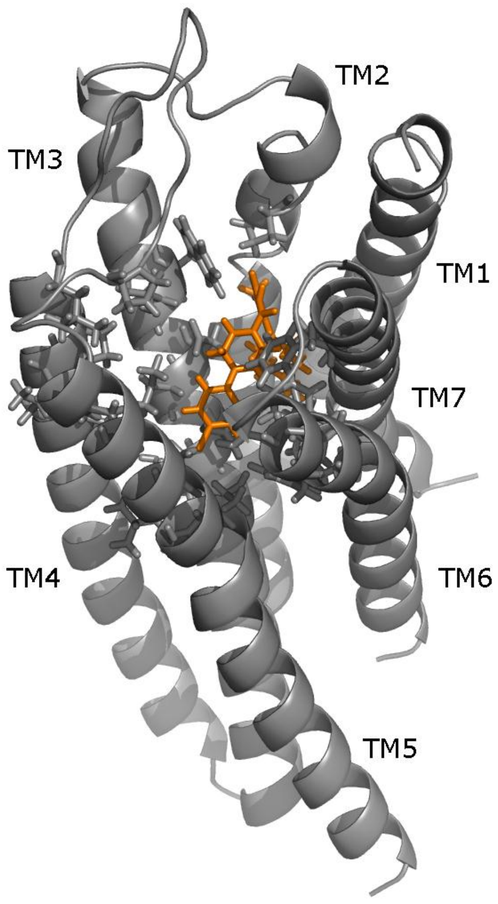


Figure 1. Visualization of 5-HT6 receptor model created on CXCR4 template, with docked active ligand (CHEMBL372453).

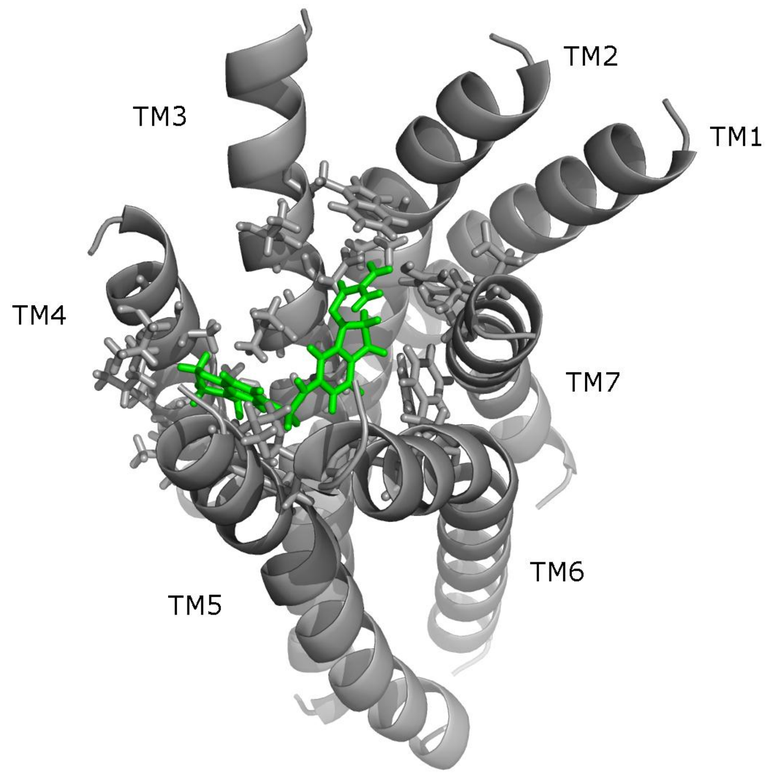
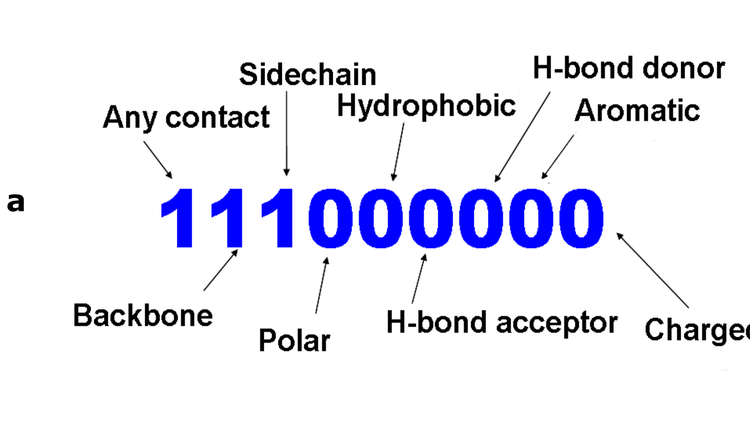
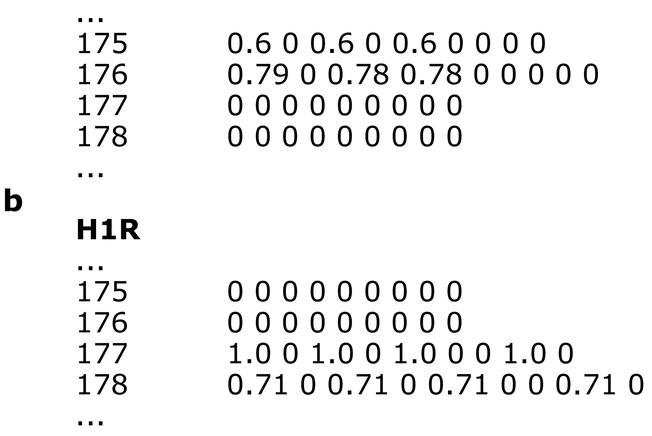


Figure 2. Visualization of H1 crystal structure, with docked active ligand (CHEMBL64067).





5-HT_6R (CXCR4 tempate)

...	
175	0.6 0 0.6 0 0.6 0 0 0 0
176	0.79 0 0.78 0.78 0 0 0 0 0
177	0 0 0 0 0 0 0 0 0
178	0 0 0 0 0 0 0 0 0
...	

H1R

...	
175	0 0 0 0 0 0 0 0 0
176	0 0 0 0 0 0 0 0 0
177	1.0 0 1.0 0 1.0 0 0 1.0 0
178	0.71 0 0.71 0 0.71 0 0 0.71 0
...	

Figure 3. **(a)** Fragment of SIFt describing bit positions for individual ligand-residue interactions. **(b)** Comparison of SIFt profiles.

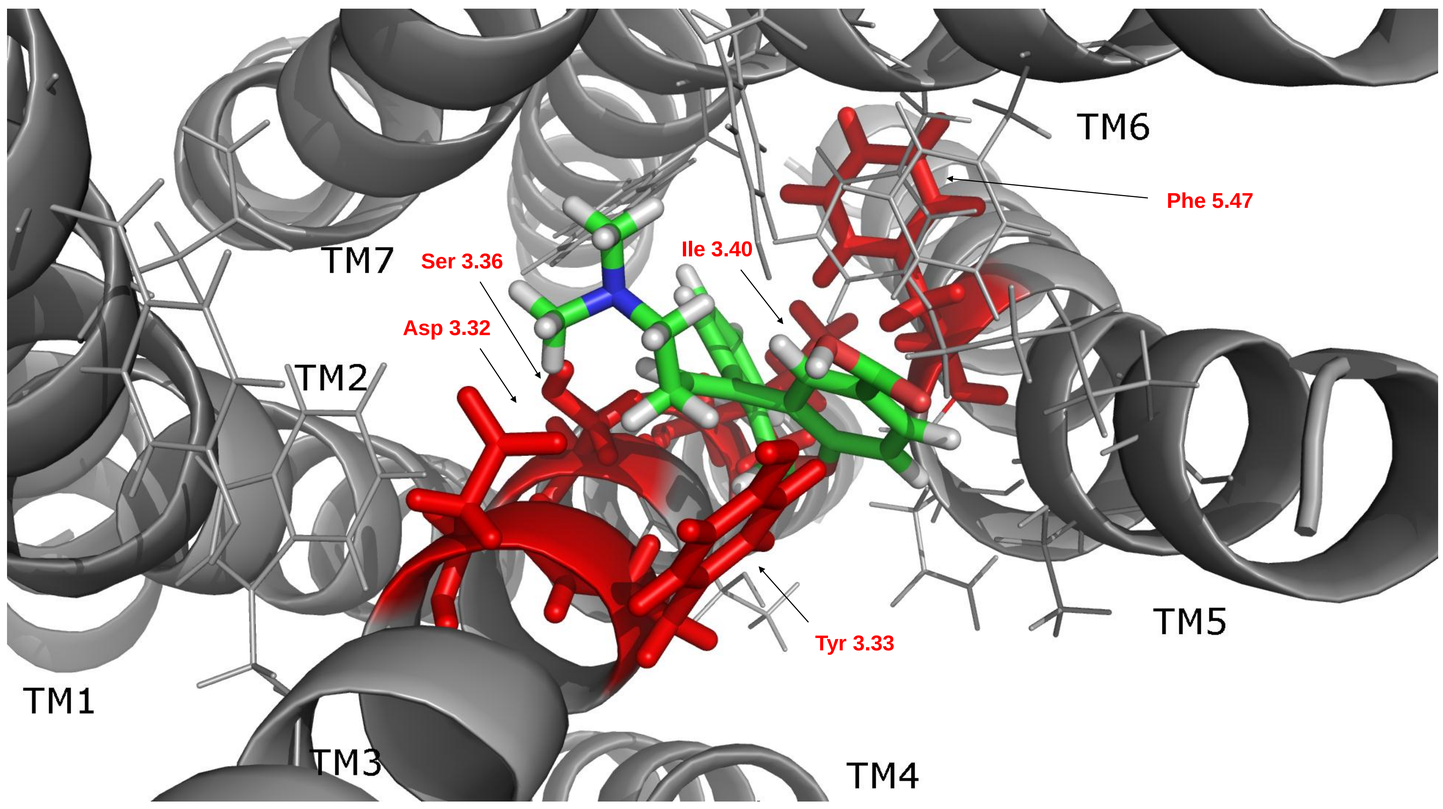


Figure 4. Visualization of H1 receptor (antitarget) with 5-HT_6 active/H1 inactive ligand docked (CHEMBL476109). SIFt for H1 profile is shown as grey lines, mismatching residues (interacting but not in profile) are shown in red; aminoacids are numbered in Ballesteros-Weinstein notation.

Literature

(1)Deng Z, Chuaqui C, Singh J *„Structural Interaction Fingerprint (SIFt): A Novel Method for Analyzing Three-Dimensional Protein-Ligand Binding Interactions”,* J. Med. Chem. 2004, 47, 337 -344
(2)Mordalski S, Kosciolek T, Kristiansen K, Sylte I, Bojarski A J *„Protein binding site analysis by means of Structural Interaction Fingerprint patterns”*

Acknowledgments

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