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BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS  
FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY

# In silico methodologies aiding fragment-based drug discovery

Thesis summary

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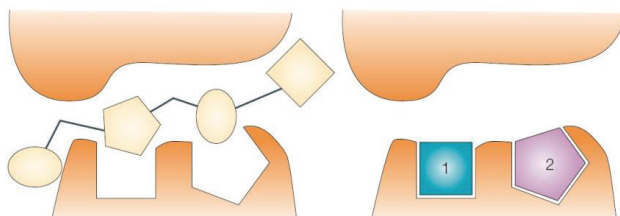
2014



# 1. Introduction and background

Fighting and preventing diseases and developing solutions for unmet medical needs are the primary goals of pharmaceutical research. However, the drug discovery process is lengthy and costly and it is burdened by high attrition rates. The analysis of recently patented compounds and launched drugs revealed that physico-chemical parameters have a great impact on pharmacokinetic and pharmacodynamic properties of drugs, one of the major reasons of attrition.<sup>1</sup> It was shown that compounds have increased molecular mass and lipophilicity, termed 'molecular obesity', which is associated with lower oral absorption, adverse effects and *in vivo* toxicology liabilities through the promiscuity of the compounds.

Fragment-based drug discovery (FBDD) is a recently emerged and quickly spreading technology due to its speed and inherent ability to control the various parameters important in the multi-dimensional optimization process of drug discovery.<sup>2</sup> FBDD is now seen as a method capable of reducing attrition and providing drug candidates even for new biological targets that were previously thought to be intractable. It involves the selection, screening and optimization of molecular fragments. Fragments are polar compounds of low molecular weight and low complexity that are able to make optimal interactions with the protein target, thus being better starting points for medicinal chemistry optimization as opposed to lead-like or drug-like molecules identified in high-throughput screening (Fig. 1). However, due to the intrinsically lower



**Figure 1.** A low quality HTS hit (left) and high quality fragment hits (right).<sup>2</sup>

<sup>1</sup> Leeson, P.D., St-Gallay, S.A. *Nat. Rev. Drug Discov.* **2011**, 10, 749.

<sup>2</sup> Rees, D.C., Congreve, M., Murray, C.W., Carr, R. *Nat. Rev. Drug Discov.* **2004**, 3, 660.

affinity specialized biophysical screening methods with usually lower throughput and a different mindset in their optimization is needed. Vemurafenib, the first approved drug discovered using FBDD, was marketed in 2011 and its idea-to-approval time was only 6 years.<sup>3</sup>

Since most of the reported fragment optimization projects utilize structural information of the biological target obtained by X-ray diffraction or NMR spectroscopy, computer-aided drug design (CADD) methodologies are also increasingly useful to support and guide fragment hit identification and optimization. *In silico* methods can be effectively used in all phases of FBDD starting from fragment selection for screening, prioritization of hits to structure-guided optimization from hits to leads and drug candidates.

Computational methods are used to analyze data from screening campaigns and to set up rules for fragment library selection from corporate or vendor compound collections such as the widely used 'Rule of Three' (MW < 300 Da, logP < 3, number of H-bond donors and acceptors ≤ 3) proposed by Congreve et al.<sup>4</sup> Retrosynthetic and fragment frequency analyses of natural products or marketed drugs can enrich fragment libraries with privileged scaffolds and attractive chemical structures for medicinal chemistry optimization. Full chemical space enumeration up to 17 non-hydrogen atoms has also facilitated *de novo* fragment-based drug discovery.

As experimental fragment screening usually faces throughput limitations, efficient methods for virtual fragment screening are also needed in order to enrich biologically active fragments in the screened library. Molecular docking is the usual method of choice for virtual fragment screening. It has been demonstrated that currently available docking software have sufficient sampling capabilities to generate experimentally observed fragment binding modes, however, scoring errors often preclude selection of the right one from the pool of nearly isoenergetic poses.<sup>5</sup> To overcome this and to improve binding affinity ranking, more computationally intensive rescoring methods have been applied in FBDD. Also protein flexibility

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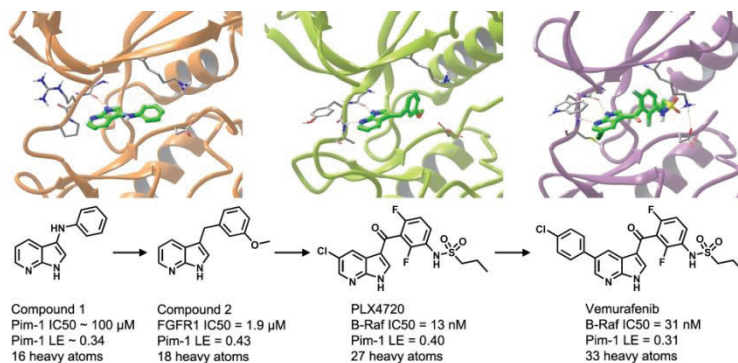
<sup>3</sup> Tsai, J., Lee, J.T., Wang, W. et al. *Proc. Natl. Acad. Sci. USA* **2008**, 105, 3041.

<sup>4</sup> Congreve, M., Carr, R., Murray, C., Jhoti, H. *Drug Discov. Today* **2003**, 8, 876.

<sup>5</sup> Sándor, M., Kiss, R., Keserű, G.M. *J. Chem. Inf. Model.* **2010**, 50, 1165.

is known to play an important role in fragment binding, however, its effect has not been extensively investigated in virtual fragment screening. There are numerous reports for successful virtual fragment screening campaigns against enzyme targets with hit rates up to around 50%, and recently de Graaf et al.<sup>6</sup> and Carlsson et al.<sup>7</sup> demonstrated successful virtual fragment screening campaigns against G protein-coupled receptors (GPCRs) as well, namely the histamine H<sub>1</sub> and H<sub>3</sub> receptors and the adenosine A<sub>2A</sub> receptor. GPCRs are a family of membrane embedded proteins featuring a seven-transmembrane alpha-helical fold and recognizing a wide variety of interacting partners outside the cell ranging from photons and ions to small molecules, lipids, peptide hormones, and other proteins. Recent elucidation of GPCR structures made it possible to apply structure-based computational modeling to this important pharmaceutical target family and enabled comparative modeling of yet unknown GPCR structures.

Fragment optimization is also usually guided by structure-based computational methods. As an example, the optimization of Vemurafenib is shown in Fig. 2. The iterative process of *de novo* FBDD generally consists of enumeration of the possible chemical space around the seed fragment and scoring of the resulting virtual



**Figure 2.** Optimization of Vemurafenib from the azaindole hit by growing.<sup>3</sup>

<sup>6</sup> de Graaf, C., Kooistra, A.J., Vischer, H.F. et al. *J. Med. Chem.* **2011**, 54, 8195.

<sup>7</sup> Chen, D., Ranganathan, A., Ijzerman, A.P., Siegal, G., Carlsson, J. *J. Chem. Inf. Model.* **2013**, 53, 2701.

compounds using a suitable fitness function, which can incorporate affinity, synthetic accessibility, diversity, novelty, druglikeness and ADMET property predictions. From the two main fragment optimization strategies, growing (of a single fragment hit group-by-group) and linking (of multiple experimentally identified proximally bound fragments), the latter seems to face more synthetic challenges and thus computational methods guiding this process are especially needed. Simple ligand efficiency and lipophilic efficiency metrics predictive of pharmacokinetic and safety liabilities have also been devised to aid the control of molecular parameters during optimization. LE (the contribution of each heavy atom to the binding free energy), LLE (the separation between binding affinity and logP) and LELP (the ratio of logP and LE) are among the most widely used and predictive metrics for successful optimization.<sup>8</sup>

Working in the CADD team in the Discovery Chemistry Laboratory at Gedeon Richter Plc. I studied available and developed new computational methodologies useful for aiding fragment-based drug discovery focusing my work on GPCR fragment hit identification and optimization.

In the first part of the work my aim was to evaluate different protocols for fragment virtual screening on GPCR targets. This work started with method development on small molecule data sets and the results were subsequently used in a fragment screening setup. Since structural information on GPCRs is still restricted to a few targets, the use of experimentally determined structures as well as homology models in virtual small molecule and fragment screening was evaluated. The effect of incorporating protein conformational flexibility into both methodologies was also studied and compared to using a single structure for virtual screening. While method development in the small molecule setup was performed on retrospective data sets, prospective fragment screening was carried out and the obtained fragment hits can be used in a further work as starting points for optimization.

In the second part of the work my aim was to study computational methodologies applicable for finding starting points

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<sup>8</sup> Hopkins, A.L., Keserű, G.M., Leeson, P.D., Rees, D.C., Reynolds, C.H. *Nat. Rev. Drug Discov.* **2014**, 13, 105.

for fragment linking. Therefore besides primary site (or hot spot) fragment screening I evaluated the performance of a sequential docking protocol for identifying fragments bound in possible secondary sites of proteins. This work also started with method development on a small molecule data set and when results were encouraging, a fragment data set was also compiled and performance of the protocol was tested. During model development another potentially interesting application emerged, namely the prediction of cytochrome P450 metabolic enzyme activators. Taking second-site fragment screening forward I have used the protocol to identify fragments for linking inside the binding pocket of the D<sub>3</sub> dopamine receptor and also assessed the selectivity of the synthesized compounds against the D<sub>2</sub> dopamine receptor on a structural basis.

## 2. Methods

In the first part of the work the homology models of the human histamine H<sub>4</sub> and the serotonin 5HT<sub>6</sub> receptors were constructed based on suitable structural templates from the Protein Data Bank using the Prime module in the Schrödinger modeling software suite. Literature homology models and X-ray structures of the dopamine D<sub>3</sub> and the chemokine CXCR<sub>4</sub> receptors were prepared for docking using the Protein Preparation Wizard in the Schrödinger suite, binding site parameters were calculated using SiteMap. They were also used as starting structures for all-atom membrane embedded unbiased molecular dynamics simulation using the NAMD software and the trajectories were analyzed and clustered using the AmberTools package. The starting structures and representative frames from the simulation were evaluated in terms of retrospective docking-based virtual screening enrichment over the GDD (GPCR Decoy Database) ligand-decoy set both as single structures and in ensemble docking paradigm. Docking was performed using the Glide module of the Schrödinger suite. A fragment library was selected from the Gedeon Richter proprietary compound collection using ChemAxon cheminformatics tools and generally accepted fragment criteria. These were used in prospective virtual fragment screening against

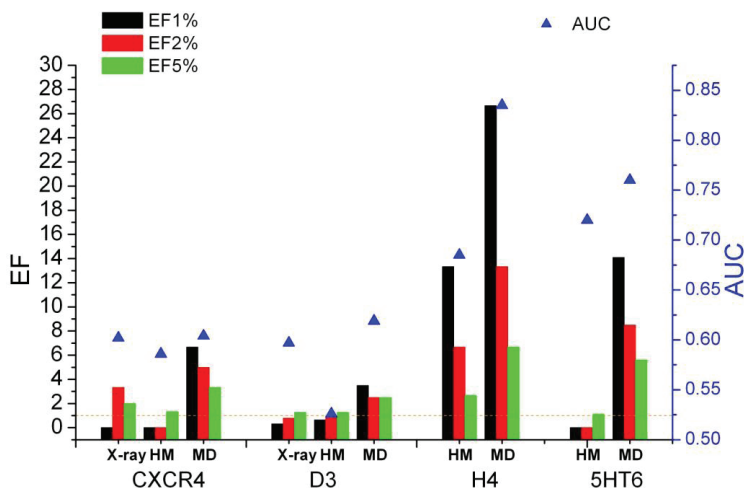
the same structural models of the dopamine D<sub>3</sub> and the histamine H<sub>4</sub> receptors both in single structure and in ensemble docking paradigm. Virtual fragment hits were measured in radioligand binding assays and results were analyzed in terms of validated hit rates, ligand efficiency metrics, novelty and binding mode robustness.

In the second part of the work ternary and higher order protein-ligand complexes were compiled from the Protein Data Bank using a self-written script, and structures of protein - linked fragment complexes were also compiled from the literature. Structures were prepared using the Protein Preparation Wizard. A simple sequential docking protocol using the Glide module was set up using the Python scripting API of the Schrödinger package. The protocol was used to dock multiple drug-like and subsequently fragment-like ligands into the protein structures and the results were analyzed in terms of docking success rates, self-docking and cross-docking RMSDs of ligand heavy atom positions and visual inspection of the docked binding modes. Finally, the protocol was used to dock two focused virtual fragment libraries assembled from the Gedeon Richter compound collection into the binding site of the dopamine D<sub>3</sub> receptor as well as a homology model of the dopamine D<sub>2</sub> receptor constructed using the Prime module. Best scoring fragments were virtually linked and the linked compounds were synthesized and tested in radioligand binding assays. Their binding interactions and observed selectivities were assessed on a structural basis.

## 3. Results

### 3.1 Virtual screening for orthosteric ligands

The performance of different receptor models was assessed by retrospective enrichment studies on the GDD data set using enrichment factor (EF), receiver operating characteristic (ROC), and area under the ROC curve (AUC) values for the X-ray structures, homology models and approximately 30-30 systematically selected as well as clustering-based representative receptor conformations from the MD trajectories of all four investigated GPCR targets.



**Figure 3.** Enrichment factors (colored bars) and AUC values (blue triangles) for the CXCR<sub>4</sub>, D<sub>3</sub>, H<sub>4</sub>, and 5HT<sub>6</sub> structures obtained with X-ray, homology model (HM), and the best molecular dynamics frame (MD).

As can be seen from Fig. 3 the best single structures from the MD simulation were always superior to the initial models, regardless of the target and the evaluation method (EF or AUC). Among the initial structures only the H<sub>4</sub> homology model was able to select actives from decoys with an enrichment factor of 13.3 at 1% of the ranked ligand set. It is suggested that during MD simulation a “consensus binding pocket” is formed, which is not entirely refined around the original ligand but can host and score multiple diverse active chemotypes. The robustness of the enrichment study was tested using two sample t-tests among the homology models, X-ray structures, and best MD models after dividing the original ligand set into random subsets containing one third of the actives and one third of the decoys ten times. The difference between both the homology model and the X-ray structure compared to the best MD snapshot was significant for the D<sub>3</sub> case and for the H<sub>4</sub>, CXCR<sub>4</sub> and 5HT<sub>6</sub> cases the difference between the homology model and the MD frame was significant. The difference between overall enrichments among the target classes are similar to those found by others in the literature. In order to assess the relationship between the binding

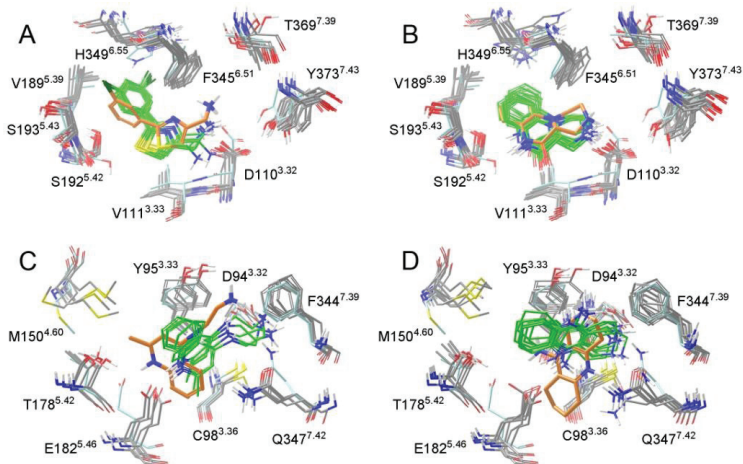
site properties and enrichment values, SiteMap descriptors were generated for all the MD frames but no strong correlation was found between these descriptors and enrichment. Also clustering and systematic MD frame selections showed similar performance and ensemble evaluation of the docking results using all the possible receptor combinations of an ensemble size up to 6 did not significantly improve the outcome.

Next, prospective virtual fragment screening of the Gedeon Richter fragment library was performed against the available structural models of the dopamine D<sub>3</sub> receptor and the histamine H<sub>4</sub> receptor. For the single structures it was straightforward to select the top 50 fragments by GlideScore ranking for biological testing. For ensemble docking two different data fusion methods were considered. It was confirmed that both rank-by-rank and consensus scoring schemes provide highly overlapping selection of top fragments and approximately 50 fragments were subjected to biological testing. In the case of D<sub>3</sub> 25 virtual hits provided higher than 20% inhibition at 10 μM, corresponding to a combined hit rate of 27%. Out of these 9 came from the crystal structure docking run (18% hit rate) and 18 from the ensemble docking run (32% hit rate)

**Table 1.** Experimental binding affinities of selected fragment hits of the D<sub>3</sub> and H<sub>4</sub> receptor and their LE and LELP values. The origin of the hits is indicated by + signs.

cpd	structure	target	K <sub>i</sub> / μM	LE	LELP	XRD/HM	MD
1		D <sub>3</sub>	0.17	0.66	3.7		+
2		D <sub>3</sub>	0.50	0.57	1.2	+	+
4		D <sub>3</sub>	1.1	0.63	0.7		+
10		H <sub>4</sub>	12.6	0.45	2.1	+	
15		H <sub>4</sub>	32.9	0.36	5.4	+	+
18		H <sub>4</sub>	75.1	0.37	2.3		+

with only 2 overlapping compounds. Compounds **2** and **4** were the most favorable in terms of ligand efficiency ( $LE = -RT\ln(K_i)/HA$ , higher than 0.3 is desired) and lipophilic efficiency ( $LELP = \text{clogP}/LE$ , lower than 10 is desired). Similarity searches in the ChEMBL bioactivity database also revealed them to be novel chemotypes for dopamine receptors. See Table 1 for summarized data. In the case of  $H_4$  somewhat fewer, 15 virtual hits provided higher than 20% inhibition in the biological assay at 10  $\mu\text{M}$ , corresponding to a combined hit rate of 18%. Out of these 11 came from the homology model docking run (22% hit rate) and 8 from the ensemble docking run (16% hit rate) with 4 overlapping compounds. The lower hit rate and the lower binding affinities indicate a difference in the chemical tractability of the two receptors. Fragments **10** and **18** showed favorable LE and LELP values and **15** and **18** proved to be novel chemotypes for histamine receptors. Both X-ray structure and homology model were capable of providing useful hits in virtual screening, and in this particular case the homology model performed even better than the crystal structure. The superiority of the ensemble docking approach was not witnessed in this work. Predicted binding modes of selected hits are depicted in Fig. 4.

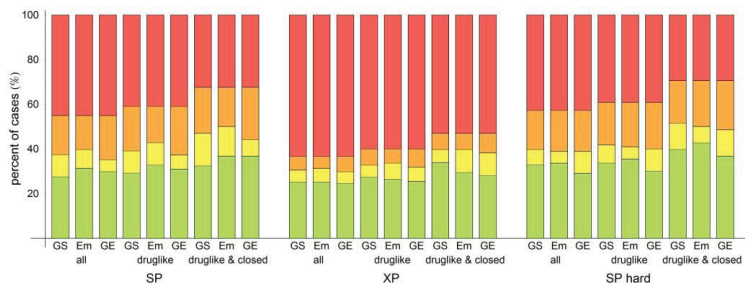


**Figure 4.** Interaction modes of selected fragment hits. A) **1** and B) **2** in the  $D_3$  binding pocket; C) **10** and D) **18** in the  $H_4$  binding pocket. Single structure docked fragment poses are shown in orange and ensemble docked poses in green skeletons.

In the case of the D<sub>3</sub> receptor it was found that docked poses of the active fragments provided very similar binding modes in multiple representative receptor conformations from MD simulation and also the X-ray structure. In the case of the H<sub>4</sub> receptor higher variability among docked poses in the ensemble approach and homology model docking was seen, which is in line with the lower affinities and ligand efficiencies of the ligands.

### 3.2 Virtual screening for secondary site ligands

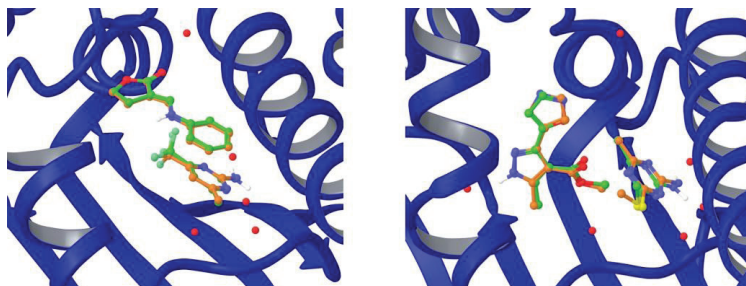
In this part of the work performance of a sequential docking protocol was evaluated for modeling cooperatively bound ligands in the binding sites of 129 ternary and higher order protein complexes compiled from the Protein Data Bank. It was found that mean RMSD of top poses were somewhat higher in this data set than those for single ligand docking as expected for docking ligands significantly smaller than their respective binding sites. Success rate of the first docking step was 78% (a pose with RMSD < 2.0 Å to the experimental binding mode is found) and it was found that if the first ligand was docked successfully, then the second docking step was also successful in 70% of the cases. If the first RMSD was over 2.0 Å, 86% of the second ligands also failed to dock successfully. The expectation value of the number of successful docking runs was 1.37, meaning that docking of more than two ligands was highly unlikely to give reliable results. Two experimental binding conformations were recovered in 55% of the cases. The impact of using different scoring functions in docking as well as ligand and binding site properties on the success rates were investigated. GlideScore (GS), Emodel (Em) and Glide Energy (GE) scoring functions with normal precision docking (SP), extra precision (XP) and SP hard (no scaling of the van der Waals radii of nonpolar ligand atoms) protocols were investigated. Druglikeness of ligands was assessed by Lipinski's Rule of Five (MW < 500 Da, logP < 5, number of H-bond donors and acceptors ≤ 5). Binding site enclosure was assessed by the *enclosure* parameter calculated by SiteMap. A site with *enclosure* > 0.78 was classified as closed. Success rates of docking two ligands with different protocols are shown in Fig. 5.



**Figure 5.** Cumulative success rates obtained in at least two consecutive docking steps with different protocols and subsets. Top pose success rates in green, top 3 pose in yellow, all poses in orange, unsuccessful in red.

The extra precision method performed inferior to the default SP protocol, and the SP hard protocol provided only slight improvements. Drug-like ligands performed only slightly better in multiple docking settings, but considering only drug-like ligands in closed binding sites the success rates increased to 68%.

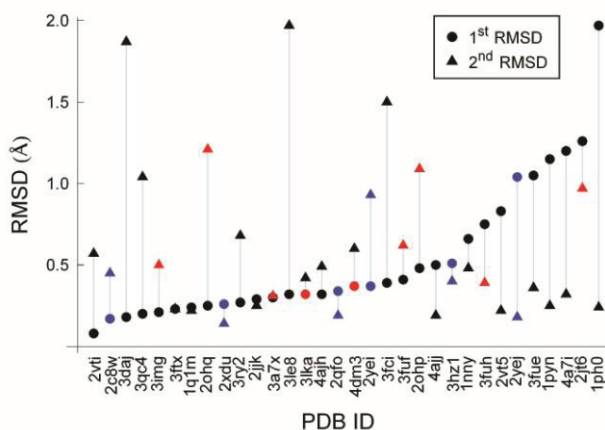
Two pharmacologically relevant subsets of the data set were investigated in more detail: the cytochrome P450 enzyme family, which is responsible for drug metabolism and mediates the majority of drug-drug interactions and the heat shock protein 90- $\alpha$  (HSP90) chaperone, which is investigated as an anti-cancer target. The former were represented by 9 structures in the data set and the latter by 5 fragment-bound complexes. In the cytochrome P450 subset the SP and SP hard protocols with Emodel scoring provided successful docked poses for all except one ligand. In the HSP90



**Figure 6.** Representative binding modes of ligands in HSP90 complexes (left: 2qfo, right: 2yej). Docked ligand is shown in green skeleton, co-crystallized ligand in orange skeleton, waters are shown as red spheres.

subset all fragment-like ligands could be docked with RMSDs lower than or close to 1 Å but only if conserved water molecules from the crystal structures were retained. It is also known from the literature that these waters play an important role in mediating protein-ligand interactions. Representative docking results are shown in Fig. 6.

Encouraged by the results of the previous study a fragment data set was also compiled: 32 complex structures of cooperatively bound or synthetically linked fragments were collected from the literature and the sequential docking protocol was applied to the two fragment ligands. Self-docking results are shown in Fig. 7. As can be

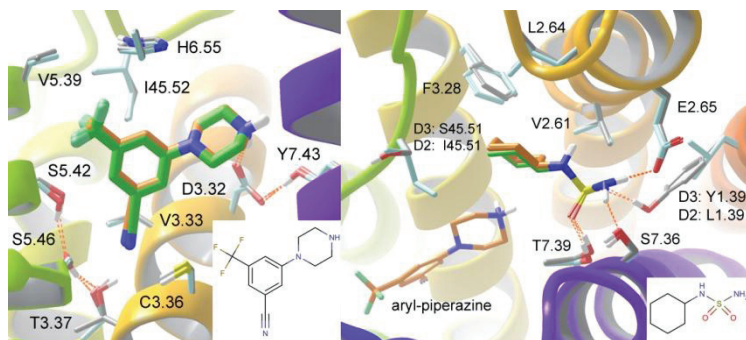


**Figure 7.** Multiple fragment docking results obtained by sequential docking. Plot markers are colored red for docking steps with scoring errors ( $E_{\text{model rank}} > 1$ ) and blue for complexes where structural waters were included in grid generation.

seen, the default sampling of Glide SP was sufficient in all of the examples: a pose was always found with RMSD < 2.0 Å to the experimental binding conformation. Furthermore, in 49 out of the 64 docking steps (77%) a pose with RMSD < 1.0 Å, and in 39 cases (59%) a pose with RMSD < 0.5 Å were found. High docking accuracy is especially important for virtual linker design in fragment optimization. In the first docking step only 2 fragments were not ranked top out of the 32 examples (6%). In the second docking step, there were 7 cases with scoring error (22%). It was shown that this lower success rate in the second docking step can originate from the

lower specificity of the secondary binding sites as opposed to primary ‘hot spot’ sites. Based on the case studies multiple docking was proposed to aid X-ray structure elucidation when fragments are screened in cocktails. Cross-docking simulations were performed for 7 targets. Performance for the first fragments was only slightly poorer compared to self-docking, while docking of the second fragments proved to be more challenging: 75% of the docking runs were successful and for 46% a pose with RMSD < 1.0 Å was found.

Finally the sequential docking methodology was applied for fragment docking and linking to the D<sub>3</sub> crystal structure and a D<sub>2</sub> homology model since selective D<sub>3</sub> antagonists or partial agonists are investigated in the treatment of schizophrenia, depression and bipolar mania. Docking of the first focused library of basic fragments produced similar binding modes as found by others in the literature (see Fig. 8), identical in D<sub>3</sub> and D<sub>2</sub> in line with the conserved nature of the primary binding site. Among the fragments docked to the secondary binding site a cyclohexylaminosulfonamide fragment produced a very robust binding mode and seemed to feature a hydrogen bond with Tyr1.39 in the D<sub>3</sub> crystal structure, which was not present in the D<sub>2</sub> homology model, as the corresponding amino acid is a leucine (shown in Fig. 8). Three linked molecules were synthesized and indeed when this fragment was linked to the primary site aryl-piperazine, the resulting compound showed high affinity and 55-fold selectivity towards the D<sub>3</sub> receptor.



**Figure 8.** Binding modes of the top primary (left) and secondary site fragments (right). D<sub>3</sub> and D<sub>2</sub> binding sites are overlaid in grey and light blue carbons respectively and docked poses of the ligands in orange and green carbons respectively.

## 4. Thesis points

1) I have shown that single frames selected by systematic sampling or clustering from all-atom POPC membrane-embedded unbiased ns timescale molecular dynamics simulation trajectories using the ff99SB+GAFF force field outperform X-ray structures and homology models in virtual screening against G protein-coupled receptors (GPCRs) and that ensemble evaluation does not further improve virtual screening performance [T1].

2) I have shown that GPCR X-ray structures, homology models and structural ensembles from molecular dynamics trajectories can be used in prospective virtual fragment screening. I have identified novel GPCR fragment starting points for medicinal chemistry optimization with good physico-chemical properties and ligand efficiencies using virtual fragment screening [T2].

3) I developed and validated a novel sequential docking methodology for identifying starting points for fragment linking using a data set of 129 X-ray structures with multiple bound ligands. In the best protocol 68 % of the experimental structures could be reproduced and even better performance was achieved for pharmacologically relevant cytochrome P450 structures and fragment-bound structures of the HSP90 protein [T3].

4) I found that the developed sequential docking methodology has outstanding performance on fragments using a data set of 32 X-ray structures with cooperatively bound or linked fragments. I have shown that sampling performance is sufficient for multiple fragment docking but fragment scoring could be improved for less specific second site binders, in line with the 'hot spot' hypothesis [T4].

5) I demonstrated the applicability of the sequential fragment docking methodology in a prospective setup and identified fragment hits for linking inside the binding pocket of a GPCR, namely the human dopamine D<sub>3</sub> receptor. The three synthesized linked compounds have high affinity to the D<sub>3</sub> receptor and their selectivity against the dopamine D<sub>2</sub> receptor subtype could be explained on a structural basis [T5].

## 5. Applications

Virtual fragment screening against GPCR targets has not yet been extensively investigated, only a few reports can be found in the literature. In the present work I have investigated different protocols for prospective virtual fragment screening and the results can be applied by others in the scientific community when designing fragment screening projects. I have shown that not only X-ray structures but also homology models of GPCRs based on reasonably close templates are also useful for virtual fragment screening, which is an important fact given the still low structural coverage of the GPCR protein family. The novel fragment ligands of the dopamine D<sub>3</sub> and histamine H<sub>4</sub> receptors identified in the present work have favorable biological and physico-chemical properties and can be progressed to fragment optimization projects.

Multiple ligand docking is an interesting field since present docking software can usually only handle the conformational searching of a single molecule. Attempts have been made to simultaneously perform the conformational search of multiple entities, but in the present work I have shown that a sequential docking protocol shows similar performance and requires no tweaking of the existing software. The protocol performs especially well for primary and secondary site fragment docking since there seems to be a natural order of fragment binding first to protein 'hot spots' and subsequently to secondary binding sites. These findings encourage virtual secondary site fragment screening and virtual fragment linking methodologies. As a first example I have used the methodology to design a selective D<sub>3</sub> receptor ligand by fragment linking, and this approach can be extended to further targets as well.

## 6. Publications

### 6.1 Papers

T1. Tarcsay, Á., Paragi, G., Vass, M., Jójárt, B., Bogár, F., Keserű, G.M. The impact of molecular dynamics sampling on the performance of virtual screening against GPCRs. *J. Chem. Inf. Model.* **2013**, 53, 2990-2999. (IF: 4.304)

T2. Vass, M., Schmidt, É., Horti, F., Keserű, G.M. Virtual fragment screening on GPCRs: a case study on dopamine D<sub>3</sub> and histamine H<sub>4</sub> receptors. *Eur. J. Med. Chem.* **2014**, 77, 38-46. (IF: 3.499)

T3. Vass, M., Tarcsay, Á., Keserű, G.M. Multiple ligand docking by Glide: implications for virtual second-site screening. *J. Comput. Aided Mol. Des.* **2012**, 26, 821-834. (IF: 3.172)

T4. Vass, M., Keserű, G.M. Fragments to link. A multiple docking strategy for second site binders. *MedChemComm* **2013**, 4, 510-514. (IF: 2.722)

T5. Vass, M., Ágai-Csongor, É., Horti, F., Keserű, G.M. Multiple fragment docking and linking in primary and secondary pockets of dopamine receptors. *ACS Med. Chem. Lett.* Submitted. (IF: 3.311)

### 6.2 Book chapter

1. Keserű, G.M., Makara, G., Vass, M. Fragment-based methods in drug design. in *In Silico Drug Discovery and Design: Theory, Methods, Challenges and Applications*, ed. C. Cavasotto. Taylor & Francis Group, LLC. Accepted.

### 6.3 Oral presentations

1. Vass, M., Tarcsay, Á., Keserű, G.M. Ligandumok kooperatív kötődésének *in silico* modellezése. Kémiai előadói napok **2010**, Szeged.

2. Vass, M., Tarcsay, Á., Keserű, G.M. Cooperative docking with Glide. Magyar Schrödinger Felhasználói Találkozó **2011**, Budapest.

3. Vass, M., Tarcsay, Á., Keserű, G.M. A Citokróm P450 heteroaktiváció *in silico* vizsgálata. Farmakoinetika és Gyógyszermetabolizmus Szimpózium **2012**, Galyatető.

4. Vass, M., Keserű, G.M. Multiple docking in support of the fragment linking strategy. Magyar Schrödinger Felhasználói Találkozó **2012**, Budapest.

5. Vass, M., Bogár, F., Jójárt, B., Keserű, G.M., Paragi, G., Tarcsay, Á. Molekuladinamikai szimulációval előállított fehérje konformációk alkalmazása G-fehérje kapcsolt receptorokon végzett virtuális szűrésekben. KeMoMo-QSAR szimpózium **2013**, Szeged.

6. Vass, M., Keserű, G.M., Schmidt, É., Horti, F. Virtuális fragmens szűrés technikák aminerg G-fehérje kapcsolt receptorokon. KeMoMo-QSAR szimpózium **2014**, Szeged.

### 6.4 Poster

1. Vass, M., Keserű, G.M. Multiple fragment docking supporting the linking strategy. Fragments **2013**, STFC Rutherford Appleton Laboratory, Oxfordshire, UK.



