A Computational Platform For Fragment Evolution

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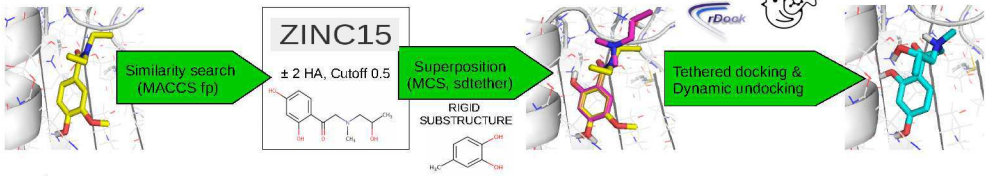
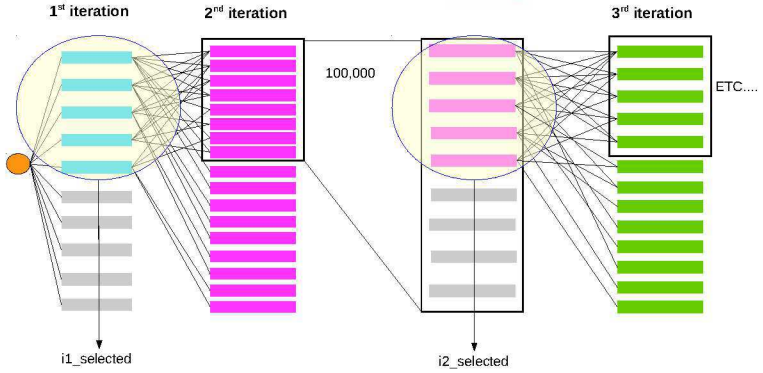
Background and motivation

Fragment-based drug design has gained ground as a hit identification strategy and is increasingly being used by researchers in industry and academia. With relatively small collections, fragment screening explores a large portion of chemical space and achieves higher hit rates than traditional drug-like collections[1]. Fragments can form optimal interactions with particular subpockets and attain better ligand efficiencies than the bigger HTS hits[1]. However, due to their size, the binding potency is usually weak, leading to the challenge of evolving it to a more potent drug-like compound. The pool of synthetically accessible and drug-like compounds that the medicinal chemists have to explore is vast and the solution is not always straightforward.

Workflow

Given an initial fragment, for which the binding mode is known (e.g. by X-ray crystallography), the protocol searches in a database for molecules that are chemically related and slightly bigger in size. These are then tethered docked to the target protein to identify those that are complementary. Dynamic undocking[2] is then applied to filter out false positives and the top candidates are selected. The process is repeated until drug-sized molecules are attained.





Aim

Here we present an automatic protocol to facilitate and direct the process of fragment evolution through navigation of the commercial chemical space, allowing at the same time some scaffold hopping to explore new molecular structures while still maintaining the important interactions intact.

Conclusions

- We have designed, implemented and validated the first version of an automated platform for fragment evolution.
- The platform can evolve a fragment hit maintaining the important interactions and binding mode, while allowing scaffold hopping.
- It can be a fast way to generate ideas for compounds to test (1 iteration per day).
- The platform is continuously improved in our group.

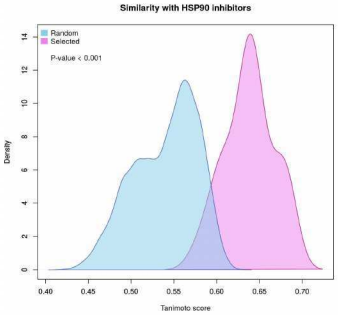
References

[1] Scott, D.E. Biochemistry, 2012, 51 (25), 4990–5003 **[2]** Ruiz-Carmona, S. Nature Chemistry, 2017, 9, 201–206 **[3]** Gehling V. S., ACS Med. Chem. Lett., 2013, 4 (9), 835-840

Validation

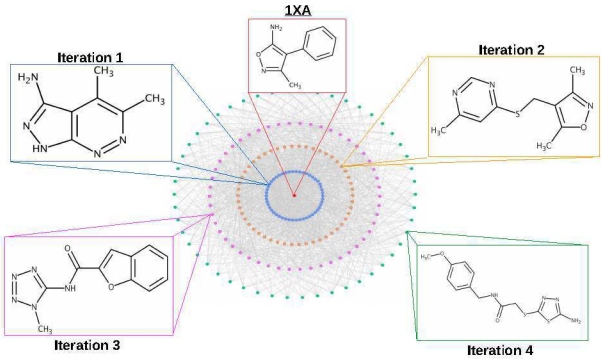
HSP90

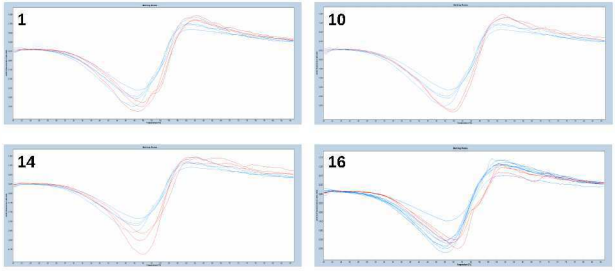
For a retrospective validation, 4 iterations of automated evolutions were carried out for 6 existing HSP90 fragments. The 50 top scoring molecules at each iteration were compared to known inhibitors of HSP90 (782 molecules with IC50/Ki ≤ 50 µM in ChEMBL20), keeping the maximum Tanimoto similarity scores and averaging them for each iteration. The same was done for random molecules (1000x) taken from ZINC15, maintaining the same range of heavy atoms as the selected ones. The distribution of these averages for both populations (selected vs. random) is represented here. The selected molecules present a clear shift towards higher values (T-test P-value = 2.067E-14). The selected molecules are not identical to any of the known HSP90 ligands, hence we have no evidence of them being active. This outcome can be explained by the relative size of the active set (782) compared to the explored chemical space (15M). Considering the difficulty of strict retrospective validation, we proceeded to validate the method prospectively with BRD4 protein.



BRD4

We applied the protocol prospectively to the bromodomain BRD4(1). Starting from a published fragment, we identified active molecules that are different from existing BRD4 inhibitors, even those that were evolved from the same fragment[3]. Selected molecules are being tested with complementary biophysical methods (DSF, SPR and ITC) and characterized by X-ray crystallography.





DSF preliminary results

Cpd	[ ]	ΔTm
1XA	50 µM	0.854
1	50 µM	1.046
10	50 µM	1.333
14	50 µM	1.315
16	10 µM	2.049