RxNfinity™ : A novel structure-based hierarchical synthon docking approach for the rapid effective search of trillion-sized libraries

Heal JR, de Souza JV, Clayton R, Ramsden N, Sheridan JM, Taylor M, Hamilton WDO
RxCelerate Ltd, Babraham Research Campus, Cambridge, UK. w: prosarx.com rxcelerate.com e: info@prosarx.com

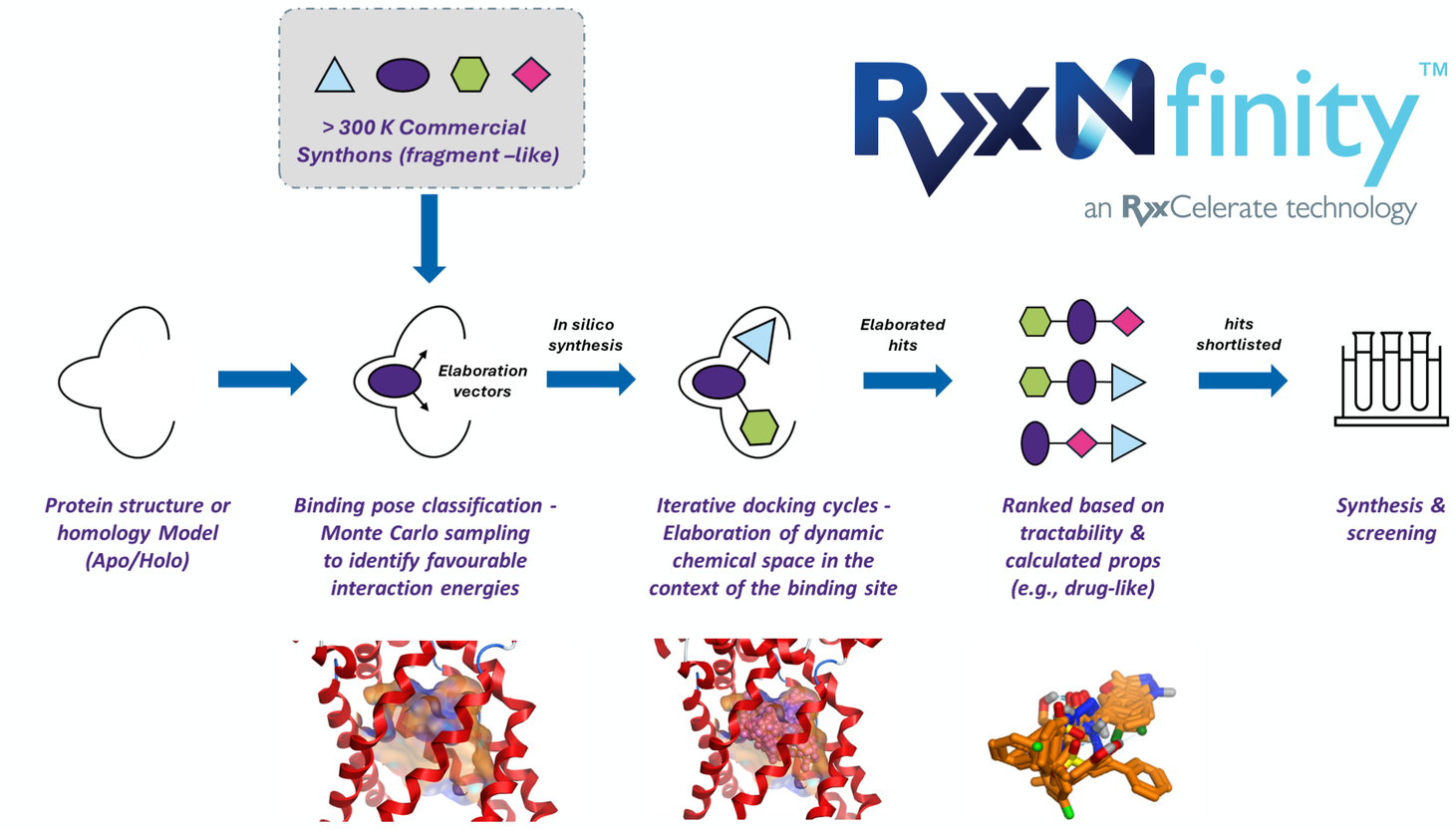
ProsaRx a division of RxCelerate

Introduction

RxNfinity™ has been developed as a novel structure-based hierarchical synthon docking approach for the rapid and dynamic virtual screening of ultra large synthesisable chemical space in the context of the binding site of the target. This new method uses commercially available libraries of small molecule synthons that are hierarchically docked to a target protein structure and elaborated according to a library of codified chemical reaction, allowing for the exploration of 3D chemical space with libraries of billions to trillions of compounds.

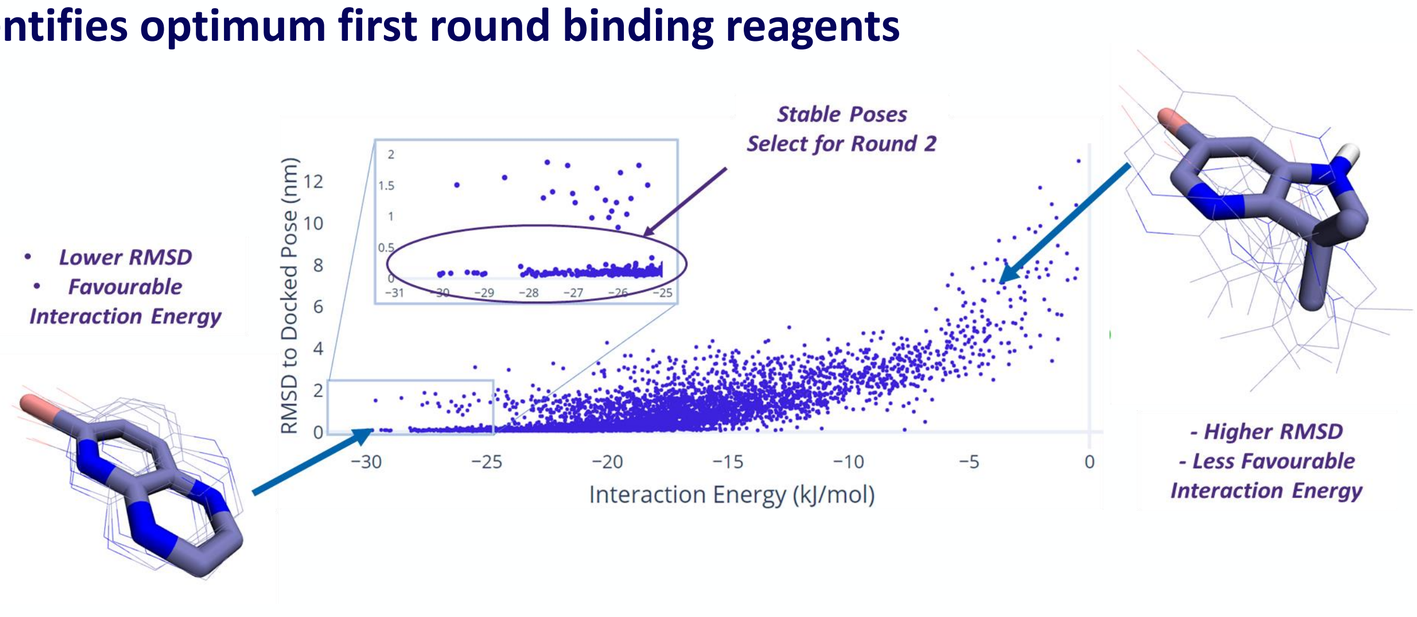
The RxNfinity™ workflow is outlined in the figure.

The overall methodology of RxNfinity™ provides the basis to rapidly design novel compounds for synthesis against protein targets with known or modelled structures. RxCelerate offer integrated services for chemistry and drug development and therefore novel chemotypes discovered using RxNfinity™ can be rapidly optimised to a lead using the same discovery team.



Monte Carlo sampling method screens and identifies optimum first round binding reagents

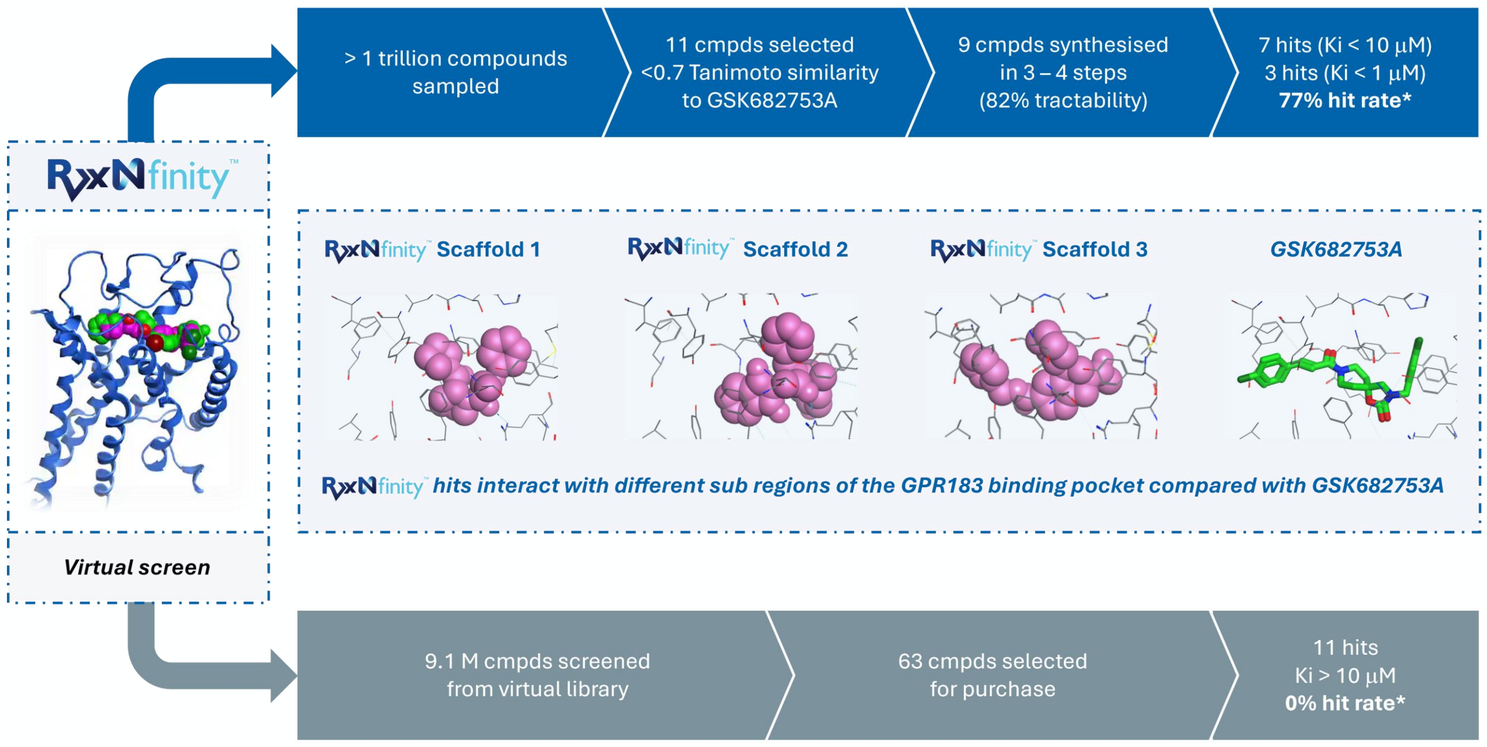
The first round of synthon docking represents a potential limitation for hierarchical docking schemes involving the synthesis of hit molecules inside the binding site of a target protein. Fragment-like synthons could be prone to errors in affinity estimation during this first round because of their small size (i.e., low MW). To overcome this issue, we developed a Monte Carlo sampling solution that ranks the first-round docking configurations.[1] Synthons showing favourable interaction energies together with a lower root-mean-square deviation (RMSD) were preferentially selected as starting points; effectively enriching the selection of synthons that can act as anchor points for virtual library enumeration within the RxNfinity™ algorithm.



Case Study with GPR183 : Discovery of novel potent scaffolds

The G protein-coupled receptor GPR183 plays a role in several immune system conditions, including SARS.[2] Hence, GPR183 antagonists are useful in modulating the immune system in the context of this disease. A co-crystal structure of GPR183 in complex with the potent inhibitor, GSK682753A, has been published.[3] RxNfinity™ was used to generate libraries of compounds in the GPR183 binding site, sampling over 1 trillion synthesisable compounds. After scoring, 11 compounds were selected for synthesis (of which 9 were synthesised). Seven of these compounds gave Ki < 10 μM (3 had Ki < 1 μM), representing a hit rate of 77%. All hits were novel and amenable to further optimisation.

For comparison, we conducted a traditional virtual screen of 9.1 M commercial compounds using the same GPR183 structure and our proprietary ProsaRx ProtoScreen platform. Whilst hits were also identified using this approach, they showed Ki values > 10 μM, highlighting the relative power of RxNfinity™ as a platform for the discovery of novel hit matter. This pattern was repeated across several other targets.



*hit defined as a compound generating a Ki value of less than 10 μM against GPR183

Summary

RxNfinity™ is a new hit finding platform for accelerating small molecule discovery projects based on a hierarchical docking approach. This novel approach allows for the rapid and dynamic *in silico* synthesis and virtual screening of ultra large synthesisable chemical space in the context of the binding site. Our case study for the inflammatory target, GPR183, highlights the value of this new approach for the identification of novel drug-like scaffolds that interact with different sub regions of the GPR183 binding pocket.

ProsaRx a division of RxCelerate

HIT FINDING | ARTIFICIAL INTELLIGENCE | CLIENT INTEGRATION

- Structure Based Design
- Ligand Based Design
- Virtual Screening
- Pharmacophore Screening
- Off target Prediction
- Machine Learning/AI and Development
- Protein Design and Engineering
- Antibody Design and Engineering

References
- **[1]** De Souza, et. al., CompBioChem. 2023 April 103; 107830
- **[2]** Foo CX, et. Al. Eur Respir J. 2023 Mar 9;61(3).
- **[3]** Chen H, et. Al. Structure. 2022 May 09; 30(7)