LeadBuilder
Taking a Rational Route to Leads

Rapid hit identification via virtual screening

Domainex

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Introduction

One of the keys to success in drug discovery is generating high-quality chemical starting points for lead optimisation. *LeadBuilder* is a proprietary virtual screening platform that you can access to deliver such starting points in an efficient, timely and cost-effective manner on targets for which there is sufficient precedent (i.e. a known crystal structure or existing ligands).

At its heart is our NICE (Number of Interesting Chemical Entities) virtual database of ~1.5 million compounds that has been assembled from all known commercial vendor collections totalling over 15 million compounds. This collection can be screened in as little as 2 weeks to generate a virtual hit list of 500 – 1000 compounds.

State-of-the-art technology

LeadBuilder integrates our expertise on your behalf in three areas: compound collection design, protein modelling and virtual screening. The know-how and expertise of our expert drug hunters is an essential component of our platform along with a state-of-the-art suite of software and hardware.

Client requirements

Clients are asked to disclose their disease target(s) of interest and whether they have any proprietary data (structural or ligand). Domainex is happy to search public sources of data, e.g. the PDB of known structures, on your behalf and to provide expert advice on potential strategies to adopt. This can include recommending homology modelling if the only available information is of a related target.

Key features

- Access to our expert computational chemistry expertise
- Virtual screens performed on ~1.5 million compounds in < 2 weeks
- Access to complimentary capabilities in assay biology, structural biology and medicinal chemistry

Ideal screening collection

Domainex has developed a proprietary series of computational filters to efficiently triage commercial vendor collections to identify lead-like compounds. The parameters we select on include:

- Desirable molecular properties
- Optimal physicochemical properties, e.g. good solubility
- Several interaction points with proteins
- Good predicted ADME/PK properties
- The absence of toxicophores

The Domainex NICE database is periodically updated to ensure that compounds in it remain commercially available.

Domainex will then design a series of target-site pharmacophore models based on the chosen binding pocket and/or of known ligands.

Compound acquisition and processing

Domainex typically looks to deliver 500 – 1000 virtual hits as the output of a *LeadBuilder* screen. This list can be provided to you for sourcing or Domainex is happy to source the compounds on your behalf. You then have the opportunity to access the wider services offered at Domainex:

- Analytical assessment of compounds, e.g. for purity and solubility
- Assay development and screening to rapidly generate potency values for the collection
- X-ray crystallography of your chosen target and soaking or co-crystallisation strategies to elucidate structure-ligand interactions
- Further sourcing of hits emerging from 'wet' screening to identify related analogues for further testing to build an initial picture of structure-activity relationships
- Medicinal chemistry optimisation of nominated hits to build in desired pharmaceutical properties such as potency, selectivity, favourable ADME/PK properties and novelty

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Case Studies

Case Study 1: Ligand-based virtual screening for a cellular assay

Our partner was using a cell-based assay with a read-out from a signal transduction pathway. They had identified one stimulator of the pathway, and wanted to find other compounds in order to further mechanism-of-action studies, and as potential therapeutics.

Domainex carried out a ligand-based virtual screen of the NICE database using three-point pharmacophores based on the known ligand. We selected about 100 compounds for screening, with an emphasis on those likely to show good cellular permeation. On screening this library, our client identified several hit compounds, one of which had 5x activity of the known ligand.

This work led to the filing of a patent protecting the best of the new compounds – which had commercially interesting levels of activity. Domainex also designed a follow-up medicinal chemistry programme with the aim of providing even better compounds, and also exemplifying and strengthening our partner's patent.

Case Study 2: Identification of novel potent tankyrase (PARP) inhibitors

In collaboration with the Institute of Cancer Research (ICR), Domainex used *LeadBuilder* to identify a candidate drug against the PARP family member tankyrase (which has been shown to play an important role in the Wnt signalling pathway).

LeadBuilder was used to identify hit compounds that acted as tankyrase inhibitors. Previously published crystal structures showed tankyrase in a closed form, in which the active site was inaccessible to ligands. Domainex built a homology model of tankyrase using a published crystal structure of PARP1 in an open conformation. This was used to screen Domainex's NICE database of ~1.5 million commercially available compounds, from which ~1000 compounds were purchased. 59 hits were identified with IC_{50} values between 1–10 μM.

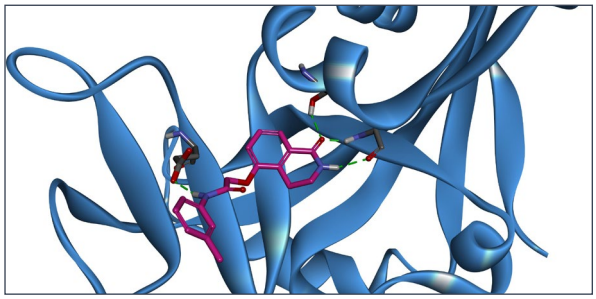

Figure 1: Ligand making hydrogen-bonds with three residues in the tankyrase model structure

A subsequent drug discovery collaboration between Domainex and ICR generated several series of potent tankyrase inhibitors with excellent selectivity over PARP1 and good DMPK properties. Lead compounds subsequently inhibited the growth of APC null tumour xenografts, and the project was successfully out-licensed to develop these compounds as anti-cancer drugs.

About Domainex

Domainex is a fully integrated drug discovery service company based at Cambridge, UK. We serve pharmaceutical, biotechnology, academic organisations and patient foundations globally. We have ambitious growth plans and are expecting to reach 110 biologists and chemists in the near future. We provide integrated services, from disease target selection to candidate drug nomination. We have a very strong reputation for contributing innovative ideas, undertaking high-quality experiments and for generating intellectual property on behalf of our clients. We strive to build strong, dynamic relationships. In 2021 we served over 60 clients from the UK, Europe, the United States, Japan and Australia and had a project renewal rate of over 80%.

How Can Domainex Help Your Drug Discovery Project?

Our highly experienced, multi-disciplined scientists – molecular biologists, protein biochemists, assay biologists, structural biologists, medicinal, computational and bio/analytical chemists, *in vitro* pharmacologists and ADME scientists – will support you to advance your drug discovery projects towards drug development effectively and efficiently. We provide customised programmes to address your specific needs at each stage of drug discovery. We draw from a wealth of expertise built up over the last 20 years across a wide range of drug targets and therapeutic areas. From our sites within Europe's leading bioscience hub at Cambridge, UK and with access to the very latest cutting-edge technologies, we are able to help you realise your goals and enrich your discovery pipeline.

Contacts

If you would like to know more about Domainex's discovery services, or speak to us regarding your own drug discovery needs, please contact us at: enquiries@domainex.co.uk

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