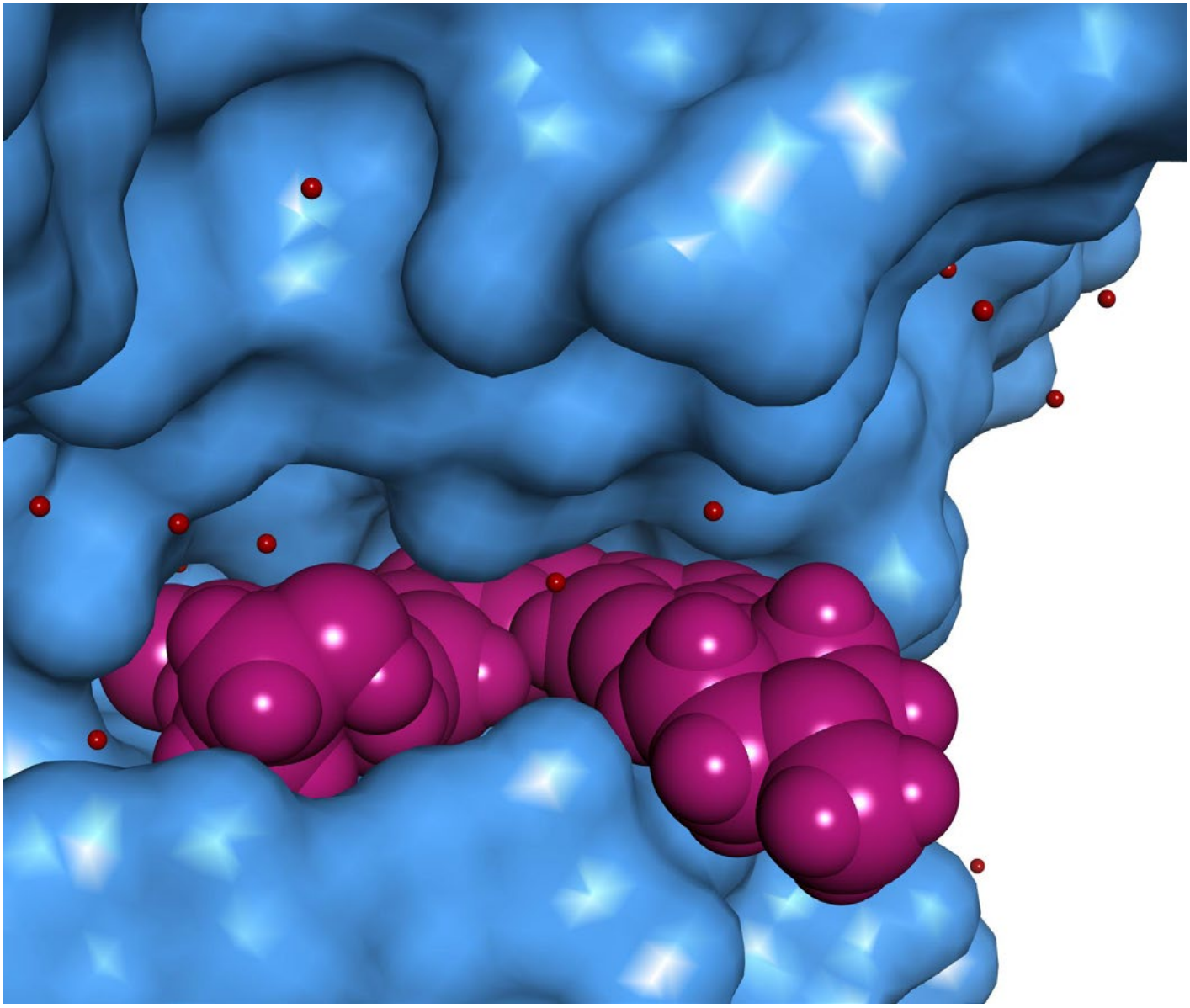
Lead Builder

Virtual screening – the key to building better leads



domainex
the faster route to drug discovery

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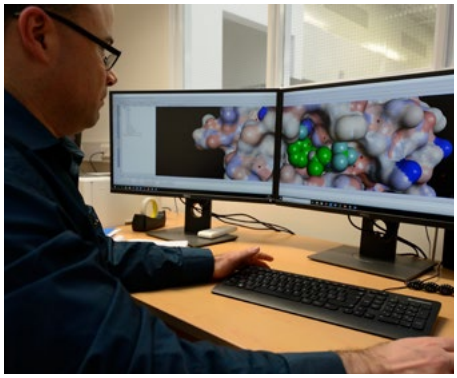
Lead Builder

Introduction

It is generally agreed that one of the critical factors influencing the likelihood of success and the speed of a small molecule drug research project are the properties of the chemical starting points. *LeadBuilder* is the proprietary lead generation platform that has been developed by Domainex to provide **rapid** and **cost-effective** access to **high-quality** hits. As such, it is particularly well-suited to the needs of emerging biotechnology and pharmaceutical companies, as well as groups engaged in Translational Research.



State-of-the-art technology

LeadBuilder integrates our capabilities in three key areas: compound collection design and selection; protein modelling; and virtual screening.

The platform encapsulates many aspects of our scientists' expertise in successful drug hunting. This know-how and experience is key to the success of the *LeadBuilder* approach, which is enabled by a state-of-the-art combination of proprietary modelling tools and commercial software from BIOVIA and CCDC.

Key features

- access to our expert computational chemistry team with an average of 20+ years' experience
- virtual screening of 1.5 million carefully selected compounds in under 2 weeks
- couple with our downstream expertise in protein expression, bioassay screening and medicinal chemistry to transform hits into clinical candidates

Ideal hit compounds

The *LibraryBuilder* module contains several databases of commercially available compounds.

We use our *CompoundProfiler* methodology to calculate molecular properties and virtual physicochemical, pharmacokinetic and toxicity profiles for these compounds. We use these assessments to rank or filter them according to their lead-like characteristics.

Perhaps the most important of our databases is the *"NICE"* virtual collection of **~1.5 million commercially available compounds** that have been carefully filtered to meet all of our criteria for an "ideal screening hit", namely: several potential points of interaction with a target protein; very favourable molecular properties; and good predicted ADME and toxicity profiles.

Virtual screening

Using our *ScreenBuilder* methodology we are able to interrogate our databases with *in silico* screens that we can develop from knowledge of your target protein, and/or any known ligands. This means that we can start with information on the target protein, or knowledge of one or more known ligands, or with data on both protein and ligand(s). *ScreenBuilder* can use a number of search protocols, including pharmacophore screens, docking, and privileged fragment recognition.

In the event that a target protein structure is not available, we are often able to use our *StructureBuilder* module to identify surrogate proteins based upon homology and active-site similarities, and to use these surrogates to develop a model of the active site of your target for virtual screening and design purposes.

Compound acquisition to clinical candidate

Informed by *LeadBuilder* data, you can then acquire the screening library in the quantities or format you need; or we can liaise with the suppliers on your behalf. Our aim is to give you quality hits by selecting what is absolutely relevant to your target from the universe of diverse, relatively-low-cost, commercially available compounds, whilst saving you the time and expense of building a large screening collection. But that is just the beginning. Using the skills of our protein scientists, assay biologists and medicinal chemists we will be with you every step of the way, as you transform hit molecules into clinical candidates.

Protein modelling

StructureBuilder
- X-ray structure
- Homology modelling

Virtual screening

ScreenBuilder

Compound collection

LibraryBuilder
- NICE collection
- Compoundprofiler

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.

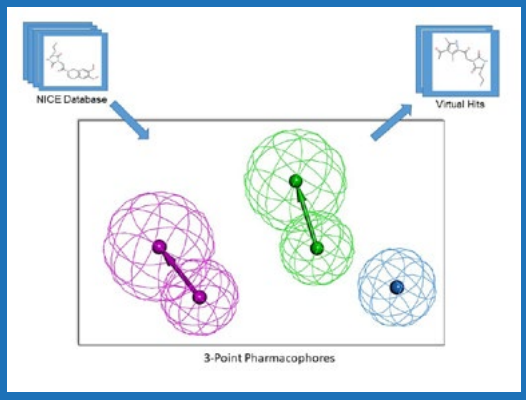


Figure 1: Ligand-based virtual screening

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).

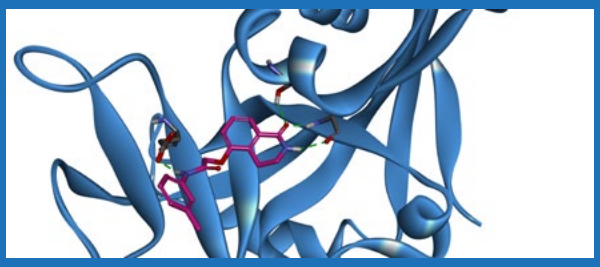


Figure 2: Ligand making hydrogen-bonds with three residues in the tankyrase model structure

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.

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 near Cambridge, UK serving pharmaceutical, biotechnology, academic and patient foundations globally. Domainex's drug discovery service business was established in 2001 and since that time has continued to expand to serve a wider range of clients across the world including UCB, FORMA Therapeutics, St George's University, The Institute of Cancer Research and Auspherix. Our expertise and commitment to providing high quality services has resulted in a strong success record in drug discovery, delivering an average of one candidate drug every year for the past six years.

How Can Domainex Help Your Drug Discovery Project?

Domainex's highly experienced molecular biologists, assay biologists, medicinal, computational and analytical chemists can be leveraged through our CRO services. Domainex provides highly efficient and well considered scientific solutions to enable successful drug discovery programmes against a wide range of drug targets. Whether your project is at an early stage of drug discovery or has already identified chemical matter, our processes have been shown to result in a 30% time-saving compared to industry standards and use less resource, allowing prudent management of your own budget.

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

Alternatively we can be contacted directly as follows:

Dr. Thomas Mander MBA
Chief Operating Officer
tom.mander@domainex.co.uk
Tel: +44 (0)1223 743174
Mob: +44 (0)7584 578024

Domainex
Chesterford Research Park
Little Chesterford
Cambridge
CB10 1XL, UK

The London BioScience
Innovation Centre
2 Royal College St
London
NW1 0NH, UK

Publications

Elliot *et al.*, (2015) Design and discovery of 3-aryl-5-substituted-isoquinolin-1-ones as potent tankyrase inhibitors *Med. Chem. Commun.*, **6**, 1687-1692

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