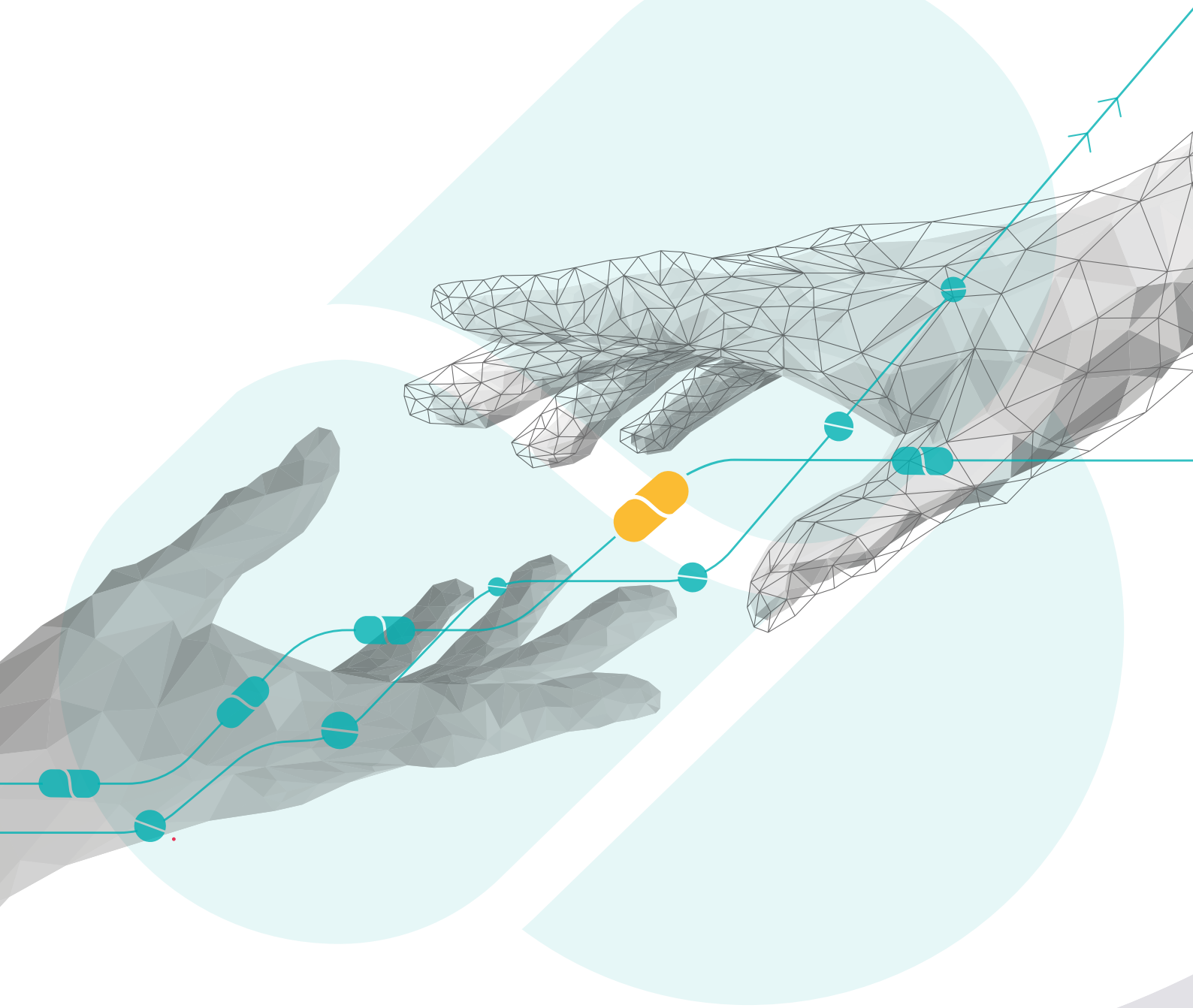
Direct to Biology

Galaxy of opportunity

Accelerate your research with Domainex's PROTAC® toolbox



Domainex

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To expedite targeted protein degrader programmes, Domainex has generated a toolbox consisting of approximately 160 partial proteolysis targeting chimeras (PROTACs®, PROTAC® is a registered trademark of Arvinas Operations, Inc., and is used under license). The toolbox is designed to be combined with Domainex's Direct-to-Biology (D2B) platform for the rapid, plate-based synthesis of PROTACs®. Each partial PROTAC® is comprised of an E3 Ligase recruiter ligand and a linker which includes a synthetic handle. The majority of the compounds are not commercially available from other vendors and are ready for immediate coupling to a protein of interest (POI) binder.

E3 Ligase Recruiters

To date most R&D in the protein degrader field has focussed on exploiting Cereblon (CRBN) and Von Hippel-Lindau tumour suppressor (VHL) E3 ligases. Where structural information is available, over half of the current clinical stage PROTACs® utilise CRBN based ligase recruiters, where the PROTAC® beyond rule-of-5 (bRo5) molecular property space is more favourable for optimisation and delivery of oral bioavailable degraders.[1]

However, for CRBN ligase recruiters, selectivity for degradation of the POI versus proteasomal degradation of neo-substrates, where the CRBN ligase recruiter acts as a molecular glue, remains a challenge. Several neo-substrates are known to play important physiological roles and their protein degradation can often lead to toxicological consequences. As an example, degradation of Spalt Like Transcription Factor 4 (SALL4) by thalidomide resulted in teratogenicity and the epidemic of severe birth defects in the late 50's-early 60's.

Given the interest in CRBN from a clinical perspective, our toolbox is biased towards CRBN-based recruiters, but with a significant subset designed to reduce potential neo-substrate protein degradation (Figure 1).

***Figure 1**: Left; E3 ligase recruiter composition. Right; proportion of CRBN recruiters designed to reduce neo-substrate protein degradation*

Linkers

It is well documented that both the linker length and its composition play an instrumental role in driving protein degradation of the POI and contributing to the property profile. As a consequence, Domainex's toolbox includes partial PROTACs® with a range of linker types including variation in length, rigidity and molecular property space (rotatable bonds, PSA, clogP, MW, ionisation state) (Figure 2). Different exit vectors (composition, position...) and multiple synthetic handles ready for coupling with POI ligands bearing different functionality are also included.

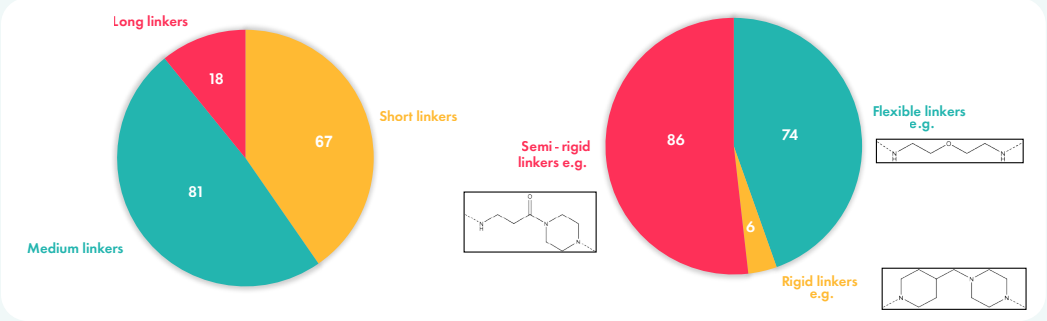

***Figure 2**: Left; Toolbox linker length composition. Right; Toolbox linker rigidity*

Reference

1.Yang et al., Drug Discovery Today, Volume 29, Issue 2, February 2024, 103865.

Case Study

Target: Aurora Kinase (overexpressed in human tumours)

JB170 is a potent and highly specific CRBN PROTAC® mediated Aurora A degrader which incorporates Alisertib as the POI lingand. As a pilot study, the acid of Alisertib was coupled to 40 amine representative examples from Domainex's PROTAC toolbox.

The plate-based chemistry was completed in less than 3 days including automated LC-MS analysis, which showed > 75% of the requisite amides were synthesized in acceptable purity. Profiling of the unpurified mixtures in a HiBiT tagged Aurora A degradation assay revealed several known and novel linker based CRBN derived compounds with DC_{50} values in the 30-150 nM range, similar to that observed with JB170 (DC_{50} 28 nM) (Table 1).

What was the successful outcome?

Selected partial PROTACs® from our toolbox were successfully used in plate-based chemistry reactions and progressed directly to a HiBiT degradation assay. Several hits, with both known and novel linkers, were identified, demonstrating the benefit of the library when combined with a D2B approach.

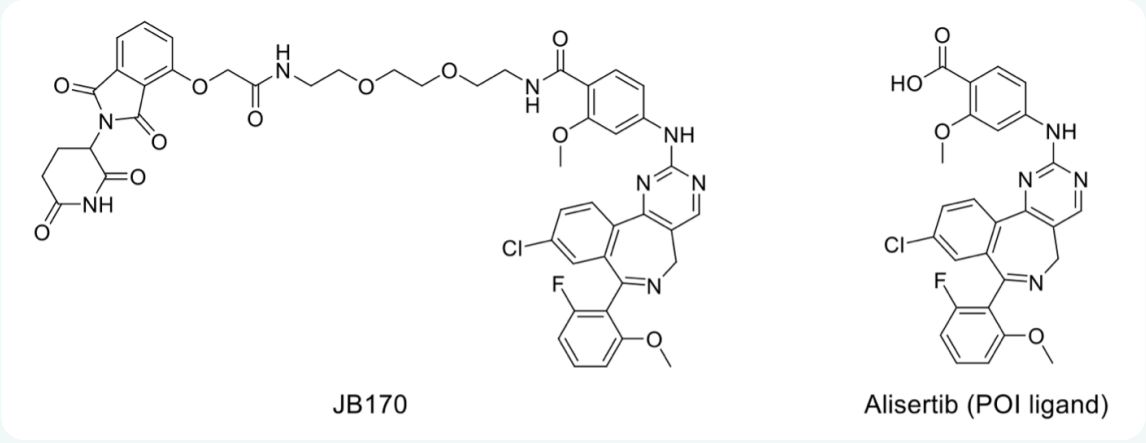

***Figure 3**: The structures of JB170 and Alisertib*

	DMX0105197	DMX0105217	DMX0105220
DC_{50} (nM)	140	36	29
MW	1025.54	861.28	993.44
ChromLogD	3.41	3.85	3.84
TPSA (Å^2)	208.1	202.5	230.2
Number of rotatable bonds	14	14	23
Number of HBD	3	4	4
Number of HBA	18	16	19
Solubility (µM)	43.8	51.4	36.8

***Table 1**: Selected hits identified from the HiBiT screen*

About Domainex

Domainex is a fully integrated drug discovery service company based in Cambridge, UK. We serve a wide range of pharmaceutical, biotechnology, academic organisations and patient foundations globally. We have ambitious growth plans and currently have over 100 scientists. 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 and work with our clients to provide customised services.

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 the pre-clinical drug discovery process. 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.

Contact

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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