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Lead Discovery Using Fragments

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Introduction

When compared to high throughput screening, fragment-based lead discovery (FBLD) is emerging as a strategy that has the potential to deliver leads more quickly and efficiently (HTS). Using sensitive biophysical approaches, small libraries of low molecular weight molecules (usually 120–250 Da) are screened in FBLD to look for weak binding. Due to their reduced size and complexity, fragments should have a lower absolute affinity than considerably greater molecular weight hits discovered by HTS. It is therefore frequently rather simple to optimise these results to promising lead compounds using structural biology. Numerous recent reviews of fragment-based techniques have been published. They provided thorough lists of instances of how lead compounds have been created starting from fragments and were directed towards medicinal chemists. In addition, examples where the beginning fragment is less than 300 Da and has a 425 mM affinity against the target are the topic of this report, which focuses on examples that have been published since these two evaluations [1].

Description

According to bioassay screening at 100 mM, a virtual screen of 10,000 primary amine fragments against dipeptidyl peptidase IV (a target for diabetes) revealed a number of hits. This fragment's X-ray structure demonstrated the predicted binding mechanism in the S1 pocket and provided the basis for a structural-based theory that ultimately resulted in the discovery of a potent class of DPP-IV inhibitors. Numerous reports on NMR fragment screening are available. Four "strong" hits for the protease FXa were discovered during the STD-NMR screening of 34 targeted fragments. Seven hits, including eight, were obtained from a 1 H-15N HSQC NMR screening of 825 fragments (200-250 Da, cLogP o2.5) against the ZipA/FtsZ complex (a target for antibacterial agents and a protein-protein interaction). The identification of an X-ray structure for the ligand-protein demonstrated binding. Identification of two fragment hits, including indolin-2-one 9, was made achievable by in silico screening against DNA gyrase and characterising potential binders by 15N HSQC NMR. One molecule with an increased potency of 25 mM (LE 14 0.33) was discovered through further analogue screening. Model research has been done using the mouse Tec kinase IV Src Homology 3 (SH3) domain [2,3].

Using a high-throughput NMR-based technique called "SAR by NMR," lead generation for the difficult protein-protein anti-cancer target Bcl-2 was investigated. Small compounds from a chemical library were tested for their ability to attach to the Bcl-XL, a member of the Bcl-2 family, big, highly lipophilic BH-3 binding groove. Thus, it was discovered that 15a and 15b bound in separate but close-by subsites within the binding groove. The two fragments were linked and optimised for potency to produce analogue 16, which was then further optimised for potency and reduced protein plasma binding to produce the preclinical candidate ABT-737. These modifications were made using structural information derived from NMR data and knowledge of key binding sites for the native binding BAK peptide. Over the past ten years, there has been a lot of research done on the difficult Hepatitis C target known as the NS3/NS4A protease-cofactor complex. Multiple fragment hits (Ki100 mM-10 mM) were found using NMR-based screening of a customised fragment library against the NS3/NS4A complex. The hits 18a and 18b were found to bind to the substrate at close-by S1-S3 and S2' substrate binding sites, according to NMR chemical shift perturbation data. These pieces were connected using this structural data to find a submicromolar lead compound (19). Unfortunately, a protein-ligand crystal structure could not be found, preventing further lead molecule optimization [4,5].

A measure of LE can be obtained by normalising the free energy of binding of a ligand to a particular protein to the size of the ligand. Since molecules are constructed from fragments, scientists were the first to compare normalised potencies of this sort and make the suggestion that they would be useful in tracking potencies. Although fragment-based discovery practitioners were keeping track of potency and molecular weight during fragment optimization, it wasn't until Hopkins coined the term LE in 2004 that it became well known. Modified definitions of LE have now been put out, and it has since been warmly adopted by researchers working on fragment-based drug discovery. The fragment optimisation process has a conceptual road map thanks to the tracking of LE. Although LE refers to entire molecules, it does not reveal whether some molecule components are more effective than others. It is typically possible to monitor the development of potency improvements and to make sure that the emerging series maintains the same binding mode during a structure-based fragment optimization effort. In these situations, matched pair comparisons of compounds enable one to attribute a change in the free energy of binding to a specific group. For a methyl analogue of compound 43 (LE 14 0.48), values higher than 0.3 suggest that the specified group is making an adequate contribution to the potency group efficiencies. The "group efficiency" is calculated by dividing the free energy change by the number of heavy atoms in the additional group [1,2].

Conclusion

Is it possible to identify medications effectively using fragment-based discovery? This is perhaps the most crucial issue to ask. It is now possible to determine if there are candidate pharmaceuticals derived from the technique that may ultimately reach the market, even though it is still too early to immediately respond to this. They have compiled all of the clinical and pre-clinical prospects and programmes for which it is publicly known that the candidate drug was discovered using fragments. Currently, six drugs made from fragments have been approved for clinical trials: PLX-204 (a PPAR inhibitor from Plexxikon), PLX-4032, AT9283 (an Aurora kinase inhibitor from Astex Therapeutics), AT7519 (a CDK inhibitor from Astex Therapeutics), and ABT-263 (a Bcl-2 inhibitor from Abbott) (B-Raf inhibitor; Plexxikon).

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Conflict of Interest

The author reported no potential conflict of interest.

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