Discovery of a Potent, Novel, and Selective Inhibitor with Catalyst

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Catalyst pharmacophore and shape technology can be used to successfully identify a novel and potent inhibitor for a disease-implicated protein. Singh *et al.* published a recent example from Biogen Idec on Type I TGF Beta receptor kinase[1].

Singh and co-workers at Biogen started with the 3D structure of SB203580, which was extracted from the crystal structure of the SB203580-p38 kinase complex (pdb code 1a9u) and aligned into the ATP binding site of TbRI. This starting compound is a known weak inhibitor of TbR1 kinase (IC50 30mM).

Using Catalyst, they identified pharmacophore features based on the binding interactions of the SB203580-p38 alignment. The shape of the bound form of SB203580 (grid of 1 Å and 50% similarity) was also generated. The combined shape+pharmacophore model was then used as a search query against a database of 200,000 commercially available compounds.

A total of 87 compounds were retrieved as hits from the database search using this query; all 87 compounds were subjected to biological testing against the kinase assay. Of the compounds identified from the database search as fitting both pharmacophore and shape constraints, compound HTS466284 was experimentally shown *in vitro* and in cell culture to be the most potent. The crystal structure of TbR1 complexed with HTS466284 was performed to confirm *in silico* findings.

Separately, researchers at Eli Lilly discovered the identical compound using conventional enzyme and cell-based assays.[2]

These results demonstrate how Catalyst technology can be a powerful shortcut to the drug discovery process, when compared to traditional high-throughput screening (HTS). This can in turn save years of painstaking work at the bench and decrease financial costs of R&D. As highlighted in the side-bar, assuming reagents and bioassay costs only (excluding labor), potential cost savings from performing smart virtual screening versus traditional screening could be as much as $299,739. Please note that this cost savings is based on assumptions of average costs and is not a statement of the exact amounts paid by the parties at hand.

References

1. Singh, J., Chuaqui, C.E., Boriack-Sjodin, P.A., et al., "Successful Shape-based Virtual Screening: The Discovery of a Potent Inhibitor of the Type I TGFb Receptor Kinase (TbRI)," *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 4355-4359.

2. Sawyer J.S., Anderson B.D., Beight D.W., *et al.*, "Synthesis and activity of new aryl- and heteroaryl-substituted pyrazole inhibitors of the transforming growth factor-beta type I receptor kinase domain," *J. Med. Chem.*, **2003**, *46*, 3953-3956.

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Industry Sector

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Key Products

Catalyst®

Workflow

1. Built Catalyst pharmacophore model
2. Built Catalyst shape model
3. Virtually screened 200,000 commercially available compounds
4. 87 hits assayed
5. 27 nM compound identified
6. Cell culture assay performed
7. Potent + novel structure + non-toxic inhibitor identified

Potential Savings of $299,739

- Cost of brute force HTS: 200,000 compounds @ $1.50 per assay = $300,000
- Cost of smart screening with Catalyst and bioassay: 87 compounds @ $3.00/assay = $261
- The difference: $300,000 - $261 = a potential savings of $299,739

Please Note:

* Based on current market knowledge, the assumption is that one brute force HTS averages $1.50, while one virtual screening followed by bioassay averages $3.00.

* The above calculation considers only the savings generated by testing fewer compounds. Clearly, more money would be saved due to the speeding up of HTS.

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