

A KINASE FOCUSED SCREENING LIBRARY

KINASet

Introduction

ChemBridge's KINASet is a collection of 12,000+ druglike, small molecule compounds selected for potential activity against kinases. Stringent druglike and desirable chemical group filters coupled with a 3D pharmacophore query method were used in selecting desirable compounds with increased probability of binding to the ATP binding region and allosteric sites of kinase targets. The KINASet collection is rationally selected from ChemBridge's EXPRESS-Pick™ Collection of 450,000+ handcrafted compounds.

KINASet Selection

The KINASet selection provides a set of EXPRESS-Pick™ compounds focused on the ATP binding region and applicable to any member of the large kinase enzyme family, including both tyrosine and serine-threonine kinases. ChemBridge developed a conceptually novel approach to the design of a general kinase-targeted library using a 3D pharmacophore query based method and allowing for additional diverse pharmacophores that could confer selectivity.

Query Generation

Low-energy conformations of 5'-O-methyladenosine were used to mimic all low-energy interactions expressed by the adenosine portion of ATP. Because the phosphate-binding regions of published ATP active-site kinase domains co-crystallized with inhibitors were not occupied, the triphosphate interactions of ATP were excluded.¹ Chem-X software was used to prepare a database of 3-point pharmacophores for the low-energy conformations of 5'-O-methyladenosine.² The pharmacophore query was then created with a modified version of Chem-X software using 3-point pharmacophores with interaction features including hydrogen bond donors, hydrogen bond acceptors, positive charge centers, aromatic ring centers, basic groups, acidic groups, and hydrophobic centers. The Chem-X database represents the likely set of possible non-phosphate interactions presented by ATP in any ATP-recognition site. Compounds that do not contain a significant number of these interaction types would be less likely to interact with an ATP recognition site.

Formats

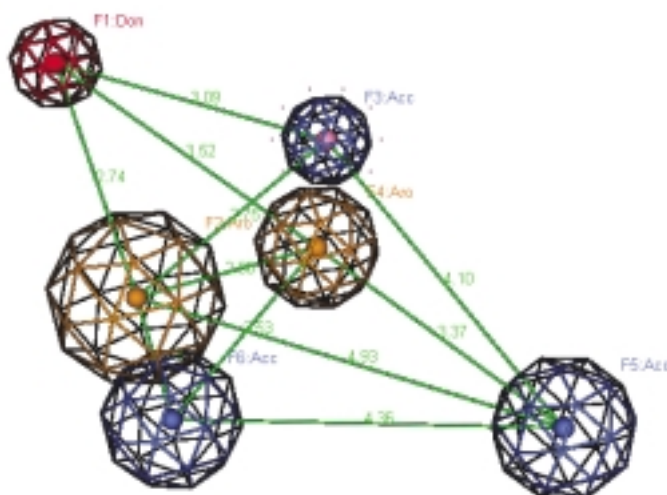
- Download and individually select from the 12,000+ KINASet selection (SDfile and ISIS db files available). Individually selected compounds are available in powder form or dissolved in DMSO.
- ChemBridge also offers the KINACore Library, a 6,000+ compound selection from our proprietary PHARMACophore Library (PCL), an internally-designed, parallel-synthesized library (PCL data provided under non-disclosure agreement).
- For a screening library with application across multiple target families, the KINASet can be expanded by adding additional EXPRESS-Pick™ compounds or DIVERSet™, CNS-Set™, Ion Channel Set, MicroFormats™ selections.

Compound Selection

The pharmacophore query was used to search a database of highly filtered EXPRESS-Pick™ compounds. The query overlap criteria were set such that half of the query pharmacophores must be present in any computational 'hits'. The other half of the pharmacophores in the hit molecules were allowed to have 'diverse' pharmacophores, which may lead to selectivity among the different of ATP-binding sites observed in nature.

Validation

The query was validated *in silico* by searching a Chem-X pharmacophore database of known kinase inhibitors. This search scored 85% of the known inhibitor compounds as 'hits' using the query. Using the same query against 70,000 compounds from a diverse library, less than 5% of the compounds scored as 'hits'. This *in silico* exercise demonstrated that the query is effective in finding known kinase inhibitors, and only a small percentage of diverse compounds are scored as hits. The same query method was applied to an in-house, parallel-synthesized, diverse library of 100,000+ compounds (PHARMACophore Library). The resulting set of 2,677 predicted hit compounds was assayed for activity against a tyrosine kinase. Multiple hits were found representing several distinct structural series.³



References

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2. Webb, T. R.; Melman, N.; Lvovskiy, D.; Ji, X.; Jacobson, K. A. The Utilization of a Unified Pharmacophore Query in the Discovery of New Antagonists of the Adenosine Receptor Family. *Bioorg. Med. Chem. Lett.* **2000**, 10, 31-34.
3. Li, R.; Xue, L.; Zhu, T.; Jiang, Q.; Cui, X.; Yan, Z.; McGee, D.; Wang, J.; Gantla, R. V.; Pickens, J.; McGrath, D.; Chucholowski, A.; Morris, S.; Webb, T. Design and Synthesis of 5-Aryl-pyridone-carboxamides as Inhibitors of Anaplastic Lymphoma Kinase. *J. Med. Chem.* **2006**, 49, 1006-1015.

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