



DIRECTED SETS FOR KINASE SCREENING

KINACore/KINASet

Introduction

ChemBridge® offers two computationally selected sets of compounds for kinase screening: The KINACore™ Library, selected from our CORE Library stock, and the KINASet™ Library, selected from our EXPRESS-Pick™ Collection stock. The libraries are based on pharmacophores generated from compounds active against kinase targets or pharmacophores from the adenosine portion of ATP. The two libraries are non-overlapping, and clients can purchase the full sets or custom-select a subset of compounds from one or both libraries.

KINACore

The KINACore Library is a computationally selected library of more than 12,000 leadlike small molecules. KINACore Library compounds are part of ChemBridge's CORE Library stock and were selected for synthesis based on similarity to 3D pharmacophore fingerprints generated from published compounds with activity against kinase targets. More than 420 novel scaffolds are represented in the KINACore Library, and in-stock analogs are available for any compound identified as a hit. The KINACore Library is divided between compounds based on pharmacophore fingerprints generated from published actives and pharmacophores generated from the adenosine portion of ATP:

- KINACore Library compounds based on published actives: Compounds showing activity against kinase targets were extracted from public, scientific databases and used to generate 3D pharmacophore fingerprints based on low energy 3D conformers. These fingerprints were then compared to the 3D pharmacophore fingerprints generated for virtual compounds based on novel scaffolds designed by ChemBridge. Virtual compounds with a high similarity to a published active fingerprint were synthesized and included in the KINACore Library selection.
- KINACore compounds based on the adenosine moiety of ATP: These compounds were selected from the CORE Library stock according to the same method used to select KINASet Library compounds from the EXPRESS-Pick Collection stock. Please refer to the description under the KINASet Library.

KINACore Library compounds may show activity against the following kinase targets based on the active molecules from which the 3D pharmacophore fingerprints were generated:

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|--------------------------------|----------------------------|-----------------------|--------------------------|
| • AdK | • CSK | • Insulin Receptor | • Serine Protease |
| • AKT, AKT1 | • EGFR | • IRAK, IRAK4 | • SRC |
| • ALK5 | • EMT/ITK/TSK | • IRR | • SYK |
| • AMPK | • erbB2 | • JAK1, JAK2, JAK3 | • TEC |
| • Aurora, Aurora2, AuroraA | • ERK, ERK2 | • JNK1, JNK2, JNK3 | • TGFR alpha, TGFR beta |
| • B-RAF | • FGFR, FGFR1, FGFR2 | • KDR | • THFR |
| • Cdc2, Cdc25B | • FLK1 | • LCK | • TIE2 |
| • CDK1, CDK2, CDK3, CDK4, CDK5 | • FLT1, FLT3 | • MEK1 | • TPK1 |
| • c-erbB-2, c-erbB-4 | • GRK2 | • Myt1 | • TRPK1 |
| • CHK1 | • GSK3 | • NIK | • TYK2, |
| • CK2 | • HER, HER3, HER4 | • P38 MAP | • VEGFR1, VEGFR2, VEGFR3 |
| • C-MET | • Histidine Protein Kinase | • PDGFR | • Wee1 |
| • CRF | • IGFR1 | • PI3K, PI4K | • ZAP70 |
| • CSFR1 | • IKK | • PKA, PKB, PKC, PKC2 | |
| | • ILK | • PLK, PLK1 | |
| | | • RAF | |

The KINASet Library is a computationally selected library of more than 11,000 druglike compounds selected for potential activity against kinases. KINASet Library compounds are part of ChemBridge's EXPRESS-Pick Collection stock and contain pharmacophores matching pharmacophore queries generated from low energy conformers of the 5'-O-methyladenosine moiety of ATP. To ensure a high-quality set of compounds, ChemBridge filtered for enhanced physicochemical properties and removed compounds with undesirable chemical groups (e.g. Michael acceptors, crown-ethers and analogs, disulfides, epoxides, etc.).

ChemBridge developed a conceptually novel approach to the design of a general kinase-targeted library using a 3D pharmacophore query-based method that allowed for additional diverse pharmacophores that could confer selectivity resulting in a selection applicable to both tyrosine and serine-threonine kinases. 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 A database of 3-point pharmacophores for the low-energy conformations of 5'-O-methyladenosine was prepared.² The pharmacophore query was then created 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 pharmacophore query was used to search the database of highly filtered EXPRESS-Pick™ Collection stock 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 ATP-binding sites observed in nature.

¹Traxler, P.; Bold, G.; Buchdunger, E.; Caravatti, G.; Furet, P.; Manley, P.; O'Reilly, T.; Wood, J.; Zimmermann, J. Tyrosine kinase inhibitors: From rational design to clinical trials. *Med. Res. Rev.* 2001, 21, 499-512.

²Webb, 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.

Format

- Download structures and custom select KINACore Library and/or KINASet Library compounds.
- Compounds can be provided in 96-well or 384-well format.
- Compounds are available dry or as DMSO solutions.



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