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™ 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.

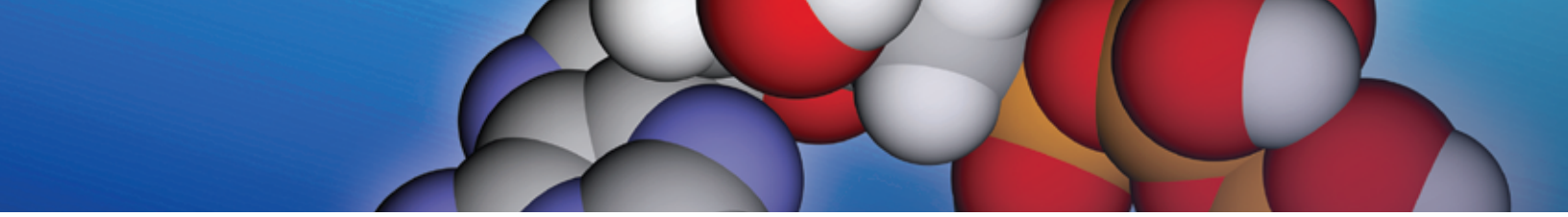
KINACore

The KINACore Library is a computationally selected library of more than 10,000 lead-like 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 380 synthetic schemes and more than 7,500 unique Bemis-Murcko scaffolds (atomic frameworks)3 are represented. 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 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:

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



KINASet

The KINASet Libary is a computationally selected library of more than 10,000 drug-like compounds selected for potential activity against kinases. KINASet Library compounds are part of ChemBridge's EXPRESS-Pick Stock and contain pharmacophores matching pharmacophore queries generated from low energy conformers of the 5′-O-methyladenosine moiety of ATP. More than 4,400 unique Bemis-Murcko scaffolds (atomic frameworks) are represented.

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.

Format

- Custom select compounds according to your requirements
- Delivery in micromole or mg amounts
- Available as DMSO solutions or dry
- Formatted according to your requirements in standard or acoustic qualified plates, in 96-well format racks, or in customer specified materials

Structures

- For files of KINACore Library and KINASet Library structures, please email sales@chembridge.com.
- ChemBridge can provide standard file versions or versions customized to the requirements of your project.

References

1. Traxler, 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.

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. Bemis GW and Murcko MA. The Properties of Known Drugs. 1. Molecular Frameworks. J Med Chem. 1996 39(15) 2887-93.

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