Measuring Kinase Small Molecule Interactions

A snapshot of TruBind Assay work completed by researchers in MSI Drug Discovery Services laboratories worldwide

SUMMARY

The Importance of Kinases

Kinase signaling pathways are principally responsible for the regulation of intracellular processes. When abnormally expressed or controlled, kinase activity can cause cellular dysregulation and contribute to the onset of several diseases, including cancer.

Challenges of Kinase Inhibitor Discovery

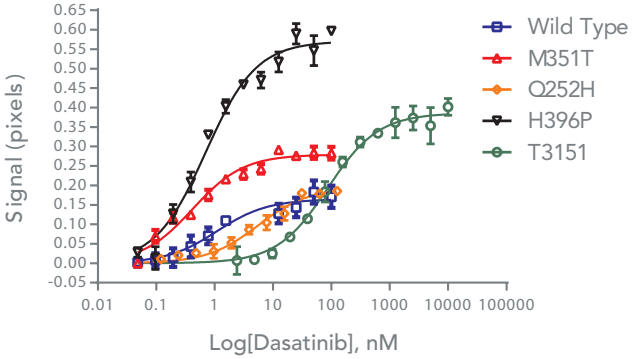
Most kinase inhibitors are Type I, ATP-competitive compounds. Type II inhibitors partially bind the ATP binding site, extending past the gatekeeper into an adjacent allosteric site present only in the inactive conformation. Compared to Type I inhibitors, Type II inhibitors exhibit advantageous pharmacological properties, including improved target specificity. Type III inhibitors bind exclusively to less-conserved allosteric sites outside the ATP pocket beyond the gatekeeper residue and are expected to have superior selectivity profiles and represent new antineoplastics.

Classical kinase inhibition assays rely upon the arrest of kinase activity and so do not lend themselves well to the discovery of Type II or Type III kinase inhibitors.

SUPPORTING DATA

BSI Advantage for Kinase Inhibitor Discovery

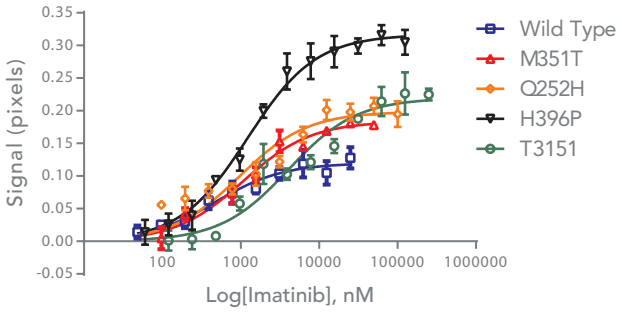
Back-Scattering Interferometry is a label-free, free-solution molecular interaction technology that has demonstrated ability to characterize small molecule – large target interactions, detect target conformational change and allosteric interactions. The unique strengths of BSI make it ideal for the study of second and third generation kinase inhibitors.



BSI analysis of Dasatinib binding against Bcr-Abl kinase Wt and mutants.

Bcr-Abl Type I & Type II Inhibitor Study

BSI was used to study the interaction of Type I (dasatinib) and Type II (imatinib) kinase inhibitors to wild type Bcr-Abl kinase as well as to Bcr-Abl H396P, M351T, Q252H, and T314I mutants. Overall assay design and performance was straight forward, making for facile determination of direct binding affinity.



BSI analysis of Imatinib binding against Bcr-Abl kinase Wt and mutants.

DATA CORRELATION & CONCLUSION

Obtained BSI kinase inhibitor affinities agreed well with previously reported IC_{50} values and are consistent with theoretical and x-ray crystallographic studies of the same systems, lending credence to the overall approach as a viable means to study potency for kinase inhibitors.

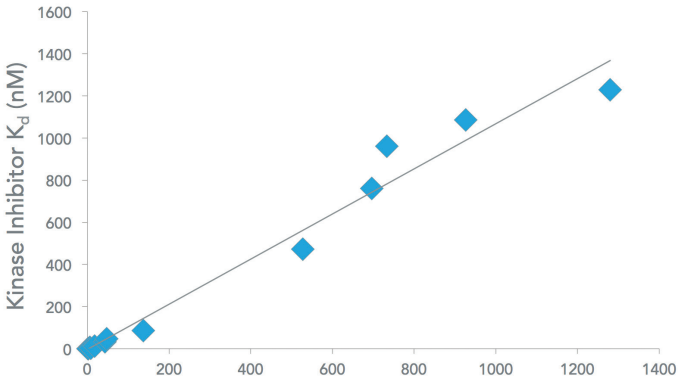


Figure 3: Correlation of BSI determined K_d vs. literature IC_{50} values derived from alternative assay technologies for the studied kinase inhibitor systems. Determined K_d values for each kinase are in high agreement with various modeling and x-ray crystallographic studies.

The demonstrated strengths of BSI to measure small molecule inhibitor binding to both active and non-activated Bcr-Abl combined with its ability to measure direct binding in allosteric systems make BSI an ideal tool for the discovery of Types II and III kinase inhibitors.

KEY BENEFITS

TruBind BSI Technology delivers key benefits in the investigation of kinase inhibitors, with no tags, no surface attachments for true binding characterization.

- Uniquely informs medicinal chemistry for complex and difficult to address targets
- Maintains target integrity: label- and tether-free, free-in-solution; target in native, or native-like, environment
- Target conformation sensitive detection
- Sensitivity to directly detect small molecule binding to large, complex targets
- Determination of mode of allosteric modulation
- Rapid assay development
- Discovery of high-value 'next-generation' therapeutic candidates

Company

Molecular Sensing, Inc. (MSI), is a commercial stage drug discovery tools and contract research services company with headquarters and drug discovery services laboratories in Nashville, Tennessee and an R&D center in Los Gatos, California, along with a European operations center near Frankfurt, Germany.

Headquarters

Molecular Sensing, Inc.
111 10th Ave, South
Suite 110
Nashville, TN 37203

ph +1 615-938-7050
fax +1 615-255-0094

info@molsense.com
www.molsense.com

North America Contacts

Technical Support
Jake Isaacs
+1 615 938-7049
rjisaacs@molsense.com

Technical Sales
Julian Abery
+1 919-724-0946
jabery@molsense.com

European Office & Contact

Molecular Sensing GmbH
Am Frauwald 10
DE 65510 Idstein
Germany
+49 6126 229050
info@molsense.de

European Operations
Wilt Peters
+49 171 7604450
wpeters@molsense.com