

VICHEM CHEMIE LTD.

THE KINASE INHIBITOR COMPANY

RESEARCH SERVICES

In vitro biology services

Assay development and hit finding:

We perform assay development, library screening and hit finding for any new kinase target. Cloning and purification of the protein can be offered as well. The high throughput screening equipment with liquid handling robots is state of the art. Available assay formats:

- Immobilized Metal Assay for Phosphochemicals (IMAP) Fluorescence polarization
- Transreener Kinase Assay with Direct Immunodetection of ADP
- Homogenous Time Resolved Fluorescence assays (HTRF)

Our Nested Chemical Library (NCL™) is an ideal hit finding tool for novel kinase targets. The compounds are tested in biochemical assays for activity against a kinase of interest. The selected and active inhibitors of a particular kinase are applied in therapeutically relevant cellular assays, in order to confirm the role of the kinase activity in this biological model. Validated hits from the NCL™ are good starting points for extended biological screening and compound optimization.

Lead optimization:

We perform a sophisticated medicinal chemistry lead generation and optimization to improve efficacy and ADMET properties of our lead compounds. The major cause of compound failure in drug development is poor pharmacokinetic profile so nowadays the use of in silico ADMET filters has become general tool in drug design. We use this kind of prefiltering of the “to be synthesized” compounds as part of our predictive QSPAR modeling approach.

During lead optimization the biological activity of the compounds is tested with biochemical kinase assays (with IC50s) and with cellular assays as described below in the

efficacy assessment section. The best optimized leads (the so called “developmental candidate” compounds) are tested in vivo and some early ADMET characterization is also performed during “drug candidate” selection but most of the DMPK (Drug Metabolism and Pharmacokinetics) and ADMET characterization is performed during “drug candidate confirmation”.

Required compound properties	Subsequent ADMET issues
Lipophilicity	• Poor solubility • CYP metabolism • Likely CYP inhibitors • Pgp substrates
Flat structure	• Poor solubility • CYP 1A2 metabolism
Hinge binder	• Amidase instability • Poor permeability
ATP-competitive	• High plasma concentrations required • Selectivity
Cell-permeable	• High permeability required

Common problems:

- Solubility
- CYP metabolism
- CYP inhibition
- Pgp substrate
- Toxicity

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