Q² Solutions®

Early Hit-to-Lead ADME Screening Bundle

Bundled Screening Assays to Accelerate Candidate Selection in Drug Discovery

In vitro ADME screening during the lead optimization stage of drug discovery positively impacts drug candidate selection with an enhanced probability of success in clinical trials. Since most new drug candidates fail during preclinical and clinical development, and the late stage of the drug development cycle can be a lengthy and costly process, any means of identifying drug candidates with optimized ADME and pharmacokinetics properties in the discovery stage will have a significant impact on the drug discovery process overall.

Focused on Solutions to Address DMPK Issues and to Enable the Success of Our Clients

Our scientists routinely conduct industry standard in vitro metabolism and DDI-based assays, including highly automated ADME in vitro screens. We can help drive your discovery phase structure activity relationship (SAR) by optimizing for ADME properties, in parallel to your receptor binding potency and selectivity, for more rapid identification of high quality drug candidates.

Metabolic stability, risk assessment for inhibiting key Cytochrome P450 enzymes, and cell permeability are three main early hit-to-lead ADME screening assays that all new chemical entities (NCEs) are tested for in the industry in effort to optimize key ADME properties.

In Vitro ADME Screening Services: Early Hit-to-Lead ADME Screening Bundle

Intrinsic Clearance Assay in Liver Microsomes

- Liver microsomes; species selectable
- Typical turnaround time is ≤10 business days
- Test article prepared at 10mM in DMSO
- Substrate and positive control incubated at 0.3μM
- Incubations performed in HLMs at a protein concentration of 0.25mg/mL
- Incubation performed using 1mM co-factor (NADPH)
- Incubation time points (+NADPH): 0, 5, 15, 30, 45 minutes
- 45 min negative control (-NADPH) for recovery assessment
- Samples analysis and quantitation by LC/MS-MS
- Deliverables: Unscaled intrinsic clearance, recovery
- Results provided via electronic spreadsheet format

CYP Single Concentration Cocktail Assay (CYP 2C9, 2D6, 3A4)

- Human Liver Microsomes (HLM)
- Typical turnaround time is ≤10 business days
- Inhibitors prepared at 10mM in DMSO
- CYP3A4 – Midazolam (5μM), CYP2D6 – Bufuralol (10μM), CYP2C9 – Diclofenac (10μM); substrates incubated as a cocktail
- Test article and positive control inhibitor incubated at 10μM
- Incubations performed in HLMs at a protein concentration of 0.05mg/mL
- Incubation performed using 1mM co-factor (NADPH)
- Incubation time: 3 minutes
- LC/MS-MS analysis using cocktail of heavy labeled internal standard for each metabolite
- A decrease in the formation of the metabolites compared to vehicle control is used to calculate a percent inhibition value
- Samples analysis and quantitation by LC/MS-MS
- Deliverables: Percent inhibition at 10μM
- Results provided via electronic spreadsheet format

In Vitro ADME Screening Services: Early Hit-to-Lead ADME Screening Bundle *continued*

MDCK II Bi-directional Permeability Assay

- MDCK II cell line (Madin-Darby Canine Kidney cells) – Sigma Aldrich (ECACC)
- Typical turnaround time is ≤15 business days
- Test article prepared at 10mM in DMSO
- Substrate and positive control incubated at 1μM in duplicate
- Incubations performed in both A:B and B:A in the presence of Cyclosporin A (P-gp inhibitor)
- Incubations carried out in cell culture incubator at 37°C/5% CO^2/95% RH
- Samples taken from the A:B plate and B:A plate following a 3 hour incubation
- A 9-pt concentration curve is prepared for quantitation of samples (2000, 1000, 500, 250, 125, 62.5, 31.3, 15.6, 7.81nM)
- Dextran Texas Red (DTR) used as monolayer integrity check
- Sample analysis and quantitation by LC/MS-MS
- Deliverables: Papp in both A:B and B:A direction, BA:AB ratio, mass balance (using both pre and post dose solutions), percent cell leakage (% DTR)
- Results provided via electronic spreadsheet format

About Q² Solutions Bioanalytical and ADME Services

Q² Solutions operates one of the world's largest and most respected bioanalytical and ADME laboratory networks. From our global locations, we serve many of the largest pharmaceutical, specialty pharmaceutical and biotechnology companies in North America, South America, Europe and Asia. Our highly trained scientists utilize a range of leading-edge technology, automation and state-of-the-art techniques.

In Vitro ADME Assays and Metabolite Identification Services in support of rapid drug discovery ADME property optimization and regulatory filings.

Bioanalytical Liquid Chromatography Mass Spectrometry (LC/MS) Services for the quantitative determination of small molecule, peptide and macromolecule therapeutics in support of pharmacokinetic (PK) studies.

Immunoassay Services for the quantitative determination of large molecule therapeutics using ligand binding technologies in support of pharmacokinetic (PK) studies. Immunogenicity assessments for pre-clinical and clinical studies including tiered based approaches, neutralizing assays and isotyping assays.

Fit-for-Purpose Biomarker Services for the quantitative determination of discovery, pre-clinical and clinical biomarkers using LC/MS, Immunoaffinity-LC/MS and Immunoassay technologies in GLP compliant facilities.

Contact us today to learn how we can help you characterize the drug disposition properties of your small molecule platforms and to enable successful drug discovery.

Contact us

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