Abstract

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Assay development of hight content metabolic stability and aldehyde oxidase benchmarking tool for drug discovery

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Abstract

Understanding the metabolism of new chemical entities at an early stage has become common practice in the pharmaceutical industry.

An automated, high throughput, in vitro assay for evaluation of the intrinsic clearance in liver microsomes, Cytochrome P450 (CYP) contribution, and metabolic soft spot identification, was developed. This assay utilizes a combination of technologies and methods including automated liquid handling, acoustic sampling, in silico prediction, and hybrid quadrupole -orbitrap mass spectrometry, to efficiently generate and deliver data both in a high throughput manner, and in a reasonable time frame early in the drug discovery process.

Aldehyde oxidase (AO) has become an important clearance pathway in recent years. Due to the subcellular location of this enzyme, first tier discovery metabolic stability assays using human liver microsomes fail to identify the contribution of AO-mediated metabolism in new chemical entities. An automated, high throughput, in vitro assay was developed as a benchmarking tool for an in vitro

- in vivo correlation of intrinsic clearance using commercial drugs known to be metabolized by AO using in vitro systems (human liver cytosol, liver S-9 fractions and human hepatocytes). This work provides a relative scale that can be used for an in vitro - in vivo correlation of AO clearance and can provide acceptance criteria as to when a potential new drug candidate that is metabolized by AO will have acceptable human clearance. This assay allows for quick structure activity relationships to guide further structural modifications for new chemical entities predicted to have AO mediated metabolism.

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Biography

Moein Masjedi has completed his PhD at the age of 29 years from Shiraz University of Medical Sciences. He is CEO of Daroosazan Sorena Exir Cosmetic Company (DSE Co.), a nanotechnology-based cosmetic manufacturing company. He has published more than 9 papers in reputed journals..

