

Inhibitor Screening by Mass Spectrometry.

Kenneth D. Greis

University of Cincinnati Genome Research Institute, 2180 E. Galbraith Road, Cincinnati, OH 45237, USA

Robust methods that monitor enzyme activity and inhibitor potency are crucial to drug discovery and development. Over the past 20 years, mass spectrometric methods have increasingly been used to measure enzyme activity and kinetics. However, for rapid screening of inhibitory compounds, various forms of fluorescence and chemiluminescence readout have continued to dominate the market. As the sensitivity, speed and miniaturization of mass spectrometry methods continue to advance, new opportunities to couple mass spectrometry with screening have come to the forefront. Mass spectrometry-based quantitative measurements are typically performed by LC-MS to eliminate buffer salts that interfere with electrospray ionization. However, MALDI-MS offers a label-free and direct readout of substrate and product, a fast sampling rate, and is tolerant of many buffer salts, reagents and compound that are typically found in enzyme reaction mixtures. In this report, a demonstration of how MALDI-MS can be used to directly measure ratios of substrates and products to produce IC_{50} curves for rapid enzyme assays and compound screening is provided. Based on the sensitivity, accuracy and speed demonstrated for this approach, MS-based methods are poised to change the landscape of screening assays and ultimately supplant other methods in much the same way that they have in the fields of protein characterization and sequencing, pharmacokinetics, and bioavailability over the past decade.