Optimization in Screening Reactive Metabolites by LC-MS/MS

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Because of potential association of drug bioactivation with idiosyncratic toxicity, screening of reactive metabolites as one of major efforts to reduce attrition rate in drug development, has increasingly become an integral part of the ADMET-guided lead optimization process in drug discovery. A general strategy includes GSH-trapping in microsomal incubations and detecting GSH adducts using LC-MS/MS. Success in detection and identification of GSH conjugates is largely relied on characteristic product ions resulting from CID-induced fragmentation of GSH moiety. It is well documented in literature that GSH conjugates undergo common neutral losses of 75 Da and 129 Da. This presentation will focus on how instrumental parameters and conjugate structures impact the formation of characteristic product ions. Examples will be presented to demonstrate how to utilize our knowledge to optimize our strategy for rapidly detecting and identifying reactive metabolites by using stable isotope trapping.