

In Vitro Bioactivation Risk Assessment (BARA) Report

Compound ID	0101	Requested by	-	Request Date	-	Experiment Date	-
Study Number	081203, 081204	Analyzed by	-	Sample Received	-	Report Date	-

A. Brief protocols

- Conditions of in vitro incubation (all concentrations are final):

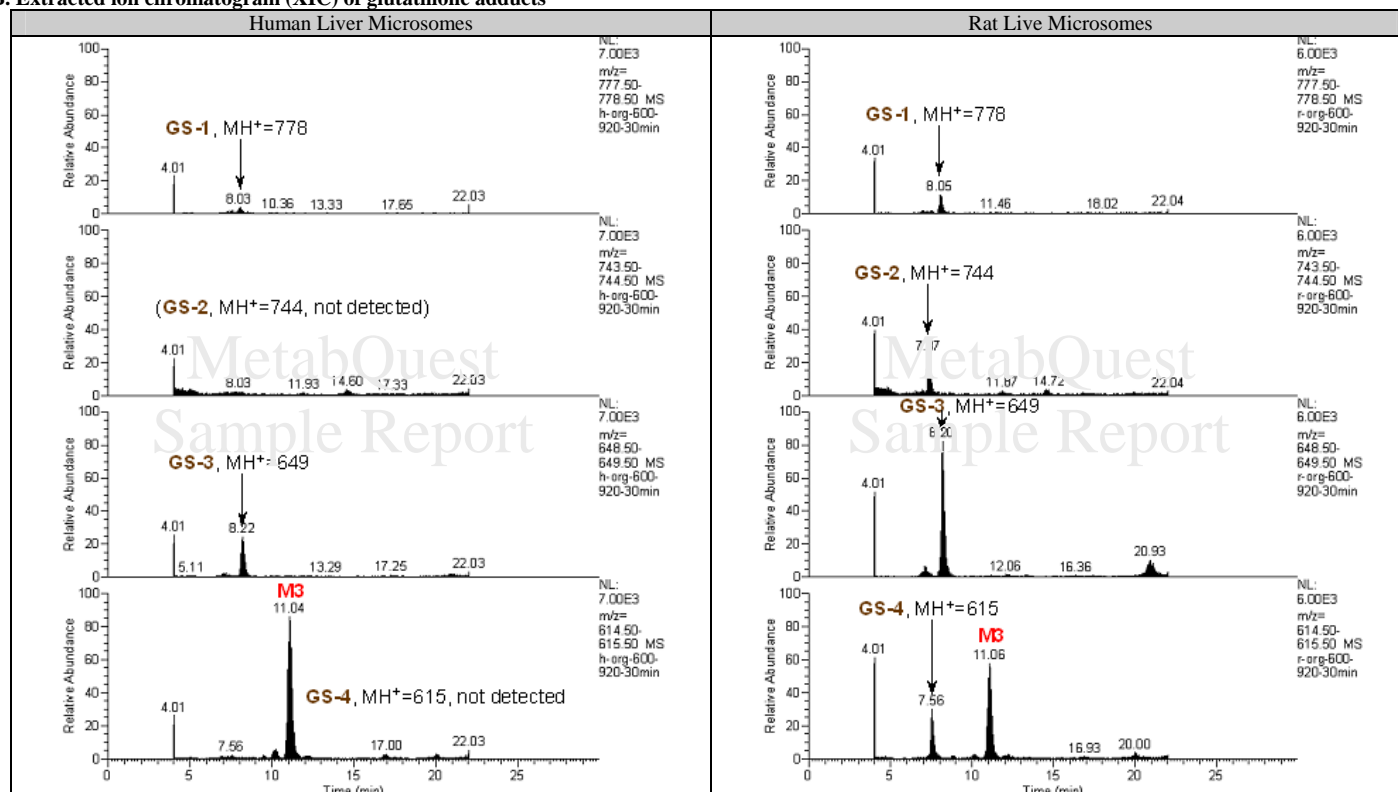
Biological matrices	Human and Rat LM	1.0 mg/mL	Solvent	KPi buffer, pH 7.4	100 mM	Glutathione	2.5 mM
Test Compound	Lapatinib	50.0 μM	Cofactor	NADPH	1.0 mM	Time/Temp.	60 min @ 37 °C

- Control is made by replacing NADPH with KPi buffer; total volume of each incubation is 500 μL;

- Incubations were quenched by addition of 500 μL of MeOH/CH₃CN (1/4, v/v) followed by centrifuge;

- Supernatant (40 μL) was then analyzed by LC-UV-MS/MS.

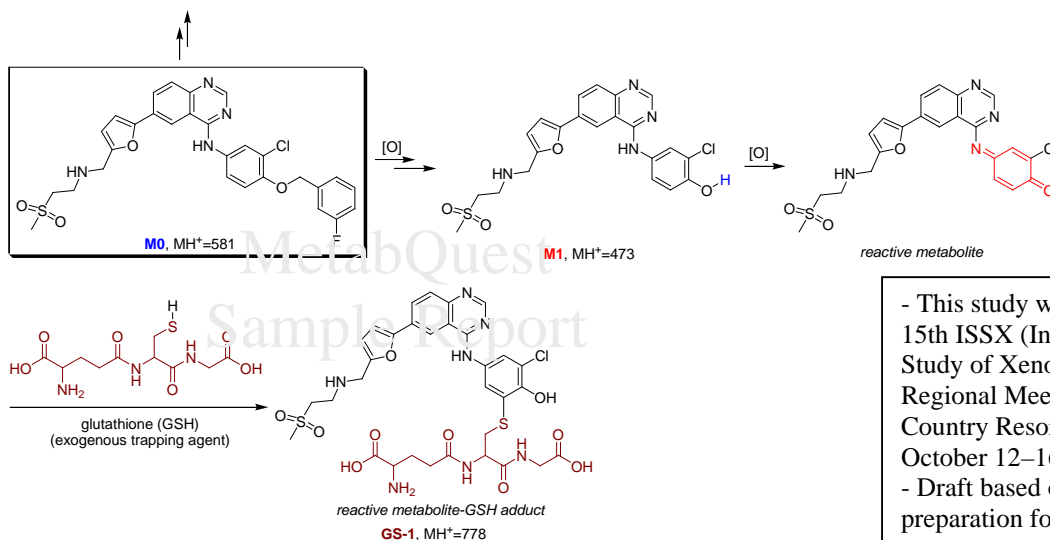
B. Extracted ion chromatogram (XIC) of glutathione adducts



C. Proposed bioactivation pathways*

GS-2, GS-3, GS-4

Elucidated Structures Not Shown Here



- This study was presented as poster at the 15th ISSX (International Society for the Study of Xenobiotics) North American Regional Meeting at San Diego's Town and Country Resort & Convention Center on October 12–16, 2008;
 - Draft based on this study is under preparation for publication.

(Detailed structural elucidation and MSⁿ data are available upon request)

* BARA with "cold" compound might lead to incomplete reactive metabolite profile. All the structures and sites of metabolism are tentative based on MS analysis.

Supporting Data

P2: Mass spectra of M0 and fragmentation analysis;

081201: 0101 HLM MetID

081202: 0101 RLM MetID

P3: Mass spectra and proposed structure of of M1;

(Mass spectra data and structures of M2, M3, M4, and M5 are not shown here)

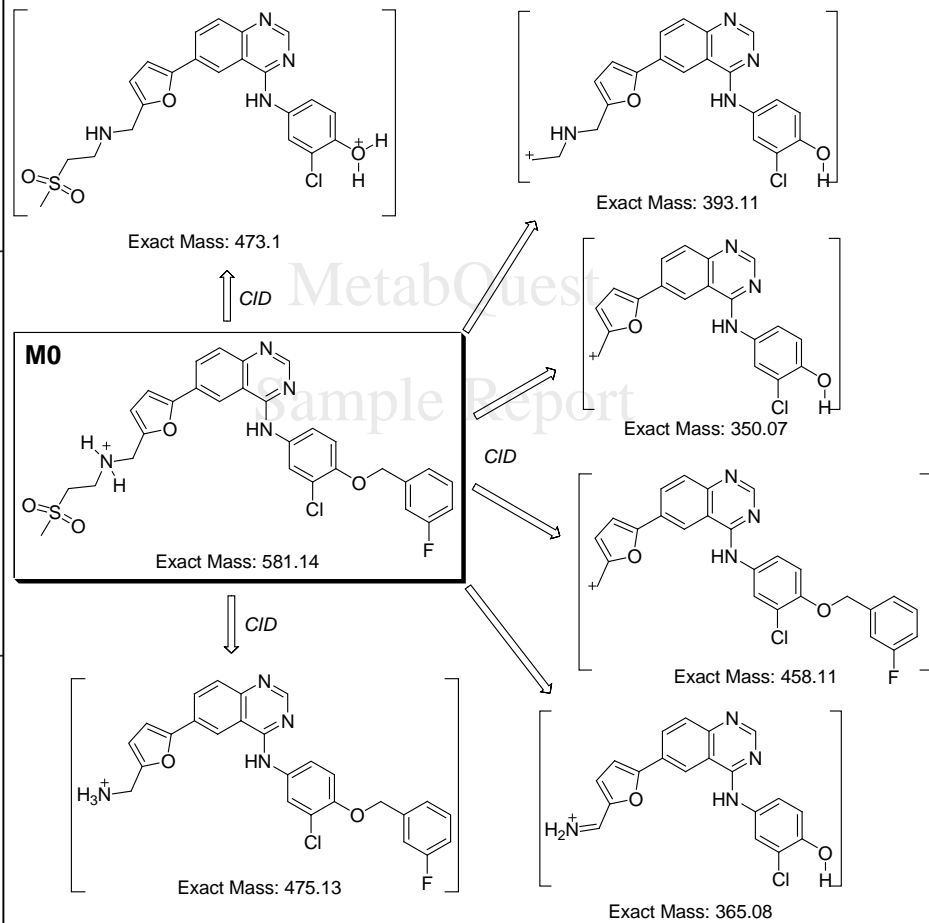
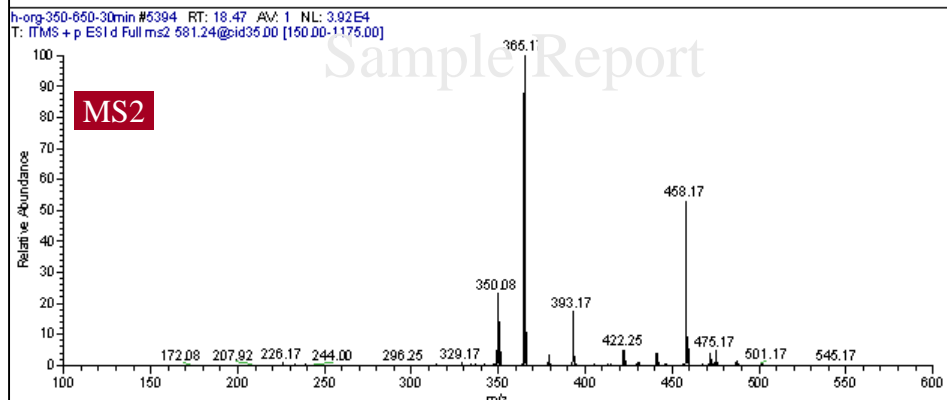
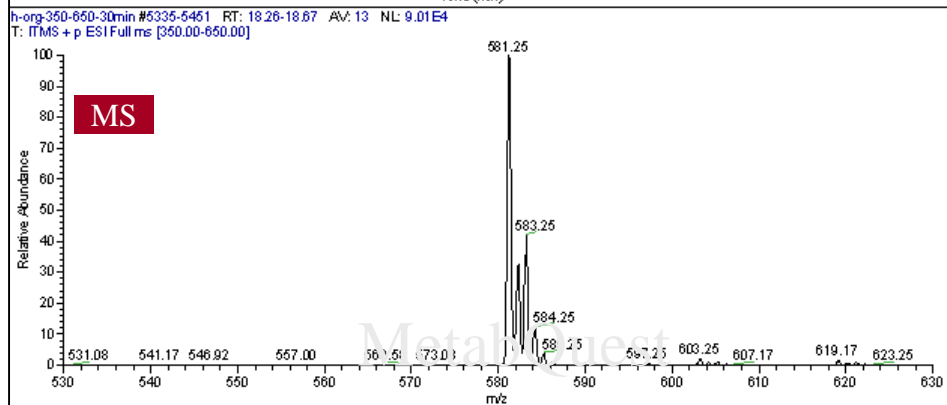
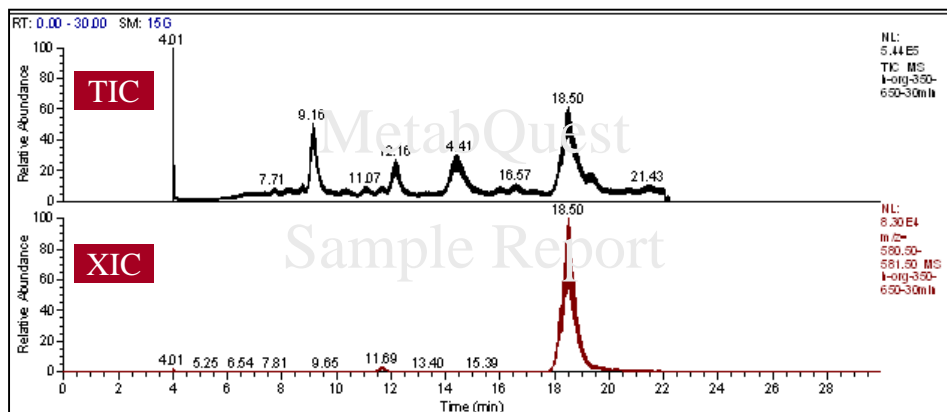
081203: 0101 HLM BARA

081204: 0101 RLM BARA

P4: Mass spectra and proposed structure of of GS-1;

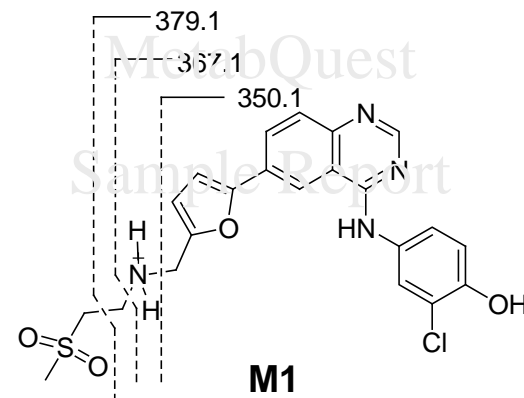
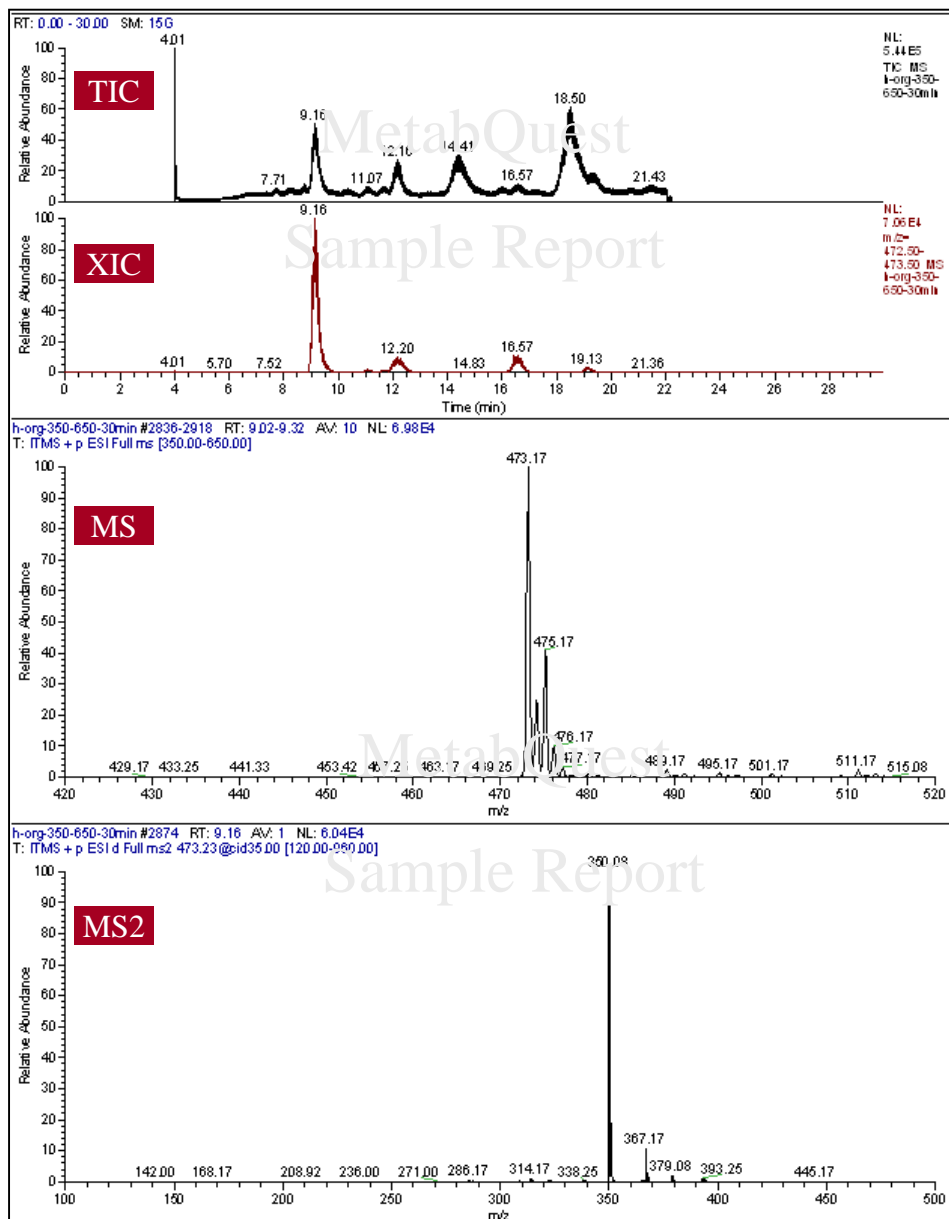
(Mass spectra data and structures of GS-2, GS-3, and GS-4 are not shown here)

M0, MH⁺=581





M1, MH⁺=473

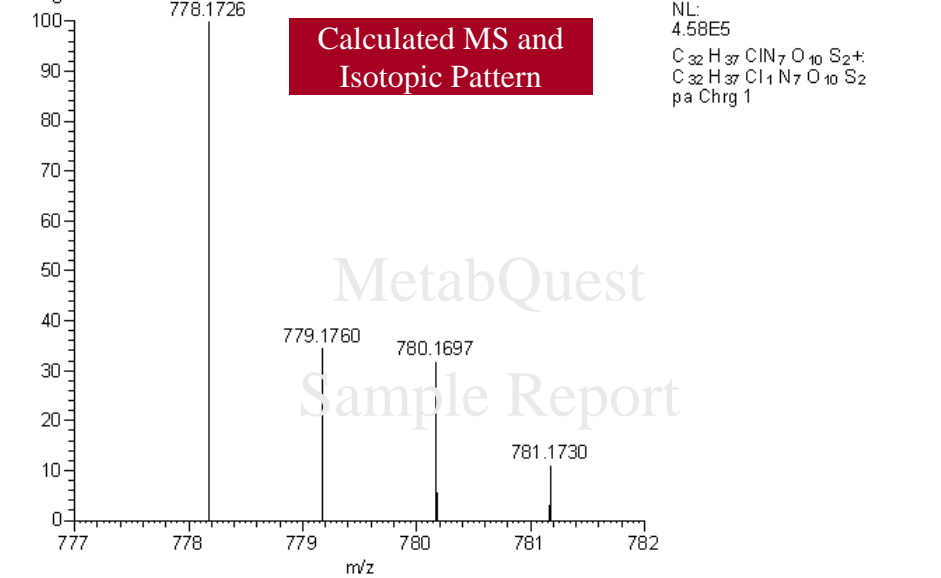
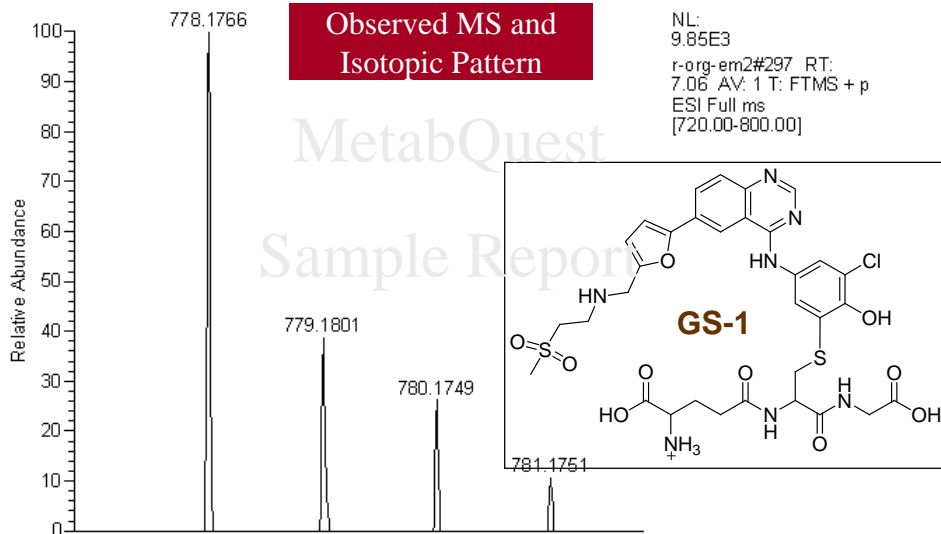




GS-1, MH⁺=778

C:\Documents and Settings\...r-org-em2

9/9/2008 4:47:48 PM



C:\Documents and Settings\...r-org-em2

9/9/2008 4:47:48 PM

