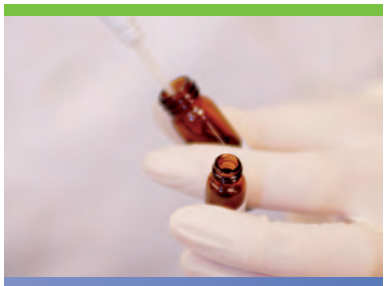
cyprotex discovery

Cloe Select Metabolite Profiling and Identification

cyprotex experts in ADME

Background Information



'We encourage the identification of differences in drug metabolism between animals used in nonclinical safety assessments and humans as early as possible during the drug development process. The discovery of disproportionate drug metabolites late in drug development can potentially cause development and marketing delays'.

FDA Guidance for Industry: Safety Testing of Drug Metabolites (February 2008)

- Understanding which metabolites are likely to be formed *in vivo* is essential for interpreting pharmacology, pharmacokinetic and toxicology data.
- Cyprotex use the Applied Biosystems Sciex QTRAP® 5500 LC-MS/MS for these studies one of the most sensitive ion traps in the industry.
- Cloe Select Metabolite Profiling and Identification service provides critical information on the formation of metabolites including, where appropriate, both Phase I and Phase II metabolism, and comparison of drug metabolism routes in different species.
- Metabolites can be investigated in a number of different matrices including microsomal incubations, hepatocyte incubations, expressed enzyme incubations or plasma samples.
- Cyprotex offers a range of metabolite profiling services depending upon the level of detail and interpretation required.

Service Options Available

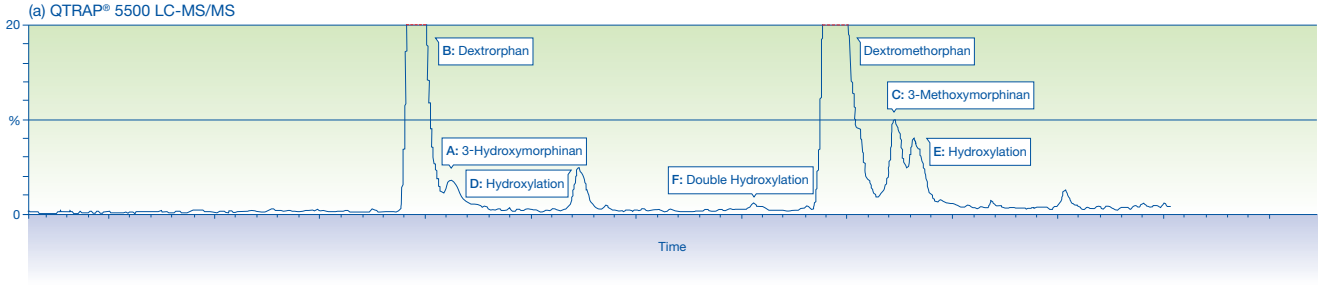
Service Option	Deliverables	Suitable for
LC-MS Metabolite Profiling	• Ion chromatogram of parent and proposed metabolites. • Name of proposed metabolites and where possible molecular formulae. • Table containing metabolite masses, absolute areas, retention time and mass difference from parent.	• Profile of metabolites formed by Phase I or Phase II metabolism. • Cross species metabolite profiling.
LC-MS/MS Metabolite Profiling	As above + • MS/MS spectra of parent and proposed metabolites. • Details of the product ion fragments of parent and any potential metabolites.	• Confirmation of metabolites identified by LC-MS scan. • Detailed metabolite characterisation including structural derivation.
Interpretation and Structural Derivation	As above + • Structural interpretation of the data based on the key fragments observed. • Detailed report containing proposed metabolite structures and expected metabolic pathways. • Expert consultation.	

To find out more contact sales@cyprotex.com

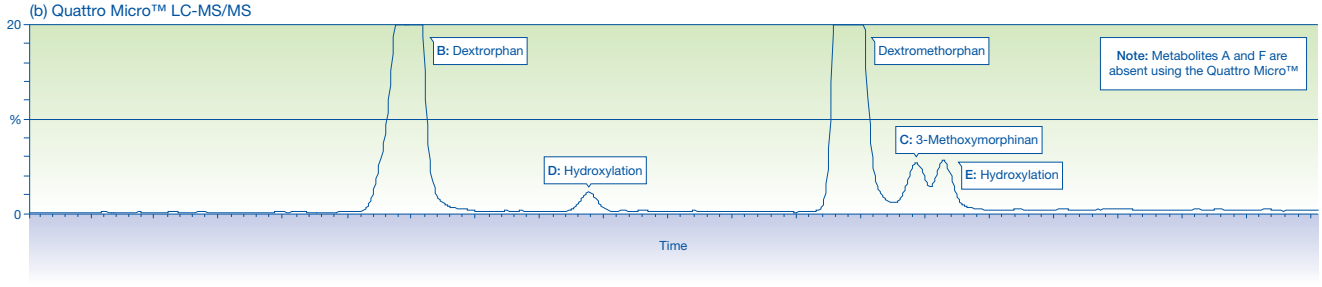
Comparison between the AB Sciex QTRAP® 5500 and the Waters Quattro Micro™ for dextromethorphan metabolism in human liver microsomes.

The AB Sciex QTRAP® 5500 LC-MS/MS detects two additional minor metabolites which were not detected using the Waters Quattro Micro™ LC-MS/MS as shown in the chromatograms below.

(a) QTRAP® 5500 LC-MS/MS

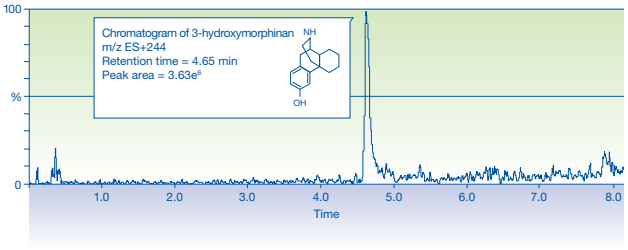


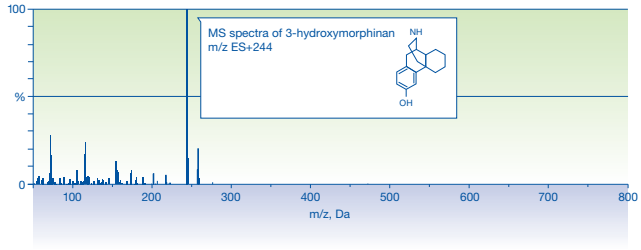
(b) Quattro Micro™ LC-MS/MS



Parent and Metabolites	Metabolite Reference	Mass difference from parent	Mode and m/z	QTRAP® 5500		Quattro Micro™	
				% Area (Sample)	% Area (Control)	% Area (Sample)	% Area (Control)
Dextromethorphan			ES + 272	57.4	99.7	59.6	100
3-Hydroxymorphinan	A	-28	ES + 244	1.27	0	Not detected	Not detected
Dextrorphan	B	-14	ES + 258	31.6	0.29	34.5	0
3-Methoxymorphinan	C	-14	ES + 258	4.09	0	2.46	0
Hydroxylation	D	+16	ES + 288	2.04	0	1.01	0
Hydroxylation	E	+16	ES + 288	3.24	0	2.46	0
Double Hydroxylation	F	+32	ES + 304	0.35	0	Not detected	Not detected

Detailed MS chromatogram and spectra are provided for metabolites:





In addition, MS/MS spectra can also be provided along with a detailed report which provides interpretation of the data: