

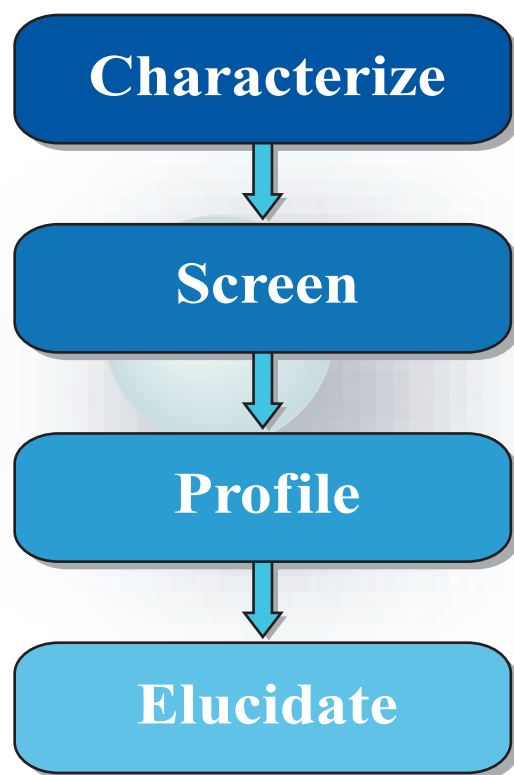


Novatia



Metabolism Analysis Services:

Drug discovery researchers have strongly emphasized the importance of obtaining qualitative measurements of their drug candidates as early as possible in the discovery process. Accelerated evaluation is “the name of the game” in everything from understanding basic ADME/Tox properties, to determining biotransformation “hot-spots”, to completing structure determination. With current technology, samples from both *in-vitro* and *in-vivo* origin can be analyzed. Novatia’s metabolism approach encompasses four basic steps that can be matched to address your specific project needs:



- Novatia’s approach begins with compound Characterization to determine pre-assay integrity and assess compound performance for all downstream metabolic assays.
- During Screening, Novatia offers various high-throughput assays such as Metabolic Stability and Half-Life Determination.
- More detailed metabolite information can be obtained using our Profiling services. Offerings range from *in-vitro* inter-species metabolic profiling to *in-vivo* metabolite identification.
- And finally, highly detailed structural information can be obtained using our Elucidation services. Novatia utilizes multi-stage MS/MS, high resolution MS and high-field capillary NMR to answer questions such as site of attachment and even complete structural assignment.

Pre-assay Characterization

Characterize

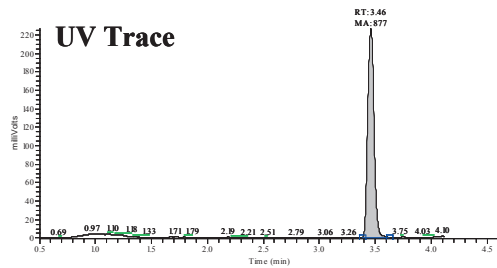
Your need for rapid turnaround time is important, but one must also pay particular attention to scientific integrity. It is equally important that you can trust the assay results from your metabolic screens. Frequently drug candidates have purity, solubility and chemical stability issues that go undetected. These can generate misleading results in the metabolic stability screen that are difficult to troubleshoot post-assay. We at Novatia advocate starting with Pre-assay Integrity Screening to characterize your compounds in the context of the assay. This is to insure quality results from your submitted samples.

The Pre-assay Integrity Screen determines the “drug candidate's” purity, stability, solubility and MS performance from two samples using LC/UV/MS: one sample dissolved in 100% organic and the other in assay buffer.

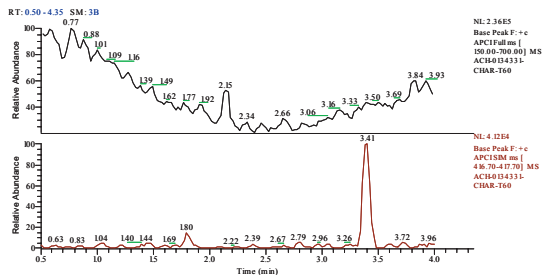
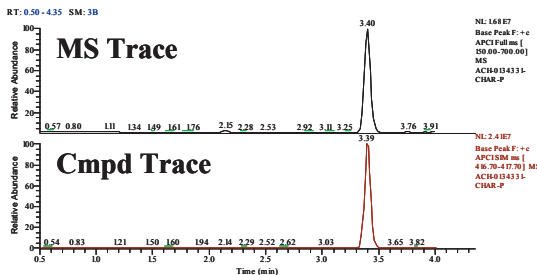
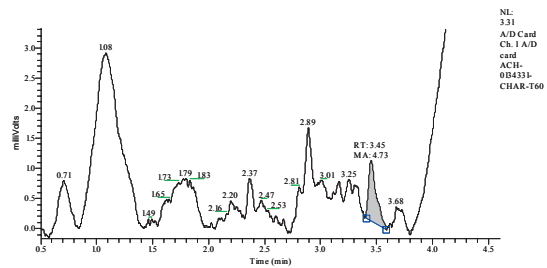
Pre-assay components are as follows:

- Purity is calculated from the organic sample based on UV %area
- Solubility is calculated from the ratio of MS and UV signals between the organic and assay buffer samples
- Stability is assessed from the appearance of additional peaks in the assay buffer sample.
- MS performance is evaluated using overall signal and observed fragmentation

Organic Solvent



Assay Buffer



Cmpd	MS CMP P	MS CMP T60	CMP MS Drop P->T60	MS CMP [] T60	UV CMP P	UV TOT P	UV CMP T60	UV TOT T60	UV % CMP P	UV % CMP T60	% CMP Drop P->T60	CMP UV Drop P->T60	UV CMP [] T60
1	5.4E+07	4.2E+05	99%	0.77	780	780	1	1	100%	100%	100%	100%	0.13
2	1.2E+08	7.5E+07	37%	0.92	412	412	280	280	100%	100%	100%	32%	0.77
3	2.5E+07	4.4E+04	100%	0.18	874	874	4	4	100%	100%	100%	100%	0.46
4	9.4E+06	7.2E+05	92%	1.75	746	760	12	12	30%	100%	102%	98%	1.01
5	6.0E+07	2.1E+07	65%	35.18	734	743	234	746	9%	31%	32%	68%	31.88

Organic VS Buffer
MS Signal LOW

+

Cmpd Peak
Purity high

+

Organic VS Buffer
UV Signal LOW

= Possible Solubility Problem

Even if you have this type of information already in-hand, it is still recommended to use Novatia's approach, which is performed just prior to any assay and designed specifically for answering questions related to in-vitro metabolism studies.

Metabolism Screening Assays

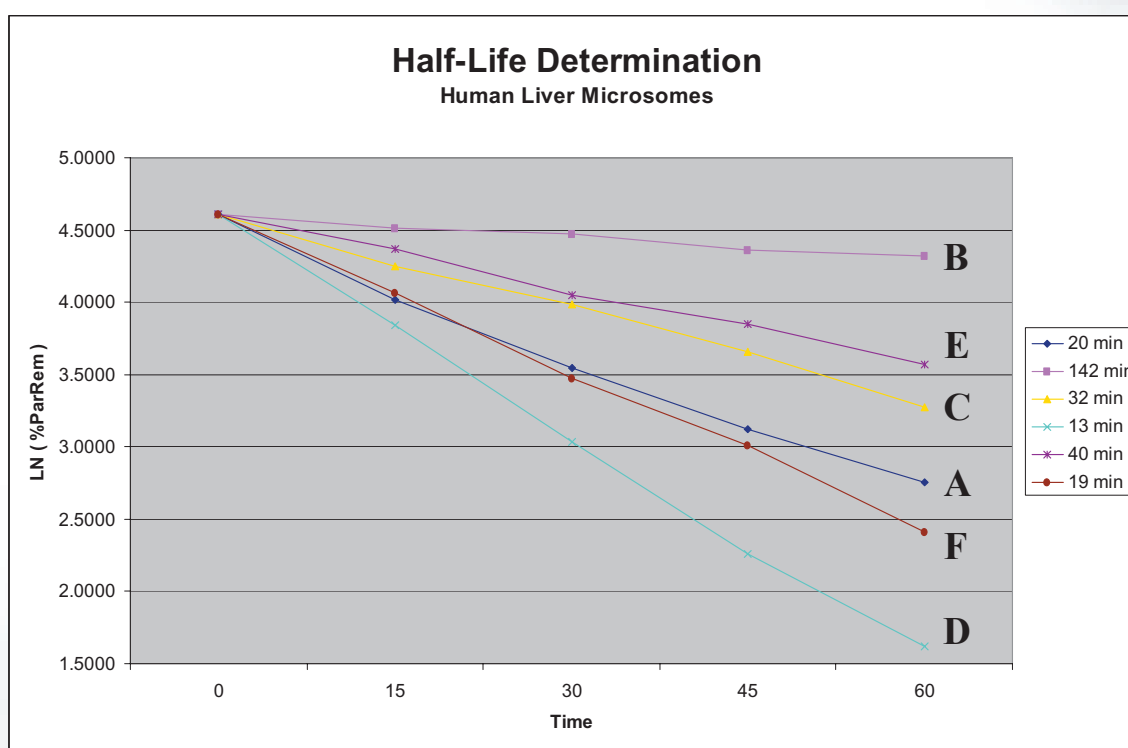
Screen

Novatia offers high-throughput *in-vitro* data of drug metabolic stability, half-life, and P450 enzyme specificity studies. We provide non-cellular and cellular assays that utilize rapid highly specific LC/MS/MS detection. Custom reports are generated which allow for rapid data evaluation. Chemists in your organization can then intelligently and quickly incorporate the information into the next synthetic series of compounds.

Assay options offered:

- Non-cellular conditions using microsomes, S9, cytosol extracts, etc. from multiple species
- Cellular conditions using fresh, cryo-preserved, and immortal hepatocytes, etc. from multiple species and cell lines
- Wide range of compound concentrations allowed
- Customized assay development and reporting

Again, all analyses are performed using high-throughput LC/MS/MS methods for speed, sensitivity, and specificity. We also encourage assay customization, which offers the best chance of integrating our results into your process. We have automated data processing routines to provide further ease of data reporting. Reporting can also be customized to meet your needs.



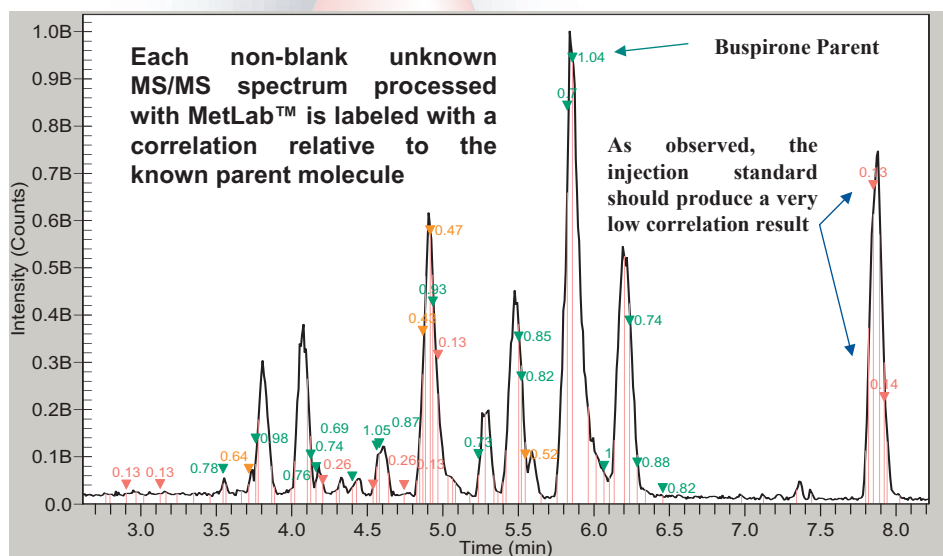
Compound	%Par Rem T0	%Par Rem T20	%Par Rem T30	%Par Rem T45	%Par Rem T60	%Par Rem T0 (LN)	%Par Rem T20 (LN)	%Par Rem T30 (LN)	%Par Rem T45 (LN)	%Par Rem T60 (LN)	m	b	R ²	T1/2
A	100.0000	55.6624	34.6154	22.7564	15.7051	4.6052	4.0193	3.5443	3.1248	2.7540	-0.0306	4.5288862	0.9919	20.1
B	100.0000	91.1765	87.6471	78.2353	75.0000	4.6052	4.5128	4.4733	4.3597	4.3175	-0.0049	4.5993868	0.9789	141.5
C	100.0000	69.7778	53.7778	38.7556	26.3111	4.6052	4.2453	3.9849	3.6573	3.2700	-0.0217	4.6042021	0.9962	31.9
D	100.0000	46.6667	20.7143	9.6032	5.0556	4.6052	3.8430	3.0308	2.2621	1.6205	-0.0503	4.5823813	0.9984	13.3
E	100.0000	79.0909	57.5000	46.8182	35.4545	4.6052	4.3706	4.0518	3.8463	3.5683	-0.0173	4.608048	0.9968	40.2
F	100.0000	58.3673	32.2449	20.3265	11.1837	4.6052	4.0668	3.4734	3.0119	2.4145	-0.0362	4.6015857	0.9988	19.0

Tabular Half-Life results for six compounds in Human Liver Microsomes.

Metabolite Profiling

Profile

It is highly desirable to obtain simultaneous identification of drug metabolites along with component profiling information for inter-species comparisons. By acquiring the full scan and MS/MS data during an LC/MS run, we are able to propose sites of biotransformation for most major metabolites and relate their relative abundance across samples. Rather than conduct slow manual interpretation at this stage, we quickly provide this time-sensitive data using our own patented software, MetLab™ Profiler. This software generates rapid interpretation and reporting of proposed metabolites in an automated fashion. The goal is to provide you with insight into compound “hot-spots” for all major metabolites in order to assist you in directing your chemistry decisions.



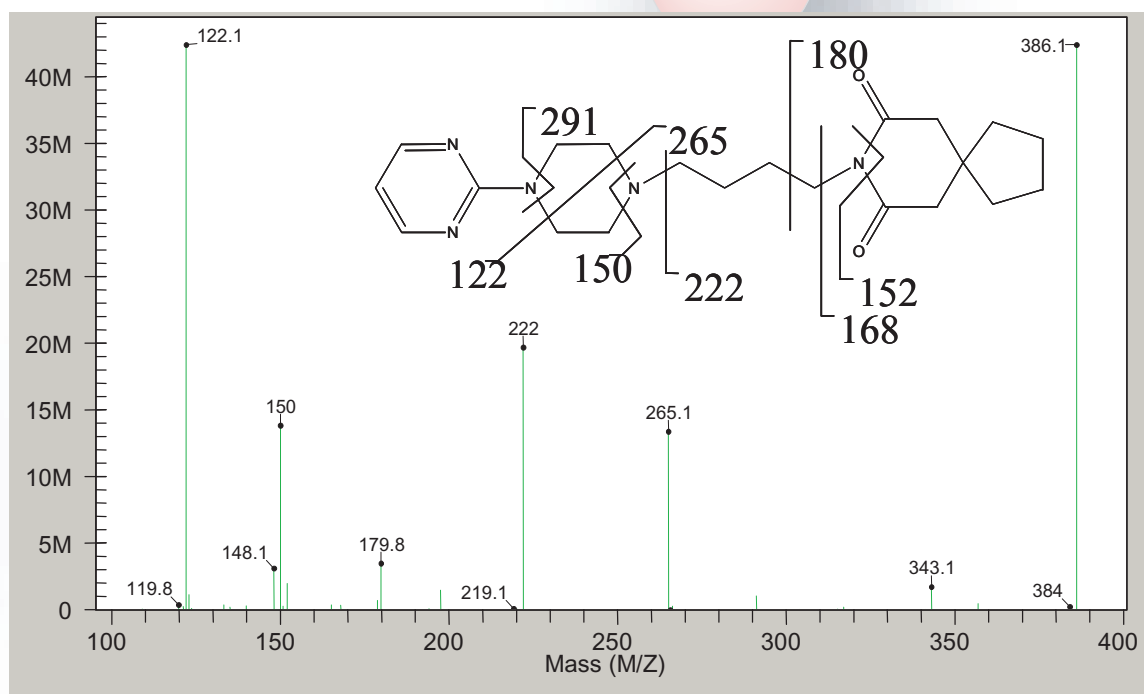
Metabolite	RT	M+H	Corr	Shifted Ions	Common Ions	Unique Ions
Dihydrox	3.54	418	High	122(+16), 150(+16), 265(+16), 222(+16)		
Dihydrox	3.72	418	Mid	122(+16), 150(+16), 222(+16)		235, 220
Hydrox	3.76	402	High	265(+16), 222(+16)	122, 150	359
Hydrox	4.12	402	High	265(+16), 222(+16), 291(+16)	122, 150	219, 220
Dihydrox	4.16	418	High	265(+16), 222(+16)	122	267, 400, 374, 220
Dihydrox	4.40	418	High	180(+16), 222(+16), 265(+16)		267, 164, 293, 374
Hydrox	4.56	402	High	222(+16), 265(+16)	122, 150	359
Dihydrox	4.58	418	High	122(+16), 150(+16), 265(+16), 222(+16)		400
Unknow	4.87	360	Mid		122, 265	343
Hydrox	4.93	402	High	222(+16), 265(+16)	122, 150	359, 342
Dihydrox	5.24	418	High	222(+16), 265(+16)		267, 293, 306, 374, 400
Hydrox	5.50	402	High	122(+16), 150(+16)	222, 265, 180	
Unknow	5.52	372	High	150(-14)	122, 222, 265	251
Paren	5.86	386	High			
Hydrox	6.24	402	High		222, 265, 122	358, 384

Buspirone metabolites found using MetLab™ Profiler.

Metabolite Elucidation

Elucidate

If detailed structural elucidation of metabolites is required, Novatia can utilize a variety of techniques such as: multi-stage MS/MS, high resolution MS, low-level component isolation and high-field capillary NMR analyses. One of our unique systems, called SepNMR, is designed to automatically isolate low-level components under conditions suitable for trace NMR analysis, thus lowering the burden for obtaining detailed structural information on critical samples. These powerful techniques can be used to answer questions ranging from biotransformation site of attachment to complete structural assignment on metabolites produced from *in-vitro* or *in-vivo* origins. The amount of detail obtained can be tailored to meet your specific project needs.



Buspirone MS/MS Substructure Template.

About Novatia and our business model:

Novatia is a company of extremely bright and innovative scientists who specialize in analytical applications. Our team has vast experience with LC/MS, NMR, HPLC, automation, data analysis, custom software development and high-throughput analysis strategies. Our main application areas are in the pharmaceutical and biotech arenas. We work with instrument vendors, instrument users, and analysis clients. We often create unique methods and technologies in the process of conducting our standard suite of contract analyses, and we try as much as possible to make those innovations commercially available to interested customers. These innovations often include experimental protocols along with custom software and/or hardware integration.

Also, particularly useful are our analytical services for those clients who do not have the relevant instrumentation and/or analytical expertise in-house. Furthermore, if a client desires to use our methods or technologies in their own shop, we will develop "a total solution" so that they too can perform the exact analysis in their own lab while using our proven methods. We therefore assist customers through our services, product offerings, consultation, and/or custom development projects.

A quick recap would be: "we'll run it for you in our lab, we'll help you run it in your lab, or we'll help you acquire it so that anybody can run it"

Of further interest?

Novatia has active and ongoing research projects with collaborators in the metabolism area. Should you be interested in collaborating with Novatia on a customized solution for your laboratory, we would be delighted to discuss it with you. Please contact us in any of the following ways:

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info@enovatia.com

* Phone:
732-274-9933

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Monmouth Junction, NJ 08852