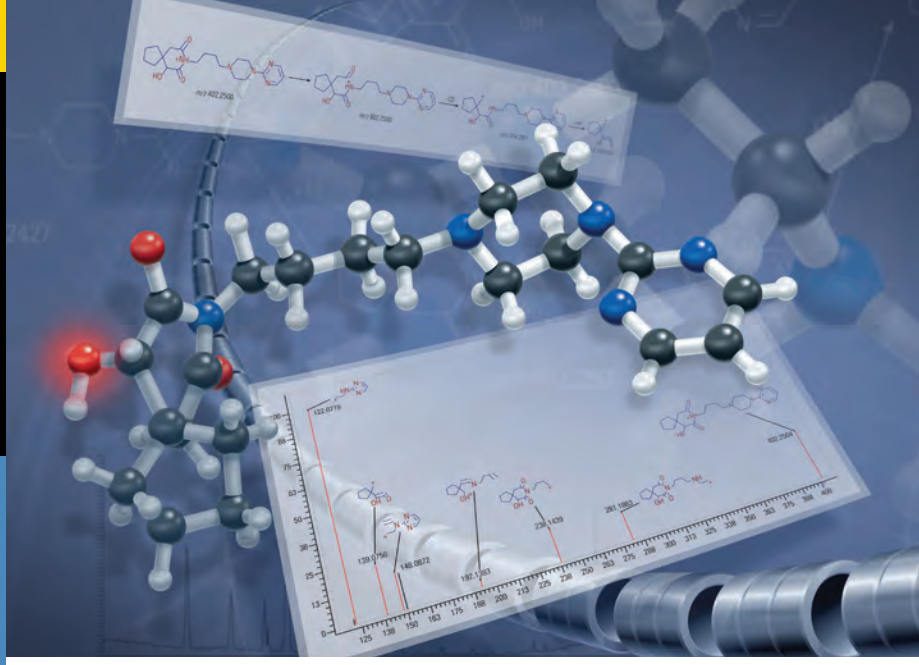
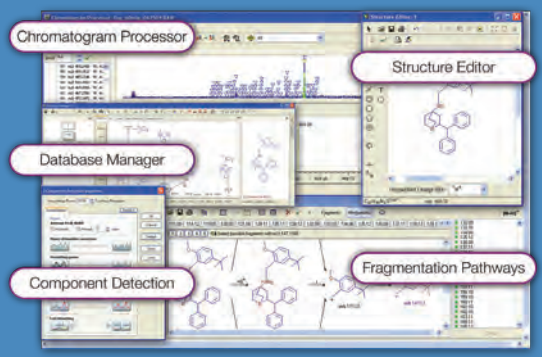
Thermo Scientific Mass Frontier Software





Chemically Intelligent Small Molecule Structural Elucidation Software for Mass Spectrometry

Thermo Scientific Mass Frontier software offers a confident path from spectra to structure through chemically intelligent structural elucidation. The software simplifies the management, evaluation, and interpretation of mass spectral data and can be used for metabolism, metabolomics, forensics, natural products, impurities, and degradants research. The software delivers several unique features to improve ease-of-use, increase throughput of analyzed compounds, reduce potential for false positives, and offer more confident structural elucidation.

- **FISh – novel screening of structurally similar compounds based on parent fragmentation pattern**
- **Unique and innovative library technology to capture and categorize the variation in MS^n data from LC/MS**
- **Ability to save current work and processing methods for automated data analysis**
- **Chemically intelligent automatic spectral annotation using user-defined or HighChem Fragmentation Library™**
- **Automatic localization of the modification site through color coding highlighting fragments common to parent compound**

Thermo Scientific Mass Frontier software offers several innovative features for the management, evaluation, and interpretation of mass spectral data not available in any other software program offered in the market place. The software provides the tools to quickly transform mass spectral data into results. Newly enhanced features offer fast, confident small molecule structural identification from MS^n data with extensive literature coverage on fragmentation mechanisms and client-server database capabilities for dynamic library searching and storage. Mass Frontier software supports all Thermo Scientific LC and GC mass spectrometers for small molecule structural elucidation and is applicable to a wide range of applications. It also complements Thermo Scientific application-specific software:

- **MetWorks metabolite identification software for the study of biotransformations**
- **MetQuest automated screening software for simultaneous quan/qual drug metabolism and pharmacokinetic analysis**
- **SIEVE differential analysis software for the study of metabolomics**
- **ExactFinder workflow software for routine targeted and general unknown screening applications**

Unparalleled Fragmentation Prediction Capabilities

Generation of Fragments and Mechanisms

Exclusive fragmentation prediction algorithms eliminate tedious and time-consuming manual spectral interpretation. Mass Frontier software accelerates confident structural elucidation by simplifying the interpretation of MS^n spectra through comprehensive fragmentation mechanism knowledge management.

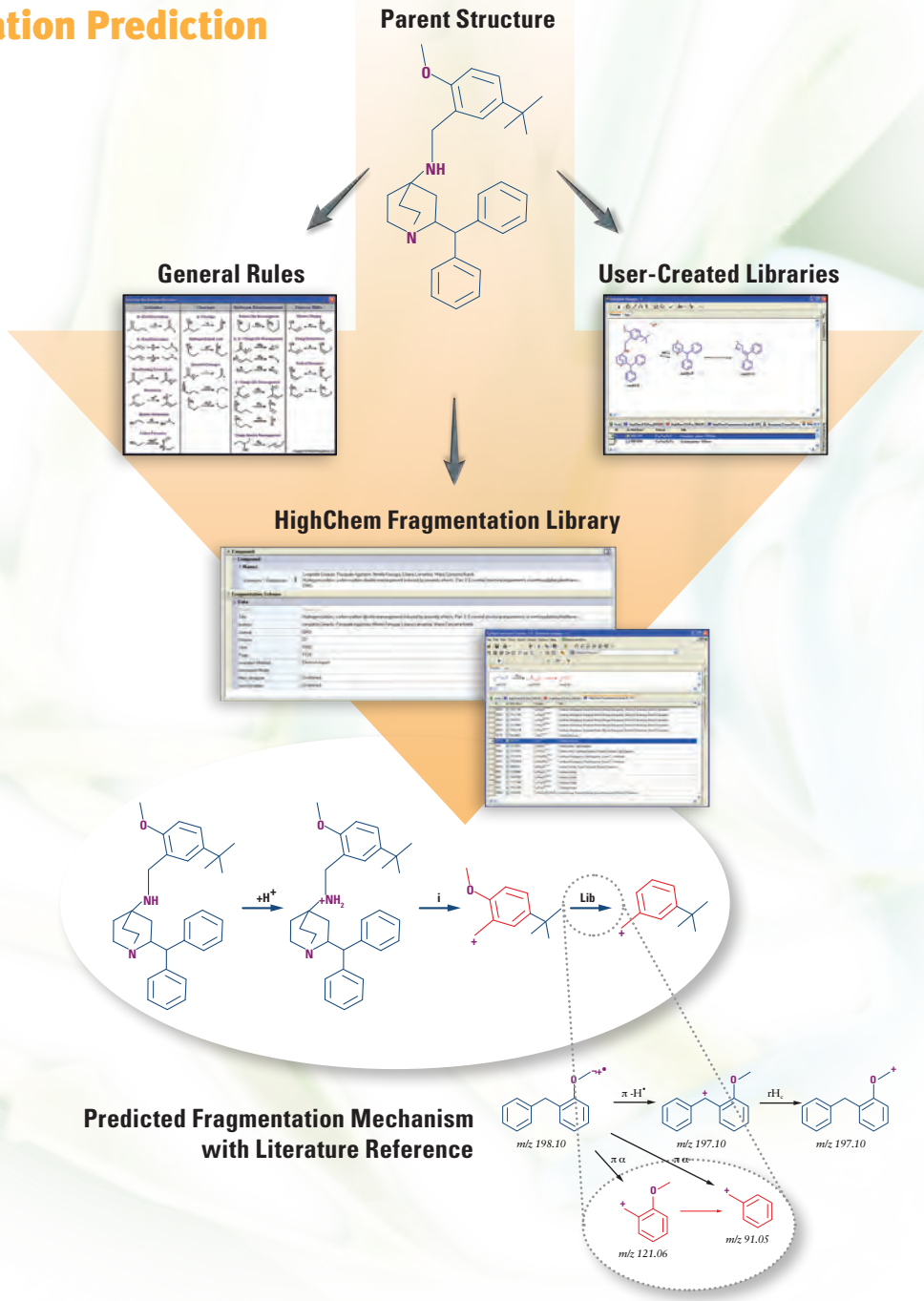
Fragments and Mechanisms – General Rules

Mass Frontier software predicts and displays comprehensive fragmentation pathways based on a set of general ionization, fragmentation, and rearrangement rules. The Fragments and Mechanisms tool automatically generates fragments from a user-supplied chemical structure. It can also generate theoretical "bar code" mass spectra, allowing the user to compare predicted and experimental mass spectra to confirm structural identity.

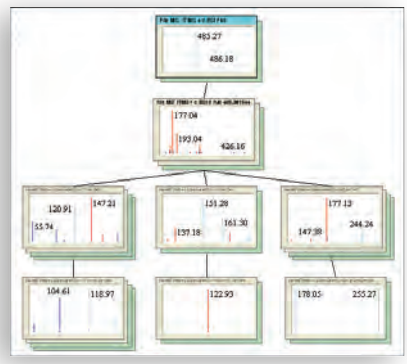
To determine the structure of unknowns, Fragments Comparator is a useful tool that compares fragments derived from different compounds. Often, two isomeric compounds can be differentiated by the presence or absence of diagnostic fragment ions. The Fragments Comparator automatically identifies common and unique fragments.

Fragmentation Library – Literature and User Defined

The predictive fragmentation capabilities of the copyrighted HighChem Fragmentation Library™ are exclusive to the program and contain fragmentation mechanisms for small molecules collated from published literature. Each mechanism, along with the chemical structures, is manually verified and saved in the library along with complementary information such as the title, authors, and source of the information. This allows the user to quickly search thousands of entries and eliminates the time lost to manual literature search. The library currently has over 120,000 literature-proposed mechanisms and together with the aforementioned general ionization, fragmentation, and rearrangement rules, serves as a knowledge base for the prediction of fragmentation pathways. In addition to the literature-based Fragmentation Library, Mass Frontier software allows the user to create their own unique libraries of customized fragmentation mechanisms, save to the database, and apply to further enhance the predictive capabilities of the program. Different groups of users can also easily share and manage their knowledge through the client-server capabilities.



Predictive fragmentation using Mass Frontier software. Clicking on "Lib" takes the user directly to the literature reference. The fragmentation mechanism pertaining to the cited literature reference is color coded for easy interpretation.



The information stored as spectral ion trees collectively and uniquely defines the structure of the molecule.

Spectral Ion Tree Libraries

Innovative Library Technology Tuned for LC/MS Spectra

Commercial GC/MS libraries can contain hundreds of thousands of compounds. The fragmentation pattern is the result of standardized ionization settings and the library quality is not overly influenced by the mass analyzer settings.

The situation is different for LC/MS where soft ionization techniques are used and fragmentation is initiated via CID in the mass analyzer. As a result, the type of instrument and analyzer settings have a profound influence on the appearance of the spectra and unlike GC/MS libraries, there are no established standard conditions under which to generate the fragmentation spectra. Users building LC/MS libraries have, therefore, had to determine their own standard experimental conditions and instrument platform to generate usable LC/MS/MS libraries. It is for these reasons that large commercial LC/MS libraries are not available.

Recognizing the need for users to be able to use and share MS/MS libraries that may have been collected under different conditions, Mass Frontier software utilizes unique and innovative library technology specially developed to capture and categorize the variation in LC/MS library spectra by allowing the storage of parallel spectra created with different collision settings. If the data were collected on an ion trap, the program also automatically stores the rich structural information of MS^n spectra in the form of spectral ion trees to help differentiate between structural isomers.

These libraries are created and shared using Mass Frontier Server Manager in SQL format for secure data storage with client-server topology. Using the Server Manager, the user can create, install, remove, delete, import, convert, back-up, and restore spectral and fragmentation libraries in one location.

Search Components and Components Editor Tools

The Search All/Selected Components tools allow the user to search detected components from a chromatogram against selected spectral libraries including user-created ones. In metabolite identification, this enables efficient knowledge management for species, matrix, or time course comparison studies. These tools are also useful for applications in the areas of forensics, toxicology, natural products, impurities, and degradants.

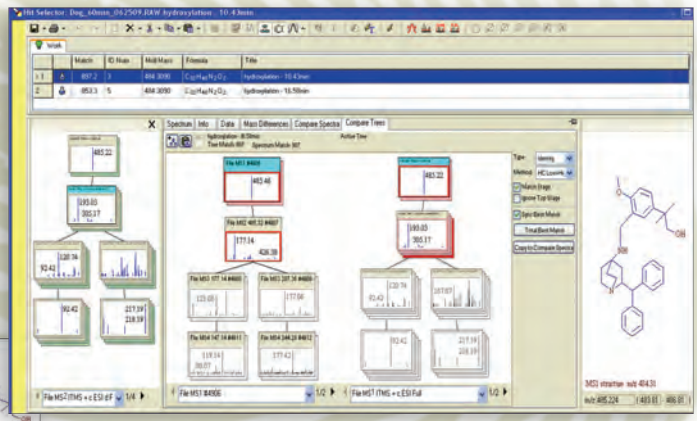
When a component search is performed, those components that are found to be similar to the library entries are highlighted. The Components Editor tool displays the search results in an active table that can be sorted by match score, retention time, *m/z* value, and molecular formula. The title for each entry from the selected library is automatically populated. A match score is assigned for each hit and clicking on an interactive eyeglass icon provides more information including the match score and visualization of spectral ion trees from both components. The user can observe the annotated nodes of the spectral ion tree from the library entry as well as use the Compare Spectra and Compare Trees tools to further examine the data.

Spectral Classification

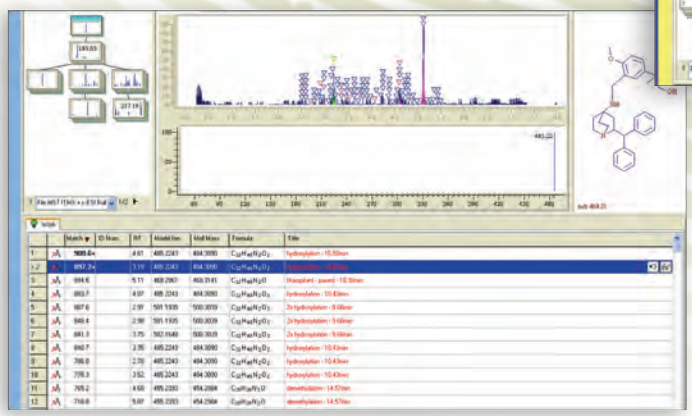
In cases where there is very little *a priori* information about the compound of interest, the user can classify the spectral library and see if the compound of interest is grouped with other classes. Mass Frontier software performs classification by comparing mass spectral data and determining spectral and structural similarities between compounds. A graphical interface simplifies viewing. The program provides three different methods for classification: Principle Component Analysis, Neural Networks, and Fuzzy Clustering.

HighChem Positive and Negative Libraries

Mass Frontier software provides spectral libraries in both positive and negative ionization modes from common pharmaceutical compounds and human metabolites. The fragments are annotated and the fragmentation mechanism schemes elucidated. The library entries include over 1,750 spectral ion trees, 14,000 spectra, and 1,000 fragmentation schemes. They establish an empirical knowledge database applicable to pharmacology, toxicology, and forensics studies.



Click on the glasses icon to view the matched library entry in the Hit Selector window.



Component search against library entries showing the table of results.

Interpreting Data with Ease

Component Detection

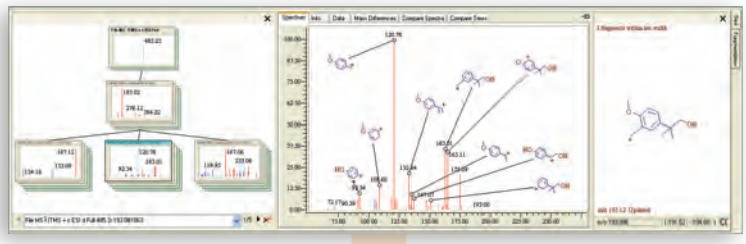
The Chromatogram Processor simplifies data analysis by providing tools for spectral deconvolution and component detection. Detected components can be copied directly to the Database Manager as individual chromatograms, spectra, or as the spectral ion tree – complete with parallel spectra. The Average and Composite spectra for each MS^n node are automatically calculated and included with each spectral ion tree diagram. This module provides visualization of the MS^n spectral ion trees for the user to easily navigate between spectral nodes and select particular spectra from MS^n experiments for detailed analysis.

Chemically Intelligent Automatic Spectral Ion Tree Annotation

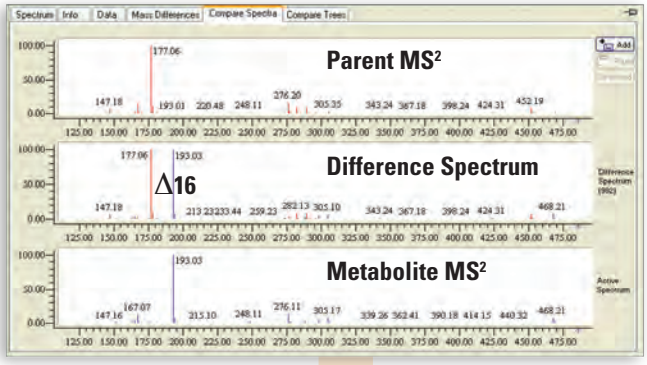
The Database Manager can rapidly confirm the putative assignment of a detected component. Simply associate a structure with a MS/MS spectrum, predict fragments and mechanisms, and then all peaks with a corresponding predicted theoretical fragment are displayed in red. Clicking on any peak displays the corresponding pathway.

If data are acquired in a Data Dependent mode, Mass Frontier software allows these interdependencies to be displayed as visual trees. Component detection automatically deconvolutes data into MS^n spectral ion trees based on the data dependent acquisition method. Unparalleled predictive fragmentation coupled with automatic deconvolution and annotation of the entire MS^n spectral ion tree facilitates the interpretation of mass spectral data. Mass Frontier software has been enhanced with new chemically intelligent tools to further accelerate this process with confidence. The program now includes an elemental composition verification step, and fragments containing unrecognized elements in comparison to the precursor ion are automatically discarded. In addition, the structures of precursor ions at various MS^n stages are automatically displayed as the user browses through the spectral ion tree to facilitate the annotation of product ions. The user also has the ability to manually annotate additional peaks under the specified threshold.

The spectral ion trees can also be manually created. Multiple instances of spectra of the same compound acquired by different experiments can be stored as parallel spectra, and a composite spectrum is automatically generated. Advanced algorithms allow the information stored among such tree structures to be searched and matched.



The entire MS^n spectra ion tree is automatically annotated using chemically intelligent tools.



Comparison of MS^2 spectra of parent and a putative metabolite to localize the site of biotransformation.

Comparison of spectral ion trees of related components to facilitate *de novo* structural elucidation.

Compare Spectra and Compare Trees Tools

The Compare Spectra tool is useful for localizing the site of biotransformation by comparing the fragmentation spectrum of a putative metabolite to that of the parent drug; for example, a composite spectrum is created that displays the difference between the parent drug spectrum and metabolite spectrum. Color coding is used to link peaks in the composite spectrum to the parent drug or metabolite. In addition, if the fragmentation data is acquired using the MS^n spectral tree mode, then two MS^n spectral trees can be compared using the innovative Compare Trees tool. This highlights the similarities between the nodes of the two components and facilitates *de novo* structural elucidation.

Comprehensive and Customizable Reporting Tools

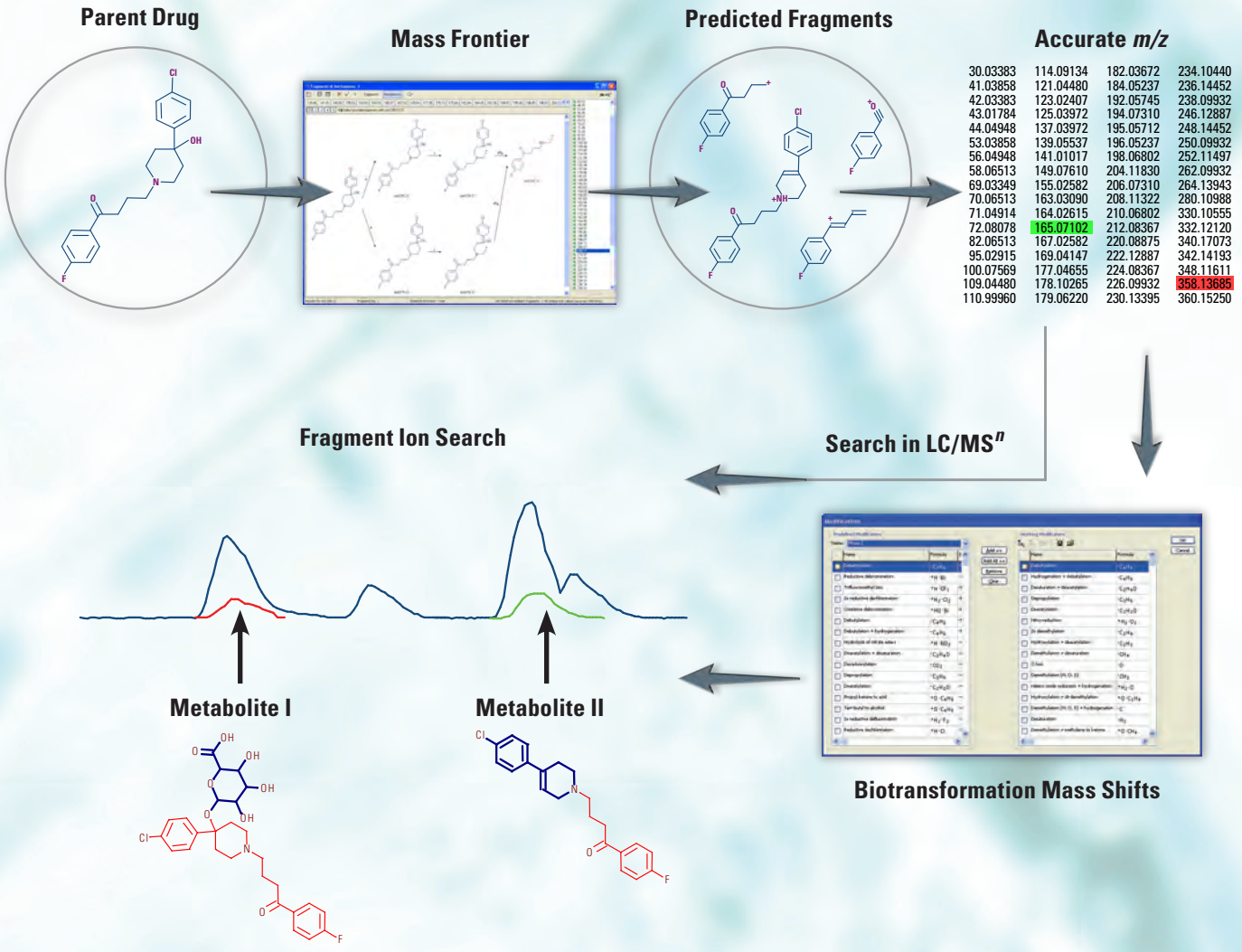
Mass Frontier software provides the user with tools to create reports in any chosen layout. A customized report can be created to include a combination of structures, spectra, list of fragment ions, and fragmentation mechanism schemes. Output of data-mining tools such as Component Editor and FISh filtered chromatograms and spectra can also be included in the report. In addition, graphics including annotated spectra, chromatograms, structures, and fragmentation mechanisms can be copied into Microsoft Office® products including PowerPoint, Word, and Excel.

Fragment Ion Search (FISh)

FISh is a novel tool that provides fast screening of structurally similar compounds based on the fragmentation pattern of the parent compound acquired either by theoretical fragment prediction or experimental MS^n spectral ion trees. It utilizes the parent compound structure to filter out the majority of matrix related background ions. Mass Frontier software provides a comprehensive user interface for FISh, allowing flexible entry of the processing parameters in a single window. The parameters can be saved as a .hcca file (HighChem chromatogram action file) for full automation where the only input data are the LC/MS raw data files and structure of the parent compound.

Fragment *m/z* vales can be conveniently entered through importing a .mol file and generating a corresponding fragment list, importing a saved list, importing a list from an active window, or selecting a user-created library. For metabolite identification, the user also has the option to extend the list of *m/z* values of predicted fragment ions by the mass shifts of expected modifications for more comprehensive detection of putative metabolites. Extensive lists of Phase I and Phase II biotransformations are provided in FISh as well as the ability to build customized lists.

In addition to filtering the structurally similar compounds, FISh can also automatically localize the modification site through color coding applied to fragments common to the parent and filtered results. The user can easily view the structural information of the filtered components by selecting a fragment *m/z* of interest and using the FISh Explanation tool. Common fragments as well as those with mass shifts from the list of biotransformations included in the FISh processing parameters will be highlighted in the parent structure.



FISh filters for related components and FISh Explanation tool facilitates localization of the site of biotransformation.

MASS FRONTIER SOFTWARE

The Ultimate Choice for Small Molecule Spectral Interpretation

Chemically Intelligent

- HighChem Fragmentation Library with extensive literature coverage
- Fragmentation prediction and generation of mechanistic pathways
- Fragment Ion Search (FISh) and FISh Explanation for structurally related components
- Automatic annotation of MS^n spectral ion trees
- Expert-annotated HighChem Positive and Negative Spectral Libraries

Easy to Use

- Capability to save work in progress, completed work, and processing methods
- Automatic recognition of Thermo data source and application of mass accuracy parameters
- Component Detection and Deconvolution of MS^n Spectral Ion Trees
- Spectra and Spectral Tree Comparison tools for assisting *de novo* structural elucidation
- Customizable and fully-searchable user libraries to store spectra, fragments, mechanisms, search results, and more

Productivity Oriented

- Unique and innovative library technology to capture and categorize the variation in MS^n data from LC/MS
- Client/Server capabilities for library sharing across networks
- Comprehensive and customizable reporting tools
- Component Search for species, matrices, or time course comparison studies
- Components Editor to sort search results by spectral ion tree similarity, retention time, *m/z* value, and molecular formula

SMALL MOLECULE STRUCTURAL ELUCIDATION SOFTWARE FOR A WIDE RANGE OF APPLICATIONS

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