Analytical and Chemical Knowledge Management Software for Drug Metabolism Science

Graham A. McGibbon,
Karim Kassam, and Susan Ling

Advanced Chemistry Development,
Inc., (ACD/Labs),
Toronto, Ontario, Canada

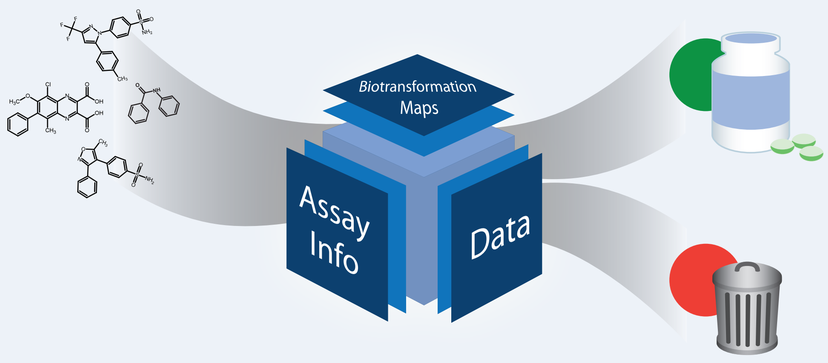

Figure 1: Analytical and Chemical Knowledge Management software supports data to decisions.

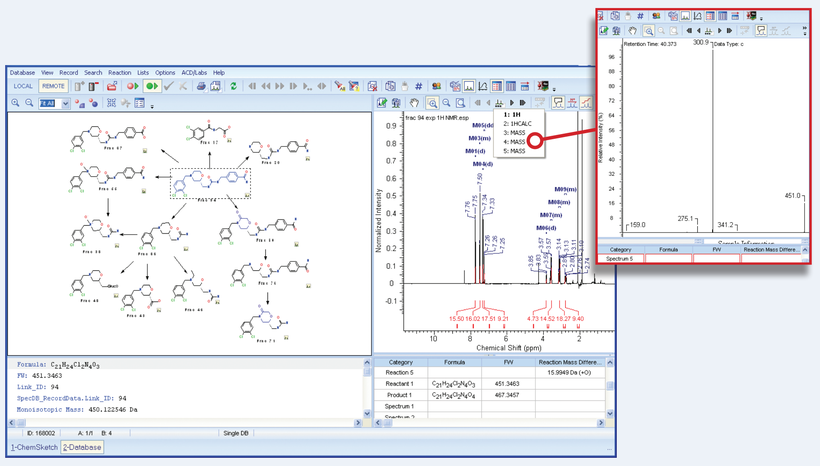

Figure 2: One view of the ACD/Labs knowledge management interface displaying an example biotransformation schema for a compound previously reported in the literature[1] along with an associated proton NMR spectrum and mass spectrum.

Abstract

Characterizing metabolite structures and metabolic pathways is essential to understanding the potential biological implications of compounds in drug discovery.

For over 16 years, ACD/Labs has facilitated discovery by offering cutting edge scientific software for the management of chemical structures, reactions, analytical data, and prediction of properties.

Herein we describe a unique enterprise software platform that enables effective management and dissemination biotransformation pathways. This software accommodates discrete or indeterminate structures, associated analytical data, and supporting information. The information is highly searchable and can be integrated with existing informatics infrastructure. It can also be extended to incorporate the many property prediction modules offered by ACD/Labs to better anticipate and avoid unwanted liabilities.

Introduction

The fate of pharmaceutical drugs in the discovery and development pipeline hinges on biotransformation pathways and the outcome of metabolite safety profiles. How best to secure and share knowledge gained from metabolite projects is a question faced by all organizations considering the disconnected nature of data acquisition and project efforts across multiple teams.

Relating biotransformation pathways to analytical and chemical information, typically generated by different research groups within remote geographic locations, has previously been a major challenge. Losing valuable information as people come and go further hinders drug development as organizations cope with lengthy and research-intensive metabolite projects.

A novel approach to knowledge management enables organizations to store, link, and access analytical and chemical data in ways not previously possible. ACD/Labs knowledge management system combines advanced interpretation of analytical data including NMR, MS, and chromatography with powerful algorithms for predicting chemical information such as physichochemical, ADME, and toxicity properties. Unifying this information and making it readily accessible leads to greater insight into metabolites and metabolism projects, Figure 1.

The Knowledge Management System

The determination of metabolite structures and creation of biotransfomation schema usually begins with the acquisition of analytical data, particularly from LC/MS instruments. Processing the data using the advanced extraction and interpretation algorithms, such as ACD/IntelliXtract, can facilitate finding and characterizing metabolites. The proposed structures, pathways, and spectral interpretations are then readily retained and can be effectively managed, visualized, and searched within the ACD/Labs knowledge management system.

Additional analytical, chemical, and biological data are associated with chemical structure, accessible to review with a simple mouse click. The stored spectra are retained with interpretations, not just as archived data allowing the features of the spectra to be readily investigated.

Individual records can accommodate single structures or complex pathways with multiple steps of metabolism or sharing common structures, both of which can be seen in the case of Frac 38. In the example record, one of the primary metabolites was assigned as an N-oxide. In case the site of oxidation wasn't immediately established, one can store the structure as a Markush representation.

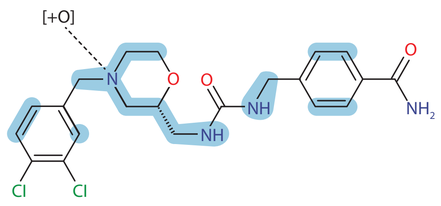

Figure 3: A Markush structure indicating oxidative metabolism. Keep track of a chemical entity even if a specific site of metabolism is undetermined.

This capability is invaluable for structures elucidated over the course of more than one sample analysis. This legacy knowledge helps to speed up interpretation and avoid mistaken elucidations in the future. Structures and reactions in the schema are searchable in a variety of ways. For instance, search a particular structure against the database to find if it has been proposed in previous experiments or projects. Alternatively, a partial structure can be selected and substructure search performed. Figure 2 features two six-member rings matching the morpholin-3-one substructure highlighted in blue along with the parent compound following such a search. Structure searches may be confined to look only for parents/reactants or metabolites/products. Furthermore, to refine searches a structure search may be preceded or followed by searches of other data fields. The query shown in Figure 4 exemplifies a search for records satisfying multiple disparate criteria simultaneously. One can thus readily focus on information for a particular species or biological matrix, and look to support tentative structure assignments by searching for similar reactions among legacy information.

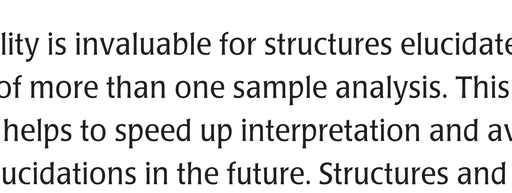

Figure 4: Search dialog box indicating potential choices involving multiple data criteria

Enhancing Knowledge by Predicting Metabolism and Identifying Safety Concerns

Identifying safety concerns and detrimental physical properties for drug candidates and potential metabolites helps avoid compounds with liabilities. Using log*P*, log*D*, solubility, and pK_a for predicting ADME properties such as permeability, oral bioavailability, and distribution is well documented. Software enabling the prediction of physicochemical, ADME, and toxicology properties from molecular structure is available from ACD/Labs and can readily be applied to the structures stored in the biotransformation schema.

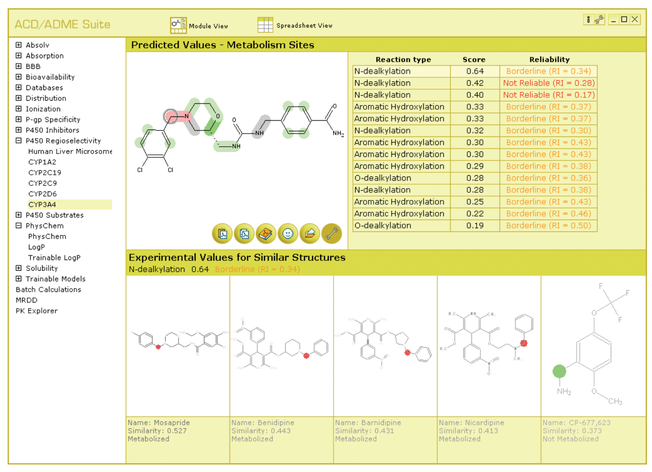

Figure 5: Prediction of Cytochrome P450 regioselectivity for parent compound indicating dealkylation.

Predicted risk associated with metabolite vulnerabilities can be used to help redesign and select more promising candidates for further and more rigorous testing. Hepatic metabolism by cytochrome P450 enzymes is the major clearance route for xenobiotics. Using *in silico* tools such as ACD/Labs cytochrome P450 predictive modules, one can identify whether compounds will be substrates and/or inhibitors of the five major drug metabolizing enzymes—CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2. Furthermore, the software predicts the most likely sites of metabolism in human liver microsomes. These predictors also offer the ability to incorporate experimental data, which extends chemical space coverage and serves to improve prediction accuracy as results accrue.

Since biotransformations can lead to either an increase or decrease in toxicity, accessory data about metabolites is an interesting and often vital part of complete compound assessment.

Conclusion

ACD/Labs knowledge management software provides the distinctive ability to store analytical data from multiple techniques generated by a wide variety of instruments in many different formats. Centralized data in a corporate database is easily shared across an organization, and knowledge can be accessed through a wide range of reporting and search options including structure, substructure, similarity, properties, and metadata.

Unique ways of linking analytical, chemical, and structure information leads to improved project management, increases the confidence in structural elucidations, helps to avoid errors in elucidation, and enables the prediction and incorporation of related safety data.

Retaining legacy information in a coherent manner and all in one place offers a better chance at identifying metabolites sooner, without replicating work, and facilitates information sharing and collaboration across the organization. Reporting is easier, and valuable information is protected from loss.

Overall, such a knowledge management system contributes invaluably to an organization's retention of information and enables individual scientists to access and leverage legacy kmowledge that helps to identify metabolites faster and to make better decisions around the safety and fate of compounds.

References

1. G.J. Dear, A.D. Roberts, C. Beaumont, S.E. North, *J. Chrom.* B, 876(2), 182-190, 2008.

ACD/Labs

Advanced Chemistry Development Inc.
Tel: (416) 368-3435
Fax: (416) 368-5596
Toll Free: 1-800-304-3988
Email: info@acdlabs.com
www.acdlabs.com