Efficient Chiral Screening and Purification in Support of Medicinal Chemistry

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INTRODUCTION

In recent years, the intrinsic nature of drug discovery has placed tremendous emphasis on the discovery chemists' ability to deliver high purity novel molecular entities while at the same time maintaining aggressive synthesis goals. Currently, within the pharmaceutical industry, it has been conservatively established that nearly 40% of the drugs under development are chiral. Chiral pharmaceuticals offer a great advantage to the industry not only in terms of activity and cost, but also in terms of establishing and defending intellectual properties. Enantiomeric purification of chiral compounds is thus a critical challenge in drug development and discovery. Compounds are typically purified in the discovery process rather than using chiral-specific synthesis due primarily to the development time differential. Medicinal chemistry groups can produce a very large number of compounds per year, putting a significant time pressure on chiral preparative labs to avoid bottlenecks in purification of compounds. The typical approach to development is chiral stationary phase (CSP) selectivity screening for a given sample followed by optimization of promising systems. This approach is efficient in terms of human effort, but frequently results in slow sample turnaround, making the medicinal chemists wait for days and sometimes weeks for the purified material. In the separations laboratory, this approach incurs an additional cost in terms of instrument and compound time. Furthermore, when compounds are found to be problematic for the standard CSPs, considerable time can be spent investigating alternative systems. If a process can be used to target given selectivities in advance, initial screens can be tailored to the compound in question based on appropriate structural queries, increasing the probability of success initially and minimizing the time and cost of purification.

PROPOSED WORKFLOW OF CHIRAL PURIFICATION

The concepts of chiral screening and databasing, combined with workflow automation, were applied to streamline the chiral sample purification and speed up the sample turnaround. Figure 1 illustrates the overall workflow of the separations laboratory that services medicinal chemists and processes on average 60–70 samples per week. The following describes some of the specific parts of the workflow (marked A–D on Figure 1) in further detail.

A) Sample Submission

Structural queries that will be conducted at the Separations laboratory require that specific structural information becomes readily available to the chromatographers. Workflow automation enables the Sample login screen (Figure 2) that a chemist can complete at their own desktop, as well as an automated response e-mail that informs the chemist when the purification is completed.

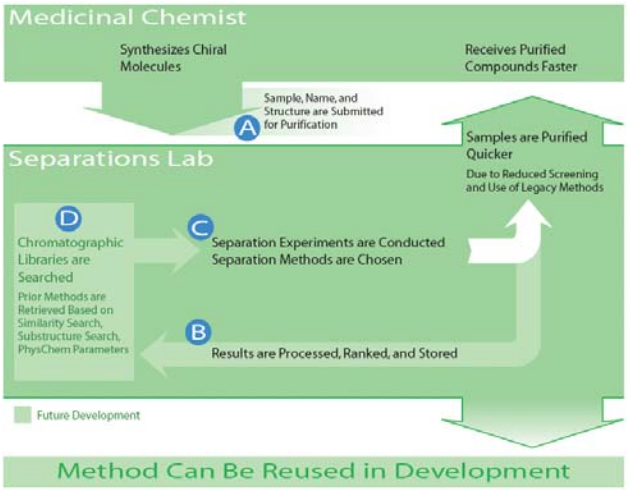

Figure 1: Proposed chiral purification workflow

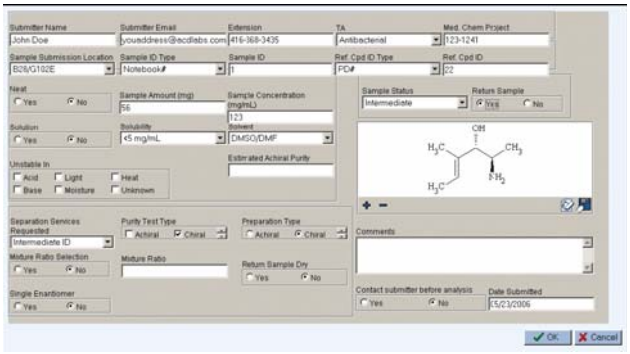

Figure 2: Medicinal chemists submit their samples and provide relevant information to the separations lab through the login screen shown.

B) Application Databasing by the Separations Group

These Databases link chemical structures with chromatographic methods and other information in order to find prior data for similar structures.[1,2] Substructure and structure similarity searches may be augmented through queries on physicochemical parameters for given analytes, as well as other types of queries. The resulting "hits" for similar compounds give method information that can be used to choose chromatographic starting points, significantly streamlining method development. An example of such a chromatographic application database is ACD/ChromManager, shown in Figure 3.

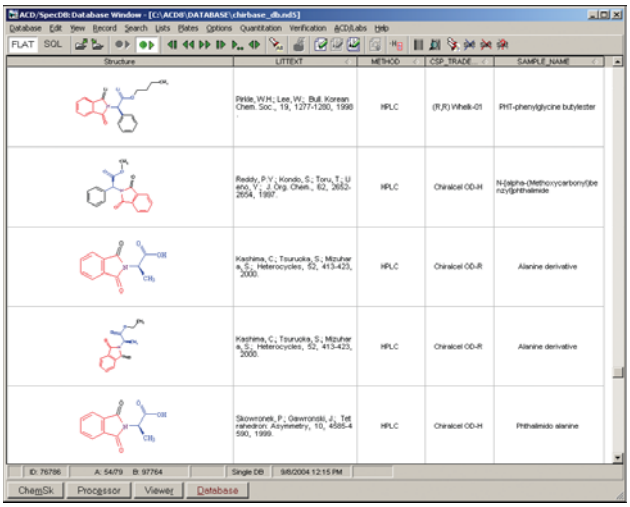

Figure 3: Chromatographic methods can be retrieved based on substructure searches as well as ranked by structure similarity.

A significant challenge faces the chromatographer intending to create a comprehensive application database. Chromatographic laboratories remain significantly fragmented in terms of data environment. It is typical to find at least four chromatography data systems in a given laboratory, in addition to a molecule registry and sample management software. Each system contains valuable information; in order to create a useful application database, the data must be united. Manual re-entry of this data is not a viable solution in most laboratories; the realities of modern laboratories are such that inefficiencies cannot be tolerated.

C) Uniting Chromatographic and Other Data

One of the challenges with a heterogeneous data environment is that each chromatographic data system writes proprietary files and/or databases. Data must be homogenized prior to incorporation into a common knowledge base. ChromManager directly supports native file formats for many Chromatography Data Systems. In addition, ASCII and AIA standard data formats provide an alternative avenue to data support. In this case, standard data formats were utilized. Export utilities in Empower and Thar were used to write the standard datafiles, and also to write a separate report file that includes chromatographic parameters. A custom ACD/ChemBasic application was used to parse the report file, writing parameters into appropriate fields of the new database. The result was a data reconciliation system that takes chromatographic data from different chromatography data systems, and attaches parameters appropriately. The parameters are attached without user intervention.

One of the key objectives of the project was the creation of databases with little or no effort on the part of the chromatographer. In this context, any manual input of data was deemed to be unacceptable; all data included in the database was required to be extracted from existing data collection systems. For this project, data was contained in three locations: the sample login system (samples/structures); Waters® Empower™ projects; and Thar Chromatogram Browser (C-Browse) files (chromatograms and chromatographic parameters). The proprietary sample login system was configured to write Structure Data Files (SDFs) containing chemical structures and initial sample information. Empower and C-Browse are configured using reporting options to write both standard chromatogram files and parameter reports. The databasing process is automated, with ACD/Automation Server performing periodic "sweeps" of the data directories and automatically

reconciling the applicable data. The dataflow is shown in Figure 4. This will reduce the onus on the chromatographer to archive separations, but it will also ensure that applications are made available with essentially zero time lag.

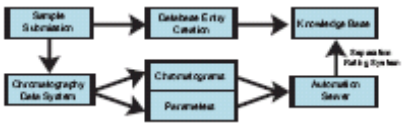

Figure 4: Dataflow schematic

D) The Future—Rating Chromatographic Selectivity

A ChemBasic application was used to evaluate the selectivity for the chromatograms. The algorithm for this was based on the premise that chiral chromatograms are very simple, and thus selectivity can be measured by the resolution of the two largest significant peaks. The result of the algorithm was a rating of selectivity (good/poor) and the creation of an associated user data field. Based on the use of this field, it is possible for queries to reject methods that show no selectivity prior to performing structure similarity or other searches. On the other hand, the inclusion of unsuccessful screens eliminates the risk of redundant work in the lifetime of the compound. Subsequent method developers need not rerun experiments in order to discount CSPs. While this algorithm works well for samples that are free from impurities that are unrelated to the chiral separation, achiral impurities can impair its effectiveness. The accuracy of the separation ratings can be increased through the future incorporation of chemometrics in conjunction with hyphenated detection. This is targeted for future implementation.

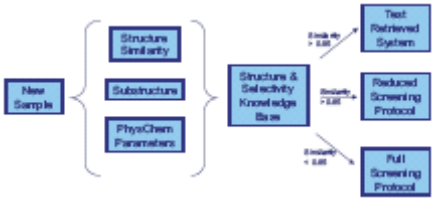

Figure 5: An approach to tailoring chiral screening based on retrieved methods.[3]

Presently, we are working on accumulating a sufficient knowledge base of the chiral separations that reflects the specific chemistry within our laboratories. After such data is accumulated, we'll be able to implement the automatic generation of screening/injection protocols based on the database queries (Figure 5). A few minutes after selectivity is shown, the information will be available to the organization.

CONCLUSION

Application databasing can increase the efficiency of chiral method development when working with novel compounds as well as forming a repository of method selectivity history for specific samples within an organization. Almost all chromatographic labs exist as heterogeneous data environments. It is beneficial to connect the disparate systems using a combination of standard data formats, proprietary format support, and custom scripts. In this case, the creation of ACD/ChromManager databases was demonstrated, collecting and reconciling data from sample registration, Waters Empower, and Thar C-Browse software. Implementation of such a data handling process, combined with structure-based screening of the previously used methods will help significantly reduce the number of method development experiments run in the separations lab, and deliver the purified chiral samples in a short period of time, eliminating the purification bottleneck.

ACKNOWLEDGEMENTS

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REFERENCES

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3. Michael McBrien, Robin Martin, Peter Frank, Frank Riley, Efficient Chiral Application Screening and Databasing, poster, HPLC 2005, Stockholm, Sweden.