A Freely Accessible, Internet-Based Human Drug Metabolism Database (hDMdb)

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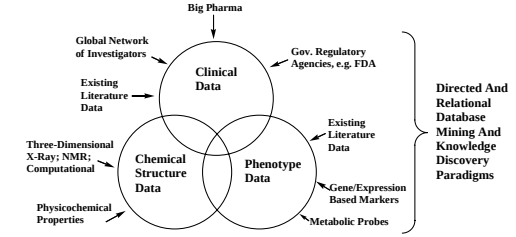
ABSTRACT

The hDMdb project was initiated by the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Pharmacology (IUPHAR), as well as by the International Council of Scientific Unions (ICSU), to establish a non-profit, Internet database of metabolic transformations that are done by humans on xenobiotic compounds. Three fields of data are being interfaced within the database: (i) Chemical name, property and structural-related information pertaining to each xenobiotic and metabolite; (ii) Metabolic biotransformation-related information pertaining to various biological parameters of the study or exposure, along with analytical and statistical details associated with the assays or assessments that were involved; and, (iii) Genetic and phenotype-related information relative to observed patterns of metabolism for each case. Investigators will be able to turn to the database as a collection of standard data that will allow: (i) Explicit name or structure searching to learn about the human metabolism of known compounds or to validate new drug metabolism research assays in terms of their ability to predict clinical outcomes; (ii) Two-dimensional (2D) and 3D substructure searching to identify analogous metabolic occurrences relative to novel compounds undergoing development as new drugs; and, (iii) Statistically derived probability rankings to be made about competing metabolic possibilities for any given compound.

PURPOSE

- **To be readily available on the Internet, it will warehouse drug metabolism and drug metabolism-related drug-drug interaction data that can be queried by any visitor via a non-profit format.**
- **Will allow explicit structure searching to readily provide information about specific compounds and to allow for the selection of the most relevant standards across a variety of structural themes that can then be used to validate proprietary drug metabolism screens and screens intended to assess drug-drug interactions.**
- **Will allow substructure searching to identify analogous metabolic occurrences and drug-drug interactions within humans relative to proprietary compounds undergoing drug development.**
- **Will have large number of biotransformation and drug-drug interaction entries so that statistically derived probability assessments can be made about metabolic possibilities including that of competing and complimentary biotransformation pathways as well as drug-drug interaction possibilities.**
- **Will be relational in nature so that any type of searching paradigm can be deployed to identify novel relationships across all or selected segments of the data, e.g. potential correlations between a certain set of structural parameters with potential metabolic occurrences or with likelihoods for a particular type of drug-drug interaction.**
- **Will be updated on a periodic basis, including that of filling presently unoccupied data fields being reserved so as to also be able to include enhanced pharmacogenetic data as the latter is expected to unfold reasonably soon relative to human drug metabolism data.**

INFORMATIONAL FIELDS



STATUS

A prototype database has been assembled on a dedicated server housing Academic Oracle using JAVA programming. Numerous connectivity tables have been devised to address the extensive chemical, pharmacological and phenotype information areas deemed to be important for the hDMdb (see Table 1). This server also hosts Microsoft's SQL server database engine wherein a portion of the hDMdb has also been placed to allow for progression to a web application "demo model." A mock-up of the anticipated homepage has also been devised (see Figure 1). For the demo prototype, metabolism data for paclitaxel (Figure 2) from several literature reports have been entered into the database and several model questions have been developed to demonstrate the database's potential utility (see Table 2).

A web application that interacts with the implemented tables of the hDMdb via a second, dedicated server housing SUN Microsystem's application server 7 has been set-up as a part of the working portion of the demo model. The JCHEM package (www.jcm.com) has been adopted for drawing and displaying chemical structures. This JAVA-based package also provides very user-friendly side features for substructure and similarity searching. Although structures are initially being handled via two-dimensional display (2D), this software can also accommodate 3D (see Figure 3) for the approach that will be used to gradually mature structures from 2D to 3D).

The double-server system has been set-up within the University of Toledo's (UT's) Information Science building which offers a segregated and controlled environment with back-up power system for computers (Figure 4). An Information Technologist, assigned to assist this project, has established appropriate firewall protection systems to prevent unauthorized alteration of the database via either UT's Intranet or the Internet. The substantial JAVA programming effort and initial web application activities have been accomplished through the hands of advanced graduate students who were interested in informatics.

Procedures have been outlined for how data will be entered into the database initially and a plan has also been suggested for the future wherein much broader participation is anticipated (See Tables 3 and 4, respectively).

TABLE 1. PARAMETERS FOR INCLUSION IN THE hDMdb

Xenobiotic

1. **Unique identification number assigned by UT: hDMDB Cmpd #**
2. **Common name; Proprietary name(s); Chemical name (including stereochemistry); CAS # (Entry checklist items)**
3. **General chemical class, e.g. benzodiazapine, oxypropanolamine, etc. (evolving menu)**
4. **Functional group(s) (from menu)**
5. **Chemical structure – 2D and 3D (will want to be able to search by both explicit and substructure 2D and 3D) (3D's history)**
6. **Number asymmetric centers; Marketed stereoforms(s)**
7. **MLog P or Clog P value (value's history)**
8. **"Rule of 5" parameters," i.e. molecular formula/MW, # H-bond donors & # H-bond acceptors**
9. **3D Parameters, e.g. molecular volume/surface area and degree of planarity**
10. **Pharmacological class, i.e. efficacy and/or toxicity (from menus) (up to 3)**
11. **Prodrug, soft drug or standard agent**

Metabolism

1. **hDMDB Cmpd # (s) and hDMDB Study # (see below)**
2. **Route(s) of administration (from menu); If other than i.v., bioavailability**
3. **Dose amount (standardized units) and protocol (from menu)**
4. **Half-life value (from menu/value's history)**
5. **Volume of distribution (from menu/value's history)**
6. **Other PK parameters (from menu)**
7. **Metabolic event(s) (from menu)**
8. **Metabolite(s) structure – 2D and 3D (same comment as above)**
9. **Chirality(ies) (from menu)**
10. **Metabolite(s') activity(ies) (from menu)**
11. **Enzyme(s) involved (only if part of in vivo study itself)**
12. **Parent and metabolite ratios and/or percentages**
13. **Parent and metabolite routes of excretion (from menu)**
14. **Overall mass balance (value's history, e.g. radiolabel – where)**
15. **Sampling type(s) (from menu)**
16. **Analytical method(s) (from menu)**

Study

1. **hDMDB Study #**
2. **Population size**
3. **Population general profile (race, sex, age, health)**
4. **Population phenotype(s): Intrinsic (from menu) and elicited (present and future categorizations for both)**
5. **Non-ordinary inclusion or exclusion criteria (potential red flags even if not queried by user)**
6. **Other xenobiotics on board (presence of known/suspected metabolic inhibitors or inducers pose potential red flags) (menu for known agents)**
7. **Prior exposures to other xenobiotics, including herbals/nutraceuticals and foodstuffs**
8. **Location(s) of study (from menu map)**
9. **Statistical treatment (from menu/history)**

Source

1. **hDMDB Study #**
2. **Complete reference citation according to standardized format, e.g. authors, title of publication or report, journal title or document type, year, volume, inclusive pages (Entry checklist items)**
3. **Lead author contact information**
4. **Affiliated institutions**
5. **Sponsoring bodies**
6. **Language**
7. **Abstract: As part of database so as to be searchable by key word(s)**
8. **Hyperlink to entire ejournal entry when available**
9. **Mechanism to upload PDF file (when readily available) into a working space associated with (but distinct from) the database so that it can be used for internal communications/records ONLY and NOT for distribution to external users**

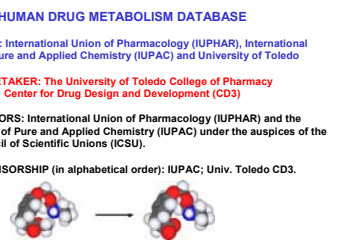


FIGURE 1. MOCK-UP OF ANTICIPATED HOMEPAGE.

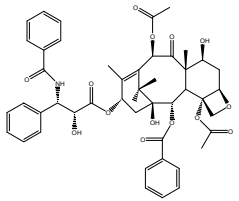
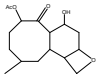


FIGURE 2. 2D VERSION OF PACLITAXEL USED WITHIN THE DATABASE FOR DEMO PURPOSES.

TABLE 2. MODEL QUSTIONS FOR THE hDMdb PROTOTYPE

1. **How is paclitaxel metabolized?**
2. **How are anti-mitotic anticancer agents metabolized?**
3. **How might my novel structure be metabolized? My novel structure is as follows:**



4. **How are oxetanes metabolized?**
5. **Under what circumstances are esters not metabolized?**
6. **Is there a relationship between PK half-life and the number of hydrogen-bonding groups present in drugs that have a MW between 250 and 500?**
7. **What types of molecular systems are susceptible to aliphatic hydroxylation?**
8. **How can one analyze for the possible metabolic occurrences that might accompany paclitaxel-like analogs?**
9. **What metabolism studies involving chemotherapeutic agents of any type have utilized human populations of at least 100 subjects?**
10. **What papers pertaining to human drug metabolism have been published or sponsored by Bristol Myers Squibb?**

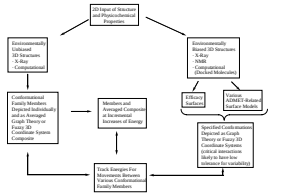


FIGURE 3. HANDLING CHEMICAL STRUCTURES.

This figure depicts the quick entry and gradual maturation of structures. Structure entry would be initiated by a simple 2D depiction and then subjected to more rigorous experimental and computational studies. Note that structures would be evolved in both an unbiased and in several environmentally biased formats. The highest structural tier would represent tracking the energies required for various conformational movements that members would take when going from one family to another. Search engines, in turn, would also provide for a variety of flexible paradigms involving physical properties with both full and partial (sub)structure searching capabilities using pattern overlap/recognition, similarity/dissimilarity, CoMFA, etc.

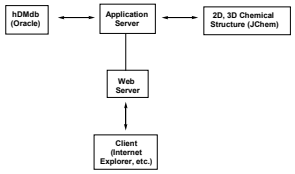


FIGURE 4. WEB APPLICATION ARCHITECTURE.

For initial construction, a dual server system is being deployed to allow access of the human drug metabolism database (hDMdb) via the Internet. Metabolism data is being housed within an Oracle (relational) database and chemical structures are being handled separately via JChem (ChemAxon Ltd.) which allows for both 2D and 3D manipulation. JAVA programming is being done throughout with HTML extending to the Internet.

TABLE 3. SUBMISSION OF INFORMATION FOR THE HDMDB (PRESENT PLAN)

- Only data from studies or exposures involving intact humans should be considered; Studies using human tissue, extracts etc. should NOT be included
- Only original articles or reports should be considered, i.e. NO REVIEW ARTICLES or SECONDARY NEWS REPORTS SHOULD BE ENTERED.
- Check "Cmpd" listing to see if previously entered studies have already included the xenobiotic(s) covered in the present study. If so, then use existing "hDMDB Cmpd #(s)" at the top of the section of the submission form pertaining to "Xenobiotic." If not, then this section of the form must also be completed as part of the submission.
- Fill-out the **hard-copy submission form** and place it in a manila folder. INCLUDE ONE COMPLETE COPY OF THE ARTICLE OR REPORT THAT DETAILS THE STUDY.
- Give the folder to either one of the College's Center Directors (i.e. KAB or PWE) who will inspect the submission documents folder, sign-off on its correctness, and then forward the folder to the designated data entry individual(s).
- Data will be entered only by selected individual(s) who will also be in charge of sequentially assigning the hDMDB Cmpd and Study #s as appropriate for new information.
- After data entry, a printout of the available database information relative to ONLY that particular study will be added to the manila folder and the folder returned to the Center Director signatory who will double-check the entry and then place the folder into the hardcopy repository to be located within the CD3.

TABLE 4. SUBMISSION OF INFORMATION FOR THE hDMDB (FUTURE PLAN)

- Will utilize **esubmission** strategy via the Internet that maintains quality control checkpoints, e.g. submission of on-line form and complete ecopy of published article or internal report.
- Will partner with major drug metabolism-related journals for simultaneous publication (post peer review) in journal and incorporation into DB.
- May also partner with the USA FDA, the UK CSM, and the EC's equivalent body for simultaneous incorporation into DB upon approval of an NDA, etc.
- May also partner with toxicological/epidemiological informational gathering organizations so as to gain ongoing access to a broader range of human exposures to xenbiotics.
- Will continually seek to enhance the ease of the esubmission process, e.g. automatic generation of IUPAC compound name and automated calculation of molecular formula, MW, Clog P, H-bond donor and H-bond acceptor values subsequent to entry of a 2D chemical structure.

CONCLUSION

Given the magnitude of this project, resources beyond what has been initially supplied by the volunteer-driven, non-profit organizations (ICSU, IUPHAR and IUPAC), are now required to fine-tune the prototype, purchase Oracle for use on the Web (public domain) rather than in just an academic setting, and bring this project to completion. Once assembled in final form, maintenance should then be able to be accomplished within an academic setting (University of Toledo Center for Drug Design and Development) wherein student interests toward such participation has been extremely high.

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