Exploring Metabolic Outcomes and Toxic Effects

DiscoveryGate[SM]
Version 1.4 SP2
Workshop Guide

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Workshop Guide

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POWERING *the process of* INVENTION

Exploring Metabolic Outcomes and Toxic Effects

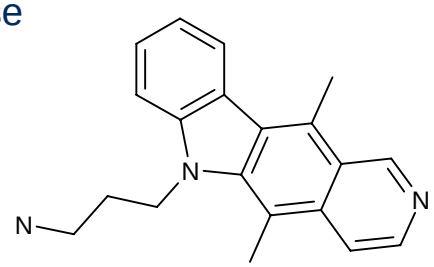
Key points

- In this workshop, you will use DiscoveryGate to access the MDL Metabolite and Toxicity databases to retrieve information on metabolic outcomes and toxic effects.

Notes

Workshop objectives

- Determine potential metabolic outcomes for a novel compound by searching the MDL Metabolite Database
- Determine the likely toxic effects associated with the parent compound and anticipated metabolites by searching the MDL Toxicity Database



Ellipticine, 6-(3-aminopropyl)-, dihydrochloride

Key points

- The compound of interest is shown on the slide. This is a novel compound for which you wish to determine potential metabolic outcomes and likely toxic effects.
- You will be searching the MDL Metabolite Database and the MDL Toxicity Database for answers.

Notes

MDL Metabolite Database

- Xenobiotic transformations abstracted semiannually since 1991 from the top 60 journals containing metabolism studies
- Metabolic schemes from *Biotransformation of Drugs* and *Pharmacokinetics*, research studies covering 1901 to 1990
- Non-proprietary metabolism studies from new drug applications published by the US Food and Drug Administration

Key points

- MDL Metabolite Database covers a range of metabolic schemes, including medicinal drugs, agricultural chemicals, industrial chemicals, and environmental contaminants.
- Metabolism information about a parent compound often comes from multiple sources. The MDL Metabolite Database makes it easy to make cross-study comparisons.
- The database is organized into metabolic schemes, allowing you to investigate outcomes occurring in multiple known pathways.
- The MDL Metabolite Database is updated semiannually.

Notes

MDL Toxicity Database

- Registry of Toxic Effects of Chemical Substances (RTECS) database, containing data on over 150,000 registered substances
- Chemical Carcinogenesis Risk Information System (CCRIS) produced by the National Cancer Institute
- GENE-TOX database produced by the US Environmental Protection Agency

Key points

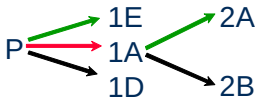
- The MDL Toxicity Database provides access to toxicological profiles on over 150,000 registered toxicological substances.
- This database uniquely consolidates toxic effects from multiple studies with a substance's chemical structure, giving scientists the ability to closely examine relationships between structural features and toxicity.
- *In vitro* and *in vivo* data in six specific toxicological categories are captured: acute toxicity, mutagenicity, skin/eye irritation, tumorigenicity and carcinogenicity, reproductive effects, and multiple-dose effects.
- The MDL Toxicity Database is updated quarterly.

Notes

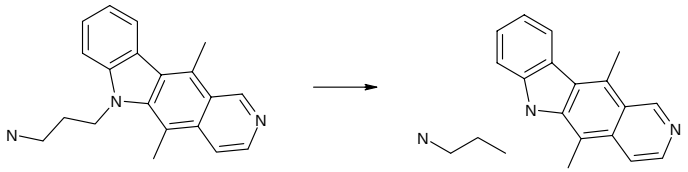
Search for desired compound

The ellipticine compound is thought to be novel, but the first strategy is to see if it is present in the Metabolite database. The database contains:

- Parent compounds and metabolic schemes



- Transformations and associated molecules

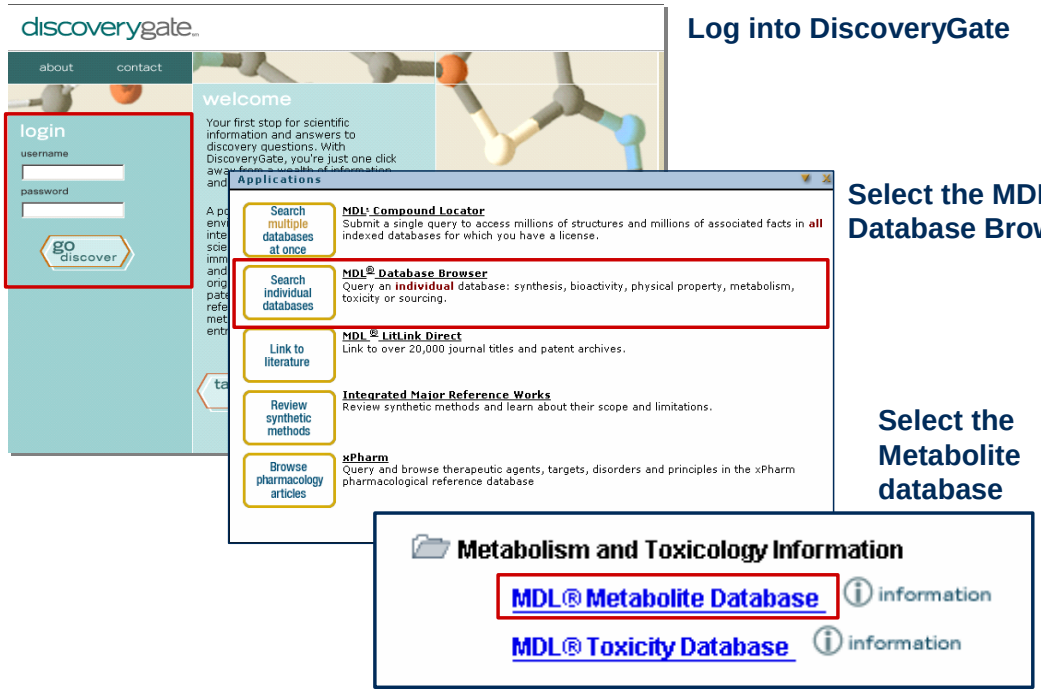


Key points

- The database entries in Metabolite are organized into schemes. Each scheme consists of a unique parent molecule, all metabolites of that parent molecule, and the transformations between molecules.
- Metabolic transformations are represented as reaction equations.
- You can search the database using molecule or transformation information.
- Each molecule or transformation has associated chemical and biological data.
- Our first task will be to see if the compound of interest can be found in the database as a parent molecule.

Notes

Launch the application and database



Log into DiscoveryGate

Select the MDL Database Browser

Select the Metabolite database

Key points

- Launch your web browser. Enter the URL: www.discoverygate.com.
- Enter your user name and password, and then click "go discover."
- On the DiscoveryGate home page, click MDL Database Browser to launch the application. A list of licensed databases for your site will be displayed.
- Click MDL Metabolite Database to choose the Metabolite database.

Notes

Summary

Perform the following:

- Launch MDL DiscoveryGate
- Open the Metabolite database

Key points

- Perform the steps summarized on the slide.

Practice steps

1. Launch your web browser.
2. Enter the URL, www.discoverygate.com.
3. Enter your user name and password, including the Company ID, if prompted.
4. Click **go discover**.
5. From the DiscoveryGate home page, click **MDL Database Browser**.
6. From the list of available databases, click **MDL Metabolite Database**.

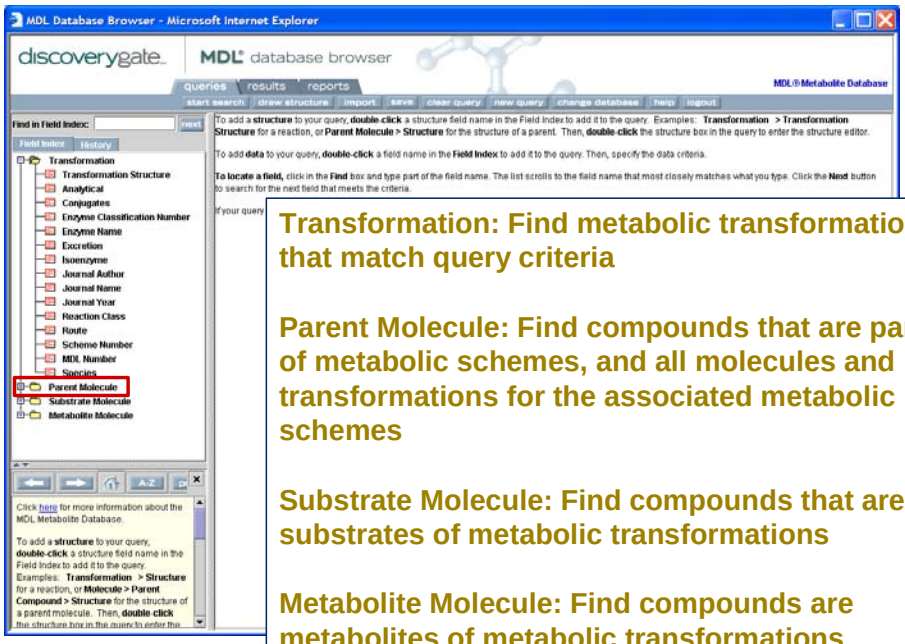
Choose search type

Key points

- You can choose to create a reaction structure query, or search by properties selected from the available fields of data.
- Custom search allows you to create queries containing target information for molecule structure, reaction structure, or property query fields.

Notes

Metabolite directories



Transformation: Find metabolic transformations that match query criteria

Parent Molecule: Find compounds that are parents of metabolic schemes, and all molecules and transformations for the associated metabolic schemes

Substrate Molecule: Find compounds that are substrates of metabolic transformations

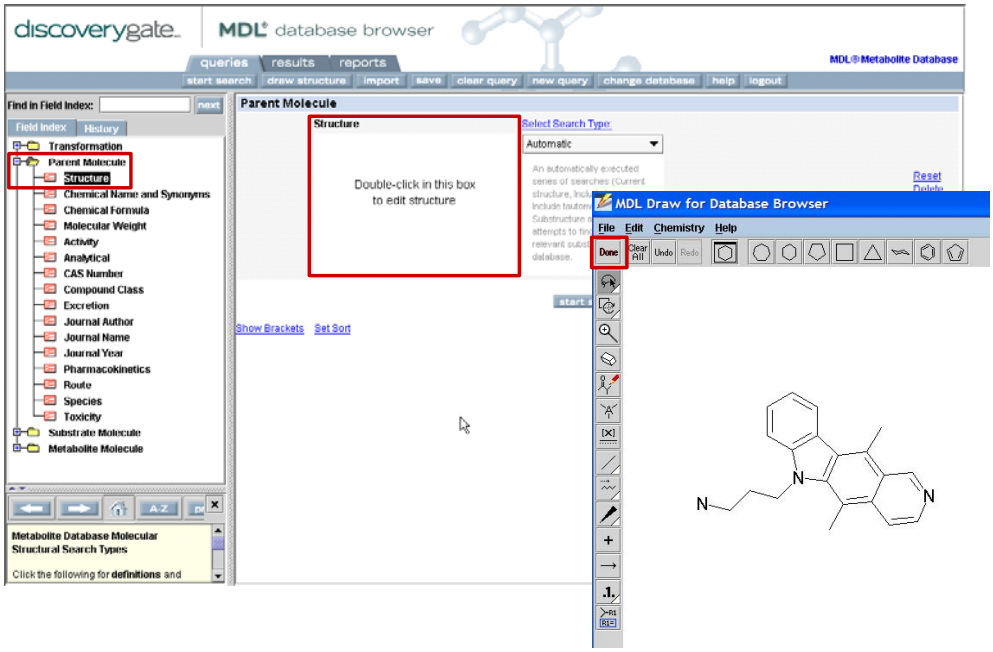
Metabolite Molecule: Find compounds are metabolites of metabolic transformations

Key points

- The Field Index allows you to choose query fields from four directories: Transformation, Parent Molecule, Substrate Molecule, and Metabolite Molecule.
- You want to search for a parent molecule by structure, so we will use the Parent Molecule directory.

Notes

Create the query structure

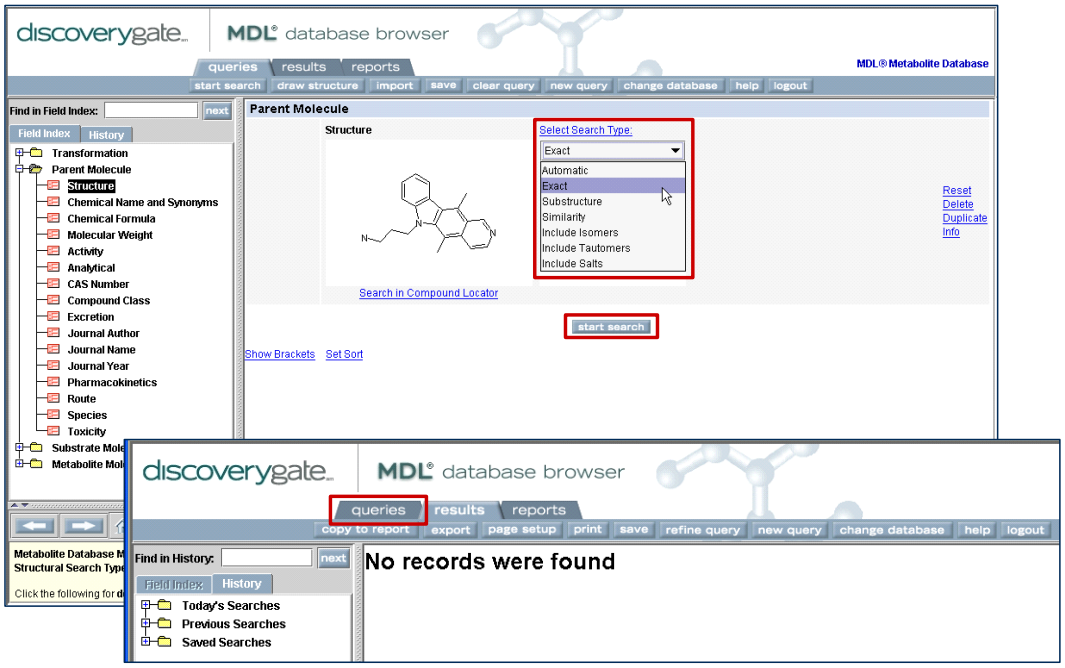


Key points

- You need to add a structure parameter to the query area, and draw the structure of interest.
- Query fields are added by double-clicking the field in the Field Index tree.
- Double-click the structure box to launch MDL Draw. Click Done to transfer the structure back to the Database Browser query window.

Notes

Conduct an exact match search



Key points

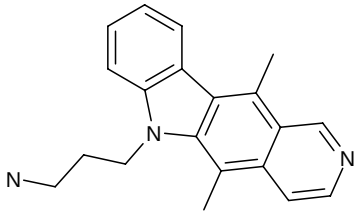
- Choose Exact from the Select Search Type drop-down list.
- These search parameters will search for a compound that exactly matches the structure query that we provide, and that is also the parent molecule of a metabolic scheme.
- If it finds such a parent compound, it will retrieve that compound. It will also retrieve all transformations in the metabolic schemes of that parent compound.
- The query finds no hits. This result is not unexpected, as this particular ellipticine compound is thought to be novel.
- We will search for similar compounds, and see if the metabolic outcomes for those compounds might be relevant.

Notes

Summary

Perform the following:

- Using the Parent Molecule structure field, create an exact match structure query for this structure



- Conduct the search

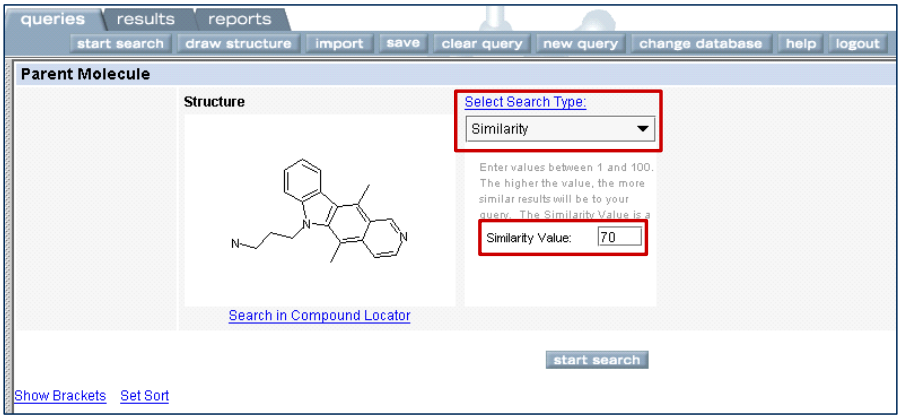
Key points

- The slide above summarizes how to search for the compound of interest as a parent compound in a metabolic scheme.

Practice steps

1. In the “Select the Search of Interest” window, click **Custom Search**.
2. In the Field Index window, expand the **Parent Molecule** directory. Double-click **Structure**.
3. Double-click the structure box to launch MDL Draw. Draw the structure shown on the slide.
4. Choose **File > Save As**. Name the structure **Ellipticine.mol**. Click **Save**.
5. Click **Done** to transfer the structure to the Database Browser query window.
6. In the Select Search Type drop-down list, choose **Exact**.
7. Click **start search**. The search returns no hits.
8. Click the **queries** tab to return to the query window.

Conduct a similarity search

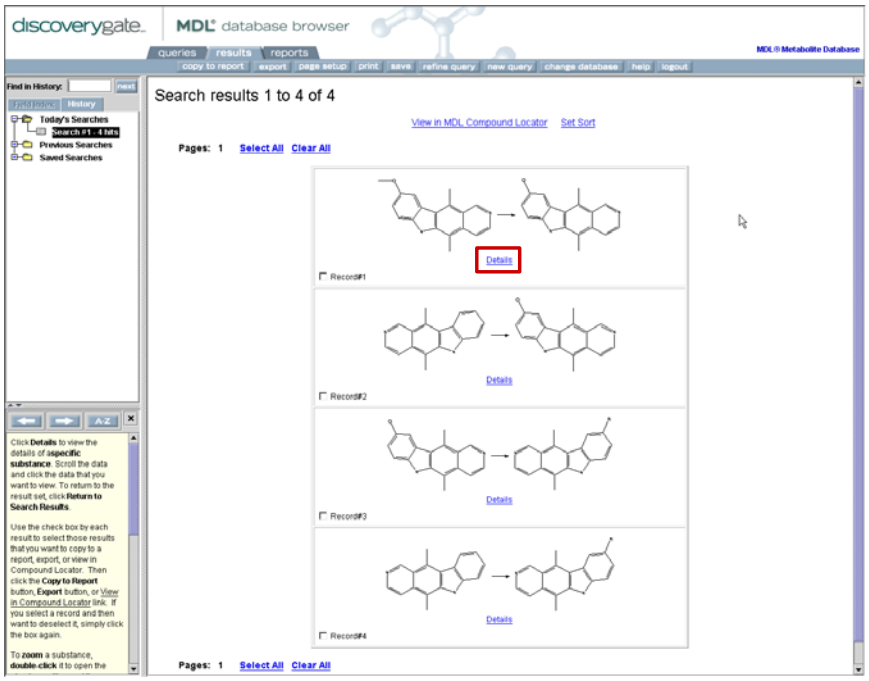


Key points

- A molecule similarity search retrieves compounds that are structurally similar to the query structure. You provide a similarity value between 1 and 100 (the higher the number, the greater the similarity to the query).
- Similarity searching is based on structure keys. A structure key indicates a specific structural feature, such as an aromatic ring or an aryl heteroatom.
- The degree of structural similarity depends on the number of structure keys that a structure has in common with the query.

Notes

View results

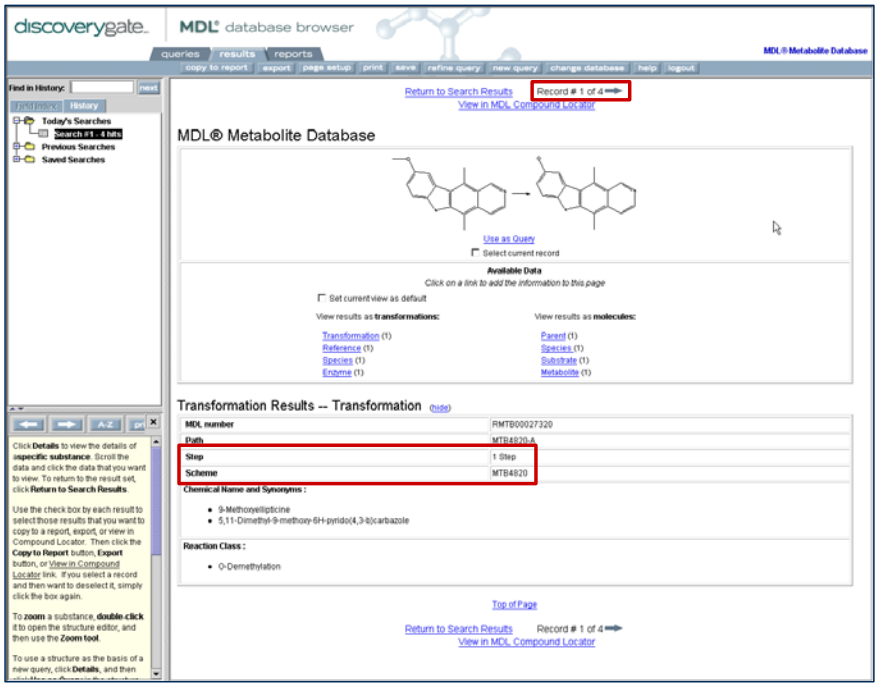


Key points

- The similarity search retrieves four transformations.
- The parent compound shown here contains the same heterocyclic system as in the compound of interest.
- Note that the second and fourth transformations share the same substrate molecule, and the substrate for the third transformation is the same as the metabolite of the second. These three transformations constitute a metabolic scheme.
- Click the Details link to see additional information for a transformation.

Notes

View results for first transformation

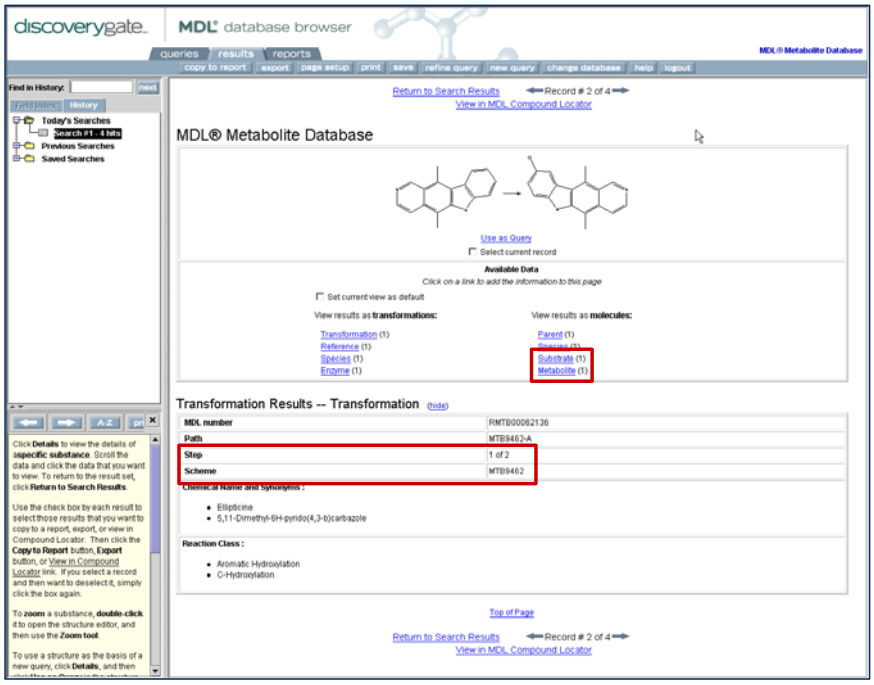


Key points

- The details page shows information about the transformation.
- The scheme in which the transformation exists is identified. Note that this is a 1 Step scheme. The demethylation of the Parent molecule is the entire scheme. There are no further identified transformations of the metabolite molecule.
- Click the right arrow next to "Record X of Y" to view the next transformation.

Notes

View results for second transformation

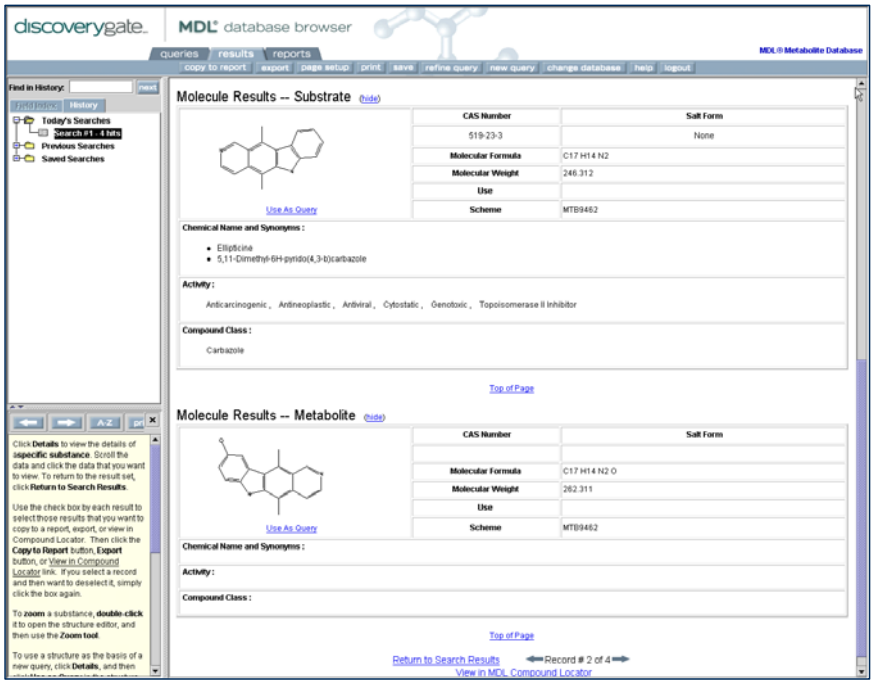


Key points

- The second transformation is in a different scheme, and is the first step of a two-step transformation pathway.
- Available data for the transformation is organized into information relevant to transformations, and information relevant to molecules.
- Click a link to add the relevant details to the display. The display automatically scrolls down to the new details.
- Click Top of Page to return to the top and add additional details.

Notes

View molecule data for transformation



Key points

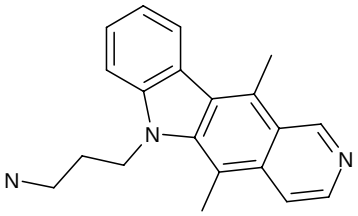
- The transformation Reference, Species, and Enzyme links contain information relevant to this specific transformation.
- The molecule Parent and Species links cite information relevant to the entire scheme. Citations in the molecule Species link can be for any transformation in the scheme.
- The Substrate link displays information about the substrates in the scheme. The parent molecule is also a substrate.
- The Metabolite link displays information about the metabolites. The metabolite in one transformation can be a substrate in the next.

Notes

Summary

Perform the following:

- Conduct a similarity search for Parent molecules, using the similarity value 70, for the same structure as used before



- View details for the transformations returned by the query

R

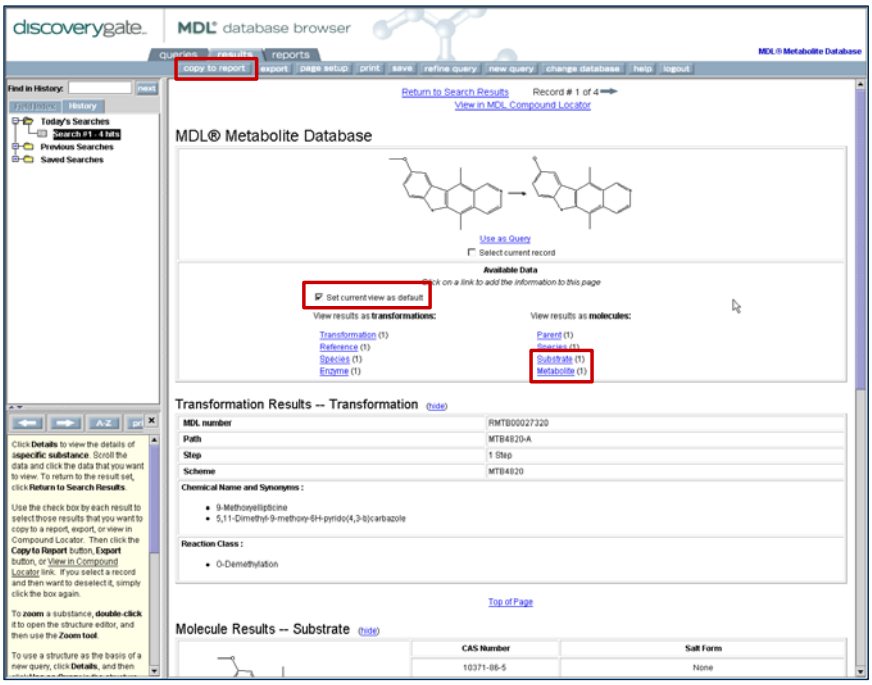
Key points

- The slide above summarizes how to search for metabolic schemes in which the parent compound is structurally similar to the compound of interest, and how to view the data associated with the scheme transformations.

Practice steps

1. In the Select Search Type drop-down list, choose **Similarity**.
2. In the Similarity Value box, type **70**. Click **start search**.
3. In the Search Results window, click **Details** for the first transformation.
4. Click the right arrow next to Record # 1 of 4 to view the second transformation.
5. Click the molecule **Substrate** link. Click **Top of Page**. Click the molecule **Metabolite** link.
6. Click **Return to Search Results** to return to the list of transformations.

Set view for a report

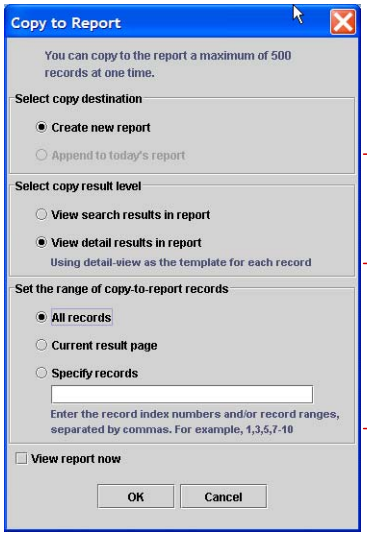


Key points

- Check the "Set current view as default" check box to apply current settings to all records you view.
- The displayed records can also be copied into a report.
- Click the "copy to report" button to create a report from the currently displayed records and details.

Notes

Create a report



Create a new report, or add data to an existing report

Add summary results only, or include details defined by a report view

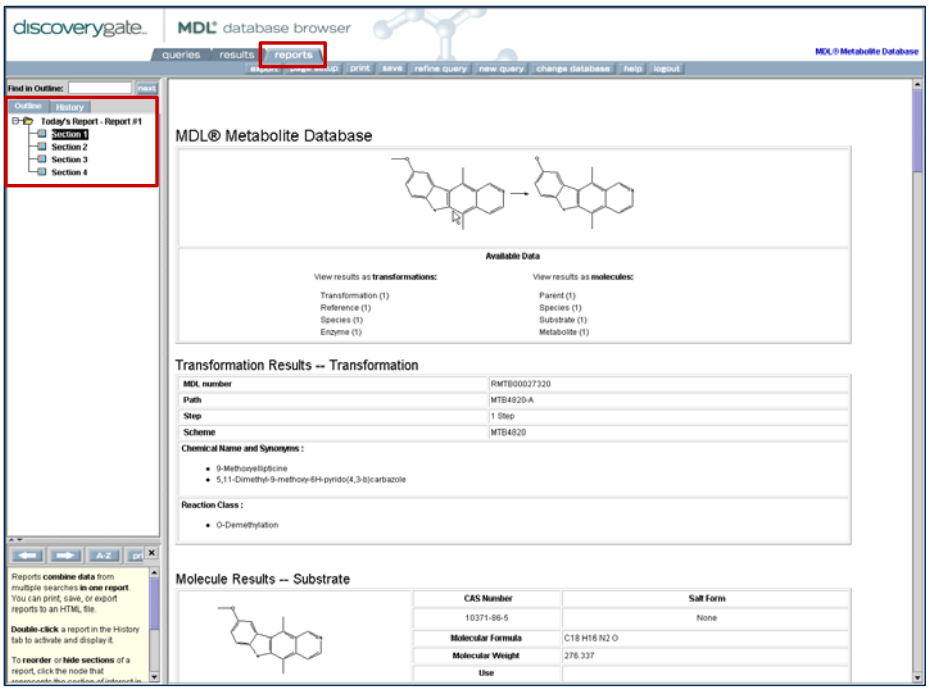
Choose which retrieved records to include in the report

Key points

- Select the settings for the report.
- If you choose to include multiple records, each record and its selected details will be put into a separate report section.

Notes

View a report section

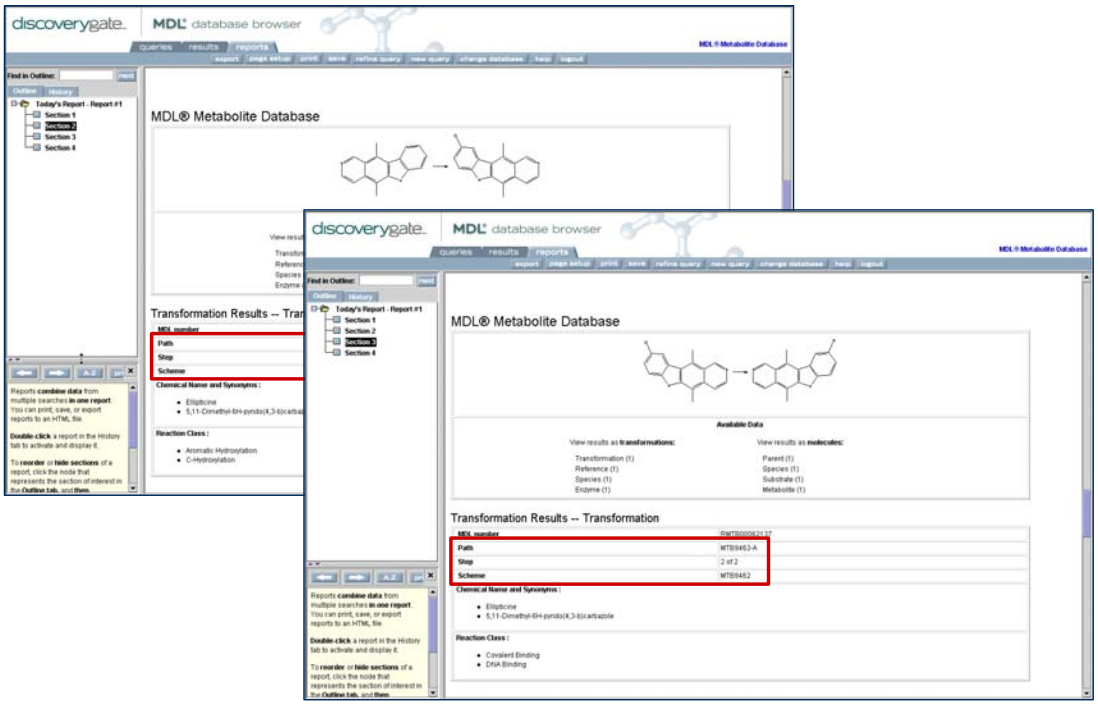


Key points

- Click the reports tab to view reports.
- Section 1 contains the summary and details information for the first of the four transformations.

Notes

View a metabolic scheme



Key points

- Click Section 2 in the Outline to view the second transformation.
- The Transformation details include the Scheme identifier, and the Path and Step for this transformation within the scheme.
- View additional sections to trace a transformation pathway. Each pathway also includes a summary transformation for the entire pathway.

Notes

Summary

Perform the following:

- Create and set a report view
- Create a report
- View transformations in a metabolic scheme

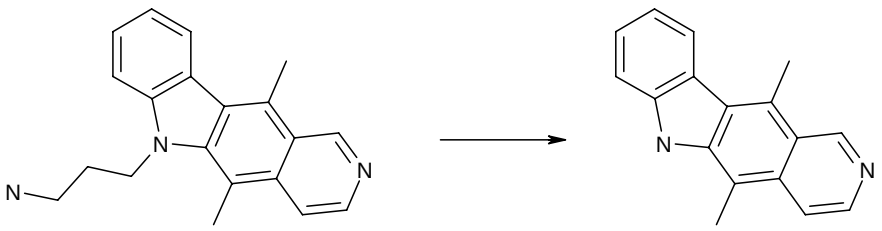
Key points

- The slide above summarizes how to copy records to a report, and view the data associated with a scheme.

Practice steps

1. Check the **Set current view as default** check box.
2. Click the **copy to report** button.
3. In the Copy to report window, choose **Create new report** for the copy destination.
4. For the "copy result level," choose **View detail results in report**. For the "range of copy-to-report records," choose **All records**.
5. Click **OK**.
6. Click the reports tab. Scroll to view information for Section 1.
7. Click **Section 2** in the outline. Note the Path and Step information for this transformation.
8. Sequentially click the remaining Sections in the Outline. Note the Path and Step information for each transformation.

How likely is this biotransformation?



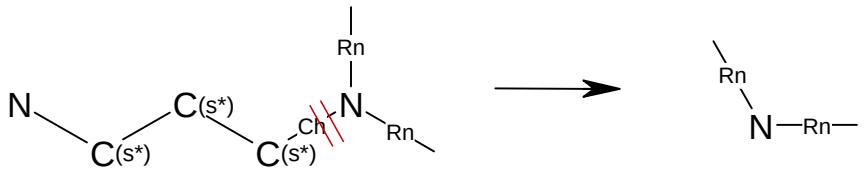
If the dealkylation of our compound can be reasonably expected, then the second scheme documents the metabolic fate of the anticipated metabolite.

Key points

- We saw in the first transformation that a compound similar to our original compound underwent a demethylation reaction.
- If our compound were to undergo a similar dealkylation reaction (pictured above), then the second scheme that we retrieved depicts a further metabolic outcome.
- Our next task is to determine how likely it would be for this biotransformation to occur. Rather than conduct a similarity search for similar transformations, we will conduct a search for transformations that have the same specific substructures and reaction type of interest. This type of search is called a transformation substructure search.

Notes

Design query to test hypothesis



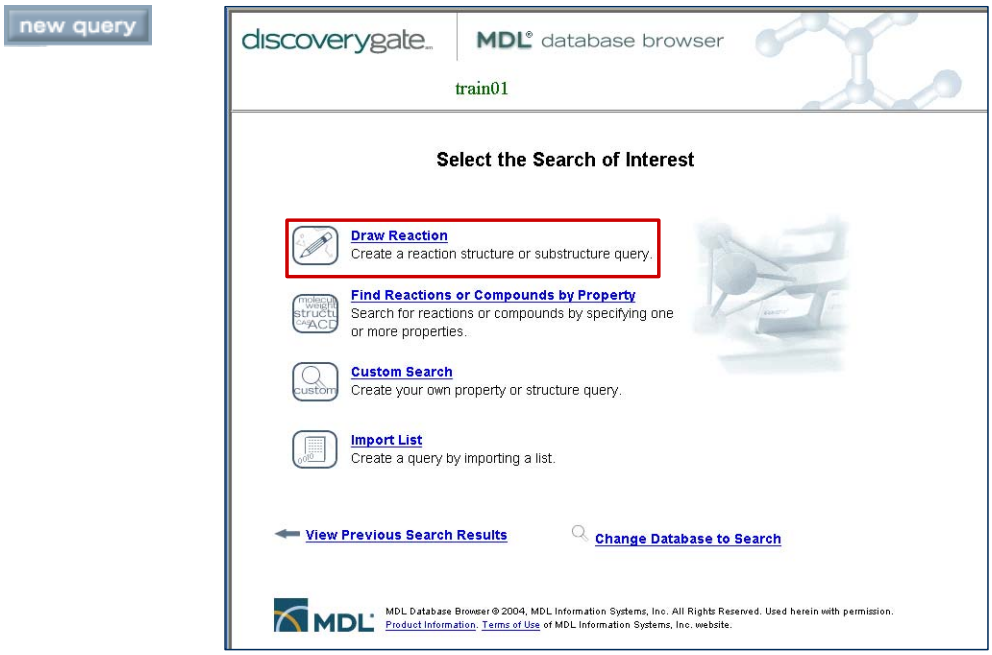
- Ring topology (Rn) allows rings of any size
- Chain topology (Ch) prevents fused ring systems
- Substitution count (s*) prevents unwanted substitution
- Reacting center (Breaks) specifies reaction bond site

Key points

- The transformation substructure query that we will use is depicted above.
- In the transformations that we retrieve, the substrate must contain a heterocyclic system, with an acyclic group containing at least three carbons and one nitrogen attached to the ring nitrogen.
- During the reaction, the bond attaching the acyclic group to the ring must be broken.
- The resulting metabolite contains a heterocyclic system that includes nitrogen.

Notes

Create a new query

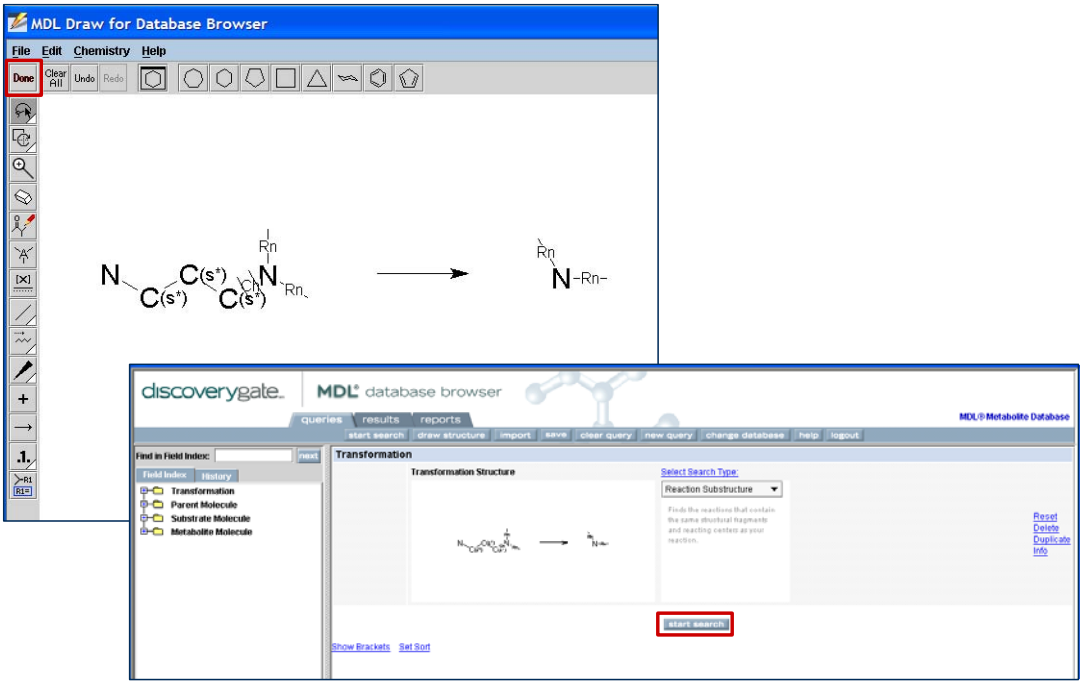


Key points

- When you click the “new query” button, you return to the Select the Search of Interest window.
- Click “Draw Reaction” to create a reaction query.

Notes

Transformation substructure query

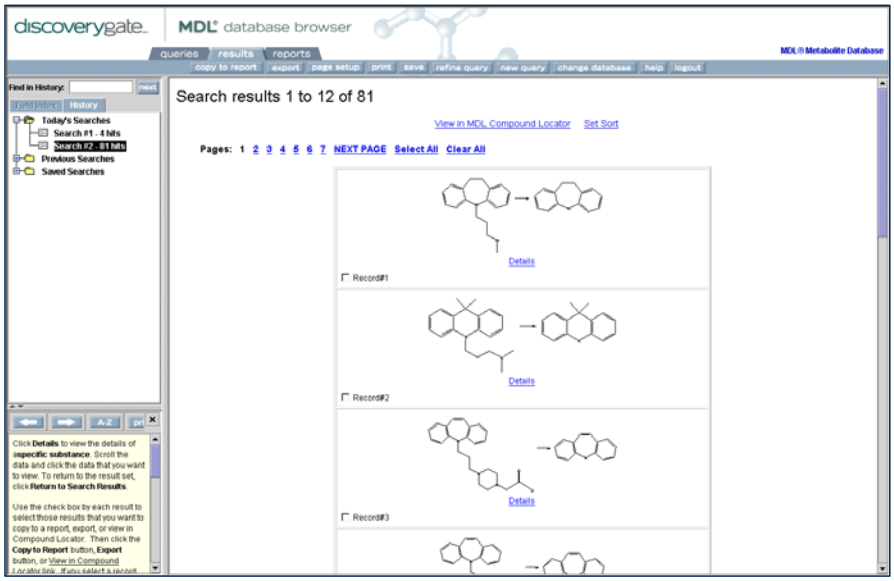


Key points

- Draw the reaction query and transfer it to the query form.
- Choose Reaction Substructure as the search type, and then initiate the search.

Notes

Results support dealkylation reaction



Key points

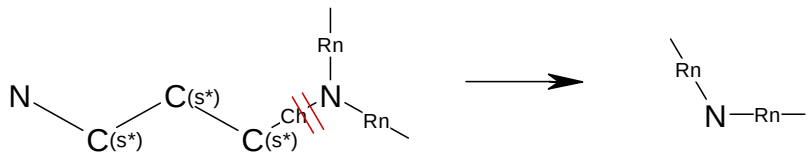
- The transformation substructure search returns more than 80 hits.
- Review of the hits indicates that the dealkylation reaction is probably reasonable to expect.

Notes

Summary

Perform the following:

- Conduct a transformation substructure search using the following query



- View some of the transformations retrieved

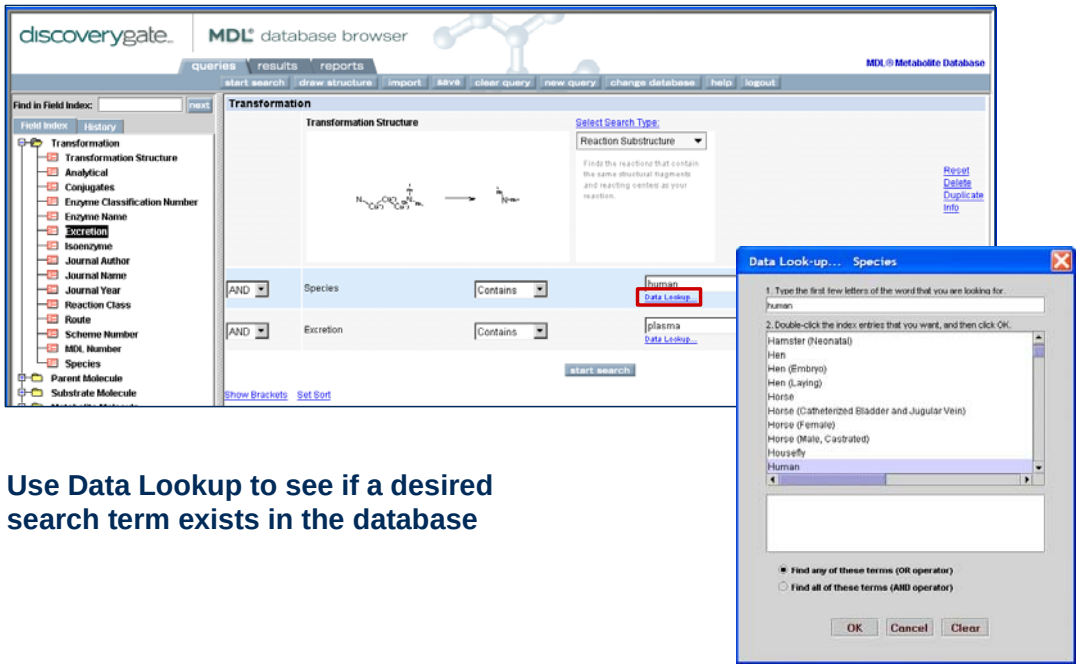
Key points

- The slide above summarizes how to conduct a search for transformations that have the same specific substructures and reaction type of interest.

Practice steps

1. Click **new query** to go to the Select the Search of Interest window.
2. Click **Draw Reaction** to open an MDL Draw window.
3. Draw the reaction shown on the slide. Click **Done** to transfer the structure to the Database Browser query window.
4. Click **start search**.
5. View some of the transformations retrieved.

Add data criteria to test relevance



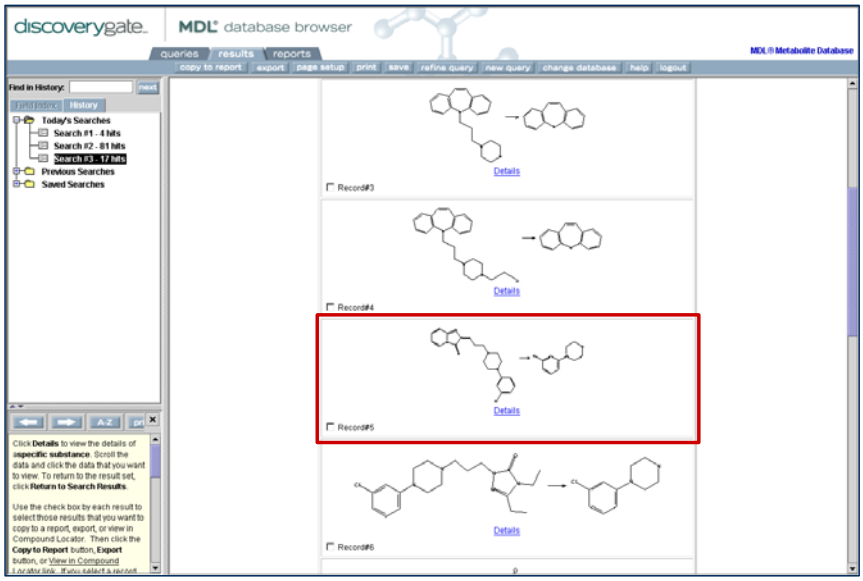
Use Data Lookup to see if a desired search term exists in the database

Key points

- To test the relevance of the transformations retrieved, you want to add data criteria to the transformation substructure search.
- You want to see if any of the transformations were observed in human studies and through plasma excretion.
- Double-click a data field in the Field Index to add it to the query.
- The Data Lookup link allows you to see if a search term exists in the database, before using it as part of your query.

Notes

Plasma excretion data in humans

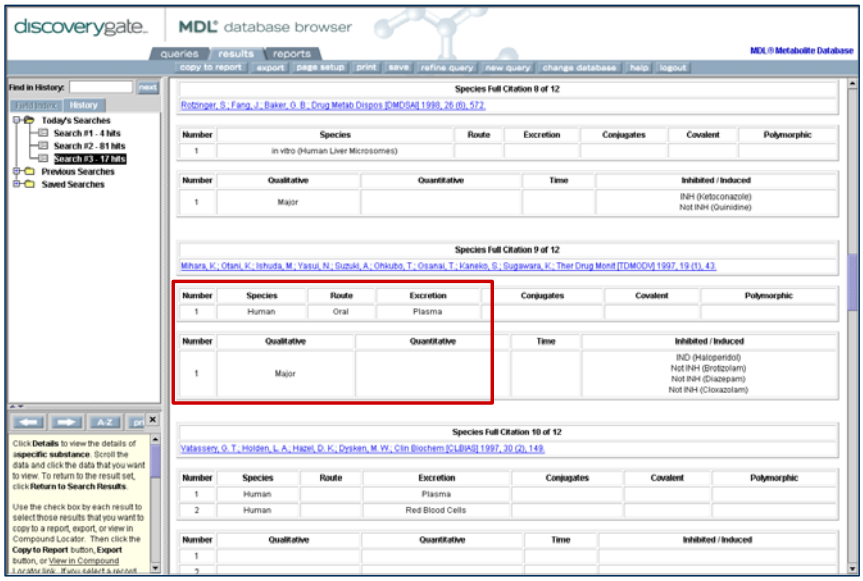


Key points

- The search retrieves 17 transformations in which blood level concentrations of dealkylated metabolites have been determined.

Notes

View concentrations of metabolites



Key points

- View the Species details to see the reported plasma levels for each citation and species in which it has been determined.

Notes

Summary

Perform the following:

- Add the following data criteria to the query

  Transformation Species contains human

  Transformation Excretion contains plasma

- View some of the transformations retrieved

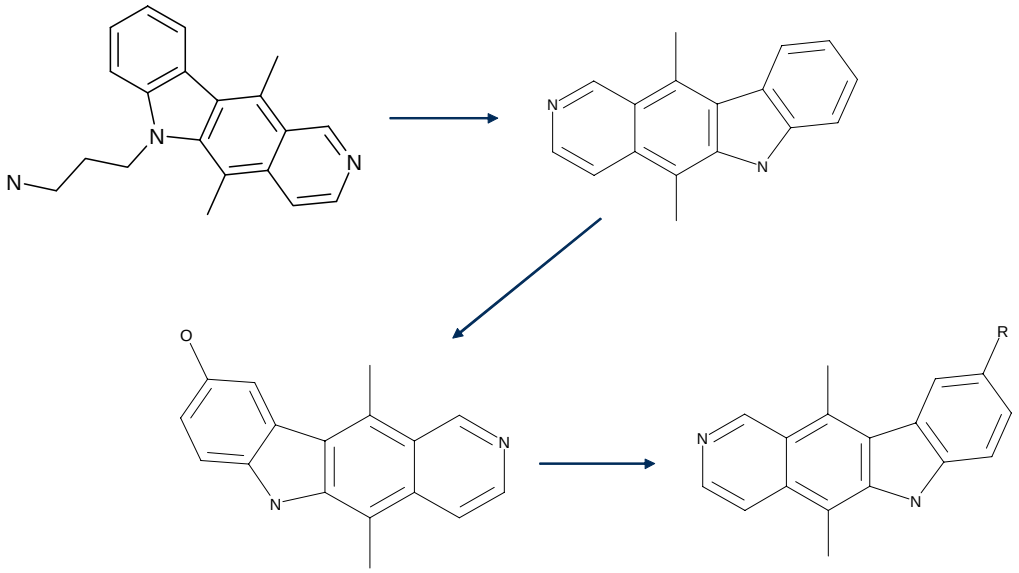
Key points

- The slide above summarizes how to refine the relevance of the transformations retrieved by adding data criteria to the search.

Practice steps

1. Click **queries** to return to the query form.
2. In the Field Index, click the **+** to expand the Transformation folder.
3. Double-click the **Species** field to add it to the query window. Verify that **Contains** is selected in the data operator drop-down list. Type **Human** in the Data text box.
4. Double-click the **Excretion** field to add it to the query window. Verify that **Contains** is selected in the data operator drop-down list. Type **Plasma** in the Data text box.
5. Click **start search**.
6. Click **Details** for the fifth transformation.
7. Click the transformation **Species** link to view excretion details.
8. View details for some of the other transformations.

Proposed metabolic pathway



Key points

- Based on what we have seen thus far, we propose a metabolic transformation of our compound (shown above).
- Next we will go on to consider the toxic effects of the parent and metabolites.

Notes

Consider toxic effects

Strategy:

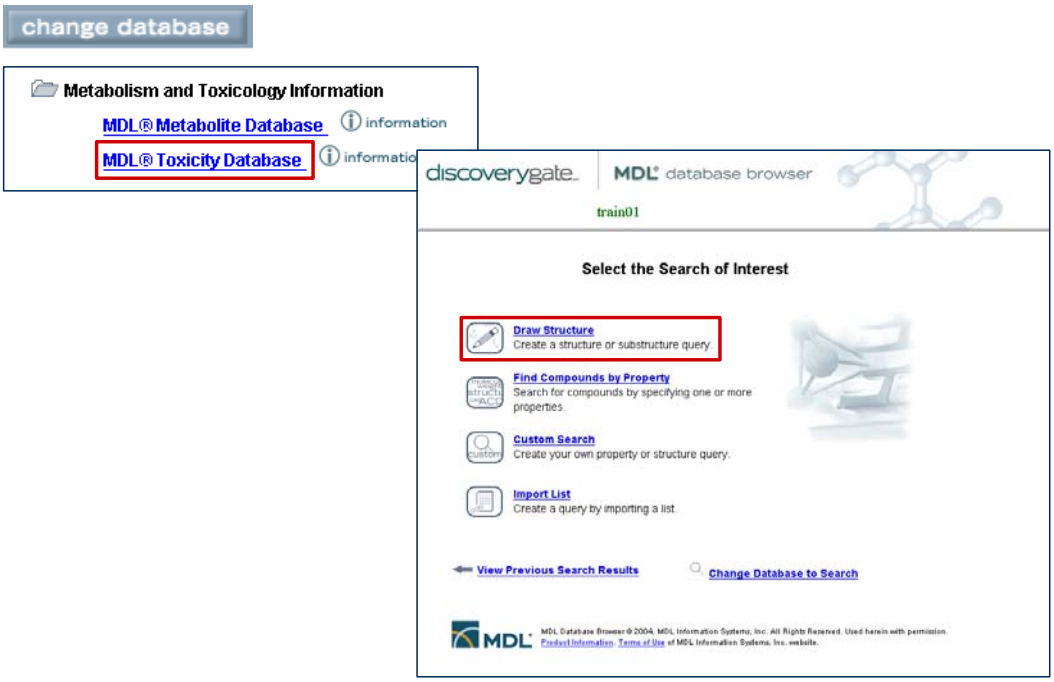
- Conduct an exact match to see if the compound is present in the MDL Toxicity Database
- If no match, conduct a similarity search
- View toxicity data for similar compounds to determine likely toxic effects of metabolites

Key points

- Our strategy for determining the toxicity of our compound and its metabolites is outlined above.

Notes

Change Database

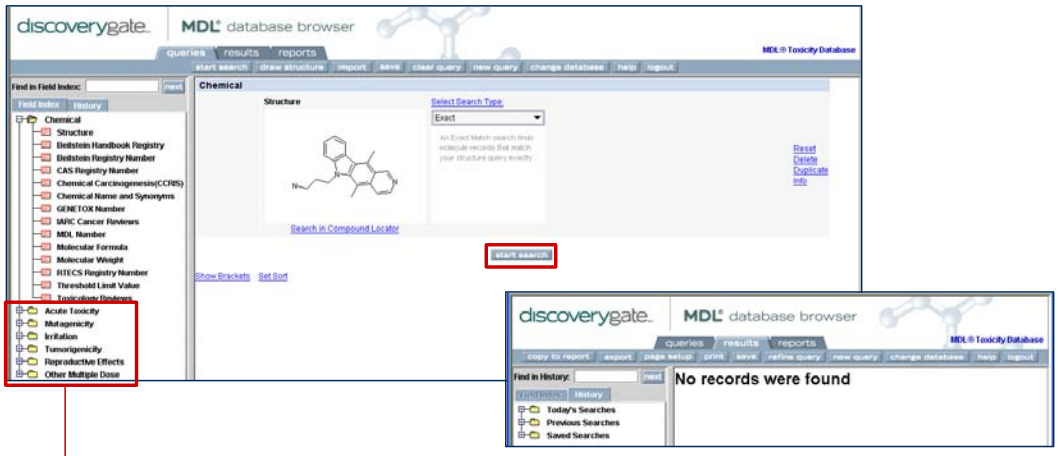


Key points

- When you change databases within the Database Browser, DiscoveryGate automatically logs you into the new database.
- When you select Draw Structure as the Search of Interest, an MDL Draw window is opened. You can draw the Ellipticine structure, or open the structure you saved earlier in this workshop.

Notes

Conduct exact match search



Data queries in the Toxicity database can be conducted for 6 types of toxic effects. These are listed as separate directories in the Field Index tree.

Key points

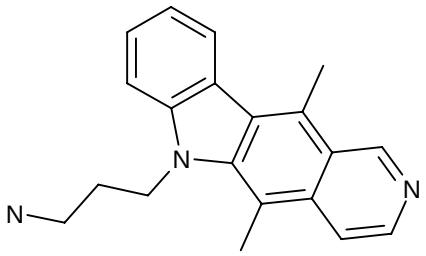
- The Chemical directory in the Field Index allows you to specify structure queries and other criteria associated with the chemical substance.
- The six toxic effects directories allow you to conduct queries for specific types of toxic effects.
- You conducted a search for the specific compound of interest in the Toxicity Database and found no hits. The next task will be to search for similar compounds.

Notes

Summary

Perform the following:

- Change to the MDL Toxicity Database
- Conduct an exact match structure search for the following compound



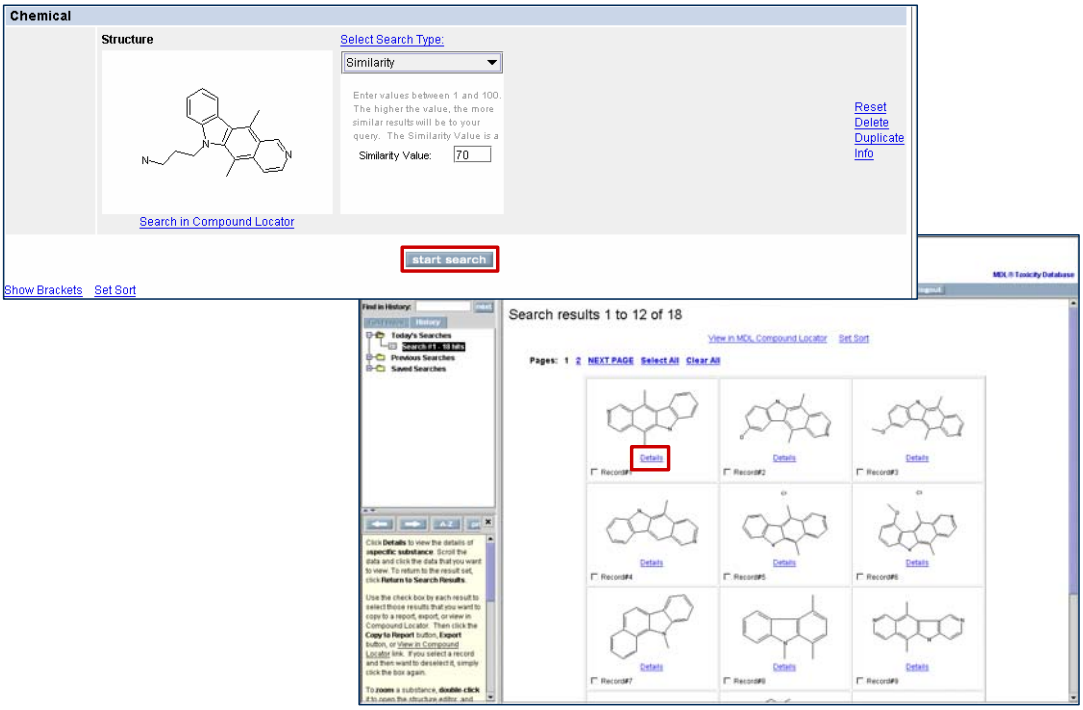
Key points

- The slide above summarizes how to search the Toxicity database for a specific compound.

Practice steps

1. Click the **change database** button.
2. Click the **MDL Toxicity Database** link.
3. In the Select the Search of Interest window, click the **Draw Structure** link.
4. Choose **File > Open**, and open the Ellipticine.mol file you saved earlier in the workshop.
   – or –
   Draw the structure shown on the slide.
5. Click **Done** to transfer the structure to the Database Browser query form.
6. Select **Exact** from the search type drop-down list.
7. Click **start search**.

Conduct similarity search

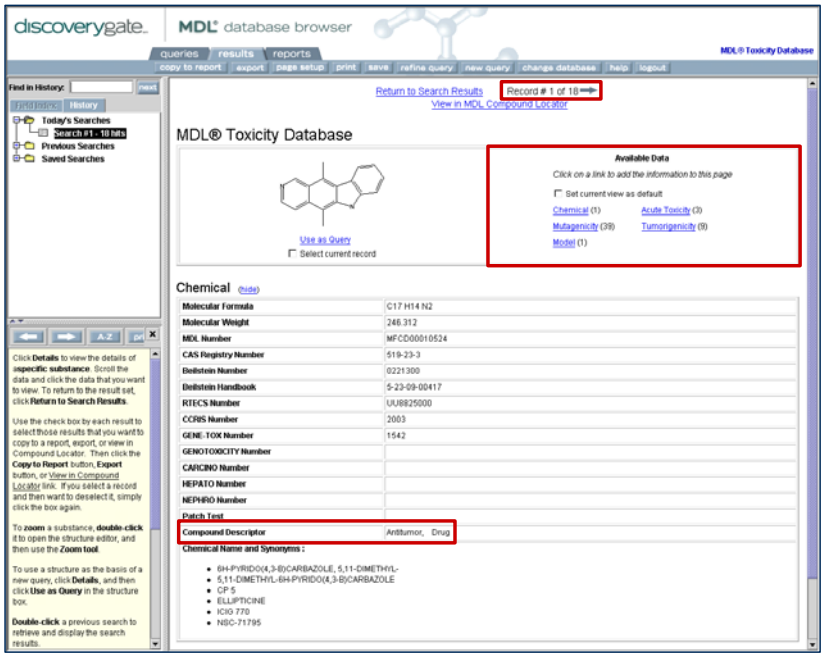


Key points

- This search will retrieve compounds that are structurally similar to the query.
- In this case, we are using 70 as the similarity value. If the search retrieves too few hits, you can reduce the similarity value. If the search retrieves too many hits, you can increase the similarity value.

Notes

Results of similarity search

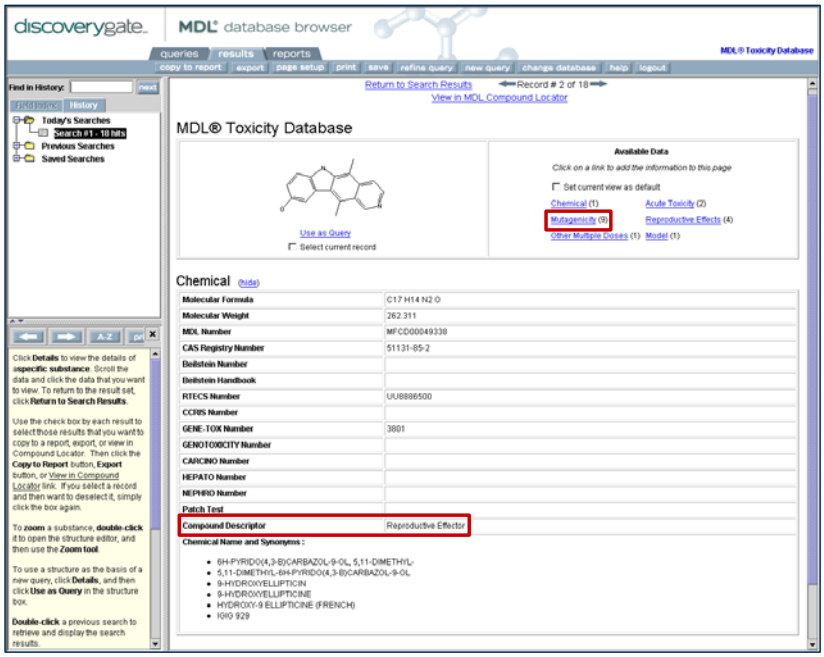


Key points

- The similarity search retrieves 18 compounds.
- Note that this first compound is the N-dealkylated compound from our metabolic scheme.
- Note the large number of mutagenicity results (39 experiments), which might indicate unacceptably adverse effects.
- The compound descriptors are Antitumor and Drug.

Notes

View next compound

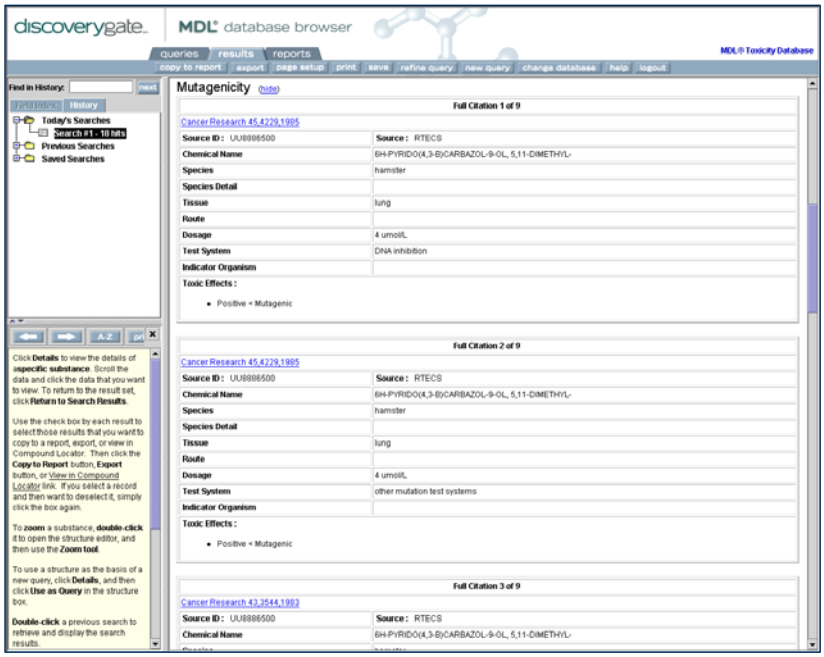


Key points

- The second compound on the list is the anticipated oxidation product from our proposed metabolic scheme.
- This compound is described as a Reproductive Effector.

Notes

Mutagenicity data



Key points

- As we look at the Mutagenicity data, we see that it exhibits mutagenicity at dosages in micromolar amounts.

Notes

Summary

Perform the following:

- Conduct a similarity search using the similarity value 70 for the same compound used before
- View the available toxicity categories for the first compound retrieved
- View the second compound on the list and its available data, particularly the mutagenicity data

Key points

- The slide above summarizes how to search for compounds that are structurally similar to the compound of interest and view the search results.

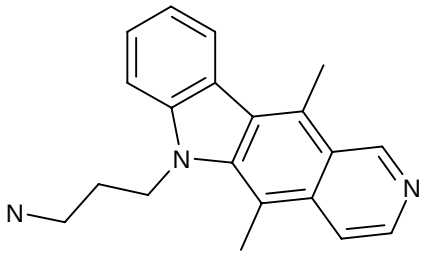
Practice steps

1. Click the **queries** tab.
2. Select **Similarity** from the search type drop-down list. Enter **70** as the Similarity Value.
3. Click **start search**.
4. Click the **Details** link for compound 1.
5. Click the links for **Acute Toxicity**, **Mutagenicity**, and **Tumorigenicity** to see the available data for the second compound.
6. Click the right arrow to view the next compound.
7. Click the link for **Mutagenicity**.

Conclusion

In this workshop, we determined:

- Potential metabolic outcomes for a novel compound
- Likely toxic effects for the parent compound and its anticipated metabolites



Ellipticine, 6-(3-aminopropyl)-, dihydrochloride

Key points

- We used different search strategies to find relevant data when a specific compound is not present in the database (similarity searching, substructure searching), as well as strategies for testing the relevance of our search results (adding data criteria).

Notes