

Leadscope structure drawing editor

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Leadscope Technical Support

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Leadscope structure drawing editor

Overview

The Leadscope structure drawing editor is an easy-to-use graphical user interface for creating an electronic representation of a chemical structure or a structure query. It is embedded throughout Leadscope applications in context sensitive areas. For example, an option to draw a chemical structure is provided when you apply models/alerts, as shown in Figure 1.

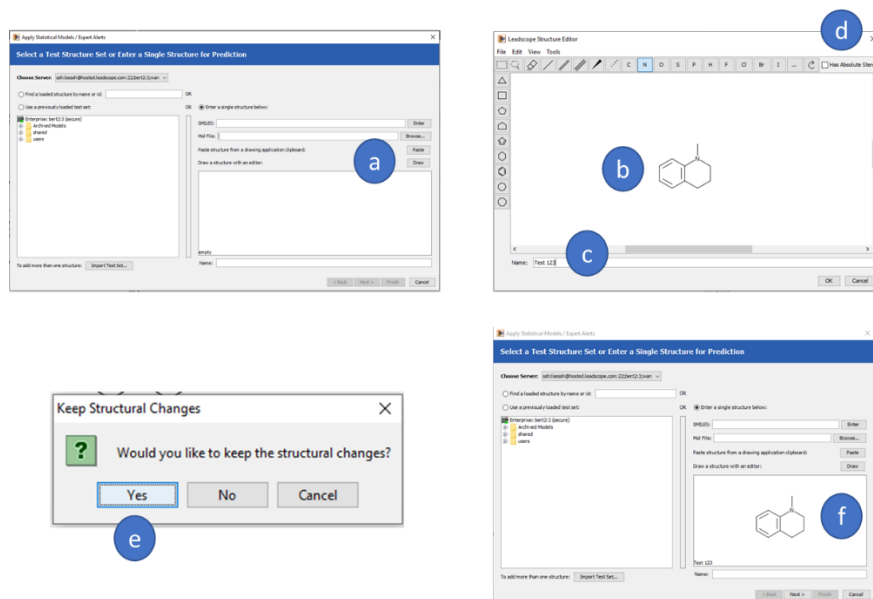


Figure 1: Using the structure drawing editor when applying models/alerts

A “Draw” option (Figure 1a) is included when applying a model or alert. Clicking on this button will launch the structure drawing editor which can be used to graphically generate a chemical structure (Figure 1b) as well as to enter a name for the chemical (Figure 1c). Once the structure is drawn, closing, or exiting the editor (for example by clicking on the × (Figure 1d) or selecting “OK”) will display a “Would you like to keep structural changes” dialog. Selecting “Yes” (Figure 1e) will then save the drawn structure within Leadscope (Figure 1f).

The structure drawing editor is included in many areas including:

- Adding new “Possible reactive features” in the model/alert “Explain” function
- Performing an expert review of “Potentially reactive features” as part of a hazard assessment based on a protocol
- Performing a structure-based search (substructure, similarity, exact or family)
- In the read-across tool to both enter a target chemical as well as to identify similar chemicals using the category approach (i.e., issuing a substructure search)
- With the Leadscope project structure classification tool and the Leadscope feature list editor to classify a set of chemical structures by substructure searches

In addition, the structure drawing editor is also available as a standalone tool from the Window’s program menu.

Drawing chemicals

The structure drawing user interface includes templates to support common operation, as shown in Figure 2.

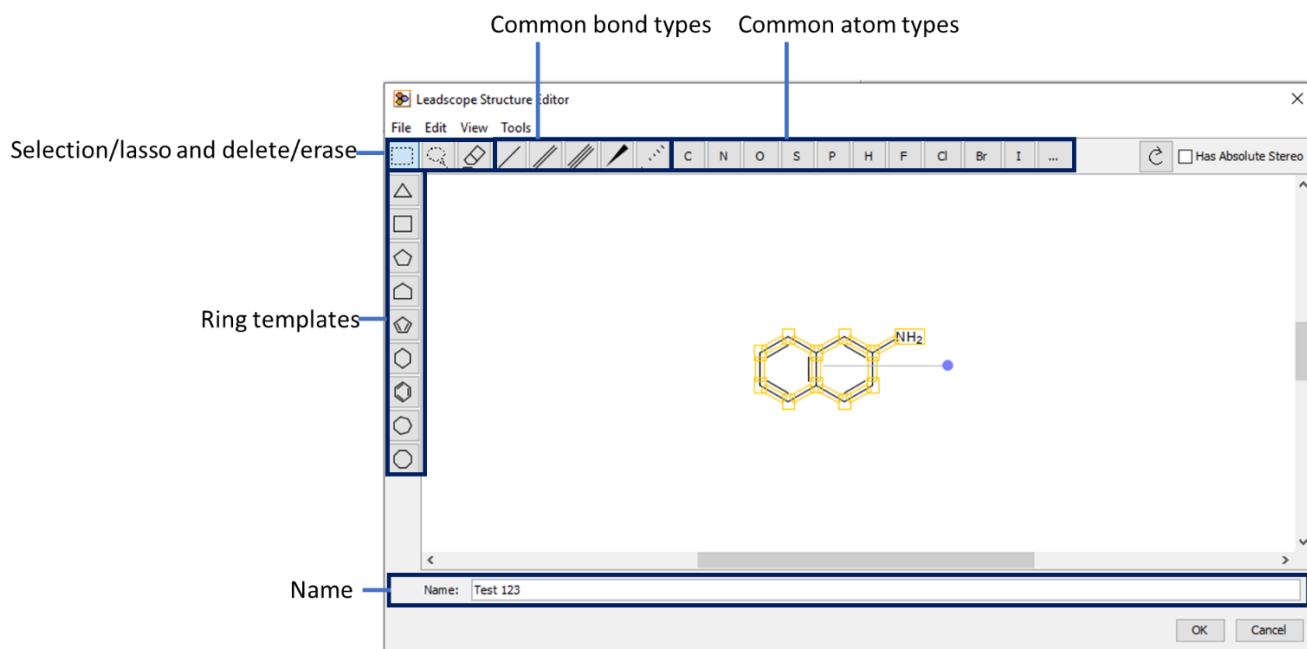


Figure 2: Common elements to support structure drawing

Common 3-7 membered aliphatic and aromatic rings are represented on the left side of the screen ("Ring templates" in Figure 2). Once a ring has been selected, clicking on the main drawing area will then render the ring (as illustrated in Figure 3a). Additional rings can be fused to an already drawn ring by again selecting a ring template then clicking on a bond in the ring already drawn (as shown in Figure 3b). An additional ring connected by a single bond can be added to structure by clicking on an atom (as shown in Figure 3c).

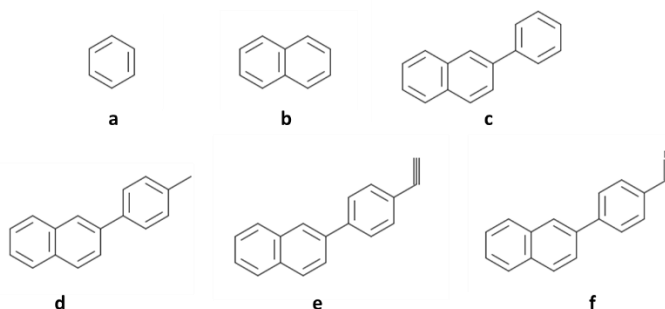


Figure 3: Drawing a chemical structure

Single, double, and triple bonds as well as up and down stereo bonds are shown in the "Common bond types" area in Figure 2. After selecting the bond type, single clicking in the drawing area will render the new bond (as shown in Figure 3d and 3e). Bonds can be added to an existing structure by either single clicking on an atom or single clicking at the same time moving the mouse to render the new bond in the

desired position. It is also possible to change a bond type by first selecting the bond (from the “Common bond type” area in Figure 2) then clicking on the existing structure bond (as shown in Figure 3e). An alternative way of changing a bond type (when the single bond type is selected) is to single click on the bond (single bonds will change to double; double to triple; and triple to single).

Ten common atoms are shown towards the top of the screen (“Common atom types” in Figure 2). Other atom types are available by clicking on the “...” button. After selecting the atom type, click in the drawing area, including on an atom already rendered, to add or change to the selected atom type (as shown in Figure 3f).

Individual atoms or bonds can be selected by single clicking on them when the selection/lasso (shown in Figure 2) option is selected (they will be highlighted in yellow as shown in Figure 4a). There are also two lassos (shown in Figure 2) that can be used to select either the whole chemical structure or a portion of the structure. After selecting the lasso, click and move the mouse at the same time to define the selected area. The selected area will be highlighted in yellow (Figure 4b). If the whole structure was selected, as shown in Figure 4c, an additional blue object will appear that allows you to rotate the chemical structure. Next to the two lasso options is an eraser (Figure 2) to remove atoms and/or bonds. Once selected, clicking on an atom or bond will remove them. The eraser can also be used on the selected portion of the chemical structure (the delete button has the same effect).

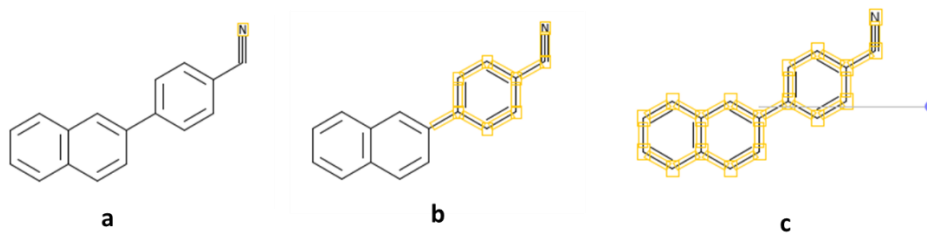


Figure 4: Highlight an atom (a), a portion of the chemical (b) and the whole chemical (c)

If there are multiple chemical structures in the drawing panel, it is possible to select one of the structures and move it over atoms and/or bonds of another. This will allow you to form a larger chemical structure including fused and spiro ring systems. Once the selected structure is close to any atoms and/or bonds of another structure, the atom(s) that will be combined are highlighted with a magenta box (as illustrated in Figure 5). The position and atom types of the stationary (non-selected) structure will be kept when the merge is completed.

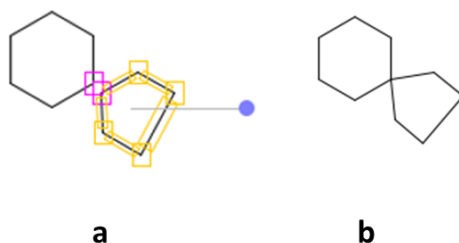
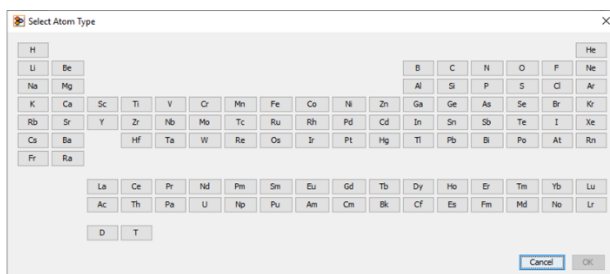


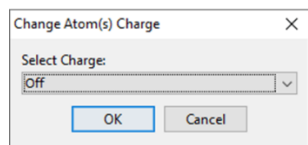
Figure 5: Joining two distinct structures

Any selected atoms and bonds can be further manipulated using the right click option. For atoms there are four options, and each option displays a dialog box (shown in Figure 6) where any selection can be made:

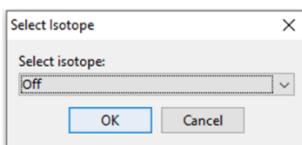
1. Change atom(s) type (dialog shown in Figure 6a)
2. Change atom(s) charge (dialog shown in Figure 6b)
3. Change atom(s) isotope (dialog shown in Figure 6c)
4. Change atom(s) valence (dialog shown in Figure 6d)



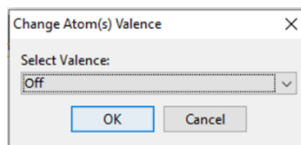
a



b



c



d

Figure 6: Options for setting atom type (a), charge (b), isotope (c) and valence (d)

Similarly for bonds, there is a single option “Change bond(s) type” which will display a dialog box to make the selection. There are six options to select from: Single Bond, Double Bond, Triple Bond, Up Bond, Down Bond, and Double Bond Stereo. Double Bond Stereo are displayed with the double bond shown with a thicker bond.

It is also possible to select atoms or bond types for a selected set of atoms and bonds.

As shown in Figure 2, there is an addition “Has Absolute Stereo” which can be applied to the chemical structure.

File menu


There are four file menus (“File”, “Edit”, “View”, and “Tools”) that provide additional capabilities for uploading, saving, creating reports, copy-and-paste, and manipulation of the chemical structures.

The **file** menu has several options:

- **New structure:** Creates a blank structure drawing panel
- **Open or add SD/MOL File:** Opens or adds a new chemical structure from either a MOL file or the first entry in an SD file
- **Add SMILES:** Add a depiction of a SMILES string to the drawing panel
- **Publish report:** Save a PDF or Word (RTF format) document to the file system
- **Print to PDF:** Creates and launches a PDF document of the chemical structure to print

- **Close:** Closes the application

The **edit** menu has several options:

- **Undo:** This will undo the last action (also available from the  button on the main page)
- **Cut, copy, paste, and delete:** Options to copy to or from the clipboard or delete the selected chemical structure
- **Select all**
- **Set and clear date**

The **view** menu has several visualization options for a drawn chemical (such as the chemical shown in Figure 7a):

- **Show (or hide) implicit hydrogens** (see Figure 7b)
- **Show (or hide) atom numbers** (see Figure 7c)

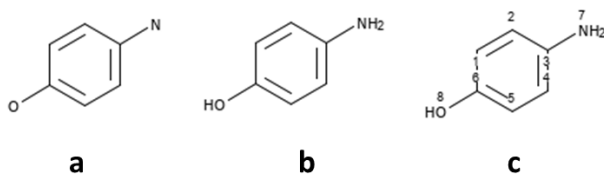


Figure 7: Visualization options

The **tools** menu has several options:

- **Change atom(s) type, charge, isotope, valence:** There are four options to make changes to any atom, which are the same as the right click functions described earlier
- **Change bonds(s) type:** It is possible to select a bond type
- **Reverse stereo bond direction**
- **Regenerate coordinates:** perform 2D coordinate generation on the selected structures
- **Apply structural transform(s):** A series of structural transformations are available from the dialog shown in Figure 8 -
 - o **Remove stereo:** convert stereo bonds to non-stereo form
 - o **Remove non-transition metal bonds:** delete any bonds to metals not transition metals
 - o **Remove isotopes:** strip isotopes from the structure
 - o **Remove radicals:** remove radical electrons from atoms
 - o **Remove salts:** strip all salts from the structure based on the list of organic and inorganic salts
 - o **Remove duplicate fragments:** strip unconnected duplicate fragments from structures
 - o **Remove water fragments:** remove any H₂O, OH⁻, H₃O⁺ fragments from a structure
 - o **Neutralize charged structure:** replace charged fragments with neutral species
 - o **Remove charge (forcibly):** remove charges including zwitterions
 - o **Remove spurious charges:** remove charges when implicit Hs are present
 - o **Remove specified (abnormal) atom valences:** remove valence spec if not nominal
 - o **Pentavalent nitrogens (make charge-separated):** replace pentavalent nitrogen fragments with charge-separated fragments

- **Pentavalent nitrogen (make charge separated):** convert charge-separated nitrogen fragments into fragments pentavalent form
- **Aromatize keto-amine tautomers:** aromatize cyclic amines where adjacent ketone group infer aromaticity of the ring.
- **Fix bad stereo-centers:** Attempt to fix a bad stereo-center by changing bond direction
- **Denormalize aromatic bonds:** transform aromatic bond types to Kekulé format
- **Dates (add missing):** add a modification date to structures
- **Convert to SAR form:** neutralize the structure and strip salts
- **Re-assign atom numbers:** Consecutively renumber atoms starting with 1
- **Validate:** Includes options to validate (1) all (includes all checks), (2) no stereo (only valence and general connectivity checking), and (3) no stereo or valence (only general connectivity checking)
- **Highlight:** Options to highlight on the drawn chemical structure (shown in Magenta) (1) stereo centers, (2) double bond stereo, (3) aromaticity and tautomers, (4) aromaticity, (5) tautomers, (5) all atoms and bonds and (7) none. Examples are shown in Figure 9.
- **Find overlapping atoms and bonds**

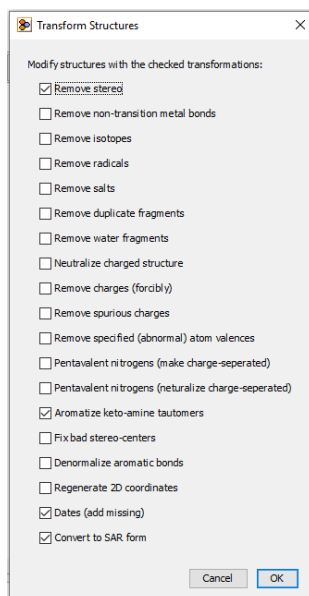


Figure 8: Structural transformation options

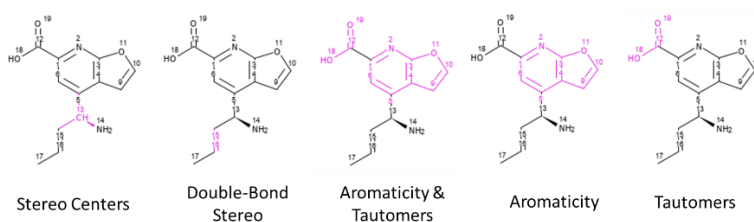


Figure 9: Examples of structure highlighting

Drawing substructure queries

The structure drawing editor, depending on where it is launched from, can specify additional restrictions on atoms, bonds as well as sets of bonds to support precise substructure searching. This option is available as part of the search tool to perform a substructure search and when specifying features to analyze a set of chemical structures by.

In addition to using atom types (as discussed previously), it is also possible to define generic atoms. This is performed in the customized “Select Atom Type” dialog shown in Figure 10 (launched either from a right click action over an atom, via the “...” button on the main screen or via the Tools menu when an atom is selected). It is possible to define a generic list on-the-fly by selecting any atoms. For example, in Figure 10, Cl and Br were selected by single clicking on the symbols. The symbol is deselected by clicking on it again. The dialog also includes a series of pre-defined generic atom symbols shown towards the bottom of the dialog: A (Any atom except hydrogen), Q (any atom except hydrogen or carbon), Ar (aromatic carbon), Ak (alkyl carbon), Ht (aromatic heteroatom), M (any metal atom), and X (F, Cl, Br, or I). It is also possible to either include or exclude the selected atom types (shown at the top of the dialog).

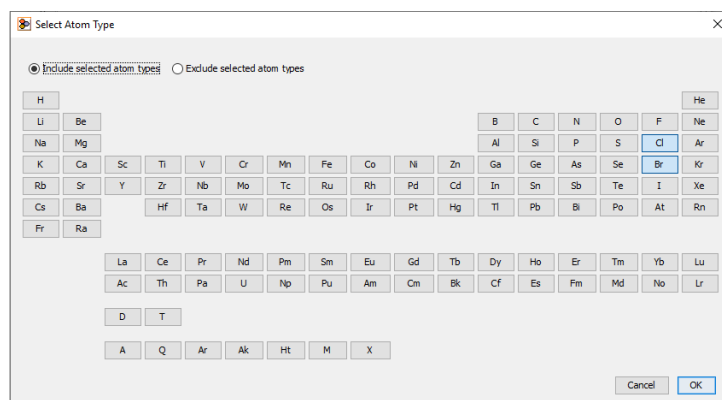


Figure 10: Customized “Select Atom Type” dialog including generic atom

The dialog for selecting bonds has also been extended to support substructure queries (launched either from a right click action over a bond or via the Tools menu when a bond is selected). In addition to the standard list of bonds (as discussed previously), a number of new bond types are included: any bond, aromatic bond, single or double bond, single or aromatic bond, and double or aromatic bond. The visual representation of these query bond types is shown in Figure 11.

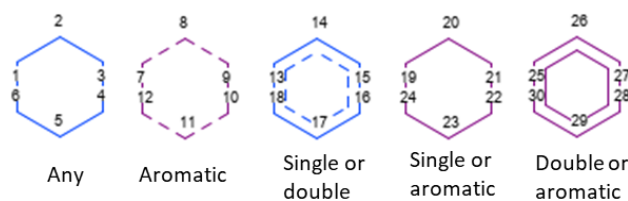


Figure 11: Depiction of the query bond types

By right clicking over an atom, it is possible to define additional restrictions on each atom to support substructure searching by selecting the “Change Atom Query Restrictions...” (this option is also available from the Tools menu). Once selected, the full list of atom query restrictions (also known as pattern modifiers) is displayed (as shown in Figure 12a). This dialog allows you to add a new restriction (“New”), modify an existing restriction (“Edit”) and delete a restriction altogether (“Remove”). When adding a new restriction, a pull-down list of restrictions is available and once a restriction is selected, context sensitive parameter will be shown in order to define each restriction (as shown in Figure 12b).

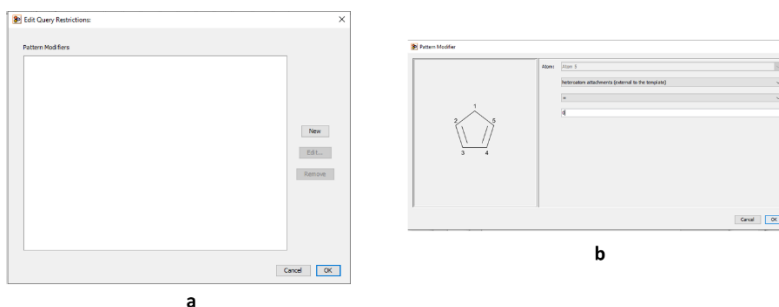


Figure 12: Adding a new atom restriction

The following atom restrictions are binary consideration (no further parameters need to be defined):

- **Is acyclic**
- **Is cyclic**
- **Is aryl**
- **Is not aryl**
- **Is closed to substitution**
- **Double bond stereo is considered**

The following atom restrictions require an integer value to be set. For example, the option “Heteroatom attachments (external to the template)” can be set to equal 0 which translates to the restriction that the query atom will match a substance in the database where there is no adjacent heteroatom (except those heteroatoms defined in the query or template). It is also possible to change the operator from “=”, to “>”, “<”, or “!” (where “!” stands for not equal to). In addition, comma separated values can be specified such as the number of hydrogens is equal to 1 or 2. The following restrictions follow this pattern:

- **Charge**
- **Double bond attachments (external to the template)**
- **Double bond attachments to heteroatoms (external to the template)**
- **Heteroatom attachments (external to the template)**
- **Number of hydrogens**
- **Ring size(s)**
- **Valence**

There are a number of additional restrictions:

- **Ring bond count:** This can be used to ensure an atom is not part of a ring, is part of an isolated ring, or part of a more complex ring system. There are 6 options:

- Has no ring bond count check
- Has no ring bonds
- Has ring bond count as drawn
- Has ring bond count of 2
- Has ring bond count of 3
- Has ring bond count of 4 or more
- **Substitution count:** This restriction can be used to specify how many explicit substitutions an atom is attached to (including substitution that are defined in the query or template). There are 8 options:
 - Has no substitution check
 - Has no substitutions
 - Has substitutions as drawn
 - Has 1 substitution
 - Has 2 substitution
 - Has 3 substitution
 - Has 4 substitution
 - Has 5 substitution
- **Unsaturated atom.** This restriction has options “On” or “Off”.

It is possible to place restrictions on individual bonds by hovering over a bond and right clicking, then selecting “Change bond query restrictions”. There are three options that operate in the same way as the atom restrictions:

- **Is acyclic**
- **Is cyclic**
- **Ring size(s)**

There is another option available through the Tools menu “Edit Query Restrictions”. This tool allows for atom and bond restrictions to be added, edited, or removed (as above). It also includes an option “Bond Set Modifier” where one or more bonds can be specified as “is acyclic”, “is cyclic”. It is also possible for the bonds selected to define the number of single, double, triple, single/double, double/aromatic, double/aromatic bond.

Atom, bond, or bond set restrictions will be shown visually in a new panel that will appear at the bottom of the structure drawing editor, as shown in Figure 13.

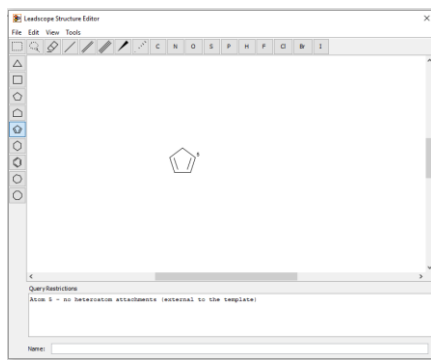


Figure 13: Panel displaying the restrictions on the atoms and bonds

There are several shortcuts to place restrictions on atoms and bonds directly (i.e., without going through the atom/bond restriction specification dialog). By right clicking on any atom(s) without restrictions on whether they are closed or open to substitution, there is an option to “Close atom(s) to substitution”. Similarly, for atom(s) that designated as closed to substitution, there is a shortcut to “Open Atom(s) to Substitution”, which will remove any such restrictions. Another shortcut available for atom(s) or bond(s) drawn as a chain is to explicit assign them as acyclic (so they only match acyclic atom(s)/bond(s) in the database chemicals) – “Restrict Atom(s) [or Bond(s)] to Acyclic Only”. Where the atom(s) or bond(s) are designated as acyclic, there is a right click option to remove such restrictions – “Allow Atom(s) [or Bond(s)] to be cyclic or acyclic”.