# Control Substitution and Ring Fusion in STNext Structure Searches

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STNext®

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CAS®
A DIVISION OF THE AMERICAN CHEMICAL SOCIETY

# Agenda

- Structure databases and structure search options on STNext
- Node and bond attributes
- Opening and closing structure queries: SSS versus CSS
- Summary

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- **Structure databases and structure search options on STNext**
- Node and bond attributes
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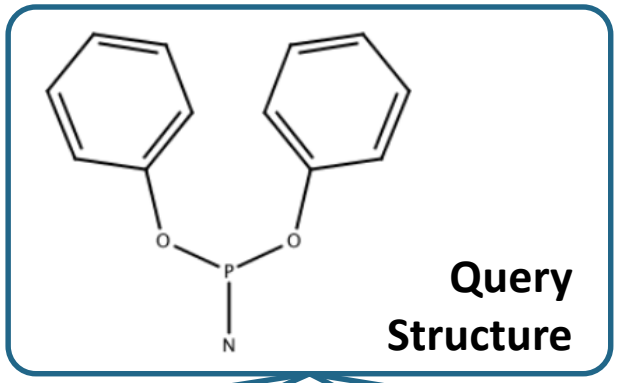
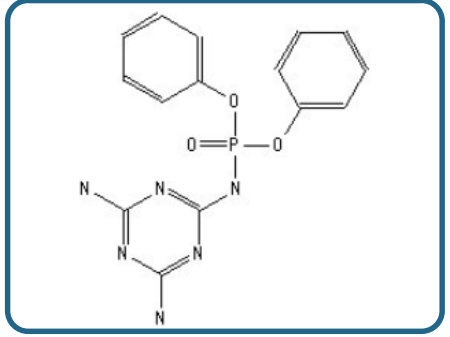
# Structure databases on STNext



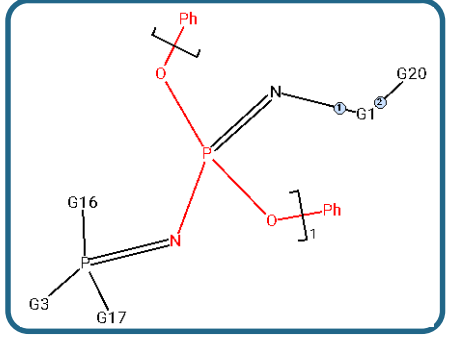

Each file has
unique content

Adjust query structure for
comprehensive retrieval

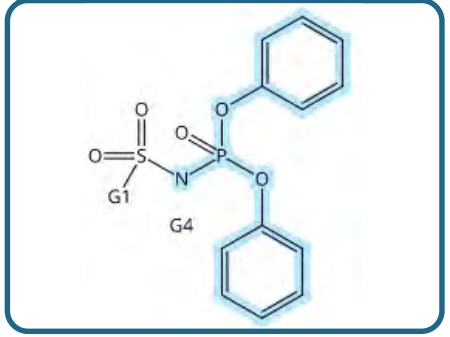
**DCR**
≈ 3.7 M structures



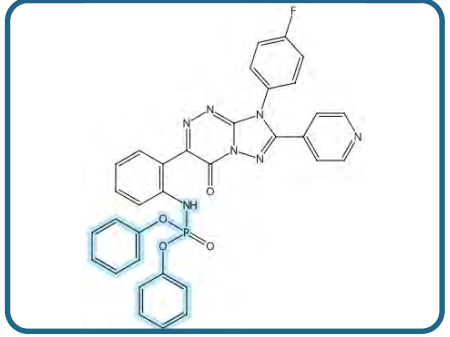
**DWPIM**
≈ 2.3 M structures




**MARPAT**
≈ 1.3 M structures




**CAS Registry**
≈ 156 M structures



# Structure search options on STNext

| Structure Search Type | Retrieval | Use variables |
|---|---|---|
| EXA (exact) | Stereoisomers, charged, and isotopically labeled structures | No |
| FAM (family) | EXA + salts, mixtures | No |
| CSS (closed subtructure search) | EXA + FAM + substances with no substitutions at open nodes unless the query is specified for substitution | Yes |
| SSS (substructure search) | EXA + FAM + CSS + analogs and derivatives of a core structure | Yes |

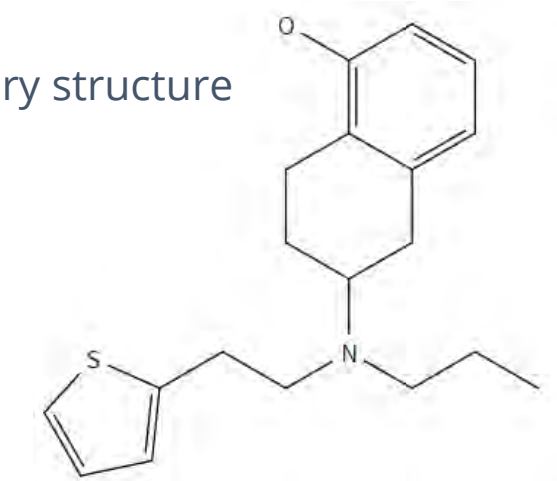
REGISTRY, DCR

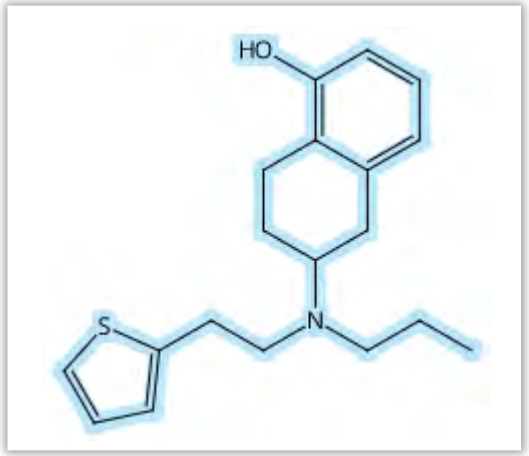
DWPIM, MARPAT

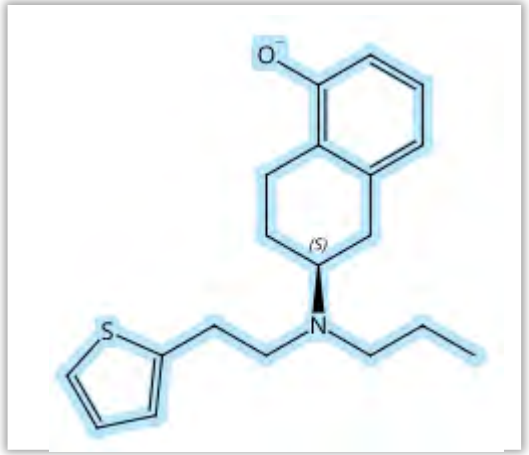
# Structure search options on STNext: **EXACT**

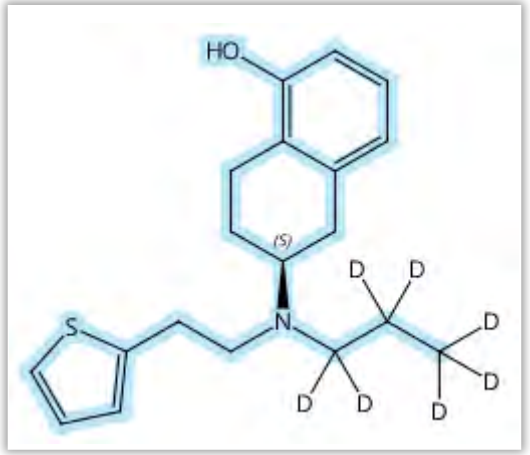
| Structure Search Type | Retrieval |
|---|---|
| EXA (exact) | Stereoisomers, charged, and isotopically labeled structures |

Query structure



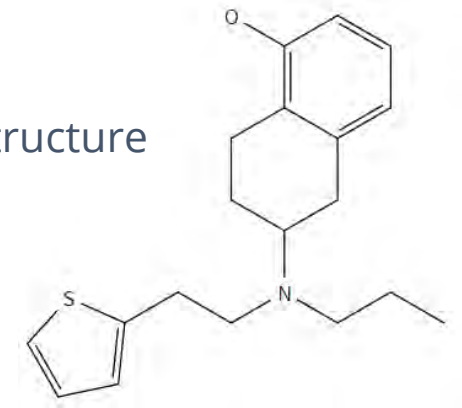



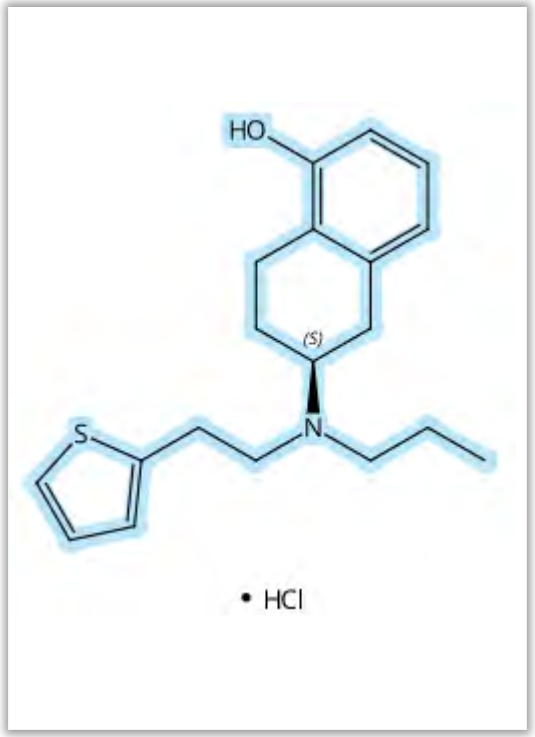



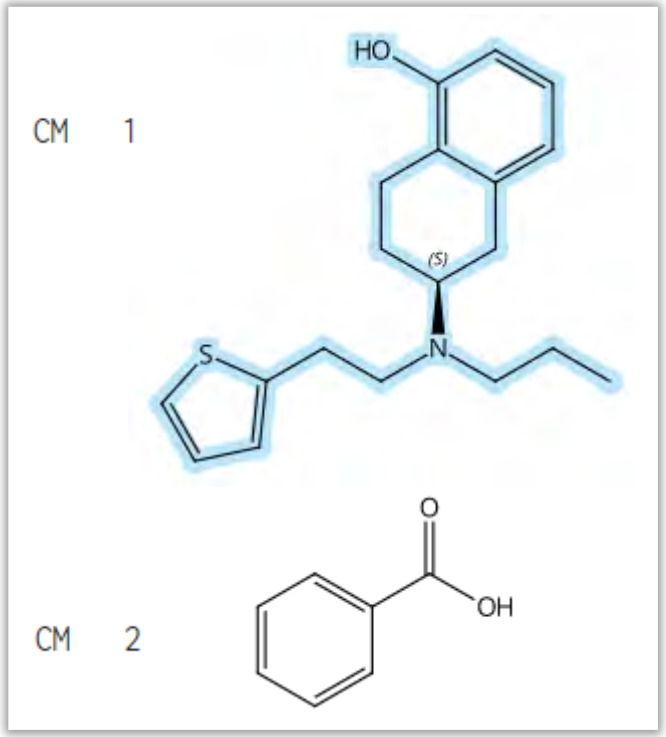
# Structure search options on STNext: **FAMILY**

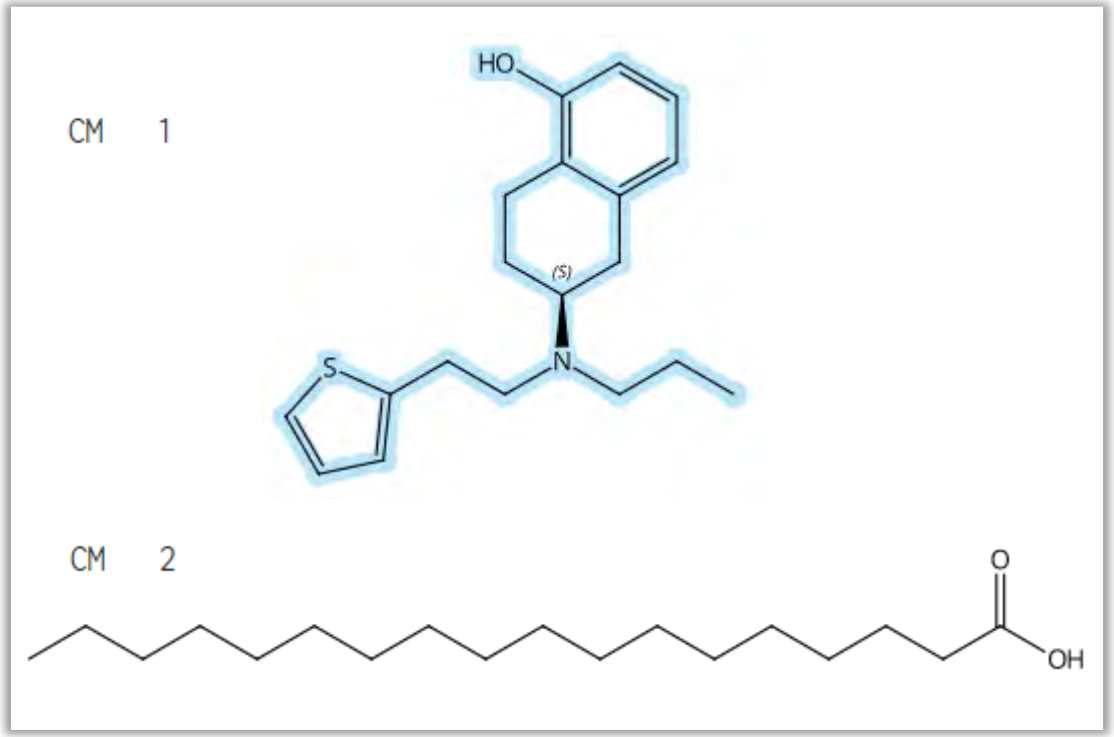
| Structure Search Type | Retrieval |
|---|---|
| FAM (family) | EXA + salts, mixtures |

Query structure



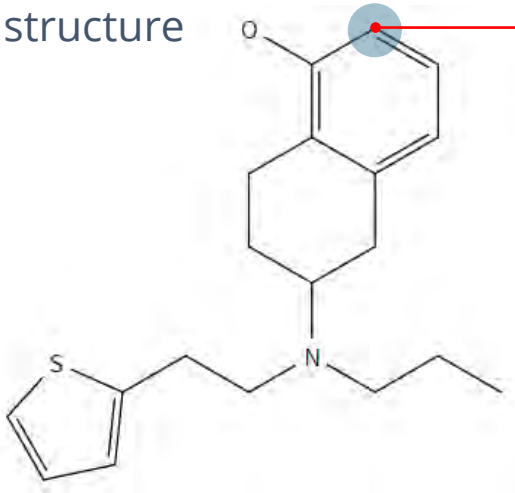



# What is the non-hydrogen count?

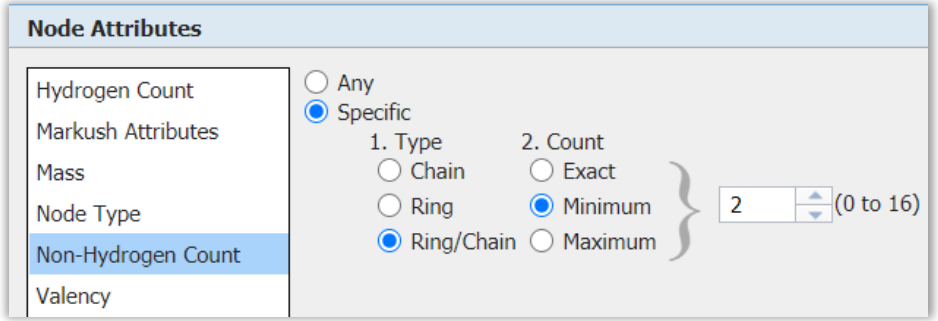
- The non-hydrogen count is the number non-hydrogen atoms attached to a specific atom (node)
- Existing connections are considered, e.g. every carbon atom in a cyclohexane ring has a non-hydrogen count of 2, because it has 2 neighbouring atoms.
- You can allow for or force substitution in **CSS or SSS** searches by altering the non-hydrogen count of one or more atom nodes

Query structure




This carbon is connected to two other carbon atoms, so its non-H count is 2

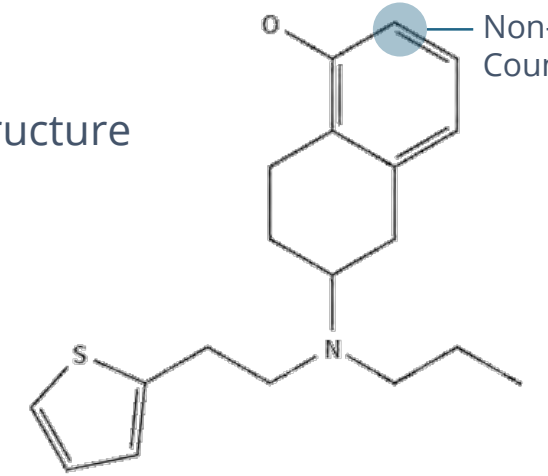
If we set this count to **min. 2**, we will also be able to retrieve substances with a substituent at this position

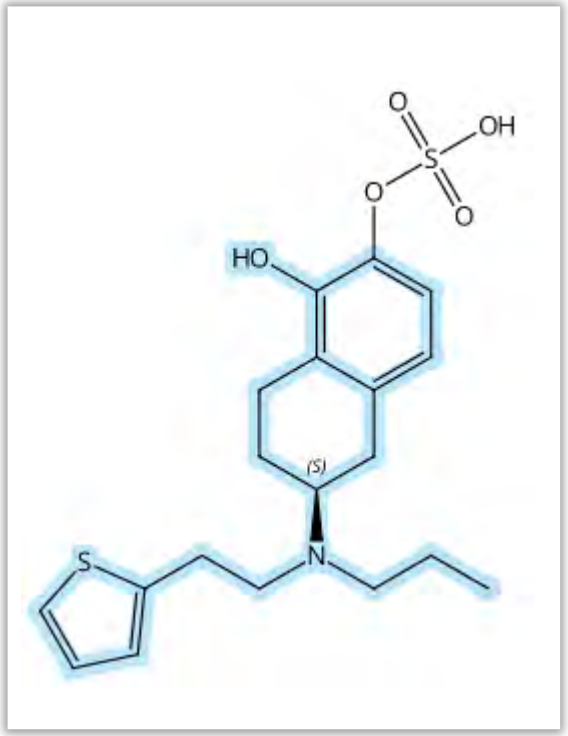


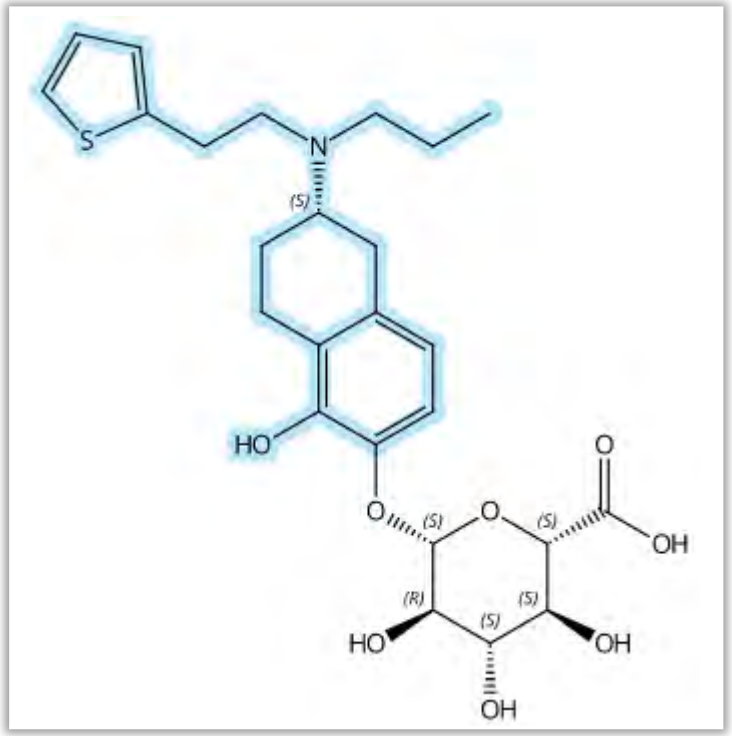
# Structure search option: CLOSED SUBSTRUCTURE

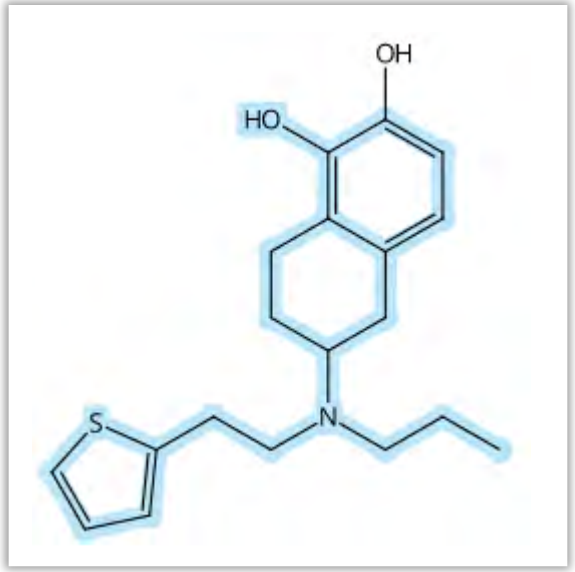
| Structure Search Type | Retrieval |
|---|---|
| CSS (closed sub-structure search) | EXA + FAM + substances with no substitutions at open nodes unless the query is specified for substitution |

Query structure



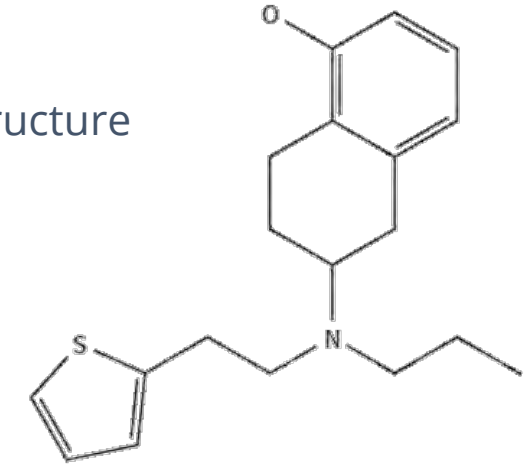



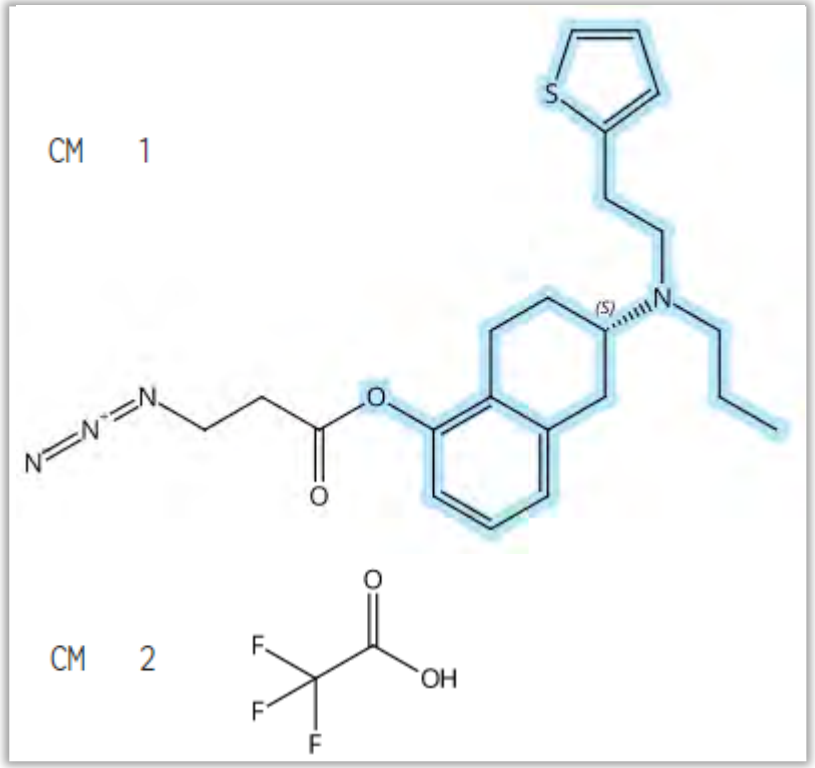



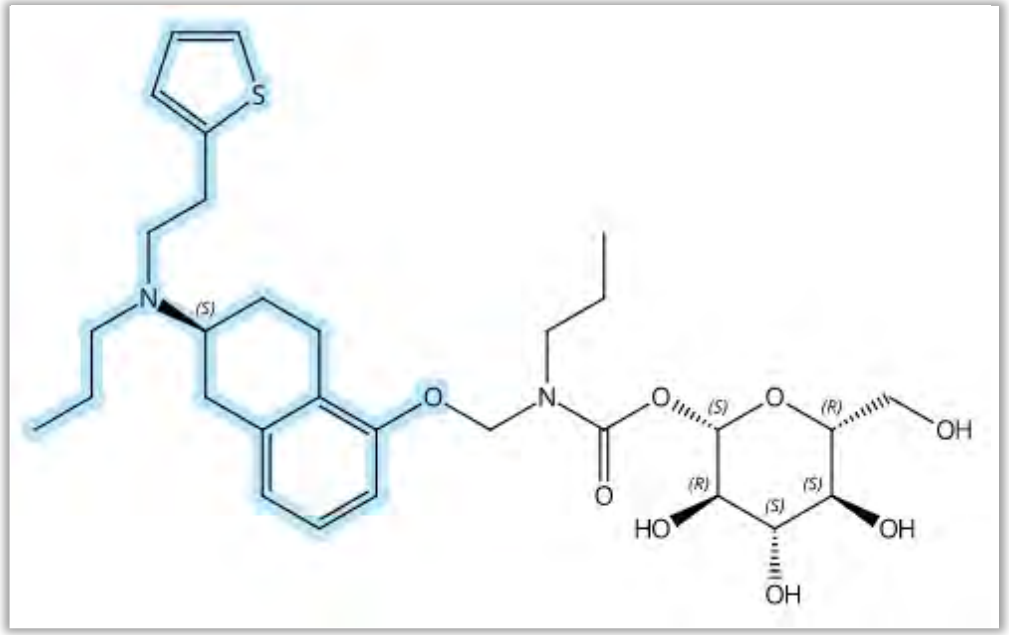
# Structure search option: SUBSTRUCTURE SEARCH

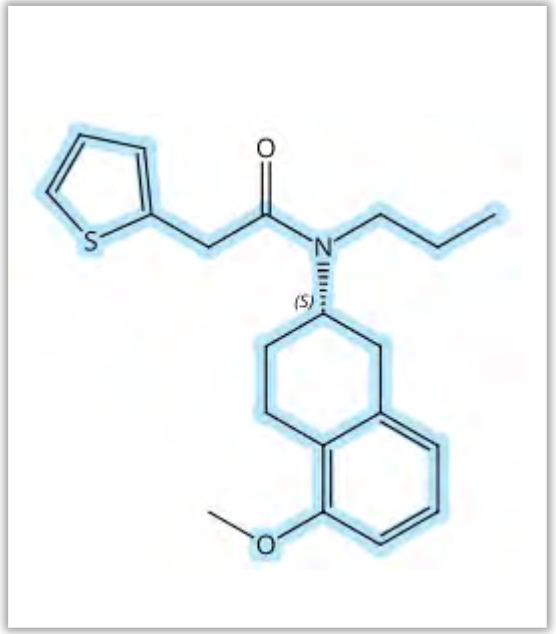
| Structure Search Type | Retrieval |
|---|---|
| SSS (substructure search) | EXA + FAM + CSS + analogs and derivatives of a core structure |

Query structure







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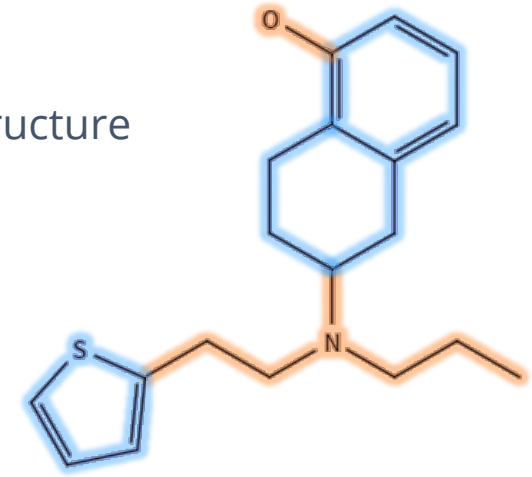
# Substructure search option: **node attributes**

| Structure Search Type | Retrieval |
| --- | --- |
| SSS (substructure search) | EXA + FAM + CSS + analogs and derivatives of a core structure |

Query structure



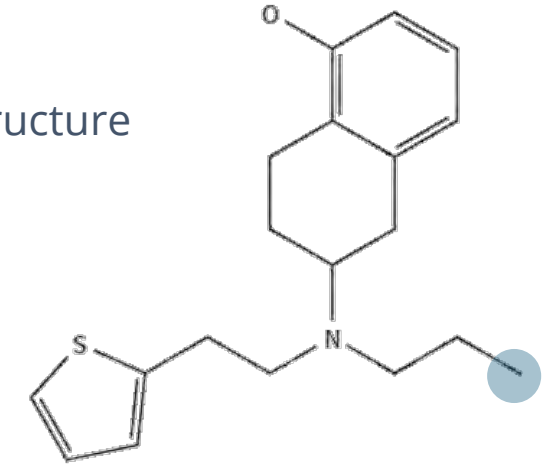

The default assumptions for atom retrieval depends on the location of an atom in the substructure query:

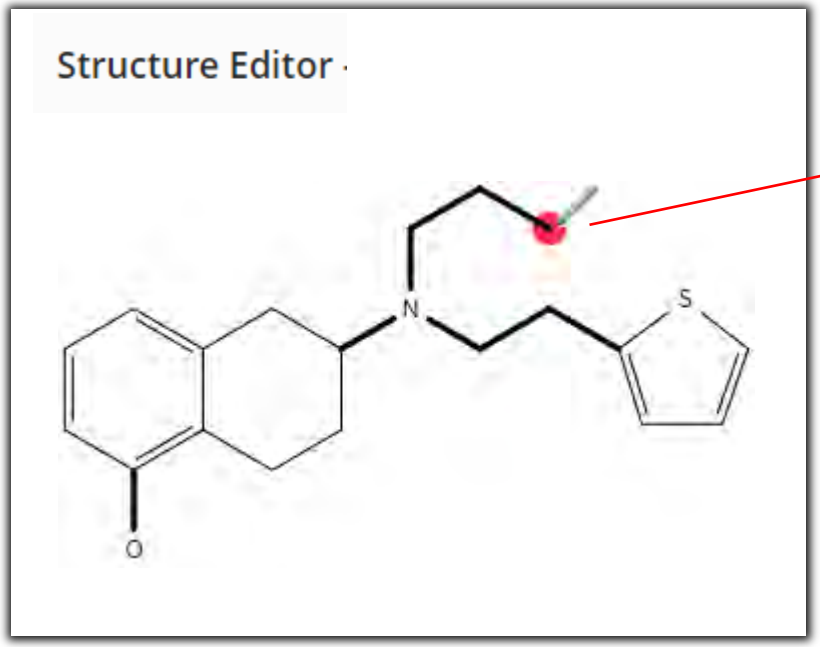
**Atom of a chain will always be part of a chain.**

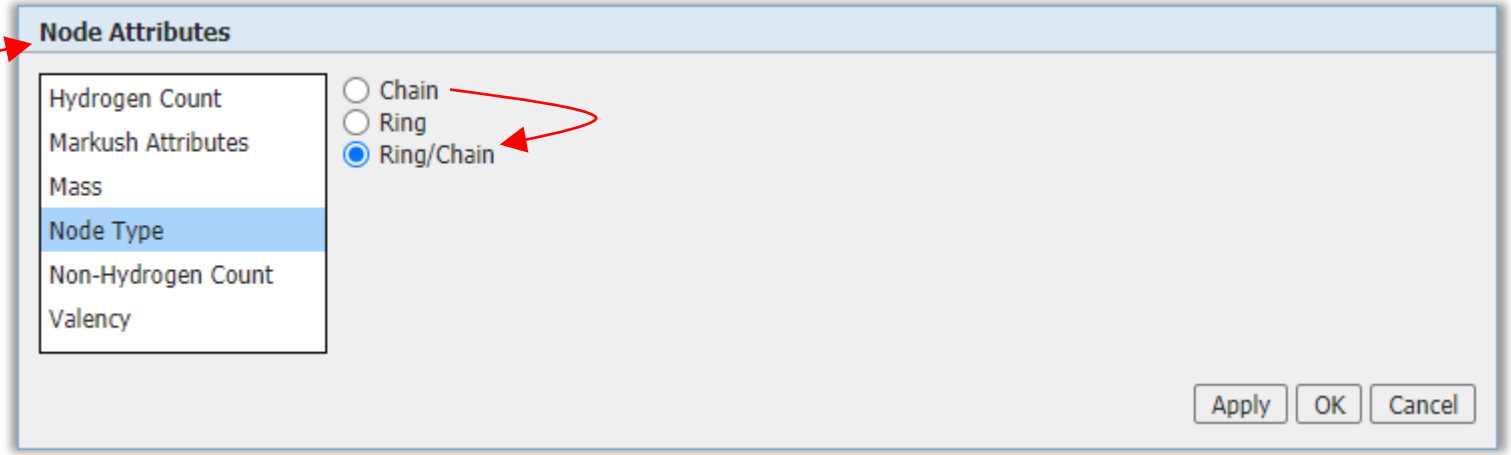
**Atom of a ring will always be part of a ring.**

# Assign non-default attributes: **Node attributes**

Query structure

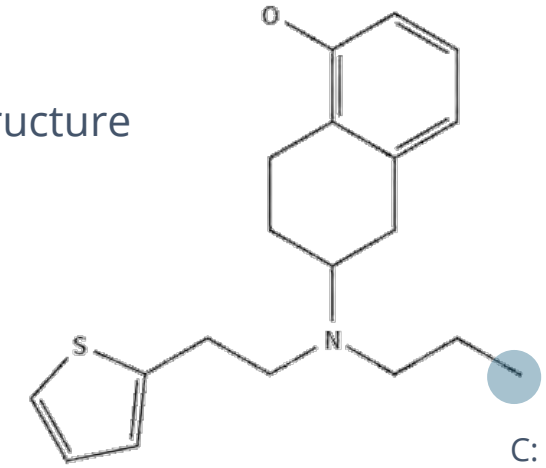


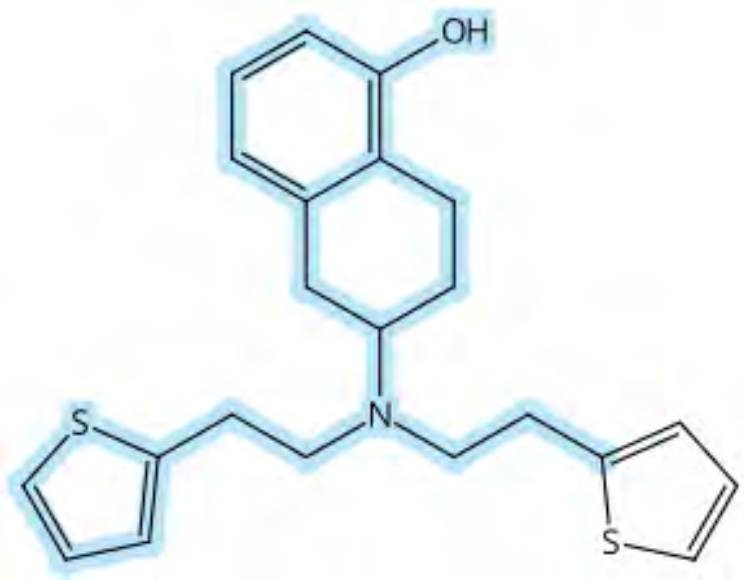



# Assign non-default attributes: **Node attributes**

Query structure




C: Ring/Chain




Additional substance records if chain atoms are set to ring/chain!

# Bonding attributes

- Each bond in a substructure query has three parameters assigned to it:
  - **Bond type**
  - **Single/double/triple/unspecified bond**
  - **Bond value**
- Default settings can be modified!

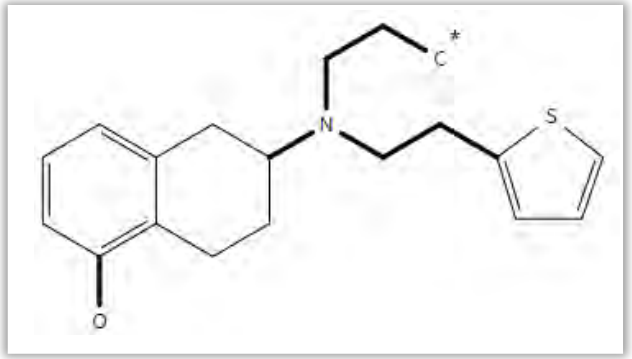
# Bonding attributes

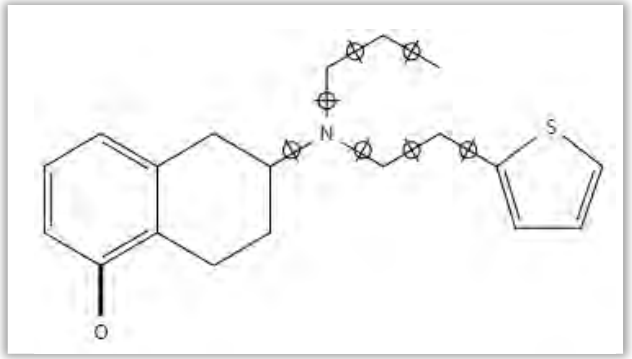
- Each bond in a substructure query has three parameters assigned to it:
  - **Bond type**
  - Single/double/triple/unspecified bond
  - Bond value

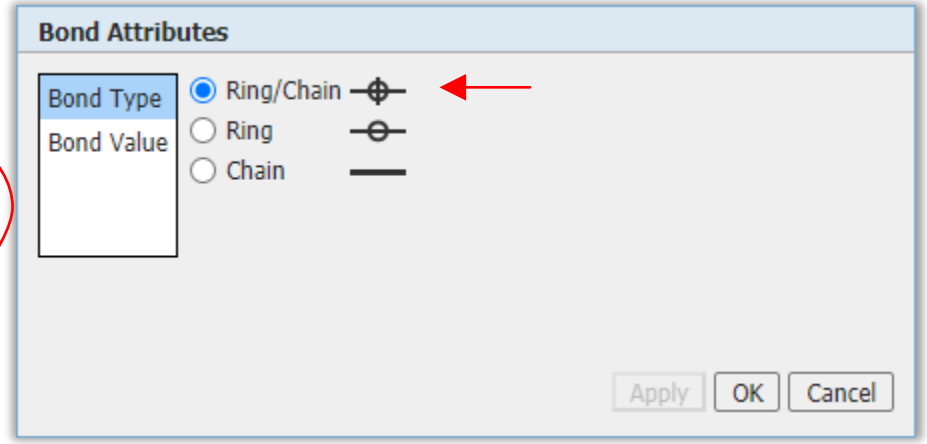
| Bond type | RETRIEVED STRUCTURES |
|---|---|
| Chain | The bond will always be part of a chain |
| Ring | The bond will always be part of a ring |
| Ring/Chain | The bond will be part of a ring or chain |

# Bonding attributes

- To allow ring formation, the bond attributes can be changed with a right mouse click on the bond to be changed (you can use the lasso or marquee tools to select a multiple bonds at once).



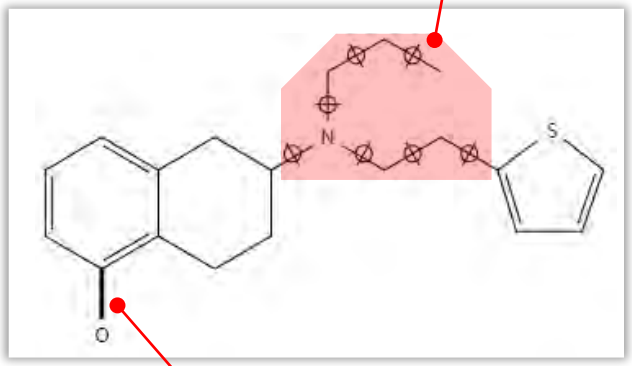




Changing the bond type to Ring/Chain also automatically changes the atom nodes at either end of the bond to Ring/Chain.

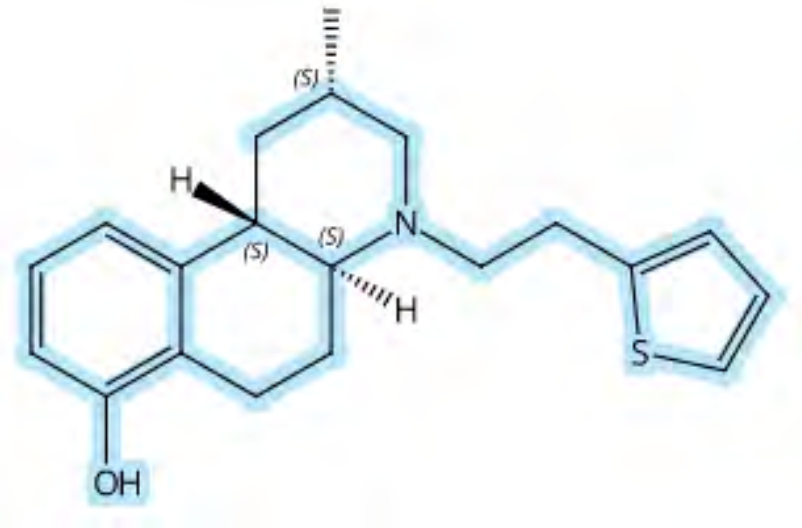
# Substructure search option: **bond attributes**

Nodes and bonds are set to Ring/Chain




Bold printed bonds indicate bond type set to chain

Additional records




(**!**) Marpat does not allow for ring/chain bonds. Draw two structures, one with chain the other one with ring bonds

Check the settings and consider what might be lost or would be gained when changing bond characteristics

# Bond attributes

- Each bond in a substructure query has three parameters assigned to it:
  - Bond type
  - **Single/double/triple/unspecified bond**
  - Bond value


Single
Double
Triple
Unspecified
Stereo Up
Stereo Down
Double Stereo Up
Double Stereo Down
Double EZ Stereo

Use unspecified bonds whenever unsure about the bonding pattern

# Bond attributes

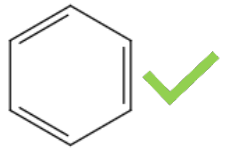
- Each bond in a substructure query has three parameters assigned to it:
  - Bond type
  - Single/double/triple/unspecified bond
  - **Bond value**
    The bond values are automatically adjusted by the structure editor to maximize retrieval of a structure query. Check the settings and consider what might have been lost or would be gained when changing bond characteristics

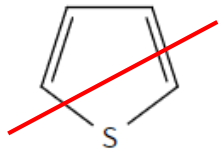
| Bond value | RETRIEVED STRUCTURES |
|---|---|
| Exact | Exact bonds will be retrieved (either single, double or triple) |
| Normalized | Normalized bonds will be retrieved |
| Exact/Normalized | Exact or Normalized bonds will be retrieved (either single, double, triple or normalized) |

# What are normalized bonds?

Certain structural moieties in the structure databases get normalized bonds assigned.
The below definitions are true for **CAS Registry and MARPAT**:

- Normalized bonds are assigned to rings with an even number of atoms that contain alternating single and double bonds






Normalized is not synonymous with aromatic!

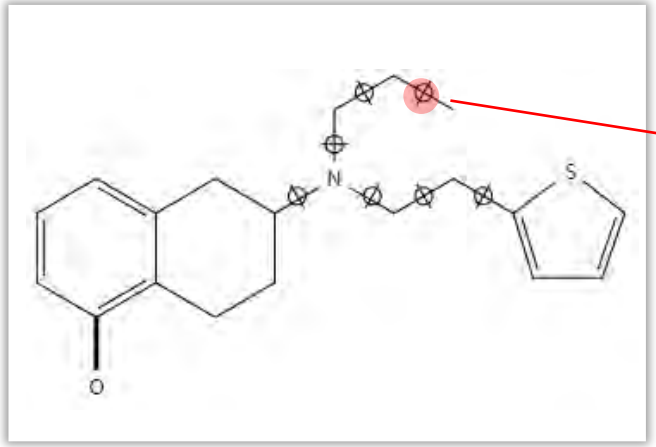
- Tautomers: H(1)-(2)=(3) <-> (1)=(2)-(3)H **|** Central atom (2) is connected to two hetero atoms (1) and (3)
  - 2 may be: C, N, P, As, Sb, S, Se, Te, Cl, Br, I
  - 1 and 3 may be: N, O, S, Se, Te
  - A double bond can be drawn between one of the hetero atoms (1 and 3) and the central atom (2)
  - A single bond can be drawn between the central atom (2) and the other hetero atom (3 or 1)
  - One of the hetero atoms (1 or 3) has at least one hydrogen, hydrogen isotope or charge

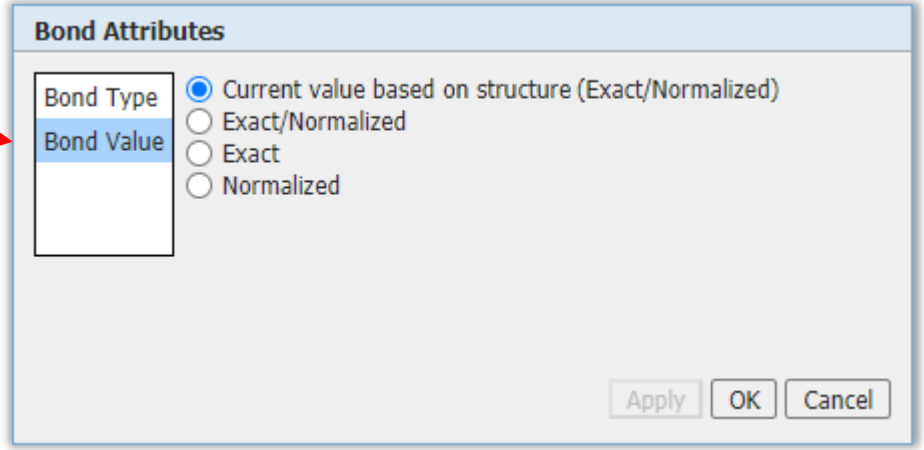
- (**!**) Keto-Enol tautomers are not indexed with normalized bonds, both variants should be searched

**DCR** applies similar rules as above (some exceptions, e.g. nitro group with normalized bonds in DCR).
**DWPIM** definitions in the DWPIM manual: https://stn.products.fiz-karlsruhe.de/sites/default/files/X/4.pdf
For questions please contact the STN helpdesk.

# Bonding attributes

- Each bond in a substructure query has three characteristics assigned to it:
  - Bond type
  - Single/double/triple/unspecified bond
  - **Bond value**
    The bond values are automatically adjusted to maximize the answers by a query.
    Check the settings and consider what might have been lost or would be gained when changing bond characteristics




Changing the bond type to Ring/Chain automatically adjusts the bond value to Exact/Normalized

# Summary: Default assumptions for nodes and bonds

- Default assumptions are made about the rings and chains in a structure query
- These assumptions determine the types of answers retrieved by a substructure search
- Default assumptions can be modified
- Changes of bonds from Chain to Ring/Chain automatically changes atoms from chain to Ring/Chain

| FOR THE STRUCTURAL FEATURE IN THE SEARCH QUERY | THE DEFAULT ASSUMPTION IS TO RETRIEVE STRUCTURE MATCHES WITH THE |
|---|---|
| Ring systems | Ring system as drawn<br>Ring system as part of a larger ring system |
| Atom in a chain | Atom in a chain only |
| Bond in a chain | Bond in a chain only |

# Agenda

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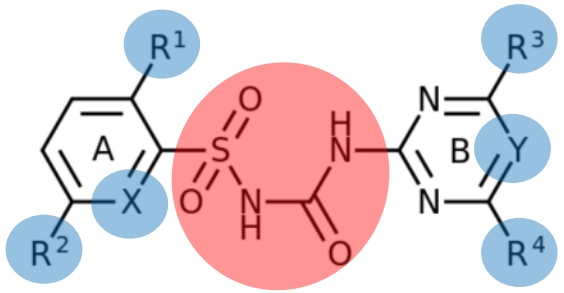
- Node and bond attributes
- **Opening and closing structure queries: SSS versus CSS**
- Summary

# Close a structure query: From SSS to CSS




Formula of active sulfonylurea herbicides, showing the sulfonylurea backbone itself in red and the side chains that distinguish each compound in blue (X, Y = CH or N).

- Sulfonylureas are a class of organic compounds used in medicine and agriculture
- As herbicides they mostly act by interfering with plant biosynthesis of certain amino acids (e.g. valine, isoleucine, and leucine)

Search Question: Explore sulfonylureas derived from the above structure
Substitutions on ring A are only allowed at position R1, X=C

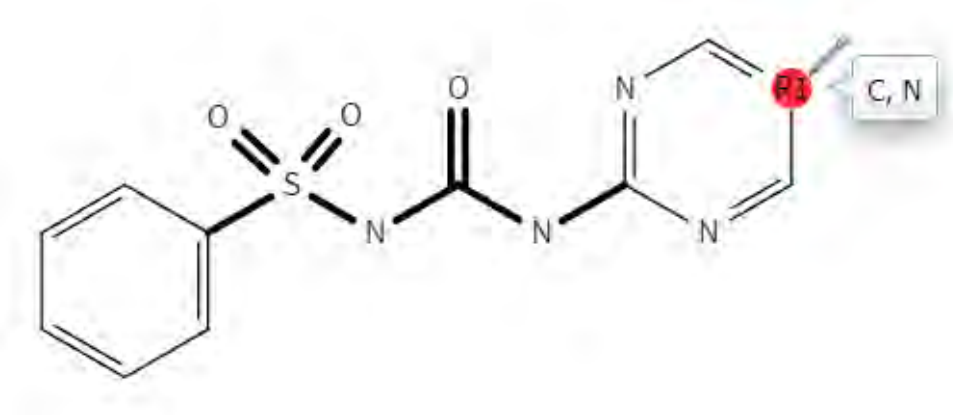
Solution 1: Perform SSS, 4 nodes on ring A are locked
Solution 2: Perform CSS, open specific sites to allow for substitution

# Options to prevent substitution

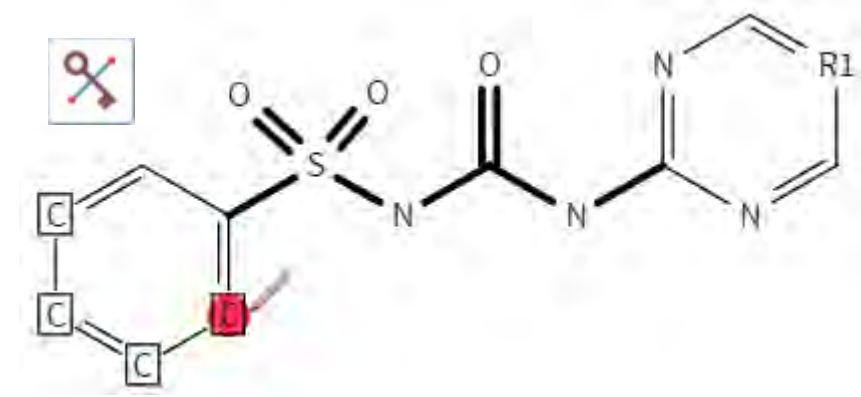
- Use **Lock Atoms**  to block substitution in a **SSS search**
- Use appropriate Shortcuts  , they often have implicit hydrogens and block substitution in an SSS search
- Modify the Hydrogen count attribute
- Modify the **Non-Hydrogen Count** attribute
- Perform a **CSS search** and open specific atom nodes only

# Use **lock atoms** to block substitution | SSS

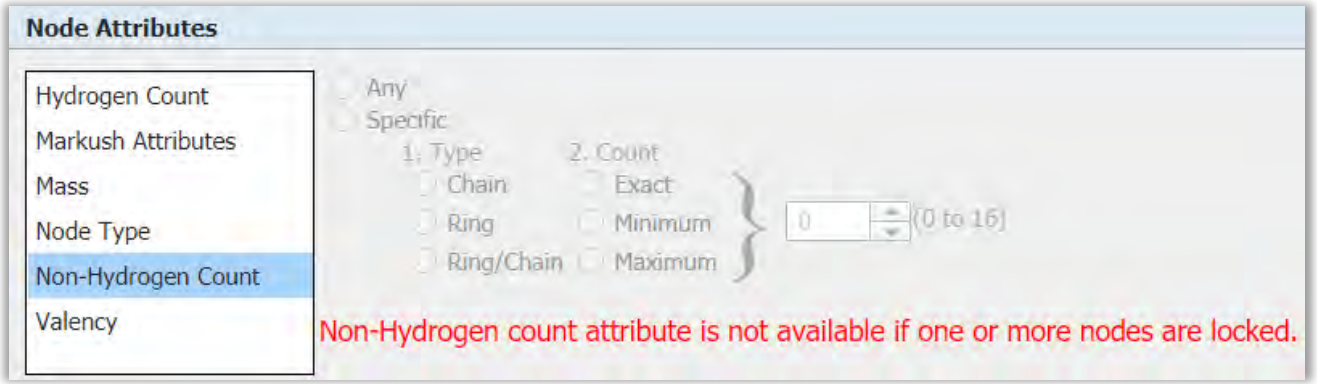
1




2



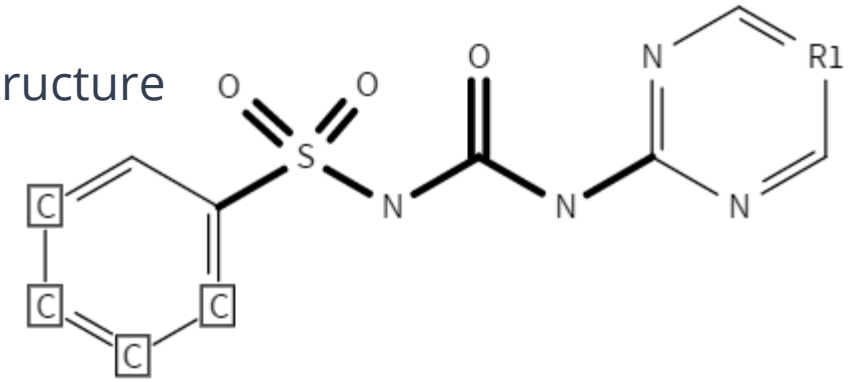

Use lock atoms to block any substituents except hydrogen



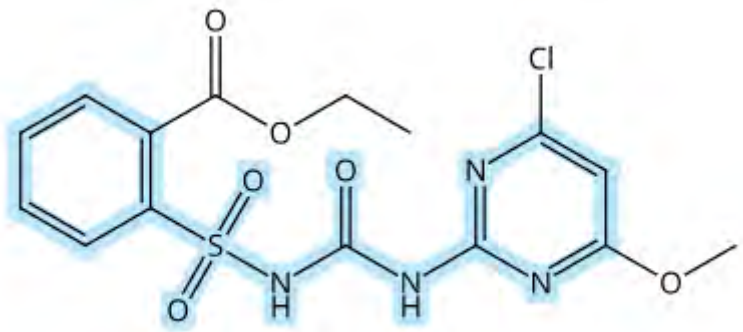

**Lock atoms** automatically sets a non-hydrogen count (exact=2 in this case), so this parameter is not available anymore

# Adjust attributes for enhanced retrieval | SSS

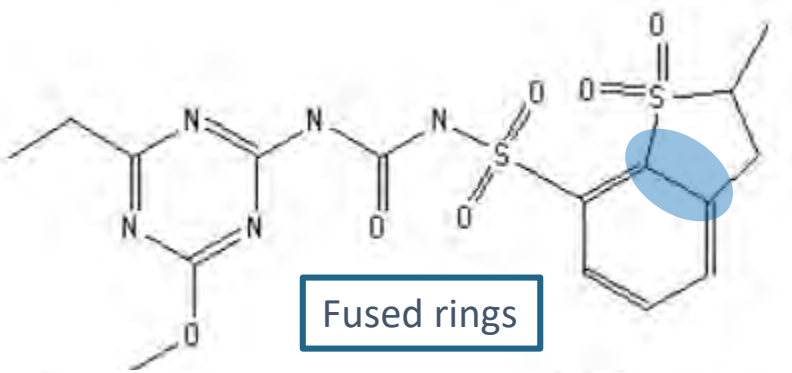
Query structure



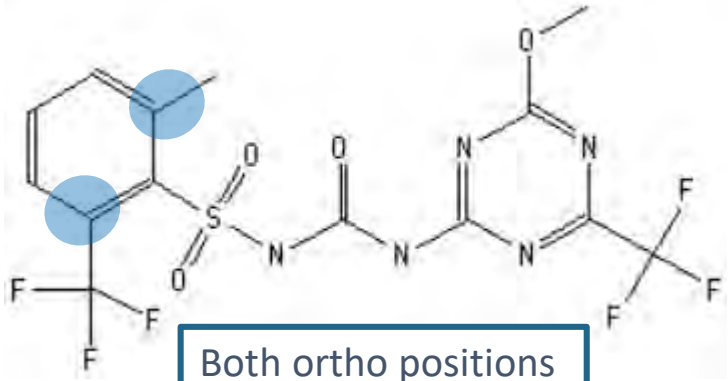
Hits



Additional records if the 4 nodes are not blocked:



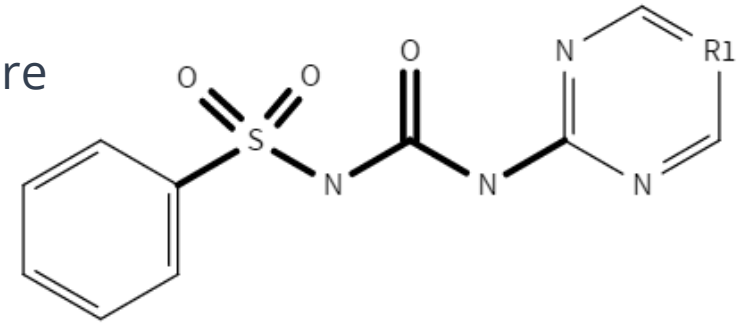
Fused rings



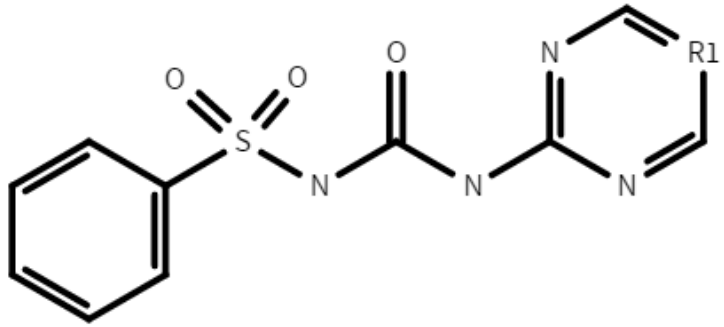
Both ortho positions substituted

# Ring Lock prevents ring fusion or ring formation | SSS

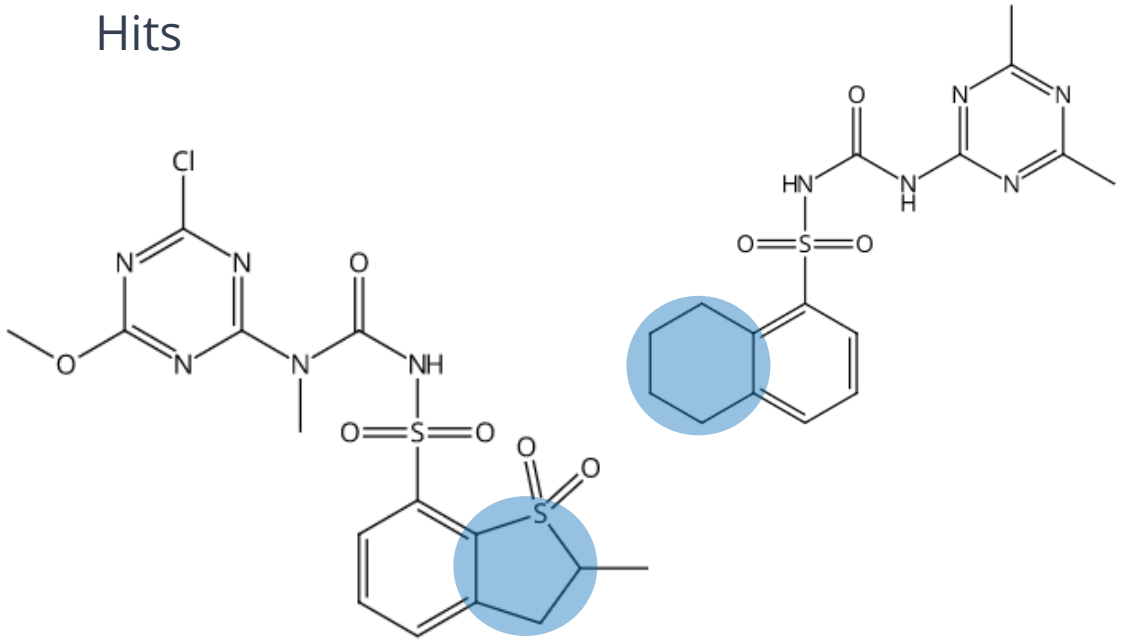
Query structure



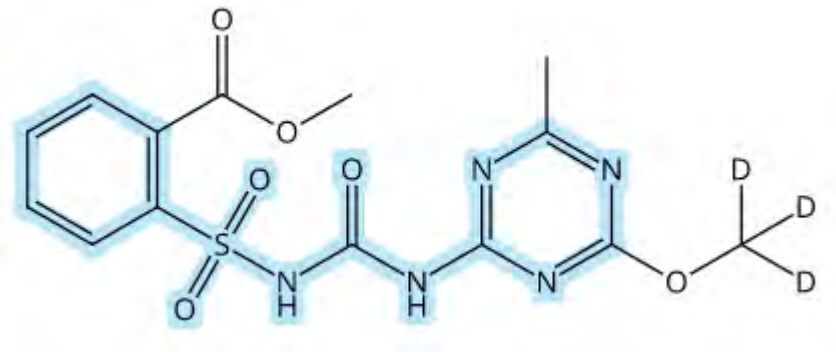

Query structure with ring lock:




Hits

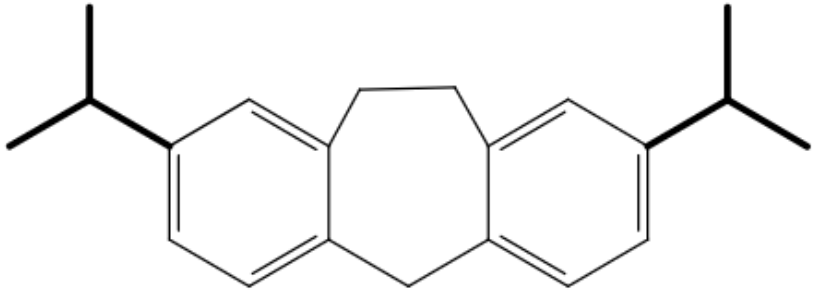


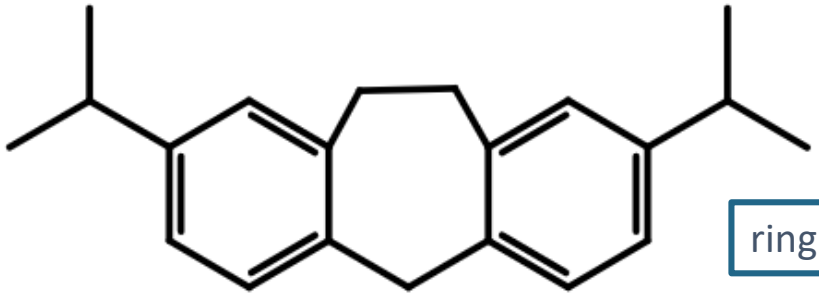

Hits:



# Ring lock also blocks spiro systems | SSS

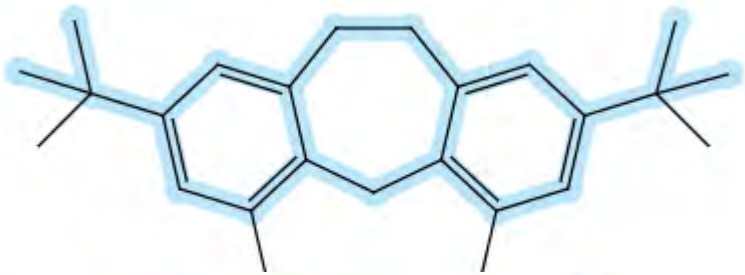
Query structure

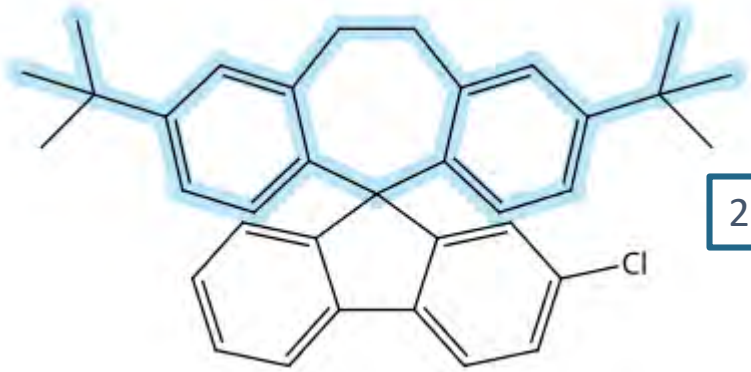




ring system locked

Hits



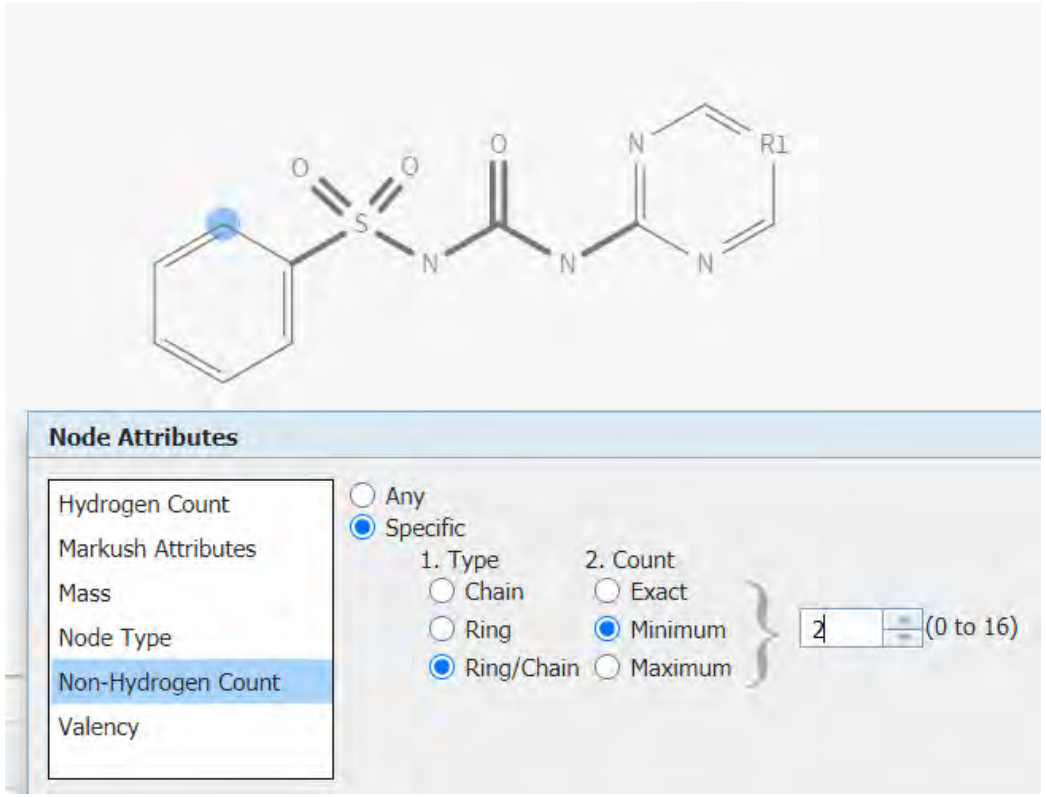



23 hits

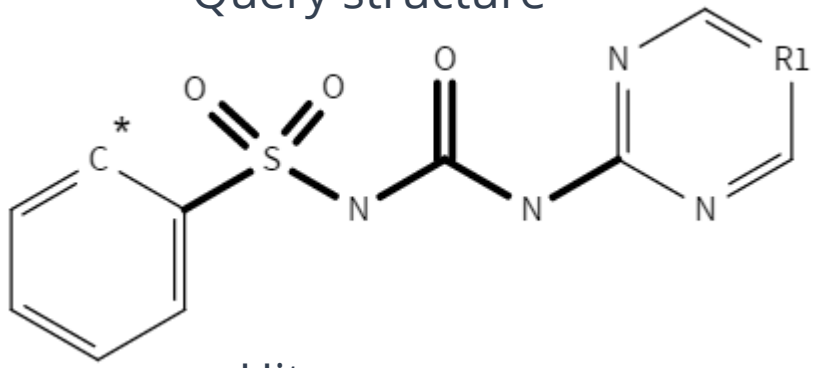
10 hits

# Specify open positions with CSS

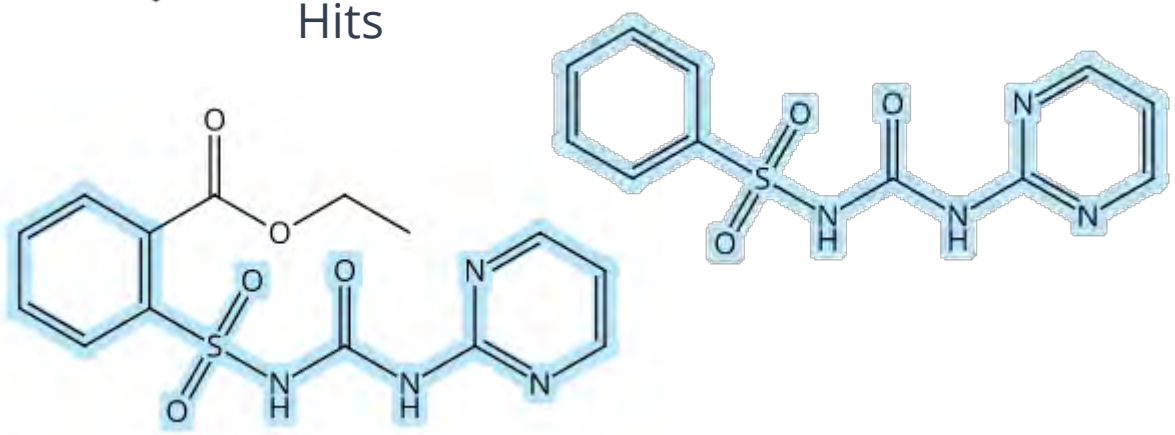
- A CSS by default blocks all non-hydrogen substituents but allows to use variables such as user-defined R-groups or STN variables. This query uses user-defined R1={C,N}
- If substitution is wanted, you must set it in the editor




Query structure

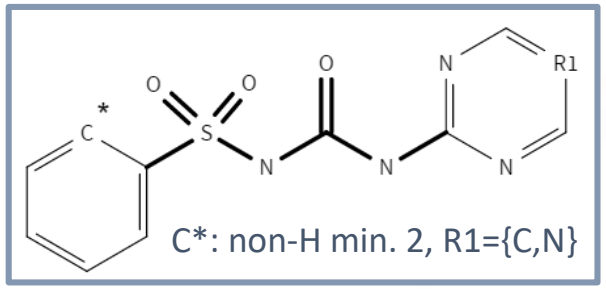


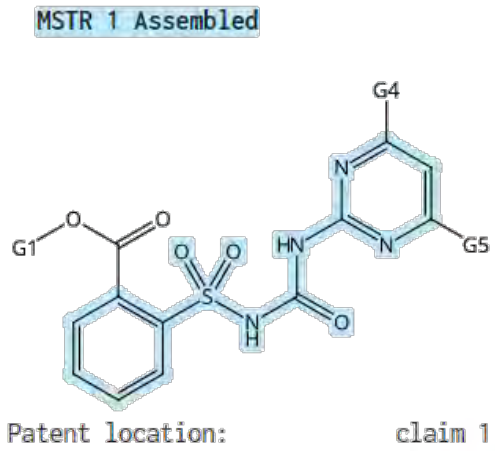
Hits

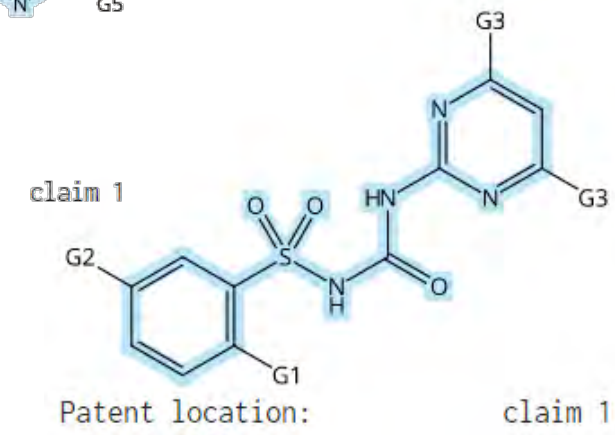


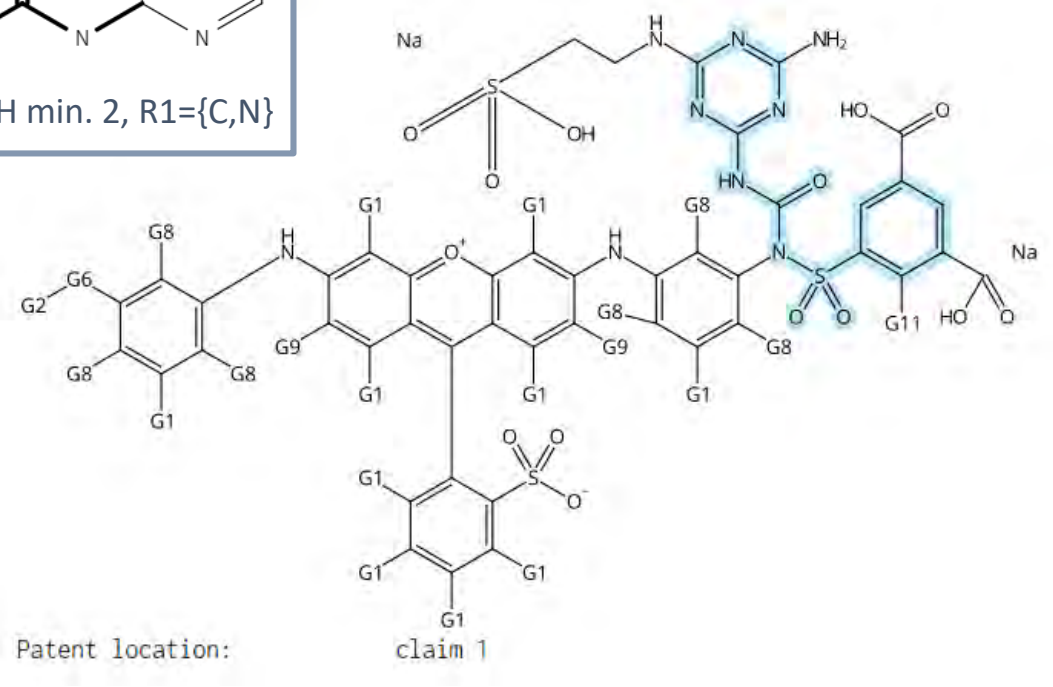
# CSS is the first best option for Markush searches

- Consider using CSS in Markush searches
- Results will be very close to the drawn structure
- You can still use variables
- Define open positions if desired




CSS search in Marpat: 107 patents

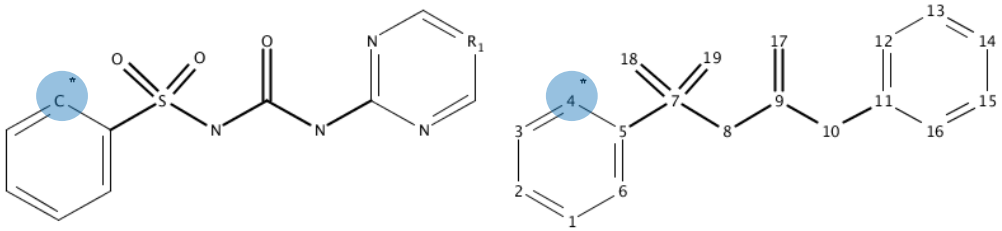
SSS search in Marpat: 523 patents

# Where to check structural parameters?

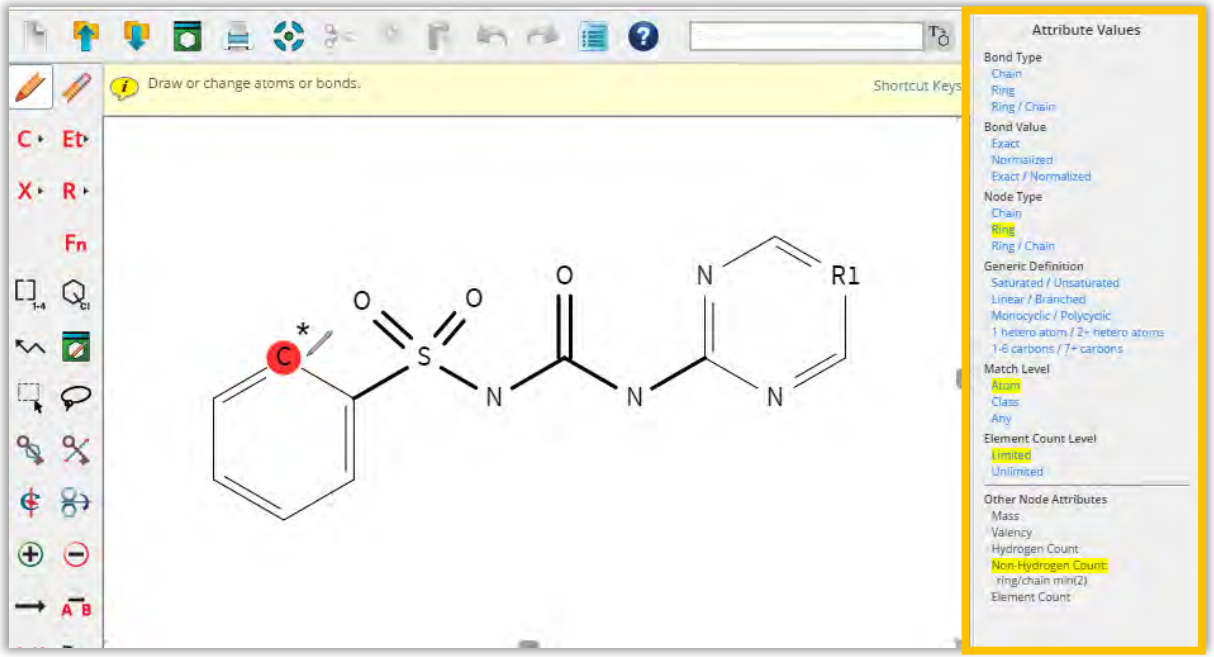
All attributes are displayed after uploading the structure

Use the Attribute Values Panel to check structural attributes when editing the structure

```
=>
Uploading structure file: 2020_0144_Structure
```



```
R-Group Definitions
R1: C,N
Node Attributes
Ring Nodes : 1  2  3  4  5  6  11  12  13  15  16
Chain Nodes : 7  8  9  10  17  18  19
Non H Count
Ring/Chain, Minimum (2) : 4
Bond Attributes
Ring Bonds : 1-2  2-3  3-4  4-5  5-6  6-1  11-12  12-13  13-14  14-15  15-16  16-11
Chain Bonds : 5-7  7-8  7-18  7-19  8-9  9-10  9-17  10-11
Normalized Bonds : 1-2  2-3  3-4  4-5  5-6  6-1
Exact/Normalized Bonds : 5-7  7-8  7-18  7-19  8-9  9-10  9-17  10-11  11-12  12-13  13-14  14-15  15-16  16-11
Markush Attributes
Match Level (ATOM) : 1  2  3  4  5  6  11  12  13  15  16
Match Level (CLASS) : 7  8  9  10  17  18  19
Element Count Level (LIMITED) : 1  2  3  4  5  6  7  8  9  10  11  12  13  15  16  17  18  19
```



# Summary

- STNext offers precision tools to adjust substitution in structure queries
- Ring and bond parameters will influence your structure search results
- Use lock atoms and lock rings to block substitution and prevent ring formation/fusion in substructure searches
- Keep in mind that structure shortcuts (e.g. Me) might block substitution
- Use predefined or self-defined variables in SSS and CSS searches
- Closed substructure searches will block substitution unless specified otherwise
- Make use of the non-hydrogen count to precisely define substitution patterns and selectively open positions in CSS searches

# Contact Us

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