Searching the PDB for drugs that bind to Christmas Factor

PDBe provides a range of services for exploring the binding of small molecules such as drugs, co-factors, co-enzymes, and prosthetic groups to biomacromolecules.

As an introduction to some of the services available, this mini-tutorial uses PDBe tools to explore compounds in the PDB archive that are chemically similar to the **benzothiophene** derivatives bound to **Christmas Factor** in PDB entries **3lc3** and **3lc5**.

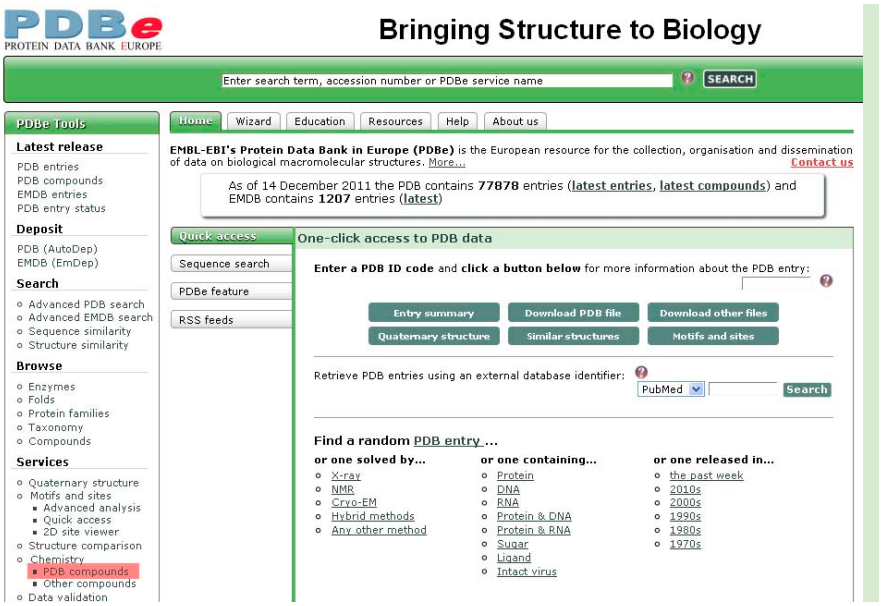
The search methods it shows should be of general use to you as you explore small molecules in PDB structures.

Small molecules are dealt with in the PDB archive as formally equivalent to macromolecular residues. Each one is given a unique **three-letter code** but these are often arbitrary and so you can't necessarily guess what the compound might be from the code.

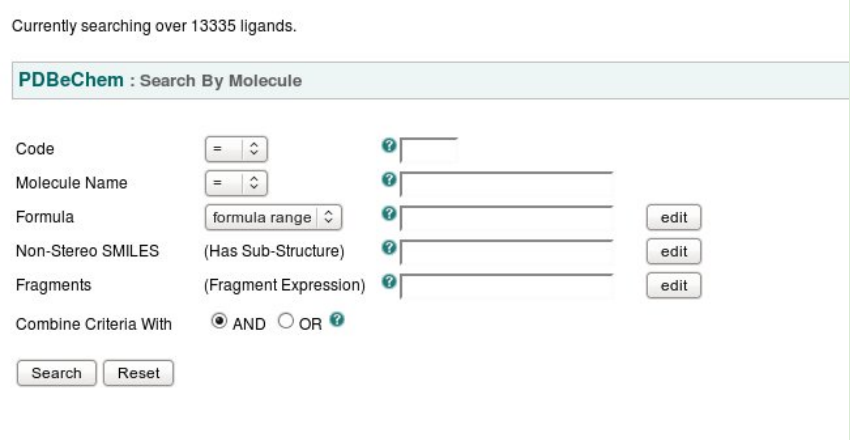
To start searching small molecules using PDBeChem, click on the link in the PDBe Services menu on the PDBe home page under **Services > Chemistry > PDB Compounds** (highlighted in red, **screenshot 1**).

Screenshot 1.
The PDB compounds link on the PDBe home page.

From here you get a search menu where you can search using five separate options, each of which has a separate input box (see **screenshot 2**).



Screenshot 2.
The Chemical Components search page



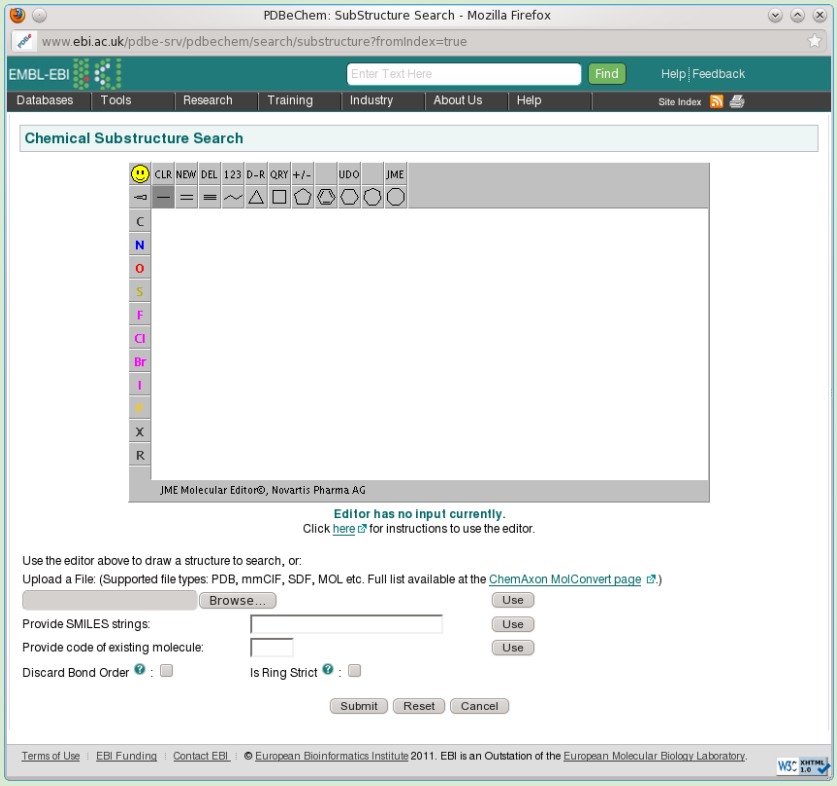
The first option on the search page is useful if you actually know the **three letter code** of the small molecule you're interested in, and the second if you know the molecule name. In both cases, changing the pull-down menu to the left of the input box from '**=**' to '**like**' means the search results will find hits **containing** the term you've input, rather than **matching it exactly**. So entering **MSE** for example takes you straight to the Chemical Component page for Selenomethionine.

The third option allows you to input the molecules formula into the search box, so searching for '**C6 H12 O6**' will find all the hexose sugars. This search box defaults to **formula range** but you can also explicitly define a range. Inputting '**C6-7 H12 O6'**, for example, will find all those molecules containing six or seven carbons, twelve hydrogens, six oxygens.

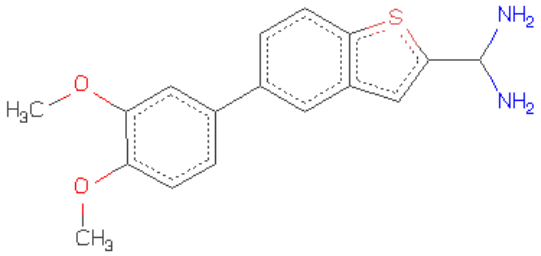
For our purpose in this tutorial, it is the next search option '**non-stereo SMILES**' which is most useful. In this search box you can input the SMILES string of the molecule, or molecule fragment of interest. SMILES stands for **Simplified Molecular-Input Line-Entry Specification**. For more information about SMILES, see this link: http://www.daylight.com/smiles/

More than likely, you won't know the SMILES string of your small molecule, so instead click the '**edit'** button to the right of the option '**non-stereo SMILES**' input box. This will open up another window with the **JME** molecular editor tool (**screenshot 3**). You'll find a link with tips on how to use the editor just below the sketch box.

Screenshot 3.
The Molecular Editor for Chemical Substructure Search



PDB entry 3lc3 contains the inhibitor 1-[5-(3,4-dimethoxyphenyl)-1-benzothiophen-2-yl] methanediamine (shown **graphically** below).



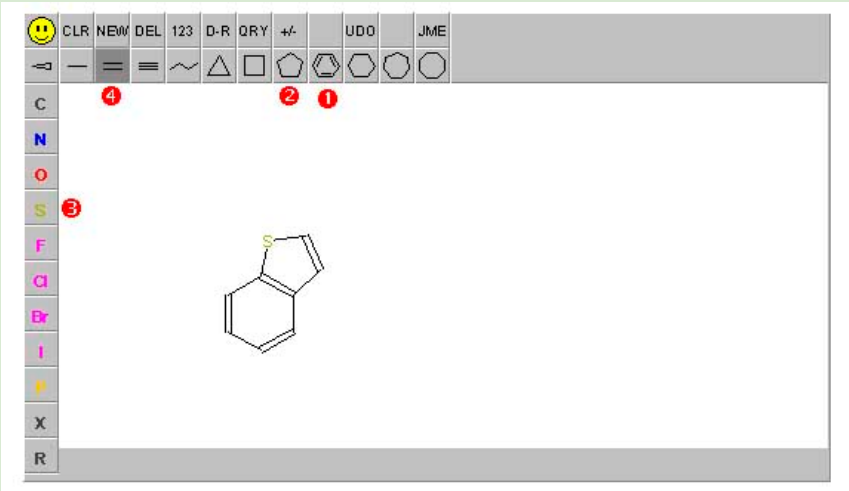
Let's sketch just the double-ringed **benzothiophene** moiety in the editor.

Firstly, select the **benzene ring** icon and drag it into the editor (number **1** in **screenshot 4** below).

Next, select the 5 membered ring (number **2** in **screenshot 4**) and while hovering over a bond in the benzene ring, click the mouse to fuse this second ring to the bezene ring. Now select 'S' from the left-hand side menu (number **3** in **screenshot 4**) and click the mouse over the right place in the 5-membered ring to swap the carbon for a sulphur.

Finally, select the the double bond icon and add a double bond into the 5 membered ring to form benzothiophene.

Screenshot 4. Building the benzothiophene rings



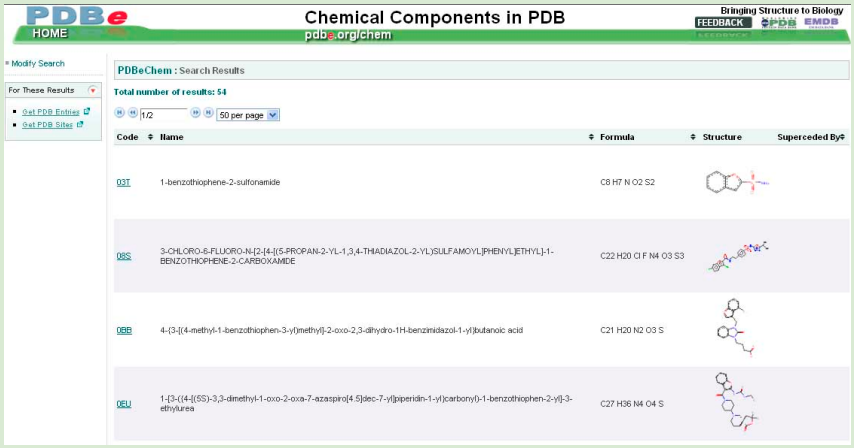
Now hit '**submit**' to take you back to the search page. You will see that the **SMILES** string for what you've drawn has been automatically filled in to the input box.

There are other useful options in the editor tool. For example you can upload a molecule to alter in the editor, which might make it more easy if you want to search for a complex fragment. You can also decide whether you want to search for fragments as **part** of a ring or optionally to **disregard** bond order.

Once the SMILES string has been automatically generated on the **PDBeChem** search page press **'Search'** to find all those small molecules in the **PDB chemical component** dictionary that contain this **benzothiophene** group.

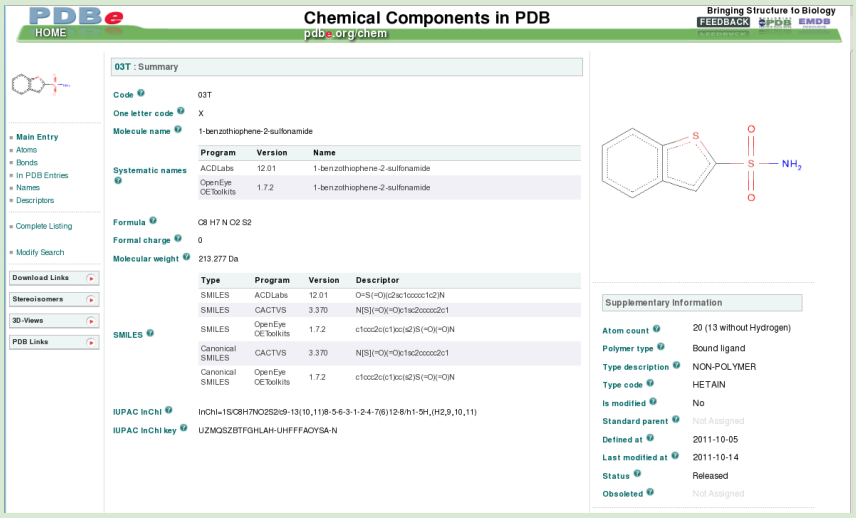
You will see a results page similar to that below (**screenshot 5**). This show that there are over 50 molecules containing this group, listed with the **three letter code**, the molecule's name, and an image of the structure. Hovering over the image will give you a larger view.

Screenshot 5.
The PDBeChem search results.



From the search results, you can click the **three letter code** to take you to a descriptive page for each ligand (for example, **03T**, whose page is shown in **screenshot 6**) and from here you can see useful information about each molecule.

Screenshot 6.
Chemical Component Summary page for 0T3



The Chemical Component Summary page contains the names and synonyms of the molecule as well as several different chemical descriptors, formula and molecular weight. The links to the left allow you to explore the atom names and bonds in the molecule, and to see a list of PDB entries which contain the molecule.

The '**Download Links**' section is where you can down load the coordinates of the molecule, and its dictionary should you want to use this molecule in your own structure determination.