Predicting drug activity

Drug-like properties

In modern drug discovery the potential of a new compound is often investigated initially without making it or testing it. The likelihood that a compound will have useful therapeutic activity (sometimes called its 'druglikeness') is predicted from its molecular structure.

A medicinal drug should have a suitable balance of solubility in water and in non-polar solvents. It should be sufficiently soluble in:

- water so that it can be carried around the body in the bloodstream;
- non-polar solvents so that it can pass through cell membranes (which consist of a phospholipid bilayer) into cells.

The relative solubility is traditionally given as the partition coefficient, *P*, of the substance between octan-1-ol and water.[1] Solubility in water can be estimated from the number of groups in the molecule that can hydrogen-bond compared with the non-polar parts of the molecule, e.g. hydrocarbon side chains. The more there are, the more water soluble the compound is likely to be.

The size of the molecule is also important. Most drugs enter cell membranes by passive transport (diffusion). The rate of passive transport depends on the size of the molecules. It is known that about 80% of known medicinal drugs consist of small molecules with relative molecular masses of less than 450.

The molecules also need to have groupings that have known chemical or pharmacological properties. These groups are called pharmacophores.

Rules of druglikeness

In 1997, Christopher Lipinski proposed a set of rules for druglikeness. His general observation was that most medicinal drugs had relatively small, lipophilic molecules. This led to the Lipinski's Rule of Five which says that a molecule of an orally active drug usually obeys at least three of the following four criteria:

- not more than 5 hydrogen bond donors, e.g. an alcohol group, -OH, or an amine group (primary, $-NH_2$, or secondary, -NHR);
- not more than 10 hydrogen bond acceptors, nitrogen atoms, N, or oxygen atoms, O;
- a relative molecular mass of less than 500;
- an octanol-water partition coefficient log*P* not greater than 5.

The origin of the rule's name comes from the fact that all numbers are multiples of five. This became a commonly used way of evaluating the potential of a substance as a medicinal drug. However, additional features that increase druglikeness have been suggested, including:

- log *P* in −0.4 to +5.6 range;
- molar refractivity from 40 to 130 (molar refractivity is a measure the overall polarity of a molecule);
- relative molecular mass from 160 to 500;
- number of atoms from 20 to 70;
- polar surface area no greater than 1.40 nm^2.

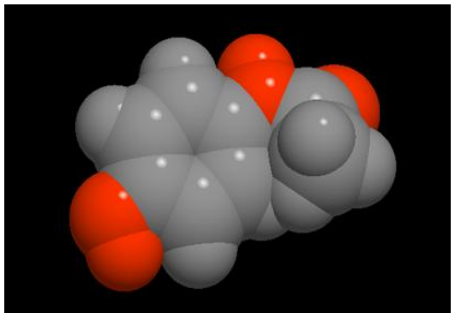


Figure 1 The red areas show the polar surface area of a paracetamol molecule

[1] See *Partition and distribution coefficients*.

Calculating drug-like properties

There are a number of fairly simple to use computer programmes that allow desirable drug-like properties of compounds to be calculated. Most use drawing programmes so that the structure of a molecule can be created, followed by an analysis of that structure to provide calculated pharmacokinetic properties.

The drawing tools take a little practice to use, but similar principles apply to them all. Together with molecular model building they provide a good way of visualising molecules and beginning to understand their properties. All require Java.

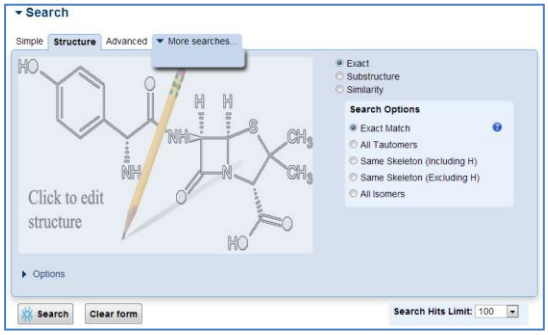
ChemSpider (http://www.chemspider.com/About.aspx?)

From the website:

ChemSpider is a free chemical structure database providing fast access to over 25 million structures, properties and associated information. By integrating and linking compounds from more than 400 data sources, ChemSpider enables researchers to discover the most comprehensive view of freely available chemical data from a single online search. It is owned by the Royal Society of Chemistry.

It may take a while to get used to using it, but here is a brief sample of what you can do.

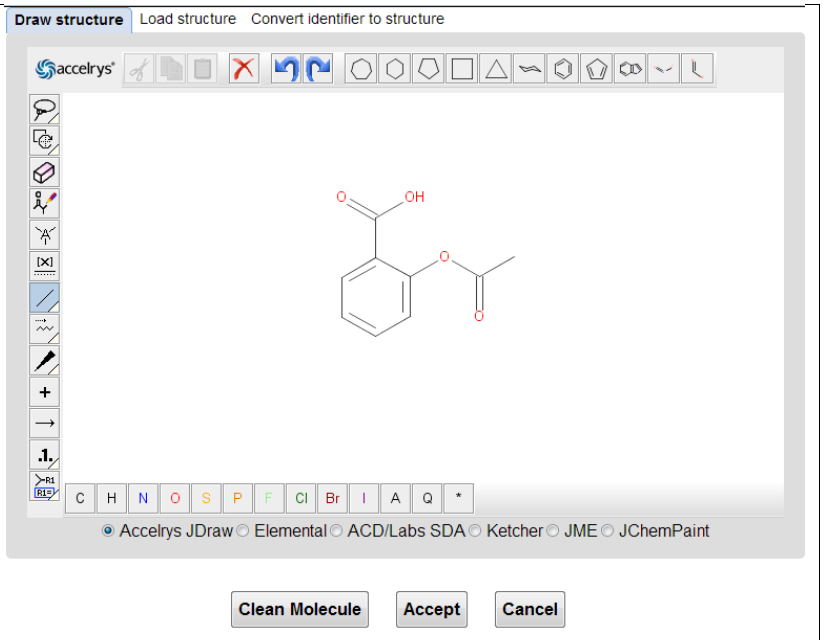
Navigate to *Structure search*. You will see a screen like the one on the right. Click on *Search* and then *Click to edit structure* to open a drawing programme. There are six to choose from:

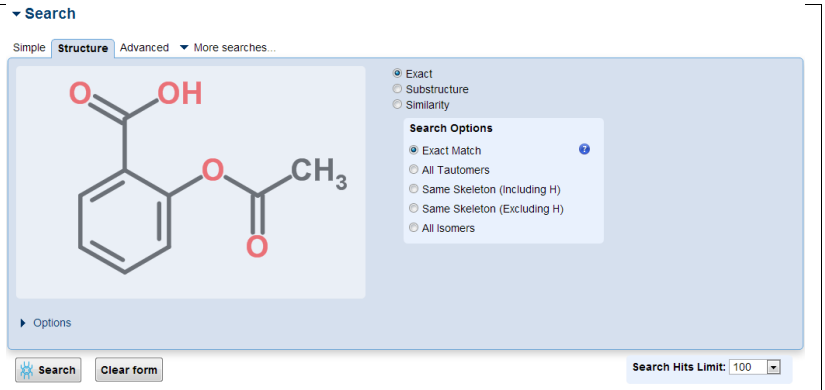
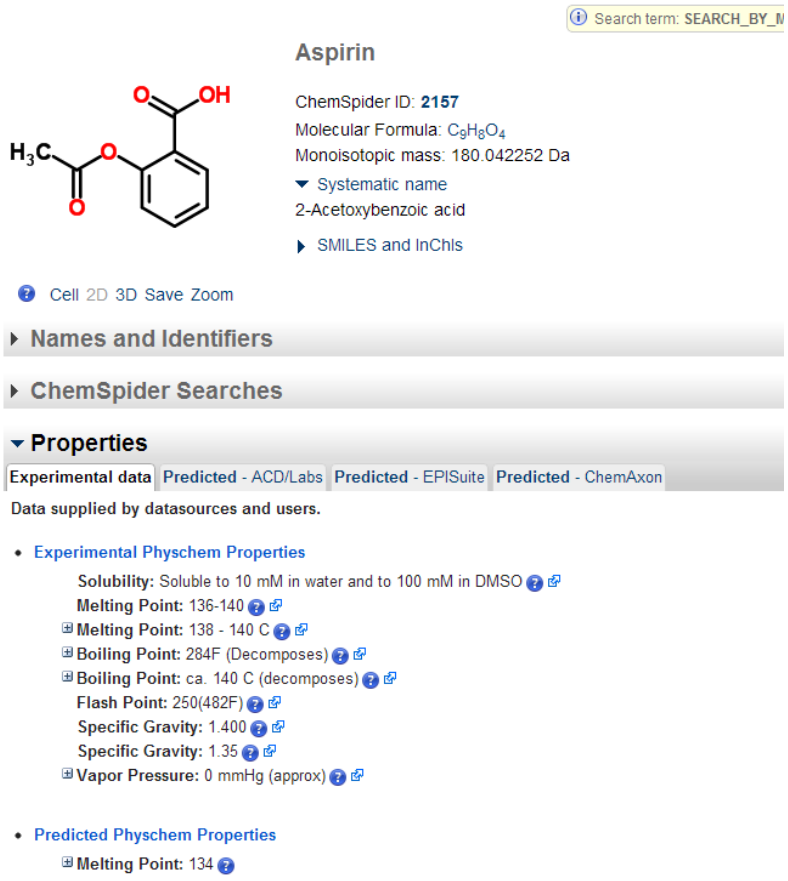


- Accelrys JDraw
- Elemental
- ACD/Labs SDA
- Ketcher
- JME
- JChemPaint

The following search was carried out using Accelrys JDraw.

1. The structure of aspirin was drawn.



2. When the drawing was finished, *Accept* was clicked and this screen appeared:	
3. Click on Search and programme finds the molecule in its database and displays stored data about the molecule. By navigating the *Properties* menu you can find: • Experimental data; • Predicted data - three prediction programmes are available: ○ ACD/Labs ○ EPISuite ○ ChemAxon	

It takes practice, but it does allow the user to modify the structure of a molecule and obtain a prediction of those physiochemical properties important to drug activity and effectiveness.

OSIRIS Property Explorer (http://www.organic-chemistry.org/prog/peo/)

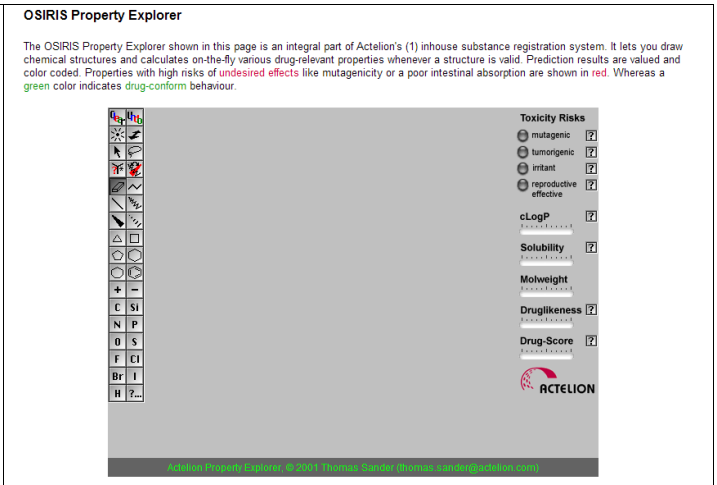
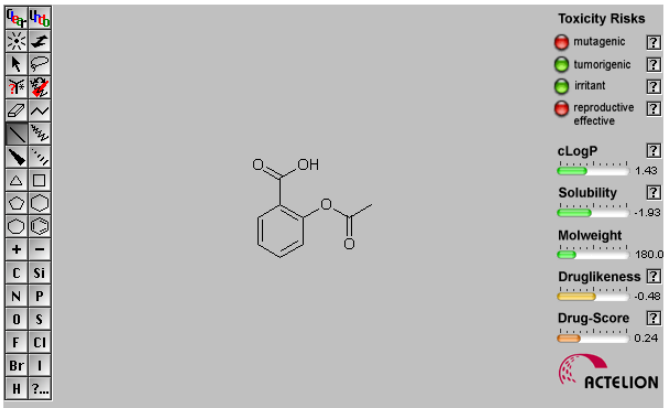
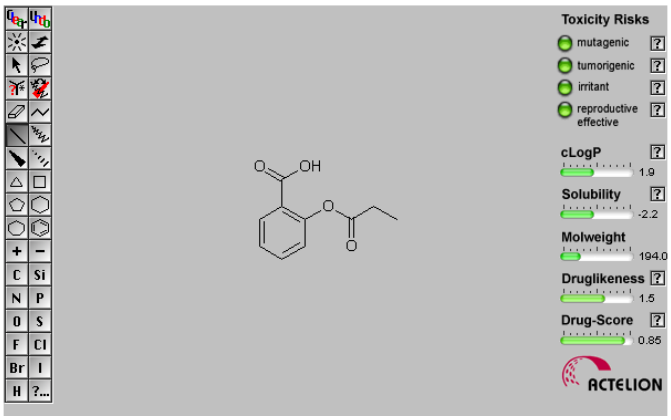
This is another drawing package combined with an extensive database. Unlike any of the predictive tools accessible via ChemSpider, OSIRIS makes a calculation of 'druglikeness'.

From the website:

There are many approaches around that assess a compound's druglikeness partially based on topological descriptors, fingerprints of MDL struture keys or other properties as cLogP and molecular weights. Our approach is based on a list of about 5300 distinct substructure fragments with associated druglikeness scores.

A computer-programme analyses the structure of a molecule and assesses the proportion of fragments that are associated with drug-like properties. For full details, visit the website.

Here is an example of what might be done.

1. This is the blank screen.	
2. The structure of aspirin is drawn and information appears about: • toxicity risks; • cLog*P;* • solubility; • molweight (relative molecular mass); • druglikeness; • drug score. The druglikeness of aspirin (2-ethanoyloxybenzoic acid) is calculated as −0.48.	
3. Modifying the structure by adding a methyl group to the ethanoyloxy- chain to make 2-propanoyloxybenzoic acid gives a dramatic change in druglikeness. The druglikeness of 3-propanoyloxy-benzoic acid) is calculated as +1.5. Interestingly, much higher than aspirin.	

Finding out

What are the limitations of drug property predictors?