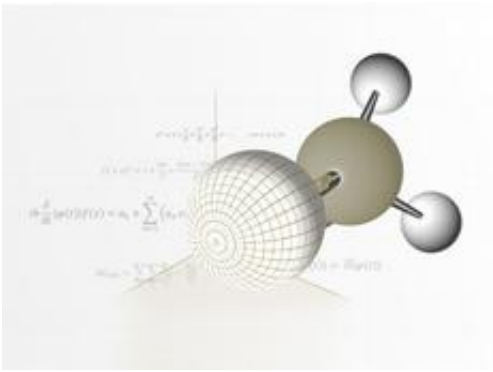
The computer knows its chemistry

March 16 2012, By Fabio Bergamin



The computer-assisted development of new active ingredients uses mathematical molecular descriptions and models from which a required pharmacological activity can be predicted. Credit: Gisbert Schneider, Max Pillong / ETH Zurich

New software developed by ETH Zurich researchers has learned important rules of chemistry. The scientists can use it to simulate the chemical synthesis of molecules in a computer and develop completely new medicines based on them.

Medicines are more and more often being developed by computer. This means chemists increasingly try out first of all on the screen something they afterwards replicate in actual practice in the laboratory. The computer acts as their playground and simulator, e.g. to find an active ingredient that binds perfectly to the specific structure of one of the body's own proteins so it can suppress its activity, for example.

Whereas in the past chemists carried out such a computer-aided active ingredient search mainly by combing through data bases containing a limited number of candidate molecules to find which of them was most suitable, ETH Zurich researchers led by Gisbert Schneider, Professor at the Institute of Pharmaceutical Sciences, are now going one step further: they have developed a program that has memorised important rules of organic chemistry and can use it to build new active ingredient molecules from first principles. The researchers call it “de-novo design”.

Molecules never seen before

This has immensely expanded the possibilities for scientists searching for active ingredients. Practically all imaginable molecules are now available to the researchers as virtual candidate active ingredients. Schneider says, “It gives us access to molecules that no chemist has ever synthesised or seen before.”

Schneider’s computer program can assemble molecules virtually on the modular principle and can compare them with existing molecules and calculate how well they fulfil the conditions defined by the researchers. The program can also modify molecules, thus gradually improving them in a process that resembles evolution, until finally the program delivers to the user the information about an optimised candidate active ingredient. To enable it to do this, the software knows a series of basic chemical modules and almost 60 of the most important reaction steps in organic chemistry. Schneider says, “They are intentionally nowhere near all the reactions that exist. We have taught the program only the ones that are widely used by chemists and which in their experience also promise success.”

The synthesis route is also taken into account

Schneider sees a big advantage in this, since comparable computer programs developed in the past 25 years sometimes produced random molecules irrespective of whether they were synthesizable at a reasonable cost. Because Schneider's program takes into account not only the finished molecule but also the route by which it could be synthesized in actual practice, it leads to active ingredients that really can also be prepared easily by laboratory synthesis.

The software has also passed its first practical test. Via the conventional computer-assisted method – searching in a molecule data base - Schneider's work group found an active ingredient molecule that inhibits one of the body's own enzymes involved in cell division. Thanks to the new software, they succeeded in finding another active ingredient with a structure completely different to the existing one. It has the same activity, but the advantage that it has not yet been patented. The aim is that one day they will be able to use this active ingredient in cancer therapy.

Also attractive for the industry

The search for active ingredients that have not yet been patented will then be an important area for the use of Schneider's software in the future as well. It is also important to find successor substances for medicines whose patent protection has expired.

In addition the computer simulation allows not only the desired activity of a substance to be tested, against a protein for example, but also possible side-effects against other proteins. Therefore the program will simplify the search for active ingredients – for example new antibiotics – that are required to have the highest possible activity and small side-effects.

This also makes the new software extremely attractive to the

pharmaceutical industry. A few companies are already using the program. ETH Zurich issues appropriate licences.

More information: Hartenfeller M, et al: DOGS: Reaction-Driven de novo Design of Bioactive Compounds. *PLoS Computational Biology* 2012, 8: e1002380, doi: 10.1371/journal.pcbi.1002380

Provided by ETH Zurich