

Era of the drug engineer

The majority of drug compounds are not sitting targets waiting to be 'hunted down', but have to be carefully engineered. X-ray crystallography is proving to be one of the most important drug discovery technologies.

In the past, chemists and biologists involved in drug discovery often proudly proclaimed that they were 'drug hunters'. While the term implies a strong purpose, it also conjures up a picture of individuals with large-calibre rifles from whom the hunted has little chance of escape. In the context of drug R&D, the term 'hunting' is no longer appropriate as it infers that the drug already exists and is just waiting to be found. This may be true when the drug candidate is a natural product, but the majority of drug compounds did not pre-exist, but had to be carefully engineered. The term 'drug engineer' would therefore seem more appropriate.

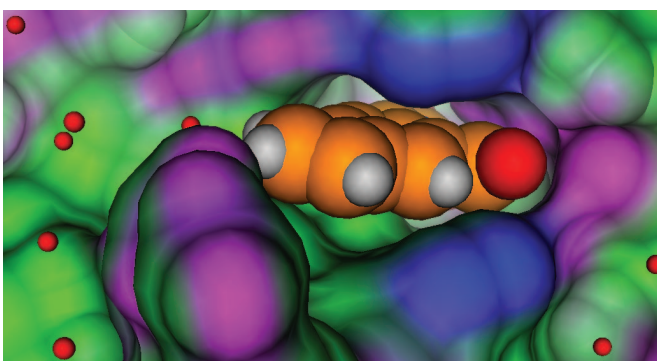
In silico methods

A feature of modern engineering is the use of in silico methods for prototyping, and this is also true for drug R&D. An example is the variety of computational methods that are now employed to aid drug design from in silico ADMET through to high-throughput docking. However, for these in silico methods to be successful, they need to be based on high-quality data.

In a recent survey conducted by Evotec OAI at the 2003 Drug Discovery Technology meeting in Boston, X-ray structure-based design was rated as the most useful drug discovery technology by 82 per cent of respondents. This technique is particularly suited to the optimisation of compounds for non-membrane bound protein targets, and has been used to great effect in the creation of HIV protease inhibitors that are now on the market.

The insight provided by X-ray crystallography into the interaction between a small molecule drug and its target can be used in the following two ways:

- **Virtual screening.** The three-dimensional structure of the ligand (drug) binding site can be used to search – by in silico docking studies – for compounds within virtual compound libraries or collections of commercially available compounds for molecules whose shape and molecular characteristics complement those of the binding site. Evotec OAI has developed a very efficient virtual screening capability, and has successfully identified active molecules of novel chemical structure.
- **Iterative structure-based design.** Arguably the most useful aspect of X-ray crystallography is where it is used to guide the medicinal chemistry optimisation of an initial screening hit or lead molecule. An X-ray crystal structure of this hit molecule bound to the target protein is then obtained. Using this information, the medicinal chemist will then synthesise analogues, making modifications to increase interaction with the target



X-ray crystallography provides Evotec OAI's medicinal chemists with valuable insights into the interaction between drug molecules and their biological targets

protein and/or to alter the drug-like properties (for example, increasing aqueous solubility) without reducing the affinity of the analogue compounds for the protein. Once an analogue has been synthesised, its X-ray structure bound to the target protein is obtained in order to determine whether it binds in the manner that was expected. This new structure will in turn lead to new hypotheses and analogue synthesis. The key is to have the X-ray crystallography closely coupled to the medicinal and computational chemistry with fast turnaround times between synthesis and structure determination.

To address the challenges of rational drug design, Evotec OAI has complemented its existing capabilities by adding X-ray crystallography, which will be utilised in combination with virtual screening. This will provide a powerful platform within its full range of drug discovery and development solutions. It will also help its medicinal chemists to act as 'drug engineers', undertaking iterative structure-based drug design programmes for the benefit of customers. ■

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