Rational drug design — designing a molecule that binds to a target

In the second part of our science article on rational drug design, Adam Todd, Roz Anderson and Paul W. Groundwater describe how a molecule that binds to a target is designed, using angiotensin-converting enzyme as a worked example to illustrate the process.

Following on from the first article (PJ, 4 July 2009, p19), in which the role of pharmacists in drug design was discussed, the development of rational drug design software using molecular modelling techniques has helped revolutionise the development of new drugs. Software-aiding rational drug design has been around since the early 1980s but, since it takes around 10 to 15 years to get a drug from concept to market, the results have only appeared recently.

Examples of this approach include donepezil, an anticholinesterase inhibitor, used in the treatment of Alzheimer’s disease and developed using quantitative structure–activity relationship studies (QSAR), and indinavir and nelfinavir, both HIV-1 protease inhibitors, developed using structure-based drug design.

The process

There are generally two methods used in structure-based drug design to generate a lead compound — de novo design and the in silico screening of databases. De novo design involves creating a molecule from scratch to fit a given target, such as a receptor or enzyme, and this can be a challenging and time-consuming process.

The in silico screening of databases, however, uses databases consisting of drug-like molecules, which are screened against a particular target. There are several large readily available commercial databases that can be downloaded free of charge from the internet. These databases consist of thousands of drug-like compounds that can be purchased directly and this approach offers the advantage that potential lead compounds can be identified, sourced, and tested quickly.

Key residues

Angiotensin-converting enzyme was chosen as the target in this article because it is well characterised and there is much information available on its binding site interactions for inhibitors. In this case, the crystal structure of ACE in complex with captopril, the first orally active ACE inhibitor, was used.

When a compound is designed to bind to a given target, it is essential to establish which residues are required for binding, so the first step in the design process was to identify the key ACE residues for interaction with the bound ligand, in this case, captopril.

ACE is a metalloprotease enzyme whose catalytic mechanism is dependent on a zinc ion. In common with previous studies, this work shows there are six key interactions between captopril and ACE, the most significant being the favourable interaction between the thiol group of captopril and the zinc ion of ACE. These molecular interactions “lock” captopril into the active site of ACE, thereby inhibiting its activity.

In agreement with the current literature, the other residues of ACE found to interact with captopril are glutamine-A281, histidine-A353, lysine-A511, histidine-A513 and tyrosine-A520.

Interestingly, the binding modes of the other ACE inhibitors, lisinopril and enalapril, have also been elucidated and indicate that captopril, lisinopril and enalapril all bind to ACE in a similar way, by interacting with the same six key residues, as outlined above. Lisinopril and enalapril, however, interact with the essential zinc ion of ACE through a carboxylate group, rather than a thiol group, as is observed with captopril.

The pharmacophore model

The next step in the process was to develop a model from the key-interacting residues that contains important structural information about the drug target. The resulting pharmacophore is considered to be an important tool in rational drug design.

Using Catalyst, a specialist drug design software developed by Accelrys, the six residues of ACE were used to generate a pharmacophore model, which was then used as a tool to generate lead compounds with the potential to inhibit ACE.

The pharmacophore model acts as a three-dimensional map and outlines interaction sites where potential compounds can bind (Figure 1). This model was then screened against an in silico database of drug-like molecules from the Maybridge screening collection. Compounds that fitted the 3D map were categorised as hits and these were stored and selected for further investigation.

Since the pharmacophore model was generated from the six key molecular interactions between ACE and the bound ACE inhibitors, it would be expected that any compound fit-
The compound appears to fit the 3D interaction map generated from captopril. Figure 2: Compound 1 matched to the pharmacophore model of ACE. This screening since there was a possibility that it might have poor oral bioavailability if it does not comply. Nevertheless, Lipinski’s rule of five is a useful filter to focus on the discovery process. The rule of five is named accordingly because the cut-off point for each parameter is a multiple of five. It predicts that a compound may have poor oral bioavailability if it meets any of the following criteria:

- More than 10 hydrogen bond acceptors
- More than five hydrogen bond donors
- A molecular weight above 500
- A log P of more than five

Therefore, any hit compound that met any of Lipinski’s criteria was removed from the screen since there was a possibility that it would have poor oral bioavailability.

Once hit compounds were filtered, the remaining compounds were then inspected in silico to see how well they matched the 3D pharmacophore model (Figure 2). Compounds that fit the interaction sites of the pharmacophore were then chosen as candidates for biological testing in order to evaluate their activity. The worked example in Figure 2 with ACE showed that compound 1 fits the pharmacophore model and would, therefore, be a good candidate to investigate inhibitory activity against ACE.

Finally, compound 1 was compared in silico to the ACE inhibitor captopril to allow evaluation of possible binding modes (Figure 3), showing that compound 1, identified using structure-based drug design, could bind to ACE in a similar manner to captopril and supporting the idea that compound 1 may have good ACE inhibiting properties.

Conclusion
At the end of this drug design process, a set of drug-like molecules, which interact with the key residues of ACE, were identified. One of these structures, compound 1, binds to ACE in a similar way to captopril, suggesting that it may have good ACE-inhibiting properties and so is a good candidate for biological testing. Structure-based drug design is a common method used by the pharmaceutical industry to discover a lead compound. Its use in drug discovery should help the move away from serendipity into a more structured and focused environment but, having said that, luck still certainly has an important part to play in drug discovery.

In conclusion, structure-based drug design has been used to design a compound with the potential to inhibit ACE. Discovering a lead compound is, however, only the first step in the long and complicated process of getting a drug from concept to the market. Many more steps, such as biological testing, toxicity, pharmacokinetics, pre-formulation and formulation studies, need to be overcome before a drug moves into the clinical phase in preparation for the market, and pharmacists can also play a key role in all of these processes.

References