HL Importance of stereochemistry in drug design and action (2)

COMBINATORIAL CHEMISTRY

Drug companies possess 'libraries' of compounds which have been screened for drug activity. In the past it could take many years to build up such a library as the substances were synthesized, purified, and screened by traditional methods. The advent of very sensitive techniques, such as mass spectrometry, to identify extremely small amounts of substances has lead to the development of 'combinatorial libraries'. In combinatorial chemistry very large numbers of related compounds can be prepared quickly. One way is to use computer controlled syringes to carry out repetitive chemical techniques but much use is now made of solid phase organic chemistry.

The starting material for the reaction is covalently bonded to very small beads (100 micrometres diameter) of polystyrene-based resin. A process called 'mix and split' is then used. Imagine the process for just three amino acids. After the first coupling, all the resin beads are then split into individual portions for the next step so that when reacted again all the nine possible combinations of dipeptides are formed. After another step all 27 possible combinations of tripeptides have been formed. If the process is scaled up for all the 20 naturally occurring amino acids then each cycle produces 400 dipeptides, 8000 tripeptides, and 160 000 tetrapeptides, etc. By using a large excess of the second and subsequent amino acids the reaction can be made to give a high yield. The final products can be purified easily by filtering off the beads from the reaction mixture and washing. Preliminary screening for drug activity can then take place either *in vitro* or *in vivo* by measuring the ability of a compound to affect enzymes and bind to receptor cells.

This process was done first for amino acids but has been extended to cover many other types of active molecules, such as those containing the benzodiazepine group in depressants to form very large combinatorial libraries. Once a particular substance is identified as potentially useful it can be made on a larger scale. In the future it may become unnecessary to actually make the initial compounds. By knowing the exact shape both of the active site on the enzyme or receptor and the shapes of the active groups within a potential drug the use of virtual computer modelling can produce a virtual library.