ChemFactsheet

www.curriculum-press.co.uk Number 168

Combinatorial Chemistry

This is a technique developed by the pharmaceutical industry. It has been designed to *reduce the time and costs involved in researching and producing new drugs*.

Combinatorial chemistry enables pharmaceutical chemists to *accelerate the process of chemical synthesis*.

A drug candidate is a compound which shows the correct properties to be effective in the prevention or treatment of an illness, and is then submitted for further clinical testing.

A compound library is a collection of compounds which are to be screened for drug activity.

Huge numbers of compounds can be synthesized and screened for new and relevant bioactivities. From this compound library, compounds of interest can be further tested in preclinical trials. Compounds showing the correct properties (referred to as 'drug candidates') can then be subject to the various clinical tests which are needed to ascertain whether the compound is safe for use and effective against a target illness.

A drug target is a biochemical structure or molecule in the patient which is crucial to the development of the disease, that is if the drug can 'hit' and disable the target, then the patient can get well.

In the past, pharmaceutical companies would most often use natural products which were isolated from animals or plants, and which were known to be biologically active. They would then try to make chemical changes in these to produce compounds of increased potency or effectiveness in curing the target illness, while ensuring that there were no nasty side effects (such as organ damage, sickness, tiredness, depression etc.) Each chemical change was done individually and the resulting compound was then purified using crystallisation, distillation or chromatography. This way of developing new drugs was very time consuming and costly, as only very small numbers of compounds could be synthesised at any one time.

Combinatorial chemistry helps drug companies find new drug candidates quickly and save money on preclinical development.

Combinatorial chemistry involves the simultaneous synthesis of large numbers of molecules, each having its own distinct structure, but which have a structural relationship to each other.

An analog is a drug with a structure which is related to that of another drug, but which may have a very different biochemical effect.

A large number of different analogs can be synthesised at the same time using the same reaction conditions. This is very much less time consuming than in the past when new compounds were made individually.

Combinatorial chemistry uses a range of chemically related compounds, and then combines each of these with a different range of chemically related compounds. In general the same reaction conditions and the same equipment can be used.

For example if we have a range of chemical compounds with related chemical structures, and call these C_1 C_2 C_3 C_4 and another range of compounds with related chemical structures D_1 D_2 D_3 D_4, a chemist may react each of the range $C_{1\text{ to }4}$ with each of the range $D_{1\text{ to }4}$ resulting in the compounds:

C_1D_1 C_1D_2 C_1D_3 C_1D_4 C_2D_1 C_2D_2 C_2D_3 C_2D_4 C_3D_1
C_3D_2 C_3D_3 C_3D_4 C_4D_1 C_4D_2 C_4D_3 C_4D_4

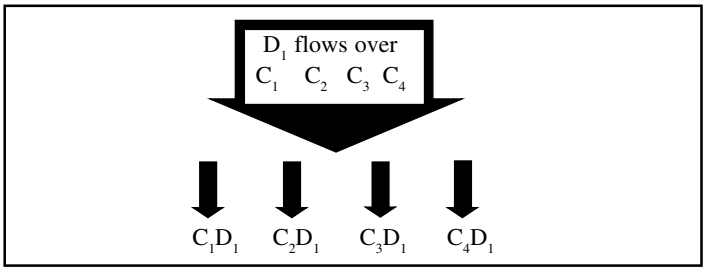
The chemist now has sixteen compounds synthesised under the same chemical conditions and in the same reaction equipment rather than just one made by reacting C with D. The new compounds may be synthesised as a mixture or as a series of individual parallel reactions.

This works because there is a huge range of organic compounds each of which could be potentially suited as a new drug, and which differ only very slightly from each other. Very tiny differences give rise to very different biochemical reactions in the human body.

Having obtained the compounds, the chemist can then separate and purify them. Each of these new compounds can then be tested to see how effective it is against a target illness, and also note any side effects which individual compounds may have. Rapid screening of compounds is now possible as methods involving measuring the ability of a compound to affect enzymes and bind to receptors of cells have been developed. This enables suitable drug candidates to be rapidly identified.

In practice the range of compounds related to C would be far larger than four, as would those related to D, and so hundreds of new compounds can be synthesised in a short time. (New compounds = number of compounds related to C multiplied by number of compounds related to D.) Also, there is a wide range of ways of achieving the required reactions.

Parallel Synthesis



The compounds C_1D_1 C_2D_1 C_3D_1 and C_4D_1 can be formed in *separate parallel reaction vessels*, with C_1 C_2 C_3 and C_4 in solution.

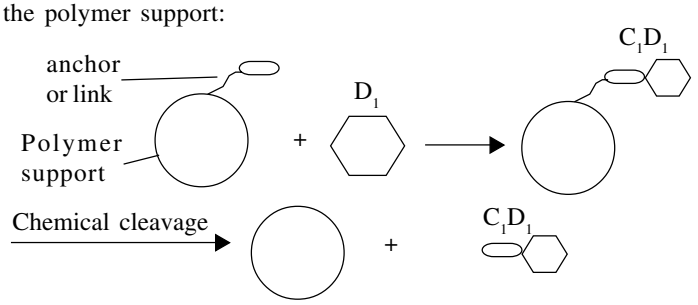
The solvent is removed from the new compounds which have been synthesised. Alternatively, C_1 C_2 C_3 and C_4 may be attached to solid supports and then detached from the supports. In practice there are many more reaction vessels, for example a hundred or more may be used, and many more than four variants of the C related and D related compounds are used. Thus many hundreds or thousands of compounds are synthesised in a short time (during which in the past only a few compounds would have been made).

The Synthesis of Compounds by Using a Solid Support

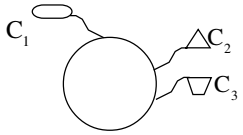
The support is usually a cross-linked polymer or plastic resin which will not react under the conditions which are being used for the reaction.One of the reactants is anchored to the support. The other reactant flows over the support and reacts with the one anchored to the support.The new compound is then chemically removed or cleaved from the solid support.

The polymer may be made up of beads which form a gel when exposed to the solvent. The mobile reactant will then diffuse through the gel to reach the reactant attached inside the polymer beads. This has the advantage of giving a large surface area in which the reactants may come together as most of the bead can be reacted with relatively little polymer support (sometimes called the polymer backbone).

For example using the reactants C_1 and D_1 with C_1 initially linked to the polymer support:



More than one C compound can be linked to the polymer support, for example C_1, C_2, C_3 may be linked. so that C_1D_1, C_2D_1 and C_3D_1 would be produced simultaneously.



[Note: There are other ways of showing the link for example a zig-zag line or linking oval may be used, so read examination questions with care.]

Chemical synthesis involving more than two types of starting compound can be achieved by adding further stages to the process, for example using compounds $E_{1\ to\ 4}$ to form compounds of the type CDE and then compounds $F_{1\ to\ 4}$ to form compounds of the type CDEF would add two further stages. The maximum number of different compounds which could be formed would then equal two hundred and fifty six.

In practice not all of these may be able to be synthesised or be of interest. However, hundreds or thousands of compounds are formed because many more than four variants of each set of closely related compounds (C, D, E, and F) are available and are used.

The Synthesis of Polypeptides

Polypeptides may be synthesised by combinatorial chemical methods. A —CH_2Cl group is the link attached to the resin. The —COOH group of the first amino acid is bonded to this group. The —NH_2 group of the second amino acid must be temporarily protected in order to prevent it bonding with other molecules of the same amino acid.

A solution of the second amino acid is then added to the resin to form a dipeptide. The protecting group is removed from the second amino acid and a solution of a third amino acid with protected —NH_2 group is added. The third amino acid bonds to the second amino acid and the protecting group of the third amino acid is removed. This can be repeated using any sequence of amino acids until the required polypeptide is produced. The polypeptide is then released from the resin by breaking the link.

A lead compound is a compound which has exhibited some activity as a drug.

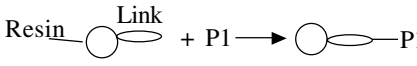
It is then used as a basis to make structures closely related to it, to find a derivative of it which is more effective and/or has fewer side effects. The idea is of *a compound that leads on to a better one*.

Practice Questions

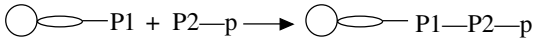
1. Computer controlled apparatus using robots for combinatorial chemical synthesis consists of 8 rows of 12 reaction vessels. Given 8 different alcohols and 12 different carboxylic acids, how many esters could be simultaneously synthesised? (1 mark)
2. Describe how you might arrange to synthesise dipeptides using combinatorial chemistry on a solid support. (3 marks)
3. Aspirin is a well known analgesic which has the negative side effect that it causes stomach irritation. How might combinatorial chemistry be used to attempt to find a similar compound which has the correct analgesic effect but does not give the negative side effect. (3 marks)

Answers

1. 96
2. An example explanation would be:
   Peptide one = P1, Peptide two = P2, Peptide 2 with protecting group = P2—p.The solid support is a resin with a link which will react to attach peptide one.
   A protecting group p, is bonded to the –NH_2 group of the second peptide to prevent it from reacting with other P2 molecules of the same amino acid rather than the P1 ones bonded to the resin.



(one mark for support and link with P1 correctly added)



(one mark for P2 correctly added)

The excess reactant is then washed away, the link broken, and the protecting group removed to give

+ P1—P2 (Dipeptide) + p

(one mark for correct cleavage step)

3. A lead compound, for example the precursor of aspirin (2-hydroxybenzenecarboxylic acid), could be chosen and used in reactions with a series of closely related compounds. (one mark) The chemicals would be delivered by computer controlled syringes (robots) to individual reaction vessels. (one mark) These reactions would give as products many different compounds each very similar to aspirin. (one mark) Preliminary tests would then be carried out using enzymes or cell cultures to find effective compounds. Promising compounds could then be further tested. (one mark)

[Key mark / worthy ideas are underlined and a maximum of three marks awarded.]

Acknowledgements: *This Factsheet was researched and written by Christine Collier.* ***Curriculum Press, Bank House, 105 King Street, Wellington, Shropshire, TF1 1NU. ISSN 1351-5136***