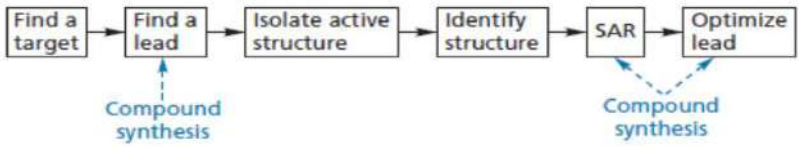
Combinatorial and parallel synthesis

The full set of compounds produced by Combinatorial and parallel synthesis is called a ***compound library***

Lec. 7

Combinatorial and parallel synthesis in medicinal chemistry projects



- The procedures used in combinatorial synthesis are designed to produce mixtures of different compounds within each reaction vessel, whereas those used in parallel synthesis produce a single product in each vessel.

Solid phase techniques

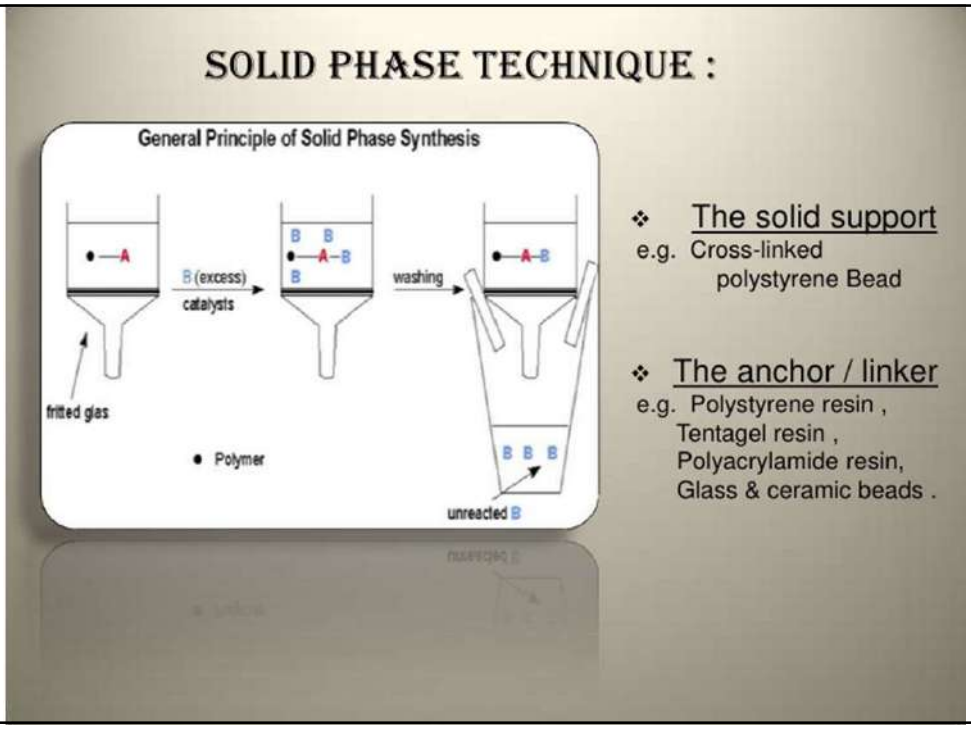
➢Solid phase techniques can be used to carry out reactions where the starting material is linked to a solid support, such as a resin bead.

Advantages:

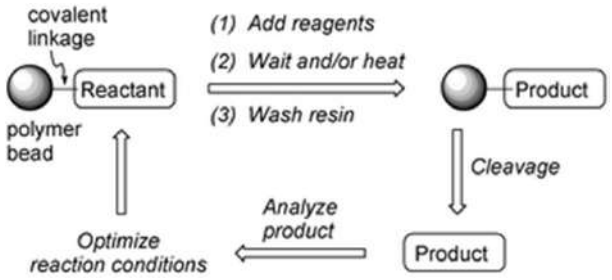
➢excess reagents or unbound by-products from each reaction can be easily removed by washing the resin.

➢large excesses of reagents can be used to drive the reactions to completion (greater than 99%).

➢intermediates in a reaction sequence are bound to the bead and do not need to be purified.



Solid phase techniques



Solid phase techniques

Advantages:

- the polymeric support can be regenerated and reused.
- automation is possible.
- if a combinatorial synthesis is being carried out, a range of different starting materials can be bound to separate beads. The individual beads can be separated at the end of the experiment to give individual products.

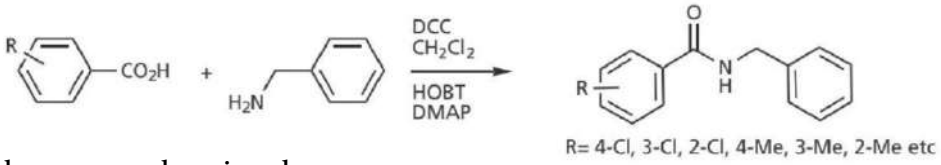
The essential requirements for solid phase synthesis

- a cross-linked insoluble **polymeric support** which is **inert** to the synthetic conditions (e.g. a resin bead);
- an **anchor or linker** covalently linked to the resin—the anchor has a reactive functional group that can be used to attach a substrate.
- a **bond** linking the substrate to the linker, which will be stable to the reaction conditions used in the synthesis;
- a **means of cleaving** the product or the intermediates from the linker.
- **protecting groups** for functional groups not involved in the synthetic route

Parallel synthesis

- a reaction is carried out in a series of wells such that each well contains a single product. This method is a 'quality rather than quantity'
- often used for focused lead optimization studies.
- typical medicinal chemist may synthesize one or two new entities a week.
- With parallel synthesis, that **same researcher** can synthesize a dozen or more pure molecules.
- can be carried out on **solid phase** and also be carried out **in solution** "solution phase organic synthesis (SPOS)"
- many techniques to facilitate SPOS. Eg. Amide synthesis.

eg. Amide synthesis



Conventionally, a work-up procedure involves:

1. Washing the organic solution with aqueous acid.
2. Separate the two layers and organic layer is washed with an aqueous base.
3. Separate the two layers , and then the organic layer is treated with a drying agent such as magnesium sulphate.
4. The drying agent is filtered off and then the solvent is removed to afford the crude amide.
5. Purification then has to be carried out by crystallization or chromatography.

In parallel synthesis variety of useful techniques can also be used to minimize the work-up procedure:

1. Equipment miniaturization: This enable one to perform up to 24 reactions followed by 24 simultaneous evaporations on a normal heater stirrer unit.
2. Multiple parallel or sequential automated chromatography units
3. Microwave reactors can dramatically speed up reaction times.

Combinatorial synthesis

- In combinatorial synthesis, mixtures of compounds are deliberately produced in each reaction vessel,
- The structures in each reaction vessel of a combinatorial synthesis are not separated and purified, but are tested for biological activity as a whole.
- Active mix .....one or more cpd active or false positive.
- Inactive mix .... then there is no need to continue studies on that mixture and it is stored.
- Overall, there is an economy of effort, as a negative result for a mixture of 100 compounds saves the effort of synthesizing, purifying, and identifying each component of that mixture.

The mix and split method in combinatorial synthesis

- Mix and split strategy used to minimize the effort involved and to maximize the number of different structures obtained.
- NO. of possible dipeptides.

By using mix and split method:

Each individual bead may contain a large number of molecules, but all the molecules on that bead are identical

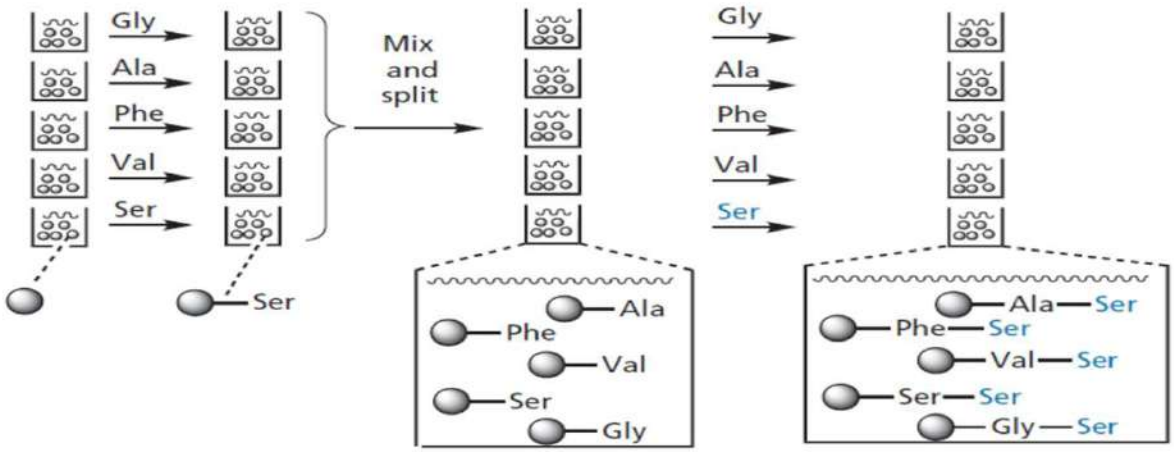
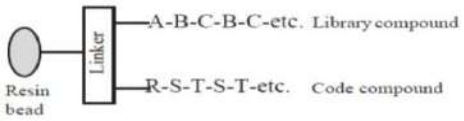


FIGURE 16.29 Synthesis of five different dipeptides using the mix and split strategy.

Structure determination of the active compound(s)

Tagging:

two molecules are built up on the same bead. One of these is the intended structure, the other is a molecular tag (usually a peptide or oligonucleotide) which will act as a code for each step of the synthesis.



Key:

Building block	Code compound
A	R
B	S
C	T

Compounds used for tagging must satisfy a number of criteria:

(1) The concentration of the tag should be just sufficient for its analysis, that is, the majority of the linkers should be occupied by the combinatorial synthesis.

(2) The tagging reaction must take place under conditions that are compatible with those used for the synthesis of the library compound.

(3) It must be possible to separate the tag from the library compound.

(4) Analysis of the tag should be rapid and accurate using methods that could be automated.

Table 5.2 The use of oligonucleotides to encode amino acids in peptide synthesis

Amino acid	Structure	Oligonucleotide code
Glycine (Gly)	NH_2 CH_2COOH	CACATG
Methionine (Met)	$CH_3SCH_2CH_2CH(NH_2)COOH$	ACGGTA