COMBINATORIAL CHEMISTRY

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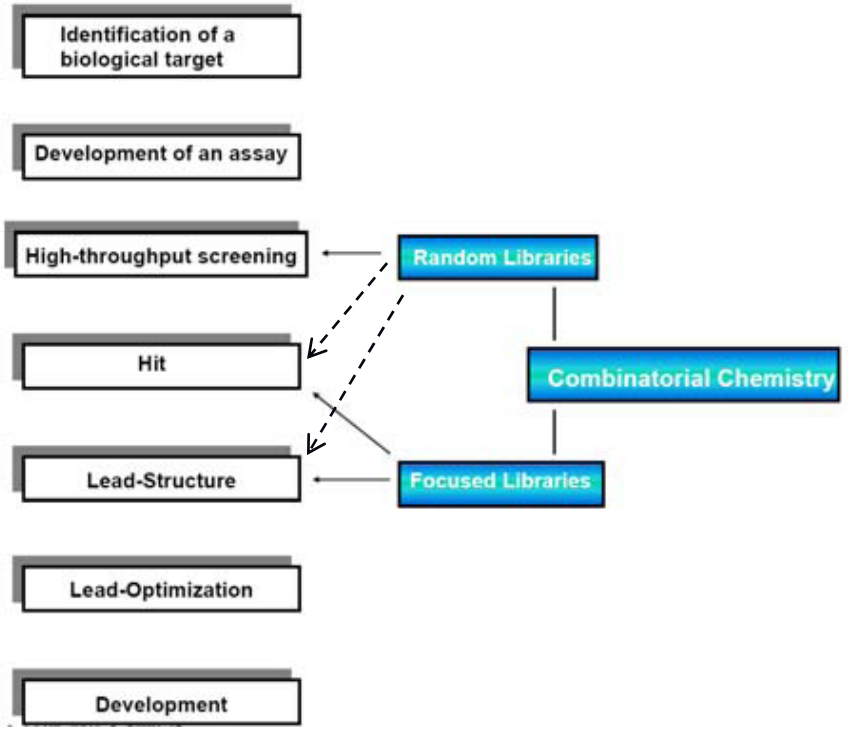
- Definition: the synthesis of chemical compounds as ensembles (libraries) and the screening of those libraries for compounds with desirable properties
- Potentially speedy route to new drugs, catalysts, and other compounds and materials
- Technique invented in the late 1980s and early 1990s to enable tasks to be applied to many molecules simultaneously

- Establishment of Libraries
  - Unbiased libraries (Random libraries)
    - Typically a common chemical core (starting point scaffold)
    - Large number of building blocks (highly diverse)
    - Many targets
    - Generating ”lead” structures
    - > 5.000 compounds
    - Solid phase synthesis (one bead screening if possible)
  - Directed libraries
    - Again a common chemical core
    - Limited number of building blocks (structural similar)
    - Directed towards a specific target
    - Used to optimize ”lead” structures
    - << 5.000 compounds
    - Solid phase synthesis, synthesis in solution



SOLID-PHASE SYNTHESIS

- The reaction is carried out on a solid support such as resin beads. The bead is treated with different starting materials, which bound together. Then it is mixed with another reagent to get product.
- Solid support: it is depend upon the type of reaction.

  Ex: polystyrene
- Linker: that sites between our compound and solid support

  Ex: wang resin, rink resin
- Protecting groups: these are important for blocking and regenerating certain functional group in a reaction sequence.

  Ex: FMOC, TBOC

- Combinatorial synthesis on solid support is usually carried out using either parallel synthesis and mix procedures

Parallel synthesis:

- In this method the compounds are prepared in separate vessel but at the same time that is in parllel.

Mix and split technique:

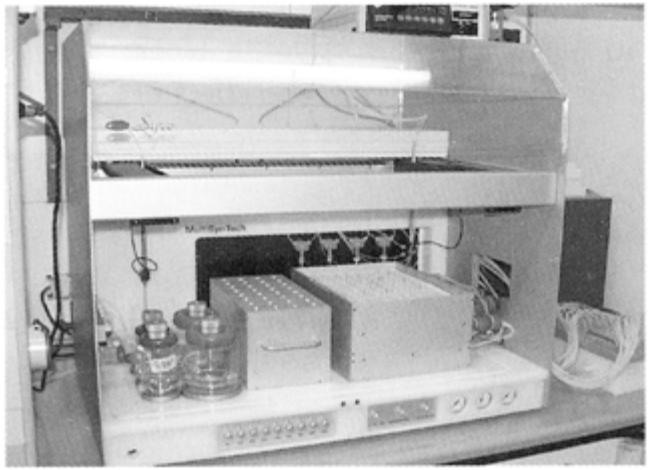
- May be used to make both large and small combinatorial libraries using relatively few reaction steps.
- The history of the bead is traced by using suitable encoding method or deconvulsion.

SOLUTION PHASE SYNTHESIS

- Reaction proceeds in Solution. Can be used to produce libraries that consist of single compounds or mixtures.
- Single compound libraries are prepared using parallel synthesis.
- Easy characterization of intermediates as well as end pruduct.
- No limitations in attachment point .
- Faster validation times relative to solid phase synthesis.
- Standard analytical protocols can be used to characterize products between each reaction step
- Difficult to drive the reaction towards the product, extensive purification is needed

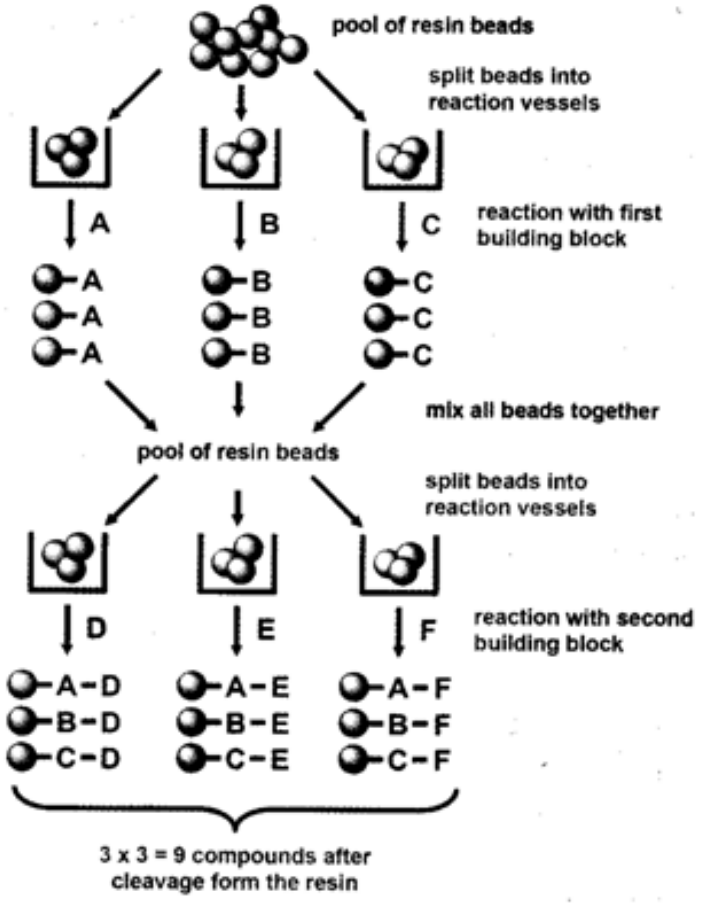
PARALLEL SYNTHESIS

- Each compund is prepared in a specific vessel (on pins or Tea-bags)
- Array of reaction vessels (96 well plates -> each well other compound)
- Automated control of reactions -> easy to keep track of each compound
- High yields
- Useful for epitope mapping
- Just applicable when small number of positions are being varied -> small libraries



PREPARATION OF LIBRARIES

- Pool/Split Synthesis
  - Good to generate large libraries
  - Labeling required to keep track of each compound
  - Beads (resin) are split into different vessels
  - Then reacted, shuffled, and split again.
  - 1000 compund library prepared from 10 building blocks in each step → 30 reaction steps. (1110 steps for parallel synthesis)



HIGH THROUGHPUT SCREENING

- Combinatorial synthesis produces a large quantity of structure in a very short time period, biological testing should be carried out quickly and automatically. The technique used by this system is known as HTS.
- Compounds are automatically tested and analyzed on a plate containing 96 small wells with the capacity of 0.1ml .
- In HTS 1536 well with capacity of 1-10µl only used.

APPLICATIONS

- Drug Discovery - Lead Optimization
- Lead identification libraries < 10 000
- Lead optimization libraries 1000-2000
- Lead optimization via focussed libraries based on a privileged structure
- Both solution and solid-phase synthesis


THANK YOU