Organic Pharmaceutical Chemistry IV

Fifth Stage

Lecture 13

Solid Phase Chemistry

- Advantages
  - excess of reagents can be used to drive reactions to completion
  - purification procedures achieved by simple filtrations which can be easily automated
  - Well suited for making large libraries

Solid Phase Chemistry

- Disadvantages
  - development of reaction conditions requires more work than in solution reactions
  - Solid support are more sensitive to steric effects
  - reactions are more difficult to monitor

Solid Phase Chemistry

- Some what in between
  - ❑overall costs for the synthesis of large libraries can compare favorably with solution synthesis
  - ❑linker molecules have to be designed which are compatible with the polymeric matrix and the chemistry used for library synthesis

Solution Phase Chemistry

- Advantages
  - ❖most reactions and reagents have been studied in solution
  - ❖usually no excess of reagents have to be used
  - ❖solvent effects can be studied and altered readily
  - ❖steric effects are usually less pronounced in solution and can be overcome more easily by using more drastic reaction conditions
  - ❖reaction conditions are usually adapted to a large variety of substituents

Solution Phase Chemistry

- Disadvantages
  - extensive and time consuming
  - chromatographic purification procedures are often necessary
  - side products have to be separated and analyzed
  - automation usually requires more initial effort

Solid phase synthesis versus synthesis in solution

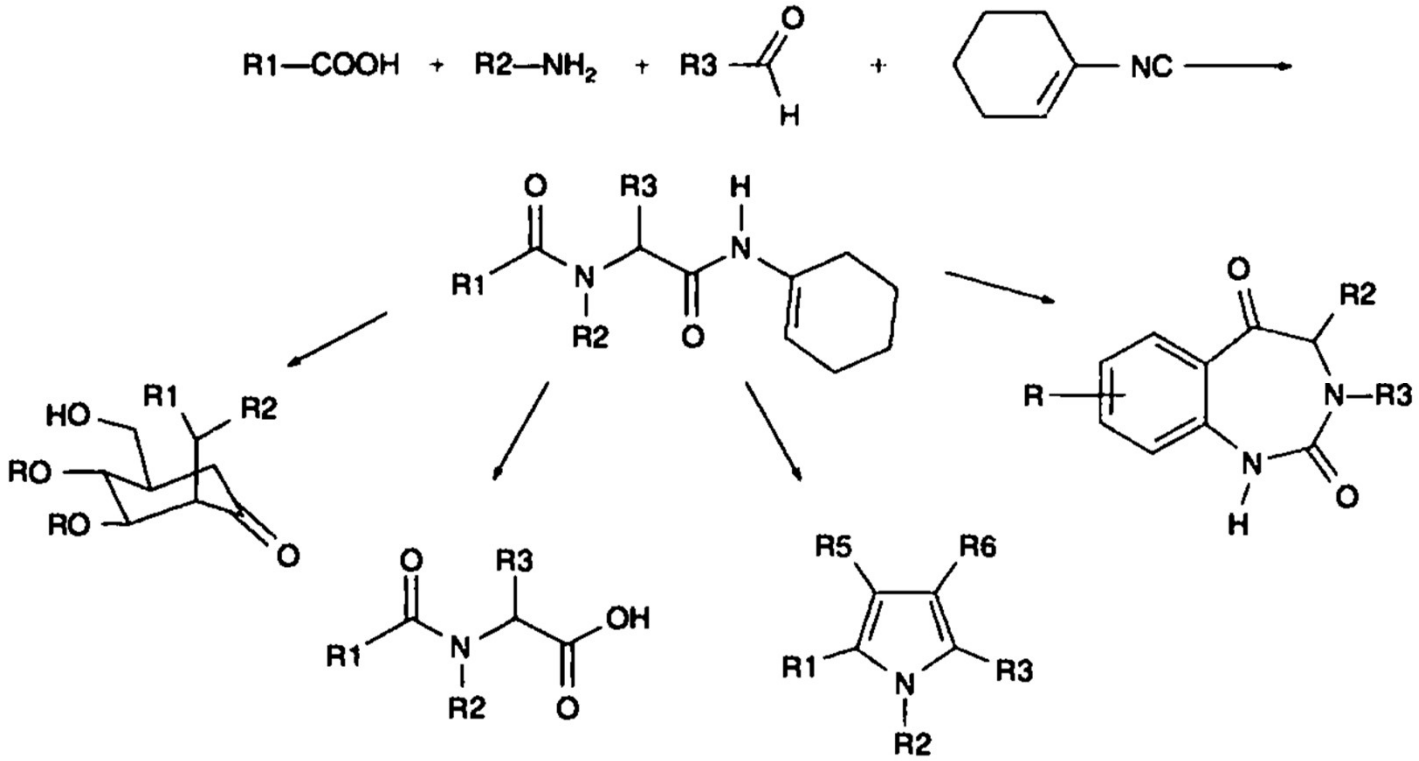
Solid-phase chemistry

- ***large libraries***
- ***split mixed synthesis***
- ***linear approaches***

Solution-phase chemistry

- ***Small libraries***
- ***parallel synthesis***
- ***convergent approaches***

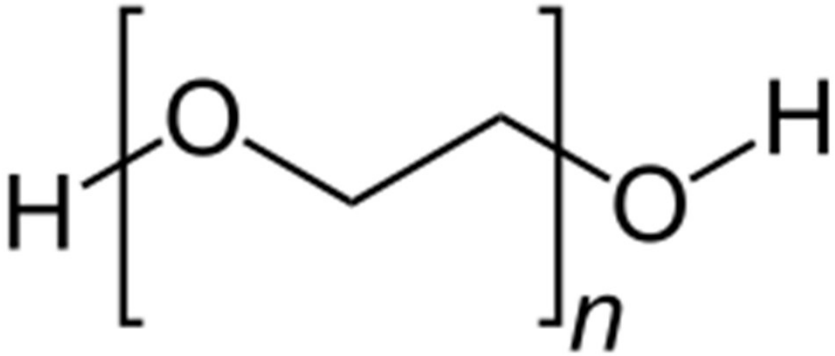
Example on solution phase

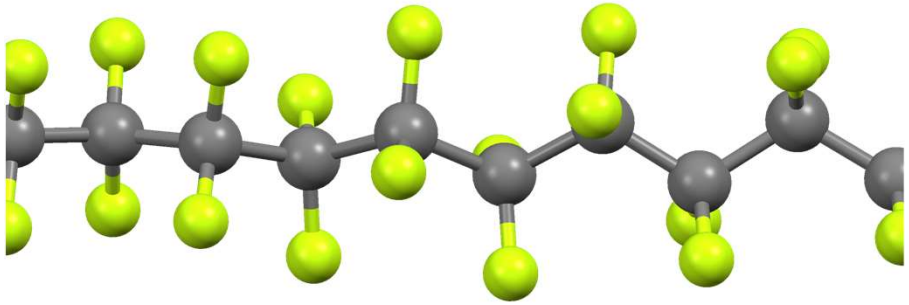


Intermediate synthesis

- Polyethylene glycol
- Dendrimers
- Fluorous phases
- Complementary DNA

Intermediate synthesis





Pooling Strategies

1. ***<u>One-bead one-compound strategy</u>***
   - Specific quantity of beads is allocated for each possible structure in the library:

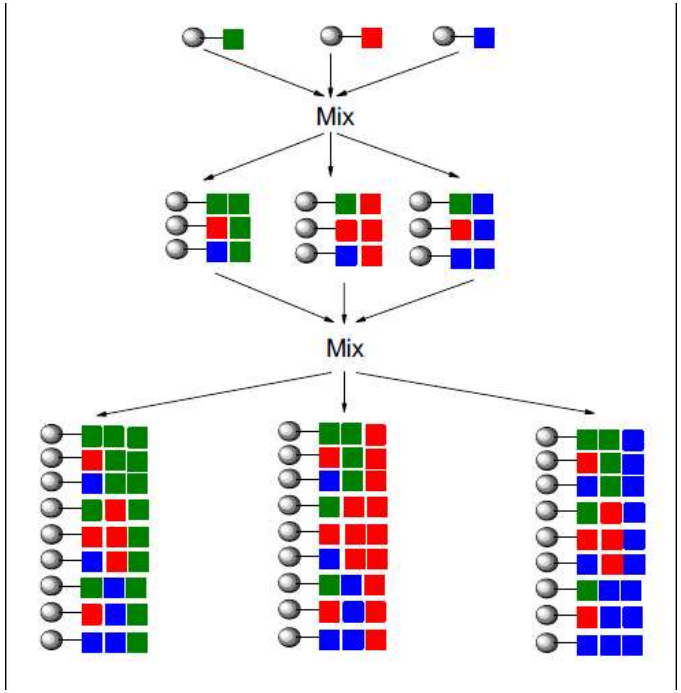
   \+ the simplicity of analysis and screening

   \- Keeping the beads separate

   \- deal with a large number of syntheses in parallel

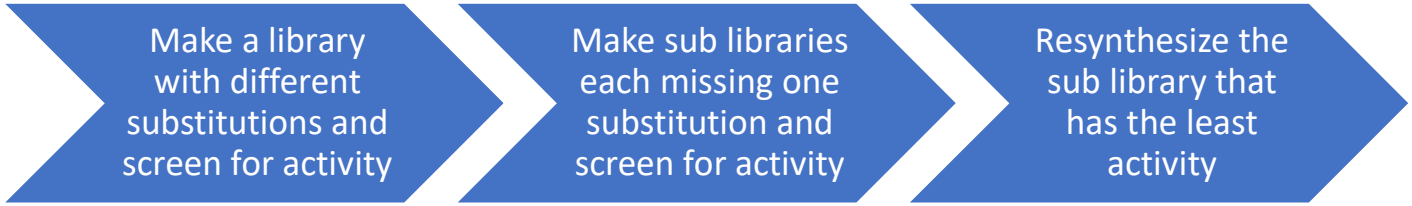
Pooling Strategies

2. ***Iterative deconvolution***



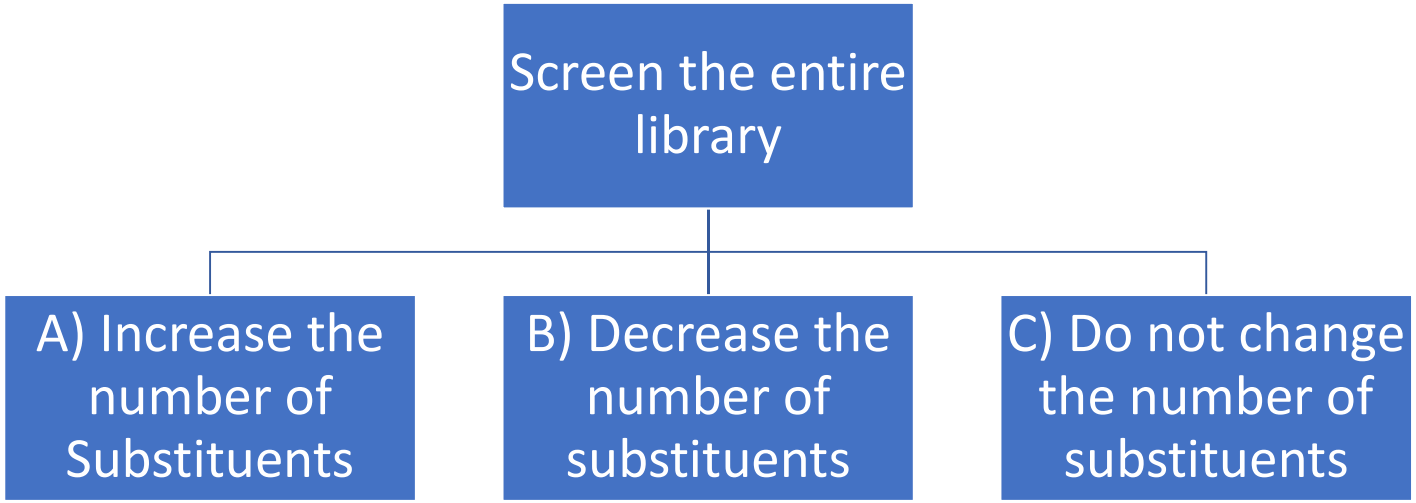
Pooling Strategies

3. ***Subtractive deconvolution***



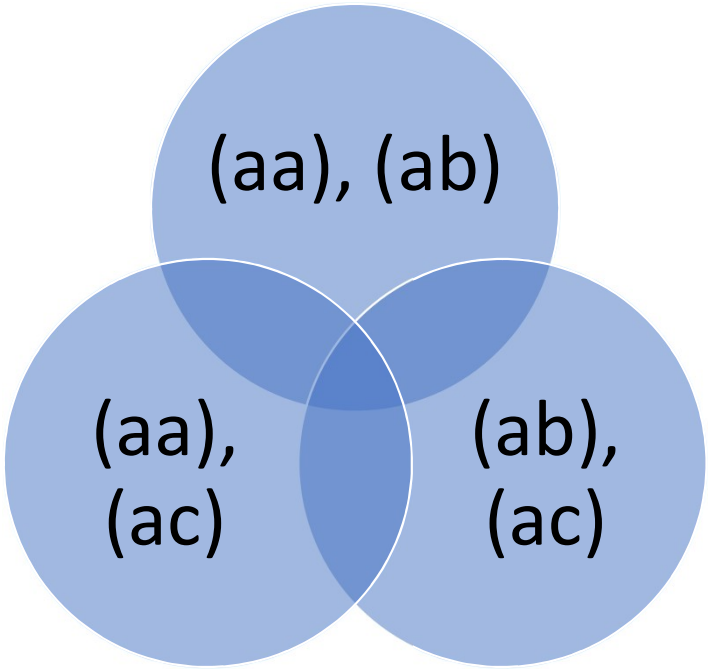
Pooling Strategies

4. <u>Bogus-coin detection</u>



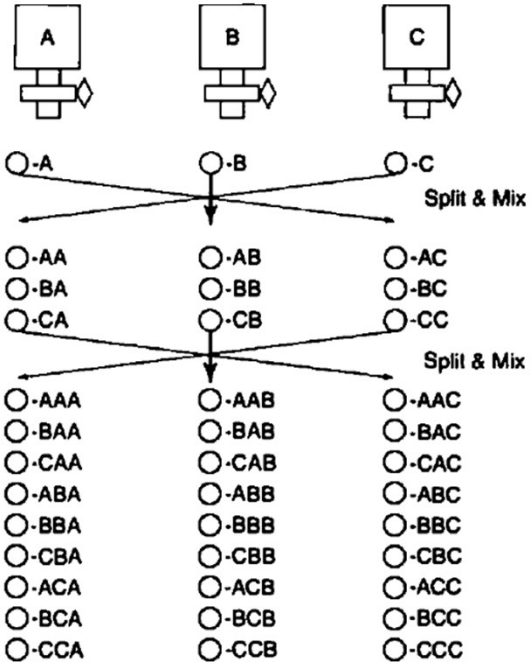
Pooling Strategies

5. <u>Orthogonal pooling</u>



Pooling Strategies

6. ***Positional scanning***



Problems with mixtures

× Complex mixtures with only one or a few active structures can have solubility problems

× The inactive compounds contribute to the total ionic concentration but not to the activity

× Compounds that have a common scaffold will have many active species (false positive)

× Partial binding of inactive structures can sometimes prevent an active structure from showing full activity (false negative)