Combinatorial Chemistry

Drug discovery process

	Target Discovery	Target Validation	Lead Compound Identification	Lead Compound Optimization	Preclinical Development	Clinical Trials
Average Length	1-3 years				1.5 years	6-7 years
Average Cost	$196 million				$122 million	$1-2.5 billion*
Goal(s)	Identification of a molecule involved in a disease ▸ Identify the target: a molecule integral to gene regulation or intracellular signaling ▸ Ensure the target is "druggable" and its activity can be modulated by another compound	▸ Validate initial hypothesis through gene knockdowns ▸ Test antibody interactions ▸ Modulate the drug's affinity to target by changing molecular structure	Generation of molecule(s) that can interact with the target previously identified ▸ Test drug mechanism of action ▸ Initial safety tests conducted in cell culture ▸ Test pharmacokinetics and pharmacodynamics	Compound modifications for increased effectiveness and safety ▸ Alter design of molecule to prevent off-target effects ▸ Optimize dosage and introduction route (oral, injection) ▸ Conduct tests for drug's uptake by 3D cell culture systems	Drug testing *in vivo* for side effects and safety ▸ Test drug in alternate cell lines, and *in vivo*: most commonly mouse and rat research models ▸ Plan for either small- or large-scale production if approved ▸ Document and mediate side effects	New drug approval by the FDA or EMA ▸ File IND to begin trials ▸ Includes three phases of human testing ▸ FDA conducts reviews and approvals after phase III ▸ Continued monitoring for dosage and safety

* This amount is highly dependent on spending associated with drugs that end up failing at some point in the trials

https://www.taconic.com/taconic-insights/quality/drug-development-process.html

Drug discovery process

- Lead compound: A lead compound is a representative of a compound series with sufficient potential to progress to a full drug development programme
- Lead discovery: Lead discovery is the process of identifying active new chemical entities (NCEs), which by subsequent modification may be transformed into a clinically useful drug.
- Lead optimization: The synthetic modification of a biologically active compound, to fulfil all stereoelectronic, physicochemical, pharmacokinetic and toxicological properties required for clinical usefulness.

What is Combinatorial Chemistry?

- Combinatorial Chemistry is a synthetic strategy which, utilising different techniques, aims at the rapid synthesis of large collections (libraries) of compounds

- The goal of the combinatorial chemistry is to synthesize, purify, chemically analyze & biologically test the all the structures in the library using few synthetic experiments

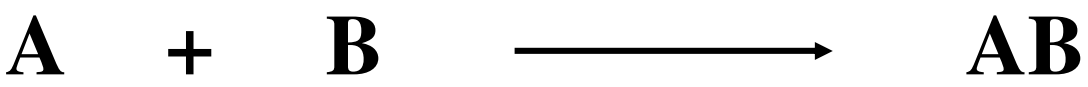
Basic characteristics of Combichem:

Combinatorial Chemistry prepares

- **a large number of different compounds**
- **simultaneously**
- **under identical reaction**
- **in a systematic manner**

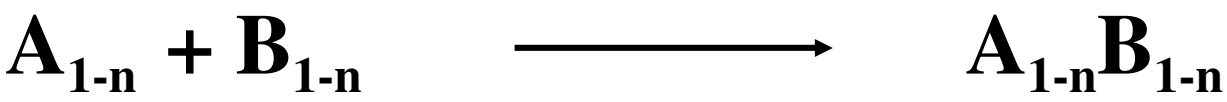
Conventional Vs combinatorial

Conventional Synthesis:



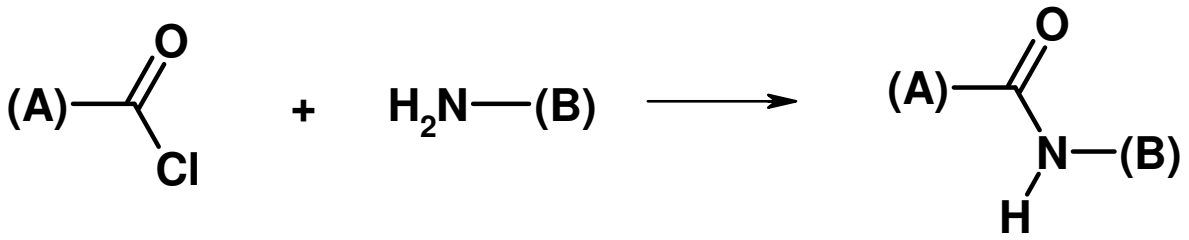
one reactant (A) reacts with another reactant (B) to yield one product AB

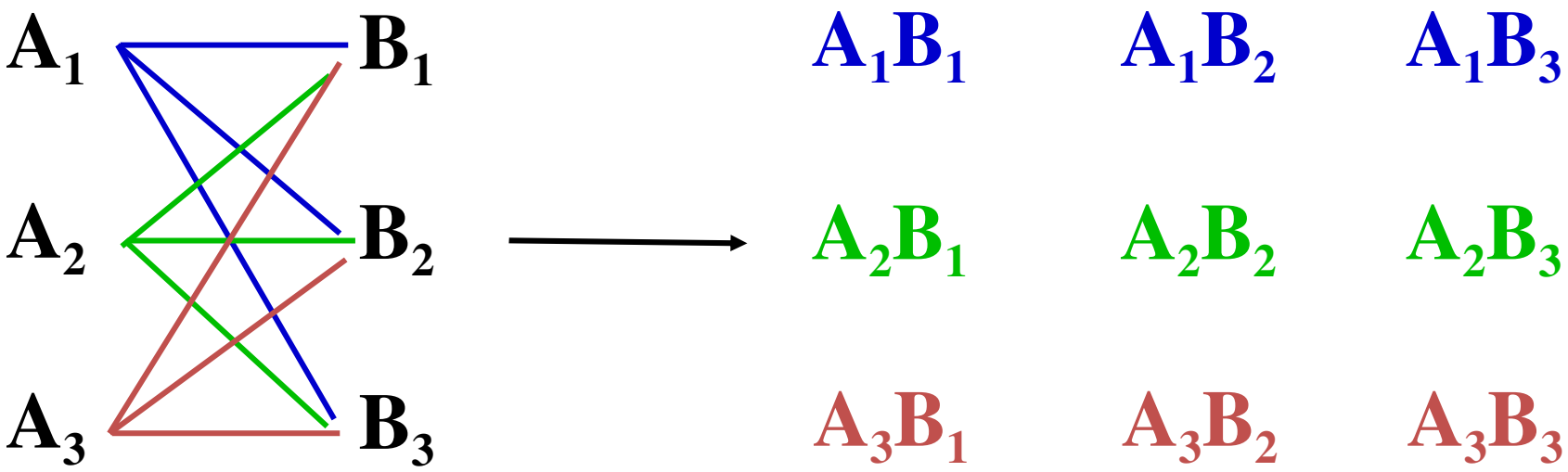
Combinatorial Synthesis:



Different building blocks of type A react combinatorially with different building blocks of type B to yield a combinatorial library

Combinatorial Synthesis:





Why Combinatorial Chemistry?

- large numbers of compounds promise to increase the chance of finding hits/leads
- Faster lead generation
- Low risk of failure
- systematic variations in parent structure increase the chance to find Structure-Activity Relationships (SAR)
- hits can be followed up more rapidly

Combinatorial Libraries:

- **Library refers to a collection of molecules.**
- **Two common types of chemical libraries-**

1) A generic library (scaffold based):-

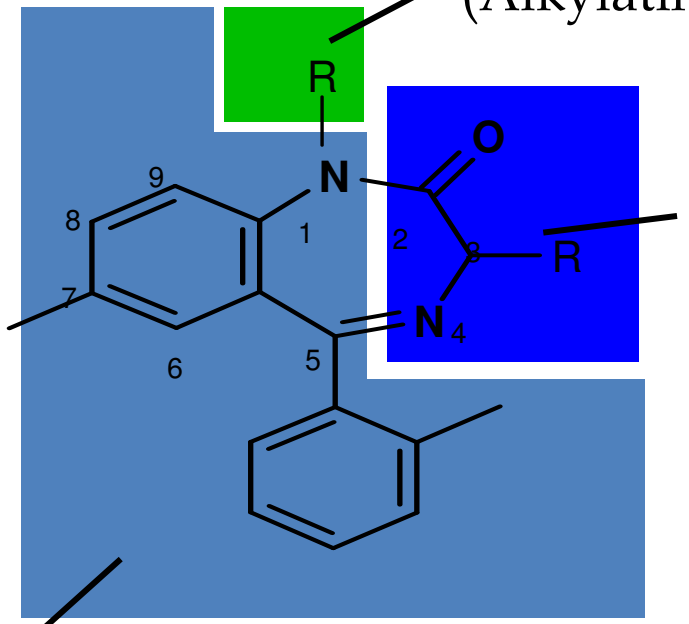
-based on a single parent or scaffold sructure & multiple substituents or residues

2) A mixture based (Backbone-based) libraries :-

-Containg a variety of structure types

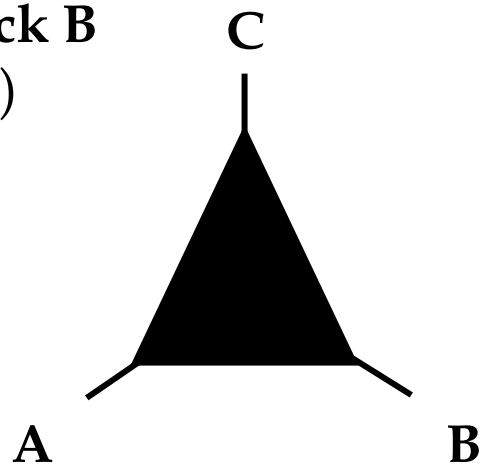
Scaffold-based libraries:

(Example: benzodiazepines)



Building block C
(Alkylating agents)

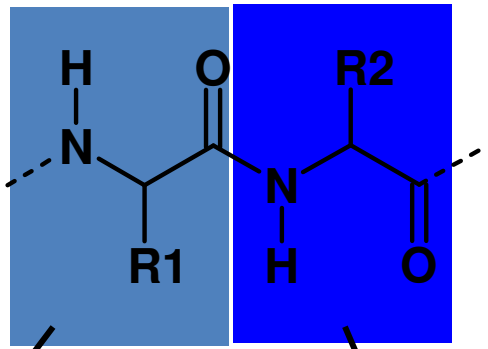
Building block B
(Amino acids)



Building block A
(2-Aminobenzophenones)

Backbone-based (mixture) libraries:

(Example: peptides)



Building block A
(Amino acid)

Building block B
(Amino acid)

A — B

LIBRARY SYNTHESIS

Two Major Approaches

- **Split & Mix**

  "Real Combinatorial Chemistry"

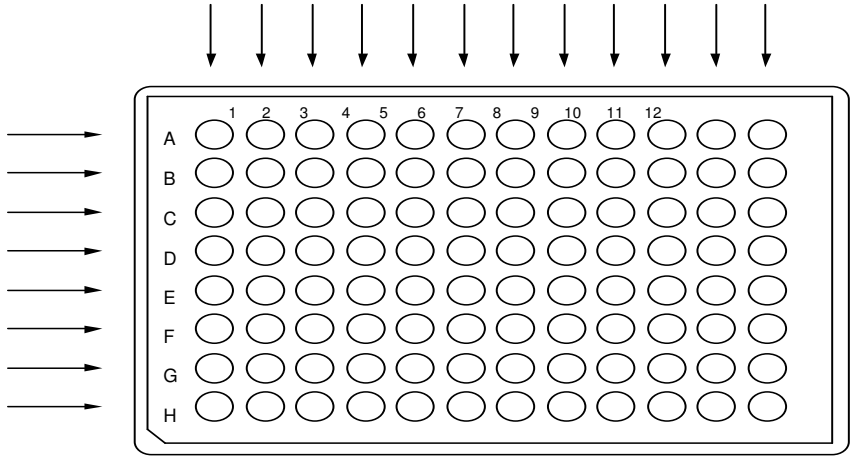
- **Array Synthesis**

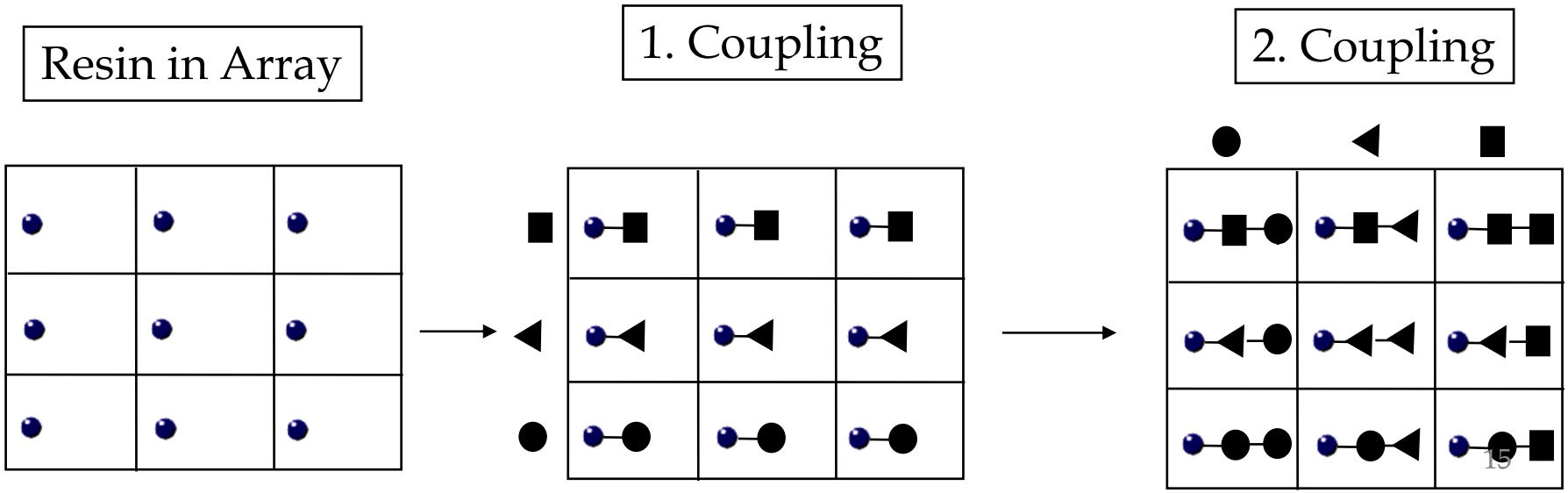
  "Parallel Synthesis'

Array-based Synthesis Stratergy:

Parallel synthesis

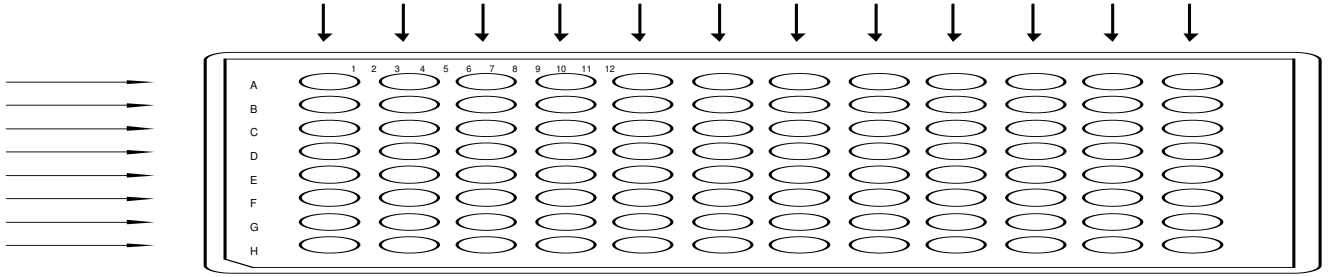
- Use array of plastic pins
- (8 x 12 array) →20 reagents →within 1 or 2 reactions →gives 96 different products.

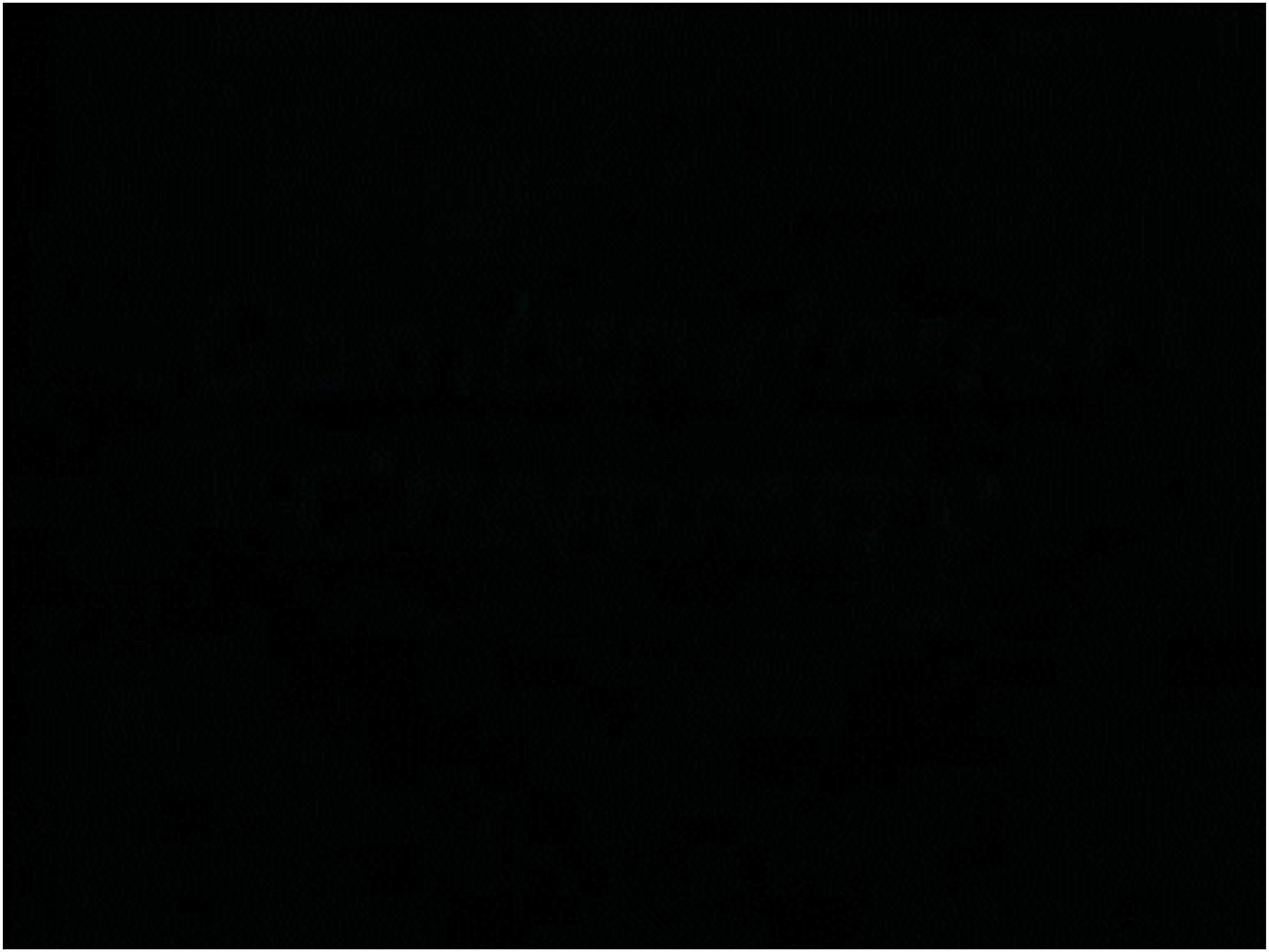




parallel synthesis

- Synthesis is carried out on polystyrene pins(act as solid-phase support)
- Pins are compatible with 96 well micro titer plates.
- Each individual well could contain a different amino acid and coupling reagent.
- Syntheses on pins are **carried out in parallel** (by immersing these pins into individual reaction vessel)
- Washing & protecting group removal can be performed in a reaction bath
- **Adv :-** Useful for epitope mapping and overlapping peptide sequences.



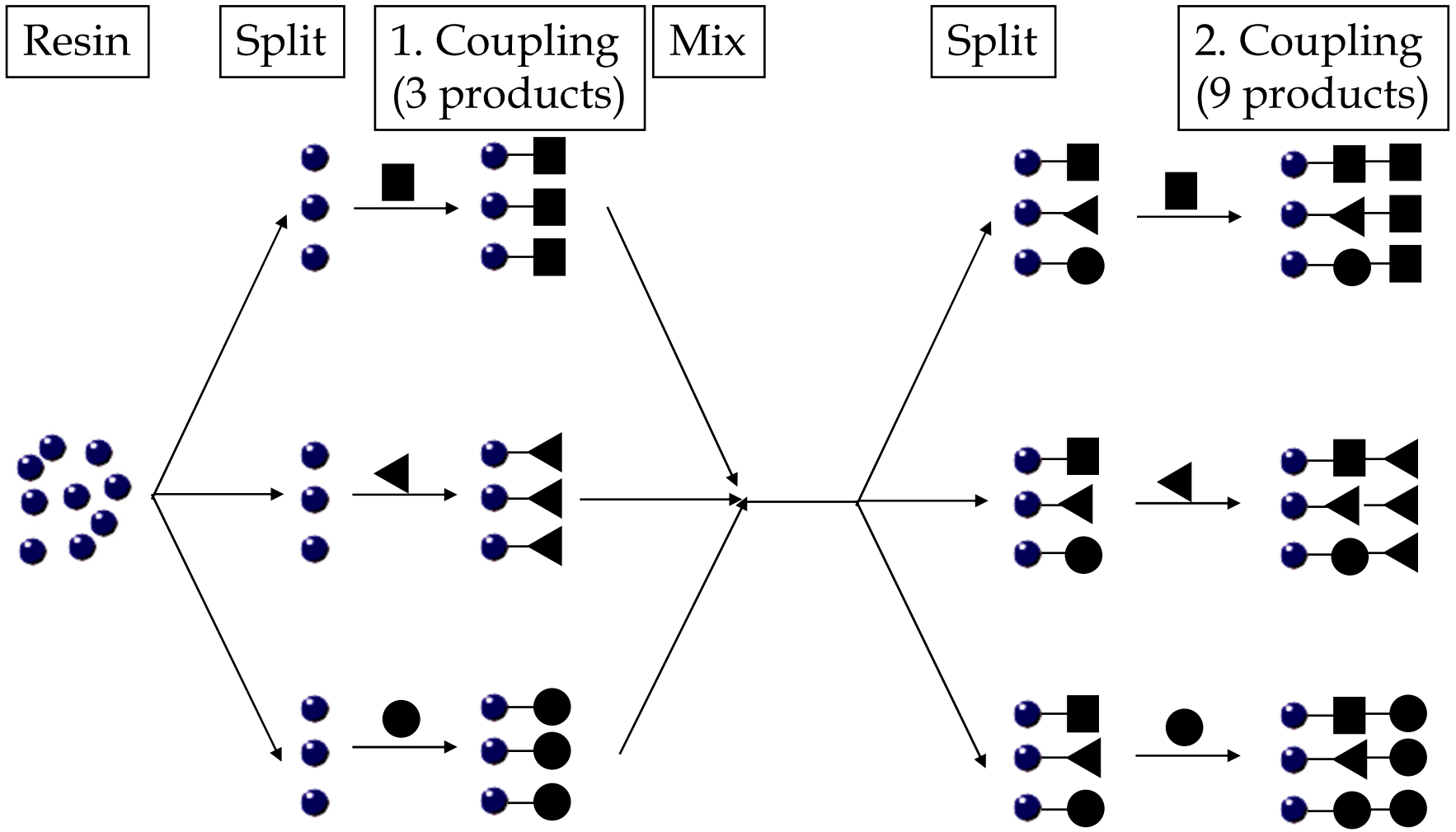


Houghton's Tea Bag procedure

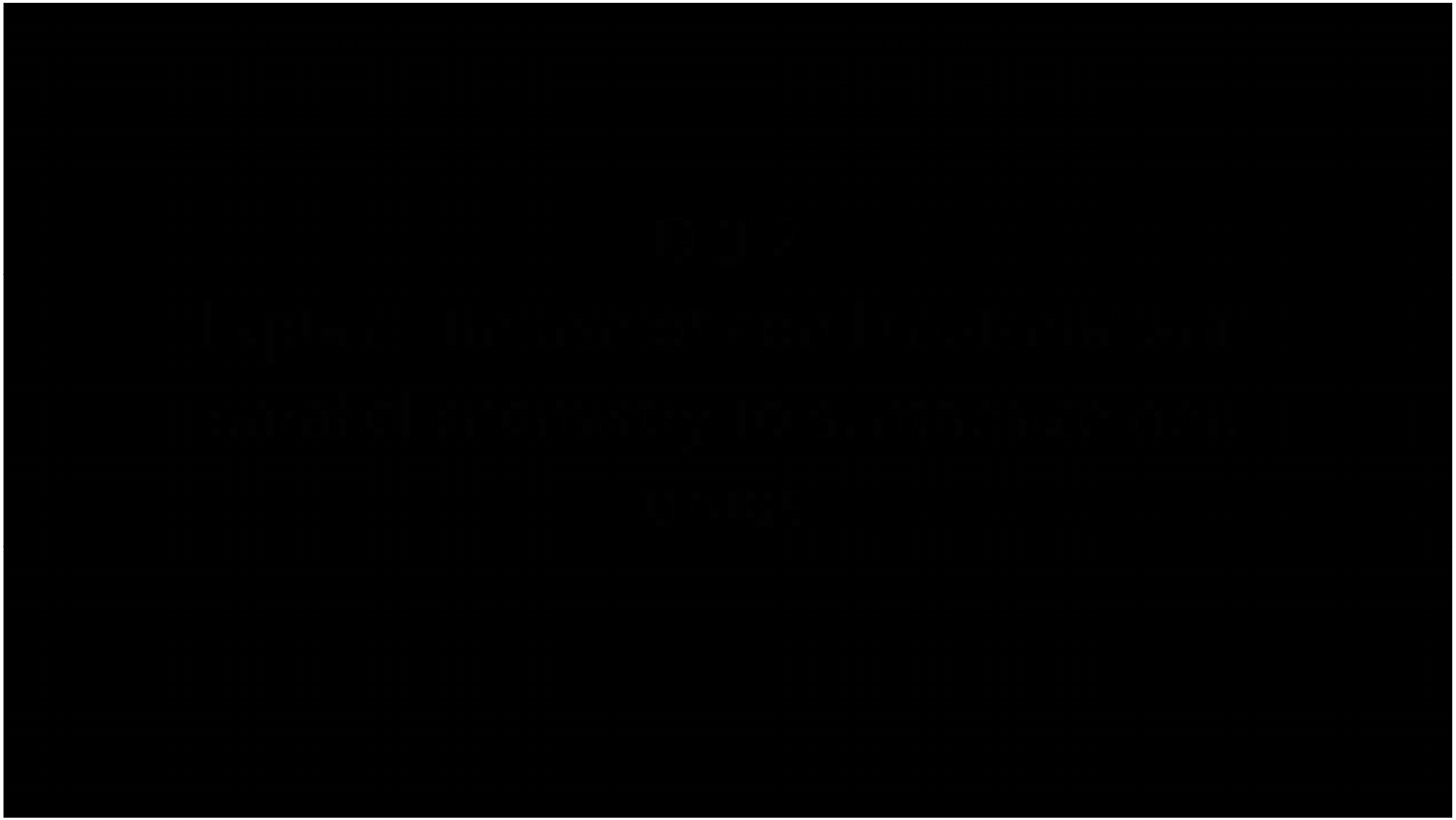
Alternative approach to parallel synthesis.

- Initially, the resin (~100 mg) is distributed into individual polypropylene meshed bags & each bag is sealed & labeled
- The tea bag are then distributed in to individual reaction vessel & resin is acylated with special Amino acid .
- The tea bag can then redistributed into fresh reaction vessel for the addition of next amino acid
- The cycle repeated until the desire peptide length is achieved

The Split-mix Synthesis Strategy:



The Split-mix Synthesis Strategy



The Split-mix Synthesis Strategy:

➢A more rigorous approach to generating libraries.

Resin is split into n equal portions.

• To create library with 3 possible amino acids at a position, split resin into 3 equal portions.

• Each aliquot of resin is coupled separately with 1 of the 3 different amino acids.

•Aliquots are then recombined after coupling reaction.

•Resin is split again into 3 equal aliquots. Each aliquot containing an equimolar mixture of the 3 different amino-acyl resins.

• A second round of coupling reactions similar to the first.

• The process can be repeated until the peptides in the library have reached the desired size.