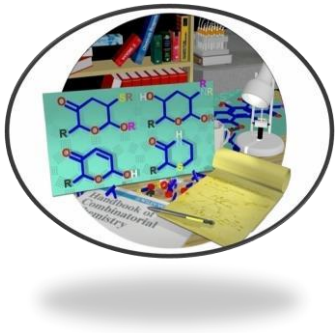
Lec7: Combinatorial Chemistry:
Introduction



Introduction:

- Combinatorial Chemistry is a new method developed by academics and researchers to reduce the time and cost of producing effective, marketable and competitive new drugs.

Introduction:

•Scientists use Combinatorial Chemistry to create large numbers of molecules that can be detected efficiently.

Introduction:

- This technique has captured the attention of many areas such as Pharmaceutical chemistry, Biotechnology and Agrochemistry.

Definition:

- Combinatorial chemistry is a technique by which large numbers of different but structurally similar molecules are produced rapidly and submitted for pharmacological assay.

Definition:

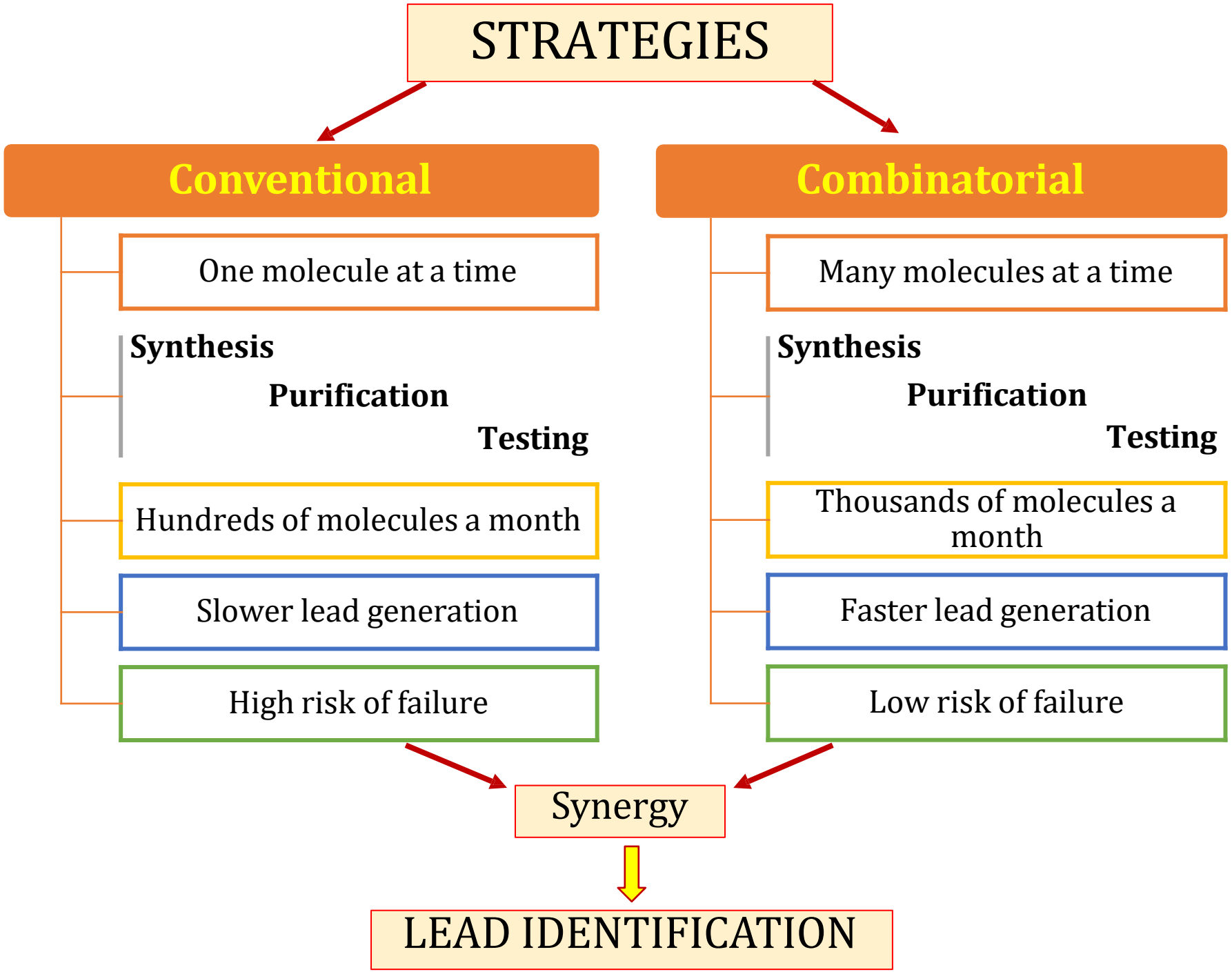
- This technique uses the same reaction conditions with the same reaction vessels to produce a large range of analogues.
- Technique invented in the late 1980s and early 1990s to enable tasks to be applied to many molecules simultaneously

Example:

- For instance, let's assume that we have two alcohols named **A** and **B**. These alcohols are utilized to form esters by the reaction with three carboxylic acids named **A, B,** and **C**.
- So, the expected products would be (**2*****3** = **6**) as follows:

1. ***A - A***
2. ***A - B***
3. ***A - C***
4. ***B - A***
5. ***B - B***
6. ***B - C***

- ***What if you have 5 alcohols and 6 carboxylic acids?***


STRATEGIES
Conventional
One molecule at a time
Synthesis
Purification
Testing
Hundreds of molecules a month
Slower lead generation
High risk of failure
Combinatorial
Many molecules at a time
Synthesis
Purification
Testing
Thousands of molecules a month
Faster lead generation
Low risk of failure
Synergy
LEAD IDENTIFICATION

Applications:

1. Applications of combinatorial chemistry are very wide. Scientists use combinatorial chemistry to create large populations of molecules that can be screened efficiently.

Applications:

2. By producing larger, more diverse compound libraries, companies increase the probability that they will find novel compounds of significant therapeutic and commercial value.

Applications:

3. Provides a stimulus for robot-controlled and immobilization strategies that allow high-throughput and multiple parallel approaches to drug discovery

Advantages:

A. Fast:

Combinatorial approach can give rise to million of compound in same time as it will take to produce one compound by traditional method of synthesis .

Advantages:

B. Economical:

A negative result of mixture saves the effort of synthesis, purification & identification of each compound

Advantages:

C. Easy:

Isolation purification & identification of active molecule from combinatorial library is relatively easy.

Advantages:

D. Drug Discovery:

Mixed Combinatorial synthesis produces chemical pool. Probability of finding a molecule in a random screening process is *proportional* to the number of molecules subjected to the screening process.

Advantages:

E. Drug Optimization:

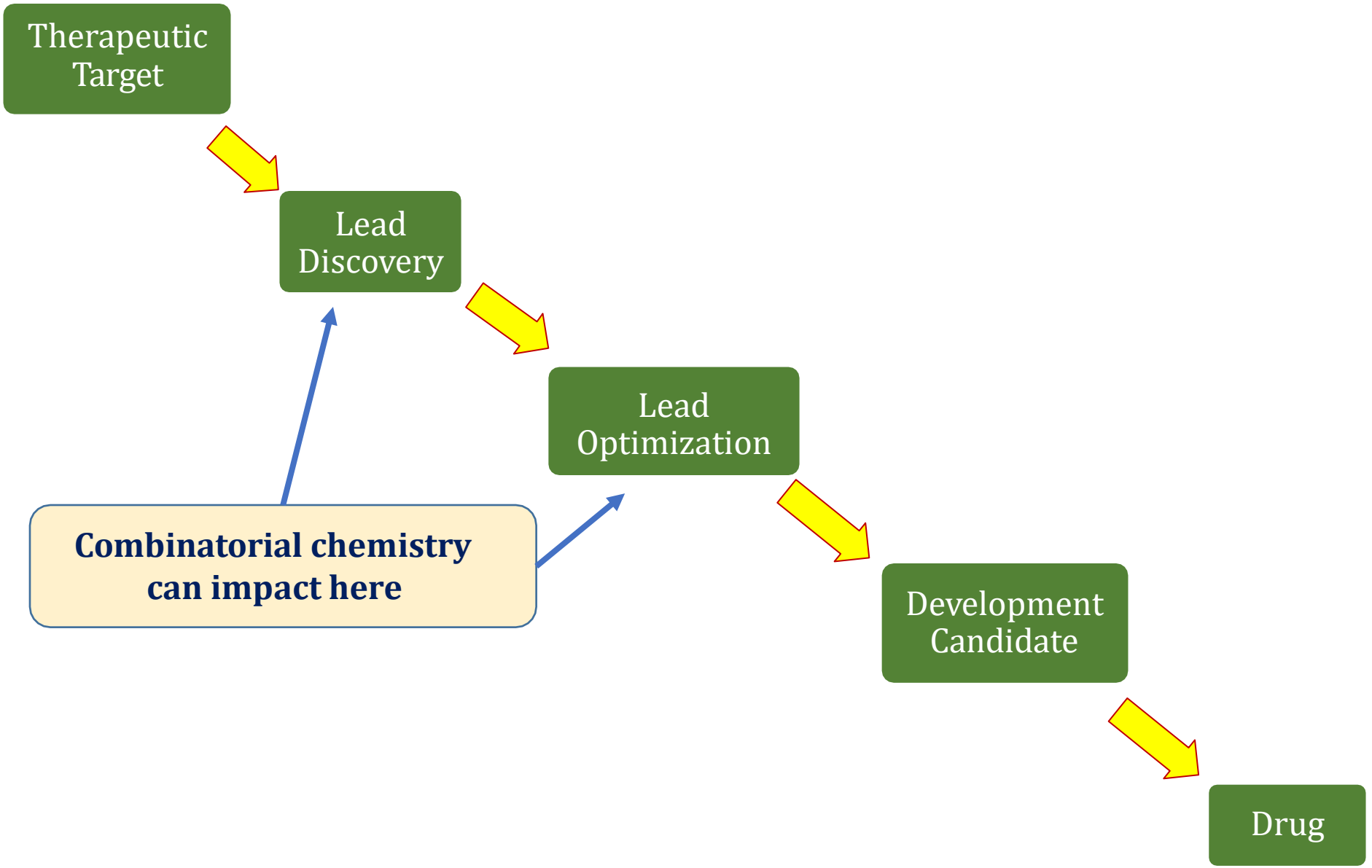
Parallel synthesis produces analogues with slight differences which is required for lead optimization

Disadvantages:

1. Efficiency is highly affected by compound's size, solubility and function group.

2. Compounds produced tend to be Achiral of Racemic.

Combinatorial Chemistry within drug design



Combinatorial Chemistry within drug design

Impact at lead discovery:

A. Traditionally lead drugs were found from:

i. Natural products.
ii. Synthetic custom crafted organic molecules made in small numbers.
iii. Analogues of known actives (analogue me-toos)

Me-too *drug: A drug that is structurally very similar to already known drugs, with only minor differences.*

Combinatorial Chemistry within drug design

B. High Throughput screening (HTS) requires large numbers of compounds to fuel the discovery process

C. As an alternative to traditional synthesis many compounds rapidly constructed was needed.

References:

- Wilson and Gisvold Textbook of Organic Medicinal and Pharmaceutical Chemistry; Delgado JN, Remers WA, (Eds.); 12th ed., 2011.

- An introduction to Medicinal chemistry,3rd edition, Graham L.Patric