SYNTHESIS IN DRUG DESIGN

LEAD DISCOVERY

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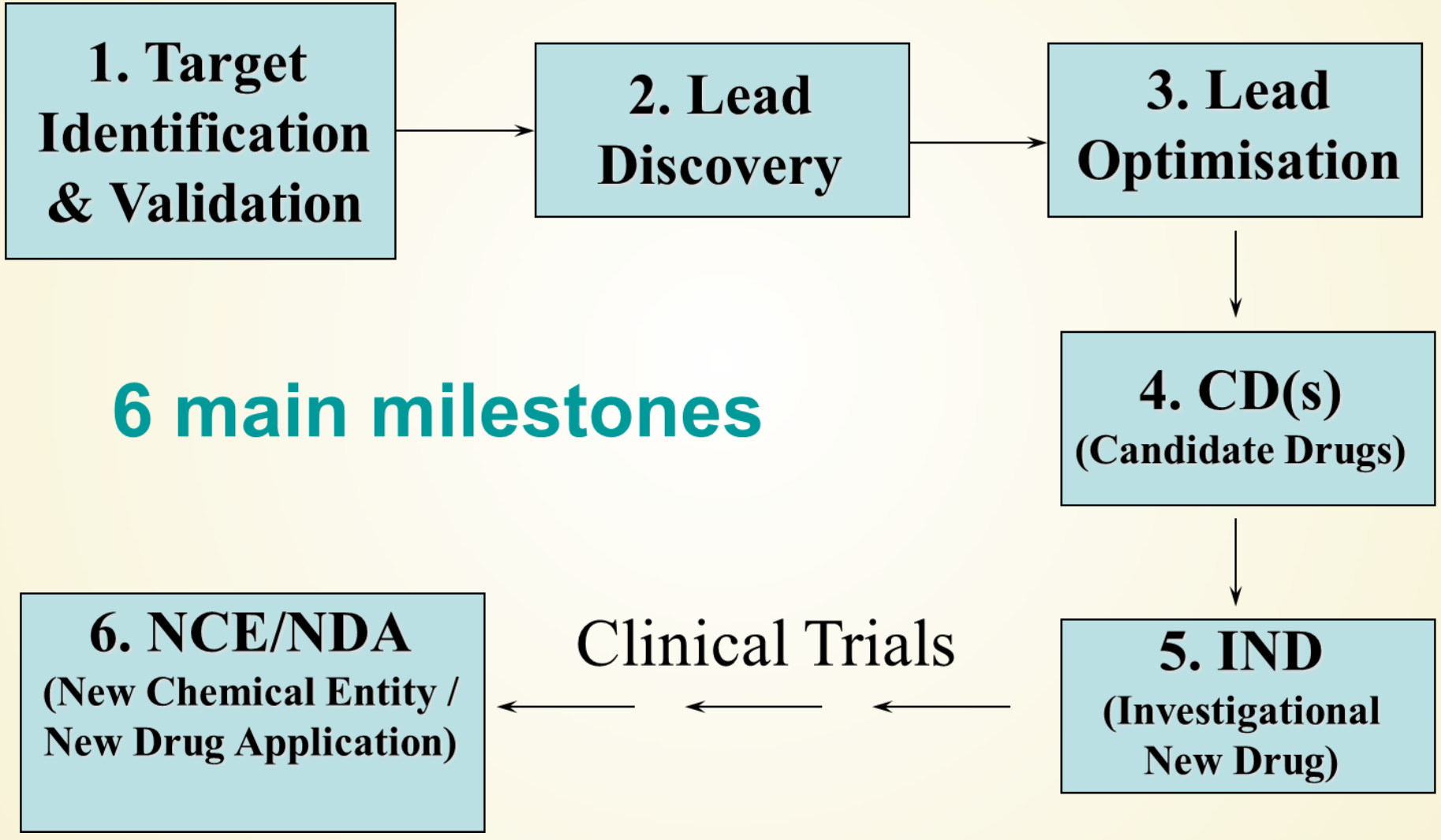
Drug Design - Course Hub

NEW DRUG DEVELOPMENT



6 main milestones

LEAD DISCOVERY

High throughput screening against a validated target is a common way to find a lead compound

- need a large ***'library'*** of compounds to screen (eg. millions of compounds!)
- libraries can be derived from various sources (purchased or in-house):
  - *natural products* - eg. NatureBank
  - *combinatorial chemistry* (CombiChem)
  - *parallel synthesis*

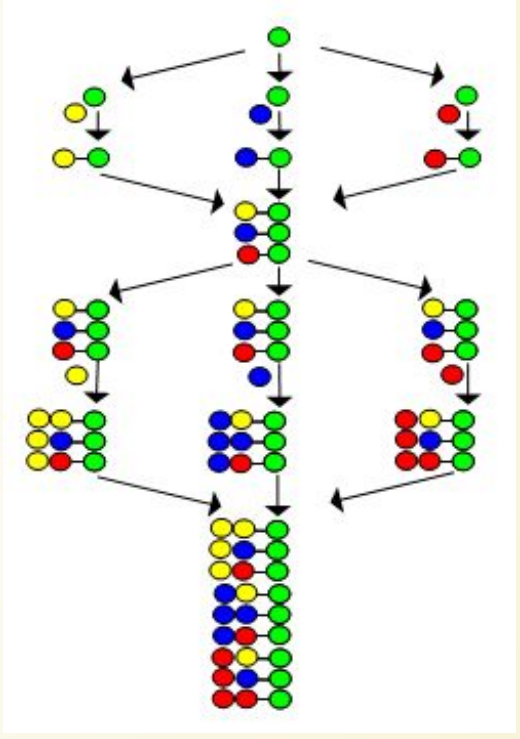
COMPOUNDS AUSTRALIA

Compounds Australia is Australia's only dedicated compound management facility. It brings together chemists (who have molecules) with biologists (who have targets).

- Libraries:
  - *Open Academic collection:* >19,500 pure compounds
  - *Open Scaffolds collection:* >33,000 pure compounds
  - *Open Drugs collection:* >2,500 FDA-approved drugs

COMBINATORIAL CHEMISTRY

CombiChem uses synthetic techniques to make large numbers (up to millions) of molecules quickly. Often the compounds are generated, and even tested, as mixtures, requiring ***deconvolution*** to identify the active component(s).



COMBINATORIAL CHEMISTRY - SOLID-PHASE SYNTHESIS

- History of solid-phase synthesis:
  - **1963** - Merrifield published first 'solid-phase' synthesis technique - peptides.
  - **1984** - Nobel prize in Chemistry
  - **Today** - Solid-phase peptide synthesis (SPPS) is standard method up to 70 amino acids

MERRIFIELD SPPS

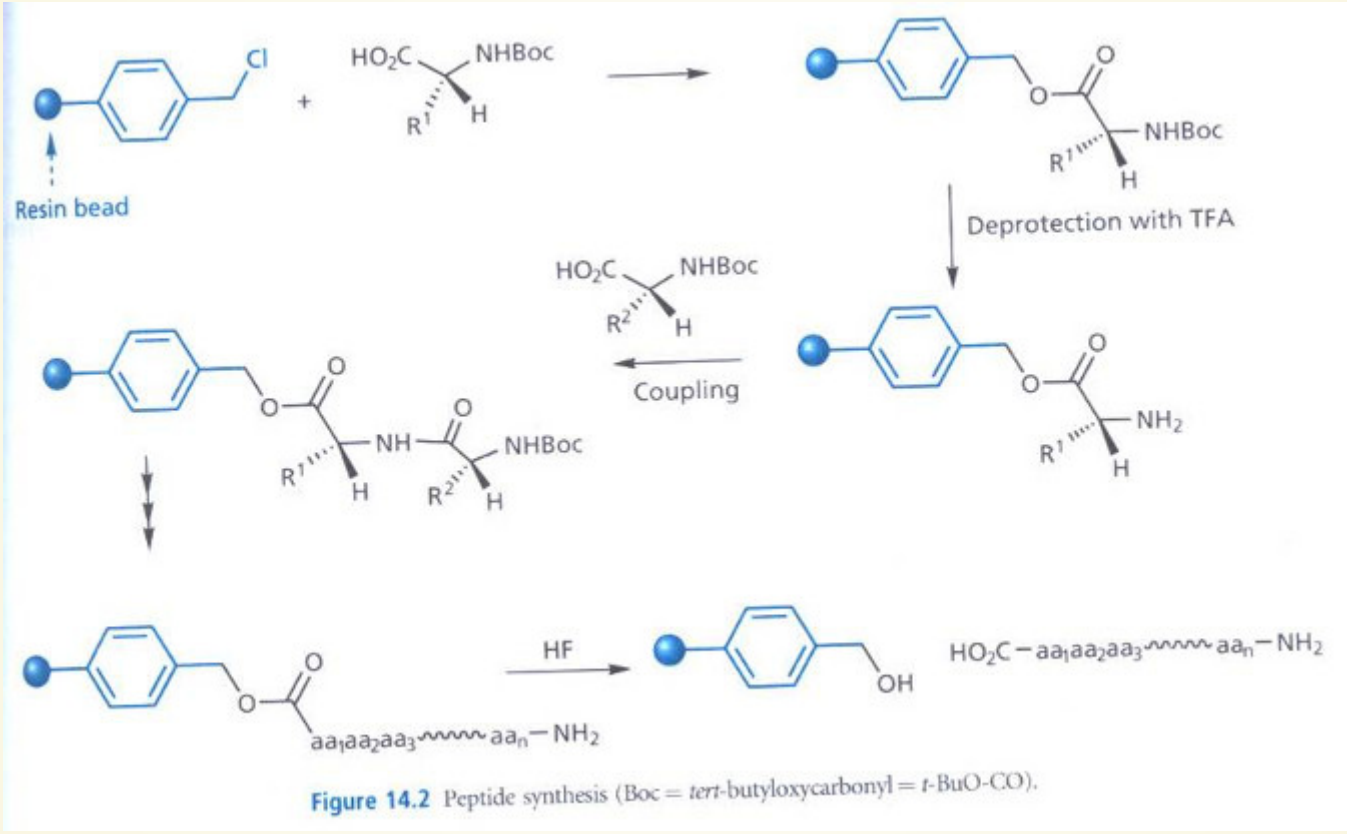


Figure 14.2 Peptide synthesis (Boc = *tert*-butyloxycarbonyl = *t*-BuO-CO).

Image from "An Introduction to Medicinal Chemistry" by Graham L. Patrick

POLYMER RESIN SWELLS IN ORGANIC SOLVENT

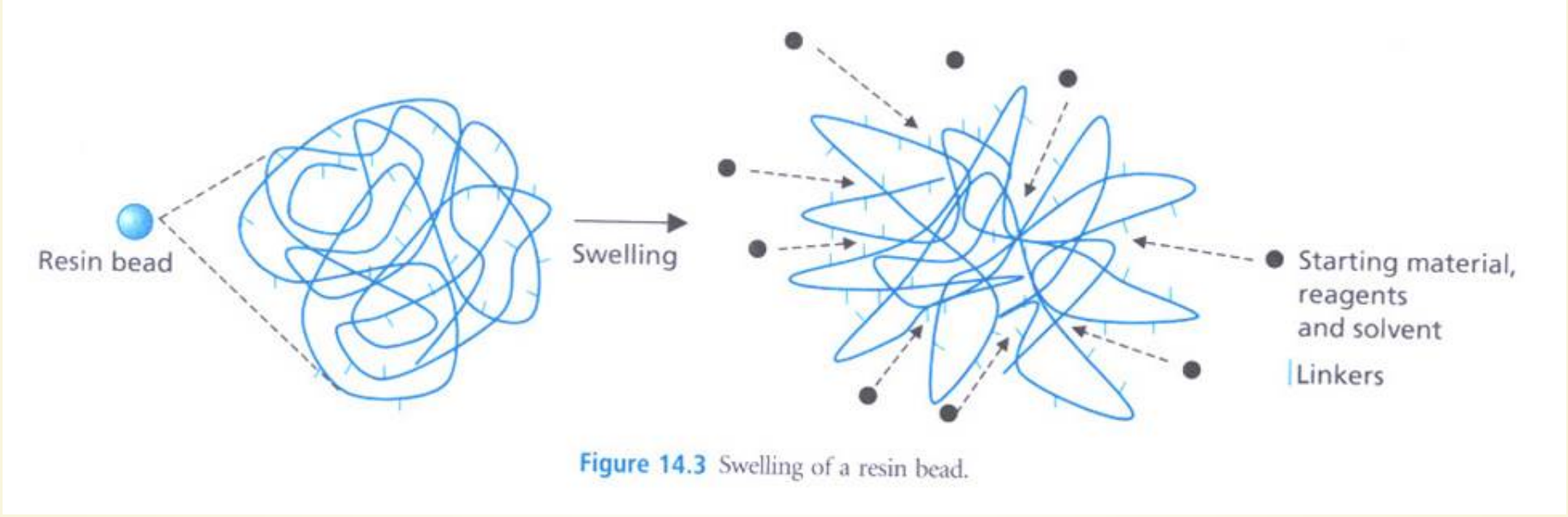


Figure 14.3 Swelling of a resin bead.

Image from "An Introduction to Medicinal Chemistry" by Graham L. Patrick

SPS COMBICHEM STRATEGY

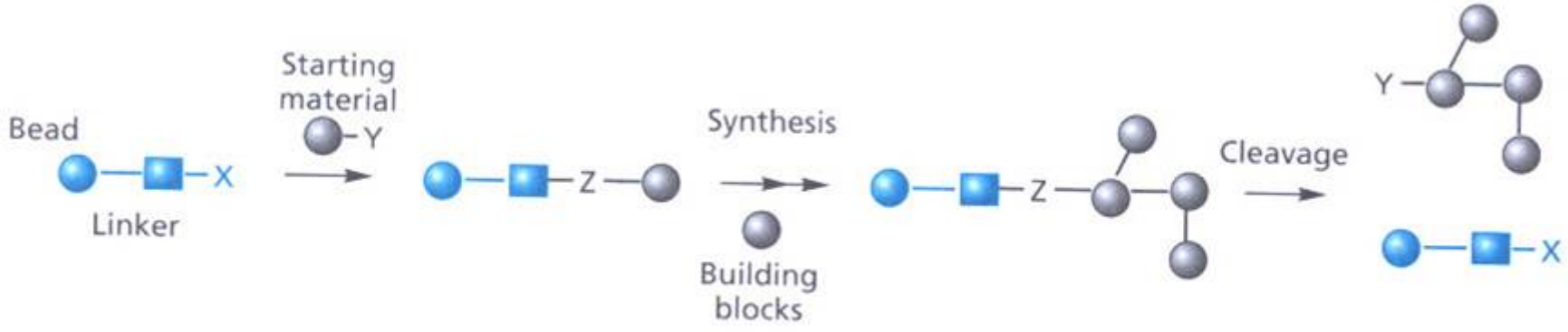
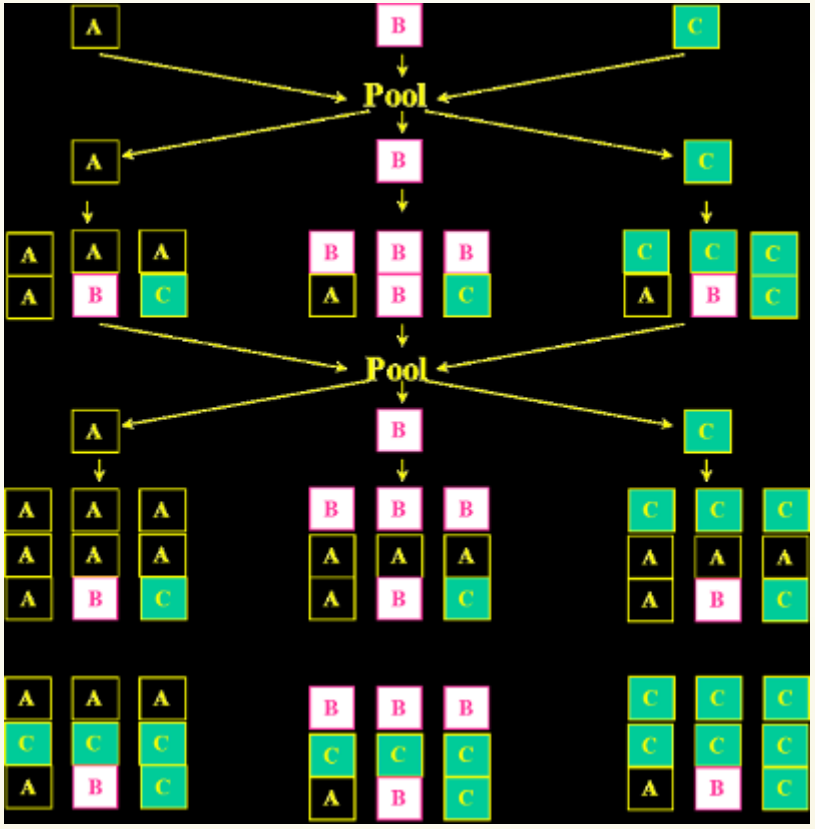


Figure 14.4 Anchor/linker. X, Y, Z are functional groups.

Image from "An Introduction to Medicinal Chemistry" by Graham L. Patrick

SPLIT AND POOL COMBICHEM STRATEGY



SCREENING METHODS

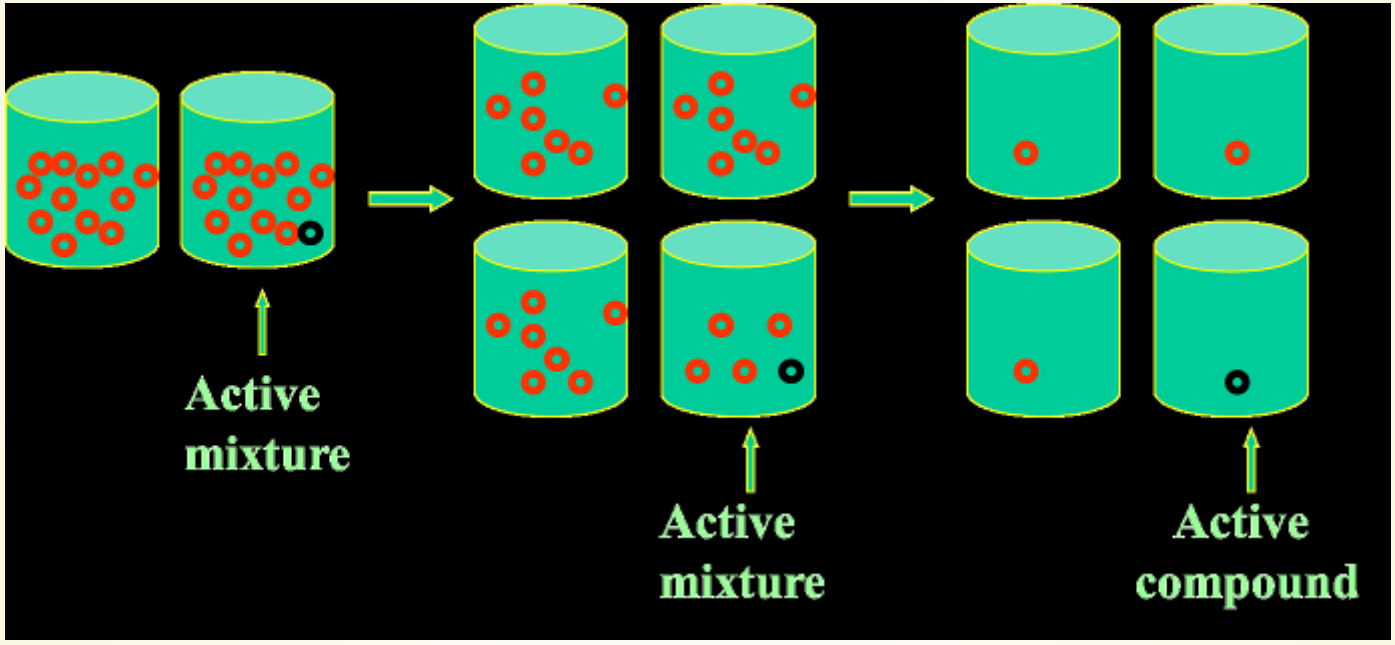
'**on-bead**': screen resin-bound products ; *or*

'**off-bead**': release products from resin, then screen in solution

HOW TO DETERMINE STRUCTURE OF ACTIVE(S) IN MIXTURE?

- **direct structure determination** - eg. peptide sequencing
  - a 100-μm bead contains ~ 100 pmole of peptide
- **tagging** - at each step the bead is modified with a unique molecular tag
- **deconvolution** - successively narrow down candidate structures

DECONVOLUTION



“Combinatorial Chemistry” N.K. Terrett, Oxford University Press, New York, 1998

WHY AREN'T WE SWIMMING IN DRUGS?

In the 1990's, the pharmaceutical industry was awash with optimism about the impact of CombiChem on the discovery of new drugs

- access to large compound numbers became easily achievable
- *however*, high hopes for CombiChem were attenuated by a lacklustre flow through to new drugs

WHY?

QUESTION:

HOW MANY SMALL, ORGANIC MOLECULES ARE POSSIBLE?

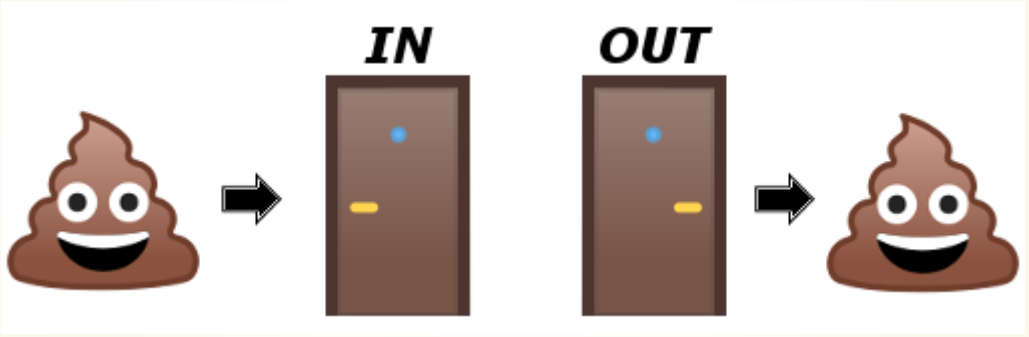
(C, H, N, O, S; $M_W < 500$)

ESTIMATE:

10^{60}!!!

NOTE: THERE ARE ESTIMATED TO BE 10^{78} TO 10^{82} ATOMS IN THE KNOWN, OBSERVABLE UNIVERSE!

The art and practice of structure-based drug design: A molecular modeling perspective. Bohacek, R. S.; McMartin, C.; Guida, W. C. *Med. Res. Rev.* **1996**, *16*, 3-50.

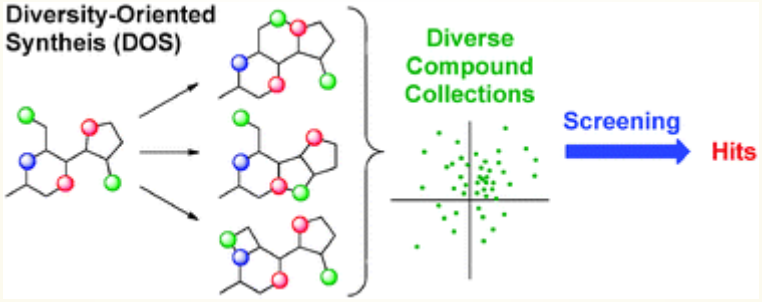

IN
OUT

INTELLIGENT LIBRARY DESIGN

- compounds that are easy to make aren't necessarily good drug leads
- without careful design, CombiChem libraries can lack chemical diversity
  - ie. large number of highly similar compounds
- efforts to intelligently design screening libraries include '**Diversity-oriented synthesis**' (DOS)

DIVERSITY-ORIENTED SYNTHESIS

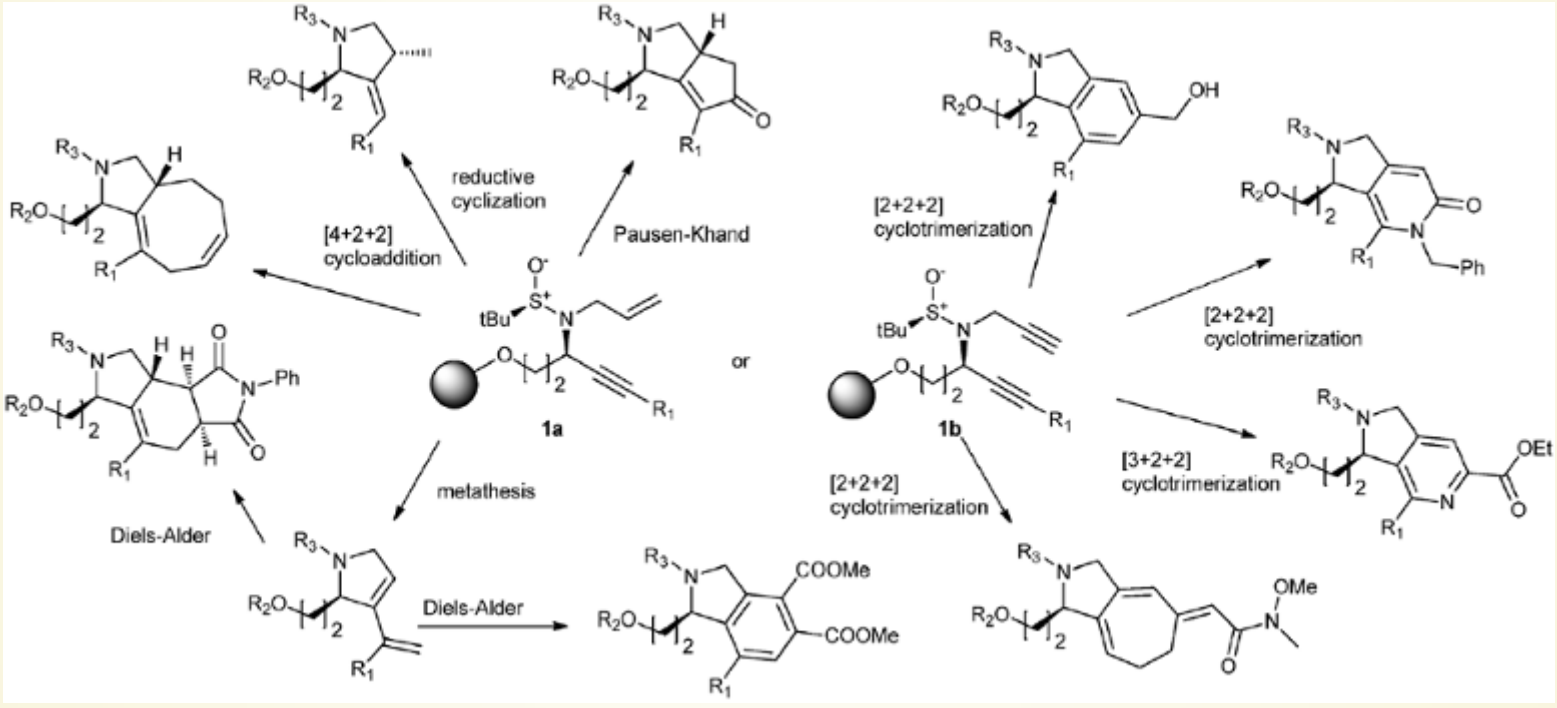
- aims to generate structural diversity efficiently



Chem. Soc. Rev., **2012**, *41*, 4444-4456.

DOS EXAMPLE

- diverse chemical structures from two simple starting materials



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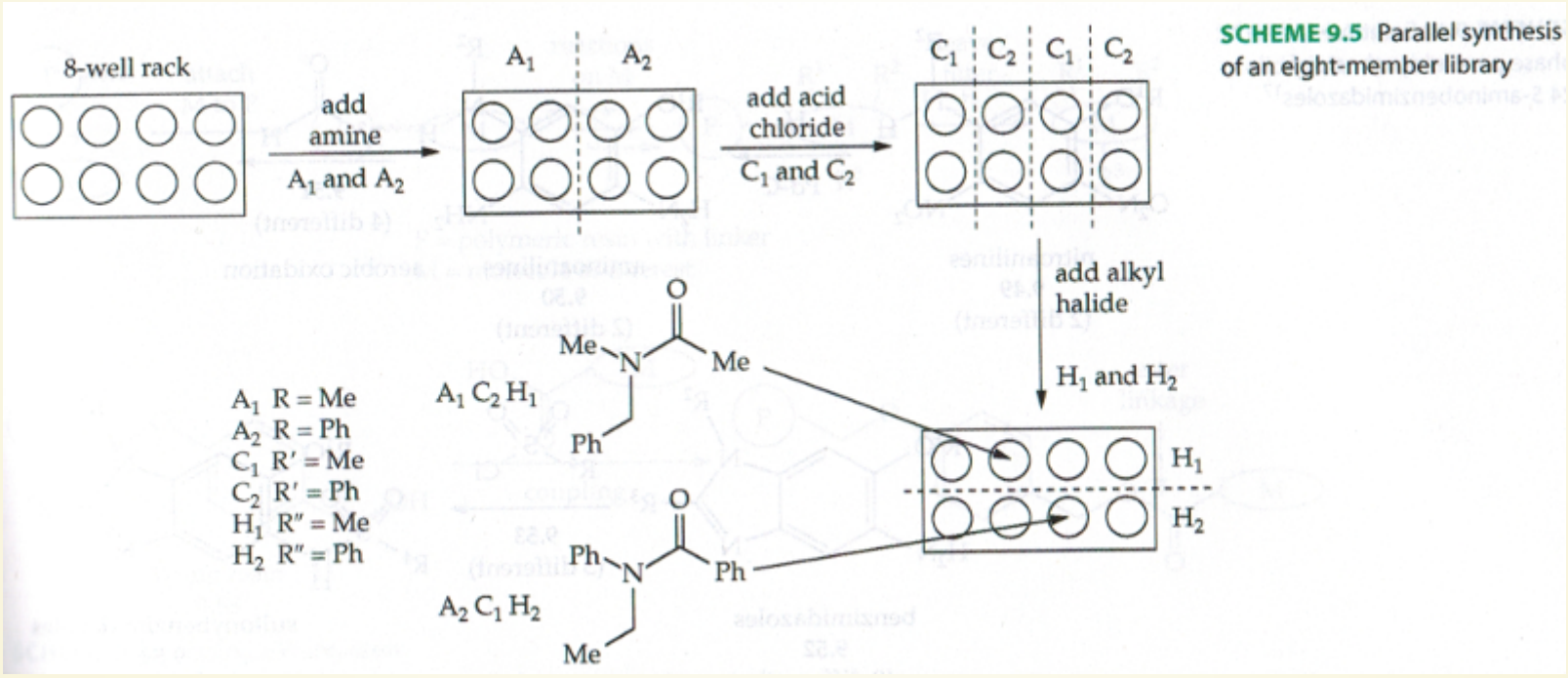
PARALLEL SYNTHESIS

- series of reactions are carried out in series of wells - *analogues*
- each well contains **one** product



SCHEME 9.5 Parallel synthesis of an eight-member library

PARALLEL SYNTHESIS

- can be done in solution or on solid phase
- technical innovations speed up synthesis
  - microwave vs. conventional heating
  - reaction 'carousels'

PARALLEL VS COMBICHEM SPLIT-POOL

Split-Pool	Parallel
large # molecules	moderate # molecules
picomole quantities	mmol easily achieved
deconvolution of mixtures	immediate SAR data
synergism/antagonism in screening mixtures	single compound per well

SUMMARY:

Synthetic libraries can be formed through combinatorial chemistry or parallel synthesis techniques.

- Advantages and disadvantages of each
- **Intelligent design** of compound libraries essential
  - ensure that library members are drug-like (or 'lead-like')
  - aim for high diversity