Combinatorial Diversity in Nature

20 natural amino acids yield

400 dipeptides

8,000 tripeptides ...

64,000,000 hexapeptides and, in principle,

$10^{400}$ proteins with MW $\approx 30$ kD

100 chemically modified amino acids yield

e.g. $1,000,000,000,000,000$ hexapeptides,

and ... 4 nucleic bases encode all organisms!
Number of organic molecules with MW < 500 (C, H, O, N, P, S, F, Cl, Br, I)

1 000 000 000 000 000 000 000 000 000 000 000
000 000 000 000 000 000 000 000 000 000 000
000 000 000 000 000 000 000 000 000 000 000
000 000 000 000 000 000 000 000 000 000 000

or more or less ....

Principles of Combinatorial Chemistry

Combinatorial Chemistry generates a multitude of chemically related ("congeneric") compounds, so-called "combinatorial libraries"

In the last years, combinatorial chemistry in drug research changed more and more to automated parallel synthesis and parallel purification.
Classical organic synthesis:

\[
\text{NH}_2 \text{CH}_3 + \text{COOMe} = \text{NH}_2 \text{CH}_3 \text{OMe}
\]

1 educt \(\times\) 1 educt = 1 product

Combinatorial synthesis:

\[
\text{R}_1 \text{NH}_2 + \text{ClR}_2 = \text{N} \text{R}_1 \text{R}_2
\]

e.g. 50 educts \(\times\) 20 educts = 1,000 products

Multistep combinatorial synthesis:

e.g. 50 \(\times\) 20 \(\times\) 20 educts = 20,000 products

Multicomponent reaction (e.g. Ugi reaction):

\[
\text{R}_1\text{NH}_2 + \text{R}_2\text{CHO} + \text{R}_3\text{NC} + \text{R}_4\text{COOH} = \text{R}_4\text{N} \text{N} \text{R}_1 \text{R}_2 \text{H} \text{R}_3
\]

e.g. 50 \(\times\) 20 \(\times\) 5 \(\times\) 200 educts = 1 million products

Combinatorial Library

Building blocks with 68 different residues in 10 positions (\(R_1\) - \(R_{10}\) are 5, 10, 10, 4, 2, 5, 5, 2, 5, and 20 residues) generate a library of 20 million different compounds. Consideration of both steric centers (*) increases this number by a factor of four, i.e. to 80 million different compounds.
Solid Phase Synthesis: Beads

Cross-linked polystyrene
(0.1-1.5% divinylbenzene)

Functionalization of the beads by chloromethylation and further chemical reactions

Tentagel Beads (Polystyrene, Grafted with Polyoxyethylene), Rapp Polymers, Tübingen, Germany
The Principle of Solid Phase Synthesis

- bead (40-80 µm) and linker
- scaffold with functional groups
- three-step synthesis
- immobilization
- cleavage
- immobilized product
- product

The Combination of Scaffolds and Building Blocks

- 3 building blocks A₁-A₃
- 3 building blocks B₁-B₃
- yield 9 products A₁B₁ – A₃B₃.

In the same manner, 10 x 10 x 10 building blocks yield 1,000 products A₁B₁C₁ – A₁₀B₁₀C₁₀.
"Split and Combine" Method for Library Synthesis

3 Mixtures with 9 different compounds in each reaction vessel
Linkers: Merrifield and Wang linkers

1. Merrifield resin
   - Cl
   - \( \text{OH} \)

2. Wang resin ("Wang linker")
   - \( \text{O} \)
   - \( \text{R} \) (several steps)

3. RCOOH (product) 50% TFA

Linkers: a) Merrifield Peptide Synthesis

1. HCl / CH\(_3\)COOH
2. Boc-NHCHR\(_1\)COO\(^{-}\) / DCCI

Dipeptide
Other linkers

- Rink acid linker
- Trityl linker
- protected Rink amide linker
- protected Sieber linker

Safety catch linkers

- Stable: $\text{S} - \text{O} - \text{R}$
- Labile: $\text{SO}_2 - \text{O} - \text{R}$
- Base: $\text{SO}_2$ + $\text{R} - \text{OH}$

- Product: $\text{N} - \text{O} - \text{R}$
- $\text{OH}^-$: product-COOH
- $\text{HNR}_1\text{R}_2$: product-CONR$_1$R$_2$

$\text{R} = \text{H}$: stable
$+ \text{CH}_2\text{N}_2 \rightarrow \text{R} = \text{CH}_3$: labile
Traceless (safety catch) linker

NH

O

R

stable

Cu(OAc)$_2$

NH$_2$

Polymer-supported solution phase syntheses
Polymeric reagents

reagent

C

A + B → A-B

Solid Phase-Supported Synthesis of (±)-Epibatidine

1. NMe$_3$BH$_4$
2. NMe$_3$RuO$_4$
3. NMe$_3$OH + MeNO$_2$
4. OTBS
5. NMe$_3$BH$_4$
6. Mesyl-Cl
7. NMe$_3$BH$_4$
8. E$t$_2$N$_2$N-tBu
9. basic epimerization

(±) 85% endo
(±)-Epibatidine
(exo:endo = 3:1)

Solid Phase-Supported Synthesis of (±)-Oxomaritidine and (±)-Epimaritidine


Polymeric scavengers for building blocks, side products and reagents

A + excess B → A-B + B → A-B + X-B

reagent
C
A + B → A-B + C → A-B + X-C

A + B → A-B + side → A-B + X-D
Scavenger Reagents: Ion Exchange Resins, Polymeric Acids and Bases, Isocyanates, etc.

- 1 equivalent
- 1.2 equivalents

Resin capture strategy

A + B → A-B + C + side product D

Resin capture with an ion exchange resin

H₂N-R → SO₃⁻ → SO₃⁻ H₃N⁺-R → H₂N-R

(Amberlite ion exchange resin)

Catch and release strategy

B₁ + B₂ → B + C + side product D
Catch and release strategy, using a traceless linker

Milestones in the History of Multicomponent Reactions

A. Strecker (1850)

\[
\text{NH}_3 + \text{HCN} + \text{RCHO} \rightarrow \text{R} = \text{CN} + \text{R}_2\text{NH} + \text{H}_2\text{O}
\]

A. R. Hantzsch (1890)

\[
\text{NH}_3 + \text{R}_1\text{Cl} + \text{HOOCR} + \text{H}_2\text{O} \rightarrow \text{R}_1\text{NH} + \text{R}_2\text{COOR} + \text{H}_2\text{O}
\]

P. Biginelli (1893)

\[
\text{R}_1\text{CHO} + \text{H}_2\text{NNH}_2 + \text{R}_2\text{COR} \rightarrow \text{R}_1\text{NH} + \text{R}_2\text{COOR} + \text{H}_2\text{O}
\]

C. Mannich (1912)

\[
\text{CH}_2\text{O} + \text{R}_1\text{R}_2\text{NH} + \text{R}_3\text{COR} \rightarrow \text{R}_1\text{NH} + \text{R}_2\text{COOR} + \text{H}_2\text{O}
\]
M. Passerini (1921)

$$R_1NC + R_2CHO + R_3COOH \rightarrow R_3O \quad R_2NHR_1$$

H. T. Bucherer (1934)

$$HCN + NH_3 + CO_2 + RCHO \rightarrow R_2NH\quad R_3S\quad R_4COO$$

F. Asinger (1958)

$$NH_3 + R_1O\quad R_2CHO + R_3SH \rightarrow R_2N\quad R_3S\quad R_4O$$

I. Ugi (1959)

$$R_1NH_2 + R_2CHO + R_3NC + R_4COOH \rightarrow R_4N\quad R_2O\quad R_3O\quad R_1N$$

Complex Molecules from Multicomponent Reactions

$$\text{4 steps} \quad \text{e.g.} \quad \text{S. L. Schreiber, Science 287, 1964-1969 (2000)}$$

The Generation of Scaffold Diversity


The Generation of Scaffold Diversity

\[ \text{R}_1\text{C} \equiv \text{C}^- + \text{R}_2\text{O} + \text{R}_3\text{NH}_2 \rightarrow \text{Three component Ugi reaction} \]

Increasing Diversity of Combinatorial Libraries

courtesy of Drs. M. Mann, W. Sauer, Serono, Geneva ©

References