

Organic Pharmaceutical Chemistry IV

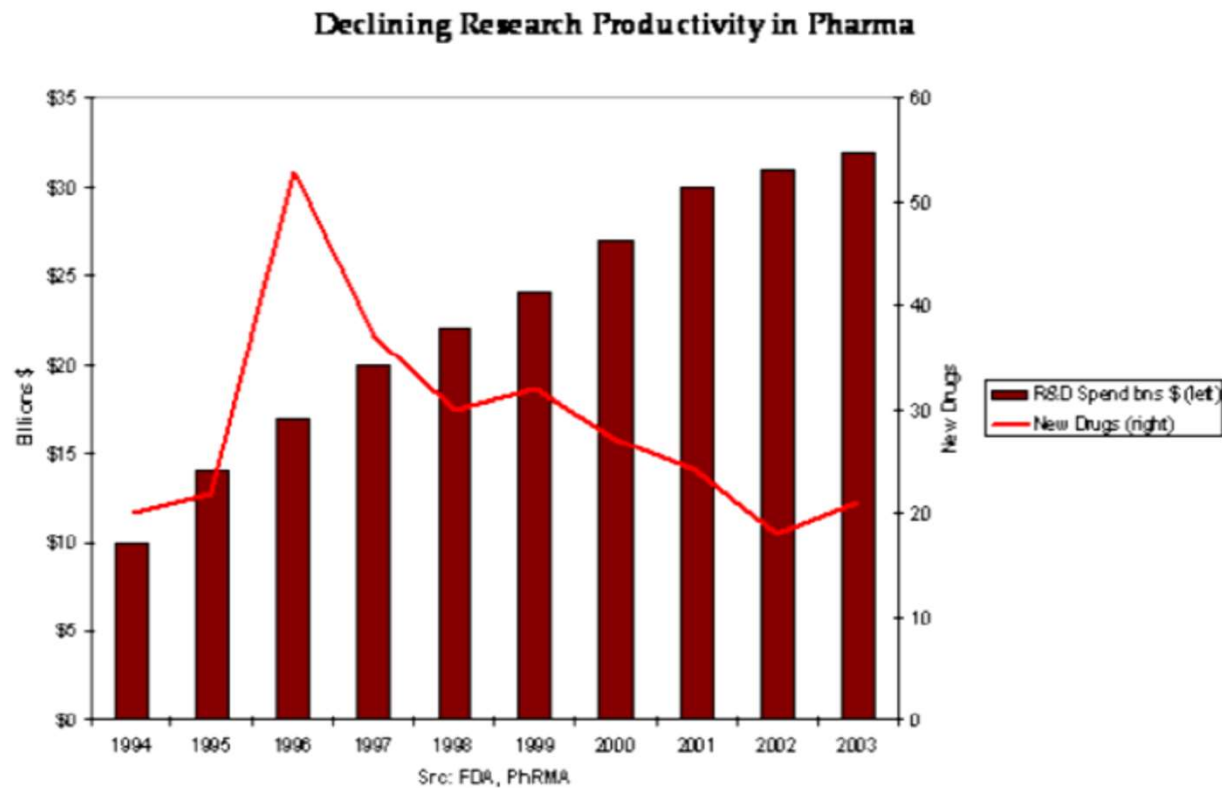
Fifth Stage

Lecture 11

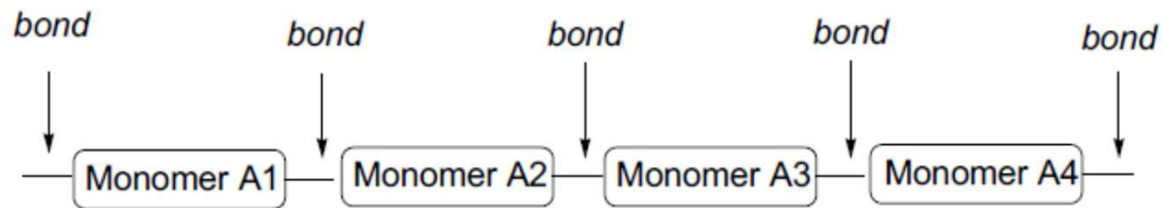
Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry

John H. Block
John M. Beale, Jr.
Eleventh Edition
2004

Why combinatorial Chemistry?

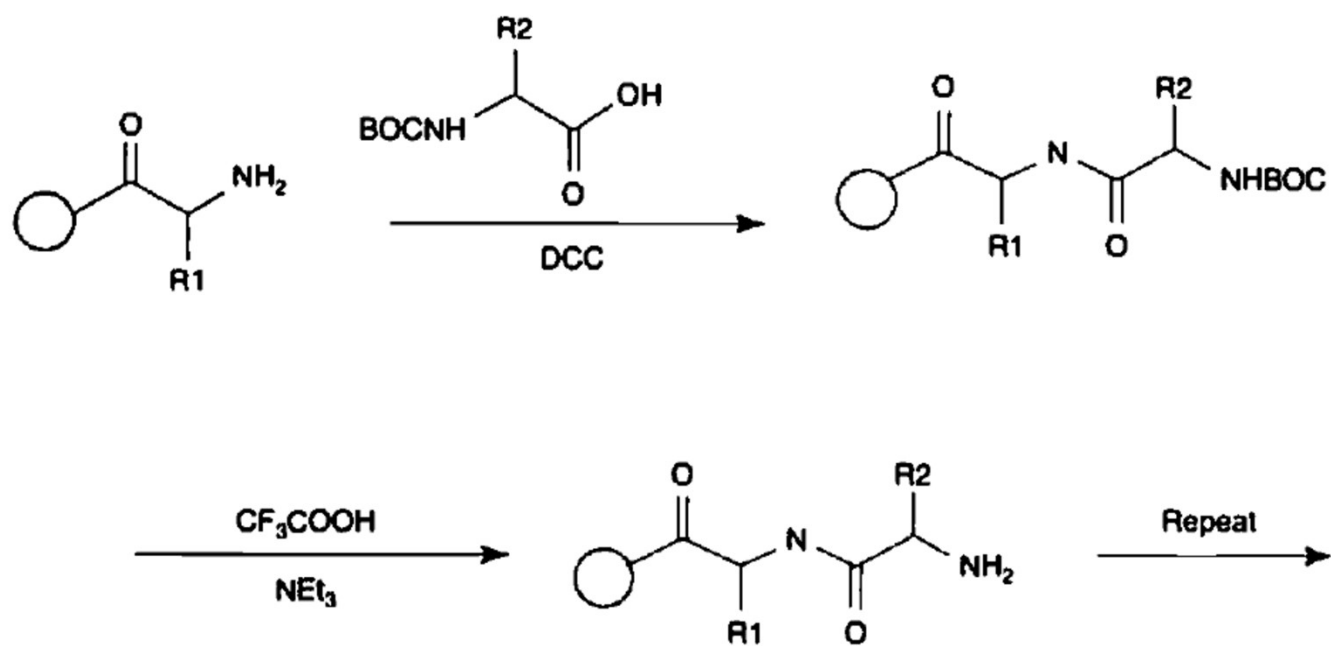


Combinatorial Synthesis of Peptides



<i>monomers</i>	<i>bond formation</i>	<i>polymers</i>
amino acids	amide bond	peptides, proteines
nucleotides	phosphorester bond	oligonucleotides
mono- and disaccharides	glycosidic bond	polysaccharides

Bruce Merrifield and the Nobel Prize



Importance of Peptides as drugs

- Peptides as drugs have a long history and started around 1920 with the discovery of insulin
- Insulin, oxytocin, gonadotropin-releasing hormone, vasopressin
- Endogenous peptides act as hormones, neurotransmitters, growth factors and antibacterial agents
- Most messengers of endocrine signaling pathways are peptides
- Most endogenous peptides and most successful peptide drugs are agonists

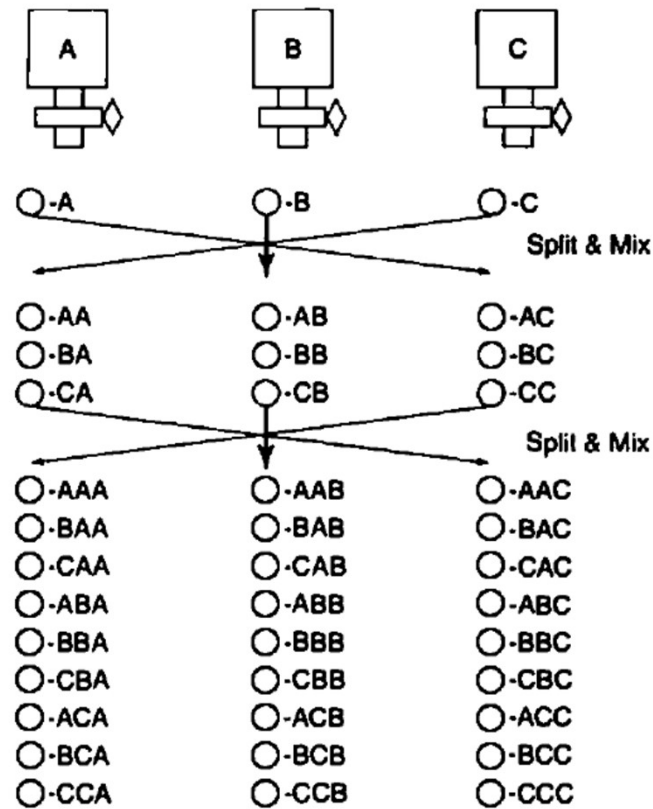
Weaknesses of Peptides as drugs

- Peptides are generally membrane-impermeable
- Peptides are usually administered subcutaneously (sc) or intravenously (iv)
- Peptides are unable to cross the blood brain barrier (BBB)
- Peptides are biologically unstable
- The manufacturing costs of peptides is generally higher than for small molecules

Strengths of Peptides as Drugs

- Peptides are generally highly potent and selective
- Most constituents of the innate immune system are peptides
- Lower toxicity issues as compared to small molecules

Split and Mix



Compound mixtures versus single compounds

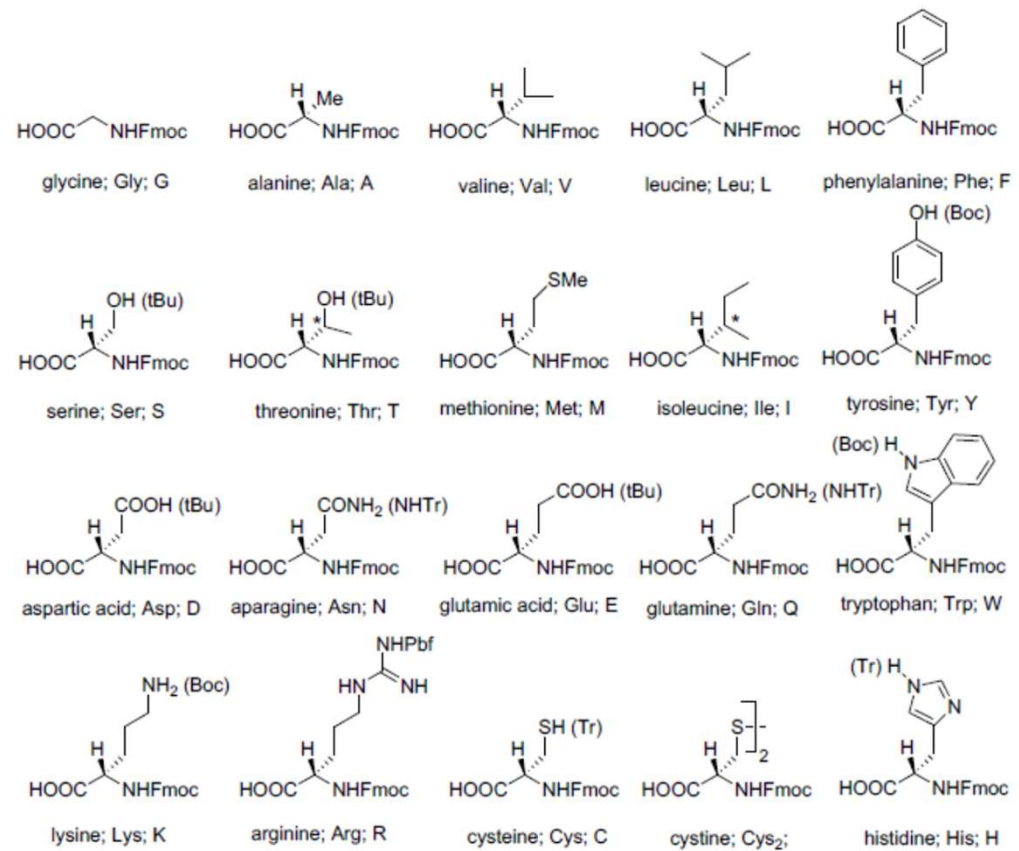
Compound mixtures

- Mixtures of products synthesized in one reaction in equimolar ratio
- compound mixtures can reduce the screening effort in expensive and laborious screens
- compounds in mixtures can interfere with one another; prone to false positive hits

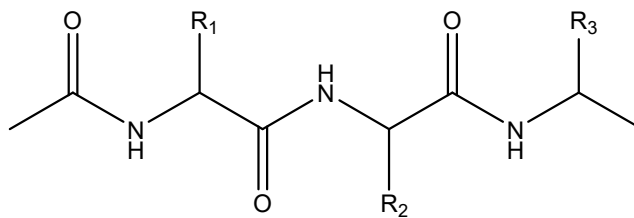
Single compounds

- Synthesis on solid supports without final purification
- Synthesis in solution followed by high-throughput preparative HPLC-purification
- Trend today: screening of single compounds

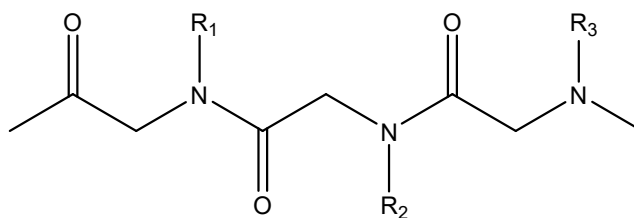
Amino Acids



Peptoids



Peptide



Peptoid

Peptoids vs Peptides

Peptides

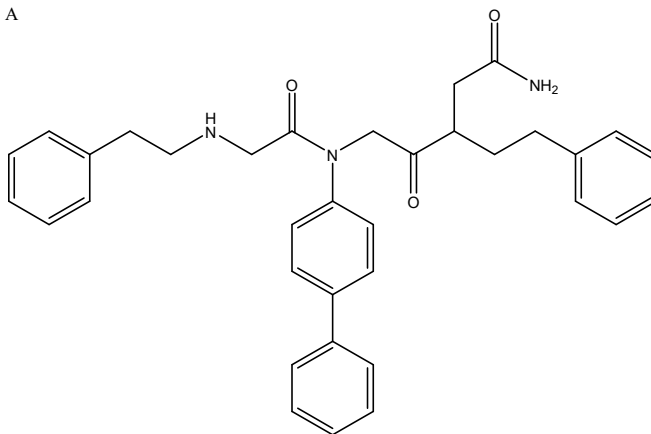
- Less stable
- More hydrogen bond donor
- Less flexible backbone

Peptoids

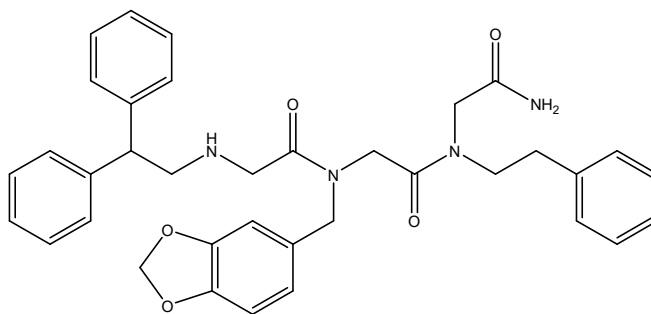
- Protease stability increased
- Less hydrogen bond donor
- More flexible backbone

Peptoids

A



B





Questions

1. Illustrate the Merrifield discovery
2. Enumerate 3 top-selling non-insulin peptides
3. What are the differences between Peptides and Peptoids? Support your answer with structures
4. Give 2 examples on biologically active Peptoids (with structures)
5. Why it's difficult to get high-throughput chemistry to deliver drugs consistently?