

Peptidomimetics

Peptides in Nature

- Importance:
- as neurotransmitters, hormones and physiological modulators,
 - involved in a variety of diseases
- Function:
- influence on signal transduction mediated through receptors
- Relevance:
- agents that can imitate or block the biological functions of bioactive peptides (agonists or antagonists)
→ therapeutic agents
- Drawback:
- poor pharmacokinetic properties (absorption, stability, duration of action)
 - poor specificity / selectivity

Design of Peptidomimetics

- Definition:
- A compound containing non-peptidic structural elements that is capable of mimicking or antagonizing the biological action(s) of a natural parent peptide
- Requirements:
- few (or no) peptide bonds
 - low molecular weight
 - similar pharmacophore → analogous binding mode

Design of Peptidomimetics

- Modifications:**
- removal of amino acids
 - Ala scan
 - D-amino acids
 - unnatural side chains
 - peptide backbone modifications
 - cyclizations
 - templates that induce secondary structures

Application:

Asp—Arg—Val—Tyr—Ile—His—Pro—Phe—His—Leu¹⁰

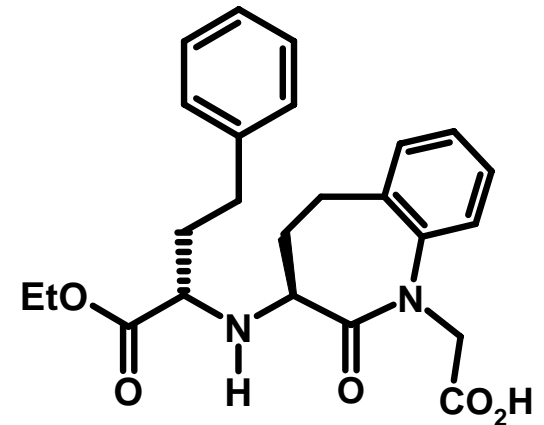
Angiotensin I



ACE

Asp—Arg—Val—Tyr—Ile—His—Pro—Phe

Angiotensin II



ACE Inhibitor
(Benzazeprile)

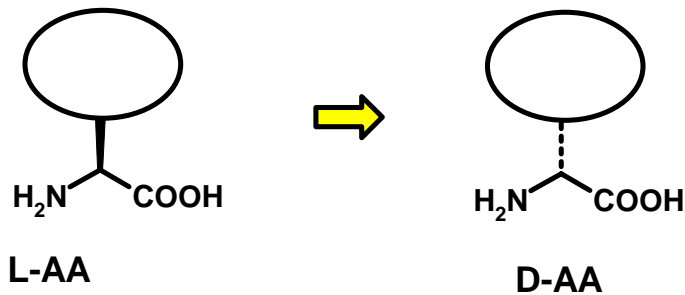
Removal of amino acids

Reduction of the molecular weight → recognition of bioactive parts
→ removal of molecular garbage
→ improvement of bioavailability

Ala scan

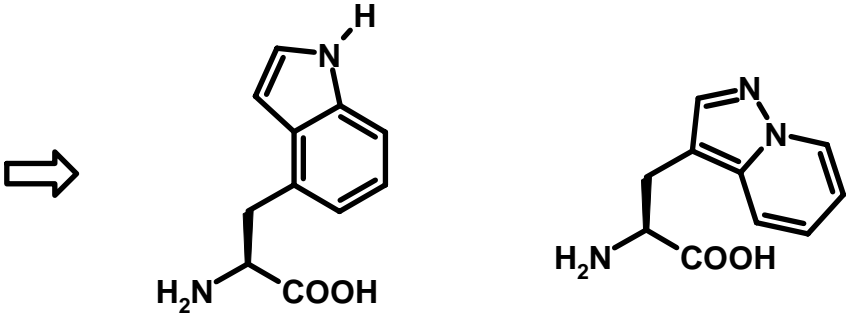
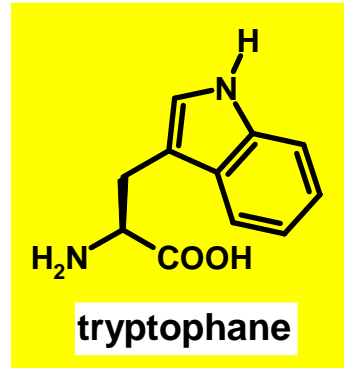
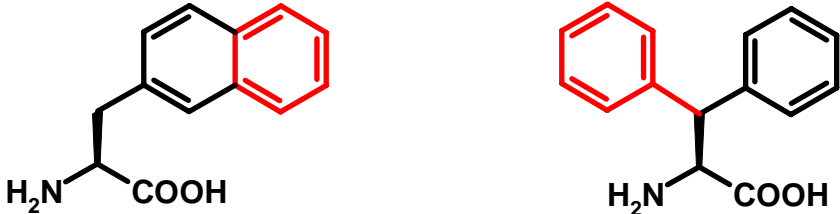
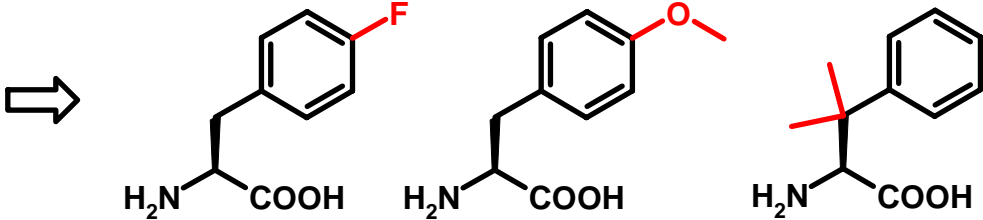
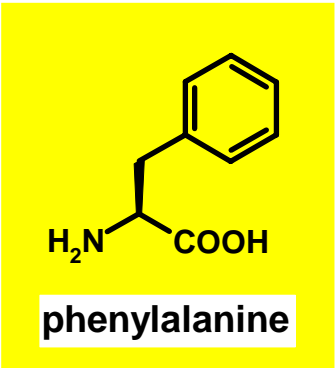
Subsequent exchange of the amino acid residues by alanine
→ selection of pharmacophoric side chains

D-Amino acids



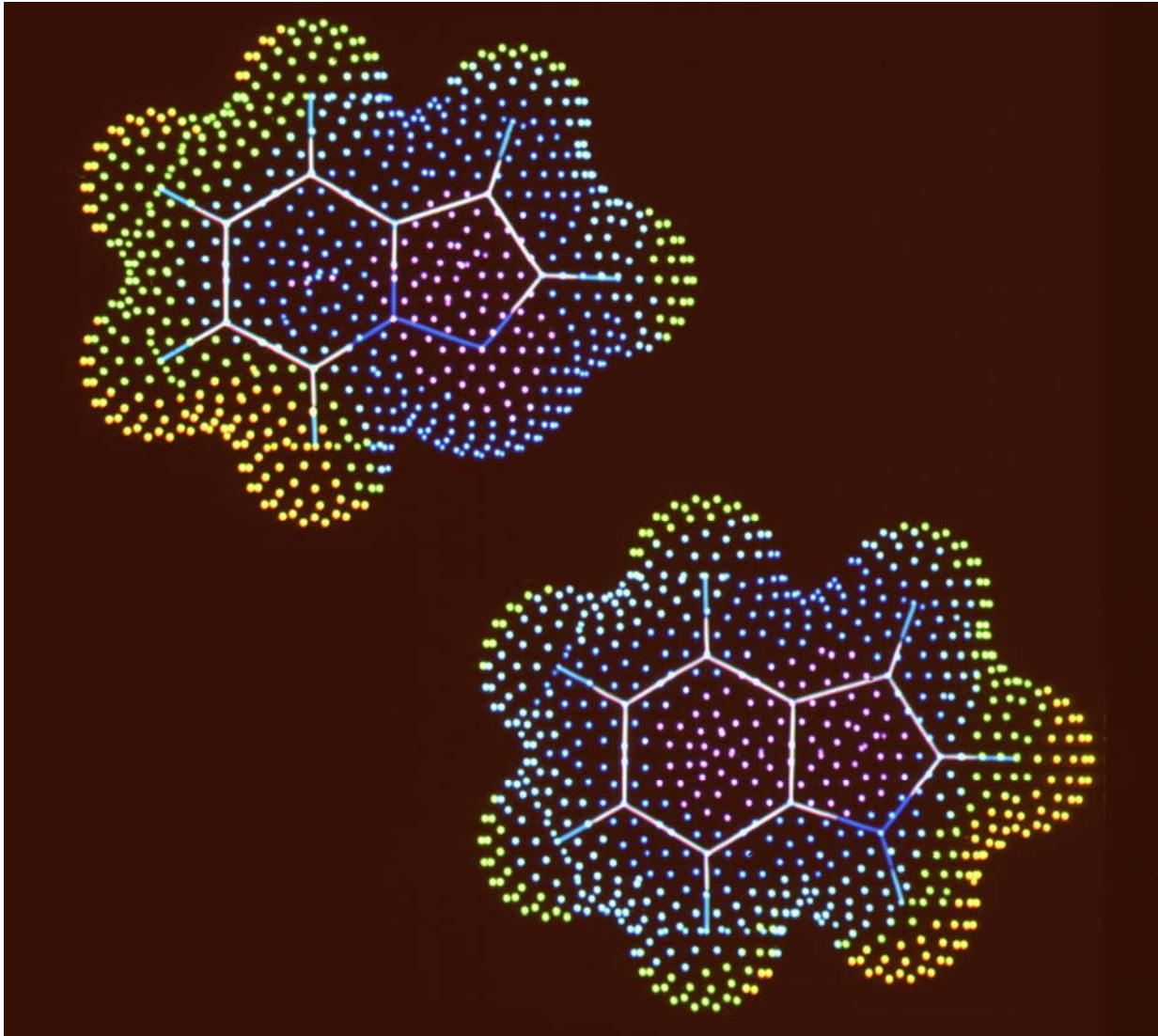
Exchange of the amino acid residues by enantiomers
→ selection of pharmacophoric side chains
→ increase of metabolic stability
→ stabilization of secondary structures
(D-AA in pos. $i+1$ → β -turn)

Unnatural side chains → non-proteinogenic amino acids



Bioisosteric replacement: tryptophane / 7a-azatryptophane

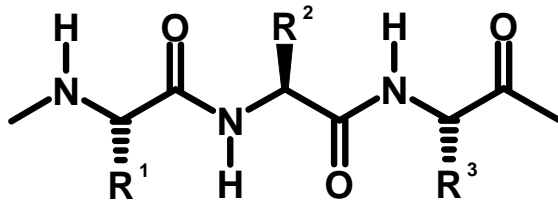
- loss of the heterocyclic H-bond donor
- different MEP maps



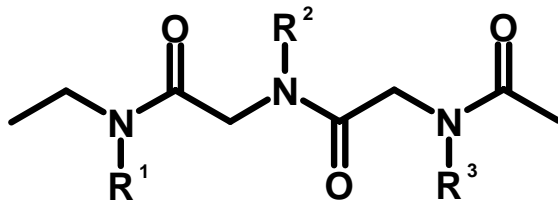
Peptide backbone modifications

Peptoids = N-substituted oligoglycines

- Advantages:
- metabolic resistance toward proteases
 - easily accessible
 - high conformational flexibility
 - achiral



peptide

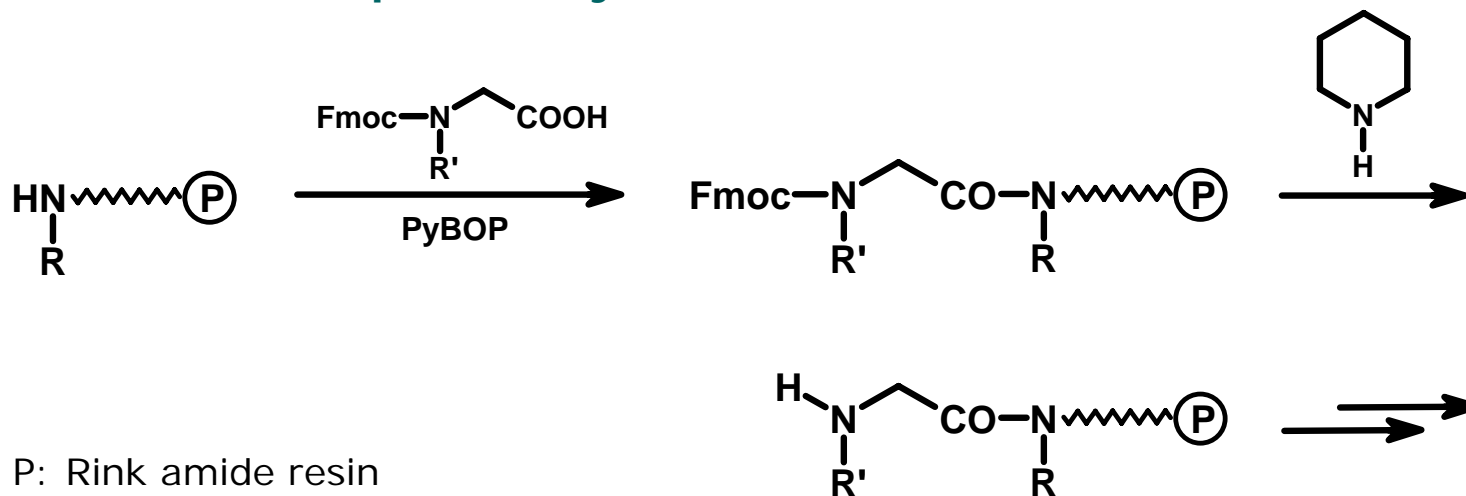


peptoid



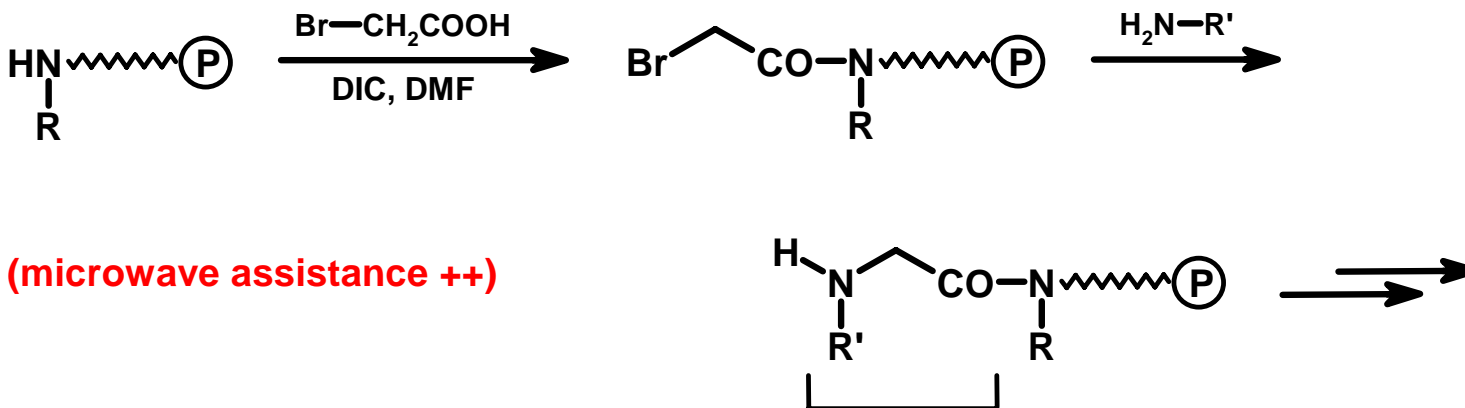
retro sequence

Fmoc based sequential synthesis



P: Rink amide resin

Submonomer approach



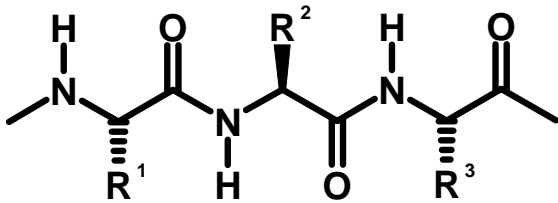
(microwave assistance ++)

Peptide backbone modifications

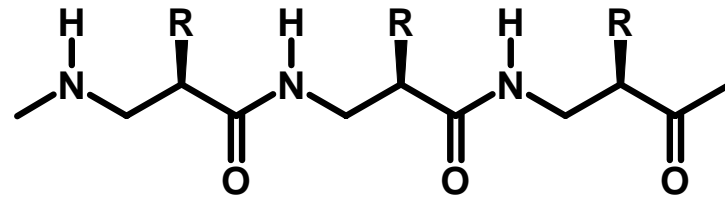
β -Peptides = peptide homologues obtained by insertion of a CH₂ group in every AA residue

properties:

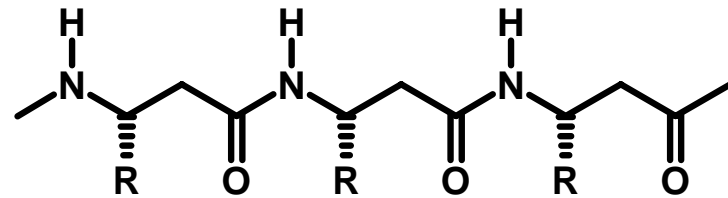
- metabolic resistance toward proteases
- easily accessible by a SPPS type approach
- high tendency to form **foldamers**
(*oligomers that adopt predictable and well-defined conformations*)
- two classes of β -AA: β 2 and β 3



peptide



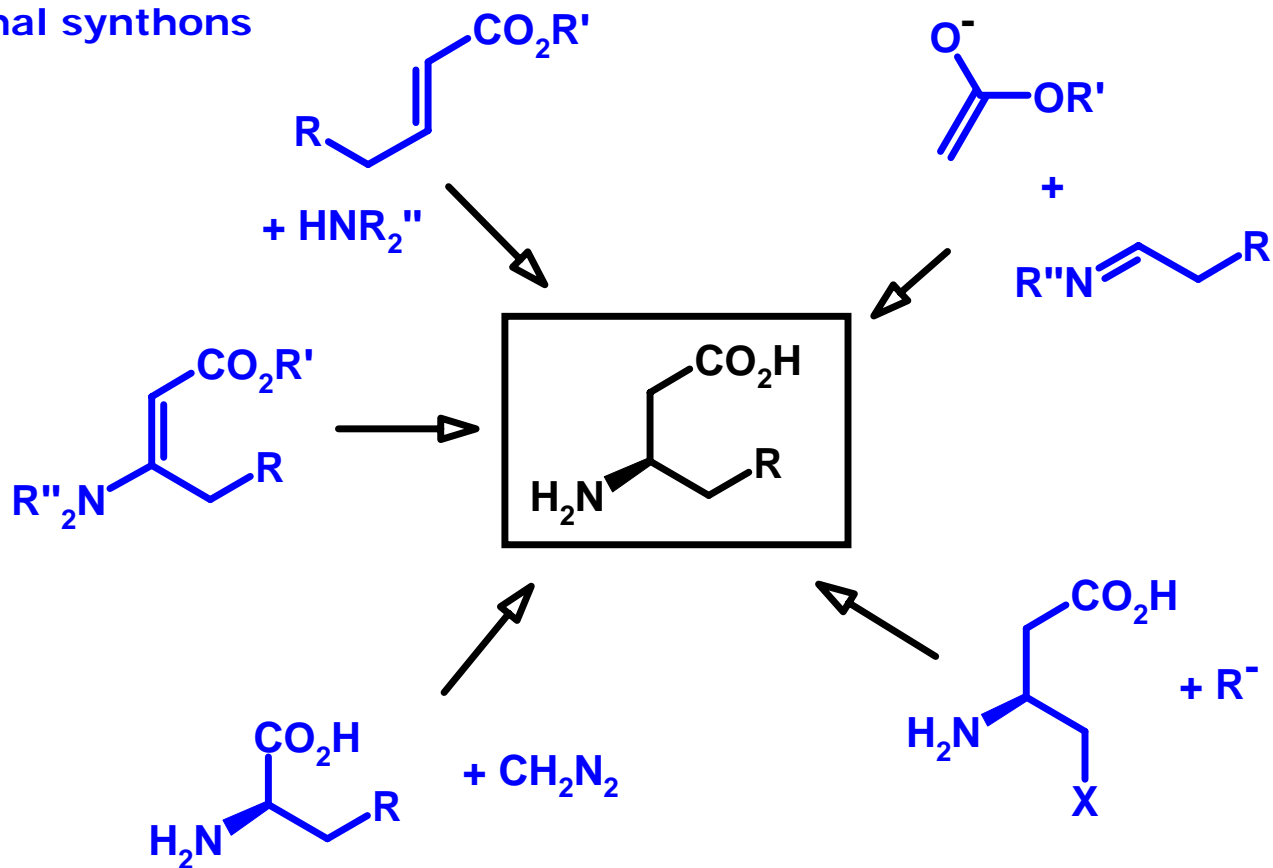
β^2 -peptide



β^3 -peptide

Synthetic approaches to β -amino acids

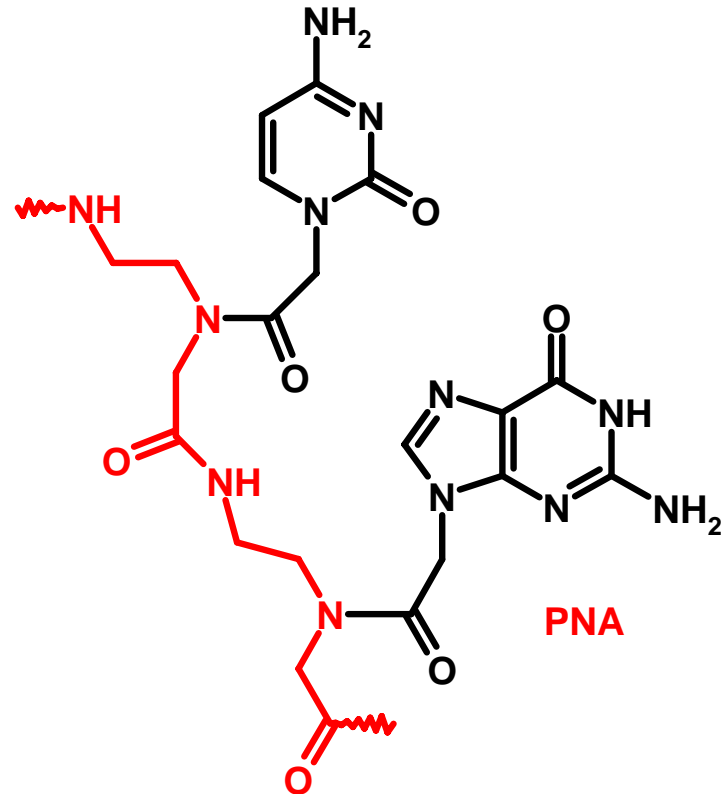
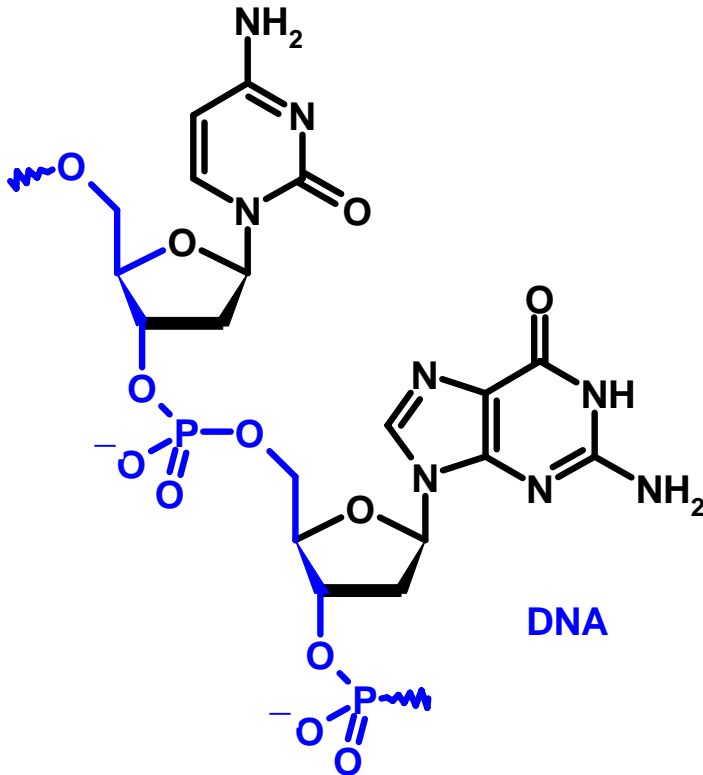
Formal synthons



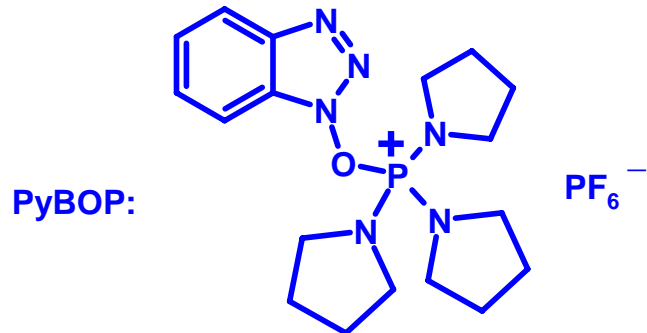
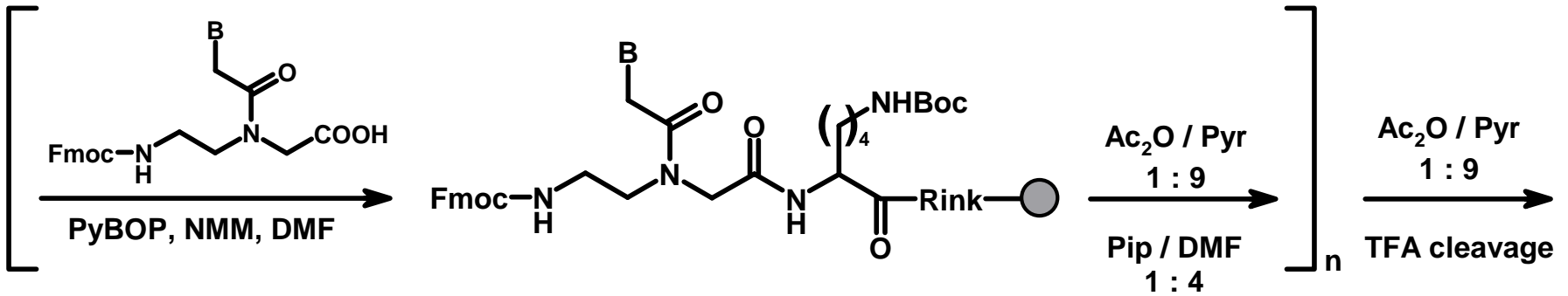
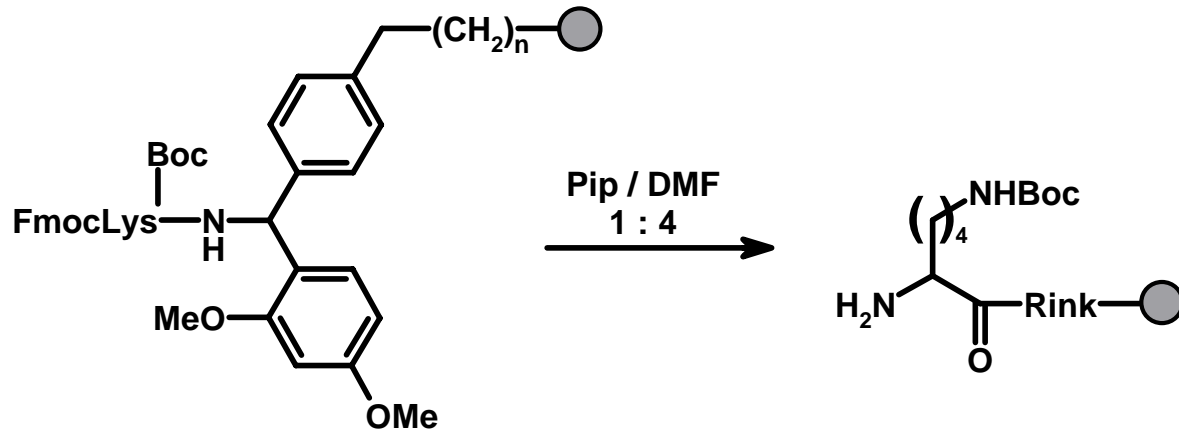
Peptide backbone modifications

PNAs

- = peptide nucleic acids (no peptides, no acids !)
- replacement of the ribose-phosphate backbone of DNA by aminoethylglycine
 - easily accessible
 - formation of highly stable DNA – PNA double strands



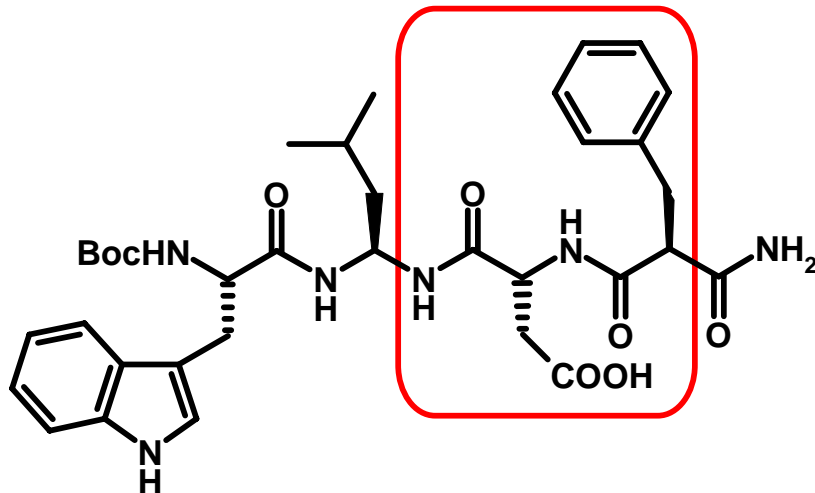
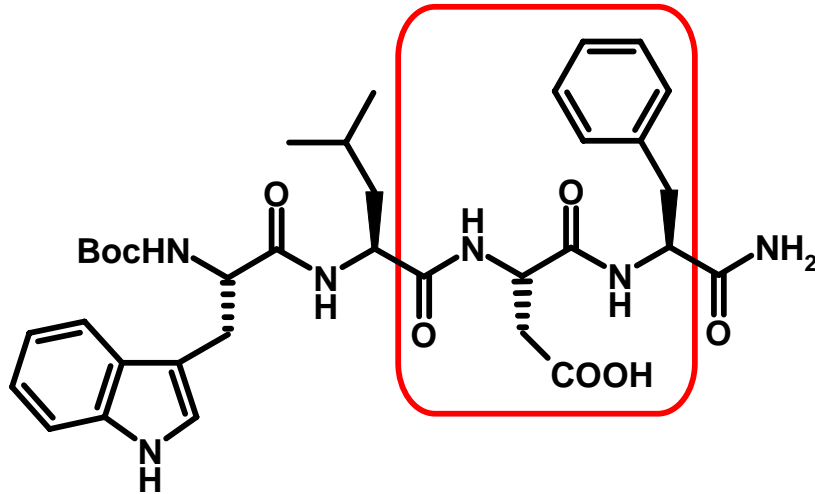
Solid phase supported PNA synthesis



Peptide backbone modifications

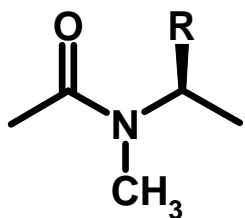
Retro-inverso isomers

- inversion of the sequence and configuration
- modification is done on the full peptide or on a part of the sequence

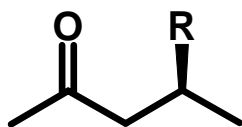


Peptide backbone modifications

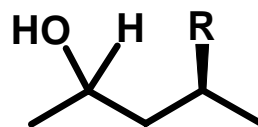
Further examples:



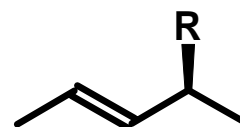
N-methyl



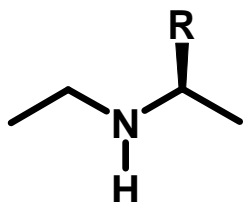
ketomethylene



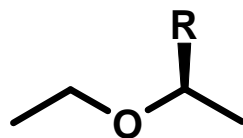
hydroxyethylene



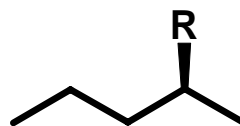
(E)-ethylene



reduced amide



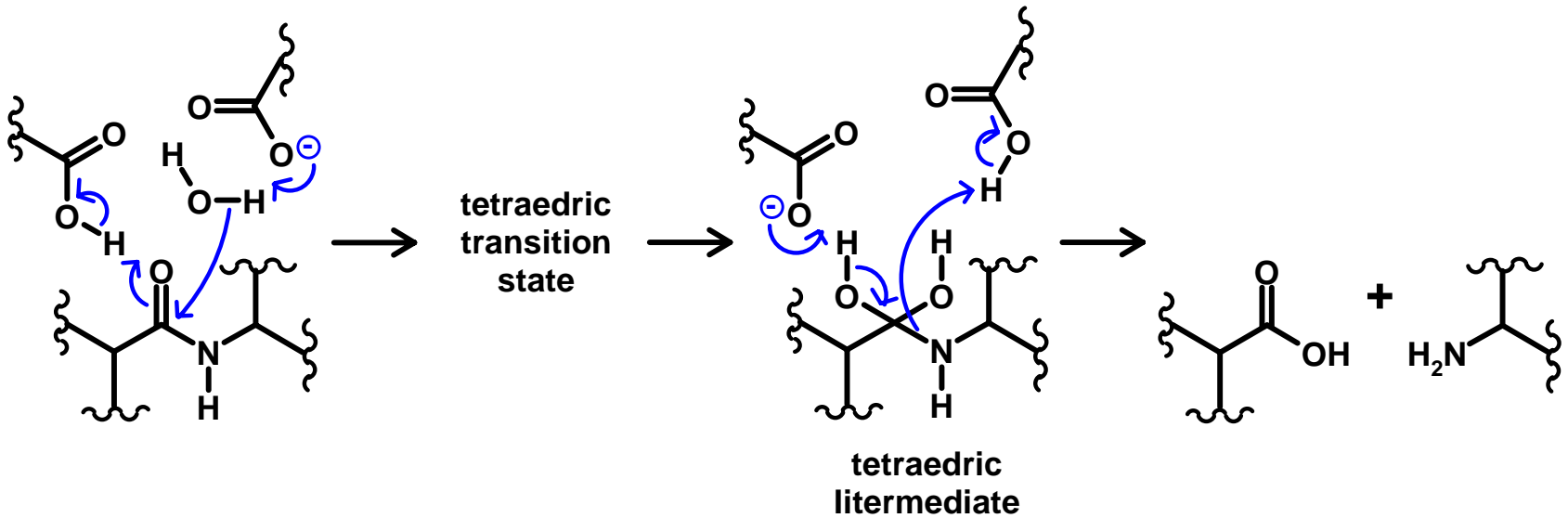
ether



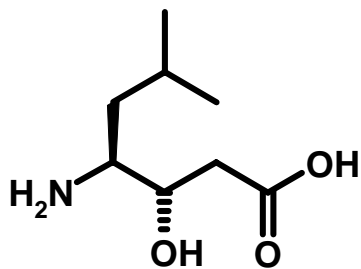
carba

Application: HIV protease inhibitors

Aspartylprotease function:

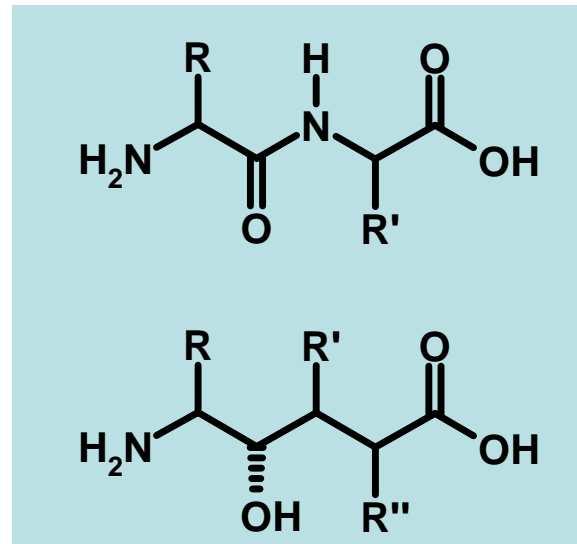


Statin: partial structure of pepstatin = aspartyl protease inhibitor
= hydroxyethylene bioisostere → „transition state mimetic“



dipeptide

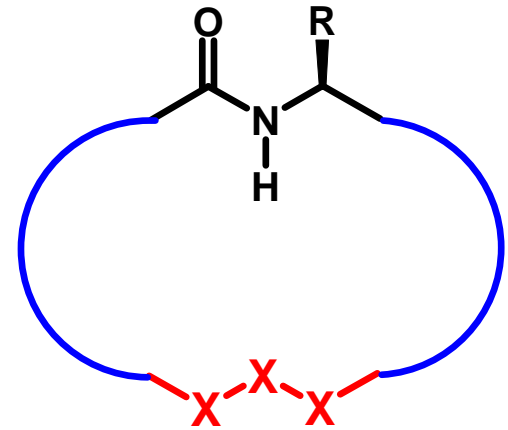
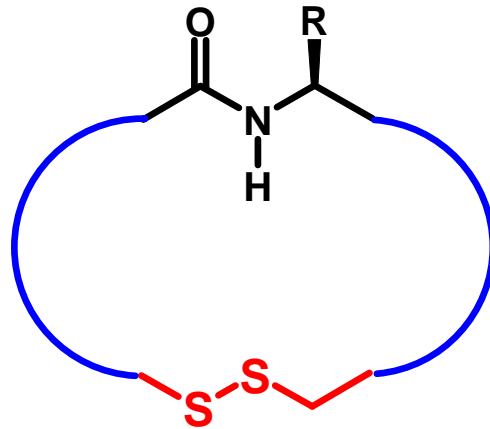
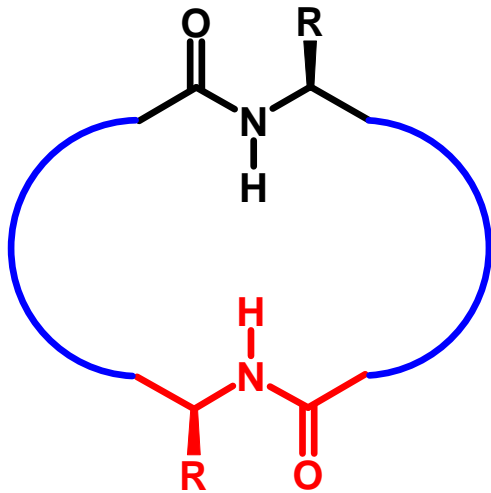
better: **hydroxypropylene bioisostere**
→ **Indinavir**



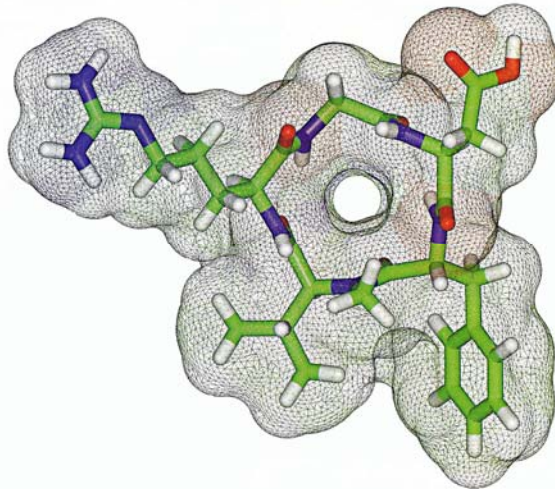
Cyclizations

Consequences:

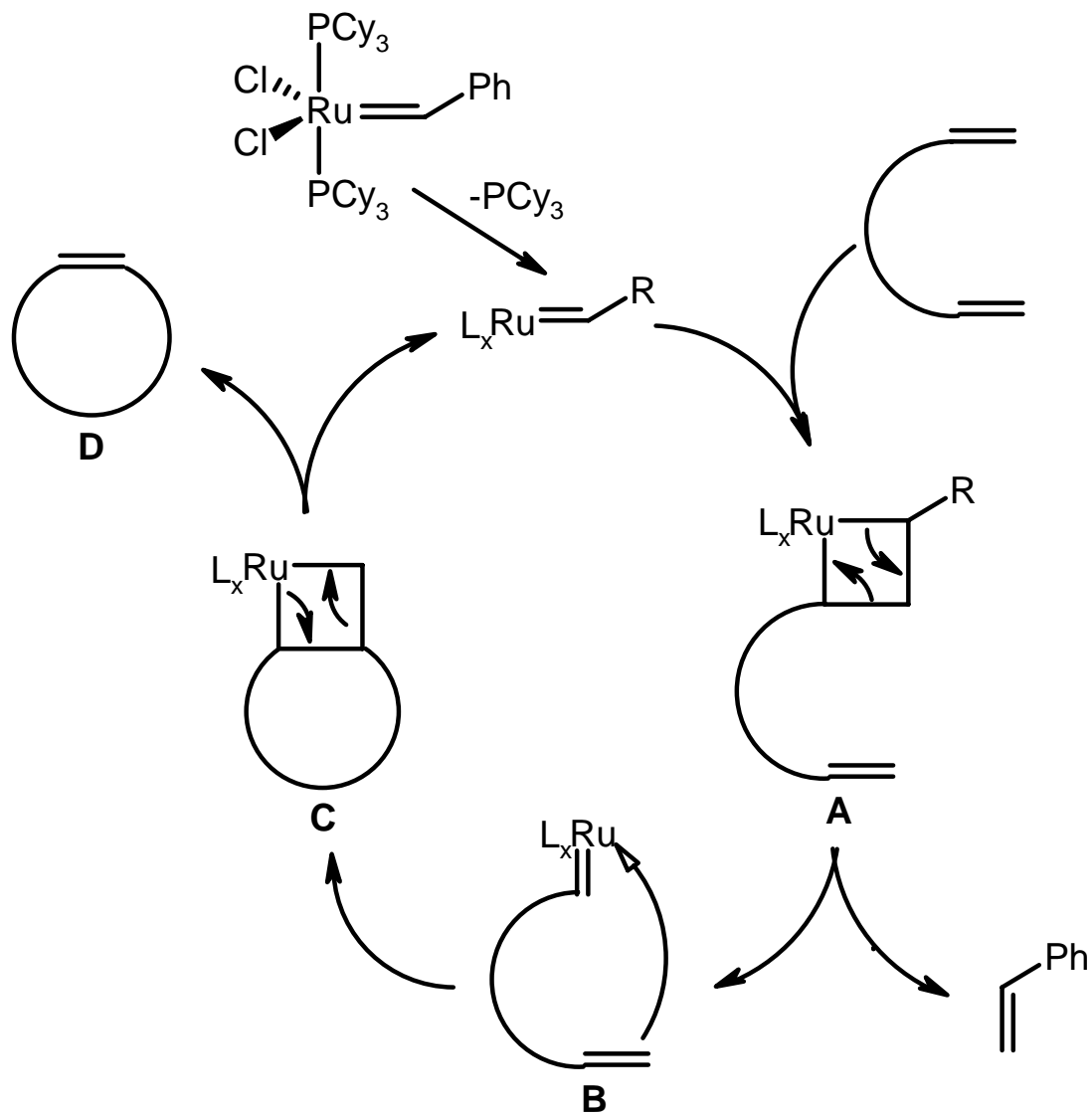
- increase of lipophilicity
- stability towards amino- and carboxypeptidases
- conformational restriction



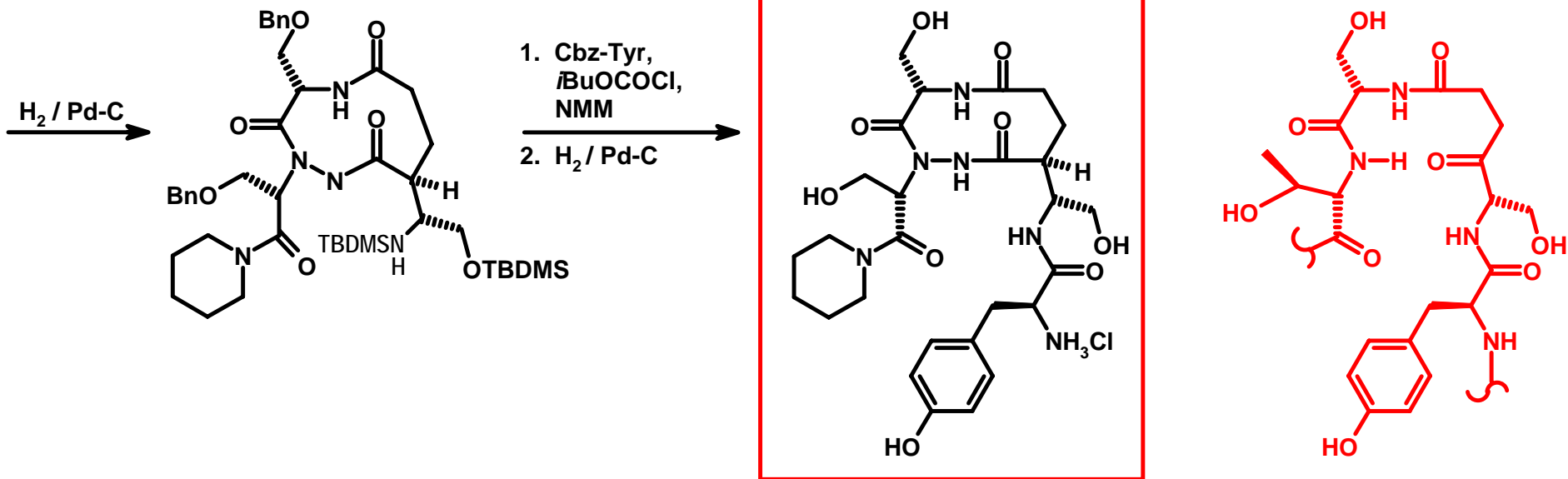
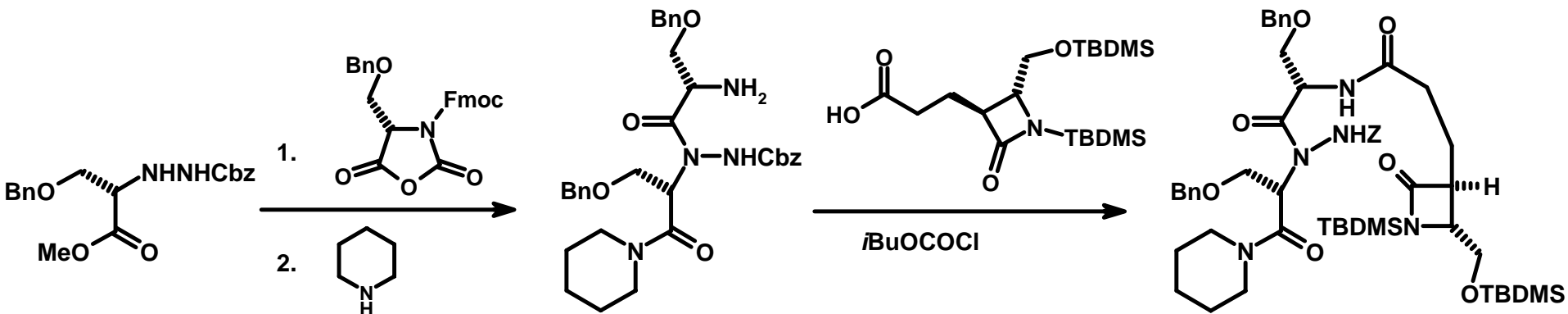
Example:
pentacyclic RGD mimetic



Ring closing metathesis reaction



Application: discovery of the first low-molecular antibody mimetic



Templates that induce secondary structures

Secondary structures of proteins: α -helices

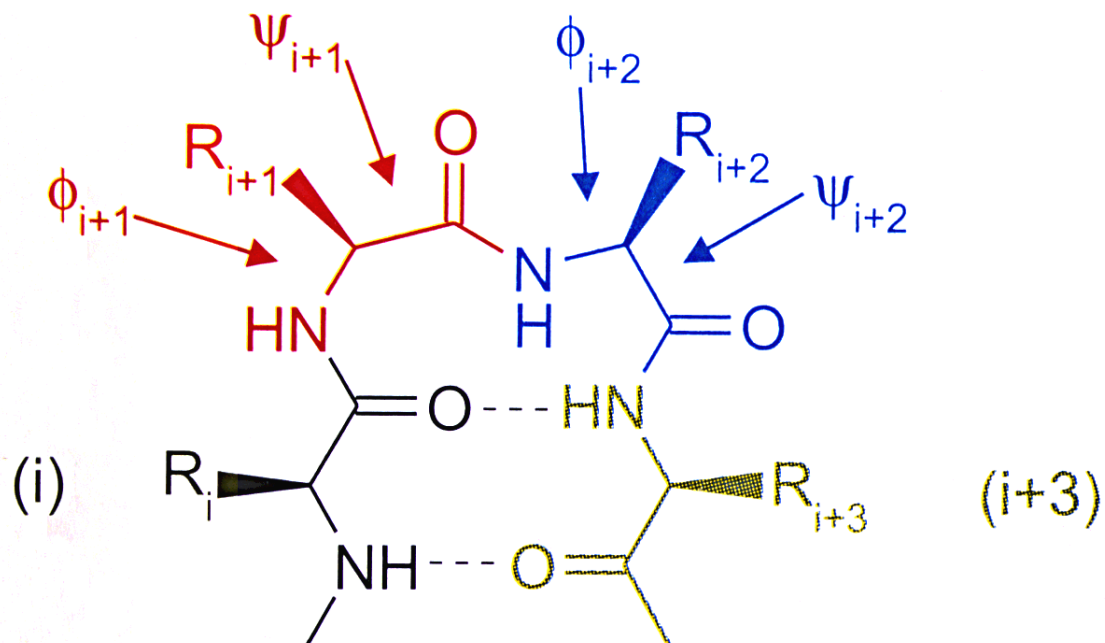
β -sheets

reverse turns – most important motif for biological recognition

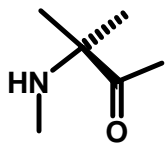
reverse turn mimetics – most important for drug discovery

β -turns:

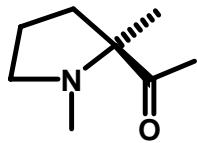
- tetrapeptide unit causing reversal of direction
- distance between $C_{\alpha i}$ and $C_{\alpha i+3} < 7\text{\AA}$
- less important:
 - γ -turns (3 AA involved)
 - α -turns (5 AA involved)



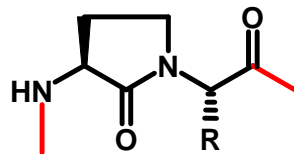
Templates that induce secondary structures



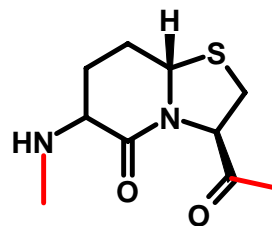
Aib



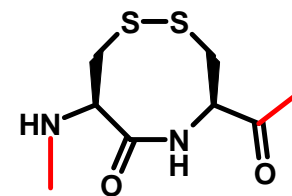
Pro



Freidinger lactam

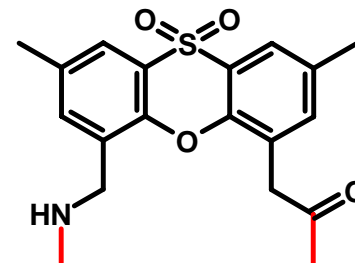
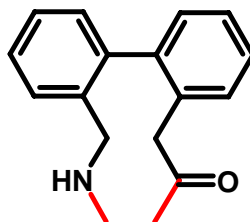
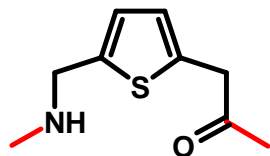
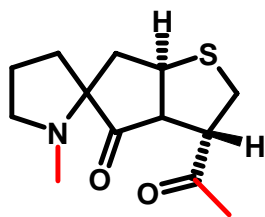
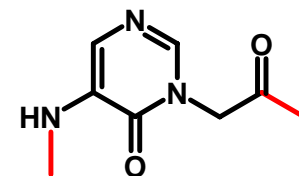
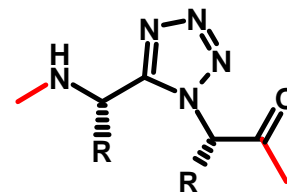
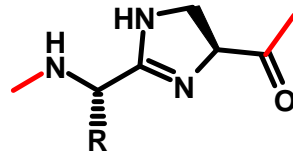
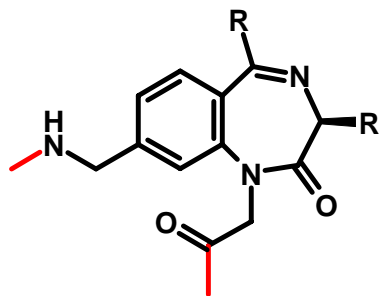
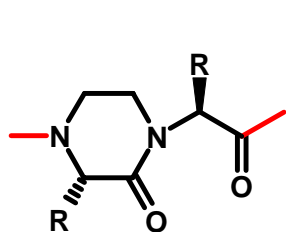


Fused lactam

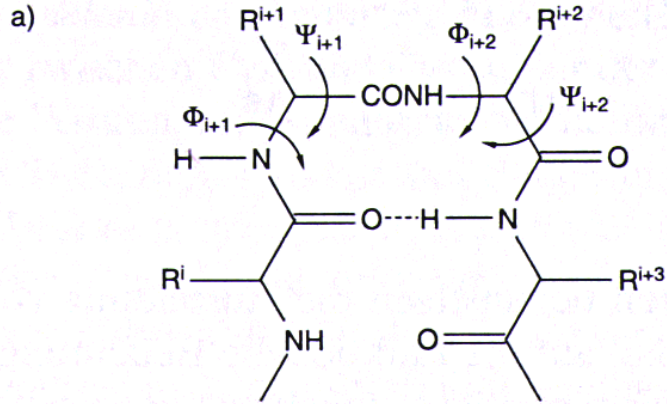


cis-peptidomimetic

Further examples:



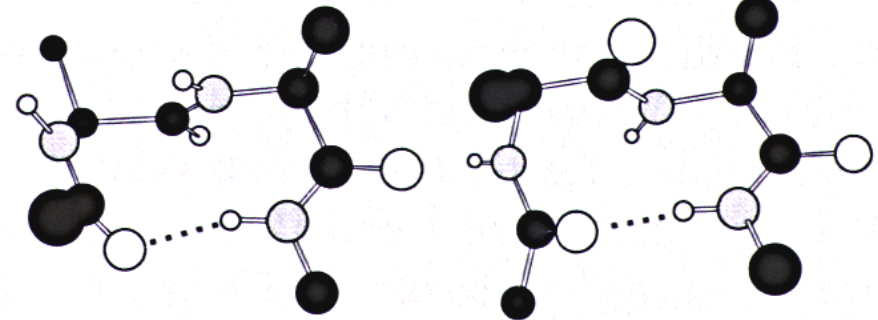
Classification of β -turns



b)

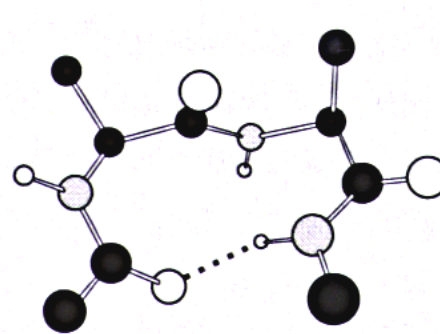
Konformation	Φ_{i+1}	Ψ_{i+1}	Φ_{i+2}	Ψ_{i+2}
	alle in Grad			
β I-Schleife	-60	-30	-90	0
β I'-Schleife	60	30	90	0
β II-Schleife	-60	120	80	0
β II'-Schleife	60	-120	-80	0
β VIa-Schleife	-60	120	-90	0
β VIb-Schleife	-120	120	-60	150

c)

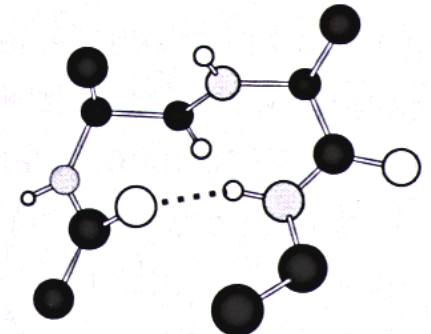


β I-Schleife

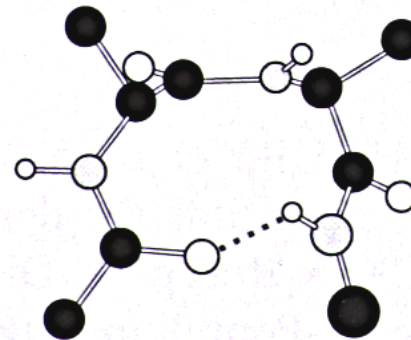
β I'-Schleife



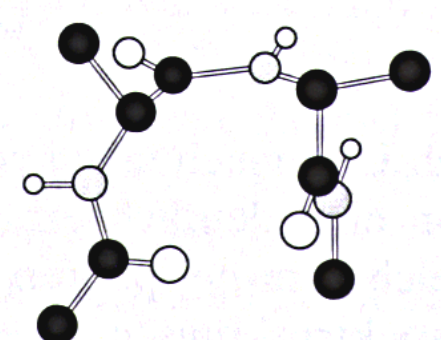
β II-Schleife



β II'-Schleife



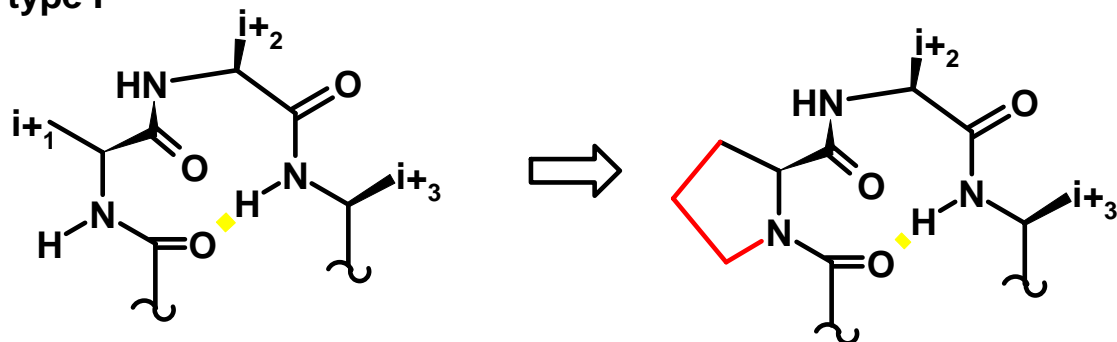
β VIa-Schleife



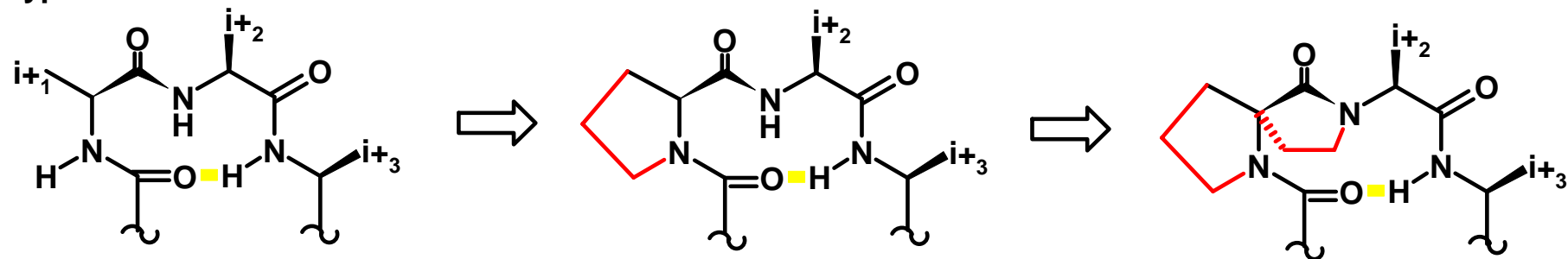
β VIb-Schleife

Most efficient conformational restrictions

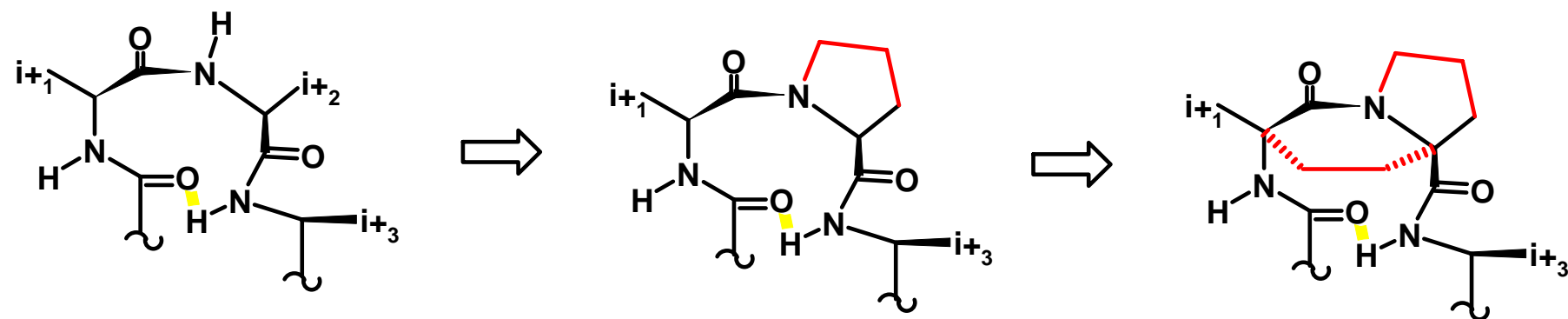
type I



type II



type VIa



Synthesis of a spirocyclic Freidinger lactam

