

Organic Pharmaceutical Chemistry IV

Fifth Stage

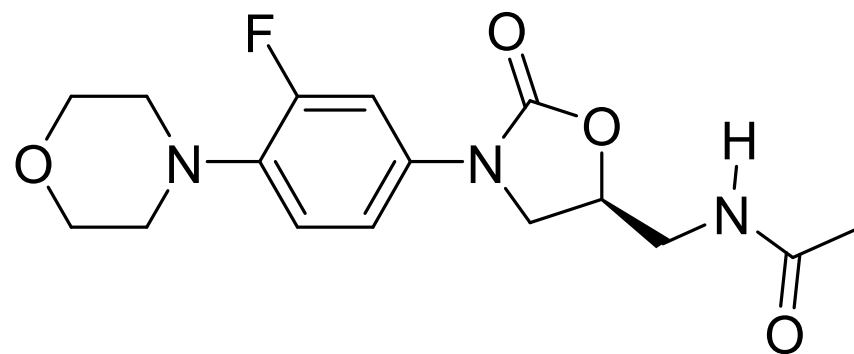
Lecture 12

Drug-ability or Drug-like

- The Lipinski rule of 5
 - <5 H-bond donors
 - <10 H-bond acceptors
 - <500 MW
 - <5 cLogP

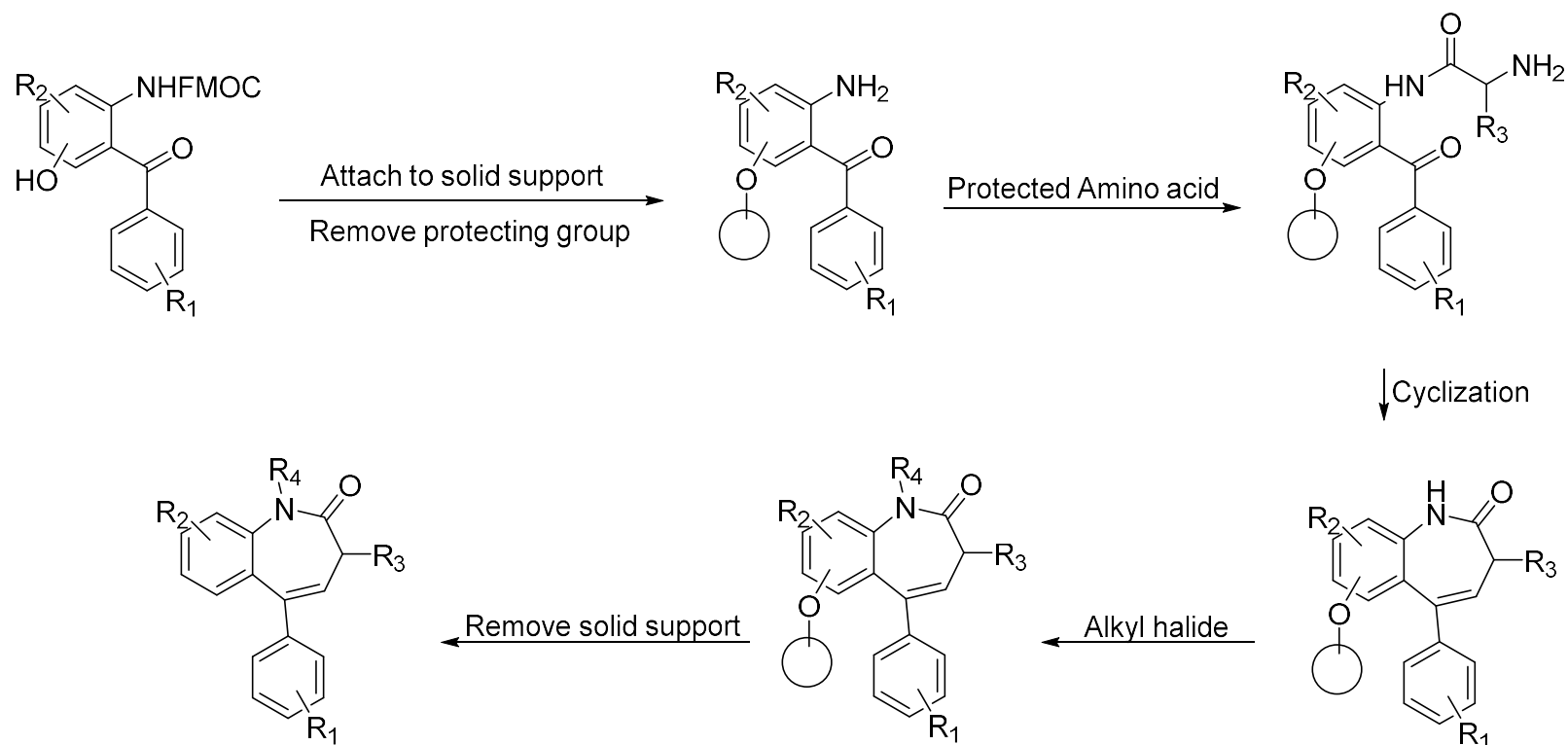
Example

- MW: 337.35 (ok)
- cLogP < 5 (ok)
- H-bond acceptors: 8 (ok)
- H-bond donor: 1 (ok)

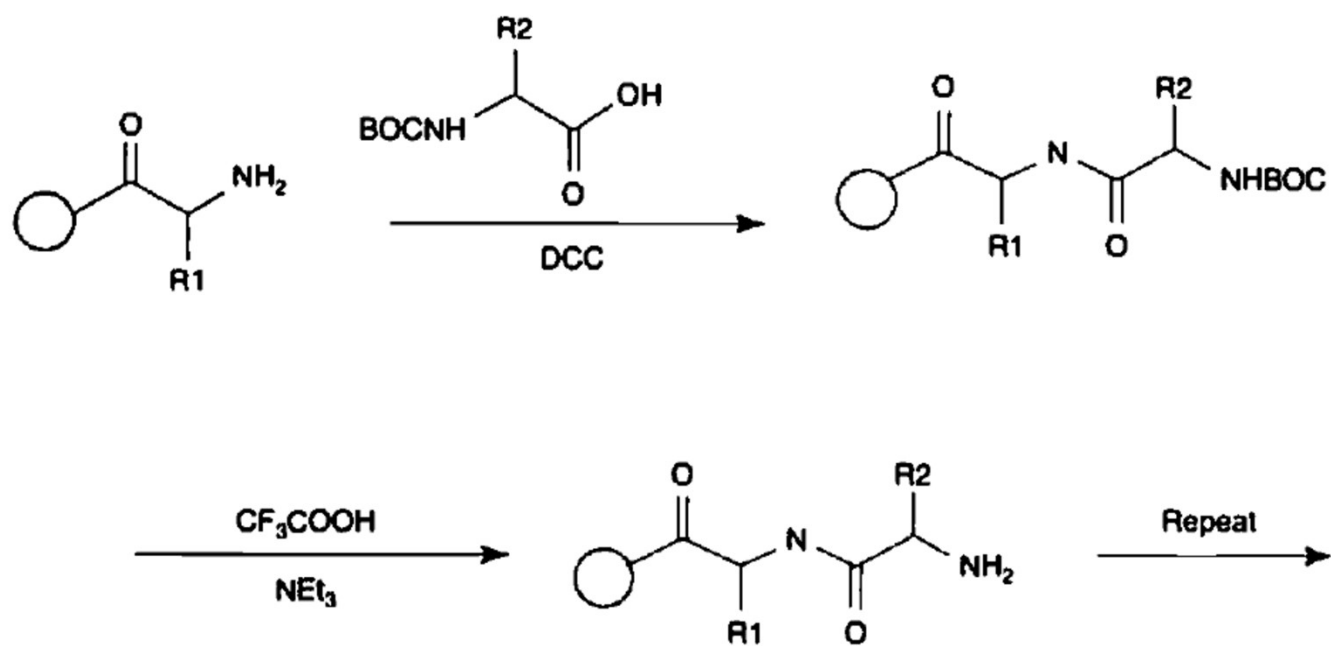


Linezolid: C₁₆H₂₀FN₃O₄

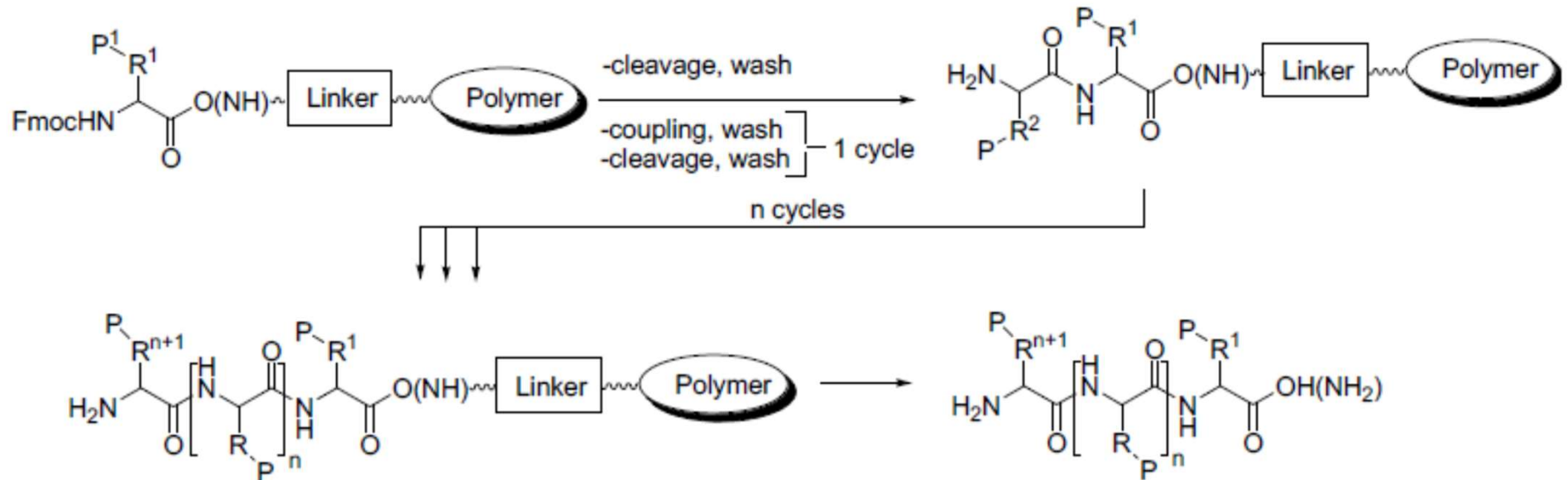
Benzodiazepines



Bruce Merrifield and the Nobel Prize



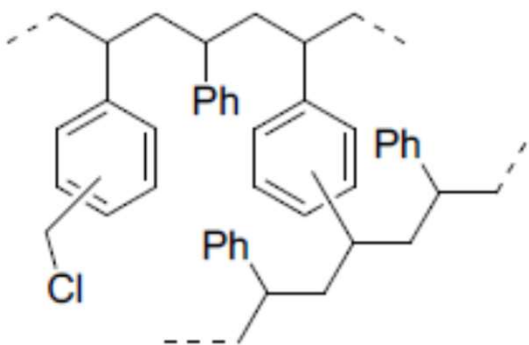
Supports and Linkers



Supports

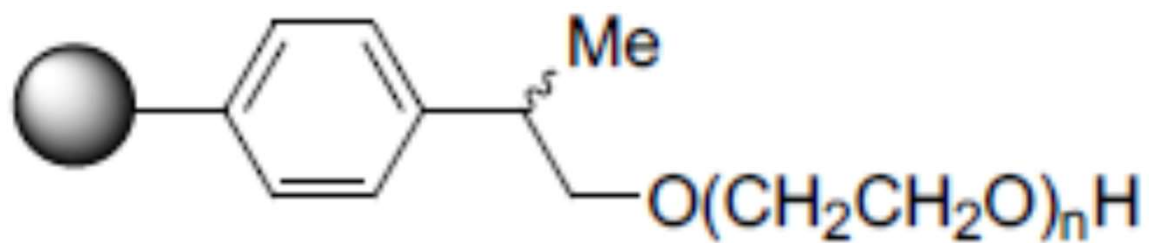
- Polymer beads 10 to 750 μm in diameter
- Swell in organic solvents
 - Expand the available area for attachment of the product
- Inert
 - Except the functional group to which the molecule is attached

Solid Support examples



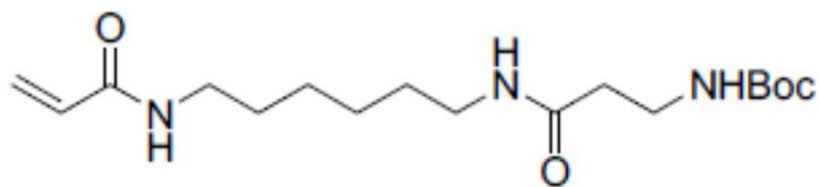
- **Polystyrene resins:**
Polystyrene cross-linked with divinyl benzene

Solid
Support
examples



- ***TentaGel resins***: Polystyrene in which some of the phenyl groups have polyethylene glycol (PEG) attached in the para position

Solid Support examples





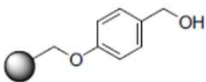
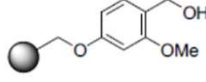
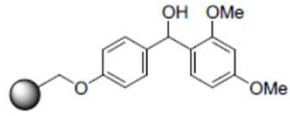
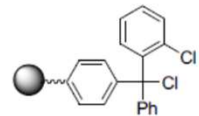
- **Polyacrylamide resins**: they swell better in polar solvents and more closely resemble biological materials

Linkers

- Must be stable under the reaction conditions
- Allow room for rotational movement of the molecule attached to it
- Easily cleavable

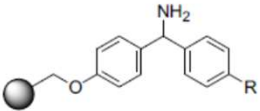
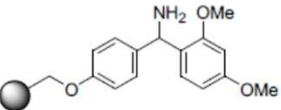
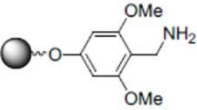
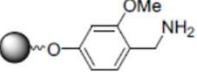
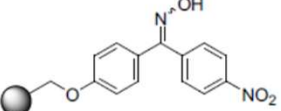
Linkers

2. Linkers for releasing carboxylic acids

| structure | abbreviation | cleavage conditions | reference |
|---|------------------------------------|---------------------------------------|---|
|  | Merryfield resin | HF, CF ₃ SO ₃ H | <i>J. Am. Chem. Soc.</i> 1963 , 85, 2149 |
|  | hydroxymethyl-PS | HF, CF ₃ SO ₃ H | |
|  | Wang resin | 95% TFA | <i>J. Am. Chem. Soc.</i> 1973 , 95, 1328 |
|  | Sasrin ^R resin (Bachem) | 1% TFA | <i>Tetrahedron Lett.</i> 1988 , 29, 4005 |
|  | Rink resin | 1% TFA | <i>Tetrahedron Lett.</i> 1987 , 28, 3787 |
|  | chloro-trityl resin (Barlos) | | <i>Tetrahedron Lett.</i> 1989 , 30, 3943 |

Linkers

2. Linkers for releasing amides

| structure | abbreviation | cleavage conditions | reference |
|---|--------------------------|--|---|
|  | BHA (R=H) MBHA (R=Me) | HF, CF ₃ SO ₃ H | <i>J. Org. Chem.</i> 1985 , 50, 5291 <i>Peptides.</i> 1981 , 2, 85 |
|  | Rink resin | 95% TFA | <i>Tetrahedron Lett.</i> 1987 , 28, 3787 |
|  | PAL resin | TFA | <i>Int. J. Prot. Pept. Res.</i> 1987 , 30, 206 |
|  | | TFA | <i>Tetrahedron Lett.</i> 1997 , 38, 7325 |
|  | Kaiser oxime resin | NH ₃ primary and secondary amines NH ₂ NH ₂ x 1H ₂ O | <i>J. Org. Chem.</i> 1980 , 45, 1295 |

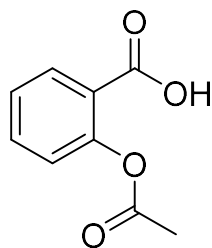
Some specialized linkers

- **Traceless linkers**: can be cleaved from the resin with no residual functionality left
- **Safety-catch linkers**: are inert to the synthesis conditions but have to be chemically transformed to allow final liberation of the product from the resin
- **Linkers sensitive to UV light**
- **Enzyme sensitive linkers**

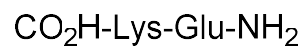


Questions

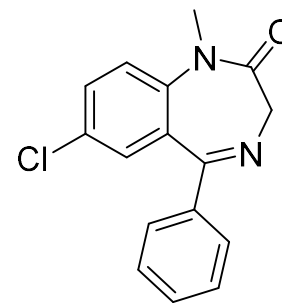
1. What are the Lipinski's rules of five?
2. Name three different types of solid supports (support your answer with structures)
3. List one linker for releasing amide and one for releasing carboxylic acid (Provide names, structures, and cleavage conditions)
4. Please determine number of H-bond donors and acceptors of the following molecules:



1



2



3