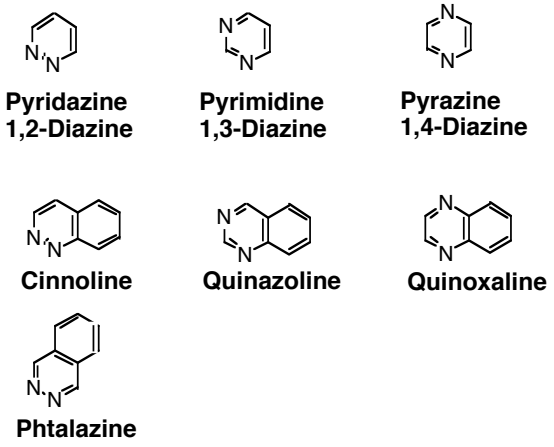
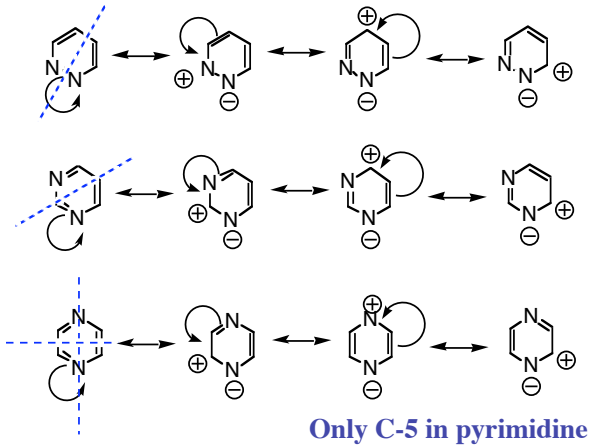
Chapter 10 - 11
Diazines





Only C-5 in pyrimidine
NOT elctron def.

Diazines

-Reacts less readily with electrophiles than pyridine

-Reacts easily with nucleophiles (additions / substitutions)

-Reacts with nucleophilic radicals (Minisci)

-Reacts as dienes in DA cycloadd. (less aromatic than pyridine)

Reactions with electrophiles

-Protonation

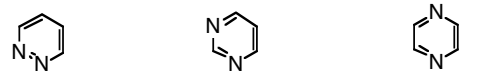
-N-alkylation

-Ox. to N-oxides (H_2O_2, peracids)

} **c.f. pyridines**

-Pract. no E-fil Ar subst. (C-5 pyrimidine)

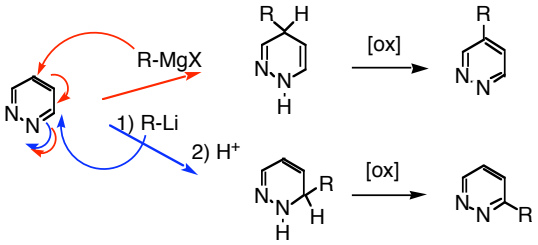
-Halogenation by add. / elim. mechanisms



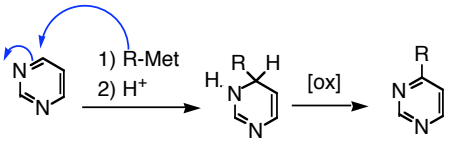
weaker bases than pyridine

Reactions with nucleophiles

Addition - Rearomatization

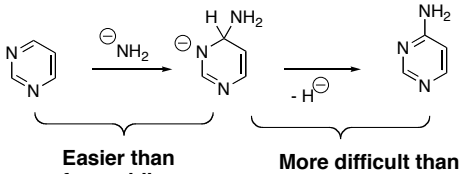


1,2- add
1,4-add



RMet: RLi, RMgX
[ox]: DDQ, $KMnO_4$

Add. av NH_2^- (Chichibabin)

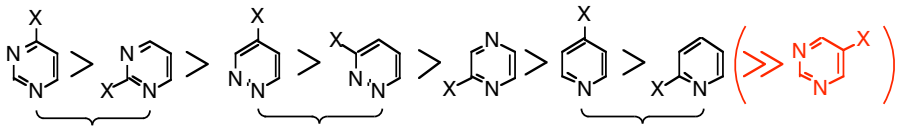


Easier than for pyridine

More difficult than for pyridine (less aromatic comp.)

Substitution on halodiazines

Reactivity:



Pyrimidines — Close in reactivity

Pyridazines

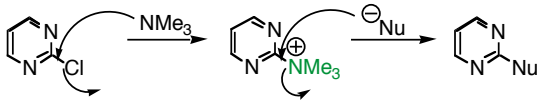
Pyrazines

Pyridines

Nucleophiles:
-ammonia / amines
-thiolates
-malonates etc.
-water / alchohols / alchoxides

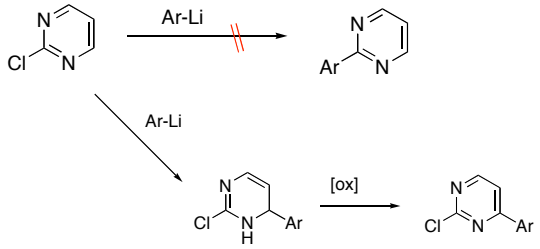
rel. soft

Leaving groups:
-halogen
-OMe
-SO_2Me

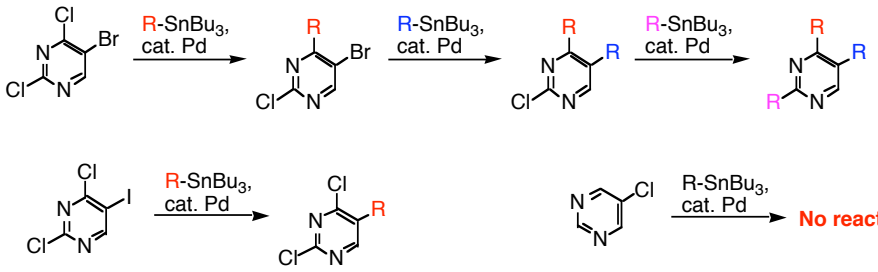


Better leav. group

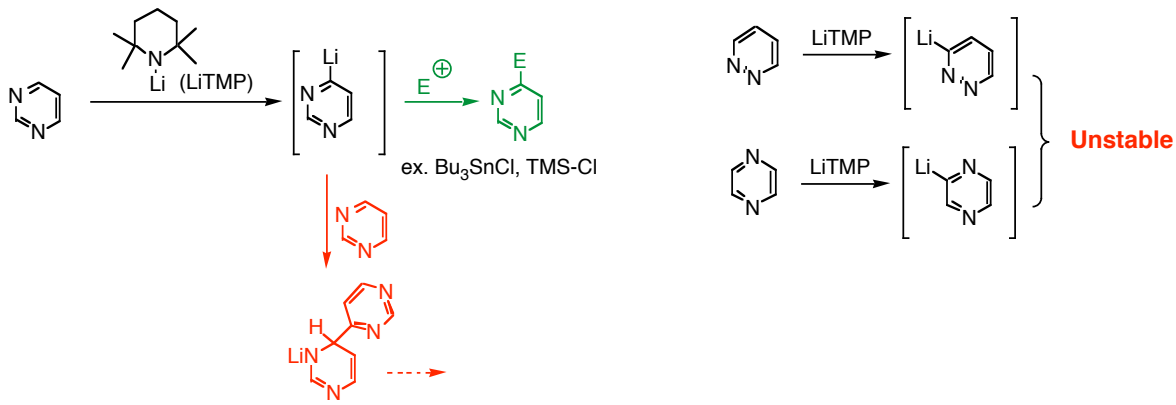
With hard Nu:

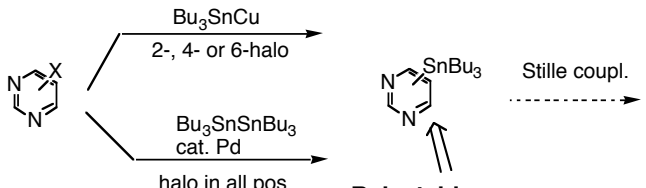


Pd-cat. couplings



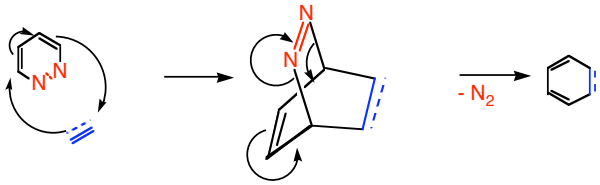
Metallation

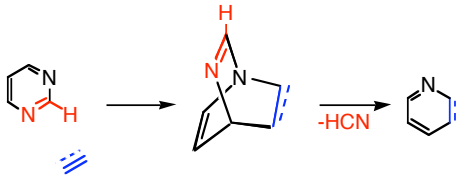


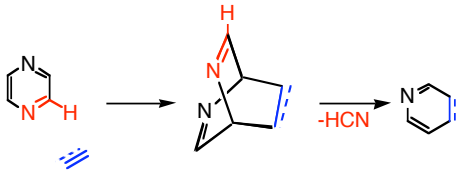


Rel. stable,
can be prepared without Pyr-Li as intermed.

Cycloadditions (DA)

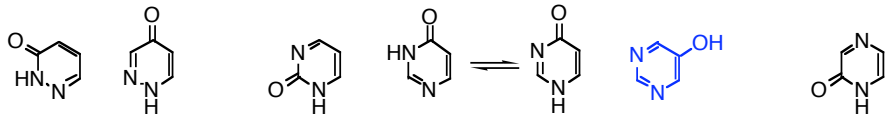


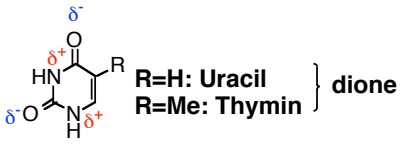


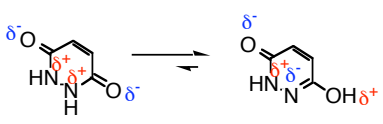


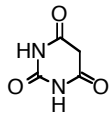
Oxydiazines

Structure - Tautomerism







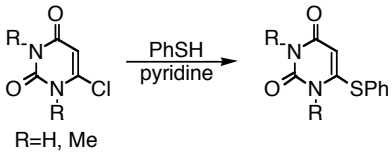


Barbitursyre: Trione

React. with E-files

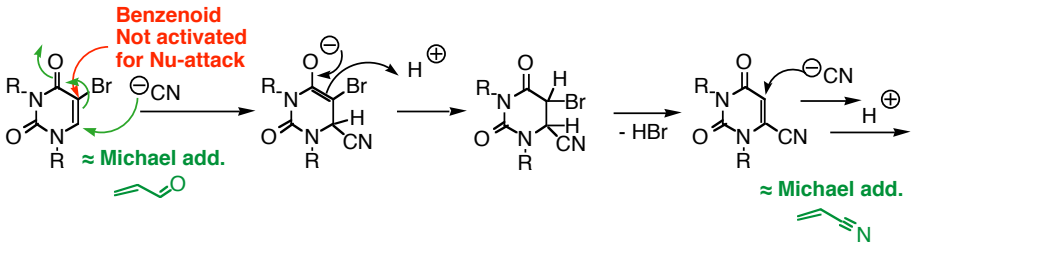
More electron rich, reacts easier with E-files than diazines
"OH" o/p directing

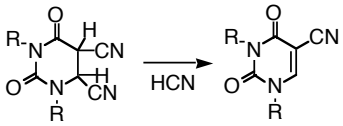
React. with Nu-files



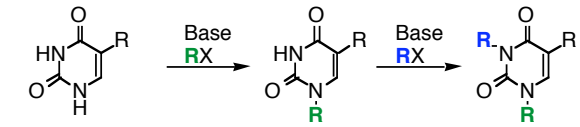
Nu Ar subst

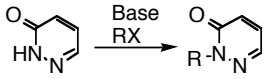
More complex mech.:





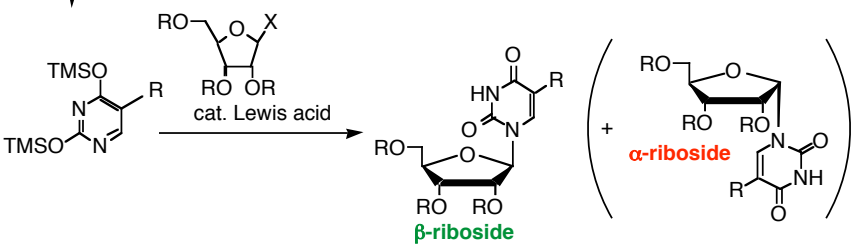
N-Deprotonation / Alkylation

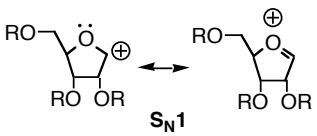




R=H: Uracil
R=Me: Thymin

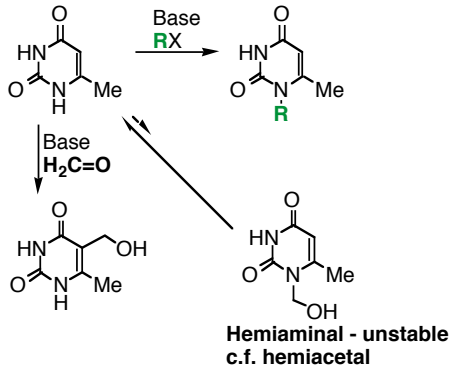
O-silylation / N-alkylation



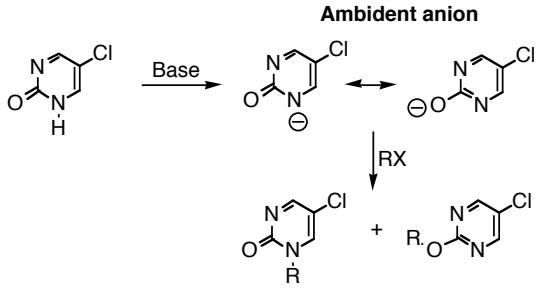


N-Deprotonation / Alkylation

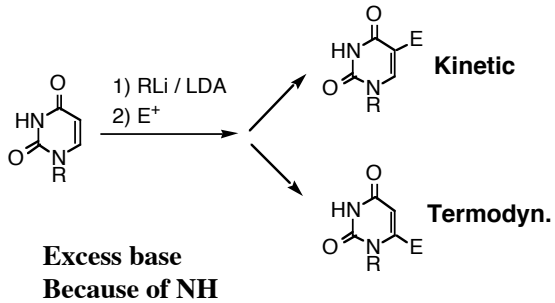
N-alkylation / C-alkylation



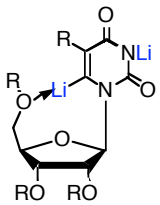
N-alkylation / O-alkylation



C-Deprotonation / Metallation

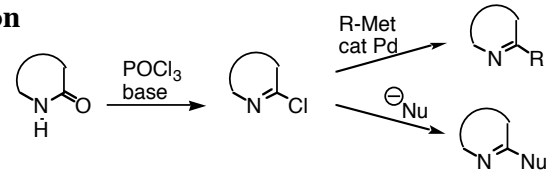


Excess base
Because of NH

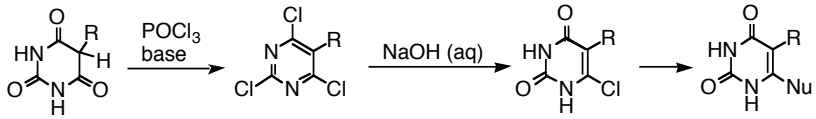


Replacement of oxygen

Halogenation

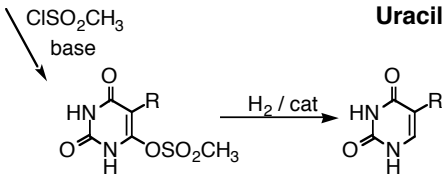


c.f. Pyridones

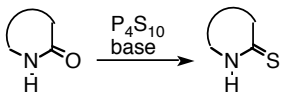


Uracil derivatives

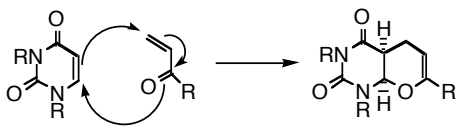
R≠H: Barbiturate



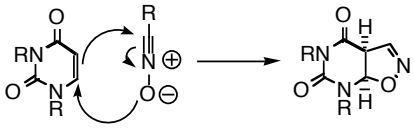
Oxo → thio



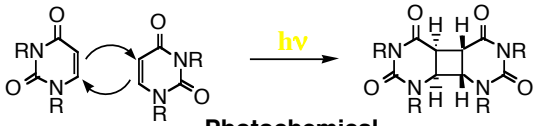
Cycloadditions



Dienophile in DA

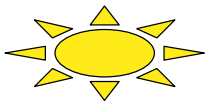


React. with 1,3-dipol



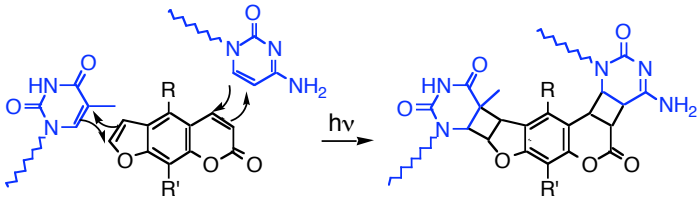
Photochemical
[2+2]

+ isomers



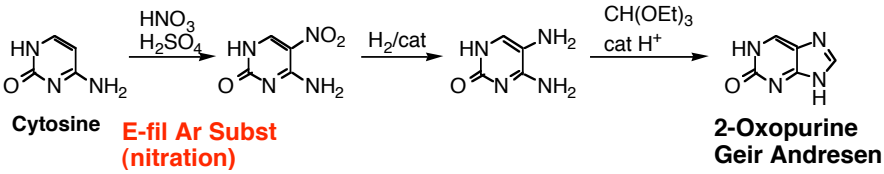
Cancer

Psoralenes - Psoriasis



Aminodiazines

- Exists as aminodiazines (not imino…)
- -NR2 electron donor: Stronger bases
- -NR2 electron donor: Participates easier in E-fil Ar subst.
- Diazotation reactions
- Dimroth rearrangement

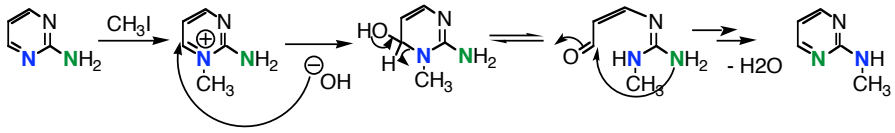


Cytosine

E-fil Ar Subst (nitration)

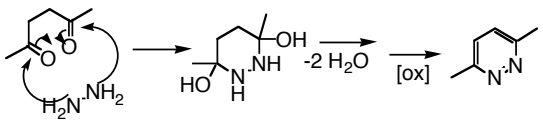
2-Oxopurine
Geir Andresen

Dimroth

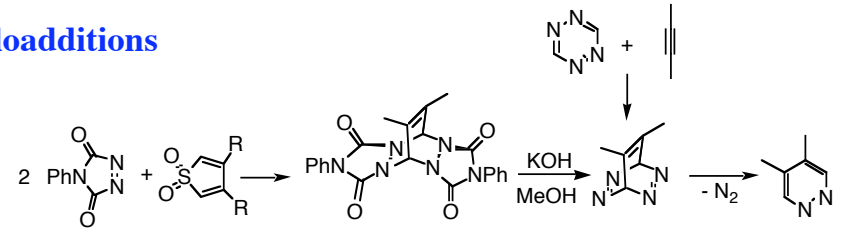


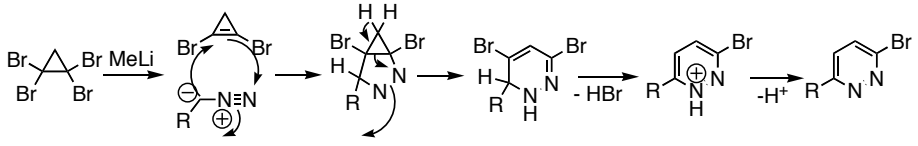
Synthesis of Pyridazines

Carbonyl condensations



Cycloadditions

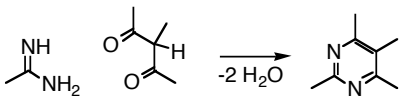


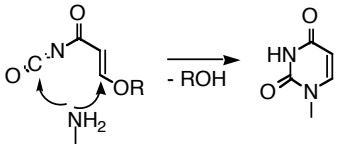


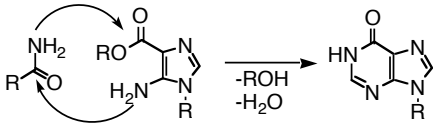
Diazoalkane

Synthesis of Pyrimidines

Carbonyl condensations etc.







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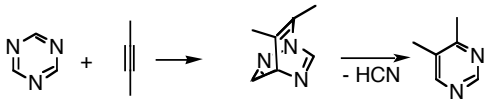
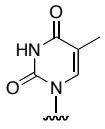
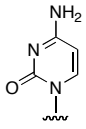


Bioactive Pyrimidines

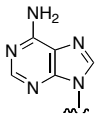
DNA bases



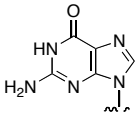
Thymine



Cytosine

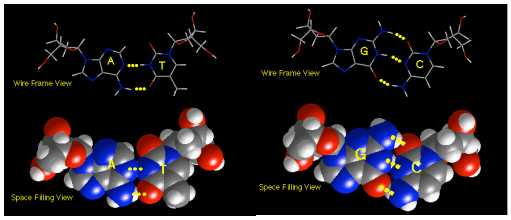


Adenine

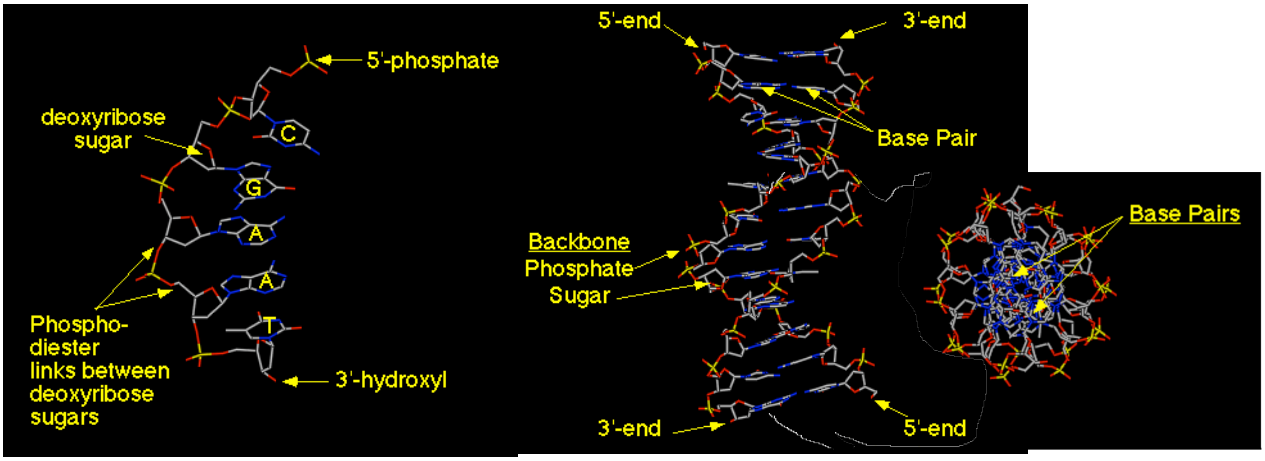


Guanine

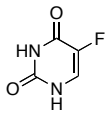
Base pairs



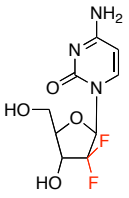
Double α-helix



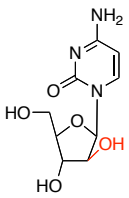
Anticancer comp.



5-FU

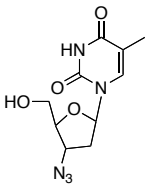


Gemcitabin

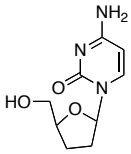


Cytarabine (ARA-C)

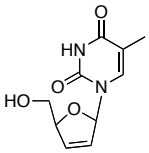
Antivirals

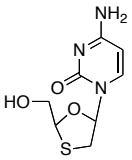


AZT



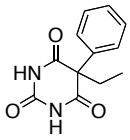
ddC



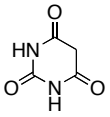


HIV (RT -inhibitors)

Barbiturates (old sedatives)



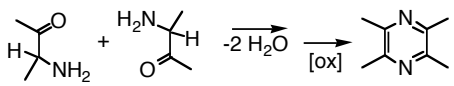
i.e. Phenobarbital

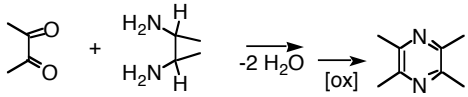


Barbituric acid
pKa 4.0

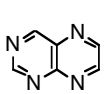
Synthesis of Pyrazines

Carbonyl condensations etc.

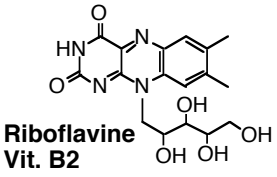




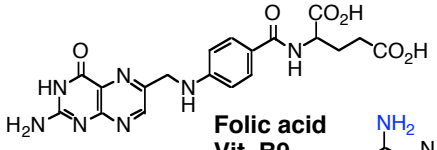
Bioactive Pyrazines: Pteridines



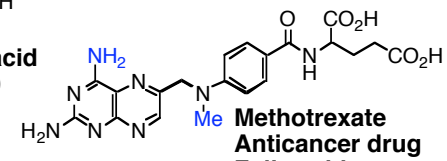
Pteridine



Riboflavine
Vit. B2

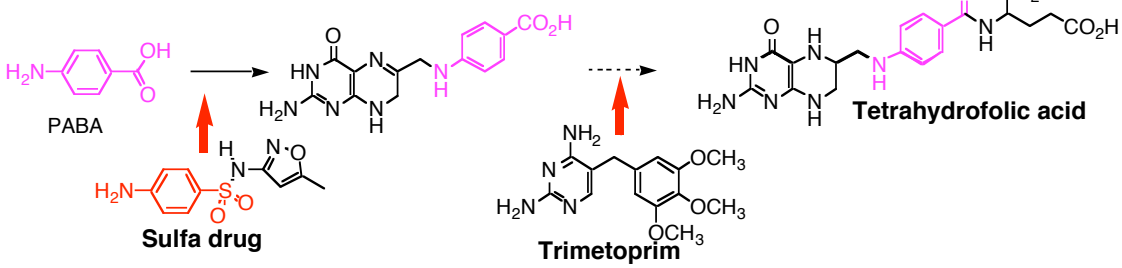


Folic acid
Vit. B9



Methotrexate
Anticancer drug
Folic acid antagonist

Bacteria synthesize folic acid



PABA

Sulfa drug

Trimetoprim

Tetrahydrofolic acid