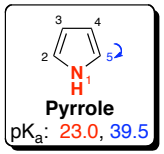
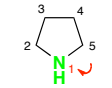
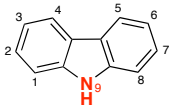
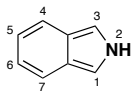
Essentials of Heterocyclic Chemistry-I

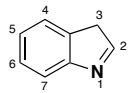
Deprotonation of N–H, Deprotonation of C–H, Deprotonation of Conjugate Acid

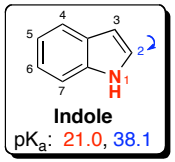



Pyrrolidine
pKa: 11.3,44


Carbazole
pKa: 19.9


Isoindole

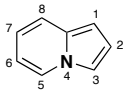

3H-Indole

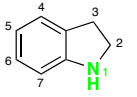


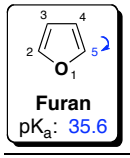

3-Pyrroline

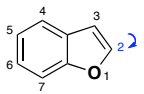

2H-Pyrrole

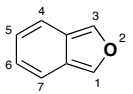

2-Pyrroline


Indolizine


Indoline
pKa: 4.9

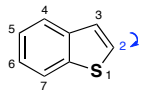


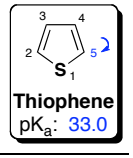

Benzofuran
pKa: 33.2

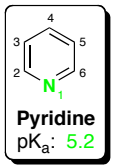

Isobenzofuran

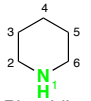

2H-Pyran

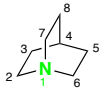

4H-Pyran

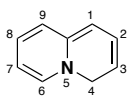

Benzo[b]thiophene
pKa: 32.4

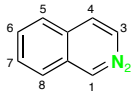


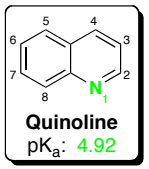


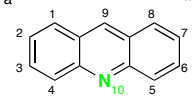

Piperidine
pKa: 11.2

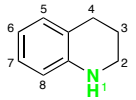

Quinuclidine
pKa: 11.0

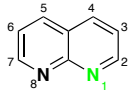

4H-Quinolizine

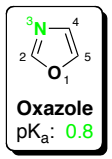

Isoquinoline
pKa: 5.4



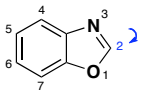

Acridine
pKa: 5.6

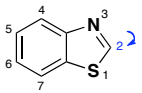

Tetrahydroquinoline
pKa: 5.0


1,8-Naphthyridine
pKa: 3.39

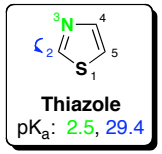


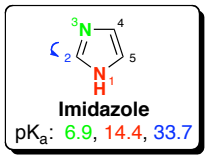

Isoxazole
pKa: –3


Benzoxazole
pKa: 24.4


Benzthiazole
pKa: 27.0

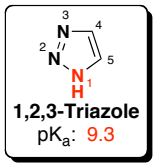

Isothiazole
pKa: –0.5

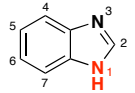


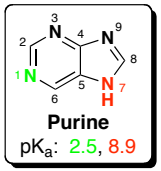



2-Imidazoline


1,3,4-Thiadiazole
pKa: –4.9




Benzimidazole
pKa: 16.4




Imidazolidine

Tetrazole
pKa: 4.9

1,2,4-Triazole
pKa: 2.2, 10.3, 26.2

Phenothiazine

1,3-Dioxolane

Thiomorpholine

1,3,5-Trithiane

1,4-Dithiane

Phenoxazine

2-Pyrazoline

Pyrazolidine

Quinazoline

Cinnoline

Pteridine

Phthalazine

1,2,4-Triazine
pKa: <0

1,3,5-Triazine
pKa: <0

Piperazine

Quinoxaline

Phenazine

1H-Indazole

Effects of Substitution on Pyridine Basicity:

	Me	^{t}Bu	NH_2	NHAc	OMe	SMe	Cl	Ph	vinyl	CN	NO_2	$CH(OH)_2$
2-position	6.0	5.8	6.9	4.1	3.3	3.6	0.7	4.5	4.8	–0.3	–2.6	3.8
3-position	5.7	5.9	6.1	4.5	4.9	4.4	2.8	4.8	4.8	1.4	0.6	3.8
4-position	6.0	6.0	9.2	5.9	6.6	6.0	3.8	5.5	5.5	1.9	1.6	4.7

Lithiation Positions: First, Second

Sites of Electrophilic Substitution: Major, Minor

Lipinski Rule of Five:

Christopher Lipinski (retired from Pfizer) formulated a set of criteria fulfilled in most orally available drugs.

1. No more than **five** hydrogen bond donors.
2. No more than **ten** hydrogen bond acceptors.
3. A molecular weight under **500**.
4. A LogP (partition coefficient) value under **five**.

Heterocyclic Aromaticity Values:

	% (of PhH)	β-value		% (of PhH)	β-value
pyridine	82	0.058	indole		0.047
tetrazole	80		benzothiophene		0.044
pyrazole	61		imidazole	43	0.042
quinoline	61	0.052	pyrrole	37	0.039
isoquinoline		0.051	benzofuran		0.036
pyrazine	75	0.049	thiophene	45	0.032
1,2,5-triazole	71		isoindole		0.029
pyrimidine	67	0.049	furan	12	0.007
pyridazine	65		isobenzofuran		0.002

Medicinal Chemistry Glossary:

ED_{50}: Dose required to yield maximum therapeutic effect in 50% of test animals.

Efficacy: Description of the relative intensity with which agonists vary in the response they produce, even with similar affinity.

Homologue: A compound belonging to a series of compounds differing from each other by a repeating unit (i.e. a CH_2, a peptide residue, etc.).

Intrinsic activity: The maximal stimulatory response induced by a compound relative to that of a given reference comopund.

LD_{50}: Dose required to kill 50% of test animals.

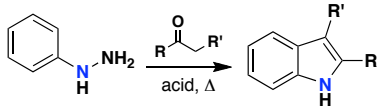
Partition coefficient (LogP): Log_{10} of the ratio of a compound's concentration in 1-octanol vs. water at equilibrium. A LogP<0 means that a compound is more soluble in water than in 1-octanol.

Pharmacophore: The ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or block) its biological response. This is not a real molecule or moiety, but rather an abstract concept that is considered the largest common denominator shared by a set of active molecules.

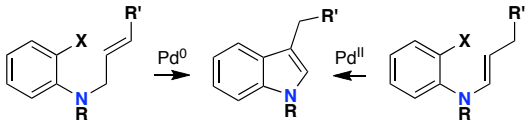
Potency: The dose of a drug required to produce a specific effect of given intensity as compared to a standard reference.

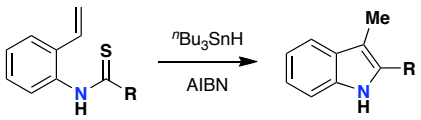
Therapeutic index: LD_{50}/ED_{50}

Indoles:

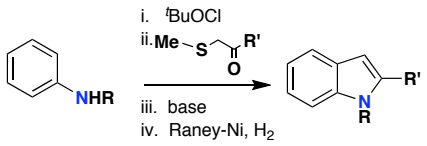


Fischer Indole Synthesis

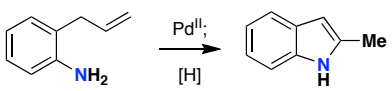




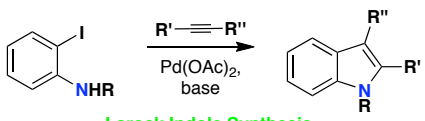
Fukuyama Indole Synthesis



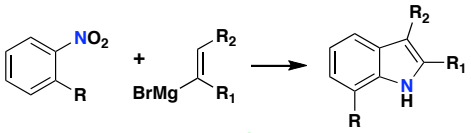
Gassman Indole Synthesis



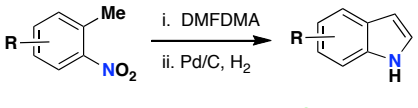
Hegedus Indole Synthesis



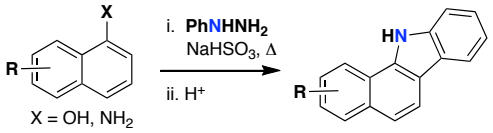
Larock Indole Synthesis



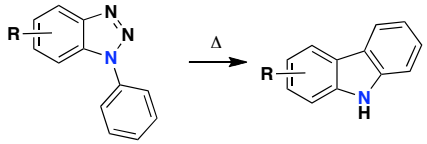
Bartoli Indole Synthesis



Batcho-Leimgruber Indole Synthesis

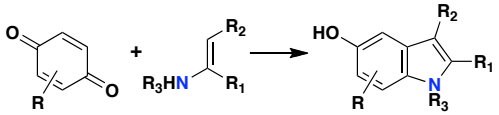


Bucherer Carbazole Synthesis

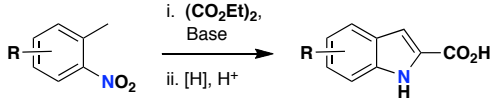


Graebe-Ullmann Carbazole Synthesis

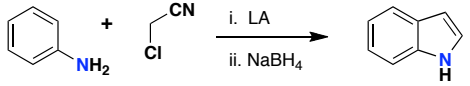
Madelung Indole Synthesis



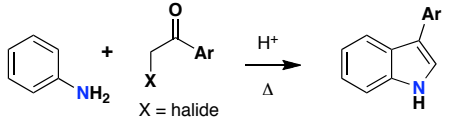
Nenitzescu Indole Synthesis



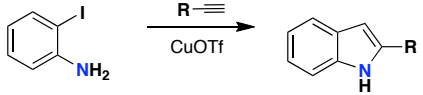
Reissert Indole Synthesis



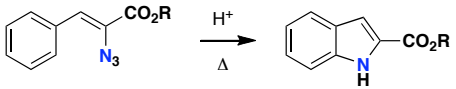
Sugasawa Indole Synthesis



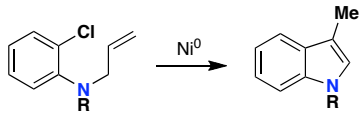
Bischler Indole Synthesis



Castro Indole Synthesis

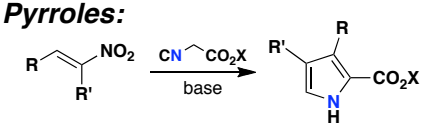


Hemetsberger Indole Synthesis

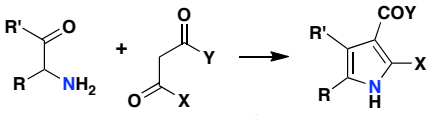


Mori-Ban Indole Synthesis

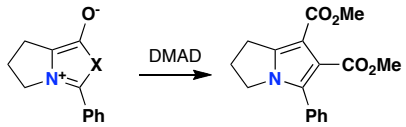
Pyrroles:



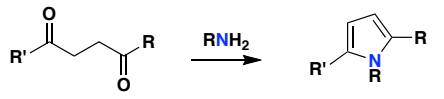
Barton-Zard Pyrrole Synthesis



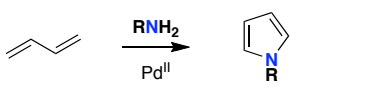
Knorr Pyrrole Synthesis

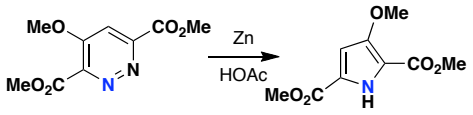


Huisgen Pyrrole Synthesis

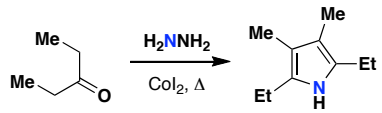


Paal-Knorr Pyrrole Synthesis

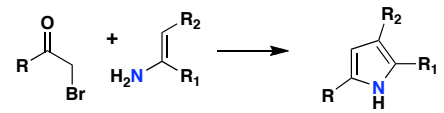




Boger Pyrrole Synthesis

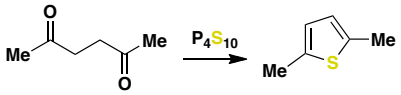


Piloty Pyrrole Synthesis

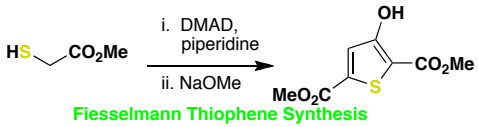


Hantzsch Pyrrole Synthesis

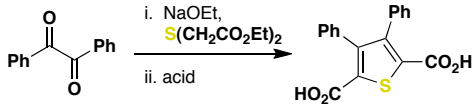
Thiophenes:



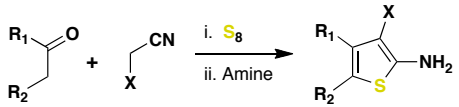
Paal Thiophene Synthesis



Fiesselmann Thiophene Synthesis

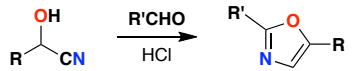


Hinsberg Thiophene Synthesis

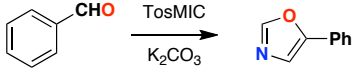


Gewald Aminothiophene Synthesis

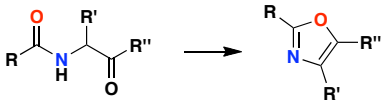
Oxazoles and Isoxazoles:



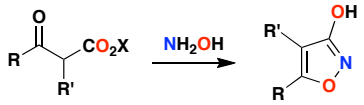
Fisher Oxazole Synthesis



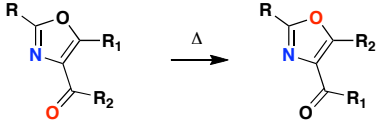
van Leusen Oxazole Synthesis



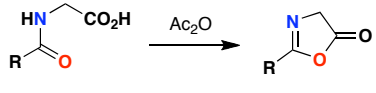
Robinson-Gabriel Oxazole Synthesis



Claisen Isoxazole Synthesis



Cornforth Rearrangement



Erlenmeyer-Plöchl Azlactone Synthesis