Nitrogen Containing Heterocycles

✓ Higher-Membered Ring Systems - Saturated
6-membered systems – piperidines, dihydropyridines

- **Meperidine**
  - Piperidine
  - Relieves pain, narcotic analgesic

- **Amlodipine**
  - Dihydropyridine
  - Ca²⁺ channel blocker, Antihypertensive, antianginal

- **Uracil**
  - Pyrimidine
  - One of the bases of RNA and DNA

- **Phenobarbital**
  - Pyrimidine
  - Controls epilepsy, seizures, as a sedative to relieve anxiety

- **Ciprofloxacin**
  - Piperazine
  - Antibacterial (anthrax)

- **Phenmetrazine**
  - Morpholine
  - Appetite suppressant, CNS stimulant, Amphetamine-like

- **Pentazocine**
  - Octahydroazepine
  - Pain reliever
Nitrogen Containing Heterocycles

Higher-Membered Ring Systems - Saturated

Tautomerism in Barbituric Acids – Enhanced Acidity of -NH

Urea group (neutral)

Imide group (acidic)

Keto form

Enol form

Barbituric Acid (Keto form)

Barbituric Acid (Enol form)

pK$_A$ ~4.1
Nitrogen Containing Heterocycles

✓ Unsaturated Ring Systems

5-membered ring systems

- Imidazole (1,3-diazole)
- Pyrazole (1,2-diazole)
- Oxazole (1,3-oxazole)
- Isoxazole (1,2-oxazole)

- Imidazoline (1,3-diazoline)
- Imidazolidine (1,3-diazidine)
- Oxazoline (1,3-oxazoline)
- Oxazolidine (1,3-oxazolidine)

Partly/fully saturated ring structures here are only for reference

Resonance in imidazole – the movement of a hydrogen

\[
\text{H} \quad \text{H}
\]
Nitrogen Containing Heterocycles

✓ Unsaturated Ring Systems

Examples of these ring systems in drugs

- Sulfisoxazole: sulfa-drug, anti-bacterial
- Metronidazole: anti-bacterial, anti-protozoan
- Celecoxib: COX-2 inhibitor, anti-inflammatory
Heterocycles

✓ Unsaturated Ring Systems Containing Sulfur

5-membered ring systems

- Tetrahydrothiophene (thiolane)
- Thiophene (Thiole)
- 1,3-thiazole

Methapyrilene
Anti-histaminic

Ceftizoxime
Anti-biotic

Thiazolsulfone
anti-malarial
More Complex Unsaturated Ring Systems

- the 1,3,4- and 1,2,5-thiadiazoles
- the 1,3,4-triazoles
- the 1,2,3,5-tetrazoles

- sulfamethizole: Anti-bacterial, Anti-protozoan
- timolol: Anti-hypertensive
- fuconazole: Anti-fungal
- losartan: Anti-hypertensive
Heterocycles

✓ More Complex Unsaturated Ring Systems

➢ 6-membered and higher heterocycles

Pyridine  pyridazine  pyrimidine  pyrazine

Quinoline  present in ……
Isoquinoline
Coumarin
Quinazoline
Pteridine

Chloroquine  (antimalarial)
Praziquantel  (anti-worm)
Warfarin  (anticoagulant)
Prazosin  (antihypertensive)
Triamterene  (antihypertensive)

Indole  present in ……
Isoindole
Benzimidazole
Benzoazole
Benzthiazole

Tryptophan  (common AA)
LSD  (hypnotic)
Omeprazole  (anti-ulcer)
Chlorozoxazone  (relieves pain)
Ethoxzolamide  (diuretic)
Heterocycles

✓ More Complex Unsaturated Ring Systems

- 6-membered and higher heterocycles

<table>
<thead>
<tr>
<th>Heterocycle</th>
<th>Function</th>
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</table>
| Indole      | present in .....
| Isoindole   | LSD (common AA, hypnotic) |
| Benzimidazole | Omeprazole (anti-ulcer) |
| Benzoxazole | Chlorozoxazine (relieves pain) |
| Benzthiazole | Ethozolamide (diuretic) |

<table>
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</table>
| 1,2,4-benzothia diazin-1,1,1-dioxide | present in .....
| 3H-1,4-Benzo diazepine | Chlorothiazone (antihypertensive) |
| 1,3-Dihydro-2H-1,4-benzodiazepin-2-one | Chlo mindset (sedative, hypnotic) |
| Phenothiazine | Diazepam (sedative, anxiolytic) |
| Acridine | Chloropromazine (anxiolytic) |
| 5H-dibenz [b,f]azepine | Quinocrine (antibiotic) |
| Imipramine | (anti-depressants) |
Heterocycles

Electrophilic Aromatic Substitution in Heterocycles

- Heterocycles generally react well with electrophiles; better than benzene (except for pyridines)
- Their stability to metabolic enzymes is generally lower than their carbocyclic analogs
- EAS occurs at the 2-position of 5-membered heterocycles
- EAS occurs at the 3-position of 6-membered heterocycles