NON-PHENOTHIAZINE DOPAMINE ANTAGONISTS:
The Dibenzoaxazepines and Related Compounds

MC Objective: Describe the chemical properties of the dibenzoaxepines (and related heterocyclic compounds):

- Structure: Analogues of the phenothiazines in which the central ring is replaced with a seven membered diazepine (X=N) or isosteric oxazepine (X=O) or thiazepine (X=S) ring. Note that these drugs contain a “piperazine” side chain (at C-11) but this differs in its position and chemical nature from the piperazine phenothiazines.

- Chemical Properties:
  - Terminal piperazine nitrogen is the most basic nitrogen atom in these structures (Do you know why?)! This basic, tertiary amine and is required for DA receptor binding. This amine group thus is ionized at physiologic pH and serves as a site for salt formation):
  - Lipophilic tricyclic structure with the ability to exist in non-ionized form: Ring system required for DA receptor binding and facilitates distribution to the CNS and other tissues.
• Members of the dibenzoxazepine (and isosteric heterocycle) so-called “atypical antipsychotic” class:

Clozapine (Clozaril) (Dibenzdiazepine)

Olanzapine (Zyprexa) (Dibenzdiazepine)

Quetiapine (Seroquel) (Dibenzthiazepine)

Loxapine (Loxitane) (Dibenzoxazepine)

MC Objective: Describe the relationship between chemical properties of the dibenzoxazepines (and related compounds) and key pharmacologic properties:

Clozapine Properties:
- Low DA affinity/Potency < Phenothiazine Piperazines ("Atypical")
- Low EPS < Phenothiazine Piperazines
- Low prolactin secretion
- Higher Sedation > Phenothiazine Piperazines
- Higher AntiAch >> Phenothiazine Piperazines
- Higher Hypotension >> Phenothiazine Piperazines
- 5-HT-2 Antagonism ("Atypical")
- Seizure potential (limits use to alternative)
- Agranulocytosis risk (monitor)
**Olanzapine**

- Low DA affinity/Potency < Phenothiazine Piperazines ("Atypical")
- Low EPS < Phenothiazine Piperazines
- Higher Sedation > Phenothiazine Piperazines
- Higher AntiAch >> Phenothiazine Piperazines
- Higher Hypotension >> Phenothiazine Piperazines
- More potent 5-HT-2 Antagonism than clozapine ("Atypical")
- No agranulocytosis reported

**Loxapine**

- Intermediate DA affinity < Phenothiazine Piperazines ("Atypical")
- Intermediate EPS (>Clozapine) < Phenothiazine Piperazines
- Lower Sedation <= Phenothiazine Piperazines
- Low AntiAch = Phenothiazine Piperazines
- Low Hypotension = Phenothiazine Piperazines
- 5-HT-2 Antagonism??? ("Atypical")

**Quetiapine**

- Low DA affinity/Potency < Phenothiazine Piperazines ("Atypical")
- Low EPS < Phenothiazine Piperazines
- Some prolactin secretion
- Intermediate Sedation >= Phenothiazine Piperazines
- Low AntiAch = Phenothiazine Piperazines
- Higher Hypotension > Phenothiazine Piperazines
- More potent 5-HT-2 Antagonism than clozapine ("Atypical")

**MC Objective:** Describe the relationship between chemical properties of the dibenzoxazepines (and related compounds) and key pharmacokinetic properties:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Bioav</th>
<th>Time to peak</th>
<th>VD</th>
<th>PPB</th>
<th>Metabolism</th>
<th>Renal</th>
<th>Fecal</th>
<th>Elim T1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>27-50% (FP)</td>
<td>2.3-3 hrs</td>
<td>6 L/Kg</td>
<td>97%</td>
<td>Extensive</td>
<td>50% as mets</td>
<td>30% as Mets</td>
<td>8-12 hrs</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>60% (FP)</td>
<td>6 hrs</td>
<td>1000L</td>
<td>Extensive</td>
<td>57%</td>
<td>30%</td>
<td>21-54 hrs</td>
<td></td>
</tr>
<tr>
<td>Loxapine</td>
<td>Low (FP)</td>
<td>1-2 hr</td>
<td>Extensive</td>
<td>30-40% as mets</td>
<td>50% as mets</td>
<td>4 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>60% (FP)</td>
<td>6 hrs</td>
<td>1000L</td>
<td>Extensive</td>
<td>57%</td>
<td>30</td>
<td>21-54 hrs</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>9% (FP)</td>
<td>1.5 hrs</td>
<td>10L/Kg</td>
<td>83%</td>
<td>Extensive</td>
<td>70%</td>
<td>20%</td>
<td>6 hrs</td>
</tr>
</tbody>
</table>
- **Absorption**: All of the dibenzoxazepine derivatives are well absorbed (>90%) from the GI tract (small intestine) by passive mechanisms due to their high lipophilicity, and yield peak plasma levels within several hours.

- **Oral Bioavailability**: All of the dibenzoxazepine derivatives display relatively low oral bioavailabilities due to extensive first pass (FP) metabolism. The large aromatic tricyclic structure and terminal groups serves as good sites for metabolic reactions, mainly CYP oxidations (See metabolism below).

- **Distribution**: As lipophilic basic compounds (ionization equilibrium) all of the dibenzoxazepine derivatives are widely distributed and readily enter the CNS. The lipophilic tricyclic structure also favors plasma protein binding.

- **Elimination**: The dibenzoxazepine derivatives are eliminated in both the urine and the feces, mainly as metabolites. The excretion is relatively “balanced” due to the lipophilic nature of these drugs and some of its metabolites, and the polarity of other metabolites (see metabolite structures in the figures that follow).

- **Metabolism**: The primary metabolic pathways the dibenzoxazepine derivatives undergo are OND, AH, N-Ox and glucuronidation. The primary metabolic pathways for these drugs are listed and shown in the figure that follow on the next several pages:

  Clozapine: major metabolites desmethylclozapine-active (both CYP1A2 and CYP3A4) and clozapine N-oxide-inactive (CYP3A4) and hydroxylated (inactive)

  Olanzapine: The primary metabolic pathways for olanzapine are direct glucuronidation (inactive) and oxidation to desmethyl (inactive) mediated by CYP1A2, CYP2D6, and the flavin-containing monoxygenase system. CYP2D6 appears to be a minor pathway

  Quetiapine: Primarily metabolized by sulfoxidation and oxidation with the CYP3A4 isoenzyme primarily responsible. Twenty metabolites of quetiapine have been identified; the 7-hydroxylated metabolite and the N-dealkylated metabolite are pharmacologically active

  Loxapine: N-desmethyl loxapine (active), 8-hydroxyloxapine (active), 8-hydroxydesmethyl-loxapine
Metabolism of Clozapine

Clozapine (Clozail)

N-Desmethyl (Active: 5-HT/DA): $t_{1/2} = 13$ hrs

N-Oxde (Inactive): $t_{1/2} = 7$ hrs

Phenols (Inactive): $t_{1/2} = ??$
Metabolism of Quetiapine

Quetiapine (Seroquel) → CYP → N-Dealkyl metabolite (Active)

Metabolism of Olanzapine

Olanzapine (Zyprexa) → CYP1A2 (major) → 4'-Desmethyl (Inactive)

10-N-Glucuronide (Inactive)
NON-PHENOTHIAZINE DOPAMINE ANTAGONISTS: HALOPERIDOL AND THE BUTYROPHENONES

MC Objective: Describe the development of the butyrophenone (haloperidol-type) antipsychotic agents:

- The butyrophenones are analogues of the analgesic meperidine in which the N-methyl group was replaced with larger, more lipophilic propiophenone or butyrophenone moiety. This substitution, particularly butyrophenone, resulted in the emergence of DA receptor antagonist activity.
- Replacement of the ester with a hydroxyl group and halogenation of the aromatic rings resulted in enhancement of DA receptor antagonist activity as observed for haloperidol.
- The hydroxyl group of haloperidol can be converted to a lipophilic ester moiety to yield a prodrug for IM injection that produces therapeutic blood levels of drug for up to 4 weeks.
• Benzimidazolone derivatives of the butyrophenones show enhanced DA receptor antagonist activity. Droperidol: Used as a sedative-neuroleptic and in combination with the analgesic fentanyl (Innovar) for sedation and angesia

**MC Objective:** Describe the chemical properties of the butyrophenone antipsychotics:

- Basic tertiary amine (piperidine) is the most basic nitrogen atom in these structures (Do you know why?)! This basic, tertiary amine and is required for DA receptor binding. This amine group thus is ionized at physiologic pH and serves as a site for salt formation:

- Lipophilic (halogenated rings) with the ability to exist in non-ionized form: Ring systems required for DA receptor binding and facilitates distribution to the CNS.
- p-F or p-substituent of similar electronegativity (CF3) required for optimal affinity
- Lengthening, shortening or branching of the butyl side chain reduces activity
- Carbonyl important, but can be replaced by CH-Ar as in the diarylpiperidines

![Haloperidol](image.png)

**MC Objective:** Describe the relationship between chemical properties of the butyrophenones and key pharmacologic properties:

**Haloperidol:**

- High DA affinity/Potency =/> Phenothiazine Piperazines
- High EPS = Phenothiazine Piperazines
- Low Sedation ≤ Phenothiazine Piperazines
- Low AntiAch = Phenothiazine Piperazines
- Low Hypotension = Phenothiazine Piperazines

**MC Objective:** Describe the relationship between chemical properties of the butyrophenones and key pharmacokinetic properties:

**Haloperidol:**

- Oral Bioavailability: 60-70%
- Time to peak plasma levels: 2-6 hours
- Vd: 1300L
- PPB: 90%
- CNS: High
- Metabolism: Reduction to alcohol, OND and beta-oxidation (see next page)
- Metabolic variability: Asians less reduction to active alcohol (3x lower alcohol levels)
- Renal Excretion: 33-40%
- Fecal Excretion: 15%
- Elimination Half-life: 21 hours
Metabolism of Haloperidol

Haloperidol

Reduction

Oxidation (OND)

Oxidation (OND)

Reduction Oxidation (OND)

Glycine Conjugation
NON-PHENOTHIAZINE DOPAMINE ANTAGONISTS:
DIPHENYLBUTYLPIPERIDINES

MC Objective: Describe the development of the diphenylbutylpiperidine (pimozide-type) antipsychotic agents:

- Analogue of the butyrophenones in which the ketone group is replaced with an arylmethine (-CHAr) group. Note that each of the diphenyllbutylpiperidines are analogues of a corresponding butyrophenone:

  ![Chemical Structures]

  - Haloperidol
  - Penfluridol
  - Droperidol
  - Pimozide (Orap)
  - Spiperone
  - Fluspirilene

- Chemical Properties:
  - Piperidiine nitrogen is the most basic nitrogen atom in these structures (Do you know why?)! This basic, tertiary amine and is required for DA receptor binding. This amine group thus is ionized at physiologic pH and serves as a site for salt formation.

  - Lipophilic multicyclic structure with the ability to exist in non-ionized form: Ring system required for DA receptor binding and facilitates distribution to the CNS and other tissues.
MC Objective: Describe the relationship between chemical properties of the diphenylbutylpiperidines and key pharmacologic properties:

**Pimozide Properties:**

- High DA affinity/Potency => Phenothiazine Piperazines
- High EPS = Phenothiazine Piperazines
- Moderate Sedation => Phenothiazine Piperazines
- Moderate AntiAch > Phenothiazine Piperazines
- Low Hypotension = Phenothiazine Piperazines
- Longer-acting than Haloperidol
- Arrhythmias (prolongs QT interval)

MC Objective: Describe the relationship between chemical properties of the diphenylbutylpiperidines and key pharmacokinetic properties:

**Pimozide**

- Oral Bioavail: >50% (1st pass)
- Time to Peak: 6-8 hours
- Distribution: Not much published data. Distribute well to CNS
- Metabolism: By CYP 3A (potential drug interactions) to 4, 4-bis-(4-fluorophenyl) butyric acid, 1-(4-piperidyl)-2-benzimidazolinone, and others. Rate of metabolism SLOWER than haloperidol (longer action)
- Renal Excretion: 38-45%, Fecal Excretion: ?
- Elimination Half-life: 53-55 hours

![Pimozide (Orap) structure](image)

Butyric Acid metabolite (Inactive)
NON-PHENOTHIAZINE DOPAMINE ANTAGONISTS: DIHYDROINDOLONES

**MC Objective:** Describe the chemical properties of the dihydroindolone (molindone-type) antipsychotics:

- Some structural similarity to the butyrophenones and other non-phenothiazine antipsychotics.

- Morpholine nitrogen is the most basic nitrogen atom in this structures (Do you know why?)! This basic, tertiary amine and is required for DA receptor binding. This amine group thus is ionized at physiologic pH and serves as a site for salt formation.

- Lipophilic multicyclic structure with the ability to exist in non-ionized form: Ring system required for DA receptor binding and facilitates distribution to the CNS and other tissues.

**MC Objective:** Describe the relationship between chemical properties of the the dihydroindolone (molindone-type) antipsychotics and key pharmacologic properties:

**Molindone Properties:**

- Lower DA affinity/Potency < Phenothiazine Piperazines
- Intermediate EPS <= Phenothiazine Piperazines
- Moderate Sedation = Phenothiazine Piperazines
- Low AntiAch = Phenothiazine Piperazines
- Low Hypotension = Phenothiazine Piperazines
- Agranulocytosis risk (monitor)

**MC Objective:** Describe the relationship between chemical properties of the dihydroindolone (molindone-type) antipsychotics and key pharmacokinetic properties:

**Molindone**

- Oral Bioavail: ?
- Time to Peak: 1.5 hours
- Distribution: Little published data. Good CNS penetration
- Metabolism: 36 recognized metabolites of Molindone
- Renal Excretion: Only 2%, Fecal Excretion: ?
- Elimination Half-life: ?
NON-PHENOTHIAZINE DOPAMINE ANTAGONISTS: BENZISOXAZOLES

MC Objective: Describe the chemical properties of the benzisoxazole (Risperidone-type) antipsychotics:

- Some structural similarity to the butyrophenones and other non-phenothiazine antipsychotics.
- Piperidine nitrogen is the most basic nitrogen atom in this structure (Do you know why?)! This basic, tertiary amine is required for DA receptor binding. This amine group thus is ionized at physiologic pH and serves as a site for salt formation.
- Lipophilic multicyclic structure with the ability to exist in non-ionized form: Ring system required for DA receptor binding and facilitates distribution to the CNS and other tissues.

MC Objective: Describe the relationship between chemical properties of the benzisoxazole (Risperidone-type) antipsychotics and key pharmacologic properties:

Risperidone Properties:
- High DA affinity/Potency ≥ Phenothiazine Piperazines
- Low EPS < Phenothiazine Piperazines
- Low Sedation < Phenothiazine Piperazines
- Low AntiAch =/< Phenothiazine Piperazines
- Moderate Hypotension > Phenothiazine Piperazines
- High Affinity for 5-HT-2 and D-2 receptors (ratio SDA = 5) and alpha-1 and 2 receptors and histamine H-1 receptors
MC Objective: Describe the relationship between chemical properties of the benzisoxazole (Risperidone-type) antipsychotics and key pharmacokinetic properties:

**Risperidone**

- Oral Bioavail: 70% (Some reduction by first pass)
- Time to Peak: 1 hr (rapid absorption)
- Distribution: Highly protein bound (90%) and good CNS distribution
- Metabolism: Risperidone is metabolized by cytochrome P450IID ring hydroxylation with a second minor pathway of N-dealkylation (see below). The ring hydroxylation reaction is sensitive to the “debrisoquine hydroxylation-type” genetic polymorphism. The main ring hydroxylation product, **9-hydroxyrisperidone**, is approximately equi-effective to the parent compound in terms of receptor binding activity
- Renal Excretion and Fecal Excretion: ??
- Elimination Half-life: 20-30 hrs
NON-PHENOTHIAZINE DOPAMINE ANTAGONISTS: BENZISOTHIAZOLES

MC Objective: Describe the properties of the benzisothiazole (Ziprasidone-type) antipsychotics:

- Some structural similarity to the benzisoxazoles and other non-phenothiazine antipsychotics. Approved in US currently
- Piperazine nitrogen is the most basic nitrogen atom in this structures (Do you know why?)! This basic, tertiary amine and is required for DA receptor binding. This amine group thus is ionized at physiologic pH and serves as a site for salt formation
- Lipophilic multicyclic structure with the ability to exist in non-ionized form: Ring system required for DA receptor binding and facilitates distribution to the CNS and other tissues.
- Pharmacology of Ziprasidone:
  - D-2, D-3 and 5-HT-2 receptor antagonist
  - Little or no EPS
  - Little orthostatic hypotension
  - Antidepressant and antianxiety activity

- Pharmacokinetics of Ziprasidone
  - Oral Bioavail: 60%
  - Time to Peak: 4-5 hrs
  - Vd: 2.3 L/Kg
  - PPB: 99%
  - Metabolism: CYP3A4-mediated reactions yielding the sulfone, sulfoxide and OND metabolites which are inactive as 5HT-2A and D2 receptor antagonists.
  - Elimination Half-life: 4-5 hr
NON-PHENOTHIAZINE DOPAMINE ANTAGONISTS: INDOLE-PIPERIDINES

MC Objective: Describe the properties of the indolepiperidine (Sertindole-type) antipsychotics:

- Some structural similarity to the diphenylbutylpiperazines and other non-phenothiazine antipsychotics. **Not available in US currently**
- Piperidine nitrogen is the most basic nitrogen atom in this structures (Do you know why?)! This basic, tertiary amine and is required for DA receptor binding. This amine group thus is ionized at physiologic pH and serves as a site for salt formation
- Lipophilic multicyclic structure with the ability to exist in non-ionized form: Ring system required for DA receptor binding and facilitates distribution to the CNS and other tissues.
- Pharmacology of Sertindole (Serlect)
  - D-2 and 5-HT-2 receptor antagonist
  - Little or no EPS
- Pharmacokinetics of Sertindole (Serlect)
  - Oral Bioavail: 74%
  - Time to Peak: 10 hrs
  - Vd: 20-40 L/Kg
  - PPB: 99%
  - Metabolism by CYP450 2D6 and 3A isoenzymes to form dehydrosertindole which is active and accounts for 40% of the metabolites, Norsertindole which is inactive and accounts for 20% of the metabolites and Hydroxy metabolites of unknown structure.
  - Elimination Half-life: 55-90 hours
## Select Dosage and Pharmacologic Parameters of Antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic agent</th>
<th>Approx equiv. dose (mg)</th>
<th>Adult daily dosage range (mg)</th>
<th>Sedation</th>
<th>EPS</th>
<th>Anti-ACh</th>
<th>Orthostatic Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenothiazines: Aliphatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>100</td>
<td>30 to 800</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Promazine</td>
<td>200</td>
<td>40 to 1200</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Trifluromazine</td>
<td>25</td>
<td>60 to 150</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Phenothiazines: Piperazine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>2</td>
<td>0.5 to 40</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>10</td>
<td>12 to 64</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>15</td>
<td>15 to 150</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>5</td>
<td>2 to 40</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Phenothiazines: Piperidines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>50</td>
<td>30 to 400</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>100</td>
<td>150 to 800</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Thioxanthenes:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiothixene</td>
<td>4</td>
<td>8 to 30</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Butyrophenone (Phenylbutylpiperadines):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>1 to 15</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Diphenylbutylpiperadines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td>0.3- 0.5</td>
<td>1 to 10</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Dihydroindolones:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molindone</td>
<td>10</td>
<td>15 to 225</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Dibenzoxazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loxapine</td>
<td>15</td>
<td>20 to 250</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>50</td>
<td>300 to 900</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Thienbenzodiazepine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5</td>
<td>5 to 20</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Dibenzothiazepine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>50</td>
<td>50 to 800</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td><strong>Benzisoxazoles:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>4</td>
<td>4 to 16</td>
<td>+</td>
<td>++</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

+++ = High incidence of side effects ++ = Moderate incidence of side effects + = Low incidence of side effects *(over the therapeutic dose range)*. At doses > 10 mg/day, risperidone's EPS profile is similar to typical antipsychotics.
NON-PHENOTHIAZINE DOPAMINE ANTAGONISTS: BENZAMIDES

PABA

\[
\begin{align*}
\text{O-MeO-Procainamide} & \quad \text{Local anesthetic and antiemetic} \\
\text{Metoclopramide} & \quad \text{DA antagonist: CNS Penetration} \\
& \quad \text{Antiemetic and antipsychotic activity} \\
\text{Pyrrolidinyl Benzamides} & \\
R = NH_2: \text{Sulpiride: Neuroleptic, Low EPS and sedation} \\
R = CH_2CH_3: \text{Sultopride: Neuroleptic, High EPS and sedation} \\
\text{Remoxipride (Pyrrolidinyl Benzamides)}
\end{align*}
\]