

Drugs Acting on CNS

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Depressant Drugs

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Antipsychotic Drugs (Major Tranquilizers)

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- Antipsychotic drugs are used to manage psychosis:
 - ✓ Schizophrenia.
 - ✓ Bipolar disorder.
- Idiopathic.
- Increased dopamine activity (mesolimbic).
- D₂-antagonism is the major mechanism.
- Extrapyramidal symptoms (typical drugs).
- Unsteady Parkinson's disease-type movement.

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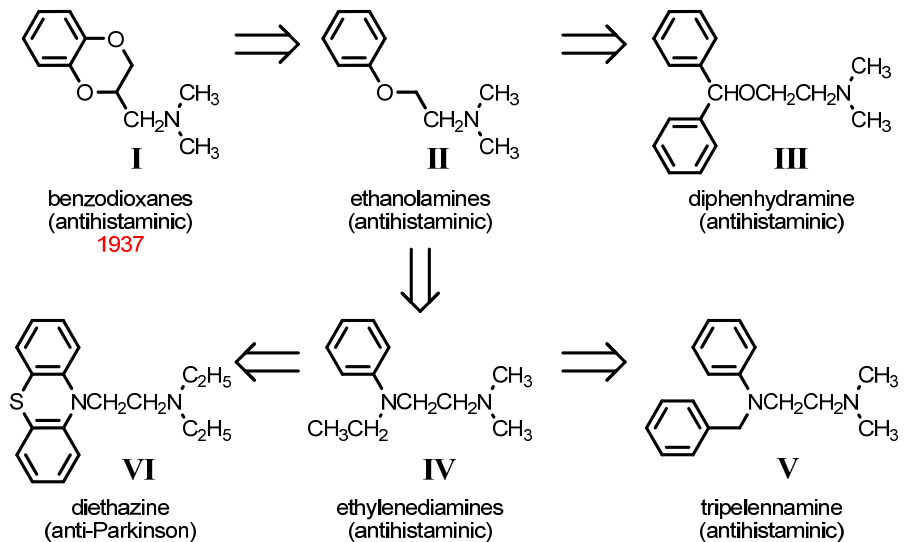
- The major 4 dopamine pathways in the brain:
 - ✓ Mesolimbic (Behavioral response).
 - ✓ Nigrostriatal (Production of movement).
 - ✓ Mesocortical (Motivation & Emotional response).
 - ✓ Tuberoinfundibular (Prolactin secretion).

- Other CNS receptors systems are involved:
 - ✓ Acetylcholine.
 - ✓ Histamine.
 - ✓ Norepinephrine.
 - ✓ Serotonin.
- Specially for atypical drugs.

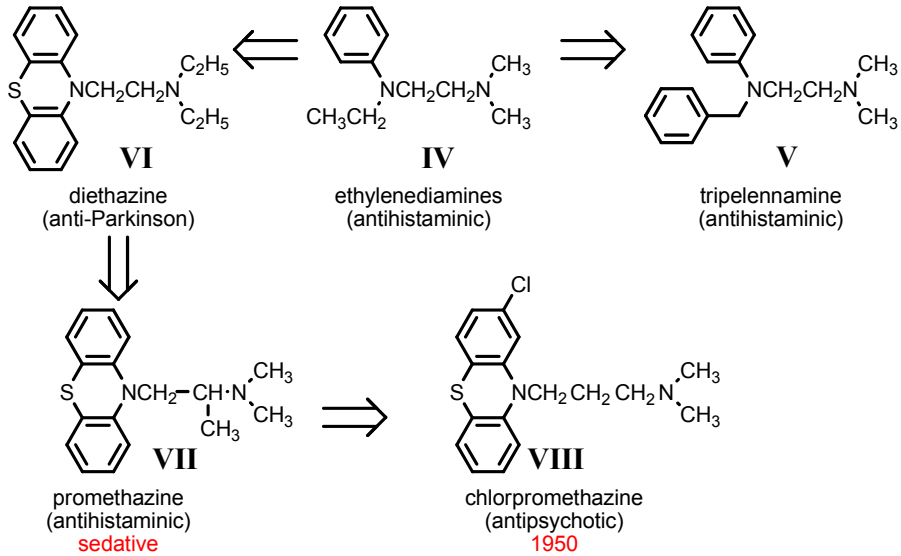
Classification of Antipsychotic Agents

- **Typical:**
 - ✓ Phenothiazine & thioxanthene derivatives.
 - ✓ Butyrophenone derivatives.
- **Atypical:**
 - ✓ Benzamide derivatives.
 - ✓ Benzazepine derivatives.
 - ✓ Benzisoxazole & benzisothiazole derivatives.

Development of Typical Antipsychotics

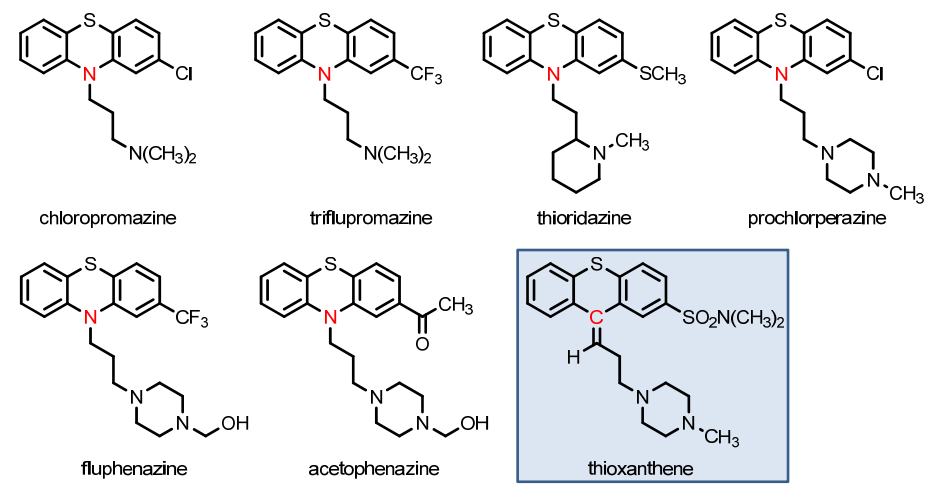


Cont.



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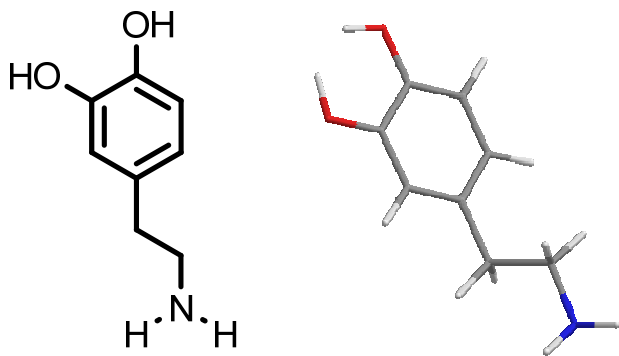
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Structure-Activity Relationships

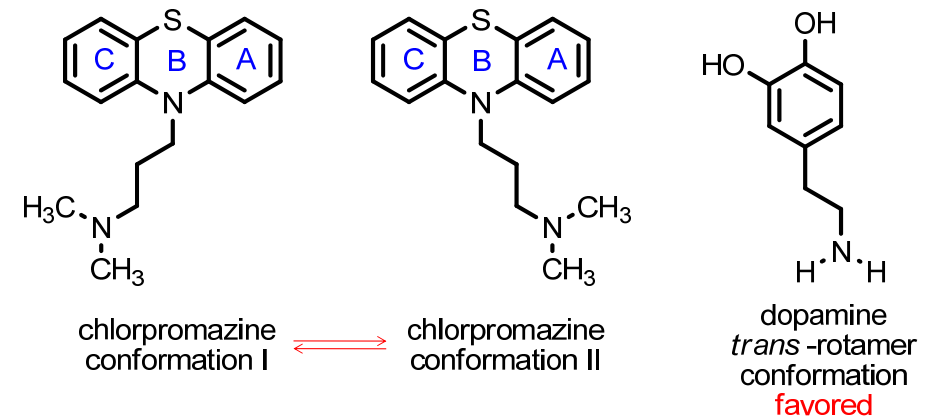


- Dopamine *trans*-rotamer conformation.
- Favored.

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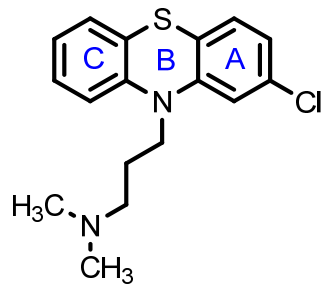
Structure-Activity Relationships



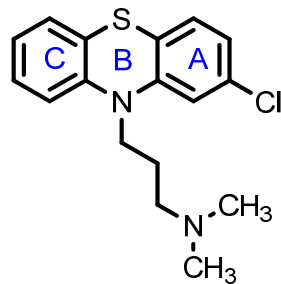
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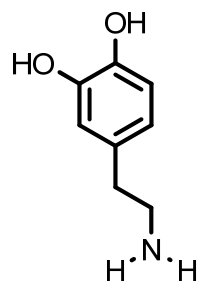
Structure-Activity Relationships



chlorpromazine
conformation I
disfavored

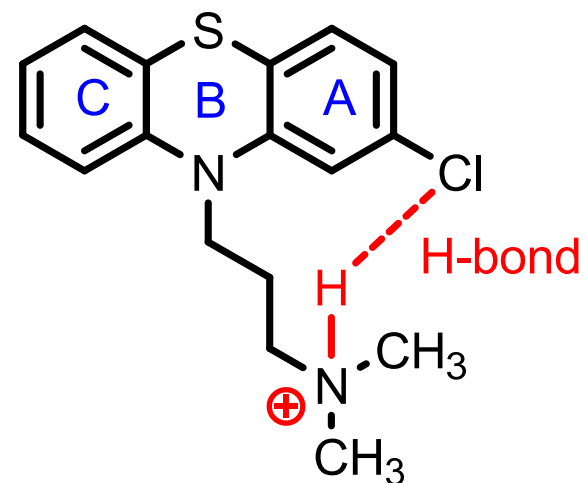


chlorpromazine
conformation II
favored

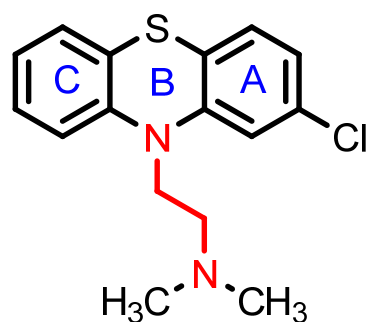


dopamine
trans-rotamer
conformation
favored

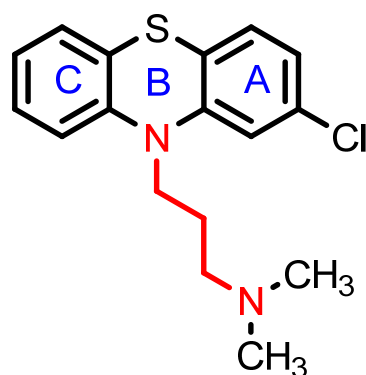
Structure-Activity Relationships



Structure-Activity Relationships

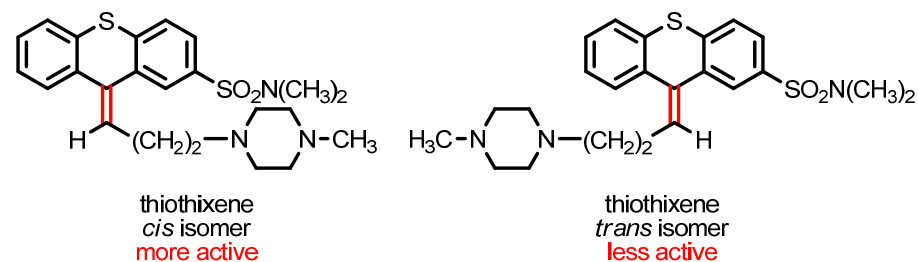


inactive



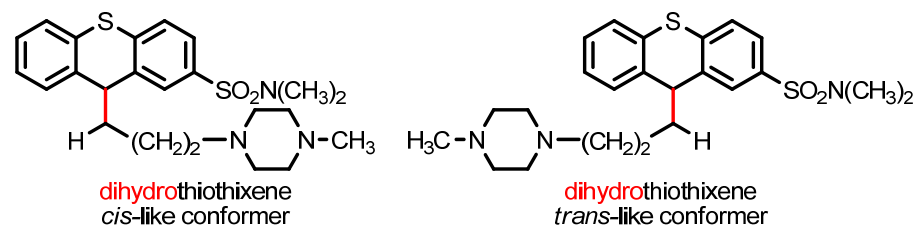
chlorpromazine
active

Structure-Activity Relationships



thiothixene
cis isomer
more active

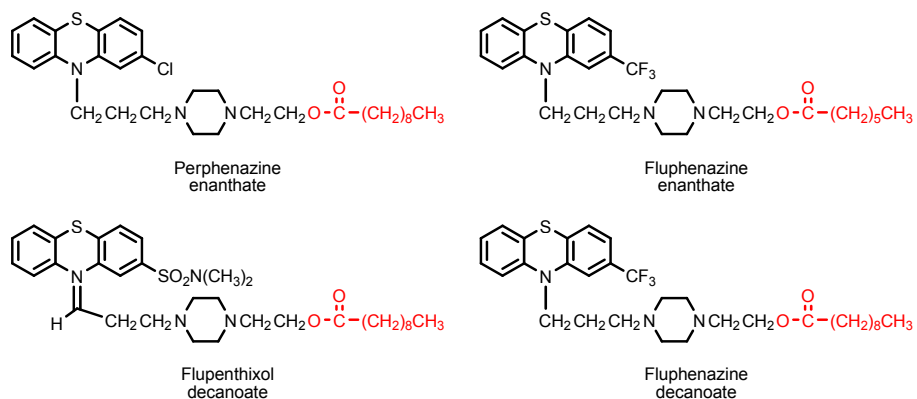
thiothixene
trans isomer
less active



dihydrothiothixene
cis-like conformer

dihydrothiothixene
trans-like conformer

Structure-Activity Relationships

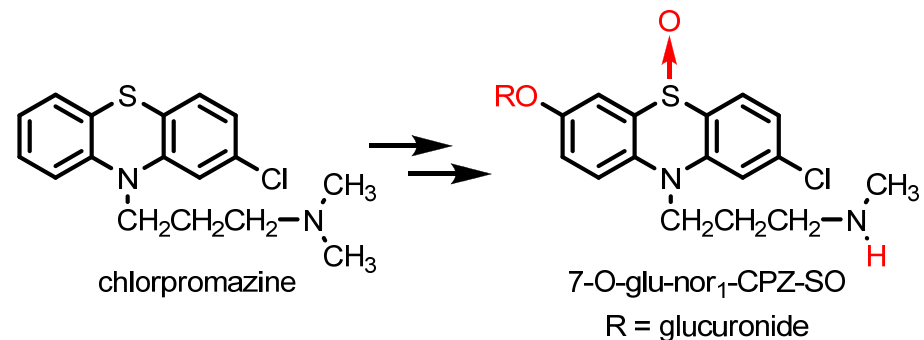


- Long duration!
- Route of administration?

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Metabolism of Chlorpromazine

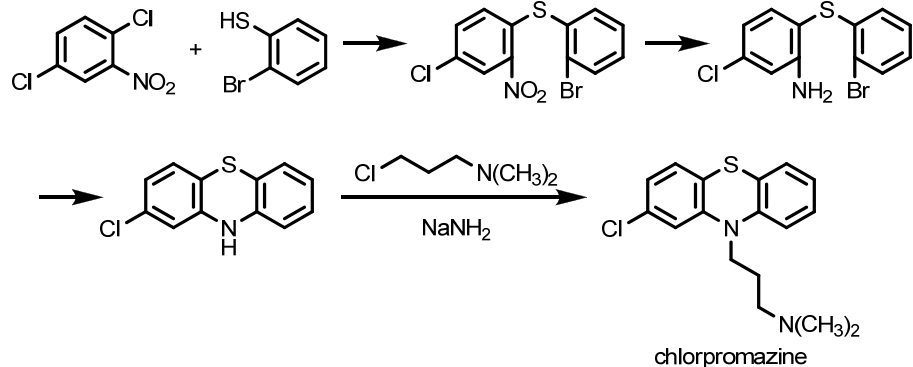


- More than 30 metabolites!

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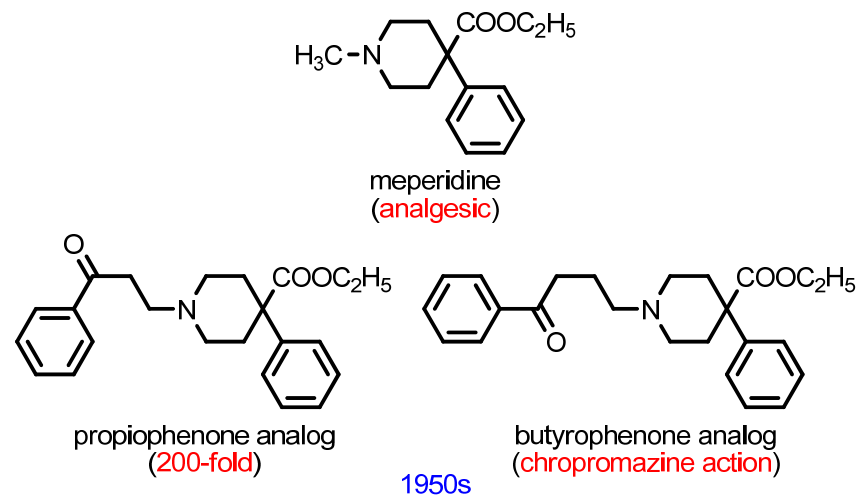
Synthesis of Chlorpromazine



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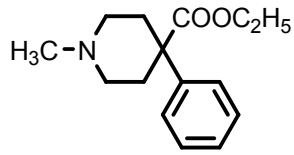
Development of Butyrophenone Neuroleptics (typical)



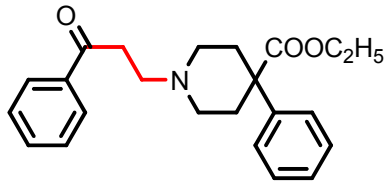
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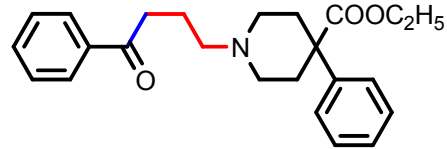
Development of Butyrophenone Neuroleptics



meperidine
(analgesic)



propiophenone analog
(200-fold)

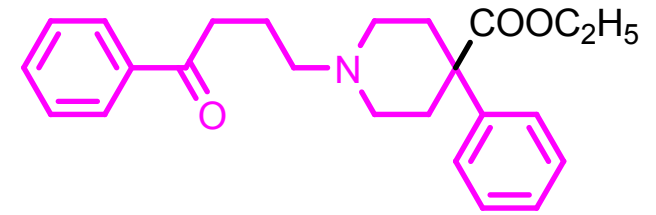


butyrophenone analog
(chropromazine action)

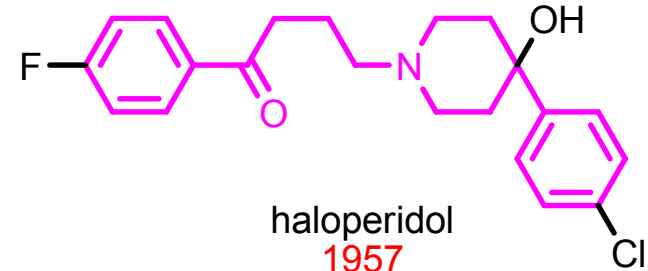
1950s

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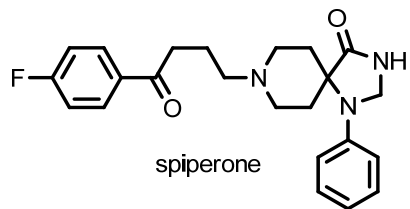
butyrophenone analog
1950s



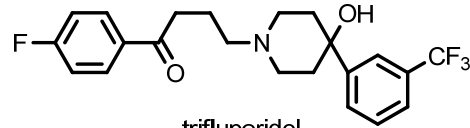
haloperidol
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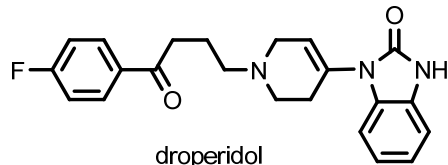
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spiperone



trifluoperidol

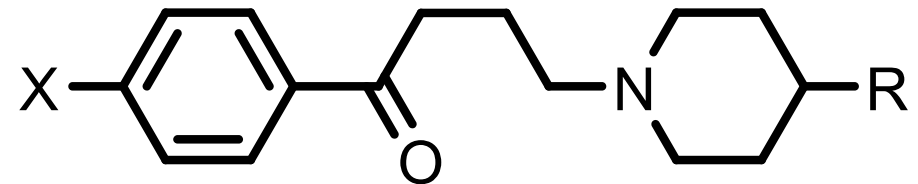


droperidol

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Structure-Activity Relationships

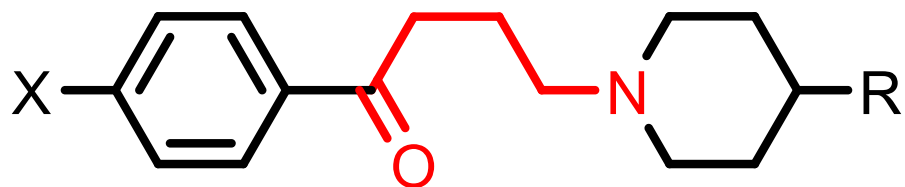


X = F or OCH₃

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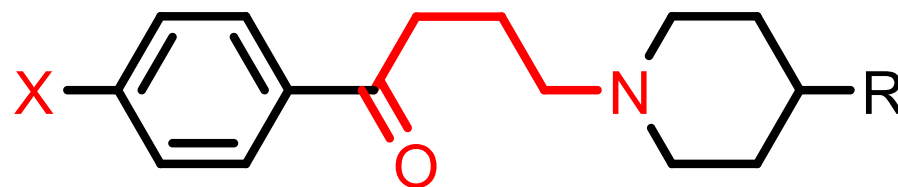
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Structure-Activity Relationships



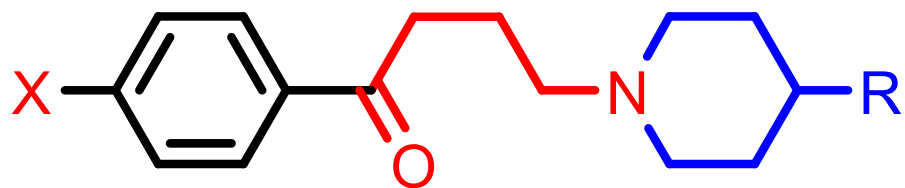
X = F or OCH₃

Structure-Activity Relationships



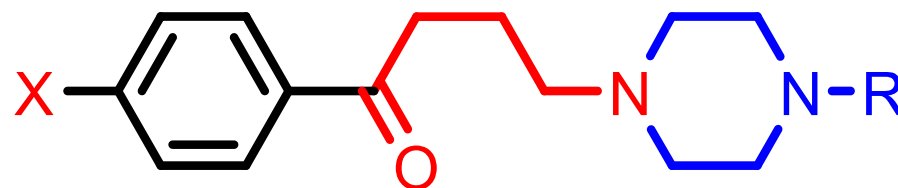
X = F or OCH₃

Structure-Activity Relationships



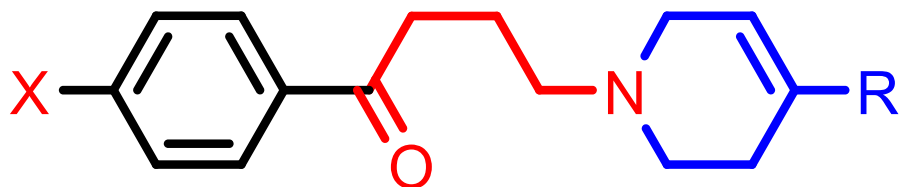
X = F or OCH₃

Structure-Activity Relationships



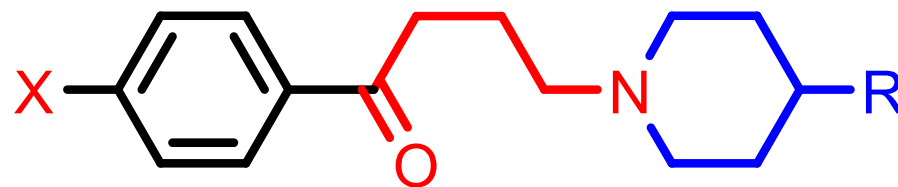
X = F or OCH₃

Structure-Activity Relationships



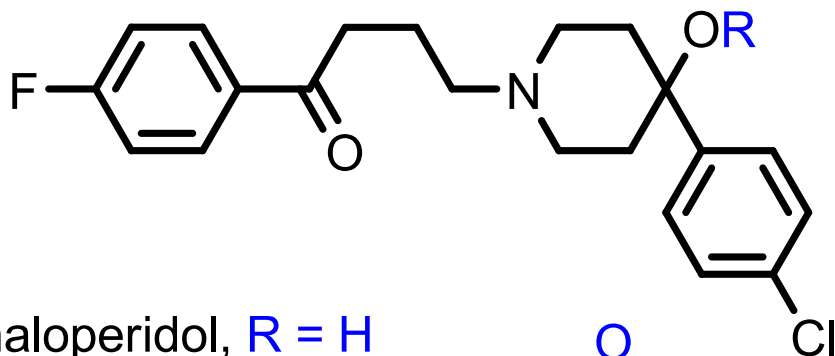
X = F or OCH₃

Structure-Activity Relationships



X = F or OCH₃

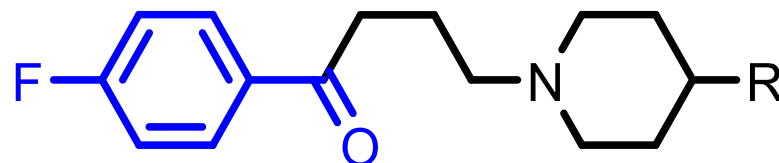
Structure-Activity Relationships



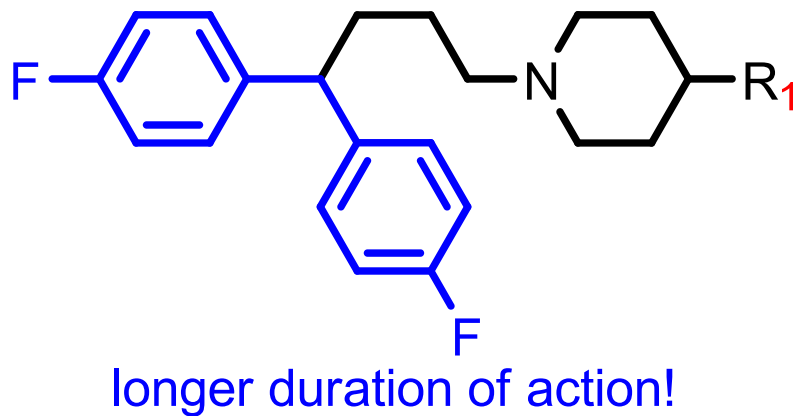
haloperidol, R = H

haloperidol decanoate, R = $\text{C}(=\text{O})(\text{CH}_2)_8\text{CH}_3$

Structure-Activity Relationships

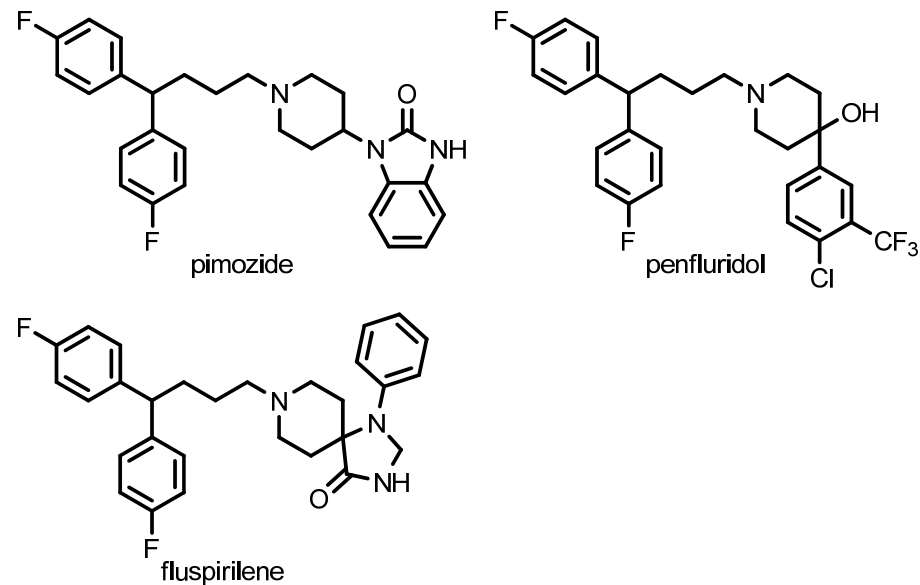


Structure-Activity Relationships



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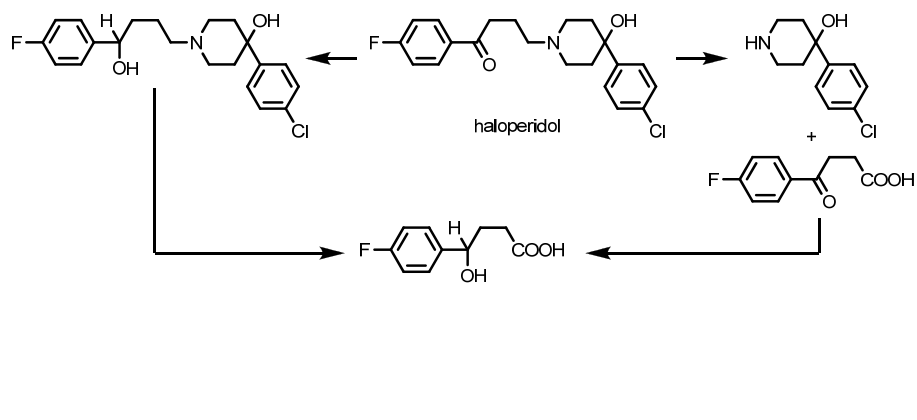
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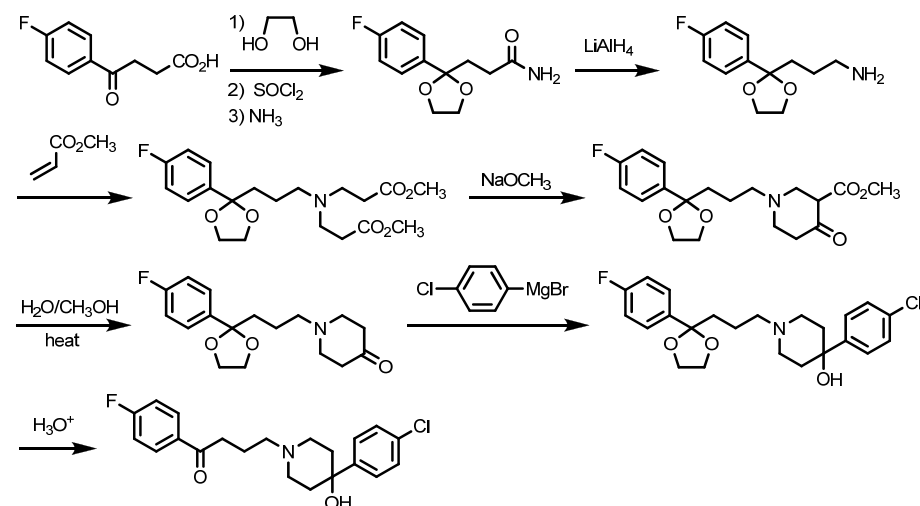
Metabolism of Haloperidol



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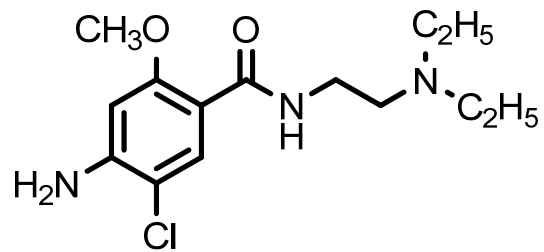
Synthesis of Haloperidol



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Benzamide Derivatives (atypical)



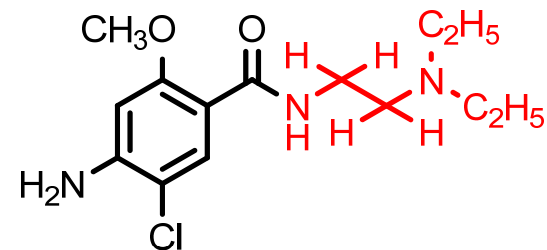
metoclopramide

- Local anesthetic & antiemetic properties.
- Neuroleptic properties & Anticholinesterase properties.
- Blockade of D_2/D_3 , M_3 , $5-HT_{1A}$, $5-HT_3$.

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Benzamide Derivatives

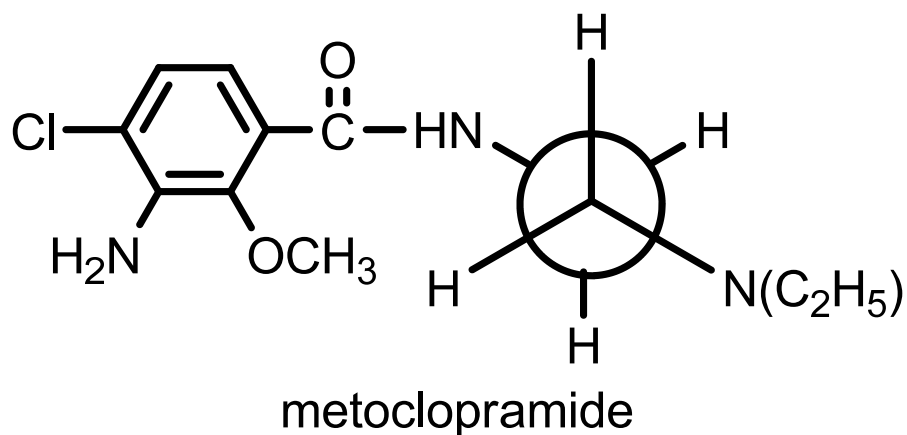


metoclopramide

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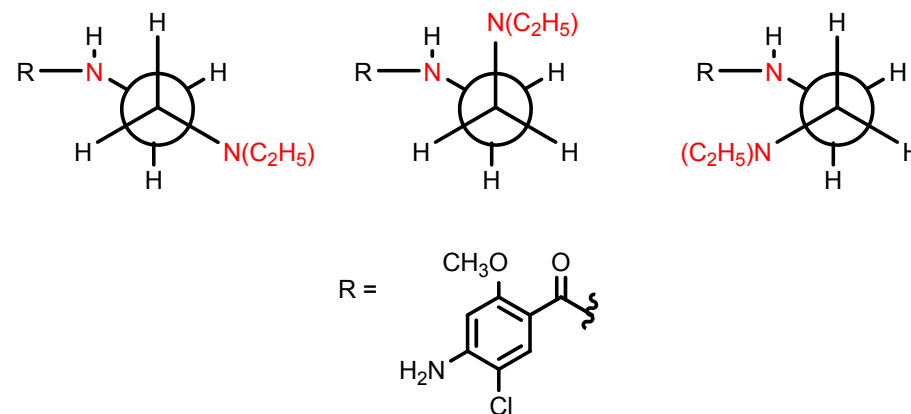
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metoclopramide

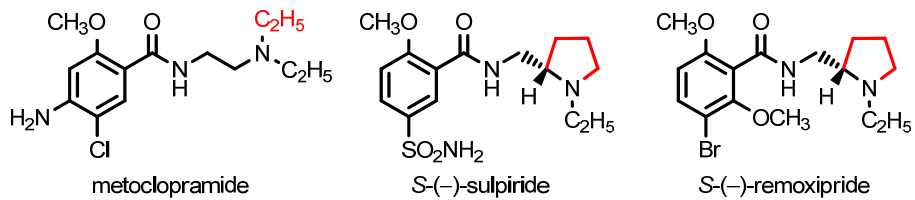
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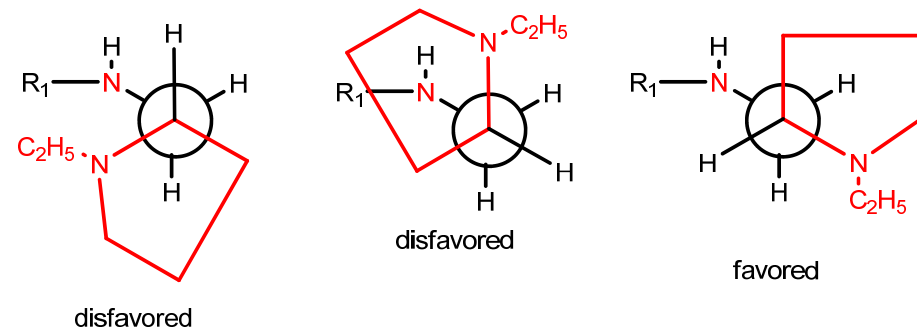
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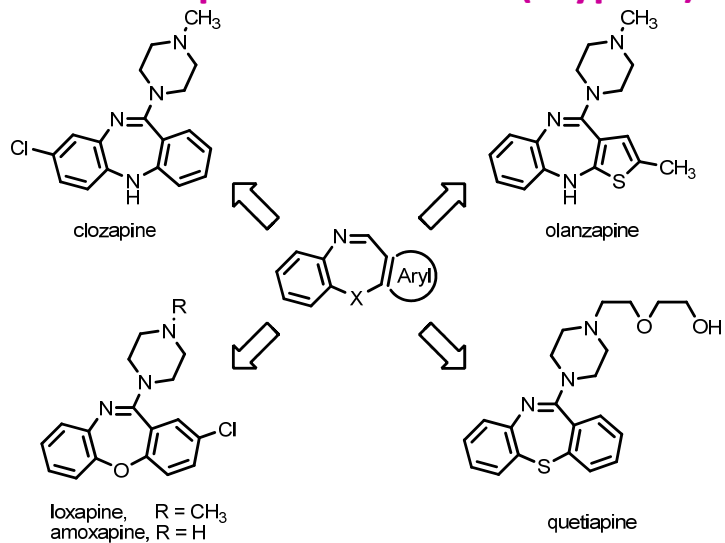
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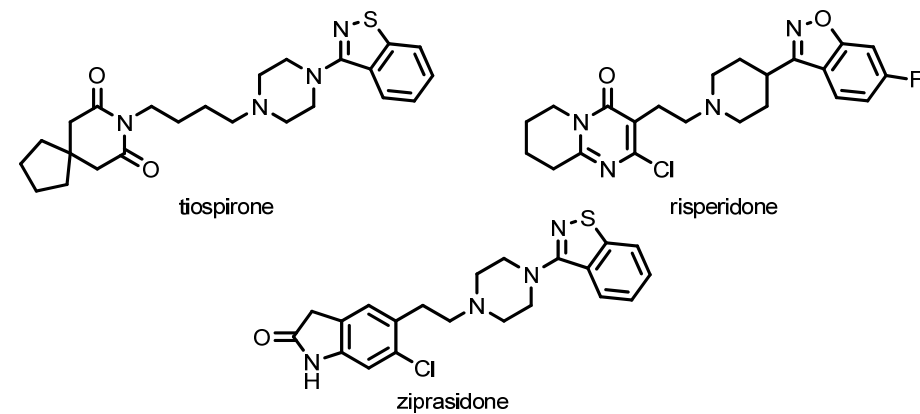
Benzazepine Derivatives (atypical)



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Benzisoxazole & Benzisothiazole Derivatives (atypical)



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