

Drugs Acting on CNS

Antidepressant Drugs

- Depression is an illness that involves the body, mood, and thoughts and affects the way one eats and sleeps, the way one feels about oneself, and the way one thinks about things.
- It often interferes with normal functioning, causing pain and suffering not only to themselves but also to those around them.
- Depression ranks among the top 5 diseases in the Western countries.

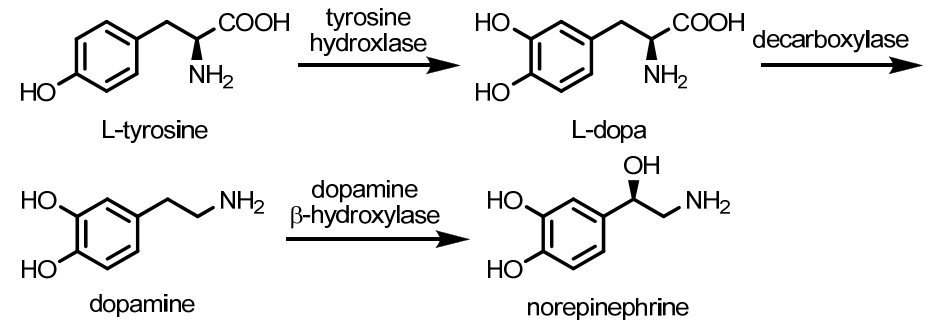
Type of Depressive Disorders

- Major depression.
- Dysthymia.
- Bipolar Disorder (Manic-Depressive Illness).
- Seasonal affective disorder.
- Adjustment disorder with depressed mood.

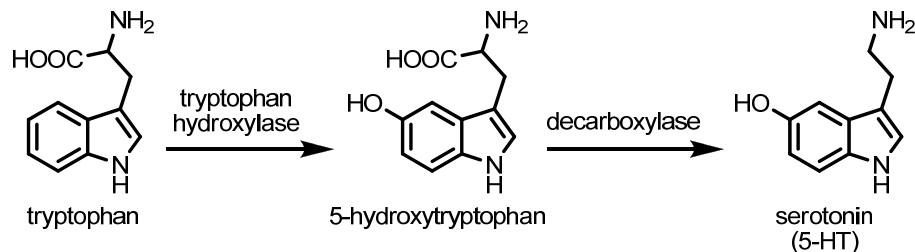
Biological Basis of Depression

- Monoamine Hypothesis (deficiency in 5-HT and/or NE).
- Receptor Sensitivity Hypothesis (depletion).
- Permissive Hypothesis (5-HT/NE).
- Hormonal Hypothesis.

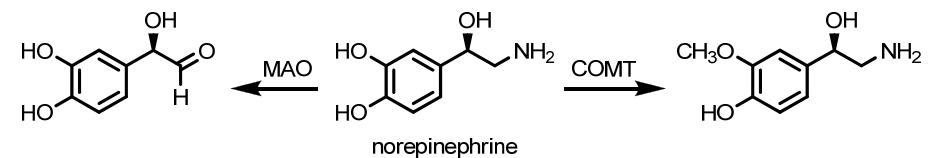
Biosynthesis of Norepinephrine (NE)



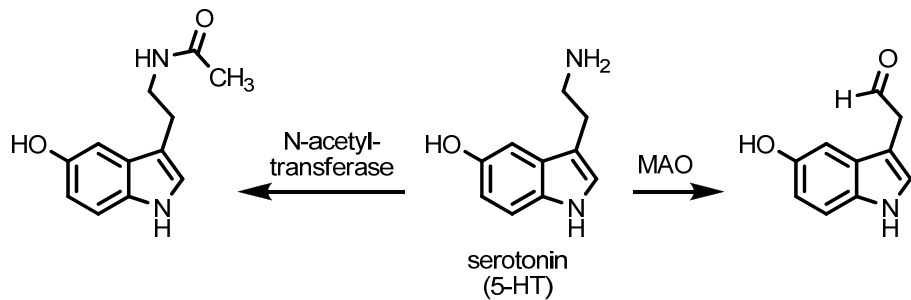
Biosynthesis of Serotonin (5-HT)



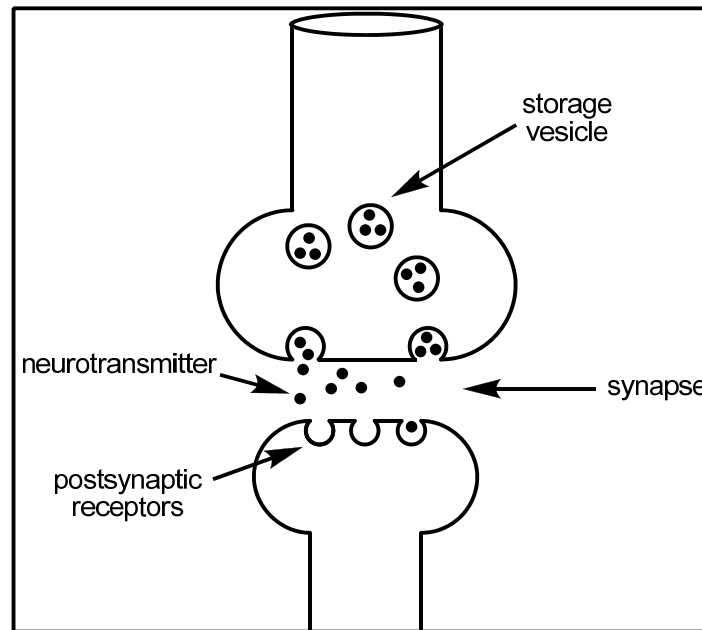
Metabolism of Norepinephrine (NE)



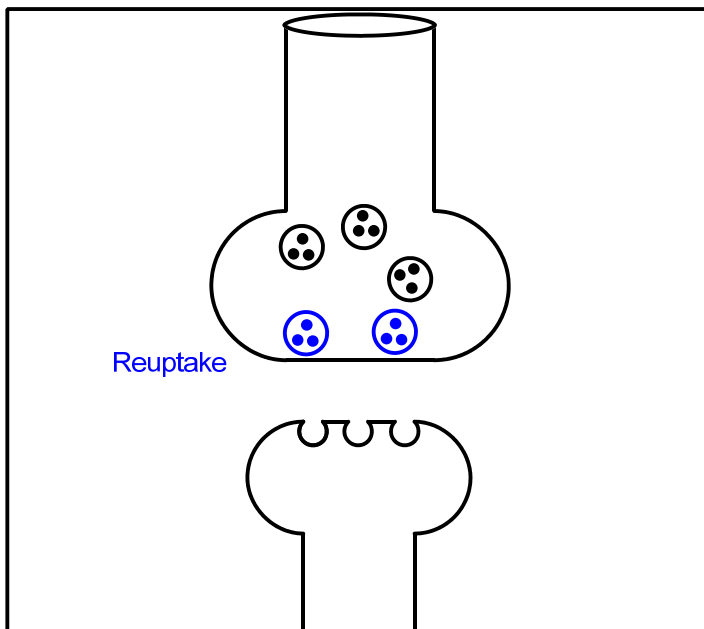
Metabolism of Serotonin (5-HT)



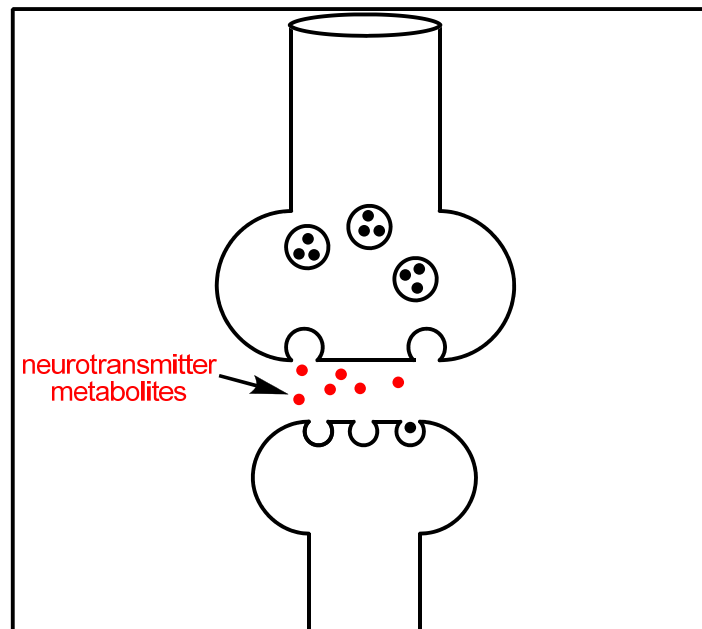
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General Approaches to Treatment of Depression

- Inhibition of the reuptake of NE and 5-HT.
- Inhibition of the metabolism of NE and 5-HT.

General Classification of Antidepressant Drugs

- NE & 5-HT Reuptake Inhibitors.
- Monoamine Oxidase inhibitors (MAOIs).

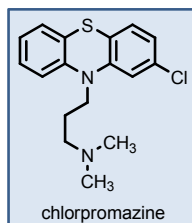
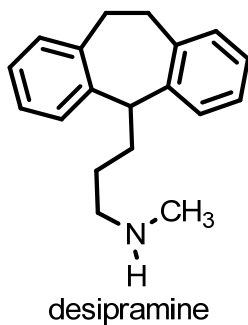
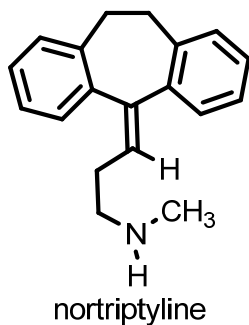
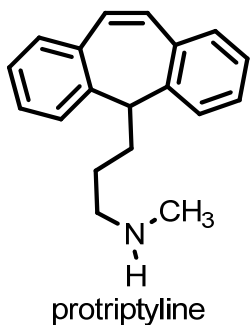
Reuptake Inhibitors

- Selective Norepinephrine Reuptake Inhibitors (SNRIs).
- Selective Serotonin Reuptake Inhibitors (SSRIs).
- Norepinephrine & Serotonin Reuptake Inhibitors (NSRIs).

Selective Norepinephrine Reuptake Inhibitors

- Tricyclic Secondary Amines Antidepressants.
- Nontricyclic Secondary Amines Antidepressants.

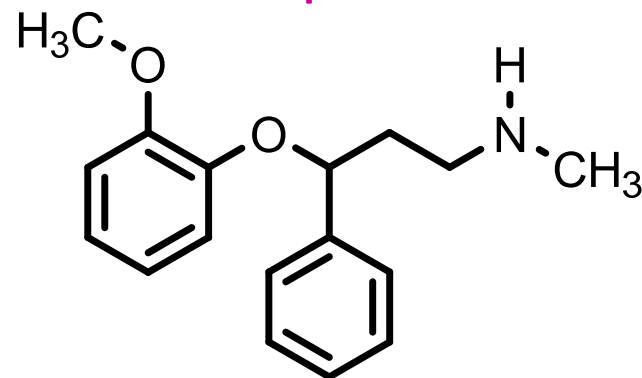
Tricyclic Secondary Amines Antidepressants



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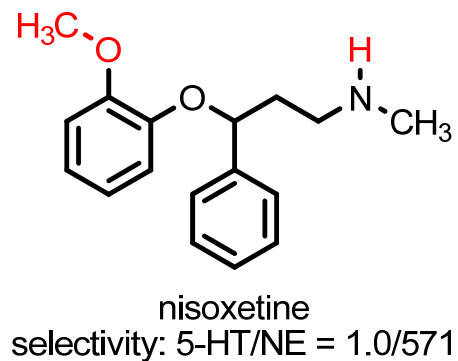
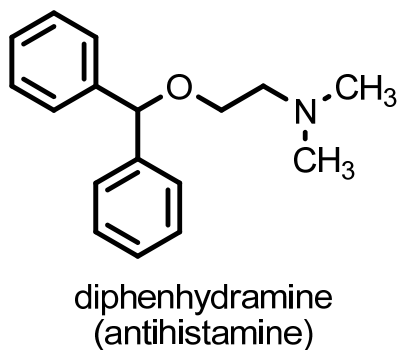
Nontricyclic Secondary Amines Antidepressants



nisooxetine
Lilly, 1970s

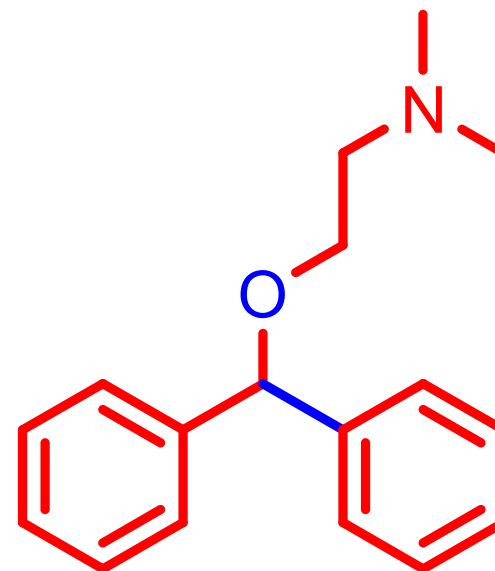
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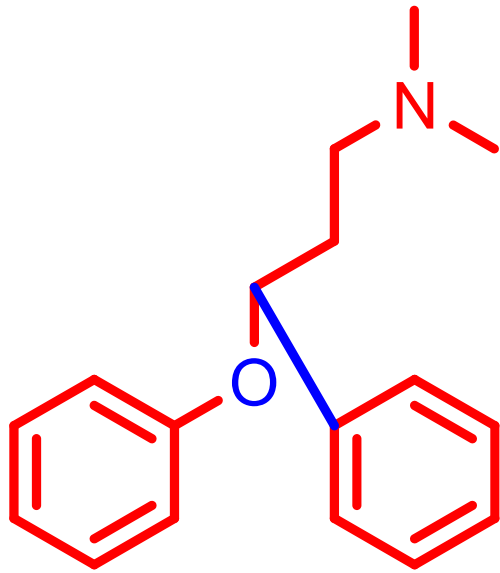
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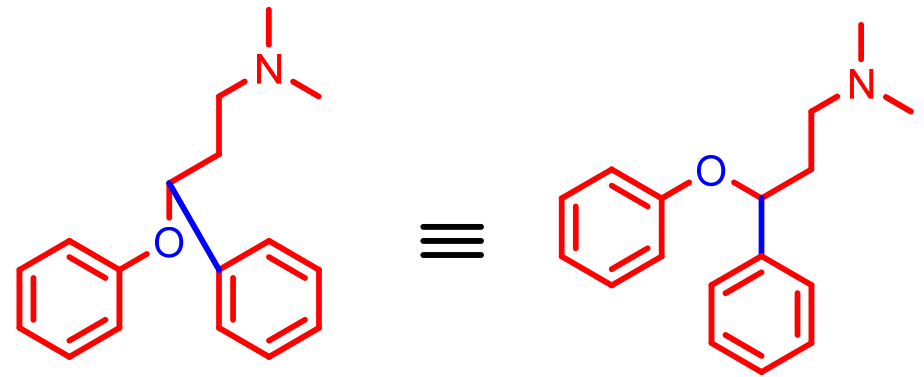
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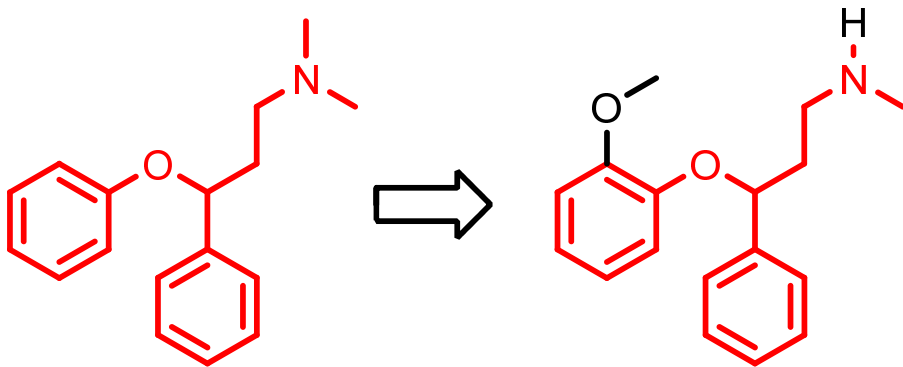
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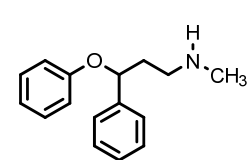
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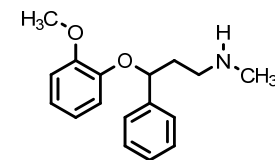
nisoxetine
Lilly

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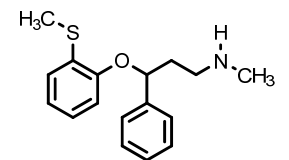
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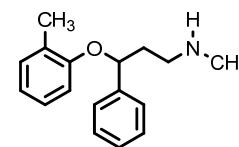
selectivity: 5-HT/NE = 2.0/1.0



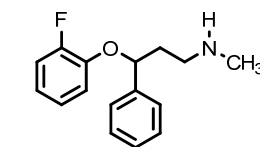
selectivity: 5-HT/NE = 1.0/571



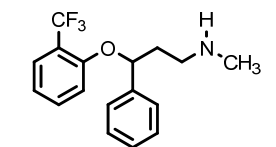
selectivity: 5-HT/NE = 1.0/510



selectivity: 5-HT/NE = 1.0/115



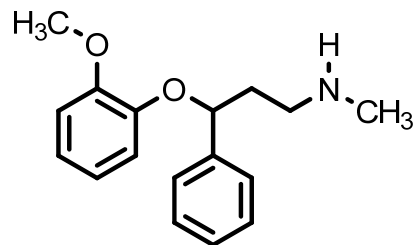
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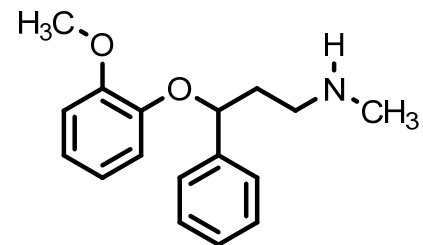
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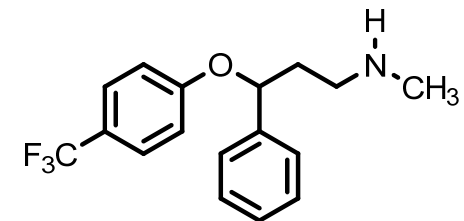
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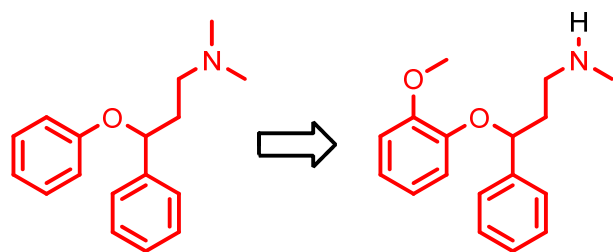
nisoxetine
selectivity: 5-HT/NE = 1.0/571
not marketed



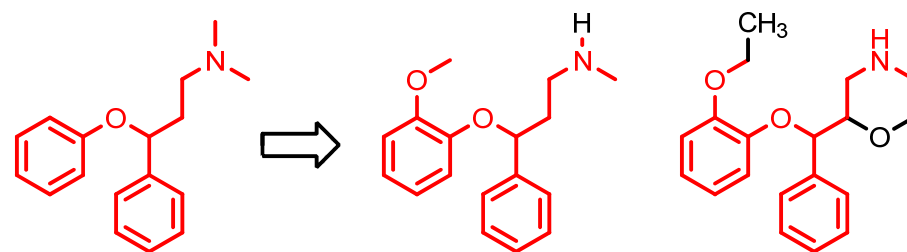
nisoxetine
selectivity: 5-HT/NE = 1.0/571
not marketed



fluoxetine
selectivity: 5-HT/NE = 159/1.0

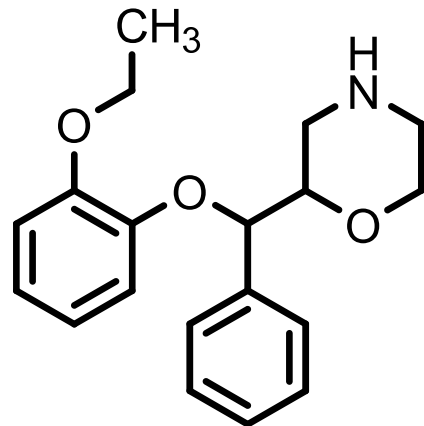


nisoxetine
Lilly

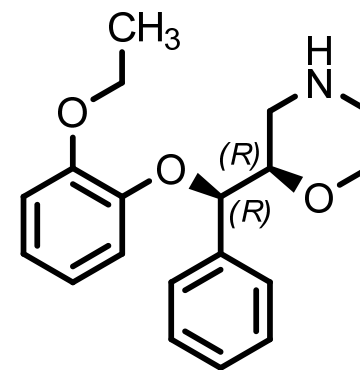


nisoxetine
Lilly

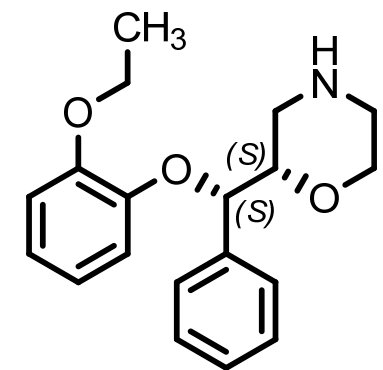
reboxetine
Pharmacia
(now Pfizer)



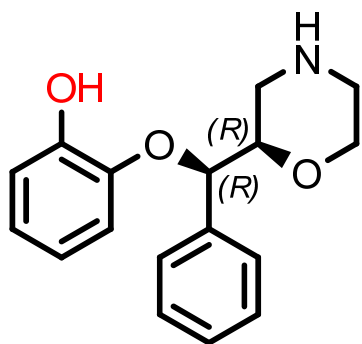
RS,RS-reboxetine



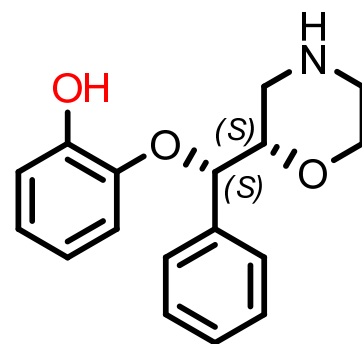
R,R-reboxetine



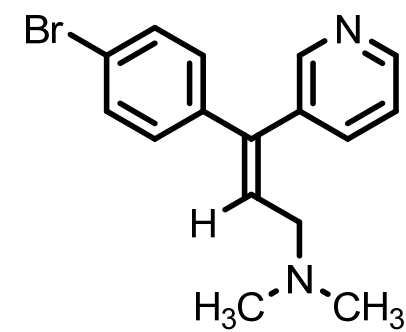
S,S-reboxetine
more active



major metabolite of
R,R-reboxetine



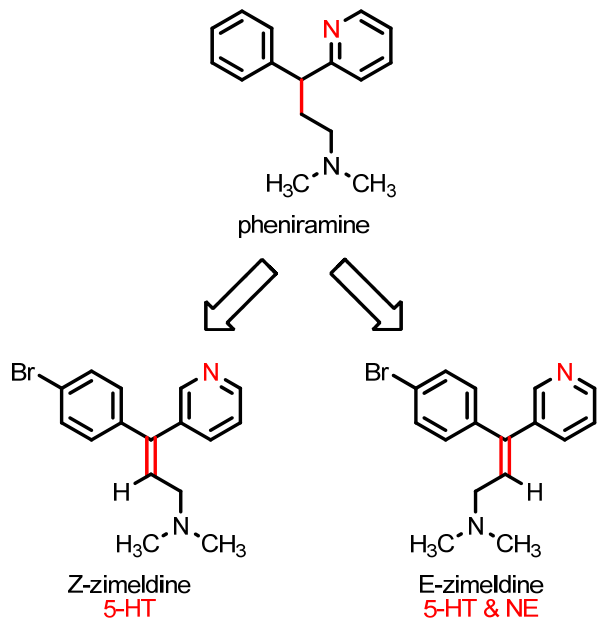
major metabolite of
S,S-reboxetine



Z-zimeldine

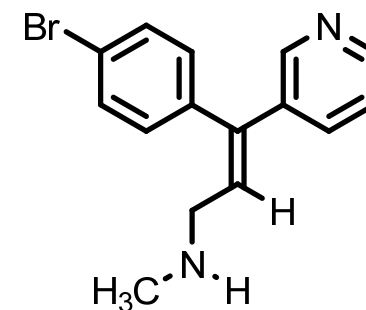
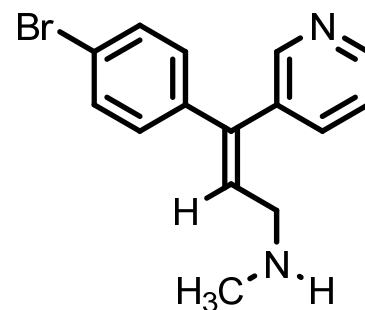
- Initial breakthrough (1960s to 1970s).
- Highly selective for SERT.

Selective Serotonin Reuptake Inhibitors



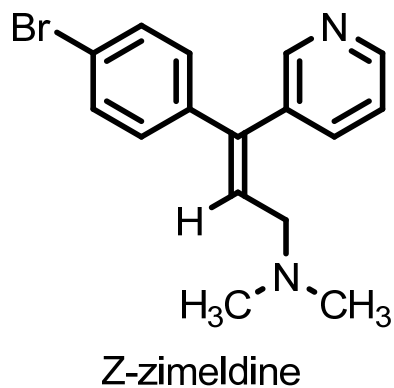
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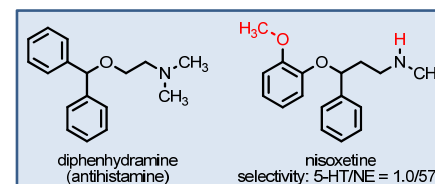
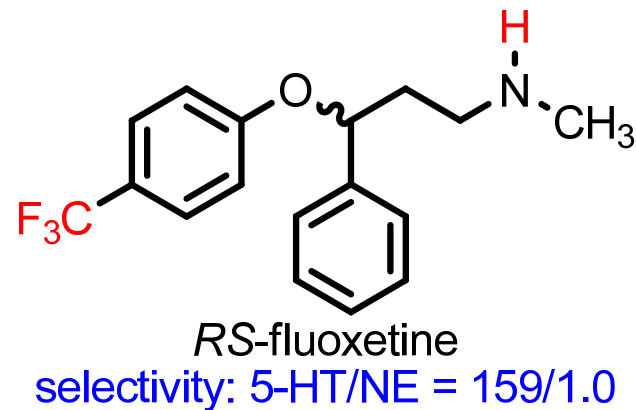
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- Autoimmune disorder (withdrawn in 1983).

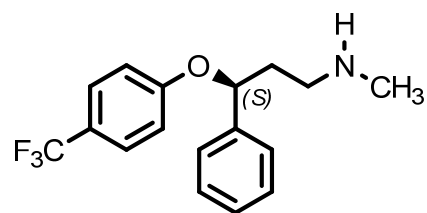
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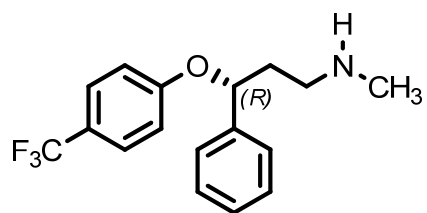


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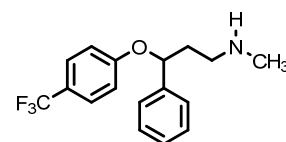
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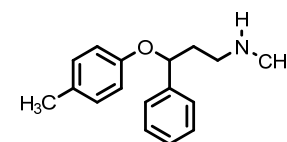
S-fluoxetine



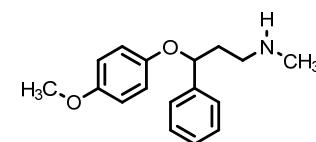
R-fluoxetine



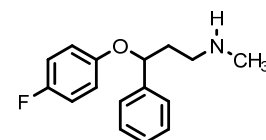
selectivity: 5-HT/NE = 159/1.0



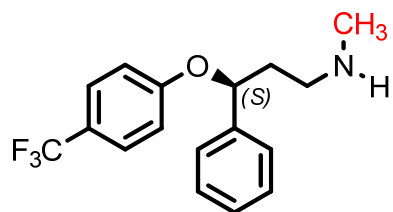
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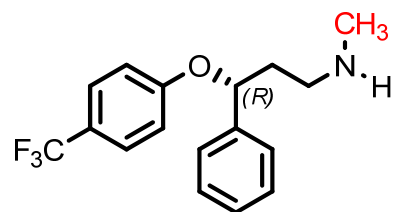
selectivity: 5-HT/NE = 17/1.0



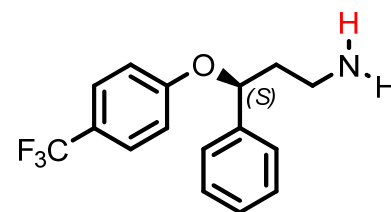
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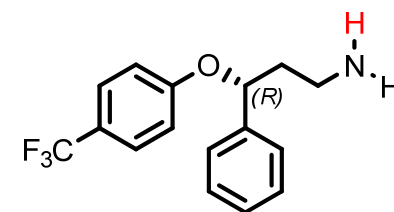
S-fluoxetine



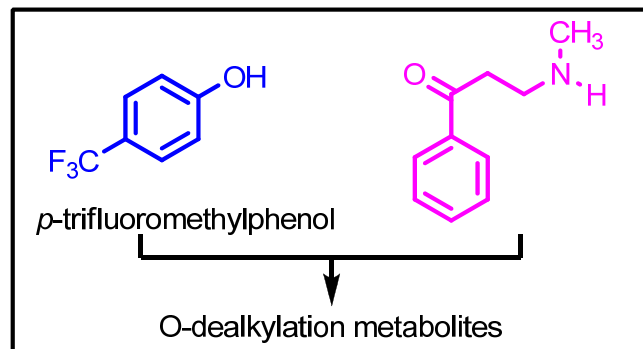
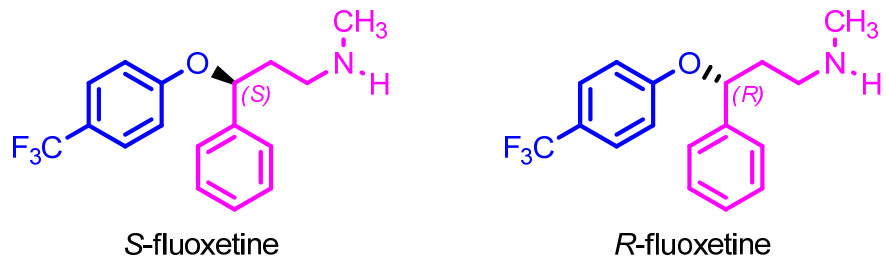
R-fluoxetine



S-norfluoxetine



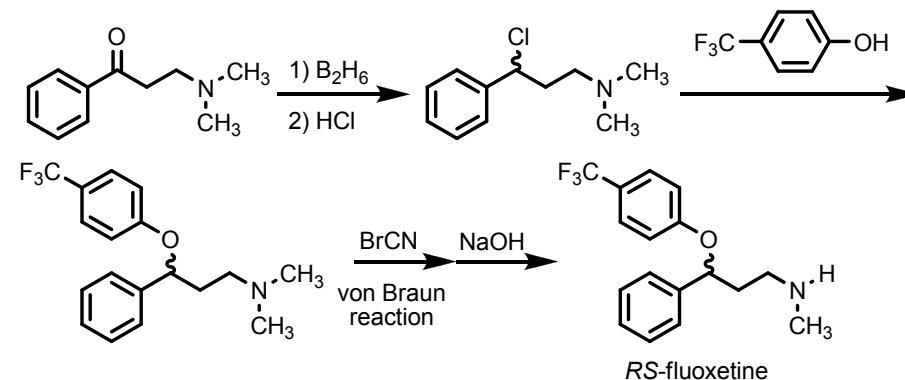
R-norfluoxetine



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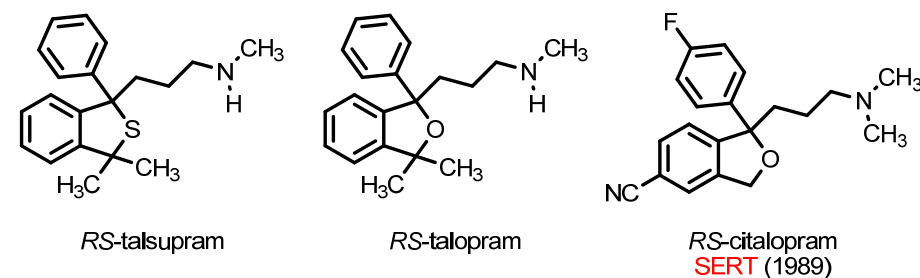
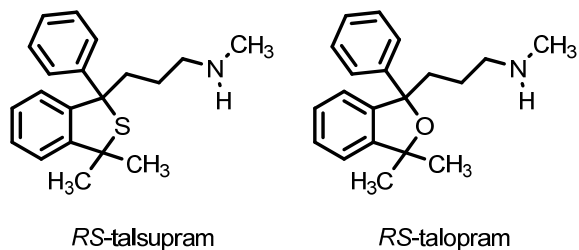
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Racemic Synthesis of Fluoxetine



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- Were designed for NET (Lundbeck)!
- Potent SNRIs.
- Suicide attempt (studies were discontinued).

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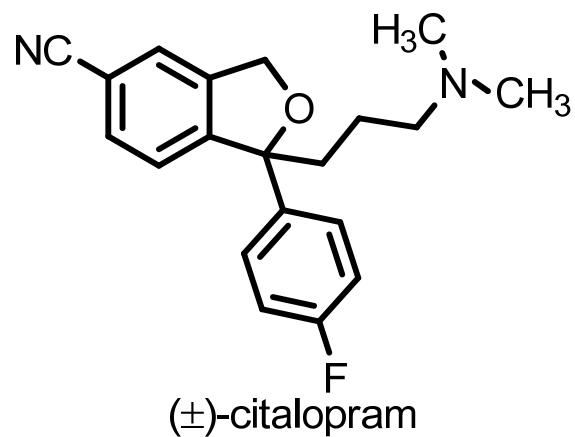
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- Citalopram is a highly selective SSRI.
- The patent expired in 2003.

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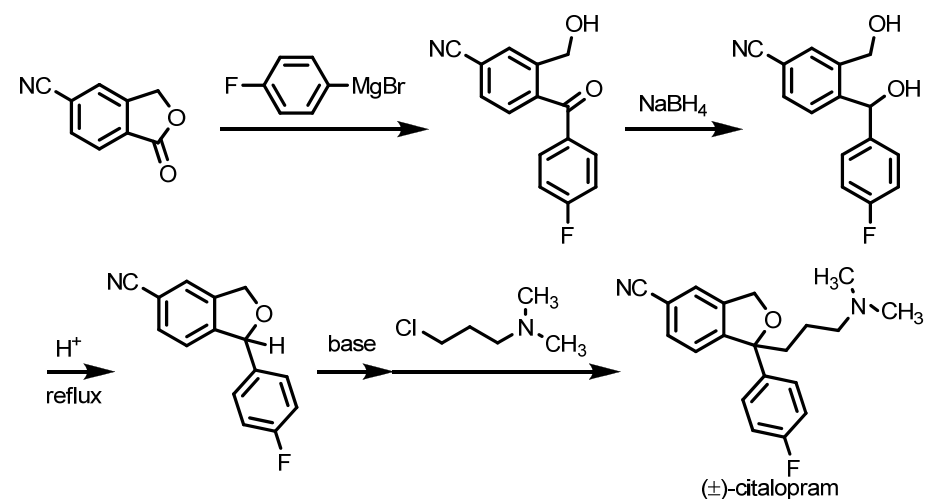
Retrosynthetic Analysis of Citalopram



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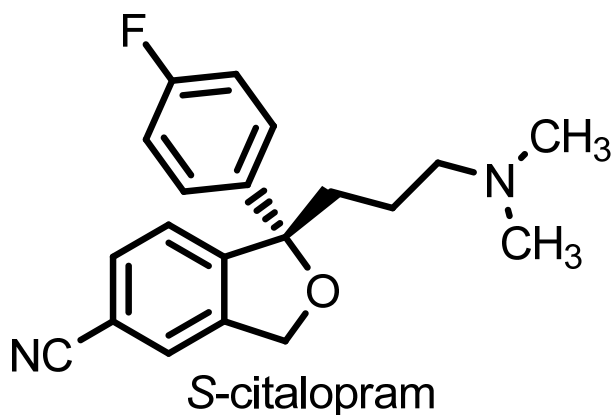
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Racemic Synthesis of Citalopram



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- Two-fold more active than the (±)-citalopram.
- 27 times more potent than R-enantiomer.
- New patent (Lundbeck).

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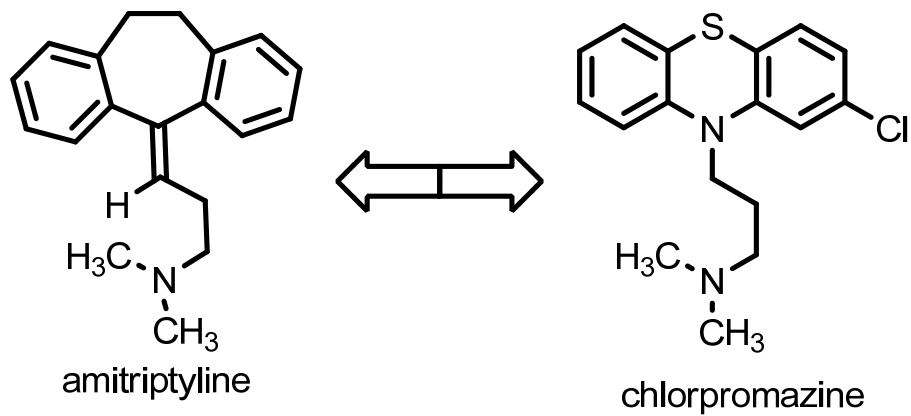
Norepinephrine & Serotonin Reuptake Inhibitors

- Tricyclic Tertiary Amines Antidepressants.
- Nontricyclic NSRIs Antidepressants.

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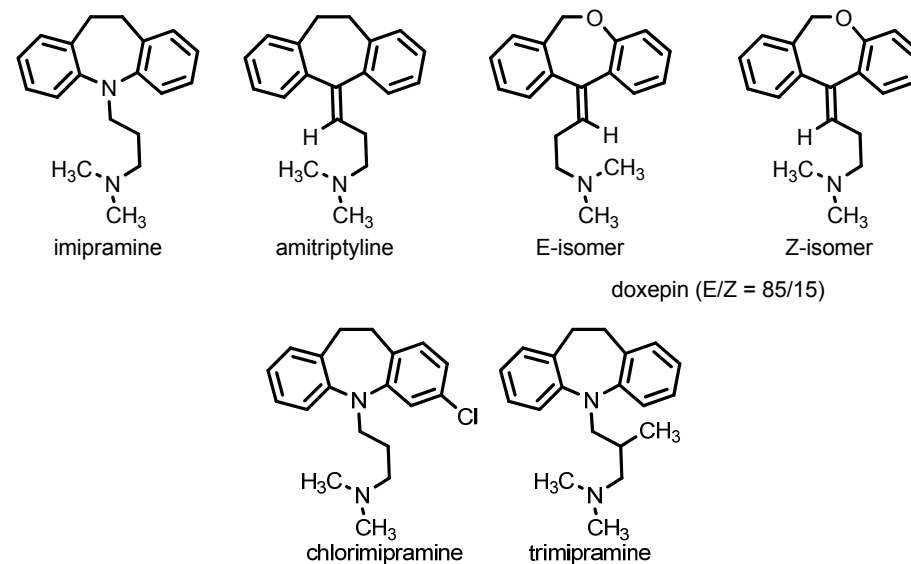
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Tricyclic Tertiary Amines Antidepressants



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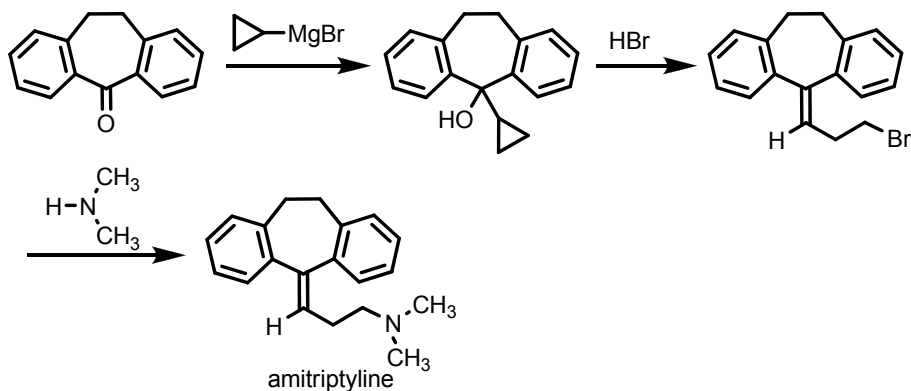
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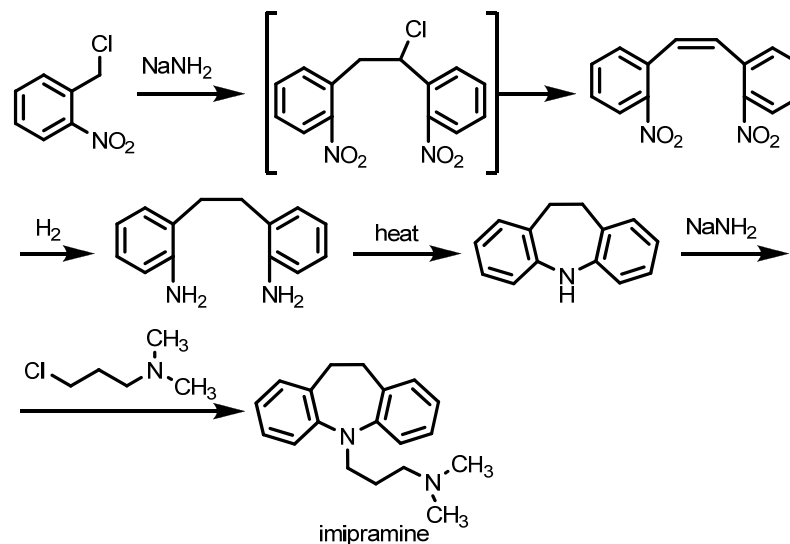
Synthesis of Amitriptyline



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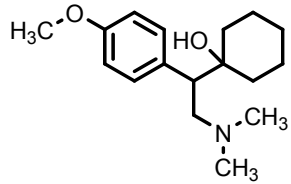
Synthesis of Imipramine



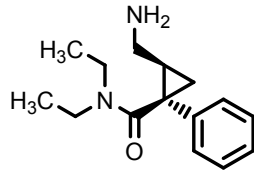
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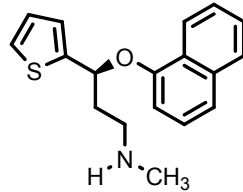
Nontricyclic NSRIs Antidepressants



(±)-venlafaxine



(±)-*cis*-milnacipran

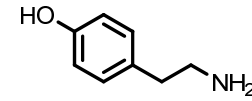


S-(+)-duloxetine

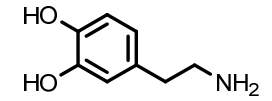
Monoamine Oxidase Inhibitors (MAOIs)



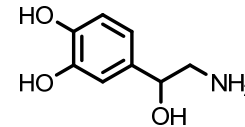
serotonin



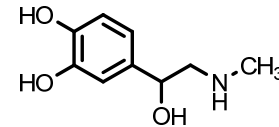
tyramine



dopamine



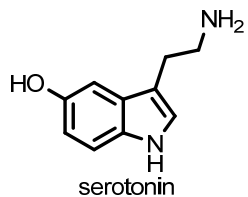
norepinephrine



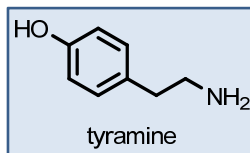
epinephrine

- Increase the availability of NE and 5-HT.
- Two isoforms: MAO-A and MAO-B.

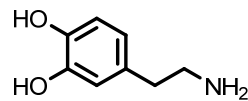
Monoamine Oxidase Inhibitors (MAOIs)



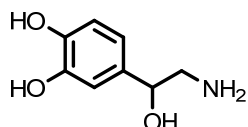
serotonin



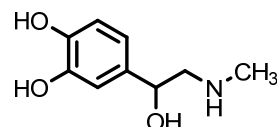
tyramine



dopamine

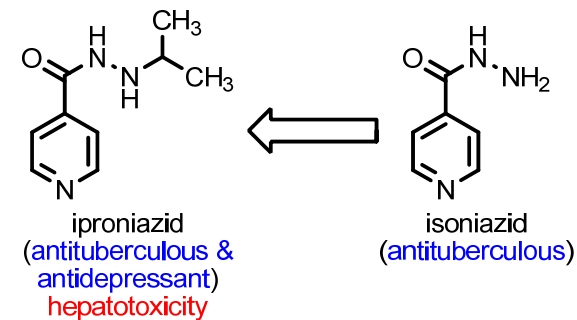


norepinephrine



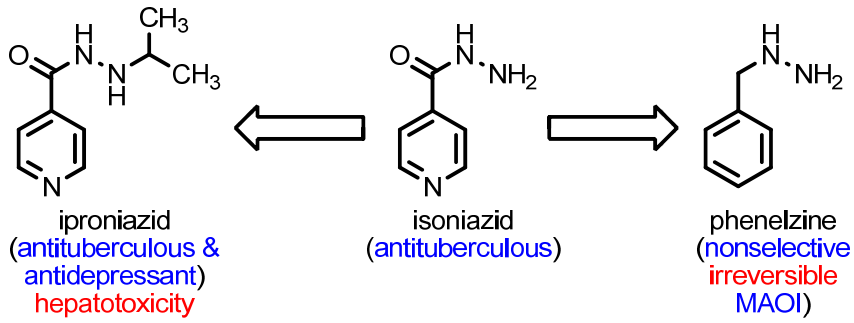
epinephrine

- Potent vasoconstrictor (Hypertension crises).
- Irreversible inhibition of MAO-A.



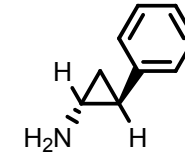
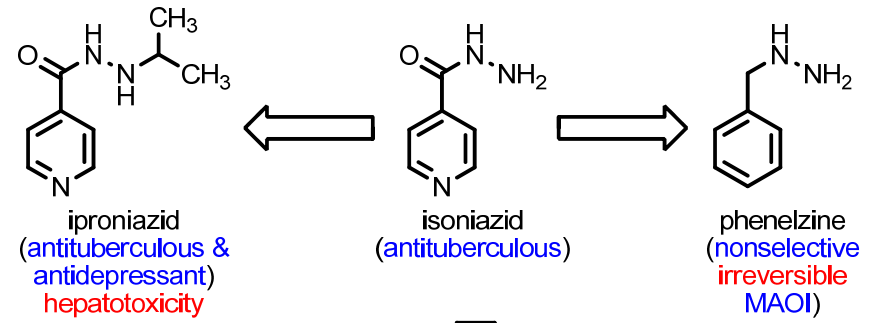
iproniazid
(antituberculous & antidepressant)
hepatotoxicity

isoniazid
(antituberculous)



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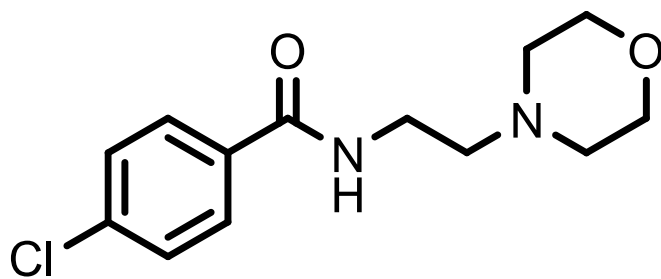


tranylcypromine
 (nonselective irreversible MAOI)

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Selective Reversible MAO-A Inhibitors



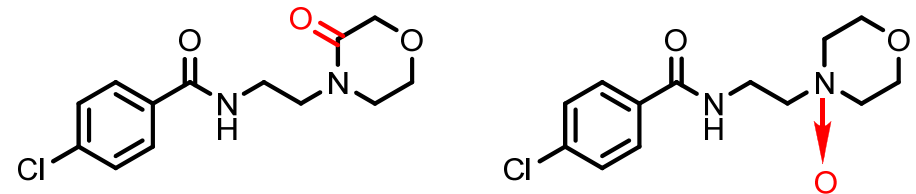
moclobemide
 ($pK_a = 6.2$)

- No dietary restriction!

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Metabolism of Moclobemide



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Synthesis of Moclobemide

