

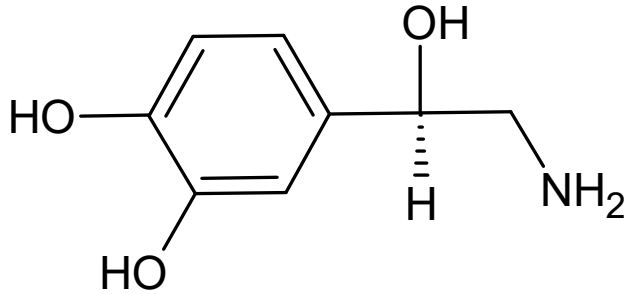
Antidepressants

- often life-saving drugs

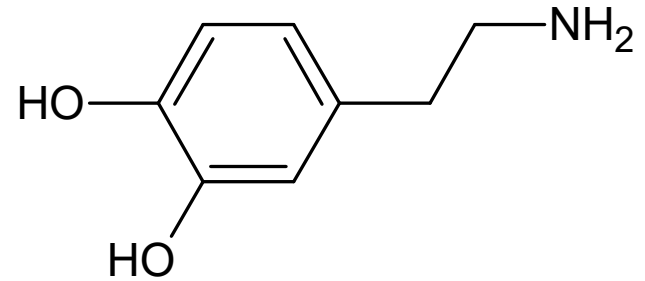
Possible classification of antidepressants

1. Non-selective monoamines reuptake inhibitors (tricyclic and tetracyclic antidepressants)
2. Monoaminooxidases (MAO) inhibitors
 - 2.1 Non-selective MAO inhibitors
 - 2.2 Selective MAO A inhibitors
3. Selective serotonin and noradrenaline reuptake inhibitors (SSNRI)
4. Selective serotonin reuptake inhibitors (SSRI)
5. Dual-serotonergic antidepressants
6. Selective noradrenaline reuptake inhibitors (SNRI)
7. Alkaline metals salts

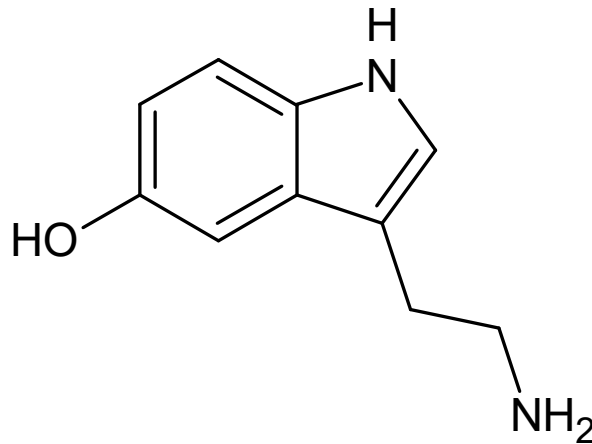
Amines involved in effects of antidepressants



4-[(1*R*)-2-amino-1-hydroxyethyl]benzene-1,2-diol
noradrenaline (norepinephrine)



4-(2-aminoethyl)benzene-1,2-diol
dopamine

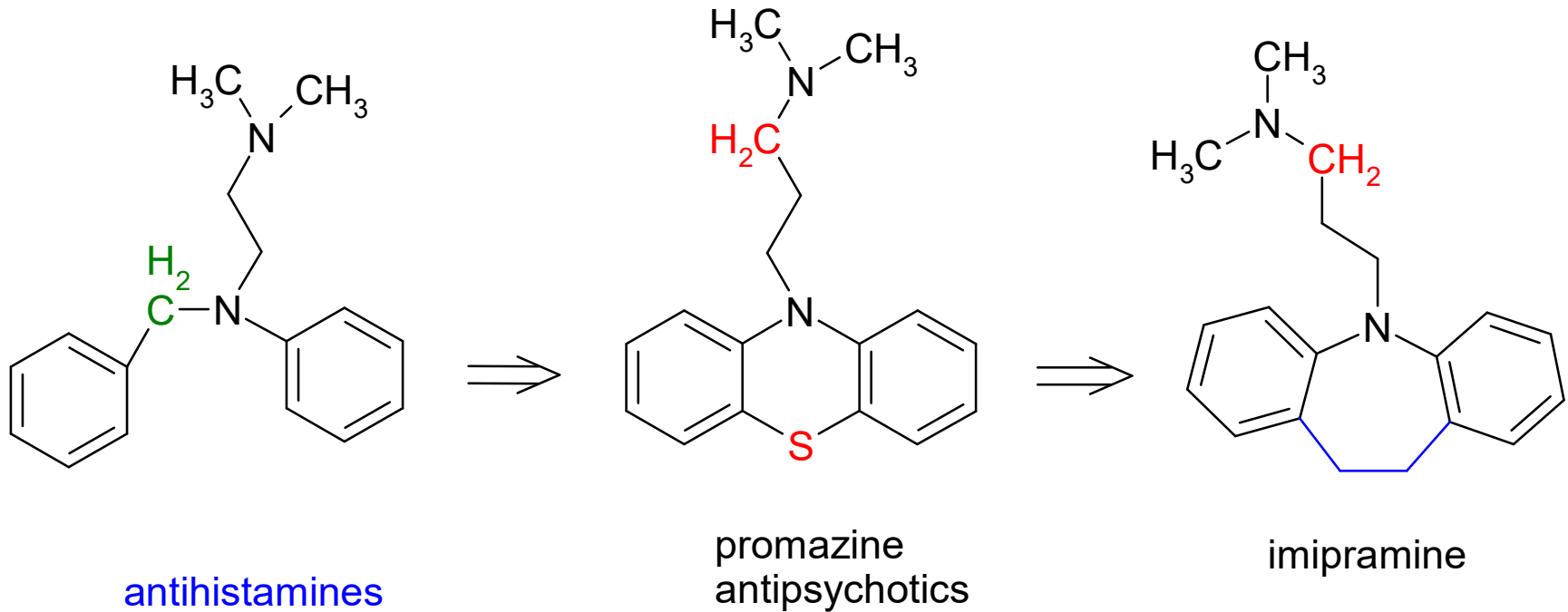


3-(2-aminoethyl)-1*H*-indol-5-ol
serotonin

1. Non-selective monoamines reuptake inhibitors (tricyclic antidepressants)

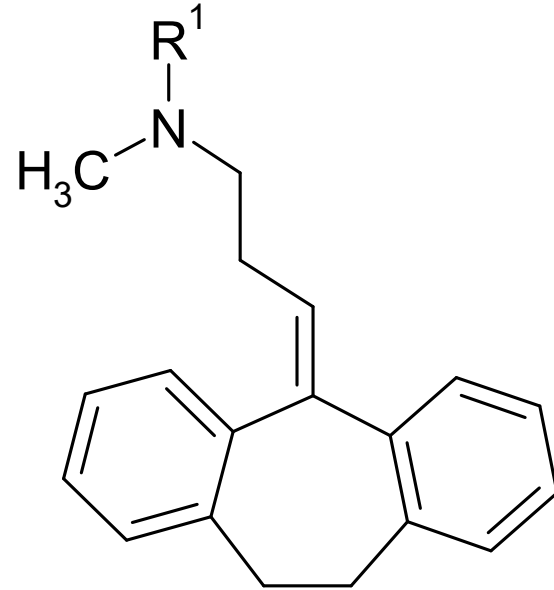
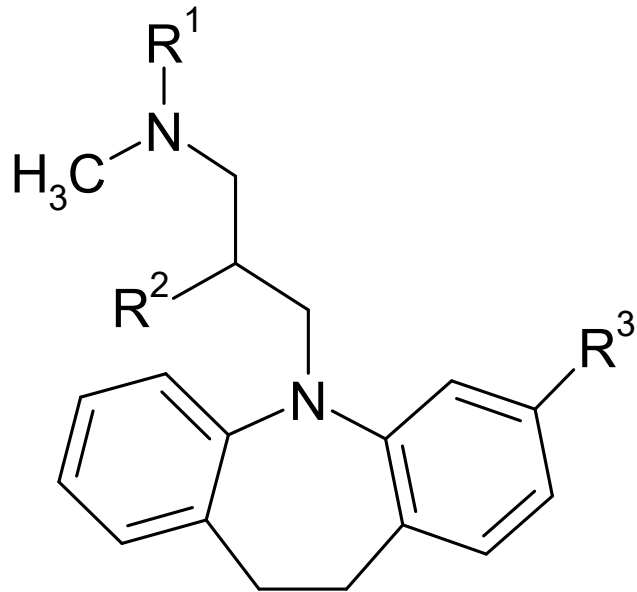
- inhibit reuptake of serotonin and noradrenaline

Genesis (derivation) of tricyclic antidepressants



1st and 2nd generations of tricyclic antidepressants

- act inhibitory also on M, H₁, α₁, α₂, 5-HT₂ receptors
- 2nd gen. increases more amount of NA than 5-HT in synapsis, 1st gen. reversely



R¹=-CH₃ R²=R³=-H

Tofranil®

R¹= R²=R³=-H

R¹= R²=-H R³=-Cl

Anafranil®

R¹= R²=-CH₃ R³=-H

Surmontil®

imipramine

desipramine

clomipramine

trimipramine

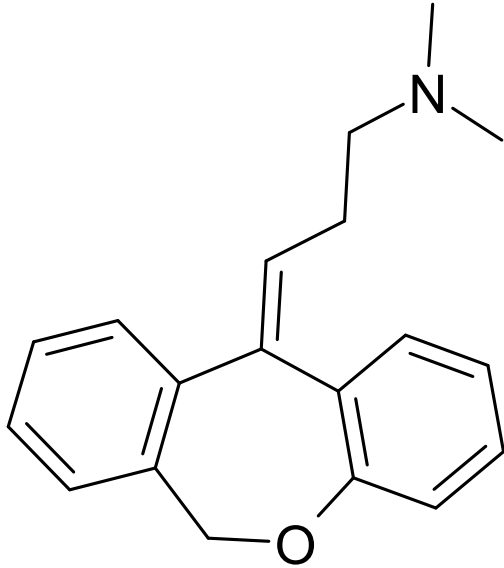
R¹=-CH₃ **amitriptyline**

Elavil®, Endep®

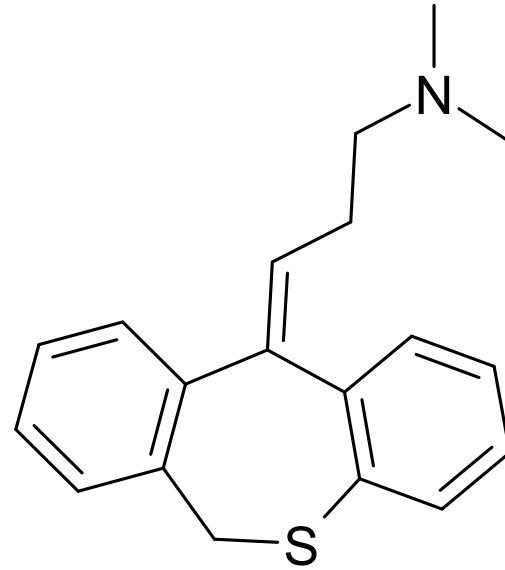
R¹=-H **nortriptyline**

Pamelor®

1st generation of tricyclic antidepressants



cidoxepin [INN]
syn. doxepin [USAN]



dosulepin [INN]
syn. dothiepin [USAN]
Prothiaden ® 25

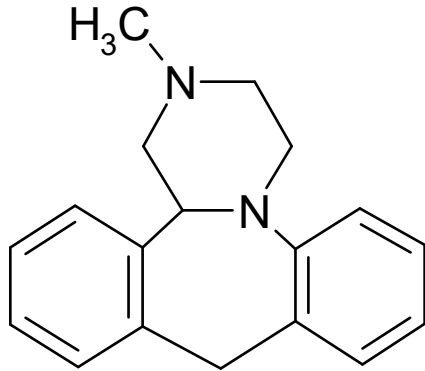
Mechanism of action:

- Inhibition of neurotransmitters reuptake
- Immediate effect = $>\uparrow$ NA and 5-HT in synapsis.
- After longer period treatment (2 - 4 weeks) = $>$
 - \downarrow of activity β and \downarrow 5-HT₂ rp.
 - \downarrow of release and return of NA
 - \downarrow NA-stimulated cAMP level in the brain
 - \uparrow sensitivity of 5-HT receptors
 - * „Adaptive responses“ *
- as long as 4 weeks of treatment are needed for full activity

Unwanted effects of tricyclic antidepressants due to antagonist action on various receptors:

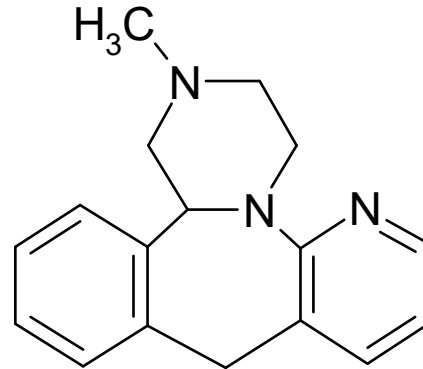
- M(uscarine) rp. - dry in the mouth, bad accommodation, tachycardia, problems with emiction, forgetting
- H₁ rp. - sedation, increase of body weight
- 5-HT₂ - increase of appetite and body weight
- α_1 - orthostatic hypotension, reflex tachycardia

Tetracyclic antidepressants (or „thymoleptics of 2nd generation“)



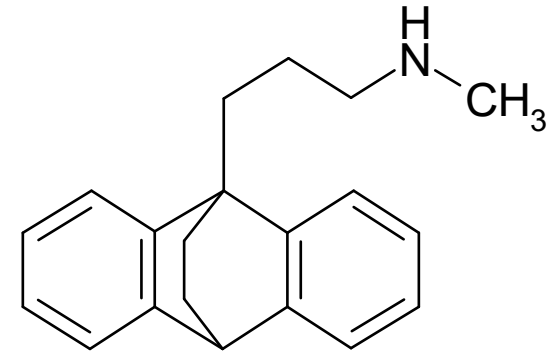
mianserin

- minimal activity on monoamines reuptake from synapses, quite selective antagonists of α_2 -adrenergic receptors which inhibit noradrenaline release



mirtazapine

Esprital ® , Mirtazapin ® *firm*



maprotiline

inhibits reuptake of noradrenaline mainly

- moderate anticholinergic effects, significant antihistamine ones (sedative)

Ludiomil ®

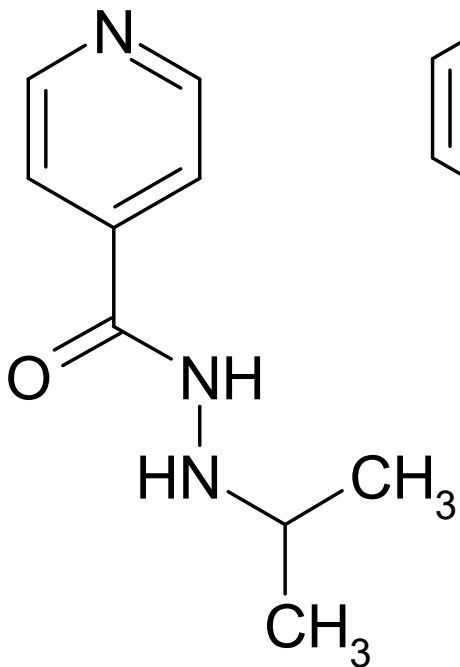
• inhibits also α_1 -rp. \Rightarrow
 \downarrow blood pressure
Lerivon ® , Miabene ®

2. Monoaminoxidases (MAO) inhibitors – also thymoeretics

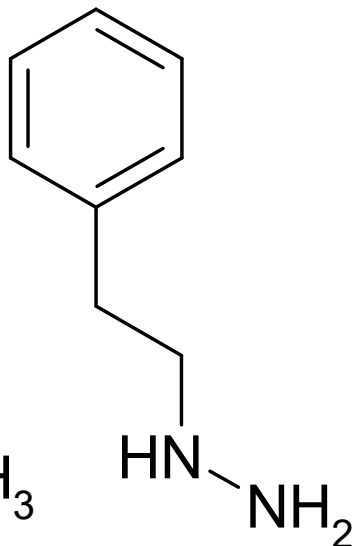
- MAOs = enzymes oxidatively degrading catecholamines
- discovered in 1950th
- potent but less used due to their lower security (interactions, unwanted effects)
- frequent occurrence of drug interactions
- most frequently used if other treatment methods failed
- AE: orthosthesis, sedation, sexual dysfunctions, body weight increase

- type A (MAO-A) decomposes mainly serotonin and less also noradrenaline
- typ B (MAO-B) decomposes various phenylethylamine including dopamine

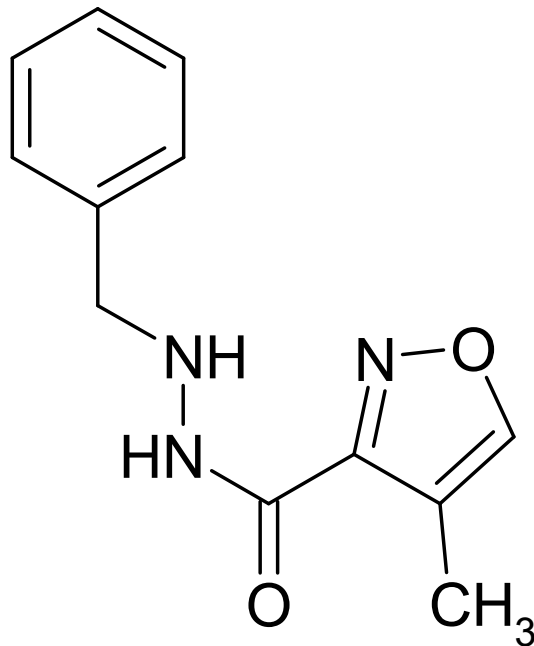
2.1 Non-selective MAO inhibitors



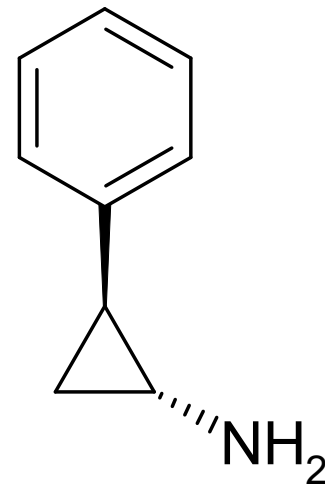
isonicotinic acid N'-
isopropylhydrazide
iproniazid



1-(2-phenylethyl)hydrazine
phenelzine

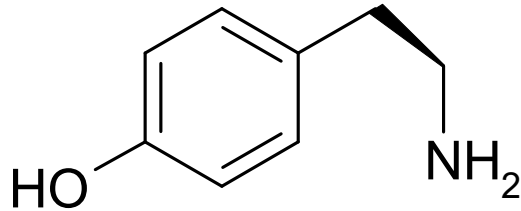


4-methylisoxazole-3-
karboxylic acid N'-
benzylhydrazide
isocarboxazid



trans-2-
phenylcyclopylamin
transylcypromine

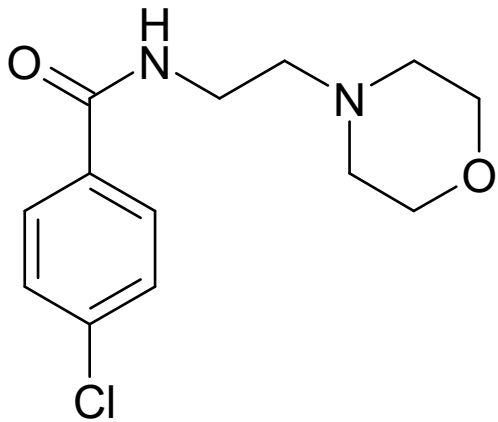
•dangerous interaction with „exciting amines“ in food (maturing cheeses, red wines) especially tyramine \Rightarrow \uparrow blood pressure to hypertension crisis



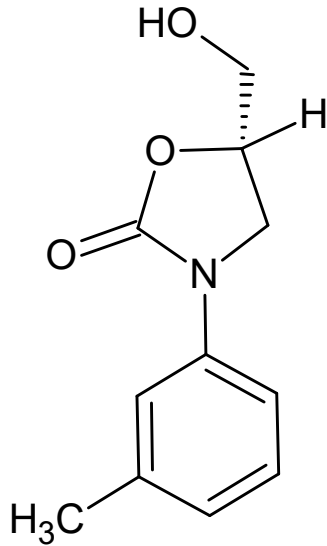
tyramine

2.2 Selective MAO A inhibitors

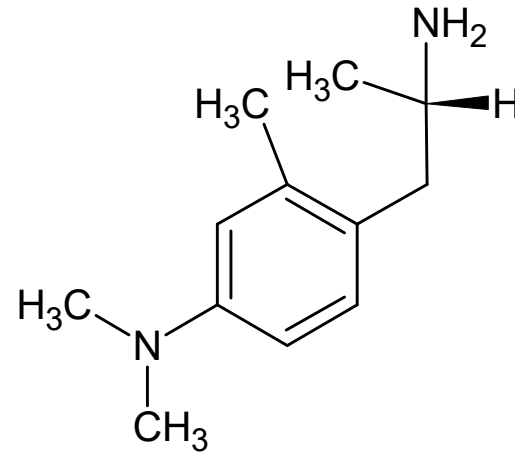
- MAO A decomposes mainly endogenous noradrenaline (NA) and serotonin (5HT)



moclobemide
N-(2-morpholinoethyl)-4-chlorobenzamide
Aurorix®



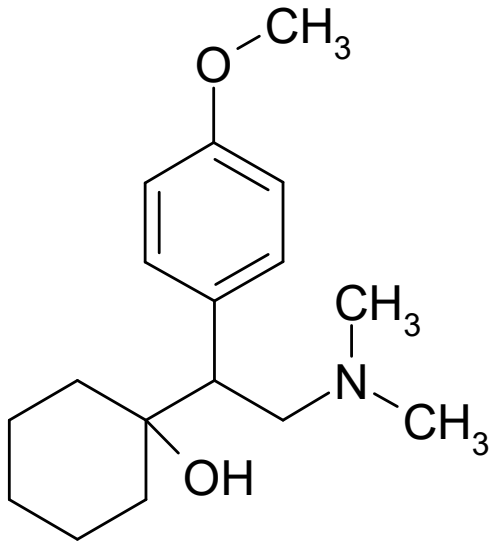
toloxatone



amiflamine

3. Serotonin and noradrenaline reuptake inhibitors (SNRI)

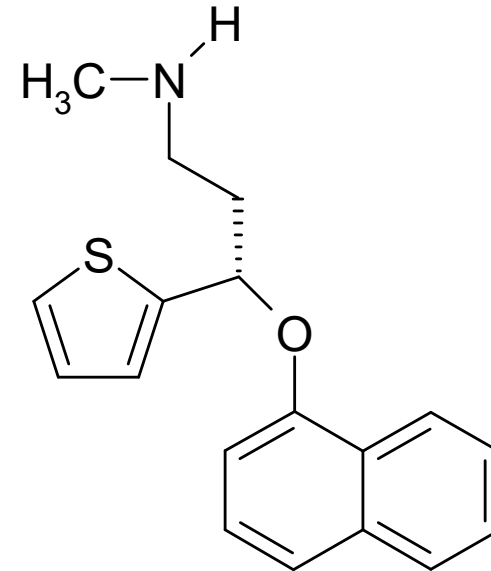
·indirect central agonists of both adrenergic and 5HT receptors



1-[2-(dimethylamino)-1-(4-methoxyphenyl)
ethyl]cyclohexanol

venlafaxine

Argofan ® , Apo-Venlafaxin ® , Velaxin ® ...

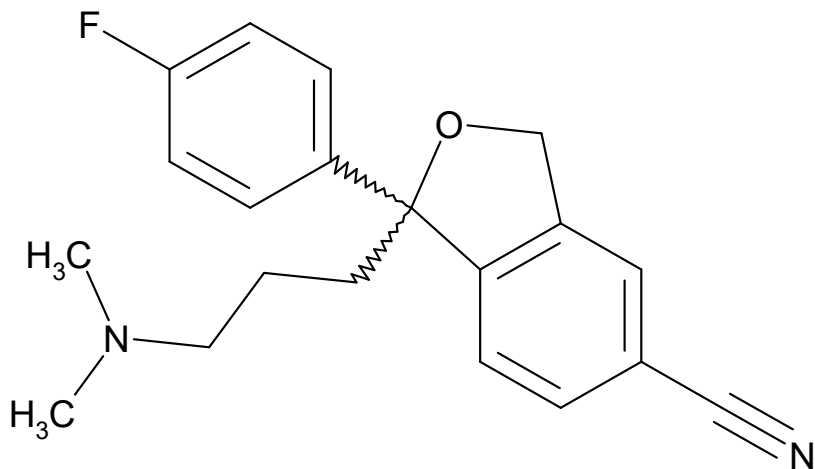


(3S)-1-methylamino-3-(1-naphtyloxy)-3-
(thiophene-2-yl)propane

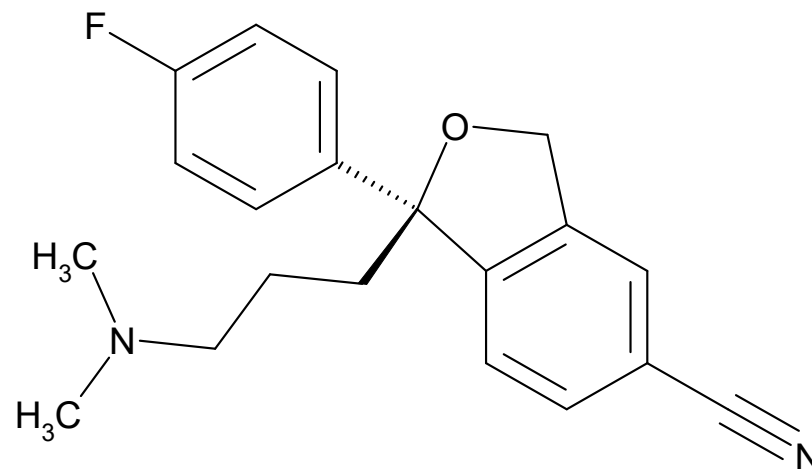
duloxetine

Cymbalta ® , Xeristar ®

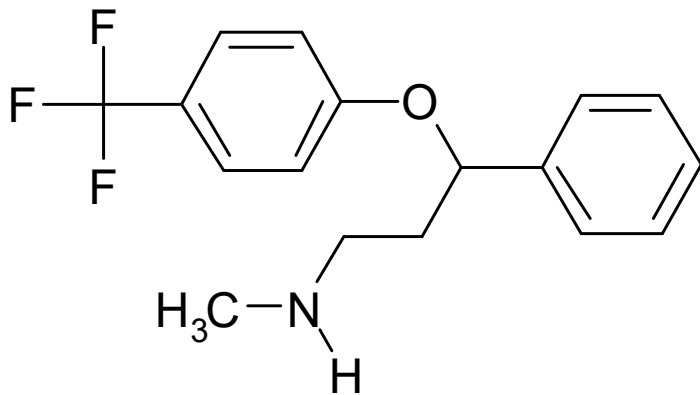
4. Selective serotonin reuptake inhibitors (SSRI)



citalopram
Citalex®



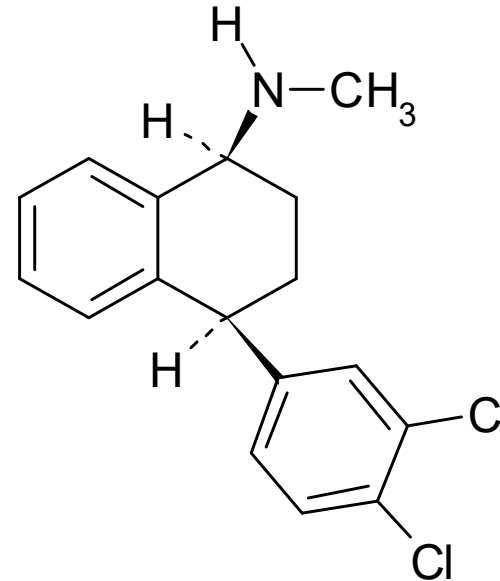
escitalopram
(S)-citalopram
Depresinal ® , Elicea ®



3-(4-trifluorophenoxy)-3-phenyl-
1-methylaminopropane

fluoxetine

Deprex[®], Floxet[®], Fluocim[®],
Fluval[®] ...

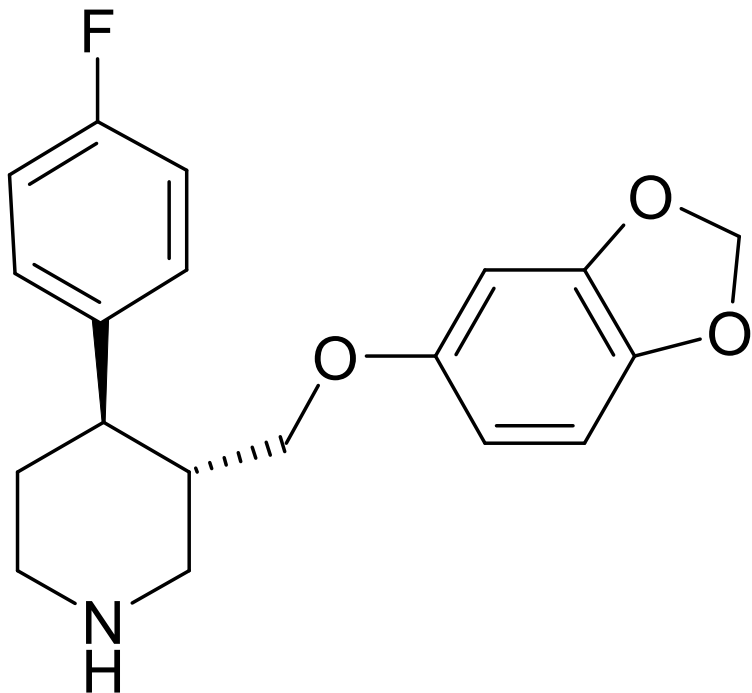


(1S,4S)-4-(3,4-dichlorophenyl)-1-methylamino-
1,2,3,4-tetrahydronaphthalene

sertraline

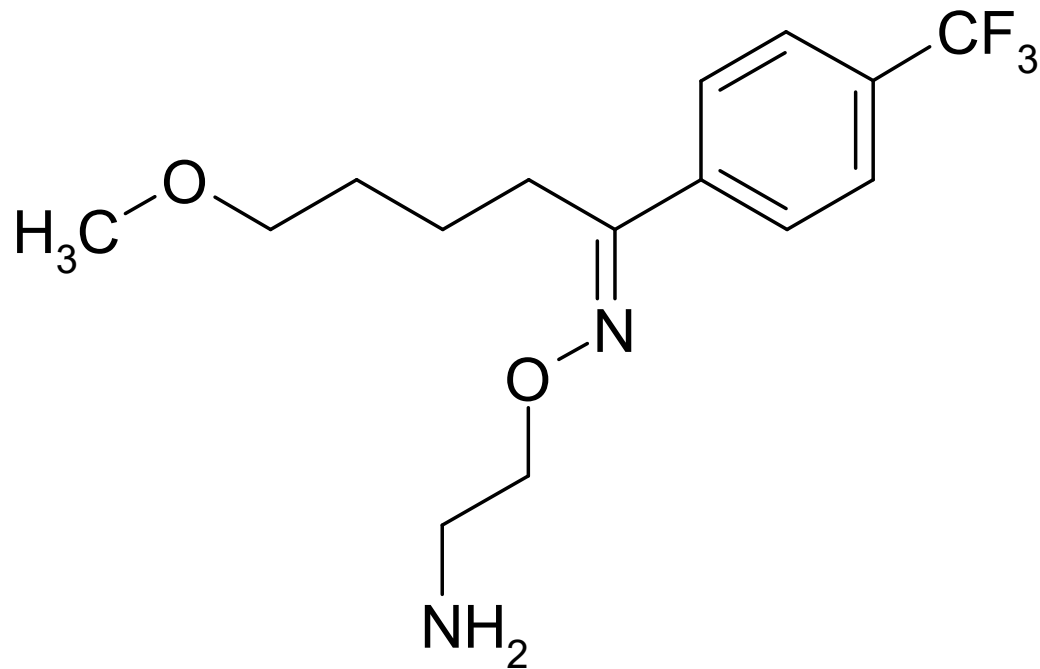
Asentra[®], Serlift[®], Setralax[®], Zoloft[®] ...

- slightly activates, can disturb the sleep if administered in the evening, increase of tension and anxiety possible, long half time – no problems with an omission of a single dose



paroxetine

Arketis ® , Parolex ®

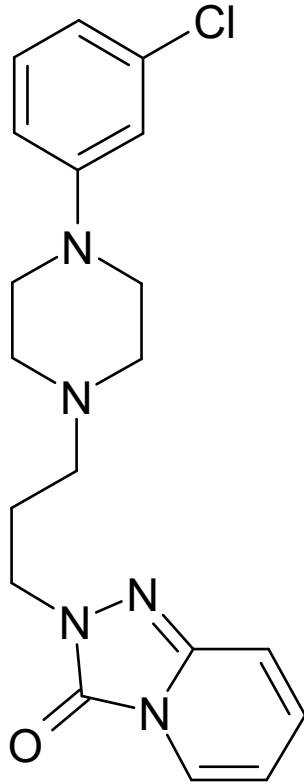


fluvoxamine

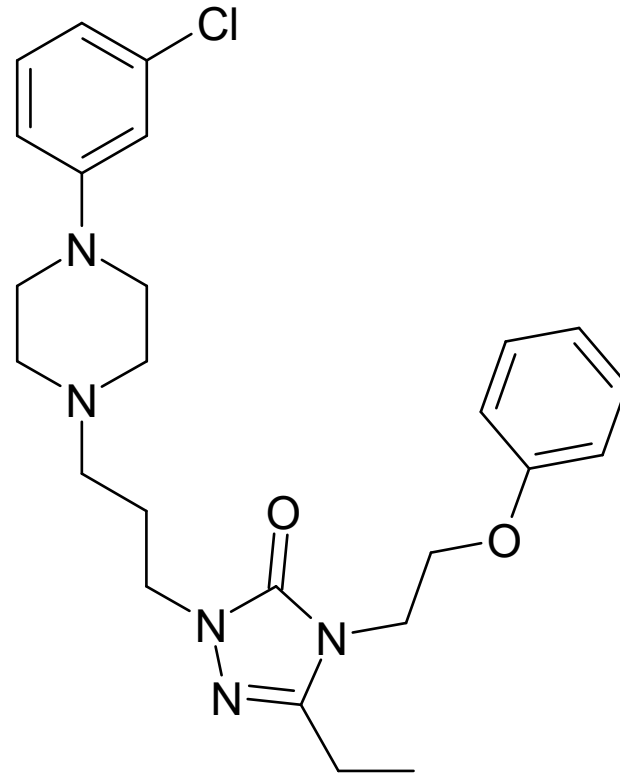
- attenuating effects, administration in the evening, suitable for inquiet patients, inhibition of suicidal turns

Fevarin ®

5. Dual-serotonergic antidepressants



trazodone



nefazodone

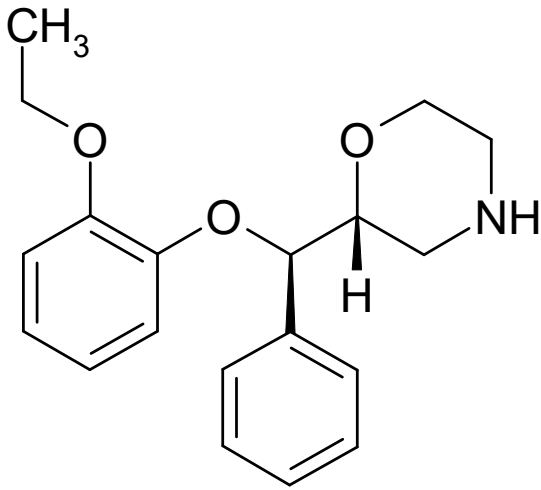
- serotonin reuptake inhibitors and simultaneously 5-HT₂ receptor antagonists

- markedly sedative

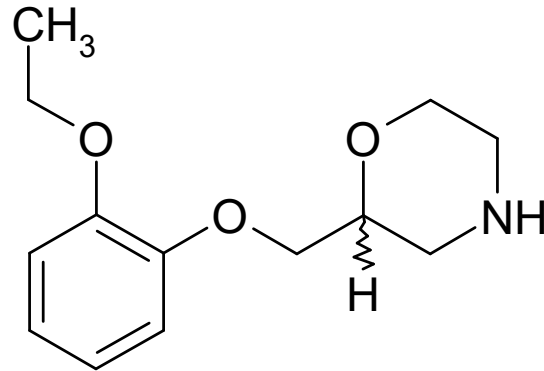
Trittico AC ®

- also inhibits NA reuptake

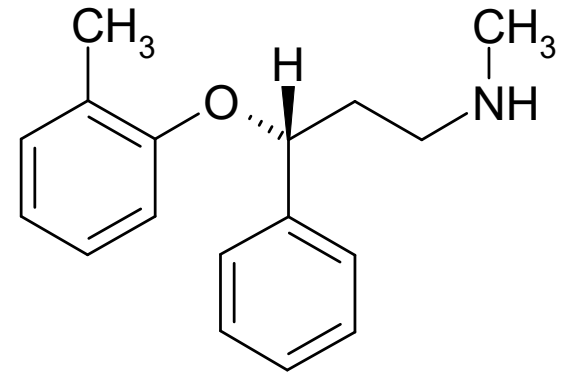
6. Selective noradrenaline reuptake inhibitors (SNRI)



reboxetine
•*R,R*



viloxazine
•racemate



atomoxetine
•*R*
Strattera®

- effective in motivation and interest stimulation
- enhance effect of sympathomimetics
- AE : tachycardia, tremor

7. Alkaline metals salts

Li⁺

- mostly often Li₂CO₃
- treatment of bipolar illness (formerly manio-depressive syndrome)
- high toxicity, low difference between therapeutic and toxic doses, plasmatic levels monitoring necessary

Rb⁺

- total amount in the body 400 – 900 mg
- potentiates noradrenergic and dopaminergic transmission of nervous impulses in CNS
- evidences of antidepressant effects