Antidepressants

- often life-saving drugs

Possible classification of antidepressants

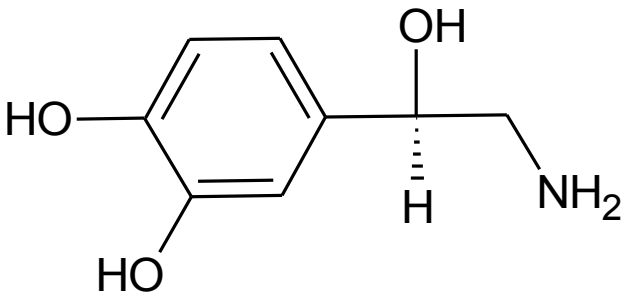
1. Non-selective monoamines reuptake inhibitors (tricyclic and tetracyclic antidepressants)
2. Monoaminooxidases (MAO) inhibitors

2.1 Non-selective MAO inhibitors

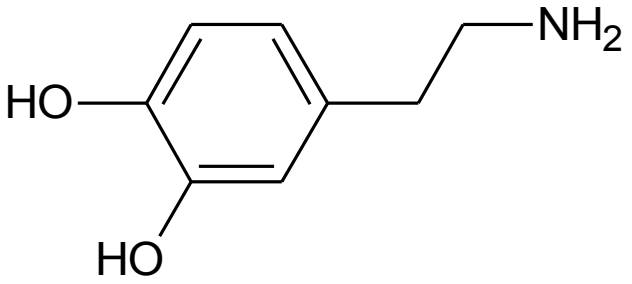
2.2 Selective MAO A inhibitors

3. Selective serotonine and noradrenaline reuptake inhibitors (SSNRI)
4. Selective serotonine reuptake inhibitors (SSRI)
5. Dual-serotoninergic antidepressants
6. Selective noradrenaline reuptake inhibitors (SNRI)
7. Alkaline metals salts

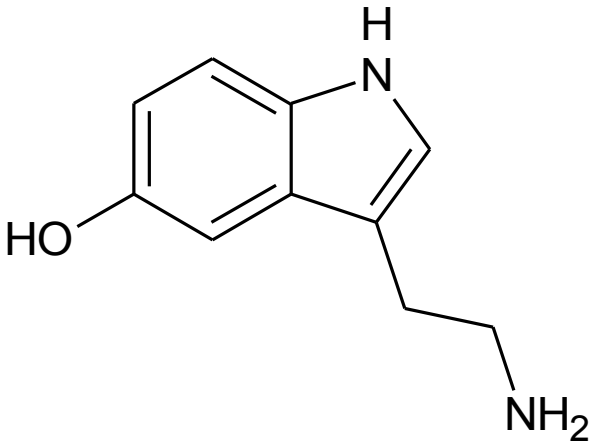
Amines involved in effects of antidepressants



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



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

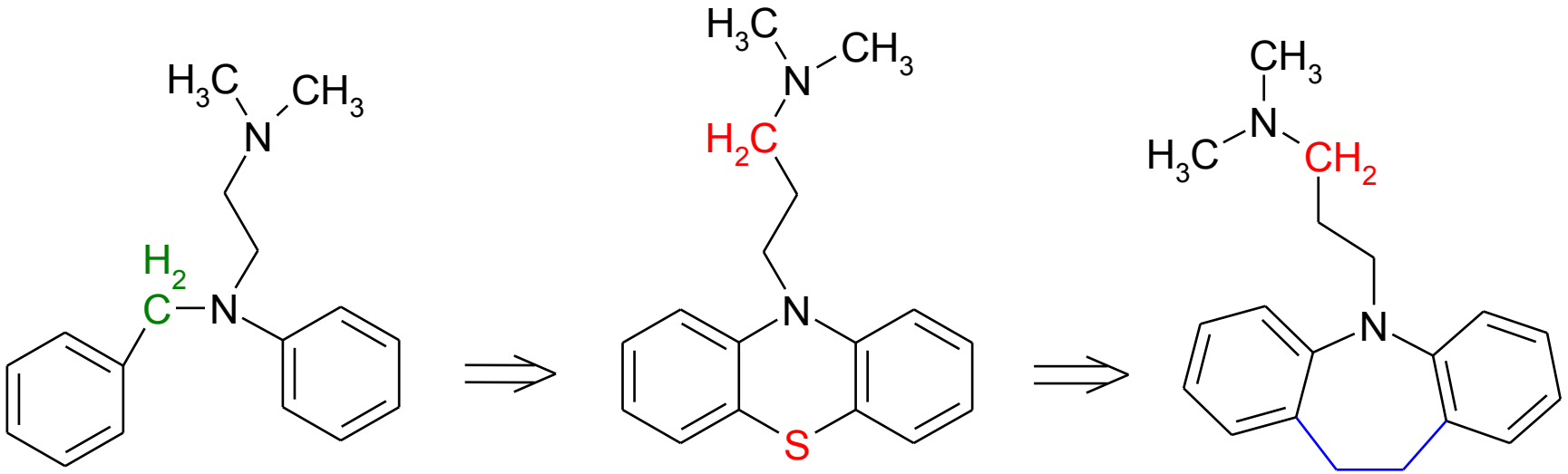


3-(2-aminoethyl)-1*H*-indol-5-ol
serotonine

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

- inhibit reuptake of serotonine and noradrenaline

Genesis (derivation) of tricyclic antidepressants



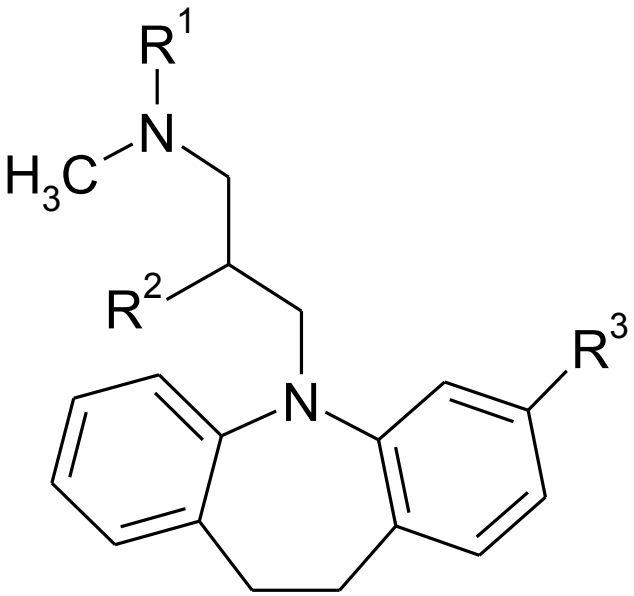
antihistamines

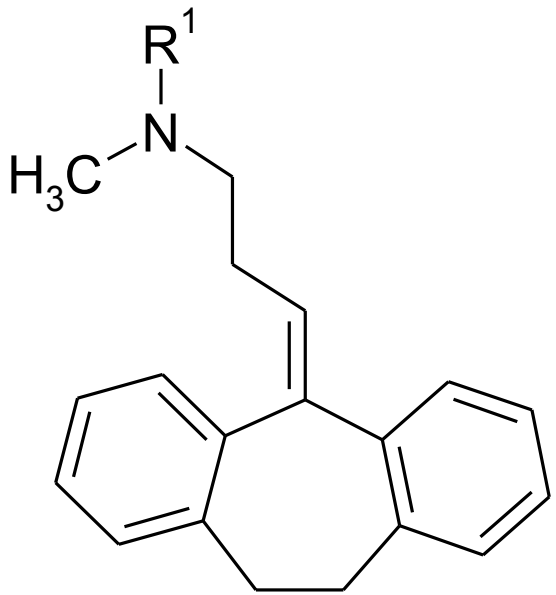
promazine
antipsychotics

imipramine

1st and 2nd generations of tricyclic antidepressants

- act innhibitory also on M, H_1, α_1, α_2, 5-HT_2 receptors
- 2nd gen. increases more amount of NA than 5-HT in synapsis, 1st gen. reversely





R^1=-CH_3 R^2=R^3=-H **imipramine**
Tofranil®

R^1= R^2=R^3=-H **desipramine**

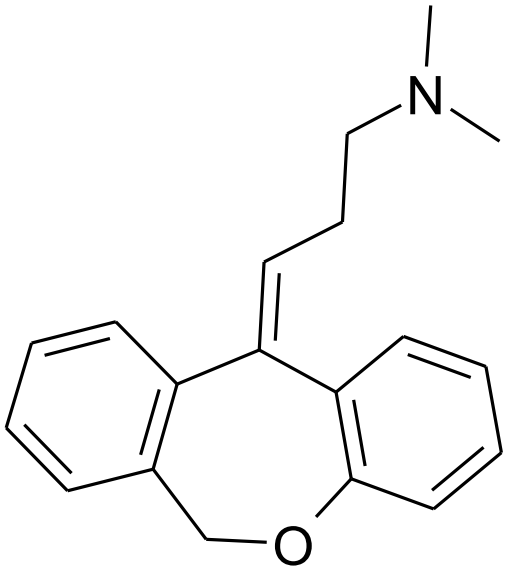
R^1= R^2=-H R^3=-Cl **clomipramine**
Anafranil®

R^1= R^2=-CH_3 R^3=-H **trimipramine**
Surmontil®

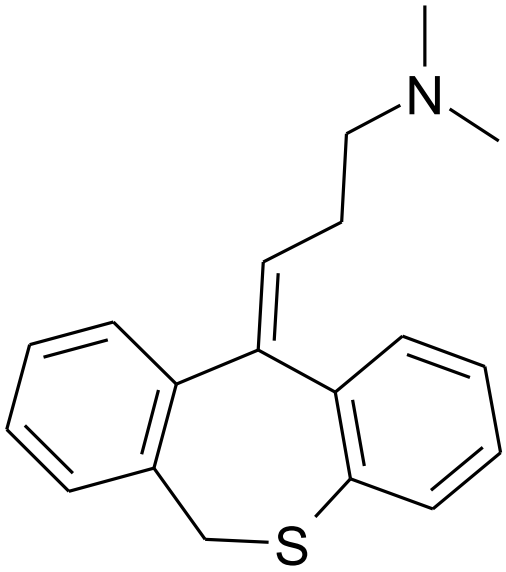
R^1=-CH_3 **amitriptyline**
Elavil®, Endep®

R^1=-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 = >↑ NA and 5-HT in synapsis.
- After longer period treatment (2 - 4 weeks) = >

↓ of activity β and ↓5-HT_2 rp.

↓ of release and return of NA

↓ NA-stimulated cAMP level in the brain

↑ sensitivity of 5-HT receptors

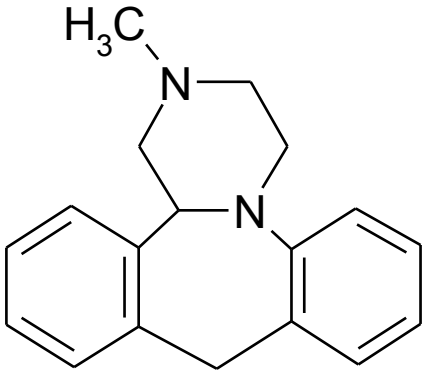
* „Adaptive responses“ *

- as long as 4 weeks of treatment are needed for full activity

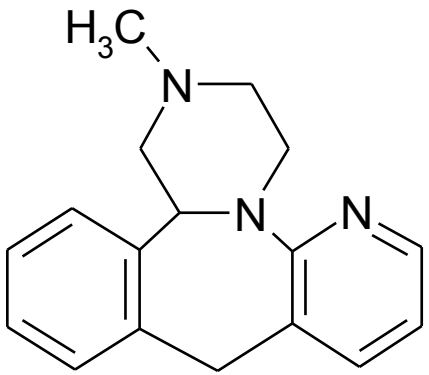
Unwanted effects of tricyclic antidepressants due to antagonist action on various receptors:

- M(uscarine) rp. - dry in the mouth, bad accomodation, tachycardia, problems with emiction, forgeting
- H_1 rp. - sedation, increase of body weight
- 5-HT_2- increase of appetite and body weight
- α_1 - orthostatic hypotension, reflex tachycardia

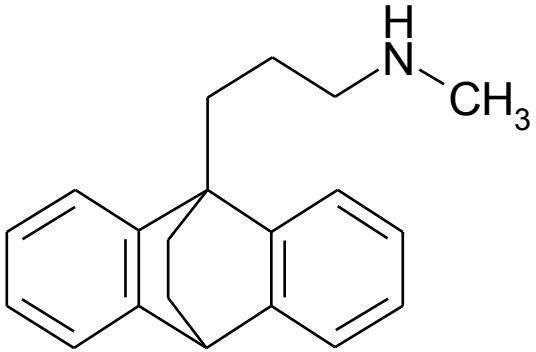
Tetracyclic antidepressants
(or „thymoleptics of 2nd generation“)



mianserin



mirtazapine



maprotiline
inhibits reuptake of noradrenaline mainly
•moderate anicholinergic effects, significant antihistamine ones (sedative)
Ludiomil ®

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

•inhibits also α_1-rp. ⇒ ↓ blood pressure
Lerivon ® , Miabene ®

Esprital ® , Mirtazapin ® *firm*

2. Monoaminooxidases (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 occurence of drug interactions

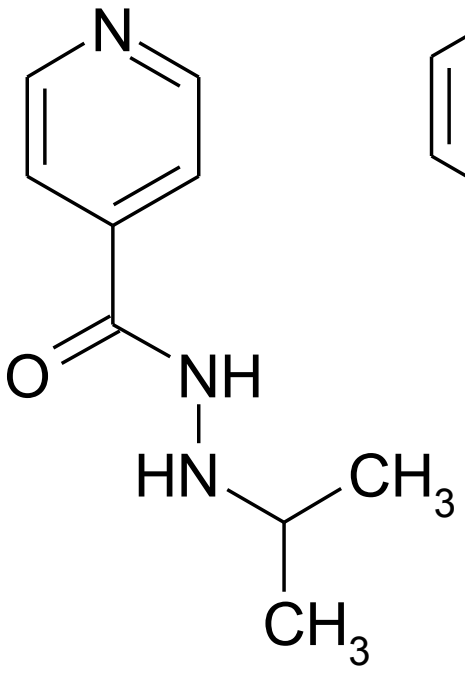
– most frequently used if other treatment methods failed

– AE: orthosthasis, sedation, sexual dysfunctions, body weight increase

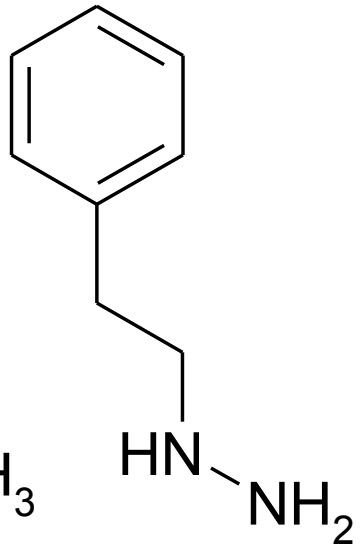
– type A (MAO-A) decomposes mainly serotonine and less also noradrenaline

– typ B (MAO-B) decomposes various phenylethylamine including dopamine

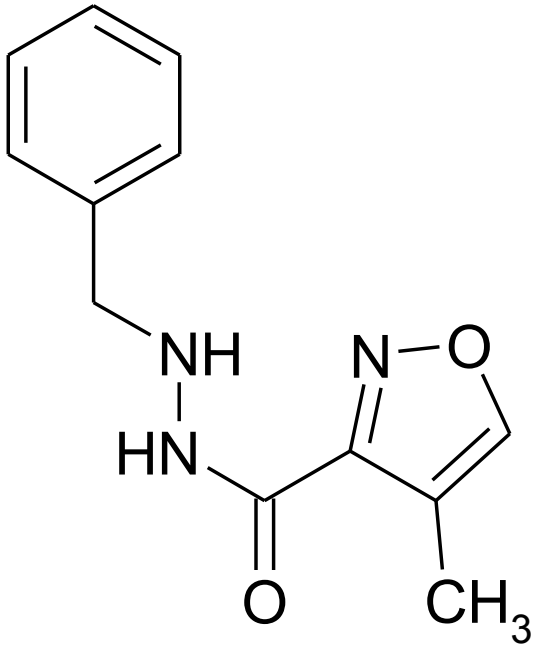
2.1 Non-selective MAO inhibitors



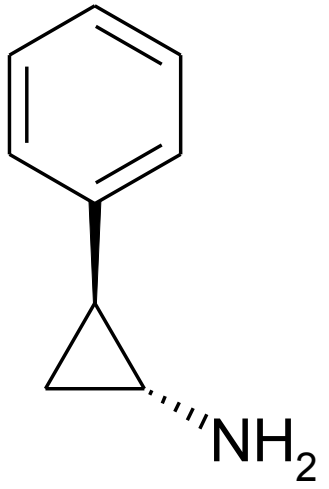
isonicotinic acid N´-isopropylhydrazide
iproniazid



1-(2-phenylethyl)hydrazine
phenelzine

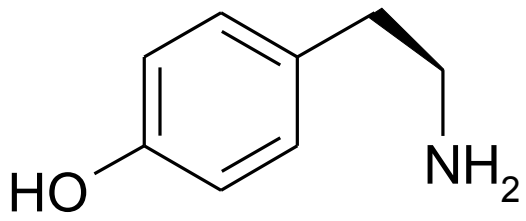


4-methylisoxazole-3-karboxylic acid N´-benzylhydrazide
isocarboxazid



trans-2-phenylcyklopylamin
tranylcypromine

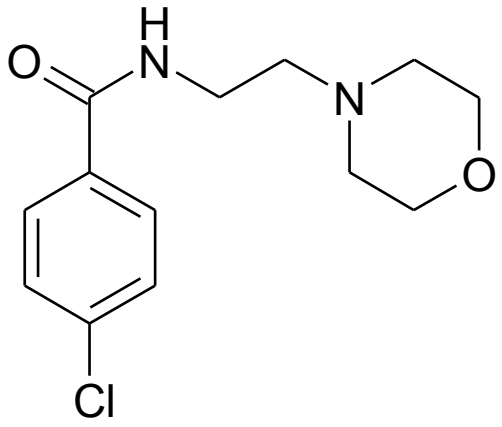
•dangerous interaction with „exciting amines“ in food (maturing cheeses, red wines) especially tyramine ⇒↑ blood pressure to hypertension crisis

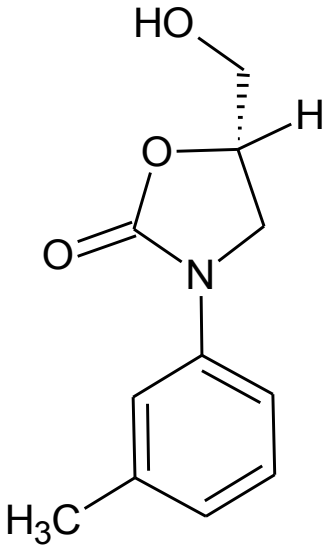


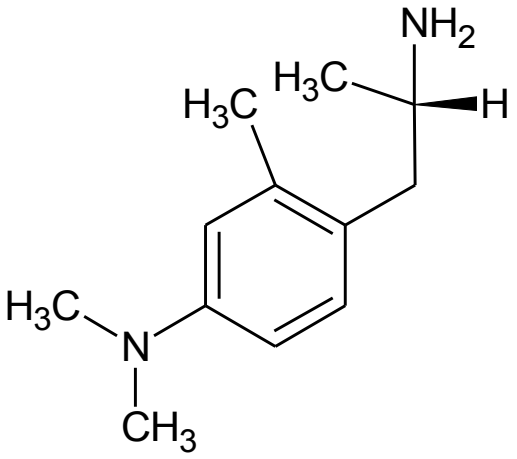
tyramine

2.2 Selective MAO A inhibitors

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







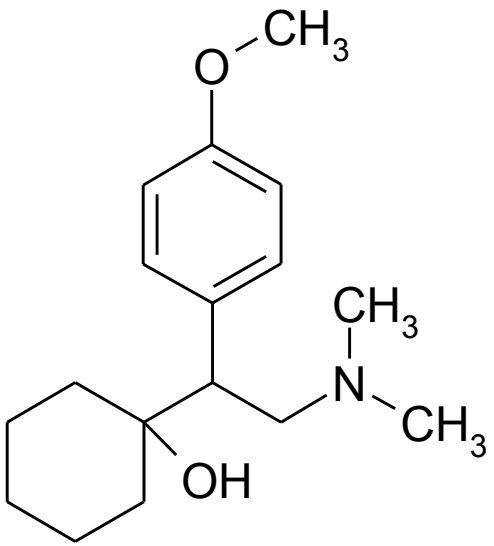
moclobemide
N-(2-morfolinoethyl)-4-chlorobenzamide
Aurorix ®

toloxatone

amiflamine

3. Serotonine and noradrenaline reuptake inhibitors (SNRI)

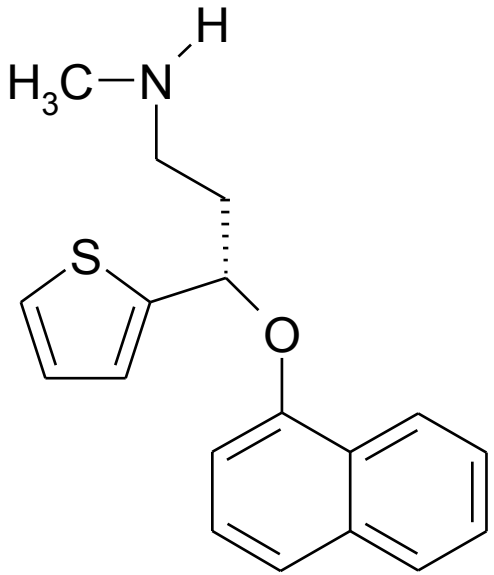
·indirect central agonists of both adrenergic and 5HT receptors



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

venlafaxine

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

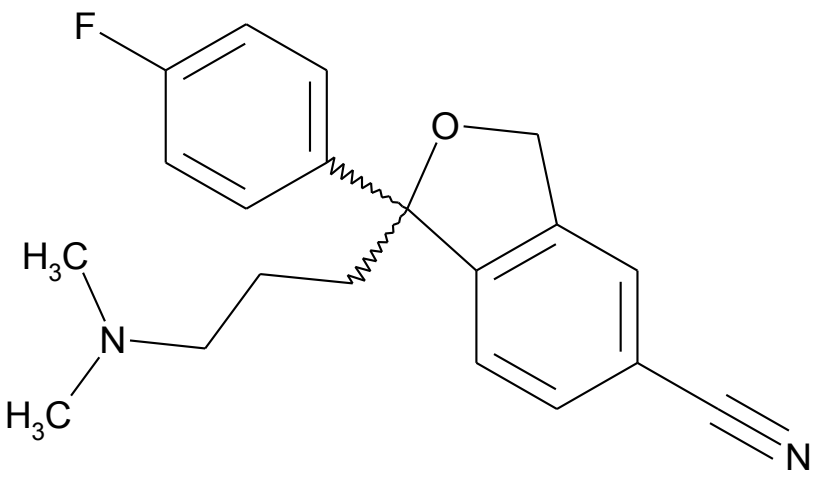


(3S)-1-methylamino-3-(1-naphtyloxy)-3-(thiophene-2-yl)propane

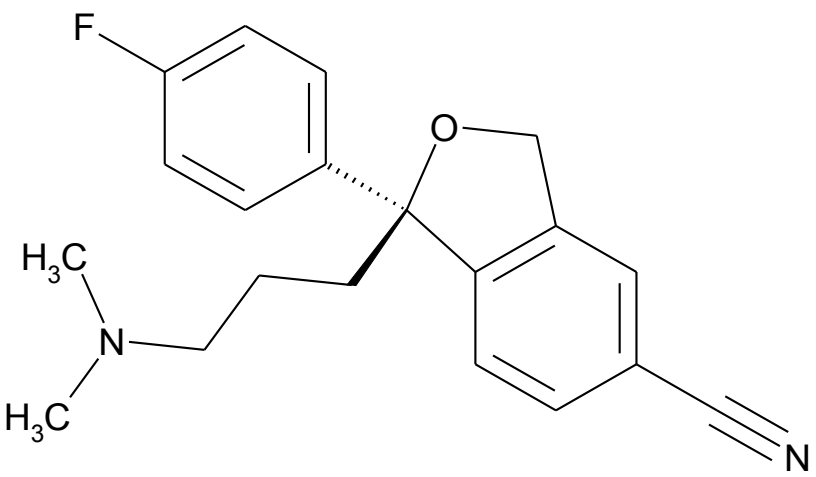
duloxetine

Cymbalta ® , Xeristar ®

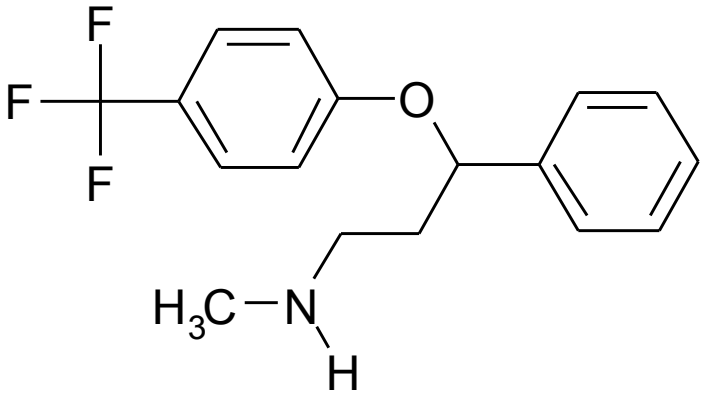
4. Selective serotonine reuptake inhibitors (SSRI)



citalopram
Citalex®



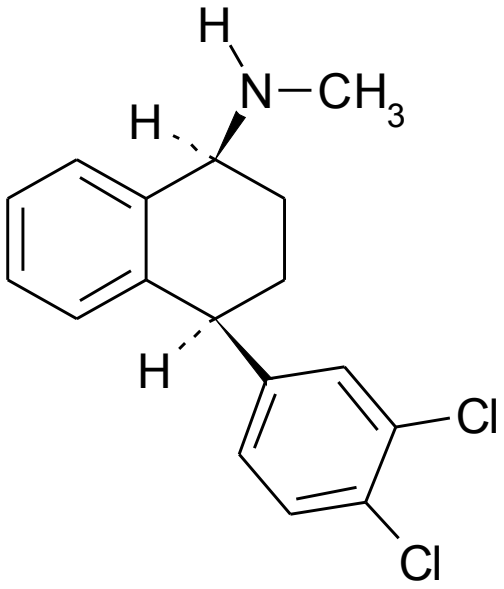
escitalopram
(*S*)-citalopram
Depresinal ® , Elicea ®



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

fluoxetin

Deprex®, Floxet®, Fluocim®, Fluval® …

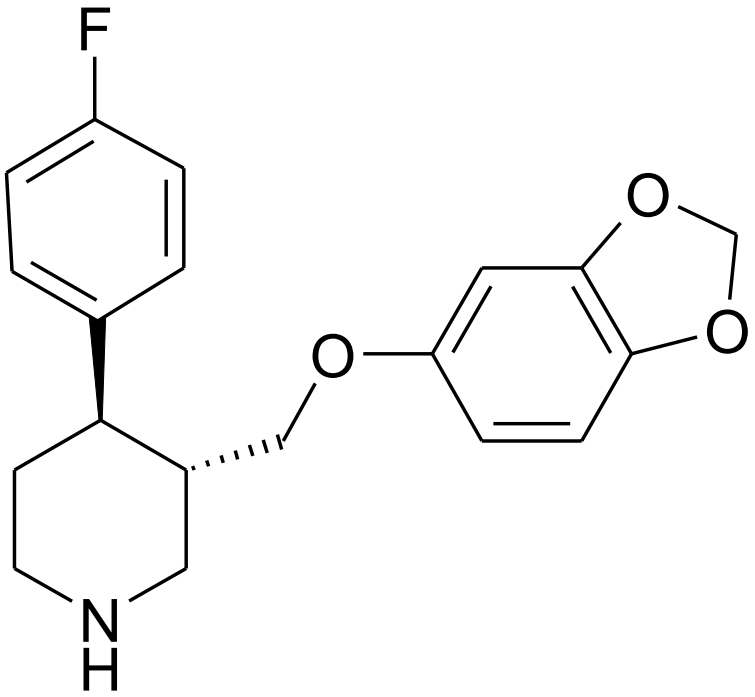


(1S,4S)-4-(3,4-dichlorophenyl)-1-methylamino-1,2,3,4-tetrahydronaphtalene

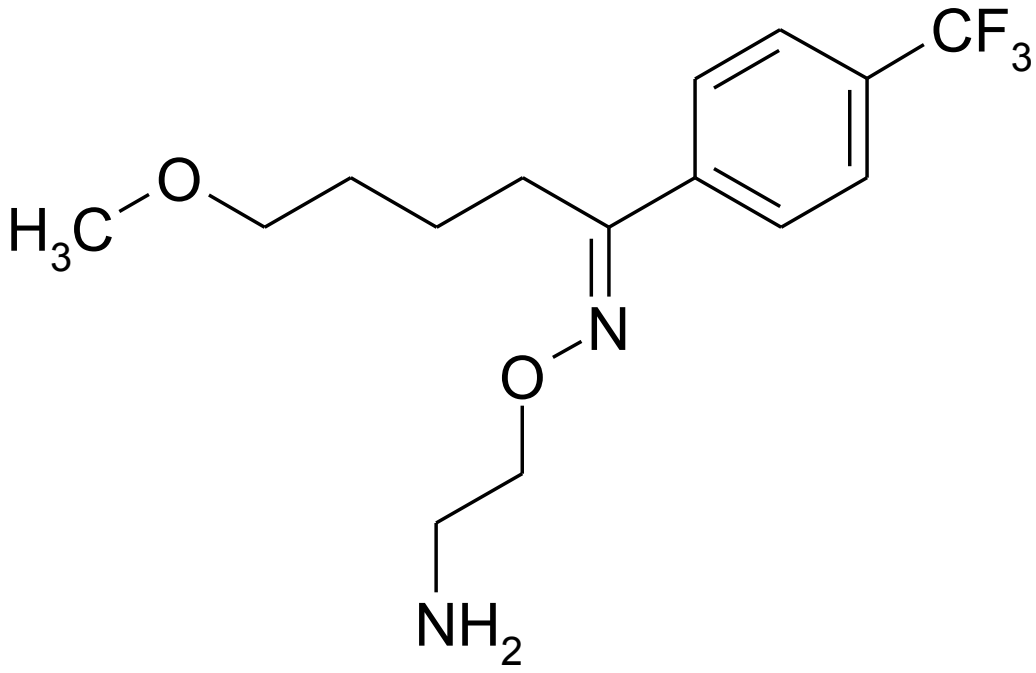
sertralin

Asentra®, Serlift®, Setralex®, 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



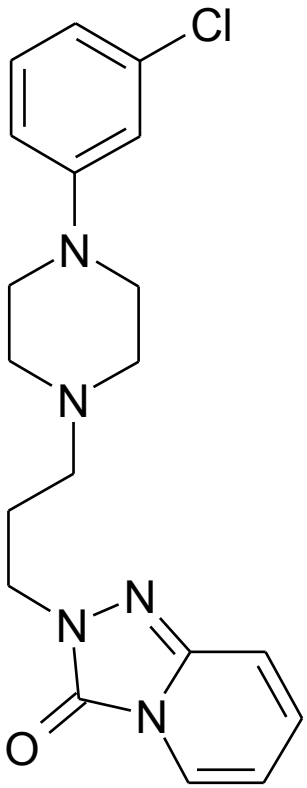
paroxetine
Arketis ® , Parolex ®



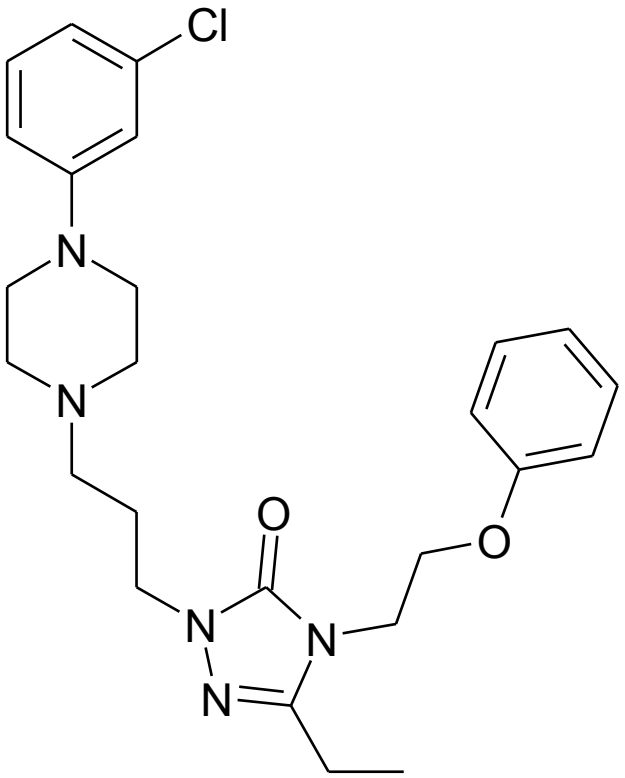
fluvoxamine

•attenuating effects, administration in the evening, suitable for inquiet patients, inhibition of suicidal turns
Fevarin ®

5. Dual-serotoninergic antidepressants



trazodone

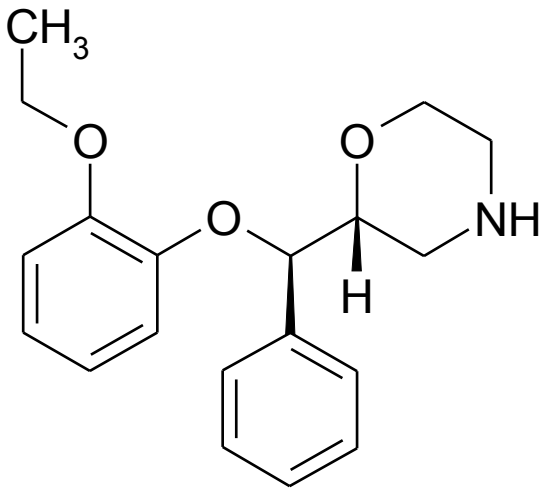


nefazodone

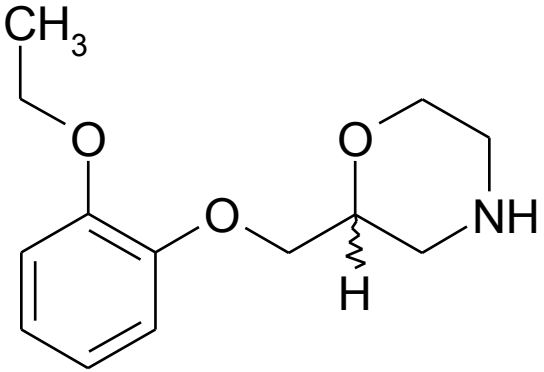
- serotonine reuptake inhibitors and simultaneously 5-HT_2 receptor antagonists
- also inhibits NA reuptake
- markedly sedative

Trittico AC ®

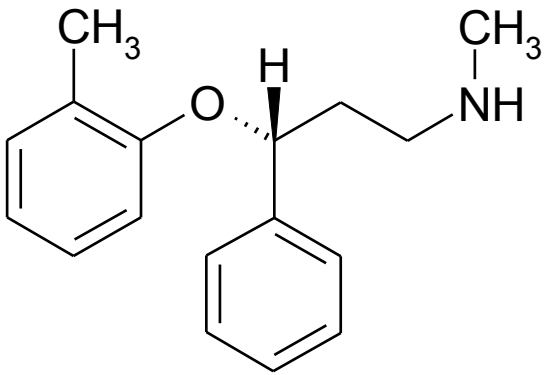
6. Selective noradrenaline reuptake inhibitors (SNRI)



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 Li_2CO_3
- 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