Antidepressants

- often life-saving drugs

A possible classification of antidepressants

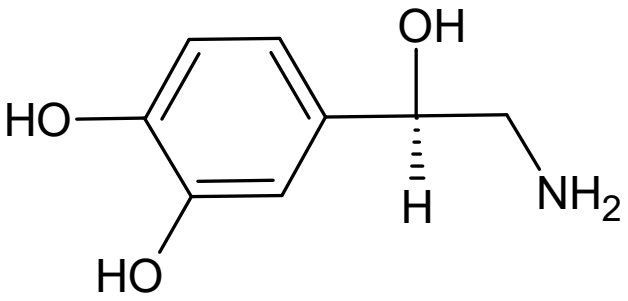
1. Non-selective monoamines reuptake inhibitors (tricyclic and tetracyclic antidepressants)
2. Monoaminooxidases (MAO) inhibitors

2.1 Non-selective MAO inhibitors

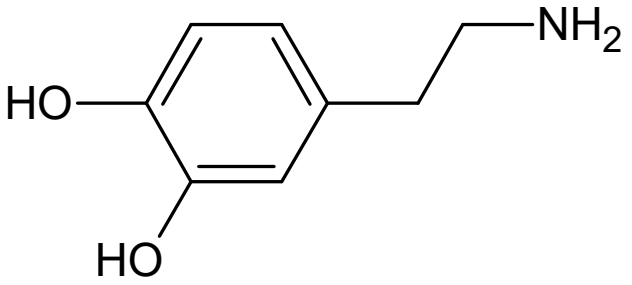
2.2 Selective MAO A inhibitors

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. Selective noradrenaline and dopamine reuptake inhibitors
8. Melatoninergic agonists
9. “Other” tricyclic antidepressants
10. Alkaline metals salts

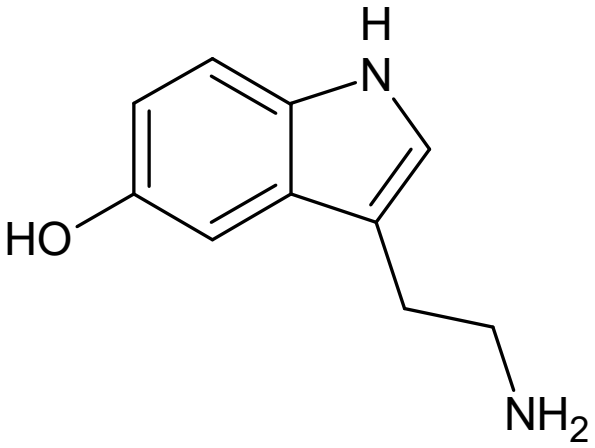
Amines mainly involved in effects of antidepressants



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



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

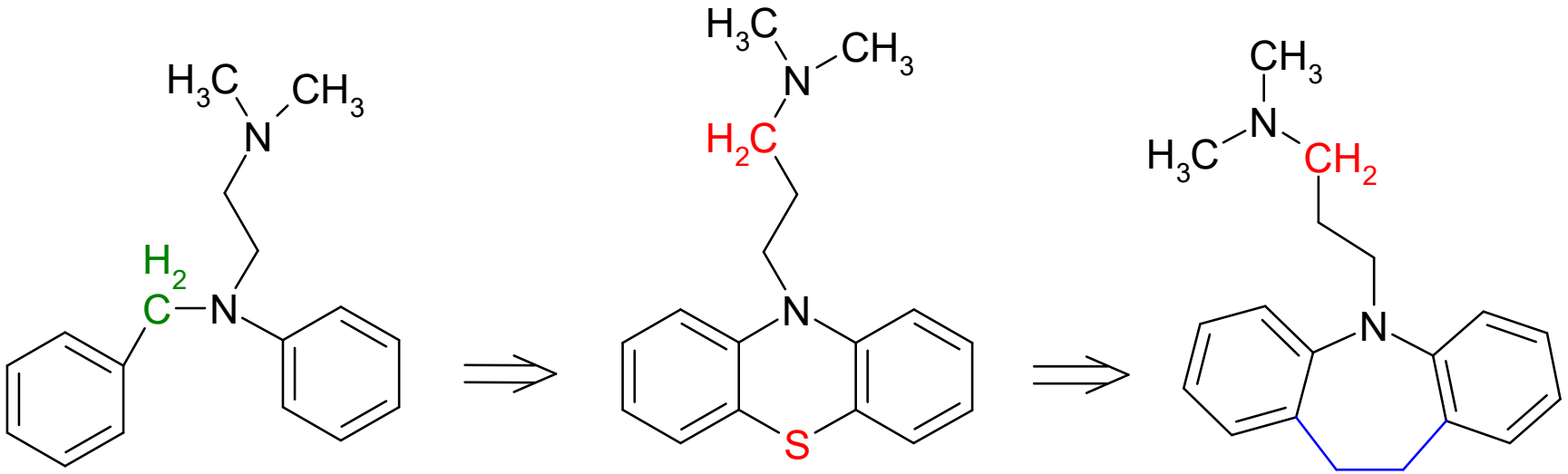


3-(2-aminoethyl)-1*H*-indol-5-ol
serotonine

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

- inhibit reuptake of serotonine and noradrenaline

Genesis (derivation) of tricyclic antidepressants



antihistamines

promazine
antipsychotics

imipramine

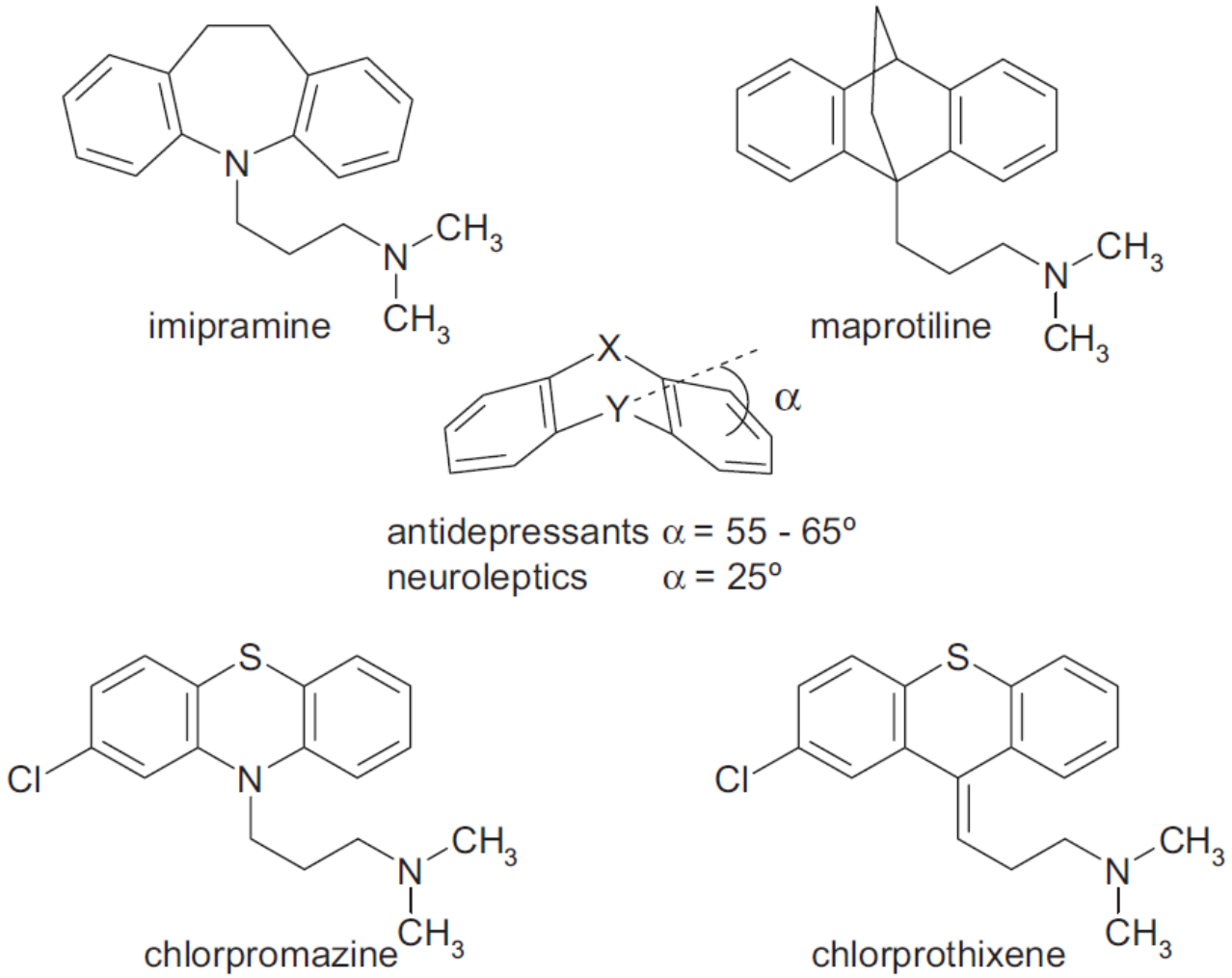
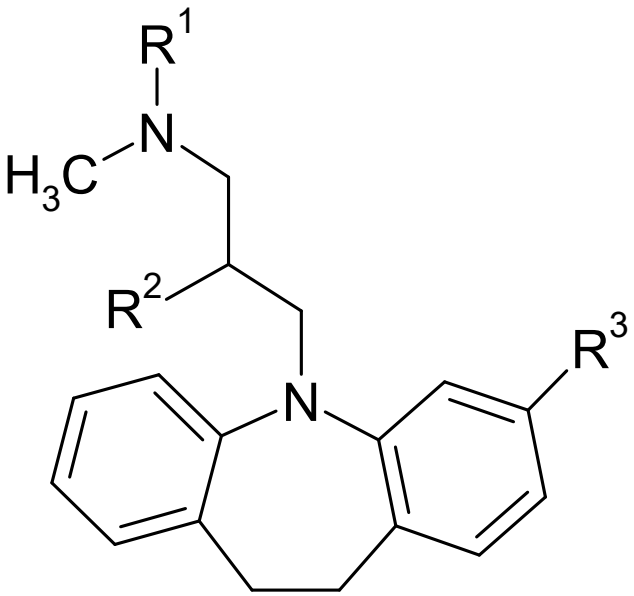
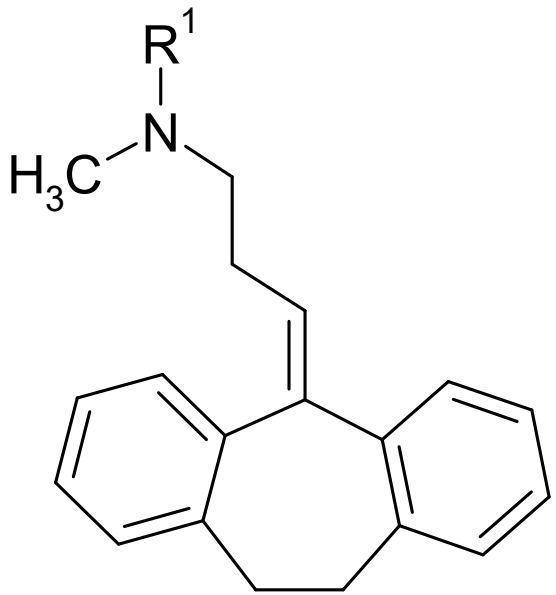


Fig. 1.5 The tricyclic antidepressants (imipramine and maprotiline) are characterized by a dihedral angle of 55° to 65° between the two benzo rings; this angle is only 25° for the tricyclic neuroleptics (chlorpromazine, chlorprothixene) [12].

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**

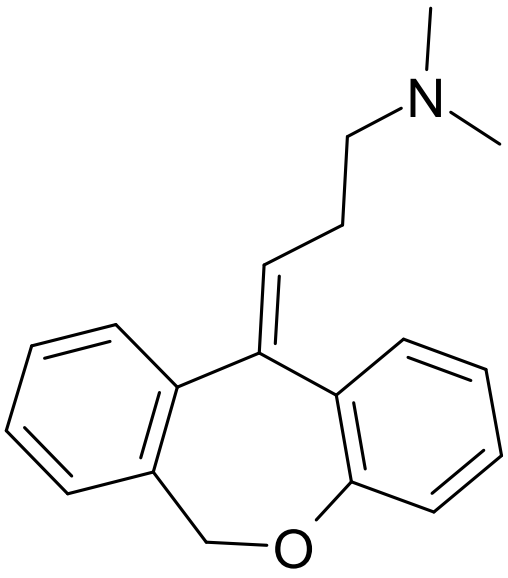
R^1= R^2=-H R^3=-Cl **clomipramine**
Anafranil®

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

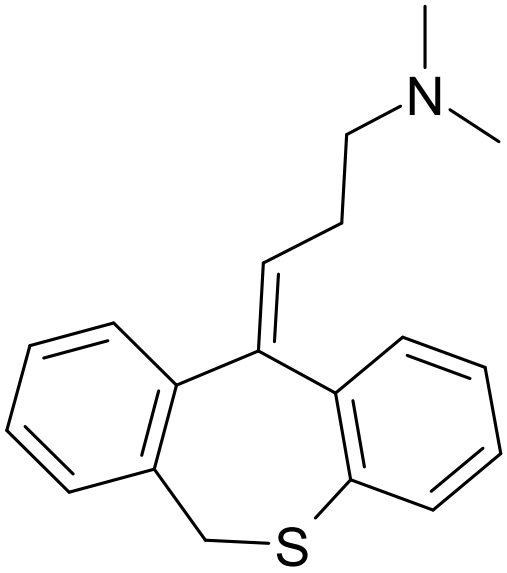
R^1=-CH_3 **amitriptyline**
Elavil®, Endep®

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

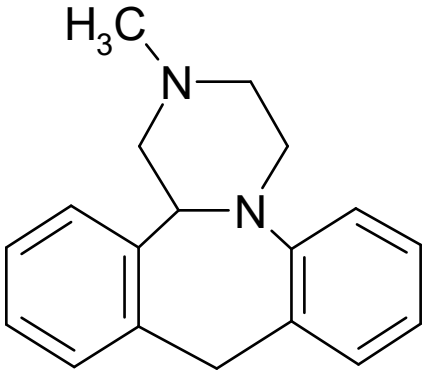
* „Adaptive responses“ *

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

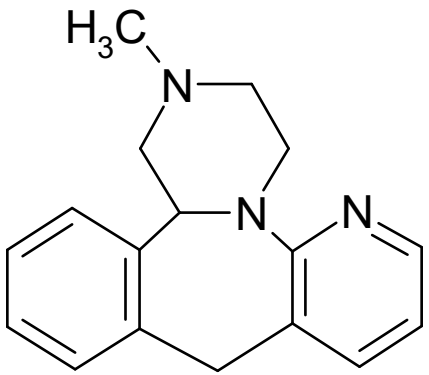
Unwanted effects of tricyclic antidepressants due to antagonist action on various receptors:

- 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

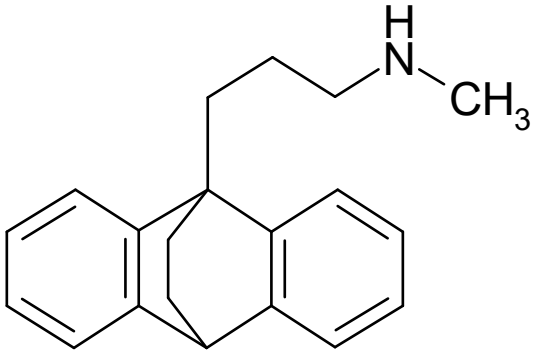
Tetracyclic antidepressants
(or „thymoleptics of 2nd generation“)



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. $\Rightarrow$
$\downarrow$ 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

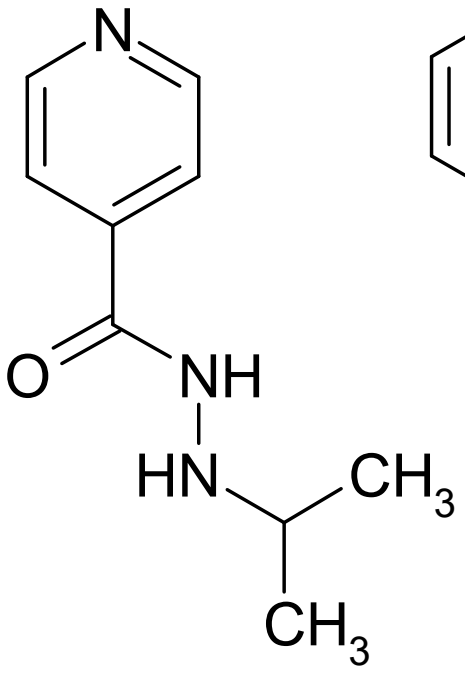
– most frequently used if other treatment methods failed

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

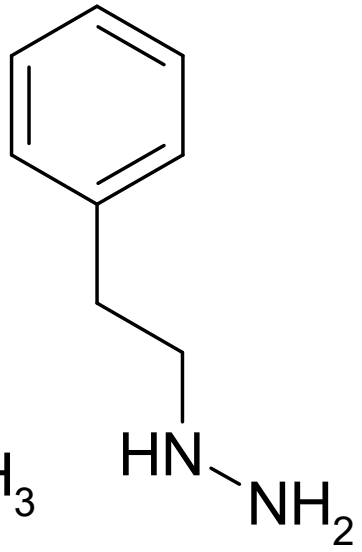
– type A (MAO-A) decomposes mainly serotonine and less also noradrenaline

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

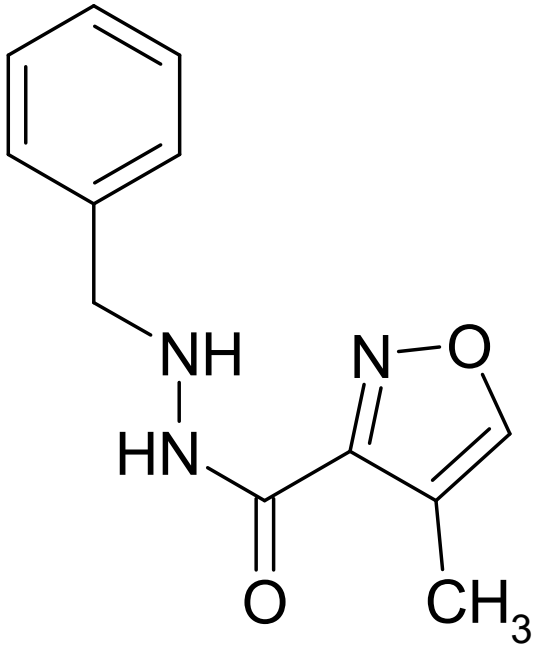
2.1 Non-selective MAO inhibitors



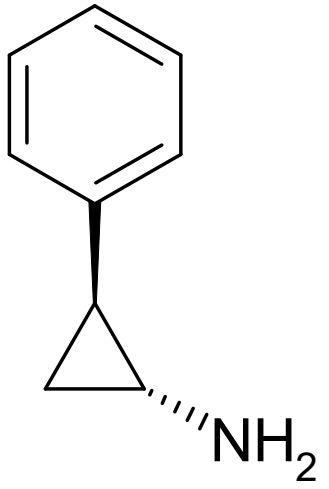
isonicotinic acid N´-isopropylhydrazide
iproniazid



1-(2-phenylethyl)hydrazine
phenelzine

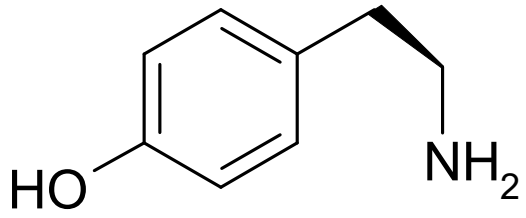


4-methylisoxazole-3-karboxylic acid N´-benzylhydrazide
isocarboxazid



trans-2-phenylcyklopylamin
tranylcypromine

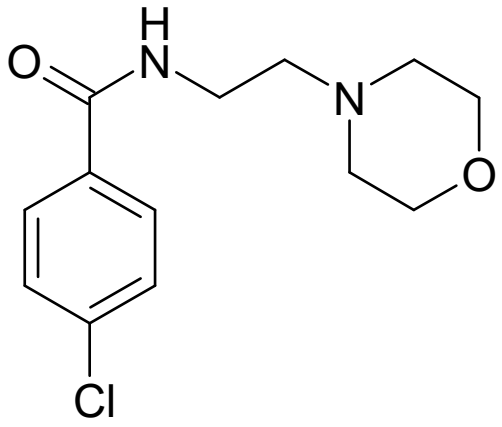
•dangerous interaction with „exciting amines“ in food (maturing cheeses, red wines) especially tyramine ⇒↑ blood pressure to hypertension crisis

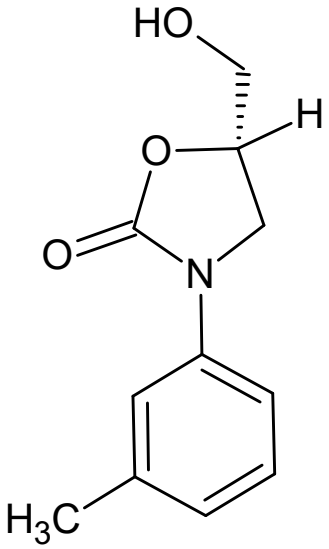


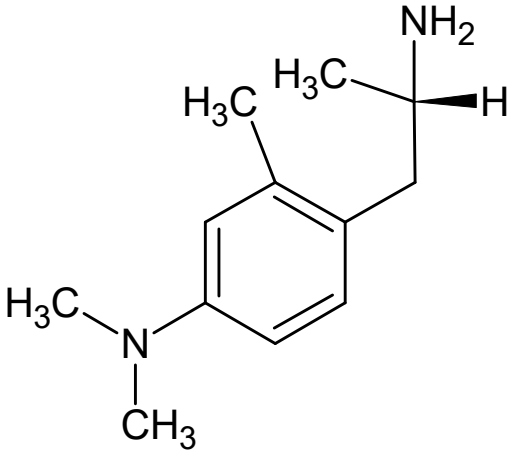
tyramine

2.2 Selective MAO A inhibitors

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







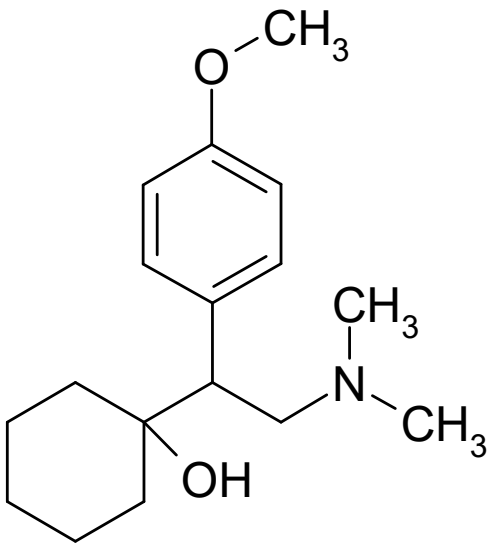
moclobemide
N-(2-morfolinoethyl)-4-chlorobenzamide
Aurorix ®

toloxatone

amiflamine

3. Serotonine and noradrenaline reuptake inhibitors (SNRI)

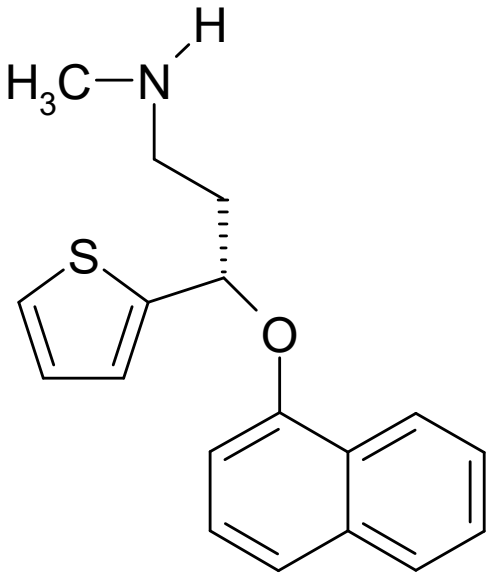
·indirect central agonists of both adrenergic and 5HT receptors



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

venlafaxine

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

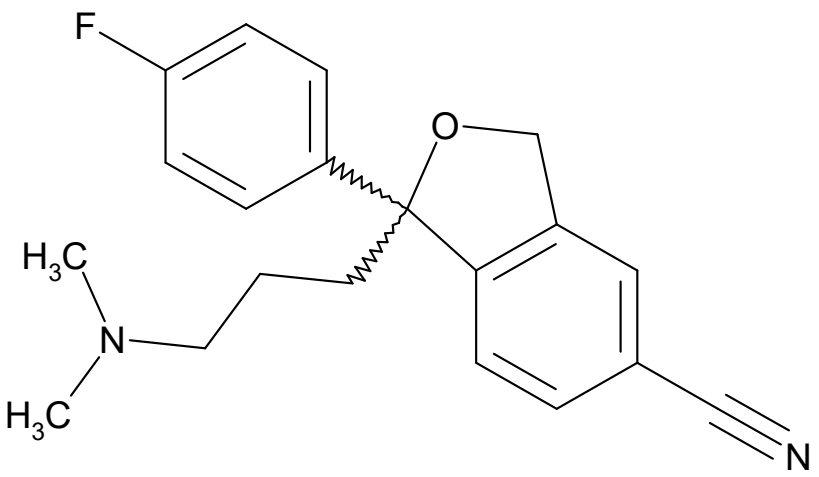


(3S)-1-methylamino-3-(1-naphtyloxy)-3-(thiophene-2-yl)propane

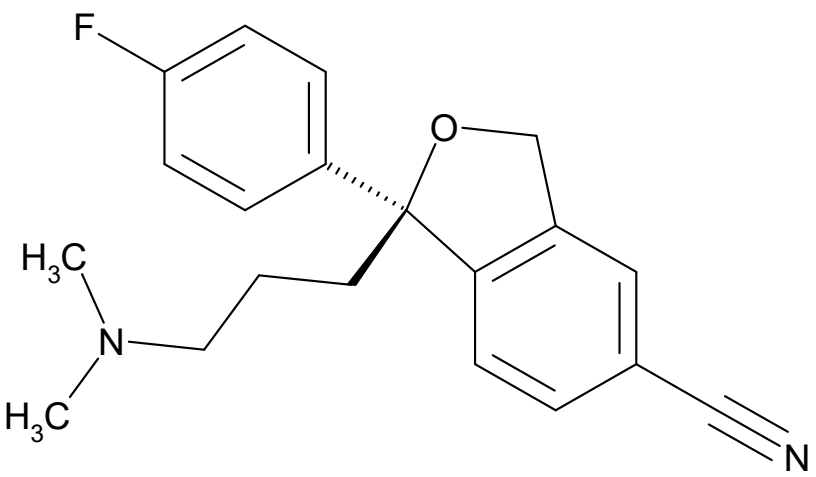
duloxetine

Cymbalta ® , Xeristar ®

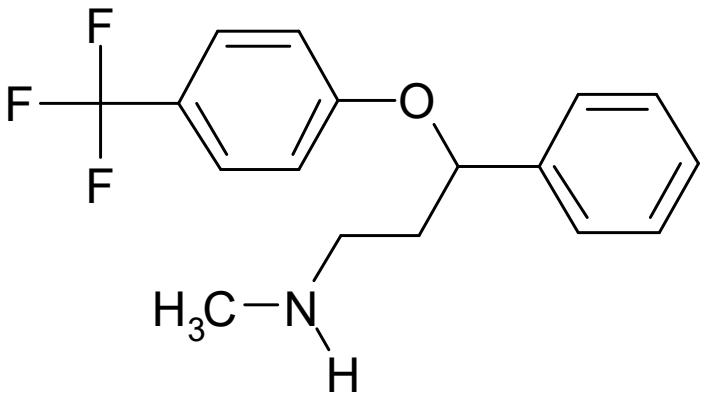
4. Selective serotonine reuptake inhibitors (SSRI)



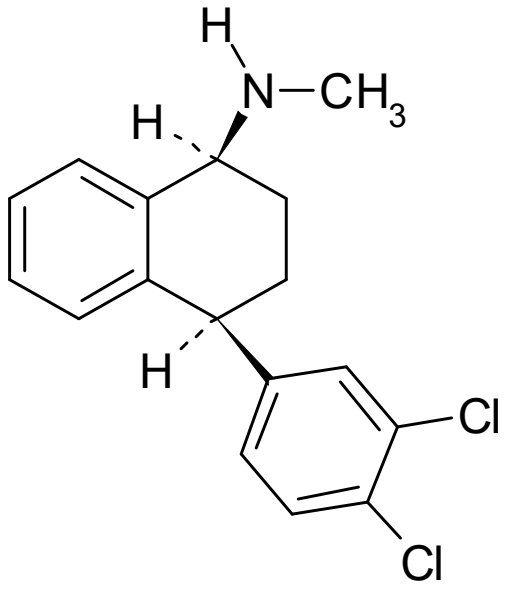
citalopram
Citalex®



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

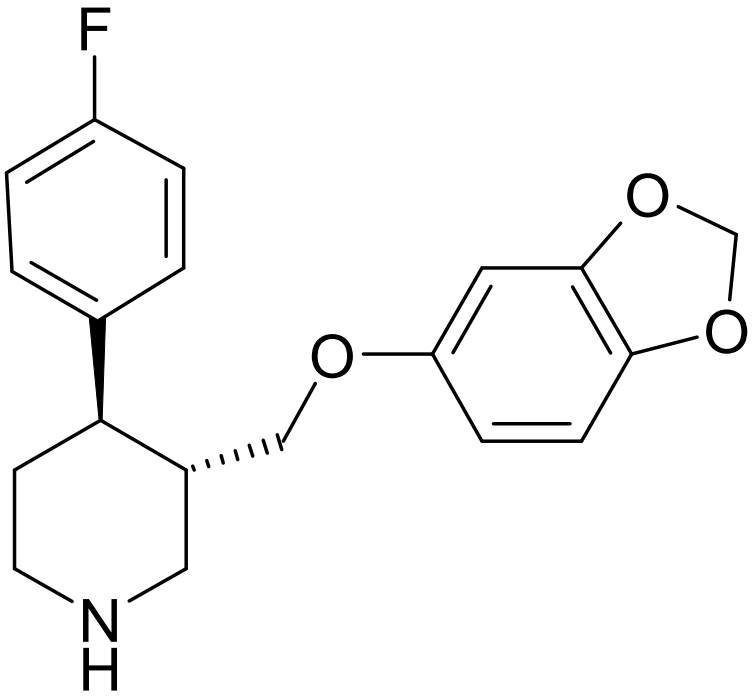


3-(4-trifluorophenoxy)-3-phenyl-1-methylaminopropane
fluoxetin
Deprex®, Floxet®, Fluocim®, Fluval® …

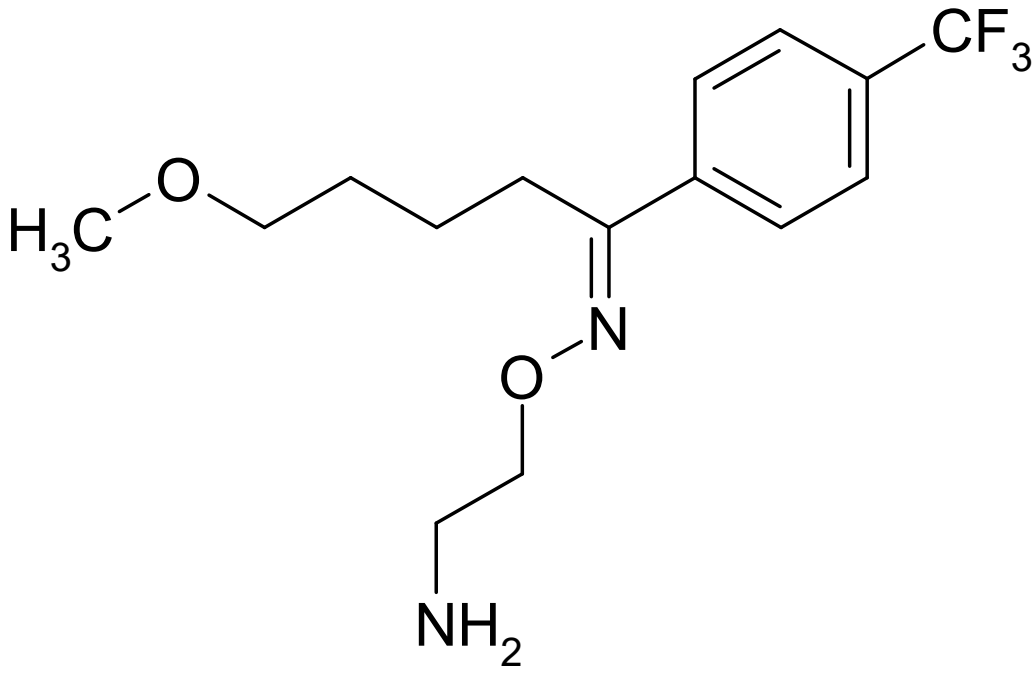


(1S,4S)-4-(3,4-dichlorophenyl)-1-methylamino-1,2,3,4-tetrahydronaphtalene
sertralin
Asentra®, Serlift®, Setralex®, Zoloft® …

•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



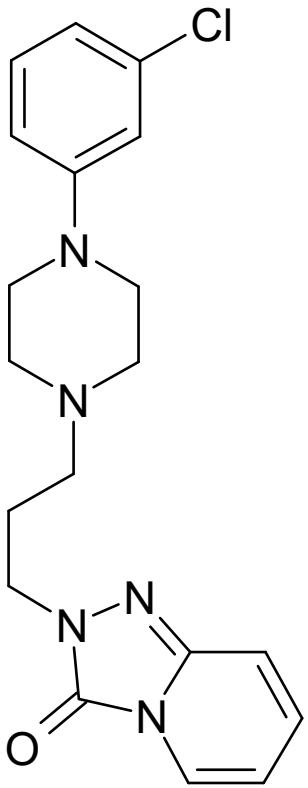
paroxetine
Arketis ® , Parolex ®



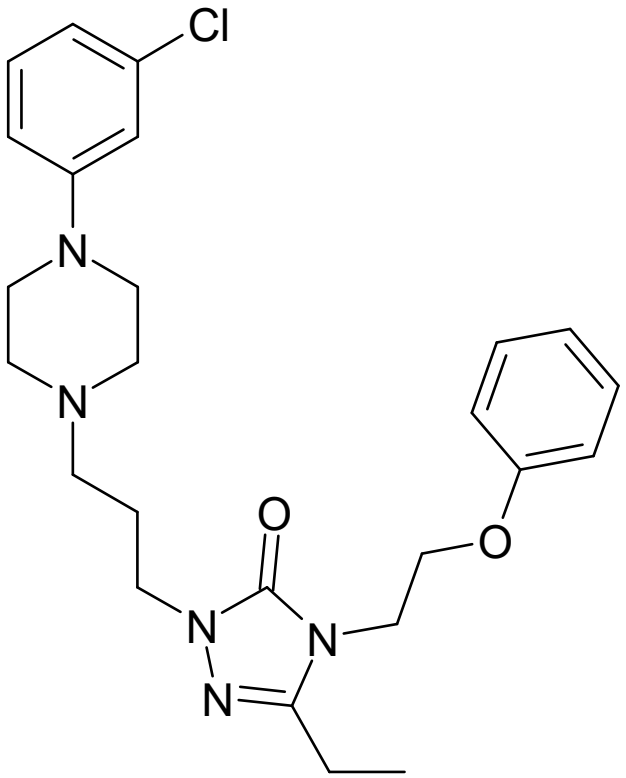
fluvoxamine

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

5. Dual-serotoninergic antidepressants



trazodone

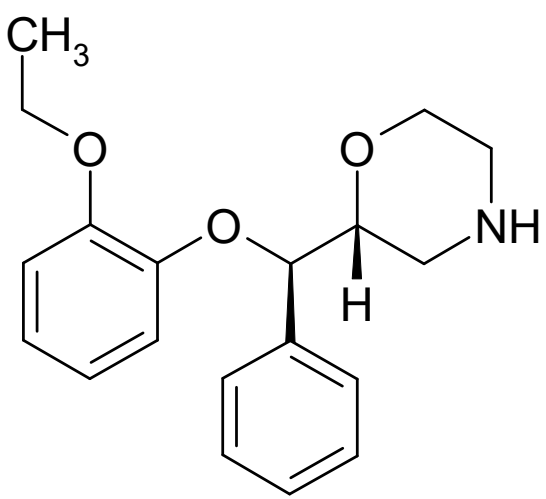


nefazodone

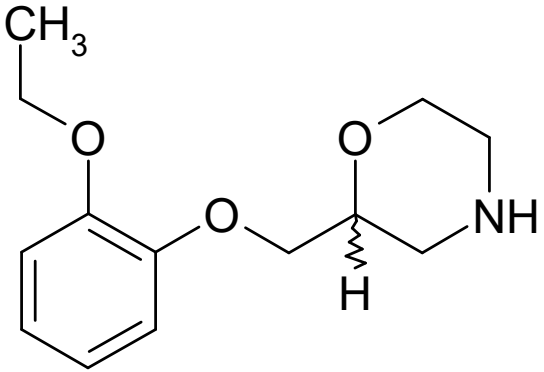
- serotonine reuptake inhibitors and simultaneously 5-HT_2 receptor antagonists
- also inhibits NA reuptake
- markedly sedative

Trittico AC ®

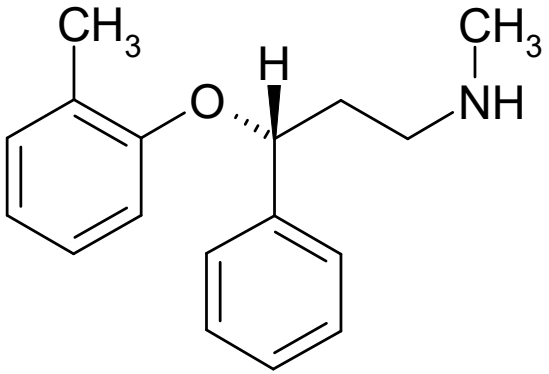
6. Selective noradrenaline reuptake inhibitors (SNRI)



reboxetine
•*R,R*



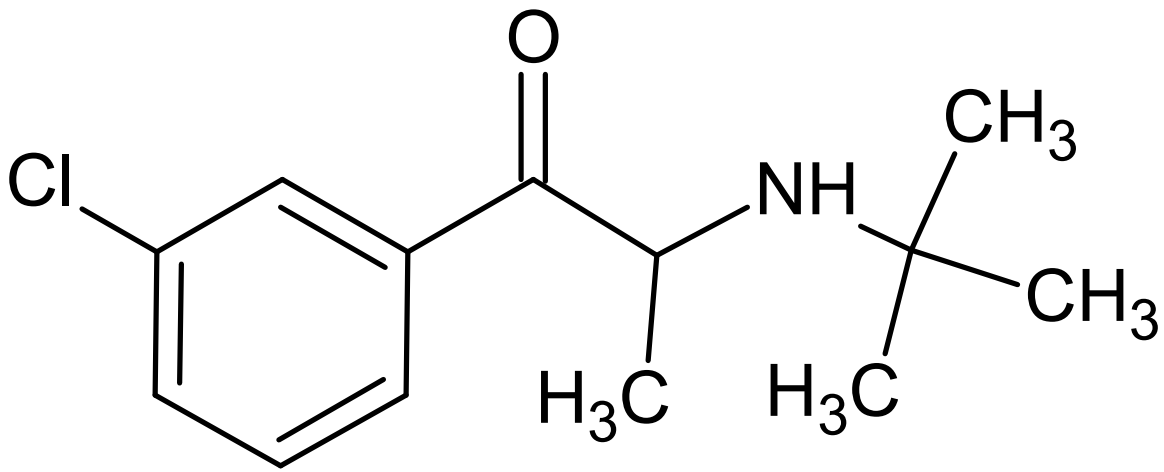
viloxazine
•racemate



atomoxetine
•*R*
Strattera ®

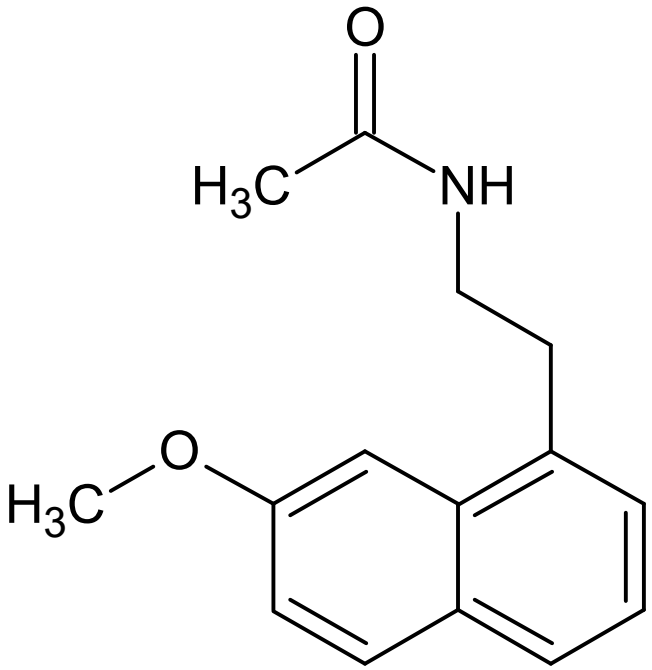
•effective in motivation and interest stimulation
•enhance effect of sympathomimetics
•AE : tachycardia, tremor

7. Selective noradrenaline and serotonine reuptake inhibitors



bupropion
Elontril ®, Welard ®, Bupropion+Pharma ® ...
•also treatment of nicotine abuse

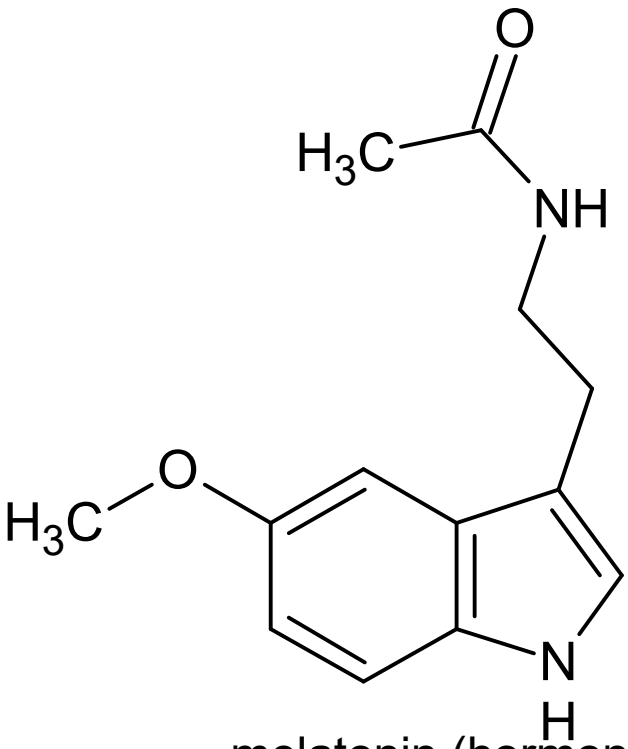
8. Melatoninergic agonists



agomelatine

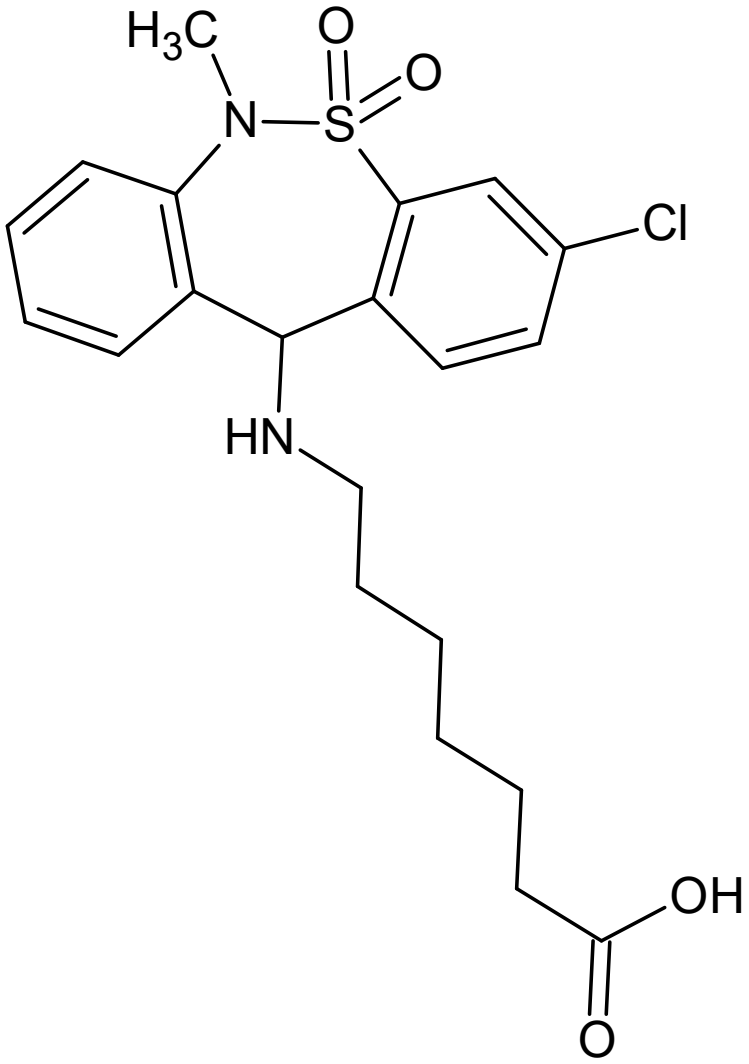
- MT_1 and MT_2 melatonin receptors agonist
- 5-HT_{2C} receptor antagonist

Valdoxan ®



melatonin (hormone)

9. „Other“ tricyclic antidepressants



tianeptine
Coaxil ®, Atinepte ®

- in animals
  - stimulates spontaneous activity of pyramide cells of hippocampus and accelerates their regeneration after functional inhibition
  - increases speed of serotonine reuptake by brain cortex and hippocampus neurons
- *in vitro*
  - no affinity to monoaminergic receptors and doesn´t inhibit 5-HT, NA or dopamine absorption
  - may modulate synaptic glutamatergic transmission.
- in humans:
  - effect to symptoms related to depression
  - effect to mood disorders; classified to a central position between sedative and stimulating antidepressants
  - significant effect to somatic problems, mainly gastrointestinal ones linked with anxiety and mood disorders
  - no effect to
    - vigility
    - cholinergic system (no anticholinergic symptoms)

10. 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