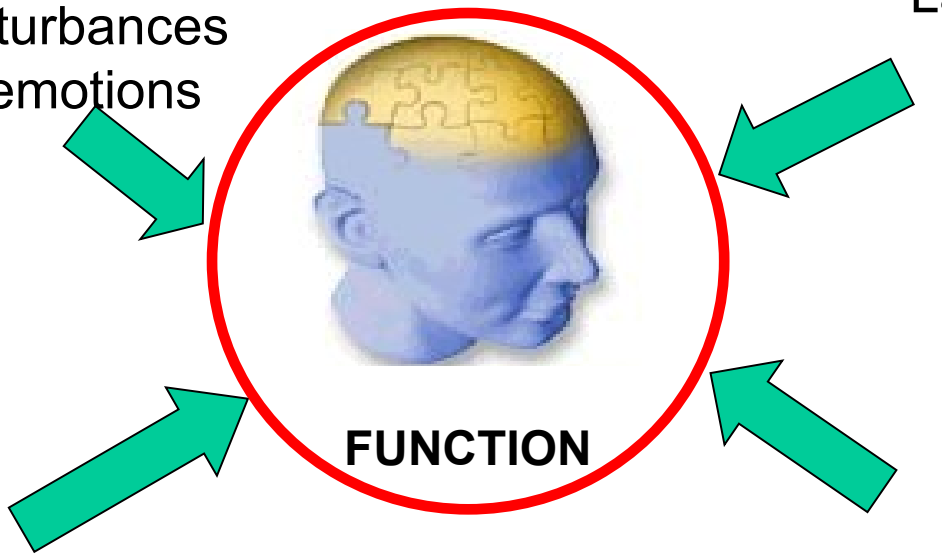
Neuroleptics = antipsychotics = „major tranquilizers“: drugs for treatment, or better for attenuation of symptoms of schizophrenic psychoses

Schizophrenia - symptoms

Positive Symptoms
Hallucinations
Delusions (bizarre, persecutory)
Disorganized Thought
Perception disturbances
Inappropriate emotions

Negative Symptoms
Blunted emotions
Anhedonia
Lack of feeling



Cognition
New Learning
Memory

Mood Symptoms
Loss of motivation
Social withdrawal
Insight
Demoralization
Suicide

Historic and alternative treatment of schizophrenia

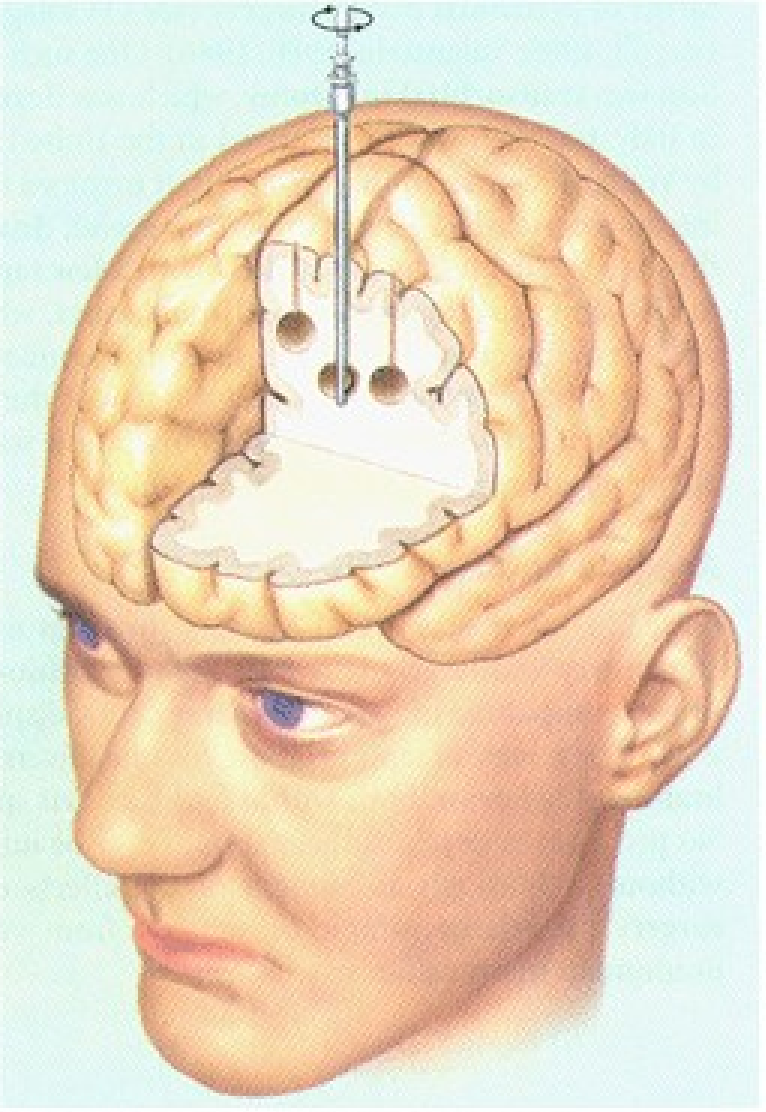
- insuline coma
- electrocovulsions
- prefrontal lobotomy
  - Egas Moniz, 50 000 lobotomies, 1935 Nobel prize
  - patients were just calmer, but also more sluggish and apathetic

► Prefrontal Lobotomy Procedure of Moniz and Lima

The Prefrontal Lobotomy Procedure of Moniz and Lima

The leucotome was inserted 6 times into the patient's brain with the cutting wire retracted.

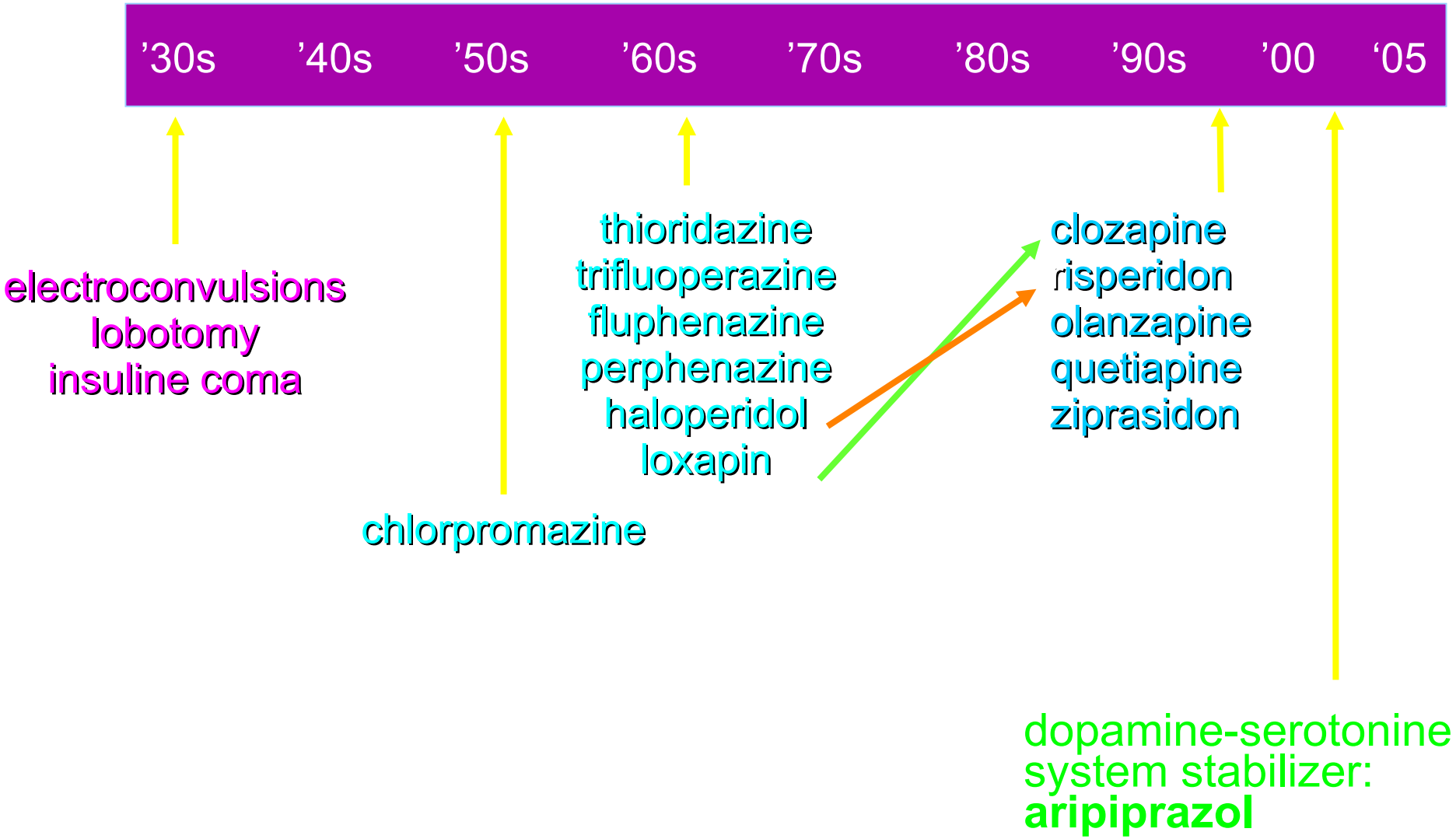
After each insertion the cutting wire was extruded and the leucotome rotated to cut out a core of tissue.

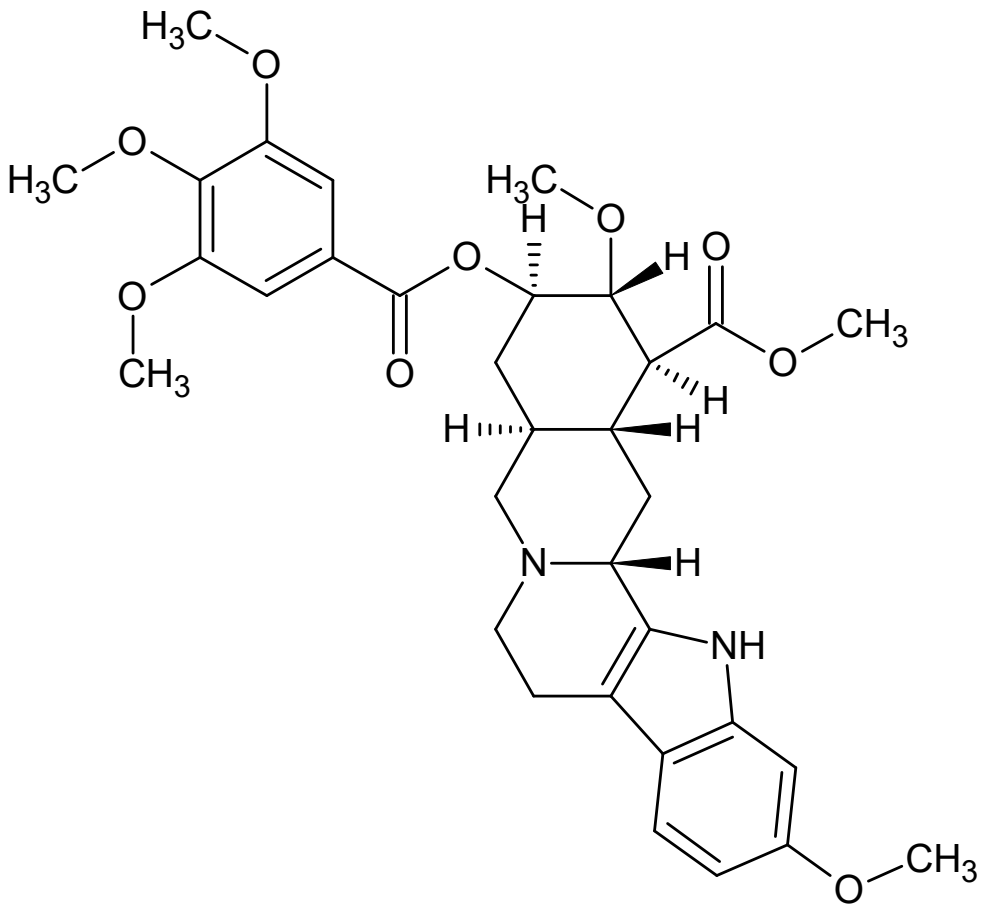


Schizophrenia Pathophysiology

	Schizophrenia Pathophysiology	Pharmacologic Profile of APDs
Past	Excess dopaminergic activity	Dopamine D_2-receptor antagonists
Present	Renewed interest in the role of serotonin (5-HT)	Combined 5-HT_2/D_2 antagonists
Future	Imbalance in cortical communication and cortical-midbrain integration, involving multiple neurotransmitters	More selective antagonists Mixed agonist/antagonists Neuropeptide analogs

Evolution of therapy of schizophrenic psychoses



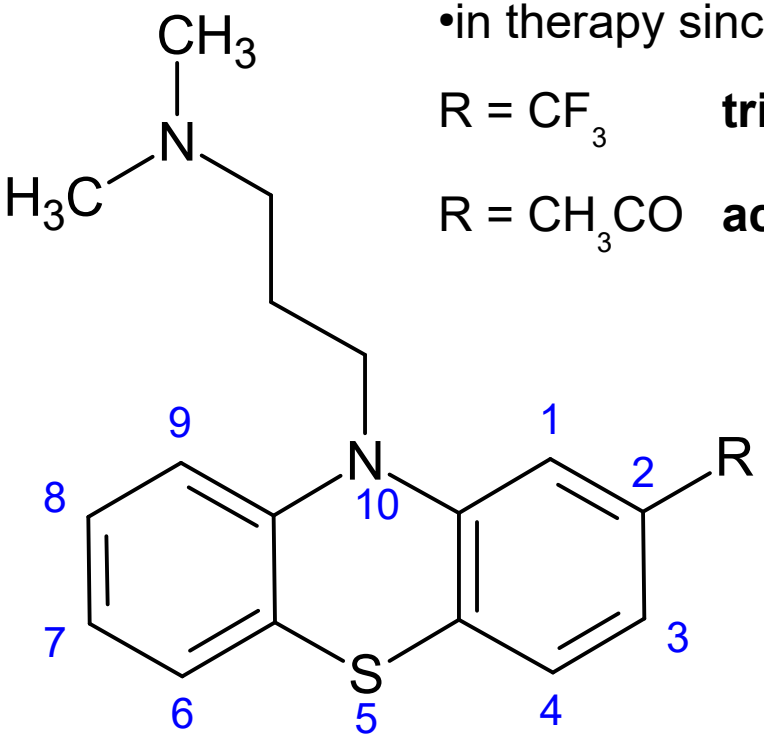


reserpine

- *Rauwolfia serpentina*
- inhibition of noradrenaline uptake into storing vesicles ⇒ decrease of catecholamines levels in both central and periphereal neuronal ends
- antipsychotic
- antihypertensive
- high toxicity

„Typical“ antipsychotics

Phenothiazines with unbranched aminopropane side chain



R = H **promazine**

R = CH_3 **chlorpromazine** Plegomazin®

•Henri Labroit, French military surgeon: causes „artifitial hibernation“

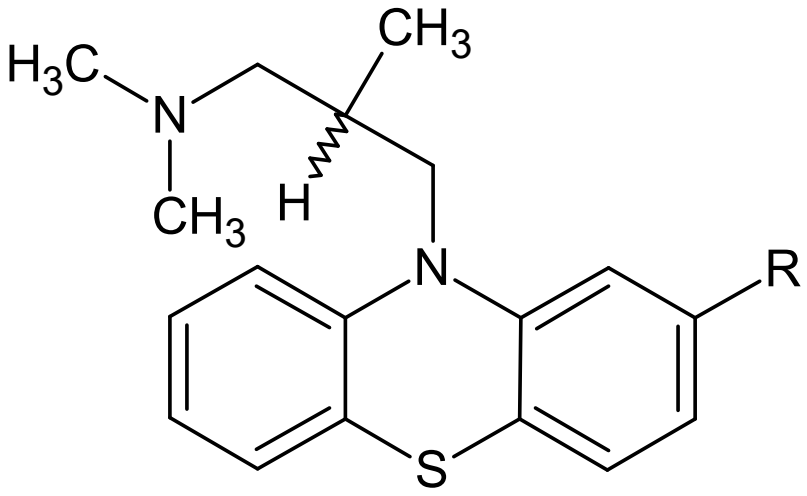
•in therapy since 1953

R = CF_3 **triflupromazine**

R = CH_3CO **acepromazine**

H. Labroit

Phenothiazines with branched aminoalkane side chain



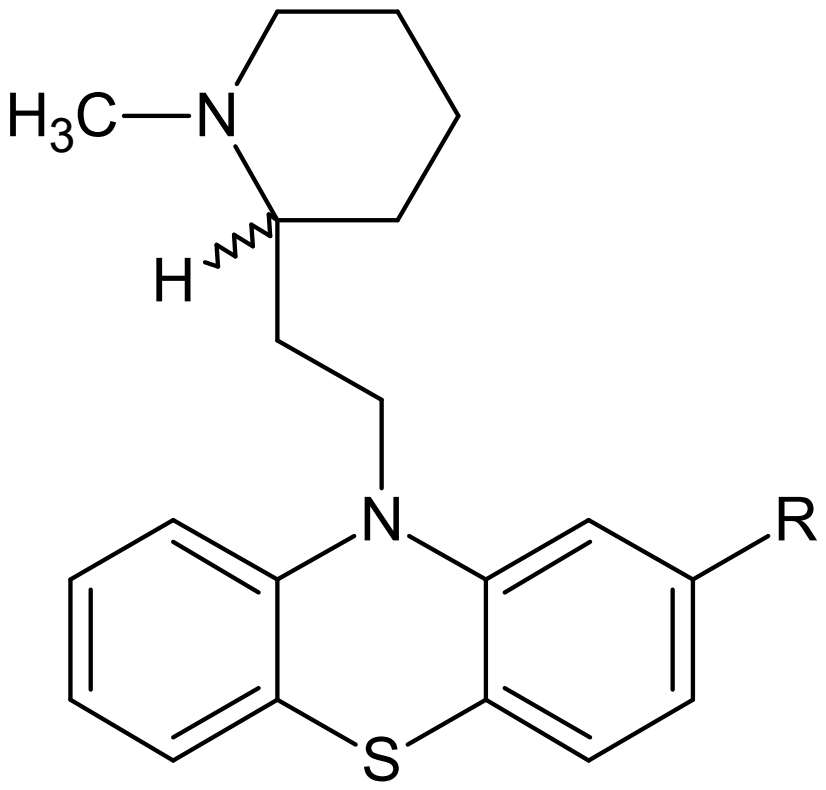
R = H **alimemazine**

R = C≡N **cyamemazine**

R = OCH_3; R-(-) **levomepromazine**

Tisercin®

Phenothiazines with 2-(piperidine-2-yl)ethyl side chain

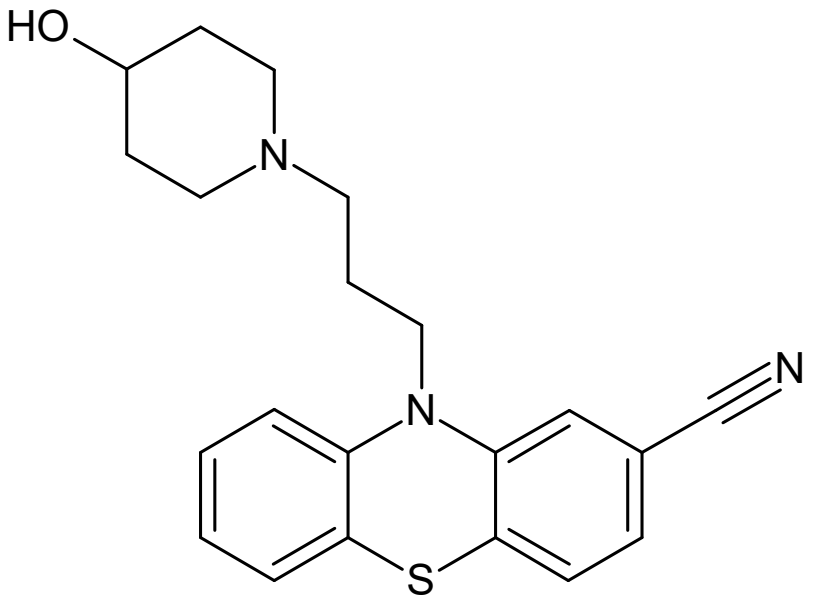


R = CH_3S **thioridazine**

- also antimicrobial activity: *Mycobacterium tuberculosis, Listeria monocytogenes*
- in some developing countries used as an antituberculotic

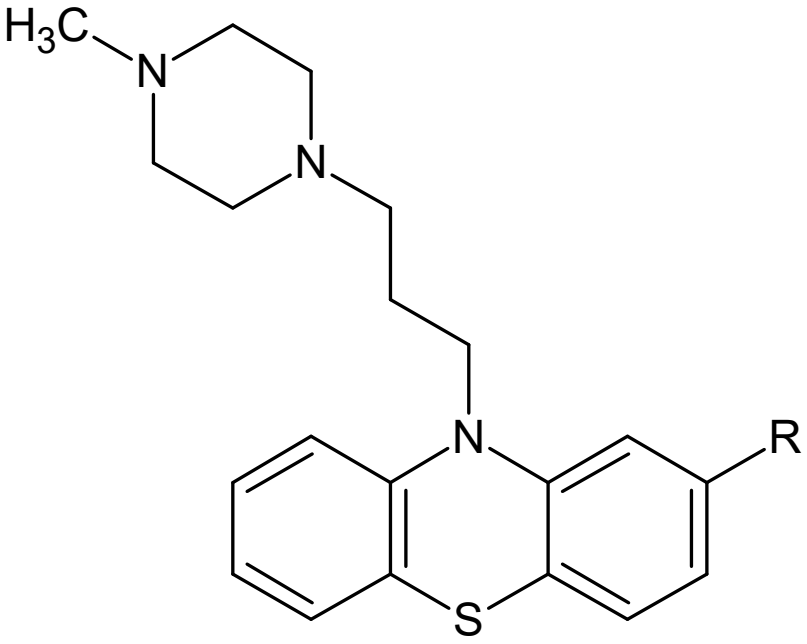
R = CH_3SO **mesoridazine**

Phenothiazines with 3-(piperidine-1-yl)propyl side chain



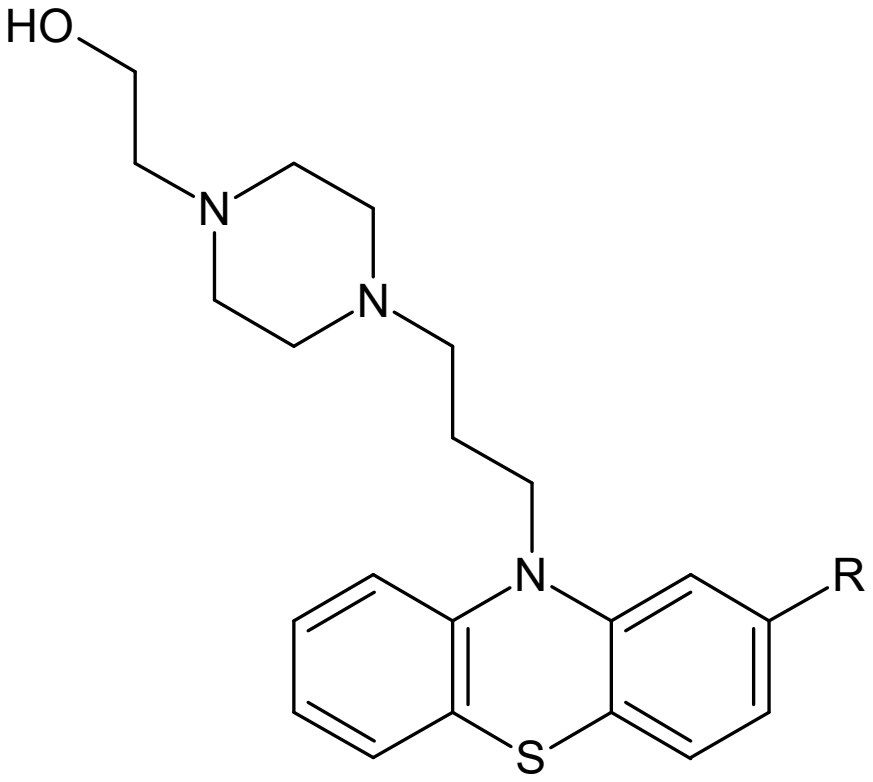
periciazine
syn. propericiazine
•AE: hypersensitivity of sensual perception

Perazine series: phenothiazines with 3-(piperazin-3-yl)propyl side chain



R = H **perazine**

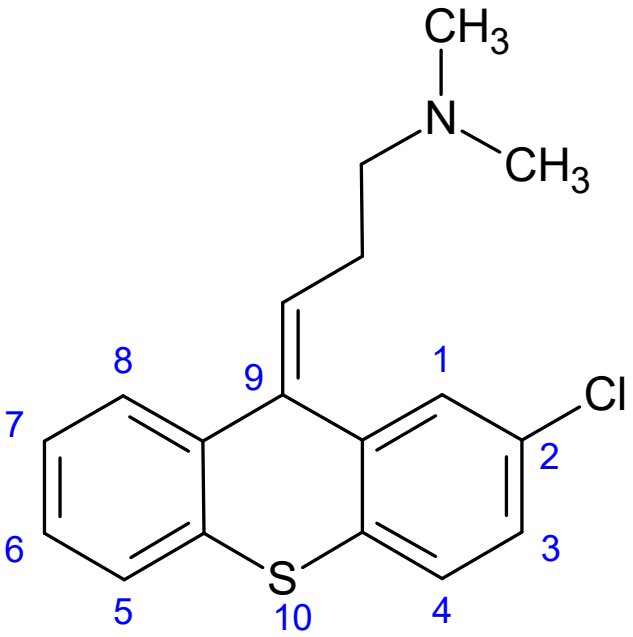
R = CF_3 **trifluperazine**



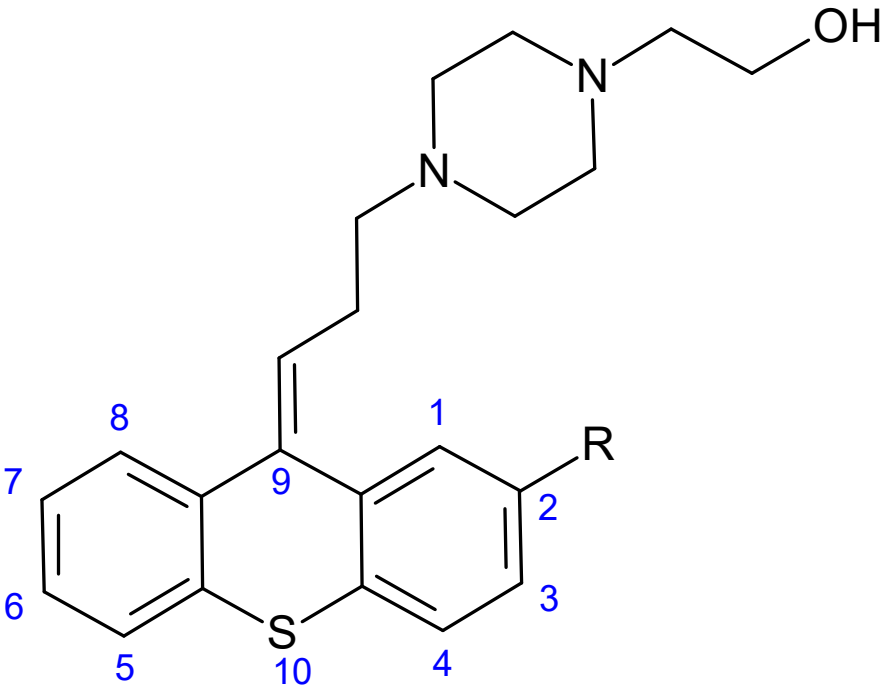
R = Cl **perphenazine**

R = CF_3 **fluphenazine** Moditen Depot® inj. sol.

Thioxanthenes: isosteric analogues of phenothiazines



chlorprothixene
•*Z*-isomer
Chlorprothixen Léčiva®



R = Cl

•mixture *E/Z:* **clopenthixol**

•*Z*-isomer: **zuclopenhtixol**

Cisordinol®

R = CF_3 **flupenthixol** Fluanxol®

•mixture *E/Z*

Structure-activity relatioships (SAR) of phenothiazines and thioxanthenes

1. linking chain between N(10) and the basic substiuent:

- propyl is optimal; compounds with butyl nearly inactive, ethyl ⇒ antihistamine activity
- any substituent in pos. 1 of the side alkyl lowers the activity
- methyl or phenyl in pos. 2 do not decrease the activity while more bulky aliphatic substituents do
- many various substitutions can be proceeded in pos. 3; basic N is often a part of a ring

2. substituent in pos. 2 of the tricyclic ring

- the highest effect is linked with electron-accepting lipophilic substituents (-Cl, -CF_3,-CN), activity increases with lipophilicity and electron-accepting properties, electrondor substituents (-OCH_3, -SCH_3) lower activity

3. tricyclic ring

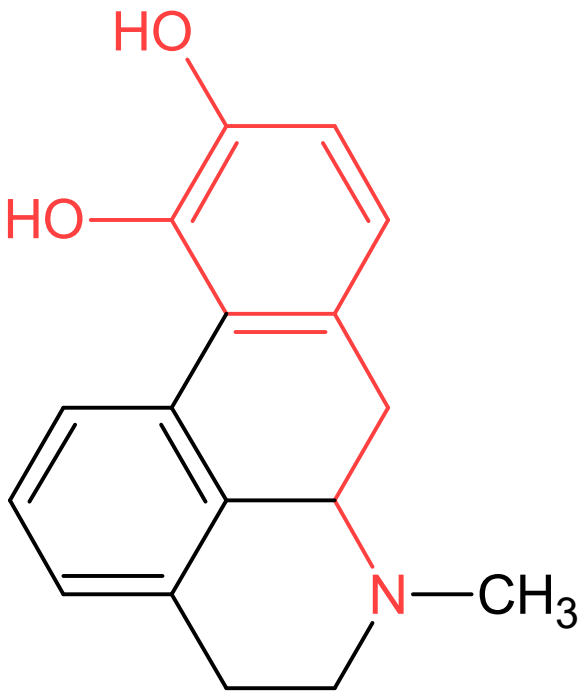
- disubstitution lowers activity, ring opening completely removes it
- substitution of S with C, O, Se etc. lowers activity; substitution of N(10) lowers activity except that with alkylidene substituted C(⇒ thioxanthenes)
- isosteric substitution C(2) with N keeps activity (⇒2-azafenothiazines)
- in thioxanthenes, compounds with *Z*-configuration on double bond going out from C(9) have higher activity than *E*-isomeres

4. modification of amino group of side chain

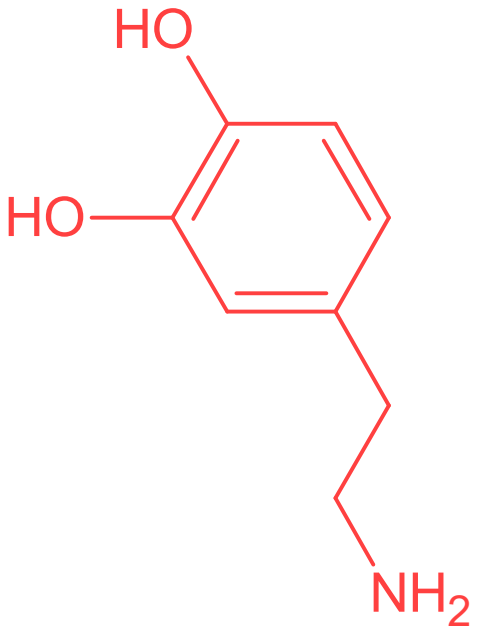
- tertiary amines (pK_a 8-10) have maximumum activity
- methyls on nitrogen lead to higher activity than longer alkyls; receptor is long and narrow which is shown by tolerance of phenyl in pos. 2 of the chain
- amino group can be part of a ring; pyrrolidine, piperidine and morpholine belong to useful cyclic substituents; compounds with piperazine are the most active ones

Mechanism of action of tricyclic antipsychotics

- reversible block of D_2-subtype of dopamine receptor
- evidence of relationship between antipsychotic antagonism against dopamine agonist apomorphine (displacement of apomorphine from this receptor) and dopamine accumulation in brain



apomorphine

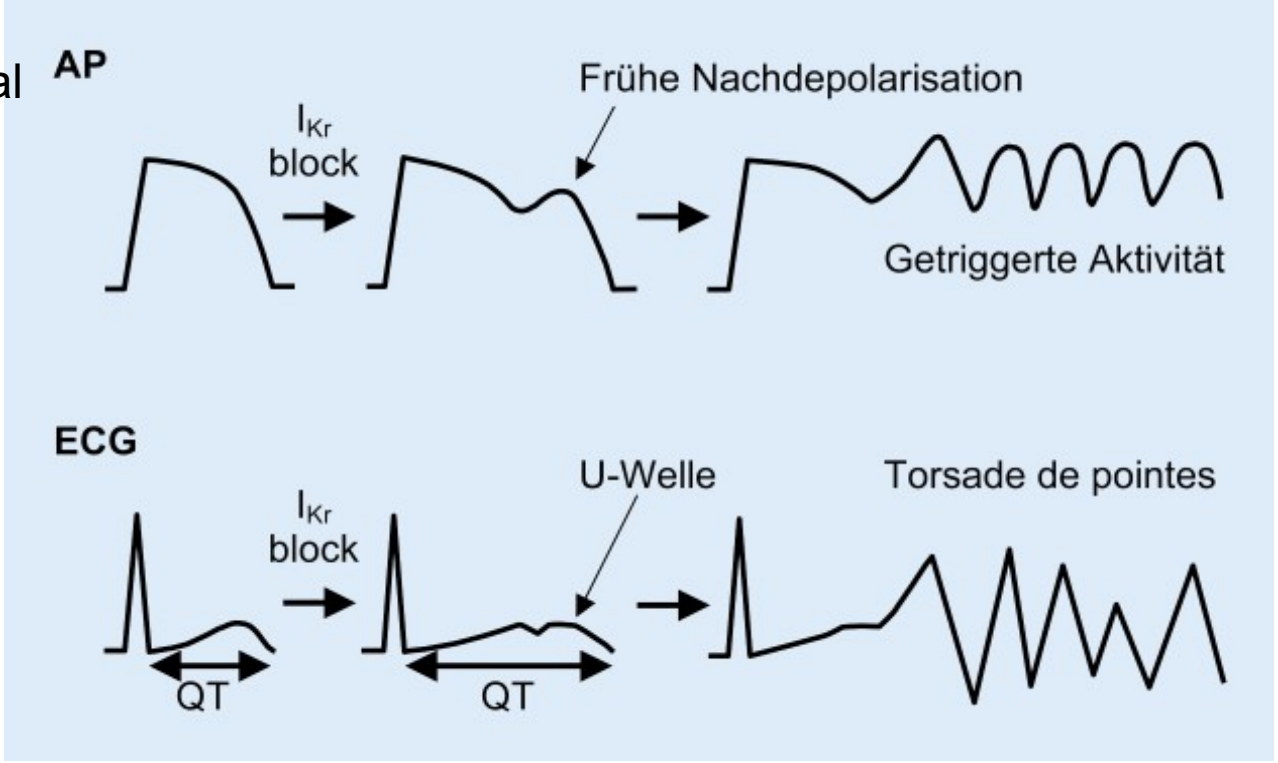


dopamine

Unwanted effects of phenothiazines and thioxanthenes

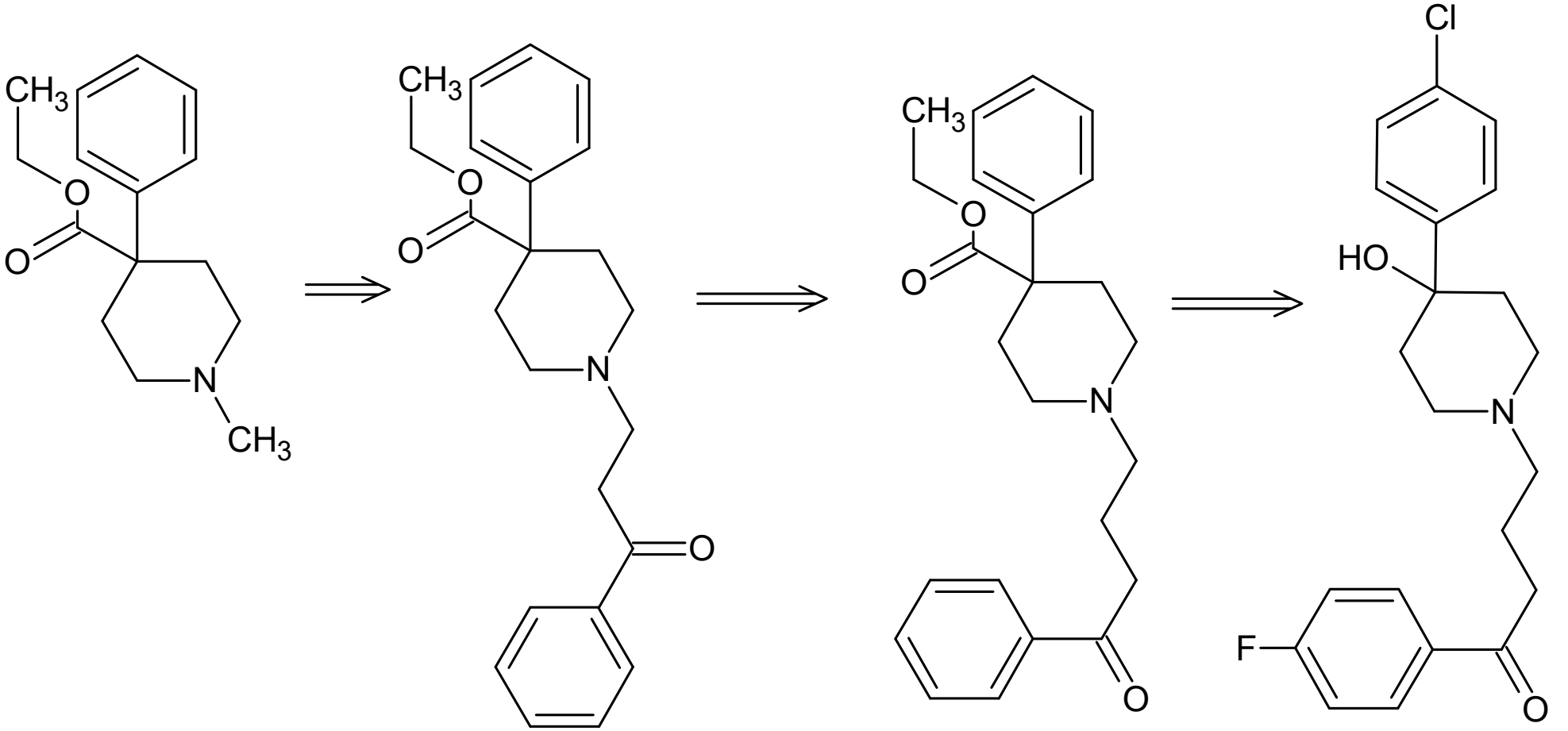
- Parkinsonian = extrapyramidal syndrome – caused by relative excess of acetylcholine in CNS over dopamine
- cardiovacular system: dysrythmias of type of Torsade de pointes (TdP; „bundle of spikes“) - begins with QT-interval elongation on ECG due to K^+-channels block – can lead to cardiac arrest and sudden death (mostly thioridazine)
- „amplified“ vision (lights and colours more intensive, objects bigger)

AP = action potential
I_{Kr} = stream through K^+ channel



„Typical“ neuroleptics: butyrophenones a diphnylbutylpiperidines

Origin of butyrophenones



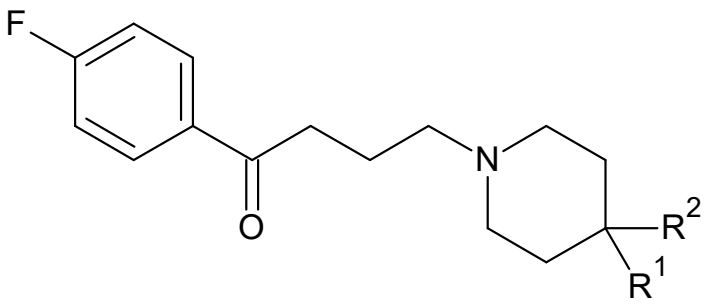
pethidine
opioid analgesic

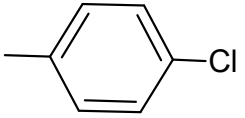
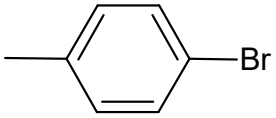
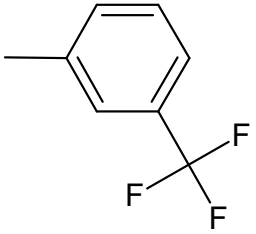
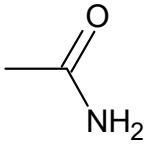
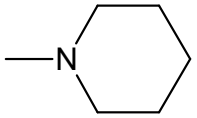
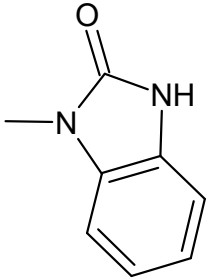
propiophenone
analogue of pethidine
• 200x highest analgesic activity

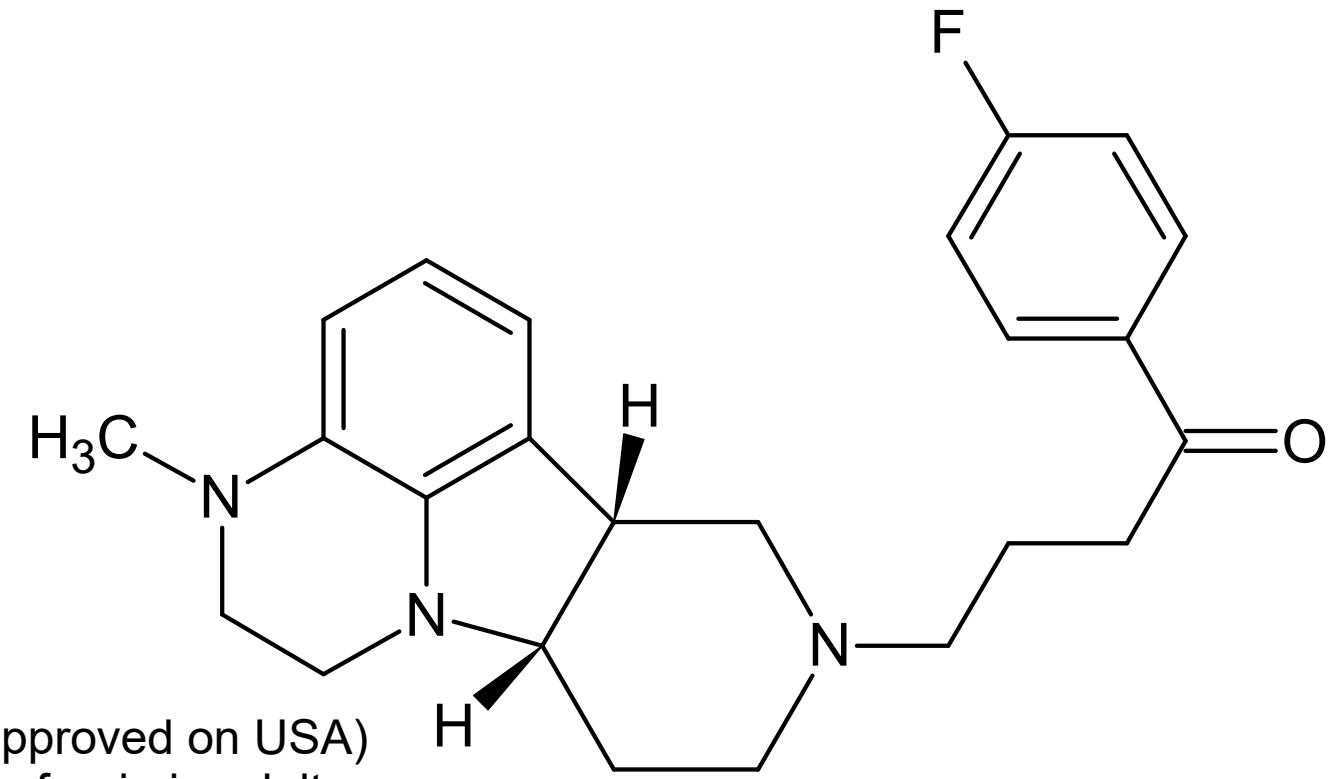
butyrophenonone analogue of pethidine
•analg. activity comparable to pethidine, other activities similar to chlorpromazine

haloperidol
•prototype = lead compound of butyrophenone antipsychotics
•10x more active than chlorpromazine

Butyrophenones

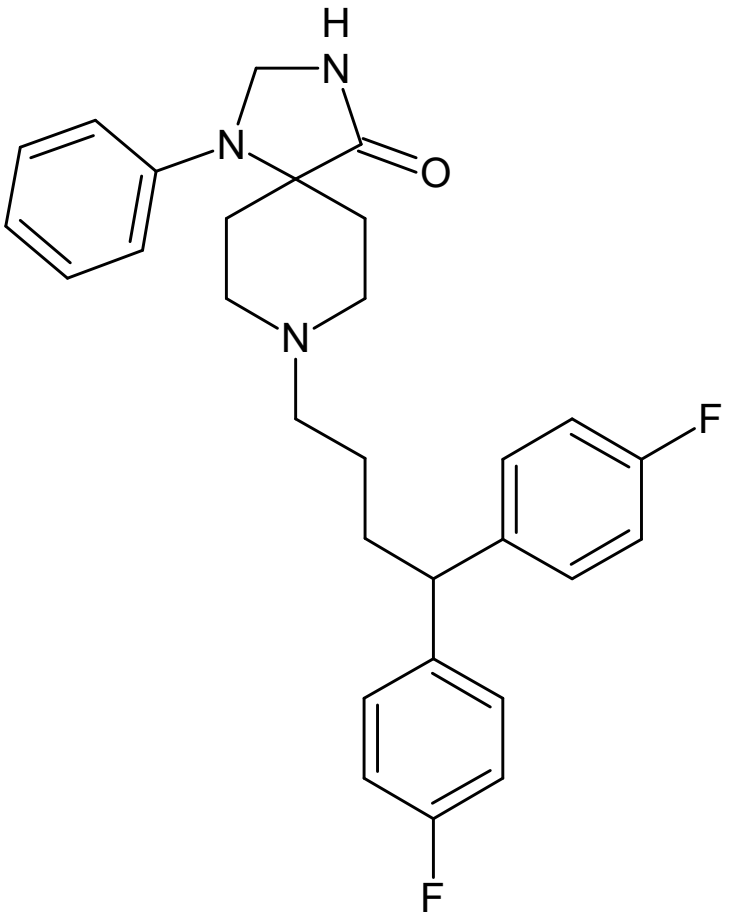


R^1	R^2	INN	LP
OH	CH_3	**melperone**	Buronil
OH		**haloperidol**	Haloperidol Richter
OH		**bromperidol**	
OH		**trifluorperidol**	
		**pipamperone**	
H		**benperidol**	

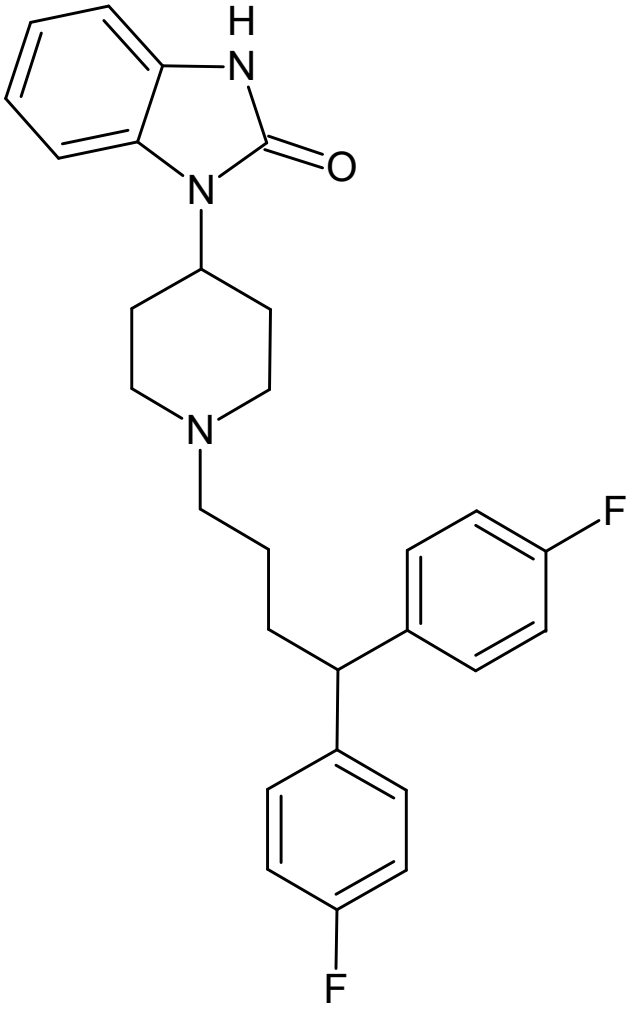


lumateperon
syn. ITI-007
•Caplyta® cps. (approved on USA)
•indications: schizofrenia in adults
• $5HT_{2a}$ antagonist
•partial agonist at na presynaptic D_2
•antagonist at postsynaptic D_2
•blocator of 5HT transport
•glutamate receptor
•low affinity to α_{1a} a α_{1b}, $5HT_{2c}$, and D_4
•does not bind to M
• good results in clinical studies for schizofrenia, depression, bipolar disorder, behavior and sleeping problems, agitation in depression and autism

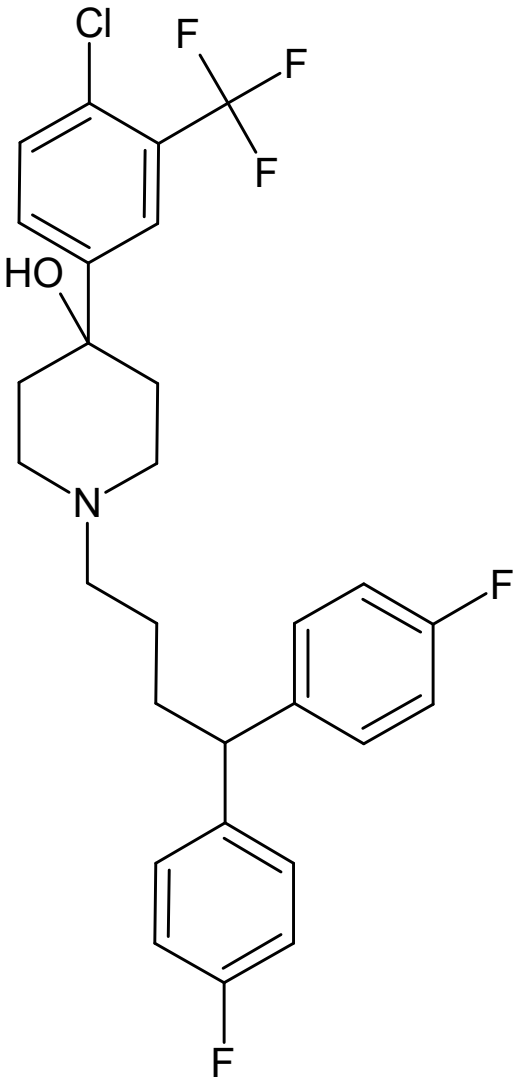
Diphenylbutylpiperidines



fluspirilen



pimozid



penfluridol

Butyrophenones and diphenylbutylpiperidines

Usage:

•treatment of schizophrenia

•neuroleptanalgesia (antipsychotic + opioid analgesic instead genaral anaesthesia)

Unwanted effect:

•similar to phenothiazines a thixanthenes but no extrapyramide syndrom

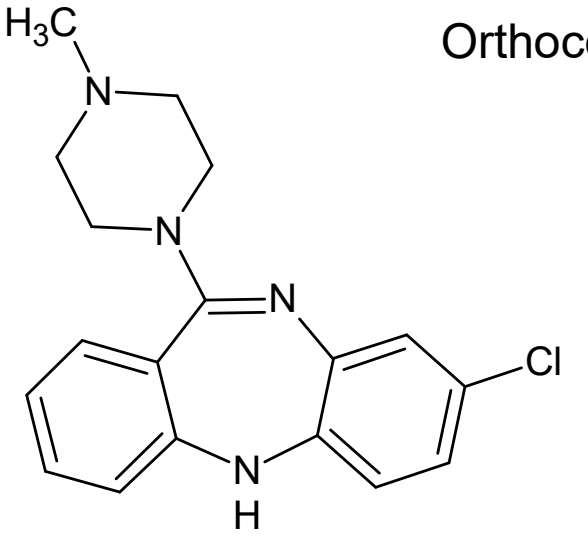
„Atypical“ neuroleptics

•influence serotoninergic system in addition to the dopaminergic one

Tricyclic compounds

MARTA (= multi acting receptor targeted agents)

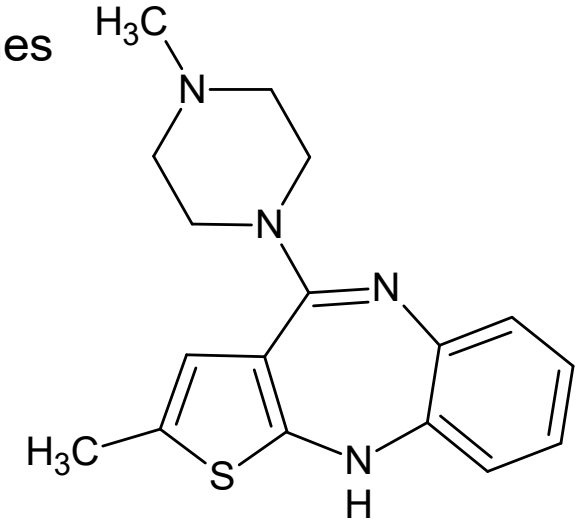
Orthocondensed diazepines



8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine

clozapine

Closapin Desitin®, Leponex®



2-methyl-4-(4-methylpiperazin-1-yl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine

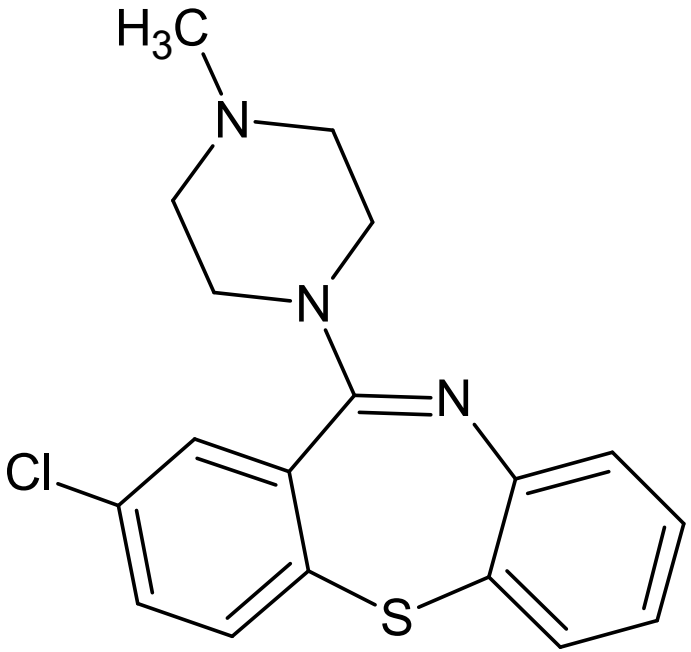
olanzapine

Zalasta®, Zyprexa® ...

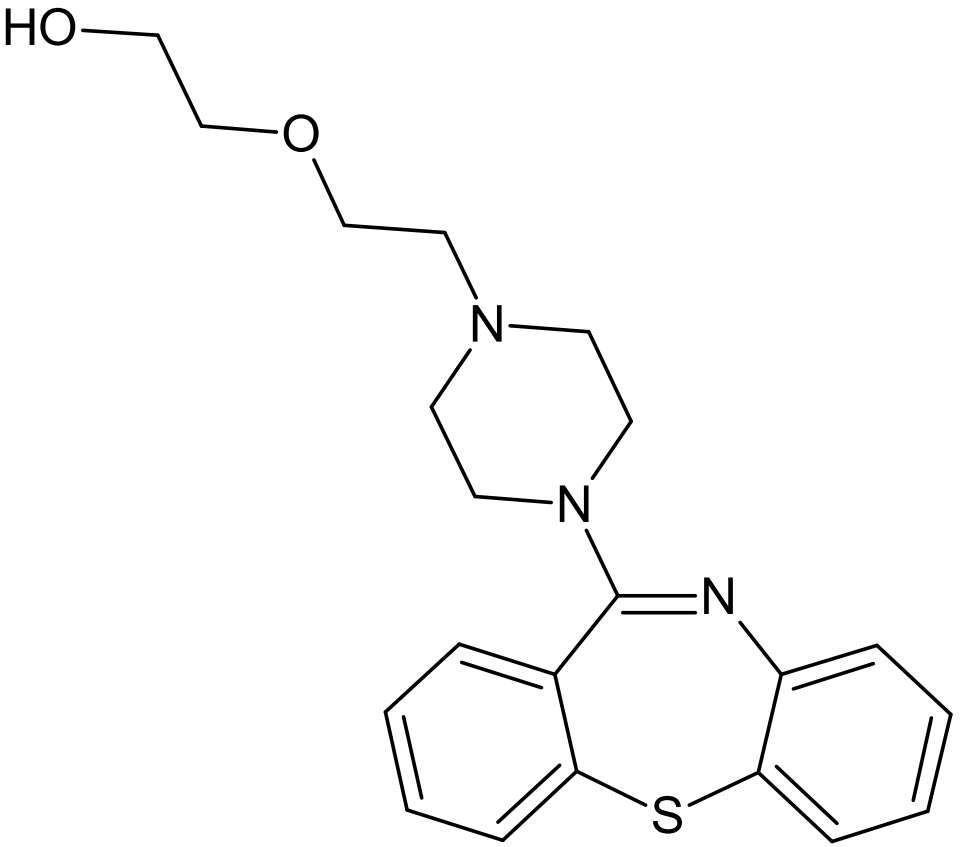
Tricyclic compounds

MARTA (= multi acting receptor targeted agents)

Orthokondensed thiazepines



clothiapine



quetiapine
Derin®, Uxippra® ...

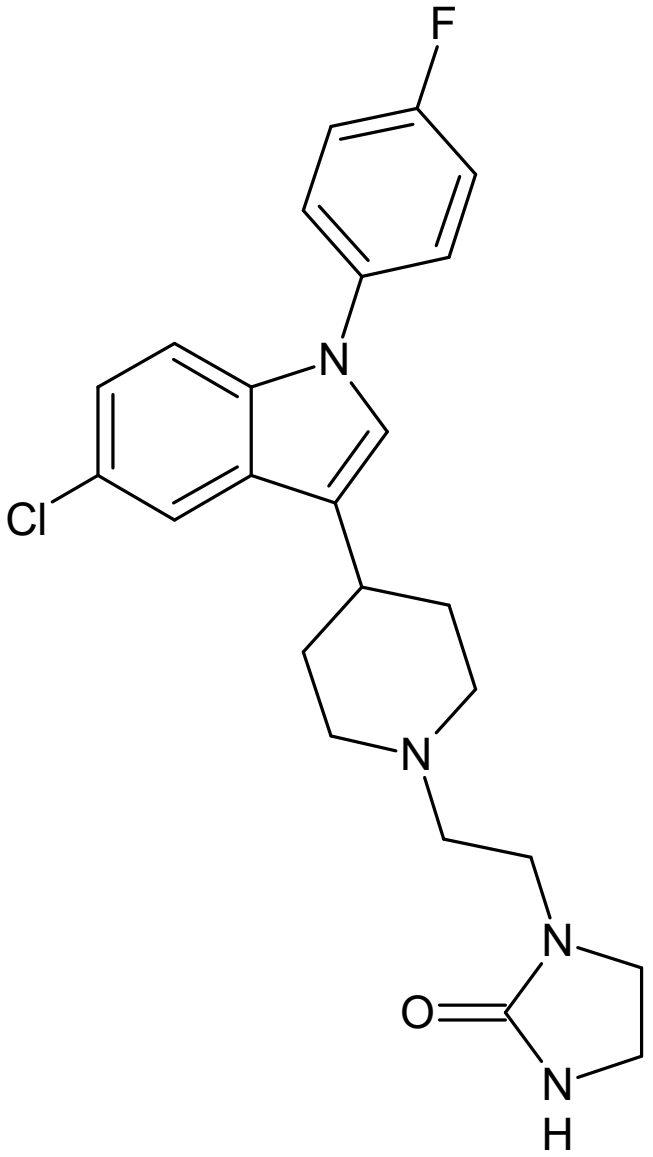
Mechanism of action of tricyclic atyp. neuroleptics (MARTA):

- serotonine antagonists on 5-$HT_{2A/2C}$ receptor subtype
- strong afinity to dopaminergic receptors but weak to D_2 subtype

Unwanted effects:

- agranulocytosis
- cardiovascular system: orthostatic hypotension, TdP dysrhytmias

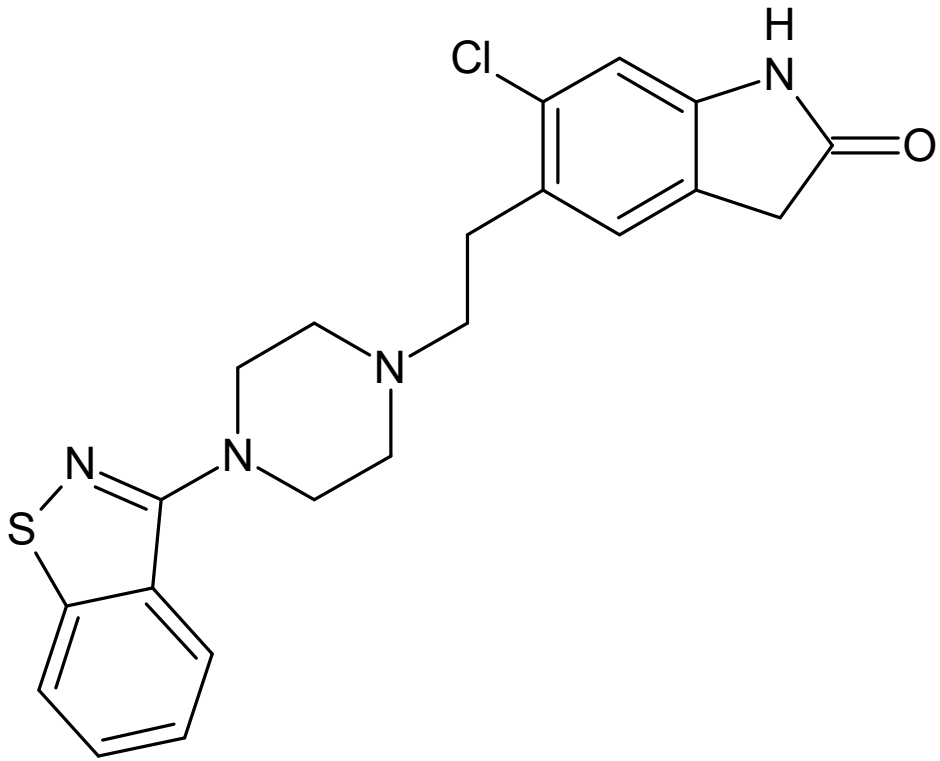
Indol derivatives



sertindole

- 5-HT_2 and D_2-rp. antagonist

Serdolect®

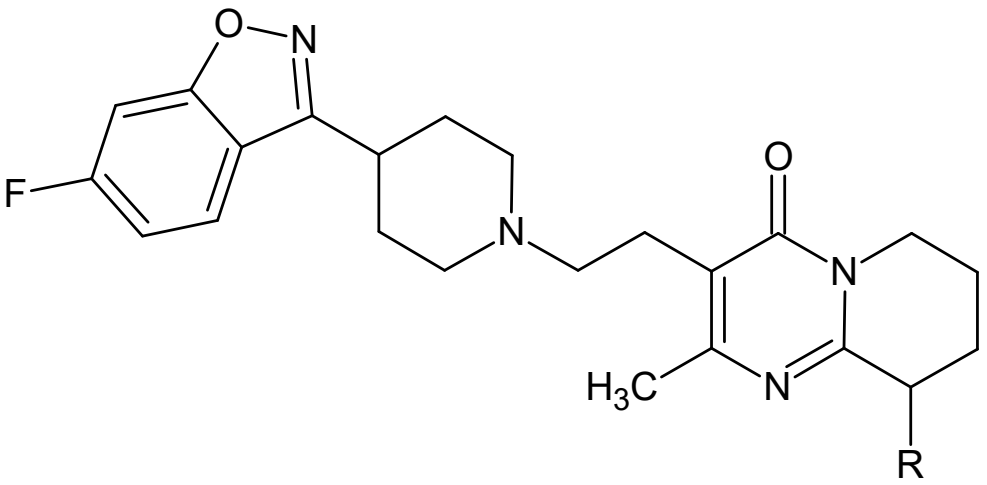


ziprasidone

- D_2-antagonist
- extrapyramidal syndrome occurs but less than in „typical“ antipsychotics

Zeldox®, Zypsila® ...

Benzoisoxazole derivatives

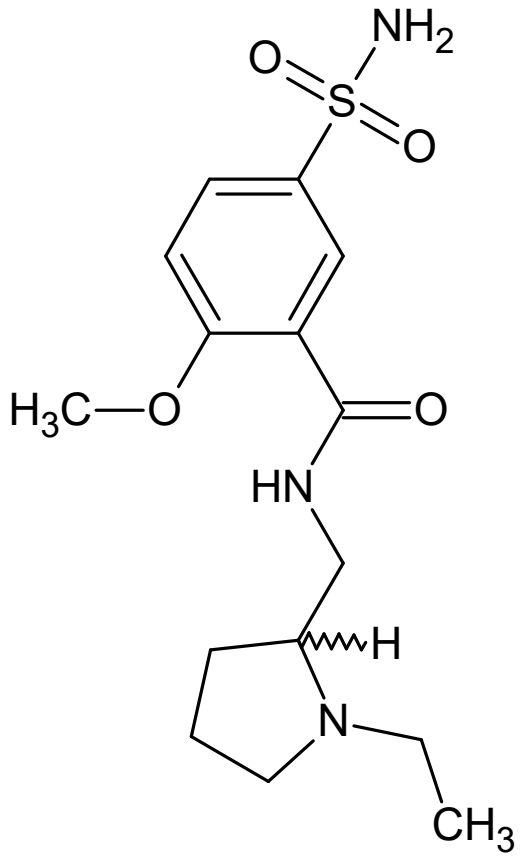


R = H **risperidone** Ridoner®, Rigenin® ...

R = OH **paliperidone** Invega®

- selectively block D_2 and 5-HT_2 receptors
- inhibit both positive and negative syndroms
- AE & toxicity: somnolence, ECG changes, altered perception

Benzamide derivatives

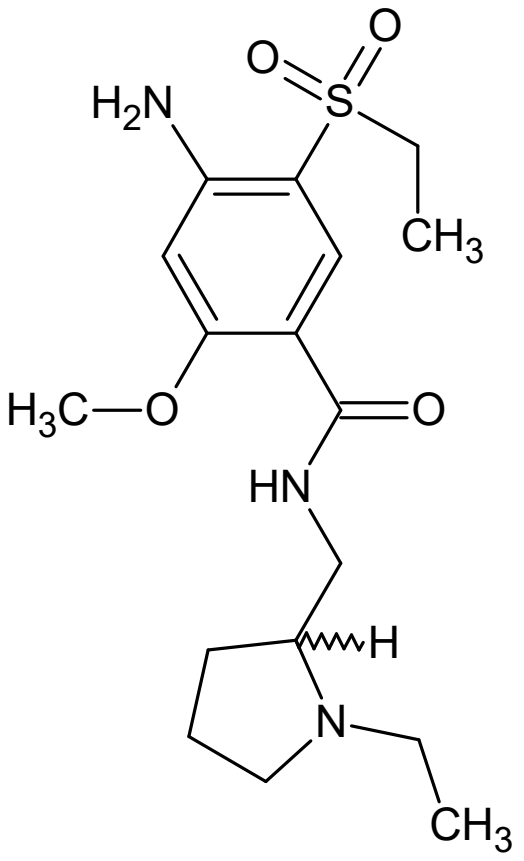


R,S-(±): **sulpiride**

Dogmatil®, Sulpirol® ...

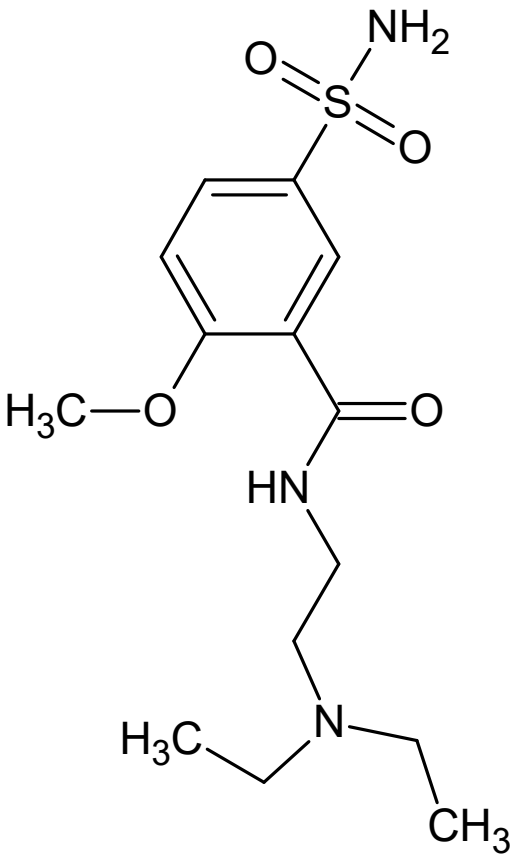
- selective antagonist of D_2-receptor
- in lower doses antidepressant – inhibit presynaptic D_2-receptors, in higher doses postsynaptic ones ⇒ antipsychotic

S-(-): **levosulpiride**



amisulpride

Amilia®, Deniban® ...



tiapride

Tiapra®, Tiapridal® ...