Drugs affecting the central nervous system

Neuroleptics

Neuroleptics are mainly used in the treatment of schizophrenia and in the manic phase of manic-depressive psychosis, accompanied by strong excitation and aggression.

Schizophrenia

Schizophrenia (Bleuler's disease) - one of the most common psychic diseases. It appears in about 1.0% of the human population and affects 40–50% of patients treated in mental hospitals.

The term schizophrenia, introduced by E. Bleuler in 1911, was derived from the Greek "schizo" (split) and "phren" (mind, will, heart).

The diagnostic criteria of schizophrenia require two or more of the following characteristic symptoms to be present for a significant proportion of time during a one-month period: delusions, hallucinations, disorganized speech, or grossly disorganized or catatonic behavior.

The following **symptoms** are **observed in schizophrenia**:

- **axial symptoms**, which are common for different forms of schizophrenia,
- **additional symptoms**, which vary in different forms of schizophrenia.

The **axial symptoms** involve disturbances in the patient's emotions and thinking processes, for example:

- autism (withdrawal from reality expressed as the person's inability to communicate properly or form relationships),
- diminishing interest in the surrrounding world,
- decreased physical activity,
- thinking disturbance (absent-mindedness, illogical thinking).

In what is classified as simple or undifferentiated schizophrenia only the axial symptoms are observed.

In **paranoid schizophrenia**, in addition to the axial symptoms, delusions in which a person believes that he/she being persecuted are observed. It is the most common form of schizophrenia (up to 80% of all cases).

In **catatonic schizophrenia** the symptoms range from excitement or hypokinesia to catatonic stupor.

In **hebephrenic schizophrenia** euphoric mood and clowning can sometimes appear.

Other kinds of schizophrenia include schizoaffective psychosis and manic-depressive psychosis (proceeding cyclically with remission periods), pseudoneurotic psychosis and child schizophrenia.

The onset of schizophrenia is often observed as early as adolescence and the disease lasts throughout the person's life. In patients suffering from schizophrenia, before the first phase of severe symptoms, personality disorders defined as schizoid personality are observed.

The causes and pathogenesis of schizophrenia have not been fully explained. The majority of psychiatrists think that schizophrenia has a genetic origin but it is also believed that the causes of schizophrenia can be attributed to certain relationships existing in the patient's family, especially in his or her childhood.

This is the reason that the patient's stay in a mental hospital may lead to the most acute symptoms of schizophrenia, particularly the schizophrenic defect.

The mechanism of action of neuroleptics

In patients suffering from schizophrenia the metabolism of dopamine in the brain is disturbed.

An excess of this neurotransmitter in **the mesolimbic system** causes the so-called positive symptoms of schizophrenia, whereas dopamine deficiency in the **prefrontal cortex** is responsible for what is called the negative symptoms.

The positive symptoms include:

- **hallucinations** (often of paranoid nature, usually in the form of voices, often perceived by the schizophrenic as calling),
- **thinking disorders** in which strange trains of thought lead to irrational conclusions and a which are often connected with the conviction that thoughts are being sent or received by an outside agent.

The negative symptoms manifest themselves as:

- the patient's breaking his ties with friends
- the patient's superficial emotional reactions.

Some **hypotheses** point to the role of the cholinergic system **in the pathomechanism of schizophrenia**.

One of them focuses on the importance of the region Ch5 and Ch6. Ch5 and Ch6 cholinergic neurons activate dopaminergic neurons in the substantia nigra and the abdominal tegmentum by stimulating muscarinic and nicotinic receptors and affecting the thalamus and the reticular structure.

Another hypothesis emphasises the role of nicotinic receptors (subunit α7). Because of that it is suggested that nicotine can be helpful in the treatment of schizophrenia. However, as nicotine demonstrates many adverse effects, safe and selective agonists of nicotinic receptors should be found.

The antipsychotic action of neuroleptics consists in blocking dopamine D_2 receptors in the mezolimbic system.

There is a strong correlation between the affinity of neuroleptics for dopamine D_2 receptors and the therapeutic dose of a neuroleptic.

The majority of neuroleptics block not only dopamine D_2 receptors but also demonstrate affinity for the receptors of other neurotransmitters.

No correlation between the dose and neuroleptic activity has been found for any other receptors, including the D_1 type.

The hypothesis that neuroleptics show antipsychotic action by blocking dopamine D_2 receptors was confirmed recently when new drugs, such as sulpiride and remoxipride, were obtained.

These drugs are relatively selective D_2-antagonists and dopamine D_2 receptors are the only possible target for them.

The blocking of other receptors by different neuroleptics must not be ignored during therapy because it is responsible for some adverse effects of neuroleptics.

For example, the blocking of α_1 receptors decreases blood pressure and when H_1 receptors are blocked sedative action is observed.

“Atropinic” action is caused by the blocking of muscarinic receptors.

Almost all neuroleptics are also antagonists for 5-HT_2 receptors. The role of these mechanisms has not been fully explained yet.

Neuroleptics also influence the concentration and turnover of GABA.

This influence varies. For example, haloperidol decreases the turnover of GABA in the striatum, whereas clozapine increases the turnover of GABA in the substantia nigra. It is possible that the action of neuroleptics on the GABA-ergic system is responsible for their undesirable influence on the functions of the extrapyramidal system.

Most neuroleptics interrupt dopaminergic transmission by blocking postsynaptic D_2 receptors in different brain regions.

The blockage of D_2 receptors in the mesolimbic tract is responsible for the antipsychotic action of neuroleptics, whereas in the striatum and/or in the nigrostriatial tract such blocking increases the concentration of prolactin in plasma and disturbs the function of the extrapyramidal tract.

Because of the many adverse effects of neuroleptics there are efforts to find new drugs which can:

- block selectively D_2 receptors,
- act selectively on the limbic structure,
- act indirectly on the dopaminergic system via other neurotransmitter systems.

It also thought that drugs demonstrating ago-antagonistic action on the dopaminergic system can have beneficial therapeutic action.

The classification of neuroleptics

Neuroleptics differ in their chemical structure, potency and adverse effects.

As regards chemical structure, neuroleptics are divided into the following groups:

Typical neuroleptics

- Tricyclic neuroleptics (phenothiazine, thioxanthene)
- Butyrophenone derivatives and
- Diphenylbutylopiperidine derivatives,

Atypical neuroleptics

- Tricyclic neuroleptics - dibenzazepine derivatives
- Benzamide derivatives,
- Indole derivatives,
- Benzisoxazoles,
- Quinoline derivatives

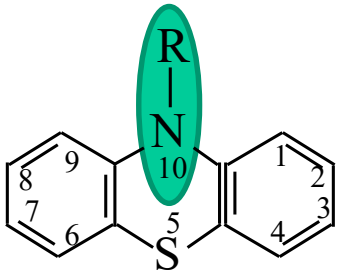
DRUGS (The potency of neuroleptics; Chlorpromazine = 1)
I. Neuroleptics with weak action
Perazine (0.5), Promazine (0.5), Sulpiride (0.5), Thioridazine (0.5) Chlorprothixene (0.7), Levomepromazine(0.7), Prothipendil (0.7)
II. Neuroleptics with medium action
Chlorpromazine (1), Clopentixol (2-3), Dixirazine (2-3), Triflupromazine (2-3) Pericazine (5)
III. Neuroleptics with strong action
Perphenazine (10), Trifluperazine (10-20)
IV. Neuroleptics with very strong action
Pimozide (20-50), Reserpine (20-50), Fluphenazine (50), Haloperidol (50), Trifluperidol (~100), Benperidol (~200)

Table10.3. The classification of neuroleptics into generations

Generations/Drugs	Years
First Generation	
Chlorpromazine, Reserpine	1950
Haloperidol, Fluphenazine, Thioridazine	
Benzamides, Thioxanthenes	1960
Second Generation	
Clozapine	1970
Zotepine	1980
Risperidon, Amisulpride, Olanzapine, Quetiapine	1990
Ziprasidon	2000
Third Generation	
Aripiprazole	2004

The chemical structure and action of neuroleptics
Tricyclic phenothiazine neuroleptics

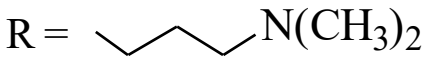
All phenothiazine neuroleptics contain a **substituent in position 10**, which is **responsible for antipsychotic action** and is the basis for international names.



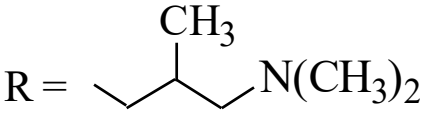
R = -H; Phenothiazine

Three groups of neuroleptics are recognised according to the chemical structure of the substituent in position 10:

❑ Alkylaminosubstituted neuroleptics

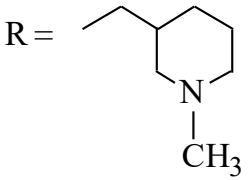


Promazines

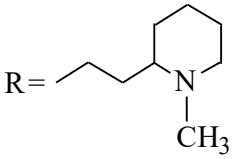


Meprazines

❑ Piperidylalkylsubstituted neuroleptics

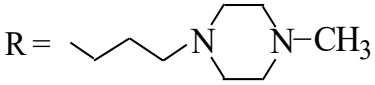


Pecazines

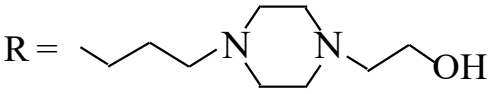


Ridazines

❑ Piperazinylalkylsubstituted neuroleptics

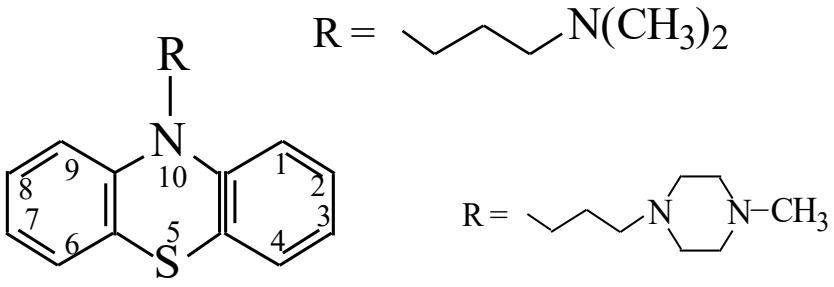


Perazines

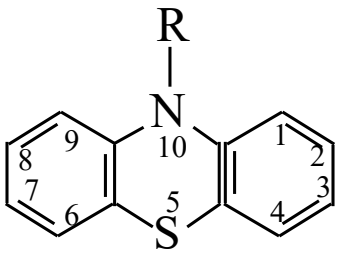


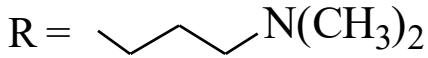
Phenazines

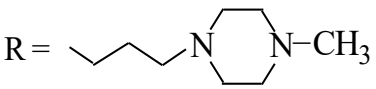
For the **antipsychotic activity of phenothiazines** the **presence of a nitrogen atom in the chain in position 10 and the distance of three carbon atoms between two nitrogen atoms** (a phenothiazine nitrogen atom and a chain nitrogen atom) are essential.



- Phenothiazines with two carbon atoms separating the two nitrogen atoms lack antipsychotic efficacy.
- Compounds such as promethazine are primarily antihistaminic agents.
- One or two atoms of nitrogen can be built into the alycyclic system of piperidine, for example.
- The antipsychotic action of phenothiazine depends on the size of the substituent in position 10. The greater the subsituent, the smaller dose of a drug is needed to obtain the desired therapeutic effect.



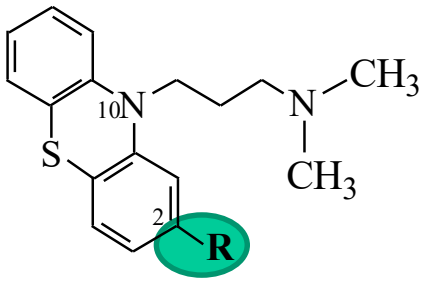




Further modification, by introducing a **lipophilic substituent in position 2 of phenothiazine**, increases the activity of phenothiazine neuroleptics.

The influence of substituents in position 2 on the activity of phenothiazine derivatives can be presented as follows:

$H < Cl < COCH_3 < CF_3 < SO_2N(CH_3)_2 < COC_3H_7$



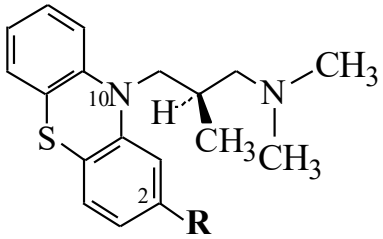
Promazine; R = -H; PROMAZIN

10-[3-(dimethylamino)propyl]phenothiazine

Chlorpromazine, R = -Cl, FENACTIL

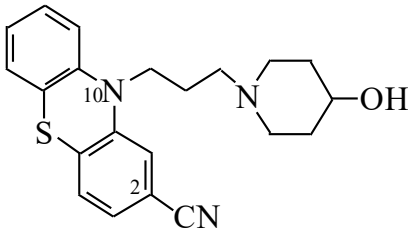
Triflupromazine, R = -CF_3; VESPRIN

Acepromazine, R -CO-CH_3; PLEGICIL

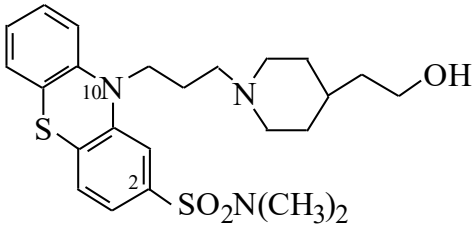


Levopromazine, R = -OCH_3; TISERCIN;

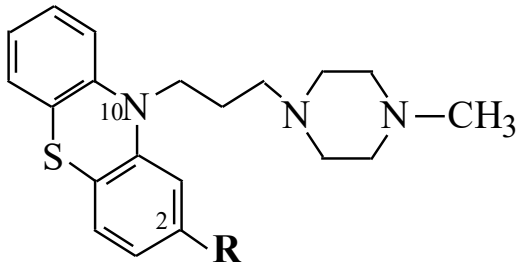
Cyamemazine, R = -CN



Periciazine



Pipotiazine

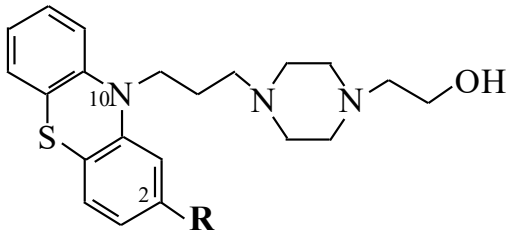


Perazine, R = H, PERAZYNA, PERNAZINUM;

Prochlorperazine, R = -Cl; CHLOROPERAZINUM

Trifluoperazine, R = CF_3; STELAZINE

Thioproperazine, R = $-SO_2-N(CH_3)_2$; MAJEPTIL;



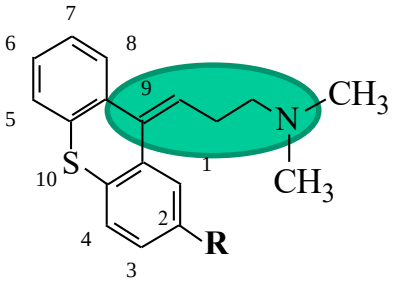
Perphenazine, R = -Cl, TRILAFON

Fluphenazine, R = $-CF_3$, MIRENIL

Tricyclic thioxanthene neuroleptics

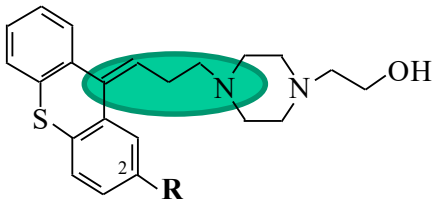
The chemical structure of thioxanthene is similar to that of phenothiazine derivatives.

A **distance of three carbon atoms between the C9 atom of thioxanthene and the nitrogen atom** in the chain is observed. The presence of a double bond causes geometric isomerism. *Cis* isomer acts much more strongly than *trans* isomer.



Chlorprothixene, R = Cl; CHLORPROTYKSEN,

(*Z*-)3-(2-Chloro- 9*H*-thioxanthen-9-ylidene)-*N*,*N*-dimethylpropan-1-amine



Clopenthixol, *Zuclopentixol*; R = -Cl; CLOPIXOL

Flupentixol, R = -CF_3; FLUANXOL

The substituents in position 9 and 2 demonstrate a similar effect on the antipsychotic activity of thioxanthene neuroleptics as phenothiazine derivatives.

Thioxanthene derivatives are safer than phenothiazine neuroleptics. They act more weakly on the extrapyramidal system.

It is probably caused by simultaneous antagonistic action on dopamine D_1 and D_2 receptors.

Thioxanthene derivatives show different potency of sedative or stimulating action.

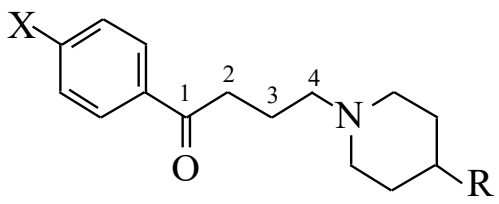
In comparison with phenothiazine derivatives, thioxanthene derivatives do not intensify depression and some of them (flupentixol) demonstrate significant antidepressive action.

Butyrophenone neuroleptics

Butyrophenone neuroleptics demonstrate the following **properties**:

- lack of cholinolytic or antihistaminic action,
- weak adrenolytic action,
- a strong side effect on the extrapyramidal system,
- the possibility of increasing depression,
- sedative action.

All butyrophenone derivatives displaying high neuroleptic potency have the following general structure:

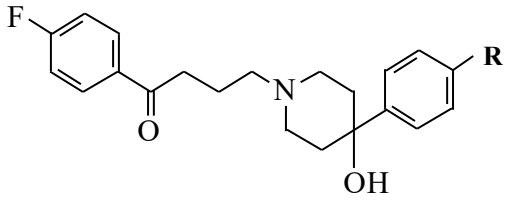


X = -F or –OCH_3

The **attachment of a tertiary amino group to the fourth carbon atom** of the butyrophenone skeleton is essential for neuroleptic activity. Lengthening, shortening, or branching of the three-carbon atom propyl chain decreases neuroleptic potency.

Replacement of the keto moiety (e.g. with thioketone, olefinic or phenoxy groups or reduction of the carbonyl group to a keto group) decreases neuroleptic potency.

In addition, the most potent butyrophenone compounds have a **fluorine substituent in the para position of the benzene ring**.[27]



Haloperidol, R = Cl; HALOPERIDOL

4-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone

Bromperidol; R = Br

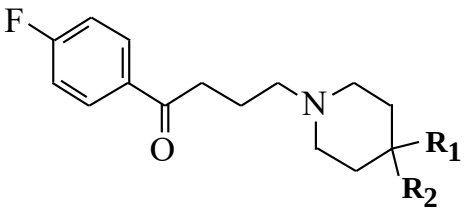
Trifluoroperidol; R = CF_3

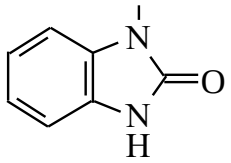
Moperon; R = CH_3

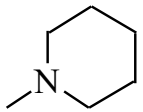
Haloperidol was introduced into the treatment of psychosis in Europe in 1958 and the United States in 1967.

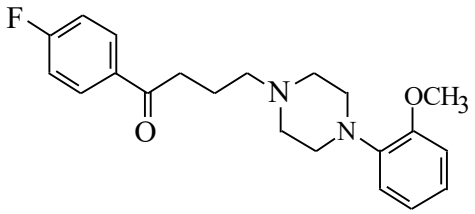
It is administered as an alternative drug to phenothiazine derivatives and is also used for the manic phase of bipolar (manic depressive) disorder.

Haloperidol decanoate has been introduced as depot maintenance therapy.

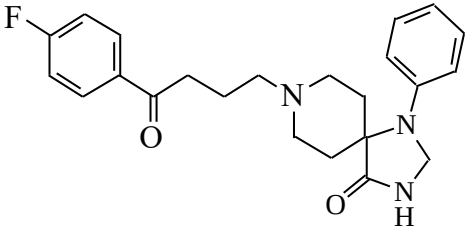


Benperidol, R_1 =  R_2 = H

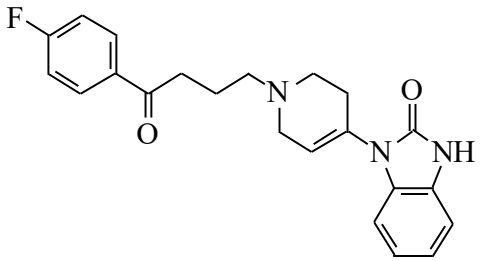
Pipamperone, R_1 =  R_2 = -CO-NH_2



Fluanisone, SEDALANDE



Spiperone, SPIROPITAN



Droperidol, INAPSINE, INNOVAR

Droperidol is a short-acting, sedating butyrophenone. It is used in anesthesia for its sedating and antiemetic effects and sometimes in psychiatric emergencies as a sedative-neuroleptic.

Droperidol is often administered together with the potent opioid analgesic fentanyl for preanesthetic sedation and anesthesia (neuroleptoanalgesia).

Then, although the patient does not feel any pain and does not remember his surgery, he can answer simple questions and respond to basic commands.

This kind of anesthesia is used for small surgical operations and diagnostic procedures, for example endoscopy.

Diphenylbutylpiperidine neuroleptics

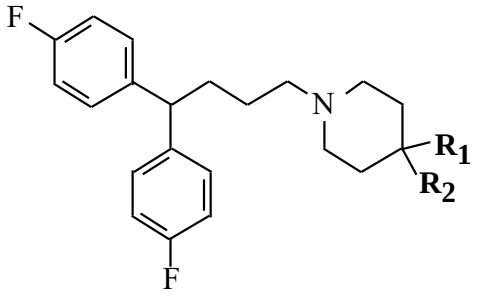
Modification of the haloperidol butyrophenone side chain by replacement of the keto function with a 4-flurophenylmethane moiety results in diphenylbutylpiperidine neuroleptics, such as pimozide, penfluridol and fluspirilene. The **diphenylbutylpiperidine neuroleptics** have a longer duration time than the butyrophenone analogs. They

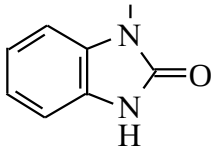
- have high affinity for D_2 receptors and demonstrate strong antipsychotic action,
- act energisingly,
- demonstrate strong unwanted action on the extrapyramidal system,
- show very weak adrenolytic activity,
- do not show cholinolytic or antihistaminic action.

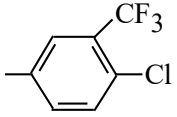
All of them are effective in the control of schizophrenia and, in particular, pimozide has proven useful in the treatment of the acute form of schizophrenia and in reducing the rate of relapse in chronic schizophrenic patients.

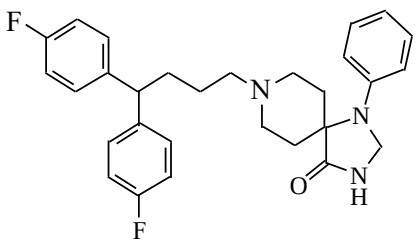
The duration time of pimozide is approx. 24 h. It is very slowly metabolised.

Pimozide is also used to treat Tourette's syndrome, a movement disorder characterized by facial tics, grimaces, strange uncontrollable sounds, and sometimes the involuntary shouting of obscenites. Chronic treatment of Tourette's syndrome with haloperidol or pimozide may cause irreversible tardive dyskinesia.



Pimozide, R_1 =  R_2 = H

Penfluridol R_1 =  R_2 = OH



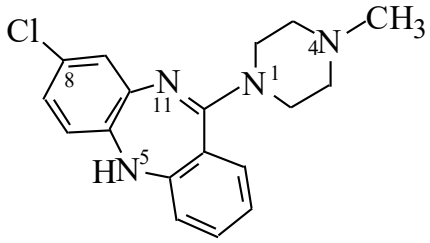
Fluspirilene

Tricyclic dibenzazepine neuroleptics

Dibenzazepine neuroleptics, in comparison with classical neuroleptics, have only weak extrapyramidal action.

It is believed that such activity can be caused by:

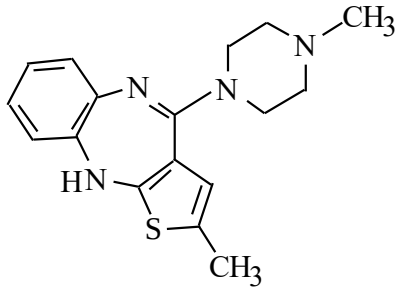
- simultaneous blocking of D_2 and D_1 receptors,
- anticholinergic action,
- stronger action on the mesolimbic system than on the extrapyramidal system.



Clozapine, CLOZAPINE, LEPONEX

8-Chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine

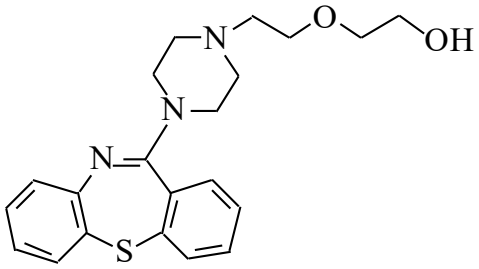
Clozapine shows relatively low affinity for D_1 and D_2 receptors and moderate affinity for D_4 receptors in comparison with its affinity for adrenergic α_1 and α_2 receptors, H_1, M_1 and 5-HT_2 receptors, so the antipsychotic action of clozapine can be caused by its interaction with these receptors.



Olanzapine, ZOLAFREN, ZYPREXA

2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thiene[2,3-*b*][1,5]benzodiazepine

Olanzapine, similarly to clozapine, shows some anxiolytic action. It is used in the treatment of acute and chronic psychosis.
It can be used once a day.

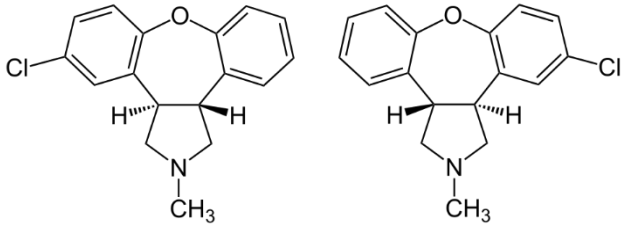


Quetiapine, SEROQUEL

Quetiapine is an atypical antipsychotic drug, with strong affinity for $5HT_2$ receptors and less affinity for D_1 and D_2 receptors. That is probably responsible for its greater effectiveness and weaker extrapyramidal effects.

Quetiapine demonstrates also high affinity for adrenergic α_2 receptors and only slight affinity for muscarinic and benzodiazepine receptors. In contrast to typical antipsychotic drugs, long-term use of quetiapine does not result in the hypersensitivity of D_2 receptors.

Asenapine



(3a*RS*,12b*RS*)-*rel*-5-Chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole

Asenapine shows high affinity (pKi) for numerous receptors, including the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{5A}, 5-$HT_{6,}$ and 5-HT_7 receptors, the α_1- , α_{2A}, $_{2B}$, $_{2C}$-adrenergic receptors, D_1, D_2, D_3, D_4, H_1 and H_2. It has much lower affinity (pKi < 5) for the muscarinic ACh receptors. Asenapine behaves as a partial agonist at the 5-HT_{1A} receptors.

Long-acting neuroleptics

The duration of action of many of the neuroleptics with a free hydroxyl moiety can be considerably prolonged by the preparation of long-chain fatty acid esters.

Long-acting neuroleptics for IM injection include:

fluphenazine enanthate (time of action 1-2 weeks),

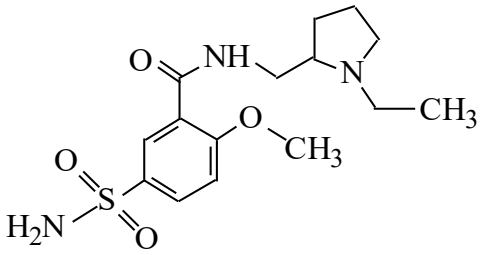
fluphenazine decanoate (time of action 2-3 weeks),

perphenazine enanthate (time of action 1-2 weeks),

thioxanthene enanthate (time of action 1-2 weeks).

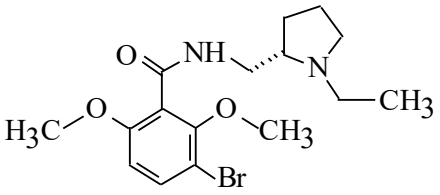
They demonstrate less adverse effects than the unesterified precursors. Additionally, the possibility of treating patients with a single IM injection every 1-2 weeks or 2-3 weeks is more comfortable for them.

Benzamide neuroleptics

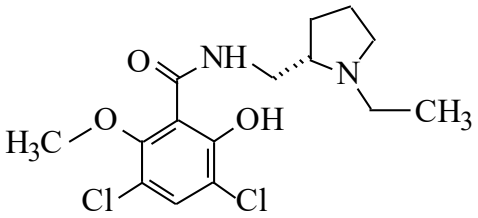


Sulpiride, SULPIRYD, DOGMATIL

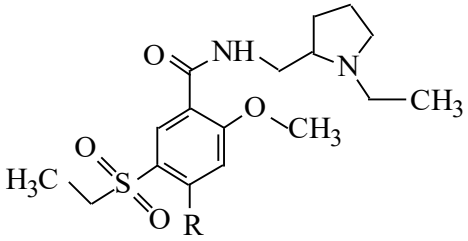
5-(Aminosulfonyl)-*N*-[(1-ethyl-pyrrolidyn-2-yl)methyl]-2-methoxybenzamide



Remoxipride

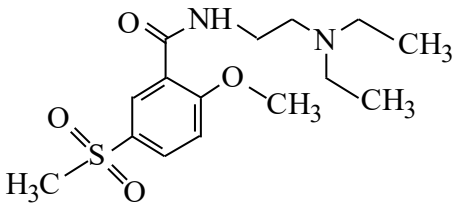


Raclopride



Sultopride, R = H; TOPRAL;

Amisulpride, R = NH_2; SOLIAN



Tiapride, DOPARID, TIAPRIDAL

The **benzamide derivatives** are relatively selective antagonists for D_2 receptors in the mesolimbic tract. Their influence on the extrapyramidal structures is not significant. However, they increase the level of prolactine in plasma. For example remoxipride shows this action to a lesser degree than sulpiride.

Sulpiride is a neuroleptic with an antidepressive component. It improves the patient's mood and acts antiemetically.

Sulpiride is used in the therapy of neurosis, migraine, vertigo, psychosomatic disorders, acute and chronic psychosis.

- Ethanol increases the action of sulpiride, whereas levodopa decreases it. Sulpiride enhances the action of drugs acting depressively on the CNS, such as opioids, benzodiazepines, barbiturates, most antihistaminic drugs and antihypertonic drugs.
- The action of sulpiride depends on dosage. In small doses, it blocks primarily presynaptic dopamine receptors, increasing the release of dopamine, whereas in high doses it inhibits pre- and postsynaptic dopamine receptors.

Remoxipride is used for the treatment of acute and chronic types of schizophrenia, which are accompanied mainly by such symptoms as delusions, hallucinations and disturbance of thinking. Remoxipride is not used in patients under 18 years of age.

Remoxipride, raclopride and sulpiride show relatively small affinity for receptors of other neurotransmitters, such as serotonin, noradrenaline, acetylcholine, histamine and GABA.

The potency of sultopride may be illustrated as follows: sedative (strong) > antidelusive (moderate) > antiautistic (weak). It does not influence the autonomic system and its action on the extrapyramidal system is moderate.

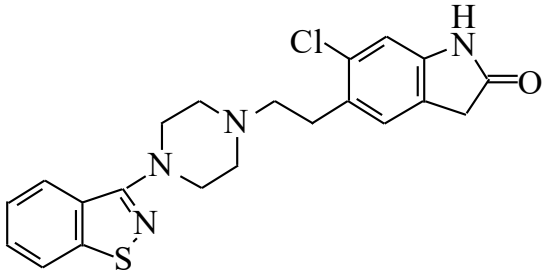
Sultopride is used for the treatment of delusion psychosis with motor excitation, and in the alcohol psychosis.

Amisulpride acts energisingly, antiautistically and antidelusively. Its influence on the extrapyramidal system is not significant. Amisulpride is used in the therapy of delusion syndromes, characterized by decreased acivity and depressed mood.

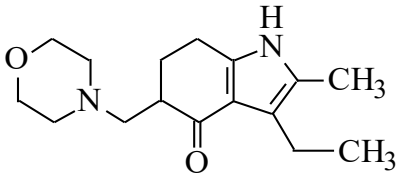
Tiapride is indicated in the states of aggression and excitation, and in choreic movement disturbances.

Tiapride increases the action of drugs acting depressively on the CNS, such as hypnotic and sedative drugs, analgesics, anaesthetics and hypotensive drugs.

Indole neuroleptics



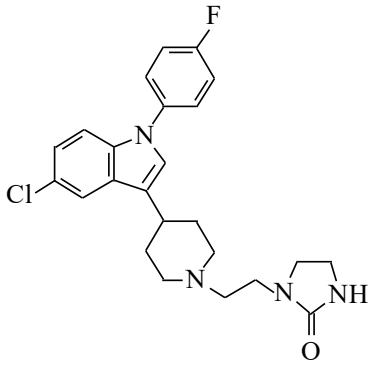
Ziprasidone, ZELDOX



Molindone, MODAN

Ziprasidone shows high affinity for 5-HT_{2A} receptors. Its affinity for D_2 receptors is approx. 10-times lower than for 5-HT_{2A}. Ziprasidone also acts on 5-HT_{2C}, 5-HT_{1D} and 5-HT_{1A} receptors to the same or a higher degree than on D_2 receptors. As it inhibits the reuptake of serotonin and noradrenaline from the synaptic cleft, it also demonstrates antidepressive activity.

Molindone, a tetrahydroindolone derivative, is a neuroleptic with mainly energising action. Apart from neurolepic activity antidepressive activity is also observed.



Sertindole, SERDOLECT

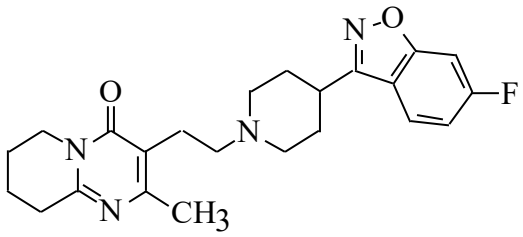
1-[2-[4[[5-Chloro-1-(*p*-fluorophenyl)indol-3-yl]-piperidinyl]ethyl]imidazolidin-2-on

Sertindole shows high affinity for serotonin 5-HT_2 receptors, low affinity for adrenergic α_1 receptors and almost no affinity for dopamine D_2 receptors.

It is approximately as effective as haloperidol in the treatment of acute and chronic schizophrenia, but produces fewer extrapyramidal side effects.

Sertindole is a relatively nonsedative long-acting neuroleptic, whose action lasts several days.

Benzisoxazol and benzisothiazole neuroleptics



Risperidone, RISPOLEPT, RISPERDAL

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino-]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-a]-pyrimidin-4-one

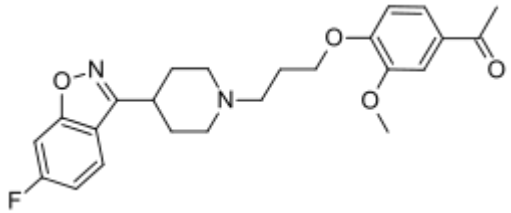
Risperidone is a 5-HT_2/D_2 receptor antagonist and has relatively high affinity for histamine H_1 and adrenergic α_1/α_2 receptors.

The anti-serotoninergic effects of risperidone are believed to un-inhibit dopaminergic neurotransmission in the striatum and cortex, reducing the severity of D_2 antagonists-induced extrapyramidal side effects and alleviating the negative symptoms of schizophrenia, while maintaining a blockade of limbic system D_2 receptors.

One of risperidone metabolites is 9-hydroxyrisperidone (Paliperidone), which shows the same activity as risperidone but has longer half-time (24 h) than risperidone (3 h).

Risperidone is effective in the treatment of delusive and negative symptoms, in both acute and chronic types of psychosis.

Iloperidone

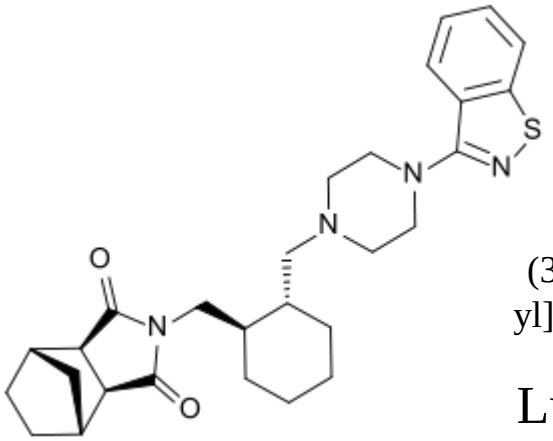


1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1- piperidinyl]propoxy]-3-methoxyphenyl]ethanone

It exhibits high (nM) affinity to serotonin $5HT_{2A}$, dopamine D_2 and D_3, moderate affinity for dopamine D_4, serotonin $5HT_6$, $5HT_7$ and noradrenaline α_1 receptors, and low affinity for the serotonin $5HT_{1A}$, dopamine D_1 and histamine H_1 receptors.

Iloperidone produces less severe extrapyramidal side effects than haloperidol. It causes significant weight gain like haloperidon and risperidone.

Lurasidone

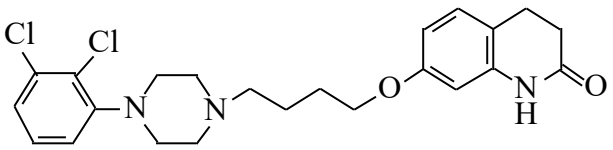


(3a*R*,4*S*,7*R*,7a*S*)-2-[((1*R*,2*R*)-2-{[4-(1,2-benzisothiazol-3-yl)-piperazin-1-yl]methyl}cyclohexyl)methyl]hexahydro-1*H*-4,7-methanisoindol-1,3-dione

Lurasidone acts as an antagonist of the following sites: $\alpha_{1,\ 2A,2C}$, D_1, D_2, $5\text{-}HT_{2A,\ 2C,\ 7,}$ and as a partial agonist of $5\text{-}HT_{1A}$ receptor.

The most common side effects: somnolence, akathisia, nausea, parkinsonism, agitation and weight gain.

Quinoline neuroleptics



Aripiprazole; 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy]3,4-dihydro-2(1*H*)-quinolinone

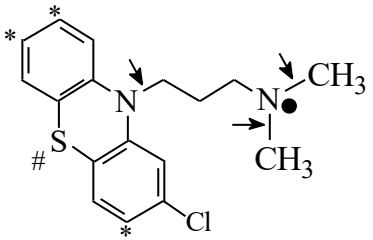
Aripiprazole belongs to a new class of neuroleptics defined as stabilizers of the dopamine system. This group of drugs shows partial affinity for dopamine and serotonin receptors. It is thought that partial agonists of dopamine receptors can stabilize the dopaminergic system without inducing low levels of dopamine, which is responsible for intolerance of other atypical antipsychotic drugs.

Aripiprazole reduces dopamine levels in the mesolimbic system, which results in its antipsychotic effects. It also has high affinity for dopamine D_2 and D_3 receptors and is a partial agonist of dopamine D_2 receptors.

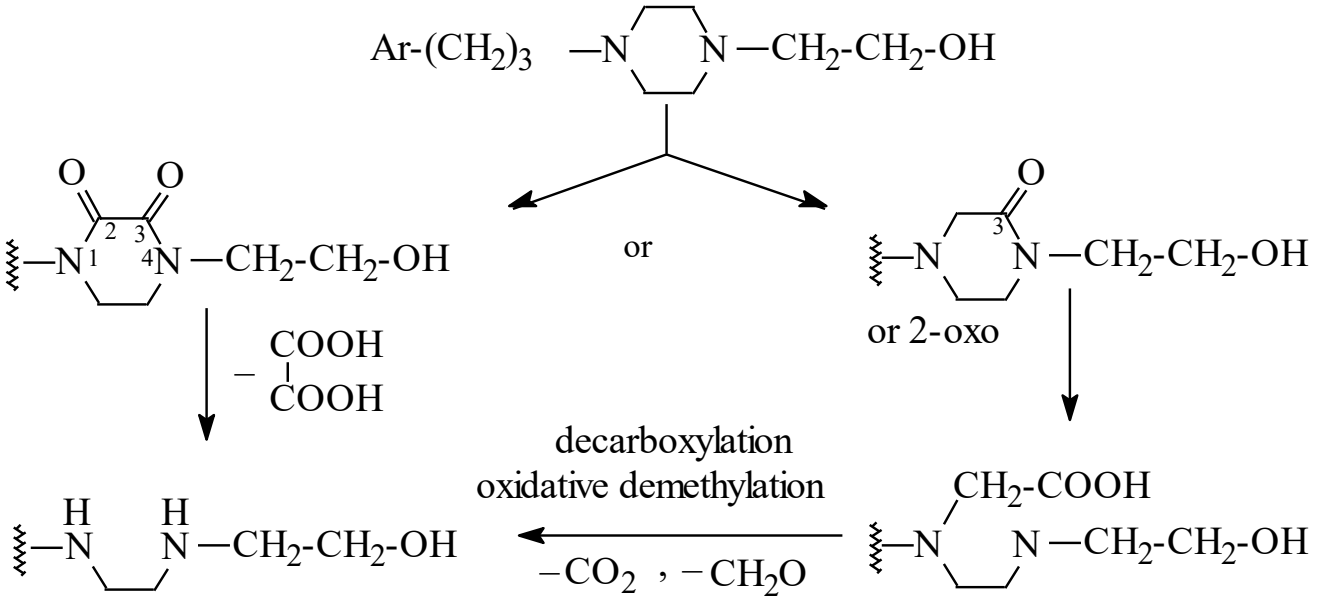
The metabolism of neuroleptics

Dimethylaminoalkyl-substituted phenothiazines, best exemplified by chloropromazine, are intensively metabolised during the first passage in the liver. The biotransformation of chloropromazine involves the following reactions: S- and N-oxidation, C-hydroxylation, the coupling of metabolites with glucuronic acid, and N-dealkylation. A combination of such processes leads to more than 100 identified metabolites.

There is evidence that 7-hydroxylated derivatives and possibly other hydroxylated derivatives as well as the mono- and di-demethylated products (nor_1-chloropromazine and nor_2-chloropromazine) are active in vivo and at dopamine D_2 receptors, whereas the sulfoxide is inactive.



In the case of piperazine derivatives, in addition to S- and N-oxidation, C-hydroxylation and N-dealkylation reactions, the opening of the piperazine ring is observed. Two possible mechanisms of this reaction are presented below.

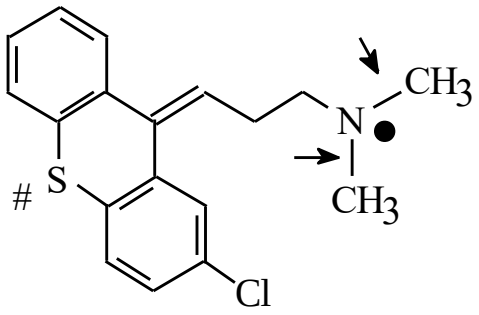


The oldest thioxanthene neuroleptic is chlorprothixene.

Similarly to phenothiazines, it is metabolized during the first passage in the liver, mainly as a result of S- and N-oxidation and N-demethylation.

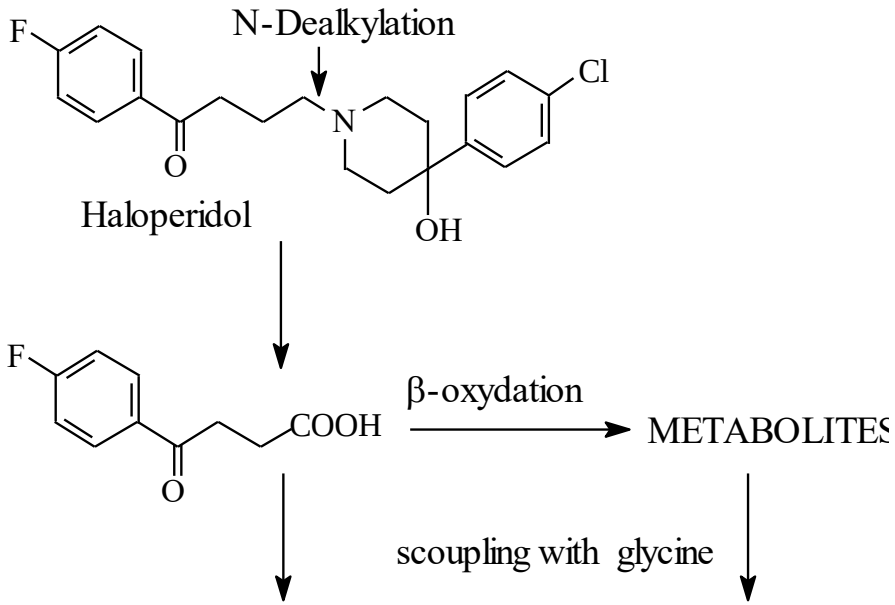
The demethylation to first-order amine occurs relatively slowly. In therapy *cis* isomer is used.

The transformation of *cis* isomer to *trans* isomer is either insignificant or does not occur.

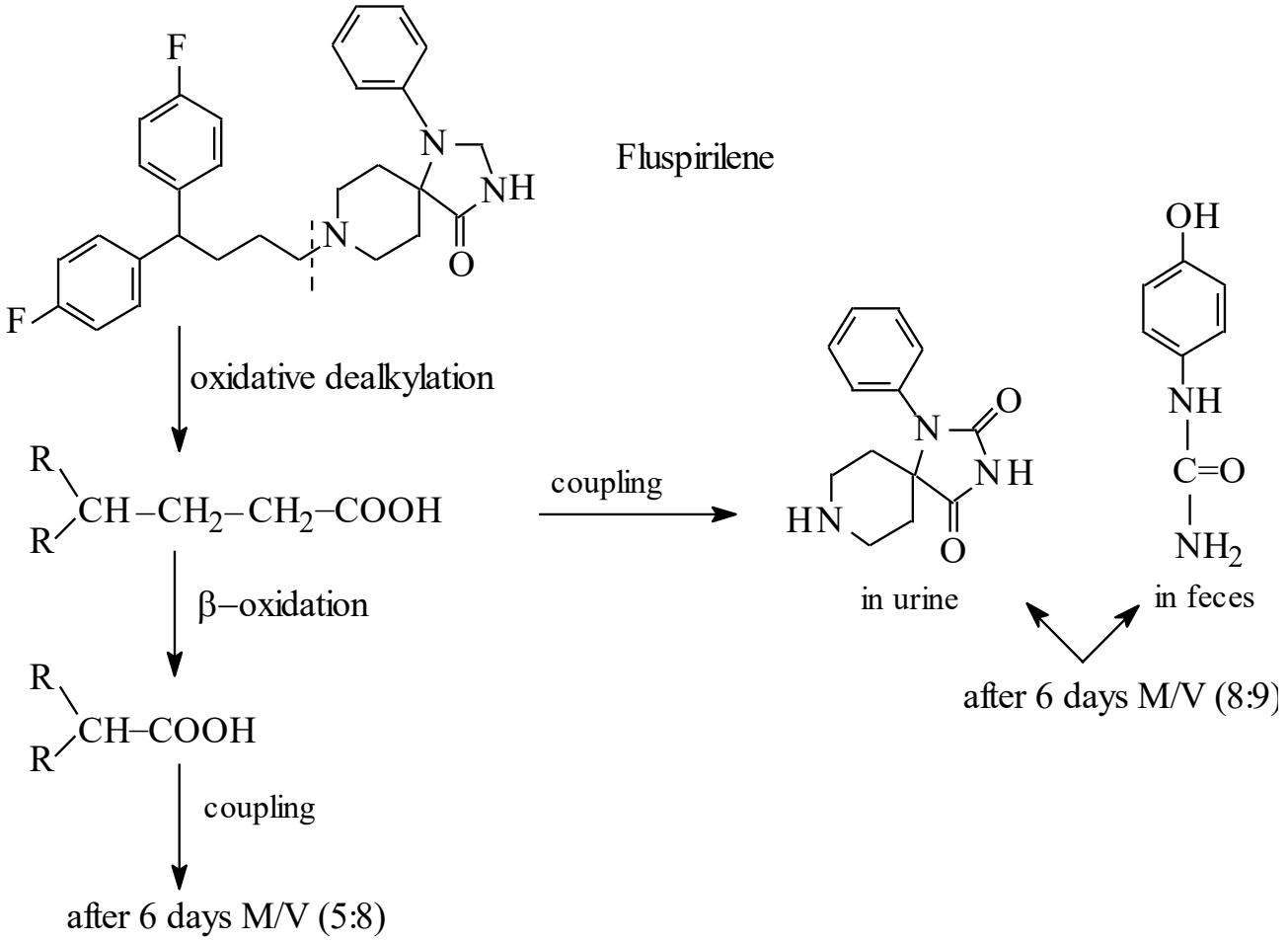


The biotransformation of haloperidol (butyrophenone derivative) and fluspirilene (diphenylpiperidine derivative) occurs as a result of oxidative dealkylation and βoxidation of primary products.

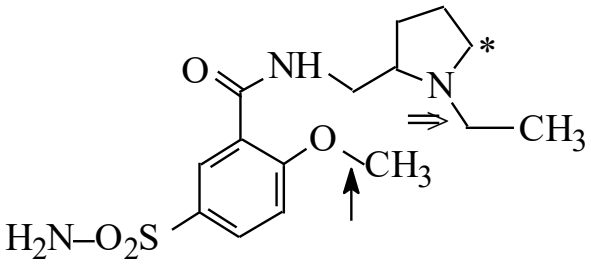
The intermediate and final metabolites are coupled with glycine. The reaction of coupling with glucuronic acid and C-hydroxylation are not observed.



In the case of fluspirilene, parallel to oxidative dealkylation, oxidation in position 2 of the imidazoline ring, the opening of the imidazoline ring and C4-hydroxylation are observed.



Sulpiride is: O-demethylated, N-dealkylated, * C-hydroksylated



The adverse effects of neuroleptics

The most common adverse effects of the majority of antipsychotic drugs are

- **extrapyramidal motor disturbance** and
- **endocrine disturbance** (increased release of prolactine), which are connected with the blocking of dopaminergic receptors
- **sedation, hypotension and an increase in body weight** are also often observed.

The adverse effects of neuroleptics

- When the phenothiazine derivatives are administered, **cholestatic jaundice** can appear.
- Other adverse effects - **xerostomia, blurred vision and hypotension** are caused by the blocking of receptors for other neurotransmitters, especially α-adrenergic and muscarinic receptors.
- The **malignant neurotic syndrome** occurs rarely and is a very serious complication. It is similar to malignant hyperthermia, which is sometimes observed during the administration of anesthetics and can cause the patient's death because of renal or circulatory insufficiency.

- Some neuroleptics cause **agranulocytosis**. Clozapine often leads to leukopenia and because of that regular blood testing is necessary. The second- and third-generation neuroleptics demonstrate significantly fewer adverse effects than the classical, first-generation neuroleptics.
- Although neuroleptics of the first generation effectively alleviate disturbances of mental functions, such as delusions or acoustic hallucinations, they also cause many adverse effects, including parkinsonism. Additionally, they do not reduce certain symptoms, for example depression, activity deficit or disturbances of cognitive functions (attention and memory).

- Drugs of the next generations are effective not only in therapy of psychotic states but also in the treatment of depression and improve cognitive functions without causing secondary effects.
- In the treatment of schizophrenia, relapses of the disease are the main problem. They are reported in 40-60% of patients with severe schizophrenia treated with the classical neuroleptics and in 25% of patients treated with neuroleptics of new generations.
- Because of the adverse effects and ineffectiveness of neuroleptics used at present in some kinds there are efforts to find new, safer and more effective drugs improving the patient's mental activity.