NEUROLEPTICS (ANTIPSYCHOTICS) DRUGS

Zeynep Ates-Alagoz, Ph.D

Ankara University, Faculty of Pharmacy

Department of Pharmaceutical Chemistry

CLASSIFICATION OF ANTIPSYCHOTIC DRUGS

More than 20 different antipsychotic drugs are available for clinical use, but with certain exceptions the differences between them are minor.

An important distinction is drawn between the main group, often referred to as classical or typical antipsychotic drugs, atypical (newer) antipsychotic drugs

“Atypical” commonly refers to the diminished tendency of some newer compounds to cause unwanted motor side-effects.

Their pharmacological profile somewhat different from that of “classical” pre-1980 drugs (phenothiazines, thioxanthines and butyrophenones).

Although the underlying cause of psychosis is unknown, treatment with neuroleptic drugs usually results in a specific improvement in psychotic sings and symptoms and does not simply cause sedation or reduce agitation.

Modern antipsychotic drugs allow many schizophrenics to lead productive lives outside hospitals or less restrictive lives within hospitals.

MECHANISM OF ACTION

-The antipsychotic drugs probably **owe their therapeutic effects mainly to blockade of D2 receptors.**

PHARMACOKINETICS

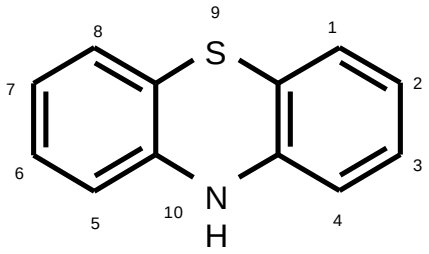
Most neuroleptic drugs are highly lipophilic, bind to proteins, and tend to accumulate in highly perfused tissues.

Half-lives are generally long, and so a single daily dose is effective.

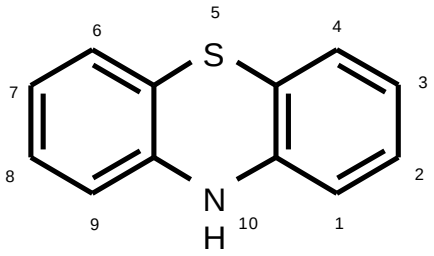
An esterified derivate of fluphenazine requires dosing only once every few weeks.

After long-term treatment and drug administration is stopped, therapeutic effects may outlast significant blood concentrations by days or weeks.

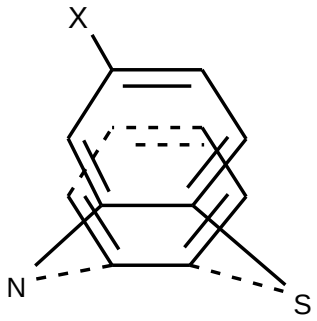
I- PHENOTHAZINE DERIVATIVES



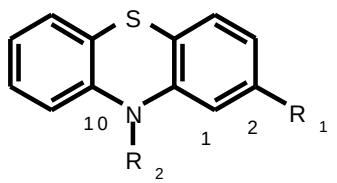
Beilstein sistemi

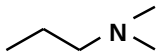
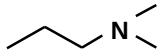
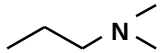


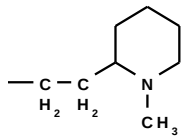
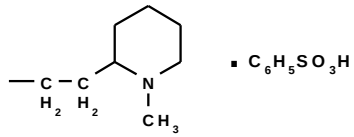
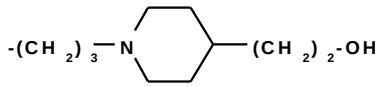
Chemical abstracts system

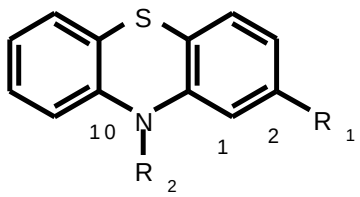


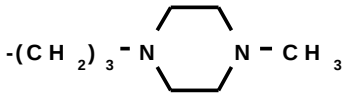
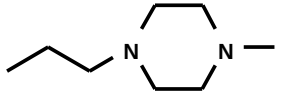
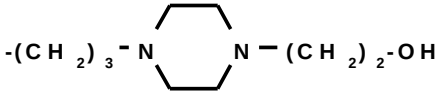
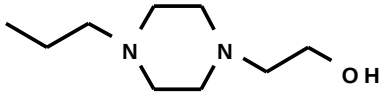
The angle between the two benzene rings is 159º for chlorpromazine and 141º for perphenazine. The phenothiazine ring is not essential for the antipsychotic effect.



Dialkilamino propil yanzinciri taşıyanlar	R_1	R_2
Promazin 10-(3-Dimetilaminopropil)fenotiyazin	-H	
Klorpromazin (Largactil (R) tb. amp.) 2-Kloro-10-(3-dimetilaminopropil)fenotiyazin	-Cl	
Triflupromazin 2-Trifluorometil-10-(3-dimetilaminopropil)fenotiyazin	$-CF_3$	

Piperidino propil yanzinciri taşıyanlar	R_1	R_2
Tiyoridazin (Mellerettes (R) drj., gtt. günümüzde Türkiye'de üretilmiyor) 2-Metilmerkapto-10-[2-N-metil-2-piperidil)etil]fenotiyazin	$-SCH_3$	
Mezoridazin (Lidanil (R) drj. günümüzde Türkiye'de üretilmiyor) 2-Metilsülfinil-10-[2-N-metil-2-piperidil)etil]fenotiyazin benzensülfonat	$-SOCH_3$	
Piperasetazin (günümüzde üretilmiyor) 2-Asetil-10-[3-[4-(2-hidroksietil)piperidil]propil]fenotiyazin	$-COCH_3$	



Piperazino propil yanzinciri taşıyanlar	R_1	R_2
Trifluoperazin (Stilizan(R) drj. 1mg) 2-Trifluorometil-10-[3-(4-metilpiperazinil)propil]fenotiyazin	$-CF_3$	
Tietilperazin 2-Etilmerkapto-10-[3-(4-metilpiperazinil)propil]fenotiyazin	$-SC_2H_5$	
Perfenazin 2-Kloro-10-[3-[4-(2-hidroksietil)piperazinil]propil]fenotiyazin	$-Cl$	
Flufenazin (Proliksin decanoate retard(R) amp.) 2-Trifluorometil-10-[3-[4-(2-hidroksietil)piperazinil]propil]fenotiyazin	$-CF_3$	

- Chlorpromazine is used for agitation, nausea and vomiting, dementia, hiccups, migraine, mania, psychosis, schizophrenia.

- Thioridazine is the derivative with the most cardiotoxic side effect.

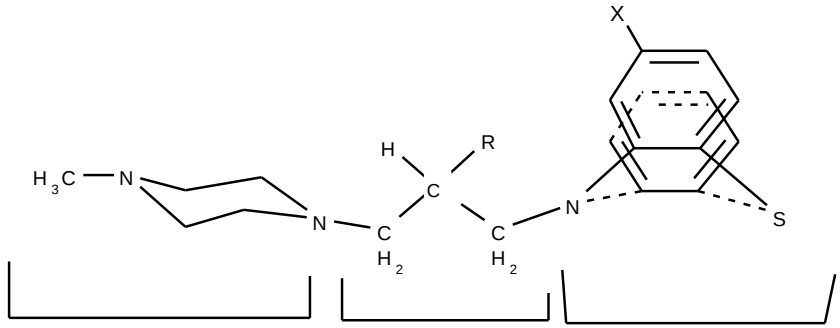
- Mesoridazine is the metabolite of thioridazine. Within typical antipsychotics, its extrapyramidal side effects are minimal. Pigmentation in the retina may be seen, which limits its use.

Contraindications: Epilepsy, pregnancy, parkinson, hepatic disease, fever, breast cancer, breastfeeding, heart disease, etc.

- The medication should not be stopped suddenly.

- All antipsychotics may cause coma in patients that have a liver disease.

PHENOTHIASINE-DOPAMINE RECEPTOR INTERACTION



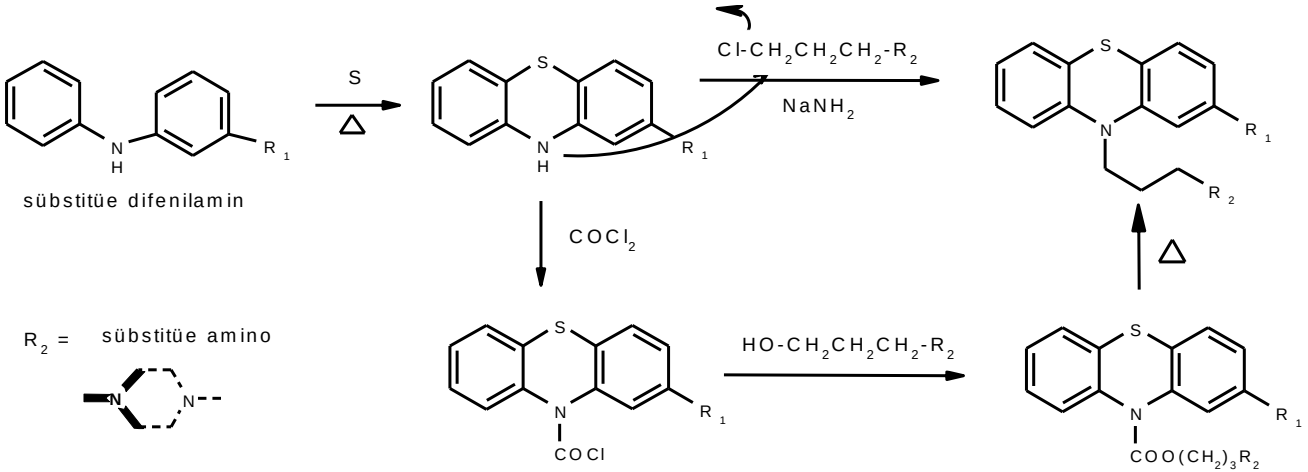
Region A: if the first nitrogen is substitue with - CH3, still same effect,
-If -H or > -CH3, the effect is reduced,
-piperazine ring increases the effect.

Region B: Maximum activity with 3 carbon chains
-R = -H, neuroleptic effect is high,
-R = -CH3, the neuroleptic effect is decreased,
antihistaminic and antipruritic effects are increased,
- R = phenyl, dimethylamino causes lost of the activity

Region C : substituent X does not interact directly with the receptor,
- X = -Cl, -COCH3, -CF3, -SO2N (CH3) 2, etc , ↑ activity
-only substitution of the 2nd position is increased the activity.

GENERAL SYNTHESIS

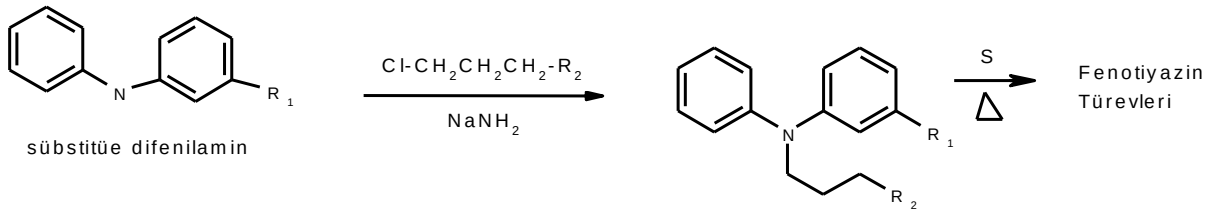
I-



sübstitüe difenilamin

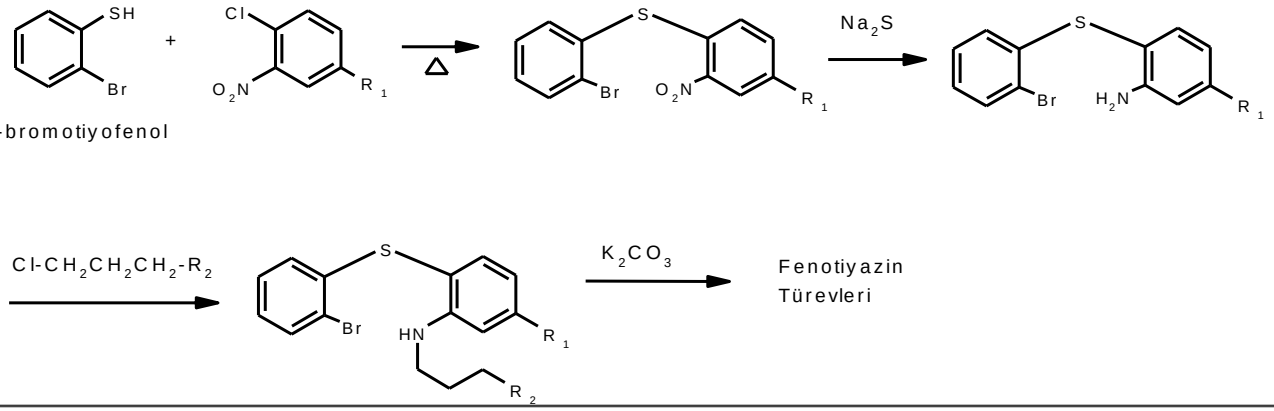
R_2 = sübstitüe amino

II-



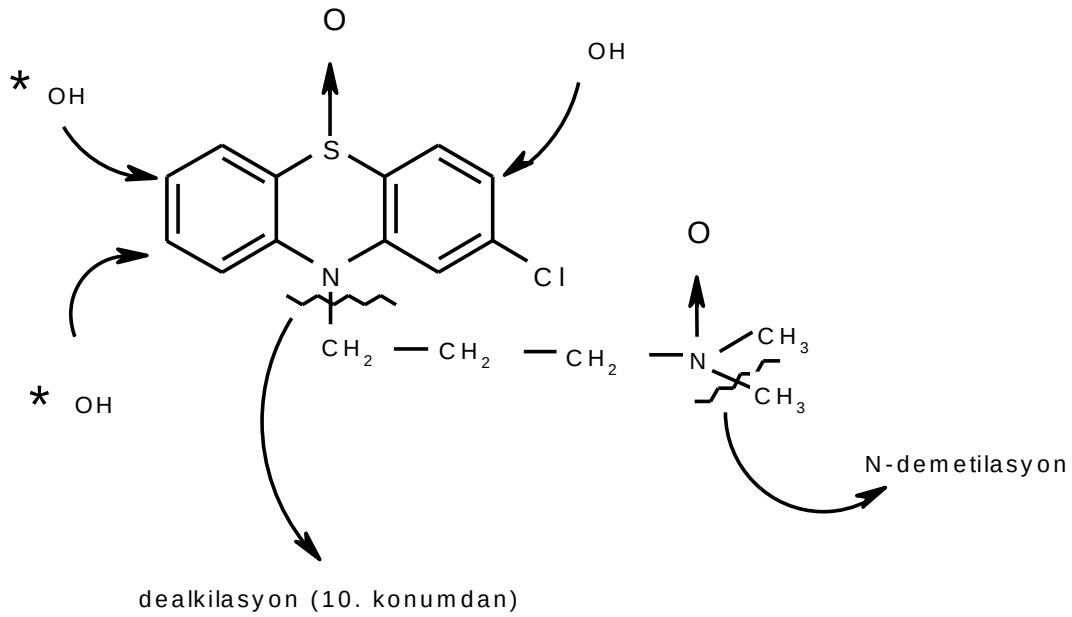
sübstitüe difenilamin

III-

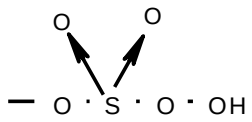


2-bromotiyofenol

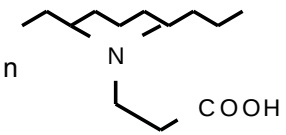
Metabolism of Chlorpromazine



7. konumdan önce hidroksillenir, sonra sülfat konjugatı veya -OCH_3 oluşur.

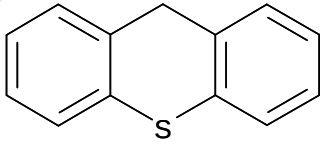


oksidatif deaminasyon



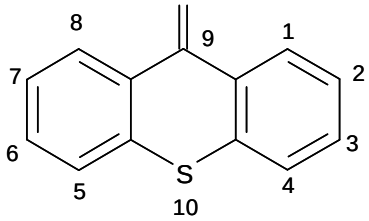
* aktif metabolitleri

II- THYOXANTENE DERIVATIVE COMPOUNDS



O ⟹ ksanten

CH_2 ⟹ antrasen



•They are not in a planar structure.

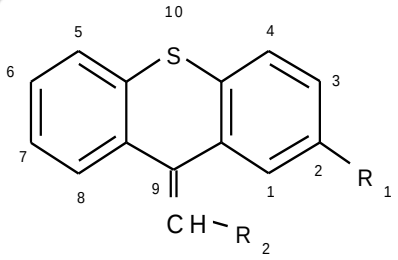
•Substitution with -CH3 at the eighth position leads to no activity.

•Substitution at the second position is important for causing the E / Z isomerism.

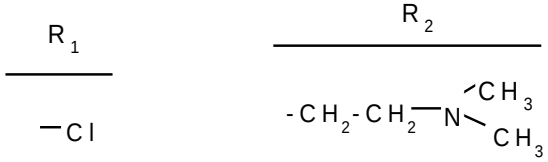
• If the = bond in the 9. position is saturated, the central depressant effect disappears.

•Cis isomers are more effective.

•They have no advantages over phenothiazine derivatives, their pharmacological effects and side effects are similar.



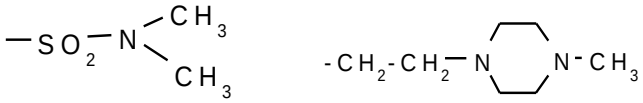
Klorprotiksen



2-kloro-9-(3-dimetilaminopropiliden) tiyoksanten

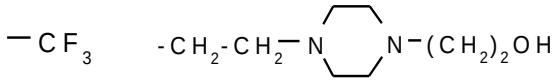
Tiyotiksen

[günümüzde üretilmiyor]



2-(dimetilaminosülfonil)-9-(3-(4-metilpiperazinil) propiliden)tiyoksanten

Flupentiksol



[Fluanksol (R) tb., IM amp.]

$H_3C(CH_2)_8COOH$ = dekanoik asit

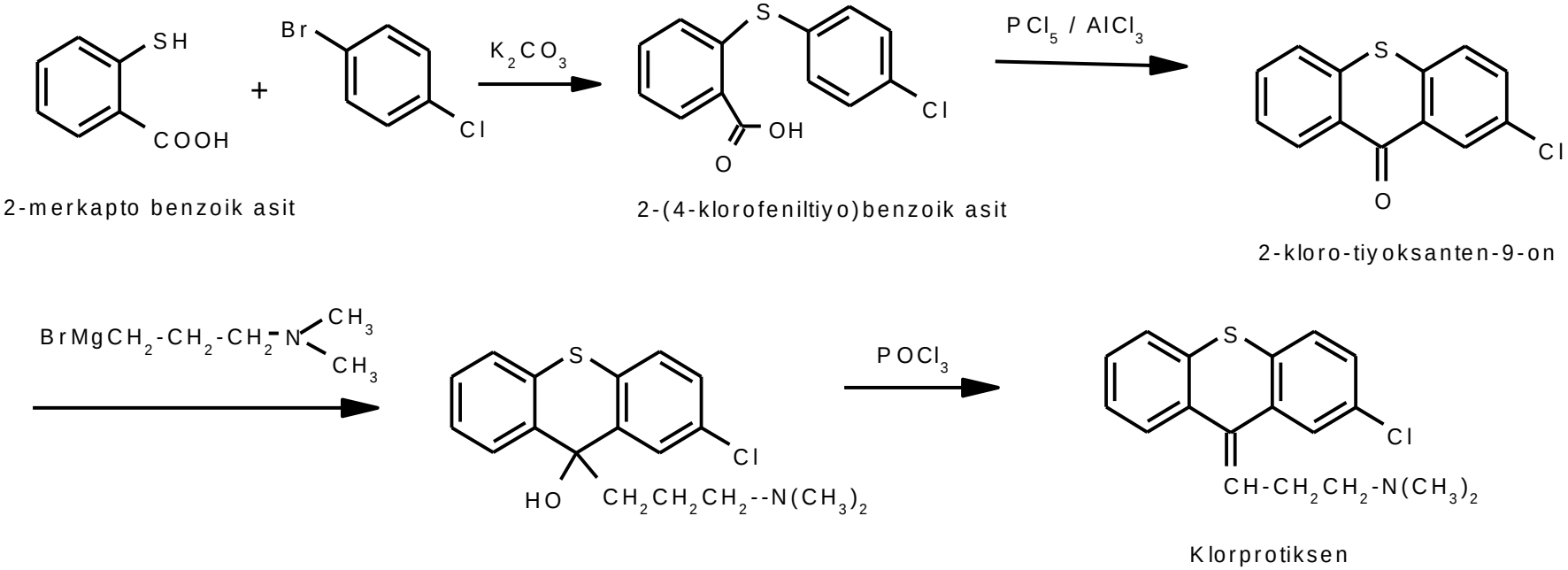
-Flupentixol decanoate is used in the preparation of long lasting injectable preparations.

-It is also used for antidepressant purposes.

-It also has Antiautistic and activating properties.

-After N-dealkylation, S- and N-oxidation, they are usually excreted via the kidneys.

Synthesis of Chloroprothixene



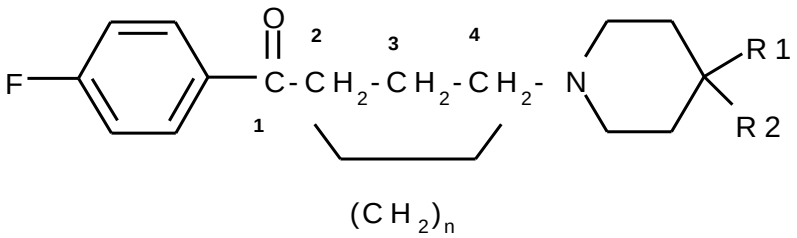
2-merkapto benzoik asit

2-(4-klorofeniltiyo)benzoik asit

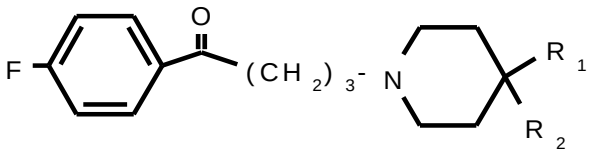
2-kloro-tiyoksanten-9-on

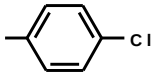
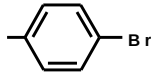
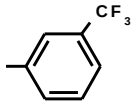
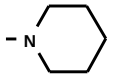
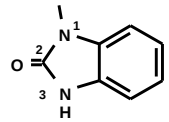
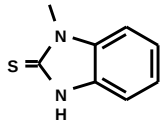
Klorprotiksen

III- FLUOROBUTYROPHENON DERIVATIVES

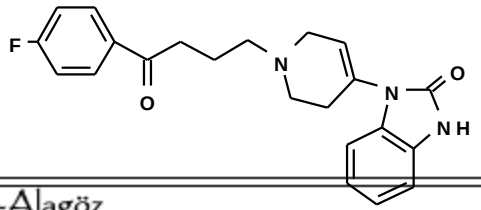


- p-fluorobutyrophenone is essential for the activity. If –F is replaced with -Cl, -Br, -OCH_3, -CH_3 etc., activity is reduced.
- Phenyl can be substituted with thienyl
- Maximum activity is obtained in the presence of carbonyl. Activity disappears with sulfonyl.
- With the n = 3, the highest activity is obtained, but the activity is reduced by branching.
- If N atom is a member of the piperidine system, maximum activity is observed.
- R2 : must be aromatic. It may be connected directly or via a methylene bridge.
- Metabolism pathways include reduction of the carbonyl group, oxidative deamination, and then acetylation of the piperidine ring.



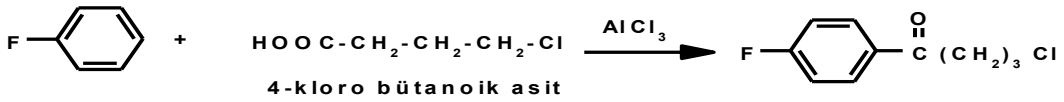
	R_1	R_2
Melperon (Buronon(R) drj. günümüzde Türkiye'de üretilmiyor) 4'-Fluoro-4-(4-metilpiperidinil)butirofenon	-H	$-CH_3$
Haloperidol (Norodol(R) amp., drj., tb.) 4'-Fluoro-4-[4-(4-klorofenil)-4-hidroksipiperidinil)butirofenon	-OH	
Bromperidol 4'-Fluoro-4-[4-(4-bromofenil)-4-hidroksipiperidinil)butirofenon	-OH	
Trifluperidol 4'-Fluoro-4-[4-(3-trifluorometilfenil)-4-hidroksipiperidinil)butirofenon	-OH	
Pipamperon 4'-Fluoro-4-[4-(1-piperidinil)-4-karboksamidopiperidinil]butirofenon	$-CONH_2$	
Benperidol 4'-Fluoro-4-[4-(2-okso-2,3-dihidrobenzimidazolil)piperidinil]butirofenon	-H	
Timiperon 4'-Fluoro-4-[4-(2-tiyokso-2,3-dihidrobenzimidazolil)piperidinil]butirofenon	-H	

Droperidol (Dehydrobenzperidol (R) amp.)
4'-Fluoro-4-[4-(2-okso-**2,3-dihidro**benzimidazolil)-**3,4-dehidro**piperidinil]butirofenon



Fluorobutirofenon Türevlerinin Genel Sentezleri

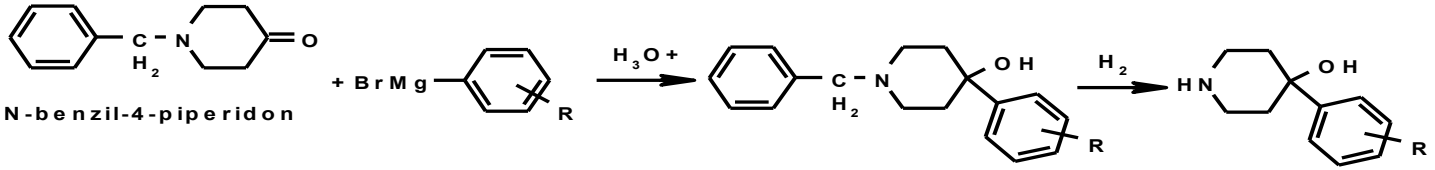
I. Basamak =



4-kloro bütanoik asit

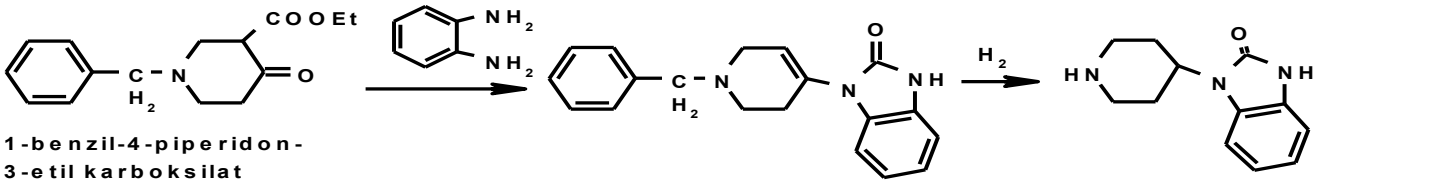
4'-fluoro-4-klorobütirofenon

II. Basamak =(Haloperidol, bromperidol, trifluperidol için)



N-benzil-4-piperidon

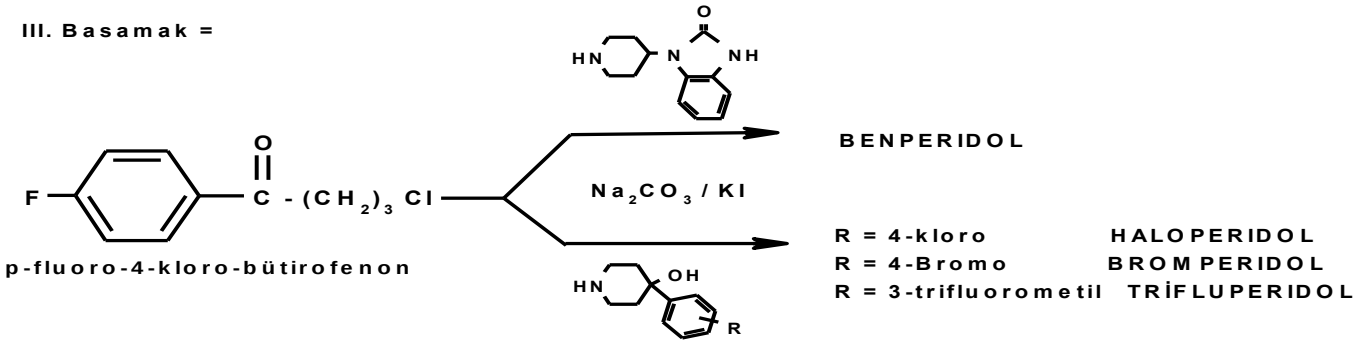
Benperidol için:



1-benzil-4-piperidon-3-etil karboksilat

4-(2-okso-2,3-dihidro-benzimidazolil)-piperidin

III. Basamak =



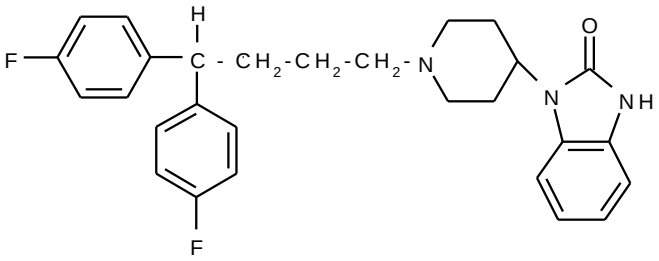
p-fluoro-4-kloro-bütirofenon

BENPERIDOL

R = 4-kloro HALOPERIDOL
R = 4-Bromo BROMPERIDOL
R = 3-trifluorometil TRİFLUPERIDOL

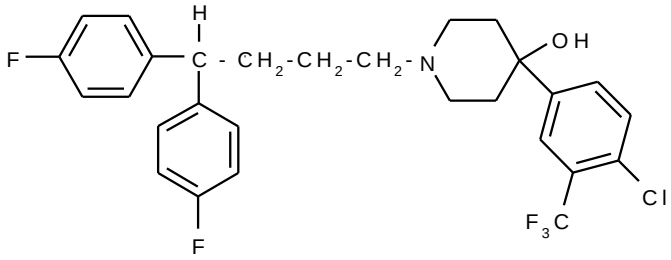
IV- DIPHENYBUTYL PIPERIDIN DERIVATIVES

Pimozid (Nörofren(R) tb.)



1-[1-[4,4-Bis(4-fluorofenil)bütil]-4-piperidinil]-1,3-dihidro-2H-benzimidazol-2-on

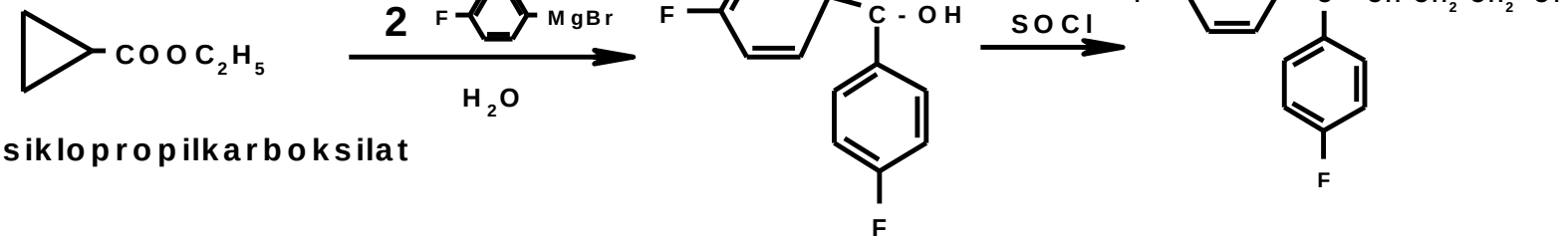
Penfluridol



1-[4,4-Bis(4-fluorofenil)bütil]-4-[4-kloro-3-trifluoro-metilfenil]-4-hidroksipiperidin

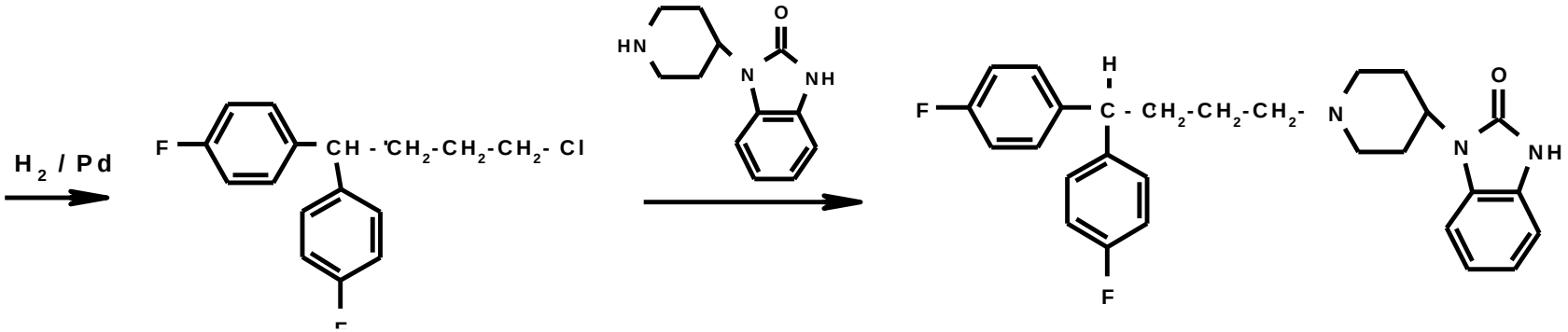
They have a long acting periods.

More selective effect on dopaminergic receptors.



Etil siklopropilkarboksilat

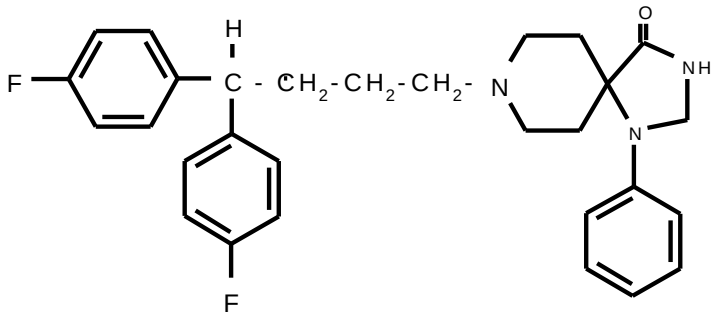
Bis-(4-fluorofenil)-siklopropil hidroksimetan



4-[bis(4-fluorofenil)]bütilklorür

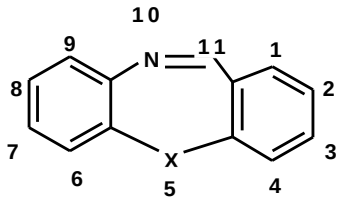
Pimozid

Fluspirilen



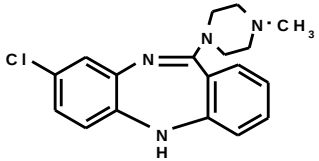
Fluspirilene is a long-acting injectable antipsychotic agent used for chronic schizophrenia.

V- Dibenzodiazepine and Dibenzooxazepine Derivatives



X = O, CH_2, S, N

Klozapin (Leponex (R) tb., Clonex (R) tb.)



8-kloro-11-(4-metilpiperazin)-5H-dibenzo [b,e] 1,4-diazepin

Loksapin ⟹ 5. konumunda -O- taşır

-Because clozapine is more effective at D1 and D4 receptors, side effects are less pronounced.

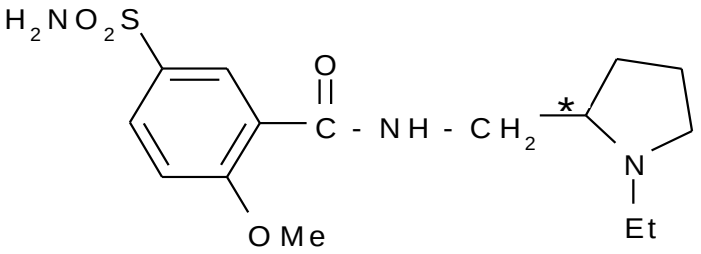
-35 mg clozapine = 100 mg chlorpromazine

-It is contraindicated in agranulocytosis, dialysis, bone marrow depression, chemotherapy, coma, under 1 year of age, and leukemia.

The efficacy and side effects of clozapine and loxapine are different each other.

VI - Benzamit Türevleri

Sulpirit < Meresa(R), Zeprid(R) tb., cap., amp.,)



N-[(1-etil-2-pirrolidinil)metil]-5-aminosülfonil-2-metoksi benzamit

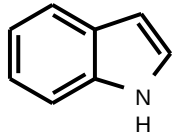
Sultopirit ⟹ aminosülfonil (NH_2-SO_2-) yerine etilsülfonil taşır (Et - SO_2 -)

-Levojir enantiomer (ℓ, -) is responsible from efficacy.

-Sulpirit is used in depressive disorders, vertigo and schizophrenia.

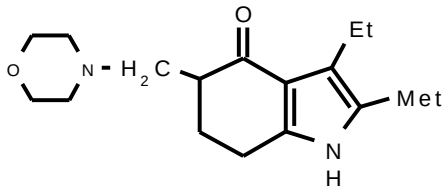
- It is selective for D2.

VII - İndol Türevleri

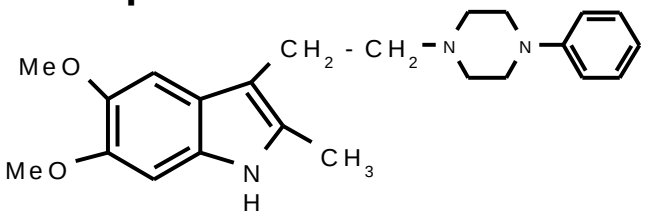


indol

Molindon



Oksipertin



Molindon is similar to phenothiazines.

Extrapyramidal side effects are stronger and anticholinergic effects are less.