Lead Modification (or Lead Optimization)

Objectives: Once a lead compound has been identified it must be systematically altered to obtain the desired properties (maximize the therapeutic index and minimize side effects). Alternatively, a known agonist or substrate can be structurally modified to make an antagonist or an inhibitor by maintaining the structural characteristics associated with binding and specificity but not "activation" of the biological activity (e.g. the HIV protease inhibitors where the lead compound was the substrate). At the end of this lecture the student will know the concepts of therapeutic index and of the pharmacophore, based on the opioids, and the traditional methods used for optimization of lead compounds to improve their biological activity.

Oral contraceptives are an example

biochemical pathway: regulation of menstration and pregnancy
steriods (e.g. progesterone) identified as mediating compounds; therefore used as lead compounds
modification of physiological steroids leads to active agents (contraceptives)

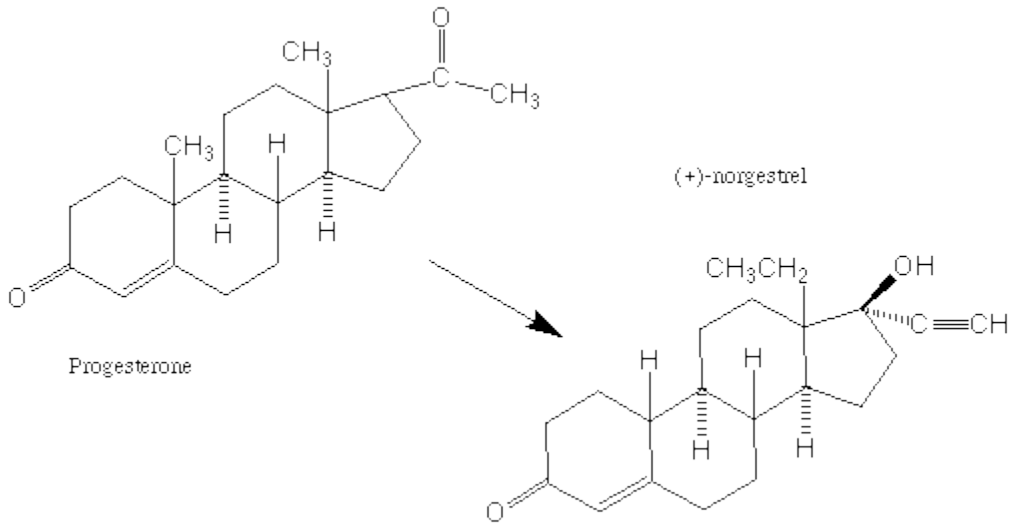


Figure 1) Structures of progesterone and (+)-norgestrel

Therapeutic index (therapeutic ratio)

measure of the ratio of undesirable to desirable drug effects (**multiple bioassays**)
in vivo: LD_{50}/EC_{50} = therapeutic index
LD_{50}: the lethal dose for 50 % of the test animals
EC_{50}: the effective dose that produces the maximum therapeutic effect in 50% of the test animals

the larger the therapeutic index the greater the safety of the drug: **goal of lead optimization**

Pharmacophore (similar to SAR with sulfa drugs)

Functional group types (e.g. hydrogen bond donors, acceptors, hydrophobic regions) and the spatial arrangement of those groups on a molecule that interact with the receptor and are responsible for binding and biological activity.

Ideally separate the binding pharmacophore from the activity pharmacophore to design a compound that binds but does not cause the biological activity (antagonist). For example, with the opioids, determine the individual pharmacophores for the analgesic and addictive properties.

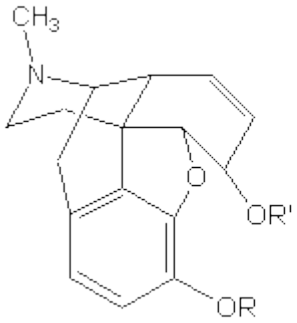
First identify the pharmacophore and then design compounds that systematically deviate from the pharmacophore to obtain desired efficacy.

Pharmacophore identification via functional group modification

1) systematically alter or remove portions of the molecule
2) identify regions essential for activity (or different types of activities)
3) note that pharmacological data is sometimes ambiguous (i.e. data is not clear cut yes or no, but often somewhere in between), requiring care when interpreting relationships of structure to activity.

Opioids as an example (morphine)

Note that physiological substrates for opioid receptors were not known for many years (endorphins, enkephalins, dynorphins and others).



Morphine: R = H, R' = H

Codeine: R = CH_3, R' = H

Heroin: R = $COCH_3$, R'=$COCH_3$

Figure 2) Structure of morphine, codeine and heroin

1) Remove tetrahydrofuran ring and hydroxyl at R'

i) levorphanol
ii) 3-4 times more potent as an analgesic than morphine
iii) maintains addictive properties
iv) therefore, tetrahydofuran ring and R' hydroxyl not essential for activity

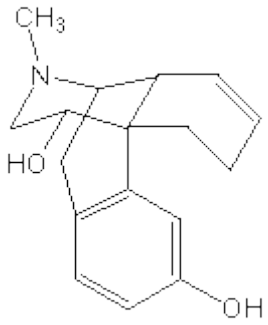


Figure 3) Structure of levorphanol

2) Removal of half of the cylcohexene ring

i) benzomorphan: partial separation of analgesic and addictive properties
ii) cyclazocine and pentazocine: much lower addictive properties
iii) therefore, cyclohexene ring contributes to the addictive properties

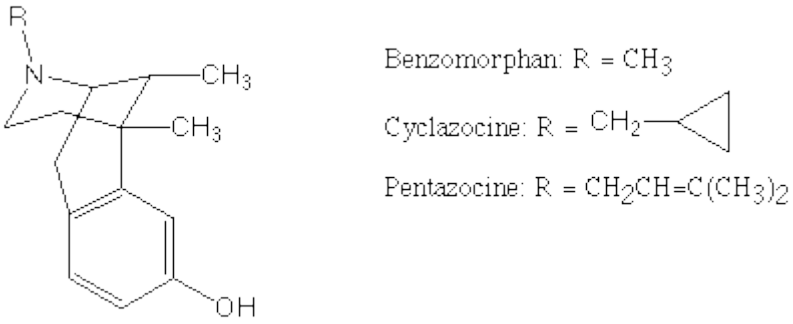


Figure 4) Structures of benzomorphan, cyclazocine and pentazocine

3) Removal of all fused rings

i) Demerol: 10-12% potency of morphine
ii) therefore, final fused ring not essential for analgesic activity

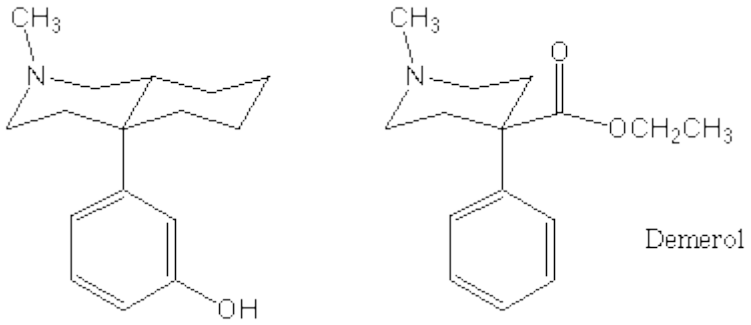


Figure 5) Structure of Demerol and related compound

3b) Analgesic activity is still retained in many acyclic analogs due to the ability of those compounds to assume a conformation similar to that of the cyclohexane ring

i) Darvon: 1/2 to 2/3 as potent as codeine
ii) Methadone: as potent an analgesic as morphine: less, but, still addictive
iii) therefore, conformation of the substituents, not the rings themselves are important for activity

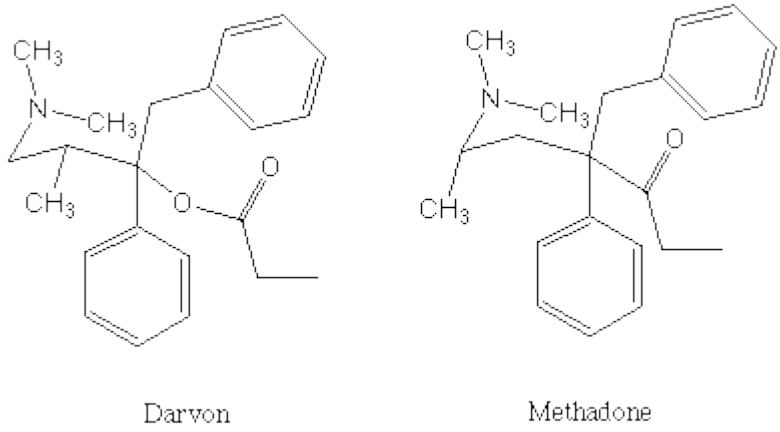


Figure 6) Structures of Darvon and Methadone

Based on these studies the **pharmacophore** of the opioids is shown below. Note that the six-membered ring that contains the nitrogen is not explicitly required for activity, just the conformational properties (space filling) associated with that type of functional group are required.

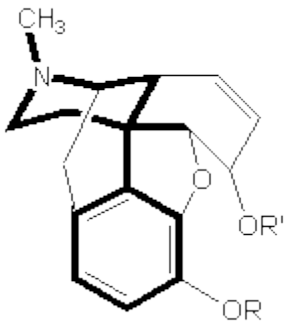


Figure 7) Structure of opioid pharmacophore (in bold, including the benzene ring at the bottom of the structure)

Note that the opioid pharmacophore presented above is based on analysis of the activity of the drug and drug analogs. A pharmacophore can also be determined based on the structure of the receptor binding site of a drug (opposite approach which will be discussed later in the course). This will be performed in the Target-Based Drug Design portion of the course.

Increase rigidity and/or structural complexity

etorphine
two-carbon bridge
substituent not in morphine
1000x more potent than morphine
used in veterinary medicine to tranquilize large animals

buprenorphine
10 - 20 times more potent than morphine
low addictive potential
recently indicated as a therapeutic agent for the treatment of heroin addiction

see http://www.nida.nih.gov/ResearchReports/Heroin/heroin5.html

rigidity increases potency (if the rigid conformation is the active conformation!)

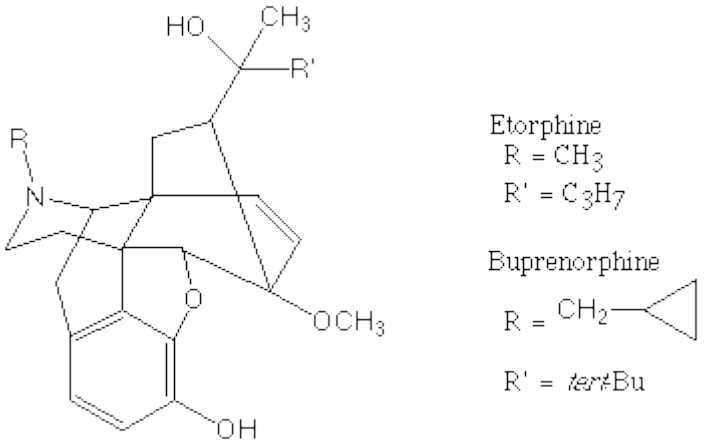


Figure 8) Structures of etorphine and buprenorphine

Functional group modification

Antihypertensive versus diuretic biological activities (note the sulfa drug pharmacophore)

Chlorothiazide
- antihypertensize
- strong diuretic

Diazoxide
- antihypertensize
- no diuretic activity

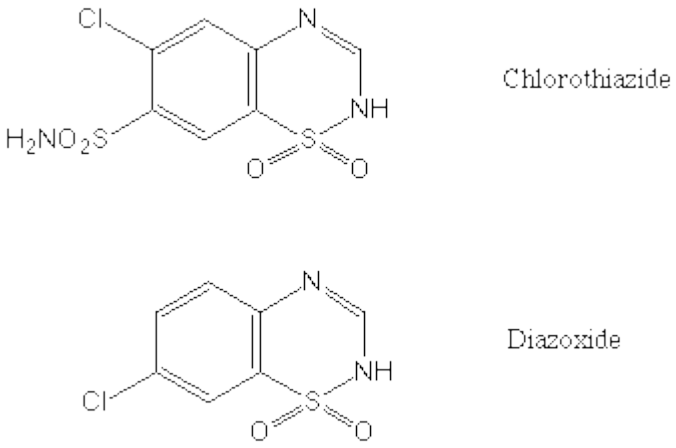


Figure 9) Structures of Chlorothiazide and Diazoxide

Need more systematic approaches to obtain information on the pharmacophore
(versus the 10,000 synthesized compounds with the sulfanilamides)

Homologation

i) Series of compounds that differ by a constant unit; generally a CH_2 group $-(CH_2)_n-$ where n is varied.
ii) Typically, an increase followed by a decrease in potency; note that the number of CH_2 groups associated with the maximum potency differs for the series of compounds under study.
iii) Changes in activity often associated with solubility/absorption issues. This will be discussed in more detail later in the quantitative structure activity relationship (QSAR) section of the course.
iv) Micelle formation of amphiphilic (lipid-like) compounds, therefore, not available to bind at receptor. This occurs when nonpolar tails are long and polar head groups are present.

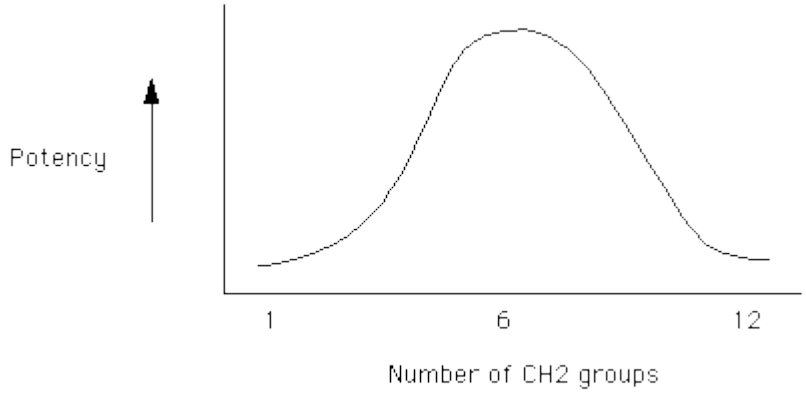
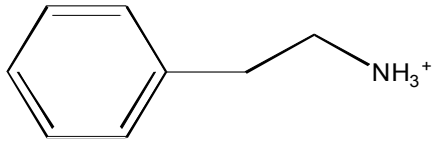


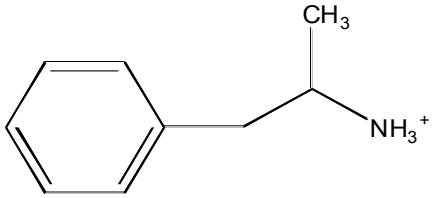
Figure 10) Relationship of potency to the number of methylene groups

Chain branching of aliphatic chains

i) Tends to make compounds more lipophilic
ii) Increased size of R-group could effect receptor binding
iii) Phenethylamine: good monoamine oxidase (MAO) substrate (therefore readily degraded) versus α-methylphenethylamine (amphetamine), which is a poor substrate
iv) Upon going from phenethylamine to amphetamine both the bioavailability and activity is altered.



Phenethyleneamine



Amphetamine

Figure 11) Structures of phenethylamine and α-methylphenethylamine (amphetamine)

Primary amines (Phenethylamine and amphetamine) are often more active than secondary amines.

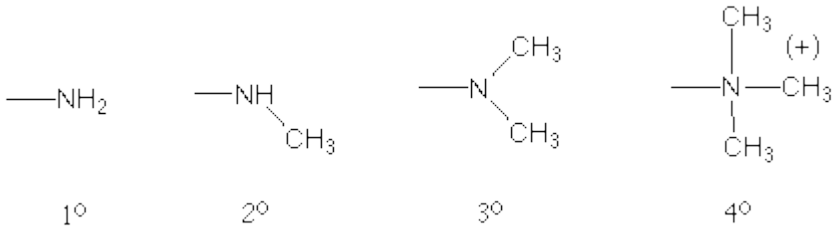


Figure 12) Primary through quarternary amines. Note that the aliphatic amines are generally protonated at physiological pH.

Note that the aliphatic amines are generally protonated at physiological pH.

Chain branching (continued)

Changing 10-aminoalkylphenothiazine R groups

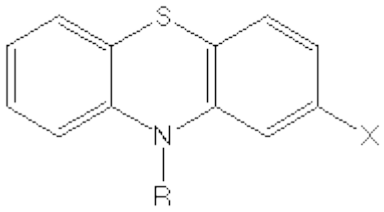


Figure 13) Structure of unsubstituted 10-aminoalkylphenothiazine

1) -$CH_2CH(CH_3)N(CH3)_2$ (promethazine)
2) -$CH_2CH_2N(CH_3)_2$ (diethazine)
   for 1 and 2: antispasmodic and antihistaminic
3) -$CH_2CH_2CH_2N(CH_3)_2$ (promazine)
   decreased antispasmodic and antihistaminic activities
   has sedative and tranquilizing activities
4) -$CH_2CH(CH_3)CH_2N(CH_3)_2$ (trimeprazine)
   reduced tranquilizing activity
   antipruritic (anti-itch) activity

Ring-Chain Transformations

Change alkyl substituent into cyclic analogs (or vice versa)
Promazines: the following 2 drugs, chloropromazine and an analog, are equivalent as animal tranquilizers

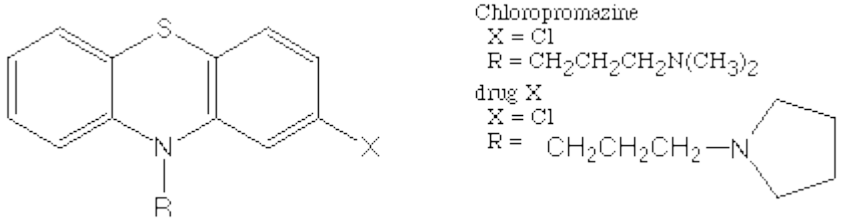


Figure 14) Structures of chloropromazine and an analog with cyclic substitutent at the R position

The following two drugs, trimeprazine and methdilazine, are equivalent as antipruritic agents in humans

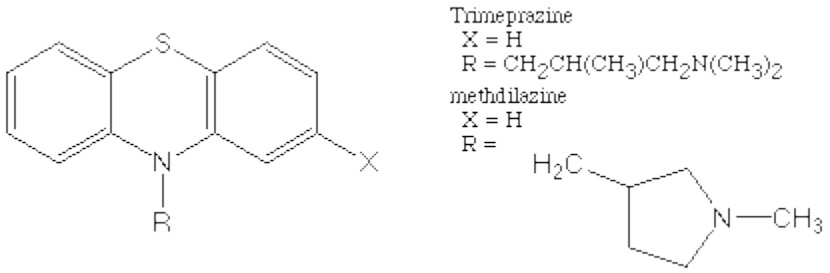


Figure 15) Structures of trimeprazine and methdilazine

Isosteres

i) Functional groups with similar properties (structural or chemical, such as hydrogen bonding ability).
ii) Often used to modify lead compound activity (i.e. fine tune biological activity) in order to
minimize toxicity
alter metabolism
maximize bioavailability

Classical isosteres

i) groups that have the same number of valence electrons but may have different numbers of atoms
ii) atoms, ions or molecules in which the peripheral layers of electrons can be considered identical

Examples of classical isosteres

Univalent atoms and groups (note the same number of total or valence electrons)
Series A) CH_3 NH_2 OH F Cl
Series B) Cl PH_2 SH
Series C) Br *i*-Propyl
Series D) I *t*-Butyl

Bivalent atoms and groups
Series A) -CH_2- -NH- -O- -S- -Se-
Series B) -$COCH_2R$ -CONHR -CO_2R -COSR

Trivalent atoms and groups
Series A) -CH= -N=
Series B) -P= -As=

Tetravalent atoms
Series A) C Si
Series B) =C= =N=(+) =P=(+)

Ring equivalents (functional groups that are in the rings)
Series A) -CH=CH- -S- (e.g. benzene versus thiophene)
Series B) -CH= -N= (e.g. benzene versus pyridine)
Series C) -O- -S- $-CH_2-$ -NH- (e.g. tetrahydrofuran vs. tetrahydrothiophene vs. cyclopentane vs. pyrrolidine)

(Nonclassical) **Bioisosteres**

i) Not included with classical isosteres
ii) Will contain at least one similar physical property, although structures can differ significantly
iii) Properties considered in bioisosteres

size
shape
electronic distribution
hydrophobicity
pK_a
chemical reactivity
hydrogen bonding capacity

ring to chain transformations can be considered isosteric replacements

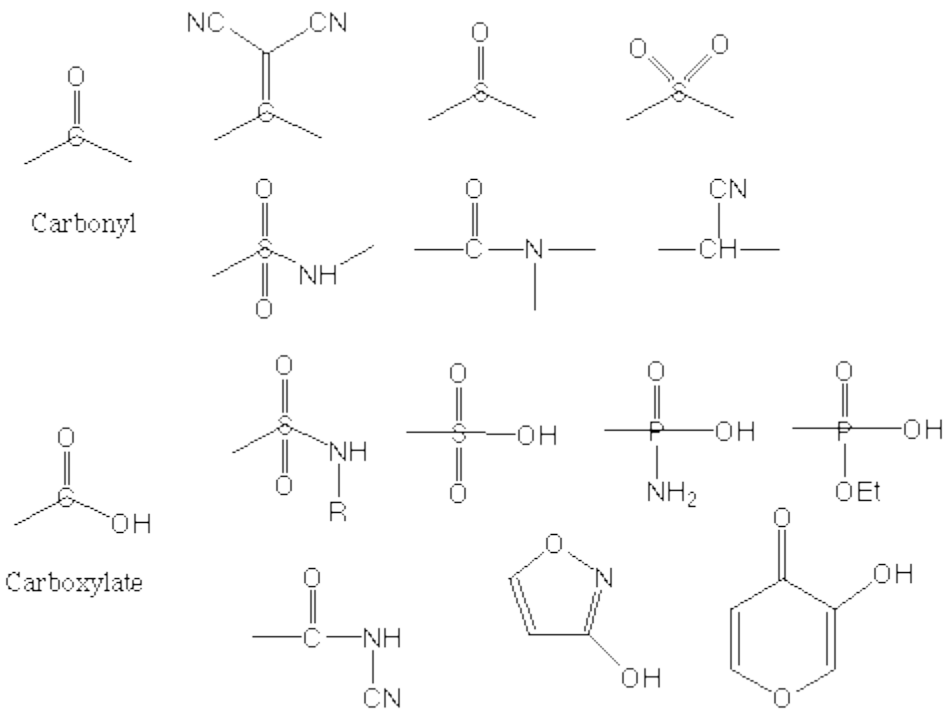


Figure 16) Examples of bioisosteres for the carbonyl and carboxylate groups

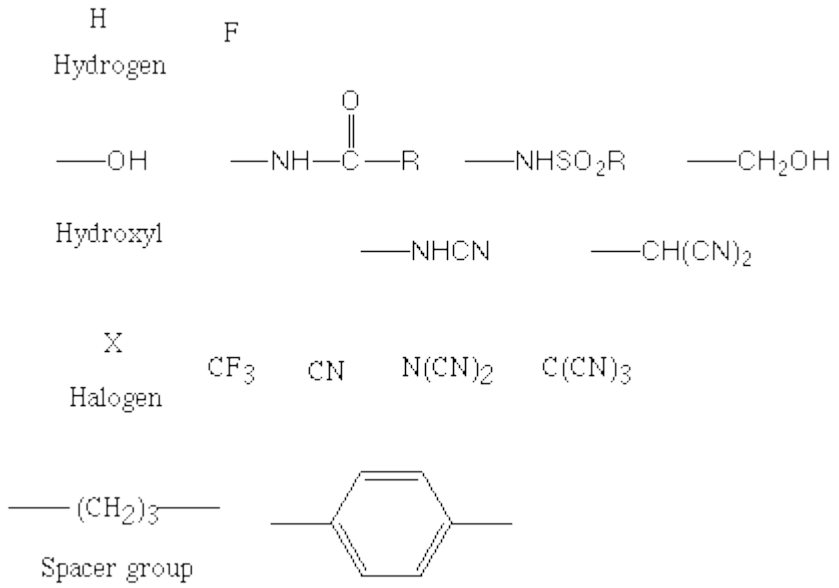


Figure 17) Examples of bioisosteres for hydrogen, hydroxyl groups, halogens, and a methylene spacer

Use of bioisosteres allows for testing the biological role of functional groups

i) Structural
change size, shape or hydrogen bonding
ii) Receptor interactions
all possible changes except hydrophobicity
iii) Pharmacokinetics (absorption, transport and excretion)
change hydrophobicity, pK_a, hydrogen bonding
iv) Metabolism (actually part of pharmacokinetics)
change chemical reactivity (oxidation, glycosylation etc.)

Example: sulfur atom to -CH=CH- or $-CH_2CH_2-$ in 10-aminoalkylphenothiazine

Normally a neuroleptic (antipsychotic) yields compounds with antidepressant activity

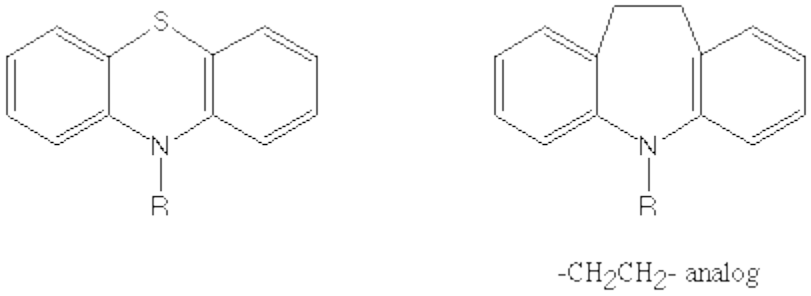


Figure 18) Comparison of 10-aminoalkylphenothiazine and the $-CH_2CH_2-$ analog