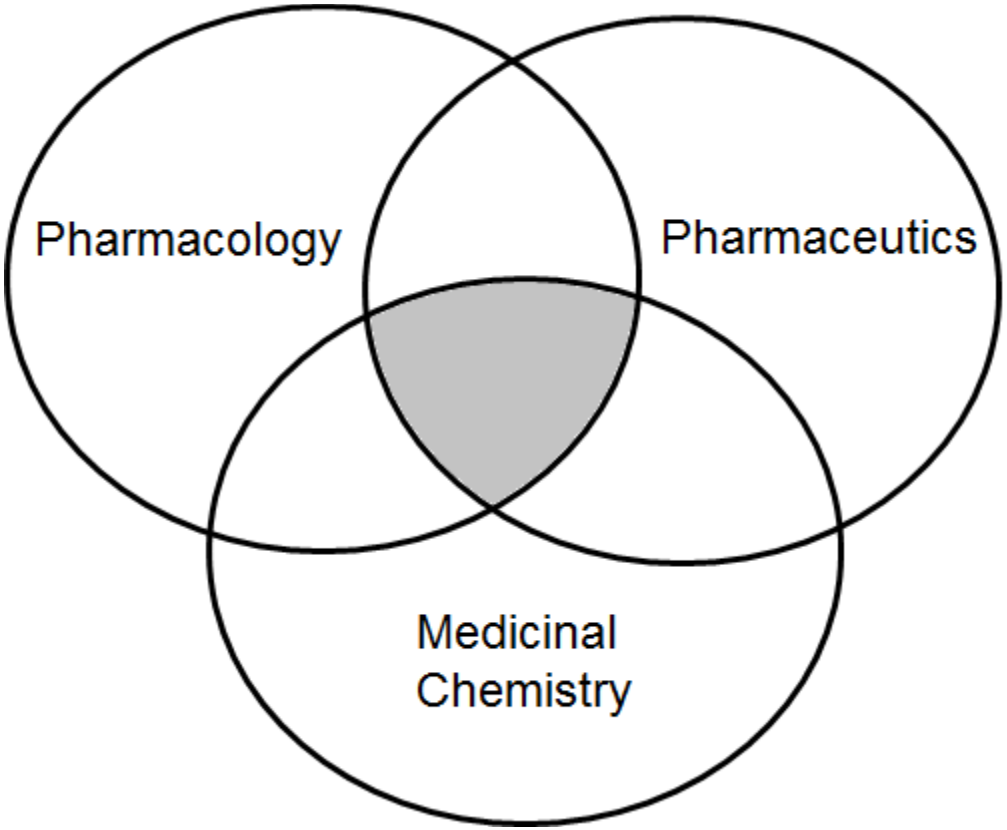
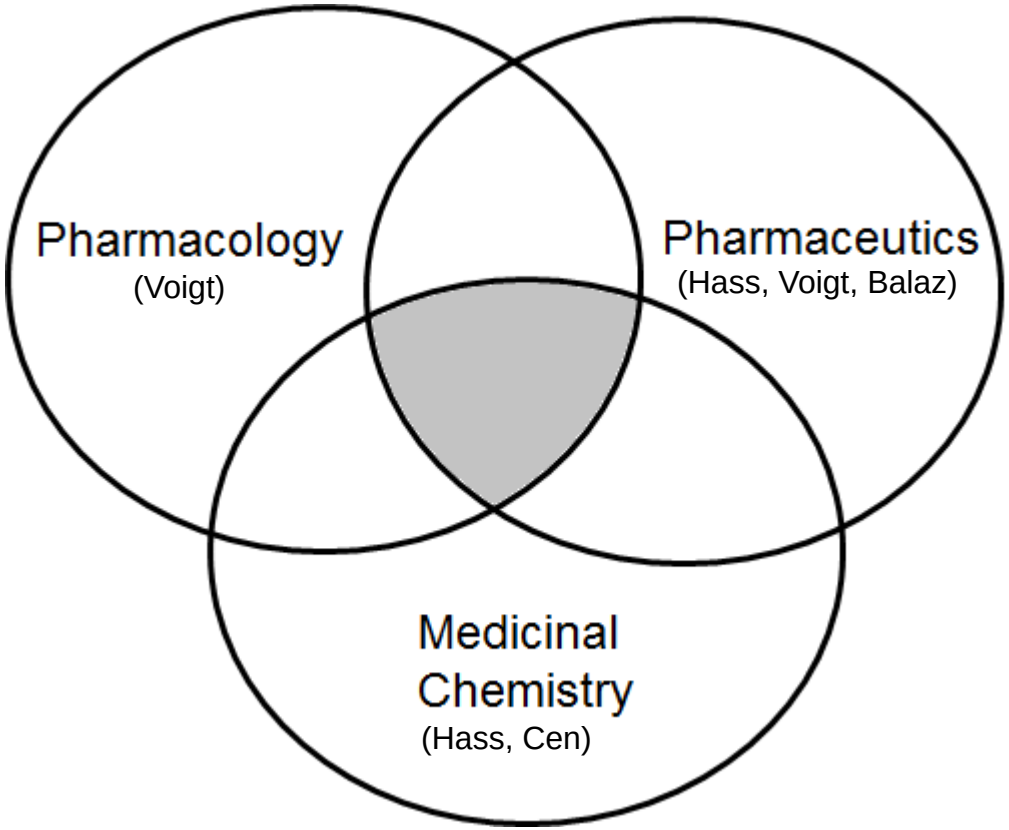
Foundations of Pharmaceutical Science



Foundations of Pharmaceutical Science



Medicinal Chemistry

Discipline of chemistry focused on the influence of chemical structure on the delivery and pharmacological activity and metabolism of drug molecules

Related Disciplines:

- Organic Chemistry
- Biochemistry
- Pharmacology
- Pharmaceutics

Medicinal Chemistry

Organic Chemistry

- Drug Structure (Functional Groups, Stereochemistry, Physiochemical Properties)
- Structure-Activity Relationships
- Drug Design and Development

Biochemistry

- Drug Transport
- Enzymes and Enzyme Activity
- Endogenous Compounds

Pharmacology (Pharmacodynamics)

- Drug-Receptor Interactions and Signal Transduction
- Dose-Response (Potency, Efficacy)
- Mechanism of Action

Pharmaceutics (ADME; Pharmacokinetics)

- Drug administraton and absorption
- Drug distribution
- Drug metabolism and excretion

Bioavailability

- The extent (how much) and the rate (how fast) that the active drug or drug metabolite reaches the systemic circulation/target site of action. action.

- Factors influencing bioavailability
  - **Drug structure/physiochemical properties**
  - Mode of administration
  - Formulation
  - Drug/food interactions
  - Disease state
  - Individual metabolic differences

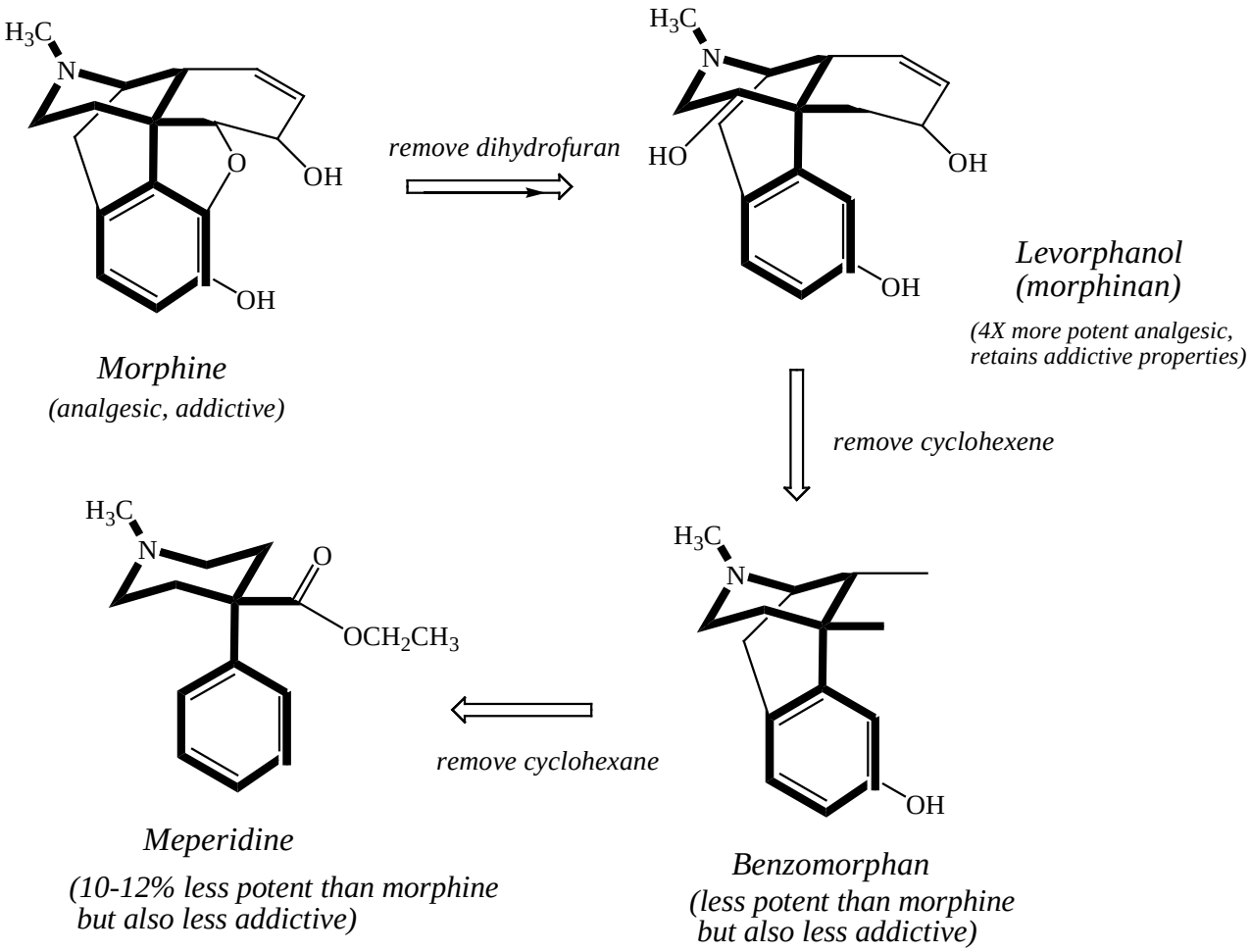
Chemical Structure & Pharmacologic Activity

Pharmacophore

The minimum structural elements, functional groups and 3D arrangement of a compound necessary to cause a biological response

Non-essential parts of the molecule are referred to as auxophore(s)

Pharmacophore revealed through systematic structural modification and pharmacologic testing


H3C
N
O
OH
OH
remove dihydrofuran
H3C
N
HO
OH
OH
Levorphanol
(morphinan)
(4X more potent analgesic,
retains addictive properties)
Morphine
(analgesic, addictive)
remove cyclohexene
H3C
N
O
OCH2CH3
H3C
N
OH
remove cyclohexane
Meperidine
(10-12% less potent than morphine
but also less addictive)
Benzomorphan
(less potent than morphine
but also less addictive)

Influence of Drug Structure

Physiochemical properties of drugs refers to the influence of functional groups on:

polarity

ionization

solubility

molecular shape

These factors influence pharmacokinetics and pharmacodynamics

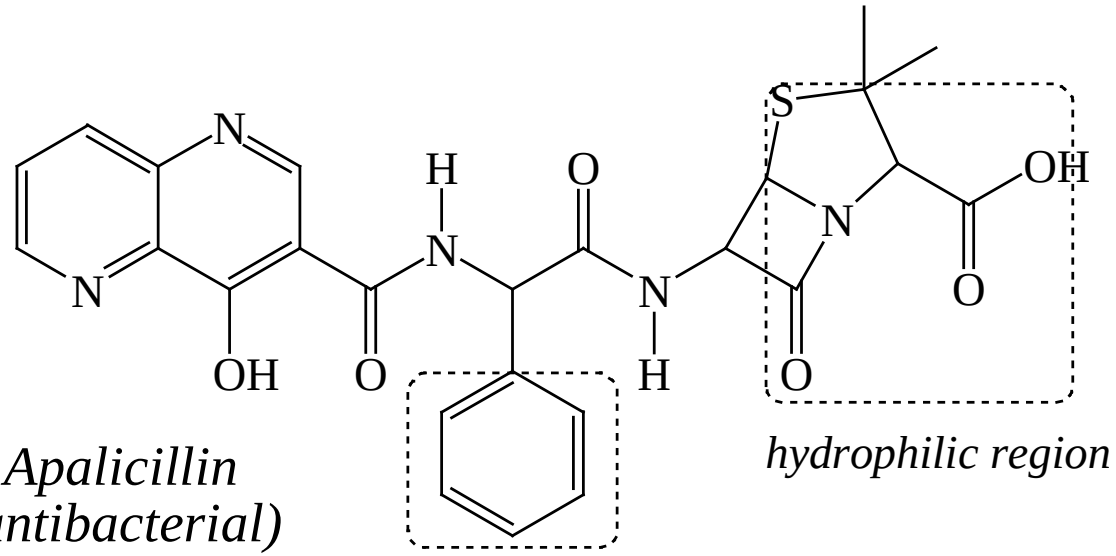
Drug Polarity

Polarity of a drug refers to the extent of charge separation in a molecule.

- Factors that decrease polarity *(lipophilic)*
  - Hydrocarbon elements

- Factors that increase polarity of a drug include: *(hydrophilic)*
  - Formal charges (ionization)
  - Polar covalent bonds
  - Lone pair electrons
  - Hydrogen bonding

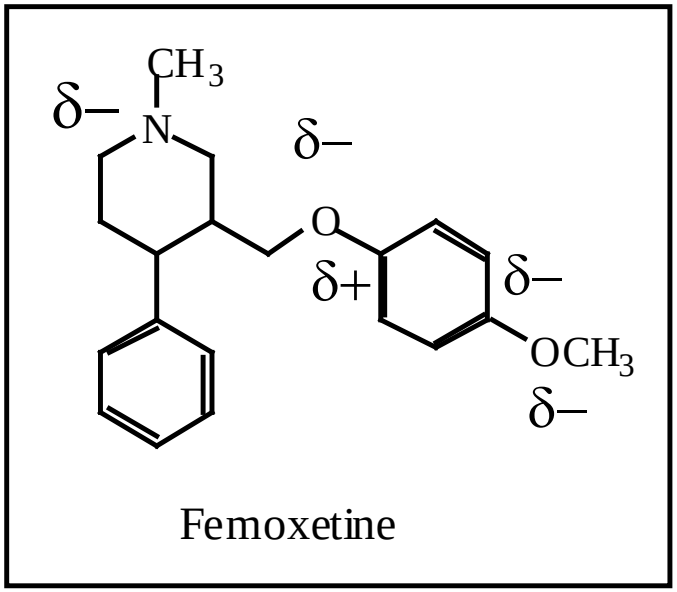
Drug Polarity



Apalicillin (antibacterial)

Both lipophilic and hydrophilic regions are present within most drug molecules

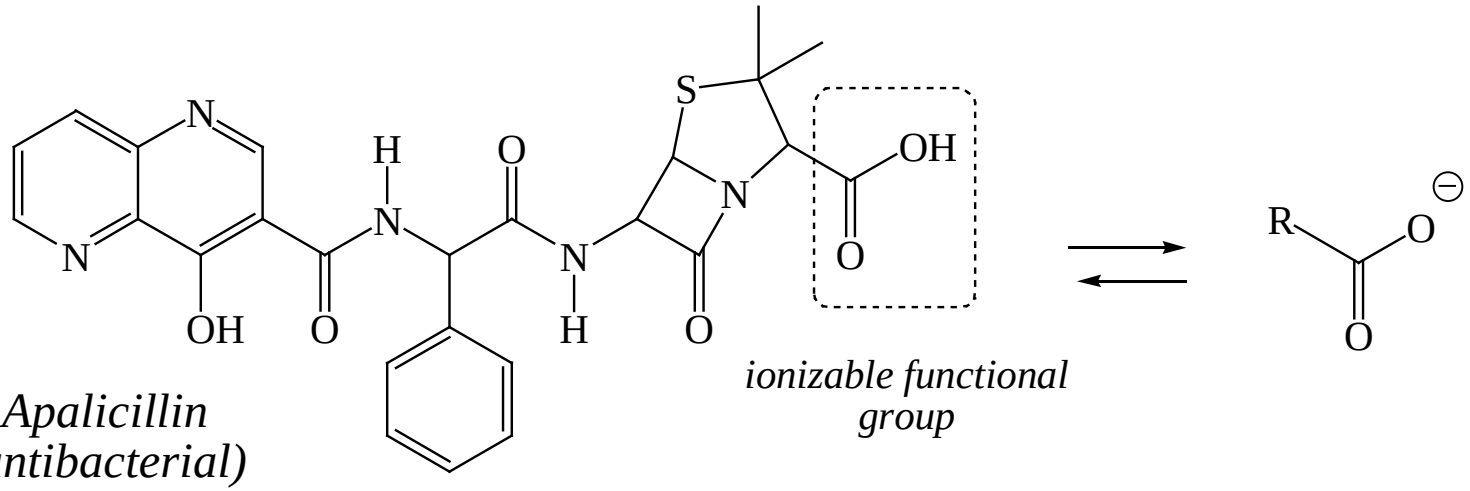
Drug Polarity



Femoxetine

Polar covalent bonds and lone pair electrons contribute to drug polarity

Drug Polarity

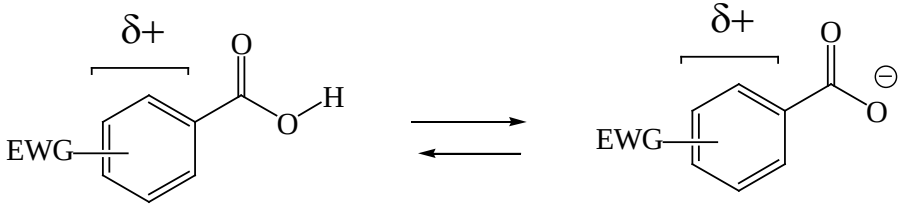


Apalicillin (antibacterial)

ionizable functional group

Ionizable functional groups have the potential of contributing to polarity by generating a formal charge

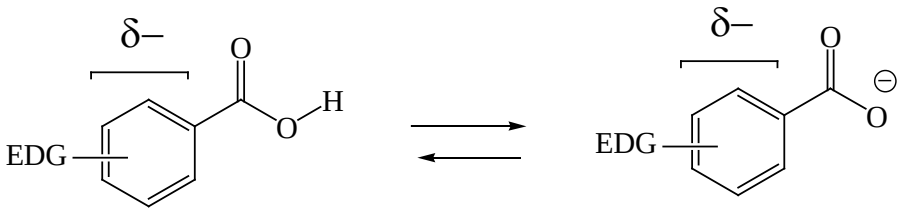
Drug Polarity



EWG = electron-withdrawing group
(i.e., nitro)

decrease electron density around ring by resonance or inductive effects

EWG: Stabilizes conjugate base
increases Ka, decreases pKa



EDG = electron-donating group
(i.e., halogens)

increase electron density around ring by resonance or inductive effects

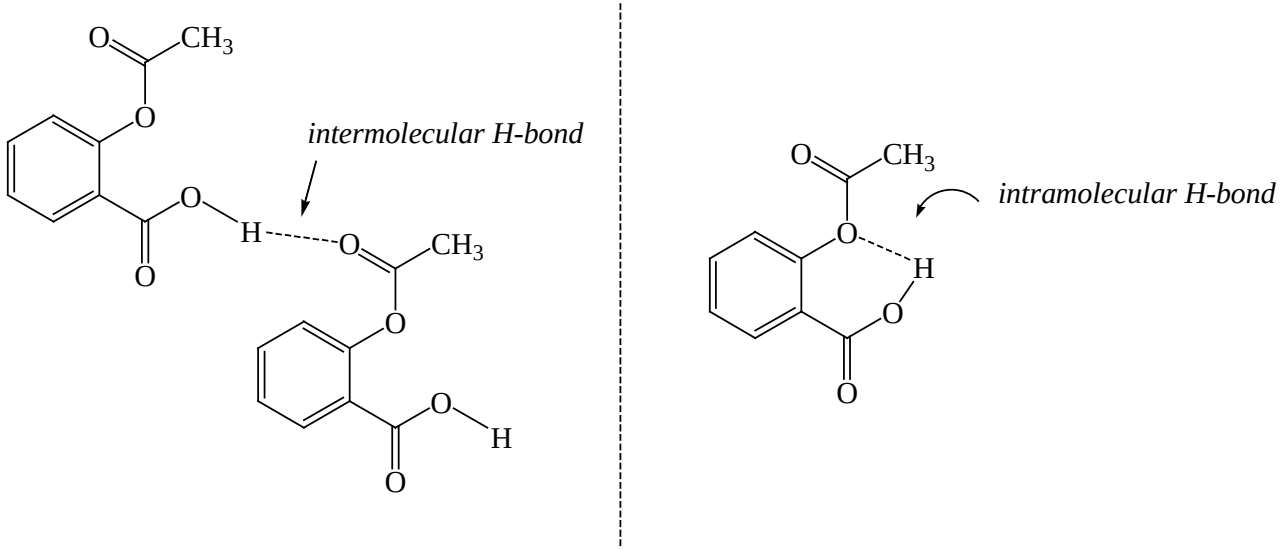
EDG: Destabilizes conjugate base
decreases Ka, increases pKa

Substituents can influence pKa and ionization

Drug Polarity

Hydrogen bonding

H-bonds are weak interactions that occur between a H atom (bonded to an electronegative element) and the lone pair electrons of another atom within the same molecule (intramolecular) or another molecule (intermolecular).



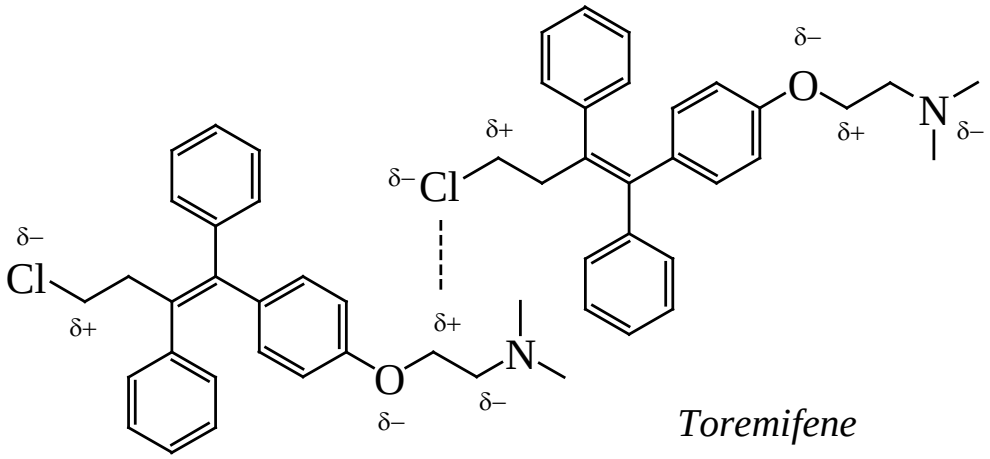
Polarity and Non-Covalent Bonding Interactions

- Non-covalent interactions are weak interactions between functional groups of like polarity within (intra) or between (inter) molecules

- Types of non-covalent interactions include:
  - H-bonds
  - Dipole-dipole
  - Ion-dipole
  - Hydrophobic Interactions

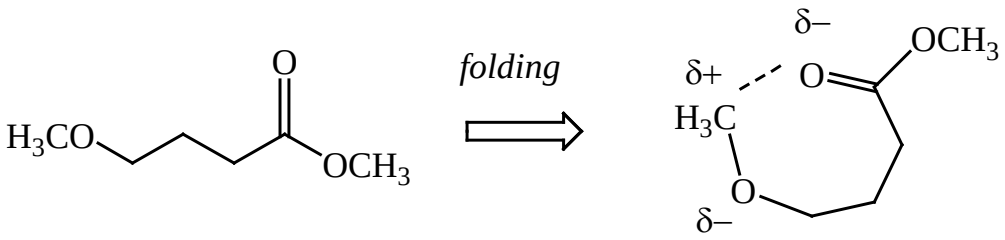
Polarity and Non-Covalent Bonding Interactions

Dipole-Dipole



Toremifene

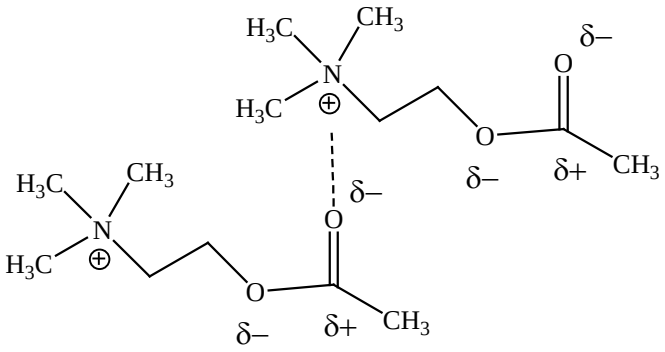
Intermolecular



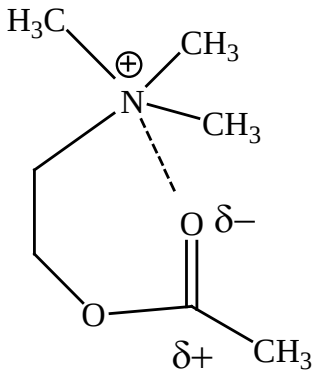
Intramolecular

Polarity and Non-Covalent Bonding Interactions

Ion-Dipole



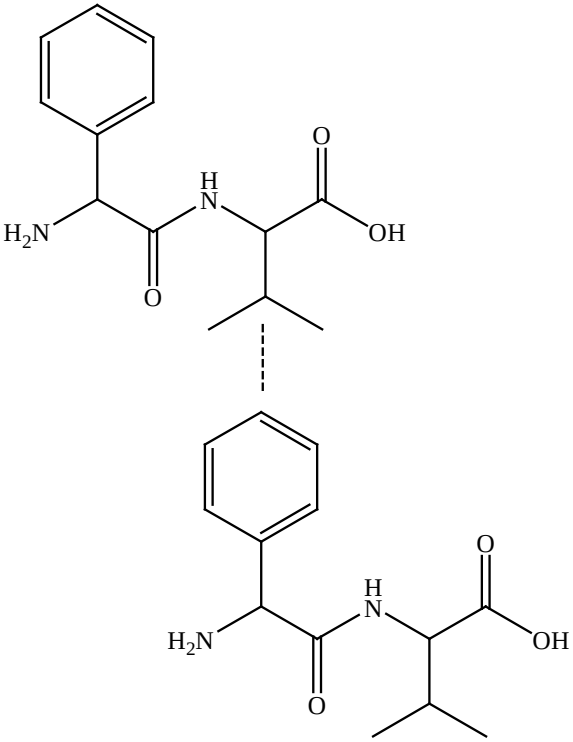
Intermolecular



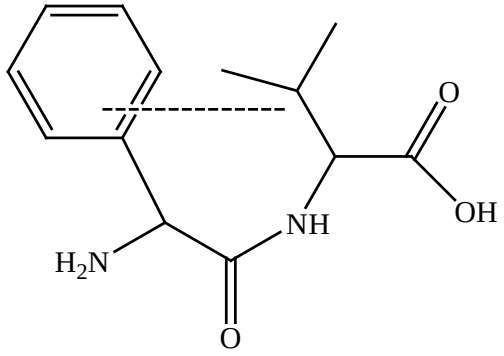
Intramolecular

Polarity and Non-Covalent Bonding Interactions

Hydrophobic



Intermolecular



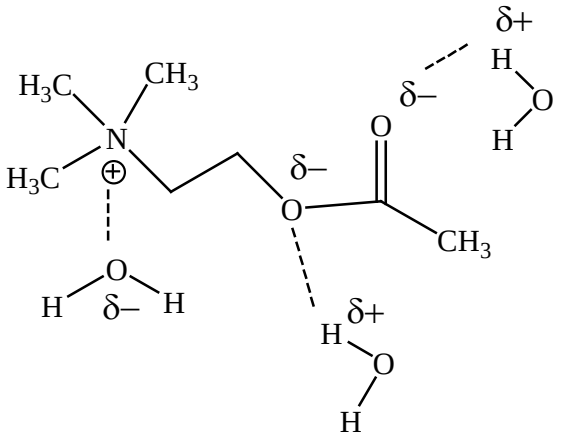
Intramolecular

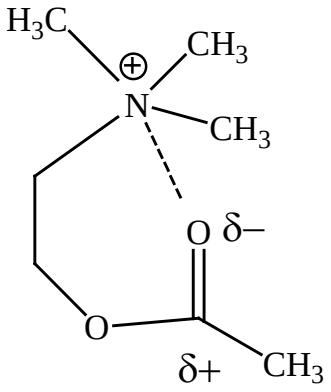
Polarity and Water Solubility

Hydrogen bonding and ion-dipole bonding contribute to water solubility

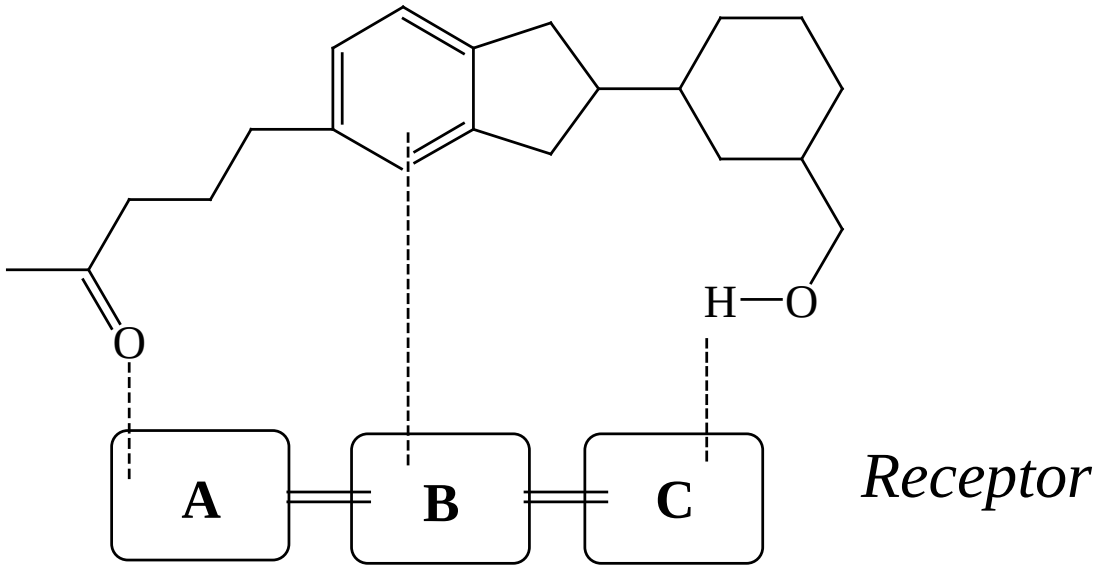
Intermolecular H-bonding between drug functional groups and water increases water solubility

Intramolecular H-bonding or ion dipole bonding within a drug does not allow solvation by water and diminishes water solubility





Molecular Shape



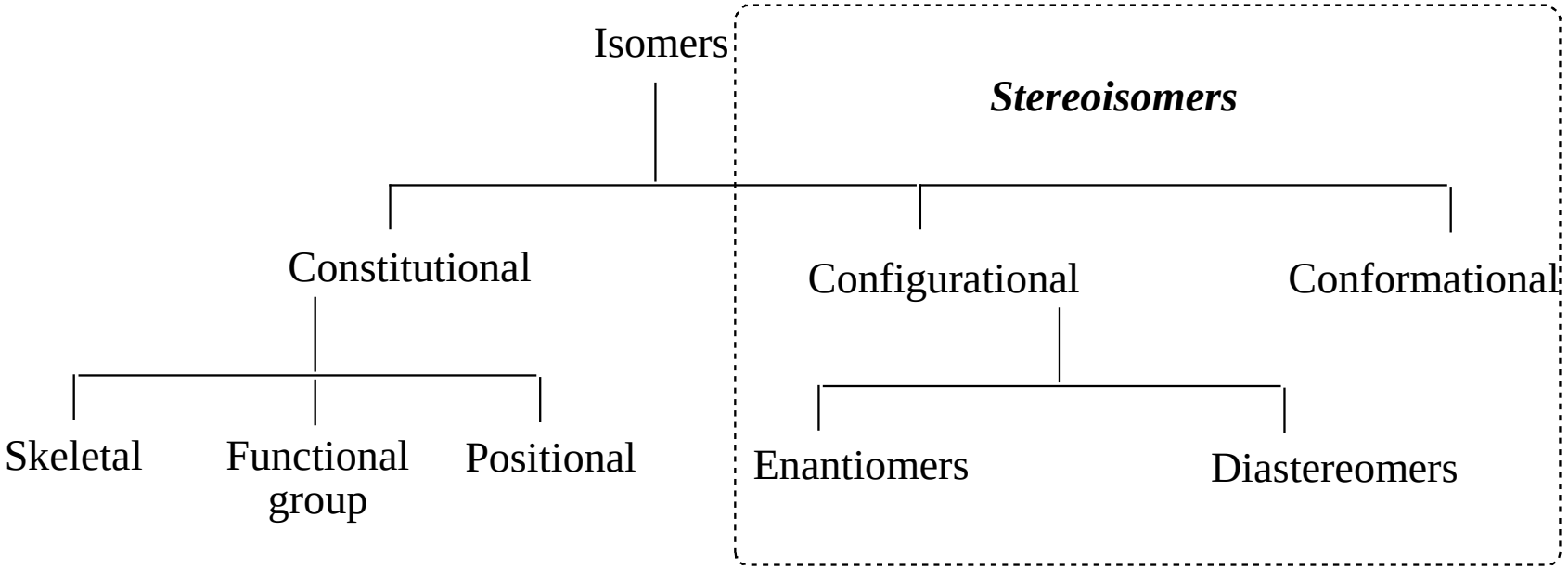
Specific functional groups on drug bind to specific sites on receptor.
Groups must be oriented properly to accommodate specific binding

Molecular Shape

- Spatial arrangement of functional groups influences physiochemical properties of drugs

- Isomers, molecules with the same molecular formula but different structural arrangement of atoms, have different physiochemical and pharmacologic properties

Isomers

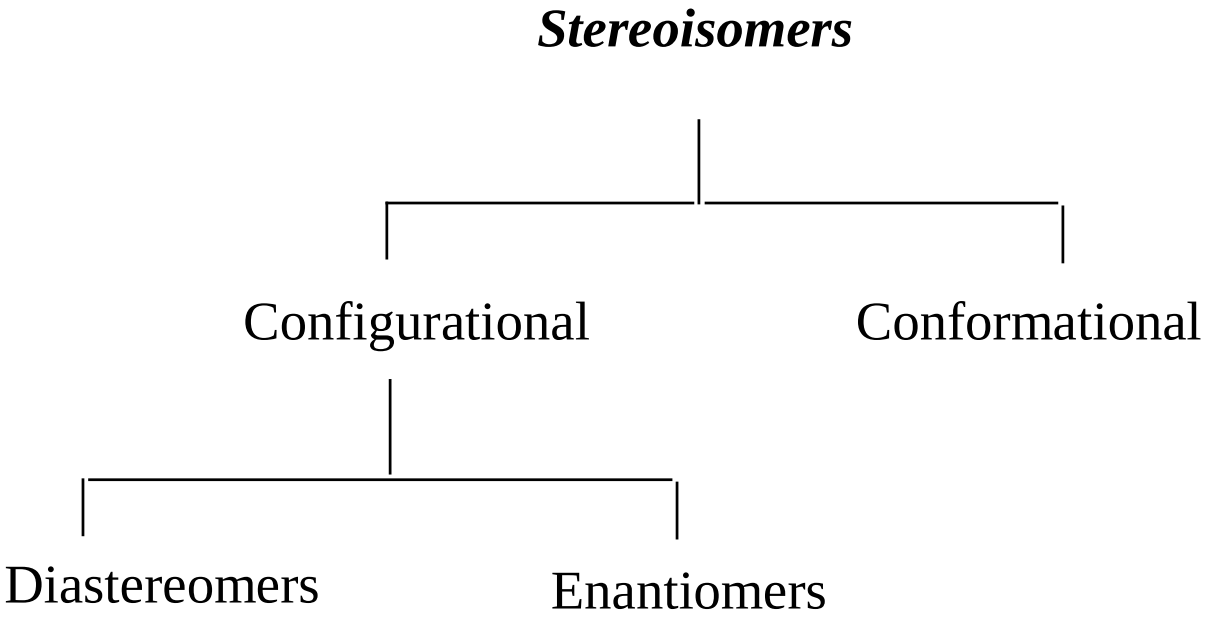


Drug isomers have the same molecular formula with a different arrangement of atoms

Stereochemistry

- Two general types of stereoisomers:
  - Configurational: same structural formula except different arrangement of atoms around a chiral element in the molecule (enantiomers, diastereomers, cis/trans isomers)
  - Conformational: same structural formula different spatial arrangements due to rotation around sigma bonds

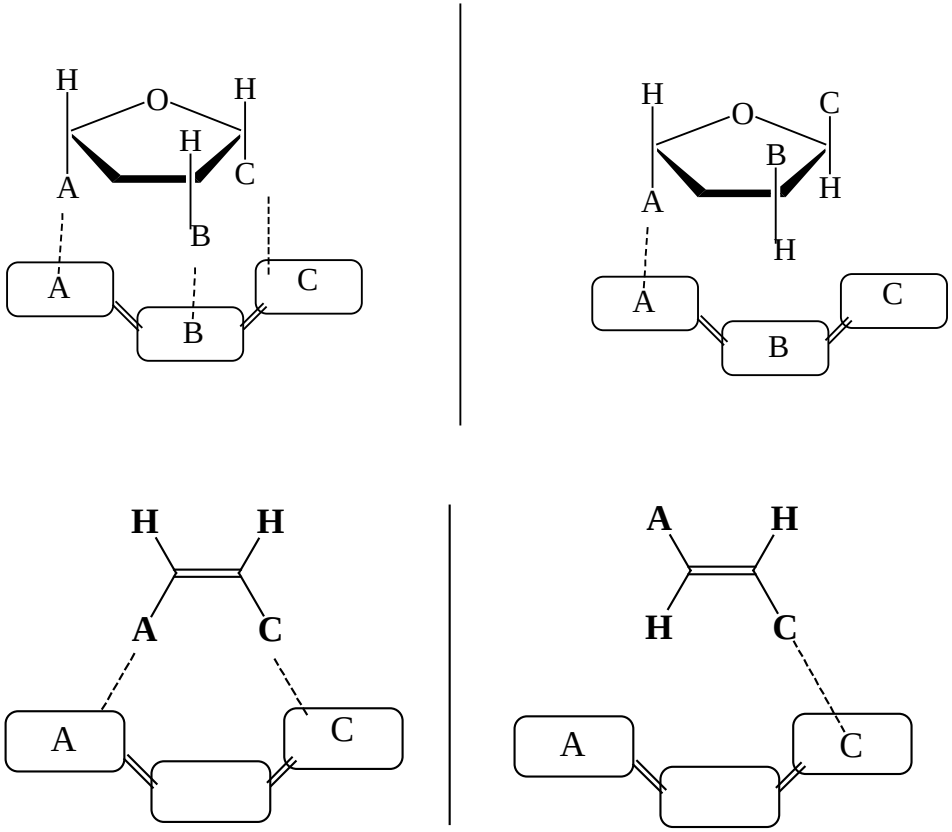
Stereochemistry



Geometric Isomers

(cis/trans; E/Z; syn/anti)

Differences in 3D orientation of functional groups results in different receptor binding



Enantiomers

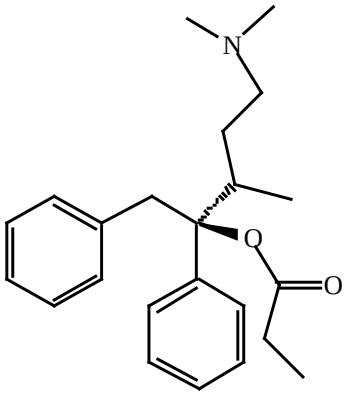
- Non-superimposable mirror image isomers that arise due to the chirality of an atom or of the overall molecule. Referred to as R/S, D/L or *d/l* (dextro/levo) isomers

- Enantiomers have identical physical properties (i.e., energy, boiling point, melting point, densities, etc.) except that they rotate the plane of polarized light in different directions.

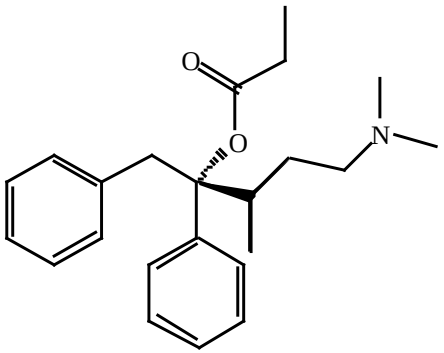
- Enantiomeric drugs do not necessarily have the same biological activity, and often have very different biological activity.

- Many drugs are sold as racemic mixtures. Racemic mixtures are 50:50 mixtures of enantiomers. FDA requires that individual enantiomers be separated and tested for biological activity even if the drug is to be sold as a racemate.

Enantiomers



(+) propoxyphene
(DARVON)

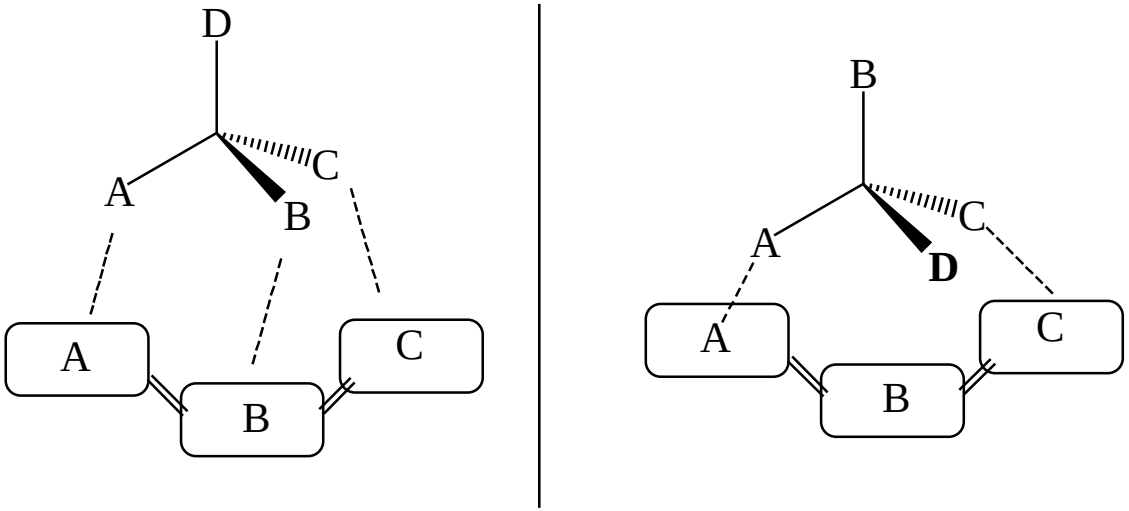


(-) levopropoxyphene
(NOVRAD)

- *d*- Propoxyphene (DARVON) and *l*- propoxyphene (NOVRAD) are enantiomers

- The d- isomer (trade name DARVON) is a narcotic analgesic. Its l- enantiomer is NOVRAD which is an antitussive agent (cough suppressant)

Enantiomers

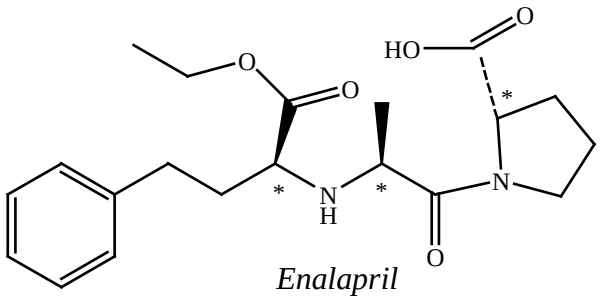


Differences in 3D orientation of functional groups around chiral center results in different receptor binding and different pharmacological activity

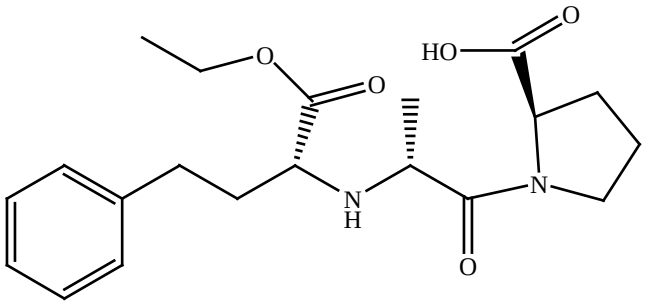
Diastereomers

- Diastereomers are non-superimposable, non-mirror image stereoisomers.
- Diastereomers arise in molecules with more than one chiral center or chiral element
- Diastereomers have different physical properties and different pharmacological activity

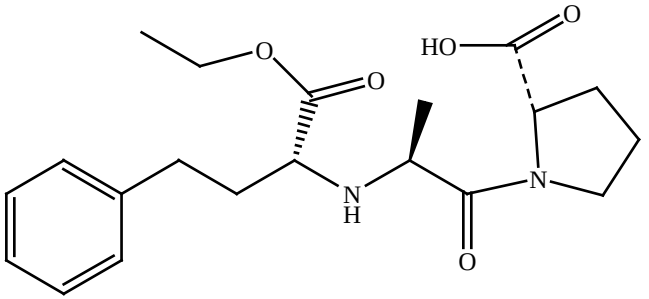
Enantiomers & Diastereomers



Enalapril
(antihypertensive)



enantiomer of enalapril



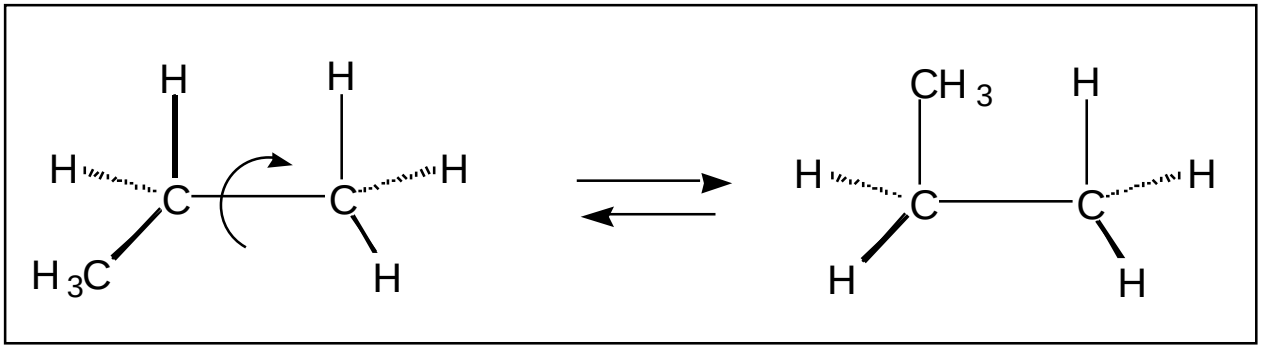
diastereomer of enalapril

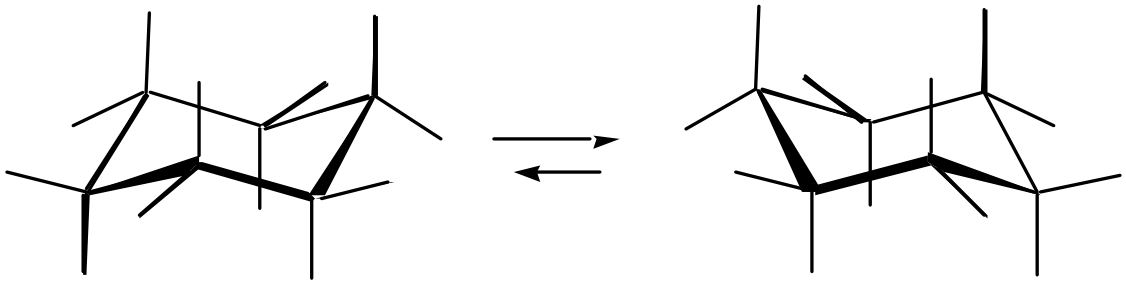
Molecules with more than one chiral center can have both enantiomers and diastereomers.

Conformational Isomers

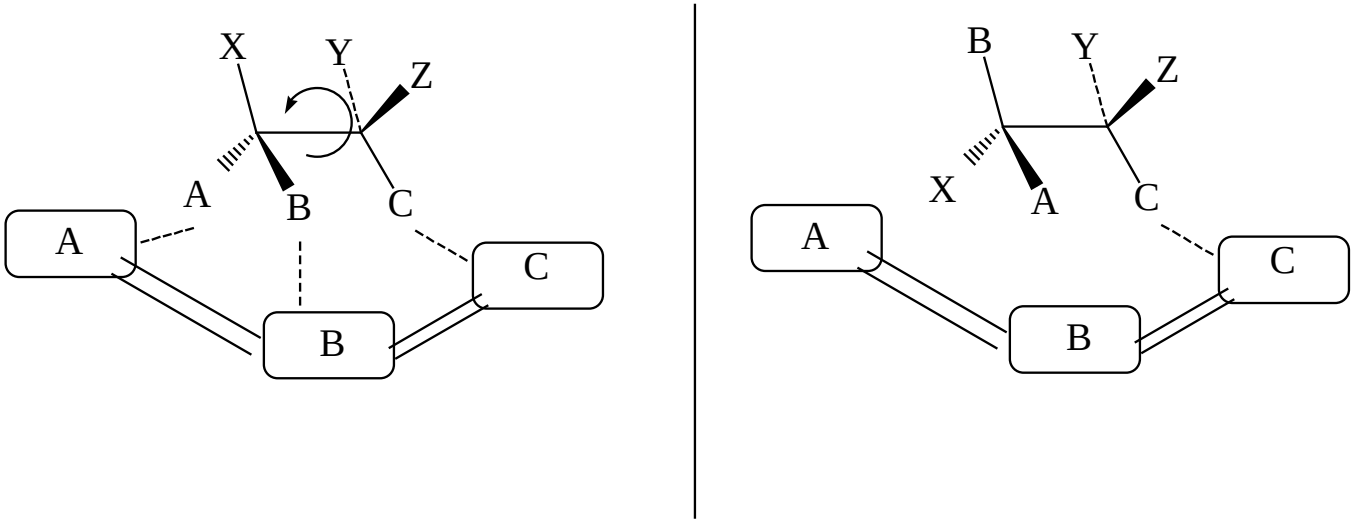
- Conformers are isomers which arise due to ***rotation*** about a carbon-carbon single bond.
- Rotation around carbon-carbon single bonds may occur without any breaking of covalent bonds.
- Some conformers or conformational isomers may experience unfavorable interactions which give rise to higher energy conditions.

Conformational Isomers



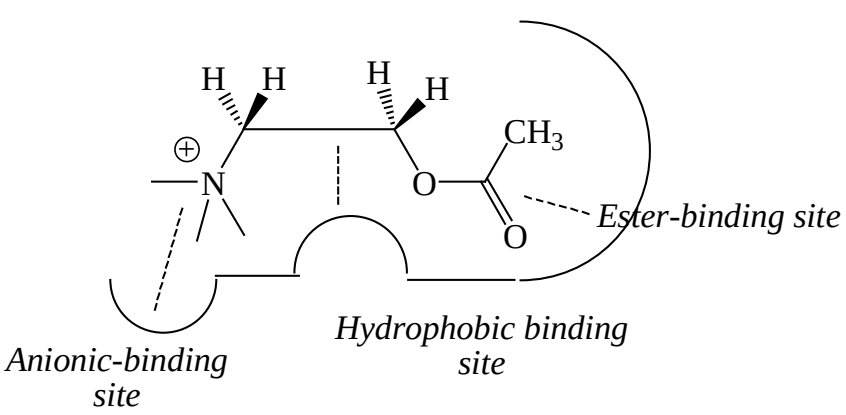


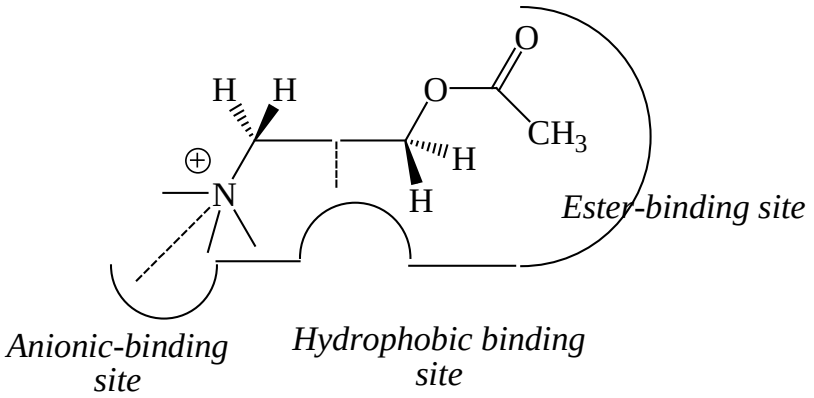
Conformational Isomers



Conformational Isomers

Acetylcholine conformers





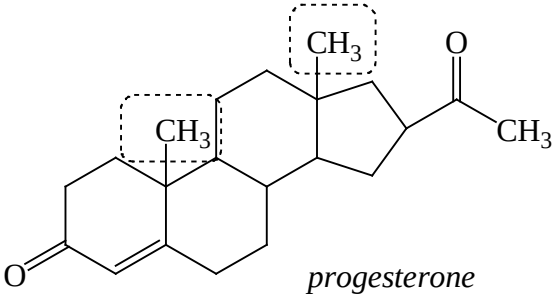
Structure Activity Relationships (SAR)

- Structurally specific drugs (majority)
  - act at a specific target site such as a receptor or enzyme to produce a biological effect
  - modification of structure gives rise to modification in activity (SAR)

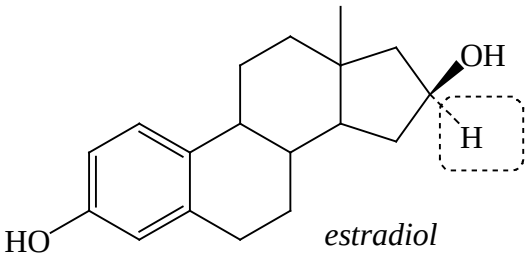
- Structurally nonspecific drugs
  - no specific site of action
  - less dependence of activity on specific drug structure

Drug Discovery
Structure Modification

Endogenous

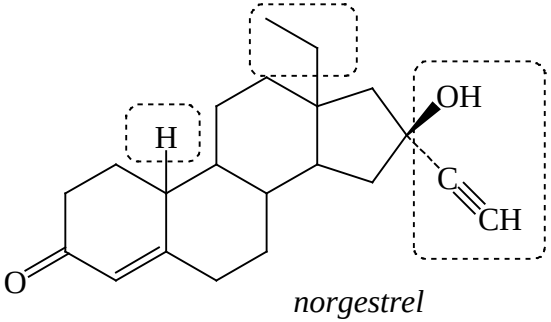


progesterone

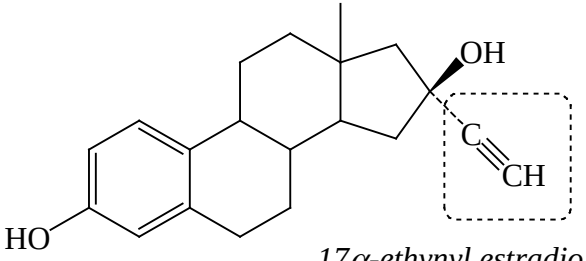


estradiol

Synthetically Modified



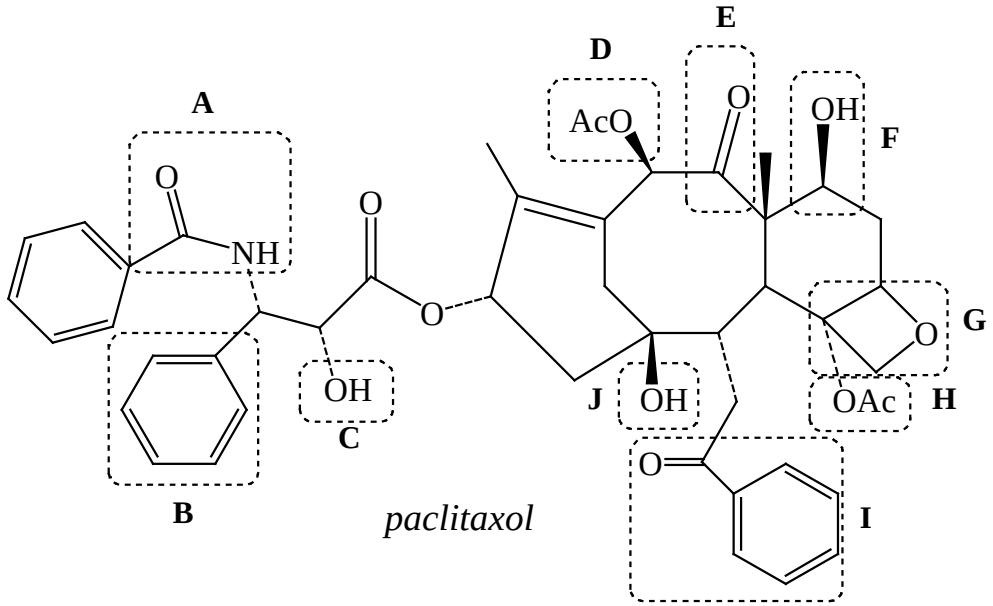
norgestrel



17α-ethynyl estradiol

Highlighted portions of molecules illustrate auxophores

Structure Activity Relationships (SAR)



A	N-acyl group required	**F**	Change of stereochemistry or esterification does not change activity
B	Phenyl or analog required	**G**	Oxetane or other small ring required for activity
C	Free hydroxyl or hydrolyzable group required	**H**	Removal of acetoxy reduces activity; other acyl analogs have improved activity
D	Acetoxy may be removed w/out loss of activity	**I**	Acyloxy required; substituted benzyloxy improves activity
E	Reduction of ketone improves activity slightly	**J**	Removal of hydroxyl reduces activity slightly

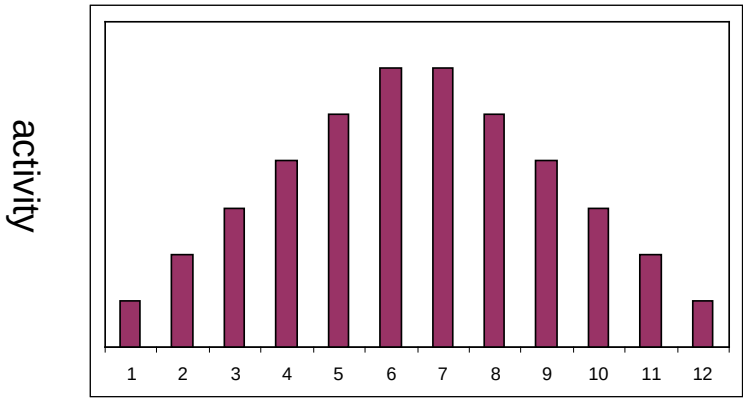
Qualitative and Quantitative SAR

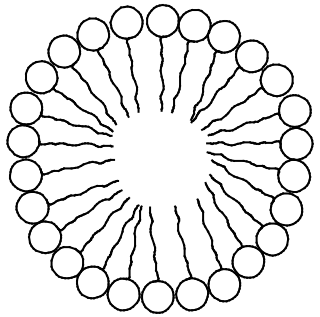
- Structural Modification of Lead Compounds (Qualitative SAR)
  - Homologation
  - Chain branching
  - Ring/chain transformations
  - Positional isomerization
  - Bioisosterism (“functional group equivalents”)

- Structural modification results in changes to pharmacodynamics (affinity, efficacy, potency) and pharmacokinetics (ADME)

Structural Modification of Lead Compounds
Homologation

- Homologation refers to progressive increases in hydrocarbon chain length ($-CH_2$ units; methyl, ethyl, propyl, etc)
- General trend is an increase followed by a decrease in activity that correlates with lipophilicity (log P)
- Increase in activity correlates with greater bioavailability. Decrease in activity occurs when reduced water solubility interferes with transport in aqueous media or formation of micelles

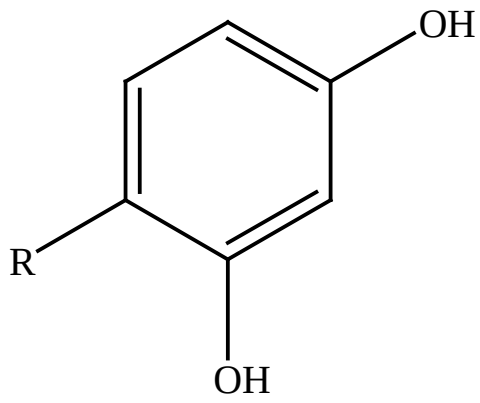




micelle

Structural Modification of Lead Compounds

Homologation



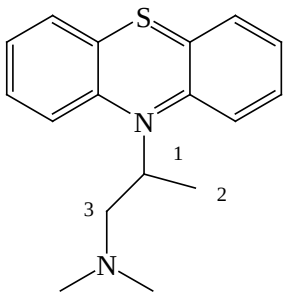
4-Alkylresorsinol antibacterial activity

R = n-propyl (5%); n-butyl (22%);
n-pentyl (33%); n-hexyl (51%);
n-heptyl (30%); n-octyl (0%)

Structural Modification of Lead Compounds
Chain Branching

- Branching imposes steric changes that affect receptor binding
- Chain branching in the aminoalkylphenothiazines promethazine and promazine results in binding to different receptors

promethazine



branched

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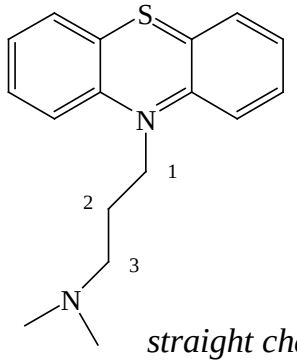
promazine

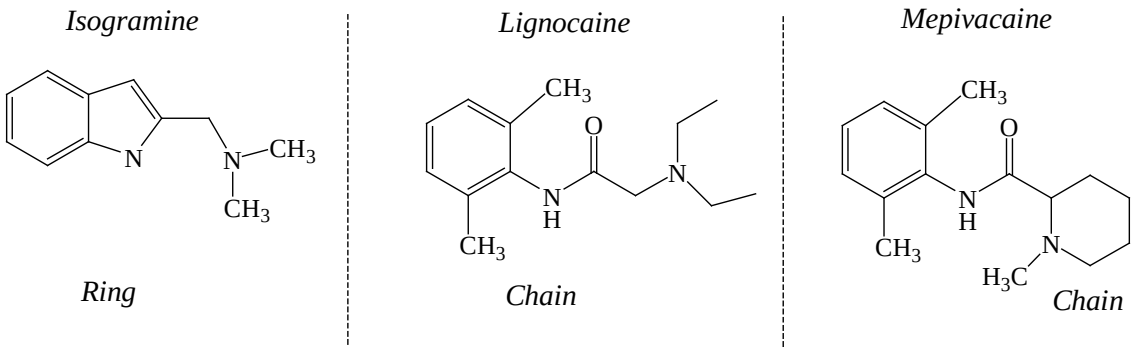


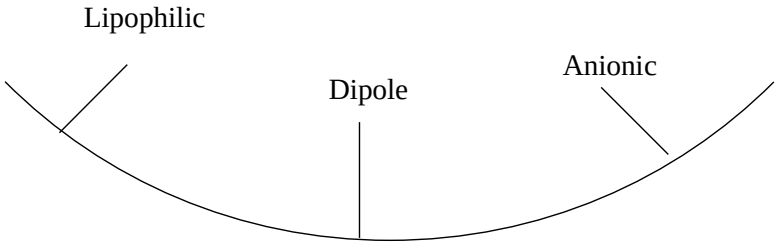
straight chain

ANTIPSYCHOTIC

Structural Modification of Lead Compounds
Ring Chain Transformations

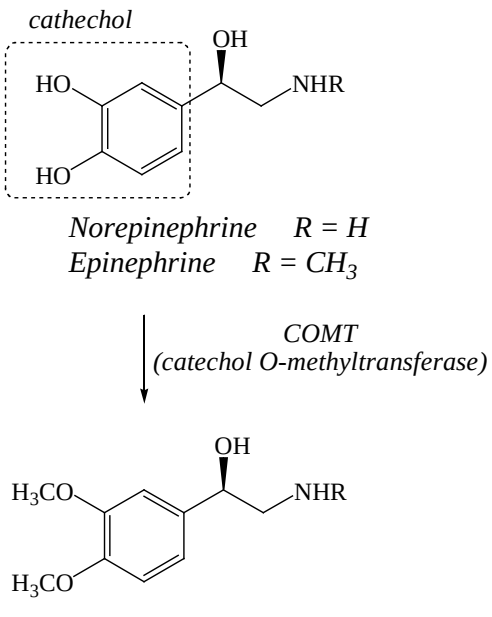
- Ring chain transformations generally provide conformational rigidity (in the ring) and conformational flexibility (in the chain)
- Ring structures in local anesthetics enhance binding at active sites in the receptor by “holding” groups in place

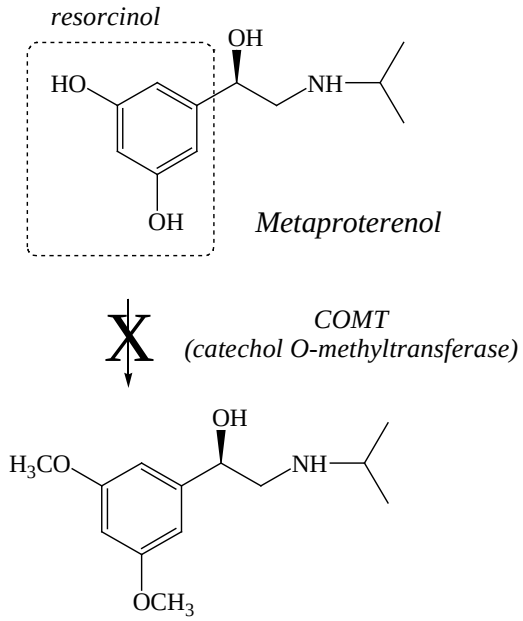




Structural Modification of Lead Compounds
Positional Isomerization

- Altering the position of functional groups modifies receptor binding and changes pharmacokinetics
- Replacement of the cathechol moeity of adrenergic agents with a resorcinol moeity enhances selectivity for β_2-adrenergic receptors
- Resorcinol derivatives have longer duration of action since the COMT enzyme does not metabolize these compounds



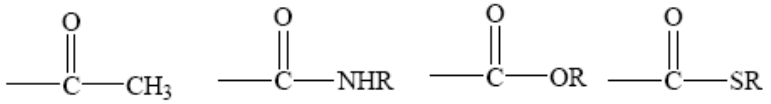
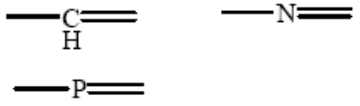
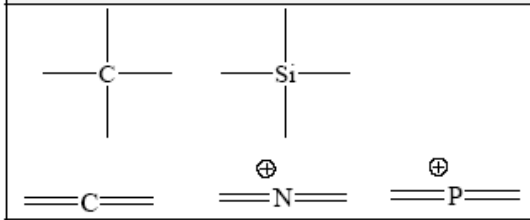
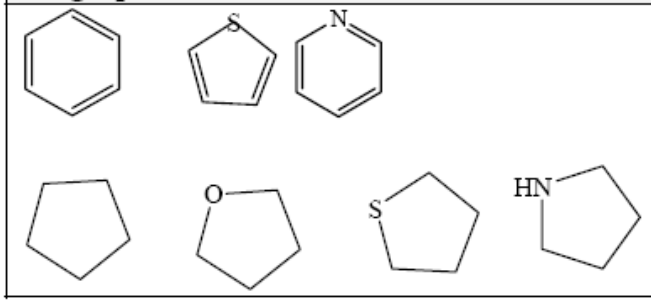


Structural Modification of Lead Compounds
Bioisosterism

- Bioisosteres are substituents or functional groups with steric and electronic similarities that produce broadly similar biological properties
- Two types of bioisosteres
  - Classical isosteres
  - Non-classical isosteres

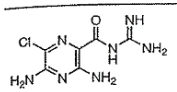
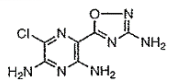
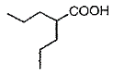
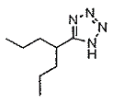
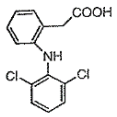
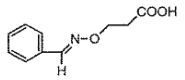
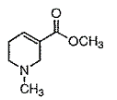
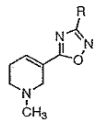
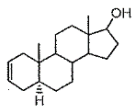
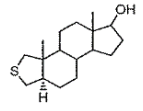
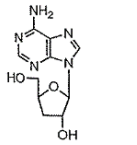
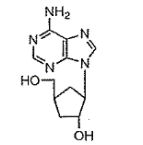
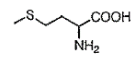
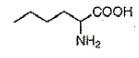
Structural Modification of Lead Compounds

Bioisosterism

Univalent
CH_3, NH_2, OH, F, Cl Cl, PH2, SH Br, iso-Pr I, t-Bu
Bivalent
$-CH_2-$, -NH-, -O-, -S-, -Se- 
Trivalent

Tetravalent

Ring equivalents


Structural Modification of Lead Compounds
Bioisosterism

Table 2.10. Nonclassical Bioisosteric Replacements

Compound	Bioisosteric Replacement
	
	
	
	
	
	
	

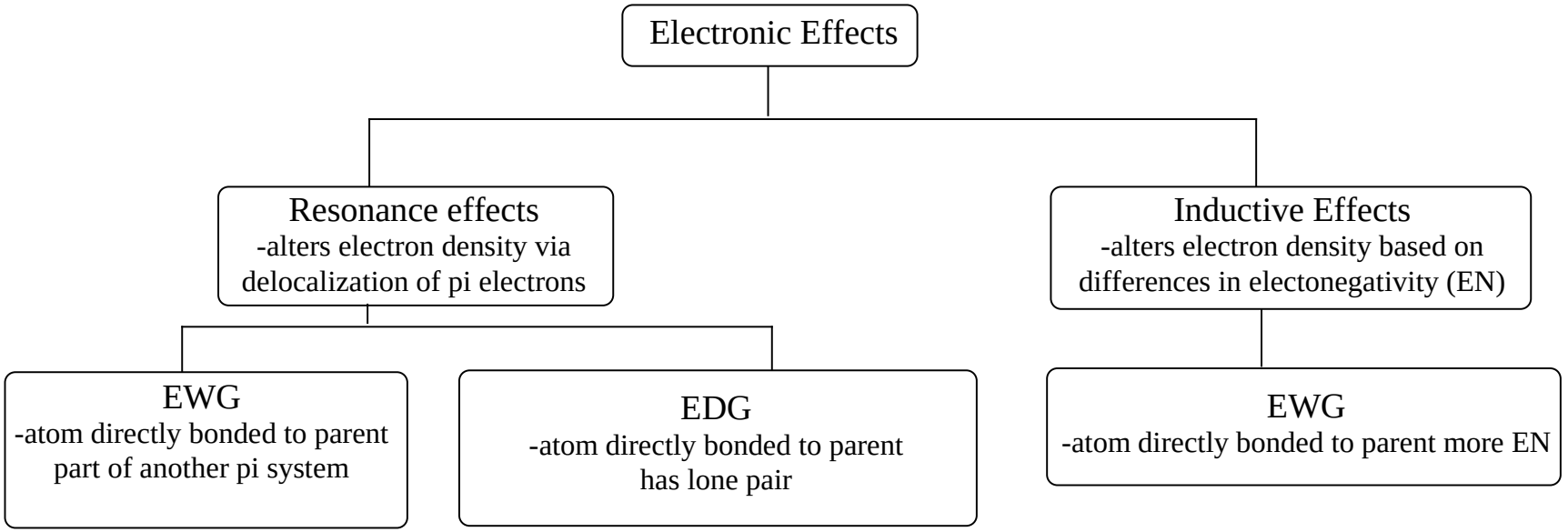
- Non-classical Isosteres
  - substitution of substituents with groups not defined by classical isosteric terms but still bear steric and electronic similarities

Quantitative Structure Activity Relationships

- Electronic effects (Hammett equation)
  - assigns value (σ) to substituents to account for electron donating/electron withdrawing character of substituents based on inductive and resonance effects
- Lipophilicity and partition coefficient (Hansch equation)
  - assigns value (P) to molecules to account for lipophilic character
- Steric Effects (Taft Equation)
  - assigns value (E) to substituents to account for steric effects

Quantitative Structure Activity Relationships

Electronic effects (Hammett equation)

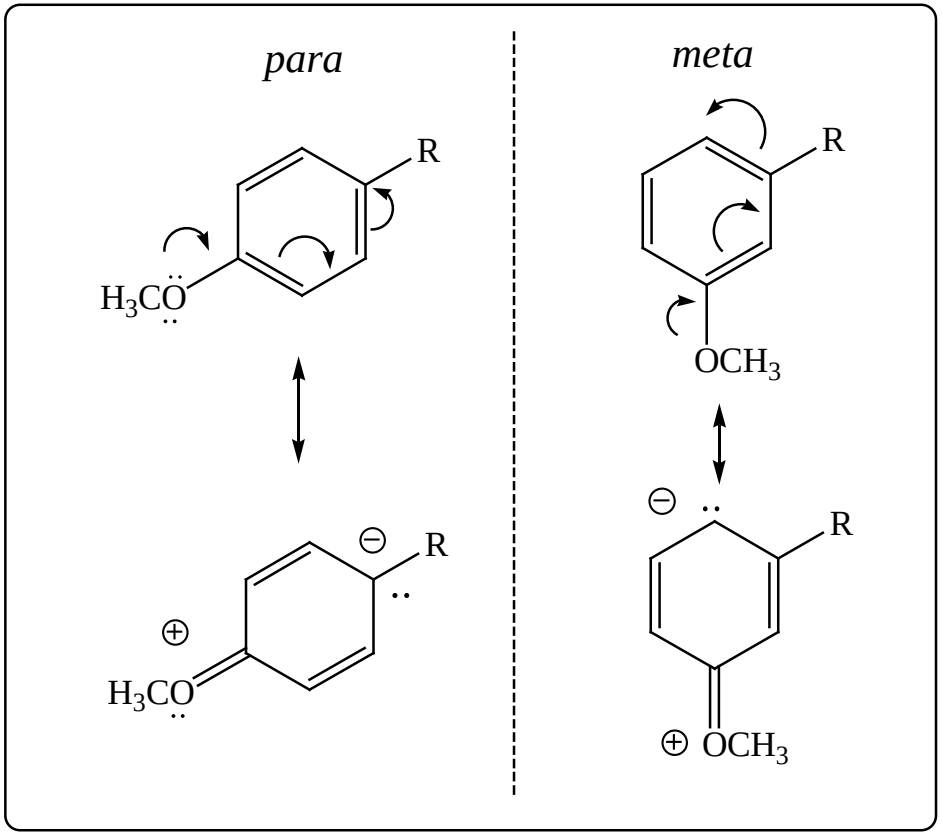


EWD = electron-withdrawing group
EDG = electron-donating group

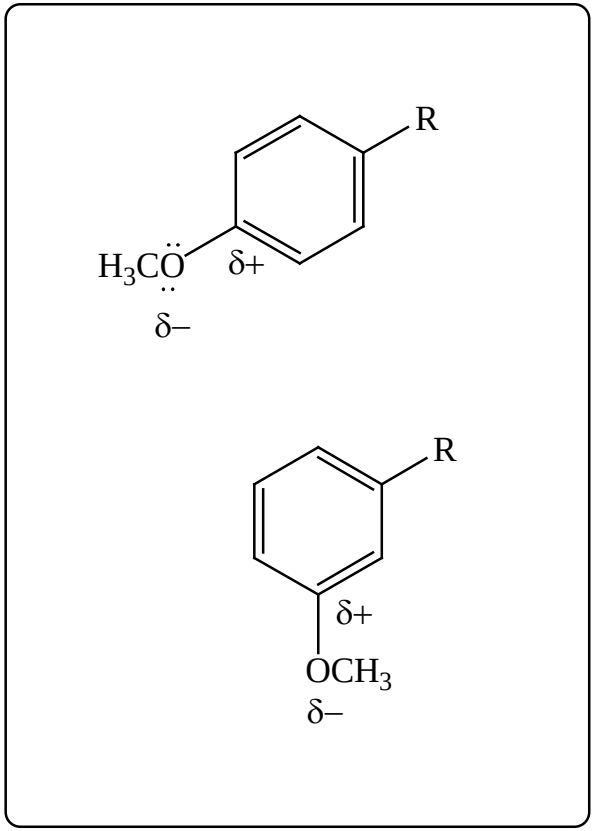
Quantitative Structure Activity Relationships

Electronic effects (Hammett equation)

RESONANCE



INDUCTION

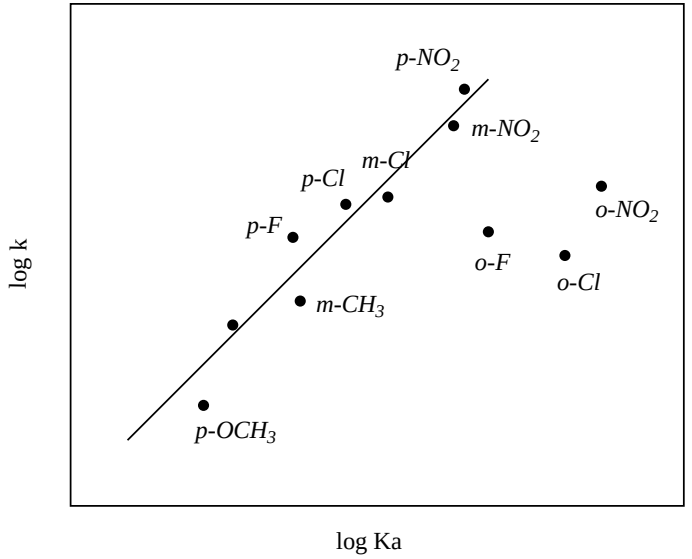


Both inductive and resonance effects contribute to a substituent's ability to be an EDG or EWG.

Quantitative Structure Activity Relationships

Electronic effects (Hammett equation)

- For meta and para substituted benzoic acids, Hammett showed a linear relationship between the ED-ability/EW ability of a substituent and the Ka of the acid (ortho- skewed by steric effects and does not correlate)



$$\frac{\log k_s}{\log k_0} = \sigma\rho$$

σ = electronic parameter (substituent)
ρ = reaction constant

k_s = rate of ionization for substituent
k_0 = rate of ionization for H

Quantitative Structure Activity Relationships

Electronic effects (Hammett equation)

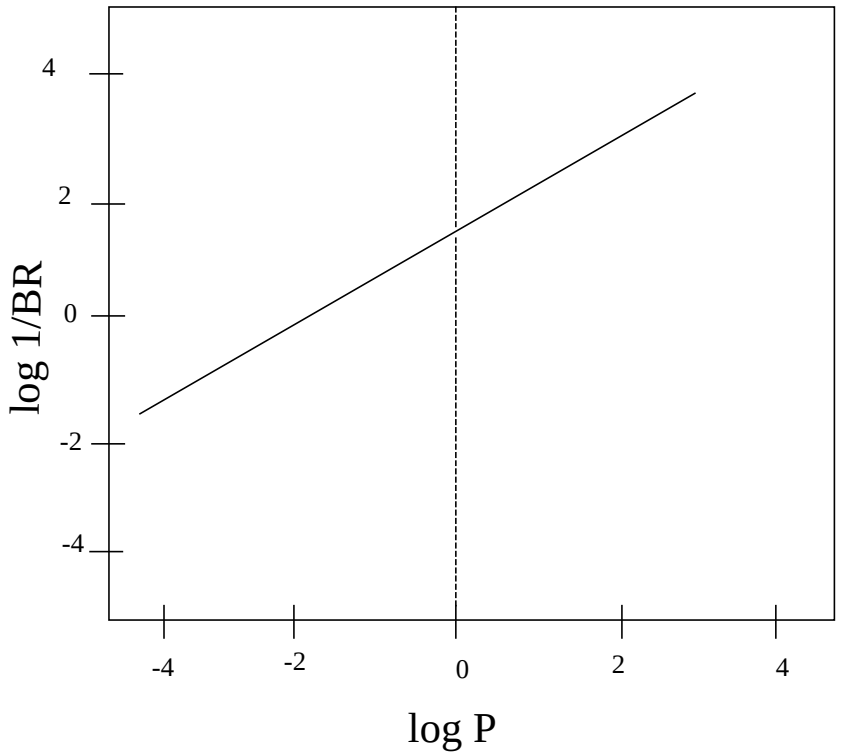
- The σ values are used to predict electron-donating and electron-withdrawing character of substituents in drugs
- The σ_{meta} values follow inductive trend; σ_{para} follow resonance trend
- Values are additive and constitutive

Substituent	Abbreviation	σ meta	σ para
acetamido-	AcNH-	0.21	-0.01
acetoxy-	AcO-	0.39	0.31
acetyl-	Ac-	0.38	0.50
amino-	NH_2-	-0.16	-0.66
bromo-	Br-	0.39	0.23
tert-butyl-	$(CH_3)_3C$-	-0.10	-0.20
chloro-	Cl-	0.37	0.23
cyano-	NC-	0.56	0.66
ethoxy-	EtO-	0.10	-0.24
ethyl-	Et-	-0.07	-0.15
fluoro-	F-	0.34	0.06
hydrogen	H-	0.00	0.00
hydroxy-	HO-	0.12	-0.37
methoxy-	MeO-	0.12	-0.27
methyl-	Me-	-0.07	-0.17
nitro-	NO_2-	0.71	0.78
phenyl-	Ph-	0.06	-0.01
trifluoromethyl	F_3C-	0.43	0.54
trimethylamino-	$(CH_3)_3N^+$-	0.88	0.82

Quantitative Structure Activity Relationships

Lipophilicity and Partition Coefficient

- Partition coefficient (lipophilicity) can be correlated with biological activity
- Three models
  - linear
  - parabolic
  - bilinear



Quantitative Structure Activity Relationships

Lipophilicity and Partition Coefficient (Hansch)

- Lipophilic character of specific substituents can be determined and correlated with the partition coefficient

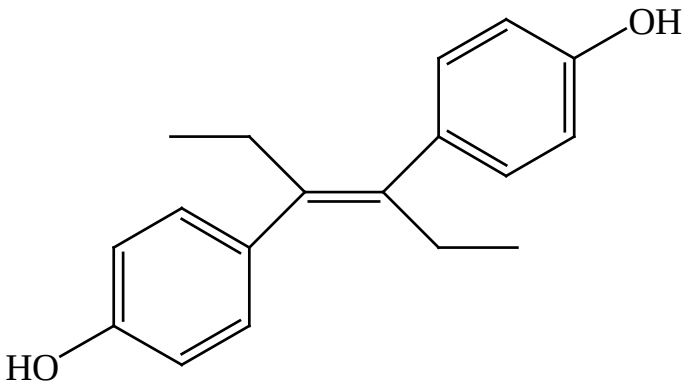
- The value π is used to indicate lipophilic character of specific substituents

Substituent	π
H	0.00
$-CH_3$	0.56
$-CH_2CH_3$	1.02
$-CH_2CH_2CH_3$	1.55
$-C(CH_3)_3$	1.53
$-OCH_3$	-0.02
$-NH_2$	-1.23
-F	0.14
-Cl	0.71
-Br	0.86
-I	1.12
$-CF_3$	0.88
-OH	-0.67
$-COCH_3$	-0.55
$-NHCOCH_3$	-0.97
$-NO_2$	-0.8
-CN	-0.57

Quantitative Structure Activity Relationships

Lipophilicity and Partition Coefficient (Hansch) equation)

The partition coefficient (lipophilicity) of a compound can be calculated from π values of its substituents



diethylstibestrol

$$\log P = 2\pi CH_3 + 2\pi CH_2 + \pi CH{=}CH + 2\log P_{PhOH}$$

$$= 2(0.50) + 2(0.50) + 0.69 + 2(1.46)$$
$$= 5.61$$

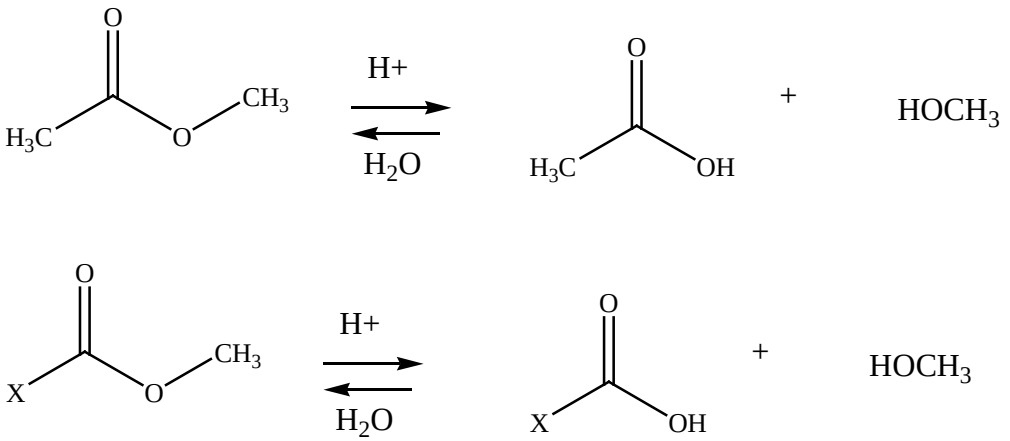
Experimental log P = 5.07

Quantitative Structure Activity Relationships
Steric Effects (Taft Equation)

- Taft Equation

  $-E_s$ represents the steric contribution of a particular group based on rates of hydrolysis α-substituted acetates

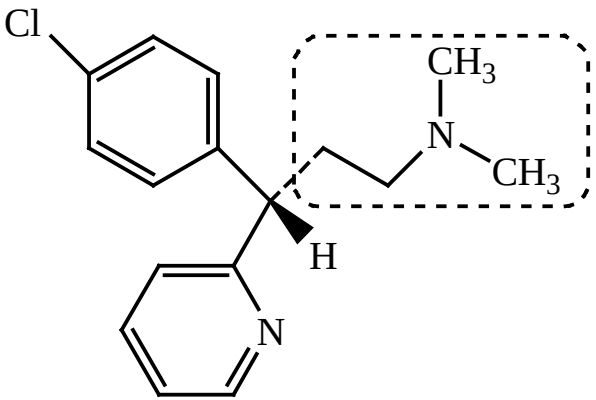
$$Es = \log k_{xCO2Me} - \log k_{methyl\ acetate}$$



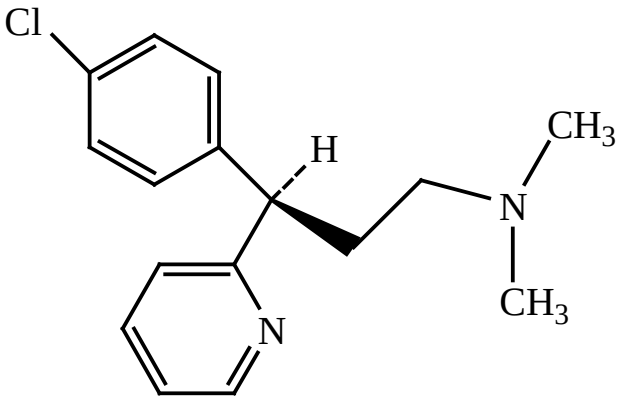
k = rate constant for acid catalyzed hydrolysis

Quantitative Structure Activity Relationships
Steric Effects (Taft Equation)

How does changing the sterics affect potency?



S(+)-dexchlorpheniramine



R(-)-dexchlorpheniramine

The S-enantiomer is 200 times more potent than the R as ^{1}H receptor antagonist.