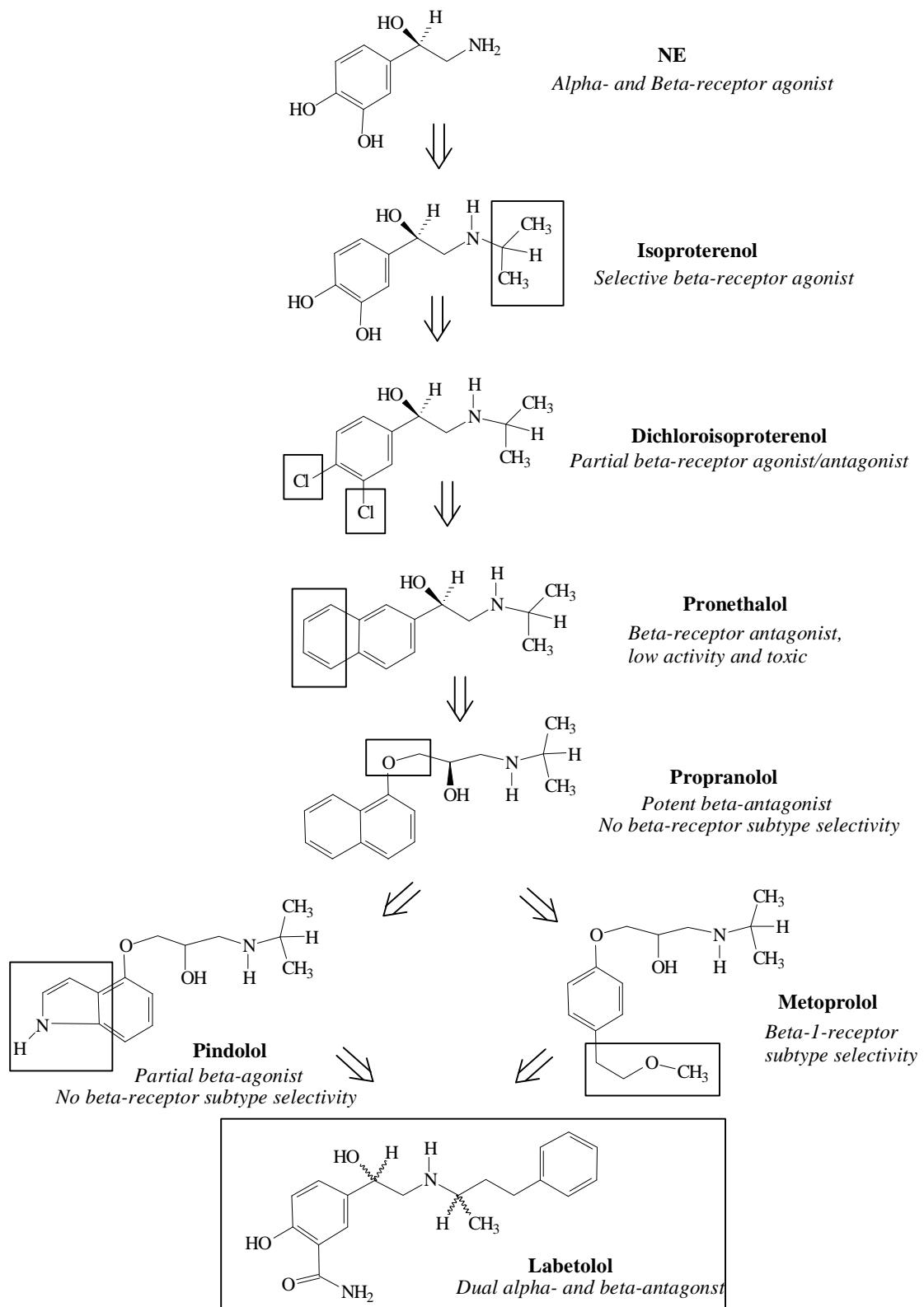


**ADRENERGIC RECEPTOR ANTAGONISTS:
BETA RECEPTOR BLOCKERS**

MC Objective: Describe the development of beta antagonists ("beta blockers") from the agonist norepinephrine (NE):

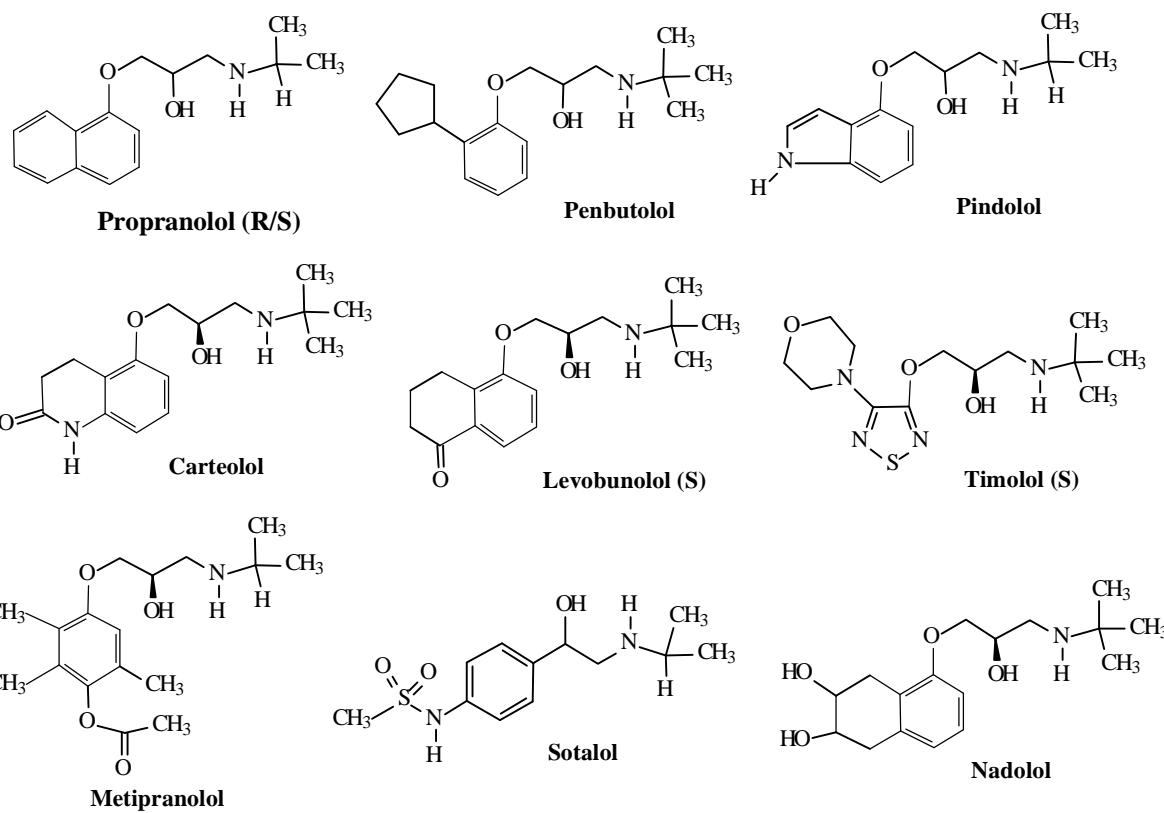


MC Objective: Based on their structures, would the beta-blockers be expected to be relatively receptor selective? YES. They do not produce significant blockade of alpha-adrenergic receptors (alpha-1 or alpha-2), histamine receptors, muscarinic receptors or dopamine receptors.

MC/PC Objective: Identify which beta blockers are classified as "non-selective":

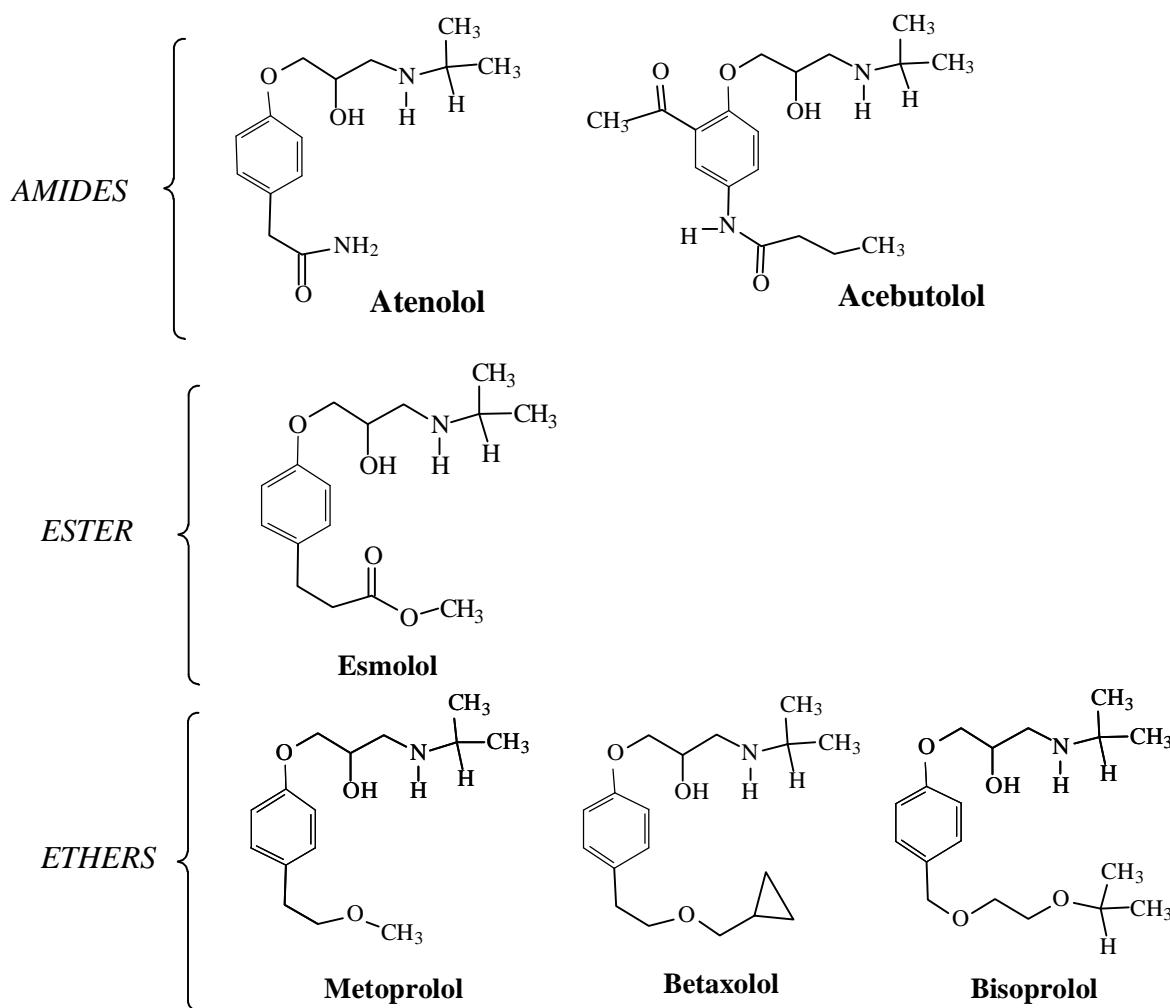
- The “non-selective” classification refers to those beta-blockers capable of blocking BOTH beta-1 and beta-2 receptors with equivalent efficacy. These drugs DO NOT have clinically significant affinity for other neurotransmitter receptors (alpha, dopamine, histamine, acetylcholine, etc.).
- ALL of these beta-blockers (**except satolol**) consist of an aryloxypropanolamine side chain linked to an aromatic or “heteroaromatic” ring which is “ortho” substituted.
- ALL of these beta-blockers differ in the specific chemical nature of the aromatic or heteroaromatic ring as shown below:

THE 'NON-SELECTIVE' BETA-BLOCKERS



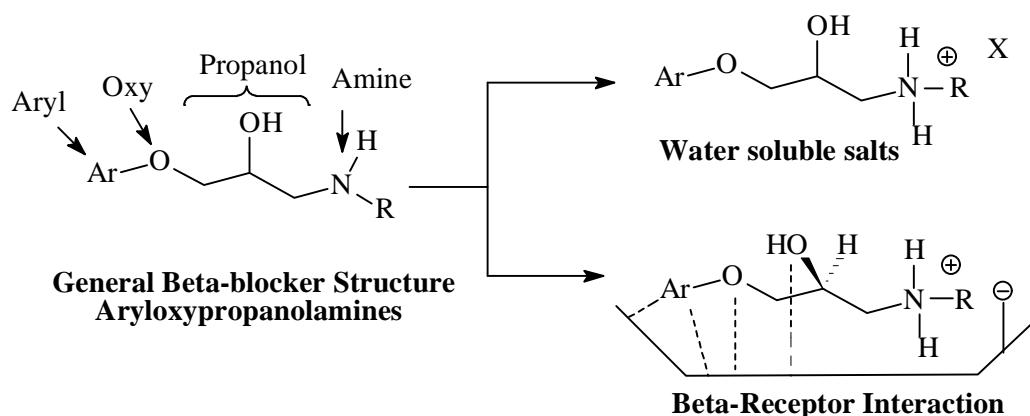
MC/PC Objective: Identify which beta blockers are classified as "beta-1-selective":

- It should be noted that the "beta-1-selective" antagonists bind to BOTH beta-receptor subtypes, but display higher affinity at beta-1 versus beta-2 receptors. These drugs DO NOT have clinically significant affinity for other neurotransmitter receptors (alpha, dopamine, histamine, acetylcholine, etc.).
- What therapeutic advantage(s) may beta-1 selective agents over non-selective beta-blockers?
- ALL of the "beta-1-selective" beta blockers have an aryloxypropanolamine side chain like the "non-selective" blockers, but they differ in that this group is linked to an aromatic ring containing a polar 4-substituent (amide, ester or ether). This 4-polar functional group is the primary structural difference between the selective and non-selective beta-blockers.
- Based on the nature of the polar 4-substituent the "beta-1-selective" blockers are subclassified as amides, esters and ethers as shown below:



MC Objective: Most beta-blockers are classified as “aryloxypropanolamines”:

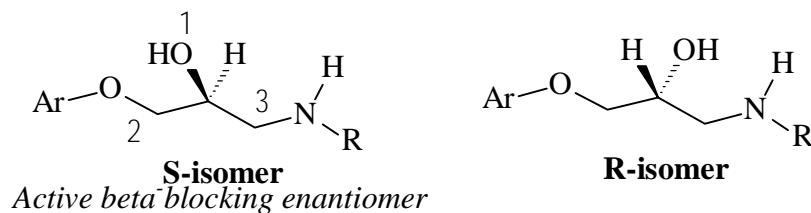
- They consist of an aromatic/heteroaromatic ring (aryl) linked to an oxygen atom (oxy) which is bound to a propanol side chain linked to an amine. While the majority of beta-blockers contain these structural elements, NOT ALL DO see later!)
- All of these compounds are basic, secondary amines. The amino group is important because:
 1. These compounds are marketed as stable, solid salt forms of the amine
 2. These compounds are predominantly ionized at physiologic pH (pKa 9)
 3. The protonated amine group is required for beta-receptor binding
 4. The amine is a major site of drug metabolism and hence drug inactivation.



MC Objective: Characterize the nature of the N-substituent in the aryloxypropanol-amine beta-blockers?

- ALL of the beta-blockers are secondary amines and the N-substituent is either an isopropyl or tertiary butyl group. As noted in earlier chapters, this substituent affords optimal affinity and some selectivity for beta-receptors (over alpha receptors)

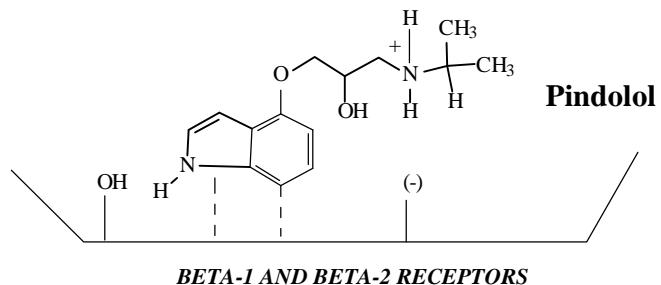
MC Objective: The aryloxypropanolamine beta-blockers are “chiral”.



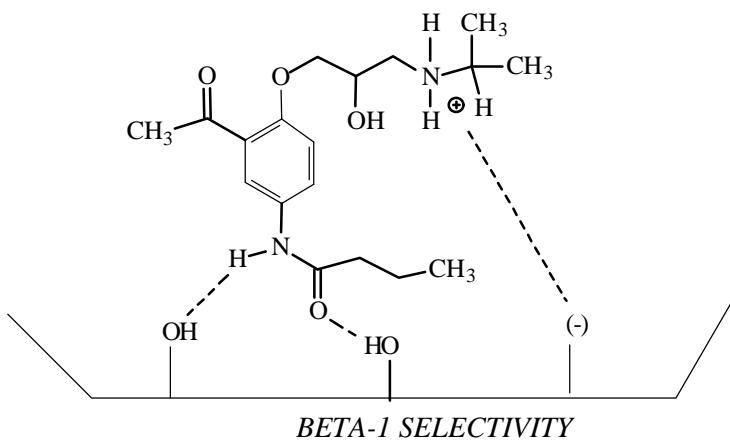
- All of the aryloxypropanolamine beta-blockers have a chirality carbon atom in the propanol side chain. Thus two enantiomeric forms are possible for each drug. Typically the S-enantiomers have the higher affinity ("more active) for beta-receptors.
- All beta-blockers currently available are marketed as racemic mixtures except timolol and levobunolol which are available as the active, S-enantiomers

MC Objective: What structural feature varies the most in the different aryloxypropanolamine beta-blockers and how does this account for differences in pharmacologic activity?

- Generally, heteroaromatic aryloxypropanolamines (pindolol, carteolol, timolol) have higher binding affinities for beta receptors than non-heteroaromatics due to additional interactions with complementary sites on the receptor as shown for pindolol below:

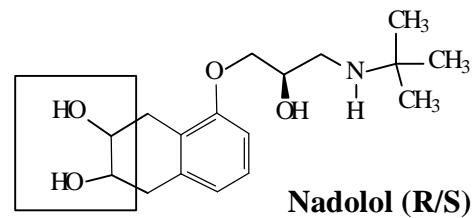
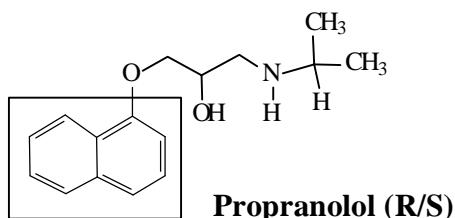


- Generally aryl substituents influence whether an aryloxypropanolamine has intrinsic sympathomimetic activity (ISA), or ability to function as partial agonists. Those beta-blockers with "ortho" substituents on the aromatic ring are likely to have ISA, but this is not an absolute rule. Note that pindolol, carteolol, penbutolol and acebutolol display the highest level of ISA, although other "ortho" substituted derivatives such as propranolol do not display significant ISA.
- Generally ALL beta-1 selective blockers contain a substituent with a dipolar functionality (amide, ester or ether group) at the 4-position. Generally non-selective beta-blockers of the aryloxy-propanolamine type lack an appropriately positioned 4-polar group and are not selective. Beta-1 selectivity probably results from these compounds being able to bind to additional complementary functionality on the beta-1 receptor - functionality that is NOT PRESENT on the beta-2 receptor. This is illustrated in the cartoon below:



- Based on the overall structure of the aryl moiety, aryloxypropanolamine beta-blockers differ in their lipophilicity. Analyzing the functionality of the aryl groups in these compounds, rationalize their subclassification as:
 - Highly lipophilic (least polar functionality): Propranolol, penbutolol
 - Low lipophilicity (most polar functionality): Nadolol, atenolol
 - Intermediate lipophilicity: all others!

NOTE: The differences in polarity between propranolol (high lipophilicity) and nadolol (low lipophilicity) should be evident by comparing these two structures. Both structures have a common propanolamine side chain except that propranolol has a N-isopropyl group and nadolol has an N-t-butyl group. This relatively minor structural difference in the propanolamine side chain would not account for the large difference in lipophilicities between these two compounds. The most significant structural differences between propranolol and nadolol are the substituents that comprise the "aryl" group. In propranolol the aryl group is a planar, fully aromatic moiety consisting of carbon and hydrogen atoms only (no polar atoms or groups). In nadolol the aryl group has two very polar hydroxyl (OH) groups capable of dipolar interactions with other like groups. As a result of this difference, nadolol is substantially more polar than propranolol:



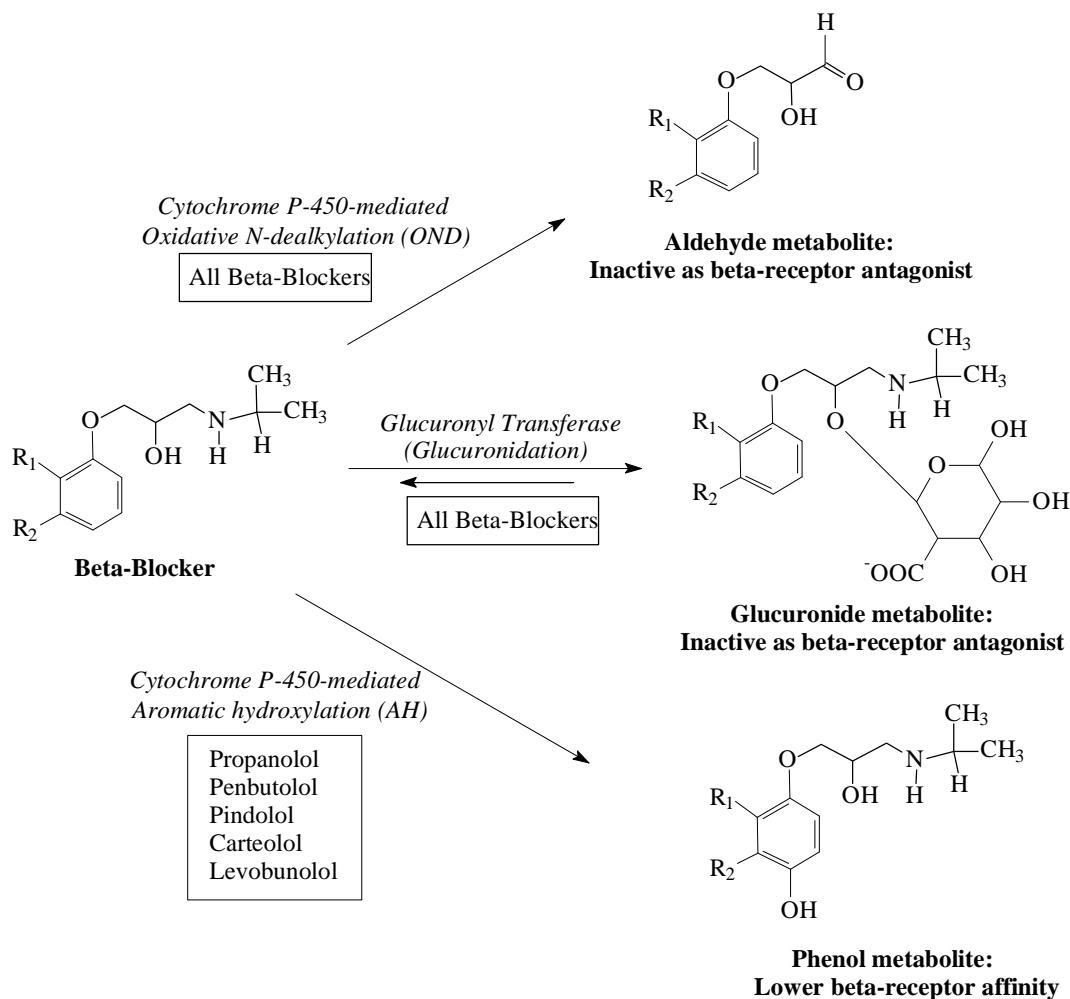
Non-polar aryl group: High lipophilicity

Polar aryl group: Low lipophilicity

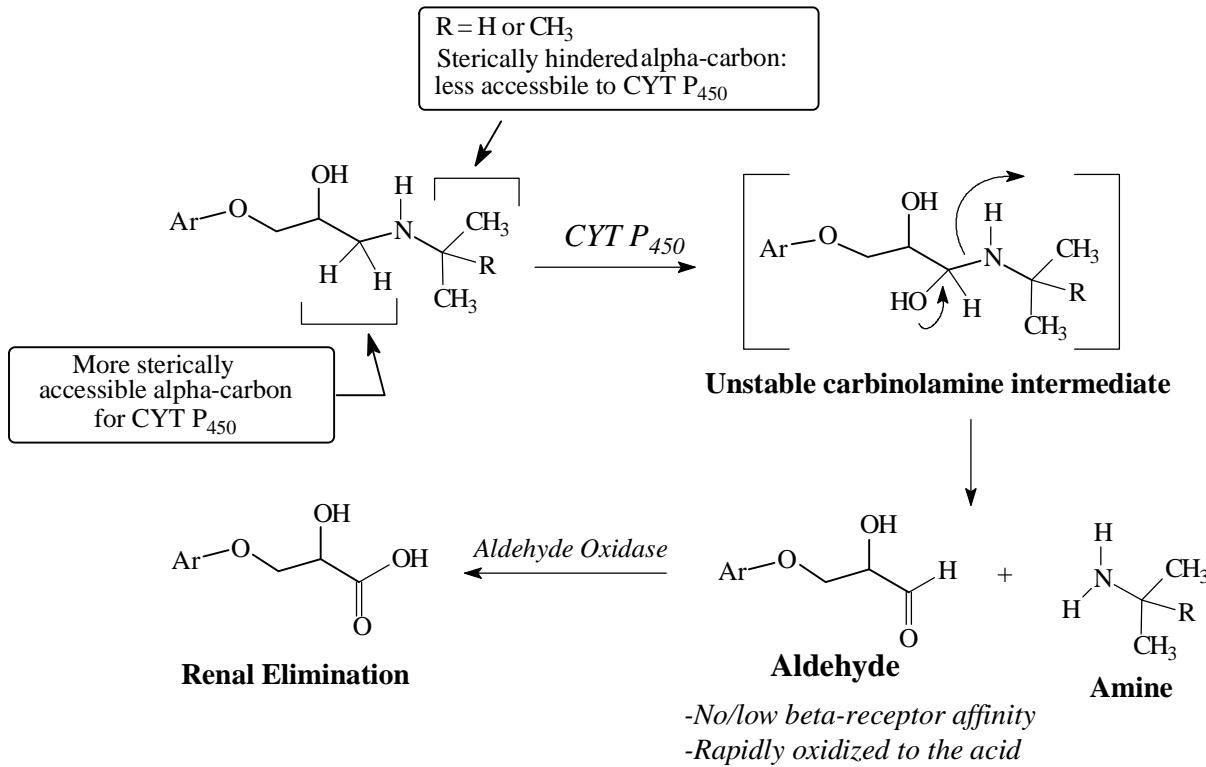
MC Objective: The differing lipophilicities (determined primarily by the aryl group) of the aryloxypropanolamine beta blockers is important therapeutically because it influences the following properties:

- Extent and rate of Absorption from the GI tract
- Nature and Extent of metabolism
- Degree of plasma protein binding
- CNS distribution
- Route of elimination
- Dosing in special patients
- Inter-patient variability
- Therapeutic indication

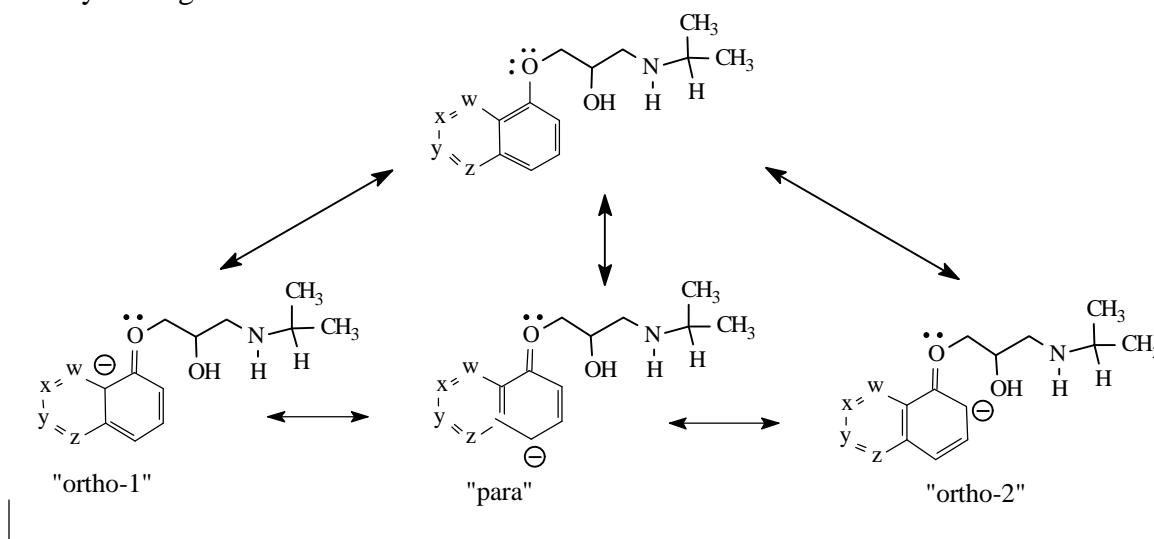
MC Objective: Most beta-blockers are subject to three metabolic processes, but to differing degrees. These are oxidative N-dealkylation (OND), propanol OH glucuronidation and aromatic ring hydroxylation (AH) as shown below:



MC Objective: The mechanism of the oxidative N-dealkylation (OND) pathway and the role of drug structure in this metabolic reaction: ALL beta-blockers may undergo OND, but typically more lipophilic, sterically unhindered drugs are metabolized more readily by this pathway. Since beta-blockers contain two carbons alpha to the side chain nitrogen, the sterically less hindered alpha-carbon is oxidized more readily (see below). Also the OND products formed are inactive as beta-blockers and are oxidized readily to the corresponding acid metabolites which are eliminated renally:

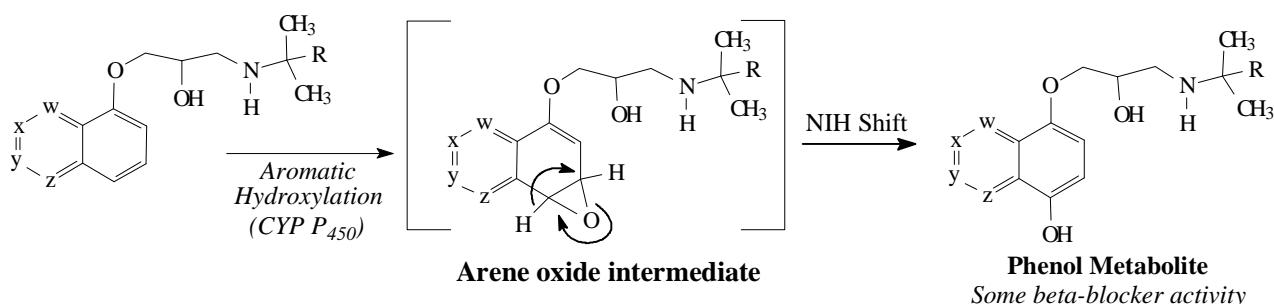


MC Objective: The mechanism of the aromatic hydroxylation (AH) metabolic pathway and the role of drug structure: Beta-blockers with aryl substituents consisting of "para"-unsubstituted aromatic rings (such as propranolol, penbutolol, pindolol, carteolol, levobunolol and nadolol) may undergo AH. Typically the more lipophilic aromatic, planar blockers (propranolol) are metabolized to a greater extent by AH. In these compounds, the "para" position is the preferred site of oxidation because it is both electron rich and sterically unhindered. Accordingly, since the beta-1 selective blockers contain "para" substituents (for selectivity) and hindered "ortho" positions, they do not readily undergo AH.



Resonance structures showing distribution of charge, and that the "para" position is the least sterically hindered site with high negative charge

Electron density is important for efficient oxidation to the arene oxide which rearranges to the hydroxy metabolite (a phenol, actually) as shown below:

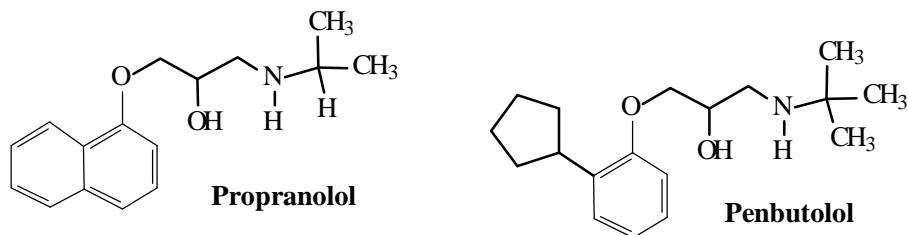


NOTE: IT IS IMPORTANT TO NOTE THAT NOT ALL BETA-BLOCKERS ARE METABOLIZED TO THE SAME EXTENT BY THE OND, AH and GLUCURONIDATION PATHWAYS SHOWN ABOVE. ALSO MANY BETA-BLOCKERS ARE SUBJECT TO UNIQUE (ADDITIONAL) METABOLIC PATHWAYS AS WELL (AS DISCUSSED MORE BELOW)!!!

MC/PK Objective: The pharmacokinetic properties of the aryloxypropanolamines are summarized in the tables on the following pages (pages 16-17). Note that most of these compounds differ from each in one or more pharmacokinetic property. Students are not required to memorize the data provided in these tables. Students will, however, be expected to explain the differences in properties and relate these to structure as discussed below.

MC/PK Objective: Compare the different beta-blockers in terms of their relative oral bioavailability:

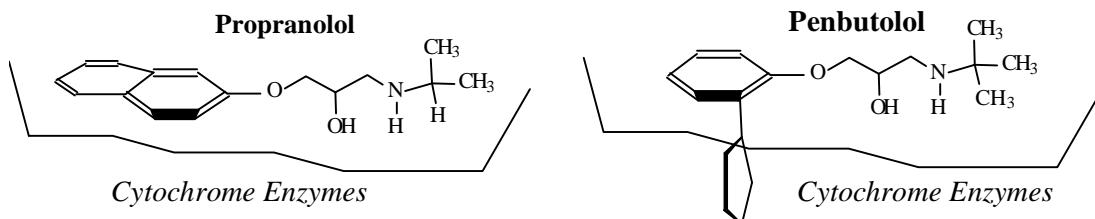
- Factors that determine the oral bioavailability of a drug product include:
 - Formulation
 - Solubility in the GI contents (water solubility)
 - Stability in the GI tract (acid and enzymes)
 - *Lipophilicity (passive absorption from the small intestine)*
 - *Metabolic stability: resistance to first pass metabolism*
- All of the beta-blockers are formulated for optimal absorption and are sufficiently water soluble and stable in the gut. These factors do not typically account for the differences observed in oral bioavailability (see Tables). The differences oral bioavailability between beta-blockers results from differences in lipophilicity (and absorption) and extent of first pass metabolism!
- Lipophilic Beta-blockers and Absorption: The two beta blockers which have the highest relative lipophilicities are propranolol and penbutolol. The compounds have aryl groups consisting only of non-polar hydrocarbon functionality as shown below. As a result of their high lipophilicities these two beta-blockers are nearly completely



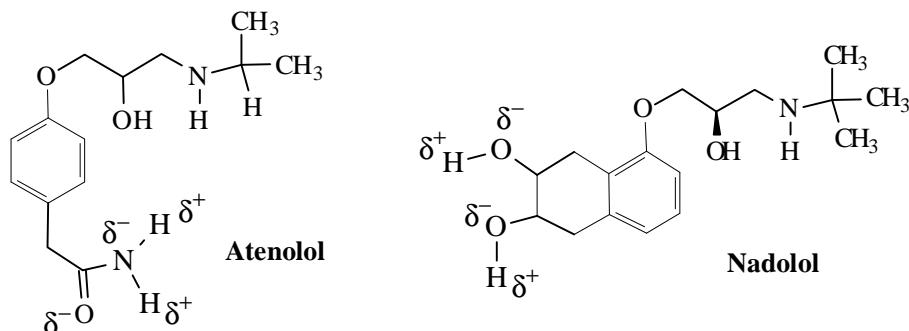
(100%) absorbed from the GI tract:

- Lipophilic Beta-blockers and Oral Bioavailability: In spite of their similar absorption, propranolol has significantly lower (and more variable) oral bioavailability than penbutolol. The difference in bioavailability is directly attributable to differences in first pass metabolism and extent of metabolism. Propranolol with its fully aromatic and planar aryl group is a good substrate for cytochrome enzymes and is efficiently and extensively metabolized as it passes through the liver (after absorption). Thus its oral bioavailability is reduced. Penbutolol has a bulky tetrahedral cyclopentane group on its aryl moiety and thus is

not as good a substrate for cytochrome enzymes. It is metabolized more slowly and thus has higher oral bioavailability as indicated by the cartoon below. Thus the primary factor limiting the oral bioavailability of propranolol is first pass metabolism!

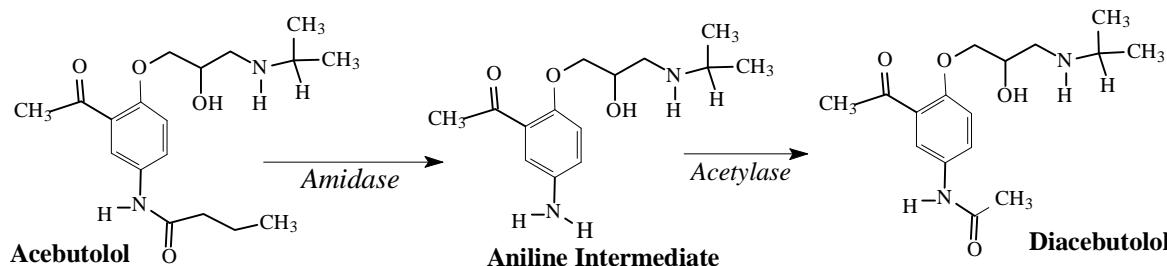


- Polar Beta-blockers and Absorption: The two beta-blockers with the lowest relative lipophilicities (highest polarities) are nadolol and atenolol. The polarity of these compounds results from the presence of dipolar functional groups on their aryl moieties. Note that nadolol has two polar OH groups while atenolol has polar primary amide NHs and a carbonyl (C=O). As a result of their polarity, neither of these compounds are as efficiently absorbed from the GI tract as propranolol or penbutolol (see Pharmacokinetic Tables). Thus atenolol and nadolol have low relative oral bioavailabilities (<60%) as a result of limited absorption from the GI tract:



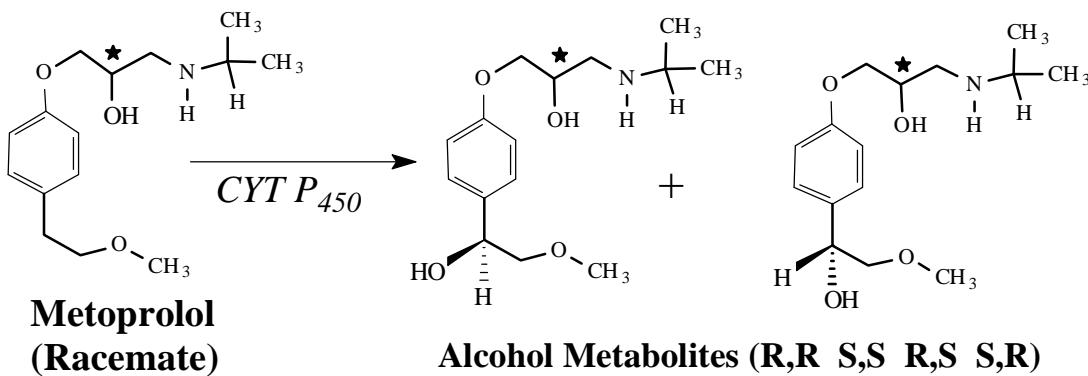
- Beta-blockers of Intermediate Lipophilicity and Absorption: All other beta-blockers are less lipophilic than propranolol, but more lipophilic than nadolol or atenolol. These compounds have more net polar functionality than propranolol or penbutolol, but less net polar functionality than nadolol or atenolol. Thus, even though these compounds are less lipophilic than propranolol, they are sufficiently lipophilic to be well absorbed from the GI tract as evidenced by the disposition data in the Tables (absorption range of 80-100%)
- Beta-blockers of Intermediate Lipophilicity and Oral Bioavailability: All of the beta-blockers of intermediate lipophilicity, except acebutolol, metoprolol and esmolol, have relatively high oral bioavailability (75-100%). These compounds (minus the exceptions) are *sufficiently lipophilic* to be absorbed, and are not significantly metabolized by first pass enzymatic processes. The exceptions to this trend, acebutolol, metoprolol and esmolol, are discussed more below.

- **Oral Bioavailability of Acebutolol:** The amide beta-blocker acebutolol has relatively low oral bioavailability in spite of good lipophilicity and GI absorption due to extensive first pass metabolism. This compound is significantly metabolized because it contains an "aromatic amide" (anilide) which can be hydrolyzed by hepatic esterases as shown below. Also, the hydrolysis product ("anilide intermediate") is readily conjugated by acetylase to yield diacebutolol which is an active and beta-1 selective beta-blocker! Because of this metabolic profile, acebutolol has relatively low oral bioavailability, but the primary metabolite is active and has a longer half-life than the parent drug! This is another case where half-life of a drug is not necessarily an indicator of duration of effect!

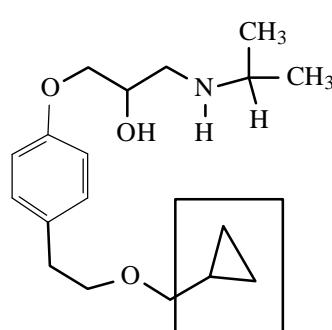


The other relevant question here is why isn't the other amide beta-blocker atenolol subject to the significant first pass hydrolytic metabolism like acebutolol. This is discussed below in a later objective.

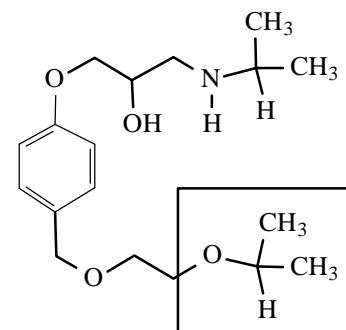
- **Oral Bioavailability of Metoprolol:** The ether beta-blocker metoprolol also has relatively low oral bioavailability in spite of good lipophilicity and absorption from the GI tract due to extensive first pass metabolism. In this compound the benzylic carbon of the 4-substituent is a substrate for cytochrome oxidation to yield the benzylic alcohol metabolites shown below. As much as 50% of the oral dose is metabolized by this pathway, and the alcohol metabolites are significantly less active as beta-blockers.



- The metabolic process metoprolol undergoes can complicate drug therapy for several reasons:
 1. Metoprolol is marketed as a racemate (R and S in propanolamine side chain) and when the drug undergoes benzylic oxidation, a second chiral center is introduced. Thus 4 different stereoisomeric alcohol drug products may form (see Figure above)!
 2. Metoprolol oxidative metabolism is “polymorphic”, meaning that patients with good metabolic capacity will extensively metabolize the drug by benzylic oxidation (“extensive metabolizers”), while those with poor metabolic capacity will not metabolize the drug to the same degree (“poor metabolizers”). As of this differential metabolism and the decrease in beta-blocking activity associated with metabolism, the therapeutic actions of a given dose of metoprolol will persist significantly longer in “poor metabolizers” (therapeutic half-life difference)!
- The other relevant question here is why aren’t the other ether beta-blockers (betaxolol, bisoprolol) subject to the significant first pass benzylic oxidative metabolism observed for metoprolol? In these compounds additional alkyl bulk (cyclopropane or methyl group) has been built into the 4-substituent chain and this retards oxidative metabolism at the benzylic carbon by a steric mechanism

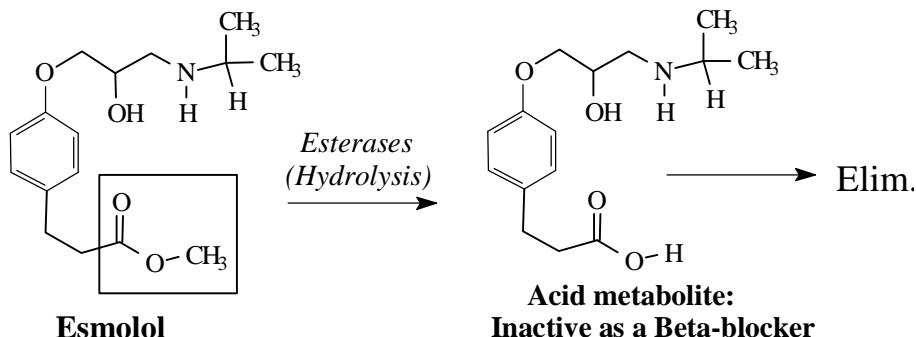


Betaxolol



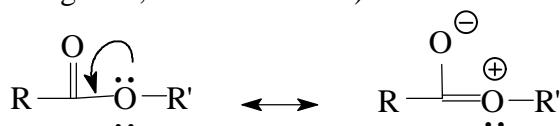
Bisoprolol

- Oral Bioavailability of Esmolol: Esmolol is NOT used orally. It is a “soft drug” designed for IV administration and short duration. As an ester it is metabolized rapidly by esterases and this hydrolysis inactivates the drug, yielding short, controlled beta-blockade!

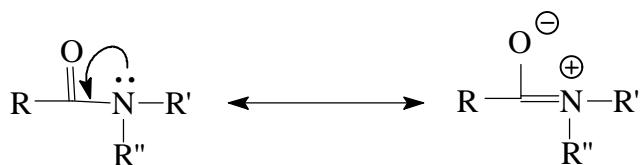


General MC Objective: Explain the difference in susceptibility to hydrolysis for esmolol, acebutolol and atenolol?

Beta-blocker structure and metabolism by hydrolysis: Several of the beta-1 selective blockers contain functional groups susceptible to hydrolysis. Generally esters (such as esmolol) are hydrolyzed more readily than amides because the ester carbonyl is more reactive than the amide carbonyl, and esterases are present in most tissues and plasma. The ester carbonyl is more reactive than amide carbonyls because there is **LESS resonance** contribution of the “ether” oxygen to the carbonyl to stabilize the carbonyl carbon to electrophilic attack. Alternatively, amide carbonyls are less reactive because the nitrogen atom can provide **GREATER** resonance stabilization to the carbonyl through electron donation. This difference between esters and amides results from the electronegativity difference between oxygen (more electronegative, less donation) and nitrogen (less electronegative, more donation) as illustrated in the resonance cartoon below:



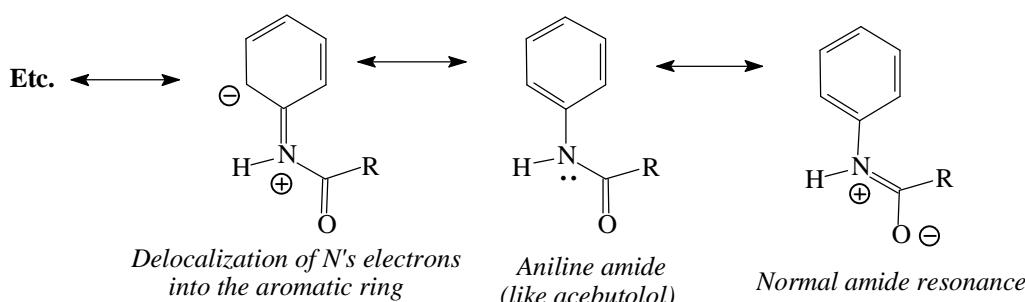
Esters: Less resonance stabilization



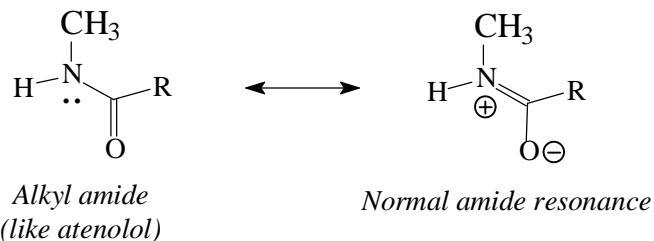
Amides: Greater resonance stabilization

Thus esmolol (and most ester drugs) is hydrolyzed more readily than the amide beta-blockers (acebutolol and atenolol) and, in fact, it possesses little oral activity due to rapid hydrolysis. Remember esmolol was designed this way to have a drug with “controlled action” by injection.

While amides generally hydrolyze more slowly than esters, amides of different electronic and steric nature will hydrolyze at different rates. For example, amides in which the nitrogen atom is linked to an aromatic ring (anilines, such as acebutolol) generally will hydrolyze more readily than alkyl amides (nitrogen connected to an sp^3 carbon, such as atenolol). This is because in anilines the resonance contribution of the nitrogen toward the carbonyl is reduced by “competing” delocation into the conjugated aromatic ring as shown below:



In alkyl amides (such as atenolol) the nitrogen can only donate electron density to the carbonyl by resonance. Thus there is greater donation in alkyl amides, more resonance stabilization and lower reactivity compared to aniline amides:



MC Objective: Most of the beta-blockers undergo some “secondary metabolism”, usually by O-glucuronidation, aromatic hydroxylation (AH) and/or oxidative N-dealkylation (OND) as described earlier.

- “Secondary metabolism” results from the drug circulating through the body and entering and re-entering tissues with metabolic enzymes such as the liver. Thus while drugs such as penbutolol, timolol, pindolol, carteolol, betaxolol and bisoprolol may not be extensively (or efficiently) metabolized upon “first pass” through the liver, continued exposure to enzymes of metabolism will result in the gradual formation of metabolites. Not all of the beta-blockers are equally susceptible to secondary metabolism because they may not distribute as well into tissues of metabolism, or the drugs may not be as efficiently bound and metabolized by enzymes. For example, the heteroaromatic beta-blockers carteolol and pindolol do undergo metabolism by AH, OND and glucuronidation over time (at a slower rate than propranolol), and some of the metabolites are inactive (OND and glucuronide), while some retain activity (AH). Also betaxolol and bisoprolol undergo slow (“secondary” metabolism mainly by O-glucuronidation. Furthermore, all of the AH, OND and glucuronide metabolites are more polar than the parent drugs and tend to be eliminated more readily by renal mechanisms.
- The more polar beta-blockers nadolol and atenolol do not distribute well to the tissues of metabolism and are not good substrates for metabolic enzymes. Hence they are metabolized to a lesser extent than the beta-blockers of high or intermediate lipophilicity.

MC/PK Objective: Elimination profiles of the beta-blockers and their metabolites (see Tables):

- Most of the beta-blockers are eliminated renally as the parent drug and more polar metabolites. The more lipophilic beta-blockers that are not extensively metabolized (penbutolol, timolol) may also have a significant biliary component to elimination. Based on this elimination profile:

Do beta-blocker doses need to be adjusted in patients with significant renal impairment? Do beta-blocker doses need to be adjusted in patients with significant hepatic impairment?

MC/PK Objective: The relationship between beta-blocker structure and drug distribution (see Tables):

- Plasma protein binding: All of the beta-blockers have a similar aryloxypropanolamine group, but differ in the nature of the substituents on the "aryl" group. These substituents, as discussed above, determine relative lipophilicities. As a **general** rule within a structural series (a series of compounds where only ONE portion of the molecule is varied), enhanced lipophilicity results in enhanced plasma protein binding, CNS distribution, etc. Thus:
 - Propranolol and penbutolol are among the most highly protein bound (>90%) beta-blockers, and distribute most readily to the CNS
 - Nadolol and atenolol display the lowest protein binding (<30%) of the beta-blockers, and distribute most slowly to the CNS

MC/PK Objective: The relationship between beta-blocker structure, extent of metabolism and plasma protein binding and half-life? In the beta-blocker series, half-life primarily is a function of rate and extent of metabolism, how metabolism alters activity, and route and rate of elimination. Plasma protein binding does not significantly influence half-life in this series of drugs. Consider the example below:

- Even though propranolol is highly protein bound, it has a relatively short half-life (3-5 hrs) due to efficient and extensive metabolism. The metabolites are either inactive or less active, and are more readily eliminated than the parent drug.
- In spite of low protein binding (<30%), nadolol has a relatively long half-life (>20 hrs). This results primarily from the resistance of this drug to metabolic inactivation.
- Acebutolol has a relatively short plasma half-life (3-4 hours), but a relatively long therapeutic half-life (>10 hours) because it yields an active metabolite that is eliminated more slowly than the parent drug.
- Metoprolol's half-life is highly variable because it undergoes polymorphic metabolism and the metabolites formed are less active and more readily eliminated than the parent drug.
- Betaxolol and bisoprolol have relatively long half-lives because they are relatively slowly metabolized and the main metabolites formed (glucuronides) are reversible.

It is important to note that while these factors may contribute to the half-life of all systemic administered drug, the *relative contributions* of these factors may differ for different drug classes!

PC/MC Objective: Summarize the therapeutic properties of the aryloxypropanol-amine beta-blockers based on their pharmacologic and chemical properties:

- Why do the beta-blockers have utility in the treatment of hypertension, glaucoma, arrhythmias, etc?
- Why should beta-blockers, particularly non-selective ones, be avoided in patients with respiratory diseases?
- Why should beta-blockers be used with caution in diabetics?
- How should beta-blocker therapy be modified if the patient is suffering from CNS side effects such as insomnia, nightmares and confusion on current therapy?
- Why should beta-blocker therapy be decreased slowly rather than withdrawn abruptly?
- Why may calcium channel blockers potentiate the actions of beta-blockers when these drugs are used concurrently?
- Which other drugs may interact significantly with beta-blockers?

Pharmacokinetic Summary of the Non-Selective Beta-Blockers:

Beta-Blocker	Relative Lipoph.	% Absorbed	First Pass Metabolism	%Oral Bioavail	Seconday metabolism	Elimination Profile	%PPB	Half-life, hr
Propranolol	High	100	High (OND+AH)	30-50	Some	>90% as urinary metabolites	90	3-5 (8-11)
Penbutolol	High	100	Minimal	100	Some (AH+Ogluc)	Renal and bile as parent and metabolites	80-98	5
Timolol	Interm	90	Minimal	75	Some	Renal and bile as parent and metabolites	10	4
Pindolol	Interm	95	Moderate (OND+AH)	100	Some (AH+Ogluc)	>60% as urinary metabolites	40	3-4
Carteolol	Interm	80	Moderate (OND+AH)	85	Some: (AH+Ogluc)	30-50% as urinary metabolites	20-30	6
Nadolol	Low	30	Minimal	30	Minimal	Urine: Not metabolized	30	20-24

Notes:

- Absorption is a function of lipophilicity. Drugs with intermediate to high lipophilicity are well absorbed!
- First pass metabolism is a function of compound structure, propranolol is lipophilic and well absorbed, but as a planar aromatic molecule binds with high affinity to cytochrome enzymes and is extensively metabolized (low oral bioavailability). Penbutolol is well absorbed and does not bind as well to cytochrome enzymes, so it undergoes less 1st pass metabolism.
- Oral Bioavailability is a function of absorption (lipophilicity) and extent of 1st pass metabolism.
- Other notes: In class discussion

Pharmacokinetic Summary of the Selective Beta-1 Blockers:

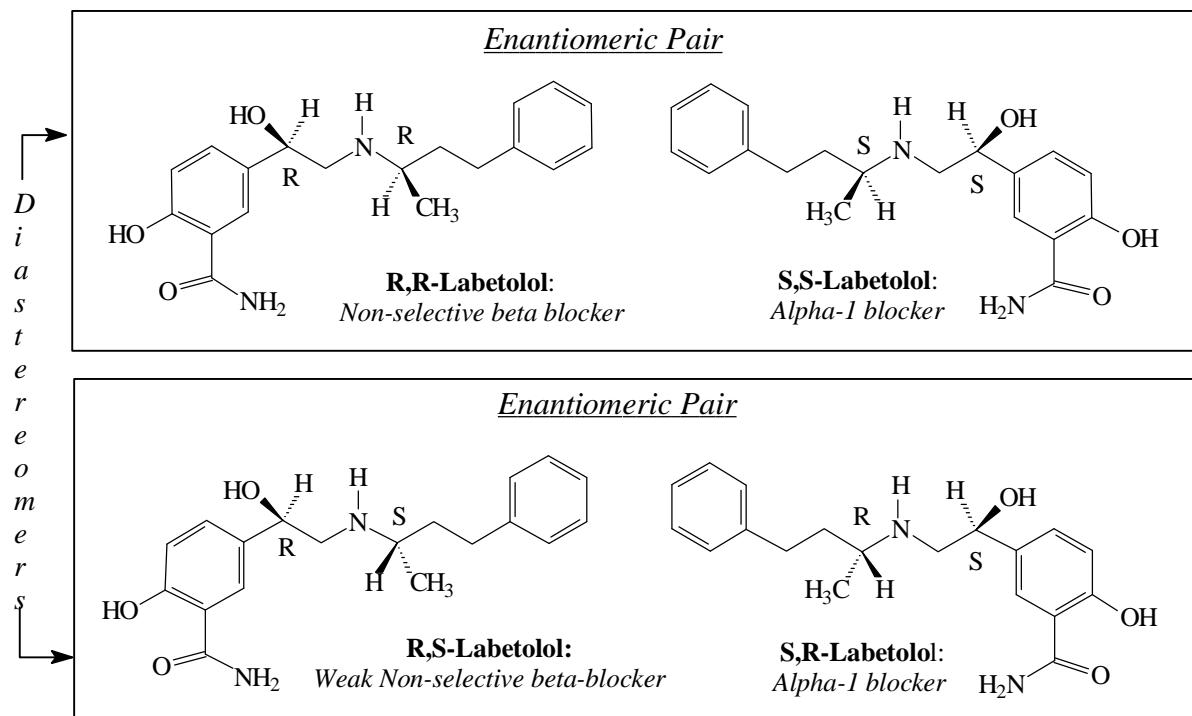
Beta-Blocker	Relative Lipoph.	% Absorbed	First Pass Metabolism	%Oral Bioavail	Seconday metabolism	Elimination Profile	%PPB	Half-life, hr
Acebutolol	Interm	90	Extensive Hydrol+N-acetylation (diacebutolol)	20-60	Minimal	Mainly metabolites in urine	25	Parent: 3-4 Diacebutolol: 8-13:
Atenolol	Low	50	Minimal	50-60	Minimal	Mainly parent in urine	<20	6-9
Esmolol	Interm	NA (IV)	NA (IV)	NA	Extensive: "Soft Drug"	Mainly metabolite in urine	55	0.15
Metoprolol	Interm	95	Extensive (OND + BO) BO: genetically controlled	40-50	Some	Mainly metabolites in urine	12	3-7
Betaxolol	Interm	100	Minimal	90	Significant: O-Gluc	Mainly metabolites in urine	50	14-22
Bisoprolol	Interm	>90	Minimal	80	Significant: O-Gluc + Chain Oxid	Metabolites and Parent in urine	30	9-12

Notes:

- Acebutolol is an aromatic amide and is readily hydrolyzed to an aniline metabolite which undergoes N-acetyl conjugation to yield an active, long-lived metabolite (diacebutolol). This metabolic pathway does not inactivate the drug!
- Esmolol is designed as a short-acting "soft drug". As an ester it is readily hydrolyzed to an inactive acid, which accounts for its lack of oral activity and short duration
- Metoprolol undergoes genetically-dependent benzylic oxidation (BO) to yield diastereomeric benzyl alcohols of varying activity at beta-receptors.

MC/PC Objective: Modification of structure of NE by 3-amido substitution and N-(α -methyl)aralkyl substitution as illustrated by labetalol yields a “dual alpha- and beta-receptor blocking” drug:

- The structural modifications of labetalol allow for binding and antagonist action at both alpha- and beta-receptors. Why may it be desirable therapeutically to have a drug with such “dual” adrenergic receptor blocking activity?
- Labetalol contains two chiral centers and is marketed as a mixture of four stereoisomeric forms - two pairs of enantiomers (non-superimposable mirror images) as shown below. Each member of each enantiomeric pair (R,R/S,S and R,R/S,R) is a diastereomer of each member of the other enantiomeric pair. The enantiomers have the same chemical properties, but diastereomers have different physicochemical properties:

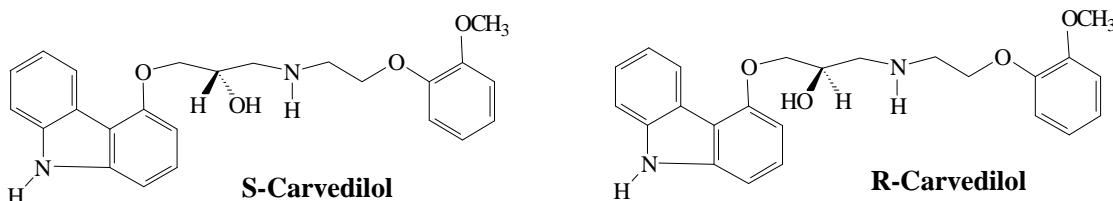


- The different stereoisomers of labetalol display similar/different adrenergic receptor binding profiles as shown above. The R,R- and to a lesser extent R,S-diastereomers have the highest affinity and antagonist activity at beta-receptors. Note that neither of these stereoisomers are beta-1 selective! The S,S- and S,R-diastereomers have the highest affinity and antagonist activity at alpha-1 receptors, and are selective for alpha-1 versus alpha-2 receptors. Based on the overall receptor affinity and potency, the predominant action expressed by all four labetalol stereoisomers is beta-antagonism.

- The oral bioavailability of the labetalol relatively low (20%) due primarily to extensive first pass metabolism involving glucuronidation. Extensive metabolism also results in labetalol having a relatively short duration of action.

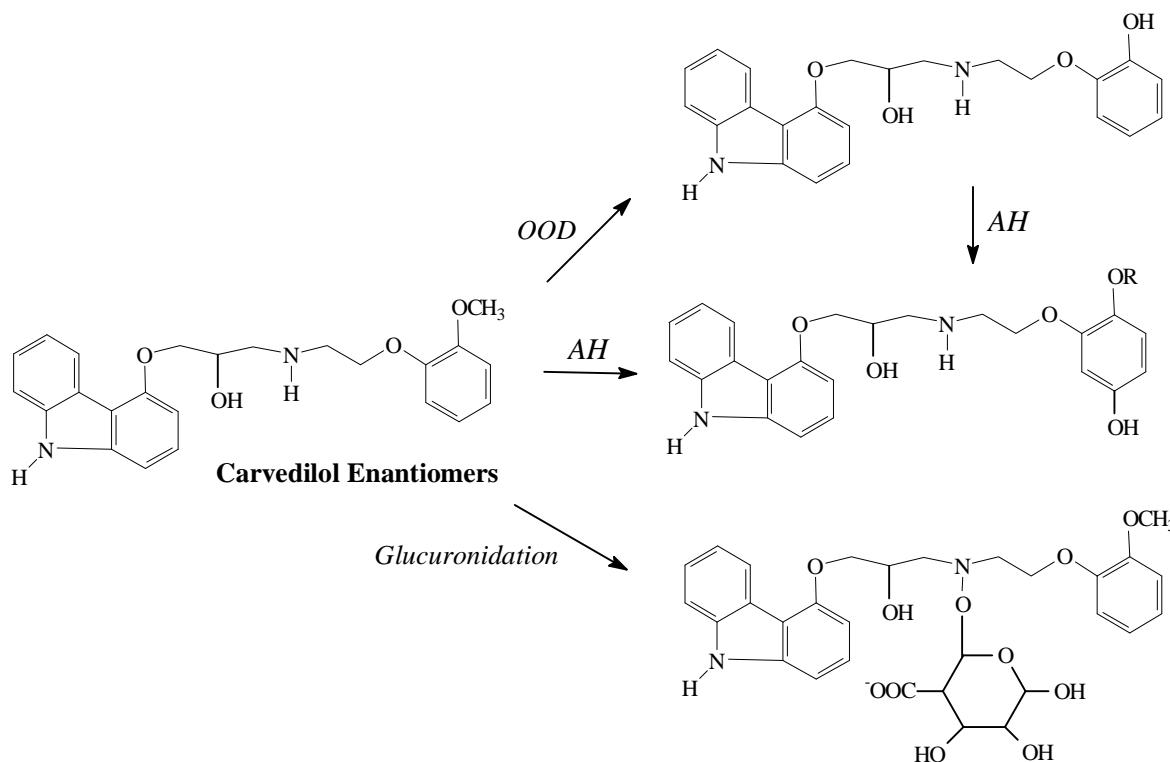
MC/PC Objective: How has the structure of a typical aryloxypropanolamine beta-blocker been modified to yield a “dual alpha- and beta-receptor blocking” drug as illustrated by carvedilol?

- The aryloxypropanolamine and N-aralkyl moieties present in carvedilol allow for binding and antagonist action at both alpha- and beta-receptors.
- Carvedilol contains one chiral center and exists as a mixture of R- and S-stereoisomers. How many stereoisomers exist and what is the stereochemical relationship between the stereoisomers?



- The carvedilol stereoisomers display different adrenergic receptor binding profiles. The S-enantiomer has higher affinity and antagonist activity at beta-receptors than the R-enantiomer, but is NOT beta-subreceptor selective. The S-enantiomer also has alpha-1 receptor blocking activity and is selective for alpha-1 versus alpha-2 receptors.
- The R-enantiomer only has affinity and antagonist activity at alpha-1 receptors and is selective for alpha-1 versus alpha-2 receptors. The R-enantiomer's alpha-1 antagonist activity is equal to that of the S-enantiomer.
- Overall, carvedilol has higher alpha-1 and beta-blocking activity than labetalol. Also, based on the receptor binding profile described above, the predominant pharmacologic action expressed by carvedilol is beta-antagonism.
- The oral bioavailability of the carvedilol is relatively low (ca. 30%) due primarily to extensive first pass metabolism by the enzymatic pathways described below. Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R-carvedilol about 2-3 times higher than S- carvedilol following oral administration. The primary P450 enzymes responsible for the metabolism of both R- and S-carvedilol are CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2 and 2E1. Thus the potential exists for drug interactions when racemic carvedilol is used concurrently with other drugs metabolized by these enzymes.
- The primary metabolic processes carvedilol undergoes include oxidative O-demethylation (OOD) and aromatic hydroxylation (AH) mediated by the cytochrome isozymes, and direct glucuronidation of the parent drug or glucuronidation of the

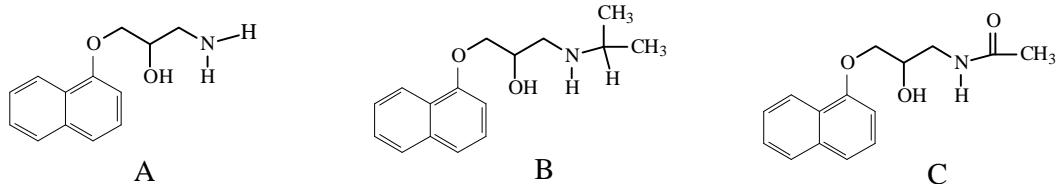
OOD and AH oxidation metabolites as shown below. These metabolic reactions are similar to those observed for other aryloxypropanolamine beta-blockers. The OOD and AH metabolites retain beta-receptor blocking activity; in fact the 4-hydroxyphenyl metabolite (AH) is more than 13 times more potent than the parent compound as a beta-blocker



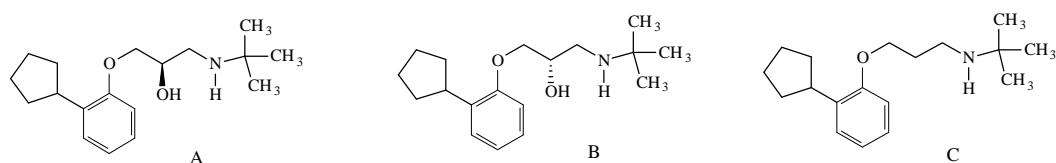
- Because of differences in metabolic rates, the mean apparent terminal elimination half-life for R-carvedilol is 5-9 hours versus 7-11 hours for the S-enantiomer.

ADDITIONAL QUESTIONS AND PROBLEMS

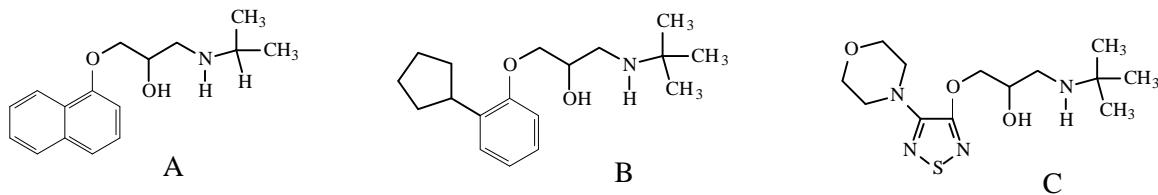
1. The role of the amino moiety of the aryloxypropanolamines in beta-receptor binding: Which compound below has the highest beta-receptor affinity?



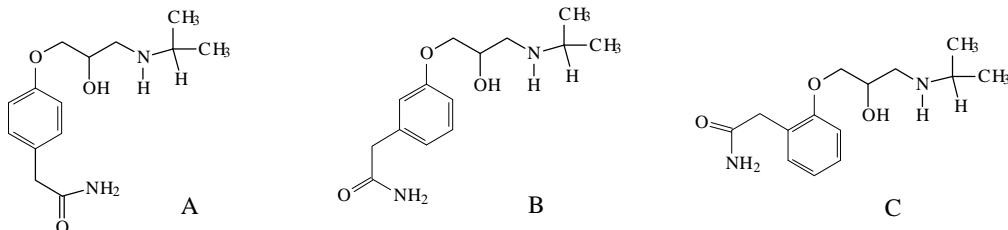
2. The role of chirality and the side chain hydroxyl group: Which compound below has the highest beta-receptor affinity?



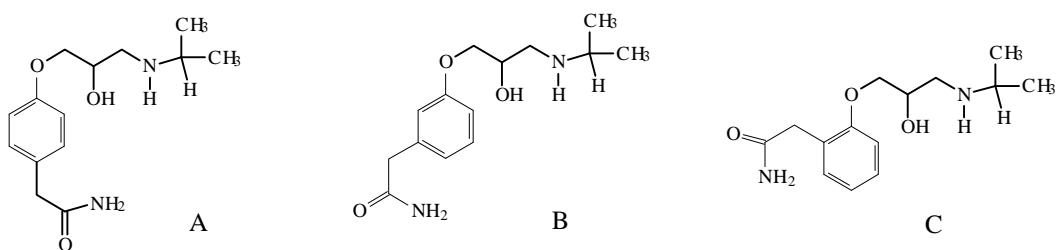
3. The role heteroaromatic aryl groups in activity: Which compound below has the highest beta-receptor affinity?



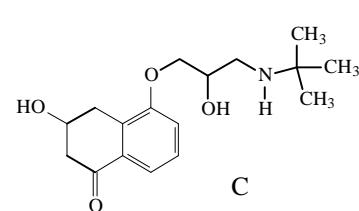
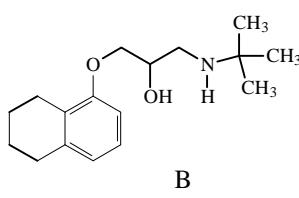
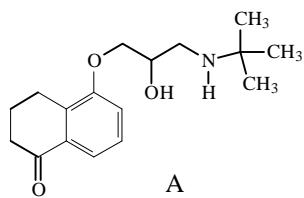
4. The role of the aryl group in intrinsic sympathomimetic activity (ISA): Which compound below is mostly likely to have ISA?



5. The role of the aryl group in beta-1 receptor selectivity: Which compound below has the highest beta-1 receptor selectivity?



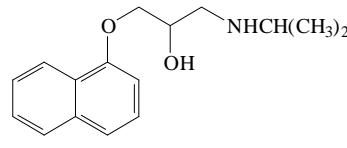
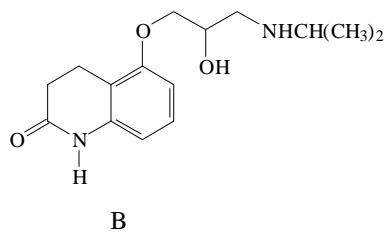
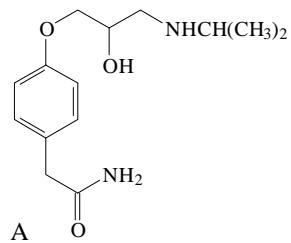
6. Beta-blocker structure and lipophilicity: Rank the following compounds in terms of lipophilicity (high, intermediate and low):



7. For the compounds in questions 6. above, answer the following question:

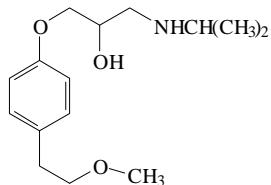
- Which would distribute to the CNS most readily?.....A or B or C
- Which would undergo the highest degree of 1st pass metabolism?.....A or B or C
- Which would be most highly bound to plasma proteins?.....A or B or C
- Which would be beta-1 receptor selective?.....A or B or C or None
- Which may undergo cytochrome-mediated OND?.....A or B or C or None
- Which may undergo aromatic hydroxylation by CYP P450?.....A or B or C or None
- Which may undergo metabolism by hydrolysis?.....A or B or C or None
- Which would be absorbed most efficiently from the GI tract?.....A or B or C

8. Analyze the structures of the compounds shown below and circle the appropriate response or responses. There may be more than one correct answer, or no correct answer ("None"):



- Which compounds are chiral?.....A B C None
- Which compounds have intrinsic sympathomimetic activity?.....A B C None
- Which compound has the greatest beta-1 receptor selectivity?.....A B C
- Which compound is most lipophilic?.....A B C
- Which compounds are metabolized by aromatic hydroxylation?.....A B C None
- Which compound is most extensively absorbed from the GI tract?.....A B C
- Which compounds are capable of functioning as beta-2 antagonists?....A B C None
- Which compounds may be metabolized by cytochrome OND?.....A B C None
- Which compound would distribute most readily to the CNS?.....A B C None
- Which compound is most polar?.....A B C
- Which compound has the highest oral bioavailability?.....A B C
- Which compound is most highly bound by plasma proteins?.....A B C
- Which compound may be safest in patients with respiratory disease....A B C

9. Draw the metabolites formed by cytochrome-mediated benzylic oxidation of metoprolol. Why is the half-life of metoprolol longer in “poor metabolizers”? Also, explain why even though Metoprolol is relatively lipophilic, is displays relatively low oral bioavailability (40-50%).



10. Explain why even though Acebutolol has a half-life of 3-4 hours, its therapeutic effects may persist for more than 10 hours. Be sure to use structures in your answer!

