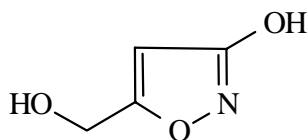


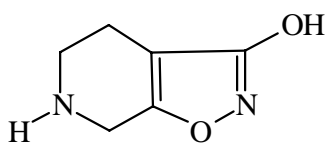
GABA RECEPTOR LIGANDS AND THE BENZODIAZEPINES

I. GABA Receptor Agonists

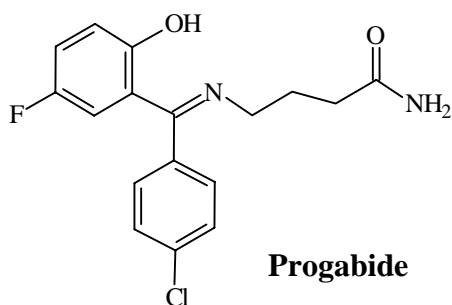


Muscimol

- Natural product obtained from *Amanita muscaria*
- Ten-fold greater affinity than GABA (0.9 nM vs 9.4 nM for GABA)

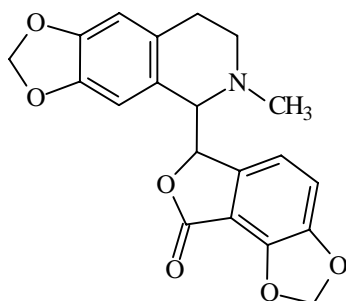


Gaboxadol (THIP)



Progabide

II. GABA Receptor Antagonists

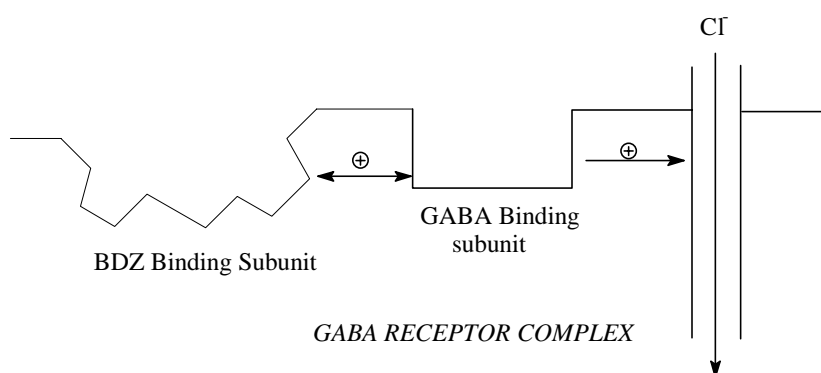


(+)-Bicuculline

- Natural Product
- Binds to all GABA receptor subtypes
- Chemically unstable: Undergoes lactone hydrolysis

III. The GABA Receptor Complex and Benzodiazepines Receptors:

γ -Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS), eliciting its physiological effects through interaction with several distinct classes of cell-surface receptors: GABA_A and GABA_B and GABA_C receptors. The GABA_A receptor is the most abundant and is a member of the superfamily of ligand-gated ion channels. The interaction of GABA with this receptor determines the opening of the intrinsic chloride ion selective channel, which is followed by an increase in chloride flux, with the result of a hyperpolarization of the neuronal cell membrane and a concomitant decrease in neuronal transmission. The physiologic actions resulting from GABAergic transmission are covered in detail in the Pharmacology Notes.

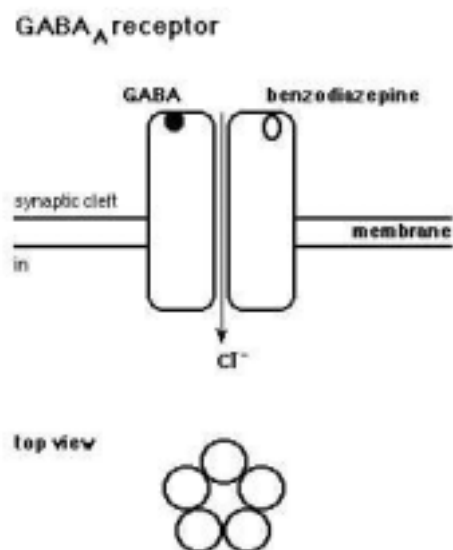


The GABA_A receptor complex also has other distinct, high-affinity binding sites able to modulate the channel function, such as the benzodiazepine receptor (BzR), the picrotoxin site, the barbiturate site and sites that bind neurosteroids, and ethanol. All of these other sites are "allosteric" and function as modulatory sites that regulate GABA affinity.

Among the allosteric receptor sites the sites for the benzodiazepines (Bz) are of prime importance since these ligands have been employed widely as anxiolytic/anticonvulsant agents since the 1960s. Studies of molecular biology have suggested that the GABA_A/BzR complex is a **heteropentameric** protein polymer constituted principally from α , β and γ subunits. At present, a total of 16 subunits (6 α , 4 β , 3 γ , 1 δ , and 2 ρ) have been isolated and identified from the CNS (15 of these have been found in the mammalian CNS). Recent studies of recombinant GABA_A/BzR have shown that the presence of α , β and γ subunits is necessary to constitute a fully functional benzodiazepine receptor/GABA/chloride ion channel which mimics the pharmacological, biochemical, and electrophysiological properties of a native receptor. From recombinant studies it appears that receptors constructed from α , β , and γ subunits most closely resemble the pharmacological profile of a native BzR subtypes obtained from mammalian tissues:

- Receptor subtypes comprised of an α 1 with β 2 γ 2 subunits resembling the activity of the classical Bz-1 receptor subtype and found in the cerebellum (and elsewhere).

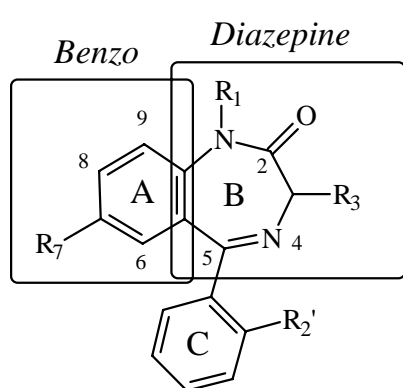
- Receptor subtypes comprised of $\alpha 2$ -, $\alpha 3$ - or $\alpha 5\beta 2\gamma 2$ subunits mimic the activity of the Bz-2 receptor that is found principally in the cortex, hippocampus, and spinal cord.
- The Bz-3 receptors, constitute the "peripheral" receptors since they have been identified in the brain as well as in a wide range of peripheral tissues; their subcellular location has been reported to be mainly mitochondrial, and hence, this receptor is also termed "mitochondrial benzodiazepine receptor". Although the structure and pharmacological role of the BZ3 receptors remains to be fully clarified, some evidence indicates their involvement in important cellular functions such as the production of neurosteroids.



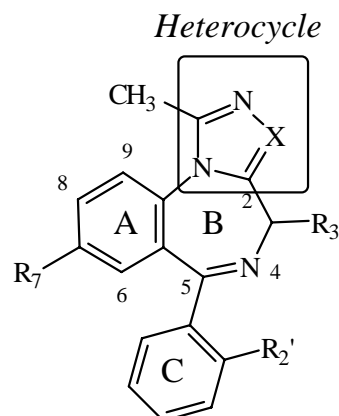
So far, a total of at least six receptor subtypes, BzR1-BzR6, have been cloned and sequenced from mammalian brain, which derive from the combination of different subunits. The extensive molecular diversity of GABA_A/BzRs that results from these subunits has been implicated in the multiple pharmacological properties elicited by ligands which lack subtype selectivity, such as diazepam. Furthermore, the regional heterogeneity of the GABA_A/BzR complex has been suggested as another basis for the multiplicity of pharmacological properties of BzR ligands. The identification of BzR subtype-selective ligands would provide agents with which to determine the relationship between physiological activity and BzR subtype. This may result in new subtype-selective agents for the treatment of anxiety, sleep disorders, convulsions, or memory deficits as well as decrease the potential for side effects. This is important since in recent years, the use of benzodiazepines has declined, due to the increasing unacceptability of their side effects, such as sedation, dizziness, interaction with alcohol, and the risk of dependence with long-term use. For these reasons, current research is directed toward the search for novel non-benzodiazepine tranquilizers devoid of the unwanted side effects associated with the classic benzodiazepines. For example, it would be useful to have partial agonists with anxiolytic and anticonvulsant properties in the absence of myorelaxant or sedative-hypnotic activity, or to have partial inverse agonists which can enhance general memory-learning and block or reverse the effects of barbiturate toxicity but are devoid of proconvulsant or convulsant activity.

IV. Benzodiazepines as Allosteric GABA Receptor Allosteric Modulators:

A. General Structure: See product List on the next page for individual Drug Structures!



Traditional Benzodiazepines
(1-Phenyl-1,4-benzodiazepin-2-one)

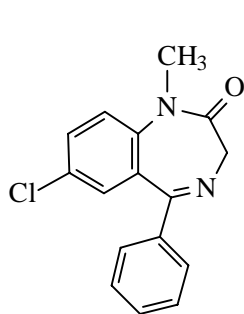


Imidazolo-benzodiazepines, X = CH
Triazolo-benzodiazepines, X = N

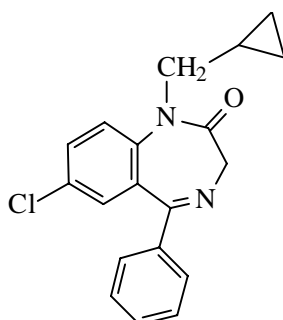
- Rings A, B and C are required for BDZ-receptor binding activity:
- Ring A participates in "pi-pi stacking " interactions with a complimentary functionality on the receptor
 - An electron withdrawing group at R₇ (usually Cl or NO₂) is required for optimal receptor affinity
 - Substitution on other positions of this ring may decrease activity
- Ring C contributes to BDZ-receptor binding through hydrophobic and steric interactions:
 - Position R₂' may be unsubstituted or contain a halogen atoms. Halogenation (F, Cl) generally increases BDZ activity
 - Substitution on other positions of this ring may decrease activity (4')
- Ring B is required for optimal BDZ-receptor binding, BUT
 - Neither the amide C=O or N-alkyl groups (R₁) directly contribute to binding. **R₁ can be H, CH₃, or relatively small alkyl groups.**
 - **Amide can be replaced with an amidine group as in chlordiazepoxide**
 - **Amide can be replaced with heterocycle such as imidazole or triazole**
 - The 3-position may be unsubstituted (R₃ = H) or hydroxylated (R₃ = OH)
 - The 4-5-imino group is not required for activity
- **Substituents at positions 1, 3 and to a lesser extent 7 influence pharmacokinetics as described in the sections that follow!**

BENZODIAZEPINE PRODUCTS

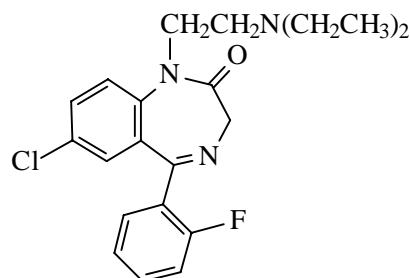
N-1-Substituted-3-Unsubstituted Benzodiazepines ("Diazepams")



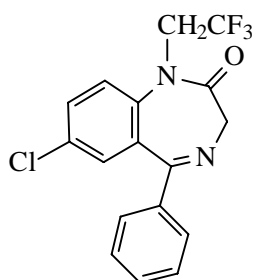
Diazepam



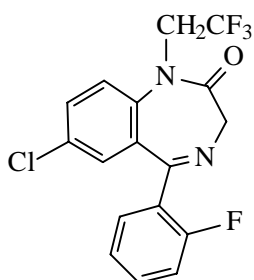
Prazepam



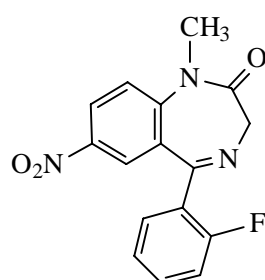
Flurazepam



Halazepam

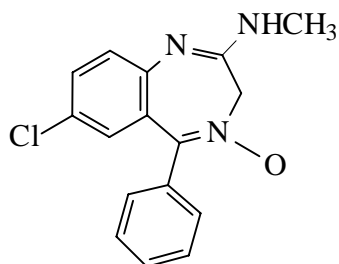


Quazepam



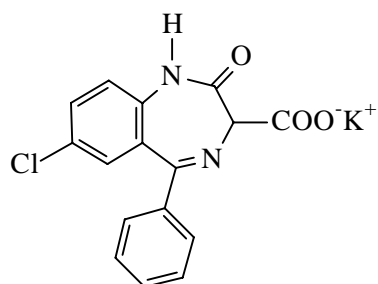
Flunitrazepam

Aminidino-N-oxide Benzodiazepines (Chlordiazepoxide)



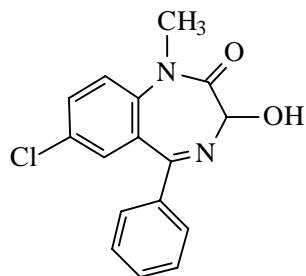
Chlordiazepoxide

3-Carboxyl-N-1-Unsubstituted Benzodiazepines (Chlorazepate)



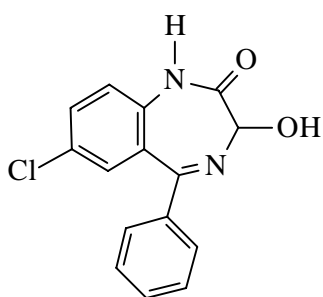
Chlorazepate

N-1-Substituted-3-Hydroxy Benzodiazepines ("N-Alkyl-Oxazepam")

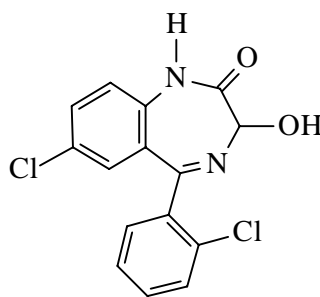


Temazepam

N-1-Unsubstituted-3-Hydroxy Benzodiazepines ("Oxazepam")

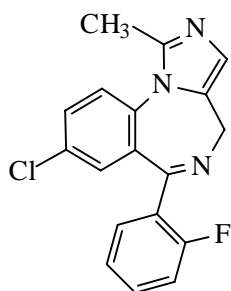


Oxazepam



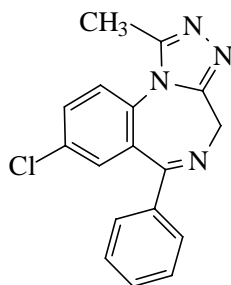
Lorazepam

Imidazo-Benzodiazepines

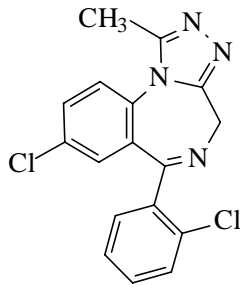


Midazolam

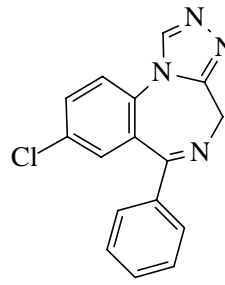
Triazolo-Benzodiazepines



Alprazolam



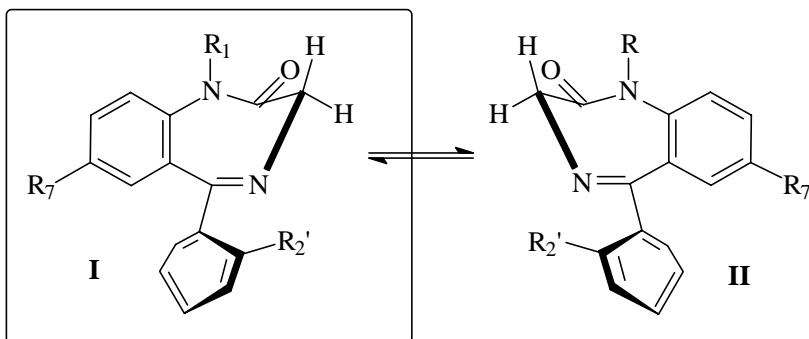
Triazolam



Estazolam

B. Benzodiazepine Stereochemistry

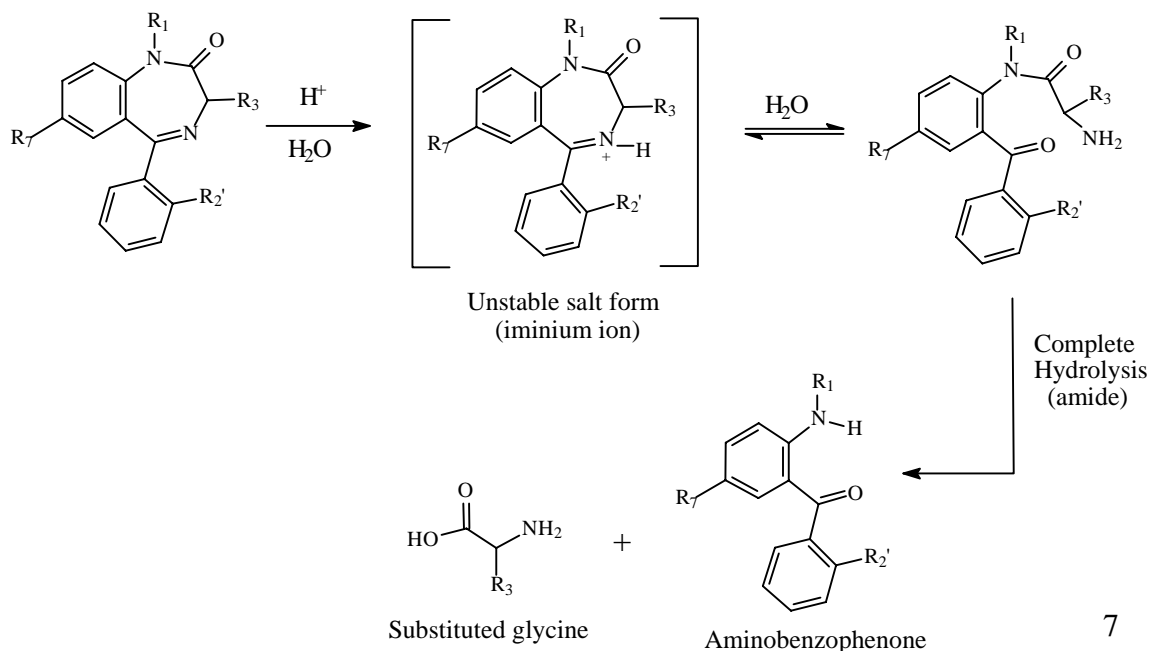
Most (BUT NOT ALL!) BDZs do not have a chiral center, but the 7-membered B ring in these compounds may adopt one of two energetically preferred boat conformations (I and II below) which are enantiomeric relative to each other. Some studies suggest conformation I is preferred for BZD receptor binding:



C. Benzodiazepine Lipophilicity: As a class the benzodiazepines are relatively lipophilic compounds due to their high hydrocarbon content and presence of halogen atoms. Also, most (not all) benzodiazepines do not behave as acids or bases under physiologic conditions and thus are not ionized. The role of lipophilicity in drug activity is discussed in more detail in the sections that follow.

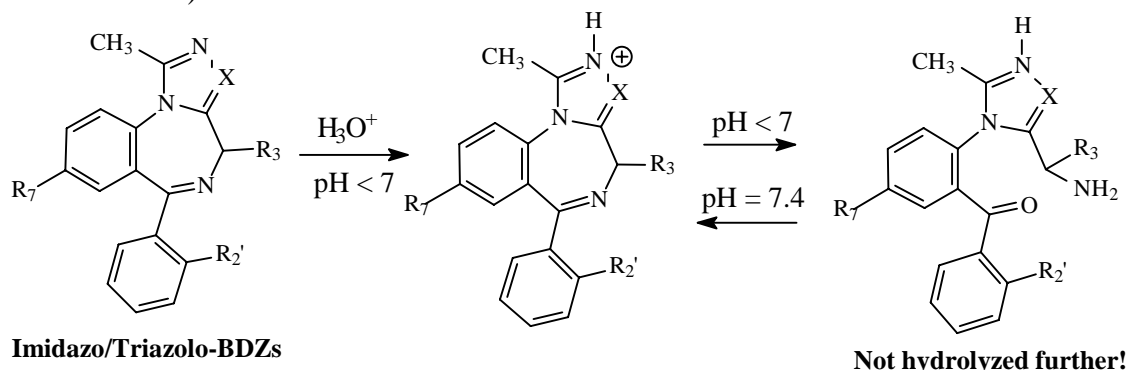
D. Basicity and Reactivity of the “Traditional Benzodiazepines”

- The BDZs are weak organic bases with the most basic nitrogen being the imine N4 (amide at positions 1,2 is non-basic). Thus BDZ salts can only be formed with strong acids. Unfortunately, such strong acid salts are unstable and readily undergo sequential hydrolyses, first at the imine bond and then at the amide to yield inactive products. **The first hydrolysis reaction (imine hydrolysis) is reversible, however the second (amide hydrolysis) eliminates GABA receptor activity.**



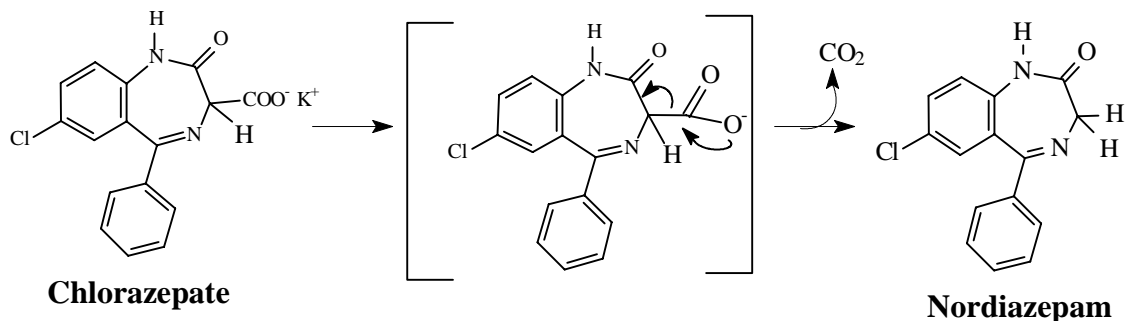
E. Basicity and Reactivity of the "Imidazo- and Triazolo-Benzodiazepines"

- The tricyclic benzodiazepines **differ** from most of the "traditional benzodiazepines" in that they have a more basic nitrogen atom (or more) in their additional ring structure (imidazole or triazole ring). This (these) nitrogen atoms typically are not sufficiently basic to be protonated (ionized) at physiologic pH, but they are sufficiently basic to yield water soluble salts when treated with strong acids.
- The salts formed from the heterocyclic benzodiazepines are more stable than salts formed from the traditional drugs!** When placed in aqueous media the heterocyclic salts may undergo imine hydrolysis similar to the traditional agents (see above), however no further hydrolysis (to inactive products) can occur since the heterocyclic compounds no longer have an acid labile amide group; in these compounds the amide was replaced with the heterocyclic group. Thus at acidic pHs imine hydrolysis may occur as shown below but the reaction does not proceed, and at physiologic pH (post-injection) reformation of the benzodiazepine ring is favored (as shown below):



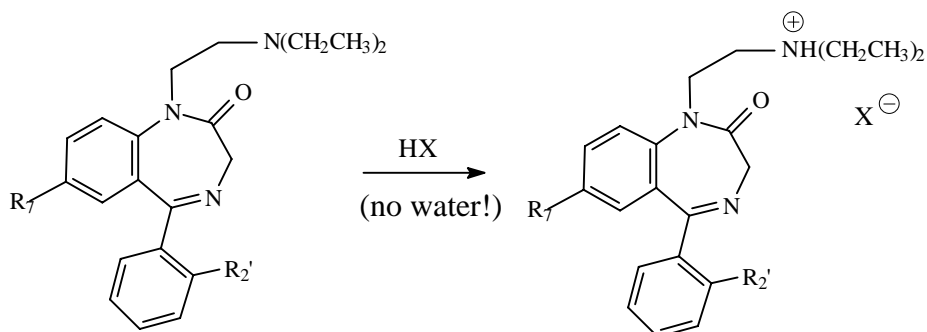
F. Clorazepate and the 3-Carboxylate Benzodiazepines: Prodrugs:

- The 3-carboxylate benzodiazepines are unique in that they contain a 3-COO⁻M⁺ functionality which allows for water solubility. These drugs, of which **chlorazepate** is the prototype, function as water soluble prodrugs for the more traditional benzodiazepines. When administered (orally) they are readily protonated in the upper GI tract and spontaneously decarboxylate (loss of CO₂) as shown below to yield an active benzodiazepine which is absorbed from the gut. **This is a chemical reaction and not an enzyme-catalyzed reaction!**



G. Flurazepam and the 1-Alkylamino Benzodiazepines

- Flurazepam differs from other traditional benzodiazepines in that it contains a 1-(diethylamino)ethyl side chain. The nitrogen atom in this side chain is a typically tertiary amine and is relatively basic (pKa about 9). Thus this nitrogen serves as a basic center for salt formation as shown below:

H. Benzodiazepine Formulations

- Oral: Parent drug or HCl salt (for basic BDZs)
- Injectables: Those benzodiazepines that do not provide stable salts (most of the traditional agents) are relatively water insoluble. Thus preparation of water soluble injection forms requires the use of co-solvents such as water with PEG 400, propylene glycol or 2% benzyl alcohol

Benzodiazepine	Formulation
Diazepam	Parent Drug: Tablets, Oral Solution Injection: 40% propylene glycol, 10% ethyl alcohol, etc
Oxazepam	Parent Drug: Tablets and Capsules
Lorazepam	Parent Drug: Tablets and oral Solution Injection: PEG 400, propylene glycol, 2% benzyl alcohol.
Halazepam	Parent Drug: Tablets
Prazepam	Parent Drug: Tablets
Clorazepate	DiK: Capsules and Tablets
Flurazepam	HCl: Capsules
Temazepam	Parent Drug; Capsules
Clonazepam	Parent Drug: Tablets
Chlordiazepoxide	HCl: Tablets and Capsules Powder for Injection
Quazepam	Parent Drug: Tablets
Estazolam	Parent Drug: Tablets
Alprazolam	Parent Drug: Tablets and oral Suspension
Midazolam	HCl: Syrup and Injection
Triazolam	Parent Drug: Tablets

I. Benzodiazepine Pharmacokinetics

- Oral administration: Most BDZs are relatively weak bases and relatively lipophilic, resulting in fairly rapid and complete absorption from the GI tract. Absorption from other sites (IM) may be more erratic due to the lipophilicity of these compounds. Generally the rate of absorption from the GI tract is dependent on the lipophilicity of the BDZ. For example, diazepam is absorbed very rapidly, while oxazepam and clonazepam are absorbed more slowly.
- Distribution: BDZs are highly protein bound (70-99%) but rapidly distribute to CNS. They cross the BBB by passive diffusion, thus the rate of CNS distribution correlates with lipophilicity (diazepam is "appropriately" lipophilic).
- Duration of Action: The duration of BDZ action is dependent largely on the rate and nature of metabolism, which is dependent on the structure of the drug. Differences in duration are accounted for by structural differences involving primary N-1 and C-3-substitution and metabolism as detailed in the Metabolism Section. For example, compare diazepam and flurazepam (both N-substituted, non-C3-OH benzodiazepines) to oxazepam and lorazepam (N-unsubstituted, C3-OH benzodiazepines). **It is also important to note that BDZs do not induce the metabolism of other drugs (unlike barbiturates).**
- BDZ's characterized by a rapid distributive phase (alpha-half-life, usually short, 1 hr) and longer elimination phase (beta-half-life which may be days). Plasma BDZ concentrations do not necessarily correlate with clinical effect. **The duration of action is often determined by the half-life of active intermediate metabolites rather than the half-life of the parent drug (see sections that follow!)**
- BDZs and their metabolites may accumulate, especially upon repeated dosing. This may result in a delay in the appearance of adverse reactions, and extension the clinical effect beyond discontinuation of the drug. This creates concerns for hepatically impaired patients, elderly, etc.
- With advancing age the intermediate **oxidative pathways** for BDZ metabolism slow more than the conjugative pathways. Thus the use of BDZs which require oxidative metabolism prior to conjugation and clearance (long-acting BDZs) should be avoided in the elderly.

Pharmacokinetics/Biodisposition of the Benzodiazepines**SEE STRUCTURES ON PAGES 5-6!!!!**

BDZ	ppl, hr (oral)	Rate of Onset	Elim. t_{1/2}, hrs	Duratn, hrs	Indications
"Diazepam"(N-1-Substituted BDZs)					
Diazepam	0.5-2	Very fast	20-80	>48 (L)	A, SH, IA, AC
Halazepam	1-3	Interm-Slow	14	>48 (L)	A, SH
Prazepam	6	Slow	30-100	>48 (L)	A
Flurazepam				>24 (L)	SH
Quazepam				>24 (L)	SH
Chlordiazepoxide	0.5-4	Interm	5-30	>48 (L)	A, SH, AD
"Nordiazepam" (N-1-Unsubstituted BDZs)					
Clorazepate	1-2	Fast	30-100	>48 (L)	A, SH, AC
Clonazepam	1-2	Interm-Slow	18-50	>48 (L)	A, AC
N1-Alkyl "Oxazepam"(N-1Subst-3-OH-BDZs)					
Temazepam				6-24 (I)	SH
"Oxazepam" (N-1-Unsubst-3-OH-BDZs)					
Oxazepam	2-4	Interm-Slow	5-20	12-18 (I)	A, SH
Lorazepam	1-6	Interm	10-20	12-18 (I)	A, SH, IA, AC
"ImidazoBDZs"					
Midazolam				<6 (S)	SH, IA
"Triazolo-BDZs"					
Triazolam				<6 (S)	SH
Estazolam				6-24 (I)	SH
Alprazolam			6-12	24 (I)	A, SH, AD

A=Anxiety

SH=Sedative/Hypnotic

IA= Induction of anesthesia

AC=Anticonvulsant

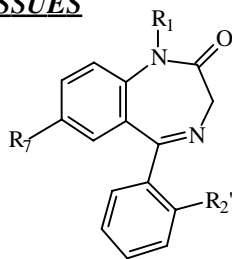
AD=Antidepressant

General Scheme of Benzodiazepine Structure and Biodisposition

PLASMA AND PERIPHERAL TISSUES

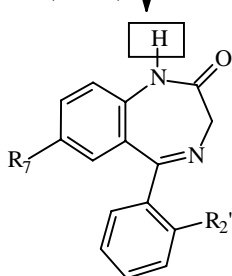
**N1-Substituted-(3-Unsubstituted)
Benzodiazepines**

$R_1 = \text{CH}_3, \text{CH}_2\text{-c-C}_3\text{H}_5, \text{CH}_2\text{CF}_3,$
or $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$



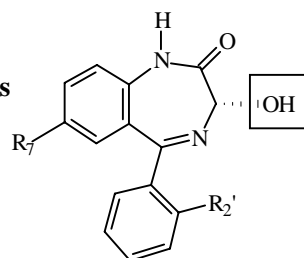
*CYP*₄₅₀
(OND)

**"Nordiazepam" Metabolites
(ACTIVE)**

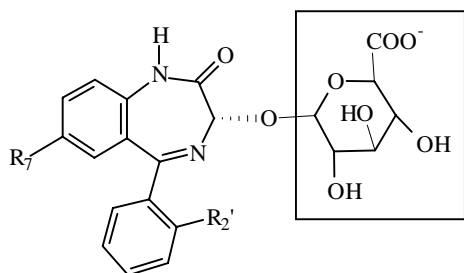


*CYP*₄₅₀
(C-3 Oxidation)

**"Oxazepam" Metabolites
(ACTIVE)**



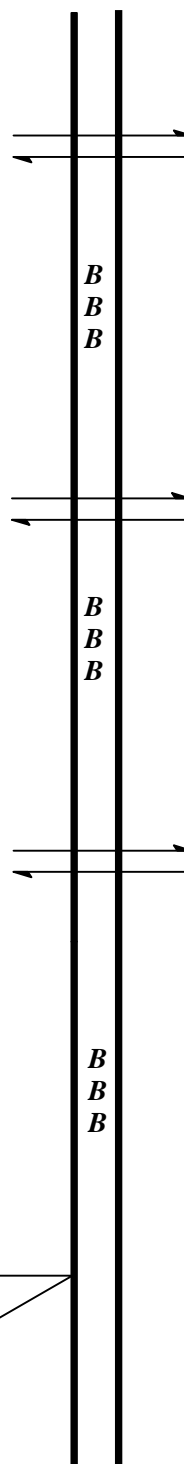
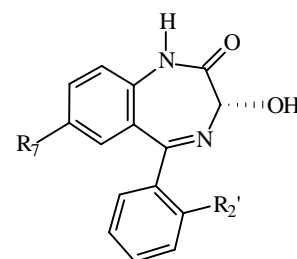
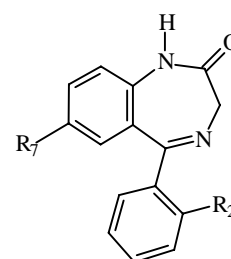
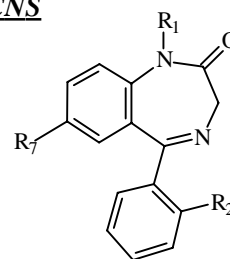
Glucuronyl
Transferase



**BDZ-3-O-Glucuronides
(INACTIVE)**

ELIMINATION

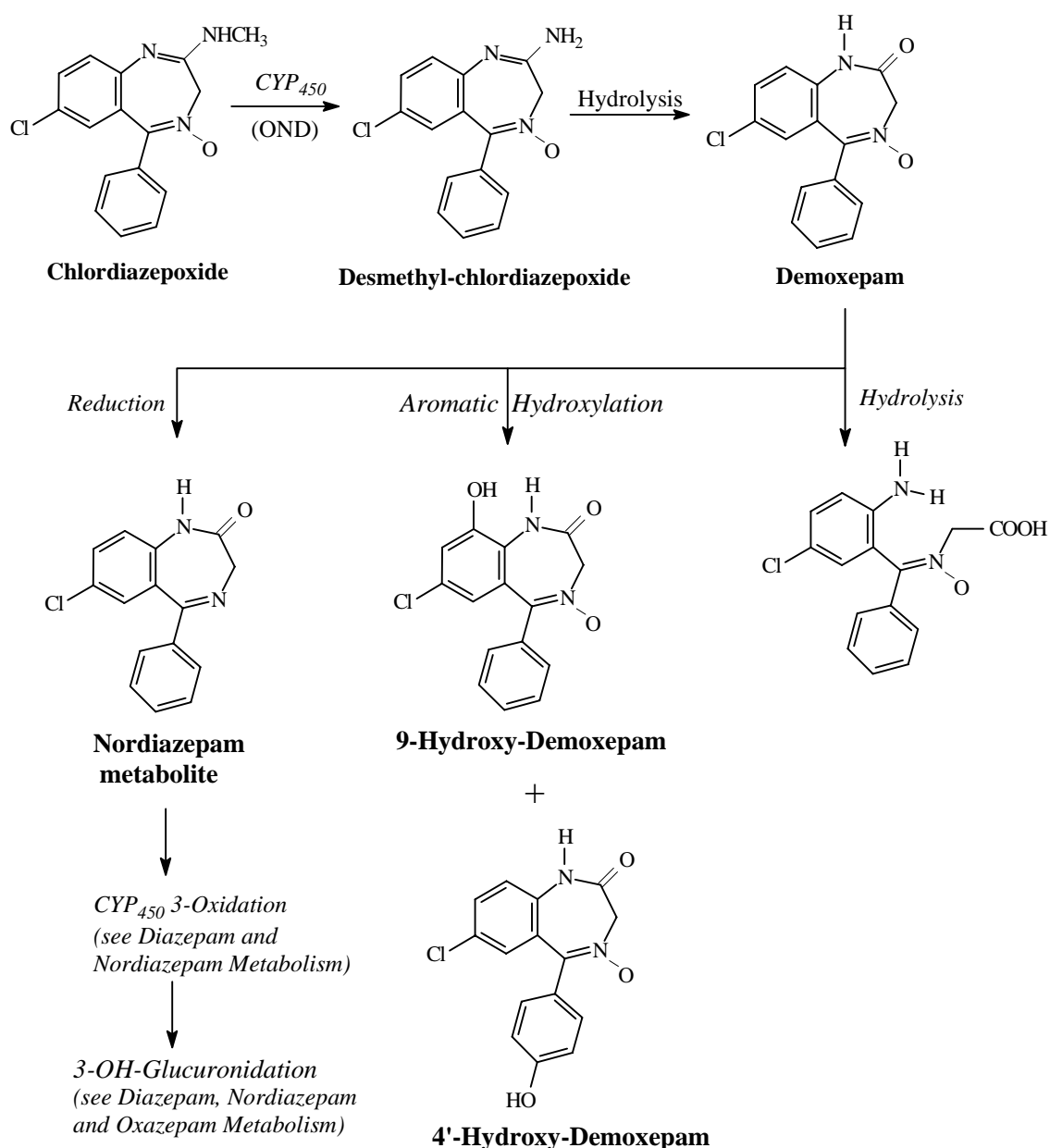
CNS



J. Metabolism of the Benzodiazepines

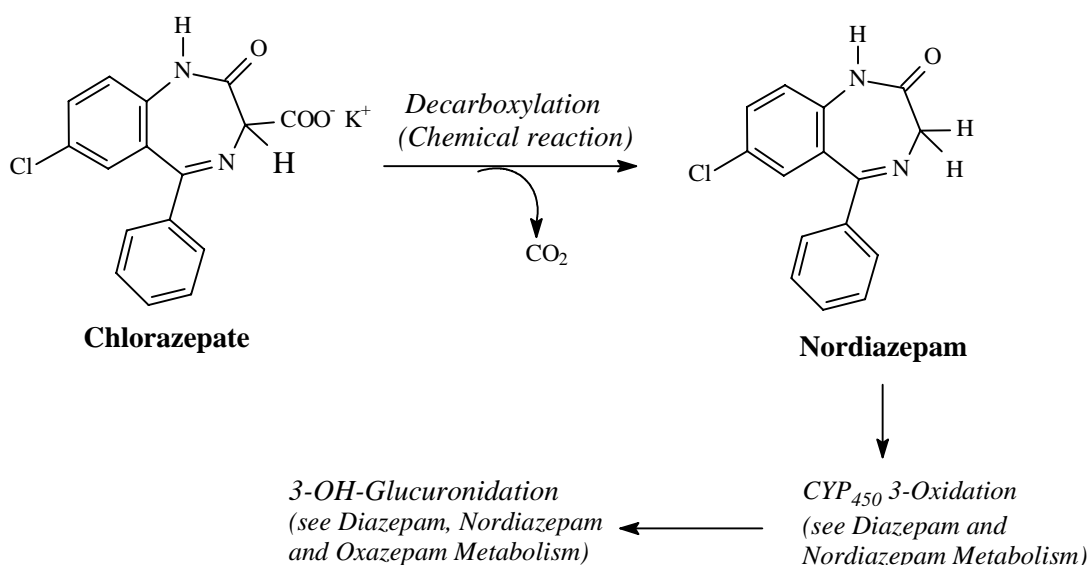
1. *Metabolism of Chlordiazepoxide/Amidine BDZs: (Interm Onset, Long Duration)*

Chlordiazepoxide is well absorbed after oral administration, but slowly and erratically absorbed from IM injection sites. This drug is metabolized to active benzodiazepine metabolites in a series of reactions beginning with CYP-mediated OND-demethylation of the amidine group. This "desmethyl"metabolite is slowly hydrolyzed to demoxepam which can undergo three different reactions: 1). hydrolysis to an inactive ring opened form, 2). aromatic hydroxylation to phenol metabolites that retain some activity and 3). Reduction to an active "nordiazepam" metabolite. The nordiazepam metabolite may be further oxidized to an active "oxazepam" metabolite that can be conjugated as a glucuronide which is inactive and eliminated:



2. Chlorazepate and 3-Carboxy-BDZ Metabolism (Fast Onset, Long Duration):

Chlorazepate and 3-carboxyl benzodiazepines have a 3-acidic group from which salts can be formed. These products undergo spontaneous decarboxylation in the GI tract (and other tissues) to yield "nordiazepam" intermediates. This is a chemical reaction (not enzymatic or metabolic)! that occurs because the anionic charge formed from decarboxylation can be stabilized by resonance through the adjacent amide carbonyl and imine. The nordiazepam formed is active as a BZ-ligand and is oxidized by CYP-isozymes to an "oxazepam" metabolite that is also active. The oxazepam metabolite may be conjugated as a glucuronide which is inactive and eliminated. Because this compound gives rise to several active, relatively long-lived metabolites, it has a long duration of action!



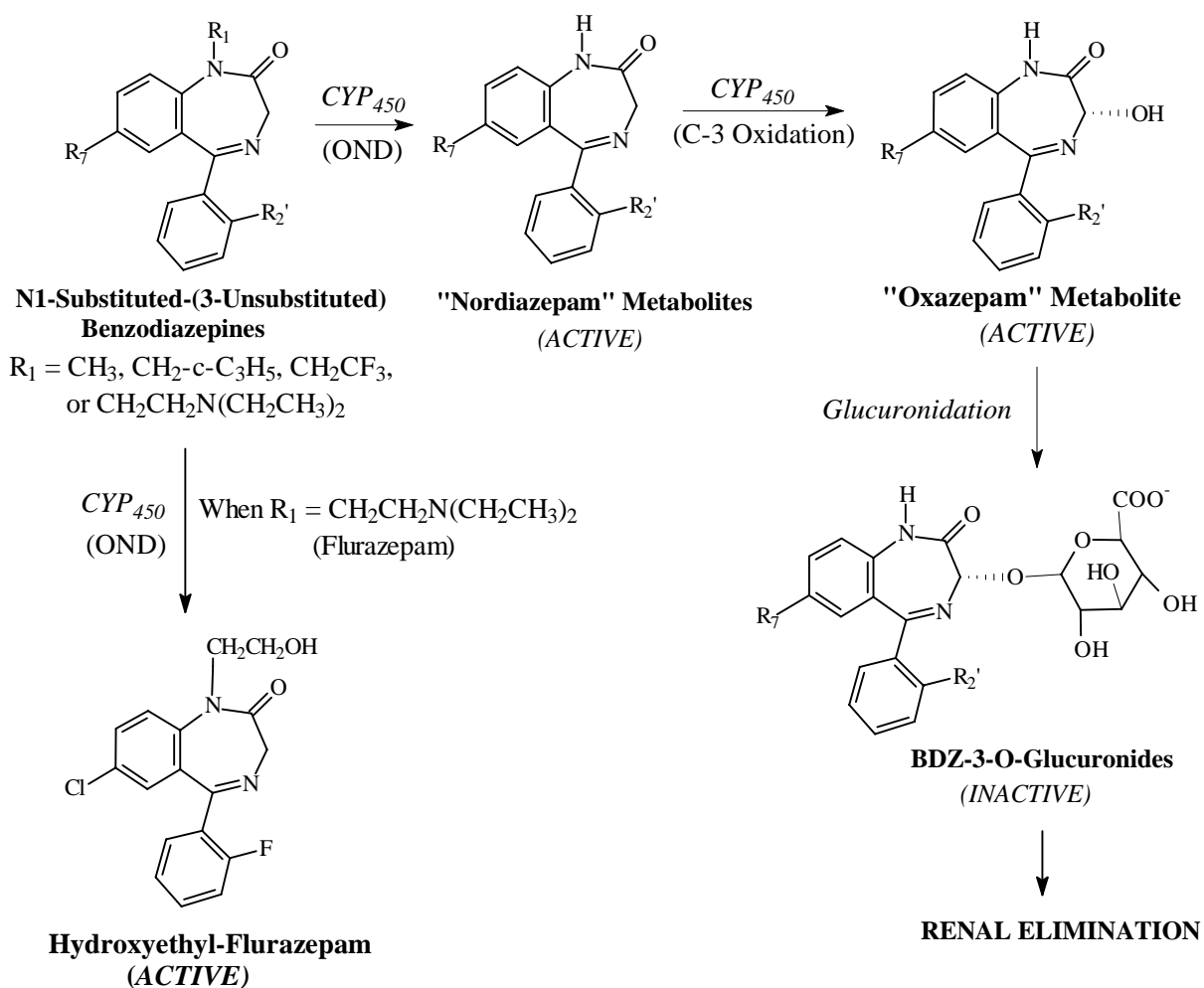
3. Metabolism of the N-1-Substituted-3-Unsubstituted Benzodiazepines ("Diazepams"): Slow to fast onset and Long Duration!

The N-1-Substituted-3-unsubstituted benzodiazepines or "diazepams" are variably absorbed and distributed to the CNS based on their solubility and lipophilicity. All of these share the common property of long duration. This is a result of the formation of several active metabolites including the corresponding "nordiazepams" and "oxazepams" as shown in the Figure on the next page. Each of these N-1-Substituted-3-unsubstituted benzodiazepines undergo sequential oxidative metabolism, first at N-1 to yield active "nordiazepam" metabolites, then at the C-3 position to yield active "oxazepam" metabolites. Each of these metabolites can penetrate the BBB and enter the CNS and bind to BZ receptors on the GABA complex and thus are active. Each of these metabolites are also lipophilic enough to be reabsorbed from the kidney or during biliary cycling. Only after these benzodiazepines are metabolized to glucuronide conjugates is BZ-activity lost and the drug eliminated. **Thus these compounds have long "effective" half-lives. It should also be noted that one of these compounds, flurazepam, can also undergo OND reactions in its N-1 diethylamino side chain (see next page). One**

of the primary metabolites formed from this pathway, the hydroxyethyl metabolite, is also an active BZ-receptor ligand!

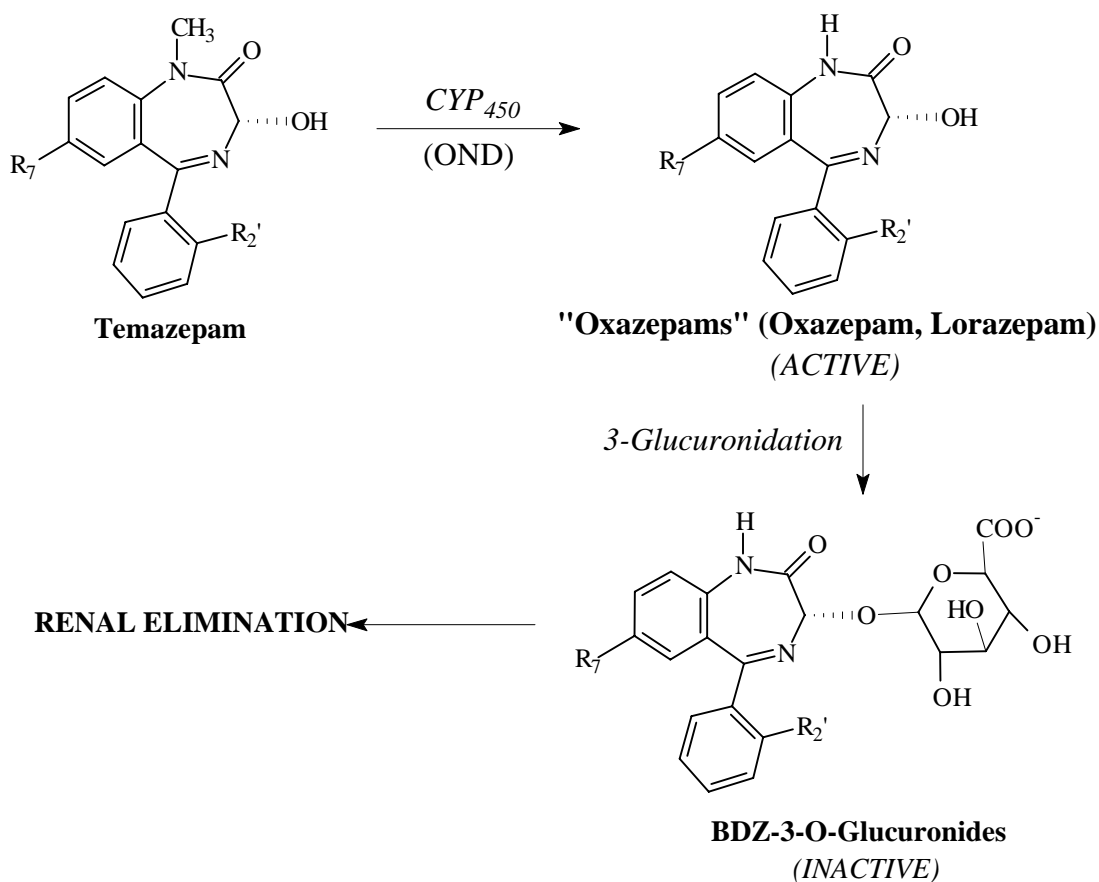
It is important to note that the clearance of the N-1-substituted-3-unsubstituted benzodiazepines, as well as the amidine and 3-carboxyl benzodiazepines discussed above, is dependent on oxidative metabolism (largely hepatic metabolism). Thus elderly patients and others with impaired hepatic function will clear these drugs more slowly than benzodiazepines that do not require oxidation for clearance (see the "oxazepam" below). In other words, these benzodiazepines will have substantially longer half-lives and may accumulate in patients with impaired or limited hepatic function!

It is also important to note that **ONLY** benzodiazepines with "oxidizable" N-1 substituents undergo N-1 oxidative dealkylation and that is why the carbon substituent bound to N-1 contains at least one (usually two) hydrogen atoms. Benzodiazepine derivatives lacking hydrogen substituents on the carbon bound to N-1 could not undergo this metabolic process!!!!



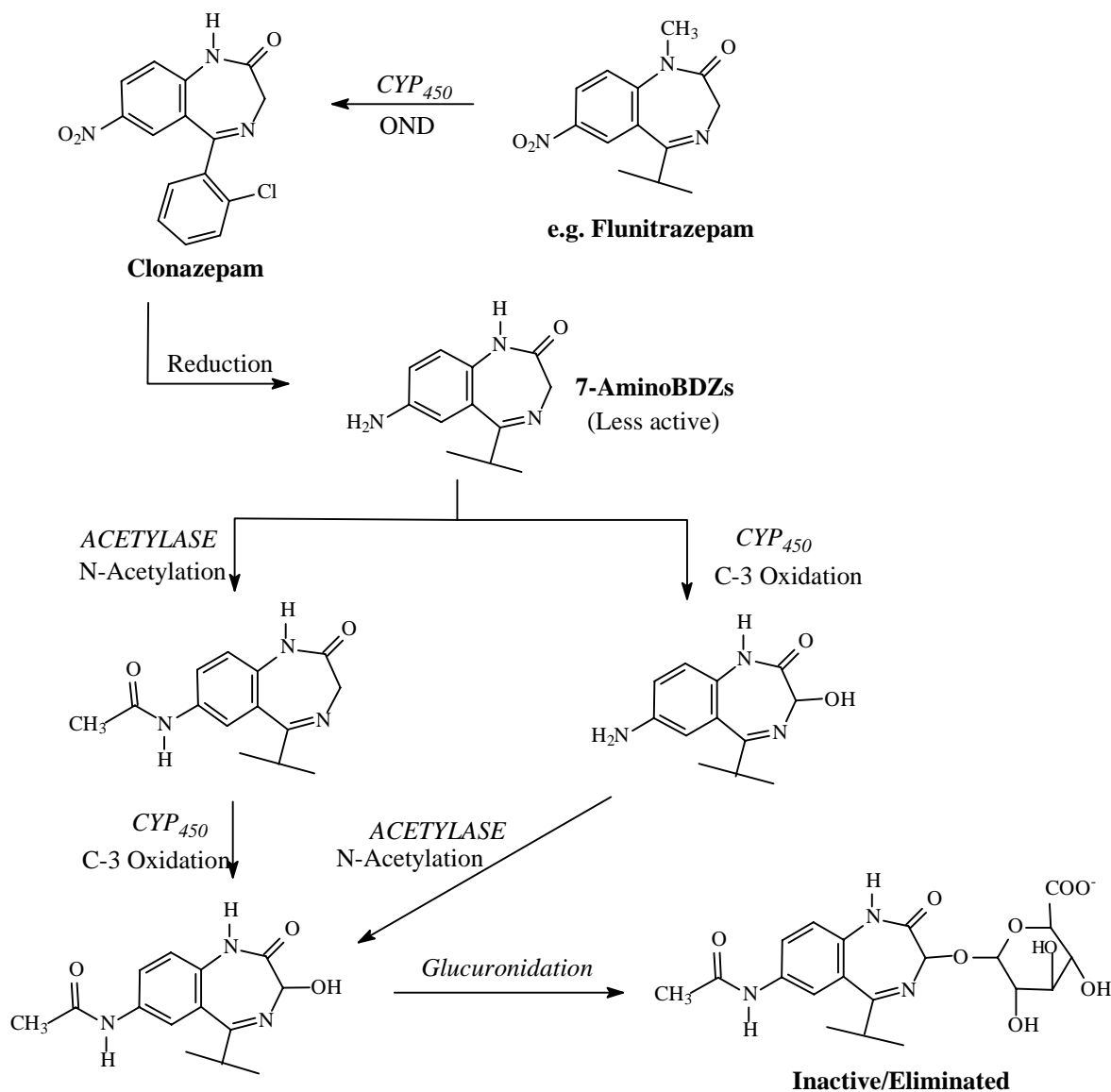
4. Metabolism of the C-3-Hydroxy-Substituted Benzodiazepines (“Oxazepam”): Slow to intermediate onset, Intermediate duration of action)

- The C-3-Hydroxy-substituted benzodiazepines are more polar than the N-1-substituted-3-unsubstituted benzodiazepines and generally have a slower onset. Also, since they all contain a 3-hydroxyl group in their structure, they can be **directly** conjugated as inactive glucuronides and eliminated. Thus they have a significantly shorter duration of action than the N-1-substituted-3-unsubstituted benzodiazepines discussed above. One consequence of this difference in metabolism is that the oxazepam may be safer to use in the elderly and other patients with compromised oxidative metabolic capacity!



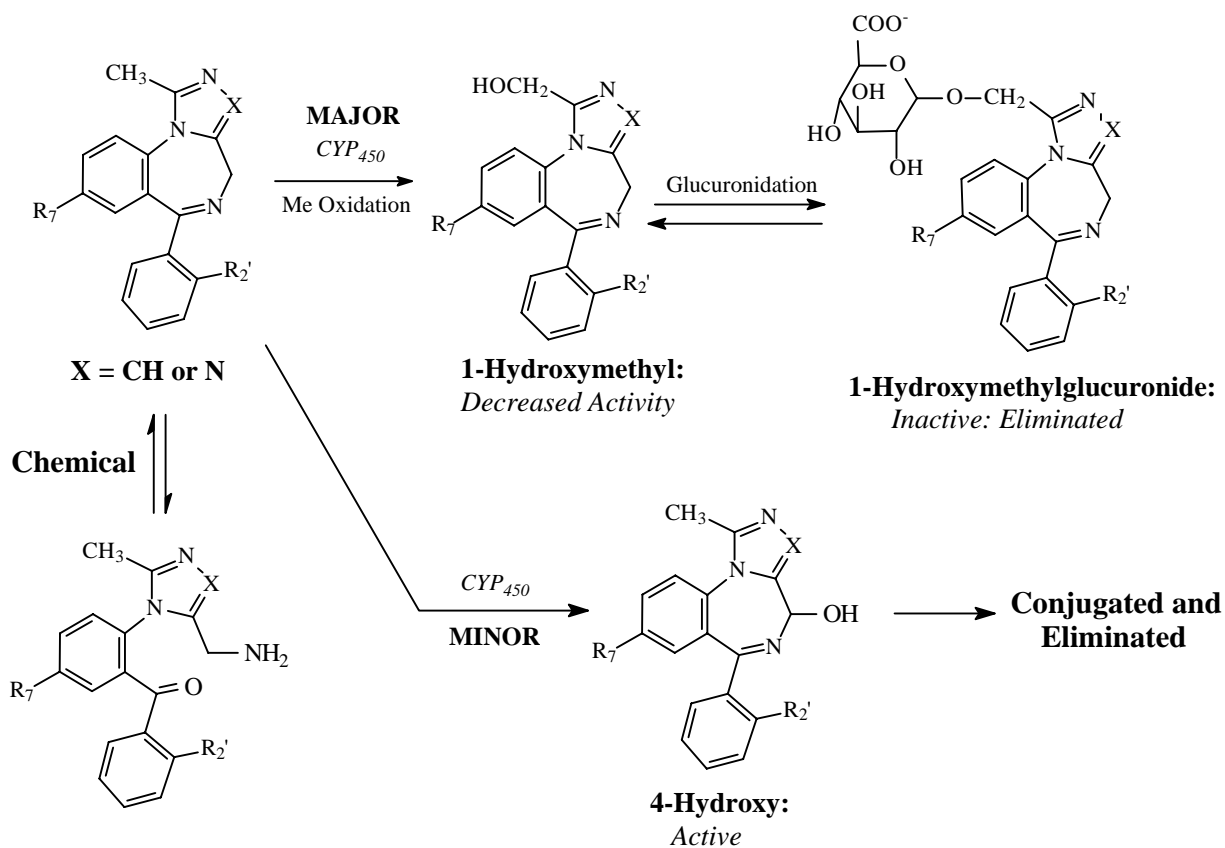
5. Metabolism of the 7-Nitro-benzodiazepines: Slow to intermediate onset and Long duration

As indicated in the metabolic scheme below, the 7-nitro-benzodiazepines can undergo the same metabolic reactions as other benzodiazepines of comparable functionality including OND at N-1 (when a N-1 substituent is present), C-3-Oxidation and glucuronide conjugation of the C-3-OH metabolite. And again, the intermediate "nordiazepam" and "oxazepam" metabolites are active as BZ-receptor ligands, and these compounds thus have relatively long duration of action. The 7-nitro benzodiazepines also can undergo reduction of the 7-nitro group to the corresponding aniline (7-amino) as shown in the figure below. The 7-amino metabolites are typically less active than the parent nitro compounds (see structure-activity requirement), and can be conjugated by acetylation (also less active). Thus complex, inactive metabolites eventually form from these compounds:



6. Metabolism of the Tricyclic Benzodiazepines: Relatively rapid onset, Intermediate to short duration.

These compounds are relatively lipophilic and thus are rapidly absorbed and diffuse into the CNS. Metabolism of the tricyclic benzodiazepines typically follows a different pathway than the "traditional" benzodiazepines. All of these compounds **except estazolam** have a "benzylic type" methyl group at the 1-position of the imidazole or triazole ring and this group is subject to rapid cytochrome-mediated oxidation as shown below. This 1-hydroxymethyl metabolite retains activity, but in most cases (**except alprazolam**) is rapidly conjugated as an inactive glucuronide and eliminated. Thus these compounds have intermediate to short duration of action. These compounds may also be oxidized at the available carbon in the benzodiazepine ring (as shown below), but this pathway appears to be relatively minor. Also some levels of the "ring-opened" benzophenone may exist in plasma (and appear in urine) but this merely reflects the



equilibrium form discussed earlier.

Thus the relative duration for the azole BDZs is: estazolam, alprazolam (intermediate) > triazolam, midazolam (relatively short)!

K. Benzodiazepine Drug Interactions

1. Pharmacologic Interactions:

Alcohol and drugs that produce CNS depression (eg, barbiturates, narcotics) may increase the CNS effects (eg, impaired psychomotor function, sedation) of the benzodiazepines.

2. Pharmacokinetic Interactions:

Antacids, H₂-antagonists and proton pump inhibitors may reduce the GI absorption of benzodiazepines by elevated gastric pH. It appears that as gastric pH increases, benzodiazepine solubility decreases, resulting in poorer diffusion and ultimately absorption from the GI tract

Drugs that **inhibit** cytochrome isozymes (cimetidine, contraceptives, disulfiram, fluoxetine, isoniazid, ketoconazole, metoprolol, propoxyphene, propranolol, valproic acid) may inhibit the oxidative metabolism (N-1 OND and C-3 oxidation) of benzodiazepines. This is particularly significant for N-1-substituted-3-unsubstituted benzodiazepines since they require two oxidation reactions prior to conjugation and elimination. Such an interaction may result in increased benzodiazepine-related CNS effects (sedation, impaired psychomotor function, etc.).

Drugs that alter the activity of glucuronyl transferase may alter the clearance of 3-hydroxybenzodiazepines ("oxazepam") and other benzodiazepines that are metabolized to 3-hydroxybenzodiazepines. For example, probenecid may interfere with 3-hydroxybenzodiazepine conjugation in the liver, possibly resulting in a more prolonged effect.

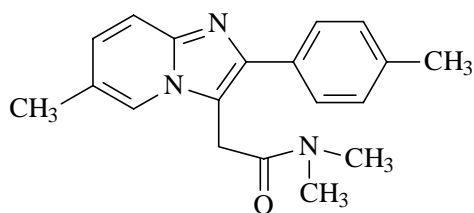
L. Benzodiazepine Adverse Reactions: *See Pharmacology Notes!*

- General Toxicity: Low
- CNS: Drowsiness, dizziness, ataxia, impaired psychomotor function, amnesia, weight gain and "paradoxical effects" (aggression, anxiety, etc.)
- Respiratory Depression: Minimal!
- Cardiovascular: Minimal (slight BP decreases)
- Skeletal Muscle: Some relaxation
- Tolerance and Dependence:

NON-BENZODIAZEPINE GABA RECEPTOR LIGANDS

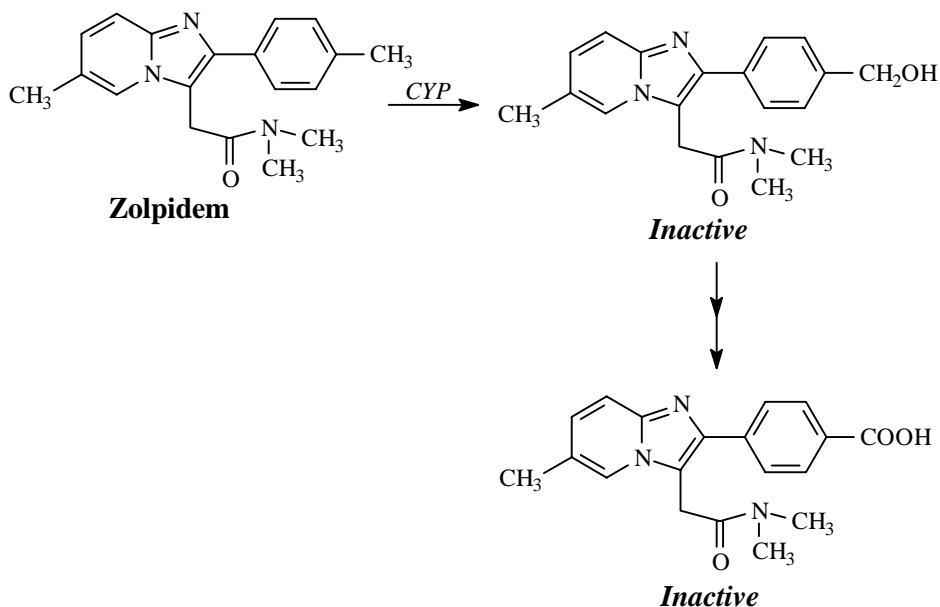
A. Zolpidem (Ambien)

- Zolpidem is an imidazopyridine sedative-hypnotic (insomnia) that is structurally unrelated to the barbiturates and benzodiazepines. Pharmacologically, zolpidem binds to the omega-1 subclass of benzodiazepine receptors (GABA_A) in the brain, presumably without binding to peripheral benzodiazepine receptors. This has been corroborated by the observation that zolpidem has little or no muscle relaxant properties. It has a rapid onset and short duration of action, and is said to have a more favorable adverse effect profile than the benzodiazepines and preliminary clinical data suggest that tolerance may not develop as readily to the drug. Thus, zolpidem may have less abuse potential than the benzodiazepines.



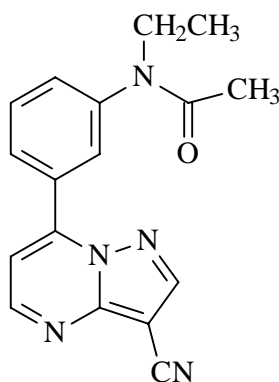
Zolpidem

- Pharmacokinetics:
 - Rapid absorption but some first pass and secondary metabolism to inactive alcohol and then acid as shown below. Thus half-life increases in the elderly and patients with hepatic disease (from 3 to 10 hours). Also the potential exists for **drug interactions** with other drugs that inhibit or competes with zolpidem for oxidative enzymes
 - Highly protein bound: Potential for drug interactions
 - Eliminated primarily as metabolites (conjugates) by non-renal routes. Reduce dose in hepatic (but not renal) impairment!



B. Zaleplon (Sonata)

- Zaleplon is a nonbenzodiazepine hypnotic from the pyrazolopyrimidine class and thus is not directly related in structure to the benzodiazepines, barbiturates, or other drugs with known hypnotic properties. Zaleplon interacts with the GABA-BZ receptor complex, and similar to the benzodiazepines modulate the GABA-BZ receptor chloride channel macromolecular complex to produce its sedative actions. Like zolpidem, zaleplon binds selectively to the brain omega-1 receptor situated on the alpha subunit of the GABA-A receptor complex and potentiates t-butyl-bicyclophosphorothionate (TBPS) binding. Studies of binding of zaleplon to purified GABA-A receptors ($\alpha 1\beta 1\gamma 2$ [omega-1] and $\alpha 2\beta 1\gamma 2$ [omega-2]) have shown that zaleplon has a low affinity for these receptors, with preferential binding to the omega-1 receptor.



Zaleplon (Sonata)

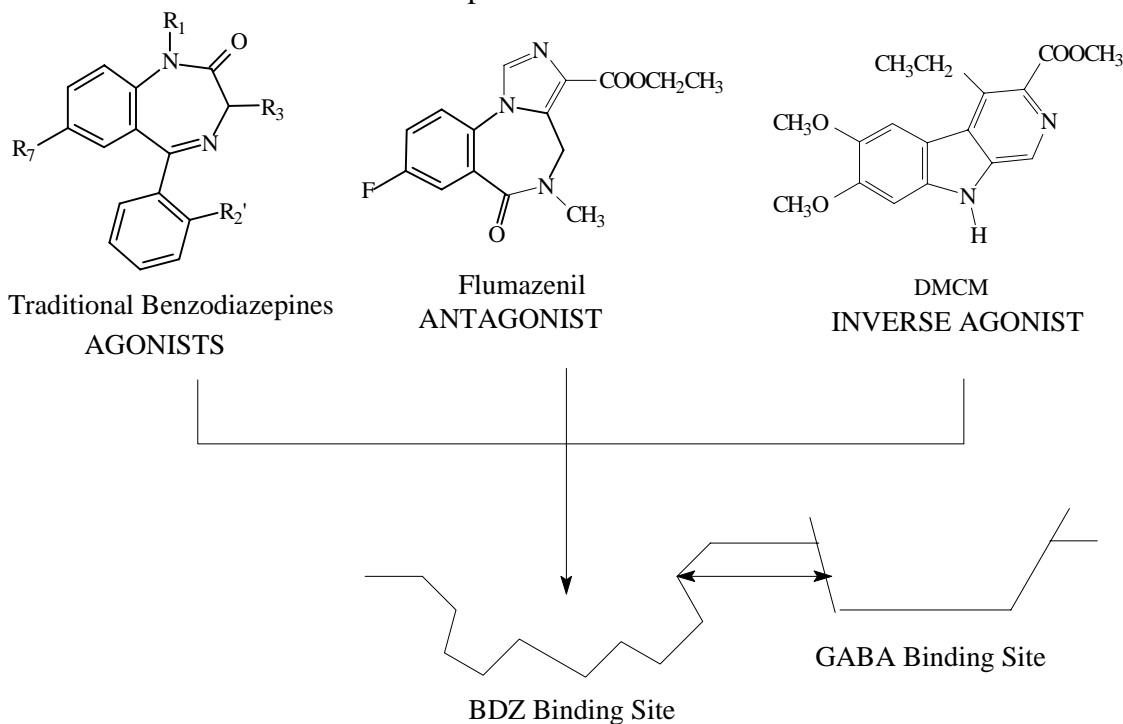
- Zaleplon is rapidly and almost completely absorbed following oral administration. Peak plasma concentrations are attained within an hour after oral administration. Although zaleplon is well absorbed, its absolute bioavailability is only about 30% because it undergoes significant first pass metabolism. A high-fat/heavy meal prolongs the absorption of zaleplon.
- Distribution: Zaleplon is a lipophilic compound with a volume of distribution of $\gg 1.4$ L/kg following IV administration, indicating substantial distribution into extravascular tissues. The in vitro plasma protein binding is $\gg 60\%$ and is independent of zaleplon concentration over the range of 10 to 1000 ng/ml. Zaleplon is uniformly distributed throughout the blood with no extensive distribution into red blood cells.
- Metabolism: After oral administration, zaleplon is extensively metabolized with $<1\%$ of the dose excreted unchanged in urine. Zaleplon is primarily metabolized by aldehyde oxidase to form 5-oxo-zaleplon. Zaleplon is metabolized to a lesser extent by CYP3A4 to form desethylzaleplon, which is quickly converted, presumably by aldehyde oxidase, to 5-oxo-desethylzaleplon. These oxidative metabolites are then converted to glucuronides and eliminated in the urine. All of zaleplon's metabolites

are pharmacologically inactive. Caution with drugs that are inducers (rifampin) or inhibitors (i.e. cimetidine) of CYP3A4

- Excretion: Following oral or IV administration, zaleplon is rapidly eliminated with a mean half-life of \gg 1 hour. Assuming normal hepatic blood flow and negligible renal clearance of zaleplon, the estimated hepatic extraction ratio of zaleplon is \gg 0.7, indicating that zaleplon is subject to high first-pass metabolism. Approximately 70% of the dose is recovered in urine within 48 hours (71% recovered within 6 days), nearly all as zaleplon metabolites and their glucuronides. An additional 17% is recovered in feces within 6 days, most as 5-oxo-zaleplon. Based on this elimination profile, dose should be reduced in instances of significant hepatic impairment, but not renal impairment. Do not use in severe hepatic impairment!
- ADRs and caution: use prior to bedtime

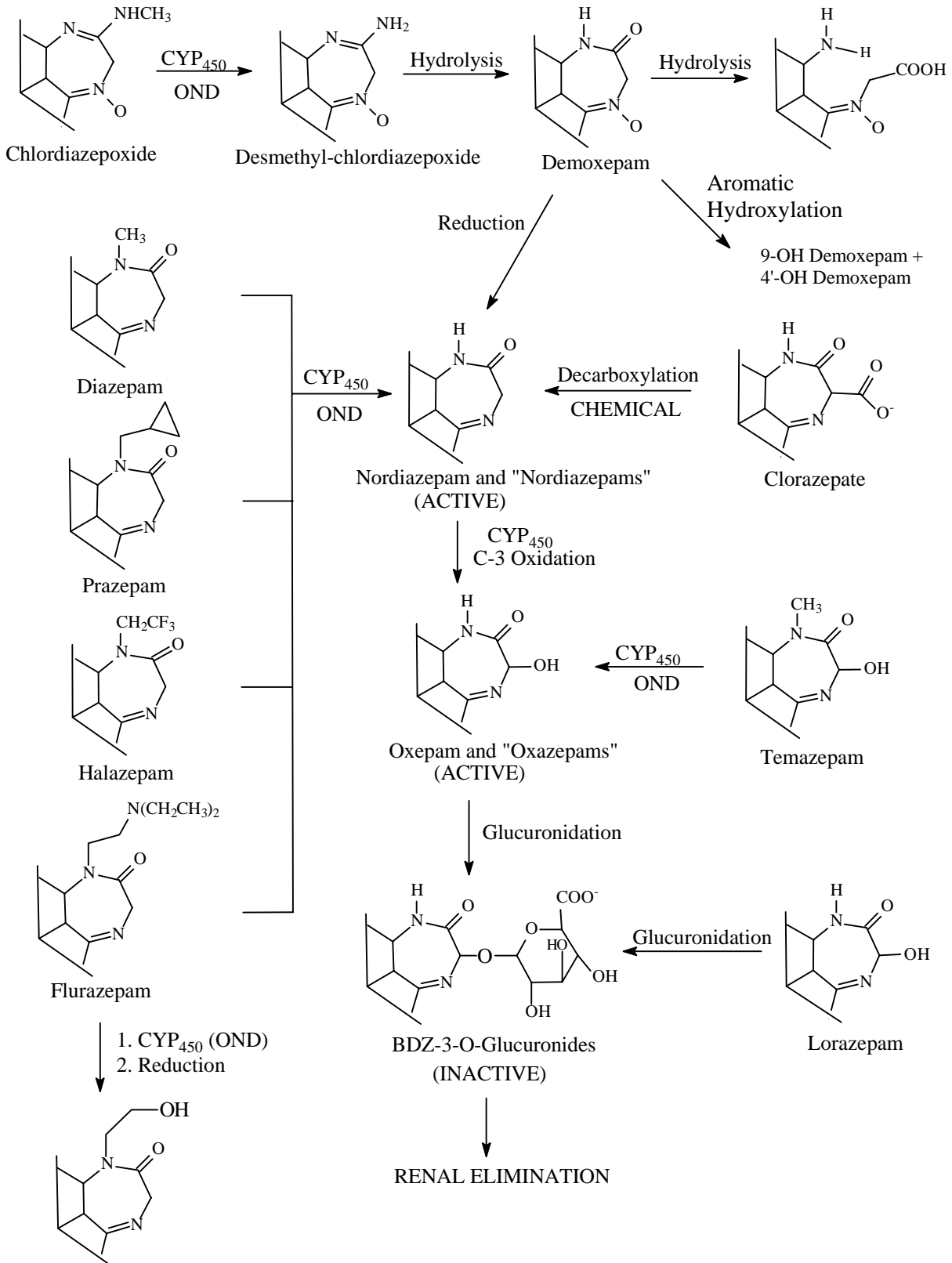
GABA RECEPTOR LIGANDS AND BENZODIAZEPINE ANTAGONISTS AND INVERSE AGONISTS

- Inverse Agonists (DMCM): Drugs that bind to the BZ-receptors but have the opposite pharmacologic action as a benzodiazepine agonist. Thus compounds like DMCM are convulsive and anxiogenic. These are largely experimental agents
- Benzodiazepine Competitive Antagonists (Flumazenil): Drugs that bind to the BZ-receptor but do not produce BZ-like stimulation (lack intrinsic BZ-receptor activity). These compounds have utility in antagonizing the sedative, cognitive, motor and anesthetic actions of the benzodiazepines



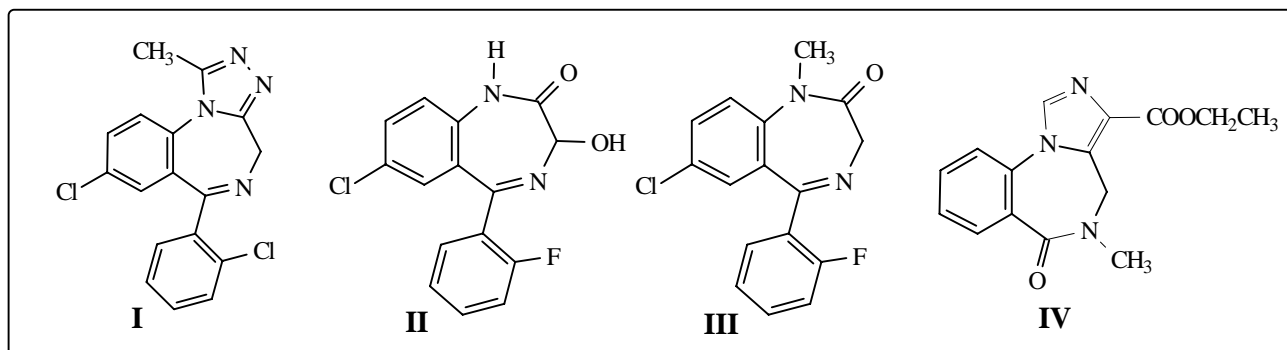
- The primary clinical uses for Flumazenil appear to be in the treatment of benzodiazepine overdose or mixed overdose, and the reversal of postoperative sedation from benzodiazepine anesthetics. The drug may also be used to prevent tolerance or treat withdrawal reactions from benzodiazepines. Single exposures to flumazenil during the last week of benzodiazepine therapy have been shown to prevent tolerance, and periodic doses may prevent subsequent withdrawal responses. Epileptic patients may benefit from the prevention of benzodiazepine tolerance
 - Administered IV and produces antagonist effects within minutes. It is ineffective orally due to rapid first pass metabolism by ester hydrolysis. Oral administration **not appropriate** for most indications!
 - Short half-life (<1 hr) due to rapid hydrolysis to the inactive acid and oxidative-N-demethylation. Eliminated in the urine as metabolites (98%).

SUMMARY OF THE METABOLISM OF TRADITIONAL BENZODIAZEPINES



Sample Exam Questions, Benzodiazepine Drugs

Answer questions 1-8 below for the following benzodiazepine derivatives (I-IV):



1. Which of the benzodiazepine derivatives shown above (I-IV) produce their therapeutic effects via interaction with benzodiazepine receptors on the GABA receptor complex?
 - A. Only IV
 - B. Only II and III
 - C. Only I, II and III
 - D. All of the benzodiazepines above (I-IV)
 - E. None of the benzodiazepines above

2. Which of the benzodiazepine derivatives shown above (I-IV) can produce sedation as either a desired effect or side effect?
 - A. Only I
 - B. Only I and II
 - C. Only II and III
 - D. Only I, II and III
 - E. All of the benzodiazepines above (I-IV)

3. Which of the benzodiazepine derivatives shown above (I-IV) could be formulated as stable, water soluble salts for IV administration?
 - A. Only I
 - B. Only I and IV
 - C. Only II and III
 - D. Only I, II and III
 - E. None of the benzodiazepines above (I-IV)

4. Which of the benzodiazepine derivatives shown above (I-IV) require metabolic activation before they can express their therapeutic activity?
 - A. Only IV
 - B. Only III
 - C. Only II and III
 - D. Only I and III
 - E. None of the benzodiazepines above (I-IV)

5. Which relative order below (A-E) correctly ranks the duration of therapeutic effect (from longest to shortest) for benzodiazepines I-IV shown above?
 - A. III > I > II > IV
 - B. III > II > I > IV
 - C. III > IV > II > I
 - D. IV > III > I > II
 - E. I > IV > III > II

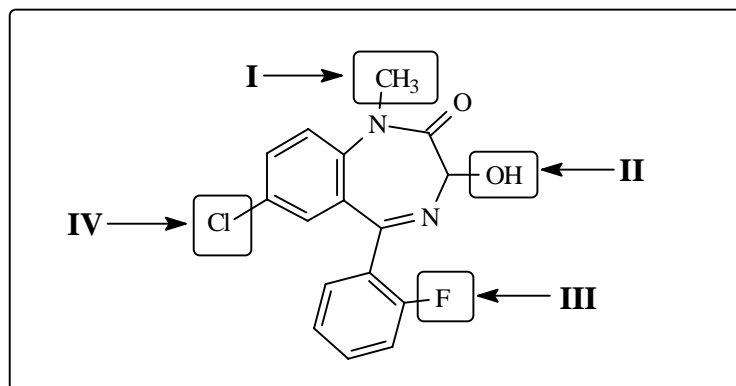
6. Which of the benzodiazepine derivatives shown above (I-IV) are ultimately cleared as glucuronide conjugates (more than one metabolic step may occur before glucuronidation)?
 - A. Only II
 - B. Only II and III
 - C. Only I, II and III
 - D. Only II, III and IV
 - E. All of the benzodiazepines above (I-IV)

7. Which of the benzodiazepine derivatives shown above (I-IV) undergo cytochrome-mediated oxidative N-alkylation?
 - A. Only III
 - B. Only III and IV
 - C. Only I and III
 - D. Only I, III and IV
 - E. All of the benzodiazepines above (I-IV)

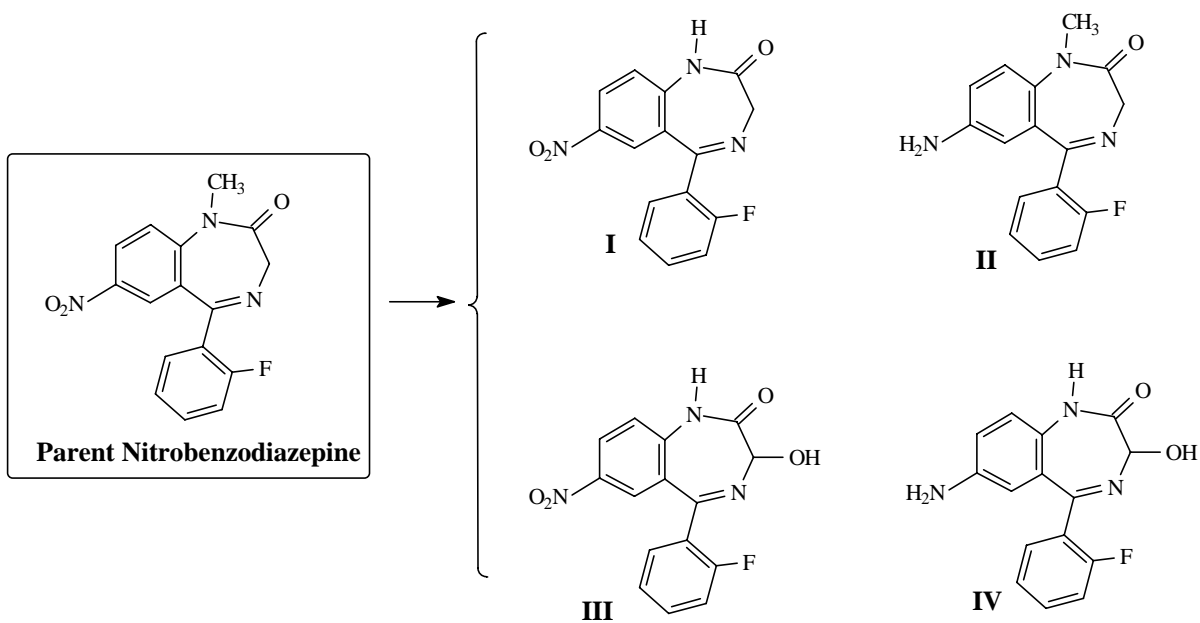
8. Which of the benzodiazepine derivatives shown above (I-IV) would be appropriate for the treatment of insomnia in an elderly patient with moderate hepatic impairment?
 - A. Only I
 - B. Only II
 - C. Only I and II
 - D. Only I and IV
 - E. Only I, II and IV

9. Which functional groups circled (I-IV) in the benzodiazepine compound shown below are necessary for this drug to bind to benzodiazepine receptors and express its therapeutic effect?

- A. Only III
 B. Only IV
 C. Only III and IV
 D. Only II, III and IV
 E. All (I-IV) are necessary



10. Which of the metabolites (I-IV) would be as therapeutically effective as the parent nitrobenzodiazepine shown below?



- A. Only I
 B. Only I and II
 C. Only I and III
 D. Only I, III and IV
 E. All of the metabolites (I-IV)