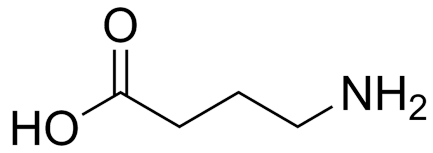
Anxiolytics

major inhibitory neurotransmitter

GABA



gamma amino butyric acid

made from glutamic acid

Low [GABA] is associated with anxiety disorders

- Benzodiazepines enhance effects of GABA

- Alcohol + Barbiturates also interact with GABA receptors

low levels of GABA associated with epilepsy

GABA Receptors

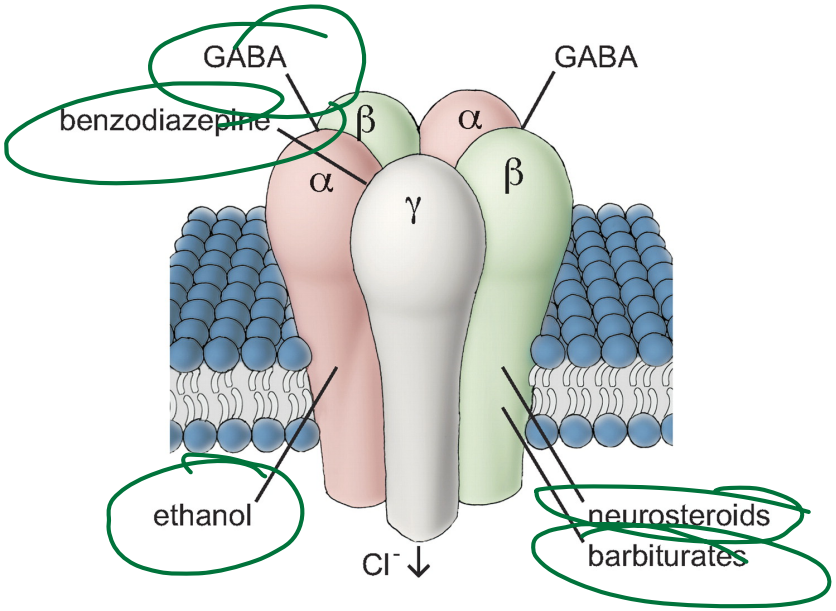
Binding of GABA opens a Cl^- channel

- Cl^- moves in
- hyperpolarization
- destimulatory

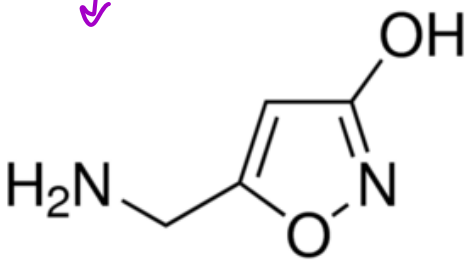
Drugs that open these are

Sedatives- decrease anxiety

hypnotics- cause sleepiness



Agonist: muscimol (amanita mushrooms)



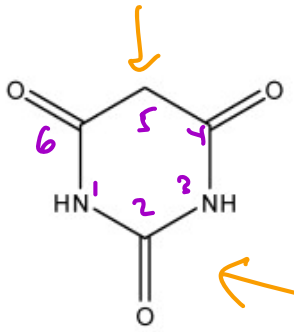
different binding sites

major classes

Barbiturates

Benzodiazepines

Barbiturates



← Based on barbituric acid

← Barbituric acid not active will tautomerize

Put R groups in 5 position

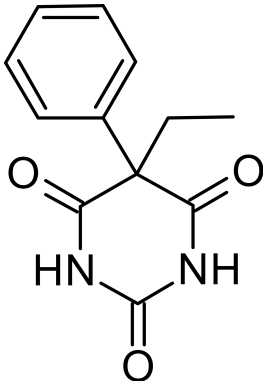
- Can cause physical dependence

- low TI

- Suppresses REM sleep

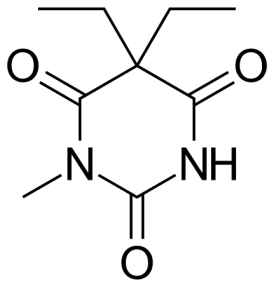
← ionizes won't cross BBB

Long Lasting Barbiturates — 6 or more hours



Phenobarbital (luminal)

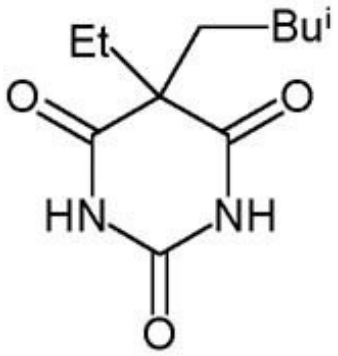
- anticonvulsant
- epilepsy



methbarbital

- epilepsy

Intermediate Acting ~6 ish hours

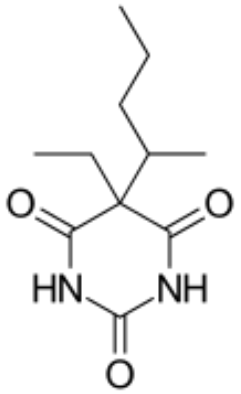


Amytal

- used for insomnia

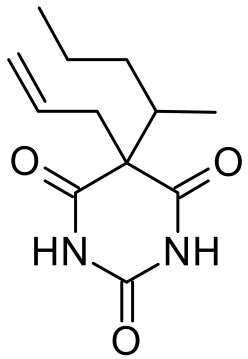
- sedative

Short Acting <3 hrs 3ish hours



Pentobarbital

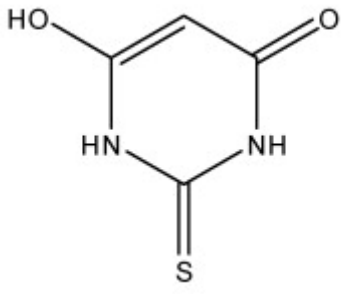
- insomnia
- vet use euthanasia



Secobarbital (Seconal)

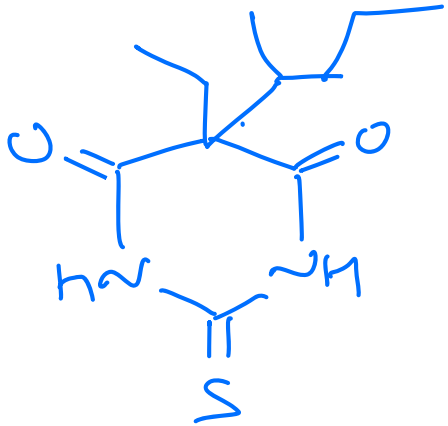
- pre surgery sedative
- insomnia

Thiobarbiturates



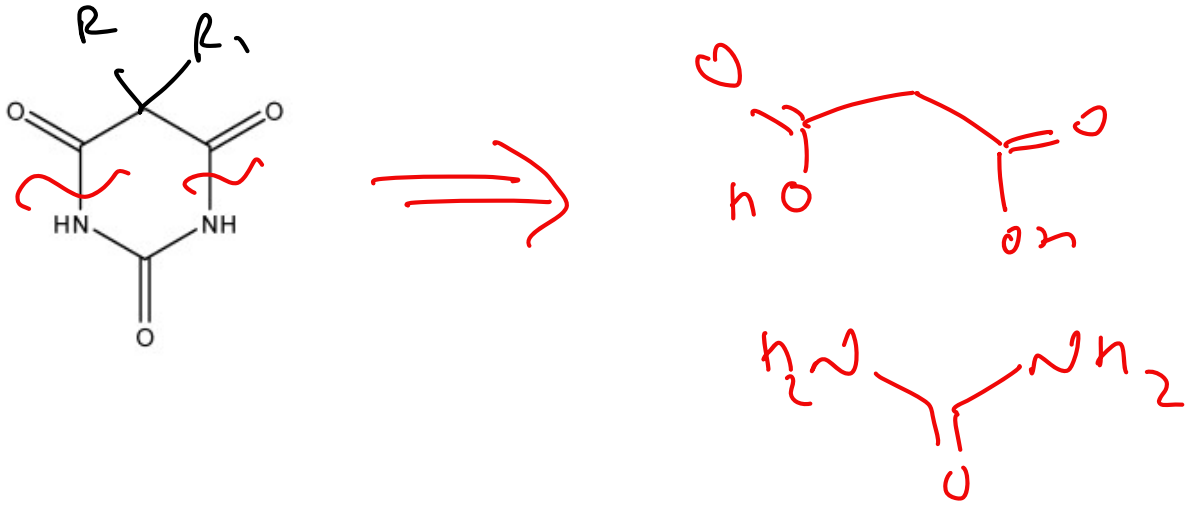
thiobarbituric acid

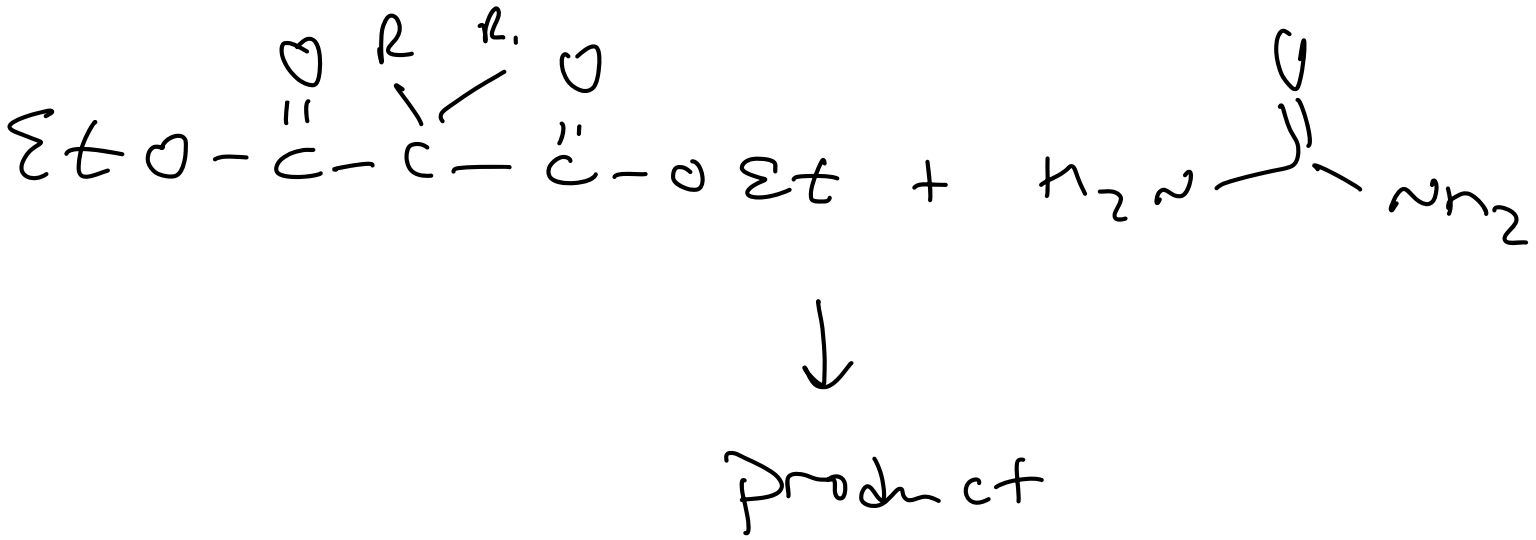
very short acting



thiopental (sodium pentathol)

Barbiturate Synthesis (Grimaux's Synthesis)

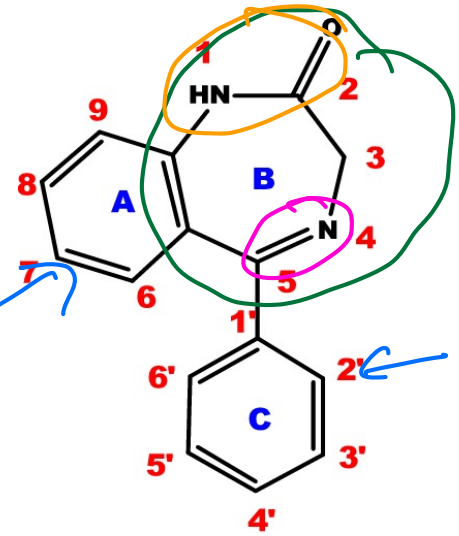




Safer than barbiturates

Benzodiazepines

Anxiolytic
Induce sleep
Anesthetic
Anticonvulsants



7 membered
imino lactam ring

Ring A must be aromatic or heteroaromatic

Substitution
1, 3, 7, 2'

OH here slows rate of absorption

Put EW stuff here often Cl⁻

Benzodiazepine Mode of Action

Primary site of action = GABA receptor

Secondarily inhibits reuptake of adenosine

has a role in Ach release

At high levels binds Ca^{2+} + Na^{+} Channels

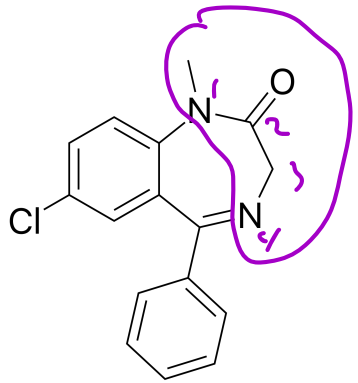
Lipophilic - deposits in fat

deposited drug gets slowly released

can have residual next day

effects

Diazepam (Valium)



a 1,4 Benzodiazepines

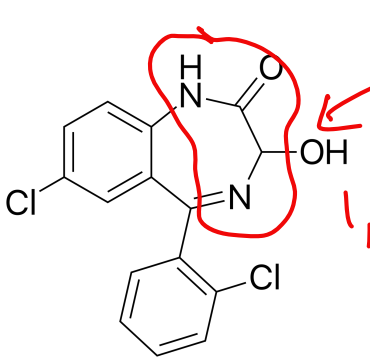
nonpolar

anxiety

anticonvulsant

surgery premedication

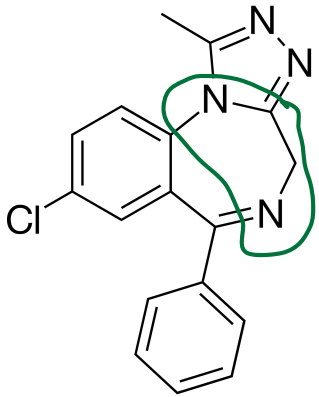
Lorazepam (Ativan)



hydroxyl makes more quickly metabolized

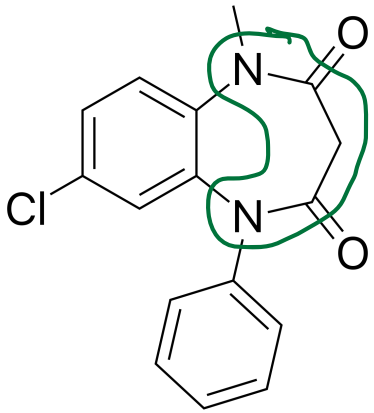
1,4 BZ

Alprazolam (Xanax)



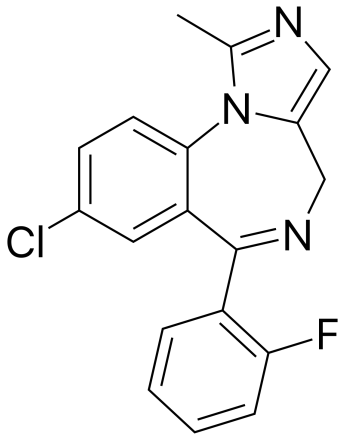
1,4

Clobazam



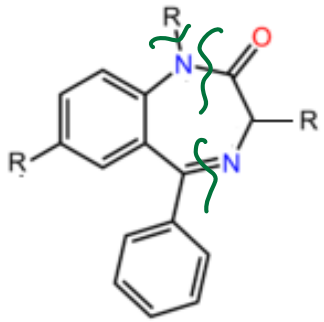
1,5 Bz

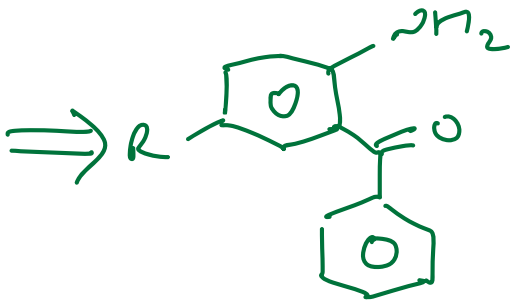
Midazolam (versed)

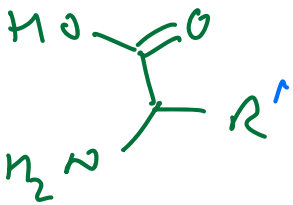


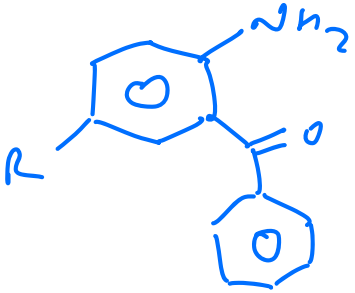
used before surgery

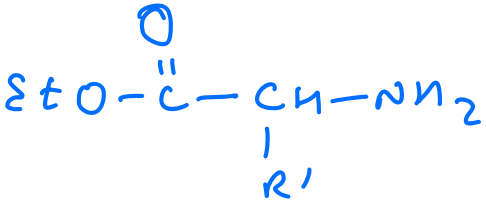
Benzodiazepine Synthesis

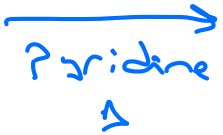


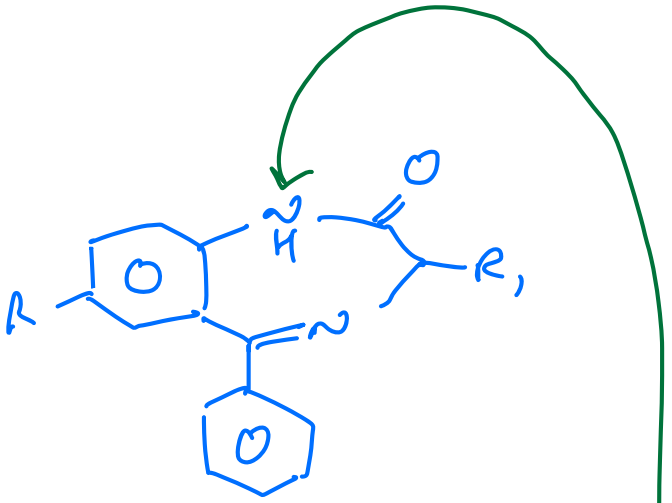




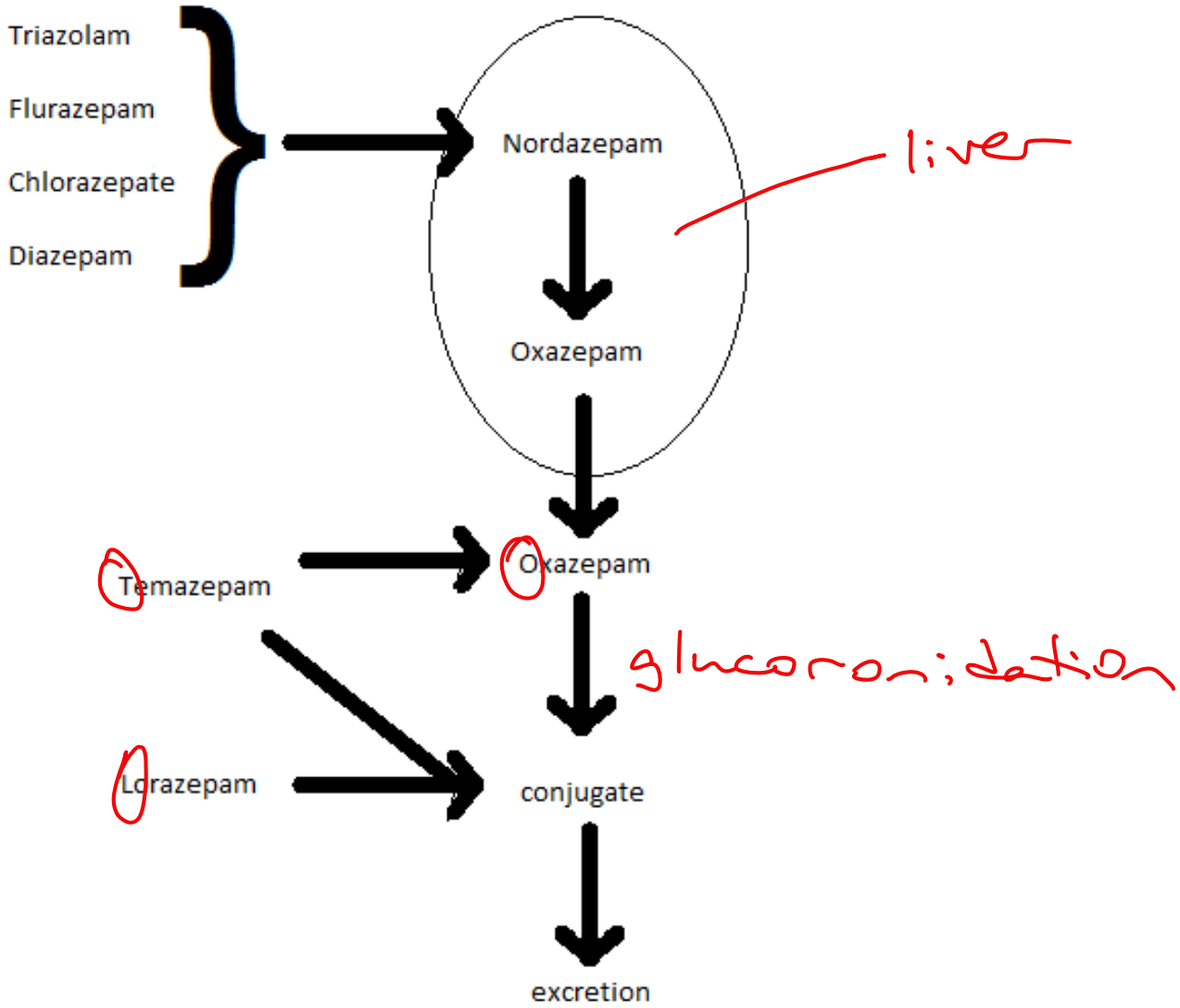




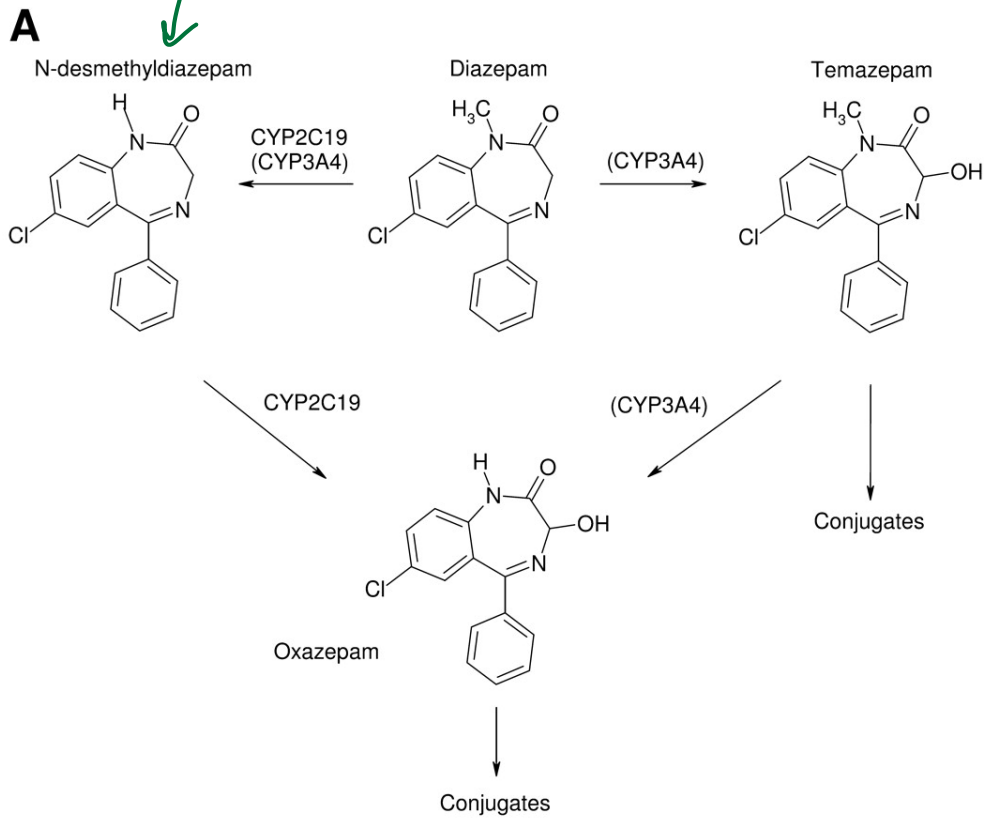


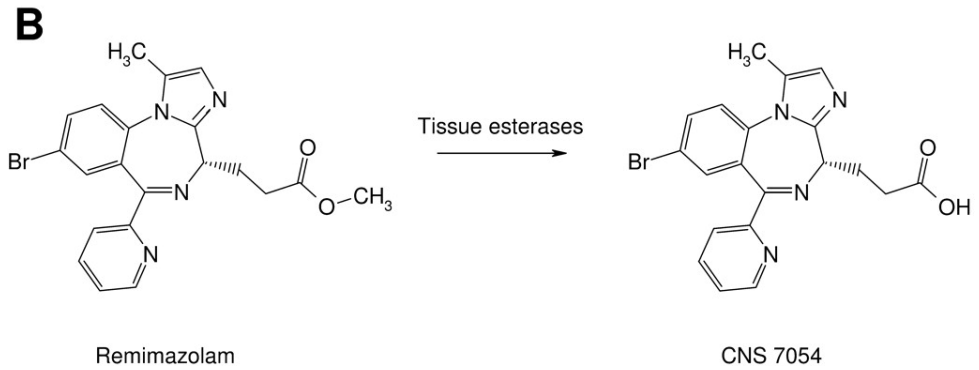


Add R group here


Triazolam
Flurazepam
Chlorazepate
Diazepam
Nordazepam
Oxazepam
liver
Temazepam
Oxazepam
glucoronidation
Lorazepam
conjugate
excretion

nordazepam

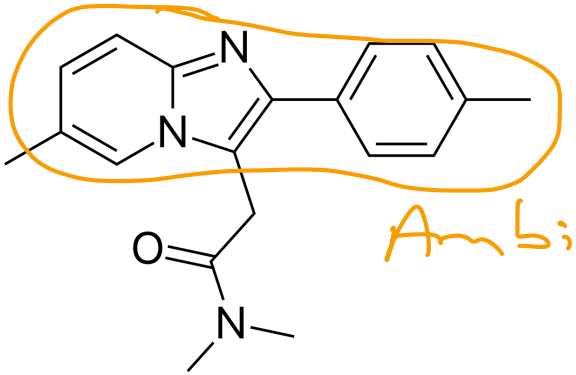

A
N-desmethyldiazepam
Diazepam
Temazepam
CYP2C19
(CYP3A4)
(CYP3A4)
CYP2C19
(CYP3A4)
Conjugates
Oxazepam
Conjugates


B
Tissue esterases
Remimazolam
CNS 7054

Nonbenzodiazepine $GABA_A$ agonists

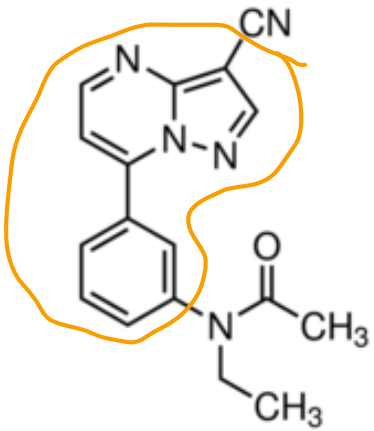
lipophilic
easily absorbed
Short acting sedative hypnotics

Zolpidem



Ambien

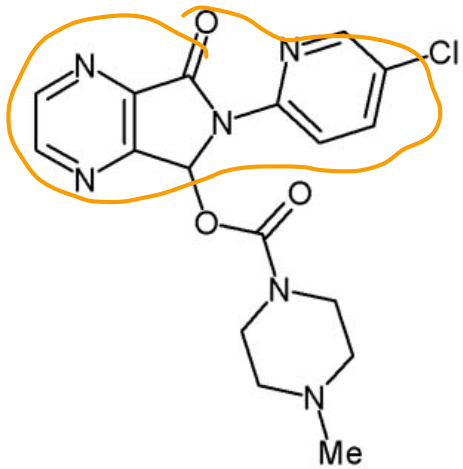
Zaleplon



Sonata

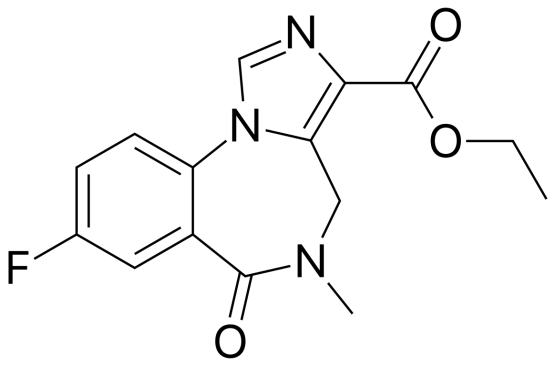
Zopiclone

Imovane



GABA Antagonist

Flumzenil



used for barbiturate overdose