SAR of Benzodiazepines

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Learning Objectives

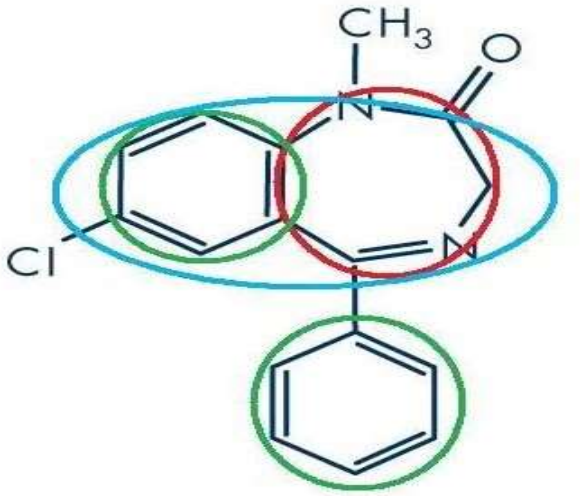
The learning objectives are…..

1. To study the chemistry of benzodiazepines.
2. To understand the SAR of Benzodiazepines.
3. To know the different examples of Benzodiazepines
4. To understand the mechanism of action

Chemistry of Benzodiazepines

✓All benzodiazepines have a benzene ring attached to a diazepine ring.

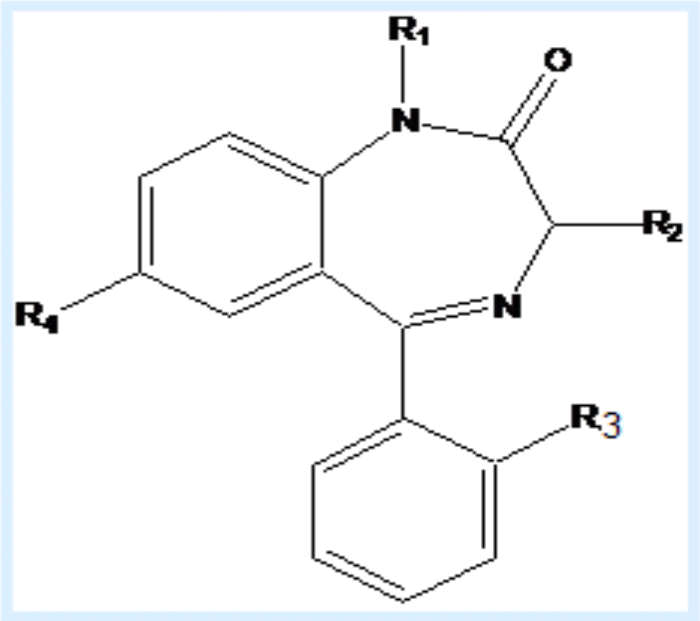
✓In the green circles are benzene rings and in the red circle is a diazepine ring, with the whole 1,4-benzodiazepine system being in the blue ring (the 1 and 4 denote the position of the nitrogen atoms in the ring

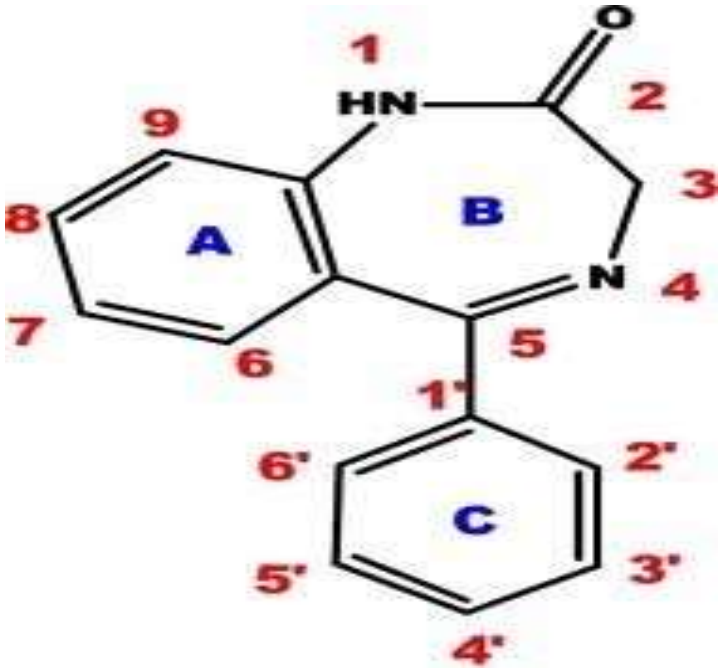


Chemistry of Benzodiazepines

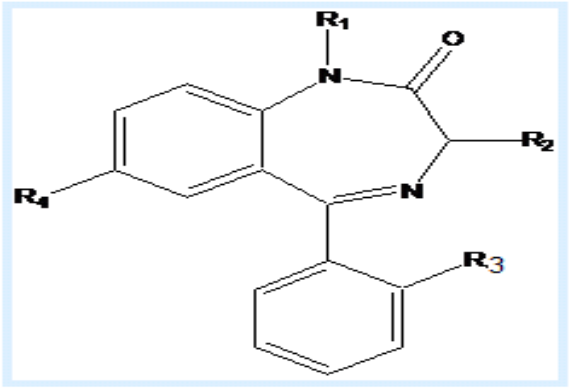
✓Different benzodiazepines have been developed through chemical substitutions at two major positions on the benzodiazepine structure

✓Therefore, all benzodiazpines are simply variations on the same core chemical structure.





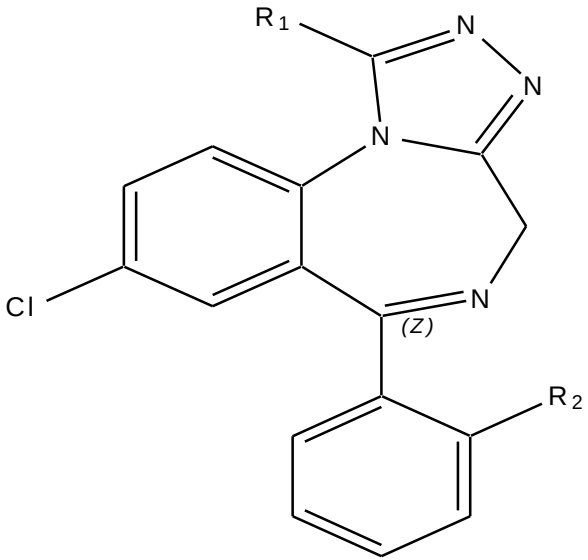
Examples of Benzodiazepines



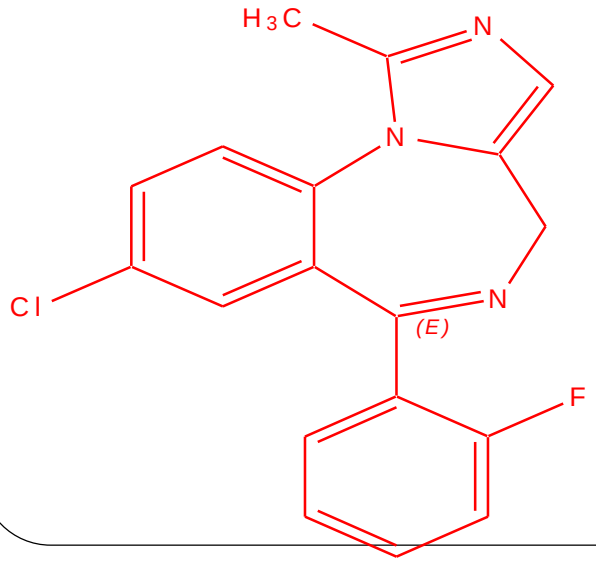
	R1	R2	R3	R4
a	CH3	H	H	Cl
b	CH3	H	F	Cl
c	H	H	H	NO2
d	H	H	Cl	NO2

a. diazepam b.flutoprazepam c. nitrazepam d. clonazepam

Modification: (triazole or imidazole) estazolam, alprazolam, trizolam and midazolam



	R1	R2
estazolam	H	H
alprazolam	CH_3	H
trizolam	CH_3	Cl
Midazolam	CH_3	F

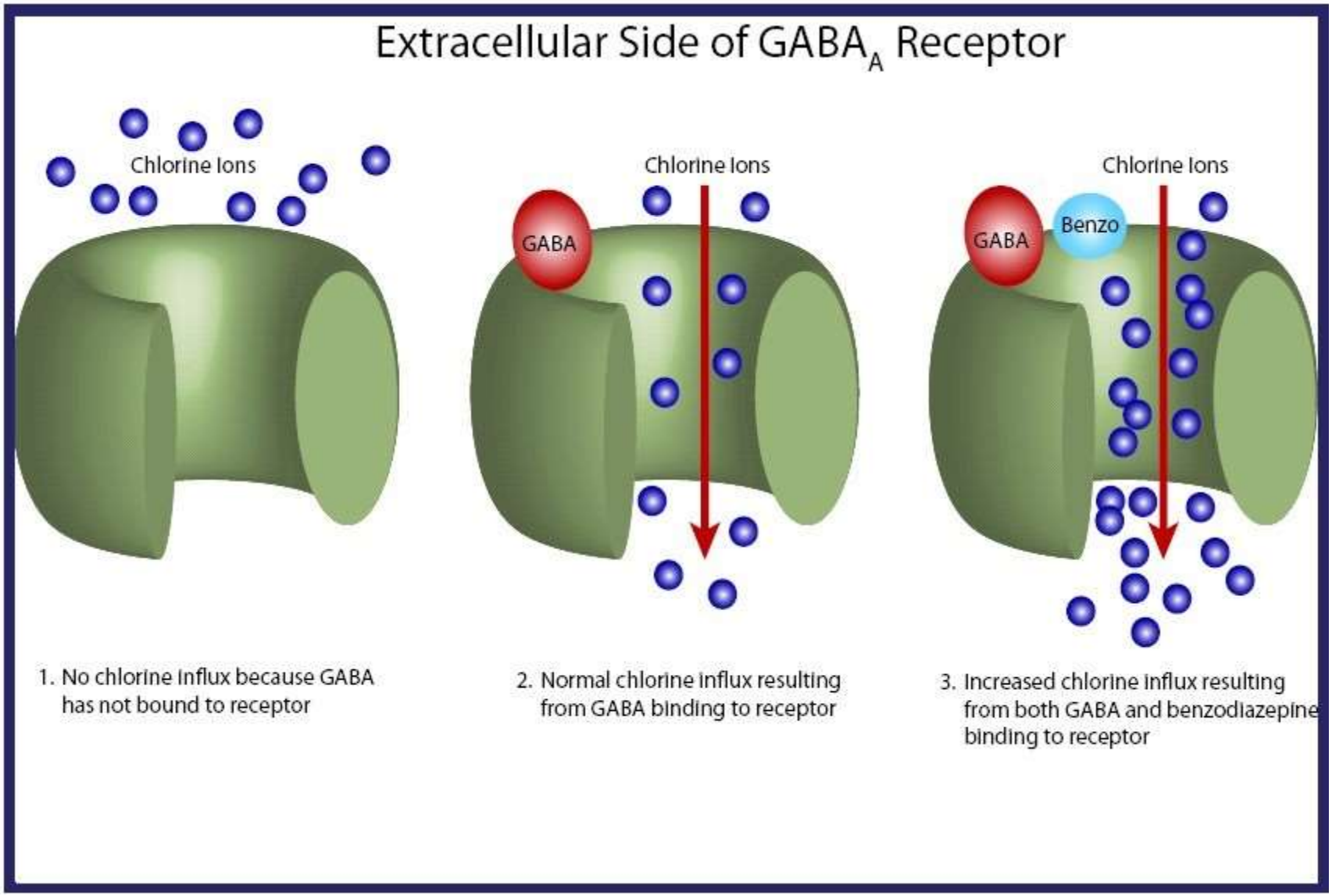


midazolam

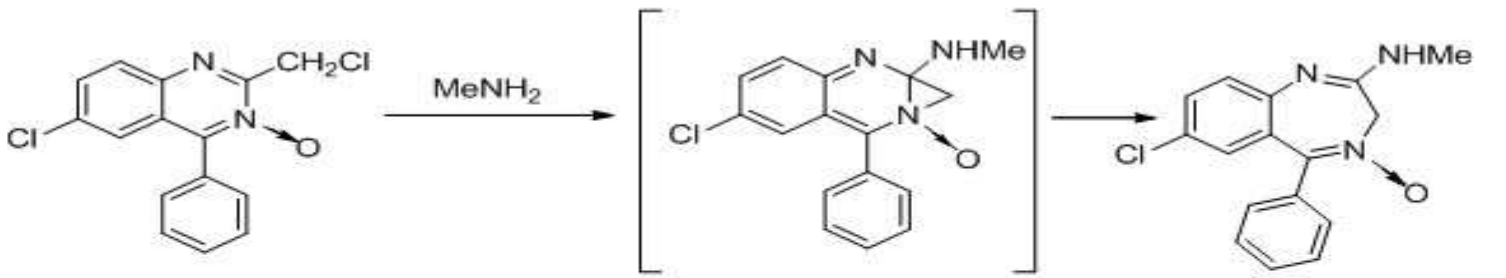
Reflection Question

1. Explain the chemistry of Benzodizepines
2. Enlist various examples of benzodizepines

Mechanism of action



Chemical synthesis of Librium

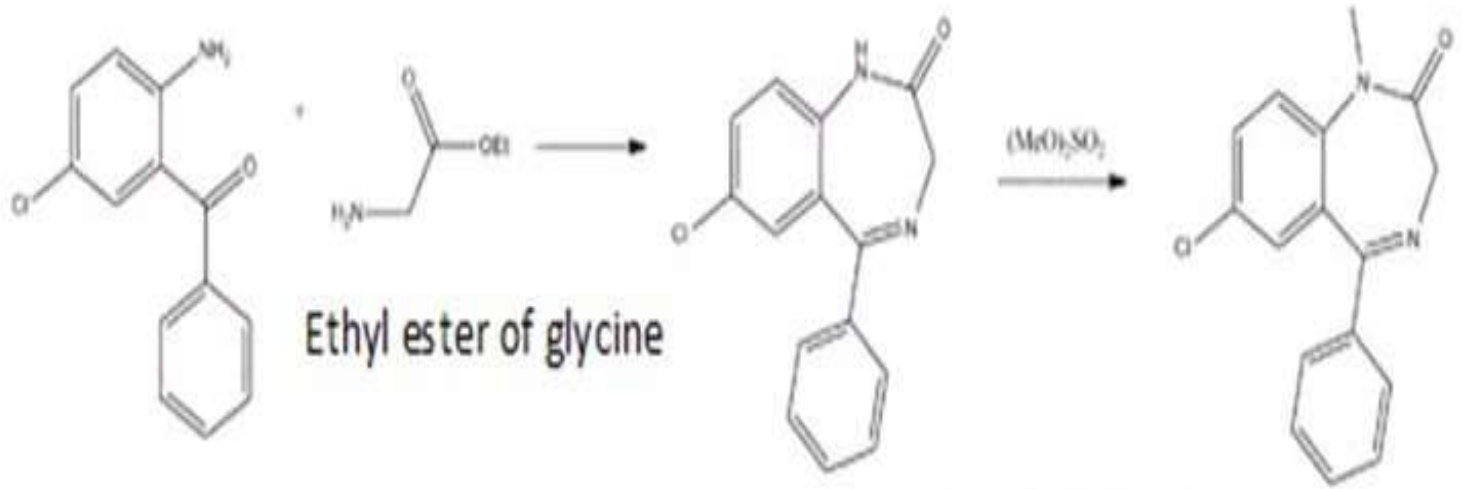


6-chloro-2 chloromethyl
-4-phenylquinazoline-3
-oxide

Chlordiazepoxide

Librium

Chemical synthesis of diazepam



2-amino-5-chlorobenzophenone

Diazepam

Structure- activity relationship:

- The electron attractive substituents on ring A enforce the activity NO2>Br>CF3>Cl

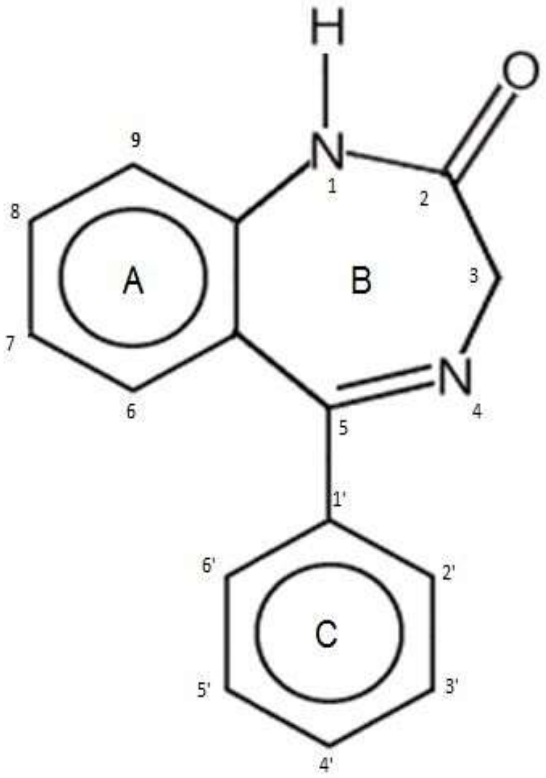
- Ring B is necessary for activity
- The electron attractive substituents with small volume on benzene ring of C-5 will enforce the activity

- The hydrolysis of amide and imine

Structure- activity relationship:

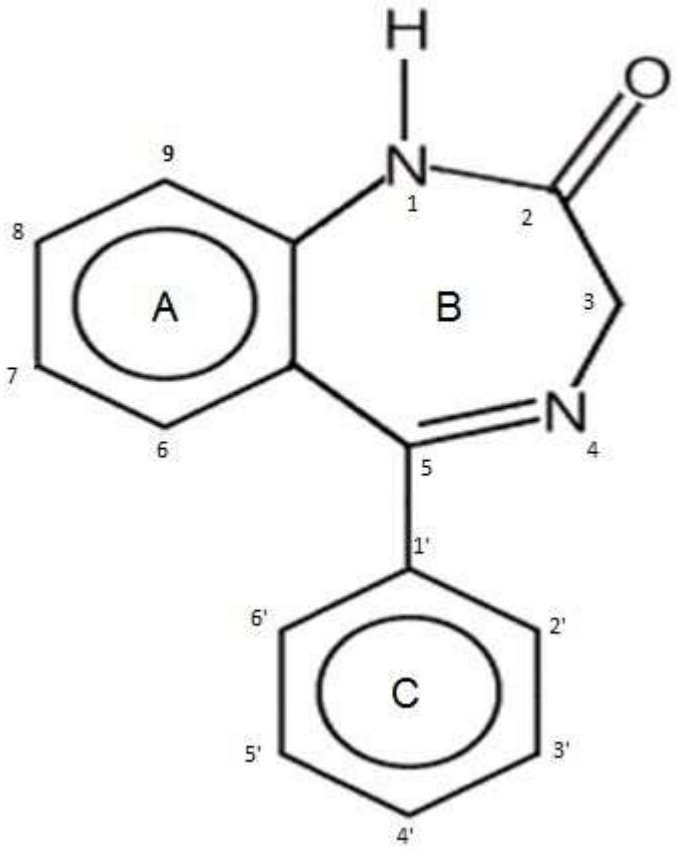
Ring A

1. The minimum requirement for 5-phenyl 1,4 benzodiaipin 2one derivatives to BZR include an aromatic or hetroaromatic ring
2. It is believed to participate in pi-pi bonding with aromatic residue of aromatic amino acids of the receptor
3. The substitution on this ring produces varied effect on binding with the receptor, however such effects are not predictable on the basis of electronic and stearic properties



Structure- activity relationship:

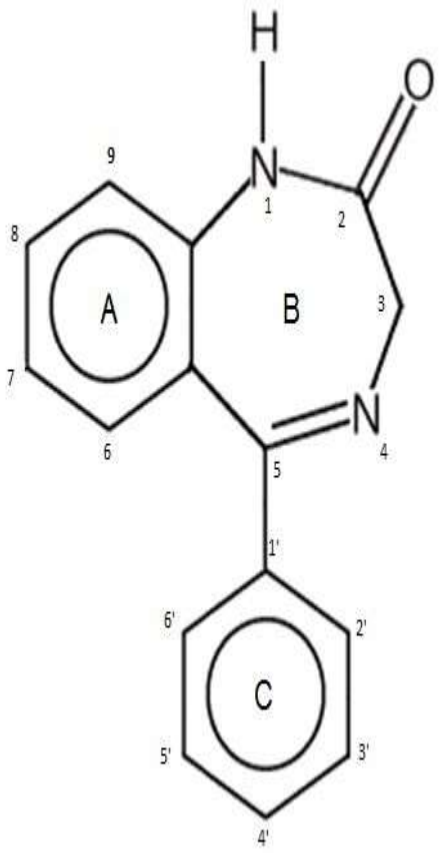
4. An electronegative group (halo or nitro) substituted at 7-position markedly increase activity and binding affinity
5. Substitution on 6,8 and 9 decrease the activity
6. On the other hand 1-4 diazepine derivative having ring A replaced with hetrocyclic ring have weak activity and affinity as compared to phenyl derivatives



Structure- activity relationship:

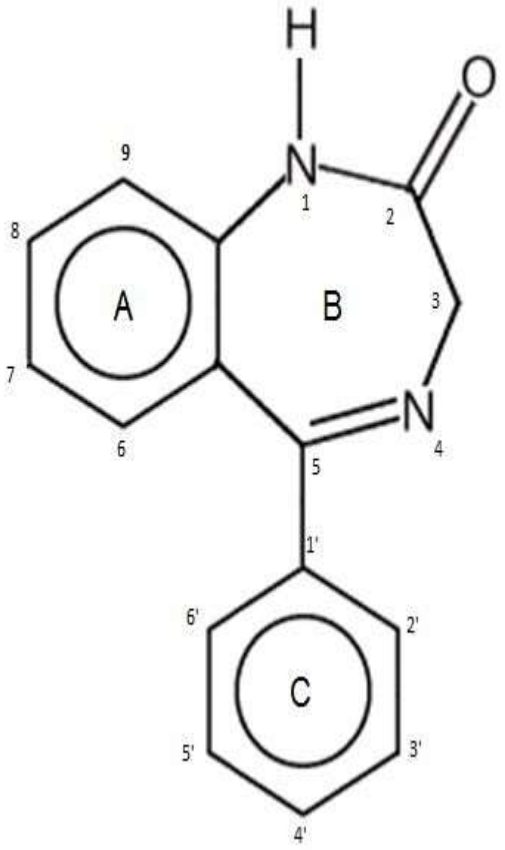
Ring B

1. A proton accepting group (carbonyl oxygen) at 2-position of ring B is necessary to interact with receptor histidine residue that act as proton donor and help in ligand binding.
2. Electron donating group must be in the same plane with electronegative group on ring A, favoring a coplanar spatial orientation of two moieties Substitution of O with S effect selective binding GABA BZR sub-populations but anxiolytic activity is maintained
3. Substitution 3-position methylene or imine nitrogen is sterically unfavorable
4. Derivatives having 3-hydroxy moiety have comparable potency to non-hydroxylated analogue but are excreted faster



Structure- activity relationship:

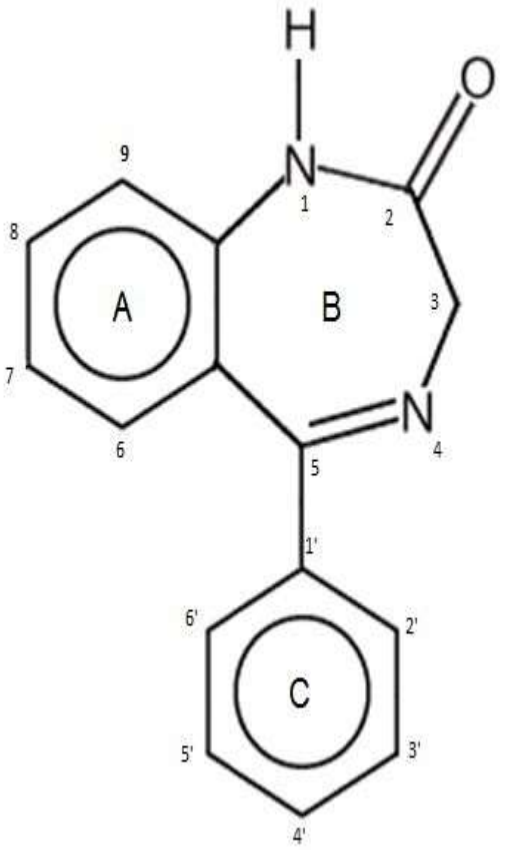
5. Esterification of 3-hydroxy moiety is possible without loss of activity
6. 1-poition amide nitrogen and its substituent are not required for in vitro binding with BZR because many N-alkyl side chains don't decrease BZR affinity Neither 4,5 double bond nor the nitrogen of 4-position is required for activity
7. If C=N is reduced BZR affinity is decreased but the derivatives again oxidized in the body to C=N



Structure- activity relationship:

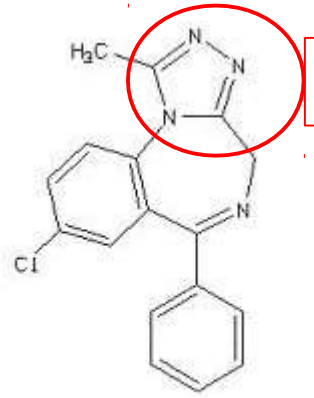
Ring C

1. The 5-phenyl ring C is not required for binding to the BZR in vitro, however, this aromatic ring contribute favorable hydrphobic or steric interactions to receptor binding and its relationship to ring A
2. Substitution at 4' (para position) is unfavorable for activity, however, ortho substitution is not detrimental to agonist activity



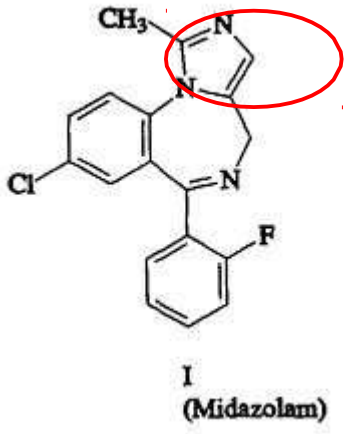
Structure- activity relationship:

3. Annelating the 1,2 bond of ring B with an additional electron rich ring such as triazole (alprazolam) or imidazole (midazolam) results in pharmacologically active benzodiazepine derivatives with high affinity to BZR



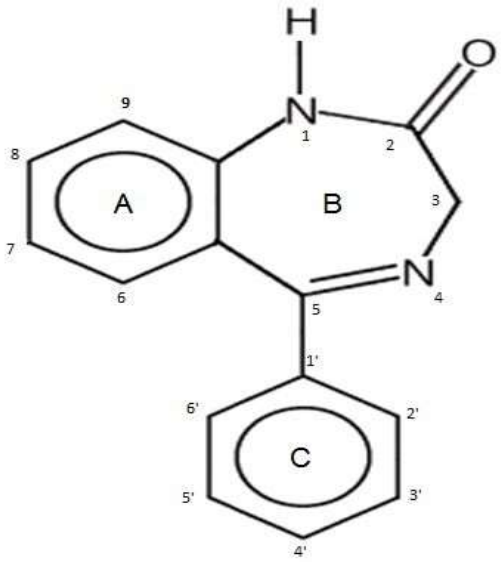
triazole

Alprazolam



I
(Midazolam)

imidazole



Reflection Question

1. Explain SAR Benzodizepines.
2. Write the mechanism of action of benzodizepines

For any queries contact : mohitepb@gmail.com

Thank you