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

Therefore, all benzodiazepines are simply variations on the same core chemical structure.
Examples of Benzodiazepines

![Benzodiazepine structure]

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH3</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
</tr>
<tr>
<td>b</td>
<td>CH3</td>
<td>H</td>
<td>F</td>
<td>Cl</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>NO2</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>NO2</td>
</tr>
</tbody>
</table>

a. diazepam  b. flutoprazepam  c. nitrazepam  d. clonazepam
Modification: (triazole or imidazole) estazolam, alprazolam, trizolam and midazolam

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
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<tbody>
<tr>
<td>estazolam</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>alprazolam</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>trizolam</td>
<td>CH₃</td>
<td>Cl</td>
</tr>
<tr>
<td>Midazolam</td>
<td>CH₃</td>
<td>F</td>
</tr>
</tbody>
</table>
1. Explain the chemistry of Benzodizepines
2. Enlist various examples of benzodizepines
Mechanism of action

1. No chlorine influx because GABA has not bound to receptor
2. Normal chlorine influx resulting from GABA binding to receptor
3. Increased chlorine influx resulting from both GABA and benzodiazepine binding to receptor
Chemical synthesis of Librium

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

Chlordiazepoxide
Librium
Chemical synthesis of diazepam

- Ethyl ester of glycine
- Dimethylsulfate
- 2-amino-5-chlorobenzophenone

Diazepam
The electron attractive substituents on ring A enforce the activity $\text{NO}_2 > \text{Br} > \text{CF}_3 > \text{Cl}$

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
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.
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 heterocyclic 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
5. Esterification of 3-hydroxy moiety is possible without loss of activity

6. 1-position 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.
Ring C

1. The 5-phenyl ring C is not required for binding to the BZR in vitro, however, this aromatic ring contributes favorable hydrophobic 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
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.
Reflection Question

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

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