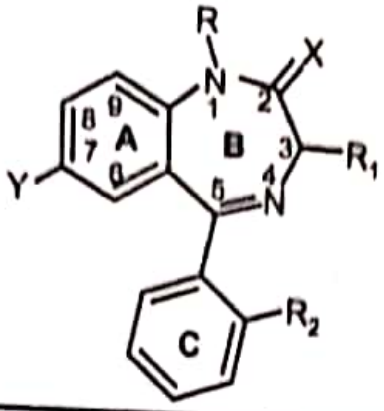


At N-1
Nitrogen at N-1 is essential for bio-activity.

At C-2
Electron accepting groups like O/S is needed for bio-activity. Replacement of S with O results in long duration of action.

Fusion of new ring at 1 and 2 positions with pyrrole (Diazolo benzodiazepine), imidazole (Triazolo benzodiazepine) are comparatively more bioactive.

From C-6 to C-9
For good bioactivity, positions 6, 8 and 9 should not be substituted.

At C-7
Electron-attracting groups Cl, Br, $CONH_2$, CF_3, NO_2, CN are required for activity.

Strong electron attracting group shows better activity.

$Br < Cl < CONH_2 < CF_3$

At C-3
Alkyl substitution at C-3 position increase lipophilicity.
Presence of polar groups like –OH, –COOH etc. improve pharmacokinetics.
3-OH group favour glucuronide formation and decrease duration of action.

At N-4 and C-5
Conversion of double bond to single bond and shifting of double bond at 3,4 position decreases bio-activity.

At C-5
Phenyl ring at C-5 position promotes bio-activity.

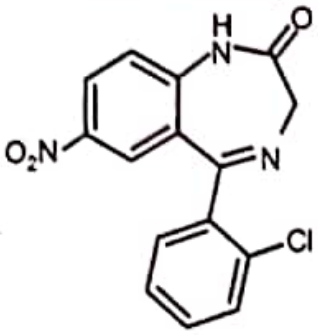
Single ortho substitution (R_2 group) or Di ortho substitution with electron attracting group for example: Cl, Br, CF_3 increases bioactivity.

Para substitution decreases bio-activity.

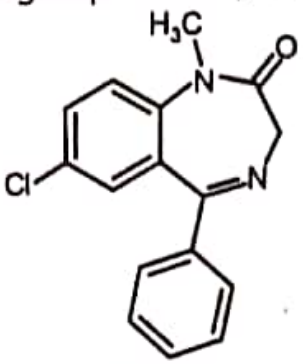
Three rings A, B and C are required for pharmacological activity. Rings A and C are involved in binding with GABA receptor directly by forming pi-pi stacking and through hydrophobic/stearic interactions. Ring B facilitates hydrogen bonding interactions and, is essential for bioactivity.

4.6.1.1 At Position 1

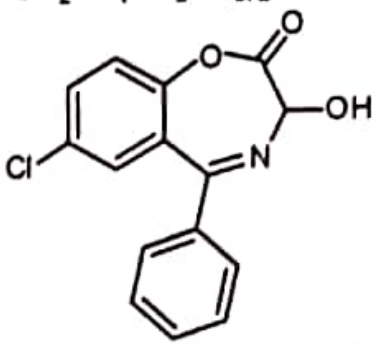
The presence of nitrogen atom at N-1 is essential for bioactivity. N-H can be substituted with $-CH_3$, or relatively small alkyl groups like $-H$, $-CH_2-CF_3$, $-CH_2-CH_2-N(CH_2CH_3)_2$



Clonazepam

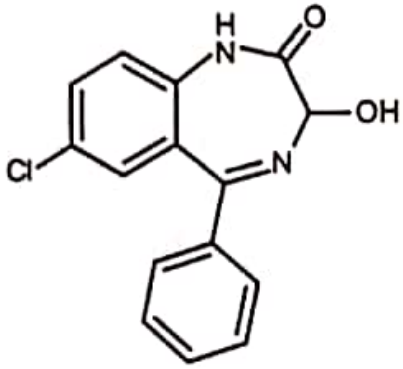


Diazepam

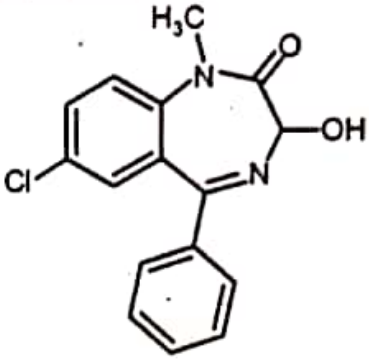


Not active

Methyl substitution enhances lipophilicity and rapid onset of action.



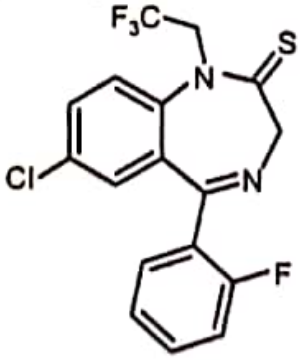
Oxazepam
Peak Onset (hrs) 2-3



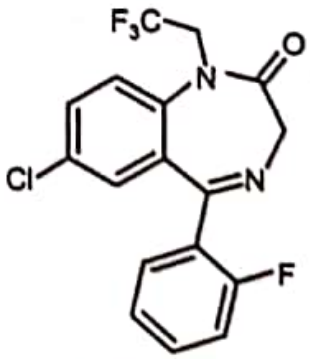
Temazepam
Peak Onset (hrs) 0.75-1.5

4.6.1.2 At Position 2

Carbonyl group or thiocarbonyl group at position 2 is required for bioactivity. For example, C=O group containing 2-Oxo quazepam is eliminated slowly as compare to C=S containing Quazepam and having a long duration of action.



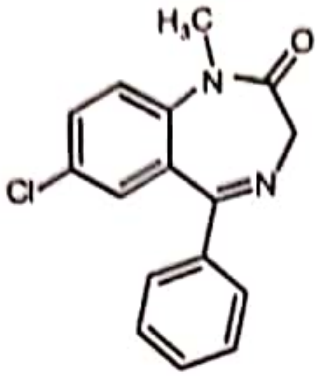
Quazepam



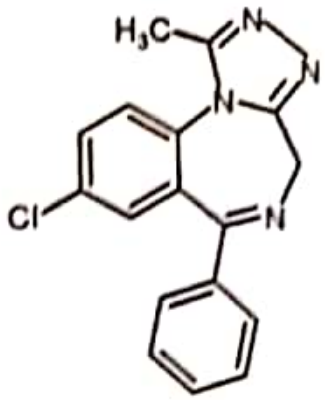
2-Oxoquazepam

Onset of action	1.8 hrs	-
Duration of action	39.3 hrs	40.2 hrs

Fusion of Benzodiazepine with a pyrrole and Imidazole ring at position 1 and 2 results in an increase in pharmacological activity (Potency).



Diazepam



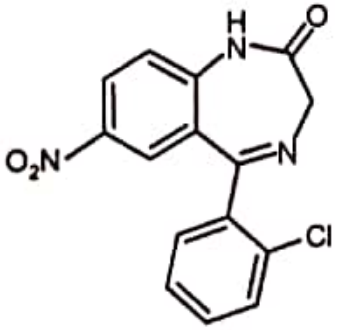
Alprazolam

Dose	5 mg	0.5 mg

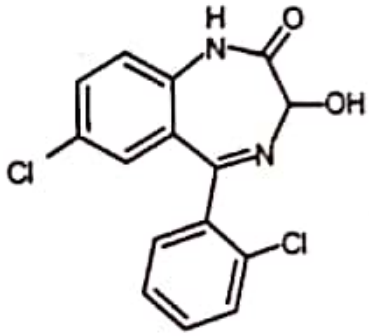
The C=O, C=S and fused benzodiazepines serve as a proton acceptor for the histidine-102 residue of GABA receptor, forming hydrogen bond interaction.

4.6.1.3 At Position 3

The presence of polar groups, for example, –OH by glucuronide formation and excreted easily, hereby, decreases the duration of action (short half life).



Clonazepam

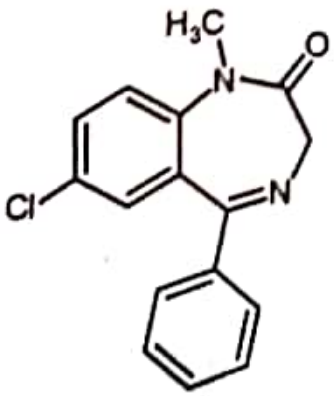


Lorazepam

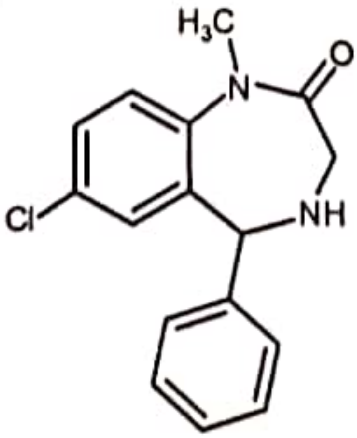
Onset of action	1-4 hrs	1-1.5 hrs
Duration of action	18-39 hrs	10-20 hrs

4.6.1.4 At Position 4

Saturation of 4, 5 double bond leads to a loss in bioactivity and delocalization of a double bond to 3, 4 also result in a loss of activity. For improved sedative and hypnotic activity, a total number of carbon atom present two groups at the C-5 position should not be less than 4 and not more than 10.



Diazepam



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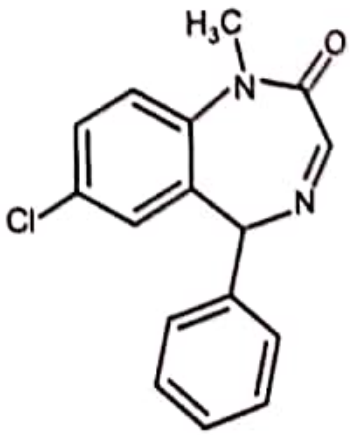
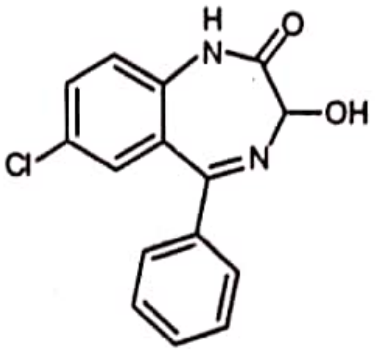
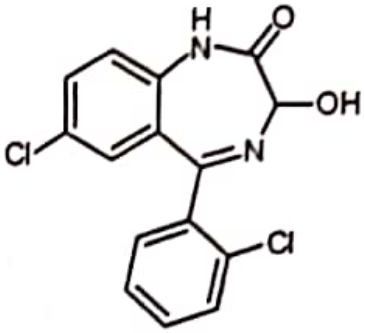


Inactive

4.6.1.5 At Position 5

Electron attracting halo substituents like F, Cl at the *ortho-* or *diortho-* (2' , 6') positions of Phenyl ring is preferred for potent activity (low dose).



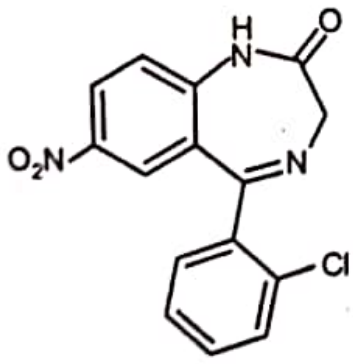


Dose	Oxazepam 15 mg	Lorazepam 1 mg

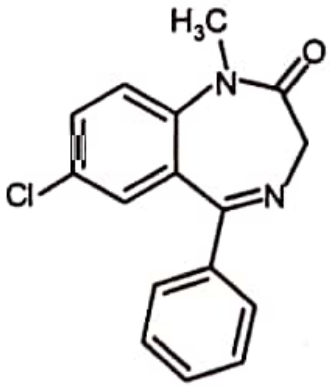
Substitutions at *meta* and *para* positions are not preferred.

4.6.1.6 At Position 6-9

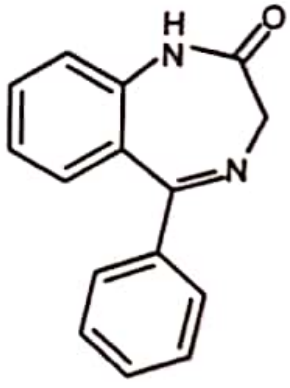
Substitution of phenyl ring with heterocyclic ring may lead to a loss in activity. Substitutions on 6, 8 and 9 decreases the activity. Position 7 may contain an electronegative atom like Br, Cl or NO_2 for biological activity.



Clonazepam



Diazepam



Inactive