

# Drugs Acting on CNS

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

1

# Depressant Drugs

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

2

# Anxiolytic Drugs (Minor Tranquilizers)

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

3

## Anxiety & Anxiety Disorders

- Psychological and physiological disorders.
- An unpleasant feeling that is associated with one or more of:
  - ✓ Uneasiness.
  - ✓ Apprehension.
  - ✓ Fear.
  - ✓ Worry.

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

4

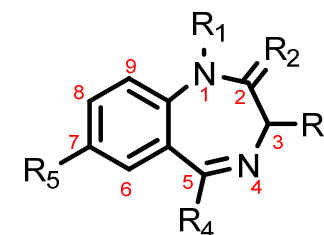
## Pathophysiology of Anxiety

- Some neurotransmitters are involved:
  - ✓ GABA.
  - ✓ Norepinephrine.
  - ✓ Serotonin.

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

5

## Benzodiazepines



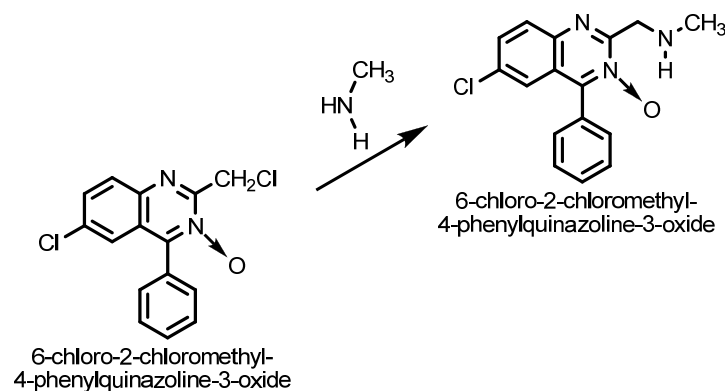
benzodiazepine

- Prototypic anti-anxiety agents.
- They target the GABA-A receptor.
- They are the most effective anxiolytics.

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

6

## Development of Benzodiazepines

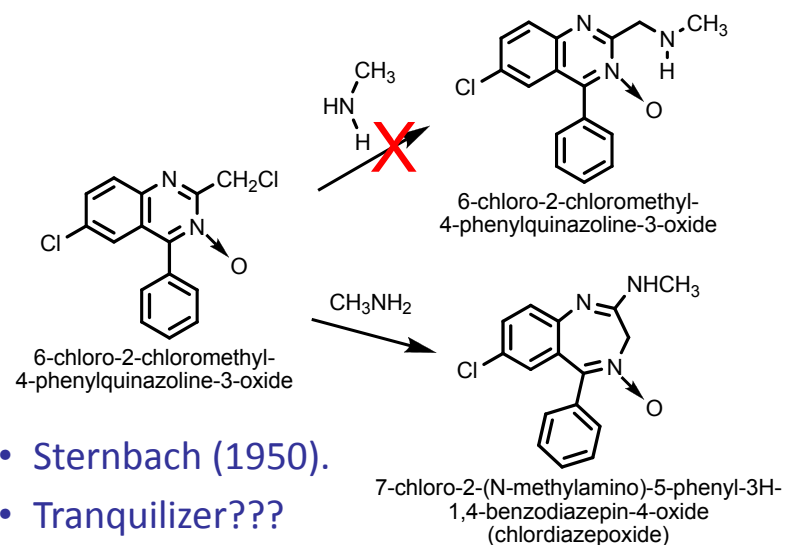


- Sternbach (1950).
- Tranquilizer???

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

7

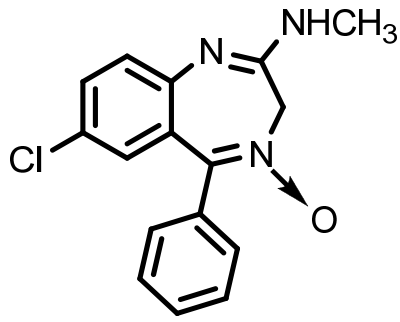
## Development of Benzodiazepines



- Sternbach (1950).
- Tranquilizer???

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

8

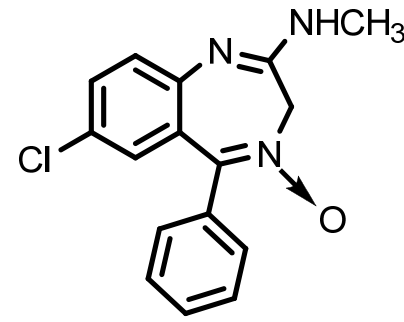


chlordiazepoxide  
**Librium (1960)**

- Good sedative and hypnotic activity.
- Improper physicochemical properties.

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

9

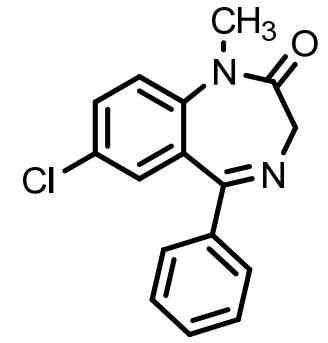


chlordiazepoxide  
**Librium (1960)**

- N-oxide is not important for activity.
- Diazepam is a popular anxiolytic drug.

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

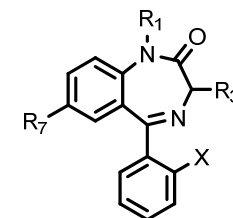
10



diazepam  
**Valium (1963)**  
**3 to 10-fold more active**

## Clinically Used Benzodiazepines

- More than 20.
- Two classes.



Class A Benzodiazepines

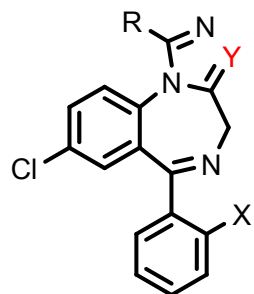
Generic name	R <sub>1</sub>	R <sub>3</sub>	R <sub>7</sub>	X
Clonazepam	H	H	NO <sub>2</sub>	Cl
Clorazepate	H	COOK	Cl	H
Diazepam	CH <sub>3</sub>	H	Cl	H
Flurazepam	CH <sub>2</sub> CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	H	Cl	F
Halazepam	CH <sub>2</sub> CF <sub>3</sub>	H	Cl	H
Lorazepam	H	OH	Cl	Cl
Oxazepam	H	OH	Cl	H
Temazepam	CH <sub>3</sub>	OH	Cl	H

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

11

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

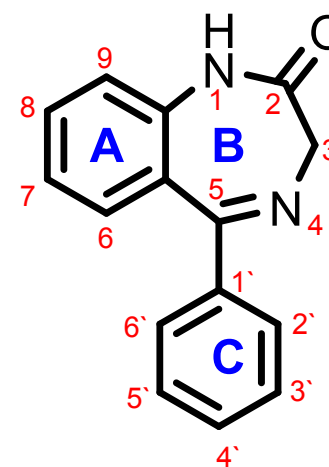
12



Class B Benzodiazepines

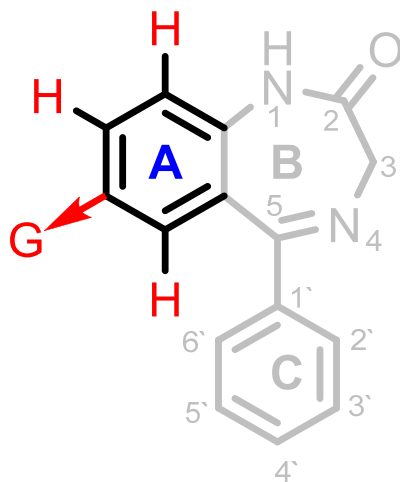
Generic name	R	X	Y
Alprazolam	CH <sub>3</sub>	H	N
Estazolam	H	H	N
Midazolam	CH <sub>3</sub>	F	CH
Triazolam	CH <sub>3</sub>	Cl	N

## Structure-Activity Relationships



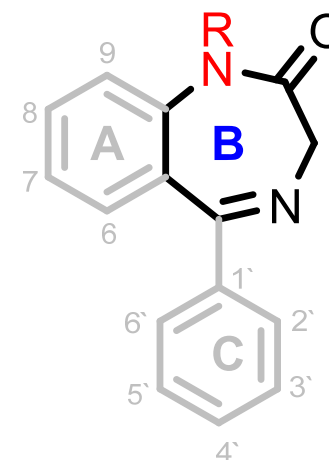
- 5-phenyl-1,4-benzodiazepin-2-one.

## Structure-Activity Relationships



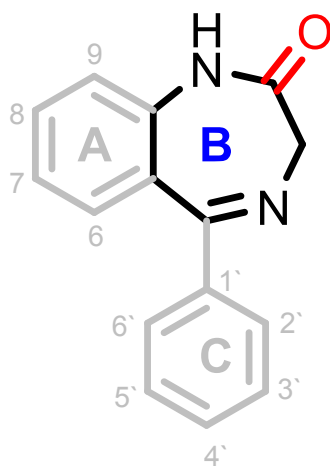
- Increases anxiolytic activity.

## Structure-Activity Relationships



- Bulky substituents decrease affinity to BZR.

## Structure-Activity Relationships

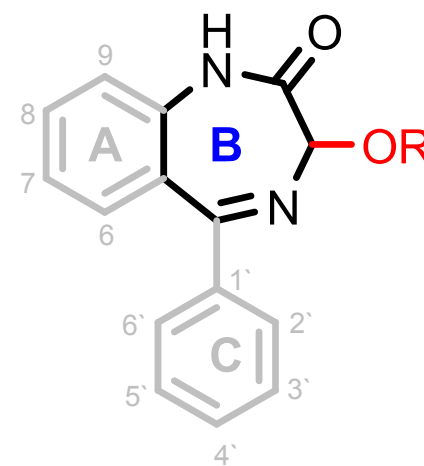


- Coplanar proton accepting group (with ring A).

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

17

## Structure-Activity Relationships

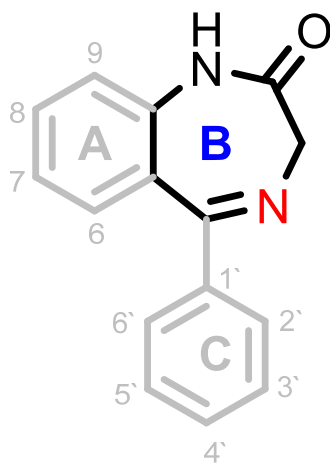


- 3-OH increases the potency (esters).

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

18

## Structure-Activity Relationships

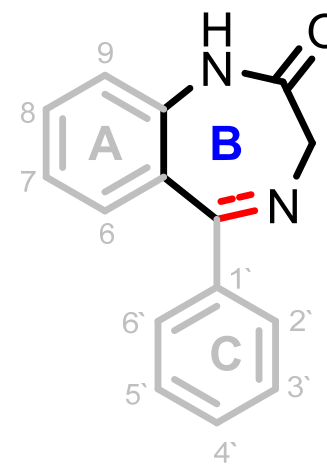


- 4-Nitrogen is not required for activity.

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

19

## Structure-Activity Relationships



- C-N shows a reduced in vitro activity!!!

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

20

## Structure-Activity Relationships



- Bioisosteric replacement at 1,2-bond of ring B?

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

21

## Structure-Activity Relationships



s-Triazolo[4,3a][1,4]-benzodiazepine

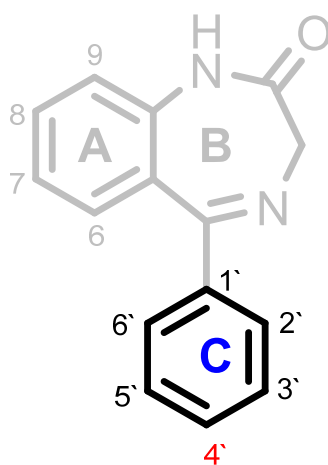
Imidazo[1,5a][1,4]-benzodiazepine

- Annulation (construction of a new ring).
- Electron rich group increases anxiolytic activity!

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

22

## Structure-Activity Relationships

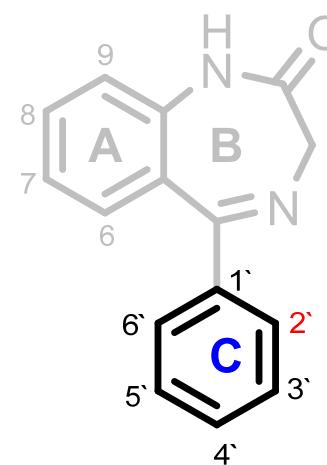


- 4'-Substitution is sterically not favored.

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

23

## Structure-Activity Relationships



- 2'-Substitution is not detrimental to activity.

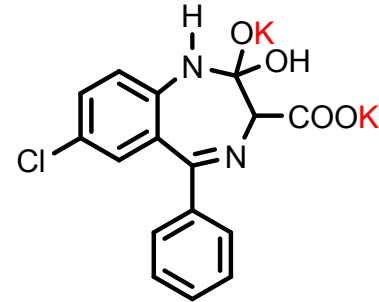
Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

24

## Pharmacokinetic Properties: Absorption & Distribution

- BZDs have higher partition coefficients.

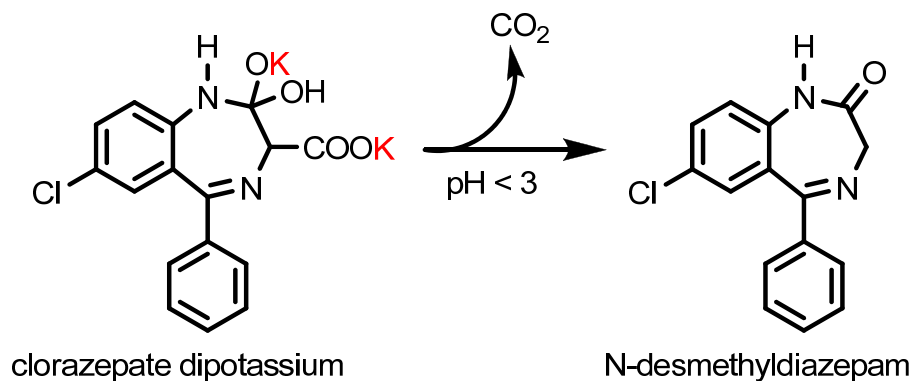
## Pharmacokinetic Properties: Absorption & Distribution



clorazepate dipotassium

- Clorazepate dipotassium is a water-soluble prodrug.

## Pharmacokinetic Properties: Absorption & Distribution

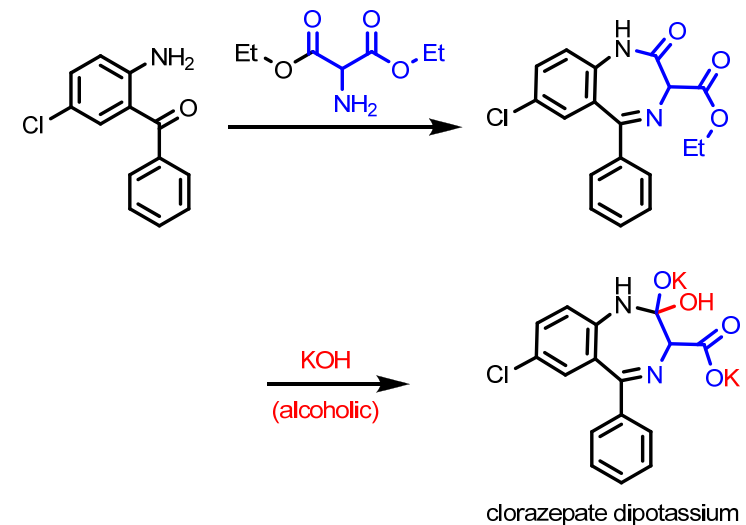


clorazepate dipotassium

N-desmethyldiazepam

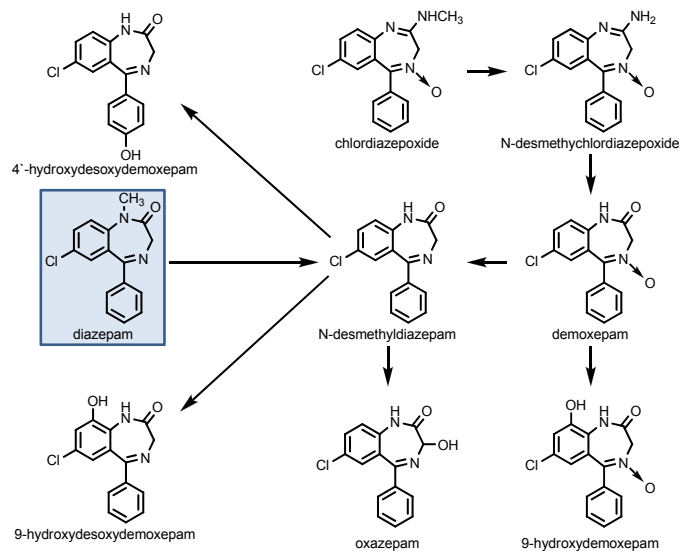
- Clorazepate dipotassium is a water-soluble prodrug.

## Synthesis of Clorazepate Dipotassium



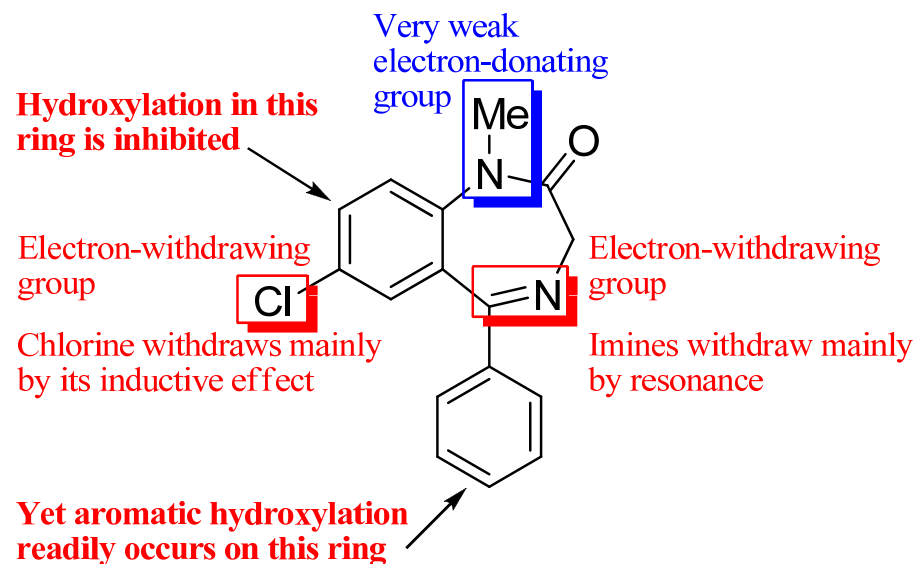
clorazepate dipotassium

## Pharmacokinetic Properties: Metabolism



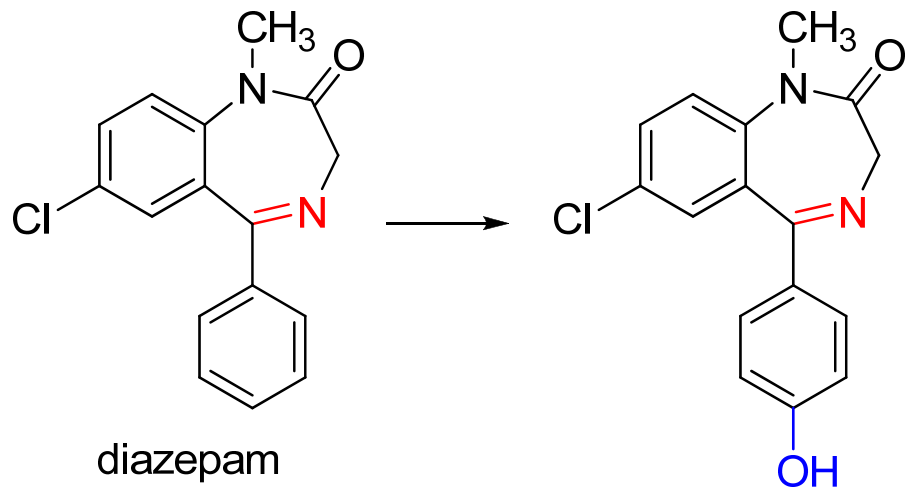
Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

29



Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

30

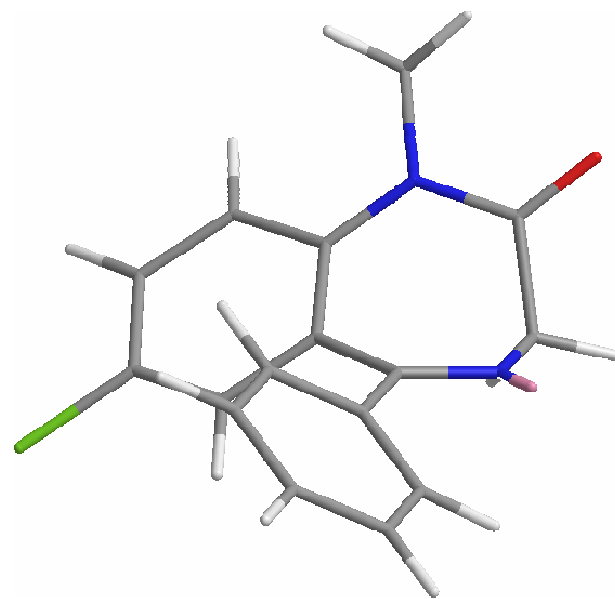


diazepam

- Why C=N is not acting as an electron withdrawing group!!?

Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

31



Associate Prof. Magdi A. Mohamed, Faculty of Pharmacy, University of Khartoum (2014)

32