

AL Chemistry Group Project 6S

Topic: Drug development - Clonazepam

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Clonazepam



Introduction

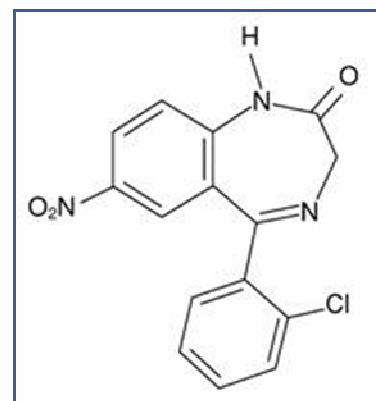
Clonazepam, also named as Klonopin, is used to relieve panic attacks by decreasing abnormal electrical activity in the brain. It is available as an orally disintegrating tablet containing 0.125 mg, 0.25 mg, 0.5 mg, 1 mg or 2 mg clonazepam.

IUPAC Name:

5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one

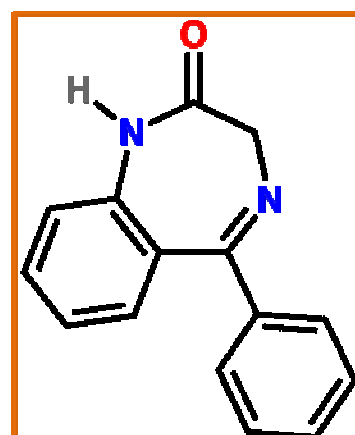
Molecular weight: 315.72

Appearance: light yellow crystalline powder

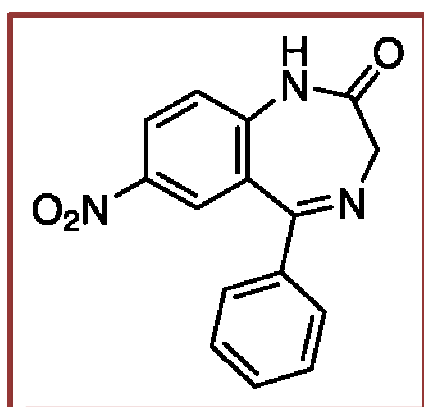


(I) lead compound discovery

Nitrazepam is a type of benzodiazepine drug whose core chemical structure is the fusion of a benzene ring and a diazepine ring. The first benzodiazepine, chlordiazepoxide, was discovered in 1955, and many chemical modifications were done based on its core structure afterwards.



The core structure of



Structure of nitrazepam

of benzodiazepine.

One of the earliest chemical modifications applied on the benzodiazepine nucleus was the **introduction of nitro group**, which were carried out by **Sternbach and his colleagues**. They prepared several nitro compounds and one of the successful, **nitrazepam**, was proved to be much more potent than chlordiazepoxide in both mice and cats. The success has offered chemists the opportunity of subsequent structural variation

(II)Molecular modification:

Clonazepam is a chlorinated derivative of nitrazepam. Therefore, it is a chloro-nitrobenzodiazepine. It differs from nitrazepam with the **substitution of a chlorine atom**.

Clonazepam, 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepine-2-one, is synthesized by following a standard scheme of making derivatives of 1,4-benzodiazepines, with the exception that the acceptor nitro group (in this example) on C7 of the benzodiazepine system is introduced at the last stage of synthesis:

1. The synthesis of clonazepam begins with 2-chloro-2'-nitrobenzophenone, which is reduced to

2-chloro-2'-aminobenzophenone by hydrogen over Raney nickel.

2. The amino derivative is amidated by 2-bromoacetyl bromide to give the bromacetamide and is further

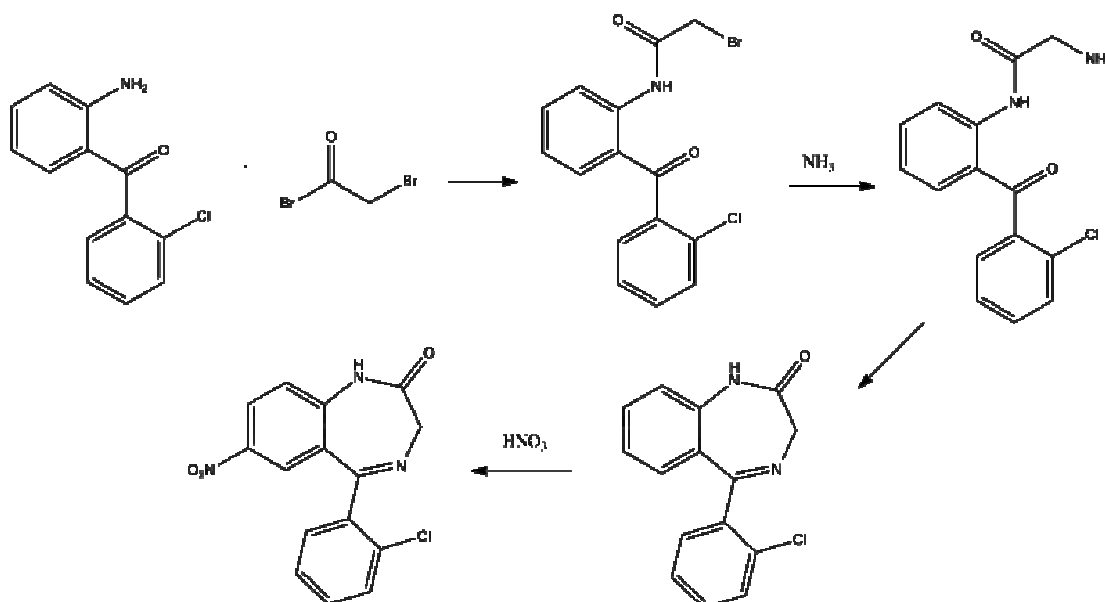
converted into aminoacetamide upon reaction with ammonia.

3. Upon reaction of this with pyridine, it is cyclized into

5-(2-chlorophenyl)-2,3-dihydro-1H-1,4-

benzodiazepine-2-one. The nitration of the resulting product in mild conditions (potassium nitrate in

sulfuric acid) results in clonazepam.



Clonazepam has an unusually long half-life of 18–50 hours which is longer than half-life of nitrazepam(15-38 hours), making it be generally considered as the long-acting benzodiazepines.

Studies show that long-term use of nitrazepam will increase the risk of developing cancer. However, carcinogenicity studies still have not been conducted with Clonazepam.

Clonazepam have a fast onset of action and high effectiveness rate. Maximum plasma concentrations of Clonazepam are reached within 1 to 4 hours after oral administration, which is much faster than nitrazepam that reaches peak blood concentrations in 3 hours.

(III)Formulation development:

Clonazepam is available as tablets and orally disintegrating tablets (wafers), oral solution (drops), as well as solution for injection or intravenous infusion.

The inactive ingredients of Clonazepam tablet include anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium lauryl sulfate. Additionally, the 0.5 mg tablets contain D&C Yellow No. 10 Aluminum Lake. The 1 mg tablets contain D&C Yellow No. 10 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake

(IV)Safety tests and human trials

Source: Par Pharmaceutical, Inc

(i) Aim: To study the deficiency diseases caused by the use of clonazepam during pregnancy

There were totally three studies. Clonazepam was administered orally to pregnant rabbits during the period of organogenesis at doses of **0.2 mg/kg/day** in study 1, **1.5**

mg/kg/day in study 2 and 10 mg/kg/day in study 3. (The maximum recommended human dose for seizure disorders is 20 mg/day, while the maximum dose for panic disorder is 4 mg/day, on a mg/m² basis)

Result:

In all dosage groups, a similar pattern of malformations such as cleft palate, open eyelid, fused sternebrae and limb defects were observed. Reductions in maternal weight gain occurred at dosages of 5 mg/kg/day or greater and reduction in embryo-fetal growth occurred in one study at a dosage of 10 mg/kg/day.

Conclusion:

Clonazepam is not suitable to be prescribed to pregnant patients.

(ii) Aim: To test the effectiveness of clonazepam in treating panic disorder

Adult outpatients who were diagnosed of panic disorder, DSM-III-R, with or without agoraphobia are chosen in these studies to test whether clonazepam is efficacious to their disorder. There are totally two studies, which are both double-blind and placebo-controlled.

Study 1 was a **fixed-dose** study which last for 9-week and were divided into 4 phases : a 1-week placebo lead-in, a 3-week upward titration, a 6-week fixed dose and finally a 7-week discontinuance phase. It involves clonazepam doses of 0.5, 1, 2, 3 or 4 mg/day or placebo

Study 2 was a **flexible-dose** study which last for 6-week and were divided three phases: a 1-week placebo lead-in, a 6-week optimal-dose and a 6-week discontinuance phase. It involves clonazepam doses range of 0.5 to 4 mg/day or placebo, and the mean clonazepam dose during the optimal dosing period was 2.3 mg/day.

RESULT:

In study 1, a significant difference was observed consistently for the **1 mg/day** group from placebo group. The difference between the 1 mg dose group and placebo

group in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 74% of patients receiving clonazepam 1 mg/day were free of full panic attacks, compared to 56% of placebo-treated patients.

In study 2, the difference between clonazepam and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 62% of patients receiving clonazepam were free of full panic attacks, compared to 37% of placebo-treated patients.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of race or gender.

Most Common Adverse Events (≥1%) Associated with Discontinuation of Treatment

Adverse Event	clonazepam(n=574)	Placebo(n=294)
Somnolence	7%	1%
Depression	4%	1%
Dizziness	1%	<1%
Nervousness	1%	0%
Ataxia	1%	0%
Intellectual Ability Reduced	1%	0%

Incidence of Most Commonly Observed Adverse Events* in Acute Therapy in Pool of 6- to 9-Week Trials

Adverse Event	clonazepam (n=574)	Placebo(n=294)
Somnolence	37%	10%
Depression	7%	1%
Coordination Abnormal	6%	0%
Ataxia	5%	0%

*Treatment-emergent events for which the incidence in the clonazepam patients was ≥5% and at least twice that in the placebo patients.

**Incidence of Most Commonly Observed Adverse Events* in
Acute Therapy in Pool of 6- to 9-Week Trials**

Adverse Event (Genentech Preferred Term)	Clonazepam (N=574)	Placebo (N=294)
Somnolence	37%	10%
Depression	7%	1%
Coordination Abnormal	6%	0%
Ataxia	5%	0%

Conclusion:

Clonazepam is significantly more effective than placebo in treating panic disorder on change from baseline in panic attack frequency.

Dosage and administration

It is recommended that the initial dose for adult patients with panic disorder is 0.25 mg , then may increase to the target dose for most patients of 1 mg/day after 3 days. The recommended dose of 1 mg/day is based on the results from the studies, in which showed the most optimal effect.

Higher doses of 2, 3 and 4 mg/day in that study were less effective and were associated with more adverse effects. Nevertheless, some individual patients may benefit from doses of up to a maximum dose of 4 mg/day, and in those cases, the dose may be increased in increments of 0.125 to 0.25 mg every 3 days until panic disorder is under control or until side effects make further undesired increases. For the sake of convenience of somnolence, administration of one dose at bedtime is desirable.

(V)Approval for marketing:

On **August 3, 2005**, Par Pharmaceutical Companies, Inc. announced that its wholly-owned subsidiary, Kali Laboratories, Inc. has received final approval from the U.S. Food and Drug Administration for its Abbreviated New Drug Application for clonazepam orally disintegrating tablets (ODT)

0.5 mg — 1/2 KLONOPIN (front)
ROCHE (scored side)



1 mg — 1 KLONOPIN (front)
ROCHE (reverse side)



2 mg — 2 KLONOPIN (front)
ROCHE (reverse side)

