Clonazepam

- relieve panic attacks

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
lead compound discovery

- **Nitrazepam** -- a type of benzodiazepine

There was a group of scientists: **Sternbach and his colleagues**

They tried to modify benzodiazepine, one of which is the introduction of nitro group.
several nitro compounds were prepared and **nitrazepam** is one of the successful products

much more potent than chlordiazepoxide in both mice and cats.

**Molecular modification**

- a chloro-nitrobenzodiazepine (a chlorinated derivative of nitrazepam)

- differs from nitrazepam with the substitution of a chlorine atom
• IUPAC: 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepine-2-one

• synthesized by derivatives of 1,4-benzodiazepines

• the acceptor nitro group (NO$_2$) on C7 of the benzodiazepine system is introduced at the last stage of synthesis

1. 2-chloro-2'-nitrobenzophenone $\rightarrow$ is reduced to 2-chloro-2'-aminobenzophenone by hydrogen over Raney nickel

2. amidated by 2-bromoacetyl bromide to give the bromacetamide
3. converted into aminoacetamide upon reaction with ammonia

4. cycled into 5-(2-chlorophenyl)-2,3-dihydro-1H-1,4-benzodiazepine-2-one

5. nitration of the resulting product in mild conditions (potassium nitrate in sulfuric acid)

DONE!
Clonazepam VS Nitrazepam

Clonazepam

• longer half-life: 18–50 hours
• No carcinogenicity studies have been conducted
• faster onset of action and higher effectiveness rate: maximum plasma concentrations are reached within 1 to 4 hours after oral administration

Nitrazepam

• half-life: 15-38 hours
• Long-term use will increase the risk of developing cancer.
• maximum plasma concentrations are reached within 3 hours after oral administration

Formulation development

• available as tablets, orally disintegrating tablets (wafers), oral solution (drops), solution for injection or intravenous infusion
• inactive ingredients of Clonazepam tablet:
  – anhydrous lactose
  – colloidal silicon dioxide
  – magnesium stearate
  – microcrystalline cellulose
  – pregelatinized starch
  – sodium lauryl
  – colourings

(IV) Safety tests and human trials

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

• (ii) Aim: To test the effectiveness of clonazepam in treating panic disorder
Clonazepam was administered orally to pregnant rabbits

- 0.2 mg/kg/day
- 1.5 mg/kg/day
- 10 mg/kg/day

**Result 1**

- ALL babies show malformations:
  - cleft palate, open eyelid, fused sternebrae or limbs
  - Fused legs
Result 2

- dosages of 5 & 10 mg/kg/day: reductions in maternal weight gain
- dosage of 10 mg/kg/day: reduction in embryo-fetal growth

Conclusion
fixed-dose study
- 9-week & 4 phases:
  - 1-week placebo lead-in
  - 3-week upward titration,
  - 6-week fixed dose
  - 7-week discontinuance phase.
  - doses of 0.5, 1, 2, 3 or 4 mg/day or placebo

flexible-dose study
- 6-week & 3 phases
  - 1-week placebo lead-in
  - 6-week optimal-dose
  - 6-week discontinuance phase.
  - doses range of 0.5 to 4 mg/day or placebo
  - mean clonazepam dose during the optimal dosing period was 2.3 mg/day.

Result: fixed-dose study
- 1 mg/day group shows the most significant effect

→ 74% free of full panic attacks

→ placebo-treated patients: 56%
Result: flexible-dose study

Patients receiving clonazepam
⇒ 62% of patients: free of full panic attacks
⇒ of placebo-treated patients: 37%

Conclusion:

• Clonazepam is significantly more effective than placebo in treating panic disorder on change from baseline in panic attack frequency.
(V) Approval for marketing:

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