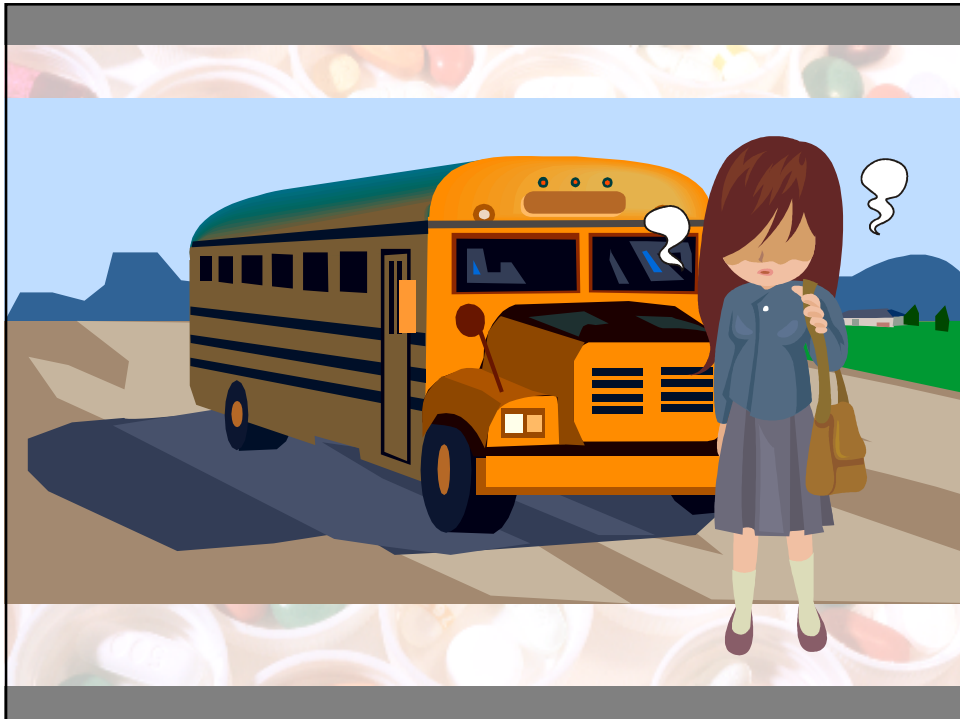


Drug Development



Xanax



- Also called Alprazolam
- IUPAC name:
8-chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine
- 1,4 benzodiazepine is a class of **central nervous system-active compounds**
- The structural formula:
 $C_{17}H_{13}ClN_4$

- Molecular weight:
308.76
- Appearance:
white, crystalline powder
- m.p. :
at about 225 °C
- Solubility:
soluble in organic solvent; insoluble in water



Lead Compound Discovery

- Xanax is a derivative of an antidepressant which is similar to other earlier antidepressants (e.g. Librium).
- it has a group called benzodiazepines (which was thought to be ineffective in treating panic disorder).
- Panic disorder was widespread among the populace.
- It was perceived to be rare and only treatable with tricyclic antidepressants.



Upjohn first took the indication as panic disorder at the behest of a young psychiatrist, David Sheehan.

- Sheehan knew patients were responsive to benzodiazepines .
- So he suggested Xanax to be marketed for anxiety disorders .
- **It was proved to be a better and less toxic antidepressant** than its counterparts.



- The first group of patients were impressed.
- A few of those patients even pooled their money and purchased stock in Upjohn.

Time line for drug development

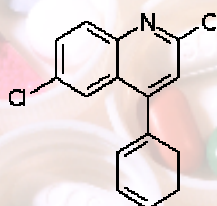
Year	Event
1970s	Xanax was first developed by Upjohn Laboratories of Kalamazoo, Michigan.
October 29, 1969	The drug was covered under U.S. Patent 3,987,052.
October 19, 1976	The drug was granted.
1981	<ol style="list-style-type: none">1. First group of patients were tested.2. It was approved and released by the USFDA.

Year	Event
September 1993	The patent was expired.
1995	Upjohn was acquired by Pharmacia.
1995-2002	The Xanax Extended Release (XANAX-XR) in 0.5,1,2,or 3mg was developed (just one dose/ day).
2002	Pfizer Pharmaceuticals acquired Pharmacia and Upjohn.
2002-NOW	It was produced and marketed by Pfizer Pharmaceuticals.

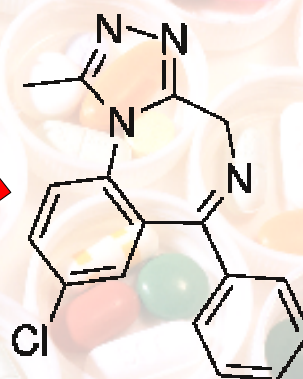
Molecular modification

- soluble in alcohol
- insoluble in water

Starting compound:



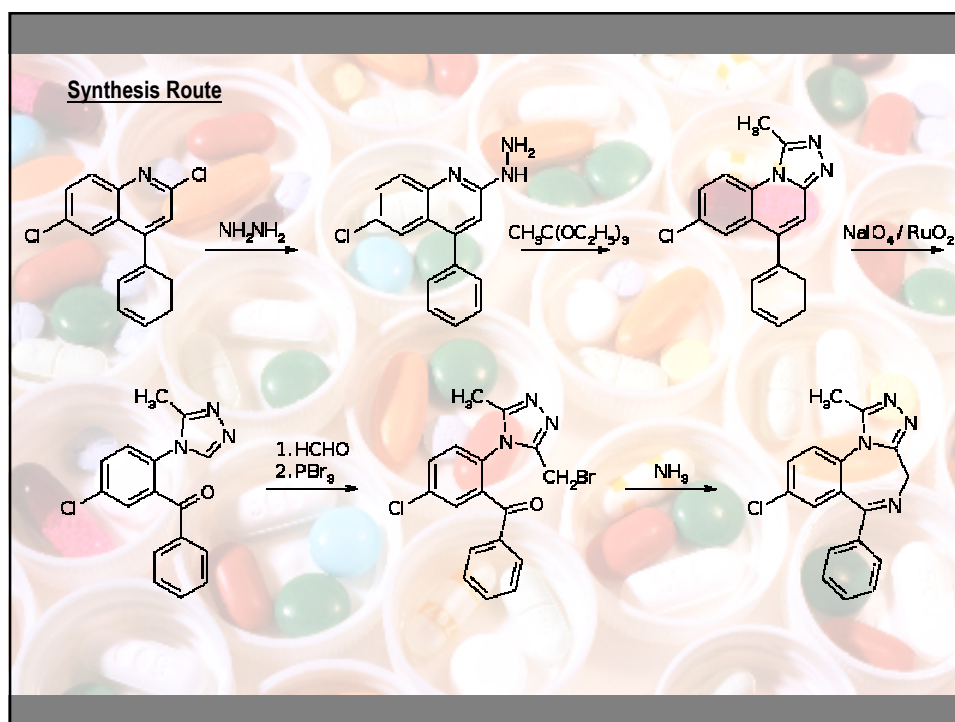
Structural formula:



- is a chemical **analog of triazolam**
- differs by the **absence of a chlorine atom** in the *o*-position of the 6-phenyl ring
- **synthesis** is **similar to that of triazolam**
- 2,6-dichloro-4-phenylquinoline is used in the reaction with hydrazine to give 6-chloro-2-hydrazino-4-phenylquinoline
- **boiling the product with triethyl orthoacetate in xylene**, the heterocyclization is lead into a triazole derivative



- Undergo **oxidative cleavage using sodium periodate** and **ruthenium dioxide** in an acetone-water system
- Oxymethylation of formaldehyde and **subsequent substitution of the resulting hydroxyl group by phosphorus tribromide** would produce 2-[4-(3'-methyl-5'-bromomethyl-1,2,4-triazolo)]-5-chlorobenzophenone
- Alprazolam is given in the **substitution of the bromine atom with an amino group using ammonia** and the spontaneous intramolecular **heterocyclization**



Formulation Development

- Some benzodiazepines **have to be taken 2 to 4 times a day**. Patients often feel anxious before it's time to take the next dose.
- Because the medicine's effects can wear off between doses if not taken as directed by their doctors.
- XANAX-XR is then developed** in 2002 to give a once-daily formula, which avoid them miss a dose by mistake.
- Each XANAX Tablet, for oral administration, contains **0.25, 0.5, 1 or 2 mg of alprazolam**.

Formulation Development

- the 0.5 mg tablet contains FD&C Yellow No. 6 and the 1 mg tablet contains FD&C Blue No. 2.

Active ingredients:	alprazolam
Inactive ingredients:	Cellulose Corn starch Docusate sodium Lactose Magnesium stearate Silicon dioxide Sodium benzoate

Safety Test and Human trials

- **Laboratory Tests**

- Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice. Clinically, all benzodiazepines cause a **dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.**

Gender

- Gender has **no effect** on the pharmacokinetics of alprazolam.

Cigarette Smoking

- Alprazolam concentrations may be **reduced by up to 50%** in smokers compared to non-smokers.

Pregnancy

- It should be considered that the child born of a mother who is receiving benzodiazepines may be **at some risk for withdrawal symptoms from the drug** during the postnatal period. Also, **neonatal flaccidity and respiratory problems** have been reported in children born of mothers who have been receiving benzodiazepines.

Pediatric Use

- **Safety and effectiveness** of Xanax in individuals **below 18 years of age have not been established.**

Nursing Mothers

- Benzodiazepines are known to be **excreted in human milk**. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their **infants to become lethargic and to lose weight**. As a general rule, nursing should not be undertaken by mothers who must use Xanax.

Geriatric Use

- The **elderly may be more sensitive** to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. **The smallest effective dose of Xanax should be used in the elderly** to preclude the development of ataxia and oversedation.

Human Trials

- XANAX is refined to minimize the side effect
- **was significantly better than placebo** at each of the evaluation periods of these **4-week studies** as judged by the following psychometric instruments: Physician's Global Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient's Global Impressions and Self-Rating Symptom Scale.



	Xanax	PLACEBO	Refined Xanax
Number of Patients	565	505	565
% of Patients Reporting:			
Central Nervous System			
Drowsiness	41.0	21.6	15.1
Light-headedness	20.8	19.3	1.2
Depression	13.9	18.1	2.4
Headache	12.9	19.6	1.1
Confusion	9.9	10.0	0.9
Insomnia	8.9	18.4	1.3
Nervousness	4.1	10.3	1.1
Syncope	3.1	4.0	/
Tiredness/Sleepiness	/	/	1.8

	Xanax	PLACEBO	Refined Xanax
Gastrointestinal			
Dry Mouth	14.7	13.3	0.7
Constipation	10.4	11.4	0.9
Diarrhea	10.1	10.3	1.2
Nausea/Vomiting	9.6	12.8	1.7
Increased Salivation	4.2	2.4	/
Cardiovascular			
Tachycardia/Palpitations	7.7	15.6	0.4
Hypotension	4.7	2.2	/
Sensory			
Blurred Vision	6.2	6.2	0.4
Musculoskeletal			
Rigidity	4.2	5.3	/
Tremor	4.0	8.8	0.4

	Xanax	PLACEBO	Refined Xanax
Cutaneous			
Dermatitis/Allergy	3.8	3.1	0.6
Other			
Nasal Congestion	7.3	9.3	/
Weight Gain	2.7	2.7	/
Weight Loss	2.3	3.0	/

/ : not reported

Xanax caused **less side effects** than Placebo in most of the cases, while the refined Xanax caused the least effects

In conclusion, **Xanax is a better drug** than Placebo and the refined Xanax is better than Xanax.



Approval for marketing

- Panic disorder was officially classified as a distinct psychiatric entity for the first time in 1980 by the American Psychological Association (APA)'s Diagnostic and Statistical Manual.
- **In 1981, the U.S. Food and Drug Administration (FDA) approved Xanax** for the treatment of Panic Disorder.

Now

- It has become one of the **most prescribed** psychotropic drugs
- Available under **more than 40 brand names** on market
- In Latin-American Countries, Xanax is prescribed as “Tafil” or other brand names are used in other countries



- Xanax is a **famous medication** indicated **for panic disorder**. There are many brands manufacturing it. For example, it is available under Alganax, Alzolam, Xanor and so on.

Reference Links

- <http://www.pmmmedia.com/Xanax.htm>
- <http://en.wikipedia.org/wiki/Alprazolam>
- <http://www.medicinenet.com/alprazolam/article.htm>
- <http://en.wikipedia.org/wiki/Alprazolam>
- <http://www.drugs.com/pro/xanax.html>
- <http://www.pillsatwork.com/anti-anxiety/xanax/prescription-info/full-article/>

Thank you !



7S Chak Choi Wai
Luk Ka Po
Wong Pui Yee
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