

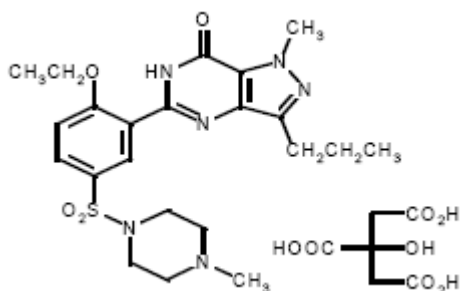
Chemistry Project on Sildenafil

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Introduction:

Sildenafil, sold as Viagra, is a drug used to treat erectile dysfunction and pulmonary arterial hypertension (PAH).

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate and has the following structural formula:



Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 666.7.

It was developed and is being marketed by the pharmaceutical company Pfizer. It acts by inhibiting cGMP specific phosphodiesterase type 5, an enzyme that regulates blood flow in the penis. Since becoming available in 1998, sildenafil has been the prime treatment for erectile dysfunction; its primary competitors on the market are tadalafil (Cialis) and vardenafil (Levitra).

Compound Discovery:

Sildenafil was synthesized by a group of pharmaceutical chemists working at Pfizer's Sandwich, Kent, research facility in England. It was initially studied for use in hypertension (high blood pressure) and angina pectoris (a symptom of ischaemic heart disease). The first clinical trials were conducted in Morrision Hospital in Swansea. Phase I clinical trials under the direction of Ian Osterloh suggested that the drug had little effect on angina, but that it could induce marked penile erections. Pfizer therefore decided to market it for erectile dysfunction, rather than for angina. The drug was patented in 1996, approved for use in erectile dysfunction by the US Food and Drug Administration on March 27, 1998, becoming the first oral treatment approved to treat erectile dysfunction in the United States, and offered for sale in the United States later that year.

Molecular Modification:

In the manufacture of Viagra, besides the active ingredient, sildenafil citrate, each viagra tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose, triacetin, and FD & C Blue #2 aluminum lake.

Formulation development:

The synthesis of sildenafil has nine steps:

- Methylation of 3-propylpyrazole-5-carboxylic acid ethyl ester with hot dimethyl sulfate.
- Hydrolysis with aqueous NaOH to free acid.
- Nitration with oleum/fuming nitric acid.
- Carboxamide formation with refluxing thionyl chloride/NH₄OH.
- Reduction of nitro group to amino.
- Acylation with 2-ethoxybenzoyl chloride.
- Cyclization.
- Sulfonation to the chlorosulfonyl derivative.
- Condensation with 1-methylpiperazine.

Trial test for human:

In clinical trials, the most common adverse effects of sildenafil use included headache, flushing, dyspepsia, nasal congestion and impaired vision, including photophobia and blurred vision. Some sildenafil users have complained of seeing everything tinted blue (cyanopsia). Some complained of blurriness and loss of peripheral vision. In July 2005, the U.S. Food and Drug Administration found that sildenafil could lead to vision impairment in rare cases and a number of studies have linked sildenafil use with nonarteritic anterior ischemic optic neuropathy

While in the trial test for its product, Viagra, it was administered to over 3700 patients (aged 19-87 years) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

The results are as follow:

Adverse Event	Percentage of Patients Reporting Event
Headache	16%
Flushing	10%
Dyspepsia	7%
Nasal Congestion	4%
Urinary Tract Infection	3%

Abnormal Vision	3%
Diarrhea	3%
Dizziness	2%
Rash	2%

The adverse events were generally transient and mild to moderate in nature.

Approval for market:

The FDA approved Viagra on March 27, 1998. Viagra is the first oral pill to treat impotence, a dysfunction that affects millions of men in the United States. Viagra is manufactured by Pfizer Pharmaceuticals, New York, NY.

The approval of Viagra is because of the follow reasons:

- In clinical trials, Viagra has shown effectiveness for organic, psychogenic, and mixed erectile dysfunction.
- Expected to be the first oral therapy indicated for erectile dysfunction, Viagra is well tolerated.
- Viagra works only in response to sexual stimulation and restores natural function.
- It is nonsurgical and noninvasive: alternative treatments currently available include implants, devices, and injections.
- Viagra tablets are taken only on an as-needed basis as a single dose, approximately an hour in advance of the desired therapeutic effect.

The end