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Vardenafil

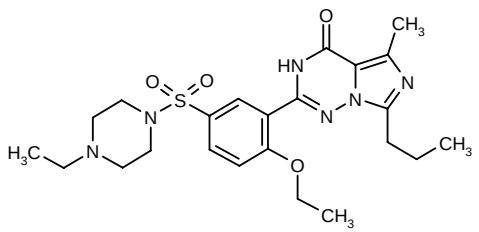
Prop INN

Treatment of Erectile Dysfunction

Phosphodiesterase 5 Inhibitor

Bay-38-9456

2-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one



$C_{23}H_{32}N_6O_4S$ Mol wt: 488.6098

CAS: 224785-90-4
CAS: 224789-15-5 (as dihydrochloride)
CAS: 224785-91-5 (as monohydrochloride)

EN: 276900

Synthesis

Cyclization of 2-ethoxybenzamidine (I) with 2-butyramidopropionic acid (II) and ethoxalyl chloride (III) by means of DMAP in refluxing pyridine gives 2-(2-ethoxyphenyl)-5-methyl-7-propyl-3,4-dihydroimidazo-[5,1-*f*][1,2,4]triazin-4-one (IV), which is sulfonated with chlorosulfonic acid to provide the sulfonyl chloride (V). Finally, this compound is condensed with 1-ethylpiperazine (VI) in dichloromethane (1). Scheme 1.

Introduction

Sexual dysfunction encompasses several conditions which involve disturbances in sexual desire and the psychophysiological processes within the sexual response cycle (2). Sexual disturbances affecting men include erectile dysfunction, ejaculatory dysfunction and male orgasmic disorder while those affecting women include female sexual arousal disorder, female orgasmic disorder and vaginismus; hypoactive sexual desire disorder, sexual aversion disorder and dyspareunia can affect both sexes (2). The estimated prevalence of sexual disorders is high with up to 30 million men in the U.S. and over 100 million men worldwide suffering from some form of erectile dysfunction (2, 3). The incidence of sexual dysfunction increases with age and studies suggest that approximately 15-25% of 65-year-old men suffer from erectile dysfunction as compared to only 5% of men aged 40 years (2).

While female sexual dysfunction remains elusive, most cases of male sexual dysfunction are treatable. Phosphodiesterase type 5 (PDE5) is a member of the cyclic nucleotide superfamily of hydrolyzing enzymes that specifically cleaves the key second messenger cyclic guanosine monophosphate (cGMP). Researchers initially focused on PDE5 as a target for the treatment of angina and hypertension. However, with the discovery of the PDE5 inhibitor sildenafil (Viagra™) and its proven efficacy as a treatment for erectile dysfunction, researchers and clinicians have refocused there efforts in the search for a treatment for sexual dysfunction, particularly erectile dysfunction. PDE5 is the predominant cGMP-hydrolyzing enzyme present in the corpus cavernosum and may be the crucial inducer of the erectile process. Sexual stimulation causes nitric oxide (NO) to be released from nonadrenergic, noncholinergic neurons innervating the corpus cavernosum. NO, in turn, activates soluble guanylyl cyclase which converts GTP to cGMP. If there is insufficient NO released, the appropriate levels of cGMP required to relax vascular muscle allowing accumulation of blood in the erectile chambers of the penis are not achieved and the result is the inability to achieve erection. However, if PDE5 is inhibited, conversion of cGMP to the inactive GMP can be prevented, thus allowing cGMP to reach appropriate levels necessary for adequate blood accumulation. PDE5 inhibitors are effective only in combination with sexual stimulation which activates the release of endogenous NO (2, 4, 5).

The launch of the prototypical inhibitor sildenafil citrate in 1998 altered the direction of drug development for the treatment of sexual dysfunction. A Table listing PDE5 inhibitors currently under development for the treatment of sexual dysfunction has recently been published (5). An additional compound, vardenafil (Bay 38-9456), has shown excellent PDE5 inhibitory activity and was chosen for further development.

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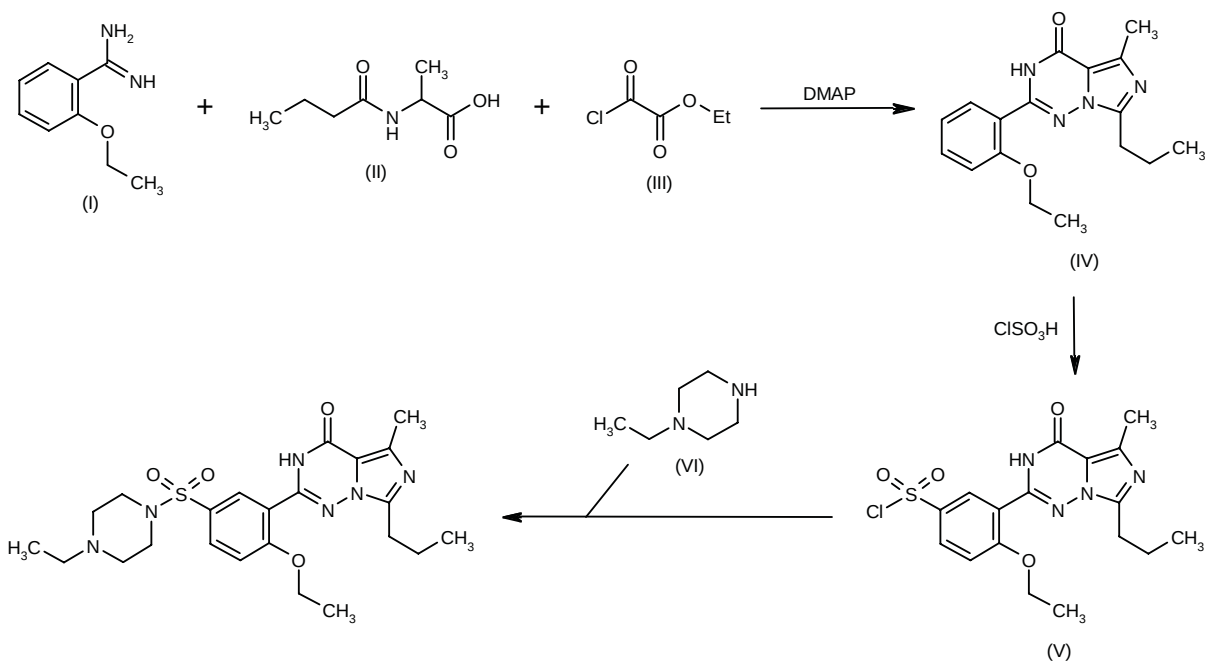
Scheme 1: Synthesis of Vardenafil



Pharmacological Actions

Vardenafil potently and selectively inhibited PDE5. An IC_{50} value of 0.7 nM was obtained against PDE5 as compared to values of 180 nM, > 10 μM, 2.5 μM, 4 μM and 157 nM obtained for the agent against PDE1, -2, -3, -4 and -6, respectively. Further *in vitro* studies using freshly isolated corpora cavernosa slices (free from the tunica albuginea) from chinchilla rabbits revealed that vardenafil dose-dependently increased cGMP concentrations in this tissue. While sodium nitroprusside (SNP) at a dose of 1 μM only increased cGMP tissue levels by 30%, 1 μM vardenafil increased cGMP 3-fold over control values; cotreatment with SNP and vardenafil resulted in a 7-fold increase in cGMP levels over controls. No effects on tissular cAMP levels were detected (6).

Vardenafil (0.1-3 mg/kg i.v.) was shown to dose-dependently induce penile erections in a manner similar to sildenafil in an *in vivo* study conducted in conscious rabbits. Coadministration of SNP significantly enhanced the effects of vardenafil, reducing the minimal effective dose to 0.01 mg/kg (i.v.). L-NAME suppressed the effects of both vardenafil and sildenafil (7).

Pharmacokinetics and Tolerability

Several studies have examined the pharmacokinetics of vardenafil in both healthy subjects and subjects with erectile dysfunction of no established organic cause.

A randomized, double-blind, placebo-controlled, single-dose, group-comparison study conducted in 9 healthy male subjects (18-45 years) reported that oral vardenafil at doses of 5, 10, 20, 40 or 80 mg was rapidly absorbed; the median t_{max} and $t_{1/2}$ values were 0.625-0.75 h and 3.3-5 h, respectively, for all doses. The pharmacokinetics of vardenafil were nonlinear since the mean AUC_{norm} for doses of 5-40 mg and 80 mg were 246 and 469 g·h/l, respectively, and the C_{max},norm value was 82 g/l for all doses. Vardenafil was well tolerated with 27 mild to moderate adverse events reported, of which 19 were in the vardenafil group and 8 were in the placebo group. Of those adverse events seen in patients given vardenafil, 9 and 3 cases were considered possibly and probably drug-related, respectively. The agent had no effect on heart rate, systolic and diastolic blood pressure, ECGs or laboratory parameters (8).

Comparable pharmacokinetics and tolerability were reported for single-dose vardenafil (10 and 20 or 20 and 40 mg p.o.) administered to subjects (n = 42) with erectile dysfunction of no known organic cause participating in 2 randomized, double-blind, placebo-controlled, 3-fold crossover studies. Vardenafil was rapidly absorbed with a median t_{max} of 0.66-0.92 h obtained for all doses; plasma elimination $t_{1/2}$ values were 3.9-4.8 h. The pharmacokinetics of vardenafil were nonlinear since the mean AUC_{norm} values for doses of 10-20 mg and 40 mg were 271 and 335 g·h/l, respectively, and the $C_{max,norm}$ value was 82 g/l for all doses. Single dosing was well tolerated. In the study involving doses of 10 and 20 mg, only 19 and 10% of the subjects given the respective vardenafil doses

Box 1: Safety, tolerability and pharmacokinetics of vardenafil in patients with erectile dysfunction (9) [Prous Science CSline database].

Design	Multicenter, crossover, randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Patients with erectile dysfunction of no established organic cause (n = 42)
Treatments	Study I: Vardenafil, 10 mg p.o. Vardenafil, 20 mg p.o. Placebo Study II: Vardenafil, 20 mg p.o. Vardenafil, 40 mg p.o. Placebo
Adverse Events	Study I: V10: 19% [headache, flush, nasal congestion] V20: 10% [headache, flush, nasal congestion] P: 5% [headache, flush, nasal congestion] Study II: V20: 48% [headache, flush, nasal congestion] V40: 67% [headache, flush, nasal congestion] P: 48% [headache, flush, nasal congestion]
Results	Physical examination, heart rate, systolic and diastolic blood pressure, ECG parameters and laboratory parameters were not significantly altered
Conclusions	Single oral doses of 10, 20 or 40 mg of vardenafil were safe and well tolerated in patients with erectile dysfunction of no established organic cause

Box 2: Safety, tolerability and pharmacokinetics of multiple-dose vardenafil in healthy volunteers (10) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Healthy volunteers (n = 12)
Treatments	Vardenafil, 40 mg p.o. o.d. x 14 d (n = 8) Placebo (n = 4)
Adverse Events	V: 4/8 (50%) [headache] P: 2/4 (50%) [headache]
Results	Physical examination, heart rate, systolic and diastolic blood pressure, ECG parameters and laboratory parameters were not clinically significantly influenced by vardenafil
Conclusions	Vardenafil was safe and well tolerated in healthy volunteers

developed treatment emergent adverse events as compared to 5% in placebo. In the study employing 20 and 40 mg doses, 48 and 67% of the subjects given the respective doses and 48% of the subjects on placebo experienced treatment emergent adverse events. The incidence of those adverse events such as headache, flush and nasal congestion that were concluded to be possibly or probably drug-related, was higher in subjects receiving the 40 mg dose as compared to 20 mg and placebo; the incidence of all other adverse events was similar in all study groups. No effects on heart rate, systolic and diastolic blood pressure, ECGs or laboratory parameters were observed (9) (Box 1).

The pharmacokinetics and tolerability of multiple vardenafil dosing (40 mg once daily for 14 days) was examined in a randomized, double-blind, placebo-controlled, group-comparison study conducted in 12 healthy male subjects (18-45 years). No accumulation of the agent was detected since the geometric C_{max} and AUC_{τ} values obtained on days 1 and 14 were 24 and 31 μg/l, respectively, and 95 and 111 μg·h/l, respectively. Similarly, absorption (t_{max} = 0.6 and 0.5 h on days 1 and 14, respectively) and elimination rates ($t_{1/2}$ = 3.8 and 4.1 h, respectively) were unaltered following multiple dosing. Multiple vardenafil dosing was well tolerated with similar adverse events observed in both treatment and placebo groups. The most common adverse event was headache seen in 4/8 subjects receiving vardenafil and 2/4 subjects given placebo. Once again, no clinically significant effects of the agent were seen on heart rate, systolic and diastolic blood pressure, ECGs or laboratory parameters (10) (Box 2).

Box 3: Erectile response on visual sexual stimulation after treatment with vardenafil or placebo (11) [Prous Science CSline database].

Design	Double-blind, randomized, placebo-controlled, crossover clinical study
Population	Male patients with erectile dysfunction (n = 21)
Treatments	Vardenafil, 20 mg p.o. s.d. Vardenafil, 40 mg p.o. s.d. Placebo
Results	Duration (min) of rigidity > 60% at penis tip: B40* (48.74) ≥ B20* (48.71) > P (12.76) [*p <0.001 *vs.* P] Duration (min) of rigidity > 80% at penis tip: B40* (22.6) ≥ B20* (18.45) > P (5.23) [*p <0.001 *vs.* P]
Conclusions	Vardenafil at doses of 20 and 40 mg was an effective oral therapy for male erectile dysfunction

Clinical Studies

Results from a randomized double-blind, placebo-controlled, 3-fold crossover trial conducted in 21 patients with erectile dysfunction showed the efficacy of vardenafil (20 and 40 mg p.o.) on the erectile response (as measured using Rigiscan™) to visual sexual stimulation (3 20-min periods of 20 min separated by 20 min and starting 20 min postdosing). As compared to placebo (12.76 ± 15.11 min), 20 and 40 mg vardenafil significantly increased the duration of rigidity of > 60% at the tip of the penis (48.71 ± 30.35 and 48.74 ± 26.68 min, respectively). In addition, the 20 and 40 mg doses of vardenafil also significantly increased the duration of rigidity of > 80% at the tip of the penis as compared to placebo (18.45 ± 21.57 and 22.60 ± 21.71 min, respectively, vs. 5.23 ± 8.66 min). Vardenafil was also superior to placebo in terms of rigidity and tumescence activity units and for the same parameters at the base of the penis. No significant differences were observed between the 20 and 40 mg doses (11) (Box 3).

Vardenafil is starting phase III trials and is expected to be launched in November 2002 (12).

Manufacturer

Bayer AG (DE).

References

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