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Sildenafil (Viagra™): Synthesis Step by Step and its Pharmaceutical Importance in Diabetic Patients with Erectile Dysfunction

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Abstract

Objective: Sildenafil is a selective inhibitor of phosphodiesterase 5 (PDE5) and is the first agent with this mode of action for the treatment of male erectile dysfunction. There has recently been an explosion of interest in sexual dysfunction. Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity. This article aims to discuss in details the commercial synthesis of Sildenafil as published by the Pfizer research group and describe critically the role of Sildenafil in diabetic neuropathic patients with erectile dysfunction.

Method: A computer as well as manual search was made to collect the relevant data published in various peer-reviewed journals on Viagra™.

Results: The synthesis of Sildenafil serves as an excellent example of the demands of commercial chemistry. Also, the serendipitous discovery of this drug's positive effect on sexual performance has revolutionized the management of erectile dysfunction. Although the literature is spare, Tadalafil has a longer half-life than Sildenafil and therefore may be recommended as the choice of preference. Contraindications for their use include the use of nitrates, unstable angina, recent myocardial infarction or complicated congestive heart failure (CHF). Other oral agents including apomorphine, Phentolamine and trazodone have also been proposed to treat ED with some adverse effects.

Conclusion: Our data in this review portrays accurately using Sildenafil for restoring sexual functions in diabetic neuropathic population. Other limitations include a great potential for misuse and costly.

Keywords: Viagra™; Sildenafil; Synthesis; Erectile dysfunction; Tadalafil

Introduction

The causes of erectile dysfunction are many, endocrine disorders neuropathy, vascular disease, diabetes control nutrition, psychogenic factors, as well as drugs used in the treatment of these complications all play a role [1]. The National Institute of Health Consensus Panel reported that ED affects as many as 30 million men in the United States [2]. Diabetes mellitus is strongly associated with the development of ED, with a reported prevalence of ED of 35-90% in those with diabetes in different populations [3]. The pathophysiology of ED in diabetes is multifactorial. Under normal circumstances, both biological and psychological factors work synchronously resulting in an erection [4]. Based on questionnaire responses by 1709 men, 35% of men reported moderate to complete ED. Overall prevalence rates were 39% in men 40 years of age, 48% in those 50 years of age, 57% in those 60 years of age, and 67% in those 70 years of age [5]. Therefore, this sector of population heavily uses a variety of medicines ranging from herbal to modern drugs. Similiarly, they are also suggested different types of psychological, social and behavioral therapies. Nevertheless, most of them remain sexual performance of an individual. Surprisingly, Sildenafil as compared with other related drugs received enhanced media attention. Also, several studies on patients with specific disorders such as diabetes mellitus, hypertension, spinal cord injury, multiple sclerosis and depression have also shown Sildenafil to be effective. This article was aimed to discuss in details Viagra™ synthesis step by step and explain its effect in diabetic patient with erectile dysfunction.

Synthesis of Viagra™

Before Viagra there was no orally active therapy for male erectile dysfunction and Sildenafil was tested against hypertension and later against angina with little success. Rumor has it that the male patients involved in the clinical studies were reluctant to discontinue the tests without apparent reason [6]. The chemical development of the commercial route to Sildenafil also serves as an excellent example of different issues that need to be considered when moving from drug discovery to commercial quantities. This problem is therefore based on the commercial synthesis of Sildenafil as published by the Pfizer research group [7].

First step

Pyrazole are very common parts of commercially available pharmaceuticals, agrochemicals and dyestuffs. The reaction of β-diketones with hydrazines is the most widely used method to synthesize pyrazoles. The reaction proceeds via the formation of hydrazone **A** [8] which on subsequent cyclization and dehydration produces the corresponding pyrazole **2** (Figure 1).

This method usually has the disadvantage that with unsymmetrical diketones generally a mixture of isomer pyrazoles is formed. Here the authors report no other isomer probably because of the great electronic

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differences of the two ketones being substituted with an ester vs. an alkyl group (Chart 1).

Second step

Me_2SO_4 is used under basic condition as source of a methyl nucleophile. It can thus transform alcohols into methyl ethers or transform amines into the methylamine (Figure 2). Usually a phase transfer catalyst such as tetrabutylammonium iodide is added to the aqueous basic solution [9]. Other reagent to create methyl ethers includes iodomethane or trimethoxonium tetrafluoroborate (Meerwien's reagent) [10]. Ester hydrolysis can proceed under acidic (saponification) conditions to the carboxylic acid. In this case aqueous NaOH is used. The order of reaction, methylation before saponification, both under basic conditions, is presumably important since the free acid would again methylated by Me_2SO_4.

Third step

Nitration is one step of the classical example of electrophilic aromatic substitution as taught in introductory organic chemistry courses. When (hetero) aromatic compounds are treated with a mixture of nitric and sulfuric acid, nitronium ions (NO_2^+) are the electrophilic species. Aromatic heterocycles are divided into two general groups by their electronic properties and the resulting reactivity. Six-membered (pyridine-type) heteroaromats are electron poor (π-deficient) and thus their reactivity is affected by electron-withdrawing effect of the heteroatom [11]. Six-membered heteroatomats therefore react fast with nucleophiles and often not in an electrophilic substitution. Five-membered (pyrrole-type) hetereoarmtic compounds are electron rich (π-excessive) and the lone pair of the heteroatom is part of the localized aromatic system. These compounds therefore react easily with electrophiles. Pyrazole belongs to the group of five-membered electron rich heterocycles and contains a pyrrole type nitrogen which releases electron into the aromatic system. However, its second nitrogen is of the pyridine-type and deactivates the ring by its electron-withdrawing properties. Usually pyrazole reacts with electrophiles very well in the 4 position is sterically available making the intrinsic selectivity irrelevant [12]. This reaction is the most dangerous in the commercial synthesis since it requires at least 50°C to start, and once the reaction starts it is very exothermic. This would increase the heat under adiabatic conditions still further until at 120°C the carboxylic acid would decarboxylate in another exothermic reaction creating CO_2 gas thus increasing the pressure in the reactor. The research group at Pfizer designed the process to minimize the risk by dividing the procedure into three steps: first the pyrazole **3** was dissolved in conc. H_2SO_4, next the fuming nitric acid was mixed with conc. H_2SO_4 and added to the pyrazole depending on the conversion (Figure 3).

Fourth step

The formation of amides is one of the most important reactions in organic chemistry, especially since peptides contain amide bonds between the amino acids. Since carboxylic acids are not reactive towards nucleophilc substitution they have to be activated first. One of the simplest methods is the transformation of the acid into the acid halide. This can be afforded by thionyl chloride ($SOCl_2$). The addition of catalytic amounts of DMF enhances the reactivity by forming a Vilsmeyer intermediate, which can also be isolated and used in the formation of acid chloride [13]. Another mild and simple method to generate acid halides involves the use of triphenylphosphine and CCl_4 creating the acid chloride and triphenylphosphine oxide [14]. In the described transformation the created acid chloride is attacked by aqueous ammonia as nucleophile to create the amide **5** in excellent yield.

In the medicinal chemistry route to Sildenafil, the nitro group in **5** was reduced using $SnCl_2$ and hydrochloric acid in ethanol; in the commercial route this was changed to the application of H_2 under palladium catalysis in ethyl acetate (Figure 4). Since stannous compounds are highly toxic to the aqueous waste stream from the reduction would have been hard to purify. The heterogeneous

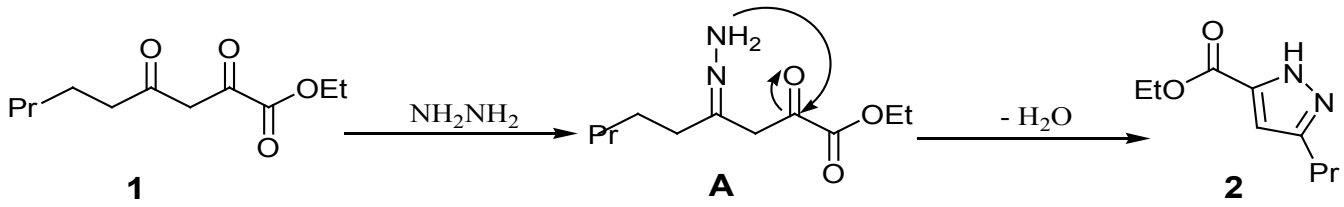

Chart 1: Mechanism of synthesis of ethyl 3-propyl-1H-pyrazole-5-carboxylate.

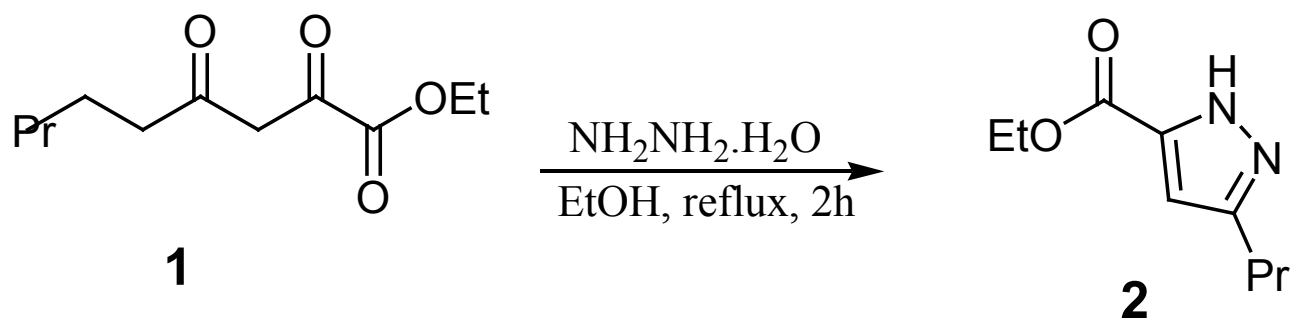

Figure 1: Synthesis of ethyl 3-propyl-1H-pyrazole-5-carboxylate **(2)**.

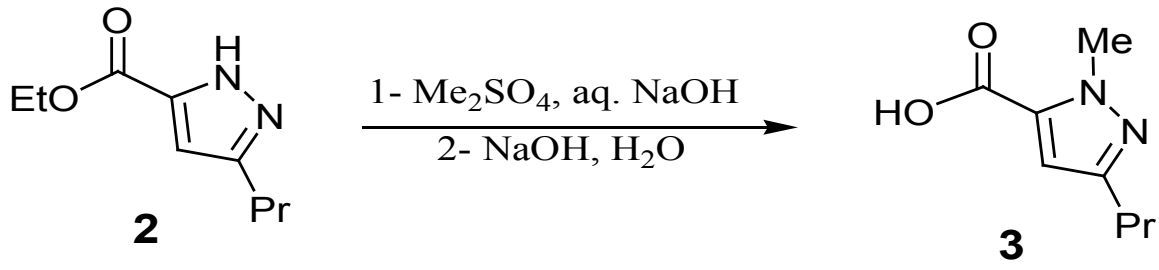

Figure 2: Synthesis of 1-methyl-3-propyl-1H-pyrazole-5-arboxylic acid **(3)**.

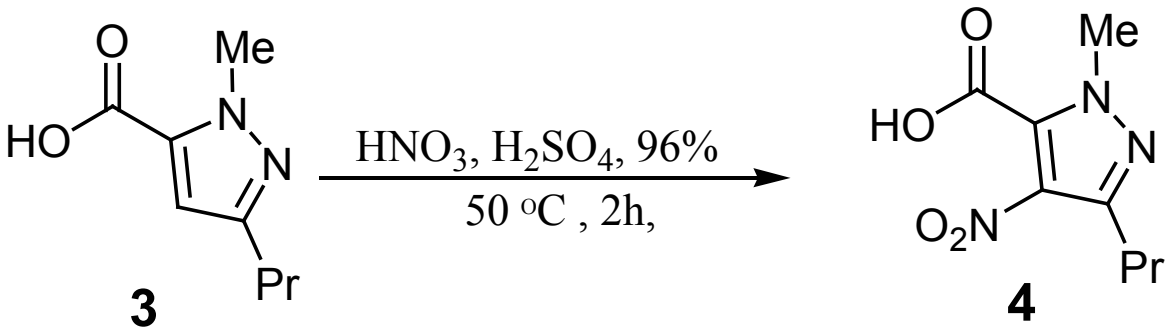

Figure 3: Synthesis of 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid **(4)**.

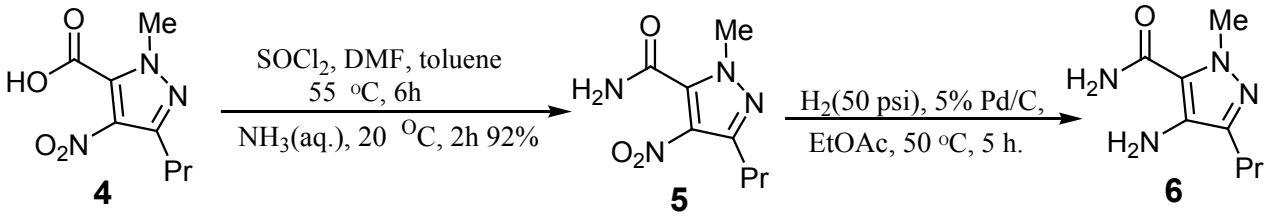

Figure 4: Synthesis of 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxamide **(5)** and 4-amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide **(6)**.

catalysis of palladium on charcoal in ethyl acetate leaves no residues and therefore the solution containing **6** could be used directly in the following coupling step.

Fifth step

Molten 2-ethoxybenzoic acid (**7**) was added to a mixture of chlorosulfonic acid and thionyl chloride while keeping the reaction temperature below 25°C in this straightforward electrophilic aromatic substitution the ethoxy group directs the electrophile towards the ortho and para position whereas the carboxylic acid directs meta giving an overall selectivity for the attack at C-5. It was necessary to add thionyl chloride to transform the intermediate sulfonic acid into the sulfonyl chloride. After quenching with ice water the product **8** could simply be precipitated and washed with water (Figure 5). The benzoic acid chloride, which was probably formed intermediately by thionyl chloride, was hydrolyzed in the work-up, too.

Sixth step

In this simple step, the sulfonyl chloride **8** can be slurred in H_2O directly as the wet filter cake from the previous reaction. N-methylpiperazine is added and the nucleaphilic substitution takes place below 20°C. The title compound again can be crystallized out of the water solution and isolated by simple filtration (Figure 6).

Seventh step

N,N'-Carbonyldiimidazole (CDI) is another reagent to activate carboxylic acids for nucleaphilic substitution at the carbonyl group [9]. Imidazole moiety in **10** now serves as a good leaving and the desired amide was formed via the usual addition elimination mechanism (Figure 7). One of the advantages of using this more expensive way of activation is the possibility to run the nitro reduction, acid activation and acylation in ethyl acetate. Thus, the bond between imidazole nitrogen and carbonyl carbon in (CDI) is not as strong as an amide bond, making it easy to cleave. Amide bonds are one of the strongest connections in organic molecules and necessary for stability of peptides. Interestingly, nature uses enzymes that contain histidine (the imidazole amino acid) in the active site to cleave amides with imidazole.

The final step

The primary amide is deprotonated by the base tert-butoxide making it more nucleophilic. The nitrogen will then act as nucleophile and attack the other amide carbon closing the ring. Isomerization will lead to the pyrimidone ring in Sildenafil concluding this synthesis. This last step involves only water soluble solvents and reagents and the final

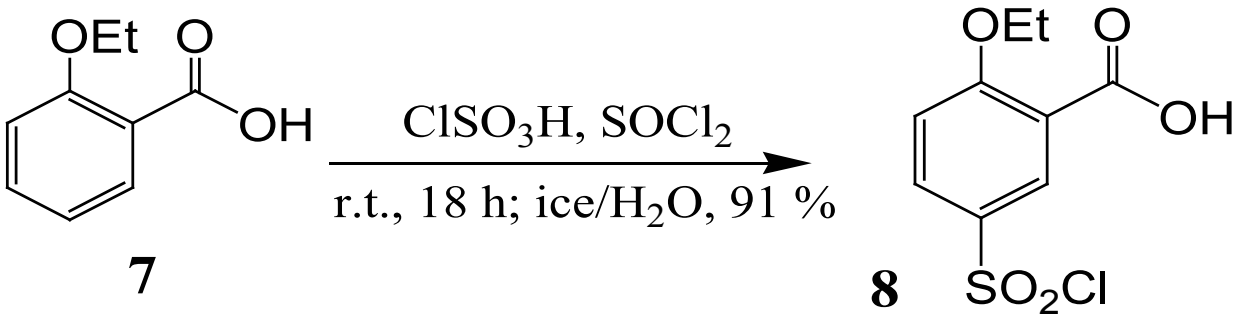

Figure 5: Synthesis of 5-(chlorosulfonyl)-2-ethoxybenzoic acid **(8)**.

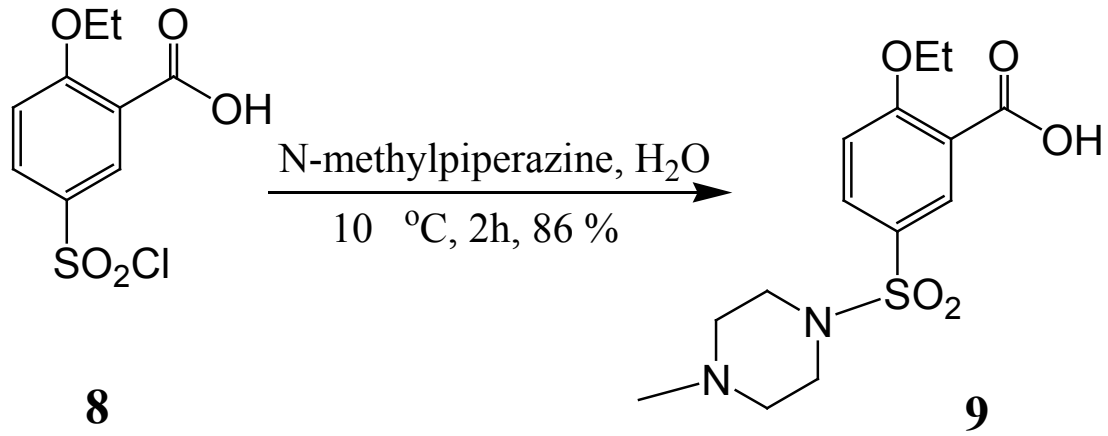

Figure 6: Synthesis of 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl) benzoic acid **(9)**.

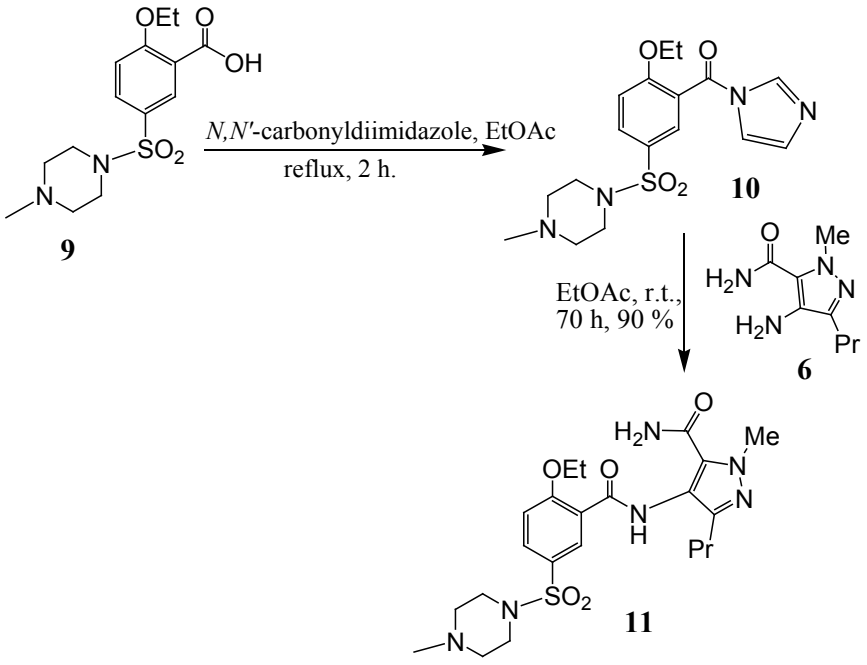

Figure 7: Synthesis of (2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl)(1H-imidazol-1-yl)methanone **(10)** and 4-(2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl) benzamido)-1-methyl-3-propyl-1H-pyrazole-5-carboxamide **(11)**.

product again precipitates out of the aqueous solution upon reaching pH 7.5 (Figure 8). No further purification is necessary and clinical quality Viagra™ is obtained directly from the filtration (Chart 2).

Summary of the Sequence of Viagra™ Synthesis

Before highlighting its mode of action and effects in diabetic patients with erectile dysfunction, the understanding of normal physiology of penile erection is warranted.

Physiology of Erection

The complete sexual response cycle has the following phases.1-appetitive, 2-excitement, 3-orgasm and 4-resolution phase [15]. The physiology of penile erection (Figure 9) is under the dynamic control of the central nervous system. The sympathetic nervous system through adrenergic pathway during flaccid stage of penis keeps smooth muscles of the paired corpora cavernous contracted. Hence, in this state penis receives the minimal blood supply. The two corpora cavernosa are the erectile chambers of the penis. Sexual desire-arousal stimulates parasympathetic nervous systems, that is, cholinergic pathway which in turn initiates the relaxation of the smooth muscle cells both within the corpora cavernosa and arteries.

Consequently, the penile tumescence develops which is the filling of spongy tissue in the erectile chambers by rapid arterial blood flow. Further full rigidity ensues when veins within these chambers are compressed. As a result, the outflow of blood is restricted and the penile rigidity and erection is maintained [16]. Thus, physiology of erection is mediated essentially by neurovascular components, complemented by hormonal, molecular and psychological factors.

Mode of Action of Sildenafil

Sildenafil is potent and specific phosphodiesterase type 5 (PDE 5) inhibitors [17]. Since then, oral Sildenafil citrate (Viagra) has become the preferred mode of treatment by patients in surveys worldwide. Sildenafil citrate (Viagra) is competitive inhibitors that resemble cGMP (the substrate) and bind to the active site of PDE5, which maintains intracavernosal levels of cGMP, subsequently producing vasodilatation

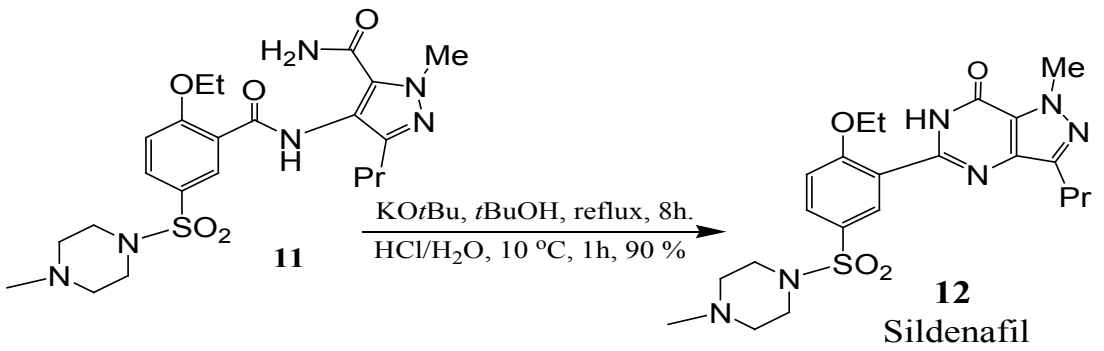

Figure 8: Synthesis of 5-(2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one **(12)**.

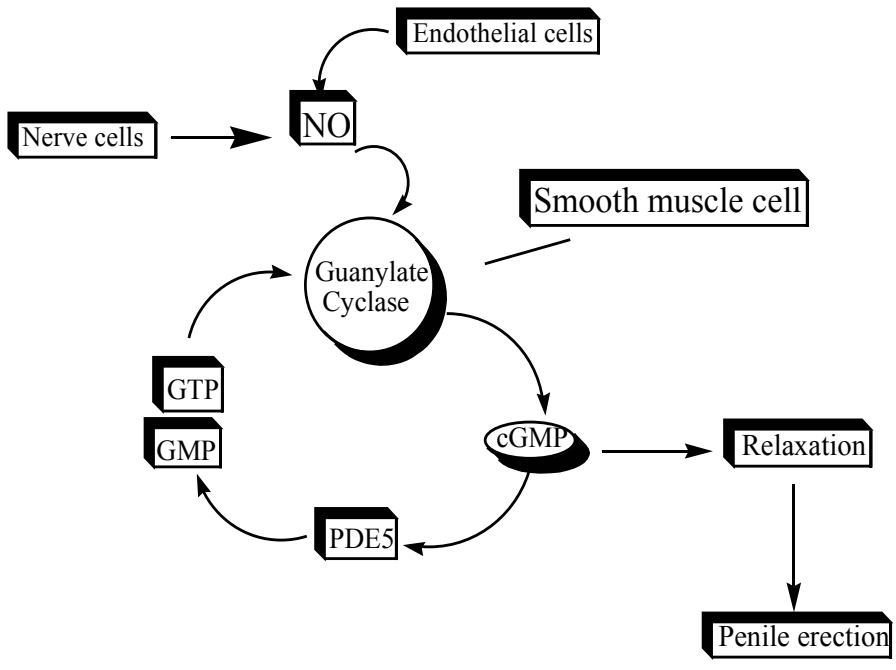

Figure 9: Normal physiology of erection.

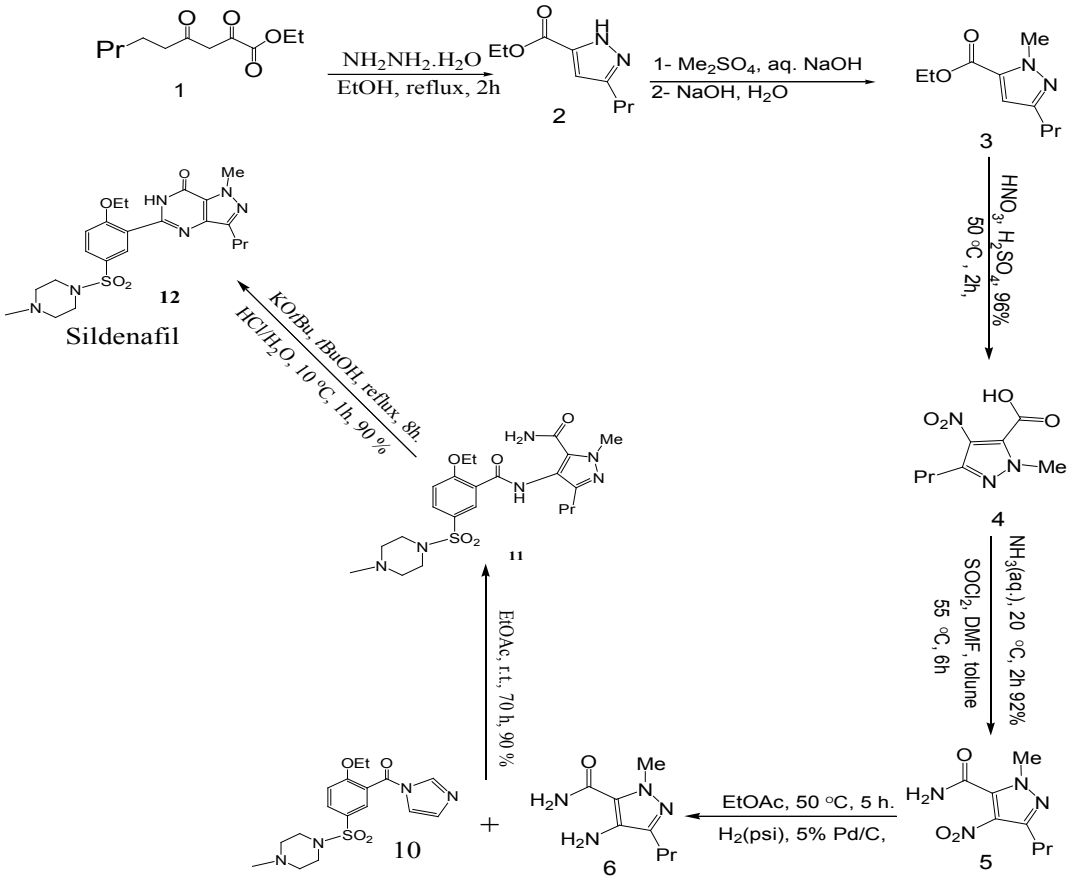

Chart 2: Summary of the sequence of Viagra™ synthesis.

and penile erection.

It was hypothesized that the inhibition of PDE5 will prolong penile tumescence and so erection. Sildsnafil is noted to inhibition PDE5 enzyme system (Figure 10) and thus reported to sustain penile erection [17].

Nine different PDE isoenzymes (PDE1 to PDE9) have been described and found to be present at various concentrations in human tissues [18]. Previous studies have shown that mRNA coding for cAMP-specific PDE (PDE4A) isoforms are present in mature rat and mouse germ cells [19] and the expression of these isoforms is maximal in round spermatids and is maintained in mature spermatozoa [20]. Nitric oxide synthase and two distinct PDE isoforms (PDE1 and PDE4) are present in human sperm cells [21,22].

It has recently been shown that some medicines can leave men permanently infertile and there are no treatments that will start sperm production again. Other medicines only have a short-term effect on sperm production. Once these medicines are stopped, sperm production should return [23]. This fertility dysfunction can be successfully treated with Sildenafil. In cases of predicted ED, cryopreservation of semen collected at an earlier non-stressful period can also be utilized if sperm retrieval fails. The optimal strategy for sperm collection in patients with temporary ED was investigated by comparing fresh semen, cryopreserved sperm, and frozen oocytes on the day of oocyte pick-up in IVF embryo transfer [24]. The recommended dose of Sildenafil (Viagra) is 50 mg once per day approximately 60 minutes before sexual activity with the lasting effects up to 4 hours. Based on efficacy and tolerability the minimum and maximum recommended doses are 25 and 100 mg. respectively [25].

Correlation between sildenafil citrate and seminal parameters in diabetic neuropathic men

Direct evidence for a neuropathic etiology of diabetic erectile dysfunction comes from studies that show structural changes in autonomic nerve fibers supplying the corpora cavernosa [26]. Emission disturbances that occur in diabetes are associated with involvement of the sympathetic fibers that sub serve the seminal vesicle, vas deferens and bladder trigone [27]. Testicular anesthesia, presence of a neurogenic bladder and a delayed bulbocavernous reflex latency are indirect evidence for a neuropathic etiology of patient's complaints. Failure of ejaculation secondary to emission disturbances due to sympathetic denervation of the vas deferens is another manifestation of autonomic neuropathy, usually seen in more advanced stage [28]. As DM has profound effects on the neuroendocrine axis, in men, both Diabetes mellitus-1 (DM1) and DM2 have long been recognized as major risk factors for sexual and reproductive dysfunction. This primarily includes impotence/erectile dysfunction (ED), ejaculatory (retrograde ejaculation) and orgasmic problems, as well as low desire (reduced libido), but impaired spermatogenesisis is also associated with DM [29].

Instances of complete absence of sperm are most readily explained by retrograde ejaculation [30]. Motility disturbances of sperm have previously been observed in diabetics with autonomic neuropathy [31].

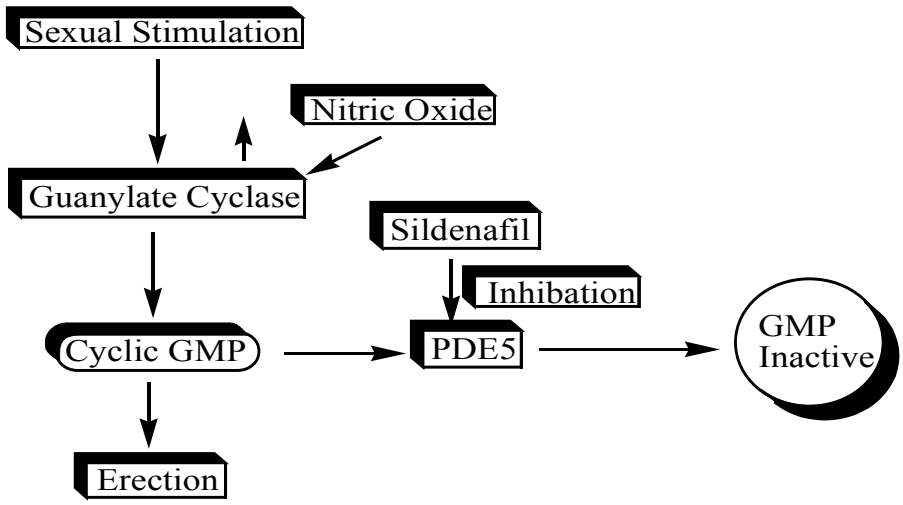

Figure 10: Mechanism of Sildenafil action.

DNA damage, sperm head abnormalities as well as abnormal sperm function and impaired sperm DNA integrity have been proven to be caused by the effects of environmental contaminants on the epididymis [32]. Ultimately, male infertility may be the result of exposure to any combination of factors such as chemical toxins, smoking and alcohol abuse, poor diet and a lack of exercise and obesity, different types of stress, and the increasing prevalence of cellphone and ionizing radiation.

Obesity essentially impinges on the male reproductive system and fertility through its effects on ED and impaired semen parameters. Several scholars have reported a correlation between obesity and ED. Corona et al. [33] presented evidence showing that 96.5% of their subjects with metabolic syndrome (MetS), which is characteristic of abdominal obesity, exhibited ED [33]. A direct proportional relationship between the increasing severity of obesity and the severity of ED was reported. Buvat and Lemaire [34] did not find any elevation, but Du Plessis et al. [35] showed that increase in estrogen and decrease in testosterone levels negatively affects spermatogenesis as well as regular testicular function. Inhibin B levels are directly related to normal spermatogenesis and thus the low levels of this protein observed in obese males result in abnormal spermatogenesis [36]. The dysregulation of the axis is shown because, despite the low Inhibin B levels observed in obese males, there is no compensatory increase in Follicle Stimulating Hormone (FSH) levels as expected. Increased estrogen levels further contribute to the negative feedback effect on the hypothalamus and lead to decreased gonodoliberin and gonadotropin release [37].

In spite of the advancing knowledge in recent years regarding the nature and treatment of diabetes, including its complications, subject of diabetic neuropathy with special reference to fertility parameters has become more confused and is still probably one of the most common complication in diabetics, and yet it remains poorly understood and inadequately explored [38]. The recommended dose of Viagra is from 25 to 100 mg as needed approximately 1 hour before sexual activity. In some individuals, the onset of activity may be seen as early as 11 to 19 minutes, but this is not the norm. The usual starting dose is 50 mg. The maximum recommended dose is 100 mg, and the maximum dosing frequency is once daily. A starting dose of 25 mg can be considered for patients older than age 65 years as well as for patients with severe hepatic cirrhosis or severe renal impairment [39,40].

Side Effects of Sildenafil

The recommended dose of Sildenafil (Viagra) is 50 mg once per day approximately 60 minutes before sexual activity with the lasting effects up to 4 hours. Based on efficacy and tolerability the minimum and maximum recommended doses are 25 and 100 mg, respectively [41,42]. Do not prescribe Sildenafil citrate to patients with unstable CAD who needs nitrates [43]. Assess the need for treadmill testing in select patients. Initial monitoring of blood pressure (BP) after the administration of Sildenafil citrate may be indicated in men with complicated congestive heart failure (CHF). α-blockers should not be used in combination with Sildenafil citrate because of the risk of orthostatic hypotension [43]. Furthermore, treatment with Sildenafil is well tolerated and is associated with minimal adverse events (example, headache, flushing, and dyspepsia) that rarely cause discontinuation of treatment [44].

Kim et al. [45] as well as those of others, Glina et al. [46] demonstrate do not prescribe Sildenafil citrate to patients with unstable CAD who need nitrates. Assess the need for treadmill testing in select patients. Initial monitoring of blood pressure (BP) after the administration of Sildenafil citrate may be indicated in men with complicated congestive heart failure (CHF). α-blockers should not be used in combination with Sildenafil citrate because of the risk of orthostatic hypotension [47].

In addition, low sperm count with an increased percentage of non-motile or dead sperm have also been reported [48], however did not observe a reduction in sperm count although they did notice decrease in sperm motility in 50% of the patients [49].

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Overdose

There are more than two dozen, randomized, double-blind, placebo-controlled studies involving this agent [51]. It produces positive results regardless of the etiology of ED. It has been studied

in patients with DM, CAD, post coronary artery bypass graft (post-CABG), spinal cord injury, depression, hypertension, prostate cancer post-prostatectomy, benign prostate enlargement post-transurethral resection of the prostate (TURP), patients on hemodialysis, as well as recipients of renal transplants. Results vary according to the underlying condition causing ED in the first place, ranging from 50% to 85% [52].

In healthy volunteers, a single dose of 800 mg/day of Sildenafil caused similar adverse effects as reported earlier. However, their incidence rates were higher. In cases of overdoses, standard supportive measures should be considered. Renal dialysis is of no value as Sildenafil is highly bound to plasma proteins and also not eliminated in the urine [53].

Sildenafil and Carcinogensis

In scientifically conducted studies in animals, Sildenafil was not shown to have carcinogenic or mutagenetic effects. Similarly, it does cause any impairment in fertility in animal studies. In healthy human volunteers, Sildenafil, 100 mg, did not cause any abnormal sperm motility or morphological changes. Sildenafil is not indicated in pediatric population, in pregnant women (probably first, second and third trimester) and in premenopausal women without pregnancy. In pregnancy category B, when rats and rabbits were exposed to Sildenafil, 200 mg/kg/day, no teratogenecity, embryo toxicity or teratoxicity was observed [53]. In pregnant women or otherwise, Sildenafil should be avoided as there is no sufficient data form well-conducted studies.

Alternative Drug: Tadalafil

The first major trial of the effects of Tadalafil (Cialis) in ED was published in 2001 [54]. In a trial of 220 Western European men with ED, Tadalafil 20 mg provided successful sexual intercourse to 74%, compared to 30% of those treated with placebo [55]. Improved sexual satisfaction with Tadalafil 10 and 20 mg has also been reported in men with mild, moderate and severe ED [56,57]. In comparison with short-acting agent Sildenafil, the major differences, which are evident from comparing trials with either Sildenafil or Tadalafil, are that there is no requirement to take Tadalafil one hour before sexual intercourse, and sexual activity can be initiated between 30 minutes and 24 hours after dosing [58]. This probably allows more choice about the onset of sexual intercourse with Tadalafil than Sildenafil. From the above described literature information it is now clear that these PDE-5 inhibitors are effective, well tolerated and safe in most patients, with adverse effects limited as previously noted [59]. The long term safety and tolerability of Tadalafil was confirmed by Kloner et al. [60]. Sildenafil and Tadalafil both are selective inhibitors of PDE5 [61]. These are rapidly absorbed after oral administration. The absolute bio-availability for Sildenafil is about 40%, whereas the absolute bioavailability of Tadalafil has not been reported to date. Both the phosphodiesterase inhibitors have a rapid onset of action. In men who respond to Sildenafil, within 20 minutes of Sildenafil dosing, 51% had an erection that led to successful intercourse (placebo, 30%) [62]. Also, in the home setting, 51% of men taking Tadalafil 20 mg had at least one successful intercourse attempt within 30 minutes (placebo, 35%) [63,64].

Kovanecz et al. [65] found most recognized improvement with both Sildenafil and Tadalafil in the frequency of penetration and the maintenance of erections after penetration, the mean score for the erectile-function domain of International Index, and the percentage of men reporting better erection, although in all the cases, men treated with Tadalafil showed greater sexual responses than the Sildenafil treated men in comparison with the controls. These results are in conformity with the above described Tadalafil responses in the patients of different ED etiologies. Surprisingly the men treated with Tadalafil showed a significantly greater sexual desire than the Sildenafil treated men who had a normal level of sexual desire, as might be expected with reference to another study with the men having ED who enter a clinical trial [66,67] and Sildenafil did not alter that level. A greater sexual desire in the Tadalafil treated men may be interpreted as its long acting mode of action and excess accumulation in the plasma.

Dietary Supplements and Erectile Dysfunction

Ginkgo biloba

A study with 60 patients who had failed papaverine injections (50 mg or less) were treated with an extract of *Ginkgo biloba*, 60 mg for 12 to 18 months. After 6 months, 50% of the patients reported improvement in erectile function [68]. A placebo-controlled randomized trial using 240 mg of *Ginkgo biloba* extract daily for 24 weeks in patients with vasculogenic ED did not demonstrate significant differences between the groups [69].

L-Arginine

L-Arginine is an amino acid that is the precursor to NO. In a randomized, double-blind, placebo-controlled trial, a formulation of L-arginine aspartate and pine bark/Pycnogenol (Prelox®) or placebo was randomly given over six months to 124 men aged 30 to 50 who had moderate erectile dysfunction. Scores on the International Index of Erectile Function improved significantly in the men who took the supplement, reflecting an improvement in erectile function, along with some evidence that erectile function continues to improve the longer the therapy is used [70].

Intracavernosal and Intraurethral Therapy

Alprostadil (Prostaglandin E1, caverject, medicated urethral system for erection)

Prostaglandin E1 (PGE1) exerts a number of pharmacologic effects including systemic vasodilatation, inhibitory actions on platelet aggregation, and relaxation of smooth muscle. PGE1 binds to PGE receptors and causes a relaxation response mediated by cyclic adenosine monophosphate (cAMP). It can be administered intracavernosally or intraurethrally [71,72]. It has been used in combination with papaverine, and the combination was superior to PGE1 alone. The intracavernosal administration seems to be more effective than transurethral (Medicated Urethral System for Erection, MUSE) [73]. MUSE should be administered in 1-mg doses, applied intraurethrally. Responses to intracavernosal injections (Caverject) as high as 80% may be expected in patients with organic ED with a dose of 20 μg, and much lower to MUSE (35% to 43%). Injections are given with 27-to 30-gauge needles. The administration of PGE1 is usually reserved as an alternative in patients who have contraindications to or failed the use of phosphodiesterase 5 (PDE5) inhibitors. The possible side effects include penile fibrosis, priapism, urethral pain or bleeding, hypotension, or syncopal episodes.

Papaverine

Papaverine is a nonspecific phosphodiesterase inhibitor that increases cAMP and cGMP levels in penile erectile tissue [74]. It produces smooth muscle relaxation and vasodilatation. It decreases the resistance to arterial inflow and increases the resistance to venous outflow. It is highly effective in psychogenic and neurogenic ED but not vasculogenic ED. It has been commonly used in combination with Phentolamine (Regitine). Major side effects include priapism,

corporeal fibrosis, and possible elevation of liver transaminases.

Phentolamine (Regitine)

Phentolamine is a competitive α-adrenergic receptor antagonist. When used alone, Phentolamine does not produce rigid erections; when it is combined with papaverine, success rates range from 63 to 87 percent [75,76]. Most urologists prescribe a combination of 30 mg of papaverine and 0.5 to 1 mg of Phentolamine and the usual dose ranges from 0.1 to 1 ml. The side effects of Phentolamine include hypotension and reflex tachycardia.

Moxisylyte chlorohydrate

Moxisylyte chlorohydrate is an α-blocking agent. In a study where, 156 subjects received either alprostadil or moxisylyte in a dose-escalating fashion, alprostadil had much better success rates (81% versus 46%) [77].

Chlorpromazine (Thorazine)

Chlorpromazine has α-blocking properties, and it is cheaper than Phentolamine (Regitine). Chlorpromazine has been shown to be a useful substitute for Phentolamine when used in combination with PGE1 [78].

Vasoactive Intestinal Polypeptide (VIP)

VIP is currently an investigational drug in the United States. Decreased concentration of VIP has been reported in the penile tissue of men with ED. VIP is believed to play a role in the erectile process. It is ineffective when administered alone but can be quite effective in combination with Phentolamine (Regitine). In a small study of 52 subjects with organic ED, 100% of them achieved an erection sufficient for intercourse [79]. Further studies into the effectiveness of VIP may be needed.

Testosterone

Patients who have low testosterone levels may benefit substantially from replacement. Men may expect significant improvements in libido, self-esteem, and overall energy levels. Additionally, testosterone is necessary for NO generation in the penile tissue. The different testosterone preparations include injections such as testosterone enanthate (Delatestryl) and cypionate (Depo-Testosterone), given as an intramuscular (IM) injection in doses of 100 to 200 mg, every 2 weeks on average. They also include transdermal testosterone patches (Androderm and Testoderm, 5 mg/d) or transdermal gel (AndroGel 5-g packets, one daily; or Testim 1% testosterone gel, one packet daily). Testosterone gel preparations provide physiologic replacement of testosterone and are preferred over depot IM injections [80]. Moreover, testosterone gel taken with Sildenafil may be beneficial in improving erectile function in hypogonadal men with erectile dysfunction who are unresponsive to Sildenafil alone [81].

Conclusion

The synthesis of Sildenafil serves as an excellent example of the demands of commercial chemistry. The route described contains all of the desired attributes required in chemical development, namely a safe, robust route, a convergent synthesis and high yielding process. The authors managed to improve the yield from 7.5% in the medicinal chemistry to 75.8% overall from pyrazole [8]. The synthesis also has an exceptionally low environmental impact. Only toluene and ethyl acetate are organic waste while the other solvents (ethanol and tert-butanol) can be treated in the water plants. The synthesis has been reassembled to make it more convergent and to put clean steps at the end of the process. This synthesis also gives a small glimpse at the chemistry of heterocyclic compounds. Most active compounds in today's pharmaceuticals or agrochemicals include heterocycles, as well as most vitamins and natural products. The chemistry of heterocycles is thus very important and lectures or textbooks should be consulted [11]. The relevant data published in various peer-reviewed journals suggested that there is a major point of difference between the short-acting agent Sildenafil and the longer acting Tadalafil. This probably allows more choice about the onset of sexual intercourse with Tadalafil than with Sildenafil. The dosing instructions for Sildenafil are that patients take Sildenafil one hour before sexual activity, whereas those for Tadalafil suggest that sexual activity can be initiated between 30 minutes and 24 hour after dosing. Tadalafil has a longer half-life than Sildenafil and therefore may be recommended as the choice of preference. The data reported in this review provides strong evidence of using Sildenafil citrate in a diabetic neuropathic population for the purpose of restoring sexual functions. Further, Sildenafil be further investigated as a new class of autonomically acting drug. The future course of events will decide whether Sildenafil could prevent realistically the tragedies of the bedroom or cause more fatal events in the bedroom. Meanwhile, the researchers should direct their efforts in developing a drug with safe and better clinical profile, which could be used in patients with erectile dysfunctions who can lead to a better quality of sexual life. Also, each hospital in Egypt should organize a workshop on Sildenafil in order to discuss its fatal events.

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