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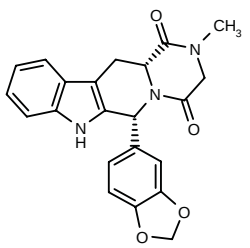
IC-351

Treatment of Erectile Dysfunction
Treatment of Female Sexual Dysfunction
Phosphodiesterase 5 Inhibitor

GF-196960
Cialis™

(6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-methyl-1,2,3,4,6,7,12,12a-octahydropyrazino[2',1':6,1]pyrido[3,4-*b*]indole-1,4-dione



$C_{22}H_{19}N_3O_4$ Mol wt: 389.4091

CAS: 171596-29-5

EN: 251999

Synthesis

Cyclization of D-tryptophan methyl ester (I) with piperonal (II) by means of TFA in dichloromethane gives, after separation of the undesired *trans*-isomer by flash chromatography, the (1*R*,3*R-cis*)-pyrido-indole derivative (III). The acylation of (III) with chloroacetyl chloride (IV) and $NaHCO_3$ in chloroform yields the chloroacetyl derivative (V), which is finally cyclized with methylamine in methanol (1-3). Scheme 1.

Description

White crystals, m.p. < 302-3 °C; $[\alpha]_D^{20}$ +65.2° (c 1.15, $CHCl_3$).

Introduction

Sexual dysfunction is defined as a series of conditions involving disturbances in sexual desire and the psychophysiological processes within the sexual response cycle (4). Sexual dysfunction affecting men includes 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 (4). It is estimated that the prevalence of sexual disorders is high. It is believed that up to 30 million men in the U.S. suffer from some form of erectile dysfunction and over 100 million men suffer from the disorder worldwide. One study surveying young adults reported that 40 and 60% of the women and 30 and 50% of the men experienced reduced libido and difficulties in arousal, respectively (4, 5). Moreover, the incidence of sexual dysfunction is known to increase with age. For example, approximately 15-25% of 65-year-old men suffer from erectile dysfunction as compared to only 5% of men aged 40 years (4).

While female sexual dysfunction remains elusive, most cases of male sexual dysfunction are treatable. Several drugs have been marketed for the treatment of male sexual dysfunction, including Caverject®, Muse®, Edex®, Viridal®, Vasomax®, Viagra™ and the Chinese herbal medicine Weige.

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) which is the primary cGMP-hydrolyzing enzyme. Researchers originally focused on PDE5 as a target for the treatment of angina and hypertension. However, with the discovery of sildenafil (Viagra™) and its efficacy as a treatment for erectile dysfunction, researchers and clinicians have refocused their approaches for the treatment of sexual dysfunction, particularly that of erectile dysfunction. PDE5 is the predominant cGMP-hydrolyzing enzyme present in the corpus cavernosum and may be the key 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,

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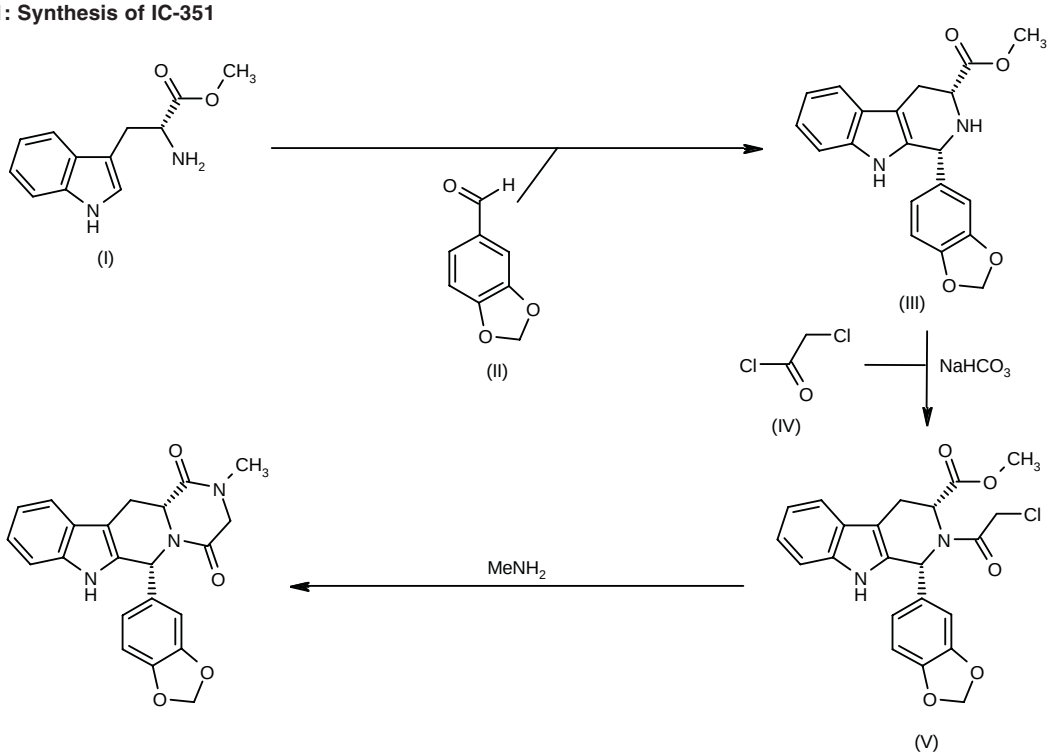
Scheme 1: Synthesis of IC-351



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 (4, 6).

Sildenafil citrate is the prototypical inhibitor and its launch in 1998 changed the course of drug development for the treatment of sexual dysfunction. Other PDE5 inhibitors currently under development for the treatment of male and female sexual dysfunction are shown in Table I (7). IC-351 (Cialis™) has shown excellent PDE5 inhibitory activity and was chosen for further development.

Pharmacological Actions

IC-351 displayed excellent *in vitro* activity by inhibiting a human recombinant PDE5 with an IC_{50} value of 2 nM. The agent also increased cGMP levels (EC_{50} = 0.2 μM) in a study using rat aortic smooth muscle cells in which particulate guanylyl cyclase was stimulated with ANF (100 nM for 10 min) (3).

Clinical Studies

Several clinical trials have investigated the efficacy of IC-351 against both male erectile dysfunction and female arousal disorder.

Results from a multicenter, randomized, double-blind, placebo-controlled study with a 3-week, drug-free, run-in period and conducted in 294 (mean age = 52.4 years) men with mild to moderate erectile dysfunction, showed the safety and efficacy of daily IC-351 administration (10, 25, 50 or 100 mg/day for 3 weeks). All doses resulted in a significant increase in responses to question 3 (penetration ability) and 4 (ability to maintain erection during intercourse) of the International Index of Erectile Dysfunction (IIEF) as compared to placebo (mean changes: 1.45-1.66 and 1.79-2.10 *vs.* 0.25 and 0.51 for placebo for questions 3 and 4, respectively). IC-351-treated patients also showed a significant increase in all IIEF domain scores as compared to placebo and a significant increase in the number of satisfying intercourse attempts for both patient and partner also significantly increased with the agent. According to global assessment question (GAQ) scores, improved erections were reported in 81-90% of the patients on IC-351 as compared to 38% on placebo. IC-351 was well tolerated with no significant changes in laboratory parameters, ECG, vital signs or color vision observed. The most common adverse events were headache, back pain, myalgia and dyspepsia (8) (Box 1).

Table I: PDE5 inhibitors launched and under investigation for sexual dysfunction. (Prous Science Drug R&D Backgrounders database).

Drug Name	Company	Indication	Status
Sildenafil Citrate (*Viagra*)	Pfizer	Male sexual dysfunction Female sexual dysfunction	Launched 1998 Phase II
IC-351 (*Cialis*)	Icos/Lilly	Male sexual dysfunction Female sexual dysfunction	Phase III Phase II
Vardenafil	Bayer	Male sexual dysfunction	Phase III
UK-343664	Pfizer	Male sexual dysfunction	Phase II
UK-357903	Pfizer	Male sexual dysfunction	Phase II
E-8010	Eisai	Male sexual dysfunction	Phase I
TA-1790	Tanabe Seiyaku	Male sexual dysfunction	Phase I
BMS-341400	Bristol-Myers Squibb	Male sexual dysfunction	Preclinical
DA-8159	Dong-A	Male sexual dysfunction	Preclinical
EMD-221829	Merck KGaA	Male sexual dysfunction	Preclinical
FR-229934	Fujisawa; TAP	Male sexual dysfunction	Preclinical
T-1032	Tanabe Seiyaku	Male sexual dysfunction	Preclinical

Box 1: Safety and efficacy of IC-351 in erectile dysfunction (8) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with mild to moderate erectile dysfunction (n = 294)
Treatments	IC-351, 10, 25, 50 or 100 mg p.o. o.d. x 3 wks Placebo
Adverse Events	Headache, back pain, myalgia, dyspepsia
Results	International Index of Erectile Function score, success in attaining erection, change: I (1.45-1.66) > P (0.25) [$p \leq 0.0001$]; success in maintaining erection: I (1.79-2.10) > P (0.51) [$p \leq 0.0001$] Number of satisfying intercourse attempts significantly increased by I [$p \leq 0.0001$] Patients (%) reporting improvement of erections on the Global Assessment Question scores: I (81-90) > P (38) [$p \leq 0.0001$]
Conclusions	IC-351 administered daily in the dose range of 10-100 mg was safe and generally well tolerated and improved patients' erectile function and sexual satisfaction

Similar safety and efficacy for IC-351 were demonstrated in 2 other multicenter, randomized, double-blind, placebo-controlled trials. In a study with a 3-week, treatment-free, run-in period conducted in 179 men (mean age = 55.9 years; subjects with diabetes mellitus or a history of radical proctectomy were excluded), IC-351 (2, 5, 10 or 25 mg) was taken on-demand over a 3-week period. All doses significantly improved responses to question 3 (mean changes: 0.61-1.32 *vs.* –0.26) and the erectile function domain (4.06-9.39 *vs.* 0.97) of the IIEF as compared to placebo. In addition, doses of 5-25 mg significantly improved responses to question 4 (0.78-1.70 *vs.* 0.25). The number of satisfying intercourse attempts for both patient and partner was also significantly increased with the agent and, according to GAQ scores, improved erections were reported in 51% (2 mg) to 81% (10 and 25 mg) of the patients on IC-351 as compared to 17% on placebo. IC-351 was well tolerated with no significant changes in laboratory parameters, ECG, vital signs or color vision observed. The most common adverse events were headache and dyspepsia (9) (Box 2).

Another similar study with a 4-week, drug-free, run-in period involving 212 men with mild to severe erectile dysfunction taking IC-351 (2-25 mg) on-demand for 8 weeks showed that doses of 5-25 mg significantly improved patient scores on questions 3 and 4 and the erectile function, orgasmic function and overall satisfaction domains of the IIEF; Sexual Encounter Profile (SEP) diary endpoints were also significantly improved. The most common adverse events (headache, back pain and dyspepsia) were dose-dependent and mild to moderate (10).

The efficacy of IC-351 in enhancing penile erections as assessed by Rigiscan™ penile plethysmography was also examined in response to visual sexual stimulation in a double-blind, placebo-controlled, single crossover study in 44 patients with mild to moderate erectile dysfunction. The study included a single-blind, placebo, run-in period to exclude extreme responders (> 80% rigidity for > 10 min or inability to achieve 20% rigidity or more for 2 min

Box 2: Safety and efficacy of IC-351 in erectile dysfunction (9) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with erectile dysfunction (n = 179)
Treatments	IC-351, 2, 5, 10 or 25 mg p.o. on-demand x 3 wks Placebo
Adverse Events	Headache, dyspepsia
Results	International Index of Erectile Function, success in attaining an erection domain score, change: IC (0.61-1.32) *vs.* P (–0.26) [$p \leq 0.0001$ for all doses *vs.* P] Success in maintaining an erection domain score, change: IC (0.78-1.70) > P (0.25) [$p \leq 0.0001$ for all doses except 2 mg *vs.* P] Erectile function domain score, mean change: IC (4.06-9.39) > P (0.97) [$p \leq 0.0001$ for all doses *vs.* P] The percentage of successful intercourse attemps as well as the number of satisfying intercourse attempts for both patients and partner were significantly increased by IC [$p \leq 0.0001$] Patients (%) reporting improvement of erections on the Global Assessment Question scores: IC25* (81) = IC10* (81) > IC2* (51) > P (17) [$p \leq 0.0001$ *vs.* P]
Conclusions	On-demand IC-351 was safe, well tolerated and improved erectile function

or longer). Patients received the agent (100 mg) and were subjected to plethysmography during visual sexual stimulation. As compared to placebo, IC-351 significantly increased the duration of erection at the base of the penis with 55% rigidity or greater (9.3 ± 12.66 *vs.* 1.43 ± 6.34 min) and the mean increase in the area under the rigidity curve at the base of the penis was significantly greater (723.8 ± 830 *vs.* 179 ± 558.7) in treated patients; similar significant effects were seen at the tip of the penis. Significantly more patients (86%) given IC-351 reported enhanced erections as compared to placebo and a significant change in the patients' median rating was observed with IC-351 treatment as compared to placebo and at baseline (4 [rigid and bendable] *vs.* 2 [partial erection]) (11).

The efficacy of IC-351 as a treatment for female arousal disorder is being investigated in 2 clinical trials; results are not yet available. The first trial is a double-blind, placebo-controlled, crossover study conducted in normal healthy women. Following IC-351 (1-20 mg) or placebo dosing, women are subjected to visual, tactile and/or olfactory stimuli and vaginal blood flow is subsequently measured by vaginal photoplethysmography. Subject genital response including throbbing, tingling and arousal is also being observed (12).

The second study in women is a double-blind, placebo-controlled trial involving 200 women with mild to moderate acquired female arousal disorder. Subjects are being administered IC-351 (5, 10 or 20 mg) or placebo daily or on-demand for up to 3 months. Efficacy will be based on answers to the 5 domains (including arousal) of the Female Sexual Functioning Index given at baseline and at each monthly visit and on sexual experiences assessed using an event diary which focuses on arousal and sexual satisfaction (12).

IC-351 (Cialis™) continues to undergo phase III trials as a treatment for male erectile dysfunction and phase II trials as a treatment for female sexual dysfunction (13).

Manufacturer

Lilly ICOS L.L.C. (US), a joint venture between ICOS Corp. (US) and Eli Lilly and Co. (US).

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