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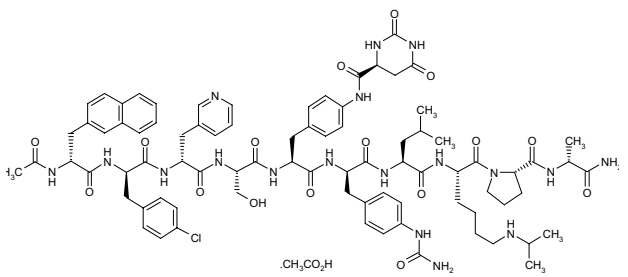
Degarelix Acetate

Prop INNM

GnRH Antagonist
Prostate Cancer Therapy

FE-200486

N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-4-[2,6-dioxohexahydropyrimidin-4(*S*)-ylcarboxamido]-L-phenylalanyl-4-ureido-D-phenylalanyl-L-leucyl-N^6-isopropyl-L-lysyl-L-prolyl-D-alaninamide acetate



$C_{84}H_{107}ClN_{18}O_{18}$
Mol wt: 1692.3116

CAS: 214766-78-6 (as free base)

EN: 274806

Abstract

Gonadotropin-releasing hormone (GnRH) analogues possess potent antiproliferative and antimetastatic effects and are an attractive hormonal therapeutic option to control the growth and spread of prostate cancer through testosterone ablation. GnRH agonists cause the suppression of gonadal steroidogenesis via down-regulation of the GnRH receptor, an effect which occurs within 2-3 weeks of dosing and is preceded by an initial flare in gonadotropin production which may transiently worsen a condition. In contrast, GnRH antagonists exert more marked inhibitory activity, which occurs immediately postdosing and without the adverse flare effects. However, clinical development of GnRH antagonists has been slow due to poor bioavailability. In an attempt to design potent, orally active, nonpeptide small-molecule GnRH receptor antagonists with increased binding affinity and bioavailability, degarelix acetate (FE-200486) was identified. Degarelix displayed increased solubility in water, long-lasting effects and weak histamine-releasing properties and was therefore chosen for further development as a treatment for prostate cancer.

Synthesis

Degarelix can be synthesized by two related methods: 1) *N*-Boc-D-alanine (I) is coupled to the resin using diisopropyl carbodiimide and 1-hydroxybenzotriazole to afford resin (II). Subsequent cleavage of the Boc protecting group by means of trifluoroacetic acid provides the D-alanine-bound resin (III). Sequential coupling and deprotection cycles are carried out with the following protected amino acids: *N*-Boc-L-proline (IV), *N*-α-Boc-N^6-isopropyl-N^6-carbobenzoxy-L-lysine (VI) and *N*-Boc-L-leucine (VIII) to afford the respective peptide resins (V), (VII) and (IX). *N*-α-Boc-D-4-(Fmoc-amino)phenylalanine (X) is coupled to (IX), yielding resin (XI). Cleavage of the side-chain Fmoc protecting group with piperidine in DMF gives the aniline derivative (XII). After conversion to the corresponding urea by treatment with *tert*-butyl isocyanate, the Boc group is cleaved with trifluoroacetic acid to produce resin (XIII). Further coupling with *N*-α-Boc-L-4-(Fmoc-amino)phenylalanine (XIV), followed by Fmoc deprotection with piperidine, furnishes (XV). The aniline derivative (XV) is acylated with L-hydroorotic acid (XVI) to yield, after Boc group cleavage, resin (XVII). Coupling of (XVII) with *N*-Boc-L-serine(*O*-benzyl) (XVIII) and subsequent deprotection gives (XIX). Peptide (XIX) is sequentially coupled with *N*-α-Boc-D-(3-pyridyl)alanine (XX) and *N*-Boc-D-(4-chlorophenyl)alanine (XXII) to furnish, after the corresponding deprotection cycles with TFA, the resins (XXI) and (XXIII), respectively. The coupling of resin (XXIII) with *N*-Boc-D-(2-naphthyl)alanine (XXIV) as before gives, after the corresponding deprotection cycle with trifluoroacetic acid, resin (XXV). The peptide resin (XXV) is acetylated with Ac_2O and finally deprotected and cleaved from the resin by treatment with HF to provide the target peptide (1, 2). Scheme 1.

2) Alternatively, after coupling of the peptide resin (XIII) with α-Boc-L-4-(Fmoc-amino)phenylalanine (XIV), the Fmoc protecting group is not removed, yielding resin (XXVI). Subsequent coupling cycles with amino acids (XVIII), (XX), (XXII) and (XXIV) as above finally produces resin (XXVII). The Fmoc group is then deprotected by treatment with piperidine, and the resulting aniline is acylated with L-hydroorotic acid (XVI) to provide resin (XXVIII), which is finally cleaved and deprotected by treatment with HF (1, 2). Scheme 2.

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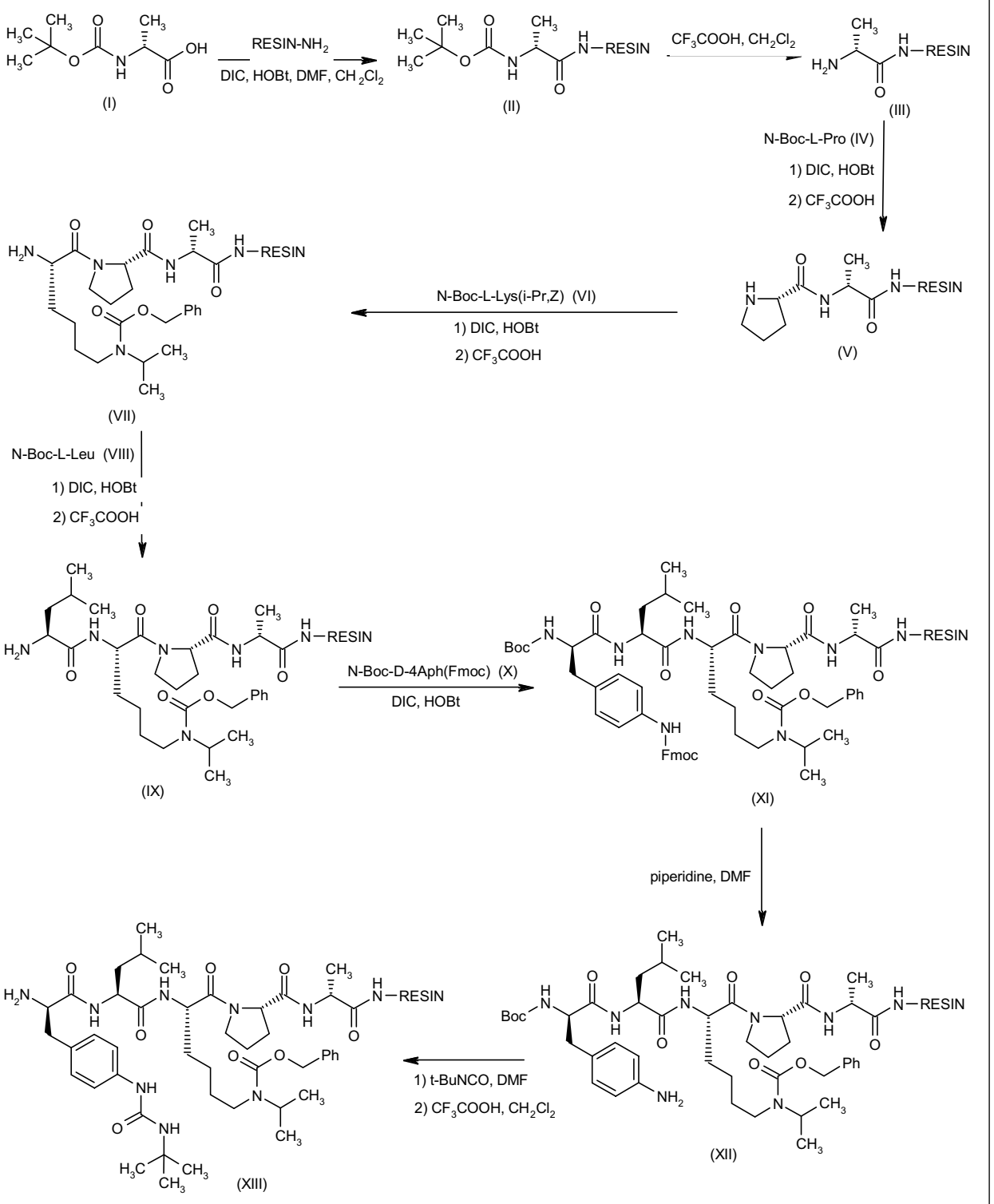
Scheme 1: Synthesis of Degarelix



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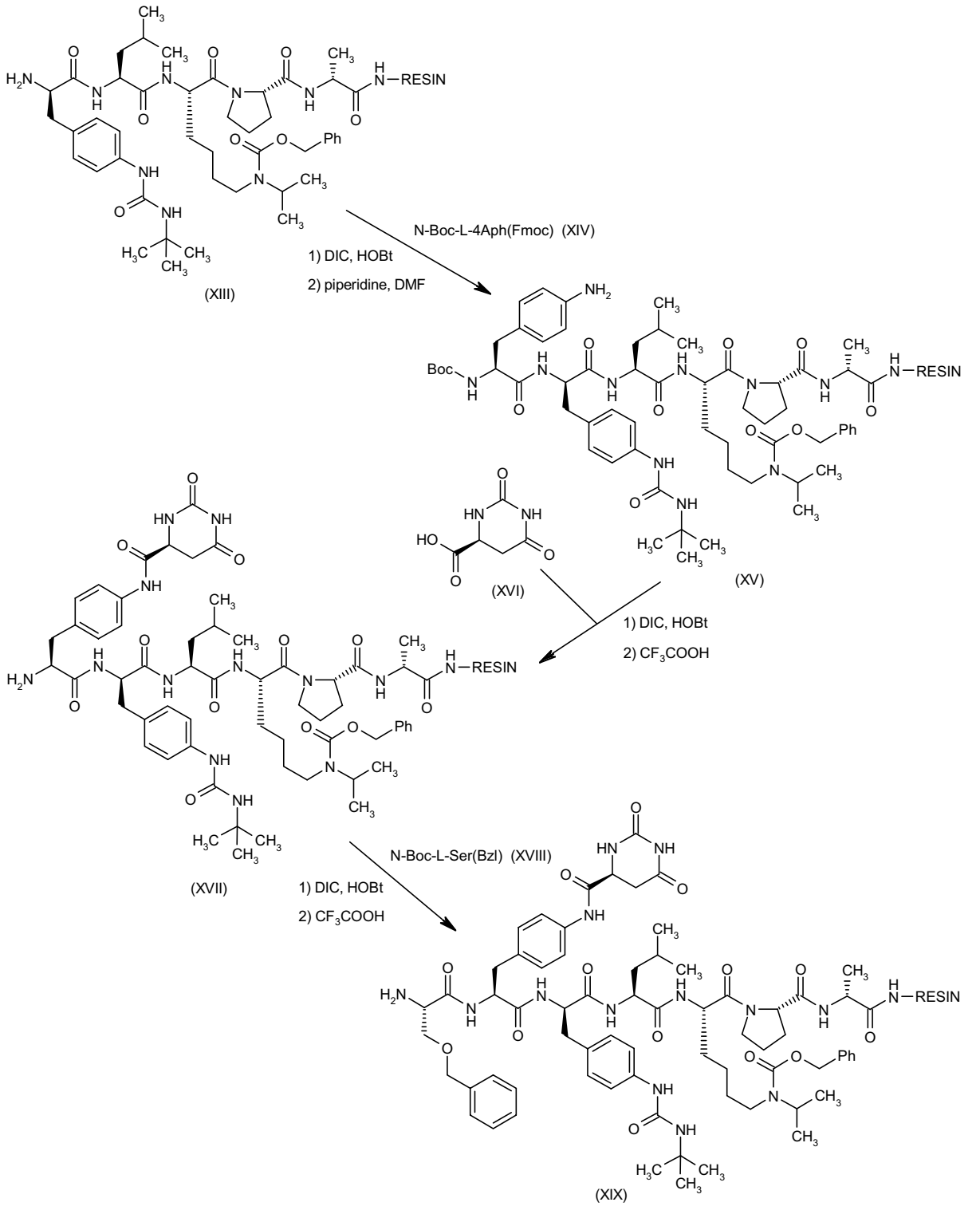
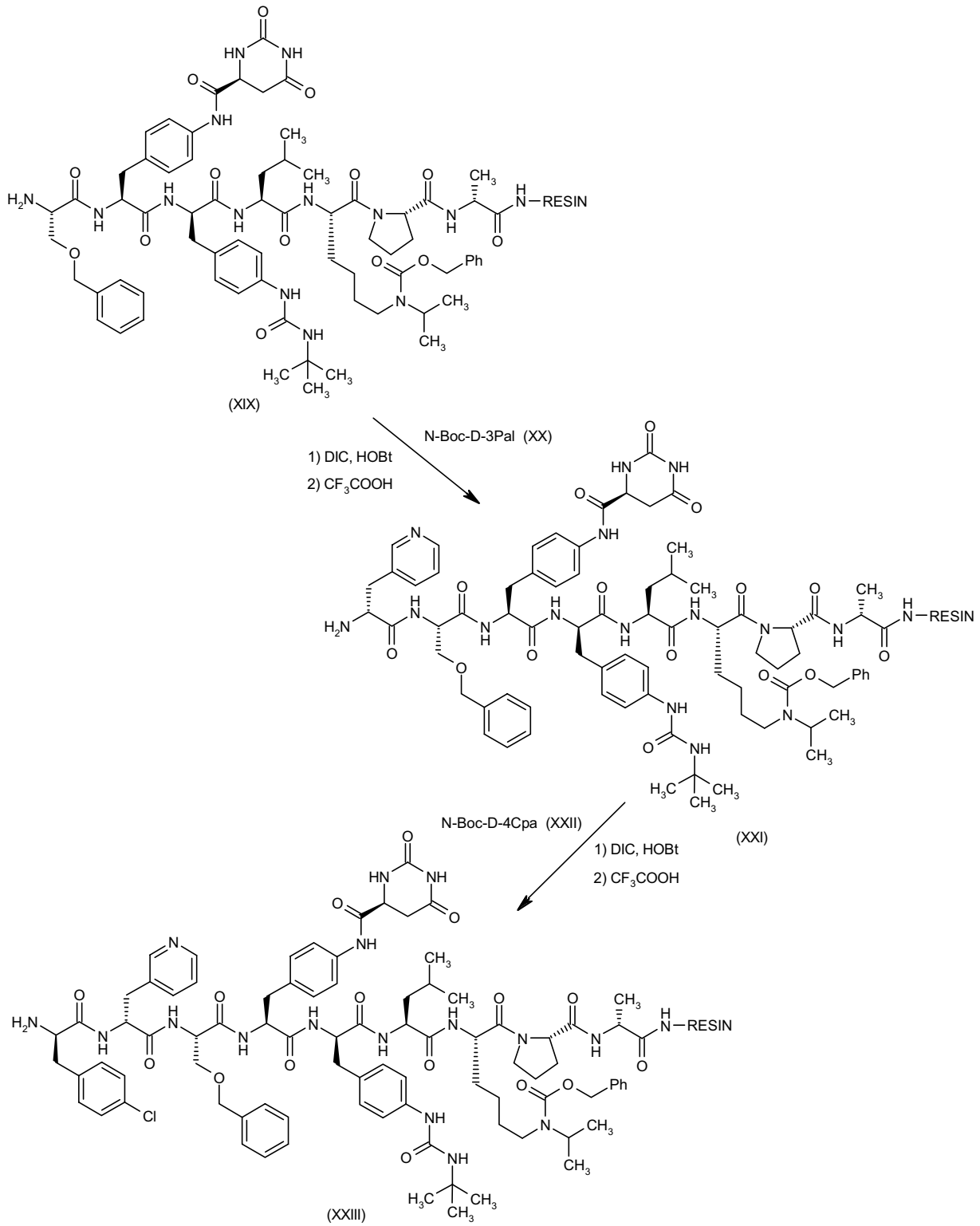


Scheme 1: Synthesis of Degarelix (cont.)



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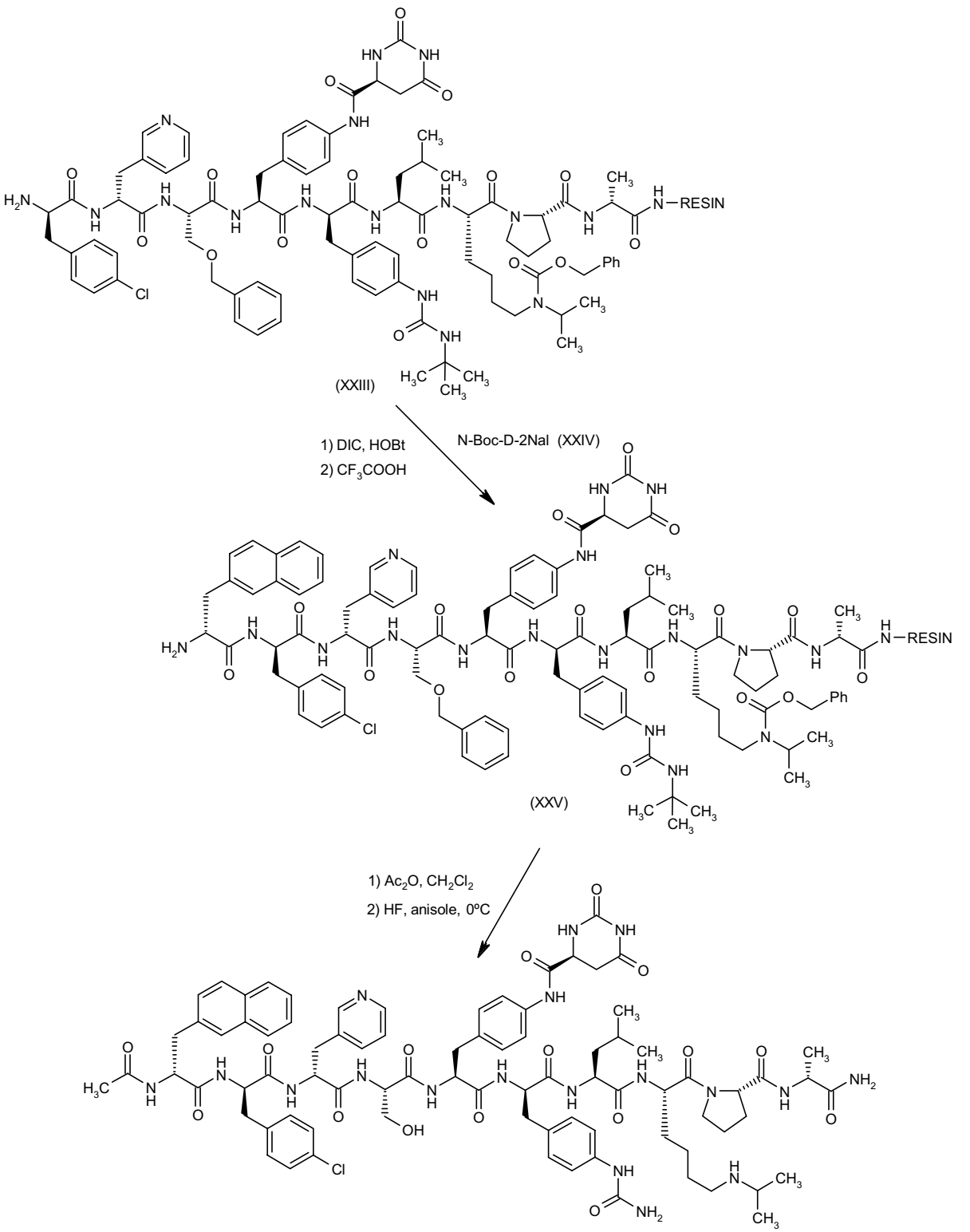
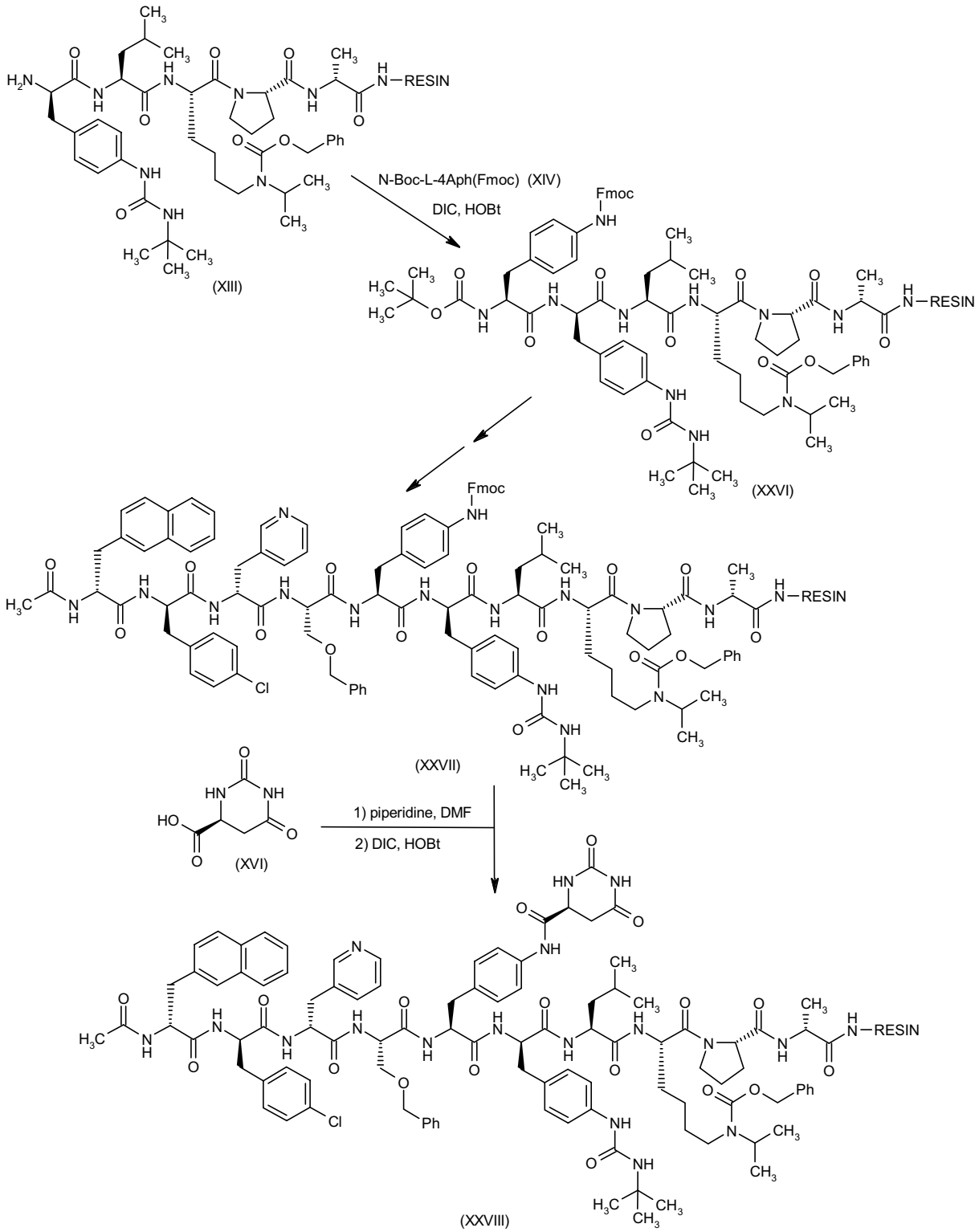
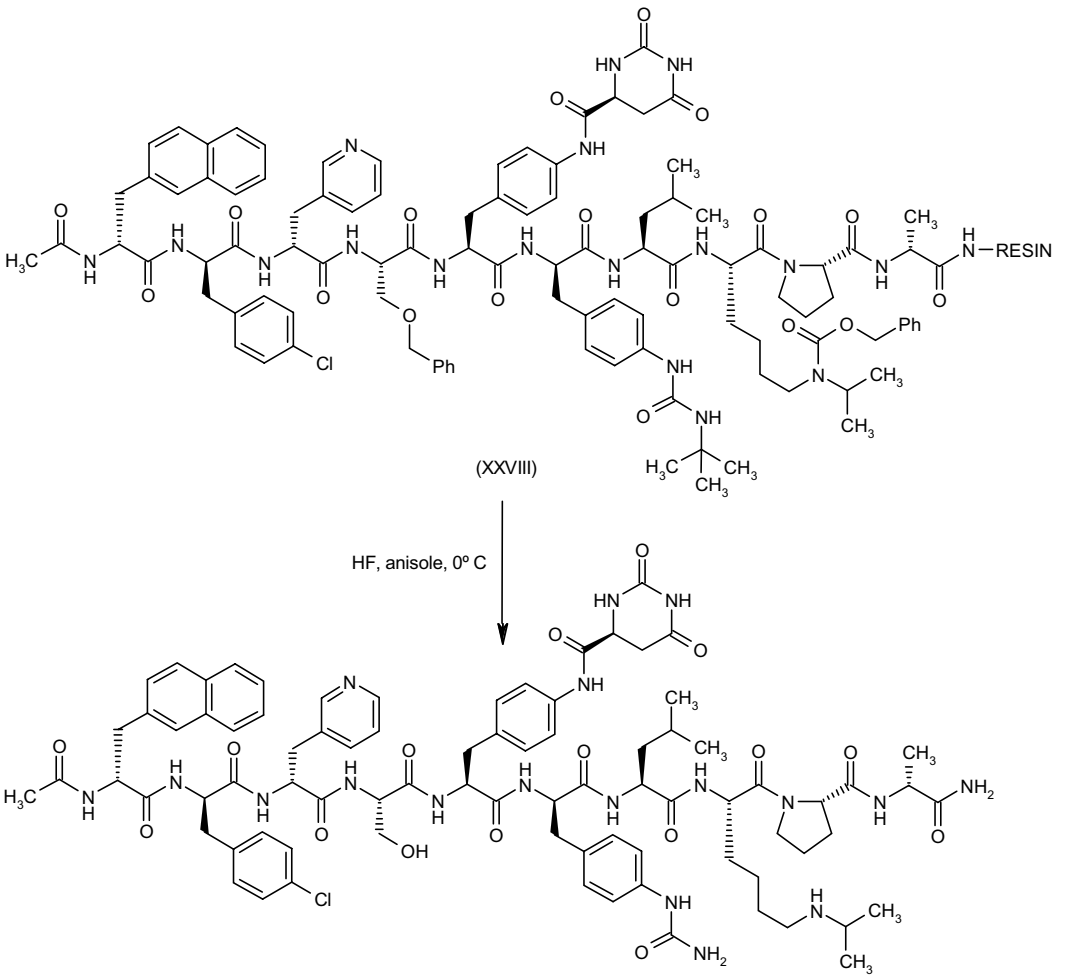


Scheme 2: Synthesis of Degarelix



Scheme 2: Synthesis of Degarelix (cont.)



Background

Cancer of the prostate gland is the second most frequently diagnosed cancer in men, accounting for 11.7% of all new cases. Prostate cancer can grow very slowly and remain undetected for years, or it can be highly aggressive and rapidly metastasizing. Approximately 80% of all prostate cancers are androgen-dependent. However, with time and upon androgen withdrawal via chemical castration, tumors progress to an androgen-independent stage known as hormone-refractory prostate cancer (HRPC). HRPC has very few therapeutic options and those which are available are mostly palliative. An extremely lethal form of prostate cancer is metastatic and heterogeneously composed of both androgen-dependent and androgen-independent malignant cells (3-6).

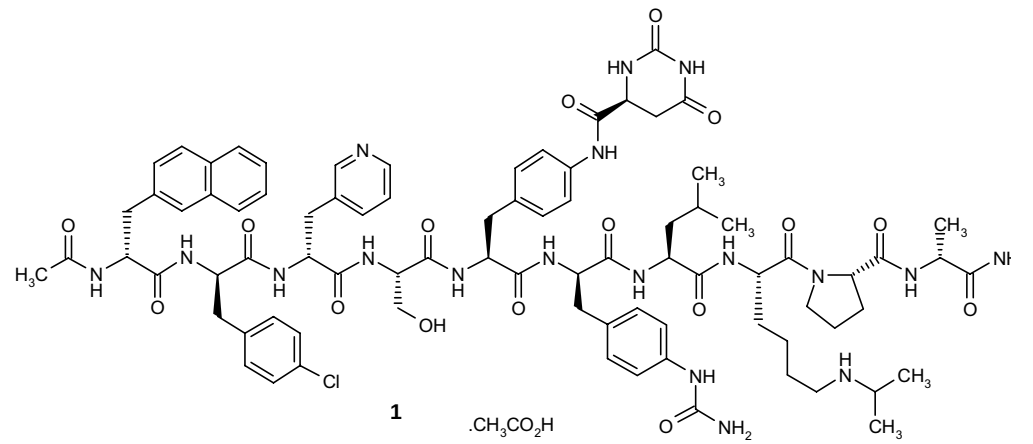
It is essential to detect prostate cancer early when it is still in an androgen-dependent stage and several treatment options are available. Therapeutic agents currently available include antiandrogens, aromatase inhibitors, estrogens, progesterones, gonadotropin-releasing hormone (GnRH) analogues and several conventional antimitotic chemotherapeutics (*e.g.*, estramustine phosphate sodium, mitoxantrone hydrochloride, docetaxel) and radiotherapeutics. Particular attention has been concentrated on GnRH analogues as an option for hormonal therapy to control the growth and spread of prostate cancer through testosterone ablation. GnRH analogues exhibit potent antiproliferative activity and antimetastatic effects via inhibition of the activity of the plasminogen activator (PA) system. Thus, the development of GnRH analogues is an extremely attractive clinical strategy for the treatment of prostate tumors, even those cases that progress to an androgen-independent stage (3, 7).

GnRH is a hypothalamic decapeptide amide that is secreted in a pulsatile manner to regulate a number of reproductive processes in both men and women. The

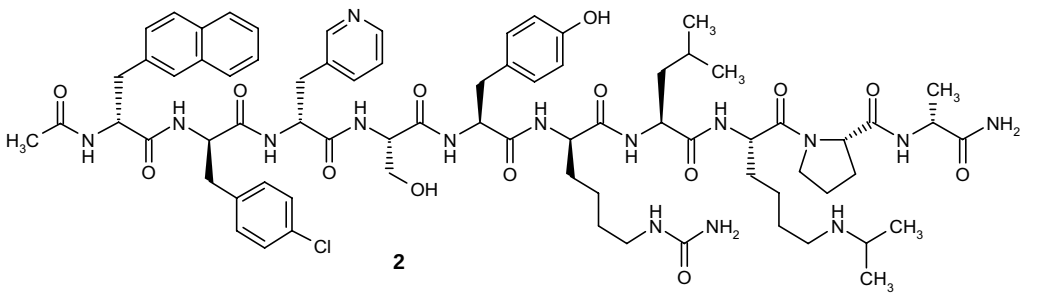
hormone binds to its G-protein-coupled receptor on the anterior pituitary, where it induces the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), two peptides responsible for mediating gonadal steroidogenesis and gametogenesis. GnRH analogues include both agonists and antagonists and have been shown to be beneficial in several hormone-dependent diseases, such as breast cancer, endometriosis, uterine leiomyoma, uterine fibrosis, precocious puberty, benign prostatic hyperplasia (BPH) and prostate cancer. GnRH agonists cause the suppression of gonadal steroidogenesis via internalization and subsequent down-regulation and desensitization of the GnRH receptor, which results in biochemical castration after 2-3 weeks of treatment. However, this effect is preceded by an initial surge or flare in gonadotropin production, which may transiently worsen a condition before improving it. In contrast, GnRH antagonists produce benefits immediately following administration. Treatment results in rapid and complete suppression of gonadotropin levels without induction of the clinical flare seen with GnRH agonists. Moreover, GnRH antagonists are associated with more marked inhibitory effects as compared to GnRH agonists (3, 8-11). GnRH antagonists currently under active development for the treatment of prostate cancer are shown in Table I.

Table I: GnRH antagonists under active development for the treatment of prostate cancer (from Prous Science Integrity ®)

Drug	Source	Phase
1. Degarelix acetate	Ferring	III
2. Teverelix	Ardana Bioscience	II
3. Ozarelix	AEterna Zentaris/Spectrum Pharmaceuticals	II



1 .CH_3CO_2H



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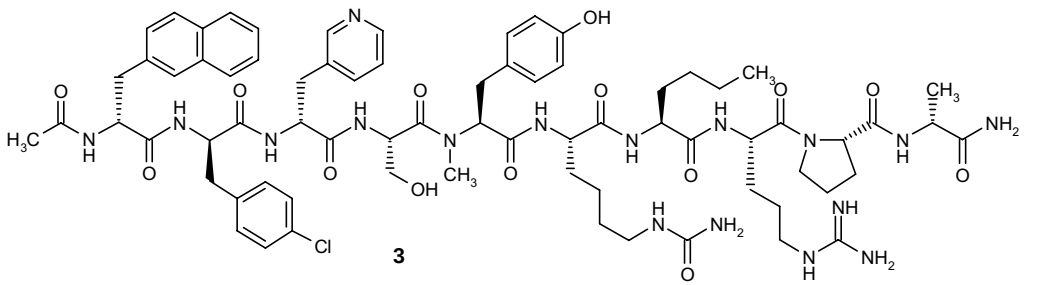

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Unfortunately, the clinical development of GnRH antagonists has been relatively slow due to both the histamine-releasing activity of these agents and their poor bioavailability as a consequence of low solubility and a propensity to form gels. Thus, researchers have continued to search for longer acting GnRH antagonist formulations that would be effective for the treatment of pathologies such as prostate cancer. In an attempt to increase binding affinity for the GnRH receptor and bioavailability at the administration site, and to stabilize the molecule against enzymatic degradation and delay elimination, degarelix acetate (FE-200486) was discovered and shown to have increased solubility in water, long-lasting effects and weak histamine-releasing properties. Degarelix was therefore chosen for further development as a treatment for prostate cancer (2, 12).

Preclinical Pharmacology

Degarelix was shown to be water-soluble (> 50 mg/ml) with a low propensity to form gels. The agent could diffuse at high concentrations in a manner similar to that observed for slow-release formulations of peptides. Degarelix displayed high affinity and potency at the GnRH receptor (pA_2 = 8.8; IC_{50} = 3 nM), as shown in a reporter gene assay in HEK-293 cells expressing the human GnRH receptor and a stably integrated luciferase reporter gene. Moreover, the agent was very long acting, as demonstrated in a castrated male rat assay in which LH secretion was inhibited by more than 80% at 96 h after s.c. administration of 50 μg (2).

Administration of the agent (0.3-10 μg/kg s.c.) to castrated male rats resulted in dose-dependent and reversible suppression of plasma LH; the minimal effective dose (MED) was 3 μg/ml and a dose of 10 μg/kg resulted in significant suppression of LH for up to 12 h postdosing. The duration of significant LH suppression seen in castrated rats injected with 12.5, 50 and 200 μg/kg s.c degarelix increased with dose (1, 2 and 7 days, respectively). At a dose of 2 mg/kg s.c., it completely suppressed plasma LH and testosterone in castrated and intact rats and ovariectomized rhesus monkeys for more than 40 days. The duration of action in both intact and castrated rats was longer than that of abarelix, ganirelix, cetrorelix and azaline B. For example, in intact rats, a single s.c. injection of 2 mg/kg inhibited plasma testosterone levels for 57 days as compared to 1, 1 and 14 days, respectively, for ganirelix, abarelix and azaline B. Plasma concentrations were maintained above 5 ng/ml up to day 41 postdosing, after which levels began to decrease and plasma LH levels began to rise, until full recovery at day 84 when degarelix plasma levels fell below 3 ng/ml (2, 12-14).

Degarelix was less potent than other GnRH antagonists in inducing histamine release from isolated rat peritoneal mast cells and isolated fresh human skin preparations. The EC_{50} value for degarelix in mast cells was 170 μg/ml as compared to 1.3, 11, 19 and 100 μg/ml, respectively, for cetrorelix, ganirelix, azaline B and abarelix. Concentrations of 3, 30 and 300 μg/ml resulted in a relative histamine release response rate in human skin of –2%, 3% and 27%, respectively, as compared to 56%, 143% and 362%, respectively, for abarelix and 67%, 404% and 279%, respectively, for cetrorelix (2, 12, 15).

The antitumor activity of degarelix was demonstrated in male Copenhagen rats grafted s.c. with androgen-dependent rat Dunning R3327H prostatic adenocarcinoma. Treatment with degarelix (2 mg/kg s.c. once/month) starting when tumors reached 300-350 mm^3 resulted in complete suppression of plasma testosterone; blockade was similar to that observed in surgically castrated rats. In addition, degarelix and surgical castration comparably and significantly suppressed tumor growth (mean tumor volume at day 55 = 450 and 494 mm^3, respectively, *vs.* 3217 mm^3 in controls). In addition, tumors from castrated or degarelix-treated animals exhibited significantly lower mean histological scores, indicating a greater degree of differentiation as compared to controls (5.8 and 5.4, respectively, *vs.* 6.6) (16, 17).

Degarelix also exerted antitumor activity in rats bearing 7, 12-dimethylbenz[*a*]anthracene (DMBA)-induced hormone-dependent mammary tumors. Treatment of tumor-bearing animals with degarelix s.c. resulted in dose-dependent, rapid, sustained and reversible suppression of estradiol production required for tumor growth (18).

A 3-month sustained-release formulation of degarelix was produced specifically for the indication of prostate cancer in which the agent was incorporated into a biodegradable polymeric carrier, poly(DL-lactide-*co*-glycolide (PLGA) microparticles. When tested in the castrated male rat model for inhibition of LH secretion, increasing doses of this formulation (0.4, 1 and 1.5 mg/kg s.c.) resulted in a faster onset of inhibition, more potent suppression and more prolonged duration of action. LH suppression observed with the highest dose was sustained for over 36 days, which was 1 week more than that observed with the same dose of unformulated degarelix (19, 20).

Pharmacokinetics and Metabolism

The pharmacokinetics of s.c. and i.m. degarelix (0.25-1.5 mg/kg; solution strength = 1.25-40 mg/ml; volume = 0.15-2.9 ml) were examined in male beagle dogs. A 2-compartment model best described the pharmacokinetics obtained following both s.c. and i.m. dosing. The model included a fast first-order input function to describe the rapid initial increase in plasma levels and a slow first-order input to describe the prolonged absorption profile. Degarelix was more rapidly absorbed following i.m. as compared to s.c. administration (C_{max} = 64 and 31 ng/ml, respectively, following a dose of 0.5 mg/kg, reached at about 2 and 3.7 h, respectively, postdosing). The slow absorption half-life was about 11 days (268 h). The relative fraction absorbed was dependent on the concentration of the dosing solution, such that when the concentration was increased from 1.25 to 40 mg/ml, the absorbed

fraction was reduced by about 50%; the rate of initial absorption was also dependent on the concentration of the dosing solution, such that slower absorption was observed with higher concentrations (21).

Population pharmacokinetic/pharmacodynamic modeling of a single i.v. infusion of degarelix was described. Comparison of the two nonlinear programs NONMEM and NLME revealed that more accurate results were produced with NONMEM. A 3-compartment disposition model best described the results, with first-order elimination from the central compartment equal to that of two peripheral compartments (22).

A population pharmacokinetic model was also described using NONMEM for an s.c. depot formulation of degarelix. The model used two concentric spherical compartments for s.c. absorption together with a 2-compartment disposition model. The model predicted that the volume effect on s.c. release was more evident at low injection volumes and reduced at high injection volumes. In addition, the dose-concentration effect on bioavailability would be reduced with increasing doses (23).

A study using NONMEM and data from 60 male volunteers reported flip-flop pharmacokinetics for single s.c. doses of degarelix and a long terminal half-life of 47 days. A mechanism-based model was constructed to describe the degarelix/LH/testosterone interaction. Continuous suppression of LH/testosterone resulted in GnRH receptor downregulation, with an estimated 93% reduction in receptor density during full testosterone suppression and a mean receptor residence time (MRT) of 4.5 days (24).

Clinical Studies

An open-label, randomized phase I trial in 36 healthy young males examined the pharmacokinetics, pharmacodynamics and safety of single-dose degarelix (1.5, 6, 15 or 30 μg/kg at 5 μg/ml i.v. over 15-45 min at a constant rate, or 20 mg at 5 mg/ml i.m. or s.c.). Treatment was well tolerated regardless of administration route. No serious adverse events were reported. Treatment with i.v., i.m. or s.c. degarelix rapidly suppressed plasma LH and testosterone. Castrate testosterone levels (< 0.5 ng/ml) were achieved in 21 of the 24 subjects who received 15 or 30 μg/ml or 20 mg; 16 of these subjects reached these levels within 24 h of dosing. Median testosterone levels at 24 h postdosing were 0.36-0.47 ng/ml. Following i.v. administration, testosterone levels were suppressed for only a few days. However, testosterone suppression in 5 subjects receiving i.m. or s.c. degarelix lasted for more than 4 weeks. According to noncompartmental analysis of pharmacokinetics, the half-life for i.v. degarelix was shorter than that of i.m. or s.c. degarelix (14 h *vs.* 3-4 weeks) (25). Table II summarizes the results from this study and several of those that follow.

A randomized, double-blind, placebo-controlled, dose-escalating study in 8 healthy eugonadal young men examined the efficacy, tolerability and pharmacokinetics of single s.c. doses of degarelix (0.5-40 mg). Treatment was well tolerated, with no serious adverse events reported. The most frequent adverse events were mild, transient injection-site reactions. Noncompartmental analysis of pharmacokinetics showed a terminal $t_{1/2}$ that suggested slow release of the agent, possibly due to *in situ* formation of an s.c. sustained-release depot. Dose-dependent decreases in serum testosterone levels were observed, with concentrations dropping to castration levels (< 0.5 ng/ml) within 24 h. Testosterone levels maintained below 0.5 ng/ml for more than 2 months in subjects administered the highest dose. Treatment also reduced serum dihydrotestosterone, LH and FSH levels (26).

Single s.c. doses of degarelix (120-320 mg; concentrations of 20-60 mg/ml) were shown to be well tolerated and rapidly effective in a multicenter, randomized, dose-escalating phase II study in 172 patients with prostate cancer (PSA > 2 ng/ml; median testosterone = 4.16 ng/ml; median PSA = 38 ng/ml). A total of 169 patients were evaluable up to day 28 and none of the patients withdrew due to adverse events. The most common adverse events were related to androgen deprivation. Injection-site pain and erythema were reported in 5% and 3% of the patients, respectively. Efficacy was affected by both dose and concentrations, such that higher doses caused better testosterone suppression, although lower concentrations for a given dose resulted in a better response. The best response was observed with an initial dose of 240 mg. In this cohort, 96% of the patients had testosterone levels below 0.5 ng/ml at days 3 and 28 (27).

The efficacy and safety of different s.c. degarelix dosing regimens (initiation doses on days 0 and 3 followed by maintenance doses every 28 days [day 0/day 3/day 28]; group A: 80/80/40 mg; group B: 40/40/40 mg; group C: 80/0/20 mg) were examined in a multicenter, randomized, dose-finding study conducted in 129 patients with prostate cancer (PSA = 20 ng/ml or more; median testosterone = 4.1 ng/ml; median PSA = 61 ng/ml). Twenty-seven patients were withdrawn due to protocol violations or for reasons other than lack of efficacy; of these, 6 withdrew due to adverse events, of which the most frequent were related to androgen deprivation. One hundred and two patients were evaluable. Testosterone was suppressed by 6 months to below 0.5 ng/ml in 87.5%, 72.2% and 58.8% of the patients in the respective dosing groups. The most effective regimen was concluded to 80/80/40 mg, which resulted in 97.5% of the patients displaying testosterone levels below 0.5 ng/ml after 3 days; these low levels were sustained for the first 28 days. At 5 weeks, serum PSA was decreased by 90% as compared to baseline (28, 29).

The efficacy of s.c. degarelix (initiation doses of 200 or 240 mg followed by maintenance doses of 80, 120 and 160 mg every 28 days) was demonstrated in a 1-year, multicenter, randomized study conducted in 187 patients with prostate cancer (PSA = 2 ng/ml or greater; median testosterone = 4.4 ng/ml; median PSA = 28 ng/ml). Treatment was well tolerated, with no testosterone surge or systemic allergic reactions reported. Twelve patients withdrew due to adverse events, the majority of which were related to androgen deprivation. Of those patients

Table II: Clinical studies of degarelix acetate (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Open	Degarelix, 1.5 µg/kg i.v. over 15-45 min (n=6) Degarelix, 6 µg/kg i.v. over 15-45 min (n=6) Degarelix, 15 µg/kg i.v. over 15-45 min (n=6) Degarelix, 30 µg/kg i.v. over 15-45 min (n=6) Degarelix, 20 mg s.c. (n=6) Degarelix, 20 mg i.m. (n=6)	36	Degarelix was well tolerated and rapidly decreased plasma testosterone levels to values below 0.5 ng/ml in healthy male volunteers	25
Cancer, prostate	Randomized Multicenter	Degarelix, 80 mg s.c. on d 0 → 80 mg s.c. on d 3 → 40 mg s.c. 1x/28 d [starting on d 28] x 6 mo (n=32) Degarelix, 40 mg s.c. on d 0 → 40 mg s.c. s.d. on d 3 → 40 mg s.c. 1x/28 d [starting on d 28] x 6 mo (n=36) Degarelix, 80 mg s.c. on d 0 → 20 mg s.c. 1x/28 d [starting on day 28] x 6 mo (n=34)	129	Degarelix showed efficacy in reducing plasma levels of testosterone and prostate-specific antigen levels in patients with prostate cancer. Most adverse events found with degarelix were associated with androgen deprivation	28, 29
Cancer, prostate	Randomized Multicenter	Degarelix, 200 mg s.c. → 80 mg s.c. 1x/28 d x 1 y Degarelix, 200 mg s.c. → 120 mg s.c. 1x/28 d x 1 y Degarelix, 200 mg s.c. → 160 mg s.c. 1x/28 d x 1 y Degarelix, 240 mg s.c. → 80 mg s.c. 1x/28 d x 1 y Degarelix, 240 mg s.c. → 120 mg s.c. 1x/28 d x 1 y Degarelix, 240 mg s.c. → 160 mg s.c. 1x/28 d x 1 y	187	Degarelix was well tolerated and demonstrated rapid and sustained reductions in testosterone and prostate-specific antigen levels in patients with prostate cancer. No evidence of testosterone surge or systemic allergic reactions was seen	30

receiving the higher initiation dose, 92% at day 3 and 95% at day 28 displayed testosterone levels of 0.5 ng/ml or less. All patients given the 160-mg maintenance dose had testosterone levels of 0.5 ng/ml or less from day 28 to day 364. By days 14 and 28, PSA levels decreased by 66% and 84%, respectively; the median time to a PSA reduction of 90% was 8 weeks (94% and 96% decreases, respectively, after 12 and 24 weeks of treatment) (30, 31).

Degarelix is currently undergoing phase III development for the treatment of prostate cancer. Several studies have been initiated to evaluate the long-term safety and tolerability of different dosing regimens of s.c. degarelix in patients with prostate cancer. In addition, a randomized, open-label, multicenter, parallel-assignment study is recruiting approximately 150 patients with prostate cancer to examine the safety, efficacy and pharmacokinetics of three different 3-month degarelix dosing regimens, and another open-label, multicenter, randomized, comparative phase III study is currently recruiting approximately 675 prostate cancer patients to examine the safety and efficacy of 1-month degarelix s.c. dosing regimens (80 and 160 mg) compared to depot leuprolide (7.5 mg) (32-38).

Source

Ferring Pharmaceuticals A/S (DK).

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