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CCC: 0377-8282/98

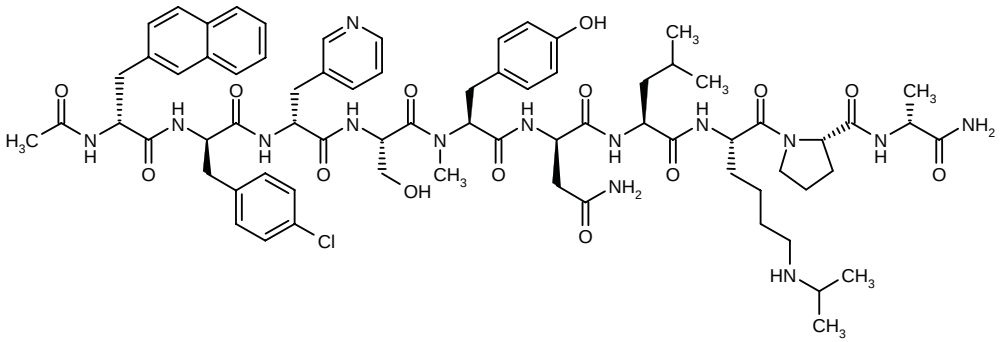
Abarelix

Prop INN

Antineoplastic
LHRH Antagonist

PPI-149
R-3827

N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-*N*-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-N^6-isopropyl-L-lysyl-L-prolyl-D-alanylamide



$C_{72}H_{95}ClN_{14}O_{14}$

Mol wt: 1416.079

CAS: 183552-38-7

EN: 251979

Synthesis

Abarelix was synthesized by a typical coupling cycle for peptide synthesis using Boc-amino acids and a methylbenzhydrylamine (MBHA) resin on a Beckman Model 990 peptide synthesizer (1). Scheme 1.

Introduction

Analogs of luteinizing hormone releasing hormone (LHRH), also known as gonadotropin (GnRH), are used in the treatment of conditions in which hormone modulation is beneficial to the resolution of disease, *e.g.*, breast cancer or endometriosis in women and prostate cancer or BPH in men. Within the class of LHRH analogs, both agonists and antagonists are known to be capable of accomplishing the same goals, although via different mechanisms. The administration of an LHRH agonist causes an initial surge in testosterone levels, followed 3-4 weeks thereafter by inhibition of the production of LH and suppression of testosterone and dihydrotestosterone to target levels. LHRH antagonists, in contrast, produce a rapid and complete suppression of testosterone levels. To date, however, all LHRH analogs on the market are agonists, or so-called superagonists.

As stated above, the use of LHRH superagonists, such as leuprolide and goserelin, in the treatment of prostate cancer leads to stimulation of LHRH receptors prior to their desensitization. This is associated with undesirable increases in levels of the male hormones androgen and gonadotropin, and requires the administration of an antiandrogen such as flutamide for the reversal of the same. The use of antiandrogens is itself associated with undesirable effects, however. Thus, the suggestion has been made that a pure LHRH antagonist alone would be sufficient, and indeed preferable, for the treatment of prostate cancer, especially in the case of patients with late-stage cancer, in whom the undesirable surge in hormone levels and resulting stimulation of cancer growth would have unfortunate consequences. Few compounds of this nature have been studied to date. Asta Medica's cetrorelix (SB-75) [I] is in clinical testing for the treatment of prostate cancer and other hormone-related cancers, but is under development primarily for the indications of assisted reproduction (preregistered), BPH (phase II) and uterine myoma (phase II). The company also has another compound, antarelix (formerly called teverelix) [II] in preclinical testing (2). Earlier this year, Abbott and TAP investigators reported that the LHRH antagonist A-84861 [III] had been selected for clinical testing for prostate cancer and other hormone-dependent conditions (3).

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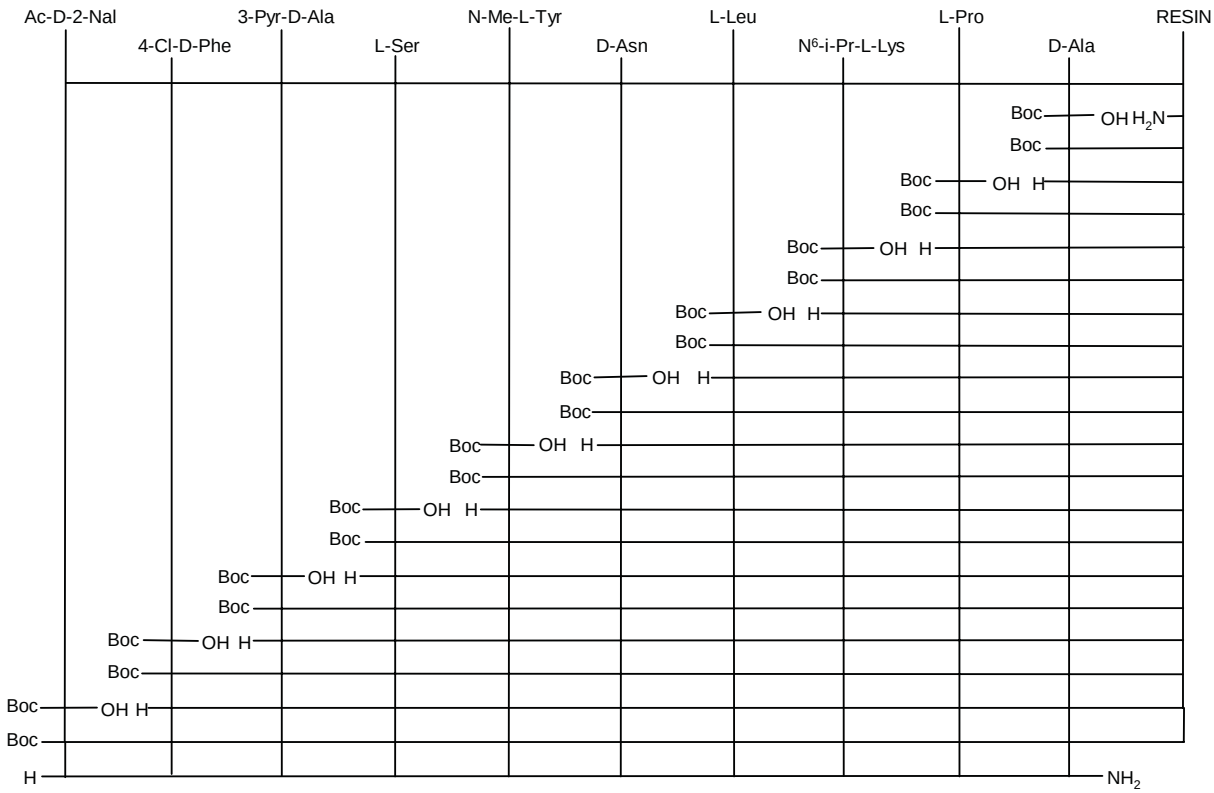
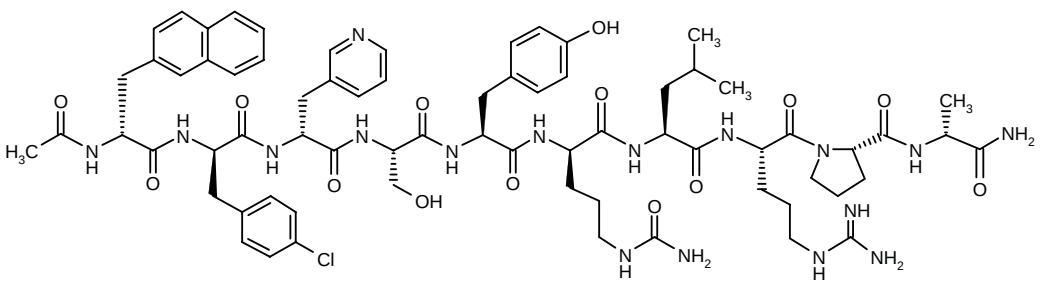
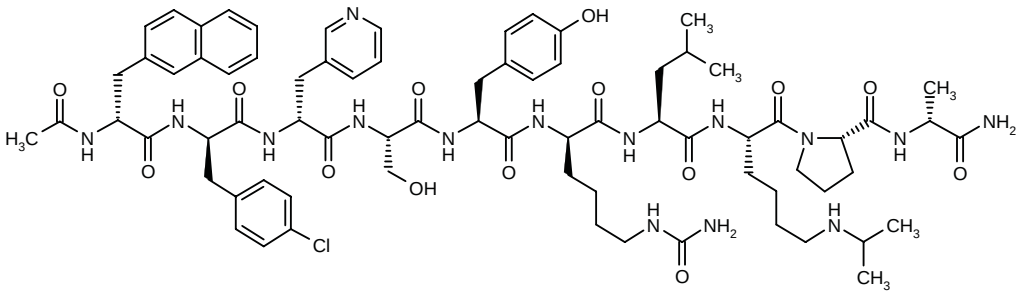
Scheme 1: Synthesis of Abarelix

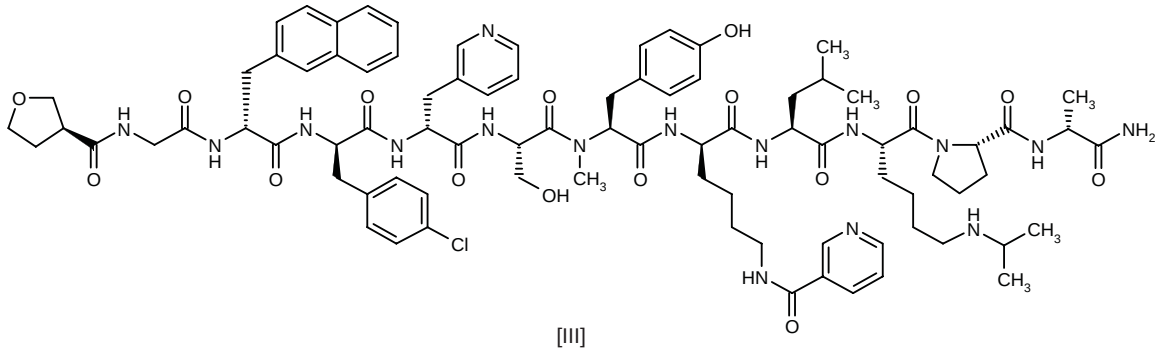




[I]



[II]



[III]

In the search for a pure LHRH antagonist with low concomitant histamine-releasing activity, scientists at Praecis (then called Pharmaceutical Peptides Inc.) discovered the lead compound PPI-149 (abarelix) and selected it for further evaluation.

Pharmacological Actions

In vitro in established laboratory assays, abarelix was shown to bind with high affinity to LHRH receptors (k_D = 1 nM); in a high-throughput functional assay, the compound behaved as a pure LHRH antagonist, blocking the agonist effects of D-His^6-GnRH (pA_2 = 11). The low histamine-releasing activity of the compound was also demonstrated *in vitro*, with this effect seen only at high concentrations (EC_{50} = 100 mg/ml) in rat peritoneal macrophages. Finally, abarelix was shown to have good water solubility. Taken together, these findings indicate the potential utility of abarelix in gonadal hormone ablation (4).

In a preclinical study, adult male rats were administered abarelix in combination with an LHRH agonist in order to determine whether the title compound could inhibit the testosterone surge normally associated with administration of the agonist. Abarelix (15 or 50 μg/kg/day) was administered to rats by continuous osmotic minipump for periods ranging from 15-28 days. A second pump releasing the LHRH agonist leuprolide (1.8 μg/kg/day) was implanted subsequently, such that the dosing periods for the two drugs overlapped for 0, 1 or 7 days. When abarelix was administered for 28 days, followed by removal of the first pump prior to initiation of dosing with leuprolide (no overlap), plasma testosterone levels were suppressed to castrate levels and no surge was experienced upon initiation of dosing with leuprolide. This result was also see when the two drugs overlapped for a period of 1 or 7 days (5).

In another preclinical study, this in male cynomolgus monkeys, abarelix (0, 30, 100 or 300 μg/kg/day) was administered by subcutaneous osmotic minipump for 28 days. On the last day of the dosing period, the minipump was removed and monkeys were administered a single depot dose of leuprolide at a dose level (0.16 mg/kg i.m.) 1.6 times higher than that used in prostate cancer patients. At the dose of 100 μg/kg/day, abarelix induced rapid and complete chemical castration of the monkeys as early as the second day of treatment, and effectively prevented the surge in testosterone normally produced by leuprolide (5).

Using a specially developed depot formulation of abarelix, the therapeutic activity, pharmacokinetics and pharmacodynamics of the compound were evaluated in male dogs. The monthly administration of abarelix depot (1.2-3.0 mg/kg s.c. or i.m.) for 6 months resulted in immediate and sustained inhibition of testosterone to castrate levels. Histological examination of the testes and prostates of dogs treated with the compound for 3 months showed that spermatogenesis was inhibited completely, together with a reduction in the size and secretory activity of the prostate. Histology of the prostates and testes of animals that were treated for 3 months and then left untreated for another 3 months was indistinguishable from that of untreated dogs; at the end of the 6-month period, spermatogenesis in the testes had recovered fully and the size and secretory activity of prostates were completely normal. Thus, the effects of abarelix are fully reversible upon discontinuation of treatment (6).

Clinical Studies

In a clinical study enrolling 36 patients with localized prostate cancer, abarelix (50 μg/kg/day s.c.) was administered for periods of 4-12 weeks prior to brachytherapy or radiation therapy. Mean prostate gland volume decreased by 25% with respect to baseline after just 4 weeks on abarelix, with another 15% reduction obtained during weeks 4 and 8. Androgen ablation was experienced immediately in all patients administered the LHRH antagonist, with sustained decreases in testosterone levels throughout the dosing period. PSA and gonadotropin levels also decreased significantly, with medical castration sustained throughout the treatment period in all patients at this dose. Abarelix was extremely well tolerated and did not produce localized or systemic hypersensitivity (7) (Box 1).

In another clinical study, abarelix was administered to 26 prostate cancer patients at doses of 30-50 μg/kg/day s.c. for 28 days. Testosterone and DHT levels decreased immediately and remained low in all patients adminis-

Box 1: Prostate-reducing activity of abarelix (7).

Study Design	Open clinical trial
Study Population	Patients with prostate cancer (n = 36)
Intervention Group	Abarelix, 50 μg/kg/day s.c. x 4-12 weeks
Adverse Effects	No adverse effects were noted
Significance of Results	Prostate gland reduction at 4 weeks, 25% Prostate gland reduction at 8 weeks, 40%
Conclusions	Abarelix rapidly reduces prostate volume, PSA and gonadotropin levels in patients with prostate cancer

Source: Prous Science CTLine database.

Box 2: Efficacy and safety of abarelix in patients with prostate cancer (8, 9).

Study Design	Open clinical trial
Study Population	Patients with prostate cancer (n = 26)
Intervention Groups	Abarelix, 30 μg/kg/day s.c. x 28 days (n = 13) Abarelix, 50 μg/kg/day s.c. x 28 days (n = 13)
Significance of Results	Time to castration: A30, 72 h; A50, 48 h
Conclusions	Abarelix rapidly clears testosterone/dehydrotestosterone from blood in < 2 days and induces a rapid fall in PSA levels with extremely good tolerability

Source: Prous Science CTLine database.

Box 3: Efficacy of abarelix SR in patients with prostate cancer (10).

Study Design	Open clinical trial
Study Population	Patients with prostate cancer (n = 40)
Intervention Groups	Abarelix depot, 10-100 mg i.m. or s.c. 1x/14-28 days x 1 month → 1x/28 days
Significance of Results	Time to castration: A75-100, 24 h
Conclusions	Abarelix SR rapidly reduces androgen and gonadotropin levels within 24 h with no initial surge as observed with GnRH superagonists

Source: Prous Science CTLine database.

tered abarelix; at the lower dose, chemical castration was achieved in 92% of the patients within 72 h, while at the higher dose, 100% of the patients were castrate within 48 h of beginning abarelix treatment. PSA levels decreased rapidly and in a dose-related fashion, parallel to chemical castration. The compound was also well tolerated in this patient group, with a significantly lower incidence of hot flashes than seen with later LHRH superagonist therapy (8, 9) (Box 2).

Another study in 40 patients with prostate cancer compared the efficacy of abarelix sustained-release depot formulation (10-100 mg i.m. or s.c.), given every 14 or 28 days during the first month and then every 28 days thereafter, to that of leuprolide and goserelin. Over the dose range of 75-100 mg, abarelix depot administration led to the immediate and sustained suppression of androgens to castrate levels, without an initial androgen surge. Subsequent dosing of the compound (20-75 mg) at month 2 resulted in maintenance of these low levels. Administration of the LHRH superagonists, in contrast, caused total testosterone and LH levels to increase from baseline during the first 2-4 weeks, prior to achieving androgen ablation. Abarelix depot was well tolerated (10) (Box 3).

Abarelix has completed phase II testing and will soon progress to phase III (11).

Formulations

Abarelix has been developed as a sustained-release formulation for administration over prolonged periods of time, ranging from several days to several months. The compound and a carrier macromolecule, preferably carboxymethylcellulose (CMC), are associated into a tight, stable complex that allows the loading of a high concentration of abarelix into the formulation. Preclinical studies in rats and dogs demonstrated the feasibility of this approach. In dogs receiving monthly i.m. or s.c. injections of the abarelix-CMC complex (1.2 mg/kg on day 1; 0.3 or 0.6 mg/kg on day 29; 1.2 mg/kg on day 57), castrate levels of testosterone (< 0.6 ng/ml) were obtained within 24 h of drug administration. These levels were maintained at or near the same level throughout the first month, regardless of route of administration. Testosterone levels remained at this low level in 75% of the treated dogs immediately before the second dose was administered on day 29. Following the second dose of abarelix – regardless of dose level –, castrate levels of testosterone were maintained for more than 20 days in 30/35 dogs treated, and by day 57, 21/35 dogs remained castrate. Plasma concentrations of abarelix remained constant for 28 days after the third dose was administered, with testosterone levels still suppressed to castrate levels in 30/35 dogs on day 85 of the treatment period. Thus, administration of this abarelix formulation was shown to rapidly, effectively and safely suppress plasma testosterone levels and to maintain said levels for an extended period of time (12).

A long-term (6 months) study evaluated the safety and efficacy of the abarelix-CMC formulation in dogs. In this study, animals were initially administered a dose of 1.2 mg/kg abarelix by the s.c. or i.m. route, followed by 5 subsequent doses of 0.3, 0.6 or 1.2 mg/kg given every 28 days. Again, abarelix suppressed plasma testosterone levels in a rapid and long-lasting manner, in this case for periods of up to 6 months (12).

Manufacturer

Praecis Pharmaceuticals, Inc. (US); licensed to Roche for the U.S. and other markets and to Synthélabo for Europe and other territories (13).

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