PEPTIDES IN CANCER RESEARCH

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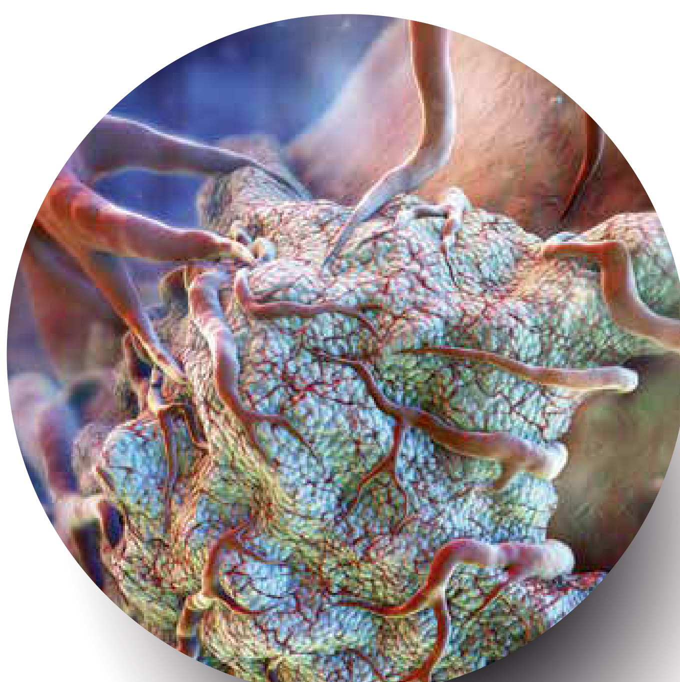

PEPTIDE-BASED CANCER THERAPEUTICS

This brochure discusses the potential use of peptides as anticancer drugs highlighting current scenario and future prospects. Some peptides are also used as diagnostic tools for cancer detection.

G-protein-coupled receptors are most important targets in drug development. Many of them are overexpressed in tumor cells. Amongst them, the GnRH receptor is the target of a considerable number of GnRH agonists and antagonists used in cancer management. GnRH (gonadotropin-releasing hormone) or LHRH (luteinizing hormone-releasing hormone) is a decapeptide produced in in the hypothalamus and released in a pulsatile fashion into the pituitary portal circulation. Prolonged non-pulsatile administration of LHRH leads to downregulation of LH and FSH secretion, followed by a suppression of gonadal steroid synthesis. For this reason, longer-acting GnRH agonists as well as antagonists are used for the treatment of hormone-dependent breast and prostate cancers.

Most neuroendocrine tumors show a marked overexpression of somatostatin receptors, especially of sst2, which instigated the development of somatostatin agonists as octreotide. These compounds also play an important role in diagnosis.

Bombesin/gastrin-releasing peptide receptors can be overexpressed in malignant cells. Antagonists of these peptides inhibit tumor growth.

Active immunization by peptide vaccines is another promising strategy to fight cancer.

Introduction

Cancer is characterized by uncontrolled division of cells and the ability of these cells to invade other tissues leading to the formation of tumor mass, to vascularization and, finally, to metastasis (spread of cancer to other parts of the body). Though angiogenesis (growth of new blood vessels from existing vessels) is a normal and vital process during growth and development, it is also a fundamental step in the transition of tumors from a dormant state to a malignant one. So, angiogenesis inhibitors have been used to suppress tumor cell growth. Chemotherapy is one of the classical approaches to treat cancer, a cytotoxic agent is delivered to the cancer cells. The main problem with conventional chemotherapy is its inability to administer the correct amount of drug directly to cancer cells without affecting normal cells. Drug resistance, altered biodistribution, biotransformation and premature clearance are also common problems. Targeted chemotherapy and drug delivery techniques are emerging as a powerful method to circumvent such problems. This will allow the selective and effective localization of drugs at pre-defined targets (e.g. overexpressed receptors) while restricting its access to normal cell thus maximizing therapeutic index and reducing toxicity. The discovery of further receptors abnormally expressed in cancer cells and tumor-related peptides and proteins is expected to lead to a 'new wave' of more effective and selective anti-cancer drugs in the future.

The "biologics" approach to cancer therapy includes application of proteins, monoclonal antibodies and peptides. Monoclonal antibodies (mAb) and large protein ligands have two major limitations compared to peptides: poor delivery to tumors due to their large size and a dose-limiting toxicity in liver and bone marrow due to nonspecific uptake into the reticuloendothelial system. The use of such macromolecules has therefore been restricted to vascular targets present on the luminal side of the tumor vessel endothelium and to hematological malignancies.

Peptides possess many advantages such as small size, ease of synthesis and modification, they are biocompatible and can penetrate tumor tissue. Their proteolytic degradation can be conveniently prevented by chemical modifications such as incorporation of D-amino acids or cyclization. Properties of bicyclic peptides are even better and comparable to those of antibody drugs.

The peptide drugs currently available on the market can be classified as analogs and antagonists of peptide hormones or tumor targeting agents carrying radionuclides.

LHRH (GnRH) Agonists and Antagonists

The first example for the introduction of peptide drugs into cancer therapy is the use of LHRH (luteinizing hormone-releasing hormone) analogs. Schally et al. developed the first GnRH agonists which later were applied in the treatment of prostate and breast cancer. Since then, peptides such as buserelin, leuprolide, goserelin, histrelin, and triptorelin have been developed and approved in cancer therapy. Depot formulations of these peptides allow for a more efficacious and convenient treatment of patients with prostate cancer. Administration of these peptides effects a down-regulation of GnRH receptors in the pituitary, leading to an inhibition of follicle-stimulating hormone (FSH) and LH release, and a concomitant decrease in testosterone production.

The introduction of LHRH antagonists as cetrorelix resulted in therapeutic improvement over agonists as they cause an immediate and dose-related inhibition of LH and FSH by competitive blockade of the LHRH receptors. To date, many potent GnRH antagonists are available for therapeutic use in patients suffering from prostate cancer. A

MODIFICATION AT POSITION 6 WITH A D-AMINO ACID YIELDS POTENT LONG-ACTING LHRH AGONISTS

PEPTIDE	SEQUENCE	INDICATION
GnRH		
GONADORELIN	Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2	none in cancer therapy
GnRH Agonists		
BUSERELIN	Pyr-His-Trp-Ser-Tyr-D-Ser(tBu)-Leu-Arg-Pro-NHEt	Prostate cancer
GOSERELIN	Pyr-His-Trp-Ser-Tyr-D-Ser(tBu)-Leu-Arg-Pro-Azagly-NH_2	Prostate and breast cancer
HISTRELIN	Pyr-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NHEt	Prostate and breast cancer
LEUPROLIDE	Pyr-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt	Prostate and breast cancer
TRIPTORELIN	Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2	Prostate and breast cancer
GnRH Antagonists		
ABARELIX	Ac-D-2-Nal-D-4-Cpa-D-3-Pal-Ser-N-Me-Tyr-D-Asn-Leu-Lys(isopropyl)-Pro-D-Ala-NH_2	Prostate cancer
CETRORELIX	Ac-D-2-Nal-4-chloro-D-Phe-β-(3-pyridyl)-D-Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2	Prostate and breast cancer
DEGARELX	Ac-D-2-Nal-D-4-Cpa-D-3-Pal-Ser-4-amino-Phe(L-4,5-dihydroorotyl)-4-ureido-D-Phe-Leu-Lys(isopropyl)-Pro-D-Ala-NH_2	Prostate cancer
OZARELIX	Ac-D-2-Nal-D-4-Cpa-D-3-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH_2	Prostate cancer
TEVERELIX	Ac-D-2-Nal-D-4-Cpa-D-3-Pal-Ser-Tyr-D-Hci-Leu-Lys(isopropyl)-Pro-D-Ala-NH_2	Prostate cancer

Table1. LHRH agonists and new generation antagonists available in the market.

list of such agonists and antagonists available in the market can be found in Table 1

Somatostatin Analogs in Cancer Therapy
Apart from the use of peptidic LHRH agonists and antagonists for treating cancer, somatostatin analogs are the only approved cancer therapeutic peptides in the market. Potent agonists of somatostatin (SRIF) including octreotide (sandostatin) have been developed for the treatment of acromegaly, gigantism and thyrotropinoma associated with carcinoid syndrome, and diarrhea in patients with vasoactive intestinal peptide-secreting tumors (VIPomas). Lanreotide, another long-acting analog of somatostatin, is used in the management of acromegaly and symptoms caused by neuroendocrine tumors.

Most neuroendocrine tumors (NETs) feature a strong overexpression of somatostatin receptors, mainly of subtype 2 (sst2). Currently, five somatostatin receptor subtypes (sst) are known (sst1-5). The density of these receptors on tumor tissue is vastly higher than on healthy tissue. Therefore, sst are attractive targets for delivery of radionuclides employing appropriately modified somatostatin analogs. Introduced in the late 1980s by Sandoz, [^{111}In-DTPA]-octreotide (pentetreotide, Octreoscan®), rapidly became the gold standard for diagnosis of sst-positive NETs. Numerous peptide-based tumor-imaging agents targeting sst have been developed over the past decades. Octreoscan® and NeoTect® (technetium-99m-labeled depreotide, cyclo(MePhe-Tyr-D-Trp-Lys-Val-Hcy(CH_2CO-β-Dap-Lys-Cys-Lys-NH_2)) are the only radiopeptide tracers on the market approved by the FDA. An octreotide scan or octreoscan is a scintigraphic method used to find carcinoids and other types of tumors and to localize sarcoidosis. DTPA-Octreotide, after radiolabeling with indium-111, is injected into a vein and travels through

THE FIVE KNOWN SOMATOSTATIN RECEPTORS ARE ATTRACTIVE TARGETS FOR TUMOR DIAGNOSIS AND THERAPY

the bloodstream. The radioactive octreotide attaches to tumor cells that have receptors for somatostatin. A radiation-measuring device detects the radioactive octreotide, and generates images showing the precise location of the tumor in the body.
The principle also works in cancer therapy. Peptide receptor radionuclide therapy (PRRT) combines appropriately modified octreotide with a radionuclide, which will bind to carcinoid tumor cells with overexpressed somatostatin receptors. Once bound, the targeted radiation will kill the malignant cells the peptide is bound to.
The complex between radionuclide and peptide has to be stable, especially if the radiopeptide is used in therapy. Cyclic chelators as DOTA bind (radio)nuclides as ^{68}Ga, ^{90}Y, or ^{177}Lu more tightly, so (Tyr^{3})-DOTA-octreotide (DOTATOC, edotreotide) can be used in diagnosis and therapy of NETs. This also holds true for the C-terminal acid, DOTA-octreotate (DOTATATE).
Somatostatin agonists vary in receptor selectivity: Lanreotide shows high affinity for sst2 and somewhat less to sst5. Pasireotide, another SRIF agonist, binds less selectively and thus mimics the natural ligand more closely.

Peptide Vaccines

Active immunization seems to be the most promising strategy to treat cancer though many approaches based on the employment of immune cells or immune molecules have been followed. This method of treating cancerous cells relies on vaccines consisting of peptides derived from the amino acid sequence of candidate tumor-associated or specific antigens. Tumor cells express antigens known as tumor-associated antigens (TAAs) that can be recognized by the T-cells of the host's immune system. A considerable number of TAAs could be identified and characterized. TAAs can be injected into cancer patients in an attempt to induce a systemic immune response that may result in the destruction of the cancer cells. Any protein/peptide produced in a tumor cell that has mal structure due to mutation can act as a tumor antigen. Such abnormal proteins are produced due to mutations in the corresponding gene. Hence, clinical studies have been initiated to assess the therapeutic potential of active immunization or vaccination with TAA peptides in patients with metastatic cancer. So far, only a limited number of TAA peptides,

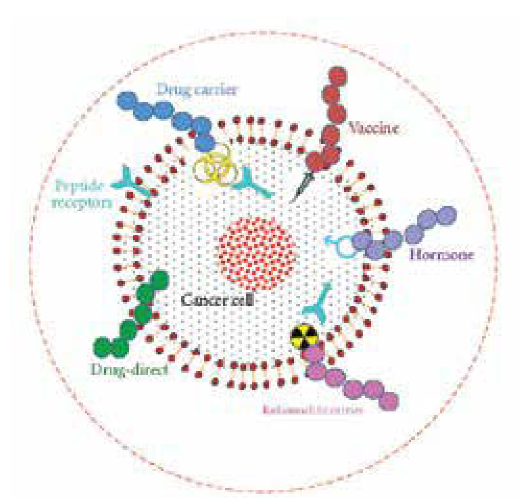

Figure1. Different treatment options of cancer using peptides. Peptides can be used as: anti-cancer drug, cytotoxic drug carrier, vaccine, hormone, radionuclide carrier and drug target (cancer drugs can be targeted towards tumor associated peptides or peptide receptors.
(J. Thundimadathil, J. Amino Acids 2012, 13 (2012))

mostly those recognized by CD8 (+) T-cells in melanoma patients, have been clinically tested. Several melanoma TAAs have been identified and are being evaluated as peptide-based cancer vaccines in clinical trials around the world.
Recent advances in the field of molecular biology have enabled the rapid identification of dozens of candidate TAAs for several important human cancers

Current Status and Future of Peptide Based Anti-Cancer Agents
The application of peptides as direct therapeutic agents, in targeted drug delivery and as diagnostic tools in cancer biology is growing. Among many improvements in targeted and controlled delivery of therapeutics, specifically binding peptides have emerged as the most valuable non-immunogenic approach to target cancer cells. Various cancer treatment options using peptides are summarized in Figure 1.
The RGD peptide iRGD (CRGDKGPDC) is able to specifically recognize and penetrate cancerous tumors but not normal tissues. The development of similar peptides with extraordinary tumor-penetrating properties will definitely make substantial improvements in cancer treatment in future. Chlorotoxin (Bachem product H-6086, a 36 amino acid peptide isolated from scorpion venom) has a higher affinity for glioma cells than for non-neoplastic and normal brain cells This preferential binding has allowed the development of new methods for the treatment and diagnosis of brain cancer. Anti-angiogenesis as a therapeutic approach led to renewed interest in cilengitide. This integrin inhibitor, a cyclic RGD peptide, is being evaluated as non-small-cell lung cancer therapeutic in clinical trials.
Bombesin/gastrin-releasing peptide (BN/GRP) peptides were shown to bind selectively to the G-protein–coupled receptors on the cell surface, stimulating the growth of various malignancies in murine and human cancer models. Thus, it has been proposed that the secretion of BN/GRP by neuroendocrine cells might be responsible for the development and progression of prostate cancer to androgen independence. GRP is widely distributed in lung and gastrointestinal tracts. It is produced in small cell lung cancer (SCLC), breast, prostatic, and pancreatic cancer, and functions as a growth factor. The involvement of bombesin-like peptides in the pathogenesis of a wide range of human tumors, their function as autocrine/paracrine tumoral growth factors, and the high incidence of BN/GRP receptors in various human cancers prompted the design and synthesis of BN/GRP receptor (GRPR) antagonists such as RC-3095, RC-3940-II, and RC-3950.
Currently, many researchers are focusing on the development of GHRH (growth hormone releasing hormone - a hypothalamic polypeptide) antagonists as potential anti-cancer therapeutics since GHRH is produced by various human tumors, including prostate cancer, and seems to exert an autocrine/paracrine stimulatory effect on them. Another promising approach for the therapy of prostate cancer consists of the use of cytotoxic analogues of GnRH, bombesin, and somatostatin, which can be targeted to receptors for these peptides in prostate cancers and their metastases. For example, a potential drug candidate, AEZS-108 consists of a peptide LHRH, coupled to the chemotherapeutic agent doxorubicin to directly target cells that express GnRH receptors, specifically, prostate cancer cells.

There is a tremendous effort to discover angiogenesis inhibitors, based on polypeptides as the safest and least toxic therapy for diseases associated with abnormal angiogenesis. A number of ongoing clinical trials in this area focus on peptides derived from: extracellular matrix proteins, growth factors and growth factor receptors, coagulation cascade proteins, chemokines, Type I Thrombospondin domain containing proteins and serpins.

Peptides will make a huge impact in the area of cancer diagnosis and therapy in the near future.

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PEPTIDES FOR CANCER RESEARCH OFFERED BY BACHEM

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BUSERELIN AND IMPURITIES

(Des-Gly^{10},D-Ser(tBu)^{6},Pro-NHEt^{9})-LHRH (Buserelin)
H-4224
<EHWSYs(tBu)-LRP-NHEt

(Des-Gly^{10},D-His^{2},D-Ser(tBu)^{6},Pro-NHEt^{9})-LHRH ((D-His^{2})-Buserelin)
H-8780
<EhWSYs(tBu)-LRP-NHEt

(Des-Gly^{10},D-Pyr^{1},D-Ser(tBu)^{6},Pro-NHEt^{9})-LHRH ((D-Pyr^{1})-Buserelin)
H-8775
<eHWSYs(tBu)-LRP-NHEt

(Des-Gly^{10},D-Ser^{4},D-Ser(tBu)^{6},Pro-NHEt^{9})-LHRH ((D-Ser^{4})-Buserelin)
H-8785
<EHWsYs(tBu)-LRP-NHEt

(Des-Gly^{10},D-Tyr^{5},D-Ser(tBu)^{6},Pro-NHEt^{9})-LHRH ((D-Tyr^{5})-Buserelin)
H-8790
<EHWSys(tBu)-LRP-NHEt

GOSERELIN AND IMPURITIES

(D-Ser(tBu)^{6},Azagly^{10})-LHRH (Goserelin)
H-6395
<EHWSYs(tBu)-LRP-Azagly-NH$_2$

(D-Ser(tBu)^{6},Azagly^{10})-LHRH (Goserelin (free base))
H-7296
<EHWSYs(tBu)-LRP-Azagly-NH$_2$

(Glu^{1},D-Ser(tBu)^{6},Azagly^{10})-LHRH ((Glu^{1})-Goserelin)
H-6652
EHWSYs(tBu)-LRP-Azagly-NH$_2$

(D-His^{2},D-Ser(tBu)^{6},Azagly^{10})-LHRH ((D-His^{2})-Goserelin)
H-5796
<EhWSYs(tBu)-LRP-Azagly-NH$_2$

(D-Ser(tBu)^{6},D-Leu^{7},Azagly^{10})-LHRH ((D-Leu^{7})-Goserelin)
H-5418
<EHWSYs(tBu)-lRP-Azagly-NH$_2$

(Ser(Ac)^{4},D-Ser(tBu)^{6},Azagly^{10})-LHRH ((Ser(Ac)^{4})-Goserelin)
H-6646
<EHWS(Ac)-Ys(tBu)-LRP-Azagly-NH$_2$

(Ser(tBu)^{6},Azagly^{10})-LHRH ((Ser(tBu)^{6})-Goserelin)
H-6644
<EHWSYS(tBu)-LRP-Azagly-NH$_2$

(D-Ser^{4},D-Ser(tBu)^{6},Azagly^{10})-LHRH ((D-Ser^{4})-Goserelin)
H-5654
<EHWsYs(tBu)-LRP-Azagly-NH$_2$

(D-Ser^{6},Azagly^{10})-LHRH ((D-Ser^{6})-Goserelin)
H-6266
<EHWSYsLRP-Azagly-NH$_2$

(D-Tyr^{5},D-Ser(tBu)^{6},Azagly^{10})-LHRH ((D-Tyr^{5})-Goserelin)
H-5734
<EHWSys(tBu)-LRP-Azagly-NH$_2$

(Des-Gly^{10},D-Ser(tBu)^{6},Pro-NHNH$_2^{9}$)-LHRH ((Des-carboxamide)-Goserelin)
H-5762
<EHWSYs(tBu)-LRP-NHNH$_2$

(Des-Pyr^{1},D-Ser(tBu)^{6},Azagly^{10})-LHRH ((Des-Pyr^{1})-Goserelin)
H-6648
HWSYs(tBu)-LRP-Azagly-NH$_2$

HISTRELIN, ANALOGS AND FRAGMENTS

(Des-Gly^{10},D-His(Bzl)^{6},Pro-NHEt^{9})-LHRH (Histrelin)
H-9210
<EHWSYh(Bzl)-LRP-NHEt

(Des-Gly^{10},His(Bzl)^{6},Pro-NHEt^{9})-LHRH ((His(Bzl)^{6})-Histrelin)
H-4656
<EHWSYH(Bzl)-LRP-NHEt

(Des-Gly^{10},D-His^{2},D-His(Bzl)^{6},Pro-NHEt^{9})-LHRH ((D-His^{2})-Histrelin)
H-4652
<EhWSYh(Bzl)-LRP-NHEt

(Des-Gly^{10},D-His(Bzl)^{6},D-Leu^{7},Pro-NHEt^{9})-LHRH ((D-Leu^{7})-Histrelin)
H-4658
<EHWSYh(Bzl)lRP-NHEt

(Des-Gly^{10},D-Ser^{4},D-His(Bzl)^{6},Pro-NHEt^{9})-LHRH ((D-Ser^{4})-Histrelin)
H-4704
<EHWsYh(Bzl)-LRP-NHEt

(Des-Gly^{10},D-Tyr^{5},D-His(Bzl)^{6},Pro-NHEt^{9})-LHRH ((D-Tyr^{5})-Histrelin)
H-4654
<EHWSyh(Bzl)-LRP-NHEt

(D-His(Bzl)^{6})-LHRH (1-7) (free acid) (Histrelin (1-7))
H-4804
<EHWSYh(Bzl)-L

(D-His(Bzl)^{6},Pro-NHEt^{9})-LHRH (4-9) (Histrelin (4-9))
H-4802
SYh(Bzl)-LRP-NHEt

LEUPROLIDE AND IMPURITIES

(Des-Gly^{10},D-Leu^{6},Pro-NHEt^{9})-LHRH (Leuprolide)
H-4060
<EHWSYlLRP-NHEt

(Des-Gly^{10},D-Leu^{6},[$^{13}C_6$]Leu^{7},Pro-NHEt^{9})-LHRH (([$^{13}C_6$]Leu^{7})-Leuprolide)
H-6258
<EHWSYl[$^{13}C_6$]LRP-NHEt

((D-Leu^{6})-LHRH (1-8) (free acid) ((Des-Pro-NHEt^{9})-Leuprolide)
H-6398
<EHWSYlLR

(D-Leu^{6},Pro-NHEt^{9})-LHRH (4-9) (Leuprolide (4-9))
H-4008
SYlLRP-NHEt

(Des-Gly^{10},D-His^{2},D-Leu^{6},Pro-NHEt^{9})-LHRH ((D-His^{2})-Leuprolide)
H-4316
<EhWSYlLRP-NHEt

(Des-Gly^{10},D-His^{2},D-Ser^{4},D-Leu^{6},Pro-NHEt^{9})-LHRH ((D-His^{2},D-Ser^{4})-Leuprolide)
H-6638
<EhWsYlLRP-NHEt

(Des-Gly^{10},D-Leu^{6},D-Leu^{7},Pro-NHEt^{9})-LHRH ((D-Leu^{7})-Leuprolide)
H-4636
<EHWSYllRP-NHEt

(Des-Gly^{10},D-Leu^{6},Orn^{8},Pro-NHEt^{9})-LHRH ((Orn^{8})-Leuprolide)
H-6716
<EHWSYlL-Orn-P-NHEt

LEUPROLIDE AND IMPURITIES (CONTINUED)

(Des-Gly^{10},D-Pyr^{1},D-Leu^{6},Pro-NHEt^{9})-LHRH ((D-Pyr^{1})-Leuprolide)
H-6642
<eHWSYlLRP-NHEt

(Des-Gly^{10},D-Ser^{4},D-Leu^{6},Pro-NHEt^{9})-LHRH ((D-Ser^{4})-Leuprolide)
H-6168
<EHWsYlLRP-NHEt

(Des-Gly^{10},D-Trp^{3},D-Leu^{6},Pro-NHEt^{9})-LHRH ((D-Trp^{3})-Leuprolide)
H-6636
<EHwSYlLRP-NHEt

(Des-Gly^{10},D-Tyr^{5},D-Leu^{6},Pro-NHEt^{9})-LHRH ((D-Tyr^{5})-Leuprolide)
H-4638
<EHWSylLRP-NHEt

(Des-Gly^{10},Des-Ser^{4},D-Leu^{6},Pro-NHEt^{9})-LHRH ((Des-Ser^{4})-Leuprolide)
H-6714
<EHWYlLRP-NHEt

(Des-Gly^{10},Leu^{6},Pro-NHEt^{9})-LHRH ((Leu^{6})-Leuprolide)
H-6402
<EHWSYLLRP-NHEt

(Des-Gly^{10},Ser(Ac)^{4},D-Leu^{6},Pro-NHEt^{9})-LHRH ((Ser(Ac)^{4})-Leuprolide)
H-6172
<EHWS(Ac)-YlLRP-NHEt

(Des-Pyr^{1},Des-Gly^{10},D-Leu^{6},Pro-NHEt^{9})-LHRH ((Des-Pyr^{1})-Leuprolide)
H-6166
HWSYlLRP-NHEt

TRIPTORELIN, ANALOGS AND FRAGMENTS

(D-Trp^{6})-LHRH (Triptorelin Acetate salt)
H-4075
<EHWSYwLRPG-NH$_2$ (Acetate salt)

(D-Trp^{6})-LHRH (Triptorelin Pamoate salt)
H-6150
<EHWSYwLRPG-NH$_2$ (Pamoate salt)

(D-Trp^{6})-LHRH (Triptorelin (free acid))
H-3078
<EHWSYwLRPG

(D-His^{2},D-Trp^{6})-LHRH ((D-His^{2})-Triptorelin)
H-4642
<EhWSYwLRPG-NH$_2$

(D-Trp^{6},D-Leu^{7})-LHRH ((D-Leu^{7})-Triptorelin)
H-4648
<EHWSYwlRPG-NH$_2$

(D-Ser^{4},D-Trp^{6})-LHRH ((D-Ser^{4})-Triptorelin)
H-4644
<EHWsYwLRPG-NH$_2$

(Trp^{6})-LHRH ((Trp^{6})-Triptorelin)
H-4578
<EHWSYWLRPG-NH$_2$

(D-Trp^{6})-LHRH-Leu-Arg-Pro-Gly amide
H-4582
<EHWSYwLRPGLRPG-NH$_2$

(D-Tyr^{5},D-Trp^{6})-LHRH ((D-Tyr^{5})-Triptorelin)
H-4646
<EHWSywLRPG-NH$_2$

(D-Trp^{6})-LHRH (1-6) amide (Triptorelin (1-6) amide)
H-4574
<EHWSYw-NH$_2$

Formyl-(D-Trp^{6})-LHRH (2-10) (Formyl-Triptorelin (2-10))
H-4576
For-HWSYwLRPG-NH$_2$

(D-Trp^{6})-LHRH (2-10) ((Des-Pyr^{1})-Triptorelin)
H-6404
HWSYwLRPG-NH$_2$

LHRH ANTAGONISTS

Cetrorelix
H-6682
Ac-D-2Nal-D-4Cpa-D-3Pal-SY-D-Cit-LRPa-NH_2

Degarelix*
H-7428
Ac-D-2Nal-D-4Cpa-D-3Pal-S-4-amino-Phe(L-4,5-dihydroorotyl)-4-ureido-D-Phe-LK(isopropyl)-Pa-NH_2

Ozarelix*
H-7384
Ac-D-2Nal-D-4-Cpa-D-3Pal-S-N-Me-Y-D-Hci-Nle-RPa-NH_2

SOMATOSTATIN, AGONISTS AND ANTAGONISTS

Somatostatin-14
H-1490
AGCKNFFWKTFTSC

([ring-D_5]Phe^6)-Somatostatin-14
H-7246
AGCKNF($^2H_5$)FWKTFTSC

BIM-23627
H-5886
F(4Cl)c-2Pal-WKVC-2Nal-NH_2

Cyclo-Somatostatin (Somatostatin Antagonist)
H-2485
c(7Aha-FwKT(Bzl))

Lanreotide (BIM-23014)
H-9055
D-2Nal-CYwKVCT-NH_2

Octreotide acetate salt (SMS 201-995)
H-5972
fCFwKTC-ThrOl

Octreotide pamoate salt
H-8346
fCFwKTC-ThrOl

([ring-D_5]Phe^3)-Octreotide
H-7238
fC($^2H_5$)FwKTC-ThrO

Octreotide trifluoroacetate salt (Dimer, Antiparallel)
H-7376
$(fCFwKTC\text{-}ThrO)_2$

Octreotide trifluoroacetate salt (Dimer, Parallel)
H-7374
$(fCFwKTC\text{-}ThrO)_2$

DOTA-(Tyr^3)-Octreotate (DOTATATE)
H-6318
DOTA-fCYwKTCT

Pasireotide* **NEW**
(SOM230)
H-7542
c(-Hyp(2-aminoethylcarbamoyl)-Phg-wKY(Bzl)F)

Tyr-(D-Dab^4,Arg^5,D-Trp^8)-cyclo-Somatostatin-14 (4-11) (KE 108)
H-6276
Y-c(D-Dab-RFFwKTF)

(D-Phe^5,Cys^{6,11},N-Me-D-Trp^8)-Somatostatin-14 (5-12) amide ((N-Me-D-Trp^4)-Octreotate amide)
H-5648
fCY(NMe-w)KTCT

Vapreotide (RC-160)
H-6634
fCYwKVCW-NH_2

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BOMBESIN AND BOMBESIN/GRP ANTAGONISTS

Bombesin
H-2155
pEQRLGNQWAVGHLM-NH_2

(Lys[3])-Bombesin
H-2160
pEQKLGNQWAVGHLM-NH_2

(Leu[13]-psi(CH_2NH)Leu[14])-Bombesin (BIM 26028)
H-7075
pEQRLGNQWAVGHL(Ψ[CH_2NH])L-NH_2

(D-Phe[12])-Bombesin
H-3038
pEQRLGNQWAVGfLM-NH_2

(D-Phe[6],Leu-NHEt[13],des-Met[14])-Bombesin (6-14) (DPDMB)
H-3042
fQWAVGHL-NHEt

(D-Phe[6],Leu[13]-psi(CH_2NH)p-chloro-Phe[14])-Bombesin (6-14)
H-3028
fQWAVGHL(Ψ[CH_2NH])F(4-Cl)-NH_2

(Tyr[4])-Bombesin
H-2165
pEQRYGNQWAVGHLM-NH_2

(Tyr[4],D-Phe[12])-Bombesin
H-9065
pEQRYGNQWAVGfLM-NH_2

(D-2-Nal[5],Cys[6,11],Tyr[7],D-Trp[8],Val[10],2-Nal[12])-Somatostatin-14 (5-12) amide (BIM 23042)
H-2126
D-2Nal-CYwKVC-Nal-NH

Acetyl-GRP (20-26) (human, porcine, canine)
H-6705
Ac-HWAVGHL-NH_2

(Deamino-Phe[19],D-Ala[24],D-Pro[26]-psi(CH_2NH)Phe[27])-GRP (19-27) (human, porcine, canine) (BW-10, BW2258U89)
H-2756
Deamino-FHWAVaHpo(Ψ[CH_2NH])F-NH_2

GHRH/ NEUROTENSIN/ SUBSTANCE P

Phenylacetyl-(D-Arg[2,28],p-chloro-Phe[6],Arg[9],Abu[15],Nle[27],Homoarg[29])-GRF (1-29) amide (human) (JV-1-36)
H-4884
Phac-YrDAIF(4Cl)TNRYRKVL-Abu-QL-SARKLLQDI-Nle-r-Har-NH_2

Phenylacetyl-(D-Arg[2,28],p-chloro-Phe[6],Homoarg[9,29],Tyr(Me)[10],Abu[15], Nle[27])-GRF (1-29) amide (human) (JV-1-38)
H-4886
Phac-YrDAIF(4Cl)TN-Har-Y(Me)RKVL-Abu-QLSARKLLQDI-Nle-r-Har-NH_2

(Lys[8]-psi(CH_2NH)Lys[9])-Neurotensin (8-13) (JMV-449)
H-8370
K(Ψ[CH_2NH])KPYIL

(D-Arg[1],D-Pro[2],D-Trp[7,9],Leu[11])-Substance P ((D-Pro[2])-Spantide)
H-1930
rpKPQQwFwLL-NH_2

(D-Arg[1],D-Trp[5,7,9],Leu[11])-Substance P
H-3992
rPKPwQwFwLL-NH_2

(Arg[6],D-Trp[7,9],N-Me-Phe[8])-Substance P (6-11) (Antagonist G)
H-1510
Rw(MeF)wLM-NH_{22}

Ac-Trp-3,5-bis(trifluoromethyl)benzyl ester (L-732,138, Substance P Antagonist)
E-3135

VIP/PACAP

PACAP-38 (6-38) (human, chicken, mouse, ovine, porcine, rat)
H-2734
FTDSYSRYRKQMAVKKYLAAVLG-KRYKQRVKNK-NH_2

Acetyl-(D-Phe[2],Lys[15],Arg[16],Leu[27])-VIP (1-7)-GRF (8-27) (PG 97–269)
H-7286
D-2Nal-CYw-Orn-VC-2Nal-NH_2

Myristoyl-(Lys[12,27,28])-VIP-Gly-Gly-Thr (free acid)
H-7292
Myr-HSDAVFTDNYTKLRKQMAVK-KYLNSIKKGGT

VIP Antagonist
H-9935
KPRRPYTDNYTRLRKQMAVKKYLN-SILN-NH_2

EPITOPES

Ovalbumin (257-264) (chicken)
H-4866
SIINFEKL

Ovalbumin (323-339) (chicken, japanese quail)
H-5532
ISQAVHAAHAEINEAGR

Cytochrome C (88-104) (domestic pigeon)
H-6016
KAERADLIAYLKQATAK

Collagen Type IV α3 Chain (185-203)
H-4208
CNYYSNSYSFWLASLNPER

Peptide 46
H-4054
GSRAHSSHLKSKKGQSTSRHKK

Peptide 74
H-8545
TMRKPRCGNPDVAN

VARIOUS

Chlorotoxin
H-6086
MCMPCFTTDHQMARKCDDCCGGK-GRGKCYGPQCLCR-NH_2

H-Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys-OH (CTT, MMP-2/MMP-9 Inhibitor III)
H-4736
CTTHWGFTLC

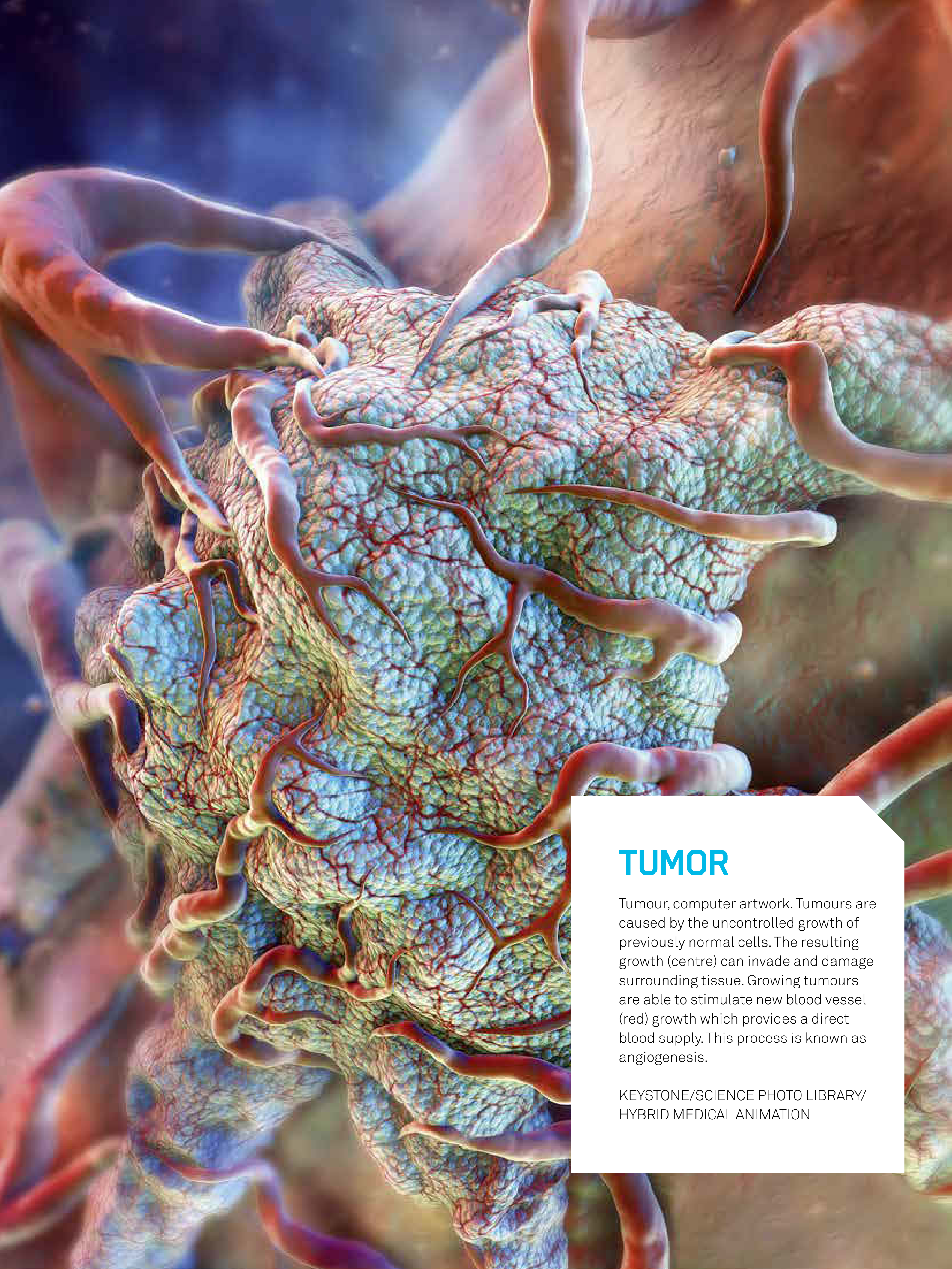
Grb2 SH2 Domain Ligand
H-2708
(pY)VNV

Human CMV pp65 (495-503)
H-6218
NLVPMVATV

Tumor Targeted Pro-Apoptotic Peptide
H-6104
CNGRCGGklaklakklaklak-NH_2

Urinary Trypsin Inhibitor Fragment
H-2692
RGPCRAFI

Z-Val-Ala-DL-Asp-fluoromethyl-ketone
N-1510
Z-VAD-FMK



TUMOR

Tumour, computer artwork. Tumours are caused by the uncontrolled growth of previously normal cells. The resulting growth (centre) can invade and damage surrounding tissue. Growing tumours are able to stimulate new blood vessel (red) growth which provides a direct blood supply. This process is known as angiogenesis.

KEYSTONE/SCIENCE PHOTO LIBRARY/ HYBRID MEDICAL ANIMATION

API PRODUCTS

Bachem is the world´s leading independent manufacturer of peptide active pharmaceutical ingredients (APIs) and a well established manufacturer of small molecules APIs. Each year, Bachem manufactures hundreds of batches of drug substance for projects in clinical trials and for products on the market.

Bachem is currently involved in more than 150 cGMP development projects targeting NCEs and Bachem offers a range of more than 30 generic drug substances. We have the capacity to produce peptide APIs from gram scale up to annual quantities of hundreds of kilograms and small molecules APIs from gram scale up to annual quantities of tens of tons. Our GMP manufacturing facilities are located in Switzerland and the United States and are regularly inspected by the FDA and local authorities.

In addition to more than 45 years of experience in the manufacture of drug substance, Bachem also has a strong regulatory background and we are well prepared to fully support you with the required regulatory documentation such as drug master files (DMFs). For complex development projects we support you with dedicated project teams comprising of our experts from R&D, production, quality control, quality assurance and regulatory affairs. A team of experienced Business Development Managers and Generics Managers look forward to working with you for your future requirements.

GENERIC APIs

Buserelin
H-4224-GMP
<EHWSYs(tBu)-LRP-NHEt

Gonadorelin Acetate
H-4005-GMP
<EHWSYGLRPG-NH_2 (Acetate salt)

Goserelin Acetate
H-6395-GMP
<EHWSYs(tBu)-LRP-Azagly-NH_2

Leuprolide Acetate
H-4060-GMP
<EHWSYlLRP-NHEt

Triptorelin Acetate
H-4075-GMP
<EHWSYwLRPG-NH_2 (Acetate salt)

Triptorelin Pamoate
H-6150-GMP
<EHWSYwLRPG-NH_2 (Pamoate salt)

IMPURITIES OF THE LEUPRORELIN PH. EUR. MONOGRAPH

Impurity A
(D-Ser^{4})-Leuprolide
H-6168
<EHWsYlLRP-NHEt

Impurity B
(D-His^{2})-Leuprolide
H-4316
<EhWSYlLRP-NHEt

Impurity C
(Leu^{6})-Leuprolide
H-6402
<EHWSYLLRP-NHEt

Impurity D
(Ser(Ac)^{4})-Leuprolide
H-6172
<EHWS(Ac)YlLRP-NHEt

Impurity E
(D-Trp^{3})-Leuprolide
H-6636
<EHwSYlLRP-NHEt

Impurity F
(D-His^{2},D-Ser^{4})-Leuprolide
H-6638
<EhWsYlLRP-NHEt

Impurity G
(D-Tyr^{5})-Leuprolide
H-4638
<EHWSylLRP-NHEt

Impurity H
(D-Leu^{7})-Leuprolide
H-4636
<EHWSYllRP-NHEt

Impurity I
(D-Pyr^{1})-Leuprolide
H-6642
<eHWSYlLRP-NHEt

IMPURITIES OF THE GOSERELIN PH. EUR. MONOGRAPH

Impurity A
(D-Ser^4)-Goserelin
H-5654
<EHWsYs(tBu)-LRP-Azagly-NH_2

Impurity B
(Ser(tBu)^6)-Goserelin
H-6644
<EHWSYS(tBu)-LRP-Azagly-NH_2

Impurity E
(Pro-$NHNH_2$^{9})-Buserelin
H-5762
<EHWSYs(tBu)-LRP-$NHNH_2$

Impurity F
(D-Tyr^5)-Goserelin
H-5734
<EHWSys(tBu)-LRP-Azagly-NH_2

Impurity G
(D-His^2)-Goserelin
H-5796
<EhWSYs(tBu)-LRP-Azagly-NH_2

Impurity K
(Ser(Ac)^4)-Goserelin
H-6646
<EHWS(Ac)-Ys(tBu)-LRP-Azagly-NH_2

Impurity L
(D-Leu^7)-Goserelin
H-5418
<EHWSYs(tBu)-lRP-Azagly-NH_2

IMPURITIES OF THE BUSERELIN PH. EUR. MONOGRAPH

Impurity A
(D-His^2)-Buserelin
H-8780
<EhWSYs(tBu)-LRP-NHEt

Impurity B
(D-Ser^4)-Buserelin
H-8785
<EHWsYs(tBu)-LRP-NHEt

Impurity D
(D-Tyr^5)-Buserelin
H-8790
<EHWSys(tBu)-LRP-NHEt

Impurity E
(D-Pyr^1)-Buserelin
H-8775
<eHWSYs(tBu)-LRP-NHEt

SOMATOSTATIN AND AGONISTS

Somatostatin
H-1490-GMP
<EhWSYs(tBu)-LRP-NHEt

Lanreotide
H-9055-GMP
<EHWsYs(tBu)-LRP-NHEt

Octreotide Acetate
H-5972-GMP
<EHWSys(tBu)-LRP-NHEt

Pasireotide Acetate*
4047875
<eHWSYs(tBu)-LRP-NHEt

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BACHEM

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