PEPTIDES IN CANCER RESEARCH

BACHEM

PIONEERING PARTNER FOR PEPTIDES
PEPTIDE-BASED CANCER THERAPEUTICS

This brochure discusses the potential use of peptides as anti-cancer 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 the hypothalamus and released in a pulsatile fashion into the pituitary portal circulation. Prolonged non-pulsatile administration of LHRH leads to down-regulation 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 cetorelix 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 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-Hcyl(CH₂CO-β-Dap-Lys-Cys-Lys-NH₂)) are the only radiopeptide tracers on the market approved by the FDA. An octreotide scan or octreoscan is a scintigraphic method used...
THE FIVE KNOWN SOMATOSTATIN RECEPTORS ARE ATTRACTIVE TARGETS FOR TUMOR DIAGNOSIS AND THERAPY

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

Cancer Research

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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, mostly those recognized by CD8 (+) T-cells in melanoma patients, have been clinically tested. Several melanoma TAs 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 cingitide. 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.
REFERENCES

L.J. Hofland et al.
Somatostatin analogs: clinical application in relation to human somatostatin receptor subtypes.

J.C. Reubi et al.
Somatostatin receptors and their subtypes in human tumors and in peritumoral vessels.
Metabolism 45, 39-41 (1996)

A.V. Schally
Luteinizing hormone-releasing hormone analogs: their impact on the control of tumorigenesis.
Peptides 20, 1247-1262 (1999)

W.A. Breeman et al.
Somatostatin receptor-mediated imaging and therapy: basic science, current knowledge, limitations and future perspectives.

S.V. Le et al.
PAC1 and PACAP expression, signaling, and effect on the growth of HCT8, human colonic tumor cells.

C. Borghouts et al.
Current strategies for the development of peptide-based anti-cancer therapeutics.

L.K. Kvols and E.A. Woltering
Role of somatostatin analogs in the clinical management of non-neuroendocrine solid tumors.
Anticancer Drugs 17, 601-608 (2006)

R.T. Dorsam and J.S. Gutkind
G-protein-coupled receptors and cancer.

S. Fister et al.
Gonadotropin-releasing hormone type II antagonists induce apoptotic cell death in human endometrial and ovarian cancer cells in vitro and in vivo.
Cancer Res. 67, 1750-1756 (2007)

L. Vujanovic and L.H. Butterfield
Melanoma cancer vaccines and anti-tumor T cell responses.

C. Doehn et al.
Degarelix for prostate cancer.
Expert Opin. Investig. Drugs 18, 851-860 (2009)

F. Goel et al.
LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women.
Cochrane Database Syst. Rev. CD004562 (2009)

A. Hackshaw
Luteinizing hormone-releasing hormone (LHRH) agonists in the treatment of breast cancer.
Expert Opin. Pharmacother. 10, 2633-2639 (2009)

F. Klug et al.
Characterization of MHC ligands for peptide based tumor vaccination.

G. Mezö and M. Manea
Luteinizing hormone-releasing hormone antagonists.
Expert Opin. Ther. Pat. 19, 1771-1785 (2009)

R.M. Myers et al.
Cancer, chemistry, and the cell: molecules that interact with the neurotensin receptors.

E.D. Deeks
Histrelin: in advanced prostate cancer.
Drugs 70, 623-630 (2010)

F. Hohla and A.V. Schally
Targeting gastrin releasing peptide receptors: New options for the therapy and diagnosis of cancer.
Cell Cycle 9, 1738-1741 (2010)

P. Whelan
Triptorelin embonate: a 6-month formulation for prostate cancer.
Expert Opin. Pharmacother. 11, 2929-2932 (2010)

D. Wild et al.
First clinical evidence that imaging with somatostatin receptor antagonists is feasible.
J. Nucl. Med. 52, 1412-1417 (2011)

B.L.R. Kam et al.
Lutetium-labelled peptides for therapy of neuroendocrine tumours.

K.P. Koopmans and A.W. Glaude-mans
Rationale for the use of radiolabelled peptides in diagnosis and therapy.

P. Limonta et al.
GnRH receptors in cancer: from cell biology to novel targeted therapeutic strategies.
Endocr. Rev. 33, 784-811 (2012)

P.W. Moody et al.
Pituitary adenylate cyclase-activating polypeptide causes tyrosine phosphorylation of the epidermal growth factor receptor in lung cancer cells.

P.K. Nanda et al.
Bombesin analogues for gastrin-releasing peptide receptor imaging.

J. Thundimadathil
Cancer treatment using peptides: Current therapies and future prospects.

F. Barbieri et al.
Peptide receptor targeting in cancer: the somatostatin paradigm.
Int. J. Pept. 2013, 926295 (2013)
R.A. Feelders et al.
Pasireotide, a multi-somatostatin receptor ligand with potential efficacy for treatment of pituitary and neuroendocrine tumors.
*Drugs Today (Barc.)* 49, 89-103 (2013)

E. Harford-Wright et al.
The potential for substance P antagonists as anti-cancer agents in brain tumours.
*Recent Pat. CNS Drug. Discov.* 8, 13-23 (2013)

O. Keskin and S. Yalcin
A review of the use of somatostatin analogs in oncology.
*Onco Targets Ther.* 6, 471-483 (2013)

E. Harford-Wright et al.
The potential for substance P antagonists as anti-cancer agents in brain tumours.
*Recent Pat. CNS Drug. Discov.* 8, 13-23 (2013)

F.G. Rick et al.
Agonists of luteinizing hormone-releasing hormone in prostate cancer.
*Expert Opin. Pharmacother.* 14, 2237-2247 (2013)

N.D. Shore et al.
New considerations for ADT in advanced prostate cancer and the emerging role of GnRH antagonists.

U.W. Tunn et al.
Six-month leuprorelin acetate depot formulations in advanced prostate cancer: a clinical evaluation.

R. Varshney et al.
(68)Ga-labeled bombesin analogs for receptor-mediated imaging.
*Recent Results Cancer Res.* 194, 221-256 (2013)

Z. Yu et al.
An update of radiolabeled bombesin analogs for gastrin-releasing peptide receptor targeting.

O. Abdel-Rahman et al.
Somatostatin receptor expression in hepatocellular carcinoma: prognostic and therapeutic considerations.

A. Accardo et al.
Receptor binding peptides for target-selective delivery of nanoparticles encapsulated drugs.

V. Ambrosini et al.
The use of gallium-68 labeled somatostatin receptors in PET/CT imaging.
*PET Clin.* 9, 323-329 (2014)

R. Baldelli et al.
Somatostatin analogs therapy in gastroenteropancreatic neuroendocrine tumors: current aspects and new perspectives.
*Front. Endocrinol. (Lausanne)* 5, 7 (2014)

N.J. Carter and S.J. Keam
Degarelix: a review of its use in patients with prostate cancer.
*Drugs* 74, 689-712 (2014)

K. Mander et al.
*Recent Pat. CNS Drug Discov.* 9, 110-121 (2014)

C. Morgat et al.
Targeting neuropeptide receptors for cancer imaging and therapy: perspectives with bombesin, neurotensin, and neuropeptide-Y receptors.

J.W. Moul
Utility of LHRH antagonists for advanced prostate cancer.

R. Coveñas and M. Muñoz
Cancer progression and substance P.

M. Muñoz and R. Coveñas
Targeting NK-1 Receptors to Prevent and Treat Pancreatic Cancer: a New Therapeutic Approach.
*Cancers (Basel)* 7, 1215-1232 (2015)

Y. Nishimura et al.
Cancer immunotherapy using novel tumor-associated antigenic peptides identified by genome-wide cDNA microarray analyses.

J. Yang et al.
Composite peptide-based vaccines for cancer immunotherapy (Review).

B. Tang et al.
Vasoactive intestinal peptide receptor-based imaging and treatment of tumors (Review).
*Int. J. Oncol.* 44, 1023-1031 (2014)

Z. Blumenfeld and A. Evron
Preserving fertility when choosing chemotherapy regimens - the role of gonadotropin-releasing hormone agonists.

L. Dardevet et al.
Chlorotoxin: a helpful natural scorpion peptide to diagnose glioma and fight tumor invasion.
*Toxins (Basel)* 7, 1079-1101 (2015)

M. Muñoz and R. Coveñas
Targeting NK-1 Receptors to Prevent and Treat Pancreatic Cancer: a New Therapeutic Approach.
*Cancers (Basel)* 7, 1215-1232 (2015)

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*Cancers (Basel)* 7, 1215-1232 (2015)
A choice of our products. Besides peptides, Bachem offers enzyme substrates, inhibitors, amino acid derivatives and other compounds for numerous applications in cancer research.
**BUSERELIN AND IMPURITIES**

- **(Des-Gly\text{\textsuperscript{10}}, D-Ser(tBu)\text{\textsuperscript{6}}, Pro-NH\text{\textsubscript{Et}})-LHRH (Buserelin)**  
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- **(Des-Gly\text{\textsuperscript{10}}, D-Pyr\text{\textsuperscript{1}}, D-Ser(tBu)\text{\textsuperscript{6}}, Pro-NH\text{\textsubscript{Et}}\text{\textsuperscript{7}})-LHRH (D-(D-Pyr\text{\textsuperscript{1}})-Buserelin)**  
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**GOSERELIN AND IMPURITIES**

- **(D-Ser(tBu)\text{\textsuperscript{4}}, Azagly\text{\textsuperscript{10}})-LHRH (Goserelin)**  
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- **(D-Ser(tBu)\text{\textsuperscript{9}}, Azagly\text{\textsuperscript{10}})-LHRH (Goserelin (free base))**  
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- **(Glu\text{\textsuperscript{1}}, D-Ser(tBu)\text{\textsuperscript{6}}, Azagly\text{\textsuperscript{10}})-LHRH ((Glu\text{\textsuperscript{1}})-Goserelin)**  
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- **(D-His\text{\textsuperscript{3}}, D-Ser(tBu)\text{\textsuperscript{5}}, Azagly\text{\textsuperscript{10}})-LHRH ((D-His\text{\textsuperscript{3}})-Goserelin)**  
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- **(Ser(Ac)\text{\textsuperscript{4}}, D-Ser(tBu)\text{\textsuperscript{6}}, Azagly\text{\textsuperscript{10}})-LHRH ((Ser(Ac)\text{\textsuperscript{4}})-Goserelin)**  
  H-6666  
  <EHWS(Ac)-Ys(tBu)-LRP-Azagly-NH\text{\textsubscript{2}}

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### HISTRELIN, ANALOGS AND FRAGMENTS

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### LEUPROLIDE AND IMPURITIES

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LEUPROLIDE AND IMPURITIES (CONTINUED)

(D-Trp$^5$)-LHRH (Triptorelin Acetate salt)
H-4075
<EHWSYWLRPG-NH$_2$ (Acetate salt)

(D-Trp$^5$)-LHRH (Triptorelin Pamoate salt)
H-6150
<EHWSYWLRPG-NH$_2$ (Pamoate salt)

(D-Trp$^5$)-LHRH (Triptorelin free acid))
H-3078
<EHWSYWLRPG

(D-His$^8$,D-Trp$^5$)-LHRH ((D-His$^8$)-Triptorelin)
H-4642
<EHWSYWLRPG-NH$_2$

(D-Trp$^6$,D-Leu$^9$)-LHRH ((D-Leu$^9$)-Triptorelin)
H-4648
<EHWSYWLRPG-NH$_2$

(D-Ser$^4$,D-Trp$^5$)-LHRH ((D-Ser$^4$)-Triptorelin)
H-4644
<EHWSYWLRPG-NH$_2$

(D-Trp$^5$)-LHRH ([(D-Trp$^5$)-Triptorelin)
H-4578
<EHWSYWLRPG-NH$_2$

(D-Trp$^5$)-LHRH-Leu-Arg-Pro-Gly amide
H-4582
<EHWSYWLRPGLRPG-NH$_2$

(D-Tyr$^5$,D-Trp$^5$)-LHRH ((D-Tyr$^5$)-Triptorelin)
H-4846
<EHWSYWLRPG-NH$_2$

(D-Trp$^5$)-LHRH (1-6) amide (Triptorelin (1-6) amide)
H-4574
<EHWSYW-NH$_2$

Formyl-(D-Trp$^9$)-LHRH (2-10) (Formyl-Triptorelin (2-10))
H-4576
For-HWSYWLRPG-NH$_2$

(D-Trp$^9$)-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-NH₂

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-NH₂

**SOMATOSTATIN, AGONISTS AND ANTAGONISTS**

Somatostatin-14  
H-1490  
AGCKNFFWKFTFTSC

([ring-D₅]Phe⁶)-Somatostatin-14  
H-7246  
AGCKNF(2H5)FWKTFTSC

BIM-23627  
H-5886  
F(4Cl)c-2Pal-WKVC-2Nal-NH₂

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

Lanreotide  
(BIM-23014)  
H-9055  
D-2Nal-CywKVCT-NH₂

Octreotide acetate salt  
(SMS 201-995)  
H-5972  
fCFwKTC-ThrO₁

Octreotide pamoate salt  
H-8346  
fCFwKTC-ThrO₁

([ring-D₅]Phe³)-Octreotide  
H-7238  
fC(2H5)FwKTC-ThrO

Octreotide trifluoroacetate salt  
(Dimer, Antiparallel)  
H-7376  
(fCFwKTC-ThrO)₂

Octreotide trifluoroacetate salt  
(Dimer, Parallel)  
H-7374  
(fCFwKTC-ThrO)₂

DOTA-(Tyr³)-Octreotide  
(DOTATATE)  
H-6318  
DOTA-fCYwKTCT

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

Tyr-(D-Dab⁴,Arg⁵,D-Trp⁸)-cyclo-Somatostatin-14 (4-11)  
(KE 108)  
H-6276  
Y-c(D-Dab-RFFwKTF)

(D-Phe⁸,Cys⁶,¹¹,N-Me-D-Trp⁸)-Somatostatin-14 (5-12) amide  
( (N-Me-D-Trp⁸)-Octreotide amide)  
H-5648  
fCY(NMe-w)KTCT

Vapreotide  
(RC-160)  
H-6634  
fCYwKVCT-NH₂

* Bachem provides this product solely for uses within the scope of any statute or law providing for an immunity, exemption, or exception to patent infringement ("Exempted Uses"), including but not limited to 35 U.S.C. § 271(e)(1) in the United States, the Bolar type exemption in Europe, and any corresponding exception to patent infringement in any other country. It is the sole responsibility of the purchaser or user of this product, and the purchaser or user of this product agrees to engage only in such Exempted Uses, and to comply with all applicable intellectual property laws and/or regulations. The purchaser of this product agrees to indemnify Bachem against all claims in connection with the performance of the respective commercial agreement (e.g. supply agreement) and possible infringements of intellectual property rights.
## BOMBESIN AND BOMBESIN/GRP ANTAGONISTS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bombesin</td>
<td>H-2155</td>
<td>pEQRLGNQWAVGHLM-NH₂</td>
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<tr>
<td>(Lys³)-Bombesin</td>
<td>H-2160</td>
<td>pEQKLGNQWAVGHLM-NH₂</td>
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<tr>
<td>(Leu¹³-psi(CH₂NH)Leu¹⁴)-Bombesin (BIM 26028)</td>
<td>H-7075</td>
<td>pEQRLGNQWAVGHLM(Ψ(CH₂NH))L-NH₂</td>
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<tr>
<td>(D-Phe¹⁰)-Bombesin</td>
<td>H-3038</td>
<td>pEQRLGNQWAVGHLM-NH₂</td>
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<tr>
<td>(D-Phe⁶,Leu-NHet¹³,des-Met¹⁴)-Bombesin (6-14) (DPDDBM)</td>
<td>H-3042</td>
<td>fQWAVGHLM-NH₂</td>
</tr>
<tr>
<td>(D-Phe⁶,Leu¹³-psi(CH₂NH)p-chloro-Phe¹⁴)-Bombesin (6-14)</td>
<td>H-3028</td>
<td>fQWAVGHLM(Ψ(CH₂NH))F(4-Cl)-NH₂</td>
</tr>
<tr>
<td>(Tyr⁴)-Bombesin</td>
<td>H-2165</td>
<td>pEQRYGNQWAVGHLM-NH₂</td>
</tr>
<tr>
<td>(Tyr⁴,D-Phe¹⁰)-Bombesin</td>
<td>H-9065</td>
<td>pEQRYGNQWAVGHLM-NH₂</td>
</tr>
<tr>
<td>(D-2-Nal⁵,Cys⁶,⁸,Tyr⁷,D-Trp⁸,Val¹⁰,2-Nal¹²)-Somatostatin-14 (5-12) amide (BIM 23042)</td>
<td>H-2126</td>
<td>D-2Nal-CyKVC-Nal-NH₂</td>
</tr>
<tr>
<td>Acetyl-GRP (20-26) (human, porcine, canine)</td>
<td>H-6705</td>
<td>Ac-HWAVGHLM-NH₂</td>
</tr>
<tr>
<td>(Deamino-Phe¹⁸,D-Ala¹⁴,D-Pro²⁸-psi(CH₂NH)Phe³⁷)-GRP (19-27) (human, porcine, canine) (BW-10, BW2258U89)</td>
<td>H-2756</td>
<td>Deamino-FHWAVAHPo(Ψ(CH₂NH))F-NH₂</td>
</tr>
<tr>
<td>Phenylacetyl-(D-Arg²⁻⁸,p-chloro-Phe⁴,Arg⁸,Abu¹⁸,Nle⁶⁺²⁺,Homoarg²⁸)-GRF (1-29) amide (human) (JV-1-36)</td>
<td>H-4884</td>
<td>Phac-YrDAIF(4Cl)TNRYRKVL-Abu-QLSARKLQDI-Nle-r-Har-NH₂</td>
</tr>
<tr>
<td>Phenylacetyl-(D-Arg²⁻⁸,p-chloro-Phe⁴,Homoarg⁴⁻²⁺,Tyr(Me)¹⁰,Abu¹⁸, Nle²⁸⁺)-GRF (1-29) amide (human) (JV-1-38)</td>
<td>H-4886</td>
<td>Phac-YrDAIF(4Cl)TN-Har-Y(Me)RKVL-Abu-QLSARKLQDI-Nle-r-Har-NH₂</td>
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<tr>
<td>(Lys⁸-psi(CH₂NH)Lys⁹)-Neurotensin (8-13) (JMV-449)</td>
<td>H-8370</td>
<td>K(Ψ(CH₂NH))KPYIL</td>
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<tr>
<td>(D-Arg⁴,D-Pro⁴,D-Trp⁷⁻⁸,Leu¹¹)-Substance P</td>
<td>H-1930</td>
<td>rpKPQoFwLL-NH₂</td>
</tr>
<tr>
<td>(D-Arg⁴,D-Trp⁴⁻⁸,⁷⁻⁸,Leu¹¹)-Substance P</td>
<td>H-3992</td>
<td>rPKPwFwLL-NH₂</td>
</tr>
<tr>
<td>(Arg⁴,D-Trp⁷⁻⁸,N-Me-Phe⁻⁸)-Substance P (6-11) (Antagonist G)</td>
<td>H-1510</td>
<td>Rw(MeF)wLM-NH₂</td>
</tr>
<tr>
<td>(Arg⁴,D-Trp⁷⁻⁸,N-Me-Phe⁻⁸)-Substance P (6-11) (Antagonist G)</td>
<td>H-1510</td>
<td>Rw(MeF)wLM-NH₂</td>
</tr>
<tr>
<td>Ac-Trp⁻³⁻⁸-bis(trifluoromethyl)benzyl ester (L-732,138, Substance P Antagonist)</td>
<td>E-3135</td>
<td></td>
</tr>
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</table>

## GHRH/NEUROTENSIN/SUBSTANCE P

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Phenylacetyl-(D-Arg²⁻⁸,p-chloro-Phe⁴,Arg⁸,Abu¹⁸,Nle⁶⁺²⁺,Homoarg²⁸)-GRF (1-29) amide (human) (JV-1-36)</td>
<td>H-4884</td>
<td>Phac-YrDAIF(4Cl)TNRYRKVL-Abu-QLSARKLQDI-Nle-r-Har-NH₂</td>
</tr>
<tr>
<td>Phenylacetyl-(D-Arg²⁻⁸,p-chloro-Phe⁴,Homoarg⁴⁻²⁺,Tyr(Me)¹⁰,Abu¹⁸, Nle²⁸⁺)-GRF (1-29) amide (human) (JV-1-38)</td>
<td>H-4886</td>
<td>Phac-YrDAIF(4Cl)TN-Har-Y(Me)RKVL-Abu-QLSARKLQDI-Nle-r-Har-NH₂</td>
</tr>
<tr>
<td>(Lys⁸-psi(CH₂NH)Lys⁹)-Neurotensin (8-13) (JMV-449)</td>
<td>H-8370</td>
<td>K(Ψ(CH₂NH))KPYIL</td>
</tr>
<tr>
<td>(D-Arg⁴,D-Pro⁴,D-Trp⁷⁻⁸,Leu¹¹)-Substance P</td>
<td>H-1930</td>
<td>rpKPQoFwLL-NH₂</td>
</tr>
<tr>
<td>(D-Arg⁴,D-Trp⁴⁻⁸,⁷⁻⁸,Leu¹¹)-Substance P</td>
<td>H-3992</td>
<td>rPKPwFwLL-NH₂</td>
</tr>
<tr>
<td>(Arg⁴,D-Trp⁷⁻⁸,N-Me-Phe⁻⁸)-Substance P (6-11) (Antagonist G)</td>
<td>H-1510</td>
<td>Rw(MeF)wLM-NH₂</td>
</tr>
<tr>
<td>(Arg⁴,D-Trp⁷⁻⁸,N-Me-Phe⁻⁸)-Substance P (6-11) (Antagonist G)</td>
<td>H-1510</td>
<td>Rw(MeF)wLM-NH₂</td>
</tr>
<tr>
<td>Ac-Trp⁻³⁻⁸-bis(trifluoromethyl)benzyl ester (L-732,138, Substance P Antagonist)</td>
<td>E-3135</td>
<td></td>
</tr>
</tbody>
</table>
**VIP/PACAP**

- **PACAP-38** (6–38) (human, chicken, mouse, ovine, porcine, rat)
  - H-2734
  - FTDSYSRYRKQMAVKKYLAVALG-KRYKQVKNK-NH₂
- **Acetyl-(D-Phe⁶,Lys¹⁵,Arg¹⁶,Leu²⁷)-VIP (1–7)–GRF (8–27) (PG 97–269)**
  - H-7286
  - D-2NaL-CWy-Orn-VC-2NaL-NH₂
- **Myristoyl-(Lys¹³,²⁷,²⁸)-VIP-Gly-Gly-Thr (free acid)**
  - H-7292
  - Myr-HSDAVFTDNYTKLRKQMAVK-KYLNISKKGGT
- **VIP Antagonist**
  - H-9935
  - KPRRPYTDNYTRLKQMAVKKYNL-SILN-NH₂

**EPITOPES**

- **Ovalbumin (257–264) (chicken)**
  - H-4866
  - SIINFEKL
- **Ovalbumin (323–339) (chicken, japanese quail)**
  - H-5532
  - ISQAVHAAHAEEINEAGR
- **Cytochrome C (88–104) (domestic pigeon)**
  - H-6016
  - KAERADLIAYLQATAK
- **Collagen Type IV α3 Chain (185–203)**
  - H-4208
  - CNYYSNSYSFWLASLNPER
- **Peptide 46**
  - H-4054
  - GSRAHSSHLKSKQGQSRSRHKK
- **Peptide 74**
  - H-8545
  - TMRKPRCGNPDVAN

**VARIOUS**

- **Chlorotoxin**
  - H-6086
  - MCMPCFTTDHQMARKCDCCGGK-GRGKCYGPQCLCR-NH₂
- **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)VNYV
- **Human CMV pp65 (495–503)**
  - H-6218
  - NLVPMVATV
- **Tumor Targeted Pro-Apoptotic Peptide**
  - H-6104
  - CNGRCGklaklaklaklaklaklakh-NH₂
- **Urinary Trypsin Inhibitor Fragment**
  - H-2692
  - RGPCRAFI
- **Z-Val-Ala-DL-Asp-fluoromethyl-ketone**
  - N-1510
  - Z-VAD-FMK
Tumor, computer artwork. Tumors are caused by the uncontrolled growth of previously normal cells. The resulting growth (centre) can invade and damage surrounding tissue. Growing tumors are able to stimulate new blood vessel (red) growth which provides a direct blood supply. This process is known as angiogenesis.

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HYBRID MEDICAL ANIMATION
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 close to 50 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

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<tr>
<th>Name</th>
<th>Code</th>
<th>Formula</th>
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<tbody>
<tr>
<td>Buserelin</td>
<td>H-4224-GMP</td>
<td>&lt;EHWSYs(tBu)-LRP-NH₂t</td>
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<tr>
<td>Gonadorelin Acetate</td>
<td>H-4005-GMP</td>
<td>&lt;EHWSYGLRPG-NH₃ (Acetate)</td>
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<tr>
<td>Goserelin Acetate</td>
<td>H-6395-GMP</td>
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<tr>
<td>Leuprolide Acetate</td>
<td>H-4060-GMP</td>
<td>&lt;EHWSYILRP-NH₂t</td>
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<tr>
<td>Triptorelin Acetate</td>
<td>H-4075-GMP</td>
<td>&lt;EHWSYwLRPG-NH₃ (Acetate)</td>
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<tr>
<td>Triptorelin Pamoate</td>
<td>H-6150-GMP</td>
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# IMPURITIES OF THE LEUPROLELIN PH. EUR. MONOGRAPH

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<tr>
<th>Impurity A</th>
<th>(D-Ser⁴)-Leuprolide</th>
<th>H-6168</th>
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<tr>
<td>Impurity B</td>
<td>(D-His²)-Leuprolide</td>
<td>H-4316</td>
<td>&lt;EHWSYILRP-NH₂t</td>
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<td>Impurity C</td>
<td>(Leu⁶)-Leuprolide</td>
<td>H-6402</td>
<td>&lt;EHWSYLLRP-NH₂t</td>
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<tr>
<td>Impurity D</td>
<td>(Ser(Ac)⁴)-Leuprolide</td>
<td>H-6172</td>
<td>&lt;EHWS(Ac)YLRP-NH₂t</td>
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<td>Impurity E</td>
<td>(D-Trp³)-Leuprolide</td>
<td>H-6636</td>
<td>&lt;EHWSYILRP-NH₂t</td>
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<tr>
<td>Impurity F</td>
<td>(D-His²,D-Ser⁴)-Leuprolide</td>
<td>H-6638</td>
<td>&lt;EHWSYILRP-NH₂t</td>
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<tr>
<td>Impurity G</td>
<td>(D-Tyr⁵)-Leuprolide</td>
<td>H-4638</td>
<td>&lt;EHWSYILRP-NH₂t</td>
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<td>Impurity H</td>
<td>(D-Leu⁷)-Leuprolide</td>
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<td>&lt;EHWSYILRP-NH₂t</td>
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<tr>
<td>Impurity I</td>
<td>(D-Pyr³)-Leuprolide</td>
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**IMPURITIES OF THE GOSERELIN PH. EUR. MONOGRAPH**

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<tr>
<th>Impurity B</th>
<th>(Ser(tBu)⁹)-Goserelin</th>
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<tr>
<th>Impurity E</th>
<th>(Pro-NHNH₂⁹)-Buserelin</th>
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<table>
<thead>
<tr>
<th>Impurity F</th>
<th>(D-Tyr⁵)-Goserelin</th>
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<tr>
<th>Impurity G</th>
<th>(D-His⁴)-Goserelin</th>
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**IMPURITIES OF THE BUSERELIN PH. EUR. MONOGRAPH**

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<tbody>
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<tr>
<th>Impurity B</th>
<th>(D-Ser⁴)-Buserelin</th>
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<thead>
<tr>
<th>Impurity D</th>
<th>(D-Tyr⁵)-Buserelin</th>
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<tbody>
<tr>
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<th>Impurity E</th>
<th>(D-Pyr¹)-Buserelin</th>
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**SOMATOSTATIN AND AGONISTS**

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<tr>
<th>Somatostatin</th>
<th>H-1490-GMP</th>
<th>&lt;EhWYSys(tBu)-LRP-NHEt</th>
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<th>Lanreotide</th>
<th>H-9055-GMP</th>
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<table>
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<tr>
<th>Octreotide Acetate</th>
<th>H-5972-GMP</th>
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</table>

| Pasireotide Acetate* | 4047875 | <eHWSYSys(tBu)-LRP-NHEt |

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