ANTIMICROBIAL PEPTIDES

BACHEM

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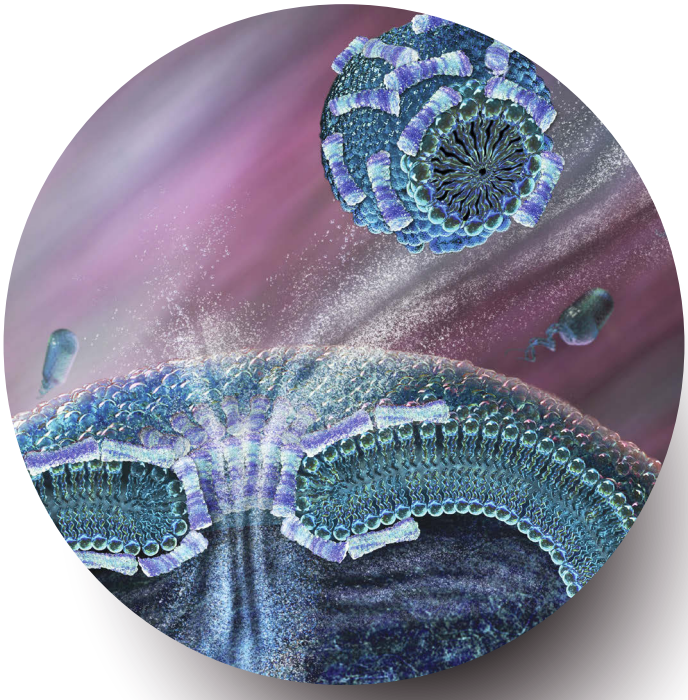

ANTIMICROBIAL PEPTIDES OFFERED BY BACHEM

Ribosomally synthesized antimicrobial peptides (AMPs) constitute a structurally diverse group of molecules found virtually in all organisms. Most antimicrobial peptides contain less than 100 amino acid residues, have a net positive charge, and are membrane active. They are major players in the innate immune defense but can also have roles in processes as chemokine induction, chemotaxis, inflammation, and wound healing. In addition to their antimicrobial effects, many of them show antiviral and antineoplastic activities.

INTRODUCTION

AMPs are a heterogeneous group of relatively small molecules usually containing less than a hundred amino acids. They were first described in the 1960's by Zeya and Spitznagel in polymorphonuclear leukocyte lysosomes.
To date, more than 2600 AMPs have been identified and registered in databases (e.g. http://aps.unmc.edu/AP/main.php). They are produced by nearly all groups of organisms, including bacteria, fungi, plants, and animals. Many vertebrate AMPs are secreted by epithelial surfaces such as the tracheal, lingual, or intestinal mucosa of mammals or the skin of amphibia. Some are expressed in neutrophils, monocytes, and macrophages.
AMPs are involved in both animal and plant immune defense systems. Constitutively expressed or induced they play a key role in the first line of defense against microbial intruders.

Structure/Classification
AMPs can be classified on the basis of their amino acid composition and structure. Two major groups of AMPs can be distinguished. The first group consists of linear molecules which either tend to adopt α-helical structure or are enriched in certain amino acids such as arginine, glycine, histidine, proline, and tryptophan. The second group consists of cysteine-containing peptides which can be divided into single or multiple disulfide structures. In many cases, the presence of disulfide bridges is required for antimicrobial activity.
Most AMPs are cationic peptides, but there are also anionic peptides such as dermcidin, an aspartic acid-rich peptide from human and maximin H5 from amphibian skin. Other non-cationic AMPs include fragments from neuropeptide precursor molecules such as proenkephalin A, aromatic dipeptides primarily isolated from dipteran larvae, or peptides derived from oxygen-binding proteins from arthropod or annelid species.

Mode of Action
Most AMPs act by provoking an increase in plasma membrane permeability. They preferentially target microbial versus mammalian cells. Selectivity is influenced by several factors such as differences in membrane composition: membranes of many bacterial pathogens contain negatively charged lipid moieties such as phosphatidylglycerol (PG), cardiolipin, and phosphatidylserine (PS), whereas mammalian membranes, commonly enriched in phosphatidylethanolamine (PE), phosphatidylcholine (PC) and sphingomyelin, are generally neutral in net charge. The presence of sterols such as cholesterol and ergesterol within the membrane may be a further means by which AMPs can distinguish between mammalian or fungal cells and prokaryotes.
A first step in the mechanism of membrane permeabilization is the electrostatic interaction between the positively charged AMP with the negatively charged membrane surface of the microorganism. Subsequent disruption of the membrane by creation of pores within the microbial membrane ultimately results in cell death of the organism due to leakage of ions, metabolites, cessation of membrane-coupled respiration, and biosynthesis. Several models for pore formation such as the Barrel-Stave, the Toroidal or Wormhole Model, and the Carpet Model have been proposed (Fig. 1).

The Barrel-Stave Model
The Barrel-Stave model describes a mechanism in which AMPs form a barrel-like pore within the bacterial membrane with the individual AMPs or AMP complexes being the staves. Arranged in this manner, the hydrophobic regions of the AMPs point outwards towards the acyl chains of the membrane whereas the hydrophilic areas form the pore.

other example for changing the surface net charge is the production of cationic lysine-substituted phosphatidylglycerol (L-PG) found in certain *Staphylococcus aureus* strains. In Gram-negative bacteria, addition of 4-aminoarabinose (Ara4N) to the phosphate group of the lipid A backbone or increased acylation of lipopolysaccharides (LPS) are important mechanisms of AMP resistance.

MOST AMPs ACT BY PROVOKING AN INCREASE IN PLASMA MEMBRANE PERMEABILITY

The Toroidal Pore or Wormhole Model
The pores described by this model differ from those of the Barrel-Stave model. Primarily, the outer and inner leaflet of the membrane are not intercalated in the transmembrane channel.

The Carpet Model
A different mechanism is proposed in the Carpet model where AMPs first cover the outer surface of the membrane and then disrupt the membrane like detergents by forming micelle-like units.

Certain AMPs penetrate the bacterial membrane without channel formation. They act on intracellular targets by e.g. inhibiting nucleic acid and/or protein synthesis.

Resistance
Resistance to AMPs can either be constitutive or inducible. Inherited resistance mechanisms include altered surface charge, active efflux, production of peptidases or trapping proteins, and modification of host cellular processes. For instance, *Staphylococcus aureus* manages to reduce the overall cell surface charge by esterification of the cell wall component teichoic acid with D-alanine and thereby increases its resistance against human AMPs. An-

Exposure to AMPs may also induce stress responses by which microorganisms try to survive. Inducible regulatory mechanisms have been described in a variety of organisms. For instance, the PhoP/PhoQ regulon in *Salmonella* has been demonstrated to regulate transcriptional activation of surface and secretory proteins, enzymes that modify lipopolysaccharide, lipid and protein constituents of the outer membrane and proteases that likely degrade certain AMPs.

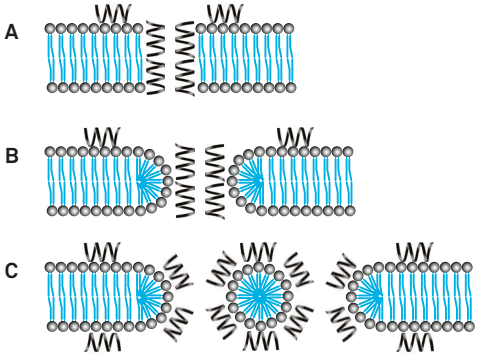

Fig. 1.
Mode of Action

A Barrel-Stave Model
B Toroidal Pore or Wormhole Model
C Carpet Model

	Examples
Linear cationic α-helical peptides	Andropin from insects Bombinin from amphibians Buforin II from amphibians CAP18 from rabbits Cepropins from insects Cecropin P1 from the pig intestinal parasitic nematode, *Ascaris suum* Ceratotoxin from insects Dermaseptin from amphibians LL-37 from human Magainin from amphibians Melittin from insects Pleurocidin from *Pseudopleuronectes americanus*
Cationic peptides enriched for specific amino acids	
Glycine-containing peptides	Hymenoptaecin from honeybees
Glycine- and proline-containing peptides	Coleoptericin from beetles Holotricin from beetles
Histidine-containing peptides	Histatins from humans and some higher primates
Proline-containing peptides	Abaecin from honeybees
Proline- and arginine-containing peptides	Apidaecins from honeybees Bactenicins from cattle Drosocin from *Drosophila* PR-39 from pigs
Proline- and phenylalanine-containing peptides	Prophenin from pigs
Tryptophan-containing peptides	Indolicidin from cattle
Anionic and cationic peptides that contain cysteine and form disulfide bonds	
1 Disulfide bond	Brevinins
2 Disulfide bonds	Protegrins from pigs
3 Disulfide bonds	α-Defensins from human, rabbits and rats β-Defensins from humans, cattle, mice, rats, pigs, goats and poultry θ-Defensin from the rhesus monkey Insect defensins (Defensin-A from *Aedes aegypti*)
4 Disulfide bonds	Antifungal defensins from plants Drosomycin from *Drosophila*
Anionic peptides	Dermcidin from human skin Maximin H5 from amphibian skin
Anionic and cationic peptide fragments derived from precursor proteins	Antimicrobial domains from bovine α-lactalbumin, human hemoglobin, lysozyme, and ovalbumin Aromatic dipeptides from dipteran larvae Casocidin I from human casein Enkelytin from proenkaphalin A Lactoferricin from lactoferrin

adapted from K.A. Brogden, Nat. Rev. Microbiol. 3, 238-250 (2005)

IMPORTANT FAMILIES OF AMPs

Bombinins
Bombinins constitute a family of AMPs produced in fire-bellied toads (*Bombina* species) active against Gram-negative and Gram-positive bacteria and fungi. Bombinins, bombinin-like peptides (BLPs), and Bombinin H molecules are found in the species *Bombina bombina*, *Bombina variegata*, and *Bombina orientalis*, whereas the homologous maximins and maximin H peptides are derived from the giant fire-bellied toad *Bombina maxima*.
Bombinin H peptides contain either 17 or 20 amino acid residues and are more hydrophobic than bombinins, some of them contain D-alloisoleucine at position 2. They exhibit lower antibacterial activity than bombinins but, in contrast to them, they possess haemolytic activity.

Cathelicidins
Members of this family are amphipathic, cationic peptides with a broad-spectrum antimicrobial activity. Cathelicidins typically act by disrupting the integrity of bacterial membranes. They are characterized by an evolutionary conserved N-terminal cathelin-like domain of approximately 99-114 amino acid residues linked to a C-terminal antimicrobial domain of 12-100 residues that can be released upon proteolytic processing.
Members of this family include linear peptides amongst them a number of proline-rich AMPs that show different types of proline repeat motifs (Bac5, Bac7, PR-39, prophenins) and the tryptophan-rich indolicidin characterized by three regularly spaced proline residues.
The protegrins (PG-1 to PG-5) contain two disulfide bridges and an amidated C-terminus.
Cathelicidins have been found in every mammalian species examined. In human, LL-37 (Product H-7298) is the only member of the cathelicidin family. The peptide consists of 37 amino acids and contains two leucine residues at the N-terminus. It is proteolytically cleaved from the 18 kDa precursor protein human cathelicidin antimicrobial protein CAP-18. LL-37 is primarily produced by phagocytic leucocytes and epithelial cells, and is involved in various processes such as direct killing of microorganisms, binding and neutralizing LPS, chemotaxis and chemokine induction, regulation of inflammatory responses, and wound healing. Its production is influenced by several factors such as microbial products, host cytokines, vitamin D_3, and availability of oxygen.
LL-37 orthologues in mouse and rat are CRAMP (mouse) (Product H-6526) and CRAMP (rat), respectively.

Cecropins
Cecropins were first isolated from the giant silk moth *Hyalophora cecropia*. They can form amphipathic, α-helical structures and are structurally related to other cecropins as bactericidin, lepidopteran, and sarcotoxin. Cecropin P1 (Product H-5718), found in pig intestine, also belongs to this family.
Most cecropins show broad-spectrum antibacterial activity. Cecropin A (Product H-3094) and B (Product H-3096) have also been demonstrated to possess tumoricidal activity against mammalian leukemia, lymphoma, and carcinoma cell lines.

Ceratotoxins
This family consists of cationic α-helical amphipathic peptides expressed in the female reproductive accessory glands of the Mediterranean fruit fly *Ceratitis capitata*.
The production of the peptides is enhanced by mating.
Ceratotoxin A and ceratotoxin B are 29 amino acid peptides differing in two amino acids. Ceratotoxin C and D consist of 32 and 36 amino acids, respectively.
The peptides of this family are active against Gram-negative as well as Gram-

positive bacteria and are supposed to act via the Barrel-Stave model. Ceratotoxin A has been shown to be mainly antibacterial for Gram-negative organisms.

Defensins
Defensins are small cysteine-rich cationic peptides containing three or four disulfide bridges. They have been isolated from molluscs, acari, arachnids, insects, mammals, and plants. They are further divided into families on the basis of the spatial distribution of their cysteine residues.
Three families, the α-, β- and θ-defensins, can be distinguished in mammals. α- and β-defensins are characterized by antiparallel β-sheet structures stabilized by three disulfide bonds. The θ-defensins are found in rhesus monkey and some other non-human primates but not in human, chimpanzee and gorilla. They consist of two nine amino acid peptides derived from different precursor proteins joined by head-to-tail cyclization. Invertebrate and plant defensins contain three or four disulfide bridges, respectively. Insect and mammalian defensins are mainly active against bacteria while most plant defensins possess antifungal activity.

Dermaseptins
The peptides of the dermaseptin family are closely related and consist of 28-34 amino acids. They were originally isolated from skin extracts of the South American arboreal frog *Phyllomedusa sauvagei* and contain a conserved tryptophan residue at position 3. Dermaseptins exhibit broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria.

Histatins
Histatins are histidine-rich and mostly cationic peptides found in the saliva of humans and some higher primates. They are active against a broad-spectrum of bacteria and fungi.
The antifungal activity of the human salivary peptide histatin-5 has been extensively studied and is supposed to be due to inhibition of mitochondrial respiration and the formation of reactive oxygen species. Histatin-5 has also been shown to inhibit both host-derived and bacterial proteolytc enzymes involved in peridontal diseases.
Histatin-8 (Product H-1422), a peptide from human parotid secretion, has been shown to inhibit hemagglutination activity of *Porphyromonas gingivalis* 381, a Gram-negative bacterium involved in certain forms of periodontal disease. The peptide may function as a binding domain for the hemagglutinins of *Porphyromonas gingivalis* during agglutination.

Magainins
Magainins constitute a family of linear amphipathic cationic AMPs discovered in the skin of *Xenopus laevis*. The two closely related members of this family, magainin I (Product H-6565) and magainin II (Product H-6570) differ merely in two positions and are 23 amino acids in length. Magainins exhibit broad-spectrum antimicrobial activity against Gram-negative and Gram-positive bacteria, fungi and protozoa and are also cytotoxic for many murine and human cancer cell lines.

CONCLUSIONS

The structures of AMPs represent a unique source for the targeted exploration of new applications in the therapy of microbial and viral infection, cancer, and sepsis. Modern synthetic methods will allow the relatively cheap and accurate production of lead compounds and peptide candidates. The achievements in peptide library generation, analytical methods as mass spectrometry, and screening and formulation technologies may contribute to solve intrinsic problems associated with the use of AMPs as therapeutic agents such as susceptibility to proteases and host toxicity.
Bachem has considerable expertise and long-standing experience in peptide synthesis. With our capacity to upscale the production of simple and modified peptides, we are the partner of choice for the pharmaceutical industries.

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ANTIMICROBIAL PEPTIDES

Antimicrobial peptides are produced by plants and most organisms throughout the animal kingdom including humans. AMPs protect against a broad range of infectious agents, as bacteria, fungi, and viruses.

CATHELIN-RELATED ANTIMICROBIAL (CRAMP) PEPTIDES

CRAMP (mouse)
H-6526
GLLRKGGEKIGEKLK-KIGQKIKNFFQKLVPQPEQ

CRAMP-18 (mouse)
H-6528
GEKLKKIGQKIKNFFQKL

CECROPINS

Cecropin A
H-3094
KWKLFKKIEKVGQNIRDGIIKAGPAVAV-VGQATQIAK-NH_2

Cecropin A (1-7)-Melittin A (2-9) amide
H-5948
KWKLFKKIGAVLKVL-NH_2

Cecropin A (1-8)-Melittin (1-18) amide
H-4314
KWKLFKKIGIGAVLKVLTTGLPALIS-NH_2

Cecropin B
H-3096
KWKVFKKIEKMGRNIRNGIVKAGPAIAVL-GEAKAL-NH_2

Cecropin B (free acid) NEW
H-7696
KWKVFKKIEKMGRNIRNGIVKAGPAIAVL-GEAKAL

Cecropin P1
H-5718
SWLSKTAKKLENSAKKRISEGIAIAIQG-GPR

DEFENSINS

Corticostatin I (rabbit)
(Defensin NP 3A (rabbit))
H-9045
GICACRRRFCPNSERFSGYCRVNGA-RYVRCCSRR
(Disulfide bonds between Cys^3 and Cys^{31}/Cys^5 and Cys^{20}/Cys^{10} and Cys^{30})

α-Defensin 6
H-6566
AFTCHCRRSCYSTEYSYGTCTVMGINHRF-CCL
(Disulfide bonds between Cys^4 and Cys^{31}/Cys^6 and Cys^{20}/Cys^{10} and Cys^{30})

Defensin HNP-1 (human)
H-9855
ACYCRIPACIAGERRYGTCIYQGRLWAFCC
(Disulfide bonds between Cys^2 and Cys^{31}/Cys^4 and Cys^{19}/Cys^9 and Cys^{29})

Defensin HNP-2 (human)
H-9005
CYCRIPACIAGERRYGTCIYQGRLWAFCC
(Disulfide bonds between Cys^1 and Cys^{29}/Cys^3 and Cys^{18}/Cys^8 and Cys^{28})

Defensin HNP-3 (human)
H-9860
DCYCRIPACIAGERRYGTCIYQGRLWAFCC
(Disulfide bonds between Cys^2 and Cys^{30}/Cys^4 and Cys^{19}/Cys^9 and Cys^{29})

rec β-Defensin 1 (human)
H-5584

β-Defensin 2 (human) NEW
H-8256
GIGDPVTCLKSGAICHPVFCPRRYKQI-GTCGLPGTKCCKKP
(Disulfide bonds, air oxidized)

rec β-Defensin 2 (human)
H-5586

Retrocyclin-1 (RC-100)
H-6126
c(GICRCICGRGICRCICGR)
(Disulfide bonds between Cys^3 and Cys^{16}/Cys^5 and Cys^{14}/Cys^7 and Cys^{12})

HEPCIDINS

Hepcidin-20 (human)
H-7358
ICIFCCGCCHRSKCGMCCKT
(Disulfide bonds, air oxidized)

Hepcidin-22 (human)
H-7362
FPICIFCCGCCHRSKCGMCCKT
(Disulfide bonds, air oxidized)

Hepcidin-24 (human)
H-7378
THFPICIFCCGCCHRSKCGMCCKT
(Disulfide bonds, air oxidized)

Hepcidin-25 (human)
H-5926
DTHFPICIFCCGCCHRSKCGMCCKT
(Disulfide bonds between Cys^{7} and Cys^{23}/Cys^{10} and Cys^{13}/Cys^{14} and Cys^{22})

Biotinyl-Hepcidin-25 (human)
H-6674
Biotinyl-DTHFPICIFCCGCCHRSKC-GMCCKT
(Disulfide bonds between Cys^{7} and Cys^{23}/Cys^{10} and Cys^{13}/Cys^{14} and Cys^{22})

Hepcidin-1 (mouse)
H-7364
DTNFPICIFCCKCCNNSQCGICCKT
(Disulfide bonds between Cys^{7} and Cys^{23}/Cys^{10} and Cys^{22}/Cys^{11} and Cys^{19}/Cys^{13} and Cys^{14})

LL-37 AND FRAGMENTS

LL-37
H-7298
LLGDFFRKSKEKIGKEFKRIVQRIKDFL-RNLVPRTES

LL-37 (37-1) NEW
H-7898
SETRPVLNRLFDKIRQVIRKFEKGIKEK-SKRFFDGLL

Biotinyl-LL-37 NEW
H-7906
Biotinyl-LLGDFFRKSKEKIGKE-FKRIVQRIKDFLRNLVPRTES

Biotinyl-εAhx-LL-37 (scrambled) NEW
H-7896
Biotinyl-εAhx-GLKLRFEFSKIKGEFLKTP EVRFRDIKLKDNRISVQR

LL-37 amide
H-6224
LLGDFFRKSKEKIGKEFKRIVQRIKDFL-RNLVPRTES-NH_2

Biotinyl-LL-37 amide
H-6692
Biotinyl-LLGDFFRKSKEKIGKE-FKRIVQRIKDFLRNLVPRTES-NH_2

5-FAM-LL-37 (scrambled) NEW
H-7888
5-FAM-GLKLRFEFSKIKGEFLKTPEVR-FRDIKLKDNRISVQR

Tyr-LL-37 NEW
H-7902
YLLGDFFRKSKEKIGKEFKRIVQRIKDFL-RNLVPRTES

LL-37 FK-13 NEW
H-7868
FKRIVQRIKDFLR

LL-37 FKR NEW
H-7874
FKRIVQRIKDFLRNLVPRTES

LL-37 GKE NEW
H-7872
GKEFKRIVQRIKDFLRNLVPR

LL-37 LLG NEW
H-7878
LLGDFFRKSKEKIGKEFKRIV

ANTIBIOTIC DESTROYING BACTERIA

Computer illustration showing antimicrobial peptides penetrating a bacterium's membrane (lower centre) according to the carpet model. A micelle forms from the microbial lipid bilayer (the fatty molecules), and the cell is punctured.

KEYSTONE/SCIENCE PHOTO LIBRARY/ NICOLLE R. FULLER

LL-37 RKS NEW
H-7882
RKSKEKIGKEFKRIVQRIKDFL-RNLVPRTES

LL-37 SKE NEW
H-7884
SKEKIGKEFKRIVQRIKDFLR

KR-12 (human)
H-6688
KRIVQRIKDFLR-NH_2

Biotinyl-KR-12 (human)
H-7904
KRIVQRIKDFLR

MAGAININS

Magainin I
H-6565
GIGKFLHSAGKFGKAFVGEIMKS

Magainin II
H-6570
GIGKFLHSAKKFGKAFVGEIMNS

MELITTINS

Cecropin A (1-7)-Melittin A (2-9) amide
H-5948
KWKLFKKIGAVLKVL-NH_2

Cecropin A (1-8)-Melittin (1-18) amide
H-4314
KWKLFKKIGIGAVLKVLTTGLPALIS-NH_2

Melittin
H-4310
GIGAVLKVLTTGLPALISWIKRKRQQ-NH_2

Melittin (free acid) NEW
H-7646
GIGAVLKVLTTGLPALISWIKRKRQQ

PSEUDIN PEPTIDES AND ANALOGS

Pseudin-2
H-6586
GLNALKKVFQGIHEAIKLINNHVQ

(Lys^{18})-Pseudin-2
H-6588
GLNALKKVFQGIHEAIKKINNHVQ

TUFTSIN AND ANALOGS

Macrophage Inhibitory Peptide
(Tuftsin (1-3))
H-4300
TKP

H-Thr-Lys-Pro-Pro-Arg-OH
H-5045
TKPPR

Tuftsin
H-5035
TKPR

(3,4-Dehydro-Pro^3)-Tuftsin
H-8515
TKΔPR

(Lys(Z)^2)-Tuftsin
H-5025
TK(Z)PR

MISCELLA-NEOUS

ACV
H-4204
Aad(Cv)

Bis-ACV
H-6015
$(Aad(Cv))_2$

Bactenecin
H-9585
RLCRIVVIRVCR
(Disulfide bond)

Beauvericin
H-2135
Cyclo(-D-α-hydroxyisovaleryl-N-Me-Phe)$_3$

Cyclo(-Leu-Pro)
G-1750
c(LP)

Dermaseptin
H-1294
ALWKTMLKKLGTMALHAGKAAL-GAAADTISQGTQ

Dermcidin-1L (human)
H-7316
SSLLEKGLDGAKKAVGGLGKLGK-DAVEDLESVGKGAVHDVKDVLDSVL

Endotoxin Inhibitor
H-1382
KTKCKFLKKC
(Disulfide bond)

Epinecidin-1
H-7228
GFIFHIIKGLFHAGKMIHGLV-NH_2

Extracellular Death Factor
H-6592
NNWNN

Histatin-8
H-1422
KFHEKHHSHRGY

IDR-1
H-6518
KSRIVPAIPVSLL-NH_2

Indolicidin
H-1234
ILPWKWPWWPWRR-NH_2

Lactoferricin B (4-14) (bovine) NEW
H-7688
RRWQWRMKKLG

Lactoferricin B25
H-7388
FKCRRWQWRMKKLGAPSITCVRRAF
(Disulfide bond)

Lysozyme C (46-61) (chicken)
H-6024
NTDGSTDYGILQINSR

Parasin I
H-4542
KGRGKQGGKVRAKAKTRSS

Penetratin
H-7514
RQIKIWFQNRRMKWKK-NH_2

Ranalexin
H-1612
FLGGLIKIVPAMICAVTKKC
(Disulfide bond)

Sapecin
H-2246
ATCDLLSGTGINHSACAAHCLLRGNRG-GYCNGKAVCVCRN
(Disulfide bonds between Cys^3 and Cys^{30}/Cys^{16} and Cys^{36}/Cys^{20} and Cys^{38})

Seminalplasmin Fragment (SPF) Analog
H-1636
PKLLKTFLSKWIG

Tachyplesin I
H-1202
KWCFRVCYRGICYRRCR-NH_2
(Disulfide bonds between Cys^3 and Cys^{16}/Cys^7 and Cys^{12})

H-Tyr-Ser-Pro-Trp-Thr-Asn-Phe-OH
(RIP (free acid))
H-5296
YSPWTNF

BACHEM

PIONEERING PARTNER FOR PEPTIDES

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