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**TITLE: NOVEL PEPTIDE, A METHOD FOR ITS PREPARATION AND A
PHARMACEUTICAL COMPOSITION CONTAINING THE PEPTIDE**

FIELD OF THE INVENTION

5 The invention relates to a biologically active peptide; a novel pharmaceutical composition containing the peptide; a method for preparing the peptide; and, uses of the peptide.

BACKGROUND OF THE INVENTION

10 Hormones are known to control the metabolic processes both in growing and mature organisms. Peptides often act as hormones. They are not only hormonally active themselves but regulate the action of other hormones, which control the vital activity of the organism. However, the potential of such natural compounds is limited. Therefore, many scientific laboratories have tried to develop methods for preparing
15 synthetic derivatives of natural peptides, which are more active than their natural analogues (EP 0136720, 1984; EP 0137904, 1984). Moreover, new peptides have been synthesized, which are absent in the organism but have unique properties. Among them there is a special group of physiologically active peptides directly or indirectly controlling the action
20 of hormones such as the growth hormone. Some of these active peptides increase the growth hormone level in blood (PCT 89/07111, 1989; PCT 91/16923, 1991) while others suppress the hormone (FR 2235701, 1978; FR 2532308, 1982).

25 A peptide which activates the growth of the epidermal layer in man (PCT 90/13570, 1990), and a metal-containing peptide, which has a significant stimulating effect on hair growth in warm-blooded animals (PCT 91/07431, 1991) have been synthesized. Another peptide analogue has been reported to facilitate hair removal in animals (FR 2487677, 1982).

30 Different peptide compositions evidently make it possible to control metabolic processes. The most promising task is, however, the development of compounds and preparations with many-sided actions.

 At present, there are only a few peptides with comprehensive

action, for instance, the analogue of the P substance described in U.S. Patent No. 4,680,283. The peptide synthesized as described in the patent has a range of useful properties. It acts as a biostimulator, and has an analgesic effect similar to that of morphine.

5 Many studies have shown the importance of synthesizing peptides with opiate-like properties. Unfortunately, the production of morphine-like compounds from natural sources is limited by the complexity of the manufacturing processes (US 4,042,682, 1977). This circumstance became a reason for creating an arsenal of synthetic analogues (US 4,681,871, 1987; 10 EP 0112036, 1983; EP 0221019, 1986).

Some opiate-like peptides have become known and clinically used in the treatment of brain ischemia (DE 3447720, 1985; US 4,684,624, 1987), for pain relief in pregnant women (EP 0099173, 1984), and only as analgesics. They are reported to be especially effective when used in 15 combination with conventional drug therapy in many diseases (EP 096592, 1983; EP 0099286, 1984; US 4,123,523, 1987).

However, the known synthetic peptides cannot completely satisfy all medical requirements, since they do not have the necessary combination of properties, which would increase their effectiveness. 20 Furthermore, many of them are effective only in large doses that can cause side effects.

SUMMARY OF THE INVENTION

The present inventor has identified a peptide which has a wide range of biological action. In particular, the peptide has been found to 25 influence physiological processes such as weight gain, activities of the epithelium growth zone, hair growth, wound healing, and to stimulate reparative and anabolic processes, and exert analgesic effects.

Broadly stated the present invention relates to a peptide of the formula I

30 X-Tyr-Y-Phe-Z-A I

wherein X is hydrogen, arginine, D-arginine, ornithine, D-ornithine,

lysine, D-lysine, homoarginine, D-homoarginine, citrulline, D-citrulline; Tyr is tyrosine; Y is D-alanine, D-valine, D-leucine, D-isoleucine, D-phenylalanine, D-asparagine, D-tryptophan, D-proline, D-serine, D-threonine, D-tyrosine, D-hydroxyproline, D-cysteine, D-cysteyl-cysteine, D-methionine, D-lysine, D-homoarginine, D-arginine, D-histidine, D-aspartic acid, D-glutamic acid, D- β -alanine, or D-ornithine; Phe is phenylalanine; Z is alanine, D-alanine, valine, D-valine, leucine, D-leucine, isoleucine, D-isoleucine, phenylalanine, D-phenylalanine, asparagine, D-asparagine, glycine, glutamine, D-glutamine, tryptophan, D-tryptophan, proline, D-proline, serine, D-serine, threonine, D-threonine, tyrosine, D-tyrosine, hydroxyproline, D-hydroxyproline, cysteine, D-cysteine, cysteyl-cysteine, cysteine-D-cysteine, D-cysteine-cysteine, D-cysteine-D-cysteine, methionine, D-methionine, lysine, D-lysine, arginine, D-arginine, histidine, D-histidine, aspartic acid, D-aspartic acid, glutamic acid, D-glutamic acid, β -alanine, D- β -alanine, ornithine, or D-ornithine; and A is hydroxyl or substituted amide ($C_1 - C_3$).

The invention also relates to analogs of the peptides of the invention and cyclized peptides. The term "peptide" or "peptides" used herein includes these analogs and cyclized peptides.

The invention also relates to a pharmaceutical composition comprising one or more peptides of the invention and a pharmaceutically acceptable carrier.

The invention still further relates to the use of a peptide of the Formula I to modulate physiological processes such as weight gain, activities of the epithelium growth zone, hair growth, wound healing, and to stimulate reparative and anabolic processes, and exert analgesic effects.

Further, the invention relates to a method of modulating physiological processes such as weight gain, activities of the epithelium growth zone, hair growth, and wound healing. The invention also

relates to a method of stimulating reparative and anabolic processes, and exerting analgesic effects.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned previously, the present invention relates to a peptide of the formula I



wherein X is hydrogen, arginine, D-arginine, ornithine, D-ornithine, lysine, D-lysine, homoarginine, D-homoarginine, citrulline, D-citrulline; Tyr is tyrosine; Y is D-alanine, D-valine, D-leucine, D-isoleucine, D-phenylalanine, D-asparagine, D-tryptophan, D-proline, D-serine, D-threonine, D-tyrosine, D-hydroxyproline, D-cysteine, D-cysteyl-cysteine, D-methionine, D-lysine, D-homoarginine, D-arginine, D-histidine, D-aspartic acid, D-glutamic acid, D- β -alanine, or D-ornithine; Phe is phenylalanine; Z is alanine, D-alanine, valine, D-valine, leucine, D-leucine, isoleucine, D-isoleucine, phenylalanine, D-phenylalanine, asparagine, D-asparagine, glycine, glutamine, D-glutamine, tryptophan, D-tryptophan, proline, D-proline, serine, D-serine, threonine, D-threonine, tyrosine, D-tyrosine, hydroxyproline, D-hydroxyproline, cysteine, D-cysteine, cysteyl-cysteine, cysteine-D-cysteine, D-cysteyl-cysteine, D-cysteine-D-cysteine, methionine, D-methionine, lysine, D-lysine, arginine, D-arginine, histidine, D-histidine, aspartic acid, D-aspartic acid, glutamic acid, D-glutamic acid, β -alanine, D- β -alanine, ornithine, or D-ornithine; and, A is hydroxyl or substituted amide ($\text{C}_1 - \text{C}_3$). A preferred peptide of the invention comprises Arg-Tyr-D-Ala-Phe-

Gly.

The following standard abbreviations for the amino acid residues are used throughout the specification: Ala - alanine; Cys - cysteine; Asp - aspartic acid; Glu - glutamic acid; Phe - phenylalanine; Gly - glycine; His - histidine; Ile - isoleucine; Lys - lysine; Leu - leucine; Met - methionine; Asn - asparagine; Pro - proline; Gln - glutamine; Arg - arginine; Ser - serine; Thr - threonine; Val - valine; Trp - tryptophan; Tyr - tyrosine; and Orn - ornithine.

The peptides of the invention may also include analogs of the peptide of the Formula I which may include, but are not limited to the peptide of the Formula I containing one or more amino acid insertions. Amino acid insertions may consist of a single amino acid residue or sequential amino acids. Analogs of the peptide of the invention exhibit the activity characteristic of the peptide and may further possess additional advantageous features such as increased bioavailability, stability, or reduced host immune recognition.

The invention further includes cyclic derivatives of the peptides of the invention. Cyclization allows the peptide to assume a more favorable conformation. Cyclization of the peptides may be achieved using techniques known in the art. In particular, disulfide bonds may be formed between two appropriately spaced components having free sulfhydryl groups. The bonds may be formed between side chains of amino acids, non-amino acid components or a combination of the two.

The invention also includes a peptide of the invention conjugated with a selected protein, or a selectable marker (see below) to produce fusion proteins:

Peptides of the invention may be converted into pharmaceutical salts by reacting with inorganic acids including hydrochloric acid, sulfuric acid, hydrobromic acid, phosphoric acid, etc., or organic acids including formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic

acid, salicylic acid, benzenesulfonic acid, and toluenesulfonic acids.

5 The peptides of the invention may be prepared using recombinant techniques. Nucleic acid molecules which encode a peptide of the invention may be incorporated in a known manner into an expression vector which ensures good expression of the peptide. Suitable expression
10 vectors include but are not limited to cosmids, plasmids, or modified viruses so long as the vector is compatible with the host cell used. The expression vectors contain a nucleic acid molecule encoding a peptide of the invention and regulatory sequences necessary for the transcription and translation of the inserted protein-sequence. Regulatory sequences
15 may be obtained from a variety of sources, such as bacterial, fungal, viral, mammalian, or insect genes (See the regulatory sequences described in Goeddel, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA (1990). The selection of regulatory sequences is dependent on the host cell chosen, and may be readily accomplished by one of ordinary skill in the art. Sequences, including an origin of replication, additional DNA restriction sites, enhancers, and sequences conferring inducibility of transcription may also be incorporated into the expression vector.

20 A selectable marker gene which facilitates the selection of transformed or transfected host cells may also be included in the recombinant expression vector. Examples of selectable marker genes are genes encoding proteins such as G418 and hygromycin which confer resistance to certain drugs, β -galactosidase, chloramphenicol
25 acetyltransferase, and firefly luciferase. It will be appreciated that the selectable markers may be introduced on a separate vector from the nucleic acid.

30 Genes may also be included in the recombinant expression vectors which encode a fusion portion which provides increased expression of the recombinant peptide; increased solubility of the recombinant peptide; and/or aid in the purification of the recombinant peptide by acting as a

ligand in affinity purification. In particular, a proteolytic cleavage site may be inserted to allow separation of the recombinant peptide from the fusion portion after purification of the fusion protein.

5 A recombinant expression vector may be introduced into a host cell to produce a transformant host cell. Transformant host cells include prokaryotic and eukaryotic cells transformed or transfected with a recombinant expression vector of the invention. The terms "transformed with", "transfected with", "transformation" and "transfection" include the introduction of nucleic acid (e.g. a vector) into
10 a host cell by one of many techniques known in the art. Examples of methods for transforming and transfecting host cells may be found in Sambrook et al. (Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press (1989)), and other laboratory textbooks.

15 Suitable host cells include prokaryotic and eukaryotic host cells. In particular, the peptides of the invention may be expressed in bacterial cells such as *E. coli*, insect cells (using baculovirus), yeast cells or mammalian cells. Other suitable host cells are described in Goeddel, Gene Expression Technology: Methods in Enzymology 185, Academic
20 Press, San Diego, CA (1991).

In the alternative, the peptides of the invention may be prepared by chemical synthesis using techniques known in the chemistry of proteins such as solid phase synthesis (Merrifield, 1964, J. Am. Chem. Assoc. 85:2149-2154) or synthesis in homogenous solution (Houbenweyl,
25 1987, Methods of Organic Chemistry, ed. E. Wansch, Vol. 15 I and II, Thieme, Stuttgart).

According to an embodiment of the present invention, the peptide of the formula (I) is synthesized by step-by-step building of the peptide chain beginning with the C-terminal amino acid Z in the form of a
30 substituted amide or an amino acid with a protected carboxyl group. N-protected phenylalanine is then attached using the method of activated ethers or mixed anhydrides and the N-protecting group is removed. The

next amino acid is attached using the method of activated ethers or mixed anhydrides and detaching the N-protected group. The following N-protected amino acid is then added using the same procedure. When the chain building is completed, the tetra- or penta-peptide is deblocked, the peptide is obtained by hydrogenolysis in the presence of the Pd catalyst, and the final product is isolated. The peptide prepared using this process is a white powder with a yellowish or greyish tinge, soluble in water, substantially insoluble in alcohol and substantially insoluble in chloroform.

N-terminal or C-terminal fusion proteins comprising a peptide of the invention conjugated with other molecules such as proteins or selectable markers may be prepared by fusing, through recombinant techniques, the N-terminal or C-terminal of the peptide, and the sequence of a selected protein or selectable marker with a desired biological function. The resulting fusion proteins contain the peptide fused to the selected protein or marker protein as described herein.

Monoclonal or polyclonal antibodies specific for the peptides of the invention may be prepared using conventional methods. For example, the preparation of monoclonal antibodies can be carried out as described in Goding, J.W., *Monoclonal Antibodies: Principles and Practice*, 2nd Ed., Academic Press, London, 1986.

The peptides of the invention may be labelled using conventional methods with various enzymes, fluorescent materials, luminescent materials and radioactive materials. Suitable enzymes, fluorescent materials, luminescent materials, and radioactive material are well known to a person skilled in the art.

The present invention offers peptides that can be used for experimental purposes and in medicine. The peptides and pharmaceutical compositions containing the peptides have significant opiate-like effects and accordingly may be used as an analgesic, hypnotic, and diaphoric, and in spasmodic conditions. The peptides exhibit an anabolic effect: they increase body weight, stimulate the activity of the

growth zone and growth of the epidermal layer, including hair. The biostimulating properties of the claimed peptide are manifested in wound healing and reparative processes.

5 The peptides of the invention can be formulated into pharmaceutical compositions for administration to subjects in a therapeutically active amount and in a biologically compatible form suitable for administration *in vivo* i.e. a form of the peptides to be administered in which any toxic effects are outweighed by the therapeutic effects.

10 The peptides may be administered to humans and animals in a therapeutically active amount. A therapeutically active amount is defined as an amount of the active ingredient i.e. peptides, effective, at dosages and for periods of time necessary to achieve the desired result. A therapeutically active amount of a peptide may vary according to factors
15 such as the disease state, age, sex, and weight of the individual. Dosage regime may be altered to provide the optimum therapeutic response.

 The peptides may be administered by injection (subcutaneous, intravenous, etc.), oral administration, inhalation, transdermal application, or rectal administration, preferably by injection or oral
20 administration. Depending on the route of administration, the peptides in the pharmaceutical compositions may be coated in a material to protect them from the action of enzymes. Organic substances may also be included in the compositions to prolong the pharmacologic actions of the peptides. Examples of such organic substances include non-antigenic
25 gelatin, carboxymethylcellulose, sulfonate or phosphate ester of alginic acid, dextran, polyethylene glycol and other glycols, phytic acid, polyglutamic acid, and protamine.

 The pharmaceutical compositions of the invention can be prepared by per se known methods for the preparation of
30 pharmaceutically acceptable compositions which can be administered to subjects, such that an effective quantity of a peptide is combined in a mixture with a pharmaceutically acceptable vehicle. Examples of

pharmaceutically acceptable vehicles are described in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985).

5 Compositions for injection include, albeit not exclusively, the peptides in association with one or more pharmaceutically acceptable vehicles or diluents, and contained in buffered solutions with a suitable pH and iso-osmotic with the physiological fluids. Any pharmaceutically suitable diluent can be used in the composition for injections: distilled water, physiological or a salt solution, and/or a buffer solution. The
10 composition for injections may be prepared by conventional volume-weight procedure. A certain amount of the peptide is diluted to the necessary volume with a diluent or solvent. Then the solution is filtered through sterilized filters, bottled or ampouled. The resultant solution is a stable transparent liquid, and does not contain any chemical or other
15 impurities.

In a preferred embodiment of the invention, the composition generally contains 0.001 or 0.1% (preferably 0.001-0.01%) of the peptide. The percentage also depends on the medicinal form - solution or a solid form. The preferred pharmaceutical composition is made by mixing the
20 carrier and the peptide at the temperature of 40 - 70°C. The composition is stable in solution for 24 hours (3 years) at the temperature 70°C (20°C), respectively.

Solid form preparations for oral administration can be made in the form of tablets, powders, capsules. It may contain a medium for the
25 active substance and other additives, including dyes, aromas, etc. The peptide percentage may be from 0.001% to 0.1% and usually depends on the type of the composition for oral use.

The utility of the peptides and pharmaceutical compositions of the invention may be confirmed in *in vivo* animal experimental model
30 systems

The following non-limiting example is illustrative of the present invention:

EXAMPLE

Table I presents physical and chemical characteristics of some derivatives of the peptide (general structure I): R_{fA} in the system (butanol:acetic acid:water = 3:1:1), R_{fB} in the system (chloroform:methanol:32% acetic acid = 60:45:20) and $[\alpha]_D$.

Biological studies of the claimed peptide showed its comprehensive action. The peptide proved to be non-toxic. The peptide toxicity (LD_{50}) was studied in 24 white mice weighing 18 g. The animals received the same diet and were kept in the same conditions. Half of the animals in each group were male mice and the other half were female mice. Twenty-four hours before the experiment and during it the animals were housed in a vivarium with a constant temperature and ventilation. Two hours before the experiment the animals were deprived of water and food. The animals were divided into four groups, 6 mice each. Mice of groups 1, 2 and 3 were injected intraperitoneally with 0.2 ml of water solution of the peptide in the dose of 800, 1100 and 1400 mg/kg, respectively. Control animals (group 4) were injected with the same volume of physiological solution. The observation period lasted 7 days after the injections, then LD_{50} was calculated. No changes were observed in the animals' general state or behaviour both immediately after injections and throughout the observation period. The peptide injections did not cause pain syndromes. No animals died in the period. The animals had normal weight gains, weight factors of the organs varied within the physiological norm.

The results of the study showed that intraperitoneal injections of the peptide in the doses of 800, 1100 and 1400 mg/kg did not cause any toxic effect and even high doses of the peptide were well tolerated by the animals.

Having illustrated and described the principles of the invention in a preferred embodiment, it should be appreciated to those skilled in the art that the invention can be modified in arrangement and detail

without departure from such principles. We claim all modifications coming within the scope of the following claims.

5 All publications, patents and patent applications referred to herein are incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

Table 1

	R_{α}	R_{β}	$[\alpha]^{20}_D$ c=1, 10% AcOH
1	2	3	4
H- Arg-Tyr-D-Ala-Phe- Gly -OH	0,54	0,71	+43,0
H- Arg-Tyr-D-Orn-Phe- Gly -OH	0,19	0,25	+36,2
H- Arg-Tyr-D-Ala-Phe-D-Ala-OH	0,56	0,75	+47,0
H- Arg-Tyr-D-Orn-Phe-D-Ala-OH	0,16	0,74	+10,0
H- Arg-Tyr-D-Arg-Phe-D-Ala-OH	0,18	0,30	+43,8
H- Arg-Tyr-D-Arg-Phe-D-Ala-NH ₂	0,52	0,83	+40,7
H-D-Arg-Tyr-D-Arg-Phe-D-Ala-NH ₂	0,52	0,83	+ 5,0
H- Orn-Tyr-D-Ala-Phe-D-Ala-OH	0,58	0,81	+36,0
H-D-Orn-Tyr-D-Ala-Phe-D-Ala-OH	0,52	0,83	+ 5,0
H- Lys -Tyr-D-Lys-Phe- Gly -OH	0,15	0,23	+29,0
H-D-Lys-Tyr-D-Lys-Phe- Gly -OH	0,15	0,23	+ 3,5
H- Har -Tyr-D-Arg-Phe-D-Ala-NH ₂	0,51	0,84	+40,7
H-D-Har-Tyr-D-Arg-Phe-D-Ala-NH ₂	0,51	0,84	+17,1
H- Cyt -Tyr-D-Arg-Phe-D-Ala-NH ₂	0,48	0,62	
H-D-Cyt-Tyr-D-Arg-Phe-D-Ala-NH ₂	0,48	0,62	
H-Tyr-D-Ala-Phe- Gly -OH	0,56	0,70	+10,1
H-Tyr-D-Lys-Phe- Gly -OH	0,59	0,71	+30,3
H-Tyr-D-Har-Phe- Gly -OH	0,60	0,84	+24,7
H-Tyr-D-Orn-Phe- Gly -OH	0,57	0,71	+33,8
H-Tyr-D-Arg-Phe- Gly -OH	0,59	0,73	+27,0
H-Tyr-D-Orn-Phe-D-Glu-OH	0,55	0,73	+35,3
H-Tyr-D-Arg-Phe-D-Glu-OH	0,60	0,77	+27,7
H-Tyr-D-Orn-Phe-D-Ala-NH ₂	0,63	0,80	+10,6
H-Tyr-D-Arg-Phe-D-Ala-NH ₂	0,60	0,78	+11,3
H-Tyr-D-Val-Phe-D-Ala-NH ₂	0,43	0,69	
H-Tyr-D-Leu-Phe-D-Ala-NH ₂	0,41	0,58	
H-Tyr-D-Ile-Phe-D-Ala - NH ₂	0,40	0,57	
H-Tyr-D-Phe-Phe-D-Ala-NH ₂	0,42	0,71	
H-Tyr-D-Asn-Phe-D-Ala-NH ₂	0,40	0,63	
H-Tyr-D-Trp-Phe-D-Ala-NH ₂	0,38	0,56	
H-Tyr-D-Pro-Phe-D-Ala-NH ₂	0,41	0,70	
H-Tyr-D-Ser-Phe-D-Ala-NH ₂	0,54	0,74	
H-Tyr-D-Thr-Phe-D-Ala-NH ₂	0,55	0,76	
H-Tyr-D-Tyr-Phe-D-Ala-NH ₂	0,48	0,61	
H-Tyr-D-Hyp-Phe-D-Ala-NH ₂	0,43	0,71	
H-Tyr-D-Cys-Phe-D-Ala-NH ₂	0,43	0,62	
H-Tyr-D-Cys-Cys-Phe-D-Ala-OH	0,40	0,65	
H-Tyr-D-Met-Phe-D-Ala-NH ₂	0,44	0,58	
H-Tyr-D-His-Phe-D-Ala-NH ₂	0,45	0,70	
H-Tyr-D-Asp-Phe-D-Ala-NH ₂	0,51	0,69	
H-Tyr-D-Glu-Phe-D-Ala-NH ₂	0,55	0,73	
H-Tyr-D-β-Ala-Phe-D-Ala-NH ₂	0,48	0,59	
H- Arg -Tyr-D-Ala-Phe- Ala -OH	0,53	0,70	+38,4
H- Arg -Tyr-D-Ala-Phe- Val -OH	0,50	0,73	+24,8
H- Arg -Tyr-D-Ala-Phe-D-Val-OH	0,50	0,73	- 0,4

Table 1 cont'd

1	2	3	4
H- Arg -Tyr-D-Ala-Phe- Leu -OH	0,51	0,72	+36,3
H- Arg -Tyr-D-Ala-Phe-D-Leu-OH	0,51	0,72	- 0,8
H- Arg -Tyr-D-Ala-Phe- Ile -OH	0,51	0,73	+33,6
H- Arg -Tyr-D-Ala-Phe-D-Ile -OH	0,51	0,73	+ 4,3
H- Arg -Tyr-D-Ala-Phe- Phe -OH	0,52	0,69	
H- Arg -Tyr-D-Ala-Phe-D-Phe-OH	0,52	0,69	
H- Arg -Tyr-D-Ala-Phe- Asn -OH	0,48	0,68	
H- Arg -Tyr-D-Ala-Phe-D-Asn-OH	0,48	0,68	
H- Arg -Tyr-D-Ala-Phe- Gln -OH	0,50	0,70	
H- Arg -Tyr-D-Ala-Phe-D-Gln-OH	0,50	0,70	
H- Arg -Tyr-D-Ala-Phe- Trp -OH	0,51	0,71	
H- Arg -Tyr-D-Ala-Phe-D-Trp-OH	0,51	0,71	
H- Arg -Tyr-D-Ala-Phe- Pro -OH	0,53	0,72	
H- Arg -Tyr-D-Ala-Phe-D-Pro-OH	0,53	0,72	
H- Arg -Tyr-D-Ala-Phe- Ser -OH	0,52	0,71	
H- Arg -Tyr-D-Ala-Phe-D-Ser-OH	0,52	0,71	
H- Arg -Tyr-D-Ala-Phe- Thr -OH	0,51	0,68	
H- Arg -Tyr-D-Ala-Phe-D-Thr-OH	0,51	0,68	
H- Arg -Tyr-D-Ala-Phe- Tyr -OH	0,54	0,74	
H- Arg -Tyr-D-Ala-Phe-D-Tyr-OH	0,54	0,74	
H- Arg -Tyr-D-Ala-Phe- Hyp -OH	0,52	0,73	
H- Arg -Tyr-D-Ala-Phe-D-Hyp-OH	0,52	0,73	
H- Arg -Tyr-D-Ala-Phe- Cys -OH	0,50	0,63	
H- Arg -Tyr-D-Ala-Phe-D-Cys-OH	0,50	0,63	
H- Arg -Tyr-D-Ala-Phe-Cys-Cys-OH	0,48	0,65	
H- Arg-Tyr-D-Ala-Phe-Cys-D-Cys-OH	0,48	0,65	
H-Arg-Tyr-D-Ala-Phe-D-Cys-Cys-OH	0,48	0,65	
H-Arg-Tyr-D-Ala-Phe-D-Cys-D-Cys-OH	0,48	0,65	
H- Arg -Tyr-D-Ala-Phe- Met -OH	0,55	0,70	+38,4
H- Arg -Tyr-D-Ala-Phe-D-Met-OH	0,55	0,70	+ 8,3
H- Arg -Tyr-D-Ala-Phe- Lys -OH	0,58	0,74	+18,3
H- Arg -Tyr-D-Ala-Phe-D-Lys-OH	0,58	0,74	-12,1
H- Arg -Tyr-D-Ala-Phe- Arg -OH	0,16	0,65	
H- Arg -Tyr-D-Ala-Phe-D-Arg-OH	0,16	0,65	
H- Arg -Tyr-D-Ala-Phe- His -OH	0,18	0,58	
H- Arg -Tyr-D-Ala-Phe-D-His-OH	0,18	0,58	
H- Arg -Tyr-D-Ala-Phe- Asp -OH	0,48	0,63	
H- Arg -Tyr-D-Ala-Phe-D-Asp-OH	0,48	0,63	
H- Arg -Tyr-D-Ala-Phe- Glu -OH	0,51	0,74	
H- Arg -Tyr-D-Ala-Phe-β-Ala -OH	0,51	0,74	
H- Arg -Tyr-D-Ala-Phe-D-β-Ala-OH	0,16	0,58	
H- Arg -Tyr-D-Ala-Phe- Orn -OH	0,58	0,73	
H- Arg -Tyr-D-Ala-Phe-D-Orn-OH	0,58	0,73	



WE CLAIM:

1. A peptide of the formula I

X-Tyr-Y-Phe-Z-A

I

wherein X is hydrogen, arginine, D-arginine, ornithine, D-ornithine,
 5 lysine, D-lysine, homoarginine, D-homoarginine, citrulline, D-citrulline;
 Tyr is tyrosine; Y is D-alanine, D-valine, D-leucine, D-isoleucine, D-
 phenylalanine, D-asparagine, D-tryptophan, D-proline, D-serine, D-
 threonine, D-tyrosine, D-hydroxyproline, D-cysteine, D-cysteyl-cysteine,
 D-methionine, D-lysine, D-homoarginine, D-arginine, D-histidine, D-
 10 aspartic acid, D-glutamic acid, D- β -alanine, or D-ornithine; Phe is
 phenylalanine; Z is alanine, D-alanine, valine, D-valine, leucine, D-
 leucine, isoleucine, D-isoleucine, phenylalanine, D-phenylalanine,
 asparagine, D-asparagine, glycine, glutamine, D-glutamine, tryptophan,
 D-tryptophan, proline, D-proline, serine, D-serine, threonine, D-
 15 threonine, tyrosine, D-tyrosine, hydroxyproline, D-hydroxyproline,
 cysteine, D-cysteine, cysteyl-cysteine, cysteine-D-cysteine, D-cysteyl-
 cysteine, D-cysteine-D-cysteine, methionine, D-methionine, lysine, D-
 lysine, arginine, D-arginine, histidine, D-histidine, aspartic acid, D-
 20 aspartic acid, glutamic acid, D-glutamic acid, β -alanine, D- β -alanine,
 ornithine, or D-ornithine; and A is hydroxyl or substituted amide (C_1 -
 C_3).

2. A pharmaceutical composition comprising one or more peptides of
 the formula I as claimed in claim 1 and a pharmaceutically acceptable
 vehicle.

- 25 3. The composition as claimed in claim 2, wherein the composition
 comprises from about 0.001 weight percent to about 0.1 weight percent of





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the peptide.

4. Use of a peptide as claimed in claim 1 in the preparation of a pharmaceutical composition for modulating physiological processes such as weight gain, activities of the epithelium growth zone, hair growth, wound healing, and to stimulate reparative and anabolic processes, and exert analgesic effects.
5. A method for modulating one or more physiological processes such as weight gain, activities of the epithelium growth zone, hair growth, wound healing, and reparative and anabolic processes comprising administering an effective amount of a peptide of the formula I as claimed in claim 1.
6. A peptide consisting essentially of the sequence Arg-Tyr-D-Ala-Phe-Gly.
7. A method for relieving pain comprising administering an effective amount of a peptide of the formula I as claimed in claim 1.

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