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54. **TÍTULO** ANAL[illegible]OS ANTAGONISTAS DE GH-RH

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71. **SOLICITANTE** THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND y THE UNITED STATES OF AMERICA REPRESENTED BY THE DEPARTMENT OF VETERANS AFFAIRS

DOMICILIO NEW ORLEANS, U.S.A.

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ANALOGOS ANTAGONISTAS DE GH-RH

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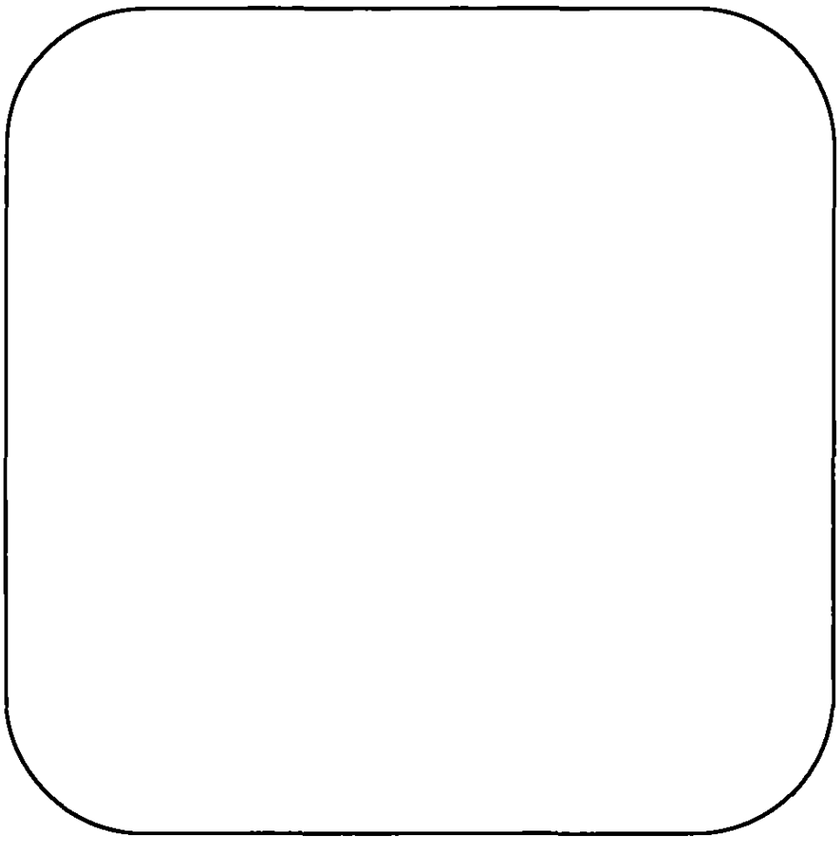
10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 463.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

(11) **FIGURA CARACTERÍSTICA**



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(54) Title: ANTAGONISTIC ANALOGS OF GH-RH (2003)

(57) Abstract: There is provided a novel series of synthetic antagonistic analogs of hGH-RH(1-29)NH_2. These analogs inhibit the activity of endogenous hGH-RH on the pituitary GH-RH receptors, and therefore prevent the release of growth hormone. The analogs also inhibit the proliferation of human cancers through a direct effect on the cancer cells. The higher inhibitory potencies of the new analogs, as compared to previously described ones, results from replacement of various amino acids.

ANTAG NISTIC ANAL GS OF GH-RH (2003)

Field Of Invention

This invention was made in part with Government support from the Medical Research Service of the Veterans Affairs Department. The Government has certain rights in this application (VA No. 03-084, assigned July 25, 2003).

The present invention relates to novel synthetic peptides that inhibit the release of growth hormone from the pituitary in mammals as well as inhibit the proliferation of human cancers through a direct effect on the cancer cells, and to therapeutic compositions containing these novel peptides.

BACKGROUND OF THE INVENTION

Growth hormone-releasing hormone (GH-RH) is a peptide belonging to the secretin/glucagon family of neuroendocrine and gastrointestinal hormones, a family that also includes vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating peptide (PACAP) and others. Human GH-RH (hGH-RH) peptide is comprised of 44 amino acid residues. The best known site of production of GH-RH is the hypothalamus, but it was found that various peripheral organs also synthesize it. hGH-RH is also produced, sometimes in large quantities, by human malignant tissues (cancers) of diverse origin.

GH-RH exerts various physiological and pathophysiological functions. Hypothalamic GH-RH is an endocrine releasing hormone that, acting through specific GH-RH receptors on the pituitary, regulates the secretion of pituitary growth hormone (GH). The physiological functions of GH-RH in extrapituitary tissues are less clear. However, there is increasing evidence for the role of GH-RH as an autocrine/paracrine growth factor in various cancers. Splice variant (SV) receptors for GH-RH, different from those expressed in the pituitary, have been described in a wide range of human cancers and in some normal peripheral organs. The actions of tumoral autocrine/paracrine GH-RH could be exerted on these receptors. In addition, receptors for VIP and other, as yet unidentified receptors of this family, could all be targets of local GH-RH.

In view of the role of GH-RH as an endocrine regulator of GH release, novel therapeutic strategies, based on the use of agonistic and antagonistic analogs of GH-RH, have been devised for the treatment of various pathological conditions.

GH is a polypeptide having 191 amino acids that stimulates the production of different growth factors, e.g. insulin-like growth factor I (IGF-I), and consequently promotes growth of numerous tissues (skeleton, connective tissue, muscle and viscera) and stimulates various physiological activities (raising the synthesis of nucleic acids and proteins, and raising lipolysis, but lowering urea secretion). Release of pituitary GH is under the control of releasing and inhibiting

factors secreted by the hypothalamus, the primary releasing factors being GH-RH and ghrelin, and the main inhibiting factor being somatostatin.

GH has been implicated in several diseases. One disease in which GH is involved is acromegaly, in which excessive levels of GH are present. The abnormally enlarged facial and extremity bones, and the cardiovascular symptoms of this disease can be treated by administering a GH-RH antagonist. Further diseases involving GH are diabetic retinopathy and diabetic nephropathy. The damage to the retina and kidneys respectively in these diseases, believed to be due to hypersecretion of GH, results in blindness or reduction in kidney function. This damage can be prevented or slowed by administration of an effective GH-RH antagonist.

In an effort to intervene in these disease and other conditions, some investigators have attempted to control GH and IGF-I levels by using analogs of somatostatin, an inhibitor of GH release. However, somatostatin analogs, if administered alone, do not suppress GH or IGF-I levels to a desired degree. If administered in combination with a GH-RH antagonist, somatostatin analogs will suppress IGF-I levels much better.

However, the main applications of GH-RH antagonists are in the field of cancer (reviewed in Schally AV and Varga JL, Trends Endocrinol Metab 10: 383-391, 1999; Schally AV et al, Frontiers Neuroendocrinol 22: 248-291, 2001; Schally AV and Comaru-Schally AM, In: Kufe DW, Pollock RE, Weichselbaum RR, Bast Jr. RC, Gansler TS, Holland JF, Frei III E, Eds. Cancer Medicine, 6th ed. Hamilton, Ontario: BC. Decker, Inc., 2003, p.911-926). GH-RH antagonists inhibit the proliferation of malignancies by indirect endocrine mechanisms based on the inhibition of pituitary GH release and resulting in the decrease of serum levels of GH and IGF-I, as well as by direct effects on the tumor tissue.

GH-RH and its tumoral splice variant (SV) receptors are present in human cancers of the lung, prostate, breast, ovary, endometrium, stomach, intestine, pancreas, kidney, and bone (see Halmos G et al, Proc Natl Acad Sci USA 97: 10555-10560, 2000; Rekasi Z et al, Proc Natl Acad Sci USA 97: 10561-10566, 2000; Schally AV et al, Frontiers Neuroendocrinol 22: 248-291, 2001; Schally AV and Comaru-Schally AM, in: Kufe DW, Pollock RE, Weichselbaum RR, Bast Jr. RC, Gansler TS, Holland JF, Frei III E, Eds. Cancer Medicine, 6th ed. Hamilton, Ontario: BC. Decker, Inc., 2003, p.911-926). Tumoral GH-RH has been shown or it is suspected to act as an autocrine growth factor in these malignancies. Antagonistic analogs of GH-RH can inhibit the stimulatory activity of GH-RH and exert direct antiproliferative effects in vitro on cancer cells, and in vivo on tumors. Direct antiproliferative effects of GH-RH antagonists are exerted on tumoral receptors (binding sites). In addition to the specific tumoral SV receptors for GH-RH, receptors for VIP and other, as yet unidentified receptors of this family, are targets of GH-RH antagonists.

In addition to endocrine inhibitory effects on serum GH and IGF-I, GH-RH antagonists have been found to reduce the autocrine and paracrine production of several tumor growth factors and/or downregulate their receptors. These growth factors include IGF-I, IGF-II, GH, vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF), Thus, a disruption of the autocrine/paracrine stimulatory loops based on these growth factors contributes to the efficacy of GH-RH antagonists as antitumor agents.

IGF-I and IGF-II are autocrine/paracrine growth factors with potent mitogenic effects on various cancers. IGF-I is also an endocrine growth factor, and elevated levels of serum IGF-I are considered an epidemiological risk factor for the development of prostate cancer, lung cancer, and colorectal cancer. The involvement of IGF-I (somatomedin-C) in breast cancer, prostate cancer, colon cancer, bone tumors and other malignancies is well established. Nevertheless, autocrine/paracrine control of proliferation by IGF-II is also a major factor in many tumors. IGF-I and IGF-II exert their proliferative and anti-apoptotic effects through the common IGF-I receptor. The receptors for IGF-I are present in primary human breast cancers, prostate cancers, lung cancers, colon cancers, brain tumors, pancreatic cancers, and in renal cell carcinomas. In several experimental cancers, such as those of the bone, lung, prostate, kidney, breast, ovary, intestine, pancreas, and brain, treatment with GH-RH antagonists produces a reduction in IGF-I and/or IGF-II levels, concomitant to inhibition of tumor growth (reviewed in Schally AV and Varga JL, Trends Endocrinol Metab 10: 383-391, 1999; Schally AV et al, Frontiers Neuroendocrinol 22: 248-291, 2001; Schally AV and Comaru-Schally AM, In: Kufe DW, Pollock RE, Weichselbaum RR, Bast Jr. RC, Gansler TS, Holland JF, Frei III E, Eds. Cancer Medicine, 6th ed. Hamilton, Ontario: BC. Decker, Inc., 2003, p.911-926). In some cases, the expression of IGF-I receptors was also decreased by GH-RH antagonists. Thus the disruption of endocrine and autocrine/paracrine stimulatory loops dependent on IGF-I and IGF-II contributes to the antitumor effect of GH-RH antagonists.

In MXT breast cancer model, treatment with GH-RH antagonists inhibited tumor growth, reduced the mRNA level for GH and the concentration of GH peptide in tumors, and inhibited the mRNA expression for GH receptors (Szepeshazi K et al, Endocrinology 142: 4371-4378, 2001). GH was shown to act as a growth factor for MXT murine mammary carcinoma cells, MCF-7 human breast cancer cells and other tumor cell lines. Thus the inhibitory activity of GH-RH antagonists on local and serum GH levels contributes to their antitumor effect.

GH-RH antagonists have been shown to inhibit the mRNA levels and protein concentrations of VEGF in human androgen-sensitive and androgen-independent prostate cancer models (Letsch M et al, Proc Natl Acad Sci USA 100: 1250-1255, 2003; Plonowski A et al, Prostate 52: 173-182, 2002) and this phenomenon contributes to their antitumor effect, since VEGF plays an important stimulatory role in the neovascularization and growth of various tumors. Moreover, it was found that a GH-RH antagonist inhibited the VEGF secretion and proliferation of

normal murine endothelial cells, apparently through a direct effect on these cells in vitro (Siejka A et al, Life Sci 72: 2473-2479, 2003).

Scientists have investigated various modifications of GH-RH to elucidate the relationship of the structure of GH-RH to its activity on the pituitary receptors, in an effort to provide synthetic congeners with improved agonistic or antagonistic properties. Thus, it was early established that GH-RH fragment comprising residues 1 to 29, or GH-RH(1-29), is the minimum sequence necessary for biological activity on the pituitary. This fragment retains 50% or more of the potency of native GH-RH. Subsequently, many synthetic analogs of GH-RH, based on the structure of hGH-RH(1-29)NH_2 peptide, were prepared. hGH-RH(1-29)NH_2 has the following amino acid sequence:

Tyr-Ala-Asp-Ala-Ile^5-Phe-Thr-Asn-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg^{20}-Lys-Leu-Leu-Gln-Asp^{25}-Ile-Met-Ser-Arg^{29}-NH_2

A considerable number of patents and articles in the open literature disclose analogs of GH-RH which either act as agonists of GH-RH (i.e. act to stimulate the release of GH) or as antagonists of GH-RH (i.e. act to inhibit the release of GH) on the pituitary. Most of these peptides are derived from the GH-RH(1-29) peptide sequence, with specific structural modifications which account for their enhanced agonistic or antagonistic properties on the pituitary receptors. However, apart from a few exceptions, it is not known how these analogs would behave on cancer cells that express GH-RH receptors different from those found in the pituitary. Only a few published scientific studies tried to elucidate the structure-activity relationships and characterize the direct antagonistic (or agonistic) effects of GH-RH analogs on cancer cells and tumors (see Rekasi Z et al, Endocrinology 141: 2120-2128, 2000; Halmos G et al, Proc Natl Acad Sci USA 97: 10555-10560, 2000; Rekasi Z et al, Proc Natl Acad Sci USA 97: 10561-10566, 2000; Kiaris H et al, Proc Natl Acad Sci USA 99: 196-200, 2002), and no issued patents have dealt with this issue so far. Consequently, very little is known about the structural features in GH-RH analogs required for a direct antagonistic action on tumor cells.

The first described GH-RH antagonist, [Ac-Tyr^1,D-Arg^2]hGH-RH(1-29)NH_2, which is generally termed as the "standard antagonist" in the literature, was found to prevent the activation of rat anterior pituitary adenylate cyclase by hGH-RH(1-29)NH_2. The same peptide blocked the action of GH-RH on its receptors in the pituitary and hypothalamus, and inhibited the pulsatile growth hormone secretion. The standard antagonist was also evaluated clinically (Ocampo-Lim B et al, J Clin Endocrinol Metab 81: 4396-4399, 1996; Jaffe CA et al, J Clin Endocrinol Metab 82: 634-637, 1997). Large doses of this antagonist (400 µg/kg) eliminated nocturnal GH secretion in normal subjects and inhibited the response to GH-RH. The standard GH-RH antagonist also reduced GH levels in a patient with acromegaly. However, for clinical use, much more potent antagonists of GH-RH are required.

The inventions mentioned below disclose GH-RH analogs with antagonistic or agonistic properties on the pituitary receptors for GH-RH. However it was not reported and not investigated whether these analogs could exert direct effects on tumor cells.

US Patent 4,659,693 discloses GH-RH antagonistic analogs which contain certain N,N'-dialkyl-omega-guanidino alpha-amino acyl residues in position 2 of the GH-RH(1-29) sequence.

Published application WO 91/16923 reviews earlier attempts to alter the secondary structure of hGH-RH by modifying its amino acid sequence. These earlier attempts include: *replacing* Tyr1, Ala^2, Asp^3 *or* Asn^8 *with their D-isomers; replacing* Asn^8 *with* L- *or* D-Ser, D-Arg, Asn, Thr, Gln or D-Lys; replacing Ser^9 with Ala to enhance amphiphilicity of the region; and replacing Gly^{15} with Ala or Aib. When R^2 in the analogs is D-Arg, and R^8, R^9, and R^{15} are substituted as indicated above, antagonistic activity is said to result. These antagonistic peptides are said to be suitable for administration as pharmaceutical compositions to treat conditions associated with excessive levels of GH, e.g., acromegaly.

The antagonistic activity of the hGH-RH analogue "[Ser^9-psi[CH_2-NH]-Tyr^{10}]hGH-RH(1-29)" of US Patent 5,084,555 was said to result from the pseudopeptide bond (i.e., a peptide bond reduced to a [CH_2-NH] linkage) between the R^9 and R^{10} residues. However, the antagonistic properties of [Ser^9-psi[CH_2-NH]-Tyr^{10}]hGH-RH(1-29) were said to be inferior to the standard antagonist, [N-Ac-Tyr^1, D-Arg^2]hGH-RH(1-29)-NH_2.

US Patent 5,550,212, US Patent 5,942,489, and US Patent 6,057,422, assigned to the same assignee as the present application, disclose analogs of hGH-RH(1-29)NH_2 said to have enhanced antagonistic properties and prolonged duration of action regarding the inhibition of GH-RH-evoked GH release. These properties are believed to result from replacement of various amino acids and acylation with aromatic or nonpolar acids at the N-terminus of GH-RH(1-29)NH_2. The tumor inhibitory properties of antagonists featured in US Patent 5,942,489 and US Patent 6,057,422 have been demonstrated by using nude mice bearing xenografts of experimental human cancer models. It is noted that in US Patent 5,550,212, and in US Patent 5,942,489, R^9 is always Ser, while R^{11} and R^{20} can be either Arg, D-Arg, or Cit. In the case of US Patent 6,057,422, R^9 can be either Arg, Har, Lys, Orn, D-Arg, D-Har, D-Lys, D-Orn, Cit, Nle, Tyr(Me), Ser, Ala, or Aib, while R^{11} and R^{20} are always Arg.

SUMMARY OF THE INVENTION

There is provided a novel series of synthetic analogs of hGH-RH(1-29)NH_2 and hGH-RH(1-30)NH_2. These analogs inhibit the release of growth hormone from the pituitary in mammals as well as inhibit the proliferation of human cancers through a direct effect on the cancer cells. The

stronger inhibitory potencies of the new analogs, as compared to previously described ones, results from replacement of various amino acids.

The invention principally relates to peptides comprising the formulae:

R_1-A^0-A^1-A^2-Asp-Ala-A^5-A^6-Thr-A^8-A^9-A^{10}-A^{11}-A^{12}-Val-Leu-A^{15}-A^{16}-Leu-Ser-A^{19}-A^{20}-A^{21}-A^{22}-Leu-Gln-Asp-Ile-A^{27}-A^{28}-A^{29}-A^{30}-R_2

wherein R_1 is a member of the group consisting of a) PhAc, Hca, Dat, IndAc, Ipa, 1-Nac, 2-Nac, 1-Npr, 2-Npr, Ibu; $CH_3(CH_2)_nCO$, or $HOOC(CH_2)_nCO$, where n is an integer from 2 to 20, and b) any other straight chain, cyclic, branch chain, saturated, unsaturated or poly unsaturated aliphatic carboxyl group of 8-14 carbon atoms and any carbocyclic or heterocyclic aromatic carboxyl group of 3-8 carbon atoms containing up to one atom each of the group S, N, and O in the heterocyclic ring,

A^0 is Phe, D-Phe, Arg, D-Arg, or a carbon-nitrogen single bond,

A^1 is Tyr or His,

A^2 is D-Arg or D-Cit,

A^5 is Ile or Val,

A^6 is Phe, Tyr, Nal, or Phe(Y), in which Y=F, Cl, Br, or I,

A^8 is Asn, D-Asn, Cit, D-Cit, Gln, D-Gln, Ser, D-Ser, Thr, D-Thr, Ala, D-Ala, Abu, D-Abu, or Aib,

A^9 is His, D-His, Amp, D-Amp, Gup, or D-Gup,

A^{10} is Tyr, Tyr(Et), Tyr(Me); Phe(Y), in which Y=H, F, Cl, Br, or I; Amp, His, Cha, Chg, Bpa, Dip, Trp, Trp(For), Tpi, 1-Nal, 2-Nal, 3-Pal, 4-Pal, Phe(NH_2), or Phe(NO_2),

A^{11} is His, D-His, Arg, D-Arg, Cit, Har, D-Har, Amp, D-Amp, Gup, or D-Gup,

A^{12} is Lys, D-Lys, Orn, D-Orn, Har, D-Har, Cit, D-Cit, Nle, or Ala,

A^{15} is Gly, Ala, Abu, Aib, Nle, Gln, Cit, or His,

A^{16} is Gln or Arg,

A^{19} is Ala or Abu,

A^{20} is His, D-His, Arg, D-Arg, or Cit,

A^{21} is Lys, D-Lys, Orn, D-Orn, Cit, or D-Cit,

A^{22} is Leu, Ala or Aib,

A^{27} is Met, Leu, Nle, Abu, or D-Arg,

A^{28} is Arg, D-Arg, Har, D-Har, Ser, Asn, Asp, Ala, Abu, or Cit,

A^{29} is Arg, D-Arg, Har, D-Har, Cit, D-Cit, or Agm,

A^{30} is Arg, D-Arg, Har, D-Har, Cit, D-Cit, Agm, or is a carbon-nitrogen or carbon-oxygen single bond,

R_2 is $-NH_2$, $-NH-NH_2$, $-NH-OH$, $-NHR_3$, $-NR_3R_4$, $-OH$, or $-OR_3$, in which R_3 and R_4 are any of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkinyl, C_{7-16} phenylalkyl, $-C_6H_5$, or $-CH(C_6H_5)_2$;

provided that if A^{29} is Agm then A^{30} and R_2 are absent, and if A^{30} is Agm then R_2 is absent,

and pharmaceutically acceptable salts thereof.

Among the preferred embodiment are peptides in the formula above wherein one or both of A^{11} and A^{20} are other than Arg, D-Arg, or Cit.

Specifically, the principal peptides falling under this genus are :

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 67

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 68

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, His^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 69

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 70

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 71

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 72

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 73

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 74

[1-Nac-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 75

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 76

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 77

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 78

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 79

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 80

[$HOOC(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 81

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 82

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 86

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 87

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 88

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 89

[1-Nac-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 91

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 92

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 93

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, His^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 94

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 95

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 96

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 97

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 98

[$CH_3(CH_2)_{10}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 99

[Hca -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 100

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHMe Peptide 101

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 102

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 103

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 104

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 105

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 106

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 107

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 108

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 109

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 110

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 111

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 112

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 113

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 114

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 115

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 116

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 117

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 118

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 119

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 120

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 121

Closely related peptides which do not fall under the foregoing generic structural formula include:

$[CH_3(CH_2)_4CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 2

$[HOOC(CH_2)_4CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 3

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 4

$[HOOC(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 5

$[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 6

$[HOOC(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 7

$[CH_3(CH_2)_{10}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 8

$[HOOC(CH_2)_{10}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 9

$[CH_3(CH_2)_{12}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 10

$[HOOC(CH_2)_{12}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 11

$[CH_3(CH_2)_{14}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 12

$[HOOC(CH_2)_{14}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 13

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D\text{-}Arg^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 14

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{8}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 15

[$CH_3(CH_2)_{14}$CO-Phe^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{8}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 16

[$CH_3(CH_2)_{14}$CO-D-Phe^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{8}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 17

[PhAc-Arg^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{8}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 18

[PhAc-D-Arg^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{8}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 19

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 21

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Cit^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 22

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Arg^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 23

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Cit^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 24

[HOOC$(CH_2)_{12}$CO-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Cit^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 25

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, D-Ala^{8}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 26

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Abu^{8}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 27

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 28

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 30

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 31

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, His^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 32

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Cha^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 33

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tpi^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 34

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 35

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 36

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNH_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 37

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Trp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 38

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNO_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 39

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, 3-Pal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 40

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 41

[PhAc-His^{1}, D-Arg^{2}, Tyr^{6}, Har^{9}, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 42

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Har^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 43

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 45

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 46

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 47

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 48

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Aib^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 49

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Orn^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 50

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29)
Peptide 51

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29)
Peptide 52

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2 Peptide 53

[Dat-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2
Peptide 54

[Ipa-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2
Peptide 55

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NHEt Peptide 56

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, D-Arg^{29}, Har^{30}]hGH-RH(1-30)NH_2 Peptide 57

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, D-Arg^{30}]hGH-RH(1-30)NH_2 Peptide 58

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30) Peptide 59

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30) Peptide 60

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 62

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Har^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 63

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Amp^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 64

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Cit^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 65

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 84

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 85

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 90

It is noted that the amino acid residues from 30 through 44 of the native GH-RH molecule do not appear to be essential to activity; nor does their identity appear to be critical. Therefore, it appears that the addition of some or all of these further amino acid residues to the C-terminus of the hGH-RH(1-29)NH_2 and hGH-RH(1-30)NH_2 analogs of the present invention will not affect the efficacy of these analogs as GH-RH antagonists. If some or all of these amino acids were added to the C-terminus of the hGH-RH(1-29)NH_2 analogs, the added amino acid residues could be the same as residues 30 through 44 in the native hGH-RH sequence or reasonable equivalents.

Synthetic Methods.

The synthetic peptides are synthesized by a suitable method such as by exclusive solid phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution phase synthesis.

When the analogs of this invention are synthesized by solid-phase method, the C-terminus residue (here, A^{29} or A^{30}) is appropriately linked (anchored) to an inert solid support (resin) while bearing protecting groups for its alpha amino group (and, where appropriate, for its side chain functional group). After completion of this step, the alpha amino protecting group is removed from the anchored amino acid residue and the next amino acid residue, A^{28} or A^{29} respectively, is added having its alpha amino group (as well as any appropriate side chain functional group) suitably protected, and so forth. The N-terminus protecting groups are removed after each residue is added, but the side chain protecting groups are not yet removed. After all the desired amino acids have been linked in the proper sequence, the peptide is cleaved from the support and freed from all side chain protecting group(s) under conditions that are minimally destructive towards residues in the sequence. This is be followed by a careful purification and scrupulous characterization of the synthetic product, so as to ensure that the desired structure is indeed the one obtained.

It is particularly preferred to protect the alpha amino function of the amino acids during the coupling step with an acid or base sensitive protecting group. Such protecting groups should have the properties of being stable in the conditions of peptide linkage formation, while being readily removable without destruction of the growing peptide chain and without racemization of any of the chiral centers contained therein. Suitable alpha amino protecting groups are Boc and Fmoc.

Medical Applications.

The hGH-RH antagonist peptides, or salts of these peptides, may be formulated in pharmaceutical dosage forms containing effective amounts thereof and administered to humans or animals for therapeutic or diagnostic purposes. The peptides may be used to suppress GH levels and to treat conditions associated with excessive levels of GH, e.g., diabetic retinopathy and nephropathy, and acromegaly. Also provided are methods for treating these diseases by administration of a composition of the invention to an individual needing such treatment. The main uses of GH-RH antagonists are, however, in the field of cancer, for example human cancers of the lung, prostate, breast, ovary, endometrium, stomach, colon, pancreas, kidney, bone, and brain where the receptors for GH-RH, IGF-I/IGF-II, or GH are present, and that depend on stimulation by growth factors such as GH-RH, IGF-I, IGF-II, GH, or VEGF.

DETAILED DESCRIPTION F THE PREFERRED EMBODIMENTS

A. Abbreviations

The nomenclature used to define the peptides is that specified by the IUPAC-IUB Commission on Biochemical Nomenclature wherein, in accordance with conventional representation, the amino group at the N-terminus appears to the left and the carboxyl group at the C-terminus appears to the right. The term "natural amino acid" as used herein means one of the common, naturally occurring L-amino acids found in naturally occurring proteins: Gly, Ala, Val, Leu, Ile, Ser, Thr, Lys, Arg, Asp, Asn, Glu, Gln, Cys, Met, Phe, Tyr, Pro, Trp and His. When the natural amino acid residue has isomeric forms, it is the L-form of the amino acid that is represented herein unless otherwise expressly indicated.

Non-coded amino acids, or amino acid analogues, are also incorporated into the GH-RH antagonists. ("Non-coded" amino acids are those amino acids which are not among the approximately 20 natural amino acids found in naturally occurring proteins.) When these non-coded amino acids, or amino acid analogues, have isomeric forms, it is the L-form of the amino acid that is represented unless otherwise expressly indicated.

Abbreviations used herein are:

Abu	alpha-aminobutyric acid
Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
Agm	agmatine
Aib	alpha-aminoisobutyric acid
All	allyl
Alloc	allyloxycarbonyl
Amp	para-amidino-phenylalanine
Bpa	para-benzoyl-phenylalanine
Boc	tert-butyloxycarbonyl
Bom	benzyloxymethyl
2BrZ	2-bromo-benzyloxycarbonyl
Bzl	benzyl
Cha	cyclohexylalanine
Chg	cyclohexylglycine
cHx	cyclohexyl
Cit	citrulline (2-amino-5-ureidovaleric acid)
2ClZ	2-chloro-benzyloxycarbonyl
Dat	des-amino-tyrosine

DCM	dichloromethane
DIC	N,N'-diisopropylcarbodiimide
DIEA	diisopropylethylamine
Dip	(3,3-diphenyl)alanine
DMF	dimethylformamide
Et	ethyl
Fm	fluorenylmethyl
Fmoc	fluorenylmethoxycarbonyl
For	formyl
GH	growth hormone
GH-RH	GH releasing hormone
Gup	para-guanidino-phenylalanine
Har	homoarginine
HBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexaflourophosphate
Hca	hydrocinnamoyl
Hca-OH	hydrocinnamic acid
hGH-RH	human GH-RH
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
Ibu	isobutyryl
IndAc	indole-3-acetyl
Ipa	indole-3-propionyl
MBHA	para-methylbenzhydrylamine
Me	methyl
MeOH	methanol
MeCN	acetonitrile
Nac	naphthylacetyl
Nal	naphthylalanine
Nle	norleucine
NMM	N-methylmorpholine
Npr	naphthylpropionyl
Orn	ornithine
Pal	pyridylalanine
PAM	phenylacetamidomethyl
Ph	phenyl
PhAc	phenylacetyl
PhAc-OH	phenylacetic acid
Phe(pCl)	para-chloro-phenylalanine
Phe(pNH_2)	para-amino-phenylalanine

$Phe(pNO_2)$	para-nitro-phenylalanine
rGH-RH	rat GH-RH
RP-HPLC	reversed phase HPLC
SPA	para-sulfonyl-phenoxyacetyl
TFA	trifluoroacetic acid
Tos	para-toluenesulfonyl
Tpi	1,2,3,4-tetrahydronorharman-3-carboxylic acid
Tyr(Me)	O-methyl-tyrosine
Tyr(Et)	O-ethyl-tyrosine
Z	benzyloxycarbonyl

B. The GH-RH Analogs

The hGH-RH analogs of the present invention were designed to increase the antagonistic effects at the pituitary level, and/or at the tumoral level. Some of these analogs, such as Peptide 4, Peptide 7, Peptide 21, Peptide 30, Peptide 31, Peptide 37, Peptide 41, Peptide 42, Peptide 62, Peptide 67, and Peptide 69 possess high endocrine antagonistic potencies, causing a very effective and long lasting inhibition of the GH release stimulated by hGH-RH(1-29)NH_2 in vitro and in vivo, and exhibit high binding affinities to the pituitary GH-RH receptors. Some analogs, such as Peptide 4, Peptide 5, Peptide 7, Peptide 11, Peptide 22, Peptide 35, Peptide 36, Peptide 39, Peptide 41, Peptide 62, Peptide 67, Peptide 69, Peptide 70, Peptide 72, Peptide 76, Peptide 77, Peptide 79, Peptide 80, Peptide 86, Peptide 95, Peptide 96, and Peptide 97, show elevated tumor inhibitory potencies and display extremely high binding affinities to the tumoral receptors for GH-RH. The peptides of the present invention were also designed to improve their chemical and metabolic stabilities.

The following embodiments are specially preferred as having remarkable bioactivity:

$[CH_3(CH_2)_4CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]$hGH-RH(1-29)$NH_2$

Peptide 2

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]$hGH-RH(1-29)$NH_2$

Peptide 4

$[HOOC(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]$hGH-RH(1-29)$NH_2$

Peptide 5

$[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]$hGH-RH(1-29)$NH_2$

Peptide 6

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 7

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 11

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 14

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 15

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 21

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 22

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Abu^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 27

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 28

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 30

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 31

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 35

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 36

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Phe(pNH_2)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 37

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNO$_2$)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$
Peptide 39

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$
Peptide 41

[PhAc-His^1, D-Arg^2, Tyr^6, Har^9, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$
Peptide 42

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 46

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 62

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$
Peptide 67

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$
Peptide 68

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, His^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$
Peptide 69

[CH$_3$(CH$_2$)$_8$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 70

[HOOC(CH$_2$)$_8$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 71

[HOOC(CH$_2$)$_{12}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 72

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 73

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 74

[1-Nac-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 75

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 76

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 77

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 78

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 79

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 80

[$HOOC(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 81

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 82

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 84

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 85

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 86

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 87

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 88

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 89

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 90

[1-Nac-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 91

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 92

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 93

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, His^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 94

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 95

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 96

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 97

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 98

[$CH_3(CH_2)_{10}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 99

[Hca -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 100

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHMe Peptide 101

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 102

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 103

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 104

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 105

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 106

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 107

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 108

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 109

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 110

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 111

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 112

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 113

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 114

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 115

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 116

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 117

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 118

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 119

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 120

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 121

Thirty very preferred embodiments have the formulae:

$CH_3(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 4

$HOOC(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 5

$HOOC(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 7

$HOOC(CH_2)_{12}CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 11

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Cit^{8}-Arg^{9}-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 21

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Cit^{8}-Cit^{9}-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 22

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Arg^{9}-Amp^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 30

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Amp^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 31

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-2-Nal^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 35

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Dip^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 36

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Phe(pNH_2)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 37

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Phe(pNO_2)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 39

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Tyr(Et)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 41

PhAc-His^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Tyr^{6}-Thr^{7}-Asn^{8}-Har^{9}-Bpa^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 42

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NHEt

Peptide 46

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Tyr(Me)^{10}-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 62

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Amp^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 67

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-His^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 69

$CH_3(CH_2)_6CO$-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Amp^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 70

$HOOC(CH_2)_{12}CO$-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Amp^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 72

$CH_3(CH_2)_6CO$-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Cit^{8}-Amp^{9}-Tyr(Me)^{10}-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 76

$HOOC(CH_2)_{12}CO$-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Cit^{8}-Amp^{9}-Tyr(Me)^{10}-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 77

$CH_3(CH_2)_6CO$-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Cit^{8}-His^{9}-Tyr(Et)^{10}-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

Peptide 79

$CH_3(CH_2)_6CO$-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Ala^{8}-His^{9}-Tyr(Et)^{10}-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 80

$HOOC(CH_2)_{12}CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 82

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-His^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 86

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-His^9-$Tyr(Et)^{10}$-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 92

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Orn^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Orn^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 95

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Orn^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-His^{20}-Orn^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 96

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NHEt Peptide 97

Under well-established convention, these may be abbreviated as follows:

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 4

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 5

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 7

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 11

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 21

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 22

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 30

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 31

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 35

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 36

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNH_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 37

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNO_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 39

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 41

[PhAc-His^1, D-Arg^2, Tyr^6, Har^9, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 42

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 46

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 62

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 67

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, His^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 69

$[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Amp^8, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 70

$[HOOC(CH_2)_{12}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Amp^8, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 72

$[CH_3(CH_2)_8CO\text{ -}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 76

$[HOOC(CH_2)_{12}CO\text{ -}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 77

$[CH_3(CH_2)_8CO\text{ -}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Cit^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 79

$[CH_3(CH_2)_8CO\text{ -}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 80

$[HOOC(CH_2)_{12}CO\text{ -}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 82

$[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 86

$[CH_3(CH_2)_8CO\text{ -}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 92

$[CH_3(CH_2)_8CO\text{ -}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 95

$[CH_3(CH_2)_8CO\text{ -}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ Peptide 96

$[CH_3(CH_2)_8CO\text{ -}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NHEt$ Peptide 97

C. Method of Preparation

1. Overview of Synthesis

The peptides are synthesized by suitable methods such as by exclusive solid phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution phase synthesis. For example, the techniques of exclusive solid-phase synthesis are set forth in the textbook "Solid Phase Peptide Synthesis", J.M. Stewart and J.D. Young, Pierce Chem. Company, Rockford, Illinois, 1984 (2nd. ed.), and M. Bodanszky, "Principles of Peptide Synthesis", Springer Verlag, 1984. The hGH-RH antagonist peptides are preferably prepared using solid phase synthesis, such as that generally described by Merrifield, J.Am.Chem.Soc., 85 p. 2149 (1963), although other equivalent chemical syntheses known in the art can also be used as previously mentioned.

The synthesis is carried out with amino acids that are protected at their alpha amino group. Urethane type protecting groups (Boc or Fmoc) are preferably used for the protection of the alpha amino group.

In solid phase synthesis, the N-alpha-protected amino acid moiety which forms the aminoacyl group of the final peptide at the C-terminus is attached to a polymeric resin support via a chemical link. After completion of the coupling reaction, the alpha amino protecting group is selectively removed to allow subsequent coupling reactions to take place at the amino-terminus, preferably with 50% TFA in DCM when the N-alpha-protecting group is Boc, or by 20% piperidine in DMF when the N-alpha-protecting group is Fmoc. The remaining amino acids with similarly Boc or Fmoc-protected alpha amino groups are coupled stepwise to the free amino group of the preceding amino acid on the resin to obtain the desired peptide sequence. Because the amino acid residues are coupled to the alpha amino group of the C-terminus residue, growth of the synthetic hGH-RH analogue peptides begins at the C terminus and progresses toward the N-terminus. When the desired sequence has been obtained, the peptide is acylated at the N-terminus, and it is removed from the support polymer.

Each protected amino acid is used in excess (2.5 or 3 equivalents) and the coupling reactions are usually carried out in DCM, DMF or mixtures thereof. The extent of completion of the coupling reaction is monitored at each stage by the ninhydrin reaction. In cases where incomplete coupling is determined, the coupling procedure is repeated, or a capping by acetylation of unreacted amino groups is carried out, before removal of the alpha amino protecting group prior to the coupling of the next amino acid.

Typical synthesis cycles are shown in Table I and Table II.

TABLE I.

Protocol for a Typical Synthetic Cycle Using Boc-strategy

Step	Reagent	Mixing Time (min)
1. Deprotection	50% TFA in DCM	5+25
	DCM wash	1
	2-propanol wash	1
2. Neutralization	5% DIEA in DCM	1
	DCM wash	1
	MeOH wash	1
	5% DIEA in DCM	3
	MeOH wash	1
	DCM wash (3 times)	1
3. Coupling	3 eq. Boc-amino acid in DCM or DMF + 3 eq. DIC or the preformed HOBt ester of the Boc-amino acid	60
	MeOH wash (3 times)	1
	DCM wash (3 times)	1
4. Acetylation (if appropriate)	Ac_2O in pyridine (30%)	10+20
	MeOH wash (3 times)	1
	DCM wash (3 times)	1

TABLE II.

Protocol for a Typical Synthetic Cycle Using Fmoc-strategy

Step	Reagent	Mixing Time (min)
1. Deprotection	20% piperidine in DMF	5+15
	DMF wash (3 times)	1
2. Coupling	3 eq. Fmoc-amino acid in DMF + 3 eq. DIC or + 3 eq. HBTU + 3 eq. HOBt + 6 eq. DIEA	60

	DMF wash (3 times)	1
3. Acetylation	3 eq. 1-acetylimidazole in DMF	30
(if appropriate)	DMF wash (3 times)	1

After completion of the synthesis, the cleavage of the peptide from the resin can be effected using procedures well known in peptide chemistry.

2. Choice of the Support Polymer

The hGH-RH antagonist peptides may be synthesized on a variety of support polymers, i.e. MBHA, Merrifield, PAM, Rink amide or Wang resins. The peptides can also be synthesized on aminomethyl, MBHA, or other resins that have been previously derivatized with suitable linkers. Examples of such linkers are the base-labile 4-hydroxymethyl benzoic acid (HMBA) linker for the attachment of C-terminal carboxyl groups or the acid-labile para-sulfonyl-phenoxyacetyl (SPA) linker which permits the attachment of agmatine through its guanidino group.

When peptides with an amidated C-terminus are synthesized by using Boc strategy, the preferred resin is MBHA. Attachment of the C-terminal amino acid to this resin can be accomplished by the standard DIC-mediated coupling method described in Table I.

In order to prepare peptides with a C-terminal ethylamide (-NHEt) modification, the Merrifield resin or HMBA-MBHA resin can be used in conjunction with the Boc strategy. Loading of the C-terminal amino acid onto the Merrifield resin is done by coupling mediated by potassium fluoride (KF) or cesium salt at elevated temperature.

For the synthesis of peptides having Agm at the C-terminus, it is preferred that the support phase is MBHA resin or an aminomethyl resin. The guanidino group of Boc-Agm is joined to the support polymer through a stable, but readily cleavable linker such as the para-sulfonyl-phenoxyacetyl (SPA) moiety. The alpha-amino-Boc-protected Agm is reacted with the chlorosulfonyl phenoxyacetic acid Cl-SO_2-C_6H_4-O-CH_2-COOH to form Boc-Agm-SO_2-C_6H_4-O-CH_2-COOH. This compound is then coupled to the support polymer e.g. to MBHA resin using DIC or HBTU-HOBt-DIEA as activating reagent to yield Boc-Agm-SPA-MBHA.

3. Amino Acid Derivatives Used

Bifunctional amino acids, i.e. those not having side chain functional groups, are mostly used in the form of their N-alpha Boc- or Fmoc- derivatives for synthesis. Thus, Boc-Gly-OH or Fmoc-Gly-OH is typically used for incorporating the Gly residue. The naturally occurring

bifunctional amino acids are Gly, Ala, Val, Leu, Ile, Phe, and Pro, and some well-known non-coded bifunctional amino acids used in this invention are Abu, Aib, and Nle.

Some of the amino acid residues of the peptides have side chain functional groups which are reactive with reagents used in coupling or deprotection. When such side chain groups are present, suitable protecting groups are joined to these functional groups to prevent undesirable chemical reactions occurring during the reactions used to form the peptides. The following general rules are followed in selecting a particular side chain protecting group: (a) the protecting group preferably retains its protecting properties and is not split off under coupling conditions, (b) the protecting group should be stable under conditions for removing the alpha amino protecting group at each step of the synthesis, (c) the side chain protecting group must be removable upon the completion of the synthesis of the desired amino acid sequence, under reaction conditions that will not undesirably alter the peptide chain.

When Boc-amino acids are used in the synthesis, the reactive side chain functional groups can be protected as follows: Tos or nitro (NO_2) for Arg and Har; cHx or Fm for Asp and Glu; Bom for His; 2ClZ or Fmoc for Lys and Orn; Bzl for Ser and Thr; For for Trp; and 2BrZ for Tyr. The side chains of Asn and Gln are unprotected. In the case of Fmoc synthesis, the reactive side chain functional groups can be protected by other appropriate protective groups as follows: 2,2,4,6,7-pentamethyl-dihydrobenzofurane-5-sulfonyl (Pbf) or bis-Boc for Arg and Har; tert-butyl (tBu) for Asp and Glu; no protective group or trityl (Trt) protection for Asn and Gln; Trt for His; Boc or 4-methoxytrityl (Mmt) for Lys and Orn; tBu or Trt for Ser and Thr; Boc for Trp; and tBu or 2-chlorotrityl (2ClTrt) for Tyr.

In addition to the widely known coded and non-coded amino acids mentioned above, some of the peptides of this application contain less common non-coded amino acids such as para-amidino-phenylalanine (Amp); para-guanidino-phenylalanine (Gup); cyclohexylalanine (Cha); 1,2,3,4-tetrahydronorharman-3-carboxylic acid (Tpi); (2-naphthyl)alanine (2-Nal); (3,3-diphenyl)alanine (Dip); para-amino-phenylalanine [Phe(pNH_2)]; para-nitro-phenylalanine [Phe(pNO_2)]; (3-pyridyl)alanine (3-Pal); O-ethyl-tyrosine [Tyr(Et)]; and para-benzoyl-phenylalanine (Bpa). These amino acid residues are incorporated into the peptides by coupling the suitable protected amino acid derivatives. A non-exclusive list of such protected amino acid derivatives that can be used is as follows: Boc-Amp(Alloc)-OH, Boc-Amp-OH, Fmoc-Amp(Alloc)-OH, Fmoc-Amp-OH, Boc-Gup(Tos)-OH, Boc-Gup-OH, Fmoc-Gup($Boc)_2$-OH, Fmoc-Gup-OH, Boc-Cha-OH, Boc-Tpi-OH, Boc-2-Nal-OH, Boc-Dip-OH, Boc-Phe(pNH-Z)-OH, Boc-Phe(pNO_2)-OH, Boc-3-Pal-OH, Boc-Tyr(Et)-OH, and Boc-Bpa-OH. The protected derivatives of noncoded amino acids mentioned above are commonly available from several commercial suppliers, including Bachem (King of Prussia, PA), Peptides International (Louisville, KY), Novabiochem (San Diego, CA), Advanced ChemTech (Louisville, KY), and RSP Amino Acid Analogues DBA (Worcester, MA).

4. Stepwise Coupling of Amino Acid Residues

Utilizing the above mentioned support polymers and after loading of the C-terminal amino acid or Agm residue, the peptide itself may suitably be built up by solid phase synthesis in the conventional manner. Each protected amino acid is coupled in about a three-fold molar excess, with respect to resin-bound free amino residues, and the coupling may be carried out in a medium such as DMF—DCM (1:1) or in DMF or DCM alone. The selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as coupling reagents are N,N'-diisopropyl carbodiimide (DIC), or HBTU combined with HOBt in the presence of DIEA. The success of the coupling reaction at each stage of the synthesis is preferably monitored by the ninhydrin reaction. In cases where incomplete coupling occurs, either the coupling procedure is repeated, or the resin-bound unreacted amino residues are acetylated using a capping reagent, before removal of the alpha amino protecting group. Suitable capping reagents are 1-acetylimidazole and Ac_2O—pyridine.

Final acylation of the N-terminus of the peptide with monocarboxylic acids is done in the same way as the previous couplings, with the difference that the appropriate carboxylic acid is used instead of an amino acid. When dicarboxylic acids are attached to the N-terminus and it is desired that only one –COOH group reacts with the amino terminus of the peptide (that is, monoamides of these acids are prepared), the anhydrides of the respective dicarboxylic acids can be used for coupling. The cyclic anhydrides of many dicarboxylic acids are commercially available; in other cases the pre-formed anhydrides of these acids are prepared by treatment with DIC and used for coupling.

5. Cleavage of the Peptide from the Support Polymer and Removal of the Side-Chain Protecting Groups

When the synthesis is complete, the peptide is cleaved from the support phase and its side-chain protecting groups are removed.

In cases where peptides with an amidated C-terminus (-$CONH_2$) or with a C-terminal carboxyl group (-COOH) are prepared by Boc strategy on an MBHA, Merrifield, or PAM resin, the removal of the peptide from the resin is performed by treatment with a reagent such as liquid hydrogen fluoride (HF). This is also the case for peptides synthesized on the Boc-Agm-SPA-MBHA resin. In some instances, the liquid HF also cleaves all the remaining side chain protecting groups. However, if side chain protecting groups resistant to HF treatment are present on the peptide, additional cleavage steps should be performed in order to remove these protecting groups. Thus, Fm and Fmoc protecting groups are removed by treatment with 20% piperidine in DMF, while All and Alloc groups are removed by treatment with $Pd(PPh_3)_4$ catalyst and nucleophilic scavengers, prior to or after the HF treatment.

Suitably, the dried and protected peptide-resin is treated with a mixture consisting of 1.0 mL m-cresol and 10 mL anhydrous hydrogen fluoride per gram of peptide-resin for 60-120 min at 0°C to cleave the peptide from the resin as well as to remove the HF-labile side chain protecting groups. After the removal of the hydrogen fluoride under a stream of nitrogen and vacuum, the free peptides are precipitated with ether, filtered, washed with ether and ethyl acetate, extracted with 50% acetic acid, and lyophilized.

In cases where peptides with an ethylamide (–NHEt) C-terminus are prepared by Boc strategy on the Merrifield or HMBA-MBHA resin, the protected peptides are first cleaved from the resin by ethylamine ($EtNH_2$) mediated aminolysis. Suitably, liquid $EtNH_2$ is transferred into a cooled, heavy-walled glass flask that contains the dried and protected peptide-resin. The quantity of liquid $EtNH_2$ should be sufficient to cover the peptide-resin. The flask is stoppered, and shaken with the liquid $EtNH_2$ for 3.5 hours at room temperature in order to allow for the reaction to take place. After this, the flask is cooled in a dry ice bath, opened, and the liquid $EtNH_2$ is filtered off the solid residue that contains a mixture of resin and cleaved peptide, the peptide still having the protecting groups attached. The solid residue is dried and subjected to HF treatment as described above, in order to remove the side chain protecting groups of the peptide.

6. Purification

The purification of the crude peptides can be effected using procedures well known in peptide chemistry. For example, purification may be performed on a MacRabbit HPLC system (Rainin Instrument Co. Inc., Woburn, MA) with a Knauer UV Photometer and a Kipp and Zonen BD40 Recorder using a Vydac 218TP510 reversed-phase column (10 x 250 mm, packed with C18 silica gel, 300 Å pore size, 5 µm particle size) (The Separations Group Inc., Hesperia, CA). The column is eluted with a solvent system consisting of (A) 0.1% aqueous TFA and (B) 0.1% TFA in 70% aqueous MeCN in a linear gradient mode (e.g., 30-55% B in 120 min). The eluent is monitored at 220 nm, and fractions are examined by analytical HPLC using a Hewlett-Packard Model HP-1090 liquid chromatograph and pooled to give maximum purity. Analytical HPLC is carried out on a Vydac 218TP52 reversed-phase column (2 x 250 mm, C18, 300 Å, 5 µm) using isocratic elution with a solvent system consisting of (A) and (B) defined above. The peaks are monitored at 220 and 280 nm. The peptides are judged to be substantially (>95%) pure by analytical HPLC. Molecular masses are checked by electrospray mass spectrometry, and the expected amino acid compositions are confirmed by amino acid analysis.

D. Pharmaceutical Compositions and Mode of Administration

The peptides of the invention may be administered in the form of pharmaceutically acceptable, nontoxic salts, such as acid addition salts. Illustrative of such acid addition salts are

hydrochloride, hydrobromide, sulphate, phosphate, fumarate, gluconate, tannate, maleate, acetate, trifluoroacetate, citrate, benzoate, succinate, alginate, pamoate, malate, ascorbate, tartarate, and the like. Particularly preferred antagonists are salts of low solubility, e.g., pamoate salts and the like. These exhibit long duration of activity.

The compounds of the present invention are suitably administered to subject humans or animals subcutaneously (s.c.), intramuscularly (i.m.), or intravenously (i.v); intranasally or by pulmonary inhalation; by transdermal delivery; or in a depot form (e.g., microcapsules, microgranules, or cylindrical rod like implants) formulated from a biodegradable suitable polymer (such as D,L-lactide-coglycolide), the former two depot modes being preferred. Other equivalent modes of administration are also within the scope of this invention, i.e., continuous drip, cutaneous patches, depot injections, infusion pump and time release modes such as microcapsules and the like. Administration is in any physiologically acceptable injectable carrier, physiological saline being acceptable, though other carriers known to the art may also be used.

The peptides are preferably administered parenterally, intramuscularly, subcutaneously or intravenously with a pharmaceutically acceptable carrier such as isotonic saline. Alternatively, the peptides may be administered as an intranasal spray with an appropriate carrier or by pulmonary inhalation. One suitable route of administration is a depot form formulated from a biodegradable suitable polymer, e.g., poly-D,L-lactide-coglycolide as microcapsules, microgranules or cylindrical implants containing dispersed antagonistic compounds.

The amount of peptide needed depends on the type of pharmaceutical composition and on the mode of administration. In cases where human subjects receive solutions of GH-RH antagonists, administered by i.m. or s.c. injection, or in the form of intranasal spray or pulmonary inhalation, the typical doses are between 2-20 mg/day/patient, given once a day or divided into 2-4 administrations/day. When the GH-RH antagonists are administered intravenously to human patients, typical doses are in the range of 8-80 µg/kg of body weight/day, divided into 1-4 bolus injections/day or given as a continuous infusion. When depot preparations of the GH-RH antagonists are used, e.g. by i.m. injection of pamoate salts or other salts of low solubility, or by i.m. or s.c. administration of microcapsules, microgranules, or implants containing the antagonistic compounds dispersed in a biodegradable polymer, the typical doses are between 1-10 mg antagonist/day/patient.

E. Therapeutic Uses of GH-RH Antagonists

The most important therapeutic applications of GH-RH antagonists are expected to be in the field of oncology and endocrinology. Some of the GH-RH antagonists act predominantly at the pituitary level and have stronger endocrine effects, inhibiting the GH-RH-evoked GH release, and ultimately decreasing the serum levels of GH and IGF-I. Other GH-RH antagonists act

predominantly at the tumor level, by blocking the tumoral receptors for GH-RH, reducing the production of various autocrine/paracrine tumor growth factors (such as IGF-I, IGF-II, GH, VEGF, FGF) and/or downregulating their receptors, and thus exert stronger inhibitory effects on tumor growth. These antagonists can also be used as carrier systems linked to radionuclides for tumor localization or therapy, or conjugated to chemotherapeutic agents or toxins. Such hybrid compounds can be actively targeted to cancer for diagnostic or therapeutic purposes. Yet other GH-RH antagonists act by multiple mechanisms of action, that is by endocrine mechanisms and by direct effects on tumors at the same time. Thus, the main therapeutic indications of various GH-RH antagonists differ based on their preferential mechanism of action.

Analogs of GH-RH with antagonistic action on the pituitary can be used in situations where it is beneficial to suppress serum levels of GH and IGF-I. Thus they are indicated for the therapy of endocrine disorders characterized by excessive production of GH and IGF-I, as well as for the treatment of cancers that express receptors for IGF-I, IGF-II, or GH, and the proliferation of which is stimulated by these growth factors.

Somatostatin analogs and GH antagonists are also available for the treatment of endocrine conditions caused by GH and IGF-I. However, GH-RH antagonists offer unique therapeutical benefits unobtainable by the use of somatostatin analogs and GH antagonists. These benefits are due to the multiple mechanisms of action of GH-RH antagonists, namely that they exert GH- and IGF-I-independent direct effects on tumors and other target sites, in addition to inhibiting the endocrine axis for GH and IGF-I. GH-RH antagonists may be given alone or together with somatostatin analogs, a combination which more completely suppresses GH and IGF-I levels. An undesired side-effect of GH antagonists, which can be avoided by the administration of GH-RH antagonists, is the elevation of serum GH levels through a feed-back mechanism.

One disease caused by excess growth hormone is acromegaly, which is manifested in an abnormal enlargement of the bones of the face and extremities. GH-RH antagonists could alleviate the clinical manifestations of acromegaly, e.g. the enlargement of facial and extremity bones, the enlargement of heart, and other structural and functional abnormalities of the cardiovascular system. The GH-RH antagonists may also be used to treat diabetic retinopathy (the main cause of blindness in diabetics) and diabetic nephropathy, in which damage to the eye and kidney respectively is thought to be due to GH. Diabetic patients can also benefit from the increased insulin sensitivity produced by GH-RH antagonists, an effect linked to the ability of these compounds to reduce the GH and IGF-I levels. In addition, since they inhibit GH release, GH-RH antagonists can be used to slow down the progression of muscular dystrophy.

Drugs with anti-growth factor properties such as GH-RH antagonists can also be of benefit in controlling or slowing down the progression of some clinicopathologic processes in conditions such as idiopathic pulmonary fibrosis, systemic sclerosis and hypertrophic cardiomyopathy, where

the present medical therapies have relatively little to offer. In addition, no drug therapy has been shown to be effective in decreasing the incidence of restenosis after percutaneous transluminal coronary angioplasty (PTCA) and new approaches must be devised, including the use of GH-RH antagonists. Some gynecologic conditions, such as myoma, endometriosis, and polycystic ovary syndrome, can also be treated with GH-RH antagonists in combination with luteinizing hormone-releasing hormone (LH-RH) agonists or antagonists. GH-RH antagonists are also available for treatment of benign prostatic hyperplasia (BPH), and hyperplastic and benign proliferative disorders of other normal organs in which the GH-RH receptors are present.

However, the main applications of GH-RH antagonists are in the field of cancer. GH-RH antagonists, especially those with strong direct effects at the tumor level, are indicated for the inhibition of growth of primary tumors and for the suppression of their metastatic spread. Since the antiproliferative effects of GH-RH antagonists are exerted by several mechanisms, these compounds are available for the treatment of a large variety of cancers, such as those that depend on autocrine/paracrine and endocrine stimulation by GH-RH, IGF-I, IGF-II, GH, VEGF, and FGF.

GH-RH antagonists are available for the treatment of tumors that express GH-RH receptors and use GH-RH as an autocrine/paracrine growth factor. Such malignancies include, but are not limited to, cancers of the lung, prostate, breast, ovary, endometrium, stomach, intestine, pancreas, kidney, bone, liver, as well as glioblastomas, pheochromocytomas, melanomas, and lymphomas. By blocking the tumoral receptors for GH-RH, these antagonists prevent the stimulatory action of GH-RH, resulting in inhibition of tumor growth.

One advantage of GH-RH antagonists over somatostatin analogs is based on the fact that GH-RH antagonists may be utilized for suppression of tumors which do not have somatostatin receptors but express the tumoral receptors for GH-RH, for example human osteogenic sarcomas.

Malignancies that express the IGF-I receptors, and depend on IGF-I and/or IGF-II as growth factors, are available for therapy with GH-RH antagonists. These malignancies include, among others, lung cancers, prostatic, breast, ovarian, endometrial, gastric, colorectal, pancreatic, renal, and hepatic cancers, sarcomas, and brain tumors. The ability of GH-RH antagonists to decrease serum IGF-I levels, inhibit the autocrine/paracrine production of IGF-I and/or IGF-II in the tumor tissue, and downregulate the expression level of IGF-I receptor, is beneficial for cancer therapy.

Breast cancers and other types of cancer that depend on GH as a growth factor, can be treated with GH-RH antagonists. The ability of GH-RH antagonists to reduce serum GH levels, inhibit the autocrine production of GH, and downregulate GH receptor expression, beneficiate the treatment of certain breast cancers and other types of tumors as well.

GH-RH antagonists are available as inhibitors of angiogenesis, in view of their inhibitory activity on the synthesis of VEGF by tumor tissues and normal endothelial cells, and considering their antiproliferative effect on endothelial cells. Thus GH-RH antagonists could be beneficial for the treatment of those tumors that strongly depend on VEGF and neoangiogenesis.

EXAMPLES

The present invention is described in connection with the following examples which are set forth for the purposes of illustration only. In the examples, optically active protected amino acids in the L-configuration are used except where specifically noted.

The following Examples set forth suitable methods of synthesizing the novel GH-RH antagonists by the solid-phase technique.

EXAMPLE I

$CH_3(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-Phe(pCl)^6-Thr^7-Ala^8-His^9-Tyr(Et)^{10}-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 (Peptide 80)

{[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2}

The synthesis is conducted in a stepwise manner using manual solid phase peptide synthesis equipment. Briefly, para-methylbenzhydrylamine (MBHA) resin (Bachem, King of Prussia, PA) (720 mg, 0.50 mmol) is neutralized with 5% DIEA in DCM and washed according to the protocol described in Table I. The solution of Boc-Har(NO_2)-OH (500 mg, 1.5 mmol) in DMF-DCM (1:1) is shaken with the neutralized resin and DIC (235 µL, 1.5 mmol) in a manual solid phase peptide synthesis apparatus for 1 hour. After the completion of the coupling reaction is proved by negative ninhydrin test, the deprotection and neutralization protocols described in Table I are performed in order to remove the Boc protecting group and prepare the peptide-resin for coupling of the next amino acid. The synthesis is continued and the peptide chain is built stepwise by coupling the following protected amino acids in the indicated order on the resin to obtain the desired peptide sequence: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH.

These protected amino acid residues (also commonly available from Bachem) are represented above according to a well accepted convention. The suitable protecting group for the

side chain functional group of particular amino acids appears in parentheses. The OH groups in the above formulae indicate that the carboxyl terminus of each residue is free.

The protected amino acids (1.5 mmol each) are coupled with DIC (235 µL, 1.5 mmol) with the exceptions of Boc-Asn-OH and Boc-Gln-OH which are coupled with their preformed HOBt esters. After removal of the N^{α}-Boc protecting group from Tyr^1, the peptide is acylated overnight with octanoic acid [$CH_3(CH_2)_6COOH$] (475 µL, 3 mmol) using DIC (235 µL, 1.5 mmol) as a coupling agent.

In order to cleave the peptide from the resin and deprotect it, a portion of 130 mg of the dried peptide resin is stirred with 0.5 mL m-cresol and 5 mL hydrogen fluoride (HF) at 0 °C for 2 hours. After evaporation of the HF under a stream of nitrogen and in vacuo, the residue is washed with dry diethyl ether and ethyl acetate. The cleaved and deprotected peptide is dissolved in 50% acetic acid and separated from the resin by filtration. After dilution with water and lyophilization, 75 mg crude product is obtained.

The crude peptide is checked by analytical HPLC using a Hewlett-Packard Model HP-1090 liquid chromatograph with a Supelco Discovery HS C18 reversed-phase column (2.1 mm x 5 cm, packed with C18 silica gel, 120 Å pore size, 3 µm particle size) (Supelco, Bellefonte, PA) and linear gradient elution (e.g., 40-70% B), with a solvent system consisting of (A) 0.1% aqueous TFA and (B) 0.1% TFA in 70% aqueous MeCN. For purification by semipreparative HPLC, 75 mg of crude peptide is dissolved in AcOH/H_2O, stirred, filtered and applied on a Beckman Ultraprep ODS column (21.2 mm x 15 cm, packed with C18 silica gel, 300 Å pore size, 10 µm particle size). The column is eluted with a solvent system described above in a linear gradient mode (e.g., 40-60% B in 120 min); flow rate 10 mL/min. The eluent is monitored at 220 nm, and fractions are examined by analytical HPLC. Fractions with purity higher than 95% are pooled and lyophilized to give 7.7 mg pure product. The analytical HPLC is carried out on a Supelco C18 reversed-phase column described above using isocratic elution with a solvent system described above with a flow rate of 0.2 mL/min. The peaks are monitored at 220 and 280 nm. The product is judged to be substantially (>95%) pure by analytical HPLC. Molecular mass is checked by electrospray mass spectrometry, and the expected amino acid composition is confirmed by amino acid analysis.

Peptide 2, Peptide 4, Peptide 6, Peptide 8, Peptide 10, Peptide 12, Peptide 14, Peptide 16, Peptide 17, Peptide 79, Peptide 86, Peptide 92, Peptide 93, Peptide 94, Peptide 95, Peptide 96, Peptide 104, and Peptide 105 are synthesized in the same manner as Peptide 80, except that these peptides also contain other amino acid substitutions and other acyl moieties originating from fatty acids at their N-terminl.

For the synthesis of Peptide 2, the chemical structure of which is [$CH_3(CH_2)_4CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH,

Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_4COOH$.

For the synthesis of Peptide 4, the chemical structure of which is $[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_8COOH$.

For the synthesis of Peptide 6, the chemical structure of which is $[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_8COOH$.

For the synthesis of Peptide 8, the chemical structure of which is $[CH_3(CH_2)_{10}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_{10}COOH$.

For the synthesis of Peptide 10, the chemical structure of which is $[CH_3(CH_2)_{12}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH,

Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_{12}COOH$.

For the synthesis of Peptide 12, the chemical structure of which is $[CH_3(CH_2)_{14}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_{14}COOH$.

For the synthesis of Peptide 14, the chemical structure of which is $[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D\text{-}Arg^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_8COOH$.

For the synthesis of Peptide 16, the chemical structure of which is $[CH_3(CH_2)_{14}CO\text{-}Phe^0, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Phe-OH, followed by acylation with $CH_3(CH_2)_{14}COOH$.

For the synthesis of Peptide 17, the chemical structure of which is $[CH_3(CH_2)_{14}CO\text{-}D\text{-}Phe^0, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH,

Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-D-Phe-OH, followed by acylation with $CH_3(CH_2)_{14}COOH$.

For the synthesis of Peptide 79, the chemical structure of which is $[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 86, the chemical structure of which is $[CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 92, the chemical structure of which is $[CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 93, the chemical structure of which is $[CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Cit^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Cit-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 94, the chemical structure of which is

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, His^{15}, His^{20}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-His(Bom)-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 95, the chemical structure of which is

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 96, the chemical structure of which is

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 104, the chemical structure of which is $[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 105, the chemical structure of which is $[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-*D*-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

HF cleavage and deprotection, and subsequent purification by semipreparative HPLC of Peptide 2, Peptide 4, Peptide 6, Peptide 8, Peptide 10, Peptide 12, Peptide 14, Peptide 16, Peptide 17, Peptide 79, Peptide 86, Peptide 92, Peptide 93, Peptide 94, Peptide 95, Peptide 96, Peptide 104, and Peptide 105 are done as described in the case of Peptide 80. The purified compounds are judged to be substantially (>95%) pure by analytical HPLC. Their molecular masses are checked by electrospray mass spectrometry, and the expected amino acid compositions are confirmed by amino acid analysis.

EXAMPLE II

$HOOC(CH_2)_{12}CO\text{-}Tyr^1\text{-}D\text{-}Arg^2\text{-}Asp^3\text{-}Ala^4\text{-}Ile^5\text{-}Phe(pCl)^6\text{-}Thr^7\text{-}Asn^8\text{-}Arg^9\text{-}Tyr^{10}\text{-}Arg^{11}\text{-}Lys^{12}\text{-}Val^{13}\text{-}Leu^{14}\text{-}Abu^{15}\text{-}Gln^{16}\text{-}Leu^{17}\text{-}Ser^{18}\text{-}Ala^{19}\text{-}Arg^{20}\text{-}Lys^{21}\text{-}Leu^{22}\text{-}Leu^{23}\text{-}Gln^{24}\text{-}Asp^{25}\text{-}Ile^{26}\text{-}Nle^{27}\text{-}D\text{-}Arg^{28}\text{-}Har^{29}\text{-}NH_2$ (Peptide 11)

$\{[HOOC(CH_2)_{12}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2\}$

The synthesis is conducted in a stepwise manner using manual solid phase peptide synthesis equipment. Briefly, MBHA resin (Bachem, King of Prussia, PA) (720 mg, 0.50 mmol) is neutralized with 5% DIEA in DCM and washed according to the protocol described in Table I. The solution of Boc-Har(NO_2)-OH (500 mg, 1.5 mmol) in DMF-DCM (1:1) is shaken with the neutralized resin and

DIC (235 µL, 1.5 mmol) in a manual solid phase peptide synthesis apparatus for 1 hour. After the completion of the coupling reaction is proved by negative ninhydrin test, the deprotection and neutralization protocols described in Table I are performed in order to remove the Boc protecting group and prepare the peptide-resin for coupling of the next amino acid. The synthesis is continued and the peptide chain is built stepwise by coupling the following protected amino acids in the indicated order on the resin to obtain the desired peptide sequence: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH. The protected amino acids (1.5 mmol each) are coupled with DIC (235 µL, 1.5 mmol) with the exceptions of Boc-Asn-OH and Boc-Gln-OH which are coupled with their preformed HOBt esters.

After removal of the N^{α}-Boc protecting group from Tyr^1, the peptide is acylated with the pre-formed symmetrical anhydride of 1,12-dodecanedicarboxylic acid which is prepared as follows. For synthesis on the scale of 0.5 mmol peptide, 388 mg (1.5 mmol) 1,12-dodecanedicarboxylic acid [$HOOC(CH_2)_{12}COOH$] is dissolved in 5 to10 mL of DMF-DCM (1:1), 235 µL (1.5 mmol) DIC is added to this solution, and the mixture is allowed to stand at room temperature for 30 min. After this period of time, the mixture is transferred into the synthesis vessel containing the peptide-resin with a free amino terminus on Tyr^1, and acylation is carried out overnight.

In order to cleave the peptide from the resin and deprotect it, a portion of 274 mg of the dried peptide resin is stirred with 0.5 mL m-cresol and 5 mL hydrogen fluoride (HF) at 0 °C for 2 hours. After evaporation of the HF under a stream of nitrogen and in vacuo, the residue is washed with dry diethyl ether and ethyl acetate. The cleaved and deprotected peptide is dissolved in 50 % acetic acid and separated from the resin by filtration. After dilution with water and lyophilization, 160 mg crude product is obtained.

The crude peptide is checked by analytical HPLC using a Hewlett-Packard Model HP-1090 liquid chromatograph with a Supelco Discovery HS C18 reversed-phase column (2.1 mm x 5 cm, packed with C18 silica gel, 120 Å pore size, 3 µm particle size) (Supelco, Bellefonte, PA) and linear gradient elution (e.g., 50-80% B), with a solvent system consisting of (A) 0.1% aqueous TFA and (B) 0.1% TFA in 70% aqueous MeCN. For purification by semipreparative HPLC, 160 mg of crude peptide is dissolved in $AcOH/H_2O$, stirred, filtered and applied on a Beckman Ultraprep ODS column (21.2 mm x 15 cm, packed with C18 silica gel, 300 Å pore size, 10 µm particle size). The column is eluted with a solvent system described above in a linear gradient mode (e.g., 50-70% B in 120 min); flow rate 10 mL/min. The eluent is monitored at 220 nm, and fractions are examined by analytical HPLC. Fractions with purity higher than 95% are pooled and lyophilized to give 6.0 mg pure product. The analytical HPLC is carried out on a Supelco C18 reversed-phase column described above using isocratic elution with a solvent system described above with a flow rate of 0.2 mL/min. The peaks are monitored at 220 and 280 nm. The product is judged to be

substantially (>95%) pure by analytical HPLC. Molecular mass is checked by electrospray mass spectrometry, and the expected amino acid composition is confirmed by amino acid analysis.

Peptide 3, Peptide 5, Peptide 7, Peptide 9, Peptide 13, Peptide 25, Peptide 81, Peptide 82, Peptide 88, Peptide 102, Peptide 108, and Peptide 109 are synthesized in the same manner as Peptide 11, except that these peptides also contain other amino acid substitutions and other acyl moieties originating from dicarboxylic acids at their N-termini.

For the synthesis of Peptide 3, the chemical structure of which is [$HOOC(CH_2)_4CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_4COOH$.

For the synthesis of Peptide 5, the chemical structure of which is [$HOOC(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_6COOH$.

For the synthesis of Peptide 7, the chemical structure of which is [$HOOC(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_6COOH$.

For the synthesis of Peptide 9, the chemical structure of which is [$HOOC(CH_2)_{10}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{10}COOH$.

For the synthesis of Peptide 13, the chemical structure of which is
[$HOOC(CH_2)_{14}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,
the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{14}COOH$.

For the synthesis of Peptide 25, the chemical structure of which is
[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,
the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Cit-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 81, the chemical structure of which is
[$HOOC(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,
the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_8COOH$.

For the synthesis of Peptide 82, the chemical structure of which is

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 88, the chemical structure of which is

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 102, the chemical structure of which is

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 108, the chemical structure of which is

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-

His(Bom)-OH, Boc-Dip-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 109, the chemical structure of which is $[HOOC(CH_2)_{12}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

HF cleavage and deprotection, and subsequent purification by semipreparative HPLC of Peptide 3, Peptide 5, Peptide 7, Peptide 9, Peptide 13, Peptide 25, Peptide 81, Peptide 82, Peptide 88, Peptide 102, Peptide 108, and Peptide 109 are done as described in the case of Peptide 11. The purified compounds are judged to be substantially (>95%) pure by analytical HPLC. Their molecular masses are checked by electrospray mass spectrometry, and the expected amino acid compositions are confirmed by amino acid analysis.

EXAMPLE III

$PhAc\text{-}Tyr^1\text{-}D\text{-}Arg^2\text{-}Asp^3\text{-}Ala^4\text{-}Ile^5\text{-}Phe(pCl)^6\text{-}Thr^7\text{-}Asn^8\text{-}Har^9\text{-}Tyr(Me)^{10}\text{-}His^{11}\text{-}Lys^{12}\text{-}Val^{13}\text{-}Leu^{14}\text{-}Abu^{15}\text{-}Gln^{16}\text{-}Leu^{17}\text{-}Ser^{18}\text{-}Ala^{19}\text{-}Arg^{20}\text{-}Lys^{21}\text{-}Leu^{22}\text{-}Leu^{23}\text{-}Gln^{24}\text{-}Asp^{25}\text{-}Ile^{26}\text{-}Nle^{27}\text{-}D\text{-}Arg^{28}\text{-}Har^{29}\text{-}NH_2$

(Peptide 62)

$\{[PhAc\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2\}$

The synthesis is conducted in a stepwise manner using manual solid phase peptide synthesis equipment. Briefly, para-methylbenzhydrylamine (MBHA) resin (Bachem, King of Prussia, PA) (720 mg, 0.50 mmol) is neutralized with 5% DIEA in DCM and washed according to the protocol described in Table I. The solution of Boc-Har(NO_2)-OH (500 mg, 1.5 mmol) in DMF-DCM (1:1) is shaken with the neutralized resin and DIC (235 µL, 1.5 mmol) in a manual solid phase peptide synthesis apparatus for 1 hour. After the completion of the coupling reaction is proved by negative ninhydrin test, the deprotection and neutralization protocols described in Table I are performed in order to remove the Boc protecting group and prepare the peptide-resin for coupling of the next amino acid. The synthesis is continued and the peptide chain is built stepwise by coupling the following protected amino acids in the indicated order on the resin to obtain the desired peptide sequence: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-

Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH. The protected amino acids (1.5 mmol each) are coupled with DIC (235 µL, 1.5 mmol) with the exceptions of Boc-Asn-OH and Boc-Gln-OH which are coupled with their preformed HOBt esters. After removal of the N^{α}-Boc protecting group from Tyr^1, the peptide is acylated with phenylacetic acid (PhAc-OH) (272 mg, 2 mmol) using DIC (313 µL, 2 mmol).

In order to cleave the peptide from the resin and deprotect it, a portion of 286 mg of the dried peptide resin is stirred with 0.5 mL m-cresol and 5 mL hydrogen fluoride (HF) at 0 °C for 2 hours. After evaporation of the HF under a stream of nitrogen and in vacuo, the residue is washed with dry diethyl ether and ethyl acetate. The cleaved and deprotected peptide is dissolved in 50 % acetic acid and separated from the resin by filtration. After dilution with water and lyophilization, 155 mg crude product is obtained.

The crude peptide is checked by analytical HPLC using a Hewlett-Packard Model HP-1090 liquid chromatograph with a Supelco Discovery HS C18 reversed-phase column (2.1 mm x 5 cm, packed with C18 silica gel, 120 Å pore size, 3 µm particle size) (Supelco, Bellefonte, PA) and linear gradient elution (e.g., 40-70% B), with a solvent system consisting of (A) 0.1% aqueous TFA and (B) 0.1% TFA in 70% aqueous MeCN. For purification by semipreparative HPLC, 155 mg of crude peptide is dissolved in AcOH/H_2O, stirred, filtered and applied on a Beckman Ultraprep ODS column (21.2 mm x 15 cm, packed with C18 silica gel, 300 Å pore size, 10 µm particle size). The column is eluted with a solvent system described above in a linear gradient mode (e.g., 40-60% B in 120 min); flow rate 12 mL/min. The eluent is monitored at 220 nm, and fractions are examined by analytical HPLC. Fractions with purity higher than 95% are pooled and lyophilized to give 13.3 mg pure product. The analytical HPLC is carried out on a Supelco C18 reversed-phase column described above using isocratic elution with a solvent system described above with a flow rate of 0.2 mL/min. The peaks are monitored at 220 and 280 nm. The product is judged to be substantially (>95%) pure by analytical HPLC. Molecular mass is checked by electrospray mass spectrometry, and the expected amino acid composition is confirmed by amino acid analysis.

Peptide 15, Peptide 18, Peptide 19, Peptide 21, Peptide 22, Peptide 23, Peptide 24, Peptide 26, Peptide 27, Peptide 28, Peptide 32, Peptide 33, Peptide 34, Peptide 35, Peptide 36, Peptide 37, Peptide 38, Peptide 39, Peptide 40, Peptide 41, Peptide 42, Peptide 43, Peptide 53, Peptide 54, Peptide 55, Peptide 57, Peptide 58, Peptide 63, Peptide 65, Peptide 69, Peptide 84, Peptide 85, Peptide 90, and Peptide 91 are synthesized in the same manner as Peptide 62, except that these peptides also contain other substitutions.

For the synthesis of Peptide 15, the chemical structure of which is

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-

Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 18, the chemical structure of which is [PhAc-Arg^0, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 19, the chemical structure of which is [PhAc-D-Arg^0, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-D-Arg(Tos)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 21, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 22, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH,

Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Cit-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 23, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-D-Arg(Tos)-OH, Boc-Har(NO$_2$)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 24, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-D-Arg(Tos)-OH, Boc-Har(NO$_2$)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Cit-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 26, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, D-Ala^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO$_2$)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-D-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 27, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Abu^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO$_2$)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH,

Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Abu-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 28, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Cit-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 32, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, His^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-His(Bom)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 33, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Cha^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Cha-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 34, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tpi^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH,

Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tpi-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 35, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-2-Nal-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 36, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Dip-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 37, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNH_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Phe(pNH-Z)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 38, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Trp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH,

Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Trp(For)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 39, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNO_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Phe(pNO_2)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 40, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, 3-Pal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-3-Pal-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 41, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Et)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 42, the chemical structure of which is [PhAc-His^1, D-Arg^2, Tyr^6, Har^9, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH,

Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Bpa-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Tyr(2BrZ)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-His(Bom)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 43, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Har^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Har(NO_2)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 53, the chemical structure of which is [Hca-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with hydrocinnamic acid (Hca-OH).

For the synthesis of Peptide 54, the chemical structure of which is [Dat-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with des-amino-tyrosine (Dat).

For the synthesis of Peptide 55, the chemical structure of which is

[Ipa-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with indole-3-propionic acid (Ipa-OH).

For the synthesis of Peptide 57, the chemical structure of which is

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, D-Arg^{29}, Har^{30}]hGH-RH(1-30)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with Hca-OH.

For the synthesis of Peptide 58, the chemical structure of which is

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, D-Arg^{30}]hGH-RH(1-30)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with Hca-OH.

For the synthesis of Peptide 63, the chemical structure of which is

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Har^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-

Har(NO_2)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 65, the chemical structure of which is

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Cit^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Cit-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 69, the chemical structure of which is

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, His^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-His(Bom)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 84, the chemical structure of which is

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 85, the chemical structure of which is

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 90, the chemical structure of which is

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Cit-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 91, the chemical structure of which is

[1-Nac-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with 1-naphthylacetic acid (1-Nac-OH).

HF cleavage and deprotection, and subsequent purification by semipreparative HPLC of Peptide 15, Peptide 18, Peptide 19, Peptide 21, Peptide 22, Peptide 23, Peptide 24, Peptide 26, Peptide 27, Peptide 28, Peptide 32, Peptide 33, Peptide 34, Peptide 35, Peptide 36, Peptide 37, Peptide 38, Peptide 39, Peptide 40, Peptide 41, Peptide 42, Peptide 43, Peptide 53, Peptide 54, Peptide 55, Peptide 57, Peptide 58, Peptide 63, Peptide 65, Peptide 69, Peptide 84, Peptide 85, Peptide 90, and Peptide 91 are done as described in the case of Peptide 62. The purified compounds are judged to be substantially (>95%) pure by analytical HPLC. Their molecular masses are checked by electrospray mass spectrometry, and the expected amino acid compositions are confirmed by amino acid analysis.

EXAMPLE IV

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Amp^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2

(Peptide 67)

{[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2}

The synthesis is conducted in a stepwise manner using manual solid phase peptide synthesis equipment. Briefly, para-methylbenzhydrylamine (MBHA) resin (Bachem, King of Prussia, PA) (720 mg, 0.50 mmol) is neutralized with 5% DIEA in DCM and washed according to the protocol described in Table I. The solution of Boc-Har(NO_2)-OH (500 mg, 1.5 mmol) in DMF-DCM (1:1) is shaken with the neutralized resin and DIC (235 µL, 1.5 mmol) in a manual solid phase peptide synthesis apparatus for 1 hour. After the completion of the coupling reaction is proved by negative ninhydrin test, the deprotection and neutralization protocols described in Table I are performed in order to remove the Boc protecting group and prepare the peptide-resin for coupling of the next amino acid. The synthesis is continued and the peptide chain is built stepwise by coupling the following protected amino acids in the indicated order on the resin to obtain the desired peptide sequence: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH. The protected, noncoded amino acid Boc-Amp(Alloc)-OH is commercially available from RSP Amino Acid Analogues, Inc. (Worcester, MA). The protected amino acids (1.5 mmol each) are coupled with DIC (235 µL, 1.5 mmol), with the exceptions of Boc-Amp(Alloc)-OH, Boc-Asn-OH and Boc-Gln-OH which are coupled with 569 mg HBTU + 203 mg HOBt + 522 µL DIEA (1.5 : 1.5 : 3 mmol). After removal of the N^{α}-Boc protecting group from Tyr^{1}, the peptide is acylated with phenylacetic acid (PhAc-OH) (272 mg, 2 mmol) using DIC (313 µL, 2 mmol). The finished peptidyl resin, with all the side-chain protecting groups still attached, is washed 3x with DCM, 3x with MeOH, and dried under high vacuum.

The peptide-resin is then subjected to Pd(0)-catalyzed removal of the Alloc protecting group from the Amp^{9} residue of the peptide chain, by using the procedure described in the Novabiochem (San Diego, CA) Catalog 2002/2003. A portion of 255 mg peptidyl resin, with an estimated peptide content of 0.033 mmol, is weighed into a test tube and the tube is sealed with a rubber septum. The test tube is flushed with a stream of argon (Ar) gas delivered from a needle inserted through the septum. 116 mg $Pd(PPh_3)_4$ (0.1 mmol, or 3 equiv. relative to the Alloc groups present on the peptidyl resin) is weighed into another dry test tube, 4-5 mL of $CHCl_3$—AcOH—N-methylmorpholine (37:2:1 vol:vol:vol) is added, the catalyst is dissolved by bubbling a stream of Ar through the solution, and the tube is sealed with a rubber septum. This solution is transferred using an Ar flushed gas-tight syringe to the tube containing the resin, and the resulting mixture is left to stand for 2 hours with an occasional gentle agitation. Next, the resin is transferred to a sintered glass funnel and washed consecutively with 0.5% DIEA in DMF (to neutralize the resin) and

sodium diethyldithiocarbamate (0.5% w/w) in DMF (to remove the catalyst). After another wash with MeOH, the resin is dried again prior to HF cleavage of the peptide.

Cleavage of the peptide from the MBHA resin with a concomitant removal of the remaining protecting groups is achieved by HF treatment, as described in Examples I-III. Subsequent work-up and HPLC purification, performed as described in Examples I-III, yields 11.6 mg of pure Peptide 67 (>95% purity by analytical HPLC). Molecular mass is checked by electrospray mass spectrometry, and the expected amino acid composition is confirmed by amino acid analysis.

Peptide 30, Peptide 31, Peptide 64, Peptide 68, Peptide 73, Peptide 74, and Peptide 75 are synthesized in the same manner as Peptide 67, except that these peptides also contain other substitutions.

For the synthesis of Peptide 30, the chemical structure of which is [PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Amp(Alloc)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 31, the chemical structure of which is [PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Amp(Alloc)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 64, the chemical structure of which is [PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Amp^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Amp(Alloc)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-

Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 68, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Amp(Alloc)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 73, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 74, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 75, the chemical structure of which is [1-Nac-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH,

Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with 1-naphthylacetic acid (1-Nac-OH).

Deprotection, cleavage from the resin, and subsequent purification by semipreparative HPLC of Peptide 30, Peptide 31, Peptide 64, Peptide 68, Peptide 73, Peptide 74, and Peptide 75 are done as described in the case of Peptide 67. The purified compounds are judged to be substantially (>95%) pure by analytical HPLC. Their molecular masses are checked by electrospray mass spectrometry, and the expected amino acid compositions are confirmed by amino acid analysis.

EXAMPLE V

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NHEt

(Peptide 46)

{[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt}

The synthesis is conducted in a stepwise manner using manual solid phase peptide synthesis equipment. Briefly, Merrifield resin (Bachem, King of Prussia, PA) (3.0 g, with a substitution of 0.6 mmol/g) is pre-swollen in DCM, washed 3x times with DMF, then a solution of 2390 mg Boc-Har(Tos)-OH (5.4 mmol, corresponding to 3x molar excess) in 20-30 mL DMF and 314 mg solid KF (5.4 mmol, 3x molar excess) is added, in order to load the first amino acid onto the resin. The resin is shaken with the above mixture for 4 hours at 80 °C, and then the resin is filtered and washed as follows: 3x DMF, 3x DMF-water (1:1) (to remove the KF), 3x DMF, 3x DCM, and 3x MeOH. The resin is dried in vacuum for 24 hours to reach a constant weight. The weight of the dry resin with the first amino acid loaded [Boc-Har(Tos)-Merrifield resin] exceeds 3.5 g, indicating that the yield of loading is better than 70%.

1.5 g of Boc-Har(Tos)-Merrifield resin (approx. 0.5 mmol) is pre-swollen in DCM, and after deprotection with 50% TFA in DCM and neutralization with 5% DIEA in DCM, the peptide chain is built stepwise by coupling the following protected amino acids in the indicated order on the resin to obtain the desired peptide sequence: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH. In this synthesis, Boc-Har(Tos)-OH is used instead of Boc-Har(NO_2)-OH, since the nitro protected guanidino group is known to be attacked by bases such as ethylamine used in this synthesis, and partial decomposition of Har to Lys could occur with Boc-Har(NO_2)-OH. The protected amino acids (1.5 mmol each) are coupled with DIC (235 µL, 1.5 mmol) with the

exceptions of Boc-Asn-OH and Boc-Gln-OH which are coupled with their preformed HOBt esters. After removal of the N^{α}-Boc protecting group from Tyr^{1}, the peptide is acylated with phenylacetic acid (PhAc-OH) (272 mg, 2 mmol) using DIC (313 µL, 2 mmol), washed with DCM and MeOH, and dried.

In order to cleave the protected peptide from the resin by ethylamine ($EtNH_2$) mediated aminolysis and to obtain it with an ethylamide modification (-NHEt) at the C-terminus, a portion of 250 mg dry peptide resin is added into a round-bottom flask made of heavy-wall glass, the flask is placed in a dry ice-methanol cooling bath inside a well-ventilated fume hood, and liquid $EtNH_2$ (b.p.=16.6 °C, from Aldrich, shipped in metallic cylinder) is transferred into the flask in an amount sufficient to cover the peptide resin. The flask is stoppered, warmed to room temperature (caution: pressure develops inside), and shaken for 3 hours and 30 min in order to allow for the reaction to take place. After this time, the flask is placed again in the cooling bath, opened, and the liquid $EtNH_2$ is filtered off the solid residue that contains a mixture of resin and cleaved peptide, the peptide still having the protecting groups attached. After this procedure, the solid residue is subjected to vacuum overnight to remove any residual $EtNH_2$ and the humidity adsorbed.

The dry residue containing the cleaved, protected peptide is placed in the HF treatment apparatus and HF cleavage of the protecting groups is performed by treatment with 5 mL HF at 0 °C for 2 hours, in the presence of 0.5 mL m-cresol as scavenger. After evaporation of the HF under a stream of nitrogen and in vacuo, the residue is washed with dry diethyl ether and ethyl acetate. The cleaved and deprotected peptide is dissolved in 50 % acetic acid and separated from the resin by filtration. After dilution with water and lyophilization, 90-110 mg of crude product is typically obtained.

The peptide is purified by semipreparative HPLC and the eluting fractions are examined by analytical HPLC as described in Examples I-III. Fractions with purity higher than 95% are pooled and lyophilized to give 5 to 10 mg of pure Peptide 46. Molecular mass is checked by electrospray mass spectrometry, and the expected amino acid composition is confirmed by amino acid analysis.

Peptide 45, Peptide 47, Peptide 48, Peptide 49, Peptide 50, Peptide 56, Peptide 97, Peptide 98, Peptide 99, Peptide 100, Peptide 101, Peptide 106, Peptide 110, Peptide 113, Peptide 114, Peptide 115, Peptide 118, Peptide 119, Peptide 120, and Peptide 121 are synthesized in the same manner as Peptide 46, except that these peptides also contain other substitutions.

For the synthesis of Peptide 45, the chemical structure of which is [Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-

OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with Hca-OH.

For the synthesis of Peptide 47, the chemical structure of which is

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with Hca-OH.

For the synthesis of Peptide 48, the chemical structure of which is

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 49, the chemical structure of which is

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Aib^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Aib-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 50, the chemical structure of which is

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Orn^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-

Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 56, the chemical structure of which is

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^8, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with Hca-OH.

For the synthesis of Peptide 97, the chemical structure of which is

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_8COOH$.

For the synthesis of Peptide 98, the chemical structure of which is

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_8COOH$.

For the synthesis of Peptide 99, the chemical structure of which is

[$CH_3(CH_2)_{10}CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_{10}COOH$.

For the synthesis of Peptide 100, the chemical structure of which is

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with Hca-OH.

For the synthesis of Peptide 101, the chemical structure of which is

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHMe,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 106, the chemical structure of which is

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 110, the chemical structure of which is [HOOC(CH_2)$_{12}$CO -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with HOOC(CH_2)$_{12}$COOH.

For the synthesis of Peptide 113, the chemical structure of which is [CH_3(CH_2)$_8$CO -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with CH_3(CH_2)$_8$COOH.

For the synthesis of Peptide 114, the chemical structure of which is [CH_3(CH_2)$_8$CO -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with CH_3(CH_2)$_8$COOH.

For the synthesis of Peptide 115, the chemical structure of which is [CH_3(CH_2)$_8$CO -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH,

Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 118, the chemical structure of which is

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 119, the chemical structure of which is

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 120, the chemical structure of which is

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 121, the chemical structure of which is [$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt,

the following protected amino acids are coupled in the indicated order on the Merrifield resin: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-$Phe(pNO_2)$-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

Ethylamine mediated cleavage from the resin of Peptide 45, Peptide 47, Peptide 48, Peptide 49, Peptide 50, Peptide 56, Peptide 97, Peptide 98, Peptide 99, Peptide 100, Peptide 106, Peptide 110, Peptide 113, Peptide 114, Peptide 115, Peptide 118, Peptide 119, Peptide 120, and Peptide 121, as well as methylamine mediated cleavage from the resin of Peptide 101, followed by their deprotection by HF, and subsequent purification by semipreparative HPLC, are done as described in the case of Peptide 46. The purified compounds are judged to be substantially (>95%) pure by analytical HPLC. Their molecular masses are checked by electrospray mass spectrometry, and the expected amino acid compositions are confirmed by amino acid analysis.

EXAMPLE VI

Hca-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Har^9-$Tyr(Me)^{10}$-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-Agm^{30}

Peptide 59

{[Hca-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30)}

The synthesis is conducted in a stepwise manner using manual solid phase peptide synthesis equipment. The starting material of the synthesis is Boc-agmatine-N^G-sulfonyl-phenoxyacetyl-MBHA (Boc-Agm-SPA-MBHA) resin with a substitution of 0.3 mmol/g, which was obtained commercially from California Peptide Research, Inc. (Napa, CA). The synthesis of this resin has been described in U.S. Pat. No. 4,914,189 and in the scientific literature (Zarandi M, Serfozo P, Zsigo J, Bokser L, Janaky T, Olsen DB, Bajusz S, Schally AV, Int. J. Peptide Protein Res. 39: 211-217, 1992), hereby incorporated by reference. Briefly, Boc-Agm-SPA-MBHA resin (1.67 g, 0.50 mmol) is pre-swollen in DCM and then the deprotection and neutralization protocols described in Table I are performed in order to remove the Boc protecting group and prepare the peptide-resin for coupling of the next amino acid. The synthesis is continued and the peptide chain is built stepwise by coupling the following protected amino acids in the indicated order on the resin to obtain the desired peptide sequence: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-$Har(NO_2)$-OH,

Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH. The protected amino acids (1.5 mmol each) are coupled with DIC (235 µL, 1.5 mmol) with the exceptions of Boc-Asn-OH and Boc-Gln-OH which are coupled with their preformed HOBt esters. After removal of the N^{α}-Boc protecting group from Tyr^{1}, the peptide is acylated with hydrocinnamic acid (Hca-OH) (300 mg, 2 mmol) using DIC (313 µL, 2 mmol).

In order to cleave the peptide from the resin and deprotect it, a portion of 250 mg of the dried peptide resin is stirred with 0.5 mL m-cresol and 5 mL hydrogen fluoride (HF) at 0 °C for 2 hours. After evaporation of the HF under a stream of nitrogen and in vacuo, the residue is washed with dry diethyl ether and ethyl acetate. The cleaved and deprotected peptide is dissolved in 50 % acetic acid and separated from the resin by filtration. After dilution with water and lyophilization, 100-110 mg of crude product is typically obtained.

The peptide is purified by semipreparative HPLC and the eluting fractions are examined by analytical HPLC as described in Examples I-III. Fractions with purity higher than 95% are pooled and lyophilized to give 5 to 10 mg of pure Peptide 59. Molecular mass is checked by electrospray mass spectrometry, and the expected amino acid composition is confirmed by amino acid analysis.

Peptide 51, Peptide 52, and Peptide 60 are synthesized in the same manner as Peptide 59, except that these peptides also contain other substitutions.

For the synthesis of Peptide 51, the chemical structure of which is
[Hca-Tyr^{1}, D-Arg^{2}, $Phe(pCl)^{6}$, Har^{9}, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29),
the following protected amino acids are coupled in the indicated order on the Boc-Agm-SPA-MBHA resin: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with Hca-OH.

For the synthesis of Peptide 52, the chemical structure of which is
[PhAc-Tyr^{1}, D-Arg^{2}, $Phe(pCl)^{6}$, Har^{9}, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29),
the following protected amino acids are coupled in the indicated order on the Boc-Agm-SPA-MBHA resin: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

For the synthesis of Peptide 60, the chemical structure of which is [PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30), the following protected amino acids are coupled in the indicated order on the Boc-Agm-SPA-MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with PhAc-OH.

HF cleavage and deprotection, and subsequent purification by semipreparative HPLC of Peptide 51, Peptide 52, and Peptide 60 are done as described in the case of Peptide 59. The purified compounds are judged to be substantially (>95%) pure by analytical HPLC. Their molecular masses are checked by electrospray mass spectrometry, and the expected amino acid compositions are confirmed by amino acid analysis.

EXAMPLE VII

$CH_3(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-Phe(pCl)^6-Thr^7-Asn^8-Amp^9-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Peptide 70

{[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2}

All synthetic steps prior to coupling of the N-terminal acyl moiety to the peptide-resin are performed as described in Example IV. After removal of the N^{α}-Boc protecting group from Tyr^1, the peptide (0.5 mmol) is acylated overnight with octanoic acid [$CH_3(CH_2)_6COOH$] (475 µL, 3 mmol) using DIC (235 µL, 1.5 mmol) as a coupling agent. The finished peptidyl resin, with all the side-chain protecting groups still attached, is washed 3x with DCM, 3x with MeOH, and dried under high vacuum.

Subsequently, the peptidyl resin is subjected to Pd(0)-catalyzed removal of the Alloc protecting group from the Amp^9 residue of the peptide chain, as described in Example IV. The peptide resin is then washed with MeOH and dried, prior to HF cleavage of the peptide.

Cleavage of the peptide from the MBHA resin with a concomitant removal of the remaining protecting groups is achieved by HF treatment, as described in Examples I-III. Subsequent work-up and HPLC purification are performed as described in Examples I-III. After HF treatment of 300 mg dry peptidyl resin, 192 mg crude lyophilized peptide is obtained, the HPLC purification of which yields 17.1 mg pure Peptide 70 (>95% purity by analytical HPLC). Molecular mass is checked by electrospray mass spectrometry, and the expected amino acid composition is confirmed by amino acid analysis.

Peptide 76, Peptide 78, Peptide 87, Peptide 103, Peptide 111, and Peptide 112 are synthesized in the same manner as Peptide 70, except that these peptides also contain other substitutions.

For the synthesis of Peptide 76, the chemical structure of which is $[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 78, the chemical structure of which is $[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 87, the chemical structure of which is $[CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_6COOH$.

For the synthesis of Peptide 103, the chemical structure of which is $[CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_8COOH$.

For the synthesis of Peptide 111, the chemical structure of which is

$[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_8COOH$.

For the synthesis of Peptide 112, the chemical structure of which is

$[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $CH_3(CH_2)_8COOH$.

Deprotection, cleavage from the resin, and subsequent purification by semipreparative HPLC of Peptide 76, Peptide 78, Peptide 87, Peptide 103, Peptide 111, and Peptide 112 are done as described in the case of Peptide 70. The purified compounds are judged to be substantially (>95%) pure by analytical HPLC. Their molecular masses are checked by electrospray mass spectrometry, and the expected amino acid compositions are confirmed by amino acid analysis.

EXAMPLE VIII

$HOOC(CH_2)_{12}CO\text{-}Tyr^1\text{-}D\text{-}Arg^2\text{-}Asp^3\text{-}Ala^4\text{-}Ile^5\text{-}Phe(pCl)^6\text{-}Thr^7\text{-}Asn^8\text{-}Amp^9\text{-}Tyr(Me)^{10}\text{-}Arg^{11}\text{-}Lys^{12}\text{-}Val^{13}\text{-}Leu^{14}\text{-}Abu^{15}\text{-}Gln^{16}\text{-}Leu^{17}\text{-}Ser^{18}\text{-}Ala^{19}\text{-}Arg^{20}\text{-}Lys^{21}\text{-}Leu^{22}\text{-}Leu^{23}\text{-}Gln^{24}\text{-}Asp^{25}\text{-}Ile^{26}\text{-}Nle^{27}\text{-}D\text{-}Arg^{28}\text{-}Har^{29}\text{-}NH_2$ Peptide 72

{[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^8, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2}

All synthetic steps prior to coupling of the N-terminal acyl moiety to the peptide-resin are performed as described in Example IV. After removal of the N^{α}-Boc protecting group from Tyr^1, the peptide is acylated with the pre-formed symmetrical anhydride of 1,12-dodecanedicarboxylic acid which is prepared as follows. For synthesis on the scale of 0.5 mmol peptide, 388 mg (1.5 mmol) 1,12-dodecanedicarboxylic acid [$HOOC(CH_2)_{12}COOH$] is dissolved in 5 to10 mL of DMF-DCM (1:1), 235 µL (1.5 mmol) DIC is added to this solution, and the mixture is allowed to stand at room temperature for 30 min. After this period of time, the mixture is transferred into the synthesis vessel containing the peptide-resin with a free amino terminus on Tyr^1, and acylation is carried out overnight. The finished peptidyl resin, with all the side-chain protecting groups still attached, is washed 3x with DCM, 3x with MeOH, and dried under high vacuum.

Subsequently, the peptidyl resin is subjected to Pd(0)-catalyzed removal of the Alloc protecting group from the Amp^8 residue of the peptide chain, as described in Example IV. The peptide resin is then washed with MeOH and dried, prior to HF cleavage of the peptide.

Cleavage of the peptide from the MBHA resin with a concomitant removal of the remaining protecting groups is achieved by HF treatment, as described in Examples I-III. Subsequent work-up and HPLC purification are performed as described in Examples I-III. After HF treatment of 150 mg dry peptidyl resin, 82 mg crude lyophilized peptide is obtained, the HPLC purification of which yields 2.5 mg pure Peptide 72 (>95% purity by analytical HPLC). Molecular mass is checked by electrospray mass spectrometry, and the expected amino acid composition is confirmed by amino acid analysis.

Peptide 71, Peptide 77, Peptide 89, Peptide 107, Peptide 116, and Peptide 117 are synthesized in the same manner as Peptide 72, except that these peptides also contain other substitutions.

For the synthesis of Peptide 71, the chemical structure of which is

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^8, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_8COOH$.

For the synthesis of Peptide 77, the chemical structure of which is

$[HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 89, the chemical structure of which is

$[HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 107, the chemical structure of which is

$[HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 116, the chemical structure of which is

$[HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-

His(Bom)-OH, Boc-Dip-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

For the synthesis of Peptide 117, the chemical structure of which is $[HOOC(CH_2)_{12}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$,
the following protected amino acids are coupled in the indicated order on the MBHA resin: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-$Phe(pNO_2)$-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, followed by acylation with $HOOC(CH_2)_{12}COOH$.

Deprotection, cleavage from the resin, and subsequent purification by semipreparative HPLC of Peptide 71, Peptide 77, Peptide 89, Peptide 107, Peptide 116, and Peptide 117 are done as described in the case of Peptide 72. The purified compounds are judged to be substantially (>95%) pure by analytical HPLC. Their molecular masses are checked by electrospray mass spectrometry, and the expected amino acid compositions are confirmed by amino acid analysis.

EXAMPLE IX

Aqueous Solution for Intramuscular Injection

$[PhAc\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ (Peptide 67) 500.0 mg

Gelatin, nonantigenic	5.0 mg
Water for injection q.s.	ad 100.0 mL

The gelatin and GH-RH antagonist Peptide 67 are dissolved in water for injection, then the solution is sterile filtered.

EXAMPLE X

Long Acting Intramuscular Injectable Formulation (Sesame Oil Gel)

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ (Peptide 80)

	10.0 mg
Aluminum monostearate, USP	20.0 mg
Sesame oil q.s.	ad 1.0 mL

The aluminum monostearate is combined with the sesame oil and heated to 125 °C with stirring until a clear yellow solution forms. This mixture is then autoclaved for sterility and allowed to cool. The GH-RH antagonist Peptide 80 is then added aseptically with trituration. Particularly preferred antagonists are salts of low solubility, e.g., pamoate salts and the like. These exhibit long duration of activity.

EXAMPLE XI

Long Acting Intramuscular (IM) Injectable-Biodegradable Polymer Microcapsules

Microcapsules are made from the following:

25/75 glycolide/lactide copolymer (0.5 intrinsic viscosity)	99%
$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$ (Peptide 96)	1%

25 mg of the above microcapsules are suspended in 1.0 mL of the following vehicle:

Dextrose	5.0%
CMC, sodium	0.5%
Benzyl alcohol	0.9%
Tween 80	0.1%
Water, purified q.s.	ad 100%

EXAMPLE XII

Biological Activity in Endocrine and Oncological Assays

The peptides of the present invention were tested in assays in vitro and in vivo for their ability to inhibit the $hGH\text{-}RH(1\text{-}29)NH_2$ induced GH release. Binding affinities of the compounds to the tumoral GH-RH receptors were also measured. The antitumor activities of the peptides and their inhibitory effects on serum IGF-I and on the tumoral IGF system were evaluated in various cancer models in vivo.

Superfused Rat Pituitary System

The analogs were tested in vitro in a test described earlier (S. Vigh and A.V. Schally, Peptides 5:241-347, 1984) with modification (Z. Rekasi and A.V. Schally, P.N.A.S. 90:2146-2149, 1993).

Briefly, the cells are preincubated with peptides for 9 minutes (3mL) at various concentrations. Immediately after the incubation, 1 nM $hGH\text{-}RH(1\text{-}29)NH_2$ is administered for 3 minutes (1mL) [0 minute response]. To check the duration of the antagonistic effect of the analogue, 1 nM $hGH\text{-}RH(1\text{-}29)NH_2$ is applied 30, 60, 90, and 120 minutes later for 3 minutes [30, 60, 90, 120 min responses]. Net integral values of the GH responses are evaluated. GH responses are compared to and expressed as percent of the original GH response induced by 1

nM GH-RH(1-29)NH_2. The effect of the new antagonists are compared to that of [Ac-Tyr^1, D-Arg^2]hGH-RH(1-29)NH_2, the "Standard antagonist".

Radioimmunoassays (RIA) for GH, IGF-I, and IGF-II

Rat GH levels in aliquots of undiluted and diluted superfusion samples were measured by double-antibody radioimmunoassay using materials supplied by the National Hormone and Pituitary Program, Baltimore, Maryland. The results of RIA were analyzed with a computer program developed in our Institute (V. Csernus and A.V. Schally, in Neuroendocrine Research Methods, Harwood Academic (Greenstein, B.D. ed., London, pp. 71-109, 1991), hereby incorporated by reference.

For the measurement of GH and IGF-I levels in the serum, as well as IGF-I and IGF-II concentrations in the cytosol fraction of tumors, blood samples and tumor samples were collected and processed as described (Braczkowski R, Schally AV, Plonowski A, Varga JL, Groot K, Krupa M, Armatis P, Cancer 95: 1735-1745, 2002), hereby incorporated by reference. Briefly, blood samples are centrifuged to separate the serum, tumors are homogenized and centrifuged to separate the cytosol fraction. Serum GH is then measured by the double-antibody RIA method. Before measurement by RIA, IGF-I and IGF-II are extracted from serum and cytosol fractions using an acid-ethanol cryoprecipitation method that eliminates most of the IGF binding proteins, which can interfere with the RIA. IGF-I concentration is measured by RIA using IGF-I as a standard and goat anti-IGF-I antibody (both from DSL Inc., Webster, TX). IGF-II concentration is measured by RIA using human recombinant IGF-II (Bachem) as a standard and anti-IGF-II monoclonal antibody (Amano International Enzyme, Troy, VA).

In all RIA measurements, inter-assay variation was less than 15% and intra-assay variation was less than 10%.

Tumoral GH-RH Receptor Binding Assay

Ligand competition assays with ^{125}I-labeled GH-RH antagonist JV-1-42 were used to determine the binding affinities of GH-RH analogs to the GH-RH receptor isoforms on membrane fractions of human PC-3 prostate tumors. The methods used have been described in detail (Halmos G, Schally AV, Varga JL, Plonowski A, Rekasi Z, Czompoly T, Proc Natl Acad Sci USA 97: 10555-10560, 2000; Halmos G, Schally AV, Czompoly T, Krupa M, Varga JL, Rekasi Z, J Clin Endocrinol Metab 87: 4707-4714, 2002), hereby incorporated by reference. Briefly, radioiodinated derivatives of JV-1-42 are prepared by the chloramine-T method. PC-3 tumors, grown as xenografts in nude mice, are used to prepare crude membranes. PC-3 membrane homogenates are incubated with [^{125}I]JV-1-42 and increasing concentrations (10^{-12} to 10^{-6} M) of nonradioactive antagonist peptides as competitors. The pellet is separated by centrifugation and counted for radioactivity in a gamma-counter. The final binding affinities are estimated by K_i (dissociation constant of the inhibitor-receptor complex) and are determined by the Ligand PC and McPherson computer programs of Munson and Rodbard (P.J. Munson and D. Rodbard, Anal. Biochem. 107: 220-239, 1980). Relative affinities (R.A.) compared to reference peptides such as JV-1-36 or JV-

1-38, are calculated as the ratio of K_i of the reference peptide to the K_i of the tested GH-RH antagonist.

Results of Superfusion Assays

The results of the in vitro antagonistic activities tested in superfused rat pituitary system are summarized in Table III. As it can be seen from these data, the substitutions present in the molecules cause a much increased and protracted inhibitory effect on the GH-RH-elicited GH release in vitro, as compared to the standard antagonist.

TABLE III.

Inhibition of GH Release in Superfused Rat Pituitary System

Antagonist	Dose (nM)	GH response (% of control) 0 min	30 min	60 min	90 min	120 min
Standard antagonist:	100	38	98	81		
JV-1-36*	30	36	21	25	29	29
	10	80	42	60	64	85
JV-1-38*	30	59	32	28	34	31
Peptide 2	30	18	13	18	25	51
Peptide 3	30	52	61	56	70	149
Peptide 4	30	5	0	12	8	18
Peptide 5	30	22	20	23	27	27
Peptide 6	30	56	22	12	15	19
Peptide 7	30	23	13	11	14	14
Peptide 8	30	37	31	48	44	40
Peptide 9	30	47	43	66	63	58
Peptide 10	30	60	30	36	37	44
Peptide 11	30	14	24	29	34	32
Peptide 12	30	35	30	35	51	43
Peptide 13	30	87	77	76	71	73
Peptide 15	30	28	13	11	36	21
Peptide 16	30	40	62	78	73	61
Peptide 17	30	29	51	68	73	61
Peptide 18	30	21	71	61	75	63
Peptide 19	30	62	64	66	82	74
Peptide 21	30	0	13	33	43	37
Peptide 22	30	22	26	27	45	N/A
Peptide 23	30	55	40	41	47	41
Peptide 24	30	56	13	18	34	60

Peptide 26	30	20	43	66	48	44
Peptide 27	30	19	15	23	23	61
Peptide 28	30	68	7	8	20	34
Peptide 30	30	18	11	7	7	8
Peptide 30	10	60	24	34	32	53
Peptide 31	30	7	1	2	4	3
Peptide 31	10	57	31	37	36	37
Peptide 32	30	28	43	69	76	N/A
Peptide 33	30	97	89	78	97	82
Peptide 35	30	91	57	80	66	72
Peptide 36	30	104	90	112	97	120
Peptide 37	30	33	12	15	15	19
Peptide 39	30	63	54	36	37	36
Peptide 40	30	42	29	26	36	30
Peptide 41	30	47	16	14	15	16
Peptide 42	30	52	7	9	8	13
Peptide 43	30	82	74	102	72	51
Peptide 45	30	91	100	100	100	99
Peptide 45	30	100	100	100	N/A	N/A
Peptide 46	30	91	28	31	56	30
Peptide 48	30	22	21	44	44	47
Peptide 49	30	83	76	90	87	120
Peptide 50	30	57	65	69	74	67
Peptide 51	30	64	36	31	N/A	N/A
Peptide 51	30	52	43	57	56	58
Peptide 51	30	87	35	46	51	61
Peptide 52	30	86	13	45	26	55
Peptide 53	30	43	42	40	36	46
Peptide 55	30	93	63	96	61	93
Peptide 56	30	76	83	92	80	68
Peptide 58	30	78	53	56	47	N/A
Peptide 58	30	94	53	57	64	64
Peptide 58	30	64	41	59	50	69
Peptide 59	30	72	49	46	38	N/A
Peptide 59	30	61	50	48	47	N/A
Peptide 59	30	93	43	60	57	76
Peptide 59	30	47	27	37	44	47
Peptide 60	30	73	27	34	56	42
Peptide 60	30	87	29	65	36	63
Peptide 62	30	20	16	14	21	21

Peptide 63	30	53	47	49	51	N/A
Peptide 64	30	59	54	70	50	56
Peptide 65	30	67	80	89	97	79
Peptide 67	30	28	15	18	20	23
Peptide 68	30	37	22	33	29	33
Peptide 69	30	9	12	18	18	25

*reference compounds, subject to U.S. Patent 6,057,422

Results of Tumoral GH-RH Receptor Binding Assay

As seen in Table IV and Table V, respectively, the substitutions present in the molecules cause a substantial increase in their binding affinities to the GH-RH receptor isoforms on PC-3 tumor membranes, as compared to the binding affinities of the reference compounds.

TABLE IV.

Relative Affinities (R.A.) of GH-RH Antagonists to Membrane Receptors on PC-3 Human Prostate Cancers

Peptide	R.A.
JV-1-36*	1
Peptide 11	1.3
Peptide 6	0.6
Peptide 7	12
Peptide 4	53
Peptide 5	4
Peptide 22	10
Peptide 43	0.09

*reference compound, subject to U.S. Patent 6,057,422

TABLE V.

Relative Affinities (R.A.) of GH-RH Antagonists to Membrane Receptors on PC-3 Human Prostate Cancers

Peptide	R.A.
JV-1-38*	1
Peptide 31	0.2
Peptide 36	11
Peptide 41	5

Peptide 42	0.6
Peptide 62	62
Peptide 67	71
Peptide 69	59

*reference compound, subject to U.S. Patent 6,057,422

Effect of GH-RH antagonists on PC-3 human prostate cancer xenografts in nude mice

Experiment 1:

Male nude mice were implanted s.c. with 3 mm^3 pieces of PC-3 human hormone-independent prostate cancer tissue on both flanks. When tumors reached a volume of approx. 50 mm^3, the mice were divided into 5 experimental groups with 7 to 8 animals in each group and received single daily injections for 28 days as follows: 1. Control (vehicle solution); 2. JV-1-38 (10 µg/day s.c.); 3. Peptide 31 (10 µg/day s.c.); 4. Peptide 67 (10 µg/day s.c.); 5. Peptide 62 (10 µg/day s.c.). Tumor volumes were measured twice a week. The experiment was ended on day 29 by sacrificing the mice under isoflurane anesthesia. Resulting tumors were cleaned, weighed, and snap-frozen until further analyses. Trunk blood was collected from the abdominal aorta and serum was separated for RIA measurement of IGF-I. Statistical analyses of the measurement results were done by two-tailed t-test; data are presented as the means ± S.E.

Experiment 2:

Experiment 2 was similar to Experiment 1, with the difference that Experiment 2 was started when PC-3 tumors had grown to approximately 30 mm^3 in volume. At this time, the animals were divided into 8 experimental groups with 8 animals in each group, and received single daily injections for 28 days as follows: 1. Control (vehicle solution); 2. JV-1-38 (10 µg/day s.c.); 3. Peptide 46 (5 µg/day s.c.); 4. Peptide 77 (5 µg/day s.c.); 5. Peptide 76 (5 µg/day s.c.); 6. Peptide 70 (5 µg/day s.c.); 7. Peptide 79 (5 µg/day s.c.); 8. Peptide 80 (5 µg/day s.c.). Further details of Experiment 2 are the same as for Experiment 1.

Experiment 3:

Male nude mice were implanted s.c. with 3 mm^3 pieces of PC-3 human hormone-independent prostate cancer tissue on both flanks. When tumors reached a volume of approximately 65 mm^3, the mice were divided into 7 experimental groups with 8 to 9 animals in each group and received single daily injections for 28 days as follows: 1. Control (vehicle solution); 2. JV-1-38 (10 µg/day s.c.); 3. Peptide 35 (10 µg/day s.c.); 4. Peptide 36 (10 µg/day s.c.); 5. Peptide 37 (10 µg/day s.c.); 6. Peptide 39 (10 µg/day s.c.); 7. Peptide 41 (10 µg/day s.c.). Tumor volumes were measured twice a week. The experiment was ended on day 28 by sacrificing the mice under isoflurane anesthesia. Resulting tumors were cleaned, weighed, and snap-frozen until further analyses. Trunk blood was collected from the abdominal aorta and serum was separated for RIA

measurement of IGF-I. Statistical analyses of the measurement results were done by ANOVA followed by Fisher test; data are presented as the means ± S.E.

Experiment 4:

All experimental details of Experiment 4 are the same as for Experiment 3, with the following difference. When tumors reached a volume of approximately 55 mm^3, the mice were divided into 5 experimental groups with 8 to 9 animals in each group and received single daily injections for 28 days as follows: 1. Control (vehicle solution); 2. Peptide 80 (5 µg/day s.c.); 3. Peptide 86 (5 µg/day s.c.); 4. Peptide 95 (5 µg/day s.c.); 5. Peptide 96 (5 µg/day s.c.). Further details of Experiment 4 are the same as for Experiment 3.

Results

Experiment 1:

Among the GH-RH antagonists tested, Peptide 67 and Peptide 62 exerted a stronger inhibitory effect on the growth of PC-3 tumors than the reference peptide JV-1-38, subject to U.S. Patent 6,057,422 (Table VI). The peptides of the present invention also more potently suppressed IGF-I levels in the serum and IGF-II levels in the tumors, as compared to JV-1-38 (Table VII).

TABLE VI.

Experiment 1: Effect of Treatment with GH-RH Antagonists on PC-3 Human Prostate Cancer Xenografts in Nude Mice

Group	Tumor volume (mm^3)		Tumor weight (mg)	Tumor volume doubling time
	Initial	Final (% inhibition)	(% inhibition)	(days)
Control	50.0±7.86	501±111	378±84.0	8.97±0.71
JV-1-38	49.2±8.37	291±80.4 (42%)	239±58.0 (37%)	12.3±1.04*
Peptide 31	49.1±12.5	363±92.8 (28%)	237±53.3 (37%)	14.0±2.69
Peptide 67	46.8±8.11	200±39.5* (60%)	150±22.1* (60%)	17.0±3.51*
Peptide 62	56.1±18.2	215±50.4 (57%)	199±51.7 (47%)	18.4±4.96*

*p<0.05 vs. control.

TABLE VII.

Experiment 1: Effect of Treatment with GH-RH Antagonists on the Serum Levels of IGF-I and the Tumor Concentrations of IGF-II in Nude Mice Bearing Xenografts of PC-3 Human Prostate Cancer

Group	Serum IGF-I (ng/mL) (% inhibition)	Tumor IGF-II (pg/mg protein) (% inhibition)
Control	149±10.4	219±64.7
JV-1-38	147±8.49 (1%)	208±43.3 (5%)
Peptide 31	133±16.7 (11%)	130±56.0 (41%)
Peptide 67	128±10.6 (14%)	139±89.2 (37%)
Peptide 62	141±8.86 (5%)	N.I.

N.I., not investigated.

Experiment 2:

Peptide 46, Peptide 77, Peptide 76, Peptide 70, Peptide 79, and Peptide 80 of the present invention, used at a dose of 5 µg/day, decreased the tumor volumes and tumor weights of PC-3 cancers by 20-64%, and increased the tumor volume doubling times by up to 101% of the control value (Table VIII). The effects of Peptide 77, Peptide 70, Peptide 79, and Peptide 80 were statistically significant on one or more of these tumor parameters. In contrast, reference peptide JV-1-38, subject to U.S. Patent 6,057,422, did not decrease the tumor volume, and only caused a slight and non-significant inhibition of 10% in the weight of PC-3 tumors, when used at a double dose of 10 µg/day (Table VIII). In addition, Peptide 70, Peptide 79, and Peptide 80 of the present invention significantly decreased serum IGF-I levels by 31%-42%, but peptide JV-1-38 had no effect (Table IX).

TABLE VIII.

Experiment 2: Effect of Treatment with GH-RH Antagonists on PC-3 Human Prostate Cancer Xenografts in Nude Mice

Group	Tumor volume (mm^3)		Tumor weight (mg)	Tumor volume doubling time
	Initial	Final (% inhibition)	(% inhibition)	(days)

Control	28.4±4.2	351±84.9	283±72.1	8.3±0.7
JV-1-38	29.3±3.8	351±72.9 (0%)	254±52.0 (10%)	8.7±0.7
Peptide 46	26.6±2.7	246±93.7 (30%)	188±66.1 (34%)	11.2±1.3
Peptide 77	27.2±3.2	192±44.1 (45%)	138±34.3 (51%)	10.7±0.8*
Peptide 76	26.8±3.4	232±30.8 (34%)	226±48.3 (20%)	9.4±0.6
Peptide 70	26.5±3.7	199±40.4*# (43%)	119±25.3*# (58%)	12.6±2.5
Peptide 79	29.1±4.3	139±49.4*# (60%)	153±54.5 (46%)	13.6±1.8*#
Peptide 80	24.8±2.2	128±38.9*# (64%)	137±46.1* (52%)	16.7±4.3*#

*p<0.05 vs. control; #p<0.05 vs. JV-1-38.

TABLE IX.

Experiment 2: Effect of Treatment with GH-RH Antagonists on the Serum Levels of IGF-I in Nude Mice Bearing Xenografts of PC-3 Human Prostate Cancer

Group	Serum IGF-I (ng/mL)	(% inhibition)
Control	262±18.1	
JV-1-38	293±28.0	0%
Peptide 46	288±17.9	0%
Peptide 77	276±16.8	0%
Peptide 76	260±29.7	1%
Peptide 70	175±12.9***	33%
Peptide 79	181±19.8**	31%
Peptide 80	152±7.83***	42%

**p<0.01 vs. control; ***p<0.001 vs. control.

Experiment 3:

All peptides tested significantly inhibited the growth of PC-3 tumors at the dose of 10 µg/day. Peptide 35, Peptide 36, and Peptide 39 had more potent antitumor effect than reference peptide JV-1-38 (Table X).

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TABLE X.

Experiment 3: Effect of Treatment with GH-RH Antagonists on PC-3 Human Prostate Cancer Xenografts in Nude Mice

Group	Tumor volume (mm^3)		Tumor weight (mg)	Tumor volume doubling time
	Initial	Final (% inhibition)	(% inhibition)	(days)
Control	71.1±10.5	678±172	700±152	10.6±0.96
JV-1-38	68.3±8.08	276±48.7** (66%)	386±62.9* (45%)	18.2±1.84
Peptide 35	65.7±11.3	261±52.9** (68%)	286±58.9* (59%)	17.0±2.32
Peptide 36	68.0±11.7	214±72.6** (76%)	361±89.6* (48%)	18.7±3.83
Peptide 37	60.0±13.0	323±68.0* (57%)	440±104 (37%)	12.7±2.03
Peptide 39	66.7±11.2	271±109** (66%)	247±55.4* (65%)	19.6±2.10
Peptide 41	66.7±12.5	341±107* (54%)	579±188 (17%)	28.2±9.85

*p<0.05 vs. control; **p<0.01 vs. control.

Experiment 4:

All four peptides, administered at a dose of 5 µg/day, significantly inhibited the growth of PC-3 tumors in nude mice. Peptide 96 had the strongest antitumor effect in this experiment (Table XI). Serum IGF-I levels were also inhibited in all groups treated with antagonists, the effects of Peptide 86 and Peptide 96 being statistically significant (Table XII).

TABLE XI.

Experiment 4: Effect of Treatment with GH-RH Antagonists on PC-3 Human Prostate Cancer Xenografts in Nude Mice

Group	Tumor volume (mm^3)		Tumor weight (mg)	Tumor volume doubling time
	Initial	Final (% inhibition)	(% inhibition)	(days)

Control	56.3±10.8	1137±351	1451±343	7.3±0.52
Peptide 80	53.2±10.1	398±68.7*	752±150*	10.7±1.28*
		68%	48%	
Peptide 86	56.1±8.67	397±71.8*	643±94.9**	12.1±1.40**
		68%	56%	
Peptide 95	60.9±12.2	393±79.8*	666±131*	12.5±1.80*
		69%	54%	
Peptide 96	56.2±13.3	301±65.2**	489±114**	11.0±0.87**
		77%	66%	

*p<0.05 vs. control; **p<0.01 vs. control.

TABLE XII.

Experiment 4: Effect of Treatment with GH-RH Antagonists on the Serum Levels of IGF-I in Nude Mice Bearing Xenografts of PC-3 Human Prostate Cancer

Group	Serum IGF-I (ng/mL)	(% inhibition)
Control	165±10.2	
Peptide 80	136±15.3	18%
Peptide 86	118±8.94*	28%
Peptide 95	127±17.5	23%
Peptide 96	114±15.5*	31%

*p<0.05 vs. control.

Effect of GH-RH antagonist on HT-29 human colon cancer xenografts in nude mice

HT-29 human colon cancers were transplanted sc. into male nude mice. 19 days after transplantation, the mice were divided into two groups of 10 animals each, and the treatment was started. Mice in the treatment group received single daily injections of Peptide 67 sc. at a dose of 10 µg/day for 62 days, while the control group was injected with the vehicle solvent. Tumors were measured regularly, and tumor volume was calculated. The mice were sacrificed at the end of experiment and tumor weights were measured.

Results

Treatment with Peptide 67 for 62 days caused a significant inhibition of 56.3% in the volumes and 53.9% in the weights of HT-29 tumors growing in nude mice, as compared to the control group (Table XIII).

TABLE XIII.

Effect of Treatment with GH-RH Antagonist Peptide 67 on HT-29 Human Colon Cancer Xenografts in Nude Mice

Group	Final tumor volume (mm^3)	Tumor weight (mg)
Control	2792±643	3112±543
Peptide 67	1218±320*	1434±405*

*p<0.05 vs. control

Effect of GH-RH antagonists on DMS-153 human small cell lung carcinomas (SCLC) xenografted into nude mice

Male nude mice were implanted s.c. with 3 mm^3 pieces of DMS-153 human SCLC tissue. When tumors reached a volume of approx. 100 mm^3 the mice were divided into 3 experimental groups of 6-8 animals each and received the following treatment for 6 weeks: group 1 (control), vehicle solution; group 2, Peptide 67 (10 µg/day s.c.); group 3, Peptide 31 (10 µg/day s.c.). Tumor volumes were recorded twice a week. At the end of treatment, mice were anesthetized with isoflurane, killed by decapitation, trunk blood was collected for measurement of serum IGF-I, and tumors were excised and weighed. Data are presented as means ± S.E. Data were evaluated by one way ANOVA and the Student-Newman-Keuls test.

Results

Tumor weights were significantly decreased in animals that received treatment with either GH-RH antagonist, Peptide 67 or Peptide 31, as compared to controls (Table XIV). Tumor volumes were also significantly smaller in the group that received Peptide 67. In addition, both antagonists significantly reduced the serum levels of IGF-I as compared to those in the control animals (Table XIV). The expression of mRNA for IGF-II was likewise inhibited by both antagonists, the level of expression being 100±1.5% in the control group, 78.0±44.3% in the group treated with Peptide 67, and 42.7±18.5% in the group that received Peptide 31. The inhibitory effect of Peptide 31 on the IGF-II mRNA expression was statistically significant ($p<0.01$ vs. control).

TABLE XIV.

Effect of Treatment with GH-RH Antagonists on DMS-153 Human SCLC Xenografts in Nude Mice and on the Serum IGF-I Levels

Group	Tumor weight (g) (% inhibition)	Tumor volume (mm^3) Initial	Tumor volume (mm^3) Final (% inhibition)	Serum IGF-I (ng/mL) (% inhibition)
Control	2.31±0.25	112±13	3641±431	169.0±9.9
Peptide 67	1.60±0.19* (31%)	132±24	2650±30* (28%)	117.9±17.2* (30%)
Peptide 31	1.58±0.11* (32%)	138±20	3329±180 (10%)	118.4±12.5* (30%)

*p<0.05 vs. control

Effect of GH-RH antagonists on H-69 human SCLC xenografted into nude mice

Male nude mice were implanted s.c. with 3 mm^3 pieces of H-69 human SCLC tissue. When tumors reached a volume of approx. 80 mm^3 the mice were divided into 4 experimental groups of 7-8 animals each and received the following treatment for 4 weeks: group 1 (control), vehicle solution; group 2, Peptide 67 (10 µg/day s.c.); group 3, Peptide 31 (10 µg/day s.c.); group 4, Peptide 72 (10 µg/day s.c.). Tumor volumes were recorded twice a week. At the end of treatment, mice were anesthetized with isoflurane, killed by decapitation, and tumors were excised and weighed. Data are presented as means ± S.E. Data were evaluated by one way ANOVA and the Student-Newman-Keuls test.

Results

All GH-RH antagonists, given as single daily injections at a dose of 10 µg/day, significantly inhibited the growth of H-69 tumors in nude mice. Among the compounds tested, Peptide 72 had the strongest antiproliferative effect (Table XV).

TABLE XV.

Effect of Treatment with GH-RH Antagonists on H-69 Human SCLC Xenografts in Nude Mice

Group	Tumor volume (mm^3)	
	Initial	Final (% Inhibition)
Control	81±13	2350±189
Peptide 67	82±10	501±35* (76%)
Peptide 31	80±6	832±23* (67%)
Peptide 72	81±9	308±23* (90%)

*p<0.001 vs. control

We claim:

1. A peptide selected from the group having the formulae:

R_1-A^0-A^1-A^2-Asp-Ala-A^5-A^6-Thr-A^8-A^9-A^{10}-A^{11}-A^{12}-Val-Leu-A^{15}-A^{16}-Leu-Ser-A^{19}-A^{20}-A^{21}-A^{22}-Leu-Gln-Asp-Ile-A^{27}-A^{28}-A^{29}-A^{30}-R_2

wherein R_1 is a member of the group consisting of a) PhAc, Hca, Dat, IndAc, Ipa, 1-Nac, 2-Nac, 1-Npr, 2-Npr, Ibu; $CH_3(CH_2)_nCO$, or $HOOC(CH_2)_nCO$, where n is an integer from 2 to 20, and b) any other straight chain, branch chain, saturated, unsaturated or poly unsaturated aliphatic carboxyl group of 2-30 carbon atoms and any carbocyclic or heterocyclic aromatic carboxyl group of 3-8 carbon atoms containing at least one atom of the group S, N, and O in the heterocyclic ring,

A^0 is Phe, D-Phe, Arg, D-Arg, or a carbon-nitrogen single bond,

A^1 is Tyr or His,

A^2 is D-Arg or D-Cit,

A^5 is Ile or Val,

A^6 is Phe, Tyr, Nal, or Phe(Y), in which Y=F, Cl, Br, or I,

A^8 is Asn, D-Asn, Cit, D-Cit, Gln, D-Gln, Ser, D-Ser, Thr, D-Thr, Ala, D-Ala, Abu, D-Abu, or Aib,

A^9 is His, D-His, Amp, D-Amp, Gup, or D-Gup,

A^{10} is Tyr, Tyr(Et), Tyr(Me); Phe(Y), in which Y=H, F, Cl, Br, or I; Amp, His, Cha, Chg, Bpa, Dip, Trp, Trp(For), Tpi, 1-Nal, 2-Nal, 3-Pal, 4-Pal, Phe(NH_2), or Phe(NO_2),

A^{11} is His, D-His, Arg, D-Arg, Cit, Har, D-Har, Amp, D-Amp, Gup, or D-Gup,

A^{12} is Lys, D-Lys, Orn, D-Orn, Har, D-Har, Cit, D-Cit, Nle, or Ala,

A^{15} is Gly, Ala, Abu, Aib, Nle, Gln, Cit, or His,

A^{16} is Gln or Arg,

A^{19} is Ala or Abu,

A^{20} is His, D-His, Arg, D-Arg, or Cit,

A^{21} is Lys, D-Lys, Orn, D-Orn, Cit, or D-Cit,

A^{22} is Leu, Ala or Aib,

A^{27} is Met, Leu, Nle, Abu, or D-Arg,

A^{28} is Arg, D-Arg, Har, D-Har, Ser, Asn, Asp, Ala, Abu, or Cit,

A^{29} is Arg, D-Arg, Har, D-Har, Cit, D-Cit, or Agm,

A^{30} is Arg, D-Arg, Har, D-Har, Cit, D-Cit, Agm, or is a carbon-nitrogen or carbon-oxygen single bond,

R_2 is $-NH_2$, $-NH-NH_2$, $-NH-OH$, $-NHR_3$, $-NR_3R_4$, $-OH$, or $-OR_3$, in which R_3 and R_4 are any of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkinyl, C_{7-16} phenylalkyl, $-C_6H_5$, or $-CH(C_6H_5)_2$;

provided that if A^{29} is Agm then A^{30} and R_2 are absent, and if A^{30} is Agm then R_2 is absent,

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein one or both of A^{11} and A^{20} are other than Arg, D-Arg, or Cit.

3. A compound of claim 1 selected from the group consisting of:

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 67

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 68

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, His^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 69

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 70

[$HOOC(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 71

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 72

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 73

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 74

[1-Nac-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 75

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 76

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 77

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 78

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 79

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 80

$[HOOC(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 81

$[HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 82

$[CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 86

$[CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 87

$[HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 88

$[HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 89

[1-Nac-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 91

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 92

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Cit^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 93

$[CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, His^{15}, His^{20}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 94

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH$-RH(1-29)NH_2 Peptide 95

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 96

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 97

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 98

$[CH_3(CH_2)_{10}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 99

[Hca -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 100

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHMe Peptide 101

$[HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 102

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 103

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 104

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 105

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 106

$[HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 107

$[HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 108

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Hls^9, $Phe(pNO_2)^{10}$, Hls^{11}, Orn^{12}, Abu^{15}, Hls^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 109

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, Hls^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 110

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 111

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 112

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 113

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, Hls^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 114

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Hls^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, Hls^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 115

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 116

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, Hls^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 117

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, Hls^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 118

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 119

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 120

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 121

4. A compound of claim 3 selected from the group consisting of :

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 67

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, His^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 69

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 70

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 72

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 76

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 77

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 79

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 80

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 86

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 95

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 96

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 97

5. A compound selected from the group consisting of:

$[CH_3(CH_2)_4CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 2

$[HOOC(CH_2)_4CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 3

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 4

$[HOOC(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 5

$[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 6

$[HOOC(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 7

$[CH_3(CH_2)_{10}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 8

$[HOOC(CH_2)_{10}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 9

$[CH_3(CH_2)_{12}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 10

$[HOOC(CH_2)_{12}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 11

$[CH_3(CH_2)_{14}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 12

$[HOOC(CH_2)_{14}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 13

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D\text{-}Arg^{29}]hGH\text{-}RH(1\text{-}29)NH_2$
Peptide 14

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^8, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 15

[$CH_3(CH_2)_{14}$CO-Phe^0, D-Arg^2, Phe(pCl)^6, Arg^8, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 16

[$CH_3(CH_2)_{14}$CO-D-Phe^0, D-Arg^2, Phe(pCl)^6, Arg^8, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 17

[PhAc-Arg^0, D-Arg^2, Phe(pCl)^6, Arg^8, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 18

[PhAc-D-Arg^0, D-Arg^2, Phe(pCl)^6, Arg^8, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 19

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 21

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 22

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 23

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 24

[HOOC$(CH_2)_{12}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 25

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, D-Ala^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 26

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Abu^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 27

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Peptide 28

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 30

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 31

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, His^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 32

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Cha^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 33

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tpl^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 34

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 35

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 36

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNH_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 37

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Trp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 38

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNO_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 39

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, 3-Pal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 40

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 41

[PhAc-His^1, D-Arg^2, Tyr^6, Har^9, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 42

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Har^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 43

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 45

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 46

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 47

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 48

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Alb^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Peptide 49

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Orn^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Peptide 50

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29)
Peptide 51

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29)
Peptide 52

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2 Peptide 53

[Dat-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2
Peptide 54

[Ipa-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2
Peptide 55

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NHEt Peptide 56

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, D-Arg^{29}, Har^{30}]hGH-RH(1-30)NH_2 Peptide 57

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, D-Arg^{30}]hGH-RH(1-30)NH_2 Peptide 58

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30) Peptide 59

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30) Peptide 60

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 62

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Har^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 63

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Amp^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 64

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Cit^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 65

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 84

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 85

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 90

6 . A peptide of claim 5 selected from the group consisting of:

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 4

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 5

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^8, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 7

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^8, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 11

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 22

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 35

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 38

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Phe(pNO_2)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 39

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Et)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 41

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Peptide 62

7. A peptide of claim 5 selected from the group consisting of;

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^8, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 4

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^8, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 7

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 21

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^8, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 30

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Peptide 31

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNH$_2$)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 37

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 41

[PhAc-His^1, D-Arg^2, Tyr^6, Har^9, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 42

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Peptide 62

8. The use of a compound of any of claims 1, , or 5 for the production of a pharmaceutical composition for suppressing levels of GH in a patient in need of same.

9. The use of a compound of any of claims 1, , or 5 for the production of a pharmaceutical composition for suppressing IGF-I or IGF-II levels in the tumor tissue of a patient having a cancer carrying receptors for IGF-I.

10. The use of a compound of any of claims 1, or 5 for the production of a pharmaceutical composition for suppressing VEGF levels in the tumor tissue of a patient having a cancer.

11. The use of a compound of any of claims 1, or 5 for the production of a pharmaceutical composition for suppressing levels of IGF-I in a patient in need of same.

12. The use of a compound of any of claims 1, or 5 for the production of a pharmaceutical composition for suppressing serum IGF-I levels in a patient having a cancer carrying receptors for IGF-I.

13. The use of a compound of any of claims 1, or 5 for the production of a pharmaceutical composition for suppressing GH levels in a patient having a cancer carrying receptors for IGF-I or GH.

14. The use of a compound of any of claims 1, or 5 for the production of a pharmaceutical composition for blocking GH-RH receptors in a patient having a cancer carrying receptors for GH-RH.

15. The method of suppressing levels of GH in a patient in need of same by administering to said patient a suppressively effective amount of a compound of any of claims 1, or 5.

16. The method of suppressing IGF-I or IGF-II levels in the tumor tissue of a patient having a cancer carrying receptors for IGF-I by administering to said patient a suppressively effective amount of a compound of any of claims 1, or 5.

17. The method of suppressing VEGF levels in the tumor tissue of a patient having a cancer by administering to said patient a suppressively effective amount of a compound of any of claims 1, or 5.

18. The method of suppressing levels of IGF-I in a patient in need of same by administering to said patient a suppressively effective amount of a compound of any of claims 1, or 5.

19. The method of suppressing serum IGF-I levels in a patient having a cancer carrying receptors for IGF-I by administering to said patient a suppressively effective amount of a compound of any of claims 1, or 5.

20. The method of suppressing GH levels in a patient having a cancer carrying receptors for IGF-I or GH by administering to said patient a suppressively effective amount of a compound of any of claims 1, or 5.

21. The method of the treatment of a patient having a cancer carrying receptors for GH-RH by administering to said patient an amount of a compound of any of claims 1, or 5 effective to block said GH-RH receptors

22. A pharmacologically administrable composition for the suppression of levels of GH in a patient consisting essentially of a compound of claim 1, or 5 and a pharmacologically acceptable carrier.

23. A pharmacologically administrable composition for the suppression of –IGF-I or IGF-II levels in the tumor tissue of a patient having a cancer carrying receptors for IGF-I consisting essentially of a compound of claim 1, or 5 and a pharmacologically acceptable carrier.

24. A pharmacologically administrable composition for the suppression of VEGF levels in the tumor tissue of a patient having a cancer consisting essentially of a compound of claim 1, or 5 and a pharmacologically acceptable carrier.

25. A pharmacologically administrable composition for the suppression of levels of IGF-I in a patient consisting essentially of a compound of claim 1, or 5 and a pharmacologically acceptable carrier.

26. A pharmacologically administrable composition for the suppression of GH levels in a patient having a cancer carrying receptors for IGF-I or GH consisting essentially of a compound of claim 1, or 5 and a pharmacologically acceptable carrier.

27. A pharmacologically administrable composition for the suppression of IGF-I levels in a patient having a cancer carrying receptors for IGF-I consisting essentially of a compound of claim 1, or 5 and a pharmacologically acceptable carrier.

28. A pharmacologically administrable composition for blocking receptors for GH-RH in a patient having a cancer carrying receptors for GH-RH consisting essentially of a compound of claim 1, or 5 and a pharmacologically acceptable carrier.

ANÁLOGOS ANTAGONISTAS DE GH-RH

Campo de la Invención

La presente invención se refiere a péptidos sintéticos novedosos que inhiben la liberación de la hormona de crecimiento desde la glándula pituitaria en mamíferos, así como también inhiben la proliferación de cánceres humanos a través del efecto directo sobre las células cancerosas. También, se refiere a composiciones terapéuticas que contienen a esos péptidos novedosos.

ANTECEDENTES DE LA INVENCIÓN

La hormona liberadora de la hormona de crecimiento (GH-RH) es un péptido que pertenece a la familia secretina/glucagón de las hormonas neuroendocrinas y gastrointestinales, una familia que también incluye al péptido vasoactivo intestinal (VIP), al péptido activador de ciclasa adenilato de la pituitaria (PACAP) y otros. El péptido GH-RH humano (hGH-RH) está compuesto de 44 residuos de amino ácidos. El sitio mejor conocido de producción de GH-RH es el hipotálamo, pero se encontró que varios órganos periféricos también lo sintetizan. El péptido hGH-RH también es producido, a veces en grandes cantidades, por tejidos humanos malignos (cánceres) de diverso origen.

La GH-RH ejerce varias funciones fisiológicas y patofisiológicas. La GH-RH hipotalámica es una hormona liberadora endocrina que, actuando a través de receptores específicos en la pituitaria, regula la secreción de la hormona pituitaria del crecimiento (GH). Las funciones fisiológicas de la GH-RH en tejidos extra-pituitarios están menos claras. Sin embargo, hay evidencia creciente del papel de la GH-RH como un factor de crecimiento autocrino/paracrino, en varios cánceres. Se han descrito variantes ensambladas (SV) de receptores de GH-RH, diferentes de los expresados en la pituitaria, en un amplio rango de cánceres humanos y en algunos órganos periféricos normales. Puede ejercerse acciones autocrinas/paracrinas tumorales de GH-RH en

esos receptores. Además, los receptores del VIP y otros, receptores todavía no identificados de esta familia, podrían ser, todos, objetivos de la GH-RH local.

En vista del papel de la GH-RH como regulador endocrino de la liberación de GH, se han diseñado estrategias terapéuticas novedosas, basadas en el uso de análogos agonísticos y antagonísticos de la GH-RH, para el tratamiento de varias condiciones patológicas.

La GH es un polipéptido de 191 amino ácidos que estimula la producción de diferentes factores de crecimiento, por ejemplo, el factor de crecimiento I del tipo insulina y que promueve subsiguientemente el crecimiento de numerosos tejidos (esqueleto, tejido conectivo, músculo y vísceras) y estimula varias actividades fisiológicas (elevando la síntesis de ácidos nucleicos y proteínas y elevando la lipólisis, pero disminuyendo la secreción de urea). La liberación de la GH de la pituitaria está bajo el control de factores liberadores e inhibidores secretados por el hipotálamo, los factores liberadores primarios son GH-RH y grelina y, el principal factor inhibidor es la somatostatina.

Se ha implicado a la GH en varias enfermedades. Una enfermedad en que está implicada la GH es la acromegalia, en la cual están presentes niveles excesivos de GH. Los huesos faciales y de las extremidades anormalmente alargados y los síntomas cardiovasculares de esta enfermedad pueden tratarse administrando un antagonista de la GH-RH. Enfermedades adicionales implicando a la GH son la retinopatía diabética y la neuropatía diabética. El daño a la retina y a los riñones respectivamente en estas enfermedades que, se cree, se deben a una hipersecreción de GH, resultan en ceguera o reducción de la función renal. Este daño puede prevenirse o retardarse por administración de un antagonista efectivo de la GH-RH.

En un esfuerzo para intervenir en esta enfermedad y otras condiciones, algunos investigadores han intentado controlar los niveles de la GH y del IGF-I usando análogos de somatostatina, un inhibidor de liberación de la GH. Sin embargo, los análogos de somatostatina, si se administran solos, no suprimen los niveles de la GH y

del IGF-I hasta un grado deseado. Si se administran con un antagonista de la GH-RH, los análogos de somatostatina suprimirán mucho mejor los niveles del IGF-I.

Sin embargo, las aplicaciones principales de los antagonistas de la GH-RH están en el campo del cáncer (revisado en Schally, A.V. y Varga, J.L., Trends Endocrinol. Metab. 10: 383-391, 1999; Schally, A.V. y colaboradores, Frontiers Neuroendocrinol. 22: 248-291, 2001; Schally, A.V. y Comaru-Schally, A.M., en Kufe D.W., Pollock, R.E., Weichselbaum, R.R, Blast Jr., R.C., Gansler, T.S., Holland, J.F., Frei III, E., Editores, Cancer Medicine, 6ª ed. Hamilton, Ontario: B.C. Decker, Inc. 2003, p 911-926). Los antagonistas de la GH-RH inhiben la proliferación de tejidos malignos por mecanismos endocrinos indirectos basados en la inhibición de la liberación de la GH pituitaria, resultando en la disminución de los niveles de GH e IGF-I en el suero, así como por efectos directos sobre el tejido del tumor.

Los receptores de la GH-RH y su variante tumoral ensamblada (SV) están presentes en cánceres humanos del pulmón, próstata, mamas, ovarios, endometrio, estómago, intestino, páncreas, riñón y hueso (ver, Halmos, G y colaboradores, Proc. Natl. Acad. Sci. USA 97: 10555-10560, 2000; Rekasi, Z. y colaboradores, Proc. Natl. Acad. Sci. USA 97: 10561-10566, 2000; Schally, A.V. y colaboradores, Frontiers Neuroendocrinol. 22: 248-291, 2001; Schally, A.V. y Comaru-Schally, A.M., en Kufe D.W., Pollock, R.E., Weichselbaum, R.R, Blast Jr., R.C., Gansler, T.S., Holland, J.F., Frei III, E., Editores, Cancer Medicine, 6ª ed. Hamilton, Ontario: B.C. Decker, Inc. 2003, p. 911-926). Se ha demostrado o se sospecha que la GH-RH tumoral actúa como un factor de crecimiento autocrino en esos tejidos malignos. Los análogos antagonistas de GH-RH pueden inhibir la actividad estimulante de la GH-RH y ejercer efectos anti-proliferativos, *in vitro*, en células cancerosas e, *in vivo*, en tumores. Los efectos anti-proliferativos directos se ejercen sobre receptores tumorales (sitios de acoplamiento). Además de los receptores tumorales específicos SV para la GH-RH, los receptores para VIP y otros receptores, todavía no identificados de esta familia son el objetivo de los antagonistas de la GH-RH.

Además de los efectos inhibidores endocrinos de la GH y del IGF-I del suero, se encontró que los antagonistas de la GH-RH reducen la producción autocrina y paracrina de varios factores de crecimiento tumoral y/o disminuyen la regulación de sus receptores. Esos factores de crecimiento incluyen IGF-I, IGF-II, GH, factor de crecimiento endotelial vascular (VEGF) y factor de crecimiento del fibroblasto (FGF). Así, una disturbación de los circuitos estimulantes basados en esos factores de crecimiento contribuye a la eficacia de los antagonistas de la GH-RH como agentes anti-tumorales.

Los IGF-I e IGF-II son factores de crecimiento autocrinos/paracrinos, con potentes efectos mitogénicos en varios cánceres. El IGF-I también es un factor de crecimiento endocrino y se considera que niveles elevados de IGF-I en el suero son un factor de riesgo epidemiológico en el desarrollo del cáncer de próstata, cáncer pulmonar y cáncer colorectal. Está bien establecida la implicación del IGF-I (somatomedina-C) en los cánceres de mamas, próstata, colon, tumores de hueso y otras condiciones malignas. Sin embargo, el control de la proliferación autocrina/paracrina por el IGF-II, también es un factor principal en muchos tumores. El IGF-I y el IGF-II ejercen sus efectos proliferativos y anti-apoptóticos, a través del receptor común del IGF-I. Los receptores del IGF-I están presentes en cánceres primarios de mamas humanos, de próstata, de pulmón, de colon, de cerebro, pancreáticos y en carcinomas de células renales. En varios cánceres experimentales, tales como los de hueso, pulmón, próstata, riñón, mamas, ovarios, intestino, páncreas y cerebro, el tratamiento con antagonistas de la GH-RH produce una reducción en los niveles de IGF-I e IGF-II, concomitante con la inhibición del crecimiento del tumor (revisado en Schally, A.V. y Varga, J.L., Trends Endocrinol. Metab. 10: 383-391, 1999; Schally, A.V. y colaboradores, Frontiers Neuroendocrinol. 22: 248-291, 2001; Schally, A.V. y Comaru-Schally, A.M., en Kufe D.W., Pollock, R.E., Weichselbaum, R.R, Blast Jr., R.C., Gansler, T.S., Holland, J.F., Frei III, E., Editores, Cancer Medicine, 6ª ed. Hamilton, Ontario: B.C. Decker, Inc. 2003, p 911-926). En algunos casos, la expresión de los receptores del

IGF-I también disminuyó por los antagonistas de la GH-RH. Así, la disrupción de los circuitos estimulantes endocrinos y autocrinos/paracrinos dependientes de IGF-I e IGF-II contribuye a los efectos anti-tumorales de los antagonistas de GH-RH.

En el modelo MXT de cáncer de mamas, el tratamiento con antagonistas inhibió el crecimiento tumoral, redujo el nivel de mARN de la GH y la concentración del péptido GH en los tumores e inhibió la expresión del mARN de los receptores de GH (Szepeshazi, K. y colaboradores, Endocrinology 142: 4371-4378, 2001). La GH demostró actuar como un factor de crecimiento para las células de carcinoma mamario murino MXT, células mamarias cancerosas humanas y otras líneas de células tumorales. Así, la actividad inhibitoria de los antagonistas de GH-RH sobre los niveles locales y de suero de GH, contribuyen a su efecto anti-tumor.

Se ha demostrado que los antagonistas de la GH-RH inhiben los niveles de mARN y las concentraciones de proteína del VEGF en modelos de cáncer de próstata humano, sensibles a andrógenos y andrógeno-independientes (Letsch, M. y colaboradores, Proc. Natl. Acad. Sci. USA 100: 1250-1255, 2003; Plonowski, A. y colaboradores, Prostate 52: 173-182, 2002) y, este fenómeno contribuye a su efecto anti-tumoral, ya que el VEGF juega un importante papel estimulador en la neovascularización y crecimiento de varios tumores. Más aún, se encontró que un antagonista de la GH-RH inhibió la secreción del VEGF y la proliferación de células endoteliales normales murinas, aparentemente a través de un efecto directo sobre esas células *in vitro* (Siejka, A. y colaboradores, Life Sci. 72: 2473-2479, 2003).

Los científicos han investigados varias modificaciones de la GH-RH para elucidar la relación de la estructura de la GH-RH con su actividad sobre los receptores de la pituitaria, en un esfuerzo para proveer congéneres sintéticos con propiedades agonísticas o antagonísticas. Así, se estableció precozmente que el residuo de GH-RH comprendiendo a los residuos 1 a 29 o GH-RH(1-29) es la secuencia mínima necesaria para la actividad biológica en la pituitaria. Este fragmento retiene 50% o más de la potencia de la GH-RH nativa. Subsiguientemente, se preparó muchos análogos

sintéticos de la GH-RH, basados en la estructura del péptido hGH-RH(1-29)NH_2. El hGH-RH(1-29)NH_2 tiene la siguiente secuencia de amino ácidos:

Tyr-Ala-Asp-Ala-Ile^5-Phe-Thr-Asn-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg^{20}-Lys-Leu-Leu-Gln-Asp^{25}-Ile-Met-Ser-Arg^{29}-NH_2

Un número considerable de patentes y artículos de la literatura abierta describen análogos de la GH-RH que actúan tanto como agonistas de GH-RH (es decir, actúan para estimular la liberación de la GH), como antagonistas de la GH-RH (es decir, actúan inhibiendo la liberación de la GH) en la pituitaria. La mayor parte de esos péptidos se derivan de la secuencia del péptido GH-RH(1-29), con modificaciones estructurales específicas, que explican sus propiedades agonistas o antagonísticas en los receptores de la pituitaria. Sin embargo, aparte de unas pocas excepciones, no se sabe cómo se comportarán esos análogos sobre células de cáncer que expresan receptores diferentes de aquellos encontrados en la pituitaria. Solo unos pocos estudios científicos publicados tratan de elucidar las relaciones estructura-actividad y caracterizar los efectos antagonísticos (o agonistas) de los análogos de la GH-RH en células cancerosas y tumores (ver, Rekasi, Z. y colaboradores, Endocrinology 141: 2120-2128, 2000; Halmos, G. y colaboradores, Proc. Natl. Acad. Sci. USA 97: 10555-10560, 2000; Rekasi, Z. y colaboradores, Proc. Natl. Acad. Sci. USA 97: 10561-10566, 2000; Kiaris, H. y colaboradores, Proc. Natl. Acad. Sci. USA 99: 196-200, 2002) y ninguna patente concedida ha tratado esta materia, hasta ahora. Consecuentemente, se sabe muy poco sobre las características estructurales de los análogos de GH-RH requeridos para una acción antagonística directa sobre células tumorales.

Se encontró que el primer antagonista descrito de la GH-RH, [Ac-Tyr^1, D-Arg^2[hGH-RH(1-29)NH_2, que generalmente se designa como el "antagonista estándar" en la literatura, prevenía la activación del ciclasa adenilato de la pituitaria anterior, en ratas, por el hGH-RH(1-29)NH_2. El mismo péptido bloqueaba la acción de la GH-RH en

sus receptores en la pituitaria y en el hipotálamo e inhibía la secreción pulsátil de la hormona de crecimiento. El antagonista estándar también se evaluó clínicamente (Ocampo-Lim, B. y colaboradores, J. Clin. Endocrinol. Metab. 81: 4396-4399, 1996; Jaffe, C.A. y colaboradores, J. Clin. Endocrinol. Metab. 82: 634-637, 1997). Grandes dosis de este antagonista (400 µg/kg) eliminaban la secreción nocturna de GH en sujetos normales e inhiblan la respuesta a la GH-RH. El antagonista estándar de la GH-RH, también reducía los niveles de GH en un paciente con acromegalia. Sin embargo, para uso clínico, se requiere antagonistas de GH-RH mucho más potentes.

Las invenciones mencionadas más adelante, describen análogos de GH-RH con propiedades antagonísticas o agonísticas en los receptores de GH-RH. Sin embargo, no se ha informado ni investigado si esos análogos podrían ejercer efectos directos sobre células tumorales.

La Patente de los EE. UU. N° 4.659.693 describe análogos antagonistas de la GH-RH que contienen ciertos residuos de N,N'-dialquil-omega-guanidino alfa-amino acil, en la posición 2 de la secuencia GH-RH(1-29).

La solicitud publicada WO 91/16923 revisa intentos tempranos para alterar la estructura secundaria de hGH-RH modificando su secuencia de amino ácidos. Esos intentos tempranos incluyen: el reemplazo de Tyr1, Ala^2, Asp^3 o Asn^8 con sus D-isómeros; el reemplazo de Asn^8 con L- o D-Ser, D- Arg, Asn, Thr, Gln o D-Lys; el reemplazo de Ser^9 con Ala para aumentar la anfifilicidad de la región; y el reemplazo de Gly^{15} con Ala o Aib. Cuando R^2 en los análogos es D-Arg y R^8, R^9 y R^{15} están sustituidos como se indicó anteriormente, se dice que se produce actividad antagonística. Se dice que estos péptidos antagonistas son adecuados para administración como composiciones farmacéuticas para tratar condiciones asociadas con niveles excesivos de GH-RH, por ejemplo, la acromegalia.

La actividad antagonística del análogo de hGH-RH "[Ser^9-psi[CH_2NH]-Tyr^{10}]hGH-RH(1-29)" de la Patente de los EE. UU. N° 5.084.555, se dijo, fue resultante del enlace pseudopeptídico (es decir, un enlace peptídico reducido a un enlace

[CH_2NH]) entre los residuos R^9 y R^{10}. Sin embargo, las propiedades antagonísticas de [Ser^9-psi[CH_2NH]-Tyr^{10}]hGH-RH(1-29), se dijo, eran inferiores al antagonista estándar, [N-Ac-Tyr^1, D-Arg^2]hGH-RH(1-29)-NH_2.

La Patente de los EE. UU. N° 5.550.212, la Patente de los EE. UU. N° 5.924.489 y la Patente de los EE. UU. N° 6.057.422, asignadas al mismo asignatario que la presente solicitud, describen análogos de hGH-RH(1-29), que se dice, tienen propiedades antagonísticas mejoradas y acción de duración prolongada, con respecto a la inhibición de la liberación de GH evocada por GH-RH. Se cree que esas propiedades resultan del reemplazo de varios amino ácidos y acilación con ácidos aromáticos o no-polares en el N-terminal de GH-RH(1-29)NH_2. Las propiedades inhibidoras de tumor de los antagonistas caracterizados en la Patente de los EE. UU. N° 5.942.489 y en la Patente de los EE. UU. N° 6.057.422 se demostraron usando xenoinjertos de modelos de cáncer humano en ratas desnudas. Se destaca que en la Patente de los EE. UU. N° 5.550.212 y en la Patente de los EE. UU. N° 5.942.489, R^9 siempre es Ser, mientras R^{11} y R^{20} pueden ser tanto Arg, D-Arg, como Cit. En el caso de la Patente de los EE. UU. N° 6.057.422, R^9 puede ser tanto Arg, Har, Lys, Orn, D-Arg, D-Har, D-Lys, D-Orn, Cit, Nle, Tyr(Me), Ser, Ala o Aib, mientras R^{11} y R^{20} siempre son Arg.

RESUMEN DE LA INVENCIÓN

Aquí se provee una novedosa serie de análogos sintéticos de hGH-RH(1-29)NH_2 y hGH-RH(1-30)NH_2. Estos análogos inhiben la liberación de la hormona de crecimiento desde la pituitaria en muchos mamíferos, así como inhiben la proliferación de cánceres humanos a través de un efecto directo sobre las células cancerosas. Las potencias inhibidoras más fuertes de los nuevos análogos, en comparación con los previamente descritos, resultan del reemplazo de varios amino ácidos.

Principalmente, la invención se refiere a péptidos que comprenden la fórmula:

R_1-A^0-A^1-A^2-Asp-Ala-A^5-A^6-Thr-A^8-A^9-A^{10}-A^{11}-A^{12}-Val-Leu-A^{15}-A^{16}-Leu-Ser-A^{19}-A^{20}-A^{21}-A^{22}-Leu-Gln-Asp-Ile-A^{27}-A^{28}-A^{29}-A^{30}-R_2

en que R_1 es un miembro del grupo que consiste de a) PhAc, Hca, Dat, IndAc, Ipa, 1-Nac, 2-Nac, 1-Npr, 2-Npr, Ibu; $CH_3(CH_2)_nCO$ o $HOOC(CH_2)_nCO$, en que n es un entero desde 2 hasta 20 y b) es cualquier otro grupo carboxílico alifático, de 6-14 átomos de carbono, de cadenas rectas, cíclicas, ramificadas, saturados, insaturados o poli-insaturados y cualquier grupo carboxilo, carbocíclico o heterocíclico aromático, de 3-8 átomos de carbono, conteniendo hasta un átomo cada uno de los grupos S, N y O en el anillo heterocíclico,

A^0 es Phe, D-Phe, Arg, D-Arg o un enlace simple carbono-nitrógeno,

A^1 es Tyr o His,

A^2 es D-Arg o D-Cit,

A^5 es Ile o Val,

A^6 es Phe, Tyr, Nal, o Phe(Y), en que Y=F, Cl, Br, o I,

A^8 es Asn, D-Asn, Cit, D-Cit, Gln, D-Gln, Ser, D-Ser, Thr, D-Thr, Ala, D-Ala, Abu, D-Abu, o Aib,

A^9 es His, D-His, Amp, D-Amp, Gup, o D-Gup,

A^{10} es Tyr, Tyr(Et), Tyr(Me); Phe(Y), en que Y=H, F, Cl, Br, o I; Amp, His, Cha, Chg, Bpa, Dip, Trp, Trp(For), Tpi, 1-Nal, 2-Nal, 3-Pal, 4-Pal, Phe(NH_2), o Phe(NO_2),

A^{11} es His, D-His, Arg, D-Arg, Cit, Har, D-Har, Amp, D-Amp, Gup, o D-Gup,

A^{12} es Lys, D-Lys, Orn, D-Orn, Har, D-Har, Cit, D-Cit, Nle, o Ala,

A^{15} es Gly, Ala, Abu, Aib, Nle, Gln, Cit, o His,

A^{16} es Gln o Arg,

A^{19} es Ala o Abu,

A^{20} es His, D-His, Arg, D-Arg, o Cit,

A^{21} es Lys, D-Lys, Orn, D-Orn, Cit, o D-Cit,

A^{22} es Leu, Ala o Aib,

A^{27} es Met, Leu, Nle, Abu, o D-Arg,

A^{28} es Arg, D-Arg, Har, D-Har, Ser, Asn, Asp, Ala, Abu, o Cit,

A^{29} es Arg, D-Arg, Har, D-Har, Cit, D-Cit, o Agm,

A^{30} es Arg, D-Arg, Har, D-Har, Cit, D-Cit, Agm, o es un enlace simple carbono-nitrógeno o carbono-oxígeno,

R_2 es $-NH_2$, $-NH-NH_2$, $-NH-OH$, $-NHR_3$, $-NR_3R_4$, $-OH$, o $-OR_3$, en que R_3 y R_4 son cualquiera de alquil C_{1-10}, alquenil C_{2-10}, alquinil C_{2-10}, fenilalquil C_{7-16}, $-C_6H_5$, o $-CH(C_6H_5)_2$;

con la salvedad que si A^{29} es Agm, entonces A^{30} y R_2 están ausentes y si A^{30} es Agm, entonces R_2 está ausente;

y las sales farmacéuticamente aceptables de los mismos.

Entre las modalidades preferidas están los péptidos en la fórmula anterior, en que uno o ambos de A^{11} y A^{20} no son Arg, D-Arg ni Cit.

Específicamente, los principales péptidos que caen bajo este género son:

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 67

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 68

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, His^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 69

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 70

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 71

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 72

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 73

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 74

[1-Nac-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 75

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 76

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 77

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 78

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 79

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 80

[$HOOC(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 81

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 82

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 86

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 87

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 88

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 89

[1-Nac-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 91

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 92

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Cit^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 93

$[CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, His^{15}, His^{20}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 94

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 95

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 96

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHEt Péptido 97

$[CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHEt Péptido 98

$[CH_3(CH_2)_{10}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHEt Péptido 99

[Hca -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHEt Péptido 100

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHMe Péptido 101

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 102

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 103

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 104

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 105

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 106

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 107

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 108

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 109

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 110

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 111

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 112

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 113

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 114

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 115

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 116

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 117

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 118

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 119

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 120

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 121

Los péptidos estrechamente relacionados, que no están comprendidos en la formula genérica estructural anterior, incluyen:

[$CH_3(CH_2)_4CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 2

[$HOOC(CH_2)_4CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 3

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 4

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 5

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 6

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 7

[$CH_3(CH_2)_{10}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 8

[$HOOC(CH_2)_{10}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 9

[$CH_3(CH_2)_{12}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 10

[$HOOC(CH_2)_{12}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 11

[$CH_3(CH_2)_{14}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 12

[$HOOC(CH_2)_{14}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 13

[$CH_3(CH_2)_8$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2 Péptido 14

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2 Péptido 15

[$CH_3(CH_2)_{14}$CO-Phe^0, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 16

[$CH_3(CH_2)_{14}$CO-D-Phe^0, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 17

[PhAc-Arg^0, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 18

[PhAc-D-Arg^0, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 19

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 21

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 22

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2 Péptido 23

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2 Péptido 24

[HOOC$(CH_2)_{12}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 25

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, D-Ala^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 26

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Abu^{8}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 27

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2 Péptido 28

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 30

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 31

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, His^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 32

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Cha^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 33

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tpi^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 34

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 35

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 36

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNH$_2$)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 37

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Trp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 38

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNO$_2$)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 39

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, 3-Pal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 40

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 41

[PhAc-His^{1}, D-Arg^{2}, Tyr^{6}, Har^{9}, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 42

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Har^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 43

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 45

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 46

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt

Péptido 47

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt

Péptido 48

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Aib^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 49

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Orn^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 50

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29) Péptido 51

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29) Péptido 52

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2 Péptido 53

[Dat-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2 Péptido 54

[Ipa-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2 Péptido 55

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[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NHEt Péptido 56

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, D-Arg^{29}, Har^{30}]hGH-RH(1-30)NH_2 Péptido 57

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, D-Arg^{30}]hGH-RH(1-30)NH_2 Péptido 58

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30) Péptido 59

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30) Péptido 60

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 62

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Har^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 63

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Amp^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 64

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Cit^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 65

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 84

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 85

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 90

Se destaca que los residuos de amino ácidos, desde el 30 hasta el 44, de la molécula nativa de la GH-RH, no parecen ser esenciales a la actividad; ni parece que su identidad sea crítica. Por lo tanto, parece que la adición de algunos o de todos estos residuos de amino ácidos adicionales al C-terminal de los análogos de hGH-RH(1-29)NH_2 y hGH-RH(1-30)NH_2 de la presente invención, no afectará la eficacia de esos análogos como antagonistas de GH-RH. Si algunos o todos esos amino ácidos se agregaran al C-terminal de los análogos hGH-RH(1-29)NH_2, los residuos de amino ácidos agregados podrían ser los mismos que los residuos 30 a 44 de la secuencia nativa hGH-RH o sus equivalentes razonables.

Métodos de Síntesis

Los péptidos sintéticos se preparan por un método adecuado de síntesis, tal como las técnicas de fase sólida exclusiva, por técnicas de fase sólida parcial, por condensación de fragmentos o por síntesis clásica de fase en solución.

Cuando los análogos de esta invención se sintetizan por el método de fase sólida, el residuo del C-terminal (aquí, A^{29} o A^{30}) está apropiadamente enlazado (anclado) a un soporte sólido inerte (resina), mientras lleva grupos protectores para su grupo alfa amino (y, en donde sea adecuado, para su grupo funcional de cadena lateral). Después de completar este paso, se remueve el grupo protector alfa amino del

residuo de amino ácido anclado y, el próximo residuo de amino ácido, A^{28} o A^{30}, respectivamente, se agrega teniendo a su grupo alfa amino (así como a cualquier grupo funcional de cadena lateral), adecuadamente protegido y, así sucesivamente. Los grupos protectores del N-terminal se remueven después de agregar cada residuo, pero no se remueven todavía los grupos protectores de la cadena lateral. Después que se han enlazado todos los amino ácidos deseados, en la secuencia adecuada, se separa el péptido desde su soporte y se lo libera de todos los grupos protectores de las cadenas laterales, bajo condiciones que sean mínimamente destructivas hacia los residuos en la secuencia. Esto se sigue con una purificación cuidadosa y caracterización escrupulosa del producto sintético, para asegurar que la estructura deseada es, sin duda, la obtenida.

Es particularmente preferido proteger a la función alfa amino de los amino ácidos durante el paso de acoplamiento, con un grupo protector sensible a ácido o a base. Tales grupos protectores deberían tener propiedades de ser estables en las condiciones de formación de enlaces peptídicos, y al mismo tiempo, ser fácilmente removibles, sin destrucción de la cadena creciente de péptidos y sin racemización de ninguno de los centros quirales contenidos allí. Los grupos protectores alfa amino adecuados son Boc y Fmoc.

Aplicaciones Médicas

Los péptidos antagonistas hGH-RH o las sales de esos péptidos pueden formularse en formas de dosificación farmacéuticas conteniendo cantidades efectivas de las mismas y administrarse a humanos o a animales con propósitos terapéuticos o de diagnóstico. Puede usarse a los péptidos para suprimir niveles de GH y para tratar condiciones asociadas con niveles excesivos de GH, por ejemplo, retinopatía diabética y neuropatía y acromegalia. También se provee métodos para tratar esas enfermedades por administración de una composición de la invención a un individuo necesitado de tal tratamiento. Los usos principales de los antagonistas de GH-RH

están, sin embargo, en el campo del cáncer, por ejemplo, los cánceres humanos de pulmón, próstata, mamas, ovario, endometrio, estómago, colon, páncreas, riñón, hueso y cerebro, en donde están presentes los receptores para GH-RH, IGF-I/IGF-II y que dependen de la estimulación por factores de crecimiento tales como GH-RH, IGF-I, IGF-II, GH o VEGF.

DESCRIPCIÓN DETALLADA DE LAS MODALIDADES PREFERIDAS

A. Abreviaturas

La nomenclatura usada para definir los péptidos es la especificada por la Comisión IUPAC-IUB sobre Nomenclatura Bioquímica, en la cual, de acuerdo con la representación convencional, el grupo amino en el N-terminal aparece a la izquierda y el grupo carboxilo en el C-terminal, aparece a la derecha. El término "amino ácido natural", como se usa aquí, significa uno de los L-amino ácidos de ocurrencia natural encontrados en proteínas de ocurrencia natural: Gly, Ala, Val, Leu, Ile, Ser, Thr, Lys, Arg, Asp, Asn, Glu, Gln, Cys, Met, Phe, Tyr, Pro, Trp e His. Cuando el residuo de amino ácido natural tiene formas isoméricas, la representada aquí es la forma L del amino ácido, a menos que se especifique expresamente en contrario.

Los amino ácidos no-codificados o análogos de amino ácidos, también se incorporan dentro de los antagonistas de GH-RH. (Los amino ácidos "no-codificados" son aquellos amino ácidos que no están entre los aproximadamente 20 amino ácidos naturales encontrados en proteínas de ocurrencia natural). Cuando esos amino ácidos no-codificados o análogos de amino ácidos tienen formas isoméricas, la forma L del amino ácido es la que se representa, a menos que se indique expresamente en contrario.

Las abreviaturas usadas aquí son:

Abu	ácido alfa-aminobutírico
Ac	acetil
AcOH	ácido acético

Ac_2O	anhídrido acético
Agm	agmantina
Aib	ácido alfa-aminoisobutírico
All	alil
Alloc	aliloxicarbonil
Amp	para-amidino-fenilalanina
Bpa	para-benzoíl-fenilalanina
Boc	ter-butiloxicarbonil
Bom	benciloxicarbonil
2BrZ	2-bromo-benciloxicarbonil
Cha	ciclohexilalanina
Chg	ciclohexilglicina
cHx	ciclohexil
Cit	citrulina (ácido 2-amino-5-ureidovalérico)
2ClZ	2-cloro-benciloxicarbonil
Dat	des-amino-tirosina
DCM	diclorometano
DIC	N,N'-diisopropilcarbodiimida
DIEA	diisopropiletilamina
Dip	(3,3-difenil)alanina
DMF	dimetilformamida
Et	etil
Fm	fluorenilmetil
Fmoc	fluorenilmetoxicarbonil
For	formil
GH	hormona de crecimiento
GH-RH	hormona liberadora de GH
Gup	para-guanidino-fenilalanina

Har	homoarginina
HBTU	hexafluorofosfato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio
Hca	hidrocinamoil
Hca-OH	ácido hidrocinámico
hGH-RH	GH-RH humano
HOBt	1-hidroxibenzotriazol
HPLC	cromatografía líquida de alto desempeño
Ibu	isobutiril
IndAc	indol-3-acetil
Ipa	indol-3-propionil
MBHA	para-metilbencidrilamina
Me	metil
MeOH	metanol
MeCN	acetonitrilo
Nac	naftilacetil
Nal	naftilalanina
Nle	norleucina
NMM	N-metilmorfolina
Npr	naftilpropionil
Orn	ornitina
Pal	piridilalanina
PAM	fenilacetoamidometil
Ph	fenil
PhAc	fenilacetil
PhAc-OH	ácido fenilacético
Phe(pCl)	para-cloro-fenilalanina
Phe(pNO_2)	para-nitro-fenilalanina

rGH-RH	GH-RH de rata
RP-HPLC	HPLC en fase reversa
SPA	para-sulfonil-fenoxiacetil
TFA	ácido trifluoroacético
Tos	para-toluensulfonil
Tpi	ácido 1,2,3,4-tetrahidronorharman-3-carboxílico
Tyr(Me)	O-metil-tirosina
Tyr(Et)	O-etil-tirosina
Z	benciloxicarbonil

B. Los análogos de GH-RH

Los análogos de hGH-RH de la presente invención se diseñaron para aumentar los efectos antagonísticos a nivel de la pituitaria y/o a nivel tumoral. Algunos de esos análogos, tales como el Péptido 4, Péptido 7, Péptido 21, Péptido 30, Péptido 31, Péptido 37, Péptido 41, Péptido 42, Péptido 62, Péptido 67 y Péptido 69 poseen altas potencias antagonísticas endocrinas, causando una inhibición muy efectiva y de larga duración en la liberación de GH estimulada por hGH-RH(1-29)NH_2, *in vitro* e *in vivo*, exhibiendo altas afinidades de ligado con los receptores pituitarios de GH-RH. Algunos análogos, tales como el Péptido 4, Péptido 5, Péptido 7, Péptido 11, Péptido 22, Péptido 35, Péptido 36, Péptido 39, Péptido 41, Péptido 62, Péptido 67, Péptido 69, Péptido 70, Péptido 72, Péptido 76, Péptido 76, Péptido 77, Péptido 79, Péptido 80, Péptido 86, Péptido 95, Péptido 96 y Péptido 97 muestran potencias elevadas de inhibición tumoral y exhiben afinidades altamente ligadoras con los receptores tumorales de GH-RH. Los péptidos de la presente invención también se diseñaron para mejorar sus estabilidades químicas y metabólicas.

Las siguientes modalidades son especialmente preferidas, porque tienen bioactividad notable:

[$CH_3(CH_2)_4CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 2

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 4

[$HOOC(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 5

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 6

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 7

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 11

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2 Péptido 14

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2 Péptido 15

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 21

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Cit^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 22

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Abu^{8}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 27

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2

Péptido 28

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 30

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 31

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 35

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 36

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNH_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 37

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNO_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 39

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 41

[PhAc-His^{1}, D-Arg^{2}, Tyr^{6}, Har^{9}, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 42

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 46

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 62

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 67

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 68

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, His^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 69

[$CH_3(CH_2)_6CO$-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 70

[$HOOC(CH_2)_8CO$-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 71

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 72

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 73

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 74

[1-Nac-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 75

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 76

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 77

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 78

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 79

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 80

[$HOOC(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 81

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 82

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 84

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 85

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 86

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 87

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 88

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 89

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 90

[1-Nac-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 91

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 92

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 93

[$CH_3(CH_2)_6CO$-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, His^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 94

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 95

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 96

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 97

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 98

[$CH_3(CH_2)_{10}CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 99

[Hca -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 100

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHMe Péptido 101

[$HOOC(CH_2)_{12}CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 102

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, Amp^{9}, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 103

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 104

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 105

[$CH_3(CH_2)_6CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 106

[$HOOC(CH_2)_{12}CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, Amp^{9}, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 107

[$HOOC(CH_2)_{12}CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 108

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 109

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 110

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido·111

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 112

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 113

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 114

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 115

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 116

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 117

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[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 118

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 119

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 120

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 121

Treinta modalidades muy preferidas tienen la fórmula:

$CH_3(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 4

$HOOC(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 5

$HOOC(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 7

$HOOC(CH_2)_{12}CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 11

PhAc-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Cit^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 21

PhAc-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Cit^8-Cit^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 22

PhAc-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Arg^9-Amp^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 30

PhAc-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Har^9-Amp^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 31

PhAc-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Har^9-2-Nal^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 35

PhAc-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-Har^9-Dip^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 36

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Phe(pNH$_2$)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH$_2$ Péptido 37

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Phe(pNO$_2$)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH$_2$ Péptido 39

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Tyr(Et)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH$_2$ Péptido 41

PhAc-His^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Tyr^{6}-Thr^{7}-Asn^{8}-Har^{9}-Bpa^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH$_2$ Péptido 42

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NHEt Péptido 46

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Tyr(Me)^{10}-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH$_2$ Péptido 62

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Amp^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH$_2$ Péptido 67

PhAc-Tyr[1]-D-Arg[2]-Asp[3]-Ala[4]-Ile[5]-Phe(pCl)[6]-Thr[7]-Asn[8]-His[9]-Tyr(Me)[10]-Arg[11]-Lys[12]-Val[13]-Leu[14]-Abu[15]-Gln[16]-Leu[17]-Ser[18]-Ala[19]-Arg[20]-Lys[21]-Leu[22]-Leu[23]-Gln[24]-Asp[25]-Ile[26]-Nle[27]-D-Arg[28]-Har[29]-NH_2 Péptido 69

$CH_3(CH_2)_6CO$-Tyr[1]-D-Arg[2]-Asp[3]-Ala[4]-Ile[5]-Phe(pCl)[6]-Thr[7]-Asn[8]-Amp[9]-Tyr(Me)[10]-Arg[11]-Lys[12]-Val[13]-Leu[14]-Abu[15]-Gln[16]-Leu[17]-Ser[18]-Ala[19]-Arg[20]-Lys[21]-Leu[22]-Leu[23]-Gln[24]-Asp[25]-Ile[26]-Nle[27]-D-Arg[28]-Har[29]-NH_2 Péptido 70

$HOOC(CH_2)_{12}CO$-Tyr[1]-D-Arg[2]-Asp[3]-Ala[4]-Ile[5]-Phe(pCl)[6]-Thr[7]-Asn[8]-Amp[9]-Tyr(Me)[10]-Arg[11]-Lys[12]-Val[13]-Leu[14]-Abu[15]-Gln[16]-Leu[17]-Ser[18]-Ala[19]-Arg[20]-Lys[21]-Leu[22]-Leu[23]-Gln[24]-Asp[25]-Ile[26]-Nle[27]-D-Arg[28]-Har[29]-NH_2 Péptido 72

$CH_3(CH_2)_6CO$-Tyr[1]-D-Arg[2]-Asp[3]-Ala[4]-Ile[5]-Phe(pCl)[6]-Thr[7]-Cit[8]-Amp[9]-Tyr(Me)[10]-His[11]-Lys[12]-Val[13]-Leu[14]-Abu[15]-Gln[16]-Leu[17]-Ser[18]-Ala[19]-Arg[20]-Lys[21]-Leu[22]-Leu[23]-Gln[24]-Asp[25]-Ile[26]-Nle[27]-D-Arg[28]-Har[29]-NH_2 Péptido 76

$HOOC(CH_2)_{12}CO$-Tyr[1]-D-Arg[2]-Asp[3]-Ala[4]-Ile[5]-Phe(pCl)[6]-Thr[7]-Cit[8]-Amp[9]-Tyr(Me)[10]-His[11]-Lys[12]-Val[13]-Leu[14]-Abu[15]-Gln[16]-Leu[17]-Ser[18]-Ala[19]-Arg[20]-Lys[21]-Leu[22]-Leu[23]-Gln[24]-Asp[25]-Ile[26]-Nle[27]-D-Arg[28]-Har[29]-NH_2 Péptido 77

$CH_3(CH_2)_6CO$-Tyr[1]-D-Arg[2]-Asp[3]-Ala[4]-Ile[5]-Phe(pCl)[6]-Thr[7]-Cit[8]-His[9]-Tyr(Et)[10]-His[11]-Lys[12]-Val[13]-Leu[14]-Abu[15]-Gln[16]-Leu[17]-Ser[18]-Ala[19]-Arg[20]-Lys[21]-Leu[22]-Leu[23]-Gln[24]-Asp[25]-Ile[26]-Nle[27]-D-Arg[28]-Har[29]-NH_2 Péptido 79

$CH_3(CH_2)_6CO$-Tyr[1]-D-Arg[2]-Asp[3]-Ala[4]-Ile[5]-Phe(pCl)[6]-Thr[7]-Ala[8]-His[9]-Tyr(Et)[10]-His[11]-Lys[12]-Val[13]-Leu[14]-Abu[15]-Gln[16]-Leu[17]-Ser[18]-Ala[19]-Arg[20]-Lys[21]-Leu[22]-Leu[23]-Gln[24]-Asp[25]-Ile[26]-Nle[27]-D-Arg[28]-Har[29]-NH_2 Péptido 80

$HOOC(CH_2)_{12}CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 82

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-His^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 86

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Asn^8-His^9-$Tyr(Et)^{10}$-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 92

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Orn^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Orn^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 95

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Orn^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-His^{20}-Orn^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 96

$CH_3(CH_2)_8CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NHEt Péptido 97

Bajo convención bien establecida, esos pueden abreviarse como sigue:

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 4

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 5

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 7

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 11

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 21

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 22

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 30

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 31

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 35

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 36

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNH$_2$)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 37

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNO$_2$)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 39

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 41

[PhAc-His^{1}, D-Arg^{2}, Tyr^{6}, Har^{9}, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 42

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 46

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 62

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 67

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, His^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 69

[CH$_3$(CH$_2$)$_6$CO-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 70

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 72

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 76

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 77

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 79

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 80

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 82

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 86

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 92

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 95

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 96

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 97

C. Método de Preparación

1.- Perspectiva General de la Síntesis

Los Péptidos se sintetizan con métodos adecuados, tales como las técnicas de fase sólida exclusiva, técnicas de fase sólida parcial, por condensación de fragmentos o por síntesis clásica de fase en solución. Por ejemplo, las técnicas de fase sólida exclusiva se describen en el libro de texto "Solid Phase Péptido Synthesis", J.M. Stewart y J.D. Young, Pierce Chem. Company, Rockford, Illinois, 1984 (2a. ed.), y M. Bodanszky, "Principles of Péptido Synthesis", Springer Verlag, 1984. Los péptidos antagonistas de hGH-RH se preparan preferiblemente usando síntesis de fase sólida, tal como la que se describe, en general, por Merrifield, J. Am. Chem. Soc., 85 p. 2149 (1963), aunque también pueden usarse otras síntesis químicas equivalentes, conocidas en el arte, como se mencionó previamente.

La síntesis se efectúa con amino ácidos protegidos en su grupo alfa amino. Preferiblemente, se usan grupos protectores del tipo uretano (Boc o Fmoc) para la protección del grupo alfa amino.

En la síntesis en fase sólida, la mitad del amino ácido protegida por N-alfa, que forma al grupo aminoacil del péptido final, en el C-terminal se une a un soporte de resina polimérica, vía un enlace químico. Después de completar la reacción de acoplamiento, el grupo protector alfa amino se remueve selectivamente para permitir que se efectúen las subsiguientes reacciones de acoplamiento en el terminal-amino, preferiblemente con 50% de TFA en DCM cuando el grupo protector N-alfa es Boc o, con 20% de piperidina en DMF cuando el grupo protector N-alfa es Fmoc. Los

restantes amino ácidos con similares grupos protectores Boc o Fmoc se acoplan en pasos al grupo amino libre del amino ácido precedente, sobre la resina, para obtener la secuencia de péptidos deseada. Debido a que los residuos de amino ácidos se acoplan con el grupo alfa amino del residuo del C-terminal, el crecimiento de los péptidos sintéticos de análogos de hGH-RH empieza en el C-terminal y progresa hacia el N-terminal. Cuando se ha obtenido la secuencia deseada, se acila el péptido en el N-terminal y se lo remueve del polímero de soporte.

Cada amino ácido protegido se usa en exceso (2,5 a 3 equivalentes) y las reacciones de acoplamiento se efectúan, usualmente, en DCM, DMF o mezclas de las mismas. La cantidad de completamiento de la reacción de acoplamiento se monitorea en cada etapa mediante la reacción de ninhidrina. En casos en que se determina un acoplamiento incompleto, se repite el procedimiento de acoplamiento o se efectúa una coronación por acetilación de los grupos amino sin reaccionar, antes de la remoción del grupo protector alfa amino, previo al acoplamiento del siguiente amino ácido.

Los ciclos de síntesis típicos se muestran en los Cuadros I y II.

CUADRO I.

Protocolo para un Ciclo de Síntesis Típico usando la Estrategia-Boc

Paso	Reactivo	Tiempo de mezclado (minutos)
1. Desprotección	50% de TFA en DCM	5 + 25
	Lavado con DCM	1
	Lavado en 2-propanol	1
2. Neutralización	5% DIEA con DCM	1
	Lavado con DCM	1
	Lavado con MeOH	1
	5% DIEA en DCM	3
	Lavado con MeOH	1
	Lavado con DCM (veces)	1
3. Acoplamiento	3 equivalentes de amino ácido-Boc en DCM o DMF + 3 equivalentes de DIC o del éster HOBt preformado del amino ácido-Boc	60
	Lavado con MeOH (3 veces)	1
	Lavado con DCM (3 veces)	1

4. Acetilación	Ac_2O en piridina (30%)	10 + 20
(sí adecuado)	Lavado con MeOH (3 veces)	1
	Lavado con DCM (3 veces)	1

CUADRO II

Protocolo para un Ciclo de Síntesis Típico usando Estrategia-Fmoc

Paso	Reactivo	Tiempo de mezclado (minutos)
1. Desprotección	20% de piperidina en DMF	5 + 15
	Lavado con DMF (3 veces)	1
2. Acoplamiento	3 equivalentes de amino ácido-Fmoc en DMF + 3 equivalentes de DIC o + 3 equivalentes de HBTU + 3 equivalentes de HOBT + 6 equivalentes de DIEA	60
	Lavado con DMF (3 veces)	1
3. Acetilación (sí adecuado)	3 equivalentes de 1-acetilimidazol en DMF	30
	Lavado con DMF (3 veces)	1

Después de completar la síntesis, la separación del péptido desde la resina puede efectuarse usando procedimientos bien conocidos en la química de los péptidos.

2.- Selección del Soporte de Polímero

Los antagonistas de los péptidos de hGH-RH pueden sintetizarse sobre una variedad de polímeros de soporte, por ejemplo, resinas MBHA, Merrifield, PAM, amida Rink o Wang. Los péptidos también pueden sintetizarse sobre aminometil, MBHA u otras resinas, previamente derivatizadas con ligadores adecuados. Los ejemplos de tales ligadores son el ligador ácido 4-hidroximetil benzoico (HMBA), sensible a base, para el acoplamiento de los grupos carboxil del C-terminal o, el ligador

para-sulfonil-fenoxiacetilo (SPA), sensible a ácido, que permite el acoplamiento de agmantina a través de su grupo guanidino.

Cuando los péptidos con un C-terminal amidado se sintetizan usando la estrategia Boc, la resina preferida es MBHA. Puede lograrse el acoplamiento del C-terminal del amino ácido a esta resina mediante el método de acoplamiento estándar mediado por DIC, descrito en el Cuadro I.

Para preparar péptidos con una modificación de etilamina en el C-terminal puede usarse la resina de Merrifield o la resina HMBA-MBHA, en conjunto con la estrategia Boc. La carga del amino ácido con C-terminal, sobre la resina de Merrifield, se efectúa por acoplamiento mediado por fluoruro de potasio (KF) o sal de cesio, a temperatura elevada.

Para la síntesis de péptidos que tienen Agm en el C-terminal, se prefiere que la fase de soporte sea resina MBHA o una resina de aminometilo. El grupo guanidino de Boc-Agm se une al polímero de soporte mediante un ligador estable, pero fácilmente separable, tal como la mitad de para-sulfonil-fenoxiacetilo (SPA). El alfa-amino de la Agm, protegido por Boc, se hace reaccionar con ácido clorosulfonil fenoxiacético, Cl-SO_2-C_6H_4-O-CH_2-COOH, para formar Boc-Agm-SO_2-C_6H_4-CH_2-COOH. Este compuesto se acopla luego con el polímero de soporte, por ejemplo, con la resina MBHA, usando DIC o HBTU-HOBt-DIEA como reactivo activador, para dar Boc-Agm-SPA-MBHA.

Los amino ácidos bifuncionales, es decir, aquellos que no tienen grupos funcionales en la cadena lateral, se usan principalmente en forma de sus derivados N-alfa Boc- o Fmoc-, para la síntesis. Así, se usa típicamente Boc-Gly-OH o Fmoc-Gly-OH, para incorporar el residuo Gly. Los amino ácidos bifuncionales de ocurrencia natural son Gly, Ala, Val, Leu, Ile, Phe y Pro y, algunos amino ácidos bifuncionales, no codificados, bien conocidos, que se usan en esta invención son Abu, Aib y Nle.

Algunos de los residuos de amino ácidos de los péptidos tienen grupos funcionales en la cadena lateral que reaccionan con los reactivos usados en el

acoplamiento o desprotección. Cuando tales grupos de cadena lateral están presentes, los grupos protectores adecuados se ligan a esos grupos funcionales para prevenir reacciones químicas indeseables, que ocurren durante las reacciones usadas para formar a los péptidos. Se siguen las siguientes reglas generales para seleccionar a un grupo protector de cadena lateral particular: (a) preferiblemente, el grupo protector retiene sus propiedades protectoras y no se separa bajo las condiciones de acoplamiento; (b) el grupo protector debería ser estable bajo condiciones para remover al grupo protector alfa amino, en cada paso de la síntesis; (c) el grupo protector de la cadena lateral debe ser removible al completar la síntesis de la secuencia de amino ácidos deseada, bajo condiciones de reacción que no alteren indeseablemente a la cadena de péptidos.

Cuando se usan Boc-amino ácidos en la síntesis, los grupos funcionales reactivos de la cadena lateral pueden protegerse como sigue: Tos o nitro (NO_2) para Arg y Har; cHx o Fm para Asp y Glu; Bom para His; 2ClZ o Fmoc para Lys y Orn; Bzl para Ser y Thr; For para Trp; y 2BrZ para Tyr. Las cadenas laterales de Asn y Gln están desprotegidas. En el caso de síntesis Fmoc, los grupos funcionales reactivos de la cadena lateral pueden protegerse por otros grupos protectores adecuados, como sigue: 2,2,4,6,7-pentametil-dihidrobenzofurán-5-sulfonilo (Pbf) o bis-Boc para Arg y Har; ter-butil (tBu) para Asp y Glu; sin grupo protector o con protección de tritil (Trt) para Asn y Gln; Trt para His; Boc o 4-metoxitritil (Mmt) para Lys y Orn; tBu o Trt para Ser y Thr; Boc para Trp; y rBu o 2-clorotritil (2ClTrt) para Tyr.

Además de los bien conocidos amino ácidos, codificados y no-codificados antedichos, algunos de los péptidos de esta solicitud contienen amino ácidos no-codificados menos comunes, tales como para-amidino-fenilalanina (Amp); para-guanidino-fenilalanina (Gup); ciclohexilalanina (Cha); ácido 1,2,3,4-tetrahidronorharman-3-carboxílico (Tpi); (2-naftil)alanina (2-Nal); (3,3-difenil)alanina (Dip); para-amino-fenilalanina [Phe(pNH_2)]; para-nitro-fenilalanina [Phe(pNO_2)]; (3-piridil)alanina (3-Pal); O-etil-tirosina [Tyr(Et)]; y para-benzoíl-fenilalanina (Bpa). Estos residuos de amino

ácidos se incorporan dentro de los péptidos, acoplando los derivados de amino ácido adecuadamente protegidos. Una lista no exclusiva de tales derivados de amino ácidos protegidos que puede usarse es como sigue: Boc-Amp(Alloc)-OH, Boc-Amp-OH, Fmoc-Amp(Alloc)-OH, Fmoc-Amp-OH, Boc-Gup(Tos)-OH, Boc-Gup-OH, Fmoc-Gup(Boc)$_2$-OH, Fmoc-Gup-OH, Boc-Cha-OH, Boc-Tpi-OH, Boc-2-Nal-OH, Boc-Dip-OH, Boc-Phe(pNH-Z)-OH, Boc-Phe(pNO_2)-OH, Boc-3-Pal-OH, Boc-Tyr(Et)-OH y Boc-Bpa-OH. Los derivados protegidos de amino ácidos no-codificados, antedichos están comúnmente disponibles en varios abastecedores comerciales, incluyendo Bachem (King of Prussia, PA), Péptidos International (Louisville, KY), Novabiochem (San Diego, CA), Advanced ChemTech (Louisville, KY) y RSP Amino Acid Analogues DBA (Worcester, MA).

4.- Acoplamiento Paso-a Paso de Residuos de Amino Ácidos

Utilizando los polímeros de soporte antedichos y después de cargar el C-terminal del amino ácido o el residuo de Agm, el péptido mismo puede acumularse por síntesis en fase sólida, en la forma convencional. Cada amino ácido protegido se acopla en alrededor de un exceso molar de tres veces, con respecto a los residuos libres de amino ácidos destinados a la resina y, el acoplamiento puede efectuarse en un medio tal como DMF-DCM (1:1) o en DMF o DCM solas. La selección de un reactivo acoplador adecuado está dentro del entrenamiento del arte. Los reactivos acopladores, particularmente adecuados son N,N'-diisopropil carbodiimida (DIC) o HBTU, combinada con HOBt, en presencia de DIEA. El éxito de la reacción de acoplamiento, en cada etapa de la síntesis, se monitorea preferiblemente por la reacción de ninhidrina. En casos en que ocurre acoplamiento incompleto, se repite el procedimiento de acoplamiento o se acetilan los residuos de amino ácidos sin reaccionar destinados a la resina, usando un reactivo coronador, antes de la remoción del grupo protector alfa amino. Los reactivos coronadores adecuados son 1-acetilimidazol y Ac_2O-piridina.

La acilación final del N-terminal del péptido con ácidos mono-carboxílicos se efectúa en la misma forma que en los acoplamientos precedentes, con la diferencia que se usa el ácido carboxílico adecuado en lugar de un amino ácido. Cuando se acoplan ácidos di-carboxílicos al N-terminal y se desea que solo un grupo –COOH reaccione con el terminal amino del péptido (esto es, se preparan mono-amidas de esos ácidos), se puede usar los anhídridos de los respectivos ácidos di-carboxílicos para el acoplamiento. Los anhídridos cíclicos de muchos ácidos di-carboxílicos están comercialmente disponibles; en otros casos, se preparan los anhídridos pre-formados de esos ácidos por tratamiento con DIC y se usan para el acoplamiento.

5. Separación del Péptido desde el Polímero de Soporte y Remoción de los Grupos Protectores de la Cadena Lateral.

Cuando se completa la síntesis, el péptido se separa de la fase de soporte y se remueven sus grupos protectores de las cadenas laterales.

En casos en que los péptidos con C-terminal amidado (-$CONH_2$) o con un grupo carboxílo (-COOH) en el C-terminal se preparan con la estrategia Boc en resina MBHA, Merrifield o PAM, la remoción del principal desde la resina se efectúa por tratamiento con un reactivo tal como fluoruro de hidrógeno líquido (HF). Este también es el caso para péptidos sintetizados sobre la resina Boc-Agm-SPA-MBHA. En algunas instancias, el HF líquido también separa a todos los grupos protectores remanentes de la cadena lateral. Sin embargo, si los grupos protectores de la cadena lateral, resistentes al tratamiento con HF están presentes en el péptido, deberá efectuarse pasos adicionales de separación para remover a esos grupos protectores. Así, los grupos protectores Fm y Fmoc se remueven por tratamiento con 20% de piperidina en DMF, mientras los grupos All y Alloc se remueven por tratamiento con catalizador $Pd(PPh_3)_4$ y eliminadores nucleofílicos, antes o después del tratamiento con HF.

Adecuadamente, el conjunto péptido-resina protegido se trata con una mezcla consistente de 1,0 ml de m-cresol y 10 ml de fluoruro de hidrógeno anhidro, por

gramo de péptido-resina, durante 60-120 minutos, a 0°C, para separar al péptido de la resina, así como para remover a los grupos protectores de la cadena lateral sensibles a HF. Después de la remoción del fluoruro de hidrógeno bajo una corriente de nitrógeno y vacío, los péptidos libres se precipitan con éter, se filtran, se lavan con éter y acetato de etilo, se extraen con ácido acético al 50% y se liofilizan.

En los casos en que se preparan péptidos con un C-terminal de etilamina (-NHEt), con la estrategia Boc, sobre resina Merrifield o HMBA-MBHA, primero se separan los péptidos desde la resina, por aminolisis con etilamina ($EtNH_2$). Adecuadamente, se transfiere la $EtNH_2$ líquida a un matraz de vidrio de paredes gruesas, enfriado, que contiene al conjunto de péptido-resina, protegido y secado. La cantidad de $EtNH_2$ líquida debería ser suficiente para cubrir al conjunto péptido-resina. Se tapona el matraz y se lo agita con la $EtNH_2$ líquida durante 3,5 horas, a temperatura ambiente, para permitir que se efectúe la reacción. Después de esto, se enfría el matraz en un baño de hielo seco, se abre y se separa la $EtNH_2$, por filtración del residuo sólido que contiene una mezcla de resina y péptido separados, en que el péptido todavía tiene unidos los grupos protectores. Luego, el residuo sólido se seca y se lo somete a tratamiento con HF, como se describió anteriormente, para remover del péptido a los grupos protectores de la cadena lateral.

6.- <u>Purificación</u>

La purificación de los péptidos crudos puede efectuarse usando procedimientos bien conocidos en la química de péptidos. Por ejemplo, la purificación puede efectuarse en un sistema HPLC de MacRabbit (Rainin Instrument Co., Inc., Woburn, MA), con un fotómetro Knauer UV y un registrador Kipp y Zonen BD40, usando una columna Vydac 218TP510, (10 x 250 mm, empacada con sílica gel C18, tamaño de poros 300 Å, tamaño de partículas 5 µm), (The Separations Group, Inc,. Hesperia, CA), en fase reversa. La columna se eluye con un sistema de solventes que consiste de (A) TFA al 0,1% acuoso y (B) TFA al 0,1% en MeCN acuoso al 70%, en un modo de

gradiente linear (es decir, 30-35% de B en 120 minutos). Se monitorea el eluyente a 220 nm y se examinan las fracciones mediante HPLC analítica, usando un equipo Hewlett-Packard Modelo HP-1090, para cromatografía líquida y combinando para dar máxima pureza. La HPLC analítica se efectúa en una columna Vydac 218P52 (2 x 250 mm, C18, 300 Å, 5 µm), en fase reversa, usando elución isocrática con un sistema de solventes que consiste de los (A) y (B) anteriormente definidos. Los picos se monitorean a 220 y 280 nm. Se considera que los péptidos están substancialmente puros (>95%) por la HPLC analítica. Se revisan las masas moleculares mediante espectrometría de masa por electro-aspersión y se confirman las composiciones esperadas de los amino ácidos por análisis de los mismos.

D. Composiciones Farmacéuticas y Modo de Administración

Puede administrarse los péptidos de la invención en forma de sales no tóxicas, farmacéuticamente aceptables, tales como las sales de adición de ácido. Los ejemplos ilustrativos de tales sales de adición de ácido son hidrocloruro, hidrobromuro, sulfato, fosfato, fumarato, gluconato, tanato, maleato, acetato, trifluoroacetato, citrato, benzoato, succinato, alginato, pamoato, malato, ascorbato, tartrato y similares. Los antagonistas particularmente preferidos son las sales de baja solubilidad, por ejemplo, las sales pamoato y similares. Estas exhiben actividad de larga duración.

Los compuestos de la presente invención se administran adecuadamente a sujetos humanos o animales, en forma subcutánea (s.c.), intramuscular (i.m.) o intravenosa (i.v.); intranasalmente o por inhalación pulmonar; por entrega transdermal; o en forma de depósito (es decir, implantes de micro-cápsulas, micro-gránulos o del tipo de barritas cilíndricas), formuladas desde un polímero adecuadamente bio-degradable (tal como D,L-lactato-co-glicólido), siendo preferidos los dos modos de depósito anteriores. Otros modos equivalentes de administración, también están dentro del alcance de esta invención, por ejemplo, goteo continuo, parches cutáneos, inyecciones de depósitos, bomba de infusión y modos de liberación extendida, tales como las micro-

cápsulas y similares. La administración se efectúa con cualquier vehículo inyectable, farmacéuticamente aceptable, siendo aceptable la solución salina fisiológica, aunque también puede usarse otros vehículos conocidos en el arte.

Preferiblemente, los péptidos se administran parenteral, intramuscular, subcutánea o intravenosamente, con un vehículo farmacéuticamente aceptable, tal como solución salina isotónica. Alternativamente, los péptidos pueden administrarse como aspersión intranasal con un vehículo adecuado o por inhalación pulmonar. Una ruta adecuada de administración es en forma de depósito, formulada con un polímero adecuadamente bio-degradable, por ejemplo, poli D,L-lactato-coglicólido, como implantes de micro-cápsulas, micro-gránulos o cilindros, conteniendo a los compuestos antagonistas adecuadamente dispersos.

La cantidad necesaria de péptido depende del tipo de composición farmacéutica y del modo de administración. En casos en que los sujetos humanos reciben soluciones de antagonistas de la GH-RH, administrados por inyección i.m. o s.c. o en forma de aspersión intranasal o inhalación pulmonar, las dosis típicas están entre 2-20 mg/día/paciente, dadas una vez al día o divididas en 2 a 4 administraciones/día. Cuando se administran los antagonistas de GH-RH intravenosamente a pacientes humanos, las dosis típicas están en el rango de 8-80 µm/kg de peso corporal diarias, divididas en 1-4 inyecciones diarias o dadas como infusión continua. Cuando se usan preparaciones de antagonistas de GH-RH, en forma de depósito, por ejemplo, como inyección i.m. de sales pamoato u otras sales de baja solubilidad o, por administración i.m. o s.c. de micro-cápsulas, micro-gránulos o implantes conteniendo a los compuestos antagonistas dispersados en un polímero bio-degradable, las dosis típicas están entre 1-10 mg del antagonista por día y por paciente.

E. Usos Terapéuticos de los Antagonistas de GH-RH

Se espera que las aplicaciones terapéuticas más importantes de los antagonistas de GH-RH estén en el campo de la oncología y de la endocrinología.

Algunos de los antagonistas de la GH-RH actúan, predominantemente, a nivel de la pituitaria y tienen efectos endocrinos más fuertes, inhibiendo la liberación de la GH evocada por GH-RH y disminuyendo, últimamente, los niveles de la GH y del IGF-I, en el suero. Otros antagonistas de la GH-RH actúan predominantemente a nivel tumoral, al bloquear los receptores de la GH-RH tumorales, reduciendo la producción de varios de los factores de crecimiento autocrinos/paracrinos del tumor (tales como el IGF-I, IGF-II, GH, VEGF, FGF) y/o regulando hacia abajo a sus receptores y, de esta manera, ejerciendo efectos inhibidores más fuertes en el crecimiento del tumor. Estos antagonistas también pueden usarse como sistemas vehiculares, unidos a radionucleidos, para terapia o localización del tumor o, conjugados con agentes quimio-terapéuticos o toxinas. Tales compuestos híbridos pueden dirigirse activamente hacia el objetivo canceroso, con propósitos de diagnóstico o terapéuticos. Aún otros antagonistas de GH-RH actúan a través de mecanismos múltiples de acción, esto es mediante mecanismos endocrinos y simultáneamente, por efectos directos sobre los tumores. De esta manera, las principales indicaciones terapéuticas para varios de los antagonistas de la GH-RH difieren, basadas en sus mecanismos preferenciales de acción.

Puede usarse los análogos de la GH-RH, con acción antagonística sobre la pituitaria, en situaciones en que es beneficioso suprimir los niveles de GH e IGF-I en el suero. Así, ellos están indicados para la terapia en desórdenes endocrinos, caracterizados por producción excesiva de GH e IGF-I, así como para el tratamiento de cánceres que expresan receptores de IGF-I, IGF-II o GH y en que se estimulan por estos factores de crecimiento.

También están disponibles los análogos de somatostatina y los antagonistas de GH, para el tratamiento de condiciones endocrinas causadas por GH e IGF-I. Sin embargo, los antagonistas de GH-RH ofrecen beneficios terapéuticos únicos, no obtenibles con el uso de análogos de somatostatina y antagonistas de GH. Estos beneficios se deben a los múltiples mecanismos de acción de los antagonistas de GH-

RH, específicamente, porque ejercen efectos directos, independientes de la GH e IGF-I, sobre tumores y otros sitios objetivo, además de inhibir el eje endocrino para la GH e IGF-I. Los antagonistas de GH-RH pueden darse solos o en conjunto con análogos de somatostatina, una combinación que suprime más completamente los niveles de GH e IGF-I. Un efecto colateral, indeseable, de los antagonistas de GH, que puede evitarse por la administración de antagonistas de GH-RH, es la elevación de los niveles de GH en el suero, a través de un mecanismo de retro-alimentación.

Una enfermedad causada por exceso de hormona de crecimiento es la acromegalia, que se manifiesta por un alargamiento anormal de los huesos de la cara y extremidades. Los antagonistas de la GH-RH podrían aliviar las manifestaciones clínicas de la acromegalia, es decir, el alargamiento de los huesos faciales y de las extremidades, el agrandamiento del corazón y otras anormalidades estructurales y funcionales del sistema cardiovascular. Los antagonistas de GH-RH también pueden usarse para tratar la retinopatía diabética (la causa principal de ceguera en diabéticos) y la neuropatía diabética, en las cuales, se piensa, que el daño al ojo y al riñón, respectivamente, se debe a la GH. Los pacientes diabéticos también pueden beneficiarse del aumento de la sensibilidad a la insulina producido por los antagonistas de GH-RH, un efecto ligado a la capacidad de estos compuestos para reducir los niveles de GH e IGF-I. Además, ya que inhiben la liberación de GH, los antagonistas de GH-RH pueden usarse para retardar la progresión de la distrofia muscular.

Las drogas con propiedades anti-factor de crecimiento, tales como los antagonistas de GH-RH, también pueden ser beneficiosas para controlar o retardar la progresión de algunos procesos clínico-patológicos, en condiciones tales como la fibrosis pulmonar idiopática, esclerosis sistémica y cardiomiopatía hipertrófica, en las cuales las actuales terapias médicas tienen relativamente poco que ofrecer. Además, no se ha demostrado ninguna terapia con drogas que sea efectiva para disminuir la incidencia de restenosis después de angioplastía coronaria transluminal percutánea (PTCA) y deben diseñarse nuevas aproximaciones, incluyendo el uso de los

antagonistas de GH-RH. Algunas condiciones ginecológicas, tales como miomas, endometriosis y síndrome de ovario poliquístico, también pueden tratarse con antagonistas de GH-RH, en combinación con agonistas y antagonistas de la hormona liberadora de la hormona luteinizante (LH-RH). También están disponibles los antagonistas de GH-RH para el tratamiento de la hiperplasia benigna de la próstata (BPH) y los desórdenes proliferativos, hiperplásicos y benignos, de otros órganos normales, en los cuales están presentes los receptores de GH-RH.

Sin embargo, las principales aplicaciones de los antagonistas de GH-RH están en el campo del cáncer. Los antagonistas de GH-RH, especialmente aquellos con fuertes efectos directos a nivel tumoral, están indicados para inhibir el crecimiento de tumores primarios y para suprimir su esparcimiento metastático. Ya que los efectos antiproliferativos de los antagonistas de GH-RH se ejercen a través de varios mecanismos, esos compuestos están disponibles para el tratamiento de una gran variedad de cánceres, tales como aquellos que dependen de la estimulación autocrina/paracrina y endocrina por la GH-RH, IGF-I, IGF-II, GH, VRGF y FGF.

Los antagonistas de GH-RH están disponibles para el tratamiento de tumores que expresan receptores de GH-RH y usan a la GH-RH como un factor de crecimiento autocrino/paracrino. Tales enfermedades malignas incluyen, pero sin que sea limitación, los cánceres de pulmón, próstata, mamas, ovarios, endometrio, estómago, intestinos, páncreas, riñones, huesos, hígado, así como glioblastomas, feocromocitomas, melanomas y linfomas. Al bloquear los receptores tumorales de la GH-RH, esos antagonistas previenen la acción estimuladora de la GH-RH, resultando en inhibición del crecimiento del tumor.

Una ventaja de los antagonistas de GH-RH sobre los análogos de somatostatina, se basa en el hecho que los antagonistas de GH-RH pueden utilizarse para la supresión de tumores que no tienen receptores para somatostatina, pero que expresan a los receptores tumorales de la GH-RH, por ejemplo, los sarcomas osteogénicos humanos.

Las enfermedades malignas que expresan receptores de IGF-I y, que dependen de los IGF-I e IGF-II como factores de crecimiento, pueden tratarse con terapias de antagonistas de GH-RH. Esas enfermedades malignas incluyen, entre otras, a los cánceres de pulmón, próstata, mamas, ovarios, endometrio, gástricos, colorectales, pancreáticos, renales y hepáticos, a los sarcomas y tumores cerebrales. La capacidad de los antagonistas de GH-RH para disminuir los niveles de IGF-I en el suero, inhibir la producción autocrina/paracrina de los IGF-I e IGF-II en el tejido tumoral y regular hacia abajo al nivel de expresión del receptor de IGF-I, es beneficiosa para la terapia contra el cáncer.

Los cánceres de mamas y otros tipos, que dependen de la GH como factor de crecimiento pueden tratarse con antagonistas de GH-RH. La capacidad de los antagonistas de GH-RH para reducir los niveles de GH en el suero, inhiben la producción autocrina de la GH y regulan hacia abajo la expresión del receptor de GH, beneficiándole tratamiento de ciertos cánceres de mamas, así como también de otros tipos de tumores.

Los antagonistas de GH-RH están disponibles como inhibidores de angiogénesis, en vista de su actividad inhibitoria de la síntesis de VEGF en tejidos tumorales y células endoteliales normales y considerando su efecto antiproliferativo sobre células endoteliales. De esta manera, los antagonistas de GH-RH podrían ser beneficiosos en el tratamiento de aquellos tumores que dependen fuertemente del VEGF y de la neoangiogénesis.

La presente invención se describe en conexión con los siguientes Ejemplos, que se presentan solo con propósitos de ilustración. En los Ejemplos, se usan amino ácidos protegidos, óptimamente activos con configuración L, excepto cuando se indique expresamente.

Los siguientes Ejemplos describen métodos de síntesis de los novedosos antagonistas de GH-RH, mediante la técnica de fase sólida.

EJEMPLO I

$CH_3(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-$Phe(pCl)^6$-Thr^7-Ala^8-His^9-$Tyr(Et)^{10}$-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 (Péptido 80)

{[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2}

La síntesis se efectuó en forma escalonada, usando equipo manual, en fase sólida, para síntesis de péptidos. Brevemente, se neutralizó resina para-metilbencildrilamina (MBHA) (Bachem, King of Prusia, PA) (720 mg, 0,50 mmol) con DIEA al 5% en DCM y se lavó de acuerdo con el protocolo descrito en el Cuadro I. Se agitó la solución de Boc-Har(NO_2)-OH (500 mg, 1.5 mmol) en DMF-DCM (1:1) con la resina neutralizada y DIC (235 µl, 1,5 mmol), durante 1 hora, en un aparato manual de síntesis de péptidos, manual, de fase sólida. Después de completar la reacción de acoplamiento, probada por la prueba negativa de ninhidrina, se efectúan los protocolos de desprotección y neutralización descritos en el Cuadro I, para remover al grupo protector Boc y preparar al conjunto péptido-resina para acoplarlo con el próximo amino ácido. Se continúa la síntesis y se construye la cadena de péptidos, paso a paso, acoplando los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina, para obtener la secuencia deseada de péptidos: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH.

Estos residuos de amino ácidos protegidos (también comúnmente disponibles en Bachem) están representados previamente, de acuerdo con una convención bien aceptada. El grupo protector adecuado para el grupo funcional de la

cadena lateral de amino ácidos particulares, aparece entre paréntesis. Los grupos OH en la fórmula anterior indican que el terminal carboxilo de cada residuo está libre.

Los amino ácidos protegidos (1,5 mmol de cada uno) se acoplan con DIC (235 µl, 1,5 mmol), con las excepciones de Boc-Asn-OH y Boc-Gln-OH, los que se acoplan con sus ésteres HOBt preformados. Después de la remoción del grupo protector N^{α}-Boc de Tyr^{1}, se acila el péptido durante la noche, con ácido octanoico $CH_3(CH_2)_6$-COOH] (475 µl, 3 mmol), usando DIC (235 µl, 1,5 mmol), como agente acoplador.

Para separar al péptido de la resina y desprotegerlo, se agita una porción de 130 mg del conjunto péptido-resina seco, con 0,5 ml de m-cresol y 5 ml de fluoruro de hidrógeno (HF), a 0°C, durante 2 horas. Después de evaporrar el HF bajo una corriente de nitrógeno y en vacío, se lava el residuo con éter dietílico seco y acetato de etilo. El péptido separado y desprotegido se disuelve en ácido acético al 50% y se separa de la resina por filtración. Después de diluirlo con agua y liofilización, se obtiene 75 mg del producto crudo.

Se revisa el péptido crudo por HPLC analítica, usando cromatografía líquida Hewlwtt-Packard Modelo HP-1090, con columna C18 Supelco Discovery HS (2,1 mm x 5 cm, empacada con sílica gel C18, tamaño de poros 120 Å, tamaño de partículas 3 µm) (Supelco, Bellefonte, PA)y gradiente linear de elución (es decir, 40-70% B), con un sistema de solventes consistiendo de (A) 0,1% TFA acuoso y (B) 0,1% TFA en MeCN acuoso al 70%. Para purificación por HPLC semi-preparativa, se disuelve 75 mg del péptido crudo en $AcOH/H_2O$, se agita, se filtra y se aplica a una columna Beckman Ultraprep ODS (21,2 mm x 15 cm, empacada con sílica gel C18, tamaño de poros 300 Å, tamaño de partículas 10 µm). La columna se eluye con el sistema de solventes anteriormente descrito, en modo de gradiente linear (por ejemplo, 40-60% B en 120 minutos); tasa de flujo 10 ml/minuto. Se monitorea el eluyente a 220 nm y las fracciones se examina por HPLC analítica. Las fracciones con pureza mayor de 95% se combinan y liofilizan, para dar 7,7 mg del producto puro. La HPLC analítica

se efectúa en una columna Supelco C18, en fase reversa, anteriormente descrita, usando elución isocrática con un sistema de solventes anteriormente descrito, con una tasa de flujo de 0,2 ml/minuto. Los picos se monitorean a 220 y 280 nm. El producto se juzga como substancialmente puro (>95% de pureza) por HPLC analítica. La masa molecular se revisa por espectrometría por electro-aspersión de masa y se confirma la composición esperada de amino ácido por análisis de los mismos.

Se sintetiza al: Péptido 2, Péptido 4, Péptido 6, Péptido 8, Péptido 10, Péptido 12, Péptido 14, Péptido 16, Péptido 17, Péptido 79, Péptido 86, Péptido 92, Péptido 93, Péptido 94, Péptido 95, Péptido 96, Péptido 104 y Péptido 105, en la misma forma que el Péptido 80, excepto que estos péptidos también contienen otras substituciones de amino ácidos y otras mitades de acil originadas por ácidos grasos en su N-terminales.

Para la síntesis del Péptido 2, cuya estructura es: $[CH_3(CH_2)_4CO\text{-}Tyr^1$, D-$Arg^2$, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acopla a los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_4COOH$.

Para la síntesis del Péptido 4,, cuya estructura química es: $[CH_3(CH_2)_8CO\text{-}Tyr^1$, D-$Arg^2$, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-

Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_8COOH$.

Para la síntesis del Péptido 6, cuya estructura química es:

$[CH_3(CH_2)_8CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_8COOH$.

Para la síntesis del Péptido 8, cuya estructura química es:

$[CH_3(CH_2)_{10}CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido de acilación con $CH_3(CH_2)_{10}COOH$.

Para la síntesis del Péptido 10, cuya estructura química es: [$CH_3(CH_2)_{12}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_{12}COOH$.

Para la síntesis del Péptido 12, cuya estructura química es: [$CH_3(CH_2)_{14}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_{14}COOH$.

Para la síntesis del Péptido 14, cuya estructura química es: [$CH_3(CH_2)_6$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-

Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_8COOH$.

Para la síntesis del Péptido 16, cuya estructura química es: $[CH_3(CH_2)_{14}CO\text{-}Phe^0, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Phe-OH, seguido por acilación con $CH_3(CH_2)_{14}COOH$.

Para la síntesis del Péptido 17, cuya estructura química es: $[CH_3(CH_2)_{14}CO\text{-}D\text{-}Phe^0, D\text{-}Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-D-Phe-OH, seguido por acilación con $CH_3(CH_2)_{14}COOH$.

Para la síntesis del Péptido 79, cuya estructura química es: [$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 86, cuya estructura química es: [$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los siguientes amino aos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 92, cuya estructura química es: [$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-

OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 93, cuya estructura química es: $[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Cit^{15}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]$hGH-RH(1-29)$NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Cit-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 94, cuya estructura química es: $[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, His^{15}, His^{20}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]$hGH-RH(1-29)$NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-His(Bom)-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 95, cuya estructura química es:

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$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 96, cuya estructura química es:

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 104, cuya estructura química es:

$[CH_3(CH_2)_6CO\text{-}Tyr^1, D\text{-}Arg^2, Phe(pCl)^6, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D\text{-}Arg^{28}, Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH,

Boc-His(Bom)-OH, Boc-Dip-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 105, cuya estructura química es: [$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

La separación y desprotección por HF y la subsiguiente purificación por HPLC semipreparativa del Péptido 2, Péptido 4, Péptido 6, Péptido 8, Péptido 10, Péptido 12, Péptido 14, Péptido 16, Péptido 17, Péptido 79, Péptido 86, Péptido 92, Péptido 93, Péptido 94, Péptido 95, Péptido 96, Péptido 104 y Péptido 105, se efectúa como se describió en el caso del Péptido 80. Los compuestos purificados se juzgan substancialmente puros (>95%) por HPLC analítica. Sus masas moleculares se revisan por espectrometría de electro-aspersión de masa y se confirman las composiciones esperadas de amino ácidos por análisis de los mismos.

EJEMPLO II

$HOOC(CH_2)_{12}CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-Phe(pCl)^6-Thr^7-Asn^8-Arg^9-Tyr^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 (Péptido 11)

{[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2}

La síntesis se efectuó en forma escalonada, usando equipo manual, en fase sólida, para síntesis de péptidos. Brevemente, se neutralizó resina MBHA (Bachem, King of Prusia, PA) (720 mg, 0,50 mmol) con DIEA al 5% en DCM y se lavó de acuerdo con el protocolo descrito en el Cuadro I. Se agitó la solución de Boc-$Har(NO_2)$-OH (500 mg, 1.5 mmol) en DMF-DCM (1:1) con la resina neutralizada y DIC (235 µl, 1,5 mmol), durante 1 hora, en un aparato manual de síntesis de péptidos, en fase sólida. Después de completar la reacción de acoplamiento, probada por la prueba negativa de ninhidrina, se efectúan los protocolos de desprotección y neutralización descritos en el Cuadro I, para remover al grupo protector Boc y preparar al conjunto péptido-resina para acoplarlo con el próximo amino ácido. Se continúa la síntesis y se construye la cadena de péptidos, paso a paso, acoplando los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina, para obtener la secuencia deseada de péptidos: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH. Los amino ácidos protegidos (1,5 mmol de cada uno) se acoplan con DIC (235 µl, 1,5 mmol), con las excepciones de Boc-Asn-OH y Boc-Gln-OH, que se acoplan con sus ésteres HOBt preformados.

Después de la remoción del grupo protector N^{α}-Boc de Tyr^1, el péptido se acila con el anhídrido simétricamente preformado del ácido 1,12-dodecandicarboxílico, que se prepara como sigue. Para síntesis a escala de 0,5 mmol del péptido, se disuelve 388 mg (1,5 mmol) del ácido 1,12-dodecandicarboxílico [$HOOC(CH_2)_{12}COOH$] en 5 a 10 ml de DMF-DCM (1:1), a esta solución se agrega 235 µl (1,5 mmol) de DIC y se deja reposar la mezcla a temperatura ambiente, durante 30 minutos. Después de

este período de tiempo, se transfiere la mezcla al recipiente de síntesis conteniendo el conjunto péptido-resina, con un amino-terminal libre en Tyr^1 y se efectúa la acilación durante la noche.

Para separar al péptido de la resina y desprotegerlo, se agita una porción de 274 mg de la resina del péptido seco con 0,5 ml de m-cresol y 5 ml de HF a 0°C, durante 2 horas. Después de evaporar al HF bajo una corriente de nitrógeno y vacío, se lava el residuo con éter dietílico seco y acetato de etilo. Se disuelve el péptido separado y desprotegido en ácido acético al 50% y se separa de la resina por filtración. Después de dilución con agua y liofilización, se obtiene 160 mg del producto crudo.

El péptido crudo se revisa por HPLC analítica, usando cromatografía líquida con un aparato Hewlett-Packard Modelo HP-2090, con una columna Supelco Discovery HS C18 (2,1 mm x 5 cm, empacada con sílica gel C18, tamaño de poros 120 Å, tamaño de partículas 3 µm), en fase reversa (Supelco, Belléfonte, PA) y elución con gradiente linear (es decir, 50-80% de B), con un sistema de solventes consistente de (A) 0,1% TFA acuoso y (B) 0,1% TFA en MeCN acuoso al 70%. Para purificación por HPLC semi-preparativa, se disuelve 160 mg del péptido crudo en $AcOH/H_2O$, se agita, se filtra y se aplica a una columna Beckman Ultraprep ODS (21,2 mm x 15 cm, empacada con sílica gel C18, tamaño de poros 300 Å, tamaño de partículas 10 µm). La columna se eluye con el sistema de solventes anteriormente descrito, en modo de gradiente linear (es decir, 50-70% de B durante 120 minutos): tasa de flujo 10 ml/minuto. El eluyente se monitorea a 220 nm y las fracciones se examinan por HPLC analítica. Las fracciones con una pureza mayor de 95% se combinan y liofilizan, para dar 6,0 mg del producto puro. La HPLC analítica se efectúa en una columna Supelco C18, en fase reversa, anteriormente descrita, usando elución isocrática con el sistema de solventes anteriormente descrito, con una tasa de flujo de 0,2 ml/minuto. Los picos se monitorean a 220 y 280 nm. Se juzga que el producto es substancialmente puro (>95% de pureza) por HPLC analítica. La masa molecular se revisa por espectrometría

de masa por electro-aspersión y se confirma la composición esperada de amino ácidos por análisis de los mismos.

Se sintetiza al Péptido 3, Péptido 5, Péptido 7, Péptido 9, Péptido 13, Péptido 25, Péptido 81, Péptido 82, Péptido 88, Péptido 102, Péptido 108 y Péptido 109 en la misma forma quie el Péptido 11, excepto que esos péptidos también contienen otras sustituciones de amino ácido y otras mitades de acil originadas desde ácidos dicarboxílicos en su N-terminales.

Para la síntesis del Péptido 3, cuya estructura química es: [$HOOC(CH_2)_4CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_4COOH$.

Para la síntesis del Péptido 5, cuya estructura química es: [$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-

Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_8COOH$.

Para la síntesis del Péptido 7,, cuya estructura química es:

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_8COOH$.

Para la síntesis del Péptido 9, cuya estructura química es:

[$HOOC(CH_2)_{10}CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{10}COOH$.

Para la síntesis del Péptido 13, cuya estructura química es:

[$HOOC(CH_2)_{14}CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre

resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{14}COOH$.

Para la síntesis del Péptido 25, cuya estructura química es:

[$HOOC(CH_2)_{12}$CO-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Cit-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 81, cuya estructura química es:

[$HOOC(CH_2)_8$CO -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH,

Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_8COOH$.

Para la síntesis del Péptido 82, cuya estructura química es: [$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 88, cuya estructura química es: [$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 102, cuya estructura química es: [$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos

protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 108, cuya estructura química es:

[$HOOC(CH_2)_{12}$CO-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 109, cuya estructura química es:

[$HOOC(CH_2)_{12}$CO-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-

OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Se efectùa la separaciòn con HF y la desprotección y subsiguiente purificación de los Péptido 3, Péptido 5, Péptido 7, Péptido 9, Péptido 13, Péptido 25, Péptido 81, Péptido 82, Péptido 88, Péptido 102, Péptido 108 y Péptido 109 por HPLC semi-preparativa, como se describiò para el Péptido 11. Se juzga que los compuestos son substancialmente puros (>95%) por HPLC analìtica. Sus masas moleculares se revisan por espectrometrìa de masa por electro-aspersiòn y las composiciones esperadas de los amino ácidos se confirman por análisis de los mismos.

EJEMPLO III

PhAc-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-Phe(pCl)^6-Thr^7-Asn^8-Har^9-Tyr(Me)^{10}-His^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 (Péptido 62)

{[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2}

La síntesis se efectuó en forma escalonada, usando equipo manual, en fase sólida, para síntesis de péptidos. Brevemente, se neutralizó resina para-metilbencildrilamina (MBHA) (Bachem, King of Prusia, PA) (720 mg, 0,50 mmol) con DIEA al 5% en DCM y se lavó de acuerdo con el protocolo descrito en el Cuadro I. Se agitó la solución de Boc-Har(NO_2)-OH (500 mg, 1.5 mmol) en DMF-DCM (1:1) con la resina neutralizada y DIC (235 µl, 1,5 mmol), durante 1 hora, en un aparato manual de síntesis de péptidos, de fase sólida. Después de completar la reacción de acoplamiento, probada por la prueba negativa de ninhidrina, se efectúan los protocolos de desprotección y neutralización descritos en el Cuadro I, para remover al grupo protector Boc y preparar al conjunto péptido-resina para acoplarlo con el próximo amino ácido. Se continúa la síntesis y se construye la cadena de péptidos, paso a paso,

acoplando los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina, para obtener la secuencia deseada de péptidos: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH. Los amino ácidos protegidos (1,5 mmol de cada uno) se acoplan con DIC (235 µl, 1.5 mmol) con las excepciones de Boc-Asn-OH y Boc-Gln-OH, los que se acoplancon sus ésteres preformados de HOBt. Después de la remociòn del grupo protector N^{α}-Boc de Tyr^{1}, el péptido se acila con ácido fenilacètico (PhAc-OH) (272 mg, 2 mmol) usando DIC (313 µl, 2 mmol).

Para separar al péptido de la resina y desprotegerlo, se agita una porción de 286 mg de la resina-péptido seco, con 0,5 ml de m-cresol y 5 ml de HF a 0°C, durante 2 horas. Después de la evaporación del HF , bajo una corriente de nitrógeno y vacio, se lava el residuo con éter dietílico y acetato de etilo. Se disluelve el péptido separado y desprotegido, en ácido acètico al 50% y se separa de la resina por filtración. Después de diluir con agua y liofilizaciòn, se obtiene 115 mg de producto crudo.

El péptido crudo se revisa por HPLC analítica usando cromatografía líquida con un aparato Hewlett-Packard Modelo HP-1090 con una columna Supelco Discovery HS C18, (2.1 mm x 5 cm, empacada con C18 sílica gel, tamaño de poros 120 Å; tamaño de partículas 3 µm) (Supelco, Bellefonte, PA) y una elución en gradiente lineal (es decir, 40-70% de B), con un sistema de solventes consistente de (A) 0.1% TFA acuoso y (B) 0.1% TFA en 70% MeCN acuoso. Para purificación por HPLC semi-preparativa, se disuelve 155 mg del péptido crudo en AcOH/H_2O, se agita, se filtra yse aplica a una columna Beckman Ultraprep ODS (21.2 mm x 15 cm, empacada con C18 sílica gel, tamaño de poros 300 Å, tamaño de partículas 10 µm). La columna se eluye con el sistema de solventes anteriormente descrito, en modo de gradiente lineal (es decir, 40-

60% de B in 120 minutos); tasa de flujo 12 ml/minuto. El eluyente se monitorea a 220 nm y las fracciones se examinan por HPLC analítica. Las fracciones con pureza mayor de 95% se combinan y liofilizan, para dar 13.3 mg de producto puro. La HPLC analítica se efectùa en una columna Supelco C18, en fase reversa, anteriormente descrita usando eluciòn isocrática con el sistema de solventes anteriormente descrito, a una tasa de flujo de 0.2 ml/min. Los picos se monitorean a 220 y 280 nm. Se juzga que el producto es substancialmente puro (>95%) por HPLC analítica. Las masas moleculares se revisan por espectrometría de masa por electro-aspersión y la composición esperada de los amino ácidos se confirma por análisis de los mismos.

Se sintetiza al Péptido 15, Péptido 18, Péptido 19, Péptido 21, Péptido 22, Péptido 23, Péptido 24, Péptido 26, Péptido 27, Péptido 28, Péptido 32, Péptido 33, Péptido 34, Péptido 35, Péptido 36, Péptido 37, Péptido 38, Péptido 39, Péptido 40, Péptido 41, Péptido 42, Péptido 43, Péptido 53, Péptido 54, Péptido 55, Péptido 57, Péptido 58, Péptido 63, Péptido 65, Péptido 69, Péptido 84, Péptido 85, Péptido 90 y Péptido 91, de la misma forma que al Péptido 62, excepto que esos péptidos también contienen otras substituciones.

Para la síntesis del Péptido 15, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 18, cuya estructura química es.

[PhAc-Arg^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 19, cuya estructura química es:

[PhAc-D-Arg^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-D-Arg(Tos)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 21, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH,

Boc-Arg(Tos)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 22, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Cit^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Cit-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 25, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Arg^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 24, cuya estructura química es:

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Cit^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Cit-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 26, cuya estructura química es:

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, D-Ala^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-D-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 27, cuya estructura química es:

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Abu^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH,

Boc-Arg(Tos)-OH, Boc-Abu-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 28, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Cit-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 32, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, His^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-His(Bom)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 33, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Cha^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina

MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Cha-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 34, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tpi^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tpi-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 35, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-2-Nal-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-

OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 36, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Dip-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 37, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNH_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Phe(pNH-Z)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 38, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Trp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina

MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Trp(For)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 39, cuya estructura química es:

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNO_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Phe(pNO_2)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 40, cuya estructura química es:

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, 3-Pal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-3-Pal-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-

OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 41, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Et)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 42, cuya estructura química es:

[PhAc-His^{1}, D-Arg^{2}, Tyr^{6}, Har^{9}, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Bpa-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Tyr(2BrZ)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-His(Bom)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 43, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Har^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-

Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Har(NO_2)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 53, cuya estructura química es:

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con ácido hidrocinámico (Hca-OH).

Para la síntesis del Péptido 54, cuya estructura química es:

[Dat-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con des-amino-tirosina (Dat).

Para la síntesis del Péptido 55, cuya estructura química es:

[Ipa-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con ácido indol-3-propiónico (Ipa-OH).

Para la síntesis del Péptido 57, cuya estructura química es:

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, D-Arg^{29}, Har^{30}]hGH-RH(1-30)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con Hca-OH.

Para la sínytesis del Péptido 58, cuya estructura química es:

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, D-Arg^{30}]hGH-RH(1-30)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-D-Arg(Tos)-OH, Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-

OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con Hca-OH.

Para la síntesis del Péptido 63, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Har^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Har(NO_2)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 65, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Cit^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Cit-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 69, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, His^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-His(Bom)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 84, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 85, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH,

Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 90, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2,

se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Cit-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 91, cuya estructura química es:

[1-Nac-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con ácido 1-naftilacético (1-Nac-OH).

La separación con HF, desprotección y subsiguiente purificación por HPLC semi-preparativa del Péptido 15, Péptido 18, Péptido 19, Péptido 21, Péptido 22,

Péptido 23, Péptido 24, Péptido 26, Péptido 27, Péptido 28, Péptido 32, Péptido 33, Péptido 34, Péptido 35, Péptido 36, Péptido 37, Péptido 38, Péptido 39, Péptido 40, Péptido 41, Péptido 42, Péptido 43, Péptido 53, Péptido 54, Péptido 55, Péptido 57, Péptido 58, Péptido 63, Péptido 65, Péptido 69, Péptido 84, Péptido 85, Péptido 90 y Péptido 91 se efectúan como se describió en el caso del Péptido 62. Los compuestos purificados se juzgan substancialmente puros (>95%) por HPLC analítica. Sus masas moleculares se revisan por espectrometría de masa por electro-aspersión y las composiciones esperadas de los amino ácidos se confirman por análisis de los mismos.

EJEMPLO IV

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Amp^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 (Péptido 67)

{[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2}

La síntesis se efectuó en forma escalonada, usando equipo manual, en fase sólida, para síntesis de péptidos. Brevemente, se neutralizó resina para-metilbencildrilamina (MBHA) (Bachem, King of Prusia, PA) (720 mg, 0,50 mmol) con DIEA al 5% en DCM y se lavó de acuerdo con el protocolo descrito en el Cuadro I. Se agitó la solución de Boc-Har(NO_2)-OH (500 mg, 1.5 mmol) en DMF-DCM (1:1) con la resina neutralizada y DIC (235 µl, 1,5 mmol), durante 1 hora, en un aparato manual de síntesis de péptidos de fase sólida. Después de completar la reacción de acoplamiento, probada por la prueba negativa de ninhidrina, se efectúan los protocolos de desprotección y neutralización descritos en el Cuadro I, para remover al grupo protector Boc y preparar al conjunto péptido-resina para acoplarlo con el próximo amino ácido. Se continúa la síntesis y se construye la cadena de péptidos, paso a paso, acoplando los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina, para

obtener la secuencia deseada de péptidos: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH. El amino ácido protegido, no-codificado Boc-Amp(Alloc)-OH está comercialmente disponible en RSP Amino Acid Analogues, Inc. (Worcester, MA). Los amino ácidos protegidos (1,5 mmol de cada uno) se acoplan con DIC (235 µl, 1,5 mmol), con las excepciones de Boc-Amp(Alloc)-OH, Boc-Asn-OH y Boc-Gln-OH, que se acoplan con 569 mg HBTU + 203 mg HOBt + 522 µl DIEA (1.5 : 1.5 : 3 mmol). Después de la remoción del grupo protector de Tyr^1, el Péptido se acila con ácido fenilacético (PhAc-OH) (272 mg, 2 mmol), usando DIC (313 µl, 2 mmol). La peptidil resina terminada, con todos los grupos protectores de la cadena lateral todavía unidos, se lava 3x con DCM, 3x con MeOH y se seca bajo alto vacío.

El conjunto péptido-resina se somete entonces a remoción catalizada por Pd(0) del grupo protector Alloc desde el residuo de Amp^9 de la cadena de péptido, usando el procedimiento descrito en el Catálogo 2002/2003 de Novabiochem (San Diego, CA). Se pesa una porción de 255 mg de peptidil resina, con un contenido estimado de 0,033 mmol, dentro de un tubo de ensayo y el tubo se sella con una membrana de goma. Luego, el tubo se enjuaga con una corriente de gas argón (Ar) entregada mediante una aguja insertada a través de la membrana. Se pesa 116 mg de $Pd(PPh_3)_4$ (0,1 mmol o 3 equivalentes, en relación con los grupos Alloc presentes en la peptidil resina), en otro tubo de ensayo y se agrega 1-5 ml de $CHCl_3$-AcOH-N-metilmorfolina (37:2:1 vol:vol:vol), el catalizador se disuelve haciendo burbujear una corriente de Ar a través de la solución y el tubo se sella con una membrana de goma. Se transfiere esta solución usando una jeringa hermética, enjuagada con Ar, al tubo que contiene a la resina y la mezcla resultante se deja reposar durante 2 horas, con una

suave agitación ocasional. En seguida, se transfiere la resina a un embudo de vidrio sinterizado y se lava consecutivamente con DIEA al 0,5% en DMF (para neutralizar a la resina) y con dietilditiocarbamato de sodio (0,5% p/p) en DMF (para remover al catalizador). Después de otro lavado con MeOH, se seca nuevamente la resina antes de la separación con HF del péptido.

La separación del péptido desde la resina MBHA, con una remoción concomitante de los restantes grupos protectores se logra con tratamiento con HF, efectuada como se describió en los Ejemplos I-III, produce 11,6 mg del Péptido 67 puro (>95% de pureza, determinada por HPLC analítica). La masa molecular se revisa por espectrometría de masa por electro-aspersión y se confirma la composición esperada de los amino ácidos por análisis de los mismos.

Se sintetiza el Péptido 30, Péptido 31, Péptido 64, Péptido 68, Péptido 73, Péptido 74 y Péptido 75 en la misma forma que el Péptido 67, excepto que esos péptidos también contienen otras substituciones.

Para la síntesis del Péptido 30, cuya estructura química es: [PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Amp(Alloc)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 31, cuya estructura química es: [PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Amp(Alloc)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 64, cuya estructura química es: [PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Amp^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Amp(Alloc)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 68, cuya estructura química es: [PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH,

Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Amp(Alloc)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 73, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 74, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Amp^{9}, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 75, cuya estructura química es: [1-Nac-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Amp^{9}, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con ácido 1-naftilacético (1-Nac-OH).

Se efectúa la separación desde la resina y la subsiguiente purificación por HPLC semi-preparativa de Péptido 30, Péptido 31, Péptido 64, Péptido 68, Péptido 73, Péptido 74 y Péptido 75 como se describió para el caso del Péptido 67. Se juzga que los compuestos purificados son substancialmente puros (>95%) por HPLC analítica. Sus masas moleculares se revisan por espectrometría de masas por electro-aspersión y las composiciones esperadas de los amino ácidos se confirman por análisis de los mismos.

EJEMPLO V

PhAc-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NHEt (Péptido 46)

{[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt}

La síntesis se efectuó en forma escalonada, usando equipo manual, en fase sólida, para síntesis de péptidos. Brevemente, se pre-hinchó resina Merrifield (Bachem, King of Prusia, PA) (3,0 g, con una sustitución de 0,6 mmol/g) en DCM y se

lavó 3 veces con DMF, luego se agregó una solución de 2.390 mg de Boc-Har(Tos)-OH (5,4 mmol, correspondiente a 3 veces un exceso molar), para cargar al primer aminoao sobre la resina. Se agitó la resina con la mezcla anterior durante 4 horas a 80°C y luego se filtró y lavó como sigue: 3x de DMF, 3x de DMF-agua (1:1) (para remover el KF), 3x de DMF, 3x de DCM y 3x de MeOH. Se secó al vacío la resina durante 24 horas hasta alcanzar un peso constante. El peso de la resina seca, cargada con el primer amino ácido [Boc-Har(Tos)-resina Merrifield] excedió los 3,5 g, indicando que el rendimiento de la carga fué mayor de 70%.

Se pre-hinchó 1,5 g de Boc-Har(Tos)-resina Merrifield (aproximadamente 0,5 mmol) en DCM y después de la desprotección con TFA al 50% en DCM y neutralización con DIEA al 5% en DCM, se construyó paso a paso la cadena de péptidos, acoplando los siguientes amino ácidos protegidos, en el orden indicado, sobre la resina, para obtener la secuencia deseada de péptidos: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH. En esta síntesis, se usó Boc-Har(Tos)-OH en lugar de Boc-Har(NO_2)-OH, ya que se sabe que el grupo guanidino protegido por nitro será atacado por bases tales como etilamina, usadas en la síntesis y podría ocurrir descomposición parcial de Har a Lys con Boc-Har(NO_2)-OH. Se acoplan los amino ácidos protegidos (1,5 mmol de cada uno) con DIC (235 µl, 1,5 mmol), con las excepciones de Boc-Asn-OH y Boc-Gln-OH, que se acoplan con sus ésteres HOBt preformados. Después de la remoción del grupo protector N^{α}-Boc de Tyr^1, se acila el péptido con ácido fenilacético (PhAc-OH) (272 mg, 2 mmol), usando DIC (313 µl, 2 mmol), se lava con DCM y MeOH y se seca.

Para separar el péptido protegido de la resina, por aminolisis mediada por etilamina ($EtNH_2$) y obtenerlo con modificación de etilamina (-NHEt) en el C-terminal, se

agrega una porción de 250 mg de conjunto péptido-resina dentro de un matraz de fondo redondo, con paredes de vidrio grueso, el matraz se coloca en un baño enfriador de hielo seco-metanol, dentro de una campana extractora bien ventilada y se transfiere $EtNH_2$ líquida (punto de ebullición = 16,6°C, disponible en Aldrich, envasada en un cilindro metálico) dentro del matraz, en una cantidad suficiente para cubrir al péptido-resina. Se tapona el matraz, se lo calienta a temperatura ambiente (precaución: se desarrolla presión dentro) y se agita durante 3 horas y 30 minutos, para permitir que se efectúe la reacción. Después de este tiempo, el matraz se coloca nuevamente en el baño enfriador, se abre y se filtra la $EtNH_2$ del residuo sólido, que contiene una mezcla de la resina y del péptido separado, el péptido todavía con sus grupos protectores unidos. Después de este procedimiento, se somete al vacío al residuo sólido durante la noche, para remover cualquier $EtNH_2$ residual y adsorber la humedad.

El residuo seco, conteniendo al péptido protegido y separado, se coloca en el aparato para tratamiento con HF y se efectúa la separación de los grupos protectores tratándolo con 5 ml de HF a 0°C, durante 2 horas, en presencia de 0,5 ml de m-cresol, como eliminador. Después de evaporar el HF bajo una corriente de nitrógeno y en vacío, se lava el residuo con éter dietílico seco y acetato de etilo. Se disuelve el péptido separado y desprotegido en ácido acético al 50% y se lo separa de la resina por filtración. Después de dilución con agua y liofilización, se obtiene típicamente 90 a 110 mg del producto crudo.

El péptido se purifica por HPLC semi-preparativa y las fracciones eluídas se examinan por HPLC analítica, como se describió en los Ejemplos I-III. Las fracciones con pureza mayor de 95% se combinan y liofilizan, para dar 5 a 10 mg del Péptido 46 puro. La masa molecular se revisa por espectrometría de masa por electro-aspersión y la composición esperada de los amino ácidos se confirma por análisis de los mismos.

Se sintetiza el Péptido 45, Péptido 47, Péptido 48, Péptido 49, Péptido 50, Péptido 56, Péptido 97, Péptido 98, Péptido 99, Péptido 100, Péptido 101, Péptido 106,

Péptido 110, Péptido 113, Péptido 114, Péptido 115, Péptido 118, Péptido 119, Péptido 120 y Péptido 121 en la misma forma que el Péptido 46, excepto que esos péptidos también contienen otras substituciones.

Para la síntesis del Péptido 45, cuya estructura química es:

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con Hca-OH.

Para la síntesis del Péptido 47, cuya estructura química es:

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con Hca-OH.

Para la síntesis del Péptido 48, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield:

Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, Boc-Arg(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 49, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Aib^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Aib-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 50, cuya estructura química es:

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Orn^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 56, cuya estructura química es: [Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(Tos)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con Hca-OH.

Para la síntesis del Péptido 97, cuya estructura química es: [$CH_3(CH_2)_8CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_8COOH$.

Para la síntesis del Péptido 98, cuya estructura química es: [$CH_3(CH_2)_8CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-

Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_8COOH$.

Para la síntesis del Péptido 99, cuya estructura química es:

[$CH_3(CH_2)_{10}CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_{10}COOH$.

Para la síntesis del Péptido 100, cuya estructura química es:

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con Hca-OH.

Para la síntesis del Péptido 101, cuya estructura química es: [$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHMe, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 106, cuya estructura química es: [$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 110, cuya estructura química es: [$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH,

Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 113, cuya estructura químico es:

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 114, cuya estructura química es:

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 115, cuya estructura química es:

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 118, cuya estructura química es:

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 119, cuya estructura química es:

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH,

Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 120, cuya estructura química es:

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 121, cuya estructura química es:

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt, se acoplan los amino ácidos protegidos, en el orden indicado, sobre resina Merrifield: Boc-Har(Tos)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-Amp-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

La separación, mediada por etilamina, de la resina del Péptido 45, Péptido 47, Péptido 48, Péptido 49, Péptido 50, Péptido 56, Péptido 97, Péptido 98, Péptido 99, Péptido 100, Péptido 106, Péptido 110, Péptido 113, Péptido 114, Péptido 115, Péptido 118, Péptido 119, Péptido 120, y Péptido 121, así como la separación, mediada por metilamina, de la resina del Péptido 101, seguida por su desprotección por HF y la subsiguiente purificación por HPLC semi-preparativa, se efectúa como se describió para el Péptido 46. Se juzga que los compuestos purificados son substancialmente puros (>95%) por HPLC analítica. Sus masas moleculares se revisan por espectrometría de masa por electro-aspersión y las composición esperadas de los amino ácidos se confirman por análisis de los mismos.

EJEMPLO VI

Hca-Tyr^{1}-D-Arg^{2}-Asp^{3}-Ala^{4}-Ile^{5}-Phe(pCl)^{6}-Thr^{7}-Asn^{8}-Har^{9}-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-Agm^{30} Peptide 59

{[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30)}

La síntesis se efectuó en forma escalonada, usando equipo manual de síntesis de péptidos en fase sólida. El material inicial para la síntesis fue resina Boc-agmantina-N^{G}-sulfonil-fenoxiacetil-MBHA (Boc-Agm-SPA-MBHA), con una substitución de 0,3 mmol/g, obtenida comercialmente de California Peptide Research, Inc. (Napa, CA). La síntesis de esta resina está descrita en la Patente de los EE. UU. N° 4.914.189 y en la literatura científica (Sarandi, M., Serfozo, P., Sigo, J., Boxer, L., Janaky, T., Olsen, D.B., Bajusz, S., Schally, A.V., Int. J. Peptide Protein Res. 39: 211-217, 1992), que se incorpora aquí por referencia. Brevemente, se pre-hinchó la resina Boc-Agm-SPA-MBHA (1,67 g, 0,50 mmol) en DCM y luego se efectuó los protocolos de desprotección y neutralización descritos en el Cuadro I, para remover al grupo protector Boc y preparar el conjunto resina-péptido para el coplamiento del próximo amino ácido.

Se continuó la síntesis y se acumuló escalonadamente la cadena de péptidos acoplando los siguientes amino ácidos, en el orden indicado, sobre la resina, para obtener la secuencia de péptidos deseada: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH.

Se acopló los amino ácidos protegidos (1,5 mmol de cada uno) con DIC (235 µl, 1,5 mmol), con las excepciones de Boc-Asn-OH y Boc-Gln-OH, los que se acoplaron con sus ésteres HOBt preformados. Después de remover el grupo protector N^{α}-Boc de Tyr^{1}, se aciló el péptido con ácido hidrocinámico (Hca-OH) (300 mg, 2 mmol), usando DIC (313 µl, 2 mmol).

Para separar al péptido de la resina y desprotegerlo, se agitó una porción de 250 mg del conjunto péptido-resina seca, con 0,5 ml de m-cresol y 5 ml de HF a 0°C, durante 2 horas. Después de evaporar al HF bajo una corriente de nitrógeno y en vacío, se lavó el residuo con éter dietílico seco y acetato de etilo. El péptido separado y desprotegido se disolvió en ácido acético al 50% y se separó de la resina por filtración. Después de diluirlo con agua y liofilización,se obtuvo típicamente 100-110 mg del producto crudo.

El péptido se purificó por HPLC semi-preparativa y las fracciones de elución se examinaron por HPLC analítica, como se describió en los Ejemplos I-III. Las fracciones con una pureza mayor de 95% se combinaron y liofilizaron, para dar 5 a 10 mg del Péptido 59 puro. Las masas moleculares se revisaron por espectrometría de masa por electro-aspersión y la composición esperada del amino ácido se confirmó por análisis del mismo.

Se sintetizó el Péptido 51, Péptido 52 y Péptido 60, en la misma forma que el Péptido 59, excepto que esos péptidos también contienen otras substituciones.

Para la síntesis del Péptido 51, cuya estructura química es: [Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29), se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina Boc-Agm-SPA-MBHA: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con Hca-OH.

Para la síntesis del Péptido 52, cuya estructura química es: [PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29), se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina Boc-Agm-SPA-MBHA: Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

Para la síntesis del Péptido 60, cuya estructura química es: [PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30), se acopló los siguientes amino ácidos protegidos, en el orden

indicado, sobre resina Boc-Agm-SPA-MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Har(NO_2)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con PhAc-OH.

La separación, desprotección y subsiguiente purificación por HPLC semi-preparativa del Péptido 51, Péptido 52 y Péptido 60 se efectuó como se describió en el caso del Péptido 59. Se juzgó que los compuestos purificados eran substancialmente puros (>95%) por HPLC analítica. Sus masas moleculares se revisaron por espectrometría de masa por electro-aspersión y las composiciones esperadas de los amino ácidos se confirmaron por análisis de los mismos.

EJEMPLO VII

$CH_3(CH_2)_6CO$-Tyr^1-D-Arg^2-Asp^3-Ala^4-Ile^5-Phe(pCl)^6-Thr^7-Asn^8-Amp^9-Tyr(Me)^{10}-Arg^{11}-Lys^{12}-Val^{13}-Leu^{14}-Abu^{15}-Gln^{16}-Leu^{17}-Ser^{18}-Ala^{19}-Arg^{20}-Lys^{21}-Leu^{22}-Leu^{23}-Gln^{24}-Asp^{25}-Ile^{26}-Nle^{27}-D-Arg^{28}-Har^{29}-NH_2 Péptido 70

{[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2}

Todos los pasos de síntesis anteriores al acoplamiento de la mitad de acil del N-terminal con el péptido-resina, se efectuaron como se describió en el Ejemplo IV. Después de remover al grupo protector N^{α}-Boc desde Tyr^1, se aciló el péptido (0,5 mmol) durante la noche, con ácido octanoico [$CH_3(CH_2)_6COOH$] (475 µl, 3 mmol) usando DIC (235 µl, 1,5 mmol) como agente acoplador. La peptidil resina terminada, con todos los grupos protectores de la cadena lateral todavía unidos, se lavó 3x con DCM, 3x con MeOH y se secó bajo alto vacío.

Subsiguientemente, la peptidil resina se sometió a remoción del grupo protector Alloc, catalizada por Pd(0), desde el residuo de Amp^9, de la cadena de péptidos, como se describió en el Ejemplo IV. El conjunto péptido-resina se lavó luego con MeOH y se secó, antes de la separación con HF del péptido.

Se logró la separación del péptido de la resina MBHA, con la remoción concomitante del resto de los grupos protectores, por tratamiento con HF, como se describió en los Ejemplos I-III. El trabajo subsiguiente y purificación por HPLC se efectuó como se describió en los Ejemplos I-III. Después del tratamiento con HF de 300 mg de peptidil resina seca, se obtuvo 192 mg de péptido crudo liofilizado, cuya purificación produjo 17,1 mg de Péptido 70 puro (>95% de pureza por HPLC analítica). La masa molecular se revisó por espectrometría de masa por electro-aspersión y, la composición esperada del amino ácido se confirmó por análisis del mismo.

Se sintetizó el Péptido 76, Péptido 87, Péptido 103, Péptido 111 y el Péptido 112 en la misma forma que el Péptido 70, excepto que esos péptidos también contienen otras substituciones.

Para la síntesis del Péptido 76, cuya estructura química es: $[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 78, cuya estructura química es: [$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 87, cuya estructura química es: [$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 103, cuya estructura química es: [$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH,

Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 111, cuya estructura química es:

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

Para la síntesis del Péptido 112, cuya estructura química es:

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, Amp^9, Phe(pNO_2)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $CH_3(CH_2)_6COOH$.

La desprotección, separación desde la resina y subsiguiente purificación por HPLC semi-preparativa del Péptido 76, Péptido 78, Péptido 87, Péptido 103, Péptido 111 y Péptido 112 se efectuó como se describió en el caso del Péptido 70. Se juzgó que los compuestos purificados eran substancialmente puros (>95%) por HPLC analítica. Sus masas moleculares se revisaron por espectrometría de masa por electro-aspersión y las composiciones esperadas de los amino ácidos se confirmaron por análisis de los mismos.

En la misma forma que con el Péptido 72, se sintetizó al Péptido 72, Péptido 77, Péptido 89, Péptido 107, Péptido 116 y Péptido 117, excepto que esos péptidos también contienen otras substituciones.

Para la síntesis del Péptido 71, cuya estructura química es: [$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Amp^9, $Tyr(Me)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Asn-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_8COOH$.

Para la síntesis del Péptido 77, cuya estructura química es: [$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^6, Amp^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-Arg(Tos)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-

OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Me)-OH, Boc-Amp(Alloc)-OH, Boc-Cit-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 89, cuya estructura química es: $[HOOC(CH_2)_{12}CO\text{-}Tyr^1$, D-$Arg^2$, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Lys(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 107, cuya estructura química es: $[HOOC(CH_2)_{12}CO\text{-}Tyr^1$, D-$Arg^2$, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]hGH\text{-}RH(1\text{-}29)NH_2$, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-$Har(NO_2)$-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Tyr(Et)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 116, cuya estructura química es:

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Dip-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

Para la síntesis del Péptido 117, cuya estructura química es: [$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2, se acopló los siguientes amino ácidos protegidos, en el orden indicado, sobre resina MBHA: Boc-Har(NO_2)-OH, Boc-D-Arg(Tos)-OH, Boc-Nle-OH, Boc-Ile-OH, Boc-Asp(OcHx)-OH, Boc-Gln-OH, Boc-Leu-OH, Boc-Leu-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Ala-OH, Boc-Ser(Bzl)-OH, Boc-Leu-OH, Boc-Gln-OH, Boc-Abu-OH, Boc-Leu-OH, Boc-Val-OH, Boc-Orn(2ClZ)-OH, Boc-His(Bom)-OH, Boc-Phe(pNO_2)-OH, Boc-Amp(Alloc)-OH, Boc-Ala-OH, Boc-Thr(Bzl)-OH, Boc-Phe(pCl)-OH, Boc-Ile-OH, Boc-Ala-OH, Boc-Asp(OcHx)-OH, Boc-D-Arg(Tos)-OH, Boc-Tyr(2BrZ)-OH, seguido por acilación con $HOOC(CH_2)_{12}COOH$.

La desprotección, separación desde la resina y subsiguiente purificación por HPLC semi-preparativa del Péptido 71, Péptido 77, Péptido 89, Péptido 107, Péptido 116 y Péptido 117 se efectuó como se describió en el caso del Péptido 72. Se juzgó que los compuestos purificados eran substancialmente puros (>95%) por HPLC analítica. Sus masas moleculares se revisaron por espectrometría de masa por electro-aspersión y las composiciones esperadas de los amino ácidos se confirmaron por análisis de los mismos.

EJEMPLO IX

Solución acuosa para Inyección Intramuscular

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Amp^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 (Péptido 67) 500.0 mg

Gelatina, no-antigénica 5.0 mg

Agua para inyección q.s. a 100.0 mL

La gelatina y el Péptido 67, antagonista de GH-RH, se disolvieron en agua para inyección, luego la solución se filtró en forma estéril.

EJEMPLO X

Formulación Inyectable Intramuscular de Larga Duración

[$CH_3(CH_2)_8CO$ -Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{8}, His^{9}, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 (Péptido 80) 10.0 mg

Monoestearato de Aluminio, USP 20.0 mg

Aceite de sésamo q.s. a 1.0 mL

Se combinó el monoestearato de aluminio con el aceite de sésamo y se calentó a 125°C, con agitación, hasta que se formó una solución amarilla clara. Esta mezcla se sometió a esterilización en autoclave y se la dejó enfriar. El Péptido 80, antagonista de GH-RH, se agregó asépticamente, con trituración. Los antagonistas preferidos son las sales de baja solubilidad, por ejemplo, sales pamoato y similares. Estas exhiben una actividad de larga duración.

EJEMPLO XI

Micro-cápsulas de Polímero Biodegradable – Inyectables Intramuscularmente (IM) de Larga Duración

Las micro-cápsulas se preparan de lo siguiente:

25/75 co-polímero de glycolato/lactato (0.5, viscosidad intrínsica)	99%
[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 (Péptido 96)	1%

Se suspendió 25 mg de las mocro-cápsulas anteriores en 1,0 ml del siguiente vehículo:

Dextrosa	5.0%
CMC, sodio	0.5%
Alcohol bencílico	0.9%
Tween 80	0.1%
Agua, purificada q.s.	a 100%

EJEMPLO XII

Actividad Biológical en Ensayos Endocrinos y Oncológicos

Se probó los péptidos de la presente invención en ensayos *in vitro* e *in vivo*, en su capacidad para inhibir a la liberación de GH inducida por hGH-RH(1-29)NH_2. También se midió las afinidades de unión de los compuestos con los receptores tumorales de GH-RH. Las actividades anti-tumorales de los péptidos y sus efectos inhibidores sobre el IGF-I del suero y en el IGF de sistema tumoral se evaluó en varios modelos de cáncer, *in vivo*.

Sistema de Pituitaria de Rata Superfundido

Se probó a los análogos *in vitro*, con una prueba anteriormente descrita (S. Vigh y A.V. Schally, Peptides 5: 241-347, 1984) modificada (Z-Rekasi y A.V. Schally, P.N.A.S. 90: 2146-2149, 1963).

Brevemente, se pre-incubó a las células con los péptidos durante 9 minutos (3 ml), a varias concentraciones. Inmediatamente después de la incubación, se administró 1 nM de hGH-RH(1-29)NH_2 (1 ml) durante 3 minutos [respuesta a los 0 minutos]. Para evaluar la duración del efecto antagonístico del análogo, se aplicó 1 nM de hGH-RH(1-29)NH_2 a los 30, 60, 90 y 120 minutos después, durante 3 minutos [respuestas a los 30, 60, 90 y 120 minutos]. Se evaluó los valores integrales netos de las respuestas de GH. Se comparó con las respuestas de GH-RH y se expresaron como porcentaje de la respuesta original inducida por 1 nM de hGH-RH(1-29)NH_2. Se comparó el efecto de los nuevos antagonistas con la del "Antagonista estándar" [Ac-Tyr^1, D-Arg^2] hGH-RH(1-29)NH_2.

Radioinmunoensayos (RIA) para GH, IGF-1 e IGF-II

Se midió niveles de GH de ratas, en alícuotas de muestras de superfusión, no-diluidas y diluidas, mediante radioinmunoensayo de doble-anticuerpo, usando materiales suministrados por el National Hormone and Pituitary Program, Baltimore, Maryland. Los resultados de RIA se analizaron con un programa para computador, desarrollado en nuestro Instituto (V. Csernus y A.V. Schally, en Neuroendocrine Research Methods, Harwood Academia (Greenstein, B.D., editor, Londres, pp. 71-109, 1991), que se incorpora aquí por referencia.

Para la medición de los niveles de GH e IGF-I en el suero, así como las concentraciones de IGF-I e IGF-II en la fracción citosol de los tumores, se recolectó muestras de sangre y muestras de tumores, las que se procesaron como se describió (Braczkowski, R., Schally, A.V., Plonowski, A., Varga, J.L., Groot, K., Krupa, M., Armatis, P., Cancer 95: 1735-1745, 2002), incorporado aquí por referencia. Brevemente, se centrifugó muestras de sangre para separar el suero, los tumores se homogenizaron y centrifugaron para separar a la fracción citosol. Luego, se midió la GH del suero por el método RIA de doble anticuerpo. Antes de la medición por RIA, se extrajo el IGF-I e IGF-II de las fracciones de suero y citosol, usando un método de

crioprecipitación por ácido-etanol, que elimina la mayoría de las proteínas ligadoras de IGF, que podrían interferir con el RIA. Se midió la concentración de IGF-I por RIA, usando IGF-I como estándar y anticuerpo de cabra anti-IGF-I (ambos de DSL, Inc., Webster, TX). Lac9 de IGF-II se midió por RIA, usando IGF-II recombinante humano (Bachem) como estándar y anticuerpo monoclonal anti-IGF-II (Amano Internacional Enzyme, Troy, VA).

En todas las mediciones RIA, la variación inter-ensayos fue menor de 15% y, la variación intra-ensayo fue menor de 10%.

Ensayo de Ligazón de Receptor de GH-RH Tumoral

Se usó los ensayos de competencia de ligandas con el antagonista de GH-RH JV-1-42, marcado con I^{125} para determinar las afinidades de ligazón de los análogos de GH-RH con las isoformas de receptor de GH-RH en fracciones de membrana de tumores prostáticos PC-3 humanos. Los métodos usados se han descrito en detalle (Halmos, G. Schally, V.A., Varga, J.L., Plonowski, A., Rekasi, Z., Czompoly, T., Proc. Natl. Acad. Sci. USA 97: 10555-10560, 2000; Halmos, G., Schally, A.V., Czompoli, T., Krupa, M., Varga, J.L., Rekasi, Z., J. Clin. Endocrinol. Metab. 87: 4707-47-14, 2002), incorporados aquí por referencia. Brevemente, se preparó los derivados radioyodinados de JV-1-42 por el método de la cloramina-T. Los tumores PC-3, que crecieron como xenoinjertos en ratas desnudas, se usaron para preparar membranas crudas. Los homogenados de membrana de PC-3 se incubaron con [^{125}I]JV-1-42 y concentraciones crecientes (10^{-12} hasta 10^{-6} M)de péptidos antagonistas no radioactivos como competidores. Se separó el pellet por centrifugación y se contó la radioactividad en un contador gamma. Se estimó las afinidades de ligazón finales por K_i (constante de disociación del complejo inhibir-receptor) y se determinaron por los programas de computador Liganda PC y McPherson, de Munson y Rodbard (P.J. Munson y D. Rodbard, Anal. Biochem. 107: 220-239, 1980). Se calculó las afinidades

relativas (R.A.) con péptidos de referencia tales como JV-1-36 o JV-1-38, como la relación de K_i del péptido de referencia con la K_i del antagonista de GH-RH probado.

Resultados de los Ensayos de Superfusión

Los resultados de las actividades antagonísticas probadas, in vitro, en el sistema de pituitaria de rata superfundido, se resumen en el Cuadro III. Como puede verse de esos datos, las substituciones presentes en las moléculas causan un efecto inhibidor mucho más aumentado y prolongado en la liberación *in vitro* de GH elicitada por GH-RH, en comparación con el antagonista estándar.

CUADRO III

Inhibición de la Liberación de GH en Sistema de Pituitaria de Rata Superfundido

Antagonista	Dosis (nM)	Respuesta de GH (% del Testigo)				
		0 min	30 min	60 min	90 min	120 min
Antagonista Estándar	100	38	98	81		
JV-1-36*	30	36	21	25	29	29
	10	80	42	60	64	85
JV-1-38*	30	59	32	28	34	31
Péptido 2	30	18	13	18	25	51
Péptido 3	30	52	61	56	70	149
Péptido 4	30	5	0	12	8	18
Péptido 5	30	22	20	23	27	27
Péptido 6	30	56	22	12	15	19
Péptido 7	30	23	13	11	14	14
Péptido 8	30	37	31	48	44	40
Péptido 9	30	47	43	66	63	58
Péptido 10	30	60	30	36	37	44
Péptido 11	30	14	24	29	34	32
Péptido 12	30	35	30	35	51	43
Péptido 13	30	87	77	76	71	73
Péptido 15	30	28	13	11	36	21
Péptido 16	30	40	62	78	73	61
Péptido 17	30	29	51	68	73	61
Péptido 18	30	21	71	61	75	63
Péptido 19	30	62	64	66	82	74
Péptido 21	30	0	13	33	43	37
Péptido 22	30	22	26	27	45	N/A
Péptido 23	30	55	40	41	47	41
Péptido 24	30	56	13	18	34	60
Péptido 26	30	20	43	66	48	44

Péptido 27	30	19	15	23	23	61
Péptido 28	30	68	7	8	20	34
Péptido 30	30	18	11	7	7	8
Péptido 30	10	60	24	34	32	53
Péptido 31	30	7	1	2	4	3
Péptido 31	10	57	31	37	36	37
Péptido 32	30	28	43	69	76	N/A
Péptido 33	30	97	89	78	97	82
Péptido 35	30	91	57	80	66	72
Péptido 36	30	104	90	112	97	120
Péptido 37	30	33	12	15	15	19
Péptido 39	30	63	54	36	37	36
Péptido 40	30	42	29	26	36	30
Péptido 41	30	47	16	14	15	16
Péptido 42	30	52	7	9	8	13
Péptido 43	30	82	74	102	72	51
Péptido 45	30	91	100	100	100	99
Péptido 45	30	100	100	100	N/A	N/A
Péptido 46	30	91	28	31	56	30
Péptido 48	30	22	21	44	44	47
Péptido 49	30	83	76	90	87	120
Péptido 50	30	57	65	69	74	67
Péptido 51	30	64	36	31	N/A	N/A
Péptido 51	30	52	43	57	56	58
Péptido 51	30	87	35	46	51	61
Péptido 52	30	86	13	45	26	55
Péptido 53	30	43	42	40	36	46
Péptido 55	30	93	63	96	61	93
Péptido 56	30	76	83	92	80	68
Péptido 58	30	78	53	56	47	N/A
Péptido 58	30	94	53	57	64	64
Péptido 58	30	64	41	59	50	69
Péptido 59	30	72	49	46	38	N/A
Péptido 59	30	61	50	48	47	N/A
Péptido 59	30	93	43	60	57	76
Péptido 59	30	47	27	37	44	47
Péptido 60	30	73	27	34	56	42
Péptido 60	30	87	29	65	36	63
Péptido 62	30	20	16	14	21	21
Péptido 63	30	53	47	49	51	N/A
Péptido 64	30	59	54	70	50	56
Péptido 65	30	67	80	89	97	79
Péptido 67	30	28	15	18	20	23
Péptido 68	30	37	22	33	29	33
Péptido 69	30	9	12	18	18	25

*compuestos de referencia, materia de la Patente de los EE. UU. N° 6.057.422

Resultados del Ensayo de Ligazón al Receptor de GH-RH Tumoral

Como se ve en los Cuadros IV y V, respectivamente, las substituciones presentes en las moléculas causan un aumento substancial en sus afinidades de

ligazón con las isoformas de receptor de GH-RH en membranas de tumores PC-3, en comparación con las afinidades de ligazón de los compuestos de referencia.

CUADRO IV

Afinidades Relativas (R.A.) de Antagonistas de GH-RH con Receptores de Membrana en Cánceres de Próstata PC-3 Humanos

Péptido	R.A.
JV-1-36*	1
Péptido 11	1.3
Péptido 6	0.6
Péptido 7	12
Péptido 4	53
Péptido 5	4
Péptido 22	10
Péptido 43	0.09

*compuesto de referencia, materia de la Patente de los EE. UU. N° 6.057.422

CIADRO V

Afinidades Relativas (R.A.) de Antagonistas de GH-RH con Receptores de Membrana en Cánceres de Próstata PC-3 Humanos

Péptido	R.A.
JV-1-38*	1
Péptido 31	0.2
Péptido 36	11
Péptido 41	5
Péptido 42	0.6
Péptido 62	62
Péptido 67	71
Péptido 69	59

*compuesto de referencia, materia de la Patente de los EE. UU. N° 6.057.422

Efecto de los antagonistas de GH-RH sobre xenoinjertos de cáncer PC-3 de próstata humano en ratas desnudas

Experimento 1:

Se implantó subcutáneamente a ratas desnudas macho con pedazos de 3 mm^3 de tejido de cáncer PC-3 de próstata humano, independiente de hormona, en ambos

costados. Cuando los tumores alcanzaron un volumen de aproximadamente 50 mm^3, se dividió a las ratas en 5 grupos experimentales, con 7 a 8 animales en cada gpy recibieron una inyección diaria, durante 28 días, como sigue: 1.- Testigo (solución de vehículo); 2.- JV-1-38 (10 µg/día s.c.); 3.- Péptido 31 (10 µg/día s.c.); 4.- Péptido 67 (10 µg/día s.c.); 5.- Péptido 62 (10 µg/día s.c.). Se midió los volúmenes de los tumores dos veces a la semana. Se terminó el experimento en el día 29, sacrificando a las ratas bajo anestesia de Isoflurano. Los tumores resultantes se limíaron, pesaron y se congelaron instantáneamente para análisis posterior. Se recolectó sangre del tronco, de la aorta abdominal y se separó el suero para medición, por RIA, del IGF-I. El análisis estadístico de los resultados de las mediciones se efectuó por la prueba de t de dos colas; los datos se presentan como las medias ± Error Estándar.

Experimento 2:

El Experimento 2 fue similar al Experimento 1, con la diferencia que el Experimento 2 se inició cuando los tumores PC-3 habían crecido a un volumen de aproximadamente 30 mm^3. En ese momento, se dividió a los animales en 8 grupos experimentales, con 8 animales por grupo, que recibieron una inyección diaria durante 28 días, como sigue: 1.- Testigo (solución de vehículo); 2.- JV-1-38 ((10 µg/día s.c.); 3.- Péptido 46 (5 µg/día s.c.); 4.- Péptido 77 (5 µg/día s.c.); 5.- Péptido 76 (5 µg/día s.c.); 6.- Péptido 70 (5 µg/día s.c.); 7.- Péptido 79 (5 µg/día s.c.); 8.- Péptido 80 (5 µg/día s.c.). Los detalles adicionales del Experimento 2 son los mismos del Experimento 1.

Experimento 3:

Se implantó subcutáneamente porciones de 3 mm^3 de tejido de cáncer de próstata PC-3 humano, independiente de hormonas, en ambos costados de ratas desnudas macho. Cuando los tumores alcanzaron un volumen de aproximadamente 65 mm^3, se dividió a las ratas en 7 grupos experimentales, con 8-9 animales por grupo, los que recibieron una inyección diaria durante 28 días, como sigue: 1.- Testigo (solución de vehículo); 2.-

JV-1-38 (10 µg/día s.c.); 3.- Péptido 35 (10 µg/día s.c.); 4.- Péptido 36 (10 µg/día s.c.); 5.- Péptido 37 (10 µg/día s.c.); 6.- Péptido 39 (10 µg/día s.c.); 7.- Péptido 41 (10 µg/día s.c.). Se midió los volúmenes de los tumores dos veces por semana. El Experimento se terminó en el día 28, sacrificando las ratas bajo anestesia con Isofluorano. Los tumores resultantes se lavaron, pesaron y se congelaron instantáneamente hasta análisis adicional. Se recolectó sangre del tronco, de la aorta abdominal y se separó el suero para mediciones RIA del IGF-I. Se efectuó el análisis estadístico de los resultados de las mediciones por ANOVA, seguido por la prueba de Fisher; los datos se presentan como medias ± el Error Estándar.

Todos los detalles del Experimento 4 son los mismos del Experimento 3, con la siguiente diferencia. Cuando los tumores alcanzaron un volumen de aproximadamente 55 mm^3, se dividió a las ratas en 5 grupos experimentales, con 8-9 animales por grupo, los que recibieron una inyección diaria durante 28 días, como sigue: 1.- Testigo (solución de vehículo); 2.- Péptido 80 (5 µg/día s.c.); 3.- Péptido 86 (5 µg/día s.c.); 4.- Péptido 95 (5 µg/día s.c.); 5.- Péptido 96 (5 µg/día s.c.). Los detalles adicionales del Experimento 4 son los mismos del Experimento 3.

Resultados

Experimento 1:

Entre los antagonistas de GH-RH probados, el Péptido 67 y el Péptido 62 ejercieron un efecto inhibidor más fuerte sobre el crecimiento de los tumores PC-3 que el péptido de referencia JV-1-38, materia de la Patente de los EE. UU. N° 6.057.422 (Cuadro VI). Los péptidos de la presente invención también suprimieron con más potencia los niveles de IGF-I en el suero y los niveles de IGF-II en los tumores, en comparación con el JV-1-38 (Cuadro VII).

CUADRO VI.

Experimento 1: Efecto del Tratamiento con Antagonistas de GH-RH sobre Xenoinjertos de Cáncer PC-3 Prostático Humano en Ratas Desnudas

Grupo	Volumen del Tumor (mm^3)		Peso del Tumor (mg) (% de inhibición)	Tiemp para Doblar el Volumen del Tumor (días)
	Inicial	Final (% inhibición)		
Tetigo	50,0 ± 7,86	501 ± 111	378 ± 84,0	8,97 ±0,71
JV-1-38	49,2 ± 8,37	291 ± 80,4 (42%)	239 ± 58,0 (37%)	12,3 ± 1,04*
Péptido 31	49,1 ± 12,5	363 ± 92,8 (28%)	237 ± 53,3 (37%)	14,0 ± 2,69
Péptido 67	46,8 ± 8,11	200 ± 39,5* (60%)	150 ± 22,1* (60%)	17,0 ± 3,51*
Péptido 62	56,1 ± 18,2	215 ± 50,4 (57%)	199 ± 51,7 (47%)	18,4 ± 4,96*

* p<0,05 vs. Testigo

CUADRO VII

Experimento 1: Efecto del Tratamiento con Antagonistas de GH-RH sobre los Niveles de IGF-I en el Suero y las Concentraciones de IGF-II en los tumores de Ratas Desnudas con Xenoinjertos de Cáncer Prostático PC-3 Humano

Grupo	IGF-I en el Suero (ng/ml) (% inhibición)	IGF-II del Tumor (pg/mg de proteína) (% inhibición)
Testigo	149 ± 10,4	219 ± 64,7
JV-1-38	147 ± 8,49 (1%)	208 ± 43,3 (5%)
Péptido 31	133 ± 16,7 (11%)	130 ± 56,0 (41%)
Péptido 67	128 ± 10,6 (14%)	139 ± 69,2 (37%)
Péptido 62	141 J 8,86 (5%)	N.I.

N.I., no investigado

Experimento 2:

Cuando se usó el Péptido 46, Péptido 77, Péptido 76, Péptido 70, Péptido 79, y Péptido 80 de la presente invención, a una dosis de 5 µg/día, estos disminuyeron los volúmenes y pesos de los tumores de cánceres PC-3, en 20- 64% y aumentaron el tiempo para doblar el volumen de los tumores en hasta 101% del valor del testigo (Cuadro VIII). Los efectos del Péptido 77, Péptido 70, Péptido 79 y Péptido 80 fueron estadísticamente significativos en uno o más de esos parámetros de tumores. En contraste, el péptido de

referencia JV-1-38, materia de la Patente de los EE. UU. N° 6.057.422, no disminuyó el volumen del tumor y solo causó una inhibición leve y no-significativa de 10% en el peso de tumores PC-3, cuando se usó al doble de la dosis de 10 µg/día (Cuadro VIII). Además, el Péptido 70, el Péptido 79 y el Péptido 80 de la presente invención disminuyeron significativamente los niveles de IGF-I en el suero, por 31-42%, mientras el precursor JV-1-38 no tuvo efecto (Cuadro IX).

CUADRO VIII

Experimento 2: Efecto del Tratamiento Antagonistas de GH-RH sobre Xenoinjertos de Cáncer Prostático PC-3 Humano en Ratas Desnudas

Grupo	Volumen del Tumor (mm^3)		Peso del Tumor (mg) (% inhibición)	Tiempo para doblar el Volumen del Tumor (días)
	Inicial	Final (% de inhibición)		
Testigo	28,4 ± 4,2	351 ± 84,9	283 ± 72,1	8,3 ± 0,7
JV-1-38	29,3 ± 3,8	351 ± 79,2 (0%)	254 ± 52,0 (10%)	8,7 ± 0,7
Péptido 46	26,6 ± 2,7	246 ± 93,7 (30%)	188 ± 66,1 (34%)	11,2 ± 1,3
Péptido 77	27,2 ± 3,2	192 ± 44,1 (45%)	138 ± 34,3 (51%)	10,7 ± 0,8*
Péptido 76	26,8 ± 3,4	232 ± 30,8 (34%)	226 ± 48,3 (20%)	9,4 ± 0,6
Péptido 70	26,5 ± 3,7	199 ± 40,4*# (58%)	119 ± 25,3*# (58%)	12,6 ± 2,5
Péptido 79	29,1 ± 4,3	139 ± 49,4*# (60%)	153 ± 54,5 (46%)	13,6 ± 1,8*#
Péptido 80	24,8 ± 2,2	128 ± 38,9*# (64%)	137 ± 46,1* (52%)	16,7 ± 4,3*#

*p<0,05 vs. Testigo; # p<0,05 vs. JV-1-38.

CUADRO IX.

Experimento 2: Efecto del Tratamiento con Antagonistas de GH-RH sobre los Niveles de IGF-I en el Suero en Ratas Desnudas con Xenoinjertos de Cáncer PC-3 Prostático Humano

Grupo	IGF-I en el Suero (ng/ml)	(% de Inhibición)
Testigo	262 ± 18,1	
JV-1-38	293 ± 29,0	0
Péptido 46	288 ± 17,9	0
Péptido 77	276 ± 16,8	0
Péptido 76	260 ± 29,7	1
Péptido 70	175 ± 12,9***	33
Péptido 79	181 ± 19,8**	31
Péptido 80	152 ± 7,83***	42

**p<0,01 vs. Testigo; ***p<0,001 vs. Testigo.

Experimento 3:

Todos los Péptidos probados inhibieron el crecimiento de tumores PC-3, a una dosis de 10 µg/día. El Péptido 35, Péptido 36 y el Péptido 39 tuvieron un efecto anti-tumoral más potente que el Péptido de referencia JV-1-38 (Cuadro X).

CUADRO X.

Experimento 3: Efecto del Tratamiento con Antagonistas de GH-RH sobre Xenoinjertos de Cáncer PC-3 Prostático Humano en Ratas Desnudas

Grupo	Volumen del Tumor (mm^3)		Peso del Tumor (mg) (% de Inhibición)	Tiempo para doblar el Volumen del Tumor (días)
	Inicial	Final (% de Inhibición)		
Testigo	71,1 ±10,5	678 ± 172	700 ± 152	10,6 ± 0,96
JV-1-38	68,3 ± 8,08	276 ± 48,7** (66%)	386 ± 62,9* (45%)	18,2 ± 1,84
Péptido 35	65,7 ± 11,3	261 ± 52,9** (68%)	286 ± 58,9* (59%)	17,0 ± 2,32
Péptido 36	68,0 ± 11,7	214 ± 72,6** (76%)	361 ± 89,6* (48%)	18,7 ± 3,83
Péptido 37	60,0 ± 13,0	323 ± 68,0* (57%)	440 ± 104 (37%)	12,7 ± 2,03
Péptido 39	66,7 ± 11,2	271 ± 109** (66%)	247 ± 55,4* (65%)	19,6 ± 2,10
Péptido 41	66,7 ± 12,5	341 ± 107* (54%)	579 ± 188 (17%)	28,2 ± 9,85

*p<0,05 vs. Testigo; **p<0,01 vs. Testigo.

Experimento 4:

Todos los cuatro péptidos, administrados a una dosis de 5 µg/día inhibieron significativamente el crecimiento de tumores PC-3 en rata desnudas. El Péptido 96 tuvo el efecto anti-tumoral más fuerte en este Experimento (Cuadro XI). Los niveles de IGF-I en el suero, también se inhibieron en todos los grupos tratados con antagonistas; el efecto del Péptido 86 y del Péptido 96 fue estadísticamente significativo (Cuadro XII).

CUADRO XI.

Experimento 4: Efecto del Tratamiento con Xenoinjertos de Cáncer PC-3 Prostático Humano en Ratas Desnudas

Grupo	Volumen del Tumor (mm^3)		Peso del Tumor (mg) (% Inhibición)	Tiempo para doblar el Volumen del Tumor (días)
	Inicial	Final (% Inhibición)		
Testigo	56,3 ± 10,8	1.137 ± 351	1.451 ± 343	7,3 ± 0,52
Péptido 80	53,2 ± 10,1	398 ± 68,7* (68%)	752 ± 150* (48%)	10,7 ± 1,28*
Péptido 86	56,1 ± 8,67	397 ± 71,8* (68%)	643 ± 94,9** (56%)	12,1 ± 1,40**
Péptido 95	60,9 ± 12,2	393 ± 79,8* (69%)	666 ± 131* (54%)	12,5 ± 1,80*
Péptido 96	56,2 ± 13,3	301 ± 65,2** (77%)	489 ± 114** (66%)	11,0 ± 0,87**

*p<0,05 vs. Testigo; **p<0,01 vs. Testigo.

CUADRO XII.

Experimento 4: Efecto del Tratamiento con Antagonistas de GH-RH sobre los niveles de IGF-I en el Suero de Ratas Desnudas con Xeroinjertos de Càncer Prostàtico PC-3 Humano

Grupo	IGF-I en el Suero (ng/ml)	(% de Inhibición)
Testigo	165 ± 10,2	
Péptido 80	136 ± 15,3	18
Péptido 86	118 ± 8,94*	28
Péptido 95	127 ± 17,5	23
Péptido 96	114 ± 15,5*	31

*p<0,05 vs. Testigo.

Efecto del Antagonista de GH-RH sobre Xenoinjertos de Càncer de Colon HT-29 Humano en Ratas Desnudas

Se transplantò cànceres de colon HT-29 humano, s.c. dentro de ratas desnudas. Después de 19 días del transplante, se dividió a las ratas en dos grupos de 10 animales cada uno y se inició el tratamiento. Las ratas en el grupo de tratamiento recibieron una inyección diaria del Péptido 67, s.c., a una dosis de 10 µg/día, durante 62 días, mientras el grupo Testigo fue inyectado solo con el solvente vehicular. Al final del experimento, se sacrificó a las ratas y se pesó los tumores.

Resultados

El tratamiento con el Péptido 67, durante 62 días, causó una inhibición significativa de 56,3% en los volúmenes y de 53,9% en los pesos, de los tumores HT-29 que crecían en ratas desnudas, en comparación con el grupo Testigo (Cuadro XIII).

CUADRO XIII.

Efecto del Tratamiento con el Antagonista de GH-RH, Péptido 67, sobre Xenoinjertos de Cáncer de Colon HT-29 Humano, en Ratas Desnudas

Grupo	Volumen Final del Tumor (mm^3)	Peso del Tumor (mg)
Testigo	2.792 ± 643	3.112 ± 543
Péptido 67	1.218 ± 320*	1.434 ± 405*

*p<0,05 vs. Testigo

Efecto de los Antagonistas de GH-RH sobre Carcinomas de Células Pequeñas Pulmonares DMS-153 Humanos (SCLC), Xenoinjertadas en Ratas Desnudas

Se implantó s.c. en ratas desnudas macho, piezas de 3 mm^3 de tejido humano SCLC DMS-153. Cuando los tumores alcanzaron un volumen de aproximadamente 100 mm^3, se dividió a las ratas en 3 grupos experimentales de 6-8 animales cada uno, los que recibieron tratamiento durante 6 semanas: grupo 1 (Testigo), solución vehicular; grupo 2, Péptido 67 (10 µg/día s.c.); grupo 3, Péptido 31 (10 µg/día s.c.). Se registró el volumen de los tumores dos veces a la semana. Al final del experimento, se anestesió a las ratas con Isofluorano, se las sacrificó por decapitación, se recolectó sangre del tronco para medición del IGF-I del suero y se separó y pesó a los tumores. Los datos se presentan como medias ± Error Estándar. Se evaluó los datos mediante ANOVA en un sentido y la prueba de Student-Newman-Keuls,

Resultados

Los pesos de los tumores disminuyeron significativamente en animales que recibieron tratamiento, tanto con el Antagonista de GH-RH, Péptido 67 o Péptido 31, en comparación con el Testigo (Cuadro XIV). El volumen de los tumores también fue significativamente más pequeño en el grupo que recibió el Péptido 67. Además, ambos antagonistas redujeron significativamente los niveles de IGF-I en el suero, en comparación con los animales testigo (Cuadro XIV). La expresión del mARN de IGF-IIfue similarmente inhibida por ambos antagonistas, siendo su nivel de expresión 100 ± 1,5% en el grupo testigo, 78,0 ± 44,3% en el grupo tratado con el Péptido 67 y 42,7 ± 18,5%, en el grupo que recibió el Péptido 31. El efecto inhibidor del Péptido 31, en la expresión del mARN del IGF-II fue estadísticamente significativo ($p<0,01$ vs. Testigo)

CUADRO XIV.

Efecto del Tratamiento con Antagonistas de GH-RH sobre Xenoinjertos de SCLC Humano DMS-153 en los Niveles de IGF-I del Suero, en Ratas Desnudas

Grupo	Peso del Tumor (g)	Volumen del Tumor (mm^3)		IGF-I en el Suero (ng/ml)
		Inicial	Final (% Inhibición)	
Testigo	2,31 ± 0,25	112 ± 13	3.641 ± 431	169,0 ± 9,9
Péptido 67	1,60 ± 0,19*	132 ± 24	2.650 ± 30* (28%)	117,9 ± 17,2* (30%)
Péptido 31	1,58 ± 0,11* (32%)	138 ± 20	3.329 ± 180 (10%)	118,4 ± 12,5* (30%)

*$p<0,05$ vs. Testigo

Efecto de los Antagonistas de GH-RH sobre SCLC H-69 Humano Xenoinjertados dentro de Ratas Desnudas

Se implantó sub-cutáneamente piezas de 3 mm^3 de tejido SCLC H-69 humano, en ratas desnudas macho. Cuando los tumores alcanzaron un volumen de aproximadamente 80 mm^3, se dividió a las ratas en 4 grupos experimentales de 7-8 animales por grupo, los que recibieron el siguiente tratamiento, durante 4 semanas: grupo 1 (testigo), solución de vehículo; grupo 2, Péptido 67 (10 µg/día s.c.); grupo 3, Péptido 31 (10 µg/día s.c.); grupo 4, Péptido 72 (10 µg/día s.c.). Se registró los volúmenes de los tumores dos veces a la semana. Al final del tratamiento, se anestesió a las ratas con Isoflurano, se las sacrificó por decapitación y se separó y pesó a los tumores. Los datos se presentan como medias ± Error Estándar. Los datos se evaluaron por ANOVA en un sentido y la prueba de Student-Newman-Keuls.

Resultados

Todos los antagonistas de GH-RH, administrados como una sola inyección diaria, a una dosis de 10 µg/día, inhibieron significativamente el crecimiento

de los tumores H-69, en ratas desnudas. Entre los compuestos probados, el Péptido 72 mostró el efecto inhibidor más fuerte (Cuadro XV).

CUADRO XV.

Efecto del Tratamiento con antagonistas de GH-RH sobre Xenoinjertos de SCLC H-69 Humano en Ratas Desnudas

Grupo	Volumen del Tumor (mm^3)	
	Inicial	Final (% Inhibición)
Testigo	81 ± 13	2.350 ± 189
Péptido 67	82 ± 10	501 ± 35* (76%)
Péptido 31	80 ± 6	832 ± 23* (67%)
Péptido 72	81 ± 9	308 ± 23* (90%)

*p<0,001 vs. Testigo

REIVINDICACIONES

1. Un péptido seleccionado del grupo que tiene la fórmula

R_1-A^0-A^1-A^2-Asp-Ala-A^5-A^6-Thr-A^8-A^9-A^{10}-A^{11}-A^{12}-Val-Leu-A^{15}-A^{16}-Leu-Ser-A^{19}-A^{20}-A^{21}-A^{22}-Leu-Gln-Asp-Ile-A^{27}-A^{28}-A^{29}-A^{30}-R_2

En donde R_1 es un miembro del grupo que consiste de a) PhAc, Hca, Dat, IndAc, Ipa, 1-Nac, 2-Nac, 1-Npr, 2-Npr, Ibu; $CH_3(CH_2)nCO$, o $HOOC(CH_2)_nCO$, en donde n es un entero de 2 a 20, y b) cualquier otra cadena recta, cadena ramificada, saturada, no saturada o grupo carboxilo alifático poli insaturado de 2-30 átomos de carbono y cualquier grupo carboxilo aromático carbocíclico o heterocíclico de 3-8 átomos de carbono que contienen al menos un átomo del grupo S, N, y O en el anillo heterocíclico,

A^0es Phe, D-Phe, Arg, D-Arg, o un enlace sencillo carbono-nitrógeno

A^1es Tyr o His,

A^2es D-Arg o D-Cit,

A^5es Ile o Val,

A^6es Phe, Tyr, Nal, o Phe(Y), en el que Y=F, Cl, Br, o I,

A^8es Asn, D-Asn, Cit, D-Cit, Gln, D-Gln, Ser, D-Ser, Thr, D-Thr, Ala, D-Ala, Abu, D-Abu, o Aib,

A^9es His, D-His, Amp, D-Amp, Gup, o D-Gup,

A^{10}es Tyr, Tyr(Et), Tyr(Me); Phe(Y), en el que Y=H, F, Cl, Br, o I; Amp, His, Cha, Chg, Bpa, Dip, Trp, Trp(For), Tpi, 1-Nal, 2-Nal, 3-Pal, 4-Pal, Phe(NH_2), o Phe(NO_2),

A^{11}es His, D-His, Arg, D-Arg, Cit, Har, D-Har, Amp, D-Amp, Gup, o D-Gup,

A^{12}es Lys, D-Lys, Orn, D-Orn, Har, D-Har, Cit, D-Cit, Nle, o Ala,

A^{15}es Gly, Ala, Abu, Aib, Nle, Gln, Cit, o His,

A^{16}es Gln o Arg,

A^{19}es Ala o Abu,

A^{20}es His, D-His, Arg, D-Arg, o Cit,

A^{21}es Lys, D-Lys, Orn, D-Orn, Cit, o D-Cit,

A^{22}es Leu, Ala o Aib,

A^{27}es Met, Leu, Nle, Abu, o D-Arg,

A^{28}es Arg, D-Arg, Har, D-Har, Ser, Asn, Asp, Ala, Abu, o Cit,

A^{29}es Arg, D-Arg, Har, D-Har, Cit, D-Cit, o Agm,

A^{30}es Arg, D-Arg, Har, D-Har, Cit, D-Cit, Agm, o es un enlace sencillo carbón-nitrógeno o carbón oxígeno,

R_2 es $-NH_2$, $-NH-NH_2$, -NH-OH, $-NHR_3$, $-NR_3R_4$, -OH, o $-OR_3$, en el que R_3 y R_4 son cualquiera de alquilo C_{1-10}, alquenilo C_{2-10}, alquinilo C_{2-10}, fenilalquilo C_{7-16}, $-C_6H_5$- o $-CH(C_6H_5)_2$;

dado que si A^{29} es Agm entonces A^{30} y R_2 están ausentes, y si A^{30} es Agm entonces R_2 está ausente, y sales farmacéuticamente de estos

2. El compuesto de la reivindicación 1 en donde uno o ambos de A^{11} y A^{20} son diferentes de Arg, D-Arg, o Cit.

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3. Un compuesto de la reivindicación 1 seleccionado del grupo que consiste de:

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 67

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 68

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, His^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 69

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 70

[$HOOC(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 71

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 72

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 73

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 74

[1-Nac-Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 75

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 76

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 77

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 78

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 79

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 80

[$HOOC(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 81

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 82

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 86

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 87

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 88

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 89

[1-Nac-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 91

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 92

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 93

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, His^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 94

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 95

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 96

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHEt Péptido 97

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHEt Péptido 98

$[CH_3(CH_2)_{10}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHEt Péptido 99

[Hca -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHEt Péptido 100

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHMe Péptido 101

$[HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 102

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 103

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 104

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 105

$[CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NHEt Péptido 106

$[HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 107

$[HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, $Har^{29}]$hGH-RH(1-29)NH_2 Péptido 108

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 109

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 110

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 111

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 112

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Tyr(Et)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 113

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 114

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, His^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 115

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 116

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 117

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 118

[$CH_3(CH_2)_8CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 119

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, Dip^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 120

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, $Phe(pCl)^6$, Ala^8, Amp^9, $Phe(pNO_2)^{10}$, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 121

4. Un compuesto de la reivindicación 3 seleccionado del grupo que consiste de:

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 67

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, His^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 69

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 70

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Amp^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 72

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 76

[$HOOC(CH_2)_{12}CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, Amp^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 77

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Cit^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 79

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 80

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 86

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 95

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Orn^{12}, Abu^{15}, His^{20}, Orn^{21}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 96

[$CH_3(CH_2)_6CO$ -Tyr^1, D-Arg^2, Phe(pCl)^6, Ala^8, His^9, Tyr(Et)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 97

5. Un compuesto de la reivindicación 3 seleccionado del grupo que consiste de:

[$CH_3(CH_2)_4CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 2

[$HOOC(CH_2)_4CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 3

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 4

[$HOOC(CH_2)_6CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 5

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 6

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 7

[$CH_3(CH_2)_{10}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 8

[$HOOC(CH_2)_{10}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 9

[$CH_3(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 10

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 11

[$CH_3(CH_2)_{14}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 12

[$HOOC(CH_2)_{14}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 13

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2

Péptido 14

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[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Péptido 15

[$CH_3(CH_2)_{14}$CO-Phe^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 16

[$CH_3(CH_2)_{14}$CO-D-Phe^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 17

[PhAc-Arg^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 18

[PhAc-D-Arg^{0}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 19

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 21

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Cit^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 22

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Arg^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Péptido 23

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Cit^{9}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Péptido 24

[$HOOC(CH_2)_{12}$CO-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Cit^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 25

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, D-Ala^{8}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 26

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Abu^{8}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 27

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Cit^{8}, Abu^{15}, Nle^{27}, Har^{28}, D-Arg^{29}]hGH-RH(1-29)NH_2
Péptido 28

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 30

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 31

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, His^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 32

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Cha^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 33

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tpl^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 34

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 35

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 36

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNH_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 37

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Trp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 38

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Phe(pNO_2)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 39

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, 3-Pal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 40

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 41

[PhAc-His^{1}, D-Arg^{2}, Tyr^{6}, Har^{9}, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2

Péptido 42

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Har^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 43

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Péptido 45

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Péptido 46

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Péptido 47

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Arg^{9}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Péptido 48

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Alb^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt
Péptido 49

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Orn^{12}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NHEt Péptido 50

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29)
Péptido 51

[PhAc-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Agm^{29}]hGH-RH(1-29)
Péptido 52

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2 Péptido 53

[Dat-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2
Péptido 54

[Ipa-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NH_2
Péptido 55

[Hca-Tyr^{1}, D-Arg^{2}, Phe(pCl)^{6}, Har^{9}, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Har^{30}]hGH-RH(1-30)NHEt Péptido 56

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[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, D-Arg^{29}, Har^{30}]hGH-RH(1-30)NH_2 Péptido 57

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, D-Arg^{30}]hGH-RH(1-30)NH_2 Péptido 58

[Hca-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30) Péptido 59

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}, Agm^{30}]hGH-RH(1-30) Péptido 60

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 62

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Har^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 63

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Amp^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 64

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Cit^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 65

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 84

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, His^{20}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 85

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Cit^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 90

6. Un péptido de la reivindicación 5 seleccionado del grupo que consiste de:

[$CH_3(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 4

[$HOOC(CH_2)_6CO$-Tyr^1, D-Arg^2, Phe(pCl)^6, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 5

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[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 7

[$HOOC(CH_2)_{12}CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 11

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Cit^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 22

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, 2-Nal^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 35

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, Dip^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 36

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Phe(pNO_2)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 39

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Et)^{10}$, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 41

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, $Tyr(Me)^{10}$, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2 Péptido 62

7. Un péptido de la reivindicación 5 seleccionado del grupo que consiste de;

[$CH_3(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 4

[$HOOC(CH_2)_8CO$-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 7

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Cit^8, Arg^9, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 21

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Arg^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 30

[PhAc-Tyr^1, D-Arg^2, $Phe(pCl)^6$, Har^9, Amp^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH_2
Péptido 31

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Phe(pNH$_2$)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$
Péptido 37

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Et)^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$
Péptido 41

[PhAc-His^1, D-Arg^2, Tyr^6, Har^9, Bpa^{10}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$
Péptido 42

[PhAc-Tyr^1, D-Arg^2, Phe(pCl)^6, Har^9, Tyr(Me)^{10}, His^{11}, Abu^{15}, Nle^{27}, D-Arg^{28}, Har^{29}]hGH-RH(1-29)NH$_2$ Péptido 62

8. El uso de un compuesto de cualquiera de las reivindicaciones 1 o 5 para la producción de una composición farmacéutica para suprimir niveles de GH en un paciente en necesidad del mismo.

9. El uso de un compuesto de cualquiera de las reivindicaciones 1 o 5 para la producción de una composición farmacéutica para suprimir niveles de IGF-I IGF-II en el tejido de tumor de un paciente que tiene receptores que llevan cáncer para IGF-I.

10. El uso de un compuesto de cualquiera de las reivindicaciones 1 o 5 para la producción de una composición farmacéutica para suprimir niveles de VEGF en el tejido de tumor de un paciente que tiene un cáncer.

11. El uso de un compuesto de cualquiera de las reivindicaciones 1 o 5 para la producción de una composición farmacéutica para suprimir niveles de IGF-I en un paciente en necesidad del mismo.

12. El uso de un compuesto de cualquiera de las reivindicaciones 1 o 5 para la producción de una composición farmacéutica para suprimir niveles IGF-I de suero en un paciente que tiene receptores que llevan cáncer para IGF-I.

13. El uso de un compuesto de cualquiera de las reivindicaciones 1 o 5 para la producción de una composición farmacéutica para suprimir niveles de GH en un paciente que tiene receptores que llevan cáncer para IGF-I o GH.

14. El uso de un compuesto de cualquiera de las reivindicaciones 1 o 5 para la producción de una composición farmacéutica para bloquear los receptores de GH-RH en un paciente que tiene receptores que llevan cáncer para GH-RH.

15. El método de suprimir niveles de GH en un paciente en necesidad del mismo al administrar a dichos pacientes una cantidad supresora efectiva de un compuesto de cualquiera de las reivindicaciones 1 o 5.

16. El método de suprimir niveles de IGF-I o IGF-II en el tejido de tumor de un paciente que tiene receptores que llevan cáncer para IGF-I al administrar a dicho paciente una cantidad supresora efectiva de un compuesto de cualquiera de las reivindicaciones 1 o 5.

17. El método de suprimir niveles VEGF en el tejido de tumor de un paciente que tiene un cáncer al administrar a dicho paciente una cantidad supresora efectiva de un compuesto de cualquiera de las reivindicaciones 1 o 5..

18. El método de suprimir niveles de IGF-I en un paciente en necesidad del mismo al administrar a dicho paciente una cantidad supresora efectiva de un compuesto de cualquiera de las reivindicaciones 1 o 5.

19. El método de suprimir niveles de IGF-I de suero en un paciente que tiene receptores que llevan cáncer para IGF-I al administrar a dicho paciente una cantidad supresora efectiva de un compuesto de cualquiera de las reivindicaciones 1 o 5.

20. El método de suprimir niveles de GH en un paciente que tiene receptores que llevan cáncer para IGF-I o GH al administrar a dicho paciente una cantidad supresora efectiva de un compuesto de cualquiera de las reivindicaciones 1 o 5.

21. El método de tratamiento de un paciente que tiene un receptor que lleva cáncer para GH-RH al administrar a dicho paciente una cantidad efectiva de un compuesto de cualquiera de las reivindicaciones 1 o 5 efectiva para bloquear dichos receptores GR-RH.

22. Una composición farmacológicamente administrable para la supresión de niveles de GH en un paciente que consiste esencialmente de un compuesto de la reivindicación 1 o 5 y un portador farmacológicamente aceptable.

23. Una composición farmacológicamente administrable para la supresión de niveles de -IGF-I o IGF-II en el tejido de tumor de un paciente que tiene receptores que llevan cáncer para IGF-I que consiste esencialmente de un compuesto de la reivindicación 1 o 5 y un portador farmacológicamente aceptable.

24. Una composición farmacológicamente administrable para la supresión de niveles VEGF en el tejido de tumor de un paciente que tiene un cáncer que consiste esencialmente de un compuesto de la reivindicación 1 o 5 y un portador farmacológicamente aceptable.

25. Una composición farmacológicamente administrable para la supresión de niveles de IGF-I en un paciente que consiste esencialmente de un compuesto de la reivindicación 1 o 5 y un portador farmacológicamente aceptable.

26. Una composición farmacológicamente administrable para la supresión de niveles de GH en un paciente que tiene receptores que llevan cáncer para IGF-I o GH que consiste esencialmente de un compuesto de la reivindicación 1 o 5 y un portador farmacológicamente aceptable.

27. Una composición farmacológicamente administrable para la supresión de niveles de IGF-I en un paciente que tiene receptores que llevan cáncer para IGF-I que consiste esencialmente de un compuesto de la reivindicación 1 o 5 y un portador farmacológicamente aceptable.

28. Una composición farmacológicamente administrable para bloquear receptores para GH-RH en un paciente que tiene receptores que llevan cáncer para Gh-RH que consiste esencialmente de un compuesto de la reivindicación 1 o 5 y un portador farmacológicamente aceptable.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 7,514
FECHA : ENERO 30 DE 2006

SUPERINDUSTRIA Y COMERCIO
Radicacion : [illegible] Folios: 269
Fecha (AMD): [illegible]
Tramite : 011 PCT-ORIENT 3/9 FASE RADI 411 PRESENTAC
Dependencia: [illegible] DIVISION DE NUEVAS CREACIONES

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	36494410	30/01/2006	43,526,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 15773-84-0019

270

264

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (✓) MODELO DE UTILIDAD ( )	( )	( )
-Indicación de que se solicita la concesión de una patente.	( )	(✓)
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
-Descripción de la invención.	( )	(✓)
-Dibujos de ser estos pertinentes.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	(✓)
COMPLETA (✓) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
ESQUEMA DE TRAZADO ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: _____

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO

REFERENCIA	Radicación No.	6 10723
	Solicitud internacional	US2004/024183
	Fecha inicio fase nacional	05/02/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	3829

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

3. La solicitud no contiene el poder debidamente otorgado por la sociedad "The administrators of the tulane educational fund", con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante.

4. Debe aclarar el nombre del solicitante, por cuanto la publicación internacional difiere del petitorio presentado en fase nacional.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación No.:6 10723

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 13 MAR 2006
jramos


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