Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-128571

54. **TÍTULO** Derivados de matostina y utilización de los mismo

51. **CLASIFICACIÓN INTERNACIONAL** A 61 K 38/00

71. **SOLICITANTE** Takeda Pharmaceutical Company limited

DOMICILIO 540045 OSAKA, JAPAN

74. **APODERADO** Emilio Ferrero
CC 938.014. de Osaka

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-1285 71- -00000-0000
Fec: 2006-12-22 11:28:50 Dep: 2020 RECEPCION ADUANES
Tip: 11 PATENTES II
Eve: 376 FASE NACIONAL
Act 411 PATENTACION Folios: 78

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

(2) SOLICITANTE (71)

Nombre: **TAKEDA PHARMACEUTICAL COMPANY LIMITED**
sociedad constituida y existente bajo las leyes de Japón.

Dirección: 1-1, Doshomachi 4-chome
Chuo-ku, Osaka-shi
541045 Osaka
Japón

Domicilio: 541045 Osaka
Japón

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

(3) REPRESENTANTE APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@camvp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

(4) INVENTOR (ES) (72)

1. **Chieko KITADA**
c/o Osaka Plant of TAKEDA PHARMACEUTICAL COMPANY LIMITED,
17-85, Jusohonmachi 2-chome
Yodogawa-ku, Osaka-shi,
Osaka 532-8686
Japón

2. **Taiji ASAMI**
c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED
10, Wadai, Tsukuba-shi
Ibaraki 3004293
Japón

3. **Naoki NISHIZAWA**
c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED,
10, Wadai, Tsukuba-shi
Ibaraki 300-4293
Japón

(5) PCT (86)

Solicitud Internacional No. PCT/JP2005/012021 Fecha: 23 de junio de 2005
Publicación Internacional No. WO 2006/001499 A2 Fecha: 5 de enero de 2006

(6) Título (54)

DERIVADOS DE METASTINA Y UTILIZACIÓN DE LOS MISMOS

(7) Clasificación Internacional (51) C07K 14/47

(8) Prioridad SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	25 de junio de 2004	2004-187671
JP	15 de diciembre de 2004	2004-363311

(9) Comprobante de pago N .: 06-94.102 **Fecha:** 11 de diciembre de 2006

2

10 **Anex s:**

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 463.000.oo.
- [ ] Comprobante de pago por reivindicación de prioridad.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] 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.
- [x] Otros: VER HOJA DE DOCUMENTOS ANEXOS

11 **FIGURA CARACTERÍSTICA**

12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

JDF

1

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2006/001499 A2
2. ☒ Extracto de publicación.

NO SE PRESENTARON MODIFICACIONES EN FASE INTERNACIONAL

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTA, D - COLOMBIA

179

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

Fe

C

14656
08085

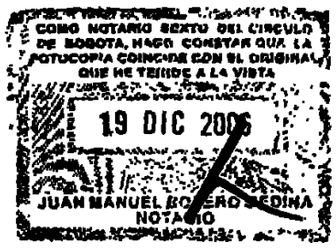
Yo (nosotros), abajo firmado (s)/I (we), the undersigned
TAKEDA PHARMACEUTICAL COMPANY LIMITED
domiciliado (s) en/of 1-1, Doshomachi 4-chome,
Chuo-ku, Osaka-shi, Osaka Japan

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª Nº 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª Nº 72 .35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will entail the cessation of the representation by the first, second or third alternate who is acting at such time.

In addition, I (we) grant a Power of Attorney in favor of the above named attorneys to the effect I (we) authorize said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit


COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
19 DIC 2006
JUAN MANUEL ROJERO MEDINA
NOTARIO

5

promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir, este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

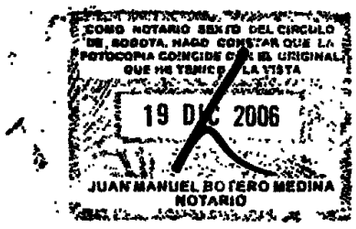
Dado y firmado hoy/Given and signed this 14th day of December, 2004

en/in Osaka, Japan

por/by

Firma Hiroshi Akimoto Ph. D. Signature
Executive Director
Member of the Board, General Manager,
Intellectual Property Dept.
Authorized Signing Officer

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
19 DIC 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO


COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
19 DIC 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Kiyoomi FUJITA
3. acting in the capacity of — Notary Public of the Osaka Legal Affairs Bureau
4. bears the seal/stamp of — Kiyoomi FUJITA, Notary Public

Certified

5. at **Osaka**
6. DEC. 17. 2004
7. by the **Ministry of Foreign Affairs**
8. No. 04149
9. Seal/stamp:
10. Signature:

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
19 DIC 2006
JUAN MANUEL ROTERO MEDINA
NOTARIO

Tsutomu HIGUCHI

For the Minister for Foreign Affairs

7

大阪法務局所属　公証人役場

認証登簿　平成１６年 第　334　　号

嘱託人 武田薬品工業株式会社 常務取締役　知的財産部長 秋元浩

は、本職の面前でこの証書に署名した。

よって、その署名が本人の自筆であることを証する。

平成　１６　年　１２　月１４　日

大阪市西区江戸堀１丁目１０番８号（帝人殖産ビル内）

公証人　**藤 田 清 臣**　役場において

大阪法務局所属

公 証 人

藤田清臣

COMO NOTARIO SUPLENTO DEL CIRCULO DE BOGOTA, DC. CONSTA QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PRESENTADO A LA VISTA

19 DIC 2006

JUAN MANUEL BOTERO MEDINA
NOTARIO

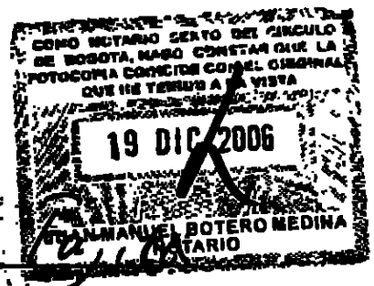
8

REGISTER NUMBER 334 / 2004

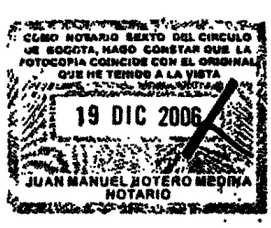
I hereby certify that this document was signed before me and that the signature appearing on the same is the true signature of Hiroshi Akimoto, Ph. D., Executive Director, Member of the Board, General Manager, Intellectual Property Department of Takeda Pharmaceutical Company Limited.

Dated this 14th day of December, 2004

10-8, Edobori 1-chome,
Nishi-ku, Osaka, Japan.



Kiyoomi Fujita
Notary attached
to The Osaka Legal
Affairs Bureau


CLARO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
19 DIC 2006
JUAN MANUEL HOTERO MEDINA
NOTARIO

9

THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPAN.
FAX : (06)6944-6248 TEL : (06)6944-6411
URL : http://www.osaka.cci.or.jp/

November 17, 2004

To whom it may concern:

CERTIFICATE OF MEMBERSHIP

This is to certify that the undermentioned company is registered as a member of this Chamber.

Company name: Takeda Pharmaceutical Company Limited

(The former company name in English was Takeda Chemical Industries, Ltd. until June 29, 2004.)

Address: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

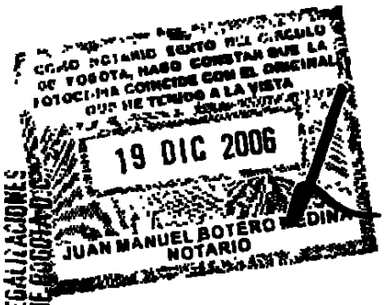
Membership Number: KT-01-00080

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
19 DIC 2006
JUAN MANUEL OTERO MEDINA NOTARIO

The Osaka Chamber of Commerce & Industry

Yoshinobu Kobayashi
Authorized Signatory

A [illegible]149



2005 FEB -4 A 2:37

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

JEFE DE RELACIONES
EXTERIORES

085749

FIRMA APARECE EN EL
DESEMPEÑO
FUNCIONES INDICADAS

EMBAJADA DE COLOMBIA - SECCION CONSULAR

Tokio, Japón, DICIEMBRE 20, 2004
No. 299

El encargado de las funciones consulares de Colombia

CERTIFICA:

Que el (la) Señor(a) YOSHINOBU KOBAYASHI, quien autoriza el presente documento , es la persona legalmente facultada para representar en la fecha señalada al (a la) CAMARA DE COMERCIO E INDUSTRIA, OSAKA y que la firma y sello que en el documento aparecen como suyos son las que usa y acostumbra para sus actos oficiales.

El Encargado de Funciones Consulares no asume responsabilidad alguna por el contenido del documento.

Firma del Encargado de Funciones Consulares

Derechos: US$23.oo

RAFAEL RICARDO OROZCO
Segundo Secretario

10

総第 3603 号

証　　明

大阪法務局所属公証人　藤田清臣

平成 16年12 月14 日付

平成16年 登簿 第 334 号

この認証の付与は，在職中の公証人がその権限に基づいてしたものであり，かつ，その押印は，真実のものであることを証明する。

平成16年12月17日
平成　　年　　月　　日

大阪法務局長　梅津和宏

CONO NOTARIO SEXTO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
19 DIC 2004
NOTARIO EUTERO MEDINA

CERTIFICATE

This is to certify that the annexed Notarial Certificate has been executed by Notary,duly authorized and practising in Osaka, Japan, and that the Official seal appearing on the same is genuine.

Date 04.12.17

Director of the Osaka Legal Affairs Bureau

11

TRADUCCIÓN OFICIAL No. 02.04/05b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento por medio del cual **TAKEDA PHARMACEUTICAL COMPANY LIMIMTED** domiciliado en el 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, Japón, otorga derechos de Representación y Poder a los Doctores EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PÁEZ, tpa. 23555; y GERMÁN CAVELIER, tpa. 832, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia.

Dado y firmado el 14 de diciembre de 2004 en Osaka, Japón.

Firma Ilegible

Firma Hiroshi Akimoto Ph. D.
Director Ejecutivo
Miembro de la Junta, Gerente General,
Departamento de Propiedad Intelectual
Signatario Autorizado

REGISTRO NÚMERO 334 / 2004

Por el presente certifico que este documento fue firmado ante mí y que la firma que aparece en mismo es la firma auténtica de Hiroshi Akimoto, Ph. D., Director Ejecutivo, Miembro de la Junta, Gerente General, Departamento de Propiedad Intelectual de Takeda Pharmaceutical Company Limited.

NOTARIO ... DEL CIRCULO ... CONSTAR QUE LA ... COINCIDE CON EL ... 19 DIC 2004 ... JUAN MANUEL BOTERO MEDINA NOTARIO

Expedido hoy 14 de diciembre de 2004

10-8, Edobori 1-chome

Nishi-ku, Osaka, Japón

Firma ilegible

Kiyoomi Fujita
Notario adjunto a la
Oficina de Asuntos Legales de Osaka

DOCUMENTO ANTERIOR EN JAPONÉS

(Anexo)

Texto en Japonés

CERTIFICADO

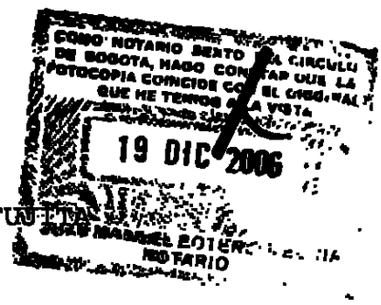
El presente es para certificar que el Certificado Notarial anexo ha sido suscrito por un notario debidamente autorizado y en ejercicio en Osaka, Japón, y que el sello oficial que aparece en el mismo es auténtico.

Fecha: 04.12.17

Director de la Oficina de Asuntos Legales de Tokio

APOSTILLA

(Convention de La Haye du 5 octubre 1961)



1. País: **JAPÓN**
   Este documento público
2. ha sido firmado por Kiyoomi FUJITA
3. actuando en calidad de Director de la Oficina de Asuntos Legales de Tokio
4. lleva el sello/estampilla de Kiyoomi FUJITA, Notario Público

La Cámara de Comercio e Industria de Osaka

Firma Ilegible

Yoshinobu Kobayashi

Signatario Autorizado

(Respaldo)

Certificado No. 299 del 20 de diciembre de 2004 expedido por la EMBAJADA DE COLOMBIA en Tokio, Japón, en donde se certifica que YOSHINOBU KOBAYASHI está legalmente facultado para firmar a nombre de la Cámara de Comercio e Industria de Osaka y que su firma en el anterior documento es auténtica.

Firmado por RAFAEL RICARDO OROZCO, Segundo Secretario.

Pagados los derechos consulares.

Legalización de la firma anterior con el **No. 085749** expedida por el Jefe de Legalizaciones del Ministerio de Relaciones Exteriores en Santafe de Bogotá el 4 de febrero de 2005.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ/ID-6472/WPCL002G/COLO 14656-845-001-0

JUAN MANUEL BOTERO MEDINA
NOTARIO

DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

54

Certificado

5. en **Osaka** 6. DIC 17 DE 2004

7. por el **Ministerio de Relaciones Exteriores**

8. **No. 04149**

DIEGO F. VARGAS
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

9. **Sello/estampilla** 10. **Firma:**

MINISTERIO DE RELACIONES EXTERIORES JAPÓN

Firma Ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores

LA CÁMARA DE COMERCIO E INDUSTRIA DE OSAKA
2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPÓN
FAX: (06) 6944-6248 TEL: 6944-6411
URL: http://www.osaka.cci.or.jp/

Noviembre 17 de 2004

A quién pueda interesar:

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TUVO A LA VISTA
19 DIC 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

CERTIFICADO DE MEMBRESÍA

El presente es para certificar que la siguiente compañía está registrada como miembro de esta Cámara.

Nombre de la compañía: Takeda Pharmaceutical Company Limited

(El nombre anterior de la compañía en inglés fue Takeda Chemical Industries, Ltd. hasta el 29 de junio de 2004.)

Dirección: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japón

Número de Membresía: KT-01-00080

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) Q:
Dieer Leeeeeeo
Cobyo
CORRESPONDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA, 06 FEB 2005

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

MINISTERIO DE
RELACIONES EXTERIORES

08 FEB -8 P 2:39

313391

DIRECCION DE LEGALIZACIONES
BOGOTA D.C.

LA SECRETARIA APARTE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
19 DIC 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2006 (05.01.2006)

PCT

(10) International Publication Number
WO 2006/001499 A2

(51) International Patent Classification[7]: C07K 14/47

(21) International Application Number:
PCT/JP2005/012021

(22) International Filing Date: 23 June 2005 (23.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2004-187671 25 June 2004 (25.06.2004) JP
2004-363311 15 December 2004 (15.12.2004) JP

(71) Applicant *(for all designated States except US)*: TAKEDA PHARMACEUTICAL COMPANY LIMITED [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, 5408645 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KITADA, Chieko [JP/JP]; c/o Osaka Plant of TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5320024 (JP). ASAMI, Taiji [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 10, Wadai, Tsukuba-shi, Ibaraki, 3004293 (JP). NISHIZAWA, Naoki [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 10, Wadai, Tsukuba-shi, Ibaraki, 3004293 (JP).

(74) Agents: KOBAYASHI, Hiroshi et al.; c/o ABE, IKUBO & KATAYAMA, Fukuoka Bldg. 9th Fl., 8-7, Yaesu 2-chome, Chuo-ku, Tokyo, 1040028 (JP).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/001499 A2

(54) Title: METASTIN DERIVATIVES AND USE THEREOF

(57) Abstract: The invention provides stable metastin derivatives having excellent biological activities (a cancer metastasis suppressing activity, a cancer growth suppressing activity, etc.). By modifying the constituent amino acids of metastin with specific modifying groups, metastin derivatives having more improved blood stability, etc. than native metastin and showing excellent cancer metastasis suppressing activity or cancer growth suppressing activity have been found. Furthermore, it has been found that these metastin derivatives exhibit effects of suppressing gonadotropic hormone secretion, suppressing sex hormone secretion, etc., which are wholly different from the effects heretofore known.

DESCRIPTION

METASTIN DERIVATIVES AND USE THEREOF

TECHNICAL FIELD

The present invention relates to metastin derivatives and use thereof.

BACKGROUND ART

Human-derived metastin (also termed KiSS-1 peptide) (WO 00/24890) and rat or mouse-derived metastin (WO 01/75104) are known. Also, sustained released preparations containing metastin are known (WO 02/85399).

Reportedly, metastin has an effect of suppressing cancer metastasis and is therefore effective for preventing or treating cancers (for example, lung cancer, gastric cancer, liver cancer, pancreatic cancer, colorectal cancer, rectal cancer, colonic cancer, prostate cancer, ovarian cancer, cervical cancer, breast cancer, renal cancer, bladder cancer, brain tumor, etc.); metastin also has an effect of controlling pancreatic function and is effective for preventing or treating pancreatic diseases (e.g., acute or chronic pancreatitis, pancreatic cancer, etc.); and metastin further has an effect of controlling placental function and is effective for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or abnormal delivery (WO 00/24890; WO 01/75104; WO 02/85399).

DISCLOSURE OF THE INVENTION

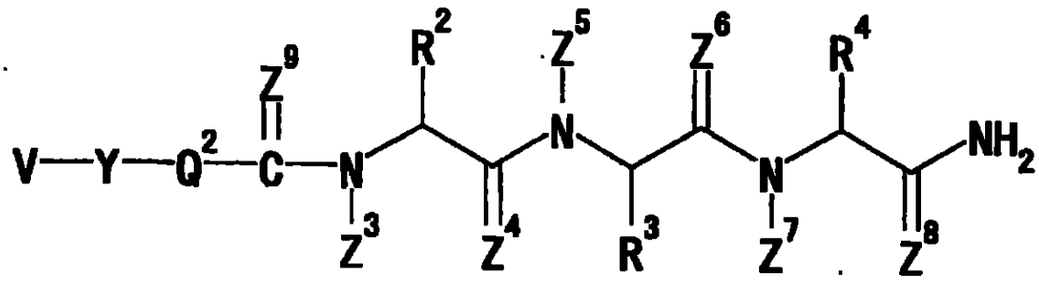
The present invention aims at providing stable metastin derivatives having excellent biological activities (a cancer metastasis suppressing activity, a cancer growth suppressing activity, etc.).

The present inventors have made extensive studies to solve the foregoing problems and as a result, have found that by modifying the amino acids, which constitute metastin, with a specific modifying group, unexpectedly metastin derivative show improved blood stability, etc. as compared to native metastin and further exhibit an excellent cancer metastasis suppressing activity or a cancer growth suppressing activity. The present inventors have further found that unexpectedly these metastin derivatives have an effect of suppressing gonadotropic hormone secretion, an effect of suppressing sex hormone secretion, etc., which are totally different from the effects known so far. Based on these findings, the present inventors have continued further

investigations and come to accomplish the present invention.

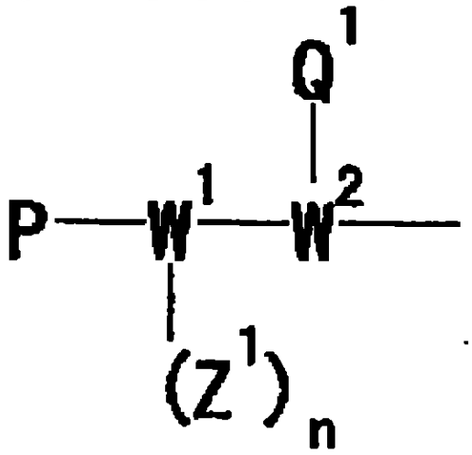
That is, the present invention provides the following features and so on.

(1) A metastin derivative (II) represented by formula:

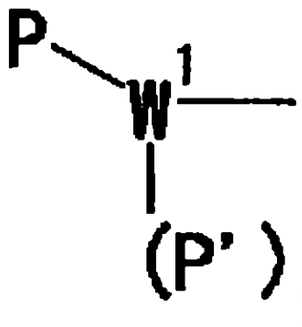


[wherein;

V represents a group represented by formula:



or a group represented by formula:



n represents 0 or 1;

W^1 represents N, CH or O (provided that when W^1 is N or CH, n represents 1 and when W^1 is O, n represents 0);

W^2 represents N or CH;

Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group;

Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

R^2 represents (1) hydrogen atom or (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group;

R^3 represents (1) a C_{1-4} alkyl group having an optionally substituted basic group and optionally having an additional substituent, (2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent, (3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substitnent, or (4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent;

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the

group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, or (3) O;

Y represents a group represented by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, or –CH=CH-, which may optionally be substituted with a C_{1-6} alkyl group; and,

Z^9 represents hydrogen atom, O or S; and,

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

(wherein:

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino group, which groups may optionally be substituted with a substituent containing an optionally substituted cyclic group;

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S;

J^3 through J^6 each represents hydrogen atom or a C_{1-3} alkyl group;

Q^3 through Q^6 each represents a C_{1-4} alkyl group, which may

optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused cyclic group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7,

(7) an optionally substituted amino group,

(8) an optionally substituted guanidino group,

(9) an optionally substituted hydroxyl group,

(10) an optionally substituted carboxyl group,

(11) an optionally substituted carbamoyl group, and

(12) an optionally substituted sulfhydryl group,

or hydrogen atom;

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5 or J^6 and Q^6 may be combined together, or, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, or Y^3 and Q^6 may be combined together, to form a ring;

Y^1 through Y^3 each represents a group represented by formula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (wherein J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group); and,

Z^{10} represents hydrogen atom, O or S);

(4) a group represented by formula:

J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$-

(wherein:

J^1 and J^2, each has the same significance as described above;

J^7 through J^9 have the same significance as for J^3;

Q^7 through Q^9 have the same significance as for Q^3;

Y^2 and Y^3 each has the same significance as described above;

Z^{10} has the same significance as described above;

J^7 and Q^7, J^8 and Q^8 or J^9 and Q^9 may be combined together, or, J^2 and Q^7, Y^2 and Q^8 or Y^3 and Q^9 may be combined together, to form a ring);

(5) a group represented by formula:

J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$-

(wherein:

J^1 and J^2 have the same significance as described above represents;

J^{10} and J^{11} have the same significance as for J^3;

Q^{10} and Q^{11} have the same significance as for Q^3;

Y^3 has the same significance as described above;

Z^{10} has the same significance as described above; and,

J^{10} and Q^{10} or J^{11} and Q^{11} may be combined together, or J^2 and Q^{10} or Y^3 and Q^{11} may be combined together, to form a ring);

(6) a group represented by formula:

J^1-J^2-$C(J^{12})(Q^{12})C(=Z^{10})$-

(wherein;

J^1 and J^2 have the same significance as described above;

J^{12} has the same significance as for J^3;

Q^{12} has the same significance as for Q^3;

Z^{10} has the same significance as described above; and,

J^{12} and Q^{12} may be combined together, or J^2 and Q^{12} may be combined together, to form a ring); or,

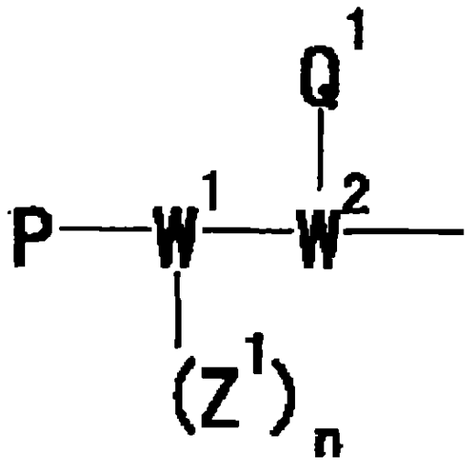
(7) a group represented by formula:

J^1-

(wherein:

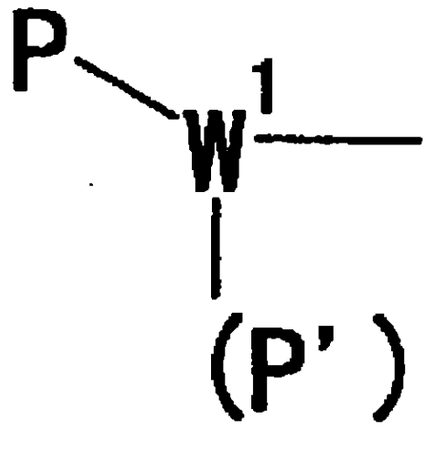
J^1 has the same significance as described above)] (provided that a peptide consisting of the amino acid sequence of 1-54, 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54, 41-54, 42-54, 43-54, 44-54, 45-54, 46-54, 47-54, 48-54 or 49-54 in the amino acid sequence represented by SEQ ID NO: 1 is excluded), or a salt thereof.

(2) The metastin derivative (II) according to (1), wherein V is a group represented by formula:



(wherein each symbol has the same significance as defined in (1)), or a salt thereof.

(3) The metastin derivative (II) according to (1), wherein V is a group represented by formula:



(wherein each symbol has the same significance as defined in (1)), or a salt thereof.

The present invention further provides the following features, and so on.

(4) A prodrug of the metastin derivative (II) according to (1) or a salt thereof.

(5) A pharmaceutical comprising the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(6) The pharmaceutical according to (5), which is an agent for suppressing cancer metastasis or an agent for suppressing cancer growth.

(7) The pharmaceutical according to (5), which is an agent for preventing or treating

cancer.

(8) The pharmaceutical according to (5), which is an agent for controlling pancreatic function.

(9) The pharmaceutical according to (5), which is an agent for preventing or treating acute or chronic pancreatitis or pancreatic cancer.

(10) The pharmaceutical according to (5), which is an agent for controlling placental function.

(11) The pharmaceutical according to (5), which is an agent for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

(12) The pharmaceutical according to (5), which is an agent for improving gonadal function.

(13) The pharmaceutical according to (5), which is an agent for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus.

(14) The pharmaceutical according to (5), which is an agent for inducing or stimulating ovulation.

(15) The pharmaceutical according to (5), which is a gonadotropic hormone secretagogue agent or a sex hormone secretagogue agent.

(16) The pharmaceutical according to (5), which is an agent for preventing or treating Alzheimer's disease or moderate cognitive impairment.

(17) A method for suppressing cancer metastasis or cancer growth, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(18) A method for preventing or treating cancer, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(19) A method for controlling pancreatic function, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(20) A method for preventing or treating acute or chronic pancreatitis or pancreatic cancer, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(21) A method for controlling placental function, which comprises administering to a

mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(22) A method for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(23) A method for improving gonadal function, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(24) A method for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(25) A method for inducing or stimulating ovulation, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(26) A method for promoting gonadotropic hormone secretion or promoting sex hormone secretion, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(27) A method for preventing or treating Alzheimer's disease or moderate cognitive impairment, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(28) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for suppressing cancer metastasis or an agent for suppressing cancer growth.

(29) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating cancer.

(30) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for controlling pancreatic function.

(31) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating acute or chronic pancreatitis or pancreatic cancer.

(32) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for controlling placental function.

(33) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

(34) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for improving gonadal function.

(35) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus.

(36) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for inducing or stimulating ovulation.

(37) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture a gonadotropic hormone secretagogue agent or a sex hormone secretagogue agent.

(38) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating Alzheimer's disease or moderate cognitive impairment.

(39) A pancreatic glucagon secretagogue agent comprising the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(40) An agent for promoting urine formation comprising the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(41) An agent for preventing or treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity, comprising the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(42) A method for promoting pancreatic glucagon secretion, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(43) A method for promoting urine formation, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(44) A method for preventing or treating obesity, hyperlipemia, type II diabetes

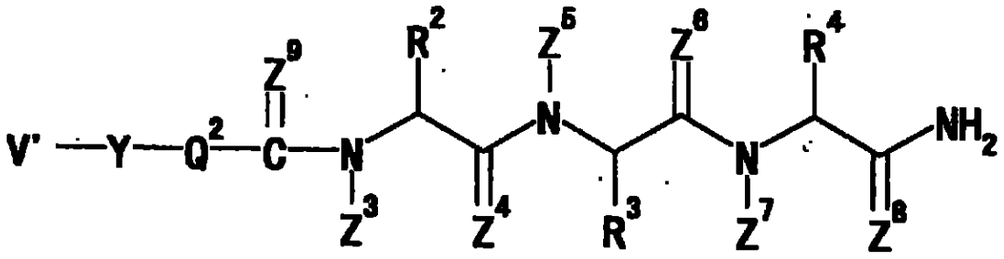
mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(45) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture a pancreatic glucagon secretagogue agent.

(46) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for promoting urine formation.

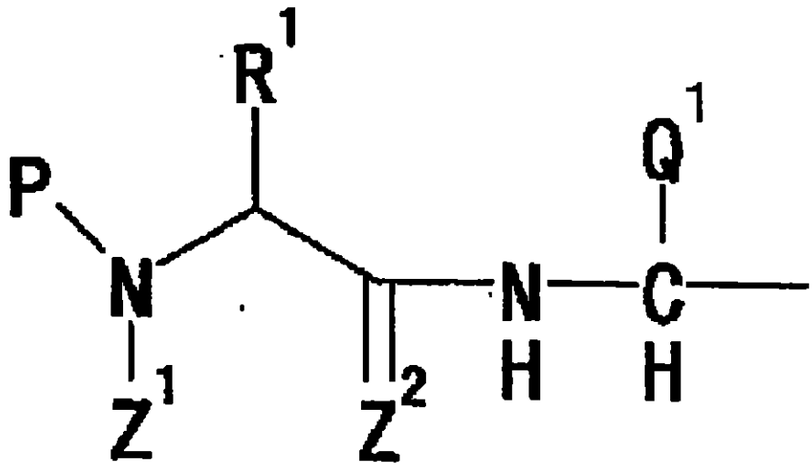
(47) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity.

(48) An agent for suppressing gonadotropic hormone secretion or an agent for suppressing sex hormone secretion comprising the metastin derivative (III) represented by formula:

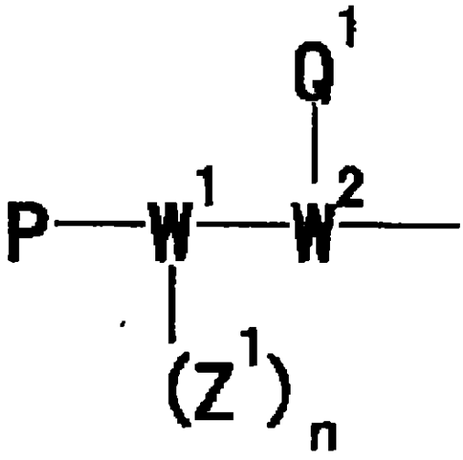


[wherein:

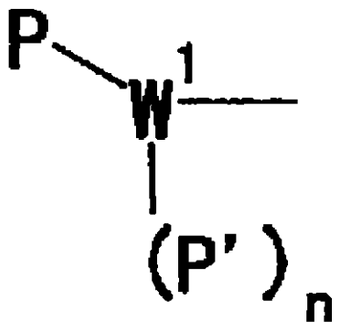
V' represents a group represented by formula:



a group represented by formula:



or a group represented by formula:



n represents 0 or 1;

W^1 represents N, CH or O (provided that W^1 is N or CH, n represents 1, and when W^1 is O, n represents 0);

W^2 represents N or CH;

Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group;

Z^2, Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

R^1 represents (1) hydrogen atom, (2) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group, (3) a cyclic or linear C_{1-10} alkyl group or (4) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (5) an optionally substituted aromatic cyclic group;

R^2 represents (1) hydrogen atom or (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group;

R^3 represents (1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent, (2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent, (3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent, or (4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent;

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having

carbon atoms not greater than 7;

Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, or (3) O; Y represents a group represented by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, or –CH=CH-, which may optionally be substituted with a C_{1-6} alkyl group; and,

Z^9 represents hydrogen atom, O or S; and,

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

(wherein:

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino group, which groups may optionally be substituted with a substituent

containing an optionally substituted cyclic group;

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S;

J^3 through J^6 each represents hydrogen atom or a C_{1-3} alkyl group;

Q^3 through Q^6 each represents a C_{1-4} alkyl group, which may optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused cyclic group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7,

(7) an optionally substituted amino group,

(8) an optionally substituted guanidino group,

(9) an optionally substituted hydroxyl group,

(10) an optionally substituted carboxyl group,

(11) an optionally substituted carbamoyl group, and

(12) an optionally substituted sulfhydryl group,

or hydrogen atom;

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5 or J^6 and Q^6 may be combined together, or, Z^1 and R^1, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, or Y^3 and Q^6 may be combined together, to form a ring;

Y^1 through Y^3 each represents a group represented by formula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (wherein J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group); and,

Z^{10} represents hydrogen atom, O or S);

(4) a group represented by formula:

J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$-

(wherein:

J^1 and J^2, each has the same significance as described above;

J^7 through J^9 have the same significance as for J^3;

Q^7 through Q^9 have the same significance as for Q^3;

Y^2 and Y^3 each has the same significance as described above;

Z^{10} has the same significance as described above;

J^7 and Q^7, J^8 and Q^8 or J^9 and Q^9 may be combined together, or, J^2 and Q^7, Y^2 and Q^8 or Y^3 and Q^9 may be combined together, to form a ring);

(5) a group represented by formula:

J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$-

(wherein:

J^1 and J^2 have the same significance as described above represents;

J^{10} and J^{11} have the same significance as for J^3;

Q^{10} and Q^{11} have the same significance as for Q^3;

Y^3 has the same significance as described above;

Z^{10} has the same significance as described above; and,

J^{10} and Q^{10} or J^{11} and Q^{11} may be combined together, or J^2 and Q^{10} or Y^3 and Q^{11} may be combined together, to form a ring);

(6) a group represented by formula:

J^1-J^2-$C(J^{12})(Q^{12})C(=Z^{10})$-

(wherein;

J^1 and J^2 have the same significance as described above;

J^{12} has the same significance as for J^3;

Q^{12} has the same significance as for Q^3;

Z^{10} has the same significance as described above; and

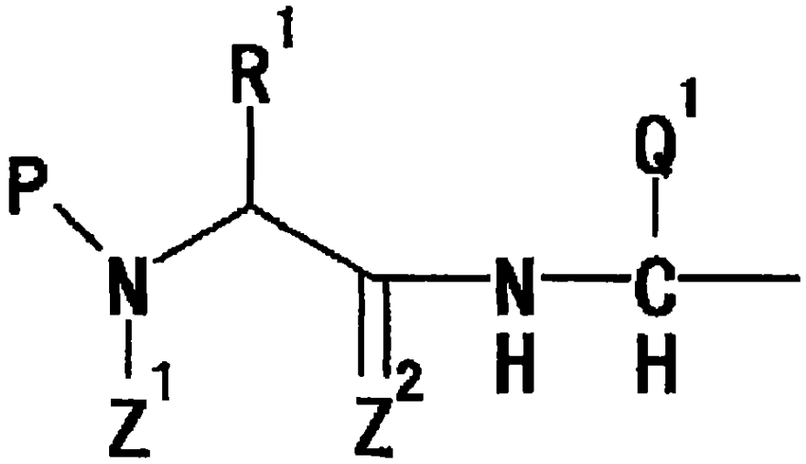
J^{12} and Q^{12} may be combined together, or J^2 and Q^{12} may be combined together, to form a ring); or,

(7) a group represented by formula:

J^1- (wherein J^1 has the same significance as described above)] or a salt thereof, or a prodrug thereof.

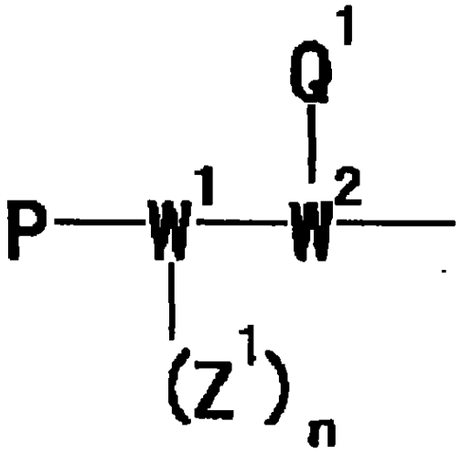
(49) The agent according to (48), wherein the metastin derivative (III) is the metastin derivative (II) according to (1).

(50) The agent according to (48), wherein V' is a group represented by formula:



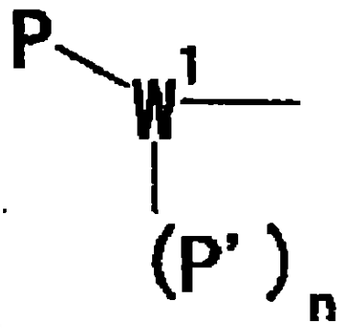
(wherein each symbol has the same significance as described in (48)).

(51) The agent according to (48), wherein V' is a group represented by formula:



(wherein each symbol has the same significance as described in (48)).

(52) The agent according to (48), wherein V' is a group represented by formula:



(wherein each symbol has the same significance as described in claim 48).

(53) The agent according to (48), wherein the metastin derivative (III) is:

(1) D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 141),

(2) D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 174),

(3) 3-(3-Indolyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 260),

(4) 3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 269),

(5) 2-(indol-3-yl)ethylcarbamoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 279),

(6) D-Tyr-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 286),

(7) D-Tyr-Asn-Trp-Asn-Ser-PheΨ(CSNH)Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 296),

(8)TyrΨ(CH_2NH)Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 300),

(9) D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 303),

(10) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 305),

(11) D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F) -NH_2 (Compound No. 318),

(12) D-Tyr-Asn-Trp-Asn-Ser-PheΨ(NHCO)Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 319),

(13) 3-(3-Pyridyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound

No. 322),

(14) 4-Imidazoleacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 323),

(15) GuAmb-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 332),

(16) GuAmb-Phe-Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 333),

(17) GuAmb-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 334),

(18) 3-(3-Indolyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 339),

(19) Benzoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 341),

(20) Indole-3-acetyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 345),

(21) Ac-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 346),

(22) Benzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 353),

(23) 3-(3-Indolyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 354),

(24) Ac-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 358),

(25) 2-(Indol-3-yl)ethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 364),

(26) 2-(Indol-3-yl)ethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 369),

(27) (2S)-2-acethoxy-3-phenylpropionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 373),

(28) (2S)-2-(3-Indolylprpionyloxy)-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 379),

(29) (2S)-2-Benzoyloxy-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 380),

(30) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 385),

(31) 3-(3-Pyridyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 386),

(32) Dibenzylcarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 393),

(33) Benzylphenethylcarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 417),

(34) Benzoyl-PheΨ(NHCO)Gly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 423),

(35) Benzoyl-AzaPhe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 431),

(36) 3-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 432),

(37) 2-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 435),

(38) 4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 436),

(39) Propionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 437),

(40) Isobutyryl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 438),

(41) Cyclohexanecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 439),

(42) Phenylacetyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 440),

(43) Benzoyl-Pya(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 441),

(44) 6-Methylnicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 445),

(45) Pyrazinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 446),

(46) Cyclopropanecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 447),

(47) Trifluoroacetyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 448),

(48) Benzoyl-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 449),

(49) Cyclopropanecarbonyl-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 451),

(50) (R)-3-hydroxy-2-methylpropionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 452),

(51) 2-Hydroxyisobutyryl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 453),

(52) 3-Furancarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 454),

(53) Pyrrole-2-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 455),

(54) 4-Imidazolecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 459),

(55) 6-Hydroxynicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 462),

(56) 6-Chloronicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 463),

(57) 6-(Trifluoromethyl)nicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 464),

(58) Dimethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 467),

(59) 1-Azetidinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 468),

(60) 4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 471),

(61) 4-Aminobenzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 472),

(62) 4-Aminomethylbenzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 473),

(63) Pyrrole-3-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 474),

(64) Pyrimidine-4-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 475),

(65) Pyrimidine-2-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 479),

(66) Pyridazine-4-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 480),

(67) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Trp-NH_2 (Compound No. 481),

(68) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Lys-Phe-NH_2 (Compound No. 487),

(69) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Phe-NH_2 (Compound No. 488),

(70) D-Tyr-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 490),

(71) D-Tyr-D-Pya(4)-Asn-Trp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 491),

(72) D-Tyr-D-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 492),

(73) D-Tyr-D-Pya(4)-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 493),

(74) D-Tyr-D-Pya(4)-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 496),

(75) D-Tyr-D-Pya(4)-Asn-Ser-Cha-Ala-Leu-Arg(Me)-Trp-NH_2 (Compound No. 497),

(76) D-Tyr-D-Pya(4)-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 498),

(77) 3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 499),

(78) 3-Phenylpropionyl-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 500),

(79) D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 501),

(80) D-Tyr-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 502),

(81) D-Tyr-D-Trp-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 503),

(82)6-Aminocaproyl-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 504),

(83) 3-Phenylpropionyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 505),

(84) 3-Phenylpropionyl-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 506),

(85) 3-Phenylpropionyl-Asn-Ser-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 507),

(86) 3-Phenylpropionyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 508),

(87) Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 509),

(88)Ac-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 510),

(89) D-Tyr-D-Trp-Ala-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 511),

(90) D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 512),

(91) D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 513),

(92) D-Tyr-D-Phe-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 514),
(93) D-Tyr-D-Pya(4)-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 515),
(94) des(1)-Ac-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10 (Compound No. 516),
(95) des(1-3)-3-Phenylpropionyl-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 517),
(96)des(1-3)-3-Phenylpropionyl-[Cha6,Arg(Me)9,Trp10]MS10 (Compound No. 518),
(97) des(1-3)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 519),
(98) des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10 (Compound No. 521),
(99) des(1-3)-Benzoyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 522),
(100) des(1-3)-Benzoyl-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 523),
(101) des(1-3)-3-Phenylpropionyl-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 524),
(102) des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 527),
(103) des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 528),
(104) des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 529),
(105) des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 530),
(106) des(1-3)-3-Phenylpropionyl-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 531),
(107) des(1-3)-3-Phenylpropionyl-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 532),
(108) des(1-3)-3-Phenylpropionyl-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 533),
(109) des(1-3)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 534),
(110) des(1-3)-2-Naphthoyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 535),
(111) [Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 536),
(112) Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 537),

(113) Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 538),

(114) des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 539),

(115) des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 540),

(116) D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 541),

(117) D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 542),

(118) des(1-3)-Benzoyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 545),

(119) des(1-3)-3-Phenylpropionyl-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 546),

(120) des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 547),

(121) des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10 (Compound No. 548),

(122) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 550),

(123) Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 551),

(124) D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 552),

(125) D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 553),

(126) D-Arg-[β-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 554),

(127) D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 555),

(128) D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 556),

(129)
D-Arg-D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 557),

(130) des(1)-Ac-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 558),

(131) des(1-2)-3-(4-Hydroxyphenyl)propionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 559),

(132) D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 561),

(133) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 562),

(134) des(1)-Ac-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 563),

(135) des(1)-Ac-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 564),

(136) des(1)-Benzoyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 565),

(137) des(1)-Cyclopropanecarbonyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 566),

(138) des(1)-Butyryl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 567),

(139) Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 568),

(140) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,6Ψ7,CH2NH,Arg(Me)9,Trp10]MS10 (Compound No. 569),

(141) des(1)-Me-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 570),

(142) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10 (Compound No. 571),

(143) des(1)-[D-Trp2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 572),

(144) des(1)-Ac-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 573),

(145) des(1)-Ac-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 576),

(146) des(1)-Ac-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 577),

(147) des(1)-Ac-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 578),

(148) des(1)-Ac-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 579),

(149) des(1)-Ac-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 580),

(150) des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 584),

(151) des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 585),

(152) des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 586),

(153) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10 (Compound No. 589),

(154) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi10]MS10 (Compound No. 590),

(155) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10 (Compound No. 591),

(156) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10 (Compound No. 592),

(157) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10 (Compound No. 594),

(158) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Cha10]MS10 (Compound No. 595),

(159) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Leu10]MS10 (Compound No. 596),

(160) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 597),

(161) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10 (Compound No. 598),

(162) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10 (Compound No. 599),

(163) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10 (Compound No. 600),

(164) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10 (Compound No. 601),

(165) des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 Compound No. 602),

(166) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 603),

(167) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10 (Compound No. 604),

(168) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10 (Compound No. 605),

(169) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10 (Compound No. 607),

(170) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10 (Compound No. 608),

(171) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10 (Compound No. 609),

(172) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10 (Compound No. 610),

(173) des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 611),

(174) des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 612),

(175) des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 613),

(176) des(1)-Amidino-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 614),

(177) des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 615),

(178) des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 616),

(179) des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 617),

(180) des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 618),

(181) des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 619),

(182) des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 620),

(183) des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 621)

(184) des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 622),

(185) des(1)-Ac-[D-Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 623),

(186) des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 624),

(187) des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 625),

(188) des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 626),

(189) des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 627),

(190) des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 628),

(191) des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 629),

(192) des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 630),

(193) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 631),

(194) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 632),

(195) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 633),

(196) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 634),

(197) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 635),

(198) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,NMePhe6,AzaGly7,Arg(Me)9,Trp10]MS10

(Compound No. 636),

(199) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 637),

(200) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 638),

(201) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10 (Compound No. 639),

(202) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10 (Compound No. 641),

(203) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10 (Compound No. 642),

(204) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10 (Compound No. 643),

(205) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10 (Compound No. 644),

(206) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10 (Compound No. 645),

(207) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10 (Compound No. 646),

(208) des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 647),

(209) [Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 648),

(210) Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 649),

(211) [D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 650),

(212) Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 651),

(213) pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 652),

(214) des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 653),

(215) des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound

No. 654),

(216) des(1)-Ac-[D-Tyr2,D-Trp3,NMeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 655),

(217) des(1)-Ac-[D-Tyr2,D-Trp3,NMeSer5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 656),

(218) des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 657),

(219) des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 658),

(220) des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 659),

(221) des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 660),

(222) des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 661),

(223) des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 662),

(224) des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 663),

(225) des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 664),

(226) des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 665),

(227) des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 666),

(228) des(1-2)-Hexanoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 667),

(229) des(1-2)-Cyclohexanecarbonyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 668),

(230) des(1-2)-Benzoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 669),

(231) des(1-2)-3-Pyridinepropionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 670),

(232) des(1-2)-Adipoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 671),

(233) des(1)-Ac-[D-Tyr2,NMeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound

No. 672),

(234) des(1-2)-6-Aminocaproyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 674),

(235) [D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 675)

(236) Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 676)

(237) Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10 (Compound No. 677)

(238) Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10 (Compound No. 678)

(239) des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 679)

(240) des(1-2)-Glycoloyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (CompoundNo. 680)

(241) des(1)-Glycoloyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 681)

(242) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10 (Compound No. 682)

(243) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10 (Compound No. 685)

(244) des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 686)

(245) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10 (Compound No. 688)

(246) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10 (CompoundNo. 689)

(247) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 691)

(248) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 692)

(249) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 693)

(250) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 694)

(251) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10

(Compound No. 695)

(252) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 696)

(253) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10 (Compound No. 698)

(254) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10 (Compound No. 699)

(255) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,,Arg(Me)9,Trp10]MS10 (Compound No. 700)

(256) des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10 (CompoundNo. 701)

(257) des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 702)

(258) des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NMe2)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 703).

(54) The agent according to (48) to (53), which is a down-regulating agent for gonadotropic hormone or sex hormone.

(55) The agent according to (48) to (53), which is a down-regulating agent for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9.

(56) The agent according to (48) to (55), which is an agent for preventing or treating hormone-dependent cancer.

(57) A method for suppressing gonadotropic hormone secretion or suppressing sex hormone secretion, which comprises administering to a mammal an effective dose of the metastin derivative (III) according to (48) or a salt thereof, or a prodrug thereof.

(58) A method for down regulating gonadotropic hormone or sex hormone, which comprises administering to a mammal an effective dose of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof.

(59) A method for down regulating human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9, which comprises administering to a mammal an effective dose of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof.

(60) A method for preventing or treating hormone-dependent cancer, which comprises administering to a mammal an effective dose of the metastin derivative according to

(48) or a salt thereof, or a prodrug thereof.

(61) Use of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof to manufacture an agent for suppressing gonadotropic hormone secretion or an agent for suppressing sex hormone secretion.

(62) Use of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof to manufacture a down-regulating agent for gonadotropic hormone or sex hormone.

(63) Use of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof to manufacture a down-regulating agent for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9.

(64) Use of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating hormone-dependent cancer.

(65) A metastin derivative represented by formula:

XX0-XX2-XX3-XX4-XX5-XX6-AzaGly-XX8-XX9-XX10-NH_2

(wherein :

XX0 represents formyl, C_{1-6} alkanoyl, cyclopropanecarbonyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 4-(D-arginylamino)butyryl, 3-(4-Hydroxyphenyl)propionyl, glycyl, tyrosyl, acetylglycyl, acetyltyrosyl, D-tyrosyl, acetyl-D-tyrosyl, pyroglutamyl, 3-(pyridine-3-yl)propionyl, adipoyl or 6-aminocaproyl;

XX2 represents Tyr, D-Tyr, D-Ala, D-Leu, D-Phe, D-Lys, D-Trp or bond arm;

XX3 represents Trp, Pro, 4-pyridylalanine, Tic, D-Trp, D-Ala, D-Leu, D-Phe, D-Lys, D-Glu, D-2-pyridylalanine, D-3-pyridylalanine or D-4-pyridylalanine;

XX4 represents Asn, 2-amino-3-ureidopropion acid, N^{β}-formyldiaminopropionic acid or N^{β}-acetyldiaminopropionic acid;

XX5 represents Ser, Thr or Val;

XX6 represents Phe, Tyr, Trp, Tyr(Me), Thi, Nal(2), Cha, 4- pyridylalanine or 4-fluorophenylalanine;

AzaGly represents azaglycine;

XX8 represents Leu, Nva or Val;

XX9 represents Arg, Orn, Arg(Me) or Arg(symMe2);

XX10 represents Phe, Trp, 2-naphthylalanine, 2-thienylalanine, tyrosine or 4-fluorophenylalanine), or a salt thereof.

(66) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No.

305),

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 385),

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 501),

Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 509),

D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 512),

Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 516),

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 540),

D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 541),

Benzoyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 545),

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-PheΨ(CSNH)NH_2(Compound No. 548),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 552),

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 553),

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 555),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558),

3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 559),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562),

Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 564),

Cyclopropanecarbonyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 566),

Butyryl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 567),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571),

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579),

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 580),

Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 584),

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2 (Compound No. 590),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2 (Compound No. 591),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2 (Compound No. 599),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2 (Compound No. 600),

Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 602),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(symMe2)-Trp-NH_2 (Compound No. 608),

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612),

Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613),

Ac-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 615),

Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 616),

Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 617),

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618),

Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 621),

Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 623),

Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 625),

Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 626),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627),

Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 629),

Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 630),

Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 635),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2 (Compound No. 642),

Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 648),

Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 649),

D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 650),

Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 651),

pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 652),

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 657),

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658),

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660),

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 662),

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663),

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 666),

Hexanoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 667),

3-Pyridinepropionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 670),

Adipoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 671),

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 672),

6-Aminocaproyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 674), or salts thereof.

(67) Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound

No. 552),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558),

3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 559),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571),

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579),

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592),

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612),

Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613),

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638),

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658),

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660),

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663), or salts thereof.

(68) The agent according to (48) above, which is an agent for potentiating immunity (prophylactic agent for infection after bone-marrow transplant, an agent for potentiating immunity intended for cancer).

(69) The agent according to (48) above, which is a prophylactic/therapeutic agent for bulbospinal muscular atrophy.

(70) The agent according to (48) above, which is a prophylactic/therapeutic agent for protecting ovary.

(71) The agent according to (48) above, which is a prophylactic/therapeutic agent for benign prostate hypertrophy (BPH).

(72) The agent according to (48) above, which is a prophylactic/therapeutic agent for gender identity disorder.

(73) The agent according to (48) above, which is a prophylactic/therapeutic agent for in vitro fertilization (IVF).

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows evaluation of the chemotaxis inhibition activity of Compound Nos. 322, 305, 303, 286, 232 and 141 using hOT7T175-expressed CHO cells. On the abscissa, FBS- designates the absence of FBS, FBS+ designates the presence of FBS, 322 designates the addition of Compound No. 322, 305 designates the addition of Compound No. 305, 303 designates the addition of Compound No. 303, 286 designates the addition of Compound No. 286, 232 designates the addition of Compound No. 232, 141 designates the addition of Compound No. 141, (1-54) designates the addition of metastin (1-54), and (45-54) designates the addition of metastin45-54. The ordinate denotes a relative activity when the chemotactic activity in the presence of FBS is made 100%.

FIG. 2 shows evaluation of the tumor growth inhibition activity of Compound No. 322 and Metastin (1-54) using tumor-bearing mice with human colonic carcinoma-derived cell line SW620, wherein the value indicates (mean value) ± (standard error). Symbols open diamond, open circle, closed circle and closed square designate the results obtained when Vehicle (distilled water), Compound No. 322 (0.1 mM), Compound No. 322 (1 mM), and Metastin (Metastin 1-54) were added, respectively. The abscissa denotes the number of days after injection. The bar on the abscissa designates a dosing period. The ordinate denotes a tumor size (mm^3).

FIG. 3 shows evaluation of the tumor growth inhibition activity of Compound No. 305 and Metastin (1-54) using tumor-bearing mice with human colonic carcinoma-derived cell line SW620, wherein the value indicates (mean value) ± (standard error). Symbols open diamond, open circle, closed circle and closed square designate the results obtained when Vehicle (distilled water), Compound No. 305 (0.1 mM), Compound No. 305 (1 mM), and Metastin (Metastin 1-54) were added, respectively. The abscissa denotes the number of days after injection. The bar on the

abscissa designates a dosing period. The ordinate denotes a tumor size (mm^3).

FIG. 4 shows the results obtained by monitoring changes in blood glucose level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle, closed triangle, closed circle and closed diamond designate blood glucose level in the saline group, the 17 nmol/kg metastin group, the 80 nmol/kg metastin group and the 170 nmol/kg metastin group, respectively. The value indicates (mean ± SE) (n = 5). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group and symbol ** designates that the P-value is 0.01 or less, when compared to the saline group.

FIG. 5 shows the results obtained by monitoring changes in blood glucagon level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate blood glucagon level in the saline group and the 80 nmol/kg metastin group, respectively. The value indicates (mean ± SE) (n = 6-9). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group and symbol ** designates that the P-value is 0.01 or less, when compared to the saline group.

FIG. 6 shows the results obtained by monitoring changes in blood insulin level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate blood insulin level in the saline group and the 80 nmol/kg metastin group, respectively. The value indicates (mean ± SE) (n = 6-9).

FIG. 7 shows the results obtained by monitoring changes in blood corticosterone level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate blood corticosterone level in the saline group and the 80 nmol/kg metastin group, respectively. The value indicates (mean ± SE) (n = 4-5).

FIG. 8 shows the results obtained by monitoring changes in thyroid hormone (T3) level in blood when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate thyroid hormone (T3) level in blood in the saline group and the 80 nmol/kg metastin group, respectively. The value indicates (mean ± SE) (n = 4-5).

FIG. 9 shows the results obtained by monitoring changes in blood glucose level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate blood glucose level in the saline group

and the 80 nmol/kg metastin group, respectively. The value indicates (mean ± SE) (n = 6-9). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group

FIG. 10 shows the results obtained by monitoring changes in blood glucose level when a metastin derivative was intravenously injected into rats under no anesthesia. In the figure, symbols open circle, closed circle and closed triangle designate blood glucose level in the saline group, the 80 nmol/kg KiSS1-305 group and the 80 nmol/kg metastin group, respectively. The value indicates (mean ± SE) (n = 5). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group and symbol ** designates that the P-value is 0.01 or less, when compared to the saline group.

FIG. 11 shows the results obtained by monitoring changes in blood glucagon level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle, closed circle and closed triangle designate blood glucagon level in the saline group and the 80 nmol/kg KiSS1-305 (Compound No. 305) group, the 80 nmol/kg KiSS1-322 (Compound No. 322) group, respectively. The value indicates (mean ± SE) (n = 5). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group.

FIG. 12 shows the level of estradiol contained in the rat plasma. In the figure, the ordinate and the abscissa denote the estradiol level and the drug receiving groups, respectively.

FIG. 13 shows the level of progesterone contained in the rat plasma. In the figure, the ordinate and the abscissa denote the estradiol level and the drug receiving groups, respectively.

FIG. 14 shows changes in the blood FSH level in immature rat by metastin injection.

FIG. 15 shows changes in the blood LH level in immature rat by metastin injection.

FIG. 16 shows changes in the blood progesterone level in immature rat by metastin injection.

FIG. 17 shows changes in the blood FSH level in rat by metastin injection.

FIG. 18 shows changes in the blood LH level in rat by metastin injection.

FIG. 19 shows changes in the blood testosterone level in rat by metastin injection.

FIG. 20 shows the number of oocytes per individual rat in each group measured in TEST EXAMPLE 13. In the figure, symbol closed diamond designates data for per individual rat and symbol closed square designates a mean value in each group.

FIG. 21 shows the blood estradiol level in each dosing group measured in TEST EXAMPLE 13. In the figure, symbol closed triangle designates data for per individual rat and symbol closed square designates a mean value in each group.

FIG. 22 shows the blood progesterone level in each group measured in TEST EXAMPLE 13. In the figure, symbol closed triangle designates data for per individual rat and symbol closed square designates a mean value in each group.

BEST MODE OF EMBODIMENTS OF THE INVENTION

In the formulae described above, n represents 0 or 1; W^1 represents N, CH or O (provided that W^1 is N or CH, n represents 1, and when W^1 is O, n represents 0); W^2 represents N or CH; Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group; and Z^2, Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

wherein, when Z^2, Z^4, Z^6 or Z^8 represents hydrogen atom, a structure of the moiety represented by $>C=Z^2$, $>C=Z^4$, $>C=Z^6$ or $>C=Z^8$ each indicates a structure of $>CH_2$.

The C_{1-3} alkyl group used includes methyl group, ethyl group, propyl group and isopropyl group.

W^1 is preferably N and W^2 is preferably CH.

Preferred combinations of Z^1 through Z^8 further include the cases that Z^1 and Z^3 represent hydrogen atom, each of Z^5 and Z^7 represents hydrogen atom or a C_{1-3} alkyl group and each of Z^2, Z^4, Z^6 and Z^8 represents O or S.

More preferably, the combinations of Z^1 through Z^8 include:

(a) the case where Z^1 is hydrogen atom, Z^3 is hydrogen atom, Z^5 is hydrogen atom and Z^7 is hydrogen atom, and Z^2 is O, Z^4 is O, Z^6 is O and Z^8 is O;

(b) the case where Z^1 is hydrogen atom, Z^3 is hydrogen atom, Z^5 is hydrogen atom and Z^7 is hydrogen atom, and Z^2 is O, Z^4 is O, Z^6 is O and Z^8 is S;

(c) the case where Z^1 and Z^3 are hydrogen atom and Z^5 is hydrogen atom, Z^7 is methyl group and Z^2 is O, and Z^4 is O, Z^6 is O and Z^8 is O; etc. Among these cases, (a) and (b) are preferred.

R^1 represents (1) hydrogen atom, (2) a C_{1-8} alkyl group optionally substituted

with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group, (3) a cyclic or linear C_{1-10} alkyl group or (4) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (5) an optionally substituted aromatic cyclic group. Inter alia, preferred R^1 includes (1) hydrogen atom or (2) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group, more preferably includes (1) hydrogen atom or (2) a C_{1-8} alkyl group substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group.

The "C_{1-8} alkyl group" used includes, for example, a linear C_{1-8} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc., and a cyclic C_{3-8} alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. C_{1-3} alkyl groups such as methyl, ethyl, etc. are particularly preferred.

The "optionally substituted carbamoyl group" used includes, for example, carbamoyl, a mono-C_{1-6} alkylcarbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), a di-C_{1-6} alkylcarbamoyl group (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), a mono- or di-C_{6-14} arylcarbamoyl group (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), a mono- or di-5- or 7-membered heterocyclic carbamoyl group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.) and the like.

The "optionally substituted hydroxyl group" used includes, for example, hydroxy group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-14} aryloxy group, an optionally substituted C_{7-16} aralkyloxy group, etc. The "optionally substituted C_{1-6} alkoxy group," "optionally substituted C_{6-14} aryloxy group" and "optionally substituted C_{7-16} aralkyloxy group" used are those of the "optionally substituted C_{1-6} alkoxy group," "optionally substituted C_{6-14} aryloxy group" and "optionally substituted C_{7-16} aralkyloxy group" in Substituent group A, which will be later described.

The "aromatic cyclic group" in "optionally substituted aromatic cyclic group" includes, for example, an aromatic hydrocarbon group, aromatic heterocyclic group, an aromatic fused cyclic group, an aromatic fused heterocyclic group, etc.

The "aromatic hydrocarbon group" used includes, for example, a C_{6-14} aryl group such as phenyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, cyclooctatetraenyl, etc.

The "aromatic heterocyclic group" used includes, for example, a 5- to 14-membered, preferably 5- to 10-membered, more preferably 5- or 6-membered aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specific examples are thienyl (e.g., 2-thienyl, 3-thienyl), furyl (e.g., 2-furyl, 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), isothiazolyl (e.g., 3-isothiazolyl), isooxazolyl (e.g., 3-isooxazolyl), etc.

The "aromatic fused cyclic group" used includes a C_{8-14} aromatic fused cyclic group such as naphthyl (e.g., 1-naphthyl, 2-naphthyl), anthryl (e.g., 2-anthryl, 9-anthryl) and the like.

The "aromatic fused heterocyclic group" used includes, for example, a 5- to 14-membered (preferably 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms, or a monovalent group formed by removing one optional hydrogen atom from a 7- to 10-membered aromatic bridged-hetero ring in 5- to 14-membered (preferably 5- to 10-membered) ring containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specific examples of these groups used are quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), 2-benzothiazolyl, benzo[b]thienyl, (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl), benzo[b]furanyl (e.g., 2-benzo[b]furanyl, 3-benzo[b]furanyl) and the like.

The "substituent" used for the "aromatic cyclic group" includes a substituent selected from the Substituent group A, which will be later described.

For R^1, there are used hydrogen atom, carbamoylmethyl, 2-carbamoylethyl, hydroxymethyl, 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thienylmethyl, 3-thienylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-indolemethyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclohexylmethyl, phenyl, acetoxymethyl, methoxymethyl, etc., preferably, hydroxymethyl, 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 3-indolemethyl, methyl, isobutyl, etc., and more preferably, hydroxymethyl, 1-hydroxyethyl, etc.

R^2 represents (1) hydrogen atom, (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group. Among them, preferred are (1) hydrogen atom, (2) a cyclic or linear C_{1-10} alkyl group, or (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group. In particular, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group is preferred.

The cyclic C_{1-10} alkyl group used includes, for example, a C_{3-8} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

Examples of the linear C_{1-10} alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonanyl, decanyl, etc.

The C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group used includes, for example, a C_{3-7} cycloalkyl-C_{1-3} alkyl group such as cyclopentylmethyl, cyclohexylmethyl, etc.

Examples of R^2 include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclohexylmethyl, benzyl, hydroxymethyl, 2-carbamoylethyl, tert-pentyl, etc.; among them, preferred are methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc., more preferably, propyl, isopropyl, isobutyl, etc.

R^3 represents:

(1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent,

(2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent,

(3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an

additional substituent, or,

(4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent.

The "optionally substituted basic group" used includes, for example, (1) a guanidino group optionally having 1 or 2 substituents from a C_{1-6} alkyl, a C_{1-6} acyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, acetyl, propionyl, etc.), etc., (2) an amino group optionally having 1 to 3 substituents from a C_{1-6} alkyl, a C_{1-6} acyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, acetyl, propionyl, etc.), etc., (3) a C_{1-6} alkylcarbonylamino group (e.g., acetamido) optionally substituted with a guanidino group optionally having 1 or 2 substituents from a C_{1-6} alkyl, a C_{1-6} acyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, acetyl, propionyl, etc.), etc., (4) a C_{1-6} alkylcarbonylamino group (e.g., acetamido) optionally substituted with an amino group optionally having 1 to 3 substituents from a C_{1-6} alkyl, a C_{1-6} acyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, acetyl, propionyl, etc.), etc. Among them, preferred are guanidino, N-methylguanidino, N,N-dimethylguanidino, N,N'-dimethylguanidino, N-ethylguanidino, N-acetylguanidino, amino, N-methylamino, N,N-dimethylamino, aminoacetamido, guanidinoacetamido, amidino, etc.

The "additional substituent" other than the "optionally substituted basic group" used includes a substituent selected from the Substituent group A later described.

Examples of the "C_{1-8} alkyl group" used are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

The "aralkyl group" used includes, for example, a C_{7-16} aralkyl group such as benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 2-biphenylylmethyl, 3-biphenylylmethyl, 4-biphenylylmethyl, etc.

The "non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7" used includes, for example, a C_{3-7} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "non-aromatic heterocyclic group of carbon atoms not greater than 7" used includes, for example, a 5- to 10-membered non-aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 1 to 7 carbon atoms, etc. Specifically examples used are pyrrolidinyl (e.g.,

1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl (e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholino, thiomorpholino, etc.

Examples of the "C_{1-4} alkyl group" used include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.

For R^3, there are used, for example, (1) 3-guanidinopropyl, 3-(N-methylguanidino)propyl, 3-(N,N-dimethylguanidino)propyl, 3-(N,N'-dimethylguanidino)propyl, 3-(N-ethylguanidino)propyl, 3-(N-propylguanidino)propyl, 3-(N-acetylguanidino)propyl, 4-guanidinobutyl, 4-(N-methylguanidino)butyl, 2-guanidinoethyl, 2-(N-methylguanidino)ethyl, 4-aminobutyl, 4-(N-methylamino)butyl, 4-(N,N-dimethylamino)butyl, 3-aminopropyl, 2-aminoethyl, aminomethyl, aminoacetamidomethyl, guanidinoacetamidomethyl, 2-(guanidinocarbonyl)ethyl, (2) 4-guanidinobenzyl, 4-aminobenzyl, (3) 4-guanidinocyclohexylmethyl, 4-aminocyclohexylmethyl, (4) 1-amidinopiperidin-4-ylmethyl, 4-pyridylmethyl, etc., preferably, 3-guanidinopropyl, 3-(N-methylguanidino)propyl, 3-(N,N-dimethylguanidino)propyl, 3-(N,N'-dimethylguanidino)propyl, 3-(N-ethylguanidino)propyl, 3-(N-propylguanidino)propyl, 3-(N-acetylguanidino)propyl, 4-guanidinobutyl, 4-(N-methylguanidino)butyl, 2-guanidinoethyl, 2-(N-methylguanidino)ethyl, 4-aminobutyl, 4-(N-methylamino)butyl, 4-(N,N-dimethylamino)butyl, 3-aminopropyl, 2-aminoethyl, 4-aminobenzyl, aminoacetamidomethyl, guanidinoacetamidomethyl, etc., and more preferably, 3-guanidinopropyl, 3-(N-methylguanidino)propyl, 3-(N,N-dimethylguanidino)propyl, 3-(N,N'-dimethylguanidino)propyl, 3-(N-ethylguanidino)propyl, 3-(N-acetylguanidino)propyl, 4-guanidinobutyl, 4-(N-methylguanidino)butyl, 2-guanidinoethyl, 4-aminobutyl, etc.

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group

consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7; and preferably, a C_{1-4} alkyl group substituted with a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7; and,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7.

Examples of the "C_{1-4} alkyl group" used include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.

The "C_{6-12} aromatic hydrocarbon group" used includes, for example, a monocyclic C_{6-12} aromatic hydrocarbon group such as phenyl, cyclooctatetraenyl, etc.

The "5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" used includes, for example, a 5- to 14-membered, preferably 5- to 10-membered, more preferably 5- or 6-membered monocyclic aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 1 to 7 carbon atoms. Specific examples used are thienyl (e.g., 2-thienyl, 3-thienyl), furyl (e.g., 2-furyl, 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl),

pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl), etc.

The "C_{8-14} aromatic fused cyclic group" used includes, for example, naphthyl (e.g., 1-naphthyl, 2-naphthyl), anthryl (e.g., 2-anthryl, 9-anthryl), etc.

The "optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" includes, for example, a 5- to 14-memberd (preferably 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms, or a monovalent group formed by removing one optional hydrogen atom from a 7- to 10-membered aromatic bridged-hetero ring in 5- to 14-membered (preferably 5- to 10-membered) ring containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specific examples used are quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), 2-benzothiazolyl, benzo[b]thienyl, (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl), benzo[b]furanyl (e.g., 2-benzo[b]furanyl, 3-benzo[b]furanyl), etc.

The "non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7" used includes, for example, a C_{3-7} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "non-aromatic heterocyclic group of carbon atoms not greater than 7" used includes, for example, a 5- or 10-membered non-aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms, in addition to 1 to 7 carbon atoms, such as pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl (e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholino, thiomorpholino, etc.

The substituents used for these "C_{6-12} aromatic hydrocarbon group," "5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "C_{8-14} aromatic fused cyclic group," "5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting

of nitrogen, oxygen and sulfur atoms," "non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7" and "non-aromatic heterocyclic group of carbon atoms not greater than 7" include, for example, substituents selected from oxo, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{3-8} cycloalkyl, an optionally substituted C_{6-14} aryl, an optionally substituted C_{7-16} aralkyl, an optionally substituted C_{1-6} alkoxy, hydroxy, an optionally substituted C_{6-14} aryloxy, an optionally substituted C_{7-16} aralkyloxy, mercapto, an optionally substituted C_{1-6} alkylthio, an optionally substituted C_{6-14} arylthio, an optionally substituted C_{7-16} aralkylthio, an optionally substituted amino[amino, an optionally substituted mono- or di-C_{1-6} alkyl-amino (e.g., methylamino, dimethylamino, ethylamino, diethylamino, propylamino, isopropylamino, etc.), an optionally substituted mono- or di-C_{2-6} alkenyl-amino (e.g., vinylamino, propenylamino, isopropenylamino), an optionally substituted C_{2-6} alkynylamino (e.g., 2-butyn-1-yl-amino, 4-pentyn-1-yl-amino, 5-hexyn-1-yl-amino), an optionally substituted mono- or di-C_{3-8} cycloalkyl-amino (e.g., cyclopropylamino, cyclohexylamino), an optionally substituted C_{6-14} arylamino (e.g., phenylamino, diphenylamino, naphthylamino), an optionally substituted C_{1-6} alkoxyamino (e.g., methoxyamino, ethoxyamino, propoxyamino, isopropoxyamino), formylamino, an optionally substituted C_{1-6} alkylcarbonylamino (e.g., acetylamino, propionylamino, pivaloylamino, etc.), an optionally substituted C_{3-8} cycloalkylcarbonylamino (e.g., cyclopropylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino, etc.), an optionally substituted C_{6-14} aryl-carbonylamino (e.g., benzoylamino, naphthoylamino, etc.), an optionally substituted C_{1-6} alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, etc.), an optionally substituted C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), an optionally substituted C_{6-14} arylsulfonylamino (e.g., phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino, etc.)], formyl, carboxy, an optionally substituted C_{1-6} alkylcarbonyl (e.g., acetyl, propionyl, pivaloyl, etc.), an optionally substituted C_{3-8} cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, 1-methyl-cyclohexyl-carbonyl, etc.), an optionally substituted C_{6-14} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), an optionally substituted C_{7-16} aralkylcarbonyl (e.g., phenylacetyl, 3-phenylpropionyl,

etc.), an optionally substituted 5- to 7-membered heterocyclic carbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., nicotinoyl, isonicotinoyl, thenoyl, furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, etc.), an optionally esterified carboxyl, an optionally substituted carbamoyl group, an optionally substituted C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.), an optionally substituted C_{1-6} alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, etc.), an optionally substituted C_{6-14} arylsulfonyl (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl, etc.), an optionally substituted C_{6-14} arylsulfinyl (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl, etc.), an optionally substituted C_{1-6} alkylcarbonyloxy (e.g., acetoxy, propionyloxy, etc.), an optionally substituted C_{6-14} aryl-carbonyloxy (e.g., benzoyloxy, naphthylcarbonyloxy, etc.), an optionally substituted C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), an optionally substituted a mono-C_{1-6} alkylcarbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.), an optionally substituted di-C_{1-6} alkylcarbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), an optionally substituted a mono- or di-C_{6-14} arylcarbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), an optionally substituted heterocyclic group, sulfo, sulfamoyl, sulfinamoyl, sulfenamoyl, or a group of 2 or more (e.g., 2 or 3) of these substituents combined, and the like (Substituent group A). The number of the substituents is not particularly limited but these rings may have 1 to 5, preferably 1 to 3 substituents in substitutable positions, and when there are two or more substituents, each substituent may be the same or different.

The "optionally esterified carboxyl used in the Substituent group A includes, for example, an optionally substituted C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), an optionally substituted C_{6-14} aryloxy-carbonyl (e.g., phenoxycarbonyl, etc.), an optionally substituted C_{7-16} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like.

The "C_{1-6} alkyl" in the "optionally substituted C_{1-6} alkyl" used in the Substituent group A includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

The "C_{2-6} alkenyl" in the "optionally substituted C_{2-6} alkenyl" used in the Substituent group A includes, for example, vinyl, propenyl, isopropenyl, 2-buten-1-yl,

4-penten-1-yl, 5-hexen-1-yl, etc.

The "C_{2-6} alkynyl" in the "optionally substituted C_{2-6} alkynyl" used in the Substituent group A includes, for example, 2-butyn-1-yl, 4-pentyn-1-yl, 5-hexyn-1-yl, etc.

The "C_{3-8} cycloalkyl" in the "optionally substituted C_{3-8} cycloalkyl" used in the Substituent group A includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The C_{6-14} aryl in the optionally substituted C_{6-14} aryl used in the Substituent group A includes, for example, phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl, etc.

The "C_{7-16} aralkyl" in the "optionally substituted C_{7-16} aralkyl" used in the Substituent group A includes, for example, benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 2-biphenylylmethyl, 3-biphenylylmethyl, 4-biphenylylmethyl), etc.

The "C_{1-6} alkoxy" in the "optionally substituted C_{1-6} alkoxy" used in the Substituent group A includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.

The "C_{6-14} aryloxy" in the "optionally substituted C_{6-14} aryloxy" used in the Substituent group A includes, for example, phenyloxy, 1-naphthyloxy, 2-naphthyloxy, etc.

The "C_{7-16} aralkyloxy" in the "optionally substituted C_{7-16} aralkyloxy" used in the Substituent group A includes, for example, benzyloxy, phenethyloxy, etc.

The "C_{1-6} alkylthio" in the "optionally substituted C_{1-6} alkylthio" used in the Substituent group A includes, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.

The "C_{6-14} arylthio" in the "optionally substituted C_{6-14} arylthio" used in the Substituent group A includes, for example, phenylthio, 1-naphthylthio, 2-naphthylthio, etc.

The "C_{7-16} aralkylthio" in the "optionally substituted C_{7-16} aralkylthio" used in the Substituent group A includes, for example, benzylthio, phenethylthio, etc.

The substituents used in the Substituent group A for these "C_{1-6} alkoxy-carbonyl," "C_{1-6} alkyl group," "C_{2-6} alkenyl," "C_{2-6} alkynyl," "C_{1-6} alkoxy," "C_{1-6} alkylthio," C_{1-6} alkyl-amino," C_{2-6} alkenyl-amino," "C_{2-6} alkynylamino," C_{1-6}

alkoxyamino," "C_{1-6} alkylcarbonyl," "C_{1-6} alkylsulfonyl," "C_{1-6} alkylsulfinyl," "C_{1-6} alkylcarbonylamino," "C_{1-6} alkoxy-carbonylamino," "C_{1-6} alkylsulfonylamino," "C_{1-6} alkylcarbonyloxy," "C_{1-6} alkoxy-carbonyloxy," "mono-C_{1-6} alkylcarbamoyloxy" and "di-C_{1-6} alkylcarbamoyloxy" include 1 to 5 substituents selected from, for example, a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom), carboxy, hydroxy, amino, a mono- or di-C_{1-6} alkylamino, a mono- or di-C_{6-14} arylamino, a C_{3-8} cycloalkyl, a C_{1-6} alkoxy, a C_{1-6} alkoxy-carbonyl, a C_{1-6} alkylthio, a C_{1-6} alkylsulfinyl, a C_{1-6} alkylsulfonyl, the optionally esterified carboxyl described above, carbamoyl, thiocarbamoyl, a mono-C_{1-6} alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), a di-C_{1-6} alkylcarbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), a mono- or di-C_{6-14} arylcarbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), a mono- or di-5- to 7-membered heterocyclic carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.) and the like.

The substituents used in the Substituent group A for the "C_{6-14} aryloxy-carbonyl," "C_{7-16} aralkyloxy-carbonyl," "C_{3-8} cycloalkyl," "C_{6-14} aryl," "C_{7-16} aralkyl," "C_{6-14} aryloxy," "C_{7-16} aralkyloxy," "C_{6-14} arylthio," "C_{7-16} aralkylthio," C_{3-8} cycloalkyl-amino, C_{6-14} arylamino, "C_{3-8} cycloalkylcarbonyl," "C_{6-14} aryl-carbonyl," "C_{7-16} aralkylcarbonyl," "5- to 7-membered heterocyclic carbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms," "C_{6-14} arylsulfonyl," "C_{6-14} arylsulfinyl," "C_{3-8} cycloalkylcarbonylamino," "C_{6-14} aryl-carbonylamino," "C_{6-14} arylsulfonylamino," "C_{6-14} aryl-carbonyloxy" and "mono- or di-C_{6-14} arylcarbamoyloxy" include 1 to 5 substituents selected from, for example, a halogen atom, hydroxy, carboxy, nitro, cyano, the optionally substituted C_{1-6} alkyl described above, the optionally substituted C_{2-6} alkenyl described above, the optionally substituted C_{2-6} alkynyl described above, the optionally substituted C_{3-8} cycloalkyl described above, the optionally substituted C_{1-6} alkoxy described above, the optionally substituted C_{1-6} alkylthio described above, the optionally substituted C_{1-6} alkylsulfinyl described above, the optionally substituted C_{1-6} alkylsulfonyl described above, the optionally esterified carboxyl described above, carbamoyl, thiocarbamoyl, a mono-C_{1-6} alkylcarbamoyl, a di-C_{1-6} alkylcarbamoyl, a mono- or di-C_{6-14} arylcarbamoyl, a mono- or di-5- to 7-membered heterocyclic

carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms, and the like.

The "optionally substituted heterocyclic group" used in the Substituent group A includes, for example, a 5- to 14-membered (monocyclic, bicyclic or tricyclic) heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which may optionally be substituted with a halogen atom, hydroxy, carboxy, nitro, cyano, the optionally substituted C_{1-6} alkyl described above, the optionally substituted C_{2-6} alkenyl described above, the optionally substituted C_{2-6} alkynyl described above, the optionally substituted C_{3-8} cycloalkyl described above, the optionally substituted C_{6-14} aryl described above, the optionally substituted C_{1-6} alkoxy described above, the optionally substituted C_{1-6} alkylthio described above, the optionally substituted C_{6-14} arylthio described above, the optionally substituted C_{7-16} aralkylthio described above, the optionally substituted C_{1-6} alkylsulfinyl described above, the optionally substituted C_{6-14} arylsulfinyl described above, the optionally substituted C_{1-6} alkylsulfonyl described above, the optionally substituted C_{6-14} arylsulfonyl described above, the optionally esterified carboxyl described above, carbamoyl, thiocarbamoyl, a mono-C_{1-6} alkylcarbamoyl, a di-lower alkylcarbamoyl, a mono- or di-C_{6-14} arylcarbamoyl, a mono- or di-5- or 7-membered heterocyclic carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms, or the like; , preferably (i) a 5- to 14-membered (preferably, 5- to 10-membered) aromatic heterocyclic group, (ii) a 5- to 10-membered non-aromatic heterocyclic group or (iii) a monovalent group formed by one optional hydrogen atom from 7- to 10-membered bridged-hetero ring, and more preferably, a 5-memberedaromatic heterocyclic group. Specifically used are an aromatic heterocyclic group such as thienyl (e.g., 2-thienyl, 3-thienyl), furyl (e.g., 2-furyl, 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), 2-benzothiazolyl, benzo[b]thienyl, (e.g., 2-benzo[b]thienyl,

3-benzo[b]thienyl), benzo[b]furanyl (e.g., , 2-benzo[b]furanyl, 3-benzo[b]furanyl), etc., a non-aromatic heterocyclic group such as pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl (e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholino, thiomorpholino, etc.

The "optionally substituted carbamoyl group" used in the Substituent group A includes a carbamoyl group, which may optionally be substituted with the optionally substituted C_{1-6} alkyl described above, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{3-8} cycloalkyl, an optionally substituted C_{6-14} aryl, an optionally substituted heterocyclic group, etc., and specific examples are carbamoyl, thiocarbamoyl, a mono-C_{1-6} alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkylcarbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{1-6} alkyl(C_{1-6} alkoxy)carbamoyl (e.g., methyl(methoxy)carbamoyl, ethyl(methoxy)carbamoyl), a mono- or di-C_{6-14} arylcarbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), a mono- or di-5- to 7-memberedheterocyclic carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.), a 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, hexamethyleneiminocarbonyl), and the like.

The "optionally substituted amino" used in the Substituent group A includes an amino, which may optionally be substituted with 1 or 2 groups selected from the optionally substituted C_{1-6} alkyl, the optionally substituted C_{2-6} alkenyl described above, the optionally substituted C_{2-6} alkynyl described above, the optionally substituted C_{3-8} cycloalkyl described above, the optionally substituted C_{6-14} aryl described above, the optionally substituted C_{1-6} alkoxy described above described above, formyl, the optionally substituted C_{1-6} alkylcarbonyl described above, the optionally substituted C_{3-8} cycloalkylcarbonyl described above, the optionally substituted C_{6-14} aryl-carbonyl described above, the optionally substituted C_{1-6} alkoxy-carbonyl described above, the optionally substituted C_{1-6} alkylsulfonyl described above, an optionally substituted C_{6-14} arylsulfonyl) and the like.

More preferably, the substituents for the "C_{6-12} aromatic hydrocarbon group,"

"5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "C_{8-14} aromatic fused cyclic group," "5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7" and "non-aromatic heterocyclic group of carbon atoms not greater than 7" are a halogen atom, hydroxy, a C_{1-6} alkoxy, an optionally halogenated C_{1-6} alkyl, an optionally halogenated C_{1-6} alkoxy, amino, nitro, cyano, etc.

Examples of R^4 used include:

(1) "a C_{1-4} alkyl group having an optionally substituted C_{6-12} aromatic hydrocarbon group" such as benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 4-chlorobenzyl, 3,4-difluorobenzyl, 3,4-dichlorobenzyl, pentafluorobenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, 3-trifluoromethylbenzyl, 4-aminobenzyl, 4-nitrobenzyl, 4-cyanobenzyl, phenethyl, etc.;

(2) "a C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" such as 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thienylmethyl, 3-thienylmethyl, 4-thiazolylmethyl, etc.;

(3) "a C_{1-4} alkyl group having an optionally substituted C_{8-14} aromatic fused cyclic group" such as 1-naphthylmethyl, 2-naphthylmethyl, inden-2-ylmethyl, etc.;

(4) "a C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" such as 3-indolemethyl, 1-formylindol-3-ylmethyl, 3-benzo[b]thienylmethyl, 2-quinolylmethyl, etc.;

(5) "a C_{1-4} alkyl group having an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7" such as cyclohexylmethyl, cyclopentylmethyl, indan-2-ylmethyl, etc.;

(6) "a C_{1-4} alkyl group having an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7" such as 4-piperidinylmethyl, tetrahydrofurfuryl, tetrahydrofuran-2-yl, tetrahydropyran-3-yl, indolin-3-yl, etc., preferably, benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 4-hydroxybenzyl, 4-aminobenzyl,

4-nitrobenzyl, 4-chlorobenzyl, 4-methoxybenzyl, 4-cyanobenzyl, 3-trifluoromethylbenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, pentafluorobenzyl, 3-pyridylmethyl, 4-pyridylmethyl, 3-indolemethyl, 1-formylindol-3-ylmethyl, 3-benzo[b]thienylmethyl, 2-quinolylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, cyclohexylmethyl, phenethyl, etc., and more preferably, benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 4-hydroxybenzyl, 4-aminobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-methoxybenzyl, 4-cyanobenzyl, 3-trifluoromethylbenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, pentafluorobenzyl, 3-pyridylmethyl, 4-pyridylmethyl, 3-indolemethyl, 3-benzo[b]thienylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, cyclohexylmethyl, etc.

Q^1 represents a C_{1-4} alkyl group optionally substituted with a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7; and

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7; and the same substituents as in R^4 are used.

Examples of Q^1 include:

(1) "a C_{1-4} alkyl group having an optionally substituted C_{6-12} aromatic hydrocarbon group" such as benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 4-chlorobenzyl, 3,4-difluorobenzyl, 3,4-dichlorobenzyl, pentafluorobenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, 4-trifluoromethylbenzyl, 4-aminobenzyl, 4-nitrobenzyl, 4-cyanobenzyl, phenethyl, etc.;

(2) "a C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" such as 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thienylmethyl, 3-thienylmethyl, 4-thiazolylmethy,

etc.;

(3)" a C_{1-4} alkyl group having optionally substituted C_{8-14} aromatic fused cyclic group," such as 1-naphthylmethyl, 2-naphthylmethyl, inden-2-ylmethyl;

(4) "a C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" such as 3-indolemethyl, 1-formylindol-3-ylmethyl, 3-benzo[b]thienylmethyl, 2-quinolylmethyl, etc.;

(5) "a C_{1-4} alkyl group having an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7" such as cyclohexylmethyl, cyclopentylmethyl, indan-2-ylmethyl, etc.;

(6) "a C_{1-4} alkyl group having an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7" such as 4-piperidinylmethyl, tetrahydrofurfuryl, tetrahydrofuran-2-yl, tetrahydropyran-3-yl, indolin-3-yl, etc.; preferably, cyclohexylmethyl, benzyl, 4-fluorobenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, pentafluorobenzyl, 2-pyridylmethyl, 4-pyridylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-indolemethyl, 2-thienylmethyl, etc. and more preferably, benzyl, 4-fluorobenzyl, cyclohexylmethyl, etc.

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, or (3) O.

Examples of the "C_{1-4} alkyl group" used are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.

Preferably, Q^2 is CH_2, $CH(CH_3)$, $CH(CH_2OH)$, NH, or the like.

Y represents a group represented by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, or –CH=CH-, which may optionally be substituted with a C_{1-6} alkyl group.

Examples of the "C_{1-6} alkyl group" used are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl; etc.

Preferably, Y is a group represented by formula: -CONH-, -CSNH-, -NHCO-, $-CH_2NH-$, $-CH_2O-$, -COO- or -CSO- (more preferably, the group represented by formula: -CONH-, -CSNH-, -NHCO- or $-CH_2NH-$).

Z^9 represents hydrogen atom, O or S, preferably O or S;

wherein, when Z^9 represents hydrogen atom, a structure of the moiety represented by $>C=Z^9$ indicates a structure of $>CH_2$.

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula: J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$- (wherein each symbol has the same significance as described above);

(4) a group represented by formula: -J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$- (wherein each symbol has the same significance as described above);

(5) a group represented by formula: J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$- (wherein each symbol has the same significance as described above);

(6) a group represented by formula: J^1-J^2-$C(J^{12})(Q^{12})C(=Z^{10})$- (wherein each symbol has the same significance as described above); or,

(7) a group represented by formula:J^{1}- (wherein J^1 has the same significance as described above).

Specific examples of the "optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence represented by SEQ ID NO: 1" used include:

(1) Asn-

(2) Trp Asn-,

(3) Asn Trp Asn-,

(4) Tyr Asn Trp Asn-,

(5) Asn Tyr Asn Trp Asn-,

(6) Pro Asn Tyr Asn Trp Asn-,

(7) Leu Pro Asn Tyr Asn Trp Asn-,

(8) Asp Leu Pro Asn Tyr Asn Trp Asn-,

(9) Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(10) Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(11) Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(12) Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(13)Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(14) Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(15) Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(16) Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(17) Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(18) Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(19) Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(20) Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(21) Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(22) Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(23) Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(24) Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(25) Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(26) His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(27) Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(28) Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(29) Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(30) Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(31) Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(32) Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val

Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(33) Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(34) Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(35) Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(36) Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(37) Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(38) Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(39) Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(40) Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(41) Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(42) Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(43) Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(44) Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-;

(45) Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(46) Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu

Pro Asn Tyr Asn Trp Asn-,

(47) Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(48) Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-, etc.

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino group, which groups may optionally be substituted with a substituent containing an optionally substituted cyclic group.

The "cyclic group" used includes, for example, "an optionally substituted an aromatic hydrocarbon group," "an optionally substituted aromatic heterocyclic group," "an optionally substituted an aromatic fused cyclic group," "an optionally substituted an aromatic fused heterocyclic group," "an optionally substituted non-aromatic cyclic hydrocarbon group," "an optionally substituted non-aromatic heterocyclic group", etc., and as the "aromatic hydrocarbon group," "aromatic heterocyclic group," "aromatic fused cyclic group" and "aromatic fused heterocyclic group," the same groups given above are used.

The "non-aromatic cyclic hydrocarbon group" used includes, for example, a C_{3-6} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "non-aromatic heterocyclic group" used includes, for example, a 5- or 10-membered non-aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 1 to 7 carbon atoms such as pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl (e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholino, thiomorpholino, etc.

The substituent optionally present on the "cyclic group" includes the same substituents given for the Substituent group A described above.

The "C_{1-15} acyl group" used includes, for example, formyl, a C_{1-14} alkylcarbonyl (e.g., a C_{1-6} alkylcarbonyl such as acetyl, propionyl, pivaloyl, etc.) and the

like.

Examples of the "C_{1-15} alkyl group" used include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonanyl, decanyl, etc.

Examples of the "C_{6-14} aryl group" used include phenyl, 1-naphthyl, 2-naphthyl, biphenyl, etc.

(1) The C_{1-15} acyl group, which may optionally be substituted with a substituent containing a cyclic group, includes (i) formyl, (ii) a C_{1-14} alkylcarbonyl (e.g., a C_{1-6} alkylcarbonyl such as acetyl, propionyl, pivaloyl, etc.), (iii) a C_{3-8} cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, 1-methylcyclohexylcarbonyl, etc.), (iv) a C_{3-8} cycloalkyl-C_{1-6} alkylcarbonyl (e.g., cyclopropylacetyl, cyclopentylacetyl, cyclohexylacetyl, etc.), (v) a C_{6-14} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), a C_{6-14} aralkylcarbonyl (e.g., phenylacetyl, 3-phenylpropionyl, etc.), (vi) a 5- to 7-membered monocyclic heterocyclic carbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., nicotinoyl, isonicotinoyl, thenoyl, furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, etc.), (vii) a 5- to 7-membered monocyclic heterocyclic-C_{1-6} alkylcarbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridylacetyl, 4-pyridylacetyl, 2-thienylacetyl, 2-furylacetyl, morpholinoacetyl, thiomorpholinoacetyl, piperidin-2-acetyl, pyrrolidine-2-ylacetyl, etc.), (viii) a 5- to 14-membered (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic carbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (e.g., 2-indolecarbonyl, 3-indolecarbonyl, 2-quinolylcarbonyl, 1-isoquinolylcarbonyl, 2-benzo[b]thienylcarbonyl, 2-benzo[b]furanylcarbonyl, etc.), (ix) a 5- to 14-membered (preferably 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic-C_{1-6} alkylcarbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (e.g., 2-indoleacetyl, 3-indoleacetyl, 2-quinolylacetyl, 1-isoquinolylacetyl, 2-benzo[b]thienylacetyl, 2-benzo[b]furanylacetyl, etc.), etc., preferably, acetyl, 2-indolecarbonyl, 3-indolecarbonyl, 3-indoleacetyl, 3-indolepropionyl, 2-indolinecarbonyl, 3-phenylpropionyl, diphenylacetyl, 2-pyridinecarbonyl, 3-pyridinecarbonyl, 4-pyridinecarbonyl, 1-pyridinioacetyl,

2-pyridineacetyl, ,3-pyridineacetyl, ,4-pyridineacetyl, 3-(1-pyridinio)propionyl, 3-(pyridin-2-yl)propionyl, 3-(pyridin-3-yl)propionyl, 3-(pyridin-4-yl)propionyl, 4-imidazoleacetyl, cyclohexanecarbonyl, 1-piperidineacetyl, 1-methyl-1-piperidinioacetyl, 4-piperidinecarbonyl, 2-pyrimidinecarbonyl, 4-pyrimidinecarbonyl, 5-pyrimidinecarbonyl, 2-pyrimidineacetyl, 4-pyrimidineacetyl, 5-pyrimidineacetyl, 3-(pyrimidine-2-yl)propionyl, 3-(pyrimidine-4-yl)propionyl, 3-(pyrimidine-5-yl)propionyl, butanoyl, hexanoyl, octanoyl, D-glucuronyl, amino-(4-hydroxyphenyl)acetyl), etc.

(2) The C_{1-15} alkyl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a mono- or di-C_{1-15} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonanyl, decanyl), (ii) a mono- or di-C_{3-8} cycloalkyl (e.g., cyclopropyl, cyclopentyl, etc.), (iii) a mono- or di-C_{3-8} cycloalkyl-C_{1-7} alkyl (e.g., cyclopropylmethyl, cyclopentylmethyl, cyclohexylethyl, etc.), (iv) a mono- or di-C_{7-15} aralkyl (e.g., benzyl, phenethyl, etc.), (v) a mono- or di-5- to 7-membered monocyclic heterocyclic-C_{1-6} alkyl group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridylmethyl, 4-pyridylmethyl, 2-thienylmethyl, furfuryl, etc.), (vi) a mono- or di-5- to 14-membered (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic-C_{1-6} alkyl group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (e.g., 2-indolemethyl, 3-indolemethyl, 3-(indol-3-yl)propyl, 2-quinolylmethyl, 1-isoquinolylmethyl, 2-benzo[b]thienylmethyl, 2-benzo[b]furanylmethyl, etc.), etc., preferably, methyl, ethyl, benzyl, 3-(indol-3-yl)propyl, etc.

(3) The C_{6-14} aryl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, a C_{6-14} aryl group (e.g., phenyl, naphthyl, biphenyl), which may optionally be substituted with (i) a C_{6-14} carbocyclic group (e.g., cycloalkyl, phenyl, 1-naphthyl, 2-naphthyl, etc.), (ii) a 5- to 7-membered monocyclic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridyl, 2-thienyl, etc.), (iii) a 5- to 14-membered containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic group (e.g., 2-indolyl, 3-indolyl, 2-quinolyl, 1-isoquinolyl,

2-benzo[b]thienyl, 2-benzo[b]furanyl, etc.), etc.

(4) The optionally substituted carbamoyl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) carbamoyl, (ii) a mono- or di-C_{1-15} alkylcarbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, (iii) a mono- or di-C_{3-8} cycloalkyl-carbamoyl (e.g., cyclopropylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl, etc.), (iv) a mono- or di-C_{3-8} cycloalkyl-C_{1-6} alkyl-carbamoyl (e.g., cyclopropylmethylcarbamoyl, cyclopentylmethylcarbamoyl, 2-cyclohexylethylcarbamoyl, etc.) (v) a mono- or di-C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, etc.), a mono- or di-C_{6-14} aralkyl-carbamoyl (e.g., benzylcarbamoyl, phenethylcarbamoyl, etc.), (vi) a mono- or di-5- to 7-membered monocyclic heterocyclic carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridinecarbamoyl, 2-thiophenecarbamoyl, piperidin-3-ylcarbamoyl, etc.), (vii) a mono- or di-5- to 7-membered monocyclic heterocyclic-C_{1-6} alkylcarbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridylmethylcarbamoyl, 2-(pyridin-2-yl)ethylcarbamoyl, 2-(piperidin-1-yl)ethylcarbamoyl, etc.), (viii) a mono- or di-5- to 14-membered containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic carbamoyl (e.g., 4-indolecarbamoyl, 5-indolecarbamoyl, 3-quinolylcarbamoyl, 5-quinolylcarbamoyl, etc.), (ix) a mono- or di-5- to 14-membered (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic-C_{1-6} alkylcarbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (e.g., benzimidazole-2-ylmethylcarbamoyl, 2-(indol-3-yl)ethylcarbamoyl, etc.), (x) a 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, hexamethyleneiminocarbonyl, etc.), (xi) a C_{1-15} acylcarbamoyl (the C_{1-15} acyl herein has the same significance as for the "C_{1-15} acyl group" in the "C_{1-15} acyl group used, which may optionally be substituted with a substituent containing a cyclic group"), (xii) a C_{1-15} alkylaminocarbamoyl (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group"), (xiii) a C_{6-14} arylaminocarbamoyl (the C_{6-14} aryl group herein has the same significance as for the "C_{6-14} aryl group, which may optionally be substituted with a substituent containing a

cyclic group"), etc., preferably, 2-(indol-3-yl)ethylcarbamoyl, etc.

(5) The carboxyl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a C_{1-15} alkyloxycarbonyl (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., tert-butyloxycarbonyl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), (ii) a C_{6-14} aryloxycarbonyl (the C_{6-14} aryl herein has the same significance as for the "C_{6-14} aryl group" in the "C_{6-14} aryl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., phenoxycarbonyl), etc.

(6) The sulfino group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a C_{1-15} alkylsulfonyl (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., benzylsulfonyl), (ii) a C_{6-14} arylsulfonyl (the C_{6-14} aryl herein has the same significance as for the "C_{6-14} aryl group" in the "C_{6-14} aryl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., tosyl), etc.

(7) The amidino group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) amidino, (ii) a C_{1-15} alkylamidino (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., N-methylamidino), (iii) a C_{1-15} acylamidino (the C_{1-15} acyl herein has the same significance as for the "C_{1-15} acyl group" in the "C_{1-15} acyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., N-acetylamidino), etc.

(8) The glyoxyloyl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a C_{1-15} alkyloxalyl (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., ethyloxalyl), (ii) a C_{6-14} aryloxalyl (the C_{6-14} aryl herein has the same significance as for the "C_{6-14} aryl group" in the "C_{6-14} aryl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., phenyloxalyl), etc.

(9) The amino group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a C_{1-15} alkylamino (the

C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group."

Among those described above, J^1 is preferably hydrogen atom, formyl, acetyl, 3-indolecarbonyl, 3-(indol-3-yl)propionyl, 3-phenylpropionyl, diphenylacetyl, 3-(pyridin-3-yl)propionyl, 4-imidazoleacetyl, cyclohexanecarbonyl, 1-piperidineacetyl, 1-methyl-1-piperidinioacetyl, 4-piperidinecarbonyl, hexanoyl, amino-(4-hydroxyphenyl)acetyl, D-glucuronyl, 2-(indol-3-yl)ethylcarbamoyl, tert-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl, amidino, 4-guanidomethylbenzoyl, benzoyl, 3-indoleacetyl, benzyloxycarbonyl, tosyl, phenyl, benzyl, phenethyl, 3-pyridinecarbonyl, 2-pyridinecarbonyl, 4-pyridinecarbonyl, propionyl, isobutyryl, phenylacetyl, 2-methylnicotinoyl, 5-methylnicotinoyl, 6-methylnicotinoyl, pyrazinecarbonyl, cyclopropanecarbonyl, trifluoroacetyl, (R)-3-hydroxy-2-methylpropionyl, 2-hydroxyisobutyryl, 3-furancarbonyl, pyrrole-2-carbonyl, 4-imidazolecarbonyl, 6-hydroxynicotinoyl, 6-chloronicotinoyl, 6-(trifluoromethyl)nicotinoyl, dimethylcarbamoyl, 1-azetidinecarbonyl, 2-azetidinecarbonyl, 4-aminobenzoyl, 4-aminomethylbenzoyl, pyrrole-3-carbonyl, pyrimidine-4-carbonyl, pyrimidine-2-carbonyl, pyridazine-4-carbonyl, 6-aminocaproyl, glycyl, glycylglycyl, glycylglycylglycyl, alanylalanylalanyl, alanylalanylalanylalanyl, acetylglycyl, acetylglycylglycyl, acetylglycylglycylglycyl, acetylalanylalanylalanyl, acetylalanylalanylalanylalanyl, D-arginylglycyl, D-arginylglycylglycyl, D-arginylglycylglycylglycyl, D-arginylalanylalanylalanyl, D-arginylalanylalanylalanylalanyl, acetyl-D-arginylglycyl, acetyl-D-arginylglycylglycyl, acetyl-D-arginylglycylglycylglycyl, acetyl-D-arginylalanylalanylalanyl, acetyl-D-arginylalanylalanylalanylalanyl, cyclopropanecarbonyl, cyclopentanecarbonyl, cyclobutanecarbonyl, cyclohexanecarbonyl, 1-naphthoyl, 2-naphthoyl, arginyl, arginylarginyl, 6-(arginylamino)caproyl, 6-(D-arginylamino)caproyl, 6-(D-arginyl-D-arginylamino)caproyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 3-(D-arginylamino)propionyl, 4-(D-arginylamino)butyryl, 4-(D-arginyl-D-arginylamino)butyryl, 4-(D-arginyl-D-arginyl-D-arginylamino)butyryl, 3-(4-hydroxyphenyl)propionyl, butyryl, methyl, adipoyl, pyroglutamyl, glycoloyl, etc., and more preferably used are hydrogen atom, formyl, acetyl, propionyl,

3-indolecarbonyl, 3-(indol-3-yl)propionyl, 3-phenylpropionyl, 3-(pyridin-3-yl)propionyl, 4-imidazoleacetyl, cyclohexanecarbonyl, hexanoyl, amino-(4-hydroxyphenyl)acetyl, 2-(indol-3-yl)ethylcarbamoyl, 9-fluorenylmethoxycarbonyl, amidino, 4-guanidomethylbenzoyl, benzoyl, 3-indoleacetyl, benzyl, phenethyl, 3-pyridinecarbonyl, 2-pyridinecarbonyl, 4-pyridinecarbonyl, isobutyryl, phenylacetyl, 6-methylnicotinoyl, pyrazinecarbonyl, cyclopropanecarbonyl, trifluoroacetyl, (R)-3-hydroxy-2-methylpropionyl, 2-hydroxyisobutyryl, 3-furancarbonyl, pyrrole-2-carbonyl, 4-imidazolecarbonyl, 6-hydroxynicotinoyl, 6-chloronicotinoyl, 6-(trifluoromethyl)nicotinoyl, dimethylcarbamoyl, 1-azetidinecarbonyl, 4-aminobenzoyl, 4-aminomethylbenzoyl, pyrrole-3-carbonyl, pyrimidine-4-carbonyl, pyrimidine-2-carbonyl, pyridazine-4-carbonyl, 6-aminocaproyl, cyclopropanecarbonyl, 2-naphthoyl, arginyl, 6-(arginylamino)caproyl, 6-(D-arginylamino)caproyl, 6-(D-arginyl-D-arginylamino)caproyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 3-(D-arginylamino)propionyl, 4-(D-arginylamino)butyryl, 4-(D-arginyl-D-arginylamino)butyryl, 4-(D-arginyl-D-arginyl-D-arginylamino)butyryl, 3-(4-hydroxyphenyl)propionyl, butyryl, adipoyl, pyroglutamyl, etc.

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S.

The "C_{1-6} alkyl group" used includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

Preferably, J^2 is NH.

J^3 through J^{12} each represents hydrogen atom or a C_{1-3} alkyl group.

The "C_{1-3} alkyl group" used includes methyl, ethyl, propyl, isopropyl, etc.

Preferably, J^3 is hydrogen atom.

Preferably, J^4 is hydrogen atom.

Preferably, J^5 is hydrogen atom.

Preferably, J^6 is hydrogen atom.

Preferably, J^7 is hydrogen atom.

Preferably, J^8 is hydrogen atom.

Preferably, J^9 is hydrogen atom.

Preferably, J^{10} is hydrogen atom.

Preferably, J^{11} is hydrogen atom.

Preferably, J^{12} is hydrogen atom.

Q^3 through Q^{12} each represents a C_{1-4} alkyl group, which may optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7;

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

(7) an optionally substituted amino group;

(8) an optionally substituted guanidino group;

(9) an optionally substituted hydroxyl group;

(10) an optionally substituted carboxyl group;

(11) an optionally substituted carbamoyl group; and,

(12) an optionally substituted sulfhydryl group;

or hydrogen atom.

Preferably, Q^3 through Q^9 include a C_{1-4} alkyl group having a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7;

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

(7) an optionally substituted amino group;

(8) an optionally substituted guanidino group;

(9) an optionally substituted hydroxyl group;

(10) an optionally substituted carboxyl group;

(11) an optionally substituted carbamoyl group; and,

(12) an optionally substituted sulfhydryl group;

or hydrogen atom.

The "optionally substituted C_{6-12} aromatic hydrocarbon group," "optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "optionally substituted C_{8-14} aromatic fused cyclic group," "optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7" and "optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7" used are the same as those given above.

(1) As the C_{1-4} alkyl group having an optionally substituted C_{6-12} aromatic hydrocarbon group, there are used, for example, benzyl, 4-hydroxybenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 4-aminobenzyl, etc.

(2) As the C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, there are used, for example, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 4-imidazolemethyl, etc.

(3) As the C_{1-4} alkyl group having an optionally substituted C_{8-14} aromatic fused cyclic group, there are used, for example, 1-naphthylmethyl, 2-naphthylmethyl, etc.

(4) As the C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, there are used, for example, 3-indolemethyl, 1-formylindol-3-ylmethyl, 2-quinolylmethyl, etc.

(5) As the C_{1-4} alkyl group having an optionally substituted non-aromatic cyclic

hydrocarbon group having carbon atoms not greater than 7, there are used, for example, cyclohexylmethyl, etc.

(6) As the C_{1-4} alkyl group having an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7, there are used, for example, piperidin-1-ylmethyl, etc.

(7) As the C_{1-4} alkyl group having an optionally substituted amino group, there are used, for example, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 4-acetamidobutyl, etc.

(8) As the C_{1-4} alkyl group having an optionally substituted guanidino group, there are used, for example, 3-guanidinopropyl, 3-(N-tosyl)guanidinopropyl, etc.

(9) As the C_{1-4} alkyl group having an optionally substituted hydroxyl group, there are used, for example, hydroxymethyl, 1-hydroxyethyl, benzyloxymethyl, etc.

(10) As the C_{1-4} alkyl group having an optionally substituted carboxyl group, there are used, for example, carboxylmethyl, 2-carboxylethyl, benzyloxycarbonylmethyl, etc.

(11) As the C_{1-4} alkyl group having an optionally substituted carbamoyl group, there are used, for example, carbamoylmethyl, 2-carbamoylethyl, xanthylcarbamoyl, etc.

(12) As the C_{1-4} alkyl group having an optionally substituted sulfhydryl group, there are used, for example, sulfhydrylmethyl, 2-(methylsulfhydryl)ethyl, etc.

(13) As the unsubstitued C_{1-4} alkyl group, there are used, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.

Preferably, Q^3 is hydrogen atom, 4-hydroxybenzyl, 3-pyridylmethyl, 4-pyridylmethyl, methyl, isobutyl, hydroxymethyl, carboxymethyl, 4-aminobutyl, etc., and more preferably, 4-hydroxybenzyl, 3-pyridylmethyl, 4-pyridylmethyl, etc.

Preferably, Q^4 includes carbamoylmethyl, 2-carbamoylethyl, 4-hydroxybenzyl, 4-imidazolemethyl, isobutyl, hydroxymethyl, 1-hydroxyethyl, carboxymethyl, 4-aminobutyl, etc., and more preferably, carbamoylmethyl, 2-carbamoylethyl, 4-hydroxybenzyl, etc.

Preferably, Q^5 includes benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 4-aminobenzyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-indolemethyl, 1-formylindol-3-ylmethyl, 2-quinolylmethyl, cyclohexylmethyl, hydroxymethyl, 1-hydroxyethyl, methyl, isopropyl, isobutyl, sec-butyl, carboxymethyl, 4-aminobutyl, etc., more preferably,

benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 4-aminobenzyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-indolemethyl, 2-quinolylmethyl, cyclohexylmethyl, 1-hydroxyethyl, isopropyl, isobutyl, sec-butyl, etc.

Preferably, Q^6 is methyl, hydroxymethyl, 1-hydroxyethyl, carbamoylmethyl, 2-carbamoylethyl, etc., more preferably, carbamoylmethyl, etc.

Preferably, Q^7 is 4-hydroxybenzyl, carbamoylmethyl, 3-pyridylmethyl, methyl, isobutyl, benzyl, 4-aminobutyl, 3-indolemethyl, etc., more preferably, 4-hydroxybenzyl, etc.

Preferably, Q^8 is benzyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-naphthylmethyl, 3-indolemethyl, hydroxymethyl, cyclohexylmethyl, sec-butyl, 1-hydroxyethyl, methyl, methyl, isobutyl, 4-aminobutyl, 3-carboxypropyl, etc., more preferably, 4-pyridylmethyl, 3-indolemethyl, sec-butyl, etc.

Preferably, Q^9 is hydrogen atom, methyl, ethyl, hydroxymethyl, 1-hydroxyethyl, carbamoylmethyl, 2-carbamoylethyl, ureidomethyl, acetamidomethyl, formamidemethyl, methylcarbamoylmethyl, dimethylcarbamoylmethyl, etc., more preferably, carbamoylmethyl, ureidomethyl, etc.

Preferably, Q^{10} is 4-hydroxybenzyl, 3-indolemethyl, methyl, 1-hydroxyethyl, 3-guanidinopropyl, etc., more preferably, 3-indolemethyl, etc.

Preferably, Q^{11} is carbamoylmethyl, etc.

Preferably, Q^{12} is methyl, carbamoylmethyl, etc., more preferably, carbamoylmethyl, etc.

Y^1 through Y^3 each represents a group represented by formula: $-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group).

As the C_{1-3} alkyl group represented by J^{13} and J^{14}, there is used methyl, ethyl, propyl or isopropyl.

J^{13} is hydrogen atom.

J^{14} is hydrogen atom.

Y^1 is preferably a group represented by formula: -CONH- or $-CH_2NH-$, etc.

Y^2 is preferably a group represented by formula: -CONH- or $-CH_2NH-$, etc.

Y^3 is preferably a group represented by formula: -CONH-, etc..

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5, J^6 and Q^6, J^7 and Q^7, J^8 and Q^8, J^9 and Q^9, J^{10} and Q^{10}, J^{11} and Q^{11}, and J^{12} and Q^{12} may be combined together to form a ring. In this

case, for example, cyclopentane, cyclohexane, piperidine, etc. are formed by $C(J^3)(Q^3)$, $C(J^4)(Q^4)$, $C(J^5)(Q^5)$, $C(J^6)(Q^6)$, $C(J^7)(Q^7)$, $C(J^8)(Q^8)$, $C(J^9)(Q^9)$, $C(J^{10})(Q^{10})$, $C(J^{11})(Q^{11})$ or $C(J^{12})(Q^{12})$.

Z^1 and R^1, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, Y^3 and Q^6, J^2 and Q^7, Y^2 and Q^8, Y^3 and Q^9, J^2 and Q^{10}, Y^3 and Q^{11}, and J^2 and Q^{12} (preferably, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, Y^3 and Q^6, J^2 and Q^7, Y^2 and Q^8, Y^3 and Q^9, J^2 and Q^{10}, Y^3 and Q^{11}, and J^2 and Q^{12}) may be combined together to form a ring. Alternatively, the ring formed may be optionally substituted, or annealed.

In the case where Z^1 and R^1, J^2 and Q^3, J^2 and Q^7, J^2 and Q^{10}, or J^2 and Q^{12} may be combined together to form a ring, for example, azetidine, pyrrolidine, piperidine or thiazolidine is formed by Z^1-N-CH-R^1, J^2-$C(J^3)(Q^3)$, J^2-$C(J^7)(Q^7)$, J^2-$C(J^{10})(Q^{10})$ or J^2-$C(J^{12})(Q^{12})$. Alternatively, the ring formed may be optionally substituted, or annealed. Z^1-N-CH-R^1 is preferably azetidine, pyrrolidine, 4-hydroxypyrrolidine, piperidine, etc.

In the case where Y^1 and Q^4, Y^2 and Q^5, Y^3 and Q^6, Y^2 and Q^8, Y^3 and Q^9, or Y^3 and Q^{11} may be combined together to form a ring, for example, pyrrolidine-2-carbonyl, piperidin-2-carbonyl or thiazolidine-4-carbonyl is formed by $Y^1C(J^4)(Q^4)$, $Y^2C(J^5)(Q^5)$, $Y^3C(J^6)(Q^6)$, $Y^2C(J^8)(Q^8)$, $Y^3C(J^9)(Q^9)$, or $Y^3C(J^{11})(Q^{11})$. Alternatively, the ring formed may be optionally substituted, or annealed.

Preferred examples of the group represented by formula: J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$- include:

Tyr Asn Trp Asn-,
Tyr Asn Trp D-Asn-,
Tyr Asn D-Trp Asn-,
Tyr D-Asn Trp Asn-,
D-Tyr Asn Trp Asn-,
Tyr Lys Trp Asn-,
Tyr Asp Trp Asn-,
Tyr Tyr Trp Asn-,
Tyr Leu Trp Asn-,
Tyr Asn Ala Asn-,
Tyr Asn Leu Asn-,
Tyr Asn Ser Asn-,
Tyr Asn Asp Asn-,

Tyr Asn Lys Asn-,
Ala Asn Trp Asn-,
Leu Asn Trp Asn-,
Ser Asn Trp Asn-,
Asp Asn Trp Asn-,
Lys Asn Trp Asn-,
Tyr Asn Trp(For)Asn-,
D-Tyr Asn D-Trp Asn-,
D-Tyr Asn Ala Asn-,
D-Tyr Asn Ser Asn-,
D-Tyr Asn Cha Asn-,
D-Tyr Asn Thr Asn-,
D-Tyr Asn Ile Asn-,
D-Tyr Gln Trp Asn-,
D-Tyr Thr Trp Asn-,
D-Tyr Asn Val Asn-,
D-Tyr D-Asn Trp Asn-,
D-Tyr D-Asn D-Trp Asn-,
D-Tyr Asn Phe Asn-,
D-Tyr Asn Nal(1) Asn-,
D-Tyr Asn Nal(2) Asn-,
D-Tyr Asn Phe(2Cl) Asn-,
D-Tyr Asn Phe(3Cl) Asn-,
D-Tyr Asn Phe(4Cl) Asn-,
D-Tyr Asn Phe($4NH_2$) Asn-,
D-Tyr Asn Pya(3) Asn-,
D-Tyr D-Asn Phe Asn-,
D-Tyr D-Asn Cha Asn-,
D-Tyr D-Asn Thr Asn-,
D-Tyr Asn Pya(2) Asn-,
D-Tyr Asn Pya(4) Asn-,
D-Tyr D-Ser Trp Asn-,
D-Tyr D-His Trp Asn-,
D-Pya(3) D-Asn Cha Asn-,

D-Pya(3) D-Tyr Cha Asn-,
TyrΨ(CH_2NH)Asn Trp Asn-,
D-Tyr AsnΨ(CH_2NH)Trp Asn-,
TyrΨ(CH_2NH)Asn D-Trp Asn-,
D-Tyr Asn Ala(2-Qui) Asn-,
D-Tyr Asn D-Pya(4) Asn-,
D-Tyr D-Asn Pya(4) Asn-,
Tyr D-Asn Cha Asn-,
Dap D-Tyr Asn Trp Asn-
Arg D-Tyr D-Pya(4) Asn-
Arg Arg D-Tyr D-Pya(4) Asn-
Arg Acp D-Tyr D-Pya(4) Asn-
D-Arg Acp D-Tyr D-Trp Asn-
D-Arg D-Arg Acp D-Tyr D-Trp Asn-
Ac D-Arg Acp D-Tyr D-Trp Asn-
D-Dap Acp D-Tyr D-Trp Asn-
D-Nle Acp D-Tyr D-Trp Asn-
D-Arg β-Ala D-Tyr D-Trp Asn-
D-Arg γ-Abu D-Tyr D-Trp Asn-
D-Arg D-Arg γ-Abu D-Tyr D-Trp Asn-
D-Arg D-Arg D-Arg γ-Abu D-Tyr D-Trp Asn-
Gly D-Tyr D-Trp Asn-
Ac Gly D-Tyr D-Trp Asn-
D-Tyr D-Tyr D-Trp Asn-
Ac D-Tyr D-Tyr D-Trp Asn-
pGlu D-Tyr D-Trp Asn-
Tyr D-Tyr D-Trp Asn-
Ac Tyr D-Tyr D-Trp Asn-, and the like.

Preferred examples of the group represented by formula: J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$- include:
Fmoc Asn Trp Asn-,
D-Asn Trp Asn-,
D-Tyr Trp Asn-,
D-Tyr D-Trp Asn-,

D-Tyr Ser Asn-,
D-Tyr Thr Asn-,
D-Tyr Ile Asn-,
D-Tyr Phe Asn-,
D-Tyr Nal(2) Asn-,
D-Pya(3) Phe Asn-,
D-Pya(3) Trp Asn-,
D-Tyr D-Pya(4) Asn-,
D-Asn Cha Asn-
D-Tyr D-Pya(4) Ala-
D-Tyr D-Pya(4) Thr-
D-Tyr Pya(4) Ala-
D-Tyr D-Trp Ala-
D-Tyr D-Trp Abu-
D-Tyr D-Phe Ala-6-Aminocaproyl-
D-Tyr D-Pya(4) Asn-
Ac D-Tyr D-Pya(4) Asn-
Benzoyl D-Tyr D-Trp Asn-
Cyclopropanecarbonyl D-Tyr D-Trp Asn-
Butyryl D-Tyr D-Trp Asn-
Me D-Tyr D-Trp Asn-
Ac D-Tyr D-Trp Gln-
Ac D-Tyr D-Trp Ser-
Ac D-Tyr D-Trp Thr-
Ac D-Tyr D-Trp Alb-
Ac D-Tyr D-Trp Dap(Ac)-
Ac D-Tyr D-Trp Dap(For)-
Ac D-Tyr Trp Asn-
Ac D-NMeTyr D-Trp Asn-
For D-Tyr D-Trp Asn-
Propionyl D-Tyr D-Trp Asn-
Amidino D-Tyr D-Trp Asn-
Ac D-Ala D-Trp Asn-
Ac D-Leu D-Trp Asn-

Ac D-Phe D-Trp Asn-
Ac D-Nal(1) D-Trp Asn-
Ac D-Nal(2) D-Trp Asn-
Ac D-Lys D-Trp Asn-
Ac D-Glu D-Trp Asn-
Ac D-Tyr D-Ala Asn-
Ac D-Tyr D-Leu Asn-
Ac D-Tyr D-Phe Asn-
Ac D-Tyr D-Thr Asn-
Ac D-Tyr D-Lys Asn-
Ac D-Tyr D-Glu Asn-
Ac D-Tyr D-Trp Asp-
Ac D-Tyr D-Trp D-Asn-
Ac D-Tyr D-Trp NMeAsn-
Ac D-Tyr Pro Asn-
Ac D-Tyr D-Pya(2) Asn-
Ac D-Tyr D-Pya(3) Asn-
Ac D-Tyr D-Pro Asn-
Ac D-Tyr Tic Asn-
Ac Tyr Trp Asn-
Ac D-Tyr NMeTrp Asn-
Glycoloyl D-Tyr D-Trp Asn-
Ac D-Tyr D-Trp Gly-
Ac D-Tyr D-Trp Dap-
Ac D-Tyr D-Trp Asp(NHMe)-
Ac D-Tyr D-Trp Asp(NMe2)-, and the like.

Preferred examples of the group represented by formula: J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$- include:
Fmoc Trp Asn-,
Boc Tyr Asn-,
Tyr Asn-,
D-Trp Asn-,
Ac Trp Asn-,
Amidino Trp Asn-,

Ac Ala Asn-,
Ac Arg Asn-,
Ac Thr Asn-
D-Tyr D-Pya(4)-
3-(4-Hydroxyphenyl)propionyl D-Trp Asn-
D-Trp Asn-
Ac D-Trp Asn-
Hexanoyl D-Trp Asn-
Cyclohexanecarbonyl D-Trp Asn-
Benzoyl D-Trp Asn-
3-Pyridinepropionyl D-Trp Asn-
Adipoyl D-Trp Asn-
6-Aminocaproyl D-Trp Asn-
Amidino D-Trp Asn-
Glycoloyl D-Trp Asn-, and the like.

Preferred examples of the group represented by formula: J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})- include:
Fmoc Asn-,
3-(Indol-3-yl)propionyl Asn-,
3-Indolecarbonyl Asn-,
3-Indoleacetyl Asn-,
4-(Indol-3-yl)butyryl Asn-,
Diphenylacetyl Asn-,
Hexanoyl Asn-,
Cyclohexanecabonyl Asn-,
2-(Indol-3-yl)ethylcabamoyl Asn-,
3-(3-Pyridyl)propionyl Asn-,
4-Imidzoleacetyl Asn-,
Piperidinecarbonyl Asn-,
1-Piperidineacetyl Asn-,
1-Methyl-1-piperidinioacetyl Asn-,
1-Pyridinioacetyl Asn-,
D-Glucuronyl Asn-,
3-Phenylpropionyl Asn-,

Ac D-Phe D-Trp Asn-

Ac D-Nal(1) D-Trp Asn-

Ac D-Nal(2) D-Trp Asn-

Ac D-Lys D-Trp Asn-

3-Phenylpropionyl Ala-,

Benzoyl Asn-,

Ac Asn-,

Cyclopropanecarbonyl Asn-,

2-Naphthoyl Asn-, and the like.

Preferred examples of the group represented by formula: J^{1-} include:

hydrogen atom,

GuAmb-,

3-(3-Indolyl)propionyl-,

3-(3-Pyridyl)propionyl-,

Benzoyl-,

Indole-3-carbonyl-,

Indole-3-acetyl-,

Ac-,

Hexanoyl-,

Z-,

Tos-,

3-Phenylpropionyl-,

2-(Indol-3-yl)ethylcarbamoyl-,

Benzyl-,

Phenethyl-,

2-Pyridinecarbonyl-,

4-Pyridinecarbonyl-,

Propionyl-,

Isobutyryl-,

Cyclohexanecarbonyl-,

Phenylacetyl-,

2-Methylnicotinoyl-,

5-Methylnicotinoyl-,

6-Methylnicotinoyl-,

Pyrazinecarbonyl-,

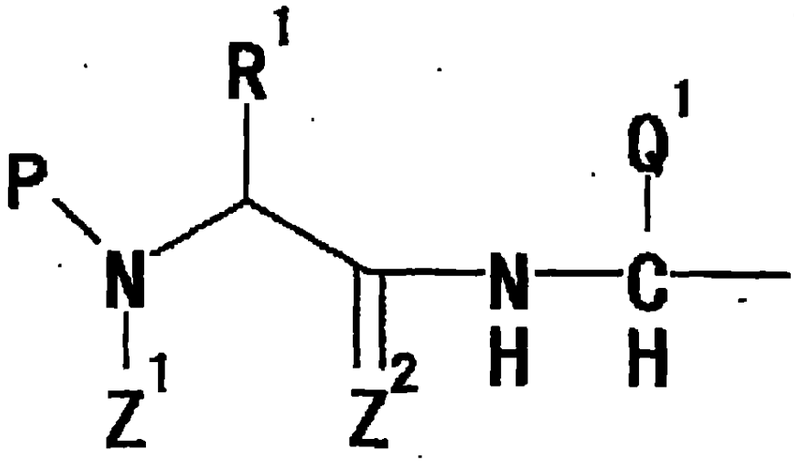
Cyclopropanecarbonyl-,

Trifluoroacetyl-,

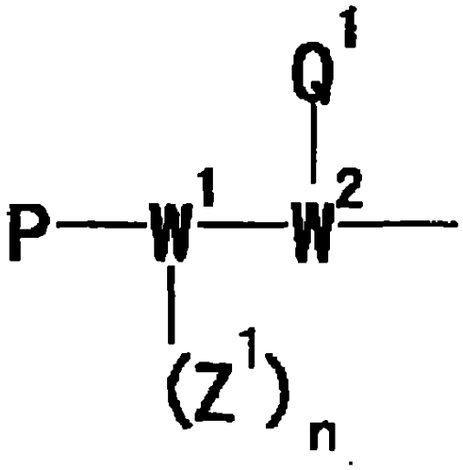
(R)-3-hydroxy-2-methylpropionyl-,

2-Hydroxyisobutyryl-,
3-Furancarbonyl-,
Pyrrole-2-carbonyl-,
4-Imidazolecarbonyl-,
6-Hydroxynicotinoyl-,
6-Chloronicotinoyl-,
6-(Trifluoromethyl)nicotinoyl-,
Dimethylcarbamoyl-,
1-Azetidinecarbonyl-,
2-Azetidinecarbonyl-,
4-Aminobenzoyl-,
4-Aminomethylbenzoyl-,
Pyrrole-3-carbonyl-,
Pyrimidine-4-carbonyl-,
Pyrimidine-2-carbonyl-,
Pyridazine-4-carbonyl-, and the like.

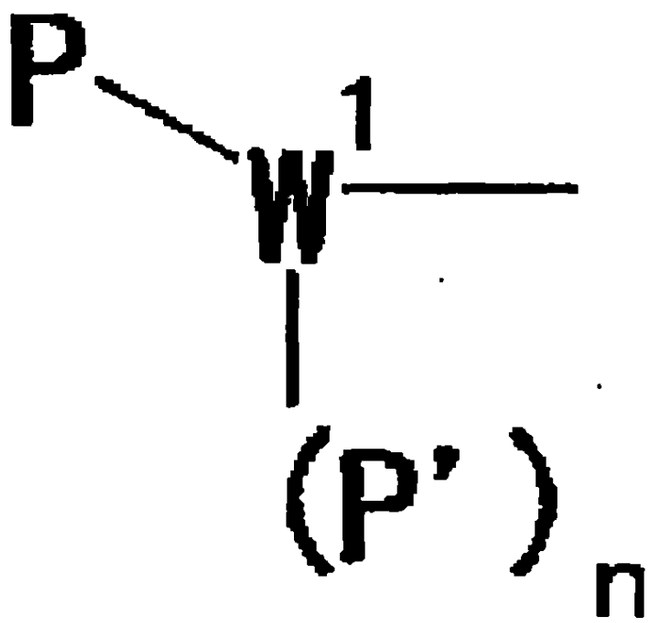
The metastin derivatives (I) in the metastin derivatives (III) of the present invention, wherein V' represents the group represented by formula:



(wherein each symbol has the same significance as defined above) are a class of compound disclosed in the specification filed as PCT/JP03/16978, whereas the metastin derivatives (II), wherein V' represents the group represented by formula:



(wherein each symbol has the same significance as defined above), or the group represented by formula:



(wherein each symbol has the same significance as defined above) are novel compounds.

In the metastin derivatives (III), all compounds that the groups shown by the respective symbols are optionally combined are preferably used. Among them, the compounds shown by Compound Numbers below (TABLES 1 through 11) are

preferred.

MS10 :Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

1 2 3 4 5 6 7 8 9 10

Compound No. 17: [Pya(4)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Pya(4)-NH_2

Compound No. 18: [Tyr(Me)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Tyr(Me)-NH_2

Compound No. 19: [Phe(2F)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(2F)-NH_2

Compound No. 23: [Tyr5]MS10

Tyr-Asn-Trp-Asn-Tyr-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 24: [Leu5]MS10

Tyr-Asn-Trp-Asn-Leu-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 30: Acetyl-MS10

Acetyl-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 31: Fmoc-MS10

Fmoc-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 38: [D-Ser5]MS10

Tyr-Asn-Trp-Asn-D-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 39: [D-Asn4]MS10

Tyr-Asn-Trp-D-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 40: [D-Trp3]MS10

Tyr-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 41: [D-Asn2]MS10

Tyr-D-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 42: [D-Tyr1]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 44: [Lys9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Lys-Phe-NH2

Compound No. 45: [Ala8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Ala-Arg-Phe-NH_2

Compound No. 50: [Ala7]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Ala-Leu-Arg-Phe-NH_2

Compound No. 51: [NMePhe10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-NMePhe-NH_2

Compound No. 53: des(1-3)-Fmoc-MS10

Fmoc-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 54: des(1-2)-Fmoc-MS10

Fmoc-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 55: des(1)-Fmoc-MS10

Fmoc-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 56: [Lys2]MS10

Tyr-Lys-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 57: [Asp2]MS10

Tyr-Asp-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 58: [Tyr2]MS10

Tyr-Tyr-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 59: [Leu2]MS10

Tyr-Leu-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 60: [Pya(3)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Pya(3)-NH_2

Compound No. 61: [Phe(4F)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4F)-NH_2

Compound No. 67: [Ala3]MS10

Tyr-Asn-Ala-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 68: [Leu3]MS10

Tyr-Asn-Leu-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 69: [Ser3]MS10

Tyr-Asn-Ser-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 70: [Asp3]MS10

Tyr-Asn-Asp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 71: [Lys3]MS10

Tyr-Asn-Lys-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 72: [Ala1]MS10

Ala-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 73: [Leu1]MS10

Leu-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 74: [Ser1]MS10

Ser-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 75: [Asp1]MS10

Asp-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 76: [Lys1]MS10

Lys-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 77: [Phe(4CN)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4CN)-NH_2

Compound No. 78: [Trp(For)3, Phe(4CN)10]MS10

Tyr-Asn-Trp(For)-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4CN)-NH_2

Compound No. 79: [Hph10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Hph-NH_2

Compound No. 81: [NMeArg9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-NMeArg-Phe-NH_2

Compound No. 82: [Arg(Me)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 83: [Arg(asy Me_2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(asyMe_2)-Phe-NH_2

Compound No. 87: des(4-5)-Boc-MS10

Boc-Tyr-Asn-Trp-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 88: des(4-5)-MS10

Tyr-Asn-Trp-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 90: [Lys9,9Ψ10,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-LysΨ(CH_2NH)Phe-NH_2

Compound No. 91: [8Ψ9,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-LeuΨ(CH_2NH)Arg-Phe-NH_2

Compound No. 97: [Har9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Har-Phe-NH_2

Compound No. 98: [Lys(Me_2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Lys(Me_2)-Phe-NH_2

Compound No. 101: [Ser7]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Ser-Leu-Arg-Phe-NH_2

Compound No. 105: [Nle8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Nle-Arg-Phe-NH_2

Compound No. 107: [Val8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Val-Arg-Phe-NH_2

Compound No. 109: [Tyr10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Tyr-NH_2

Compound No. 110: [Nal(2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Nal(2)-NH_2

Compound No. 111: [Phe(F5)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(F5)-NH_2

Compound No. 112: [Cha10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Cha-NH_2

Compound No. 114: des(1-3)-3-(3-Indolyl)propionyl-MS10

3-(3-Indolyl)propionyl-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 121: des(1-4)-[Trp5]MS10

Trp-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 123: [NMeLeu8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-NMeLeu-Arg-Phe-NH_2

Compound No. 126: [NMeSer5]MS10

Tyr-Asn-Trp-Asn-NMeSer-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 127: [D-Asn4,NMePhe6]MS10

Tyr-Asn-Trp-D-Asn-Ser-NMePhe-Gly-Leu-Arg-Phe-NH_2

Compound No. 128: [10Ψ,CSNH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-PheΨ(CSNH)NH_2

Compound No. 129: [Arg(symMe_2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(symMe_2)-Phe-NH_2

Compound No. 130: [Phe(4Cl)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4Cl)-NH_2

Compound No. 131: [Phe(4NH_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4NH_2)-NH_2

Compound No. 132: [Phe(4NO_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4NO_2)-NH_2

Compound No. 133: [Nal(1)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Nal(1)-NH_2

Compound No. 134: [Trp10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Trp-NH_2

Compound No. 137: [Nle9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Nle-Phe-NH_2

Compound No. 138: [Cit9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Cit-Phe-NH_2

Compound No. 140: [Arg(Me)9,NMePhe10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-NMePhe-NH_2

Compound No. 141: [D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 142: [D-Tyr1,D-Trp3,Arg(Me)9]MS10

D-Tyr-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 143: [D-Trp3,Arg(Me)9]MS10

Tyr-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 144: des(1-3)-Fmoc-[Arg(Me)9]MS10

Fmoc-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 145: des(1-2)-Fmoc-[Arg(Me)9]MS10

Fmoc-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 146: [10Ψ,CSNH,D-Tyr1]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-PheΨ(CSNH)NH_2

Compound No. 150: [Tyr6]MS10

Tyr-Asn-Trp-Asn-Ser-Tyr-Gly-Leu-Arg-Phe-NH_2

Compound No. 151: [Nal(1)6]MS10

Tyr-Asn-Trp-Asn-Ser-Nal(1)-Gly-Leu-Arg-Phe-NH_2

Compound No. 152: [Nal(2)6]MS10

Tyr-Asn-Trp-Asn-Ser-Nal(2)-Gly-Leu-Arg-Phe-NH_2

Compound No. 153: [Phe(F5)6]MS10

Tyr-Asn-Trp-Asn-Ser-Phe(F_5)-Gly-Leu-Arg-Phe-NH_2

Compound No. 154: [Phe(4F)6]MS10

Tyr-Asn-Trp-Asn-Ser-Phe(4F)-Gly-Leu-Arg-Phe-NH_2

Compound No. 156: [Cha6]MS10

Tyr-Asn-Trp-Asn-Ser-Cha-Gly-Leu-Arg-Phe-NH_2

Compound No. 163: [6Ψ7,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-PheΨ(CH_2NH)Gly-Leu-Arg-Phe-NH_2

Compound No. 165: [Dap(Gly)9]-MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Dap(Gly)-Phe-NH_2

Compound No. 166: [6Ψ7,CSNH]MS10

Tyr-Asn-Trp-Asn-Ser-PheΨ(CSNH)Gly-Leu-Arg-Phe-NH_2

Compound No. 169: [D-Tyr1,Ala3,Arg(Me)9]MS10

D-Tyr-Asn-Ala-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 170: [D-Tyr1,Ser3,Arg(Me)9]MS10

D-Tyr-Asn-Ser-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 171: [D-Tyr1,Cha3,Arg(Me)9]MS10

D-Tyr-Asn-Cha-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 172: [D-Tyr1,Cha6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 173: [D-Tyr1,Ala7,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Ala-Leu-Arg(Me)-Phe-NH_2

Compound No. 174: [D-Tyr1,Arg(Me)9,Trp10]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 176: [AzaGly7]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg-Phe-NH_2

Compound No. 181: [D-Tyr1,Cha3,6,Arg(Me)9]MS10

D-Tyr-Asn-Cha-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 182: [D-Tyr1,Cha3,6,Arg(Me)9,Trp10]MS10

D-Tyr-Asn-Cha-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 183: [Phe(4NH_2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Phe(4NH_2)-Phe-NH_2

Compound No. 184: [Phe(4-Guanidino)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Phe(4-Guanidino)-Phe-NH_2

Compound No. 185: [Dap(GnGly)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Dap(GnGly)-Phe-NH_2

Compound No. 186: [Trp(For)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Trp(For)-NH_2

Compound No. 187: [Abu8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Abu-Arg-Phe-NH_2

Compound No. 189: [Ala(3-Bzt)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Ala(3-Bzt)-NH_2

Compound No. 190: [D-Tyr1,Cha3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 191: [D-Tyr1,Ser3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ser-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 192: [D-Tyr1,Arg(Et)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Et)-Phe-NH_2

Compound No. 193: [D-Tyr1,Arg(n-Pr)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(n-Pr)-Phe-NH_2

Compound No. 194: [D-Tyr1,Arg(Ac)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Ac)-Phe-NH_2

Compound No. 197: [Phe(3F)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3F)-NH_2

Compound No. 198: [Phe(3,4F_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3,4F_2)-NH_2

Compound No. 199: [Phe(3,4Cl_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3,4Cl_2)-NH_2

Compound No. 200: [Phe(3CF_3)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3CF_3)-NH_2

Compound No. 201: [Ala(2-Qui)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Ala(2-Qui)-NH_2

Compound No. 203: [D-Tyr1,Cha6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 204: [D-Tyr1, Ala7, Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Ala-Leu-Arg(Me)-Phe-NH_2

Compound No. 205: [D-Tyr1,Thr3,Arg(Me)9]MS10

D-Tyr-Asn-Thr-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 206: [D-Tyr1,Ile3,Arg(Me)9]MS10

D-Tyr-Asn-Ile-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 207: [D-Tyr1,Ser4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Ser-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 208: [D-Tyr1,Thr4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Thr-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 209: [D-Tyr1,Gln4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Gln-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 210: [D-Tyr1,Ala4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Ala-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 211: [D-Tyr1,Thr5,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Thr-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 212: [D-Tyr1,Ala5,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ala-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 213: [D-Tyr1,Val8,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Val-Arg(Me)-Phe-NH_2

Compound No. 214: [D-Tyr1,Gln2,Arg(Me)9]MS10

D-Tyr-Gln-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 215: [D-Tyr1,Thr2,Arg(Me)9]MS10

D-Tyr-Thr-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 216: des(1)-[D-Asn2,Arg(Me)9]MS10

D-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 217: des(1)-[D-Tyr2,Arg(Me)9]MS10

D-Tyr-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 218: [N($(CH_2)_3$Gn)]Gly9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-N($(CH_2)_3$Gn)Gly-Phe-NH_2

Compound No. 220: [Arg(Et)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Et)-Phe-NH_2

Compound No. 221: [D-Tyr1,Thr3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 222: des(1)-[D-Tyr2,AzaGly7,Arg(Me)9]MS10

D-Tyr-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 223: des(1-2)-[D-Trp3,Arg(Me)9]MS10

D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 224: des(1)-[D-Tyr2,D-Trp3,Arg(Me)9]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 225: des(1)-[D-Asn2,D-Trp3,Arg(Me)9]MS10

D-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 226: des(1)-[D-Tyr2,Ser3,Arg(Me)9]MS10

D-Tyr-Ser-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 227: des(1)-[D-Tyr2,Thr3,Arg(Me)9]MS10

D-Tyr-Thr-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 228: des(1)-[D-Tyr2,Ile3,Arg(Me)9]MS10

D-Tyr-Ile-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 229: [D-Tyr1,Val3,Arg(Me)9]MS10

D-Tyr-Asn-Val-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 230: [D-Tyr1,D-Asn2,Arg(Me)9]MS10

D-Tyr-D-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 231: [D-Tyr1,D-Asn2,D-Trp3,Arg(Me)9]MS10

D-Tyr-D-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 232: [D-Tyr1,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 233: [D-Tyr1,Ile3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ile-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 234: [D-Tyr1,Val3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Val-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 235: [D-Tyr1,Ala3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ala-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 236: [D-Tyr1,D-Trp3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 237: [D-Tyr1,D-Asn2,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 238: [D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 239: des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Ser-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 240: des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Ile-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 241: des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 242: des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 244: [D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 245: [D-Tyr1,Nal(1)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Nal(1)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 246: [D-Tyr1,Nal(2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Nal(2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 247: [D-Tyr1,Phe(2Cl)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe(2Cl)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 248: [D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe(3Cl)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 249: [D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe(4Cl)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 250: [D-Tyr1,Phe(4NH2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe(4NH_2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 251: [D-Tyr1,Pya(3)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pya(3)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 252: [D-Tyr1,D-Ala3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-D-Ala-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 253: [D-Tyr1,Pro3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pro-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 254: des(1)-[D-Tyr2,Phe3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 255: des(1)-[D-Tyr2,Nal(2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Nal(2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 256: des(1)-[D-Pya(3)2,Phe3,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 257: [D-Tyr1,D-Asn2,Phe3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 258: [D-Pya(3)1,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 259: [D-Ala1,AzaGly7,Arg(Me)9]MS10

D-Ala-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 260: des(1-3)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9]MS10

3-(3-Indolyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 261: [7Ψ8,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-GlyΨ(CH_2NH)Leu-Arg-Phe-NH_2

Compound No. 265: des(1-3)-Indole-3-carbonyl-[AzaGly7,Arg(Me)9]MS10

Indole-3-carbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 266: des(1-3)-Indole-3-acetyl-[AzaGly7,Arg(Me)9]MS10

Indol-3-acetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 267: des(1-3)-4-(3-Indolyl)butyryl-[AzaGly7,Arg(Me)9]MS10

4-(3-Indolyl)butyryl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 268: des(1-3)-Diphenylacetyl-[AzaGly7,Arg(Me)9]MS10

Diphenylacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 269: des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9]MS10

3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 270: [D-Tyr1,Phe3,Ser-Phe5,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe-Asn-Ser-Phe-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 271: des(1-2)-[AzaGly7,Arg(Me)9]MS10

Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 272: des(1-2)-Acetyl-[AzaGly7,Arg(Me)9]MS10

Acetyl-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 273: des(1-2)-Amidino-[AzaGly7,Arg(Me)9]MS10

Amidino-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 274: des(1-2)-Acetyl-[Ala3,AzaGly7,Arg(Me)9]MS10

Acetyl-Ala-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 275: des(1-2)-Acetyl-[Arg3,AzaGly7,Arg(Me)9]MS10

Acetyl-Arg-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 276: des(1-2)-Acetyl-[Thr3,AzaGly7,Arg(Me)9]MS10

Acetyl-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 277: des(1-3)-n-Hexanoyl-[AzaGly7,Arg(Me)9]MS10

n-Hexanoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 278: des(1-3)-Cyclohexanecarbonyl-[AzaGly7, Arg(Me)9]MS10

Cyclohexanecarbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 279: des(1-3)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10

2-(indol-3-yl)ethylcarbamoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 281: [D-Tyr1,Pya(2)6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Pya(2)-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 282: [D-Tyr1,Pya(4)6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Pya(4)-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 283: [D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 284: [D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 285: [D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pya(2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 286: [D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 287: [D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Ser-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 288: [D-Tyr1,D-His2,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-His-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 289: des(1)-[D-Pya(3)2,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 290: [D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 291: [D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-D-Tyr-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 293: [4Ψ5,CH_2NH]MS10

Tyr-Asn-Trp-AsnΨ(CH_2NH)Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 294: [1Ψ2,CH_2NH]MS10

TyrΨ(CH_2NH)Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 295: [2Ψ3,CH_2NH]MS10

Tyr-AsnΨ(CH_2NH)Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 296: [6Ψ7,CSNH,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-PheΨ(CSNH)Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 297: [D-Tyr1,Thr5,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 298: [D-Tyr1,D-Asn2,Thr5,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 299: [1Ψ2,CH_2NH,AzaGly7,Arg(Me)9]-MS10

TyrΨ(CH_2NH)Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 300: [1Ψ2,CH_2NH,D-Trp3,AzaGly7,Arg(Me)9]-MS10

TyrΨ(CH_2NH)Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 301: [D-Tyr1,Ala(2-Qui)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ala(2-Qui)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 302: [D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 303: [D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 304: [D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 305: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 306: [D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Pya(4)-D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 307: [7Ψ8,CH_2NH,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-GlyΨ(CH_2NH)Leu-Arg(Me)-Phe-NH_2

Compound No. 308: [6Ψ7,CH_2NH,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-PheΨ(CH_2NH)Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 310: [Nar9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Nar-Phe-NH_2

Compound No. 311: [Nar(Me)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Nar(Me)-Phe-NH_2

Compound No. 312: [Har(Me)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Har(Me)-Phe-NH_2

Compound No. 313: [Dab9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Dab-Phe-NH_2

Compound No. 314: [Orn9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Orn-Phe-NH_2

Compound No. 315: des(1)-[D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 316: [D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

D-Tyr-D-Asn-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 317: [D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 318: [D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 319: [6Ψ7,NHCO,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-PheΨ(NHCO)Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 322: des(1-3)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10

3-(3-Pyridyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 323: des(1-3)-4-Imidazoleacetyl-[AzaGly7,Arg(Me)9]MS10

4-Imidazoleacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 324: des(1-3)-4-Piperidinecarbonyl-[AzaGly7,Arg(Me)9]MS10

Piperidinecarbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 325: des(1-3)-1-Piperidineacetyl-[AzaGly7,Arg(Me)9]MS10

1-Piperidineacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 326: des(1-3)-1-Methylpiperidinio-1-acetyl-[AzaGly7,Arg(Me)9]MS10

1-Methylpiperidino-1-acetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 327: des(1-3)-1-Pyridinioacetyl-[AzaGly7,Arg(Me)9]MS10

1-Pyridinoacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 328: des(1-3)-D-Glucuronyl-[AzaGly7,Arg(Me)9]MS10

D-Glucuronyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 375:2-Aminoethyl-Gly-[D-Tyr1,Arg(Me)9]MS10

2-Aminoethyl-Gly-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 385: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 386: des(1-3)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

3-(3-Pyridyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 387:Dap-[D-Tyr1,Arg(Me)9]MS10

Dap-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 397:Methylthiocarbamoyl-Sar-[D-Tyr1,Arg(Me)9]MS10

Methylthiocarbamoyl-Sar-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 400:

(S)-1-(Quinolin-8-yl-carbamoyl)-4-thiapentylcarbamoyl-[D-Tyr1,Arg(Me)9]MS10

(S)-1-(Quinolin-8-yl-carbamoyl)-4-thiapentylcarbamoyl-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 481: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Trp-NH_2

Compound No. 486: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Orn9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Orn-Phe-NH_2

Compound No. 487: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Lys9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Lys-Phe-NH_2

Compound No. 488: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Phe-NH_2

Compound No. 489: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har(Me)9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har(Me)-Phe-NH_2

Compound No. 490: des(1)-[D-Tyr2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 491: des(1)-[D-Tyr2,D-Pya(4)3,Trp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Trp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 492: des(1)-[D-Tyr2,D-Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 493: des(1)-[D-Tyr2,D-Pya(4)3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 494: des(1,4)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 495: des(1-3)-[D-Tyr4,Pya(4)5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-Pya(4)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 496: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 497: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Ala7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Cha-Ala-Leu-Arg(Me)-Trp-NH_2

Compound No. 498: des(1)-[D-Tyr2,D-Pya(4)3,Ile5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 499: des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 500:

des(1-3)-3-Phenylpropionyl-[Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 501: des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 502: des(1)-[D-Tyr2,Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 503: des(1)-[D-Tyr2,D-Trp3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 504: [Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 505:

des(1-3)-3-Phenylpropionyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 506:

des(1-3)-3-Phenylpropionyl-[Ile5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 507:

des(1-3)-3-Phenylpropionyl-[Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 508:

des(1-3)-3-Phenylpropionyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 509: des(1-3)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 510: des(1-3)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 511:

des(1)-[D-Tyr2,D-Trp3,Ala4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Ala-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 512: des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 513: des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 514: des(1)-[D-Tyr2,D-Phe3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Phe-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 515: des(1)-[D-Tyr2,D-Pya(4)3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 516: des(1)-Ac-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 517:

des(1-3)-3-Phenylpropionyl-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 518: des(1-3)-3-Phenylpropionyl-[Cha6,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 519: des(1-3)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Phenylacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 521: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg-Phe-NH_2

Compound No. 522: des(1-3)-Benzoyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 523: des(1-3)-Benzoyl-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 524: des(1-3)-3-Phenylpropionyl-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 527: des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 528: des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 529: des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Tle-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 530: des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Phg-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 531: des(1-3)-3-Phenylpropionyl-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Pic(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 532: des(1-3)-3-Phenylpropionyl-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 533: des(1-3)-3-Phenylpropionyl-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-D-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 534: des(1-3)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Cyclopropanecarbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 535: des(1-3)-2-Naphthoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Naphthoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 536: [Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 537: Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 538: Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 539: des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 540: des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 541:

D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 542:

D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 545: des(1-3)-Benzoyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 546:

des(1-3)-3-Phenylpropionyl-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 547:

des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 548: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-PheΨ(CSNH)NH_2

Compound No. 550: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 551:

Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 552:

D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 553:

D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 554:

D-Arg-[β-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-β-Ala-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 555:

D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 556:

D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS

10

D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 557:

D-Arg-D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tr

p10]MS10

D-Arg-D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH

2

Compound No. 558: des(1)-Ac-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 559:

des(1-2)-3-(4-Hydroxyphenyl)propionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me

)9,Trp10]MS10

3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 561:

D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 562:

des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 563:

des(1)-Ac-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 564: des(1)-Ac-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 565:

des(1)-Benzoyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 566:

des(1)-Cyclopropanecarbonyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,
Trp10]MS10

Cyclopropanecarbonyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 567:

des(1)-Butyryl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Butyryl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 568:

Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 569:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,6Ψ7,CH_2NH,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-PheΨ(CH_2NH)Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 570: des(1)-Me-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Me-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 571: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 572: des(1)-[D-Trp2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 573:

des(1)-Ac-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 576: des(1)-Ac-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Gln-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 577: des(1)-Ac-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Ser-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 578: des(1)-Ac-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 579: des(1)-Ac-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 580:

des(1)-Ac-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 584:

des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 585:

des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 586: des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 589:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

Compound No. 590: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2

Compound No. 591: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2

Compound No. 592:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 594:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Hph-NH_2

Compound No. 595: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Cha10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Cha-NH_2

Compound No. 596: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Leu10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Leu-NH_2

Compound No. 597:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 598: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 599: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2

Compound No. 600: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2

Compound No. 601: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 602:

des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 603:

des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 604: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Tos)-Trp-NH_2

Compound No. 605:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(NO2)-Trp-NH_2

Compound No. 607:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)asym-Trp-NH_2

Compound No. 608:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)sym-Trp-NH_2

Compound No. 609: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Et)-Trp-NH_2

Compound No. 610:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys(Me2)-Trp-NH_2

Compound No. 611: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 612: des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 613:

des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 614:

des(1)-Amidino-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Amidino-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 615: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 616: des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 617: des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 618: des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 619: des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(1)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 620: des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(2)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 621: des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 622: des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Glu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 623: des(1)-Ac-[D-Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 624: des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 625: des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 626: des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 627: des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 628: des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Thr-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 629: des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 630: des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 631:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Ala-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 632:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Leu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 633:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Lys-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 634:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Glu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 635:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 636:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,MePhe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-MePhe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 637:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 638:

des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 639: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys-Trp-NH_2

Compound No. 641:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ala-Arg(Me)-Trp-NH_2

Compound No. 642:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

Compound No. 643:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Phe-Arg(Me)-Trp-NH_2

Compound No. 644:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ser-Arg(Me)-Trp-NH_2

Compound No. 645: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har-Trp-NH_2

Compound No. 646: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har(Me)-Trp-NH_2

Compound No. 647:

des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 648: [Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 649: Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 650: [D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 651:

Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 652:

des(1)-pGlu-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 653:

des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-D-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 654:

des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-D-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 655:

des(1)-Ac-[D-Tyr2,D-Trp3,MeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-MeAsn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 656:

des(1)-Ac-[D-Tyr2,D-Trp3,MeSer5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-MeSer-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 657: des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 658:

des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 659:

des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-allo-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 660:

des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 661: des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 662: des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 663: des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 664: des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 665: des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 666: des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 667:

des(1-2)-Hexanoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Hexanoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 668:

des(1-2)-Cyclohexanecarbonyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Cyclohexanecarbonyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 669: des(1-2)-Benzoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 670:

des(1-2)-3-Pyridinepropionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Pyridinepropionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 671: des(1-2)-Adipoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Adipionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 672:

des(1)-Ac-[D-Tyr2,NMeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 674:

des(1-2)-6-Aminocaproyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

6-Aminocaproyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 675: [D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 676: Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 677:

Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Nva-Arg(Me)-Trp-NH_2

Compound No. 678:

Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ile-Arg(Me)-Trp-NH_2

Compound No. 679: des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Amidino-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 680:

des(1-2)-Glycoloyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Glycoloyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 681:

des(1)-Glycoloyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Glycoloyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 682:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Gln-Arg(Me)-Trp-NH_2

Compound No. 685: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 686: des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Gly-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 688: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Pya(4)-Trp-NH_2

Compound No. 689:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-D-Trp-NH_2

Compound No. 691:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 692:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 693:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr(Me)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 694:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Nal(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 695:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Thi-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 696:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 698:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Abu-Arg(Me)-Trp-NH_2

Compound No. 699:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-γMeLeu-Arg(Me)-Trp-NH_2

Compound No. 700: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Aib-Arg(Me)-Trp-NH_2

Compound No. 701: des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 702:
des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asp(NHMe)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 703:
des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NMe2)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asp(NMe2)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

However, the metastin derivatives (III) of the present invention do not include a peptide (native human metastin or its partial peptides) consisting of the following amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1, i.e., the amino acid sequence of 1-54 (Compound No. 1), 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54 (Compound No. 2), 41-54, 42-54 (Compound No. 32), 43-54, 44-54, 45-54 (Compound No. 3), 46-54 (Compound No. 4), 47-54, 48-54 or 49-54.

In the metastin derivatives (II), all compounds that the groups shown by the respective symbols are optionally combined are preferably used. Among them, the compounds shown by Compound Numbers below are preferred.

Compound No. 332: des(1-5)-GuAmb-[AzaGly7,Arg(Me)9]MS10
GuAmb-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 333: des(1-5)-GuAmb-[Arg(Me)9]MS10
GuAmb-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 334: des(1-5)-GuAmb-[AzaGly7,Arg(Me)9,Trp10]MS10
GuAmb-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 339: des(1-5)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9]MS10
3-(3-Indolyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 340: des(1-5)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10
3-(3-Pyridyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 341: des(1-5)-Benzoyl-[AzaGly7,Arg(Me)9]MS10
Benzoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 344: des(1-5)-Indole-3-carbonyl-[AzaGly7,Arg(Me)9]MS10
Indole-3-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 345: des(1-5)-Indole-3-acetyl-[AzaGly7,Arg(Me)9]MS10

Indole-3-acetyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 346: des(1-5)-Ac-[AzaGly7,Arg(Me)9]MS10

Ac-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 347: des(1-5)-n-Hexanoyl-[AzaGly7,Arg(Me)9]MS10

n-Hexanoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 348: des(1-5)-Z-[AzaGly7,Arg(Me)9]MS10

Z-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 349: des(1-5)-Tos-[AzaGly7,Arg(Me)9]MS10

Tos-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 351: des(1-5)-Benzoyl-MS10

Benzoyl-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 352: des(1-5)-3-(3-Indolyl)propionyl-MS10

3-(3-Indolyl)propionyl-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 353: des(1-5)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 354: des(1-5)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

3-(3-Indolyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 358: des(1-5)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 362: des(1-6)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9]MS10

3-Phenylpropionyl-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 364: des(1-5)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10

2-(Indol-3-yl)ethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 366: des(1-5)-n-Hexanoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

n-Hexanoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 367: des(1-5)-Z-[AzaGly7,Arg(Me)9,Trp10]MS10

Z-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 368: des(1-5)-Tos-[AzaGly7,Arg(Me)9,Trp10]MS10

Tos-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 369: des(1-5)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-(Indol-3-yl)ethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 373:

des(1-6)-(2S)-2-acetoxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

(2S)-2-acetoxy-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 374: des(1-6)-Z-[AzaGly7,Arg(Me)9,Trp10]MS10

Z-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 378: des(1-6)-Diphenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Diphenylacetyl-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 379: des(1-6)-(2S)-2-(3-Indolylprpionyloxy)-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

(2S)-2-(3-Indolylprpionyloxy)-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 380: des(1-6)-(2S)-2-Benzoyloxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

(2S)-2-Benzoyloxy-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 392: des(1-5)-Benzoyl-[Ala6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Ala-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 393: des(1-6)-Dibenzylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Dibenzylcarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 408: des(1-6)-1-Oxo-isochroman-3-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

1-Oxo-isochroman-3-carbonyl-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 412: des(1-6)-(2R)-2-Benzoyloxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

(2R)-2-Benzoyloxy-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 417: des(1-6)-Benzylphenethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzylphenethylcarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 421: des(1-5)-Benzoyl-[6Ψ7,CH2O,Arg(Me)9,Trp10]MS10

Benzoyl-PheΨ(CH2O)Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 423: des(1-5)-Benzoyl-[6Ψ7,NHCO,Arg(Me)9,Trp10]MS10

Benzoyl-PheΨ(NHCO)Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 428: des(1-6)-Dibenzylaminocarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Dibenzylaminocarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 431: des(1-5)-Benzoyl-[AzaPhe6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-AzaPhe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 432: des(1-5)- 3-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 434: des(1-7)-Dibenzylaminocarbamoylacetyl-[Arg(Me)9,Trp10]MS10

Dibenzylaminocarbamoylacetyl-Leu-Arg(Me)-Trp-NH_2

Compound No. 435: des(1-5)-2-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 436: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 437: des(1-5)-Propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Propionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 438: des(1-5)-Isobutyryl-[AzaGly7,Arg(Me)9,Trp10]MS10

Isobutyryl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 439: des(1-5)-Cyclohexanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Cyclohexanecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 440: des(1-5)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Phenylacetyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 441: des(1-5)-Benzoyl-[Pya(2)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Pya(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 442: des(1-5)-Benzoyl-[Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 443: des(1-5)-2-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Methylnicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 444: des(1-5)-5-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

5-Methylnicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 445: des(1-5)-6-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

6-Methylnicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 446: des(1-5)-Pyrazinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrazinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 447: des(1-5)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Cyclopropanecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 448: des(1-5)-Trifluoroacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Trifluoroacetyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 449: des(1-5)-Benzoyl-[Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 450: des(1-5)-Benzyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 451: des(1-5)-Cyclopropanecarbonyl-[Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Cyclopropanecarbonyl-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 452: des(1-5)-(R)-3-hydroxy-2-methylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

(R)-3-hydroxy-2-methylpropionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 453: des(1-5)-2-Hydroxyisobutyryl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Hydroxyisobutyryl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 454: des(1-5)-3-Furancarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Furancarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 455: des(1-5)-Pyrrole-2-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrrole-2-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 459: des(1-5)-4-Imidazolecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Imidazolecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 460: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Val8,Arg(Me)9,Trp10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

Compound No. 461: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Nal(2)10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

Compound No. 462: des(1-5)-6-Hydroxynicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

6-Hydroxynicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 463: des(1-5)-6-Chloronicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

6-Chloronicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 464: des(1-5)-6-(Trifluoromethyl)nicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

6-(Trifluoromethyl)nicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 466: des(1-5)-2-Azetidinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Azetidinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 467: des(1-5)-Dimethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Dimethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 468: des(1-5)-1-Azetidinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

1-Azetidinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 471: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 472: des(1-5)-4-Aminobenzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Aminobenzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 473: des(1-5)-4-Aminomethylbenzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Aminomethylbenzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 474: des(1-5)-Pyrrole-3-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrrole-3-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 475: des(1-5)-Pyrimidine-4-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrimidine-4-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 477: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Orn9,Trp10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Orn-Trp-NH_2

Compound No. 478: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Har9,Trp10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Har-Trp-NH_2

Compound No. 479: des(1-5)-Pyrimidine-2-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrimidine-2-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 480: des(1-5)-Pyridazine-4-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyridazine-4-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 481: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Trp-NH_2

Compound No. 486: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Orn9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Orn-Phe-NH_2

Compound No. 487: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Lys9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Lys-Phe-NH_2

Compound No. 488: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Phe-NH_2

Compound No. 489: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har(Me)9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har(Me)-Phe-NH_2

Compound No. 490: des(1)-[D-Tyr2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 491: des(1)-[D-Tyr2,D-Pya(4)3,Trp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Trp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 492: des(1)-[D-Tyr2,D-Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 493: des(1)-[D-Tyr2,D-Pya(4)3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 494: des(1,4)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 495: des(1-3)-[D-Tyr4,Pya(4)5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-Pya(4)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 496: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 497: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Ala7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Cha-Ala-Leu-Arg(Me)-Trp-NH_2

Compound No. 498: des(1)-[D-Tyr2,D-Pya(4)3,Ile5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 499: des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 500:

des(1-3)-3-Phenylpropionyl-[Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 501: des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 502: des(1)-[D-Tyr2,Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 503: des(1)-[D-Tyr2,D-Trp3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 504: [Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 505:

des(1-3)-3-Phenylpropionyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 506: des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 507:

des(1-3)-3-Phenylpropionyl-[Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 508:

des(1-3)-3-Phenylpropionyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 509: des(1-3)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 510: des(1-3)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 511:

des(1)-[D-Tyr2,D-Trp3,Ala4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Ala-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 512: des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 513: des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 514: des(1)-[D-Tyr2,D-Phe3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Phe-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 515: des(1)-[D-Tyr2,D-Pya(4)3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 516: des(1)-Ac-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 517:

des(1-3)-3-Phenylpropionyl-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 518: des(1-3)-3-Phenylpropionyl-[Cha6,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 519: des(1-3)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Phenylacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 521: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg-Phe-NH_2

Compound No. 522: des(1-3)-Benzoyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 523:

des(1-3)-Benzoyl-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 524:

des(1-3)-3-Phenylpropionyl-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 527: des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 528: des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 529: des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Tle-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 530: des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Phg-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 531:

des(1-3)-3-Phenylpropionyl-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Pic(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 532:

des(1-3)-3-Phenylpropionyl-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 533:

des(1-3)-3-Phenylpropionyl-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-D-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 534: des(1-3)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Cyclopropanecarbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 535: des(1-3)-2-Naphthoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Naphthoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 536: [Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 537: Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 538: Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 539: des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 540: des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 541:

D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 542:

D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 545: des(1-3)-Benzoyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 546:

des(1-3)-3-Phenylpropionyl-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 547:

des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 548: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-PheΨ(CSNH)NH_2

Compound No. 550: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 551:

Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 552:

D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 553:

D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 554:

D-Arg-[β-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-β-Ala-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 555:

D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 556:
D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 557:
D-Arg-D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Arg-D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 558: des(1)-Ac-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 559:
des(1-2)-3-(4-Hydroxyphenyl)propionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 561:
D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Arg-Acp-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 562:
des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 563:
des(1)-Ac-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 564: des(1)-Ac-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 565:
des(1)-Benzoyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Benzoyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 566:
des(1)-Cyclopropanecarbonyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Cyclopropanecarbonyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 567:

des(1)-Butyryl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Butyryl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 568:

Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 569:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,6Ψ7,CH_2NH,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-PheΨ(CH_2NH)Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 570: des(1)-Me-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Me-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 571: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 572: des(1)-[D-Trp2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 573:

des(1)-Ac-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 576: des(1)-Ac-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Gln-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 577: des(1)-Ac-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Ser-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 578: des(1)-Ac-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 579: des(1)-Ac-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 580:

des(1)-Ac-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 584:

des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 585:

des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 586: des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 589: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

Compound No. 590: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi(2)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2

Compound No. 591: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2

Compound No. 592: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 594: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Hph-NH_2

Compound No. 595: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Cha10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Cha-NH_2

Compound No. 596: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Leu10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Leu-NH_2

Compound No. 597: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 598: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 599: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2

Compound No. 600: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2

Compound No. 601: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 602: des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 603:
des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Pya(4)-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 604: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Tos)-Trp-NH_2
Compound No. 605:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(NO2)-Trp-NH_2
Compound No. 607:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)asym-Trp-NH_2
Compound No. 608:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)sym-Trp-NH_2
Compound No. 609: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Et)-Trp-NH_2
Compound No. 610:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys(Me2)-Trp-NH_2
Compound No. 611: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 612: des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 613:
des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 614:
des(1)-Amidino-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Amidino-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 615: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 616: des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 617: des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 618: des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 619:

des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(1)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 620:

des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(2)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 621: des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 622: des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Glu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 623: des(1)-Ac-[D-Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 624: des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 625: des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 626: des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 627: des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 628: des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Thr-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 629: des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 630: des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 631:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Ala-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 632:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Leu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 633:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Lys-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 634:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Glu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 635:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 636:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,NMePhe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-MePhe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 637:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 638:

des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 639: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys-Trp-NH_2

Compound No. 641:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ala-Arg(Me)-Trp-NH_2

Compound No. 642:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

Compound No. 643:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Phe-Arg(Me)-Trp-NH_2

Compound No. 644:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ser-Arg(Me)-Trp-NH_2

Compound No. 645: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har-Trp-NH_2

Compound No. 646: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har(Me)-Trp-NH_2

Compound No. 647:

des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 648: [Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 649: Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9;Trp10]MS10

Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 650: [D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 651:

Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 652:

pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 653:

des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-D-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 654:

des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-D-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 655:

des(1)-Ac-[D-Tyr2,D-Trp3,NMeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-NMeAsn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 656:

des(1)-Ac-[D-Tyr2,D-Trp3,NMeSer5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-NMeSer-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 657: des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 658:

des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 659:

des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-allo-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 660:

des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 661: des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 662: des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 663: des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 664: des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 665: des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 666: des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 667:

des(1-2)-Hexanoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Hexanoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 668:

des(1-2)-Cyclohexanecarbonyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Cyclohexanecarbonyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 669: des(1-2)-Benzoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 670:

des(1-2)-3-Pyridinepropionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Pyridinepropionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 671: des(1-2)-Adipoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Adipoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No.: des(1)-Ac-[D-Tyr2,NMeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 674 :
des(1-2)-6-Aminocaproyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
6-Aminocaproyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 675: [D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 676: Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 677:
Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Nva-Arg(Me)-Trp-NH_2
Compound No. 678:
Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ile-Arg(Me)-Trp-NH_2
Compound No. 679: des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Amidino-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 680:
des(1-2)-Glycoloyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Glycoloyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 681:
des(1)-Glycoloyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Glycoloyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 682:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Gln-Arg(Me)-Trp-NH_2
Compound No. 685: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 686: des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Gly-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 688: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Pya(4)-Trp-NH_2
Compound No. 689:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-D-Trp-NH_2
Compound No. 691:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 692:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 693:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr(Me)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 694:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Nal(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 695:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Thi-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 696:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 698:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Abu-Arg(Me)-Trp-NH_2

Compound No. 699:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-γMeLeu-Arg(Me)-Trp-NH_2

Compound No. 700: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Aib-Arg(Me)-Trp-NH_2

Compound No. 701: des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 702:

des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp(NHMe)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 703:

des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NMe2)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp(NMe2)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

For metastin derivatives (II), preferably used are metastin derivatives represented by the formula:

XX0-XX2-XX3-XX4-XX5-XX6-AzaGly-XX8-XX9-XX10-NH_2

(wherein :

XX0 represents formyl, C_{1-6} alkanoyl (e.g., acetyl, propionyl, butyryl, hexanoyl, and so on; preferably acetyl, propionyl, butyryl; more preferably acetyl), cyclopropanecarbonyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 4-(D-arginylamino)butyryl, or 3-(4-Hydroxyphenyl)propionyl, glycyl. tyrosyl, acetylglycyl, acetyltyrosyl, D-tyrosyl, acetyl-D-tyrosyl, pyroglutamyl, 3-(pyridine-3-yl)propionyl, adipoyl or 6-aminocaproyl (preferably acetyl and the like);

XX2 represents Tyr, D-Tyr, D-Ala, D-Leu, D-Phe, D-Lys, D-Trp or bond arm (preferably D-Tyr or bond arm; more preferably D-Tyr);

XX3 represents Trp, Pro, 4-pyridylalanine, Tic, D-Trp, D-Ala, D-Leu, D-Phe, D-Lys, D-Glu, D-2-pyridylalanine, D-3-pyridylalanine or D-4-pyridylalanine (preferably D-Trp or D-4-pyridylalanine);

XX4 represents Asn, 2-amino-3-ureidopropion acid, N^{β}-formyldiaminopropionic acid or N^{β}-acetyldiaminopropionic acid (preferably Asn);

XX5 represents Ser, Thr or Val (preferably Ser or Thr);

XX6 represents Phe, Tyr, Trp, Tyr(Me), Thi, Nal(2), Cha, 4-pyridylalanine or 4-fluorophenylalanine (preferably Phe or 4-fluorophenylalanine);

AzaGly represents azaglycine;

XX8 represents Leu, Nva or Val (prerferably Leu);

XX9 represents Arg, OrnArg(Me), or Arg(symMe2) (preferably Arg(Me));

XX10 represents Phe, Trp, 2-naphthylalanine, 2-thienylalanine, tyrosine or 4-fluorophenylalanine (preferably Phe or Trp)), or a salt thereof. Further, compounds represented by the following compound number are preferred:

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 552),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558),

3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compound No. 559),
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571),
Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579),
Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592),
For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612),
Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613),
Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618),
Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637),
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638),
Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658),
Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660),
Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663), or salts thereof.

The metastin derivatives (II) of the present invention or their salts or prodrugs have excellent blood stability, in addition to excellent effects of suppressing cancer metastasis and cancer growth, and are useful as agents for preventing or treating cancers (for example, lung cancer, gastric cancer, liver cancer, pancreatic cancer, colorectal cancer, rectal cancer, colonic cancer, prostate cancer, ovarian cancer, cervical cancer, breast cancer, etc.). The metastin derivatives (II) of the present invention or their salts or prodrugs have an effect of controlling pancreatic function and are useful as agents for

preventing or treating pancreatic diseases (e.g., acute or chronic pancreatitis, pancreatic cancer, etc.). The metastin derivatives (II) of the present invention or their salts or prodrugs have an effect of controlling placental function and are useful as agents for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

Moreover, the metastin derivatives (II) of the present invention or their salts or prodrugs have effects of increasing sugar level, promoting pancreatic glucagon secretion and promoting urine formation, and are useful as agents for preventing or treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity.

In addition, the metastin derivatives (II) of the present invention or their salts or prodrugs have excellent activities of promoting gonadotropic hormone secretion, promoting sex hormone secretion, inducing ovulation or stimulating ovulation, and are useful as low toxic and stable agents, e.g., agents for improving gonadal function, agents for preventing or treating hormone-dependent cancer (e.g., prostate cancer, breast cancer, etc.), infertility, endometriosis, early puberty, myoma of the uterus, etc., agents for inducing or stimulating ovulation, gonadotropic hormone secretagogue agents, contraceptives, sex hormone secretagogue agents, or the like.

Furthermore, the metastin derivatives (II) of the present invention or their salts or prodrugs are useful as agents for preventing or treating Alzheimer's disease, moderate cognitive impairment, etc.

The metastin derivatives (III) [including the metastin derivatives (II) and the metastin derivatives (I)] of the present invention or their salts or prodrugs are useful as agents for suppressing gonadotropic hormone secretion or sex hormone secretion; down-regulating agents for gonadotropic hormone or sex hormone; down-regulating agents for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9; agents for preventing or treating hormone-dependent cancers (e.g., prostate cancer, breast cancer, etc.; particularly, hormone-sensitive prostate cancer, hormone-sensitive prostate cancer, etc.); agents for preventing or treating endometriosis; agents for inhibiting ovarian follicular maturation; menstrual cycle-suspending agents; agents for treating myoma of the uterus; agents for

treating early puberty; contraceptives, etc.

In addition, the metastin derivatives (III) [including the metastin derivatives (II) and the metastin derivatives (I)] of the present invention or their salts or prodrugs are useful as an agent for potentiating immunity (prophylactic agent for infection after bone-marrow transplant, an agent for potentiating immunity intended for cancer); a prophylactic/therapeutic agent for bulbospinal muscular atrophy; an agent for protecting ovary; a prophylactic/therapeutic agent for benign prostate hypertrophy (BPH); a prophylactic/therapeutic agent for gender identity disorder; or an agent for in vitro fertilization (IVF). In addition, it is useful as a prophylactic/therapeutic agent for infertility, hypogonadism, oligospermia, azoospermia, aspermia, asthenospermia, or necrospermia. Further, it is useful for hormone-dependent diseases such as prostate cancer, uterine cancer, breast cancer, sex hormone dependent cancer like hypohysial tumor, prostate gland enlargement, endometriosis, uterine fibroid, early puberty, dysmenorrhea, amenorrhea, menstrual syndrome, multilocular ovary syndrome, postoperative relapse of the above-mentioned cancers, metastasis of the above-mentioned cancers, hypopituitarism, dwarfism (the case where the secretion of growth hormone was compromised associating with hyposecretion of pituitary hormone), menopausal disorder, indefinite complaint, sex hormone dependent disorders such as calcium phosphor bone metabolic disorders. It is applicable for contraception (or infertility when rebound effects after cessation of the drug are utilized).

Furthermore, metastin per se, DNA encoding metastin, etc. are also useful as agents for suppressing gonadotropic hormone secretion or sex hormone secretion; down-regulating agents for gonadotropic hormone or sex hormone; down-regulating agents for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9; agents for preventing or treating hormone-dependent cancers (e.g., prostate cancer, breast cancer, etc.; particularly, hormone-sensitive prostate cancer, hormone-sensitive prostate cancer, etc.); agents for preventing or treating endometriosis; agents for inhibiting ovarian follicular maturation; menstrual cycle-suspending agents; agents for treating myoma of the uterus; agents for treating early puberty; contraceptives, etc.

BEST MODE FOR CARRYING OUT THE INVENTION

The metastin derivatives (I) and (II) of the present invention can be prepared by publicly known methods for peptide synthesis. As the methods for peptide synthesis,

for example, either solid phase synthesis or liquid phase synthesis may be used. That is, the partial peptide or amino acids that can constitute the peptide of the present invention are repeatedly condensed with the remaining part to give the product having a desired sequence. Where the product has protecting groups, these protecting groups are removed to give the desired peptide. Publicly known methods for condensation and removal of the protecting groups are described in (i) to (v) below.

(1) M. Bodanszky & M.A. Ondetti: Peptide Synthesis, Interscience Publishers, New York (1966)

(2) Schroeder & Luebke: The Peptide, Academic Press, New York (1965)

(3) Nobuo Izumiya, et al.: *Peptide Gosei-no-Kiso to Jikken* (Basics and experiments of peptide synthesis), published by Maruzen Co. (1975)

(4) Haruaki Yajima & Shumpei Sakakibara: *Seikagaku Jikken Koza* (Biochemical Experiment) 1, *Tanpakushitsu no Kagaku* (Chemistry of Proteins) IV, 205 (1977)

(5) Haruaki Yajima, ed.: *Zoku Iyakuhin no Kaihatsu* (A sequel to Development of Pharmaceuticals), Vol. 14, Peptide Synthesis, published by Hirokawa Shoten

After completion of the reaction, the product may be purified and isolated by a combination of conventional purification methods such as solvent extraction, distillation, column chromatography, liquid chromatography and recrystallization to give the partial peptide of the present invention. When the peptide obtained by the above methods is in a free form, the peptide can be converted into an appropriate salt by a publicly known method; when the protein is obtained in a salt form, it can be converted into its free form by publicly known methods.

For condensation of the protected amino acids or peptides, a variety of activation reagents for protein synthesis may be used, but trisphosphonium salts, tetramethyluronium salts, carbodiimides, etc. are particularly preferred. Examples of trisphosphonium salts include benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP), bromotris(pyrrolidino) phosphonium hexafluorophosphate (PyBroP) and 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP), examples of tetramethyluronium salts include 2-(1H-benzotriazol-1-yl)-1,1,3,3-hexafluorophosphate (HBTU), 2-(7-azabenzotriazol-1-yl)-1,1,3,3-hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU),

2-(5-norbornene-2,3-dicarboxyimido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU) and O-(N-succimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU); examples of carbodiimides include DCC, N,N'-diisopropylcarbodiimide (DIPCDI) and N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI.HCl); etc. For condensation using these reagents, the addition of racemization inhibitors (e.g., HONB, HOBt, HOAt, HOOBt, etc.) is preferred. Solvents used in condensation may be appropriately chosen from solvents that are known to be usable for condensation. For example, acid amides such as anhydrous or hydrous N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, etc., halogenated hydrocarbons such as methylene chloride, chloroform, etc., alcohols such as trifluoroethanol, phenol, etc., sulfoxides such as dimethyl sulfoxide, etc., tertiary amines such as pyridine, etc., ethers such as dioxane, tetrahydrofuran, etc., nitriles such as acetonitrile, propionitrile, etc., esters such as methyl acetate, ethyl acetate, etc., or suitable mixtures thereof, etc. are used. The reaction temperature is appropriately chosen from the range known to be applicable to peptide binding reactions and is normally suitably chosen from the range of about -20°C to 50°C. The activated amino acid derivatives are used generally in 1.5 to 6 times excess. In the case of solid phase synthesis, the condensation is examined using the ninhydrin reaction; when the condensation is insufficient, the condensation can be completed by repeating the condensation reaction without removal of the protecting groups. When the condensation is yet insufficient even after repeating the reaction, the unreacted amino acids are acylated with acetic anhydride or acetylimidazole to cancel any adverse effect on the subsequent reaction.

Examples of the protecting groups used to protect amino groups in the starting amino acids include Z, Boc, tert-pentyloxycarbonyl, isobornyloxycarbonyl, 4-methoxybenzyloxycarbonyl, Cl-Z, Br-Z, adamantyloxycarbonyl, trifluoroacetyl, phthaloyl, formyl, 2-nitrophenylsulphenyl, diphenylphosphinothioyl, Fmoc, trityl, etc. Examples of protecting groups for a carboxyl group include, in addition to the C_{1-6} alkyl group, C_{3-8} cycloalkyl group and C_{7-14} aralkyl group for R described above, allyl, 2-adamantyl, 4-nitrobenzyl, 4-methoxybenzyl, 4-chlorobenzyl, phenacyl group, benzyloxycarbonylhydrazide, tert-butoxycarbonylhydrazide, tritylhydrazide, etc.

The hydroxyl group of serine and threonine can be protected, for example, by esterification or etherification. Examples of groups suitable for this esterification include a lower (C_{2-4}) alkanoyl group such as acetyl group, an aroyl group such as benzoyl group, etc. and a group derived from organic acid. Examples of a group suitable

for the etherification include benzyl group, tetrahydropyranyl group, tert-butyl group, trytyl group (Trt), etc.

Examples of groups for protecting the phenolic hydroxyl group of tyrosine include Bzl, Cl_2-Bzl, 2-nitrobenzyl, Br-Z, tert-butyl, etc.

Examples of groups used to protect the imidazole moiety of histidine include Tos, 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr), DNP, Bom, Bum, Boc, Trt, Fmoc, etc.

Examples of protecting groups for a guanidino group of arginine include Tos, Z, 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr), p-methoxybenzenesulfonyl (MBS), 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc), mesitylene-2-sulfonyl (Mts), 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf), Boc, Z, NO_2, etc.

Examples of protecting groups for side chain amino group of lysine include Z, Cl-Z, trifluoroacetyl, Boc, Fmoc, Trt, Mtr, 4,4-dimethyl-2,6-dioxocyclohexylideneyl (Dde), etc.

Examples of protecting groups for indolyl of tryptophan include formyl (For), Z, Boc, Mts, Mtr, etc.

A protecting group for asparagine and glutamine include Trt, xanthyl (Xan), 4,4'-dimethoxybenzhydryl (Mbh), 2,4,6-trimethoxybenzyl (Tmob), etc.

Examples of the activated carboxyl groups in the starting materisl include the corresponding acid anhydrides, azides, activated esters [esters with alcohols (e.g., pentachlorophenol, 2,4,5-trichlorophenol, 2,4-dinitrophenol, cyanomethyl alcohol, p-nitrophenol, HONB, N-hydroxysuccimide, 1-hydroxybenzotriazole (HOBt) or 1-hydroxy-7-azabenzotriazole (HOAt)], etc. As the amino acids in which the amino groups in the starting material are activated, the corresponding phosphoric amides are employed.

To eliminate (split off) the protecting groups, there are used catalytic reduction under hydrogen gas flow in the presence of a catalyst such as Pd-black or Pd-carbon; an acid treatment with anhydrous hydrogen fluoride, methanesulfonic acid, trifluoromethanesulfonic acid, trifluoroacetic acid, trimethylsilane bromide (TMSBr), trimethylsilyl trifluoromethanesulfonate, tetrafluoroboric acid, tris(trifluoro)boron, boron tribromide or a mixed solution thereof, a base treatment with diisopropylethylamine, triethylamine, piperidine, piperazine, etc., and reduction with sodium in liquid ammonia. The elimination of protecting groups by the acid treatment described above is carried out generally at a temperature of approximately -20°C to

40°C. In the acid treatment, it is efficient to add a cation scavenger such as anisole, phenol, thioanisole, m-cresol, p-cresol, etc., dimethylsulfide, 1,4-butanedithiol, 1,2-ethanedithiol, etc. Furthermore, 2,4-dinitrophenyl group known as the protecting group for the imidazole of histidine is removed by a treatment with thiophenol. Formyl group used as the protecting group of the indole of tryptophan is removed by the aforesaid acid treatment in the presence of 1,2-ethanedithiol, 1,4-butanedithiol, etc. as well as by a treatment with an alkali such as a dilute sodium hydroxide solution, dilute ammonia, etc.

Protection of functional groups that should not be involved in the reaction of the starting materials, protecting groups, removal of the protecting groups and activation of functional groups involved in the reaction may be appropriately chosen from publicly known groups and publicly known means.

In another method for obtaining the amides of the peptide, for example, the α-carboxyl group of the carboxy terminal amino acid is first protected by amidation; the peptide chain is then extended from the amino group side to a desired length. Thereafter, a peptide in which only the protecting group of the N-terminal α-amino group in the peptide chain has been removed from the peptide and a peptide (or an amino acid) in which only the protecting group of the C-terminal carboxyl group has been eliminated are prepared. The two peptides are condensed in a mixture of the solvents described above. The details of the condensation reaction are the same as described above. After the protected peptide obtained by the condensation is purified, all the protecting groups are removed by the method described above to give the desired crude peptide. This crude peptide is purified by various known purification means. Lyophilization of the major fraction gives the amide of the desired peptide.

When the metastin derivatives (I) and (II) of the present invention are present as a configurational isomer, a diastereomer, a conformer or the like, each can be isolated by the separating and purifying means described above, if desired. In addition, when the compound of the present invention is racemic, it can be separated into an S isomer and an R isomer by the conventional optical resolving means.

When the metastin derivatives (I) and (II) of the present invention have steric isomers, the present invention includes both of these isomers alone and the isomers present as a mixture thereof.

In addition, the metastin derivatives (I) and (II) of the present invention may be hydrated or non-hydrated.

The metastin derivatives (I) and (II) of the present invention may be labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S), etc.

Throughout the present specification, the peptides are represented in accordance with the conventional way of describing peptides, that is, the N-terminus (amino terminus) at the left hand and the C-terminus (carboxyl terminus) at the right hand. In the peptides, the C-terminus is usually in the form of an amide ($-CONH_2$), a carboxyl group (-COOH), a carboxylate ($-COO^-$), an alkylamide (-CONHR) or an ester (-COOR) and the amide ($-CONH_2$) is particularly preferred. Examples of the ester or alkylamide as R include a C_{1-6} alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, etc.; a C_{3-8} cycloalkyl group such as cyclopentyl, cyclohexyl, etc.; a C_{6-12} aryl group such as phenyl, α-naphthyl, etc.; a C_{7-14} aralkyl group such as a phenyl-C_{1-2}-alkyl group, e.g., benzyl, phenethyl, etc., or an α-naphthyl-C_{1-2}-alkyl group such as α-naphthylmethyl, etc.; pivaloyloxymethyl group, which are widely used as an ester for oral use, and the like.

Examples of a salt of the metastin derivative (I) of the present invention include a metal salt, a salt with ammonium, a salt with an organic base, a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid, and the like. Preferred examples of the metal salt include alkali metal salts such as sodium salts, potassium salts, etc.; alkaline earth metal salts such as calcium salts, magnesium salts, barium salts, etc.; aluminum salts; and the like. Preferred examples of the salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. Preferred examples of the salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. Preferred examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. Preferred examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferred examples of salts with acidic amino acids include salts with aspartic, glutamic acid, etc.

Among them, pharmaceutically acceptable salts are preferable. For example, when the compound has an acidic functional group, inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g., calcium salt,

magnesium salt, barium salt, etc.), ammonium salts, etc. are preferable. When the compound has a basic functional group, salts with inorganic acids with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc., and salts with organic acids such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, etc. are preferable.

A prodrug of the metastin derivative (III) or a salt thereof (hereinafter sometimes simply referred to as the metastin derivative (III) of the present invention) means a metastin derivative that is converted into the metastin derivative (III) of the present invention under physiological conditions or with a reaction due to an enzyme, a gastric acid, etc., in the living body. That is, the prodrug of the present invention is a metastin derivative that undergoes enzymatic oxidation, reduction, hydrolysis, etc. to be converted into the metastin derivative (III) of the present invention, or a metastin derivative that undergoes hydrolysis, etc. by gastric acid, etc. to be converted into the metastin derivative (III) of the present invention.

The prodrugs of the metastin derivative (I) of the present invention or salts thereof (hereinafter sometimes simply referred to as the metastin derivative (I) of the present invention) and the prodrugs of the metastin derivative (II) of the present invention or salts thereof (hereinafter sometimes simply referred to as the metastin derivative (II) of the present invention), which can be used, are the same as those described for the prodrugs of the metastin derivative (III) of the present invention.

Examples of the prodrugs of the metastin derivatives (III) of the present invention include metastin derivatives wherein an amino group of the metastin derivative (III) of the present invention is substituted with an acyl, an alkyl, phosphoric acid, etc. (e.g., metastin derivatives wherein an amino group of the metastin derivative (III) of the present invention is substituted with eicosanoyl, alanyl, pentylaminocarbonyl (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, tert-butyl, etc); metastin derivatives wherein a hydroxy group of the metastin derivative (I) of the present invention is substituted with an acyl, an alkyl, phosphoric acid, boric acid, etc. (e.g., metastin derivatives wherein an hydroxy group of the metastin derivative (III) of the present invention is substituted with acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl, dimethylaminomethylcarbonyl, etc.); and metastin derivatives wherein a carboxyl group of the metastin derivative (III) of the present invention is substituted with ester, amide,

etc. (e.g., metastin derivatives wherein a carboxyl group of the metastin derivative (III) of the present invention is substituted with ethyl ester, phenyl ester, carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, cyclohexyloxycarbonylethyl ester, methylamide, etc); and the like. These metastin derivatives can be produced from the metastin derivative (I) of the present invention by per.se known methods.

The prodrugs of the metastin derivative (III) of the present invention may be those that are converted into the metastin derivative (III) of the present invention under the physiological conditions as described in "Pharmaceutical Research and Development", Vol. 7 (Drug Design), pages 163-198, published 1990 by Hirokawa Publishing Co.

The metastin derivatives (I), (II) or (III) of the present invention or their salts or prodrugs (hereinafter sometimes simply referred to as the compound of the present invention) possess a cancer metastasis suppressing activity or a cancer growth suppressing activity. Thus, the metastin derivatives are useful for pharmaceuticals such as agents for preventing or treating all cancers (e.g., lung cancer, gastric cancer, liver cancer, pancreas cancer, colorectal cancer, rectal cancer, colonic cancer, prostate cancer, ovarian cancer, cervical cancer, breast cancer, etc.).

The compounds of the present invention also possess the effect of controlling pancreatic function and are thus useful as agents for preventing or treating various pancreatic diseases (e.g., acute or chronic pancreatitis, pancreatic cancer, etc.) as agents for controlling pancreatic function.

The compounds of the present invention also possess the effect of controlling placental function and are thus useful as pharmaceuticals for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery, as agents for controlling placental function.

Furthermore, the compounds of the present invention possess the effects of increasing sugar level, promoting pancreatic glucagon secretion and promoting urine formation and are thus useful as pharmaceuticals such as hyperglycemic agents, pancreatic glucagon secretagogue agents or agents for promoting urine formation, which are useful for preventing or treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy,

diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity.

In addition, the compounds of the present invention also possess the effects of promoting gonadotropic hormone (e.g., FSH, LH, etc.) secretion, promoting sex hormone [e.g., androgens (e.g., testosterone, androstenedione, etc.), estrogens (e.g., estradiol, estrone, etc.), progesterones, etc.] secretion, improving gonadal function and inducing or stimulating ovulation, as well as a sexual maturation effect, etc., and hence, can be used as agents for improving gonadal function, agents for inducing or stimulating ovulation, gonadotropic hormone secretagogue agents or sex hormone secretagogue agents, or agents for preventing or treating hormone-dependent cancers [e.g., prostate cancer, breast cancer, etc.], infertility [e.g., irregular menstruation, dysmenorrhea, amenorrhea, weight loss-induced amenorrhea, secondary amenorrhea, anovulation, hypoovarianism, hypogonadism, spermatogenetic failure, hypogonadism (e.g., impotence, etc.), genital atrophy, testicular atrophy, testicular function disorder, azoospermia, hypoandrogenemia, etc.], endometriosis, early puberty, myoma of the uterus, etc.

Furthermore, the prodrugs of the metastin derivative (I) or (II) of the present invention or salts thereof are useful as agents for preventing or treating Alzheimer's disease, moderate cognitive impairment, etc.

Moreover, the compounds of the present invention have excellent blood stability, as compared to native metastin such as metastin 54 (1-54) or metastin 10 (45-54).

The metastin derivatives (III) [including the metastin derivatives (II) and the metastin derivatives (I)] of the present invention or their salts or prodrugs are useful as agents for suppressing gonadotropic hormone secretion or sex hormone secretion; down-regulating agents for gonadotropic hormone (e.g., FSH, LH) or sex hormone [e.g., androgen (e.g., testosterone, androstenedione), estrogen (e.g., estradiol, estorone), progesterone];in particular, it is useful for suppressing gonadotropic hormone secretion or sex hormone secretion via down-regulation of gonadotropic hormone or sex hormone (wherein, the down-regulation of gonadotropic hormone or sex hormone may be pulse loss of LHRH or depletion of LHRH) or down-regulation of human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9; as agents for preventing or treating hormone-dependent cancers (e.g., prostate cancer,

breast cancer, etc.; particularly, hormone-sensitive prostate cancer, hormone-sensitive prostate cancer, etc.); agents for preventing or treating endometriosis; agents for inhibiting ovarian follicular maturation; menstrual cycle-suspending agents; agents for treating myoma of the uterus; agents for treating early puberty; or as contraceptives, etc.

Where the metastin derivative (III) of the present invention [including the metastin derivative (II) and the metastin derivative (I)] or its salt or prodrug, metastin per se, or DNA encoding metastin, etc. have normal agonist activity, an effective dose of the metastin derivative sufficient to suppress the secretion of gonadotropic hormone or sex hormone is administered at the site or tissue where the therapeutic effects are to be exerted, so that the metastin derivative is present in a dose more than required (i.e., the metastin derivative is administered in an excess over the normal effective dose, at which the metastin derivative exerts the effects of suppressing cancer metastasis, suppressing cancer growth, etc.; or the gonadotropic hormone secretagogue agent, the effect of promoting sex hormone secretion, etc.) to exhibit the effects of suppressing gonadotropic hormone secretion or sex hormone secretion. Specific examples include sustained or continuous administration of the normal effective dose (including an administration technique to gradually release the pharmaceutical ingredients by bolus administration); and the like. Further when the metastin derivative (III) of the present invention [including the metastin derivative (II) and the metastin derivative (I)] or its salt or the prodrug thereof, etc. have a sufficient agonist activity more than required (a super-agonist activity), it becomes possible to sustain the activities more than exhibited by the necessary dose at the site or tissue where the therapeutic effect are to be exhibited. It is therefore sufficient even by normal effective dose administration to suppress the secretion of gonadotropic hormone or sex hormone, whereby the effect of suppressing gonadotropic hormone secretion or sex hormone secretion is exhibited.

That is, the metastin derivative (III) [including the metastin derivative (II) and the metastin derivative (I)] or its salt or prodrug, or metastin per se, metastin-encoding DNA, etc. are administered in an effective dose sufficient to suppress the secretion of gonadotropic hormone or sex hormone. Consequently, it becomes possible to keep the metastin derivative, etc. present in a dose more than the necessary dose or sustain the activity more than exhibited by the necessary dose, at the site or tissue where the pharmaceutical effects are to be exhibited, resulting in exerting the effect of suppressing gonadotropic hormone secretion or sex hormone secretion.

The pharmaceutical compositions comprising the compounds of the present

invention are low toxic and thus can be safely administered orally or parenterally (e.g., topically, rectally, intravascularly, etc.) either directly as they are or in the form of pharmaceutical preparations such as tablets (including dragees and film-coated tablets), powdery dosage forms, granules, capsules (including soft capsules), liquid dosage forms, injections, suppositories, sustained release dosage forms, etc.

The compound of the present invention is contained in the pharmaceutical preparation of the present invention in about 0.01 to about 100 wt%, based on the total weight of the preparation.

A dose of the compound of the present invention may vary depending upon subject to be administered, target organ, conditions, route of administration, etc., and in oral administration, the compound is generally administered to the patient with cancer (as 60 kg body weight) in a daily dose of about 0.1 to about 100 mg, preferably about 1.0 to about 50 mg and more preferably about 1.0 to about 20 mg. In parenteral administration, a single dose of the compound may vary depending upon subject to be administered, target organ, conditions, route of administration, etc., and in the form of an injectable dosage form, it is advantageous to administer the compound to the patient with cancer (as 60 kg body weight) generally in a daily dose of about 0.01 to about 30 mg, preferably about 0.1 to about 20 mg, and more preferably about 0.1 to about 10 mg. For other animal species, the corresponding dose as converted per 60 kg weight can be administered.

Pharmacologically acceptable carriers, which may be used in manufacturing the pharmaceutical preparation of the present invention, include various organic or inorganic carrier substances conventionally used as materials for pharmaceutical preparations. These substances include, e.g., an excipient, a lubricant, a binder and a disintegrating agent in a solid dosage form, and a solvent, a dissolution aid, a suspending agent, an isotonizing agent, a buffer, a soothing agent, etc. in a liquid dosage form. In addition, conventional additives such as a preservative, an antioxidant, a colorant, a sweetener, an adsorbent, a wetting agent, etc. can be appropriately used in suitable amounts, if necessary.

Examples of excipients include, e.g., lactose, saccharose, D-mannitol, starch, cornstarch, crystalline cellulose, light anhydrous silicic acid, etc.

Examples of useful lubricants include, e.g., magnesium stearate, calcium stearate, talc, colloidal silica, etc.

Examples of binders include, e.g., crystalline cellulose, saccharose,

D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, sodium carboxymethylcellulose, etc.

Examples of disintegrating agents include, e.g., starch, carboxymethylcellulose, carboxymethylcellulose calcium, sodium carboxymethyl starch, L-hydroxypropylcellulose, etc.

Examples of solvents include, e.g., water for injection, alcohol, propylene glycol, Macrogol, sesame oil, corn oil, olive oil, etc.

Examples of dissolution aids include, e.g., polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

Examples of suspending agents include, e.g., surfactants such as stearyltriethanolamine, sodium laurylsulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerine monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, etc.

Examples of isotonizing agents include, e.g., glucose, D-sorbitol, sodium chloride, glycerine, D-mannitol, etc.

Examples of buffers include, e.g., buffering solutions of a phosphate, acetate, carbonate, citrate, etc.

Examples of soothing agents include, e.g., benzyl alcohol, etc.

Examples of preservatives include, e.g., p-hydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

Examples of antioxidants include, e.g., a sulfite, ascorbic acid, α-tocopherol, etc.

Furthermore, the compound of the present invention can be used in combination with drugs other than the compound of the present invention.

Examples of the drugs, which can be used in combination with the compound of the present invention (hereinafter referred to as a combination drug), include chemotherapeutic agents for treating cancer, hormonal therapeutic agents, immunotherapeutic agents, etc.

Examples of "chemotherapeutic agents" include, e.g., alkylating agents, antimetabolites, anticancer antibiotics, and plant-derived anticancer agents.

Examples of "alkylating agents" include, e.g., nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, estramustine sodium phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, carboquone, adozelesin, cystemustine, bizelesin, etc.

Examples of "antimetabolites" include, e.g., mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emmitefur, etc.), aminopterin, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, etc.

Examples of "anticancer antibiotics" include, e.g., actinomycin D, actinomycin C, mitomycin C, chromomycin A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, etc.

Examples of "plant-derived anticancer agents" include, e.g., etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, etc.

Examples of "hormonal therapeutic agents" include, e.g., fosfestrol, diethylstylbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, etc.), pill dosage forms, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin, Leuprorelin, etc.), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane, etc.), anti-androgens (e.g., flutamide, bicartamide, nilutamide, etc.), 5α-reductase inhibitors

(e.g., finasteride, epristeride, etc.), adrenocorticohormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone, etc.), androgen synthesis inhibitors (e.g., abiraterone, etc.), retinoid and drugs that retard retinoid metabolism (e.g., liarozole, etc.), and among them, LH-RH agonists (e.g., goserelin acetate, buserelin, Leuprorelin, etc.) are preferable.

Examples of "immunotherapeutic agents (BRM)" include, e.g., picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, Corynebacterium parvum, levamisole, polysaccharide K, procodazole, etc.

The combined use of the compound of the present invention and a combination drug results in, for example, the following excellent effects.

(1) The dose of the compound of the present invention can be reduced when compared with the dose when administered alone.

(2) A combination drug with the compound of the present invention can be chosen depending on the condition (mild, severe, etc.) of a patient.

(3) A combination drug, whose functional mechanism is different from that of the compound of the present invention, can be chosen so that a treatment period can be set longer.

(4) A combination drug, whose functional mechanism is different from that of the compound of the present invention, can be chosen so that sustained therapeutic effects can be achieved.

(5) A synergistic effect can be obtained by the combined use of the compound of the present invention and a combination drug.

In addition, the compound of the present invention can reduce values of testosterone to emasculate level immediately after medication. Thus when the combination drug such as LH-RH agonist (e.g., goserelin acetate, buserelin, Leuprorelin etc.; preferably Leuprorelin) uses in combination with the compound of the present invention, the values of testosterone can be reduced to emasculate level immediately after medication of the compound of the present invention. Further, since the combined use of the combination drug such as LH-RH agonist (e.g., goserelin acetate, buserelin, Leuprorelin etc.; preferably Leuprorelin) and the compound of the present invention results in prolonged preservation of hormone-dependent period, it can advantageously be used.

Hereinafter, the combined use of Compound (I) of the present invention and a combination drug is referred to as "the combined preparation of the present invention."

When the combined preparation of the present invention is used, a dosing period of the compound of the present invention and the combination is not restricted; the compound of the present invention or its pharmaceutical composition and a combination drug or its pharmaceutical composition may be administered to the subject to be administered either simultaneously or at certain time intervals. The dose of a combination drug may be modified according to the dose used clinically and may be appropriately chosen depending upon subject to be administered, route for administration, disease, combination, etc.

A mode for administration of the combined preparation of the present invention is not particularly limited, but it is sufficient that the compound of the present invention is used in combination with a combination drug at the time of administration. For such mode of administration, there are, for example, (1) administration of a simple dosage form obtained by mixing the compound of the present invention and a combination drug together at the same time, (2) simultaneous administration of two dosage forms prepared separately from the compound of the present invention and a combination drug through the same route for administration, (3) administration of two dosage forms prepared separately from the compound of the present invention and a combination drug at certain time intervals through the same route for administration, (4) simultaneous administration of two dosage forms prepared separately from the compound of the present invention and a combination drug through different routes for administration, (5) administration of two dosage forms prepared separately from the compound of the present invention and a combination drug at certain time intervals (e.g., administration of the compound of the present invention and a combination drug in this order, or administration in a reversed order) through different routes for administration, etc.

The combined preparation of the present invention is low toxic and thus can be safely administered orally or parenterally (e.g., topically, rectally, intravascularly, etc.) either directly as they are or in the form of pharmaceutical preparations such as tablets (including dragees and film-coated tablets), powdery dosage forms, granules, capsules (including soft capsules), liquid dosage forms, injections, suppositories, sustained release dosage forms, etc., which are obtained by mixing the compound of the present invention or (and) a combination drug described above with pharmacologically acceptable carriers. Injectable dosage forms can be administered intravenously,

intramuscularly or subcutaneously, into the organ, or directly at the focus.

Pharmacologically acceptable carriers, which may be used to manufacture the combined preparation of the present invention, include various organic or inorganic carrier substances conventionally used as materials for pharmaceutical preparations. These substances include, e.g., an excipient, a lubricant, a binder and a disintegrating agent in a solid dosage form, and a solvent, a dissolution aid, a suspending agent, an isotonizing agent, a buffer, a soothing agent, etc. in a liquid dosage form. In addition, conventional additives such as a preservative, an antioxidant, a colorant, a sweetener, an adsorbent, a wetting agent, etc. can be appropriately used in suitable amounts, if necessary.

Examples of excipients include, e.g., lactose, saccharose, D-mannitol, starch, cornstarch, crystalline cellulose, light anhydrous silicic acid, etc.

Examples of useful lubricants include, e.g., magnesium stearate, calcium stearate, talc, colloidal silica, etc.

Examples of binders include, e.g., crystalline cellulose, saccharose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, sodium carboxymethylcellulose, etc.

Examples of disintegrating agents include, e.g., starch, carboxymethylcellulose, carboxymethylcellulose calcium, sodium carboxymethyl starch, L-hydroxypropylcellulose, etc.

Examples of solvents include, e.g., water for injection, alcohol, propylene glycol, Macrogol, sesame oil, corn oil, olive oil, etc.

Examples of dissolution aids include, e.g., polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

Examples of suspending agents include, e.g., surfactants such as stearyltriethanolamine, sodium laurylsulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerine monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, etc.

Examples of isotonizing agents include, e.g., glucose, D-sorbitol, sodium chloride, glycerine, D-mannitol, etc.

Examples of buffers include, e.g., buffering solutions of a phosphate, acetate, carbonate, citrate, etc.

Examples of soothing agents include, e.g., benzyl alcohol, etc.

Examples of preservatives include, e.g., p-hydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

Examples of antioxidants include, e.g., a sulfite, ascorbic acid, α-tocopherol, etc.

In the combined preparation of the present invention, a ratio of the compound of the present invention to a combination drug may be appropriately chosen depending upon subject to be administered, route for administration, disease, combination, etc.

For example, the amount of the compound of the present invention contained in the combined preparation of the present invention varies depending on the dosage form of the preparation, but is usually about 0.01 to 100% by weight, preferably about 0.1 to 50% by weight, and more preferably about 0.5 to 20% by weight, based on the total weight of the preparation.

The amount of a combination drug contained in the combined preparation of the present invention varies depending on the dosage form of the preparation, but is usually about 0.01 to 100% by weight, preferably about 0.1 to 50% by weight, and more preferably about 0.5 to 20% by weight, based on the total weight of the preparation.

The amount of additives such as a carrier, etc. contained in the combined preparation of the present invention varies depending on the dosage form of the preparation, and is usually about 1 to 99.99% by weight, preferably about 10 to 90% by weight, based on the total weight of the preparation.

These amounts may be the same, also when the compound of the present invention and a combination drug are separately prepared, respectively.

These preparations can be manufactured by per se publicly known methods generally used conventionally.

For example, an injectable dosage form can be prepared by dissolving, suspending or emulsifying the compound of the present invention or a combination drug in a dispersing agent (e.g., Tween 80 (manufactured by Atlas Powder Company, USA), HCO 60 (manufactured by Nikko Chemicals Co., Ltd.), polyethylene glycol, carboxymethyl cellulose, sodium alginate, etc.), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite), a surfactant (e.g., polysorbate 80, macrogol, etc.), a solubilizing agent (e.g., glycerin, ethanol, etc.), a buffering agent (e.g., phosphoric acid or its alkali metal salt,

citric acid or its alkali metal salt, etc.), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose, etc.), a pH adjusting agent (e.g., hydrochloric acid, sodium hydroxide, etc.), a preservative (e.g., ethyl p-oxybenzoate, benzoic acid, methylparabene, propylparabene, benzyl alcohol, etc.), a solubilizer (e.g., concentrated glycerin, meglumine, etc.), a dissolution aid (e.g., propylene glycol, saccharose, etc.), a soothing agent (e.g., glucose, benzyl alcohol, etc.), a vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc., a dissolution aid such as propylene glycol or the like to prepare into an oily injection.

An oral dosage form can be produced in a conventional manner by adding to the compound of the present invention or a combination drug, for example, an excipient (e.g., lactose, saccharose, starch, etc.), a disintegrating agent (e.g., starch, calcium carbonate, etc.), a binder (e.g., starch, gum arabic, carboxymethyl cellulose, polyvinylpyrrolidone, hydroxypropyl cellulose, etc.), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000, etc.) and other additives, compressing the resulting mixture and, if necessary, coating the compressed product for the purpose of taste masking, enteric degradation or sustained release by techniques per se publicly known. Coating agents for this purpose include, for example, hydroxypropylmethyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, polyoxyethylene glycol, Tween 80, Prulonic F68, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, Eudragit (manufactured by Rohm Company, Germany, methacrylic acid/acrylic acid copolymer) and dyes (e.g., iron oxide, titanium dioxide). The oral dosage form may be either a rapid release dosage form or a sustained release dosage form.

For example, in a suppository, the compound of the present invention or a combination drug is prepared into an oily or aqueous solid, semi-solid or liquid composition by techniques per se publicly known. Oily bases used for the composition described above include glycerides of higher fatty acids [e.g., cacao butter, uitepsols (manufactured by Dynamite Nobel Company, Germany), etc.], moderate fatty acids [e.g., miglyols (manufactured by Dynamite Nobel Company, Germany), etc.], vegetable oils (e.g., sesame oil, soybean oil, cottonseed oil, etc.), and the like. Aqueous bases include, for example, polyethylene glycols and propylene glycol. Bases for aqueous gels include, for example, natural rubbers, cellulose derivatives, vinyl polymers, acrylic polymers, etc.

Examples of the sustained release dosage form above include sustained release

microcapsules, and the like.

Sustained release microcapsules can be obtained by per se publicly known methods, and are preferably prepared in the form of, e.g., a sustained release dosage form by the method [2] shown below and administered.

Preferably, the compound of the present invention is prepared into a dosage form for oral administration such as a solid dosage form (e.g., powdery dosage form, granules, tablets, capsules) or into a dosage form for rectal administration such as a suppository, etc. A dosage form for oral administration is particularly preferred.

A combination drug can be prepared into the dosage form described above, depending on the kind of drug.

Hereinafter, [1] an injectable preparation of the compound of the present invention or a combination drug and its production, [2] a sustained release or immediate release preparation of the compound of the present invention or a combination drug and its production and [3] a sublingual, buccal or rapid oral disintegrating preparations of the compound of the present invention or a combination drug and its production will be specifically described.

[1] Injectable Preparation and its Production

An injectable preparation obtained by dissolving the compound of the present invention or a combination drug in water is preferred. The injectable preparation may contain a benzoate and/or a salicylate.

The injectable preparation is obtained by dissolving the compound of the present invention or a combination drug and optionally a benzoate and/or a salicylate in water.

Examples of the benzoate and/or salicylate described above include an alkali metal salt such as sodium and potassium salts, etc., an alkaline earth metal salt such as calcium and magnesium salts, etc., an ammonium salt, a meglumine salt, a salt of an organic acid such as trometamol, and the like.

The concentration of the compound of the present invention or a combination drug in the injectable preparation is about 0.5 to 50 w/v %, preferably about 3 to 20 w/v %. The concentration of the benzoate and/or salicylate is 0.5 to 50 w/v %, preferably 3 to 20 w/v %.

Furthermore, additives generally used in an injectable preparation such as a stabilizer (ascorbic acid, sodium pyrosulfite, etc.), a surfactant (polysorbate 80,

macrogol, etc.), a solubilizing agent (glycerin, ethanol, etc.), a buffering agent (phosphoric acid and its alkali metal salt, citric acid and its alkali metal salt, etc.), an isotonizing agent (sodium chloride, potassium chloride, etc.), a dispersing agent (hydroxypropylmethyl cellulose, dextrin), a pH adjusting agent (hydrochloric acid, sodium hydroxide, etc.), a preservative (ethyl p-oxybenzoate, benzoic acid, etc.), a solubilizer (concentrated glycerin, meglumine, etc.), a dissolution aid (propylene glycol, saccharose, etc.), a soothing agent (glucose, benzyl alcohol, etc.) are appropriately added to the preparation. Any of these additives is added in an amount generally used in an injectable preparation.

The injectable preparation is adjusted to pH of 2 to 12, preferably 2.5 to 8.0 by adding a pH adjusting agent.

The injectable preparation is obtained by dissolving both the compound of the present invention or a combination drug and optionally a benzoate and/or salicylate, and, if necessary, the above additives in water. These components may be dissolved in any order according to the same manner as in a conventional injectable preparation.

An aqueous solution for injection is preferably warmed, and used as an injectable preparation after filtration sterilization by filtration or autoclaved as in a conventional injectable preparation to provide for an injectable preparation.

An aqueous injectable preparation is preferably autoclaved, e.g., at 100 to 121°C for 5 to 30 minutes.

Moreover, the preparation may be in a solution form to which antibacterial activity is imparted to be usable as a multiple dosage form in divided dosing.

[2] Sustained Release or Immediate Release Preparation and its Production

A preferred sustained release preparation comprises a core comprising the compound of the present invention or a combination drug, which is optionally coated with a water-insoluble material or a swelling polymer. For example, a sustained release preparation for oral administration of a once-daily dosage form is preferred.

Examples of the water-insoluble material used for the coating agent include cellulose ethers such as ethyl cellulose, butyl cellulose, etc., cellulose esters such as cellulose acetate, cellulose propionate, etc., polyvinyl esters such as polyvinyl acetate, polyvinyl butyrate, etc., acrylic acid polymers such as an acrylic acid/methacrylic acid copolymer, a methyl methacrylate copolymer, an ethoxyethyl methacrylate/cinnamoethyl methacrylate/aminoalkyl methacrylate copolymer, a polyacrylic acid, a polymethacrylic acid, a methacrylic acid alkylamide copolymer, a

poly(methyl methacrylate), a polymethacrylate, an aminoalkyl methacrylate copolymer, a poly(methacrylic anhydride), a glycidyl methacrylate copolymer, in particular, a series of Eudragits (Rohm & Pharma) such as Eudragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO (ethyl acrylate/methyl methacrylate/chlorotrimethyl methacrylate/ethyl ammonium copolymer) and Eudragit NE-30D (methyl methacrylate/ethyl acrylate copolymer), etc., hydrogenated oils such as hydrogenated castor oil (e.g., LUBRI WAX (Freund Industrial Co., Ltd.), etc.), waxes such as carnauba wax, a fatty acid glycerin ester, paraffin, etc., polyglycerin fatty acid esters, etc.

The swelling polymer is preferably a polymer having an acidic removable group and exhibiting pH-dependent swelling, and a polymer having an acidic removable group, which undergoes a less swelling at an acidic pH such as in the stomach but is swollen extensively at a neutral pH such as in the small and large intestines, is preferred.

Examples of such a polymer having an acidic removable group and exhibiting pH-dependent swelling include a crosslinked polyacrylic acid polymer such as Carbomers 934P, 940, 941, 974P, 980, 1342, etc., polycarbophil and calcium polycarbophil (all manufactured by BF Goodrich Chemicals), Hivis Wakos 103, 104, 105 and 304 (all manufactured by Wako Pure Chemical Industries, Ltd.), etc.

The coating agent used in the sustained release preparation may further contain a hydrophilic material.

Examples of the hydrophilic material include a polysaccharide which may have a sulfate group, such as pullulan, dextrin, alkali metal alginates, etc., a polysaccharide having a hydroxyalkyl group or a carboxyalkyl group such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, etc., methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, etc.

The amount of the water-insoluble material contained in the coating agent of the sustained release preparation is about 30 to about 90% (w/w), preferably about 35 to about 80% (w/w), more preferably about 40 to about 75% (w/w), and the swelling polymer content is about 3 to about 30% (w/w), preferably about 3 to about 15% (w/w). The coating agent may further contain a hydrophilic material, and the amount of the hydrophilic material contained in the coating agent is about 50% (w/w) or less, preferably about 5 to about 40% (w/w), more preferably about 5 to about 35% (w/w). As used herein, the % (w/w) above is used to mean a % by weight based on the coating agent composition, which is the remainder of the coating agent solution after removing

any solvent (e.g., water, a lower alcohol such as methanol, ethanol, etc.).

The sustained release preparation is manufactured by preparing a core containing a drug as illustrated below, followed by coating the resulting core with a coating agent solution obtained by heat-melting a water-insoluble material or a swelling polymer or by dissolving or dispersing such a material in a solvent.

I. Preparation of Drug-Containing Core

The shape of a core containing a drug to be coated with a coating agent (hereinafter sometimes simply referred to as a core) is not specifically limited but preferably prepared into a particulate shape such as granules, fine granules, or the like.

When the core is granules or fine granules, they have a mean particle size of preferably about 150 to about 2,000 μm, more preferably about 500 to about 1,400 μm.

The core can be prepared in a conventional manner. For example, a drug is mixed with a suitable excipient, binder, disintegrating agent, lubricant, stabilizer, etc., and then subjected to wet extrusion granulation, fluidized bed granulation, or the like.

The drug content in the core is about 0.5 to about 95% (w/w), preferably about 5.0 to about 80% (w/w), more preferably about 30 to about 70% (w/w).

Examples of the excipient contained in the core include a saccharide such assaccharose, lactose, mannitol, glucose, etc., starch, crystalline cellulose, calcium phosphate, cornstarch, etc. Among them, crystalline cellulose and cornstarch are preferred.

Examples of the binder used include polyvinyl alcohol, hydroxypropyl cellulose, polyethylene glycol, polyvinyl pyrrolidone, Pluronic F68, gum arabic, gelatin, starch, etc. Examples of the disintegrating agent include calcium carboxymethyl cellulose (ECG505), sodium croscarmellose (Ac-Di-Sol), crosslinked polyvinyl pyrrolidone (crospovidone), a low substituted hydroxypropyl cellulose (L-HPC), etc. Among them, hydroxypropyl cellulose, polyvinyl pyrrolidone and a low substituted hydroxypropyl cellulose are preferred. Examples of the lubricant and the anticoagulant include talc, magnesium stearate and its inorganic salts, and examples of the lubricant include polyethylene glycol, etc. Examples of the stabilizer include an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid, etc.

In addition to the technique described above, the core can be prepared by using other techniques such as an tumbling granulation technique, a pan coating technique, a fluidized bed coating technique and a melt granulation technique, wherein a drug or a mixture of the drug with an excipient, a lubricant, etc. is portionwise added to inert

carrier particles as seeds for the core with spraying a binder dissolved in a suitable solvent such as water, a lower alcohol (e.g., methanol, ethanol, etc.) or the like. Examples of the inert carrier particles include those prepared fromsaccharose, lactose, starch, crystalline cellulose and waxes, and, preferably, these carriers have a mean particle size of about 100 μm to about 1,500 μm.

In order to separate the drug contained in the core from a coating agent, the surface of the core may be covered with a protective material. Examples of the protective material include the hydrophilic material described above and water-insoluble material. The preferred protective material is polyethylene glycol or a polysaccharide having a hydroxyalkyl group or a carboxyalkyl group, more preferably, hydroxypropylmethyl cellulose and hydroxypropyl cellulose. The protective material may contain, as a stabilizer, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid, etc., and a lubricant such as talc. When the protective material is used, the amount thereof to be coated is about 1 to about 15% (w/w), preferably about 1 to about 10% (w/w), more preferably about 2 to about 8% (w/w) based on the core.

The protective material can be coated by a conventional coating method and specifically, the core is spray-coated with the protective material by a fluidized bed coating technique, a pan coating technique, etc.

II. Coating of Core with Coating Agent

The core obtained in I above is coated with a coating agent solution prepared by melt-heating the water-insoluble material and pH-dependent swelling polymer described above and a hydrophilic material or by dissolving or dispersing them in a solvent to obtain a sustained release preparation.

As a coating method of the core with the coating agent solution, there are, for example, spray-coating, etc.

The composition ratio of the water-insoluble material, swelling polymer and hydrophilic material in the coating agent solution can be appropriately chosen to be within the amounts of the respective components contained in the coating.

The amount of the coating agent is about 1 to about 90% (w/w), preferably about 5 to about 50% (w/w), more preferably about 5 to about 35% (w/w) based on the core (excluding the protective material coating).

As the solvent for the coating agent solution, water and an organic solvent can be used alone or as a mixture thereof. When a mixture is used, the ratio of water and the

organic solvent (water/organic solvent: a weight ratio) may vary with the range of 1 to 100%, and is preferably 1 to about 30%. The organic solvent is not particularly limited so far as it can dissolve the water-insoluble material, and examples of the solvent include a lower alcohol such as methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, etc., a lower alkanone such as acetone, acetonitrile, chloroform, methylene chloride, etc. Among them, a lower alcohol is preferred, with ethyl alcohol and isopropyl alcohol being more preferred. Water and a mixture of water and an organic solvent are used preferably as solvents for the coating agent solution. In this case, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid, etc. may be added to the coating agent solution, if necessary, for the purpose of stabilizing the coating agent solution.

To carry out the coating by spray coating, the coating can be made using a conventional coating method. Specifically, the core is sprayed with a coating agent solution by a fluidized bed coating technique, a pan coating technique, or the like. At this time, a lubricant such as talc, titanium oxide, magnesium stearate, calcium stearate, light silicic anhydride, etc., and a plasticizer such as glycerin fatty ester, hardened castor oil, triethyl citrate, cetyl alcohol, stearyl alcohol, etc. may also be added.

After coating with a coating agent, an antistatic agent such as talc may also be admixed, if necessary.

The immediate release preparation may be a liquid (solution, suspension, emulsion, etc.) or a solid (particles, pills, tablets, etc.). An oral preparation and a parenteral preparation such as an injectable preparation may be used, and an oral preparation is preferred.

The immediate release preparation may usually contain a carrier, additives and an excipient (hereinafter sometimes abbreviated as excipients) which are conventionally used in the pharmaceutical field, in addition to a drug which is an active ingredient. The pharmaceutical excipients are not specifically limited so long as they are excipients conventionally used in the pharmaceutical field. Examples of the excipient for an oral solid preparation include lactose, starch, corn starch, crystalline cellulose (Avicel PH101, manufactured by Asahi Kasei Corporation, etc.), powdered sugar, granulated sugar, mannitol, light silicic anhydride, magnesium carbonate, calcium carbonate, L-cysteine, etc., with corn starch and mannitol being preferred. Any of these excipients may be employed alone or in combination with each other. The amounts of the excipients are, for example, about 4.5 to about 99.4 w/w %, preferably about 20 to

about 98.5 w/w %, more preferably about 30 to about 97 w/w %, based on the total weight of the immediate release preparation.

The content of drug in the immediate release preparation may appropriately be selected from about 0.5% through about 95%, preferably about 1% through about 60% to whole amount of the immediate release preparation.

When the immediate release preparation is an oral solid preparation, the preparation contains a disintegrating agent in addition to the components described above. Examples of the disintegrating agent include calcium carboxymethylcellulose (ECG505 manufactured by GOTOKU CHEMICAL Co., Ltd.), sodium croscarmellose (for example, Ac-Di-Sol manufactured by Asahi Kasei Corporation), crospovidone (for example, COLIDON CL manufactured by BASF), low-substituted hydroxypropyl cellulose (Shin-Etsu chemical Co., Ltd.), carboxymethyl starch (MATSUTANI CHEMICAL INDUSTRY Co., Ltd.), sodium carboxymethyl starch (EXORITAB manufactured by KIMURA SANGYO), partial α starch (PCS manufactured by Asahi Kasei Corporation), etc. For example, the disintegrating agent that disintegrates granules by water absorption or swelling upon contact with water, or forming a channel between the active component comprising the core and an excipient can be used. Any of these disintegrating agents can be used alone or in combination with each other. The amount of the disintegrating agent used may be appropriately chosen depending upon the type and the amount of the drug used or a particular preparation design for the intended release performance. For example, the amount is about 0.05 to about 30 w/w %, preferably about 0.5 to about 15 w/w % based on the total weight of the immediate release preparation.

When the immediate release preparation is an oral solid preparation, the preparation may optionally contain additives conventionally used in a solid preparation, in addition to the components described above. Examples of the additives include binders (for example, sucrose, gelatin, powdery gum arabic, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose, polyvinyl pyrrolidone, pullran, dextrin, etc.), lubricants (polyethylene glycol, magnesium stearate, talc, light silicic anhydride (for example, aerosil (NIPPON AEROSIL)), surfactants (for example, anionic surfactants such as sodium alkylsulfate, nonionic surfactants such as polyoxyethylene fatty ester, polyoxyethylene sorbitan fatty ester, polyoxyethylene castor oil derivatives, etc.), colorants (for example, tar colorants, caramel, colcothar, titanium oxide, riboflavins), if necessary, corrigents (for example,

sweeteners, flavors, etc.), adsorbents, preservatives, wetting agents, antistatic agents, etc. Furthermore, an organic acid such as tartaric acid, citric acid, succinic acid, fumaric acid or the like can also be added as a stabilizer.

As the binder above, hydroxypropyl cellulose, polyethylene glycol and polyvinyl pyrrolidone, etc. are preferably used.

The immediate release preparation can be prepared by mixing the components described above and kneading the mixture, if necessary, and then molding according to a conventional technique for making pharmaceutical preparations. The mixing above can be carried out in a conventional manner, e.g., by mixing, kneading, etc. Specifically, where the immediate release preparation is in the form of particles, the preparation can be prepared by mixing components with a vertical granulator, a multi-purpose kneader (HATA IRON WORKS CO., LTD), a fluidized bed granulator FD-5S (POWREX CORPORATION) or thee like, and then granulating the resulting by wet extrusion granulation or fluidized bed granulation by a technique similar to that for preparing the core of the sustained release preparation described above.

The immediate release preparation and the sustained release preparation thus obtained can be compounded, as they are, or, together with appropriate pharmaceutical excipients, in pharmaceutical preparations separately in a conventional manner to prepare respective preparations for administering in combination with each other simultaneously or at certain time intervals. Alternatively, both preparations may be compounded in a single dosage form for oral administration (e.g., granules, fine granules, tablets, capsules) as they are, or, together with appropriate pharmaceutical excipients. Both preparations in the form of granules or fine granules may also be filled in a single capsule for oral administration.

[3] Sublingual, Buccal or Rapid Oral Disintegrating Preparation and its Production

A sublingual, buccal or rapid oral disintegrating preparation may be in the form of a solid preparation such as a tablet, or may be in the form of an oral mucosal patch (film).

The sublingual, buccal or rapid oral disintegrating preparation is preferably a preparation containing the compound of the present invention or a combination drug and an excipient. The preparation may also contain auxiliary agents such as a lubricant, an isotonizing agent, a hydrophilic carrier, a water-dispersible polymer, a stabilizer, etc. Further for the purpose of promoting the absorption and enhancing the bioavailability, the preparation may also contain β-cyclodextrin or β-cyclodextrin derivatives (e.g.,

hydroxypropyl-β-cyclodextrin, etc.).

Examples of the above excipient include lactose, saccharose, D-mannitol, starch, crystalline cellulose, light silicic anhydride, etc. Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica, etc., with magnesium stearate and colloidal silica being preferred. Examples of the isotonizing agent include sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerin and urea, with mannitol being particularly preferred. As the hydrophilic carrier, there are, for example, a swelling hydrophilic carrier such as crystalline cellulose, ethyl cellulose, crosslinked polyvinyl pyrrolidone, light silicic anhydride, silicic acid, dicalcium phosphate, calcium carbonate, etc., with crystalline cellulose (e.g., microcrystalline cellulose, etc.) being preferred. As the water-dispersible polymer, there are, for example, a gum (e.g., tragacanth gum, acacia gum, guar gum), alginate (e.g., sodium alginate), cellulose derivatives (e.g., methyl cellulose, carboxymethylcellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose), gelatin, water-soluble starch, polyacrylic acid (e.g., carbomer), polymethacrylic acid, polyvinyl alcohol, polyethylene glycol, polyvinyl pyrrolidone, polycarbophil, ascorbate palmitate salt, etc., with hydroxypropylmethyl cellulose, polyacrylic acid, alginate, gelatin, carboxymethylcellulose, polyvinyl pyrrolidone and polyethylene glycol being preferred. Hydroxypropylmethyl cellulose is particularly preferred. As the stabilizer, there are, for example, cysteine, thiosorbitol, tartatic acid, citric acid, sodium carbonate, ascrobic acid, glycine, sodium sulfite, etc., with citric acid and ascorbic acid being particularly preferred.

The sublingual, buccal or rapid oral disintegrating preparation can be prepared by mixing the compound of the present invention or a combination drug and an excipient by a method per se known. Furthermore, if desired, the auxiliary agents described above, such as the lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer, colorant, sweetener, preservative, etc. may also be admixed. After mixing the components described above simultaneously or at certain time intervals, the mixture is compressed into tablets to obtain the sublingual, buccal or oral quick disintegration tablet. In order to obtain a suitable hardness, a solvent such as water, an alcohol, etc. can be used to moisturize or wet the components before or after tabletting, followed by drying.

In preparing the oral mucosal patch (film), the compound of the present invention or a combination drug and the water-dispersible polymer (preferably,

hydroxypropyl cellulose, hydroxypropylmethyl cellulose), excipient, etc. described above are dissolved in a solvent such as water, etc. and then the resulting solution is cast into a film. In addition, additives such as a plasticizer, a stabilizer, an antioxidant, a preservative, a colorant, a buffering agent, a sweeteners, etc. may be added to the preparation. A glycol such as polyethylene glycol, propylene glycol, etc. may be added to impart an appropriate elasticity to a film, and a bioadhesive polymer (e.g., polycarbophile, carbopol) may also be added to enhance the adhesion of the film to the oral mucosal lining. The casting can be carried out by pouring a solution onto a non-adhesive surface, spreading the solution using a coater such as a doctor blade in a uniform thickness (preferably, approximately 10 to 1000 microns), and then drying the solution to form a film. The film thus formed is dried at room temperature or while warming, and then cut into pieces each having a desired surface area.

A preferred rapid oral disintegrating preparation is, for example, a rapid diffusion preparation in a solid network form, which comprises the compound of the present invention or a combination drug and a water-soluble or water-diffusible carrier inert to the compound of the present invention or the combination drug. The network is formed by sublimating a solvent from a solid composition comprising a solution of the compound of the present invention or a combination drug in a suitable solvent.

In addition to the compound of the present invention or a combination drug, the composition of the rapid oral disintegrating preparation may preferably contain a matrix-forming agent and a secondary component.

Examples of the matrix-forming agent include gelatins, dextrins and animal or vegetable proteins from soybean, wheat, psyllium seed, etc.; gummy materials such as gum arabic, guar gum, agar, xanthane gum, etc.; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinyl pyrrolidones; materials derived from gelatin-gum arabic complexes, etc. The matrix-forming agent further includes saccharides such as mannitol, dextrose, lactose, galactose, trehalose, etc.; cyclic saccharides such as cyclodextrins, etc.; inorganic salts such as sodium phosphate, sodium chloride, aluminum silicate, etc.; amino acids having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine, L-phenylalanine, etc.

One or more matrix-forming agents can be incorporated into a solution or suspension before solidification. The matrix-forming agents may be present in addition to a surfactant, or may be present in the absence of a surfactant. The matrix-forming

agents serve not only to form a matrix itself, but also assist to maintain diffusion of the compound of the present invention or a combination drug in the solution or suspension.

The composition may contain a secondary component such as a preservative, an antioxidant, a surfactant, a thickening agent, a colorant, pH adjusting agent, a flavor, a sweetener, a taste masking agent, etc. As the suitable colorant, there are, for example, iron oxide red, black and yellow, FD & C dyes available from ERIS & EVERALD such as FD & C Blue No. 2 and FD & C Red No. 40, etc. Examples of the suitable flavor include mint, raspberry, licorice, orange, lemon, grape fruit, caramel, vanilla, cherry, grape flavor and a combination thereof. Examples of the suitable pH adjusting agent include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Examples of the suitable sweetener include aspartame, acesulfame K and thaumatine. Examples of the suitable taste masking agent include sodium bicarbonate, ion exchange resins, cyclodextrin inclusion compounds, adsorbents and microencapsulated apomorphine.

The preparation generally contains the compound of the present invention or a combination drug in an amount of about 0.1 to about 50% by weight, preferably about 0.1 to about 30% by weight and, preferably, the preparation (the sublingual tablet, buccal, etc. described above) allows 90% or more of the compound of the present invention or a combination drug to be dissolved (in water) within a time period of about 1 to about 60 minutes, preferably about 1 minute to about 15 minutes, more preferably about 2 minutes to about 5 minutes, or is a rapid oral disintegrating preparation which disintegrates within about 1 to about 60 seconds, preferably about 1 to about 30 seconds, more preferably about 1 to about 10 seconds, after being placed in the oral cavity.

The amount of the above excipient is about 10 to about 99% by weight, preferably about 30 to about 90% by weight based on the total weight of the preparation. The amount of β-cyclodextrin or β-cyclodextrin derivative is about 0 to about 30% by weight based on the total weight of the preparation. The amount of the lubricant is about 0.01 to about 10% by weight, preferably about 1 to about 5% by weight based on the total weight of the preparation. The amount of the isotonizing agent is about 0.1 to about 90% by weight, preferably about 10 to about 70% by weight based on the total weight of the preparation. The amount of the hydrophilic carrier is about 0.1 to about 50% by weight, preferably about 10 to about 30% by weight based on the total weight of the preparation. The amount of the water-dispersible polymer is about 0.1 to

about 30% by weight, preferably about 10 to about 25% by weight based on the total weight of the preparation. The amount of the stabilizer is about 0.1 to about 10% by weight, preferably about 1 to about 5% by weight based on the total weight of the preparation. If necessary, the preparation described above may further contain additives such as a colorant, a sweetener, a preservative, etc.

A dose of the combined preparations of the present invention varies depending upon kind of the compound of the present invention, age, body weight, conditions, dosage form, route for administration, dosing period, etc.

A dose of the compound of the present invention may vary depending upon subject to be administered, target organ, conditions, route of administration, etc., and in oral administration, the compound is generally administered to the patient with cancer (as 60 kg body weight) in a daily dose of about 0.1 to about 100 mg, preferably about 1.0 to about 50 mg and more preferably about 1.0 to about 20 mg. In parenteral administration, a single dose of the compound may vary depending upon subject to be administered, target organ, conditions, route of administration, etc., and in the form of an injectable dosage form, it is advantageous to administer the compound to the patient with cancer (as 60 kg body weight) generally in a daily dose of about 0.01 to about 30 mg, preferably about 0.1 to about 20 mg, and more preferably about 0.1 to about 10 mg. For other animal species, the corresponding dose as converted per 60 kg weight can be administered. Of course, the dose may vary depending on individual conditions as described above; in such a case, a dose less than the dose given above may be sufficient, or may be higher than the range above.

It is possible to set any range of a dose for the combination drug, so long as it causes no adverse side effects. A daily dose of the combination drug may vary depending on the severity of disease, subject's age, sex, body weight and susceptibility, the dosing period and intervals, the characteristics, formulation, type and active components of the pharmaceutical preparation, etc. and is not particularly limited. For example, in oral administration, the dose is about 0.001 to 2000 mg, preferably about 0.01 to 500 mg, and more preferably about 0.1 to 100 mg in terms of a drug; usually, this dose is administered by dividing 1 to 4 times per day.

When the pharmaceutical preparations of the present invention are administered, the compound of the present invention and a combination drug may be administered at the same time. Alternatively, a combination drug is first administered and then the compound of the present invention is administered, or the compound of the

present invention is first administered and then a combination drug is administered. When they are administered at certain time intervals, the intervals vary depending on the active component to be administered, dosage form and route of administration; when a combination drug is first administered, the compound of the present invention may be administered within 1 minute to 3 days, preferably 10 minutes to 1 day, more preferably 15 minutes to 1 hour after the administration of the combination drug. When the compound of the present invention is first administered, a combination drug may be administered within 1 minute to 1 day, preferably 10 minutes to 6 hours, more preferably 15 minutes to 1 hour after the administration of the compound of the present invention.

As a preferred method of administration, for example, about 0.001 to 200 mg/kg of a combination drug in the form of an oral dosage preparation is administered orally and, after about 15 minutes, about 0.005 to 0.5 mg/kg of the compound of the present invention in the form of a parenteral preparation is administered parenterally as a daily dose.

As the metastins, there are used, for example, human metastin described in WO 00/24890, mouse or rat metastin described in WO 01/75104, etc.

Specific examples of human metastin include a peptide containing the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 and consisting of 8 to 54 amino acid residues, and the like.

The "peptide containing the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 and consisting of 8 to 54 amino acid residues" may be any peptide, as far as it is a peptide containing the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 and consisting of 8 to 54 amino acid residues, but means that these peptides have substantially the same physiological activity (e.g., a receptor binding activity, a signal transduction action, a sugar level elevating action, a pancreatic glucagon secretion promoting action, a urine formation promoting action, etc.). Specifically, there are used (i) a peptide having the amino acid sequence represented by SEQ ID NO: 1, (ii) a peptide having the N-terminal 47-54 amino acid sequence at the C terminus in the amino acid sequence represented by SEQ ID NO: 1 and consisting of 8 to 54 amino acid residues, etc.

More specifically, human metastin used includes (i) a peptide consisting of the amino acid sequence represented by SEQ ID NO: 1 (human metastin 54 (1-54)), (ii) a

peptide consisting of the N-terminal 40-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 15 (40-54); SEQ ID NO: 15), (iii) a peptide consisting of the N-terminal 45-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 10 (45-54); SEQ ID NO: 16), (iv) a peptide consisting of the N-terminal 46-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 9 (46-54); SEQ ID NO: 17), (v) a peptide consisting of the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by (human metastin 8 (47-54); SEQ ID NO: 18), etc.

As mouse metastin (A), there are used, for example, (i) a peptide containing the N-terminal 134-141 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 3 and consisting of 8 to 52 amino acid residues. Specific examples of mouse metastin (A) used include (i) a peptide consisting of the N-terminal 90-141 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 3, (ii) a peptide consisting of the N-terminal 132-141 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 3, (iii) a peptide consisting of the N-terminal 127-141 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 3, and the like.

As mouse metastin (B), there are used, for example, (i) a peptide containing the N-terminal 138-145 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 5 and consisting of 8 to 52 amino acid residues. Specific examples of mouse metastin (B) used include (i) a peptide consisting of the N-terminal 94-145 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 5, and the like.

As rat metastin, there are used, for example, (i) a peptide containing the N-terminal 112-119 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 7 and consisting of 8 to 52 amino acid residues. Specific examples of rat metastin used include (i) a peptide consisting of the N-terminal 68-119 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 7, (ii) a peptide consisting of the N-terminal 110-119 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 7, (iii) a peptide consisting of the N-terminal 105-119 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 7, and the like.

Throughout the specification, the metastins are represented in accordance with the conventional way of describing peptides, that is, the N-terminus (amino terminus) at

the left hand and the C-terminus (carboxyl terminus) at the right hand. In the peptide represented by SEQ ID NO: 1, the C-terminus may be in any form of a carboxyl group (-COOH), a carboxylate (-COO-), an amide ($-CONH_2$) and an ester (-COOR). Herein, examples of the ester group shown by R include a C_{1-6} alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, etc.; a C_{3-8} cycloalkyl group such as cyclopentyl, cyclohexyl, etc.; a C_{6-12} aryl group such as phenyl, α-naphthyl, etc.; a C_{7-14} aralkyl such as a phenyl-C_{1-2} alkyl group, e.g., benzyl, phenethyl, etc.; an α-naphthyl-C_{1-2} alkyl group such as α-naphthylmethyl, etc.; pivaloyloxymethyl group, which are widely used as an ester for oral use, and the like.

Furthermore, the metastins include peptides, wherein the amino group at the N-terminal methionine residue is protected with a protecting group (e.g., a C_{1-6} acyl group such as a C_{2-6} alkanoyl group, e.g., formyl group, acetyl group, etc.); those wherein the N-terminal region is cleaved in vivo and the glutamyl group thus formed is pyroglutaminated; those wherein a substituent (e.g., -OH, -SH, amino group, imidazole group, indole group, guanidino group, etc.) on the side chain of an amino acid in the molecule is protected with a suitable protecting group (e.g., a C_{1-6} acyl group such as a C_{2-6} alkanoyl group, e.g., formyl group, acetyl group, etc.), or conjugated peptides such as glycopeptides bound to sugar chains.

For salts of the metastins of the present invention, preferred are salts with physiologically acceptable acids (e.g., inorganic acids or organic acids) or bases (e.g., alkali metal salts), etc., especially physiologically acceptable acid addition salts. Examples of such salts include salts with, for example, inorganic acids (e.g., hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid); salts with organic acids (e.g., acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid) and the like.

As the DNAs encoding metastins, there are used, for example, DNAs encoding human metastin described in WO 00/24890, DNAs encoding mouse or rat metastin described in WO 01/75104, etc.

The DNAs encoding the metastins may be any of genomic DNA, genomic DNA library, cDNA derived from the cells and tissues described above, cDNA library derived from the cells and tissues described above and synthetic DNA. The vector to be used for the library may be any of bacteriophage, plasmid, cosmid and phagemid. The DNA may also be directly amplified by reverse transcriptase polymerase chain reaction

(hereinafter abbreviated as RT-PCR) using the total RNA or mRNA fraction prepared from the cells and tissues described above.

The DNA encoding human metastin, mouse metastin precursor (A), mouse metastin precursor (B) or rat metastin precursor may be any DNA, so long as each is a DNA containing a base sequence represented by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8, or a DNA having a base sequence hybridizable to the base sequence represented by any base sequence represented by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 under highly stringent conditions and encoding the human metastin, mouse metastin (A), mouse metastin (B) or rat metastin described above.

Specific examples of the DNA hybridizable to the base sequence represented by any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 under highly stringent conditions include DNAs containing a base sequence having at least about 70% homology, preferably at least about 80% homology, more preferably at least about 90% homology and the most preferably at least about 95% homology, to the base sequence represented by any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8.

Homology in the base sequence can be measured under the following conditions (an expectation value = 10; gaps are allowed; filtering = ON; match score = 1; mismatch score = -3) using the homology scoring algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool).

The hybridization can be carried out by per se publicly known methods or by modifications of these methods, for example, according to the method described in Molecular Cloning, 2nd (J. Sambrook et al., Cold Spring Harbor Lab. Press, 1989). A commercially available library may also be used according to the instructions of the attached manufacturer's protocol. Preferably, the hybridization can be carried out under highly stringent conditions.

The highly stringent conditions used herein are, for example, those in a sodium concentration at about 19 to 40 mM, preferably about 19 to 20 mM at a temperature of about 50 to 70°C, preferably about 60 to 65°C. In particular, hybridization conditions in a sodium concentration of about 19 mM at a temperature of about 65°C are most preferred.

Specifically, as the DNA encoding the human metastin consisting of the amino acid sequence represented by SEQ ID NO: 1, the DNA consisting of the base sequence

represented by SEQ ID NO: 2 is used. Accordingly, for the base sequence encoding the human metastin consisting of the various amino acid sequences described above, a base sequence corresponding to each of the partial amino acid sequences in the amino acid sequence represented by SEQ ID NO: 1 may be chosen from the base sequence represented by SEQ ID NO: 2.

As the DNA encoding the mouse metastin precursor (A) comprising the amino acid sequence represented by SEQ ID NO: 3, there are employed a DNA consisting of the base sequence represented by SEQ ID NO: 4, and the like. Accordingly, for the base sequence encoding the mouse metastin precursor (A) consisting of the various amino acid sequences described above, a base sequence corresponding to each of the partial amino acid sequences in the amino acid sequence represented by SEQ ID NO: 3 may be chosen from the base sequence represented by SEQ ID NO: 4.

As the DNA encoding the mouse metastin precursor (B) comprising the amino acid sequence represented by SEQ ID NO: 5, there are employed a DNA consisting of the base sequence represented by SEQ ID NO: 6, and the like. Accordingly, for the base sequence encoding the mouse metastin precursor (B) consisting of the various amino acid sequences described above, a base sequence corresponding to each of the partial amino acid sequences in the amino acid sequence represented by SEQ ID NO: 5 may be chosen from the base sequence represented by SEQ ID NO: 6.

As the DNA encoding the rat metastin comprising the amino acid sequence represented by SEQ ID NO: 7, there are employed a DNA consisting of the base sequence represented by SEQ ID NO: 8, and the like. Accordingly, for the base sequence encoding the rat metastin consisting of the various amino acid sequences described above, a base sequence corresponding to each of the partial amino acid sequences in the amino acid sequence represented by SEQ ID NO: 7 may be chosen from the base sequence represented by SEQ ID NO: 8.

More specifically, for the peptide consisting of the amino acid sequence represented by SEQ ID NO: 1 (human metastin 54 (1-54)), a DNA containing the base sequence represented by SEQ ID NO: 2, etc. is used.

For the peptide consisting of the N-terminal 40-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 15 (40-54); SEQ ID NO: 15), a DNA containing the base sequence represented by SEQ ID NO: 19, etc. is used.

For the peptide consisting of the N-terminal 45-54 amino acid sequence in the

amino acid sequence represented by SEQ ID NO: 1 (human metastin 10 (45-54); represented by SEQ ID NO: 16), a DNA containing the base sequence represented by SEQ ID NO: 20, etc. is used.

For the peptide consisting of the N-terminal 46-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 9 (46-54); represented by SEQ ID NO: 17), a DNA containing the base sequence represented by SEQ ID NO: 21, etc. is used.

For the peptide consisting of the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 8 (47-54); represented by SEQ ID NO: 18), a DNA containing the base sequence represented by SEQ ID NO: 22, etc. is used.

As the metastin receptor, its partial peptides or salts thereof, there are used, for example, a human metastin receptor, its partial peptides or salts thereof described in WO 00/24890, a mouse or rat human metastin receptor, its partial peptides or salts thereof described in WO 01/75104, etc.

Specifically, the metastin receptor includes a protein containing the same or substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, etc.

The amino acid sequence which has substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13 includes, for example, an amino acid sequence having at least about 70% homology, preferably at least about 80% homology, more preferably at least about 90% homology, and most preferably at least about 95% homology, to the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13.

Homology of the amino acid sequences can be determined under the following conditions (an expectation value = 10; gaps are allowed; matrix = BLOSUM62; filtering = OFF) using a homology scoring algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool).

As the protein having substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, preferred is a protein having substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13 and having the activity of the same nature as that of a protein consisting of the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, etc.

As the activity of substantially the same nature, there are, for example, a ligand binding activity, a signal transduction activity, and the like. The "substantially the same nature" is used to mean that the nature of these activities is equivalent in terms of quality. Thus, the activities such as a ligand binding activity, a signal transduction activity, etc. are preferably equivalent (e.g., about 0.01 to 100 times, preferably about 0.1 to 10 times, more preferably 0.5 to 2 times), but differences in degree such as a level of these activities, quantitative factors such as a molecular weight of the protein may be present and allowable.

The activities such as a ligand binding activity, a signal transduction activity, etc. can be assayed by per se publicly known method with modifications and may be determined according to methods of determining a ligand or screening methods described in, e.g., WO 00/24890 or WO 01/75104.

Examples of the metastin receptor used include proteins comprising (1) (i) the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, of which at least 1 or 2 (preferably about 1 to about 30, more preferably about 1 to about 10 and most preferably several (1 or 2)) amino acids are deleted; (ii) the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, to which at least 1 or 2 (preferably about 1 to about 30, more preferably about 1 to about 10 and most preferably several (1 or 2)) amino acids are added; (iii) the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, in which at least 1 or 2 (preferably about 1 to about 30, more preferably about 1 to about 10 and most preferably several (1 or 2)) amino acids are inserted; (iv) the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, in which at least 1 or 2 (preferably about 1 to about 30, more preferably about 1 to about 10 and most preferably several (1 or 2)) amino acids are substituted by other amino acids; or (v) a combination of these amino acid sequences; and the like.

Throughout the specification, the metastin receptors are represented in accordance with the conventional way of describing peptides, that is, the N-terminus (amino terminus) at the left hand and the C-terminus (carboxyl terminus) at the right hand. In the metastin receptors including the metastin receptor represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, the C-terminus may be in any form of a carboxyl group (-COOH), a carboxylate (-COO-), an amide ($-CONH_2$) and an ester (-COOR). Herein, examples of the ester group shown by R include a C_{1-6} alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, etc.; a C_{3-8} cycloalkyl group such as

cyclopentyl, cyclohexyl, etc.; a C_{6-12} aryl group such as phenyl, α-naphthyl, etc.; a C_{7-14} aralkyl such as a phenyl-C_{1-2} alkyl group, e.g., benzyl, phenethyl, etc.; an α-naphthyl-C_{1-2} alkyl group such as α-naphthylmethyl, etc.; and pivaloyloxymethyl group, which are widely used as an ester for oral use, and the like.

Where the metastin receptors contain a carboxyl group (or a carboxylate) at a position other than the C-terminus, the carboxyl group may be amidated or esterified and such amides or esters are also included within the receptor protein of the present invention. In this case, the ester group used may be the same group as the C-terminal esters described above.

Furthermore, the metastin receptors include those wherein the amino group at the N-terminal methionine residue is protected with a protecting group (e.g., a C_{1-6} acyl group such as a C_{2-6} alkanoyl group, e.g., formyl group, acetyl group, etc.); those wherein the N-terminal region is cleaved in vivo and the glutamyl group thus formed is pyroglutaminated; those wherein a substituent (e.g., -OH, -SH, amino group, imidazole group, indole group, guanidino group, etc.) on the side chain of an amino acid in the molecule is protected with a suitable protecting group (e.g., a C_{1-6} acyl group such as a C_{2-6} alkanoyl group, e.g., formyl group, acetyl group, etc.), or conjugated proteins such as glycoproteins bound to sugar chains.

Specific examples of the metastin receptors include human metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 9, rat metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 11, mouse metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 13, etc.

The partial peptides of the metastin receptor (hereinafter sometimes simply referred to as the partial peptide) may be any peptide, so long as they are partial peptides of the metastin receptor described above; there are used those such as protein molecules of the metastin receptor, which are the sites exposed outside the cell membrane, and having a ligand binding activity.

Specifically, the partial peptide of the metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13 is a peptide containing the parts analyzed to be extracellular domains (hydrophilic domains) in the hydrophobic plotting analysis. A peptide containing a hydrophobic domain in part can be used as well. In addition, the peptide may contain each domain separately or a plurality of domains together.

In the metastin receptor, preferred partial peptides are those having the number of amino acids of at least 20, preferably at least 50, and more preferably at least 100, in the amino acid sequence described above, which constitutes the metastin receptor.

The partial peptide may be a peptide having the amino acid sequence described above, of which at least 1 or 2 (preferably about 1 to about 10 and more preferably several (1 or 2)) amino acids are deleted; to which at least 1 or 2 (preferably about 1 to about 10 and more preferably several (1 or 2)) amino acids are added; or, in which at least 1 or 2 (preferably about 1 to about 10 and more preferably several (1 or 2)) amino acids are substituted by other amino acids.

In the partial peptide, the C terminus may be any form of a carboxyl group (-COOH), a carboxylate (-COO-), an amide ($-CONH_2$) and an ester (-COOR), as in the metastin receptor described above.

Furthermore, the partial peptides include peptides, wherein the amino group at the N-terminal methionine residue is protected with a protecting group; those wherein the N-terminal region is cleaved in vivo and the glutamyl group thus formed is pyroglutaminated; those wherein a substituent on the side chain of an amino acid in the molecule is protected with a suitable protecting group, or conjugated peptides such as glycopeptides bound to sugar chains, as in the metastin receptors described above.

For salts of the metastin receptor or the partial peptide, preferred are salts with physiologically acceptable acids, especially physiologically acceptable acid addition salts. Examples of the salts include salts with, for example, inorganic acids (e.g., hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid); salts with organic acids (e.g., acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid) and the like.

As the DNA encoding the metastin receptor or its partial peptides, there are used, for example, a DNA encoding the human metastin receptor or its partial peptides described in WO 00/24890, a DNA encoding the mouse or rat human metastin receptor or its partial peptides described in WO 01/75104, etc.

The DNAs encoding the metastin receptor or its partial peptides may be any of genomic DNA, genomic DNA library, cDNA derived from the cells and tissues described above, cDNA library derived from the cells and tissues described above and synthetic DNA. The vector to be used for the library may be any of bacteriophage, plasmid, cosmid and phagemid. The DNA may also be directly amplified by reverse

transcriptase polymerase chain reaction (hereinafter abbreviated as RT-PCR) using the total RNA or mRNA fraction prepared from the cells and tissues described above.

Specifically, the DNA encoding human metastin receptor, mouse metastin receptor or rat metastin receptor may be any DNA, so long as it is a DNA containing each base sequence represented by SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14, or a DNA containing a base sequence hybridizable to the base sequence represented by SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14 under highly stringent conditions and encoding a receptor having the activity of substantially the same nature (e.g., a ligand binding activity, a signal transduction activity, etc.) as that of the human metastin receptor, mouse metastin receptor or rat metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14.

Examples of the DNA hybridizable to the base sequence represented by any of SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14 include DNAs containing a base sequence having at least about 70% homology, preferably at least about 80% homology, more preferably at least about 90% homology and the most preferably at least about 95% homology, to the base sequence represented by any of SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14.

Homology in the base sequence can be measured under the following conditions (an expectation value = 10; gaps are allowed; filtering = ON; match score = 1; mismatch score = -3) using the homology scoring algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool).

The hybridization can be carried out by per se publicly known methods or by modifications of these methods, for example, according to the method described in Molecular Cloning, 2nd (J. Sambrook et al., Cold Spring Harbor Lab. Press, 1989), etc. A commercially available library may also be used according to the instructions of the attached manufacturer's protocol. Preferably, the hybridization can be carried out under highly stringent conditions.

The highly stringent conditions used herein are, for example, those in a sodium concentration at about 19 to 40 mM, preferably about 19 to 20 mM at a temperature of about 50 to 70°C, preferably about 60 to 65°C. In particular, hybridization conditions in a sodium concentration of about 19 mM at a temperature of about 65°C are most preferred.

More specifically, as the DNA encoding the human metastin receptor

consisting of the amino acid sequence represented by SEQ ID NO: 9, the DNA consisting of the base sequence represented by SEQ ID NO: 10 is used.

As the DNA encoding the rat metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 11, the DNA consisting of the base sequence represented by SEQ ID NO: 12 is used.

As the DNA encoding the mouse metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 13, the DNA consisting of the base sequence represented by SEQ ID NO: 14 is used.

The metastin receptors, their partial peptides or salts thereof and the DNAs encoding the metastin receptors or their partial peptides can be obtained or produced by the methods described in WO 00/24890 or WO 01/75104.

The present invention will be described in detail by referring to EXAMPLES, FORMULATION EXAMPLES AND TEST EXAMPLES, but is not deemed to be limited thereto, and any modification may be made without departing from the scope of the present invention.

In the following EXAMPLES, the term "room temperature" normally means a temperature of about 10°C to 35°C. In percentages, the yield is shown by mol/mol% and the solvent used in chromatography by vol%, and the remaining by wt%. In proton NMR spectra, data on OH, NH protons, etc. that are broad and unidentified are not shown.

The other abbreviations used in the specification mean as follows.

Abbreviation	Description
10Ψ,CSNH:	C-terminal-$CONH_2$ at the 10-position is substituted with -$CSNH_2$.
1Ψ2,CH_2NH:	The -CONH- bond between the 1- and 2-positions is substituted with the -CH_2NH- bond.
2Ψ3,CH_2NH:	The -CONH- bond between the 2- and 3-positions is substituted with the -CH_2NH- bond.
3Ψ4,CH_2NH:	The -CONH- bond between the 3- and 4-positions is substituted with the -CH_2NH- bond.
4Ψ5,CH_2NH:	The -CONH- bond between the 4- and 5-positions is substituted with the -CH_2NH- bond.
6Ψ7,CSNH:	The -CONH- bond between the 6- and 7-positions is substituted with the -CSNH- bond.
6Ψ7,NHCO:	The -CONH- bond between the 6- and 7-positions is substituted with

the -NHCO- bond.

6Ψ7,CH_2NH: The -CONH- bond between the 6- and 7-positions is substituted with the -CH_2NH- bond.

6Ψ7,CH_2O: The -CONH- bond between the 6- and 7-positions is substituted with the -CH_2O- bond.

7Ψ8,CH_2NH: The -CONH- bond between the 7- and 8-positions is substituted with the -CH_2NH- bond.

8Ψ9,CH_2NH: The -CONH- bond between the 8- and 9-positions is substituted with the -CH_2NH- bond.

9Ψ10,CH_2NH: The -CONH- bond between the 9- and 10-positions is substituted with the -CH_2NH- bond.

Abu : 2-aminobutanic acid

Ac : acetyl

Acp : 6-aminocaproic acid

AcOEt : ethyl acetate

AcOH : acetic acid

Aib : α-aminoisobutanoic acid

Ala(2-Qui) : 2-quinolylalanine

Ala(3-Bzt) : 3-benzothienylalanine

Alb : Albizziin 2-amino-3-ureidopropion acid

Arg(Ac): N^{ω}-acetylarginine

Arg(Boc_2,Me) : $N^{\omega,\omega'}$-bis-tert-butoxycarbonyl-N^{ω}-methylarginine

Arg(Et) : N^{ω}-ethylarginine

Arg(Me) : N^{ω}-methylarginine

Arg(asyMe_2) or Arg(Me_2)asym : asymmetric-$N^{\omega,\omega}$-dimethylarginine

Arg(symMe_2) or Arg(Me_2)sym : symmetric-$N^{\omega,\omega'}$-dimethylarginine

Arg(NO_2) : N^{ω}-methylarginine

Arg(n-Pr) : N^{ω}-propylarginine

Arg(Tos) : N^{ω}-tosylarginine

Asp(NHMe) : N^{ω}-methylasparagine

Asp(Nme2) : N^{ω}-dimethylasparagine

AzaGly : azaglycine

AzaPhe : azaphenylalanine

Aze(2) : azetidine-2-carboxylic acid

β-Ala : β-alanine
Boc : tert-butoxycarbonyl
Boc_2O : di-tert-butyl dicarbonate
Br-Z : 2-bromobenzyloxycarbonyl
Bu^t : tert-butyl
Bzl : benzyl
CDI : 1,1'-carbonyldiimidazole
Cha : cyclohexylalanine
CIP : 2-chloro-1,3-dimethylimidazolium tetrafluoroborate
Cit : citrulline
Clt resin : 2-chlorotrytyl resin
Cl-Z : 2-chlorobenzyloxycarbonyl
Dab : 2,4-diaminobutanoic acid
Dap : 2,3-diaminopropionic acid
Dap(Ac) : N^{β}-acetyldiaminopropionic acid
Dap(For) : N^{β}-formyldiaminopropionic acid
Dap(Gly) : N^{β}-glycyldiaminopropionic acid
Dap(GnGly) : N^{β}-(N-guanidinoglycyl)diaminopropionic acid
DCM : dichloromethane
DEA : diethylamine
DIEA : N,N-diisopropylethylamine
DIPCDI : 1,3-diisopropylcarbodiimide
DMAP : 4-dimethylaminopyridine
DMF : N,N-dimethylformamide
EDT : 1,2-ethanedithiol
Fmoc : 9-fluorenylmethoxycarbonyl
For : formyl
γ-Abu : 4-aminobutanoic acid
γ-MeLeu : γ-methylleucine
Gn : guanidino
GuAmb : 4-guanidinomethylbenzoyl
Har : homoarginine
Har(Me) : N^{ω}-methylhomoarginine
HOAt : 1-hydroxy-7-azabenzotriazole

HOBt : 1-hydroxybenzotriazole
HONB : N-hydroxy-5-norbornene-2,3-dicarboxamide
Hph : homophenylalanine
Hyp : trans-4-hydroxyproline
IndPr : 3-(indol-3-yl)propionyl
Lys(Me_2) : $N^{\alpha,\varepsilon}$-dimethyllysine
MBHA : p-methylbenzhydrylamine
MeOH : methanol
Mtt : 4-methyltrytyl
N((CH_2)$_3$Gn)Gly : N-(3-guanidinopropyl)glycine
Nal(1) : 1-naphthylalanine
Nal(2) : 2-naphthylalanine
Nar : norarginine
Nar(Me) : N^{ω}-methylnorarginine
Nle : norleucine
NMeArg : N^{α}-methylarginine
NMeAsn : N^{α}-methylasparagine
NMeLeu : N^{α}-methylleucine
NMePhe : N^{α}-methylphenylalanine
NMeSer : N^{α}-methylserine
NMeTrp : N^{α}-methyltryptophan
NMeTyr : N^{α}-methyltyrosine
Nva : Norvaline
Orn : ornithine
Orn(Mtt) : N^{δ}-(4-methyltrytyl)ornithine
PAL : 5-(4-(9-fluorenylmethoxycarbonyl)aminomethyl3,5-dimethoxy-phenoxy)valeric acid
Pbf : 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
pGlu : pyroglutamic acid
Phe(2Cl) : 2-chlorophenylalanine
Phe(2F) : 2-fluorophenylalanine
Phe(3,4Cl_2) : 3,4-dichlorophenylalanine
Phe(3,4F_2) : 3,4-difluorophenylalanine
Phe(3CF_3) : 3-trifluoromethylphenylalanine

Phe(3Cl) : 3-chlorophenylalanine
Phe(3F) : 3-fluorophenylalanine
Phe(4Cl) : 4-chlorophenylalanine
Phe(4CN) : 4-cyanophenylalanine
Phe(4F) : 4-fluorophenylalanine
Phe(4Gn) : 4-guanidinophenylalanine
Phe(4NH_2) : 4-aminophenylalanine
Phe(4NO_2) : 4-nitrophenylalanine
Phe(4CN) : 4-cyanophenylalanine
Phe(F_5) : pentafluorophenylalanine
PheΨ(CH_2O)Gly : The -CONH- bond between Phe and Gly is substituted with the -CH_2O- bond.
PheΨ(CSNH)-NH_2 : The C-terminal phenylalanylamide is substituted with the phenylalanylthioamide.
Phg : phenylglycine
PhOH : phenol
PhSMe : thioanisole
Pip(2) : 2-aminopipecolinic acid
Pro : proline
Pya(2) : 2-pyridylalanine
Pya(3) : 3-pyridylalanine
Pya(4) : 4-pyridylalanine
PyAOP : (7-azabenzotriazole-1-yloxy)-tris(pyrrolidino)phosphonium hexafluorophosphate
PyBOP : (benzotriazole-1-yloxy)-tris(pyrrolidino)phosphonium hexafluorophosphate
PyBrop : bromo-tris(pyrrolidino)phosphonium hexafluorophosphate
Sar : N-methylglycine
Ser(Ac) : O-acetylserine
Ser(Me) : O-methylserine
Thi : 2-thienylalanine
Tic : 1,2,3,4-tetrahydroisoquinoline-2-caarboxylic acid
TIS : triisopropylsilane
Tle : tert-leucine

Tos : tosyl

Trp(For) : N^{in}-formyltryptophan

Trt : trytyl

Tyr(Me) : O-methyltyrosine

TyrΨ(CH_2NH)Asn : The -CONH- bond between Tyr and Asn is substituted with the -CH_2NH- bond.

TFA : trifluoroacetic acid

TFE : trifluoroethanol

Z : benzyloxycarbonyl

In the specification and drawings, the codes of bases and amino acids are denoted in accordance with the IUPAC-IUB Commission on Biochemical Nomenclature or by the common codes in the art, examples of which are shown below. For amino acids that may have the optical isomer, L form is presented unless otherwise indicated.

DNA : deoxyribonucleic acid

cDNA : complementary deoxyribonucleic acid

A : adenine

T : thymine

G : guanine

C : cytosine

Y : thymine or cytosine

N : thymine, cytosine, adenine or guanine

R : adenine or guanine

M : cytosine or adenine

W : thymine or adenine

S : cytosine or guanine

RNA : ribonucleic acid

mRNA : messenger ribonucleic acid

dATP : deoxyadenosine triphosphate

dTTP : deoxythymidine triphosphate

dGTP : deoxyguanosine triphosphate

dCTP : deoxycytidine triphosphate

ATP : adenosine triphosphate

EDTA : ethylenediaminetetraacetic acid
SDS : sodium dodecyl sulfate
TFA : trifluoroacetic acid
EIA : enzyme immunoassay

Gly or G : glycine
Ala or A : alanine
Val or V : valine
Leu or L : leucine
Ile or I : isoleucine
Ser or S : serine
Thr or T : threonine
Cys or C : cysteine
Met or M : methionine
Glu or E : glutamic acid
Asp or D : aspartic acid
Lys or K : lysine
Arg or R : arginine
His or H : histidine
Phe or F : phenylalanine
Tyr or Y : tyrosine
Trp or W : tryptophan
Pro or P : proline
Asn or N : asparagine
Gln or Q : glutamine
pGlu : pyroglutamic acid

The sequence identification numbers in the sequence listing of the specification indicates the following sequence, respectively.

SEQ ID NO: 1

This shows the amino acid sequence of human-derived metastin (Metastin).

SEQ ID NO: 2

This shows the base sequence of DNA encoding human metastin.

SEQ ID NO: 3

This shows the amino acid sequence of mouse metastin precursor (A).

SEQ ID NO: 4

This shows the base sequence of DNA encoding mouse metastin precursor (A), which is the base sequence contained in plasmid pCMV-mKiSS-1 harbored on transformant Escherichia coli DH10B/pCMV-mKiSS-1.

SEQ ID NO: 5

This shows the amino acid sequence of mouse metastin precursor (B).

SEQ ID NO: 6

This shows the base sequence of DNA encoding mouse metastin precursor (B), which is the base sequence contained in plasmid pCR2.1-mKiSS-1.4A harbored on transformant Escherichia coli DH5α/pCR2.1-mKiSS-1.4A.

SEQ ID NO: 7

This shows the amino acid sequence of rat-derived metastin precursor.

SEQ ID NO: 8

This shows the base sequence of DNA encoding rat metastin precursor.

SEQ ID NO: 9

This shows the amino acid sequence of human OT7T175 (metastin receptor).

SEQ ID NO: 10

This shows the base sequence of DNA encoding human OT7T175 (metastin receptor).

SEQ ID NO: 11

This shows the amino acid sequence of rat OT7T175 (metastin receptor).

SEQ ID NO: 12

This shows the base sequence of DNA encoding rat OT7T175 (metastin receptor).

SEQ ID NO: 13

This shows the amino acid sequence of mouse OT7T175 (metastin receptor).

SEQ ID NO: 14

This shows the base sequence of DNA encoding mouse OT7T175 (metastin receptor).

SEQ ID NO: 15

This shows the amino acid sequence of human metastin 15 (40-54).

SEQ ID NO: 16

This shows the amino acid sequence of human metastin 10 (45-54) (MS10).

SEQ ID NO: 17

This shows the amino acid sequence of human metastin 9 (46-54).

SEQ ID NO: 18

This shows the amino acid sequence of human metastin 8 (47-54).

SEQ ID NO: 19

This shows the base sequence of DNA encoding human metastin 15 (40-54).

SEQ ID NO: 20

This shows the base sequence of DNA encoding human metastin 10 (45-54).

SEQ ID NO: 21

This shows the base sequence of DNA encoding human metastin 9 (46-54).

SEQ ID NO: 22

This shows the base sequence of DNA encoding human metastin 8 (47-54).

The transformant *Escherichia coli* DH10B/pCMV-mKiSS-1 has been on deposit since January 24, 2000 with International Patent Organisms Depository, National Institute of Advanced Industrial Science and Technology (the former Ministry of International Trade and Industry, Agency of Industrial Science and Technology, National Institute of Bioscience and Human Technology (NIBH)), located at Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki (postal code 305-8566), Japan as the Accession Number FERM BP-7003 and since December 16, 1999 with Institute for Fermentation (IFO), located at 2-17-85 Juso-Honmachi, Yodogawa-ku, Osaka-shi, Osaka, Japan, as the Accession Number IFO 16348.

The transformant *Escherichia coli* DH5α/pCR2.1-mKiSS-1.4A has been on deposit since March 6, 2000 with International Patent Organisms Depository, National Institute of Advanced Industrial Science and Technology (the former Ministry of International Trade and Industry, Agency of Industrial Science and Technology, National Institute of Bioscience and Human Technology (NIBH)), located at Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki (postal code 305-8566), Japan as the Accession Number FERM BP-7073 and since February 16, 2000 with Institute for Fermentation (IFO), located at 2-17-85 Juso-Honmachi, Yodogawa-ku, Osaka-shi, Osaka, Japan, as the Accession Number IFO 16360.

In the present invention, Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2 (SEQ ID NO: 16) is referred to as metastin 10 (Metastin10), i.e., MS10.

In EXAMPLES later described, the N-terminal Tyr and the C-terminal Phe in

MS10 are counted as the 1- and 10-positions, respectively.

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
1 2 3 4 5 6 7 8 9 10

For example, [Hph10]MS10 of Compound No. 79 (EXAMPLE 1) means a peptide wherein the C-terminal Phe (10-position) of MS10 is substituted with Hph.

For example, des(1)-MS10 of Compound No. 4 means a peptide wherein the N-terminal Tyr (1-position) is deleted.

For example, des(1-3)-Fmoc-MS10 of Compound No. 53 means a peptide wherein the N-terminal Tyr-Asn-Trp (1 to 3-positions) is deleted and the amino group of Asn at the 4-position is modified and protected with Fmoc.

[EXAMPLE 1]

(Synthesis Process A): Preparation of [Hph10]MS10 (Compound No. 79)

Using 51 mg of Fmoc-Hph-PAL resin (sub. 0.39 mmol/g), which was prepared by introducing Fmoc-Hph into commercially available PAL resin, the peptide chain was extended on a multiple peptide synthesizer ACT-396 to give Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)Hph-PAL resin. To 18.2 mg of the resin, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added and the mixture was shaken for 2 hours. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution was performed with eluants A/B: 73/27-63/37 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 2.6 mg of white powders.

Mass spectrum $(M+H)^+$ 1316.5 (Calcd. 1316.7)

Elution time on HPLC: 20.6 min

Elution conditions

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 2]

(Synthesis Process B): Preparation of [Trp(For)10]MS10 (Compound No. 186)

Using 379 mg of Fmoc-Arg(Pbf)-O-Clt resin (sub. 0.33 mmol/g), which was prepared by introducing Fmoc-Arg(Pbf)-OH into commercially available 2-chlorotritylchloride resin (Clt resin,1.33 mmol/g), the peptide chain was extended on ABI 433A to give 540 mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)-O-Clt resin. To 270 mg of the peptide, 10 mL of AcOH/TFE/DCM (1/1/8) was added the mixture was shaken for 30 minutes. After the resin was removed by filtration, the solvent was concentrated and the residue was dissolved in AcOEt. The solution was then washed with satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether-petroleum ether was added to the residue to give 68 mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)-OH as the precipitate. To 22 mg of the peptide, 4 mg of HCl H-Trp(For)-NH_2 (prepared by treating Boc-Trp(For)-NH_2 with 9.7 N HCl/dioxane at 0°C for 30 minutes), 10 mg of PyAOP, 5 mg of HOAt and 11 μL of DIEA were added. The mixture was stirred for 15 hours. After the solvent was concentrated, chloroform-diethyl ether was added to the residue to give Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)Trp(For)-NH_2 as the precipitate. To the peptide, 1 mL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added and the mixture was stirred for 2 hours. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 73/27-63/37 using eluant A: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 2.0 mg of white powders.

Mass spectrum $(M+H)^+$ 1369.3 (Calcd. 1369.6)

Elution time on HPLC: 19.6 min

Elution conditions

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 3]

(Synthesis Process C): Preparation of [10Ψ,CSNH]MS10 (Compound No. 128)

After 264 mg of Boc-Phe-NH_2 was dissolved in 20 mL of THF, 1.62 g of Lawesson's reagent was added to the solution, followed by stirring for 24 hours. Insoluble matters were removed by filtration, the solvent was concentrated and the concentrate was dissolved in AcOEt. The solution washed over satd. $NaHCO_3$ aq. solution and then satd: NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography. Diethyl ether-petroleum ether was added to give 275 mg (yield 98%) of (S)-2-tert-Butoxycarbonylamino-3-phenylpropanethioamide (Boc-PheΨ(CSNH)-NH_2) as the precipitate. After 42 mg of the peptide was treated at 0°C with 9.7 N HCl to remove Boc, the removal of Fmoc with 10% DEA/DMF treatment followed by condensation by the PyBOP/HOBt method were repeated to give 66 mg of Fmoc-LeuArg(Pbf)PheΨ(CSNH)-NH_2 (yield 93%). To 17mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGly-OH prepared as in EXAMPLE 2, H-LeuArg(Pbf)PheΨ(CSNH)-NH_2 (prepared by treating 14 mg of Fmoc-LeuArg(Pbf)PheΨ(CSNH)-NH_2 with 10% DEA/DMF), 9 mg of PyBrop, 3 mg of HOAt and 7 mL of DIEA were added and the mixture was stirred for 15 hours. After the solvent was concentrated, chloroform-diethyl ether was added thereto for precipitation. To 10 mg of the product, 100 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added and the mixture was stirred for 2 hours. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 72/28-62/38 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 1.0 mg of white powders.

Mass spectrum $(M+H)^+$ 1318.4 (Calcd. 1318.6)

Elution time on HPLC: 21.8 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 4]

(Synthesis Process D): Preparation of [6Ψ7,CH_2NH]MS10 (Compound No. 163)

Using 321 mg of Fmoc-Phe-PAL resin, which was prepared by introducing Fmoc-Phe into commercially available PAL resin, the peptide chain was extended on ABI 433A to give Fmoc-LeuArg(Pbf)Phe-PAL resin. To a half volume of the peptide, Fmoc-Gly was condensed to give 190 mg of Fmoc-GlyLeuArg(Pbf)Phe-PAL resin. After 76 mg of the product was subjected to Fmoc deprotection, 2 mL of DMF, 50 μL of AcOH, 46 mg of Fmoc-Phe-H and 8 mg of $NaBH_3CN$ were added thereto, followed by shaking an hour. After the resin washed, 2 mL of DMF, 22 μL of DIEA and 18 μL of Z-Cl were added thereto and the mixture was shaken for 3 hours. After the resin washed, the peptide chain was extended on ABI 433A to give Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheΨ(CH_2NZ)GlyLeuArg(Pbf)Phe-PAL resin. Under ice cooling, 46 μL of TMS-Br, 42 μL of PhSMe, 38 μL of m-cresol, 18 μL of EDT and 227 μL of TFA were added to 15 mg of the peptide an the mixture was stirred for 2 hours. After the solvent was removed by distillation, diethyl ether was added to the residue, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 72/28-62/38 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 2.0 mg of white powders.

Mass spectrum $(M+H)^+$ 1288.7 (Calcd. 1288.7)

Elution time on HPLC: 18.2 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

(REFERENCE EXAMPLE 1)

Preparation of N-methyl-N,N'-Bis-Boc-1-guanylpyrazole

Under a nitrogen flow, 720 mg of 60% NaH in oil was dissolved in 20 mL of dry DMF and 20 mL of dry DMF solution of 5.59 g of N,N'-Bis-Boc-1-guanylpyrazole commercially available was added to the solution at 0°C, followed by stirring for 10 minutes. After 1.68 mL of methyl iodide was added thereto, the mixture was stirred at room temperature for 24 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography (ethyl acetate/n-hexane = 1/4) using silica gel 60 (200 mL) to give 5.35 g (yield 91.6%) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole.

^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (br s, 1H), 7.69 (br s, 1H), 6.42 (dd, 1H, J=2.7, 1.5 Hz), 3.25 (s, 3H), 1.53 (s, 9H), 1.30 (s, 9H)

Elemental analysis as $C_{15}H_{24}N_4O_4$

Calcd.: C, 55.54; H, 7.46; N, 17.27

Found: C, 55.36; H, 7.48; N, 17.06

Rf1: 0.64, Rf2: 0.79

Developing solvent for TLC: Rf1 (ethyl acetate/n-hexane = 1/2), Rf2 (methanol/chloroform = 2/98)

Elution time on HPLC: 26.7 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-20/80, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (40 mins.)

Flow rate: 1.0 ml/min.

(REFERENCE EXAMPLE 2)

Preparation of N-methyl-N,N'-Bis-Z-1-guanylpyrazole

In an argon atmosphere, 40 mg of 60% NaH in oil was dissolved in 5 mL of

dry DMF and 5 mL of dry DMF solution of 380 mg of N,N'-Bis-Z-1-guanylpyrazole commercially available was added to the solution at 0°C, followed by stirring for 10 minutes. After 125 μL of methyl iodide was added thereto, the mixture was stirred at room temperature for 15 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated to give 393 mg of the crude product. From the crude product 170 mg was purified by flush column chromatography (ethyl acetate/n-hexane = 1/4) using silica gel 60 (75 mL) to give 152 mg (yield 89.5%) of N-methyl-N,N'-bis-Z-1-guanylpyrazole.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (br s, 1H), 7.61 (d, 1H, J=1.0Hz), 7.37-7.32 (m, 4H), 7.29-7.26 (m, 4H), 7.16-7.13 (m, 2H), 6.36 (dd, 1H, J=2.8, 1.6 Hz), 5.18 (s, 2H), 5.04 (s, 2H), 3.22 (s, 3H)

Elemental analysis as $C_{21}H_{20}N_4O_4$

Calcd.: C, 64.28; H, 5.14; N, 14.28

Found: C, 64.09; H, 5.24; N, 14.43

Rf1: 0.50, Rf2: 0.86

Developing solvent for TLC: Rf1(ethyl acetate/n-hexane=1/2), Rf2(methanol/chloroform=2/98)

Elution time on HPLC: 28.9 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-20/80, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (40 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 5]

(Synthesis Process E): Preparation of [Arg(Me)9]MS10 (Compound No. 82)

Using 480 mg of Fmoc-Phe-Rink Amide MBHA resin, which was prepared by introducing Fmoc-Phe into Rink Amide MBHA resin commercially available, the peptide chain was extended on ABI 433A to give 1080 mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuOrn(Mtt)Phe-Rink Amide MBHA resin. To 540 mg of the peptide, 10 mL of TFA/TIS/DCM (1/5/94) was added and the mixture was shaken for 50 minutes. The resin washed and then dried. After 2 mL of DMF, 49 mg of N-methyl-N,N'-bis-Boc-1-guanylpyrazole prepared in REFERENCE EXAMPLE 1 and 87 μL of DIEA were added to 2/5 volume of the resin,

the mixture was shaken for 15 hours to give 220 mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Boc$_2$,Me)Phe-Rink Amide MBHA resin. To 50 mg of the peptide, 1 mL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added and the mixture was stirred for 2 hours. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 74/26-64/36 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 10.5 mg of white powders.

Mass spectrum $(M+H)^+$ 1316.5 (Calcd. 1316.7)

Elution time on HPLC: 20.1 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

N-Methyl-N,N'-bis-Boc-1-guanylpyrazole used to convert the amino acid at the 9-position into N^{ω}-methylated Arg in this EXAMPLE is a reagent useful for producing peptides containing N^{ω}-methylated Arg, and is advantageously used also in general peptides to produce peptides containing N^{ω}-methylated Arg characterized by reacting N-methyl-N,N'-bis-Boc-1-guanylpyrazole with Orn in peptides followed by deprotection.

Furthermore, blood stability is improved by converting Arg into N^{ω}-methylated Arg not only in the N^{ω}-methylated Arg-containing peptide obtained in this EXAMPLE but also in general peptides. Therefore, substituents on the side chain of N^{ω}-methylated Arg are useful for a method of enhancing blood stability, which comprises converting Arg in a peptide into N^{ω}-methylated Arg.

Moreover, a method of enhancing blood stability, which comprises introducing one or two (preferably one) alkyl group, preferably C_{1-4} alkyl group, more preferably methyl group into the side chain of Arg in the Arg-containing peptide, may be provided. Herein, the Arg-containing peptide includes, for example, a peptide having a partial

peptide characterized by the structure -Arg-XXX-, wherein XXX represents an amino acid having optionally substituted aromatic ring group into the side chain, preferably Phe, Trp, Tyr, etc.

The N^{ω}-methylated Arg-containing peptides can also be produced using not only N-methyl-N,N'-bis-Boc-1-guanylpyrazole but N-methyl-N,N'-bis-Z-1-guanylpyrazole prepared in REFERENCE EXAMPLE 2.

[EXAMPLE 6]

(Synthesis Process F): Preparation of [6Ψ7,CSNH]MS10 (Compound No. 166)

In 10 mL of DMF, 503 mg of HCl H-Gly-OBu^t was dissolved and 1162 mg of Fmoc-Phe, 608 mg of HOBt, 1874 mg of PyBOP and 784 μL of DIEA were added at 0°C, followed by stirring for 4 hours. The solvent was concentrated and the concentrate was dissolved in AcOEt. The solution was then washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether-petroleum ether was added to give 1.48 g (yield 99%) of Fmoc-PheGly-OBu^t as the precipitate. After 250 mg of the product was dissolved in 10 mL of toluene, 404 mg of Lawesson's reagent was added to the solution, followed by stirring at 80°C for 2 hours. The solvent was concentrated and the concentrate was dissolved in AcOEt. The solution was then washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography. Diethyl ether-petroleum ether was added to the eluate to give 207 mg (yield 80%) of Fmoc-PheΨ(CSNH)Gly-OBu^t as the precipitate. To 103 mg of the product, TFA/H_2O (95/5) was added and the mixture was stirred for an hour. After the solvent was concentrated, diethyl ether was added to give 82.4 mg (yield 90%) of Fmoc-PheΨ(CSNH)Gly-OH as the precipitate. Using Fmoc-Phe-PAL resin, which was prepared by introducing Fmoc-Phe into commercially available PAL resin, the peptide chain was extended on ABI 433A and 80 mg of Fmoc-LeuArg(Pbf)Phe-PAL resin thus extended was subjected to Fmoc deprotection. Then 35 mg of Fmoc-PheΨ(CSNH)Gly-OH, 47 mg of PyBrop, 14 mg of HOAt and 35 μL of DIEA were added to the resin, followed by shaking for 15 hours. After the resin washed, the peptide chain was extended on ABI 433A to give Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheΨ(CSNH)GlyLeuArg(Pbf)Phe-PAL resin. To 15 mg of the product, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, followed by stirring for 2 hours. Diethyl ether was added to

the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 77/23-57/43 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 1.0 mg of white powders.

Mass spectrum $(M+H)^+$ 1318.7 (Calcd. 1318.6)

Elution time on HPLC: 20.8 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 7]

(Synthesis Process G): Preparation of [AzaGly7]MS10 (Compound No. 176)

Using 321 mg of Fmoc-Phe-PAL resin, which was prepared by introducing Fmoc-Phe into commercially available PAL resin, the peptide chain was extended on ABI 433A and 80 mg of Fmoc-LeuArg(Pbf)Phe-PAL resin thus extended was subjected to Fmoc deprotection. After 2 mL of THF and 16 mg of CDI were added, the mixture was shaken for 2 hours. Then 6 μL of hydrazine monohydrate was added to the mixture. The mixture was shaken for an hour and the resin was then washed. After 39 mg of Fmoc-Phe, 93 mg of PyBrop, 27 mg of HOAt and 105 μL of DIEA were added to the system, followed by shaking for 2 hours. After the resin washed, the peptide chain was extended on ABI 433A to give Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Pbf)Phe-PAL resin. To 25 mg of the product, 1 mL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, followed by shaking for 2 hours. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 74/26-64/36 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC

using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 5.5 mg of white powders.

Mass spectrum $(M+H)^+$ 1303.3 (Calcd. 1303.6)

Elution time on HPLC: 18.9 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 8]

(Synthesis Process H): Preparation of [D-Tyr1,AzaGly7,Arg(Me)9]MS10 (Compound No. 232)

Fmoc-Phe,Fmoc-Orn(Mtt) was introduced into 4 g (0.55mmol/g) of Rink Amide MBHA resin commercially available to prepare Fmoc-Orn(Mtt)-Phe- Rink Amide MBHA resin, and 50 mL of TFA/TIS/DCM (1/5/94) was added to the resin, followed by shaking for 50 minutes. After the resin washed, 40 mL of DCM and 2.27 g of N-methyl-N,N'-bis-Boc-1-guanylpyrazole prepared in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 9. The mixture was shaken for 15 hours to give 4.74 g of Fmoc-Arg(Boc_2,Me)Phe-Rink Amide MBHA resin. Separately, 145 mg of Fmoc-$NHNH_2$ HCl was suspended in 10 mL of THF. Under ice cooling, 89 mg of CDI and 87 mL of DIEA were added to the suspension, followed by stirring at room temperature for an hour. Under ice cooling, a solution of 224 mg of H-Leu-OBu^t HCl in 5 mL of DMF 5 mL was added to the mixture. While reverting to room temperature, the mixture was stirred for 18 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography to give 230 mg (yield 99%) of Fmoc-AzaGly-Leu-OBu^t. To 187 mg of the product, 10 mL of TFA/H_2O (9/1) was added, followed by stirring for an hour. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether was added to give 143 mg of Fmoc-AzaGly-Leu-OH as the precipitate (yield 87%). The resulting Fmoc-AzaGly-Leu-OH, Trt-Phe was introduced into Fmoc-Arg(Boc_2,Me)Phe-Rink

Amide MBHA resin. To the thus prepared Trt-Phe-AzaGly-Leu-Arg(Boc_2,Me)Phe-Rink Amide MBHA resin, 50 mL of TFA/TIS/DCM (1/5/94) was added and the mixture was shaken for 50 minutes. After the resin washed and neutralized, Fmoc-Ser(Bu^t) and then Fmoc-Asn(Trt) were introduced thereinto. Using 80.3mg of the resulting Fmoc-Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin, the peptide chain was extended to give 97.2 mg of H-D-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin.

To the resin obtained, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added, followed by stirring for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 76/24-66/34 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized to give 11.7 mg of white powders.

Mass spectrum $(M+H)^+$ 1317.0 (Calcd. 1317.6)

Elution time on HPLC: 21.0 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm).

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 9]

(Synthesis Process I): Preparation of des(1-3)-3-(3-pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10 (Compound No. 322)

After 48.2 mg of Fmoc-Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin prepared in EXAMPLE 8 was subjected to Fmoc deprotection, the resin was treated with 15.2 mg of 3-(3-pyridyl)propionic acid commercially available, 15.9μL of DIPCDI and 200 μL of 0.5M HOAt/DMF at room temperature for 90 minutes. After the resin obtained washed and dried, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT

(80/5/5/5/2.5/2.5) was added to the resin, followed by stirring for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 80/20-60/40 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized to give 6.0 mg of white powders.

Mass spectrum $(M+H)^+$ 987.4 (Calcd. 987.5)

Elution time on HPLC: 8.1 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 10]

(Synthesis Process J): Preparation of des(1-2)-Amidino-[AzaGly7,Arg(Me)9]MS10 (Compound No. 273)

After Fmoc-Trp(Boc) was introduced into 48.2 mg of Fmoc-Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin prepared in EXAMPLE 8, the resin was subjected to Fmoc deprotection to give H-Trp(Boc)Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin. The resin obtained was treated in DMF with 29.3 mg of N,N'-bis-Boc-1-guanylpyrazole and 34.8 μL of DIEA for 14 hours to give Amidino-Trp(Boc)Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin. After the resin obtained washed and dried, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added, followed by stirring for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 78/22-58/42 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A

column (20 x 250 mm). The fractions containing the product were collected and lyophilized to give 0.6 mg of white powders.

Mass spectrum $(M+H)^+$ 1082.3 (Calcd. 1082.6)

Elution time on HPLC: 11.4 min

Elution conditions:

Column: YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 11]

(Synthesis Process K): Preparation of [6Ψ7,NHCO,D-Tyr1,Arg(Me)9]MS10 (Compound No. 319)

In 30 mL of MeCN, 5.99 g of Z-Phe was dissolved and 3.94 g of HONB and 4.59 g of WSCD HCl were added to the solution at 0°C, followed by stirring at room temperature for 4 hours. While keeping at 0°C, 3.4 mL of 25% NH_3 aq. solution and 10 mL of DMF were added to the mixture, followed by stirring for 4 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether was added to give 1.48 g (yield 99%) of Z-Phe-NH_2 as the precipitate. After 1.94 g of [Bis(trifluoroacetoxy)iodo]benzene was dissolved in 20 mL of MeCN and 5 mL of H_2O, 890 mg of Z-Phe-NH_2 prepared above and 972 μL of pyridine were added to the precipitate at 0°C, followed by stirring at room temperature for 15 hours. After the solvent was concentrated, the concentrate was subjected to liquid-liquid separation with diethyl ether-1N HCl aq. solution and the 1N HCl aq. solution layer was concentrated and then dried. Its half volume was dissolved in 5 mL of DMF, and 486 μL of mono-tert-butyl malonate and 540 mg of HOBt were added to the solution. Then, 2.08 g of PyBOP and 1394 μL of DIEA were added at 0°C to the mixture, followed by stirring at room temperature for 15 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography. Diethyl ether-petroleum ether was added to give 304 mg (yield 33%) of Z-PheΨ(NHCO)Gly-OBu^t as the precipitate. After 154 mg of the product was dissolved

in 20mL of MeOH, 10% Pd-C was added to the solution, followed by catalytic hydrogenation for 2 hours in a hydrogen flow. After removal of the catalyst by filtration, the solvent was concentrated and dried. The residue was dissolved in 10 mL of MeCN 10 mL and 152 mg of Fmoc-OSu and 78 μL of DIEA were added to the solution, followed by stirring for 15 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether-petroleum ether was added to give 127 mg (yield 68%) of Fmoc-PheΨ(NHCO)Gly-OBu^t as the precipitate. Fmoc-Leu was introduced into 63 mg of Fmoc-Arg(Boc$_2$,Me)Phe-Rink Amide MBHA resin prepared in EXAMPLE 10. After Fmoc deprotection, Fmoc-PheΨ(NHCO)Gly-OH (prepared by treating 25 mg of Fmoc-PheΨ(NHCO)Gly-OBu^t with TFA for 3 minutes), 300 μL of 0.5M HOAt, 78 mg of PyAOP and 52 μL of DIEA were added to the resin, followed by shaking for 6 hours. After the resin washed, 2 mL of DMF, 9 μL of DIEA and 12 μL of Ac_2O were added to the resin, followed by shaking for 30 minutes. After the resin washed, the peptide chain was extended on ABI 433A to give Boc-D-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheΨ(NHCO)GlyLeuArg(Boc$_2$,Me)Phe-Rink Amide MBHA resin. To 34 mg of the product, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, followed by stirring for 2 hours. Ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 76/24-66/34 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 0.7 mg of white powders.

Mass spectrum $(M+H)^+$ 1316.3 (Calcd. 1316.7)

Elution time on HPLC: 18.7 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 12]

(Synthesis Process L): Preparation of [N((CH$_2$)$_3$Gn)Gly9]-MS10 (Compound No. 218)

Using 192 mg of Fmoc-Phe-Rink Amide MBHA resin, the peptide chain was extended on ABI 433A to give Fmoc-GlyPhe-Rink Amide MBHA resin. After a 1/4 volume of the product was subjected to Fmoc deprotection, 2 mL of DMF, 50 μL of AcOH, 5 mg of Boc-β-Ala-H and 16 mg of NaBH$_3$CN were added thereto and the mixture was shaken for 30 minutes. After the resin washed, 71 mg of Fmoc-Leu, 56 mg of CIP, 27 mg of HOAt and 105 mL of DIEA were added, followed by shaking for 15 hours. After the resin washed, the peptide chain was extended on ABI 433A to give Z-Tyr(Bzl)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuN((CH$_2$)$_3$NHBoc)GlyPhe-Rink Amide MBHA resin. To the product, 1 mL of TFA/PhOH/H$_2$O/TIS/EDT (87.5/5/2.5/2.5/2.5) was added and the mixture was stirred for 2 hours. After the resin was removed by filtration and then concentrated, ether was added to the concentrate. A half volume of the resulting precipitate was dissolved in 500 μL of DMF, 9 mg of 1H-pyrazole-1-carboxamidine hydrochloride and 22 mL of DIEA were added to the solution, followed by stirring for 15 hours. The solvent was distilled off and ether was added to precipitate. Under ice cooling, 60 μL of PhSMe, 56 μL of m-cresol, 26 μL of EDT, 337 μL of TFA and 65 μL of TMSBr were added to the mixture, followed by stirring for 2 hours. After the solvent was distilled off, ether was added to the residue, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 74/26-64/36 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 1.8 mg of white powders.

Mass spectrum $(M+H)^+$ 1302.5 (Calcd. 1302.7)

Elution time on HPLC: 18.6 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 13]

(Synthesis Process M): Preparation of MS10 (Compound No. 3)

Commercially available p-methyl BHA resin (0.77 mmole/g resin) was charged in a reaction tank of peptide synthesizer ABI 430A. Thereafter, Boc-Phe.Boc-Arg(Tos), Boc-Leu.Boc-Gly, Boc-Phe.Boc-Ser(Bzl), Boc-Asn.Boc-Trp(For) and Boc-Asn.Boc-Tyr(Br-Z) were introduced into the resin in this order according to the Boc-strategy (DCC-HOBt) peptide synthesis to give the desired protected peptide resin. The resin, 0.11 g, was stirred at 0°C for 60 minutes in 10 ml of anhydrous hydrogen fluoride containing 1 ml of p-cresol and 1.2 ml of 1,4-butanediol. Thereafter the hydrogen fluoride was distilled off in vacuum. Diethyl ether was added to the residue and the precipitate was filtrated. To the precipitate 50% acetic acid aqueous solution was added for extraction and insoluble matters were removed. After the extract was sufficiently concentrated, the concentrate was applied to Sephadex (trade name) G-25 column (2.0 x 80 cm) filled with 50% acetic acid aqueous solution followed by development with the same solvent. The main fractions were collected and lyophilized to give 40 mg of white powders. A half volume of the powders was applied to column chromatography (2.6 x 60 cm) packed with LiChroprep (trade name) RP-18 followed by washing with 200 ml of water containing 0.1% TFA. Then linear density gradient elution was performed with 300 ml of 0.1% TFA in water and 300 ml of 0.1% TFA-containing 33% acetonitrile. The main fractions were collected and lyophilized to give 2.2 mg of the desired peptide.

Mass spectrum (M+H) 1302.5 (Calcd. 1302.6)

Elution time on HPLC: 18.7 min

Elution conditions:

Column: Wakosil-II 5C18T 4.6 x 100 mm

Eluant: linear density gradient elution with eluants A/B = 95/5-45/55, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 14]

(Synthesis Process N): Preparation of des(1-3)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10 (Compound No. 279)

Fmoc-Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Me,Boc$_2$)Phe-Rink-Amide MBHA resin prepared in EXAMPLE 8 was subjected to Fmoc deprotection. To 64 mg (20 μmol) of H-Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Me,Boc$_2$)Phe-Rink Amide MBHA

resin, 1.5 mL of THF and 13 mg of CDI were added, followed by shaking for 2 hours. After 32 mg of tryptamine hydrochloride, 28 μL of DIEA and 500 μL of DMF were added to the mixture, followed by shaking for 24 hours. Thereafter the resin washed to give

2-(Indol-3-yl)ethylcarbamoyl-Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Me,Boc$_2$)Phe-Rink Amied MBHA resin. To 15 mg of the product, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, followed by stirring for 2 hours. Ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 69/31-59/41 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 1.1 mg of white powders.

Mass spectrum $(M+H)^+$ 1040.2 (Calcd. 1040.5)

Elution time on HPLC: 20.1 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 15]

Preparation of Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin

Commercially available Rink Amide MBHA resin, 5 g (0.4 mmol/g), was swollen in DMF, and treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained washed with DMF, Trp(Boc) was introduced by treating the resin at room temperature with 4.213 g (8 mmol) of Fmoc-Trp(Boc)-OH, 1.272 mL (8 mmol) of DIPCDI and 16 mL (8 mmol) of 0.5M HOAt/DMF solution for 90 minutes to give Fmoc-Trp(Boc)-Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 2 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. After the resin obtained washed and swollen with DCM, 50 mL of TFA/TIS/DCM (1/5/94) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated

until yellow coloration caused by free Mtt group in a TFA/TIS/DCM (1/5/94) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 1.946 g (6 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give 6.195 g of Fmoc-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The resin was divided in half and the Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin (1 mmol) to give H-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin (1 mmol).

Separately, 1.745 g (6 mmol) of Fmoc-NHNH$_2$ HCl was suspended in 20 mL of DMF-THF (4:1). Under ice cooling, 973 mg (6 mmol) of CDI and 2.09 mL (12 mmol) of DIEA were added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 3.314 g of Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin.

[EXAMPLE 16]

(Synthesis Process O): Preparation of des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 385)

After 100 mg (0.03 mmol) of Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin was swollen in DMF, the resin was treated with 2 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained washed with DMF, Phe was introduced by treating the resin with 77.5 g (0.2 mmol) of Fmoc-Phe-OH, 31.8 μL (0.2 mmol) of DIPCDI and 0.4 mL (0.2 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes. In a similar manner, Ser(^{t}Bu) and Asn(Trt) were introduced to give Fmoc-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin. The obtained resin was subjected to Fmoc deprotection and treated with 77.6 mg (0.2 mmol) of Fmoc-$_D$-Pya(4)-OH, 104.2 mg (0.2 mmol) of PyAOP, 400 μL

(0.2 mmol) of 0.5M HOAt/DMF and 174.2 μL (0.2 mmol) of DIEA at room temperature for 90 minutes to introduce $_D$-Pya(4) and then $_D$-Tyr(^{t}Bu), followed by Fmoc deprotection. Thus, 135 mg of H-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin was obtained.

To the resin obtained, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added, followed by stirring for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 15 ml/min with eluants A/B: 79/21-69/31 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm). The fractions containing the product were collected and lyophilized. The white powders obtained were dissolved in 10 mL of water and 100 μL of ion exchange resin BioRAD AG1 x 8 AcO^- form was added to the solution. While manually stirring the solution sometimes, the reaction solution was settled for an hour. The solution was filtered through a membrane filter to remove the resin and give 6.6 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1204.5 (Calcd. 1204.6)

Elution time on HPLC: 8.2 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 17]

(Synthesis Process P): Preparation of des(1-6)-Dibenzylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 393)

After 35.2 mg (0.015 mmol) of Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin was swollen in DMF, the resin was treated with 2 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. Separately, 19.2 μL (0.1 mmol) of dibenzylamine was dissolved in THF. Under ice cooling, 16.2 mg (0.1 mmol) of CDI and 2.6 μL (0.015

mmol) of DIEA were added to the solution, followed by stirring at room temperature for an hour. After Fmoc deprotection, the resulting solution was added to H-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin, followed by stirring at room temperature for 15 hours.

To Bzl_2NCO-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin obtained, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added, and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 8 ml/min. with eluants A/B: 63/37-53/47 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized. The white powders obtained were dissolved in 10 mL of water and 100 μL of ion exchange resin BioRAD AG1 x 8 AcO^- form was added to the solution. While manually stirring the solution sometimes, the reaction solution was settled for an hour. The solution was filtered through a membrane filter to remove the resin and give 2.2 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 768.7 (Calcd. 768.4)

Elution time on HPLC: 16.9 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 18]

(Synthesis Process Q): Preparation of des(1-5)-Benzoyl-[6Ψ7,CH2O,Arg(Me)9,Trp10]MS10 (Compound No. 421)

After 1.80 g of Z-Phe was dissolved in 20 mL of MeOH, 〒 73 mg of DMAP and 1.38 g of WSCD HCl were added to the solution at 0°C, followed by stirring at 4°C for 12 hours. The solvent was concentrated and the concentrate was dissolved in AcOEt. The solution was then washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated to

give Z-Phe-OMe as oil. After dissolving in 20 mL of dry THF, 196 mg of $LiBH_4$ was added to the solution, followed by stirring at room temperature for 15 hours. The solvent was concentrated and the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and ether-petroleum ether was added to the concentrate to give 1.45 g (yield 85%) of Z-Phe-ol as the precipitate. After 60 mg of 60% NaH was suspended in 10 mL of dry THF, 285 mg of Z-Phe-ol, 264 mg of 18-crown-6 and 1.48 mL of tert-butyl bromoacetate were added to the solution at 0°C. While reverting to room temperature, the mixture was stirred for 15 hours. After the solvent was distilled off in vacuum, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography to give 217 mg (yield 54%) of Z-PheΨ(CH_2O)Gly-OBu^t as oil. After 160 mg of Z-PheΨ(CH_2O)Gly-OBu^t was dissolved in 20 mL of MeOH, 10% Pd-C was added to the solution, followed by catalytic hydrogenation for 3 hours in a nitrogen flow. The catalyst was removed by filtration and the solvent was concentrated followed by drying. The concentrate was dissolved in 15 mL of DCM, and 114 mg of Fmoc-Cl and 139 μL of DIEA were added to the solution, followed by stirring for 12 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography. Diethyl ether-petroleum ether was added to give 150 mg (yield 77%) of Fmoc-PheΨ(CH_2O)Gly-OBu^t as the precipitate. To the precipitate, were added 31 mg (15 μmol) of H-LeuArg(Me,Boc_2)Trp(Boc)-Rink amide MBHA resin obtained in a manner similar to the process of EXAMPLE 15, 19 mg of Fmoc-PheΨ(CH_2O)Gly-OH (prepared by treating Fmoc-PheΨ(CH_2O)Gly-OBu^t with 50% TFA/DCM for an hour), 180 μL of 0.5M HOAt, 42 mg of PyBrop and 47 μL of DIEA. The mixture was shaken for 18 hours. After the resin washed, 5 mL of 20% piperidine/DMF was added to the resin, followed by stirring at room temperature for 30 minutes. After the resin washed, 9 μL of benzoyl chloride, 13 μL of DIEA and 1 mL of DMF 1 were added to the resin, followed by stirring at room temperature for 2 hours. After the resin washed and dried, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added to the resin, followed by stirring for 2 hours. Ether was added to the reaction solution, the resulting

precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 75/25-65/35 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 2.5 mg of white powders.

Mass spectrum $(M+H)^+$ 782.2 (Calcd. 782.4)

Elution time on HPLC: 22.1 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 19]

(Synthesis Process R): Preparation of des(1-7)-Dibenzylaminocarbamoylacetyl-[Arg(Me)9,Trp10]MS10 (Compound No. 434)

After 1.54 mL of mono-tert-butyl malonate, 1.08 g of fluorenylmethanol and 61 mg of DMAP were dissolved in 20 mL of DCM 20, 1.15 g of WSCD HCl was added to the solution, followed by stirring at room temperature for 24 hours. The solvent was distilled off in vacuum, the residue was dissolved in AcOEt. The solution was then washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography to give 1.62 g (yield 96%) of tert-butyl fluorenylmethyl malonate. In 20 mL of TFA, 61 mg of tert-butyl fluorenylmethyl malonate was dissolved and the solution was stirred at room temperature for 2 hours. After the solvent was distilled off in vacuum, the residue was dissolved in AcOEt, followed by washing with satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and purified by flush column chromatography to give 850 mg (yield 67%) of mono-fluorenylmethyl malonate. After 5 mL of 20% piperidine/DMF was added to 46 mg (15 μmol) of Fmoc-LeuArg(Me,Boc_2)Trp(Boc)-Rink amide MBHA resin prepared in a manner similar to EXAMPLE 15, the solution was shaken at room temperature for 30 minutes. After the resin washed, 42 mg of

mono-fluorenylmethyl malonate, 70 mg of PyBrop, 300 μL of 0.5M HOAt/DMF, 52 μL of DIEA and 1 mL of DMF were added to the resin, and the mixture was shaken for 15 hours. After this procedure was repeated twice, 8 μL of Ac_2O, 5 μL of DIEA and 2 mL of DCM were added, followed by stirring at room temperature for 30 minutes. After the resin washed and then dried, 5 mL of 20% piperidine/DMF was added to a half of the resin, followed by stirring at room temperature for 30 minutes. After the resin washed, 13 mg of dibenzylhydrazine, 28 mg of PyBrop, 120 μL of 0.5M HOAt/DMF, 21 μL of DIEA and 1 mL of DMF were added to the resin, followed by shaking for 15 hours. After the resin washed and then dried, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added to the resin, followed by stirring for 2 hours. Ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (120 minutes) was performed with eluants A/B: 83/17-63/37 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 21.6 mg of white powders.

Mass spectrum $(M+H)^+$ 767.6 (Calcd. 767.4)

Elution time on HPLC: 14.5 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 20]

(Synthesis Process S): Preparation of des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 436)

After 340.1 mg (0.1 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin was swollen in DMF, the resin was treated in 20 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained washed with DMF and treated with 155.0 mg (0.4 mmol) of Fmoc-Phe-OH, 63.6 μL (0.4 mmol) of DIPCDI and 0.8 mL (0.4 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to introduce

Phe. After Fmoc-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin obtained was subjected to Fmoc deprotection and then treated with 49.2 mg (0.4 mmol) of 4-Pyridinecarboxylic acid, 63.6 μL (0.4 mmol) of DIPCDI and 0.8 mL (0.4 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes. Then, the resin washed and dried to give 353.5 mg of 4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin. To the resulting resin, 3.5 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 15 ml/min with eluants A/B: 79/21-69/31 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm). The fractions containing the product were collected and lyophilized. The white powders obtained were dissolved in 6 mL of water and 200 μL of ion exchange resin BioRAD AG1 x 8 AcO^- form was added to the solution. While manually stirring the solution sometimes, the reaction solution was settled for an hour. The solution was filtered through a membrane filter to remove the resin and give 21.6 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 797.8 (Calcd. 797.4)

Elution time on HPLC: 8.8 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 21]

(Synthesis Process T): Preparation of des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 499)

After 170.1 mg (0.05 mmol) of Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin was swollen in DMF, the resin was treated with 5 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained washed with DMF and treated with 77.5

mg (0.2 mmol) of Fmoc-Phe-OH, 31.8 μL (0.2 mmol) of DIPCDI, and 0.4 mL (0.2 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to introduce Phe. In a similar manner, Ser(^{t}Bu) and Asn(Trt) were introduced to give Fmoc-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was subjected to Fmoc deprotection and then treated with 30.0 mg (0.2 mmol) of phenylpropionic acid, 31.8 μL (0.2 mmol) of DIPCDI and 0.4 mL (0.2 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes. Then, the resin washed and dried to give 209.6 mg of 3-Phenylpropionyl-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin. To the resin obtained, 1.5 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 8 ml/min with eluants A/B: 71/29-61/39 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized. The white powders obtained were dissolved in 10 mL of water and 125 μL of ion exchange resin BioRAD AG1 x 8 AcO^- form was added to the solution. While manually stirring the solution sometimes, the reaction solution was settled for an hour. The solution was filtered through a membrane filter to remove the resin and give 5.2 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1025.3 (Calcd. 1025.5)

Elution time on HPLC: 13.6 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 22]

(Synthesis Process U): Preparation of des(1-5)-Benzoyl-[AzaPhe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 431)

After 500 mg (2.56 mmol) of benzylhidrazine.2HCl was dissolved in DCM, the solution was cooled to -78°C on dry ice. Then, 727.1 mg (3.33 mmol) of Boc_2O and 0.982 ml (5.64 mmol) of DIEA were added to the solution. Dry ice was removed and the mixture was stirred for 30 minutes. After confirming by TLC that the reaction proceeded, 327 µl (2.82 mmol) of benzoyl chloride and 580.4 µl (3.33 mmol) of DIEA were added to the mixture, followed by stirring at room temperature overnight. Citric acid crystals were added to the reaction solution and the mixture was concentrated. A 10% citric acid aqueous solution was added to the mixture. The precipitated residue was extracted with AcOEt and the extract washed with 10% citric acid aqueous solution, 5% $NaHCO_3$ aq. solution and then satd. NaCl aq. solution, followed by drying over anhydrous Na_2SO_4. The residue obtained was crystallized from ether-hexane (1:1) to give 435.5 mg of white crystals.

After 46.3 mg (0.015 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-NH-Rink Amide MBHA resin was swollen in DMF, the resin was treated with 5 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained washed with DMF and treated in THF with 3.65 mg (0.023 mmol) of CDI at room temperature for an hour. Separately, 32.6 mg (0.1 mmol) of the white powders above were treated with 0.3 ml of 4N HCl/dioxane for an hour. The solvent was then distilled off and the residue washed with ether. The residue obtained was dissolved in THF, and 17.4 µl (0.1 mmol) of DIEA was added to the solution. The resulting solution was added to the resin, followed by stirring overnight. The resin washed and dried to give 29.5 mg of Benzoyl-AzaPhe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-NH-Rink Amide MBHA resin. To the resin obtained,

0.5 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 8 ml/min with eluants A/B: 66/34-56/44 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized to give 3.2 mg of white powders.

Mass spectrum $(M+H)^+$ 797.7 (Calcd. 797.4)

Elution time on HPLC: 15.3 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 23]

(Synthesis Process V): Preparation of des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10 (Compound No. 548)

Fmoc-Leu-OH was introduced into commercially available 2-chlorotritylchloride resin. After Fmoc deprotection, 5 mL of THF and 162 mg of CDI were added to 403 mg of Fmoc-Leu-O-Clt resin (sub. 0.62 mmol/g) obtained. The mixture was shaken for an hour. After 97 μL of hydrazine monohydrate was added to the system, the mixture was shaken for 2 hours and the resin was then washed. To the resin, 581 mg of Fmoc-Phe, 699 mg of PyBrop, 3 mL of 0.5M HOAt/DMF solution and 784 μL of DIEA were added, followed by shaking for 12 hours. After the resin washed, the peptide chain was extended on ABI 433A to give 0.47 g of Boc-$_D$-Tyr(Bu^t)$_D$-Pya(4)Asn(Trt)Ser(Bu^t)PheAzaGlyLeu-O-Clt resin. To the resin, 10 mL of AcOH/TFE/DCM (1/1/8) was added, followed by shaking for 30 minutes. The resin was removed by filtration and the solvent was concentrated. The residue was dissolved in chloroform and the resulting solution washed with satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and AcOEt-diethyl ether was added to the concentrate to give 320 mg (yield 98%) of Boc-$_D$-Tyr(Bu^t)$_D$-Pya(4)Asn(Trt)Ser(Bu^t)PheAzaGlyLeu-OH as the precipitate. On the other hand, 5 mL of 4N HCl/AcOEt was added to 264 mg (1 mmol) of Boc-Phe-NH_2 under ice cooling, followed by stirring for 30minutes. The solvent was distilled off and ether was then added for precipitation. The precipitate was dissolved in 20 mL of DMF, and 455 mg of Fmoc-Orn(Boc), 540 mg of HOBt, 382 mg of WSCD.HCl and 348 μL of DIEA were added to the solution, followed by stirring for 6 hours. After the solvent was distilled off in vacuum, the residue was dissolved in ethyl acetate and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated. Ether-petroleum ether

was added to the concentrate to give 594.4 mg (yield 99%) of Fmoc-Orn(Boc)-Phe-NH_2 as the precipitate. Under ice cooling, 5 mL of 4N HCl/AcOEt was added to 132 mg of the product, followed by stirring for 30 minutes. After the solvent was distilled off, ether was added to give 111.1 mg (yield 94%) of Fmoc-Orn-Phe-NH_2.HCl as the precipitate. The precipitate was dissolved in 3 mL of chloroform/TFE (3/1), and 194 mg of N-methyl-N,N'-Bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 and 105 μL of DIEA were added to the solution, followed by stirring for 24 hours. After the solvent was distilled off, ether-petroleum ether was added to give 108.5 mg (yield 72%) of Fmoc-Arg(Boc_2,Me)-Phe-NH_2 as the precipitate. In 5 mL of THF, 38 mg of the product was dissolved and 142 mg of Lawesson's Reagent was added to the solution, followed by stirring for 15 hours. After the solvent was distilled off in vacuum, the residue was dissolved in ethyl acetate and the solution washed with $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated. After purification by flush column chromatography, ether-petroleum ether was added to give 18.7 mg (yield 48%) of Fmoc-Arg(Me,Boc_2)-PheΨ(CSNH)-NH_2 as the precipitate. To 11 mg of the product, 1 mL of 10% DEA/DMF was added and the mixture was stirred for 2 hours. After the solvent was distilled off, the residue was dissolved in 1 mL of DMF, and 18 mg of Boc-D-Tyr(Bu^t)-D-Pya(4)-Asn(Trt)-Ser(Bu^t)-Phe-AzaGly-Leu-OH previously obtained, 7.6 mg of HOBt, 5.4 mg of WSCD.HCl and 4.9 μL of DIEA were added to the solution, followed by stirring for 15 hours. The solvent was distilled off and ether was added to the residue for precipitation. To the precipitate, 1 mL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, and the mixture was stirred for 2 hours. Ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 82/18-72/28 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 0.9 mg of white powders.

Mass spectrum $(M+H)^+$ 1181.5 (Calcd. 1181.6)

Elution time on HPLC: 14.9 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 24]

(Synthesis Process W): Preparation of Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 550)

After 5 g (0.4 mmol/g) of commercially available Rink Amide MBHA resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained washed with DMF, Trp(Boc) was introduced by treating the resin with 4.213 g (8 mmol) of Fmoc-Trp(Boc)-OH, 1.272 mL (8 mmol) of DIPCDI and 16 mL (8 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes. In a similar manner, Orn(Mtt) was introduced to give 2 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained washed with DCM, after swelling, 50 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 1.946 g (6 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol) to give H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol).

Separately, 2.326 g (8 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 20 mL of DMF. Under ice cooling, a suspension of 297 mg (8 mmol) of CDI in 20 mL of THF and then 2.787 mL (16 mmol) of DIEA was added to the suspension, followed by

stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 6.394 g of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

After 3.197 g (1 mmol) of the resin obtained was swollen in DMF, the resin was treated with 30 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained washed with DMF, the resin was treated with 1.806 g (4 mmol) of Trt-Phe-OH.0.5AcOEt, 2.086 g (4 mmol) of PyAOP, 8 mL (4 mmol) of 0.5M HOAt/DMF and 2.787 mL (16 mmol) of DIEA at room temperature for 90 minutes to give Trt-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin Phe. The resin obtained washed with DCM, after swelling, 30 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Trt group in a TFA/TIS/TFE/DCM (1/5/19/75) solution disappeared when the solution was added, thus the Trt group was removed. The H-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin obtained was neutralized with 5%-DIEA/DMF solution and washed with DMF. Thereafter, the resin was treated with 1.590 g (4 mmol) of Fmoc-Thr(^{t}Bu)-OH, 0.636 mL (4 mmol) of DIPCDI and 8 mL (4 mmol) of 0.5M HOAt/DMF at room temperature for 90 minutes to introduce Thr(^{t}Bu). Subsequently, the Fmoc deprotection by treatment with 30 ml of 20% piperidine/DMF solution for 20 minutes and condensation by the DIPCDI/HOAt method similar to introduction of Thr(^{t}Bu) were repeated so that Asn(Trt), $_D$-Trp(Boc), and $_D$-Tyr(^{t}Bu) were introduced to give Fmoc-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was treated with 30 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained washed to give H-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was treated with 188.7 μL (2 mmol) of Ac_2O and 348.4 μL (2 mmol) of DIEAin 20 mL of DMF at room temperature for 30 minutes to acetylate the N terminus. The resin was then washed and dried to give 4.168 g of Ac-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc

)-Rink Amide MBHA resin.

To a half of the resin obtained, i.e., 2.111 g, 15 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5 /5/2.5 /2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. After the residue was extracted with an aqueous acetic acid solution, the extract was filtered to remove the resin and lyophilized to give crude peptide powders. With respect to the remaining half of the resin, deprotection was performed under the same conditions to give about 650 mg of crude peptide powders in total. About 50 mg each of the crude peptide obtained was purified by applying sequentially to linear density gradient elution (60 minutes) at a flow rate of 15 ml/min with eluants A/B: 71/29-61/39 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm). The fractions containing the product were collected and lyophilized to give 255.5 mg of white powders as the purified sample.

All of the white powders were dissolved in 200 mL of aqueous acetonitrile solution and 492 μL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour. The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 225.3 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1298.7 (Calcd. 1298.6)

Elution time on HPLC: 15.6 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 25]

: Preparation of Ac-des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 562)

After 5.455 g (0.455 mmol/g) of commercially available Rink Amide MBHA

resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, Trp(Boc) was introduced by treating the resin with 6.319 g (12 mmol) of Fmoc-Trp(Boc)-OH, 1.908 mL (12 mmol) of DIPCDI and 24 mL (12 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to give Fmoc-Trp(Boc)- Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 3 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was washed with DCM, after swelling, 75 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 40 mL of DCM-TFE (4:1) and 2.919 g (9 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol) to give H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol).

Separately, 3.489 g (12 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 30 mL of DMF. Under ice cooling, a suspension of 1.849 mg (11.4 mmol) of CDI in 20 mL of THF and then 4.181 mL (24 mmol) of DIEA was added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 8.2496 g of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

After 2.646 g (1 mmol) of the resin obtained was swollen in DMF, the resin was treated with 30 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, the resin was treated with 1.630 g (4 mmol) of Trt-Phe-OH, 2.086 g (4 mmol) of PyAOP, 8 mL (4 mmol) of 0.5M

HOAt/DMF and 2.787 mL (16 mmol) of DIEA at room temperature for 90 minutes to give Trt-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin Phe. The resin obtained was washed with DCM, after swelling, 30 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Trt group in a TFA/TIS/TFE/DCM (1/5/19/75) solution disappeared when the solution was added, thus the Trt group was removed. The H-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin obtained was neutralized with 5%-DIEA/DMF solution and washed with DMF. Thereafter, the resin was treated with 1.590 g (4 mmol) of Fmoc-Thr(^{t}Bu)-OH, 0.636 mL (4 mmol) of DIPCDI and 8 mL (4 mmol) of 0.5M HOAt/DMF at room temperature for 90 minutes to introduce Thr(^{t}Bu). Subsequently, the Fmoc deprotection by treatment with 30 ml of 20% piperidine/DMF solution for 20 minutes and condensation by the DIPCDI/HOAt method similar to introduction of Thr(^{t}Bu) were performed to give Fmoc-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was Fmoc-deprotected. Then the resin was treated with 1.476 g (3.8 mmol) of Fmoc-$_D$-Pya(4)-OH, 2.086 mg (4 mmol) of PyAOP, 8 mL of 0.5 M HOAt/DMF (4 mmol) and 2.439 mL of DIEA (14 mmol) at room temperature for 90 minutes to introduce $_D$-Pya(4). Susequently, by the DIPCDI/HOAt method similar to introduction of Thr(^{t}Bu), $_D$-Tyr(^{t}Bu) was introduced to the resin to give Fmoc-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was treated with 30 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained was washed to give H-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was treated with 188.7 μL (2 mmol) of Ac_2O and 348.4 μL (2 mmol) of DIEA in 20 mL of DMF at room temperature for 30 minutes to acetylate the N terminus. The resin was then washed and dried to give 1 mmol of Ac-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

To the resin obtained, 30 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the

supernatant was removed. This procedure was repeated twice for washing. After the residue was extracted with an aqueous acetic acid solution, the extract was filtered to remove the resin and lyophilized to give 949.0 mg of crude peptide powders. About 50 mg each of the crude peptide obtained was purified by applying to preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm) at a flow rate of 15 ml/min sequencially with initial eluants A/B: 90/10 for 8 minutes, A/B: 75/25, wherein it took 7 minutes to increase the concentration, and linear density gradient elution (60 minutes) with eluants A/B: 75/25-65/35 using eluant A: 0.05% TFA in water and eluant B: 0.05% TFA-containing acetonitrile. The fractions containing the product were collected and lyophilized to give 361.1 mg of white powders as the purified sample.

All of the white powders obtained were dissolved in 200 mL of aqueous acetonitrile solution and 1.434 mL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour. The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 309.3 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1260.4 (Calcd. 1260.4)

Elution time on HPLC: 15.5 min

Elution conditions:

Column Wakosil-II 5C18 HG (4.6 x 100 mm).

Eluant: linear density gradient elution with eluants A/B = 100/0-50/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA as eluant B (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 26]

: Preparation of Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10 (Compound No. 571)

After 2.5 g (0.4 mmol/g) of commercially available Rink Amide MBHA resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, Phe was introduced by treating the resin with 1.550 g (4 mmol) of Fmoc-Phe-OH, 0.636 mL (4 mmol) of DIPCDI and 8 mL (4 mmol) of 0.5M

HOAt/DMF solution at room temperature for 90 minutes to give Fmoc-Phe- Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 1 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was washed with DCM, after swelling, 25 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Phe-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 0.973 g (3 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin (1 mmol) to give H-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin (1 mmol).

Separately, 1.163 g (4 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 10 mL of DMF. Under ice cooling, a suspension of 0.568 mg (3.5 mmol) of CDI in 10 mL of THF and then 1.307 mL (7.5 mmol) of DIEA was added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 3.134 g of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin.

Using this resin, 1.94 g of Trt-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin obtained by the condensation of Trt-Phe-OH 0.5AcOEt in similar to EXAMPLE 24, was washed with DCM. After swelling, 12 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until brownish yellow coloration caused by free Trt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Trt group was removed. By washing the resin, 1.66 g of H-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin were obtained. Using 553 mg of the resin obtained, peptide chain was extended with the

peptide synthesizer ABI-433A (Fmoc/DCC/HOBt) to give H-D-Tyr(But)-D-Trp(Boc)-Asn(Trt)-Thr(But)-Phe-AzaGly-Leu-Arg(Boc2,Me)-Phe-Rink amide MBHA resin. To this product, 5 mL of DMF, 111 mg of AcONB and 44 ml of DIEA was added and the resin was shaken for two hours. The resin was dried after washing to give 0.78 g of Ac-D-Tyr(But)-D-Trp(Boc)-Asn(Trt)-Thr(But)-Phe-AzaGly-Leu-Arg(Boc2,Me)-Phe-Rink amide MBHA resin. To the resin, 6 mL of TFA/thioanisole/m-cresol/H2O/TIS/EDT (80/5/5/5/2.5/2.5) was added and the resin was shaken for two hours. After removal of the resin by filtration, solvent was distilled off. By adding diethylether, precipitation was obtained. After centrifugation, washing by removal of the supernatant was repeated twice, and the residues were extracted with acetate solution. After the resin was removed by filtration, the fraction was purified by applying to preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm) at a flow rate of 15 ml/min sequencially with linear density gradient elution (60 minutes) with eluants A/B: 71/29-61/39 using eluant A: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile. The fractions containing the product were collected and lyophilized to give white powders as the purified sample. The purified sample was lyophilized. The crude peptide obtained in the similar manner using 553 mg of H-Phe-AzaGly-Leu-Arg(Boc2,Me)-Phe-Rink amide MBHA resin was purified on preparative HPLC to give total 237.6 mg of purified sample as white powders.

The white powders obtained, 236.1 mg were dissolved in 200 mL of aqueous acetonitrile solution and 935 μL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour. The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 204.6 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1259.5 (Calcd. 1259.6)

Elution time on HPLC: 13.2 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA as eluant B (25

mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 27]

: Preparation of Ac-des(1)-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 579)

After 5 g (0.4 mmol/g) of commercially available Rink Amide MBHA resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, Trp(Boc) was introduced by treating the resin with 4.213 g (8 mmol) of Fmoc-Trp(Boc)-OH, 1.272 mL (8 mmol) of DIPCDI and 16 mL (8 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to give Fmoc-Trp(Boc)- Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 2 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was washed with DCM, after swelling, 50 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 1.946 g (6 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol) to give H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol).

Separately, 2.326 g (8 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 20 mL of DMF. Under ice cooling, a suspension of 1.297 mg (8 mmol) of CDI in 20 mL of THF and then 2.787 mL (16 mmol) of DIEA was added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed

by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 2 mmol of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

Using 868 mg (0.257 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin, Thr(^{t}Bu), Alb, $_D$-Trp(Boc), and $_D$-Tyr(^{t}Bu) were introduced by repeating condensation using DCC/HOBt method with ABI 433A to give a H-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Alb-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. N-terminus od the obtained resin was acetylated by treating with 111 mg (0.5 mmol) of AcONB and 87 μL (0.5 mmol) of DIEA in 5 mL of DMF at room temperature for 10 hours. Subsequently, the resin was washed and dried to give a Ac-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Alb-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rin k Amide MBHA resin.

To the resin obtained, 6 mL of TFA/ PhSMe/ m-cresol/ H_2O/ TIS/ EDT(80/ 5/ 5 /5/2.5 /2.5) was added, and the suspension was shaken for two hours. After removal of the resin by filtration, solvent was distilled off. By adding diethylether, precipitation was obtained. After centrifugation, washing by removal of the supernatant was repeated twice, and the residues were extracted with acetate solution. After the resin was removed by filtration, the fraction was purified by applying to preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm) at a flow rate of 15 ml/min sequencially with linear density gradient elution (60 minutes) with eluants A/B: 69/31-59/41 using eluant A: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile. The fractions containing the product were collected and lyophilized to give 106.5 mg of white powders as the purified sample.

All the white powders obtained were dissolved in 100 mL of aqueous acetonitrile solution and 400 μL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour. The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 97.5 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1299.5 (Calcd. 1299.6)

Elution time on HPLC: 19.0 min

Elution conditions:

Column Wakosil-II (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-50/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA as eluant B (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 28]

(Synthesis Process X): Preparation of Ac-des(1)-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 585)

After 5 g (0.4 mmol/g) of commercially available Rink Amide MBHA resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, Trp(Boc) was introduced by treating the resin with 4.213 g (8 mmol) of Fmoc-Trp(Boc)-OH, 1.272 mL (8 mmol) of DIPCDI and 16 mL (8 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to give Fmoc-Trp(Boc)- Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 2 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was washed with DCM, after swelling, 50 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 1.946 g (6 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol) to give H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol).

Separately, 2.326 g (8 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 20 mL of DMF. Under ice cooling, a suspension of 1.297 mg (8 mmol) of CDI in 20 mL of THF and then 2.787 mL (16 mmol) of DIEA was added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 2 mmol of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

Using 868 mg (0.257 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin, Thr(^{t}Bu), Dap(Mtt), D-Trp(Boc) and D-Tyr(^{t}Bu) were introduced by repeating condensation using DCC/HOBt method with ABI 433A to give a H-D-Tyr(^{t}Bu)-D-Trp(Boc)-Dap(Mtt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc) -Rink Amide MBHA resin. N-terminus od the obtained resin was acetylated by treating with 111 mg (0.5 mmol) of AcONB and 87 μL (0.5 mmol) of DIEA in 5 mL of DMF at room temperature for 4 hours. Subsequently, the resin was washed and dried to give a Ac-D-Tyr(^{t}Bu)-D-Trp(Boc)-Dap(Mtt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

To the resin obtained, 6 mL of TFA/ PhSMe/ m-cresol/ H_2O/ TIS/ EDT(80/ 5/ 5 /5/2.5 /2.5) was added, and the suspension was shaken for two hours. After removal of the resin by filtration, solvent was distilled off. By adding diethylether, precipitation was obtained. After centrifugation, washing by removal of the supernatant was repeated twice, and the residues were extracted with acetate solution. After the resin was removed by filtration, the fraction was purified by applying to preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm) at a flow rate of 15 ml/min sequencially with linear density gradient elution (60 minutes) with eluants A/B: 71/29-61/39 using eluant A: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile. The fractions containing the product were collected and lyophilized to give 106.5 mg of white powders as the purified sample.

All the white powders obtained were dissolved in 100 mL of aqueous acetonitrile solution and 400 μL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour.

The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 58.3 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1284.7 (Calcd. 1284.6)

Elution time on HPLC: 17.9 min

Elution conditions:

Column Wakosil-II (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-50/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA as eluant B (25 mins.)

Flow rate: 1.0 ml/min.

The structures of compounds synthesized as in EXAMPLES 1 to 24 and physicochemical properties of these compounds are shown in TABLES 1 to 11, below.

[TABLE 1]

Comp. No.		M+H+ (obs.)	M+H+ (cal.)	HPLC (min.)	HPLC mode	Synth Proc
1	Motsutin	5858.4	5858.5	18.1	d	M
2	Lys-Asp-Leu-Pro-Asn-MS10	1888.8	1888.8	18.5	d	M
3	MS10	1302.5	1302.6	14.7	d	M
4	des(1)-MS10	1139.6	1139.6	16.1	d	M
17	[Pya(4)10]MS10	1303.6	1303.6	14.7	d	M
18	[Tyr(Me)10]MS10	1332.7	1332.7	17.7	d	M
19	[Phe(2F)10]MS10	1320.8	1320.6	17.9	d	M
23	[Tyr3]MS10	1378.8	1378.6	18.8	d	M
24	[Leu6]MS10	1328.7	1328.7	19.8	d	M
30	Acetyl-MS10	1344.8	1344.6	20.2	b	A
31	Fmoc-MS10	1564.8	1564.7	23.1	b	A
35	[D-Ser5]MS10	1302.8	1302.6	11.9	c	A
39	[D-Asn4]MS10	1302.8	1302.6	11.8	c	A
40	[D-Trp1]MS10	1302.8	1302.6	11.8	c	A
41	[D-Asn3]MS10	1302.8	1302.6	11.7	c	A
42	[D-Tyr1]MS10	1302.8	1302.6	11.4	c	A
44	[Lys2]MS10	1274.8	1274.6	11.7	c	A
45	[Ala8]MS10	1288.5	1288.6	10.0	c	A
50	[Ala7]MS10	1316.3	1316.7	12.8	c	A
51	[NMePhe10]MS10	1316.3	1316.7	22.7	a	A
53	des(1-3)-Fmoc-MS10	1081.2	1081.5	27.3	a	A
54	des(1-2)-Fmoc-MS10	1247.4	1247.6	29.9	a	A
55	des(1)-Fmoc-MS10	1361.6	1361.6	29.2	a	A
56	[Lys2]MS10	1316.8	1316.7	16.8	d	M
57	[Asp5]MS10	1303.7	1303.6	17.7	d	M
58	[Tyr3]MS10	1351.7	1351.7	18.2	d	M
59	[Leu6]MS10	1301.8	1301.7	18.2	d	M
60	[Pya(3)10]MS10	1303.6	1303.6	14.7	d	M
61	[Phe(4F)10]MS10	1320.8	1320.6	18.9	d	M
67	[Ala3]MS10	1187.4	1187.6	8.3	a	A
68	[Leu1]MS10	1229.6	1229.6	11.1	a	A
69	[Ser5]MS10	1203.5	1203.6	8.9	a	A
70	[Asp5]MS10	1231.6	1231.6	9.0	a	A
71	[Lys2]MS10	1244.8	1244.7	8.1	a	A
72	[Ala1]MS10	1210.5	1210.6	11.1	a	A
73	[Leu1]MS10	1232.8	1232.7	12.5	c	A
74	[Ser1]MS10	1228.8	1228.6	10.8	a	A
75	[Asp1]MS10	1254.4	1254.6	11.0	a	A

[TABLE 2]

76	[Lys1]MS10	1287.6	1287.7	10	c	A
77	[Phe(4CN)10]MS10	1327.5	1327.6	17.2	d	M
78	[Trp(For)3, Phe(4CN)10]MS10	1355.6	1355.6	17.4	d	M
79	[Hph10]MS10	1316.5	1316.7	20.8	a	A
81	[NMeArg8]MS10	1316.2	1316.7	23.3	a	A
82	[Arg(Me)9]MS10	1316.5	1316.7	20.1	a	E
83	[Arg(Me2)asy9]MS10	1330.4	1330.7	21.3	a	A
87	des(4-5)-Boc-MS10	1201.6	1201.6	22.5	d	M
88	des(4-5)-MS10	1101.5	1101.5	18.6	d	M
90	[Lys9,9Ψ10,CH2NH]MS10	1280.6	1280.7	19.8	a	D
91	[8Ψ9,CH2NH]MS10	1288.7	1288.7	20.5	a	D
97	[Har9]MS10	1316.3	1316.7	11.9	c	A
98	[Lys(Me2)9]MS10	1302.6	1302.7	11.5	c	A
101	[Ser7]MS10	1332.6	1332.6	11.8	c	A
105	[Nle8]MS10	1302.3	1302.6	11.9	c	A
107	[Val8]MS10	1288.5	1288.6	11	c	A
109	[Tyr10]MS10	1408.4	1408.7	10.2	c	A
110	[Nal(2)10]MS10	1332.4	1332.6	13.5	c	A
111	[Phe(F5)10]MS10	1392.2	1392.6	13.5	c	A
112	[Cha10]MS10	1308.4	1308.7	13.4	c	A
114	des(1-3)-3-(3-Indolyl)propionyl-MS10	1010.5	1010.5	13.8	c	A+I
121	des(1-4)-[Trp5]MS10	824.3	824.5	22.5	d	M
123	[NMeLeu8]MS10	1316.7	1316.7	12.7	c	A
126	[NMeSer8]MS10	1317	1316.7	11.8	c	A
127	[D-Asn4,NMePhe6]MS10	1316.7	1316.7	11.8	c	A
128	[10Ψ,CSNH]MS10	1318.4	1318.6	21.8	a	C
129	[Arg(Me2)sy9]MS10	1331.2	1330.7	20.9	a	A
130	[Phe(4CO)10]MS10	1338.4	1338.6	13.1	c	A
131	[Phe(4NH2)10]MS10	1317.4	1317.6	8.3	c	A
132	[Phe(4NO2)10]MS10	1347.4	1347.6	12.2	c	A
133	[Nal(1)10]MS10	1382.6	1382.7	13.5	c	A
134	[Trp10]MS10	1341.5	1341.6	12	c	A
137	[Nle9]MS10	1259.4	1259.6	15.3	c	A

139	[CR8]MS10	1303.4	1303.6	12.2	a	A
140	[Arg(Me)8,NMePhe10]MS10	1330.4	1330.7	21	a	E
141	[D-Tyr1,Arg(Me)8]MS10	1316.5	1316.7	20.2	a	E
142	[D-Tyr1,D-Trp3,Arg(Me)8]MS10	1316.7	1316.7	20.1	a	E
143	[D-Trp3,Arg(Me)8]MS10	1316.7	1316.7	20.3	a	E
144	des(1-3)-Fmoc-[Arg(Me)8]MS10	1076.2	1076.5	28	a	E
145	des(1-2)-Fmoc-[Arg(Me)8]MS10	1261.2	1261.5	28.8	a	E

[TABLE 3]

148	[10Ψ,CSNH,D-Tyr1]MS10	1318.4	1318.6	21.4	a	C
150	[Tyr6]MS10	1318.4	1318.6	10.2	a	A
151	[Nal(1)6]MS10	1352.6	1352.7	13.5	a	A
152	[Nal(2)6]MS10	1352.6	1352.7	13.6	a	A
153	[Phe(F5)6]MS10	1392.5	1392.6	13.7	a	A
154	[Phe(4F)6]MS10	1320.6	1320.6	12.3	a	A
155	[Cha6]MS10	1308.2	1308.5	13.2	a	A
163	[8Ψ7,CH2NH]MS10	1288.7	1288.7	18.2	a	D
165	[Dap(Gly)6] MS10	1289.6	1289.6	10.2	a	E
166	[8Ψ7,CSNH]MS10	1318.7	1318.6	20.9	a	F
168	[D-Tyr1,Ala3,Arg(Me)6]MS10	1202.1	1201.6	9.0	a	E
170	[D-Tyr1,Ser3,Arg(Me)6]MS10	1218.2	1217.6	8.8	a	E
171	[D-Tyr1,Cha3,Arg(Me)6]MS10	1284.2	1283.7	12.1	a	E
172	[D-Tyr1,Cha5,Arg(Me)6]MS10	1402.9	1322.7	13.1	a	E
173	[D-Tyr1,Ala7,Arg(Me)6]MS10	1410.9	1330.7	12.2	a	E
174	[D-Tyr1,Arg(Me)6,Trp10]MS10	1338.3	1338.7	11.7	a	E
176	[AzaGly7]MS10	1303.3	1303.6	18.9	a	D
181	[D-Tyr1,Cha3,6,Arg(Me)6]MS10	1370.6	1370.6	13.9	a	E
182	[D-Tyr1,Cha3,5,Arg(Me)6,Trp10] MS10	1328.2	1328.7	21.3	a	E
183	[Phe(4NH2)6]MS10	1325.2	1305.6	18.4	a	A
184	[Phe(4-Guanidino)6]MS10	1350.4	1350.6	18.7	a	E
185	[Dap(OrnGly)6]MS10	1331.2	1331.6	18.1	a	E
186	[Trp(For)10]MS10	1369.3	1369.6	19.6	a	B
187	[Abu6]MS10	1274.4	1274.6	10.4	a	A
189	[Ala(3-Bzt)10]MS10	1388.4	1388.6	13.4	a	A
190	[D-Tyr1,Cha3,AzaGly7,Arg(Me)6] MS10	1284.5	1284.7	18.3	a	H
191	[D-Tyr1,Ser3,AzaGly7,Arg(Me)6] MS10	1218.4	1218.6	16.8	a	H
192	[D-Tyr1,Arg(Et)6]MS10	1330.6	1330.7	18.8	a	E
193	[D-Tyr1,Arg(n-Pr)6]MS10	1344.8	1344.7	19.4	a	E
194	[D-Tyr1,Arg(Ac)6]MS10	1346.1	1344.6	18.8	a	E
197	[Phe(3F)10]MS10	1320.6	1320.6	12.2	a	A
198	[Phe(3,4F2)10]MS10	1338.7	1338.6	12.7	a	A
199	[Phe(3,4Cl2)10]MS10	1370.6	1370.6	13.1	a	A
200	[Phe(3CF3)10]MS10	1370.6	1370.6	13.1	a	A
201	[Ala(3-Cu)10]MS10	1353.4	1353.6	8.8	a	A
203	[D-Tyr1,Cha5,Arg(Me)6]MS10	1322.4	1322.7	12.9	a	E
204	[D-Tyr1, Ala7, Arg(Me)6]MS10	1330.4	1330.7	11.7	a	E
205	[D-Tyr1,Thr3,Arg(Me)6]MS10	1231.4	1231.6	8.0	a	E
206	[D-Tyr1,Ile3,Arg(Me)6]MS10	1243.6	1243.7	10.1	a	E
207	[D-Tyr1,Ser4,Arg(Me)6]MS10	1288.5	1288.6	11.7	a	E

[TABLE 4]

208	[D-Tyr1,Thr4,Arg(Me)5][MS10	1303.4	1303.7	12.0	a	E
209	[D-Tyr1,Gln4,Arg(Me)5][MS10	1330.8	1330.7	11.8	a	E
210	[D-Tyr1,Ala4,Arg(Me)5][MS10	1273.7	1273.6	12.3	a	E
211	[D-Tyr1,Thr5,Arg(Me)5][MS10	1330.7	1330.7	11.7	a	E
212	[D-Tyr1,Ala5,Arg(Me)5][MS10	1300.5	1300.7	12.1	a	E
213	[D-Tyr1,Val5,Arg(Me)5][MS10	1302.5	1302.6	10.4	a	E
214	[D-Tyr1,Gln5,Arg(Me)5][MS10	1330.5	1330.7	11.4	a	E
215	[D-Tyr1,Thr2,Arg(Me)5][MS10	1303.4	1303.7	11.9	a	E
216	des(1)-[D-Asn2,Arg(Me)5][MS10	1153.5	1153.6	11.1	a	E
217	des(1)-[D-Tyr2,Arg(Me)5][MS10	1202.4	1202.6	12.3	a	E
218	[N[(CH2)3Gn,]Gly6][MS10	1302.5	1302.7	18.6	a	L
220	[Arg(Et)5][MS10	1330.7	1330.7	18.5	a	E
221	[D-Tyr1,Thr3,AzaGly7,Arg(Me)5] MS10	1233.5	1232.6	18.1	a	H
222	des(1)-[D-Tyr2,AzaGly7,Arg(Me)5][MS10	1203.5	1203.6	19.3	a	H
223	des(1-2)-[D-Trp3,Arg(Me)5][MS10	1038.5	1038.5	11.9	a	E
224	des(1)-[D-Tyr2,D-Trp3,Arg(Me)5][MS10	1202.4	1202.6	12.2	a	E
225	des(1)-[D-Asn2,D-Trp3,Arg(Me)5][MS10	1153.5	1153.6	11.1	a	E
226	des(1)-[D-Tyr2,Ser3,Arg(Me)5] MS10	1103.5	1103.6	9.5	a	E
227	des(1)-[D-Tyr2,Thr3,Arg(Me)5] MS10	1117.5	1117.6	9.8	a	E
228	des(1)-[D-Tyr2,Ile3,Arg(Me)5][MS10	1129.5	1129.6	11.5	a	E
229	[D-Tyr1,Val3,Arg(Me)5][MS10	1229.5	1229.6	9.7	a	E
230	[D-Tyr1,D-Asn2,Arg(Me)5][MS10	1316.5	1316.7	11.5	a	E
231	[D-Tyr1,D-Asn2,D-Trp3,Arg(Me)5][MS10	1316.2	1316.7	11.7	a	E
232	[D-Tyr1,AzaGly7,Arg(Me)5][MS10	1317.9	1317.6	21.9	a	H
233	[D-Tyr1,Ile3,AzaGly7,Arg(Me)5] MS10	1244.1	1244.7	20.9	a	H
234	[D-Tyr1,Val3,AzaGly7,Arg(Me)5] MS10	1230.5	1230.6	20.6	a	H
235	[D-Tyr1,Ala3,AzaGly7,Arg(Me)5] MS10	1202.5	1202.6	20.5	a	H
236	[D-Tyr1,D-Trp3,AzaGly7,Arg(Me)5][MS10	1317.5	1317.6	20.9	a	H
237	[D-Tyr1,D-Asn2,AzaGly7,Arg(Me) 5][MS10	1317.5	1317.6	20.9	a	H
238	[D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)5][MS10	1317.5	1317.6	20.6	a	H
239	des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)5][MS10	1104.1	1104.6	19.0	a	H
240	des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)5][MS10	1130.1	1130.6	20.3	a	H
241	des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)5][MS10	1118.0	1118.6	20.3	a	H
242	des(1)-[D-Tyr2,D-Trp3,AzaGly7, Arg(Me)5][MS10	1202.9	1203.6	21.2	a	H
244	[D-Tyr1,Phe3,AzaGly7,Arg(Me)5] MS10	1278.6	1278.6	10.5	a	H
245	[D-Tyr1,Nal(1)3,AzaGly7,Arg(Me) 5][MS10	1328.5	1328.7	12.3	a	H
246	[D-Tyr1,Nal(2)3,AzaGly7,Arg(Me) 5][MS10	1328.7	1328.7	12.3	a	H
247	[D-Tyr1,Phe(2CO2)3,AzaGly7,Arg(Me)5] MS10	1316.6	1316.6	11.3	a	H

[TABLE 5]

248	[D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)8] MS10	1312.5	1312.8	11.8	c	H
249	[D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)8] MS10	1312.5	1312.8	11.7	c	H
250	[D-Tyr1,Phe(4NH2)3,AzaGly7, Arg(Me)8]MS10	1293.4	1293.8	7.8	a	H
251	[D-Tyr1,Pya(3)3,AzaGly7,Arg(Me) 8]MS10	1279.4	1279.8	7.8	a	H
252	[D-Tyr1,D-Ala3,AzaGly7,Arg(Me) 8]MS10	1202.4	1202.8	8.5	a	H
253	[D-Tyr1,Pro3,AzaGly7,Arg(Me)8] MS10	1228.4	1228.8	8.5	a	H
254	des(1)-[D-Tyr2,Phe3,AzaGly7, Arg(Me)8]MS10	1184.4	1184.8	11.8	c	H
255	des(1)-[D-Tyr2,Nal(2)3,AzaGly7, Arg(Me)8]MS10	1214.5	1214.8	13.7	c	H
256	des(1)-[D-Pya(3)2,Phe3,AzaGly7, Arg(Me)8]MS10	1149.3	1149.8	8.5	a	H
257	[D-Tyr1,D-Asn3,Phe3,AzaGly7, Arg(Me)8]MS10	1276.5	1276.8	10.9	c	H
258	[D-Pya(3)1,AzaGly7,Arg(Me)8] MS10	1302.3	1302.8	10.1	c	H
259	[D-Ala1,AzaGly7,Arg(Me)8]MS10	1225.5	1225.8	10.7	c	H
260	des(1-3)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)8]MS10	1025.2	1025.5	13.7	c	I
261	[7下8,CH2NH]MS10	1288.1	1288.7	17.2	a	D
262	des(1-3)-Indole-3-carbonyl-[AzaGly7,Arg(Me)8]MS10	997.3	997.5	12.6	c	I
263	des(1-3)-Indole-3-acetyl-[AzaGly7,Arg(Me)8]MS10	1011.3	1011.5	12.7	c	I
264	des(1-3)-4-(3-Indolyl)butyryl-[AzaGly7, Arg(Me)8]MS10	1039.3	1039.5	14.4	a	I
265	des(1-3)-Diphenylacetyl-[AzaGly7,Arg(Me)8]MS10	1049.5	1049.5	15.7	a	I
266	des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)8]MS10	999.7	999.5	13.5	c	I
270	Endo-Phe5a-[D-Tyr1,Phe3,Aza Gly7,Arg(Me)8]MS10	1425.9	1425.7	13.4	a	H
271	des(1-2)-[AzaGly7,Arg(Me)8]MS10	1040.5	1040.5	10.4	a	H
272	des(1-2)-Acetyl-[AzaGly7, Arg(Me)8]MS10	1082.5	1082.6	12.8	c	H
273	des(1-2)-Amidino-[AzaGly7, Arg(Me)8]MS10	1083.3	1083.6	11.4	c	J
274	des(1-2)-Acetyl-[Ala3,AzaGly7, Arg(Me)8]MS10	967.3	967.5	9.5	c	H
275	des(1-2)-Acetyl-[Arg3,AzaGly7, Arg(Me)8]MS10	1082.5	1082.6	8.5	a	H
276	des(1-2)-Acetyl-[Thr3,AzaGly7, Arg(Me)8]MS10	997.5	997.5	9.4	a	H
277	des(1-3)-n-Hexanoyl-[AzaGly7, Arg(Me)8]MS10	952.5	952.5	13.4	c	I
278	des(1-3)-Cyclohexanecarbonyl-[AzaGly7, Arg(Me)8]MS10	964.3	964.5	13.2	c	I
279	des(1-3)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)8]MS10	1040.2	1040.5	20.1	a	N
281	[D-Tyr1,Pya(2)3,Arg(Me)8]MS10	1317.5	1317.8	7.8	c	E
282	[D-Tyr1,Pya(4)3,Arg(Me)8]MS10	1317.2	1317.8	8.0	c	E

[TABLE 6]

283	[D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9][MS10	1294.3	1294.7	12.3	a	H
284	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9][MS10	1232.2	1232.6	8.8	a	H
285	[D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9][MS10	1278.2	1278.6	7.9	a	H
286	[D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9][MS10	1278.2	1278.6	7.7	a	H
287	[D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9][MS10	1290.1	1290.6	11.4	a	H
288	[D-Tyr1,D-His2,AzaGly7,Arg(Me)9][MS10	1340.2	1340.7	10.3	a	H
289	des(1)-[D-Pya(3)2,AzaGly7,Arg(Me)9][MS10	1188.2	1188.6	10.0	a	H
290	[D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9][MS10	1298.8	1298.7	10.9	a	H
291	[D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9][MS10	1317.4	1316.7	12.0	a	H
292	[4▼5,CH2NH][MS10	1258.1	1258.7	18.4	a	D
294	[1▼2,CH2NH][MS10	1258.4	1258.7	18.2	a	D
295	[2▼3,CH2NH][MS10	1258.1	1258.7	18.2	a	D
296	[6▼7,CSNH,D-Tyr1,Arg(Me)9] MS10	1332.1	1332.8	20.8	a	F
297	[D-Tyr1,Thr3,AzaGly7,Arg(Me)9] MS10	1331.2	1330.7	11.3	a	H
298	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9][MS10	1331.1	1330.7	11.8	a	H
299	[1▼2,CH2NH,AzaGly7,Arg(Me)9] MS10	1303.4	1302.7	11.3	a	D+H
300	[1▼2,CH2NH,D-Trp3,AzaGly7,Arg(Me)9] MS10	1303.4	1303.7	10.8	a	D+H
301	[D-Tyr1,Ala(3-Cha)3,AzaGly7,Arg(Me)9][MS10	1329.4	1329.8	9.0	a	H
302	[D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9][MS10	1279.4	1279.6	7.5	a	H
303	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9][MS10	1279.4	1279.6	7.8	a	H
304	[D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9][MS10	1279.4	1279.6	7.7	a	H
305	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9][MS10	1165.4	1165.6	8.0	a	H
306	[D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9][MS10	1299.5	1299.5	10.8	a	H
307	[7▼8,CH2NH,D-Tyr1,Arg(Me)9] MS10	1302.2	1302.7	17.9	a	D+E
308	[6▼7,CH2NH,D-Tyr1,Arg(Me)9] MS10	1302.3	1302.7	18.1	a	D+E
310	[Nva6][MS10	1288.8	1288.6	18.4	a	E
311	[Nva(Me)9][MS10	1302.3	1302.8	19.5	a	E
312	[Hse(Me)9][MS10	1330.2	1330.7	18.8	a	E
313	[Dab6][MS10	1245.1	1245.6	19.3	a	A
314	[Orn6][MS10	1260.2	1259.6	19.3	a	A
315	des(1)-[D-Asn2,Cha3,AzaGly7,Arg(Me)9][MS10	1121.3	1121.6	11.4	a	H
316	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10][MS10	1250.5	1250.6	17.0	a	H
317	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10][MS10	1297.4	1297.6	18.4	a	H
318	[D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10][MS10	1235.4	1235.6	18.0	a	H

[TABLE 7]

319	[8Ψ7,NHCO,D-Tyr1,Arg(Me)9] MS10	1316.3	1316.7	18.7	a	K
322	des(1-3)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10	987.4	987.5	8.1	a	I
323	des(1-3)-4-Imidazoleacetyl-[AzaGly7,Arg(Me)9]MS10	962.5	962.5	7.9	a	I
324	des(1-3)-4-Piperidinecarbonyl-[AzaGly7,Arg(Me)9]MS10	965.5	965.5	7.7	a	I
325	des(1-3)-1-Piperidineacetyl-[AzaGly7, Arg(Me)9]MS10	979.5	979.5	8.5	a	I
326	des(1-3)-1-Methylpiperidine-1-acetyl-[AzaGly7,Arg(Me)9]MS10	993.4	993.6	8.7	a	I
327	des(1-3)-1-Pyridiniumacetyl-[Aza Gly7,Arg(Me)9]MS10	973.4	973.5	8.1	a	I
328	des(1-3)-D-Glucuronyl-[AzaGly7, Arg(Me)9]MS10	1030.2	1030.5	7.5	a	I
332	des(1-5)-GuAmb-[AzaGly7,Arg(Me)9]MS10	825.5	825.5	9.5	a	H+J
333	des(1-5)-GuAmb-[Arg(Me)9]MS10	827.5	827.5	10.5	a	E+J
334	des(1-5)-GuAmb-[AzaGly7,Arg(Me)9,Trp10]MS10	867.5	867.5	10.3	a	H+J
339	des(1-5)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9]MS10	824.5	824.5	18.0	a	S
340	des(1-5)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10	786.4	786.4	8.5	a	S
341	des(1-5)-Benzoyl-[AzaGly7,Arg(Me)9]MS10	757.2	757.4	14.8	a	S
344	des(1-5)-Indole-3-carboxyl-[AzaGly7,Arg(Me)9]MS10	796.5	796.4	14.5	a	S
345	des(1-5)-Indole-3-acetyl-[AzaGly7,Arg(Me)9]MS10	810.5	810.4	15.2	a	S
346	des(1-5)-Ac-[AzaGly7,Arg(Me)9]MS10	695.5	695.4	10.7	a	S
347	des(1-5)-n-Hexanoyl-[AzaGly7,Arg(Me)9]MS10	751.7	751.5	16.2	a	S
348	des(1-5)-Z-[AzaGly7,Arg(Me)9]MS10	787.5	787.4	16.7	a	S
349	des(1-5)-Tos-[AzaGly7,Arg(Me)9]MS10	807.5	807.4	15.9	a	S
351	des(1-5)-Benzoyl-MS10	742.4	742.4	15.1	a	A+I
352	des(1-5)-3-(3-Indolyl)propionyl-MS10	809.5	809.4	16.2	a	A+I
353	des(1-5)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	788.4	788.4	15.0	a	S
354	des(1-5)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	863.4	863.5	16.2	a	S

380	des(1-5)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10	734.4	734.4	11.2	a	S
382	des(1-5)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9]MS10	838.4	838.4	12.5	a	S
384	des(1-5)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10	839.5	839.5	15.5	a	N
386	des(1-5)-n-Hexanoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	790.5	790.5	16.5	a	S
387	des(1-5)-Z-[AzaGly7,Arg(Me)9,Trp10]MS10	826.5	826.4	16.8	a	S
388	des(1-5)-Tos-[AzaGly7,Arg(Me)9,Trp10]MS10	846.5	846.4	16.9	a	S
389	des(1-5)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	878.5	878.5	16.1	a	N

[TABLE 8]

373	des(1-4)-(2S)-2-acetoxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	735.5	735.4	13.8	a	S
374	des(1-4)-2-[AzaGly7,Arg(Me)9,Trp10]MS10	679.5	679.4	31.2	a	S
375	2-Aminoethyl-Gly-[D-Tyr1,Arg(Me)9]MS10	1416.4	1416.7	17.3	a	E
376	des(1-4)-Diphenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10	739.4	739.4	15.9	a	S
379	des(1-4)-(2S)-2-(3-Indolylpropionyloxy)-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	864.7	864.5	16.2	a	S
380	des(1-4)-(2S)-2-Benzoyloxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	797.8	797.4	17.2	a	S
385	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1204.4	1204.6	8.3	a	O
386	des(1-4)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	1026.4	1026.2	8.5	a	I
387	Dap-[D-Tyr1,Arg(Me)9]MS10	1402.7	1402.7	17.0	a	E
392	des(1-4)-Benzoyl-[Ala8,AzaGly7,Arg(Me)9,Trp10]MS10	720.5	720.4	11.4	a	S
393	des(1-4)-Dibenzylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	769.7	769.4	16.9	a	P
397	Methylthiocarbamoyl-Ser-[D-Tyr1,Arg(Me)9]MS10	1461.2	1460.7	20.0	a	E
400	(S)-1-(Quinolin-8-yl-carbamoyl)-4-chlorobutylcarbamoyl-[D-Tyr1,Arg(Me)9]MS10	1617.8	1617.7	21.7	a	E
408	des(1-4)-1-Oxo-isochroman-3-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	719.1	718.4	11.3	a	S

412	des(1-5)-CFO-2-Benzyloxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	796.5	797.4	17.1	s	S
417	des(1-5)-Benzylphenethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	782.9	782.4	17.5	s	P
421	des(1-5)-Benzoyl-[8▼7,CH2O,Arg(Me)9,Trp10]MS10	782.5	782.4	22.1	s	Q
423	des(1-5)-Benzoyl-[8▼7,NHCO,Arg(Me)9,Trp10]MS10	795.4	795.4	16.5	s	I+K
429	des(1-5)-Dibenzylaminocarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	783.5	783.4	17.0	s	P
431	des(1-5)-Benzoyl-[AzaPhe8,AzaGly7,Arg(Me)9,Trp10]MS10	797.7	797.4	16.3	c	U
432	des(1-5)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	797.5	797.4	9.2	s	S
434	des(1-7)-Dibenzylaminocarbamoylacetyl-[Arg(Me)9,Trp10]MS10	797.5	797.4	14.5	s	R
435	des(1-5)-2-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	797.7	797.4	14.1	s	S
436	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	797.5	797.4	8.5	s	S
437	des(1-5)-Propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	748.7	748.4	14.4	s	S
438	des(1-5)-Isobutyryl-[AzaGly7,Arg(Me)9,Trp10]MS10	762.4	762.4	13.7	s	S
439	des(1-5)-Cyclohexanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	802.5	802.5	16.3	s	S

[TABLE 9]

440	des(1-5)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10	810.1	810.4	15.8	c	S
441	des(1-5)-Benzoyl-[Pya(2)8,AzaGly7,Arg(Me)9,Trp10]MS10	797.8	797.4	9.5	c	S
442	des(1-5)-Benzoyl-[Pya(4)8,AzaGly7,Arg(Me)9,Trp10]MS10	797.8	797.4	9.1	c	S
443	des(1-5)-2-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	811.8	811.4	9.9	c	S
444	des(1-5)-5-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	811.8	811.4	9.2	c	S
445	des(1-5)-6-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	811.4	811.4	8.6	c	S
446	des(1-5)-Pyrazinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	798.4	798.4	12.4	c	S
447	des(1-5)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	785.9	786.5	13.0	c	S
448	des(1-5)-Trifluoroacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10	788.8	788.4	14.8	c	S
449	des(1-5)-Benzoyl-[Cha8,AzaGly7,Arg(Me)9,Trp10]MS10	802.9	802.5	17.2	c	S
450	des(1-5)-Benzyl-[AzaGly7,Arg(Me)9,Trp10]MS10	782.7	782.4	11.2	c	H+D
451	des(1-5)-Cyclopropanecarbonyl-[Cha8,AzaGly7,Arg(Me)9,Trp10]MS10	785.9	786.5	15.1	c	S
452	des(1-5)-(R)-3-hydroxy-2-methylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	777.8	778.4	11.4	c	S
453	des(1-5)-2-Hydroxyisobutyryl-[AzaGly7,Arg(Me)9,Trp10]MS10	777.8	778.4	11.8	c	S
454	des(1-5)-3-Furoylcarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	786.8	786.4	13.7	c	S
455	des(1-5)-Pyrrole-2-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	785.7	785.4	13.9	c	S
456	des(1-5)-4-Imidazolecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	786.6	786.4	8.5	c	S
457	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Val8,Arg(Me)9,Trp10]MS10	783.5	783.4	9.7	c	S
458	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Nal(2)10]MS10	809.5	809.4	11.1	c	S
459	des(1-5)-6-Hydroxynicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	813.8	813.4	10.2	c	S
460	des(1-5)-6-Chloronicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	831.8	831.4	14.3	c	S
461	des(1-5)-6-(Trifluoromethyl)nicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	865.7	865.4	15.8	c	S
462	des(1-5)-2-Azetidinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	775.8	776.4	8.8	c	H
463	des(1-5)-Dimethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	763.7	763.4	12.5	c	H+N
464	des(1-5)-1-Azetidinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	775.4	775.4	12.8	c	H+N
471	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9]MS10	758.8	758.5	8.1	c	S
472	des(1-5)-4-Aminobenzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	811.8	811.4	11.2	c	H
473	des(1-5)-4-Aminomethylbenzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	825.8	825.5	9.5	c	H

[TABLE 10]

474	des(1-5)-Pyrrole-3-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	755.5	755.4	12.2	a	S
475	des(1-5)-Pyrimidine-4-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	768.5	768.4	12.2	a	S
477	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Orn8,Trp10]MS10	741.5	741.3	8.6	a	G+I
478	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Har8,Trp10]MS10	797.5	797.4	8.6	a	G+I
479	des(1-5)-Pyrimidine-2-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	768.5	768.4	11.5	a	S
480	des(1-5)-Pyridazine-4-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	768.5	768.4	10.7	a	S
481	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har8,Trp10]MS10	1204.6	1204.6	8.2	a	G
482	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Orn8]MS10	1108.6	1108.6	13.6	a	G
487	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Lys8]MS10	1123.6	1123.6	13.5	a	G
488	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9]MS10	1165.6	1165.6	14.1	a	G
489	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har(Me)9]MS10	1179.6	1179.6	13.9	a	G
490	des(1)-[D-Tyr2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1165.6	1165.6	7.6	a	H
491	des(1)-[D-Tyr2,D-Pya(4)3,Trp5,AzaGly7,Arg(Me)9,Trp10]MS10	1302.6	1302.6	17.2	a	O
492	des(1)-[D-Tyr2,D-Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1161.9	1161.6	14.3	a	O
493	des(1)-[D-Tyr2,D-Pya(4)3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10	1191.9	1191.6	14.2	a	O
494	des(1,4)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1090.9	1090.6	8.4	a	O
495	des(1-3)-[D-Tyr4,Pya(4)5,AzaGly7,Arg(Me)9,Trp10]MS10	1003.9	1003.5	7.6	a	O
496	des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Arg(Me)9,Trp10]MS10	1209.6	1209.7	10.4	a	E
497	des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Ala7,Arg(Me)9,Trp10]MS10	1223.7	1223.7	10.5	a	E
498	des(1)-[D-Tyr2,D-Pya(4)3,Ile5,AzaGly7,Arg(Me)9,Trp10]MS10	1230.7	1230.7	16.8	a	O
499	des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	1028.5	1028.5	13.8	a	T
500	des(1-3)-3-Phenylpropionyl-[Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	982.5	982.5	15.1	a	T
501	des(1)-[D-Tyr2,D-Pya(4)3,Thr6,AzaGly7,Arg(Me)9,Trp10]MS10	1218.7	1218.6	14.2	a	O
502	des(1)-[D-Tyr2,Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1161.4	1161.6	14.0	a	O

503	des(1)-[D-Tyr2,D-Trp3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1198.3	1199.6	17.8	e	O
504	[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1276.6	1276.5	8.1	c	H
505	des(1-3)-3-Phenylpropionyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1040.0	1039.5	13.9	c	T
506	des(1-3)-3-Phenylpropionyl-[Ile5,AzaGly7,Arg(Me)9,Trp10]MS10	1062.0	1061.6	17.8	c	T
507	des(1-3)-3-Phenylpropionyl-[Trp5,AzaGly7,Arg(Me)9,Trp10]MS10	1084.2	1084.5	13.7	c	T

[TABLE 11]

508	des(1-3)-3-Phenylpropionyl-[Phe(4F)8,AzaGly7,Arg(Me)9,Trp10]MS10	1043.2	1043.5	14.1	a	T
509	des(1-3)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	997.8	997.5	12.4	a	T
510	des(1-3)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10	935.9	935.5	9.5	a	T
511	des(1)-[D-Tyr2,D-Trp3,Ala4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1213.6	1213.6	17.9	a	O
512	des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1256.7	1256.6	17.0	a	O
513	des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10	1213.6	1213.6	18.5	a	O
514	des(1)-[D-Tyr2,D-Phe3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1160.6	1160.6	17.9	a	O
515	des(1)-[D-Tyr2,D-Pya(4)3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10	1216.6	1216.6	15.7	a	O
	a:0-70% AcCN/35min, flow1ml/min, Wakosil-II 5C18 HG (4.6 x 100mm)					
	b:0-70% AcCN/35min, flow1ml/min, YMC ODS AM-301 (4.6 x 100mm)					
	c:20-70% AcCN/25min, flow1ml/min, YMC ODS AM-301 (4.6 x 100mm)					
	d:5-75% AcCN/35min, flow1ml/min, Wakosil-II 5C18 HG (4.6 x 100mm)					
	e:0-50% AcCN/25min, flow1ml/min, Wakosil-II 5C18 HG (4.6 x 100mm)					
	Only compound no. 1 represents M+ value.					

The structures of compounds synthesized as in EXAMPLES 1 to 24 and physicochemical properties of these compounds are shown in TABLE 12 below.

[TABLE 12]

Comp. No.		M+H+ (obs.)	M+H+ (cal.)	HPLC (min.)	HPLC mode
516	Ac-des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1207.8	1207.6	9.2	c
517	des(1-3)-3-Phenylpropionyl-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10	1051.6	1051.5	13.7	c
518	des(1-3)-3-Phenylpropionyl-[Cha6,Arg(Me)9,Trp10]MS10	1030.5	1030.6	15.8	c
519	des(1-3)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10	1011.5	1011.5	12.7	c
521	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10	1151.5	1151.6	13.4	c
522	des(1-3)-Benzoyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1011.9	1011.5	12.7	c
523	des(1-3)-Benzoyl-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1029.9	1029.5	13.3	c
524	des(1-3)-3-Phenylpropionyl-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10	1036	1035.6	15.8	c
527	des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10	1230.5	1230.6	14.3	c
528	des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10	1214.7	1214.6	15.7	c
529	des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10	1230.7	1230.7	16.5	c
530	des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10	1250.6	1250.6	16.8	c
531	des(1-3)-3-Phenylpropionyl-[Pip(2)5,AzaGly7,Arg(Me)9,Trp10]MS10	1049.6	1049.6	16.4	c
532	des(1-3)-3-Phenylpropionyl-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10	1021.8	1021.5	14.4	c
533	des(1-3)-3-Phenylpropionyl-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10	1035.7	1035.6	15.2	c
534	des(1-3)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	961.6	961.5	10.7	c
535	des(1-3)-2-Naphthoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	1047.6	1047.5	14.7	c
536	[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1360.3	1360.7	14	a
537	Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1516.5	1516.8	13.4	a
538	Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1473.8	1473.8	13.9	a
539	des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10	1254.7	1254.7	18.7	a
540	des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10	1242.4	1242.6	11.8	c
541	D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1525.8	1525.8	16.7	a
542	D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1681.9	1681.9	16.3	a
545	des(1-3)-Benzoyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1015.7	1015.5	13	c
546	des(1-3)-3-Phenylpropionyl-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10	1067.6	1067.5	15.2	c
547	des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10	1246.6	1246.7	9.4	c
548	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10	1181.5	1181.6	14.9	a
550	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.7	1298.6	13.6	c
551	Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1567.8	1567.8	12.4	a
552	D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1455.8	1455.8	11.5	a
553	D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1482.5	1482.8	13.3	c
554	D-Arg-[b-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1483.7	1483.8	16.5	a
555	D-Arg-[g-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1497.7	1497.8	16.6	a
556	D-Arg-D-Arg-[g-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1654	1653.9	15.7	a

557	D-Arg-D-Arg-D-Arg-[g-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1809.8	1810	15.6	a
558	Ac-des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10	1284.6	1284.6	13.3	c
559	3-(4-Hydroxyphenyl)propionyl-des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1241.3	1241.6	14.4	c
561	D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10	1482.8	1482.8	17.5	a
562	Ac-des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.4	1260.4	16.8	a
563	Ac-des(1)-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10	1280.6	1280.6	19.1	a
564	Ac-des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10	1296.5	1296.7	19.9	a
565	Benzoyl-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1360.8	1360.7	15.7	a
566	Cyclopropanecarbonyl-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1324.8	1324.7	14.5	c
567	Butyryl-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1326.8	1326.7	14.8	a
568	Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1454.7	1454.7	17.2	a
569	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,8Ψ7,CH2NH,Arg(Me)9,Trp10]MS10	1283.7	1283.7	17.7	a
570	Me-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1270.6	1270.6	16.5	a
571	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10	1259.5	1259.6	13.2	c
572	des(1)-[D-Trp2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1227.6	1227.6	10.1	c
573	Ac-des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10	1255.6	1255.6	19.4	a
576	Ac-des(1)-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	18.2	a
577	Ac-des(1)-[D-Tyr2,D-Trp3,Sor4,AzaGly7,Arg(Me)9,Trp10]MS10	1257.7	1257.6	18.8	a
578	Ac-des(1)-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10	1271.6	1271.6	18.8	a
579	Ac-des(1)-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10	1299.5	1299.6	19	a
580	Ac-des(1)-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.4	1298.6	19.3	a

Comp. No.	Structure	M+H+ (obs.)	M+H+ (cal.)	HPLC (min.)	HPLC mode	Syn. Proc.
584	des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10	1298.7	1298.6	18.7	e	X
585	des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10	1284.7	1284.6	17.9	e	X
586	des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10					W
589	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10	1309.6	1309.6	15.2	c	W
590	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi10]MS10	1265.5	1265.6	13.4	c	W
591	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10	1275.5	1275.6	12.2	c	W
592	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1277.5	1277.6	14	c	W
594	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10	1273.8	1273.6	14.6	c	W
597	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.7	14.1	c	W
598	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10	1297.5	1297.6	18.5	e	H+W
599	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10	1242.4	1242.6	17.8	e	G+W
600	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10	1284.7	1284.6	17.9	e	G+W
601	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10	1297.6	1297.6	18.2	e	H+W
602	des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1312.7	1312.7	19	e	W
603	des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS1	1260.6	1260.6	15.3	e	W
604	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Toc)9,Trp10]MS10	1438.6	1438.6	20.5	e	G+W
605	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10	1329.4	1329.6	18.7	e	G+W
607	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10	1312.8	1312.7	18.1	e	W
608	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10	1312.3	1312.7	18.1	c	W
609	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10	1312.8	1312.7	17.7	e	W
610	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10	1284.9	1284.7	17.7	e	G+W
611	des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.9	1260.6	14.4	e	W
612	des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1284.7	1284.6	17.8	a	T+W
613	des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1312.6	1312.7	18.3	e	T+W
614	des(1)-Amidino-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.4	1298.7	16.9	e	J+W
615	des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1299	1298.6	13.9	c	W
616	des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1206.8	1206.4	13.1	c	W
617	des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1248.9	1248.7	15.5	c	W
618	des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1282.7	1282.6	15.8	a	W
619	des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1332.6	1332.7	17.6	a	W
620	des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1332.4	1332.7	17.7	c	W
621	des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1263.5	1263.7	11.3	c	W
622	des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1264.6	1264.4	12.7	c	W
623	des(1)-Ac-[D-Tyr2,Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.9	1298.6	14.2	c	W
624	des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.8	1260.6	10.2	c	W

625	des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1183.8	1183.6	11.4	c	W
626	des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1226	1225.6	13.3	c	W
627	des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1259.9	1259.6	13.8	c	W
628	des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1213.9	1213.6	11.1	c	W
629	des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1240.9	1240.7	10.1	c	W
630	des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1241.9	1241.6	11.2	c	W
631	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10	1222.9	1222.6	11.6	c	W
632	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10	1265	1264.7	13.5	c	W
633	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10	1279.8	1279.7	10.4	c	W
634	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10	1280.8	1280.6	11.5	c	W
635	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10	1299.9	1299.6	10.5	c	W
636	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,MePhe6,AzaGly7,Arg(Me)9,Trp10]MS10	1312.4	1312.7	15.4	c	W
637	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1316.5	1316.6	14.4	c	W
638	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1278.6	1278.6	10.7	c	W
639	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10	1256.9	1256.6	17.5	c	G+W
640	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,D-Leu8,Arg(Me)9,Trp10]MS10	1298.7	1298.6	17.6	e	W
641	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10	1256.9	1256.6	16.5	e	W
642	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10	1284.5	1284.6	17.4	a	W
643	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10	1332.4	1332.6	18.3	a	W
644	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10	1272.9	1272.6	16.5	e	W
645	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Hsr9,Trp10]MS10	1299.1	1298.6	17.7	e	G+W
646	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Hsr(Me)9,Trp10]MS10	1313.1	1312.7	17.9	e	W
647	des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1299.9	1298.6	18.2	e	W
648	[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1313.6	1313.7	16	a	W
649	Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1355.9	1355.7	17.4	e	W
650	[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1418.8	1419.7	16.6	e	W
651	Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1461.4	1461.7	18	e	W
652	pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1367.4	1367.7	17.6	e	W
653	des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	18.2	e	W
654	des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	17.6	e	W
655	des(1)-Ac-[D-Tyr2,D-Trp3,MeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1312.8	1312.7	18.3	e	W
656	des(1)-Ac-[D-Tyr2,D-Trp3,MeSer5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	17.8	e	W
657	des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1209.2	1209.6	12.4	c	W
658	des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.3	1260.6	10.4	c	W
659	des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	17.9	e	W
660	des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.8	1260.6	10.3	c	W

661	des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1209.8	1209.6	11.5	c	W
662	des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1271.4	1271.4	13.9	c	W
663	des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1321.7	1321.7	15.9	c	W
664	des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.7	1298.6	14.1	c	W
665	des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1093.7	1093.6	11.1	c	O
666	des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1135.7	1135.6	13.4	c	T+W
667	des(1-2)-Hexanoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1191.4	1191.6	17.2	c	T+W
668	des(1-2)-Cyclohexanecarbonyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS	1203.3	1203.6	17.1	c	T+W
669	des(1-2)-Benzoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1197.6	1197.6	16	c	T+W
670	des(1-2)-3-Pyridinepropionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS1	1226.7	1226.6	11.5	c	T+W
671	des(1-2)-Adipionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1221.6	1221.6	13.5	c	T+W
672	des(1)-Ac-[D-Tyr2,MeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1312.9	1312.7	14.5	c	W
674	des(1)-Ac-[Acp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1206.7	1206.7	11.5	c	T+W
675	[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1419.6	1419.7	16.8	e	W
676	Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1461.4	1461.7	18	e	W
677	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10	1284.9	1284.6	17.1	e	W
678	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10	1298.9	1298.6	17.8	e	W
679	des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1135.7	1135.6	11.7	c	J+W
680	des(1-2)-Glycoloyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1151.9	1151.6	12.9	c	W
681	des(1)-Glycoloyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1314.8	1314.6	13.5	c	W
682	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10	1313.9	1313.6	15.7	e	W
685	des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10	1221.8	1221.6	9.9	c	W
686	des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10	1227.8	1227.6	14.2	c	W
688	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10	1276.8	1276.6	13.8	c	W
689	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10	1298.8	1298.6	13.6	c	W
691	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10	1314.4	1314.6	12.3	c	W
692	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10	1337.5	1337.7	14	c	W
693	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10	1328.9	1328.7	13.9	c	W
694	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10	1348.9	1348.7	15.7	c	W
695	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10	1304.7	1304.6	13.6	c	W
696	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10	1304.9	1304.7	15.3	c	W
698	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10	1270.7	1270.6	16.7	e	W
699	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7, γ MeLeu8,Arg(Me)9,Trp10]MS10	1312.6	1312.7	18.4	e	W
700	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Alb8,Arg(Me)9,Trp10]MS10	1269.9	1269.6	16.8	e	E
701	des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10	1257	1256.6	16.7	e	W
702	des(1)-Ac-[D-Tyr2,D-Trp3,Asp[NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS	1312.6	1312.7	17.9	e	W

FORMULATION EXAMPLE 1:

(1) Compound No. 305	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 305, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 2

(1) Compound No. 305	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 305 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 3

(1) Compound No. 305	5.0 mg
(2) Salt	20.0 mg

(3) Distilled water to make the whole volume 2 ml

After 5.0 mg of Compound No. 305 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 4:

(1) Compound No. 550	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 550, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 5

(1) Compound No. 550	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 550 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 6

(1) Compound No. 550	5.0 mg
(2) Salt	20.0 mg
(3) Distilled water to make the whole volume	2 ml

After 5.0 mg of Compound No. 550 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 7:

(1) Compound No. 562	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 562, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 8

(1) Compound No. 562	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 562 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 9

(1) Compound No. 562	5.0 mg
(2) Salt	20.0 mg
(3) Distilled water to make the whole volume	2 ml

After 5.0 mg of Compound No. 562 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 10:

(1) Compound No. 571	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 571, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 11

(1) Compound No. 571	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 571 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 12

(1) Compound No. 571	5.0 mg
(2) Salt	20.0 mg
(3) Distilled water to make the whole volume 2 ml	

After 5.0 mg of Compound No. 571 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 13:

(1) Compound No. 579	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 579, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 14

(1) Compound No. 579	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 579 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 15

(1) Compound No. 579	5.0 mg
(2) Salt	20.0 mg
(3) Distilled water to make the whole volume	2 ml

After 5.0 mg of Compound No. 579 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 16:

(1) Compound No. 585	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 585, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 17

(1) Compound No. 585	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 585 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 18

(1) Compound No. 585	5.0 mg
(2) Salt	20.0 mg

(3) Distilled water to make the whole volume 2 ml

After 5.0 mg of Compound No. 585 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

TEST EXAMPLE 1

Assay for hOT7T175 receptor binding activity

(1) Preparation of Cy-5-labeled metastin (40-54)

A synthetic peptide having 40-54 amino acid sequence in the amino acid sequence of metastin, into which Cy-5 was introduced via the ε-amino group of lysine located at the amino terminus and the carboxyl terminus was amidated, was prepared in accordance with the synthesis technique Amersham Bioscience, Inc. Using this synthetic peptide, a test for binding inhibition was carried out.

Sequence: (Cy-5)-KDLPNYNWNSFGLRF-NH_2

(2) Test for binding inhibition using a test compound, Cy-5-labeled metastin (40-54) and h0T7T175-expressed CHO cell

h0T7T175-Expressed CHO cells were cultured in MEM-α medium (nucleic acid-free) containing 10% dialyzed serum. The medium was removed and the adhered cells were washed with PBS. Then, PBS containing 5 mM EDTA was added and the cells were scraped from a flask with a cell scraper.

After centrifugation, the cells were suspended at 1.11×10^5cells/ml in assay buffer (10 mM HEPES pH 7.4, 140 mM NaCl, 2.5 mM $CaCl_2$, 3 mM $MgCl_2$, 0.5% BSA, 0.01% NaN_3) and Cy-5-labeled metastin (40-54) was added to the suspension in a final concentration of 1 nM. To each well of a 96-Well Black Clear Bottom Microplate (Applied Biosystems, Inc.), 10 μL of assay buffer containing 1% dimethylsulfoxide was added to examine total binding, 10 μL of 10 μM non-labeled peptide (having the same amino acid sequence as that of labeled one) solution diluted with assay buffer to examine non-specific binding, and 10 μL of a test compound diluted with assay buffer to examine a binding inhibition activity of the test compound, and furthermore, 90 μL each of the cell suspension was dispensed to each well. After an hour, the level of Cy-5-labeled metastin (40-54) bound to the cells was determined by the FMAT 8100 HTS system (Applied Biosystems, Inc.). Specific binding is calculated as non-specific binding subtracted from total binding. The binding inhibition activity of a test compound is shown by a ratio of the value obtained by subtracting a measured value in presence of a test compound from the total binding to the specific binding. The receptor binding activity of test compound is shown in TABLES 13 through 18.

[TABLE 13]

Compound Number		IC50(M)
1	Metastin	1.7E-07
3	MS10	6.5E-09
4	des(1)-MS10	2.6E-07
17	[Pya(4)10]MS10	6.6E-12
18	[Tyr(Me)10]MS10	7.7E-09
19	[Phe(2F)10]MS10	8.6E-08
23	[Tyr5]MS10	4.0E-07
24	[Leu5]MS10	8.3E-10
30	Acetyl-MS10	3.1E-08
31	Fmoc-MS10	9.3E-07
32	Leu-Pro-Asn-MS10	2.5E-08
38	[D-Asn4]MS10	8.3E-07
40	[D-Trp3]MS10	1.9E-08
41	[D-Asn2]MS10	2.1E-07
42	[D-Tyr1]MS10	6.7E-08
44	[Lys9]MS10	1.9E-07
50	[Ala7]MS10	1.9E-07
54	des(1-2)-Fmoc-MS10	4.5E-07
57	[Asp2]MS10	1.0E-07
58	[Tyr2]MS10	1.8E-08
59	[Leu2]MS10	3.4E-07
60	[Pya(3)10]MS10	1.7E-07
61	[Phe(4F)10]MS10	1.3E-08
67	[Ala3]MS10	2.7E-08
68	[Leu3]MS10	7.7E-09
69	[Ser3]MS10	8.3E-08
70	[Asp3]MS10	2.0E-07
71	[Lys3]MS10	8.6E-08
72	[Ala1]MS10	5.4E-07
73	[Leu1]MS10	2.2E-07
75	[Asp1]MS10	8.8E-07

[TABLE 14]

77	[Phe(4CN)10]MS10	7.4E-09
78	[Trp(CHO)3, Phe(4CN)10]MS10	2.6E-08
82	[Arg(Me)9]MS10	4.1E-09
83	[Arg(Me2)asy9]MS10	2.5E-08
97	[Hsr9]MS10	3.7E-07
101	[Ser7]MS10	1.0E-07
105	[Nle8]MS10	8.8E-07
107	[Val8]MS10	1.2E-07
109	[Tyr10]MS10	2.3E-08
110	[Nal(2)10]MS10	2.4E-08
111	[Phe(F5)10]MS10	1.4E-07
112	[Cha10]MS10	3.7E-07
114	dea(1-3)-3-(3-indolyl)propionyl-MS10	5.5E-07
128	[10Ψ,CSNH]MS10	5.5E-08
129	[Arg(Me2)asy9]MS10	8.3E-08
130	[Phe(4Cl)10]MS10	4.2E-08
131	[Phe(4NH2)10]MS10	1.2E-07
132	[Phe(4NO2)10]MS10	9.3E-08
133	[Nal(1)10]MS10	3.3E-07
134	[Trp10]MS10	1.1E-07
141	[D-Tyr1,Arg(Me)9]MS10	5.1E-08
142	[D-Tyr1,D-Trp3,Arg(Me)9]MS10	2.6E-08
143	[D-Trp3,Arg(Me)9]MS10	7.7E-09
145	dea(1-2)-Fmoc-[Arg(Me)9]MS10	1.2E-07
146	[10Ψ,CSNH,D-Tyr1]MS10	3.7E-07
150	[Tyr6]MS10	3.2E-07
151	[Nal(1)6]MS10	3.0E-07
152	[Nal(2)6]MS10	1.6E-07
153	[Phe(F5)6]MS10	3.9E-07
154	[Phe(4F)6]MS10	6.0E-08
158	[Cha6]MS10	4.9E-08
163	[6Ψ7,CH2NH]MS10	2.5E-07
166	[6Ψ7,CSNH]MS10	9.4E-09
169	[D-Tyr1,Ala3,Arg(Me)9]MS10	1.8E-07
170	[D-Tyr1,Ser3,Arg(Me)9]MS10	2.6E-07

[TABLE 15]

171	[D-Tyr1,Cha3,Arg(Me)9]MS10	1.1E-07
174	[D-Tyr1,Arg(Me)9,Trp10]MS10	4.2E-07
176	[AzaGly7]MS10	5.2E-08
181	[D-Tyr1,Cha3,6,Arg(Me)9]MS10	1.9E-08
182	[D-Tyr1,Cha3,6,Arg(Me)9,Trp10]MS10	9.8E-08
186	[Trp(CHO)10]MS10	4.6E-07
187	[Abu8]MS10	7.2E-07
189	[Ala(3-Bzt)10]MS10	2.3E-07
190	[D-Tyr1,Cha3,AzaGly7,Arg(Me)9]MS10	1.2E-08
191	[D-Tyr1,Ser3,AzaGly7,Arg(Me)9]MS10	3.0E-07
192	[D-Tyr1,Arg(Et)9]MS10	5.3E-07
193	[D-Tyr1,Arg(n-Pr)9]MS10	9.2E-07
194	[D-Tyr1,Arg(Ac)9]MS10	2.1E-07
197	[Phe(3F)10]MS10	1.7E-07
198	[Phe(3,4F2)10]MS10	1.7E-07
199	[Phe(3,4Cl2)10]MS10	4.7E-07
200	[Phe(3CF3)10]MS10	3.4E-07
201	[Ala(2-Qui)10]MS10	8.2E-07
203	[D-Tyr1,Cha6,Arg(Me)9]MS10	3.7E-08
204	[D-Tyr1, Ala7, Arg(Me)9]MS10	6.8E-07
205	[D-Tyr1,Thr3,Arg(Me)9]MS10	2.6E-07
206	[D-Tyr1,Ile3,Arg(Me)9]MS10	8.5E-08
208	[D-Tyr1,Thr4,Arg(Me)9]MS10	8.3E-07
210	[D-Tyr1,Ala4,Arg(Me)9]MS10	7.3E-07
211	[D-Tyr1,Thr5,Arg(Me)9]MS10	4.4E-08
212	[D-Tyr1,Ala5,Arg(Me)9]MS10	3.6E-08
213	[D-Tyr1,Val5,Arg(Me)9]MS10	1.9E-07
214	[D-Tyr1,Gln2,Arg(Me)9]MS10	3.9E-07
215	[D-Tyr1,Thr2,Arg(Me)9]MS10	2.5E-07
216	des(1)-[D-Asn2,Arg(Me)9]MS10	7.0E-07
217	des(1)-[D-Tyr2,Arg(Me)9]MS10	2.5E-07
220	[Arg(Et)9]MS10	3.3E-07
221	[D-Tyr1,Thr3,AzaGly7,Arg(Me)9]MS10	9.5E-08
222	des(1)-[D-Tyr2,AzaGly7,Arg(Me)9]MS10	3.3E-08
223	des(1-2)-[D-Trp3,Arg(Me)9]MS10	7.6E-07

[TABLE 16]

224	des(1)-[D-Tyr2,D-Trp3,Arg(Me)9]MS10	1.4E-07
225	des(1)-[D-Asn2,D-Trp3,Arg(Me)9]MS10	4.1E-07
226	des(1)-[D-Tyr2,Ser3,Arg(Me)9]MS10	1.0E-07
227	des(1)-[D-Tyr2,Thr3,Arg(Me)9]MS10	4.8E-08
228	des(1)-[D-Tyr2,Ile3,Arg(Me)9]MS10	4.0E-08
229	[D-Tyr1,Val3,Arg(Me)9]MS10	1.3E-07
230	[D-Tyr1,D-Asn2,Arg(Me)9]MS10	2.5E-07
231	[D-Tyr1,D-Asn2,D-Trp3,Arg(Me)9]MS10	5.5E-08
232	[D-Tyr1,AzaGly7,Arg(Me)9]MS10	4.9E-08
233	[D-Tyr1,Ile3,AzaGly7,Arg(Me)9]MS10	2.3E-08
234	[D-Tyr1,Val3,AzaGly7,Arg(Me)9]MS10	4.7E-08
235	[D-Tyr1,Ala3,AzaGly7,Arg(Me)9]MS10	1.0E-07
236	[D-Tyr1,D-Trp3,AzaGly7,Arg(Me)9]MS10	4.2E-08
237	[D-Tyr1,D-Asn2,AzaGly7,Arg(Me)9]MS10	2.7E-08
238	[D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)9]MS10	4.9E-08
239	des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)9]MS10	1.2E-07
240	des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)9]MS10	1.7E-08
241	des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)9]MS10	5.8E-08
242	des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9]MS10	7.0E-08
244	[D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10	7.7E-08
246	[D-Tyr1,Nal(1)3,AzaGly7,Arg(Me)9]MS10	9.8E-08
246	[D-Tyr1,Nal(2)3,AzaGly7,Arg(Me)9]MS10	7.1E-09
247	[D-Tyr1,Phe(2Cl)3,AzaGly7,Arg(Me)9]MS10	4.5E-08
248	[D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)9]MS10	5.8E-08
249	[D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)9]MS10	1.5E-07
250	[D-Tyr1,Phe(4NH2)3,AzaGly7,Arg(Me)9]MS10	3.7E-09
251	[D-Tyr1,Pya(3)3,AzaGly7,Arg(Me)9]MS10	8.7E-08
252	[D-Tyr1,D-Ala3,AzaGly7,Arg(Me)9]MS10	5.8E-07
253	[D-Tyr1,Pro3,AzaGly7,Arg(Me)9]MS10	2.7E-08
254	des(1)-[D-Tyr2,Phe3,AzaGly7,Arg(Me)9]MS10	1.1E-08
255	des(1)-[D-Tyr2,Nal(2)3,AzaGly7,Arg(Me)9]MS10	3.3E-08
256	des(1)-[D-Pya(3)2,Phe3,AzaGly7,Arg(Me)9]MS10	2.2E-08
257	[D-Tyr1,D-Asn2,Phe3,AzaGly7,Arg(Me)9]MS10	4.0E-08
258	[D-Pya(3)1,AzaGly7,Arg(Me)9]MS10	9.0E-08
259	[D-Ala1,AzaGly7,Arg(Me)9]MS10	2.5E-07

[TABLE 17]

280	des(1-3)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9]MS10	3.2E-07
281	[7? 8,CH2NH-]MS10	3.9E-07
285	des(1-3)-Indole-3-carbonyl-[AzaGly7,Arg(Me)9]MS10	9.5E-08
286	des(1-3)-Indole-3-acetyl-[AzaGly7,Arg(Me)9]MS10	2.3E-07
287	des(1-3)-4-(3-Indolyl)butyryl-[AzaGly7, Arg(Me)9]MS10	3.6E-07
288	des(1-3)-Diphenylacetyl-[AzaGly7,Arg(Me)9]MS10	5.5E-07
289	des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9]MS10	4.7E-07
270	Endo-Phe5a-[D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10	1.6E-08
271	des(1-2)-[AzaGly7,Arg(Me)9]MS10	1.2E-07
272	des(1-2)-Acetyl-[AzaGly7, Arg(Me)9]MS10	5.4E-07
273	des(1-2)-Amidino-[AzaGly7, Arg(Me)9]MS10	3.0E-07
275	des(1-2)-Acetyl-[Arg3,AzaGly7,Arg(Me)9]MS10	4.1E-07
276	des(1-2)-Acetyl-[Thr3,AzaGly7,Arg(Me)9]MS10	4.6E-07
277	des(1-3)-n-Hexanoyl-[AzaGly7,Arg(Me)9]MS10	5.4E-08
278	des(1-3)-Cyclohexanecarbonyl-[AzaGly7, Arg(Me)9]MS10	1.1E-07
279	des(1-3)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10	2.9E-08
281	[D-Tyr1,Pya(2)6,Arg(Me)9]MS10	2.3E-07
283	[D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	6.9E-10
284	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9]MS10	3.4E-08
285	[D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9]MS10	4.0E-08
286	[D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1.7E-08
287	[D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9]MS10	2.3E-09
288	[D-Tyr1,D-His2,AzaGly7,Arg(Me)9]MS10	7.2E-11
289	[D-Pya(3)2,AzaGly7,Arg(Me)9]MS10-(2-10)	8.4E-09
290	[D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1.4E-09
291	[D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9]MS10	4.1E-10
294	[1? 2,CH2NH-]MS10	3.0E-08
295	[2? 3,CH2NH-]MS10	6.8E-07
296	[6? 7,CSNH,D-Tyr1,Arg(Me)9]MS10	1.4E-08
297	[D-Tyr1,Thr5,AzaGly7,Arg(Me)9]MS10	9.3E-10
298	[D-Tyr1,D-Asn2,Thr5,AzaGly7,Arg(Me)9]MS10	2.5E-10
299	[1 Ψ 2,CH2NH,AzaGly7,Arg(Me)9]-MS10	1.2E-09
300	[1 Ψ 2,CH2NH,D-Trp3,AzaGly7,Arg(Me)9]-MS10	3.8E-09
301	[D-Tyr1,Ala(2-Qui)3,AzaGly7,Arg(Me)9]MS10	1.5E-08

[TABLE 18]

302	[D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	7.7E-09
303	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	5.0E-10
304	[D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	5.0E-09
305	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1.3E-09
306	[D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	4.4E-09
307	[7Ψ8,CH2NH,D-Tyr1,Arg(Me)9]MS10	6.4E-08
308	[8Ψ7,CH2NH,D-Tyr1,Arg(Me)9]MS10	3.5E-07
310	[Nar9]MS10	3.1E-07
311	[Nar(Me)9]MS10	4.7E-07
312	[Har(Me)9]MS10	1.0E-07
313	[Dab9]MS10	6.9E-07
314	[Orn9]MS10	4.7E-07
316	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	2.6E-08
317	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	2.1E-09
318	[D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	9.9E-10
319	[8Ψ7,NHCO,D-Tyr1,Arg(Me)9]MS10	9.7E-09
322	des(1-3)-3-Pyridylpropionyl-[AzaGly7,Arg(Me)9]MS10	5.4E-08
323	des(1-3)-4-Imidazoleacetyl-[AzaGly7,Arg(Me)9]MS10	2.8E-07
328	des(1-3)-D-Glucoronyl-[AzaGly7,Arg(Me)9]MS10	4.7E-07

TEST EXAMPLE 2

Assay for intracellular Ca ion level-increasing activity using FLIPR

In accordance with the method described in JPA 2000-312590, the intracellular Ca ion level-increasing activity was measured using FLIPR.

The stable expression cell line rOT7T175 was obtained by transduction of expression plasmid pAK-rOT175 for animal cell into CHO/dhfr$^-$ cells, using CellPhect Transfection Kit (Amersham Pharmacia Biotech, Inc.). First, 240 µL of Buffer A (attached to CellPhect Transfection Kit) was added to 9.6 µg of plasmid DNA dissolved in 240 µL of distilled water followed by stirring. After the mixture was settled for 10 minutes, 480 µL of Buffer B (attached to CellPhect Transfection Kit) was added to the mixture, which was vigorously stirred to form liposomes containing the DNA. Then, 4 x 10^5 CHO/dhfr$^-$ cells (obtained from ATCC) were inoculated on a 60 mm Petri dish. After culturing the cells in Ham's F-12 medium (Nissui Seiyaku Co., Ltd.) supplemented with 10% fetal bovine serum (BIO WHITTAKER, Inc.) at 37°C for 2

days in 5% carbon dioxide gas, 480 μL of the liposomes were dropwise added to the cells in the Petri dish. After culturing the cells at 37°C for 6 hours in 5% carbon dioxide gas, the cells were washed twice with serum-free Ham's F-12 medium and 3 μL of 15% glycerol was added to the cells in the Petri dish followed by treatment for 2 minutes. The cells were again washed twice with serum-free Ham's F-12 medium followed by incubation in Ham's F-12 medium supplemented with 10% fetal bovine serum at 37°C for 15 hours in 5% carbon dioxide gas. The cells were dispersed by trypsin treatment to recover from the Petri dish. The recovered cells were inoculated on a 6-well plate in 1.25×10^4 cells/well and began to incubate at 37°C in Dulbecco's modified Eagle medium (DMEM) medium (Nissui Seiyaku Co., Ltd.) containing 10% dialyzed fetal bovine serum (JRH BIOSCIENCES, Inc.) in 5% carbon dioxide gas. The plasmid-transfected transformed CHO cells grew in the medium but the non-transfected cells gradually died. The medium was exchanged on Days 1 and 2 to remove the cells died. Approximately 20 colonies of the transformed CHO cells that kept growing on Days 8 to 10 after the incubation were isolated. From the cells in these colonies, cells showing high reactivity with the ligand peptide metastin (hereinafter merely referred to as hOT7T175/CHO) were selected to provide for the following experiment.

The intracellular Ca ion level-increasing activity of the synthetic peptide in hOT7T175/CHO was determined using FLIPR (Molecular Devices, Inc.).

hOT7T175/CHO was subcultured in DMEM supplemented with 10% dialyzed fetal bovine serum (hereinafter abbreviated as dFBS) and provided for the experiment (hereinafter abbreviated as 10% dFBS/DMEM). The hOT7T175/CHO was suspended in 10% dFBS-DMEM in 15×10^4 cells/ml. The suspension was inoculated on a 96-well plate for FLIPR (Black Plate Clear Bottom, Coster, Inc.) at 200 μl each (3.0×10^4 cells/200 μl), followed by incubation at 37°C overnight in a 5% CO_2 incubator. The cells thus incubated were used (hereinafter simply referred to as the cell plate). Then, 21 ml of HANKS/HBSS (9.8 g of HANKS', 0.35 g of sodium hydrogencarbonate, 20 ml of 1M HEPES; after adjusting the pH to 7.4 with 1N sodium hydroxide, the mixture was subjected to sterilization through a filter), 210 μl of 250 mM Probenecid and 210 μl of fetal bovine serum (FBS) were mixed (HANKS/HBSS-Probenecid-FBS).

Furthermore, 2 vials of Fluo3-AM (50 μg/vial) were dissolved in 21 μL of dimethylsulfoxide and 21 μL of 20% Pluronic acid. The resulting solution was added to and mixed with 10 ml of HANKS/HBSS-Probenecid-FBS described above. After the culture medium was removed, the mixture was dispensed onto the cell plate in 100 μl

each/well, followed by incubation at 37°C for an hour in a 5% CO_2 incubator (pigment loading). The peptide was dissolved in dimethylsulfoxide in 1 x 10^{-3} M. The peptide solution was diluted with HANKS'/HBSS containing 2.5 mM Probenecid and 0.2% BSA. The dilution was transferred to a 96-well plate for FLIPR (V-Bottom plate, Coster, Inc.) (hereinafter referred to as a sample plate). After completion of the pigment loading onto the cell plate, the cell plate washed 4 times with wash buffer, which was obtained by adding 2.5 mM Probenecid to HANKS'/HBSS, using a plate washer to leave 100 µL of wash buffer after the washing. The cell plate and the sample plate were set in FLIPR and 0.05 ml of a sample from the sample plate was automatically transferred to the cell plate with the FLIPR device to promote the cell response. A change in intracellular calcium ion level for 180 seconds was measured with passage of time.

The intracellular Ca ion level-increasing activity [specific activity to Metastin (1-54)] is shown in TABLES 19 to 23.

142
143

[TABLE 19]

Comp. No.	Specific Act.
Metastin(1-54)	1
Metastin(46-54)	10
17	5
18	1
19	2
24	1
30	10
31	2
32	10
40	30
41	10
42	30
46	1
50	30
53	1
54	5
56	5
58	1
74	1
75	1
76	1
78	10
79	1
87	1
88	1
97	10
98	1/2
101	10
105	1
109	20
110	20
111	3
112	2
114	3
128	10
130	10
131	3
132	10
133	3
134	30
141	10
142	2
143	3
144	1
146	10
151	1
152	5
154	5
156	2
163	1
166	5
169	2
170	1
171	10
172	1
173	1

[TABLE 20]

174	10
176	5
182	5
187	1
189	10
190	10
192	1
193	1/2
194	1
197	10
198	10
199	3
200	10
201	1
203	10
204	5
205	10
206	10
207	1/2
208	1
209	1/2
210	1
211	10
212	10
213	2
214	10
215	10
216	1
217	20
220	5
222	10
224	2
225	1
226	1
227	1
228	5
229	1
230	10
231	1
232	3
233	1
234	1
235	1
236	2
237	3
238	1
241	1
242	2
244	1
245	1
246	2
247	1
248	2
249	1
250	1
254	1
255	1

[TABLE 21]

256	1
257	3
258	2
259	1
260	5
261	1
265	3
266	2
267	2
268	1
269	3
270	1
271	1
272	2
273	5
274	1
277	2
278	2
279	5
281	1/2
284	1
286	2
287	2
288	1
289	1
290	1
291	2
294	10
295	1
296	3
297	1
298	5
299	5
300	5
301	1
302	2
303	5
304	3
305	5
306	2
307	1
308	2
310	3
311	1
312	3
314	1
315	1
316	1
317	1
318	5
319	3
322	1
323	1
332	2
333	1
334	5
339	2

[TABLE 22]

340	1/5
341	2
344	1/2
345	2
346	2
347	1/2
348	1/5
349	1/5
351	1/2
352	1/3
353	10
354	10
358	2
362	1/10
364	1
366	1/3
367	1/5
368	1/2
369	2
373	2
374	1/3
375	2
378	1/2
379	2
380	5
385	10
386	7
387	1
392	1/5
393	1
397	5
400	1
406	1/3
412	1/5
417	1
421	1/3
423	5
428	1/10
431	1
432	2
434	1/10
435	10
436	5
437	2
438	3
439	2
440	1
441	1
442	1/2
443	1/2
444	1/3
445	5
446	1
447	5
448	3
449	5
450	1/3

[TABLE 23]

451	5
452	1
453	1
454	6
455	5
459	2
460	1/3
461	1/3
462	1
463	2
464	1
466	1/3
467	1
468	1
471	1
472	3
473	3
474	5
476	3
477	1/5
478	1/3
479	5
480	1
481	5
486	1/2
487	1
488	1
489	1/2
490	3
491	7
492	5
493	2
494	1/3
495	1/6
496	5
497	2
498	7
499	10
500	1
501	10
502	10
503	10
504	2
505	20
506	1
507	5
508	10
509	20
510	3
511	10
512	30
513	20
514	10
515	10

TEST EXAMPLE 3

Assay for intracellular Ca ion level-increasing activity using FLIPR

The intracellular Ca ion level-increasing activity was measured using FLIPR as in TEST EXAMPLE 2. However, (1) the evaluation in TEST EXAMPLE 2 for measuring a change in intracellular Ca ion level for 180 seconds with passage of time was changed to the evaluation for 40 seconds after initiation of the reaction. Also, (2) indication of the activity is changed to EC_{50}/MS10 EC_{50} from the specific activity to Metastin (1-54).

A part of the evaluation results are shown in TABLE 24.

145
146

[TABLE 24]

Comp. No.	Specific Act.
40	1.6
41	2.7
42	1.6
82	1.0
97	2.9
108	2.6
114	4.1
128	0.5
134	0.6
141	1.6
146	1.5
152	1.4
156	0.9
174	2.3
176	1.3
187	1.9
206	4.6
208	7.3
210	9.3
211	1.3
212	1.1
217	3.1
222	2.7
232	3.9
239	6.7
240	4.9
241	5.3
242	1.4
260	4.3
265	4.4
266	6.4

268	4.5
269	3.4
279	6.4
294	0.7
296	5.2
297	5.5
298	1.8
303	6.9
305	2.0
308	2.6
310	2.0
311	6.2
312	4.0
314	4.4
318	2.9
319	3.1
322	5.4
332	4.9
333	5.0
334	1.4
339	5.9
341	2.8
353	0.8
354	0.8
358	5.6
369	4.8
375	5.2
378	10.4
379	3.0
385	0.7
386	2.9
387	5.0
393	5.9
423	5.6

436	1.4
438	3.0
445	4.2
447	1.4
449	4.2
451	2.6
454	2.6
455	4.1
459	7.3
463	4.6
464	10.6
467	4.0
468	5.2
472	3.4
473	4.2
474	3.2
475	4.2
479	2.6
480	8.8
481	2.4
488	5.5
490	6.2
491	1.0
492	1.1
493	2.2
494	8.6
496	0.7
497	1.4
498	1.5
499	1.4
500	3.2
501	1.1
502	1.4
503	0.4

504	6.9
505	0.7
506	1.3
507	1.7
508	1.0
509	2.0
510	3.5
511	0.5
512	0.8
513	0.4
514	0.7
515	1.0
516	3.7
517	1.0
518	10.5
519	2.4
521	2.4
522	1.9
523	1.1
524	1.1
527	3.8
528	1.4
529	1.8
530	3.4
531	1.8
532	1.0
533	9.7
534	5.6
535	0.8
536	1.8
537	4.7
538	3.3
539	1.2
540	0.7

541	2.0
542	1.4
545	1.1
546	1.9
547	2.5
548	1.7
550	0.7
551	1.2
552	2.3
553	1.9
554	1.3
555	1.5
556	2.8
557	3.2
558	0.4
559	0.3
561	1.6
562	1.0
563	0.7
564	0.5
565	0.6
566	0.8
567	0.8
568	0.6
569	0.5
570	0.5
571	1.2
572	0.7
573	0.7
576	0.8
577	0.7
578	0.8
579	0.6
580	0.6

Comp. No.	Spec. Act.
584	0.4
585	0.4
586	0.3
589	2.3
590	1.4
591	1.2
592	1.1
594	2.1
595	11.4
597	0.6
598	0.5
599	0.5
600	0.3
601	2.1
602	2.4
603	1.7
604	6.3
605	3.9
607	2.2
608	2.2
609	0.9
610	1.9
611	1.7
612	0.8
613	0.4
614	0.2
615	0.7
616	1.1
617	2.4
618	1.6
619	1.5
620	1.7
621	1.3
622	2.8
623	0.6
624	1.3
625	2.8
626	2.1
627	1.8
628	4.4
629	8.4
630	4.2
631	2
632	1.1
633	2.4
634	10.5
636	1.4
637	0.8
638	1.7
639	2
641	3.6
642	3.7
643	2.5
644	2.5
645	1.1
646	1.8

647	10.8
648	1.8
649	1
650	0.6
651	0.7
652	0.9
653	1.3
654	2.9
655	4.7
656	2.9
657	1.1
658	0.4
659	0.5
660	1.1
661	8.5
662	0.7
663	0.9
664	0.6
665	1.1
666	1.1
667	1.4
668	1.2
669	0.5
670	0.9
671	3.6
672	2.1
674	2
675	0.8
676	1.4
677	0.9
678	1.1
679	1.8
680	2.5
681	1.2
682	7.3
685	4.8
686	0.6
688	9.7
689	2.3
691	1.1
692	0.7
693	1.5
694	1.7
695	0.7
696	0.5
698	2.2
699	1.3
700	0.8
701	1.4
702	0.6
703	3.7

TEST EXAMPLE 4

Assay for cell growth inhibition activity in hOT7T175-expressed CHO cells

hOT7T175-Expressed CHO cells (hereinafter hOT7T175) was cultured in DMEM supplemented with 10% dialyzed FBS (hereinafter 10% dFBS/DMEM), which was used for the following assay. hOT7T175 was suspended in 10% dFBS/DMEM at 10,000 cells/ml. The cells were plated on a 96 well plate at 100 μL each/well (1,000 cells/well), followed by culturing at 37°C -5% CO_2 incubator overnight. On the following day, the medium was removed and 90 μL of 10% dFBS/DMEM supplemented with 0.5% BSA (hereinafter, 0.5% BSA/10% dFBS/DMEM) was added. Subsequently, 10 μL of a solution of metastin or metastin derivative in 0.5% BSA/10% dFBS/DMEM was added to each well, followed by culturing at 37°C -5% CO_2 incubator for 3 days. After 10 μL of Cell Counting Kit-8 solution (Dojin Chemical Laboratory) was added to each well, incubation was performed at 37°C -5% CO_2 incubator for 4 hours, absorbance was measured at 450 nm.

The cell inhibition activities of Metastin (1-54), Metastin (45-54) and synthetic compound are shown in TABLE 25.

[TABLE 25]

Compound Number	IC50 (M)
305	8.94E-09
232	9.67E-09
286	1.83E-08
303	4.12E-08
322	7.19E-08
141	8.70E-08
1-54	2.12E-07
45-54	8.51E-06

*"1-54" and "45-54" represent Metastin(1-54) and Metastin(45-54), respectively.

TEST EXAMPLE 5

Assay for chemotaxis inhibition activity in hOT7T175-expressed CHO cells

hOT7T175-Expressed CHO cells (hereinafter hOT7T175) was cultured in DMEM supplemented with 10% dialyzed FBS (hereinafter 10% dFBS/DMEM), which

was provided for assay. Also a 24-well 6.5 mm Transwell (pore size 8.0 μm) (COSTAR) was treated with fibronectin by the following method. Specifically, 0.5 ml of 1 μg/ml bovine fibronectin (Yagai Co., Ltd.) was added to the upper and lower chambers of Transwell. After the mixture was settled at room temperature for 10 minutes, the fibronectin solution was removed and further air-dried. After hOT7T175 washed with DMEM 3 times, the cells were suspended in DMEM containing 0.5% BSA (hereinafter 0.5% BSA/DMEM) at a density of 2.5 x 10^6 cells/ml. Metastin or a metastin derivative was diluted with 0.5% BSA/DMEM. After 600 μL of 0.5% BSA/DMEM supplemented with 20% FBS (or 0.5% BSA/DMEM for negative control) was added to the lower chamber of Transwell, and 50 μL of the cell suspension and 50 μL of the metastin or a metastin derivative dilution (or 0.5% BSA/DMEM for positive control) were added to the upper chamber. After incubation at 37°C in a 5% CO_2 incubator for 7 hours, the culture medium was removed and the upper side of the filter was wiped with a cotton swap wetted with phosphate-buffered saline to remove all cells on the upper side of the filter. The filter was fixed and stained with DifQuick (International Reagents Corporation) and the cells migrated toward the lower side of the filter were counted. The chemotaxis inhibition activity is shown in FIG. 1.

TEST EXAMPLE 6

Evaluation of tumor growth inhibition activity

The tumor growth inhibition effect of Metastin (1-54) (hereinafter referred to as Metastin) and Compounds (Compound Nos. 305 and 322) in vivo using tumor-bearing mice with human colonic carcinoma-derived cell line SW620.

Alza osmotic pump (0.25 μL/hour, 14 days release, Model 1002) filled with 100 μL each of 1 mM Metastin, 0.1 mM and 1 mM Compounds dissolved in distilled water (Otsuka Joryusui K.K.) and distilled water as a vehicle was subcutaneously embedded into the back of BALB/cAnN-nu mice (6 weeks old, female, Charles River Japan, Inc.) under ether anesthesia to initiate intermittent administration for 14 days. The number of experiments was n = 10 in the Metastin group and the vehicle group and n = 11 in the both Compound groups. On the following day, human colonic carcinoma-derived cell line SW620 (ATCC) was dissolved in 20 mM phosphate-buffered saline (pH 7.2)(PBS) containing 200 μL of 0.15M NaCl at a density of 2 x 10^6cells. The resulting solution was subcutaneously injected into the left flank of the mice above. The day when the cells were injected was made Day 0. Tumor was

measured with an electronic caliper every other or 2 other days during Days 4 to 13 from the cell administration, and tumor size was calculated by the equation: (shorter diameter)^2 x longer diameter/2. As shown in FIG. 2, the Metastin group (24 nmol/day/mouse x 14 days) showed a significant effect of tumor growth inhibition on Day 6, when compared to the vehicle group. On the other hand, the Compound No. 322 group showed a significant tumor growth inhibition activity in a 1/10 dose (2.4 nmol/day/mouse x 14 days) of Metastin from Days 6 to 8. Also, the Compound No. 322 group (24 nmol/day/mouse x 14 days) receiving the same dose as that of Metastin showed a significant tumor growth inhibition activity from Days 6 to 11, when compared to the vehicle group and on Day 11, showed a significant tumor growth inhibition activity even when compared with the Metastin group. The foregoing results reveal that Metastin shows the effect of tumor growth inhibition in vivo as well and Compound No. 322 has the effect of tumor growth inhibition of 10 times higher than with Metastin.

The results of Compound No. 305 are also shown in FIG. 3. The Metastin group (24 nmol/day/mouse x 14 days) showed a significant effect of tumor growth inhibition from Days 5 to 7, when compared to the vehicle group. On the other hand, the Compound No. 305 group (2.4 nmol/day/mouse x 14 days) receiving a 1/10 dose as that of Metastin showed a significant tumor growth inhibition activity from Days 5 to 11, when compared to the vehicle group. Furthermore, the Compound No. 305 group (24 nmol/day/mouse x 14 days) receiving the same dose as that of Metastin showed a significant effect of tumor growth inhibition from Days 5 to 9 and on Day 11, when compared to the vehicle group, revealing that Compound No. 305 also shows the in vivo effect of tumor growth inhibition of 10 times higher than with Metastin.

TEST EXAMPLE 7

Effect of elevating sugar level by metastin

In order to study the effect of metastin on sugar level by peripheral administration, an operation was performed in free moving animal to collect blood. Mature Wistar male rats (weighing 210 - 230 g at the time of operation) were anesthetized by intraperitoneal injection of 50 mg/kg pentobarbital. The animal was taped dorsally to the dissection pad and the left jugular vein was exposed. A polyethylene tube SP35 (inner diameter of 0.5 mm, outer diameter of 0.9 mm, Natsume Seisakusho Co., Ltd.) was cut into a length of about 30 cm and filled up with 200

units/ml of heparinated saline. Thereafter, the tube was inserted into the jugular vein to a depth of about 4.5 cm and fixed. The other end of the tube was subcutaneously inserted into the back to expose at the jugular (back).

After the operation, the animal was maintained overnight. Prior to administration of metastin, 300 µl of blood was drawn through a 1 ml tuberculin syringe and a 25-gauge needle (both by Terumo Co., Ltd.). To prevent blood clotting, 3 µl of 300 KIU/ml aprotinin solution containing 3 mg/ml EDTA had previously been filled in the syringe. Otsuka saline or 1 mL saline solution of metastin (17, 80 or 170 nmol) was intravenously injected in a dose of 1 mL/kg through the tube. Blood was collected from the jugular vein by 300 µl each 0, 5, 15, 30 and 60 minutes starting from the intravenous injection. The collected blood was centrifuged (13,000 rpm, 5 minutes) with a high speed refrigerated centrifuge (MR-150, Tomy Seiko Co., Ltd.) to recover the supernatant (plasma). Glucose level in blood was measured using Fuji Drychem 3500 (FUJI FILM). As shown in FIG. 4, the Metastin group showed a significant effect ($p<0.005$, $n = 5$) of enhancing glucose level in blood dose-dependently (17-170 nmol/kg) from 5 minutes after the intravenous injection, when compared to the control group. In the blood glucose level, a prolonged period of time (30 minutes at maximum) for enhancing the sugar level accompanied by an increase of the maximum level was noted metastin, as the dose increased.

TEST EXAMPLE 8

Effect of promoting pancreatic glucagon secretion by metastin

In order to study the mechanism of metastin for the effect of enhancing glucose level in blood, effects of metastin on the level of blood glucagon, insulin, corticosterone and thyroid hormone (T3) known to be hormones affecting glucose level in blood were examined. An operation was performed in free moving mature Wistar male rats (weighing 260 - 300 g at the time of operation) to collect blood. After the operation, the animal was maintained overnight. Prior to administration of metastin, 300 µl of blood was drawn through a 1 ml tuberculin syringe and a 25-gauge needle (both by Terumo Co., Ltd.). To prevent blood clotting, 3 µl of 300 KIU/ml aprotinin solution containing 3 mg/ml EDTA had previously been filled in the syringe. Otsuka saline or a saline solution of metastin (80 nmol/mL) was intravenously injected in a dose of 1 mL/kg through the tube. Blood was collected from the jugular vein by 300 µl each 1, 3, 5 and 15 minutes starting from the intravenous injection. The collected blood was centrifuged

(13,000 rpm, 5 minutes) with a high speed refrigerated centrifuge (MR-150, Tomy Seiko Co., Ltd.) to recover the supernatant (plasma). Glucagon level in blood was measured using a glucagon kit "Daiichi" (Daiichi Radioisotope Laboratories Ltd.), insulin level in blood using rat insulin [^{125}I] assay system (Amersham Biosciences), corticosterone level in blood using rat corticosterone [^{125}I] assay system (Amersham Biosciences), thyroid hormone (T3) in blood using T-3.RIA beads (Dinabott Co. Ltd.), and glucose level in blood using Fuji Drychem 3500 (FUJI FILM). As shown in FIG. 5, the Metastin group showed a significant effect of enhancing glucagon level in blood 1 minute after the injection, when compared to the control group. The significant effect of enhancing glucagon level continued until 5 minutes after the injection. On the other hand, in the insulin level in blood (FIG. 6), corticosterone level in blood (FIG. 7) and thyroid hormone (T3) level in blood (FIG. 8), no change was noted by the injection of metastin. Based on these results and the observed increase in blood glucagon level followed by blood glucose level (FIG. 9), it was considered that the effect of blood glucose level by intravenous injection of metastin would be induced due to stimulation of glucagon secretion by metastin.

TEST EXAMPLE 9

Effect of elevating sugar level by metastin derivatives

The effect of metastin derivatives KiSS305 (Compound No. 305) and KiSS322 (Compound No. 322) on blood glucose level and blood glucagon level was examined. An operation was performed in free moving mature Wistar male rats (weighing 260-3000 g at the time of operation) in a manner similar to TEST EXAMPLE 1 to collect blood. After the operation, the animal was maintained overnight. Prior to administration of metastin, 300 μl of blood was drawn through a 1 ml tuberculin syringe and a 25-gauge needle (both by Terumo Co., Ltd.). To prevent blood clotting, 3 μl of 300 KIU/ml aprotinin solution containing 3 mg/ml EDTA had previously been filled in the syringe. Otsuka saline or a saline solution of metastin (80 nmol/mL) was intravenously injected in a dose of 1 mL/kg through the tube. Blood was collected from the jugular vein by 300 μl each 2, 5, 15, 30, 45 and 60 minutes starting from the intravenous injection. The collected blood was centrifuged (13,000 rpm, 5 minutes) with a high speed refrigerated centrifuge (MR-150, Tomy Seiko Co., Ltd.) to recover the supernatant (plasma). Glucose level in blood was measured using Fuji Drychem 3500 (FUJI FILM) and glucagon level in blood was measured using a glucagon kit

"Daiichi" (Daiichi Radioisotope Laboratories Ltd.), as in TEST EXAMPLE 1 or 2. As shown in FIG. 10, both compounds showed an increase in the blood glucose level. Also, both compounds showed an increase in the blood glucagon level, as shown in FIG. 11.

TEST EXAMPLE 10

Induction of ovulation by human metastin in immature rat

Equine chorionic gonadotropin (eCG, serotropin, Dainippon Pharmaceutical Co., Ltd.) was dissolved in saline (Otsuka Pharmaceutical Co., Ltd.) in a concentration of 100 IU/mL. Using a 1 ml tuberculin syringe and a 26-gauge needle (both by Terumo Co., Ltd.), eCG was subcutaneously injected into the dorsal area of female Wistar rats of 23 days old after birth (Charles River Japan, Inc.) in a dose of 10 IU/animal, during 9:30 to 10:00 AM. Following the eCG injection, the animal was grouped after 47 to 48 hours as shown below, to which groups, each drug was injected.

Group A (5 rats): Human chorionic gonadotropin (hCG, gonadotropin, Dainippon Pharmaceutical Co., Ltd.) was dissolved in saline at 100 IU/mL and the solution was subcutaneously injected into the back in a dose of 20 IU/animal.

Group B (5 rats): Human metastin was dissolved in saline at 100 nmol/mL and the solution was subcutaneously injected into the back in a dose of 20 nmol/animal.

Group C (5 rats): Human metastin was dissolved in saline at 33.3 nmol/mL and the solution was subcutaneously injected into the back in a dose of 6.67 nmol/animal.

Group D (6 rats): Saline was subcutaneously injected into the back in a dose of 200 μL/animal.

After administration of the drugs described above, the animal was sacrificed by decapitation after 24 to 25 hours to recover blood, bilateral oviducts and uterus. In collecting blood, 90 μl of 10 KIU/ml aprotinin solution (Trasylol, Bayer) containing 3 mg/ml EDTA had been previously filled in a tube for recovery to prevent blood clotting. After blood recovery, the blood was thoroughly blended and the mixture was centrifuged at 2,000G for 25 minutes. After the supernatant was recovered, the product was used as a plasma sample.

The number of oocytes was counted as follows.

Where retention of oocytes in the oviducal ampulla was confirmed by stereomicroscopic observation of the oviduct, the ampulla was punctured with a syringe with 27-gauge needle for syringe (Terumo) to retrieve the oocytes. After granulosa cells

surrounding the oocytes were removed by trypsin treatment, the number of oocytes was counted. Where retention of oocytes in the oviducal ampulla was not confirmed by stereomicroscopic observation of the oviduct, a 27-gauge needle with the polished tip for syringe was inserted into the tubal ostium and more than 400 μL of saline was flushed into the oviduct and uterine for rinsing. Then, the presence or absence of oocytes in the effluent was observed.

The number of oocytes obtained is shown in TABLE 26.

[TABLE 26]

	Group A	Group B	Group C	Group D
1	36	29	29	0
2	35	56	39	0
3	40	17	32	0
4	42	25	22	0
5	35	32	16	0
Average of Ovulation	37.6	31.8	27.6	0.00
Standard Deviation	3.21	14.65	8.91	0.00

In the table, the numbers "1" through "5" represent a number for individual rat.

In Group A, which is a multipurpose superovulation treatment group, ovulation of 37.6 oocytes in average per rat was confirmed. In Groups B and C receiving metastin, ovulation of 31.8 and 27.6 oocytes in average, respectively, were confirmed. Turning to Group D receiving saline, the number of oocytes was 0.6 in average, indicating that voluntary ovulation was little observed in the absence of ovulation stimulation.

The level of estradiol contained in the plasma collected from the rats shown in TABLE 22 was determined by radioimmunoassay (DPC-Estradiol Kit; Diagnostic Products Corporation). The results are shown in FIG. 12.

The results reveal that among Groups A, B and C, there is no difference in the

level of estradiol contained in plasma, showing that the level of estradiol was extremely high only in Group D receiving saline.

The level of progesterone contained in plasma was determined by radioimmunoassay (DPC.Progesterone; Diagnostic Products Corporation). The results are shown in FIG. 13.

The results reveal that the level of progesterone was highest in Group A and in Groups B and C, the blood level was approximately half that of Group A and that the progesterone level was extremely low in Group D.

In general, the major steroid hormone produced in rat mouse and human ovaries is estrogen in the mature phase of ovarian follicle, whereas it is progesterone after ovulation was induced. It is understood actually from the results in FIG. 12 and FIG. 13 that Group D receiving saline maintained the state where estrogen was highly produced, because of no induction of ovulation; whereas in Group A receiving hCG, production of estrogen increased. In Groups B and C, which are groups receiving Metastin, the plasma estrogen level was very low but the level of progesterone increased, indicating that metastin induced ovulation in the rat ovary via its normal ovulatory process. It is also considered that since the progesterone level in Groups B and C was lower than in Group A, metastin would have a milder ovarian stimulation.

TEST EXAMPLE 11

Gonadotropin-releasing effect of human metastin in immature rat

Human metastin dissolved in saline in a concentration of 33.3 nmol/mL was subcutaneously injected into the dorsal area of female Wistar rats of 25 days old after birth (Charles River Japan, Inc.) in a dose of 200 μL/animal, i.e., 6.67 nmol as human metastin, during 9:00 to 10:00 AM. Prior to the metastin injection and 1, 2 and 4 hours after the injection, the animal was decapitated to recover blood. In recovery of blood, 90 μl of 10 KIU/ml aprotinin solution (Trasylol, Bayer) containing 3 mg/ml EDTA had been previously filled in a centrifuging tube for recovery to prevent blood clotting. After blood recovery, the blood was thoroughly blended and the mixture was centrifuged at 2,000G for 25 minutes. After the supernatant was recovered, the product was used as a plasma sample. The levels of FSH (follicle-stimulating hormone), LH (luteinizing hormone) and progesterone contained in the plasma were determined by radioimmunoassay (Rat Follicle Stimulating Hormone (rFSH) [^{125}I] Biotrack Assay System with Magnetic Separation, Rat Luteinizing Hormone (rLH) [^{125}I] Biotrack

Assay System with Magnetic Separation, both by Amersham Bioscience, and DPC.Progesterone by Diagnostic Products Corporation).

The results obtained by monitoring changes in the FSH level in blood from the immature rat by the metastin injection are shown in FIG. 14. One hour after the metastin injection, the blood FSH level began to significantly increase and reached the maximum after 2 hours. While a decrease in the blood FSH level was noted after 4 hours, the FSH level was still maintained higher than the level prior to the injection.

The results obtained by monitoring changes in the LH level in blood from the immature rat by the metastin injection are shown in FIG. 15. Similarly to the case of FSH, the blood LH level began to significantly increase 1 hour after and reached the maximum after 2 hours. While a decrease in the blood LH level was noted after 4 hours, the LH level was still maintained higher than the level prior to the injection.

The results obtained by monitoring changes in the progesterone level in blood from the immature rat by the metastin injection are shown in FIG. 16. Reflecting the increase of blood LH level, the progesterone level began to increase slowly 1 hour after the metastin injection and showed a significantly higher level than the level prior to the injection.

The results of FIG. 14 and FIG. 15 reveal that peripheral administration of metastin induces release of gonadotropin such as FSH, LH, etc. The induction of ovulation by metastin demonstrated in TEST EXAMPLE 9 is considered to be mediated by this gonadotropin release, particularly LH release.

The effect of inducing ovulation demonstrated in TEST EXAMPLE 9 is an action in rats receiving eCG but the effect in this TEST EXAMPLE shows the results obtained using nude rats. No eCG pretreatment is required for the effect of releasing gonadotropin by metastin.

The results shown in FIG. 16 mean that the release of gonadotropin by the metastin injection imparts physiological stimulation also to the ovary, resulting in increasing the production of progesterone.

TEST EXAMPLE 12

Gonadotropin-releasing effect of human metastin in mature male rat

Human metastin dissolved in saline in a concentration of 175 nmol/mL was subcutaneously injected into the dorsal area of male Wistar rats of 11 weeks old after birth (Charles River Japan, Inc.) in a dose of 200 μL/animal, i.e., 35 nmol as human

metastin, during 10:30 to 11:30 AM. Prior to the metastin injection and 1, 2 and 4 hours after the injection, the animal was decapitated to recover blood. In recovery of blood, 300 μl of 10 KIU/ml aprotinin solution (Trasylol, Bayer) containing 3 mg/ml EDTA had been previously filled in a centrifuging tube for recovery to prevent blood clotting. After blood recovery, the blood was thoroughly blended and the mixture was centrifuged at 2,000G for 25 minutes. After the supernatant was recovered, the product was used as a plasma sample. The levels of FSH (follicle-stimulating hormone), LH (luteinizing hormone) and testosterone contained in the plasma were determined by radioimmunoassay (Rat Follicle Stimulating Hormone (rFSH) [^{125}I] Biotrack Assay System with Magnetic Separation, Rat Luteinizing Hormone (rLH) [^{125}I] Biotrack Assay System with Magnetic Separation, both by Amersham Bioscience, and DPC.Total Testosterone by Diagnostic Products Corporation).

The results obtained by monitoring changes in the blood FSH level in rat by the metastin injection are shown in FIG. 17. One hour after the metastin injection, the blood FSH level began to significantly increase and reached the maximum after 2 hours, and even after 4 hours, still maintained a higher state.

The results obtained by monitoring changes in the blood LH level in rat by the metastin injection are shown in FIG. 18. Similarly to the case of FSH, the blood LH level began to significantly increase 1 hour after and reached the maximum after 2 hours. While a decrease in the blood LH level was noted after 4 hours, the LH level was still maintained higher than the level prior to the injection.

The results obtained by monitoring changes in the blood testosterone level in rat by the metastin injection are shown in FIG. 19. The testosterone level showed a rapid increase in 1 hour after the metastin injection. While a decrease in the blood testosterone level was noted after 2 and 4 hours, the testosterone level was still maintained at both points of time higher than the level prior to the injection.

The results of FIG. 17 and FIG. 18 reveal that peripheral administration of metastin induces release of gonadotropin such as FSH, LH, etc. in male rat. In view of the results of TEST EXAMPLE 10, metastin is considered to be an extremely important factor in both female and male rats, in stimulating the release of gonadotropin.

The results shown in FIG. 19 mean that the release of gonadotropin by the metastin injection imparts physiological stimulation also to the testis, resulting in increasing the production of testosterone.

From these results it is considered that administration of metastin would

stimulate the testis mediated by release of gonadotropin. This suggests that metastin possibly affects the male reproductive function including seminal maturation, hormone secretion, etc.

TEST EXAMPLE 13

Test on stability of Compound in blood

Blood was drawn from Balb/c mouse of 8 weeks old (female), settled at 37°C for 30 minutes and centrifuged at 13000 rpm for 10 minutes to give mouse serum. The serum thus obtained was frozen-stored at -80°C.

The stability test was performed by addition of 5 nmol of Compound (5μL of aqueous solution) to 45 μL of serum and then settlement of the mixture at 37°C. The settlement was made at 3 points of time, including 2, 10 and 30 minutes. The sample after the settlement was boiled for 3 minutes and cooled on an ice bath. After 200 μL of acetonitrile/water (3/1) was added to the sample, the mixture was ultrasonicated for 5 minutes and then centrifuged at 5000 rpm for 1 minute. After 150 μL of the supernatant was diluted with 250 μL of distilled water, insoluble matters were removed by filtration through a filter having a pore size of 0.45 μm and 200 μL of the filtrate was applied on HPLC (220 nm) to determine the peak area of Compound. A ratio of the peak area to the area when Compound was treated for 0 minute under the same conditions was calculated as a mean value in 4 respective runs to determine the residual ratio. Next, by taking the calculated residual ratio on the ordinate and time on the abscissa, a graph was prepared and approximated by an exponential function. Thus, the time when the residual ratio reached 50% was calculated as a half life.

The LC-VP series manufactured by Shimadzu Corporation was used as preparative HPLC and Wakosil-II 5C18 HG (4.6 mm x 100 mm) manufactured by Wako Pure Chemical Industries, Ltd. was used as a column. Eluant A (0.1% TFA-containing water) and eluant B (0.1% TFA-containing acetonitrile) were used as eluants. Linear density gradient elution was performed at a flow rate of 1.0 ml/min. using eluants A/B: 100/0 - 0/50 (25 minutes).

Compounds tested and the $t_{1/2}$ (min) values are shown in TABLE 27.

[TABLE 27]

Compound Number	$t_{1/2}$ (min)
1	22.5
3	0.6
42	0.7
82	1.8
134	2.4
141	8.7
232	28.2
286	57.5
296	47.2
305	66.6
308	13.2
319	33.0
322	94.2

TEST EXAMPLE 14

Induction of ovulation in immature rat using metastin derivatives

Equine chorionic gonadotropin (eCG, serotropin, Dainippon Pharmaceutical Co., Ltd.) was dissolved in saline (Otsuka Pharmaceutical Co., Ltd.) in a concentration of 100 IU/mL. Using a 1 ml tuberculin syringe and a 26-gauge needle (both by Terumo Co., Ltd.), eCG was subcutaneously injected into the dorsal area of female Wistar rats of 23 days old after birth (Charles River Japan, Inc.) in a dose of 10 IU/animal, during 9:00 to 10:00 AM. Following the eCG injection, the animal was grouped after 47 to 48 hours as shown below, to which groups, each drug was injected.

Group A (5 rats): Human chorionic gonadotropin (hCG, gonadotropin, Dainippon Pharmaceutical Co., Ltd.) was dissolved in saline at 100 IU/mL and the solution was subcutaneously injected into the back in a dose of 20 IU/animal.

Group B (5 rats): Compound No. 305 was dissolved in saline at 33.3 nmol/mL and the solution was subcutaneously injected into the back in a dose of 6.7 nmol/animal.

Group C (5 rats): Compound No. 305 was dissolved in saline at 10.0 nmol/mL and the solution was subcutaneously injected into the back in a dose of 2.0 nmol/animal.

Group D (5 rats): Compound No. 322 was dissolved in saline at 33.3 nmol/mL and the solution was subcutaneously injected into the back in a dose of 6.7 nmol/animal.

Group E (5 rats): Compound No. 322 was dissolved in saline at 10.0 nmol/mL and the solution was subcutaneously injected into the back in a dose of 2.0 nmol/animal.

Group F (6 rats): Saline was subcutaneously injected into the back in a dose of 200 μL/animal.

After administration of these drugs, the animal was sacrificed by decapitation after 24 to 25 hours to recover blood, bilateral oviducts and uterus. In collecting blood, 90 μl of 10 KIU/mL aprotinin solution (Trasylol, Bayer) containing 3 mg/ml EDTA had been previously filled in a tube for recovery to prevent blood clofting. After blood recovery, the blood was thoroughly blended and the mixture was centrifuged at 2,000G for 25 minutes. After the supernatant was recovered, the product was used as a plasma sample.

The number of oocytes was counted by referring to the method described in Eur. J. Endocrinol., 138, 594-600 (1998).

Where retention of oocytes in the oviducal ampulla was confirmed by stereomicroscopic observation of the oviduct, the ampulla was punctured with a 27-gauge needle for syringe (Terumo) to retrieve the oocytes. After granulosa cells surrounding the oocytes were removed by trypsin treatment, the number of oocytes was

counted. Where retention of oocytes in the oviducal ampulla was not confirmed by stereomicroscopic observation of the oviduct, a with 27-gauge needle with the polished tip for syringe was inserted into the tubal ostium and more than 400 μL of saline was flushed into the oviduct and uterine for rinsing. Then, the presence or absence of oocytes in the effluent was observed.

The number of oocytes thus obtained is shown in FIG. 20. In Group A, which is a multipurpose superovulation treatment group, the number of oocytes was 38.0 oocytes in average per rat. In Groups B, C and D, the number of oocytes was 32.6, 29.4 and 29.6 oocytes in average, respectively, indicating that ovulation was substantially equivalent to Group A. Turning to Group E receiving 2.0 nmol of Compound No. 322, 3 out of 5 rats were ovulated and the number of oocytes was 11.6 in average, which was less than Group A. Further in Group A for negative control, no ovulation was observed.

The results of FIG. 20 reveal that for induction of ovulation equivalent to hCG, at least 2.0 nmol/animal of Compound No. 305 and at least 6.7 nmol/animal of Compound No. 322 should be administered.

The results obtained by measuring the level of estradiol contained in plasma are shown in FIG. 21. The blood estradiol level was measured by radioimmunoassay (DPC.Estradiol Kit, Iatron, Inc.). As shown in FIG. 21, no difference was found among Groups A, B, C and D in terms of estradiol and only Group F showed a high level. Group E had a tendency to show a higher level in rats with no ovulation induction.

The results obtained by measuring the level of progesterone contained in plasma are shown in FIG. 22. The blood progesterone level was measured by radioimmunoassay (DPC.Progesterone, Iatron, Inc.). As shown in FIG. 22, the blood progesterone level was highest in Group A and in Groups B, C and D, the progesterone level shows less than a half of the level in Group A. Groups E and F shows a very low level.

The results of FIG. 21and FIG. 22 reveal that more than 2.0 nmol/animal of Compound No. 305 and more than 6.7 nmol/animal of Compound No. 322 were administered to induce normal differentiation from estrogen-producing granulosa cells to progesterone-producing luteal cells. Furthermore, when Compound No. 305 or KiSS-322 was administered, the progesterone level was lower than in the hCG administration, suggesting that the stimulating effect of these derivatives on ovary would be milder than that of hCG.

TEST EXAMPLE 15

Evaluation of blood testosterone level decreasing effect of metastin peptide derivatives using mature male rat

A metastin peptide derivative (hereinafter peptide) was dissolved in distilled water (Otsuka Joryusui K.K.) to prepare 2 mM peptide solution. This peptide solution was filled in 5 ALZET osmotic pumps (Model 2001, 0.2 ml in volume, release rate: 0.001 ml/hr, DURECT Corporation). The ALZET pumps filled with the peptide solution were implanted subcutaneously in 5 CD(SD)IGS male rats of 9 weeks old after birth (Charles River Japan, Inc.) on the back under ether anesthesia by one pump for one animal. For negative control, distilled water (Otsuka Pharmaceutical Co., Ltd.) was filled in 5 ALZET osmotic pumps, which were similarly implanted in 5 male CD(SD)IGS rats (Charles River Japan, Inc.), respectively. These pump-implanted rats were fed for 6 days under normal feeding conditions. After weighing, the animal was decapitated to collect blood. After 0.03 ml/ml blood of aprotinin solution (Trasylol, Bayer) containing 0.1 mg/ml EDTA.2Na was added to blood, the mixture was centrifuged at 1,800G for 25 minutes to isolate/recover plasma. From the plasma obtained, 0.05 ml was applied to radioimmunoassay (DPC.Total Testosterone Kit, Diagnostic Products Corporation) to measure the plasma testosterone level of each rat. The value below the limit of measurement (0.04 ng/ml of plasma · level) in radioimmunoassay was treated as 0. A mean value of the testosterone levels from 5 rats receiving the peptide was calculated and a relative value (percent) of the mean value to a mean value from 5 rats receiving distilled water.

Using this evaluation method, various peptides were evaluated and a part of the results are shown in TABLES 28 and 29.

[TABLE 28]

Comp. No.	Testosterone level in Blood
334	40%
354	43%
436	35%
269	7%
386	23%
499	2%
305	2%
385	2%
492	65%
496	3%
134	50%
141	31%
176	12%

[TABLE 29]

Comp. No.	Teststerone level in Blood
505	40%
508	9%
509	2%
512	2%
515	2%
517	79%

TEST EXAMPLE 16

In a manner similar to TEST EXAMPLE 14, evaluation was made using 0.1 mM peptide solution and a part of the results obtained are shown in TABLE 30.

[TABLE 30]

Compound Number	Testosterone level in Blood
305	48%
385	33%
499	32%
512	38%
518	3%
523	72%
538	45%
540	55%
545	37%
547	65%
550	2%
551	8%
552	21%
553	39%
554	52%
556	73%
558	2%
559	17%
562	11%
564	68%
565	80%
566	89%
567	86%
571	17%

TEST EXAMPLE 17

Evaluation of metastin peptide derivatives for action of reducing testosterone level in blood using mature male rat

Peptide solutions at the concentration of 1 mM was prepared by dissolving the metastin peptide derivatives (hereinafter referred to as peptide) in 50% DMSO aqueous solution. The peptide was encapsulated in five ALZET osmotic pump (Model 2001, 0.2 ml of volume, releasing rate 0.001 ml/hr, DURECT Corporation). The ALZET pumps

encapsulated with the peptide solution were implanted to dorsal subcutaneous of five male CD (SD) IGS rat at nine weeks age (Charles River Japan,Inc.) anesthesized with ether for one pump to one rat. Separately, for negative controls, the ALZET osmotic pumps encapsulated with distilled water were implanted to five male CD (SD) IGS rat (Chairles River Japan,Inc.) The rats were bred for six days under the normal conditions. After weighing, blood was collected by decapitation. To 1 ml of blood, 0.03 ml of aprotinin (Trasylol, Byer) solution containing 0.1 g/ml EDTA 2Na was added. The plasma was isolated by centrifugation at 1,800 x g for 25 minutes and collected. The thusobtained plasma, 0.05 ml was effected by radioimmunoassay. (DPC Total Testosterone Kit, Diagnostic Products Corporation) to measure testosterone level in blood of each rat. The value beneath measuring limit of radioimmunoassay (0.04 ng/ml as concentration of plasma) was treated as zero. The mean values for testosterone level of five rats, to which the peptide was given, was calculated and the relative value (percentage) for the mean values of testosterone level of five rats, to which distilled watrer was given, was estimated. One example of the results evaluated for various peptides using this evaluation method was shown in TABLE 31.

[TABLE 31]

Comp. No.	Testosterone level in Blood
305	25
501	25
545	25
548	185
558	25
564	25
569	25
580	25
591	25
592	25
599	25
600	25
602	25
608	25
612	25
613	25
615	25
616	25
617	25
618	25
621	25
623	25
625	25
626	25
627	25
629	25
630	25
635	25
637	25
638	25
642	25
645	25
649	25
650	25
651	25
652	25
657	25
658	25
660	25
662	25
663	25
664	25
666	25
667	25
670	25
671	25
672	25
674	25
675	25
676	25
677	25

[Sequence Listing Free Text]

SEQ ID NO: 15 The C terminus is amidated.

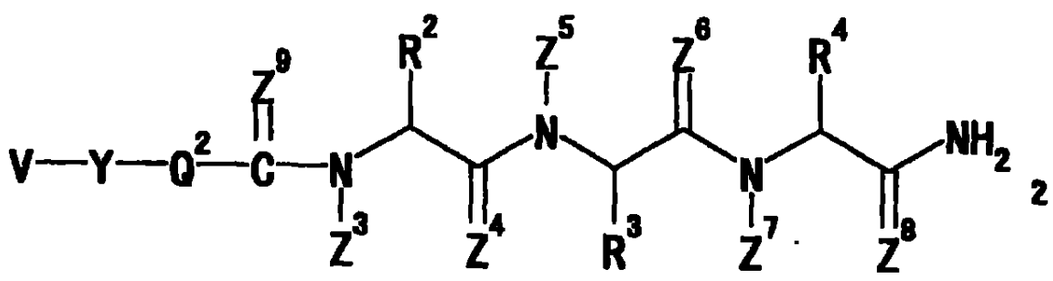
SEQ ID NO: 16 The C terminus is amidated.

SEQ ID NO: 17 The C terminus is amidated.

SEQ ID NO: 18 The C terminus is amidated.

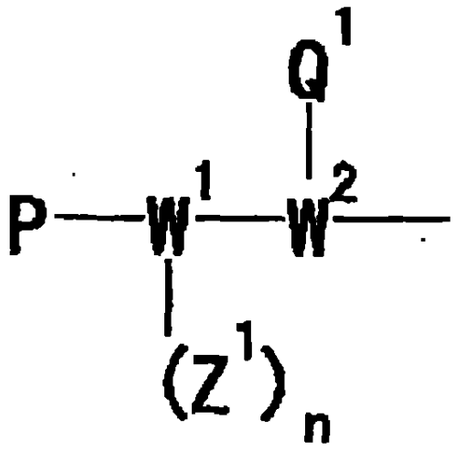
CLAIMS

1. A metastin derivative (II) represented by formula:

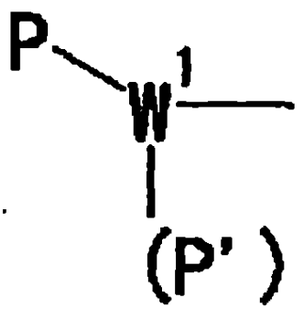


[wherein;

V represents a group represented by formula:



or a group represented by formula:



n represents 0 or 1;

W^1 represents N, CH or O (provided that when W^1 is N or CH, n represents 1 and when W^1 is O, n represents 0);

W^2 represents N or CH;

Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group;

Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

R^2 represents (1) hydrogen atom or (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group;

R^3 represents (1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent, (2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent, (3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent, or (4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent;

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an

optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, or (3) O;

Y represents a group represented by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO- or $-CH_2CH_2-$, which may optionally be substituted with a C_{1-6} alkyl group; and,

Z^9 represents hydrogen atom, O or S; and,

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

(wherein:

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino

group, which groups may optionally be substituted with a substituent containing an optionally substituted cyclic group;

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S;

J^3 through J^6 each represents hydrogen atom or a C_{1-3} alkyl group;

Q^3 through Q^6 each represents a C_{1-4} alkyl group, which may optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused cyclic group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7,

(7) an optionally substituted amino group,

(8) an optionally substituted guanidino group,

(9) an optionally substituted hydroxyl group,

(10) an optionally substituted carboxyl group,

(11) an optionally substituted carbamoyl group, and

(12) an optionally substituted sulfhydryl group, -

or hydrogen atom;

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5 or J^6 and Q^6 may be combined together, or, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, or Y^3 and Q^6 may be combined together, to form a ring;

Y^1 through Y^3 each represents a group represented by formula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (wherein J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group); and,

Z^{10} represents hydrogen atom, O or S);

(4) a group represented by formula:

J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$-

(wherein:

J^1 and J^2, each has the same significance as defined above;

J^7 through J^9 have the same significance as for J^3;

Q^7 through Q^9 have the same significance as for Q^3;

Y^2 and Y^3 each has the same significance as defined above;

Z^{10} has the same significance as defined above;

J^7 and Q^7, J^8 and Q^8 or J^9 and Q^9 may be combined together, or, J^2 and Q^7, Y^2 and Q^8 or Y^3 and Q^9 may be combined together, to form a ring);

(5) a group represented by formula:

J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$-

(wherein:

J^1 and J^2 have the same significance as defined above represents;

J^{10} and J^{11} have the same significance as for J^3;

Q^{10} and Q^{11} have the same significance as for Q^3;

Y^3 has the same significance as defined above;

Z^{10} has the same significance as defined above; and,

J^{10} and Q^{10} or J^{11} and Q^{11} may be combined together, or J^2 and Q^{10} or Y^3 and Q^{11} may be combined together, to form a ring);

(6) a group represented by formula:

J^1-J^2-$C(J^{12})(Q^{12})C(=Z^{10})$-

(wherein;

J^1 and J^2 have the same significance as defined above;

J^{12} has the same significance as for J^3;

Q^{12} has the same significance as for Q^3;

Z^{10} has the same significance as defined above; and,

J^{12} and Q^{12} may be combined together, or J^2 and Q^{12} may be combined together, to form a ring); or,

(7) a group represented by formula:

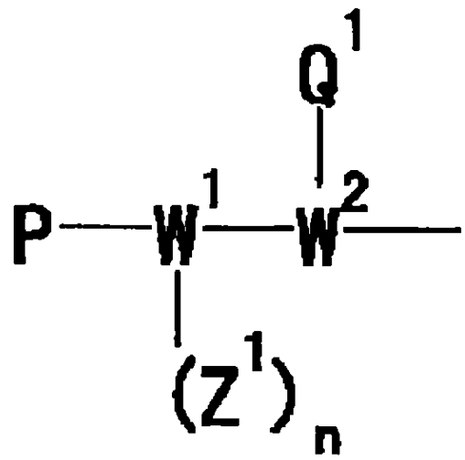
J^1-

(wherein:

J^1 has the same significance as defined above)] (provided that a peptide consisting of the amino acid sequence of 1-54, 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54, 41-54, 42-54, 43-54, 44-54,

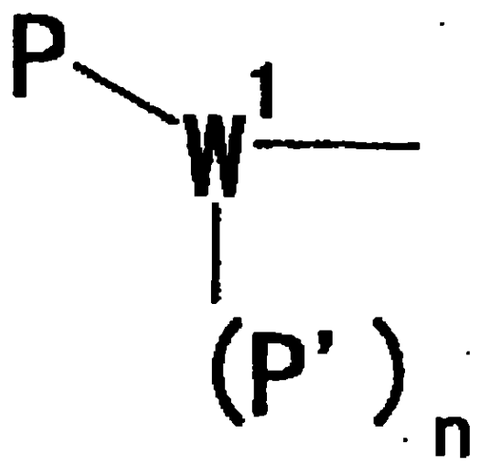
45-54, 46-54, 47-54, 48-54 or 49-54 in the amino acid sequence represented by SEQ ID NO: 1 is excluded), or a salt thereof.

2. The metastin derivative (II) according to claim 1, wherein V is a group represented by formula:



(wherein each symbol has the same significance as defined in claim 1), or a salt thereof.

3. The metastin derivative (II) according to claim 1, wherein V is a group represented by formula:



(wherein each symbol has the same significance as defined in claim 1), or a salt thereof.

4. A prodrug of the metastin derivative (II) according to claim 1 or a salt thereof.

5. A pharmaceutical comprising the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

6. The pharmaceutical according to claim 5, which is an agent for suppressing cancer metastasis or an agent for suppressing cancer growth.

7. The pharmaceutical according to claim 5, which is an agent for preventing or treating cancer.

8. The pharmaceutical according to claim 5, which is an agent for controlling placental function.

9. The pharmaceutical according to claim 5, which is an agent for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

10. The pharmaceutical according to claim 5, which is an agent for improving gonadal function.

11. The pharmaceutical according to claim 5, which is an agent for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus.

12. The pharmaceutical according to claim 5, which is an agent for inducing or stimulating ovulation.

13. The pharmaceutical according to claim 5, which is a gonadotropic hormone secretagogue agent or a sex hormone secretagogue agent.

14. The pharmaceutical according to claim 5, which is an agent for preventing or treating Alzheimer's disease or moderate cognitive impairment.

15. A method for suppressing cancer metastasis or cancer growth, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

16. A method for preventing or treating cancer, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

17. A method for controlling placental function, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

18. A method for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

19. A method for improving gonadal function, which comprises administering

to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

20. A method for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

21. A method for inducing or stimulating ovulation, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

22. A method for promoting gonadotropic hormone secretion or promoting sex hormone secretion, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

23. A method for preventing or treating Alzheimer's disease or moderate cognitive impairment, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

24. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for suppressing cancer metastasis or an agent for suppressing cancer growth.

25. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating cancer.

26. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for controlling placental function.

27. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

28. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for improving gonadal function.

29. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus.

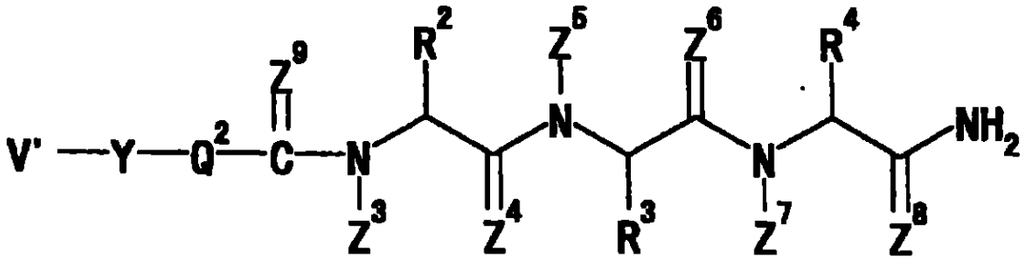
30. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for inducing or stimulating ovulation.

31. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture a gonadotropic hormone secretagogue agent or a sex

hormone secretagogue agent.

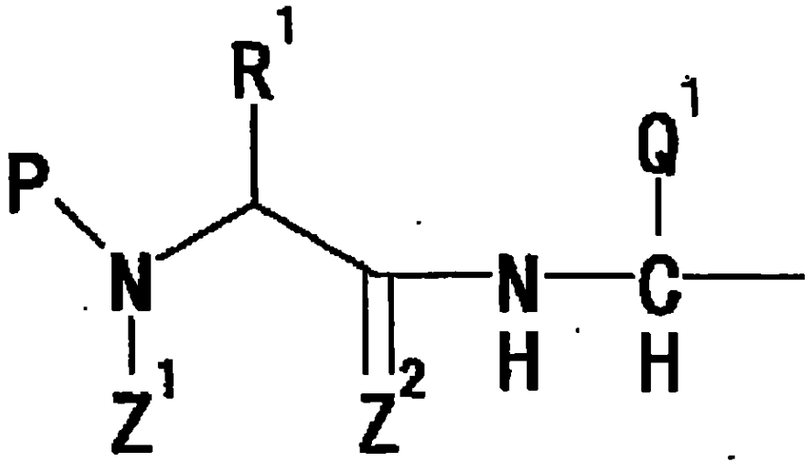
32. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating Alzheimer's disease or moderate cognitive impairment.

33. An agent for suppressing gonadotropic hormone secretion or an agent for suppressing sex hormone secretion comprising the metastin derivative (III) represented by formula:

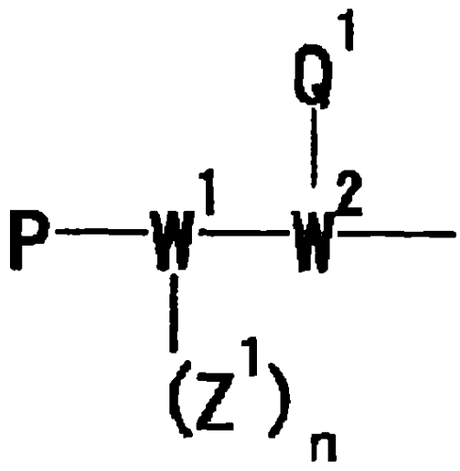


[wherein:

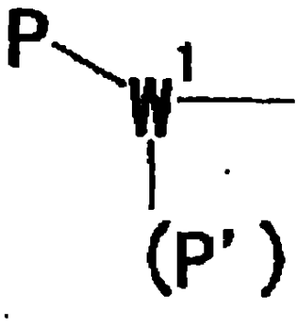
V' represents a group represented by formula:



a group represented by formula:



or a group represented by formula:



n represents 0 or 1;

W^1 represents N, CH or O (provided that W^1 is N or CH, n represents 1, and when W^1 is O, n represents 0);

W^2 represents N or CH;

Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group;

Z^2, Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

R^1 represents (1) hydrogen atom, (2) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group, (3) a cyclic or linear C_{1-10} alkyl group or (4) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (5) an optionally substituted aromatic cyclic group;

R^2 represents (1) hydrogen atom or (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group

and an optionally substituted aromatic cyclic group;

R^3 represents (1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent, (2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent, (3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent, or (4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent;

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group

consisting of carbamoyl group and hydroxyl group, or (3) O;

Y represents a group represented by formula: -CONH-, -CSNH-, -CH_2NH-, -NHCO-, -CH_2O-, -CH_2S-, -COO-, -CSO-, -CH_2CH_2-, or –CH=CH-, which may optionally be substituted with a C_{1-6} alkyl group; and,

Z^9 represents hydrogen atom, O or S; and,

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

(wherein:

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino group, which groups may optionally be substituted with a substituent containing an optionally substituted cyclic group;

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S;

J^3 through J^6 each represents hydrogen atom or a C_{1-3} alkyl group;

Q^3 through Q^6 each represents a C_{1-4} alkyl group, which may optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused cyclic group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7,

(6) an optionally substituted non-aromatic heterocyclic group having

carbon atoms not greater than 7,

(7) an optionally substituted amino group,

(8) an optionally substituted guanidino group,

(9) an optionally substituted hydroxyl group,

(10) an optionally substituted carboxyl group,

(11) an optionally substituted carbamoyl group, and

(12) an optionally substituted sulfhydryl group,

or hydrogen atom;

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5 or J^6 and Q^6 may be combined together, or, Z^1 and R^1, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, or Y^3 and Q^6 may be combined together, to form a ring;

Y^1 through Y^3 each represents a group represented by formula: -CON(J^{13})-, -CSN(J^{13})-, -C(J^{14})N(J^{13})- or -N(J^{13})CO- (wherein J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group); and,

Z^{10} represents hydrogen atom, O or S);

(4) a group represented by formula:

J^1-J^2-C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})-

(wherein:

J^1 and J^2, each has the same significance as defined above;

J^7 through J^9 have the same significance as for J^3;

Q^7 through Q^9 have the same significance as for Q^3;

Y^2 and Y^3 each has the same significance as defined above;

Z^{10} has the same significance as defined above;

J^7 and Q^7, J^8 and Q^8 or J^9 and Q^9 may be combined together, or, J^2 and Q^7, Y^2 and Q^8 or Y^3 and Q^9 may be combined together, to form a ring);

(5) a group represented by formula:

J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})-

(wherein:

J^1 and J^2 have the same significance as defined above represents;

J^{10} and J^{11} have the same significance as for J^3;

Q^{10} and Q^{11} have the same significance as for Q^3;

Y^3 has the same significance as defined above;

Z^{10} has the same significance as defined above; and,

J^{10} and Q^{10} or J^{11} and Q^{11} may be combined together, or J^2 and Q^{10} or Y^3 and Q^{11} may be combined together, to form a ring);

(6) a group represented by formula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(wherein;

J^1 and J^2 have the same significance as defined above;

J^{12} has the same significance as for J^3;

Q^{12} has the same significance as for Q^3;

Z^{10} has the same significance as defined above; and

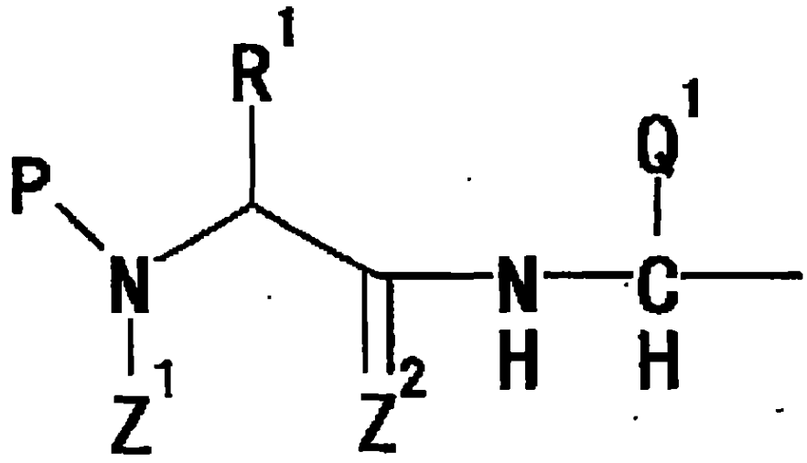
J^{12} and Q^{12} may be combined together, or J^2 and Q^{12} may be combined together, to form a ring); or,

(7) a group represented by formula:

J^1- (wherein J^1 has the same significance as defined above)] or a salt thereof, or a prodrug thereof.

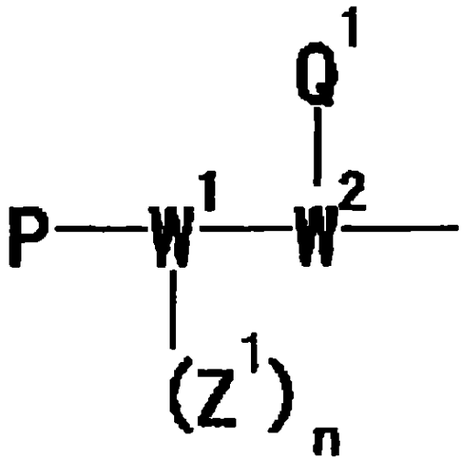
34. The agent according to claim 33, wherein the metastin derivative (III) is the metastin derivative (II) according to claim 1.

35. The agent according to claim 33, wherein V' is a group represented by formula:



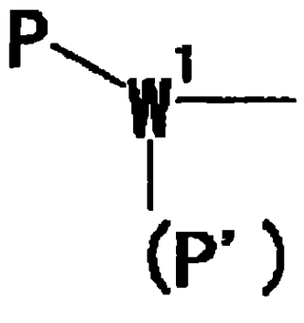
(wherein each symbol has the same significance as defined in claim 33).

36. The agent according to claim 33, wherein V' is a group represented by formula:



(wherein each symbol has the same significance as defined in claim 33).

37. The agent according to claim 33, wherein V' is a group represented by formula:



(wherein each symbol has the same significance as defined in claim 33).

38. The agent according to claims 33 to 37, which is a down-regulating agent for gonadotropic hormone or sex hormone.

39. The agent according to claims 33 to 37, which is a down-regulating agent for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9.

40. The agent according to claims 33 to 39, which is an agent for preventing or treating hormone-dependent cancer.

41. A method for suppressing gonadotropic hormone secretion or suppressing sex hormone secretion, which comprises administering to a mammal an effective dose of the metastin derivative (III) according to claim 33 or a salt thereof, or a prodrug thereof.

42. A method for down regulating gonadotropic hormone or sex hormone, which comprises administering to a mammal an effective dose of the metastin

derivative according to claim 33 or a salt thereof, or a prodrug thereof.

43. A method for down regulating human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9, which comprises administering to a mammal an effective dose of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof.

44. A method for preventing or treating hormone-dependent cancer, which comprises administering to a mammal an effective dose of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof.

45. Use of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof to manufacture an agent for suppressing gonadotropic hormone secretion or an agent for suppressing sex hormone secretion.

46. Use of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof to manufacture a down-regulating agent for gonadotropic hormone or sex hormone.

47. Use of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof to manufacture a down-regulating agent for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9.

48. Use of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating hormone-dependent cancer.

49. A metastin derivative represented by formula:

XX0-XX2-XX3-XX4-XX5-XX6-AzaGly-XX8-XX9-XX10-NH_2

(wherein :

XX0 represents formyl, C_{1-6} alkanoyl, cyclopropanecarbonyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 4-(D-arginylamino)butyryl, 3-(4-Hydroxyphenyl)propionyl, glycyl, tyrosyl, acetylglycyl, acetyltyrosyl, D-tyrosyl, acetyl-D-tyrosyl, pyroglutamyl, 3-(pyridine-3-yl)propionyl, adipoyl or 6-aminocaproyl;

XX2 represents Tyr, D-Tyr, D-Ala, D-Leu, D-Phe, D-Lys, D-Trp or bond arm;

XX3 represents Trp, Pro, 4-pyridylalanine, Tic, D-Trp, D-Ala, D-Leu, D-Phe, D-Lys, D-Glu, D-2-pyridylalanine, D-3-pyridylalanine or D-4-pyridylalanine;

XX4 represents Asn, 2-amino-3-ureidopropion acid, N^{β}-formyldiaminopropionic acid or N^{β}-acetyldiaminopropionic acid;

XX5 represents Ser, Thr or Val;

XX6 represents Phe, Tyr, Trp, Tyr(Me), Thi, Nal(2), Cha, 4- pyridylalanine or

4-fluorophenylalanine;

AzaGly represents azaglycine;

XX8 represents Leu, Nva or Val;

XX9 represents Arg, Orn, Arg(Me) or Arg(symMe2);

XX10 represents Phe, Trp, 2-naphthylalanine, 2-thienylalanine, tyrosine or 4-fluorophenylalanine), or a salt thereof.

50. D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 305),
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 385),
D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 501),
Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 509),
D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 512),
Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 516),
D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 540),
D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 541),
Benzoyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 545),
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-PheΨ(CSNH)NH_2 (Compound No. 548),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 550),
Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),
D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 552),
D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 553),
D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 555),
Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558),
3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 559),
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562),
Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 564),

Cyclopropanecarbonyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 566),
Butyryl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 567),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571),
Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579),
Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 580),
Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 584),
Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2 (Compound No. 590),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2 (Compound No. 591),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2 (Compound No, 599),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2 (Compound No. 600),
Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 602),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(symMe2)-Trp-NH_2 (Compound No. 608),
For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612),
Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613),
Ac-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 615),
Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 616),
Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 617),
Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618),
Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 621),
Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 623),
Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 625),
Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 626),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627),
Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 629),
Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 630),
Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 635),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637),
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2 (Compound No. 642),
Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 648),
Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 649),
D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 650),
Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 651),
pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 652),
Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 657),
Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658),
Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660),
Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 662),
Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663),
Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 666),
Hexanoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 667),
3-Pyridinepropionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 670),
Adipoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 671),
Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 672),
6-Aminocaproyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 674), or salts thereof.

51. Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compound No. 550),
Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),
D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 552),
Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558),
3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 559),
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571),
Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579),
Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592),
For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612),
Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613),
Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618),
Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637),
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638),
Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658),
Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660),
Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663),
or salts thereof.

52. A method of enhancing blood stability, which comprises introducing one or two alkyl groups into the side chain of Arg in the Arg-containing peptide.

53. A method of enhancing blood stability, which comprises introducing one alkyl group into the side chain of Arg in the Arg-containing peptide.

54. A method of enhancing blood stability, which comprises converting the side chain of Arg in the Arg-containing peptide to N^{ω}-alkylated Arg.

55. The method according to claims 52 through 54, wherein an alkyl group is a C_{1-4} alkyl group.

56. The method according to claims 52 through 54, wherein an alkyl group is a methyl group.

57. The method according to claims 52 through 54, wherein an Arg-containing peptide is a peptide having a partial peptide characterized by the structure -Arg-XXX-, wherein XXX represents an amino acid having optionally substituted aromatic ring group into the side chain.

58. The method according to claim 57, wherein XXX is Phe, Trp or Tyr.

FIG 1

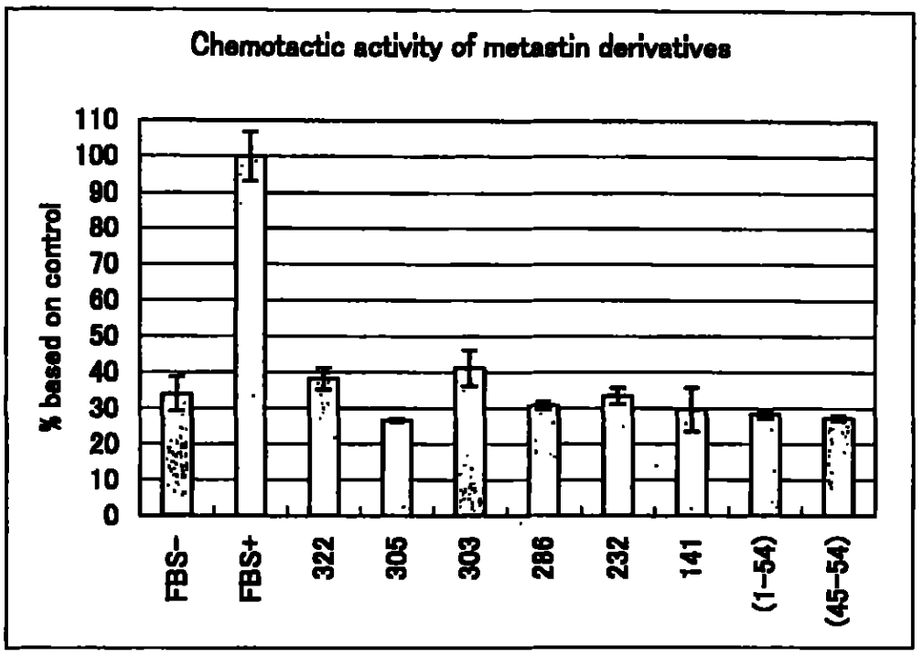

Chemotactic activity of metastin derivatives
% based on control
110
100
90
80
70
60
50
40
30
20
10
0
FBS−
FBS+
322
305
303
286
232
141
(1−54)
(45−54)

FIG 8

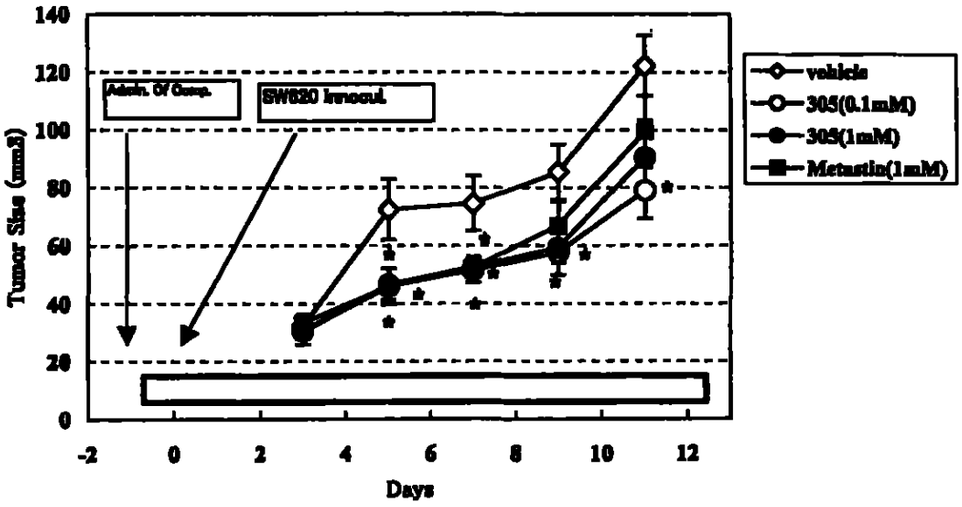

140
120
100
80
60
40
20
0
Tumor Size (mm2)
-2
0
2
4
6
8
10
12
Days
Admin. of Comp.
SW620 Inocul.
vehicle
305(0.1mM)
305(1mM)
Metastin(1mM)

FIG 5

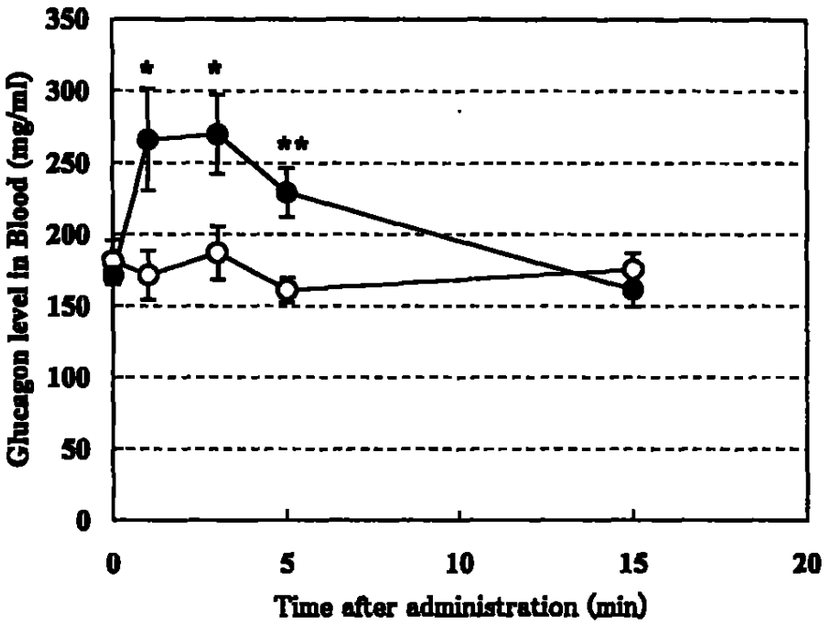

350
300
250
200
150
100
50
0
Glucagon level in Blood (mg/ml)
*
*
**
0
5
10
15
20
Time after administration (min)

FIG 7

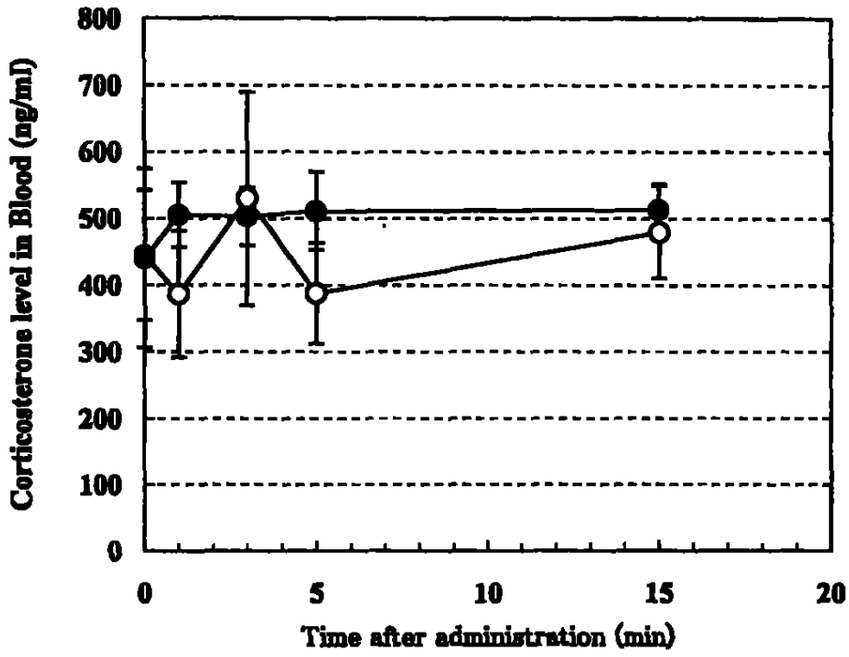

Corticosterone level in Blood (ng/ml)
800
700
600
500
400
300
200
100
0
0
5
10
15
20
Time after administration (min)

FIG 9

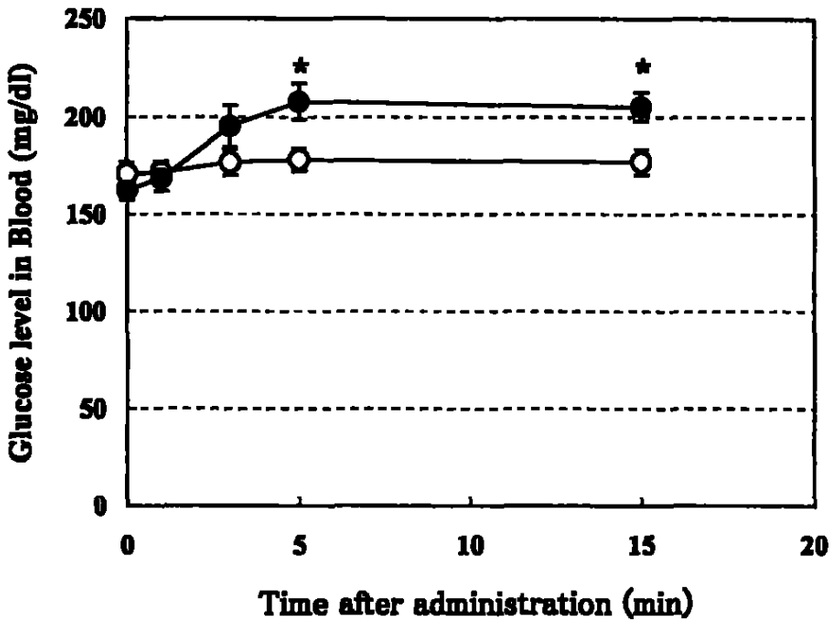

250
200
150
100
50
0
Glucose level in Blood (mg/dl)
0
5
10
15
20
Time after administration (min)
*
*

FIG 11

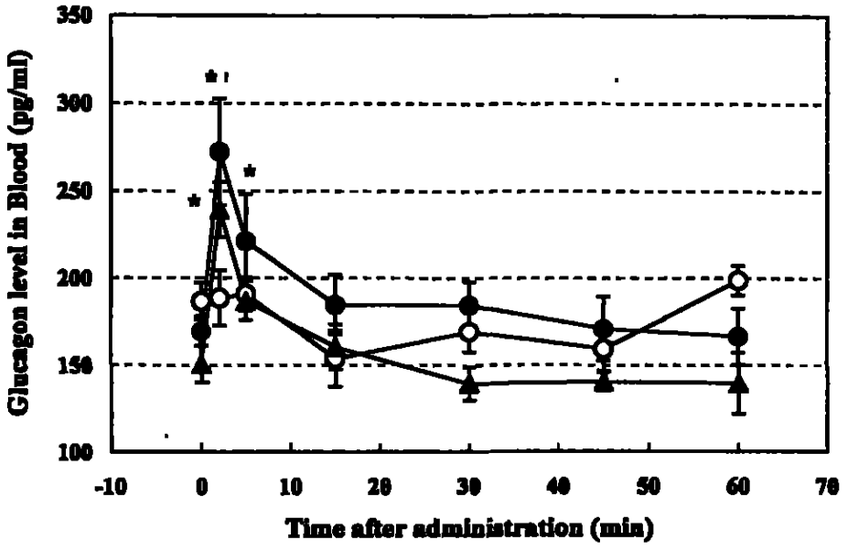

Glucagon level in Blood (pg/ml)
350
300
250
200
150
100
-10
0
10
20
30
40
50
60
70
Time after administration (min)

FIG 13

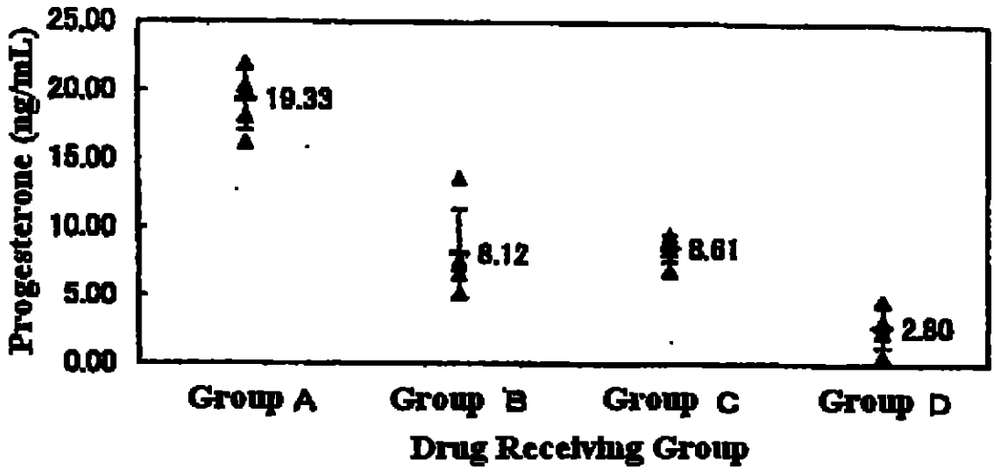

25.00
20.00
15.00
10.00
5.00
0.00
Progesterone (ng/mL)
19.39
8.12
8.61
2.80
Group A
Group B
Group C
Group D
Drug Receiving Group

FIG 15

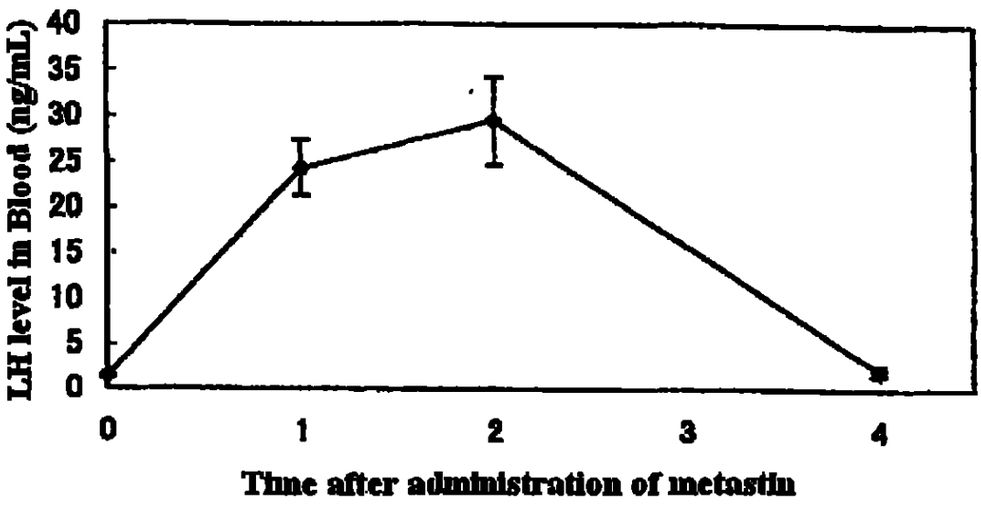

LH level in Blood (ng/mL)
40
35
30
25
20
15
10
5
0
0
1
2
3
4
Time after administration of metastin

FIG 17

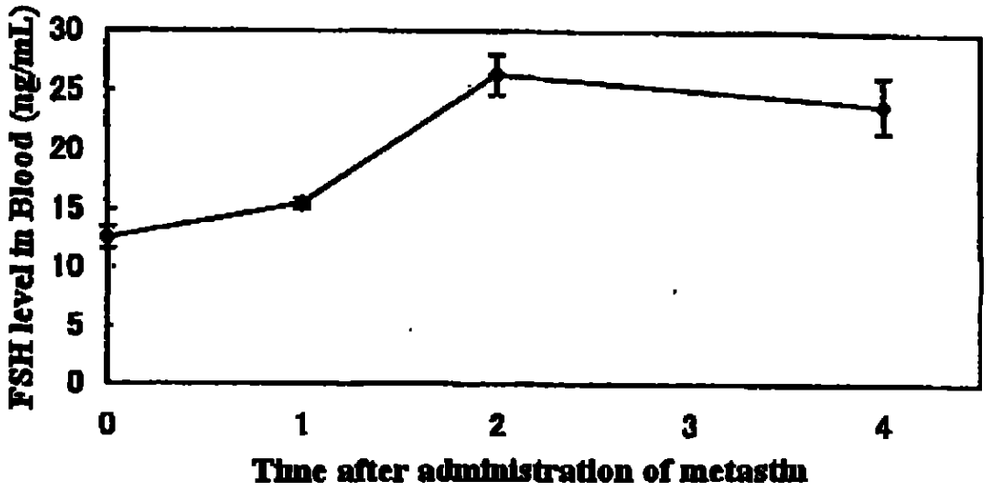

FSH level in Blood (ng/mL)
30
25
20
15
10
5
0
0
1
2
3
4
Time after administration of metastin

FIG 19

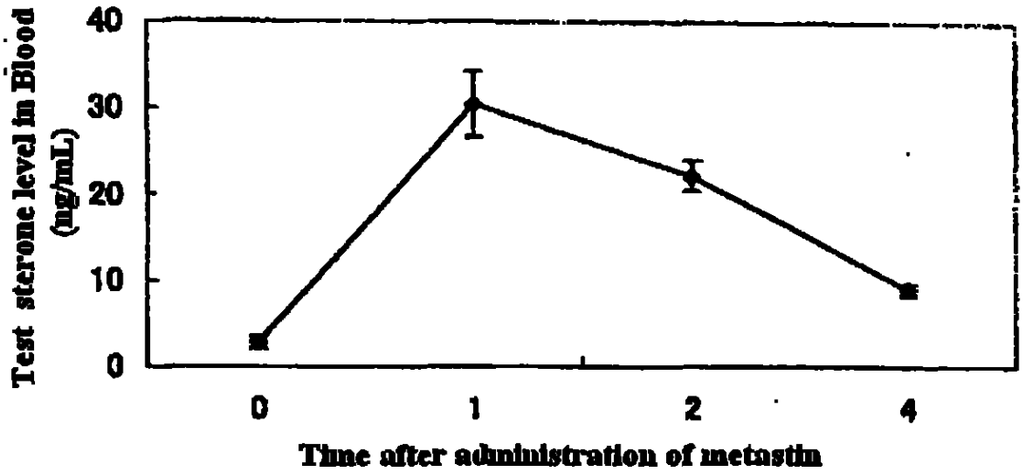
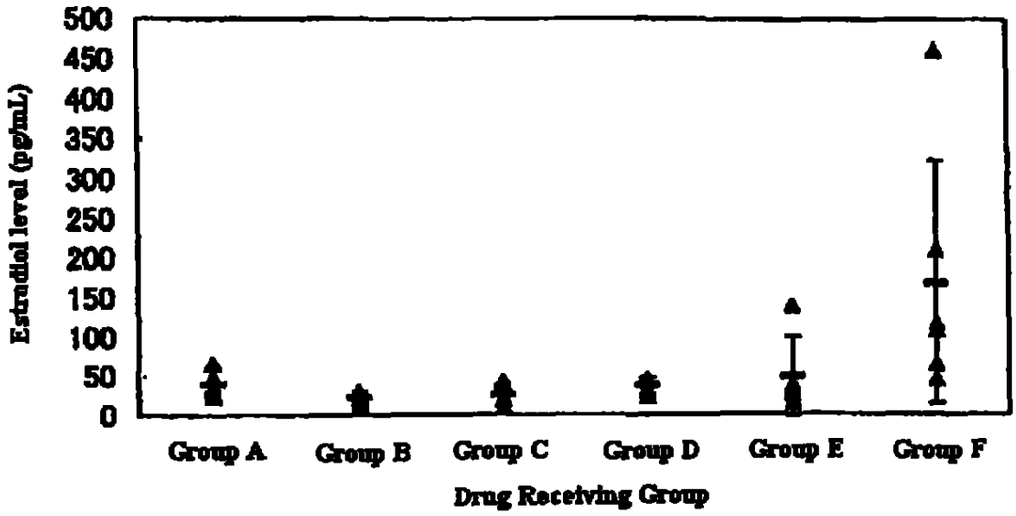

Test sterone level in Blood (ng/mL)
40
30
20
10
0
0
1
2
4
Time after administration of metastin

FIG 21


Estradiol level (pg/mL)
500
450
400
350
300
250
200
150
100
50
0
Group A
Group B
Group C
Group D
Group E
Group F
Drug Receiving Group

181
182

SEQUENCE LISTING

<110> Takeda Pharmaceutical Company, Ltd.

<120> Metastin Derivatives And Use Thereof

<130> PCT05-0008

<150> JP 2004-187671
<151> 2004-06-25

<160> 22

<210> 1
<211> 54
<212> PRT
<213> Homo sapiens

<400> 1
Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln
1 5 10 15
Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly
20 25 30
Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn
35 40 45
Ser Phe Gly Leu Arg Phe
50

<210> 2
<211> 162
<212> DNA
<213> Homo sapiens

<400> 2
ggtacttctc tgtctccgcc gccggaatct tctggttctc gtcagcagcc gggtctgtct 60
gctccgcact ctcgtcagat cccggctccg cagggtgctg ttctggttca gcgtgaaaaa 120
gacctgccga actacaactg gaactctttc ggtctgcgtt tc 162

ggaccccagg aactcgttaa tgcctgggaa aaggaatcgc ggtatgcaga gagcaagcct 240
gggtctgcag ggctgcgcgc tcgtaggtcg tcgccatgcc cgccggttga gggccccgcg 300
gggcgccagc ggcccctgtg tgcctcccgc agtcgcctga tccctgcgcc ccgcggagcg 360
gtgctggtgc agcgggagaa ggacctgtcc acctacaact ggaactcctt cggcctgcgc 420
tacggcagga ggcaggcggc gcggggcagca cggggc 456

<210> 5
<211> 156
<212> PRT
<213> Mus musculus

<400> 5

Met	Tyr	Leu	Arg	Phe	Gly	Val	Asp	Val	Cys	Ser	Leu	Ser	Pro	Trp	Lys
				5					10					15	
Glu	Thr	Val	Asp	Leu	Pro	Leu	Pro	Pro	Arg	Met	Ile	Ser	Met	Ala	Ser
			20					25					30		
Trp	Gln	Leu	Leu	Leu	Leu	Leu	Cys	Val	Ala	Thr	Tyr	Gly	Glu	Pro	Leu
		35					40					45			
Ala	Lys	Val	Ala	Pro	Leu	Val	Lys	Pro	Gly	Ser	Thr	Gly	Gln	Gln	Ser
	50					55					60				
Gly	Pro	Gln	Glu	Leu	Val	Asn	Ala	Trp	Glu	Lys	Glu	Ser	Arg	Tyr	Ala
65					70					75					80
Glu	Ser	Lys	Pro	Gly	Ser	Ala	Gly	Leu	Arg	Ala	Arg	Arg	Ser	Ser	Pro
				85					90					95	
Cys	Pro	Pro	Val	Glu	Gly	Pro	Ala	Gly	Arg	Gln	Arg	Pro	Leu	Cys	Ala
			100					105					110		
Ser	Arg	Ser	Arg	Leu	Ile	Pro	Ala	Pro	Arg	Gly	Ala	Val	Leu	Val	Gln
		115					120					125			
Arg	Glu	Lys	Asp	Leu	Ser	Thr	Tyr	Asn	Trp	Asn	Ser	Phe	Gly	Leu	Arg
	130					135					140				
Tyr	Gly	Arg	Arg	Gln	Ala	Ala	Arg	Ala	Ala	Arg	Gly				
145					150					155					

<210> 6
<211> 468
<212> DNA
<213> Mus musculus

<211> 390
<212> DNA
<213> Rattus sp.

<400> 8
atgacctcgc tggcttcttg gcagctgctg cttctcctct gtgtggcctc ttttggggag 60
ccactggcaa aaatggcacc tgtggtgaac cctgaaccca caggccaaca gtccggaccc 120
caggaactcg ttaatgcctg gcaaaagggc ccgcggtatg cagagagcaa gcctggggct 180
gcaggactgc gcgctcgccg aacatcgcca tgcccgccgg tggagaaccc cacggggcac 240
cagcggcccc cgtgtgccac ccgcagtcgc ctgatccctg cgccccgcgg atcggtgctg 300
gtgcagcgcg agaaggacat gtcagcctac aactggaact ccttttggcct gcgctacggc 360
aggaggcagg tggcgcgggc ggcacggggc 390

<210> 9
<211> 398
<212> PRT
<213> Homo sapiens

<400> 9
Met His Thr Val Ala Thr Ser Gly Pro Asn Ala Ser Trp Gly Ala Pro
1 5 10 15
Ala Asn Ala Ser Gly Cys Pro Gly Cys Gly Ala Asn Ala Ser Asp Gly
20 25 30
Pro Val Pro Ser Pro Arg Ala Val Asp Ala Trp Leu Val Pro Leu Phe
35 40 45
Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
50 55 60
Tyr Val Ile Cys Arg His Lys Pro Met Arg Thr Val Thr Asn Phe Tyr
65 70 75 80
Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val
85 90 95
Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Gly Trp Val Leu Gly Asp
100 105 110
Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala
115 120 125
Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr
130 135 140

<400> 10

atgcacaccg tggctacgtc cggacccaac gcgtcctggg gggcaccggc caacgcctcc 60
ggctgcccgg gctgtggcgc caacgcctcg gacggcccag tcccttcgcc gcgggccgtg 120
gacgcctggc tcgtgccgct cttcttcgcg gcgctgatgc tgctgggcct ggtggggaac 180
tcgctggtca tctacgtcat ctgccgccac aagccgatgc ggaccgtgac caacttctac 240
atcgccaacc tggcggccac ggacgtgacc ttcctcctgt gctgcgtccc cttcacggcc 300
ctgctgtacc cgctgcccgg ctgggtgctg ggcgacttca tgtgcaagtt cgtcaactac 360
atccagcagg tctcggtgca ggccacgtgt gccactctga ccgccatgag tgtggaccgc 420
tggtacgtga cggtgttccc gttgcgcgcc ctgcaccgcc gcacgccccg cctggcgctg 480
gctgtcagcc tcagcatctg ggtaggctct gcggcggtgt ctgcgccggt gctcgccctg 540
caccgcctgt cacccgggcc gcgcgcctac tgcagtgagg ccttccccag ccgcgccctg 600
gagcgcgcct tcgcactgta caacctgctg gcgctgtacc tgctgccgct gctcgccacc 660
tgcgcctgct atgcggccat gctgcgccac ctgggccggg tcgccgtgcg ccccgcgccc 720
gccgatagcg ccctgcaggg gcaggtgctg gcagagcgcg caggcgccgt gcgggccaag 780
gtctcgcggc tggtggcggc cgtggtcctg ctcttcgccg cctgctgggg ccccatccag 840
ctgttcctgg tgctgcaggc gctgggcccc gcggggctcc tggcacccacg cagctacgcc 900
gcctacgcgc ttaagacctg ggctcactgc atgtcctaca gcaactccgc gctgaacccg 960
ctgctctacg ccttcctggg ctcgcactic cgacaggcct tccgccgcgt ctgccccctgc 1020
gcgccgcgcc gccccccgccg ccccccgccgg cccggaccct cggaccccgc agccccacac 1080
gcggagctgc accgcctggg gtcccacccg gccccccgcca gggcgcagaa gccaggggagc 1140
agtgggctgg ccgcgcgcgg gctgtgcgtc ctgggggagg acaacgcccc tctc 1194

<210> 11
<211> 396
<212> PRT
<213> Rattus sp.

<400> 11

Met Ala Ala Glu Ala Thr Leu Gly Pro Asn Val Ser Trp Trp Ala Pro
1 5 10 15
Ser Asn Ala Ser Gly Cys Pro Gly Cys Gly Val Asn Ala Ser Asp Gly
20 25 30
Pro Gly Ser Ala Pro Arg Pro Leu Asp Ala Trp Leu Val Pro Leu Phe
35 40 45
Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
50 55 60

185
186

355 360 365

His Pro Val Arg Val Arg Thr Pro Glu Pro Gly Asn Pro Val Val Arg

370 375 380

Ser Pro Ser Val Gln Asp Glu His Thr Ala Pro Leu

385 390 395

<210> 12

<211> 1188

<212> DNA

<213> Rattus sp.

<400> 12

atggccgcag aggcgacgtt gggtccgaac gtgagctggt gggctccgtc caacgcttcg 60

ggatgcccgg gctgcggtgt caatgcctcg gatggcccag gctccgcgcc aaggccccig 120

gatgcctggc tggtgcccct gttttcgct gccctaatgt tgctggggct agtcgggaac 180

tcactggtca tcttcgttat ctgccgccac aagcacatgc agaccgtcac caatttctac 240

atcgctaacc tggcggccac agatgtcact ttccttctgt gctgcgtacc cttcaccgcg 300

ctcctctatc cgctgcccac ctgggtgctg ggagacttca tgtgcaaatt cgtcaactac 360

atccagcagg tctcggtgca agccacatgt gccacttiga cagccatgag tgtggaccgc 420

tggtacgtga ctgtgticcc gctgcgtgca cttcaccgcc gcactccgcg cctggccctg 480

actgtcagcc ttagcatctg ggtgggttcc gcagctgttt ccgccccggt gctggctctg 540

caccgcctgt cgcccgggcc tcacacctac tgcagtgagg cgtttcccag ccgtgccctg 600

gagcgcgctt tcgcgctcta caacctgctg gccctatacc tgctgccgct gctcgccacc 660

tgcgcctgct acggtgccat gctgcgccac ctgggccgcg ccgctgtacg ccccgcaccc 720

actgatggcg ccctgcaggg gcagctgcta gcacagcgcg ctggagcagt gcgcaccaag 780

gtctcccggc tggtggccgc tgtcgtcctg ctcttcgccg cctgctgggg cccgatccag 840

ctgttcctgg tgcttcaagc cctgggcccc tcgggggcct ggcaccctcg aagctatgcc 900

gcctacgcgc tcaagatctg ggctcactgc atgtcctaca gcaattctgc gctcaacccg 960

ctgctctatg ccttcciggg ttcccactic agacaggcct tctgccgcgt gtgcccctgc 1020

ggcccgcaac gccagcgtcg gccccacgcg tcagcgcact cggaccgagc cgcaccccat 1080

agtgtgccgc acagccgggc tgcgcaccct gtccgggtca ggacccccga gcctgggaac 1140

cctgtggtgc gctcgccctc tgttcaggat gaacacactg ccccactc 1188

<210> 13

<211> 396

<212> PRT

<213> Mus musculus

275 280 285
Gly Pro Ser Gly Ala Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Val
290 295 300
Lys Ile Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro
305 310 315 320
Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Cys Arg
325 330 335
Val Cys Pro Cys Cys Arg Gln Arg Gln Arg Arg Pro His Thr Ser Ala
340 345 350
His Ser Asp Arg Ala Ala Thr His Thr Val Pro His Ser Arg Ala Ala
355 360 365
His Pro Val Arg Ile Arg Ser Pro Glu Pro Gly Asn Pro Val Val Arg
370 375 380
Ser Pro Cys Ala Gln Ser Glu Arg Thr Ala Ser Leu
385 390 395

<210> 14
<211> 1188
<212> DNA
<213> Mus musculus

<400> 14
atggccaccg aggcgacatt ggctcccaat gtgacctggt gggctccgtc caacgcttca 60
ggatgcccag gctgcggtgt caacgcctcg gatgacccag gctctgcgcc aaggcccctg 120
gatgcctggc tggttcccct gttttcgct acactcatgt tgcttgggct ggtcggaaac 180
tcattggtca tctacgttat ctgccgccac aagcacatgc agacagttac caacttctac 240
atcgctaacc tggctgccac agacgtcact ttcctactgt gctgcgtgcc cttcaccgca 300
ctcctctacc cgctgcccgc ctgggtgctg ggagacttca tgtgcaaatt cgtcaactac 360
atccagcagg tctcggtgca agccacatgt gccactctga cggccatgag tgtggaccgc 420
tggtatgtga ctgtgttccc gctgcgtgca cttcaccgcc gcactccgcg cctggccctg 480
gctgtcagcc tcagcatctg ggtggggtca gcagctgtgt ccgcccccgt gctggccctg 540
caccgcctgt cgccagggcc tcgcacctac tgcagcgagg cgtttcccag ccgcgccctg 600
gagcgcgcct tcgcgctcta caacctgctg gctctatatc tgctgccgct gctcgccacc 660
tgcgcctgct acggcgccat gctgcgccac ctgggccgtg cggctgtacg ccccgcaccc 720
actgacggcg ccctgcaggg acagctgcta gcacagcgcg ccggagcagt gcgcaccaag 780
gtctcccggc tggtggccgc tgtcgtcctg ctcttcgccg cctgctgggg cccgatccag 840
ctgttcctgg tgcttcaagc cctgggcccc tcgggggcct ggcacccctg aagctatgcc 900

<400> 17
Asn Trp Asn Ser Phe Gly Leu Arg Phe
1 5 9

<210> 18
<211> 8
<212> PRT
<213> Artificial

<220>
<223> the C-terminus of the polypeptide is amide (-CONH2) form

<400> 18
Trp Asn Ser Phe Gly Leu Arg Phe
1 5 8

<210> 19
<211> 45
<212> DNA
<213> Homo sapiens

<400> 19
aaggacctgc cgaactacaa ctggaacicc ticggcctgc gcttc 45

<210> 20
<211> 30
<212> DNA
<213> Homo sapiens

<400> 20
tacaactgga actccticgg cctgcgcttc 30

<210> 21
<211> 27
<212> DNA
<213> Homo sapiens

1465611 0054
DIC 25

188
189

DERIVADOS DE METASTINA Y UTILIZACIÓN DE LOS MISMOS

CAMPO TÉCNICO

La presente invención se refiere a los derivados de metastina y la utilización de los mismos.

ANTECEDENTES TÉCNICOS

Es conocida la metastina derivada del ser humano (también denominado péptido KiSS-1) (WO 00/24890) y la metastina derivada de rata o ratón (WO 01/75104). También, son conocidas las preparaciones de liberación prolongada que contienen metastina (WO 02/85399).

Según informes, la metastina tiene el efecto de suprimir la metástasis del cáncer y por consiguiente es eficaz para prevenir o tratar cánceres (por ejemplo, cáncer pulmonar, cáncer gástrico, cáncer hepático, cáncer pancreático, cáncer colorectal, cáncer rectal, cáncer colónico, cáncer de próstata, cáncer ovárico, cáncer cervical, cáncer de pecho, cáncer renal, cáncer de vejiga, tumor cerebral, etc.); la metastina también tiene el efecto de controlar la función pancreática y es eficaz para prevenir o tratar las enfermedades pancreáticas (por ejemplo, pancreatitis aguda o crónica, cáncer pancreático, etc.); y la metastina además tiene el efecto de controlar el funcionamiento de placenta y es eficaz para prevenir o tratar coriocarcinoma, mola hidatídica, mola invasiva, aborto, hipoplasia fetal, metabolismo de glucosa anormal, metabolismo de lípido anormal o parto anormal (WO 00/24890; WO 01/75104; WO 02/85399).

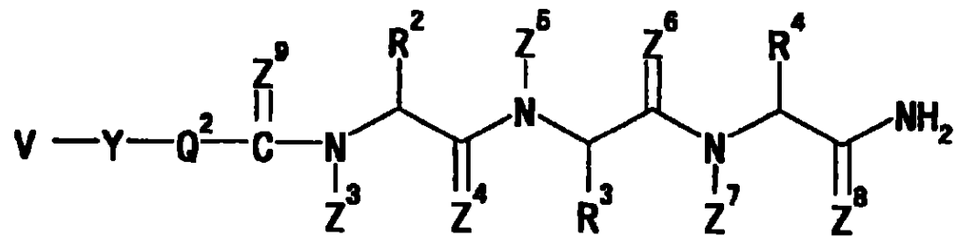
DESCRIPCIÓN DE LA INVENCIÓN

La presente invención plantea proveer derivados de metastina estables que poseen excelentes actividades biológicas (actividad que suprime la metástasis de cáncer, actividad que suprime el crecimiento del cáncer, etc.).

Los presentes inventores han realizado extensos estudios para resolver los problemas anteriores y como resultado, han encontrado que modificando los aminoácidos que constituyen la metastina con un grupo modificador específico, inesperadamente el derivado de metastina demuestra una estabilidad en sangre mejorada, etc., en comparación a la metastina natural y además exhibe una excelente actividad supresora de metástasis de cáncer o actividad supresora de crecimiento de cáncer. Los presentes inventores inesperadamente han encontrado además que estos derivados de metastina tienen el efecto de suprimir la secreción de hormona gonadotrópica, el efecto de suprimir la secreción de hormona del sexo, etc., lo cual es totalmente diferente de los efectos conocidos hasta ahora. Basados en estos hallazgos, los presentes inventores han continuado investigaciones adicionales y han realizado la presente invención.

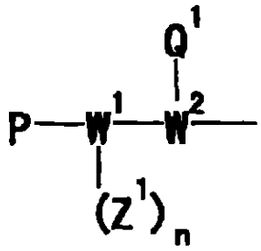
Es decir, la presente invención provee las siguientes características y actividades.

(1) Un derivado de metastina (II) representado por la fórmula:

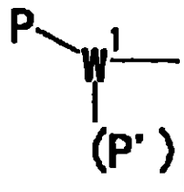


[en donde;

V representa un grupo representado por la fórmula:



o un grupo representado por la fórmula:



n representa 0 ó 1;

W^1 representa N, CH ó O (con la condición que cuando W^1 es N ó CH, n representa 1 y cuando W^1 es O, n representa 0);

W^2 representa N ó CH;

Z^1, Z^3, Z^5 y Z^7 cada uno representa un átomo de hidrógeno o un grupo alquilo C_{1-3};

Z^4, Z^6 y Z^8 cada uno representa átomo de hidrógeno, O ó S;

R^2 representa (1) átomo de hidrógeno ó (2) un grupo alquilo C_{1-10} cíclico o lineal, o (3) un grupo alquilo C_{1-10} que consiste de un grupo alquilo cíclico y un grupo de

alquilo lineal, o (4) un grupo alquilo C_{1-8} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo y un grupo cíclico aromático opcionalmente sustituido;

R^3 representa (1) un grupo alquilo C_{1-8} que posee un grupo básico opcionalmente sustituido y opcionalmente posee un sustituyente adicional, (2) un grupo aralquilo que posee un grupo básico opcionalmente sustituido y opcionalmente posee un sustituyente adicional, (3) un grupo alquilo C_{1-4} que tiene un grupo hidrocarburo cíclico no aromático de cantidad de átomos de carbono no mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional, o (4) un grupo alquilo C_{1-4} que tiene un grupo heterocíclico no aromático de cantidad de átomos de carbono no mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional;

R^4 representa un grupo alquilo C_{1-4}, el cual puede ser opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de (1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido, (2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (3) un

grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido, (4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, y (6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

Q^1 representa un grupo alquilo C_{1-4} que puede ser opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de (1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido, (2) un grupo heterocíclico aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido, (4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, y (6)

un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

Q^2 representa (1) CH_2 que puede ser opcionalmente sustituido con un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, (2) NH, el cual puede ser opcionalmente sustituido con un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, o (3) O;

Y representa un grupo representado por la fórmula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, ó -CH=CH-, que puede ser opcionalmente sustituido con un grupo alquilo C_{1-6}; y,

Z^9 representa átomo de hidrógeno, O ó S; y,

P y P', los cuales pueden ser iguales o diferentes, cada uno puede formar un anillo combinando P y P' ó P y Q^1 juntos representan:

(1) átomo de hidrógeno;

(2) un residuo de aminoácido opcional limitado de manera continua o discontinua de la terminal C de la secuencia de aminoácido 1-48 en la secuencia de aminoácido representada por SEQ ID NO: 1;

(3) un grupo representado por la fórmula:

$J^1-J^2-C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})-$

(en donde:

J^1 representa (a) átomo de hidrógeno o (b) (i) un grupo acilo C_{1-15}, (ii) un grupo alquilo C_{1-15}, (iii) un grupo arilo C_{6-14}, (iv) grupo carbamoilo, (v) grupo carboxilo, (vi) grupo sulfino, (vii) grupo amidino, (viii) grupo glioxiloilo o (ix) grupo amino, cuuos grupos pueden ser opcionalmente sustituidos con un sustituyente que contiene de un grupo cíclico opcionalmente sustituido;

J^2 representa (1) NH opcionalmente sustituido con un grupo alquilo C_{1-6}, (2) CH_2 opcionalmente sustituido con un grupo alquilo C_{1-6}, (3) O ó (4) S;

J^3 a J^6 representa átomo de hidrógeno o un grupo alquilo C_{1-3};

Q^3 a Q^6 representa un grupo alquilo C_{1-4} el cual puede tener un sustituyente opcionalmente seleccionado del grupo que consiste de:

(1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido,

(2) un grupo heterocíclico aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre,

(3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido,

(4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del

grupo que consiste de átomos de nitrógeno, oxígeno y azufre,

(5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7,

(6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7,

(7) un grupo amino opcionalmente sustituido,

(8) un grupo guanidino opcionalmente sustituido,

(9) un grupo hidroxilo opcionalmente sustituido,

(10) un grupo carboxilo opcionalmente sustituidos,

(11) un grupo carbamoilo opcionalmente sustituido, y

(12) un grupo sulfhidrilo opcionalmente sustituido,

o átomo de hidrógeno.;

Pueden combinarse entre sí J^3 y Q^3, J^4 y Q^4, J^5 y Q^5 ó J^6 y Q^6 juntos, o, pueden combinarse J^2 y Q^3, Y^1 y Q^4, Y^2 y Q^5, ó Y^3 y Q^6, para formar un anillo;

Y^1 a Y^3 representa un grupo representado por la fórmula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ ó $-N(J^{13})CO-$ (en donde J^{13} y J^{14} cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3}); y,

Z^{10} representa átomo de hidrógeno, O ó S);

(4) un grupo representado por la fórmula:

$J^1-J^2-C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})-$

(en donde:

J^1 y J^2, cada uno posee el mismo significado según lo descripto anteriormente;

J^7 a J^9 poseen el mismo significado que para J^3;

Q^7 a Q^9 poseen el mismo significado que para Q^3;

Y^2 y Y^3 cada uno posee el mismo significado según lo descripto anteriormente;

Z^{10} posee el mismo significado según lo descripto anteriormente;

Pueden combinarse entre sí J^7 y Q^7, J^8 y Q^8 ó J^9 y Q^9, ó, pueden combinarse entre sí J^2 y Q^7, Y^2 y Q^8 o Y^3 y Q^9, para formar un anillo);

(5) un grupo representado por la fórmula:

J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})-

(en donde:

J^1 y J^2 poseen el mismo significado según lo descripto anteriormente representa;

J^{10} y J^{11} poseen el mismo significado que para J^3;

Q^{10} y Q^{11} poseen el mismo significado que para Q^3;

Y^3 posee el mismo significado según lo descripto anteriormente;

Z^{10} posee el mismo significado según lo descripto anteriormente; y

Pueden combinarse entre sí J^{10} y Q^{10} ó J^{11} y Q^{11}, o pueden combinarse entre sí J^2 y Q^{10} ó Y^3 y Q^{11}, para formar un anillo);

(6) un grupo representado por la fórmula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(en donde;

J^1 y J^2 poseen el mismo significado según lo descripto anteriormente;

J^{12} posee el mismo significado de J^3;

Q^{12} posee el mismo significado de Q^3;

Z^{10} posee el mismo significado según lo descripto anteriormente; y,

Pueden combinarse entre sí J^{12} y Q^{12}, o pueden combinarse entre sí J^2 y Q^{12}, para formar un anillo); ó,

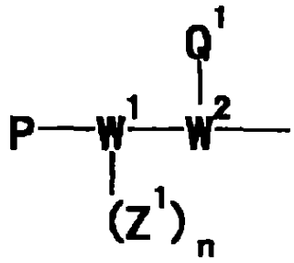
(7) un grupo representado por la fórmula:.

J^1-

(en donde:

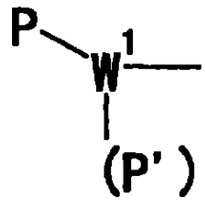
J^1 posee el mismo significado según lo descripto anteriormente)] (con la condición que un péptido que consiste en la secuencia de aminoácido de 1-54, 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54, 41-54, 42-54, 43-54, 44-54, 45-54, 46-54, 47-54, 48-54 ó 49-54 en la secuencia de aminoácido representada por SEQ ID NO.: 1 sea excluida), o una sal del mismo.

(2) Un derivado de metastina (II) de acuerdo con (1), en donde V es un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado como el definido en (1)), o una sal del mismo.

(3) Un derivado de metastina (II) de acuerdo con (1), en donde V es un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado como el definido en (1)), o una sal del mismo.

La presente invención además provee las siguientes características, y así sucesivamente.

(4) Una prodroga del derivado de metastina (II) de acuerdo con (1) o una sal del mismo.

(5) Un compuesto farmacéutico que comprende el derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(6) Un compuesto farmacéutico de acuerdo con (5) el cual es un agente para suprimir la metástasis del cáncer o un agente para suprimir el crecimiento del cáncer.

(7) Un compuesto farmacéutico de acuerdo con (5) el cual es un agente para prevenir o tratar cáncer.

(8) Un compuesto farmacéutico de acuerdo con (5) el cual es un agente por controlar la función pancreática.

(9) Un compuesto farmacéutico de acuerdo con (5) el cual

es un agente para prevenir o tratar pancreatitis aguda o crónica o cáncer pancreático.

(10) Un compuesto farmacéutico de acuerdo con (5) el cual es un agente para controlar la función de placenta.

(11) Un compuesto farmacéutico de acuerdo con (5) el cual es un agente para prevenir o tratar coriocarcinoma, mola hidatídica, mola invasiva, aborto, hipoplasia fetal, metabolismo de glucosa anormal, metabolismo de lípido anormal o inducción a parto.

(12) Un compuesto farmacéutico de acuerdo con (5) el cual es un agente por mejorar la función gonadal.

(13) Un compuesto farmacéutico de acuerdo con (5) el cual es un agente para prevenir o tratar el cáncer dependiente de hormona, infertilidad, endometriosis,, pubertad precoz o mioma de útero.

(14) Un compuesto farmacéutico de acuerdo con (5) el cual es un agente para inducir o estimular la ovulación.

(15) Un compuesto farmacéutico de acuerdo con (5) el cual es agente secretágogo de hormona gonadotrópica o un agente secretagogo de hormona del sexo.

(16) Un compuesto farmacéutico de acuerdo con (5) el cual es un agente para prevenir o tratar la enfermedad de Alzheimer o el deterioro cognoscitivo moderado.

(17) Un método para suprimir metástasis de cáncer o crecimiento de cáncer que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga

del mismo.

(18) Un método para prevenir o tratar cáncer que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(19) Un método por controlar la función pancreática que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(20) Un método para prevenir o tratar pancreatitis aguda o crónico o cáncer pancreático que comprenden administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(21) Un método por controlar el placental funciona que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(22) Un método para prevenir o tratar el choriocarcinoma, mola hidatídica, mola invasiva, aborto, hypoplasia fetal, metabolismo de glucosa anormal, metabolismo de lípido anormal o inducción de parto que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(23) Un método para mejorar la función gonadal que comprende administrar a un mamífero una dosis eficaz del

derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(24) Un método para prevenir o tratar el cáncer dependiente de hormona, infertilidad, endometriosis, pubertad precoz o mioma del útero que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(25) Un método por inducir o estimular ovulación que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(26) Un método para promover la secreción de hormona gonadotrópica o promover la secreción de hormona del sexo que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(27) Un método para prevenir o tratar la enfermedad de Alzheimer o deterioro cognoscitivo moderado que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(28) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para suprimir la metástasis de cáncer o un agente para suprimir el crecimiento del cáncer.

(29) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para prevenir o tratar el cáncer.

(30) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para controlar la función pancreática.

(31) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para prevenir o tratar pancreatitis aguda o crónica o cáncer pancreático.

(32) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para controlar la función placental.

(33) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para prevenir o tratar el coriocarcinoma, mola hidatídica, mola invasiva, aborto, hipoplasia fetal, metabolismo de glucosa anormal, metabolismo de lípido anormal o inducción al parto.

(34) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para mejorar la función gonadal.

(35) Una utilización del derivado de metastina (II) de

acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para prevenir o tratar el cáncer dependiente de hormona, infertilidad, endometriosis, pubertad precoz o mioma de útero.

(36) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para inducir o estimular la ovulación.

(37) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente secretagogo de hormona gonadotrópica o un agente secretagogo de hormona del sexo.

(38) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para prevenir o tratar la enfermedad de Alzheimer o el deterioro cognoscitivo moderado.

(39) Un agente secretagogo de glucagón pancreático que comprende el derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(40) Un agente para promover la formación de orina que comprende el derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(41) Un agente para prevenir o tratar la obesidad, hiperlipidemia, diabetes mellitus tipo II, hipoglucemia, hipertensión, neuropatía diabética, nefropatía diabética,

el retinopatía diabética, edema, perturbaciones urinarias, resistencia a insulina, diabetes inestable, atrofia grasa, la alergia a insulina, insulinoma, arteriosclerosis, desordenes trombóticos o lipotoxicidad, que comprende el derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(42) Un método para promover la secreción del glucagon pancreático que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(43) Un método para promover formación de orina que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

(44) Un método para prevenir o tratar la obesidad, hiperlipidemia, diabetes mellitus tipo II, hipoglucemia, hipertensión, neuropatía diabética, nefropatía diabética, retinopatía diabética, edema, perturbaciones urinarias, resistencia a insulina, diabetes inestable, atrofia grasa, alergia a insulina, insulinoma, arteriosclerosis, desordenes trombóticos o lipotoxicidad que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo.

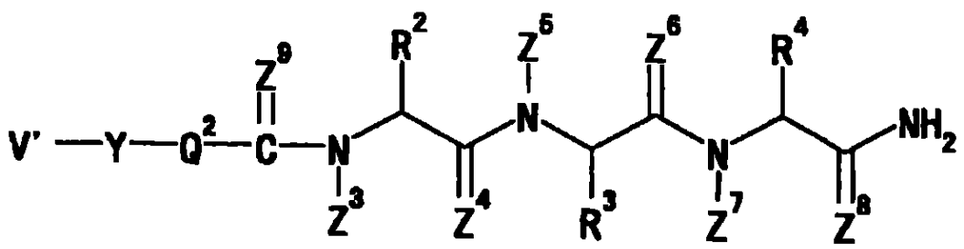
(45) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente secretagogo de glucagón

pancreático.

(46) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para promover la formación de orina.

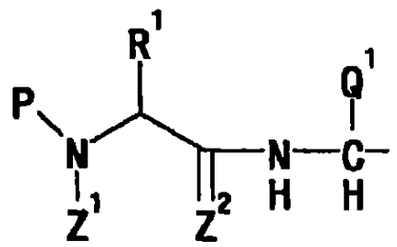
(47) Una utilización del derivado de metastina (II) de acuerdo con (1) o una sal del mismo, o una prodroga del mismo para fabricar un agente para prevenir o tratar obesidad, hiperlipidemia, diabetes mellitus tipo II, hipoglucemia, hipertensión, neuropatía diabética, nefropatía diabética, retinopatía diabética, edema, perturbaciones urinarias, resistencia a insulina, diabetes inestable, atrofia grasa, alergia a insulina, insulinoma, arteriosclerosis, desórdenes trombóticos o lipotoxicidad.

(48) Un agente para suprimir la secreción de hormona gonadotrópica o un agente para suprimir secreción de hormona del sexo que comprende el derivado de metastina (III) representado por la fórmula:

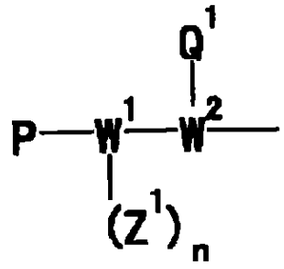


[en donde:

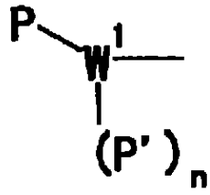
V' representa un grupo representado por la fórmula:



un grupo representado por la fórmula:



o un grupo representado por la fórmula:.



n representa 0 ó 1;

W^1 representa N, CH ó O (con la condición que W^1 es N ó CH, n representa 1, y cuando W^1 es O, n representa 0);

W^2 representa N ó CH;

Z^1, Z^3, Z^5 y Z^7 cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3};

Z^2, Z^4, Z^6 y Z^8 cada uno representa átomo de hidrógeno, O ó S;.

R^1 representa (1) átomo de hidrógeno, (2) un grupo alquilo C_{1-8} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo opcionalmente sustituido y un grupo cíclico aromático opcionalmente sustituido, (3) un grupo alquilo C_{1-10}

lineal o cíclico o (4) un grupo alquilo C_{1-10} que consiste de un grupo alquilo cíclico y un grupo alquilo lineal, o (5) un grupo cíclico aromático opcionalmente sustituido;

R^2 representa (1) átomo de hidrógeno o (2) un grupo alquilo C_{1-10} lineal o cíclico, (3) un grupo alquilo C_{1-10} que consiste en un grupo alquilo cíclico y un grupo alquilo lineal; o (4) un grupo alquilo C_{1-8} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo opcionalmente sustituido y un grupo cíclico aromático opcionalmente sustituido;

R^3 representa (1) un grupo alquilo C_{1-8} que posee un grupo básico opcionalmente sustituido y posee opcionalmente un sustituyente adicional, (2) un grupo aralquilo que posee un grupo básico opcionalmente sustituido y posee opcionalmente un sustituyente adicional, (3) un grupo alquilo C_{1-4} que no tiene un grupo hidrocarburo cíclico no aromático de una cantidad de átomos de carbono no mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional, o (4) un grupo alquilo C_{1-4} que tiene un grupo heterocíclico no aromático de una cantidad de átomos de carbono no mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional;

R^4 representa un grupo alquilo C_{1-4} que puede ser opcionalmente sustituido con un sustituyente seleccionado

del grupo que consiste de (1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido, (2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido, (4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, y (6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;.

Q^1 representa un grupo alquilo C_{1-4} que puede ser opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de (1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido, (2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido, (4) un grupo heterocíclico fusionado

aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, y (6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

Q^2 representa (1) CH_2 que puede ser opcionalmente sustituido con un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, (2) NH que puede ser opcionalmente sustituido con un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, o (3) O; Y representa un grupo representado por la fórmula:

-CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, ó -CH=CH- que puede ser opcionalmente sustituido con un grupo alquilo C_{1-6}; y,

Z^9 representa átomo de hidrógeno, O ó S; y,

P y P', los cuales pueden ser iguales o diferentes, cada uno puede formar un anillo por combinación entre sí de P y P' ó P y Q^1 y representa:

(1) átomo de hidrógeno;

(2) un residuo de aminoácido optcional continua o

discontinuamente limitado del C terminal de la secuencia de aminoácido 1-48 en la secuencia de aminoácido representada por SEQ ID NO: 1;

(3) un grupo representado por la fórmula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

(en donde:

J^1 representa (a) átomo de hidrógeno o (b) (i) un grupo acilo C_{1-15}, (ii) un grupo alquilo C_{1-15}, (iii) un grupo arilo C_{6-14}, (iv) grupo carbamoilo, (v) grupo carboxilo, (vi) grupo sulfino, (vii) grupo amidino, (viii) grupo glioxiloilo ó (ix) grupo amino, tales grupos pueden ser opcionalmente sustituidos con un sustituyente que contiene un grupo cíclico opcionalmente sustituido;

J^2 representa (1) NH opcionalmente sustituido con un grupo alquilo C_{1-6}, (2) CH_2 opcionalmente sustituido con un grupo alquilo C_{1-6}, (3) O ó (4) S;

J^3 a J^6 cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3};

Q^3 a Q^6 cada uno representa un grupo alquilo C_{1-4} que puede tener un sustituyente opcionalmente seleccionado del grupo que consiste de:

(1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido,

(2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre,

(3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido,

(4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre,

(5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7,

(6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7,

(7) un grupo amino opcionalmente sustituido,

(8) un grupo guanidino opcionalmente sustituido,

(9) un grupo hidroxilo opcionalmente sustituido,

(10) un grupo carboxilo opcionalmente sustituido,

(11) un grupo carbamoilo opcionalmente sustituido, y

(12) un grupo sulfhidrilo opcionalmente sustituido,

o átomo de hidrógeno;

Pueden combinarse entre sí J^3 y Q^3, J^4 y Q^4, J^5 y Q^5 ó J^6 y Q^6, o, pueden combinarse entre sí Z^1 y R^1, J^2 y Q^3, Y^1 y Q^4, Y^2 y Q^5, o Y^3 y Q^6, para formar un anillo;

Y^1 a Y^3 cada uno representa un grupo representado por la fórmula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ ó $-N(J^{13})CO-$ (en donde J^{13} y J^{14} cada uno representa átomo de hidrógeno o

un grupo alquilo C_{1-3}); y,

Z^{10} representa átomo de hidrógeno, O ó S);

(4) un grupo representado por la fórmula:

J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$-

(en donde:

J^1 y J^2, cada uno posee el mismo significado según lo descripto anteriormente;

J^7 a J^9 poseen el mismo significado que para J^3;

Q^7 a Q^9 poseen el mismo significado que para Q^3;

Y^2 y Y^3 cada uno posee el mismo significado según lo descripto anteriormente;

Z^{10} posee el mismo significado según lo descripto anteriormente;

Pueden combinarse entre sí J^7 y Q^7, J^8 y Q^8 ó J^9 y Q^9, o, pueden combinarse entre sí J^2 y Q^7, Y^2 y Q^8 ó Y^3 y Q^9, para formar un anillo);

(5) un grupo representado por la fórmula:

J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$-

(en donde:

J^1 y J^2 poseen el mismo significado según lo descripto anteriormente representa;

J^{10} y J^{11} poseen el mismo significado que para J^3;

Q^{10} y Q^{11} poseen el mismo significado que para Q^3;

Y^3 posee el mismo significado según lo descripto anteriormente;

Z^{10} posee el mismo significado según lo descripto anteriormente; y,

Pueden combinarse entre sí J^{10} y Q^{10} ó J^{11} y Q^{11}, o pueden combinarse entre sí J^2 y Q^{10} ó Y^3 y Q^{11}, para formar un anillo);

(6) un grupo representado por la fórmula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(en donde;

J^1 y J^2 poseen el mismo significado según lo descripto anteriormente;

J^{12} posee el mismo significado de J^3;

Q^{12} posee el mismo significado de Q^3;

Z^{10} posee el mismo significado según lo descripto anteriormente; y

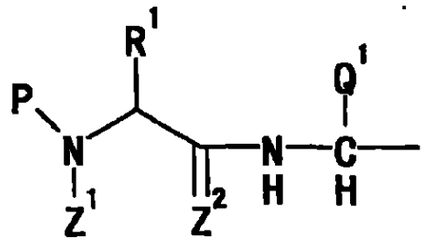
Pueden combinarse entre sí J^{12} y Q^{12}, o pueden combinarse entre sí J^2 y Q^{12}, para formar un anillo); o,

(7) un grupo representado por la fórmula:

J^1- (en donde J^1 posee el significado según lo descripto anteriormente)] o una sal del mismo, o una prodroga del mismo.

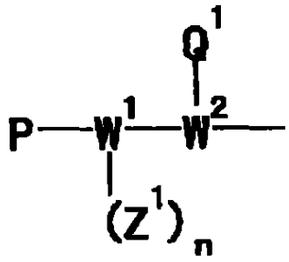
(49) Un agente de acuerdo con (48), en donde el derivado de metastina (III) es el derivado de metastina (II) de acuerdo con (1).

(50) Un agente de acuerdo con (48), en donde V' es un grupo representado por la fórmula:



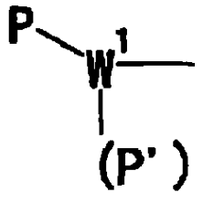
(en donde cada símbolo posee el mismo significado según lo descripto en (48)).

(51) Un agente de acuerdo con (48), en donde V' es un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado según lo descripto en (48)).

(52) Un agente de acuerdo con (48), en donde V' es un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado según lo descripto en el punto 48 precedentemente).

(53) Un agente de acuerdo con (48), en donde el derivado de metastina (III) es:

(1) D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 141),

(2) D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 174),

(3) 3-(3-Indolil)propionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 260),

(4) 3-Fenilpropionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-

NH_2 (Compuesto No. 269),

(5) 2-(indol-3-il)etilcarbamoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 279),

(6) D-Tyr-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 286),

(7) D-Tyr-Asn-Trp-Asn-Ser-Pheψ(CSNH)Gly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 296),

(8)Tyrψ(CH2NH)Asn-d-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 300),

(9) D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 303),

(10) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 305),

(11) D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compuesto No. 318),

(12) D-Tyr-Asn-Trp-Asn-Ser-Pheψ(NHCO)Gly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 319),

(13) 3-(3-Piridil)propionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 322),

(14) 4-Imidazolacetil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 323),

(15) GuAmb-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 332)

(16) GuAmb-Phe-Gly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 333)

(17) GuAmb-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 334)

(18) 3-(3-Indolil)propionil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 339)

(19) Benzoil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 341)

(20) Indol-3-acetil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 345)

(21) Ac-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 346)

(22) Benzoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 353)

(23) 3-(3-Indolil)propionil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 354)

(24) Ac-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 358)

(25) 2-(Indol-3-il)etilcarbamoil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 364)

(26) 2-(Indol-3-il)etilcarbamoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 369)

(27) (2S)-2-acetoxi-3-fenilpropionil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 373)

(28) (2S)-2-(3-Indolilpropioniloxi)-3-fenilpropionil-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 379)

(29) (2S)-2-Benzoiloxi-3-fenilpropionil-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 380)

(30) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 385),

(31) 3-(3-Piridil)propionil-Asn-Ser-Phe-AzaGly-Leu-

Arg(Me)-Trp-NH_2 (Compuesto No. 386),

(32) Dibencilcarbamoil-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 393)

(33) Bencilfenetilcarbamoil-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 417)

(34) Benzoil-Pheψ(NHCO)Gly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 423)

(35) Benzoil-AzaPhe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 431)

(36) 3-Piridincarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 432)

(37) 2-Piridincarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 435)

(38) 4-Piridincarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 436)

(39) Propionil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 437)

(40) Isobutiril-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 438)

(41) Ciclohexancarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 439)

(42) Fenilacetil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 440)

(43) Benzoil-Pya(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 441)

(44) 6-Metilnicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 445)

(45) Pirazinecarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 446)

(46) Ciclopropanecarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 447)

(47) Trifluoroacetil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 448)

(48) Benzoil-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 449)

(49) Ciclopropancarbonil-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 451)

(50) (R)-3-hidroxi-2-metilpropionil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 452)

(51) 2-Hidroxiisobutiril-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 453)

(52) 3-Furancarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 454)

(53) Pirrol-2-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 455)

(54) 4-Imidazolcarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 459)

(55) 6-Hidroxinicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 462)

(56) 6-Cloronicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 463)

(57) 6-(Trifluorometil)nicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 464)

(58) Dimetilcarbamoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 467)

(59) 1-Azetidinecarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 468)

(60) 4-Piridincarbonil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

(Compuesto No. 471)

(61) 4-Aminobenzoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 472)

(62) 4-Aminometilbenzoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 473)

(63) Pirrol-3-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 474)

(64) Pirimidin-4-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 475)

(65) Pirimidin-2-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 479)

(66) Piridazin-4-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 480)

(67) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Trp-NH_2

(Compuesto No. 481)

(68) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Lys-Phe-NH_2

(Compuesto No. 487)

(69) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Phe-NH_2

(Compuesto No. 488)

(70) D-Tyr-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

(Compuesto No. 490)

(71) D-Tyr-D-Pya(4)-Asn-Trp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 491)

(72) D-Tyr-D-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 492)

(73) D-Tyr-D-Pya(4)-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 493)

(74) D-Tyr-D-Pya(4)-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 496)

(75) D-Tyr-D-Pya(4)-Asn-Ser-Cha-Ala-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 497)

(76) D-Tyr-D-Pya(4)-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 498)

(77) 3-Fenilpropionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 499)

(78) 3-Fenilpropionil-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 500)

(79) D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 501)

(80) D-Tyr-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 502)

(81) D-Tyr-D-Trp-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 503)

(82) 6-Aminocaproil-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 504)

(83) 3-Fenilpropionil-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 505)

(84) 3-Fenilpropionil-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 506)

(85) 3-Fenilpropionil-Asn-Ser-Trp-AzaGly-Leu-Arg(Me)-Trp-

NH_2 (Compuesto No. 507)

(86) 3-Fenilpropionil-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 508)

(87) Benzoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 509)

(88) Ac-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 510)

(89) D-Tyr-D-Trp-Ala-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 511)

(90) D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 512)

(91) D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 513)

(92) D-Tyr-D-Phe-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 514),

(93) D-Tyr-D-Pya(4)-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 515)

(94) des(1)-Ac-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10 (Compuesto No. 516)

(95) des(1-3)-3-Fenilpropionil-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 517)

(96) des(1-3)-3-Fenilpropionil-[Cha6,Arg(Me)9,Trp10]MS10 (Compuesto No. 518)

(97) des(1-3)-Fenilacetil-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 519)

(98) des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10 (Compuesto No. 521)

(99) des(1-3)-Benzoil-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 522)

(100) des(1-3)-Benzoil-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 523)

(101) des(1-3)-3-Fenilpropionil-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 524)

(102) des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 527)

(103) des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 528)

(104) des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 529)

(105) des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 530)

(106) des(1-3)-3-Fenilpropionil-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 531)

(107) des(1-3)-3-Fenilpropionil-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 532)

(108) des(1-3)-3-Fenilpropionil-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 533)

(109) des(1-3)-Ciclopropancarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 534)

(110) des(1-3)-2-Naftoil-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 535)

(111) [Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 536)

(112) Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 537)

(113) Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 538)

(114) des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 539)

(115) des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 540)

(116) D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 541)

(117) D-Arg-d-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 542)

(118) des(1-3)-Benzoil-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 545)

(119) des(1-3)-3-Fenilpropionil-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 546)

(120) des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 547)

(121) des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10ψ,CSNH]MS10 (Compuesto No. 548)

(122) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 550)

(123) Ac-d-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 551)

(124) D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 552)

(125) D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 553)

(126) D-Arg-[(-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 554)

(127) D-Arg-[ψ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 555)

(128) D-Arg-d-Arg-[ψ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 556)

(129) D-Arg-d-Arg-d-Arg-[ψ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 557)

(130) des(1)-Ac-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 558)

(131) des(1-2)-3-(4-Hidroxifenil)propionil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 559)

(132) D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 561)

(133) Ac-des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 562)

(134) Ac-des(1)-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 563)

(135) Ac-des(1)-[D-Tyr2,D-

Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 564)

(136) des(1)-Benzoil-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 565)

(137) des(1)-Ciclopropancarbonil-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 566)

(138) Butiril-des(1)-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 567)

(139) Ac-[D-Arg1,D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 568)

(140) des(1)-Ac-[D-Tyr2,D-

Trp3,Thr5,6ψ7,CH2NH,Arg(Me)9,Trp10]MS10 (Compuesto No. 569)

(141) des(1)-Me-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 570)

(142) des(1)-Ac-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9]MS10 (Compuesto No. 571)

(143) des(1)-[D-Trp2,D-

Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 572)

(144) des(1)-Ac-[D-Tyr2,D-

Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 573)

(145) des(1)-Ac-[D-Tyr2,D-

Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 576)

(146) des(1)-Ac-[D-Tyr2,D-

Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 577)

(147) des(1)-Ac-[D-Tyr2,D-

Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 578)

(148) Ac-des(1)-[D-Tyr2,D-

Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 579),

(149) des(1)-Ac-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 580),

(150) des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 584),

(151) des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 585),

(152) des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 586),

(153) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10 (Compuesto No. 589),

(154) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi10]MS10 (Compuesto No. 590),

(155) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10 (Compuesto No. 591),

(156) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10 (Compuesto No. 592),

(157) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10 (Compuesto No.

594),

(158) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Cha10]MS10 (Compuesto No. 595),

(159) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Leu10]MS10 (Compuesto No. 596),

(160) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 597),

(161) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10 (Compuesto No. 598),

(162) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10 (Compuesto No. 599),

(163) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10 (Compuesto No. 600),

(164) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10 (Compuesto No. 601),

(165) des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 Compuesto No. 602),

(166) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 603),

(167) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10 (Compuesto No. 604),

(168) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10 (Compuesto No. 605),

(169) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10 (Compuesto No. 607),

(170) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10 (Compuesto No. 608),

(171) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10 (Compuesto No. 609),

(172) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10 (Compuesto No. 610),

(173) des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 611),

(174) des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 612),

(175) des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 613),

(176) des(1)-Amidino-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 614),

(177) des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 615),

(178) des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 616),

(179) des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 617),

(180) des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 618),

(181) des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 619),

(182) des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 620),

(183) des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 621)

(184) des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 622),

(185) des(1)-Ac-[D-Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 623),

(186) des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 624),

(187) des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No.

625),

(188) des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 626),

(189) des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 627),

(190) des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 628),

(191) des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 629),

(192) des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 630),

(193) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 631),

(194) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 632),

(195) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 633),

(196) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No.

634),

(197) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 635),

(198) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,NMePhe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 636),

(199) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 637),

(200) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 638),

(201) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10 (Compuesto No. 639),

(202) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10 (Compuesto No. 641),

(203) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10 (Compuesto No. 642),

(204) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10 (Compuesto No. 643),

(205) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10 (Compuesto No. 644),

(206) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10 (Compuesto No. 645),

(207) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10 (Compuesto No. 646),

(208) des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 647),

(209) [Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 648),

(210) Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 649),

(211) [D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 650),

(212) Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 651),

(213) pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 652),

(214) des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 653),

(215) des(1)-Ac-[D-Tyr2,D-Trp3,D-

Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 654),

(216) des(1)-Ac-[D-Tyr2,D-Trp3,NMeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 655),

(217) des(1)-Ac-[D-Tyr2,D-Trp3,NMeSer5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 656),

(218) des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 657),

(219) des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 658),

(220) des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 659),

(221) des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 660),

(222) des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 661),

(223) des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 662),

(224) des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 663),

(225) des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 664),

(226) des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 665),

(227) des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 666),

(228) des(1-2)-Hexanoil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 667),

(229) des(1-2)-Ciclohexancarbonil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 668),

(230) des(1-2)-Benzoil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 669),

(231) des(1-2)-3-Piridinpropionil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 670),

(232) des(1-2)-Adipoil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 671),

(233) des(1)-Ac-[D-Tyr2,NMeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 672),

(234) des(1-2)-6-Aminocaproil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No.

674),

(235) [D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 675)

(236) Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 676)

(237) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10 (Compuesto No. 677)

(238) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10 (Compuesto No. 678)

(239) des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 679)

(240) des(1-2)-Glicoloil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (CompuestoNo. 680)

(241) des(1)-Glicoloil-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 681)

(242) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10 (Compuesto No. 682)

(243) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10 (Compuesto No. 685)

(244) des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 686)

(245) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10 (Compuesto No. 688)

(246) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-

Trp10]MS10 (CompuestoNo. 689)

(247) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 691)

(248) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 692)

(249) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 693)

(250) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 694)

(251) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 695)

(252) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 696)

(253) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10 (Compuesto No. 698)

(254) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10 (Compuesto No. 699)

(255) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,,Arg(Me)9,Trp10]MS10 (Compuesto No. 700)

(256) des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10 (CompuestoNo. 701)

(257) des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 702)

(258) des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NMe2)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 703).

(54) Un agente de acuerdo con (48) a (53) el cual es un agente para regular en disminución la hormona gonadotrópica u hormona del sexo.

(55) Un agente de acuerdo con (48) a (53) el cual es un agente para regular en disminución la proteína OT7T175 humana (receptor de metastina) que consiste de la secuencia de aminoácido representada por SEQ ID NO: 9.

(56) Un agente de acuerdo con (48) a (55) el cual es un agente para prevenir o tratar cáncer dependiente de hormona.

(57) Un método para suprimir la secreción de hormona gonadotrópica o suprimir la secreción de hormona del sexo que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (III) de acuerdo con (48) o una sal del mismo, o una prodroga del mismo.

(58) Un método para regular en disminución la hormona gonadotrópica u hormona del sexo que comprende administrar a un mamífero una dosis eficaz del derivado de metastina de acuerdo con (48) o una sal del mismo, o

una prodroga del mismo.

(59) Un método para regular en disminución la proteína OT7T175 humana (receptor de metastina) que consiste en la secuencia de aminoácido representada por SEQ ID NO: 9 que comprende administrar a un mamífero una dosis eficaz del derivado de metastina de acuerdo con (48) o una sal del mismo, o una prodroga del mismo.

(60) Un método para prevenir o tratar cáncer dependiente de hormona que comprende administrar a un mamífero una dosis eficaz del derivado de metastina de acuerdo con (48) o una sal del mismo, o una prodroga del mismo.

(61) Una utilización del derivado de metastina de acuerdo con (48) o una sal del mismo, o una prodroga del mismo para fabricar un agente para suprimir la secreción de hormona gonadotrópica o un agente para suprimir la secreción de hormona del sexo.

(62) Una utilización del derivado de metastina de acuerdo con (48) o una sal del mismo, o una prodroga del mismo para fabricar un agente para regular en disminución la hormona gonadotrópica u hormona del sexo.

(63) Una utilización del derivado de metastina de acuerdo con (48) o una sal del mismo, o una prodroga del mismo para fabricar un agente para regular en disminución la proteína OT7T175 humana (receptor de metastina) que consiste en la secuencia de aminoácido representada por SEQ ID NO: 9.

(64) Una utilización del derivado de metastina de acuerdo

con (48) o una sal del mismo, o una prodroga del mismo para fabricar un agente para prevenir o tratar el cáncer dependiente de hormona.

(65) Un derivado del metastina representado por la fórmula:

XX0-XX2-XX3-XX4-XX5-XX6-AzaGly-XX8-XX9-XX10-NH_2.

(en donde:

XX0 representa formilo, alcanoilo C_{1-6}, ciclopropancarbonilo, 6-(acetil-D-arginilamino)caproilo, 6-((R)-2,3-diaminopropionilamino)caproilo, 6-(D-norleucilamino)caproilo, 4-(D-arginilamino)butirilo, 3-(4-Hidroxifenil)propionilo, glicilo, tirosilo, acetilglicilo, acetiltirosilo, D-tirosilo, acetil-D-tirosilo, piroglutamilo, 3-(piridin-3-il)propionilo, adipoilo o aminocaproilo;

XX2 representa Tyr, D-Tyr, D-Ala, D-Leu, D-Phe, D-Lys, D-Trp o brazo de enlace;

XX3 representa Trp, Pro, 4-piridilalanina, Tic, D-Trp, D-Ala, D-Leu, D-Phe, D-Lys, D-Glu, D-2-piridilalanina, D-3-piridilalanina ó D-4-piridilalanina;

XX4 representa Asn, ácido 2-amino-3-ureidopropionico, ácido N^{β}-formildiaminopropiónico o ácido N^{β}-acetildiaminopropiónico;

XX5 representa Ser, Thr o Val;

XX6 representa Phe, Tyr, Trp, Tyr(Me), Thi, Nal(2), Cha, 4-piridilalanina o 4-fluorofenilalanina;

AzaGly representa azaglicina;

XX8 representa Leu, Nva ó Val (preferentemente Leu);

XX9 representa Arg, Orn, Arg(Me), ó Arg(symMe2);

XX10 representa Phe, Trp, 2-naftilalanina, 2-tienilalanina, tirosina o 4-fluorofenilalanina), o una sal del mismo.

(66) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 305),

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 385),

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 501),

Benzoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 509),

D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 512),

Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 516),

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 540),

D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 541),

Benzoil-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 545),

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-PheΨ(CSNH)NH_2 (Compuesto No. 548),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 552),

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 553),

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 555),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 558),

3-(4-Hidroxifenil)propionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 559),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 562),

Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 564),

Ciclopropancarbonil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 566),

Butiril-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 567),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 571),

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 579),

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 580),

Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 584),

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 585),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

(Compuesto No. 589),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2

(Compuesto No. 590),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2

(Compuesto No. 591),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

(Compuesto No. 592),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2

(Compuesto No. 599),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2

(Compuesto No. 600),

Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 602),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(symMe2)-Trp-NH_2

(Compuesto No. 608),

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 612),

Propionil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 613),

Ac-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 615),

Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 616),

Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 617),

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 618),

Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 621),

Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 623),

Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 625),

Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 626),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 627),

Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 629),

Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 630),

Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 635),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 637),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 638),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

(Compuesto No. 642),

Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 648),

Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 649),

D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 650),

Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 651),

pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 652),

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 657),

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 658),

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 660),

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 662),

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 663),

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 666),

Hexanoil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 667),

3-Piridinpropionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 670),

Adipoil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 671),

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 672),

6-Aminocaproil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 674), o sales del mismo.

(67) Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 552),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 558),

3-(4-Hidroxifenil)propionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH2 (Compuesto No. 559),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 562),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 571),

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 579),

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 585),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compuesto No. 589),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compuesto No. 592),

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-

NH_2 (Compuesto No. 612),

Propionil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 613),

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 618),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 627),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 637),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 638),

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 658),

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 660),

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 663),

o sales del mismo.

(68) Un agente de acuerdo con (48) precedentemente el cual es un agente para la potenciación de la inmunidad (agente profiláctico para la infección después del trasplante de médula ósea, agente para potenciación de la inmunidad indicada para cáncer).

(69) Un agente de acuerdo con (48) precedentemente que es un agente de profilaxis/terapéutica para la atrofia muscular bulboespinal.

(70) Un agente de acuerdo con (48) precedentemente que es

un agente de profilaxis/terapéutica para proteger el ovario.

(71) Un agente de acuerdo con (48) precedentemente que es un agente de profilaxis/terapéutica para la hipertrofia benigna de la próstata (BPH).

(72) Un agente de acuerdo con (48) precedentemente que es un agente de profilaxis/terapéutica para el desorden de identidad de género.

(73) Un agente de acuerdo con (48) precedentemente que es un agente de profilaxis/terapéutica para la fertilización in vitro (IVF).

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La fig. 1 ilustra una evaluación de la actividad de inhibición de quimiotaxis de los compuestos Nros. 322, 305, 303, 286, 232 y 141 usando células CHO expresando hOT7T175. En la abscisa, FBS- designa la ausencia de FBS, FBS+ designa la presencia de FBS, 322 designa el agregado de Compuesto No. 322, 305 designa el agregado de Compuesto No. 305, 303 designa el agregado de Compuesto No. 303, 286 designa el agregado de Compuesto No. 286, 232 designa el agregado de Compuesto No. 232, 141 designa el agregado de Compuesto No. 141, (1-54) designa el agregado de metastina (1-54), y (45-54) designa el agregado de metastina 45-54. La ordenada denota una actividad relativa cuando la actividad de quimiotaxis en presencia de FBS pasa a ser de 100%.

La fig. 2 ilustra una evaluación de la actividad de

inhibición de crecimiento de tumor del Compuesto No. 322 y metastina (1-54) usando los ratones con tumor con la línea celular SW620 derivada de carcinoma humano colónico, en donde el valor indica (valor promedio) + (error típico). Los símbolos de rombo abierto, círculo abierto, círculo cerrado y cuadrado cerrado indican los resultados obtenidos cuando son agregados el vehículo (agua destilada), compuesto No. 322 (0,1 mM), compuesto No. 322 (1 mM), y Metastina (Metastina 1-54), respectivamente. La abscisa denota el número de días después de la inyección. La barra en la abscisa designa un período de dosificación. La ordenada denota el tamaño de tumor (mm^3).

La fig. 3 ilustra una evaluación de la actividad de inhibición de crecimiento de tumor con compuesto No. 305 y Metastina (1-54) usando los ratones con tumor con la línea celular SW620 derivada de carcinoma colónico humano, en donde el valor indica (valor promedio) + (error típico). Los símbolos rombo abierto, círculo abierto, círculo cerrado y cuadrado cerrado designan los resultados obtenidos cuando son agregados vehículo (agua destilada), compuesto No. 305 (0,1 mM), compuesto No. 305 (1 mM), y Metastina (Metastina 1-54), respectivamente. La abscisa denota el número de días después de la inyección. La barra en la abscisa designa un período de la dosificación. La ordenada denota un tamaño de tumor (mm^3).

La fig. 4 ilustra los resultados obtenidos supervisando los cambios en el nivel de glucosa en sangre cuando la metastina fue inyectada intravenosamente en las ratas sin ninguna anestesia. En la figura, los símbolos del círculo abierto, triángulo cerrado, círculo cerrado y rombo cerrado designan el nivel de glucosa en sangre en el grupo salino, el grupo 17 nmol/kg de metastina, el grupo 80 nmol/kg de metastina y el grupo 170 nmol/kg de metastina, respectivamente. El valor indica (promedio + SE) (n = 5). El símbolo * que designa el P-valor es 0,05 o inferior, en comparación al grupo salino y el símbolo ** designa que el P-valor es 0,01 o inferior, en comparación al grupo salino.

La fig. 5 ilustra los resultados obtenidos supervisando los cambios en el nivel de glucagon en sangre cuando la metastina es inyectada intravenosamente en las ratas sin ninguna anestesia. En la figura, los símbolos del círculo abierto y el círculo cerrado designan los niveles de glucagon en sangre en el grupo salino y grupo 80 nmol/kg de metastina, respectivamente. El valor indica (prmedio + SE) (n = 6-9). El símbolo * designa que el P-valor es 0,05 o inferior, en comparación al grupo salino y el símbolo ** designa que el P-valor es 0,01 o inferior, cuando se compara al grupo salino.

La fig. 6 ilustra los resultados obtenidos supervisando los cambios en el nivel de insulina en sangre cuando la metastina es inyectada intravenosamente

en las ratas sin ninguna anestesia. En la figura, los símbolos del círculo abierto y el círculo cerrado designan el nivel de insulina en sangre en el grupo salino y grupo 80 nmol/kg de metastina, respectivamente. El valor indica (promedio + SE) (n = 6-9).

La fig. 7 ilustra los resultados obtenidos supervisando los cambios en los niveles de corticoesterona en sangre cuando la metastina es inyectada intravenosamente en las ratas sin ninguna anestesia. En la figura, los símbolos circulo abierto y el círculo cerrado designan los niveles de corticoesterona en sangre en el grupo salino y grupo 80 nmol/kg de metastina, respectivamente. El valor indica (promedio + SE) (n = 4-5).

La fig. 8 ilustra los resultados obtenidos supervisando los cambios en el nivel de la hormona tiroidea (T3) en sangre cuando la metastina es inyectada intravenosamente en las ratas sin ninguna anestesia. En la figura, los símbolos circulo abierto y el círculo cerrado designan el nivel de la hormona tiroidea (T3) en sangre en el grupo salino y grupo 80 nmol/kg de metastina, respectivamente. El valor indica (promedio + SE) (n = 4-5).

La fig. 9 ilustra los resultados obtenidos supervisando los cambios en el nivel de glucosa de sangre cuando la metastina es inyectada intravenosamente en las ratas sin ninguna anestesia. En la figura, los símbolos

circulo abierto y círculo cerrado designan el nivel de glucosa en sangre en el grupo salino y grupo 80 nmol/kg de metastina, respectivamente. El valor indica (promedio + SE) (n = 6-9). El símbolo * designa que el P-valor es 0.05 o inferior, cuando es comparado al grupo salino.

La fig. 10 ilustra los resultados obtenidos supervisando los cambios en el nivel de glucosa en sangre cuando un derivado de metastina es inyectado intravenosamente en las ratas sin ninguna anestesia. En la figura, los símbolos circulo abierto, círculo cerrado y triángulo cerrado designan el nivel de glucosa en sangre en el grupo salino, el grupo 80 nmol/kg KiSS1-305 y grupo 80 nmol/kg de metastina, respectivamente. El valor indica (promedio + SE) (n = 5). El símbolo * designa que el P-valor es 0,05 o inferior, cuando se lo compara al grupo salino y el símbolo ** designa que el P-valor es 0,01 o inferior, cuando se lo compara al grupo salino.

La fig. 11 ilustra los resultados obtenidos supervisando los cambios en los niveles de glucagón en sangre cuando la metastina es inyectada intravenosamente en ratas sin ninguna anestesia. En la figura, los símbolos circulo abierto, círculo cerrado y triángulo cerrado designan los niveles de glucagon en sangre en el grupo salino y grupo 80 nmol/kg KiSS1-305 (Compuesto No. 305), grupo 80 nmol/kg KiSS1-322 (Compuesto No. 322), respectivamente. El valor indica (promedio + SE) (n = 5).

El símbolo * designa que el P-valor es 0,05 o inferiior, cuando se lo compara al grupo salino.

La fig. 12 ilustra el nivel de estradiol contenido en el plasma de la rata. En la figura, la ordenada y la abscisa denotan el nivel de estradiol y la droga que reciben los grupos, respectivamente.

La fig. 13 ilustra el nivel de progesterona contenido en el plasma de la rata. En la figura, la ordenada y la abscisa denotan el nivel de estradiol y la droga que reciben los grupos, respectivamente.

La fig. 14 ilustra los cambios en el nivel de FSH en la sangre en la rata inmadura por la inyección de metastina.

La fig. 15 ilustra los cambios en el nivel de LH en la sangre en la rata inmadura por la inyección de metastina.

La fig. 16 ilustra los cambios en el nivel de la progesterona en la sangre en la rata inmadura por la inyección de metastina.

La fig. 17 ilustra los cambios en el nivel de FSH en la sangre en la rata por la inyección de metastina.

La fig. 18 ilustra los cambios en el nivel de LH en la sangre de la rata por la inyección de metastina.

La fig. 19 ilustra los cambios en el nivel de testosterona de la sangre en la rata por la inyección de metastina.

La fig. 20 ilustra el número de oocitos por rata

individual en cada grupo medido en el Ejemplo de prueba 13. En la figura, el símbolo de rombo cerrado designa los datos para la rata individual y el símbolo cuadrado cerrado designa un valor promedio en cada grupo.

La fig. 21 ilustra el nivel de estradiol en la sangre en cada grupo con la dosificación medida en el Ejemplo de prueba 13. En la figura, el símbolo del triángulo cerrado designa los datos para la rata individual y el símbolo del cuadrado cerrado designa un valor promedio en cada grupo.

La fig. 22 ilustra el nivel de la progesterona en la sangre en cada grupo medido en el Ejemplo de prueba 13. En la figura, el símbolo del triángulo cerrado designa los datos para la rata individual y el símbolo del cuadrado cerrado designa un valor promedio en cada grupo.

MEJORES MODALIDADES DE REALIZACIÓN DE LA INVENCIÓN

En las fórmulae descriptas precedentemente, n representa 0 ó 1; W^1 representa N, CH u O (con la condición que W^1 es N ó CH, n representa 1, y cuando W^1 es O, n representa 0); W^2 representa N ó CH; Z^1, Z^3, Z^5 y Z^7 cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3}; y Z^2, Z^4, Z^6 y Z^8 cada uno representa átomo de hidrógeno, O ó S;

en donde, cuando Z^2, Z^4, Z^6 o Z^8 representan el átomo de hidrógeno, una estructura de la fracción representada por $>C=Z^2$, $>C=Z^4$, $>C=Z^6$ ó $>C=Z^8$ cada uno indica una estructura de $>CH_2$.

El grupo alquilo C_{1-3} utilizado incluye grupo metilo, grupo etilo, grupo propilo y grupo isopropilo.

W^1 es preferentemente N y W^2 es preferentemente CH.

Las combinaciones preferidas de Z^1 a Z^8 además incluyen los casos en donde Z^1 y Z^3 representan átomo de hidrógeno, cada uno de Z^5 y Z^7 representa átomo de hidrógeno o un grupo alquilo C_{1-3} y cada uno de Z^2, Z^4, Z^6 y Z^8 representa O ó S.

Más preferentemente, las combinaciones de Z^1 a Z^8 incluyen:

(a) el caso dónde Z^1 es átomo de hidrógeno, Z^3 es átomo de hidrógeno, Z^5 es átomo de hidrógeno y Z^7 es átomo de hidrógeno, y Z^2 es O, Z^4 es O, Z^6 es O y Z^8 es O;

(b) el caso dónde Z^1 es átomo de hidrógeno, Z^3 es átomo de hidrógeno, Z^5 es átomo de hidrógeno y Z^7 es átomo de hidrógeno, y Z^2 es O, Z^4 es O, Z^6 es O y Z^8 es S;

(c) el caso dónde Z^1 y Z^3 son átomo de hidrógeno y Z^5 es átomo de hidrógeno, Z^7 es grupo metilo y Z^2 es O, y Z^4 es O, Z^6 es O y Z^8 es O; etc. Entre estos casos, son preferibles (a) y (b).

R^1 representa (1) átomo de hidrógeno, (2) un grupo alquilo C_{1-8} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo opcionalmente sustituido y un grupo cíclico aromático opcionalmente sustituido, (3) un grupo alquilo C_{1-10} lineal o cíclico o (4) un grupo alquilo C_{1-10} que consiste

en un grupo alquilo cíclico y un grupo alquilo lineal, o (5) un grupo cíclico aromático opcionalmente sustituido. Entre otros, el R^1 preferido incluye (1) átomo de hidrógeno o (2) un grupo alquilo C_{1-8} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo opcionalmente sustituido y un grupo cíclico aromático opcionalmente sustituido, más preferentemente incluye (1) átomo de hidrógeno o (2) un grupo alquilo C_{1-8} sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo opcionalmente sustituido y un grupo cíclico aromático opcionalmente sustituido.

El "grupo alquilo C_{1-8}" usado incluye, por ejemplo, un grupo alquilo C_{1-8} lineal tal como metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, hexilo, heptilo, octilo, etc., y un grupo alquilo C_{3-8} cíclico tal como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etc. se prefiere particularmente el grupo alquilo C_{1-3} tal como metilo, etilo, etc..

El "grupo carbamoilo opcionalmente sustituido" utilizado incluye, por ejemplo, carbamoilo, grupo mono-alquilcarbamoilo C_{1-6} (por ejemplo, metilcarbamoilo, etilcarbamoilo, etc.), un grupo di-alquilcarbamoilo C_{1-6} (por ejemplo, dimetilcarbamoilo, dietilcarbamoilo,

etilmetilcarbamoilo, etc.), un grupo mono- o di-arilcarbamoilo C_{6-14} (por ejemplo, fenilcarbamoilo, 1-naftilcarbamoilo, 2-naftilcarbamoilo, etc.), un grupo mono - o dicarbamoilo heterocíclico de 5 o 7 miembros conteniendo 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, 2-piridilcarbamoilo, 3-piridilcarbamoilo, 4-piridilcarbamoilo, 2-tienilcarbamoilo, 3-tienilcarbamoilo, etc.) y lo similar.

El "grupo hidroxilo opcionalmente sustituido" usado incluye, por ejemplo, grupo hidroxilo, un grupo alcoxilo C_{1-6} opcionalmente sustituido, un grupo ariloxilo C_{6-14} opcionalmente sustituido, un grupo aralquiloxilo C_{7-16} opcionalmente sustituido, etc. Los "grupo alcoxilo C_{1-6} opcionalmente sustituido", "grupo ariloxilo C_{6-14} opcionalmente sustituido" y "grupo aralquiloxilo C_{7-16} opcionalmente sustituido" usados son aquéllos del "grupo alcoxilo C_{1-6} opcionalmente sustituido", "grupo ariloxilo C_{6-14} opcionalmente sustituido" y "grupo aralquiloxilo C_{7-16} opcionalmente sustituido" en grupo A sustituyente que se describirá más adelante.

El "grupo cíclico aromático" en el "grupo cíclico aromático opcionalmente sustituido" incluye, por ejemplo, un grupo de hidrocarburo aromático, grupo heterocíclico aromático, un grupo cíclico aromático fusionado, un grupo heterocíclico aromático fusionado, etc.

Por ejemplo, el "grupo de hidrocarburo aromático" usado incluye que un grupo arilo C_{6-14} tal como fenilo, 2-bifenililo, 3-bifenililo, 4-bifenililo, ciclooctatetraenilo, etc.,

El "grupo heterocíclico aromático" usado incluye, por ejemplo, un grupo heterocíclico aromático de 5 a 14 miembros, preferentemente de 5 a 10 miembros, más preferentemente de 5 ó 6 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono. Los ejemplos específicos son tienilo (por ejemplo, 2-tienilo, 3-tienilo), furilo (por ejemplo, 2-furilo, 3-furilo), piridilo (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo), tiazolilo (por ejemplo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo), oxazolilo (por ejemplo, 2-oxazolilo, 4-oxazolilo), pirazinilo, pirimidinilo (por ejemplo, 2-pirimidinilo, 4-pirimidinilo), pirrolilo (por ejemplo, 1-pirrolilo, 2-pirrolilo, 3-pirrolilo), imidazolilo (por ejemplo, 1-imidazolilo, 2-imidazolilo, 4-imidazolilo), pirazolilo (por ejemplo, 1-pirazolilo, 3-pirazolilo, 4-pirazolilo), piridazinilo (por ejemplo, 3-piridazinilo, 4-piridazinilo), isotiazolilo (por ejemplo, 3-isotiazolilo), isooxazolilo (por ejemplo, 3-isooxazolilo), etc.

El "grupo cíclico fusionado aromático" utilizado incluye un grupo cíclico fusionado aromático C_{8-14} tal

como naftilo (por ejemplo, 1-naftilo, 2-naftilo), antrilo (por ejemplo, 2-antrilo, 9-antrilo) y lo similar.

El "grupo heterocíclico fusionado aromático" usado incluye, por ejemplo, un grupo bicíclico o tricíclico heterocíclico aromático de 5 a 14 miembros (preferentemente 5 a 10 miembros) que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de 3 a 11 átomos de carbono, o un grupo monovalente formado eliminando un átomo de hidrógeno opcional de un anillo aromático de 7 a 10 miembros hetero conectado a un anillo de 5 a 14 miembros (preferentemente 5 a 10 miembros) que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionado de átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono. Los ejemplos específicos de estos grupos usados son quinolilo (por ejemplo, 2-quinolilo, 3-quinolilo, 4-quinolilo, 5-quinolilo, 8-quinolilo), isoquinolilo (por ejemplo, 1-isoquinolilo, 3-isoquinolilo, 4-isoquinolilo, 5-isoquinolilo), indolilo (por ejemplo, 1-indolilo, 2-indolilo, 3-indolilo), 2-benzotiazolilo, el benzo[b]tienilo, (por ejemplo, 2-benzo[b]tienilo, 3-benzo[b]tienilo), benzo[b]furanilo (por ejemplo, 2-benzo[b]furanilo, 3-benzo[b]furanilo) y lo similar.

El "sustituyente" utilizado para el "grupo cíclico aromático" incluye un sustituyente seleccionado del grupo A sustituyente que se describirá más adelante.

Para R^1, se utiliza átomo de hidrógeno, carbamoilmetilo, 2-carbamoiletilo, hidroximetilo, 1-hidroxiletilo, bencilo, 4-hidroxibencilo, 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 2-tienilmetilo, 3-tienilmetilo, 1-naftilmetilo, 2-naftilmetilo, 3-indolmetilo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, ciclohexilmetilo, fenilo, acetoximetilo, metoximetilo, etc., preferentemente, hidroximetilo, 1-hidroxietilo, bencilo, 4-hidroxibencilo, 3-indolmetilo, metilo, isobutilo, etc., y más preferentemente, hidroximetilo, 1-hidroxietilo, etc.

R^2 representa (1) átomo de hidrógeno, (2) un grupo alquilo C_{1-10} lineal o cíclico, (3) un grupo alquilo C_{1-10} que consiste en un grupo alquilo cíclico y un grupo alquilo lineal, o (4) un grupo alquilo C_{1-8} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo opcionalmente sustituido y un grupo cíclico aromático opcionalmente sustituido. Entre los mismos, los preferibles son (1) átomo de hidrógeno, (2) un grupo alquilo C_{1-10} lineal o cíclico, ó (3) un grupo alquilo C_{1-10} que consiste de un grupo alquilo cíclico y un grupo alquilo lineal. En particular es preferible el (3) un grupo alquilo C_{1-10} que consiste de un grupo alquilo cíclico y un grupo alquilo lineal.

El grupo alquilo C_{1-10} cíclico usado incluye, por

ejemplo, un grupo cicloalquilo C_{3-8} tal como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etc.

Los ejemplos del grupo alquilo C_{1-10} lineal incluyen metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, hexilo, heptilo, octilo, nonanilo, decanilo, etc.

El grupo alquilo C_{1-10} utilizado que consiste en un grupo alquilo cíclico y un grupo alquilo lineal incluye, por ejemplo, un grupo cicloalquil C_{3-7}-alquilo C_{1-3} tal como ciclopentilmetilo, ciclohexilmetilo, etc.,

Los ejemplos de R^2 incluyen metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, ciclohexilmetilo, bencilo, hidroximetilo, 2-carbamoiletilo, terc-pentilo, etc.; entre los mismos, los preferibles son metilo, etilo, propilo, isopropilo, isobutilo, sec-butilo, terc-butilo, etc., más preferentemente, propilo, isopropilo, isobutilo, etc.

R^3 representa:

(1) un grupo alquilo C1-8 que posee un grupo básico opcionalmente sustituido y opcionalmente posee un sustituyente adicional,

(2) un grupo aralquilo que posee un grupo básico opcionalmente sustituido y opcionalmente posee un sustituyente adicional,

(3) un grupo alquilo C_{1-4} que posee un grupo hidrocarburo cíclico no aromático de cantidad de átomos de carbono no

mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional, o,

(4) un grupo alquilo C_{1-4} que tiene un grupo heterocíclico no aromático de cantidad de átomos de carbono no mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional.

El "grupo básico opcionalmente sustituido" utilizado incluye, por ejemplo, (1) un grupo guanidino que opcionalmente posee 1 ó 2 sustituyentes de un alquilo C_{1-6}, un acilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, acetilo, propionilo, etc.), etc., (2) un grupo amino que opcionalmente posee 1 a 3 sustituyentes de un alquilo C_{1-6}, un acilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, acetilo, propionilo, etc.), etc., (3) un grupo alquilcarbonilamino C_{1-6} (por ejemplo, acetamido) opcionalmente sustituido con un grupo guanidino que opcionalmente tiene 1 ó 2 sustituyentes de un alquilo C_{1-6}, un acilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, acetilo, propionilo, etc.), etc., (4) un grupo alquilcarbonilamino C_{1-6} (por ejemplo, acetamido) opcionalmente sustituido con un grupo amino que opcionalmente tiene 1 a 3 sustituyentes de un alquilo C_{1-6}, un acilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, acetilo, propionilo, etc.), etc.

Entre los mismos, los preferibles son guanidino, N-metilguanidino, N,N-dimetilguanidino, N,N'-dimetilguanidino, N-etilguanidino, N-acetylguanidino, amino, N-metilamino, N,N-dimetilamino, aminoacetamido, guanidinoacetamido, amidino, etc.,

El "sustituyente adicional" distinto del "grupo básico opcionalmente sustituido" utilizado incluye un sustituyente seleccionado del grupo de substituyente A que será descripto.

Los ejemplos del "grupo alquilo C_{1-8}" utilizado son metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, hexilo, heptilo, octilo, etc.

Por ejemplo, el "grupo aralquilo" utilizado incluye un grupo aralquilo C_{7-16} tal como bencilo, fenetilo, difenilmetilo, 1-naftilmetilo, 2-naftilmetilo, 2,2-difeniletilo, 3-fenilpropilo, 4-fenilbutilo, 5fenilpentilo, 2-bifenililmetilo, 3-bifenililmetilo, 4-bifenililmetilo, etc.

El "grupo hidrocarburo cíclico no aromático de cantidad de átomos de carbono no mayor que 7" utilizado incluye, por ejemplo, un grupo cicloalquilo C_{3-7} tal como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etc.,

El "grupo heterocíclico no aromático de cantidad de átomos de carbono mayor que 7" utilizado incluye, por ejemplo, un grupo heterocíclico no aromático de 5 a 10

miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de 1 a 7 átomos de carbono, etc. Específicamente los ejemplos usados son los pirrolidinilo (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo), oxazolidinilo (por ejemplo, 2-oxazolidinilo), imidazolinilo (por ejemplo, 1-imidazolinilo, 2-imidazolinilo, 4-imidazolinilo), piperidinilo (por ejemplo, 1-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo), piperazinilo (por ejemplo, 1-piperazinilo, 2-piperazinilo), morfolino, tiomorfolino, etc.,

Los ejemplos del "grupo alquilo C_{1-4}" usado incluyen metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, etc.,

Para R^3, se utiliza, por ejemplo, (1) 3-guanidinopropilo, 3-(N-metilguanidino)propilo, 3-(N,N-dimetilguanidino)propilo, 3-(N,N'-dimetilguanidino)propilo, 3-(N-etilguanidino)propilo, 3-(N-propilguanidino)propilo, 3-(N-acetilguanidino)propilo, 4-guanidinobutilo, 4-(N-metilguanidino)butilo, 2-guanidinoetilo, 2-(N-metilguanidino)etilo, 4-aminobutilo, 4-(N-metilamino)butilo, 4-(N,N-dimetilamino)butilo, 3-aminopropilo, 2-aminoetilo, aminometilo, aminoacetamidometilo, guanidinoacetamidometilo, 2-(guanidinocarbonil)etilo, (2) 4-guanidinobencilo, 4-aminobencilo, (3) 4-guanidinociclohexilmetilo, 4-

aminociclohexilmetilo, (4) 1-amidinopiperidin-4-ilmetilo, 4-piridilmetilo, etc., preferentemente, 3-guanidinopropilo, 3-(N-metilguanidino)propilo, 3-(N,N-dimetilguanidino)propilo, 3-(N,N'-dimetilguanidino)propilo, 3-(N-etilguanidino)propilo, 3-(N-propilguanidino)propilo, 3-(N-acetilguanidino)propilo, 4-guanidinobutilo, 4-(N-metilguanidino)butilo, 2-guanidinoetilo, 2-(N-metilguanidino)etilo, 4-aminobutilo, 4-(N-metilamino)butilo, 4-(N,N-dimetilamino)butilo, 3-aminopropilo, 2-aminoetilo, 4-aminobencilo, aminoacetamidometilo, guanidinoacetamidometilo, etc., y más preferentemente, 3-guanidinopropilo, 3-(N-metilguanidino)propilo, 3-(N,N-dimetilguanidino)propilo, 3-(N,N'-dimetilguanidino)propilo, 3-(N-etilguanidino)propilo, 3-(N-acetilguanidino)propilo, 4-guanidinobutilo, 4-(N-metilguanidino)butilo, 2-guanidinoetilo, 4-aminobutilo, etc.

R^4 representa un grupo alquilo C_{1-4} que puede ser opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de:

(1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido;

(2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre.;

(3) un grupo cíclico fusionado aromático C_{8-14}

opcionalmente sustituido;

(4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre;

(5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, y

(6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7; y preferentemente, un grupo alquilo C_{1-4} sustituido con un sustituyente seleccionado del grupo que consiste de:

(1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido;

(2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre;

(3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido;

(4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre;

(5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos

de carbono no mayor que 7; y,

(6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7.

Los ejemplos del "grupo alquilo C_{1-4}" utilizados incluyen metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, etc.,

El "grupo hidrocarburo aromático C_{6-12}" utilizado incluye, por ejemplo, un grupo hidrocarburo aromático C_{6-12} monocíclico tal como fenilo, ciclooctatetraenilo, etc.,

El "grupo heterocíclico aromático de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre" utilizado incluye, por ejemplo, un grupo heterocíclico aromático monocíclico de 5 a 14 miembros, preferentemente 5 a 10 miembros, más preferentemente 5 ó 6 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de 1 a 7 átomos de carbono. Los ejemplos específicos usados son tienilo (por ejemplo, 2-tienilo, 3-tienilo), furilo (por ejemplo, 2-furilo, 3-furilo), piridilo (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo), tiazolilo (por ejemplo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo), oxazolilo (por ejemplo, 2-oxazolilo, 4-oxazolilo), pirazinilo, pirimidinilo (por ejemplo, 2-pirimidinilo, 4-pirimidinilo), pirrolilo (por ejemplo, 1-pirrolilo, 2-

pirrolilo, 3-pirrolilo), imidazolilo (por ejemplo, 1-imidazolilo, 2-imidazolilo, 4-imidazolilo), pirazolilo (por ejemplo, 1-pirazolilo, 3-pirazolilo, 4-pirazolilo), piridazinilo (por ejemplo, 3-piridazinilo, 4-pyridazinil), isotiazolilo (por ejemplo, 3-isotiazolilo), isoxazolilo (por ejemplo, 3-isoxazolilo), etc.

El "grupo cíclico fusionado aromático C_{8-14}" utilizado incluye, por ejemplo, naftilo (por ejemplo, 1-naftilo, 2-naftilo), antrilo (por ejemplo, 2-antrilo, 9-antrilo), etc.

El "grupo heterocíclico fusionado aromático 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre" incluye, por ejemplo, un grupo bicíclico o tricíclico heterocíclico aromático de 5 a 14 miembros (preferentemente 5 a 10 miembros) que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de 3 a 11 átomos de carbono, o un grupo monovalente realizado eliminando un átomo de hidrógeno opcional de un anillo aromático de 7 a 10 miembros hetero puenteado a un anillo de 5 a 14 miembros (preferentemente 5 a 10 miembros) que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono. Los ejemplos específicos usados son quinolilo (por ejemplo, 2-

quinolilo, 3-quinolilo, 4-quinolilo, 5-quinolilo, 8-quinolilo), isoquinolilo (por ejemplo, 1-isoquinolilo, 3-isoquinolilo, 4-isoquinolilo, 5-isoquinolilo), indolilo (por ejemplo, 1-indolilo, 2-indolilo, 3-indolilo), 2-benzotiazolilo, benzo[b]tienilo, (por ejemplo, 2-benzo[b]tienilo, 3-benzo[b]tienilo), benzo[b]furanilo (por ejemplo, 2-benzo[b]furanilo, 3-benzo[b]furanilo), etc.

El "grupo hidrocarburo cíclico no aromático de cantidad de átomos de carbono no mayor que 7" utilizado incluye, por ejemplo, un grupo cicloalquilo C_{3-7} tal como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etc.

El grupo heterocíclico no aromático de cantidad de átomos de carbono no mayor que 7" utilizado incluye, por ejemplo, un gruupo heterocíclico no aromático de 5 ó 10 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno, además de 1 a 7 átomos de carbono, tal como pirrolidinilo (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo), oxazolidinilo (por ejemplo, 2-oxazolidinilo), imidazolinilo (por ejemplo, 1-imidazolinilo, 2-imidazolinilo, 4-imidazolinilo), piperidinilo (por ejemplo, 1-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo), piperazinilo (por ejemplo, 1-piperazinilo, 2-piperazinilo), morfolino, tiomorfolino, etc.,

Los sustituyentes utilizados para estos "grupo hidrocarburo aromático C_{6-12}", "grupo heterocíclico aromático de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre", "grupo cíclico fusionado aromático C_{8-14}", "grupo heterocíclico funsionado aromático de 5 a 14 miembros que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre", "grupo hidrocarburo cíclico no aromático de cantidad de átomos de carbono no mayor que 7" y "grupo heterocíclico no aromático de cantidad de átomos de carbono no mayor que 7" incluyen, por ejemplo, los sustituyentes seleccionados de oxo, un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo, etc.), alquilendioxilo C_{1-3} (por ejemplo, metilendioxilo, etilendioxilo, etc.), nitro, ciano, un alquilo C_{1-6} opcionalmente sustituido, un alquenilo C_{2-6} opcionalmente sustituido, un alquinilo C_{2-6} opcionalmente sustituido, un cicloalquilo C_{3-8} opcionalmente sustituido, un arilo C_{6-14} opcionalmente sustituido, un aralquilo C_{7-16} opcionalmente sustituido, un alcoxilo C_{1-6} opcionalmente sustituido, hidroxilo, un ariloxilo C_{6-14} opcionalmente sustituido, un aralquiloxilo C_{7-16} opcionalmente sustituido, mercapto, un alquiltio C_{1-6} opcionalmente sustituido, un ariltio C_{6-14} opcionalmente sustituido, un aralquiltio C_{7-16} opcionalmente sustituido, un amino[amino opcionalmente

sustituido, un mono- o dialquil C_{1-6}-amino opcionalmente sustituido (por ejemplo, metilamino, dimetilamino, etilamino, dietilamino, propilamino, isopropilamino, etc.), un mono- o dialquenil C_{2-6}-amino opcionalmente sustituido (por ejemplo, vinilamino, propenilamino, isopropenylamino), un alquinilamino C_{2-6} opcionalmente sustituido (por ejemplo, 2-butin-1-il-amino, 4-pentin-1-il-amino, 5-hexin-1-il-amino), un mono- o di-cicloalquil C_{3-8}-amino opcionalmente sustituido (por ejemplo, ciclopropilamino, ciclohexilamino), un arilamino C6-14 opcionalmente sustituidos (por ejemplo, fenilamino, difenilamino, naftilamino), un alcoxiamino C_{1-6} opcionalmente sustituido (por ejemplo, metoxiamino, etoxiamino, propoxiamino, isopropoxiamino), formilamino, un alquilcarbonilamino C_{1-6} opcionalmente sustituido (por ejemplo, acetilamino, propionilamino, pivaloilamino, etc.), un cicloalquilcarbonilamino C_{3-8} opcionalmente sustituido (por ejemplo, ciclopropilcarbonilamino, ciclopentilcarbonilamino, ciclohexilcarbonilamino, etc.), un aril-carbonilamino C_{6-14} opcionalmente sustituido (por ejemplo, benzoilamino, naftoilamino, etc.), un alcoxi-carbonilamino C_{1-6} opcionalmente sustituidos (por ejemplo, metoxicarbonilamino, etoxicarbonilamino, propoxicarbonilamino, butoxicarbonilamino, etc.), un alquilsulfonilamino C_{1-6} opcionalmente sustituido (por ejemplo, metilsulfonilamino, etilsulfonilamino, etc.), un arilsulfonilamino C_{6-14} opcionalmente sustituido (por

ejemplo, fenilsulfonilamino, 2-naftilsulfonilamino, 1-naftilsulfonilamino, etc.)], formilo, carboxilo, un alquilcarbonilo C1-6 opcionalmente sustituidos (por ejemplo, acetilo, propionilo, pivaloilo, etc.), un cicloalquilcarbonilo C3-8 opcionalmente sustituido (por ejemplo, ciclopropilcarbonilo, ciclopentilcarbonilo, ciclohexilcarbonilo, 1-metil-ciclohexil-carbonilo, etc.), un aril-carbonilo C_{6-14} opcionalmente sustituido (por ejemplo, benzoilo, 1-naftoilo, 2-naftoilo, etc.), un aralquilcarbonilo C_{7-16} opcionalmente sustituido (por ejemplo, fenilacetilo, 3-fenilpropionilo, etc.), un carbonilo heterocíclico de 5 a 7 miembros opcionalmente sustituido que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionado de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, nicotinoilo, isonicotinoilo, tenoilo, furoilo, morfolinocarbonilo, tiomorfolinocarbonilo, piperazin-1-ilcarbonilo, pirrolidin-1-ilcarbonilo, etc.), un carboxilo opcionalmente esterificado, un grupo carbamoilo opcionalmente sustituido, un alquilsulfonilo C_{1-6} opcionalmente sustituido (por ejemplo, metilsulfonilo, etilsulfonilo, etc.), un alquilsulfinilo C_{1-6} opcionalmente sustituido (por ejemplo, metilsulfinilo, etilsulfinilo, etc.), un arilsulfonilo C6-14 opcionalmente sustituido (por ejemplo, fenilsulfonilo, 1-naftilsulfonilo, 2-naftilsulfonilo, etc.), un arilsulfinilo C_{6-14} opcionalmente sustituido (por ejemplo,

fenilsulfinilo, 1-naftilsulfinilo, 2-naftilsulfinilo, etc.), un alquilcarboniloxilo C_{1-6} opcionalmente sustituido (por ejemplo, acetoxilo, propioniloxilo, etc.), un aril-carboniloxilo C_{6-14} opcionalmente sustituido (por ejemplo, benzoiloxilo, naftilcarboniloxilo, etc.), un alcoxi-carboniloxilo C_{1-6} opcionalmente sustituido (por ejemplo, metoxicarboniloxilo, etoxicarboniloxilo, propoxicarboniloxilo, butoxicarboniloxilo, etc.), un mono- alquilcarbamoiloxilo C_{1-6} opcionalmente sustituido (por ejemplo, metilcarbamoiloxilo, etilcarbamoiloxilo, etc.), un dialquilcarbamoiloxilo C_{1-6} opcionalmente sustituido (por ejemplo, dimetilcarbamoiloxilo, dietilcarbamoiloxilo, etc.), un mono- o di-arilcarbamoiloxilo C_{6-14} opcionalmente sustituido (por ejemplo, fenilcarbamoiloxilo, naftilcarbamoiloxilo, etc.), un grupo heterocíclico opcionalmente sustituido, sulfo, sulfamoilo, sulfinamoilo, sulfenamoilo o un grupo de 2 o más (por ejemplo, 2 ó 3) de estos sustituyentes combinados, y lo similar (grupo A sustituyente). El número de sustituyentes no está limitado particularmente pero éstos anillos pueden tener 1 a 5, preferentemente 1 a 3 sustituyentes en posiciones sustituibles, y cuando hay dos o más sustituyentes, cada sustituyente pueden ser igual o diferente.

El "grupo carboxilo opcionalmente esterificado" utilizado en el grupo A sustituyente incluye, por

ejemplo, un alcoxi C_{1-6}-carbonilo opcionalmente sustituido (por ejemplo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, terc-butoxicarbonilo, etc.), un ariloxi C_{6-14}-carbonilo opcionalmente sustituido (por ejemplo, fenoxicarbonilo, etc.), un aralquiloxi C_{7-16}-carbonilo opcionalmente sustituido (por ejemplo, benciloxicarbonilo, fenetiloxicarbonilo, etc.), y lo similar.

El "alquilo C_{1-6}" en el "alquilo C_{1-6} opcionalmente sustituido" usado en el grupo A sustituyente incluye, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, hexilo, etc.,,

El "alquenilo C_{2-6}" en el "alquenilo C_{2-6} opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, vinilo, propenilo, isopropenilo, 2-buten-1-ilo, 4-penten-1-ilo, 5-hexen-1-ilo, etc.

El "alquinilo C_{2-6}" en el "alquinilo C_{2-6} opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, 2-butin-1-ilo, 4-pentin-1-ilo, 5-hexin-1-ilo, etc.,

El "cicloalquilo C_{3-8}" en el "cicloalquilo C_{3-8} opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etc.

El arilo C_{6-14} en el arilo C_{6-14} opcionalmente

sustituido utilizado en el grupo A sustituyente incluye, por ejemplo, fenilo, 1-naftilo, 2-naftilo, 2-bifenililo, 3-bifenililo, 4-bifenililo, 2-antrilo, etc.

El "aralquilo C_{7-16}" en el "aralquilo C_{7-16} opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, bencilo, fenetilo, difenilmetilo, 1-naftilmetilo, 2-naftilmetilo, 2,2-difeniletilo, 3-fenilpropilo, 4-fenilbutilo, 5-fenilpentilo, 2-bifenililmetilo, 3-bifenililmetilo, 4-bifenililmetilo), etc.

El "alcoxilo C_{1-6}" en el "alcoxilo C_{1-6} opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, metoxilo, etoxilo, propoxilo, isopropoxilo, butoxilo, isobutoxilo, sec-butoxilo, pentiloxilo, hexiloxilo, etc.

El "ariloxilo C_{6-14}" en el "ariloxilo C_{6-14} opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, feniloxilo, 1-naftiloxilo, 2-naftiloxilo, etc.

El "aralquiloxilo C_{7-16}" en el "aralquiloxilo C_{7-16} opcionalmente sustituido utilizado en el grupo A sustituyente incluye, por ejemplo, benziloxilo, fenetiloxilo, etc.

El "alquiltio C_{1-6}" en el "alquiltio C_{1-6} opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, metiltio, etiltio, propiltio, isopropiltio, butiltio, sec-butiltio, terc-

butiltio, etc.

El "ariltio C_{6-14}" en el "ariltio C_{6-14} opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, feniltio, 1-naftiltio, 2-naftiltio, etc.,

El "aralquiltio C_{7-16}" en el "aralquiltio C_{7-16} opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, benciltio, fenetiltio, etc.

Los sustituyentes usados en el grupo A sustituyente para estos "alcoxi-carbonilo C_{1-6}", "grupo alquilo C_{1-6}", "alquenilo C_{2-6}", "alquinilo C_{2-6}", "alcoxilo C_{1-6}", "alquiltio C_{1-6}", "alquil C_{1-6}-amino, "alquenil C_{2-6}-amino, "alquinilamino C_{2-6}", "alcoxiamino C_{1-6}, "alquilcarbonilo C_{1-6}", "alquilsulfonilo C_{1-6}", "alquilsulfinilo C_{1-6}", "alquilcarbonilamino C_{1-6}", "alcoxi C_{1-6}-carbonilamino", alquilsulfonilamino C_{1-6}", "alquilcarboniloxilo C_{1-6}", "alcoxi C_{1-6}-carboniloxilo", "mono- alquilcarbamoiloxilo C_{1-6}" y "dialquilcarbamoiloxilo C_{1-6}" incluyen 1 a 5 sustituyentes seleccionados de, por ejemplo, un átomo halógeno (por ejemplo, átomo de flúor, átomo de cloro, átomo de bromo, átomo de iodo), carboxilo, hidroxilo, amino, un mono- o dialquilamino C_{1-6}, un mono- o di-arilamino C_{6-14}, un cicloalquilo C_{3-8}, un alcoxilo C_{1-6}, un alcoxi-carbonilo C_{1-6}, un alquiltio C_{1-6}, un alquilsulfinilo C_{1-6}, un alquilsulfonilo C_{1-6}, carboxilo opcionalmente esterificado descripto precedentemente, carbamoilo, tiocarbamoilo, un mono-alquilcarbamoilo C_{1-6}

(por ejemplo, metilcarbamoilo, etilcarbamoilo, etc.), un di-alquilcarbamoilo C_{1-6} (por ejemplo, dimetilcarbamoilo, dietilcarbamoilo, etilmetilcarbamoilo, etc.), un mono- o diarolcarbamoilo C_{6-14} (por ejemplo, fenilcarbamoilo, 1-naftilcarbamoilo, 2-naftilcarbamoilo, etc.), un mono- o dicarbamoilo heterocíclico de 5 a 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, 2-piridilcarbamoilo, 3-piridilcarbamoilo, 4-piridilcarbamoilo, 2-tienilcarbamoilo, 3-tienilcarbamoilo, etc.) y lo similar.

Los sustituyentes utilizados en el grupo A sustituyente para el "ariloxi C_{6-14}-carbonilo", "aralquiloxi C_{7-16}-carbonilo", "cicloalquilo C_{3-8}", "arilo C_{6-14}", "aralquilo C_{7-16}", "ariloxilo C_{6-14}", "aralquiloxilo C_{7-16}", "ariltio C_{6-14}", "aralquiltio C_{7-16}", cicloalquil C_{3-8}-amino , arilamino C_{6-14}, "cicloalquilcarbonilo C_{3-8}", "aril C_{6-14}-carbonilo", "aralquilcarbonilo C_{7-16}", "carbonilo heterocíclico de 5 a 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionado de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono", "arilsulfonilo C_{6-14}", "arilsulfinilo C_{6-14}", "cicloalquilcarbonilamino C_{3-8}", "aril C_{6-14}-carbonilamino", "arilsulfonilamino C_{6-14}", "aril C_{6-14}-carboniloxilo" y "mono- o diarilcarbamoiloxilo C_{6-14}" incluyen 1 a 5 sustituyentes seleccionados de, por

ejemplo, un átomo halógeno, hidroxilo, carboxilo, nitro, ciano, alquilo C_{1-6} opcionalmente sustituido descripto anteriormente, alquenilo C_{2-6} opcionalmente sustituido descripto anteriormente, el alquinilo C_{2-6} opcionalmente sustituido descripto anteriormente, cicloaquilo C_{3-8} opcionalmente sustituido descripto anteriormente, alcoxilo C_{1-6} opcionalmente sustituido descripto precedentemente, alquiltio C_{1-6} opcionalmente sustituido descripto precedentemente, alquilsulfinilo C_{1-6} opcionalmente sustituido descripto precedentemente, alquilsulfonilo C_{1-6} opcionalmente sustituido descripto precedentemente, carboxilo opcionalmente esterificado descripto precedentemente, carbamoilo, tiocarbamoilo, un mono-alquilcarbamoilo C_{1-6}, un di- alquilcarbamoilo C_{1-6}, un mono- o diarilcarbamoilo C_{6-14}, un mono- o dicarbamoilo heterocíclico de 5 a 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono, y lo similar.

El "grupo heterocíclico opcionalmente sustituido" utilizado en el grupo A sustituyente incluye, por ejemplo, un grupo heterocíclico de 5 a 14 miembros (monocíclico, bicíclico o tricíclico) que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de átomos de carbono que pueden ser opcionalmente sustituidos con un átomo halógeno, hidroxilo, carboxilo, nitro, ciano,

alquilo C_{1-6} opcionalmente sustituido descripto anteriormente, alquenilo C_{2-6} opcionalmente sustituido descripto anteriormente, alquinilo C_{2-6} opcionalmente sustituido descripto anteriormente, cicloaquilo C_{3-8} opcionalmente sustituido descripto anteriormente, arilo C_{6-14} opcionalmente sustituido descripto precedentemente, alcoxilo C_{1-6} opcionalmente sustituido descripto precedentemente, alquiltio C_{1-6} opcionalmente sustituidos descripto precedentemente, ariltio C_{6-14} opcionalmente sustituido descripto precedentemente, aralquiltio C_{7-16} opcionalmente sustituidos descripto precedentemente, alquilsulfinilo C_{1-6} opcionalmente sustituido descripto precedentemente, arilsulfinilo C_{6-14} opcionalmente sustituido descripto precedentemente, alquilsulfonilo C_{1-6} opcionalmente sustituido descripto precedentemente, arilsulfonilo C_{6-14} opcionalmente sustituido descripto precedentemente, carboxilo opcionalmente esterificado descripto precedentemente, carbamoilo, tiocarbamoilo, mono-alquilcarbamoilo C_{1-6}, di- alquilcarbamoilo inferior, un mono- o di-arilcarbamoilo C_{6-14}, un mono- o di-carbamoilo heterocíclico de 5 o 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionado de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono, o lo similar; preferentemente (i) un grupo heterocíclico aromático de 5 a 14 miembros (preferentemente, de 5 a 10 miembros), (ii) un grupo heterocíclico no aromático de 5 a 10 miembros o (iii) un

grupo monovalente formado por un átomo de hidrógeno opcional de anillo hetero puenteado de 7 a 10 miembros, y más preferentemente, un grupo heterocíclico aromático de 5 miembros. Es usado específicamente un grupo heterocíclico aromático tal como tienilo (por ejemplo, 2-tienilo, 3-tienilo), furilo (por ejemplo, 2-furilo, 3-furilo), piridilo (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo), tiazolilo (por ejemplo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo), oxazolilo (por ejemplo, 2-oxazolilo, 4-oxazolilo), quinolilo (por ejemplo, 2-quinolilo, 3-quinolilo, 4-quinolilo, 5-quinolilo, 8-quinolilo), isoquinolilo (por ejemplo, 1-isoquinolilo, 3-isoquinolilo, 4-isoquinolilo, 5-isoquinolilo), pirazinilo, pirimidinilo (por ejemplo, 2-pirimidinilo, 4-pirimidinilo), pirrolilo (por ejemplo, 1-pirrolilo, 2-pirrolilo, 3-pirrolilo), imidazolilo (por ejemplo, 1-imidazolilo, 2-imidazolilo, 4-imidazolilo), pirazolilo (por ejemplo, 1-pirazolilo, 3-pirazolilo, 4-pirazolilo), piridazinilo (por ejemplo, 3-piridazinilo, 4-piridazinilo), isotiazolilo (por ejemplo, 3-isotiazolilo), isoxazolilo (por ejemplo, 3-isoxazolilo), indolilo (por ejemplo, 1-indolilo, 2-indolilo, 3-indolilo), 2-benzotiazolilo, benzo[b]tienilo, (por ejemplo, 2-benzo[b]tienilo, 3-benzo[b]tienilo), benzo[b]furanilo (por ejemplo, 2-benzo[b]furanilo, 3-benzo[b]furanilo), etc., un grupo heterocíclico no aromático tal como pirrolidinilo (por ejemplo, 1-

pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo), oxazolidinilo (por ejemplo, 2-oxazolidinilo), imidazolinilo (por ejemplo, 1-imidazolinilo, 2-imidazolinilo, 4-imidazolinilo), piperidinilo (por ejemplo, 1-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo), piperazinilo (por ejemplo, 1-piperazinilo, 2-piperazinilo), morfolino, tiomorfolino, etc.

El "grupo carbamoilo opcionalmente sustituido" utilizado en el grupo A sustituyente incluye un grupo carbamoilo que puede ser opcionalmente sustituido con alquilo C_{1-6} opcionalmente sustituido descripto precedentemente, un alquenilo C_{2-6} opcionalmente sustituido, un alquinilo C_{2-6} opcionalmente sustituido, un cicloalquilo C_{3-8} opcionalmente sustituido, un arilo C_{6-14} opcionalmente sustituido, un grupo heterocíclico opcionalmente sustituidos, etc., y los ejemplos específicos son carbamoilo, tiocarbamoilo, un mono-alquilcarbamoilo C_{1-6} (por ejemplo, metilcarbamoilo, etilcarbamoilo, etc.), di- alquilcarbamoilo C_{1-6} (por ejemplo, dimetilcarbamoilo, dietilcarbamoilo, etilmetilcarbamoilo, etc.), alquil C_{1-6} (alcoxi C_{1-6})carbamoilo (por ejemplo, metil(metoxi)carbamoilo, etil(metoxi)carbamoilo), un mono- o diarilcarbamoilo C_{6-14} (por ejemplo, fenilcarbamoilo, 1-naftilcarbamoilo, 2-naftilcarbamoilo, etc.), un mono- o di- carbamoilo heterocíclico de 5 a 7 miembros que contiene 1 a 4

heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, 2-piridilcarbamoilo, 3-piridilcarbamoilo, 4-piridilcarbamoilo, 2-tienilcarbamoilo, 3-tienilcarbamoilo, etc.), un carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidinilcarbonilo, hexametileniminocarbonilo), y lo similar.

El "amino opcionalmente sustituido" utilizado en el grupo A sustituyente incluye un amino que puede ser opcionalmente sustituido con 1 o 2 grupos seleccionado del alquilo C_{1-6} opcionalmente sustituido, alquenilo C_{2-6} opcionalmente sustituido descripto precedentemente, alquinilo C_{2-6} opcionalmente sustituido descripto precedentemente, cicloaquilo C_{3-8} opcionalmente sustituido descripto anteriormente, arilo C_{6-14} opcionalmente sustituido descripto precedentemente, alcoxilo C_{1-6} opcionalmente sustituido descripto anteriormente, formilo, alquilcarbonilo C_{1-6} opcionalmente sustituido descripto precedentemente, cicloalquilcarbonilo C_{3-8} opcionalmente sustituido descripto precedentemente, aril C_{6-14}-carbonilo opcionalmente sustituido descripto precedentemente, alcoxi C_{1-6}-carbonilo opcionalmente sustituido descripto precedentemente, alquilsulfonilo C_{1-6} opcionalmente sustituido descripto precedentemente, un arilsulfonilo C_{6-14} opcionalmente sustituido) y lo similar.

Más preferentemente, los sustituyentes para el "grupo hidrocarburo aromático C_{6-12}", "grupo heterocíclico aromático de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre", "grupo cíclico fusionado aromático C_{8-14}", "grupo heterocíclico fusionado aromático de 5 a 14 miembros que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre", "grupo hidrocarburo cíclico no aromático de cantidad de átomos de carbono no mayor que 7" y "grupo heterocíclico no aromático de cantidad de átomos de carbono no mayor que 7" son un átomo halógeno, hidroxilo, un alcoxilo C_{1-6}, un alquilo C_{1-6} opcionalmente halogenado, un alcoxilo C_{1-6} opcionalmente halogenado, amino, nitro, ciano, etc.

Los ejemplos de R^4 usados incluyen:

(1) "un grupo alquilo C_{1-4} que posee un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido" como bencilo, 2-fluorobencilo, 3-fluorobencilo, 4-fluorobencilo, 4-clorobencilo, 3,4-difluorobencilo, 3,4-diclorobencílico, pentafluorobencilo, 4-hidroxibencilo, 4-metoxibencilo, 3-trifluorometilbencilo, 4-aminobencilo, 4-nitrobencilo, 4-cianobencilo, fenetilo, etc.;

(2) "un grupo alquilo C_{1-4} que posee un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y

heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre como 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 2-tienilmetilo, 3-tienilmetilo, 4-thiazolilmetilo, etc.;

(3) "un grupo alquilo C_{1-4} que posee un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido" como 1-naftilmetilo, 2-naftilmetilo, inden-2-ilmetilo, etc.;

(4) "un grupo alquilo C_{1-4} que posee un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre" como 3-indolmetilo, 1-formilindol-3-ilmetilo, 3-benzo[b]tienilmetilo, 2-quinolilmetilo, etc.;

(5) "un grupo alquilo C_{1-4} que posee un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7" como ciclohexilmetilo, ciclopentilmetilo, indan-2-ilmetilo, etc.;

(6) "un grupo alquilo C_{1-4} que posee un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7" como 4-piperidinilmetilo, tetrahidrofurfurilo, tetrahidrofuran-2-ilo, tetrahidropiran-3-ilo, indolin-3-ilo, etc., preferentemente, bencilo, 2-fluorobencilo, 3-fluorobencilo, 4-fluorobencilo, 4-hidroxibencilo, 4-aminobencilo, 4-nitrobencilo, 4-clorobencilo, 4-

metoxibencilo, 4-cianobencilo, 3-trifluorometilbencilo, 3,4-diclorobencílico, 3,4-difluorobencilo, pentafluorobencilo, 3-piridilmetilo, 4-piridilmetilo, 3-indolmetilo, 1-formilindol-3-ilmetilo, 3-benzo[b]tienilmetilo, 2-quinolilmetilo, 1-naftilmetilo, 2-naftilmetilo, ciclohexilmetilo, fenetilo, etc., y más preferentemente, bencilo, 2-fluorobencilo, 3-fluorobencilo, 4-fluorobencilo, 4-hidroxibencilo, 4-aminobencilo, 4-nitrobencilo, 4-clorobencilo, 4-metoxibencilo, 4-cianobencilo, 3-trifluorometilbencilo, 3,4-diclorobencílico, 3,4-difluorobencilo, pentafluorobencilo, 3-piridilmetilo, 4-piridilmetilo, 3-indolmetilo, 3-benzo[b]tienilmetilo, 1-naftilmetilo, 2-naftilmetilo, ciclohexilmetilo, etc.

Q^1 representa un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de:

(1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido;

(2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre;

(3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido;

(4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11

átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre;

(5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7; y

(6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7; y utiliza los mismos sustituyentes como R^4.

Los ejemplos Q^1 incluyen:

(1) "un grupo alquilo C_{1-4} que posee un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido" tal como bencilo, 2-fluorobencilo, 3-fluorobencilo, 4-fluorobencilo, 4-clorobencilo, 3,4-difluorobencilo, 3,4-diclorobencílico, pentafluorobencilo, 4-hidroxibencilo, 4-metoxibencilo, 4-trifluorometilbencilo, 4-aminobencilo, 4-nitrobencilo, 4-cianobencilo, fenetilo, etc.;

(2) "un grupo alquilo C_{1-4} que tiene un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre" tal como 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 2-tienilmetilo, 3-tienilmetilo, 4-tiazolilmetilo, etc.;

(3) "un grupo alquilo C_{1-4} que posee un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido," tal como1-naftilmetilo, 2-naftilmetilo, inden-2-ilmetilo;

(4) "un grupo alquilo C_{1-4} que posee un grupo

heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre" tal como 3-indolmetilo, 1-formilindol-3-ilmetilo, 3-benzo[b]tienilmetilo, 2-quinolilmetilo, etc.;

(5) "un grupo alquilo C_{1-4} que posee un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7" como ciclohexilmetilo, ciclopentilmetilo, indan-2-ilmetilo, etc.;

(6) "un grupo alquilo C_{1-4} que posee un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7" como 4-piperidinilmetilo, tetrahidrofurfurilo, tetrahidrofuran-2-ilo, tetrahidropiran-3-ilo, indolin-3-ilo, etc.; preferentemente, ciclohexilmetilo, bencilo, 4-fluorobencilo, 4-hidroxibencilo, 4-metoxibencilo, pentafluorobenzilo, 2-piridilmetilo, 4-piridilmetilo, 1-naftilmetilo, 2-naftilmetilo, 3-indolmetilo, 2-tienilmetilo, etc. y más preferentemente, bencilo, 4-fluorobencilo, ciclohexilmetilo, etc.,

Q^2 representa (1) CH_2 que puede ser opcionalmente sustituido con un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, (2) NH que puede ser opcionalmente sustituido con un grupo

alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, o (3) O.

Los ejemplos del "grupo alquilo C_{1-4}" usados son metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, etc.,

Preferentemente, Q^2 es CH_2, $CH(CH_3)$, $CH(CH_2OH)$, NH, o lo similar.

Y representa un grupo representado por la fórmula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, ó -CH=CH-, que puede ser opcionalmente sustituido con un grupo alquilo C_{1-6}.

Los ejemplos del "grupo alquilo C_{1-6}" usados son metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, hexilo, etc.,

Preferentemente, Y es un grupo representado por la fórmula: -CONH-, -CSNH-, -NHCO-, $-CH_2NH-$, $-CH_2O-$, -COO- ó -CSO- (más preferentemente, grupo representado por la fórmula: -CONH-, -CSNH-, -NHCO- o $-CH_2NH-$).

Z^9 representa átomo de hidrógeno, O ó S, preferentemente O ó S,;

en donde, cuando Z^9 representa átomo de hidrógeno, una estructura de la fracción representada por $>C=Z^9$ indica una estructura de $>CH_2$.

P y P' los cuales pueden ser iguales o diferentes, cada uno puede formar un anillo combinando entre sí P y

P' o P y Q^1 y representa:

(1) átomo de hidrógeno;

(2) un residuo de aminoácido opcional limitado continua o discontinuamente del C terminal de la secuencia de aminoácido 1-48 en la secuencia de aminoácido representada por SEQ ID NO: 1;

(3) un grupo representado por la fórmula:

J^1-J^2-C(J^3)(Q^3)Y^1C(J^4)(Q+)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})- (en donde cada símbolo posee el mismo significado según lo descripto anteriormente).;

(4) un grupo representado por la fórmula:

-J^1-J^2-C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})- (en donde cada símbolo posee el mismo significado según lo descripto anteriormente);

(5) un grupo representado por la fórmula:

J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q11)C(=Z^{10})- (en donde cada símbolo posee el mismo significado según lo descripto anteriormente);

(6) un grupo representado por la fórmula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})- (en donde cada símbolo posee el mismo significado según lo descripto anteriormente); o,

(7) un grupo representado por el formula: J^1- (en donde J^1 posee el mismo significado según lo descripto anteriormente).

Los ejemplos específicos del "residuo de aminoácido opcional limitado continua o discontinuamente del C terminal de la secuencia de aminoácido 1-48 representado

por SEQ ID NO: 1" utilizado incluye:

(1) Asn-

(2) Trp Asn-,

(3) Asn Trp Asn-,

(4) Tyr Asn Trp Asn-,

(5) Asn Tyr Asn Trp Asn-,

(6) Pro Asn Tyr Asn Trp Asn-,

(7) Leu Pro Asn Tyr Asn Trp Asn-,

(8) Asp Leu Pro Asn Tyr Asn Trp Asn-,

(9) Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(10) Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(11) Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(12) Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(13)Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(14) Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(15) Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(16) Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(17) Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(18) Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(19) Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(20) Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp

Leu Pro Asn Tyr Asn Trp Asn-,

(21) Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(22) Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(23) Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(24) Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(25) Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(26) su Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(27) Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(28) Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(29) Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(30) Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(31) Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(32) Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(33) Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(34) Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(35) Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(36) Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(37) Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(38) Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(39) Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(40) Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(41) Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(42) Prol Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(43) Prol Pro del Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(44) Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(45) Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(46) Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(47) Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(48) Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-, etc.

J^1 representa (a) átomo de hidrógeno o (b) (i) un grupo acilo C_{1-15}, (ii) un grupo alquilo C_{1-15}, (iii) un grupo arilo C_{6-14}, (iv) grupo carbamoilo, (v) grupo carboxilo, (vi) grupo sulfino, (vii) grupo amidino, (viii) grupo glioxiloilo o (ix) grupo amino, tales grupos pueden ser opcionalmente sustituidos con un sustituyente que contiene un grupo cíclico opcionalmente sustituido.

Por ejemplo, el "grupo cíclico" utilizado incluye "un grupo hidrocarburo aromático opcionalmente sustituido", "un grupo heterocíclico aromático opcionalmente sustituido", "un grupo cíclico fusionado aromático opcionalmente sustituido", "un grupo heterocíclico fusionado aromático opcionalmente sustituido", "un grupo hidrocarburo cíclico no aromático opcionalmente sustituido", "un grupo heterocíclico no aromático opcionalmente sustituido", etc., y como el "grupo hidrocarburo aromático", "grupo heterocíclico aromático", "grupo cíclico fusionado aromático" y "grupo heterocíclico fusionado aromático", se utilizan los mismos grupos indicados precedentemente.

El "grupo hidrocarburo cíclico no aromático" utilizado incluye, por ejemplo, un grupo cicloalquilo C_{3-8} tal como ciclopropilo, ciclobutilo, ciclopentilo,

ciclohexilo, etc.

El "grupo heterocíclico no aromático" utilizado incluye, por ejemplo, un grupo heterocíclico no aromático de 5 ó 10 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de 1 a 7 átomos de carbono tal como pirrolidinilo (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo), oxazolidinilo (por ejemplo, 2-oxazolidinilo), imidazolinilo (por ejemplo, 1-imidazolinilo, 2-imidazolinilo, 4-imidazolinilo), piperidinilo (por ejemplo, 1-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo), piperazinilo (por ejemplo, 1-piperazinilo, 2-piperazinilo), morfolino, tiomorfolino, etc.,

El sustituyente opcionalmente presente en el "grupo cíclico" incluye los mismos sustituyentes indicados para el grupo A sustituyente descripto precedentemente.

El "grupo acilo C_{1-15}" usado incluye, por ejemplo, formilo, un alquilcarbonilo C_{1-14} (por ejemplo, un alquilcarbonilo C_{1-6} tal como acetilo, propionilo, pivaloilo, etc.) y lo similar.

Los ejemplos del "grupo alquilo C_{1-15}" utilizados incluyen metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, hexilo, heptilo, octilo, nonanilo, decanilo, etc.

Los ejemplos del "grupo arilo C_{6-14}" utilizados

incluyen fenilo, 1-naftilo, 2-naftilo, bifenilo, etc.,

(1) El grupo acilo C_{1-15} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico incluye (i) formilo, (ii) un alquilcarbonilo C_{1-14} (por ejemplo, un alquilcarbonilo C_{1-6} tal como acetilo, propionilo, pivaloilo, etc.), (iii) un cicloalquilcarbonilo C_{3-8} (por ejemplo, ciclopropilcarbonilo, ciclopentilcarbonilo, ciclohexilcarbonilo, 1-metilciclohexilcarbonilo, etc.), (iv) un cicloalquil C_{3-8}-alquilcarbonilo C_{1-6} (por ejemplo, ciclopropilacetilo, ciclopentilacetilo, ciclohexilacetilo, etc.), (v) un aril C_{6-14}-carbonilo (por ejemplo, benzoilo, 1-naftoilo, 2-naftoilo, etc.), un aralquilcarbonilo C_{6-14} (por ejemplo, fenilacetilo, 3-fenilpropionilo, etc.)., (vi) un carbonilo heterocíclico monocíclico de 5 a 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionado de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, nicotinoilo, isonicotinoilo, tenoilo, furoilo, morfolinocarbonilo, tiomorfolinocarbonilo, piperazin-1-ilcarbonilo, pirrolidin-1-ilcarbonilo, etc.), (vii) un alquilcarbonilo C_{1-6}-heterocíclico monocíclico de 5 a 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, 3-piridilacetilo, 4-piridilacetilo, 2-tienilacetilo, 2-

furilacetilo, morfolinoacetilo, tiomorfolinoacetilo, piperidin-2-acetilo, pirrolidin-2-ilacetilo, etc.), (viii) un carbonilo heterocíclico aromático bicíclico o tricíclico de 5 a 14 miembros (preferentemente, de 5 a 10 miembros) que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionado de los átomos de nitrógeno, azufre y oxígeno además de 3 a 11 átomos de carbono (por ejemplo, 2-indolecarbonilo, 3-indolecarbonilo, 2-quinolilcarbonilo, 1-isoquinolilcarbonilo, 2-benzo[b]tienilcarbonilo, 2-benzo[b]furanilcarbonilo, etc.), (ix) un alquilcarbonilo C_{1-6} heterocíclico aromático bicíclico o tricíclico de 5 a 14 miembros (preferentemente de 5 a 10 miembros) que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionado de los átomos de nitrógeno, azufre y oxígeno además de 3 a 11 átomos de carbono (por ejemplo, 2-indolacetilo, 3-indolacetilo, 2-quinolilacetilo, 1-isoquinolilacetilo, 2-benzo[b]tienilacetilo, 2-benzo[b]furanilacetilo, etc.), etc., preferentemente, acetilo, 2-indolecarbonilo, 3-indolecarbonilo, 3-indolacetilo, 3-indolepropionilo, 2-indolinecarbonilo, 3-fenilpropionilo, difenilacetilo, 2-piridincarbonilo, 3-piridincarbonilo, 4-piridincarbonilo, 1-piridinacetilo, 2-piridinacetilo, 3-piridinacetilo, 4-piridinacetilo, 3-(1-piridinio)propionilo, 3-(piridin-2-il)propionilo, 3-(piridin-3-il)propionilo, 3-(piridin-4-il)propionilo, 4-imidazolacetilo, ciclohexancarbonilo, 1-piperidinacetilo, 1-metil-1-piperidinioacetilo, 4-

piperidincarbonilo, 2-pirimidincarbonilo, 4-pirimidincarbonilo, 5-pirimidincarbonilo, 2-pirimidinacetilo, 4-pirimidinacetilo, 5-pirimidinacetilo, 3-(pirimidin-2-il)propionilo, 3-(pirimidin-4-il)propionilo, 3-(pirimidin-5-il)propionilo, butanoilo, hexanoilo, octanoilo, D-glucuronilo, amino-(4-hidroxifenil)acetilo), etc.

(2) Un grupo alquilo C_{1-15} utilizado, el cual puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico incluye, por ejemplo, (i) un mono- o di- alquilo C_{1-15} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, hexilo, heptilo, octilo, nonanilo, decanilo), (ii) un mono- o dicicloalquilo C_{3-8} (por ejemplo, ciclopropilo, ciclopentilo, etc.), (iii) un mono- o di- cicloalquil C_{3-8}-alquilo C_{1-7} (por ejemplo, ciclopropilmetilo, ciclopentilmetilo, ciclohexiletilo, etc.), (iv) un mono- o diaralquilo C_{7-15} (por ejemplo, bencilo, fenetilo, etc.), (v) un grupo mono- o dialquilo C1-6 heterocíclico monocíclico de 5 a 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionado de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, 3-piridilmetilo, 4-piridilmetilo, 2-tienilmetilo, furfurilo, etc.), (vi) un grupo mono- o dialquilo C_{1-6} heterocíclico aromático bicíclico o tricíclico de 5 a 14 miembros (preferentemente, de 5 a 10

miembros) que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionado de los átomos de nitrógeno, azufre y oxígeno además de 3 a 11 átomos de carbono (por ejemplo, 2-indolmetilo, 3-indolmetilo, 3-(indol-3-il)propilo, 2-quinolilmetilo, 1-isoquinolilmetilo, 2-benzo[b]tienilmetilo, 2-benzo[b]furanilmetilo, etc.), etc., preferentemente, metilo, etilo, bencilo, 3-(indol-3-il)propilo, etc.,

(3) Un grupo arilo C_{6-14} utilizado, el cual puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico incluye, por ejemplo, un grupo arilo C_{6-14} (por ejemplo, fenilo, naftilo, bifenilo) el cual puede ser opcionalmente sustituido con (i) un grupo carbocíclico C_{6-14} (por ejemplo, cicloalquilo, fenilo, 1-naftilo, 2-naftilo, etc.), (ii) un grupo heterocíclico monocíclico de 5 a 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, 3-piridilo, 2-tienilo, etc.), (iii) un grupo heterocíclico aromáticos bicíclico o tricíclico de 5 a 14 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de 3 a 11 átomos de carbono (preferentemente, de 5 a 10 miembros) (por ejemplo, 2-indolilo, 3-indolilo, 2-quinolilo, 1-isoquinolilo, 2-benzo[b]tienilo, 2-benzo[b]furanilo, etc.), etc.

(4) Un grupo carbamoilo opcionalmente sustituido utilizado, el cual puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico incluye, por ejemplo, (i) carbamoilo, (ii) un grupo mono- o di-alquilcarbamoilo C_{1-15} (por ejemplo, metilcarbamoilo, etilcarbamoilo, (iii) un mono- o di-cicloalquil C_{3-8}-carbamoilo (por ejemplo, ciclopropilcarbamoilo, ciclopentilcarbamoilo, ciclohexilcarbamoilo, etc.), (iv) un mono- o di-cicloalquil C_{3-8}-alquil C_{1-6}-carbamoilo (por ejemplo, ciclopropilmetilcarbamoilo, ciclopentilmetilcarbamoilo, 2-ciclohexiletilcarbamoilo, etc.) (v) un mono- o di-aril C_{6-14}-carbamoilo (por ejemplo, fenilcarbamoilo, etc.), un mono- o di-aralquil C_{6-14}-carbamoilo (por ejemplo, benzilcarbamoilo, fenetilcarbamoilo, etc.), (vi) un mono- o di-carbamoilo heterocíclico monocíclico de 5 a 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, 3-piridincarbamoilo, 2-tiofencarbamoilo, piperidin-3-ilcarbamoilo, etc.), (vii) un mono- o di-alquilcarbamoilo C_{1-6} heterocíclico monocíclico de 5 a 7 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de los átomos de carbono (por ejemplo, 3-piridilmetilcarbamoilo, 2-(piridin-2-il)etilcarbamoilo, 2-(piperidin-1-il)etilcarbamoilo, etc.), (viii) un mono- o di-carbamoilo

heterocíclico aromático bicíclico o tricíclico de 5 a 14 miembros que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de 3 a 11 átomos de carbono (preferentemente, de 5 a 10 miembros) (por ejemplo, 4-indolcarbamoilo, 5-indolcarbamoilo, 3-quinolilcarbamoilo, 5-quinolilcarbamoilo, etc.), (ix) un mono- o di-alquilcarbonilo C_{1-6} heterocíclico aromáticos bicíclico o tricíclico de 5 a 14 miembros (preferentemente, de 5 a 10 miembros)que contiene 1 a 4 heteroátomos de 1 ó 2 especies seleccionados de los átomos de nitrógeno, azufre y oxígeno además de 3 a 11 átomos de carbono (por ejemplo, benzimidazol-2-ilmetilcarbamoilo, 2-(indol-3-il)etilcarbamoilo, etc.), (x) un carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidinilcarbonilo, hexametileniminocarbonilo, etc.), (xi) un acilcarbamoilo C_{1-15} (el acilo C_{1-15} tiene el mismo significado en la presente en cuanto a "grupo acilo C_{1-15}" en el "grupo acilo C_{1-15} utilizado que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico"), (xii) un alquilaminocarbamoilo C_{1-15} (el alquilo C_{1-15} tiene el mismo significado en la presente con respecto al "grupo alquilo C_{1-15}" en el "grupo alquilo C_{1-15} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico"), (xiii) un arilaminocarbamoilo C_{6-14} (el grupo arilo C_{6-14} en la presente posee el mismo significado que

el del "grupo arilo C_{6-14} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico"), etc., preferentemente, 2-(indol-3-il)etilcarbamoilo, etc.,

(5) Un grupo carboxilo utilizado, el cual puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico incluye, por ejemplo, (i) un alquiloxicarbonilo C_{1-15} (el alquilo C_{1-15} tiene el mismo significado en la presente con respecto al "grupo alquilo C_{1-15}" en el "grupo alquilo C_{1-15} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico" por ejemplo, terc-butiloxicarbonilo, benciloxicarbonilo, 9-fluorenilmetoxicarbonilo), (ii) un ariloxicarbonilo C_{6-14} (el arilo C_{6-14} tiene el mismo significado en la presente con respecto al "grupo arilo C_{6-14}" en el "grupo arilo C_{6-14} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico" por ejemplo, fenoxicarbonilo), etc.

(6) Un grupo sulfino utilizado, el cual puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico incluye, por ejemplo, (i) un alquilsulfonilo C_{1-15} (el alquilo C_{1-15} tiene el mismo significado en la presente con respecto al "grupo alquilo C_{1-15}" en el "grupo alquilo C_{1-15} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico" por ejemplo, bencilsulfonilo), (ii) un arilsulfonilo C_{6-14} (el arilo C_{6-14} tiene el mismo

significado en la presente con respecto al "grupo arilo C_{6-14}" en el "grupo arilo C_{6-14} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico" por ejemplo, tosilo), etc.

(7) Un grupo amidino utilizado, el cual puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico incluye, por ejemplo, (i) amidino, (ii) un alquilamidino C_{1-15} (el alquilo C_{1-15} tiene el mismo significado en la presente con respecto al "grupo alquilo C_{1-15}" en el "grupo alquilo C_{1-15} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico" por ejemplo, N-metilamidino), (iii) un acilamidino C_{1-15} (el acilo C_{1-15} tiene el mismo significado en la presente con respecto al "grupo acilo C1-15" en el "grupo acilo C_{1-15} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico" por ejemplo, N-acetilamidino), etc.

(8) Un grupo glioxiloilo utilizado, que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico incluye, por ejemplo, (i) un alquiloxalilo C_{1-15} (el alquilo C_{1-15} tiene el mismo significado en la presente con respecto al "grupo alquilo C_{1-15}" en el "grupo alquilo C_{1-15} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico" por ejemplo, etiloxalilo), (ii) un ariloxalilo C_{6-14} (el arilo C_{6-14} tiene el mismo significado en la presente con respecto al "grupo arilo C_{6-14}" en el

"grupo arilo C_{6-14} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico" por ejemplo, feniloxalilo), etc.

(9) Un grupo amino utilizado, el cual puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico incluye, por ejemplo, (i) un alquilamino C_{1-15} (el alquilo C_{1-15} tiene el mismo significado en la presente con respecto al "grupo alquilo C_{1-15}" en el "grupo alquilo C_{1-15} que puede ser opcionalmente sustituido con un sustituyente que contiene un grupo cíclico".

Entre los descriptos anteriormente, J^1 es preferentemente átomo de hidrógeno, formilo, acetilo, 3-indolcarbonilo, 3-(indol-3-il)propionilo, 3-fenilpropionilo, difenilacetilo, 3-(piridin-3-il)propionilo, 4-imidazoleacetilo, ciclohexancarbonilo, 1-piperidinacetilo, 1-metil-1-piperidinioacetilo, 4-piperidincarbonilo, hexanoilo, amino-(4-hidroxifenil)acetilo, D-glucuronilo, 2-(indol-3-il)etilcarbamoilo, terc-butiloxicarbonilo, 9-fluorenilmetoxicarbonilo, amidino, 4-guanidometilbenzoilo, benzoilo, 3-indolacetilo, benziloxicarbonilo, tosyl, fenilo, bencilo, fenetilo, 3-piridincarbonilo, 2-piridincarbonilo, 4-piridincarbonilo, propionilo, isobutirilo, fenilacetilo, 2-metilnicotinoilo, 5-metilnicotinoilo, 6-metilnicotinoilo, pirazincarbonilo, ciclopropancarbonilo, trifluoroacetilo,

(R)-3-hidroxi-2-metilpropionilo, 2-hidroxiisobutirilo, 3-furancarbonilo, pirrol-2-carbonilo, 4-imidazolcarbonilo, 6-hidroxinicotinoilo, 6-cloronicotinoilo, 6-(trifluorometil)nicotinoilo, dimetilcarbamoilo, 1-azetidincarbonilo, 2-azetidincarbonilo, 4-aminobenzoilo, 4-aminometilbenzoilo, pirrol-3-carbonilo, pirimidin-4-carbonilo, pirimidin-2-carbonilo, piridazin-4-carbonilo, 6-aminocaproilo, glicilo, glicilglicilo, glicilglicilglicilo, alanilalanilalanilo, alanilalanilalanilalanilo, acetilglicilo, acetilglicilglicilo, acetilglicilglicilglicilo, acetilalanilalanilalanilo, acetilalanilalanilalanilalanilo, D-arginilglicilo, D-arginilglicilglicilo, D-arginilglicilglicilglicilo, D-arginilalanilalanilalanilo, D-arginilalanilalanilalanilalanilo, acetil-D-arginilglicilo, acetil-D-arginilglicilglicilo, acetil-D-arginilglicilglicilglicilo, acetil-D-arginilalanilalanilalanilo, acetil-D-arginilalanilalanilalanilalanilo, ciclopropancarbonilo, ciclopentancarbonilo, ciclobutancarbonilo, ciclohexancarbonilo, 1-naftoilo, 2-naftoilo, arginilo, arginilarginilo, 6-(arginilamino)caproilo, 6-(D-arginilamino)caproilo, 6-(D-arginil-D-arginilamino)caproilo, 6-(acetil-D-arginilamino)caproilo, 6-((R)-2,3-diaminopropionilamino)caproilo, 6-(D-norleucilamino)caproilo, 3-(D-arginilamino)propionilo, 4-

(D-arginilamino)butirilo, 4-(D-arginil-D-arginilamino)butirilo, 4-(D-arginil-D-arginil-D-arginilamino)butirilo, 3-(4-hidroxifenil)propionilo, butirilo, metilo, adipoilo, piroglutamilo, glicolilo,etc., y los utilizados más preferentemente son átomo de hidrógeno, formilo acetilo, propionilo, 3-indolcarbonilo, 3-(indol-3-il)propionilo, 3-fenilpropionilo, 3-(piridin-3-il)propionilo, 4-imidazoleacetilo, ciclohexancarbonilo, hexanoilo, amino-(4-hidroxifenil)acetilo, 2-(indol-3-il)etilcarbamoilo, 9-fluorenilmetoxicarbonilo, amidino, 4-guanidometilbenzoilo, benzoilo, 3-indolacetilo, bencilo, fenetilo, 3-piridincarbonilo, 2-piridincarbonilo, 4-piridincarbonilo, isobutirilo, fenilacetilo, 6-metilnicotinoilo, pirazinecarbonilo, ciclopropancarbonilo, trifluoroacetilo, (R)-3-hidroxi-2-metilpropionilo, 2-hidroxiisobutirilo, 3-furancarbonilo, pirrol-2-carbonilo, 4-imidazolcarbonilo, 6-hidroxinicotinoilo, 6-cloronicotinoilo, 6-(trifluorometil)nicotinoilo, dimetilcarbamoilo, 1-azetidincarbonilo, 4-aminobenzoilo, 4-aminometilbenzoilo, pirrol-3-carbonilo, pirimidin-4-carbonilo, pirimidin-2-carbonilo, piridazin-4-carbonilo, 6-aminocaproilo, ciclopropancarbonilo, 2-naftoilo, arginilo, 6-(arginilamino)caproilo, 6-(D-arginilamino)caproilo, 6-(D-arginil-D-arginilamino)caproilo, 6-(acetil-D-arginilamino)caproilo, 6-((R)-2,3-

diaminopropionilamino)caproilo, 6-(D-norleucilamino)caproilo, 3-(D-arginilamino)propionilo, 4-(D-arginilamino)butirilo, 4-(D-arginil-D-arginilamino)butirilo, 4-(D-arginil-D-arginil-D-arginilamino)butirilo, 3-(4-hidroxifenil)propionilo, butirilo, adipoilo, piroglutamilo, etc.,

J^2 representa (1) NH opcionalmente sustituido con un grupo alquilo C_{1-6}, (2) CH2 opcionalmente sustituido con un grupo alquilo C_{1-6}, (3) O ó (4) S.

El "grupo alquilo C_{1-6}" utilizado incluye metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, hexilo, etc.

Preferentemente, J^2 es NH.

J^3 a J^{12} cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3}.

El "grupo alquilo C_{1-3}" utilizado incluye metilo, etilo, propilo, isopropilo, etc.

Preferentemente, J^3 es átomo de hidrógeno.

Preferentemente, J^4 es átomo de hidrógeno.

Preferentemente, J^5 es átomo de hidrógeno.

Preferentemente, J^6 es átomo de hidrógeno.

Preferentemente, J^7 es átomo de hidrógeno.

Preferentemente, J^8 es átomo de hidrógeno.

Preferentemente, J^9 es átomo de hidrógeno.

Preferentemente, J^{10} es átomo de hidrógeno.

Preferentemente, J^{11} es átomo de hidrógeno.

Preferentemente, J^{12} es átomo de hidrógeno.

Q^3 a Q^{12} cada uno representa un grupo alquilo C_{1-4} que puede tener un sustituyente opcionalmente seleccionado del grupo que consiste de:

(1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido;

(2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre;

(3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido;

(4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre;

(5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

(6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

(7) un grupo amino opcionalmente sustituido;

(8) un grupo guanidino opcionalmente sustituido;

(9) un grupo hidroxilo opcionalmente sustituido;

(10) un grupo carboxilo opcionalmente sustituido;

(11) un grupo carbamoilo opcionalmente sustituido; y,

(12) un grupo sulfhidrilo opcionalmente sustituido;

o átomo de hidrógeno.

Preferiblemente, Q^3 a Q^9 incluyen un grupo alquilo C_{1-4} que posee un sustituyente seleccionado del grupo que consiste de:

(1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido.;

(2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre;

(3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido;

(4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre;

(5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

(6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

(7) un grupo amino opcionalmente sustituido;

(8) un grupo guanidino opcionalmente sustituido;

(9) un grupo hidroxilo opcionalmente sustituido;

(10) un grupo carboxilo opcionalmente sustituido;

(11) un grupo carbamoilo opcionalmente sustituido; y,

(12) un grupo sulfhidrilo opcionalmente sustituido;

o átomo de hidrógeno.

El "grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido", "grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre", "grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido", "grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre", "grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7" y "grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7" utilizado es igual que los indicados precedentemente.

(1) Como el grupo alquilo C_{1-4} que posee un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido, se utiliza, por ejemplo, bencilo, 4-hidroxibencilo, 2-clorobencilo, 3-clorobencilo, 4-clorobencilo, 4-aminobencilo, etc.

(2) Como el grupo alquilo C_{1-4} que posee un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y

heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, se utiliza, por ejemplo, 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 4-imidazolemetilo, etc.,

(3) Como el grupo alquilo C_{1-4} que posee un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido, se utiliza, por ejemplo, 1-naftilmetilo, 2-naftilmetilo, etc.

(4) Como el grupo alquilo C_{1-4} que posee un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, se utiliza, por ejemplo, 3-indolmetilo, 1-formilindol-3-ilmetilo, 2-quinolilmetilo, etc.,

(5) Como el grupo alquilo C_{1-4} que posee un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, se utiliza, por ejemplo, ciclohexilmetilo, etc.,

(6) Como el grupo alquilo C_{1-4} que posee un grupo heterocíclico no aromático opcionalmente sustituidos que posee una cantidad de átomos de carbono no mayor que 7, se utiliza, por ejemplo, piperidin-1-ilmetilo, etc.,

(7) Como el grupo alquilo C_{1-4} que posee un grupo amino opcionalmente sustituido, se utiliza, por ejemplo, 2-aminoetilo, 3-aminopropilo, 4-aminobutilo, 4-

acetamidobutilo, etc.

(8) Como el grupo alquilo C_{1-4} que posee un guanidino opcionalmente sustituido, se utiliza, por ejemplo, 3-guanidinopropilo, 3-(N-tosil)guanidinopropilo, etc.

(9) Como el grupo alquilo C_{1-4} que posee un grupo hidroxilo opcionalmente sustituido, se utiliza, por ejemplo, hidroximetilo, 1-hidroxietilo, benciloximetilo, etc.

(10) Como el grupo alquilo C_{1-4} que posee un grupo carboxilo opcionalmente sustituido, se utiliza, por ejemplo, carboximetilo, 2-carboxietilo, benziloxicarbonilmetilo, etc.,

(11) Como el grupo alquilo C_{1-4} que posee un grupo carbamoilo opcionalmente sustituidos, se utiliza, por ejemplo, carbamoilmetilo, 2-carbamoiletilo, xantilcarbamoilo, etc.

(12) Como el grupo alquilo C_{1-4} que posee un grupo sulfhidrilo opcionalmente sustituidos, se utiliza, por ejemplo, sulfhidrilmetilo, 2-(metilsulfhidril)etilo, etc.,

(13) Como el grupo alquilo C_{1-4} sin sustituir, se utiliza, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, etc.,

Preferiblentemente, Q^3 es átomo de hidrógeno, 4-hidroxibencilo, 3-piridilmetilo, 4-piridilmetilo, metilo, isobutilo, hidroximetilo, carboximetilo, 4-aminobutilo, etc., y más preferentemente, 4-hidroxibencilo, 3-

piridilmetilo, 4-piridilmetilo, etc.

Preferiblentemente, Q^4 incluye carbamoilmetilo, 2-carbamoiletilo, 4-hidroxibencilo, 4-imidazolemetilo, isobutilo, hidroximetilo, 1-hidroxietilo, carboximetilo, 4-aminobutilo, etc., y más preferentemente, carbamoilmetilo, 2-carbamoiletilo, 4-hidroxibencilo, etc.,

Preferentemente, Q^5 incluye bencilo, 2-clorobencilo, 3-clorobencilo, 4-clorobencilo, 4-aminobencilo, 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 1-naftilmetilo, 2-naftilmetilo, 3-indolmetilo, 1-formilindol-3-ilmetilo, 2-quinolilmetilo, ciclohexilmetilo, hidroximetilo, 1-hidroxietilo, metilo, isopropilo, isobutilo, sec-butilo, carboximetilo, 4-aminobutilo, etc., más preferentemente, bencilo, 2-clorobencilo, 3-clorobencilo, 4-clorobencilo, 4-aminobencilo, 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 1-naftilmetilo, 2-naftilmetilo, 3-indolmetilo, 2-quinolilmetilo, ciclohexilmetilo, 1-hidroxietilo, isopropilo, isobutilo, sec-butilo, etc.

Preferentemente, Q^6 es metilo, hidroximetilo, 1-hidroxietilo, carbamoilmetilo, 2-carbamoiletilo, etc., más preferentemente, carbamoilmetilo, etc.

Preferentemente, Q^7 es 4-hidroxibencilo, carbamoilmetilo, 3-piridilmetilo, metilo, isobutilo, bencilo, 4-aminobutilo, 3-indolmetilo, etc., más preferentemente, 4-hidroxibencilo, etc.

Preferentemente, Q^8 es bencilo, 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 2-naftilmetilo, 3-indolmetilo, hidroximetilo, ciclohexilmetilo, sec-butilo, 1-hidroxietilo, metilo, isobutilo, 4-aminobutilo, 3-carboxipropilo, etc., más preferentemente, 4-piridilmetilo, 3-indolmetilo, sec-butilo, etc.

Preferentemente, Q^9 es átomo de hidrógeno, metilo, etilo, hidroximetilo, 1-hidroxietilo, carbamoilmetilo, 2-carbamoiletilo, ureidometilo, acetamidometilo, formamidometilo, metilcarbamoilmetilo, dimetilcarbamoilmetilo, etc., más preferentemente, carbamoilmetilo, ureidometilo, etc.

Preferentemente, Q^{10} es 4-hidroxibencilo, 3-indolmetilo, metilo, 1-hidroxietilo, 3-guanidinopropilo, etc., más preferentemente, 3-indolmetilo, etc.,

Preferentemente, Q^{11} es carbamoilmetilo, etc.

Preferentemente, Q^{12} es metilo, carbamoilmetilo, etc., más preferentemente, carbamoilmetilo, etc.

Y^1 a Y^3 cada uno representa un grupo representado por la fórmula: $-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ ó $-N(J^{13})CO-$ (J^{13} y J^{14} cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3}).

Como el grupo alquilo C_{1-3} representado por J^{13} y J^{14}, allí es utilizado metilo, etilo, propilo o isopropilo.

J^{13} es átomo de hidrógeno.

J^{14} es átomo de hidrógeno.

Y^1 es preferentemente un grupo representado por la

fórmula: -CONH- ó $-CH_2NH-$, etc.

Y^2 es preferentemente un grupo representado por la fórmula: -CONH- ó $-CH_2NH-$, etc.

Y^3 es preferentemente un grupo representado por la fórmula: -CONH-, etc.

Pueden combinarse entre sí J^3 y Q^3, J^4 y Q^4, J^5 y Q^5, J^6 y Q^6, J^7 y Q^7, J^8 y Q^8, J^9 y Q^9, J^{10} y Q^{10}, J^{11} y Q^{11}, y J^{12} y Q^{12} para formar un anillo. En este caso, por ejemplo, se forma ciclopentano, hexametileno, piperidina, etc. por $C(J^3)(Q^3)$, $C(J^4)(Q^4)$, $C(J^5)(Q^5)$, $C(J^6)(Q^6)$, $C(J^7)(Q^7)$, $C(J^8)(Q^8)$, $C(J^9)(Q^9)$, $C(J^{10})(Q^{10})$, $C(J^{11})(Q^{11})$ o $C(J^{12})(Q^{12})$.

Z^1 y R^1, J^2 y Q^3, Y^1 y Q^4, Y^2 y Q^5, Y^3 y Q^6, J^2 y Q^7, Y^2 y Q^8, Y^3 y Q^9, J^2 y Q^{10}, Y^3 y Q^{11}, y J^2 y Q^{12} (preferentemente, J^2 y Q^3, Y^1 y Q^4, Y^2 y Q^5, Y^3 y Q^6, J^2 y Q^7, Y^2 y Q^8, Y^3 y Q^9, J^2 y Q^{10}, Y^3 y Q^{11}, y J^2 y Q^{12}) pueden combinarse entre sí para formar un anillo. Alternativamente, el anillo formado puede ser opcionalmente sustituido, o recristalizado.

En el caso en donde pueden combinarse entre sí Z^1 y R^1, J^2 y Q^3, J^2 y Q^7, J^2 y Q^{10}, ó J^2 y Q^{12} para formar un anillo, por ejemplo, se forma azetidina, pirrolidina, piperidina o tiazolidina por Z^1-N-CH-R^1, J^2-$C(J^3)(Q^3)$, J^2-$C(J^7)(Q^7)$, J^2-$C(J^{10})(Q^{10})$ o J^2-$C(J^{12})(Q^{12})$. Alternativamente, el anillo formado puede ser opcionalmente sustituido, o recristalizado. Preferentemente Z^1-N-CH-R^1 es azetidina, pirrolidina, 4-hidroxipirrolidina, piperidina, etc.

En el caso en donde pueden combinarse entre sí Y^1 y

Q^4, Y^2 y Q^5, Y^3 y Q^6, Y^2 y Q^8, Y^3 y Q^9, o Y^3 y Q^{11} para formar un anillo, por ejemplo, se forma pirrolidin-2-carbonilo, piperidin-2-carbonilo o tiazolidin-4-carbonilo por $Y^1C(J^4)(Q^4)$, $Y^2C(J^5)(Q^5)$, $Y^3C(J^6)(Q^6)$, $Y^2C(J^8)(Q^8)$, $Y^3C(J^9)(Q^9)$, ó $Y^3C(J^{11})(Q^{11})$. Alternativamente, el anillo formado puede ser opcionalmente sustituido, o recristalizado..

Los ejemplos preferidos del grupo representados por la fórmula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

incluyen:

Tyr Asn Trp Asn-,

Tyr Asn Trp D-Asn-,

Tyr Asn D-Trp Asn-,

Tyr D-Asn Trp Asn-,

D-Tyr Asn Trp Asn-,

Tyr Lys Trp Asn-,

Tyr Asp Trp Asn-,

Tyr Tyr Trp Asn-,

Tyr Leu Trp Asn-,

Tyr Asn Ala Asn-,

Tyr Asn Leu Asn-,

Tyr Asn Ser Asn-,

Tyr Asn Asp Asn-,

Tyr Asn Lys Asn-,

Ala Asn Trp Asn-,

Leu Asn Trp Asn-,

Ser Asn Trp Asn-,

Asp Asn Trp Asn-,

Lys Asn Trp Asn-,

Tyr Asn Trp(For)Asn-,

D-Tyr Asn D-Trp Asn-,

D-Tyr Asn Ala Asn-,

D-Tyr Asn Ser Asn-,

D-Tyr Asn Cha Asn-,

D-Tyr Asn Thr Asn-,

D-Tyr Asn Ile Asn-,

D-Tyr Gln Trp Asn-,

D-Tyr Thr Trp Asn-,

D-Tyr Asn Val Asn-,

D-Tyr D-Asn Trp Asn-,

D-Tyr D-Asn D-Trp Asn-,

D-Tyr Asn Phe Asn-,

D-Tyr Asn Nal(1) Asn-,

D-Tyr Asn Nal(2) Asn-,

D-Tyr Asn Phe(2Cl) Asn-,

D-Tyr Asn Phe(3Cl) Asn-,

D-Tyr Asn Phe(4Cl) Asn-,

D-Tyr Asn Phe($4NH_2$) Asn-,

D-Tyr Asn Pya(3) Asn-,

D-Tyr D-Asn Phe Asn-,

D-Tyr D-Asn Cha Asn-,

D-Tyr D-Asn Thr Asn-,

D-Tyr Asn Pya(2) Asn-,

D-Tyr Asn Pya(4) Asn-,

D-Tyr D-Ser Trp Asn-,

D-Tyr D-His Trp Asn-,

D-Pya(3) D-Asn Cha Asn-,

D-Pya(3) D-Tyr Cha Asn-,

Tyrψ(CH_2NH)Asn Trp Asn-,

D-Tyr Asnψ(CH_2NH)Trp Asn-,

Tyrψ(CH_2NH)Asn D-Trp Asn-,

D-Tyr Asn Ala(2-Qui) Asn-,

D-Tyr Asn D-Pya(4) Asn-,

D-Tyr D-Asn Pya(4) Asn-,

Tyr D-Asn Cha Asn-,

Dap D-Tyr Asn Trp Asn-

Arg D-Tyr D-Pya(4) Asn-

Arg Arg D-Tyr D-Pya(4) Asn-

Arg Acp D-Tyr D-Pya(4) Asn-

D-Arg Acp D-Tyr D-Trp Asn-

D-Arg D-Arg Acp D-Tyr D-Trp Asn-

Ac D-Arg Acp D-Tyr D-Trp Asn-

D-Dap Acp D-Tyr D-Trp Asn-

D-Nle Acp D-Tyr D-Trp Asn-

D-Arg β-Ala D-Tyr D-Trp Asn-

D-Arg γ-Abu D-Tyr D-Trp Asn-

D-Arg D-Arg γ- Abu D-Tyr D-Trp Asn-

D-Arg D-Arg D-Arg γ-Abu D-Tyr D-Trp Asn-

Gly D-Tyr D-Trp Asn-

Ac Gly D-Tyr D-Trp Asn-

D-Tyr D-Tyr D-Trp Asn-

Ac D-Tyr D-Tyr D-Trp Asn-

pGlu D-Tyr D-Trp Asn-

Tyr D-Tyr D-Trp Asn-

Ac Tyr D-Tyr D-Trp Asn-, y lo similar.

Los ejemplos preferidos del grupo representados por la fórmula:

J^1-J^2-C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})- incluyen:

Fmoc Asn Trp Asn-,

D-Asn Trp Asn-,

D-Tyr Trp Asn-,

D-Tyr D-Trp Asn-,

D-Tyr Ser Asn-,

D-Tyr Thr Asn-,

D-Tyr Ile Asn-,

D-Tyr Phe Asn-,

D-Tyr Nal(2) Asn-,

D-Pya(3) Phe Asn-,

D-Pya(3) Trp Asn-,

D-Tyr D-Pya(4) Asn-,

D-Asn Cha Asn-

D-Tyr D-Pya(4) Ala-

D-Tyr D-Pya(4) Thr-

D-Tyr Pya(4) Ala-

D-Tyr D-Trp Ala-

D-Tyr D-Trp Abu-

D-Tyr D-Phe Ala-6-Aminocaproil-

D-Tyr D-Pya(4) Asn-

Ac D-Tyr D-Pya(4) Asn-

Benzoilo D-Tyr D-Trp Asn-

Ciclopropancarbonilo D-Tyr D-Trp Asn-

Butirilo D-Tyr D-Trp Asn-

Me D-Tyr D-Trp Asn-

Ac D-Tyr D-Trp Gln-

Ac D-Tyr D-Trp Ser-

Ac D-Tyr D-Trp Thr-

Ac D-Tyr D-Trp Alb-

Ac D-Tyr D-Trp Dap(Ac)-

Ac D-Tyr D-Trp Dap(For)-

Ac D-Tyr Trp Asn-

Ac D-NMeTyr D-Trp Asn-

For D-Tyr D-Trp Asn-

Propionilo D-Tyr D-Trp Asn-

Amidino D-Tyr D-Trp Asn-

Ac D-Ala D-Trp Asn-

Ac D-Leu D-Trp Asn-

Ac D-Phe D-Trp Asn-

Ac D-Nal(1) D-Trp Asn-

Ac D-Nal(2) D-Trp Asn-

Ac D-Lys D-Trp Asn-

Ac D-Glu D-Trp Asn-

Ac D-Tyr D-Ala Asn-

Ac D-Tyr D-Leu Asn-

Ac D-Tyr D-Phe Asn-

Ac D-Tyr D-Thr Asn-

Ac D-Tyr D-Lys Asn-

Ac D-Tyr D-Glu Asn-

Ac D-Tyr D-Trp Asp-

Ac D-Tyr D-Trp D-Asn-

Ac D-Tyr D-Trp NMeAsn-

Ac D-Tyr Pro Asn-

Ac D-Tyr D-Pya(2) Asn-

Ac D-Tyr D-Pya(3) Asn-

Ac D-Tyr D-Pro Asn-

Ac D-Tyr Tic Asn-

Ac Tyr Trp Asn-

Ac D-Tyr NMeTrp Asn-

Glicoloilo D-Tyr D-Trp Asn-

Ac D-Tyr D-Trp Gly-

Ac D-Tyr D-Trp Dap-

Ac D-Tyr D-Trp Asp(NHMe)-

Ac D-Tyr D-Trp Asp(NMe2)-, y lo similar.

Los ejemplos preferidos del grupo representados por la fórmula:

J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})- incluyen:

Fmoc Trp Asn-,

Boc Tyr Asn-,

Tyr Asn-,

D-Trp Asn-,

Ac Trp Asn-,

Amidino Trp Asn-,

Ac Ala Asn-,

Ac Arg Asn-,

Ac Thr Asn-

D-Tyr D-Pya(4)-

3-(4-Hidroxifenil)propionilo D-Trp Asn-,

D-Trp Asn-

Ac D-Trp Asn-

Hexanoilo D-Trp Asn-

Ciclohexancarbonilo D-Trp Asn-

Benzoilo D-Trp Asn-

3-Piridinpropionilo D-Trp Asn-

Adipoilo D-Trp Asn-

6-Aminocaproilo D-Trp Asn-

Amidino D-Trp Asn-

Glicoloilo D-Trp Asn-, y lo similar.

Los ejemplos preferidos del grupo representados por la fórmula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})- incluyen:

Fmoc Asn-,

3-(Indol-3-il)propionilo Asn-,

3-Indolcarbonilo Asn-,

3-Indolacetilo Asn-,

4-(Indol-3-il)butirilo Asn-,

Difenilacetilo Asn-,

Hexanoilo Asn-,

Ciclohexancabonilo Asn-,

2-(Indol-3-il)etilcabamoilo Asn-,

3-(3-Piridil)propionilo Asn-,

4-Imidzolacetilo Asn-,

Piperidincarbonilo Asn-,

1-Piperidinacetilo Asn-,

1-metil-1-piperidinioacetilo Asn-,

1-Piridinioacetilo Asn-,

D-Glucuronilo Asn-,

3-Fenilpropionilo Asn-,

3-Fenilpropionilo Ala -,

Benzoilo Asn-,

Ac Asn -.,

Ciclopropanecarbonilo Asn-,

2-Naftoilo Asn-, y lo similar.

Los ejemplos preferidos del grupo representados por la fórmula: J1- incluyen:

átomo de hidrógeno,

GuAmb-,

3-(3-Indolil)propionil-,

3-(3-Piridil)propionil-,

Benzoil-,

Indol-3-carbonil-,

Indol-3-acetil-,

Ac-,

Hexanoil-,

Z-,

Tos-,

3-Fenilpropionil-,

2-(Indol-3-il)etilcarbamoil-,

bencil-,

Fenetil-,

2-Piridincarbonil-,

4-Piridincarbonil-,

Propionil-,

Isobutiril-,

Ciclohexancarbonil-,

Fenilacetil-,

2-Metilnicotinoil-,

5-Metilnicotinoil-,

6-Metilnicotinoil-,

Pirazincarbonil-,

Ciclopropancarbonil-,

Trifluoroacetil-,

(R)-3-hidroxi-2-metilpropionil-,

2-Hidroxiisobutiril-,

3-Furancarbonil-,

Pirrol-2-carbonil-,

4-Imidazolcarbonil-,

6-Hidroxinicotinoil-,

6-Cloronicotinoil-,

6-(Trifluorometil)nicotinoil-,

Dimetilcarbamoil-,

1-Azetidincarbonil-,

2-Azetidincarbonil-,

4-Aminobenzoil-,

4-Aminometilbenzoil-,

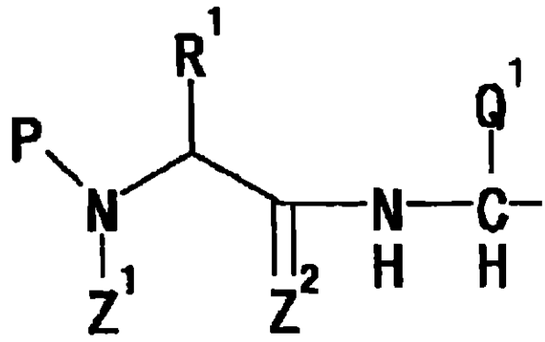
Pirrol-3-carbonil-,

Pirimidin-4-carbonil-,

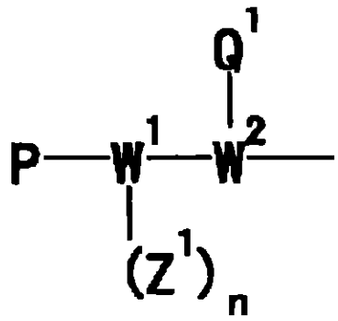
Pirimidin-2-carbonil-,

Piridazin-4-carbonil-, y lo similar.

Los derivados de metastina (I) en los derivados de metastina (III) de la presente invención, en donde V' representa un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado como el definido anteriormente) es una clase de compuesto descripta en la descripción registrada como PCT/JP03/16978, mientras que los derivados de metastina (II), en donde la V' representa un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado como el

definido anteriormente), o el grupo representado por la fórmula:

(en donde cada símbolo posee el mismo significado como el definido anteriormente) son los compuestos novedosos.

En los derivados de metastina (III), son utilizados preferentemente todos los compuestos cuyos grupos son ilustrados por los símbolos respectivos se combinan opcionalmente. Entre los mismos, son preferibles los compuestos que más adelante son ilustrados por los números de compuesto (Tablas 1 a 11).

MS10: Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

1 2 3 4 5 6 7 8 9 10

Compuesto No. 17: [Pya(4)10]MS10.

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Pya(4)-NH_2

Compuesto No. 18: [Tyr(Me)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Tyr(Me)-NH_2

Compuesto No. 19: [Phe(2F)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(2F)-NH_2

Compuesto No. 23: [Tyr5]MS10

Tyr-Asn-Trp-Asn-Tyr-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 24: [Leu5]MS10

Tyr-Asn-Trp-Asn-Leu-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 30: Acetil-MS10

Acetil-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 31: Fmoc-MS10

Fmoc-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 38: [D-Ser5]MS10

Tyr-Asn-Trp-Asn-D-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 39: [D-Asn4]MS10

Tyr-Asn-Trp-D-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 40: [D-Trp3]MS10

Tyr-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 41: [D-Asn2]MS10

Tyr-D-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 42: [D-Tyr1]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 44: [Lys9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Lys-Phe-NH_2

Compuesto No. 45: [Ala8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Ala-Arg-Phe-NH_2

Compuesto No. 50: [Ala7]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Ala-Leu-Arg-Phe-NH_2

Compuesto No. 51: [NMePhe10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-NMePhe-NH_2

Compuesto No. 53: des(1-3)-Fmoc-MS10

Fmoc-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 54: des(1-2)-Fmoc-MS10

Fmoc-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 55: des(1)-Fmoc-MS10

Fmoc-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 56: [Lys2]MS10

Tyr-Lys-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 57: [Asp2]MS10

Tyr-Asp-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 58: [Tyr2]MS10

Tyr-Tyr-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 59: [Leu2]MS10

Tyr-Leu-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 60: [Pya(3)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Pya(3)-NH_2

Compuesto No. 61: [Phe(4F)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4F)-NH_2

Compuesto No. 67: [Ala3]MS10

Tyr-Asn-Ala-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 68: [Leu3]MS10

Tyr-Asn-Leu-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 69: [Ser3]MS10

Tyr-Asn-Ser-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 70: [Asp3]MS10

Tyr-Asn-Asp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 71: [Lys3]MS10

Tyr-Asn-Lys-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 72: [Ala1]MS10

Ala-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 73: [Leu1]MS10

Leu-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 74: [Ser1]MS10

Ser-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 75: [Asp1]MS10

Asp-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 76: [Lys1]MS10

Lys-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 77: [Phe(4CN)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4CN)-NH_2

Compuesto No. 78: [Trp(For)3, Phe(4CN)10]MS10

Tyr-Asn-Trp(For)-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4CN)-NH_2

Compuesto No. 79: [Hph10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Hph-NH_2

Compuesto No. 81: [NMeArg9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-NMeArg-Phe-NH_2

Compuesto No. 82: [Arg(Me)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 83: [Arg(asy Me2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(asyMe2)-Phe-NH_2

Compuesto No. 87: el des(4-5)-Boc-MS10

Boc-Tyr-Asn-Trp-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 88: el des(4-5)-MS10

Tyr-Asn-Trp-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 90: [Lys9,9ψ10,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Lysψ(CH_2NH)Phe-NH_2

Compuesto No. 91: [8ψ9,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leuψ(CH_2NH)Arg-Phe-NH_2

Compuesto No. 97: [Har9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Har-Phe-NH_2

Compuesto No. 98: [Lys(Me2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Lys(Me2)-Phe-NH_2

Compuesto No. 101: [Ser7]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Ser-Leu-Arg-Phe-NH_2

Compuesto No. 105: [Nle8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Nle-Arg-Phe-NH_2

Compuesto No. 107: [Val8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Val-Arg-Phe-NH_2

Compuesto No. 109: [Tyr10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Tyr-NH_2

Compuesto No. 110: [Nal(2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Nal(2)-NH_2

Compuesto No. 111: [Phe(F5)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(F5)-NH_2

Compuesto No. 112: [Cha10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Cha-NH_2

Compuesto No. 114: des(1-3)-3-(3-Indolil)propionil-MS10

3-(3-Indolil)propionil-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 121: des(1-4)-[Trp5]MS10

Trp-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 123: [NMeLeu8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-NMeLeu-Arg-Phe-NH_2

Compuesto No. 126: [NMeSer5]MS10

Tyr-Asn-Trp-Asn-NMeSer-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 127: [D-Asn4,NMePhe6]MS10

Tyr-Asn-Trp-D-Asn-Ser-NMePhe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 128: [10ψ,CSNH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Pheψ(CSNH)NH_2

Compuesto No. 129: [Arg(symMe2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(symMe2)-Phe-NH_2

Compuesto No. 130: [Phe(4Cl)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4Cl)-NH_2

Compuesto No. 131: [Phe(4NH_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4NH2)-NH_2

Compuesto No. 132: [Phe(4NO_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4NO_2)-NH_2

Compuesto No. 133: [Nal(1)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Nal(1)-NH_2

Compuesto No. 134: [Trp10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Trp-NH_2

Compuesto No. 137: [Nle9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Nle-Phe-NH_2

Compuesto No. 138: [Cit9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Cit-Phe-NH_2

Compuesto No. 140: [Arg(Me)9,NMePhe10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-NMePhe-NH_2

Compuesto No. 141: [D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 142: [D-Tyr1,D-Trp3,Arg(Me)9]MS10

D-Tyr-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 143: [D-Trp3,Arg(Me)9]MS10

Tyr-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 144: des(1-3)-Fmoc-[Arg(Me)9]MS10

Fmoc-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 145: des(1-2)-Fmoc-[Arg(Me)9]MS10

Fmoc-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 146: [10ψ,CSNH,D-Tyr1]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Pheψ(CSNH)NH_2

Compuesto No. 150: [Tyr6]MS10

Tyr-Asn-Trp-Asn-Ser-Tyr-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 151: [Nal(1)6]MS10

Tyr-Asn-Trp-Asn-Ser-Nal(1)-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 152: [Nal(2)6]MS10

Tyr-Asn-Trp-Asn-Ser-Nal(2)-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 153: [Phe(F5)6]MS10

Tyr-Asn-Trp-Asn-Ser-Phe(F5)-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 154: [Phe(4F)6]MS10

Tyr-Asn-Trp-Asn-Ser-Phe(4F)-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 156: [Cha6]MS10

Tyr-Asn-Trp-Asn-Ser-Cha-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 163: [6ψ7,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-Pheψ(CH_2NH)Gly-Leu-Arg-Phe-NH_2

Compuesto No. 165: [Dap(Gly)9]-MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Dap(Gly)-Phe-NH_2

Compuesto No. 166: [6ψ7,CSNH]MS10

Tyr-Asn-Trp-Asn-Ser-Pheψ(CSNH)Gly-Leu-Arg-Phe-NH_2

Compuesto No. 169: [D-Tyr1,Ala3,Arg(Me)9]MS10

D-Tyr-Asn-Ala-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 170: [D-Tyr1,Ser3,Arg(Me)9]MS10

D-Tyr-Asn-Ser-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 171: [D-Tyr1,Cha3,Arg(Me)9]MS10

D-Tyr-Asn-Cha-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 172: [D-Tyr1,Cha6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 173: [D-Tyr1,Ala7,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Ala-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 174: [D-Tyr1,Arg(Me)9,Trp10]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 176: [AzaGly7]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg-Phe-NH_2

Compuesto No. 181: [D-Tyr1,Cha3,6,Arg(Me)9]MS10

D-Tyr-Asn-Cha-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 182: [D-Tyr1,Cha3,6,Arg(Me)9,Trp10]MS10

D-Tyr-Asn-Cha-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 183: [Phe(4NH2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Phe(4NH2)-Phe-NH_2

Compuesto No. 184: [Phe(4-Guanidino)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Phe(4-Guanidino)-Phe-NH_2

Compuesto No. 185: [Dap(GnGly)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Dap(GnGly)-Phe-NH_2

Compuesto No. 186: [Trp(For)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Trp(For)-NH_2

Compuesto No. 187: [Abu8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Abu-Arg-Phe-NH_2

Compuesto No. 189: [Ala(3-Bzt)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Ala(3-Bzt)-NH_2

Compuesto No. 190: [D-Tyr1,Cha3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 191: [D-Tyr1,Ser3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ser-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 192: [D-Tyr1,Arg(Et)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Et)-Phe-NH_2

Compuesto No. 193: [D-Tyr1,Arg(n-Pr)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(n-Pr)-Phe-NH_2

Compuesto No. 194: [D-Tyr1,Arg(Ac)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Ac)-Phe-NH_2

Compuesto No. 197: [Phe(3F)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3F)-NH_2

Compuesto No. 198: [Phe(3,4F2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3,4F2)-NH_2

Compuesto No. 199: [Phe(3,4Cl2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3,4Cl2)-NH_2

Compuesto No. 200: [Phe(3CF3)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3CF3)-NH_2

Compuesto No. 201: [Ala(2-Qui)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Ala(2-Qui)-NH_2

Compuesto No. 203: [D-Tyr1,Cha6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 204: [D-Tyr1, Ala7, Arg(Me)9]MS10,

D-Tyr-Asn-Trp-Asn-Ser-Phe-Ala-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 205: [D-Tyr1,Thr3,Arg(Me)9]MS10

D-Tyr-Asn-Thr-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 206: [D-Tyr1,Ile3,Arg(Me)9]MS10

D-Tyr-Asn-Ile-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 207: [D-Tyr1,Ser4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Ser-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 208: [D-Tyr1,Thr4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Thr-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 209: [D-Tyr1,Gln4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Gln-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 210: [D-Tyr1,Ala4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Ala-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 211: [D-Tyr1,Thr5,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Thr-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 212: [D-Tyr1,Ala5,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ala-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 213: [D-Tyr1,Val8,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Val-Arg(Me)-Phe-NH_2

Compuesto No. 214: [D-Tyr1,Gln2,Arg(Me)9]MS10

D-Tyr-Gln-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 215: [D-Tyr1,Thr2,Arg(Me)9]MS10

D-Tyr-Thr-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 216: des(1)-[D-Asn2,Arg(Me)9]MS10

D-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 217: des(1)-[D-Tyr2,Arg(Me)9]MS10

D-Tyr-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 218: [N((CH2)3Gn)] Gly9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-N((CH2)3Gn)Gly-Phe-NH_2

Compuesto No. 220: [Arg(Et)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Et)-Phe-NH_2

Compuesto No. 221: [D-Tyr1,Thr3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 222: des(1)-[D-Tyr2,AzaGly7,Arg(Me)9]MS10

D-Tyr-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 223: des(1-2)-[D-Trp3,Arg(Me)9]MS10

D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 224: des(1)-[D-Tyr2,D-Trp3,Arg(Me)9]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 225: des(1)-[D-Asn2,D-Trp3,Arg(Me)9]MS10

D-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 226: des(1)-[D-Tyr2,Ser3,Arg(Me)9]MS10

D-Tyr-Ser-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 227: des(1)-[D-Tyr2,Thr3,Arg(Me)9]MS10

D-Tyr-Thr-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 228: des(1)-[D-Tyr2,Ile3,Arg(Me)9]MS10

D-Tyr-Ile-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 229: [D-Tyr1,Val3,Arg(Me)9]MS10

D-Tyr-Asn-Val-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 230: [D-Tyr1,D-Asn2,Arg(Me)9]MS10

D-Tyr-D-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 231: [D-Tyr1,D-Asn2,D-Trp3,Arg(Me)9]MS10

D-Tyr-D-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 232: [D-Tyr1,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 233: [D-Tyr1,Ile3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ile-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 234: [D-Tyr1,Val3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Val-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 235: [D-Tyr1,Ala3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ala-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 236: [D-Tyr1,D-Trp3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 237: [D-Tyr1,D-Asn2,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 238: [D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 239: des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Ser-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 240: des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Ile-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 241: des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 242:des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 244: [D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 245: [D-Tyr1,Nal(1)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Nal(1)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 246: [D-Tyr1,Nal(2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Nal(2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 247: [D-Tyr1,Phe(2Cl)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe(2Cl)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 248: [D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe(3Cl)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 249: [D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe(4Cl)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 250: [D-Tyr1,Phe(4NH2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe(4NH2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 251: [D-Tyr1,Pya(3)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pya(3)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 252: [D-Tyr1,D-Ala3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-D-Ala-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 253: [D-Tyr1,Pro3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pro-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 254: des(1)-[D-Tyr2,Phe3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No.255:des(1)-[D-Tyr2,Nal(2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Nal(2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No.256:des(1)-[D-Pya(3)2,Phe3,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 257: [D-Tyr1,D-Asn2,Phe3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 258: [D-Pya(3)1,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 259: [D-Ala1,AzaGly7,Arg(Me)9]MS10

D-Ala-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 260: des(1-3)-3-(3-Indolil)propionil-[AzaGly7,Arg(Me)9]MS10

3-(3-Indolil)propionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 261: [7ψ8,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Glyψ(CH_2NH)Leu-Arg-Phe-NH_2

Compuesto No. 265: des(1-3)-Indole-3-carbonil-[AzaGly7,Arg(Me)9]MS10

Indole-3-carbonil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 266: des(1-3)-Indol-3-acetil-[AzaGly7,Arg(Me)9]MS10

Indol-3-acetil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 267: des(1-3)-4-(3-Indolil)butiril-[AzaGly7,Arg(Me)9]MS10

4-(3-Indolil)butiril-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 268: des(1-3)-Difenilacetil-

[AzaGly7,Arg(Me)9]MS10

Difenilacetil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 269: des(1-3)-3-Fenilpropionil-[AzaGly7,Arg(Me)9]MS10

3-Fenilpropionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 270: [D-Tyr1,Phe3,Ser-Phe5,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe-Asn-Ser-Phe-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 271: des(1-2)-[AzaGly7,Arg(Me)9]MS10

Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 272: des(1-2)-acetil-[AzaGly7,Arg(Me)9]MS10

Acetil-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 273: des(1-2)-Amidino-[AzaGly7,Arg(Me)9]MS10

Amidino-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 274: des(1-2)-acetil-[Ala3,AzaGly7,Arg(Me)9]MS10

Acetil-Ala-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 275: des(1-2)-acetil-[Arg3,AzaGly7,Arg(Me)9]MS10

Acetil-Arg-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 276: des(1-2)-acetil-[Thr3,AzaGly7,Arg(Me)9]MS10

Acetil-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 277: des(1-3)-n-Hexanoil-[AzaGly7,Arg(Me)9]MS10

n-Hexanoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 278: des(1-3)-Ciclohexancarbonil-[AzaGly7, Arg(Me)9]MS10

Ciclohexancarbonil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 279: des(1-3)-2-(Indol-3-il)etilcarbamoil-[AzaGly7,Arg(Me)9]MS10

2-(indol-3-il)etilcarbamoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 281: [D-Tyr1,Pya(2)6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Pya(2)-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 282: [D-Tyr1,Pya(4)6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Pya(4)-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 283: [D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 284: [D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 285: [D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pya(2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 286: [D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 287: [D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Ser-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 288: [D-Tyr1,D-His2,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-su-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 289: des(1)-[D-Pya(3)2,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No.290: [D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No.291: [D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-D-Tyr-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH2

Compuesto No. 293: [4ψ5,CH_2NH]MS10

Tyr-Asn-Trp-Asnψ(CH_2NH)Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 294: [1ψ2,CH_2NH]MS10

Tyrψ(CH_2NH)Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 295: [2ψ3,CH_2NH]MS10

Tyr-Asnψ(CH_2NH)Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 296: [6ψ7,CSNH,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Pheψ(CSNH)Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 297: [D-Tyr1,Thr5,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 298: [D-Tyr1,D-Asn2,Thr5,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 299: [1ψ2,CH_2NH,AzaGly7,Arg(Me)9]-MS10

Tyrψ(CH_2NH)Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 300: [1ψ2,CH_2NH,D-Trp3,AzaGly7,Arg(Me)9]-MS10

Tyrψ(CH_2NH)Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 301: [D-Tyr1,Ala(2-Qui)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ala(2-Qui)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 302: [D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No.303: [D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 304: [D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 305: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 306: [D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Pya(4)-D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 307: [7ψ8,CH_2NH,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Glyψ(CH_2NH)Leu-Arg(Me)-Phe-NH_2

Compuesto No. 308: [6ψ7,CH_2NH,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Pheψ(CH_2NH)Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 310: [Nar9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Nar-Phe-NH_2

Compuesto No. 311: [Nar(Me)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Nar(Me)-Phe-NH_2

Compuesto No. 312: [Har(Me)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Har(Me)-Phe-NH_2

Compuesto No. 313: [Dab9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Dab-Phe-NH_2

Compuesto No. 314: [Orn9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Orn-Phe-NH_2

Compuesto No. 315: des(1)-[D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 316: [D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

D-Tyr-D-Asn-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compuesto No. 317: [D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compuesto No. 318: [D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compuesto No. 319: [6ψ7,NHCO,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Pheψ(NHCO)Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 322: des(1-3)-3-(3-Piridil)propionil-[AzaGly7,Arg(Me)9]MS10

3-(3-Piridil)propionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 323: des(1-3)-4-Imidazolacetil-[AzaGly7,Arg(Me)9]MS10

4-Imidazolacetil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 324: des(1-3)-4-Piperidincarbonil-[AzaGly7,Arg(Me)9]MS10

Piperidincarbonil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 325: des(1-3)-1-Piperidinacetil-[AzaGly7,Arg(Me)9]MS10

1-Piperidinacetil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 326: des(1-3)-1-Metilpiperidinio-1-acetil-[AzaGly7,Arg(Me)9]MS10

1-Metilpiperidin-1-acetil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 327: des(1-3)-1-Piridinioacetil-[AzaGly7,Arg(Me)9]MS10

1-Piridinoacetil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 328: des(1-3)-D-Glucuronil-[AzaGly7,Arg(Me)9]MS10

D-Glucuronil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 375:2-Aminoetil-Gly-[D-Tyr1,Arg(Me)9]MS10

2-Aminoetil-Gly-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 385: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 386: des(1-3)-3-(3-Piridil)propionil-[AzaGly7,Arg(Me)9,Trp10]MS10

3-(3-Piridil)propionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 387:Dap-[D-Tyr1,Arg(Me)9]MS10

Dap-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 397:Metiltiocarbamoil-Sar-[D-Tyr1,Arg(Me)9]MS10

Metiltiocarbamoil-Sar-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 400: (S)-1-(Quinolin-8-il-carbamoil)-4-tiapentilcarbamoil-[D-Tyr1,Arg(Me)9]MS10

(S)-1-(Quinolin-8-il-carbamoil)-4-tiapentilcarbamoil-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 481: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Trp-NH_2

Compuesto No. 486: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Orn9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Orn-Phe-NH_2

Compuesto No. 487: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Lys9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Lys-Phe-NH_2

Compuesto No. 488: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Phe-NH_2

Compuesto No. 489: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har(Me)9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har(Me)-Phe-NH_2

Compuesto No. 490: des(1)-[D-Tyr2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 491: des(1)-[D-Tyr2,D-Pya(4)3,Trp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Trp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 492: des(1)-[D-Tyr2,D-Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 493: des(1)-[D-Tyr2,D-Pya(4)3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 494: des(1,4)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 495: des(1-3)-[D-Tyr4,Pya(4)5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-Pya(4)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 496: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 497: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Ala7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Cha-Ala-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 498: des(1)-[D-Tyr2,D-Pya(4)3,Ile5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 499: des(1-3)-3-Fenilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 500: des(1-3)-3-Fenilpropionil-[Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 501: des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 502: des(1)-[D-Tyr2,Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 503: des(1)-[D-Tyr2,D-Trp3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 504: [Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 505: des(1-3)-3-Fenilpropionil-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 506: des(1-3)-3-Fenilpropionil-[Ile5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 507: des(1-3)-3-Fenilpropionil-[Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 508: des(1-3)-3-Fenilpropionil-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 509: des(1-3)-Benzoil-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 510: des(1-3)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 511: des(1)-[D-Tyr2,D-Trp3,Ala4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Ala-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 512: des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 513: des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 514: des(1)-[D-Tyr2,D-Phe3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Phe-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 515: des(1)-[D-Tyr2,D-Pya(4)3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 516: des(1)-Ac-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 517: des(1-3)-3-Fenilpropionil-

[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 518: des(1-3)-3-Fenilpropionil-[Cha6,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 519: des(1-3)-Fenilacetil-[AzaGly7,Arg(Me)9,Trp10]MS10

Fenilacetil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 521: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg-Phe-NH_2

Compuesto No. 522: des(1-3)-Benzoil-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 523: des(1-3)-Benzoil-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 524: des(1-3)-3-Fenilpropionil-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 527: des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 528: des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 529: des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Tle-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 530: des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Phg-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 531: des(1-3)-3-Fenilpropionil-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Pic(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 532: des(1-3)-3-Fenilpropionil-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 533: des(1-3)-3-Fenilpropionil-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-D-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 534: des(1-3)-Ciclopropancarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Ciclopropancarbonil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 535: des(1-3)-2-Naftoil-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Naftoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 536: [Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 537: Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 538: Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 539: des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 540: des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 541: D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 542: D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 545: des(1-3)-Benzoil-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 546: des(1-3)-3-Fenilpropionil-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 547: des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 548: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10ψ,CSNH]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Pheψ(CSNH)NH_2

Compuesto No. 550: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 551: Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 552: D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 553: D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 554: D-Arg-[(-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-(-Ala-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 555: D-Arg-[γ-Abu1,D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 556: D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 557: D-Arg-D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 558: des(1)-Ac-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 559: des(1-2)-3-(4-Hidroxifenil)propionil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-(4-Hidroxifenil)propionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 561: D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 562: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 563: des(1)-Ac-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 564: des(1)-Ac-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 565: des(1)-Benzoil-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 566: des(1)-Ciclopropancarbonil-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ciclopropancarbonil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 567: des(1)-Butiril-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Butiril-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 568: Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 569: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,6ψ7,CH_2NH,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Pheψ(CH_2NH)Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 570: des(1)-Me-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Me-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 571: des(1)-Ac-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 572: des(1)-[D-Trp2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 573: des(1)-Ac-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 576: des(1)-Ac-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Gln-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 577: des(1)-Ac-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Ser-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 578: des(1)-Ac-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 579: des(1)-Ac-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 580: des(1)-Ac-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 584: des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 585: des(1)-Ac-[D-Tyr2,D-

Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 586: des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 589: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

Compuesto No. 590: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2

Compuesto No. 591: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2

Compuesto No. 592: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compuesto No. 594: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Hph-NH_2

Compuesto No. 595: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Cha10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Cha-NH_2

Compuesto No. 596: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Leu10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Leu-NH_2

Compuesto No. 597: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 598: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 599: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2

Compuesto No. 600: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2

Compuesto No. 601: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 602: des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 603: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 604: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Tos)-Trp-NH_2

Compuesto No. 605: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(NO2)-Trp-NH_2

Compuesto No. 607: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)asym-Trp-NH_2

Compuesto No. 608: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)sym-Trp-NH_2

Compuesto No. 609: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Et)-Trp-NH_2

Compuesto No. 610: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys(Me2)-Trp-NH_2

Compuesto No. 611: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 612: For-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Para-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 613: Propionyl-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Propionil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 614:

des(1)-Amidino-[D-Tyr2,D-

rp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Amidino-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 615: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 616: des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 617: des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 618: des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 619: des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(1)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 620: des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(2)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 621: des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 622: des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Glu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 623: des(1)-Ac-[D-

Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 624: des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 625: des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 626: des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 627: des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 628: des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Thr-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 629: des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 630: des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 631: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Ala-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 632: des(1)-Ac-[D-Tyr2,D-

Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Leu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 633: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Lys-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 634: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Glu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 635: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 636: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,MePhe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-MePhe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 637: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 638: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 639: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys-Trp-NH_2

Compuesto No. 641: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ala-Arg(Me)-Trp-NH_2

Compuesto No. 642: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

Compuesto No. 643: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Phe-Arg(Me)-Trp-NH_2

Compuesto No. 644: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ser-Arg(Me)-Trp-NH_2

Compuesto No. 645: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har-Trp-NH_2

Compuesto No. 646: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har(Me)-Trp-NH_2

Compuesto No. 647: des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 648: [Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 649: Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 650: [D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 651: Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 652: el pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 653: des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-D-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 654: des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-D-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 655: des(1)-Ac-[D-Tyr2,D-Trp3,MeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-MeAsn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 656: des(1)-Ac-[D-Tyr2,D-Trp3,MeSer5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-MeSer-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 657: des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 658: des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 659: des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-allo-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 660: des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 661: des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 662: des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 663: des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 664: des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 665: des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 666: des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 667: des(1-2)-Hexanoil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Hexanoil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 668: des(1-2)-Ciclohexancarbonil-[D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ciclohexancarbonil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 669: des(1-2)-Benzoil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 670: des(1-2)-3-Piridinpropionil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Piridinpropionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 671: des(1-2)-Adipoil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Adipionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 672: des(1)-Ac-[D-Tyr2,NMeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 674: des(1-2)-6-Aminocaproil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

6-Aminocaproil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 675: [D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 676: Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 677: Ac-des(1)-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Nva-Arg(Me)-Trp-NH_2

Compuesto No. 678: Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ile-Arg(Me)-Trp-NH_2

Compuesto No. 679: des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Amidino-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 680: des(1-2)-Glicoloil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Glicoloil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 681: des(1)-Glicoloil-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Glicoloil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 682: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Gln-Arg(Me)-Trp-NH_2

Compuesto No. 685: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 686: des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Gly-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 688: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Pya(4)-Trp-NH_2

Compuesto No. 689: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-D-Trp-NH_2

Compuesto No. 691: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 692: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 693: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr(Me)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 694: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Nal(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 695: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Thi-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 696: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 698: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Abu-Arg(Me)-Trp-NH_2

Compuesto No. 699: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-γMeLeu-Arg(Me)-Trp-NH_2

Compuesto No. 700: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Aib-Arg(Me)-Trp-NH_2

Compuesto No. 701: des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 702: des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp(NHMe)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 703: des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NMe2)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp(NMe2)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2.

Sin embargo, los derivados de metastina (III) de la presente invención no incluyen un péptido (metastina humana nativa o sus péptidos parciales) que consiste de la secuencia de aminoácido siguiente en la secuencia de aminoácido representada por SEQ ID NO: 1, es decir, la secuencia de aminoácido de 1-54 (Compuesto No. 1), 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54 (Compuesto No. 2), 41-54, 42-54 (Compuesto No. 32), 43-54, 44-54, 45-54 (Compuesto No. 3), 46-54 (Compuesto No. 4), 47-54, 48-54

ó 49-54.

En los derivados de metastina (II), son utilizados preferiblemente todos los compuestos cuyos grupos ilustrados por los símbolos respectivos son opcionalmente combinados. Entre los mismos, se prefieren los compuestos ilustrados por los números compuestos siguientes.

Compuesto No. 332: des(1-5)-GuAmb-[AzaGly7,Arg(Me)9]MS10

GuAmb-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 333: des(1-5)-GuAmb-[Arg(Me)9]MS10

GuAmb-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 334: des(1-5)-GuAmb-[AzaGly7,Arg(Me)9,Trp10]MS10

GuAmb-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 339: des(1-5)-3-(3-Indolil)propionil-[AzaGly7,Arg(Me)9]MS10

3-(3-Indolil)propionil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 340: des(1-5)-3-(3-Piridil)propionil-[AzaGly7,Arg(Me)9]MS10

3-(3-Pyridil)propionil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 341: des(1-5)-Benzoil-[AzaGly7,Arg(Me)9]MS10

Benzoil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 344: des(1-5)-Indol-3-carbonil-[AzaGly7,Arg(Me)9]MS10

Indole-3-carbonil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 345: des(1-5)-Indol-3-acetil-[AzaGly7,Arg(Me)9]MS10

Indole-3-acetil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 346: des(1-5)-Ac-[AzaGly7,Arg(Me)9]MS10

Ac-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 347: des(1-5)-n-Hexanoil-[AzaGly7,Arg(Me)9]MS10

n-Hexanoil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 348: des(1-5)-z-[AzaGly7,Arg(Me)9]MS10

Z-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 349: des(1-5)-Tos-[AzaGly7,Arg(Me)9]MS10

Tos-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 351: des(1-5)-Benzoil-MS10

Benzoil-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 352: des(1-5)-3-(3-Indolil)propionil-MS10

3-(3-Indolil)propionil-Phe-Gly-Leu-Arg-Phe-NH_2

Compuesto No. 353: des(1-5)-Benzoil-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 354: des(1-5)-3-(3-Indolil)propionil-[AzaGly7,Arg(Me)9,Trp10]MS10

3-(3-Indolil)propionil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 358: des(1-5)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 362: des(1-6)-3-Fenilpropionil-[AzaGly7,Arg(Me)9]MS10

3-Fenilpropionil-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 364: des(1-5)-2-(Indol-3-il)etilcarbamoil-

[AzaGly7,Arg(Me)9]MS10

2-(Indol-3-il)etilcarbamoil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 366: des(1-5)-n-Hexanoil-[AzaGly7,Arg(Me)9,Trp10]MS10

n-Hexanoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 367: des(1-5)-z-[AzaGly7,Arg(Me)9,Trp10]MS10

Z-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 368: des(1-5)-Tos-[AzaGly7,Arg(Me)9,Trp10]MS10

Tos-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 369: des(1-5)-2-(Indol-3-il)etilcarbamoil-[AzaGly7,Arg(Me)9,Trp10]MS10

2-(Indol-3-il)etilcarbamoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 373: des(1-6)-(2S)-2-acetoxi-3-fenilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10

(2S)-2-acetoxi-3-fenilpropionil-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 374: des(1-6)-z-[AzaGly7,Arg(Me)9,Trp10]MS10

Z-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 378: des(1-6)-Difenilacetil-[AzaGly7,Arg(Me)9,Trp10]MS10

Difenilacetil-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 379: des(1-6)-(2S)-2-(3-

Indolilpropioniloxi)-3-fenilpropionil-
[AzaGly7,Arg(Me)9,Trp10]MS10
(2S)-2-(3-Indolilpropioniloxi)-3-fenilpropionil-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 380: des(1-6)-(2S)-2-Benzoiloxi-3-fenilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10
(2S)-2-Benzoiloxi-3-fenilpropionil-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 392: des(1-5)-Benzoil-
[Ala6,AzaGly7,Arg(Me)9,Trp10]MS10
Benzoil-Ala-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 393: des(1-6)-Dibencilcarbamoil-
[AzaGly7,Arg(Me)9,Trp10]MS10
Dibencilcarbamoil-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 408: des(1-6)-1-Oxo-isocroman-3-carbonil-
[AzaGly7,Arg(Me)9,Trp10]MS10
1-Oxo-isocroman-3-carbonil-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 412: des(1-6)-(2R)-2-Benzoiloxi-3-fenilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10
(2R)-2-Benzoiloxi-3-fenilpropionil-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 417: des(1-6)-Bencilfenetilcarbamoil-
[AzaGly7,Arg(Me)9,Trp10]MS10
Bencilfenetilcarbamoil-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 421: des(1-5)-Benzoil-
[6ψ7,CH2O,Arg(Me)9,Trp10]MS10
Benzoil-Pheψ(CH2O)Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 423: des(1-5)-Benzoil-[6ψ7,NHCO,Arg(Me)9,Trp10]MS10

Benzoil-Pheψ(NHCO)Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 428: des(1-6)-Dibenzylaminocarbamoil-[AzaGly7,Arg(Me)9,Trp10]MS10

Dibencilaminocarbamoil-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 431: des(1-5)-Benzoil-[AzaPhe6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-AzaPhe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 432: des(1-5)-3-Piridincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Piridincarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 434: des(1-7)-Dibencilaminocarbamoilacetil-[Arg(Me)9,Trp10]MS10

Dibencilaminocarbamoilacetil-Leu-Arg(Me)-Trp-NH2

Compuesto No. 435: des(1-5)-2-Piridincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Piridincarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 436: des(1-5)-4-Piridincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Piridincarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 437: des(1-5)-Propionil-[AzaGly7,Arg(Me)9,Trp10]MS10

Propionil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 438: des(1-5)-Isobutiril-[AzaGly7,Arg(Me)9,Trp10]MS10

Isobutiril-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 439: des(1-5)-Ciclohexancarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Ciclohexancarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 440: des(1-5)-Fenilacetil-[AzaGly7,Arg(Me)9,Trp10]MS10

Fenilacetil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 441: des(1-5)-Benzoil-[Pya(2)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Pya(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 442: des(1-5)-Benzoil-[Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 443: des(1-5)-2-Metilnicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Metilnicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 444: des(1-5)-5-Metilnicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10

5-Metilnicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 445: des(1-5)-6-Metilnicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10

6-Metilnicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 446: des(1-5)-Pirazincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Pirazincarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 447: des(1-5)-Ciclopropancarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Ciclopropancarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 448: des(1-5)-Trifluoroacetil-[AzaGly7,Arg(Me)9,Trp10]MS10

Trifluoroacetil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 449: des(1-5)-Benzoil-[Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 450: des(1-5)-bencilo-[AzaGly7,Arg(Me)9,Trp10]MS10

Bencilo-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 451: des(1-5)-Ciclopropancarbonil-[Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Ciclopropancarbonil-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 452: des(1-5)-(R)-3-hidroxi-2-metilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10

(R)-3-hidroxi-2-metilpropionil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 453: des(1-5)-2-Hidroxiisobutiril-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Hidroxiisobutiril-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 454: des(1-5)-3-Furancarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Furancarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 455: des(1-5)-pirrol-2-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Pirrol-2-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 459: des(1-5)-4-Imidazolcarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Imidazolcarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 460: des(1-5)-4-Piridincarbonil-[AzaGly7,Val8,Arg(Me)9,Trp10]MS10

4-Piridincarbonil-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

Compuesto No. 461: des(1-5)-4-Piridincarbonil-[AzaGly7,Arg(Me)9,Nal(2)10]MS10

4-Piridincarbonil-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

Compuesto No. 462: des(1-5)-6-Hidroxinicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10

6-Hidroxinicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 463: des(1-5)-6-Cloronicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10

6-Cloronicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 464: des(1-5)-6-(Trifluorometil)nicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10

6-(Trifluorometil)nicotinoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 466: des(1-5)-2-Azetidinecarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Azetidinecarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 467: des(1-5)-Dimetilcarbamoil-[AzaGly7,Arg(Me)9,Trp10]MS10

Dimetilcarbamoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 468: des(1-5)-1-Azetidincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

1-Azetidincarbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 471: des(1-5)-4-Piridincarbonil-

[AzaGly7,Arg(Me)9]MS10

4-Piridincarbonil-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 472: des(1-5)-4-Aminobenzoil-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Aminobenzoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 473: des(1-5)-4-Aminometilbenzoil-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Aminometilbenzoil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 474: des(1-5)-pirrol-3-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Pirrol-3-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 475: des(1-5)-Pirimidin-4-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Pirimidin-4-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 477: des(1-5)-4-Piridincarbonil-[AzaGly7,Orn9,Trp10]MS10

4-Piridincarbonil-Phe-AzaGly-Leu-Orn-Trp-NH_2

Compuesto No. 478: des(1-5)-4-Piridincarbonil-[AzaGly7,Har9,Trp10]MS10

4-Piridincarbonil-Phe-AzaGly-Leu-Har-Trp-NH_2

Compuesto No. 479: des(1-5)-Pirimidin-2-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Pirimidin-2-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 480: des(1-5)-Pyridazine-4-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Piridazin-4-carbonil-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 481: des(1)-[D-Tyr2,D-

Pya(4)3,AzaGly7,Har9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Trp-NH_2

Compuesto No. 486: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Orn9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Orn-Phe-NH_2

Compuesto No. 487: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Lys9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Lys-Phe-NH_2

Compuesto No. 488: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Phe-NH_2

Compuesto No. 489: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har(Me)9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har(Me)-Phe-NH_2

Compuesto No. 490: des(1)-[D-Tyr2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 491: des(1)-[D-Tyr2,D-Pya(4)3,Trp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Trp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 492: des(1)-[D-Tyr2,D-Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 493: des(1)-[D-Tyr2,D-Pya(4)3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 494: des(1,4)-[D-Tyr2,D-

Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 495: des(1-3)-[D-Tyr4,Pya(4)5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-Pya(4)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 496: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 497: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Ala7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Cha-Ala-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 498: des(1)-[D-Tyr2,D-Pya(4)3,Ile5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 499: des(1-3)-3-Fenilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 500: des(1-3)-3-Fenilpropionil-[Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 501: des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 502: des(1)-[D-Tyr2,Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 503: des(1)-[D-Tyr2,D-

Trp3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 504: [Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 505: des(1-3)-3-Fenilpropionil-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 506: des(1-3)-3-Fenilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 507: des(1-3)-3-Fenilpropionil-[Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 508: des(1-3)-3-Fenilpropionil-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 509: des(1-3)-Benzoil-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 510: des(1-3)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 511: des(1)-[D-Tyr2,D-Trp3,Ala4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Ala-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 512: des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 513: des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 514: des(1)-[D-Tyr2,D-Phe3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Phe-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 515: des(1)-[D-Tyr2,D-Pya(4)3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 516: des(1)-Ac-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 517: des(1-3)-3-Fenilpropionil-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 518: des(1-3)-3-Fenilpropionil-[Cha6,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 519: des(1-3)-Fenilacetil-[AzaGly7,Arg(Me)9,Trp10]MS10

Fenilacetil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 521: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg-Phe-NH_2

Compuesto No. 522: des(1-3)-Benzoil-

[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 523: des(1-3)-Benzoil-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 524: des(1-3)-3-Fenilpropionil-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 527: des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 528: des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 529: des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Tle-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 530: des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Phg-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 531: des(1-3)-3-Fenilpropionil-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Pic(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 532: des(1-3)-3-Fenilpropionil-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-

NH_2

Compuesto No. 533: des(1-3)-3-Fenilpropionil-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-D-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 534: des(1-3)-Ciclopropancarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10

Ciclopropancarbonil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 535: des(1-3)-2-Naftoil-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Naftoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 536: [Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 537: Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 538: Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 539: des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 540: des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 541: D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 542: D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 545: des(1-3)-Benzoil-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 546: des(1-3)-3-Fenilpropionil-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Fenilpropionil-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 547: des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 548: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10ψ,CSNH]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Pheψ(CSNH)NH_2

Compuesto No. 550: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 551:

Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 552:

D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 553:

D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 554:

D-Arg-[β-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-β-Ala-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 555:

D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 556:

D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 557:

D-Arg-D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 558: des(1)-Ac-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 559: des(1-2)-3-(4-Hidroxifenil)propionil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-(4-Hidroxifenil)propionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 561: D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 562: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 563: des(1)-Ac-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 564: des(1)-Ac-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 565: Benzoil-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 566: des(1)-Ciclopropancarbonil-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ciclopropancarbonil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 567: des(1)-Butiril-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Butiril-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 568: Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 569:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,6ψ7,CH_2NH,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Pheψ(CH_2NH)Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 570: Me-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Me-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 571: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 572: des(1)-[D-Trp2,D-

Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 573: des(1)-Ac-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 576: des(1)-Ac-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Gln-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 577: des(1)-Ac-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Ser-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 578: des(1)-Ac-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 579: des(1)-Ac-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 580:

des(1)-Ac-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 584:

des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 585:

des(1)-Ac-[D-Tyr2,D-

Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 586: des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 589:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

Compuesto No. 590:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2

Compuesto No. 591:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2

Compuesto No. 592:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compuesto No. 594:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Hph-NH_2

Compuesto No. 595: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Cha10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Cha-NH_2

Compuesto No. 596: des(1)-Ac-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Leu10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Leu-NH_2

Compuesto No. 597: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 598: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 599: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2

Compuesto No. 600: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2

Compuesto No. 601: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 602: des(1)-Ac-[D-MeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-MeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 603: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 604: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Tos)-Trp-NH_2

Compuesto No. 605:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(NO2)-Trp-NH_2

Compuesto No. 607:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)asym-Trp-NH_2

Compuesto No. 608:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)sym-Trp-NH_2

Compuesto No. 609:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Et)-Trp-NH_2

Compuesto No. 610:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys(Me2)-Trp-NH_2

Compuesto No. 611: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 612: For-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Para-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH2

Compuesto No. 613: Propionyl-des(1)-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Propionil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 614: Amidino-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Amidino-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 615: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 616: des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 617: des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 618: des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 619: des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(1)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 620: des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(2)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 621: des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 622: des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Glu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 623: des(1)-Ac-[D-Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 624: des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 625: des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 626: des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 627: des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 628: des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Thr-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 629: des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 630: des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 631: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Ala-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 632: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Leu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 633: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Lys-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 634: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Glu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 635: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 636: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,MePhe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-MePhe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 637: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 638: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 639: des(1)-Ac-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys-Trp-NH_2

Compuesto No. 641: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ala-Arg(Me)-Trp-NH_2

Compuesto No. 642: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

Compuesto No. 643: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Phe-Arg(Me)-Trp-NH_2

Compuesto No. 644: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ser-Arg(Me)-Trp-NH_2

Compuesto No. 645: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har-Trp-NH_2

Compuesto No. 646: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har(Me)-Trp-NH_2

Compuesto No. 647: des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 648: [Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 649: Ac-[Gly1,D-Tyr2,D-

Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 650: [D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 651: Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 652: el pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 653: des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-D-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 654: des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-D-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 655: des(1)-Ac-[D-Tyr2,D-Trp3,MeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-MeAsn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 656: des(1)-Ac-[D-Tyr2,D-Trp3,MeSer5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-MeSer-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 657: des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 658: des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 659: des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-allo-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 660: des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 661: des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 662: des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 663: des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 664: des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 665: des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 666: des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 667: des(1-2)-Hexanoil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Hexanoil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 668: des(1-2)-Ciclohexancarbonil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ciclohexancarbonil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 669: des(1-2)-Benzoil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 670: des(1-2)-3-Piridinpropionil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Piridinpropionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 671: des(1-2)-Adipoil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Adipoil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No.: des(1)-Ac-[D-Tyr2,NMeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 674: des(1-2)-6-Aminocaproil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

6-Aminocaproil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 675: [D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 676: Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 677: Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Nva-Arg(Me)-Trp-NH_2

Compuesto No. 678: Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ile-Arg(Me)-Trp-NH_2

Compuesto No. 679: des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Amidino-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 680: des(1-2)-Glicoloil-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Glicoloil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 681: des(1)-Glicoloil-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Glicoloil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 682: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Gln-Arg(Me)-Trp-NH_2

Compuesto No. 685: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compuesto No. 686: des(1)-Ac-[D-Tyr2,D-

Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Gly-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 688: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Pya(4)-Trp-NH_2

Compuesto No. 689: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-D-Trp-NH_2

Compuesto No. 691: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 692: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 693: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr(Me)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 694: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Nal(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 695: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Thi-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 696: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 698: des(1)-Ac-[D-Tyr2,D-

Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Abu-Arg(Me)-Trp-NH_2

Compuesto No. 699: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-γMeLeu-Arg(Me)-Trp-NH_2

Compuesto No. 700: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Aib-Arg(Me)-Trp-NH_2

Compuesto No. 701: des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 702: des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp(NHMe)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compuesto No. 703: des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NMe2)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp(NMe2)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2.

Para los derivados de metastina (II), los utilizados preferiblemente son derivados de metastina representados por la fórmula:

XX0-XX2-XX3-XX4-XX5-XX6-AzaGly-XX8-XX9-XX10-NH_2

(en donde:

XX0 representa formilo, alcanoilo C_{1-6} (por ejemplo, acetilo, propionilo, butirilo, hexanoilo, y similares; preferentemente acetilo, propionilo, butirilo; más

preferentemente acetilo), ciclopropanecarbonilo, 6-(acetil-D-arginilamino)caproilo, 6-((R)-2,3-diaminopropionilamino)caproilo, 6-(D-norleucilamino)caproilo, 4-(D-arginilamino)butirilo, o 3-(4-Hidroxifenil)propionilo, glicilo, tirosilo, acetilglicilo, acetiltirosilo, D-tirosilo, acetil-D-tirosilo, piroglutamilo, 3-(piridin-3-il)propionilo, adipoilo o 6-aminocaproilo (preferentemente acetilo y lo similar);

XX2 representa Tyr, D-Tyr, D-Ala, D-Leu, D-Phe, D-Lys, D-Trp ó brazo de enlace (preferentemente D-Tyr o brazo de enlace; más preferiblemente D-Tyr);

XX3 representa Trp, Pro, 4-piridilalanina, Tic, D-Trp, D-Ala, D-Leu, D-Phe, D-Lys, D-Glu, D-2-piridilalanina, D-3-piridilalanina o D-4-piridilalanina (preferentemente D-Trp o D-4-piridilalanina);

XX4 representa Asn, ácido 2-amino-3-ureidopropiónico, ácido N^{β}-formildiaminopropiónico o ácido N^{β}-acetildiaminopropiónico (preferentemente Asn);

XX5 representa Ser, Thr o Val (preferentemente Ser o Thr);

XX6 representa Phe, Tyr, Trp, Tyr(Me), Thi, Nal(2), CHa, 4-piridilalanina o 4-fluorofenilalanina (preferentemente Phe o 4-fluorofenilalanina);

AzaGly representa azaglicina;

XX8 representa Leu, Nva ó Val (prerferiblemente Leu);

XX9 representa Arg, OrnArg(Me), o Arg(symMe2) (preferiblemente Arg(Me));

XX10 representa Phe, Trp, 2-naftilalanina, 2-tienilalanina, tirosina o 4-fluorofenilalanina (preferentemente Phe ó Trp)), o una sal del mismo. Además, se prefieren compuestos representados por el número de compuesto siguiente:

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 552),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 558),

3-(4-Hidroxifenil)propionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 559),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 562),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 571),

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 579),

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 585),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compuesto No. 589),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compuesto No. 592),

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH2 (Compuesto No. 612),

Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 613),

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 618),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 627),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 637),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 638),

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 658),

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 660),

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 663), o sales de los mismos.

Los derivados de metastina (II) de la presente invención o sus sales o prodrogas tienen una excelente estabilidad en sangre, además de efectos excelentes para suprimir metástasis de cáncer y crecimiento de cáncer, y son útiles como agentes para prevenir o tratar cánceres (por ejemplo, cáncer pulmonar, cáncer gástrico, cáncer hepático, cáncer pancreático, cáncer colorectal, cáncer

la presente invención o sus sales o prodrogas poseen excelentes actividades de promover la secreción de hormona gonadotrópica, promover la secreción de hormona del sexo, inducir ovulación o estimular ovulación, y son útiles por ser agentes estables y de baja toxicidad, por ejemplo, agentes para mejorar la función gonadal, agentes para prevenir o tratar cáncer dependiente de hormona (por ejemplo, cáncer de próstata, cáncer de pecho, etc.), infertilidad, endometriosis, pubertad precoz, mioma uterino, etc., agentes para inducir o estimular la ovulación, agente secretagogo de hormonas gonadotrópicas, anticonceptivos, agente secretagogo de hormona del sexo, o lo similar.

Además, los derivados de metastina (II) de la presente invención o sus sales o prodrogas son útiles como agentes para prevenir o tratar la enfermedad de Alzheimer, deterioro cognoscitivo moderado, etc.

Los derivados de metastina (III) [incluso los derivados de metastina (II) y los derivados de metastina (I)] de la presente invención o sus sales o prodrogas son útiles como agentes para suprimir secreción de hormona gonadotrópica o secreción de hormona del sexo; agentes para regular en decremento hormona gonadotrópica u hormona de sexo; agentes para regular en decremento la proteína OT7T175 humana (receptor de metastina) que consiste en la secuencia de aminoácido representada por SEQ ID NO: 9; agentes para prevenir o tratar cánceres

dependiente de hormonas (por ejemplo, cáncer de próstata, cáncer de pecho, etc.; particularmente, cáncer de próstata sensible a hormona, etc.); agentes para prevenir o tratar endometriosis; agentes para inhibir la maduración folicular ovárica; agentes de suspensión de ciclo menstrual; agentes para tratar mioma uterino; agentes para tratar pubertad precoz; anticonceptivos, etc.

Adicionalmente, los derivados de metastina (III) [inclusive los derivados de metastina (II) y los derivados de metastina (I)] de la presente invención o sus sales o prodrogas son útiles como agente para potenciación de la inmunidad (agente profiláctico para infección después del trasplante de hueso-médula, agente para potenciación de la inmunidad considerada para cáncer); agente de profilaxis/terapéutica para la atrofia muscular bulboespinal; agente para proteger el ovario; agente de profilaxis/terapéutica para la hipertrofia benigna de próstata (BPH); agente de profilaxis/terapéutica para el desorden de identidad de género; o agente para la fertilización "in vitro" (IVF). Además, es útil como un agente de profilaxis/terapéutica para infertilidad, hipogonadismo, oligospermia, azoospermia, aspermia, astenospermia, o necrospermia. Además, es útil para las enfermedades dependiente de hormonas tales como cáncer de próstata, cáncer uterino, cáncer de pecho, cáncer dependiente de hormona del sexo

similar al tumor hipofisial, agrandamiento de glándula próstata, endometriosis, fibroide uterino, pubertad precoz, dismenorrea, amenorrea, síndrome menstrual, síndrome de ovario multilocular, recaída postoperatoria de los cánceres mencionados precedentemente, metástasis de los cánceres mencionados precedentemente, hipopituitarismo, enanismo (caso en donde la secreción de hormona somatotrópica fue comprometido asociando con la hiposecreción de hormona pituitaria), desorden menopáusico, síntoma indefinido, desórdenes dependientes de hormona del sexo tal como los desórdenes metabólicos del hueso calcio fosforado. Son aplicables para anticoncepción (o infertilidad cuando se utiliza el efecto de rebote después de la cesación de la droga).

Además, de la metastina por sí misma, el ADN que codifica la metastina, etc. también es útil como agente para suprimir la secreción de la hormona gonadotrópica o secreción de hormona del sexo; como agente para regular en disminución la hormona gonadotrópica u hormona del sexo; como agente para regular en disminución la proteína OT7T175 humana (receptor de metastina) el cual consiste en la secuencia de aminoácido representada por SEQ ID NO: 9; como agente para prevenir o tratar cánceres dependiente de hormonas (por ejemplo, cáncer de próstata, cáncer de pecho, etc.; particularmente, cáncer de próstata sensible a hormona, cáncer de próstata sensible hormona, etc.); como agente para prevenir o tratar

endometriosis; como agente para inhibir la maduración folicular ovárica; commo agente para suspensión de ciclo menstrual; como agente para tratar mioma de útero; ó como agente para tratar la pubertad precoz; commo anticonceptivo, etc.

MEJOR MODALIDAD PARA REALIZACIÓN DE LA INVENCIÓN

Los derivados de metastina (I) y (II) de la presente invención pueden ser preparados por métodos públicamente conocidos para la síntesis de péptido. Como los métodos para la síntesis de péptido, por ejemplo, puede usarse tanto síntesis de fase sólida o síntesis de fase líquida. Es decir, los péptidos parciales o aminoácidos que pueden constituir los péptidos de la presente invención son condensados repetidamente con la parte restante para realizar un producto que posee la secuencia deseada. Cuando el producto tiene grupos protectores, estos grupos protectores son eliminados para producir el péptido deseado. Los métodos públicamente conocidos para la condensación y eliminación de los grupos protectores se describen en (i) a (v) a continuación.

(1) M. Bodanszky & M.A. Ondetti: "Peptide Sinthesys", Interscience Publishers, Nueva York (1966).

(2) Schroeder & Luebke: "Peptide", Academic Press, Nueva York (1965).

(3) Nobuo Izumiya, y col.: "Péptido Gosei-no-Kiso to Jikken" (Elementos esenciales y experimentos de síntesis de péptido), publicado por la Cía. Maruzen (1975).

(4) Haruaki Yajima & Shunpei Sakakibara: "Seikagaku Jikken Koza" (Experimento Bioquímico) 1, "Tanpakushitsu no Kagaku" (Química de Proteínas) IV, 205 (1977).

(5) Haruaki Yajima, ed.: "Zoku Iyakuhin no Kaihatsu" (Una continuación al desarrollo de farmacéuticos), Vol. 14, "Peptide Synthesis", publicada por Hirokawa Shoten.

Después de la realización de la reacción, el producto puede ser purificado y puede ser aislado por una combinación de métodos de purificación convencionales tal como la extracción por solvente, destilación, cromatografía en columna, cromatografía líquida y recristalización para producir el péptido parcial de la presente invención. Cuando los péptidos obteniso por los métodos anteriores está en una forma libre, los péptidos pueden ser convertidos en una sal apropiada por un método públicamente conocido; cuando la proteína es obtenida en una forma de sal, puede ser convertida en su forma libre por métodos públicamente conocidos.

Para la condensación de los aminoácidos o péptidos protegidos, puede usarse una variedad de reactivos de activación para síntesis de proteína, pero se prefieren particularmente las sales de trisfosfonio, sal de tetrametiluronio, carbodiimides, etc.. Los ejemplos de sales trisfosfonio incluyen hexafluorofosfato de benzotriazol-1-iloxitris(pirrolidino)fosfonio (PyBOP), bromotris(pirrolidino) hexafluorofosfato de fosfonio (PyBroP) y hexafluorophosphate de 7-azabenzotriazol-1-

iloxitris(pirrolidino)fosfonio (PyAOP), los ejemplos de sales de tetrametiluronio incluyen 2-(1H-benzotriazol-1-il)-1,1,3,3-hexafluorofosfato (HBTU), 2-(7-azabenzotriazol-1-il)-1,1,3,3-hexafluorofosfato (HATU), 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio tetraflluoroborato (TBTU), tetrafluoroborato de 2-(5-norbornen-2,3-dicarboxiimido)-1,1,3,3-tetrametiluronio (TNTU) y tetrafluoroborato de O-(N-succimidil)-1,1,3,3-tetrametiluronio (TSTU); los ejemplos de carbodiimidas incluyen DCC, N,N'-diisopropilcarbodiimida (DIPCDI) y hidrocloruro deN-etil-N'-(3-dimetilaminopropil)carbodiimide (EDCI.HCl); etc. Para la condensación que utiliza estos reactivos, es preferible el agregado de inhibidores de racemización (por ejemplo, HONB, HOBt, HOAt, HOOBt, etc.). Pueden escogerse apropiadamente los solventes utilizados en condensación de solventes que son conocidos por ser utilizables para condensación. Por ejemplo, pueden ser utilizadas amidas ácidas tales como N,N-dimetilformamida anhidra o hidratada, N,N-dimetilacetamida, N-metilpirrolidona, etc., hidrocarburos halogenados tales como cloruro de metileno, cloroformo, etc., alcoholes tales como trifluoroetanol, fenol, etc., sulfóxidos tales como dimetilsulfóxido, etc., amina tal como piridina, etc., éteres tales como dioxano, tetrahidrofurano, etc., nitrilos tales como acetonitrilo, propionitrilo, etc., ésteres tales como acetato de metilo, acetato de etilo,

etc., o mezclas convenientes de los mismos, etc.. La temperatura de reacción es elegida apropiadamente del rango conocido para ser aplicable a las reacciones de enlace de péptido y normalmente se escoge adecuadamente del rango de aproximadamente -20°C a 50°C. Los derivados de aminoácido activados generalmente se usan en exceso de 1,5 a 6 veces. En el caso de síntesis de fase sólida, la condensación es examina con reacción de ninhidrina; cuando la condensación es insuficiente, la condensación puede ser completada repitiendo la reacción de condensación sin eliminación de los grupos protectores. Cuando la condensación aún es insuficiente incluso después de repetir la reacción, los aminoácidos sin reaccionar son acilados con anhídrido acético o acetilimidazol para cancelar cualquier efecto adverso en la reacción subsiguiente.

Los ejemplos de los grupos protectores utilizados para proteger los grupos amino en los aminoácidos de comienzo incluyen Z, Boc, terc-pentiloxicarbonilo, isoborniloxicarbonilo, 4-metoxibenziloxicarbonilo, Cl-z, Br-z, adamantiloxicarbonilo, trifluoroacetilo, ftaloilo, formilo, 2-nitrofenilsulfenilo, difenilfosfinotioilo, Fmoc, tritilo, etc. los Ejemplos de los grupos protectores para un grupo carboxilo incluyen, además del grupo alquilo C_{1-6}, grupo cicloalquilo C_{3-8} y grupo aralquilo C_{7-14} para R descripto precedentemente son alilo, 2-adamantilo, 4-nitrobencilo, 4-metoxibencilo, 4-

clorobencilo, grupo fenacilo, benziloxicarbonilhidrazida, terc-butoxicarbonilhidrazida, tritilhidrazida, etc.

El grupo hidroxilo de serina y treonina puedeser protegido, por ejemplo, por esterificación o eterificación. Los ejemplos de grupos convenientes para esta esterificación incluyen un gruupo alcanoilo inferior (C_{2-4}) tal como el grupo acetilo, un grupo aroilo tal como gruupo benzoilo, etc. y un grupo derivado del ácido orgánico. Los ejemplos de un grupo conveniente para eterificación incluyen el grupo bencilo, grupo tetrahidropiranilo, grupo terc-butilo, grupo tritilo (Trt), etc.

Los ejemplos de grupos para proteger el grupo hidroxilo fenólico de tirosina incluyen Bzl, Cl_2-Bzl, 2-nitrobencilo, Br-z, terc-butilo, etc.,

Los ejemplos de grupos para proteger la fracción imidazol de histidina incluyen Tos, 4-metoxi-2,3,6-trimetilbencensulfonilo (Mtr), DNP, Bom, Vago, Boc, Trt, Fmoc, etc.

Los ejemplos de los grupos para proteger un grupo guanidino de arginina incluyen Tos, Z, 4-metoxi-2,3,6-trimetilbenzenesulfonilo (Mtr), p-metoxibencensulfonilo (MBS), 2,2,5,7,8-pentametilcroman-6-sulfonilo (Pmc), mesitileno-2-sulfonilo (Mts), 2,2,4,6,7-pentametildihidrobenzofuran-5-sulfonilo (Pbf), Boc, Z, NO_2, etc.

Los ejemplos de los grupos protectores para el grupo

amino de cadena lateral de lisina incluyen Z, Cl-Z, trifluoroacetilo, Boc, Fmoc, Trt, Mtr, 4,4-dimetil-2,6-dioxociclohexilidenilo (Dde), etc.

Los ejemplos de los grupos protectores para el indolilo de triptofano incluyen formilo (For), Z, Boc, Mts, Mtr, etc.

Un grupo protector para asparagina y glutamina incluye Trt, xantilo (Xan), 4,4'-dimetoxibenzhidrilo (Mbh), 2,4,6-trimetoxibencilo (Tmob), etc.

Los ejemplos de los grupos carboxilo activados en el material de comienzo incluyen los anhídridos ácidos correspondientes, azida, ésteres activados [ésteres con alcoholes (por ejemplo, pentaclorofenol, 2,4,5-triclorofenol, 2,4-dinitrofenol, alcohol cianometilo, p-nitrofenol, HONB, N-hidroxisuccimida, 1-hidroxibenzotriazol (HOBt) ó 1-hidroxi-7-azabenzotriazol (HOAt)], etc. Como los aminoácidos en los cuales son activados los grupos amino en el material de comienzo, son utilizadas las amidas fosfóricas correspondientes.

Para eliminar (separar) los grupos protectores, es utilizada la reducción catalítica bajo flujo de gas hidrógeno en presencia de un catalizador tal como Pd-negro o Pd-carbono; un tratamiento con ácido con ácido clorhídrico anhidro, ácido metansulfónico, ácido trifluorometansulfónico, ácido trifluoracético, bromuro de trimetilsilano (TMSBr), trifluorometansulfonato de trimetilsililo, ácido tetrafluorobórico,

tris(trifluoro)boro, tribromuro de boro o una solución mezcla de los mismos, un tratamiento a base de diisopropiletilamina, trietilamina, piperidina, piperacina, etc., y reducción con sodio en amonio líquido. La eliminación de los grupos protectores por tratamiento con ácido descripta precedentemente generalmente es realizada a una temperatura de aproximadamente -20°C a 40°C. En el tratamiento con ácido, es eficaz agregar un depurador de catión tal como anisol, fenol, tioanisol, m-cresol, p-cresol, etc., dimetilsulfuro, 1,4-butanditiol, 1,2-etaneditiol, etc. Además, el grupo 2,4-dinitrofenilo conocido como el grupo protector para el imidazol de histidina es eliminado por un tratamiento con tiofenol. El grupo formilo usado como grupo protector de indol de triptofano es eliminado por tratamiento con ácido mencionado precedentemente en presencia de 1,2-etanditiol, 1,4-butanditiol, etc. así como por un tratamiento con un álcali tal como una solución diluida de hidróxido de sodio, amonio diluido, etc.,

La protección de grupos funcionales que no deben ser involucrados en la reacción de los materiales de comienzo, grupos protectores, eliminación de los grupos protectores y activación de grupos funcionales involucrados en la reacción puede ser elegida apropiadamente de los grupos públicamente conocidos y los medios públicamente conocidos.

En otro método para obtener las amidas del péptido, por ejemplo, el grupo α-carboxilo del carboxilo del terminal aminoácido es primero protegido por amidación; entonces la cadena de péptido es extendida del lado de grupo amino a una longitud deseada. Después de esto, se prepara un péptido en el cual sólo el grupo protector de grupo término N α-amino en la cadena de péptido ha sisdo eliminado del péptido y un péptido (o un aminoácido) en el cual sólo el grupo protector del grupo carboxilo terminal C se ha eliminado. Los dos péptidos son condensados en una mezcla de solventes descripta anteriormente. Los detalles de la reacción de condensación son iguales a los descriptos anteriormente. Después que los péptidos protegidos obtenidos por condensación son purificados, todos los grupos protectores son separados por el método descrito precedentemente para dar el péptido en bruto deseado. Este péptido en bruto es purificado por los diversos medios de purificación conocidos. La liofilización de la fracción principal produce la amida del péptido deseado.

Cuando los derivados de metastina (I) y (II) de la presente invención están presentes como un isómero de configuración, un diaestereómero, un conformero o lo similar, cada uno puede ser aislado por los medios de separación y purificación descriptos precedentemente, si se desea. Adicionalmente, cuando el compuesto de la presente invención es racémico, puede ser separado en un

isómero S y un isómero R por los medios de resolución ópticos convencionales.

Cuando los derivados de metastina (I) y (II) de la presente invención tienen isómero estérico, la presente invención incluyen ambos isómeros solos y los isómero presentes como una mezcla.

Adicionalmente, los derivados de metastina (I) y (II) de la presente invención pueden ser hidratados o no hidratados.

Los derivados de metastina (I) y (II) de la presente invención pueden ser etiquetados con un isótopo (por ejemplo, ^{3}H, ^{14}C, ^{35}S), etc.

A través de la presente descripción, los péptidos se representan de acuerdo con la manera convencional para describir los péptidos, es decir, término N (terminal amino) en el lado izquierdo y el terminal C (terminal carboxilo) en el lado derecho. En los péptidos, terminal C está normalmente en la forma de una amida ($-CONH_2$), un grupo carboxilo (-COOH), un carboxilato ($-COO^-$), un alquilamida (-CONHR) o un éster (-COOR) y es particularmente preferible la amida ($-CONH_2$). Los ejemplos del éster o alquilamida como R incluyen un grupo alquilo C_{1-6} tal como metilo, etilo, n-propilo, isopropilo, n-butilo, etc.; un grupo cicloalquilo C_{3-8} tal como ciclopentilo, ciclohexilo, etc.; un grupo arilo C_{6-12} tal como fenilo, α-naftilo, etc.; un grupo aralquilo C_{7-14} tal como un grupo fenil-C_{1-2}-alquilo, por ejemplo,

bencilo, fenetilo, etc., o un grupo α-naftil-C_{1-2}-alquilo tal como α-naftilmetilo, etc.; grupo pivaloiloximetilo que es utilizado ampliamente como un éster para uso oral y lo similar.

Los ejemplos de una sal de derivado de metastina (I) de la presente invención incluyen una sal de metal, una sal con amonio, una sal con una base orgánica, una sal con ácido inorgánico, una sal con ácido orgánico, una sal con un elemento esencial o aminoácido ácido, y lo similar. Los ejemplos preferidos de la sal de metal incluyen las sales de metal alcalino tal como la sal de sodio, sal de potasio, etc.; sales de metal alcalino térreo tal como sal de calcio, sal de magnesio, sal de bario, etc.; las sales de aluminio; y lo similar. Los ejemplos preferibles de las sales con bases orgánicas incluyen las sales con trimetilamina, trietilamina, piridina, picolina, 2,6-lutidina, etanolamina, dietanolamina, trietanolamina, ciclohexilamina, diciclohexilamina, N,N'-dibenciletilendiamina, etc. Los ejemplos referibles de las sales con ácidos inorgánicos incluyen las sales con ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, etc. Los ejemplos preferibles de sales con ácidos orgánicos incluyen las sales con ácido fórmico, ácido acético, ácido ftálico, ácido trifluoracético, ácido fumárico, ácido oxálico, ácido tartárico, ácido maléico, ácido cítrico, ácido succínico, ácido málico,

ácido metansulfónico, ácido bencensulfónico, ácido p-toluensulfónico, etc. Los ejemplos preferibles de sales con aminoácidos básicos incluyen las sales con arginina, lisina, ornitina, etc., y los ejemplos preferibles de sales con aminoácidos ácidos incluyen las sales con ácido aspártico, ácido glutámico, etc.,

Entre los mismos, son preferibles las sales farmacéuticamente aceptables. Por ejemplo, cuando el compuesto tiene un grupo funcional ácido, son preferibles las sales inorgánicas tales como las sales de metal alcalino (por ejemplo, sal de sodio, sal de potasio, etc.), sal de metal alcalino térreo (por ejemplo, sal de calcio, sal de magnesio, sal de bario, etc.), las sales de amonio, etc.. Cuando el compuesto tiene un grupo funcional básico, son preferibles las sales con ácidos inorgánicos con ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, etc., y sales con ácidos orgánicos tales como ácido acético, ácido ftálico, ácido fumárico, ácido oxálico, ácido tartárico, ácido maléico, ácido cítrico, ácido succínico, ácido metansulfónico, ácido p-toluensulfónico, etc..

Una prodroga del derivado de metastina (III) o una sal del mismo (más adelante a veces denominado simplemente derivado de metastina (III) de la presente invención) significa un derivado de metastina que es reconstruido en el derivado de metastina (III) de la presente invención bajo condiciones fisiológicas o con

una reacción debido a una enzima, un ácido gástrico, etc., en el cuerpo viviente. Es decir, la prodroga de la presente invención es un derivado de metastina que sufre una oxidación, reducción, hidrólisis, enzimática etc. para ser convertido en el derivado de metastina (III) de la presente invención, o un derivado de metastina que sufre una hidrólisis, etc. por medio del ácido gástrico, etc. para ser convertido en el derivado de metastina (III) de la presente invención.

Las prodrogas del derivado de metastina (I) de la presente invención o sales de los mismos (más adelante a veces denominado simplemente el derivado de metastina (I) de la presente invención) y las prodrogas del derivado de metastina (II) de la presente invención o sales de los mismos (más adelante a veces denominado simplemente el derivado de metastina (II) de la presente invención) que pueden ser utilizados son iguales a los descriptos para las prodrogas del derivado de metastina (III) de la presente invención.

Los ejemplos de prodrogas de los derivados de metastina (III) de la presente invención incluyen los derivados de metastina en donde un grupo amino del derivado de metastina (III) de la presente invención es sustituido con un acilo, un alquilo, ácido fosfórico, etc. (por ejemplo, derivados de metastina en donde un grupo amino del derivado de metastina (III) de la presente invención es sustitudio con eicosanoilo,

alanilo, pentilaminocarbonil (5-metil-2-oxo-1,3-dioxolen-4-il)metoxicarbonilo, tetrahidrofuranoilo, pirrolidilmetilo, pivaloiloximetilo, terc-butilo, etc); los derivados de metastina en donde un grupo hidroxilo del derivado de metastina (I) de la presente invención es sustituido con un acilo, alquilo, ácido fosfórico, ácido bórico, etc. (por ejemplo, derivados de metastina en donde un grupo hidroxilo del derivado de metastina (III) de la presente invención es sustituido con acetilo, palmitoilo, propanoilo, pivaloilo, succinilo, fumarilo, alanilo, dimetilaminometilcarbonilo, etc.); y derivados de metastina en donde un grupo carboxilo del derivado de metastina (III) de la presente invención es sustituido con éster, amida, etc. (por ejemplo, derivados de metastina en donde un grupo carboxilo del derivado de metastina (III) de la presente invención es sustituido con éster de etilo, éster de fenilo, éster de carboximetilo, éster de dimetilaminometilo, éster de pivaloiloximetilo, éster de etoxicarboniloxietilo, éster de ftalidilo, éster de (5-metil-2-oxo-1,3-dioxolen-4-il)metilo, éster de ciclohexiloxicarboniletilo, metilamida, etc); y lo similar. Estos derivados de metastina pueden ser producido del derivado de metastina (I) de la presente invención mediante los métodos conocidos por sí mismos.

Las prodrogas del derivado de metastina (III) de la presente invención pueden ser aquellas que son

reconstruidas en el derivado de metastina (III) de la presente invención bajo condiciones fisiológicas tales como las descriptas en "Pharmaceutical Research and Development", Vol. 7 (Diseño de Droga), páginas 163-198, publicado en 1990 por Hirokawa Publishing Co.

Los derivados de metastina (I), (II) ó (III) de la presente invención o sus sales o prodrogas (más adelante a veces denominado simplemente el compuesto de la presente invención) poseen una actividad que suprime la metástasis de cáncer o una actividad que suprime el crecimiento de cáncer. Así, los derivados de metastina son útiles para los compuestos farmacéuticos tales como agentes para prevenir o tratar todos los cánceres (por ejemplo, cáncer pulmonar, cáncer gástrico, cáncer hepático, cáncer de páncreas, cáncer colorectal, cáncer rectal, cáncer colónico, cáncer de próstata, cáncer ovárico, cáncer cervical, cáncer de pecho, etc.).

Los compuestos de la presente invención también poseen el efecto de controlar la función pancreática y son útiles como agentes para prevenir o tratar las diversas enfermedades pancreáticas (por ejemplo, pancreatitis aguda o crónica, cáncer pancreático, etc.) como agentes para controlar la función pancreática.

Los compuestos de la presente invención también poseen el efecto de controlar la función de la placenta y así son útiles como compuestos farmacéuticos para prevenir o tratar coriocarcinoma, mola hidatídica, mola

invasiva, aborto, hipoplasia fetal, metabolismo de glucosa anormal, metabolismo de lípido anormal o inducción al parto, como agentes para controlar la función de placenta.

Además, los compuestos de la presente invención poseen efecto decreciente de nivel de azúcar, promueven la secreción del glucagón pancreático y promueven la formación de orina y así son útiles en compuestos farmacéuticos como agentes hiperglucémicos, agentes secretagogos de glucagon pancreático o agentes para promover la formación de orina los cuales son útiles para prevenir o tratar obesidad, hiperlipidemia, diabetes mellitus tipo II, hipoglucemia, hipertensión, neuropatía diabética, nefropatía diabética, retinopatía diabética, edema, perturbaciones urinarias, resistencia a insulina, diabetes inestable, atrofia grasa, alergia a insulina, insulinoma, arteriosclerosis, desórdenes trombóticos o lipotoxicidad.

Adicionalmente, los compuestos de la presente invención también poseen efectos de promoción de la secreción de la hormona gonadotrópica (por ejemplo, FSH, LH, etc.), promover la secreción de la hormona del sexo [por ejemplo, andrógenos (por ejemplo, testosterona, androestenodiona, etc.), estrógenos (por ejemplo, estradiol, teelina, etc.), progesteronas, etc.], mejorar la función gonadal e inducir o estimular la ovulación, así como un efecto de maduración sexual, etc., y por lo

tanto, pueden ser utilizados como agentes para mejorar la función gonadal, agentes para inducir o estimular la ovulación, agente secretagogo de hormona gonadotrópica o agente secretagogo de hormona del sexo, o agentes para prevenir o tratar cánceres dependientes de hormonas [por ejemplo, cáncer de próstata, cáncer de pecho, etc.], infertilidad [por ejemplo, menstruación irregular, dismenorrea, amenorrea, pérdida d peso inducido por amenorrea, amenorrea secundaria, anovulación, hipoovarismo, hipogonadismo, falla espermatogenética, hipogonadismo (por ejemplo, impotencia, etc.), atrofia genital, atrofia testicular, desorden de función testicular, azoospermia, hipoandrogenemia, etc.], endometriosis, pubertad precoz, mioma de útero, etc.,

Además, las prodrogas del derivado de metastina (I) ó (II) de la presente invención o sales de los mismos son útiles como agentes para prevenir o tratar la enfermedad de Alzheimer, deterioro cognoscitivo moderado, etc.

Además, los compuestos de la presente invención tienen una excelente estabilidad en sangre, en comparación a la metastina natural tal como la metastina 54 (1-54) o metastina 10 (45-54).

Los derivados de metastina (III) [incluyendo los derivados de metastina (II) y los derivados de metastina (I)] de la presente invención o sus sales o prodrogas son útiles como agentes para suprimir la secreción de hormona gonadotrópica o secreción de hormona del sexo; agentes

para regular en disminución la hormona gonadotrópica (por ejemplo, FSH, LH) u hormona del sexo [por ejemplo, andrógeno (por ejemplo, testosterona, androstenodiona), estrógeno (por ejemplo, estradiol, estorona), progesterona]; en particular, son útiles para suprimir la secreción de hormona gonadotrópica o secreción de hormona de sexo mediante la regulación por disminución de hormona gonadotrópica u hormona del sexo (en donde, la regulación de hormona por disminución de hormona gonadotrópica o de sexo puede ser pérdida del pulso LHRH o vaciamiento de LHRH) o regulación por disminución de proteína OT7T175 humana (receptor de metastina) que consiste en la secuencia de aminoácido representada por SEQ ID NO: 9; como agentes para prevenir o tratar cáncer dependiente de hormona (por ejemplo, cáncer de la próstata, cáncer de pecho, etc.; particularmente, cáncer de próstata sensible a hormona, cáncer de próstata sensible a hormona, etc.); agentes para prevenir o tratar endometriosis; agentes para inhibir la maduración folicular ovárica; agentes para suspensión de ciclo menstrual; agentes para tratar mioma de útero; agentes para tratar pubertad precoz; o como anticonceptivos, etc.

Cuando el derivado de metastina (III) de la presente invención [incluyendo el derivado de metastina (II) y el derivado de metastina (I)] o su sal o prodroga, metastina por sí misma, o ADN que codifica metastina, etc. tiene actividad agonista normal, es administrada una dosis

eficaz del derivado de metastina suficiente para suprimir la secreción de hormona gonadotrópica u hormona de sexo al sitio o tejido en donde serán ejercidos los efectos terapéuticos, para que el derivado de metastina esté presente en una dosis más de la requerida (es decir, el derivado del metastina es administrado en un exceso por sobre la dosis eficaz normal para que el derivado de metastina despliegue el efecto de suprimir la metástasis de cáncer, suprimir el crecimiento de cáncer, etc.; o el agente secretagogo de hormona gonadotrópica, el efecto de promover la secreción de hormona del sexo, etc.) para exhibir el efecto de suprimir la secreción de hormona gonadotrópica o secreción de hormona del sexo. Los ejemplos específicos incluyen la administración sostenida o continua de una dosis eficaz normal (incluyendo una técnica de administración para liberar los ingredientes farmacéuticos gradualmente por administración de bolo); y lo similar. Además cuando el derivado de metastina (III) de la presente invención [incluyendo el derivado de metastina (II) y el derivado de metastina (I)] o su sal o prodroga del mismo, etc. tiene una actividad más agonista de la suficientemente requerida (una actividad agonista excelente), hace posible sostener más actividades de las exhibidas por una dosis necesaria en el sitio o tejido en donde el efecto terapéutico será exhibido. Por consiguiente es suficiente incluso por la administración de una dosis eficaz normal suprimir la secreción de

hormona gonadotrópica u hormona del sexo, con lo cual se exhibe el efecto de suprimir la secreción de hormona gonadotrópica o secreción de hormona del sexo.

Es decir, el derivado de metastina (III) [incluso el derivado de metastina (II) y el derivado de metastina (I)] o su sal o prodroga, o metastina por sí misma, ADN que codifica mmetastina, etc. es administrada en una dosis eficaz suficiente para suprimir la secreción de hormona gonadotrópica u hormona del sexo. Por consiguiente, se hace posible mantener el derivado de metastina, etc. presente una dosis mayor de la dosis necesaria o sostener la actividad más de lo exhibido por la dosis necesaria, en el sitio o tejido en donde los efectos farmacéuticos serán exhibidos, resultando en el despliegue del efecto de suprimir la secreción de hormona gonadotrópica o secreción de hormona del sexo.

Las composiciones farmacéuticas que comprenden los compuestos de la presente invención son de bajo toxicidad y así pueden administrarse de manera segura oralmente o parenteralmente (por ejemplo, tópicamente, rectalmente, intravascularmente, etc.) directamente tal como están o en forma de preparaciones farmacéuticas como talbetas (incluso grageas y tabletass recubiertas con película), formas de dosis en polvo, gránulos, cápsulas (incluyendo las cápsulas blandas), formas de dosis líquidas, inyecciones, supositorios, formas de dosis de liberación prolongada, etc.,

El compuesto de la presente invención está contenido en una preparación farmacéutica de la presente invención desde aproximadamente 0,01 hasta aproximadamente 100% en peso, basado en el peso total de la preparación.

Una dosis del compuesto de la presente invención puede variar, dependiendo del sujeto a ser administrado, órgano objetivo, condiciones, vía de administración, etc., y en la administración oral, el compuesto es administrado al paciente generalmente con cáncer (como 60 kg de peso del cuerpo) en una dosis diaria desde aproximadamente 0,1 hasta aproximadamente 100 mg, preferentemente aproximadamente desde 1,0 hasta aproximadamente 50 mg y más preferentemente desde aproximadamente 1,0 hasta aproximadamente 20 mg. En la administración parental, una única dosis del compuesto puede variar, dependiendo del sujeto a ser administrado, órgano objetivo, condiciones, vía de administración, etc., y la forma de dosis inyectable, es ventajoso administrar el compuesto al paciente con cáncer (como 60 kg peso del cuerpo) generalmente en una dosis diaria desde aproximadamente 0,01 hasta aproximadamente 30 mg, preferentemente desde aproximadamente 0,1 hasta aproximadamente 20 mg, y más preferentemente desde aproximadamente 0,1 hasta aproximadamente 10 mg. Para otras especies animales, puede ser administrada la dosis correspondiente convertida a 60 kg peso.

Los vehículos farmacológicamente aceptables que

pueden ser usados para fabricar la preparación farmacéutica de la presente invención incluyen varias substancias de vehículo orgánicas o inorgánicas usadas convencionalmente como materiales para las preparaciones farmacéuticas. Por ejemplo, estas substancias incluyen un vehículo, un lubricante, un aglutinante y un agente de desintegración en una forma de dosis sólida, y un solvente, una auxiliar de disolución, agente de suspensión, un agente de isotonización, un agente amortiguador, un agente anestesiante, etc. en una forma de dosis líquida. Adicionalmente, pueden ser ustilizados apropiadamente aditivos convencionales tales como un conservante, un antioxidante, un colorante, un edulcorante, un adsorbente, un agente humectante, etc., en cantidades convenientes, si es necesario.

Por ejemplo, los ejemplos de excipients incluyen lactosa, sacarosa, D-manitol, almidón, almidón de maíz, ácido silícico anhidro ligero, celulosa cristalina, etc.

Por ejemplo, los ejemplos de lubricantes útiles incluyen estearato de magnesio, estearato de calcio, talco, sílice coloidal, etc.

Por ejemplo, los ejemplos de aglutinantes incluyen celulosa cristalina, sacarosa, D-manitol, dextrina, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona, almidón, sacarosa, gelatina, metilcelulosa, carboximetilcelulosa de sodio, etc.

Por ejemplo, los ejemplos de agentes de

desintegración incluyen almidón, carboximetilcelulosa, carboximetilcelulosa de calcio, carboximetil almidón de sodio, L-hidroxipropilcelulosa, etc.

Por ejemplo, los ejemplos de solventes incluyen agua para inyección, alcohol, propilenglicol, Macrogol, aceite de sésamo, aceite de maíz, aceite de oliva, etc.,

Por ejemplo, los ejemplos de auxiliares de disolución incluyen polietilen glicol, propilenglicol, D-manitol, benzoato de bencilo, etanol, trisaminometano, colesterol, trietanolamina, carbonato de sodio, citrato de sodio, etc.

Por ejemplo, los ejemplos de agentes de suspensión incluyen agentes tensioactivos tales como estearíltrietanolamina, laurilsulfato de sodio, lauril aminopropionato, lecitina, cloruro de benzalconio, cloruro de benzetonio, monoestearato de glicerina, etc.; polímeros hidrófilos tales como polivinil alcohol, polivinil pirolidona, carboximetilcelulosa de sodio, metilcelulosa, hidroximetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, etc.

Por ejemplo, los ejemplos de agentes de isotonización incluyen glucosa, D-sorbitol, cloruro de sodio, glicerina, D-manitol, etc.

Por ejemplo, los ejemplos de agentes amortiguadores incluyen las soluciones amortiguadoras de fosfato, acetato, carbonato, citrato, etc.

Por ejemplo, los ejemplos de agentes de anestesiado

incluyen alcohol bencílico, etc.,

Por ejemplo, los ejemplos de conservantes incluyen p-hidroxibenzoatos, clorobutanol, bencil alcohol, fenetil alcohol, ácido sórbico, ácido deshidroacético, etc.,

Por ejemplo, los ejemplos de antioxidantes incluyen sulfito, ácido ascórbico, α-tocoferol, etc.

Además, el compuesto de la presente invención puede ser utilizado en combinación con distintas drogas del compuesto de la presente invención.

Los ejemplos de las drogas que pueden ser utilizadas en combinación con el compuesto de la presente invención (más adelante denominado una droga de combinación), incluyen a los agentes quimioterapéuticos para tratar cáncer, agentes terapéuticos hormonales, agentes inmunoterapéuticos, etc.

Por ejemplo, los ejemplos de "agentes quimioterapéuticos" incluyen a los agentes de alquilación, antimetabolitos, antibióticos anticáncer, y agentes anticancer derivados de planta.

Por ejemplo, los ejemplos de "agentes de alquilación" incluyen mostaza de nitrógeno, hidrocloruro de mostaza-N-óxido de nitrógeno, clorambutilo, ciclofosfamida, ifosfamida, tiotepa, carboquone, tosilato de improsulfan, busulfan, hidrocloruro de nimustina, mitobronitol, rnelfalan, dacarbazina, ranimustina, estramustina fosfato de sodio, trietilenmelamina, carmustina, lomustina, estreptozocina, pipobroman,

etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamina, ambamustina, hidrocloruro de dibrospidio, fotemustina, prednimustina, pumitepa, ribomustin, temozolomida, treosulfan, trofosfamida, stimalamer zinostatin, carboquone, adozelesin, cistemustina, bizelesin, etc.

Por ejemplo, los ejemplos de "antimetabolitos" incluyen mercaptopurina, 6-mercaptopurina ribosida, tioinosina, metotrexato, enocitabina, citarabina, ocfosfato de citarabina, hidrocloruro de ancitabina, drogas 5-FU (por ejemplo, fluorouracilo, tegafur, UFT, doxifluridina, carmofur, gallocitabina, emmitefur, etc.), aminopterina, leucovorin de calcio, tabloid, butocina, folinato de calcio, levofolinato de calcio, cladribina, emitefur, fludarabina, gemcitabina, hidroxicarbamida, pentostatin, piritrexim, idoxuridina, mitoguazona, tiazofrina, ambamustina, etc.

Por ejemplo, los ejemplos de "antibiótico anticancer" incluyen D-actinomicina, actinomicina C, mitomicina C, cromomicina A3, hidrocloruro de bleomicina, sulfato de bleomicina, sulfato de peplomicina, hidrocloruro de daunorubicina, hidrocloruro de doxorubicina, hidrocloruro de aclarubicina, hidrocloruro de pirarubicina, hidrocloruro de epirubicina, neocarzinostatina, mitramicina, sarcomicina, carzinofilina, mitotano, hidrocloruro de zorubicina, hidrocloruro del mitoxantrona, hidrocloruro de

idarubicina, etc.

Los ejemplos de "agentes anticancer derivados de planta" incluyen, por ejemplo, etoposida, fosfato de etoposida, sulfato de vinblastina, sulfato de vincristina, sulfato de vindesina, teniposida, paclitaxel, docetaxel, vinorelbina, etc.

Los ejemplos de "agentes terapéuticos hormonales" incluyen, por ejemplo, fosfestrol, dietilestilbestrol, clorotrianiseno, acetato de medroxiprogesterona, acetato de megestrol, acetato de clormadinona, acetato de ciproterona, danazol, alilestrenol, gestrinona, mepartricin, raloxifeno, ormeloxifeno, levormeloxifeno, antiestrógenos (por ejemplo, citrato de tamoxifen, citrato de toremifeno, etc.), formas de dosis de píldora, mepitiostano, testrolactona, aminoglutetimida, agonistas de LH-RH (por ejemplo, acetato de goserelin, buserelin, leuprorelin, etc.), droloxifeno, epitiostanol, sulfonato de etinilestradiol, inhibidores de aromatasa (por ejemplo, hidrocloruro de fadrozol, anastrozol, retrozol, exemestano, vorozol, formestano, etc.), antiandrógenos (por ejemplo, flutamida, bicartamida, nilutamida, etc.), inhibidores de 5α-reductasa (por ejemplo, finasteride, epristeride, etc.), drogas de hormonas adrenocorticodes (por ejemplo, dexametasona, prednisolona, betametasone, triamcinolono, etc.), inhibidores de síntesis de andrógeno (por ejemplo, abiraterona, etc.), retinoide y drogas que retardan el metabolismo del retinoide (por

ejemplo, liarozol, etc.), y entre los mismos, son preferibles los agonistas del LH-RH (por ejemplo, acetato de goserelin, buserelin, Leuprorelin, etc.).

Los ejemplos de agentes del immunotherapeutic" (BRM) " incluyen, por ejemplo, picibanil, crestin, sizofiran, lentinan, ubenimex, interferón, interleucinas, factor estimulante de colonia de macrófago, factor estimulante de colonia de granulocito, eritropoyetina, linfotoxina, vacuna BCG, Corynebacterium parvum, levamisol, polisacárido K, procodazol, etc.,

El uso combinado del compuesto de la presente invención y una droga de combinación resulta, por ejemplo, en los excelentes efectos siguientes.

(1) La dosis del compuesto de la presente invención puede ser reducida en comparación con la dosis cuando es administrado de manera exclusiva.

(2) La combinación de una droga con el compuesto de la presente invención puede ser elegida dependiendo de la condición (moderada, severa, etc.) de un paciente.

(3) La combinación de una droga cuyo mecanismo funcional es diferente del compuesto de la presente invención, puede ser elegida para que un período de tratamiento se pueda hacer en mucho más tiempo.

(4) La combinación de una droga cuyo mecanismo funcional es diferente al compuesto de la presente invención, puede ser elegida para que puedan lograrse efectos terapéuticos prolongados.

(5) Un efecto sinérgico puede ser obtenido por el uso combinado del compuesto de la presente invención y una droga de combinación.

Adicionalmente, el compuesto de la presente invención puede reducir los valores de testosterona para medicación inmediatamente debajo del nivel de castración. Así cuane la combinación de drogas tal como agonista LH-RH (por ejemplo, acetato de goserelina, buserlina, Leuprorelina, etc., preferiblemente Leuprorelina) es utilizada en combinación con el compuesto de la presente invención, los valores de testosterona pueden ser reducidos para medicación inmediatamente debajo del nivel de castración del compuesto de la presente invención. Además, debido a que la utilización combinada de una combinación de drogas tal como agonista LH-RH (por ejemplo, acetato de goserelina, buserlina, Leuprorelina, etc., preferiblemente Leuprorelina) y el compuesto de la presente invención resulta en una conservación prolongada del período dependiente de hormona, lo cual puede ser utilizado ventajosamente.

Más adelante en la presente, la utilización combinada del compuesto (I) de la presente invención y una droga de combinación es denominado "preparación combinada de la presente invención".

Cuando la preparación combinada de la presente invención es utilizada, el período de dosificación del compuesto de la presente invención y la combinación no

están restringidos; el compuesto de la presente invención o su composición farmacéutica y una droga de combinación o su composición farmacéutica pueden ser administrados al sujeto a ser administrado tanto simultáneamente como a ciertos intervalos de tiempo. La dosis de una droga de combinación puede ser modificada según la dosis utilizada clínicamente y puede ser elegida dependiendo apropiadamente del sujeto a ser administrado, via de administración, enfermedad, combinación, etc.

Una modalidad para administración de la preparación combinada de la presente invención no está limitada en particular, pero es suficiente que el compuesto de la presente invención sea utilizado en combinación con una droga de combinación en el momento de administración. Para tal modalidad de administración, se presenta, por ejemplo, (1) la administración de una forma de dosis de bolo obtenida mezclando el compuesto de la presente invención y una droga de combinación juntos al mismo tiempo, (2) la administración simultánea de dos formas de dosis preparadas separadamente del compuesto de la presente invención y una droga de combinación a través de la misma vía de administración, (3) la administración de dos formas de dosis preparadas separadamente del compuesto de la presente invención y una droga de combinación a ciertos intervalos de tiempo a través de la misma vía para administración, (4) la administración simultánea de dos formas de dosis preparadas

separadamente del compuesto de la presente invención y una droga de combinación a través de diferentes vías para administración, (5) la administración de dos formas de dosis preparadas separadamente del compuesto de la presente invención y una droga de combinación a ciertos intervalos de tiempo (por ejemplo, administración del compuesto de la presente invención y una droga de combinación en este orden, o administración en un orden inverso) a través de vías diferentes para administración, etc.

La preparación combinada de la presente invención es de baja toxicidad y así puede ser administrada de manera segura oralmente o parenteralmente (por ejemplo, tópicamente, rectalmente, intravascularmente, etc.) tanto directamente como están o en forma de preparaciones farmacéuticas como tabletas (incluso grageas y tabletas recubiertas de película), formas de dosis polvorientas, gránulos, cápsulas (incluyendo cápsulas blandas), las formas de dosis líquidas, inyecciones, supositorios, las formas de dosis de liberación prolongada, etc., la cual se obtiene mezclando el compuesto de la presente invención o (y) una droga de combinación descripta precedentemente con vehhículos farmacológicamente aceptables. Pueden ser administradas las formas de dosis inyectables intravenosamente, intramuscularmente o subcutáneamente, en el órgano, o directamente en el foco.

Los vehículos farmacológicamente aceptables que

pueden ser usados para fabricar la preparación combinada de la presente invención incluyen diversas sustancias de vehículox orgánicas o inorgánicas utilizadas convencionalmente como materiales para preparaciones farmacéuticas. Por ejemplo, estas substancias incluyen un vehículo, un lubricante, un aglutinante y un agente de desitegración en una forma de dosis sólida, y un solvente, un auxiliar de disolución, agente de suspensión, un agente de isotonización, un amortiguador, un agente de anestesiado, etc. en una forma de dosis líquida. Adicionalmente, pueden ser usados apropiadamente aditivos convencionales tales como un conservante, un antioxidante, un colorante, un edulcorante, un adsorbente, un agente humectante, etc. en cantidades convenientes, si es necesario.

Por ejemplo, los ejemplos de excipientes incluyen lactosa, sacarosa, D-manitol, almidón, almidón de maíz, ácido silícico anhidro ligero, celulosa cristalino, etc.

Por ejemplo, los ejemplos de lubricantes útiles incluyen estearato de magnesio, estearato de calcio, talco, sílice coloidal, etc.

Por ejemplo, los ejemplos de aglutinantes incluyen celulosa cristalina, sacarosa, D-manitol, dextrina, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona, almidón, sacarosa, gelatina, metilcelulosa, carboximetilcelulosa de sodio, etc.

Por ejemplo, los ejemplos de agentes de

desintegración incluyen almidón, carboximetilcelulosa, carboximetilcelulosa de calcio, carboximetil almidón de sodio, L-hidroxipropilcelulosa, etc.

Por ejemplo, los ejemplos de solventes incluyen agua para inyección, alcohol, propilenglicol, Macrogol, aceite de sésamo, aceite de maíz, aceite de oliva, etc.

Por ejemplo, los ejemplos de auxiliares de disolución incluyen polietilén glicol, propilenglicol, D-manitol, benzoato de bencilo, etanol, trisaminometano, colesterol, trietanolamina, carbonato de sodio, citrato de sodio, etc.

Por ejemplo, los ejemplos de agentes de suspensión incluyen agentes tensioactivos tales como estеariltrietanolamina, laurilsulfato de sodio, lauril aminopropionato, lecitina, cloruro de benzalconio, cloruro de benzetonio, monoestearato de glicerina, etc.; polímeros hidrófilos tales como polivinil alcohol, polivinil pirrolidona, carboximetilcelulosa de sodio, metilcelulosa, hidroximetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, etc.

Por ejemplo, los ejemplos de agentes de isotonización incluyen glucosa, D-sorbitol, cloruro de sodio, glicerina, D-manitol, etc.,

Por ejemplo, los ejemplos de amortiguadores incluyen las soluciones amortiguadoras de fosfato, acetato, carbonato, citrato, etc.

Por ejemplo, los ejemplos de agentes de anestesiado

incluyen bencil alcohol, etc.

Por ejemplo, los ejemplos de conservantes incluyen p-hidroxibenzoatos, clorobutanol, bencil alcohol, fenetil alcohol, ácido sórbico, ácido deshidroacético, etc.

Por ejemplo, los ejemplos de antioxidantes incluyen un sulfito, ácido ascórbico, α-tocoferol, etc.

En la preparación combinada de la presente invención, una proporción del compuesto de la presente invención respecto a una droga de combinación puede ser elegida dependiendo apropiadamente del sujeto a ser administrado, vía de administración, enfermedad, combinación, etc.

Por ejemplo, la cantidad del compuesto de la presente invención contenida en la preparación combinada de la presente invención varía, dependiendo de la forma de dosis de preparación, pero normalmente es desde aproximadamente 0,01 hasta 100% en peso, preferentemente desde aproximadamente 0,1 hasta 50% en peso, y más preferentemente desde aproximadamente 0,5 hasta 20% en peso, basado en el peso total de la preparación.

La cantidad de droga de combinación contenida en la preparación combinada de la presente invención varía, dependiendo de la forma de dosis de preparación, pero normalmente es desde aproximadamente 0,01 hasta 100% en peso, preferentemente desde aproximadamente 0,1 hasta 50% en peso, y más preferentemente desde aproximadamente 0,5 hasta 20% en peso, basado en el peso total de la

preparación.

La cantidad de aditivos tales como un vehículo, etc. contenidos en la preparación combinada de la presente invención varían, dependiendo de la forma de dosis de preparación, y normalmente es desde aproximadamente 1 hasta 99,99% en peso, preferentemente desde aproximadamente 10 hasta 90% en peso, basado en el peso total de la preparación.

Estas cantidades pueden ser las mismas, aún cuando el compuesto de la presente invención y una droga de combinación, respectivamente sean preparadas separadamente.

Estas preparaciones generalmente pueden ser fabricadas mediante los métodos conocidos públicamente por sí mismos convencionalmente usados en general.

Por ejemplo, una forma de dosis inyectable puede ser preparada disolviendo, suspendiendo o emulsionando el compuesto de la presente invención o una droga de combinación en un agente de dispersión (por ejemplo, "Tween 80" (fabricó por "Atlas Powder Company", EE.UU.), HCO 60 (fabricado por la "Nikko Chemicals Co., Ltd."), polietilen glicol, carboximetil celulosa, alginato de sodio, etc.), un estabilizador (por ejemplo, ácido ascórbico, pirosulfito de sodio), un agente tensioactivo (por ejemplo, polisorbato 80, macrogol, etc.), un agente de solubilización (por ejemplo, glicerina, etanol, etc.), agente de amortiguamiento (por ejemplo, ácido fosfórico o

su sal de metal alcalino, ácido cítrico o su sal de metal alcalino, etc.), agente de isotonización (por ejemplo, cloruro de sodio, cloruro de potasio, manitol, sorbitol, glucosa, etc.), un agente para ajusatr el pH (por ejemplo, ácido clorhídrico, hidróxido de sodio, etc.), un conservante (por ejemplo, p-oxybenzoato de etilo, ácido benzoico, metilparabeno, propilparabeno, bencil alcohol, etc.), un solubilizador (por ejemplo, glicerina concentrada, metilglucamina, etc.), un auxiliar de disolución (por ejemplo, propilenglicol, sacarosa, etc.), un agente de anestesiado (por ejemplo, glucosa, bencil alcohol, etc.), un aceite vegetal tal como aceite de oliva, aceite de sésamo, aceite de semilla de algodón, aceite de maíz, etc., un auxiliar de disolución tal como propilenglicol o lo similar para preparar en una inyección aceitosa.

Una forma de dosis oral puede ser producida de una manera convencional agregando al compuesto de la presente invención o una droga de combinación, por ejemplo, un vehículo (por ejemplo, lactosa, sacarosa, almidón, etc.), un agente de desitegración (por ejemplo, almidón, carbonato de calcio, etc.), un aglutinante (por ejemplo, almidón, goma árabe, carboximetil celulosa, polivinilpirrolidona, hidroxipropil celulosa, etc.), un lubricante (por ejemplo, talco, estearato de magnesio, polietilen glicol 6000, etc.) y otros aditivos, comprimiendo la mezcla resultante y, si es necesario,

recubrir el producto comprimido con el propósito del enmascaramiento del sabor, degradación entérica o liberación prolongada por las técnicas públicamente conocidas por sí mismas. Los agentes de recubrimiento para este propósito incluyen, por ejemplo, hidroxipropilmetil celulosa, etil celulosa, hidroximetil celulosa, hidroxipropil celulosa, polioxietilen glicol, Tween 80, Prulonic F68, ftalato de acetato de celulosa, ftalato de hidroxipropilmetil celulosa, succinato de acetato de hidroximetil celulosa, Eudragit (copolímero de ácido metacrílico/acrílico fabricado por "Rohm Company", Alemania) y tintes (por ejemplo, óxido de hierro, dióxido de titanio). La forma de dosis oral puede ser una forma de dosis de liberación rápida o una forma de dosis de la liberación prolongada.

Por ejemplo, en un supositorio, el compuesto de la presente invención o una droga de combinación es preparado en un sólido aceitoso o acuoso, composición semisólida o líquida por las técnicas públicamente conocidas por sí mismas. Las bases aceitosas usadas para la composición descripta precedentemente incluyen glicéridos de ácidos grasos superiores [por ejemplo, manteca de cacao, "uitepsols" (fabricado por "Dynamite Nobel Company", Alemania), etc.], ácidos grasos moderados [por ejemplo, miglioles (fabricados por "Dynamite Nobel Company", Alemania), etc.], aceites vegetales (por ejemplo, aceite de sésamo, aceite de soja, aceite de

semilla de algodón, etc.), y lo similar. Por ejemplo, las bases acuosas incluyen polietilen glicol y propilenglicol. Por ejemplo, las bases para geles acuosos incluyen gomas naturales, derivados celulosos, polímeros de vinilo, polímeros acrílicos, etc.

Los ejemplos de la forma de dosis de liberación prolongada precedente incluyen microcápsulas de liberación prolongada, y lo similar.

Las microcápsulas de la liberación prolongada pueden ser obtenidas por por métodos públicamente conocidos por sí mismos, y son preparadas y administradas preferentemente en forma de, por ejemplo, una forma de dosis de liberación prolongada por el método [2] ilustrado más adelante.

Preferentemente, el compuesto de la presente invención es preparado en una forma de dosis para administración oral como una forma de dosis sólida (por ejemplo, forma de dosis en polvo, gránulos, tabletas, cápsulas) o en una forma de dosis para administración rectal como un supositorio, etc. Una forma de dosis para administración oral es particularmente preferida.

Una droga de combinación puede ser preparada en forma de dosis descrpita precedentemente, dependiendo del tipo de droga.

Más adelante en la presente, [1] una preparación inyectable del compuesto de la presente invención o una droga de combinación y su producción, [2] una liberación

prolongada o la preparación de liberación inmediata del compuesto de la presente invención o una droga de combinación y su producción y [3] una preparación sublingual, bucal o de desintegración oral rápida del compuesto de la presente invención o una droga de combinación y su producción será descripta específicamente.

[1] Preparación inyectable y su producción

Una preparación inyectable obtenida disolviendo el compuesto de la presente invención o una droga de combinación en agua es preferible. La preparación inyectable puede contener un benzoato y/o un salicilato.

La preparación inyectable es obtenida disolviendo el compuesto de la presente invención o una droga de combinación y opcionalmente un benzoato y/o un salicilato en agua.

Los ejemplos del benzoato y/o salicilato descriptos precedentemente incluyen una sal de metal alcalino tal como sal de sodio y potasio, etc., una sal del metal alcalino-térreo tal como sal de calcio y magnesio, etc., una sal de amonio, una sal de metilglucamina, una sal de un ácido orgánico tal como trometamol, y lo similar.

La concentración del compuesto de la presente invención o una droga de combinación en la preparación inyectable es desde aproximadamente 0,5 hasta 50% p/v, preferentemente aproximadamente 3 a 20 % p/v. La concentración del benzoato y/o salicilato es 0,5 a 50%

p/v, preferentemente 3 a 20% p/v.

Además, los aditivos utilizados generalmente en una preparación inyectable tal como un estabilizador (ácido ascórbico, pirosulfito de sodio, etc.), un agente tensioactivo (polisorbato 80, macrogol, etc.), agente de solubilización (glicerina, etanol, etc.), agente de amortiguamiento (ácido fosfórico y su sal de metal alcalino, ácido cítrico y su sal de metal alcalino, etc.), agente de isotonización (cloruro de sodio, cloruro de potasio, etc.), un agente de dispersión (hidroxipropilmetil celulosa, dextrina), un agente para ajusatr el pH (ácido clorhídrico, hidróxido de sodio, etc.), un conservante (p-oxibenzoato de etilo, ácido benzoico, etc.), un solubilizador (glicerina concentrada, metilglucamina, etc.), un auxiliar de disolución (propilenglicol, sacarosa, etc.), agente de anestesiado (glucosa, bencil alcohol, etc.) es agregado apropiadamente a la preparación. Cualquiera de estos aditivos generalmente es agregado en una cantidad utilizada en una preparación inyectable.

La preparación inyectable se ajusta al pH 2 a 12, preferentemente 2,5 a 8,0 agregando un agente para ajusatr el pH.

La preparación inyectable es obtenida disolviendo el compuesto de la presente invención o una droga de combinación y opcionalmente un benzoato y/o salicilato, y, si es necesario, los aditivos anteriores en agua.

Estos componentes pueden ser disueltos en cualquier orden según la misma modalidad de una preparación inyectable convencional.

Una solución acuosa para inyección preferentemente es calentada, y utilizada como una preparación inyectable después de esterilización por filtración mediante filtración o autoclave como en una preparación inyectable convencional para proveer una preparación inyectable.

Una preparación inyectable acuosa es preferentemente esterilizada, por ejemplo, desde 100 a 121°C durante 5 a 30 minutos.

Además, la preparación puede estar en una forma de solución a cual la actividad antibacteriana es impartida para ser utilizable como una forma de dosis múltiple en una dosificación dividida.

[2] Preparación de liberación prolongada o liberación inmediata y su producción

Una preparación de liberación prolongada preferida comprende un centro que comprende el compuesto de la presente invención o una droga de combinación que son opcionalmente recubiertos con un material insoluble en agua o un polímero del hinchazón. Por ejemplo, es preferible una preparación de liberación prolongada para administración oral de una forma de dosis una vez diaria.

Los ejemplos del material insoluble en agua usados para el agente de recubrimiento incluyen los éteres de celulosa tal como etil celulosa, butil celulosa, etc.,

los ésteres celulosos tales como acetato de celulosa, propionato de celulosa, etc., polivinil ésteres tales como el acetato de polivinilo, butirato de polivinilo, etc., los polímeros de ácido acrílico tales como un copolímero de ácido acrílico/ ácido metacrílico, un copolímero de metacrilato de metilo, un copolímero de etoxietil metacrilato/cinnamoetil metacrilato/aminoalquil metacrilato, un ácido poliacrílico, un ácido polimetacrílico, un copolímero de alquilamida de ácido metacrílico, un poli(metil metacrilato), un polimetacrilato, un copolímero de aminoalquil metacrilato, un poli(anhídrido metacrílico), un copolímero de glicidil metacrilato, en particular, una serie de Eudragit ("Rohm & Pharma") tal como Eudragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO (copolímero etil acrylato/metil metacrilato/clorotrimetil metacrilato/etil amonio) y Eudragit NE-30D (copolímero metil metacrilato/etil acrilato), etc., aceites hidrogenados tales como aceite de castor hidrogenado (por ejemplo, LUBRI WAX ("Freund Industrial Co., Ltd."), etc.), ceras tales como cera de Carnauba, un éster de glicerina de ácido graso, parafina, etc., ésteres de poliglicerin ácido graso, etc.

El polímero de agrandamiento es preferentemente un polímero que tiene un grupo ácido eliminable y exhibe un pH dependiente del agrandamiento, y un polímero que tiene un grupo ácido eliminable, el cual sufre un agrandamiento

menor a un pH ácido tal como en el estómago pero es hinchado extensivamente a un pH neutro tal como en el intestino delgado y grueso, es preferible.

Los ejemplos de tal polímero que poseen un grupo ácido eliminable y exhiben el pH dependiente al agrandamiento incluyen un polímero reticulado de ácido poliacrílico tal como Carbomers 934P, 940, 941, 974P, 980, 1342, etc., policarbophil y calcium policarbophil (todos fabricados por "BF Goodrich Chemicals"), Hivis Wakos 103, 104, 105 y 304 (todos fabricados por "Wako Pure Chemical Industries, Ltd."), etc.

El agente de recubrimiento utilizado en la preparación de la liberación prolongada puede contener además un material hidrófilo.

Los ejemplos del material hidrófilo incluyen un polisacárido que puede tener un grupo sulfato, tal como pullulan, dextrina, alginatos de metal alcalino, etc., un polisacárido que tiene un grupo hidroxialquilo o un grupo carboxialquilo como hidroxipropil celulosa, hidroxipropilmetil celulosa, carboximetilcelulosa de sodio, etc., metilo celulosa, polivinil pirrolidona, alcohol polivinil, polietilen glicol, etc.

La cantidad del material insoluble en agua contenido en el agente de recubrimiento de la preparación de liberación prolongada es desde aproximadamente 30 hasta aproximadamente 90% (p/p), preferentemente desde aproximadamente 35 hasta aproximadamente 80% (p/p), más

preferentemente aproximadamente 40 hasta aproximadamente 75% (p/p), y el volumen de polímero de agrandamiento es aproximadamente desde 3 hasta aproximadamente 30% (p/p), preferentemente desde aproximadamente 3 hasta aproximadamente 15% (p/p). El agente de recubrimiento además puede contener un material hidrófilo, y la cantidad del material hidrófilo contenido en el agente de recubrimiento es desde aproximadamente 50% (p/p) o inferior, preferentemente desde aproximadamente 5 hasta aproximadamente 40% (p/p), más preferentemente desde aproximadamente 5 hasta aproximadamente 35% (p/p). De la manera utilizada en la presente, el % (p/p) precedente es usado para significar un % en peso basado en la composición de agente de recubrimieto, el cual es el resto de la solución de agente de recubrimieto después de eliminar cualquier solvente (por ejemplo, agua, un alcohol inferior tal como metanol, etanol, etc.).

La preparación de la liberación prolongada es realizada preparando un centro que contiene una droga tal como la ilustrada precedentemente, seguido por el recubrimiento del centro resultante con una solución de agente de recubrimiento obtenido fundiendo con calor un material insoluble en agua o un polímero de agrandamiento o disolviendo o dispersando tal material en un solvente.

1. Preparación de centro que contiene droga.

La forma de un centro que contiene una droga a ser recubierta con un agente de recubrimiento (más adelante a

veces denominado simplemente un centro) no está limitada específicamente pero es preparado preferentemente en una forma de partícula tal como gránulos, gránulos finos, o lo similar.

Cuando el centro es de gránulos o gránulos finos, los mismos tienen preferentemente una dimensión de partícula media desde aproximadamente 150 hasta aproximadamente 2.000 µm, más preferentemente desde aproximadamente 500 hasta aproximadamente 1.400 µm.

El centro puede ser preparado de una manera convencional. Por ejemplo, una droga es mezclada con un vehículo conveniente, aglutinante, agente de desintegración, lubricante, estabilizador, etc., y entonces es semetida a humectación de la granulación de extrusión, granulación en lecho fluído, o lo similar.

El contenido de droga en el centro es desde aproximadamente 0,5 hasta aproximadamente 95% (p/p), preferentemente desde aproximadamente 5,0 hasta aproximadamente 80% (p/p), más preferentemente desde aproximadamente 30 hasta aproximadamente 70% (p/p).

Los ejemplos del vehículo contenido en el centro incluyen un sacárido tal como sacarosa, lactosa, manitol, glucosa, etc., almidón, celulosa cristalina, fosfato de calcio, almidón de maíz, etc. Entre los mismos, se prefieren celulosa cristalina y almidón de maíz.

Los ejemplos del aglutinante usado incluyen polivinil alcohol, hidroxipropil celulosa, polietilen

glicol, polivinil pirrolidona, Pluronic F68, goma árabe, gelatina, almidón, etc. los ejemplos del agente de desitegración incluyen carboximetil celulosa de calcio (ECG505), croscaramelosa de sodio (Ac-Di-sol), polivinil pirrolidona reticulada (crospovidona), hidroxipropil celulosa sustituida inferior (L-HPC), etc. Entre los mismos, se prefieren hidroxipropil celulosa, polivinil pirrolidona y una hidroxipropil celulosa sustituida inferior. Los ejemplos del lubricante y el anticoagulante incluyen talco, estearato de magnesio y sus sales inorgánicas, y los ejemplos del lubricante incluyen polietilen glicol, etc. Los ejemplos del estabilizador incluyen un ácido tal como el ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, ácido maléico, etc.,

Además de la técnica descrpita precedentemente, el centro puede ser preparado usando otras técnicas tales como una técnica de granulación con movimiento de rotación, una técnica de grageificación en un cilindro, una técnica de revestimiento en lecho fluido y una técnica de granulación de fusión, en donde una droga o una mezcla de la droga con un vehículo, un lubricante, etc. es agregado por partes a las partículas del vehículo inerte como semillas para el centro con el rociado de un aglutinante disuelto en un solvente conveniente tal como agua, un alcohol inferior (por ejemplo, metanol, etanol, etc.) o lo similar. Los ejemplos de las partículas de

vehículo inertes incluyen las preparadas de sacarosa, lactosa, almidón, celulosa cristalina y ceras, y, preferentemente, estos vehículos tienen una dimensión de partícula media desde aproximadamente 100 µm hasta aproximadamente 1.500 µm.

Para separar la droga contenida en el centro de un agente de recubrimiento, la superficie del centro puede ser recubierta con un material protector. Los ejemplos del material protector incluyen el material hidrófilo descrito precedentemente y el material insoluble en agua. El material protector preferido es polietilén glicol o un polisacárido que tenga un grupo hidroxialquilo o un grupo carboxialquilo, más preferentemente, hidroxipropilmetil celulosa e hidroxipropil celulosa. El material protector puede contener, como estabilizador, un ácido tal como el ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, ácido maléico, etc., y un lubricante tal como talco. Cuando el material protector es utilizado, la cantidad del mismo a ser recubierto es desde aproximadamente 1 hasta aproximadamente 15% (p/p), preferentemente desde aproximadamente 1 hasta aproximadamente 10% (p/p), más preferentemente desde aproximadamente 2 hasta aproximadamente 8% (p/p) basado en el centro.

El material protector puede ser recubierto por un método de recubrimiento convencional y específicamente, el centro es recubierto por rociado con material

protector por una técnica de revestimiento en lecho fluido, una técnica de grageificación en un cilindro, etc.

II. Recubrimiento de centro con agente de recubrimiento.

El centro obtenido en el punto 1 precedentemente es recubierto con una solución de agente de recubrimiento preparada calentando hasta la fusión del material insoluble en agua y el polímero de agrandamiento dependiente del pH descripto precedentemente y un material hidrófilo o disolviendo o dispersándolo en un solvente para obtener una preparación de la liberación prolongada.

Como un método de recubrimiento del centro con la solución de agente recubrimiento, se ejemplifica, por ejemplo, recubrimiento por rociado, etc.

La proporción de la composición del material insoluble en agua, polímero de agrandamiento y material hidrófilo en la solución de agente de recubrimiento puede ser elegida apropiadamente para estar dentro de las cantidades de los componentes respectivos contendios en el recubrimiento.

La cantidad del agente de recubrimiento es desde aproximadamente 1 hasta aproximadamente 90% (p/p), preferentemente desde aproximadamente 5 hasta aproximadamente 50% (p/p), más preferentemente desde aproximadamente 5 hasta aproximadamente 35% (p/p) basado en el centro (excluyendo la capa de material protector).

Como el solvente para la solución de agente de recubrimiento, pueden ser utilizados exclusivamente o como una mezcla de los mismos agua y un solvente orgánico. Cuando es utilizada una mezcla, la proporción de agua y solvente orgánico (solvente de agua/orgánico: una proporción en peso) puede variar dentro del rango de 1 a 100%, y es preferentemente desde 1 hasta aproximadamente 30%. El solvente orgánico no está limitado particularmente en tanto el mismo no pueda disolver el material insoluble en agua, y los ejemplos del solvente incluyen un alcohol inferior tal como alcohol metílico, alcohol etílico, alcohol isopropílico, n-butil alcohol, etc., una alcanona inferior tal como acetona, acetonitrilo, cloroformo, cloruro de metileno, etc. Entre los mismos, es preferible un alcohol inferior, siendo más preferible alcohol etílico e isopropil alcohol. Son utiliadas preferentemente agua y una mezcla de agua y un solvente orgánico como solventes para la solución de agente de recubrimiento. En este caso, un ácido tal como ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, ácido maléico, etc. puede ser agregado a la solución de agente de recubrimiento, si es necesario, con el propósito de estabilizar la solución de agente de recubrimiento.

Para realizar el recubrimiento por capa de rocío, la capa puede ser realizada utilizando un método de recubrimiento convencional. Específicamente, el centro es

rociado con una solución de agente de recubrimiento por medio de una técnica de recubrimiento en lecho fluido, una técnica de grageificación en un cilindro, o lo similar. En la actualidad, también puede agregarse un lubricante tal como talco, óxido de titanio, estearato de magnesio, estearato de calcio, anhídrido silícico ligero, etc., y un plastificador tal como éster graso de glicerina, aceite de castor endurecido, citrato de trietilo, alcohol cetílico, alcohol esteárico, etc.

Después de recubrir con un agente de recubrimiento, también puede ser mezclado un antiestático tal como talco, si es necesario.

La preparación de liberación inmediata puede ser un líquido (solución, suspensión, emulsión, etc.) o un sólido (partículas, píldoras, tabletas, etc.). Puede ser utilizada una preparación oral y una preparación parental como preparación inyectable, y es preferible una preparación oral.

La preparación de liberación inmediata normalmente puede contener un vehículo, aditivos y un excipiente (más adelante a veces denominado como excipientes) los cuales son utilizados convencionalmente en el campo farmacéutico, además de una droga la cual es un ingrediente activo. Los excipientes farmacéuticos no están limitados específicamente en tanto los mismos sean excipientes usados convencionalmente en el campo farmacéutico. Los ejemplos del vehículo para una

preparación sólida oral incluyen lactosa, almidón, almidón de maíz, celulosa cristalina (Avicel PH101, fabricado por la "Asahi Kasei Corporation", etc.), azúcar pulverizado, azúcar cristalizado, manitol, anhídrido silícico ligero, carbonato de magnesio, carbonato de calcio, L-cisteína, etc., siendo prefreibles almidón de maíz y manitol. Cualquiera de estos excipientes puede ser utilizado exclusivamente o en combinación entre sí. Las cantidades del excipientes son, por ejemplo, desde aproximadamente 4,5 hasta aproximadamente 99,4% p/p, preferentemente desde aproximadamente 20 hasta aproximadamente 98,5% p/p, más preferentemente desde aproximadamente 30 hasta aproximadamente 97% p/p, basado en el peso total de la preparación de liberación inmediata.

El volumen de droga en la preparación de liberación inmediata puede ser seleccionado desde apropiadamente 0,5% hasta aproximadamente 95%, preferentemente desde aproximadamente 1% hasta aproximadamente 60% respecto a la cantidad total de la preparación de liberación inmediata.

Cuando la preparación de liberación inmediata es una preparación sólida oral, la preparación contiene un agente de desitegración además de los componentes descriptos anteriormente. Los ejemplos del agente de desitegración incluyen carboximetilcelulosa de calcio (ECG505 fabricado por "GOTOKU CHEMICAL Co., Ltd."),

croscaramelosa de sodio (por ejemplo, Ac-Di-sol fabricado por "Asahi Kasei Corporation"), crospovidona (por ejemplo, COLIDON CL fabricado por BASF), hidroxipropil celulosa sustituida inferior ("Shin-Etsu chemical Co., Ltd."), carboximetil almidón ("MATSUTANI CHEMICAL INDUSTRY Co., Ltd."), carboximetil almidón sodio (EXORITAB fabricado por "KIMURA SANGYO"), almidón α parcial (PCS fabricado por "Asahi Kasei Corporation"), etc. por ejemplo, puede ser utilizado un agente de desitegración que desintegra los gránulos por absorción de agua o agrandamiento en contacto con agua, o formando un canal entre el componente activo que comprende el centro y un vehículo. Cualquiera de estos agentes de desintegración puede ser utilizado de manera exclusiva o en combinación entre sí. La cantidad del agente de desitegración utilizado puede ser elegida apropiadamente dependiendo del tipo y cantidad de droga usada o diseño de preparación particular para la actuación de la liberación buscada. Por ejemplo, la cantidad es desde aproximadamente 0,05 hasta aproximadamente 30% p/p, preferentemente desde aproximadamente 0,5 hasta aproximadamente 15% p/p basado en el peso total de la preparación de liberación inmediata.

Cuando la preparación de liberación inmediata es una preparación sólida oral, la preparación puede contener opcionalmente aditivos usados convencionalmente en una preparación sólida, además de los componentes descriptos

anteriormente. Los ejemplos de los aditivos incluyen los aglutinantes (por ejemplo, sacarosa, gelatina, polvo de goma árabe, metil celulosa, hidroxipropil celulosa, hidroxipropilmetil celulosa, carboximetilcelulosa, polivinil pirolidona, pullran, dextrina, etc.), lubricantes (polietilén glicol, estearato de magnesio, talco, anhídrido silícico ligero (por ejemplo, aerosil (NIPPON AEROSIL)), agentes tensioactivos (por ejemplo, agentes tensioactivos aniónicos tal como alquilsulfato de sodio, agentes tensioactivos no iónicos tal como éster graso de polioxietileno, éster graso de polioxietilén sorbitan, derivados de aceite de castor de polioxietileno, etc.), colorantes (por ejemplo, colorantes de alquitrán, caramelo, colcothar, óxido de titanio, riboflavinas), si es necesario, correctores de sabor (por ejemplo, edulcorante, saborizante, etc.), adsorbentes, conservantes, agentes humectantes, agentes antiestáticos, etc. Además, también puede agregarse un ácido orgánico tal como ácido tartárico, ácido cítrico, ácido sussínico, ácido fumárico o lo similar como un estabilizador.

Como el aglutinante precedente, es utilizado preferentemente hidroxipropil celulosa, polietilén glicol y polivinil pirolidona, etc.

La preparación de liberación inmediata puede ser preparada mezclando los componentes descriptos precedentemente y amasando la mezcla, si es necesario, y

amoldando entonces según una técnica convencional para hacer las preparaciones farmacéuticas. La mezcla precedente puede ser realizada de una manera convencional, por ejemplo, mezclando, amasando, etc. Específicamente, cuando la preparación de liberación inmediata está en forma de partículas, la preparación puede ser preparada mezclando los componentes con un granulador vertical, un amasador para uso múltiple ("HATA IRON WORKS CO., LTD."), un granulador de lecho fluído FD-5S (POWREX CORPORATION) o lo similar, y granulando el resultado por granulación de extrusión húmeda o granulación de lecho fluído por una técnica similar a ésta para preparar el centro de preparación de liberación prolongada descripto anteriormente.

La preparación de liberación inmediata y la preparación de liberación prolongada así obtenidas se pueden componer, tal como están, o, junto con excipientes farmacéuticos apropiado, se pueden componer separadamente en preparaciones farmacéuticas de una manera convencional para preparar las preparaciones respectivas para administrar entre sí en combinación o simultáneamente o a ciertos intervalos de tiempo. Alternativamente, se pueden componer ambas preparaciones en una sola forma de dosis para administración oral (por ejemplo, gránulos, gránulos finos, tabletas, cápsulas) tal como están, o, junto con excipientes farmacéuticos apropiados. También pueden llenarse ambas preparaciones en forma de gránulos o

gránulos finos en una sola cápsula para administración oral.

[3] Preparación sublingual, bucal o de desintegración oral rápida y su producción,

Una preparación sublingual, oral o de desintegración bucal rápida puede estar en forma de una preparación sólida tal como una tableta, o puede estar en forma de un parche de mucosa oral (película).

La preparación sublingual, bucal o de desintegración oral rápida es preferentemente una preparación que contiene el compuesto de la presente invención o una droga de combinación y un vehículo. La preparación también puede contener agentes auxiliares tales como un lubricante, agente de isotonización, un vehículo hidrófilo, un polímero dispersable en agua, un estabilizador, etc. Además con el propósito de promover la absorción y aumentar la biodisponibilidad, la preparación también puede contener β-ciclodextrina o derivados de β-ciclodextrina (por ejemplo, hidroxipropil-β-ciclodextrina, etc.).

Los ejemplos del vehículo anterior incluyen lactosa, sacarosa, D-manitol, almidón, celulosa cristalina, anhídrido silícico ligero, etc. Los ejemplos del lubricante incluyen estearato de magnesio, estearato de calcio, talco, sílice coloidal, etc., siendo preferibles el estearato de magnesio y sílice coloidal. Los ejemplos del agente de isotonización incluyen cloruro de sodio,

glucosa, fructosa, manitol, sorbitol, lactosa, sacarosa, glicerina y urea, siendo preferible particularmente manitol. Como el vehículo hidrófilo, hay, por ejemplo, un vehículo hidrófilo de agrandamiento tal como celulosa cristalina, etil celulosa, polivinil pirolidona reticulada, anhídrido silícico ligero, ácido silícico, fosfato de dicalcio, carbonato de calcio, etc., prefiriéndose celulosa cristalina (por ejemplo, celulosa microcristalina, etc.). Como el polímero dispersable en agua, hay, por ejemplo, una goma (por ejemplo, goma tragacanto, goma arábiga, goma guar), alginato (por ejemplo, alginato de sodio), derivados de celulosa (por ejemplo, metil celulosa, carboximetilcelulosa, hidroximetil celulosa, hidroxipropil celulosa, hidroxipropilmetil celulosa), gelatina, almidón soluble en agua, ácido poliacrílico (por ejemplo, carbomer), ácido polimetacrílico, polivinil alcohol, polietilén glicol, polivinil pirolidona, policarbofilo, sal palmitato de ascorbato, etc., siendo preferidos hidroxipropilmetil celulosa, ácido poliacrílico, alginato, gelatina, carboximetilcelulosa, polivinil pirolidona y polietilén glicol. Se prefiere particularmente hidroxipropilmetil celulosa. Como el estabilizador, hay, por ejemplo, cisteína, tiosorbitol, ácido tartatico, ácido cítrico, carbonato de sodio, ácido ascórbico, glicina, sulfito de sodio, etc., siendo preferidos particularmente el ácido cítrico y ácido

ascórbico.

La preparación sublingual, bucal o de desintegración oral rápida puede ser preparada mezclando el compuesto de la presente invención o una droga de combinación y un vehículo por un método conocido por sí mismo. Además, si se desea, los agentes auxiliares descriptos precedentemente, tales como el lubricante, agente de isotonización, vehiculo hidrófilo, polímero dispersable en agua, estabilizador, colorante, edulcorante, conservante, etc. también pueden mezclarse. Después de mezclar los componentes descriptos precedentemente simultáneamente o en ciertos intervalos de tiempo, la mezcla es comprimida en tabletas para obtener una tableta sublingual, bucal, o de desintegración rápida oral. Con la finalidad de obtener una dureza conveniente, puede ser utililzado un solvente tal como agua, un alcohol, etc. para hidratar o humectar los componentes antes o después de la formación de tableta, seguido por secado.

Para preparar el compuesto para parche de mucosa oral (película), de la presente invención o una droga de combinación y el polímero dispersable en agua (preferentemente, hidroxipropil celulosa, hidroxipropilmetil celulosa), excipiente, etc. descripto precedentemente se disuelve en un solvente tal como agua, etc. y entonces la solución resultante es moldeada en una película. Adicionalmente, pueden ser agregados a la preparación aditivos tales como un plastificador, un

estabilizador, un antioxidante, un conservante, un colorante, agente de amortiguamiento, un edulcorante, etc. Un glicol tal como polietilén glicol, propilenglicol, etc. pueden agregarse para impartir una elasticidad apropiada a una película, y un polímero bioadhesivo (por ejemplo, policarbófilo, carbopol) también puede ser agregado para mejorar la adherencia de la película al recubrimiento de mucosa oral. El moldeo puede ser realizado vertiendo una solución sobre una superficie no adhesiva, extendiendo la solución usando una recubridora como una hoja de doctor en un espesor uniforme (preferentemente, aproximadamente 10 a 1000 micrones), y luego secar la solución para formar una película. La película así formada es secada en la temperatura ambiente o calentando, y entonces es cortada en pedazos teniendo cada uno una área de superficie deseada.

Una preparación de desintegración oral rápida preferida es, por ejemplo, una preparación de difusión rápida en una forma de red sólida que comprende el compuesto de la presente invención o una droga de combinación y un vehículo inerte soluble en agua o difundible en agua junto al compuesto de la presente invención o la droga de combinación. La red es formada sublimando un solvente desde una composición sólida que comprende una solución del compuesto de la presente invención o una droga de combinación en un solvente

conveniente.

Además del compuesto de la presente invención o una droga de combinación, la composición de la preparación de desintegración rápida oral puede contener preferentemente un agente de formación de matriz y un componente secundario.

Los ejemplos del agente de formación de matriz incluyen gelatinas, dextrinas y proteínas animal o vegetales de la soja, trigo, semilla de llantén, etc.; los materiales gomosos tales como goma árabe, goma guar, gelosa, goma xantano, etc.; los polisacáridos; alginatos; carboximetilcelulosa; carragenina; dextranos; pectinas; polímeros sintéticos tales como polivinil pirrolidonas; materiales derivados de los complejos gelatina goma árabe, etc. El agente de formación de matriz incluye además sacáridos tales como manitol, glucosa, lactosa, galactosa, trehalosa, etc.; sacáridos cíclicos tal como ciclodextrinas, etc.; sales inorgánicas tales como fosfato de sodio, cloruro de sodio, silicato de aluminio, etc.; aminoácidos que tienen 2 a 12 átomos de carbono tales como glicina, L-alanina, ácido L-glutámico, ácido L-aspártico, L-hidroxiprolina, L-isoleucina, L-leucina, L-fenilalanina, etc.

Uno o más agentes de formación de matriz pueden ser incorporados en una solución o suspensión antes de la solidificación. Los agentes de formación de matriz pueden estar presentes además de un agente tensioactivo, o

pueden estar presentes en ausencia de un agente tensioactivo. Los agentes de formación de matriz no sólo sirven para formar una matriz, sino también ayudan a mantener la difusión del compuesto de la presente invención o una droga de combinación en una solución o suspensión.

La composición puede contener un componente secundario tal como un conservante, un antioxidante, un agente tensioactivo, agente de espesado, un colorante, agente para ajusatr el pH, un sabor, un edulcorante, un agente de para enmascarar el sabor, etc. Como el colorante conveniente, se indica, por ejemplo, rojo óxido de hierro, negro y amarillo, tintes FD & C disponible de ERIS & EVERALD tal como el FD & C Azul No. 2 y FD & C Rojo No. 40, etc. los ejemplos de saborizante conveniente incluyen menta, frambuesa, menta, naranja, limón, pasa de uva, caramelo, vainilla, cereza, sabor a uva y una combinación de los mismos. Los ejemplos del agente conveniente para ajustar pH incluyen ácido cítrico, ácido tartárico, ácido fosfórico, ácido clorhídrico y ácido maléico. Los ejemplos del edulcorante conveniente incluyen aspartamo, acesulfame K y taumatina. Los ejemplos del agente de enmascaramiento del sabor conveniente incluyen bicarbonato de sodio, resinas de intercambio de iones, compuestos de inclusión de ciclodextrina, adsorbentes y apomorfina microencapsulada.

La preparación generalmente contiene el compuesto de

la presente invención o una droga de combinación en una cantidad desde aproximadamente 0,1 hasta aproximadamente 50% en peso, preferentemente desde aproximadamente 0,1 hasta aproximadamente 30% en peso y, preferentemente, la preparación (tableta sublingual, bucal, etc. descripta precedentemente) permite que 90% o más del compuesto de la presente invención o una droga de combinación sea disuelta (en agua) dentro de un período de tiempo desde aproximadamente 1 hasta aproximadamente 60 minutos, preferentemente desde aproximadamente 1 minuto hasta aproximadamente 15 minutos, más preferentemente desde aproximadamente 2 minutos hasta aproximadamente 5 minutos, o es una preparación de desintegración rápida oral que se desintegra dentro desde aproximadamente 1 hasta aproximadamente 60 segundos, preferentemente desde aproximadamente 1 hasta aproximadamente 30 segundos, más preferentemente desde aproximadamente 1 hasta aproximadamente 10 segundos, después que es colocada en la cavidad oral.

La cantidad del vehículo anterior es desde aproximadamente 10 hasta aproximadamente 99% en peso, preferentemente desde aproximadamente 30 hasta aproximadamente 90% en peso basado en el peso total de la preparación. La cantidad de β-ciclodextrina o derivado de β-ciclodextrina es desde aproximadamente 0 hasta aproximadamente 30% en peso basado en el peso total de la preparación. La cantidad del lubricante es desde

aproximadamente 0,01 hasta aproximadamente 10% en peso, preferentemente desde aproximadamente 1 hasta aproximadamente 5% en peso basado en el peso total de la preparación. La cantidad del agente de isotonización es desde aproximadamente 0,1 hasta aproximadamente 90% en peso, preferentemente desde aproximadamente 10 hasta aproximadamente 70% en peso basado en el peso total de la preparación. La cantidad del vehículo hidrófilo es desde aproximadamente 0,1 hasta aproximadamente 50% en peso, preferentemente desde aproximadamente 10 hasta aproximadamente 30% en peso basado en el peso total de la preparación. La cantidad del polímero dispersable en agua es desde aproximadamente 0,1 hasta aproximadamente 30% en peso, preferentemente desde aproximadamente 10 hasta aproximadamente 25% en peso basado en el peso total de la preparación. La cantidad del estabilizador es desde aproximadamente 0,1 hasta aproximadamente 10% en peso, preferentemente desde aproximadamente 1 hasta aproximadamente 5% en peso basado en el peso total de la preparación. Si es necesario, la preparación descrpita precedentemente puede contener además aditivos tales como un colorante, un edulcorante, un conservante, etc.

La dosis de preparaciones combinadas de la presente invención varía, dependiendo del tipo de compuesto de la presente invención, edad, peso del cuerpo, condiciones, forma de dosis, via para administración, período de dosificación, etc.

Una dosis del compuesto de la presente invención puede variar, dependiendo del sujeto a ser administrado, órgano objetivo, condiciones, vía de administración, etc., y en administración oral, el compuesto es administrado generalmente al paciente con cáncer (como 60 kg de peso del cuerpo) en una dosis diaria desde aproximadamente 0,1 hasta aproximadamente 100 mg, preferentemente desde aproximadamente 1,0 hasta aproximadamente 50 mg y más preferentemente desde aproximadamente 1,0 hasta aproximadamente 20 mg. En administración parental, una sola dosis del compuesto puede variar, dependiendo del sujeto a ser administrado, órgano objetivo, condiciones, vía de administración, etc., y en la forma de dosis inyectable, es ventajoso administrar el compuesto al paciente con cáncer (como 60 kg peso del cuerpo) generalmente en una dosis diaria desde aproximadamente 0,01 hasta aproximadamente 30 mg, preferentemente desde aproximadamente 0,1 hasta aproximadamente 20 mg, y más preferentemente desde aproximadamente 0,1 hasta aproximadamente 10 mg. Para otras especies animales, la dosis correspondiente convertida para 60 kg de peso puede ser administrada. Por supuesto, la dosis puede variar, dependiendo de las condiciones individuales según lo descripto anteriormente; en tal caso, una dosis inferior de la dosis indicada precedentemente puede ser suficiente, o puede ser superior que el rango anterior.

Es posible determinar cualquier rango de una dosis para la droga de combinación, en tanto como la misma no cause ningún efecto colateral adverso. La dosis diaria de la droga de combinación puede variar, dependiendo de la severidad de la enfermedad, la edad del sujeto, sexo, peso del cuerpo y susceptibilidad, período de dosificación e intervalos, características, formulación, tipo y componentes activos de la preparación farmacéutica, etc. y no está particularmente limitada. Por ejemplo, en administración oral, la dosis es desde aproximadamente 0,001 a 2000 mg, preferentemente desde aproximadamente 0,01 a 500 mg, y más preferentemente desde aproximadamente 0,1 a 100 mg en lo que se refiere a una droga; normalmente, esta dosis es administrada dividiéndola en 1 a 4 veces por día.

Cuando son administradas las preparaciones farmacéuticas de la presente invención, el compuesto de la presente invención y una droga de combinación pueden ser administrados al mismo tiempo. Alternativamente, una droga de combinación es administrada primero y entonces el compuesto de la presente invención es administrado, o el compuesto de la presente invención es administrado primero y entonces una droga de combinación es administrada. Cuando los mismos son administrados a ciertos intervalos de tiempo, los intervalos varían, dependiendo del componente activo a ser administrado, la forma de dosis y vía de administración; cuando una droga

de combinación es administrada primero, el compuesto de la presente invención puede ser administrado dentro de 1 minuto a 3 días, preferentemente de 10 minutos a 1 día, más preferentemente de 15 minutos a 1 hora después de la administración de la droga de combinación. Cuando el compuesto de la presente invención es administrado primero, una droga de combinación puede ser administrada dentro de 1 minuto a 1 día, preferentemente de 10 minutos a 6 horas, más preferentemente de 15 minutos a 1 hora después de la administración del compuesto de la presente invención.

Como un método de administración preferido, por ejemplo, aproximadamente 0,001 a 200 mg/kg de una droga de combinación en forma de una preparación de dosificación oral es administrada oralmente y, después de aproximadamente 15 minutos, aproximadamente 0,005 a 0,5 mg/kg del compuesto de la presente invención en forma de una preparación parental es administrada parenteralmente como una dosis diaria.

Como la metastina, se utilizan, por ejemplo, las metastinas humanas descriptas en WO 00/24890, metastinas de ratón o rata descriptas en WO 01/75104, etc.,

Los ejemplos específicos de metastina humana incluyen un péptido que contiene secuencia de aminoácido 47-54 término N en la secuencia de aminoácido representada por SEQ ID NO: 1 y que consiste de 8 a 54 residuos de aminoácido, y lo similar.

El "péptido que contiene la secuencia de aminoácido 47-54 término N en la secuencia de aminoácido representada por SEQ ID NO: 1 y que consiste de 8 a 54 residuos de aminoácido" puede ser cualquier péptido, en tanto sea un péptido que contenga la secuencia de aminoácido 47-54 término N en la secuencia de aminoácido representado por SEQ ID NO: 1 y que consiste de 8 a 54 residuos de aminoácido, pero significa que estos péptidos tienen sustancialmente la misma actividad fisiológica (por ejemplo, un receptor de actividad de enlace, una acción de señal de transducción, una acción de incremento de nivel de azúcar, una acción que promueve secreción de glucagon pancreático, una acción que promueve la formación de orina, etc.). Específicamente, es utilizado (i) un péptido que tiene la secuencia de aminoácido representada por SEQ ID NO: 1, (ii) un péptido que tiene la secuencia de aminoácido 47-54 término N en el C terminal en la secuencia de aminoácido representado por SEQ ID NO: 1 y que consiste de 8 a 54 residuos de aminoácido, etc.

Más específicamente, metastina humano usada incluye (i) un péptido que consiste en la secuencia de aminoácido representada por SEQ ID NO: 1 (metastina 54 humana (1-54)), (ii) un péptido que consiste en la secuencia de aminoácido 40-54 término N en la secuencia de aminoácido representado por SEQ ID NO: 1 (metastina 15 humano (40-54); SEQ ID NO: 15), (iii) un péptido que consiste en la

secuencia de aminoácido 45-54 término N en la secuencia de aminoácido representado por SEQ ID NO: 1 (metastina 10 humana (45-54); SEQ ID NO: 16), (iv) un péptido que consiste en la secuencia de aminoácido 46-54 término N en la secuencia de aminoácido representado por SEQ ID NO: 1 (metastina 9 humana (46-54); SEQ ID NO: 17), (v) un péptido que consiste en la secuencia de aminoácido 47-54 término N en la secuencia de aminoácido representado por (metastina 8 humana (47-54); SEQ ID NO: 18), etc.

Cuando la metastina de ratón (A), es utilizada, por ejemplo, (i) un péptido que contiene la secuencia de aminoácido 134-141 término N en la secuencia de aminoácido representada por SEQ ID NO: 3 y que consiste de 8 a 52 residuos de aminoácido. Los ejemplos específicos de metastina de ratón (A) usada incluye (i) un péptido que consiste en la secuencia de aminoácido 90-141 término N en la secuencia de aminoácido representado por SEQ ID NO: 3, (ii) un péptido que consiste en la secuencia de aminoácido 132-141 término N en la secuencia de aminoácido representada por SEQ ID NO: 3, (iii) un péptido que consiste en la secuencia de aminoácido 127-141 término N en la secuencia de aminoácido representado por SEQ ID NO: 3, y lo similar.

Como la metastina de ratón (B), es utilizada, por ejemplo, (i) un péptido que contiene la secuencia de aminoácido 138-145 término N en la secuencia de aminoácido representada por SEQ ID NO: 5 y que consiste

de 8 a 52 residuos de aminoácido. Los ejemplos específicos de metastina de ratón (B) usada incluye (i) un péptido que consiste en la secuencia de aminoácido 94-145 término N en la secuencia de aminoácido representado por SEQ ID NO: 5, y lo similar.

Como la metastina de rata, es utilizada, por ejemplo, (i) un péptido que contiene la secuencia de aminoácido 112-119 término N en la secuencia de aminoácido representado por SEQ ID NO: 7 y que consiste de 8 a 52 residuos de aminoácido. Los ejemplos específicos de metastina de rata usada incluyen (i) un péptido que consiste en la secuencia de aminoácido 68-119 término N en la secuencia de aminoácido representado por SEQ ID NO: 7, (ii) un péptido que consiste en la secuencia de aminoácido 110-119 término N en la secuencia de aminoácido representado por SEQ ID NO: 7, (iii) un péptido que consiste en la secuencia de aminoácido 105-119 término N en la secuencia de aminoácido representado por SEQ ID NO: 7, y lo similar.

A través de la descripción, las metastinas se representan de acuerdo con una manera convencional para describir péptidos, es decir, término N (término amino) en la mano izquierda y C terminal (término carboxilo) en el lado derecho. En el péptido representado por SEQ ID NO: 1, el C terminal puede estar en cualquier forma de un grupo carboxilo (-COOH), un carboxilato (-COO-), una amida ($-CONH_2$) y un éster (-COOR). En la presente, los

ejemplos del grupo éster ilustrado por R incluyen un grupo alquilo C_{1-6} tal como metilo, etilo, n-propilo, isopropilo, n-butilo, etc.; un grupo cicloalquilo C_{3-8} tal como ciclopentilo, ciclohexilo, etc.; un grupo arilo C_{6-12} tal como fenilo, α-naftilo, etc.; un aralquilo C_{7-14} tal como grupo fenilalquilo C_{1-2}, por ejemplo, bencilo, fenetilo, etc.; un grupo α-naftil-alquilo C_{1-2} como α-naftilmetilo, etc.; grupo pivaloiloximetilo que es usado ampliamente como un éster para uso oral y lo similar.

Además, las metastins incluyen péptidos, en donde el grupo amino en el residuo metionina de término N es protegido con un grupo protector (por ejemplo, un grupo acilo C_{1-6} tal como un grupo alcanoilo C_{2-6}, por ejemplo, grupo formilo, grupo acetilo, etc.); aquellos en donde la región del término N son segmentados en el ser vivo y el grupo glutamilo formado así es piroglutaminado; aquéllos en donde un sustituyente (por ejemplo, -OH, -SH, grupo amino, grupo imidazol, grupo indol, grupo guanidino, etc.) en la cadena lateral de un aminoácido en la molécula es protegido con un grupo protector conveniente (por ejemplo, un grupo acilo C_{1-6} tal como un alcanoilo C_{2-6}, por ejemplo, grupo formilo, grupo acetilo, etc.), o péptidos conjugados tal como glicopéptidos unidos a cadenas de azúcar.

Para las sales de metastina de la presente invención, las preferibles son las sales con ácidos fisiológicamente aceptables (por ejemplo, ácidos

inorgánicos o ácidos orgánicos) o bases (por ejemplo, sal de metal alcalino), etc., especialmente sales de adición ácidas fisiológicamente aceptables. Los ejemplos de tales sales incluyen, por ejemplo, las sales con ácidos inorgánicos (por ejemplo, ácido clorhídrico, ácido fosfórico, ácido sulfúrico, ácido bromhídrico); las sales con ácidos orgánicos (por ejemplo, ácido acético, ácido fórmico, ácido propiónico, ácido fumárico, ácido maléico, ácido succínico, ácido tartárico, ácido cítrico, ácido málico, ácido oxálico, ácido benzoico, ácido metansulfónico, ácido bencensulfónico) y lo similar.

Como ADN codificando metastina, por ejemplo, es utilizado ADN codificando metastina humana descripta en WO 00/24890, ADN codificando metastina de ratón o rata descripto en WO 01/75104, etc.

El ADN codificando metastina puede ser cualquiera ADN genómico, ADN de biblioteca genómica, ADNc derivado de células y tejidos descriptos precedentemente, ADNc de biblioteca derivada de células y tejidos descriptos precedentemente y ADN sintético. El vector a ser usado para la biblioteca puede ser cualquiera de bacteriofago, plásmid, cósmido y fagémido. El ADN también puede ser amplificado directamente por reacción en cadena de polimerasa de transcriptasa inversa (mas adelante abreviada como RT-PCR) usando ARN total o fragmento ARNm preparado de las células y tejidos descriptos anteriormente.

El ADN codificando metastina humana, precursor de metastina de ratón (A), precursor de metastina de ratón (B) o precursor de metastina de rata puede ser cualquier ADN, en tanto cada uno sea un ADN que contiene una secuencia de base representada por SEQ ID NO: 2, SEQ ID NO,: 4, SEQ ID NO,: 6 ó SEQ ID NO: 8, o un ADN que tiene una secuencia base hibridizable a la secuencia de base representada por cualquier secuencia de base representada por SEQ ID NO: 2, SEQ ID NO,: 4, SEQ ID NO,: 6 o SEQ ID NO: 8 bajo condiciones muy severas y codificando metastina humana, metastina de ratón (A), metastina de ratón (B) o metastina de rata descripta anteriormente.

Los ejemplos específicos del ADN hibridizable a la secuencia de base representada por cualquiera de SEQ ID NO: 2, SEQ ID NO,: 4, SEQ ID NO,: 6 o SEQ ID NO: 8 bajo condiciones muy severas incluyen ADN que contienen una secuencia de base que tiene por lo menos aproximadamente 70% de homología, preferentemente por lo menos aproximadamente 80% de homología, más preferentemente por lo menos aproximadamente 90% de homología y más preferentemente por lo menos aproximadamente 95% de homología, a una secuencia de base representada por cualquiera de SEQ ID NO,: 2, SEQ ID NO,: 4, SEQ ID NO,: 6 o SEQ ID NO: 8.

La homología en la secuencia de base puede ser medida bajo las condiciones siguientes (un valor esperado = 10; se permiten huecos; filtrando = "ON"; calificación

de coincidencia = 1; calificación de desigualdad = -3) usando la el algoritmo de calificado de homología NCBI BLAST (Centro Nacional para la Información de Biotecnología Herramienta de Búsqueda de Alineación Local Básica).

La hibridación puede ser realizada por los métodos públicamente conocidos por sí mismos o por las modificaciones de estos métodos, por ejemplo, según el método descripto en "Molecular Clonning, 2nd" (J. Sambrook y col., Cold Spring Harbor Lab. Press, 1989). Una biblioteca disponible comercialmente también puede ser usada según las instrucciones adjuntas del protocolo del fabricante. Preferentemente, la hibridación puede ser llevada a cabo bajo condiciones muy severas.

Las condiciones muy severas usadas en la presente son, por ejemplo, aquéllas en una concentración de sodio hasta aproximadamente 19 a 40 mM, preferentemente aproximadamente de 19 a 20 mM a una temperatura de aproximadamente 50 a 70°C, preferentemente aproximadamente 60 a 65°C. En particular, es más preferible la condición de hibridación en una concentración de sodio de aproximadamente 19 mM a una temperatura de aproximadamente 65°C.

Específicamente, como el ADN codificando la metastina humana consiste de la secuencia de aminoácido representado por SEQ ID NO: 1, es utilizado el ADN que consiste en la secuencia de base representada por SEQ ID

NO: 2. Consiguientemente, para la secuencia de base codificando la metastina humana que consiste en las diversas secuencias de aminoácido descrpitas precedentemente, una secuencia de base que corresponde a cada una de las secuencias de aminoácido parciales en la secuencia de aminoácido representada por SEQ ID NO.: 1 puede ser elegida de la secuencia de base representada por SEQ ID NO: 2.

Como el ADN codificando al precursor de metastina de ratón (A) que comprende la secuencia de aminoácido representada por SEQ ID NO: 3, se utiliza un ADN que consiste en la secuencia de base representada por SEQ ID NO: 4, y lo similar. Consiguientemente, para la secuencia se base codificando al precursor de metastina de ratón (A) que consiste de diversas secuencias de aminoácido descripto precedentemente, puede ser elegida una secuencia de base que corresponde a cada una de las secuencicas del aminoácido parcial en la secuencia de aminoácido representada por SEQ ID NO.: 3 de la secuencia de base representada por SEQ ID NO: 4.

Como el ADN codificando al precursor de metastina de ratón (B) que comprende la secuencia de aminoácido representada por SEQ ID NO: 5, se utiliza un ADN que consiste en la secuencia de base representada por SEQ ID NO: 6, y lo similar. Consiguientemente, para la secuencia de base que codifica al precursor de metastina de ratón (B) que consiste de las diversas secuencias de aminoácido

480
481

descriptas precedentemente, se puede elegir una secuencia de base que corresponda a cada una de las secuencias de aminoácido parciales en la secuencia de aminoácido representada por SEQ ID NO.: 5 de la secuencia de base representada por SEQ ID NO: 6.

Como el ADN codificando la metastina de la rata que comprende la secuencia de aminoácido representada por SEQ ID NO: 7, se utiliza un ADN que consiste en la secuencia de base representada por SEQ ID NO: 8, y lo similar. Consiguientemente, para la secuencia de base que codifica la metastina de la rata que consiste en las diversas secuencias de aminoácido descrpitas precedentemente, una secuencia de base que corresponde a cada una de las secuencias de aminoácido parciales en la secuencia de aminoácido representada por SEQ ID NO: 7 puede ser elegida de la secuencia de base representada por SEQ ID NO: 8.

Más específicamente, para el péptido que consiste en la secuencia de aminoácido representada por SEQ ID NO.: 1 (metastina humana 54 (1-54)), se utiliza un ADN que contiene la secuencia de base representada por SEQ ID NO: 2, etc.

Para el péptido que consiste en la secuencia de aminoácido 40-54 término N en la secuencia de aminoácido representada por SEQ ID NO: 1 (metastina humana 15 (40-54); SEQ ID NO: 15), es usado un ADN que contiene la secuencia de base representada por SEQ ID NO: 19, etc.

Para el péptido que consiste en la secuencia de aminoácido 45-54 término N en la secuencia de aminoácido representado por SEQ ID NO: 1 (metastina humana 10 (45-54); representada por SEQ ID NO: 16), es usado un ADN que contiene la secuencia de base representada por SEQ ID NO: 20, etc..

Para el péptido que consiste en la secuencia de aminoácido 46-54 término N en la secuencia de aminoácido representado por SEQ ID NO: 1 (metastina humana 9 (46-54); representada por SEQ ID NO: 17), es usado un ADN que contiene la secuencia de base representado por SEQ ID NO: 21, etc.

Para el péptido que consiste en la secuencia de aminoácido 47-54 término N en la secuencia de aminoácido representada por SEQ ID NO: 1 (metastina humana 8 (47-54); representada por SEQ ID NO: 18), se usa un ADN que contiene la secuencia de base representada por SEQ ID NO: 22, etc.

Como el receptor de la metastina, se utilizan sus péptidos parciales o sales de los mismos, por ejemplo, un receptor de metastina humana, sus péptidos parciales o sales de los mismos descriptas en WO 00/24890, un receptor de metastina humano de ratón o rata, sus péptidos parciales o sales descriptas en WO 01/75104, etc.

Específicamente, el receptor de metastina incluye una proteína que contiene la misma o sustancialmente la

misma secuencia de aminoácido como la secuencia de aminoácido representada por SEQ ID NO: 9, SEQ ID NO.: 11 o SEQ ID NO.: 13, etc.

La secuencia de aminoácido que tiene sustancialmente la misma secuencia de aminoácido como la secuencia de aminoácido representada por SEQ ID NO: 9, SEQ ID NO.: 11 ó SEQ ID NO: 13 incluye, por ejemplo, una secuencia de aminoácido que tiene por lo menos aproximadamente 70% de homología, preferentemente por lo menos aproximadamente 80% de homología, más preferentemente por lo menos aproximadamente 90% de homología, y más preferentemente por lo menos aproximadamente 95% de homología, respecto a la secuencia de aminoácido representada por SEQ ID NO.: 9, SEQ ID NO.: 11 ó SEQ ID NO: 13.

La homología de las secuencias de aminoácido puede ser determinada bajo las condiciones siguientes (valor de expectativa = 10; se permiten huecos; matriz = BLOSUM62; filtrado = "OFF") usando un algoritmo de calificación de homología NCBI BLAST (Centro nacional para la información de la biotecnología herramienta de búsqueda de alineación local básica).

Como la proteína que tiene sustancialmente la misma secuencia de aminoácido como la secuencia de aminoácido representada por SEQ ID NO: 9, SEQ ID NO.: 11 ó SEQ ID NO: 13, las preferibles son una proteína que tiene sustancialmente la misma secuencia de aminoácido como la secuencia de aminoácido representada por SEQ ID NO: 9,

SEQ ID NO.: 11 o SEQ ID NO: 13 y posee la actividad de la misma naturaleza como la de una proteína que consiste en la secuencia de aminoácido representado por SEQ ID NO: 9, SEQ ID NO.: 11 o SEQ ID NO: 13, etc.,

Como la actividad de sustancialmente la misma naturaleza, por ejemplo, se indica una actividad de enlace a ligando, una actividad de señal de transducción, y lo similar. Por "sustancialmente la misma naturaleza" se aplica para significar que la naturaleza de estas actividades es equivalente en lo que se refiere a la calidad. Así, actividades tales como una actividad de enlace a ligando, una actividad de señal de transducción, etc. son preferentemente equivalentes (por ejemplo, aproximadamente de 0,01 a 100 veces, preferentemente aproximadamente de 0,1 a 10 veces, más preferentemente de 0,5 a 2 veces), pero pueden estar presentes y ser aceptables diferencias en grado tal como el nivel de estas actividades, y factores cuantitativos tales como un peso molecular de proteína.

Las actividades tales como una actividad de enlace a ligando, una actividad de señal de transducción, etc. se puede ensayar por métodos públicamente conocidos por sí mismos con modificaciones y pueden ser determinadas según los métodos de determinación de un ligando o métodos de filtrado descriptos, por ejemplo, en WO 00/24890 ó WO 01/75104.

Los ejemplos del receptor de metastina utilizado

incluyen proteínas que comprenden (1) (i) la secuencia de aminoácido representada por SEQ ID NO: 9, SEQ ID NO: 11 ó SEQ ID NO: 13, de las cuales por lo menos 1 ó 2 (preferentemente desde aproximadamente 1 hasta aproximadamente 30, más preferentemente desde aproximadamente 1 hasta aproximadamente 10 y más preferentemente varios (1 ó 2)) aminoácidos son anulados; (ii) la secuencia de aminoácido representada por SEQ ID NO: 9, SEQ ID NO: 11 ó SEQ ID NO: 13, en las cuales por lo menos 1 ó 2 (preferentemente desde aproximadamente 1 hasta aproximadamente 30, más preferentemente desde aproximadamente 1 hasta aproximadamente 10 y más preferentemente varios (1 ó 2)) aminoácidos son agregados; (iii) la secuencia de aminoácido representada por SEQ ID NO: 9, SEQ ID NO: 11 ó SEQ ID NO: 13, en donde por lo menos 1 ó 2 (preferentemente desde aproximadamente 1 hasta aproximadamente 30, más preferentemente desde aproximadamente 1 hasta aproximadamente 10 y más preferentemente varios (1 ó 2)) aminoácidos son insertados; (iv) la secuencia de aminoácido representada por SEQ ID NO: 9, SEQ ID NO: 11 ó SEQ ID NO: 13 en donde por lo menos 1 ó 2 (preferentemente desde aproximadamente 1 hasta aproximadamente 30, más preferentemente desde aproximadamente 1 hasta aproximadamente 10 y más preferentemente varios (1 ó 2)) aminoácidos son sustituidos por otros aminoácidos; o (v) una combinación de éstas secuencias de aminoácido; y lo similar.

terminal C descriptos anteriormente.

Además, los receptores de metastina incluyen aquéllos en donde el grupo amino en el residuo de metionina terminal N es protegido con un grupo protector (por ejemplo, un grupo acilo C_{1-6} tal como un grupo alcanoilo C_{2-6}, por ejemplo, grupo formilo, grupo acetilo, etc.); aquellos en donde la región del terminal N son segmentados en el ser vivo y el grupo glutamilo así formado es piroglutaminado; aquéllos en donde un sustituyente (por ejemplo, -OH, -SH, grupo amino, grupo imidazol, grupo indol, grupo guanidino, etc.) en la cadena lateral de un aminoácido en la molécula es protegido con un grupo protector conveniente (por ejemplo, un grupo acilo C_{1-6} tal como un grupo alcanoilo C_{2-6}, por ejemplo, grupo formilo, grupo acetilo, etc.), o las proteínas conjugadas tales como glicoproteínas unidas a las cadenas de azícar.

Los ejemplos específicos de los receptores de metastina incluyen receptor de metastina humana que consiste en la secuencia de aminoácido representada por SEQ ID NO: 9, receptor de metastina de rata que consiste en la secuencia de aminoácido representada por SEQ ID NO: 11, receptor de metastina de ratón que consiste en la secuencia de aminoácido representada por SEQ ID NO: 13, etc.

Los péptidos parciales del receptor de metastina (más adelante a veces denominado simplemente péptido

parcial) puede ser cualquier péptido, en tanto sean los péptidos parciales del receptor de metastina descriptos precedentemente; se utilizan aquéllos como las moléculas de proteína del receptor del metastina, los cuales son los sitios expuestas fuera de la membrana celular, y poseen una actividad de enlace a ligando.

Específicamente, péptido parcial del receptor de metastina que consiste en la secuencia de aminoácido representado por SEQ ID NO: 9, SEQ ID NO: 11 o SEQ ID NO: 13 son un péptido que contiene las partes analizadas por ser dominios extracelulares (los dominios hidrófilos) en el análisis de gráfico hidrófobo. Un péptido que en parte contiene un dominio hidrófobo también puede ser usado. Adicionalmente, los péptido pueden contener cada dominio separadamente o en una pluralidad de dominios juntos.

En el receptor de metastina, los péptidos parciales preferidos son aquéllos que poseen un número de aminoácidos de por lo menos 20, preferentemente por lo menos 50, y más preferentemente por lo menos 100, en la secuencia de aminoácido descrpita precedentemente que constituye el receptor de metastina.

Los péptidos parciales pueden ser un péptido que posee la secuencia de aminoácido descripta precedentemente, de la cual por lo menos 1 ó 2 (preferentemente desde aproximadamente 1 hasta aproximadamente 10 y más preferentemente varios (1 ó 2)) aminoácidos se anulan; a la cual por lo menos 1 ó 2

A través de la especificación, los receptores de metastina son representados de acuerdo con la modalidad convencional de descripción de péptidos, es decir, el terminal N (término amino) en el lado izquierdo y terminal C (término carboxilo) e el lado derecho. En los receptores de metastina que incluyen el receptor de metastina representado por SEQ ID NO: 9, SEQ ID NO: 11 ó SEQ ID NO: 13, el terminal C puede estar en cualquier forma del grupo carboxilo (-COOH), un carboxilato (-COO-), una amida ($-CONH_2$) y un éster (-COOR). En la presente, los ejemplos del grupo éster ilustrados por R incluyen un grupo alquilo C_{1-6} tal como metilo, etilo, n-propilo, isopropilo, n-butilo, etc.; un grupo cicloalquilo C_{3-8} tal como ciclopentilo, ciclohexilo, etc.; un grupo arilo C_{6-12} tal como fenilo, α-naftilo, etc.; un aralquilo C_{7-14} tal como un grupo fenilalquilo C_{1-2}, por ejemplo, bencilo, fenetilo, etc.; un grupo α-naftil-alquilo C_{1-2} tal como α-naftilmetilo, etc.; y grupo pivaloiloximetilo que es usado ampliamente como un éster para uso oral y lo similar.

Cuando los receptores de metastina contienen un grupo carboxilo (o un carboxilato) en una posición distinta del terminal C, el grupo carboxilo puede estar amidado o esterificado y tales amidas o ésteres también están incluidos dentro de la proteína de receptor de la presente invención. En este caso, el grupo éster usado puede ser el mismo grupo que el de los ésteres de

(preferentemente desde aproximadamente 1 hasta aproximadamente 10 y más preferentemente varios (1 o 2)) aminoácidos se agregan; o en la cual por lo menos 1 ó 2 (preferentemente desde aproximadamente 1 hasta aproximadamente 10 y más preferentemente varios (1 o 2)) aminoácidos son sustituidos por otros aminoácidos.

En el péptido parcial, el terminal C puede ser cualquier forma de un grupo carboxilo (-COOH), un carboxilato (-COO-), una amida ($-CONH_2$) y un éster (-COOR), como en el receptor de metastina descripto anteriormente.

Además, los péptidos parciales incluyen péptidos, en donde el grupo amino en el residuo de metionina terminal N es protegido con un grupo protector; aquellos en donde la región terminal N son segmentados en el ser vivo y el grupo glutamilo así formado es piroglutaminado; aquéllos en donde un sustituyente en la cadena lateral de un aminoácido en la molécula es protegido con un grupo protector conveniente, o péptidos conjugados tales como glicopéptidos unidos a las cadenas de azúcar, como en los receptores de metastina descriptos anteriormente.

Para las sales de receptor de metastina o péptido parcial, las preferidas son las sales con ácidos fisiológicamente aceptables, especialmente las sales de adición ácidas fisiológicamente aceptables. Los ejemplos de las sales incluyen las sales por ejemplo, con ácidos inorgánicos (por ejemplo, ácido clorhídrico, ácido

fosfórico, ácido sulfúrico, ácido bromhídrico); las sales con ácidos orgánicos (por ejemplo, ácido acético, ácido fórmico, ácido propiónico, ácido fumárico, ácido maléico, ácido succínico, ácido tartárico, ácido cítrico, ácido málico, ácido oxálico, ácido benzoico, ácido metansulfónico, ácido bencensulfónico) y lo similar.

Como el ADN codificando el receptor de metastina o su péptido parcial, se utiliza, por ejemplo, un ADN codificando el receptor de metastina humana o sus péptidos parciales descriptos en WO 00/24890, un ADN codificando el receptor de metastina humano de ratón o rata o su péptidos parciales descriptos en WO 01/75104, etc.

El ADN que codifica el receptor de metastina o sus péptidos parciales puede ser cualquier ADN genómico, biblioteca de ADN genómica, ADNc derivado de células y tejidos descriptos precedentemente, biblioteca de ADNc derivado de células y tejidos descriptos precedentemente y ADN sintético. El vector a ser usado para la biblioteca puede ser cualquiera de bacteriófago, plásmido, cósmido y fagémido. El ADN también puede ser amplificado directamente por reacción en cadena de polimerasa de transcriptasa inversa (más adelante abreviado como RT-PCR) usando el ARN total o fragmento de ARNm preparado de células y tejidos descriptos anteriormente.

Específicamente, el ADN codificando receptor de metastina humana, el receptor de metastina de ratón o

receptor de metastina de rata puede ser cualquier ADN, en tanto sea un ADN que contiene cada secuencia de base representada por SEQ ID NO: 10, SEQ ID NO: 12 ó SEQ ID NO: 14, o un ADN que contiene una secuencia de base hibridizable a la secuencia de base representada por SEQ ID NO: 10, SEQ ID NO: 12 ó SEQ ID NO: 14 bajo condiciones muy severas y codificando un receptor que tiene sustancialmente la misma naturaleza de actividad (por ejemplo, una actividad de enlace a ligando, una actividad de señal de transducción, etc.) como el del receptor de metastina humano, receptor de metastina de ratón o receptor de metastina de rata que consiste en la secuencia de aminoácido representado por SEQ ID NO: 10, SEQ ID NO: 12 ó SEQ ID NO: 14.

Los ejemplos del ADN hibridizable a la secuencia de base representada por cualquiera de SEQ ID NO: 10, SEQ ID NO: 12 ó SEQ ID NO: 14 incluyen ADN que contiene una secuencia de base que tiene por lo menos aproximadamente 70% de homología, preferentemente por lo menos aproximadamente 80% de homología, más preferentemente por lo menos aproximadamente 90% de homología y más preferentemente por lo menos aproximadamente 95% de homología, a la secuencia de base representada por cualquiera de SEQ ID NO: 10, SEQ ID NO: 12 ó SEQ ID NO: 14.

La homología en la secuencia de base puede medirse bajo las condiciones siguientes (valor de expectativa =

10; se permiten huecos; filtrado = "ON"; calificación de coincidencia = 1; calficación de desigualdad = -3) usando el algoritmo de calificación de homología NCBI BLAST (Centro nacional para la información de la biotecnología la herramienta de búsqueda de alineación local básica).

La hibridación puede ser realizada por métodos públicamente conocidos por sí mismos o por modificaciones de estos métodos, por ejemplo, según el método descripto e, "Molecular Clonning, 2nd" (J. Sambrook y col., Cold Spring Harbor Lab. Press, 1989), etc. Una biblioteca disponible comercialmente también puede ser usada según las instrucciones adjunto del protocolo del fabricante. Preferentemente, la hibridación puede ser realizada bajo condiciones muy severas.

Las condiciones muy severas utilizadas en la presente son, por ejemplo, aquéllas en donde la concentración de sodio es de aproximadamente 19 a 40 mM, preferentemente de aproximadamente 19 a 20 mM a una temperatura de aproximadamente 50 a 70°C, preferentemente aproximadamente de 60 a 65°C. En particular, es más preferible la condición de hibridación en una concentración de sodio de aproximadamente 19 mM a una temperatura de aproximadamente 65°C.

Más específicamente, como el ADN codificando el receptor de metastina humano consiste en la secuencia de aminoácido representado por SEQ ID NO: 9, es utilizado el ADN que consiste en la secuencia de base representada por

SEQ ID NO: 10.

Como el ADN codificando el receptor de metastina de rata que consiste en la secuencia de aminoácido representado por SEQ ID NO: 11, es utilizado el ADN que consiste en la secuencia de base representada por SEQ ID NO: 12.

Como el ADN codificando el receptor de metastina de ratón que consiste en la secuencia de aminoácido representado por SEQ ID NO: 13, es utilizado ADN que consiste en la secuencia de base representado por SEQ ID NO: 14.

Los receptores de metastina, sus péptidos parciales o sales de los mismos y ADN que codifican los receptores de metastina o sus péptidos parciales pueden ser obtenidos o pueden ser producidos por los métodos descriptos en WO 00/24890 ó WO 01/75104.

La presente invención será descripta en detalle con referencia a los EJEMPLOS, EJEMPLOS DE FORMULACIÓN Y EJEMPLOS DE PRUEBA, pero no se debe considerar limitada por los mismos, y puede ser realizada cualquier modificación sin apartarse del alcance de la presente invención.

En los EJEMPLOS siguientes, el término "temperatura ambiente" significa normalmente una temperatura de aproximadamente 10°C a 35°C. En los porcentuales, el rendimiento se ilustra en mol/mol% y el solvente utilizada en la cromatografía por % en volumen, y resto

por % en peso. En los espectros RMN de protón, no son ilustrados los datos de OH, protones NH, etc. los cuales son anchos y no identificados.

Las otras abreviaturas utilizadas en la descripción significan lo siguiente.

Abreviatura Descripción.

10ψ,CSNH: El terminal C-$CONH_2$ en posición 10 es sustituido con -$CSNH_2$.

1ψ2,CH_2NH: El enlace -CONH- entre las posiciones 1 y 2 es sustituido con el enlace -CH_2NH-.

2ψ3,CH_2NH: El enlace -CONH- entre las posiciones 2 y 3 es sustituido con el enlace -CH_2NH-.

3ψ4,CH_2NH: El enlace -CONH- entre las posiciones 3 y 4 es sustituido con el enlace -CH_2NH-.

4ψ5,CH_2NH: El enlace -CONH- entre las posiciones 4 y 5 es sustituido con el enlace -CH_2NH-.

6ψ7,CSNH: El enlace -CONH- entre las posiciones 6 y 7 es sustituido con el enlace -CSNH-.

6ψ7,NHCO: El enlace -CONH- entre las posiciones 6 y 7 es sustituido con el enlace -NHCO-.

6ψ7,CH_2NH: El enlace -CONH- entre las posiciones 6 y 7 es sustituido con el enlace -CH_2NH-.

6ψ7,CH_2O: El enlace -CONH- entre las posiciones 6 y 7 es sustituido con el enlace -CH_2O-.

7ψ8,CH_2NH: El enlace -CONH- entre las posiciones 7 y 8 es sustituido con el enlace -CH_2NH-.

8ψ9,CH_2NH: El enlace -CONH- entre las posiciones 8 y 9 es sustituido con el enlace -CH_2NH-.

9ψ10,CH_2NH: El enlace -CONH- entre las posiciones 9 y 10 es sustituido con el enlace -CH_2NH-.

Abu : ácido 2-aminobutánico

Ac : acetilo

Acp : ácido 6-aminocaproico

AcOEt : acetato de etilo

AcOH : ácido acético

Aib: : ácido α-aminoisobutanoico

Ala(2-Qui): 2-quinolilalanina

Ala(3-Bzt): 3-benzotienilalanina

Alb : Albizziin ácido 2-amino-3-ureidopropionico.

Arg(Ac) : N^{ω}-acetilarginina

Arg(Boc_2,Me) : $N^{\omega,\omega'}$-bis-terc-butoxicarbonil-N^{ω}-metilarginina

Arg(Et) : N^{ω}-etilarginina

Arg(Me) : N^{ω}-metilarginina

Arg(asyMe_2) ó Arg(Me_2)asym : asimétrica-$N^{\omega,\omega}$-dimetilarginina

Arg(symMe_2) ó Arg(Me_2)sym : simétrica-$N^{\omega,\omega'}$-dimetilarginina

Arg(NO_2) : N^{ω}-metilarginina

Arg(n-Pr) : N^{ω}-propilarginina

Arg(Tos) : N^{ω}-tosilarginina

Asp(NHMe) : N^{ω}-metilaspargina

Asp(NMe2) : N^{α}-dimetilaspargina

AzaGly : azaglicina

AzaPhe : azafenilalanina

Aze(2) : ácido azetidin-2-carboxílico

β-Ala : β-alanina

Boc : terc-butoxicarbonilo

Boc_2O : bicarbonato de di-terc-butilo.

Br-z : 2-bromobenciloxicarbonilo

Bu^t : terc-butilo

Bzl : bencilo

CDI : 1,1'-carbonildiimidazol

Cha : ciclohexilalanina

CIP :tetrafluoroborato de 2-cloro-1,3-dimetilimidazolio

Cit : citrulina

resina Clt : resina 2-clorotritilo

Cl-z : 2-clorobenciloxicarbonilo

Dab : ácido 2,4-diaminobutanoico.

Dap : ácido 2,3-diaminopropionico

Dap(Ac) : ácido de N^{β}-acetildiaminopropiónico

Dap(For) : ácido N^{β}-formildiaminopropiónico

Dap(Gly) : ácido N^{β}-glicildiaminopropiónico

Dap(GnGly) : ácido de N(-(N-guanidinoglicil)diamino-propiónico.

DCM : diclorometano

DEA : dietilamina

DIEA : N,N-diisopropiletilamina

DIPCDI	: 1,3-diisopropilcarbodiimida
DMAP	: 4-dimetilaminopiridina
DMF	: N,N-dimetilformamida
EDT	: 1,2-etanditiol.
Fmoc	: 9-fluorenilmetoxicarbonilo
For	: formilo
[γ-Abu]	: ácido 4-aminobutanoico
γ-MeLeu	: γ-metilleucina
Gn	: guanidino
GuAmb	: 4-guanidinometilbenzoilo
Har	: homoarginina.
Har(Me)	: N^{ω}-metilhomoarginina
HOAt	: 1-hidroxi-7-azabenzotriazol
HOBt	: 1-hidroxibenzotriazol
HONB	: N-hidroxi-5-norbornen-2,3-dicarboxamida
Hph	: homofenilalanina
Hyp	: trans-4-hidroxiprolina.
IndPr	: 3-(indol-3-il)propionilo
Lys(Me_2)	: $N^{\varepsilon,\varepsilon}$-dimetilisina
MBHA	: p-metilbenzhidrilamina
MeOH	: metanol
Mtt	: 4-metiltritilo
N($(CH_2)_3$Gn)Gly	: N-(3-guanidinopropil)glicina.
Nal(1)	: 1-naftilalanina
Nal(2)	: 2-naftilalanina
Nar	: norarginina

498

Nar(Me) : N^{ω}-metilnorarginina

Nle : norleucina

NMeArg : N^{α}-metilarginina

NmeAsn : N^{α}-metilasparagina

NMeLeu : N^{α}-metileucina

NMePhe : N^{α}-metilfenilalanina.

NMeSer : N^{α}-metilserina

NMeTrp : N^{α}-metiltriptofano

NMeTyr : N^{α}-metiltirosina

Nva : Norvalina

Orn : ornitina

Orn(Mtt) : N^{δ}-(4-metiltritil)ornitina

PAL : ácido 5-(4-(9-fluorenilmetoxicarbonil)aminometil-3,5-dimetoxifenoxi)valérico.

Pbf : 2,2,4,6,7-pentametildihidrobenzofuran-5-sulfonilo

pGlu : ácido piroglutámico

Phe(2Cl) : 2-clorofenilalanina

Phe(2F) : 2-fluorofenilalanina

Phe(3,4Cl_2) : 3,4-diclorofenilalanina

Phe(3,4F_2) : 3,4-difluorofenilalanina

Phe(3CF_3) : 3-trifluorometilfenilalanina.

Phe(3Cl) : 3-clorofenilalanina

Phe(3F) : 3-fluorofenilalanina

Phe(4Cl) : 4-clorofenilalanina

Phe(4CN) : 4-cianofenilalanina

Phe(4F) : 4-fluorofenilalanina

Phe(4Gn) : 4-guanidinofenilalanina

Phe($4NH_2$) : 4-aminofenilalanina

Phe($4NO_2$) : 4-nitrofenilalanina

Phe(4CN) : 4-cianofenilalanina.

Phe(F_5) : pentafluorofenilalanina

Pheψ(CH_2O)Gly : Enlace -CONH- entre Phe y Gly es sustituido con enlace -CH_2O-.

Pheψ(CSNH)-NH_2 : La fenilalanilamida terminal C es sustituida con fenilalaniltioamida.

Phg : fenilglicina.

PhOH : fenol

PhSMe : tioanisol

Pip(2) : ácido 2-aminopipecolinico

Pro : prolina

Pya(2) : 2-piridilalanina

Pya(3) : 3-piridilalanina

Pya(4) : 4-piridilalanina.

PyAOP : hexafluorofosfato de (7-azabenzotriazol-1-iloxi)-tris(pirrolidino)fosfonio.

PyBOP : (hexafluorofosfato de benzotriazol-1-iloxi)-tris(pirrolidino)fosfonio.

PyBrop : hexafluorofosfato de bromo-tris(pirrolidino)fosfonio.

Sar : N-metilglicina

Ser(Ac) : O-acetilserina

Ser(Me) : O-metilserina

Thi : 2-tienilalanina

Tic : ácido 1,2,3,4-tetrahidroisoquinolin-2-carboxílico

TIS : triisopropilsilano

Tle : terc-leucina

Tos : tosilo

Trp(For) : Nin-formiltriptofano.

Trt : tritilo

Tyr(Me) : O-metiltirosina

Tyrψ(CH_2NH)Asn : Enlace -CONH- entre Tyr y Asn es sustituido con enlace -CH_2NH-.

TFA : ácido trifluoracético.

TFE : trifluoroetanol

Z : benziloxicarbonilo.

En la descripción y dibujos, se denotan los códigos de bases y aminoácidos de acuerdo con la Comisión IUPAC-IUB de la Nomenclatura Bioquímica o por códigos comunes en la técnica, cuyos ejemplos se ilustran más adelante. Para los aminoácidos que pueden tener isómeros ópticos, la forma L se presenta a menos que sea indicado de otra manera.

ADN : ácido desoxirribonucleico

ADNc : ácido desoxirribonucleico complementario.

A : aminopurina

T : timina

G : guanina

C	: citosina
Y	: timina o citosina
N	: timina, citosina, aminopurina o guanina.
R	: aminopurina o guanina
M	: citosina o aminopurina
W	: timina o aminopurina
S	: citosina o guanina.
ARN	: ácido ribonucleico
ARNm	: ácido ribonucleico mensajero
dATP	: trifosfato de desoxiadenosina
dTTP	: trifosfato desoxitimidina.
dGTP	: trifosfato de desoxiguanosina
dCTP	: trifosfato de dedoxicitidins
ATP	: trifosfato de adenosina
EDTA	: ácido etilendiamintetraacético.
SDS	: sulfato de dodecil sodio
TFA	: ácido trifluoracético
EIA	: inmunoensayo enzimático.
Gly o G	: glicina
Ala o A	: alanina
Val o V	: valina
Leu o L	: leucina
Ile o I	: isoleucina.
Ser o S	: serina
Thr o T	: treonina
Cys o C	: cisteína
Met o M	: metionina

Glu o E : ácido glutámico.

Asp o D : ácido aspártico

Lys o K : lisina

Arg o R : arginina

His o H : histidina

Phe o F : fenilalanina.

Tyr o Y : tirosina

Trp o W : triptofano

Pro o P : prolina

Asn o N : asparagina

Gln o Q : glutamina

pGlu : ácido piroglutámico.

Los números de identificación de secuencia en el listado de secuencia de la descripción indica la secuencia siguiente, respectivamente.

SEQ ID NO: 1

Esto ilustra la secuencia de aminoácido de metastina derivada de humano (Metastina).

SEQ ID NO: 2

Esto ilustra la secuencia de base de ADN codificando metastina humana.

SEQ ID NO: 3

Esto ilustra la secuencia de aminoácido de precursor de metastina de ratón (A).

SEQ ID NO: 4

Esto ilustra la secuencia de base de ADN codificando al precursor de metastina de ratón (A) que es la

secuencia de base contenida en el plásmido pCMV-mKiSS-1 contenido en el transformante de Escherichia coli DH10B/pCMV-mKiSS-1.

SEQ ID NO: 5

Esto ilustra la secuencia de aminoácido de precursor de metastina de ratón (B).

SEQ ID NO: 6

Esto ilustra la secuencia de base de ADN codificando al precursor de metastina de ratón (B) que es la secuencia de base contenida en plásmido pCR2.1-mKiSS-1.4A contenido en el transformante de Escherichia coli DH5α/pCR2.1-mKiSS-1.4A.

SEQ ID NO: 7

Esto ilustra la secuencia de aminoácido de precursor de metastina derivado de rata.

SEQ ID NO: 8

Esto ilustra la secuencia de base de ADN codificando al precursor de metastina de rata.

SEQ ID NO: 9.

Esto ilustra la secuencia de aminoácido de OT7T175 humano (receptor de metastina).

SEQ ID NO: 10

Esto ilustra la secuencia de base de ADN codificando OT7T175 humano (receptor de metastina).

SEQ ID NO: 11

Esto ilustra la secuencia de aminoácido de rata OT7T175 (receptor de metastina).

SEQ ID NO: 12

Esto ilustra la secuencia de base de ADN codificando OT7T175 de rata (receptor de metastina).

SEQ ID NO: 13

Esto ilustra la secuencia de aminoácido de OT7T175 de ratón (receptor de metastina).

SEQ ID NO: 14

Esto ilustra la secuencia de base de ADN codificando OT7T175 de ratón (receptor de metastina).

SEQ ID NO: 15

Esto ilustra la secuencia de aminoácido de metastina humana 15 (40-54).

SEQ ID NO: 16

Esto ilustra la secuencia de aminoácido de metastina humana 10 (45-54) (MS10).

SEQ ID NO: 17

Esto ilustra la secuencia de aminoácido de metastina humana 9 (46-54).

SEQ ID NO: 18

Esto ilustra la secuencia de aminoácido de metastina humana 8 (47-54).

SEQ ID NO: 19

Esto ilustra la secuencia de base de ADN codificando la metastina humana 15 (40-54).

SEQ ID NO: 20

Esto ilustra la secuencia de base de ADN codificando la metastina humana 10 (45-54).

SEQ ID NO: 21

Esto ilustra la secuencia de base de ADN codificando la metastina humana 9 (46-54).

SEQ ID NO: 22.

Esto ilustra la secuencia de base de ADN codificando la metastina humana 8 (47-54).

El transformante de Escherichia coli DH10B/pCMV-mKiSS-1 ha estado en el depósito desde el 24 de enero de 2000 con el Depositario de Organismos de Patente Internacional, Instituto Nacional de Ciencia Industrial Avanzada y Tecnología (el primer Ministerio de Comercio Internacional e Industria, Agencia de Ciencia Industrial y Tecnología, Instituto nacional de biociencia y tecnología humana (NIBH)), localizado en Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki (código postal 305-8566), Japón como el Número de acceso FERM BP-7003 y desde el 16 de diciembre de 1999 con el Instituto para Fermentación (IFO), localizado en 2-17-85 Juso-Honmachi, Yodogawa-ku, Osaka-shi, Osaka, Japón, como el Número de acceso IFO 16348.

El transformante de Escherichia coli DH5(/pCR2.1-mKiSS-1.4A ha estado en el depósito desde el 6 de marzo del 2000 con el Depositario de Organismos de Patente Internacional, Instituto Nacional de Ciencia Industrial Avanzada y Tecnología (primer Ministerio de Comercio Internacional e Industria, Agencia de Ciencia Industrial y Tecnología, Instituto Nacional de biociencia y

tecnología humana (NIBH)), localizado en Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki (código postal 305-8566), Japón como el Número de acceso FERM BP-7073 y desde el 16 de febrero de 2000 con el Instituto para Fermentación (IFO), localizado en 2-17-85 Juso-Honmachi, Yodogawa-ku, Osaka-shi, Osaka, Japón, como el Número de acceso IFO 16360.

En la presente invención, Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2 (SEQ ID NO: 16) es denominada metastina 10 (Metastina 10), es decir, MS10.

En los Ejemplos descriptos más adelante, el Tyr terminal N y el Phe terminal C en MS10 se cuentan como las posiciones 1 y 10, respectivamente.

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2.

1 2 3 4 5 6 7 8 9 10

Por ejemplo, [Hph10]MS10 del Compuesto No. 79 (Ejemplo 1) significa un péptido en donde el Phe terminal C (posición 10) de MS10 se sustituye con Hph.

Por ejemplo, des(1)-MS10 del Compuesto No. 4 significa un péptido en donde el Tyr N terminal (posición 1) se anula.

Por ejemplo, des(1-3)-Fmoc-MS10 del Compuesto No. 53 significa un péptido en donde el Tyr-Asn-Trp terminal N (posiciones 1 a 3) se anula y el grupo amino de Asn posición 4 se modifica y es protegido con Fmoc.

[EJEMPLO 1]

(Procedimiento de síntesis A): Preparación de [Hph10]MS10 (Compuesto No. 79)

Utilizando 51 mg de resina Fmoc-Hph-PAL (sub. 0,39 mmol/g) que fue preparada introduciendo Fmoc-Hph en la resina PAL disponible comercialmente, la cadena de péptido fue extendida en un sintetizador de péptido múltiple ACT-396 para producir la resina Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)Hph-PAL. A 18,2 mg de la resina, se agregaron 200 µL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5) y la mezcla fue agitada durante 2 horas. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento estaba repetido para lavar. El residuo se extrajo con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, fue realizada la elución de pendiente de densidad lineal con eluyentes A/B: 73/27-63/37 usando: 0,1% TFA en agua y el eluyente B: 0,1% que TFA-que contiene acetonitrilo en HPLC preparativa que usa columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 2,6 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1316,5 (Calculado 1316,7).

Tiempo de elución en HPLC: 20,6 min.

Condiciones de la elución.

La columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-30/70, usando 0,1% TFA en agua

como eluyente A y acetonitrilo que contiene 0,1% TFA (35 mins.)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 2]

(Procedimiento de síntesis B): Preparación de [Trp(For)10]MS10 (Compuesto No. 186).

Utilizando 379 mg de resina de Fmoc-Arg(Pbf)-O-Clt (sub. 0,33 mmol/g), que fue preparada introduciendo Fmoc-Arg(Pbf)-OH en la resina 2-clorotritilcloruro disponible comercialmente (resina Clt, 1,33 mmol/g), la cadena de péptido fue extendida en un ABI 433A para producir de ésta manera 540 mg de resina Boc-Tir(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)FeGliLeuArg(Pbf)-O-Clt. A 270 mg del péptido, fueron agregados 10 mL de AcOH/TFE/DCM (1/1/8), la mezcla fue agitada durante 30 minutos. Después que la resina fue eliminada por filtración, el solvente fue concentrado y lugo el residuo fue disuelto en AcOEt. Entonces, la solución fue lavada con una solución acuosa saturada de NaCl. Después de secado sobre Na_2SO_4, el solvente fue concentrado y fue agregado dietil éter - éter de petróleo al residuo para producir 68 mg de Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)-OH como el precipitado. A 22 mg de péptido, fueron agregados 4 mg de HCl H-Trp(For)-NH_2 (preparado por tratamiento de Boc-Trp(For)-NH_2 con 9,7 N HCl/dioxano a 0°C durante 30 minutos), 10 mg de PyAOP, 5 mg de HOAt y

11 µL de DIEA. La mezcla fue agitada durante 15 horas. Después que el solvente fue concentrado, fue agregado cloroformo-dietil éter al residuo para producir Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)Trp (For)-NH_2 como precipitado. Al péptido, le fue agregado 1 mL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5) y la mezcla fue agitada durante 2 horas. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para el lavado. El residuo fue extractado mediante una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Luego, la pendiente de elución de densidad lineal (30 minutos) fue realizada con eluyentes A/B: 73/27-63/37 usando eluyente A: 0,1% TFA en agua y eluyente B: 0,1% que contiene TFA-acetonitrilo en HPLC preparativo utilizando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contenían el producto entonces fueron recolectadas y liofilizadas para producir 2,0 mg de polvos blancos.

Espectro de masa $(M+H)^+$ 1369,3 (Calculado 1369,6).

Tiempo de elución en HPLC: 19,6 min

Condiciones de elución

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: pendiente de elución de densidad lineal con eluyentes A/B = 100/0-30/70, usando 0,1% TFA en agua como eluyente A y acetonitrilo con 0,1% de TFA (35

mins.).

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 3]

(Procedimiento de síntesis C): Preparación de [10ψ,CSNH]MS10 (Compuesto No. 128)

Después que 264 mg de Boc-Phe-NH_2 fue disuelto en 20 mL de THF, fue agregado 1,62 g de reactivo Lawesson a la solución, seguido por agitación durante 24 horas. Las materias insolubles fueron eliminadas por filtración, el solvente fue concentrado y el concentrado fue disuelto en AcOEt. La solución fue lavada con solución acuosa salina de $NaHCO_3$. y luego con solución acousa saturada de NaCl. Después de secar sobre Na_2SO_4, el solvente fue concentrado y el concentrado fue purificado por cromatografía en columna de enrasado. Fue agregado dietil éter-éter de petróleo para producir 275 mg (rendimiento 98%) de (S)-2-terc-Butoxicarbonilamin-3-fenilpropantioamida (Boc-Pheψ(CSNH)-NH_2) como precipitado. Después fueron tratados 42 mg de péptido a 0°C con HCl 9,7 N para eliminar Boc, la eliminación de Fmoc con un tratamiento 10% de DEA/DMF seguido por condensación por el método PyBOP/HOBt fue repetido para dar 66 mg de Fmoc-LeuArg(Pbf)Pheψ(CSNH)-NH_2 (rendimiento 93%). A 17mg de Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGly-OH preparado como en el Ejemplo 2, se agregaron H-LeuArg(Pbf)Pheψ(CSNH)-NH_2 (preparado tratando 14 mg de Fmoc-LeuArg(Pbf)Pheψ(CSNH)-NH_2 con 10% DEA/DMF), 9 mg de

PyBrop, 3 mg de HOAt y 7 mL de DIEA y la mezcla fue agitada durante 15 horas. Después que el solvente fue concentrado, fue agregado a los mismos cloroformo-dietil éter para precipitación. A 10 mg del producto, fueron agregados 100 µL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5) y la mezcla fue agitada durante 2 horas. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (30 minutos) fue realizada con eluyentes A/B: 72/28-62/38 usando A: 0,1% TFA en agua y eluyente B: 0,1% de TFA-conteniendo acetonitrilo en HPLC preparativa usando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contenían el producto fueron recolectadas y liofilizadas para dar 1,0 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1318,4 (Calculado 1318,6).

Tiempo de elución en HPLC: 21,8 min.

Las condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-30/70, usando 0,1% TFA en agua como eluyente A y acetonitrilo conteniendo 0,1% TFA (35 mins.)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 4]

(Procedimiento de síntesis D): Preparación de [6ψ7,CH_2NH]MS10 (Compuesto No. 163)

Usando 321 mg de resina Fmoc-Phe-PAL, que fue preparada introduciendo Fmoc-Phe en resina PAL disponible comercialmente, la cadena de péptido fue extendida en ABI 433A para dar resina Fmoc-LeuArg(Pbf)Phe-PAL. A la mitad de volumen del péptido, fue condensado Fmoc-Gly para dar 190 mg de resina Fmoc-GlyLeuArg(Pbf)Phe-PAL. Luego que 76 mg del producto fueran sometidos a desprotección de Fmoc, fueron agregados a los mismos 2 mL de DMF, 50 µL de AcOH, 46 mg de Fmoc-Phe-h y 8 mg de $NaBH_3CN$, seguido de una agitación por una hora. Después que la resina fue lavada, fueron agregado a los mismos 2 mL de DMF, 22 µL de DIEA y 18 µL de Z-Cl y la mezcla fue agitada durante 3 horas. Después del lavado de resina, la cadena de péptido fue extendida en ABI 433A para dar resina Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)Pheψ(CH_2NZ)GlyLeuArg(Pbf)Phe-PAL. Bajo enfriamiento con hielo, fueron agregados 46 µL de Tm-Br, 42 µL de PhSMe, 38 µL de m-cresol, 18 µL de EDT y 227 µL de TFA a 15 mg de péptido y la mezcla fue agitada durante 2 horas. Después que el solvente fue eliminado por destilación, fue agregado dietil éter al residuo, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este

procedimiento fue repetido para lavado. El residuo fue extractado con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (30 minutos) fue realizada con eluyentes A/B: 72/28-62/38 usando: 0,1% TFA en agua y eluyente B: 0,1% acetonitrilo conteniendo TFA en HPLC preparativa usando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contenían el producto fueron recolectadas y liofilizadas para dar 2,0 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1288,7 (Calculado 1288,7)

Tiempo de elución en HPLC: 18,2 min

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm)

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-0/70, usando 0,1% TFA en agua como eluyente A y acetonitrilo que contiene 0,1% TFA (35 min.)

Velocidad de flujo: 1,0 ml/min.

(EJEMPLO DE REFERENCIA 1)

Preparación de N-metil-N,N'-bis-Boc-1-guanilpirazol

Bajo un flujo de nitrógeno, fueron disueltos 720 mg de NaH en aceite al 60% en 20 mL de DMF seco y fueron agregados 20 mL de solución de DMF seco en 5,59 g de N,N'-bis-Boc-1-guanilpirazol comercialmente disponible a la solución a 0°C, luego de agitación durante 10 minutos. Luego que fueran agregados a los mismos 1,68 mL de yoduro

de metilo, la mezcla fue agitada a temperatura ambiente durante 24 horas. Luego que el solvente fue destilado, el residuo fue disuelto en AcOEt y la solución fue lavada con 1N HCl acuoso, solución acousa saturada de $NaHCO_3$ y luego con solución acousa saturada de NaCl. Luego de secar sobre Na_2SO_4, el solvente fue concentrado y el concentrado fue purificado por cromatografía en columna de enrasado (acetato de etilo/n-hexano = 1/4) usando gel de sílice 60 (200 mL) para dar 5,35 g (rendimiento 91,6%) de N-metil-N,N'-bis-Boc-1-guanilpirazol.

^1H RMN (300 MHz; $CDCl_3$): δ 8,00 (br s; 1H); 7;69 (br s; 1H); 6,42 (dd; 1H; J=2,7; 1,5 Hz); 3,25 (s; 3H); 1,53 (s; 9H); 1,30 (s; 9H).

Análisis elemental como $C_{15}H_{24}N_4O_4$

Calculado: C: 55,54; H: 7,46; N: 17,27.

Encontrado: C: 55,36; H: 7,48; N: 17,06.

Rf1: 0,64, Rf2: 0,79

Solvente de desarrollo para TLC: Rf1 (acetato de etilo/n-hexano = 1/2), Rf2 (metanol/cloroformo = 2/98)

Tiempo de elución en HPLC: 26,7 min.

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-20/80, usando 0,1% TFA en agua como eluyente A y acetonitrilo el cual contiene 0,1% TFA (40 min.).

Velocidad del flujo: 1,0 ml/min.

(EJEMPLO DE REFERENCIA 2)

Preparación de N-metil-N,N'-bis-Z-1-guanilpirazolo

En una atmósfera de argón, 40 mg de 60% NaH en aceite fue disuelto en 5 mL de DMF seco y 5 mL de solución DMF seco de 380 mg de N,N'-bis-Z-1-guanilpirazolo comercialmente disponible fue agregado a 0°C, seguido por agitación durante 10 minutos. Luego fueron agregados a los mismos 125 µL de ioduro de metilo, la mezcla fue agitada a temperatura ambiente durante 15 horas. Luego el solvente fue eliminado por destilación, el residuo fue disuelto en AcOEt y la solución fue lavada con solución acuosa 1N HCl, solución acousa saturada de $NaHCO_3$ y luego con solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado para dar 393 mg del producto en bruto. Del producto en bruto fueron purificados 170 mg por cromatografía en columna de enrasado (acetato de etilo/n-hexano = 1/4) usando sílica gel 60 (75 mL) para dar 152 mg (rendimiento 89,5%) de N-metil-N,N'-bis-Z-1-guanilpirazol.

^{1}H RMN (300 MHz; $CDCl_3$): δ 7,97 (br s; 1H); 7,61 (d; 1H; J=1,0Hz); 7,37-7,32 (m; 4H); 7,29-7,26 (m; 4H); 7,16-7,13 (m; 2H); 6,36 (dd; 1H; J=2,8; 1,6 Hz); 5,18 (s; 2H); 5,04 (s, 2H); 3,22 (s; 3H)

Análisis elemental como $C_{21}H_{20}N_4O_4$

Calculado: C: 64,28; H: 5,14; N: 14,28.

Encontrado: C: 64,09; H: 5,24; N: 14,43.

Rf1: 0,50; Rf2,: 0,86.

El solvente de desarrollo para TLC: Rf1 (acetato de etilo/n-hexano = 1/2), Rf2(metanol/cloroformo=2/98)

Tiempo de elución en HPLC: 28,9 min.

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-20/80, usando 0,1% TFA en agua como eluyente A y acetonitrilo que contiene 0,1% TFA (40 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 5]

(Procedimiento de síntesis E): Preparación de [Arg(Me)9]MS10 (Compuesto No. 82)

Usando 480 mg de resina MBHA Amida Fmoc-Phe-Rink, que fue preparada introduciendo Fmoc-Phe en resina MBHA Amida Rink disponible comercialmente, la cadena de péptido fue extendida en un ABI 433A para dar 1080 mg de resina MBHA Amida Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuOrn(Mtt)Phe-Rink. A 540 mg del péptido, se agregaron 10 mL de TFA/TIS/DCM (1/5/94) y la mezcla fue agitada durante 50 minutos. La resina fue lavada y luego fue secada. Luego fueron agregados a 2/5 del volumen de resina, 2 mL de DMF, 49 mg de N-metil-N,N'-bis-Boc-1-guanilpirazol preparado en el EJEMPLO DE REFERENCIA 1 y 87 µL de DIEA, la mezcla fue agitada durante 15 horas para dar 220 mg de resina MBHA Amida Boc-

Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGliLeuArg(Boc_2, Me)Phe-Rink. A 50 mg del péptido, fue agregado 1 mL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5) y la mezcla fue agitada durante 2 horas. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (30 minutos) fue realizada con eluyentes A/B: 74/26-64/36 usando: 0,1% TFA en agua y eluyente B: 0,1% acetonitrilo conteniendo TFA en HPLC preparativa usando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 10,5 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1316,5 (Calc. 1316,7).

Tiempo de elución en HPLC: 20,1 min

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (35 min)

Velocidad de flujo: 1,0 ml/min.

N-metil-N,N'-bis-Boc-1-guanilpirazol usado para convertir el aminoácido en la posición 9 en Arg N^{ω}-

metilado en este EJEMPLO es un reactivo útil para producir péptidos que contienen Arg N^{ω}-metilado, y se usa ventajosamente también en general el péptido para producir péptidos que contienen Arg N^{ω}-metilado caracterizado por la reacción de N-metil-N,N'-bis-Boc-1-guanilpirazol con Orn en péptidos seguido por desprotección.

Además, la estabilidad en sangre es mejorada convirtiendo Arg en Arg N^{ω}-metilado no sólo en péptidos N^{ω}-metilado que contienen Arg obtenido en este EJEMPLO sino también en péptidos en general. Por consiguiente, los sustituyentes en la cadena lateral de Arg N^{ω}-metilado son útiles para un método de incremento de la estabilidad en sangre, lo cual comprende la converción de Arg en un péptido en Arg N^{ω}-metilado.

Adicionalmente, se puede proveer un método para incrementar la estabilidad en la sangre, que comprende introducir uno o dos (preferiblemente uno) grupos alquilo, preferiblemente grupo alquilo C_{1-4}, más preferiblemente grupo metilo en la cadena lateral de Arg en el péptido que contiene Arg. En la presente, el péptido que contiene Arg incluye, por ejemplo, un péptido que posee un péptido parcial caracterizado por la estructura -Arg-XXX-, en donde XXX representa un aminoácido que opcionalmente posee sustituido un grupo de anillo aromático en la cadena lateral, preferiblemente Phe, Trp, Tyr, etc.

Los péptidos que contienen Arg N^{ω}-metilado también pueden ser producidos usando no sólo N-metil-N,N'-bis-Boc-1-guanilpirazol sino también N-metil-N,N'-bis-Z-1-guanilpirazol preparado en el EJEMPLO DE REFERENCIA 2.

[EJEMPLO 6]

(Procedimiento de síntesis F): Preparación de [6ψ7,CSNH]MS10 (Compuesto No. 166)

En 10 mL de DMF, fueron disueltos 503 mg de HCl H-Gly-OBu^t y fueron agregados a 1162 mg de Fmoc-Phe, 608 mg de HOBt, 1874 mg de PyBOP y 784 μL de DIEA a 0°C, luego de agitación durante 4 horas. El solvente fue concentrado y el concentrado fue disuelto en AcOEt. La solución fue lavada entonces con una solción acuosa 1N de HCl, solución acousa saturada de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secado sobre de Na_2SO_4, el solvente fue concentrado y fue agregado dietil éter-éter de petróleo para dar 1,48 g (rendimiento 99%) de Fmoc-PheGly-OBu^t como precipitado. Después que 250 mg del producto fueran disueltos en 10 mL de tolueno, fueron agregados a la solución 404 mg del reactivo de Lawesson, seguido por agitación a 80°C durante 2 horas. El solvente fue concentrado y el concentrado fue disuelto en AcOEt. La solución fue lavada entonces con una solución acuosa de 1N HCl, solución acousa saturada de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado y el concentrado fue purificado por

cromatografía en columna de enrasado. Fue agregado al resultante dietil éter-éter de petróleo para dar 207 mg (rendimiento 80%) de Fmoc-Pheψ(CSNH)Gly-OBu^t como precipitado. A 103 mg del producto, se agregaron TFA/H2O (95/5) y la mezcla fue agitada durante una hora. Después que el solvente fue concentrado, fue agregado dietil éter para dar 82,4 mg (rendimiento 90%) de Fmoc-Pheψ(CSNH)Gly-OH como precipitado. Usando resina Fmoc-Phe-PAL, que fue preparada introduciendo Fmoc-Phe en resina PAL disponible comercialmente, la cadena de péptido fue extendida en un ABI 433A y 80 mg de resina Fmoc-LeuArg(Pbf)Phe-PAL extendida fue sometida a desprotección Fmoc. Entonces 35 mg de Fmoc-Pheψ(CSNH)Gly-OH, fueron agregados 47 mg de PyBrop, 14 mg de HOAt y 35 µL de DIEA a la resina, seguido por agitación durante 15 horas. Después del lavado de resina, la cadena de péptido fue extendida en ABI 433A para dar resina Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)Pheψ(CSNH)GlyLeuArg(Pbf)Phe-PAL. A 15 mg del producto, se agregaron 200 µL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5), luego de agitación durante 2 horas. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Luego, la elución de pendiente de densidad lineal (60 minutos) fue

realizada con eluyentes A/B: 77/23-57/43 usando: 0,1% TFA en agua y eluyente B: 0,1% acetonitrilo conteniendo TFA en HPLC preparativa usando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 1,0 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1318,7 (Calc. 1318,6).

Tiempo de elución en HPLC: 20,8 min.

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (35 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 7]

(Procedimiento de síntesis G): Preparación de [AzaGly7]MS10 (Compuesto No. 176)

Usando 321 mg de resina Fmoc-Phe-PAL, que fue preparada introduciendo Fmoc-Phe en la resina PAL disponible comercialmente, la cadena de péptido fue extendida en ABI 433A y 80 mg de resina Fmoc-LeuArg(Pbf)Phe-PAL así extendida fue sometido a desprotección Fmoc. Luego fueron agregados 2 mL de THF y 16 mg de CDI y la mezcla fue agitada durante 2 horas. Entonces 6 µL de monohidrato de hidracina fueron agregados a la mezcla. La mezcla fue agitada durante una

hora y la resina fue lavada. Luego fueron agregados al sistema 39 mg de Fmoc-Phe, 93 mg de PyBrop, 27 mg de HOAt y 105 µL de DIEA, luego de agitación durante 2 horas. Luego fue lavada la resina, la cadena de péptido fue extendida en ABI 433A para dar resina Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheAzaGliLeuArg(Pbf)Phe-PAL. A 25 mg del producto, fue agregado 1 mL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5), seguido por agitación durante 2 horas. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (30 minutos) fue realizada con eluyentes A/B: 74/26-64/36 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA conteniendo acetonitrilo en HPLC preparativa usando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 5,5 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1303,3 (Calculado 1303,6).

Tiempo de elución en HPLC: 18,9 min.

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-30/70, usando 0,1% TFA en agua

como eluyente A y 0,1% TFA que contiene acetonitrilo (35 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 8]

(Procedimiento de síntesis H): Preparación de [D-Tyr1,AzaGly7,Arg(Me)9]MS10 (Compuesto No. 232)

Fmoc-Phe,Fmoc-Orn(Mtt) fue introducido en 4 g (0,55 mmol/g) de resina MBHA Amida Rink comercialmente disponible para preparar resina MBHA Amida Fmoc-Orn(Mtt)-Phe-Rink, y fueron agregados 50 mL de TFA/TIS/DCM (1/5/94) a la resina, seguido por agitación durante 50 minutos. Luego de lavar la resina, fueron agregados a la resina 40 mL de DCM y 2,27 g de N-metil-N,N'-bis-Boc-1-guanilpirazol preparado en el EJEMPLO DE REFERENCIA 1. Fue agregado DIEA a la mezcla para ajustar el pH de la solución a 9. La mezcla fue agitada durante 15 horas para dar 4,74 g de resina MBHA Amida Fmoc-Arg(Boc_2,Me)Phe-Rink. Separadamente, 145 mg de Fmoc-$NHNH_2$ HCl fue suspendido en 10 mL de THF. Bajo enfriamiento con hielo, fueron agregados 89 mg de CDI y 87 mL de DIEA a la suspensión, seguido por agitación a temperatura ambiente durante una hora. Bajo enfriamiento con hielo, fue agregado a la mezcla 5 mL de una solución de 224 mg de H-Leu-OBut HCl en 5 mL de DMF. Cuando alcanzó la temperatura ambiente, la mezcla fue agitada durante 18 horas. Después que el solvente fue destilado, el residuo fue disuelto en AcOEt y la solución fue lavada con una

solución acuosa de 1N HCl, solución acousa saturada de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado y el concentrado fue purificado por cromatografía en columna de enrasado dar 230 mg (rendimiento 99%) de Fmoc-AzaGli-Leu-OBut. A 187 mg del producto, fue agregado 10 mL de TFA/H_2O (9/1), luego de agitación durante una hora. Después que el solvente fue destilado, el residuo fue disuelto en AcOEt y la solución lavada con solución acousa saturada de NaCl. Luego de secado sobre de Na_2SO_4, el solvente fue concentrado y fue agregado dietil éter para dar 143 mg de Fmoc-AzaGly-Leu-OH como precipitado (rendimiento 87%). El Fmoc-AzaGli-Leu-OH resultante, fue introducido Trt-Phe en resina MBHA Amida Fmoc-Arg(Boc$_2$,Me)Phe-Rink. A la así preparada resina MBHA Amida Trt-Phe-AzaGli-Leu-Arg(Boc$_2$,Me)Phe-Rink, fue agregado 50 mL de TFA/TIS/DCM (1/5/94) y la mezcla fue agitada durante 50 minutos. Luego que la resina fue lavada y neutralízada, fueron introducidos a los misma Fmoc-Ser(Bu^t) y luego Fmoc-Asn(Trt). Usando 80,3mg de resina MBHA Amida Fmoc-Asn(Trt)Ser(Bu^t)Phe-AzaGli-LeuArg(Boc$_2$,Me)Phe-Rink resultante, la cadena del péptido fue extendida para dar 97,2 mg de resina MBHA Amida H-$_D$-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)Phe-AzaGli-LeuArg(Boc$_2$,Me)Phe-Rink.

A la resina obtenida, fue agregado 1 mL de TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2,5/2,5),

seguido por agitación durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada con eluyentes A/B: 76/24-66/34 usando: 0,1% TFA en agua y el eluyente B: 0,1% acetonitrilo conteniendo TFA en HPLC preparativa usando una columna YMC SH-343-5 S-5, 120A (20 x 250 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 11,7 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1317,0 (Calc. 1317,6).

Tiempo de elución en HPLC: 21,0 min.

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (35 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 9]

(Procedimiento de síntesis I): Preparación de des(1-3)-3-(3-piridil)propionil-[AzaGli7,Arg(Me)9]MS10 (Compuesto No. 322)

Luego que 48,2 mg de resina MBHA Amida Fmoc-Asn(Trt)Ser(Bu^t)Phe-AzaGli-LeuArg(Boc_2,Me)Phe-Rink preparada en EJEMPLO 8 fue sometida a desprotección Fmoc, la resina fue tratada con 15,2 mg de ácido 3-(3-piridil)propionico disponible comercialmente, 15,9 µL de DIPCDI y 200 µL de 0,5M HOAt/DMF a temperatura ambiente durante 90 minutos. Luego que la resina obtenida fue lavada y secada, fue agregado 1 mL de TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2,5/2,5) a la resina, seguido por agitación durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada con eluyentes A/B: 80/20-60/40 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contiene acetonitrilo en HPLC preparativa usando una columna YMC SH-343-5 S-5, 120A (20 x 250 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para producir 6,0 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 987,4 (Calculado 987,5)

Tiempo de elución en HPLC: 8,1 min.

Condiciones de elución:

Columna: YMC-AM301 (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal

con eluyentes A/B = 80/20-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 10]

(Procedimiento de síntesis J): La preparación de des(1-2)-Amidin-[AzaGly7,Arg(Me)9]MS10 (Compuesto No. 273)

Luego que Fmoc-Trp(Boc) fue introducido en 48,2 mg de resina MBHA Amida Fmoc-Asn(Trt)Ser(Bu^t)Phe-AzaGli-LeuArg(Boc_2,Me)Phe-Rink la cual fue preparada en el EJEMPLO 8, la resina fue sometida a desprotección Fmoc para dar la resina MBHA Amida H-Trp(Boc)Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink. La resina obtenida fue tratada en DMF con 29,3 mg de N,N'-bis-Boc-1-guanilpirazol y 34,8 µL de DIEA durante 14 horas para dar resina MBHA Amida Amidin-Trp(Boc)Asn(Trt)Ser(Bu^t)Phe-AzaGli-LeuArg(Boc_2,Me)Phe-Rink. Luego que la resina obtenida fue lavada y secada, fue agregado 1 mL de TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2,5/2,5), seguido de agitación durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada

con eluyentes A/B: 78/22-58/42 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contiene acetonitrilo en HPLC preparativa usando una columna YMC SH-343-5 S-5, 120A (20 x 250 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 0,6 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1082,3 (Calc. 1082,6).

Tiempo de elución en HPLC: 11,4 min.

Condiciones de elución:

Columna: YMC-AM301 (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 80/20-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 11]

(Procedimiento de síntesis K): Preparación de [6ψ7,NHCO,D-Tyr1,Arg(Me)9]MS10 (Compuesto No. 319)

En 30 mL de MeCN, fueron disueltos 5,99 g de Z-Phe y 3,94 g de HONB y 4,59 g de WSCD HCl fueron agregados a la solución a 0°C, seguido por agitación a temperatura ambiente durante 4 horas. Manteniendo el sistema a 0°C, fueron agregados 3,4 mL de una solución acuosa al 25% de NH_3 y 10 mL de DMF a la mezcla, seguido por agitación durante 4 horas. Después que el solvente fue destilado, el residuo fue disuelto en AcOEt y la solución fue lavada con una solución acuosa 1N HCl, solución acousa saturada

de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secar sobre Na_2SO_4, el solvente fue concentrado y fue agregado dietil éter para dar 1,48 g (rendimiento 99%) de Z-Phe-NH_2 como precipitado. Luego que 1,94 g de [Bis(trifluoroacetoxi)iodo]benceno fueron disueltos en 20 mL de MeCN y 5 mL de H_2O, fueron agregados 890 mg de Z-Phe-NH_2 preparados anteriormente y 972 µL de piridina al precipitado a 0°C, seguido de agitación a temperatura ambiente durante 15 horas. Después que el solvente fue concentrado, la concentración fue sometida a una separación líquido-líquido con dietil éter-1N HCl en solución acuosa y la capa de la solución acuosa de 1N HCl fue concentrada y luego secada. Su volumen medio fue disuelto en 5 mL de DMF, y fueron agregados 486 µL de malonato de mono-terc-butilo y 540 mg de HOBt a la solución. Entonces, fueron agregados a la mezcla 2,08 g de PyBOP y 1394 µL de DIEA a 0°C, seguido por agitación a temperatura ambiente durante 15 horas. Después que el solvente fue destilado, el residuo fue disuelto en AcOEt y la solución fue lavada con una solución acuosa de 1N HCl, solución acousa saturada de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado y el concentrado fue purificado por cromatografía en columna de enrasado. Fue agregado dietil éter-éter de petróleo de para dar 304 mg (rendimiento 33%) de Z-Pheψ(NHCO)Gli-OBu^t como un precipitado. Después

que 154 mg del producto fueron disueltos en 20mL de MeOH, fue agregado Pd-C al 10% a la solución, seguido por hidrogenación catalítica durante 2 horas en un flujo de hidrógeno. Después que se fue eliminado el catalizador por filtración, el solvente fue concentrado y secado. El residuo fue disuelto en 10 mL de MeCN y fueron agregados 152 mg de Fmoc-OSu y 78 µL de DIEA a la solución, luego de agitación durante 15 horas. Después que el solvente fue destilado, el residuo fue disuelto en AcOEt y la solución fue lavada con una solución acuosa de 1N HCl, solución acousa saturada de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado y fue agregado dietil éter-éter de petróleo para dar 127 mg (rendimiento 68%) de Fmoc-Pheψ(NHCO)Gli-OBut como precipitado. El Fmoc-Leu fue introducido en 63 mg de resina MBHA Amida Fmoc-Arg(Boc$_2$,Me)Phe-Rink que fue preparada en el EJEMPLO 10. Luego fueron agregados desprotección Fmoc, Fmoc-Pheψ(NHCO)Gly-OH (preparado tratando 25 mg de Fmoc-Pheψ(NHCO)Gli-OBu^t con TFA durante 3 minutos), 300 µL de 0,5M HOAt, 78 mg de PyAOP y 52 µL de DIEA a la resina, luego de agitación durante 6 horas. Después que la resina fue lavada, fueron agregados 2 mL de DMF, 9 µL de DIEA y 12 µL de Ac_2O a la resina, seguido por agitación durante 30 minutos. Después que la resina fue lavada, la cadena de péptido fue extendida en ABI 433A para dar resina MBHA

Amida Boc-d-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)Pheψ(NHCO)GliLeuArg(Boc$_2$,Me)Phe-Rink. A 34 mg del producto, fueron agregados 200 µL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5), luego de agitación durante 2 horas. Fue agregado éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (30 minutos) fue realizada con eluyentes A/B: 76/24-66/34 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contenia acetonitrilo en HPLC preparativa usando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 0,7 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1316,3 (Calc. 1316,7).

Tiempo de elución en HPLC: 18,7 min.

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-0/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (35 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 12]

(Procedimiento de síntesis L): Preparación de [N((CH$_2$)$_3$Gn)Gly9]-MS10 (Compuesto No. 218)

Usando 192 mg resina MBHA Amida Fmoc-Phe-Rink, la cadena de péptido fue extendida en un ABI 433A dar resina MBHA Amida Fmoc-GlyPhe-Rink. Después que un 1/4 volumen del producto fue sometido a desprotección Fmoc, fueron agregados a los mismos 2 mL de DMF, 50 µL de AcOH, 5 mg de Boc-β-Ala-H y 16 mg de $NaBH_3CN$ y la mezcla fue agitada durante 30 minutos. Después que la resina fue lavada, fueron agregados 71 mg de Fmoc-Leu, 56 mg de CIP, 27 mg de HOAt y 105 mL de DIEA, seguido de agitación durante 15 horas. Después que la resina fue lavada, la cadena de péptido fue extendida en un ABI 433A para dar finalmente la resina MBHA Amida Z-Tyr(Bzl)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuN((CH$_2$)$_3$NHBoc)GliPhe-Rink. Al producto, le fue agregado 1 mL de TFA/PhOH/H_2O/TIS/EDT (87,5/5/2,5/2,5/2,5) y la mezcla fue agitada durante 2 horas. Después que la resina fue eliminada por la filtración y luego fue concentrada, fue agregado éter a la concentración. Una mitad de volumen del precipitado resultante fue disuelto en 500 µL de DMF, fue agregada una solución de 9 mg de clorhidrato de 1H-pirazol-1-carboxamidina y 22 mL de DIEA, seguido por agitación durante 15 horas. El solvente fue destilado y fue agregado éter para precipitar. Bajo enfriamiento con hielo, fueron agregados 60 µL de PhSMe, 56 µL de m-cresol, 26 µL de EDT, 337 µL de TFA y 65 µL de TMSBr a la

mezcla, luego de agitación durante 2 horas. Después que el solvente fue destilado, fue agregado el éter al residuo, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para el lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto luego fue filtrado para eliminar la resina. Entonces, la elución de una pendiente de densidad lineal (60 minutos) fue realizada con eluyentes A/B: 74/26-64/36 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contenia acetonitrilo, en una HPLC preparativa utilizando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para producir de ésta manera 1,8 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1302,5 (Calc. 1302,7).

Tiempo de elución en HPLC: 18,6 min

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (35 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 13]

(Procedimiento de síntesis M): La preparación de MS10 (Compuesto No. 3)

La resina de p-metil BHA disponible comercialmente

(0,77 mmol/g de resina) fue cargada en un tanque de reacción de síntesis de péptido, con ABI 430A. Luego de esto, fueron introducidos Boc-Phe.Boc-Arg(Tos), Boc-Leu.Boc-Gli, Boc-Phe.Boc-Ser(Bzl), Boc-Asn.Boc-Trp(For) y Boc-Asn.Boc-Tyr(Br-z) en la resina en este orden según la síntesis de péptido según estrategia Boc (DCC-HOBt) para dar la resina del péptido protegida deseada. La resina, 0,11 g, fue agitada a 0°C durante 60 minutos en 10 ml de ácido fluorhídrico anhidro que contiene 1 ml de p-cresol y 1,2 ml de 1,4-butandiol. Luego de esto el ácido fluorhídrico fue destilado en vacío. Fue agregado dietil éter al residuo y el precipitado fue filtrado. Al precipitado, le fue agregada una solución acuosa de ácido acético al 50% para extracción y las materias insolubles fueron eliminadas. Después que el extracto fue suficientemente concentrado, la concentración fue aplicada a una una columna Sephadex (nombre comercial) G-25 (2,0 x 80 cm) llena con una solución acuosa de ácido acético al 50% seguida por desarrollo con el mismo solvente. Las fracciones principales fueron recolectadas y liofilizadas para dar 40 mg de polvo blanco. Medio volumen del polvo fueron aplicados en una columna cromatografica (2,6 x 60 cm) envasada con LiChroprep (nombre comercial) RP-18, seguido de un lavado con 200 ml de agua que contiene 0,1% TFA. Entonces fue realizada la elución de pendiente de densidad lineal con 300 ml de 0,1% TFA en agua y 300 ml de 0,1% TFA que contenia 33% de

acetonitrilo. Las fracciones principales fueron recolectadas y liofilizadas para dar 2,2 mg del péptido deseado.

Espectro de masa $(M+H)^+$ 1302,5 (Calc. 1302,6).

Tiempo de elución en HPLC: 18,7 min

Condiciones de elución:

Columna: Wakosil-II 5C18T 4,6 x 100 mm.

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 95/5-45/55, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 14]

(Procedimiento de síntesis N): Preparación de des(1-3)-2-(Indol-3-il)etilcarbamoil-[AzaGly7,Arg(Me)9]MS10

(Compuesto No. 279)

Resina MBHA Amida Fmoc-Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Me,Boc_2)Phe-Rink preparada en el EJEMPLO 8 fue sometida a desprotección Fmoc. A 64 mg (20 µmol) de resina MBHA Amida H-Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Me,Boc_2)Phe-Rink, fueron agregados a 1,5 mL de THF y 13 mg de CDI, luego de agitación durante 2 horas. Luego 32 mg de clorhidrato de triptamina, fueron agregados 28 µL de DIEA y 500 µL de DMF a la mezcla, seguido de agitación durante 24 horas. Luego de esto la resina fue lavada para dar resina MBHA Amida 2-(Indol-3-il)etilcarbamoil-

Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Me,Boc$_2$)Phe-Rink. A 15 mg del producto, le fueron agregados 200 µL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5), luego de agitación durante 2 horas. Fue agregado éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada con eluyentes A/B: 69/31-59/41 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contenia acetonitrilo en HPLC preparativa usando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 1,1 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1040,2 (Calculado 1040,5).

Tiempo de elución en HPLC: 20,1 min

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-0/50, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 15]

Preparación de resina MBHA Amida Fmoc-AzaGly-Leu-

Arg(Boc$_2$,Me)-Trp(Boc)-Rink.

Se permitió agrandar 5 g (0,4 mmol/g) de Resina MBHA Amida Rink disponible comercialmente, en DMF, y fue tratada con 50 ml de una solución al 20% de piperidina/DMF durante 20 minutos para eliminar el grupo Fmoc. Después que la resina obtenida fue lavada con DMF, fue introducido Trp(Boc) por tratamiento de la resina a temperatura ambiente con 4,213 g (8 mmol) de Fmoc-Trp(Boc)-OH, 1,272 mL (8 mmol) de DIPCDI y 16 mL (8 mmol) de solución 0,5M de HOAt/DMF durante 90 minutos para dar la resina MBHA Amida Fmoc-Trp(Boc)-Rink. De una manera similar, fue introducido Orn(Mtt) para dar 2 mmol de la resina MBHA Amida Fmoc-Orn(Mtt)-Trp(Boc)-Rink. Después que la resina obtenida fue lavada y agrandada con DCM, fue agregado 50 mL de TFA/TIS/DCM (1/5/94), la mezcla fue agitada por 10 minutos y la solución fue destilada. Este procedimiento fue repetido hasta que la coloración amarilla causado por la falta de grupo Mtt en una solución de TFA/TIS/DCM (1/5/94) desaparece cuando la solución fue agregada, así el grupo Mtt fue eliminado.

La resina MBHA Amida Fmoc-Orn-Trp(Boc)-Rink resultante fue neutralizada con una solución al 5% de DIEA/DCM. Luego de lavar con DCM, fueron agregados a la resina 25 mL de DCM-TFE (4:1) y 1,946 g (6 mmol) de N-metil-N,N'-bis-Boc-1-guanilpirazol que fue obtenido en el EJEMPLO DE REFERENCIA 1. Fue agregada DIEA a la mezcla para ajustar el pH de la solución a 10, y la mezcla fue

agitada durante 15 horas para dar 6,195 g de resina MBHA Amida Fmoc-Arg(Boc$_2$,Me)-Trp(Boc)-Rink. Fue introducido Fmoc-Leu en la resina obtenida de la misma manera descrita anteriormente. La resina fue dividida por la mitad y el grupo Fmoc fue eliminado de la así obtenida resina MBHA Amida Fmoc-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink (1 mmol) para dar la resina MBHA Amida H-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink (1 mmol).

Separadamente, fue suspendido 1,745 g (6 mmol) de Fmoc-NHNH$_2$ HCl en 20 mL de DMF-THF (4:1). Bajo enfriamiento con hielo, fueron agregados a la suspensión 973 mg (6 mmol) de CDI y 2,09 mL (12 mmol) de DIEA, seguido por agitación a temperatura ambiente durante una hora. La solución de reacción resultante fue agregada a la resina MBHA Amida H-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink descrita antes, seguido por agitación a temperatura ambiente durante 15 horas. Luego de realizada la reacción, la resina fue lavada y secó para dar la 3,314 g de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink.

[EJEMPLO 16]

(Procedimiento de síntesis O): La preparación de des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 385)

Después que 100 mg (0,03 mmol) de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink se permiten agrandar en DMF, la resina fue tratada con 2 ml de

solución al 20% de piperidina/DMF durante 20 minutos para eliminar el grupo Fmoc. Después que la resina obtenida fue lavada con DMF, fue introducido Phe por tratamiento a la resina con 77,5 g (0,2 mmol) de Fmoc-Phe-oh, 31,8 µL (0,2 mmol) de DIPCDI y 0,4 mL (0,2 mmol) de una solución 0,5M de HOAt/DMF a temperatura ambiente durante 90 minutos. De una manera similar, fueron introducidos Ser(^{t}Bu) y Asn(Trt) para dar resina MBHA Amida Fmoc-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink. La resina obtenida fue sometida a desprotección Fmoc y fue tratada con 77,6 mg (0,2 mmol) de Fmoc-$_D$-Pya(4)-OH, 104,2 mg (0,2 mmol) de PyAOP, 400 µL (0,2 mmol) de 0,5M HOAt/DMF y 174,2 µL (0,2 mmol) de DIEA a temperatura ambiente durante 90 minutos para introducir $_D$-Pya(4) y luego D-Tyr(tBu), seguido por desprotección Fmoc. Así, fueron obtenidos 135 mg de resina MBHA Amida H-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink.

A la resina obtenida, le fue agregado 1 mL de TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2,5/2,5), luego de agitación durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido dos veces para lavarlo. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad

lineal (60 minutos) fue realizada a una velocidad del flujo de 15 ml/min con eluyentes A/B: 79/21-69/31 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contenia acetonitrilo en HPLC preparativa usando una columna YMC Pack R&D-ODS-5-B S-5 120A (30 x 250 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas. Se disolvieron los polvos blancos obtenidos en 10 mL de agua y fueron agregados a la solución 100 µL de resina de intercambio de iones BioRAD AG1 x 8 AcO^-. Mientra se agitaba a mano la solución a veces, la solución de reacción se deja en reposo durante una hora. La solución fue filtrada a través de un filtro de membrana para eliminar la resina y dar 6,6 mg de polvo blanco como el acetato.

Espectro de masa $(M+H)^+$ 1204,5 (Calculado 1204,6).

Tiempo de elución en HPLC: 8,2 min

Condiciones de elución:

Columna YMC-AM301 (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 80/20-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 17]

(Procedimiento de síntesis P): La preparación de des(1-6)-Dibencilcarbamoil-[AzaGly7,Arg(Me)9,Trp10]MS10

(Compuesto No. 393)

Después que 35,2 mg (0,015 mmol) de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink fue hinchada en DMF, la resina fue tratada con 2 ml de solución al 20% de piperidina/DMF durante 20 minutos para eliminar el grupo Fmoc. Separadamente, 19,2 µL (0,1 mmol) de dibencilamina fue disuelta en THF. Bajo enfriamiento con hielo, fue agregado 16,2 mg (0,1 mmol) de CDI y 2,6 µL (0,015 mmol) de DIEA a la solución, seguido por agitación a temperatura ambiente durante una hora. Luego de desprotección Fmoc, la solución resultante fue agregada a resina MBHA Amida H-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink, seguido por agitación a temperatura ambiente durante 15 horas.

A la resina MBHA Amida Bzl$_2$NCO-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink obtenida, fue agregado 1 mL de TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2,5/2,5), y la mezcla fue agitada durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido dos veces para lavarlo. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada a una velocidad del flujo de 8 ml/min con eluyentes A/B: 63/37-53/47 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contiene acetonitrilo en HPLC preparativa usando una columna YMC

SH-343-5' S-5, 120A (20 x 250 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas. Se disolvieron los polvos blancos obtenidos en 10 mL de agua y fue agregado a la solución 100 μL de resina intercambiadora de iones BioRAD AG1 x8 AcO^-. Mientras fue agitada a mano la solución a veces, la solución de reacción se dejó en reposo durante una hora. La solución fue filtrada a través de un filtro de membrana para eliminar la resina y dar 2,2 mg de polvo blanco como acetato.

Espectro de masa $(M+H)^+$ 768,7 (Calc. 768,4).

Tiempo de elución en HPLC: 16,9 min.

Condiciones de elución:

La columna YMC-AM301 (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 80/20-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 18]

(Procedimiento de síntesis Q): Preparación de des(1-5)-Benzoil-[6ψ7,CH_2O,Arg(Me)9,Trp10]MS10 (Compuesto No. 421)

Después que 1,80 g de Z-Phe fue disuelto en 20 mL de MeOH, fueron agregados 73 mg de DMAP y 1,38 g de WSCD HCl a la solución a 0°C, seguido por agitación a 4°C durante 12 horas. El solvente fue concentrado y el concentrado fue disuelto en AcOEt. La solución fue lavada entonces

con una solución acuosa de 1N HCl, el solución acousa saturada de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado para dar Z-Phe-OMe como aceite. Luego de disolver en 20 mL de THF seco, fue agregado a la solución 196 mg de $LiBH_4$, seguido por agitación a temperatura ambiente durante 15 horas. El solvente fue concentrado y el residuo fue disuelto en AcOEt y la solución lavada con una solución acuosa 1N HCl, solución acousa saturada de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado y fue agregado éter-éter de petróleo a la concentración para dar 1,45 g (rendimiento 85%) de Z-Phe-ol como precipitado. Después que fue suspendido 60 mg NaH al 60% en 10 mL de THF seco, fueron agregados 285 mg de Z-Phe-ol, 264 mg de 18-crown-6 y 1,48 mL de bromoacetato de terc-butilo a la solución a 0°C. Al volver a la temperatura ambiente, la mezcla fue agitada durante 15 horas. Después que el solvente fue destilado en vacío, el residuo fue disuelto en AcOEt y lavado con una solución acuosa 1N HCl, solución acousa salina $NaHCO_3$ y solución acousa saturada de NaCl. Luego de secar sobre Na_2SO_4, el solvente fue concentrado y el concentrado fue purificado por cromatografía en columna de enrasado para dar 217 mg (rendimiento 54%) de Z-Pheψ(CH_2O)Gly-OBu^t como aceite. Después que 160 mg de Z-Pheψ(CH_2O)Gly-OBu^t fue disuelto en 20 mL de MeOH, fue agregado Pd-C al 10% a la

solución, seguida por hidrogenación catalizadora durante 3 horas en un flujo de nitrógeno. El catalizador fue eliminado por filtración y el solvente fue concentrado seguido por su secado. La concentración fue disuelta en 15 mL de DCM, y fueron agregados 114 mg de Fmoc-Cl y 139 µL de DIEA a la solución, luego de agitación durante 12 horas. Después que el solvente fue destilado, el residuo fue disuelto en AcOEt y la solución lavada con una solución acuosa de 1N HCl, solución acousa saturada de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secar sobre Na_2SO_4, el solvente fue concentrado y el concentrado fue purificado por la cromatografía en columna de enrasado. Fue agregado dietil éter-éter de petróleo para dar 150 mg (rendimiento 77%) de Fmoc-Pheψ(CH_2O)Gly-OBu^t como precipitado. Al precipitado, fue agregado 31 mg (15 µmol) de resina MBHA amida H-LeuArg(Me,Boc_2)Trp(Boc)-Rink obtenida de una manera similar al proceso del EJEMPLO 15, 19 mg de Fmoc-Pheψ(CH_2O)Gly-OH (preparado tratando Fmoc-Pheψ(CH_2O)Gly-OBut con TFA/DCM al 50% durante una hora), 180 µL de 0,5M HOAt, 42 mg de PyBrop y 47 µL de DIEA. La mezcla fue agitada durante 18 horas. Después que se lavó la resina, fue agregado a la resina 5 mL de piperidina/DMF al 20%, seguido por agitación a temperatura ambiente durante 30 minutos. Después que se lavó la resina, fueron agregados a la resina 9 µL de cloruro de benzoilo, 13 µL de DIEA y 1 mL de DMF, seguido por agitación a temperatura ambiente

durante 2 horas. Después que fue lavada y secada la resina, fueron agregados a la resina 200 µL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5), luego de agitación durante 2 horas. Fue agregado éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada con eluyentes A/B: 75/25-65/35 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contiene acetonitrilo en HPLC preparativa usando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 2,5 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 782,2 (Calc. 782,4).

Tiempo de elución en HPLC: 22,1 min.

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-0/50, usando TFA 0,1% en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 19]

(Procedimiento de síntesis R): La preparación de des(1-

7)-Dibencilaminocarbamoilacetil-[Arg(Me)9,Trp10]MS10

(Compuesto No. 434)

Luego que 1,54 mL de malonato de mono-terc-butilo, fueron agregados a la solución 1,08 g de fluorenilmetanol y 61 mg de DMAP fue disuelto en 20 mL de DCM 20, 1,15 g de WSCD HCl, seguido por agitación a temperatura ambiente durante 24 horas. El solvente fue destilado en vacío, el residuo fue disuelto en AcOEt. La solución fue lavada entonces con una solución acuosa de 1N HCl, solución acousa saturada de NaHCO3 y después con una solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado y el concentrado fue purificado por cromatografía en columna de enrasado para dar 1,62 g (rendimiento 96%) de malonato de terc-butil fluorenilmetilo. En 20 mL de TFA, fueron disueltos 61 mg de malonato de terc-butil fluorenilmetilo y la solución fue agitada a temperatura ambiente durante 2 horas. Después que el solvente fue destilado al vacío, el residuo fue disuelto en AcOEt, seguido de un lavado con solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado y purificado por cromatografía en columna de enrasado para dar 850 mg (rendimiento 67%) de malonato de mono-fluorenilmetilo. Después que 5 mL de piperidina/DMF al 20% fueran agregado a 46 mg (15 μmol) de resina MBHA ámida Fmoc-LeuArg(Me,Boc_2)Trp(Boc)-Rink preparada de una manera similar a la del EJEMPLO 15, la solución se agitó a

temperatura ambiente durante 30 minutos. Después que fue lavada la resina, fueron agregados a la resina 42 mg de malonato de mono-fluorenilmetilo, 70 mg de PyBrop, 300 µL de 0,5M HOAt/DMF, 52 µL de DIEA y 1 mL de DMF, y la mezcla fue agitada durante 15 horas. Luego este procedimiento se repitió dos veces, fueron agregados 8 µL de Ac_2O, 5 µL de DIEA y 2 mL de DCM, seguido de agitación a temperatura ambiente durante 30 minutos. Luego la resina fue lavada y secada, fue agregado 5 mL de piperidina/DMF al 20% a la mitad de la resina, seguido por agitación a temperatura ambiente durante 30 minutos. Después que fue lavada la resina, fueron agregados 13 mg de dibencilhidrazina, 28 mg de PyBrop, 120 µL de 0,5M HOAt/DMF, 21 µL de DIEA y 1 mL de DMF a la resina, luego de agitación durante 15 horas. Luego la resina fue lavada y secada, fue agregado 200 µL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5) a la resina, luego de agitación durante 2 horas. Fue agregado éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (120 minutos) fue realizada con eluyentes A/B: 83/17-63/37 usando: 0,1% TFA en agua y eluyente B: 0,1% que TFA que contenia acetonitrilo en HPLC preparativa usando una columna YMC

D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 21,6 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 767,6 (Calc. 767,4).

Tiempo de elución en HPLC: 14,5 min

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 20]

(Procedimiento de síntesis S): Preparación de des(1-5)-4-Piridincarbonil-[AzaGli7,Arg(Me)9,Trp10]MS10 (Compuesto No. 436)

Después que 340,1 mg (0,1 mmol) de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink se permite agrandar en DMF, la resina fue tratada en 20 ml de solución al 20% de piperidina/DMF durante 20 minutos para eliminar el grupo Fmoc. La resina obtenida fue lavada con DMF y fue tratada con 155,0 mg (0,4 mmol) de Fmoc-Phe-OH, 63,6 µL (0,4 mmol) de DIPCDI y 0,8 mL (0,4 mmol) de solución de 0,5M HOAt/DMF a temperatura ambiente durante 90 minutos para introducir Phe. Después que la resina MBHA Amida Fmoc-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink obtenida fue sometida a desprotección Fmoc y después fue

tratada con 49,2 mg (0,4 mmol) de ácido 4-Piridincarboxílico, 63,6 µL (0,4 mmol) de DIPCDI y 0,8 mL (0,4 mmol) de solución HOAt/DMF 0,5M a temperatura ambiente durante 90 minutos. Entonces, la resina fue lavada y secada para dar 353,5 mg de resina MBHA Amida 4-Piridincarbonil-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink. A la resina resultante, fue agregado 3,5 mL de TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2,5/2,5) y la mezcla fue agitada durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido dos veces para lavarlo. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada a una velocidad del flujo de 15 ml/min con eluyentes A/B: 79/21-69/31 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contenia acetonitrilo en HPLC preparativa usando una columna YMC Pack R&D-ODS-5-B S-5 120Å (30 x 250 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas. Se disolvieron los polvos blancos obtenidos en 6 mL de agua y fue agregado a la solución 200 µL de resina intercambiadora de iones BioRAD AG1 x8 AcO^-. Mientras fue agitada a mano la solución a veces, luego la solución de reacción permanece en reposo durante una hora. La solución fue filtrada a través de un filtro de

membrana para eliminar la resina y da 21,6 mg de polvo blanco como acetato.

Espectro de masa $(M+H)^+$ 797,8 (Calculado 797,4).

Tiempo de elución en HPLC: 8,8 min.

Condiciones de elución:

La columna YMC-AM301 (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 80/20-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contiene acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 21]

(Procedimiento de síntesis T): Preparación de des(1-3)-3-Fenilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 499)

Después que 170,1 mg (0,05 mmol) de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink se permite agrandar en DMF, la resina fue tratada con 5 ml de solución al 20% piperidina/DMF durante 20 minutos para eliminar el grupo Fmoc. La resina obtenida fue lavada con DMF y fue tratada con 77,5 mg (0,2 mmol) de Fmoc-Phe-OH, 31,8 µL (0,2 mmol) de DIPCDI, y 0,4 mL (0,2 mmol) de solución de 0,5M HOAt/DMF a temperatura ambiente durante 90 minutos para introducir Phe. De una manera similar, fue introducido Ser(^{t}Bu) y Asn(Trt) para dar resina MBHA Amida Fmoc-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink. La resina obtenida fue sometida a

desprotección Fmoc y entonces fue tratada con 30,0 mg (0,2 mmol) de ácido fenilpropiónico, 31,8 µL (0,2 mmol) de DIPCDI y 0,4 mL (0,2 mmol) de solución de HOAt/DMF 0,5M a temperatura ambiente durante 90 minutos. Entonces, la resina fue lavada y secada para dar 209,6 mg de resina MBHA Amida 3-fenilpropionil-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink. A la resina obtenida, fue agregado 1,5 mL de TFA/PhSMe/m-cresol/H2O/TIS/EDT (80/5/5/5/2,5/2,5) y la mezcla fue agitada durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido dos veces para lavarlo. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada a una velocidad del flujo de 8 ml/min con eluyentes A/B: 71/29-61/39 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contenia acetonitrilo en HPLC preparativa usando una columna YMC SH-343-5 S-5 120A (20 x 250 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas. Se disolvieron los polvos blancos obtenidos en 10 mL de agua y fue agregado a la solución 125 µL de resina de intercambio de iones BioRAD AG1 x 8 AcO^-. Mientras fue agitada a mano la solución a veces, luego la solución de reacción permanece en reposo durante una hora. La solución fue filtrada a través de un filtro de membrana

para eliminar la resina y da 5,2 mg de polvo blanco como acetato.

Espectro de masa $(M+H)^+$ 1025,3 (Calc. 1025,5).

Tiempo de elución en HPLC: 13,6 min.

Condiciones de elución:

La columna YMC-AM301 (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 80/20-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA el cual además contenia acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 22]

(Procedimiento de síntesis U): Preparación de des(1-5)-Benzoil-[AzaPhe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 431)

Después que 500 mg (2,56 mmol) de bencilhidracina.2HCl fue disuelto en DCM, la solución fue enfriada a -78°C en hielo seco. Entonces, fueron agregados a la solución 727,1 mg (3,33 mmol) de Boc_2O y 0,982 ml (5,64 mmol) de DIEA. El hielo seco fue retirado y la mezcla fue agitada durante 30 minutos. Luego de confirmar por TLC el avance de la reacción, fueron agregados a la mezcla 327 µl (2,82 mmol) de cloruro de benzoilo y 580,4 µl (333 mmol) de DIEA, seguido por agitación toda la noche a la temperatura ambiente. Fueron agregados cristales de ácido cítrico a la solución de reacción y la mezcla fue concentrada. Fue agregado a la

mezcla una solución acuosa al 10% de ácido cítrico. El residuo precipitado fue extraído con AcOEt y el extracto fue lavado con una solución acuosa al 10% ácido cítrico, una solución acuosa al 5% de $NaHCO_3$ y después con una solución acousa saturada de NaCl, seguido de secado sobre Na_2SO_4 anhidro. El residuo obtenido se cristalizó de éter-hexano (1:1) para dar 435,5 mg de cristales blancos.

Después que 46,3 mg (0,015 mmol) de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-NH-Rink se permiten agrandar en DMF, la resina fue tratada con 5 ml de solución al 20% de piperidina/DMF durante 20 minutos para eliminar el grupo Fmoc. La resina obtenida fue lavada con DMF y fue tratada en THF con 3,65 mg (0,023 mmol) de CDI a temperatura ambiente durante una hora. Separadamente, 32,6 mg (0,1 mmol) del polvo blanco citado anteriormente fue tratado con 0,3 ml de 4N HCl/dioxano durante una hora. El solvente entonces fue destilado y el residuo fue lavado con éter. El residuo obtenido fue disuelto en THF, fue agregado a la solución y 17,4 µl (0,1 mmol) de DIEA. La solución resultante fue agregada a la resina, seguido por agitación toda la noche. La resina fue lavada y secada para dar 29,5 mg resina MBHA Amida Benzoil-AzaPhe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-NH-Rink.
A la resina obtenida, fueron agregados 0,5 mL de TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2,5/2,5) y la mezcla fue agitada durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado

resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido dos veces para lavarlo. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada a una velocidad de flujo de 8 ml/min con eluyentes A/B: 66/34-56/44 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contenia acetonitrilo en HPLC preparativa usando una columna YMC SH-343-5 S-5 120A (20 x 250 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 3,2 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 797,7 (Calculado 797,4).

Tiempo de elución en HPLC: 15,3 min.

Condiciones de elución:

La columna YMC-AM301 (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 80/20-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contenia acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 23]

(Procedimiento de síntesis V): Preparación de des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10ψ,CSNH]MS10 (Compuesto No. 548)

Fue introducido Fmoc-Leu-OH en resina 2-clorotritilcloruro disponible comercialmente. Luego de

desprotección de Fmoc, fue agregado 5 mL de THF y 162 mg de CDI a 403 mg de resina Fmoc-Leu-O-Clt obtenida (sub. 0,62 mmol/g). La mezcla fue agitada durante una hora. Después que 97 µL de monohidrato de hidrazina fue agregado al sistema, la mezcla fue agitada durante 2 horas y la resina fue lavada entonces. A la resina, fueron agregados 581 mg de Fmoc-Phe, 699 mg de PyBrop, 3 mL de una solución 0,5M de HOAt/DMF y 784 µL de DIEA, luego de agitación durante 12 horas. Después que fue lavada la resina, la cadena de péptido fue extendida en un ABI 433A dar 0,47 g de resina Boc-d-Tyr(Bu^t)$_D$-Pya(4)Asn(Trt)Ser(Bu^t)PheAzaGlyLeu-O-Clt. A la resina, fue agregado 10 mL de AcOH/TFE/DCM (1/1/8), luego de agitación durante 30 minutos. La resina fue eliminada por la filtración y el solvente fue concentrado. El residuo fue disuelto en el cloroformo y la solución resultante fue lavada con solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado y fue agregado AcOEt-dietil éter a la concentración para dar 320 mg (rendimiento 98%) de Boc-$_D$-Tyr(Bu^t)$_D$-Pya(4)Asn(Trt)Ser(Bu^t)PheAzaGlyLeu-OH como precipitado. Por otro lado, 5 mL de HCl/AcOEt 4N fue agregado a 264 mg (1 mmol) de Boc-Phe-NH_2 bajo enfriamiento con hielo, seguido de agitación durante 30 minutos. El solvente fue destilado y entonces fue agregado éter para precipitación. El precipitado fue disuelto en 20 mL de DMF, y fueron agregados a la solución 455 mg de Fmoc-

Orn(Boc), 540 mg de HOBt, 382 mg de WSCD.HCl y 348 µL de DIEA, luego de agitación durante 6 horas. Después que el solvente fue destilado al vacío, el residuo fue disuelto en acetato de etilo y la solución lavada con una solución acuosa de 1N HCl, solución acousa saturada de $NaHCO_3$ y después con una solución acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado. Fue agregado éter-éter de petróleo a la concentración para dar 594,4 mg (rendimiento 99%) de Fmoc-Orn(Boc)-Phe-NH_2 como precipitado. Bajo enfriamiento con hielo, 5 mL de HCl/AcOEt 4N fue agregado a 132 mg del producto, seguido de agitación durante 30 minutos. Después que el solvente fue destilado, fue agregado éter para dar 111,1 mg (rendimiento 94%) de Fmoc-Orn-Phe-NH_2.HCl como precipitado. El precipitado fue disuelto en 3 mL de cloroformo/TFE (3/1), y fueron agregados 194 mg de N-metil-N,N'-bis-Boc-1-guanilpirazol obtenido en el EJEMPLO DE REFERENCIA 1 y 105 µL de DIEA a la solución, luego de agitación durante 24 horas. Después que el solvente fue destilado, fue agregado éter-éter de petróleo para dar 108,5 mg (rendimiento 72%) de Fmoc-Arg(Boc_2,Me)-Phe-NH_2 como precipitado. En 5 mL de THF, 38 mg del producto fue disuelto y 142 mg del reactivo de Lawesson fue agregado a la solución, luego de agitación durante 15 horas. Después que el solvente fue destilado al vacío, el residuo fue disuelto en acetato de etilo y la solución lavada con una solución acuosa de $NaHCO_3$ y después con una solución

acousa saturada de NaCl. Luego de secado sobre Na_2SO_4, el solvente fue concentrado. Luego de la purificación por cromatografía en columna de enrasado, fue agregado éter-éter de petróleo para dar 18,7 mg (rendimiento 48%) de Fmoc-Arg(Me,Boc_2)-Pheψ(CSNH)-NH_2 como precipitado. A 11 mg del producto, 1 mL de DEA/DMF 10% fue agregado y la mezcla fue agitada durante 2 horas. Después que el solvente fue destilado, el residuo fue disuelto en 1 mL de DMF, y 18 mg de Boc-$_D$-Tyr(Bu^t)-$_D$-Pya(4)-Asn(Trt)-Ser(Bu^t)-Phe-AzaGly-Leu-OH previamente obtenido, fueron agregados 7,6 mg de HOBt, 5,4 mg de WSCD.HCl y 4,9 µL de DIEA a la solución, luego de agitación durante 15 horas. El solvente fue destilado y fue agregado éter al residuo para precipitación. Al precipitado, fue agregado 1 mL de TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2,5/2,5), y la mezcla fue agitada durante 2 horas. Fue agregado éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido para lavado. El residuo fue extraído con una solución acuosa de ácido acético y el extracto fue filtrado para eliminar la resina. Entonces, la elución de pendiente de densidad lineal (60 minutos) fue realizada con eluyentes A/B: 82/18-72/28 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contenia acetonitrilo en HPLC preparativa usando una columna YMC D-ODS-5-ST S-5 120A (20 x 150 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas

para dar 0,9 mg de polvo blanco.

Espectro de masa $(M+H)^+$ 1181,5 (Calculado 1181,6).

Tiempo de elución en HPLC: 14,9 min.

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-0/50, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contenia acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 24]

(Procedimiento de síntesis W): La preparación de des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

(Compuesto No. 550)

Después que 5 g (0,4 mmol/g) de resina MBHA Amida Rink disponible comercialmente se permiten agrandar en DMF, la resina fue tratada con 50 ml solución piperidina/DMF al 20% durante 20 minutos para eliminar grupo Fmoc. Después que la resina obtenida fue lavada con DMF, Trp(Boc) fue introducido por tratamiento la resina con 4,213 g (8 mmol) de Fmoc-Trp(Boc)-OH, 1,272 mL (8 mmol) de DIPCDI y 16 mL (8 mmol) de solución 0,5M HOAt/DMF a temperatura ambiente durante 90 minutos. De una manera similar, fue introducido Orn(Mtt) para dar 2 mmol resina MBHA Amida Fmoc-Orn(Mtt)-Trp(Boc)-Rink. La resina obtenida fue lavada con DCM, después de inflar, fue agregado 50 mL de TFA/TIS/TFE/DCM (1/5/19/75), la

mezcla fue agitada durante 10 minutos y la solución fue destilada. Este procedimiento fue repetido hasta que el colorido amarillo causado por el grupo Mtt en estado libre en una solución TFA/TIS/TFE/DCM(1/5/19/75) desapareciera cuando la solución fue agregada, así el grupo Mtt fue eliminado.

La resina MBHA Amida Fmoc-Orn-Trp(Boc)-Rink resultante fue neutralizada con una solución DIEA/DCM al 5%. Luego de lavar con DCM, fueron agregados a la resina 25 mL de DCM-TFE (4:1) y 1,946 g (6 mmol) de N-metil-N,N'-bis-Boc-1-guanilpirazol obtenido en el EJEMPLO DE REFERENCIA 1. Fue agregado a la mezcla DIEA para ajustar pH de la solución a 10, y la mezcla fue agitada durante 15 horas para dar la resina MBHA Amida Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink. Fue introducido Fmoc-Leu en la resina obtenida de la misma manera descripta anteriormente. El grupo Fmoc fue eliminado de la resina MBHA Amida Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink obtenida (2 mmol) para dar la resina MBHA Amida H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink (2 mmol).

Separadamente, fue suspendido 2,326 g (8 mmol) de Fmoc-$NHNH_2$.HCl en 20 mL de DMF. Bajo enfriamiento con hielo, una suspensión de 297 mg (8 mmol) de CDI en 20 mL de THF y entonces 2,787 mL (16 mmol) de DIEA fue agregado a la suspensión, seguido por agitación a temperatura ambiente durante una hora. La solución de reacción resultante fue agregada a la resina MBHA Amida H-Leu-

Arg(Boc_2,Me)-Trp(Boc)-Rink descrita anteriormente, seguido por agitación a temperatura ambiente durante 15 horas. Luego de completada la reacción, la resina fue lavada y secada para dar 6,394 g resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink.

Luego 3,197 g (1 mmol) de la resina obtenida se permite agrandar en DMF, la resina fue tratada con 30 ml de solución al 20% de piperidina/DMF durante 20 minutos para eliminar el grupo Fmoc. Luego la resina obtenida fue lavada con DMF, la resina fue tratada con 1,806 g (4 mmol) de Trt-Phe-OH.0,5AcOEt; 2,086 g (4 mmol) de PyAOP, 8 mL (4 mmol) de HOAt/DMF 0,5M y 2,787 mL (16 mmol) de DIEA a temperatura ambiente durante 90 minutos para dar resina MBHA Amida fenil Trt-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink. La resina obtenida fue lavada con DCM, después se infló, fue agregado 30 mL de TFA/TIS/TFE/DCM (1/5/19/75), la mezcla fue agitada durante 10 minutos y la solución fue destilada. Este procedimiento fue repetido hasta que coloreado amarillo causado por el grupo Trt en estado libre en una solución TFA/TIS/TFE/DCM (1/5/19/75) desapareciera cuando la solución fue agregada, así el grupo Trt fue eliminado. La resina MBHA Amida H-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink obtenida fue neutralizada con una solución de DIEA/DMF al 5% y fue lavada con DMF. Luego de esto, la resina fue tratada con 1,590 g (4 mmol) de Fmoc-Thr(^{t}Bu)-OH, 0,636 mL (4 mmol) de DIPCDI y 8 mL (4 mmol) de 0,5M HOAt/DMF a

temperatura ambiente durante 90 minutos para introducir Thr(^{t}Bu). Subsiguientemente, la desprotección de Fmoc por tratamiento con 30 ml de solución 20% de piperidina/DMF por 20 minutos y condensación por método DIPCDI/HOAt similar a la introducción de Thr(^{t}Bu) fue repetida de manera tal que Asn(Trt), $_D$-Trp(Boc), y D-Tyr(^{t}Bu) fueron introducidos para dar la resina MBHA Amida Fmoc-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink. La resina obtenida fue tratada con 30 ml de solución al 20% de piperidina/DMF durante 20 minutos para eliminar el grupo Fmoc. La resina obtenida fue lavada para dar resina MBHA Amida H-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink. La resina obtenida fue tratada con 188,7 µL (2 mmol) de Ac_2O y 348,4 µL (2 mmol) de DIEA en 20 mL de DMF a temperatura ambiente durante 30 minutos para acetilar el N terminal. La resina fue lavada entonces y secada para dar 4,168 g de resina MBHA Amida Ac-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink.

A la mitad de la resina obtenida, es decir, 2,111 g, le fue agregada 15 mL de TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5 /5/2,5/2,5) y la mezcla fue agitada durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido dos veces para lavado. Después que el residuo

fue extraído con una solución acuosa de ácido acético, el extracto fue filtrado para eliminar la resina y fue liofilizo para dar polvo de péptido en bruto. Con respecto a la mitad restante de la resina, la desprotección fue realizada bajo las mismas condiciones para dar aproximadamente 650 mg en total de péptido en bruto en forma de polvo. Aproximadamente 50 mg de cada uno de los péptidos en bruto obtenidos fueron purificados aplicando secuencialmente la elución de pendiente de densidad lineal (60 minutos) a una velocidad de flujo de 15 ml/min con eluyentes A/B: 71/29-61/39 usando: 0,1% TFA en agua y eluyente B: 0,1% TFA que contenía acetonitrilo en HPLC preparativa usando columna YMC Pack R&D-ODS-5-B S-5, 120A (30 x 250 mm). Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 255,5 mg de polvo blanco como la muestra purificada.

Todos los polvos blancos fueron disueltos en 200 mL de solución de acetonitrilo acuoso y fue agregado a la solución 492 µL de resina de intercambio de iones AG1 x 8 AcO^- que se obtuvo convirtiendo el BioRAD AG1 x 8 Cl^- disponible comercialmente en el tipo acetato de una manera convencional. Mientras fue agitada a mano la solución a veces, después la solución de reacción permanece en reposo durante una hora. La solución fue concentrada para eliminar el acetonitrilo lo mas posible. La concentración fue filtrada entonces a través de un filtro de membrana y fue liofilizada para dar 225,3 mg de

polvo blanco como acetato.

Espectro de masa $(M+H)^+$ 1298,7 (Calculado 1298,6)

Tiempo de elución en HPLC: 15,6 min

Condiciones de elución:

Columna YMC-AM301 (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 80/20-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contenia acetonitrilo (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 25]

Preparación de des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 562)

Después que 5,455 g (0,455 mmol/g) de resina MBHA Amida Rink disponible comercialmente se permite agrandar en DMF, la resina fue tratada con 50 ml de una solución al 20% de piperidina/DMF durante 20 minutos para eliminar el grupo Fmoc. Después que la resina obtenida fue lavada con DMF, fue introducido para tratamiento Trp(Boc) a la resina con 6,319 g (12 mmol) de Fmoc-Trp(Boc)-OH, 1,908 mL (12 mmol) de DIPCDI y 24 mL (12 mmol) de una solución de HOAt/DMF 0,5M a temperatura ambiente durante 90 minutos para dar resina MBHA Amida Fmoc-Trp(Boc)-Rink. De una manera similar, fue introducido Orn(Mtt) para dar 3 mmol de resina MBHA Amida Fmoc-Orn(Mtt)-Trp(Boc)-Rink. La resina obtenida fue lavada con DCM, después se infló, fue

agregado 75 mL de TFA/TIS/TFE/DCM (1/5/19/75), la mezcla fue agitada durante 10 minutos y la solución fue destilada. Este procedimiento fue repetido hasta que el coloreado amarillo causado por el grupo Mtt en estado libre en solución de TFA/TIS/TFE/DCM(1/5/19/75) desapareciera cuando la solución era agregada, así el grupo Mtt fue eliminado.

La resina MBHA Amida Fmoc-Orn-Trp(Boc)-Rink resultante fue neutralizada con una solución DIEA/DCM al 5%. Luego de lavar con DCM, fueron agregados a la resina 40 mL de DCM-TFE (4:1) y 2,919 g (9 mmol) de N-metil-N,N'-bis-Boc-1-guanilpirazol obtenido en el EJEMPLO DE REFERENCIA 1. fue agregado DIEA a la mezcla para ajustar pH de la solución a 10, y la mezcla fue agitada durante 15 horas para dar resina MBHA Amida Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink. Fue introducido Fmoc-Leu en la resina obtenida de la misma manera descrita anteriormente. El grupo Fmoc fue eliminado de la resina MBHA Amida Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink obtenida (2 mmol) para dar la resina MBHA Amida H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink (2 mmol).

Separadamente, fue suspendido 3,489 g (12 mmol) de Fmoc-$NHNH_2$.HCl en 30 mL de DMF. Bajo enfriamiento con hielo, fueron agregados una suspensión de 1,849 mg (11,4 mmol) de CDI en 20 mL de THF y luego 4,181 mL (24 mmol) de DIEA a la suspensión, seguido por agitación a temperatura ambiente durante una hora. La solución de

reacción resultante fue agregada a la resina MBHA Amida H-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink descrita anteriormente, seguido por agitación a temperatura ambiente durante 15 horas. Luego de completada la reacción, la resina fue lavada y secada para dar 8,2496 g de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink.

Luego 2,646 g (1 mmol) de la resina obtenida se permiten agrandar en DMF, la resina fue tratada con 30 ml de una solución de piperidina/DMF al 20% durante 20 minutos para eliminar el grupo Fmoc. Después que la resina obtenida fue lavada con DMF, la resina fue tratada con 1,630 g (4 mmol) de Trt-Phe-OH, 2,086 g (4 mmol) de PyAOP, 8 mL (4 mmol) de HOAt/DMF 0,5M y 2,787 mL (16 mmol) de DIEA a temperatura ambiente durante 90 minutos para dar resina MBHA Amida Trt-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Phe. La resina obtenida fue lavada con DCM, después inflada, fue agregado 30 mL de TFA/TIS/TFE/DCM (1/5/19/75), la mezcla fue agitada durante 10 minutos y la solución fue destilada. Este procedimiento fue repetido hasta que el colorido amarillo causado por el grupo Trt en estado libre desapareciera en un solución TFA/TIS/TFE/DCM (1/5/19/75) cuando la solución sea agregada, así el grupo Trt fue eliminado. La resina MBHA Amida H-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink obtenida se neutralizó con una solución de DIEA/DMF al 5% y se lavó con DMF. Luego de esto, la resina fue tratada con 1,590 g (4 mmol) de Fmoc-Thr(^{t}Bu)-OH, 0,636

mL (4 mmol) de DIPCDI y 8 mL (4 mmol) de HOAt/DMF 0,5M a temperatura ambiente durante 90 minutos para introducir Thr(^{t}Bu). Como consecuencia, la desprotección de Fmoc por tratamiento con 30 ml de una solución de piperidina/DMF al 20% durante 20 minutos y condensación por el método similar de DIPCDI/HOAt a la introducción de Thr(^{t}Bu) fue realizado para dar resina MBHA Amida Fmoc-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink. La resina obtenida fue Fmoc-desprotegido. Entonces la resina fue tratada con 1,476 g (3,8 mmol) de Fmoc-$_D$-Pya(4)-OH, 2,086 mg (4 mmol) de PyAOP, 8 mL de HOAt/DMF 0,5 M (4 mmol) y 2,439 mL de DIEA (14 mmol) a temperatura ambiente durante 90 minutos para introducir $_D$-Pya(4). A consecuencia, por el método similar de DIPCDI/HOAt a la introducción de Thr(^{t}Bu), $_D$-Tyr(^{t}Bu) fue intrdocido a la resina para dar resina MBHA Amida Fmoc-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink. La resina obtenida fue tratada con 30 ml de una solución de piperidina/DMF al 20% durante 20 minutos para eliminar el grupo Fmoc. La resina obtenida fue lavada para dar resina MBHA Amida H-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink. La resina obtenida fue tratada con 188,7 µL (2 mmol) de Ac_2O y 348,4 µL (2 mmol) de DIEA en 20 mL de DMF a temperatura ambiente durante 30 minutos a acetilato el terminado de N. La resina entonces se lavó y secó para dar 1 mmol de resina MBHA Amida Ac-$_D$-Tyr(^{t}Bu)-$_D$-

Pya(4)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink.

A la resina obtenida, le fue agregada 30 mL de TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2,5/2,5) y la mezcla fue agitada durante 90 minutos. Fue agregado dietil éter a la solución de reacción, el precipitado resultante fue centrifugado y el sobrenadante fue eliminado. Este procedimiento fue repetido dos veces para lavarlo. Después que el residuo fue extraído con una solución acuosa de ácido acético, el extracto fue filtrado para eliminar la resina y liofilizado para dar 949,0 mg de polvo de péptido en bruto. Aproximadamente 50 mg de aquel péptido en bruto obtenido fue purificado aplicando HPLC preparativa utilizando una columna YMC Pack R&D-ODS-5-B S-5 120A (30 x 250 mm) a una velocidad de flujo de 15 ml/min con eluyentes iniciales A/B: 90/10 durante 8 minutos, A/B: 75/25, el que tomó 7 minutos para aumentar la concentración, y pendiente de elución de densidad lineal (60 minutos) con eluyentes A/B: 75/25-65/35 usando eluyente A: 0,05% TFA en agua y eluyente B: 0,05% TFA-que contenia acetonitrilo. Las fracciones que contienen el producto fueron recolectadas y liofilizadas para dar 361,1 mg de polvo blanco como muestra purificada.

Todo el polvo blanco obtenido fue disuelto en 200 mL de solución acuosa de acetonitrilo y fue agregado a la solución 1,434 mL de resina de intercambio de iones AG1 x

8 AcO^- que se obtuvo convirtiendo BioRAD AG1 x 8 Cl^- disponible comercialmente en el tipo de acetato de manera convencional. Mientras fue agitada a mano la solución a veces, luego la solución de reacción permanece en reposo durante una hora. La solución fue concentrada para eliminar tanto como sea posible el acetonitrilo. La concentración fue filtrada entonces a través de un filtro de membrana y liofilizada para dar 309,3 mg de polvo blanco como acetato. Espectro de masa $(M+H)^+$ 1260,4 (Calculado 1260,4).

Tiempo de elución en HPLC: 15,5 min.

Condiciones de elución:

Columna: Wakosil-II 5C18 HG (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 100/0-50/50, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contenia acetonitrilo como el eluyente B (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 26]

Preparación de des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10 (Compuesto No. 571)

Después que 2,5 g (0,4 mmol/g) de resina MBHA Amida Rink disponible comercialmente se permiten agrandar en DMF, la resina fue tratada con 50 ml de una solución de piperidina/DMF al 20% durante 20 minutos para eliminar el grupo Fmoc. Después que la resina obtenida fue lavada con DMF, fue introducido Phe tratando la resina con 1,550 g

(4 mmol) de Fmoc-Phe-OH, 0,636 mL (4 mmol) de DIPCDI y 8 mL (4 mmol) de una solución de HOAt/DMF 0,5 M a temperatura ambiente durante 90 minutos para dar resina MBHA Amida Fmoc-Phe-Rink. De manera similar, fue introducido Orn(Mtt) para dar 1 mmol de resina MBHA Amida Fmoc-Orn(Mtt)-Trp(Boc)-Rink. La resina obtenida fue lavada con DCM, después inflada, fue agregado 25 mL de TFA/TIS/TFE/DCM (1/5/19/75), la mezcla fue agitada durante 10 minutos y la solución fue destilada. Este procedimiento fue repetido hasta que el colorido amarillo causado por El grupo Mtt en estado libre desapareciera en una solución TFA/TIS/TFE/DCM(1/5/19/75) cuando la solución sea agregada, así el grupo Mtt fue eliminado.

La resina MBHA Amida Fmoc-Orn-Phe-Rink resultante fue neutralizada con una solución de DIEA/DCM al 5%. Luego de lavar con DCM, fueron agregados a la resina 25 mL de DCM-TFE (4:1) y 0,973 g (3 mmol) de N-metil-N,N'-bis-Boc-1-guanilpirazol obtenido en el EJEMPLO DE REFERENCIA 1. DIEA fue agregado a la mezcla para ajustar pH de la solución a 10, y la mezcla fue agitada durante 15 horas para dar resina MBHA Amida Fmoc-Arg(Boc$_2$,Me)-Phe-Rink. Fue introducido Fmoc-Leu en la resina obtenida de la misma manera descrita anteriormente. El grupo Fmoc fue eliminado la resina MBHA Amida Fmoc-Leu-Arg(Boc$_2$,Me)-Phe-Rink obtenida (1 mmol) para dar resina MBHA Amida H-Leu-Arg(Boc$_2$,Me)-Phe-Rink (1 mmol).

Separadamente, 1,163 g (4 mmol) de Fmoc-NHNH$_2$.HCl

fue suspendido en 10 mL de DMF. Bajo enfriamiento con hielo, fueron agregados a la suspensión, una suspensión de 0,568 mg (3,5 mmol) de CDI en 10 mL de THF y después 1,307 mL (7,5 mmol) de DIEA, seguido por agitación a temperatura ambiente durante una hora. La solución de reacción resultante fue agregada a resina MBHA Amida H-Leu-Arg(Boc$_2$,Me)-Phe-Rink descrita anteriormente, seguido por agitación a temperatura ambiente durante 15 horas. Luego de completada la reacción, la resina fue lavada y secada para dar 3,134 g de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Phe-Rink.

Usando esta resina, 1,94 g de resina MBHA Amida Trt-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink obtenida por condensación de Trt-Phe-OH.0,5AcOEt similar a la del EJEMPLO 24, fue lavada con DCM. Luego de inflar, fue agregado 12 mL de TFA/TIS/TFE/DCM (1/5/19/75), la mezcla fue agitada durante 10 minutos y la solución fue destilada. Este procedimiento fue repetido hasta que el colorido amarillo pardo causado por el grupo Trt en estado libre desapareciera en un solución TFA/TIS/TFE/DCM(1/5/19/75) cuando la solución sea agregada, así el grupo Trt fue eliminado. Lavada la resina, fue obtenido 1,66 g de resina MBHA Amida H-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Phe-Rink. Usando 553 mg de la resina obtenida, la cadena de péptido fue extendida con un sintetizador de péptido ABI-433A (Fmoc/DCC/HOBt) para dar resina MBHA Amida H-$_D$-Tyr(Bu^t)-$_D$-Trp(Boc)-Asn(Trt)-

Thr(Bu^t)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Phe-Rink. A este producto, fueron agregados 5 mL de DMF, 111 mg de AcONB y 44 ml de DIEA y la resina fue agitada durante dos horas. La resina fue secada, luego lavada para dar 0,78 g de resina MBHA Amida Ac-D-Tyr(But)-D-Trp(Boc)-Asn(Trt)-Thr(But)-Phe-AzaGly-Leu-Arg(Boc2,Me)-Phe-Rink. A la resina fue agregado, 6 mL de TFA/tioanisolo/m-cresol/H_2O/TIS/EDT (80/5/5/5/2,5/2,5) y la resina fue agitada durante dos horas. Luego de la eliminación de la resina por filtración, el solvente fue destilado. Agregando dietiléter, fue obtenida una precipitación. Luego de centrífugar, el lavado para eliminación del sobrenadante fue repetido dos veces, y los residuos fueron extraídos con una solución de acetato. Después que la resina fue eliminada por filtración, la fracción fue purificada aplicando HPLC preparativa usando una columna YMC Pack R&D-ODS-5-B S-5 120A (30 x 250 mm) a una velocidad del flujo de 15 ml/min con una elución de pendiente de densidad lineal (60 minutos) con eluyentes A/B: 71/29-61/39 usando eluyente A: 0,1% TFA en agua y eluyente B: 0,1% TFA-que contenia acetonitrilo. Las fracciones que contenían el producto fueron recolectadas y liofilizadas para dar polvo blanco de la muestra purificada. La muestra purificada fue liofilizada. El péptido en bruto obtenido de manera similar usando 553 mg resina MBHA Amida H-Phe-AzaGly-Leu-Arg(Boc2,Me)-Phe-Rink fue purificado en HPLC preparativa para dar 237,6 mg de

muestra purificada como polvo blanco.

Unos 236,1 mg de polvos blancos obtenidos, fueron disueltos en 200 mL de solución acuosa de acetonitrilo y fue agregada a la solución 935 µL de resina de intercambio de iones AG1 x 8 AcO^- que se obtuvo convirtiendo una manera convencional BioRAD AG1x 8 Cl^- disponible comercialmente en el tipo de acetato. Mientras fue agitada a mano la solución a veces, luego la solución de reacción permaneció en reposo durante una hora. La solución fue concentrada para eliminar el acetonitrilo tanto como sea posible. Entonces la concentración fue filtrada a través de un filtro de membrana y fue liofilizada para dar 204,6 mg de polvo blanco como acetato.

Espectro de masa $(M+H)^+$ 1259,5 (Calc. 1259,6).

Tiempo de elución en HPLC: 13,2 min.

Condiciones de elución:

Columna YMC-AM301 (4,6 x 100 mm).

Eluyente: elución de pendiente de densidad lineal con eluyentes A/B = 80/20-30/70, usando 0,1% TFA en agua como eluyente A y 0,1% TFA que contenia acetonitrilo como el eluyente B (25 min)

Velocidad de flujo: 1,0 ml/min.

[EJEMPLO 27]

Preparación de Ac-des(1)-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compuesto No. 579)

Después que 5 g (0,4 mmol/g) resina MBHA Amida Rink

comercialmente disponible se permite dilatar en DMF, la resina fue tratada con 50 ml de solución 20% piperidina/DMF por 20 minutos para eliminar el grupo Fmoc. Después que la resina obtenida fue lavada con DMF, fue introducido Trp(Boc) por tratamiento de la resina con 4,213 g (8 mmol) de Fmoc-Trp(Boc)-OH, 1,272 mL (8 mmol) de DIPCDI y 16 mL (8 mmol) de 0,5M solución HOAt/DMF a temperatura ambinete oor 90 minutos para dar Fmoc-Trp(Boc)- resina MBHA Amida Rink. De una manera similar, fue introducido Orn(Mtt) para dar 2 mmol de resina MBHA Amida Fmoc-Orn(Mtt)-Trp(Boc)-Rink. La resina obtenida fue lavada con DCM, después de dilatación, 50 mL de TFA/TIS/TFE/DCM · (1/5/19/75) fueron agregados, la mezcla fue agitada por 10 minutos y la solución eliminada por destilación. Este procedimiento fue repetido hasta que la coloración amarilla causada por el grupo Mtt libre en la solución TFA/TIS/TFE/DCM(1/5/19/75) desapareció cuando la solución fue agregada, así fue eliminado el grupo Mtt.

La resina MBHA Amida Fmoc-Orn-Trp(Boc)-Rink resultante fue neutralizada con solución 5%-DIEA/DCM. Después de lavado con DCM, 25 mL de DCM-TFE (4:1) y 1,946 g (6 mmol) de N-metil-N,N'-bis-Boc-1-guanilpirazol obtenido en EJEMPLO DE REFERENCIA 1 fueron agregados a la resina. Fue agregado DIEA a la mezcla para ajustar pH de la solución a 10, y la mezcla fue agitada por 15 horas para dar MBHA resina MBHA xAmida Fmoc-Arg(Boc2,Me)-Trp(Boc)-Rink. Fue introducido Fmoc-Leu en la resina

obtenida de la misma manera que la descripta anteriormente. El grupo Fmoc fue eliminado de la resina MBHA Amida Fmoc-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink así obtenida (2 mmol) para dar resina MBHA Amida H-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink (2 mmol).

Separadamente, 2,326 g (8 mmol) de Fmoc-NHNH2.HCl fueron suspendidos en 20 mL de DMF. Bajo enfriamiento con hielo, una suspension de 1,297 mg (8 mmol) de CDI en 20 mL de THF y luego 2,787 mL (16 mmol) de DIEA fue agregado a la suspensión, seguido por agitación a temperatura ambiente por an hour. La solución de reacción resultante fue agregada a resina MBHA Amida H-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink descripta anteriormente, seguido por agitación a temperatura ambiente por 15 horas. Después de completar la reacción, la resina fue lavada y secada para dar 2 mmol de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink.

Usando 868 mg (0,257 mmol) de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink, Thr(tBu), Alb, D-Trp(Boc), y D-Tyr(tBu) fueron introducidos por repetición de condensación usando método DCC/HOBt con ABI 433A para dar una resina MBHA Amida H-D-Tyr(tBu)-D-Trp(Boc)-Alb-Ser(tBu)-Phe-AzaGly-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink. La terminal N de la resina obtenida fue acetilada por tratamiento con 111 mg (0,5 mmol) de AcONB y 87 µL (0,5 mmol) de DIEA en 5 mL de DMF a temperatura ambiente por 10 horas. Subsiguientemente, la resina fue

lavada y secada para dar una resina MBHA Amida Ac-D-Tyr(tBu)-D-Trp(Boc)-Alb-Ser(tBu)-Phe-AzaGly-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink.

A la resin obtenida, fueron agregados 6 mL de TFA/ PhSMe/ m-cresol/ H_2O/ TIS/ EDT(80/ 5/ 5 /5/2,5 /2,5), y la suspensión fue agitada por dos horas. Después de la eliminación de la resina por filtración, el solvente fue eliminado por destilación. Por agregado de dietil éter, se obtuvo el precipitado. Después de centrifugación, el lavado para eliminar el sobrenadante fue repetido dos veces, y los residuos fueron extractados con solución de acetato. Después que la resina fue eliminada por filtración, la fraction fue purificada por aplicar HPLC preparativa usando YMC Pack R&D-ODS-5-B S-5, columna 120A (30 x 250 mm) a una velocidad de circulación de 15 ml/min secuencialmente con elución de gradiente de densidad lineal (60 minutos) con eluyentes A/B: 69/31-59/41 usando eluyente A: 0,1% TFA en agua y eluyente B: 0,1% conteniendo TFA acetonitrilo. Las fracciones conteniendo el producto fueron recolectadas y liofilizadas para dar 106,5 mg de polvos blancos como la muestra purificada.

La totalidad de los polvos blancos obtenidos fue disuelta en 100 mL de solución acuosa de acetonitrilo y 400 µL de resina de intercambio de ión AG1 x 8 AcO-, la cual se obtuvo por convertir BioRAD AG1 x 8 Cl- comercialmente disponible en el tipo acetato de una manera convencional, lo cual fue agregado a the solución.

Mientras se agita manualmente la solución reacción a veces, la solución de reacción se deja establecer por una hora. La solución fue concentrada para eliminar todo lo posible posible el acetonitrilo. El concentrado luego fue filtrado a través de un filtro de membrana y fue liofilizado para dar 97,5 mg de polvo blanco como acetato.

Espectro de masa $(M+H)^+$ 1299.5 (Calculado 1299,6)

Tiempo de elución en HPLC: 19,0 min

Condiciones de elución:

Columna Wakosil-II (4.6 x 100 mm)

Eluyente: elución de gradiente de densidad lineal con eluyentes A/B = 100/0-50/50, usando 0,1% TFA en agua como eluyente A y acetonitrilo conteniendo 0,1% TFA como eluyente B (25 mins.)

Velocidad de circulación: 1.0 ml/min.

[EJEMPLO 28]

(Procedimiento de síntesis X): Preparación de Ac-des(1)-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10

(Compuesto No. 585)

Después que 5 g (0,4 mmol/g) de resina MBHA Amida Rink disponible comercialmente se hizo dilatar en DMF, la resina fue tratada con 50 ml de 20% solución piperidina/DMF por 20 minutos para eliminar el grupo Fmoc. Después que la resina obtenida fue lavada con DMF, fue introducido Trp(Boc) por tratamiento de la resina con 4,213 g (8 mmol) de Fmoc-Trp(Boc)-OH, 1,272 mL (8 mmol)

de DIPCDI y 16 mL (8 mmol) de 0,5M solución HOAt/DMF a temperatura ambiente por 90 minutos para dar resina MBHA Amida Fmoc-Trp(Boc)-Rink. De una manera similar, fue introducido Orn(Mtt) para dar 2 mmol de resina MBHA Amida Fmoc-Orn(Mtt)-Trp(Boc)-Rink. La resina obtenida fue lavada con DCM, después de la dilatación, 50 mL de TFA/TIS/TFE/DCM (1/5/19/75) fueron agregados, la mezcla fue agitada por 10 minutos y la solución fue eliminada por destilación. Este procedimiento repetido hasta que la coloración amarilla causada por el grupo Mtt libre en la solución TFA/TIS/TFE/DCM(1/5/19/75) desapareción cuando la solución fue agregada, así fue eliminado el grupo Mtt.

La resina MBHA Amida Fmoc-Orn-Trp(Boc)-Rink resultante fue neutralizada con solución 5%-DIEA/DCM. Después de lavado con DCM, 25 mL de DCM-TFE (4:1) y 1,946 g (6 mmol) de N-metil-N,N'-bis-Boc-1-guanilpirazol obtenido en EXAMPLO DE REFERENCIA 1 fue agregado a la resina. El DIEA fue agregado a la mezcla para ajustar el pH de la solución a 10, y la mezcla fue agitada por 15 horas para dar Fmoc-Arg(Boc2,Me)-Trp(Boc)-resina MBHA Amida Rink. Fmoc-Leu fue introducido dentro de la resina obtenida de la misma manera descripta precedentemente. El grupo Fmoc fue eliminado de la resina MBHA Amida Fmoc-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink así obtenida (2 mmol) para dar resina MBHA Amida H-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink (2 mmol).

Separadamente, 2,326 g (8 mmol) de Fmoc-$NHNH_2$.HCl

fue suspendido en 20 mL de DMF. Bajo enfriamiento con hielo, una suspension de 1,297 mg (8 mmol) de CDI en 20 mL de THF y luego 2,787 mL (16 mmol) de DIEA fue agregado a la suspensión, seguido por agitación a temperatura ambiente por una hora. La solución de reacción resultante fue agregada a la resina MBHA Amida H-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink descripta precedentemente, seguido por agitación a temperatura ambiente por 15 horas. Después de completar la reacción, la resina fue lavada y secada para dar 2 mmol de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink.

Usando 868 mg (0,257 mmol) de resina MBHA Amida Fmoc-AzaGly-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink, Thr(tBu), Dap(Mtt), D-Trp(Boc) y D-Tyr(tBu) fueron introducidos por condensación repetida usando método DCC/HOBt con ABI 433A para dar resina MBHA Amida H-D-Tyr(tBu)-D-Trp(Boc)-Dap(Mtt)-Ser(tBu)-Phe-AzaGly-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink. La terminal N de la resina obtenida fue acetilada por tratamiento con 111 mg (0,5 mmol) de AcONB y 87 µL (0,5 mmol) de DIEA en 5 mL de DMF a temperatura ambiente por 4 horas. Subsiguientemente, la resina fue lavada y secada para dar resina MBHA Amida Ac-D-Tyr(tBu)-D-Trp(Boc)-Dap(Mtt)-Ser(tBu)-Phe-AzaGly-Leu-Arg(Boc2,Me)-Trp(Boc)-Rink.

A la resina obtenida, fueron agregados 6 mL de TFA/ PhSMe/ m-cresol/ H_2O/ TIS/ EDT(80/ 5/ 5 /5/2,5 /2,5), y la suspension fue agitada por dos horas. Después de la

eliminación de la resina por filtración, el solvente fue eliminado por destilación. Por agregado de dietil éter, fue obtenida el precipitado. Después de centrifugación, el lavado para eliminar el sobrenadante fue repetido dos veces, y los residuos fueron extractados con solución de acetato. Después que la resina fue eliminada por filtration, la fracción fue purificada por aplicación de HPLC preparativo usando "YMC Pack R&D-ODS-5-B S-5", columna 120A (30 x 250 mm) a una velocidad de circulación de 15 ml/min secuencialmente con elución de gradiente de densidad lineal (60 minutos) con eluyentes A/B: 71/29-61/39 usando eluyente A: 0,1% TFA en agua y eluyente B: 0,1% acetonitrilo conteniendo TFA. Las fracciones conteniendo el producto fueron recolectadas y loofilizadas para dar 106,5 mg de polvo blanco como la muestra purificada.

Todos los polvos blancos obtenidos fueron disueltos en 100 mL de solución acuosa de acetonitrilo y 400 µL de resin de intercambio de ión AG1 x 8 forma AcO, el cual fue obtenido convirtiendo BioRAD AG1 x 8 forma Cl comercialmente disponible en el tipo acetato en una manera conventional, fue agregado a la solución. Mientras se agita manualmente la solución de reacción a veces, a la solución de reacción se permite establece por una hora. La solución fue concentrada para eliminar tanto acetonitrilo como sea possible. El concentrado luego fue filtrado a través de un filtro de membrana y fue

liofilizado para dar 58,3 mg de polvo blanco como acetato.

Espectro de masa $(M+H)^+$ 1284,7 (Calculado 1284,6)

Tiempo de elución en HPLC: 17,9 min

Condiciones de elución:

Columna Wakosil-II (4,6 x 100 mm)

Eluyente: elución de gradiente de densidad lineal con eluyentes A/B = 100/0-50/50, usando 0,1% TFA en agua como eluyente A y acetonitrilo conteniendo 0,1% TFA como eluyente B (25 min.)

Velocidad de circulación: 1,0 ml/min.

Las estructuras de los compuestos sintetizados de los EJEMPLOS 1 al 24 y propiedades físico-químicas de estos compuestos de ilustran en las TABLAS 1 a 11.

[TABLA 1]

Comp. No.		M+H+ (clc.)	M+H+ (exp.)	HPLC (min.)	modo HPLC	Proc Sint.
1	Metastina	5658.4	5658.5	18.1	d	M
2	Lys-Asp-Leu-Pro-Asn-MS10	1589.6	1589.9	18.6	d	M
3	MS10	1302.5	1302.8	18.7	d	M
4	des(1)-MS10	1139.6	1139.8	18.1	d	M
17	[Pya(4)10]MS10	1303.6	1303.6	14.7	d	M
18	[Tyr(Me)10]MS10	1332.7	1332.7	17.7	d	M
19	[Phe(2F)10]MS10	1320.5	1320.6	17.8	d	M
23	[Tyr3]MS10	1378.6	1378.8	18.6	d	M
24	[Leu5]MS10	1328.7	1328.7	18.8	d	M
30	Acetyl-MS10	1344.5	1344.6	29.2	b	A
31	Fmoc-MS10	1524.6	1524.7	33.1	b	A
38	[D-Ser3]MS10	1302.5	1302.8	11.8	c	A
39	[D-Asn4]MS10	1302.5	1302.8	11.6	c	A
40	[D-Trp5]MS10	1302.5	1302.8	11.5	c	A
41	[D-Asn2]MS10	1302.5	1302.6	11.7	c	A
42	[D-Tyr1]MS10	1302.5	1302.6	11.4	c	A
44	[Lys9]MS10	1274.6	1274.8	11.7	c	A
45	[Ala8]MS10	1260.5	1260.6	10.0	c	A
50	[Ala7]MS10	1316.3	1316.7	12.2	c	A
51	[NMePhe10]MS10	1316.3	1316.7	29.7	a	A
53	des(1-3)-Fmoc-MS10	1061.2	1061.5	27.3	a	A
54	des(1-2)-Fmoc-MS10	1247.4	1247.6	29.6	a	A
55	des(1)-Fmoc-MS10	1361.6	1361.6	28.2	a	A
56	[Lys2]MS10	1316.6	1316.7	16.8	d	M
57	[Asp2]MS10	1303.7	1303.8	17.7	d	M
58	[Tyr2]MS10	1351.7	1351.7	18.2	d	M
59	[Leu2]MS10	1301.8	1301.7	18.2	d	M
60	[Pya(3)10]MS10	1303.6	1303.6	14.7	d	M
61	[Phe(4F)10]MS10	1320.6	1320.6	18.0	d	M
67	[Ala3]MS10	1187.4	1187.6	9.3	c	A
68	[Leu3]MS10	1229.6	1229.6	11.1	c	A
69	[Ser3]MS10	1203.5	1203.6	8.9	c	A
70	[Asp3]MS10	1231.6	1231.6	9.9	c	A
71	[Lys3]MS10	1244.6	1244.7	8.1	c	A
72	[Ala1]MS10	1210.5	1210.6	11.1	c	A
73	[Leu1]MS10	1752.6	1752.7	12.5	c	A
74	[Ser1]MS10	1226.6	1226.6	10.9	c	A
75	[Asp1]MS10	1254.4	1254.6	11.0	c	A

[TABLA 2]

76	[Lys1]MS10	1267.6	1267.7	10	c	A
77	[Phe(4CN)10]MS10	1327.5	1327.8	17.2	d	M
78	[Trp(For)3, Phe(4CN)10]MS10	1355.6	1355.6	17.4	d	M
79	[Hph10]MS10	1316.5	1316.7	20.6	a	A
81	[NMeArg9]MS10	1316.3	1316.7	23.3	a	A
82	[Arg(Me)9]MS10	1316.5	1316.7	20.1	a	E
83	[Arg(Me2)asy9]MS10	1330.4	1330.7	21.3	a	A
87	des(4-5)-Boc-MS10	1201.6	1201.6	22.5	d	M
88	des(4-5)-MS10	1101.5	1101.5	18.6	d	M
90	[Lys9,9Ψ10,CH2NH]MS10	1280.6	1280.7	19.8	a	D
91	[8Ψ9,CH2NH]MS10	1288.7	1288.7	20.5	a	D
97	[Har9]MS10	1316.3	1316.7	11.9	c	A
98	[Lys(Me2)8]MS10	1302.6	1302.7	11.5	c	A
101	[Ser7]MS10	1332.6	1332.6	11.6	c	A
105	[Nle8]MS10	1302.3	1302.6	11.9	c	A
107	[Val8]MS10	1288.5	1288.6	11	c	A
109	[Tyr10]MS10	1408.4	1408.7	10.2	c	A
110	[Nal(2)10]MS10	1332.4	1332.6	13.5	c	A
111	[Phe(F5)10]MS10	1392.2	1392.6	13.5	c	A
112	[Cha10]MS10	1308.4	1308.7	13.4	c	A
114	des(1-3)-3-(3-Indolil)propionil-MS10	1010.5	1010.5	13.8	c	A+I
121	des(1-4)-[Trp5]MS10	824.3	824.5	22.5	d	M
123	[NMeLeu8]MS10	1316.7	1316.7	12.7	c	A
126	[NMeSer6]MS10	1317	1316.7	11.8	c	A
127	[D-Asn4,NMePhe6]MS10	1316.7	1316.7	11.8	c	A
128	[10Ψ,CSNH]MS10	1318.4	1318.6	21.8	a	C
129	[Arg(Me2)sy9]MS10	1331.2	1330.7	20.9	a	A
130	[Phe(4Cl)10]MS10	1336.4	1336.6	13.1	c	A
131	[Phe(4NH2)10]MS10	1317.4	1317.6	8.3	c	A
132	[Phe(4NO2)10]MS10	1347.4	1347.6	12.2	c	A
133	[Nal(1)10]MS10	1352.6	1352.7	13.5	c	A
134	[Trp10]MS10	1341.5	1341.6	12	c	A
137	[Nle8]MS10	1259.4	1259.6	15.3	c	A

138	[Cit9]MS10	1303.4	1303.6	12.2	c	A
140	[Arg(Me)9,NMePhe10]MS10	1330.4	1330.7	21	a	E
141	[D-Tyr1,Arg(Me)9]MS10	1316.9	1316.7	20.2	a	E
142	[D-Tyr1,D-Trp3,Arg(Me)9]MS10	1316.7	1316.7	20.1	a	E
143	[D-Trp3,Arg(Me)9]MS10	1316.7	1316.7	20.3	a	E
144	des(1-3)-Fmoc-[Arg(Me)9]MS10	1075.2	1075.5	26	a	E
145	des(1-2)-Fmoc-[Arg(Me)9]MS10	1261.2	1261.6	28.6	a	E

[TABLA 3]

146	[10Ψ,CSNH,D-Tyr1]MS10	1318.4	1318.6	21.4	a	C
150	[Tyr6]MS10	1318.4	1318.6	10.2	c	A
151	[Nal(1)6]MS10	1352.6	1352.7	13.5	c	A
152	[Nal(2)6]MS10	1352.6	1352.7	13.6	c	A
153	[Phe(F5)6]MS10	1392.5	1392.6	13.7	c	A
154	[Phe(4F)6]MS10	1320.6	1320.6	12.3	c	A
156	[Cha6]MS10	1308.2	1308.5	13.2	c	A
163	[6Ψ7,CH2NH]MS10	1288.7	1288.7	18.2	a	D
165	[Dap(Gly)8] MS10	1289.8	1289.6	18.2	a	E
166	[6Ψ7,CSNH]MS10	1318.7	1318.6	20.8	a	F
169	[D-Tyr1,Ala3,Arg(Me)8]MS10	1202.1	1201.6	9.0	c	E
170	[D-Tyr1,Ser3,Arg(Me)8]MS10	1218.2	1217.6	8.6	c	E
171	[D-Tyr1,Cha3,Arg(Me)8]MS10	1284.2	1283.7	12.1	c	E
172	[D-Tyr1,Cha6,Arg(Me)8]MS10	1402.9	1322.7	13.1	c	E
173	[D-Tyr1,Ala7,Arg(Me)8]MS10	1410.9	1330.7	12.2	c	E
174	[D-Tyr1,Arg(Me)8,Trp10]MS10	1335.3	1335.7	11.7	c	E
176	[AzaGly7]MS10	1303.3	1303.6	18.9	a	G
181	[D-Tyr1,Cha3,6,Arg(Me)8]MS10	1370.6	1370.6	13.9	c	E
182	[D-Tyr1,Cha3,6,Arg(Me)8,Trp10] MS10	1328.2	1328.7	21.3	b	E
183	[Phe(4NH2)8]MS10	1328.2	1308.6	19.4	a	A
184	[Phe(4-Guanidino)8]MS10	1350.4	1350.6	19.7	a	E
185	[Dap(GnGly)8]MS10	1331.2	1331.6	19.1	a	E
186	[Trp(For)10]MS10	1369.3	1369.6	19.6	a	B
187	[Abu6]MS10	1274.4	1274.6	10.4	c	A
188	[Ala(3-Bzt)10]MS10	1358.4	1358.6	13.4	c	A
190	[D-Tyr1,Cha3,AzaGly7,Arg(Me)8] MS10	1284.5	1284.7	19.3	a	H
191	[D-Tyr1,Ser3,AzaGly7,Arg(Me)8] MS10	1218.4	1218.6	15.9	a	H
192	[D-Tyr1,Arg(Et)8]MS10	1330.5	1330.7	18.9	a	E
193	[D-Tyr1,Arg(n-Pr)8]MS10	1344.8	1344.7	19.4	a	E
194	[D-Tyr1,Arg(Ac)8]MS10	1345.1	1344.6	18.8	a	E
197	[Phe(3F)10]MS10	1320.6	1320.6	12.2	c	A
198	[Phe(3,4F2)10]MS10	1338.7	1338.6	12.7	c	A
199	[Phe(3,4Cl2)10]MS10	1370.6	1370.6	13.1	c	A
200	[Phe(3CF3)10]MS10	1370.6	1370.6	13.1	c	A
201	[Ala(2-Qui)10]MS10	1353.4	1353.6	9.6	c	A
203	[D-Tyr1,Cha6,Arg(Me)8]MS10	1322.4	1322.7	12.9	c	E
204	[D-Tyr1, Ala7, Arg(Me)8]MS10	1330.4	1330.7	11.7	c	E
205	[D-Tyr1,Thr3,Arg(Me)8]MS10	1231.4	1231.6	8.0	c	E
206	[D-Tyr1,Ile3,Arg(Me)8]MS10	1243.6	1243.7	10.1	c	E
207	[D-Tyr1,Ser4,Arg(Me)8]MS10	1289.5	1289.6	11.7	c	E

[TABLA 4]

208	[D-Tyr1,Thr4,Arg(Me)9]MS10	1303.4	1303.7	12.0	c	E
209	[D-Tyr1,Gln4,Arg(Me)9]MS10	1330.8	1330.7	11.8	c	E
210	[D-Tyr1,Ala4,Arg(Me)9]MS10	1273.7	1273.6	12.3	c	E
211	[D-Tyr1,Thr5,Arg(Me)9]MS10	1330.7	1330.7	11.7	c	E
212	[D-Tyr1,Ala5,Arg(Me)9]MS10	1300.5	1300.7	12.1	c	E
213	[D-Tyr1,Val8,Arg(Me)9]MS10	1302.5	1302.6	10.4	c	E
214	[D-Tyr1,Gln2,Arg(Me)9]MS10	1330.5	1330.7	11.4	c	E
215	[D-Tyr1,Thr2,Arg(Me)9]MS10	1303.4	1303.7	11.9	c	E
216	des(1)-[D-Asn2,Arg(Me)9]MS10	1153.3	1153.6	11.1	c	E
217	des(1)-[D-Tyr2,Arg(Me)9]MS10	1202.4	1202.6	12.3	c	E
218	(N((CH2)3Gn))Gly8]MS10	1302.5	1302.7	18.6	a	L
220	[Arg(Et)9]MS10	1330.7	1330.7	19.5	a	E
221	[D-Tyr1,Thr3,AzaGly7,Arg(Me)9] MS10	1232.9	1232.6	16.1	a	H
222	des(1)-[D-Tyr2,AzaGly7,Arg(Me)9]MS10	1203.5	1203.5	19.3	a	H
223	des(1-2)-[D-Trp3,Arg(Me)9]MS10	1039.5	1039.5	11.0	c	E
224	des(1)-[D-Tyr2,D-Trp3,Arg(Me)9]MS10	1202.4	1202.6	12.2	c	E
225	des(1)-[D-Asn2,D-Trp3,Arg(Me)9]MS10	1153.6	1153.6	11.1	c	E
226	des(1)-[D-Tyr2,Ser3,Arg(Me)9] MS10	1103.5	1103.6	9.5	c	E
227	des(1)-[D-Tyr2,Thr3,Arg(Me)9] MS10	1117.5	1117.6	9.8	c	E
228	des(1)-[D-Tyr2,Ile3,Arg(Me)9]MS10	1129.6	1129.6	11.5	c	E
229	[D-Tyr1,Val3,Arg(Me)9]MS10	1229.5	1229.6	9.7	c	E
230	[D-Tyr1,D-Asn2,Arg(Me)9]MS10	1316.5	1316.7	11.8	c	E
231	[D-Tyr1,D-Asn2,D-Trp3,Arg(Me)9]MS10	1316.3	1316.7	11.7	c	E
232	[D-Tyr1,AzaGly7,Arg(Me)9]MS10	1317.0	1317.6	21.0	a	H
233	[D-Tyr1,Ile3,AzaGly7,Arg(Me)9] MS10	1244.1	1244.7	20.9	a	H
234	[D-Tyr1,Val3,AzaGly7,Arg(Me)9] MS10	1230.5	1230.6	20.6	a	H
235	[D-Tyr1,Ala3,AzaGly7,Arg(Me)9] MS10	1202.5	1202.6	20.5	a	H
236	[D-Tyr1,D-Trp3,AzaGly7,Arg(Me)9]MS10	1317.5	1317.6	20.9	a	H
237	[D-Tyr1,D-Asn2,AzaGly7,Arg(Me) 9]MS10	1317.6	1317.6	20.9	a	H
238	[D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)9]MS10	1317.6	1317.6	20.6	a	H
239	des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)9]MS10	1104.1	1104.6	19.0	a	H
240	des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)9]MS10	1130.1	1130.6	20.3	a	H
241	des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)9]MS10	1118.0	1118.6	20.2	a	H
242	des(1)-[D-Tyr2,D-Trp3,AzaGly7, Arg(Me)9]MS10	1202.9	1203.6	21.2	a	H
244	[D-Tyr1,Phe3,AzaGly7,Arg(Me)9] MS10	1278.6	1278.6	10.5	c	H
245	[D-Tyr1,Nal(1)3,AzaGly7,Arg(Me) 9]MS10	1328.5	1328.7	12.3	c	H
246	[D-Tyr1,Nal(2)3,AzaGly7,Arg(Me) 9]MS10	1328.7	1328.7	12.3	c	H
247	[D-Tyr1,Phe(2Cl)3,AzaGly7,Arg(Me)9] MS10	1315.5	1312.6	11.3	c	H

[TABLA 5]

248	[D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)9] MS10	1312.5	1312.6	11.6	c	H
249	[D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)9] MS10	1312.5	1312.6	11.7	c	H
250	[D-Tyr1,Phe(4NH2)3,AzaGly7, Arg(Me)9]MS10	1293.4	1293.6	7.8	c	H
251	[D-Tyr1,Pya(3)3,AzaGly7,Arg(Me) 9]MS10	1279.4	1279.6	7.8	c	H
252	[D-Tyr1,D-Ala3,AzaGly7,Arg(Me) 9]MS10	1202.4	1202.6	8.5	c	H
253	[D-Tyr1,Pro3,AzaGly7,Arg(Me)9] MS10	1228.4	1228.6	8.6	c	H
254	des(1)-[D-Tyr2,Phe3,AzaGly7, Arg(Me)9]MS10	1164.4	1164.6	11.8	c	H
255	des(1)-[D-Tyr2,Nal(2)3,AzaGly7, Arg(Me)9]MS10	1214.5	1214.6	13.7	c	H
256	des(1)-[D-Pya(3)2,Phe3,AzaGly7, Arg(Me)9]MS10	1149.3	1149.6	9.5	c	H
257	[D-Tyr1,D-Asn2,Phe3,AzaGly7, Arg(Me)9]MS10	1278.5	1278.6	10.9	c	H
258	[D-Pya(3)1,AzaGly7,Arg(Me)9] MS10	1302.3	1302.6	10.1	c	H
259	[D-Ala1,AzaGly7,Arg(Me)9]MS10	1225.5	1225.6	10.7	c	H
260	des(1-3)-3-(3-Indolil)propionil-[AzaGly7,Arg(Me)9]MS10	1025.2	1025.5	13.7	c	I
261	[7Ψ8,CH2NH]MS10	1288.1	1288.7	17.2	a	D
265	des(1-3)-Indol-3-carbonil-[AzaGly7,Arg(Me)9]MS10	997.3	997.5	12.6	c	I
266	des(1-3)-Indol-3-acetil-[AzaGly7,Arg(Me)9]MS10	1011.3	1011.5	12.7	c	I
267	des(1-3)-4-(3-Indolil)butiril-[AzaGly7, Arg(Me)9]MS10	1039.3	1039.5	14.4	c	I
268	des(1-3)-Difenilacetil-[AzaGly7,Arg(Me)9]MS10	1048.5	1048.5	15.7	c	I
269	des(1-3)-3-Fenilpropionil-[AzaGly7,Arg(Me)9]MS10	986.7	986.5	13.5	c	I
270	Endo-Phe5a-[D-Tyr1,Phe3,Aza Gly7,Arg(Me)9]MS10	1425.5	1425.7	13.4	c	H
271	des(1-2)-[AzaGly7,Arg(Me)9]MS10	1040.2	1040.5	10.4	c	H
272	des(1-2)-Acetil-[AzaGly7, Arg(Me)9]MS10	1082.3	1082.6	12.8	c	H
273	des(1-2)-Amidino-[AzaGly7, Arg(Me)9]MS10	1082.3	1082.6	11.4	c	J
274	des(1-2)-Acetil-[Ala3,AzaGly7, Arg(Me)9]MS10	997.3	997.5	9.6	c	H
275	des(1-2)-Acetil-[Arg3,AzaGly7, Arg(Me)9]MS10	1052.2	1052.6	8.5	c	H
276	des(1-2)-Acetil-[Thr3,AzaGly7, Arg(Me)9]MS10	997.2	997.5	9.4	c	H
277	des(1-3)-n-Hexanoil-[AzaGly7, Arg(Me)9]MS10	952.2	952.5	13.4	c	I
278	des(1-3)-Ciclohexanocarbonil-[AzaGly7, Arg(Me)9]MS10	964.3	964.5	13.2	c	I
279	des(1-3)-2-(Indol-3-il)etilcarbamoil-[AzaGly7,Arg(Me)9]MS10	1040.2	1040.5	20.1	a	N
281	[D-Tyr1,Pya(2)6,Arg(Me)9]MS10	1317.3	1317.6	7.8	c	E
282	[D-Tyr1,Pya(4)6,Arg(Me)9]MS10	1317.2	1317.6	8.0	c	E

[TABLA 6]

283	[D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1284.3	1284.7	12.3	c	H
284	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9]MS10	1232.2	1232.6	8.6	c	H
285	[D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9]MS10	1279.2	1279.6	7.9	c	H
286	[D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.2	1279.6	7.7	c	H
287	[D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9]MS10	1290.1	1290.6	11.4	c	H
288	[D-Tyr1,D-His2,AzaGly7,Arg(Me)9]MS10	1340.2	1340.7	10.3	c	H
289	des(1)-[D-Pya(3)2,AzaGly7,Arg(Me)9] MS10	1188.2	1188.6	10.0	c	H
290	[D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1269.5	1269.7	10.9	c	H
291	[D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9]MS10	1317.4	1316.7	12.0	c	H
293	[4Ψ5,CH2NH]MS10	1288.1	1288.7	18.4	a	D
294	[1Ψ2,CH2NH]MS10	1288.4	1288.7	19.2	a	D
295	[2Ψ3,CH2NH]MS10	1288.1	1288.7	18.2	a	D
296	[6Ψ7,CSNH,D-Tyr1,Arg(Me)9] MS10	1332.1	1332.8	20.5	a	F
297	[D-Tyr1,Thr5,AzaGly7,Arg(Me)9] MS10	1331.2	1330.7	11.3	c	H
298	[D-Tyr1,D-Asn2,Thr5,AzaGly7,Arg(Me)9]MS10	1331.1	1330.7	11.6	c	H
299	[1Ψ2,CH2NH,AzaGly7,Arg(Me)9] MS10	1303.4	1330.7	11.3	c	D+H
300	[1Ψ2,CH2NH,D-Trp3,AzaGly7,Arg(Me)9] MS10	1303.4	1303.7	10.8	c	D+H
301	[D-Tyr1,Ala(2-Qui)3,AzaGly7,Arg(Me)9]MS10	1329.4	1329.6	9.0	c	H
302	[D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.4	1279.6	7.6	c	H
303	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.4	1279.6	7.6	c	H
304	[D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.4	1279.6	7.7	c	H
305	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1165.4	1165.6	8.0	c	H
306	[D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1269.5	1269.5	10.8	c	H
307	[7Ψ8,CH2NH,D-Tyr1,Arg(Me)9] MS10	1302.2	1302.7	17.9	a	D+E
308	[6Ψ7,CH2NH,D-Tyr1,Arg(Me)9] MS10	1302.3	1302.7	18.1	a	D+E
310	[Nar9]MS10	1288.8	1288.6	19.4	a	E
311	[Nar(Me)9]MS10	1302.3	1302.6	19.5	a	E
312	[Har(Me)9]MS10	1330.2	1330.7	19.5	a	E
313	[Dab9]MS10	1246.1	1246.6	19.3	a	A
314	[Orn9]MS10	1260.2	1260.6	19.3	a	A
315	des(1)-[D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1121.3	1121.6	11.4	c	H
316	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1250.5	1250.6	17.0	a	H
317	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1297.4	1297.6	16.4	a	H
318	[D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1335.4	1335.6	19.0	a	H

588

[TABLA 7]

318	[6Ψ7,NHCO,D-Tyr1,Arg(Me)9] MS10	1316.3	1316.7	18.7	a	K
322	des(1-3)-3-(3-Pirid1()propionil-[AzaGly7,Arg(Me)9]MS10	987.4	987.5	8.1	c	I
323	des(1-3)-4-Imidazolacetil-[AzaGly7,Arg(Me)9]MS10	982.5	982.5	7.9	c	I
324	des(1-3)-4-Piperidincarbonil-[AzaGly7,Arg(Me)9]MS10	985.5	985.5	7.7	c	I
325	des(1-3)-1-Piperidinacetil-[AzaGly7, Arg(Me)9]MS10	979.5	979.5	8.5	c	I
326	des(1-3)-1-Metilpiperidinio-1-acetil-[AzaGly7,Arg(Me)9]MS10	993.4	993.6	8.7	c	I
327	des(1-3)-1-Piridiniacetil-[Aza Gly7,Arg(Me)9]MS10	973.4	973.5	8.1	c	I
328	des(1-3)-D-Glucuronil-[AzaGly7, Arg(Me)9]MS10	1030.2	1030.5	7.5	c	I
332	des(1-5)-GuAmb-[AzaGly7,Arg(Me)9]MS10	828.6	828.5	9.9	c	H+J
333	des(1-5)-GuAmb-[Arg(Me)9]MS10	827.6	827.5	10.6	c	E+J
334	des(1-5)-GuAmb-[AzaGly7,Arg(Me)9,Trp10]MS10	867.6	867.5	10.3	c	H+J
339	des(1-5)-3-(3-Indol1)propionil-[AzaGly7,Arg(Me)9]MS10	824.6	824.5	16.0	c	S
340	des(1-5)-3-(3-Pirid1()propionil-[AzaGly7,Arg(Me)9]MS10	788.4	788.6	8.5	c	S
341	des(1-5)-Benzoil-[AzaGly7,Arg(Me)9]MS10	757.2	757.4	14.8	c	S
344	des(1-5)-Indol-3-carbonil-[AzaGly7,Arg(Me)9]MS10	796.5	796.4	14.8	c	S
345	des(1-5)-Indol-3-acetil-[AzaGly7,Arg(Me)9]MS10	810.6	810.4	15.2	c	S
346	des(1-5)-Ac-[AzaGly7,Arg(Me)9]MS10	695.5	695.4	10.7	c	S
347	des(1-5)-n-Hexanoil-[AzaGly7,Arg(Me)9]MS10	751.7	751.5	16.2	c	S
348	des(1-5)-Z-[AzaGly7,Arg(Me)9]MS10	787.5	787.4	16.7	a	S
349	des(1-5)-Tos-[AzaGly7,Arg(Me)9]MS10	807.5	807.4	15.9	c	S
351	des(1-5)-Benzoil-MS10	742.4	742.4	15.1	c	A+J
352	des(1-5)-3-(3-Indol1)propionil-MS10	809.6	809.4	16.2	a	A+J
353	des(1-5)-Benzoil-[AzaGly7,Arg(Me)9,Trp10]MS10	796.4	796.4	15.0	c	S
354	des(1-5)-3-(3-Indol(1)propionil-[AzaGly7,Arg(Me)9,Trp10]MS10	863.4	863.5	16.2	c	S

358	des(1-5)-Ac [AzaGly7,Arg(Me)9 Trp10]MS10	734.4	734.4	11.2	c	S
362	des(1-5)-3-Fenilpropionil-[AzaGly7,Arg(Me)9]MS10	838.4	838.4	12.5	c	S
364	des(1-5)-2-(Indol-3-il)etilcarbamoil-[AzaGly7,Arg(Me)9]MS10	939.6	939.5	15.8	c	N
366	des(1-5)-n-Hexanoil-[AzaGly7,Arg(Me)9,Trp10]MS10	790.5	790.5	16.5	c	S
367	des(1-5)-Z-[AzaGly7,Arg(Me)9,Trp10]MS10	826.5	826.4	16.8	c	S
368	des(1-5)-Tos-[AzaGly7,Arg(Me)9,Trp10]MS10	846.6	846.4	16.0	c	S
369	des(1-5)-2-(Indol-3-il)etilcarbamoil-[AzaGly7,Arg(Me)9,Trp10]MS10	878.6	878.5	16.1	c	N

[TABLA 2]

76	[Lys1]MS10	1267.6	1267.7	10	c	A
77	[Phe(4CN)10]MS10	1327.5	1327.6	17.2	d	M
78	[Trp(For)3, Phe(4CN)10]MS10	1356.6	1355.6	17.4	d	M
79	[Hph10]MS10	1316.5	1316.7	20.6	a	A
81	[NMeArg9]MS10	1318.2	1316.7	23.3	a	A
82	[Arg(Me)9]MS10	1318.5	1316.7	20.1	a	E
83	[Arg(Me2)asy9]MS10	1330.4	1330.7	21.3	a	A
87	des(4-5)-Boc-MS10	1201.6	1201.6	22.5	d	M
88	des(4-5)-MS10	1101.5	1101.5	18.6	d	M
90	[Lys8,9Ψ10,CH2NH]MS10	1260.6	1260.7	19.5	a	D
91	[8Ψ9,CH2NH]MS10	1268.7	1268.7	20.5	a	D
97	[Har9]MS10	1316.3	1316.7	11.5	c	A
98	[Lys(Me2)9]MS10	1302.6	1302.7	11.5	c	A
101	[Ser7]MS10	1332.6	1332.6	11.6	c	A
105	[Nle8]MS10	1302.3	1302.6	11.5	c	A
107	[Val8]MS10	1288.5	1288.6	11	c	A
109	[Tyr10]MS10	1408.4	1408.7	10.2	c	A
110	[Nal(2)10]MS10	1332.4	1332.6	13.5	c	A
111	[Phe(F5)10]MS10	1392.2	1392.6	13.5	c	A
112	[Cha10]MS10	1308.4	1308.7	13.4	c	A
114	des(1-3)-3-(3-Indolil)propionil-MS10	1010.5	1010.5	13.8	c	A+I
121	des(1-4)-[Trp5]MS10	824.3	824.5	22.5	d	M
123	[NMeLeu8]MS10	1316.7	1316.7	12.7	c	A
126	[NMeSer8]MS10	1317	1316.7	11.8	c	A
127	[D-Asn4,NMePhe8]MS10	1316.7	1316.7	11.8	c	A
128	[10Ψ,CSNH]MS10	1318.4	1318.6	21.8	a	O
129	[Arg(Me2)sy9]MS10	1331.2	1330.7	20.9	a	A
130	[Phe(4Cl)10]MS10	1338.4	1338.6	13.1	c	A
131	[Phe(4NH2)10]MS10	1317.4	1317.6	8.3	c	A
132	[Phe(4NO2)10]MS10	1347.4	1347.6	12.2	c	A
133	[Nal(1)10]MS10	1352.6	1352.7	13.5	c	A
134	[Trp10]MS10	1341.5	1341.6	12	c	A
137	[Nle9]MS10	1289.4	1289.6	15.3	c	A

138	[Cit9]MS10	1303.4	1303.6	12.2	c	A
140	[Arg(Me)9,NMePhe10]MS10	1330.4	1330.7	21	a	E
141	[D-Tyr1,Arg(Me)9]MS10	1316.9	1316.7	20.2	a	E
142	[D-Tyr1,D-Trp3,Arg(Me)9]MS10	1316.7	1316.7	20.1	a	E
143	[D-Trp3,Arg(Me)9]MS10	1316.7	1316.7	20.3	a	E
144	des(1-3)-Fmoc-[Arg(Me)9]MS10	1075.2	1075.5	25	a	E
145	des(1-2)-Fmoc-[Arg(Me)9]MS10	1261.2	1261.6	28.6	a	E

[TABLA 3]

146	[10Ψ,CSNH,D-Tyr1]MS10	1318.4	1318.6	21.4	a	C
150	[Tyr6]MS10	1318.4	1318.6	10.2	c	A
151	[Nal(1)6]MS10	1352.6	1352.7	13.5	c	A
152	[Nal(2)6]MS10	1352.6	1352.7	13.6	c	A
153	[Phe(F5)6]MS10	1392.5	1392.6	13.7	c	A
154	[Phe(4F)6]MS10	1320.6	1320.6	12.3	c	A
156	[Cha6]MS10	1308.2	1308.5	13.2	c	A
163	[6Ψ7,CH2NH]MS10	1288.7	1288.7	19.2	b	D
165	[Dap(Gly)8] MS10	1289.6	1289.6	19.2	a	E
166	[6Ψ7,CSNH]MS10	1318.7	1318.6	20.8	a	F
169	[D-Tyr1,Ala3,Arg(Me)8]MS10	1202.1	1201.6	9.0	c	E
170	[D-Tyr1,Ser3,Arg(Me)8]MS10	1218.2	1217.6	8.6	c	E
171	[D-Tyr1,Cha3,Arg(Me)8]MS10	1284.2	1283.7	12.1	c	E
172	[D-Tyr1,Cha6,Arg(Me)8]MS10	1402.9	1322.7	13.1	a	E
173	[D-Tyr1,Ala7,Arg(Me)8]MS10	1410.9	1330.7	12.2	c	E
174	[D-Tyr1,Arg(Me)8,Trp10]MS10	1335.3	1335.7	11.7	c	E
176	[AzaGly7]MS10	1303.3	1303.6	18.9	a	G
181	[D-Tyr1,Cha3,6,Arg(Me)8]MS10	1370.6	1370.6	13.9	c	E
182	[D-Tyr1,Cha3,6,Arg(Me)8,Trp10] MS10	1328.2	1328.7	21.3	a	E
183	[Phe(4NH2)8]MS10	1328.2	1308.6	19.4	a	A
184	[Phe(4-Guanidino)8]MS10	1350.4	1350.6	19.7	a	E
185	[Dap(GnGly)8]MS10	1331.2	1331.6	19.1	a	E
186	[Trp(For)10]MS10	1369.3	1369.6	19.6	a	B
187	[Abu6]MS10	1274.4	1274.6	10.4	c	A
189	[Ala(3-Bzt)10]MS10	1358.4	1358.6	13.4	c	A
190	[D-Tyr1,Cha3,AzaGly7,Arg(Me)8] MS10	1284.5	1284.7	19.3	a	H
191	[D-Tyr1,Ser2,AzaGly7,Arg(Me)8] MS10	1218.4	1218.6	15.9	a	H
192	[D-Tyr1,Arg(Et)8]MS10	1330.5	1330.7	18.9	a	E
193	[D-Tyr1,Arg(n-Pr)8]MS10	1344.8	1344.7	19.4	a	E
194	[D-Tyr1,Arg(Ac)8]MS10	1345.1	1344.6	18.8	a	E
197	[Phe(2F)10]MS10	1320.6	1320.6	12.2	c	A
198	[Phe(3,4F2)10]MS10	1338.7	1338.6	12.7	c	A
199	[Phe(3,4Cl2)10]MS10	1370.6	1370.6	13.1	c	A
200	[Phe(3CF3)10]MS10	1370.8	1370.6	13.1	c	A
201	[Ala(2-Oxl)10]MS10	1353.4	1353.6	9.8	c	A
203	[D-Tyr1,Cha6,Arg(Me)8]MS10	1322.4	1322.7	12.9	c	E
204	[D-Tyr1, Ala7, Arg(Me)8]MS10	1330.4	1330.7	11.7	c	E
205	[D-Tyr1,Thr3,Arg(Me)8]MS10	1231.4	1231.6	9.0	a	E
206	[D-Tyr1,Ile3,Arg(Me)8]MS10	1243.6	1243.7	10.1	c	E
207	[D-Tyr1,Ser4,Arg(Me)8]MS10	1289.5	1289.6	11.7	c	E

[TABLA 4]

208	[D-Tyr1,Thr4,Arg(Me)9]MS10	1303.4	1303.7	12.0	c	E
209	[D-Tyr1,Gln4,Arg(Me)9]MS10	1330.8	1330.7	11.8	c	E
210	[D-Tyr1,Ala4,Arg(Me)9]MS10	1273.7	1273.6	12.3	c	E
211	[D-Tyr1,Thr5,Arg(Me)9]MS10	1330.7	1330.7	11.7	c	E
212	[D-Tyr1,Ala5,Arg(Me)9]MS10	1300.5	1300.7	12.1	c	E
213	[D-Tyr1,Val5,Arg(Me)9]MS10	1302.5	1302.6	10.4	c	E
214	[D-Tyr1,Gln2,Arg(Me)9]MS10	1330.5	1330.7	11.4	c	E
215	[D-Tyr1,Thr2,Arg(Me)9]MS10	1303.4	1303.7	11.9	c	E
216	des(1)-[D-Asn2,Arg(Me)9]MS10	1153.5	1153.6	11.1	c	E
217	des(1)-[D-Tyr2,Arg(Me)9]MS10	1202.4	1202.6	12.3	c	E
218	[N((CH2)3Gn))Gly9]MS10	1302.5	1302.7	19.6	a	L
220	[Arg(Et)9]MS10	1330.7	1330.7	18.5	a	E
221	[D-Tyr1,Thr3,AzaGly7,Arg(Me)9] MS10	1232.5	1232.6	16.1	a	H
222	des(1)-[D-Tyr2,AzaGly7,Arg(Me)9]MS10	1203.5	1203.6	19.3	a	H
223	des(1-2)-[D-Trp3,Arg(Me)9]MS10	1039.5	1039.5	11.0	c	E
224	des(1)-[D-Tyr2,D-Trp3,Arg(Me)9]MS10	1202.4	1202.6	12.2	c	E
225	des(1)-[D-Asn2,D-Trp3,Arg(Me)9]MS10	1153.6	1153.6	11.1	c	E
226	des(1)-[D-Tyr2,Ser3,Arg(Me)9] MS10	1103.5	1103.6	9.5	c	E
227	des(1)-[D-Tyr2,Thr3,Arg(Me)9] MS10	1117.3	1117.6	9.8	c	E
228	des(1)-[D-Tyr2,Ile3,Arg(Me)9]MS10	1129.6	1129.6	11.5	c	E
229	[D-Tyr1,Val3,Arg(Me)9]MS10	1229.5	1229.6	9.7	c	E
230	[D-Tyr1,D-Asn2,Arg(Me)9]MS10	1316.5	1316.7	11.8	c	E
231	[D-Tyr1,D-Asn2,D-Trp3,Arg(Me)9]MS10	1316.3	1316.7	11.7	a	E
232	[D-Tyr1,AzaGly7,Arg(Me)9]MS10	1317.0	1317.6	21.0	a	H
233	[D-Tyr1,Ile3,AzaGly7,Arg(Me)9] MS10	1244.1	1244.7	20.9	a	H
234	[D-Tyr1,Val3,AzaGly7,Arg(Me)9] MS10	1230.5	1230.6	20.6	a	H
235	[D-Tyr1,Ala3,AzaGly7,Arg(Me)9] MS10	1202.5	1202.6	20.5	a	H
236	[D-Tyr1,D-Trp3,AzaGly7,Arg(Me)9]MS10	1317.5	1317.6	20.9	a	H
237	[D-Tyr1,D-Asn2,AzaGly7,Arg(Me) 9]MS10	1317.5	1317.6	20.9	a	H
238	[D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)9]MS10	1317.6	1317.6	20.8	a	H
239	des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)9]MS10	1104.1	1104.6	19.0	a	H
240	des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)9]MS10	1130.1	1130.6	20.3	a	H
241	des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)9]MS10	1118.0	1118.6	20.3	a	H
242	des(1)-[D-Tyr2,D-Trp3,AzaGly7, Arg(Me)9]MS10	1202.9	1203.6	21.2	a	H
244	[D-Tyr1,Phe3,AzaGly7,Arg(Me)9] MS10	1278.6	1278.6	10.8	c	H
245	[D-Tyr1,Nal(1)3,AzaGly7,Arg(Me) 9]MS10	1328.5	1328.7	12.3	c	H
246	[D-Tyr1,Nal(2)3,AzaGly7,Arg(Me) 9]MS10	1328.7	1328.7	12.3	c	H
247	[D-Tyr1,Phe(2Cl)3,AzaGly7,Arg(Me)9] MS10	1315.6	1312.8	11.3	c	H

[TABLA 5]

248	[D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)9] MS10	1312.5	1312.6	11.6	c	H
249	[D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)9] MS10	1312.5	1312.6	11.7	c	H
250	[D-Tyr1,Phe(4NH2)3,AzaGly7, Arg(Me)9]MS10	1293.4	1293.6	7.8	c	H
251	[D-Tyr1,Pya(3)3,AzaGly7,Arg(Me) 9]MS10	1279.4	1279.6	7.8	c	H
252	[D-Tyr1,D-Ala3,AzaGly7,Arg(Me) 9]MS10	1202.4	1202.6	8.5	c	H
253	[D-Tyr1,Pro3,AzaGly7,Arg(Me)9] MS10	1228.4	1228.6	8.6	c	H
254	des(1)-[D-Tyr2,Phe3,AzaGly7, Arg(Me)9]MS10	1164.4	1164.6	11.8	c	H
255	des(1)-[D-Tyr2,Nal(2)3,AzaGly7, Arg(Me)9]MS10	1214.5	1214.6	13.7	c	H
256	des(1)-[D-Pya(3)2,Phe3,AzaGly7, Arg(Me)9]MS10	1149.3	1149.6	9.5	c	H
257	[D-Tyr1,D-Asn2,Phe3,AzaGly7, Arg(Me)9]MS10	1278.5	1278.6	10.9	c	H
258	[D-Pya(3)1,AzaGly7,Arg(Me)9] MS10	1302.3	1302.6	10.1	c	H
259	[D-Ala1,AzaGly7,Arg(Me)9]MS10	1225.5	1225.6	10.7	c	H
260	des(1-2)-3-(3-Indolil)propanil-[AzaGly7,Arg(Me)9]MS10	1025.2	1025.5	13.7	c	I
261	[7Ψ8,CH2NH]MS10	1288.1	1288.7	17.2	s	D
265	des(1-3)-Indol-3-carbonil-[AzaGly7,Arg(Me)9]MS10	997.3	997.5	12.8	c	I
266	des(1-3)-Indol-3-acetil-[AzaGly7,Arg(Me)9]MS10	1011.3	1011.5	12.7	c	I
267	des(1-3)-4-(3-Indolil)butiril-[AzaGly7, Arg(Me)9]MS10	1039.3	1039.5	14.4	c	I
268	des(1-3)-Difenilacetil-[AzaGly7,Arg(Me)9]MS10	1048.5	1048.5	15.7	c	I
269	des(1-3)-3-Fenilpropionil-[AzaGly7,Arg(Me)9]MS10	986.7	986.5	13.5	c	I
270	Endo-Phe5a-[D-Tyr1,Phe3,Aza Gly7,Arg(Me)9]MS10	1425.5	1425.7	13.4	c	H
271	des(1-2)-[AzaGly7,Arg(Me)9]MS10	1040.2	1040.5	10.4	c	H
272	des(1-2)-Acetil-[AzaGly7, Arg(Me)9]MS10	1082.3	1082.6	12.8	c	H
273	des(1-2)-Amidino-[AzaGly7, Arg(Me)9]MS10	1082.3	1082.6	11.4	c	J
274	des(1-2)-Acetil-[Ala3,AzaGly7, Arg(Me)9]MS10	997.3	997.5	9.8	c	H
275	des(1-2)-Acetil-[Arg3,AzaGly7, Arg(Me)9]MS10	1052.2	1052.6	8.5	c	H
276	des(1-2)-Acetil-[Thr3,AzaGly7, Arg(Me)9]MS10	997.2	997.5	9.4	c	H
277	des(1-3)-n-Hexanoil-[AzaGly7, Arg(Me)9]MS10	952.2	952.5	13.4	c	I
278	des(1-3)-Ciclohexanocarbonil-[AzaGly7, Arg(Me)9]MS10	964.3	964.5	13.2	c	I
279	des(1-3)-2-(Indol-3-il)etilcarbamoil-[AzaGly7,Arg(Me)9]MS10	1040.2	1040.5	20.1	s	N
281	[D-Tyr1,Pya(2)8,Arg(Me)9]MS10	1317.3	1317.6	7.8	c	E
282	[D-Tyr1,Pya(4)8,Arg(Me)9]MS10	1317.2	1317.6	8.0	c	E

[TABLA 6]

283	[D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1284.3	1284.7	12.3	c	H
284	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9]MS10	1232.2	1232.6	8.6	c	H
285	[D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9]MS10	1279.2	1279.6	7.9	c	H
286	[D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.2	1279.6	7.7	c	H
287	[D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9]MS10	1290.1	1290.6	11.4	c	H
288	[D-Tyr1,D-His2,AzaGly7,Arg(Me)9]MS10	1340.2	1340.7	10.3	c	H
289	des(1)-[D-Pya(3)2,AzaGly7,Arg(Me)9]MS10	1189.2	1189.6	10.0	c	H
290	[D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1269.5	1269.7	10.9	c	H
291	[D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9]MS10	1317.4	1316.7	12.0	c	H
292	[4Ψ5,CH2NH]MS10	1288.1	1288.7	18.4	a	D
294	[1Ψ2,CH2NH]MS10	1288.4	1288.7	18.2	a	D
295	[2Ψ3,CH2NH]MS10	1288.1	1288.7	18.2	a	D
296	[6Ψ7,CSNH,D-Tyr1,Arg(Me)9] MS10	1332.1	1332.8	20.5	a	F
297	[D-Tyr1,Thr5,AzaGly7,Arg(Me)9] MS10	1331.2	1330.7	11.3	c	H
298	[D-Tyr1,D-Asn2,Thr5,AzaGly7,Arg(Me)9]MS10	1331.1	1330.7	11.6	c	H
299	[1Ψ2,CH2NH,AzaGly7,Arg(Me)9] MS10	1303.4	1330.7	11.3	c	D+H
300	[1Ψ2,CH2NH,D-Trp3,AzaGly7,Arg(Me)9] MS10	1303.4	1303.7	10.8	c	D+H
301	[D-Tyr1,Ala(2-Qui)3,AzaGly7,Arg(Me)9]MS10	1329.4	1329.6	9.0	c	H
302	[D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.4	1279.6	7.6	c	H
303	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.4	1279.6	7.6	c	H
304	[D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.4	1279.6	7.7	c	H
305	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1165.4	1165.6	8.0	c	H
306	[D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1269.5	1269.5	10.8	c	H
307	[7Ψ8,CH2NH,D-Tyr1,Arg(Me)9] MS10	1302.2	1302.7	17.9	a	D+E
308	[6Ψ7,CH2NH,D-Tyr1,Arg(Me)9] MS10	1302.3	1302.7	18.1	a	D+E
310	[Nor9]MS10	1288.8	1288.6	19.4	a	E
311	[Nor(Me)9]MS10	1302.3	1302.6	19.5	a	E
312	[Hor(Me)9]MS10	1330.2	1330.7	19.5	a	E
313	[Dab9]MS10	1246.1	1246.6	19.3	a	A
314	[Orn9]MS10	1260.2	1260.6	19.3	a	A
315	des(1)-[D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1121.3	1121.6	11.4	c	H
316	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1250.5	1250.6	17.0	a	H
317	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1297.4	1297.6	16.4	a	H
318	[D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1335.4	1335.6	19.0	a	H

[TABLA 7]

319	[6▼7,NHCO,D-Tyr1,Arg(Me)9] MS10	1318.3	1318.7	18.7	a	K
322	des(1-3)-3-(3-Pyridil)propionil-[AzaGly7,Arg(Me)9]MS10	987.4	987.5	8.1	c	I
323	des(1-3)-4-Imidazolacetil-[AzaGly7,Arg(Me)9]MS10	982.5	982.5	7.9	c	I
324	des(1-3)-4-Piperidincarbonil-[AzaGly7,Arg(Me)9]MS10	985.5	985.5	7.7	c	I
325	des(1-3)-1-Piperidinacetil-[AzaGly7, Arg[Me]9]MS10	979.5	979.5	8.5	c	I
326	des(1-3)-1-Metilpiperidino-1-acetil-[AzaGly7,Arg(Me)9]MS10	993.4	993.6	8.7	c	I
327	des(1-3)-1-Piridinacetil-[Aza Gly7,Arg(Me)9]MS10	973.4	973.5	8.1	c	I
328	des(1-3)-D-Glutamil-[AzaGly7, Arg(Me)9]MS10	1030.2	1030.5	7.5	c	I
332	des(1-5)-GluAmb-[AzaGly7,Arg(Me)9]MS10	828.6	828.5	9.9	c	H+J
333	des(1-5)-GluAmb-[Arg(Me)9]MS10	827.5	827.5	10.5	a	E+J
334	des(1-5)-GluAmb-[AzaGly7,Arg(Me)9,Trp10]MS10	887.6	887.5	10.3	c	H+J
339	des(1-5)-3-(3-Indol)propionil-[AzaGly7,Arg(Me)9]MS10	824.6	824.5	16.0	c	S
340	des(1-5)-3-(3-Piridil)propionil-[AzaGly7,Arg(Me)9]MS10	786.4	786.4	8.5	c	S
341	des(1-5)-Benzoil-[AzaGly7,Arg(Me)9]MS10	757.2	757.4	14.8	c	S
344	des(1-5)-Indol-3-carbonil-[AzaGly7,Arg(Me)9]MS10	796.5	796.4	14.5	c	S
345	des(1-5)-Indol-3-acetil-[AzaGly7,Arg(Me)9]MS10	810.5	810.4	15.2	c	S
346	des(1-5)-Ac-[AzaGly7,Arg(Me)9]MS10	695.5	695.4	10.7	c	S
347	des(1-5)-n-Hexanoil-[AzaGly7,Arg(Me)9]MS10	751.7	751.5	16.2	c	S
348	des(1-5)-Z-[AzaGly7,Arg(Me)9]MS10	787.5	787.4	16.7	c	S
349	des(1-5)-Tos-[AzaGly7,Arg(Me)9]MS10	807.5	807.4	15.9	c	S
351	des(1-5)-Benzoil-MS10	742.4	742.4	15.1	c	A+J
352	des(1-5)-3-(3-Indol)propionil-MS10	809.6	809.4	16.2	c	A+J
353	des(1-5)-Benzoil-[AzaGly7,Arg(Me)9,Trp10]MS10	796.4	796.4	15.0	c	S
354	des(1-5)-3-(3-Indol)propionil-[AzaGly7,Arg(Me)9,Trp10]MS10	863.4	863.5	16.2	c	S

359	des(1-5)-As [AzaGly7,Arg(Me)9 Trp10]MS10	734.4	734.4	11.2	c	S
362	des(1-5)-3-Fen[propion]-[AzaGly7,Arg(Me)9]MS10	638.4	638.4	12.3	c	S
364	des(1-5)-2-(Indol-3-[Oct]carbamoil-[AzaGly7,Arg(Me)9]MS10	839.6	839.5	16.8	c	N
366	des(1-5)-n-Hexanoil-[AzaGly7,Arg(Me)9,Trp10]MS10	790.5	790.5	16.5	c	S
367	des(1-5)-2-[AzaGly7,Arg(Me)9,Trp10]MS10	826.5	826.4	16.8	c	S
368	des(1-5)-Tos-[AzaGly7,Arg(Me)9,Trp10]MS10	846.5	846.4	16.0	c	S
369	des(1-5)-2-(Indol-3-il)[et]carbamoil-[AzaGly7,Arg(Me)9,Trp10]MS10	878.9	878.5	16.1	c	N

[TABLA 8]

373	des(1-6)-(2S)-2-acetoxi-3-fenilpropanil-[AzaGly7,Arg(Me)9,Trp10]MS10	735.5	735.4	13.6	c	S
374	des(1-6)-Z-[AzaGly7,Arg(Me)9,Trp10]MS10	679.5	679.4	31.2	c	S
375	2-Aminoetil-Gly-[D-Tyr1,Arg(Me)9]MS10	1416.4	1416.7	17.3	e	E
376	des(1-6)-Difenilacetil-[AzaGly7,Arg(Me)9,Trp10]MS10	738.4	738.4	15.9	c	S
379	des(1-6)-(2S)-2-(3-Indolilpropioniloxi)-3-fenilpropanil-[AzaGly7,Arg(Me)9,Trp10]MS10	864.7	864.5	16.2	c	S
380	des(1-6)-(2S)-2-Benzoiloxi-3-fenilpropanil-[AzaGly7,Arg(Me)9,Trp10]MS10	787.6	787.4	17.2	c	S
385	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1204.4	1204.6	8.3	c	O
388	des(1-3)-3-(3-Piridil)propanil-[AzaGly7,Arg(Me)9,Trp10]MS10	1026.4	1026.2	8.5	c	I
397	Dap-[D-Tyr1,Arg(Me)9]MS10	1402.7	1402.7	17.0	e	E
398	des(1-6)-Benzoil-[Ala8,AzaGly7,Arg(Me)9,Trp10]MS10	720.5	720.4	11.4	c	S
399	des(1-6)-Dibencilcarbamoil-[AzaGly7,Arg(Me)9,Trp10]MS10	788.7	788.4	16.9	c	P
407	Metiltiocarbamoil-Ser-[D-Tyr1,Arg(Me)9]MS10	1481.2	1480.7	20.0	e	E
409	(S)-1-(Quinolin-8-il-carbamoil)-4-tiopentilcarbamoil-[D-Tyr1,Arg(Me)9]MS10	1817.9	1817.7	21.7	e	E
408	des(1-6)-1-Oxo-isocroman-3-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	719.1	719.4	11.3	c	S

412	des(1-5)-(2R)-2-Benzoilamino-3-Fenilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10	796.8	797.4	17.1	c	S
417	des(1-5)-Bencilfenetilcarbamoil-[AzaGly7,Arg(Me)9,Trp10]MS10	782.8	782.4	17.8	c	P
421	des(1-5)-Benzoil-[6Ψ7,CH2O,Arg(Me)9,Trp10]MS10	782.2	782.4	22.1	a	Q
423	des(1-5)-Benzoil-[6Ψ7,NHCO,Arg(Me)9,Trp10]MS10	795.4	795.4	19.8	a	I+K
428	des(1-5)-Dibencilaminoacetamoil-[AzaGly7,Arg(Me)9,Trp10]MS10	783.8	783.4	17.0	c	P
431	des(1-5)-Benzoil-[AzaPhe6,AzaGly7,Arg(Me)9,Trp10]MS10	797.7	797.4	16.3	c	U
432	des(1-5)-3-(3-Piridil)propionil-[AzaGly7,Arg(Me)9,Trp10]MS10	797.8	797.4	9.2	a	S
434	des(1-7)-Dibencilaminoacetamoilacetil-[Arg(Me)9,Trp10]MS10	797.6	797.4	14.6	a	R
435	des(1-5)-2-Piridincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	797.7	797.4	14.1	c	S
436	des(1-5)-4-Piridincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	797.8	797.4	8.8	a	S
437	des(1-5)-Propionil-[AzaGly7,Arg(Me)9,Trp10]MS10	748.7	748.4	14.4	c	S
438	des(1-5)-Isobutiril-[AzaGly7,Arg(Me)9,Trp10]MS10	762.4	762.4	13.7	c	S
439	des(1-5)-Ciclohexancarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	802.6	802.5	16.3	c	S

[TABLA 9]

440	des(1-5)-Feniacetil-[AzaGly7,Arg(Me)9,Trp10]MS10	810.1	810.4	15.6	c	S
441	des(1-5)-Benzoil-[Pya(2)8,AzaGly7,Arg(Me)9,Trp10]MS10	797.6	797.4	9.5	c	S
442	des(1-5)-Benzoil-[Pya(4)8,AzaGly7,Arg(Me)9,Trp10]MS10	797.6	797.4	9.1	c	S
443	des(1-5)-2-Metilnicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10	811.6	811.4	9.0	c	S
444	des(1-5)-5-Metilnicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10	811.5	811.4	9.2	c	S
445	des(1-5)-6-Metilnicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10	811.4	811.4	8.6	c	S
446	des(1-5)-Pirazincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	798.4	798.4	12.4	c	S
447	des(1-5)-Ciclopropancarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	785.9	786.5	13.0	c	S
448	des(1-5)-Trifluoracetil-[AzaGly7,Arg(Me)9,Trp10]MS10	788.6	788.4	14.8	c	S
449	des(1-5)-Benzoil-[Cha8,AzaGly7,Arg(Me)9,Trp10]MS10	802.6	802.5	17.2	c	S
450	des(1-5)-Bencil-[AzaGly7,Arg(Me)9,Trp10]MS10	782.7	782.4	11.2	c	H+D
451	des(1-5)-Ciclopropancarbonil-[Cha8,AzaGly7,Arg(Me)9,Trp10]MS10	785.9	786.5	15.1	c	S
452	des(1-5)-(R)-3-hidroxi-2-metilpropionil-[AzaGly7,Arg(Me)9,Trp10]MS10	777.6	778.4	11.4	c	S
453	des(1-5)-2-Hidroxiisobutiril-[AzaGly7,Arg(Me)9,Trp10]MS10	777.9	778.4	11.9	c	S
454	des(1-5)-3-Furancarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	786.8	786.4	13.7	c	S
455	des(1-5)-Pirrol-2-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	785.7	785.4	13.9	c	S
456	des(1-5)-4-Imidazolcarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	786.6	786.4	8.5	c	S
460	des(1-5)-4-Piridincarbonil-[AzaGly7,Val8,Arg(Me)9,Trp10]MS10	783.5	783.4	6.7	c	S
461	des(1-5)-4-Piridincarbonil-[AzaGly7,Arg(Me)9,Nal(2)10]MS10	809.5	809.4	11.1	c	S
462	des(1-5)-6-Hidroxinicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10	813.5	813.4	10.2	c	S
463	des(1-5)-6-Cloronicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10	831.5	831.4	14.3	c	S
464	des(1-5)-6-(Trifluorometil)nicotinoil-[AzaGly7,Arg(Me)9,Trp10]MS10	865.7	865.4	15.9	c	S
466	des(1-5)-2-Azetidincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	775.6	775.4	8.9	c	H
467	des(1-5)-Dimetilcarbamoil-[AzaGly7,Arg(Me)9,Trp10]MS10	763.7	763.4	12.5	c	H+N
468	des(1-5)-1-Azetidincarbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	775.4	775.4	12.5	c	H+N
471	des(1-5)-4-Piridincarbonil-[AzaGly7,Arg(Me)9]MS10	758.5	758.5	9.1	c	S
472	des(1-5)-4-Aminobenzoil-[AzaGly7,Arg(Me)9,Trp10]MS10	811.5	811.4	11.2	c	H
473	des(1-5)-4-Aminometilbenzoil-[AzaGly7,Arg(Me)9,Trp10]MS10	825.5	825.5	9.5	c	H

[TABLA 10]

474	des(1-5)-Pirrol-3-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	785.8	785.4	12.2	c	S
475	des(1-5)-Pirimidin-4-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	798.8	798.4	12.2	c	S
477	des(1-5)-4-Piridincarbonil-[AzaGly7,Orn8,Trp10]MS10	741.8	741.3	8.8	c	G+I
478	des(1-5)-4-Piridincarbonil-[AzaGly7,Har8,Trp10]MS10	797.8	797.4	8.6	c	G+I
479	des(1-5)-Pirimidin-2-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	798.8	798.4	11.8	c	S
480	des(1-5)-Piridazin-4-carbonil-[AzaGly7,Arg(Me)9,Trp10]MS10	798.8	798.4	10.7	c	S
481	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9,Trp10]MS10	1204.8	1204.6	8.2	c	G
486	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Orn9]MS10	1109.6	1109.6	13.6	c	G
487	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Lys9]MS10	1123.5	1123.6	13.5	c	G
488	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9]MS10	1165.6	1165.6	14.1	c	G
489	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har(Me)9]MS10	1178.6	1178.6	13.8	c	G
490	des(1)-[D-Tyr2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1165.6	1165.6	7.6	c	H
491	des(1)-[D-Tyr2,D-Pya(4)3,Trp5,AzaGly7,Arg(Me)9,Trp10]MS10	1303.6	1303.6	17.2	c	O
492	des(1)-[D-Tyr2,D-Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1161.9	1161.6	14.3	c	O
493	des(1)-[D-Tyr2,D-Pya(4)3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10	1191.9	1191.6	14.2	c	O
494	des(1,4)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1090.9	1090.6	8.4	c	O
495	des(1-3)-[D-Tyr4,Pya(4)5,AzaGly7,Arg(Me)9,Trp10]MS10	1003.9	1003.5	7.8	c	O
496	des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Arg(Me)9,Trp10]MS10	1209.8	1209.7	10.4	c	E
497	des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Ala7,Arg(Me)9,Trp10]MS10	1223.7	1223.7	10.5	c	E
498	des(1)-[D-Tyr2,D-Pya(4)3,Ile5,AzaGly7,Arg(Me)9,Trp10]MS10	1230.7	1230.7	16.8	c	O
499	des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	1025.3	1025.5	13.8	c	T
500	des(1-3)-3-Phenylpropionyl-[Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	982.5	982.5	15.1	c	T
501	des(1)-[D-Tyr2,D-Pya(4)3,Thr6,AzaGly7,Arg(Me)9,Trp10]MS10	1218.7	1218.6	14.2	c	O
502	des(1)-[D-Tyr2,Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1161.4	1161.6	14.0	c	O

503	des(1)-[D-Tyr2,D-Trp3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1198.3	1189.6	17.8	e	O
504	[Ace1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1278.6	1278.5	8.1	c	H
505	des(1-3)-3-Fenilpropionil-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1040.0	1039.5	13.9	c	T
506	des(1-3)-3-Fenilpropionil-[Ile5,AzaGly7,Arg(Me)9,Trp10]MS10	1052.0	1051.6	17.6	c	T
507	des(1-3)-3-Fenilpropionil-[Trp6,AzaGly7,Arg(Me)9,Trp10]MS10	1064.2	1064.5	13.7	c	T

[TABLA 11]

508	des(1-3)-3-Fenilpropionil-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1043.2	1043.5	14.1	c	T
509	des(1-3)-Benzoil-[AzaGly7,Arg(Me)9,Trp10]MS10	997.8	997.5	12.4	c	T
510	des(1-3)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10	935.9	935.5	9.5	c	T
511	des(1)-[D-Tyr2,D-Trp3,Ala4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1213.6	1213.6	17.9	e	O
512	des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1258.7	1258.6	17.0	e	O
513	des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10	1213.6	1213.6	18.5	e	O
514	des(1)-[D-Tyr2,D-Phe3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1160.8	1160.6	17.9	e	O
515	des(1)-[D-Tyr2,D-Pya(4)3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10	1216.6	1216.6	15.7	e	O
	a:0-70% AcCN/35min, caudal 1ml/min, Wakosil-II 5C18 HG (4.6 x 100mm)					
	b:0-70% AcCN/35min, caudal 1ml/min, YMC ODS AM-301 (4.6 x 100mm)					
	c:20-70% AcCN/25min, caudal 1ml/min, YMC ODS AM-301 (4.6 x 100mm)					
	d:5-75% AcCN/35min, caudal 1ml/min, Wakosil-II 5C18 HG (4.6 x 100mm)					
	e:0-50% AcCN/25min, caudal 1ml/min, Wakosil-II 5C18 HG (4.6 x 100mm)					
	Solo compuesto nro. 1 representa valor M+					

Las estructuras de compuestos sintetizados como en los EJEMPLOS 1 a 24 y propiedades fisicoquímicas de estos compuestos se ilustran más adelante en la TABLA 12.

[TABLA 12]

Comp. No.		MH+ (obs.)	MH+ (calc.)	HPLC (min.)	modo HPLC
516	Ac-des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1207.8	1207.5	9.8	e
517	des(1-3)-3-Fenilpropionil-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1051.6	1051.5	13.7	c
518	des(1-3)-3-Fenilpropionil-[Phe6,Arg(Me)9,Trp10]MS10	1030.8	1030.6	15.8	c
519	des(1-3)-Fenilacetil-[AzaGly7,Arg(Me)9,Trp10]MS10	1011.5	1011.5	12.7	c
521	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10	1161.6	1161.6	13.4	e
522	des(1-3)-Benzoil-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1011.9	1011.5	12.7	c
523	des(1-3)-Benzoil-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1029.9	1029.5	13.1	c
524	des(1-3)-3-Fenilpropionil-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10	1035	1035.6	15.8	c
527	des(1)-[D-Tyr2,D-Pya(4)3,Hse4,AzaGly7,Arg(Me)9,Trp10]MS10	1230.5	1230.6	14.9	e
528	[illegible]				

557	D-Arg-D-Asn-D-Arg-Lit-Asp(1)-D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1608.8	1610	15.8	a
558	Asn-des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)8,Trp10]MS10	1284.6	1284.6	12.3	c
559	3-(4-[Nitrophenyl]propionyl-des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1241.3	1241.8	14.4	a
561	D-Arg-[Asp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)8,Trp10]MS10	1482.6	1482.8	17.8	a
562	Ac-des(1)-[D-Tyr2,D-Pro4(OH),Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1260.4	1260.4	13.5	a
563	Ac-des(1)-[D-Tyr2,D-Trp3,Pro4(OH),Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1260.6	1260.6	14.1	c
564	Ac-des(1)-[D-Tyr2,D-Trp3,Val8,AzaGly7,Arg(Me)8,Trp10]MS10	1296.5	1296.7	16.9	a
565	Benzo[]-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1360.6	1360.7	15.7	a
566	Cyclopropancarbon[]-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1324.6	1324.7	14.5	c
567	Ethyl-[]-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1326.6	1326.7	14.8	c
568	Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1454.7	1454.7	17.2	a
569	Asn-des(1)-[D-Tyr2,D-Trp3,Thr5,[*]7,CH2NH,Arg(Me)8,Trp10]MS10	1282.7	1283.7	17.7	a
570	Ala-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1270.6	1270.6	16.5	c
571	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8]MS10	1259.6	1259.6	13.2	c
572	des(1)-[D-Tyr2,D-Pro4(1)3,AzaGly7,Arg(Me)8,Trp10]MS10	1227.6	1227.6	16.1	c
573	Ac-des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)8,Trp10]MS10	1255.6	1255.6	16.4	a
576	Ac-des(1)-[D-Tyr2,D-Trp3,Dhb4,AzaGly7,Arg(Me)8,Trp10]MS10	1298.6	1298.6	16.2	a
577	Ac-des(1)-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)8,Trp10]MS10	1257.7	1257.6	16.8	a
578	Ac-des(1)-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)8,Trp10]MS10	1271.6	1271.6	16.8	a
579	Ac-des(1)-[D-Tyr2,D-Trp3,Ala4,AzaGly7,Arg(Me)8,Trp10]MS10	1255.6	1255.6	19	a
580	Ac-des(1)-[D-Tyr2,D-Trp3,Ser(Me)4,AzaGly7,Arg(Me)8,Trp10]MS10	1269.4	1269.6	19.3	a

Compd. No.	Structure	[M+H]+ (obs.)	[M+H]+ (calc.)	HPLC (min.)	Grade	HPLC	Proc. Sta.
584	des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)8,Trp10]MS10	1288.7	1288.6	18.7	e		X
585	des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)8,Trp10]MS10	1284.7	1284.6	17.9	e		X
586	des(1)-Ac-[D-Tyr2,Thr3,D-Phe4,AzaGly7,Arg(Me)8,Trp10]MS10						W
589	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Nal(2)10]MS10	1309.6	1309.6	15.2	c		W
590	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Thi10]MS10	1285.5	1285.6	13.4	c		W
591	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Tyr10]MS10	1275.5	1276.6	12.2	c		W
592	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Phe(4F)10]MS10	1277.5	1277.6	14	c		W
594	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Hph10]MS10	1273.6	1273.6	14.6	c		W
597	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)8,Trp10]MS10	1288.6	1288.7	14.1	c		W
598	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)8,Trp10]MS10	1287.5	1287.6	18.5	e		H+W
599	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10	1242.4	1242.6	17.8	e		G+W
600	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10	1284.7	1284.6	17.9	e		Q+W
601	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)8,Trp10]MS10	1287.6	1287.6	18.2	e		H+W
602	des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1312.7	1312.7	19	e		W
603	des(1)-Ac-[D-Tyr2,D-Pro(4S)3,Thr5,D-Phe6,AzaGly7,Arg(Me)8,Trp10]MS10	1298.6	1298.6	16.3	e		W
604	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1438.6	1438.6	20.5	e		G+W
605	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)8,Trp10]MS10	1329.4	1329.6	18.7	e		G+W
607	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2asym)8,Trp10]MS10	1312.8	1312.7	18.1	e		W
608	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2sym)8,Trp10]MS10	1312.8	1312.7	18.1	e		W
609	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)8,Trp10]MS10	1312.8	1312.7	17.7	e		W
610	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me)2,8,Trp10]MS10	1284.9	1284.7	11.7	e		G+W
611	des(1)-Ac-[Tyr2,D-Pro(4S)3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1260.9	1260.6	14.4	e		W
612	des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1284.7	1284.6	17.8	e		T+W
613	des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1312.6	1312.7	18.3	c		T+W
614	des(1)-Acrylyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1296.4	1296.7	16.9	e		J+W
615	des(1)-Ac-[Tyr2,D-Pro(4S)3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1299	1298.6	13.9	c		W
616	des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1256.8	1256.6	13.1	c		W
617	des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1248.9	1248.7	15.5	c		W
618	des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1298.7	1298.6	15.8	c		W
619	des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1332.6	1332.7	17.6	c		W
620	des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1332.4	1332.7	17.7	c		W
621	des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1263.8	1263.7	11.3	c		W
622	des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1264.8	1264.4	12.7	c		W
623	des(1)-Ac-[D-Tyr2,Trp3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1298.9	1298.6	14.2	c		W
624	des(1)-Ac-[D-Tyr2,Pro(4S)3,Thr5,AzaGly7,Arg(Me)8,Trp10]MS10	1260.8	1260.6	10.2	c		W

625	des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1183.8	1183.6	11.4	g	W
626	des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1225	1225.6	13.3	c	W
627	des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1259.9	1259.6	13.8	c	W
628	des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1213.8	1213.6	11.1	g	W
629	des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1240.9	1240.7	10.1	c	W
630	des(1)-Ac-[D-Tyr2,D-Gln3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1241.9	1241.6	11.3	c	W
631	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1222.9	1222.6	11.8	c	W
632	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1265	1264.7	13.5	g	W
633	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1279.9	1279.7	10.4	c	W
634	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Gln6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1280.9	1280.6	11.5	c	W
635	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4)6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1299.9	1299.6	10.8	c	W
636	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,MePhe6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1313.4	1313.7	15.4	c	W
637	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1316.5	1316.6	14.4	c	W
638	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1278.6	1278.6	10.7	c	W
639	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Lys8,Trp10]MS10	1256.9	1256.6	17.5	g	G+W
640	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,D-Leu8,Arg(Me)9,Trp10]MS10	1298.7	1298.6	17.6	g	W
641	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Ala8,Arg(Me)9,Trp10]MS10	1256.9	1256.6	18.5	g	W
642	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Val8,Arg(Me)9,Trp10]MS10	1284.9	1284.6	17.4	g	W
643	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Phe8,Arg(Me)9,Trp10]MS10	1332.4	1332.6	18.3	c	W
644	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Ser8,Arg(Me)9,Trp10]MS10	1272.9	1272.6	15.8	g	W
645	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Hse8,Trp10]MS10	1280.1	1280.6	17.7	g	G+W
646	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Har(Me)9,Trp10]MS10	1313.1	1312.7	17.9	g	W
647	des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,Asn(Gly7,Arg(Me)9,Trp10]MS10	1299.9	1299.6	18.2	g	W
648	[Gly1,D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1313.8	1313.7	18	g	W
649	Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1355.9	1355.7	17.4	g	W
650	[D-Tyr1,D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1419.8	1419.7	16.8	g	W
651	Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1461.4	1461.7	18	g	W
652	pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1367.4	1367.7	17.6	g	W
653	des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1298.8	1298.6	18.2	g	W
654	des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1298.8	1298.6	17.5	g	W
655	des(1)-Ac-[D-Tyr2,D-Trp3,Hyp4,Asn5,Thr6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1312.8	1312.7	18.3	g	W
656	des(1)-Ac-[D-Tyr2,D-Trp3,Ala5,Ser6,Asn(Gly7,Arg(Me)8,Trp10]MS10	1298.8	1298.6	17.8	g	W
657	des(1)-Ac-[D-Tyr2,Pro3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1298.2	1298.6	18.4	c	W
658	des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1260.2	1260.6	19.4	c	W
659	des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1298.8	1298.6	17.9	c	W
660	des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1260.8	1260.6	19.2	g	W

661	des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1298.8	1298.6	11.5	g	W
662	des(1)-Ac-[D-Tyr2,Thr3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1271.4	1271.4	13.9	c	W
663	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1321.7	1321.7	18.9	c	W
664	des(1)-Ac-[Tyr2,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1298.7	1298.9	14.1	c	W
665	des(1-2)-[D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1083.7	1083.8	11.1	c	O
666	des(1-2)-Ac-[D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1125.7	1125.8	13.4	g	T+W
667	des(1-2)-Hyvanal-[D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1181.4	1181.8	17.2	g	T+W
668	des(1-2)-Glutathionaneurbeal-[D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS	1303.5	1303.8	17.1	g	T+W
669	des(1-2)-Bagpeal-[D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1197.6	1197.8	16	g	T+W
670	des(1-2)-2-Pyridylcarbeal-[D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1226.7	1226.8	11.6	c	T+W
671	des(1-2)-Agglycal-[D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1221.6	1221.8	13.6	g	T+W
672	des(1)-Ac-[D-Tyr2,MeTrp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1312.8	1312.7	14.6	c	W
673	des(1)-Ac-[Asp2,D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1299.7	1299.7	11.5	c	T+W
674	[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1419.8	1419.7	18.8	g	W
675	Ac-[D-Tyr2,D-Trp3,Thr5,Asn(Gly7,Arg(Me)8,Trp10]MS10	1461.4	1461.7	18	g	W

EJEMPLO DE FORMULACIÓN 1:

(1) Compuesto No. 305	10,0 mg
(2) Lactosa	60,0 mg
(3) Amidón de maíz	35,0 mg
(4) Gelatina	3,0 mg
(5) Estearato de magnesio	2,0 mg,

Una mezcla de 10,0 mg de Compuesto No. 305, 60,0 mg de lactosa y 35,0 mg de almidón de maíz granulados con 0,03 ml solución 10% gelatina acuosa (3,0 mg como gelatina) a través de cedazo malla 1 mm, secado a 40°C y filtrado de nuevo. Los gránulos así obtenidos se mezclan con 2,0 mg de estearato de magnesio y comprimidos. Las tabletas de centro resultantes se recubrieron con recubrimiento de azúcar de una suspensión acuosa de sacarosa, dióxido de titanio, talco y goma árabe. Las tabletas recubiertas fueron pulidas con cera amarilla para obtener tabletas recubiertas.

EJEMPLO DE FORMULACIÓN 2

(1) Compuesto No. 305	10,0 mg
(2) Lactosa	70,0 mg

(3) Almidón de maíz 50,0 mg

(4) Almidón soluble 7,0 mg

(5) Estearato de magnesio 3,0 mg.

Una mezcla de 10 mg de Compuesto 305 y 3,0 mg de estearato de magnesio fueron granulados con 0,07 ml de una solución acuosa de un almidón soluble (7,0 mg como almidón soluble), fueron secados, y mezclados con 70,0 mg de lactosa y 50,0 mg de almidón de maíz. La mezcla se comprime para obtener tabletas.

EJEMPLO DE FORMULACIÓN 3

(1) Compuesto No. 305 5,0 mg

(2) Sal 20,0 mg.

(3) Agua destilada para hacer 2 ml de volumen total

Después que 5,0 mg del Compuesto No. 305 y 20,0 mg de sal se disuelven en agua destilada, se agrega agua a la solución para hacer un volumen total de 2,0 ml. La solución fue filtrada y fue rellenada una ampolla de 2 ml bajo condiciones asépticas. La ampolla fue esterilizada y sellada para obtener una solución para inyección.

EJEMPLO DE FORMULACIÓN 4:

(1) Compuesto No. 550 10,0 mg

(2) Lactosa 60.0 mg

(3) Almidón de maíz 35,0 mg

(4) Gelatina 3,0 mg

(5) Estearato de magnesio 2,0 mg.

Una mezcla de 10,0 mg de compuesto No. 550, 60,0 mg de lactosa y 35,0 mg de almidón de maíz son granulados con 0,03 ml de solución acuosa 10% de gelatina (3,0 mg como gelatina) a través de un filtro de malla de 1 mm,. fue secada a 40°C y

filtrada de nuevo. Los gránulos así obtenidos son mezclados con 2,0 mg de estearato de magnesio y fueron comprimidos. Las tabletas de centro resultantes son recubiertas con recubrimiento de azúcar de una suspensión acuosa de sacarosa, dióxido de titanio, talco y goma árabe. Las tabletas recubiertas fueron pulidas con cera amarilla para obtener las tabletas recubiertas.

EJEMPLO DE FORMULACIÓN 5

(1) Compuesto No. 550	10,0 mg
(2) Lactosa	70,0 mg
(3) Almidón de maíz	50,0 mg
(4) Almidón soluble	7,0 mg
(5) Astearato de magnesio	3,0 mg,

Una mezcla de 10 mg de Compuesto 550 y 3,0 mg de estearato de magnesio es granulado con 0,07 ml de una solución acuosa de un almidón soluble (7,0 mg como almidón soluble), fue secada, y mezclada con 70,0 mg de lactosa y 50,0 mg de almidón de maíz. La mezcla fue comprimida para obtener las tabletas.

EJEMPLO DE FORMULACIÓN 6

(1) Compuesto No. 550	5,0 mg
(2) Sal	20,0 mg

(3) Agua destilada para hacer un volumen total de 2 ml

Después que 5,0 mg de Compuesto No. 550 y 20,0 mg de sal se disuelven en agua destilada, se agrega agua a la solución para hacer 2,0 ml de volumen total. La solución fue filtrada y fue rellenada una ampolla de 2 ml bajo condiciones asépticas. La ampolla fue esterilizada y sellada para obtener una solución para inyección.

EJEMPLO DE FORMULACIÓN 7:

(1) Compuesto No. 562	10,0 mg
(2) Lactosa	60,0 mg
(3) Almidón de maíz	35,0 mg
(4) Gelatina	3,0 mg
(5) Estearato de magnesio	2,0 mg,

Una mezcla de 10,0 mg de Compuesto No, 562, 60,0 mg de lactosa y 35,0 mg de almidón de maíz es granulado con 0,03 ml de 10% solución de gelatina acuosa (3,0 mg como la gelatina) a través de un filtro de malla de 1 mm, secada a 40°C y filtrada de nuevo. Los gránulos así obtenidos son mezclados con 2,0 mg de estearato de magnesio y comprimidos. Las tabletas de centro resultantes son recubiertas con recubrimiento de azúcar de una suspensión acuosa de sacarosa, dióxido de titanio, talco y goma árabe. Las tabletas recubiertas fueron pulidas con cera amarilla para obtener las tabletas recubiertas.

EJEMPLO DE FORMULACIÓN 8

(1) Compuesto No. 562	10,0 mg
(2) Lactosa	70,0 mg
(3) Almidón de maíz	50,0 mg
(4) Almidón soluble	7,0 mg
(5) Estearato de magnesio	3,0 mg,

Una mezcla de 10 mg de Compuesto 562 y 3,0 mg de estearato de magnesio es granulado con 0,07 ml de una solución acuosa de un almidón soluble (7,0 mg como almidón soluble), fue secada, y mezclada con 70,0 mg de lactosa y 50,0 mg de almidón de maíz. La mezcla fue comprimida para obtener las tabletas.

EJEMPLO DE FORMULACIÓN 9

(1) Compuesto No. 562	5,0 mg

(2) Sal 20,0 mg

(3) Agua destilada para hacer un volumen total de 2 ml.

Después quee 5,0 mg de compuesto No. 562 y 20,0 mg de sal se disuelven en agua destilada, se agrega agua a la solución para hacer un volumen total de 2,0 ml. La solución fue filtrada y fue rellenada una ampolla del 2 ml bajo condiciones asépticas. La ampolla fue esterilizada y sellada para obtener una solución para inyección.

EJEMPLO DE FORMULACIÓN 10:

(1) Compuesto No. 571 10,0 mg

(2) Lactosa 60,0 mg

(3) Almidón de maíz 35,0 mg

(4) Gelatina 3,0 mg

(5) Estearato de magnesio 2,0 mg,

Una mezcla de 10,0 mg de Compuesto No, 571, 60,0 mg de lactosa y 35,0 mg de almidón de maíz es granulado con 0,03 ml de 10% solución de gelatina acuosa (3,0 mg como gelatina) a través de un filtro de malla de 1 mm, secada a 40°C y filtrada de nuevo. Los gránulos así obtenidos son mezclados con 2,0 mg de estearato de magnesio y comprimidos. Las tabletas de centro resultantes son recubiertas con recubrimiento de azúcar de una suspensión acuosa de sacarosa, dióxido de titanio, talco y goma árabe. Las tabletas recubiertas fueron pulidas con cera amarilla para obtener las tabletas recubiertas.

EJEMPLO DE FORMULACIÓN 11

(1) Compuesto No. 571 10,0 mg

(2) Lactosa 70,0 mg

(3) Almidón de maíz 50,0 mg

(4) Almidón soluble 7,0 mg

(5) Estearato de magnesio 3,0 mg,

Una mezcla de 10 mg de Compuesto 571 y 3,0 mg de estearato de magnesio es granulado con 0,07 ml de una solución acuosa de un almidón soluble (7,0 mg como almidón soluble), fue secada, y mezclada con 70,0 mg de lactosa y 50,0 mg de almidón de maíz. La mezcla fue comprimida para obtener las tabletas.

EJEMPLO DE FORMULACIÓN 12

(1) Compuesto No. 571 5,0 mg

(2) Sal 20,0 mg

(3) agua destilada para hacer un volumen total de 2 ml.

Después que 5,0 mg que el compuesto No. 571 y 20,0 mg de sal se disuelven en el agua destilada, se agrega agua a la solución para hacer 2,0 ml al volumen total. La solución es filtrada y se rellena una ampolla de 2 ml bajo condiciones asépticas. La ampolla es esterilizada y sellada para obtener una solución para inyección.

FORMULACIÓN EJEMPLO 13:

(1) Compuesto No. 579 10,0 mg

(2) Lactosa 60,0 mg

(3) Almidón de maíz 35,0 mg

(4) Gelatina 3,0 mg

(5) Estearato de magnesio 2,0 mg,

Una mezcla de 10,0 mg de Compuesto No, 579, 60,0 mg de lactosa y 35,0 mg de almidón de maíz es granulado con 0,03 ml de 10% solución de gelatina acuosa (3,0 mg como la gelatina) a través de un filtro de malla de 1 mm, secada a 40°C y filtrada de nuevo. Los gránulos así obtenidos son mezclados con 2,0 mg de

estearato de magnesio y son comprimidos. Las tabletas de centro resultantes son recubiertas con recubrimiento de azúcar de una suspensión acuosa de sacarosa, dióxido de titanio, talco y goma árabe. Las tabletas recubiertas fueron pulidas con cera amarilla para obtener las tabletas recubiertas.

EJEMPLO DE FORMULACIÓN 14

(1) Compuesto No. 579	10,0 mg
(2) Lactosa	70,0 mg
(3) Almidón de maíz	50,0 mg
(4) Almidón soluble	7,0 mg
(5) Estearato de magnesio	3,0 mg,

Una mezcla de 10 mg de Compuesto 579 y 3,0 mg de estearato de magnesio es granulado con 0,07 ml de una solución acuosa de un almidón soluble (7,0 mg como almidón soluble), fue secado, y mezclado con 70,0 mg de lactosa y 50,0 mg de almidón de maíz. La mezcla fue comprimida para obtener las tabletas.

EJEMPLO DE FORMULACIÓN 15

(1) Compuesto No. 579	5,0 mg
(2) Sal	20,0 mg

(3) Agua destilada para hacer un volumen total de 2 ml

Después de 5,0 mg de Compuesto No. 579 y 20,0 mg de sal se disuelven en agua destilada, se agrega agua a la solución para hacer un volumen total de 2,0 ml. La solución fue filtrada y fue rellenada una ampolla de 2 ml bajo condiciones asépticas. La ampolla fue esterilizada y sellada para obtener una solución para inyección.

EJEMPLO DE FORMULACIÓN 16:

(1) Compuesto No. 585	10,0 mg

(2) Lactosa 60,0 mg

(3) Almidón de maíz 35,0 mg

(4) Gelatina 3,0 mg

(5) Estearato de magnesio 2,0 mg.

Una mezcla de 10,0 mg de Compuesto No. 585, 60,0 mg de lactosa y 35,0 mg de almidón de maíz es granulada con 0,03 ml de solución 10% de gelatina acuosa (3,0 mg como gelatina) a través de un filtro de malla de 1 mm, fue secada a 40°C y filtrada de nuevo. Los gránulos así obtenidos fueron mezclados con 2,0 mg de estearato de magnesio y comprimidos. Las tabletas de centro resultantes fueron recubiertas con recubrimiento de azúcar de una suspensión acuosa de sacarosa, dióxido de titanio, talco y goma árabe. Las tabletas recubiertas fueron pulidas con cera amarilla para obtener las tabletas recubiertas.

EJEMPLO DE FORMULACIÓN 17

(1) Compuesto No. 585 10.0 mg

(2) Lactosa 70,0 mg

(3) Almidón de maíz 50,0 mg

(4) Almidón soluble 7,0 mg

(5) Estearato de magnesio 3,0 mg,

Una mezcla de 10 mg de Compuesto 585 y 3,0 mg de estearato de magnesio es granulado con 0,07 ml de una solución acuosa de un almidón soluble (7,0 mg como almidón soluble), fue secada y mezclada con 70,0 mg de lactosa y 50,0 mg de almidón de maíz. La mezcla fue comprimida para obtener las tabletas.

EJEMPLO DE FORMULACIÓN 18

(1) Compuesto No. 585 5,0 mg

(2) Sal 20,0 mg

(3) Agua destilada para hacer un volumen total de 2 ml.

Después que 5,0 mg de Compuesto No. 585 y 20,0 mg de sal fueron disueltos en agua destilada, se agrega el agua a la solución para hacer un volumen total de 2,0 ml. La solución fue filtrada y fue rellenada una ampolla de 2 ml bajo condiciones asépticas. La ampolla fue esterilizada y sellada para obtener una solución para inyección.

EJEMPLO DE PRUEBA 1

Ensayo para la actividad de enlace a receptor hOT7T175

(1) Preparación de metastina etiquetada con Cy-5 (40-54).

Un péptido sintético que tiene secuencia de 40-54 aminoácidos en la secuencia de aminoácido de metastina en donde se introdujo Cy-5 mediante el grupo ε-amino de lisina localizada en el terminal amino y el terminal carboxilo fue amidatado, fue preparado de acuerdo con la técnica de síntesis "Amersham Bioscience, Inc". Usando este péptido sintético, una prueba para inhibición de enlace fue realizada.

Secuencia: (Cy-5)-KDLPNYNWNSFGLRF-NH_2.

(2) Prueba para inhibición de enlace usando un compuesto de prueba, metastina etiquetada con Cy-5 (40-54) y célula de CHO expresando hOT7T175.

Las células CHO expresando hOT7T175 fueron cutivadas en medio MEM-α (libre de ácido nucleico) que contiene 10% de suero dializado. El medio fue eliminado y las células adheridas se lavaron con PBS. Entonces, el PBS que contiene 5 mM EDTA fue agregado y las células se rasparon de un frasco con un raspador celular.

Después del centrifugado, las células fueron suspendidas en

1,11 x 10^5 células/ml en amortiguador de ensaye (10 mM HEPES pH 7,4, 140 mM NaCl, 2,5 mM $CaCl_2$, 3 mM $MgCl_2$, 0,5% BSA, 0,01% NaN_3) y metastina etiquetada con Cy-5 (40-54) fue agregada a la suspensión en una concentración final de 1 nM. A cada hendidura de una Microplaca de fondo claro negro de 96 hendiduras ("Applied Biosystems, Inc."), 10 µL de amortiguador de ensayo que contiene 1% dimetilsulfóxido fue agregado para examinar el enlace total, 10 µL de 10 µM de la solución diluida de péptido no etiquetado (que posee la misma secuencia de aminoácido como el etiquetado) con amortiguador de ensayo para examinar el enlace no específico, y 10 µL de un compuesto de prueba diluido con amortiguador de ensayo para examinar una actividad de inhibición de enlace del compuesto de prueba, y además, 90 µL cada una de la suspensión celular fue distribuida a cada hendidura. Después de una hora, nivel de metastina etiquetado con Cy-5 (40-54) unido a las células fue determinado por disposición HTS FMAT 8100 ("Applied Biosystems, Inc."). La actividad de enlace específica fue calculada como el enlace no específico restado del enlace total. La actividad de inhibición de enlace de un compuesto de prueba se ilustra por una proporción del valor obtenido restando un valor medido en presencia de un compuesto de prueba del enlace total respecto al enlace específico. La actividad de enlace a receptor del compuesto de prueba se ilustra en las TABLAS 13 a 18.

[TABLA 13]

Número de compuesto		IC50(M)
1	Metastina	1.7E-07
3	MS10	6.5E-09
4	des(1)-MS10	2.6E-07
17	[Pya(4)10]MS10	6.6E-12
18	[Tyr(Me)10]MS10	7.7E-09
19	[Phe(2F)10]MS10	8.6E-09
23	[Tyr5]MS10	4.0E-07
24	[Leu5]MS10	8.3E-10
30	Acetil-MS10	3.1E-08
31	Fmoc-MS10	9.3E-07
32	Leu-Pro-Asn-MS10	2.5E-08
39	[D-Asn4]MS10	8.3E-07
40	[D-Trp3]MS10	1.9E-08
41	[D-Asn2]MS10	2.1E-07
42	[D-Tyr1]MS10	5.7E-08
44	[Lys9]MS10	1.9E-07
50	[Ala7]MS10	1.9E-07
54	des(1-2)-Fmoc-MS10	4.5E-07
57	[Asp2]MS10	1.0E-07
58	[Tyr2]MS10	1.6E-08
59	[Leu2]MS10	3.4E-07
60	[Pya(3)10]MS10	1.7E-07
61	[Phe(4F)10]MS10	1.3E-08
67	[Ala3]MS10	2.7E-08
68	[Leu3]MS10	7.7E-09
69	[Ser3]MS10	8.3E-08
70	[Asp3]MS10	2.0E-07
71	[Lys3]MS10	6.6E-08
72	[Ala1]MS10	5.4E-07
73	[Leu1]MS10	2.2E-07
75	[Asp1]MS10	8.8E-07

[TABLA 14]

77	[Phe(4CN)10]MS10	7.4E-09
78	[Trp(CHO)3, Phe(4CN)10]MS10	2.5E-08
82	[Arg(Me)9]MS10	4.1E-09
83	[Arg(Me2)asy9]MS10	2.5E-08
97	[Har9]MS10	3.7E-07
101	[Ser7]MS10	1.0E-07
105	[Nle8]MS10	8.8E-07
107	[Val8]MS10	1.2E-07
109	[Tyr10]MS10	2.3E-08
110	[Nal(2)10]MS10	2.4E-08
111	[Phe(F5)10]MS10	1.4E-07
112	[Cha10]MS10	3.7E-07
114	des(1-3)-3-(3-indol1)propionil-MS10	5.5E-07
128	[10Ψ,CSNH]MS10	5.5E-08
129	[Arg(Me2)sy9]MS10	8.3E-08
130	[Phe(4Cl)10]MS10	4.2E-08
131	[Phe(4NH2)10]MS10	1.2E-07
132	[Phe(4NO2)10]MS10	9.3E-08
133	[Nal(1)10]MS10	3.3E-07
134	[Trp10]MS10	1.1E-07
141	[D-Tyr1,Arg(Me)9]MS10	5.1E-08
142	[D-Tyr1,D-Trp3,Arg(Me)9]MS10	2.6E-08
143	[D-Trp3,Arg(Me)9]MS10	7.7E-09
145	des(1-2)-Fmoc-[Arg(Me)9]MS10	1.2E-07
146	[10Ψ,CSNHD-Tyr1]MS10	3.7E-07
150	[Tyr6]MS10	3.2E-07
151	[Nal(1)6]MS10	3.0E-07
152	[Nal(2)6]MS10	1.8E-07
153	[Phe(F5)6]MS10	3.9E-07
154	[Phe(4F)6]MS10	6.0E-08
156	[Cha6]MS10	4.9E-08
183	[6Ψ7,CH2NH]MS10	2.5E-07
166	[6Ψ7,CSNH]MS10	9.4E-09
169	[D-Tyr1,Ala3,Arg(Me)9]MS10	1.6E-07
170	[D-Tyr1,Ser3,Arg(Me)9]MS10	2.6E-07

[TABLA 15]

171	[D-Tyr1,Cha3,Arg(Me)9]MS10	1.1E-07
174	[D-Tyr1,Arg(Me)9,Trp10]MS10	4.2E-07
176	[AzaGly7]MS10	5.2E-08
181	[D-Tyr1,Cha3,6,Arg(Me)9]MS10	1.9E-08
182	[D-Tyr1,Cha3,6,Arg(Me)9,Trp10]MS10	9.8E-08
186	[Trp(CHO)10]MS10	4.6E-07
187	[Abu8]MS10	7.2E-07
189	[Ala(3-Bzt)10]MS10	2.3E-07
190	[D-Tyr1,Cha3,AzaGly7,Arg(Me)9]MS10	1.2E-08
191	[D-Tyr1,Ser3,AzaGly7,Arg(Me)9]MS10	3.0E-07
192	[D-Tyr1,Arg(Et)9]MS10	5.3E-07
193	[D-Tyr1,Arg(n-Pr)9]MS10	9.2E-07
194	[D-Tyr1,Arg(Ac)9]MS10	2.1E-07
197	[Phe(3F)10]MS10	1.7E-07
198	[Phe(3,4F2)10]MS10	1.7E-07
199	[Phe(3,4Cl2)10]MS10	4.7E-07
200	[Phe(3CF3)10]MS10	3.4E-07
201	[Ala(2-Qui)10]MS10	8.2E-07
203	[D-Tyr1,Cha6,Arg(Me)9]MS10	3.7E-08
204	[D-Tyr1, Ala7, Arg(Me)9]MS10	6.8E-07
205	[D-Tyr1,Thr3,Arg(Me)9]MS10	2.6E-07
206	[D-Tyr1,Ile3,Arg(Me)9]MS10	8.5E-08
208	[D-Tyr1,Thr4,Arg(Me)9]MS10	8.3E-07
210	[D-Tyr1,Ala4,Arg(Me)9]MS10	7.3E-07
211	[D-Tyr1,Thr5,Arg(Me)9]MS10	4.4E-08
212	[D-Tyr1,Ala5,Arg(Me)9]MS10	3.6E-08
213	[D-Tyr1,Val8,Arg(Me)9]MS10	1.9E-07
214	[D-Tyr1,Gln2,Arg(Me)9]MS10	3.9E-07
215	[D-Tyr1,Thr2,Arg(Me)9]MS10	2.5E-07
216	des(1)-[D-Asn2,Arg(Me)9]MS10	7.0E-07
217	des(1)-[D-Tyr2,Arg(Me)9]MS10	2.5E-07
220	[Arg(Et)9]MS10	3.3E-07
221	[D-Tyr1,Thr3,AzaGly7,Arg(Me)9]MS10	9.5E-08
222	des(1)-[D-Tyr2,AzaGly7,Arg(Me)9]MS10	3.3E-08
223	des(1-2)-[D-Trp3,Arg(Me)9]MS10	7.6E-07

[TABLA 16]

224	des(1)-[D-Tyr2,D-Trp3,Arg(Me)9]MS10	1.4E-07
225	des(1)-[D-Asn2,D-Trp3,Arg(Me)9]MS10	4.1E-07
226	des(1)-[D-Tyr2,Ser3,Arg(Me)9]MS10	1.0E-07
227	des(1)-[D-Tyr2,Thr3,Arg(Me)9]MS10	4.8E-08
228	des(1)-[D-Tyr2,Ile3,Arg(Me)9]MS10	4.0E-08
229	[D-Tyr1,Val3,Arg(Me)9]MS10	1.3E-07
230	[D-Tyr1,D-Asn2,Arg(Me)9]MS10	2.5E-07
231	[D-Tyr1,D-Asn2,D-Trp3,Arg(Me)9]MS10	5.5E-08
232	[D-Tyr1,AzaGly7,Arg(Me)9]MS10	4.9E-08
233	[D-Tyr1,Ile3,AzaGly7,Arg(Me)9]MS10	2.3E-08
234	[D-Tyr1,Val3,AzaGly7,Arg(Me)9]MS10	4.7E-08
235	[D-Tyr1,Ala3,AzaGly7,Arg(Me)9]MS10	1.0E-07
236	[D-Tyr1,D-Trp3,AzaGly7,Arg(Me)9]MS10	4.2E-08
237	[D-Tyr1,D-Asn2,AzaGly7,Arg(Me)9]MS10	2.7E-08
238	[D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)9]MS10	4.9E-08
239	des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)9]MS10	1.2E-07
240	des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)9]MS10	1.7E-08
241	des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)9]MS10	5.6E-08
242	des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9]MS10	7.0E-08
244	[D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10	7.7E-08
245	[D-Tyr1,Nal(1)3,AzaGly7,Arg(Me)9]MS10	9.8E-08
246	[D-Tyr1,Nal(2)3,AzaGly7,Arg(Me)9]MS10	7.1E-09
247	[D-Tyr1,Phe(2Cl)3,AzaGly7,Arg(Me)9]MS10	4.5E-08
248	[D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)9]MS10	5.8E-08
249	[D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)9]MS10	1.5E-07
250	[D-Tyr1,Phe(4NH2)3,AzaGly7,Arg(Me)9]MS10	3.7E-09
251	[D-Tyr1,Pya(3)3,AzaGly7,Arg(Me)9]MS10	8.7E-08
252	[D-Tyr1,D-Ala3,AzaGly7,Arg(Me)9]MS10	5.8E-07
253	[D-Tyr1,Pro3,AzaGly7,Arg(Me)9]MS10	2.7E-08
254	des(1)-[D-Tyr2,Phe3,AzaGly7,Arg(Me)9]MS10	1.1E-08
255	des(1)-[D-Tyr2,Nal(2)3,AzaGly7,Arg(Me)9]MS10	3.3E-08
256	des(1)-[D-Pya(3)2,Phe3,AzaGly7,Arg(Me)9]MS10	2.2E-08
257	[D-Tyr1,D-Asn2,Phe3,AzaGly7,Arg(Me)9]MS10	4.0E-08
258	[D-Pya(3)1,AzaGly7,Arg(Me)9]MS10	9.0E-08
259	[D-Ala1,AzaGly7,Arg(Me)9]MS10	2.5E-07

[TABLA 17]

260	des(1-3)-3-(3-Indolil)propionil-[AzaGly7,Arg(Me)9]MS10	3.2E-07
261	[7? 8,CH2NH]MS10	3.9E-07
265	des(1-3)-Indol-3-carboxil-[AzaGly7,Arg(Me)9]MS10	9.5E-08
266	des(1-3)-Indol-3-acetil-[AzaGly7,Arg(Me)9]MS10	2.3E-07
267	des(1-3)-4-(3-Indolil)butiril-[AzaGly7, Arg(Me)9]MS10	3.6E-07
268	des(1-3)-DiFenilacetil-[AzaGly7,Arg(Me)9]MS10	5.5E-07
269	des(1-3)-3-Fenilpropionil-[AzaGly7,Arg(Me)9]MS10	4.7E-07
270	Endo-Phe5a-[D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10	1.5E-08
271	des(1-2)-[AzaGly7,Arg(Me)9]MS10	1.2E-07
272	des(1-2)-Acetil-[AzaGly7, Arg(Me)9]MS10	5.4E-07
273	des(1-2)-Amidino-[AzaGly7, Arg(Me)9]MS10	3.0E-07
275	des(1-2)-Acetil-[Arg3,AzaGly7,Arg(Me)9]MS10	4.1E-07
276	des(1-2)-Acetil-[Thr3,AzaGly7,Arg(Me)9]MS10	4.8E-07
277	des(1-3)-n-Hexanoil-[AzaGly7,Arg(Me)9]MS10	5.4E-08
278	des(1-3)-Ciclohexancarbonil-[AzaGly7, Arg(Me)9]MS10	1.1E-07
279	des(1-3)-2-(Indol-3-il)etilcarbamoil-[AzaGly7,Arg(Me)9] MS10	2.9E-08
281	[D-Tyr1,Pya(2)5,Arg(Me)9]MS10	2.3E-07
283	[D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	6.9E-10
284	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9]MS10	3.4E-08
285	[D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9]MS10	4.0E-08
286	[D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1.7E-08
287	[D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9]MS10	2.3E-09
288	[D-Tyr1,D-His2,AzaGly7,Arg(Me)9]MS10	7.2E-11
289	[D-Pya(3)2,AzaGly7,Arg(Me)9]MS10-(2-10)	8.4E-09
290	[D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1.4E-09
291	[D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9]MS10	4.1E-10
294	[1? 2,CH2NH]MS10	3.0E-08
295	[2? 3,CH2NH]MS10	6.8E-07
296	[6? 7,CSNH,D-Tyr1,Arg(Me)9]MS10	1.4E-08
297	[D-Tyr1,Thr5,AzaGly7,Arg(Me)9]MS10	9.3E-10
298	[D-Tyr1,D-Asn2,Thr5,AzaGly7,Arg(Me)9]MS10	2.5E-10
299	[1 Ψ 2,CH2NH,AzaGly7,Arg(Me)9]-MS10	1.2E-09
300	[1 Ψ 2,CH2NH,D-Trp3,AzaGly7,Arg(Me)9]-MS10	3.8E-09
301	[D-Tyr1,Ala(2-Qui)3,AzaGly7,Arg(Me)9]MS10	1.5E-08

[TABLA 18]

302	[D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	7.7E-09
303	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	5.0E-10
304	[D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	5.0E-09
305	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1.3E-09
306	[D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	4.4E-09
307	[7 Ψ 8,CH2NH,D-Tyr1,Arg(Me)9]MS10	6.4E-08
308	[6 Ψ 7,CH2NH,D-Tyr1,Arg(Me)9]MS10	3.5E-07
310	[Nar9]MS10	3.1E-07
311	[Nar(Me)9]MS10	4.7E-07
312	[Har(Me)9]MS10	1.0E-07
313	[Dab9]MS10	6.9E-07
314	[Orn9]MS10	4.7E-07
316	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	2.6E-08
317	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	2.1E-09
318	[D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	9.9E-10
319	[6 Ψ 7,NHCO,D-Tyr1,Arg(Me)9]MS10	9.7E-09
322	des(1-3)-3-Pyridylpropionyl-[AzaGly7,Arg(Me)9]MS10	5.4E-08
323	des(1-3)-4-Imidazolacetyl-[AzaGly7,Arg(Me)9]MS10	2.8E-07
328	des(1-3)-D-Glucuronyl-[AzaGly7,Arg(Me)9]MS10	4.7E-07

EJEMPLO DE PRUEBA 2

Ensayo para la actividad de incremento del nivel de ión Ca intracelular usando FLIPR

De acuerdo con el método descripto en JPA 2000-312590, la actividad de incremento del nivel de ion Ca intracelular fue medida usando FLIPR.

La expresión estable de la línea celular rOT7T175 se obtuvo por transducción de expresión de plásmido pAK-rOT175 para la célula animal en las células CHO/dhfr$^-$, usando el Equipo "CellPhect Transfection" (Amersham Pharmacia Biotech, Inc.). Primero, 240 µL de solución amortiguadora A (adjunta al Equipo "CellPhect Transfection") fueron agregados a 9,6 µg de plásmido

de ADN disuelto en 240 µL de agua destilada seguido de agitación. Después que la mezcla permanece fija durante 10 minutos, fueron agregados 480 µL más de solución amortiguadora B (adjunta al Equipo "CellPhect Transfection") a la mezcla que fue agitada vigorosamente para formar liposomas que contiene el ADN. Entonces, 4 x 10^5 células CHO/dhfr$^-$ (obtenidas de ATCC) fue inoculado en un plato Petri de 60 mm. Después de cultivar las células en medio de Ham F-12 ("Nissui Seiyaku Co., Ltd.") complementado con 10% suero fetal bovino (BIO WHITTAKER, Inc.) en 37°C durante 2 días en 5% de gas anhídrido carbónico, 480 µL de liposomas fueron agregados por gotas a las células en el plato Petri. Después de cultivar las células a 37°C durante 6 horas en 5% de gas de anhídrido carbónico, las células fueron lavadas dos veces con el medio Ham F-12 sin suero y se agregaron 3 µL de 15% glicerol a las células en el plato Petri seguido por el tratamiento durante 2 minutos. Las células fueron lavadas de nuevo dos veces con medio Ham F-12 sin suero seguido por la incubación en medio Ham F-12 complementado con 10% suero bovino fetal a 37°C durante 15 horas en 5% gas de anhídrido carbónico. Las células se dispersaron por tratamiento de tripsina para recuperarlas del plato Petri. Las células recuperadas se inocularon en una placa de 6 hendiduras en 1,25 x 10^4 células/hendidura y se empezaron a incubar a 37°C en el medio Dulbecco modificado por el medio Eagle (DMEM) ("Nissui Seiyaku Co., Ltd.") que contiene 10% de suero bovino fetal dializado (JRH BIOSCIENCES, Inc.) en 5% de gas de anhídrido carbónico. Las células CHO transformadas transfectadas por plásmido crecieron en el medio pero las células no transfectadas se murieron

gradualmente. El medio fue intercambiado en los días 1 y 2 para eliminar las células muertas. Aproximadamente 20 colonias de células CHO transformadas siguieron creciendo en los días 8 a 10 después que la incubación fue aislada. De las células en estas colonias, las células que muestran alta reactividad con el ligando de péptido de metastina (mas adelante meramente denominado hOT7T175/CHO) fueron seleccionadas para ser provistas al experimento siguiente.

La actividad de incremento de nivel de ion Ca intracelular del péptido sintético en hOT7T175/CHO fue determinada usando FLIPR (Molecular Devices, Inc.).

El hOT7T175/CHO fue subcultivado en DMEM complementado con 10% suero bovino fetal dializado (más adelante abreviado como dFBS) y provisto para el experimento (más adelante abreviado como 10% dFBS/DMEM). El hOT7T175/CHO fue suspendido en 10% dFBS-DMEM en 15 x 10^4 células/ml. La suspensión fue inoculada en una placa de 96 hendiduras para FLIPR (Black Plate Clear Bottom, Coster, Inc.) a 200 µl cada uno (3,0 x 10^4 células/200 µl), seguido de la incubación a 37°C de noche en una incubadora con 5% CO_2. Se usaron las células así incubadas (después simplemente denominada placa celular). Entonces, 21 ml de HANKS/HBSS (9,8 g de HANK, 0,35 g de carbonato hidrógeno de sodio, 20 ml de 1M HEPES; después de ajustar el pH a 7,4 con 1N hidróxido de sodio, la mezcla fue sometida a esterilización a través de un filtro), 210 µl de 250 mM Probenecid y 210 µl de suero bovino fetal (FBS) fueron mezcladoas (HANKS/HBSS-Probenecid-FBS).

Además, 2 ampollas de Fluo3-AM (50 µg/ampolla) se dis lvieron en 21 µL de dimetilsulfóxid y 21 µL de 20% ácido

Plurónico. La solución resultante fue agregada y mezclada con 10 ml de HANKS/HBSS-Probenecid-FBS descriptos anteriormente. Después que el medio de cultivo fue eliminado, la mezcla fue distribuida sobre el placa celular en 100 µl cada/hendidura, seguido de incubación a 37°C durante una hora en una incubadora con 5% de CO_2 (carga del pigmento). El péptido fue disuelto en dimetilsulfóxido en 1 x 10^{-3} M. La solución del péptido fue diluída con HANKS'/HBSS que contiene 2,5 mM de Probenecid y 0,2% BSA. La dilución fue transferida a una placa de 96 hendiduras para FLIPR (placa de fondo en "V", Coster, Inc.) (en adelante denominada como un placa de muestra). Después de la realización de la carga de pigmento sobre la placa celular, placa celular fue lavada 4 veces con solución amortiguadora de lavado que se obtuvo agregando 2,5 mM Probenecid a HANKS'/HBSS, usando a una placa de lavado para dejar 100 µL de solución amortiguadora de lavado después del lavado. La placa celular y la placa de muestra fueron fijadas en FLIPR y 0,05 ml de una muestra desde la placa de muestra fueron transferidos automáticamente a la placa celular con el dispositivo FLIPR para promover la respuesta celular. Un cambio en el nivel de ion calcio intracelular fue medido durante 180 segundos con el transcurso del tiempo. La actividad de incremento de nivel del ión Ca intracelular [actividad específica de Metastina (1-54)] se ilustra en las TABLAS 19 a 23.

[TABLA 19]

Comp. No.	Act. específica
Metastina(1-54)	1
Metastina(45-54)	10
17	5
18	1
19	2
24	1
30	10
31	2
32	10
40	30
41	10
42	30
45	1
50	30
53	1
54	5
55	5
56	1
74	1
75	1
76	1
78	10
79	1
87	1
88	1
97	10
98	1/2
101	10
105	1
109	20
110	20
111	3
112	2
114	3
128	10
130	10
131	3
132	10
133	3
134	30
141	10
142	2
143	3
144	1
146	10
151	1
152	5
154	5
156	2
163	1
166	5
169	2
170	1
171	10
172	1
173	1

[TABLA 20]

174	10
176	5
182	5
187	1
189	10
190	10
192	1
193	1/2
194	1
197	10
198	10
199	3
200	10
201	1
203	10
204	5
205	10
206	10
207	1/2
208	1
209	1/2
210	1
211	10
212	10
213	2
214	10
215	10
216	1
217	20
220	5
222	10
224	2
225	1
226	1
227	1
228	5
229	1
230	10
231	1
232	3
233	1
234	1
235	1
236	2
237	3
238	1
241	1
242	2
244	1
245	1
246	2
247	1
248	2
249	1
250	1
254	1
255	1

[TABLA 21]

256	1
257	3
258	2
259	1
260	5
261	1
265	3
266	2
267	2
268	1
269	3
270	1
271	1
272	2
273	5
274	1
277	2
278	2
279	5
281	1/2
284	1
286	2
287	2
288	1
289	1
290	1
291	2
294	10
295	1
296	3
297	1
298	5
299	5
300	5
301	1
302	2
303	5
304	3
305	5
306	2
307	1
308	2
310	3
311	1
312	3
314	1
315	1
316	1
317	1
318	5
319	3
322	1
323	1
332	2
333	1
334	5
339	2

[TABLA 22]

340	1/5
341	2
344	1/2
345	2
346	2
347	1/2
348	1/5
349	1/5
351	1/2
352	1/3
353	10
354	10
358	2
362	1/10
364	1
366	1/3
367	1/5
368	1/2
369	2
373	2
374	1/3
375	2
378	1/2
379	2
380	5
385	10
386	7
387	1
392	1/5
393	1
397	5
400	1
408	1/3
412	1/5
417	1
421	1/3
423	5
428	1/10
431	1
432	2
434	1/10
435	10
436	5
437	2
438	3
439	2
440	1
441	1
442	1/2
443	1/2
444	1/3
445	5
446	1
447	5
448	3
449	5
450	1/3

[TABLA 23]

451	5
452	1
453	1
454	6
455	5
459	2
460	1/3
461	1/3
462	1
463	2
464	1
466	1/3
467	1
468	1
471	1
472	3
473	3
474	5
475	3
477	1/5
478	1/3
479	5
480	1
481	5
486	1/2
487	1
488	1
489	1/2
490	3
491	7
492	5
493	2
494	1/3
495	1/6
496	5
497	2
498	7
499	10
500	1
501	10
502	10
503	10
504	2
505	20
506	1
507	5
508	10
509	20
510	3
511	10
512	30
513	20
514	10
515	10

EJEMPLO DE PRUEBA 3

Ensayo para la actividad de incremento de nivel del ión Ca intracelular usando FLIPR

La actividad de incremento de nivel del ión Ca intracelular fue medida usando FLIPR como en el EJEMPLO DE PRUEBA 2. Sin embargo, (1) la evaluación en la EJEMPLO DE PRUEBA 2 para medir un cambio en el nivel de ión Ca intracelular durante 180 segundos con el transcurso de tiempo cambió a la evaluación durante 40 segundos después de la iniciación de la reacción.

También, (2) la indicación de la actividad cambia a EC_{50}/MS10 EC_{50} de la actividad específica a etastina (1-54).

Una parte de los resultados de la evaluación se ilustran en TABLA 24.

[TABLA 24]

Comp. No.	Act. esp
40	1.6
41	2.7
42	1.6
82	1.0
97	2.9
109	2.6
114	4.3
126	0.5
134	0.6
141	1.6
146	1.6
152	3.4
156	0.9
174	2.3
176	1.3
187	1.9
206	4.8
208	7.3
210	9.3
211	1.3
212	3.1
217	3.1
223	2.7
232	3.9
239	6.7
240	4.9
241	5.3
242	1.4
260	4.3
265	4.1
266	6.4

268	4.5
269	3.4
279	5.4
294	0.7
296	5.2
297	5.5
298	1.8
303	0.9
305	2.0
308	2.6
310	2.0
311	0.2
312	4.0
314	4.4
318	2.9
319	3.1
322	5.4
332	4.9
333	5.0
334	1.4
339	5.9
341	2.8
353	0.8
354	0.8
358	5.8
369	4.8
375	6.2
378	10.4
379	3.0
385	0.7
386	2.9
387	5.9
393	5.9
423	5.6

436	1.4
438	3.0
445	4.2
447	1.4
449	4.2
451	2.8
454	2.5
455	4.1
459	7.3
463	4.8
464	10.5
467	4.0
468	5.2
472	3.4
473	4.2
474	5.2
475	4.2
479	2.6
480	3.3
481	2.4
488	5.5
490	6.2
491	1.8
492	1.1
493	2.1
494	3.6
496	0.7
497	1.4
498	1.5
499	1.4
500	3.2
501	1.1
502	1.4
503	0.4

504	6.9
505	0.7
506	1.3
507	1.7
508	1.0
509	2.0
510	3.5
511	0.5
512	0.8
513	0.4
514	0.7
515	1.0
516	3.7
517	1.0
518	10.5
519	2.4
521	2.4
522	1.9
523	1.1
524	1.1
527	3.3
528	1.4
529	1.8
530	3.4
531	1.8
532	1.0
533	9.7
534	5.6
535	0.8
536	1.8
537	4.7
538	3.3
539	1.2
540	0.7

541	2.0
542	1.4
545	1.1
546	1.9
547	2.5
548	1.7
550	0.7
551	1.2
552	2.3
553	1.9
554	1.3
555	1.5
556	2.5
557	3.2
558	0.4
559	0.3
561	1.6
562	1.0
563	0.7
564	0.5
565	0.4
566	0.5
567	0.3
568	0.6
569	0.5
570	0.5
571	1.2
572	0.7
573	0.7
576	0.8
577	0.7
578	0.6
579	0.6
580	0.6

Comp. No.	Act. espec.
584	0.4
585	0.4
586	0.3
589	2.3
590	1.4
591	1.2
592	1.1
594	2.1
596	11.4
597	0.6
598	0.3
599	0.5
600	0.3
601	3.1
602	2.4
603	1.7
604	6.3
605	3.9
607	2.2
608	2.2
609	0.9
610	1.8
611	1.7
612	0.8
613	0.4
614	0.8
615	0.7
616	1.1
617	2.4
618	1.8
619	1.5
620	1.7
621	1.9
622	2.8
623	0.6
624	1.2
625	2.8
626	2.1
627	1.8
628	4.4
629	3.4
630	4.2
631	2
632	1.1
633	3.4
634	10.5
635	1.4
637	0.8
638	1.7
639	2
641	3.6
642	3.7
643	2.5
644	2.8
645	1.1
646	1.8

647	10.6
648	1.6
649	1
650	0.6
651	0.7
652	0.9
653	1.3
654	2.8
655	4.7
656	2.9
657	1.1
658	0.4
659	0.6
660	1.1
661	6.5
662	0.7
663	0.8
664	0.6
665	1.1
666	1.1
667	1.4
668	1.2
669	0.5
670	0.9
671	3.6
672	2.1
674	2
675	0.8
676	1.4
677	0.3
678	1.1
679	1.8
680	2.5
681	1.2
682	7.3
685	4.8
686	0.6
688	9.7
689	2.3
691	1.1
692	0.7
693	1.5
694	1.7
695	0.7
696	0.5
698	2.2
699	1.3
700	0.8
701	1.4
702	0.6
706	3.7

EJEMPLO DE PRUEBA 4

Ensaye para la actividad de inhibición de crecimiento celular en células CHO expresando hOT7T175

Las células CHO expresando hOT7T175 (más adelante en la presente hOT7T175) fueron cultivadas en DMEM complementado con 10% FBS dïalizado (después 10% dFBS/DMEM) las cuales se utilizaron para el ensayo siguiente. El hOT7T175 fue suspendido en 10% dFBS/DMEM en 10.000 células/ml. Las células fueron colocadas una placa de 96 hendiduras a 100 µL cada/hendidura (1.000 células/hendidura), seguido por cultivo durante toda la noche a 37°C -5% de en incubadora de CO_2. En el día siguiente, el medio fue eliminado y 90 µL de 10% dFBS/DMEM complementado con 0,5% BSA (después, 0,5% BSA/10% dFBS/DMEM) fue agregado. Subsiguientemente, 10 µL de una solución de metastina o derivado de metastina en 0,5% BSA/10% dFBS/DMEM fue agregada a cada una de las hendiduras, seguido por cultivo a 37°C -5% incubadora de CO2 durante 3 días. Después que 10 µL de la solución "Cell Counting Kit-8" ("Dojin Chemical Laboratory") fueran agregados a cada una de las hendiduras, fue realizada la incubación a 37°C - 5% incubadora CO_2 durante 4 horas, fue medida la absorbencia en 450 nm.

Las actividades de inhibición celular de Metastina (1-54), Metastina (45-54) y el compuesto sintético se ilustran en TABLA 25.

[TABLA 25]

Compuesto número	IC50 (M)
305	8.94E-09
232	9.67E-09

*"1-54" y "45-54" representan Metastina (1-54) y Metastina (45-54) respectivamente

EJEMPLO DE PRUEBA 5

Ensayo para actividad de inhibición de quimiotaxis en las células CHO expresando hOT7T175

Las células CHO expresando hOT7T175 (más adelante en la presente hOT7T175) fueron cultivadas en DMEM complementado con 10% FBS dializado (después 10% dFBS/DMEM), el cual fue provisto para ensayo. También un "Transwell" de 24 hendiduras 6,5 mm (tamaño de poro 8,0 μm) (COSTAR) fue tratado con fibronectina por el método siguiente. Específicamente, 0,5 ml de 1 μg/ml fibronectina bovina (Yagai Co, Ltd.) fue agregado a las cámaras superiores e inferiores de "Transwell". Después que la mezcla permaneción estable en la temperatura ambiente durante 10 minutos, la solución de fibronectina fue eliminada y además secada por aire. Después que el hOT7T175 fue lavado con DMEM 3 veces, las células fueron suspendidas en DMEM que contiene 0,5% BSA (después 0,5% BSA/DMEM) a una densidad de 2,5 x 10^6 células/ml. La metastina o un derivado de metastina fueron diluídos con 0,5% BSA/DMEM. Después que 600 μL de 0,5% BSA/DMEM

complementado con 20% FBS (ó 0,5% BSA/DMEM para control negativo) fueron agregados a la cámara inferior de "Transwell", y 50 µL de la suspensión celular y 50 µL de metastina o una dilución derivado de metastina (o 0,5% BSA/DMEM para control positivo) fue agregada a la cámara superior. Después de incubación a 37°C en una incubadora con 5% de CO_2 durante 7 horas, el medio de cultivo fue eliminado y el lado superior del filtro fue limpiado con un trapo de algodón humedecido con la solución salina amortiguada de fosfato para eliminar todas las células en el lado superior del filtro. El filtro fue fijado y manchado con "DifQuick" ("International Reagents Corporation") y las células que emigraron hacia lado inferior del filtro fueron contadas. La actividad de inhibición de quimiotaxis se ilustra en FIG. 1.

EJEMPLO DE PRUEBA 6

Evaluación de actividad de inhibición de crecimiento de tumor

El efecto de inhibición de crecimiento de tumor de Metastina (1-54) (más adelante en la presente denominada Metastina) y los Compuestos (Compuestos Nos. 305 y 322) en el ser vivo usando ratones con tumor que poseen la línea celular SW620 derivada carcinoma colónico humano.

La bomba osmótica "Alza" (0,25 µL/hora, 14 días libre, Modelo 1002) llena con 100 µL cada uno de 1 mM Metastina, 0,1 mM y 1 mM de Compuestos disueltos en agua destilada ("Otsuka Joryusui K.K.") y agua destilada como vehículo fueron incorporados subcutáneamente en la parte de atrás de ratones BALB/cAnN-nu (6 semanas de edad, hembra, Charles River Japón, Inc.) bajo anestesia de éter para comenzar la administración

intermitente durante 14 días. El número de experimentos fue de n = 10 en grupo Metastina y grupo vehículo y n = 11 en los dos grupos Compuesto. Al día siguiente, la línea celular derivada de carcinoma colónico humano SW620 (ATCC) fue disuelta en 20 mM solución salina amortiguada de fosfato (pH 7,2)(PBS) que contiene 200 µL de 0,15M NaCl a una densidad de 2 x 10^6 células. La solución resultante fue inyectada subcutaneamente en el flanco izquierdo de los ratones. El día cuando las células fueron inyectadas era el Día 0. El tumor fue medido con un calibre electrónico cada día o a otros 2 días durante los días 4 a 13 de la administración de células, y el tamaño del tumor fue calculado por la ecuación: (diámetro más corto)^2 x diámetro más largo/2. Según se ilustra en la FIG. 2, el grupo Metastina (24 x nmol/día/ratón x 14 días) demuestra un efecto significativo de inhibición de crecimiento de tumor en el día 6, cuando se lo compara al grupo de vehículo. Por otra parte, el grupo Compuesto No. 322 demuestra una actividad significativa inhibición de crecimiento de tumor en una dosis 1/10 (2,4 x nmol/día/ratón x 14 días) de Metastina en días 6 a 8. También, el grupo de Compuesto No. 322 (24 x nmol/día/ratón x 14 días) que recibe la misma dosis de Metastina demuestra una actividad significativa de inhibición de crecimiento de tumor los días 6 a 11, cuando se la compara al grupo de vehículo y en día 11, demostró una actividad significante de inhibición de crecimiento de tumor incluso cuando se la compara con el grupo Metastina. Los resultados anteriores revelan que la Metastina demuestra un efecto de inhibición de crecimiento de tumor también en el ser vivo también y el Compuesto No. 322 tiene efecto de inhibición

de crecimiento de tumor 10 veces superior que con Metastina.

También se ilustran los resultados del Compuesto No. 305 en la FIG. 3. El grupo Metastina (24 x nmol/día/ratón x 14 días) demostró un efecto significativo de inhibición de crecimiento de tumor en días 5 a 7, cuando se lo compara al grupo de vehículo. Por otra parte, el grupo de Compuesto No. 305 (2,4 x nmol/día/ratón x 14 días) recibiendo una dosis 1/10 como el de Metastina demostraron una actividad significativa de inhibición de crecimiento de tumor los días 5 a 11, cuando se la compara al grupo de vehículo. Además, el grupo de Compuesto No. 305 (24 x nmol/día/ratón x 14 días) recibiendo la misma dosis como el de Metastina demostraron un efecto significativo de inhibición de crecimiento de tumor en días 5 a 9 y día 11, cuando se la compara al grupo de vehículo, revelando que el Compuesto No. 305 demuestra un efecto superior en el ser vivo de inhibición de crecimiento de tumor de 10 veces superior con respecto a Metastina.

EJEMPLO DE PRUEBA 7

Efecto de elevación de nivel de azúcar por metastina

Para estudiar el efecto de metastina en el nivel de azúcar por la administración periférica, fue realizada una operación en animal que se mueve libremente para recolectar sangre. Las ratas macho Wistar maduras (pesando 210 - 230 g en el momento de la operación) fueron anestesiadas por la inyección intraperitoneal de 50 mg/kg de pentobarbital. El animal fue fijado dorsalmente a la almohadilla de disección y la vena yugular izquierda fue expuesta. Un tubo de polietileno SP35 (diámetro interno de 0,5 mm, diámetro exterior de 0,9 mm, "Natsume Seisakusho Co., Ltd.")

fue cortado en una longitud de aproximadamente 30 cm y rellenado con 200 unidades/ml de solución salina heparinizada. Después de esto, el tubo fue insertado en la vena yugular a una profundidad de aproximadamente 4,5 cm y fue fijado. El otro extremo del tubo fue insertado subcutáneamente en la parte de atrás para exponer la yugular (atrás).

Después de la operación, el animal se mantuvo toda la noche. Antes de la administración de metastina, 300 µl de sangre fueron extraídos a través de una jeringa tuberculina de 1 ml y una aguja de medida 25 (ambos de "Terumo Co., Ltd."). Para prevenir coágulos de sangre, se habían llenado previamente en una jeringa 3 µl de 300 KIU/ml de solución de aprotinina que contiene 3 mg/ml de EDTA. Unos 1 mL de solución salina Otsuka o solución salina de metastina (17, 80 ó 170 nmol) fueron inyectados intravenosamente en una dosis de 1 mL/kg a través del tubo. La sangre fue recolectada de la vena yugular por 300 µl cada 0, 5, 15, 30 y 60 minutos empezando de la inyección intravenosa. La sangre recolectada fue centrifugada (13.000 rpm, 5 minutos) con un centrifugado refrigerado de gran velocidad (MR-150, Tomy Seiko Co., Ltd.) para recuperar el sobrenadante (plasma). El nivel de glucosa en sangre fue medido usando Fuji Drychem 3500 (FUJI FILM). Según se ilustra en FIG. 4, el grupo Metastina demostró un efecto significativo ($p < 0,005$, $n = 5$) de aumento del nivel de glucosa en sangre dependiente de dosis (17-170 nmol/kg) desde 5 minutos después de la inyección intravenosa, cuando se compara al grupo de control. En el nivel de glucosa de la sangre, se registró un período prolongado de tiempo (30 minutos al máximo) para aumentar el nivel de azúcar

acompañado por un aumento del nivel máximo de metastina, cuando la dosis aumentaba.

EJEMPLO DE PRUEBA 8

Efecto de promoción de la secreción de glucagon pancreática por metastina

Con la finalidad de estudiar el mecanismo de metastina para el efecto de aumento del nivel de glucosa en sangre, fue examinado el efecto de metastina en el nivel de glucagon en sangre, insulina, corticosterona y hormona tiroidea (T3) conocidas por ser las hormonas que afectan el nivel de glucosa en sangre. Una operación fue realizada a las ratas macho Wistar maduras que se mueven libremente (pesando 260 - 300 g en el momento de operación) para recolectar sangre. Después de la operación, animal se contuvo toda la noche. Antes de la administración de metastina, 300 µl de sangre fueron extraídos a través de una jeringa tuberculina de 1 ml y una aguja de medida 25 (ambos de la Terumo Co., LTd.). Para prevenir coágulo de sangre, se habían llenado previamente en la jeringa 3 µl de 300 KIU/ml solución de aprotinina que contiene 3 mg/ml EDTA. La solución Otsuka salina o una solución salina de metastina (80 nmol/mL) fue inyectada intravenosamente en una dosis de 1 mL/kg a través del tubo.

La sangre fue recolectada de la vena yugular por 300 µl cada 1, 3, 5 y 15 minutos empezando de la inyección intravenosa. La sangre recolectada fue centrifugada (13.000 rpm, 5 minutos) con un centrifugado refrigerado de gran velocidad (MR-150, Tomy Seiko Co., Ltd.) para recuperar el sobrenadante (plasma). El nivel de glucagon en sangre fue medido usando un equipo de

glucagon "Daiichi" (Daiichi Radioisotope Laboratories Ltd.), nivel de insulina en la sangre usando sistema de ensayo de insulina de la rata [^{125}I] (Amersham Biosciences), nivel de corticoesterona en sangre usando sistema de ensayo de corticoesterona de la rata [^{125}I] (Amersham Biosciences), hormona tiroidea (T3) en sangre usando cuentas T-3.RIA ("Dinabott Co., Ltd.), y nivel de glucosa en sangre usando Fuji Drychem 3500 (FUJI FILM). Como se ilustra en la FIG. 5, el grupo de Metastina demostró un efecto significativo para aumentar el nivel de glucagon en 1 minuto de sangre después de inyección, cuando se compara al grupo de control. Un efecto significativo de aumento del nivel de glucagon continuó hasta 5 minutos después de la inyección. Por otra parte, en el nivel de insulina en sangre (FIG. 6), el nivel de corticoesterona en sangre (FIG. 7) y nivel de hormona tiroidea (T3) en sangre (FIG. 8), no se nota ningún cambio por la inyección de metastina. Basados en estos resultados y del aumento observado en el nivel de glucagon de sangre seguido por el nivel de glucosa en sangre (FIG. 9), se considera que sería inducido el efecto de nivel de glucosa en sangre por la inyección intravenosa de metastina debido al estímulo de secreción de glucagon por metastina.

EJEMPLO DE PRUEBA 9

Efecto de aumento de nivel de azúcar por derivados de metastina

El efecto de derivados de metastina KiSS305 (Compuesto No. 305) y KiSS322 (Compuesto No. 322) en el nivel de glucosa de sangre y nivel de glucagon en sangre fue examinado. Una operación fue realizada en las ratas macho Wistar maduras que se mueven libremente (pesando 260-3000 g en el momento de la

operación) de una manera similar para PROBAR EJEMPLO 1 para coleccionar sangre. Después de la operación, el animal se contuvo toda la noche. Antes de la administración de metastina, 300 µl de sangre fueron extraídos a través de una jeringa tuberculina de 1 ml y una aguja de medida 25 (ambos por Terumo Co., Ltd.). Para prevenir coágulos de sangre, se había estado llenando previamente la jeringa con 3 µl de 300 KIU/ml solución de aprotinina que contiene 3 mg/ml EDTA. La solución Otsuka salina o una solución salina de metastina (80 nmol/mL) fue inyectada intravenosamente en una dosis de 1 mL/kg a través del tubo. La sangre fue recolectada de la vena yugular por 300 µl cada 2, 5, 15, 30, 45 y 60 minutos empezando de la inyección intravenosa. La sangre recolectada fue centrifugada (13.000 rpm, 5 minutos) con un centrifugador refrigerado de gran velocidad (MR-150, Tomy Seiko Co., Ltd.) para recuperar el sobrenadante (plasma). El nivel de glucosa en sangre fue medido usando Fuji Drychem 3500 (FUJI FILM) y el nivel de glucagon en sangre fue medido usando un equipo de glucagon "Daiichi" ("Daiichi Radioisotope Laboratories Ltd."), como en el EJEMPLO DE PRUEBA 1 ó 2. Como se ilustra en la FIG. 10, ambos compuestos demostraron un aumento en el nivel de glucosa en sangre. También, ambos compuestos demostraron un aumento en el nivel de glucagon en sangre, según se ilustra en la FIG. 11.

EJEMPLO DE PRUEBA 10

Inducción de ovulación por metastina humana en la rata inmadura

La gonadotropina coriónica equina (eCG, serotropina, Dainippon Pharmaceutical Co., Ltd.) fueron disueltos en solución salina (Otsuka Pharmaceutical Co., Ltd.) en una concentración de

100 IU/mL. Usando una jeringa tuberculina de 1 ml y una aguja de medida 26 (ambos por Terumo Co., Ltd.), se inyectó subcutáneamente eCG en el área dorsal de ratas Wistar hembra de 23 días de edad después del nacimiento (Charles River Japón, Inc.) en una dosis de 10 IU/animal, durante 9:30 a 10:00 AM. Siguiente a la inyección de eCG, los animales se agruparon después de 47 a 48 horas según se ilustra a continucación, en cuyos grupos, cada droga fue inyectada.

Gupo A (5 ratas): La gonadotropina coriónica humana (hCG, gonadotropina, Dainippon Pharmaceutical Co, Ltd.) se disolvió en solución salina a 100 IU/mL y la solución se inyectó subcutáneamente en la parte de atrás en una dosis de 20 IU/animal.

Grupo B (5 ratas): La metastina humana se disolvió en solución salina a 100 nmol/mL y la solución se inyectó subcutáneamente en la parte de atrás en una dosis de 20 nmol/animal.

Grupo C (5 ratas): La metastina humana se disolvió en solución salina a 33,3 nmol/mL y la solución se inyectó subcutáneamente en la parte de atrás en una dosis de 6,67 nmol/animal.

Grupo D (6 ratas): La solución salina se inyectó subcutáneamente en la parte de atrás en una dosis de 200 µL/animal.

Después de la administración de las drogas descripta precedentemente, el animal fue sacrificado por decapitación después de 24 a 25 horas para recuperar sangre, oviductos bilaterales y útero. En la sangre recolectada, 90 µl de 10

KIU/ml solución de aprotinina (Trasylol, Bayer) que contiene 3 mg/ml de EDTA se había llenado previamente en un tubo para recuperación para prevenir coágulos de sangre. Después de la recuperación de sangre, la sangre fue mezclada completamente y la mezcla fue centrifugada a 2.000G durante 25 minutos. Después el sobrenadante fue recuperado, el producto fue usado como una muestra de plasma.

El número de oocitos fue contaba de la manera siguiente.

Cuando la retención de oocitos en conducto dilatado de trompa de Falopio era confirmada por la observación del estereomicroscopio del oviducto, el conducto fue punzado con una jeringa con la aguja de medida 27 para jeringa (Terumo) para recuperar oocitos. Después que las células granulosas que rodean los oocitos fueron eliminadas por tratamiento de tripsina, el número de oocitos fue contado. Cuando la retención de oocitos en el conducto de trompa de Falopio no era confirmada por observación en estereomicroscopio del oviducto, una aguja de medida 27 con punta pulida para jeringa fue insertada en el orificio tubárico y más de 400 µL de solución salina fueron enviados al oviducto y utero para enjuagar. Entonces, fue observada la presencia o ausencia de oocitos en el efluente.

El número de oocitos obtenido se ilustra en TABLA 26.

[TABLA 26]

	Grupo A	Grupo B	Grupo C	Grupo D
1	36	29	29	0
2	35	56	39	0
3	40	17	32	0
4	42	25	22	0
5	35	32	16	0
Porciento de ovulación	37, 6	31, 8	27, 6	0. 00
Desvío estandard	3, 21	14, 65	8, 91	0. 00

En la tabla, los números "1" a "5" representan un número para cada rata individual.

En el Grupo A, el cual es un grupo de tratamiento de superovulación multipropósito, la ovulación de 37,6 oocitos en promedio por rata fue confirmada. En los Grupos B y C que reciben metastina, la ovulación de 31,8 y 27,6 oocitos en promedio, respectivamente, fue confirmada. Con respecto al Grupo D que recibe solución salina, el número de oocitos era de 0,6 en promedio, indicando que esta ovulación voluntaria observada era pequeña en ausencia de estímulo de ovulación.

El nivel de estradiol contenido en el plasma recolectado de las ratas ilustradas en TABLA 22 fue determinado por radioinmunoensayo (DPC-estradiol Kit; Diagnostic Corporation Products). Los resultados se ilustran en la FIG. 12.

Los resultados revelan que entre los Grupos A, B y C, no hay ninguna diferencia en el nivel de estradiol contenido en el plasma, demostrando que el nivel de estradiol sólo era sumamente alto en el Grupo D receptor de solución salina.

El nivel de progesterona contenido en el plasma fue

determinado por radioinmunoensayo (DPC.Progesterone; Diagnostic Corporation Products). Los resultados se ilustran en FIG. 13.

Los resultados revelan que el nivel de progesterona era más alto en el Grupo A y en Grupos B y C, el nivel sanguíneo era de aproximadamente una fracción de Grupo A y el nivel de la progesterona era sumamente bajo en el Grupo D.

En general, la hormona esteroide principal producida en los ovarios de la rata y humanos son estrógeno en la fase madura de folículo ovárico, mientras que la principal es la progesterona después que la ovulación fue inducida. Realmente se entiende de los resultados en FIG. 12 y FIG. 13 del Grupo D receptor de solución salina mantuvo el estado cuando el estrógeno era altamente producido, debido a que no hay ninguna inducción de ovulación; considerando el Grupo A receptor de hCG, la producción de estrógeno aumentó. En los Grupos B y C que son grupos receptores de Metastina el nivel de estrógeno en plasma era muy bajo pero el nivel de progesterona aumentó, indicando que la metastina induce la ovulación en el ovario de la rata mediante su proceso ovulatorio normal. También se considera que debido a que el nivel de la progesterona en los Grupos B y C era más bajo que en el Grupo A, la metastina tendría un estímulo ovárico más moderado.

EJEMPLO DE PRUEBA 11

Efecto liberador de gonadotropina de metastina humana en la rata inmadura

La Metastina humana disuelta en solución salina en una concentración de 33,3 nmol/mL fue inyectada subcutáneamente en el área dorsal de ratas Wistar hembra de 25 días de edad después

del nacimiento (Charles River Japón, Inc.) en una dosis de 200 µL/animal, es decir, 6,67 nmol como metastina humana, durante 9:00 a 10:00 AM. Antes de la inyección de metastina y 1, 2, y 4 horas después de la inyección, el animal fue decapitado para recuperar la sangre. Con la sangre recuperada, 90 µl de 10 KIU/ml de solución de aprotinina (Trasylol, Bayer) que contiene 3 mg/ml de EDTA se habían llenado previamente en un tubo de centrifugado para la recuperación para prevenir coágulos de sangre. Después de la recuperación de sangre, la sangre fue mezclada completamente y la mezcla fue centrifugada a 2.000G durante 25 minutos. Después que el sobrenadante fue recuperado, el producto fue utilizado como muestra de plasma. Los niveles de FSH (hormona folículo-estimulante), LH (hormona luteinizante) y el contenido de progesterona en el plasma fueron determinados por radioinmunoensayo (Folículo Estimulante de Hormona de Rata (rFSH) [^{125}I] "Biotrack Assay System" con separación magnética, Hormona Luteinizante Rata (rLH) [^{125}I] "Biotrack Assay System" con separación magnética, ambos por Amersham Bioscience, y "DPC.Progesterone" por "Diagnostic Corporation Products").

Los resultados obtenidos por monitoero de los cambios en el nivel FSH en sangre de la rata inmadura por inyección de metastina se ilustran en FIG. 14. Una hora después de la inyección de metastina, el nivel de FSH de sangre empezó a aumentar significativamente y alcanzó el máximo después de 2 horas. Mientras una disminución en el nivel de FSH en sangre fue notado después de 4 horas, el nivel de FSH todavía se mantuvo superior que nivel anterior a la inyección.

Los resultados obtenidos por monitoreo de los cambios en el

nivel de LH en sangre de rata inmadura por inyección de metastina se ilustran en FIG. 15. De manera semejante al caso de FSH, el nivel de LH en la sangre empezó a aumentar significativamente 1 hora después y alcanzó el máximo después de 2 horas. Mientras una disminución en el nivel de LH en la sangre era notado después de 4 horas, el nivel de LH todavía se mantuvo superior al nivel anterior a la inyección.

Los resultados obtenidos por monitoreo de los cambios en el nivel de progesterona en sangre de la rata inmadura por inyección de metastina se ilustran en FIG. 16. Reflejando el aumento del nivel LH en sangre, el nivel de progesterona empezó a aumentar despacio 1 hora después de la inyección de metastina y demuestra un nivel significativamente superior que el nivel anterior a la inyección.

Los resultados de las FIG. 14 y FIG. 15 revelan que la administración periférica de metastina induce la liberación de gonadotropina tal como FSH, LH, etc. La inducción de ovulación por metastina demostrada en el EJEMPLO DE PRUEBA 9 se considera que es inducida por esta liberación de gonadotropina, particularmente la liberación de LH.

El efecto de inducir la ovulación demostrado en el EJEMPLO DE PRUEBA 9 es una acción en las ratas del receptor eCG pero el efecto en este EJEMPLO DE PRUEBA demuestra los resultados obtenidos usando ratas desnudas. No se requiere ningún tratamiento previo de eCG para el efecto de liberación de gonadotropina por metastina.

Los resultados ilustrados en la FIG. 16 indican que la liberación de gonadotropina por inyección de metastina también

imparte estímulo fisiológico al ovario, produciendo aumento de producción de progesterona.

EJEMPLO DE PRUEBA 12

Efecto liberador de Gonadotropina de metastina humana en la rata macho madura

La Metastina humana disuelto en solución salina en una concentración de 175 nmol/mL fue inyectada subcutáneamente en el área dorsal de ratas Wistar macho de 11 semanas de edad después del nacimiento (Charles River Japón, Inc.) en una dosis de 200 µL/animal, es decir, 35 nmol como metastina humana, durante 10:30 a 11:30 AM. Antes de la inyección de metastina y 1, 2 y 4 horas después de la inyección, cada animal fue decapitado para recuperar sangre. En la recuperación de sangre, 300 µl de 10 KIU/ml de solución aprotinina (Trasylol, Bayer) que contiene 3 mg/ml de EDTA se habían llenado previamente en un tubo centrifugando para recuperación para prevenir coágulos de sangre. Después de la recuperación de sangre, la sangre fue mezclada completamente y la mezcla fue centrifugada a 2.000G durante 25 minutos. Después que el sobrenadante era recuperado, el producto fue usado como una muestra de plasma. Los niveles de FSH (hormona folículo-estimulante), LH (hormona luteinizante) y el contenido testosterona en el plasma fue determinado por radioinmunoensayo (Folículo Estimulante de Hormona de Rata (rFSH) [^{125}I] Biotrack Assay System con separación magnética, Hormona Luteinizante de Rata (rLH) [^{125}I] Biotrack Assay System con separación magnética, ambos por Amersham Bioscience, y DPC.Total Testosterone por Diagnostic Products Corporation).

Los resultados obtenidos por monitoreo de los cambios en el

nivel de FSH en la sangre en la rata por inyección de metastina se ilustran en FIG. 17. Una hora después de la inyección de metastina, el nivel de FSH en la sangre empezó a aumentar significativamente y alcanzó el máximo después de 2 horas, y aún después de 4 horas, todavía se mantuvo un estado más alto.

Los resultados obtenidos por monitoreo de los cambios en el nivel de LH en la sangre en la rata por inyección de metastina se ilustran en FIG. 18. De manera semejante al caso de FSH, el nivel de LH en la sangre empezó a aumentar significativamente 1 hora después y alcanzó el máximo después de 2 horas. Mientras una disminución en el nivel de LH en la sangre fue medido después de 4 horas, nivel de LH todavía se mantuvo superior que el nivel anterior a la inyección.

Se ilustran los resultados obtenidos por monitorieo de los cambios en el nivel de testosterona en la sangre en la rata por inyección de metastina en FIG. 19. El nivel de testosterona demostró un aumento rápido a 1 hora después de la inyección de metastina. Una disminución en el nivel de testosterona en la sangre fue notado después de 2 y 4 horas, el nivel de testosterona aún se mantuvo superior a ambos puntos de tiempo que el nivel anterior a la inyección.

Los resultados de FIG. 17 y FIG. 18 revelan que la administración periférica de metastina induce la liberación de gonadotropina tal como FSH, LH, etc. en la rata macho. En vista a los resultados del EJEMPLO DE PRUEBA 10, se considera que la metastina es un factor sumamente importante en las ratas macho y hembra, estimulando la liberación de gonadotropina.

Los resultados ilustrados en la FIG. 19 indican que la

liberación de gonadotropina por inyección de metastina también imparte estímulo fisiológico a los testículos, produciendo aumento de la producción de testosterona.

De estos resultados se considera que la administración de metastina estimularía los testículos inducida por la liberación de gonadotropina. Esto sugiere que la metastina posiblemente afecta la función reproductora masculina que incluye la maduración seminal, secreción de hormona, etc.

EJEMPLO DE PRUEBA 13

Pruebe de la estabilidad del compuesto en sangre.

La sangre fue extraída del ratón Balb/c de 8 semanas de edad (hembra), estabilizada a 37°C durante 30 minutos y centrifugada a 13.000 rpm durante 10 minutos para dar suero de ratón. Se almacena helado el suero así obtenido a -80°C.

La prueba de estabilidad se realizó por agregado de 5 nmol de Compuesto (5µL de solución acuosa) a 45 µL de suero y luego se establece la mezcla a 37°C. La estabilización fue realizada en 3 puntos de tiempo, incluyendo 2, 10 y 30 minutos. La muestra después de la estabilización fue hervida durante 3 minutos y refrigerada en un baño de hielo. Después fue agregado a la muestra 200 µL de acetonitrilo/agaua (3/1), la mezcla fue ultrasonificada durante 5 minutos y entonces centrifugada a 5,000 rpm durante 1 minuto. Después 150 µL del sobrenadante fueron diluídos con 250 µL de agua destilada, las materias insolubles fueron eliminadas por filtración a través de un filtro que tiene un tamaño de poro de 0,45 µm y 200 µL del filtrado fueron aplicados a HPLC (220 nm) para determinar el área máxima del Compuesto. Una proporción de área máxima

respecto al área cuando el Compuesto fue tratado durante 0 minuto bajo las mismas condiciones fue calculado como un valor promedio en 4 pasadas respectivas para determinar la proporción residual. Luego, tomando la proporción residual calculada en la ordenada y el tiempo en la abscisa, fue realizado un gráfico y se aproximó por una función exponencial. Así, fue calculado el tiempo cuando la proporción residual alcanzó 50% como una media vida.

La serie LC-VP fabricada por "Shimadzu Corporation" fue usada como HPLC preparativa y, Wakosil-II 5C18 HG (4,6 mm x 100 mm) fabricado por "Wako Pure Chemical Industries, Ltd." fue usada como columna. El eluyente A (0,1% agua que contiene TFA) y el eluyente B (0,1% acetonitrilo que contiene TFA) se usaron como eluyentes. La elución de pendiente de densidad lineal fue realizada a una velocidad de flujo de 1,0 ml/min. eluyentes usando A/B: 100/0 - 0/50 (25 minutos).

Los compuestos probados y los valores t1/2 (min) se ilustran en TABLA 27.

[TABLA 27]

Compuesto Número	$t_{1/2}$ (min)
1	22.5
3	0.6
42	0.7
82	1.8
134	2.4
141	8.7
232	28.2
286	57.5

EJEMPLO DE PRUEBA 14

Inducción de ovulación en rata inmadura usando los derivados de metastina

La gonadotropina coriónica equina (eCG, serotropina, Dainippon Pharmaceutical Co., Ltd.) se disolvió en solución salina (Otsuka Pharmaceutical Co., Ltd.) en una concentración de 100 IU/mL. Usando una jeringa de tuberculina de 1 ml y una aguja de medida 26 (ambos de Terumo Co., Ltd.), se inyectó subcutáneamente eCG en el área dorsal de ratas Wistar hembra de 23 días de edad después del nacimiento (Charles River Japón, Inc.) en una dosis de 10 IU/animal, durante 9:00 a 10:00 AM. Luego de la inyección del eCG, animal se agrupó después de 47 a 48 horas según se ilustra a continuación, en los grupos, cada droga fue inyectada.

Grupo A (5 ratas): gonadotropina coriónica humana (hCG, gonadotropina, Dainippon Pharmaceutical Co., Ltd.) fue disuelto en solución salina a 100 IU/mL y la solución se inyectó subcutáneamente en la parte de atrás en una dosis de 20 IU/animal.

Grupo B (5 ratas): Compuesto No. 305 fue disuelto en

solución salina a 33,3 nmol/mL y la solución fue inyectada subcutáneamente en la parte de atrás en una dosis de 6,7 nmol/animal.

Grupo C (5 ratas): Compuesto No. 305 fue disuelto en solución salina a 10,0 nmol/mL y la solución fue inyectada subcutáneamente en la parte de atrás en una dosis de 2,0 nmol/animal.

Grupo D (5 ratas): Compuesto No. 322 fue disuelto en solución salina a 33,3 nmol/mL y la solución fue inyectada subcutáneamente en la parte de atrás en una dosis de 6,7 nmol/animal.

Grupo E (5 ratas): Compuesto No. 322 fue disuelto en solución salina a 10,0 nmol/mL y la solución se inyectó subcutáneamente en la parte de atrás en una dosis de 2,0 nmol/animal.

Grupo F (6 ratas): La solución salina se inyectó subcutáneamente en la parte de atrás en una dosis de 200 µL/animal.

El animal fue sacrificado por decapitación después de 24 a 25 horas prar recuperar sangre, oviductos bilaterales y útero después de la administración de estas drogas. En la sangre recolectada, se habían llenado previamente 90 µl de 10 KIU/mL solución aprotinina (Trasylol, Bayer) que contiene 3 mg/ml EDTA en un tubo para recuperación para prevenir coágulos de sangre. Después de la recuperación de sangre, la sangre fue mezclada completamente y la mezcla fue centrifugada a 2.000G durante 25 minutos. Después que el sobrenadante era recuperado, el producto fue usado como una muestra de plasma.

El número de oocitos fue contado por referencia al método descripto en "Eur. J. Endocrinol.", 138, 594-600 (1998).

Cuando la retención de oocitos en el conducto de trompa de Falopio era confirmada por la observación del oviducto en el estereomicroscopio, el conducto fue punzado con una aguja de medida 27 para jeringa (Terumo) para recuperar oocitos. Después que las células de granulosa que rodean los oocitos fueron eliminadas por tratamiento de tripsina, el número de oocitos fue contado. Cuando la retención de oocitos en el conducto dilatado de oviducto no era confirmada por observación del oviducto en el estereomicroscopio, se insertó con una aguja de medida 27 con la punta pulida para jeringa en ostium tubal y más de 400 µL de solución salina carmesí en el oviducto y utero para enjuagar. Entonces, fue observada la presencia o ausencia de oocitos en el efluente.

El número de oocitos así obtenido se ilustra en FIG. 20. En el Grupo A que es un grupo de tratamiento de superovulación multipropósito el número de oocitos era de 38,0 oocitos en promedio por rata. En los Grupos B, C y D, el número de oocitos era 32,6, 29,4 y 29,6 oocitos en promedio, respectivamente, indicando esa ovulación que era sustancialmente equivalente al Grupo A. En cuanto al Grupo E que recibe 2,0 nmol de Compuesto No. 322, se ovularon 3 de 5 ratas y el número de oocitos era de 11,6 en promedio lo cual es inferior al Grupo A. Además en el Grupo A debido al control negativo, ninguna ovulación fue observada.

Los resultados de la FIG. 20 indican que para la inducción de ovulación equivalente al hCG, por lo menos 2,0 nmol/animal

del Compuesto No. 305 y por lo menos 6,7 nmol/animal de Compuesto No. 322 deben ser administrados.

Se ilustran los resultados obtenidos de la medición del nivel de estradiol contenido en el plasma en la FIG. 21. El nivel de estradiol de sangre fue medido por radioinmunoensayo (DPC.Estradiol Kit, Iatron, Inc.). Según lo ilustrado en la FIG. 21, ninguna diferencia se encontró entre los Grupos A, B, C y D en lo que se refiere al estradiol y sólo el Grupo F demuestra un nivel alto. El Grupo E tenía una tendencia a demostrar un nivel más alto en ratas sin inducción de ovulación.

Se ilustran los resultados obtenidos midiendo el nivel de progesterona contenido en el plasma en la FIG. 22. El nivel de progesterona en la sangre fue medido por radioinmunoensayo (DPC.Progesterone, Iatron, Inc.). Según se ilustra en la FIG. 22, el nivel de progesterona en la sangre era supeior en el Grupo A y en los Grupos B, C y D, el nivel de progesterona muestra menos de una mitad de nivel del Grupo A. Los Grupos E y F demuestran un nivel muy bajo.

Los resultados de FIG. 21 y FIG. 22 revelan que más de 2,0 nmol/animal de Compuesto No. 305 y más de 6,7 nmol/animal de Compuesto No. 322 fueron administrados para inducir la diferenciación normal de las células de granulosa productoras de estrógeno a las células luteales productoras de progesterona. Además, cuando el Compuesto No. 305 o Kiss-322 fue administrado, nivel de progesterona era más bajo que por la administración del hCG, sugiriendo que el efecto estimulante de estos derivados en el ovario sería más moderado que el del hCG.

EJEMPLO DE PRUEBA 15

Evaluación del efecto de disminución del nivel de testosterona en sangre de los derivados de péptido de metastina usando rata macho madura

Un péptido del derivado de metastina (más adelante en la presente péptido) fue disuelto en agua destilada (Otsuka Joryusui K.K.) para preparar 2 mM de solución de péptido. Esta solución de péptido fue llenada en 5 bombas osmóticas "ALZET" (Modelo 2001, 0,2 ml en volumen, relación de liberación: 0,001 ml/hr, DURECT Corporation). El llenado de bombas ALZET con la solución de péptido fue implantado subcutáneamente en 5 ratas macho CD(SD)IGS de 9 semanas de edad después del nacimiento (Charles River Japón, Inc.) en la parte de atrás bajo anestesia de éter con una bomba por animal. Para control negativo, fue llenada agua destilada (Otsuka Pharmaceutical Co., Ltd.) en 5 bombas osmóticas ALZET que se implantaron de manera semejante en 5 ratas macho CD(SD)IGS (Charles River Japón, Inc.), respectivamente. Estas ratas implantadas con bomba se alimentaron durante 6 días bajo condiciones de alimento normales. Después de ser pesados, los animales fueron decapitados para recolectar sangre. Después que 0,03 ml/ml de sangre por solución de aprotinina (Trasylol, Bayer) que contiene 0,1 mg/ml EDTA.2Na fue agregada a la sangre, la mezcla fue centrifugada a 1.800G durante 25 minutos para aislar/recuperar el plasma. Del plasma obtenido, se aplicaron 0,05 ml al radioinmunoensayo (DPC.Total Testosterone Kit, Diagnostic Products Corporation) para medir el nivel de testosterona en plasma de cada rata. El valor debajo del límite de medición (0,04 ng/ml de nivel de plasma) en radioinmunoensayo fue tratado

como 0. Un valor promedio de nivel de testosterona de 5 ratas que reciben péptido fue calculado y un valor relativo (porciento) al valor medio respecto a un valor promedio de 5 ratas que reciben agua destilada.

Usando este método de evaluación, se evaluaron los diversos péptidos y una parte de los resultados se ilustra en las TABLAS 28 y 29.

[TABLA 28]

Comp. No.	Nivel de testosterona en sangre
334	40%
354	43%
436	35%
269	7%
386	23%
499	2%
305	2%
385	2%
492	65%
496	3%
134	50%
141	31%
176	12%

[TABLA 29]

Comp. No.	Nivel de testosterona en sangre
505	40%
508	9%
509	2%
512	2%
515	2%
517	79%

EJEMPLO DE PRUEBA 16

De una manera similar al EJEMPLO DE PRUEBA 14, fue realizada la evaluación usando 0,1 mM de solución de péptido y una parte de los resultados obtenidos se ilustran en TABLA 30.

[TABLA 30]

Compuesto Número	Nivel de testosterona en la sangre
305	48%
385	33%
499	32%
512	38%
516	3%
523	72%
538	45%
540	55%
545	37%
547	65%
550	2%
551	8%
552	21%
553	39%
554	52%
555	73%
558	2%
559	17%
562	11%
564	66%
565	80%
566	89%
567	86%
571	17%

EJEMPLO DE PRUEBA 17

Evaluación de derivados de péptido de metastina para acción de reducción del nivel de testosterona en de sangre usando rata macho madura

Las soluciones de péptido a una concentración de 1 mM fueron preparadas disolviendo los derivados de péptido de metastina (más adelante en la presente denominados péptido) en solución acuosa 50% de DMSO. El péptido fue encapsulado en cinco bombas osmóticas ALZET (Modelo 2001, 0,2 ml de volumen, proporción de liberación 0,001 ml/hr, DURECT Corporation). Las bombas ALZET encapsuladas con solución de péptido se implantaron subcutáneamente al dorso de cinco ratas CD macho (SD) IGS de nueve semanas de edad (Charles River Japan,Inc.) anestesiadas con éter con una bomba por rata. Separadamente, para el control negativo, se implantaron las bombas osmóticas ALZET encapsuladas con agua destilada a cinco ratas CD macho (SD) IGS (Charles River Japan,Inc.) Las ratas se alimentaron durante seis días bajo condiciones normales. Después de ser pesadas, fue recolectada la sangre por decapitación. A 1 ml de sangre, le fue agregada 0,03 ml de aprotinina (Trasylol, Byer) en solución que contiene 0,1 g/ml EDTA 2Na. El plasma fue aislado por centrifugado a 1.800 x g durante 25 minutos y fue recolectado. Del plasma así obtenido, 0,05 ml se tomaron para radioinmunoensayo (DPC Total Testosterone Kit, Diagnostic Products Corporation) para medir el nivel de testosterona en sangre de cada rata. El valor por debajo del límite de medición de radioinmunoensayo (0,04 ng/ml como concentración de plasma) fue tratado como cero. Los valores medios para el nivel de

testosterona de cinco ratas a las cuales se administró el péptido, fue calculado y el valor relativo (porciento) para valor medio de nivel de testosterona de cinco ratas a las cuales se administró el agua destilada, fue estimado. Un ejemplo de los resultados evaluados para varios péptidos usando este método de evaluación se ilustra en la TABLA 31.

[TABLA 31]

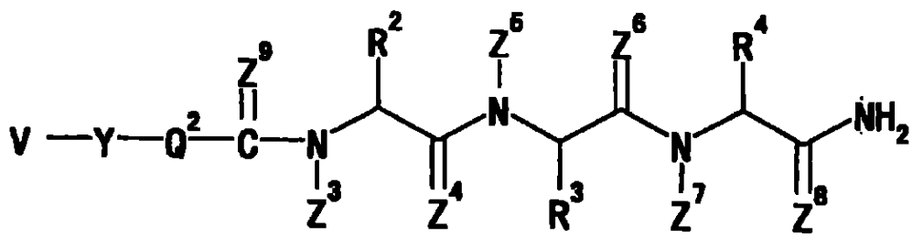
Comp. No.	Nivel testosterona en ganara
500	2%
501	2%
545	2%
548	18%
555	2%
564	2%
589	2%
590	2%
591	2%
592	2%
595	3%
598	2%
599	2%
600	2%
602	2%
608	2%
612	2%
613	2%
615	2%
616	2%
617	2%
618	2%
621	2%
623	2%
625	2%
626	2%
627	2%
629	2%
630	2%
635	2%
637	2%
638	2%
642	2%
648	2%
649	2%
650	2%
651	2%
652	2%
657	2%
658	2%
660	2%
662	2%
663	2%
664	8%
666	2%
667	2%
670	2%
671	2%
672	2%
674	2%
675	2%
676	2%
677	2%

[Listado de secuencia]

SEQ ID NO: 15	La terminal C es aminada..
SEQ ID NO: 16	La terminal C es aminada..
SEQ ID NO: 17	La terminal C es aminada..
SEQ ID NO: 18	La terminal C es aminada..

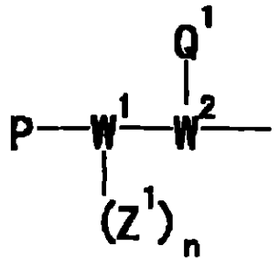
REIVINDICACIONES

1. Un derivado de metastina (II) caracterizado por que está representado por la fórmula:

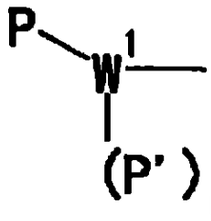


[en donde;

V representa un grupo representado por la fórmula:



o un grupo representado por la fórmula:



n representa 0 ó 1;

W^1 representa N, CH ó O (con la condición que cuando W^1 es N ó CH, n representa 1 y cuando W^1 es O, n representa 0);

W^2 representa N ó CH;

Z^1, Z^3, Z^5 y Z^7 cada uno representa un átomo de hidrógeno o un grupo alquilo C_{1-3};

Z^4, Z^6 y Z^8 cada uno representa átomo de hidrógeno, O ó S;

R^2 representa (1) átomo de hidrógeno ó (2) un grupo alquilo C_{1-10} cíclico o lineal, o (3) un grupo alquilo C_{1-10} que consiste de un grupo alquilo cíclico y un grupo de alquilo lineal, o (4)

un grupo alquilo C_{1-8} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo opcionalmente sustituido y un grupo cíclico aromático opcionalmente sustituido;

R^3 representa (1) un grupo alquilo C_{1-8} que posee un grupo básico opcionalmente sustituido y opcionalmente posee un sustituyente adicional, (2) un grupo aralquilo que posee un grupo básico opcionalmente sustituido y opcionalmente posee un sustituyente adicional, (3) un grupo alquilo C_{1-4} que tiene un grupo hidrocarburo cíclico no aromático de cantidad de átomos de carbono no mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional, o (4) un grupo alquilo C_{1-4} que tiene un grupo heterocíclico no aromático de cantidad de átomos de carbono no mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional;

R^4 representa un grupo alquilo C_{1-4}, el cual puede ser opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de (1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido, (2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido, (4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de

átomos de nitrógeno, oxígeno y azufre, (5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, y (6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

Q^1 representa un grupo alquilo C_{1-4} que puede ser opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de (1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido, (2) un grupo heterocíclico aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido, (4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, y (6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

Q^2 representa (1) CH_2 que puede ser opcionalmente sustituido con un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, (2) NH, el cual puede ser opcionalmente sustituido con un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, o (3) O;

Y representa un grupo representado por la fórmula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO- ó $-CH_2CH_2-$ que puede ser opcionalmente sustituido con un grupo alquilo C_{1-6}; y,

Z^9 representa átomo de hidrógeno, O ó S; y,

P y P', los cuales pueden ser iguales o diferentes, cada uno puede formar un anillo combinando P y P' ó P y Q^1 juntos representan:

(1) átomo de hidrógeno;

(2) un residuo de aminoácido opcional limitado de manera continua o discontinua del C terminal de la secuencia de aminoácido 1-48 en la secuencia de aminoácido representada por SEQ ID NO: 1;

(3) un grupo representado por la fórmula:
$J^1-J^2-C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})-$
(en donde:

J^1 representa (a) átomo de hidrógeno o (b) (i) un grupo acilo C_{1-15}, (ii) un grupo alquilo C_{1-15}, (iii) un grupo arilo C_{6-14}, (iv) grupo carbamoilo, (v) grupo carboxilo, (vi) grupo sulfino, (vii) grupo amidino, (viii) grupo glioxiloilo o (ix) grupo amino, cuuos grupos pueden ser opcionalmente sustituidos con un sustituyente que contiene de un grupo cíclico opcionalmente sustituido;

J^2 representa (1) NH opcionalmente sustituido con un grupo alquilo C_{1-6}, (2) CH_2 opcionalmente sustituido con un grupo alquilo C_{1-6}, (3) O ó (4) S;

J^3 a J^6 representa átomo de hidrógeno o un grupo alquilo C_{1-3};

Q^3 a Q^6 representa un grupo alquilo C_{1-4} el cual puede tener un sustituyente opcionalmente seleccionado del grupo que consiste de:

(1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido,

(2) un grupo heterocíclico aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre,

(3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido,

(4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre,

(5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7,

(6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7,

(7) un grupo amino opcionalmente sustituido,

(8) un grupo guanidino opcionalmente sustituido,

(9) un grupo hidroxilo opcionalmente sustituido,

(10) un grupo carboxilo opcionalmente sustituidos,

(11) un grupo carbamoilo opcionalmente sustituido, y

(12) un grupo sulfhidrilo opcionalmente sustituido,

o átomo de hidrógeno.;

Pueden combinarse entre sí J^3 y Q^3, J^4 y Q^4, J^5 y Q^5 ó J^6 y Q^6 juntos, o, pueden combinarse entre sí J^2 y Q^3, Y^1 y Q^4, Y^2 y Q^5, ó Y^3 y Q^6, para formar un anillo;

Y^1 a Y^3 representa un grupo representado por la fórmula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ ó $-N(J^{13})CO-$ (en donde J^{13} y J^{14} cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3}); y,

Z^{10} representa átomo de hidrógeno, O ó S);

(4) un grupo representado por la fórmula:

$J^1-J^2-C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})-$

(en donde:

J^1 y J^2, cada uno posee el mismo significado según lo descripto anteriormente;

J^7 a J^9 poseen el mismo significado que para J^3;

Q^7 a Q^9 poseen el mismo significado que para Q^3;

Y^2 y Y^3 cada uno posee el mismo significado según lo descripto anteriormente;

Z^{10} posee el mismo significado según lo descripto anteriormente;

Pueden combinarse entre sí J^7 y Q^7, J^8 y Q^8 ó J^9 y Q^9, ó, pueden combinarse entre sí J^2 y Q^7, Y^2 y Q^8 o Y^3 y Q^9, para formar un anillo);

(5) un grupo representado por la fórmula:

$J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})-$

(en donde:

J^1 y J^2 poseen el mismo significado según lo descripto anteriormente representa;

J^{10} y J^{11} poseen el mismo significado que para J^3;

Q^{10} y Q^{11} poseen el mismo significado que para Q^3;

Y^3 posee el mismo significado según lo descripto anteriormente;

Z^{10} posee el mismo significado según lo descripto anteriormente; y

Pueden combinarse entre sí J^{10} y Q^{10} ó J^{11} y Q^{11}, o pueden combinarse entre sí J^2 y Q^{10} ó Y^3 y Q^{11}, para formar un anillo);

(6) un grupo representado por la fórmula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(en donde;

J^1 y J^2 poseen el mismo significado según lo descripto anteriormente;

J^{12} posee el mismo significado de J^3;

Q^{12} posee el mismo significado de Q^3;

Z^{10} posee el mismo significado según lo descripto anteriormente; y,

Pueden combinarse entre sí J^{12} y Q^{12}, o pueden combinarse entre sí J^2 y Q^{12}, para formar un anillo); ó,

(7) un grupo representado por la fórmula:.

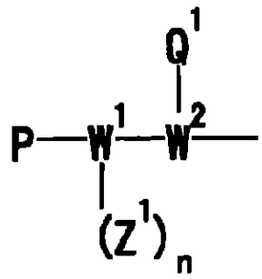
J^1-

(en donde:

J^1 posee el mismo significado según lo descripto anteriormente)] (con la condición que un péptido que consiste en la secuencia de aminoácido de 1-54, 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54, 41-54, 42-54,

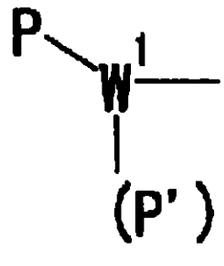
43-54, 44-54, 45-54, 46-54, 47-54, 48-54 ó 49-54 en la secuencia de aminoácido representada por SEQ ID NO.: 1 sea excluida), o una sal del mismo.

2. Un derivado de metastina (II) de acuerdo con la reivindicación 1, caracterizado por que V es un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado como el definido en reivindicación 1), o una sal del mismo.

3. Un derivado de metastina (II) de acuerdo con la reivindicación 1, caracterizado por que V es un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado como el definido en la reivindicación 1), o una sal del mismo.

4. Una prodroga caracterizada por que es un derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo.

5. Un compuesto farmacéutico caracterizado por que comprende el derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

6. Un compuesto farmacéutico de acuerdo con la

reivindicación 5, caracterizado por que es un agente para suprimir la metástasis del cáncer o un agente para suprimir el crecimiento del cáncer.

7. Un compuesto farmacéutico de acuerdo con la reivindicación 5, caracterizado por que es un agente para prevenir o tratar el cáncer.

8. Un compuesto farmacéutico de acuerdo con la reivindicación 5, caracterizado por que es un agente para controlar la función placentaria.

9. Un compuesto farmacéutico de acuerdo con la reivindicación 5, caracterizado por que es un agente para prevenir o tratar coriocarcinoma, mola hidatídica, mola invasiva, aborto, hipoplasia fetal, metabolismo de glucosa anormal, metabolismo de lípido anormal o inducción al parto.

10. Un compuesto farmacéutico de acuerdo con la reivindicación 5, caracterizado por que es un agente para mejorar la función gonadal.

11. Un compuesto farmacéutico de acuerdo con la reivindicación 5, caracterizado por que es un agente para prevenir o tratar el cáncer dependiente de hormona, infertilidad, endometriosis, pubertad precoz o mioma de útero.

12. Un compuesto farmacéutico de acuerdo con la reivindicación 5, caracterizado por que es un agente para inducir o estimular la ovulación.

13. Un compuesto farmacéutico de acuerdo con la reivindicación 5, caracterizado por que es un agente secretagogo de hormona gonadotrópica o un agente secretagogo de hormona sexual.

14. Un compuesto farmacéutico de acuerdo con la reivindicación 5, caracterizado por que es un agente para prevenir o tratar la enfermedad de Alzheimer o deterioro cognoscitivo moderado.

15. Un método para suprimir metástasis de cáncer o crecimiento de cáncer, caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

16. Un método para prevenir o tratar cáncer caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

17. Un método para controlar la funcion placental caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

18. Un método para prevenir o tratar coriocarcinoma, mola hidatídica, mol invasiva, aborto, hipoplasia fetal, metabolismo de glucosa anormal, metabolismo de lípidos anormal o inducción al parto, caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

19. Un método para mejorar la función gonadal caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

20. Un método para prevenir o tratar cáncer dependiente de hormona, infertilidad, endometriosis, pubertad precoz o mioma de útero, caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

21. Un método para inducir o estimular la ovulación, caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

22. Un método para promover la secreción de hormona gonadotrópica o promover la secreción de hormona sexual caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

23. Un método para prevenir o tratar la enfermedad de Alzheimer o el deterioro cognoscitivo moderado caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo.

24. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un agente para suprimir la metástasis del cáncer o un agente para suprimir el crecimiento del cáncer.

25. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un

agente para prevenir o tratar el cáncer.

26. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un agente para controlar la función placental.

27. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un agente para prevenir o tratar coriocarcinoma, mola hidatídica, mola invasiva, aborto, hipoplasia fetal, metabolismo de glucosa anormal, metabolismo de lípido anormal o inducción al parto.

28. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un agente para mejorar la función gonadal.

29. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un agente para prevenir o tratar el cáncer dependiente de hormona, infertilidad, endometriosis, pubertad precoz o mioma de útero.

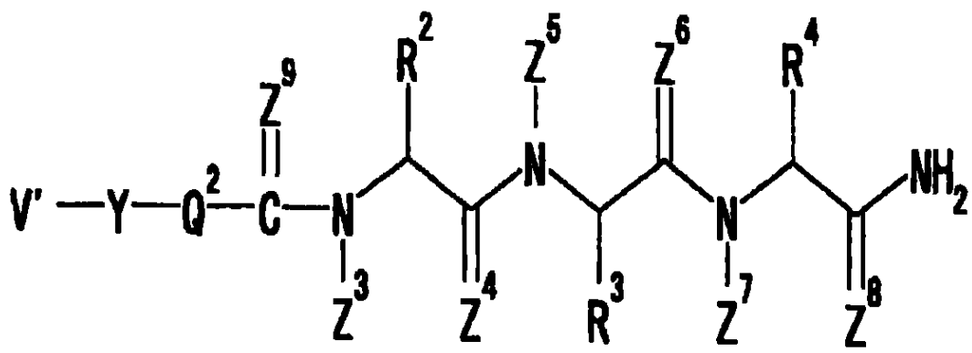
30. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un agente para inducir o estimular la ovulación.

31. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un agente secretagogo de hormona gonadotrópica o un agente

secretagogo de hormona sexual.

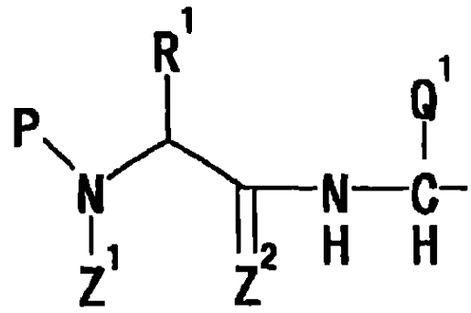
32. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un agente para prevenir o tratar la enfermedad de Alzheimer o el deterioro cognoscitivo moderado.

33. Un agente para suprimir la secreción de hormona gonadotrópica o un agente para suprimir la secreción de hormona sexual caracterizado por que comprende el derivado de metastina (III) representado por la fórmula:

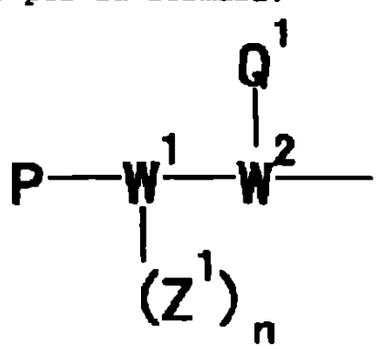


[en donde:

V' representa un grupo representado por la fórmula:



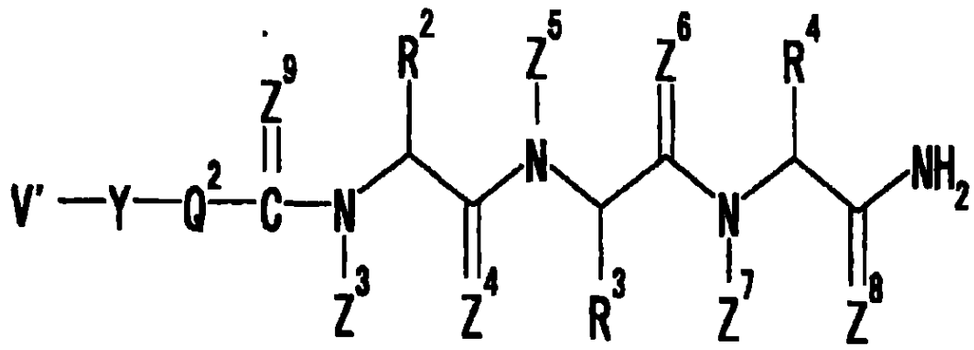
un grupo representado por la fórmula:



secretagogo de hormona sexual.

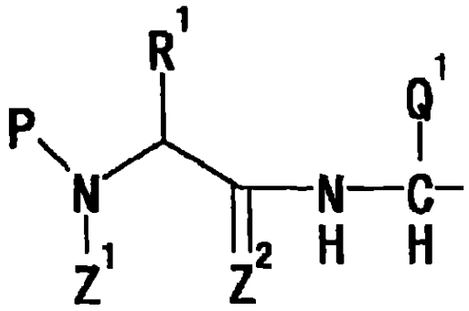
32. Una utilización del derivado de metastina (II) de acuerdo con la reivindicación 1 o una sal del mismo, o una prodroga del mismo caracterizada por que es para fabricar un agente para prevenir o tratar la enfermedad de Alzheimer o el deterioro cognoscitivo moderado.

33. Un agente para suprimir la secreción de hormona gonadotrópica o un agente para suprimir la secreción de hormona sexual caracterizado por que comprende el derivado de metastina (III) representado por la fórmula:

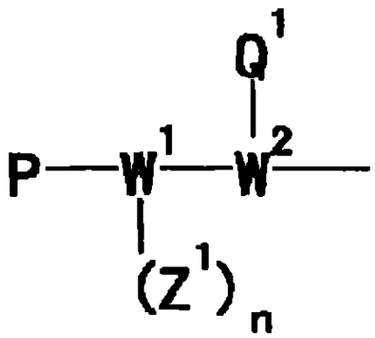


[en donde:

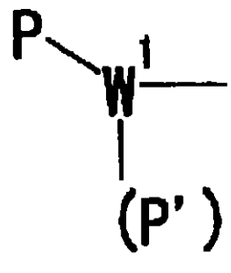
V' representa un grupo representado por la fórmula:



un grupo representado por la fórmula:



o un grupo representado por la fórmula:



n representa 0 ó 1;

W^1 representa N, CH ó O (con la condición que W^1 es N ó CH, n representa 1, y cuando W^1 es O, n representa 0);

W^2 representa N ó CH;

Z^1, Z^3, Z^5 y Z^7 cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3};

Z^2, Z^4, Z^6 y Z^8 cada uno representa átomo de hidrógeno, O ó S;.

R^1 representa (1) átomo de hidrógeno, (2) un grupo alquilo C_{1-8} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo opcionalmente sustituido y un grupo cíclico aromático opcionalmente sustituido, (3) un grupo alquilo C_{1-10} lineal o cíclico o (4) un grupo alquilo C_{1-10} que consiste de un grupo alquilo cíclico y un grupo alquilo lineal, o (5) un grupo cíclico aromático opcionalmente sustituido;

R^2 representa (1) átomo de hidrógeno o (2) un grupo alquilo C_{1-10} lineal o cíclico o (3) un grupo alquilo C_{1-10} que consiste en un grupo alquilo cíclico y un grupo alquilo lineal, o (4) un grupo alquilo C_{1-8} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de un grupo carbamoilo opcionalmente sustituido, un grupo hidroxilo opcionalmente

sustituido y un grupo cíclico aromático opcionalmente sustituido;

R^3 representa (1) un grupo alquilo C_{1-8} que posee un grupo básico opcionalmente sustituido y posee opcionalmente un sustituyente adicional, (2) un grupo aralquilo que posee un grupo básico opcionalmente sustituido y posee opcionalmente un sustituyente adicional, (3) un grupo alquilo C_{1-4} que no tiene un grupo hidrocarburo cíclico no aromático de una cantidad de átomos de carbono no mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional, o (4) un grupo alquilo C_{1-4} que tiene un grupo heterocíclico no aromático de una cantidad de átomos de carbono no mayor que 7 el cual tiene un grupo básico opcionalmente sustituido, y opcionalmente posee un sustituyente adicional;

R^4 representa un grupo alquilo C_{1-4} que puede ser opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de (1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido, (2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido, (4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, y (6) un grupo

heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;.

Q^1 representa un grupo alquilo C_{1-4} que puede ser opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de (1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido, (2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido, (4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre, (5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7, y (6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7;

Q^2 representa (1) CH_2 que puede ser opcionalmente sustituido con un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, (2) NH que puede ser opcionalmente sustituido con un grupo alquilo C_{1-4} opcionalmente sustituido con un sustituyente seleccionado del grupo que consiste de grupo carbamoilo y grupo hidroxilo, o (3) O;

Y representa un grupo representado por la fórmula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO- ó $-CH_2CH_2-$ que puede ser opcionalmente sustituido con un grupo

alquilo C_{1-6}; y,

Z^9 representa átomo de hidrógeno, O ó S; y,

P y P', los cuales pueden ser iguales o diferentes, cada uno puede formar un anillo por combinación entre sí de P y P' ó P y Q^1 y representa:

(1) átomo de hidrógeno;

(2) un residuo de aminoácido optcional continua o discontinuamente limitado del C terminal de la secuencia de aminoácido 1-48 en la secuencia de aminoácido representada por SEQ ID NO: 1;

(3) un grupo representado por la fórmula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

(en donde:

J^1 representa (a) átomo de hidrógeno o (b) (i) un grupo acilo C_{1-15}, (ii) un grupo alquilo C_{1-15}, (iii) un grupo arilo C_{6-14}, (iv) grupo carbamoilo, (v) grupo carboxilo, (vi) grupo sulfino, (vii) grupo amidino, (viii) grupo glioxiloilo ó (ix) grupo amino, tales grupos pueden ser opcionalmente sustituidos con un sustituyente que contiene un grupo cíclico opcionalmente sustituido;

J^2 representa (1) NH opcionalmente sustituido con un grupo alquilo C_{1-6}, (2) CH_2 opcionalmente sustituido con un grupo alquilo C_{1-6}, (3) O ó (4) S;

J^3 a J^6 cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3};

Q^3 a Q^6 cada uno representa un grupo alquilo C_{1-4} que puede tener un sustituyente opcionalmente seleccionado del grupo que consiste de:

(1) un grupo hidrocarburo aromático C_{6-12} opcionalmente sustituido,

(2) un grupo heterocíclico aromático opcionalmente sustituido de 5 a 14 miembros que consiste de 1 a 7 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre,

(3) un grupo cíclico fusionado aromático C_{8-14} opcionalmente sustituido,

(4) un grupo heterocíclico fusionado aromático de 5 a 14 miembros opcionalmente sustituido que consiste de 3 a 11 átomos de carbono y heteroátomos seleccionados del grupo que consiste de átomos de nitrógeno, oxígeno y azufre,

(5) un grupo hidrocarburo cíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7,

(6) un grupo heterocíclico no aromático opcionalmente sustituido que posee una cantidad de átomos de carbono no mayor que 7,

(7) un grupo amino opcionalmente sustituido,

(8) un grupo guanidino opcionalmente sustituido,

(9) un grupo hidroxilo opcionalmente sustituido,

(10) un grupo carboxilo opcionalmente sustituido,

(11) un grupo carbamoilo opcionalmente sustituido, y

(12) un grupo sulfhidrilo opcionalmente sustituido,

o átomo de hidrógeno;

Pueden combinarse entre sí J^3 y Q^3, J^4 y Q^4, J^5 y Q^5 ó J^6 y Q^6, o, pueden combinarse entre sí Z^1 y R^1, J^2 y Q^3, Y^1 y Q^4, Y^2 y Q^5, o Y^3 y Q^6, para formar un anillo;

Y^1 a Y^3 cada uno representa un grupo representado por la fórmula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ ó $-N(J^{13})CO-$ (en donde J^{13} y J^{14} cada uno representa átomo de hidrógeno o un grupo alquilo C_{1-3}); y,

Z^{10} representa átomo de hidrógeno, O ó S);

(4) un grupo representado por la fórmula:

$J^1-J^2-C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})-$

(en donde:

J^1 y J^2, cada uno posee el mismo significado según lo descripto anteriormente;

J^7 a J^9 poseen el mismo significado que para J^3;

Q^7 a Q^9 poseen el mismo significado que para Q^3;

Y^2 y Y^3 cada uno posee el mismo significado según lo descripto anteriormente;

Z^{10} posee el mismo significado según lo descripto anteriormente;

Pueden combinarse entre sí J^7 y Q^7, J^8 y Q^8 ó J^9 y Q^9, o, pueden combinarse entre sí J^2 y Q^7, Y^2 y Q^8 ó Y^3 y Q^9, para formar un anillo);

(5) un grupo representado por la fórmula:

$J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})-$

(en donde:

J^1 y J^2 poseen el mismo significado según lo descripto anteriormente representa;

J^{10} y J^{11} poseen el mismo significado que para J^3;

Q^{10} y Q^{11} poseen el mismo significado que para Q^3;

Y^3 posee el mismo significado según lo descripto

anteriormente;

Z^{10} posee el mismo significado según lo descripto anteriormente; y,

Pueden combinarse entre sí J^{10} y Q^{10} ó J^{11} y Q^{11}, o pueden combinarse entre sí J^2 y Q^{10} ó Y^3 y Q^{11}, para formar un anillo);

(6) un grupo representado por la fórmula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(en donde;

J^1 y J^2 poseen el mismo significado según lo descripto anteriormente;

J^{12} posee el mismo significado de J^3;

Q^{12} posee el mismo significado de Q^3;

Z^{10} posee el mismo significado según lo descripto anteriormente; y

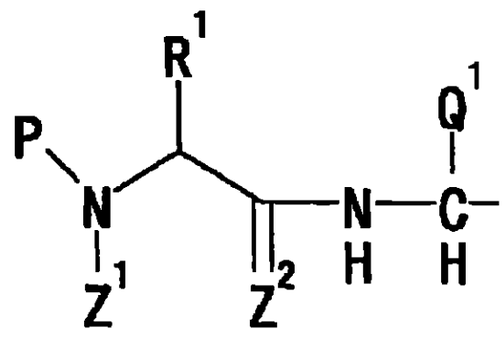
Pueden combinarse entre sí J^{12} y Q^{12}, o pueden combinarse entre sí J^2 y Q^{12}, para formar un anillo); o,

(7) un grupo representado por la fórmula:

J^1- (en donde J^1 posee el significado según lo descripto anteriormente)] o una sal del mismo, o una prodroga del mismo.

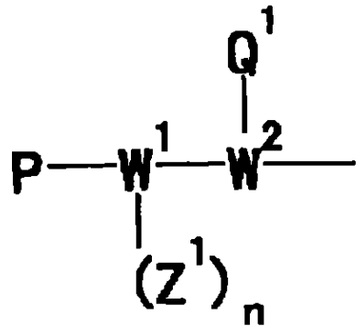
34. Un agente de acuerdo con la reivindicación 33, caracterizado por que el derivado de metastina (III) es derivado de metastina (II) de acuerdo con la reivindicación 1.

35. Un agente de acuerdo con la reivindicación 33, caracterizado por que V' es un grupo representado por la fórmula:



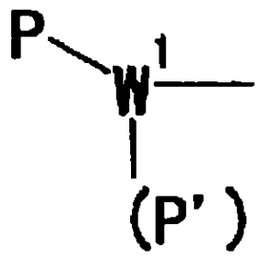
(en donde cada símbolo posee el mismo significado como el definido en reivindicación 33).

36. Un agente de acuerdo con la reivindicación 33, caracterizado por que V' es un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado como el definido en reivindicación 33).

37. Un agente de acuerdo con la reivindicación 33, caracterizado por que V' es un grupo representado por la fórmula:



(en donde cada símbolo posee el mismo significado como el definido en reivindicación 33).

38. Un agente de acuerdo con las reivindicaciones 33 a 37, caracterizado por que es un agente para regular en disminución la hormona gonadotrópica u hormona sexual.

39. Un agente de acuerdo con las reivindicaciones 33 a 37, caracterizado por que es un agente para regular en disminución la proteína OT7T175 humana (receptor de metastina) que consiste

en la secuencia de aminoácido representada por SEQ ID NO: 9.

40. Un agente de acuerdo con las reivindicaciones 33 a 39, caracterizado por que es un agente para prevenir o tratar el cáncer dependiente de hormona.

41. Un método para suprimir la secreción de hormona gonadotrópica o suprimir la secreción de hormona sexual caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina (III) de acuerdo con la reivindicación 33 o una sal del mismo, o una prodroga del mismo.

42. Un método para regular en disminución la hormona gonadotrópica u hormona sexual caracterizado por que comprende administrando a un mamífero una dosis eficaz del derivado de metastina de acuerdo con la reivindicación 33 o una sal del mismo, o una prodroga del mismo.

43. Un método para regular en disminución la proteína OT7T175 humana (receptor de metastina) que consiste en la secuencia de aminoácido representada por SEQ ID NO: 9, caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina de acuerdo con la reivindicación 33 o una sal del mismo, o una prodroga del mismo.

44. Un método para prevenir o tratar cáncer dependiente de hormona caracterizado por que comprende administrar a un mamífero una dosis eficaz del derivado de metastina de acuerdo con la reivindicación 33 o una sal del mismo, o una prodroga del mismo.

45. Una utilización del derivado de metastina de acuerdo con la reivindicación 33 o una sal del mismo, o una prodroga del mismo, caracterizada por que es para fabricar un agente para

suprimir la secreción de hormona gonadotrópica o un agente para suprimir la secreción de hormona sexual.

46. Una utilización del derivado de metastina de acuerdo con la reivindicación 33 o una sal del mismo, o una prodroga del mismo, caracterizada por que es para fabricar un agente para regular en disminución la hormona gonadotrópica u hormona sexual.

47. Una utilización del derivado de metastina de acuerdo con la reivindicación 33 o una sal del mismo, o una prodroga del mismo, caracterizada por que es para fabricar un agente para regular en disminución la proteína OT7T175 humana (receptor de metastina) que consiste en la secuencia de aminoácido representada por SEQ ID NO: 9.

48. Una utilización del derivado de metastina de acuerdo con la reivindicación 33 o una sal del mismo, o una prodroga del mismo, caracterizada por que es para fabricar un agente para prevenir o tratar el cáncer dependiente de hormona.

49. Un derivado de metastina representado por la fórmula:

XX0-XX2-XX3-XX4-XX5-XX6-AzaGly-XX8-XX9-XX10-NH_2

(en donde:

XX0 representa formilo, alcanoilo C_{1-6}, ciclopropancarbonilo, 6-(acetil-D-arginilamino)caproilo, 6-((R)-2,3-diaminopropionilamino)caproilo, 6-(D-norleucilamino)caproilo, 4-(D-arginilamino)butirilo, 3-(4-hidroxifenil)propionilo, glicilo, tirosilo, acetilglicilo, acetiltirosilo, D-tirosilo, acetil-D-tirosilo, piroglutamilo, 3-(piridin-3-il)porpionilo, adipoilo ó 6-aminocaproilo;

XX2 representa Tyr, D-Tyr, D-Ala, D-Leu, D-Phe, D-Lys D-Trp

ó brazo de enlace;

XX3 representa Trp, Pro, 4-piridilalanina, Tic, D-Trp, D-Ala, D-Leu, D-Phe, D-Lys, D-Glu D-2-piridilalanina, D-3-piridilalanina ó D-4-piridilalanina;

XX4 representa Asn, ácido 2-amino-3-ureidopropiónico, ácido N^{β}-formildiaminopropiónico ó ácido N^{β}-acetildiaminopropiónico;

XX5 representa Ser, Thr ó Val;

XX6 representa Phe, Tyr, Trp, Tyr(Me),Thi, Nal(2), Cha, 4-piridilalanina ó 4-fluorofenilalanina;

AzaGly representa azaglicina;

XX8 representa Leu, Nva ó Val;

XX9 representa Arg, Orn, Arg(Me) ó Arg(symMe2);

XX10 representa Phe, Trp, 2-naftilalanina, 2-tienilalanina, tirosina ó 4-fluorofenilalanina), ó una sal del mismo.

50. Un compuesto caracterizado por que su fórmula es:

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 305),

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 385),

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 501),

Benzoil-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 509),

D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 512),

Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 516),

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto

No. 540),

D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 541),

Benzoil-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto

No. 545),

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-

PheΨ(CSNH)NH_2(Compuesto No. 548),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto

No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 552),

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 553),

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 555),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto

No. 558),

3-(4-Hidroxifenil)propionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-

Arg(Me)-Trp-NH_2 (Compuesto No. 559),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 562),

Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto

No. 564),

Ciclopropancarbonil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-

Trp-NH_2 (Compuesto No. 566),

Butiril-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 567),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 571),

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 579),

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 580),

Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 584),

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 585),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compuesto No. 589),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2 (Compuesto No. 590),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2 (Compuesto No. 591),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compuesto No. 592),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2 (Compuesto No. 599),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2 (Compuesto No. 600),

Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 602),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(symMe2)-Trp-NH_2 (Compuesto No. 608),

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 612),

Propionil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 613),

Ac-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 615),

Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 616),

Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 617),

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 618),

Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 621),

Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 623),

Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 625),

Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 626),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 627),

Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 629),

Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 630),

Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 635),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 637),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 638),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2 (Compuesto No. 642),

Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 648),

Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 649),

D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 650),

Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 651),

pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 652),

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 657),

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 658),

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 660),

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 662),

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 663),

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 666),

Hexanoil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto

No. 667),

3-Piridinpropionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 670),

Adipoil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 671),

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 672),

6-Aminocaproil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 674), o sales del mismo.

51. Un compuesto caracterizado por que su fórmula es:

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 552),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 558),

3-(4-Hidroxifenil)propionil-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 559),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 562),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compuesto No. 571),

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 579),

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 585),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

(Compuesto No. 589),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

(Compuesto No. 592),

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 612),

Propionil-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 613),

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 618),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 627),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 637),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 638),

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 658),

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compuesto No. 660),

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compuesto No. 663), o sales de los mismos.

52. Un método para mejorar la estabilidad en sangre, caracterizado por que comprende introducir uno o dos grupos alquilo en la cadena lateral de Arg en el péptido que contiene Arg.

53. Un método para mejorar la estabilidad en sangre, caracterizado por que comprende introducir un grupo alquilo en

la cadena lateral de Arg en el péptido que contiene Arg.

54. Un método para mejorar la estabilidad en sangre, caracterizado por que comprende convertir la cadena lateral de Arg en el péptido que contiene Arg en N^{ω}-Arg alquilado.

55. Un método de acuerdo con las reivindicaciones 52 a 54, caracterizado por que el grupo alquilo es un grupo alquilo C_{1-4}.

56. Un método de acuerdo con las reivindicaciones 52 a 54, caracterizado por que el grupo alquilo es un grupo metilo.

57. Un método de acuerdo con las reivindicaciones 52 a 54, en donde el péptido que contiene Arg es un péptido que posee un péptido parcial caracterizado por que posee la estructura -Arg-XXX-, en donde XXX representa un aminoácido que posee opcionalmente un grupo anillo aromático sustituido en la cadena lateral.

58. Un método de acuerdo con la reivindicación 57, caracterizado por que XXX es Phe, Trp ó Tyr.

RESUMEN

La invención provee derivados de metastina estables que tienen actividades biológicas excelentes (una actividad supresora de metástasis del cáncer, una actividad supresora del crecimiento del cáncer, etc.). Por la modificación de los aminoácidos constitutivos de metastina con grupos modificadores específicos, se ha encontrado que los derivados de metastina han mejorado más la estabilidad en sangre, etc. con respecto a la metastina natural y demuestran una excelente actividad de supresión de metástasis de cáncer o crecimiento de cáncer. Además, se ha encontrado que estos derivados de metastina exhiben efectos de supresión de la secreción de hormona gonadotrópica, suprimiendo a la vez la secreción de hormona sexual, etc., lo cual es totalmente diferente de los efectos conocidos hasta ahora.

FIG 1

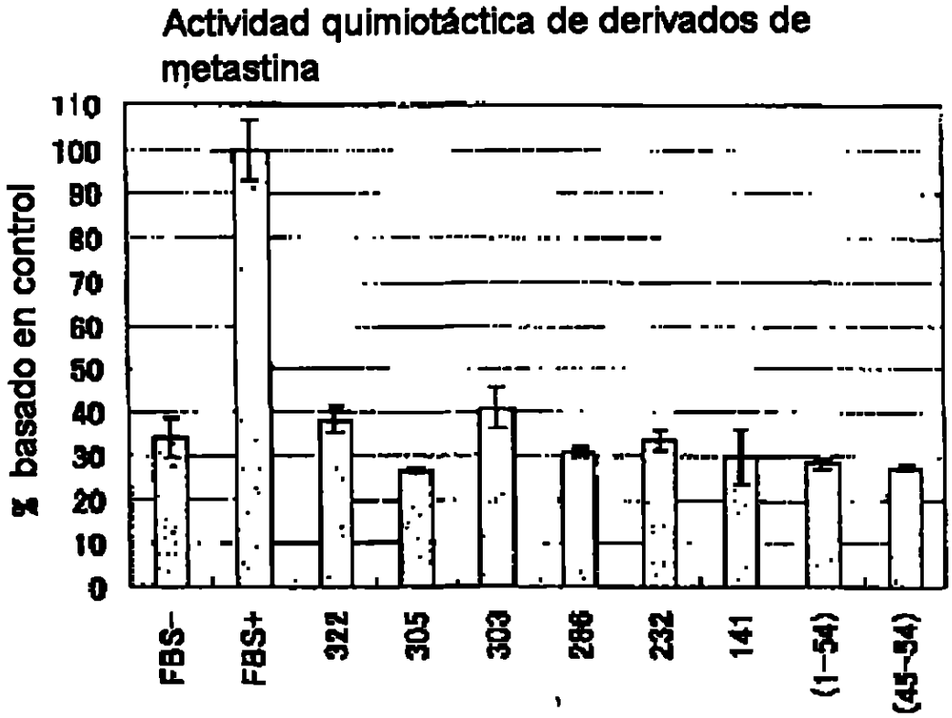

Actividad quimiotáctica de derivados de metastina
% basado en control
110
100
90
80
70
60
50
40
30
20
10
0
FBS-
FBS+
322
305
303
286
232
141
(1-54)
(45-54)

FIG 2

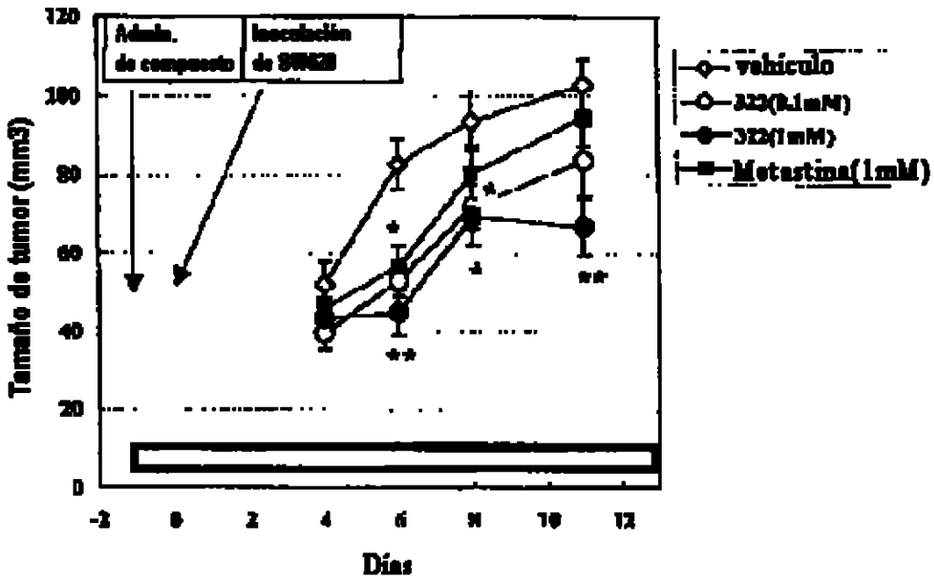


FIG 3

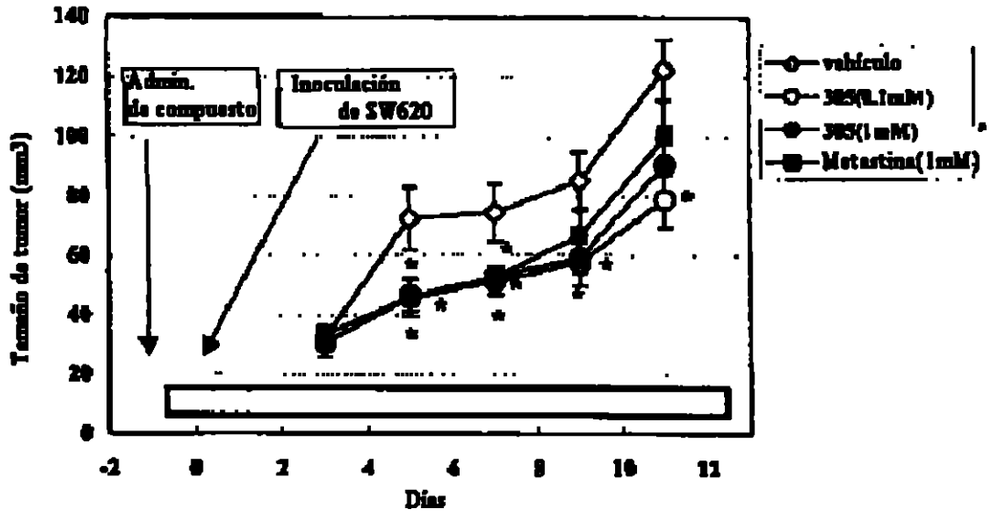

140
120
100
80
60
40
20
0
Tamaño de tumor (mm3)
Admin. de compuesto
Inoculación de SW620
-2
0
2
4
6
8
10
11
Días
vehículo
385(0.1mM)
385(1mM)
Metastina(1mM)
*

FIG 4

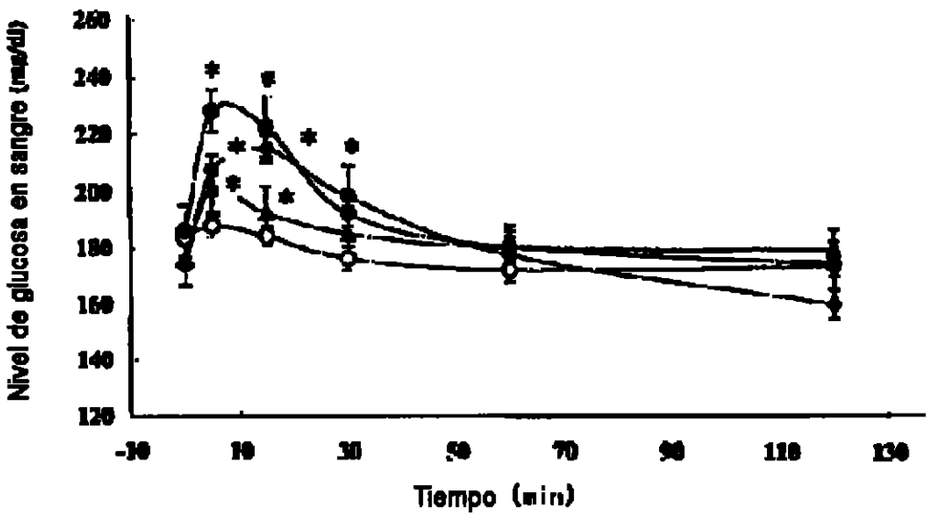

Nivel de glucosa en sangre (mg/dl)
260
240
220
200
180
160
140
120
-10
10
30
50
70
90
110
130
Tiempo (min)

FIG 5

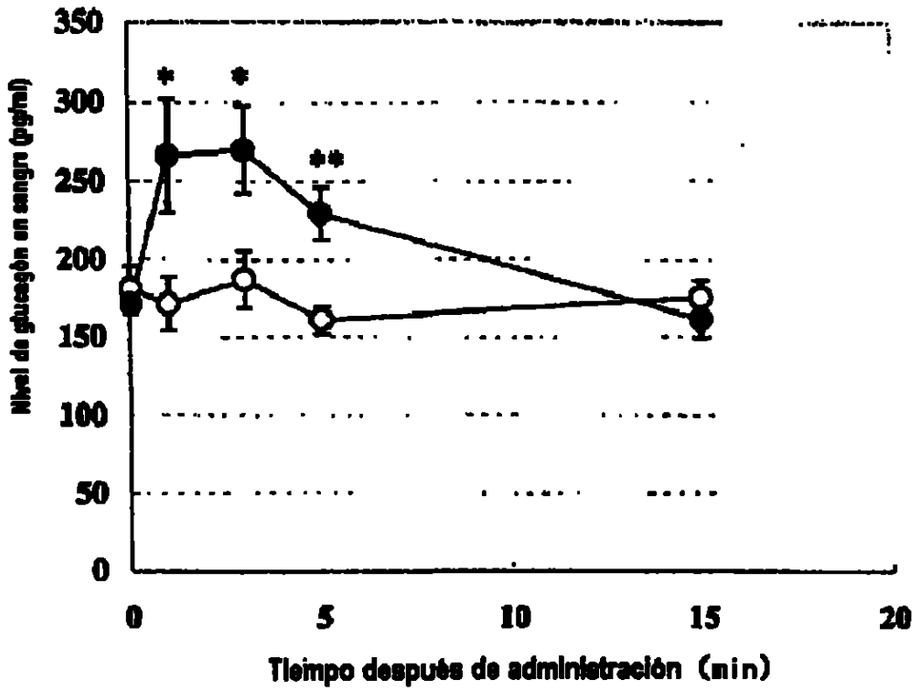

350
300
250
200
150
100
50
0
Nivel de glucagón en sangre (pg/ml)
*
*
**
0
5
10
15
20
Tiempo después de administración (min)

FIG 6

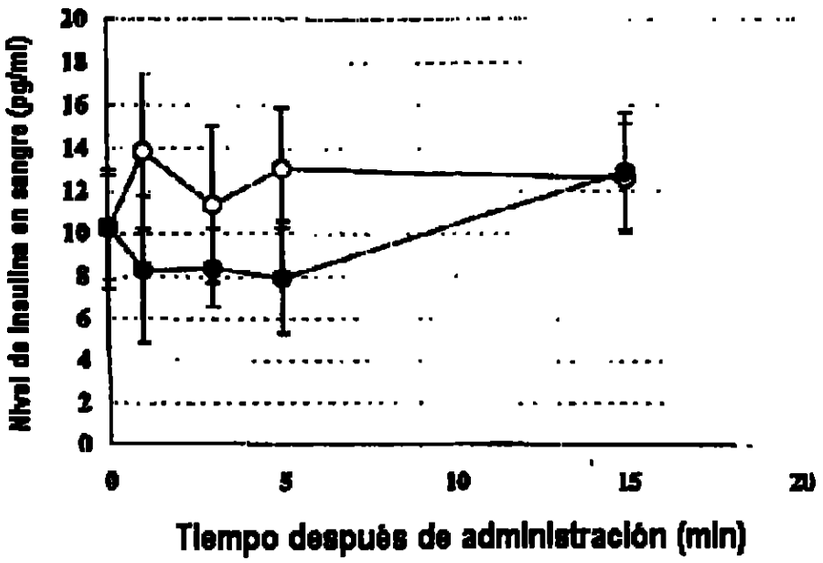

Nivel de insulina en sangre (pg/ml)
20
18
16
14
12
10
8
6
4
2
0
0
5
10
15
20
Tiempo después de administración (min)

FIG 7

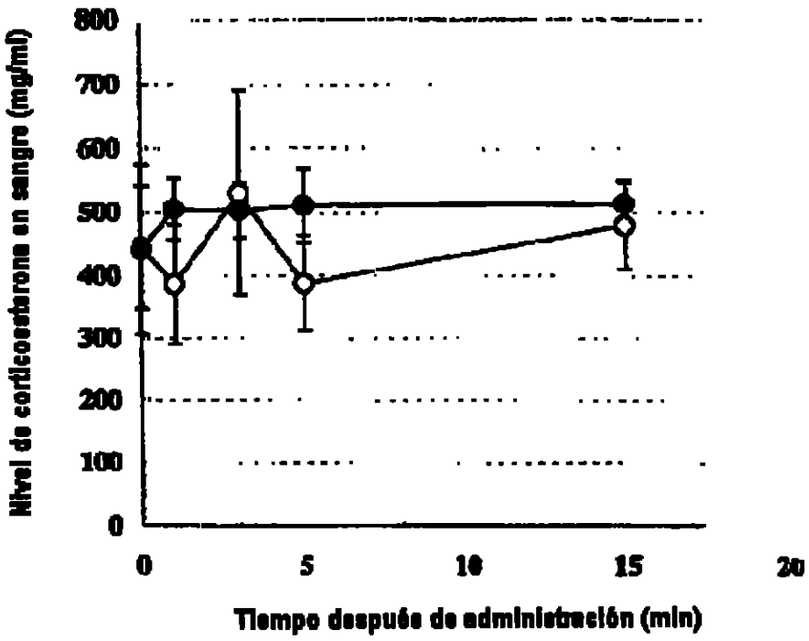

800
700
600
500
400
300
200
100
0
Nivel de corticosterona en sangre (mg/ml)
0
5
10
15
20
Tiempo después de administración (min)

FIG 8

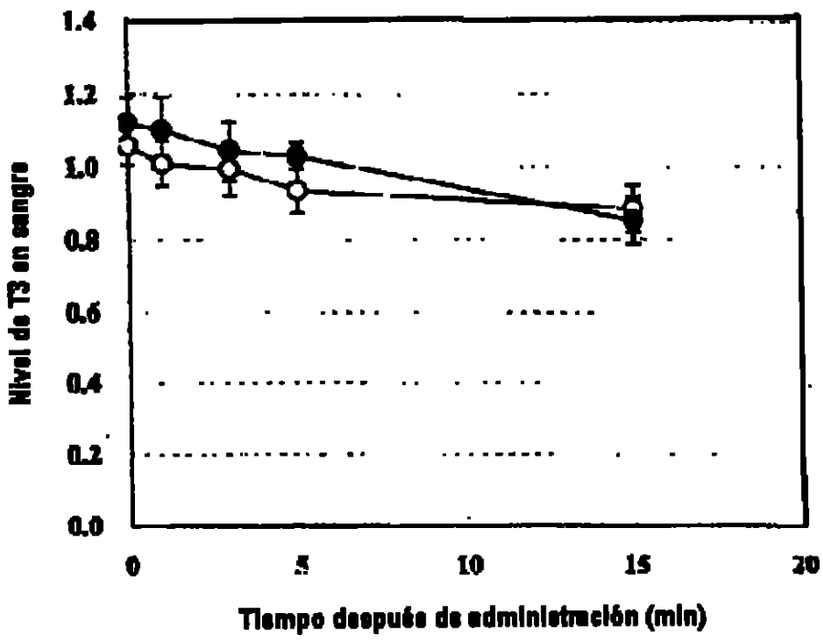

1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Nivel de T3 en sangre
0
5
10
15
20
Tiempo después de administración (min)

FIG 9

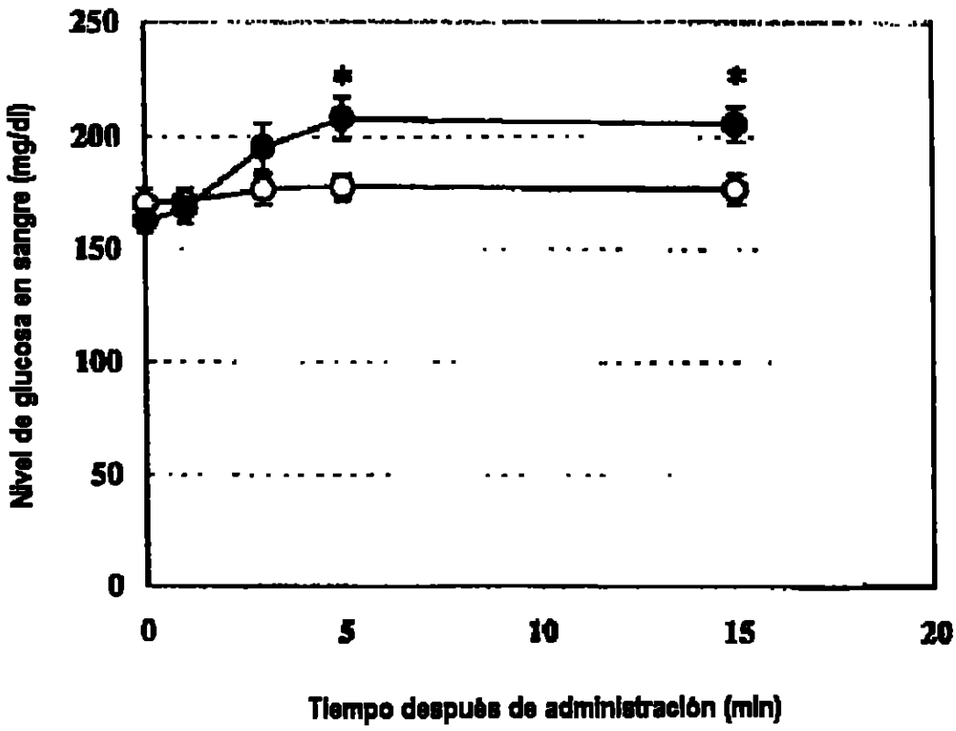

250
200
150
100
50
0
0
5
10
15
20
*
*
Nivel de glucosa en sangre (mg/dl)
Tiempo después de administración (min)

FIG 10

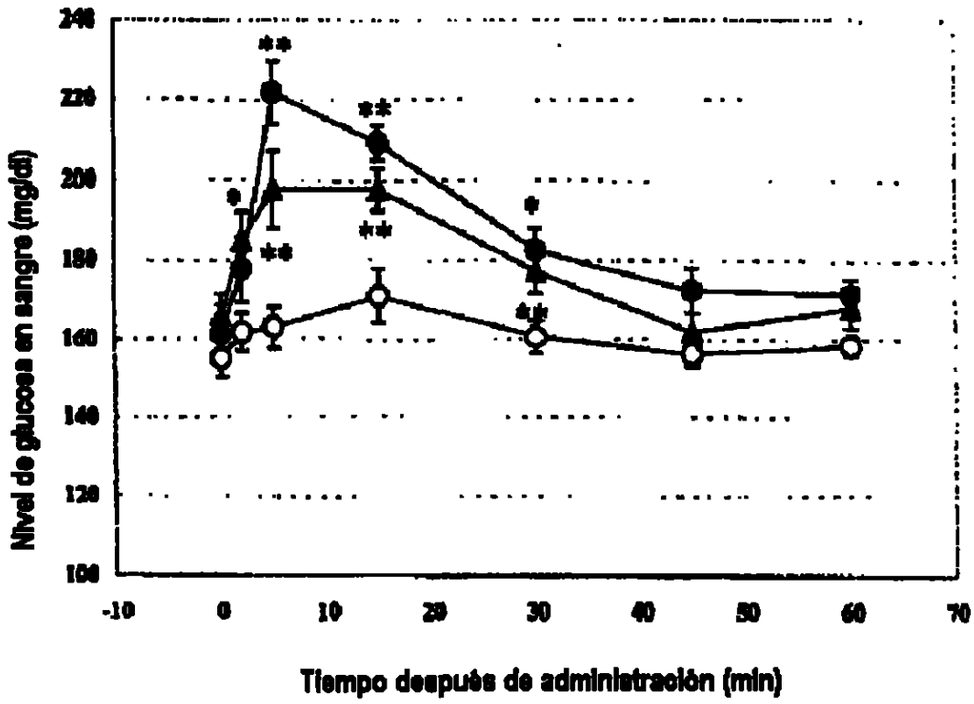

240
220
200
180
160
140
120
100
Nivel de glucosa en sangre (mg/dl)
-10
0
10
20
30
40
50
60
70
Tiempo después de administración (min)

FIG 11

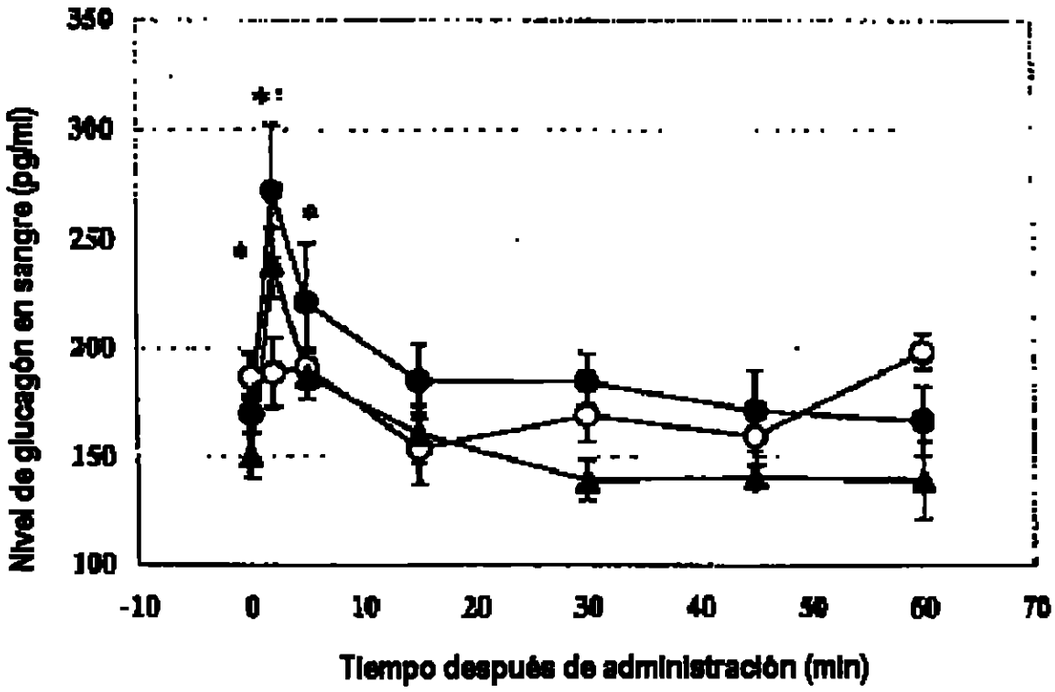

350
300
250
200
150
100
Nivel de glucagón en sangre (pg/ml)
-10
0
10
20
30
40
50
60
70
Tiempo después de administración (min)

FIG 12

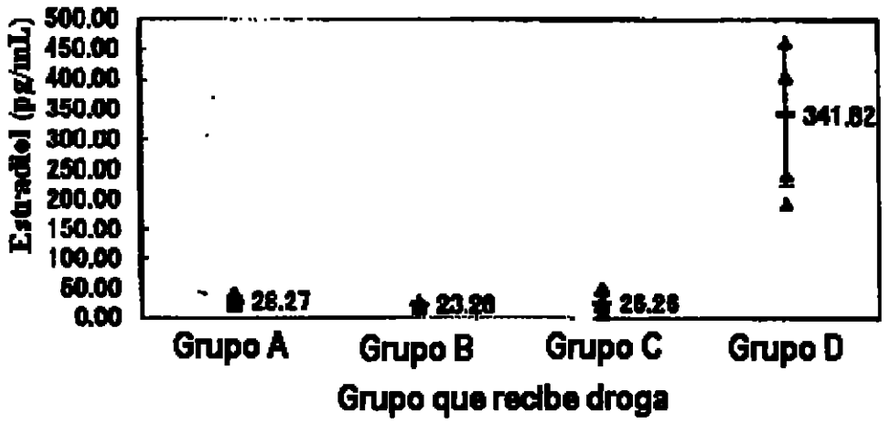

Estradiol (pg/mL)
500.00
450.00
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
26.27
23.26
26.26
341.82
Grupo A
Grupo B
Grupo C
Grupo D
Grupo que recibe droga

FIG 13

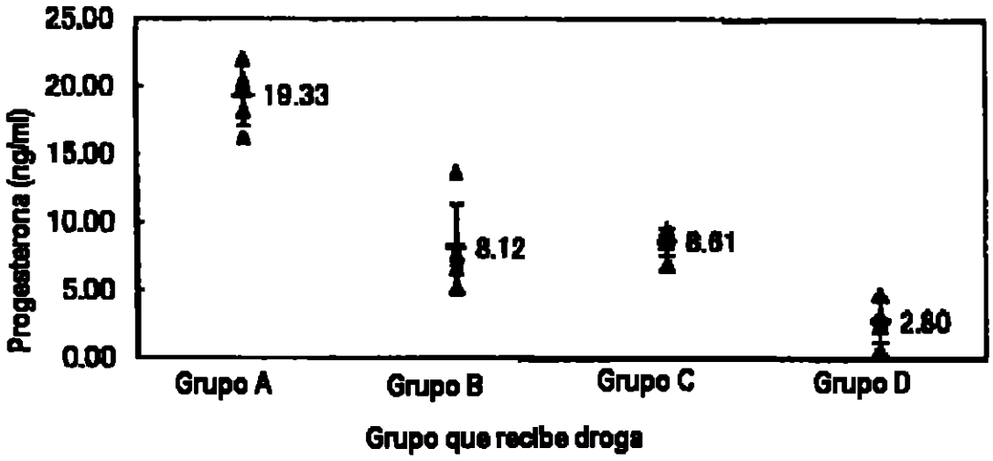

25.00
20.00
15.00
10.00
5.00
0.00
Progesterona (ng/ml)
19.33
8.12
8.61
2.80
Grupo A
Grupo B
Grupo C
Grupo D
Grupo que recibe droga

FIG 14

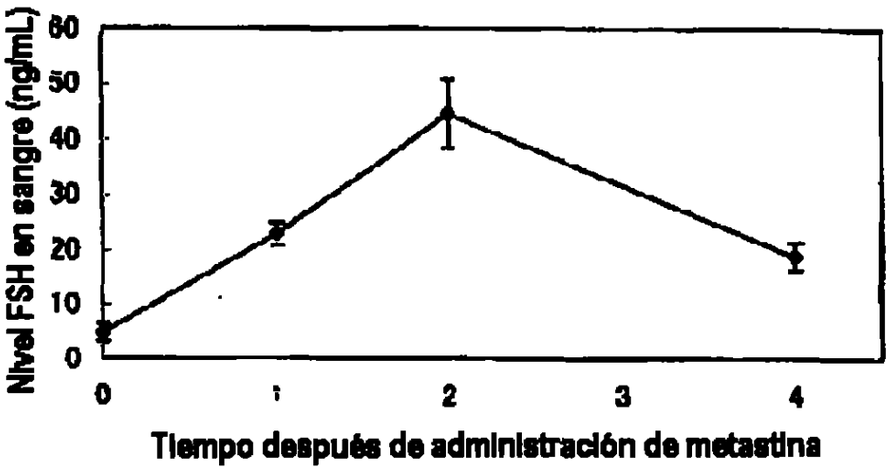

Nivel FSH en sangre (ng/mL)
60
50
40
30
20
10
0
0
1
2
3
4
Tiempo después de administración de metastina

FIG 15

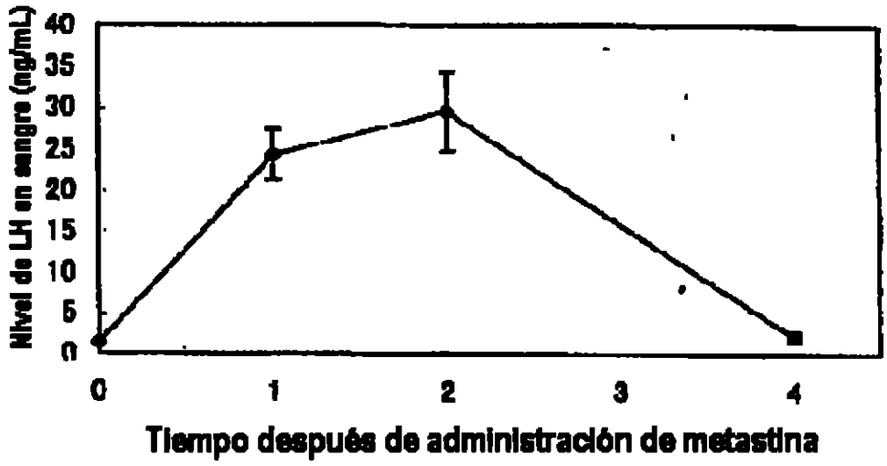

Nivel de LH en sangre (ng/mL)
40
35
30
25
20
15
10
5
0
0
1
2
3
4
Tiempo después de administración de metastina

FIG 16

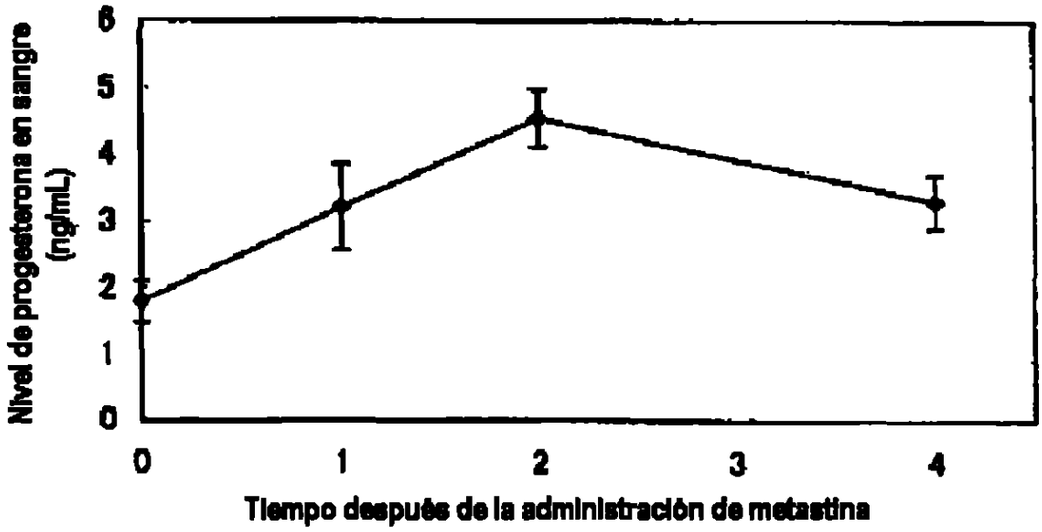

Nivel de progesterona en sangre (ng/mL)
6
5
4
3
2
1
0
0
1
2
3
4
Tiempo después de la administración de metastina

FIG 17

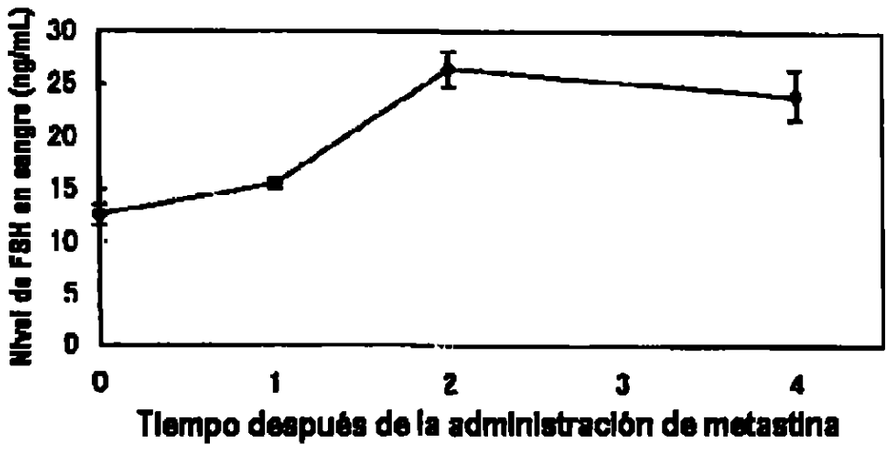

Nivel de FSH en sangre (ng/mL)
30
25
20
15
10
5
0
0
1
2
3
4
Tiempo después de la administración de metastina

FIG 18

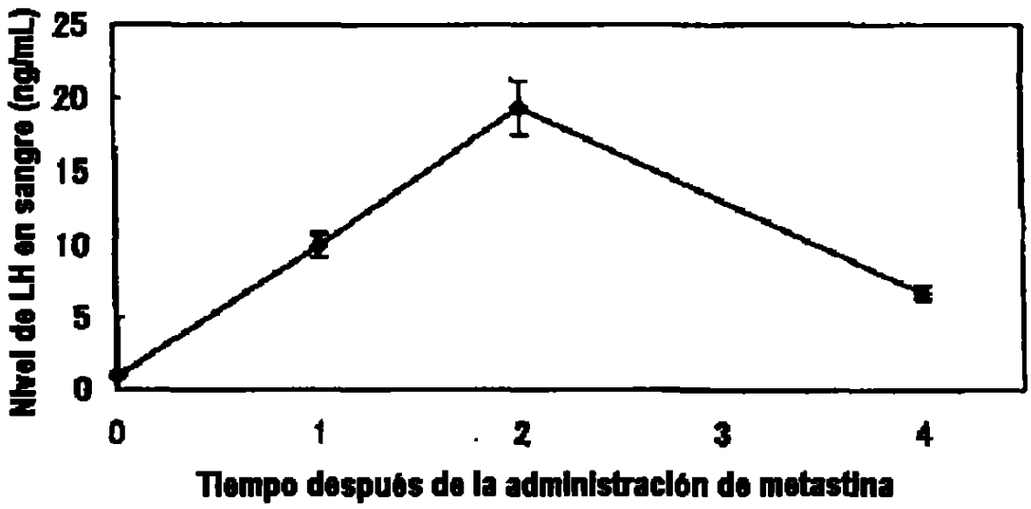

Nivel de LH en sangre (ng/mL)
25
20
15
10
5
0
0
1
2
3
4
Tiempo después de la administración de metastina

FIG 19

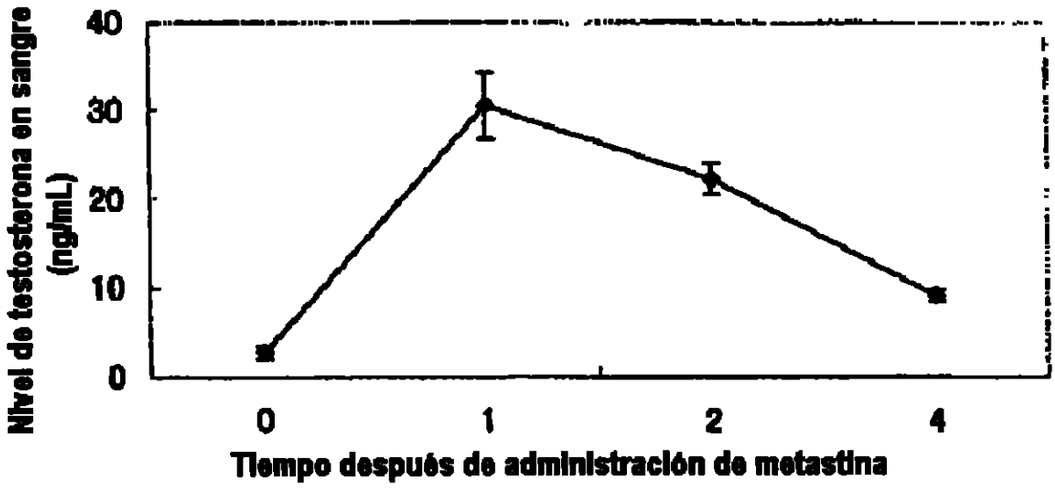

Nivel de testosterona en sangre (ng/mL)
40
30
20
10
0
0
1
2
4
Tiempo después de administración de metastina

FIG 20

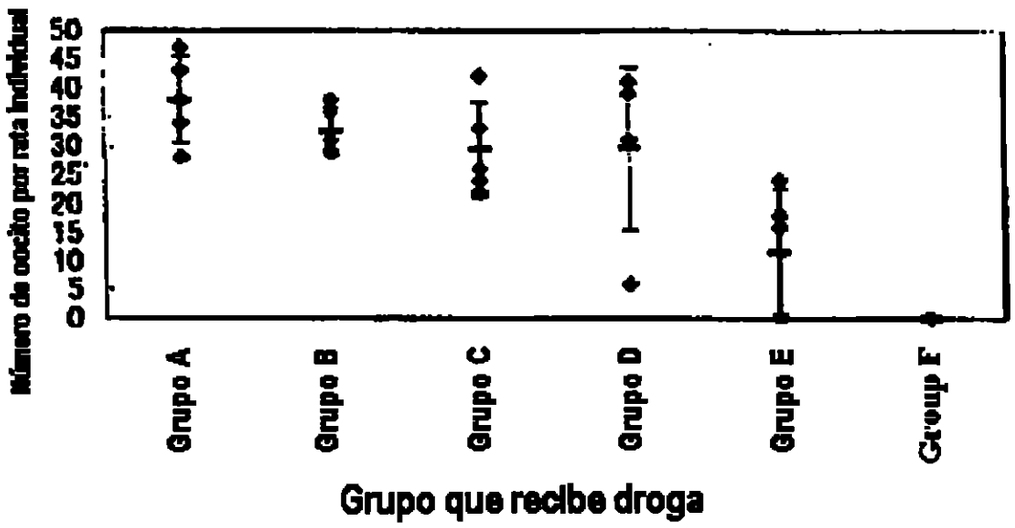

Número de cocáin por rata individual
0
5
10
15
20
25
30
35
40
45
50
Grupo A
Grupo B
Grupo C
Grupo D
Grupo E
Group F
Grupo que recibe droga

FIG 21

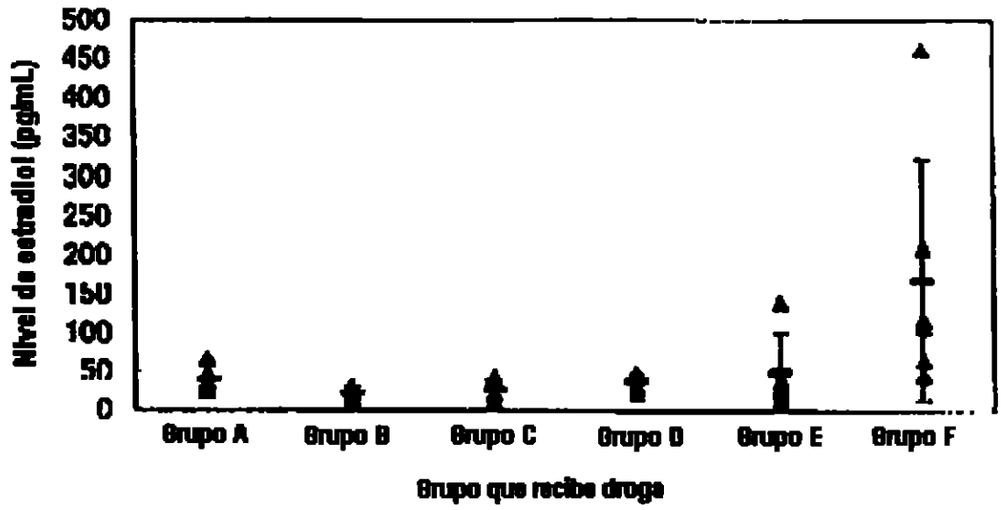
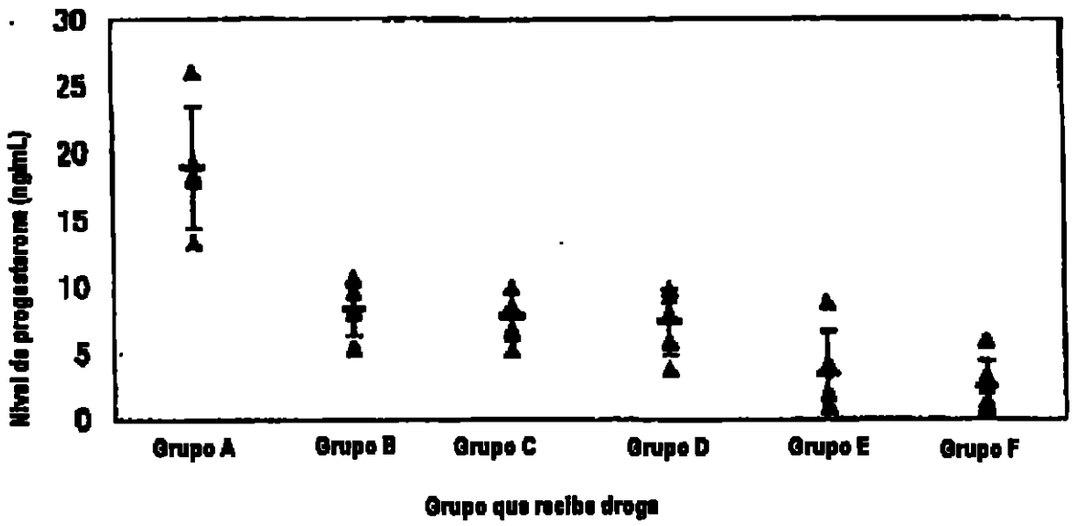

Nivel de estradiol (pg/mL)
500
450
400
350
300
250
200
150
100
50
0
Grupo A
Grupo B
Grupo C
Grupo D
Grupo E
Grupo F
Grupo que recibe droga

FIG 22


30
25
20
15
10
5
0
Nível de progesterona (ng/mL)
Grupo A
Grupo B
Grupo C
Grupo D
Grupo E
Grupo F
Grupo que recibe droga

/

LISTADO DE SECUENCIA

<110> Takeda Pharmaceutical Company, Ltd.

<120> Derivados de Metastina y su utilización

<130> PCT05-0008

<150> JP 2004-187671
<151> 2004-06-25

<160> 22

<210> 1
<211> 54
<212> PRT
<213> Homo sapiens

<400> 1
Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln
 1   5   10   15
Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly
            20   25   30
Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn
        35   40   45
Ser Phe Gly Leu Arg Phe
    50

<210> 2
<211> 162
<212> ADN
<213> Homo sapiens

<400> 2
ggtacttctc tgtctccgcc gccggaatct tctggttctc gtcagcagcc gggtctgtct 60
gctccgcact ctcgtcagat cccggctccg cagggtgctg ttctggttca gcgtgaaaaa 120
gacctgccga actacaactg gaactctttc ggtctgcgtt tc   162

/

<210> 3

<211> 152

<212> PRT

<213> Mus musculus

<400> 3

Met Tyr Leu Arg Phe Gly Val Asp Val Cys Ser Leu Ser Pro Trp Lys
5 10 15

Glu Thr Val Asp Leu Pro Leu Pro Pro Arg Met Ile Ser Met Ala Ser
20 25 30

Trp Gln Leu Leu Leu Leu Leu Cys Val Ala Thr Tyr Gly Glu Pro Leu
35 40 45

Ala Lys Val Ala Pro Gly Ser Thr Gly Gln Gln Ser Gly Pro Gln Glu
50 55 60

Leu Val Asn Ala Trp Glu Lys Glu Ser Arg Tyr Ala Glu Ser Lys Pro
65 70 75 80

Gly Ser Ala Gly Leu Arg Ala Arg Arg Ser Ser Pro Cys Pro Pro Val
85 90 95

Glu Gly Pro Ala Gly Arg Gln Arg Pro Leu Cys Ala Ser Arg Ser Arg
100 105 110

Leu Ile Pro Ala Pro Arg Gly Ala Val Leu Val Gln Arg Glu Lys Asp
115 120 125

Leu Ser Thr Tyr Asn Trp Asn Ser Phe Gly Leu Arg Tyr Gly Arg Arg
130 135 140

Gln Ala Ala Arg Ala Ala Arg Gly
145 150

<210> 4

<211> 456

<212> ADN

<213> Mus musculus

<400> 4

atgtatctga gatttggcgt tgatgtctgc agcctgagtc cctggaagga gactgtagac 60

ctgcccttc ctcccagaat gatctcaatg gcttcttggc agctgctgct tctcctctgt 120

gtcgccacct atggggagcc gctggcaaaa gtgaagcctg gatccacagg ccagcagtcc 180

/

ggaccccagg aactcgttaa tgcctgggaa aaggaatcgc ggtatgcaga gagcaagcct 240
gggtctgcag ggctgcgcgc tcgtaggtcg tcgccatgcc cgccggttga gggccccgcg 300
gggcgccagc ggcccctgtg tgcctcccgc agtcgcctga tccctgcgcc ccgcggagcg 360
gtgctggtgc agcgggagaa ggacctgtcc acctacaact ggaactcctt cggcctgcgc 420
tacggcagga ggcaggcggc gcgggcagca cggggc 456

<210> 5
<211> 156
<212> PRT
<213> Mus musculus

<400> 5

Met	Tyr	Leu	Arg	Phe	Gly	Val	Asp	Val	Cys	Ser	Leu	Ser	Pro	Trp	Lys
			5					10					15		
Glu	Thr	Val	Asp	Leu	Pro	Leu	Pro	Pro	Arg	Met	Ile	Ser	Met	Ala	Ser
		20					25					30			
Trp	Gln	Leu	Leu	Leu	Leu	Leu	Cys	Val	Ala	Thr	Tyr	Gly	Glu	Pro	Leu
	35					40					45				
Ala	Lys	Val	Ala	Pro	Leu	Val	Lys	Pro	Gly	Ser	Thr	Gly	Gln	Gln	Ser
50					55					60					
Gly	Pro	Gln	Glu	Leu	Val	Asn	Ala	Trp	Glu	Lys	Glu	Ser	Arg	Tyr	Ala
65				70					75						80
Glu	Ser	Lys	Pro	Gly	Ser	Ala	Gly	Leu	Arg	Ala	Arg	Arg	Ser	Ser	Pro
			85					90					95		
Cys	Pro	Pro	Val	Glu	Gly	Pro	Ala	Gly	Arg	Gln	Arg	Pro	Leu	Cys	Ala
		100					105					110			
Ser	Arg	Ser	Arg	Leu	Ile	Pro	Ala	Pro	Arg	Gly	Ala	Val	Leu	Val	Gln
	115					120					125				
Arg	Glu	Lys	Asp	Leu	Ser	Thr	Tyr	Asn	Trp	Asn	Ser	Phe	Gly	Leu	Arg
130					135					140					
Tyr	Gly	Arg	Arg	Gln	Ala	Ala	Arg	Ala	Ala	Arg	Gly				
145				150					155						

<210> 6
<211> 468
<212> ADN
<213> Mus musculus

/

<400> 6

atgtatctga gatttggcgt tgatgtctgc agcctgagtc cctggaagga gactgtagac 60
ctgcccctte ctcccagaat gatctcaatg gcttcttggc agctgctgct tctcctctgt 120
gtcgccacct atggggagcc gctggcaaaa gtggcacctt tggtgaagcc tggatccaca 180
ggccagcagt ccggacccca ggaactcgtt aatgcctggg aaaaggaatc gcggtatgca 240
gagagcaagc ctgggtctgc agggctgcgc gctcgtaggt cgtcgccatg cccgccggtt 300
gagggccccg cggggcgcca gcggcccctg tgtgcctccc gcagtcgcct gatccctgcg 360
ccccgcggag cggtgctggt gcagcgggag aaggacctgt ccacctacaa ctggaactcc 420
ttcggcctgc gctacggcag gaggcaggcg gcgcgggcag cacggggc 468

<210> 7
<211> 130
<212> PRT
<213> Rattus sp.

<400> 7

Met Thr Ser Leu Ala Ser Trp Gln Leu Leu Leu Leu Cys Val Ala
5 10 15
Ser Phe Gly Glu Pro Leu Ala Lys Met Ala Pro Val Val Asn Pro Glu
20 25 30
Pro Thr Gly Gln Gln Ser Gly Pro Gln Glu Leu Val Asn Ala Trp Gln
35 40 45
Lys Gly Pro Arg Tyr Ala Glu Ser Lys Pro Gly Ala Ala Gly Leu Arg
50 55 60
Ala Arg Arg Thr Ser Pro Cys Pro Pro Val Glu Asn Pro Thr Gly His
65 70 75 80
Gln Arg Pro Pro Cys Ala Thr Arg Ser Arg Leu Ile Pro Ala Pro Arg
85 90 95
Gly Ser Val Leu Val Gln Arg Glu Lys Asp Met Ser Ala Tyr Asn Trp
100 105 110
Asn Ser Phe Gly Leu Arg Tyr Gly Arg Arg Gln Val Ala Arg Ala Ala
115 120 125
Arg Gly
130

<210> 8

/

<211> 390

<212> ADN

<213> Rattus sp.

<400> 8

atgacctcgc tggcttcttg gcagctgctg cttctcctct gtgtggcctc ttttggggag 60
ccactggcaa aaatggcacc tgtggtgaac cctgaaccca caggccaaca gtccggaccc 120
caggaactcg ttaatgcctg gcaaaagggc ccgcggtatg cagagagcaa gcctggggct 180
gcaggactgc gcgctcgccg aacatcgcca tgcccgccgg tggagaaccc cacggggcac 240
cagcggcccc cgtgtgccac ccgcagtcgc ctgatccctg cgccccgcgg atcggtgctg 300
gtgcagcgcg agaaggacat gtcagcctac aactggaact cctttggcct gcgctacggc 360
aggaggcagg tggcgcgggc ggcacggggc 390

<210> 9

<211> 398

<212> PRT

<213> Homo sapiens

<400> 9

Met His Thr Val Ala Thr Ser Gly Pro Asn Ala Ser Trp Gly Ala Pro
5 10 15
Ala Asn Ala Ser Gly Cys Pro Gly Cys Gly Ala Asn Ala Ser Asp Gly
20 25 30
Pro Val Pro Ser Pro Arg Ala Val Asp Ala Trp Leu Val Pro Leu Phe
35 40 45
Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
50 55 60
Tyr Val Ile Cys Arg His Lys Pro Met Arg Thr Val Thr Asn Phe Tyr
65 70 75 80
Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val
85 90 95
Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Gly Trp Val Leu Gly Asp
100 105 110
Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala
115 120 125
Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr
130 135 140

/

Val Phe Pro Leu Arg Ala Leu His Arg Arg Thr Pro Arg Leu Ala Leu
145 150 155 160
Ala Val Ser Leu Ser Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro
165 170 175
Val Leu Ala Leu His Arg Leu Ser Pro Gly Pro Arg Ala Tyr Cys Ser
180 185 190
Glu Ala Phe Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn
195 200 205
Leu Leu Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr
210 215 220
Ala Ala Met Leu Arg His Leu Gly Arg Val Ala Val Arg Pro Ala Pro
225 230 235 240
Ala Asp Ser Ala Leu Gln Gly Gln Val Leu Ala Glu Arg Ala Gly Ala
245 250 255
Val Arg Ala Lys Val Ser Arg Leu Val Ala Ala Val Val Leu Leu Phe
260 265 270
Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu Gln Ala Leu
275 280 285
Gly Pro Ala Gly Ser Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Leu
290 295 300
Lys Thr Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro
305 310 315 320
Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Arg Arg
325 330 335
Val Cys Pro Cys Ala Pro Arg Arg Pro Arg Arg Pro Arg Arg Pro Gly
340 345 350
Pro Ser Asp Pro Ala Ala Pro His Ala Glu Leu His Arg Leu Gly Ser
355 360 365
His Pro Ala Pro Ala Arg Ala Gln Lys Pro Gly Ser Ser Gly Leu Ala
370 375 380
Ala Arg Gly Leu Cys Val Leu Gly Glu Asp Asn Ala Pro Leu
385 390 395

<210> 10
<211> 1194
<212> ADN
<213> Homo sapiens

/

<400> 10

atgcacaccg tggctacgtc cggacccaac gcgtcctggg gggcaccggc caacgcctcc 60
ggctgcccgg gctgtggcgc caacgcctcg gacggcccag tcccttcgcc gcgggccgtg 120
gacgcctggc tcgtgccgct cttcttcgcg gcgctgatgc tgctgggcct ggtggggaac 180
tcgctggtca tctacgtcat ctgccgccac aagccgatgc ggaccgtgac caacttctac 240
atcgccaacc tggcggccac ggacgtgacc ttcctcctgt gctgcgtccc cttcacggcc 300
ctgctgtacc cgctgcccgg ctgggtgctg ggcgacttca tgtgcaagtt cgtcaactac 360
atccagcagg tctcggtgca ggccacgtgt gccactctga ccgccatgag tgtggaccgc 420
tggtacgtga cggtgttccc gttgcgcgcc ctgcaccgcc gcacgccccg cctggcgctg 480
gctgtcagcc tcagcatctg ggtaggctct gcggcggtgt ctgcgccggt gctcgccctg 540
caccgcctgt cacccgggcc gcgcgcctac tgcagtgagg ccttccccag ccgcgccctg 600
gagcgcgcct tcgcactgta caacctgctg gcgctgtacc tgctgccgct gctcgccacc 660
tgcgcctgct atgcggccat gctgcgccac ctgggccggg tcgccgtgcg ccccgcgccc 720
gccgatagcg ccctgcaggg gcaggtgctg gcagagcgcg caggcgccgt gcgggccaag 780
gtctcgcggc tggtggcggc cgtggtcctg ctcttcgccg cctgctgggg ccccatccag 840
ctgttcctgg tgctgcaggc gctgggcccc gcgggctcct ggcacccacg cagctacgcc 900
gcctacgcgc ttaagacctg ggctcactgc atgtcctaca gcaactccgc gctgaacccg 960
ctgctctacg ccttcctggg ctcgcacttc cgacaggcct tccgccgcgt ctgcccctgc 1020
gcgccgcgcc gccccgccg ccccgccggg cccggaccct cggaccccgc agccccacac 1080
gcggagctgc accgcctggg gtcccacccg gccccgccca gggcgcagaa gccagggagc 1140
agtgggctgg ccgcgcgcgg gctgtgcgtc ctgggggagg acaacgcccc tctc 1194

<210> 11
<211> 396
<212> PRT
<213> Rattus sp.

<400> 11

Met Ala Ala Glu Ala Thr Leu Gly Pro Asn Val Ser Trp Trp Ala Pro
1 5 10 15
Ser Asn Ala Ser Gly Cys Pro Gly Cys Gly Val Asn Ala Ser Asp Gly
20 25 30
Pro Gly Ser Ala Pro Arg Pro Leu Asp Ala Trp Leu Val Pro Leu Phe
35 40 45
Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
50 55 60

Phe Val Ile Cys Arg His Lys His Met Gln Thr Val Thr Asn Phe Tyr
65 70 75 80
Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val
85 90 95
Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Thr Trp Val Leu Gly Asp
100 105 110
Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala
115 120 125
Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr
130 135 140
Val Phe Pro Leu Arg Ala Leu His Arg Arg Thr Pro Arg Leu Ala Leu
145 150 155 160
Thr Val Ser Leu Ser Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro
165 170 175
Val Leu Ala Leu His Arg Leu Ser Pro Gly Pro His Thr Tyr Cys Ser
180 185 190
Glu Ala Phe Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn
195 200 205
Leu Leu Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr
210 215 220
Gly Ala Met Leu Arg His Leu Gly Arg Ala Ala Val Arg Pro Ala Pro
225 230 235 240
Thr Asp Gly Ala Leu Gln Gly Gln Leu Leu Ala Gln Arg Ala Gly Ala
245 250 255
Val Arg Thr Lys Val Ser Arg Leu Val Ala Ala Val Val Leu Leu Phe
260 265 270
Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu Gln Ala Leu
275 280 285
Gly Pro Ser Gly Ala Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Leu
290 295 300
Lys Ile Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro
305 310 315 320
Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Cys Arg
325 330 335
Val Cys Pro Cys Gly Pro Gln Arg Gln Arg Arg Pro His Ala Ser Ala
340 345 350
His Ser Asp Arg Ala Ala Pro His Ser Val Pro His Ser Arg Ala Ala

703

703

355 360 365

His Pro Val Arg Val Arg Thr Pro Glu Pro Gly Asn Pro Val Val Arg

370 375 380

Ser Pro Ser Val Gln Asp Glu His Thr Ala Pro Leu

385 390 395

<210> 12

<211> 1188

<212> ADN

<213> Rattus sp.

<400> 12

atggccgcag aggcgacgtt gggtccgaac gtgagctggt gggctccgtc caacgcttcg 60

ggatgcccgg gctgcggtgt caatgcctcg gatggcccag gctccgcgcc aaggcccctg 120

gatgcctggc tggtgccccc gtttttcgct gccctaatgt tgctggggct agtcgggaac 180

tcactggtca tcttcgttat ctgccgccac aagcacatgc agaccgtcac caatttctac 240

atcgctaacc tggcggccac agatgtcact ttccttctgt gctgcgtacc cttcaccgcg 300

ctcctctatc cgctgcccac ctgggtgctg ggagacttca tgtgcaaatt cgtcaactac 360

atccagcagg tctcggtgca agccacatgt gccactttga cagccatgag tgtggaccgc 420

tggtacgtga ctgtgttccc gctgcgtgca cttcaccgcc gcactccgcg cctggccctg 480

actgtcagcc ttagcatctg ggtgggttcc gcagctgttt ccgccccggt gctggctctg 540

caccgcctgt cgcccgggcc tcacacctac tgcagtgagg cgtttcccag ccgtgccctg 600

gagcgcgctt tcgcgctcta caacctgctg gccctatacc tgctgccgct gctcgccacc 660

tgcgcctgct acggtgccat gctgcgccac ctgggccgcg ccgctgtacg ccccgcaccc 720

actgatggcg ccctgcaggg gcagctgcta gcacagcgcg ctggagcagt gcgcaccaag 780

gtctcccggc tggtggccgc tgtcgtcctg ctcttcgccg cctgctgggg cccgatccag 840

ctgttcctgg tgcttcaagc cctgggcccc tcgggggcct ggcaccctcg aagctatgcc 900

gcctacgcgc tcaagatctg ggctcactgc atgtcctaca gcaattctgc gctcaacccg 960

ctgctctatg ccttcctggg ttcccacttc agacaggcct tctgccgcgt gtgcccctgc 1020

ggcccgcaac gccagcgtcg gccccacgcg tcagcgcact cggaccgagc cgcaccccat 1080

agtgtgccgc acagccgggc tgcgcaccct gtccgggtca ggaccccccga gcctgggaac 1140

cctgtggtgc gctcgccctc tgttcaggat gaacacactg ccccactc 1188

<210> 13

<211> 396

<212> PRT

<213> Mus musculus

/

<400> 13

Met Ala Thr Glu Ala Thr Leu Ala Pro Asn Val Thr Trp Trp Ala Pro
1 5 10 15
Ser Asn Ala Ser Gly Cys Pro Gly Cys Gly Val Asn Ala Ser Asp Asp
20 25 30
Pro Gly Ser Ala Pro Arg Pro Leu Asp Ala Trp Leu Val Pro Leu Phe
35 40 45
Phe Ala Thr Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
50 55 60
Tyr Val Ile Cys Arg His Lys His Met Gln Thr Val Thr Asn Phe Tyr
65 70 75 80
Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val
85 90 95
Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Ala Trp Val Leu Gly Asp
100 105 110
Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala
115 120 / 125
Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr
130 135 140
Val Phe Pro Leu Arg Ala Leu His Arg Arg Thr Pro Arg Leu Ala Leu
145 150 155 160
Ala Val Ser Leu Ser Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro
165 170 175
Val Leu Ala Leu His Arg Leu Ser Pro Gly Pro Arg Thr Tyr Cys Ser
180 185 190
Glu Ala Phe Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn
195 200 205
Leu Leu Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr
210 215 220
Gly Ala Met Leu Arg His Leu Gly Arg Ala Ala Val Arg Pro Ala Pro
225 230 235 240
Thr Asp Gly Ala Leu Gln Gly Gln Leu Leu Ala Gln Arg Ala Gly Ala
245 250 255
Val Arg Thr Lys Val Ser Arg Leu Val Ala Ala Val Val Leu Leu Phe
260 265 270
Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu Gln Ala Leu

/

275 280 285

Gly Pro Ser Gly Ala Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Val
290 295 300

Lys Ile Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro
305 310 315 320

Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Cys Arg
325 330 335

Val Cys Pro Cys Cys Arg Gln Arg Gln Arg Arg Pro His Thr Ser Ala
340 345 350

His Ser Asp Arg Ala Ala Thr His Thr Val Pro His Ser Arg Ala Ala
355 360 365

His Pro Val Arg Ile Arg Ser Pro Glu Pro Gly Asn Pro Val Val Arg
370 375 380

Ser Pro Cys Ala Gln Ser Glu Arg Thr Ala Ser Leu
385 390 395

<210> 14
<211> 1188
<212> ADN
<213> Mus musculus

<400> 14

atggccaccg aggcgacatt ggctcccaat gtgacctggt gggctccgtc caacgcttca 60
ggatgcccag gctgcggtgt caacgcctcg gatgacccag gctctgcgcc aaggcccctg 120
gatgcctggc tggttccect gtttttcgct acactcatgt tgcttgggct ggtcggaaac 180
tcattggtca tctacgttat ctgccgccac aagcacatgc agacagttac caacttctac 240
atcgctaacc tggctgccac agacgtcact ttcctactgt gctgcgtgcc cttcaccgca 300
ctcctctacc cgctgcccgc ctgggtgctg ggagacttca tgtgcaaatt cgtcaactac 360
atccagcagg tctcggtgca agccacatgt gccactctga cggccatgag tgtggaccgc 420
tggtatgtga ctgtgttccc gctgcgtgca cttcaccgcc gcactccgcg cctggccctg 480
gctgtcagcc tcagcatctg ggtggggtca gcagctgtgt ccgccccggt gctggccctg 540
caccgcctgt cgccagggcc tcgcacctac tgcagcgagg cgtttcccag ccgcgccctg 600
gagcgcgcct tcgcgctcta caacctgctg gctctatatc tgctgccgct gctcgccacc 660
tgcgcctgct acggcgccat gctgcgccac ctgggccgtg cggctgtacg ccccgcaccc 720
actgacggcg ccctgcaggg acagctgcta gcacagcgcg ccggagcagt gcgcaccaag 780
gtctcccggc tggtggccgc tgtcgtcctg ctcttcgccg cctgctgggg cccgatccag 840
ctgttcctgg tgcttcaagc cctgggcccc tcgggggcct ggcaccctcg aagctatgcc 900

/

gcctacgcgg tcaagatctg ggctcactgc atgtcctaca gcaactcggc gctcaatccg 960
ctgctctatg ccttcctggg ttcacacttc agacaggcct tctgccgcgt gtgcccctgc 1020
tgccggcaac gccagcgccg gccccacacg tcagcgcact cggaccgagc tgcaactcac 1080
actgtgccgc acagccgtgc tgcgcaccct gtgcggatca ggagcccgga gcctgggaac 1140
cctgtggtgc gctcgccctg cgctcagagt gaacgcactg cctcactc 1188

<210> 15
<211> 15
<212> PRT
<213> Artificial

<220>
<223> el C terminal del polipéptido es amida de forma (-CONH2)

<400> 15
Lys Asp Leu Pro Asn Tyr Asn Trp Asn Ser Phe Gly Leu Arg Phe
1 5 10 15

<210> 16
<211> 10
<212> PRT
<213> Artificial

<220>
<223> el C terminal del polipéptido es amida de forma (-CONH2)

<400> 16
Tyr Asn Trp Asn Ser Phe Gly Leu Arg Phe
1 5 10

<210> 17
<211> 9
<212> PRT
<213> Artificial

<220>
<223> el C terminal del polipéptido es amida de forma (-CONH2)

/

<400> 17
Asn Trp Asn Ser Phe Gly Leu Arg Phe
1 5 9

<210> 18
<211> 8
<212> PRT
<213> Artificial

<220>
<223> el C terminal del polipéptido es amida de forma (-CONH2)

<400> 18
Trp Asn Ser Phe Gly Leu Arg Phe
1 5 8

<210> 19
<211> 45
<212> ADN
<213> Homo sapiens

<400> 19
aaggacctgc cgaactacaa ctggaactcc ttcggcctgc gcttc 45

<210> 20
<211> 30
<212> ADN
<213> Homo sapiens

<400> 20
tacaactgga actccttcgg cctgcgcttc 30

<210> 21
<211> 27
<212> ADN
<213> Homo sapiens

<400> 21

aactggaact ccttcggcct gcgcttc 27

<210> 22
<211> 24
<212> ADN
<213> Homo sapiens

<400> 22
tggaactcct tcggcctgcg cttc 24

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) 2004-187671 (32) 25/06/04 (33) JP
2004-363311 15/12/04 JP

(51) Int Cl: C07K 14/47

(71)Solicitante(s) TAKEDA PHARMACEUTICAL COMPANY LIMITED

(72) Inventor(es) CHIEKO KITADA
Y OTROS

(74) Apoderado: EMILIO FERRERO

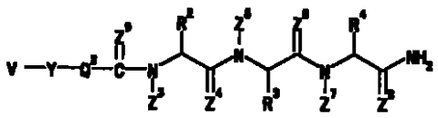
(85) Fecha límite inicio fase nacional: 25/01/2007
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 23/06/2005
No. de solicitud PCT/JP2005/012021

(87) Publicación internacional
Fecha: 05/01/2006
N° publicación: WO 2006/001499 A2

(54) *Título:* **DERIVADOS DE METASTINA Y UTILIZACIÓN DE LOS MISMOS**

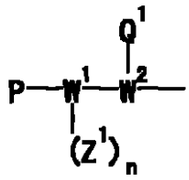
Reivindicación(es):

1. Un derivado de metastina (II) caracterizado por que está representado por la fórmula:

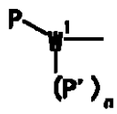


[en donde;

V representa un grupo representado por la fórmula:



o un grupo representado por la fórmula:



n representa 0 ó 1;

W^1 representa N, CH ó O (con la condición que cuando W^1 es N ó CH, n representa 1 y cuando W^1 es O, n representa 0);

W^2 representa N ó CH;

Z^1, Z^3, Z^5 y Z^7 cada uno representa un átomo de hidrógeno o un grupo alquilo C_{1-3};

710

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radi: 06-128571- -00000-0000
Fec: 2006-12-22 11:28:00 Usu: 2000 NUEVOENLAJUNES
TRL 11 PATENTEYU
Eva: 3/5 FASENAJUNAL

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 94,102
FECHA : DICIEMBRE 11 DE 2006

***** 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	55767475	11/12/2006	25,475,000.

***** 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 : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO 14656 841 015 4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-1285/1- -00000-0000
Fec: 2008-12-22 11:28:00 Dep: 2000 NUEVOS RADICADOS
Fol: 11 PATENTES
Eve: 315 PATENTE
Sel:411 PRESENTACION Folios: 711

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que 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 un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No.	06 128571
	Solicitud internacional	PCT/JP2005/012021
	Fecha inicio fase nacional	25/01/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1515

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. 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.

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.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 02 FEB. 2007
adpa10