SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-177219- -00000-0000
Fecha: 2011-12-22 17:36:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 202

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE
INVENCIÓN

TITULO: **PÉPTIDOS ESPECÍFICOS PARA RECEPTORES DE MELANOCORTINA**

SOLICITANTES: ASTRAZENECA AB

DIRECCIÓN: S-SE-151 85 Södertälje

APODERADO: CARLOS R. OLARTE

BOGOTÁ 22 de Diciembre de 2011

P2011/000207

OLARTEMOURE

OLARTE MOURE & AS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-177219- -00000-0000
Fecha: 2011-12-22 17:36:30 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 202

**PETITORIO - FORMULARIO ÚNICO DE SOLICITUD**
**PATENTE PCT**
**ENTRADA EN FASE NACIONAL** **P2011/000207**

**SOLICITUD DE:**

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

**Nombre:** **ASTRAZENECA AB;**
**Dirección:** S-151- 85 Sodertalje Suecia
**Nacionalidad o Domicilio:** Suecia.
**Lugar de Constitución:** Suecia.
**Teléfono:** **Fax:**
**E-mail:**

**IDENTIFICACIÓN**
**C.C.** [ ] **NIT** [ ]
**C.E.** [ ] **Otro** [ ]
**Cual**
**Número**

**REPRESENTANTE O APODERADO**

**Nombre:** CARLOS R. OLARTE
**Dirección:** Carrera 5 No. 34-03 Bogotá
**Teléfono:** 601-7700 **Fax:** 601-7799
**E-mail:** office@olartemoure.com

**IDENTIFICACIÓN**
**C.C.** [x] **NIT** [ ]
**C.E.** [ ] **Otro** [ ]
**Cual**
**Número** 79.782.747
**TP** 74.295

**INVENTOR (ES) (72)**

**Nombre:** **(1)** John H. DODD; **(2)** Yi-Qun SHI; **(3)** Wei YANG.
**Dirección:** **(1)** y **(2)** c/o Palatin Technologies, INC, 4-C Cedar Brook, Cedar Brook Corporate Center, Cranbury, New Jersey 08512, USA. **(3)** Palatin Technologies, INC, 4-C Cedar Brook, Cedar Brook Corporate Center, Cranbury, New Jersey 08512, USA.
**Nacionalidad o Domicilio:** (1), (2) y (3) Estadounidense.

(5) **PCT (86)**

Solicitud Internacional No. PCT/SE2010/050626 Fecha Junio 07, 2010

Publicación Internacional No. WO 2010/144038 Fecha Diciembre 16, 2010

(6) **Título (54)** **PÉPTIDOS ESPECÍFICOS PARA RECEPTORES DE MELANOCORTINA**

**Clasificación Internacional (51)** C07K 7/06; A61K 38/08; A61P 3/04.

**Prioridad**
**SI** [X] **NO** [ ]

| (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|
| US | Junio 08, 2009 | 61/184.932 |
| | | |
| | | |
| | | |

(9) **Comprobante de pago No.** 11- **Fecha** Diciembre de 2011

(10) **ANEXOS**

[X] Comprobante de pago de la tasa de presentación de la solicitud.

[X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

[X] Poderes, si fuere el caso. Adjunto copia simple. Ver expediente No. 08-129.814

[ ] 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).

[X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

[ ] Traducción del examen preliminar internacional 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 12 x 12.

[ ] 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] De ser el caso, modificaciones efectuadas a la solicitud internacional.

[X] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
**NIT : 800.176.089-2**
- / -

Industria y Comercio
SUPERINTENDENCIA

**RECIBO DE CAJA**

**No. 11 - 124764**

Bogotá D.C., Diciembre 22 de 2011 - 16:10:13

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

| TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PAGO | VR.PAGO |
|---|---|---|---|---|---|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 408396144 | 22/12/2011 | 6.281.000.00 |

*** Conceptos Pagados ***

| CANT | RENTISTICO | CONCEPTO | Vr.UNDITARIO | Vr.CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE INVENCION | 571.000.00 | 571.000.00 |
| | | | | $571.000.00 |

**SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE*****

Responsable: _____
-****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 11-177219- -00000-0000**

Fecha: 2011-12-22 17:36:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 202



3

Traducción oficial de un documento cuyo original está en inglés

No. 11426

El Ministerio de Relaciones Exteriores en Estocolmo certifica por el presente documento que Mrs. Anna-Karin Östin, de la Oficina de Registro de Compañías de Suecia, Sundsvall, ha expedido y firmado la anterior certificación en su calidad oficial.

En Estocolmo, este día 14 de Agosto de 2007.

(Firmado)

Hay un sello del Ministerio de Relaciones Exteriores de Suecia.

Hay un sello firmado de la Embajada de Sudán en Estocolmo.

Firma de Agneta S...

Y sello de ...

Firma: Mohamed Hussein.

Fecha: 20 de Agosto de 2007.

Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Certificación Notarial

Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anders Burén, debidamente autorizado para firmar en nombre de Astrazeneca AB ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex oficio:

(Firmado) Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Ministerio de Justicia

*Apostilla adjunta:*

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

| | |
|---|---|
| 1. País: | Suecia |
| | El presente documento público |
| 2. Ha sido firmado por: | Anne-Marie Bonde |
| 3. Actuando en calidad de: | Notario Público |
| 4. Lleva el sello / estampilla de: | Notario Público de Estocolmo. |
| | Certificado |
| 5. En: | Estocolmo |
| 6. El: | Día 26 de Octubre de 2007 |
| 7. Por: | Björn Sandin, Notario Público |
| 8. Bajo el No. | 4071 |
| 9. Sello / estampilla: | Björn Sandin, Notario Público de Estocolmo. |
| 10. Firma: | (Firmado) |

*Certificación:*

*Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Cert.Min. Rel."*

*Fecha: 13 de Noviembre de 2007.*

*Traductor: Jorge Enrique Sierra Reyes.*

*Licencia No. 376 de 1993, del Ministerio de Justicia.*

*Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.*

*Teléfono: (57-1) 2182308, (57-1) 6232925.*

*E-mail: treseser1@yahoo.com. No. 10-054*

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

**APOSTILLE**

**(Convention de La Haye du 5 octobre 1961)**

1. **Country : Sweden**

   **This public document**

2. **has been signed by** Anne-Marie Bonde

3. **acting in the capacity of** Notary Public

4. **bears the seal/stamp of**

   Notary Public in Stockholm

**Certified**

5. **at** Stockholm  **6. the** 26.10.2007

7. **by** Björn Sandin

   Notary Public

8. **No** 4071

9. **Seal/stamp:**  **10. Signature:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

**OLARTERAISBECK**
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olart
J. Ian Raisbec
Ana María Frie
Juan Guillermo Mour
Natalia Castr

Zayde Chahí
Simón Salina
Alexander Agudel
Camilo A. Rodrigue
Lina Mosquer
Catalina Barbastefan

Of Counse
Guillermo Chahí
Graciela Mel
Jacqueline Chaparr
Cruz E. de Moncalean

## Power of Attorney

The undersigned, AstraZeneca AB

domiciled in Vastra Malarehamnen 9 S-151 85 Sodertalje, Sweden

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications, collect refunds, desist, settle, conciliate or negotiate. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

## Poder

El suscrito,

domiciliado en

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: **Anders Burén**
**Authorized Signatory**

Date/Fecha: 24 OCTOBER 2007

City,Country/Ciudad,País: SODERTALJE

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm
hereby certify that
ANDERS BURÉN
duly authorized to sign for
ASTRAZENECA AB
has issued and signed the foregoing document.

Fee 340:- Stockholm 2007-10-26
Crowns Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

Anders Burén
Authorized Signatory

6

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

## MODEL OF NOTARIAL CERTIFICATION

| Notarial Certification | Certificación Notarial |
|---|---|
| On this date, | En esta fecha, |
| The undersigned Notary Public certifies: | el Notario Público suscrito certifica: |
| 1. That | 1. Que |
| of legal age and domiciled in | mayor de edad y domiciliado |
| signed the foregoing document. | suscribió el documento que antecede. |
| 2. That the grantor has executed the foregoing document as DULY AUTHORISED SIGNATORY of ASTRAZENECA AB | 2. Que el otorgante ha suscrito el referido documento en su carácter de de |
| 3. That ASTRAZENECA AB having its principal place of business located in SODERTALJE, SWEDEN is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes. | 4. Que con sede principal ubicada en está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social. |
| 4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal. | 4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima. |
| 5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s): | 5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s): |

1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB

2. AUTHORISATION IN FAVOUR OF SIGNATORY

NOTARY PUBLIC (Signature):
Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)
SEAL (optional)

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

851 81 Sund... Tel. 060-18 40 00 - Fax: 060 129840.
bolagsverket@bolagsverket (ilegible)

# Certificado de Existencia

Yo, Anna-Karin Östin, de Bolagsverket, la Oficina de Registro de Compañías de Suecia, certifico por medio del presente documento que

AstraZeneca AB

Registro No. 556011-7482

es una compañía debidamente constituida según las leyes de Suecia, vigente y con existencia corporativa legal hasta donde muestran los registros de esta oficina en la fecha que se indica más adelante.

En testimonio de lo anterior, he puesto mi firma y estampado el sello oficial de Bolagsverket en Sundsvall, este día 8 de Agosto del año 2007.

(Firmado) Anna-Karin Östin.

Hay un sello de Bolagsverket

Bolagsverket, la Oficina de registro de Compañías de Suecia, es el Registrador Oficial de las Compañías Limitadas y otras formas de empresas comerciales en Suecia. Antes de que se expida un Certificado de existencia, los registros radicados en esta oficina se examinan para tener la seguridad de que la compañía en cuestión llena los siguientes requerimientos:

- La compañía tiene una Junta Directiva competente
- La compañía tiene un Auditor titulado calificado.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

- La compañía ha llenado sus obligaciones con respecto a la radicación correcta de su informe anual.
- La compañía no es el sujeto de acciones legales de división de compañías, terminación o bancarrota.
- La compañía no ha sido disuelta como resultado de una fusión y no ha salido del registro por ninguna otra razón.

El Certificado está firmado por un funcionario autorizado para expedir estos y similares documentos en nombre de Bolagsverket, la Oficina de Registro de Compañías de Suecia.

Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Certificación Notarial

Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anna-Karin Östin, debidamente autorizada para firmar en nombre de la Oficina de Registro de Compañías de Suecia, ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex oficio:

(Firmado) Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

*Apostilla adjunta:*

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

| | |
|---|---|
| 1. País: | Suecia |
| | El presente documento público |
| 2. Ha sido firmado por: | Anne-Marie Bonde |
| 3. Actuando en calidad de: | Notario Público |
| 4. Lleva el sello / estampilla de: | Notario Público de Estocolmo. |
| | Certificado |
| 5. En: | Estocolmo |
| 6. El: | Día 26 de Octubre de 2007 |
| 7. Por: | Björn Sandin, Notario Público |
| 8. Bajo el No. | 4070 |
| 9. Sello / estampilla: | Björn Sandin, Notario Público de Estocolmo. |
| 10. Firma: | (Firmado) |

---

*Certificación:*

*Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Cert.Bolagsverket"*

*Fecha: 13 de Noviembre de 2007.*

*Traductor: Jorge Enrique Sierra Reyes.*

*Licencia No. 376 de 1993, del Ministerio de Justicia.*

*Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.*

*Teléfono: (57-1) 2182308, (57-1) 6232925.*

*E-mail: treseser1@yahoo.com. No. 10-053*

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Ministerio

**APOSTILLE**

**(Convention de La Haye du 5 octobre 1961)**

1. **Country :** Sweden

   **This public document**

2. **has been signed by** Anne-Marie Bonde

3. **acting in the capacity of** Notary Public

4. **bears the seal/stamp of**

   Notary Public in Stockholm

**Certified**

5. **at** Stockholm

6. **the** 26.10.2007

7. **by** Björn Sandin

   Notary Public

8. **No** 4070

9. **Seal/stamp:**

10. **Signature:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

Bolagsverket

851 81 Sundsvall
Besökare: Badhusparken
Tel: 060-18 40 00 • Fax: 060-12 98 40
bolagsverket@bolagsverket.se • bolagsverket.se

# Certificate of Good Standing

I, Anna-Karin Östin, of Bolagsverket, the Swedish Companies Registration Office, do hereby certify that

**AstraZeneca AB**
registration number **556011-7482**

is a duly incorporated company under the laws of Sweden and is in good standing and has a legal corporate existence as far as the records of this office show as of the date stated below.

In testimony hereof, I have hereunto set my hand and the official seal of Bolagsverket at Sundsvall, this 8th day of August in the year of two thousand and seven.

Anna-Karin Östin

Bolagsverket, the Swedish Companies Registration Office, is the official registrar of limited companies and other forms of business enterprise in Sweden. Before a Certificate of Good Standing is issued, the records kept by this office are examined to ensure that the following requirements are fulfilled for the company in question:

- the company has a registered competent board of directors
- the company has a registered qualified auditor
- the company has fulfilled its obligations regarding the correct filing of its annual report
- the company is not the subject of company division, winding up or bankruptcy proceedings
- the company has not been dissolved as the result of a merger and has not been struck off the register for any other reason

The Certificate is signed by an official authorized to issue these and similar documents on behalf of Bolagsverket, the Swedish Companies Registration Office.

I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm

hereby certify that

ANNA-KARIN ÖSTIN

duly authorized to sign for

THE SWEDISH COMPANIES REGISTRATION OFFICE

has issued and signed the foregoing document in original of which this is a true copy.

Fee 340:- Stockholm 2007-10-26

Crowns Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

The Ministry for Foreign Affairs in Stockholm hereby certifies that

Mr. Anna-Karin Bäck

**Swedish Companies Registration Office**, Sundsvall

has issued and signed the foregoing attestation in his official capacity

For Stockholm this 20th day of August 2007

FEE 100:- PAID

Agneta Ödeklund

SIGNATURE OF Agneta Ödeklund

AND STAMP OF : Sec MFA

SIGNATURE : Mohamed Hussein

DATE : 20-08-07

NOTARIUS PUBLICUS I STOCKHOLM — ANNE-MARIE BONDE

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 December 2010 (16.12.2010)

PCT

(10) International Publication Number
WO 2010/144038 A1

(51) International Patent Classification:
*C07K 7/06* (2006.01) *A61P 3/04* (2006.01)
*A61K 38/08* (2006.01)

(21) International Application Number:
PCT/SE2010/050626

(22) International Filing Date:
7 June 2010 (07.06.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/184,932 8 June 2009 (08.06.2009) US

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; SE-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DODD, John H.** [US/US]; Palatin Technologies, INC, 4-C Cedar Brook, Cedar Brook Corporate Center, Cranbury, New Jersey 08512 (US). **SHI, Yi-Qun** [US/US]; Palatin Technologies, INC, 4-C Cedar Brook, Cedar Brook Corporate Center, Cranbury, New Jersey 08512 (US). **YANG, Wei** [US/US]; Palatin Technologies, INC, 4-C Cedar Brook, Cedar Brook Corporate Center, Cranbury, New Jersey 08512 (US).

(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, SE-151 85 Södertälje (SE).

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

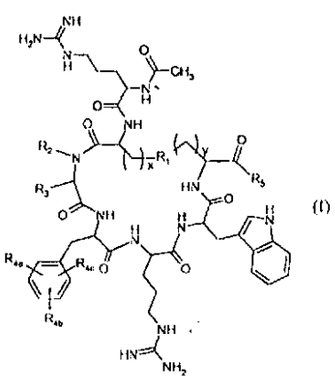
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published**:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: MELANOCORTIN RECEPTOR-SPECIFIC PEPTIDES



(I)

(57) Abstract: The invention relates to melanocortin receptor-specific cyclic peptides of Formula (I) or a pharmaceutically acceptable salt thereof, where $R_1$, $R_2$, $R_3$, $R_{4a}$, $R_{4b}$, $R_{4c}$, $R_5$, x and y are as defined in the specification. These compounds are particularly useful in the treatments of energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity, overweight and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome.

WO 2010/144038 A1

# MELANOCORTIN RECEPTOR-SPECIFIC PEPTIDES

## Technical field

The present invention relates to melanocortin receptor-specific cyclic peptides which may be used in the treatment of melanocortin receptor-mediated diseases, indications, conditions and syndromes, in particular energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity, overweight and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome.

## Background

The following discussion refers to a number of publications by author(s) and year of publication, and that due to recent publication dates certain publications are not to be considered as prior art vis-a-vis the present invention. Discussion of such publications herein is given for more complete background and is not to be construed as an admission that such publications are prior art for patentability determination purposes.

A family of melanocortin receptor types and subtypes have been identified, including melanocortin-1 receptors (MC1-R) expressed on normal human melanocytes and melanoma cells, melanocortin-2 receptors (MC2-R) for ACTH (adrenocorticotropin) expressed in cells of the adrenal gland, melanocortin-3 and melanocortin-4 receptors (MC3-R and MC4-R) expressed primarily in cells in the hypothalamus, mid-brain and brainstem, and melanocortin-5 receptors (MC5-R), expressed in a wide distribution of peripheral tissues. MC1-R has been suggested to be associated with hair and skin pigmentation and inflammation, MC2-R is believed to mediate steroidogenesis, MC3-R has been suggested to be associated with energy homeostasis, food intake, and inflammation, MC4-R is believed to control feeding behavior, energy homeostasis, and sexual function (e.g. erectile function), and MC5-R has been suggested to be involved in the exocrine gland system.

Significant work has been done in determining the structure of melanocortin receptors, including both the nucleic acid sequences encoding for the receptors and the amino acid sequences constituting the receptors. MC4-R is a G protein-coupled, 7-transmembrane receptor that is believed to be expressed primarily in the brain.

MC4-R inactivation has been shown to result in obesity (Hadley, 1999, Ann N Y Acad Sci., 885:1-21). Agouti-related protein (AgRP) is an endogeneous compound that has been suggested to be a MC antagonist or an inverse agonist on MC4-R. The α-melanocyte stimulating hormone (α-MSH) is believed to be the principle endogenous MC4-R agonist.

Also peripherally located MC4-R receptors have been suggested to be involved in the control of energy homeostasis, and the role of MC4-R signalling in the vagus nerve and its relevance for treatment of obesity and diabetes is discussed by Gautron et al, The Journal of Comparative Neurology, 518:6-24 (2010).

Peptides specific for MC4-R, and secondarily peptides specific for MC3-R, are believed to be useful in regulation of mammalian energy homeostasis, including use as agents for attenuating food intake and body weight gain. MC4-R agonist peptides are believed to be useful for treating sexual dysfunction, including male erectile dysfunction, and for decreasing food intake and body weight gain, such as for treatment of obesity. Such peptides may also be employed for decreasing voluntary ethanol consumption, treatment of drug addictions, and the like. MC4-R agonist peptides, as well as MC3-R agonist peptides, may further be employed for treatment of circulatory shock, ischemia, hemorrhagic shock, inflammatory diseases and related diseases, indications, conditions and syndromes. MC4-R antagonist peptides, by contrast, are believed to be useful for weight gain aid, such as for use in treatment of cachexia, sarcopenia, wasting syndrome or disease, and anorexia. Such peptides may also be employed for treatment of depression and related disorders. (Wikberg et al, Nature Reviews, Drug Discovery, 7, 307, (2008); Adan et al, British J. Pharm., 149, 815-827 (2006); Nogueiras et al, J. Clin., Invest., 117(11): 3475-3488 (2007); Maaser et al, Ann. N.Y. Acad. Sci., 1072, 123-134 (2006); Giuliani et al, British J. Pharm., 150, 595-603 (2007); Balbani, Expert Opin. Ther. Patents, 17(3), 287-297 (2007); and Navarro et al, Alcohol. Clin. Exp. Res., 29(6), 949-957 (2005)).

Melanocortin receptor-specific peptides include cyclic α-MSH analog peptides such as Ac-Nle-*cyclo*(-Asp-His-D-Phe-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:1) (*See* U.S. Patent Nos.

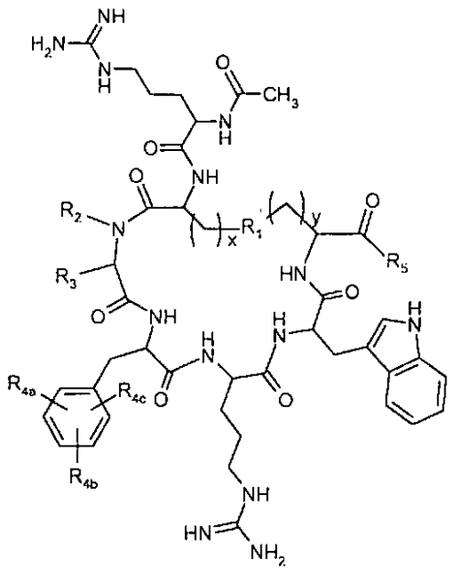
5,674,839 and 5,576,290) and Ac-Nle-*cyclo*(-Asp-His-D-Phe-Arg-Trp-Lys)-OH (SEQ ID NO:2) (*See* U.S. Patent Nos. 6,579,968 and 6,794,489). These and other melanocortin receptor-specific peptides generally contain the central tetrapeptide sequence of native α-MSH, $His^6$-$Phe^7$-$Arg^8$-$Trp^9$ (SEQ ID NO:3), or a mimetic or variation thereof, including the substitution of D-Phe for $Phe^7$. Other peptides or peptide-like compounds asserted to be specific for one or more melanocortin receptors are disclosed in U.S. Patent Nos. 5,731,408, 6,054,556, 6,350,430, 6,476,187, 6,600,015, 6,613,874, 6,693,165, 6,699,873, 6,887,846, 6,951,916, 7,008,925, and 7,176,279; in U.S. published patent application Publication Nos. 2001/0056179, 2002/0143141, 2003/0064921, 2003/0105024, 2003/0212002, 2004/0023859, 2005/0130901, 2005/0187164, 2005/0239711, 2006/0105951, 2006/0111281, 2006/0293223, 2007/0027091, 2007/0105759, 2007/0123453, 2007/0244054, and 2008/0039387; and in international patent applications nos. WO 98/27113, WO 99/21571, WO 00/05263, WO 99/54358, WO 00/35952, WO 00/58361, WO 01/30808, WO 01/52880, WO 01/74844, WO 01/85930, WO 01/90140, WO 02/18437, WO 02/26774, WO 03/006604, WO 2004/099246, WO 2004/046166, WO 2005/000338, WO 2005/000339, WO 2005/000877, WO 2005/030797, WO 2005/060985, WO2006/048449, WO 2006/048450, WO 2006/048451, WO 2006/048452, WO 2006/097526, WO 2007/008684, WO 2007/008704, and WO 2007/009894. Notwithstanding the intense scientific and pharmaceutical interest in melanocortin receptor-specific peptides, evidenced by numerous articles in the scientific literature and numerous patent applications and issued patents (Nozawa et al, Expert Opin. Ther. Patents 18(4):403-427 (2008); Bednarek et al, Expert Opin. Ther. Patents 14(3):327-336 (2004); Todorovic et al, Peptides, 26, 2026-2036 (2005); and Ujjainwalla et al, Current Topics in Med. Chem., 7, 1068-1084 (2007)), no melanocortin receptor-specific peptide has been approved as a drug for any therapeutic indication. Indeed, there are no reports of any melanocortin receptor-specific peptide for any therapeutic indication having advanced past Phase II clinical trials. There remains a significant and substantial need for melanocortin receptor-specific peptides for use in pharmaceutical applications. It is against this background that the present invention was made.

Summary of the invention

It is therefore an object of the present invention to provide novel compounds that are useful for the treatment of diseases, disorders and/or conditions responsive to modulation,

including activation, of MC4-R and/or MC3-R, in particular treatment of energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity, overweight and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome.

In one aspect, the present invention relates to a cyclic peptide of the structural Formula (I):



(I)

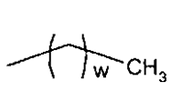
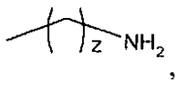
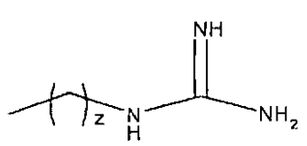
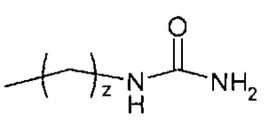
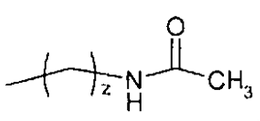
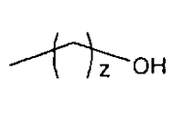
including all enantiomers, stereoisomers or diastereoisomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

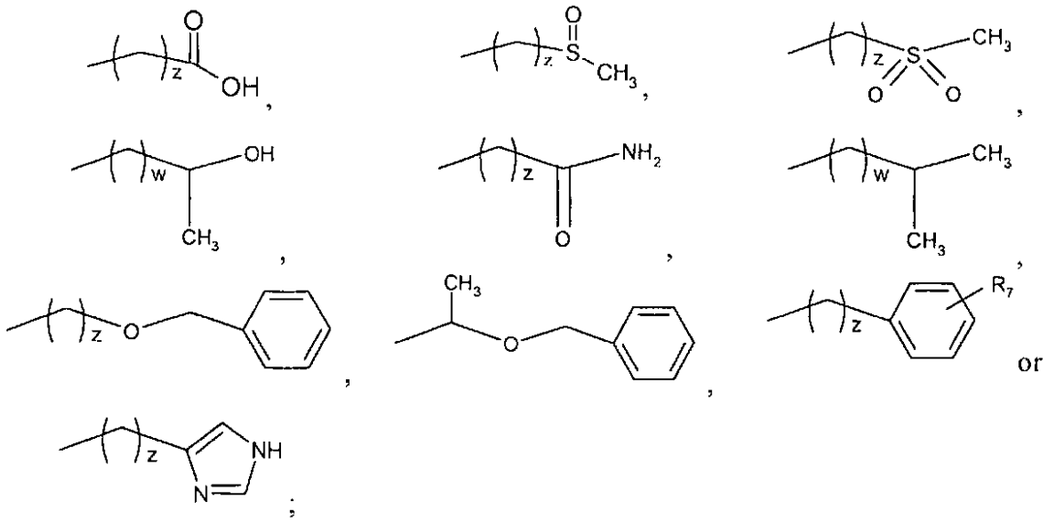
wherein:

$R_1$ is -NH-C(=O)- or -C(=O)-NH-;

$R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH;

$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from


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or

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$R_{4a}$, $R_{4b}$ and $R_{4c}$ are are each independently selected from hydrogen, halo, ($C_1$-$C_{10}$)alkyl-halo, ($C_1$-$C_{10}$)alkyl-dihalo, ($C_1$-$C_{10}$)alkyl-trihalo, ($C_1$-$C_{10}$)alkyl, ($C_1$-$C_{10}$)alkoxy, ($C_1$-$C_{10}$)alkylthio, aryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carboxy, or alkoxy-carbonyl, on the proviso that at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is not hydrogen;

$R_5$ is -OH or -N($R_{6a}$)($R_{6b}$);

$R_{6a}$ and $R_{6b}$ are each independently H or a $C_1$ to $C_4$ linear, branched or cyclic alkyl chain;

$R_7$ is -H or -C(=O)-$NH_2$;

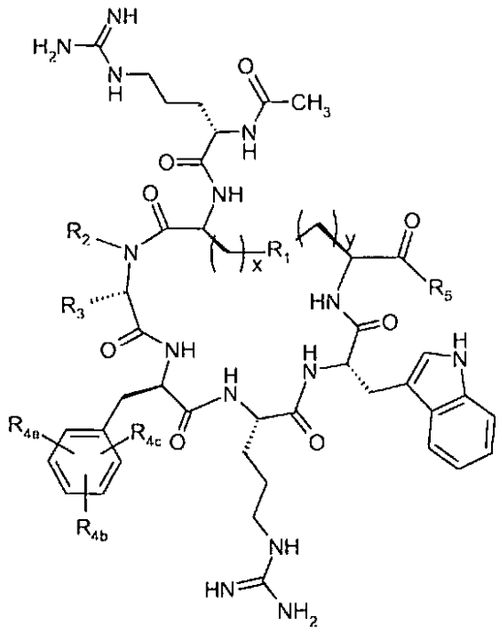
w is in each instance independently 0 to 5;

x is 1 to 5;

y is 1 to 5; and

z is in each instance independently 1 to 5.

In another aspect, the present invention relates to a cyclic peptide of Formula (I) which is of formula (II):



(II)

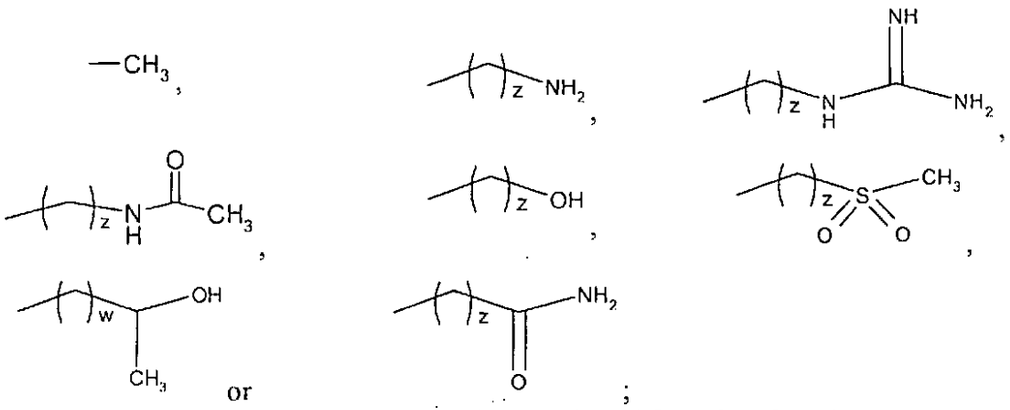
or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a cyclic peptide of Formula I, in particular of Formula (II), wherein $R_1$ is -C(=O)-NH-, x is 2 and y is 3.

In another aspect, the present invention relates to a cyclic peptide of Formula (I), in particular of Formula (II), wherein $R_1$ is -NH-C(=O)-, x is 3 and y is 2.

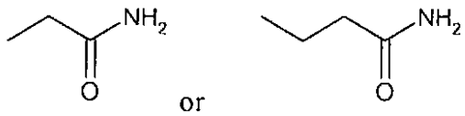
In another aspect, the present invention relates to a cyclic peptide of Formula (I), in particular of Formula (II), wherein $R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH; and

$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is



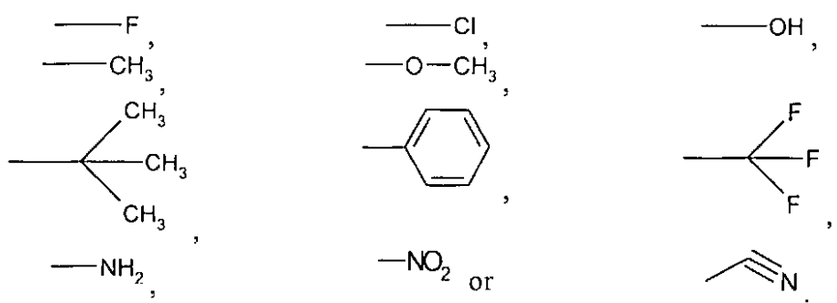
wherein w is in each instance independently selected from 0 to 5, and z is in each instance independently selected from 1 to 5.

In another aspect, the present invention relates to a cyclic peptide of Formula I, in particular of Formula (II) or (III), wherein $R_2$ is H, $R_3$ is selected from



In another aspect, the present invention relates to a cyclic peptide of Formula I, in particular of Formula (II), wherein $R_2$ is $-CH_2-$ and $R_3$ is $-(CH_2)_2-$, $R_2$ and $R_3$ together forming an unsubstituted pyrrolidine ring.

In another aspect, the present invention relates to a cyclic peptide of Formula I, in particular Formula (II), wherein at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is selected from



In another aspect, the present invention relates to a cyclic peptide of Formula I, in particular Formula (II) or (III), wherein $R_{4a}$ is in the 4 position and is -C≡N and $R_{4b}$ and $R_{4c}$ are each H.

In another aspect, the present invention relates to a cyclic peptide of Formula (I), in particular Formula (II) or (III), wherein $R_{4a}$ is in the 4 position and is -F and $R_{4b}$ and $R_{4c}$ are each H.

The peptides according to the invention are ligands of one or more of the melanocortin receptors, in particular ligands of the MC4-R, more particularly agonists (including full and partial agonists) of the MC4-R. The term "ligands" as used herein include peptides binding to the active site as well as peptides binding to one or more allosteric sites of any one of said receptors.

Thus, the peptides of the invention can be used as a medicament, in particular for the treatment of disorders, diseases, or conditions responsive to modulation of the MC3-R and/or MC4-R, and in particular disorders, diseases, or conditions responsive to the activation of the MC4-R. More particularly, the peptides of the invention are believed to attenuate food intake, body weight and/or body weight gain and are therefore believed to

be useful for treatments of energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity and overweight, and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome, in a patient in need thereof. The patient may be a human or non-human animal, in particular a human.

Peptides of the invention may have advantageous properties compared to peptides of the prior art, in particular enhanced potency and/or enhanced selectivity. These advantages may provide for corresponding useful properties in practice. For example, when used as pharmaceutical agents, peptides of the present invention may be used at a lower daily clinical dose, may have longer duration of action, and/or an improved side effect profile.

In another aspect of the invention, there is provided a method of treating disorders, diseases, or conditions responsive to modulation of the MC4-R and/or MC3-R, such as disorders, diseases, or conditions responsive to activation of the MC4-R, in particular energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity and overweight, and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome, by administering a therapeutically effective amount of a peptide of the invention to a patient in need thereof.

According to a further aspect of the invention, there is provided a method of reducing food intake, body weight and/or body weight gain by administering a pharmacologically effective amount of a peptide of the invention to an individual, such as a human, in need thereof.

According to a further aspect of the invention, there is provided a method of preventing body weight regain after weight loss by administering a pharmacologically effective amount of a peptide of the invention to an individual, such as a human, in need thereof.

In a further aspect, the invention provides the use of a peptide of Formula I in the preparation of a medicament for treatment of a disease, disorder and/or condition

responsive to activation of the MC4-R, in particular energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity and overweight, and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome.

In another aspect, the present invention provides a melanocortin receptor-specific peptide-based pharmaceutical composition for use in treatment of melanocortin receptor-mediated diseases, indications, conditions and syndromes, in particular diseases, disorders, conditions and/or syndromes responsive to modulation of MC4-R, such as activation of MC4-R, comprising a peptide of Formula I and a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a peptide-based melanocortin receptor-specific pharmaceutical composition comprising a peptide of Formula I and a pharmaceutically acceptable carrier, wherein the peptide is a selective MC4-R ligand, for use in treatment of energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity, overweight and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome.

In another aspect, the present invention provides peptides which are specific for MC4-R and which are partial or full agonists at MC4-R. In particular, the present invention provides peptides which are specific for MC4-R and which are partial agonists at MC4-R.

In another aspect, the present invention provides a specific MC4-R cyclic peptide that is effective over a significant dose range.

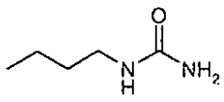
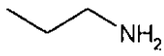
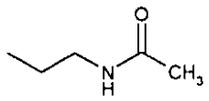
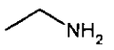
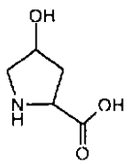
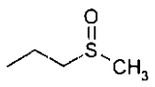
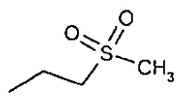
Other aspects and novel features, and the further scope of applicability of the present invention will be set forth in part in the detailed description to follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The aspects of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

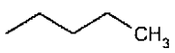
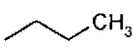
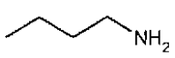
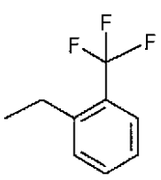
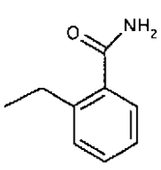
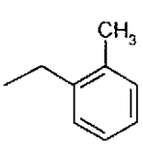
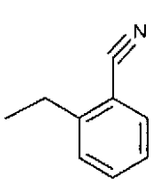
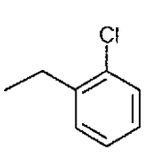
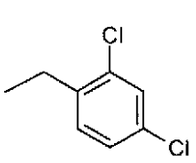
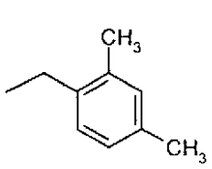
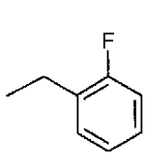
Detailed description of the invention

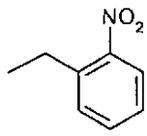
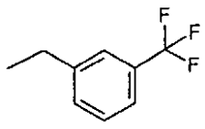
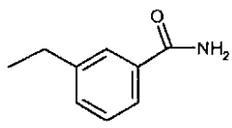
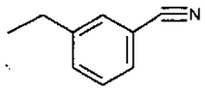
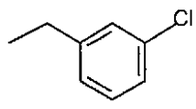
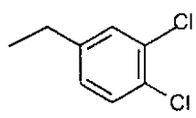
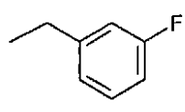
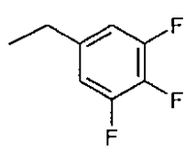
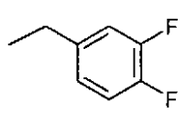
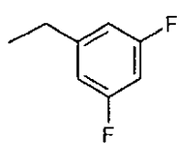
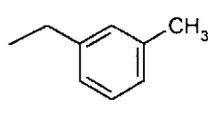
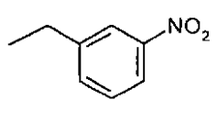
1.0 Definitions.

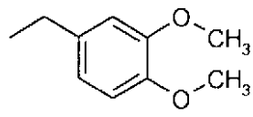
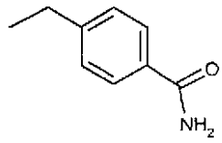
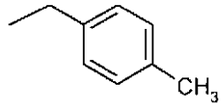
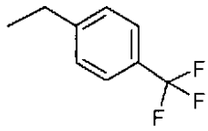
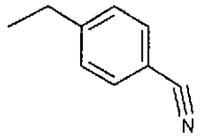
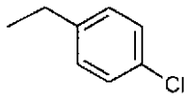
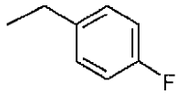
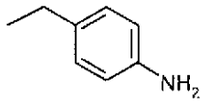
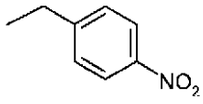
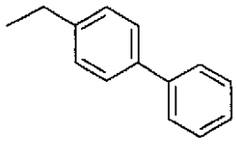
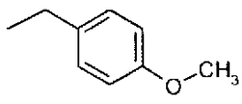
Before proceeding with the description of the invention, certain terms are defined as set forth herein.

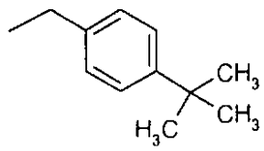
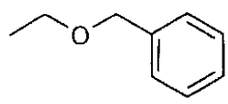
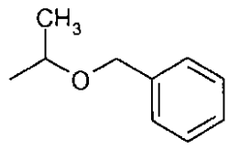
In the sequences given for the peptides according to the present invention, the amino acid residues have their conventional meaning as given in Chapter 2400 of the Manual of Patent Examining Procedure, 8th Ed. Thus, "Ala" is alanine, "Asn" is asparagine, "Asp" is aspartic acid, "Arg" is arginine, "Cys" is cysteine, "Gly" is glycine, "Gln" is glutamine, "Glu" is glutamic acid, "His" is histidine, "Ile" is isoleucine, "Leu" is leucine, "Lys" is lysine, "Met" is methionine, "Phe" is phenylalanine, , "Pro" is proline, "Ser" is serine, "Thr" is Threonine, "Trp" is tryptophan, "Tyr" is tyrosine, and "Val" is valine, and so on. It is to be understood that "D" isomers are designated by a "D-" before the three letter code or amino acid name, such that for example D-Phe is D-phenylalanine. Amino acid residues not encompassed by the foregoing have the following definitions:

| Abbreviation | Common Name | Side Chain or Amino Acid Structure |
|---|---|---|
| Cit | citrulline |  |
| Dab | diaminobutyric acid |  |
| Dab(Acetyl) | 2-amino, 4-acetylaminobutyric acid |  |
| Dap | diaminoproprionic acid |  |
| Hyp | hydroxyproline |  |
| Met(O) | methionine sulfoxide |  |
| Met($O_2$) | methionine sulfone |  |

| Abbreviation | Common Name | Side Chain or Amino Acid Structure |
|---|---|---|
| Nle | norleucine |  |
| Nva | norvaline |  |
| Orn | ornithine |  |
| Phe(2-$CF_3$) | 2-trifluoromethyl phenylalanine |  |
| Phe(2-C(=O)-$NH_2$) | 2-carbamoyl-phenylalanine |  |
| Phe(2-Me) | 2-methyl phenylalanine |  |
| Phe(2-CN) | 2-cyano phenylalanine |  |
| Phe(2-Cl) | 2-chloro phenylalanine |  |
| Phe(2,4-diCl) | 2, 4-dichloro phenylalanine |  |
| Phe(2,4-diMe) | 2, 4-dimethyl phenylalanine |  |
| Phe(2-F) | 2-flouro phenylalanine |  |

| Abbreviation | Common Name | Side Chain or Amino Acid Structure |
|---|---|---|
| Phe(2-$NO_2$) | 2-nitro phenylalanine |  |
| Phe(3-$CF_3$) | 3-triflouromethyl phenylalanine |  |
| Phe(3-C(=O)-$NH_2$) | 3-carbamoyl-phenylalanine |  |
| Phe(3-CN) | 3-cyano phenylalanine |  |
| Phe(3-Cl) | 3-chloro phenylalanine |  |
| Phe(3,4-diCl) | 3,4-dichloro phenylalanine |  |
| Phe(3-F) | 3-fluoro phenylalanine |  |
| Phe(3,4,5-triF) | 3,4,5-trifluoro phenylalanine |  |
| Phe(3,4-diF) | 3,4-difluoro phenylalanine |  |
| Phe(3,5-diF) | 3,5-difluoro phenylalanine |  |
| Phe(3-Me) | 3-methyl phenylalanine |  |
| Phe(3-$NO_2$) | 3-nitro phenylalanine |  |

| Abbreviation | Common Name | Side Chain or Amino Acid Structure |
|---|---|---|
| Phe(3,4-diOMe) | 3,4-dimethoxy phenylalanine |  |
| Phe(4-C(=O)-$NH_2$) | 4-carbamoyl-phenylalanine |  |
| Phe(4-Me) | 4-methyl phenylalanine |  |
| Phe(4-$CF_3$) | 4-trifluoromethyl phenylalanine |  |
| Phe(4-CN) | 4-cyano phenylalanine |  |
| Phe(4-Cl) | 4-chloro phenylalanine |  |
| Phe(4-F) | 4-fluoro phenylalanine |  |
| Phe(4-$NH_2$) | 4-amino phenylalanine |  |
| Phe(4-$NO_2$) | 4-nitro phenylalanine |  |
| Phe(4-Ph) | 4-phenyl phenylalanine |  |
| Phe(4-OMe) | 4-methoxy phenylalanine |  |

| Abbreviation | Common Name | Side Chain or Amino Acid Structure |
|---|---|---|
| Phe(4-tBu) | 4-*tert* butyl phenylalanine |  |
| Ser(Bzl) | O-benzyl-serine |  |
| Thr(OBzl) | O-benzyl-threonine |  |

The term "acyl" includes a group R(C=O)-, where R is an organic group, such as an alkyl, aryl, heteroaryl, carbocyclyl or heterocyclyl. Thus, when reference is made herein to a substituted acyl group, it means that said organic group (R) is substituted. An example is the acetyl group $CH_3$-C(=O)-, referred to herein as "Ac". A peptide or aliphatic moiety is "acylated" when an alkyl or substituted alkyl group as defined above is bonded through one or more carbonyl {-(C=O)-} groups. A peptide is most usually acylated at the N-terminus.

The term "alkane" includes linear or branched saturated hydrocarbons. Examples of linear alkane groups include methane, ethane, propane, and the like. Examples of branched or substituted alkane groups include methylbutane or dimethylbutane, methylpentane, dimethylpentane or trimethylpentane, and the like. In general, any alkyl group may be a substitutent of an alkane.

The term "alkene" includes unsaturated hydrocarbons that contain one or more double carbon-carbon bonds. Examples of such alkene groups include ethylene, propene, and the like.

The term "alkenyl" includes a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing at least one double bond; examples thereof include ethenyl, 2-propenyl, and the like.

The term "alkyl" includes a straight or branched chain saturated aliphatic hydrocarbon group . $C_{1-10}$ alkyl means an alkyl having from 1 to 10 carbon atoms. Non-

limiting examples of such alkyl radicals include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The term "alkyne" includes a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing at least one triple bond; examples thereof include ethyne, propyne, butyne, and the like.

The term "aryl" includes a monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 12 ring atoms, and optionally substituted independently with one or more substituents selected from alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, amino, monosubstituted amino, disubstituted amino, hydroxy, carboxy, or alkoxy-carbonyl. The term "aryl" also includes bicyclic aromatic ring systems wherein one ring is aromatic and one ring is non-aromatic (including saturated or partially saturated rings). In bicyclic aromatic ring systems, two or more ring carbons are common to two adjoining rings (the rings are "fused rings"). Examples of an aryl group include phenyl, biphenyl, indanyl, naphthyl, 1-naphthyl, and 2-naphthyl, derivatives thereof, and the like.

The term "aralkyl" includes a radical - $R^aR^b$ where $R^a$ is an alkylene (a bivalent alkyl) group and $R^b$ is an aryl group as defined above. Examples of aralkyl groups include benzyl, phenylethyl, 3-(3-chlorophenyl)-2-methylpentyl, and the like.

The term "aliphatic" includes compounds with hydrocarbon chains, such as for example alkanes, alkenes, alkynes, and derivatives thereof.

As used herein, the term "amide" includes compounds that have a trivalent nitrogen attached to a carbonyl group, i.e. $-C(=O)-NH_2$ (i.e. primary amide), $-C(=O)-NHR_c$ and $-C(=O)-NR_cR_d$, wherein each of $R_c$ and $R_d$ independently represents an organic group. When reference is made herein to a substituted amide group, it means that at least one of said organic groups ($R_c$ and $R_d$) is substituted. Examples of amides include methylamide, ethylamide, propylamide, and the like.

The term "amine" includes $-NH_2$ (i.e. an amino group), $-NHR_a$ and $-NR_aR_b$, wherein each of $R_a$ and $R_b$ independently represents an organic group. When reference is made herein to a substituted amine group, it means that at least one of said organic groups ($R_a$ and $R_b$) is substituted.

The term "nitrile" includes the functional group -C≡N.

The term "halogen" (or "halo") is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term "alkyl-halo" includes an alkyl substituted with one halogen atom, such as -$CH_2F$. The term "alkyl-dihalo" includes an alkyl substituted with two halogen atoms, such as –$CHF_2$. The term "alkyl-trihalo" includes an alkyl substituted with three halogen atoms, such as -$CF_3$.

The term "alkylthio" includes -S-alkyl wherein alkyl is as defined above. Non-limiting examples of $C_1$-$C_{10}$ alkylthio include methylthio, ethylthio, n-propylthio, iso-propylthio, and n-butylthio.

The term "nitro" is intended to include –$NO_2$.

The term "hydroxy" is intended to include –OH.

The term "alkoxy" includes -O-alkyl wherein alkyl is as defined above. $C_1$-$C_{10}$ alkoxy includes an alkyl having from 1 to 10 carbon atoms. Non-limiting examples of $C_1$-$C_{10}$ alkoxy include methoxy, ethoxy, *n*-propyloxy, *iso*-propyloxy, and 2-methyl-1-propyloxy.

The term "aryloxy" includes -O-aryl wherein aryl is as defined above.

The term "alkoxycarbonyl" includes –C(=O)-O-R, wherein R is an alkyl as defined above. Non-limiting examples of $C_1$-$C_{10}$ alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxy-carbonyl and isopentoxycarbonyl.

The term "carboxy" includes –C(=O)OH.

The term "oxo" includes =O.

The term "sulfonamide" includes a sulfonyl group connected to an amine group, i.e. –$S(=O)_2NH_2$, –$S(=O)_2NHR_a$, and –$S(=O)_2NR_aR_b$, wherein each of $R_a$ and $R_b$ independently represents an organic group. When reference is made herein to a substituted sulfonamide group, it means that at least one of said organic groups ($R_a$ and $R_b$) is substituted.

The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from

dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions utilized in the present invention encompass any composition made by admixing an active ingredient and one or more pharmaceutically acceptable carriers.

By a melanocortin receptor "agonist" is meant an endogenous substance, drug substance or compound, including a compound such as the peptides of the present invention, which can interact with a melanocortin receptor and initiate a pharmacological response, including but not limited to adenyl cyclase activation, characteristic of the melanocortin receptor.

By "α-MSH" is meant the peptide Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-$NH_2$ (SEQ ID NO:4) and analogs and homologs thereof, including without limitation NDP-α-MSH.

By "NDP-α-MSH" is meant the peptide Ac-Ser-Tyr-Ser-Nle-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val-$NH_2$ (SEQ ID NO:5) and analogs and homologs thereof.

By "$EC_{50}$" is meant the molar concentration of an agonist, including a partial agonist, which produced 50% of the maximum possible response for that agonist. By way of example, a test compound which, at a concentration of 72 nM, produces 50% of the maximum possible response for that compound as determined in a cAMP assay in an MC4-R cell expression system has an $EC_{50}$ of 72 nM. Unless otherwise specified, the molar concentration associated with an $EC_{50}$ determination is in nanomoles per liter (nM).

By "Ki (nM)" is meant the equilibrium inhibitor dissociation constant representing the molar concentration of a competing compound that binds to half the binding sites of a receptor at equilibrium in the absence of radioligand or other competitors. In general, the numeric value of the Ki is inversely correlated to the affinity of the compound for the receptor, such that if the Ki is low, the affinity is high. Ki may be determined using the equation of Cheng and Prusoff (Cheng Y., Prusoff W. H., *Biochem. Pharmacol.* 22: 3099-3108, 1973):

Ki may be expressed in terms of specific receptors (e.g., MC1-R, MC3-R, MC4-R or MC5-R) and specific ligands (e.g. α-MSH or NDP-α-MSH).

By "inhibition" is meant the percent attenuation, or decrease in receptor binding, in a competitive inhibition assay compared to a known standard. Thus, by "inhibition at 1 μM (NDP-α-MSH)" is meant the percent decrease in binding of NDP-α-MSH by addition of a determined amount of the compound to be tested, such as 1 μM of a test compound, such as under the assay conditions hereafter described. By way of example, a test compound that does not inhibit binding of NDP-α-MSH has a 0% inhibition, and a test compound that completely inhibits binding of NDP-α-MSH has a 100% inhibition. Typically, as described hereafter, a radio assay is used for competitive inhibition testing, such as with $I^{125}$-labeled NDP-α-MSH, or a lanthanide chelate fluorescent assay, such as with Eu-NDP-α-MSH. However, other methods of testing competitive inhibition are known, including use of label or tag systems other than radioisotopes, and in general any method known in the art for testing competitive inhibition may be employed in this invention. It may thus be seen that "inhibition" is one measure to determine whether a test compound attenuates binding of α-MSH to melanocortin receptors.

By "binding affinity" is meant the ability of a compound or drug to bind to its biological target, expressed herein as Ki (nM).

By "intrinsic activity" is meant the maximal stimulation (functional activity) achievable by a compound in a specified melanocortin receptor expressing cell system, such as the maximal stimulation of adenylyl cyclase. The maximal stimulation achieved by α-MSH or NDP-α-MSH is designated as an intrinsic activity of 1.0 (or 100%) and a compound capable of stimulating half the maximal activity that of α-MSH or NDP-α-MSH is designated as having an intrinsic activity of 0.5 (or 50%). A compound of this invention that under assay conditions described herein has an intrinsic activity of 0.7 (70%) or higher is classified as an agonist, a compound with intrinsic activity between 0.1 (10%) and 0.7 (70%) is classified as a partial agonist, and a compound with intrinsic activity below 0.1 (10%) is classified as inactive or having no intrinsic activity. In one aspect, the cyclic peptides of the present invention may generally be characterized as a partial agonist at MC4-R with respect to α-MSH or NDP-α-MSH.

In general, "functional activity" is a measure of the signaling of a receptor, or measure of a change in receptor-associated signaling, such as a melanocortin receptor, and in particular MC4-R or hMC4-R, upon activation by a compound. Melanocortin receptors initiate signal transduction through activation of heterotrimeric G proteins. In one aspect,

melanocortin receptors signal through $G\alpha_s$, which catalyzes production of cAMP by adenylyl cyclase. Thus determination of stimulation of adenylyl cyclase, such as determination of maximal stimulation of adenylyl cyclase, is one measure of functional activity, and is the primary measure exemplified herein. However, it is to be understood that alternative measures of functional activity may be employed in the practice of this invention, and are specifically contemplated and included within the scope of this invention. Thus, in one example intracellular free calcium may be measured, such as reported by and using the methods disclosed in Mountjoy K.G. et al., Melanocortin receptor-mediated mobilization of intracellular free calcium in HEK293 cells. *Physiol Genomics* 5:11-19, 2001, or Kassack M.U. et al., Functional screening of G protein-coupled receptors by measuring intracellular calcium with a fluorescence microplate reader. *Biomol Screening* 7:233-246, 2002. It is also possible to measure activation by measurement of the production of inositol triphosphate or diacylglycerol from phosphatidylinositol 4,5-biphosphate, such as by use of radioassays. Yet another measure of functional activity is receptor internalization, resulting from activation of regulatory pathways, such as using the methods disclosed in Nickolls S.A. et al., Functional selectivity of melanocortin 4 receptor peptide and nonpeptide agonists: evidence for ligand specific conformational states. *J Pharm Exper Therapeutics* 313:1281-1288, 2005. Yet another measure of functional activity is the exchange, and exchange rate, of nucleotides associated with activation of a G protein receptor, such as the exchange of GDP (guanosine diphosphate) for GTP (guanosine triphosphase) on the G protein α subunit, which may be measured by any number of means, including a radioassay using guanosine 5′-(γ-[$^{35}$S]thio)-triphosphate, as disclosed in Manning D.R., Measures of efficacy using G proteins as endpoints: differential engagement of G proteins through single receptors. *Mol Pharmacol* 62:451-452, 2002. Various gene-based assays have been developed for measuring activation of G-coupled proteins, such as those disclosed in Chen W. et al., A colorimetric assay from measuring activation of Gs- and Gq-coupled signaling pathways. *Anal Biochem* 226:349-354, 1995; Kent T.C. et al., Development of a generic dual-reporter gene assay for screening G-protein-coupled receptors. *Biomol Screening*, 5:437-446, 2005; or Kotarsky K. et al., Improved receptor gene assays used to identify ligands acting on orphan seven-transmembrane receptors. *Pharmacology & Toxicology* 93:249-258, 2003. The colorimetric assay of Chen et al. has been adapted for use in measuring

melanocortin receptor activation, as disclosed in Hruby V.J. et al., Cyclic lactam α-melanocortin analogues of Ac-Nle$^4$-cyclo[Asp$^5$,D-Phe$^7$,Lys$^{10}$] α-melanocyte-stimulating hormone-(4-10)-$NH_2$ with bulky aromatic amino acids at position 7 shows high antagonist potency and selectivity at specific melanocortin receptors. *J Med Chem* 38:3454-3461, 1995. In general, functional activity may be measured by any method, including methods of determining activation and/or signaling of a G-coupled receptor, and further including methods which may be hereafter developed or reported. The terms "treat," "treating" and "treatment," as used herein, contemplate an action that occurs while a patient is suffering from the specified disease, disorder and/or condition, which reduces the severity of the disease, disorder and/or condition. Moreover, the terms "treat," "treating" and "treatment," as used herein are intended to embrace therapeutic (curative), prophylactic (preventing), controlling and palliative treatment of the indicated diseases, disorders and/or conditions.

As used herein, the term "pharmacologically effective amount" (including "therapeutically effective amount") means an amount of a peptide according to the invention that is sufficient to induce a desired therapeutic or biological effect.

As used herein, the term "therapeutically effective amount" means the amount of a peptide of the invention that will elicit a biological or medical response in the mammal that is being treated by a medical doctor or other clinician.

As used herein, the term "prophylactically effective" or "preventive" means the amount of a peptide of the invention that will prevent or inhibit affliction or mitigate affliction of a mammal with a medical condition that a medical doctor or other clinician is trying to prevent, inhibit, or mitigate before a patient begins to suffer from the specified disease or disorder.

The term "diabetes" includes Type 1 Diabetes, which is insulin-dependent diabetes mellitus as diagnosed according to criteria published in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (*Diabetes Care*, Vol. 24, Supp. 1, January 2001) whereby fasting plasma glucose level is greater than or equal to 126 milligrams per deciliter and for which the primary cause is pancreatic beta cell destruction, Type 2 Diabetes, which is non-insulin-dependent diabetes mellitus as diagnosed according to criteria published in the Report of the Expert Committee on the

Diagnosis and Classification of Diabetes Mellitus whereby fasting plasma glucose level is greater than or equal to 126 milligrams per deciliter, and latent autoimmune diabetes mellitus of adults (LADA).

The term "metabolic syndrome" refers to metabolic disorders, particularly glucose and lipid regulatory disorders, including insulin resistance and defective secretion of insulin by pancreatic beta cells, and may further include conditions and states such as abdominal obesity, dyslipidemia, hypertension, glucose intolerance or a prothrombitic state, and which may further result in disorders such as hyperlipidemia, obesity, diabetes, insulin resistance, glucose intolerance, hyperglycemia, and hypertension.

2.0 Clinical Indications and Utility.

The compositions and methods disclosed herein can be used for both medical applications and animal husbandry or veterinary applications. Typically, the methods are used in humans, but may also be used in other mammals. The term "patient" is intended to denote a mammalian individual, and is so used throughout the specification and in the claims. The primary applications of the present invention involve human patients, but the present invention may be applied to laboratory, farm, zoo, wildlife, pet, sport or other animals. Clinical indications and specific utilities include the following:

2.1 Obesity and Related Metabolic Syndrome.

Peptides of Formula (I), and in particular Formula (II) or (III), have been found to be ligands of the MC4 receptor. In particular, peptides of Formula (I) are believed to be useful in treating diseases, disorders and/or conditions responsive to modulation of the MC4-R function, more particularly activation of the MC4-R, i.e. diseases, disorders and/or conditions which would benefit from agonism (including full or partial agonism) at the MC4-R, including energy homeostasis and metabolism related (such as diabetes, in particular type 2 diabetes; dyslipidemia; fatty liver; hypercholesterolemia; hypertriglyceridemia; hyperuricacidemia; impaired glucose tolerance; impaired fasting glucos; insulin resistance syndrome; and metabolic syndrome), food intake related (such as hyperphagia; binge eating; bulimia; and compulsive eating) and/or energy balance and body weight related diseases, disorders and/or conditions, more particularly such diseases, disorders and conditions characterized by excess body weight and/or excess food intake.

Peptides of Formula (I), and in particular Formula (II) or (III), are particularly believed to be useful for treatment of body weight related diseases, disorders and/or conditions characterized by excess body weight, including obesity and overweight (by promotion of weight loss, maintenance of weight loss, and/or prevention of weight gain, including medication-induced weight gain or weight gain subsequent to cessation of smoking), and diseases, disorders and/or conditions associated with obesity and/or overweight, such as insulin resistance; impaired glucose tolerance; type 2 diabetes; metabolic syndrome; dyslipidemia (including hyperlipidemia); hypertension; heart disorders (e.g. coronary heart disease, myocardial infarction); cardiovascular disorders; non-alcoholic fatty liver disease (including non-alcoholic steatohepatitis); joint disorders (including secondary osteoarthritis); gastroesophageal reflux; sleep apnea; atherosclerosis; stroke; macro and micro vascular diseases; steatosis (e.g. in the liver); gall stones; and gallbladder disorders.

Peptides of Formula (I), and in particular Formula (II) or (III), are particularly believed to be useful for treatment of obesity and type 2 diabetes, more specifically obesity.

It will be understood that there are medically accepted definitions of obesity and overweight. A patient may be identified by, for example, measuring body mass index (BMI), which is calculated by dividing weight in kilograms by height in meters squared, and comparing the result with the definitions. The recommended classifications for BMI in humans, adopted by the Expert Panel on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults, and endorsed by leading organizations of health professionals, are as follows: underweight < 18.5 $kg/m^2$, normal weight 18.5-24.9 $kg/m^2$, overweight 25-29.9 $kg/m_2$, obesity (class 1) 30-34.9 $kg/m^2$, obesity (class 2) 35-39.9 $kg/m^2$, extreme obesity (class 3) $\geq$ 40 $kg/m^2$ (Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The North American Association for the Study of Obesity (NAASO) and the National Heart, Lung and Blood Institute (NHLBI) 2000). Modifications of this classification may be used for specific ethnic groups and for children. Another alternative for assessing overweight and obesity is by measuring waist circumference. There are several proposed classifications and differences in the cutoffs based on ethnic group. For instance, according to the

classification from the International Diabetes Federation, men having waist circumferences above 94 cm (cut off for europids) and women having waist circumferences above 80 cm (cut off for europids) are at higher risk of diabetes, dyslipidemia, hypertension and cardiovascular diseases because of excess abdominal fat. Another classification is based on the recommendation from the Adult Treatment Panel III where the recommended cut-offs are 102 cm for men and 88 cm for women. However, the peptides of Formula (I) may also be used for reduction of self-diagnosed overweight and for decreasing the risk of becoming obese due to life style, genetic considerations, heredity and/or other factors.

It is believed that peptides of Formula (I), and in particular Formula (II) or (III), upon administration to an animal, including man, will reduce food intake, body weight and/or body weight gain in that animal.

Without being bound by any theory, it is believed that peptides of Formula (I), and in particular Formula (II) or (III), act by modulating appetite and/or satiety, increasing metabolic rate, reducing intake of and/or craving for fat and/or carbohydrates.

Without being bound by any theory, it is also believed that peptides of Formula (I), and in particular Formula (II) or (III), act by enhancing glucose tolerance and/or decreasing insulin resistance. It is therefore believed that peptides of Formula (I) can be useful also for treatment of type 2 diabetes in underweight and normal weight individuals as well as in overweight and obese individuals.

Peptides of the invention might also be useful for (i) prevention of organ or tissue damage caused by hypoperfusion due to vessel occlusion (e.g. caused by thrombosis), haemorrhage, trauma, surgery, haemorrhagic shock, cardiogenic shock, toxic shock or septic shock or (iii) treatment of male and female sexual dysfunctions, such as male erectile dysfunction or female sexual arousal dysfunction.

According to a further aspect of the invention, there is provided a peptide of Formula (I), and in particular Formula (II) or (III), as previously defined for use as a medicament.

In another aspect, the invention provides the use of a peptide of Formula (I), and in particular Formula (II) or (III), for treatment of diseases, disorders and/or conditions responsive to modulation of the MC4-R, such as diseases, disorders and/or conditions responsive to activation of the MC4-R, in particular energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related

diseases, disorders and/or conditions, including obesity, overweight and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome.

In a further aspect, the invention provides the use of a peptide of Formula (I), and in particular Formula (II) or (III), in the preparation of a medicament for treatment of diseases, disorders and/or conditions responsive to modulation of the MC4-R, such as activation of the MC4-R, in particular energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity, overweight and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome.

Peptides of the invention are advantageously more selective (i.e. higher affinity and/or higher specificity) for MC4-R and/or MC3-R than for MC1-R, MC2-R and MC5-R, in particular MC1-R. In particular, peptides of the invention are advantageously more selective for MC4-R than for any of MC3-R and MC1-R. Peptides of the invention are suitably at least 3-fold, in particular 10-fold, more particularly 30-fold, more selective for MC4-R than for any of MC1-R, MC2-R, MC3-R and MC5-R. Some peptides of the invention are even more than 100-fold, such as even about 150-fold, more selective for MC4-R than MC1-R as determined in the receptor binding assay described in 7.1. It is noted that the selectivity profile may affect in vivo safety and side effects obtained upon administration of the peptides.

Upon treatment of energy homeostasis and metabolism related, food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, it is desirable to reduce or eliminate unwanted side-effects that may result from MC4-R activation, such as sexual side-effects, including penile erection, and blood pressure effects.

Peptides of the invention are believed to be useful for treatment of energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity, overweight and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome, without causing substantial adverse cardiovascular effects, including a substantial increase in blood pressure.

Peptides of the invention are believed to be useful for treatment of energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity, overweight and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome, without causing substantial unwanted sexual effects resulting from MC4-R activation, such as penile erection.

It is believed that peptides of Formula I, and in particular Formula (II) or (III), possess a satisfactory pharmacological profile and promising biopharmaceutical properties, such as toxicological profile, metabolism and pharmacokinetic properties, solubility, and permeability. It will be understood that determination of appropriate biopharmaceutical properties is within the knowledge of a person skilled in the art.

3.0 Combination Therapy for Certain Indications.

The peptides, compositions and methods of the present invention may be used for treatment of any of the foregoing diseases, indications, conditions or syndromes, or any disease, indication, condition or syndrome which is melanocortin receptor mediated, by administration in combination with one or more other pharmaceutically active compounds. Such combination administration may be by means of a single dosage form which includes both a peptide of the present invention and one more other pharmaceutically active compound, such single dosage form including a tablet, capsule, spray, inhalation powder, injectable liquid or the like. Alternatively, combination administration may be by means of administration of two different dosage forms, with one dosage form containing a peptide of the present invention, and the other dosage form including another pharmaceutically active compound. In this instance, the dosage forms may be the same or different. Without meaning to limit combination therapies, the following exemplifies certain combination therapies which may be employed.

3.1 Combination Therapy for Obesity and Related Metabolic Syndrome.

One or more peptides of the invention may be combined with one or more other pharmacologically active agent(s) that is (are) useful in the treatment of various weight and feeding-related disorders, such as obesity and/or overweight, in particular other anti-obesity drugs that affect energy expenditure, glycolysis, gluconeogenesis, glucogenolysis, lipolysis, lipogenesis, fat absorption, fat storage, fat excretion, hunger and/or satiety and/or craving mechanisms, appetite/motivation, food intake, or gastrointestinal motility. Drugs

that reduce energy intake include, in part, various pharmacological agents, referred to as anorectic drugs, which are used as adjuncts to behavioral therapy in weight reduction programs.

Generally, a total dosage of the below-described obesity control agents or medications, when used in combination with one or more peptides of the present invention can range from 0.1 to 3,000 mg/day, preferably from about 1 to 1,000 mg/day and more preferably from about 1 to 200 mg/day in single or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on such factors as the potency of the compound administered, the age, weight, condition and response of the patient.

One or more peptides of the invention may be combined with one or more other pharmacologically active agent(s) that is (are) useful in the treatment of diabetes, such as other anti-diabetic drugs.

One or more peptides of the invention may in addition or alternatively further be combined with one or more other pharmacologically active agent(s) that is (are) useful in the treatment of diseases, disorders and/or conditions associated with obesity and/or overweight, such as insulin resistance; impaired glucose tolerance; type 2 diabetes; metabolic syndrome; dyslipidemia (including hyperlipidemia); hypertension; heart disorders (e.g. coronary heart disease, myocardial infarction); cardiovascular disorders; non-alcoholic fatty liver disease (including non-alcoholic steatohepatitis); joint disorders (including secondary osteoarthritis); gastroesophageal reflux; sleep apnea; atherosclerosis; stroke; macro and micro vascular diseases; steatosis (e.g. in the liver); gall stones; and gallbladder disorders.

According to a further aspect of the invention there is provided a combination treatment comprising the administration of a pharmacologically effective amount of a peptide according to the invention, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

- insulin and insulin analogues;

- insulin secretagogues, including sulphonylureas (e.g. glipizide) and prandial glucose regulators (sometimes called "short-acting secretagogues"), such as meglitinides (e.g. repaglinide and nateglinide);
- agents that improve incretin action, for example dipeptidyl peptidase IV (DPP-4) inhibitors (e.g. vildagliptin, saxagliptin, and sitagliptin), and glucagon-like peptide-1 (GLP-1) agonists (e.g. exenatide);
- insulin sensitising agents including peroxisome proliferator activated receptor gamma (PPARγ) agonists, such as thiazolidinediones (e.g. pioglitazone and rosiglitazone), and agents with any combination of PPAR alpha, gamma and delta activity;
- agents that modulate hepatic glucose balance, for example biguanides (e.g. metformin), fructose 1,6-bisphosphatase inhibitors, glycogen phopsphorylase inhibitors, glycogen synthase kinase inhibitors, and glucokinase activators;
- agents designed to reduce/slow the absorption of glucose from the intestine, such as alpha-glucosidase inhibitors (e.g. miglitol and acarbose);
- agents which antagonise the actions of or reduce secretion of glucagon, such as amylin analogues (e.g. pramlintide);
- agents that prevent the reabsorption of glucose by the kidney, such as sodium-dependent glucose transporter 2 (SGLT-2) inhibitors (e.g. dapagliflozin);
- agents designed to treat the complications of prolonged hyperglycaemia, such as aldose reductase inhibitors (e.g. epalrestat and ranirestat); and agents used to treat complications related to micro-angiopathies;
- anti-dyslipidemia agents, such as HMG-CoA reductase inhibitors (statins, e.g. rosuvastatin) and other cholesterol-lowering agents; PPARα agonists (fibrates, e.g. gemfibrozil and fenofibrate); bile acid sequestrants (e.g.cholestyramine); cholesterol absorption inhibitors (e.g. plant sterols (i.e. phytosterols), synthetic inhibitors); cholesteryl ester transfer protein (CETP) inhibitors; inhibitors of the ileal bile acid transport system (IBAT inhibitors); bile acid binding resins; nicotinic acid (niacin) and analogues thereof; anti-oxidants, such as probucol; and omega-3 fatty acids;

- antihypertensive agents, including adrenergic receptor antagonists, such as beta blockers (e.g. atenolol), alpha blockers (e.g. doxazosin), and mixed alpha/beta blockers (e.g. labetalol); adrenergic receptor agonists, including alpha-2 agonists (e.g. clonidine); angiotensin converting enzyme (ACE) inhibitors (e.g. lisinopril), calcium channel blockers, such as dihydropyridines (e.g. nifedipine), phenylalkylamines (e.g. verapamil), and benzothiazepines (e.g. diltiazem); angiotensin II receptor antagonists (e.g. candesartan); aldosterone receptor antagonists (e.g. eplerenone); centrally acting adrenergic drugs, such as central alpha agonists (e.g. clonidine); and diuretic agents (e.g. furosemide);
- haemostasis modulators, including antithrombotics, such as activators of fibrinolysis; thrombin antagonists; factor VIIa inhibitors; anticoagulants, such as vitamin K antagonists (e.g. warfarin), heparin and low molecular weight analogues thereof, factor Xa inhibitors, and direct thrombin inhibitors (e.g. argatroban); antiplatelet agents, such as cyclooxygenase inhibitors (e.g. aspirin), adenosine diphosphate (ADP) receptor inhibitors (e.g. clopidogrel), phosphodiesterase inhibitors (e.g. cilostazol), glycoprotein IIB/IIA inhibitors (e.g. tirofiban), and adenosine reuptake inhibitors (e.g. dipyridamole);
- anti-obesity agents, such as appetite suppressant (e.g. ephedrine), including noradrenergic agents (e.g. phentermine) and serotonergic agents (e.g. sibutramine), pancreatic lipase inhibitors (e.g. orlistat), microsomal transfer protein (MTP) modulators, diacyl glycerolacyltransferase (DGAT) inhibitors, and cannabinoid (CB1) receptor antagonists (e.g. rimonabant);
- feeding behavior modifying agents, such as orexin receptor modulators and melanin-concentrating hormone (MCH) modulators;
- glucagon like peptide-1 (GLP-1) receptor modulators;
- neuropeptideY (NPY)/NPY receptor modulators;
- pyruvate dehydrogenase kinase (PDK) modulators;
- serotonin receptor modulators;
- leptin/leptin receptor modulators;
- ghrelin/ghrelin receptor modulators; or

- monoamine transmission-modulating agents, such as selective serotonin reuptake inhibitors (SSRI) (e.g. fluoxetine), noradrenaline reuptake inhibitors (NARI), noradrenaline-serotonin reuptake inhibitors (SNRI), triple monoamine reuptake blockers (e.g. tesofensine), and monoamine oxidase inhibitors (MAOI) (e.g. toloxatone and amiflamine),

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable carrier to a mammal, such as man, in need of such therapeutic treatment.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of a pharmacologically effective amount of a compound according to the invention, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable carrier, with the simultaneous, sequential or separate administration of very low calorie diets (VLCD) or low-calorie diets (LCD).

4.0 Methods of Making.

In general, the peptides of the present invention may be synthesized by solid-phase synthesis and purified according to methods known in the art. Any of a number of well-known procedures utilizing a variety of resins and reagents may be used to prepare the peptides of the present invention.

The cyclic peptides of the present invention may be readily synthesized by known conventional procedures for the formation of a peptide linkage between amino acids. Such conventional procedures include, for example, any solution phase procedure permitting a condensation between the free alpha amino group of an amino acid or residue thereof having its carboxyl group and other reactive groups protected and the free primary carboxyl group of another amino acid or residue thereof having its amino group or other reactive groups protected. In a preferred conventional procedure, the cyclic peptides of the present invention may be synthesized by solid-phase synthesis and purified according to methods known in the art. Any of a number of well-known procedures utilizing a variety of resins and reagents may be used to prepare the peptides of the present invention.

The process for synthesizing the cyclic peptides may be carried out by a procedure whereby each amino acid in the desired sequence is added one at a time in succession to another amino acid or residue thereof or by a procedure whereby peptide fragments with the desired amino acid sequence are first synthesized conventionally and then condensed to provide the desired peptide. The resulting peptide is then cyclized to yield a cyclic peptide of the invention.

Solid phase peptide synthesis methods are well known and practiced in the art. In such methods the synthesis of peptides of the invention can be carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain according to the general principles of solid phase methods. These methods are disclosed in numerous references, including Merrifield, R.B., Solid phase synthesis (Nobel lecture). *Angew Chem* 24:799-810 (1985) and Barany et al., The Peptides, Analysis, Synthesis and Biology, Vol. 2, Gross, E. and Meienhofer, J., Eds. Academic Press 1-284 (1980).

In chemical syntheses of peptides, reactive side chain groups of the various amino acid residues are protected with suitable protecting groups, which prevent a chemical reaction from occurring at that site until the protecting group is removed. Also common is the protection of the alpha amino group of an amino acid residue or fragment while that entity reacts at the carboxyl group, followed by the selective removal of the alpha amino protecting group to allow a subsequent reaction to take place at that site. Specific protecting groups have been disclosed and are known in solid phase synthesis methods and solution phase synthesis methods.

Alpha amino groups may be protected by a suitable protecting group, including a urethane-type protecting group, such as benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and p-methoxybenzyloxycarbonyl (Moz) and aliphatic urethane-type protecting groups, such as t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and allyloxycarbonyl (Alloc). Fmoc are preferred for alpha amino protection.

Guanidino groups may be protected by a suitable protecting group, such as nitro, p-toluenesulfonyl (Tos), Z, pentamethylchromanesulfonyl (Pmc), adamantyloxycarbonyl,

pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) and Boc. Pbf and Pmc are preferred protecting groups for Arg.

The peptides of the invention described herein were prepared using solid phase synthesis, such as by means of a Symphony Multiplex Peptide Synthesizer (Rainin Instrument Company/Protein Technologies Inc) automated peptide synthesizer, using programming modules as provided by the manufacturer and following the protocols set forth in the manufacturer's manual.

Solid phase synthesis is commenced from the C-terminal end of the peptide by coupling a protected alpha amino acid to a suitable resin. Such starting material is prepared by attaching an alpha amino-protected amino acid by an amide linkage to a 4-(2', 4'-dimethoxylphenyl-aminomethyl-phenoxy (Rink Amide) resin, a 4-(2', 4'-dimethoxylphenyl-aminomethyl)-phenoxyacetamido-norleucyl-MBHA resin, an amino-xanthen-3-yloxy-merifiel resin (Sieber Amide) resin, or by an ester linkage to a p-benzyloxybenzyl alcohol (Wang) resin, a 2-chlorotrityl chloride resin or by other means well known in the art. Fmoc-Linker-BHA resin supports are commercially available and generally used when feasible. The resins are carried through repetitive cycles as necessary to add amino acids sequentially. The alpha amino Fmoc protecting groups are removed under basic conditions. Piperidine, piperazine, diethylamine, or morpholine (20-40% v/v) in N,N-dimethylformamide (DMF) may be used for this purpose.

Following removal of the alpha amino protecting group, the subsequent protected amino acids are coupled stepwise in the desired order to obtain an intermediate, protected peptide-resin. The activating reagents used for coupling of the amino acids in the solid phase synthesis of the peptides are well known in the art. After the peptide is synthesized, if desired, the orthogonally protected side chain protecting groups may be removed using methods well known in the art for further derivatization of the peptide.

Typically, orthogonal protecting groups are used as appropriate. For example, the peptides of the invention contain multiple amino acids with an amino group-containing side chain. In one aspect, an Allyl-Alloc protection scheme is employed with the amino acids forming a lactam bridge through their side chains, and orthogonal protecting groups, cleavable under different reactive conditions, use for other amino acids with amino group-containing side chains. Thus, for example, Fmoc-Orn(Alloc)-OH and Fmoc-Glu(OAll)-OH amino acids (Glu(OAll) refers to glutamic acid 5-allyl ester) can be employed for the

positions forming a lactam bridge upon cyclization, while other amino acids with amino group-containing side chains have a different and orthogonal protecting group, such as with Fmoc-Arg(Pbf)-OH, Fmoc-Lys(Pbf)-OH, Fmoc-Dab(Pbf)-OH or the like. Other protecting groups may be similarly employed; by way of example and not limitation, Mtt/OPp (4-methyltrityl/ 2-phenylisopropyl) can be employed with the side chains forming a lactam bridge upon cyclization, with orthogonal protecting groups being utilized for other positions that are not cleavable using conditions suitable for cleavage of Mtt/OPp.

Reactive groups in a peptide can be selectively modified, either during solid phase synthesis or after removal from the resin. For example, peptides can be modified to obtain N-terminus modifications, such as acetylation, while on resin, or may be removed from the resin by use of a cleaving reagent and then modified. Similarly, methods for modifying side chains of amino acids are well known to those skilled in the art of peptide synthesis. The choice of modifications made to reactive groups present on the peptide will be determined, in part, by the characteristics that are desired in the peptide.

In the peptides of the present invention, in one embodiment the N-terminus group is modified by introduction of an N-acetyl group. In one aspect, a method is employed wherein after removal of the protecting group at the N-terminal, the resin-bound peptide is reacted with acetic anhydride in DMF in the presence of an organic base, such aspyridine. Other methods of N-terminus acetylation are known in the art, including solution phase acetylation, and may be employed.

The peptide can, in one embodiment, be cyclized prior to cleavage from the peptide resin. For cyclization through reactive side chain moieties, the desired side chains are deprotected, and the peptide suspended in a suitable solvent and a cyclic coupling agent added. Suitable solvents include, for example DMF, dichloromethane (DCM) or 1-methyl-2-pyrrolidone (NMP). Suitable cyclic coupling reagents include, for example, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP), 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU), 2-(2-oxo-1(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or N,N'-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCCI/HOBt). Coupling is

conventionally initiated by use of a suitable base, such as N,N-diisopropylethylamine (DIPEA), sym-collidine or N-methylmorpholine (NMM).

The cyclized peptides can then be cleaved from solid phase, using any suitable reagent, such as ethylamine in DCM or various combinations of agents, such as trifluoroacetic acid (TFA), tri-isopropylsilane (TIS), dimethoxybenezene (DMB), water and the like. The resulting crude peptide is dried and remaining amino acid side chain protecting groups, if any, are cleaved using any suitable reagent, such as TFA in the presence of water, TIS, 2-mercaptopethane (ME), and/or 1,2-ethanedithiol (EDT). The final product is precipitated by adding cold ether and collected by filtration. Final purification is by reverse phase high performance liquid chromatography (RP-HPLC), using a suitable column, such as a $C_{18}$ column, or other methods of separation or purification, such as methods based on the size or charge of the peptide, can also be employed. Once purified, the peptide can be characterized by any number of methods, such as high performance liquid chromatography (HPLC), amino acid analysis, mass spectrometry, and the like.

For peptides of the present invention which have a C-terminus substituted amide derivative or N-alkyl group, synthesis may proceed by solid phase synthesis commenced from the C-terminal end of the peptide by coupling a protected alpha amino acid to a suitable resin. Such methods for preparing substituted amide derivatives on solid-phase have been described in the art. See, for example, Barn D.R. et al., Synthesis of an array of amides by aluminum chloride assisted cleavage on resin bound esters. *Tetrahedron Letters*, 37:3213-3216 (1996); DeGrado W.F. and Kaiser E.T., Solid-phase synthesis of protected peptides on a polymer bound oxime: Preparation of segments comprising the sequences of a cytotoxic 26-peptide analogue. *J. Org. Chem.*, 47:3258-3261 (1982). Such a starting material can be prepared by attaching an alpha amino-protected amino acid by an ester linkage to a p-benzyloxybenzyl alcohol (Wang) resin or an by amide linkage to a 4-(2', 4'-dimethoxylphenyl-aminomethyl-phenoxy (Rink Amide) resin by well known means. The peptide chain is grown with the desired sequence of amino acids. Before cleavage, the peptide is cyclized on the solid phase. Peptides employing a p-benzyloxybenzyl alcohol (Wang) resin may be cleaved from resin by aluminum chloride in DCM, and peptides employing a Rink Amide resin may be cleaved by mixture of TFA, TIS and water.

While synthesis has been described primarily with reference to solid phase Fmoc chemistry, it is to be understood that other chemistries and synthetic methods may be employed to make the cyclic peptides of the invention, such as by way of example and not limitation, methods employing Boc chemistry, solution chemistry, and other chemistries and synthetic methods.

5.1 Salt Form of Cyclic Peptides of the Present Invention.

It shall be understood that as used herein all references to peptides according to the invention, including a specific chemical formula or name, are intended to include all pharmaceutically acceptable salts, solvates, hydrates, polymorphs, prodrugs, metabolites, stereoisomers, and tautomeric isomers thereof.

Cyclic peptides of the present invention may be in the form of any pharmaceutically acceptable salt. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids (see "Handbook of Pharmaceutical Salts: Properties, Selection and Use", P. H. Stahl, P. G. Wermuth, IUPAC, Wiley-VCH, 2002). Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. When cyclic peptide of the present invention is basic, acid addition salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, carboxylic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric,

tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Acid addition salts of peptides of the present invention are prepared in a suitable solvent for the peptide and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic (TFA), citric, tartaric, maleic, succinic or methanesulfonic acid. The acetate, ammonium acetate and TFA acid salt forms are especially useful.

Where peptides of the present invention include an acidic moiety, suitable pharmaceutically acceptable salts may include alkali metal salts, such as sodium or potassium salts, or alkaline earth metal salts, such as calcium or magnesium salts.It is also to be understood that certain peptides of the Formula (I) can exist in solvated forms, including solvates of the free peptide or solvates of a salt of the compound, as well as unsolvated forms. The term "solvate" is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term "hydrate" is employed when said solvent is water.It is to be understood that all polymorphs, including mixtures of different polymorphs, are included within the scope of the claimed peptides.

5.2 Pharmaceutical Compositions.

The invention provides a pharmaceutical composition that includes one or more cyclic peptides of the present invention and a pharmaceutically acceptable carrier. When formulated with a pharmaceutically acceptable carrier, the compound of the invention may be present in the pharmaceutical composition in a concentration from 0.1 to 99.5%, such as from 0.5 to 95%, by weight of the total composition. The choice of carrier is within the knowledge of a person skilled in the art and depends on, for instance, the mode of administration, the dosage form, and the physical properties of the active compound, such as solubility and stability. The term "carrier" as used herein relates to a therapeutically inactive ingredient. The dosage form may be a solid, semi-solid or liquid system. The formulation may be an immediate and/or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted and programmed release formulation.

The carrier may be a liquid formulation, and is preferably a buffered, isotonic, aqueous solution. Pharmaceutically acceptable carriers also include excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like, as hereafter described.

The cyclic peptide compositions of the present invention may be formulated or compounded into pharmaceutical compositions that include at least one cyclic peptide of the present invention together with one or more pharmaceutically acceptable carriers, including excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like, as may be desired. Formulation excipients may include polyvinylpyrrolidone, gelatin, hydroxy propyl cellulose (HPC), acacia, polyethylene glycol, mannitol, sodium chloride and sodium citrate. For injection or other liquid administration formulations, water containing at least one or more buffering constituents is preferred, and stabilizing agents, preservatives and solubilizing agents may also be employed. For solid administration formulations, any of a variety of thickening, filler, bulking and carrier additives may be employed, such as starches, sugars, cellulose derivatives, fatty acids and the like. For topical administration formulations, any of a variety of creams, ointments, gels, lotions and the like may be employed. For most pharmaceutical formulations, non-active ingredients will constitute the greater part, by weight or volume, of the preparation. For pharmaceutical formulations, it is also contemplated that any of a variety of measured-release, slow-release or sustained-release formulations and additives may be employed, so that the dosage may be formulated so as to provide delivery of a peptide of the present invention over a period of time.

In general, the actual quantity of cyclic peptides of the present invention administered to a patient will vary between fairly wide ranges depending on the mode of administration, the formulation used, and the response desired.

In practical use, the cyclic peptides of the invention can be combined as the active ingredient in an admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, for example, oral, parenteral (including intravenous), urethral, vaginal, nasal, buccal, sublingual, or the like. In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating

agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets.

Because of their ease of administration, tablets and capsules represent an advantageous oral dosage unit form. If desired, tablets may be coated by standard aqueous or non-aqueous techniques. The amount of active peptide in such therapeutically useful compositions is such that an effective dosage will be obtained. In another dosage unit form, sublingual constructs may be employed, such as sheets, wafers, tablets or the like.

The tablets, pills, capsules, and the like may also contain a binder such as povidone, gum tragacanth, acacia, corn starch or gelatin; diluents; fillers such as microcrystalline cellulose; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch or alginic acid; preservatives; colorants; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be utilized as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

If formulated for oral delivery, the peptide is preferably formulated and made such that it is encased in an enteric protectant, more preferably such that it is not released until the tablet or capsule has transited the stomach, and optionally has further transited a portion of the small intestine. In the context of this application it will be understood that the term enteric coating or material refers to a coating or material that will pass through the stomach essentially intact but will disintegrate after passing through the stomach to release the active drug substance. Materials that may be used includes cellulose acetate phthalate, hydroxypropylmethyl-ethylcellulose succinate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, and methacrylic acid-methyl methacrylate copolymer. The enteric coating employed promotes dissolution of the dosage form primarily at a site outside the stomach, and may be selected such that the enteric coating dissolves at a pH of approximately at least 5.5, more preferable at a pH of from about 6.0 to about 8.0.

Any of a variety of permeation enhancers may be employed, to increase uptake in the intestines upon dissolution of the enteric coating. In one aspect, permeation enhancers

increase either paracellular or transcellular transport systems. Representative, non-limiting examples of such permeation enhancers include calcium chelators, bile salts (such as sodium cholate), and fatty acids. In some embodiments, peptides or polypeptides that act as substrates for intestinal proteases are further added.Cyclic peptides may also be administered parenterally. Solutions or suspensions of these active peptides may for instance be prepared in water mixed with for instance hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. These preparations may optionally contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that it may be administered by syringe. The form must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, a polyol, for example glycerol, propylene glycol or liquid polyethylene glycol, suitable mixtures thereof, and vegetable oils.

The cyclic peptides of the present invention may be therapeutically applied by means of nasal administration. By "nasal administration" is meant any form of intranasal administration of any of the cyclic peptides of the present invention. The peptides may be in an aqueous solution, such as a solution including saline, citrate or other common excipients or preservatives. The peptides may also be in a dry or powder formulation.

If in an aqueous solution, the cyclic peptides may be appropriately buffered by means of saline, acetate, phosphate, citrate, acetate or other buffering agents, which may be at any physiologically acceptable pH, such as from about pH 4 to about pH 7. A combination of buffering agents may also be employed, such as phosphate buffered saline, a saline and acetate buffer, and the like. In the case of saline, a 0.9% saline solution may be employed. In the case of acetate, phosphate, citrate, and the like, a 50 mM solution may be employed. In addition to buffering agents, a suitable preservative may be employed, to prevent or limit bacteria and other microbial growth. One such preservative that may be employed is 0.05% benzalkonium chloride.

In an alternative embodiment, cyclic peptides of the present invention may be administered directly into the lung. Intrapulmonary administration may be performed by means of a metered dose inhaler, a device allowing self-administration of a metered bolus of a peptide of the present invention when actuated by a patient during inspiration. Any of a variety of different techniques may be used to make dry powder microparticles, including but not limited to micro-milling, spray drying and a quick freeze aerosol followed by lyophilization.

The cyclic peptides of the present invention may be therapeutically administered by means of an injection of a sustained release formulation. In general, any of a number of injectable and biocrodible polymers may be employed in a sustained release injectable formulation. Alternatively other sustained release formulations may be employed, including formulations permitting subcutaneous injection, which other formulations may include one or more of nano/microspheres, liposomes, emulsions (such as water-in-oil emulsions), gels, insoluble salts or suspensions in oil The formulation may be such that an injection is required on a daily, weekly, monthly or other periodic basis, depending on the concentration and amount of cyclic peptide, the sustained release rate of the materials employed, and other factors known to those of skill in the art.

5.3 Routes of Administration.

If a composition including one or more peptides of the present invention is administered by injection, the injection may be intravenous, subcutaneous, intramuscular, intraperitoneal or other means known in the art.

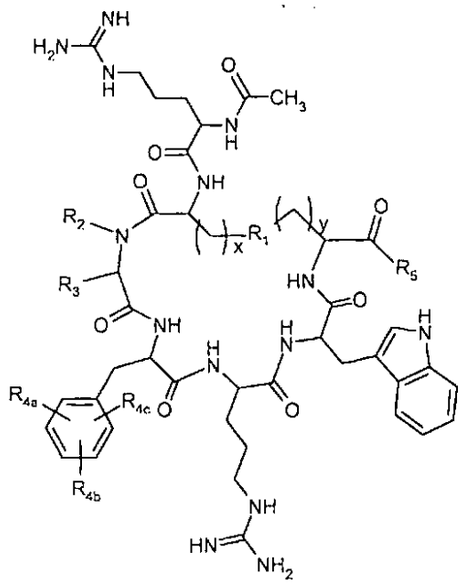
The peptides of the present invention may be formulated by any means known in the art, including but not limited to formulation as tablets, capsules, caplets, suspensions, powders, lyophilized preparations, suppositories, ocular drops, skin patches, oral soluble formulations, sprays, aerosols and the like, and may be mixed and formulated with buffers, binders, excipients, stabilizers, anti-oxidants and other agents known in the art. In general, any route of administration by which the peptides of invention are introduced across an epidermal layer of cells may be employed. Administration means may thus include administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration, urethral administration, vaginal administration, and the like.

5.4 Therapeutically Effective Amount.

In general, the actual quantity of cyclic peptide of the present invention administered to a patient will vary between fairly wide ranges depending upon the mode of administration, the patient (including weight, sex, health condition and diet), the formulation used, and the response desired. The dosage for treatment is administration, by any of the foregoing means or any other means known in the art, of an amount sufficient to bring about the desired therapeutic effect. The cyclic peptides of the present invention are highly active. For example, the cyclic peptide can be administered (as a single dose or in divided daily doses) at about 0.1, 0.5, 1, 5, 50, 100, 500, 1000 or 5000 μg/kg body weight, depending on the specific peptide selected, the desired therapeutic response, the route of administration, the formulation and other factors known to those of skill in the art.

6.0 Peptides of the Present Invention.

In one aspect, the present invention relates to a cyclic peptide of the structural Formula (I):



(I)

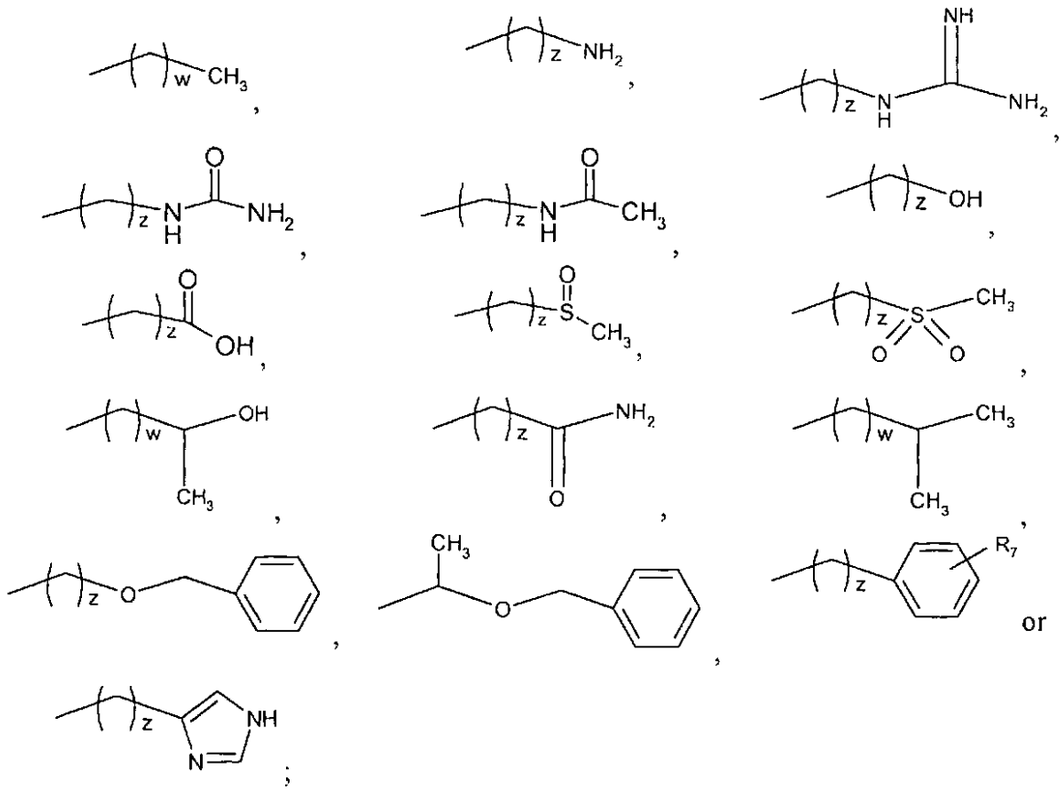
including all enantiomers, stereoisomers or diastereoisomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

$R_1$ is -NH-C(=O)- or -C(=O)-NH-;

$R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH;

$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from



or



;

$R_{4a}$, $R_{4b}$ and $R_{4c}$ are each independently selected from hydrogen, halo, ($C_1$-$C_{10}$)alkyl-halo, ($C_1$-$C_{10}$)alkyl-dihalo, ($C_1$-$C_{10}$)alkyl-trihalo, ($C_1$-$C_{10}$)alkyl, ($C_1$-$C_{10}$)alkoxy, ($C_1$-$C_{10}$)alkylthio, aryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carboxy, or alkoxy-carbonyl, on the proviso that at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is not hydrogen;

$R_5$ is -OH or $-N(R_{6a})(R_{6b})$;

$R_{6a}$ and $R_{6b}$ are each independently H or a $C_1$ to $C_4$ linear, branched or cyclic alkyl chain;

$R_7$ is -H or $-C(=O)-NH_2$;

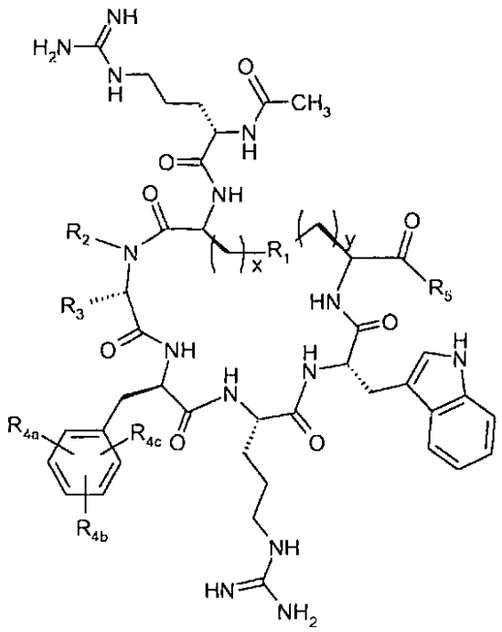
w is in each instance independently 0 to 5;

x is 1 to 5;

y is 1 to 5; and

z is in each instance independently 1 to 5.

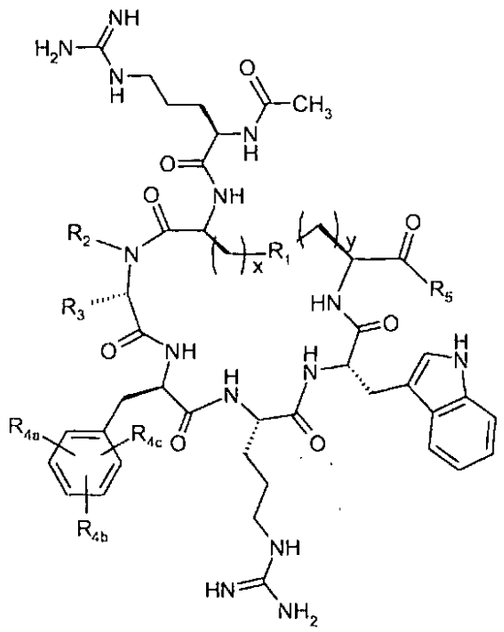
In another aspect, the present invention relates to a cyclic peptide of Formula (I) which is of formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a cyclic peptide of Formula (I) which is of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a cyclic heptapeptide which contains a core sequence derived from His-Phe-Arg-Trp within the cyclic portion, and where the amino

acid in the first position is Arg and is outside the cyclic portion. Without being bound by any theory, the Arg residue is believed to largely contribute to the low activity at MC1-R.

Further, the core sequence in the peptides of Formula I includes a substituted D-Phe. Without being bound by any theory, it is believed that the intrinsic activity may be lowered while substantially maintaining potency by using substituted D-Phe in peptides in accordance with the invention. The peptide called Ref Ex 1 (including unsubstituted D-Phe) in Table 1 can be compared with one or more of Examples 1-5, 9-11, 17, 26 and 27. It may be noted that Table 1 includes mean values.

**Table 1**

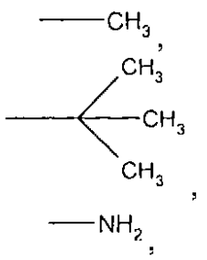
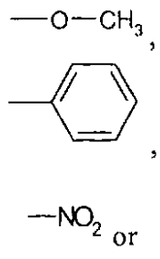
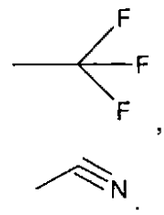
| | | | 0.1 ng/mL Doxycycline | |
|---|---|---|---|---|
| | | $K_i$ (nM) | $EC_{50}$ (nM) | Intrinsic activity (%) |
| Ref Ex 1 | Ac-Arg-cyclo(Glu-Dab-D-Phe-Arg-Trp-Orn)-$NH_2$ | 0.65 | 0.33 | 94 |
| Ref Ex 2 | Ac-Arg-cyclo(Glu-Dab-D-Phe-Arg-Trp-Orn)-OH | 8 | 3.0 | 92 |

In a further embodiment of the invention, there are provided peptides according to Formula (I), and in particular Formula (II) or (III), wherein one or more of $R_{4a}$, $R_{4b}$ and $R_{4c}$ are each independently selected from hydrogen, halo, ($C_1$-$C_{10}$)alkyl-halo, ($C_1$-$C_{10}$)alkyl-dihalo, ($C_1$-$C_{10}$)alkyl-trihalo, ($C_1$-$C_{10}$)alkyl, ($C_1$-$C_{10}$)alkoxy, phenyl, nitro, nitrile, amino or hydroxy, on the proviso that at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is not hydrogen.

In a further embodiment of the invention, there are provided peptides according to Formula (I), and in particular Formula (II) or (III), wherein one or more of $R_{4a}$, $R_{4b}$ and $R_{4c}$ are each independently selected from hydrogen, halo, ($C_1$-$C_4$)alkyl-halo, ($C_1$-$C_4$)alkyl-dihalo, ($C_1$-$C_4$)alkyl-trihalo, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, phenyl, nitro, nitrile, amino or hydroxy, on the proviso that at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is not hydrogen.

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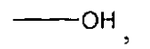
fluoro, chloro, ——OH,

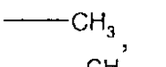
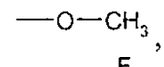
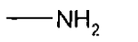
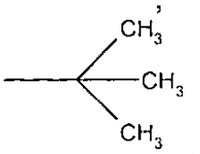
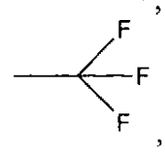
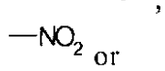
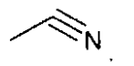






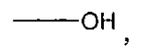

In a further embodiment of the invention, there are provided peptides according to Formula (I), and in particular Formula (II) or (III), wherein one or more of $R_{4a}$, $R_{4b}$ and $R_{4c}$ are each independently selected from hydrogen, halo, ($C_1$-$C_4$)alkyl-halo, ($C_1$-$C_4$)alkyl-dihalo, ($C_1$-$C_4$)alkyl-trihalo, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, nitro, nitrile, amino or hydroxy, on the proviso that at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is not hydrogen.

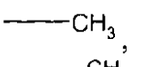
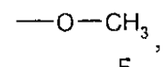
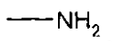
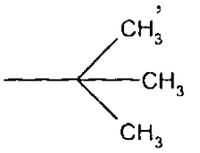
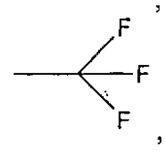
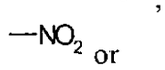
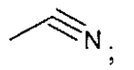
In a further embodiment of the invention, there are provided peptides according to Formula (I), and in particular Formula (II) or (III), wherein one or more of $R_{4a}$, $R_{4b}$ and $R_{4c}$ are each independently selected from

fluoro, chloro, 

In a further embodiment of the invention, there are provided peptides according to Formula (I), and in particular Formula (II) or (III), wherein $R_{4a}$, is selected from

fluoro, chloro, 

and $R_{4b}$ and $R_{4c}$ are each H.

In a further embodiment of the invention, there are provided peptides according to Formula (I), and in particular Formula (II) or (III), wherein $R_{4a}$ is selected from -C≡N or

–F, and $R_{4b}$ and $R_{4c}$ are each H.

In a particular embodiment of the invention, there are provided peptides according to Formula (I), and in particular Formula (II) or (III), wherein $R_{4a}$ is in the 4 position and is -C≡N and $R_{4b}$ and $R_{4c}$ are each H.

In another particular embodiment of the invention, there are provided peptides according to Formula (I), and in particular Formula (II) or (III), wherein $R_{4a}$ is in the 4 position and is -F and $R_{4b}$ and $R_{4c}$ are each H.

The peptides encompassed within Formula (I) contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, so that the peptides encompassed within Formula (I) can exist in different stereoisomeric forms. For both specific and generically described peptides, including the peptides encompassed within Formula (I), all forms of isomers at all chiral or other isomeric centers, including enantiomers and diastereomers, are intended to be covered herein. The peptides of the invention each include multiple chiral centers, and may be used as a racemic mixture or an enantiomerically enriched mixture, in addition to use of the peptides of the invention in enantiopure preparations. Typically, the peptides of the invention will be synthesized with the use of chirally pure reagents, such as specified L- or D-amino acids, using reagents, conditions and methods such that enantiomeric purity is maintained, but it is possible and contemplated that racemic mixtures may be made. Such racemic mixtures may optionally be separated using well-known techniques and an individual enantiomer may be used alone. In cases and under specific conditions of temperature, solvents and pH wherein peptides may exist in tautomeric forms, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form. Thus a single enantiomer of a peptide of Formula (I), which is an optically active form, can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates.

The peptides of formulas (II) and (III) are specific stereoisomeric forms of the peptides of Formula (I), but the invention should not be construed as being limited to the stereoisomeric forms encompassed by formulas (II) and (III).

The invention is further intended to include prodrugs of the present peptides, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological peptides. In general, such prodrugs will be functional derivatives of

the present peptides, which are readily convertible in vivo into a peptide of Formula (I). Prodrugs are any covalently bonded compounds, which release the active parent peptide drug of Formula (I) in vivo. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985. Typical examples of prodrugs have biologically labile protecting groups on a functional moiety, such as for example by esterification of hydroxyl, carboxyl or amino functions. Thus by way of example and not limitation, a prodrug includes peptides of Formula (I) wherein an ester prodrug form is employed, such as, for example, lower alkyl esters of the R group of Formula (I), such as where R is –OH, which lower alkyl esters may include from 1-8 carbons in an alkyl radical or aralkyl esters which have 6-12 carbons in an aralkyl radical. Broadly speaking, prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated or dephosphorylated to produce an active parent peptide drug of Formula (I) in vivo.

Certain modifications of peptides of Formula I may be made in order to enhance the half-life of the peptide (see G. Pasuta and F. M. Veronese (2007) "Polymer-drug conjugation, recent achievements and general strategies" *Progress in Polymer Science* 32 (8-9): 933-961).

The subject invention also includes peptides which are identical to those recited in Formula (I), but for the fact that one or more atoms depicted in Formula (I) are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into peptides of the invention include isotopes of hydrogen, carbon, nitrogen and oxygen, such as $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}O$ and $^{17}O$, respectively. Peptides of the present invention and pharmaceutically acceptable salts or solvates of said peptides which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled peptides of the present invention, for example those into which radioactive isotopes such as $^{3}H$ and $^{14}C$ are incorporated, may have use in a variety of assays, such as in drug and/or substrate tissue distribution assays. Substitution with heavier isotopes, such as substitution of one or more hydrogen atoms with deuterium ($^{2}H$), can provide pharmacological advantages in some instances, including increased

metabolic stability. Isotopically labeled peptides of Formula (I) can generally be prepared by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

In one embodiment of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_1$ is -C(=O)-NH-, x is 2 and y is 3.

In another embodiment of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_1$ is -C(=O)-NH-, x is 1 and y is 4.

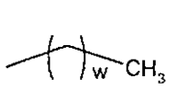
In another embodiment of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_1$ is -NH-C(=O)-, x is 3 and y is 2.

In still another embodiment of the peptides according to the Formula (I), and in particular Formula (II) or (III), $R_1$ is -NH-C(=O)-, x is 4 and y is 1.

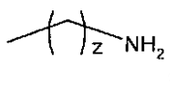
In a particular embodiment of the peptides according to the Formula (I), and in particular Formula (II) or (III), $R_1$ is -C(=O)-NH-, x is 2 and y is 3, or alternatively $R_1$ is -NH-C(=O)-, x is 3 and y is 2. More specifically, $R_1$ is -C(=O)-NH-, x is 2 and y is 3. It has surprisingly and unexpectedly been found that peptides according to the invention having a lactam bridge wherein the amide bond is positioned by means of the side chain of Glu (at the N-terminus end of the cyclic portion) and the side chain of Orn (at the C-terminus end of the cyclic portion) generally provides improved potency as determined by $EC_{50}$, in particular in the herein described low density hMC4-R system, compared to peptides wherein the amide bond is positioned by means of the side chains of Asp and Lys, but which are otherwise identical. This discovery is contrary to assertions in the prior art that the location and direction of an amide bond in the lactam bridge of melanocortin receptor specific peptides is of little importance for activity and does not interact with receptors. See, for example, Bednarek MA et al., Potent and selective peptide agonists of α-melanotropin action at human melanocortin receptor 4: their synthesis and biological evaluation *in vitro*. *Biochem. Biophys. Res. Comm.* 286:641-645 (2001).

In an embodiment of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH;

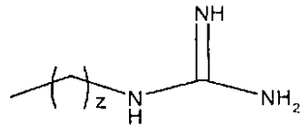
$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from



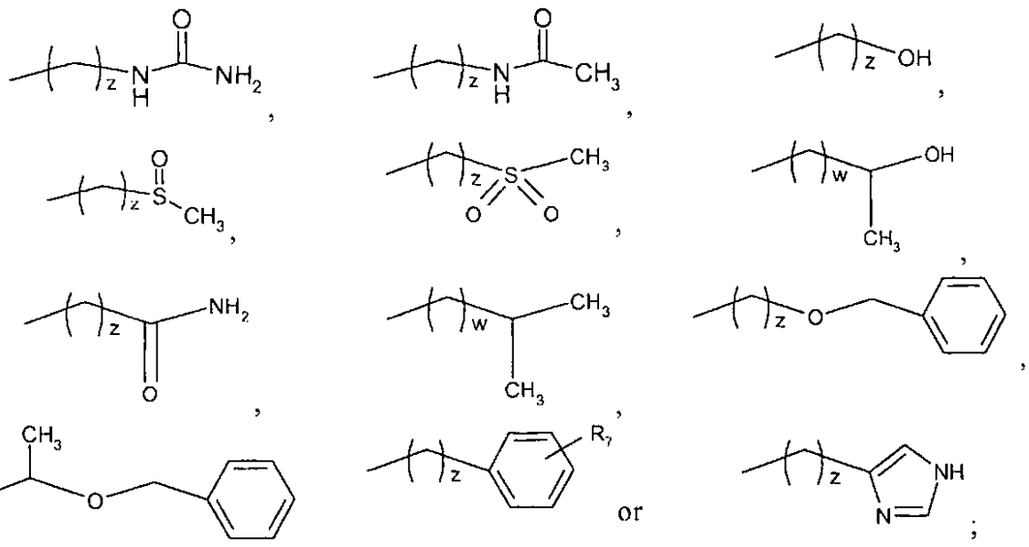
,



,



,

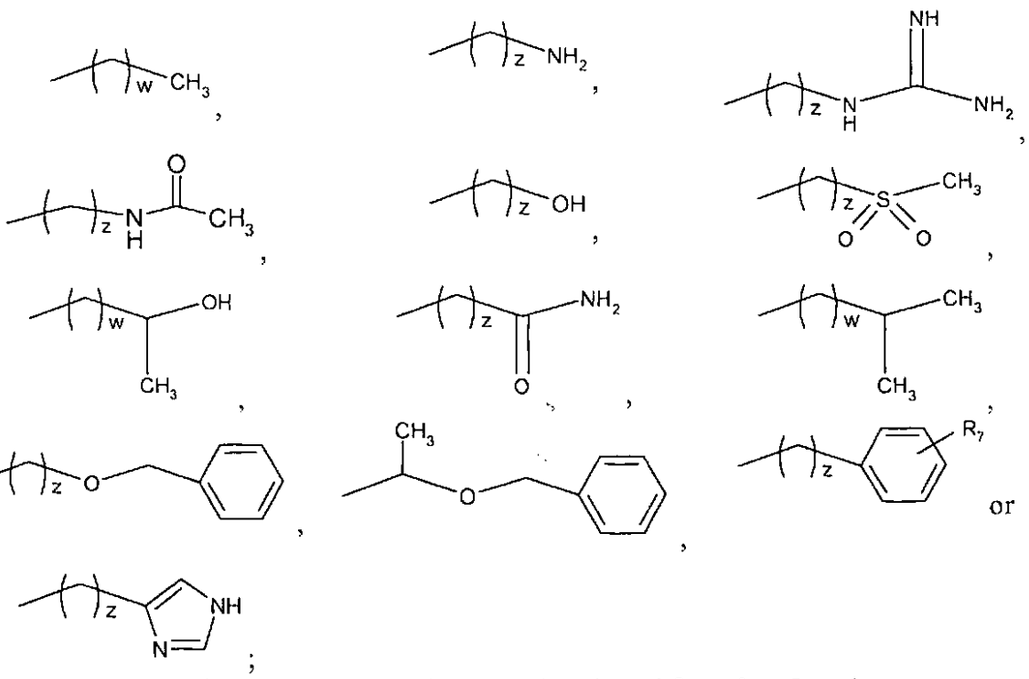


wherein w is in each instance independently selected from 0 to 5, and

z is in each instance independently selected from 1 to 5.

In an embodiment of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH;

$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from



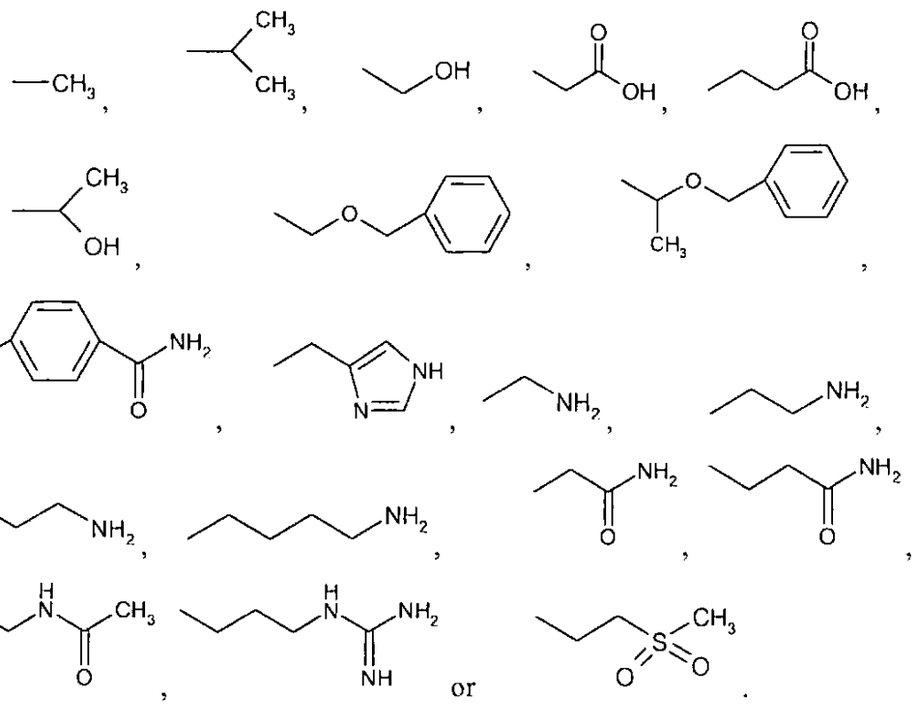
wherein w is in each instance independently selected from 0 to 5, and

z is in each instance independently selected from 1 to 5.

In an embodiment of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_2$ is H.

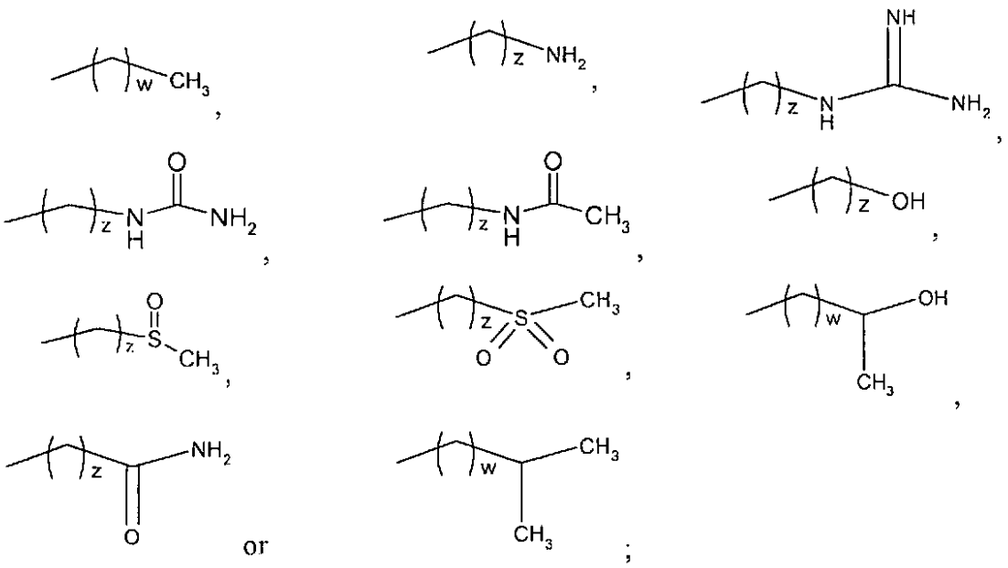
In an embodiment of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_2$ is H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH; and

$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from



Without being bound by any theory, replacing His by a non-aromatic amino acid, in particular a non-polar, small aliphatic amino acid, such as Pro or Ala, or a polar uncharged or charged amino acid, such as Lys, Asp, Gln and Asn, is believed to contribute to attenuation of blood pressure effects. Thus, the His position in the core sequence may for instance be replaced by Dab, Dab(Acetyl), Ser, Met(O), Met($O_2$), Thr, Hyp, Gln, Pro, Ala, Asn, Cit, Orn, Dap, Lys, or Arg, in particular Pro, Asn or Gln.

Thus, in a further embodiment of the invention, there are provided peptides of Formula (I), in particular of Formula (II) or (III), wherein $R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH; and $R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from

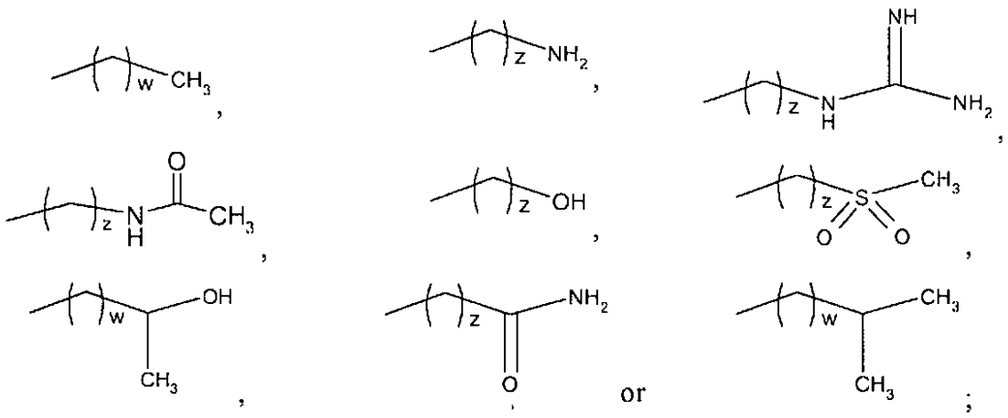


or ;

wherein w is in each instance independently selected from 0 to 5, and

z is in each instance independently selected from 1 to 5.

In a further embodiment of the invention, there are provided peptides of Formula (I), in particular of Formula (II) or (III), wherein $R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH; and $R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from

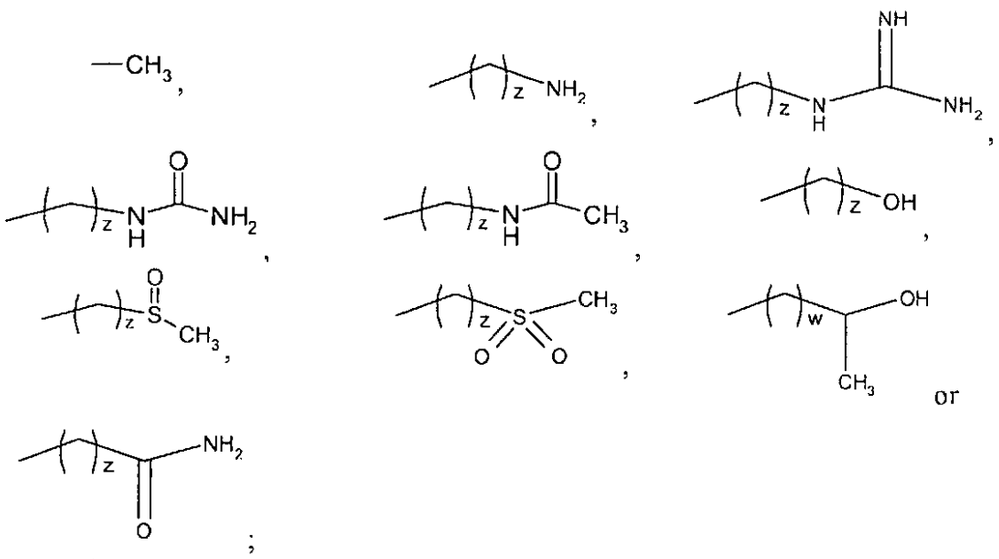


or ;

wherein w is in each instance independently selected from 0 to 5, and

z is in each instance independently selected from 1 to 5.

In a particular embodiment of the invention, there are provided peptides of Formula (I), in particular of Formula (II) or (III), wherein $R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH; and $R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from

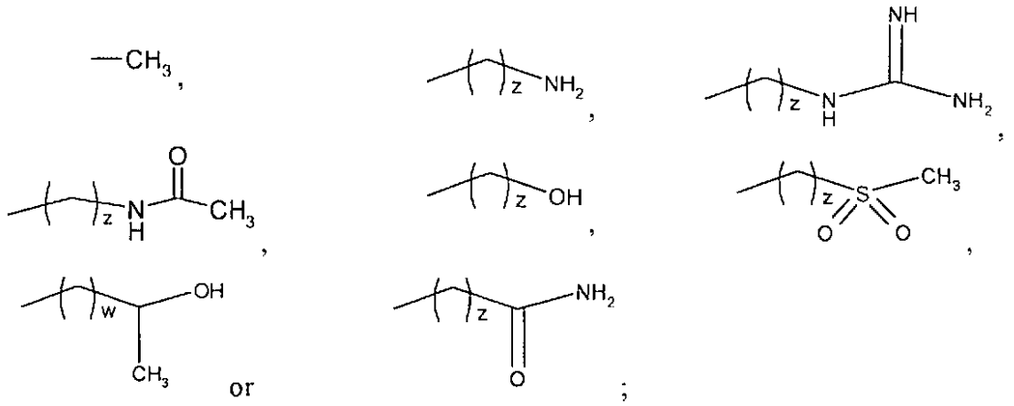


wherein w is in each instance independently selected from 0 to 5, in particular 0 to 2, such as 0, and

z is in each instance independently selected from 1 to 5, in particular 1 to 4.

In a further particular embodiment of the invention, there are provided peptides of Formula (I), in particular of Formula (II) or (III), wherein $R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH; and

$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from

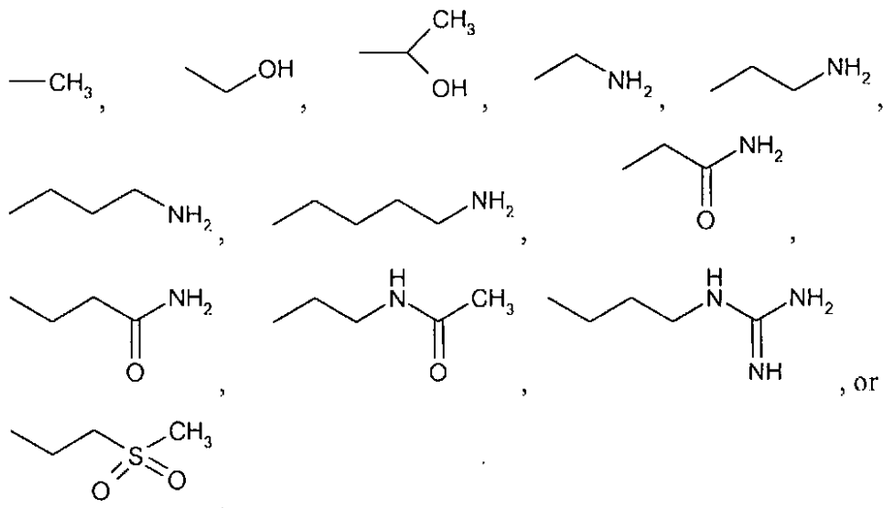


wherein w is in each instance independently selected from 0 to 5, in particular 0 to 2, such as 0, and

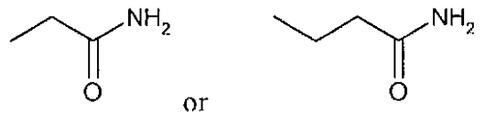
z is in each instance independently selected from 1 to 5, in particular 1 to 4.

In further embodiments of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_2$ is H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH; and

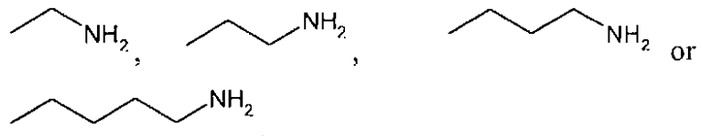
$R_3$ is selected from



In another embodiment of the invention, there are provided peptides of Formula (I), in particular of Formula (II) or (III), wherein $R_2$ is H and $R_3$ is selected from



In another embodiment of the invention, there are provided peptides of Formula (I), in particular of Formula (II) or (III), wherein $R_2$ is H and $R_3$ is selected from



In another embodiment of the invention, there are provided peptides of Formula (I), and in particular Formula (II) or (III), wherein $R_2$ is $-CH_2-$ and $R_3$ is $-(CH_2)_2-$, $R_2$ and $R_3$ together forming an unsubstituted pyrrolidine ring.

In still another embodiment of the invention, there are provided peptides of Formula (I), and in particular Formula (II) or (III), wherein $R_2$ is $-CH_2-$ and $R_3$ is $-(CH_2)_2-$, $R_2$ and $R_3$ together forming an pyrrolidine ring substituted with –OH. In a further embodiment of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_5$ is $–NH_2$ or –OH.

In a specific embodiment of the peptides according to Formula (I), and in particular Formula (II) or (III), $R_5$ is $-NH_2$.

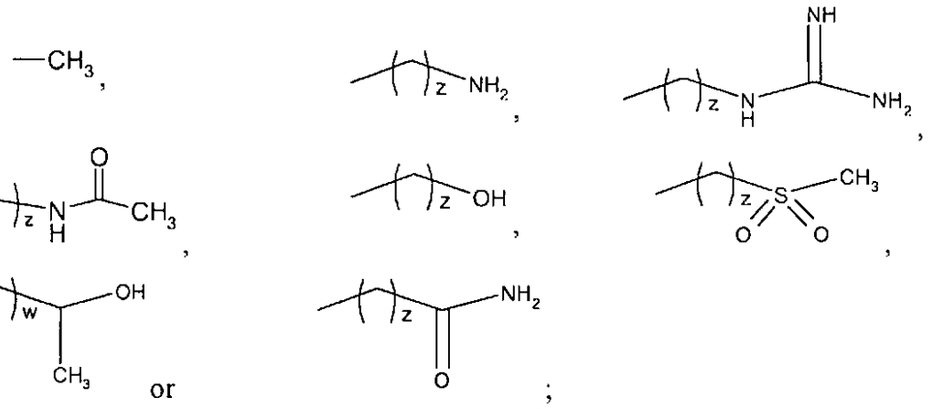
One or more of the above embodiments may be combined to provide further specific embodiments of the peptides according to the invention.

Thus, in a particular embodiment of the invention, there are provided peptides according to Formula (I), in particular Formula (II) or (III), wherein

$R_1$ is -C(=O)-NH-, x is 2 and y is 3;,

$R_2$ is -H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH;

$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from



or



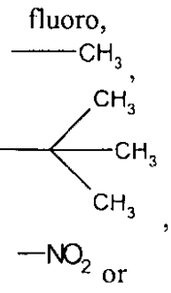
;

w is in each instance independently selected from 0 to 5;

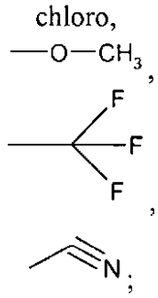
z is in each instance independently selected from 1 to 5;

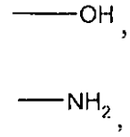
one or more of $R_{4a}$, $R_{4b}$ and $R_{4c}$ are each independently selected from

fluoro,



chloro,





or



;

and

$R_5$ is $-NH_2$ or -OH.

Some specific peptides of the invention are one or more of the following:

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:6);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:7);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:8);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2,4-diCl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:9);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,4-diCl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:10);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:11);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:12);

Ac-Arg-*cyclo*(Glu-Dab-D-Tyr-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:13);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:14);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:15);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:16);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:17);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:18);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:19);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:20);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-OMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:21);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,5-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:22);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:23);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:24);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:25);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2,4-diMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:26);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-$NO_2$)-Arg-Trp-Orn-$NH_2$ (SEQ ID NO:27);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-$NO_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:28);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-$NO_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:29);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,4-diOMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:30);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,4-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:31);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:32);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-$NH_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:33);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-tBu)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:35);

Ac-Arg-*cyclo*(Glu-Ser-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:36);

Ac-Arg-*cyclo*(Glu-Thr-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:37);

Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:38);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:39);

Ac-Arg-*cyclo*(Glu-Ser-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:40);

Ac-Arg-*cyclo*(Glu-Thr-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:41);

Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:42);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:43);

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:44);

Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:45);

Ac-Arg-*cyclo*(Glu-Ala-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:46);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:48);

Ac-Arg-*cyclo*(Glu-Thr-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:49);

Ac-Arg-*cyclo*(Glu-Ser-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:50);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51);

Ac-Arg-*cyclo*(Glu-Orn-D-Phe(2-Cl)-Arg-Trp-Orn)-OH (SEQ ID NO:54);

Ac-Arg-*cyclo*(Glu-Orn-D-Phe(3-Cl)-Arg-Trp-Orn)-OH (SEQ ID NO:60);

Ac-Arg-*cyclo*(Glu-Dab(Acetyl)-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:61);

Ac-Arg-*cyclo*(Glu-Ser-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:63);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:64);

Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:65);

Ac-Arg-*cyclo*(Glu-Dap-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:66);

Ac-Arg-*cyclo*(Glu-Dap-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:67);

Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:69);

Ac-Arg-*cyclo*(Glu-Ser-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:70);

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:71);

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72);

Ac-Arg-*cyclo*(Glu-Met($O_2$)-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:73);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:74);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:78);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(3,5-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:81);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:89);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:90);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:91);

Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-OMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:92);

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:93);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:97);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:100);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:102);

Ac-Arg-*cyclo*(Glu-Arg-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:104);

Ac-Arg-*cyclo*(Glu-Lys-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:105);

Ac-Arg-*cyclo*(Glu-Orn-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:106)

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-OH (SEQ ID NO:107);

Ac-Arg-*cyclo*(Glu-Asp-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:111);

Ac-Arg-*cyclo*(Glu-Asp-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:112);

Ac-Arg-*cyclo*(Glu-Glu-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:113);

Ac-Arg-*cyclo*(Glu-Glu-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:114);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:115);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:119);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:121); or a pharmaceutically acceptable salt of any of the foregoing.

Particularly, the invention relates to:

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:48);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:74);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:90), or a pharmaceutically acceptable salt of any of the foregoing.

Particularly, the invention also relates to:

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:91);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:97), or a pharmaceutically acceptable salt of any of the foregoing.

Particularly, the invention also relates to:

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:44);

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72),

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-OH (SEQ ID NO:107); or a pharmaceutically acceptable salt of any of the foregoing.

Some further specific peptides of the invention are:

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(4-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:75);

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:76);

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(3-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:77);

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(2-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:79);

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(3,4-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:80);

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(3,5-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:82);

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:96);

Ac-Arg-*cyclo*(Orn-Gln-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:99);

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(3,4,5-triF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:101);

Ac-Arg-*cyclo*(Orn-Gln-D-Phe(3,4,5-triF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:103);

Ac-Arg-*cyclo*(Orn-Pro-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:110);

Ac-Arg-*cyclo*(Orn-Gln-D-Phe(2-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:116);

Ac-Arg-*cyclo*(Orn-Gln-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:117);

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:118);

Ac-Arg-*cyclo*(Orn-Gln-D-Phe(2-$CF_3$)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:120);

Ac-Arg-*cyclo*(Orn-Asn-D-Phe(2-$CF_3$)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:122); or a pharmaceutically acceptable salt of any of the foregoing.

6.1 Specific peptides.

Peptides of the following structures were synthesized by the general methods described above, and except where indicated MC1-R Ki and MC4-R Ki values for each peptide were determined in competitive binding assays using [$I^{125}$]-NDP-α-MSH as described in 7.1 below. All peptides were prepared in the TFA acid salt form, except for the peptides of Examples 43, 46 and 67, which were prepared in the acetate salt form.

The syntheses of some specific peptides of the invention are illustrated below. These peptides were prepared using solid phase peptide synthesis by means of a Symphony Multiplex Peptide Synthesizer (Rainin Instrument Company/Protein Technologies Inc) automated peptide synthesizer.

Step 1: Coupling of Orn

The Sieber resin 9-Fmoc-Aminoxanthen-3-yloxy-polystyrene resin (0.39 mol/g,ChemPep Inc.,#151902) was swelled in 3 x 5 mL of DMF for 10 min. Thereafter, Fmoc was deprotected using 2 x 5 mL of 20% piperidine in DMF for 10 min. The resin was then washed in 6 x 5 mL DMF for 30 sec. 5 mL of 200 mM Fmoc-Orn(Alloc)-OH in DMF and 5 mL 200 mM HBTU containing 400 mM NMM in DMF was added and after 30 min the resin was washed with 3 x 5 mL DMF for 30 sec.

Step 2: Coupling of next 6 amino acids (AA)

The resin from step 1 was first swelled in 3 x 5 mL of DMF for 30 sec, Fmoc was deprotected using 2 x 5 mL of 20% piperidine in DMF for 10 min and then washed with 6 x 5 mL DMF for 30 sec. 5 mL of 200 mM Fmoc-AA-OH solution and 5 mL 200 mM HBTU containing 400 mM NMM in DMF was added and after 30 min the resin was washed with 3 x 5 mL DMF for 30 sec.

This step was repeated for each amino acid (AA).

Step 3: Acetylation

Fmoc was deprotected using 2 x 5 mL of 20% piperidine in DMF for 10 min and the resin was then washed with 3 x 5 mL DMF for 30 sec. Thereafter, 5 mL of 50% $Ac_2O$/DMF solution was added and after 30 min the peptide resin was washed with 3 x 5 mL DMF for 30 sec and 6 x 5 mL DCM for 30 sec.

Step 4: Allyl/Alloc Deprotection

The peptide resin (0.6 mmol) was mixed with phenylsilane (Oakwood Chemical, #S13600) (20 eq.) in 20 mL of DCM and bubbled with nitrogen for 5 min.

Tetrakis(triphenylphosphine)-palladium(0) (Strem Chemicals, Inc., #46-2150) (0.2 eq.) was added and the mixture was agitated with nitrogen for 1 hour. The procedure was repeated one time for 1 hour and an additional time for 30 min with fresh reagents. The treated peptide resin was then washed with DCM x 3 and DMF x 3.

Step 5: Lactam Formation

The lactam ring was formed on the peptide resin using TBTU (2 eq.) and ethyldiisopropylamine (DIEA) (4 eq.) in 20 mL DMF for 1 hour. A second coupling may be needed if a positive Kaiser Ninhydrin test is observed.

Step 6: Peptide Cleavage

The peptide resin (0.6 mmol) was mixed with 20 mL of 5% sodium diethyldithio-carbamate trihydrate ($NaCS_2NEt_2$, Aldrich, #228680) in DMF for 20 min and then washed with DMF x 3, DCM x 3 and diethyl ether x 2.

The resin (0.6 mmol) was then stirred in a 25 mL of TFA/TIS/H2O (90 : 5.0 : 5.0 v/v/v) for 2.5 hours. The resin was filtered. The filtrate was concentrated to about 10 mL in volume and about 140 mL of cold diethyl ether (pre-cooled to about 0 °C) was added.

The mixture was vortexed, and then placed in the refrigerator (about -4 °C) for 1 h, centrifuged for 5 min at 2800 rpm, and the ether layer was decanted.

The peptide was washed with 90 mL of cold diethyl ether (pre-cooled to about 0 °C), vortexed, centrifuged for 5 min at 2800 rpm, and ether layer decanted.

The resulting solid was dissolved in 50% AcOH/$H_2O$ and stored at room temperature overnight.

The crude peptide solution was concentrated to afford solid crude peptide for HPLC purification.

After HPLC purification, the peptide TFA salt was converted to peptide acetate salt using ion exchange (x 100 eq.). The anion exchange resin used was Dowex SBR LC NG, OH-form (Supelco, Cat# 14036-U).

**Example 46:** Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51)

The procedure described above was followed in the preparation of the title peptide.

The amino acids added in step 2 were, in the order of being coupled, Fmoc-Trp(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-D-Phe(4-CN)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OAll)-OH, and Fmoc-Arg(Pbf)-OH.

The resulting peptide was purified by HPLC (column: Atlantis dC18 OBD$^{TM}$ 19 x 100 mm (5µ, Waters part # 186001367 ) using 10% MeOH/$H_2O$ containing 0.1% TFA (solvent A) and 90% MeOH/$H_2O$ containing 0.1% TFA (solvent B). A gradient of 0%-5% of solvent B for 5 min and 5%-35% of solvent B for 30 min was used.

The peptide yield was 10%.

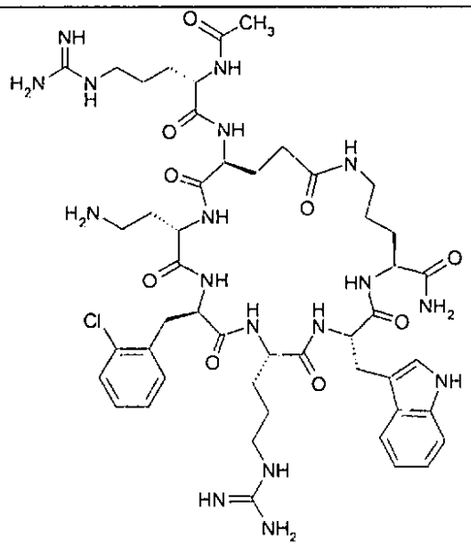
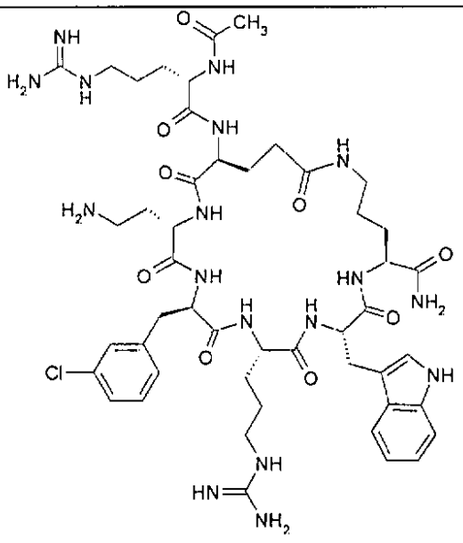
**Example 67:** Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72)

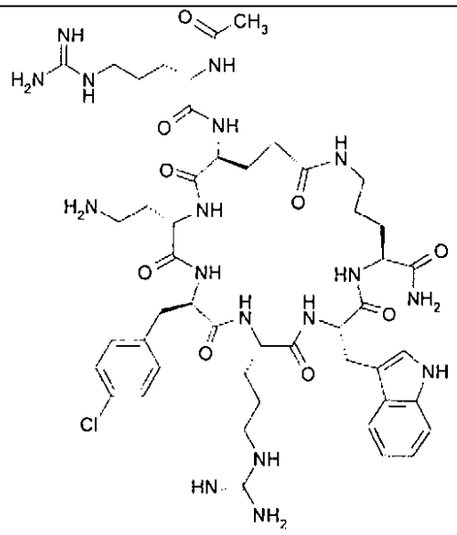
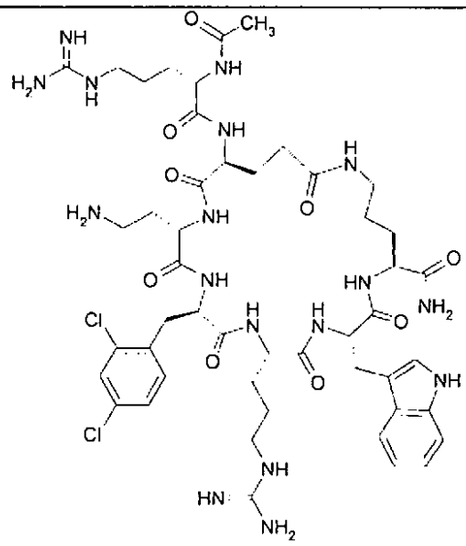
The procedure described above was followed in the preparation of the title peptide except for that 15 mL of 5% sodium diethyldithio-carbamate trihydrate in DMF, 16 mL of TFA/TIS/$H_2O$ and 90 mL + 60 mL of diethyl ether were used in step 6. Moreover, the filtrate was concentrated to 5 mL.

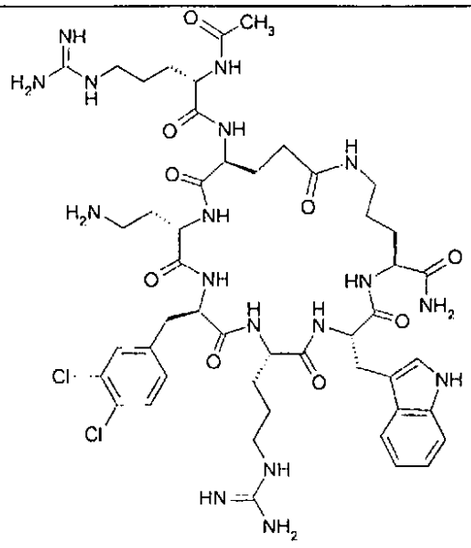
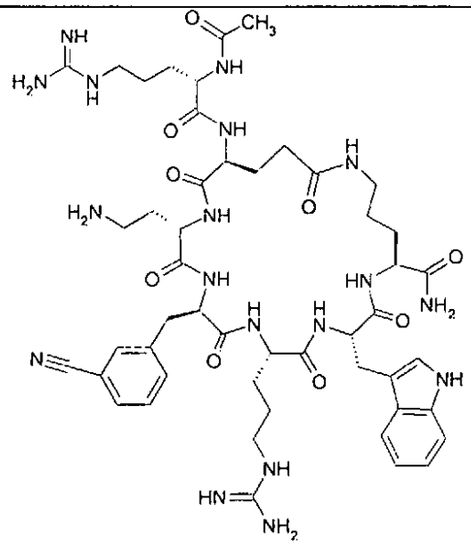
The amino acids added in step 2 were, in the order of being coupled, Fmoc-Trp(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-D-Phe(4-F)-OH, Fmoc-Pro-OH, Fmoc-Glu(OAll)-OH, and Fmoc-Arg(Pbf)-OH.

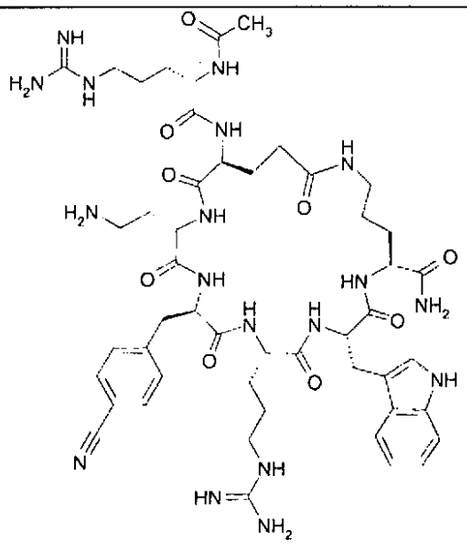
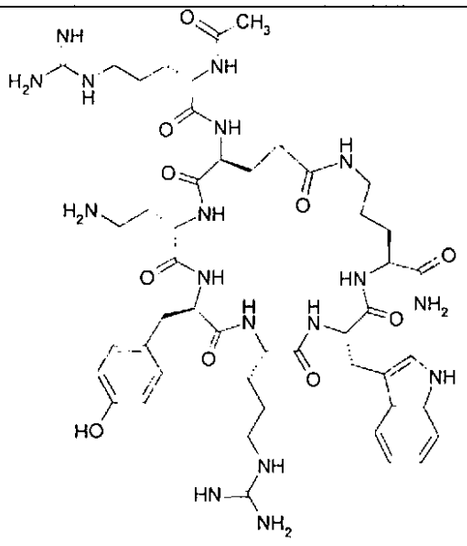
The resulting peptide was purified by HPLC (column: Atlantis dC18 OBD$^{TM}$ 19 x 100 mm (5µ, Waters part # 186001367 ) using 10% MeOH/$H_2O$ containing 0.1% TFA (solvent A) and 90% MeOH/$H_2O$ containing 0.1% TFA (solvent B). A gradient of 5%-10% of solvent B for 5 min and 10%-40% of solvent B for 30 min was used.

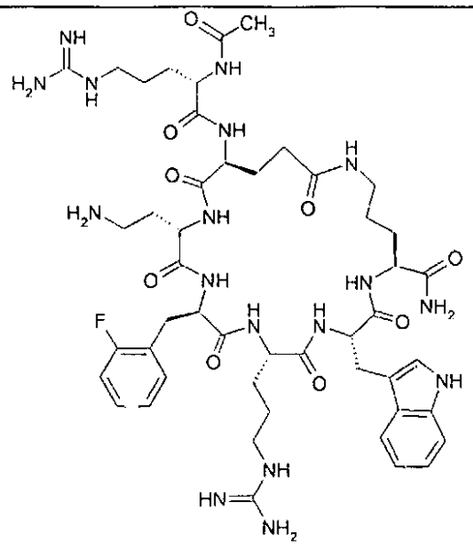
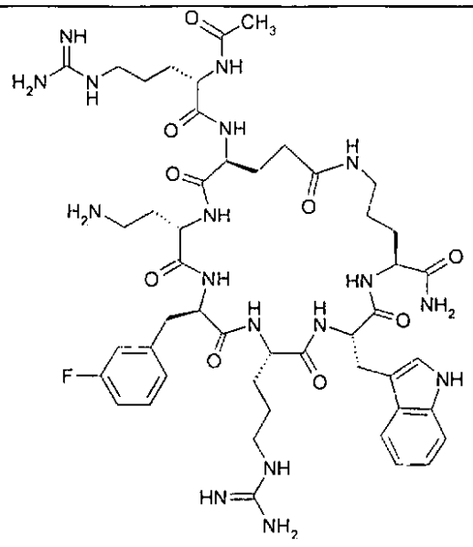
The peptide yield was 16%.

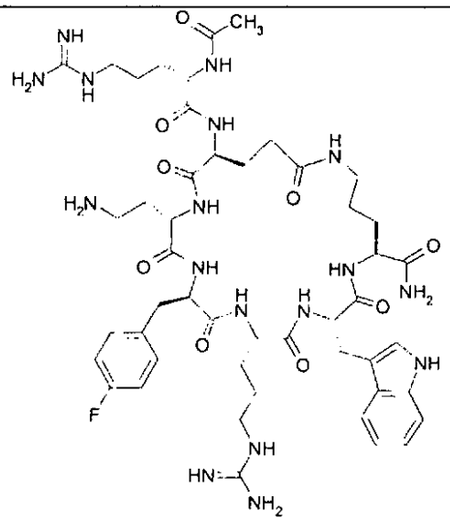
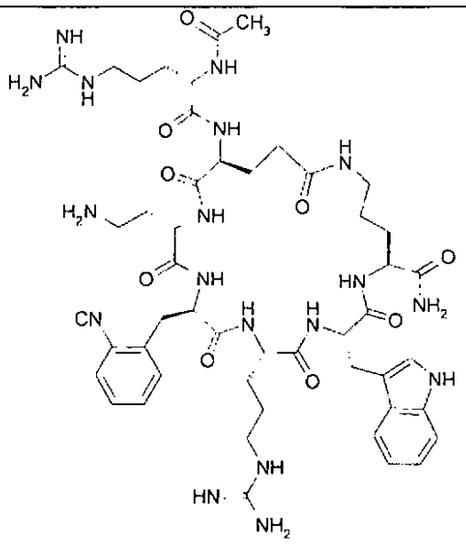
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 1 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:6) | 3 | 1 |
| 2 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:7) | 0.75 | 1 |

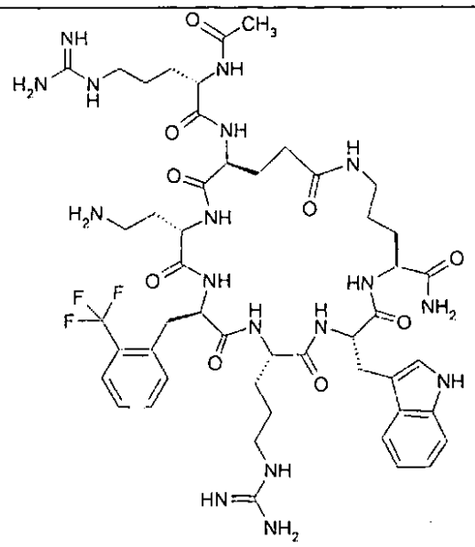
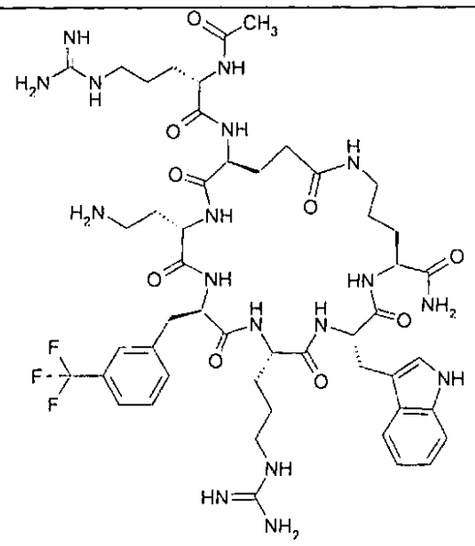
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 3 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:8) | 0.08 | 0.3 |
| 4 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2,4-diCl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:9) | 0.055 | 0.5 |

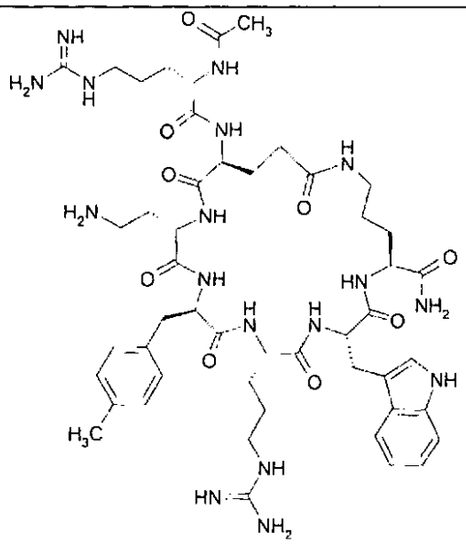
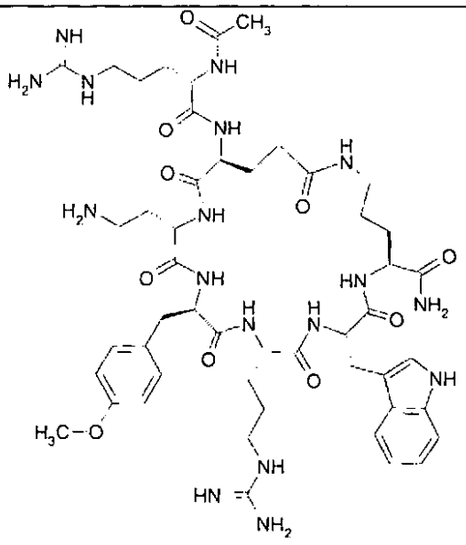
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 5 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,4-diCl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:10) | 0.055 | 0.2 |
| 6 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:11) | 33 | 43 |

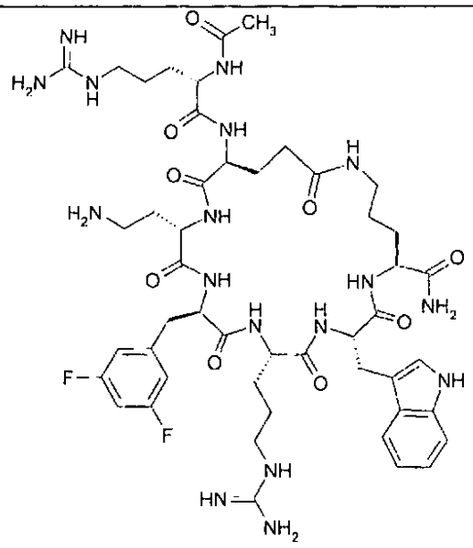
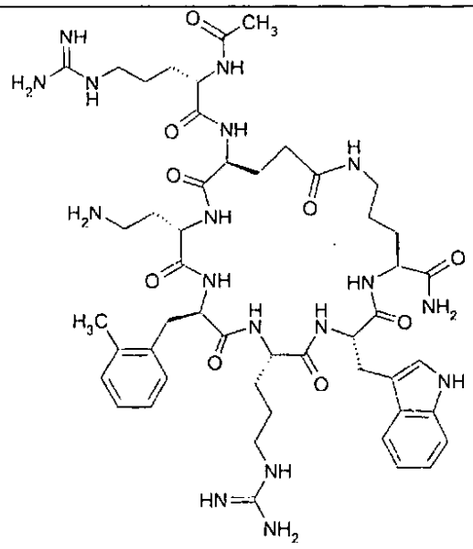
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 7 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:12) | 0.833 | 5 |
| 8 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Tyr-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:13) | 75 | 15 |

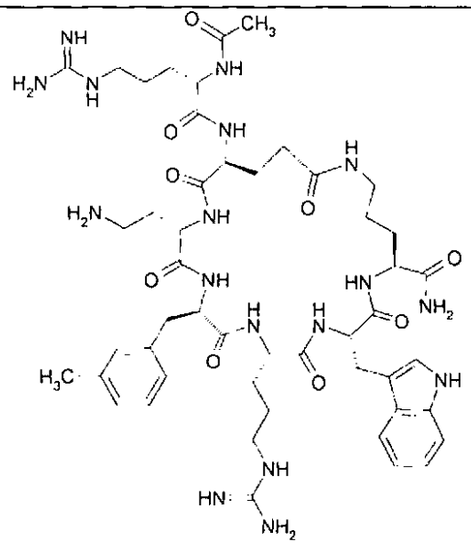
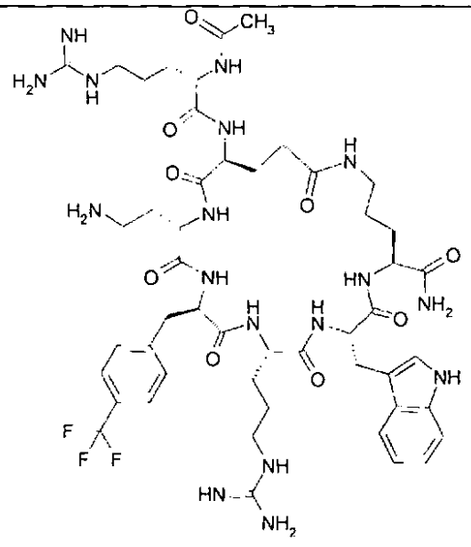
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MCI-R Ki (nM) |
|---|---|---|---|---|
| 9 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:14) | 0.7 | 0.8 |
| 10 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:15 | 2 | 2 |

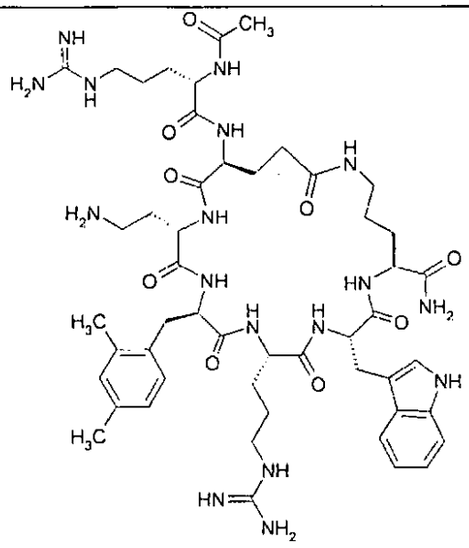
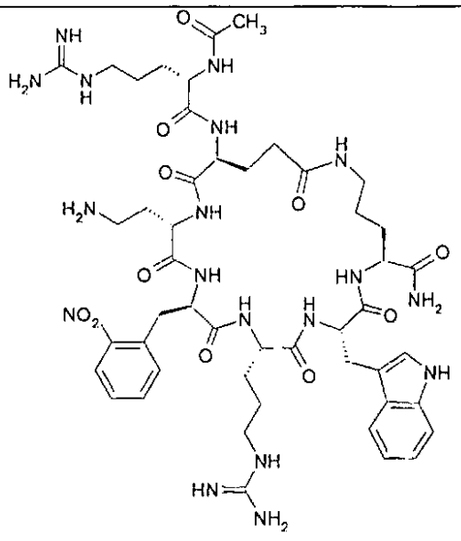
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 11 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:16) | 0.25 | 0.5 |
| 12 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:17) | 45 | 35 |

| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 13 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:18) | 0.6 | 3 |
| 14 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:19) | 0.95 | 9 |

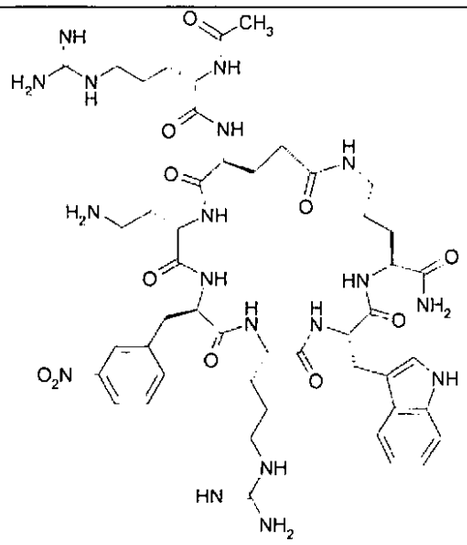
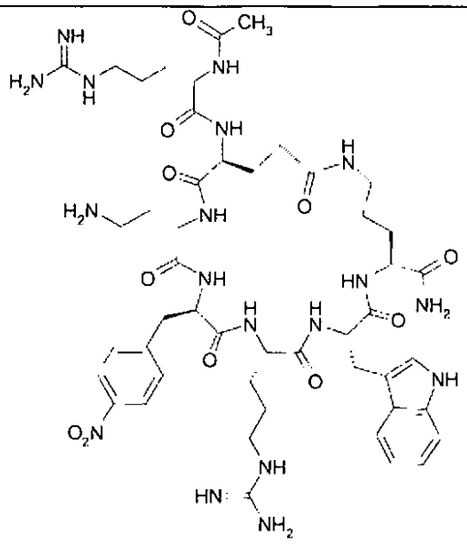
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 15 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:20) | 0.145 | 0.75 |
| 16 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-OMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:21) | 0.25 | 0.15 |

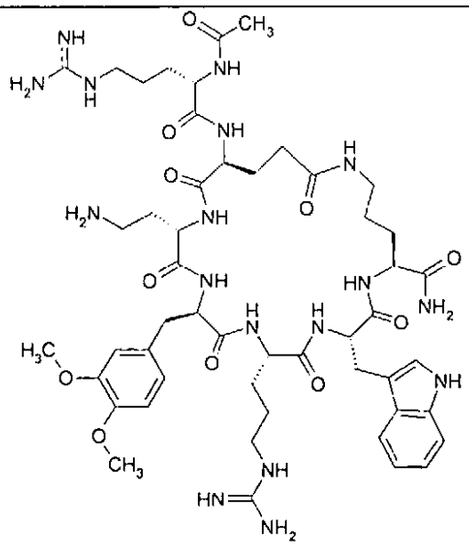
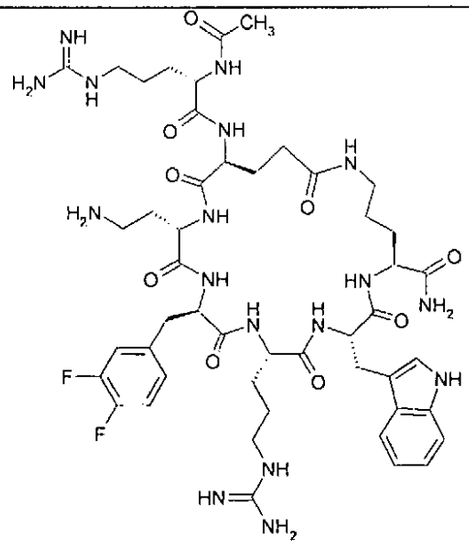
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 17 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,5-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:22) | 2 | - |
| 18 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:23) | 0.5 | - |

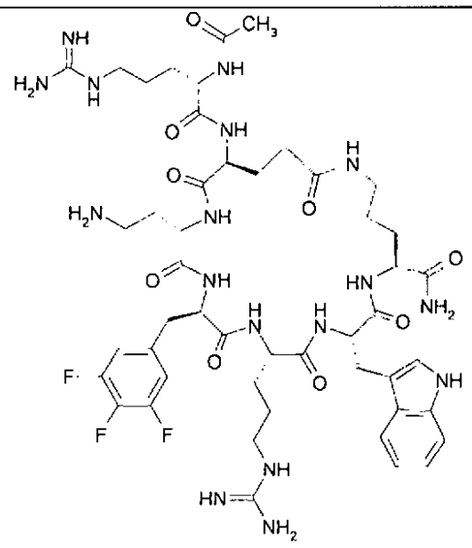
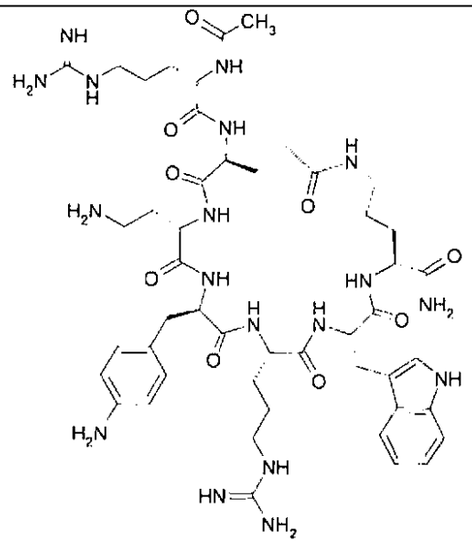
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 19 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:24) | 0.4 | - |
| 20 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:25) | 0.06 | - |

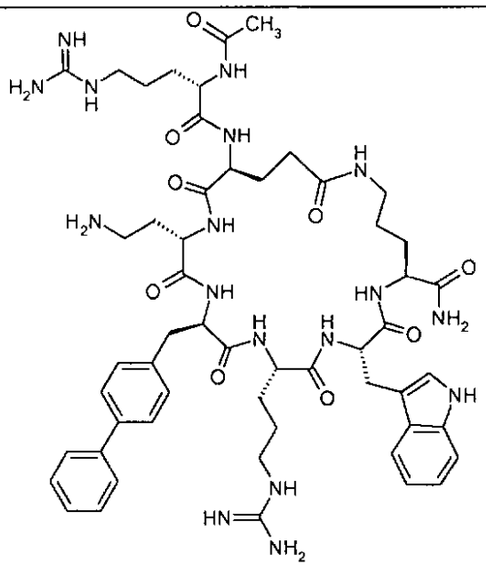
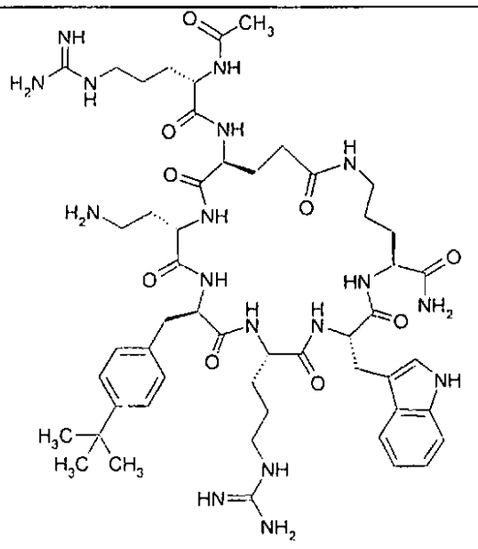
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 21 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2,4-diMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:26) | 0.085 | - |
| 22 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(2-$NO_2$)-Arg-Trp-Orn-$NH_2$ (SEQ ID NO:27) | 11 | - |

10.

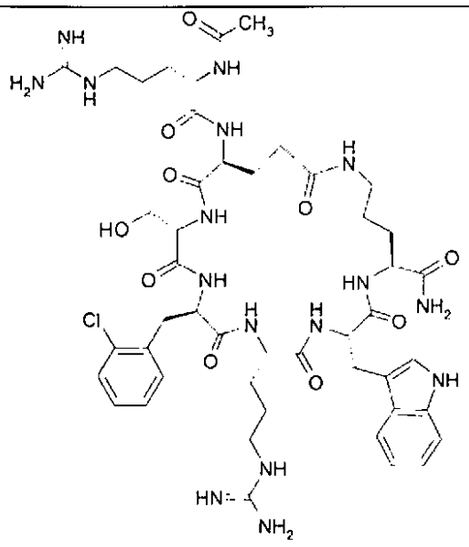
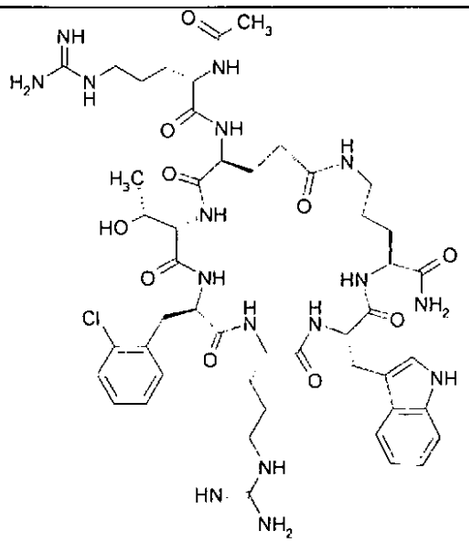
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 23 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-$NO_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:28) | 0.7 | - |
| 24 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-$NO_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:29) | 0.45 | - |

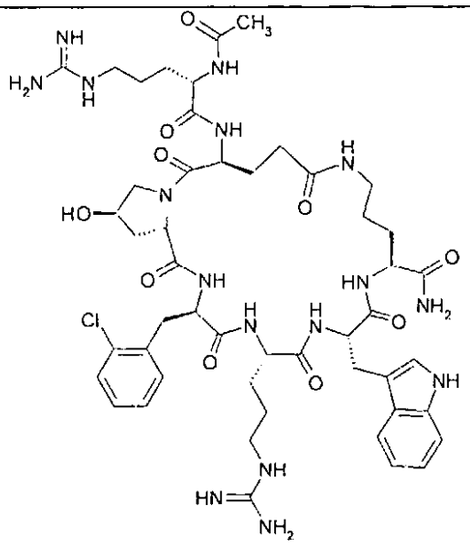
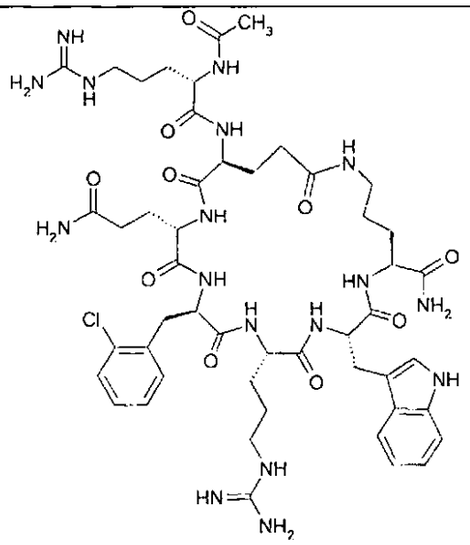
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 25 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,4-diOMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:30) | 35 | - |
| 26 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,4-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:31) | 0.3 | - |

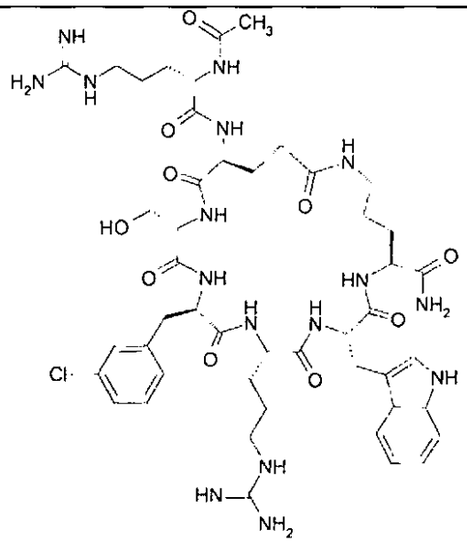
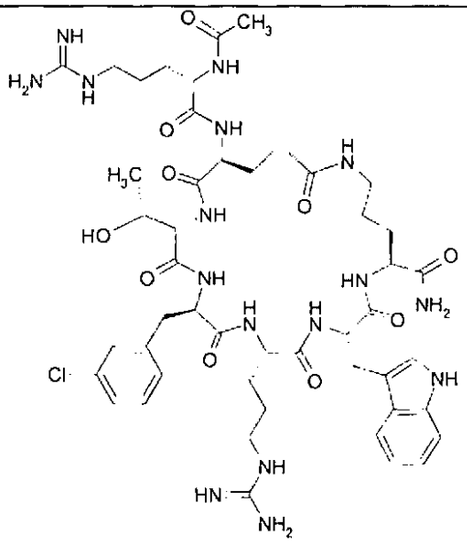
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 27 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:32) | 0.667 | - |
| 28 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-$NH_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:33) | 48 | - |

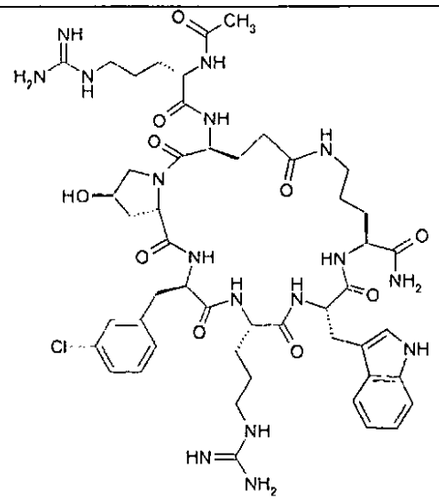
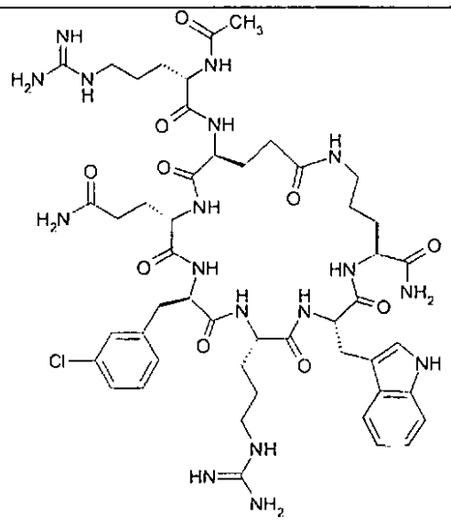
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 29 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-Ph)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:34) | 0.5 | - |
| 30 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(4-tBu)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:35) | 4 | - |

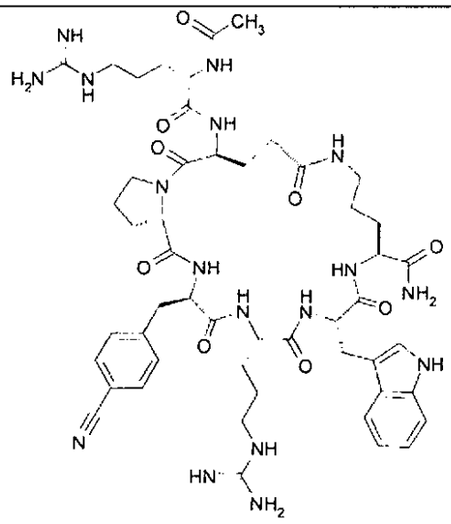
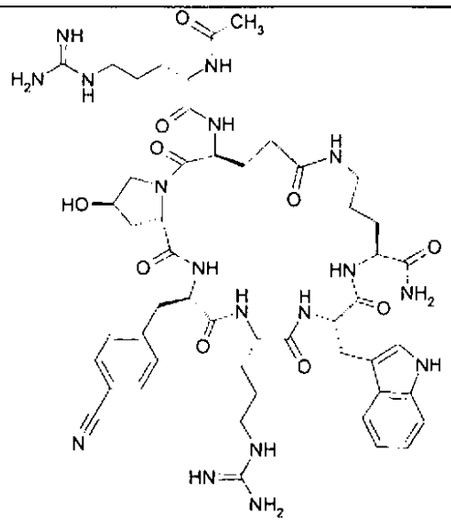
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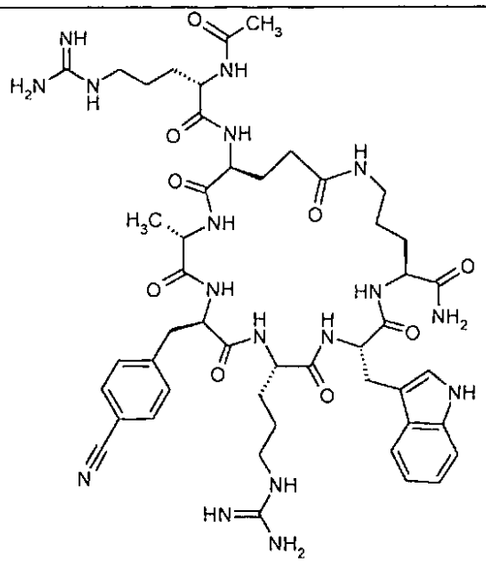
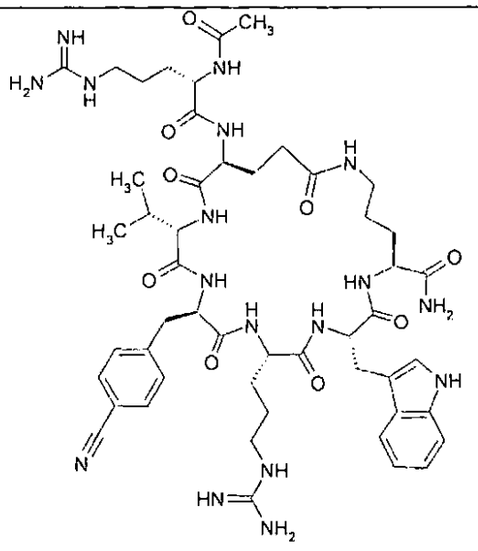
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 31 |  | Ac-Arg-*cyclo*(Glu-Ser-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:36) | 8 | 300 |
| 32 |  | Ac-Arg-*cyclo*(Glu-Thr-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:37) | 11 | 540 |

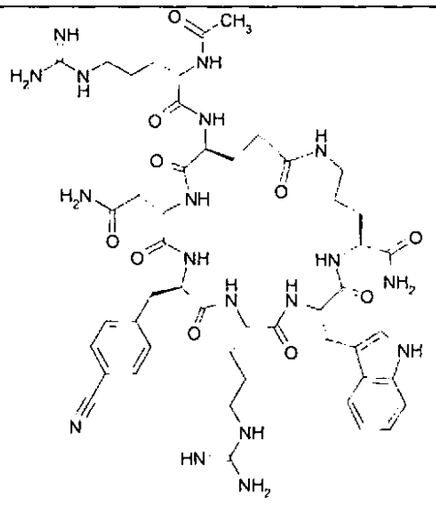
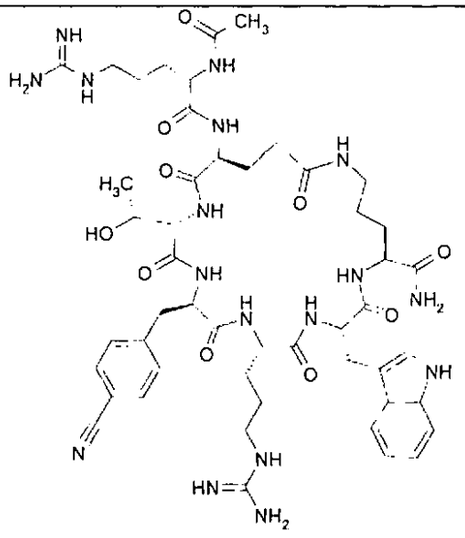
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 33 |  | Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:38) | 1 | 143 |
| 34 |  | Ac-Arg-*cyclo*(Glu-Gln-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:39) | 7 | 128 |

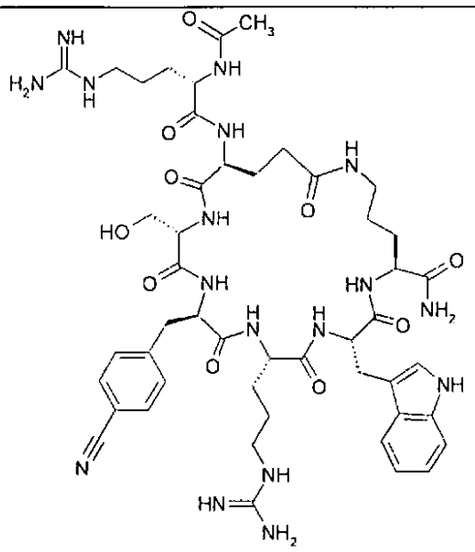
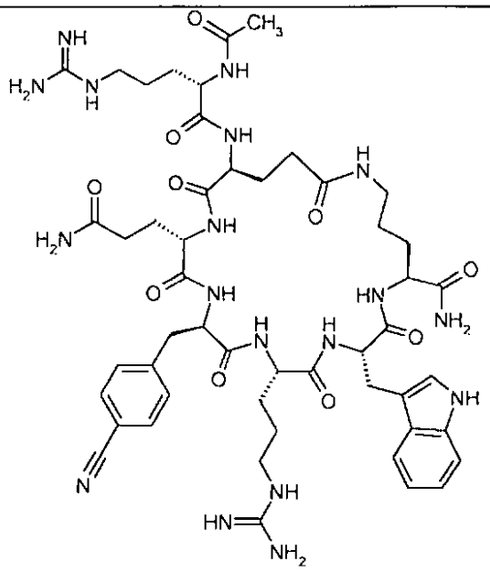
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 35 |  | Ac-Arg-*cyclo*(Glu-Ser-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:40) | 10 | 810 |
| 36 |  | Ac-Arg-*cyclo*(Glu-Thr-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:41) | 6 | 380 |

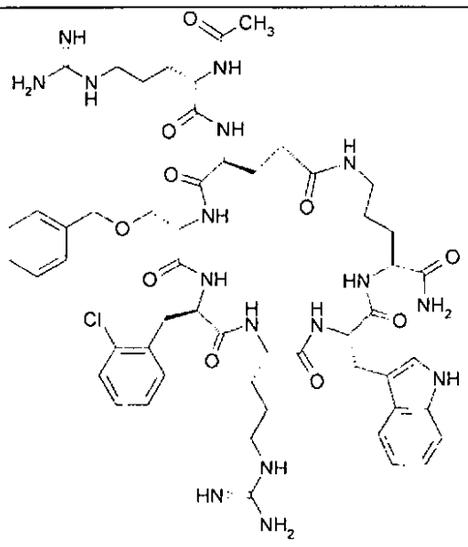
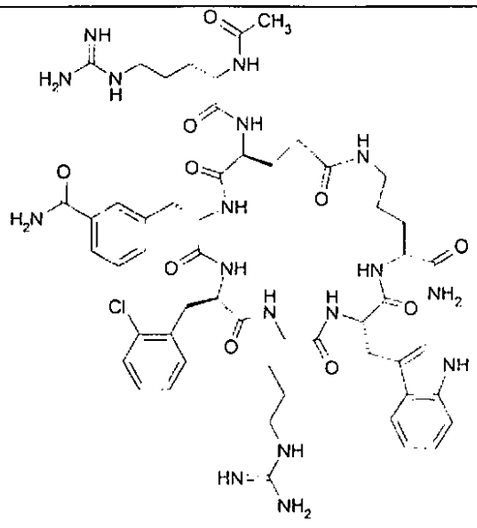
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 37 |  | Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:42) | 2 | 430 |
| 38 |  | Ac-Arg-*cyclo*(Glu-Gln-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:43) | 3 | 290 |

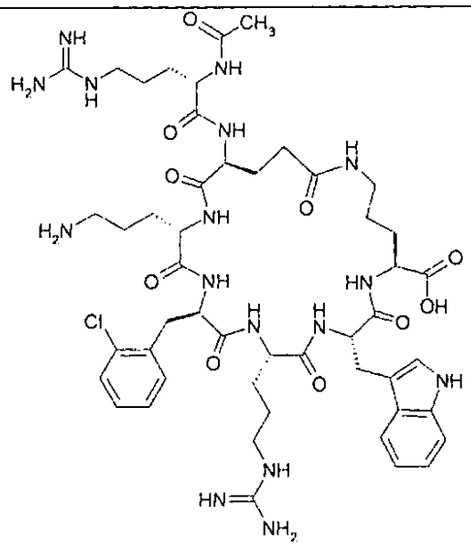
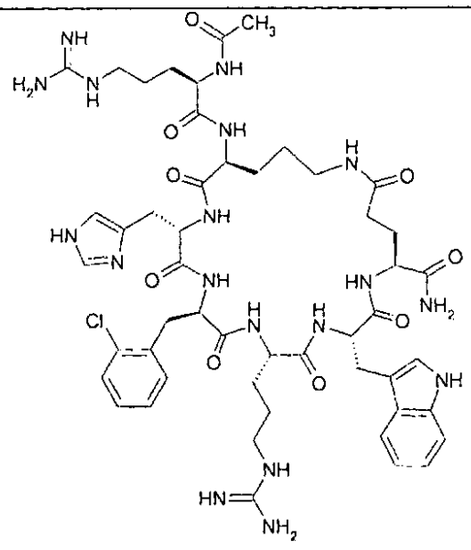
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 39 |  | Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:44) | 4 | 1550 |
| 40 |  | Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:45) | 2 | 880 |

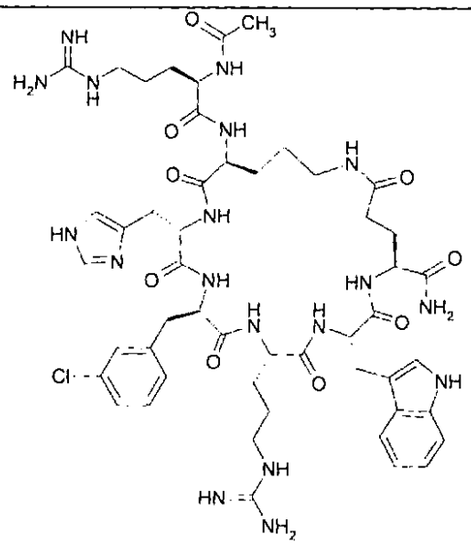
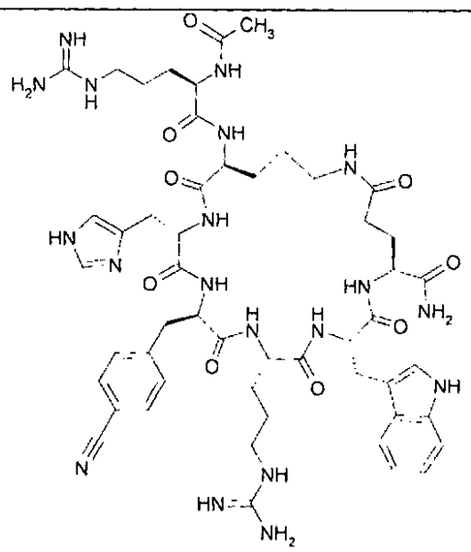
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 41 |  | Ac-Arg-*cyclo*(Glu-Ala-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:46) | 3 | 4300 |
| 42 |  | Ac-Arg-*cyclo*(Glu-Val-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:47) | 6 | 420 |

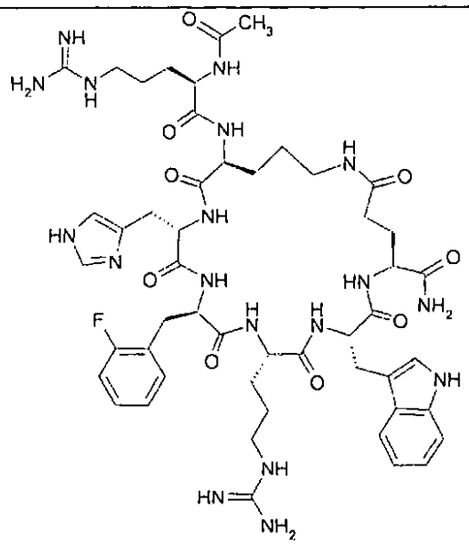
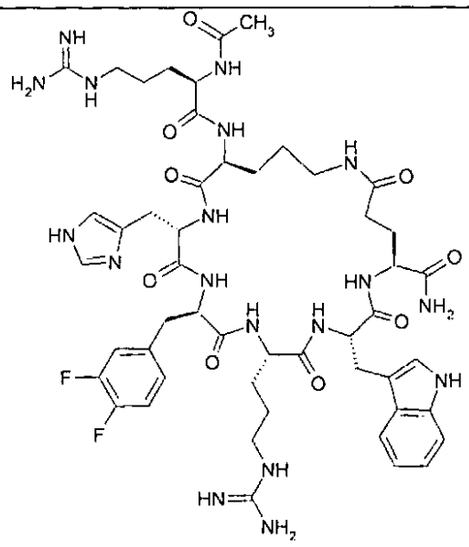
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 43 |  | Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:48) | 5 | 870 |
| 44 |  | Ac-Arg-*cyclo*(Glu-Thr-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:49) | 18 | 1625 |

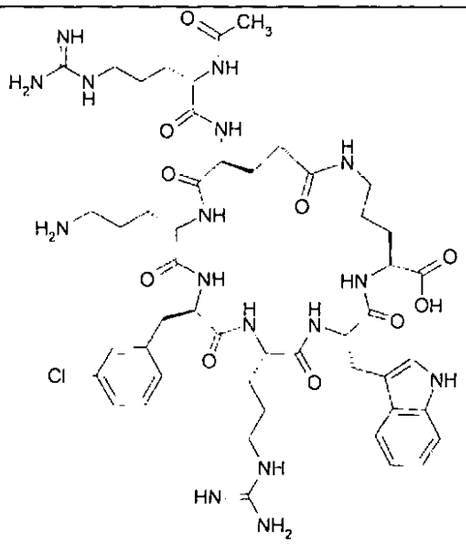
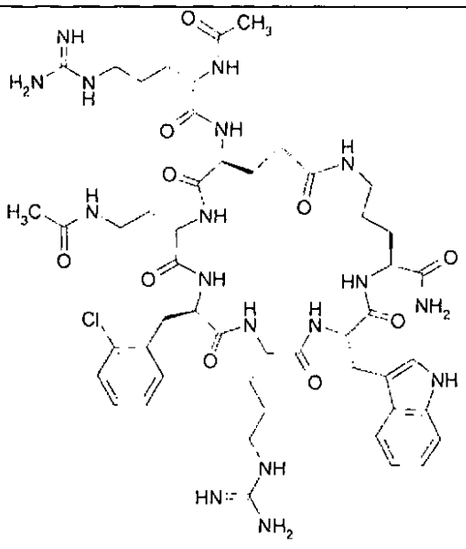
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MCI-R Ki (nM) |
|---|---|---|---|---|
| 45 |  | Ac-Arg-*cyclo*(Glu-Ser-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:50) | 10 | 10000 |
| 46 |  | Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51) | 4 | 425 |

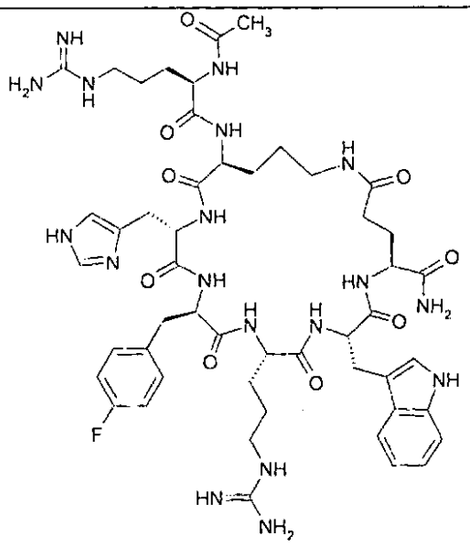
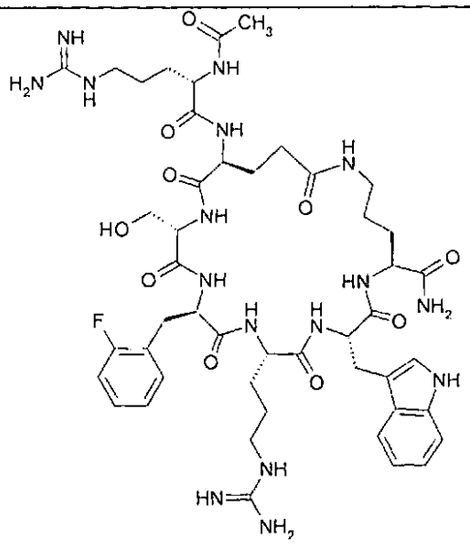
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 47 |  | Ac-Arg-*cyclo*(Glu-Ser(Bzl)-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:52) | 0.3 | 25 |
| 48 |  | Ac-Arg-*cyclo*(Glu-Phe(3-C(=O)-$NH_2$)-D-Phe(2-Cl)-D-Phe-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:53) | 15 | 545 |

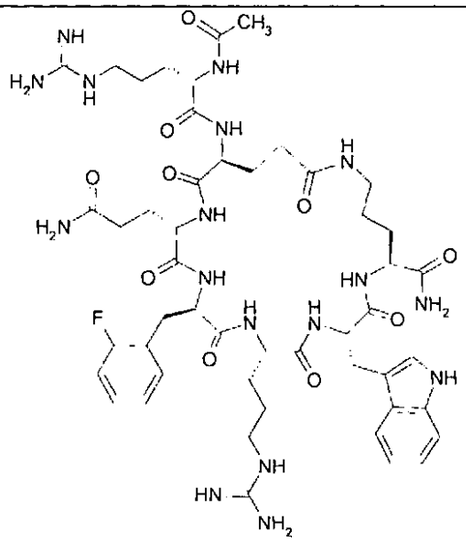
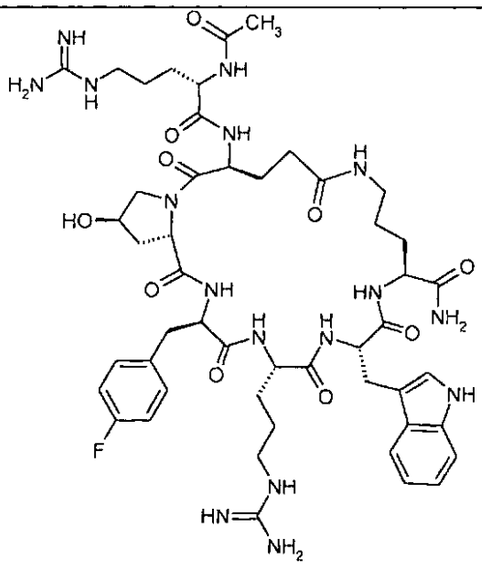
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 49 |  | Ac-Arg-*cyclo*(Glu-Orn-D-Phe(2-Cl)-Arg-Trp-Orn)-OH (SEQ ID NO:54) | 8 | 8 |
| 50 |  | Ac-D-Arg-*cyclo*(Orn-His-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:55) | 1 | 2 |

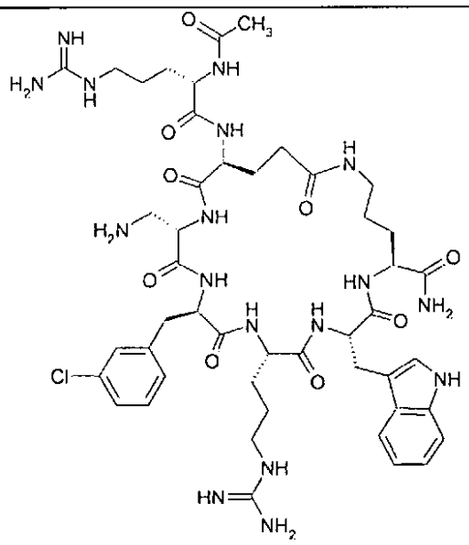
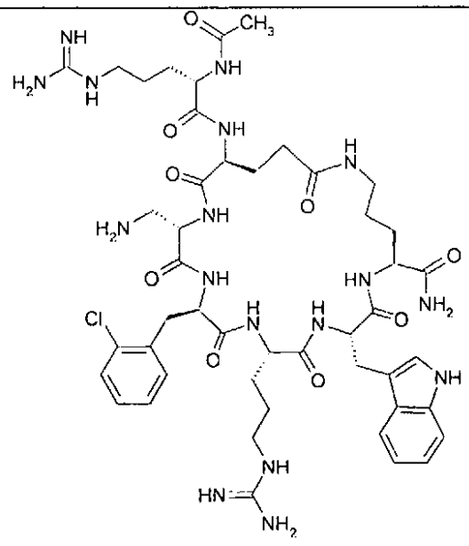
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 51 |  | Ac-D-Arg-*cyclo*(Orn-His-D-Phe(3-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:56) | 0.6 | 3 |
| 52 |  | Ac-D-Arg-*cyclo*(Orn-His-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:57) | 0.6 | 6 |

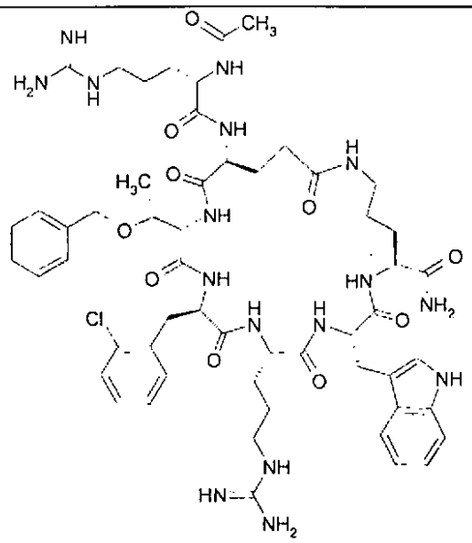
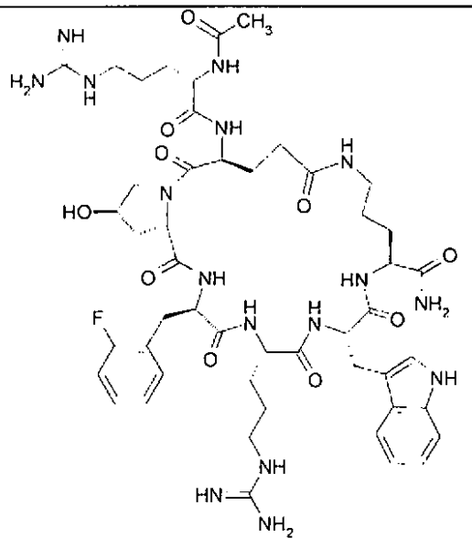
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 53 |  | Ac-D-Arg-*cyclo*(Orn-His-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:58) | 0.95 | 0.75 |
| 54 |  | Ac-D-Arg-*cyclo*(Orn-His-D-Phe(3,4-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:59) | 0.25 | 0.7 |

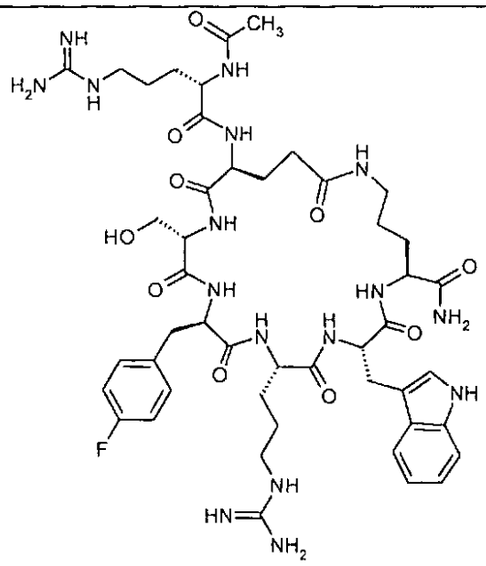
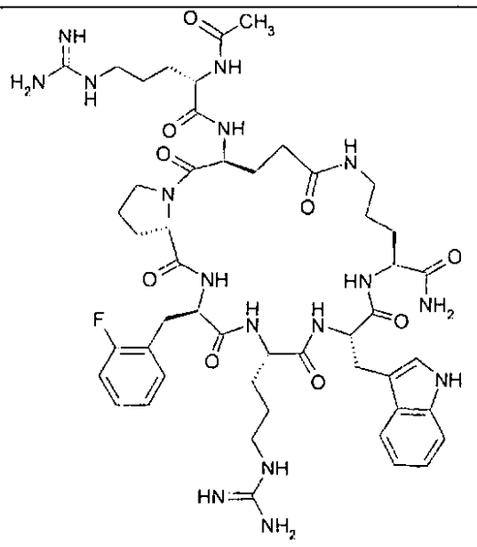
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 55 |  | Ac-Arg-*cyclo*(Glu-Orn-D-Phe(3-Cl)-Arg-Trp-Orn)-OH (SEQ ID NO:60) | 20 | 23 |
| 56 |  | Ac-Arg-*cyclo*(Glu-Dab(Acetyl)-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:61) | 11 | 30 |

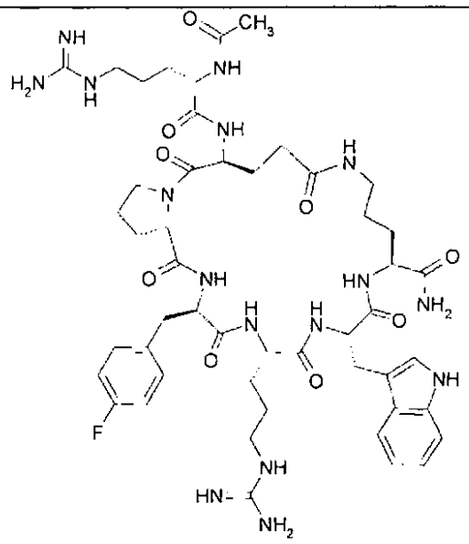
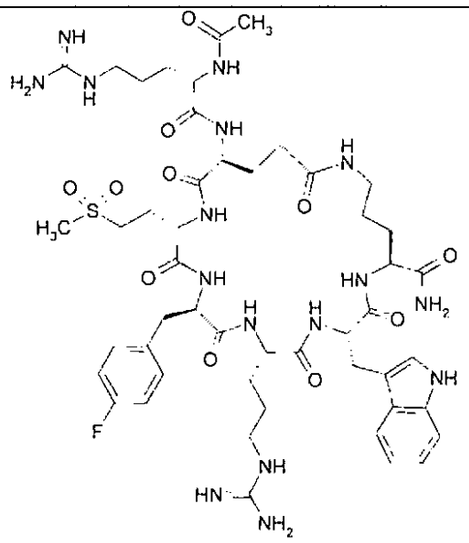
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 57 |  | Ac-D-Arg-*cyclo*(Orn-His-D-Phe(4-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:62) | 0.65 | 1 |
| 58 |  | Ac-Arg-*cyclo*(Glu-Ser-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:63) | 15 | 138 |

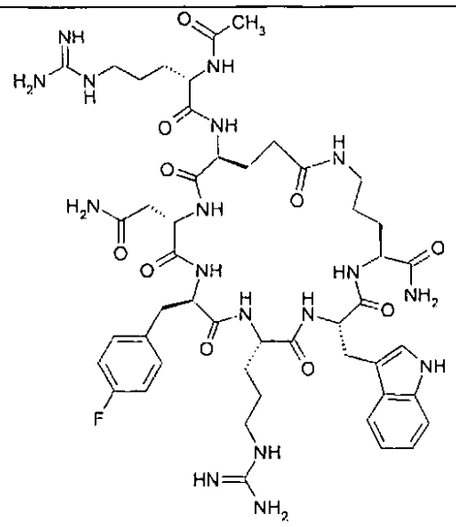
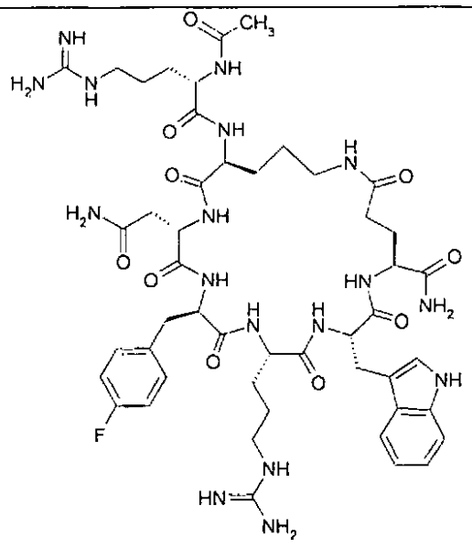
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 59 |  | Ac-Arg-*cyclo*(Glu-Gln-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:64) | 7 | 58 |
| 60 |  | Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:65) | 1 | 89 |

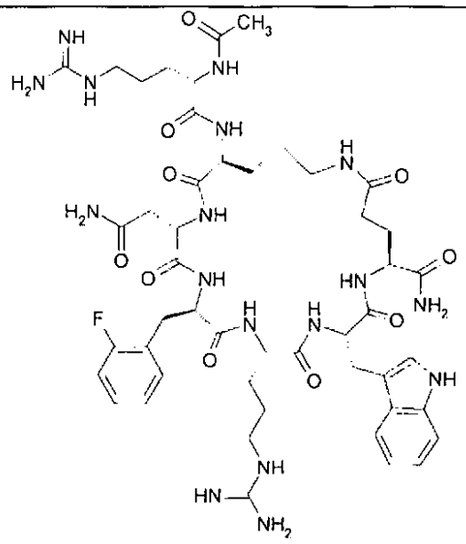
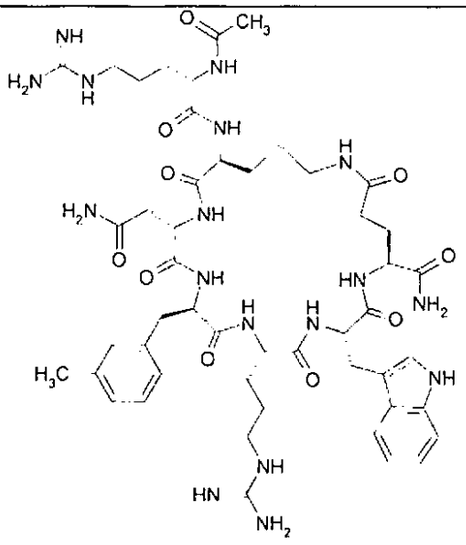
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 61 |  | Ac-Arg-*cyclo*(Glu-Dap-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:66) | 4 | 25 |
| 62 |  | Ac-Arg-*cyclo*(Glu-Dap-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:67) | 9 | 28 |

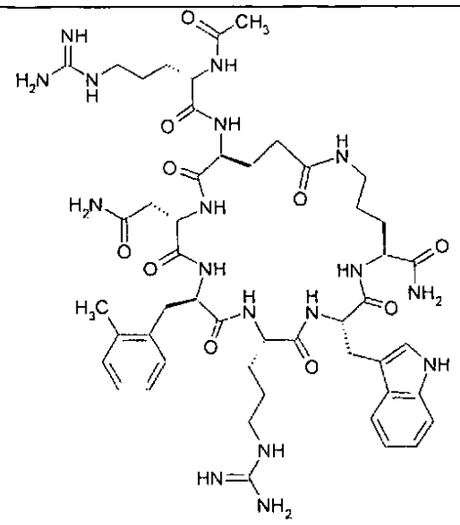
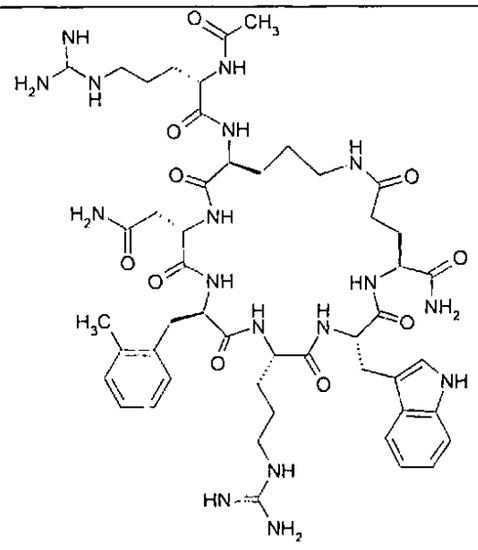
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 63 |  | Ac-Arg-*cyclo*(Glu-Thr(Bzl)-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:68) | 0.35 | 12 |
| 64 |  | Ac-Arg-*cyclo*(Glu-Hyp-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:69) | 3 | 53 |

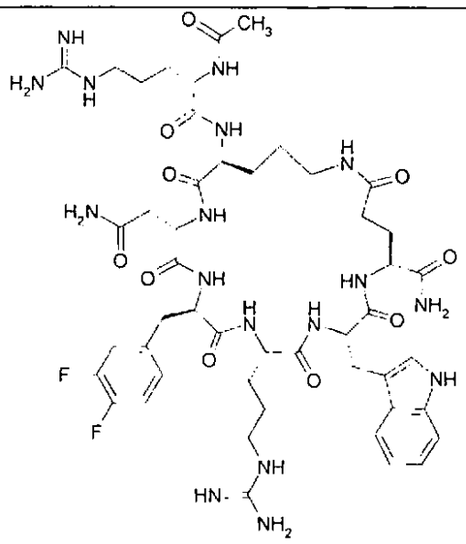
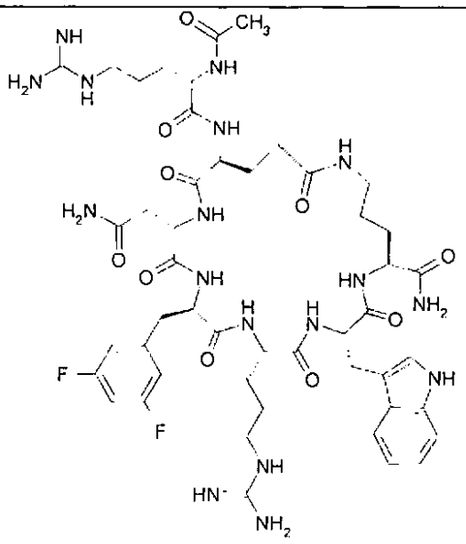
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 65 |  | Ac-Arg-*cyclo*(Glu-Ser-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:70) | 5 | 43 |
| 66 |  | Ac-Arg-*cyclo*(Glu-Pro-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:71) | 6 | 95 |

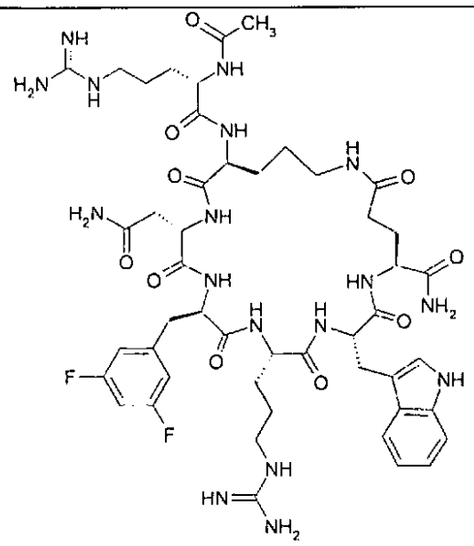
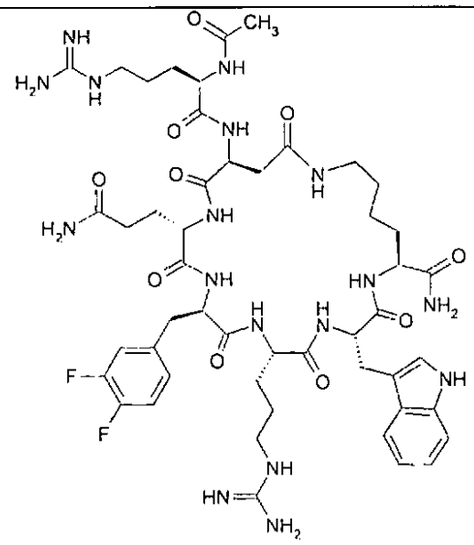
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 67 |  | Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72) | 5 | 130 |
| 68 |  | Ac-Arg-*cyclo*(Glu-Met($O_2$)-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:73) | 2 | 33 |

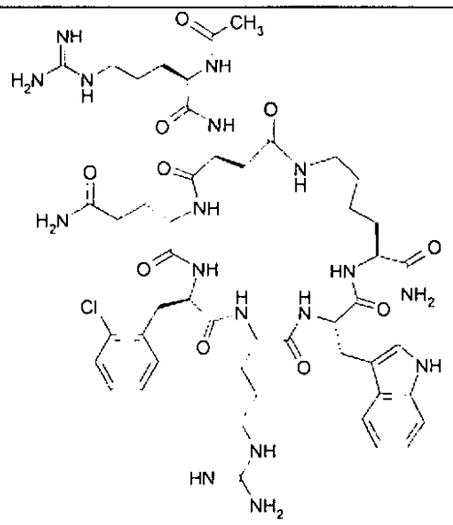
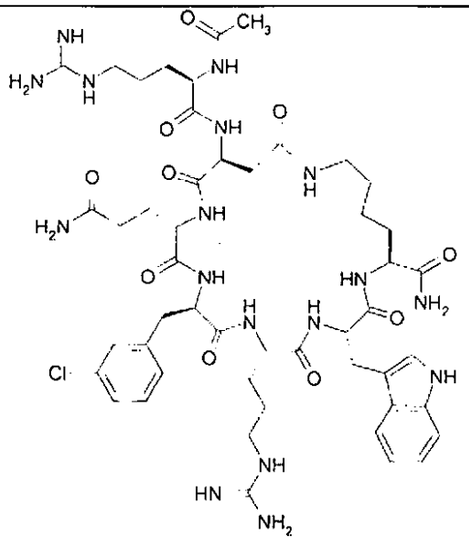
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 69 |  | Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:74) | 3 | 150 |
| 70 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(4-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:75) | 3 | 170 |

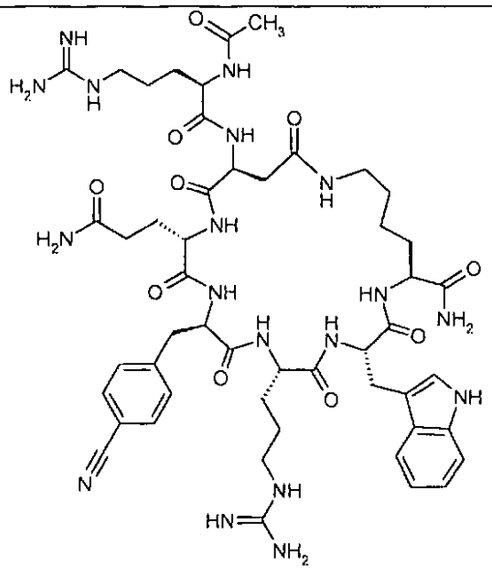
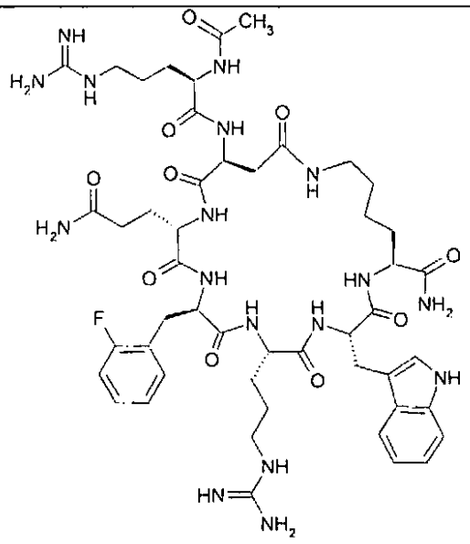
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 71 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:76) | 9 | 335 |
| 72 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(3-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:77) | 4 | 2300 |

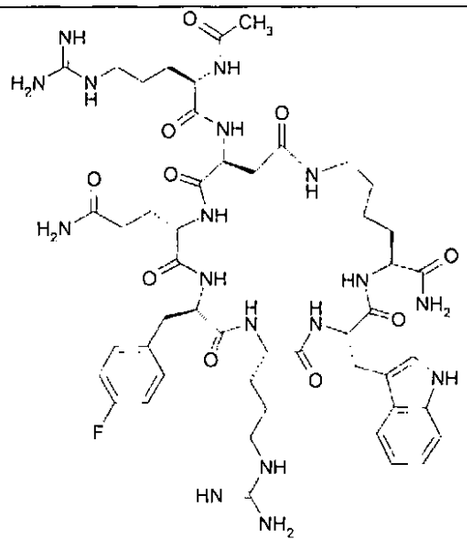
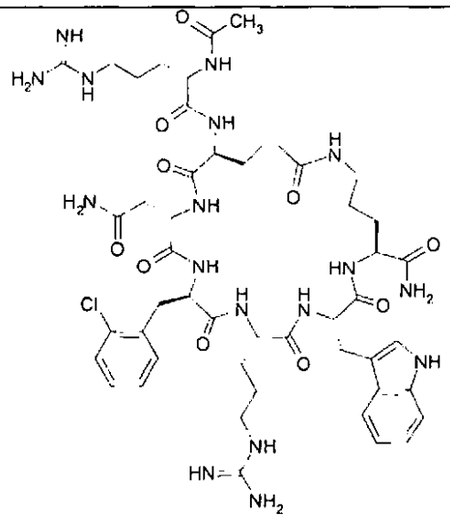
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 73 |  | Ac-Arg-*cyclo*(Glu-Asn-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:78) | 4 | 160 |
| 74 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(2-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:79) | 5 | 405 |

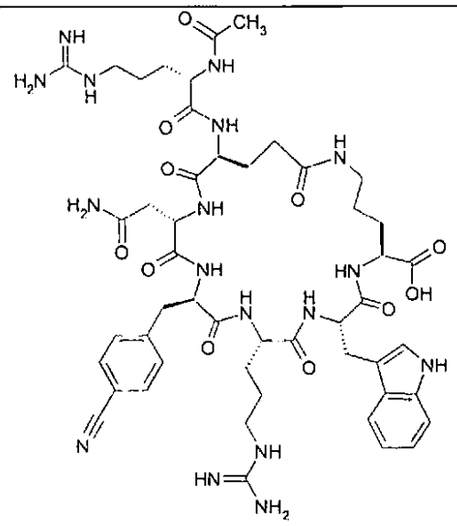
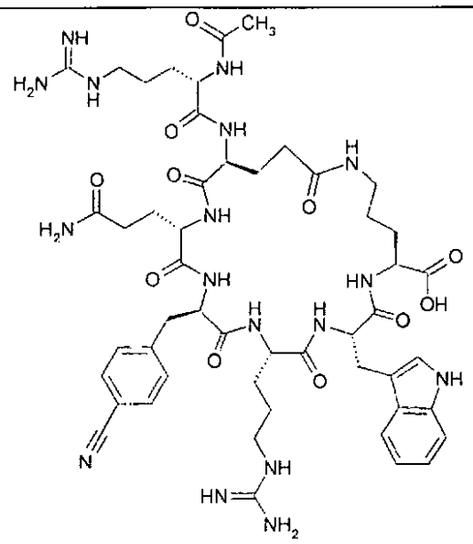
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 75 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(3,4-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:80) | 3 | 190 |
| 76 |  | Ac-Arg-*cyclo*(Glu-Asn-D-Phe(3,5-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:81) | 20 | 260 |

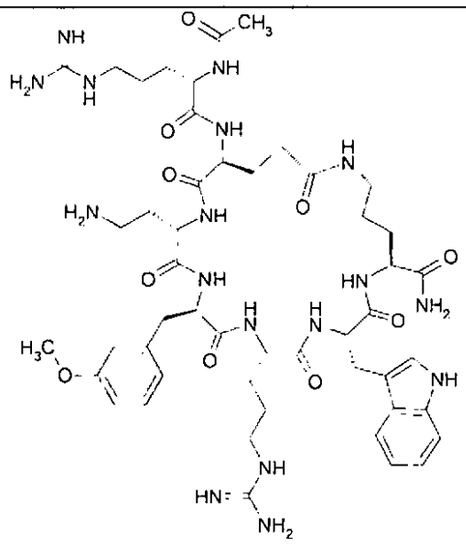
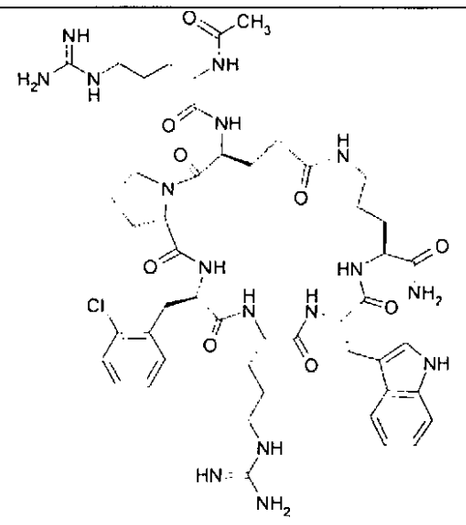
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 77 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(3,5-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:82) | 8 | 190 |
| 78 |  | Ac-D-Arg-*cyclo*(Asp-Gln-D-Phe(3,4-diF)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:83) | 8 | 515 |

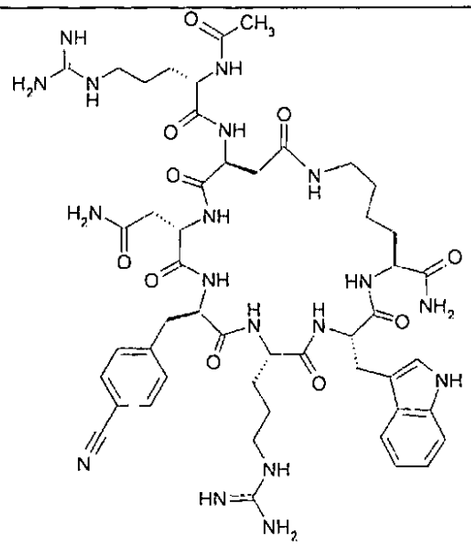
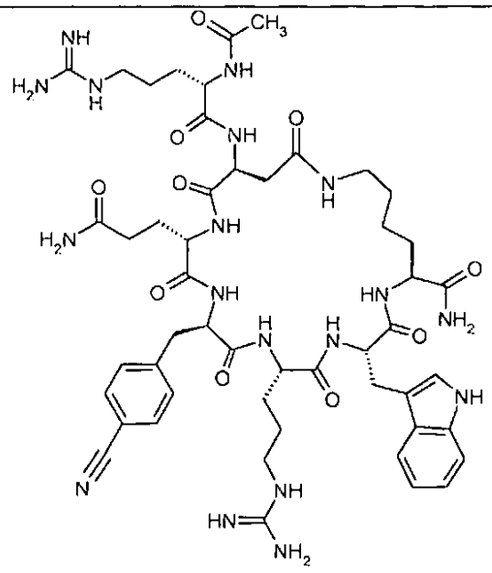
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 79 |  | Ac-D-Arg-*cyclo*(Asp-Gln-D-Phe(2-Cl)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:84) | 10 | 395 |
| 80 |  | Ac-D-Arg-*cyclo*(Asp-Gln-D-Phe(3-Cl)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:85) | 7 | 1750 |

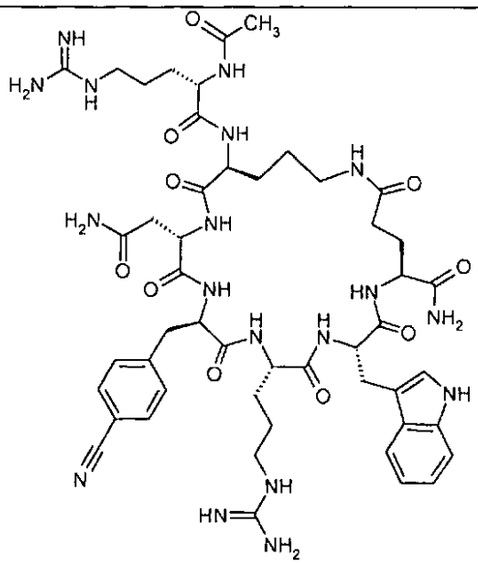
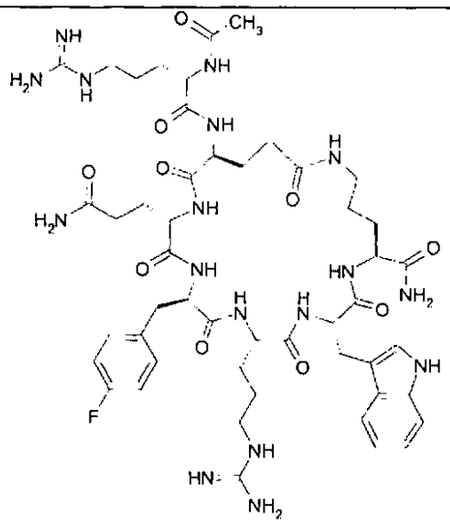
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 81 |  | Ac-D-Arg-*cyclo*(Asp-Gln-D-Phe(4-CN)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:86) | 13 | 10000 |
| 82 |  | Ac-D-Arg-*cyclo*(Asp-Gln-D-Phe(2-F)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:87) | 10 | 220 |

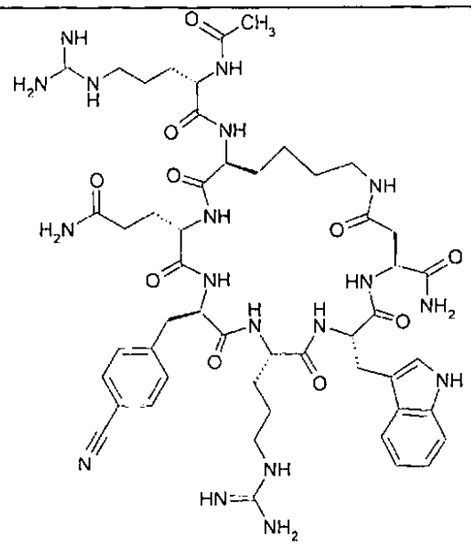
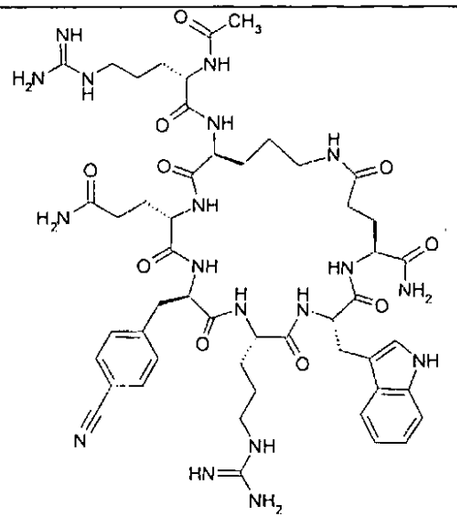
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 83 |  | Ac-D-Arg-*cyclo*(Asp-Gln-D-Phe(4-F)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:88) | 6 | 260 |
| 84 |  | Ac-Arg-*cyclo*(Glu-Asn-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:89) | 7 | 245 |

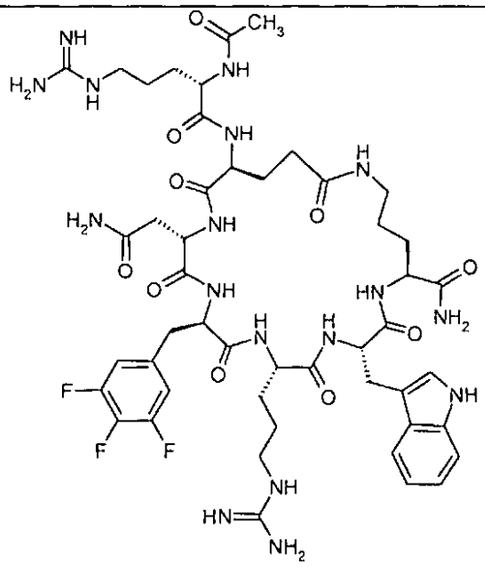
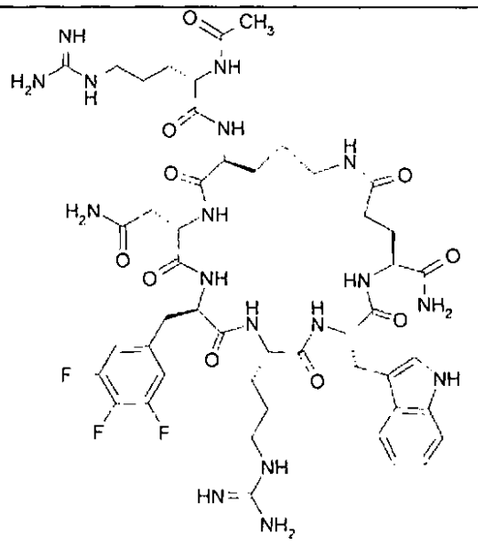
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 85 |  | Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:90) | 64 | 10000 |
| 86 |  | Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:91) | 40 | 3968 |

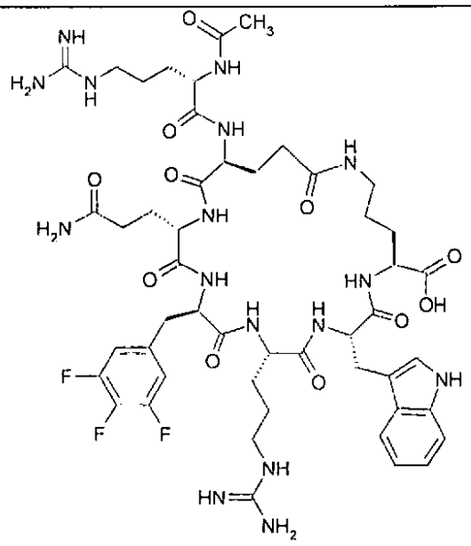
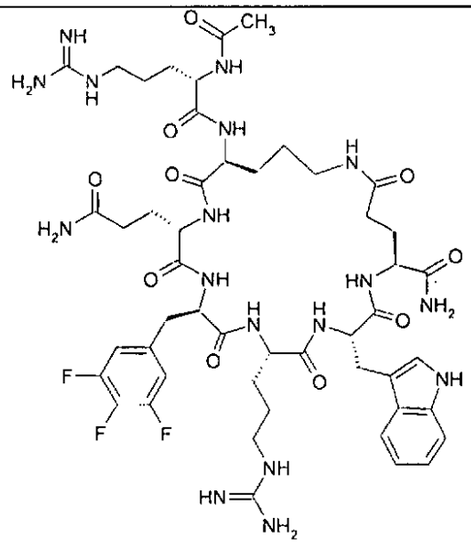
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 87 |  | Ac-Arg-*cyclo*(Glu-Dab-D-Phe(3-OMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:92) | 3 | - |
| 88 |  | Ac-Arg-*cyclo*(Glu-Pro-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:93) | 5 | - |

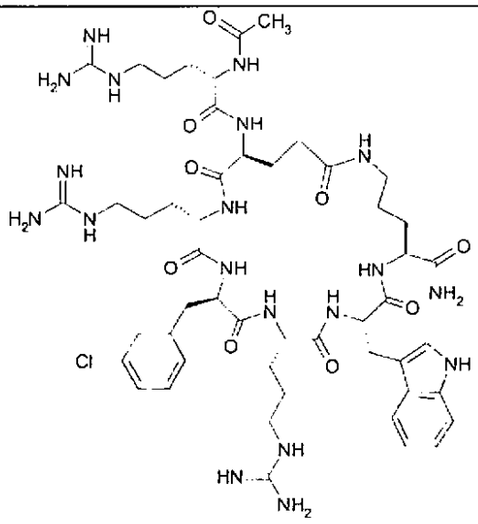
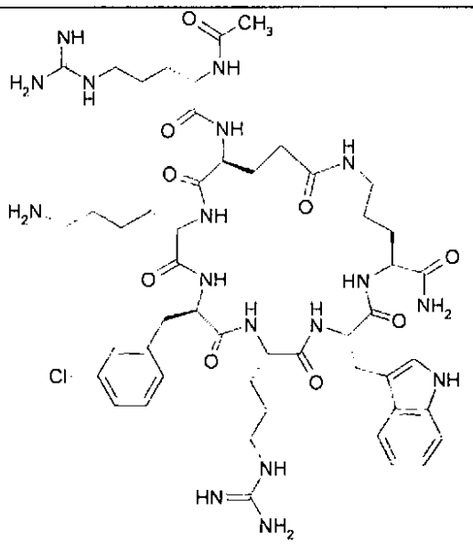
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 89 |  | Ac-Arg-*cyclo*(Asp-Asn-D-Phe(4-CN)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:94) | 48 | - |
| 90 |  | Ac-Arg-*cyclo*(Asp-Gln-D-Phe(4-CN)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:95) | 5 | - |

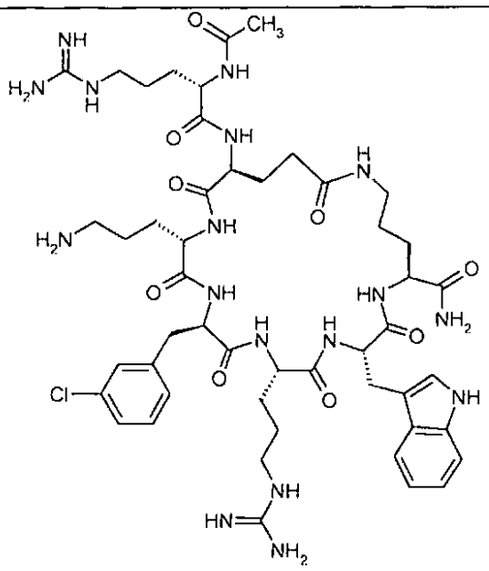
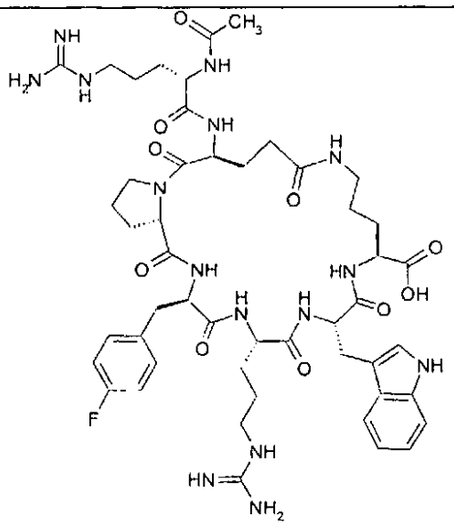
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 91 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:96) | 4 | - |
| 92 |  | Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:97) | 2 | - |

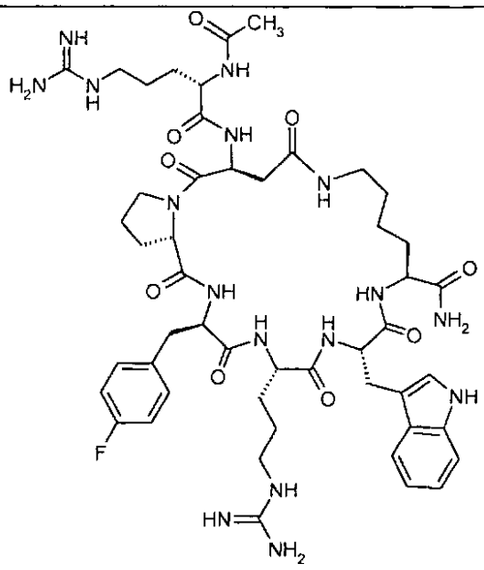
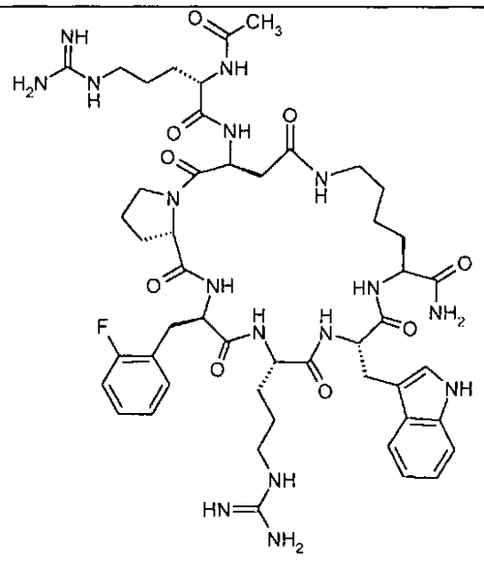
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 93 |  | Ac-Arg-*cyclo*(Lys-Gln-D-Phe(4-CN)-Arg-Trp-Asp)-$NH_2$ (SEQ ID NO:98) | 1 | - |
| 94 |  | Ac-Arg-*cyclo*(Orn-Gln-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:99) | 0.9 | - |

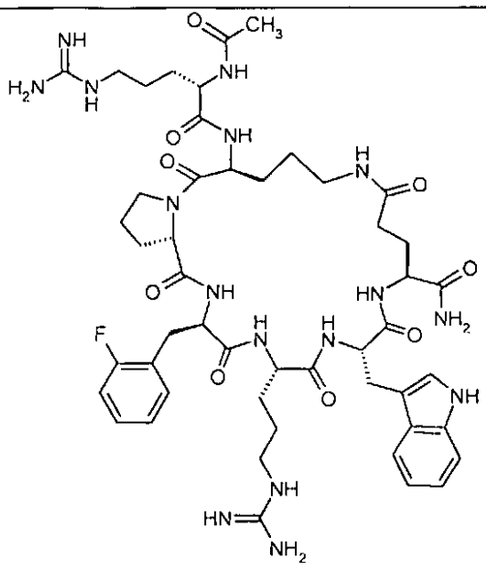
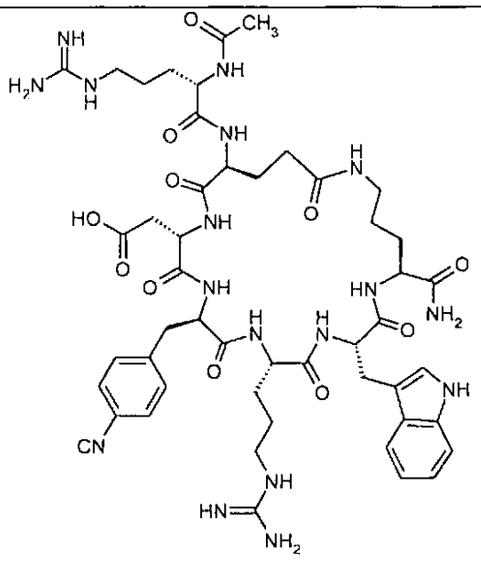
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 95 |  | Ac-Arg-*cyclo*(Glu-Asn-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:100) | 3 | - |
| 96 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(3,4,5-triF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:101) | 2 | - |

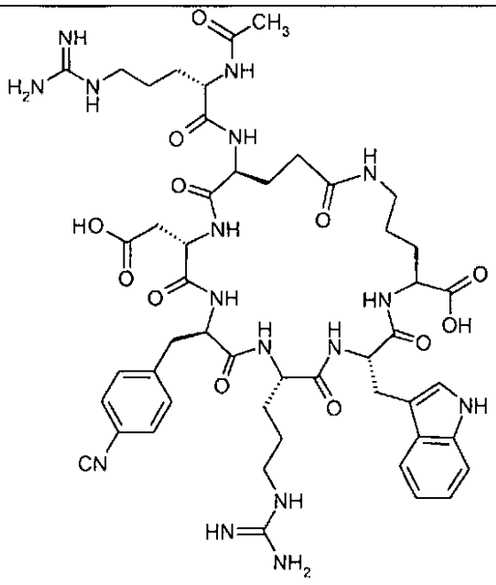
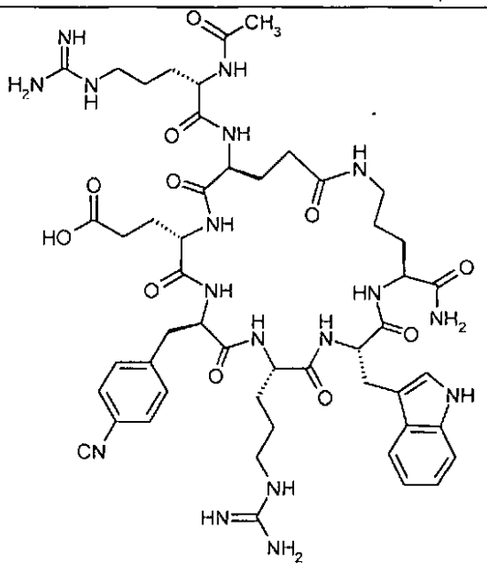
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 97 |  | Ac-Arg-*cyclo*(Glu-Gln-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:102) | 0.75 | - |
| 98 |  | Ac-Arg-*cyclo*(Orn-Gln-D-Phe(3,4,5-triF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:103) | 0.75 | - |

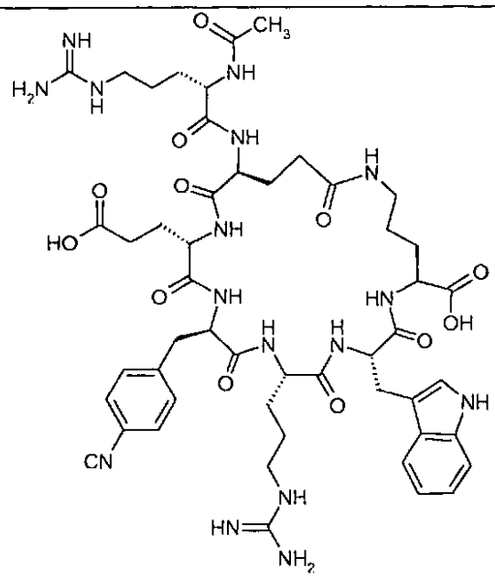
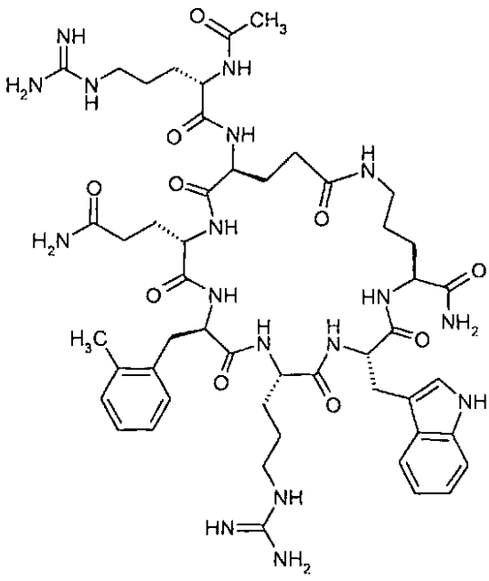
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 99 |  | Ac-Arg-*cyclo*(Glu-Arg-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:104) | 0.5 | - |
| 100 |  | Ac-Arg-*cyclo*(Glu-Lys-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:105) | 4 | - |

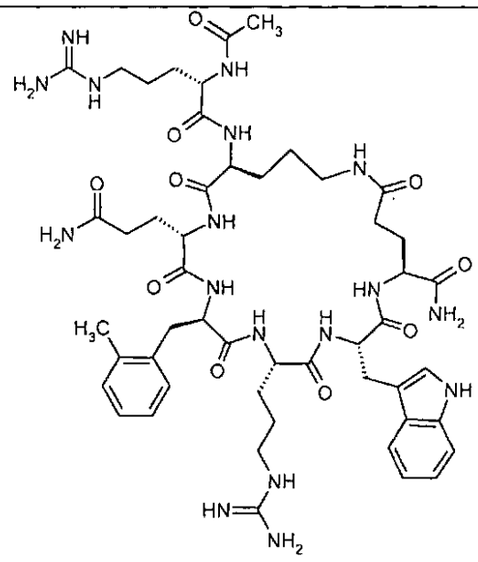
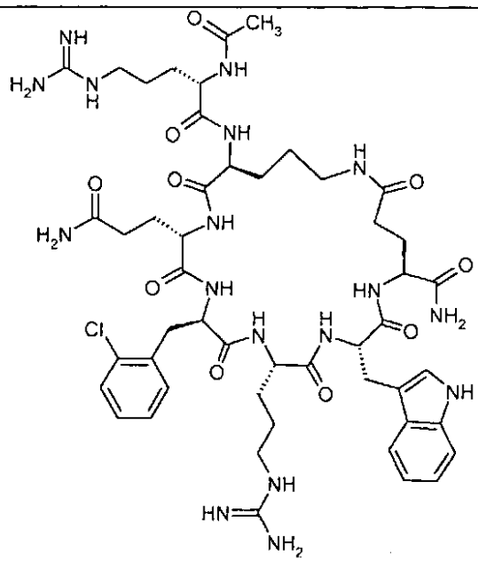
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 101 |  | Ac-Arg-*cyclo*(Glu-Orn-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:106) | 1 | - |
| 102 |  | Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-OH (SEQ ID NO:107) | 30 | 730 |

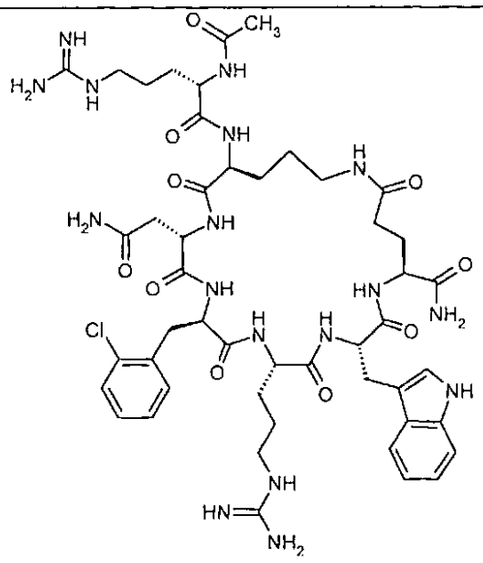
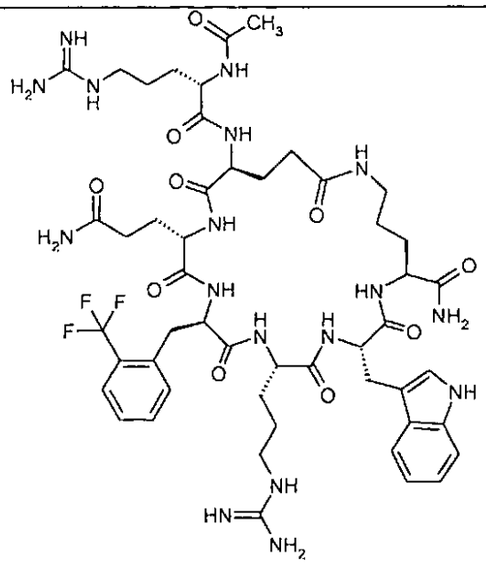
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 103 |  | Ac-Arg-*cyclo*(Asp-Pro-D-Phe(4-F)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:108) | 4 | - |
| 104 |  | Ac-Arg-*cyclo*(Asp-Pro-D-Phe(2-F)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:109) | 78 | - |

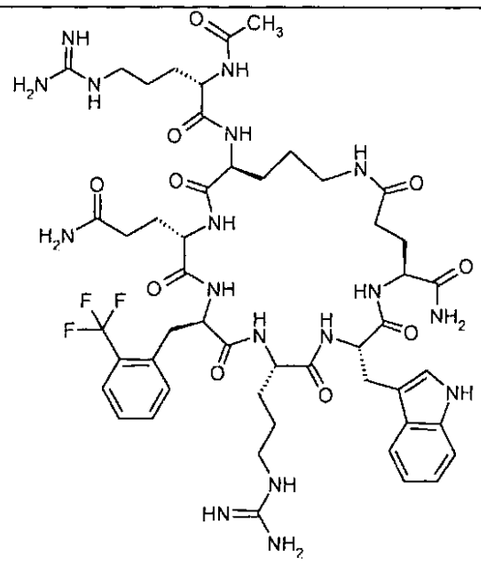
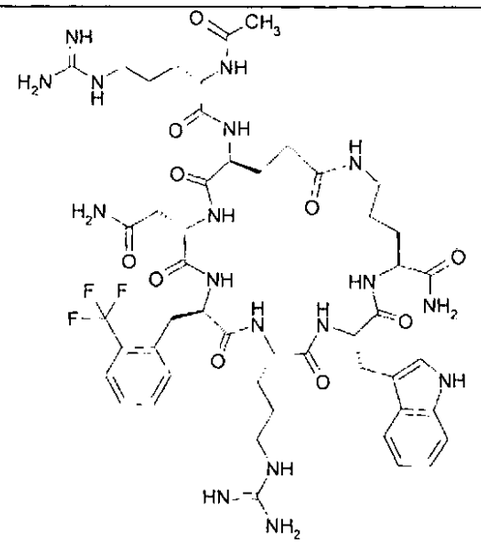
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 105 |  | Ac-Arg-*cyclo*(Orn-Pro-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:110) | 7 | - |
| 106 |  | Ac-Arg-*cyclo*(Glu-Asp-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:111) | 647 | 10000 |

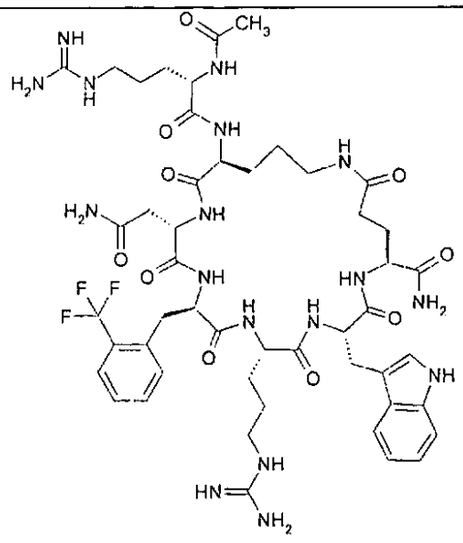
| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 107 |  | Ac-Arg-*cyclo*(Glu-Asp-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:112) | 6463 | 10000 |
| 108 |  | Ac-Arg-*cyclo*(Glu-Glu-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:113) | 128 | 10000 |

| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 109 |  | Ac-Arg-*cyclo*(Glu-Glu-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:114) | 1090 | 10000 |
| 110 |  | Ac-Arg-*cyclo*(Glu-Gln-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:115) | 5 | 105 |

| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 111 |  | Ac-Arg-*cyclo*(Orn-Gln-D-Phe(2-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:116) | 6 | 145 |
| 112 |  | Ac-Arg-*cyclo*(Orn-Gln-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:117) | 4 | 83 |

| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 113 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:118) | 7 | 255 |
| 114 |  | Ac-Arg-*cyclo*(Glu-Gln-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:119) | 8 | 93 |

| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 115 |  | Ac-Arg-*cyclo*(Orn-Gln-D-Phe(2-$CF_3$)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:120) | 4 | 235 |
| 116 |  | Ac-Arg-*cyclo*(Glu-Asn-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:121) | 7 | 380 |

| No. | Structure | Amino Acid Sequence | MC4-R Ki (nM) | MC1-R Ki (nM) |
|---|---|---|---|---|
| 117 |  | Ac-Arg-*cyclo*(Orn-Asn-D-Phe(2-$CF_3$)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:122) | 5 | 540 |

7.0 Tests and Assays Employed in Evaluation of the Peptides of the Present Invention.

The melanocortin receptor-specific peptides of this invention may be tested by a variety of assay systems and animal models to determine binding, functional status and efficacy.

7.1 Competitive Inhibition Assay using [$I^{125}$]-NDP-α-MSH.

A competitive inhibition binding assay was performed for exemplified peptides according to the invention using membrane homogenates prepared from HEK-293 cells that express recombinant hMC4-R, hMC3-R, or hMC5-R, and from B-16 mouse melanoma cells (containing endogenous MC1-R). In some instances, HEK-293 cells that express recombinant hMC1-R were employed. Assays were performed in 96 well GF/B Millipore multiscreen filtration plates (MAFB NOB10) pre-coated with 0.5% bovine serum albumin (Fraction V). Membrane homogenates were incubated with 0.2nM (for hMC4-R) 0.4 nM (for MC3-R and MC5-R) or 0.1 nM (for mouse B16 MC1-R or hMC1-R) [$I^{125}$]-NDP-α-MSH (Perkin Elmer) and increasing concentrations of test peptides of the present invention in buffer containing 25 mM HEPES buffer (pH 7.5) with 100 mM NaCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 0.3 mM 1,10-phenanthroline, and 0.2% bovine serum albumin. After incubation for 60 minutes at 37° C, the assay mixture was filtered and the

membranes washed three times with ice-cold buffer. Filters were dried and counted in a gamma counter for bound radioactivity. Non-specific binding was measured by inhibition of binding of [$I^{125}$]-NDP-α-MSH in the presence of 1 μM NDP-α-MSH. Maximal specific binding (100%) was defined as the difference in radioactivity (cpm) bound to cell membranes in the absence and presence of 1 μM NDP-α-MSH. Radioactivity (cpm) obtained in the presence of test peptides was normalized with respect to 100% specific binding to determine the percent inhibition of [$I^{125}$]-NDP-α-MSH binding. Each assay was conducted in triplicate and the actual mean values are described, with results less than 0% reported as 0%. Ki values for test peptides of the present invention were determined using Graph-Pad Prism® curve-fitting software. Results from this assay are presented herein (see 6.1). For some peptides, a mean value of more than two values is presented.

7.2 Assay for Agonist Activity.

Accumulation of intracellular cAMP was examined as a measure of the ability of peptides of the present invention to elicit a functional response in HEK-293 cells that express MC4-R. Confluent HEK-293 cells that express recombinant hMC4-R were detached from culture plates by incubation in enzyme-free cell dissociation buffer. Dispersed cells were suspended in Earle's Balanced Salt Solution containing 10 mM HEPES (pH 7.5), 1 mM $MgCl_2$, 1mM glutamine, 0.5% albumin and 0.3 mM 3-isobutyl-1-methyl-xanthine (IBMX), a phosphodiesterase inhibitor. The cells were plated in 96-well plates at a density of 0.5 x $10^5$ cells per well and pre-incubated for 10 minutes. Cells were exposed for 15 minutes at 37° C to peptides of the present invention dissolved in DMSO (final DMSO concentration of 1%) at a concentration range of 0.05 - 5000 nM in a total assay volume of 200 μL. NDP-α-MSH was used as the reference agonist. cAMP levels were determined by an HTRF® cAMP cell-based assay system from Cisbio Bioassays utilizing cryptate-labeled anti-cAMP and d2-labeled cAMP, with plates read on a Perkin-Elmer Victor plate reader at 665 and 620nM. Data analysis was performed by nonlinear regression analysis with Graph-Pad Prism® software. The maximum efficacies of test peptides of the present invention were compared to that achieved by the reference melanocortin agonist NDP-α-MSH, used as full agonist benchmark in this context.

7.3 High and Low Density hMC4-R Functional Assay.

A HEK293 cell line transfected with human MC4-R (Palatin Technologies, US, with license from the University of Michigan) was used. The human MC4-R was

introduced to HEK293 by using the T-REx™ System, Invitrogen. The T-REx™ System employs a tetracycline-regulated mammalian expression system that uses regulatory elements from the *E. coli* Tn*10*-encoded tetracycline (Tet) resistance operon. By use of the T-REx™ System, expression of the gene of interest, the human MC4-R gene, is repressed in the absence of tetracycline or doxycycline and induced in the presence of tetracycline or doxycycline (see T-REx™ System Manual, published by Invitrogen).

HEK293-T-REx-MC4-R cells were cultured in DMEM (Gibco 11965), supplemented with L-Glutamine (Gibco 25030), 10% fetal bovine serum (FBS), 200 µg/mL Zeocin (Invitrogen 46-0072) and 6 µg/mL Blasticidin (Invitrogen 46-1120) in 5% $CO_2$ and 95% humidity at 37°C. T-150 flasks of cells at 75% confluence were incubated with two concentrations of doxycycline (0.1 ng/mL to provide a low density hMC4-R system and 10 ng/mL to provide a high density hMC4-R system) in 5% $CO_2$ at 37°C for 16-18 hours to induce MC4-R expression. On the day of the assay, the cells were washed with PBS (Gibco 14190) and harvested using cell dissociation buffer (Gibco 13150-016), then centrifuged and resuspended in Hanks' Balanced Salt Solution (+Ca, +Mg) (Gibco 14025), 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (pH 7.4) (Sigma H0887), 1mM L-Glutamine (Gibco 25030), 1 mg/mL bovine serum albumin (BSA) (Sigma A3311) and 0.3 mM 3-isobutyl-1-methyl-xanthine (IBMX). Cells were then counted and volume was adjusted to 2.5 x $10^5$ cells per ml.

The cells were then dispensed into 96-well plates (BD 353916) in 198 µL (about 5 x $10^4$) cells/well and incubated for 10 minutes at 37°C. The compound to be tested was diluted with DMSO to a final concentration of 1 mM. Serial dilution was prepared in polypropylene removable 12-well library tube strips (VWR cat# 83009-682). 120 µL of the 1 mM compound stock was pipetted in the second column on the plate. Using the Janus liquid handler the compound was serially diluted 1:10 (25 µL compound + 225 µL DMSO) to a total of 9 concentrations (representing final assay concentrations ranging from $10^{-5}$ to $10^{-13}$ M).

2 µL of the standard, [Nle$^4$, D-Phe$^7$]-alpha-Melanocyte Stimulating Hormone (NDP-α-MSH), or compound was added to the 96-well plate using the Janus robotic system. All assay samples were run in duplicate (i.e. each sample was in two low dox and two high dox plates, respectively). The plates were gently shaken and incubated for 15 minutes at

37° C. The reaction was stopped by adding 15 µL of lysis buffer per well and the plates were shakened for 30 minutes at room temperature.

Agonist stimulation of the MC4-R activates adenylate cyclase, which is an enzyme that catalyses the formation 3′,5′-cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). Thus, agonist stimulation of the MC4-R increases the levels of cAMP. cAMP-levels were measured with the cAMP dynamic 2 HTRF kit (CisBio cat# 62AM4PEC; see manual published by CisBio). cAMP levels were normalised against plate controls (1% DMSO for 0%, 400 nM NDP-α-MSH for 100%) and a calibration curve ranging from 712 nM to 0.04 nM cAMP (essentially as described in the CisBio HTRF kit). The plates were incubated on a shaker at room temperature for 1 hour and read on the Perkin-Elmer Victor plate reader at 665 and 620 nm. Fluorescence ratios were then calculated as described in the CisBio HTRF kit, with GraphPad Prism software used to plot the change in fluorescence percent values versus cAMP concentration using the variable slope dose response curve and, based on calculated cAMP concentrations, to determine $EC_{50}$ values and percent activation. Results from this assay are presented herein (see 8.0).

7.4 Food Intake and Body Weight Change.

Change in food intake and body weight was evaluated for selected peptides administered by subcutaneous injection route. Male Sprague-Dawley rats were obtained from Hilltop Lab Animals, Inc. (Scottdale, PA). Animals were individually housed in conventional polystyrene hanging cages and maintained on a controlled 12 hour on/off light cycle. Water and pelleted food (ProLab RMH 2500, W.F. Fisher & Son Inc.) was provided *ad libitum*. The rats were dosed subcutaneously with vehicle (3.2% mannitol/50mM Tris buffer) or selected peptides (1.0 mg/kg). The changes in food intake for the 4 and 24 hour periods after dosing and the changes in body weight for the 24 hour period after dosing were determined. The changes in body weight and food intake for the 48 hour and 72 hour periods after dosing was also measured to determine reversal of changes in body weight and food intake effects back to baseline levels (not shown).

Food intake (FI, 0-4 h and 0-24 h) and body weight (BW, 0-24 h) results from studies with 1.0 mg/kg subcutaneously of Examples 43, 46 and 67 and corresponding vehicle controls run in parallel are shown in Table 2 below, expressed as means ± SEM (n=8-10).

**Table 2**

| Experiment | Treatment | Dose (mg/kg, s.c.) | n | FI 0-4h (g) | FI 0-24h (g) | BW change 0-24h (g) |
|---|---|---|---|---|---|---|
| 1 | Vehicle | | 10 | 10.53 ± 0.78 | 27.75 ± 1.00 | 1.49 ± 0.18 |
| 1 | Ref Ex 2 | 1.0 | 10 | 4.41 ± 0.48 | 20.84 ± 1.01 | -0.38 ± 0.46 |
| 1 | Ex 43 | 1.0 | 10 | 6.85 ± 0.55 | 24.44 ± 0.85 | 0.45 ± 0.35 |
| | | | | | | |
| 2 | Vehicle | | 8 | 7.09 ± 0.39 | 27.46 ± 1.16 | 1.96 ± 0.55 |
| 2 | Ref Ex 2 | 1.0 | 8 | 2.80 ± 0.27 | 21.81 ± 1.04 | 0.85 ± 0.45 |
| 2 | Ex 46 | 1.0 | 8 | 3.71 ± 0.68 | 20.56 ± 1.14 | -0.29 ± 0.55 |
| | | | | | | |
| 3 | Vehicle | | 8 | 7.76 ± 0.53 | 25.71 ± 0.25 | 2.25 ± 0.50 |
| 3 | Ref Ex 2 | 1.0 | 8 | 3.17 ± 0.42 | 19.98 ± 0.60 | -0.27 ± 0.48 |
| 3 | Ex 67 | 1.0 | 8 | 4.20 ± 0.66 | 21.51 ± 1.27 | -0.05 ± 0.39 |

7.5 Induction of Penile Erection.

The ability of peptides of the present invention to induce penile erection (PE) in male rats was evaluated with selected peptides. Male Sprague-Dawley rats weighing 250-300 g were kept on a 12 hour on/off light cycle with food and water *ad libitum*. All behavioral studies were performed between 9 a.m. and 4 p.m. Groups of 6-8 rats were administered peptides at a variety of doses via the subcutaneous injection route. Immediately after treatment, rats were placed into individual polystyrene cages (27 cm long, 16 cm wide, and 25 cm high) for behavioral observation, typically by remote video monitoring (High-speed Digital Video Recording System EVS-DSX-16000DVD-H with CCD cameras, Epic Systems Inc., St. Louis, MO, USA) followed by blinded off-line scoring of video recordings. Rats were observed for one hour, and the number of yawns, grooming bouts and PEs were recorded in 10-minute bins.

PE results from studies with 1.0-3.0 mg/kg subcutaneously of Examples 43, 46 and 67, along with Ref Ex 2, are shown in Table 3 below, expressed as total number of PE/rat, mean ± SEM (n=7-11) and number of rats/group showing at least one erection over the study period (% responders). Corresponding vehicle controls (3.2% mannitol/50mM Tris buffer) were run in parallel.

**Table 3**

| Treatment | Dose (mg/kg, s.c.) | n | Total number of PE/rat 0-1h | % Responders |
|---|---|---|---|---|
| Vehicle | | 11 | 1.0 ± 0.27 | 64 |
| Ref Ex 2 | 3.0 | 7 | 6.0 ± 0.44 | 100 |
| Ex 43 | 1.0 | 7 | 1.7 ± 0.36 | 29 |
| | 3.0 | 7 | 6.0 ± 0.76 | 100 |
| Ex 46 | 1.0 | 7 | 4.9 ± 1.1 | 100 |
| | 3.0 | 7 | 4.4 ± 1.1 | 86 |
| Ex 67 | 1.0 | 7 | 2.3 ± 0.42 | 86 |
| | 3.0 | 7 | 3.3 ± 1.0 | 100 |

8.0 High and Low Density hMC4-R Functional Assay Results

Exemplified peptides were tested using the high and low density hMC4-R functional assay as described in Section 7.3 above, with the results as shown in Table 4 below. Table 4 includes both single point values and mean values.

**Table 4**

| Compound | 0.1 ng/mL Doxycycline | | 10 ng/mL Doxycycline | |
|---|---|---|---|---|
| | $EC_{50}$ (nM) | Intrinsic Activity (%) | $EC_{50}$ (nM) | Intrinsic Activity (%) |
| Example 1 | 0.34 | 91 | 0.045 | 96 |
| Example 2 | 0.56 | 36 | 0.095 | 99 |
| Example 3 | 0.07 | 28 | 0.16 | 100 |
| Example 4 | - | 11 | 0.245 | 100 |
| Example 5 | - | 5 | 0.38 | 92 |
| Example 6 | 37 | 29 | 2 | 100 |
| Example 7 | 0.3 | 48 | 0.135 | 100 |
| Example 8 | 48 | 71 | 0.55 | 87 |
| Example 9 | 0.09 | 91 | 0.035 | 89 |
| Example 10 | 0.45 | 77 | 0.17 | 94 |
| Example 11 | 0.065 | 83 | 0.06 | 90 |
| Example 12 | 34 | 64 | 0.5 | 97 |
| Example 13 | 0.125 | 85 | 0.06 | 96 |

| Compound | 0.1 ng/mL Doxycycline | | 10 ng/mL Doxycycline | |
|---|---|---|---|---|
| | $EC_{50}$ (nM) | Intrinsic Activity (%) | $EC_{50}$ (nM) | Intrinsic Activity (%) |
| Example 14 | 8 | 16 | 0.4 | 93 |
| Example 15 | 0.165 | 16 | 0.2 | 90 |
| Example 16 | 0.15 | 28 | 0.16 | 97 |
| Example 17 | 0.95 | 64 | 0.12 | 95 |
| Example 18 | 0.14 | 83 | 0.085 | 97 |
| Example 19 | 0.42 | 35 | 0.22 | 97 |
| Example 20 | - | 0.5 | 0.75 | 53 |
| Example 21 | - | 8 | 0.5 | 97 |
| Example 22 | 3 | 78 | 0.2 | 93 |
| Example 23 | 2 | 17 | 0.55 | 95 |
| Example 24 | 0.7 | 15 | 0.45 | 99 |
| Example 25 | 75 | 23 | 2 | 94 |
| Example 26 | 0.125 | 74 | 0.12 | 90 |
| Example 27 | 0.7 | 37 | 0.33 | 97 |
| Example 28 | 29 | 35 | 0.6 | 94 |
| Example 29 | 3 | 14 | 0.8 | 100 |
| Example 30 | - | 2 | 25 | 9 |
| Example 31 | 7 | 33 | 0.313 | 98 |
| Example 32 | 18 | 34 | 0.543 | 96 |
| Example 33 | 1 | 41 | 0.153 | 98 |
| Example 34 | 1 | 79 | 0.137 | 97 |
| Example 35 | - | 6 | 1 | 84 |
| Example 36 | - | 8 | 1 | 89 |
| Example 37 | - | 6 | 0.55 | 90 |
| Example 38 | 2 | 31 | 0.258 | 97 |
| Example 39 | - | 4 | 1 | 79 |
| Example 40 | - | 8 | 0.5 | 93 |
| Example 41 | - | 5 | 0.8 | 84 |
| Example 42 | - | 9 | 0.5 | 84 |

| Compound | 0.1 ng/mL Doxycycline | | 10 ng/mL Doxycycline | |
|---|---|---|---|---|
| | $EC_{50}$ (nM) | Intrinsic Activity (%) | $EC_{50}$ (nM) | Intrinsic Activity (%) |
| Example 43 | 1 | 43 | 0.177 | 100 |
| Example 44 | 11 | 22 | 0.617 | 99 |
| Example 45 | - | 12 | 0.45 | 87 |
| Example 46 | 0.666 | 40 | 0.173 | 97 |
| Example 47 | 0.31 | 36 | 0.373 | 100 |
| Example 48 | - | 6 | 4 | 93 |
| Example 49 | 2 | 74 | 0.235 | 93 |
| Example 50 | 0.21 | 94 | 0.085 | 94 |
| Example 51 | 0.64 | 22 | 0.4 | 95 |
| Example 52 | 0.325 | 31 | 0.2 | 99 |
| Example 53 | 0.13 | 86 | 0.13 | 90 |
| Example 54 | 0.075 | 56 | 0.075 | 92 |
| Example 55 | 10 | 28 | 0.8 | 98 |
| Example 56 | 5 | 41 | 0.3 | 98 |
| Example 57 | 0.25 | 89 | 0.095 | 100 |
| Example 58 | 5 | 67 | 0.25 | 100 |
| Example 59 | 0.6 | 90 | 0.1 | 98 |
| Example 60 | 0.45 | 62 | 0.14 | 95 |
| Example 61 | - | 6 | 0.95 | 89 |
| Example 62 | 16 | 23 | 0.47 | 84 |
| Example 63 | 0.37 | 30 | 0.157 | 93 |
| Example 64 | 1 | 57 | 0.08 | 90 |
| Example 65 | 1 | 58 | 0.085 | 93 |
| Example 66 | 5 | 32 | 0.265 | 88 |
| Example 67 | 1 | 38 | 0.14 | 99 |
| Example 68 | 0.85 | 55 | 0.075 | 91 |
| Example 69 | 0.25 | 76 | 0.095 | 92 |
| Example 70 | 0.4 | 64 | 0.1 | 91 |
| Example 71 | 1 | 86 | 0.085 | 91 |

| Compound | 0.1 ng/mL Doxycycline | | 10 ng/mL Doxycycline | |
|---|---|---|---|---|
| | $EC_{50}$ (nM) | Intrinsic Activity (%) | $EC_{50}$ (nM) | Intrinsic Activity (%) |
| Example 72 | 3 | 11 | 0.35 | 84 |
| Example 73 | 0.587 | 86 | 0.068 | 102 |
| Example 74 | 0.943 | 68 | 0.11 | 100 |
| Example 75 | 0.65 | 43 | 0.125 | 87 |
| Example 76 | 3 | 53 | 0.135 | 85 |
| Example 77 | 3 | 34 | 0.155 | 80 |
| Example 78 | 2 | 48 | 0.2 | 89 |
| Example 79 | 4 | 48 | 0.2 | 85 |
| Example 80 | 6 | 13 | 0.65 | 86 |
| Example 81 | 4 | 23 | 0.45 | 85 |
| Example 82 | 2 | 79 | 0.095 | 95 |
| Example 83 | 0.75 | 78 | 0.075 | 94 |
| Example 84 | 0.633 | 78 | 0.09 | 97 |
| Example 85 | 15 | 36 | 0.707 | 94 |
| Example 86 | 9 | 36 | 0.483 | 96 |
| Example 87 | 1 | 64 | 0.065 | 100 |
| Example 88 | 3 | 15 | 0.35 | 89 |
| Example 89 | | 6 | 17 | 87 |
| Example 90 | 4 | 31 | 0.283 | 96 |
| Example 91 | 1 | 18 | 0.265 | 96 |
| Example 92 | 0.1 | 81 | 0.04 | 89 |
| Example 93 | 0.3 | 44 | 0.17 | 97 |
| Example 94 | 0.24 | 32 | 0.09 | 92 |
| Example 95 | 1 | 42 | 0.125 | 100 |
| Example 96 | 2 | 24 | 0.235 | 100 |
| Example 97 | 0.8 | 49 | 0.1 | 100 |
| Example 98 | 0.45 | 47 | 0.14 | 100 |
| Example 99 | 0.7 | 32 | 0.14 | 94 |
| Example 100 | 6 | 27 | 0.27 | 93 |

| Compound | 0.1 ng/mL Doxycycline | | 10 ng/mL Doxycycline | |
|---|---|---|---|---|
| | $EC_{50}$ (nM) | Intrinsic Activity (%) | $EC_{50}$ (nM) | Intrinsic Activity (%) |
| Example 101 | 0.95 | 36 | 0.14 | 93 |
| Example 102 | 18 | 30 | 0.725 | 97 |
| Example 103 | 1 | 32 | 0.13 | 100 |
| Example 104 | 191 | 16 | 10 | 100 |
| Example 105 | 3 | 35 | 0.15 | 94 |
| Example 106 | | 3 | 113 | 77 |
| Example 107 | | 4 | | 64 |
| Example 108 | | 3 | 9 | 59 |
| Example 109 | | 2 | 269 | 69 |
| Example 110 | 0.6 | 84 | 0.06 | 105 |
| Example 111 | 0.575 | 81 | 0.053 | 104 |
| Example 112 | 0.39 | 83 | 0.07 | 101 |
| Example 113 | 0.72 | 80 | 0.065 | 100 |
| Example 114 | 1 | 73 | 0.185 | 117 |
| Example 115 | 0.8 | 54 | 0.17 | 108 |
| Example 116 | 0.68 | 77 | 0.095 | 104 |
| Example 117 | 1 | 50 | 0.18 | 112 |

It is believed that peptides of the invention exhibiting an intrinsic activity of equal to or greater than about 0.1 (10%), such as greater than 0.2 (20%) or greater than about 0.3 (30%) or greater than about 0.4 (40%) or greater than about 0.5 (50%) or greater than about 0.6 (60%) %) or greater than about 0.7 (70%), or greater than about 0.8 (80%), or greater than about 0.9 (90%), or equal to or greater than about 1.0 (100%), in the above described high density hMC4-R system (i.e. HEK293TRexMC4R cells treated with 10 ng/ml doxycycline), based on maximal stimulation of adenylyl cyclase achievable by the compound in the same high density hMC4-R system where the maximal stimulation achieved by α-MSH or NDP-α-MSH is designated as an intrinsic activity of 1.0 (100%), provide agonist (full or partial) activity on the MC4 receptor.

A majority of the peptides of the Examples which were tested in the above described high density hMC4-R system (i.e. HEK293TRexMC4R cells treated with 10 ng/ml doxycycline) gave in said assay $EC_{50}$ values for cAMP production of less than 0.05 μM, such as less than 0.01 μM, and in particular less than 0.001 μM .

As seen from Table 4, peptides of the invention may lack intrinsic activity in the low density hMC4-R system and be full agonists in the high density hMC4-R system.

As further seen from Table 4, peptides of the invention may be partial agonists in the above described low density hMC4-R system and full agonists in the above described high density hMC4-R system.

As further seen from Table 4, peptides of the invention may be full agonists in both the low density hMC4-R system and in the high density hMC4-R system.

Without being bound by any theory, it is believed that peptides that either lack intrinsic activity or are partial agonists in the above described low density hMC4-R system (i.e. peptides having intrinsic activity of from 0 to 70% in the low density hMC4-R system) and are partial or full agonists in the above described high density hMC4-R system (i.e. peptides having intrinsic activity of equal to or above 10%, or above 70%, in the high density hMC4-R system) will provide no or a reduced level of sexual effects resulting from MC4 receptor activation, e.g. penile erection, compared to peptides being full agonists in both the low and the high density hMC4-R systems. As explained above, these sexual effects are considered unwanted side-effects upon treatment of energy homeostasis and metabolism related, food intake related and/or energy balance and body weight related diseases, disorders and/or conditions.

It is thus believed that peptides according to the invention possess promising MC4 receptor affinity, efficacy and potency to be useful for treatment of diseases, disorders and/or conditions responsive to activation of the MC4 receptor, in particular energy homeostasis and metabolism related (e.g. diabetes), food intake related and/or energy balance and body weight related diseases, disorders and/or conditions, including obesity, overweight and diseases, disorders and/or conditions associated with obesity and/or overweight, such as type 2 diabetes and metabolic syndrome.

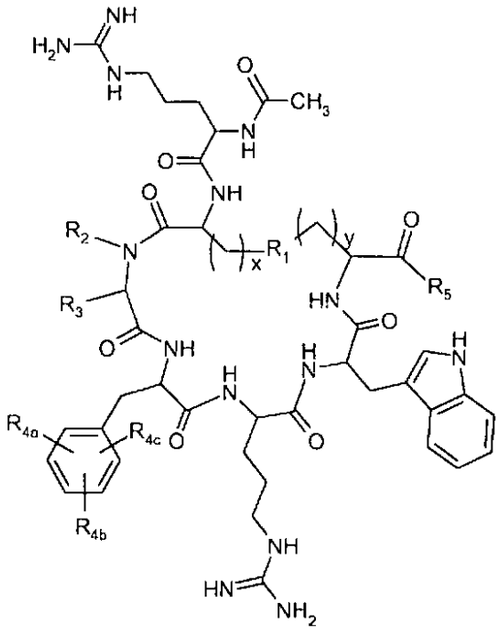
Although the invention has been described in detail with particular reference to these preferred embodiments, other embodiments can achieve the same results. Variations

and modifications of the present invention will be obvious to those skilled in the art and it is intended to cover all such modifications and equivalents.

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CLAIMS

1. A cyclic peptide of Formula (I):



(I)

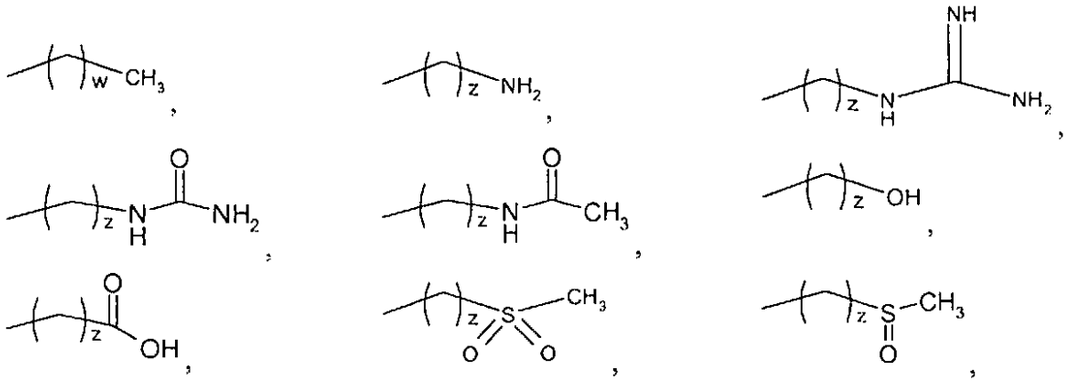
or a pharmaceutically acceptable salt thereof,

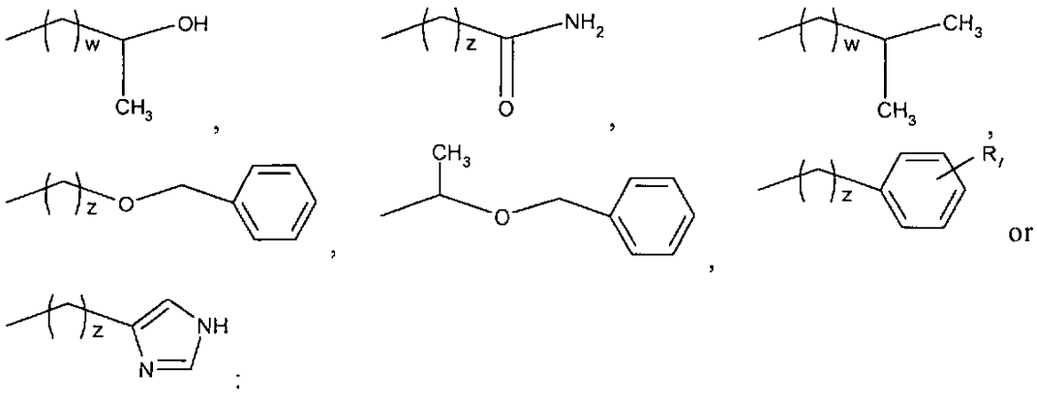
wherein:

$R_1$ is -NH-C(=O)- or -C(=O)-NH-;

$R_2$ is -H or -$CH_2$-, and if $R_2$ is -$CH_2$- forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH;

$R_3$ is -$(CH_2)_2$- if $R_2$ is -$CH_2$-, and otherwise $R_3$ is selected from





$R_{4a}$, $R_{4b}$ and $R_{4c}$ are each independently selected from hydrogen, halo, ($C_1$-$C_{10}$)alkyl-halo, ($C_1$-$C_{10}$)alkyl-dihalo, ($C_1$-$C_{10}$)alkyl-trihalo, ($C_1$-$C_{10}$)alkyl, ($C_1$-$C_{10}$)alkoxy, ($C_1$-$C_{10}$)alkylthio, aryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carboxy, or alkoxy-carbonyl, on the proviso that at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is not hydrogen;

$R_5$ is -OH or -N($R_{6a}$)($R_{6b}$);

$R_{6a}$ and $R_{6b}$ are each independently H or a $C_1$ to $C_4$ linear, branched or cyclic alkyl chain;

$R_7$ is -H or -C(=O)-$NH_2$;

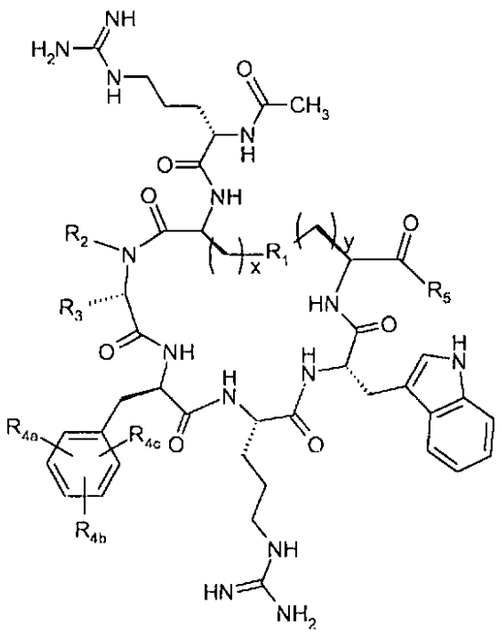
w is in each instance independently 0 to 5;

x is 1 to 5;

y is 1 to 5; and

z is in each instance independently 1 to 5.

2. The cyclic peptide of claim 1 which is of Formula (II):



(II)

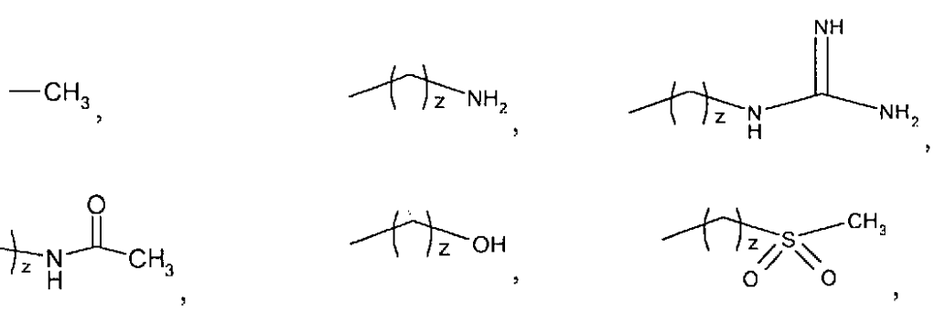
or a pharmaceutically acceptable salt thereof.

3. The cyclic peptide of claim 1 or claim 2, wherein $R_1$ is -C(=O)-NH-, x is 2 and y is 3.

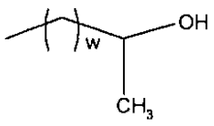
4. The cyclic peptide of claim 1 or claim 2 wherein $R_1$ is -NH-C(=O)-, x is 3 and y is 2.

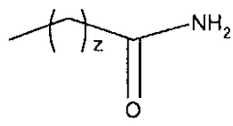
5. The cyclic peptide of any one of claims 1-4, wherein $R_2$ is H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH; and

$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from



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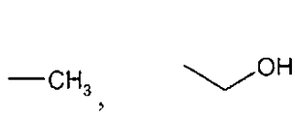


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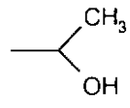
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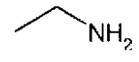
6. The cyclic peptide of any one of claims 1-4, wherein $R_2$ is H or $-CH_2-$, and if $R_2$ is $-CH_2-$ forms with $R_3$ a pyrrolidine ring, the pyrrolidine ring optionally substituted with -OH; and

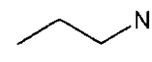
$R_3$ is $-(CH_2)_2-$ if $R_2$ is $-CH_2-$, and otherwise $R_3$ is selected from

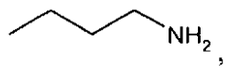


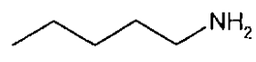
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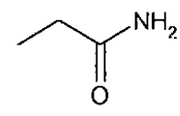

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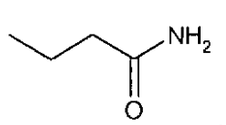
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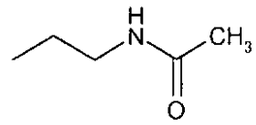
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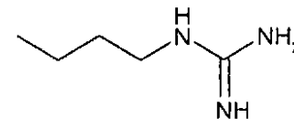
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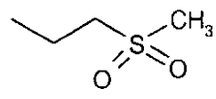
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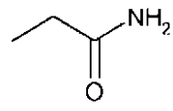
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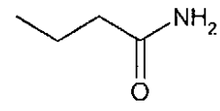
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or


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7. The cyclic peptide of any one of claims 1-4, wherein $R_2$ is H, $R_3$ is selected from



or


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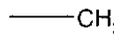
8. The cyclic peptide of any one of claims 1-4, wherein $R_2$ is $-CH_2-$ and $R_3$ is $-(CH_2)_2-$, $R_2$ and $R_3$ together forming an unsubstituted pyrrolidine ring.

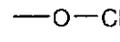
9. The cyclic peptide of any one of claims 1-8, wherein at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is independently selected from



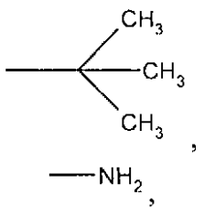
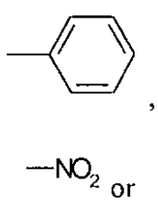
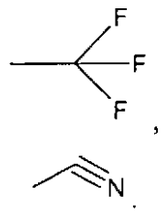
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,

10. The cyclic peptide of any one of claims 1-8, wherein at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is independently selected from hydrogen, halo, ($C_1$-$C_4$)alkyl-halo, ($C_1$-$C_4$)alkyl-dihalo, ($C_1$-$C_4$)alkyl-trihalo, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, nitro, nitrile, amino or hydroxy, on the proviso that at least one of $R_{4a}$, $R_{4b}$ and $R_{4c}$ is not hydrogen.

11. The cyclic peptide of any one of claims 1-8 wherein $R_{4a}$ is in the 4 position and is -C≡N and $R_{4b}$ and $R_{4c}$ are each H.

12. The cyclic peptide of any one of claims 1-8 wherein $R_{4a}$ is in the 4 position and is -F and $R_{4b}$ and $R_{4c}$ are each H.

13. A cyclic peptide selected from:

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:48);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:74);

Ac-Arg-*cyclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:90);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:91);

Ac-Arg-*cyclo*(Glu-Gln-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:97);

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:44);

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72);

Ac-Arg-*cyclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-OH (SEQ ID NO:107); or

a pharmaceutically acceptable salt of any of the foregoing.

14. A pharmaceutical composition comprising a cyclic peptide or a pharmaceutically acceptable salt thereof of any one of claims 1-13 and a pharmaceutically acceptable carrier.

15. A peptide according any one of claims 1-13 for use as a medicament.

16. A peptide according to any one of claims 1-13 for use in treating diseases, disorders and/or conditions responsive to activation of the MC4 receptor.

17. A peptide according to any one of claims 1-13 for use in treating diabetes; obesity; overweight; and/or diseases, disorders and/or conditions associated with obesity and/or overweight, including insulin resistance; impaired glucose tolerance; type 2 diabetes; metabolic syndrome; dyslipidemia; hyperlipidemia; hypertension; heart disorders; cardiovascular disorders; non-alcoholic fatty liver disease; joint disorders; secondary osteoarthritis; gastroesophageal reflux; sleep apnea; atherosclerosis; stroke; macro and micro vascular diseases; steatosis; gall stones; and gallbladder disorders.

18. A method of treating a disease, disorder and/or condition responsive to activation of the MC4 receptor comprising administering a therapeutically effective amount of a peptide according to any one of claims 1-13 to a patient in need thereof.

19. A method of treating diabetes, obesity, overweight and/or diseases, disorders and/or conditions associated with obesity and/or overweight, including insulin resistance; impaired glucose tolerance; type 2 diabetes; metabolic syndrome; dyslipidemia; hyperlipidemia; hypertension; heart disorders; cardiovascular disorders; non-alcoholic fatty liver disease; joint disorders; secondary osteoarthritis; gastroesophageal reflux; sleep apnea; atherosclerosis; stroke; macro and micro vascular diseases; steatosis; gall stones; and gallbladder disorders comprising administering a therapeutically effective amount of a peptide according to any one of claims 1-13 to a patient in need thereof.

20. A method of reducing food intake, body weight and/or body weight gain comprising administering a pharmacologically effective amount of a peptide according to any one of claims 1-13 to an individual in need thereof.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050626

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:A61K, A61P, C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P, X | WO 2009151383 A1 (PALATIN TECHNOLOGIES INC ET AL), 17 December 2009 (2009-12-17); claims<br>-- | 1-20 |
| A | WO 2005030797 A2 (NOVO NORDISK AS ET AL), 7 April 2005 (2005-04-07); claim 28<br>-- | 1-20 |
| A | US 7541430 B2 (SENSFUSS ULRICH ET AL), 18 October 2007 (2007-10-18); claim 23<br>--<br>---------- | 1-20 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17-09-2010 | 17-09-2010 |

| Name and mailing address of the ISA/SE | Authorized officer |
|---|---|
| Patent- och registreringsverket<br>Box 5055<br>S-102 42 STOCKHOLM<br>Facsimile No. + 46 8 666 02 86 | Carolina Gomez Lagerlöf<br>Telephone No. + 46 8 782 25 00 |

Form PCT/ISA/210 (second sheet) (July 2009)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050626

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-20
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 18-20 relate to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims). The search has been directed to the technical content of the claims.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/SE2010/050626

**Continuation of:** second sheet

**International Patent Classification (IPC)**

***C07K 7/06*** (2006.01)
***A61K 38/08*** (2006.01)
***A61P 3/04*** (2006.01)

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Use the application number as username. The password is **HDKCZJDUOA**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE2010/050626

| | | | | | | |
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| | | | | US | 20070244054 | A1 18/10/2007 |

# PÉPTIDOS ESPECÍFICOS PARA RECEPTORES DE MELANOCORTINA

## Campo técnico

La presente invención se refiere a péptidos cíclicos específicos para receptores de melanocortina que pueden utilizarse en el tratamiento de enfermedades, indicaciones, afecciones y síndromes mediados por los receptores de melanocortina, en particular enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, la diabetes), relacionados con la ingesta de alimentos y/o el equilibrio energético y relacionados con el peso corporal, incluida la obesidad, el sobrepeso y enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, tales como diabetes tipo 2 y síndrome metabólico.

## Antecedentes

Lo que sigue se refiere a distintas publicaciones por autor(es) y año de publicación y, debido a fechas de publicación recientes, ciertas publicaciones no se consideran técnica anterior con respecto a la presente invención. La descripción de dichas publicaciones en la presente se proporciona con el fin de tener un panorama más completo de los antecedentes y no debe interpretarse como una admisión de que dichas publicaciones constituyen técnica anterior a los efectos de la determinación de la patentabilidad.

Se ha identificado una familia de tipos y subtipos de receptores de melanocortina, incluidos los receptores de melanocortina-1 (MC1-R) expresados en melanocitos y células de melanoma humanos normales, los receptores de melanocortina-2 (MC2-R) para ACTH (adrenocorticotropina) expresados en células de glándula adrenal, los receptores de melanocortina-3 y melanocortina-4 (MC3-R y MC4-R) expresados principalmente en células del hipotálamo, mesencéfalo y tronco cerebral, y los receptores de melanocortina-5 (MC5-R), expresados ampliamente en tejidos periféricos. Se ha sugerido que el MC1-R se asocia con la pigmentación e inflamación del cabello y la piel, se cree que el MC2-R media la esteroidogénesis, se ha sugerido que el MC3-R se asocia con la homeostasis de la energía, la ingesta de alimentos y la inflamación, se cree que el MC4-R controla el comportamiento alimenticio, la homeostasis de la energía y la función sexual (por ejemplo,

la función eréctil) y se ha sugerido que el MC5-R participa en el sistema glandular exócrino.

Se ha trabajado abundantemente para determinar la estructura de los receptores de melanocortina, incluidas las secuencias de ácidos nucleicos que codifican los receptores y las secuencias de aminoácidos que constituyen los receptores. El MC4-R es un receptor 7-transmembrana acoplado a la proteína G que se cree se expresa principalmente en el cerebro.

Se ha demostrado que la inactivación del MC4-R resulta en obesidad (Hadley, 1999, Ann N Y Acad Sci., 885:1-21). La proteína relacionada con agouti (AgRP) es un compuesto endógeno que, según se ha sugerido, puede ser un antagonista de MC o un agonista inverso en MC4-R. Se cree que la hormona estimuladora de α-melanocitos (α-MSH) es el principal agonista de MC4-R endógeno.

Además, se ha sugerido que los receptores de MC4-R ubicados periféricamente participan en el control de la homeostasis de la energía, y el papel de la señalización de MC4-R en el nervio vago y su importancia para el tratamiento de la obesidad y la diabetes se analizan en Gautron et al, The Journal of Comparative Neurology, 518:6-24 (2010).

Se cree que péptidos específicos para MC4-R, y péptidos secundarios específicos para MC3-R, son útiles en la regulación de la homeostasis de la energía en mamíferos, incluido el uso como agentes para atenuar la ingesta de alimentos y el aumento de peso corporal. Se cree que los péptidos agonistas de MC4-R son útiles para el tratamiento de la disfunción sexual, incluida la disfunción eréctil masculina, y para reducir la ingesta de alimentos y el aumento de peso corporal, así como también para el tratamiento de la obesidad. Dichos péptidos también pueden utilizarse para reducir el consumo de etanol voluntario, para el tratamiento de adicciones a drogas y similares. Los péptidos agonistas de MC4-R, así como los péptidos agonistas de MC3-R, también pueden emplearse para el tratamiento de shock circulatorio, isquemia, shock hemorrágico, enfermedades inflamatorias y enfermedades, indicaciones, afecciones y síndromes relacionados. Por el contrario, se cree que los péptidos antagonistas de MC4-R son útiles para ayudar a aumentar de peso, como por ejemplo en el uso del tratamiento de caquexia, sarcopenia, síndrome o enfermedad de desgaste y anorexia. Dichos péptidos también pueden emplearse

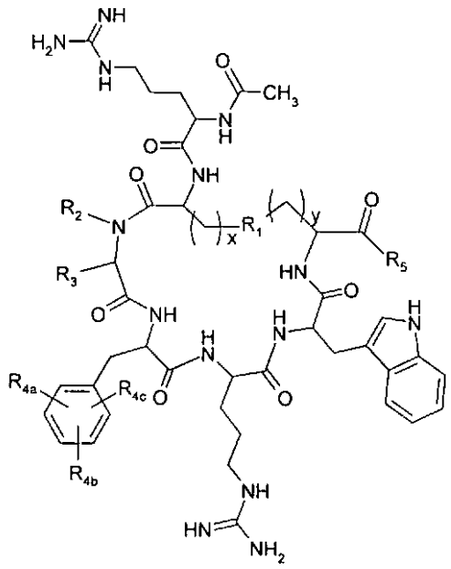
para el tratamiento de la depresión y trastornos relacionados. (Wikberg et al, Nature Reviews, Drug Discovery, 7, 307, (2008); Adan et al, British J. Pharm., 149, 815-827 (2006); Nogueiras et al, J. Clin., Invest., 117(11): 3475-3488 (2007); Maaser et al, Ann. N.Y. Acad. Sci., 1072, 123-134 (2006); Giuliani et al, British J. Pharm., 150, 595-603 (2007); Balbani, Expert Opin. Ther. Patents, 17(3), 287-297 (2007); y Navarro et al, Alcohol. Clin. Exp. Res., 29(6), 949-957 (2005)). Péptidos específicos para los receptores de melanocortina incluyen péptidos análogos a α-MSH cíclicos tales como Ac-Nle-*ciclo*(-Asp-His-D-Phe-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:1) (ver las patentes de los Estados Unidos Nos. 5.674.839 y 5.576.290) y Ac-Nle-*ciclo*(-Asp-His-D-Phe-Arg-Trp-Lys)-OH (SEQ ID NO:2) (ver las patentes de los Estados Unidos Nos. 6.579.968 y 6.794.489). Estos y otros péptidos específicos para los receptores de melanocortina generalmente contienen la secuencia de tetrapéptidos central de la α-MSH nativa, $His^6$-$Phe^7$-$Arg^8$-$Trp^9$ (SEQ ID NO:3), o un mimético o variación de la misma, incluida la sustitución de D-Phe por $Phe^7$. Otros péptidos y compuestos similares a péptidos que se indica son específicos para uno o más receptores de melanocortina se describen en las patentes de los Estados Unidos Nos. 5.731.408, 6.054.556, 6.350.430, 6.476.187, 6.600.015, 6.613.874, 6.693.165, 6.699.873, 6.887.846, 6.951.916, 7.008.925 y 7.176.279; en las publicaciones de solicitudes de patente de los Estados Unidos Nos. 2001/0056179, 2002/0143141, 2003/0064921, 2003/0105024, 2003/0212002, 2004/0023859, 2005/0130901, 2005/0187164, 2005/0239711, 2006/0105951, 2006/0111281, 2006/0293223, 2007/0027091, 2007/0105759, 2007/0123453, 2007/0244054 y 2008/0039387; y en las solicitudes de patente internacionales Nos. WO 98/27113, WO 99/21571, WO 00/05263, WO 99/54358, WO 00/35952, WO 00/58361, WO 01/30808, WO 01/52880, WO 01/74844, WO 01/85930, WO 01/90140, WO 02/18437, WO 02/26774, WO 03/006604, WO 2004/099246, WO 2004/046166, WO 2005/000338, WO 2005/000339, WO 2005/000877, WO 2005/030797, WO 2005/060985, WO2006/048449, WO 2006/048450, WO 2006/048451, WO 2006/048452, WO 2006/097526, WO 2007/008684, WO 2007/008704 y WO 2007/009894. A pesar del gran interés científico y farmacéutico en los péptidos específicos para los receptores de melanocortina, lo que queda demostrado por numerosos artículos en la bibliografía científica y en numerosas solicitudes de patente y

patentes otorgadas (Nozawa et al, Expert Opin. Ther. Patents 18(4):403-427 (2008); Bednarek et al, Expert Opin. Ther. Patents 14(3):327-336 (2004); Todorovic et al, Peptides, 26, 2026-2036 (2005); y Ujjainwalla et al, Current Topics in Med. Chem., 7, 1068-1084 (2007)), no se ha aprobado ningún péptido específico para receptores de melanocortina como fármaco para alguna indicación terapéutica. En efecto, no existen informes acerca de algún péptido específico para receptores de melanocortina para alguna indicación terapéutica que haya superado pruebas clínicas más allá de la Fase II. Sigue existiendo una necesidad importante y considerable de péptidos específicos para receptores de melanocortina para su uso en aplicaciones farmacéuticas. Es en virtud de estos antecedentes que se elaboró la presente invención.

Compendio de la invención

Es, por lo tanto, un objeto de la presente invención proporcionar compuestos novedosos que sean útiles para el tratamiento de enfermedades, trastornos y/o afecciones sensibles a la modulación, incluida la activación, de MC4-R y/o MC3-R, en particular para el tratamiento de enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, la diabetes), relacionados con la ingesta de alimentos y/o el equilibrio de energía y relacionados con el peso corporal, incluida la obesidad, el sobrepeso y enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, tales como diabetes tipo 2 y síndrome metabólico.

En un aspecto, la presente invención se refiere a un péptido cíclico de la Fórmula estructural (I):



(I)

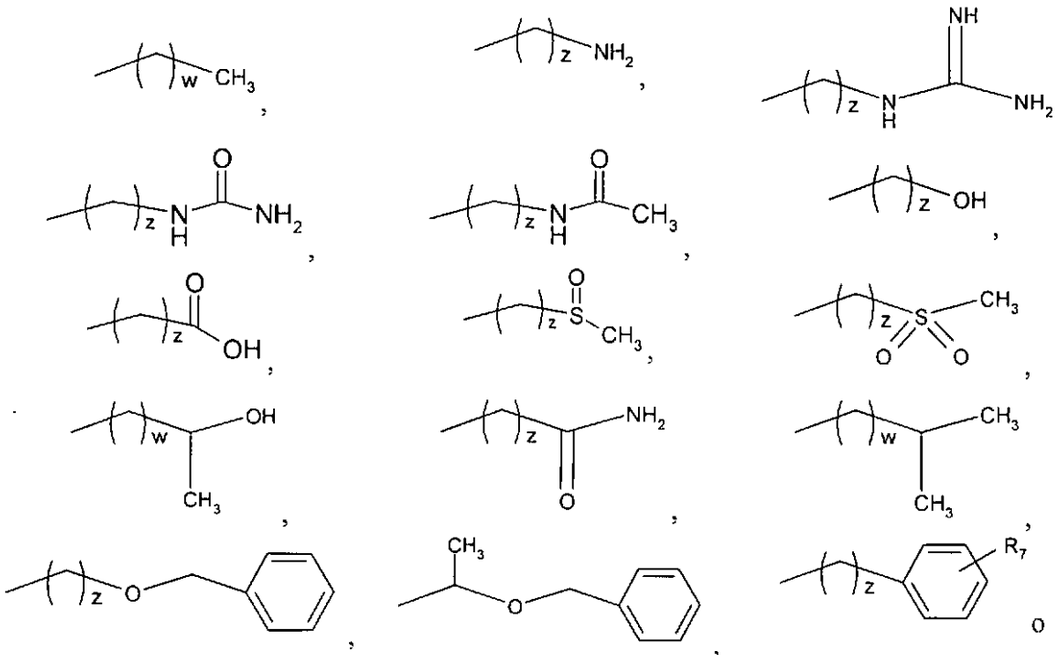
incluidos todos los enantiómeros, estereoisómeros o diastereoisómeros del mismo o a una sal farmacéuticamente aceptable de cualquiera de los anteriores.

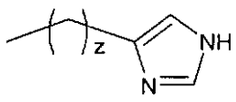
en donde:

$R_1$ es -NH-C(=O)- o -C(=O)-NH-;

$R_2$ es -H o $-CH_2-$ y, si $R_2$ es $-CH_2-$, forma con $R_3$ un anillo de pirrolidina, estando el anillo de pirrolidina opcionalmente sustituido por –OH;

$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de





;

$R_{4a}$, $R_{4b}$ y $R_{4c}$ se seleccionan cada uno independientemente de hidrógeno, halo, alquil($C_1$-$C_{10}$)-halo, alquil($C_1$-$C_{10}$)-dihalo, alquil($C_1$-$C_{10}$)-trihalo, alquilo($C_1$-$C_{10}$), alcoxi($C_1$-$C_{10}$), alquil($C_1$-$C_{10}$)tio, arilo, ariloxi, nitro, nitrilo, sulfonamida, amino, amino monosustituido, amino disustituido, hidroxi, carboxi o alcoxi-carbonilo, con la condición de que al menos uno de $R_{4a}$, $R_{4b}$ y $R_{4c}$ no sea hidrógeno;

$R_5$ es -OH o -N($R_{6a}$)($R_{6b}$);

$R_{6a}$ y $R_{6b}$ son cada uno independientemente H o una cadena de alquilo $C_1$ a $C_4$ lineal, ramificada o cíclica;

$R_7$ es -H o -C(=O)-$NH_2$;

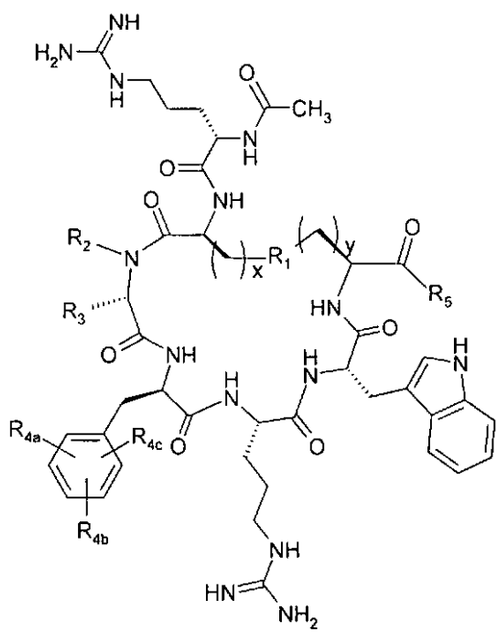
w es en cada instancia independientemente 0 a 5;

x es 1 a 5;

y es 1 a 5; y

z es en cada instancia independientemente 1 a 5.

En otro aspecto, la presente invención se refiere a un péptido cíclico de Fórmula (I) que es de Fórmula (II):



(II)

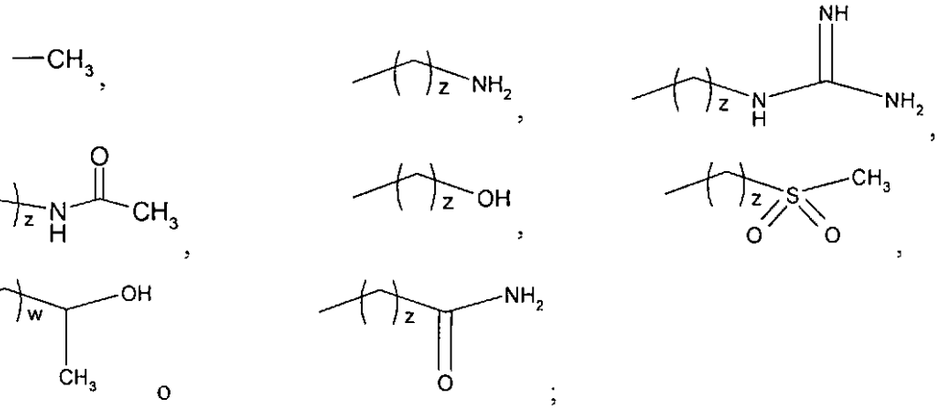
o una sal farmacéuticamente aceptable del mismo.

En otro aspecto, la presente invención se refiere a un péptido cíclico de Fórmula I, en particular de Fórmula (II), en donde $R_1$ es -C(=O)-NH-, x es 2 e y es 3.

En otro aspecto, la presente invención se refiere a un péptido cíclico de Fórmula (I), en particular de Fórmula (II), en donde $R_1$ es -NH-C(=O)-, x es 3 e y es 2.

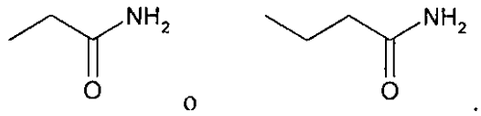
En otro aspecto, la presente invención se refiere a un péptido cíclico de Fórmula (I), en particular de Fórmula (II), en donde $R_2$ es -H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, estando el anillo de pirrolidina opcionalmente sustituido por -OH; y

$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ es



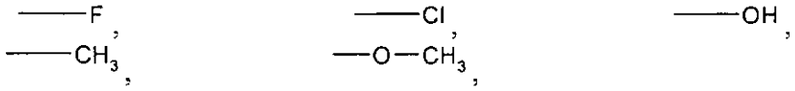
en donde w es en cada instancia independientemente seleccionado de 0 a 5, y z se selecciona en cada instancia independientemente de 1 a 5.

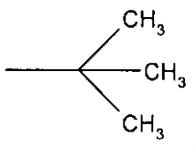
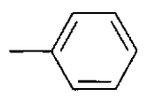
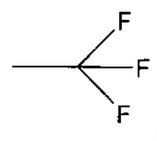
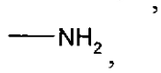
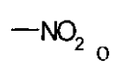
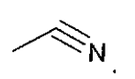
En otro aspecto, la presente invención se refiere a un péptido cíclico de Fórmula I, en particular de Fórmula (II) o (III), en donde $R_2$ es H, $R_3$ se selecciona de



En otro aspecto, la presente invención se refiere a un péptido cíclico de Fórmula I, en particular de Fórmula (II), en donde $R_2$ es $-CH_2-$ y $R_3$ es-$(CH_2)_2-$, formando $R_2$ y $R_3$ juntos un anillo de pirrolidina insustituido.

En otro aspecto, la presente invención se refiere a un péptido cíclico de Fórmula I, en particular Fórmula (II), en donde al menos uno de $R_{4a}$, $R_{4b}$ y $R_{4c}$ se selecciona de



En otro aspecto, la presente invención se refiere a un péptido cíclico de Fórmula I, en particular Fórmula (II) o (III), en donde $R_{4a}$ está en la posición 4 y es -C≡N y $R_{4b}$ y $R_{4c}$ son cada uno H.

En otro aspecto, la presente invención se refiere a un péptido cíclico de Fórmula (I), en particular Fórmula (II) o (III), en donde $R_{4a}$ está en la posición 4 y es -F y $R_{4b}$ y $R_{4c}$ son cada uno H.

Los péptidos de acuerdo con la invención son ligandos de uno o más receptores de melanocortina, en particular ligando de MC4-R, más particularmente agonistas (incluidos agonistas completos y parciales) de MC4-R. El término "ligandos", tal como se utiliza en la presente, incluye la unión de péptidos al sitio activo, así como también la unión de péptidos a uno o más sitios alostéricos de cualquiera de dichos receptores.

Por lo tanto, los péptidos de la invención pueden utilizarse como medicamento, en particular para el tratamiento de trastornos, enfermedades o afecciones sensibles a la modulación del MC3-R y/o MC4-R, y en particular trastornos, enfermedades o afecciones sensibles a la activación del MC4-R. Más particularmente, se cree que los péptidos de la invención atenúan la ingesta de alimentos, el peso corporal y/o el aumento de peso corporal y, por lo tanto, se cree que son útiles para los tratamientos de enfermedades, trastornos y/o afecciones relacionadas con la homeostasis de la energía y el metabolismo (por ejemplo, la diabetes), la ingesta de alimentos y/o el equilibrio de la energía y el peso corporal, incluida la obesidad y el sobrepeso, y enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, tal como la diabetes tipo 2 y el síndrome metabólico, en una paciente que lo necesita. El paciente puede ser un humano o un animal no humano, en particular un humano.

Los péptidos de la invención pueden tener propiedades ventajosas en comparación con los péptidos de la técnica anterior, en particular potencia mejorada y/o selectividad mejorada. Estas ventajas pueden proporcionar propiedades útiles correspondientes en la

práctica. Por ejemplo, cuando se utilizan como agentes farmacéuticos, los péptidos de la presente invención pueden utilizarse en una dosis clínica diaria más baja, pueden tener mayor duración de acción y/o un perfil de efectos secundarios mejorado.

En otro aspecto, se proporciona un método para tratar trastornos, enfermedades o afecciones sensibles a la modulación de MC4-R y/o MC3-R, tales como trastornos, enfermedades o afecciones sensibles a la activación de MC4-R, en particular enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, diabetes), ingesta de alimentos y/o equilibrio de energía y peso corporal, incluida la obesidad y/o el sobrepeso, tal como la diabetes tipo 2 y el síndrome metabólico, mediante la administración de una cantidad terapéuticamente efectiva de un péptido de la invención a un paciente que lo necesita.

De acuerdo con otro aspecto de la invención, se proporciona un método de reducción de ingesta de alimentos, peso corporal y/o aumento de peso corporal mediante la administración de una cantidad farmacológicamente efectiva de un péptido de la invención a un individuo, tal como un humano, que lo necesita.

De acuerdo con otro aspecto de la invención, se proporciona un método para evitar la recuperación de peso corporal después de una pérdida de peso mediante la administración de una cantidad farmacológicamente efectiva de un péptido de la invención a un individuo, tal como un humano, que lo necesita.

En otro aspecto, la invención proporciona el uso de un péptido de Fórmula I en la preparación de un medicamento para el tratamiento de una enfermedad, trastorno y/o afección sensible a la activación de MC4-R, en particular enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, la diabetes), la ingesta de alimentos y/o el equilibro de la energía y el peso corporal, incluida la obesidad y el sobrepeso, y enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, tales como la diabetes tipo 2 y el síndrome metabólico.

En otro aspecto, la presente invención proporciona una composición farmacéutica en base a péptidos específicos para receptores de melanocortina para utilizar en el tratamiento de enfermedades, indicaciones, afecciones y síndromes mediados por el receptor de melanocortina, en particular enfermedades, trastornos, afecciones y/o

síndromes sensibles a la modulación de MC4-R, tal como la activación de MC4-R, que comprende un péptido de Fórmula I y un portador farmacéuticamente aceptable.

En otro aspecto, la presente invención proporciona una composición farmacéutica específica para el receptor de melanocortina en base a péptidos que comprende un péptido de Fórmula I y un portador farmacéuticamente aceptable, en donde el péptido es un ligando de MC4-R selectivo, para utilizar en el tratamiento de enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, la diabetes), relacionados con la ingesta de alimentos y/o el equilibrio de energía y relacionados con el peso corporal, incluida la obesidad, el sobrepeso y enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, tales como diabetes tipo 2 y síndrome metabólico.

En otro aspecto, la presente invención proporciona péptidos que son específicos para MC4-R y que son agonistas parciales o completos en MC4-R. En particular, la presente invención proporciona péptidos que son específicos para MC4-R y que son agonistas parciales en MC4-R.

En otro aspecto, la presente invención proporciona un péptido cíclico de MC4-R que es efectivo en un rango de dosis considerable.

Otros aspectos y características nuevas y el alcance adicional de aplicación de la presente invención se indicarán en parte en la descripción detallada que sigue, y en parte serán evidentes para los expertos en la técnica tras el examen de lo que sigue, o podrán desprenderse de la puesta en práctica de la invención. Los aspectos de la invención pueden llevarse a cabo y lograrse a través de los medios y combinaciones particularmente indicados en las reivindicaciones adjuntas.

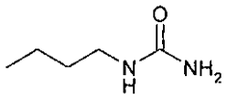
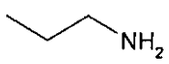
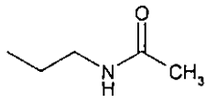
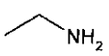
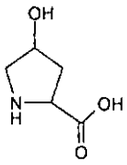
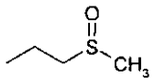
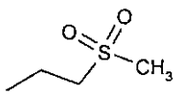
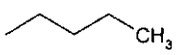
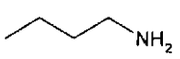
Descripción detallada de la invención

1.0 Definiciones

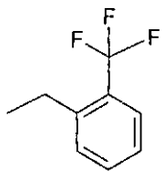
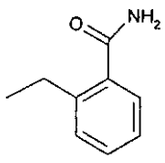
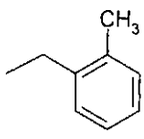
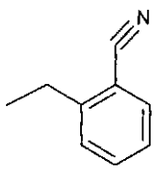
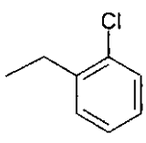
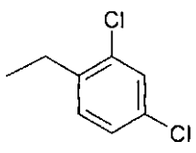
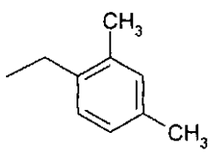
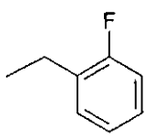
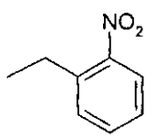
Antes de proceder con la descripción de la invención, se definen determinados términos como se indican en la presente.

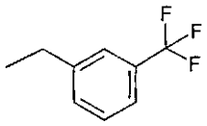
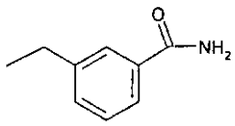
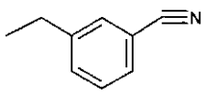
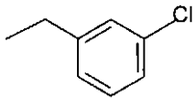
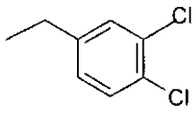
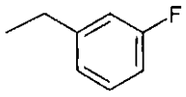
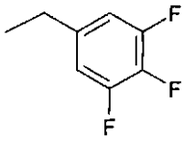
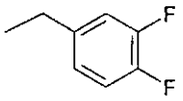
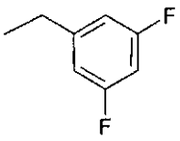
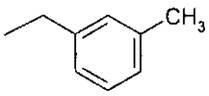
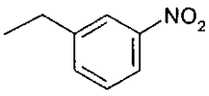
En las secuencias proporcionadas para los péptidos de acuerdo con la presente invención, los residuos de aminoácidos tienen su significado convencional, según se

proporciona en el Capítulo 2400 del Manual de Procedimiento de Examen de Patentes, 8va Ed. Por lo tanto, "Ala" es alanina, "Asn" es asparagina, "Asp" es ácido aspártico, "Arg" es arginina, "Cys" es cisteína, "Gly" es glicina, "Gln" es glutamina, "Glu" es ácido glutámico, "His" es histidina, "Ile" es isoleucina, "Leu" es leucina, "Lys" es lisina, "Met" es metionina, "Phe" es fenilalanina, "Pro" es prolina, "Ser" es serina, "Thr" es Treonina, "Trp" es triptófano, "Tyr" es tirosina, "Val" es valina, etc. Debe comprenderse que isómeros "D" se designan mediante una "D-" antes del código de tres letras o nombre de aminoácido, de forma tal que, por ejemplo, D-Phe es D-fenilalanina. Los residuos aminoácidos no comprendidos anteriormente tienen las siguientes definiciones:

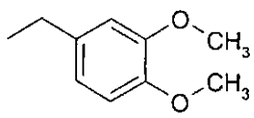
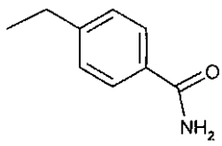
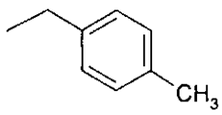
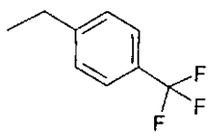
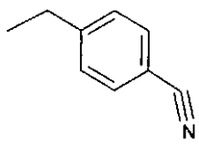
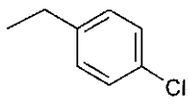
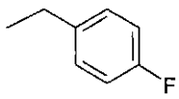
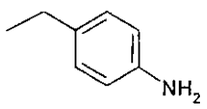
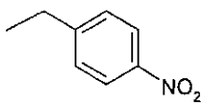
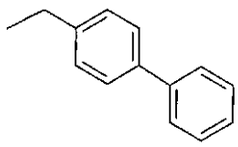
| **Abreviatura** | **Nombre común** | **Cadena lateral o estructura de aminoácidos** |
|---|---|---|
| Cit | citrulina |  |
| Dab | ácido diaminobutírico |  |
| Dab(Acetil) | ácido 2-amino, 4-acetilaminobutírico |  |
| Dap | ácido diaminopropriónico |  |
| Hip | hidroxiprolina |  |
| Met(O) | metionina sulfóxido |  |
| Met($O_2$) | metionina sulfona |  |
| Nle | norleucina |  |
| Nva | norvalina |  |
| Orn | ornitina |  |

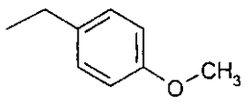
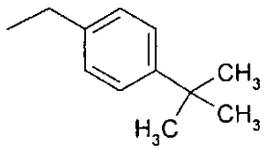
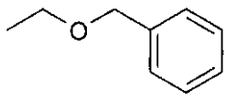
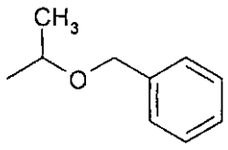
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| Abreviatura | Nombre común | Cadena lateral o estructura de aminoácidos |
|---|---|---|
| Phe(2-$CF_3$) | 2-trifluorometil fenilalanina |  |
| Phe(2-C(=O)-$NH_2$) | 2-carbamoil-fenilalanina |  |
| Phe(2-Me) | 2-metil fenilalanina |  |
| Phe(2-CN) | 2-ciano fenilalanina |  |
| Phe(2-Cl) | 2-cloro fenilalanina |  |
| Phe(2,4-diCl) | 2,4-dicloro fenilalanina |  |
| Phe(2,4-diMe) | 2,4-dimetil fenilalanina |  |
| Phe(2-F) | 2-fluoro fenilalanina |  |
| Phe(2-$NO_2$) | 2-nitro fenilalanina |  |

| Abreviatura | Nombre común | Cadena lateral o estructura de aminoácidos |
|---|---|---|
| Phe(3-$CF_3$) | 3-trifluorometil fenilalanina |  |
| Phe(3-C(=O)-$NH_2$) | 3-carbamoil-fenilalanina |  |
| Phe(3-CN) | 3-ciano fenilalanina |  |
| Phe(3-Cl) | 3-cloro fenilalanina |  |
| Phe(3,4-diCl) | 3,4-dicloro fenilalanina |  |
| Phe(3-F) | 3-fluoro fenilalanina |  |
| Phe(3,4,5-triF) | 3,4,5-trifluoro fenilalanina |  |
| Phe(3,4-diF) | 3,4-difluoro fenilalanina |  |
| Phe(3,5-diF) | 3,5-difluoro fenilalanina |  |
| Phe(3-Me) | 3-metil fenilalanina |  |
| Phe(3-$NO_2$) | 3-nitro fenilalanina |  |

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| Abreviatura | Nombre común | Cadena lateral o estructura de aminoácidos |
|---|---|---|
| Phe(3,4-diOMe) | 3,4-dimetoxi fenilalanina |  |
| Phe(4-C(=O)-$NH_2$) | 4-carbamoil-fenilalanina |  |
| Phe(4-Me) | 4-metil fenilalanina |  |
| Phe(4-$CF_3$) | 4-trifluorometil fenilalanina |  |
| Phe(4-CN) | 4-ciano fenilalanina |  |
| Phe(4-Cl) | 4-cloro fenilalanina |  |
| Phe(4-F) | 4-fluoro fenilalanina |  |
| Phe(4-$NH_2$) | 4-amino fenilalanina |  |
| Phe(4-$NO_2$) | 4-nitro fenilalanina |  |
| Phe(4-Ph) | 4-fenil fenilalanina |  |

| Abreviatura | Nombre común | Cadena lateral o estructura de aminoácidos |
|---|---|---|
| Phe(4-OMe) | 4-metoxi fenilalanina |  |
| Phe(4-tBu) | 4-*terc* butil fenilalanina |  |
| Ser(Bzl) | O-bencil-serina |  |
| Thr(OBzl) | O-bencil-treonina |  |

El término "acilo" incluye un grupo R(C=O)-, donde R es un grupo orgánico, tal como un alquilo, arilo, heteroarilo, carbociclilo o heterociclilo. Por lo tanto, cuando se hace referencia en la presente a un grupo acilo sustituido, significa que dicho grupo orgánico (R) está sustituido. Un ejemplo es el grupo acetilo $CH_3$-C(=O)-, al que se hace referencia en la presente como "Ac". Un péptido o resto alifático es "acilado" cuando un alquilo o grupo alquilo sustituido como se define anteriormente se une a través de uno o más grupos carbonilo {-(C=O)-}. Un péptido es más generalmente acilado en el extremo N.

El término "alcano" incluye hidrocarburos saturados lineales o ramificados. Los ejemplos de grupos alcano lineales incluyen metano, etano, propano y similares. Los ejemplos de grupos alcano sustituidos o ramificados incluyen metilbutano o dimetilbutano, metilpentano, dimetilpentano o trimetilpentano y similares. En general, cualquier grupo alquilo puede ser un sustituyente de un alcano.

El término "alqueno" incluye hidrocarburos insaturados que contienen uno o más enlaces dobles carbono-carbono. Los ejemplos de dichos grupos alqueno incluyen etileno, propeno y similares.

El término "alquenilo" incluye un radical hidrocarburo monovalente lineal de dos a seis átomos de carbono o un radical hidrocarburo monovalente ramificado de tres a seis

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átomos de carbono que contienen al menos un enlace doble; ejemplos de los mismos incluyen etenilo, 2-propenilo y similares.

El término "alquilo" incluye un grupo hidrocarburo alifático saturado de cadena recta o ramificada. Alquilo $C_{1-10}$ significa un alquilo que tiene 1 a 10 átomos de carbono. Los ejemplos no taxativos de dichos radicales alquilo incluyen metilo, etilo, propilo, isopropilo, butilo, sec-butilo, butilo terciario, pentilo, isopentilo, hexilo, isohexilo y similares.

El término "alquino" incluye un radical hidrocarburo monovalente lineal de dos a seis átomos de carbono o un radical hidrocarburo monovalente ramificado de tres a seis átomos de carbono que contienen al menos un enlace triple; los ejemplos del mismo incluyen etino, propino, butino y similares.

El término "arilo" incluye un radical hidrocarburo aromático monocíclico o bicíclico de 6 a 12 átomos anulares y opcionalmente independientemente sustituido por uno o más sustituyentes seleccionados de alquilo, haloalquilo, cicloalquilo, alcoxi, alquiltio, halo, nitro, acilo, ciano, amino, amino monosustituido, amino disustituido, hidroxi, carboxi o alcoxi-carbonilo.

El término "arilo" también incluye sistemas anulares aromáticos bicíclicos en donde un anillo es aromático y un anillo es no aromático (incluidos anillos saturados o parcialmente saturados). En sistemas anulares aromáticos bicíclicos, dos o más carbonos anulares son comunes a dos anillos adyacentes (los anillos son "anillos fusionados"). Los ejemplos de un grupo arilo incluyen fenilo, bifenilo, indanilo, naftilo, 1-naftilo y 2-naftilo, derivados de los mismos y similares.

El término "aralquilo" incluye un radical – $R^aR^b$ donde $R^a$ es un grupo alquileno (un alquilo bivalente) y $R^b$ es un grupo arilo como se define anteriormente. Los ejemplos de grupos aralquilo incluyen bencilo, feniletilo, 3-(3-clorofenil)-2-metilpentilo y similares.

El término "alifático" incluye compuestos con cadenas de hidrocarburo, tales como por ejemplo, alcanos, alquenos, alquinos y derivados de los mismos.

Como se utiliza en la presente, el término "amida" incluye compuestos que tienen un nitrógeno trivalente unido a un grupo carbonilo, es decir, $-C(=O)-NH_2$ (es decir, amida primaria), $-C(=O)-NHR_c$ y $-C(=O)-NR_cR_d$, en donde cada uno de $R_c$ y $R_d$

independientemente representa un grupo orgánico. Cuando se hace referencia en la presente a un grupo amida sustituido, significa que al menos uno de dichos grupos orgánicos ($R_c$ y $R_d$) está sustituido. Los ejemplos de amidas incluyen metilamida, etilamida, propilamida y similares.

El término "amina" incluye $-NH_2$ (es decir, un grupo amino), $-NHR_a$ y $-NR_aR_b$, en donde cada uno de $R_a$ y $R_b$ independientemente representa un grupo orgánico. Cuando se hace referencia en la presente a un grupo amina sustituido, significa que al menos uno de dichos grupos orgánicos ($R_c$ y $R_d$) está sustituido.

El término "nitrilo" incluye el grupo funcional $-C\equiv N$.

El término "halógeno" (o "halo") incluye los átomos halógenos fluor, cloro, bromo y yodo.

El término "alquil-halo" incluye un alquilo sustituido por un átomo de halógeno, tal como $-CH_2F$. El término "alquil-dihalo" incluye un alquilo sustituido por dos átomos de halógeno, tal como $-CHF_2$. El término "alquil-trihalo" incluye un alquilo sustituido por tres átomos de halógeno, tal como $-CF_3$.

El término "alquiltio" incluye -S-alquilo en donde alquilo es como se define anteriormente. Los ejemplos no taxativos de alquil$C_1$-$C_{10}$tio incluyen metiltio, etiltio, n-propiltio, isopropiltio y n-butiltio.

El término "nitro" incluye $-NO_2$.

El término "hidroxi" incluye -OH.

El término "alcoxi" incluye -O-alquilo en donde alquilo es como se define anteriormente. Alcoxi $C_{1-10}$ significa un alquilo que tiene 1 a 10 átomos de carbono. Los ejemplos no taxativos de alcoxi $C_1$-$C_{10}$ incluyen metoxi, etoxi, n-propiloxi, *iso*-propiloxi y 2-metil-1-propiloxi.

El término "ariloxi" incluye -O-arilo en donde arilo es como se define anteriormente.

El término "alcoxicarbonilo" incluye $-C(=O)$-O-R, en donde R es un alquilo como se define anteriormente. Los ejemplos no taxativos de alcoxicarbonilo $C_1$-$C_{10}$ incluyen metoxicarbonilo, etoxicarbonilo, isopropoxi-carbonilo e isopentoxicarbonilo.

El término "carboxi" incluye $-C(=O)OH$.

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El término "oxo" incluye =O.

El término "sulfonamida" incluye un grupo sulfonilo conectado a un grupo amina, es decir, $-S(=O)_2NH_2$, $-S(=O)_2NHR_a$ y $-S(=O)_2NR_aR_b$, en donde cada uno de $R_a$ y $R_b$ representa independientemente un grupo orgánico. Cuando se hace referencia en la presente a un grupo sulfonamida sustituido, significa que al menos uno de dichos grupos orgánicos ($R_a$ y $R_b$) está sustituido.

El término "composición", como en una composición farmacéutica, abarca un producto que comprende el/los ingrediente(s) activo(s), y el/los ingrediente(s) inerte(s) que forman el portador, así como cualquier producto que resulta, directa o indirectamente, de la combinación, complejación o acumulación de cualquiera de dos o más de los ingredientes, o de la disociación de uno o más de los ingredientes, o de otros tipos de reacciones o interacciones de uno o más ingredientes. Por lo tanto, las composiciones farmacéuticas utilizadas en la presente invención abarcan cualquier composición realizada por la mezcla de un ingrediente activo y uno o más portadores farmacéuticamente aceptables.

"Agonista" del receptor de melanocortina significa una sustancia endógena, sustancia de fármaco o compuesto, incluido un compuesto como los péptidos de la presente invención, que puede interactuar con un receptor de melanocortina e iniciar una respuesta farmacológica, incluida, a modo no taxativo, la activación por adenil ciclasa, característica del receptor de melanocortina.

"α-MSH" significa el polipéptido Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-$NH_2$ (SEQ ID NO:4) y los análogos y homólogos del mismo, incluido, a modo no taxativo, NDP-α-MSH.

"NDP-α-MSH" significa el polipéptido Ac-Ser-Tyr-Ser-Nle-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val-$NH_2$ (SEQ ID NO:5) y los análogos y homólogos del mismo.

"$CE_{50}$" es la concentración molar de un agonista, incluido un agonista parcial, que produjo 50% de la respuesta máxima posible para dicho agonista. A modo de ejemplo, un compuesto de prueba que, en una concentración de 72 nM, produce 50% de la respuesta máxima posible para dicho compuesto según se determinó en un ensayo de cAMP en un sistema de expresión celular de MC4-R tiene una $CE_{50}$ de 72 nM. A menos que se indique

lo contrario, la concentración molar asociada con una determinación de $CE_{50}$ es en nanomoles por litro (nM).

"Ki(nM)" significa la constante de disociación del inhibidor de equilibro que representa la concentración molar de un compuesto competidor que se une a la mitad de los sitios de unión de un receptor en equilibrio en ausencia de radioligando y otros competidores. En general, el valor numérico de Ki está inversamente correlacionado con afinidad del compuesto para el receptor, de forma tal que si la Ki es baja, la afinidad es alta. Ki puede determinarse utilizando la ecuación de Cheng y Prusoff (Cheng Y., Prusoff W. H., *Biochem. Pharmacol.* 22: 3099-3108, 1973).

La Ki puede expresarse en términos de receptores específicos (por ejemplo, MC1-R, MC3-R, MC4-R o MC5-R) y ligandos específicos (por ejemplo, α-MSH o NDP-α-MSH).

"Inhibición" significa la atenuación porcentual o disminución en la unión del receptor en un ensayo de inhibición competitiva comparado con un estándar conocido. Por lo tanto, "inhibición en 1 μM (NDP-α-MSH)" significa la disminución porcentual en la unión de NDP-α-MSH por adición de una cantidad determinada de un compuesto que ha de evaluarse, tal como 1 μM de un compuesto de prueba, tal como en las condiciones del ensayo que se describen más adelante. A modo de ejemplo, un compuesto de prueba que no inhibe la unión de NDP-α-MSH tiene una inhibición de 0% y un compuesto de prueba que inhibe completamente la unión de NDP-α-MSH tiene un 100% de inhibición. Generalmente, como se describe más adelante, se utiliza un ensayo de radio para pruebas de inhibición competitiva, tal como con NDP-α-MSH etiquetado con $I^{125}$, o un ensayo fluorescente de quelato de lantanida tal como con Eu-NDP-α-MSH. Sin embargo, se conocen otros métodos para evaluar la inhibición competitiva, incluido el uso de sistemas de etiqueta o rótulo en vez de radioisótopos, y en general en esta invención puede utilizarse cualquier método conocido en la técnica para evaluar la inhibición competitiva. Por lo tanto, puede verse que la "inhibición" es una medida para determinar si un compuesto de prueba atenúa la unión de α-MSH con receptores de melanocortina.

"Afinidad de unión" significa la capacidad de un compuesto o fármaco de unirse a su prueba biológica, expresada en la presente como Ki (nM).

"Actividad intrínseca" significa la estimulación (actividad funcional) máxima que puede alcanzar un compuesto en un sistema celular de expresión del receptor de

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melanocortina tal como la estimación máxima de adenilil ciclasa. La estimulación máxima alcanzada por α-MSH o NDP-α-MSH se designa como una actividad intrínseca de 1,0 (o 100%) y un compuesto capaz de estimular la mitad de la actividad máxima de α-MSH o NDP-α-MSH tiene una actividad intrínseca de 0,5 (o 50%). Un compuesto de la presente invención que en las condiciones de ensayo descrito en la presente tiene una actividad intrínseca de 0,7 (70%) o más se clasifica como un agonista, un compuesto con actividad intrínseca entre 0,1 (10%) y 0,7 (70%) se clasifica como un agonista parcial y un compuesto con una actividad intrínseca por debajo de 0,1 (10%) se clasifica como inactivo o sin actividad intrínseca. En un aspecto, los péptidos cíclicos de la presente invención pueden generalmente caracterizarse como agonista parcial en MC4-R con respecto a α-MSH o NDP-α-MSH.

En general, la "actividad funcional" es una medida de la señalización de un receptor o una medida de un cambio en la señalización asociada al receptor, tal como receptor de melanocortina y en particular MC4-R o hMC4-R, después de la activación por parte de un compuesto. Los receptores de melanocortina inician la transducción de señales a través de la activación de proteínas G heterotriméricas. En un aspecto, los receptores de melanocortina señalizan a través de $G\alpha_S$, que cataliza la producción de cAMP mediante adenilil ciclasa. Por lo tanto, la determinación de la estimulación de adenilil ciclasa, tal como la determinación de la estimulación máxima de adenilil ciclasa, es una medida de actividad funcional y es una medida primaria que se ejemplifica en la presente. Sin embargo, debe comprenderse que pueden emplearse medidas alternativas de la actividad funcional en la puesta en práctica de esta invención y se contemplan específicamente e incluyen dentro del alcance de la invención. Por lo tanto, en un ejemplo se puede medir el calcio libre intracelular, tal como se describe en Mountjoy K.G. et al., Melanocortin receptor-mediated mobilization of intracellular free calcium in HEK293 cells, *Physiol Genomics* 5:11-19, 2001, o Kassack M.U. et al., Functional screening of G protein-coupled receptors by measuring intracellular calcium with a fluorescence microplate reader, *Biomol Screening* 7:233-246, 2002, y mediante los métodos allí descritos. También es posible medir la activación mediante la medición de la producción de inositol trifosfato o diacilglicerol de fosfatidilinisitol 4,5-bifosfato, tal como mediante el uso de radioensayos. Otra medida de la actividad funcional es la internalización del receptor, lo que resulta de la actividad de vías reguladoras, tal como utilizando los métodos descritos en Nickolls S.A. et

al., Functional selectivity of melanocortin 4 receptor peptide and nonpeptide agonists: evidence for ligand specific conformational states, *J Pharm Exper Therapeutics* 313:1281-1288, 2005. Otra medida adicional de la actividad funcional es el intercambio, y la velocidad del intercambio, de los nucleótidos asociados con la activación de un receptor de proteína G, tal como el intercambio de GDP (guanosina difosfato) para GTP (guanosina trifosfato) en la subunidad α de la proteína G, que puede medirse mediante cualquier cantidad de medios, incluido el radioensayo que utiliza guanosina 5'-(γ-[$^{35}$S]tio)-trifosfato, como se describe en Manning D.R., Measures of efficacy using G proteins as endpoints: differential engagement of G proteins through single receptors, *Mol Pharmacol* 62:451-452, 2002. Se han desarrollado diversos ensayos basados en genes para medir la activación de proteínas acopladas a G, tal como las que se describen en Chen W. et al., A colorimetric assay from measuring activation of Gs- and Gq-coupled signaling pathways. *Anal Biochem* 226:349-354, 1995; Kent T.C. et al., Development of a generic dual-reporter gene assay for screening G-protein-coupled receptors. *Biomol Screening*, 5:437-446, 2005; o Kotarsky K. et al., Improved receptor gene assays used to identify ligands acting on orphan seven-transmembrane receptors. *Pharmacology & Toxicology* 93:249-258, 2003. En ensayo colorimétrico de Chen et al. se ha adaptado para utilizar en la medición de la activación del receptor de melanocortina, como se describe en Hruby V.J. et al., Cyclic lactam α-melanocortin analogues of Ac-Nle$^4$-cyclo[Asp$^5$,D-Phe$^7$,Lys$^{10}$] α-melanocyte-stimulating hormone-(4-10)-$NH_2$ with bulky aromatic amino acids at position 7 shows high antagonist potency and selectivity at specific melanocortin receptors. *J Med Chem* 38:3454-3461, 1995. En general, la actividad funcional puede medirse mediante cualquier método, incluidos los métodos para determinar la activación y/o señalización de un receptor acoplado a G, e incluye además los métodos que pueden desarrollarse o describirse más adelante. Las expresiones "tratar", "que trata" y "tratamiento", como se utilizan en la presente, contemplan una acción que ocurre mientras el paciente sufre de una enfermedad, trastorno y/o afección específico que reduce la gravedad de la enfermedad, trastorno y/o afección. Además, las expresiones "tratar" "que trata" y "tratamiento", como se utilizan en la presente, abarcan el tratamiento terapéutico (curativo), profiláctico (preventivo), de control y paliativo de las enfermedades, trastornos y/o afecciones indicados.

Como se utiliza en la presente, la expresión "cantidad farmacológicamente efectiva" (incluida "cantidad terapéuticamente efectiva") significa una cantidad de un péptido de acuerdo con la invención que es suficiente para inducir un efecto terapéutico o biológico deseado.

Como se utiliza en la presente, la expresión "cantidad terapéuticamente efectiva" significa la cantidad de un péptido de la invención que provocará una respuesta biológica o médica en el mamífero que está siendo tratado por un médico u otro facultativo.

Como se utiliza en la presente, la expresión "profilácticamente efectivo" o "preventivo" significa la cantidad de un péptido de la invención que evitará o inhibirá el dolor de un mamífero con una afección médica que el médico u otro facultativo está tratando de prevenir, inhibir o mitigar antes de que el paciente comience a sufrir de la enfermedad o trastorno especificado.

El término "diabetes" incluye Diabetes Tipo 1, que es la Diabetes mellitus insulino-dependiente según diagnóstico de acuerdo con los criterios publicados en el Informe del Comité de Expertos en Diagnóstico y Clasificación de Diabetes Mellitus (*Diabetes Care*, Vol. 24, Sup. 1, enero de 2001), según los cuales el nivel de glucosa de plasma en ayunas es mayor a 126 miligramos por decilitro y cuya primera causa es la destrucción de células beta pancreáticas, Diabetes Tipo 2, que es diabetes mellitus no insulino- dependiente según diagnóstico de acuerdo con los criterios publicados en el Informe del Comité de Expertos en Diagnóstico y Clasificación de Diabetes Mellitus, según los cuales el nivel de glucosa de plasma en ayunas es mayor o igual a 126 miligramos por decilitro, y diabetes mellitus autoinmune latente de adultos (LADA).

El término "síndrome metabólico" se refiere a trastornos metabólicos, particularmente trastornos reguladores de lípidos y glucosa, incluida la resistencia a la insulina y la secreción defectuosa de insulina por parte de las células beta pancreáticas, y puede también incluir afecciones y estados tales como obesidad abdominal, dislipidemia, hipertensión, intolerancia a la glucosa o un estado protrombótico, y que puede también resultar en trastornos tales como hiperlipidemia, obesidad, diabetes, resistencia a la insulina, intolerancia a la glucosa, hiperglicemia e hipertensión.

2.0 Indicaciones clínicas y utilidad

Las composiciones y métodos descritos en la presente pueden utilizarse para aplicaciones médicas y aplicaciones relacionadas con la cría de animales o veterinarias. Generalmente, los métodos se utilizan en humanos, pero también pueden utilizarse en otros mamíferos. El término "paciente" denota un individuo mamífero y se utiliza, por lo tanto, a lo largo de toda la memoria descriptiva y en las reivindicaciones. Las aplicaciones principales de la presente invención involucran pacientes humanos, pero la presente invención puede aplicarse a animales de laboratorio, granja, zoológico, vida salvaje, mascotas, deportes u otros. Las indicaciones clínicas y utilidades específicas incluyen lo siguiente:

2.1 Obesidad y síndrome metabólico relacionado

Se ha encontrado que los péptidos de Fórmula (I), y en particular de Fórmula (II) o (III), son ligandos del receptor MC4. En particular, se cree que los péptidos de Fórmula (I) son útiles para tratar enfermedades, trastornos y/o afecciones sensibles a la modulación de la función de MC4-R, más particularmente la activación de MC4-R, es decir, enfermedades, trastornos y/o afecciones que se beneficiarían del agonismo (incluido el agonismo completo o parcial) en MC4-R, incluidas las enfermedades, trastornos y afecciones relacionados con la homeostasis de la energía y el metabolismo (tales como diabetes, en particular de tipo 2; dislipidemia; hígado adiposo; hipercolesterolemia; hipertrigliceridemia; hiperuricacidemia; tolerancia a la glucosa alterada; glucosa en ayunas alterada; síndrome de resistencia a la insulina y síndrome metabólico), ingesta de alimentos (tal como hiperfagia; atracón; bulimia e ingesta compulsiva) y/o equilibrio de energía y peso corporal, más particularmente las enfermedades, trastornos y afecciones caracterizados por peso corporal excesivo y/o ingesta excesiva de alimentos.

Se cree particularmente que los péptidos de Fórmula (I), y en particular de Fórmula (II) o (III), son útiles para el tratamiento de enfermedades, trastornos y/o afecciones relacionados con el peso corporal caracterizados por peso corporal excesivo, incluida la obesidad y el sobrepeso (por promoción de pérdida de peso, mantenimiento de pérdida de peso y/o prevención de aumento de peso, incluido el aumento de peso inducido por medicación o aumento de peso posterior a dejar de fumar) y enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, tales como resistencia de insulina; tolerancia a la glucosa alterada; diabetes tipo 2; síndrome metabólico; dislipidemia

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(incluida hiperlipidemia); hipertensión; trastornos cardíacos (por ejemplo, enfermedad cardíaca coronaria, infarto miocárdico); trastornos cardiovasculares; enfermedad de hígado adiposo no alcohólico (incluida la esteatohepatitis no alcohólica); trastornos articulatorios (incluida la osteoartritis secundaria); reflujo gastroesofágico; apnea del sueño; aterosclerosis; accidente cerebrovascular; enfermedades macro y micro vasculares; esteatosis (por ejemplo, en el hígado); cálculos en la vesícula y trastornos de la vesícula.

Se cree particularmente que os péptidos de Fórmula (I), y en particular la Fórmula (II) o (III) son útiles para el tratamiento de obesidad y diabetes tipo 2, más específicamente obesidad.

Se comprenderá que hay definiciones médicamente aceptadas de obesidad y sobrepeso. Un paciente puede identificarse, por ejemplo, midiendo el índice de masa del cuerpo (BMI) que se calcula dividiendo el peso en kilogramos por altura en metros cuadrados, y comparando el resultado con las definiciones. Las clasificaciones recomendadas para BMI en humanos, adoptadas por el Panel de Expertos en Identificación, Evaluación y Tratamiento de Sobrepeso y Obesidad en Adultos, y aprobadas por las organizaciones líderes de profesionales de la salud, son las siguientes: Bajo peso < 18,5 $kg/m^2$, peso normal 18,5-24,9 $kg/m^2$, sobrepeso 25-29,9 $kg/m_2$, obesidad (clase 1) 30-34,9 $kg/m^2$, obesidad (clase 2) 35-39,9 $kg/m^2$, obesidad extrema (clase 3) $\geq$ 40 $kg/m^2$ (Guía Práctica de la Identificación, Evaluación y Tratamiento del Sobrepeso y Obesidad en Adultos, Asociación Norteamericana para el Estudio de la Obesidad (NAASO) y el Instituto Nacional del Corazón, Pulmones y Sangre (NIHLBI) 2000). Pueden utilizarse modificaciones de esta clasificación para grupos étnicos específicos y para niños. Otra alternativa para evaluar el sobrepeso y la obesidad es midiendo la circunferencia de la cintura. Hay varias clasificaciones y diferencias propuestas en los límites en base al grupo étnico. Por ejemplo, de acuerdo con la clasificación de la Federación Internacional de Diabetes, los hombres que tienen circunferencias de cintura por encima de los 94 cm (límite para európidos) y las mujeres que tienen circunferencias de cintura por encima de los 80 cm (límite para európidos) están en alto riesgo de diabetes, dislipidemia, hipertensión y enfermedades cardiovasculares dada a la excesiva grasa abdominal. Otra clasificación se basa en la recomendación del Panel de Tratamiento de Adultos III donde los límites recomendados son 102 cm para los hombres y 88 cm para las mujeres. Sin embargo, también pueden utilizarse los péptidos de Fórmula (I) para la reducción de

sobrepeso autodiagnosticado y para reducir el riesgo de convertirse en obeso debido al estilo de vida, las consideraciones genéticas, hereditarias y/o otros factores.

Se cree que los péptidos de Fórmula (I), y en particular de Fórmula (II) o (III), al administrarse a un animal, incluido el hombre, reducirán la ingesta de alimentos, el peso corporal y/o el aumento de peso corporal en dicho animal.

Sin estar sujeto a ninguna teoría, se cree que los péptidos de Fórmula (I) y en particular Fórmula (II) o (III), actúan modulando el apetito y/o saciedad, aumentando el índice metabólico, reduciendo la ingesta y/o las ansias de grasa y/o carbohidratos.

Sin estar sujeto a ninguna teoría, también se cree que los péptidos de Fórmula (I), y en particular de Fórmula (II) o (III), actúan mejorando la tolerancia a la glucosa y/o disminuyendo la resistencia a la insulina. Por lo tanto, se cree que los péptidos de Fórmula (I) también pueden ser útiles para tratar la diabetes tipo 2 en individuos de bajo peso y peso normal, así como también en individuos con sobrepeso y obesos.

Los péptidos de la invención también pueden ser útiles para (i) la prevención del daño a los órganos o tejidos causado por la hipoperfusión debido a la oclusión de vasos (por ejemplo, causada por trombosis), hemorragia, traumatismo, cirugía, shock hemorrágico, shock cardiogénico, shock tóxico o shock séptico o (ii) el tratamiento de disfunciones sexuales masculinas y femeninas, tales como la disfunción eréctil masculina o la disfunción de excitación sexual femenina.

De acuerdo con otro aspecto de la invención, se proporciona un péptido de Fórmula (I), y en particular de Fórmula (II) o (III), como se define anteriormente para utilizar como medicamento.

En otro aspecto, la invención proporciona el uso de un péptido de Fórmula (I), y en particular Fórmula (II) o (III), para el tratamiento de enfermedades, trastornos y/o afecciones sensibles a la modulación de MC4-R, tales como enfermedades, trastornos y/o afecciones sensibles a la activación de MC4-R, en particular enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, la diabetes), ingesta de alimentos y/o equilibro de energía y peso corporal, incluida la obesidad, sobrepeso y enfermedades, trastornos y/o afecciones asociados con la obesidad y el sobrepeso, tales como la diabetes tipo 2 y el síndrome metabólico.

En otro aspecto, la invención proporciona el uso de un péptido de Fórmula (I), y en particular Fórmula (II) o (III), en la preparación de un medicamento para el tratamiento de

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enfermedades, trastornos y/o afecciones sensibles a la modulación de MC4-R, tal como la activación de MCR-4, en particular enfermedades, trastornos y/o afecciones sensibles a la activación de MC4-R, en particular enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, la diabetes), ingesta de alimentos y/o equilibro de energía y peso corporal, incluida la obesidad, sobrepeso y enfermedades, trastornos y/o afecciones asociados con la obesidad y el sobrepeso, tales como la diabetes tipo 2 y el síndrome metabólico.

Los péptidos de la invención son ventajosamente más selectivos (es decir, tienen mayor afinidad y/o mayor especificidad) para MC4-R y/o MC3-R que para MC1-R, MC2-R y MC5-R, en particular MC1-R. En particular, los péptidos de la invención son ventajosamente más selectivos para MC4-R que para cualquiera de MC3-R y MC1-R. Los péptidos de la invención son adecuadamente al menos 3 veces, en particular 10 veces, más particularmente 30 veces, más selectivos para MC4-R que para cualquiera de MC1-R, MC2-R, MC3-R y MC5-R. Algunos péptidos de la invención son incluso más de 100 veces, tal como aun aproximadamente 150 veces, más selectivos para MC4-R que MC1-R, según se determinó en el ensayo de unión al receptor descrito en 7.1. Se observa que el perfil de selectividad puede afectar la seguridad in vivo y los efectos secundarios obtenidos con la administración de los péptidos.

Con el tratamiento de las enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo, ingesta de alimentos y/o equilibro de energía y peso corporal, se desea reducir o eliminar los efectos secundarios no deseados que pueden resultar de la activación de MC4-R, tal como los efectos secundarios sexuales, incluidos efectos en la erección peneana y la presión sanguínea.

Se cree que los péptidos de la invención son útiles para el tratamiento de las enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, diabetes), ingesta de alimentos y/o equilibro de energía y peso corporal, incluida la obesidad, sobrepeso y enfermedades, trastornos y/o afecciones asociados como la obesidad y/o el sobrepeso, tales como la diabetes tipo 2 y el síndrome metabólico, sin causar efectos cardiovasculares adversos importantes, incluido un aumento considerable de la presión sanguínea.

Se cree que los péptidos de la invención son útiles para el tratamiento de las enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el

metabolismo (por ejemplo, diabetes), ingesta de alimentos y/o equilibro de energía y peso corporal, incluida la obesidad, sobrepeso y enfermedades, trastornos y/o afecciones asociados como la obesidad y/o el sobrepeso, tales como la diabetes tipo 2 y el síndrome metabólico, sin causar efectos sexuales no deseados importantes que resulten de la activación de MC4-R, tal como la erección peneana.

Se cree que los péptidos de Fórmula I, y en particular de Fórmula (II) o (III), poseen un perfil farmacológico satisfactorio y propiedades biofarmacéuticas prometedoras, tales como perfil toxicológico, propiedades del metabolismo y farmacocinéticas, solubilidad y permeabilidad. Se comprenderá que la determinación de propiedades biofarmacéuticas apropiadas está dentro del conocimiento de un experto en la técnica.

3.0 Terapia de combinación para determinadas indicaciones.

Los péptidos, composiciones y métodos de la presente invención pueden utilizarse para el tratamiento de cualquiera de las enfermedades, indicaciones, afecciones o síndromes anteriores, o cualquier enfermedad, indicación, afección o síndrome que es mediado por el receptor de melanocortina, mediante la administración en combinación con uno o más compuestos farmacéuticamente activos. Dicha administración en combinación puede ser por medio de una forma de dosificación única que incluye un péptido de la presente invención y otro compuesto farmacéuticamente activo, incluyendo dicha forma de dosificación única un comprimido, cápsula, aerosol, inhalación, polvo, líquido inyectable o similar. Alternativamente, la administración en combinación puede ser por medio de la administración de dos formas de dosificación diferentes, conteniendo una forma de dosificación un péptido de la presente invención e incluyendo la otra forma de dosificación otro compuesto farmacéuticamente activo. En este caso, las formas de dosificación pueden ser iguales o diferentes. Sin ánimo de limitar las terapias de combinación, a continuación se ilustran determinadas terapias de combinación que pueden emplearse.

3.1 Terapia de combinación para obesidad y síndrome metabólico relacionado

Uno o más péptidos de la invención pueden combinarse con uno o más agente(s) farmacológicamente activo(s) que es/son útil(es) en el tratamiento de varios trastornos relacionados con el peso y la alimentación, tales como la obesidad y/o el sobrepeso, en particular otros fármacos que afectan el gasto de energía, glicólisis, glucogénesis, glucogenólisis, lipólisis, lipogénesis, absorción de grasa, almacenamiento de grasa, excreción de grasa, mecanismos de hambre y/o saciedad y/o ansias, apetito/motivación,

ingesta de alimentos o motilidad gastrointestinal. Los fármacos que reducen la absorción de energía incluyen, en parte, diversos agentes farmacológicos a los que se hace referencia como fármacos anoréxicos, que se utilizan como adjuntos a la terapia de comportamiento en programas de reducción de peso.

En general, una dosis total de los agentes o medicamentos de control de obesidad que se describen más adelante, cuando se utilizan en combinación con uno o más péptidos de la presente invención, pueden estar en el rango de 0,1 a 3.000 mg/día, preferiblemente de aproximadamente 1 a 1.000 mg/día y más preferiblemente de aproximadamente 1 a 200 mg/día en una dosis única o dividida en 2-4 dosis. La dosis exacta, sin embargo, es determinada por el médico tratante y depende de factores tales como potencia del compuesto administrado, edad, peso, condición y respuesta del paciente.

Pueden combinarse uno o más péptidos de la invención con uno o más agentes farmacológicamente activos que sean útiles en el tratamiento de diabetes, tales como fármacos anti-diabéticos.

Uno o más péptidos de la invención pueden además o alternativamente combinarse con uno o más agentes farmacológicamente activos que sean útiles en el tratamiento de enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, tal como resistencia a la insulina, tolerancia a la glucosa alterada; diabetes tipo 2; síndrome metabólico; dislipidemia (incluida la hiperlipidemia); hipertensión; trastornos cardíacos (por ejemplo, enfermedad cardíaca coronaria, infarto del miocardio); trastornos cardiovasculares; enfermedad del hígado adiposo no alcohólico (incluida la esteatohepatitis no alcohólica); trastornos articulatorios (incluida la osteoartritis secundaria); reflujo gastroesofágico; apnea del sueño; aterosclerosis; accidente cerebrovascular; enfermedades macro y micro vasculares; esteatosis (por ejemplo, en el hígado); cálculos en la vesícula y trastornos de la vesícula.

De acuerdo con otro aspecto de la invención se proporciona un tratamiento de combinación que comprende la administración de una cantidad farmacológicamente efectiva de un péptido de acuerdo con la invención, o una sal farmacéuticamente del mismo, opcionalmente junto con un diluyente o portador farmacéuticamente aceptable, con

la administración simultánea, secuencial o separada de uno o más de los siguientes agentes seleccionados de:

- insulina y análogos de insulina;
- secretagogos de insulina, incluidas sulfonilureas (por ejemplo, glipizida) y reguladores de glucosa prandial (a veces denominados "secretagogos de corta acción"), tal como meglitinidas (por ejemplo, repaglinida y nateglinida);
- agentes que mejoran la acción de incretina, por ejemplo inhibidores de dipeptidil peptidasa IV (DPP-4) (por ejemplo, vildagliptina, saxagliptina y sitagliptina), y agonistas de péptidos similares de glucagón 1 (GLP-1) (por ejemplo, exenatida);
- agentes de sensibilización a la insulina, incluidos los agonistas del receptor gamma activado por proliferador de peroxisoma (PPARγ), tales como tiazolidinedionas (por ejemplo, pioglitazona y rosiglitazona), y agentes con cualquier combinación de actividad de PPAR alfa, gamma y delta;
- agentes que modulan el equilibro de la glucosa hepática, por ejemplo biguanidas (por ejemplo, metformina), inhibidores de 1,6-bisfosfatasa de fructosa, inhibidores de fosforilasa de glicógeno, inhibidores de quinasa de glicógeno sintasa y activadores de glucoquinasa;
- agentes diseñados para reducir/disminuir la absorción de glucosa del intestino, tal como inhibidores de alfa-glucosidasa (por ejemplo, miglitol y acarbosa);
- agentes que antagonizan las acciones o reducen la secreción de glucagón, tales como análogos de amilina (por ejemplo, pramlintida);
- agentes que previenen la reabsorción de glucosa del riñón, tales como inhibidores del transportador de glucosa dependiente de sodio 2 (SGLT-2) (por ejemplo, dapagluflozina);
- agentes diseñados para tratar las complicaciones de la hiperglicemia prolongada, tales como inhibidores de aldosa reductasa (por ejemplo, epalrestat y ranirestat); y agentes utilizados para tratar complicaciones relacionadas con micro-angiopatías;
- agentes anti-dislipidemia, tales como inhibidores de HMG-CoA reductasa (estatinas, por ejemplo, rosuvastatina) y otros agentes que reducen el colesterol; agonistas de PPARα (fibrados, por ejemplo, gemfibrozil y fenofibrato);

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secuestrantes de ácido biliar (por ejemplo, colestiramina); inhibidores de absorción de colesterol (por ejemplo, esteroles vegetales (es decir, fitosteroles), inhibidores sintéticos); inhibidores de la proteína de transferencia de éster de colesterilo (CETP); inhibidores del sistema de transporte del ácido biliar ileal (inhibidores de IBAT); resinas de unión a ácido biliar; ácido nicotínico (niacina) y análogos del mismo; antioxidantes, tales como probucol; y ácidos grasos omega-3;

- agentes antihipertensivos, incluidos los antagonistas del receptor adrenérgico, tales como bloqueadores beta (pro ejemplo, atenolol), bloqueadores alfa (por ejemplo, doxazosina) y bloqueadores mixtos alfa/beta (por ejemplo, labetalol); agonistas del receptor adrenérgico, incluidos agonistas alfa-2 (por ejemplo, clonidina); inhibidores de la enzima de conversión de angiotensina (ACE) (por ejemplo, lisinoprilo), bloqueadores de canal de calcio, tales como dihidropiridinas (por ejemplo, nifedipina), fenilalquilaminas (por ejemplo, verapamil) y benzotiazepinas (por ejemplo, diltiazem); antagonistas del receptor de angiotensina II (por ejemplo, candesartán); antagonistas del receptor de aldosterona (por ejemplo, eplerenona); fármacos adrenérgicos con actuación central, tales como agonistas alfa centrales (por ejemplo, clonidina); y agentes diuréticos (por ejemplo, furosemida);
- moduladores de la homeostasis, incluidos antitrombóticos, tales como activadores de fibrinólisis; antagonistas de trombina; inhibidores del factor VIIa; anticoagulantes, tales como antagonistas de vitamina K (por ejemplo, warfarina), heparina y análogos de bajo peso molecular de los mismos, inhibidores del factor Xa e inhibidores directos de trombina (por ejemplo, argatrobán); agentes antiplaquetarios, tales como inhibidores de ciclooxigenasa (por ejemplo, aspirina), inhibidores del receptor de adenosina difosfato (ADP) (por ejemplo, clopidogrel), inhibidores de fosfodiesterasa (por ejemplo, cilostazol), inhibidores de la glicoproteína IIB/IIA (por ejemplo, tirofibán) e inhibidores de la reabsorción de adenosina (por ejemplo, dipridamol);
- agentes anti-obesidad, tal como supresor del apetito (por ejemplo, efedrina), incluidos agentes noradrenérgicos (por ejemplo, fentermina) y agentes serotonérgicos (por ejemplo, sibutramina), inhibidores de lipasa pancreática (por

ejemplo, orlistat), modulares de la proteína de transferencia microsomal (MTP), inhibidores de diacil glicerlaciltransferasa DGAT) y antagonistas del receptor cannabinoide (CB1) (por ejemplo, rimonabant);

- agentes modificaciones del comportamiento de alimentación, tal como modulares del receptor de orexina y modulares de la hormona de concentración de melanina (MCH);
- moduladores del receptor de péptido-1 similar a glucagón (GLP-1);
- moduladores del neuropéptido Y (NPY)/receptor de NPY;
- modulares de la piruvato deshidrogenasa quinasa (PDK);
- moduladores del receptor de serotonina;
- moduladores de letpina/ receptor de leptina;
- moduladores de grelina/ receptor de grelina; o
- agentes moduladores de la transmisión de monoamina, tales como inhibidores selectivos de la recaptación de serotonina (SSRI) (por ejemplo, fluoxetina), inhibidores de la recaptación de noradrenalina (NARI), inhibidores de la recaptación de noradrenalina-serotonina (SNRI), bloqueadores de la recaptación de monoamina triple (por ejemplo, tesofensina) e inhibidores de oxidasa de monoamina (MAOI) (por ejemplo, toloxatona y amiflamina),

o una sal, solvato, solvato de dicha sal o profármaco farmacéuticamente aceptable de los mismos, opcionalmente junto con un vehículo farmacéuticamente aceptable a un mamífero, tal como el hombre, que necesita dicho tratamiento terapéutico.

De acuerdo con otro aspecto de la invención se proporciona un tratamiento de combinación que comprende la administración de una cantidad farmacológicamente efectiva de un compuesto de acuerdo con la invención, o una sal farmacéuticamente del mismo, opcionalmente junto con un vehículo farmacéuticamente aceptable, con la administración simultánea, secuencial o separada de dietas muy bajas en calorías (VLCD) o dietas bajas en calorías (LCD).

4.0 Métodos de realización

En general, los péptidos de la presente invención pueden sintetizarse mediante síntesis en fase sólida y purificarse de acuerdo con los métodos conocidos en la técnica. Puede utilizarse cualquier procedimiento de una cantidad de procedimientos bien

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conocidos que utilizan una variedad de resinas y reactivos para preparar los péptidos de la presente invención.

Los péptidos cíclicos de la presente invención pueden sintetizarse fácilmente mediante procedimientos convencionales conocidos para la formación de una unión de péptidos entre los aminoácidos. Dichos procedimientos convencionales incluyen, por ejemplo, cualquier procedimiento de fase de solución que permita una condensación entre el grupo amino alfa libre de un aminoácido o residuo del mismo que tenga su grupo carboxilo y otros grupos reactivos protegidos y el grupo carboxilo primario libre de otro aminoácido o residuo del mismo que tiene su grupo amino u otros grupos amino protegidos. En general, los péptidos cíclicos de la presente invención pueden sintetizarse mediante síntesis en fase sólida y purificarse de acuerdo con los métodos conocidos en la técnica. Puede utilizarse cualquier procedimiento de una cantidad de procedimientos bien conocidos que utilizan una variedad de resinas y reactivos para preparar los péptidos de la presente invención.

El proceso para sintetizar los péptidos cíclicos puede llevarse a cabo mediante un procedimiento por el cual cada aminoácido en la secuencia deseada se agrega de a uno en sucesión a otro aminoácido o residuo del mismo o mediante un procedimiento por el cual los fragmentos de péptidos con la secuencia de aminoácidos deseada se sintetizan primero convencionalmente y luego se condensan para proporcionar el péptido deseado. El péptido resultante se cicliza luego para proporcionar un péptido cíclico de la invención.

Los métodos de síntesis de péptidos en fase sólida se conocen bien y se utilizan ampliamente en la técnica. En dichos métodos, la síntesis de los péptidos de la invención puede llevarse a cabo secuencialmente incorporando los residuos de aminoácidos deseados de a uno en la cadena de péptidos creciente de acuerdo con los principios generales de los métodos en fase sólida. Estos métodos se describen en numerosas referencias, incluida Merrifield, R.B., Solid phase synthesis (Conferencia Nobel). *Angew Chem* 24:799-810 (1985) y Barany et al., The Peptides, Analysis, Synthesis and Biology, Vol. 2, Gross, E. and Meienhofer, J., Eds. Academic Press 1-284 (1980).

En las síntesis químicas de los péptidos, los grupos de cadena lateral reactivos de los diversos residuos de aminoácidos están protegidos con grupos protectores adecuados, lo cual evita que una reacción química no ocurra en el sitio hasta que se extraiga el grupo protector. También es común la protección del grupo amino alfa de un residuo o fragmento

de aminoácido mientras que la entidad reacciona en el grupo carboxilo, seguida de la eliminación selectiva del grupo protector amino alfa para permitir que ocurra una posterior reacción en el sitio. Se han descrito y se conocen grupos protectores específicos en métodos de síntesis en fase sólida y métodos de síntesis en fase de solución.

Los grupos amino alfa pueden estar protegidos por un grupo protector adecuado, incluido un grupo protector del tipo uretano, tal como benciloxicarbonilo (Z) y benciloxicarbonilo sustituido, tales como grupos protectores p-clorobenciloxicarbonilo, p-nitrobenciloxicarbonilo, p-bromobenciloxicarbonilo, p-bifenil-isopropoxicarbonilo, 9-fluorenilmetoxicarbonilo (Fmoc) y p-metoxibenciloxicarbonilo (Moz) del tipo uretano alifáticos, tales como t-butiloxicarbonilo (Boc), diisopropilmetoxicarbonilo, isopropoxicarbonilo y aliloxicarbonilo (Aloc). Se prefiere Fmoc para la protección de amino alfa.

Los grupos guanidino pueden estar protegidos por un grupo protector adecuado, tal como nitro, p-toluenosulfonilo (Tos), Z, pentametilcloromanosulfonilo (Pmc), adamantiloxicarbonilo, pentametildihidrobenzofuran-5-sulfonilo (Pbf) y Boc. Pbf y Pmc son grupos protectores preferidos para Arg.

Los péptidos de la invención descritos en la presente se prepararon utilizando síntesis en fase sólida, tal como por medio de un sintetizador automatizado Symphony Multiplex (Rainin Instrument Company/Protein Technologies Inc), utilizando módulos de programación como los que proporciona el fabricante y siguiendo los protocolos indicados en el manual del fabricante.

La síntesis en fase sólida se inicia desde el extremo C-terminal del péptido acoplando un grupo amino alfa protegido por una resina adecuada. Dicho material de partida se prepara adjuntando un aminoácido amino-protegido alfa mediante un enlace amida a una resina de 4-(2',4'-dimetoxilfenil-aminometil-fenoxi (Amida Rink), una resina de 4-(2', 4'-dimetoxilfenil-aminometil)-fenoxiacetamido-norleucil-MBHA, una resina de amino-xanten-3-iloxi-merifiel (Amida Sieber), o mediante un enlace de éster a un alcohol p-benciloxibencílico (Wang), una resina de cloruro de 2-clorotritilo o por otros medios conocidos en la técnica. Los soportes de la resina BHA enlazadora de Fmoc están disponibles comercialmente y generalmente se utilizan cuando es viable. Las resinas se someten a ciclos repetitivos según sea necesario para agregar aminoácidos secuencialmente. Los grupos protectores de Fmoc amino alfa se extraen en condiciones

básicas. Pueden utilizarse a estos efectos piperidina, piperazina, dietilamina o morfolina (20-40% v/v) en N,N-dimetilformamida (DMF).

Después de la eliminación del grupo protector amino alfa, los aminoácidos protegidos posteriores se acoplan en etapas en el orden deseado para obtener una resina de péptido protegida e intermediaria. Los reactivos de activación utilizados para acoplar los aminoácidos en la síntesis en fase sólida de los péptidos se conocen bien en la técnica. Después de sintetizar el péptido, si se desea, los grupos protectores de cadena lateral ortogonalmente protegidos pueden eliminarse utilizando métodos que se conocen bien en la técnica para una mayor derivatización del péptido.

Generalmente se utilizan grupos protectores ortogonales según corresponda. Por ejemplo, los péptidos de la invención contienen aminoácidos múltiples con una cadena lateral que contiene un grupo amino. En un aspecto, se emplea un esquema de protección alilo-aloc con los aminoácidos que forman un puente de lactama a través de sus cadenas laterales, y los grupos protectores ortogonales, escindibles en diferentes condiciones de reacción, se utilizan para otros aminoácidos con cadenas laterales que contienen un grupo amino. De este modo, por ejemplo, pueden emplearse aminoácidos de Fmoc-Orn(Alloc)-OH y Fmoc-Glu(OAll)-OH (Glu(OAll) se refiere éster de 5-alilo de ácido glutámico) para las posiciones que forman un puente de lactama tras la ciclización, mientras que otros aminoácidos con cadenas laterales que contienen grupos protectores amino tienen un grupo protector ortogonal diferente, tal como con Fmoc-Arg(Pbf)-OH, Fmoc-Lys(Pbf)-OH, Fmoc-Dab(Pbf)-OH o similar. Otros grupos protectores pueden emplearse de manera similar; a modo de ejemplo y no taxativo, puede emplearse Mtt/OPp (4-metiltritilo/ 2-fenilisopropilo) con las cadenas laterales que forman un puente de lactama tras la ciclización, utilizándose grupos protectores ortogonales para otras posiciones que no son escindibles utilizando condiciones adecuadas para escisión de Mtt/OPp.

Pueden modificarse selectivamente grupos reactivos en un péptido durante la síntesis en fase sólida o después de la eliminación de la resina. Por ejemplo, los péptidos pueden modificarse para obtener modificaciones N-terminales, tales como acetilación, mientras están en la resina, o pueden extraerse de la resina para utilizar un reactivo de escisión y luego modificarse. De manera similar, los expertos en la técnica conocen bien los métodos para modificar cadenas laterales de aminoácidos de síntesis de péptidos. La

elección de las modificaciones realizadas a grupos reactivos presentes en el péptido se determinará, en parte, por las características deseadas en el péptido.

En los péptidos de la presente invención, en una realización, el grupo N-terminal se modifica por la introducción de un grupo N-acetilo. En un aspecto, se emplea un método en donde después de la eliminación del grupo protector en el extremo N-terminal, el péptido unido a la resina se hace reaccionar con anhídrido acético en DMF en presencia de una base orgánica, tal como aspiridina. Se conocen en la técnica y pueden emplearse otros métodos de acetilación en el extremo N-terminal, incluida la acetilación en fase de solución.

El péptido puede, en una realización, ciclizarse antes de la escisión de la resina del péptido. Para ciclización a través de restos de cadena lateral reactiva, las cadenas laterales deseadas no están protegidas y el péptido está suspendido en un disolvente adecuado y se agrega un agente de acoplamiento cíclico. Los disolventes adecuados incluyen, por ejemplo, DMF, diclorometano (DCM) o 1-metil-2-pirrolidona (NMP). Los reactivos de acoplamiento cíclico adecuados incluyen, por ejemplo, tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (TBTU), hexafluorofosfato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (HBTU), benzotriazol-1-il-oxi-tris(dimetilamino)fosfoniohexafluorofosfato (BOP), benzotriazol-1-il-ox-tris(pirrolidino)fosfoniohexafluorofosfato (PyBOP), tetrafluoroborato de 2-(7-aza-1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (TATU), tetrafluoroborato de 2-(2-oxo-1(2H)-piridil)-1,1,3,3-tetrametiluronio (TPTU) o N,N'-diciclohexilcarbodiimida/1-hidroxibenzotriazol (DCCI/HOBt). El acoplamiento se inicia convencionalmente mediante el uso de una base adecuada, tal como N,N-diisopropiletilamina (DIPEA), sim-colidina o N-metilmorfolina (NMM).

Los péptidos ciclizados pueden escindirse de una fase sólida utilizando cualquier reactivo adecuado, tal como etilamina en DCM o varias combinaciones de agentes, tales como ácido trifluoroacético (TFA), tri-isopropilsilano (TIS), dimetoxibenceno (DMB), agua y similares. El péptido bruto resultante se seca y los grupos protectores de cadena lateral de aminoácidos restantes, si los hay, se escinden utilizando cualquier reactivo adecuado, tal como TFA en presencia de agua, TIS, 2-mercaptopetano (ME) y/o 1,2-etanditiol (EDT). El producto final se precipita agregando éter frío y se recolecta por filtración. La purificación final es por cromatografía líquida de alto rendimiento de fase

inversa (RP-HPLC), que utiliza una columna adecuada, tal como una columna $C_{18}$, o pueden también emplearse otros métodos de separación o purificación, tales como los métodos basados en el tamaño o carga del péptido. Una vez purificado, el péptido puede caracterizarse por cualquier cantidad de métodos, tales como cromatografía líquida de alto rendimiento (HPLC), análisis de aminoácidos, espectrometría de masas y similares.

Para los péptidos de la presente invención que tienen un derivado de amida sustituido C-terminal o grupo N-alquilo, la síntesis puede proceder mediante síntesis en fase sólida iniciada desde el extremo C-terminal del péptido acoplando un aminoácido alfa protegido a una resina adecuada. Dichos métodos de preparación de derivados de amida sobre fase sólida se han descrito en la técnica. Ver, por ejemplo, Barn D.R. et al., Synthesis of an array of amides by aluminum chloride assisted cleavage on resin bound esters. *Tetrahedron Letters*, 37:3213-3216 (1996); DeGrado W.F. y Kaiser E.T., Solid-phase synthesis of protected peptides on a polymer bound oxime: Preparation of segments comprising the sequences of a cytotoxic 26-peptide analogue. *J. Org. Chem.*, 47:3258-3261 (1982). Dicho material de partida puede prepararse adjuntando un aminoácido protegido por amino alfa mediante un enlace éster a una resina de alcohol p-benciloxibencílico (Wang) o mediante un enlace amida a una resina de 4-(2',4'-dimetoxilfenil-aminometil-fenoxi (Amida Rink) mediante métodos que se conocen bien. La cadena de péptidos se cultiva con la secuencia deseada de aminoácidos. Antes de la escisión, el péptido se cicliza sobre la fase sólida. Los péptidos que emplean una resina de alcohol p-benciloxibencílico (Wang) pueden escindirse de la resina mediante cloruro de aluminio en DCM, y los péptidos que emplean una resina de Amida Rink puede escindirse mediante una mezcla de TFA, TIS y agua.

Aunque la síntesis se ha descrito principalmente con referencia a la química de Fmoc en fase sólida, debe comprenderse que pueden emplearse otros métodos químicos y sintéticos para obtener los péptidos cíclicos de la invención, tal como, a modo de ejemplo y no taxativo, los métodos químicos que emplean Boc, soluciones y otros métodos químicos y sintéticos.

5.1 Forma de sal de los péptidos cíclicos de la presente invención.

Se entenderá que, tal como se utilizan en la presente, todas las referencias a péptidos de acuerdo con al invención, incluyendo una fórmula o nombre químico específico,

pretenden incluir todas las sales, solvatos, hidratos, polimorfos, profármacos, metabolitos, estereoisómeros e isómeros tautoméricos farmacéuticamente aceptables de los mismos.

Los péptidos cíclicos de la presente invención pueden estar en forma de cualquier sal farmacéuticamente aceptable. La expresión "sales farmacéuticamente aceptables" se refiere a sales preparadas a partir de bases o ácidos no tóxicos farmacéuticamente aceptables, incluidas bases inorgánicas u orgánicas y ácidos inorgánicos u orgánicos (ver "Handbook of Pharmaceutical Salts: Properties, Selection and Use", P. H. Stahl, P. G. Wermuth, IUPAC, Wiley-VCH, 2002). Las sales derivadas de bases inorgánicas incluyen aluminio, amonio, calcio, cobre, férrico, ferroso, litio, magnesio, sales mangánicas, manganoso, potasio, sodio, zinc y similares. Particularmente se prefiere amonio, calcio, litio, magnesio, potasio y sales sódicas. Las sales derivadas de bases no tóxicas orgánicas farmacéuticamente aceptables incluyen sales de aminas primarias, secundarias y terciarias, aminas sustituidas, incluyendo aminas sustituidas naturalmente, aminas cíclicas y resinas de intercambio iónico básicas, tales como arginina, betaína, cafeína, colina, N,N'-dibenciletilenodiamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilenodiamina, N-etil-morfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, isopropilamina, lisina, metilglucamina, morfolina, piperazina, piperidina, resinas poliaminas, procaína, purinas, teobromina, trietilamina, trimetilamina, tripropilamina, trometamina y similares. Cuando un péptido cíclico de la presente invención es básico, las sales de adición de ácido pueden prepararse a partir de ácidos no tóxicos farmacéuticamente aceptables, incluyendo ácidos inorgánicos y orgánicos. Tales ácidos incluyen ácido acético, bencenosulfónico, benzoico, camforsulfónico, carboxílico, cítrico, etanosulfónico, fórmico, fumárico, glucónico, glutámico, bromhídrico, clorhídrico, isetiónico, láctico, maleico, málico, mandélico, metanosulfónico, malónico, múcico, nítrico, pamoico, pantoténico, fosfórico, propiónico, succínico, sulfúrico, tartárico, ácido p-toluenosulfónico, ácido trifluoroacético y similares. Las sales de adición de ácido de péptidos de la presente invención se preparan en un disolvente apropiado para el péptido y un exceso de un ácido, tal como ácido clorhídrico, bromhídrico, sulfúrico, fosfórico, acético, trifluoroacético (TFA), cítrico, tartárico, maleico, succínico o metanosulfónico. Las formas de sal de ácido de acetato, acetato de amonio y TFA son especialmente útiles.

Cuando los péptidos de la presente invención incluyen un resto acídico, las sales farmacéuticamente aceptables adecuadas pueden incluir sales de metales alcalinos, tales

como sales de sodio o potasio, o sales de metales alcalinotérreos, tales como sales de calcio o magnesio. También debe entenderse que ciertos péptidos de Fórmula (I) pueden existir en formas solvatadas, incluyendo solvatos del péptido libre o solvatos de una sal del compuesto, así como también formas no solvatadas. El término "solvato" se utiliza en la presente para describir un complejo molecular que comprende el compuesto de la invención y una o más moléculas disolventes farmacéuticamente aceptables, por ejemplo, etanol. El término "hidrato" se utiliza cuando dicho disolvente es agua. Debe entenderse que todos los polimorfos, incluyendo mezclas de diferentes polimorfos, están incluidos dentro del alcance de los péptidos reivindicados.

5.2 Composiciones farmacéuticas

La invención proporciona una composición farmacéutica que incluye uno o más péptidos cíclicos de la presente invención y un portador farmacéuticamente aceptable. Cuando se formula con un portador farmacéuticamente aceptable, el compuesto de la invención puede estar presente en la composición farmacéutica en una concentración de 0,1 a 99,5%, tal como 0,5 a 95%, en peso de la composición total. La elección del portador se encuentra en el campo de conocimiento de una persona experta en la técnica y depende, por ejemplo, del modo de administración, la forma de dosificación y las propiedades físicas del compuesto activo, tales como solubilidad y estabilidad. El término "portador", como se utiliza en la presente, se refiere a un ingrediente terapéuticamente inactivo. La forma de dosificación puede ser un sistema sólido, semi-sólido o líquido. La formulación puede ser de liberación inmediata y/o modificada, incluyendo formulación de liberación retardada, sostenida, por pulsos, controlada, dirigida y programada.

El portador puede ser una formulación líquida y es preferiblemente una solución acuosa, isotónica, amortiguada. Los portadores farmacéuticamente aceptables también incluyen excipientes, tales como diluyentes, portadores y similares, y aditivos tales como agentes estabilizantes, conservantes, agentes solubilizantes, amortiguadores y similares, como se describirán más adelante.

Las composiciones de péptido cíclico de la presente invención pueden formularse o prepararse en composiciones farmacéuticas que incluyen al menos un péptido cíclico de la presente invención junto con uno o más portadores farmacéuticamente aceptables, incluyendo excipientes, tales como diluyentes, portadores y similares, y aditivos tales como agentes estabilizantes, conservantes, agentes solubilizantes, amortiguadores y

similares, según se desee. Los excipientes de la formulación pueden incluir polivinilpirrolidona, gelatina, hidroxipropil celulosa (HPC), goma arábiga, polietilenglicol, manitol, cloruro de sodio y citrato de sodio. Para inyectables u otras formulaciones de administración líquida, se prefiere agua que contiene al menos uno o más constituyentes amortiguadores y también pueden utilizarse agentes estabilizantes, conservantes y agentes solubilizantes. Para formulaciones de administración sólida puede utilizarse cualquiera de una diversidad de aditivos espesantes, de carga, volumétricos y portadores, tales como almidones, azúcares, derivados de celulosa, ácidos grasos y similares. Para formulaciones de administración tópica puede utilizarse cualquiera de una diversidad de cremas, ungüentos, geles, lociones y similares. Para la mayoría de las formulaciones farmacéuticas, los ingredientes no activos constituirán la mayor parte, en peso o volumen, de la preparación. Para las formulaciones farmacéuticas, también se contempla que puede utilizarse cualquiera de una diversidad de formulaciones de liberación medida, liberación lenta o liberación sostenida y aditivos, de modo que la dosificación puede formularse de modo tal que proporcione una administración de un péptido de la presente invención durante un período de tiempo.

En general, la cantidad de péptidos cíclicos de la presente invención administrados a un paciente variará entre rangos bastante amplios, dependiendo del modo de administración, la formulación utilizada y la respuesta descada.

En la práctica, los péptidos cíclicos de la invención pueden combinarse como ingrediente activo en un aditivo con un portador farmacéutico de acuerdo con técnicas de preparación farmacéutica convencionales. El portador puede tomar una amplia diversidad de formas, dependiendo de la forma de preparación deseada para la administración, por ejemplo, oral, parenteral (incluyendo intravenosa), uretral, vaginal, nasal, bucal, sublingual o similares. En la preparación de las composiciones para forma de dosificación oral, cualquiera de los medios farmacéuticos habituales puede utilizarse, tales como, por ejemplo, agua, glicoles, aceites, alcoholes, agentes saborizantes, conservantes, agentes colorantes y similares en el caso de preparaciones líquidas orales tales como, por ejemplo, suspensiones, elixires y soluciones; o portadores tales como almidones, azúcares, celulosa microcristalina, diluyentes, agentes de granulación, lubricantes, aglutinantes, agentes de desintegración y similares en el caso de preparaciones sólidas orales tales como, por ejemplo, polvos, cápsulas duras y blandas y comprimidos.

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Debido a su facilidad de administración, los comprimidos y cápsulas representan una forma de dosificación unitaria oral ventajosa. Si se desea, los comprimidos pueden revestirse mediante técnicas acuosas y no acuosas estándar. La cantidad de péptido activo en tales composiciones terapéuticamente útiles es tal que se obtendrá una dosificación eficaz. En otra forma de dosificación unitaria, pueden utilizarse constructos sublinguales, tales como láminas, obleas, comprimidos o similares.

Los comprimidos, pastillas, cápsulas y similares también pueden contener un aglutinante tal como povidona, goma tragacanto, goma arábiga, almidón de maíz o gelatina; diluyentes; cargas tales como celulosa microcristalina; excipientes tales como fosfato dicálcico; un agente de desintegración tal como almidón de maíz, almidón de papa o ácido algínico; conservantes; colorantes; un lubricante tal como estearato de magnesio; y un agente edulcorante tal como sacarosa, lactosa o sacarina. Cuando una forma de dosificación unitaria es una cápsula, puede contener, además de los materiales del tipo anterior, un portador líquido tal como aceite graso. Pueden utilizarse otros materiales diversos como revestimientos o para modificar la forma física de la dosificación unitaria. Por ejemplo, los comprimidos pueden revestirse con goma laca, azúcar o ambas. Un jarabe o elixir puede contener, además del ingrediente activo, sacarosa como agente edulcorante, metil y propilparabenos como conservantes, un pigmento y un saborizante tal como sabor naranja o cereza.

Si se formula para administración oral, el péptido preferiblemente se formula y hace de modo que esté recubierto con un protector entérico, más preferiblemente de modo que no se libere hasta que el comprimido o cápsula haya transitado el estómago, y opcionalmente que además haya transitado una porción del intestino delgado. En el contexto de esta aplicación se entenderá que la expresión revestimiento o material entérico se refiere a un revestimiento o material que pasará a través del estómago básicamente intacto pero se desintegrará después de pasar a través del estómago para liberar el fármaco. Los materiales que puede utilizarse incluyen acetoftalato de celulosa, succinato de hidroxipropilmetiletilcelulosa, ftalato de hidroxipropilmetilcelulosa, acetoftalato de polivinilo y copolímero de ácido metacrílico-metil metacrilato. El revestimiento entérico utilizado promueve la disolución de la forma de dosificación fundamentalmente en un sitio fuera del estómago, y puede seleccionarse de modo que el revestimiento entérico se

disuelva hasta un pH de aproximadamente al menos 5,5, más preferiblemente un pH de aproximadamente 6,0 a aproximadamente 8,0.

Puede utilizarse cualquiera de una diversidad de potenciadores de la penetración para aumentar la absorción en los intestinos luego de la disolución del revestimiento entérico. En un aspecto, los potenciadores de penetración aumentan los sistemas de transporte paracelulares o transcelulares. Ejemplos representativos no taxativos de tales potenciadores de la penetración incluyen quelantes de calcio, sales biliares (tales como colato de sodio) y ácidos grasos. En algunas realizaciones, se agregan adicionalmente péptidos o polipéptidos que actúan como sustratos para proteasas intestinales. Los péptidos cíclicos también pueden administrarse parenteralmente. Las soluciones o suspensiones de estos péptidos activos pueden, por ejemplo, prepararse en agua mezclada con, por ejemplo, hidroxipropilcelulosa. Las dispersiones también pueden prepararse en glicerol, glicoles de polietileno líquidos y mezclas de los mismos en aceites. Estas preparaciones pueden contener opcionalmente a un conservante para evitar el crecimiento de microorganismos.

Las formas farmacéuticas adecuadas para uso inyectable incluyen soluciones o dispersiones acuosas estériles y polvos estériles para la preparación improvisada de soluciones o dispersiones inyectables estériles. En todos los casos, la forma debe ser estéril y debe ser fluida hasta el punto que puede administrarse mediante una jeringa. La forma debe ser estable en las condiciones de fabricación y almacenamiento y debe conservarse contra la acción contaminante de microorganismos tales como bacterias y hongos. El portador puede ser un medio disolvente o de dispersión que contenga, por ejemplo, agua, etanol, un poliol, por ejemplo glicerol, propilenglicol o polietilenglicol líquido, mezclas adecuadas de los mismos y aceites vegetales.

Los péptidos cíclicos de la presente invención pueden aplicarse terapéuticamente mediante administración nasal. Por "administración nasal" se entiende cualquier forma de administración intranasal de cualquiera de los péptidos cíclicos de la presente invención. Los péptidos pueden estar en una solución acuosa, tal como una solución que incluye solución salina, citrato u otros excipientes o conservantes comunes. Los péptidos también pueden estar en una formulación seca o en polvo.

Si están en una solución acuosa, los péptidos cíclicos pueden amortiguarse apropiadamente mediante solución salina, acetato, fosfato, citrato, acetato u otros agentes amortiguadores, los cuales pueden estar a cualquier pH fisiológicamente aceptable, tal

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como de aproximadamente pH 4 a aproximadamente pH 7. También puede utilizarse una combinación de agentes amortiguadores, tales como solución salina amortiguada por fosfato, una solución amortiguadora salina y de acetato y similares. En el caso de solución salina puede utilizarse una solución salina al 0,9%. En el caso de acetato, fosfato, citrato y similares puede utilizarse una solución de 50 mM. Además de agentes amortiguadores, puede utilizarse un conservante adecuado para evitar o limitar el crecimiento de bacterias y otros microbios. Un conservante que puede utilizarse es cloruro de benzalconio al 0,05%.

En una realización alternativa, los péptidos cíclicos de la presente invención pueden administrarse directamente en el pulmón. La administración intrapulmonar puede llevarse a cabo mediante un inhalador de dosis medidas, un dispositivo que permite la auto-administración de un bolo medido de un péptido de la presente invención cuando el paciente lo acciona durante la inspiración. Puede utilizarse una diversidad de técnicas diferentes para hacer micropartículas de polvo seco incluyendo, a modo no taxativo, micro-molienda, secado por aspersión y un aerosol de congelación rápida seguido de liofilización.

Los péptidos cíclicos de la presente invención pueden administrarse terapéuticamente mediante una inyección de una formulación de liberación sostenida. En general, puede utilizarse cualquiera de una cantidad de polímeros inyectables y bioerosionables en una formulación inyectable de liberación sostenida. Alternativamente pueden utilizarse otras formulaciones de liberación sostenida, incluyendo formulaciones que permiten la inyección subcutánea, pudiendo incluir dichas otras formulaciones una o más nano/microesferas, liposomas, emulsiones (tales como emulsiones de agua en aceite), geles, sales insolubles o suspensiones en aceite. La formulación puede ser tal de modo que se necesite una inyección diariamente, semanalmente, mensualmente u otro modo periódico, dependiendo de la concentración y cantidad de péptido cíclico, la tasa de liberación sostenida de los materiales utilizados y otros factores conocidos para aquellos expertos en la técnica.

5.3 Vías de administración

Si una composición que incluye uno o más péptidos de la presente invención se administra mediante inyección, la inyección puede ser intravenosa, subcutánea, intramuscular, intraperitoneal u otros medios conocidos en la técnica.

Los péptidos de la presente invención pueden formularse mediante cualquier medio conocido en la técnica incluyendo, a modo no taxativo, formulación como comprimidos,

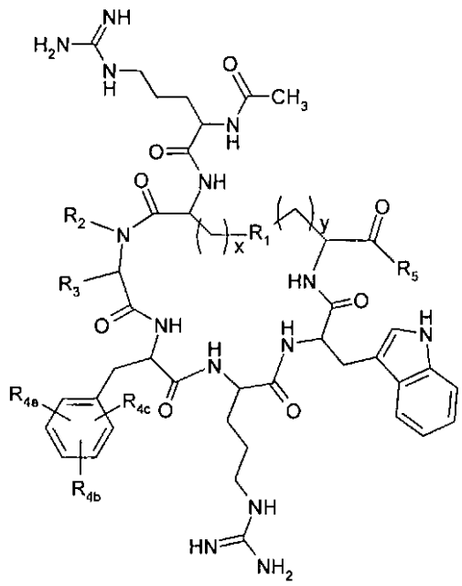
cápsulas, comprimidos oblongos, suspensiones, polvos, preparaciones liofilizadas, supositorios, gotas oculares, parches dérmicos, formulaciones solubles orales, atomizadores, aerosoles y similares, y pueden mezclarse y formularse con amortiguadores, aglutinantes, excipientes, estabilizadores, antioxidantes y otros agentes conocidos en la técnica. En general, puede utilizarse cualquier vía de administración mediante la cual los péptidos de la invención se introducen a través de una capa epidérmica de células. Los medios de administración por consiguiente pueden incluir administración a través de membranas mucosas, administración bucal, administración oral, administración dérmica, administración por inhalación, administración nasal, administración uretral, administración vaginal y similares.

5.4 Cantidad terapéuticamente efectiva

En general, la cantidad real de péptidos cíclicos de la presente invención administrados a un paciente variará entre rangos bastante amplios dependiendo del modo de administración, el paciente (incluyendo peso, sexo, condición de salud, dieta), la formulación utilizada y la respuesta deseada. La dosificación para tratamiento es la administración, mediante cualquiera de los medios anteriores o cualquier otro medio conocido en la técnica, de una cantidad suficiente para provocar el efecto terapéutico deseado. Los péptidos cíclicos de la presente invención son muy activos. Por ejemplo, el péptido cíclico puede administrarse (como una dosis única o dividido en dosis diarias) a aproximadamente 0,1, 0,5, 1, 5, 50, 100, 500, 1000 o 5000 µg/kg de peso corporal, dependiendo del péptido específico seleccionado, la respuesta terapéutica deseada, la vía de administración, la formulación y otros factores conocidos para aquellos expertos en la técnica.

6.0 Péptidos de la presente invención

En un aspecto, la presente invención se refiere a un péptido cíclico de Fórmula estructural (I):



(I)

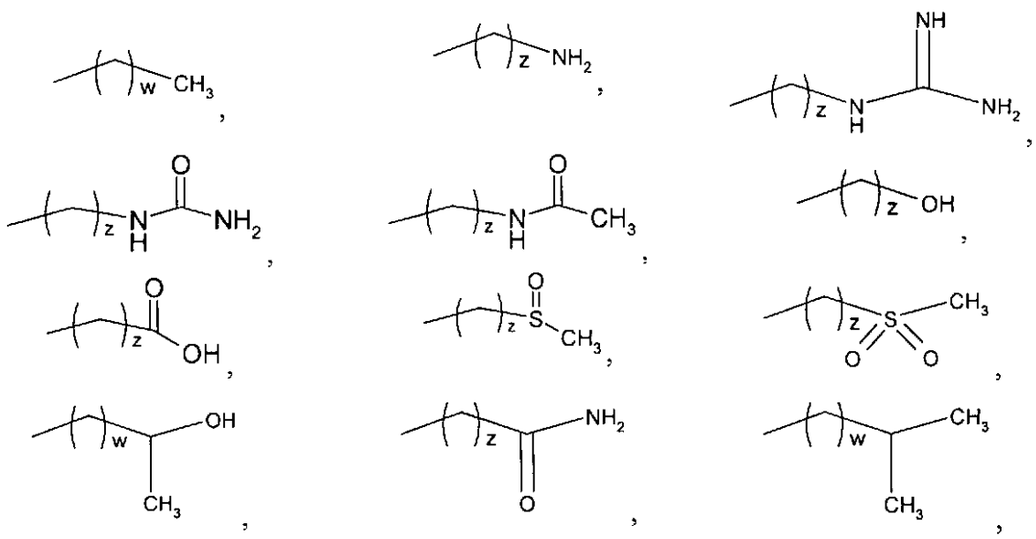
incluyendo todos los enantiómeros, estereoisómeros o diastereoisómeros del mismo, o una sal farmacéuticamente aceptable de cualquiera de los anteriores,

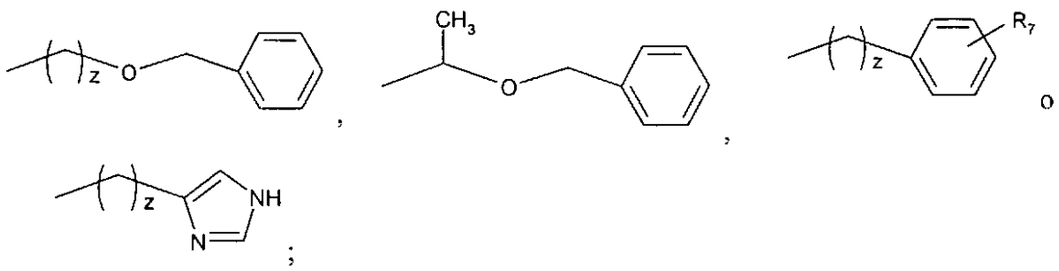
en donde:

$R_1$ es -NH-C(=O)- o -C(=O)-NH-;

$R_2$ es -H o $-CH_2-$ y, si $R_2$ es $-CH_2-$, forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH;

$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de





$R_{4a}$, $R_{4b}$ y $R_{4c}$ se seleccionan cada uno independientemente de hidrógeno, halo, alquilo($C_1$-$C_{10}$)-halo, alquilo($C_1$-$C_{10}$)-dihalo, alquilo($C_1$-$C_{10}$)-trihalo, alquilo($C_1$-$C_{10}$), alcoxi($C_1$-$C_{10}$), alquil($C_1$-$C_{10}$)tio, arilo, ariloxi, nitro, nitrilo, sulfonamida, amino, amino monosustituido, amino disustituido, hidroxi, carboxi o alcoxi-carbonilo, con la condición de que al menos uno de $R_{4a}$, $R_{4b}$ y $R_{4c}$ no sea hidrógeno;

$R_5$ es -OH o -N($R_{6a}$)($R_{6b}$);

$R_{6a}$ y $R_{6b}$ son cada uno independientemente H o una cadena alquilo de $C_1$ a $C_4$ lineal, ramificada o cílica;

$R_7$ es -H o -C(=O)-$NH_2$;

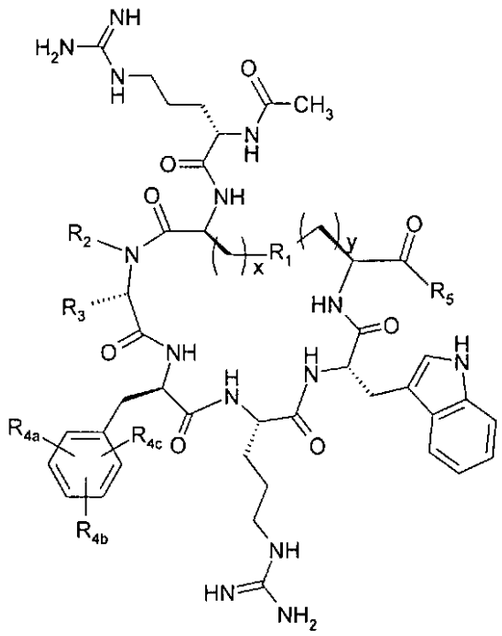
w es en cada instancia independientemente 0 a 5;

x es 1 a 5;

y es 1 a 5; y

z es en cada instancia independientemente 1 a 5.

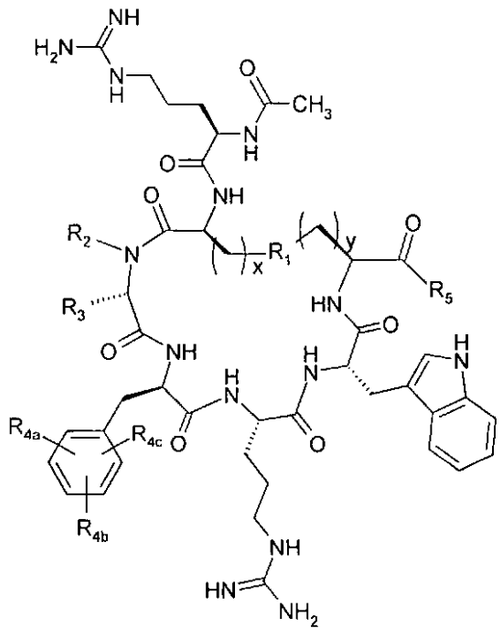
En otro aspecto, la presente invención se refiere a un péptido cíclico con la Fórmula (I) que es de la Fórmula (II):



(II)

o una sal farmacéuticamente aceptable del mismo.

En otro aspecto, la presente invención se refiere a un péptido cíclico con la Fórmula (I) que es de la Fórmula (III):



(III)

o una sal farmacéuticamente aceptable del mismo.

En un aspecto, la invención proporciona un heptapéptido cíclico que contiene una secuencia central derivada de His-Phe-Arg-Trp dentro de la porción cíclica, y donde el

aminoácido en la primera porción es Arg y está fuera de la porción cíclica. Sin estar sujeto a ninguna teoría, se cree que el residuo Arg contribuye ampliamente con la baja actividad en MC1-R.

Adicionalmente, la secuencia central en los péptidos de la Fórmula I incluye un D-Phe sustituido. Sin estar sujeto a ninguna teoría, se cree que la actividad intrínseca puede reducirse manteniendo sustancialmente, a la vez, la potencia mediante la utilización de D-Phe sustituido en péptidos de acuerdo con la invención. El péptido denominado Ej. de Ref. 1 (incluido D-Phe insustituido) en la Tabla 1 puede compararse con uno o más de los Ejemplos 1-5, 9-11, 17, 26 y 27. Puede observarse que la Tabla 1 incluye valores medios.

**Tabla 1**

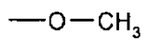
| | | | 0,1 ng/mL Doxiciclina | |
|---|---|---|---|---|
| | | $K_i$ (nM) | $CE_{50}$ (nM) | Actividad intrínseca (%) |
| Ej de Ref 1 | Ac-Arg-ciclo(Glu-Dab-D-Phe-Arg-Trp-Orn)-$NH_2$ | 0,65 | 0,33 | 94 |
| Ej de Ref 2 | Ac-Arg-ciclo(Glu-Dab-D-Phe-Arg-Trp-Orn)-OH | 8 | 3,0 | 92 |

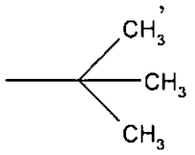
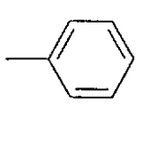
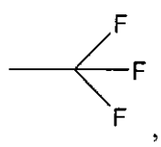
En una realización adicional de la invención se proporcionan péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), en donde uno o más de $R_{4a}$, $R_{4b}$ y $R_{4c}$ se seleccionan cada uno independientemente de hidrógeno, halo, alquilo($C_1$-$C_{10}$)-halo, alquilo($C_1$-$C_{10}$)-dihalo, alquilo($C_1$-$C_{10}$)-trihalo, alquilo ($C_1$-$C_{10}$), alcoxi ($C_1$-$C_{10}$), fenilo, nitro, nitrilo, amino o hidroxi, con la condición de que al menos uno de $R_{4a}$, $R_{4b}$ y $R_{4c}$ no sea hidrógeno.

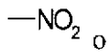
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En una realización adicional de la invención se proporcionan péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), en donde uno o más de $R_{4a}$, $R_{4b}$ y $R_{4c}$ se seleccionan cada uno independientemente de

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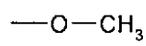
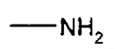
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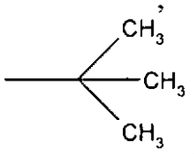
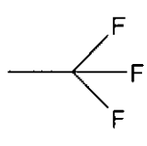
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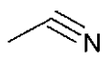
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En una realización adicional de la invención se proporcionan péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), en donde uno o más de $R_{4a}$, $R_{4b}$ y $R_{4c}$ se seleccionan cada uno independientemente de

fluoro, cloro, ,

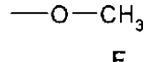
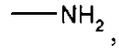
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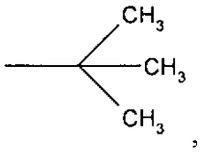
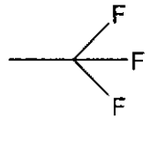
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 o  .

En una realización adicional de la invención se proporcionan péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), en donde $R_{4a}$ se selecciona de

fluoro, cloro, ,

,  ,  ,

 ,  ,



y $R_{4b}$ y $R_{4c}$ son cada uno H.

En una realización adicional de la invención se proporcionan péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), en donde $R_{4a}$ se selecciona de -C≡N o –F, y $R_{4b}$ y $R_{4c}$ son cada uno H.

En una realización adicional de la invención se proporcionan péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), en donde $R_{4a}$ está en la posición 4 y es -C≡N, y $R_{4b}$ y $R_{4c}$ son cada uno H.

En una realización adicional de la invención se proporcionan péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), en donde $R_{4a}$ está en la posición 4 y es -F y $R_{4b}$ y $R_{4c}$ son cada uno H.

Los péptidos que abarca la Fórmula (I) contienen uno o más elementos asimétricos tales como centros estereogénicos, ejes estereogénicos y similares, de modo que los péptidos que abarca la Fórmula (I) pueden existir en diferentes formas estereoisoméricas. Se pretende que, para los péptidos descritos específica y genéricamente, incluyendo los péptidos que abarca la Fórmula (I), todas las formas de isómeros en todos los centros quirales u otros centros isoméricos, incluyendo enantiómeros y diastereómeros, queden abarcados en la presente. Cada uno de los péptidos de la invención incluye múltiples centros quirales, y puede utilizarse como una mezcla racémica o una mezcla enriquecida enantioméricamente, además del uso de los péptidos de la invención en preparaciones enantioméricamente puras. Típicamente, los péptidos de la invención se sintetizarán con el uso de reactivos quiralmente puros, tales como L- o D-aminoácidos especificados, utilizando reactivos, condiciones y métodos de modo tal que la pureza enantiomérica se mantenga, pero es posible y está contemplado que se puedan hacer mezclas racémicas. Tales mezclas racémicas pueden separarse opcionalmente utilizando técnicas bien conocidas y un enantiómero individual puede utilizarse solo. En casos y en condiciones de temperatura, disolventes y pH específicos en dónde los péptidos pueden existir en formas tautoméricas, se contempla que cada forma tautomérica esté incluida dentro de esta invención, ya sea existiendo en equilibrio o predominantemente en una forma. Por consiguiente un solo enantiómero de un péptido de la Fórmula (I), que es un forma ópticamente activa, puede obtenerse mediante síntesis asimétrica, síntesis a partir de precursores ópticamente puros o mediante resolución de los racematos.

Los péptidos de las Fórmulas (II) y (III) son formas estereoisoméricas específicas de los péptidos de Fórmula (I), pero la invención no debe interpretarse como limitada a las formas estereoisoméricas que abarcan las Fórmulas (II) y (III).

Se pretende adicionalmente que la invención incluya profármacos de los presentes péptidos, los cuales en la administración sufren una conversión química mediante procesos metabólicos antes de volverse péptidos farmacológicamente activos. En general, tales profármacos serán derivados funcionales de los presentes péptidos, los cuales son fácilmente convertibles in vivo en un péptido de la Fórmula (I). Los profármacos son compuestos enlazados covalentemente, los cuales liberan el fármaco de péptido base activo de la Fórmula (I) in vivo. Los procedimientos convencionales para la selección y preparación de derivados de profármacos adecuados se describen, por ejemplo, en "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985. Los ejemplos típicos de profármacos tienen grupos protectores biológicamente lábiles en un resto funcional, como por ejemplo mediante la esterificación de funciones hidroxilo, carboxilo o amino. Por consiguiente a modo de ejemplo y no taxativo, un profármaco incluye péptidos de Fórmula (I) en donde se utiliza una forma de profármaco de éster, tal como, por ejemplo, ésteres de alquilo inferior del grupo R de la Fórmula (I), tal como donde R es –OH, pudiendo incluir los ésteres de alquilo inferior de 1-8 carbonos en un radical alquilo o ésteres de aralquilo que tienen 6-12 carbonos en un radical aralquilo. En términos generales, los profármacos incluyen compuestos que pueden oxidarse, reducirse, aminarse, desaminarse, hidroxilarse, deshidroxilarse, hidrolizarse, deshidrolizarse, alquilarse, desalquilarse, acilarse, desacilarse, fosforilarse o desfosforilarse para producir un fármaco de péptido base activo de la Fórmula (I) in vivo.

Pueden hacerse ciertas modificaciones a los péptidos de la Fórmula I para mejorar la semivida de los péptidos (ver G. Pasuta and F. M. Veronese (2007) "Polymer-drug conjugation, recent achievements and general strategies" *Progress in Polymer Science* 32 (8-9): 933-961).

La presente invención también incluye péptidos que son idénticos a aquellos que se describen en la Fórmula (I), excepto por el hecho de que uno o más átomos representados en la Fórmula (I) se reemplazan por un átomo que tiene una masa atómica o número de masa diferente a la masa atómica o número de masa generalmente encontrado en la naturaleza. Ejemplos de isótopos que pueden incorporarse a los péptidos de la invención

incluyen isótopos de hidrógeno, carbono, nitrógeno y oxígeno, tales como $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}O$ y $^{17}O$, respectivamente. Los péptidos de la presente invención y las sales o solvatos farmacéuticamente aceptables de dichos péptidos, los cuales contienen los isótopos mencionados anteriormente y/u otros isótopos de otros átomos, están dentro del alcance de esta invención. Ciertos péptidos isotópicamente marcados de la presente invención, por ejemplo aquellos en los cuales se incorporan isótopos radioactivos tales como $^{3}H$ y $^{14}C$, pueden utilizarse en una diversidad de ensayos, tales como ensayos de distribución en tejido de fármacos y/o sustratos. La sustitución con isótopos más pesados, tal como la sustitución de uno o más átomos de hidrógeno con deuterio ($^{2}H$), puede proporcionar ventajas farmacológicas en algunas instancias, incluyendo estabilidad metabólica aumentada. Los péptidos isotópicamente marcados de la Fórmula (I) pueden prepararse generalmente sustituyendo un reactivo isotópicamente marcado por un reactivo no isotópicamente marcado.

En una realización de los péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), $R_1$ es -C(=O)-NH-, x es 2 e y es 3.

En otra realización de los péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), $R_1$ es -C(=O)-NH-, x es 1 e y es 4.

En otra realización de los péptidos de acuerdo con la Fórmula (I), en particular la Fórmula (II) o (III), $R_1$ es -NH-C(=O)-, x es 3 e y es 2.

En otra realización adicional de los péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), $R_1$ es -NH-C(=O)-, x es 4 e y es 1.

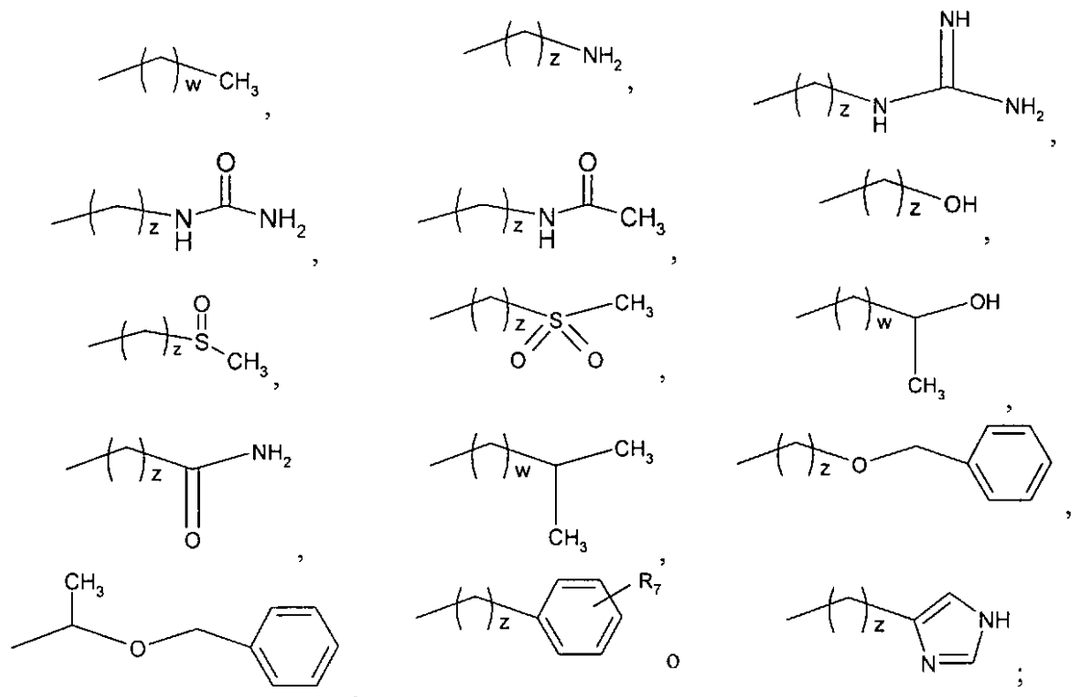
En una realización particular de los péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), $R_1$ es -C(=O)-NH-, x es 2 e y es 3, o alternativamente $R_1$ es -NH-C(=O)-, x es 3 e y es 2. Más específicamente, $R_1$ es -C(=O)-NH-, x es 2 e y es 3. Se ha descubierto en forma sorprendente e inesperada que los péptidos de acuerdo con la invención que tienen un puente de lactama en donde el enlace amida se ubica por medio de la cadena lateral de Glu (en el extremo N-terminal de la porción cíclica) y la cadena lateral de Orn (en el extremo C-terminal de la porción cíclica) generalmente proporcionan una potencia mejorada según se determina mediante $CE_{50}$, en particular en el sistema de hMC4-R de baja densidad descrito en la presente, en comparación con péptidos en donde el enlace amida se ubica por medio de las cadenas laterales de Asp y Lys, pero que de otro modo son idénticos. Este descubrimiento es contrario a las afirmaciones en la técnica

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anterior de que la ubicación y la dirección de un enlace amida en el puente de lactama de péptidos específicos para los receptores de melanocortina tienen poca importancia para la actividad y no interactúan con los receptores. Ver, por ejemplo, Bednarek MA et al., Potent and selective peptide agonists of α-melanotropin action at human melanocortin receptor 4: their synthesis and biological evaluation *in vitro*. *Biochem. Biophys. Res. Comm.* 286:641-645 (2001).

En una realización de los péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), $R_2$ es -H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH;

$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de

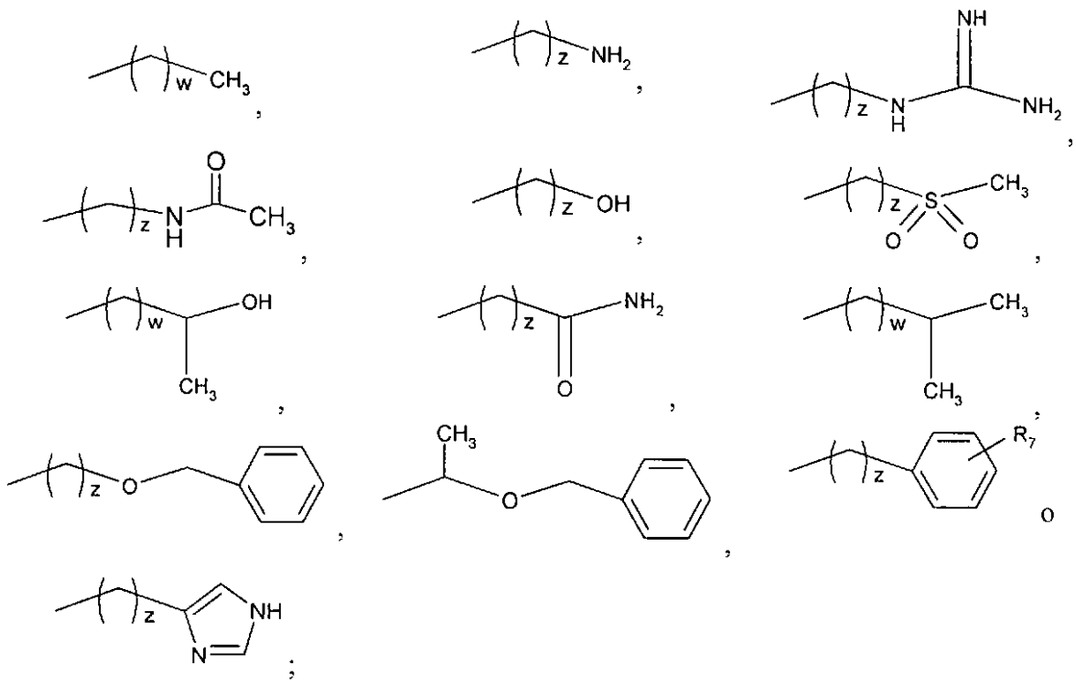


en donde w se selecciona en cada instancia independientemente de 0 a 5, y

z se selecciona en cada instancia independientemente de 1 a 5.

En una realización de los péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), $R_2$ es -H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH;

$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de



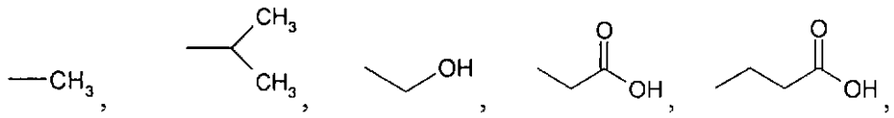
en donde w se selecciona en cada instancia independientemente de 0 a 5, y

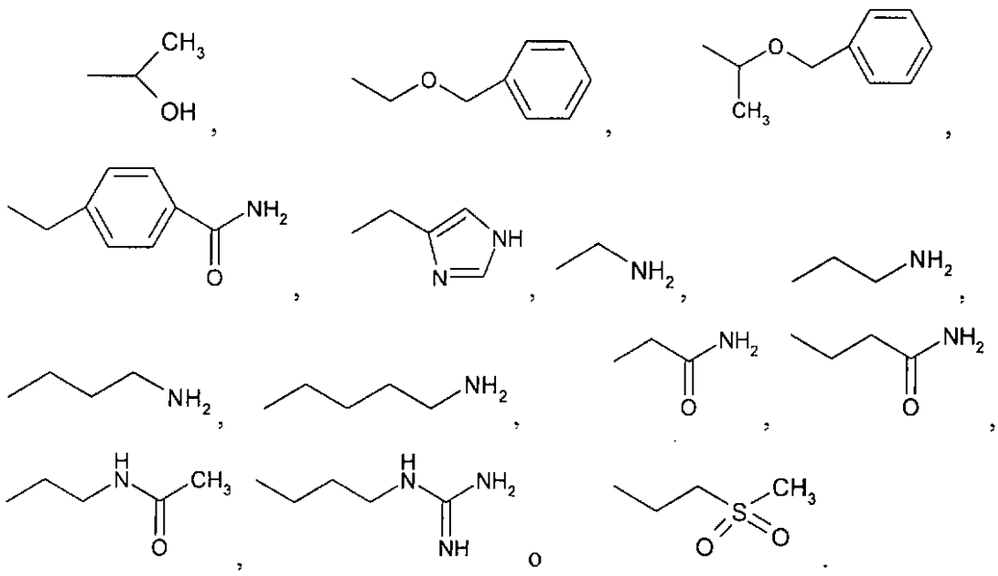
z se selecciona en cada instancia independientemente de 1 a 5.

En una realización de los péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), $R_2$ es H.

En una realización de los péptidos de acuerdo con Fórmula (I), y en particular la Fórmula (II) o (III), $R_2$ es H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH; y

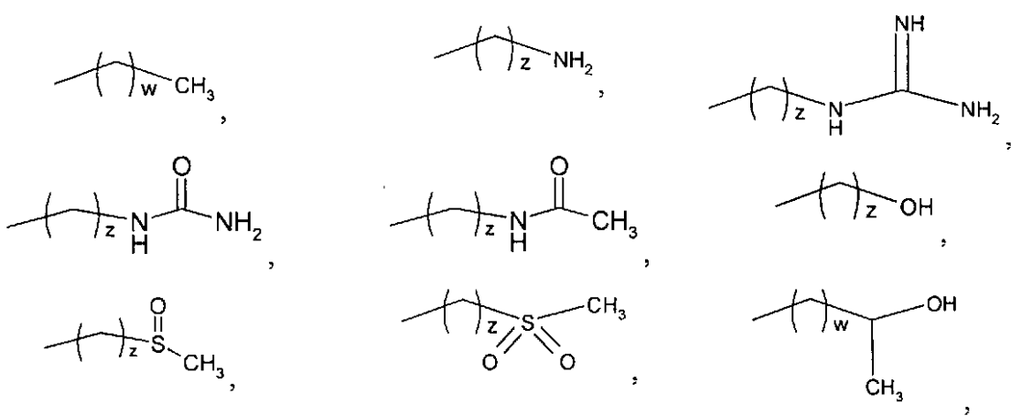
$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de

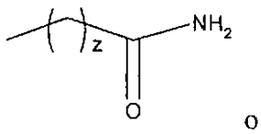
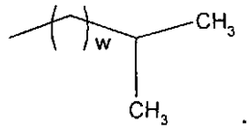




Sin estar sujeto a ninguna teoría, se cree que el reemplazo de His por un aminoácido no aromático, en particular un aminoácido alifático pequeño no polar, tal como Pro o Ala, o un aminoácido polar cargado o no cargado, tal como Lys, Asp, Gln y Asn, contribuye a la atenuación de los efectos de la presión sanguínea. Por consiguiente, la porción His en la secuencia central puede, por ejemplo, reemplazarse por Dab, Dab(Acetilo), Ser, Met(O), $Met(O_2)$, Thr, Hyp, Gln, Pro, Ala, Asn, Cit, Orn, Dap, Lys o Arg, en particular Pro, Asn o Gln.

Por consiguiente, en una realización adicional de la invención, se proporcionan péptidos de Fórmula (I), en particular de Fórmula (II) o (III), en donde $R_2$ es -H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH; y $R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de modo $R_3$ se selecciona de

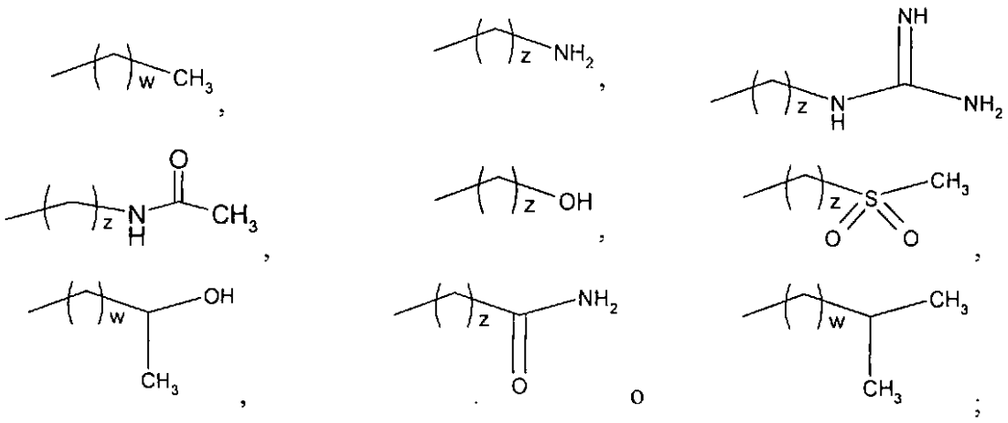


en donde w se selecciona en cada instancia independientemente de 0 a 5, y

z se selecciona en cada instancia independientemente de 1 a 5.

En una realización adicional de la invención se proporcionan péptidos de Fórmula (I), en particular de Fórmula (II) o (III), en donde $R_2$ es -H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH; y $R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de

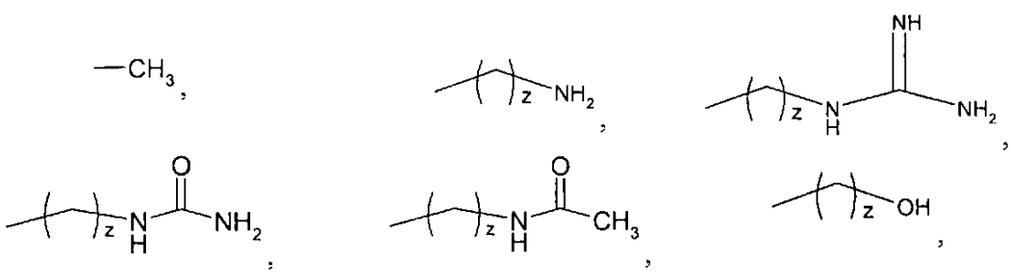


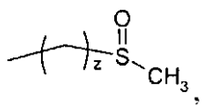
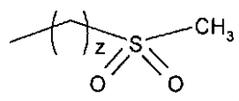
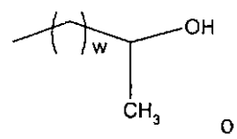
en donde w se selecciona en cada instancia independientemente de 0 a 5, y

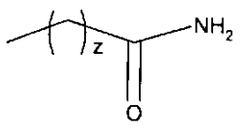
z se selecciona en cada instancia independientemente de 1 a 5.

En una realización particular de la invención, se proporcionan péptidos de Fórmula (I), en particular de Fórmula (II) o (III), en donde $R_2$ es H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH; y

$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de




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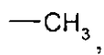
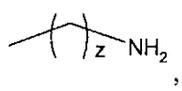
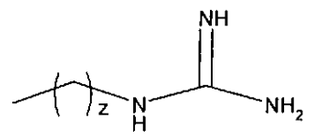

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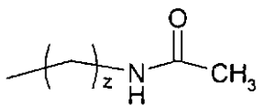
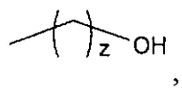
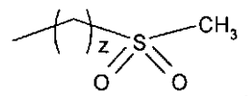
en donde w se selecciona en cada instancia independientemente de 0 a 5, en particular 0 a 2, tal como 0, y

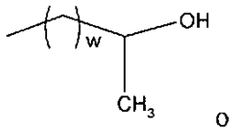
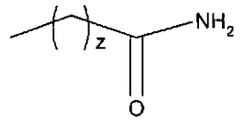
z se selecciona en cada instancia independientemente de 1 a 5, en particular 1 a 4.

En una realización adicional de la invención se proporcionan péptidos de Fórmula (I), en particular de Fórmula (II) o (III), en donde $R_2$ es H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH; y

$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de


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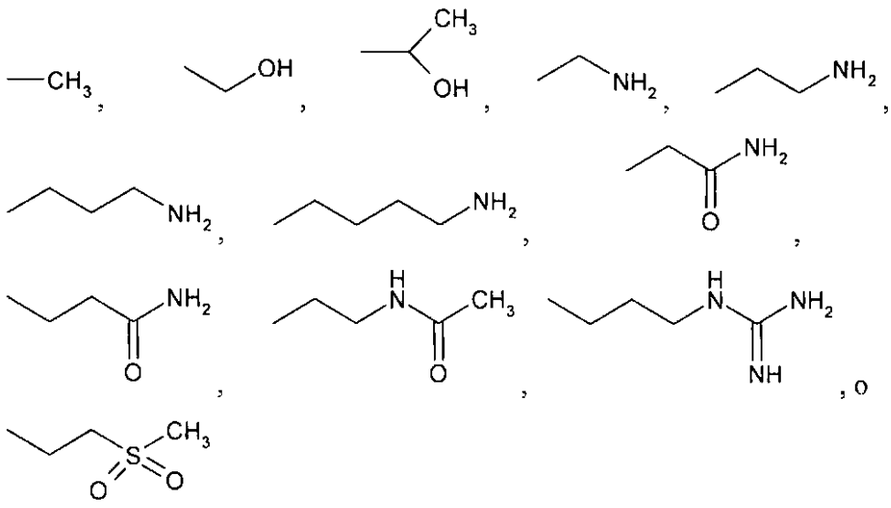

o

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en donde w se selecciona en cada instancia independientemente de 0 a 5, en particular 0 a 2, tal como 0, y

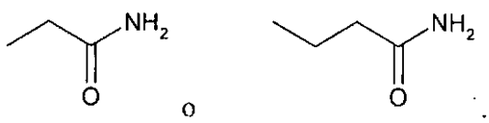
z se selecciona en cada instancia independientemente de 1 a 5, en particular 1 a 4.

En realizaciones adicionales de los péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), $R_2$ es H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH; y

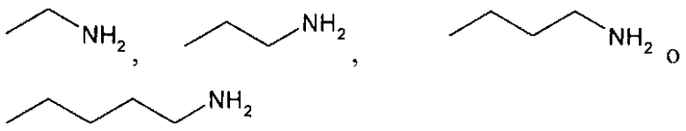
$R_3$ se selecciona de



En otra realización de la invención, se proporcionan péptidos de Fórmula (I), y en particular de Fórmula (II) o (III), en donde $R_2$ es H y $R_3$ se selecciona de



En otra realización de la invención, se proporcionan péptidos de Fórmula (I), en particular de Fórmula (II) o (III), en donde $R_2$ es H y $R_3$ se selecciona de



En otra realización de la invención, se proporcionan péptidos de Fórmula (I), y en particular de Fórmula (II) o (III), en donde $R_2$ es $-CH_2-$ y $R_3$ es $-(CH_2)_2-$, $R_2$ y $R_3$ juntos forman un anillo de pirrolidina insustituido.

En otra realización adicional de la invención, se proporcionan péptidos de Fórmula (I), y en particular de Fórmula (II) o (III), en donde $R_2$ es $-CH_2-$ y $R_3$ es $-(CH_2)_2-$, $R_2$ y $R_3$ juntos forman un anillo de pirrolidina sustituido por –OH. En una realización adicional de los péptidos de acuerdo con la Fórmula (I), y en particular la Fórmula (II) o (III), $R_5$ es $–NH_2$ u –OH.

En una realización específica de los péptidos de acuerdo con la Fórmula (I), y en particular de la Fórmula (II) o (III), $R_5$ es $–NH_2$.

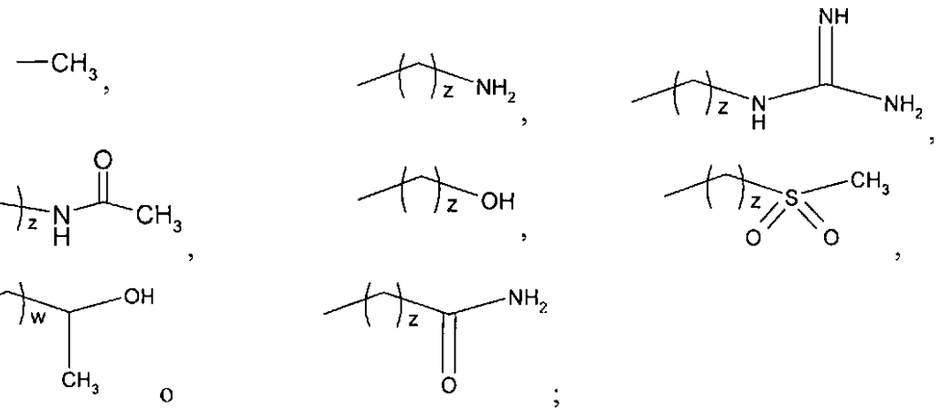
Una o más de las realizaciones anteriores pueden combinarse para proporcionar realizaciones específicas adicionales de los péptidos de acuerdo con la invención.

Por consiguiente, en una realización particular de la invención, se proporcionan péptidos de acuerdo con la Fórmula (I), y en particular de la Fórmula (II) o (III), en donde

$R_1$ es -C(=O)-NH-, x es 2 e y es 3;

$R_2$ es -H o $-CH_2-$, y si $R_2$ es $-CH_2-$ forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH;

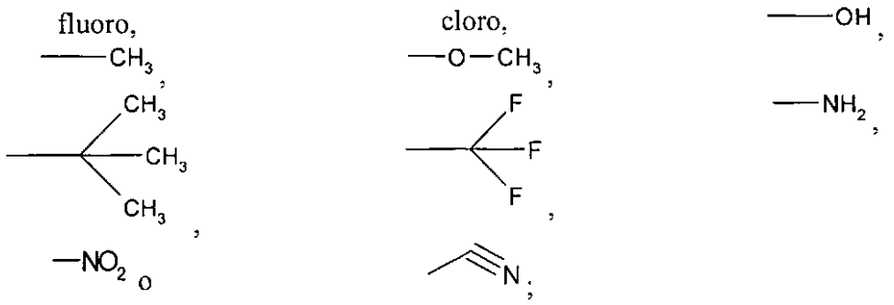
$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de



w se selecciona en cada instancia independientemente de 0 a 5;

z se selecciona en cada instancia independientemente de 1 a 5;

uno o más de $R_{4a}$, $R_{4b}$ y $R_{4c}$ se seleccionan independientemente de



y

$R_5$ es $-NH_2$ u -OH.

Algunos péptidos específicos de la invención son uno o más de los siguientes:

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:6);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:7);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:8);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2,4-diCl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:9);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,4-diCl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:10);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:11);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:12);

Ac-Arg-*ciclo*(Glu-Dab-D-Tyr-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:13);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:14);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:15);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:16);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:17);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:18);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:19);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:20);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-OMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:21);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,5-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:22);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:23);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:24);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:25);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2,4-diMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:26);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-$NO_2$)-Arg-Trp-Orn-$NH_2$ (SEQ ID NO:27);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-$NO_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:28);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-$NO_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:29);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,4-diOMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:30);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,4-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:31);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:32);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-$NH_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:33);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-tBu)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:35);

Ac-Arg-*ciclo*(Glu-Ser-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:36);

Ac-Arg-*ciclo*(Glu-Thr-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:37);

Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:38);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:39);

Ac-Arg-*ciclo*(Glu-Ser-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:40);

Ac-Arg-*ciclo*(Glu-Thr-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:41);

Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:42);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:43);

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:44);

Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:45);

Ac-Arg-*ciclo*(Glu-Ala-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:46);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:48);

Ac-Arg-*ciclo*(Glu-Thr-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:49);

Ac-Arg-*ciclo*(Glu-Ser-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:50);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51);

Ac-Arg-*ciclo*(Glu-Orn-D-Phe(2-Cl)-Arg-Trp-Orn)-OH (SEQ ID NO:54);

Ac-Arg-*ciclo*(Glu-Orn-D-Phe(3-Cl)-Arg-Trp-Orn)-OH (SEQ ID NO:60);

Ac-Arg-*ciclo*(Glu-Dab(Acetyl)-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:61);

Ac-Arg-*ciclo*(Glu-Ser-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:63);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:64);

Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:65);

Ac-Arg-*ciclo*(Glu-Dap-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:66);

Ac-Arg-*ciclo*(Glu-Dap-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:67);

Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:69);

Ac-Arg-*ciclo*(Glu-Ser-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:70);

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:71);

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72);

Ac-Arg-*ciclo*(Glu-Met($O_2$)-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:73);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:74);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:78);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(3,5-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:81);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:89);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:90);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:91);

Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-OMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:92);

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:93);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:97);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:100);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:102);

Ac-Arg-*ciclo*(Glu-Arg-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:104);

Ac-Arg-*ciclo*(Glu-Lys-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:105);

Ac-Arg-*ciclo*(Glu-Orn-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:106)

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-OH (SEQ ID NO:107);

Ac-Arg-*ciclo*(Glu-Asp-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:111);

Ac-Arg-*ciclo*(Glu-Asp-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:112);

Ac-Arg-*ciclo*(Glu-Glu-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:113);

Ac-Arg-*ciclo*(Glu-Glu-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:114);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:115);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:119);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:121); o una sal farmacéuticamente aceptable de cualquiera de los anteriores.

Particularmente, la invención se refiere a:

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:48);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:74);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:90); o una sal farmacéuticamente aceptable de cualquiera de los anteriores.

Particularmente, la invención también se refiere a:

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:91);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:97); o una sal farmacéuticamente aceptable de cualquiera de los anteriores.

Particularmente, la invención también se refiere a:

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:44);

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72),

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-OH (SEQ ID NO:107); o una sal farmacéuticamente aceptable de cualquiera de los anteriores.

Algunos de los péptidos específicos adicionales de la invención son:

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(4-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:75);

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:76);

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(3-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:77);

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(2-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:79);

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(3,4-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:80);

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(3,5-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:82);

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:96);

Ac-Arg-*ciclo*(Orn-Gln-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:99);

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(3,4,5-triF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:101);

Ac-Arg-*ciclo*(Orn-Gln-D-Phe(3,4,5-triF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:103);

Ac-Arg-*ciclo*(Orn-Pro-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:110);

Ac-Arg-*ciclo*(Orn-Gln-D-Phe(2-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:116);

Ac-Arg-*ciclo*(Orn-Gln-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:117);

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:118);

Ac-Arg-*ciclo*(Orn-Gln-D-Phe(2-$CF_3$)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:120);

Ac-Arg-*ciclo*(Orn-Asn-D-Phe(2-$CF_3$)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:122); o una sal farmacéuticamente aceptable de cualquiera de los anteriores.

6.1 Péptidos específicos

Los péptidos de las siguientes estructuras si sintetizaron mediante los métodos generales descritos anteriormente y, excepto donde se indicó, los valores de Ki de MC1-R y MC4-R para cada péptido se determinaron en ensayos de unión competitiva utilizando [$I^{125}$]-NDP-α-MSH como se describe en 7.1 a continuación. Todos los péptidos se prepararon en forma de sal de ácido de TFA, excepto los péptidos de los Ejemplos 43, 46 y 67, los cuales se prepararon en forma de sal de acetato.

Las síntesis de algunos de los péptidos específicos de la invención se ilustran a continuación. Estos péptidos se prepararon utilizando síntesis de péptidos en fase sólida por medio de un sintetizador automático de péptidos Symphony Multiplex (Rainin Instrument Company/Protein Technologies Inc).

Etapa 1: Acoplamiento de Orn

La resina Sieber 9-Fmoc-Aminoxanten-3-iloxi-poliestireno (0,39 mol/g, ChemPep Inc., No. 151902) se hinchó en 3 x 5 mL de DMF durante 10 min. Luego, se desprotegió Fmoc utilizando 2 x 5 mL de piperidina al 20% en DMF durante 10 min. La resina luego se lavó en 6 x 5 mL de DMF durante 30 segundos. Se agregaron 5 mL de Fmoc-Orn(Alloc)-OH 200 mM en DMF y 5 mL de HBTU 200 mM que contenía NMM 400 mM en DMF y después de 30 minutos la resina se lavó con 3 x 5 mL DMF durante 30 segundos.

Etapa 2: Acoplamiento de los siguientes 6 aminoácidos (AA)

La resina de la etapa 1 primero se hinchó en 3 x 5 mL de DMF durante 30 segundos, se desprotegió Fmoc utilizando 2 x 5 mL de piperidina al 20% en DMF durante 10 min y luego se lavó con 6 x 5 mL de DMF durante 30 segundos. Se agregaron 5 mL de una solución de Fmoc-AA-OH 200 mM y 5 mL HBTU 200 mM que contenía NMM 400 mM en DMF y después de 30 min la resina se lavó con 3 x 5 mL de DMF durante 30 segundos.

Esta etapa se repitió para cada aminoácido (AA).

Etapa 3: Acetilación

Se desprotegió Fmoc utilizando 2 x 5 mL de piperidina al 20% en DMF durante 10 min y la resina luego se lavó con 3 x 5 mL de DMF durante 30 segundos. Luego, se agregaron 5 mL de una solución de $Ac_2O$/DMF al 50% y después de 30 min la resina de péptido se lavó con 3 x 5 mL de DMF durante 30 segundos y 6 x 5 mL de DCM durante 30 segundos.

Etapa 4: Desprotección con alil/aloc

La resina de péptido (0,6 mmol) se mezcló con fenilsilano (Oakwood Chemical, No. S13600) (20 eq.) en 20 mL de DCM y se burbujeó con nitrógeno durante 5 min.

Se agregó Tetrakis(trifenilfosfina)-paladio(0) (Strem Chemicals, Inc., No. 46-2150) (0,2 eq.) y la mezcla se agitó con nitrógeno durante 1 hora. El procedimiento se repitió una vez durante 1 hora y un tiempo adicional de 30 min con reactivos nuevos. La resina de péptido tratada luego se lavó con DCM x 3 y DMF x 3.

Etapa 5: Formación de lactama

El anillo de lactama se formó en la resina de péptido utilizando TBTU (2 eq.) y etildiisopropilamina (DIEA) (4 eq.) en 20 mL de DMF durante 1 hora. Puede ser necesario un segundo acoplamiento si se observa una prueba de Kaiser Ninhydrin positiva.

Etapa 6: Escisión de péptido

La resina de péptido (0,6 mmol) se mezcló con 20 mL de dietilditiocarbamato de sodio trihidrato al 5% ($NaCS_2NEt_2$, Aldrich, No. 228680) en DMF durante 20 min y luego se lavó con DMF x 3, DCM x 3 y éter dietílico x 2.

Luego se agitó la resina (0,6 mmol) en 25 mL de TFA/TIS/H2O (90:5,0:5,0 v/v/v) durante 2,5 horas. Se filtró la resina. El filtrado se concentró a aproximadamente 10 mL en volumen y se agregaron aproximadamente 140 mL de éter dietílico frío (pre-enfriado hasta aproximadamente 0 °C).

La mezcla se sometió a agitación vorticial y luego se colocó en el refrigerador (aproximadamente -4 °C) durante 1 h, se centrifugó durante 5 min a 2800 rpm y la capa de éter se decantó.

El péptido se lavó con 90 mL de éter dietílico frío (pre-enfriado hasta aproximadamente 0 °C), se sometió a agitación vorticial, se centrifugó durante 5 min a 2800 rpm y la capa de éter se decantó.

El sólido resultante de disolvió en AcOH/$H_2O$ al 50% y se almacenó a temperatura ambiente durante toda la noche.

La solución de péptido bruto se concentró para proporcionar un péptido sólido bruto para purificación mediante HPLC.

Después de la purificación mediante HPLC, la sal TFA de péptido se convirtió en sal de acetato de péptido utilizando intercambio iónico (x 100 eq.). La resina de intercambio aniónico utilizada fue Dowex SBR LC NG, forma OH- (Supelco, Cat. No. 14036-U).

**Ejemplo 46:** Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51)

Se siguió el procedimiento descrito anteriormente en la preparación del péptido del título.

Los aminoácidos que se agregaron en la etapa 2 fueron, en el orden de acoplamiento, Fmoc-Trp(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-D-Phe(4-CN)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OAll)-OH y Fmoc-Arg(Pbf)-OH.

El péptido resultante se purificó mediante HPLC (columna: Atlantis dC18 OBD™ 19 x 100 mm (5µ, Waters, pieza No. 186001367) utilizando MeOH/$H_2O$ al 10% que contenía TFA al 0,1% (disolvente A) y MeOH/$H_2O$ al 90% que contenía TFA al 0,1% (disolvente B). Se utilizó una gradiente de 0%-5% del disolvente B durante 5 min y de 5%-35% del disolvente B durante 30 min.

El rendimiento de péptido fue 10%.

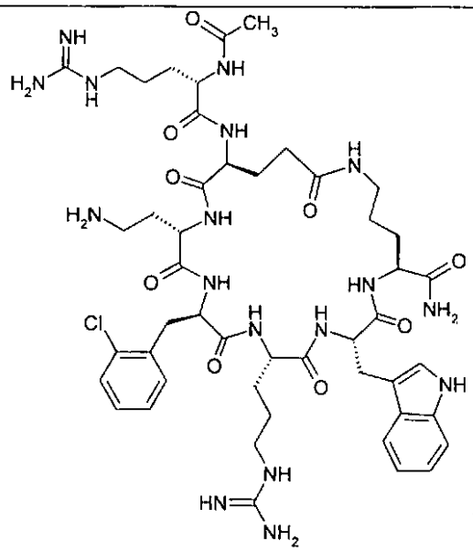
**Ejemplo 67:** Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72)

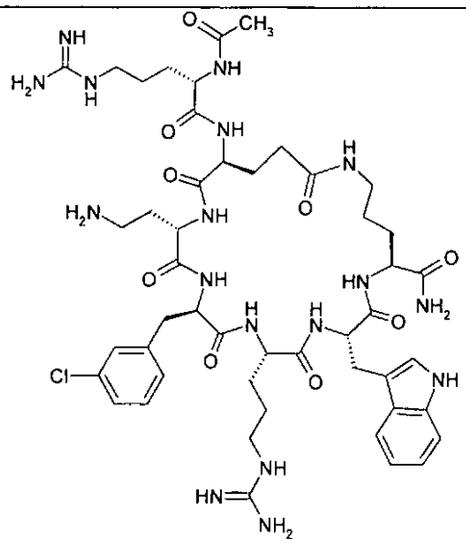
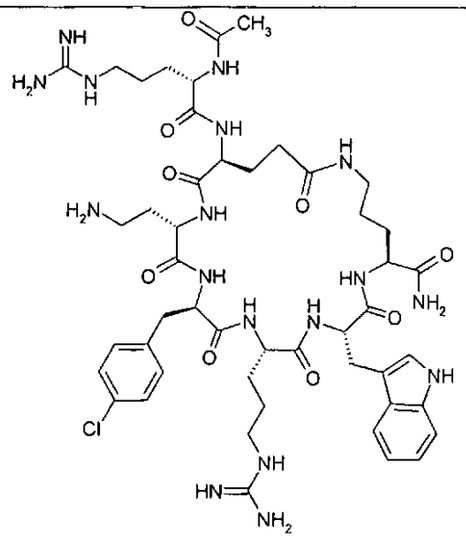
Se siguió el procedimiento descrito anteriormente en la preparación del péptido del título excepto que se utilizaron 15 mL de dietilditio-carbamato de sodio trihidrato al 5% en DMF, 16 mL de TFA/TIS/$H_2O$ y 90 mL + 60 mL de éter dietílico en la etapa 6. Además, el filtrado se concentró a 5 mL.

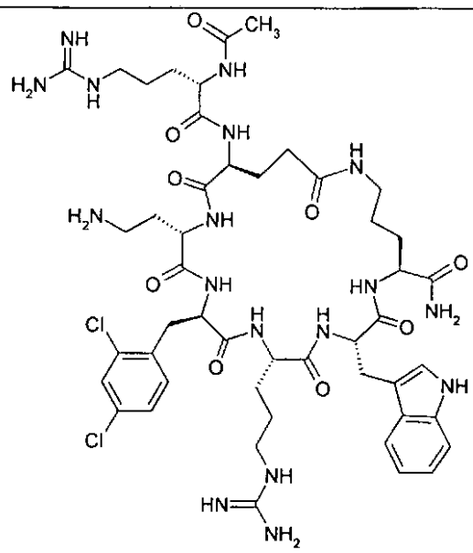
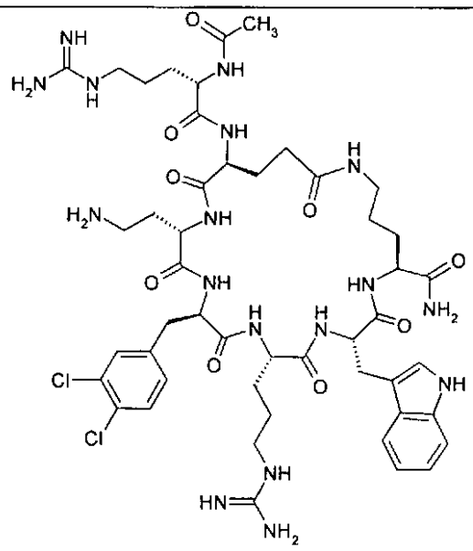
Los aminoácidos que se agregaron en la etapa 2 fueron, en el orden de acoplamiento, Fmoc-Trp(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-D-Phe(4-F)-OH, Fmoc-Pro-OH, Fmoc-Glu(OAll)-OH y Fmoc-Arg(Pbf)-OH.

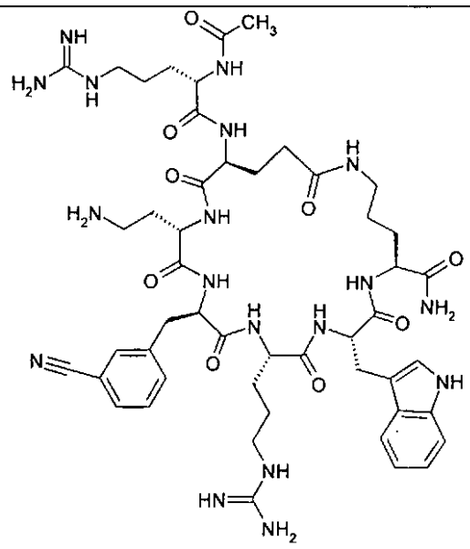
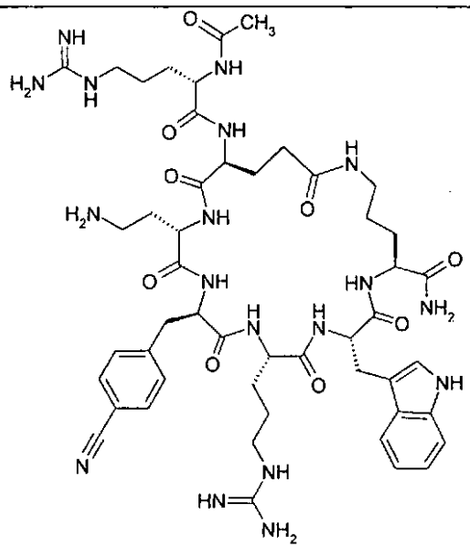
El péptido resultante se purificó mediante HPLC (columna: Atlantis dC18 OBD™ 19 x 100 mm (5µ, Waters, pieza No. 186001367) utilizando MeOH/$H_2O$ al 10% que contenía TFA al 0,1% (disolvente A) y MeOH/$H_2O$ al 90% que contenía TFA al 0,1% (disolvente B). Se utilizó una gradiente de 5%-10% del disolvente B durante 5 min y de 10%-40% del disolvente B durante 30 min.

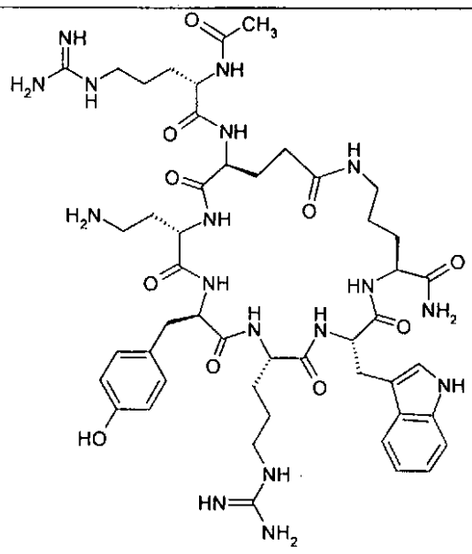
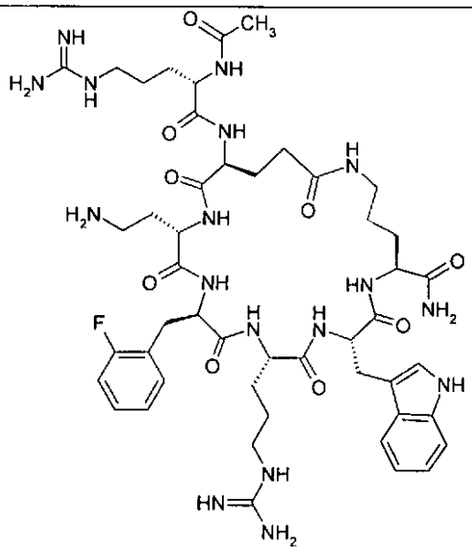
El rendimiento de péptido fue 16%.

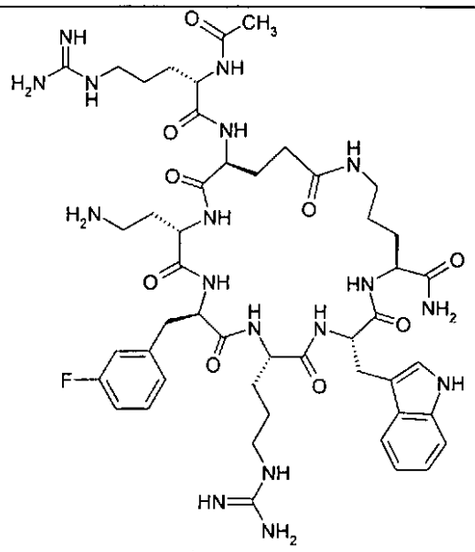
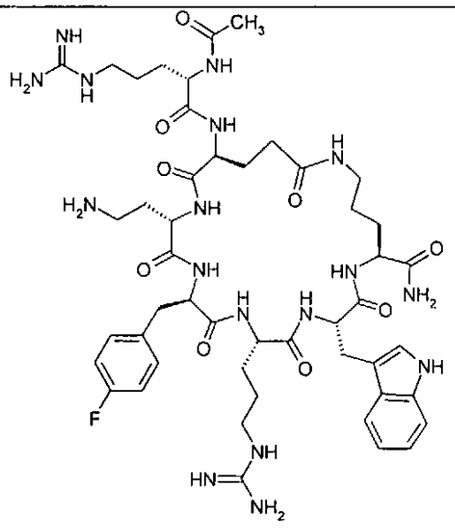
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 1 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:6) | 3 | 1 |

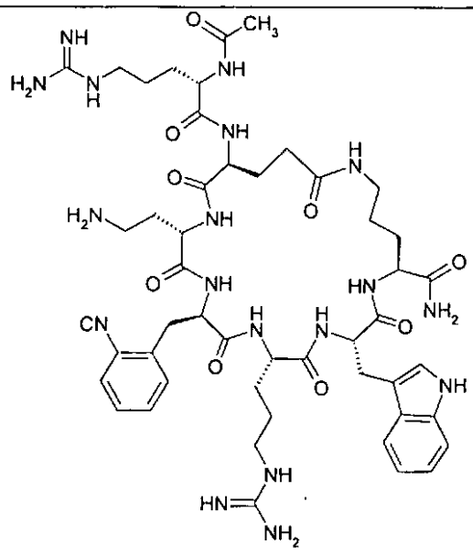
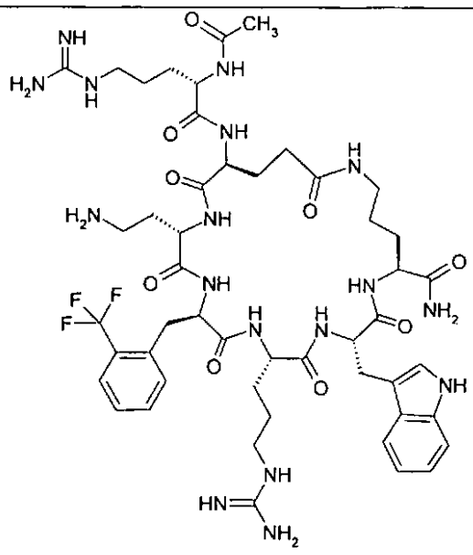
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 2 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:7) | 0,75 | 1 |
| 3 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:8) | 0,08 | 0,3 |

| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 4 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2,4-diCl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:9) | 0,055 | 0,5 |
| 5 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,4-diCl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:10) | 0,055 | 0,2 |

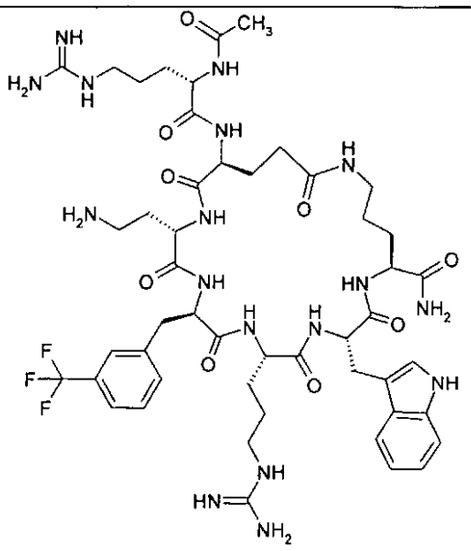
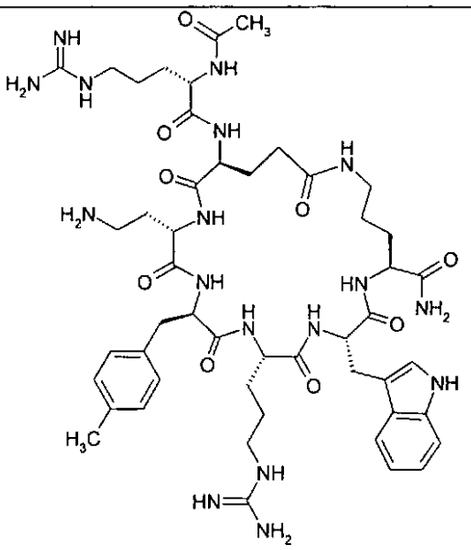
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 6 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:11) | 33 | 43 |
| 7 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:12) | 0,833 | 5 |

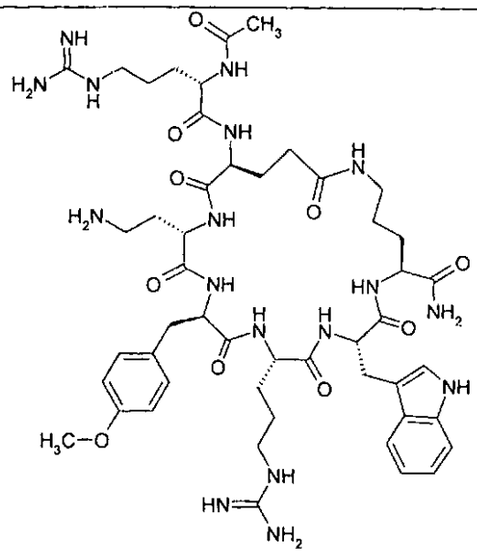
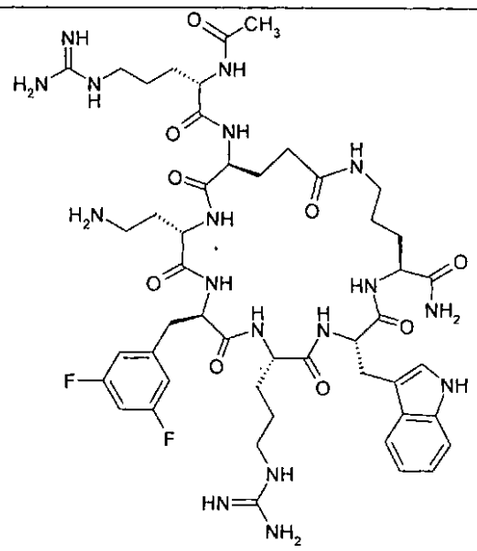
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 8 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Tyr-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:13) | 75 | 15 |
| 9 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:14) | 0,7 | 0,8 |

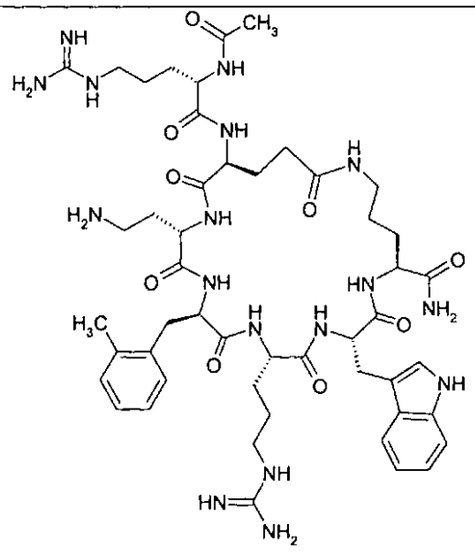
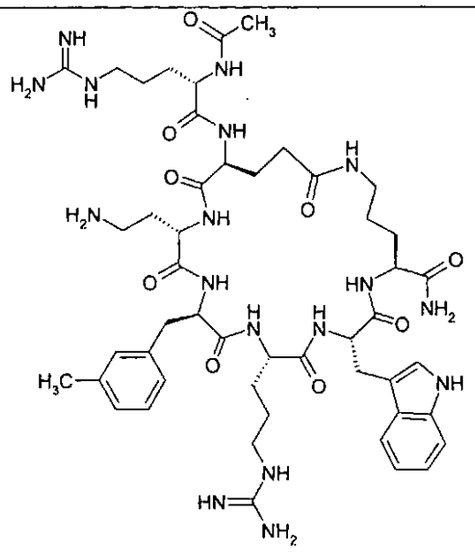
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 10 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:15) | 2 | 2 |
| 11 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:16) | 0,25 | 0,5 |

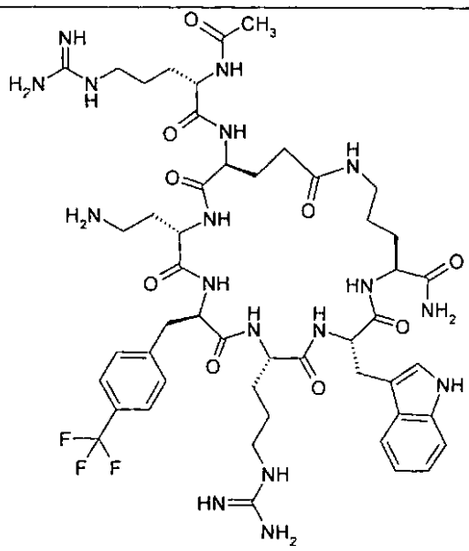
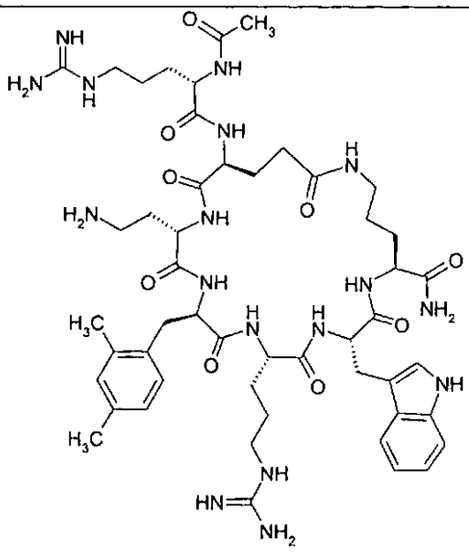
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 12 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:17) | 45 | 35 |
| 13 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:18) | 0,6 | 3 |

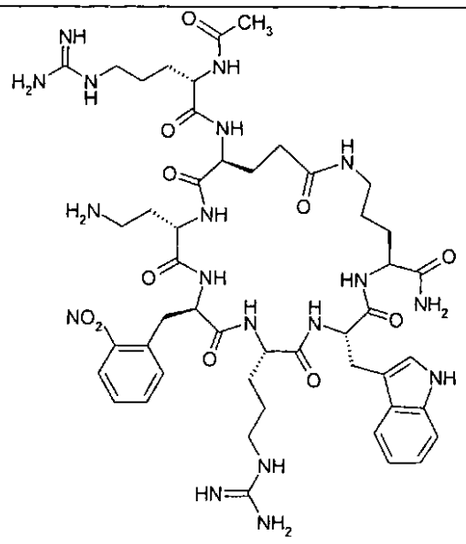
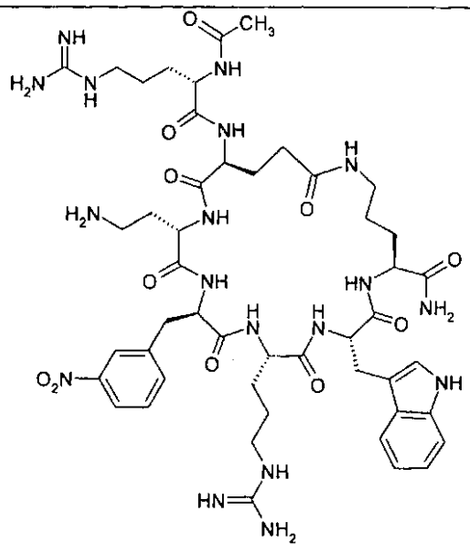
116

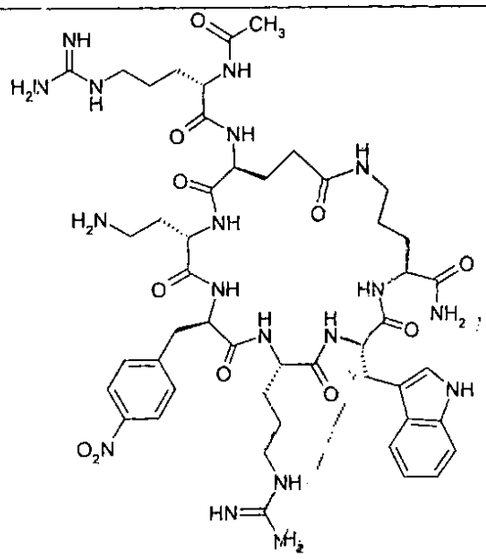
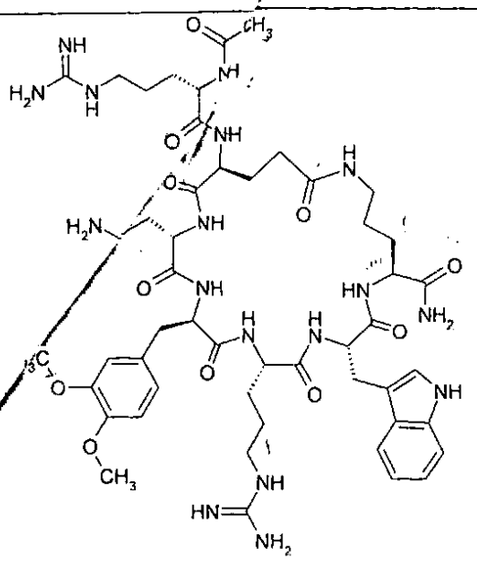
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 14 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:19) | 0,95 | 9 |
| 15 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:20) | 0,145 | 0,75 |

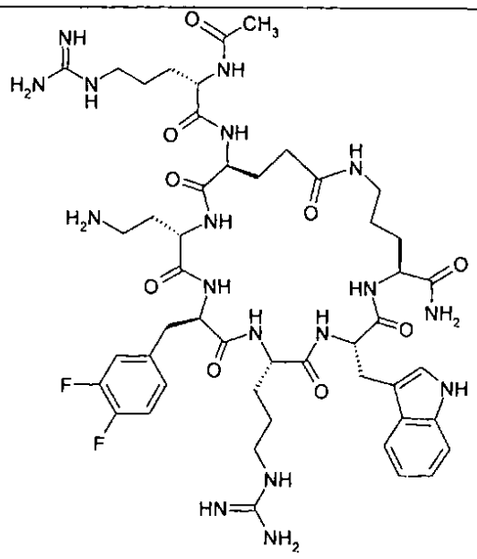
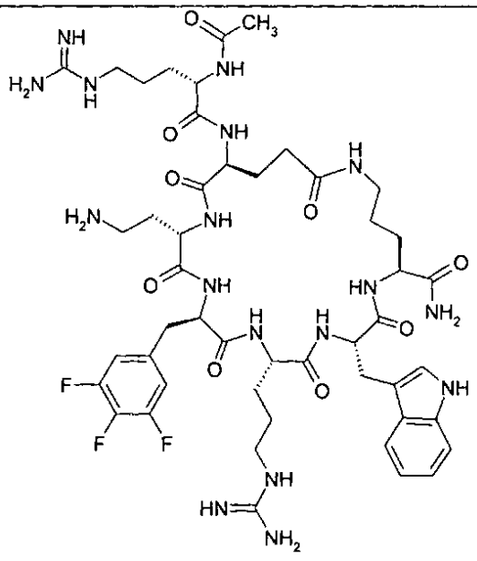
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 16 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-OMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:21) | 0,25 | 0,15 |
| 17 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,5-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:22) | 2 | - |

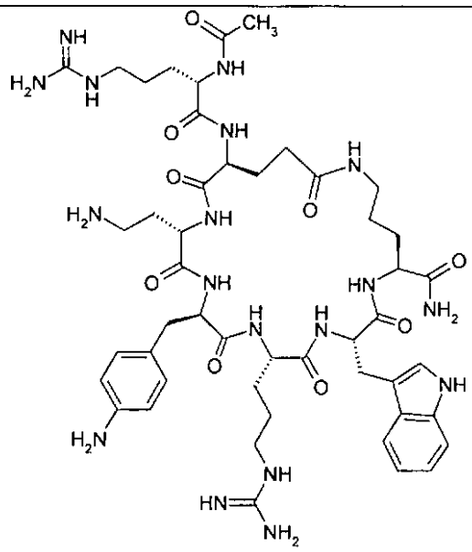
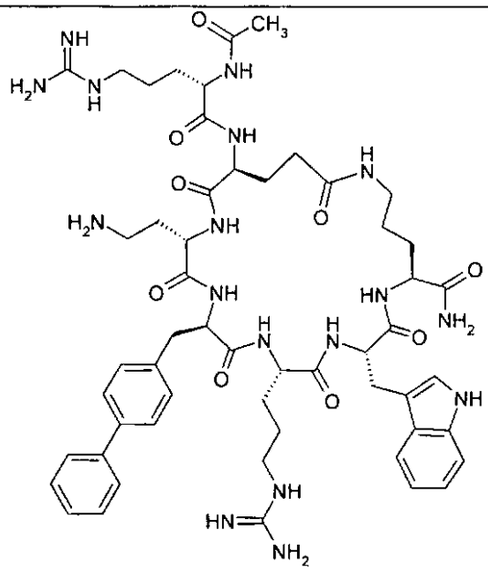
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 18 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:23) | 0,5 | - |
| 19 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:24) | 0,4 | - |

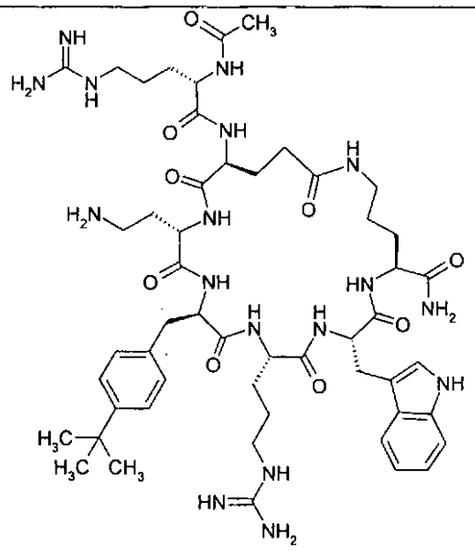
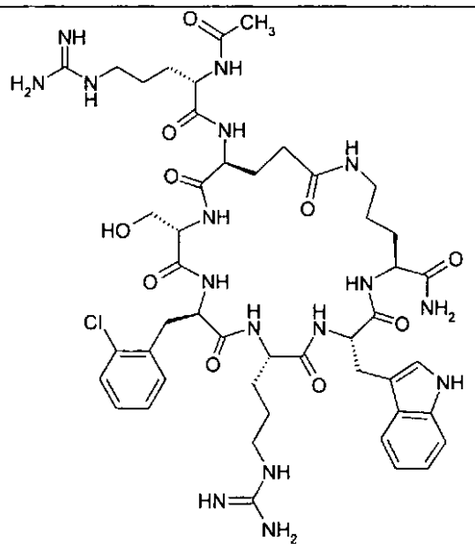
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 20 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:25) | 0,06 | - |
| 21 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2,4-diMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:26) | 0,085 | - |

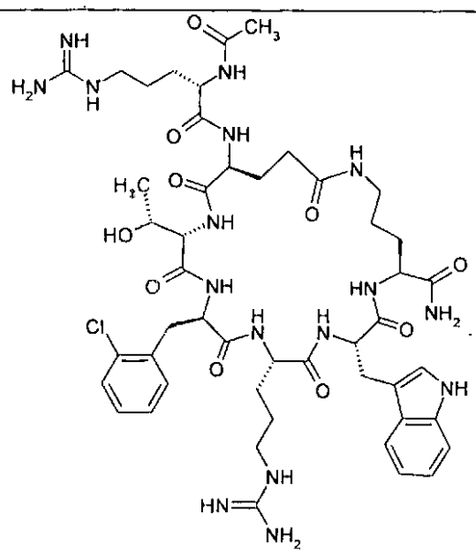
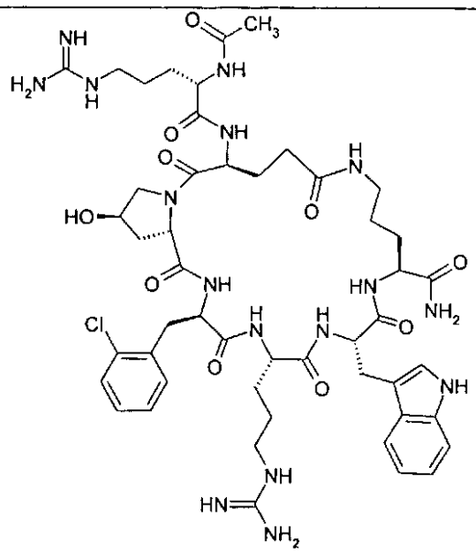
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 22 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(2-$NO_2$)-Arg-Trp-Orn-$NH_2$ (SEQ ID NO:27) | 11 | - |
| 23 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-$NO_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:28) | 0,7 | - |

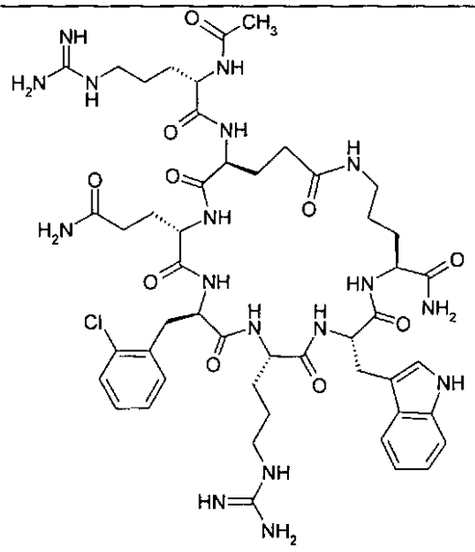
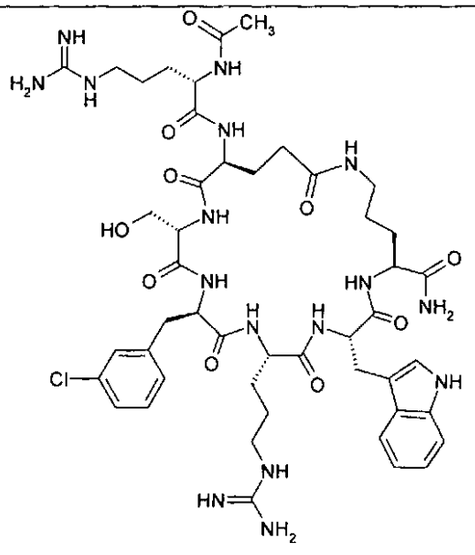
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 24 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-$NO_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:29) | 0,45 | - |
| 25 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,4-diOMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:30) | 35 | - |

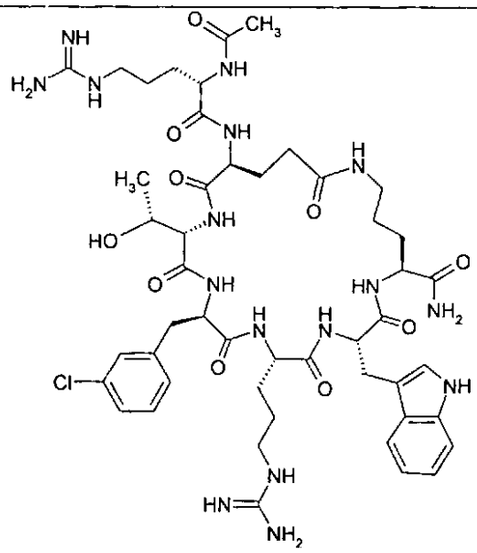
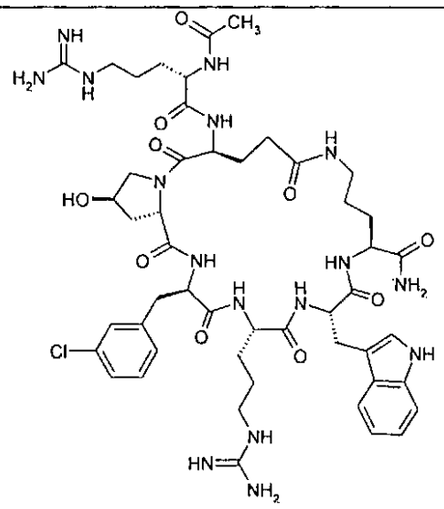
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 26 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,4-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:31) | 0,3 | - |
| 27 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:32) | 0,667 | |

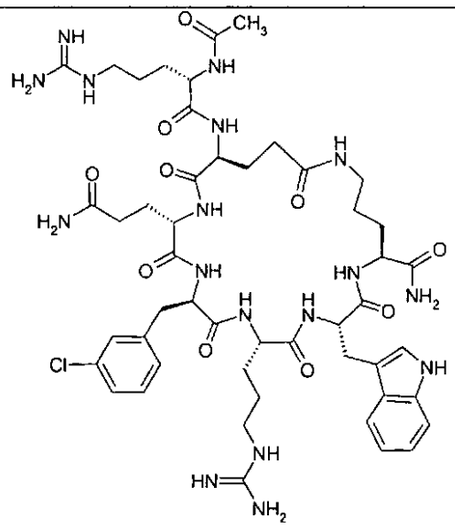
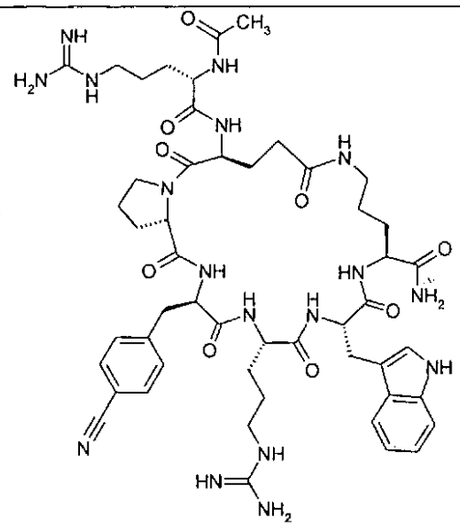
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 28 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-$NH_2$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:33) | 48 | - |
| 29 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-Ph)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:34) | 0,5 | - |

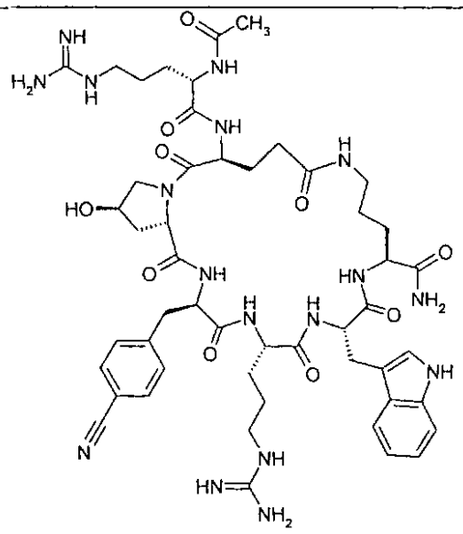
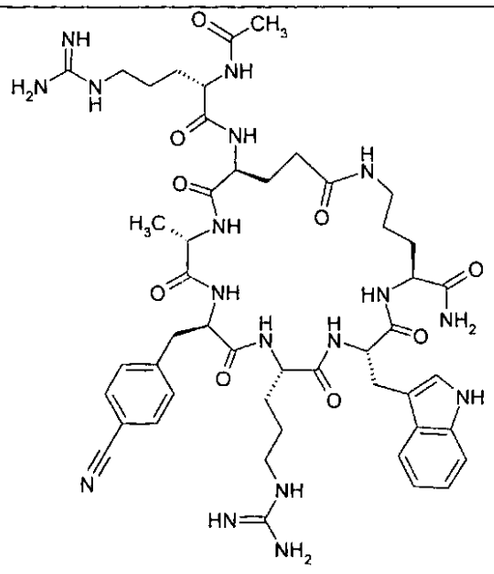
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 30 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(4-tBu)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:35) | 4 | - |
| 31 |  | Ac-Arg-*ciclo*(Glu-Ser-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:36) | 8 | 300 |

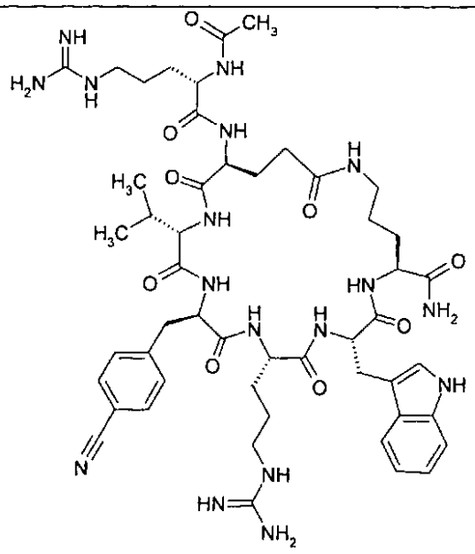
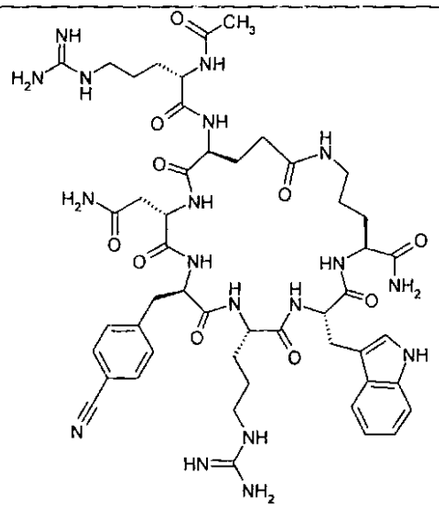
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 32 |  | Ac-Arg-*ciclo*(Glu-Thr-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:37) | 11 | 540 |
| 33 |  | Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:38) | 1 | 143 |

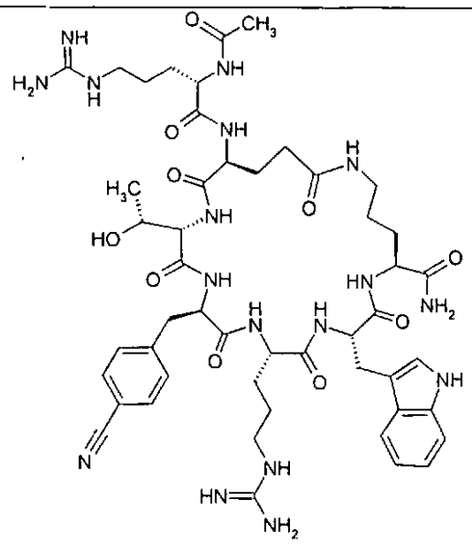
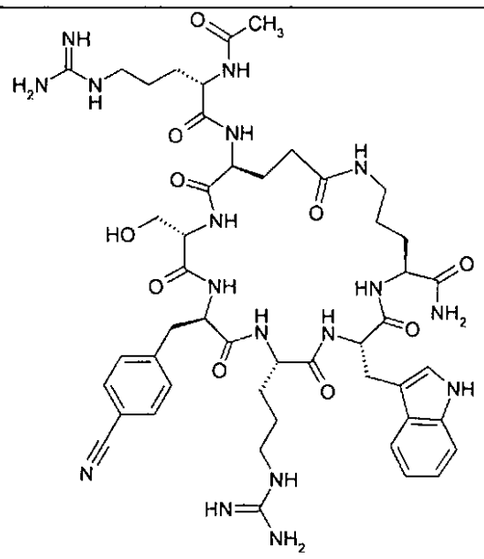
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 34 |  | Ac-Arg-*ciclo*(Glu-Gln-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:39) | 7 | 128 |
| 35 |  | Ac-Arg-*ciclo*(Glu-Ser-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:40) | 10 | 810 |

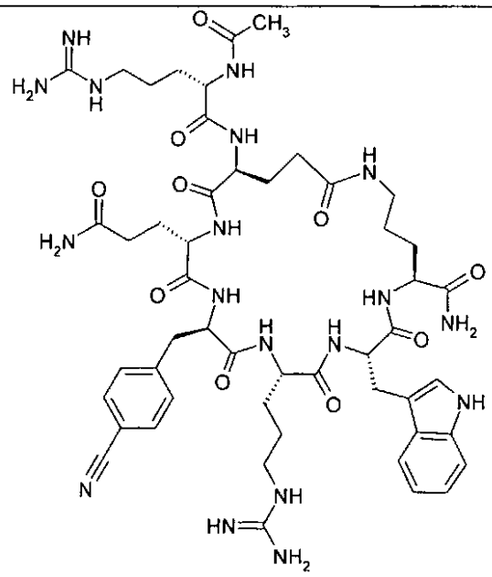
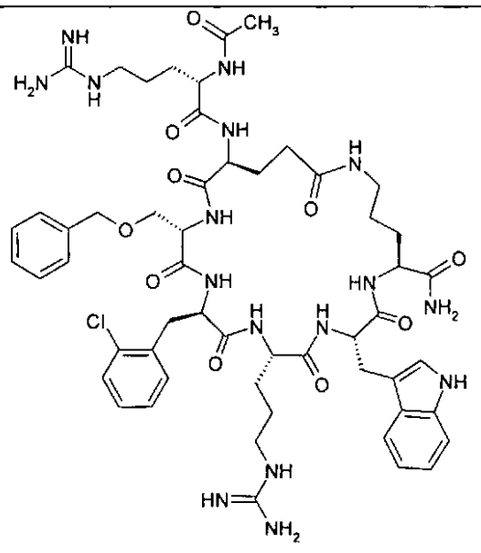
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 36 |  | Ac-Arg-*ciclo*(Glu-Thr-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:41) | 6 | 380 |
| 37 |  | Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:42) | 2 | 430 |

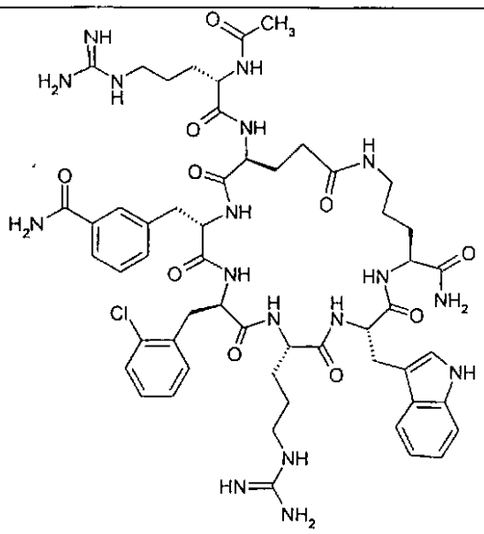
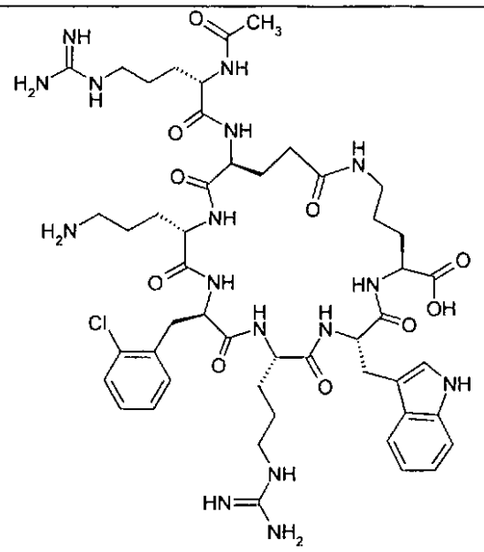
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 38 |  | Ac-Arg-*ciclo*(Glu-Gln-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:43) | 3 | 290 |
| 39 |  | Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:44) | 4 | 1550 |

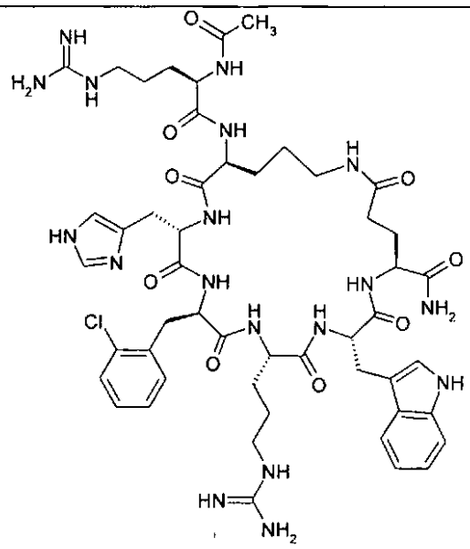
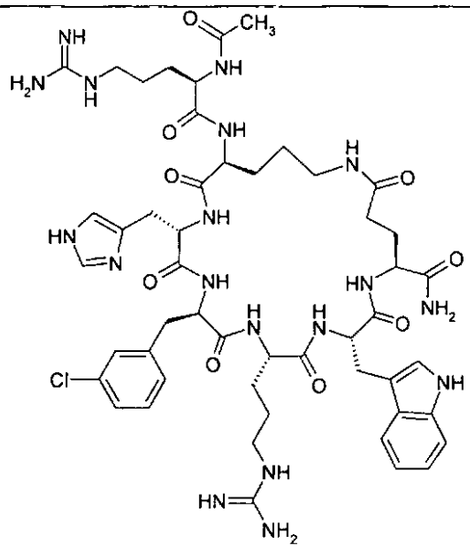
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 40 |  | Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:45) | 2 | 880 |
| 41 |  | Ac-Arg-*ciclo*(Glu-Ala-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:46) | 3 | 4300 |

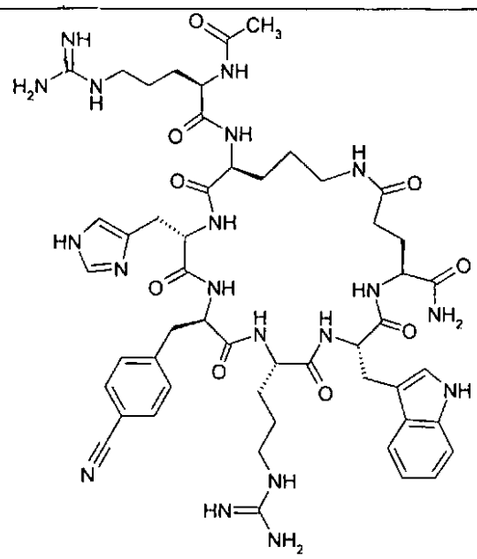
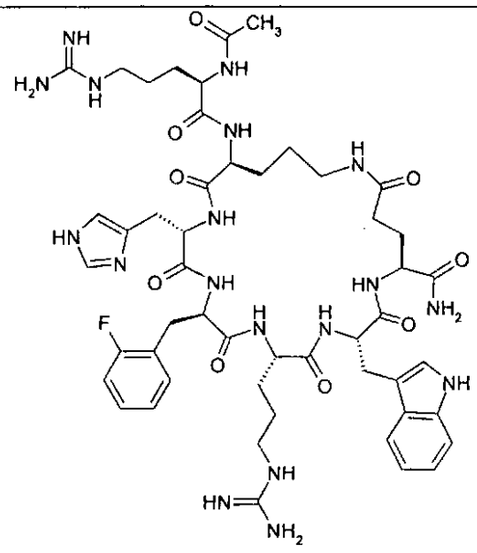
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 42 |  | Ac-Arg-*ciclo*(Glu-Val-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:47) | 6 | 420 |
| 43 |  | Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:48) | 5 | 870 |

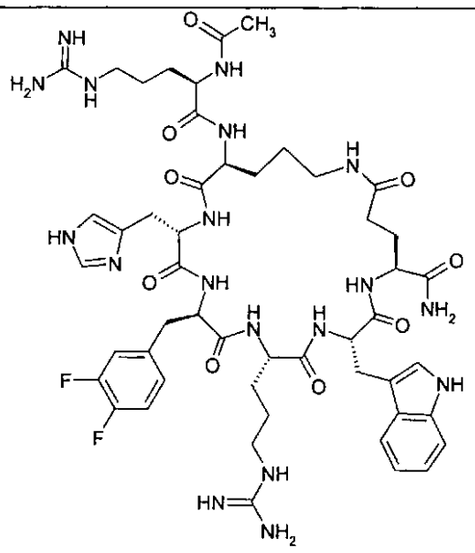
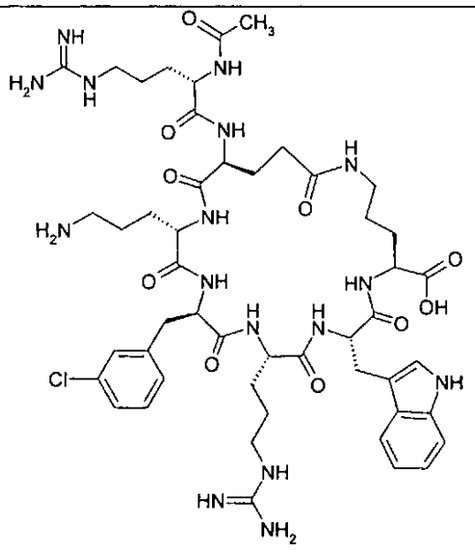
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 44 |  | Ac-Arg-*ciclo*(Glu-Thr-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:49) | 18 | 1625 |
| 45 |  | Ac-Arg-*ciclo*(Glu-Ser-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:50) | 10 | 10000 |

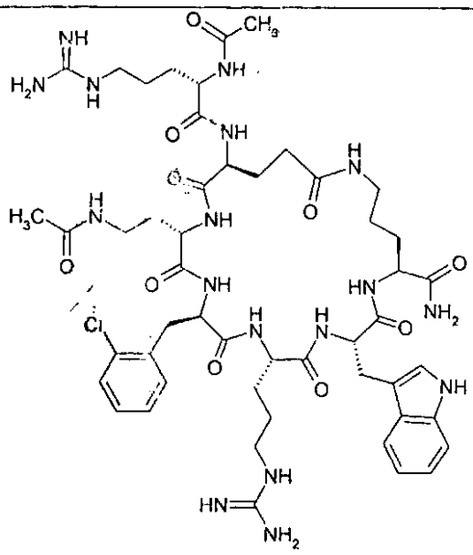
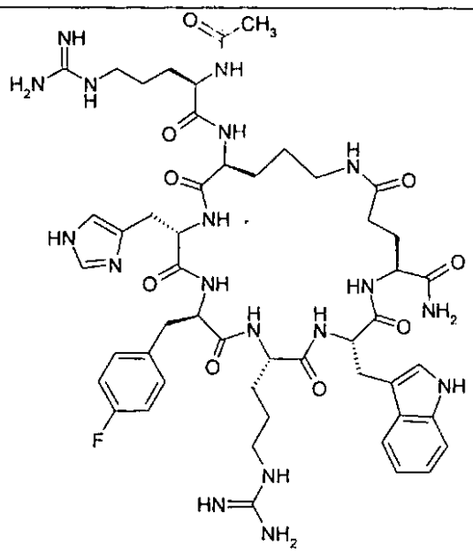
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 46 |  | Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51) | 4 | 425 |
| 47 |  | Ac-Arg-*ciclo*(Glu-Ser(Bzl)-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:52) | 0,3 | 25 |

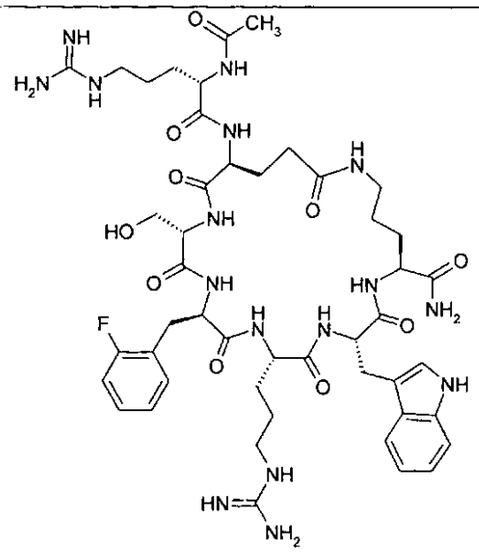
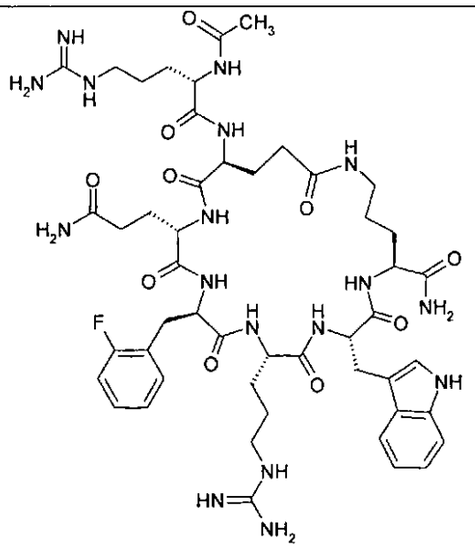
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 48 |  | Ac-Arg-*ciclo*(Glu-Phe(3-C(=O)-$NH_2$)-D-Phe(2-Cl)-D-Phe-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:53) | 15 | 545 |
| 49 |  | Ac-Arg-*ciclo*(Glu-Orn-D-Phe(2-Cl)-Arg-Trp-Orn)-OH (SEQ ID NO:54) | 8 | 8 |

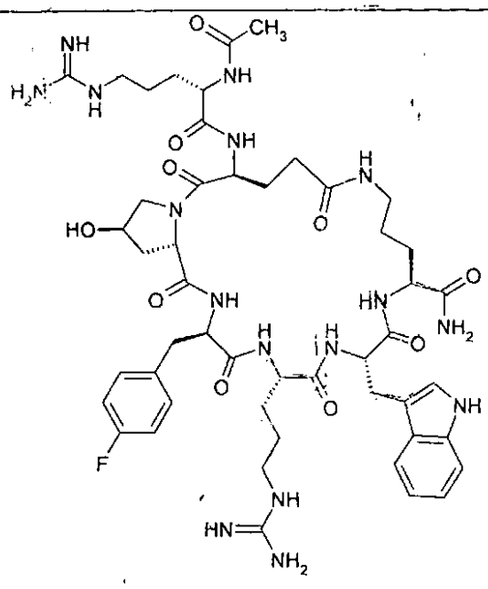
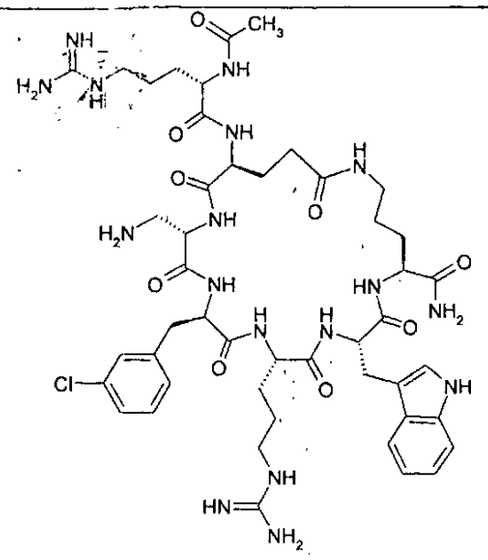
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 50 |  | Ac-D-Arg-*ciclo*(Orn-His-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:55) | 1 | 2 |
| 51 |  | Ac-D-Arg-*ciclo*(Orn-His-D-Phe(3-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:56) | 0,6 | 3 |

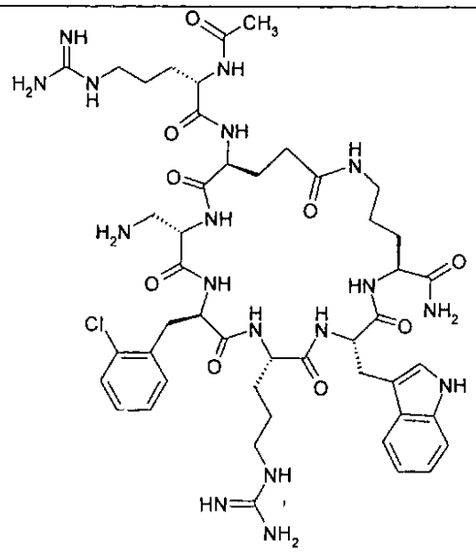
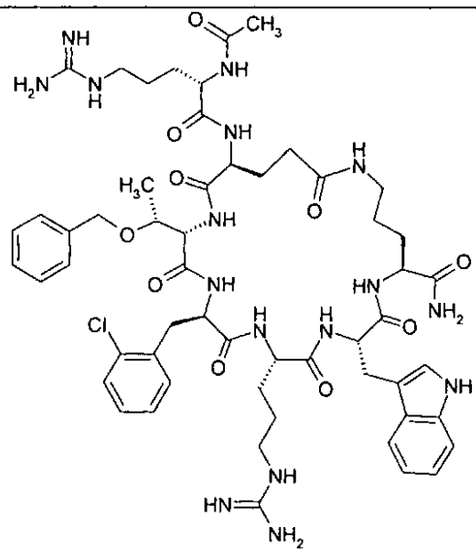
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 52 |  | Ac-D-Arg-*ciclo*(Orn-His-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:57) | 0,6 | 6 |
| 53 |  | Ac-D-Arg-*ciclo*(Orn-His-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:58) | 0,95 | 0,75 |

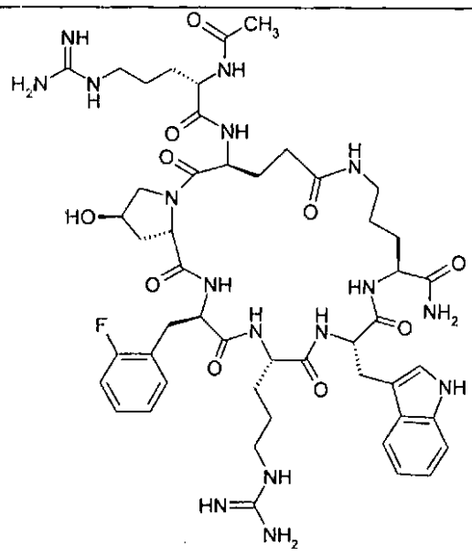
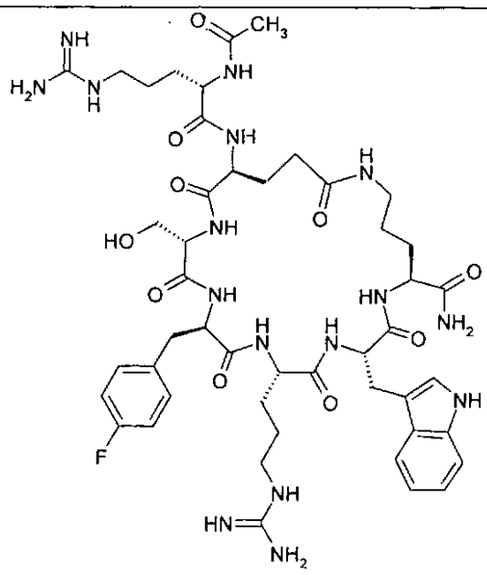
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 54 |  | Ac-D-Arg-*ciclo*(Orn-His-D-Phe(3,4-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:59) | 0,25 | 0,7 |
| 55 |  | Ac-Arg-*ciclo*(Glu-Orn-D-Phe(3-Cl)-Arg-Trp-Orn)-OH (SEQ ID NO:60) | 20 | 23 |

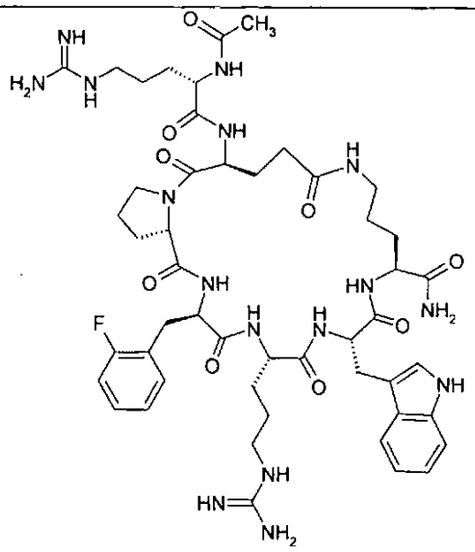
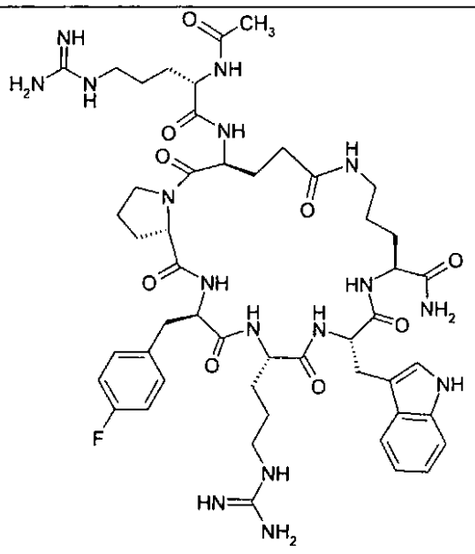
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 56 |  | Ac-Arg-*ciclo*(Glu-Dab(Acetyl)-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:61) | 11 | 30 |
| 57 |  | Ac-D-Arg-*ciclo*(Orn-His-D-Phe(4-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:62) | 0,65 | 1 |

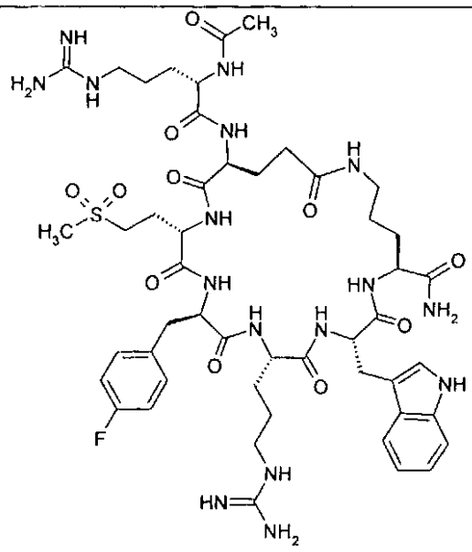
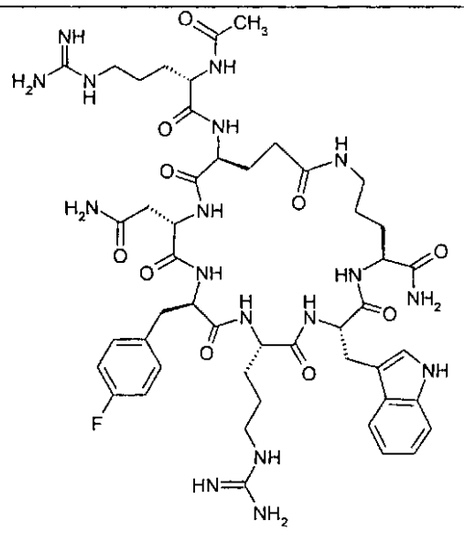
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 58 |  | Ac-Arg-*ciclo*(Glu-Ser-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:63) | 15 | 138 |
| 59 |  | Ac-Arg-*ciclo*(Glu-Gln-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:64) | 7 | 58 |

| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 60 |  | Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:65) | 1 | 89 |
| 61 |  | Ac-Arg-*ciclo*(Glu-Dap-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:66) | 4 | 25 |

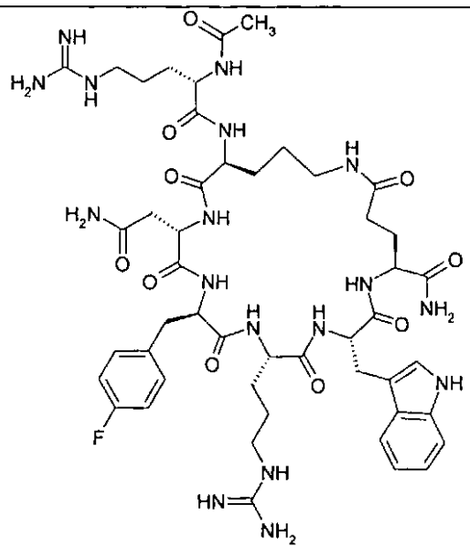
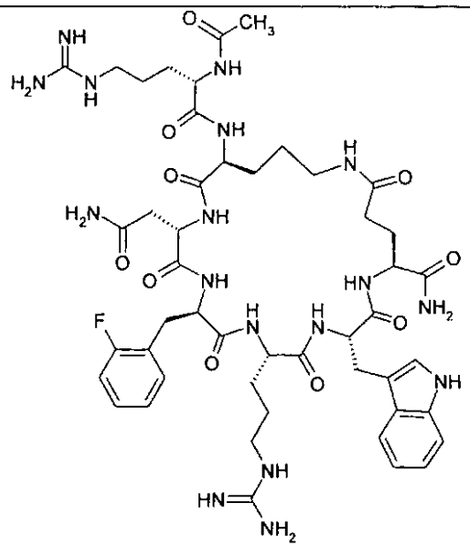
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 62 |  | Ac-Arg-*ciclo*(Glu-Dap-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:67) | 9 | 28 |
| 63 |  | Ac-Arg-*ciclo*(Glu-Thr(Bzl)-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:68) | 0,35 | 12 |

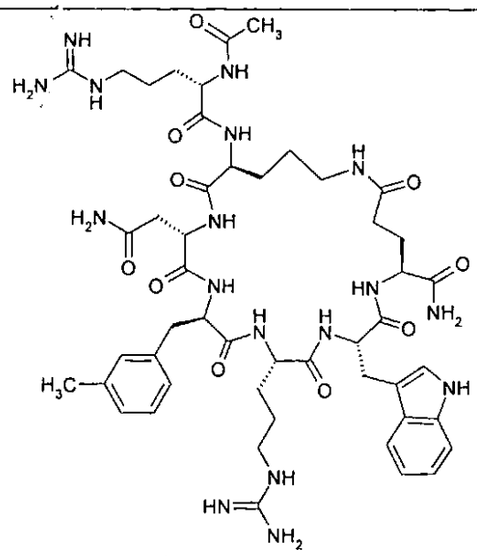
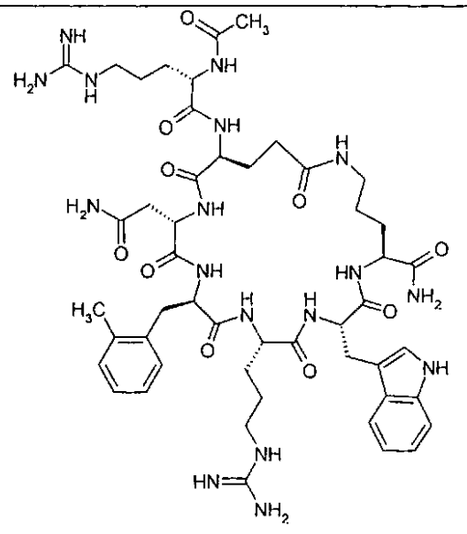
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 64 |  | Ac-Arg-*ciclo*(Glu-Hyp-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:69) | 3 | 53 |
| 65 |  | Ac-Arg-*ciclo*(Glu-Ser-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:70) | 5 | 43 |

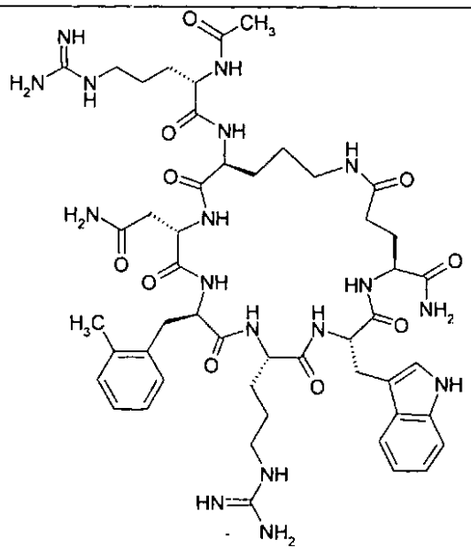
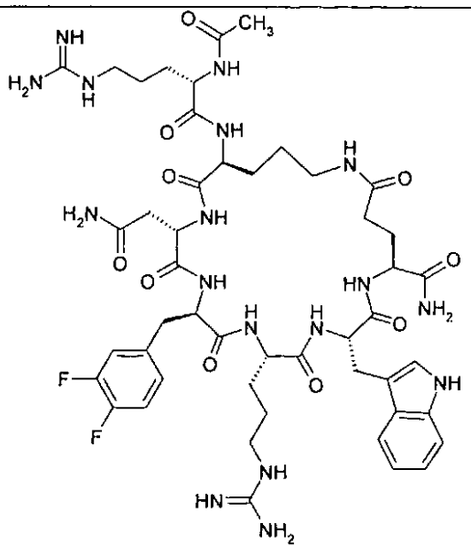
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 66 |  | Ac-Arg-*ciclo*(Glu-Pro-D-Phe(2-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:71) | 6 | 95 |
| 67 |  | Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72) | 5 | 130 |

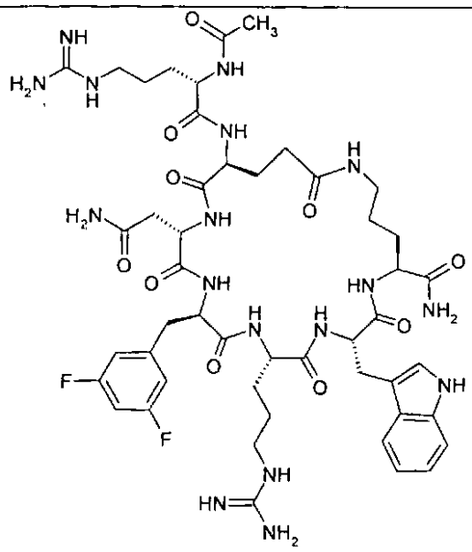
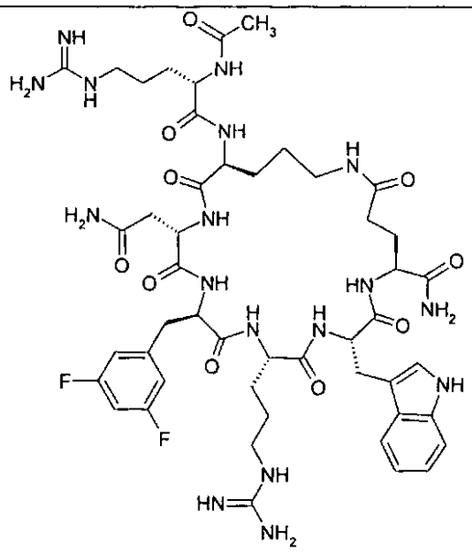
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 68 |  | Ac-Arg-*ciclo*(Glu-Met($O_2$)-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:73) | 2 | 33 |
| 69 |  | Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:74) | 3 | 150 |

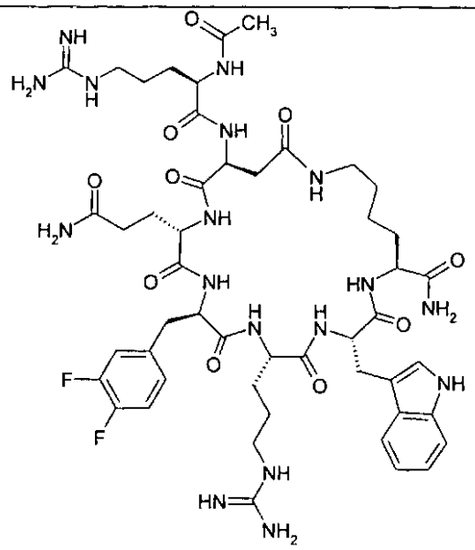
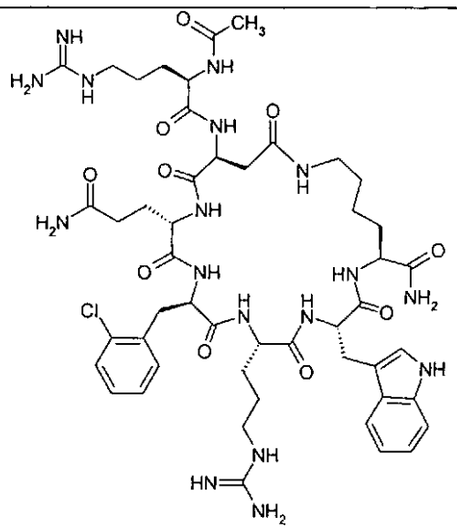
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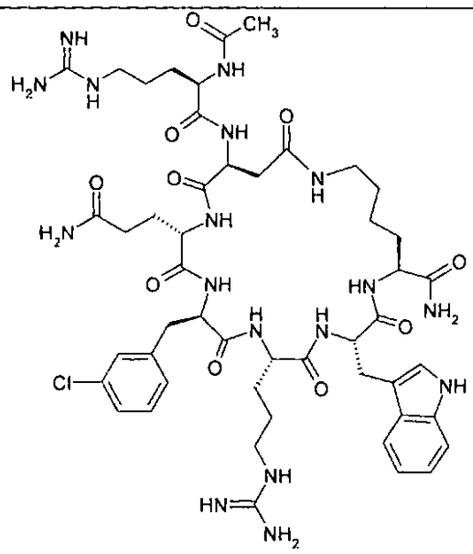
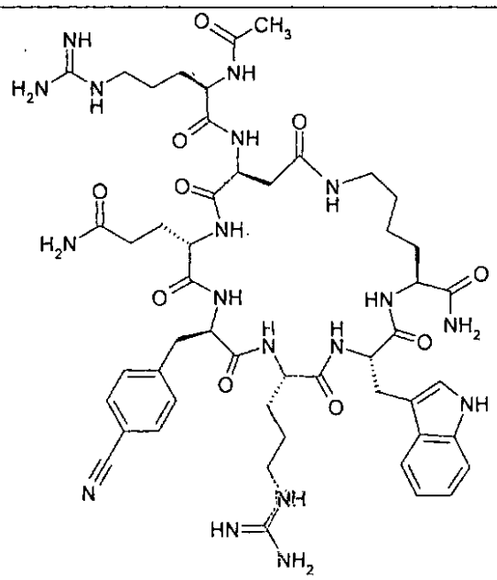
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 70 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(4-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:75) | 3 | 170 |
| 71 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:76) | 9 | 335 |

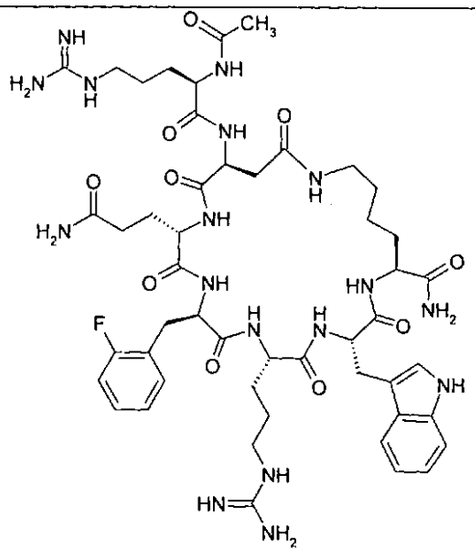
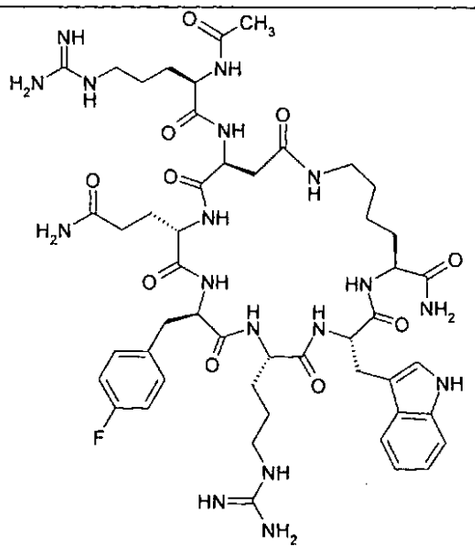
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 72 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(3-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:77) | 4 | 2300 |
| 73 |  | Ac-Arg-*ciclo*(Glu-Asn-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:78) | 4 | 160 |

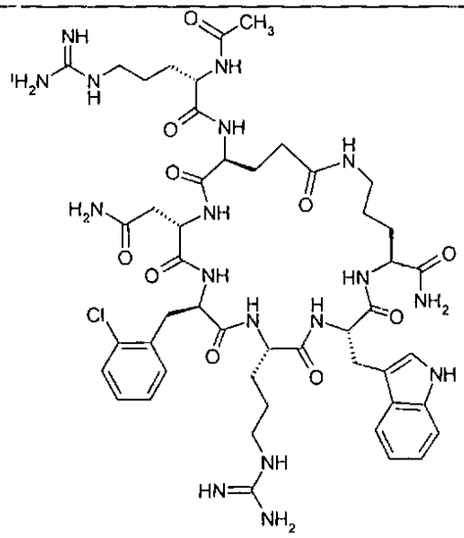
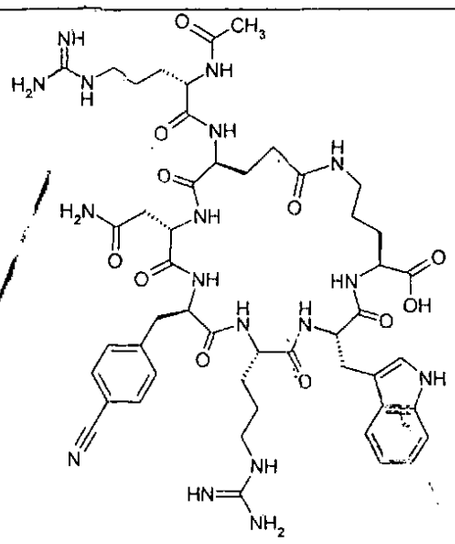
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 74 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(2-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:79) | 5 | 405 |
| 75 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(3,4-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:80) | 3 | 190 |

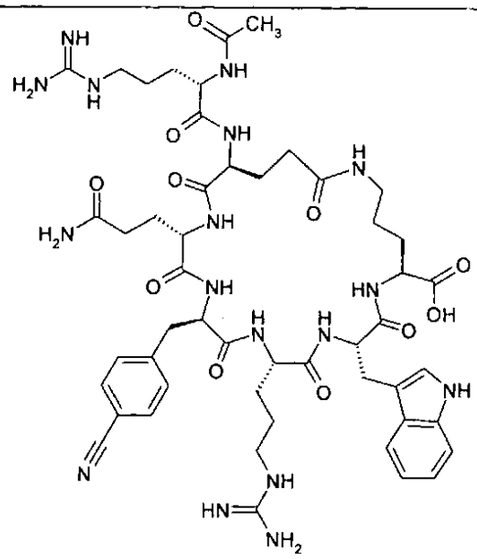
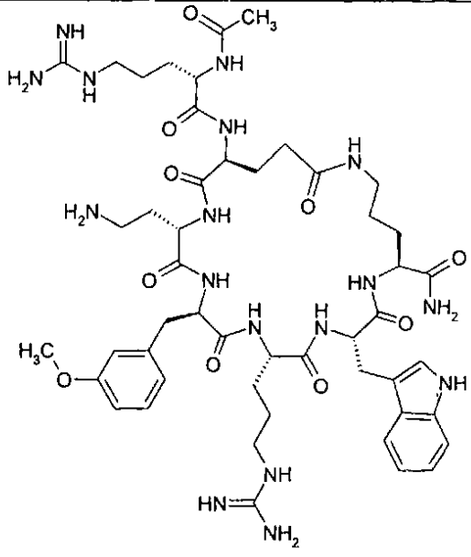
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 76 |  | Ac-Arg-*ciclo*(Glu-Asn-D-Phe(3,5-diF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:81) | 20 | 260 |
| 77 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(3,5-diF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:82) | 8 | 190 |

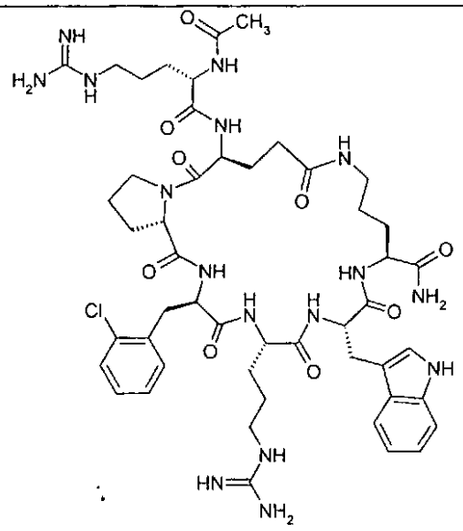
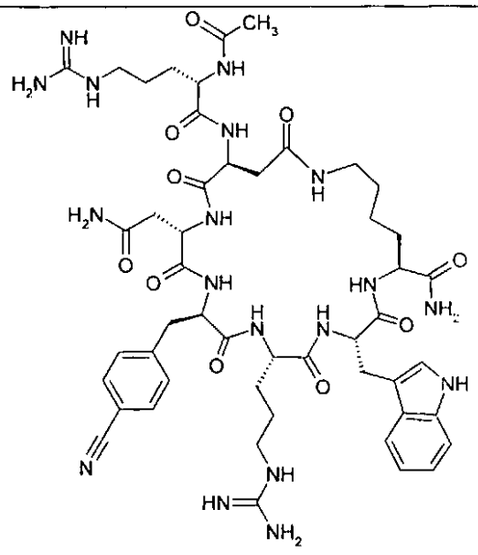
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 78 |  | Ac-D-Arg-*ciclo*(Asp-Gln-D-Phe(3,4-diF)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:83) | 8 | 515 |
| 79 |  | Ac-D-Arg-*ciclo*(Asp-Gln-D-Phe(2-Cl)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:84) | 10 | 395 |

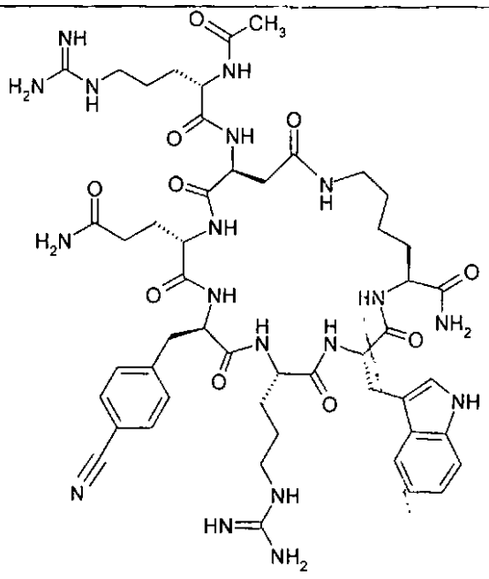
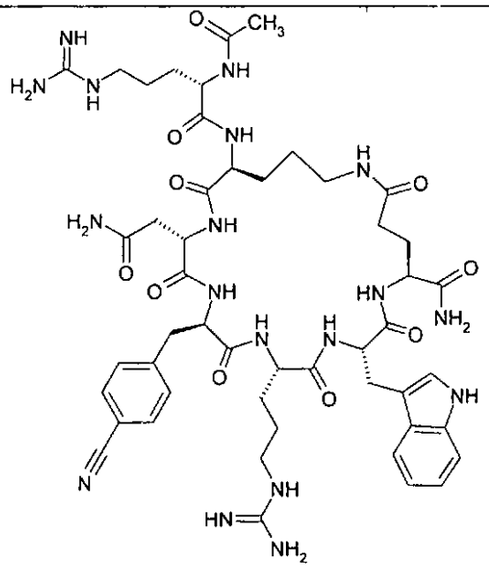
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 80 |  | Ac-D-Arg-*ciclo*(Asp-Gln-D-Phe(3-Cl)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:85) | 7 | 1750 |
| 81 |  | Ac-D-Arg-*ciclo*(Asp-Gln-D-Phe(4-CN)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:86) | 13 | 10000 |

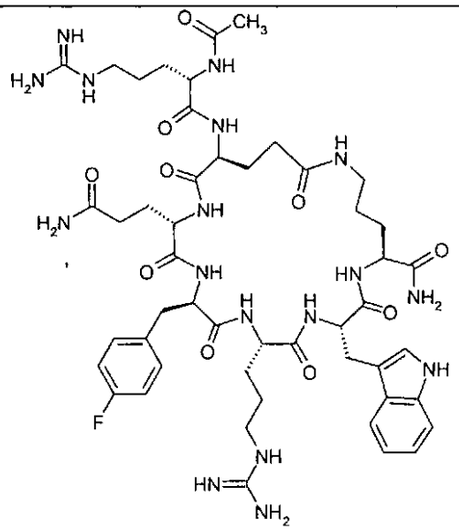
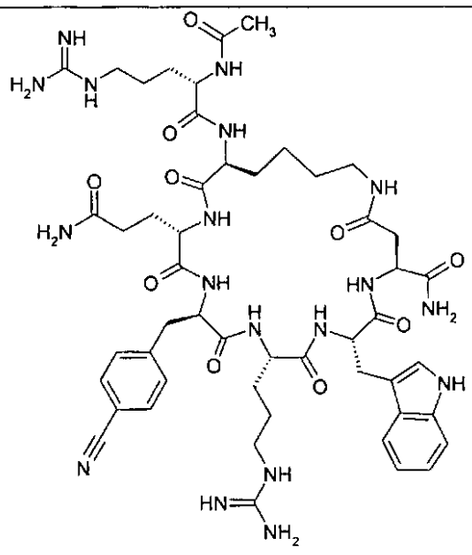
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 82 |  | Ac-D-Arg-*ciclo*(Asp-Gln-D-Phe(2-F)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:87) | 10 | 220 |
| 83 |  | Ac-D-Arg-*ciclo*(Asp-Gln-D-Phe(4-F)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:88) | 6 | 260 |

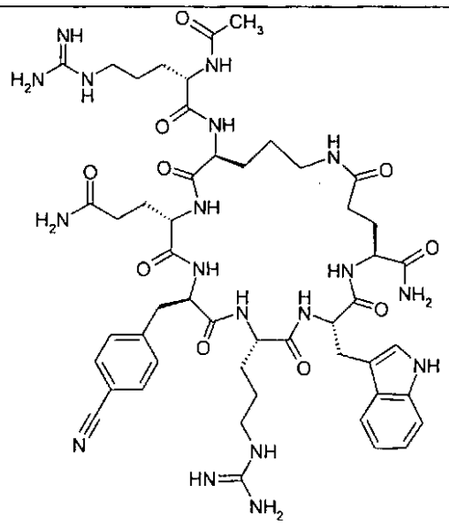
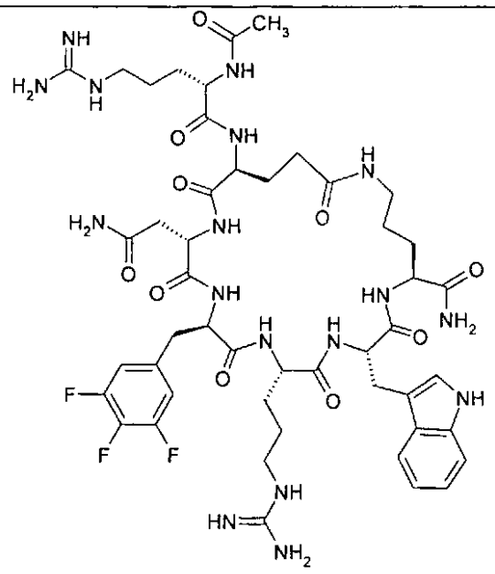
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 84 |  | Ac-Arg-*ciclo*(Glu-Asn-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:89) | 7 | 245 |
| 85 |  | Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:90) | 64 | 10000 |

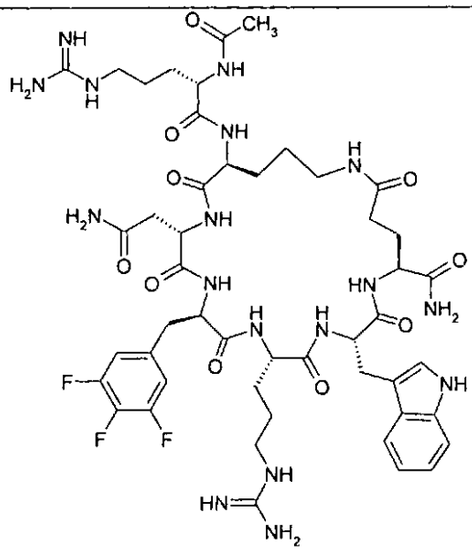
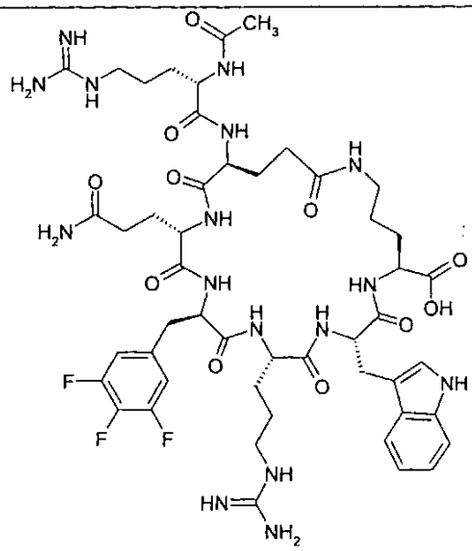
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 86 |  | Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:91) | 40 | 3968 |
| 87 |  | Ac-Arg-*ciclo*(Glu-Dab-D-Phe(3-OMe)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:92) | 3 | - |

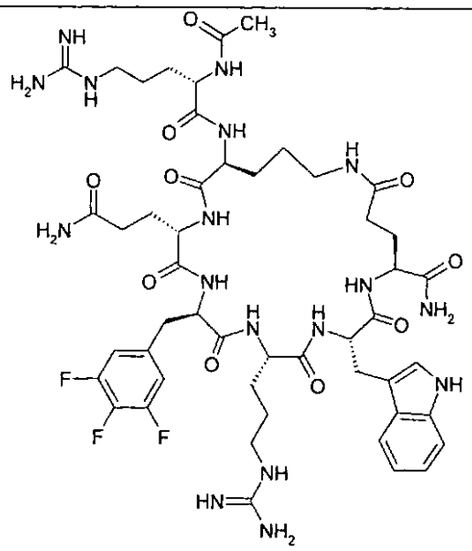
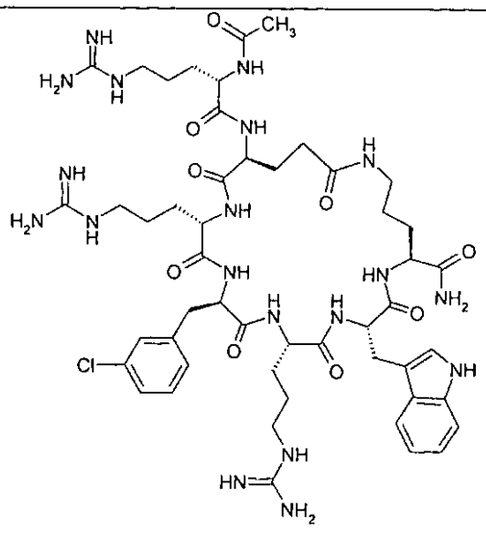
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 88 |  | Ac-Arg-*ciclo*(Glu-Pro-D-Phe(2-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:93) | 5 | - |
| 89 |  | Ac-Arg-*ciclo*(Asp-Asn-D-Phe(4-CN)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:94) | 48 | - |

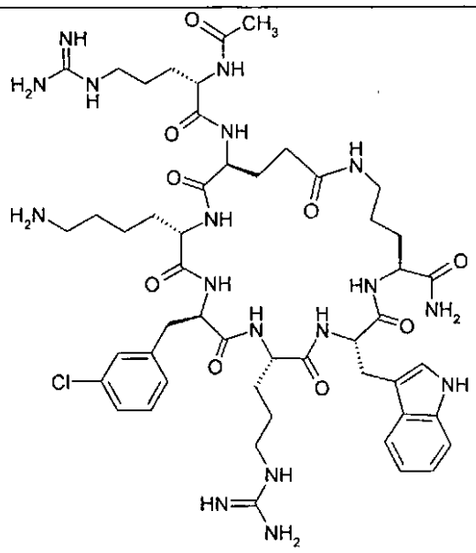
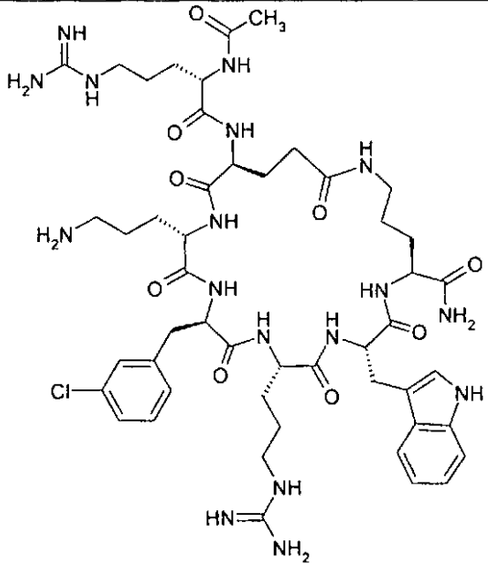
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 90 |  | Ac-Arg-*ciclo*(Asp-Gln-D-Phe(4-CN)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:95) | 5 | - |
| 91 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:96) | 4 | - |

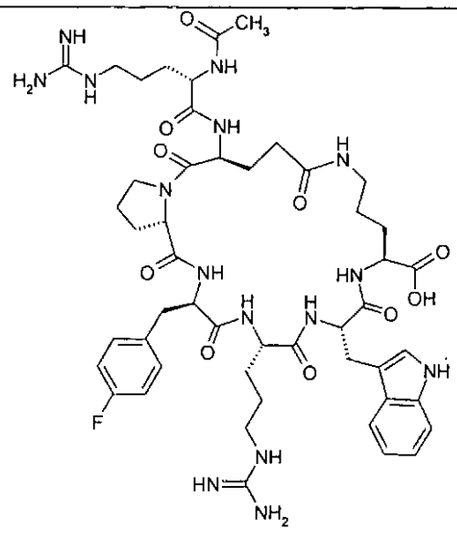
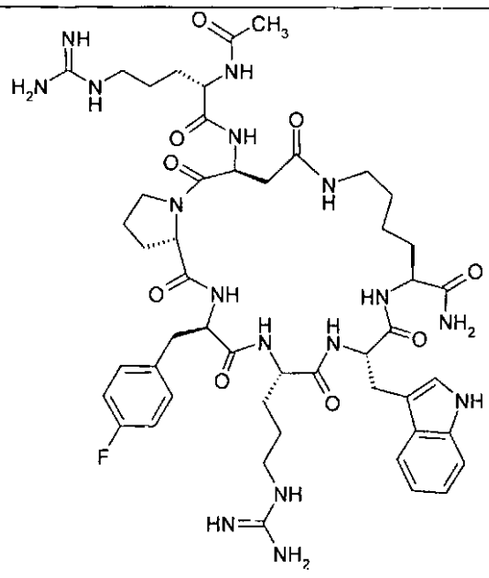
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 92 |  | Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:97) | 2 | - |
| 93 |  | Ac-Arg-*ciclo*(Lys-Gln-D-Phe(4-CN)-Arg-Trp-Asp)-$NH_2$ (SEQ ID NO:98) | 1 | - |

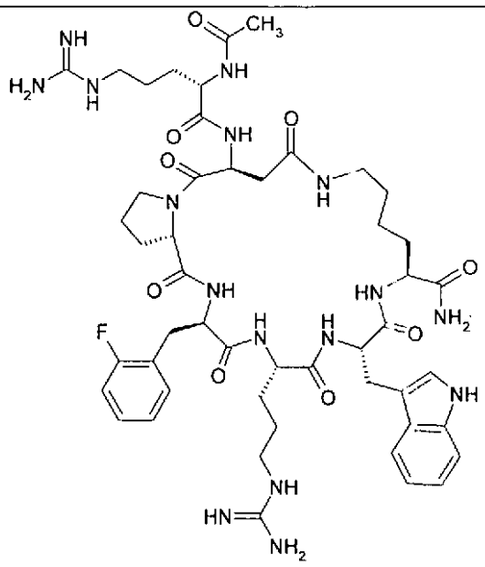
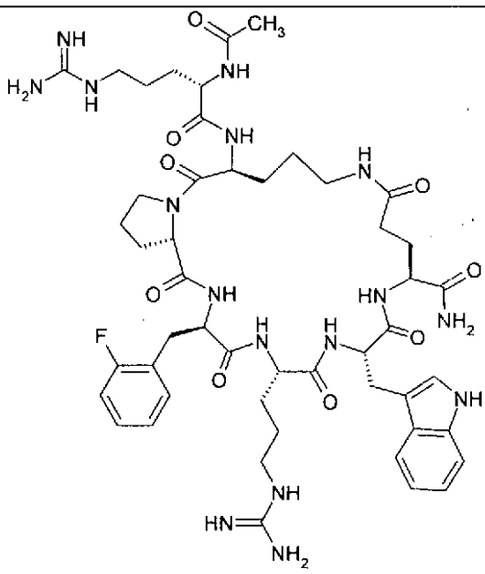
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 94 |  | Ac-Arg-*ciclo*(Orn-Gln-D-Phe(4-CN)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:99) | 0,9 | - |
| 95 |  | Ac-Arg-*ciclo*(Glu-Asn-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:100) | 3 | - |

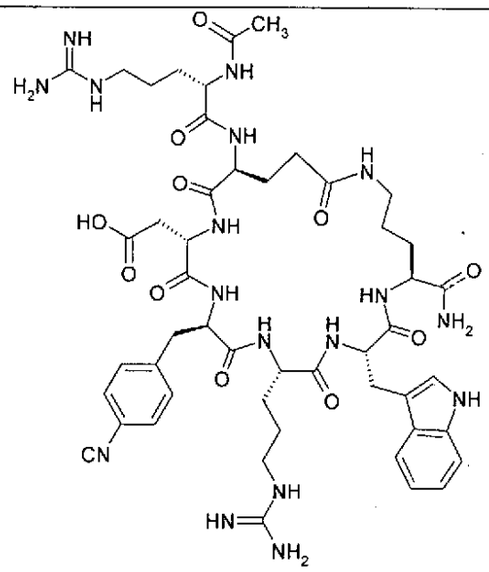
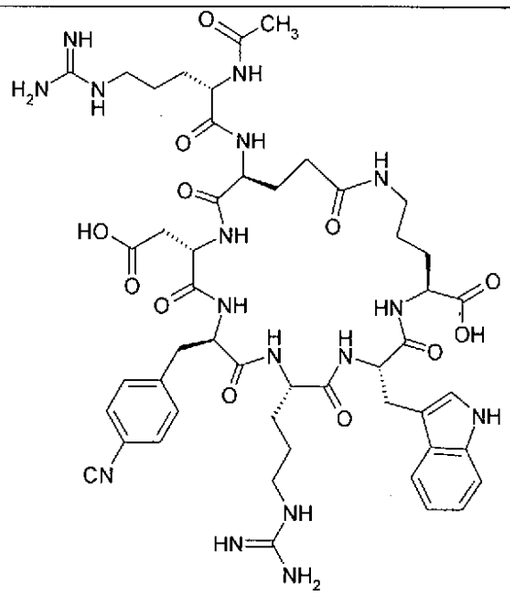
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 96 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(3,4,5-triF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:101) | 2 | - |
| 97 |  | Ac-Arg-*ciclo*(Glu-Gln-D-Phe(3,4,5-triF)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:102) | 0,75 | - |

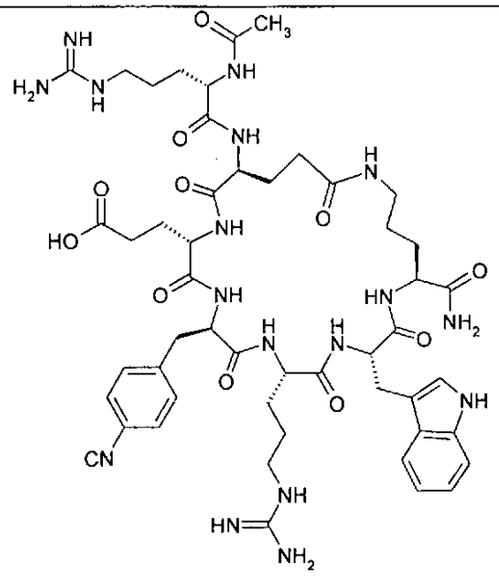
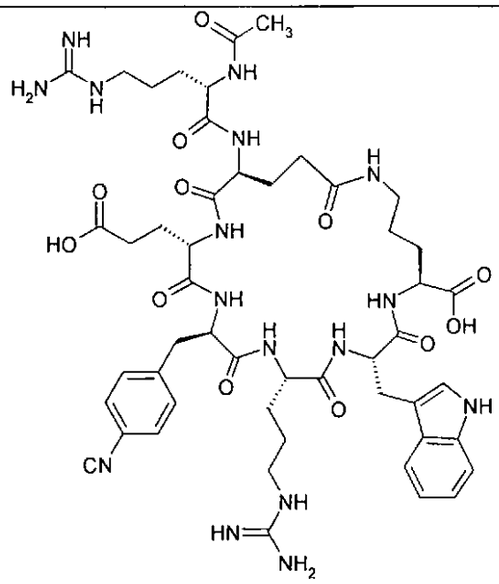
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 98 |  | Ac-Arg-*ciclo*(Orn-Gln-D-Phe(3,4,5-triF)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:103) | 0,75 | - |
| 99 |  | Ac-Arg-*ciclo*(Glu-Arg-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:104) | 0,5 | - |

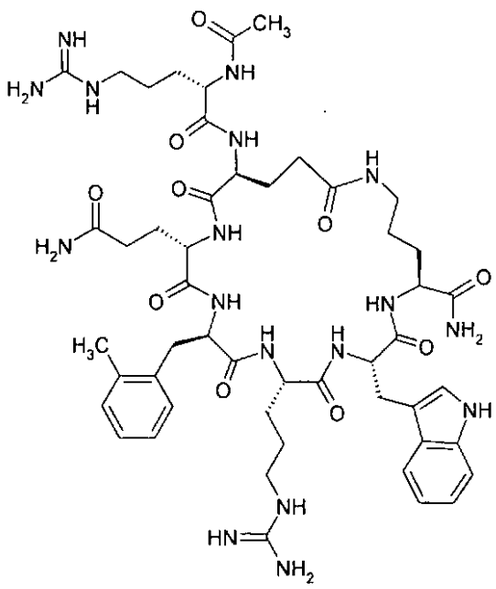
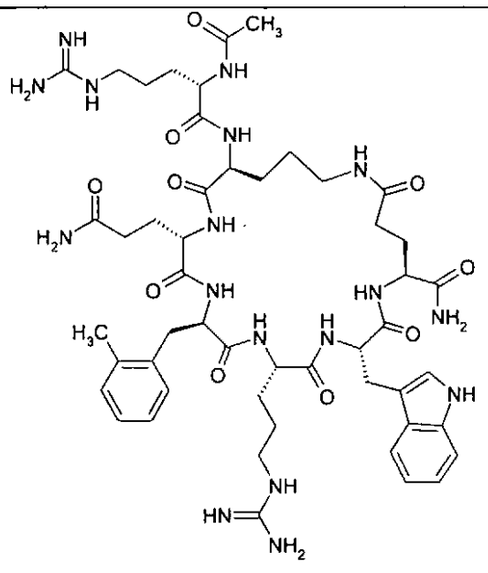
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 100 |  | Ac-Arg-*ciclo*(Glu-Lys-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:105) | 4 | - |
| 101 |  | Ac-Arg-*ciclo*(Glu-Orn-D-Phe(3-Cl)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:106) | 1 | - |

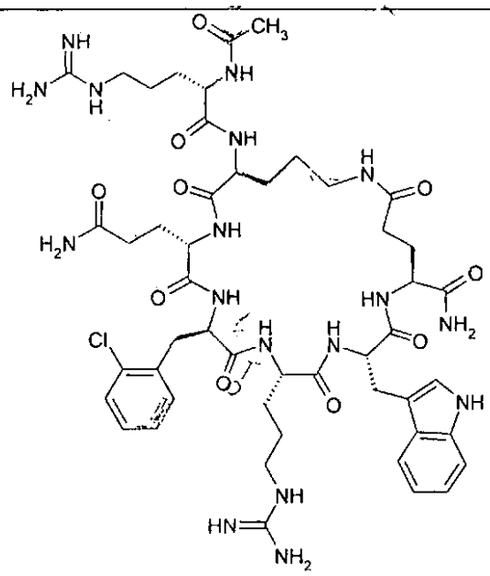
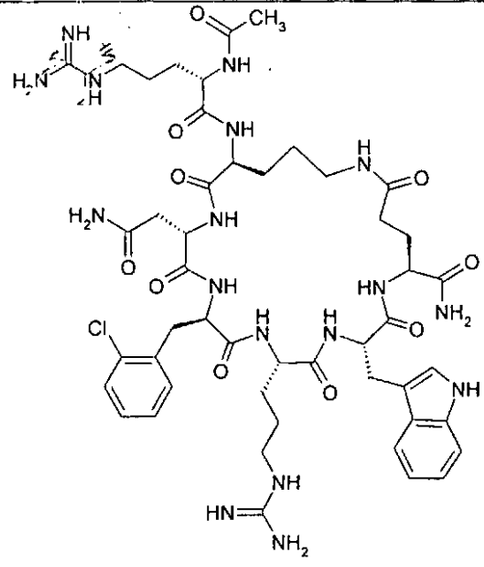
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 102 |  | Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-OH (SEQ ID NO:107) | 30 | 730 |
| 103 |  | Ac-Arg-*ciclo*(Asp-Pro-D-Phe(4-F)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:108) | 4 | - |

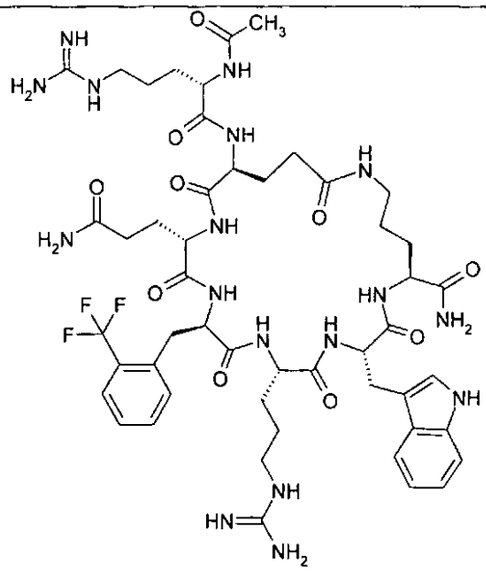
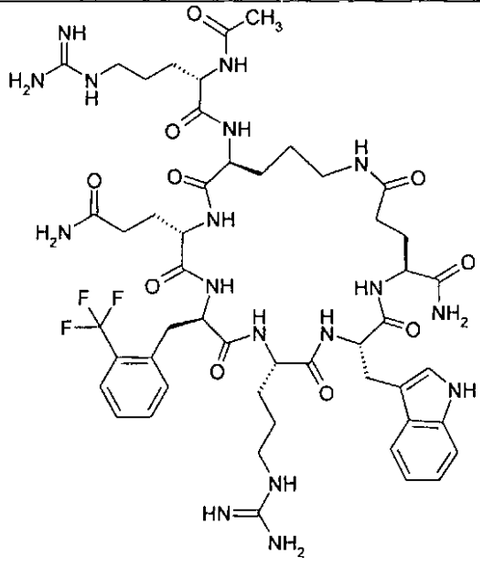
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 104 |  | Ac-Arg-*ciclo*(Asp-Pro-D-Phe(2-F)-Arg-Trp-Lys)-$NH_2$ (SEQ ID NO:109) | 78 | - |
| 105 |  | Ac-Arg-*ciclo*(Orn-Pro-D-Phe(2-F)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:110) | 7 | - |

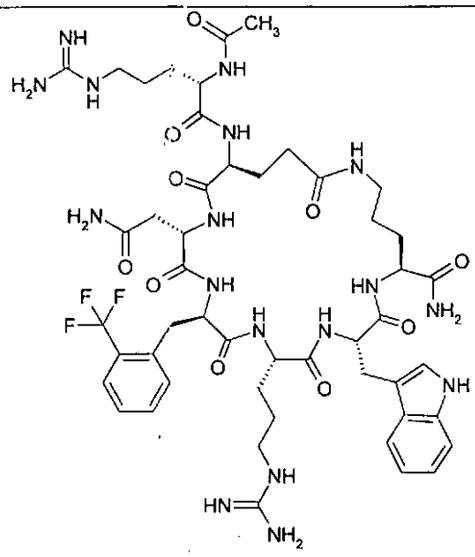
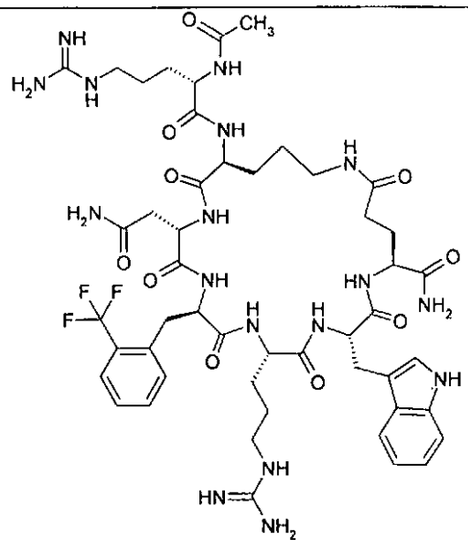
| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 106 |  | Ac-Arg-*ciclo*(Glu-Asp-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:111) | 647 | 10000 |
| 107 |  | Ac-Arg-*ciclo*(Glu-Asp-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:112) | 6463 | 10000 |

| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 108 |  | Ac-Arg-*ciclo*(Glu-Glu-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:113) | 128 | 10000 |
| 109 |  | Ac-Arg-*ciclo*(Glu-Glu-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:114) | 1090 | 10000 |

| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 110 |  | Ac-Arg-*ciclo*(Glu-Gln-D-Phe(2-Me)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:115) | 5 | 105 |
| 111 |  | Ac-Arg-*ciclo*(Orn-Gln-D-Phe(2-Me)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:116) | 6 | 145 |

| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 112 |  | Ac-Arg-*ciclo*(Orn-Gln-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:117) | 4 | 83 |
| 113 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(2-Cl)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:118) | 7 | 255 |

| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 114 |  | Ac-Arg-*ciclo*(Glu-Gln-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:119) | 8 | 93 |
| 115 |  | Ac-Arg-*ciclo*(Orn-Gln-D-Phe(2-$CF_3$)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:120) | 4 | 235 |

| No. | Estructura | Secuencia de aminoácidos | Ki MC4-R (nM) | Ki MC1-R (nM) |
|---|---|---|---|---|
| 116 |  | Ac-Arg-*ciclo*(Glu-Asn-D-Phe(2-$CF_3$)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:121) | 7 | 380 |
| 117 |  | Ac-Arg-*ciclo*(Orn-Asn-D-Phe(2-$CF_3$)-Arg-Trp-Glu)-$NH_2$ (SEQ ID NO:122) | 5 | 540 |

7.0 Pruebas y ensayos empleados en la evaluación de los péptidos de la presente invención.

Los péptidos específicos para los receptores de melanocortina de esta invención pueden evaluarse a través de distintos sistemas de ensayo y modelos animales para determinar su unión, estado funcional y eficacia.

7.1 Ensayo de inhibición competitiva utilizando [$I^{125}$]-NDP-α-MSH.

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Se realizó un ensayo de inhibición de unión competitiva para los péptidos ejemplificados de acuerdo con la invención utilizando homogenados de membrana preparados a partir de células HEK-293 que expresan hMC4-R, hMC3-R o hMC5-R recombinante y a partir de células de melanoma de ratón B-16 (que contenían MC1-R endógeno). En algunos casos se emplearon células HEK-293 que expresan hMC1-R recombinante. Los ensayos se llevaron a cabo en placas de filtración de 96 pocillos GF/B Millipore Multiscreen (MAFB NOB10) recubiertas previamente con albúmina de suero bovino al 0,5% (Fracción V). Los homogenados de membrana se incubaron con [$I^{125}$]-NDP-α-MSH 0,2nM (para hMC4-R), 0,4 nM (para MC3-R y MC5-R) o 0,1 nM (para MC1-R de B16 de ratón o hMC1-R) (Perkin Elmer) y concentraciones en aumento de péptidos de prueba de la presente invención en solución amortiguadora que contenía solución amortiguadora de HEPES 25 mM (pH 7,5) con NaCl 100 mM, $CaCl_2$ 2 mM, $MgCl_2$ 2 mM, 1,10-fenantrolina 0,3 mM y albúmina de suero bovino al 0,2%. Luego de la incubación durante 60 minutos a 37°C, la mezcla de ensayo se filtró y las membranas se lavaron tres veces con solución amortiguadora helada. Los filtros se secaron y contaron en un contador gamma para detectar la radioactividad unida. La unión no específica se midió mediante la inhibición de la unión de [$I^{125}$]-NDP-α-MSH en presencia de NDP-α-MSH 1 μM. La unión específica máxima (100%) se definió como la diferencia en radiactividad (cpm) unida a membranas celulares en ausencia y presencia de NDP-α-MSH 1 μM. La radiactividad (cpm) obtenida en presencia de péptidos de prueba se normalizó con respecto al 100% de unión específica para determinar la inhibición porcentual de la unión de [$I^{125}$]-NDP-α-MSH. Cada ensayo se llevó a cabo por triplicado y se describen los valores medios reales, reportándose los resultados menores que 0% como 0%. Los valores de Ki para los péptidos de prueba de la presente invención se determinaron utilizando el programa informático de ajuste a la curva Graph-Pad Prism®. Los resultados de este ensayo se presentan en la presente (ver 6.1). Para algunos péptidos se presenta un valor medio de más de dos valores.

7.2 Ensayo de actividad agonista.

La acumulación de cAMP intracelular se examinó como medida de la capacidad de los péptidos de la presente invención de provocar una respuesta funcional en células HEK-293 que expresan MC4-R. Se despegaron células HEK-293 confluentes que expresaban hMC4-R recombinante de placas de cultivo celular mediante incubación en solución

amortiguadora de disociación de células sin enzimas. Las células dispersadas se suspendieron en solución salina equilibrada de Earle que contenía HEPES 10 mM (pH 7,5), $MgCl_2$ 1 mM, glutamina 1mM, albúmina al 0,5% y 3-isobutil-1-metil-xantina (IBMX) 0,3 mM, un inhibidor de fosfodiesterasa. Las células se colocaron en placas de 96 pocillos con una densidad de 0,5 x $10^5$ células por pocillo y se incubaron previamente durante 10 minutos. Las células se expusieron durante 15 minutos a 37°C a péptidos de la presente invención disueltos en DMSO (concentración final de DMSO de 1%) en un rango de concentración de 0,05 - 5000 nM en un volumen de ensayo total de 200 µL. Se utilizó NDP-α-MSH como agonista de referencia. Los niveles de cAMP se determinaron mediante un sistema de ensayo en base a células de cAMP HTRF® de Cisbio Bioassays que utilizaba anti-cAMP etiquetado con criptato y cAMP etiquetado con d2, y las placas se leyeron en un lector de placas Victor de Perkin-Elmer a 665 y 620nM. El análisis de datos se llevó a cabo mediante análisis de regresión no lineal con el programa informático Graph-Pad Prism®. Las eficacias máximas de los péptidos de prueba de la presente invención se compararon con las de las alcanzados por el agonista de melanocortina de referencia NDP-α-MSH, utilizado como patrón agonista completo en este contexto.

7.3 Ensayo funcional de hMC4-R de alta y baja densidad.

Se utilizó una línea de células HEK293 transfectada con MC4-R humano (Palatin Technologies, EE.UU., con licencia de la Universidad de Michigan). El MC4-R humano se introdujo en HEK293 mediante el sistema T-REx™ de Invitrogen. El sistema T-REx™ emplea un sistema de expresión de mamíferos regulado por tetraciclina que utiliza elementos reguladores del operón de resistencia a tetraciclina (Tet) codificado por Tn*10* de *E. coli*. Mediante el uso del sistema T-REx™, la expresión del gen de interés, el gen MC4-R humano, se reprime en ausencia de tetraciclina o doxiciclina y se induce en presencia de tetraciclina o doxiciclina (ver el manual del sistema T-REx™ publicado por Invitrogen).

Se cultivaron células HEK293-T-REx-MC4-R en DMEM (Gibco 11965), complementado con L-Glutamina (Gibco 25030), suero fetal bovino al 10% (FBS), 200 µg/mL de Zeocina (Invitrogen 46-0072) y 6 µg/mL de Blasticidina (Invitrogen 46-1120) en 5% de $CO_2$ y 95% de humedad a 37°C. Se incubaron matraces T-150 de células con una confluencia del 75% con dos concentraciones de doxiciclina (0,1 ng/mL para proporcionar un sistema de hMC4-R de baja densidad y 10 ng/mL para proporcionar un sistema de hMC4-R de alta densidad) en 5% de $CO_2$ a 37°C durante 16-18 horas para inducir la

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expresión de MC4-R. En el día del ensayo las células se lavaron con PBS (Gibco 14190) y se cosecharon utilizando solución amortiguadora de disociación celular (Gibco 13150-016), luego se centrifugaron y resuspendieron en solución salina equilibrada de Hanks (+Ca, +Mg) (Gibco 14025), ácido 4-(2-hidroxietil)-1-piperazinaetanesulfónico (HEPES) 10 mM (pH 7,4) (S7n igma H0887), L-Glutamina 1mM (Gibco 25030), 1 mg/mL de albúmina de suero bovino (BSA) (Sigma A3311) y 3-isobutil-1-metil-xantina (IBMX) 0,3 mM. Las células luego se contaron y se ajustó el volumen a 2,5 x $10^5$ células por ml.

Luego las células se dispensaron en placas de 96 pocillos (BD 353916) en 198 µL (aproximadamente 5 x $10^4$) células/pocillo y se incubaron durante 10 minutos a 37°C. El compuesto a evaluar se diluyó con DMSO hasta una concentración final de 1 mM. La dilución en serie se preparó en tiras de tubo de biblioteca de 12 pocillos removibles de polipropileno (VWR cat No. 83009-682). Se pipetearon 120 µL del compuesto concentrado 1 mM en la segunda columna de la placa. Utilizando el manipulador de líquidos Janus, el compuesto se diluyó en series 1:10 (25 µL de compuesto + 225 µL de DMSO) hasta un total de 9 concentraciones (que representaban concentraciones de ensayo finales de $10^{-5}$ a $10^{-13}$ M).

Se agregaron 2 µL de la Hormona Estimuladora de [Nle$^4$, D-Phe$^7$]-alfa-Melanocito (NDP-α-MSH) estándar o compuesto a la placa de 96 pocillos utilizando el sistema robótico Janus. Todas las muestras de ensayo se realizaron por duplicado (es decir, cada muestra se encontraba en dos placas con bajo dox y dos placas con alto dox, respectivamente). Las placas se agitaron suavemente y se incubaron durante 15 minutos a 37°C. La reacción se detuvo mediante la adición de 15 µL de solución amortiguadora de lisis por pocillo y las placas se agitaron durante 30 minutos a temperatura ambiente.

La estimulación con agonistas del MC4-R activa la adenilato ciclasa, que es una enzima que cataliza la formación de adenosina monofosfato 3´,5´-cíclica (cAMP) a partir de la adenosina trifosfato (ATP). De este modo, la estimulación con agonista del MC4-R aumenta los niveles de cAMP. Los niveles de cAMP se midieron con el kit cAMP dynamic 2 HTRF (CisBio cat No. 62AM4PEC; ver manual publicado por CisBio). Los niveles de cAMP se normalizaron con respecto a los testigos de la placa (1% DMSO para 0%, NDP-α-MSH 400 nM para 100%) y una curva de calibración en el rango de cAMP 712 nM a 0,04 nM (básicamente como se describe en el kit HTRF de CisBio). Las placas se incubaron en un agitador a temperatura ambiente durante 1 hora y se leyeron en la lectora

de placas Victor de Perkin-Elmer a 665 y 620 nm. Luego se calcularon las relaciones de fluorescencia como se describe en el kit HTRF de CisBio y se utilizó el programa informático GraphPad Prism para representar gráficamente el cambio de los valores porcentuales de fluorescencia con respecto a la concentración de cAMP utilizando la pendiente variable de la curva dosis-respuesta y, en base a las concentraciones de cAMP calculadas, para determinar los valores de $CE_{50}$ y la activación porcentual. Los resultados de este ensayo se presentan en la presente (ver 8.0).

7.4 Cambio en la ingesta de alimentos y peso corporal.

El cambio en la ingesta de alimentos y en el peso corporal se evaluó para péptidos seleccionados administrados mediante inyección subcutánea. Se obtuvieron ratas macho Sprague-Dawley de Hilltop Lab Animals, Inc. (Scottdale, PA). Los animales se albergaron individualmente en jaulas colgantes de poliestireno convencionales en un ciclo de luz/oscuridad de 12 horas. Se proporcionó agua y alimento granulado (ProLab RMH 2500, W.F. Fisher & Son Inc.) *ad libitum*. Las ratas se dosificaron subcutáneamente con vehículo (3,2% manitol/solución amortiguadora Tris 50mM) o péptidos seleccionados (1,0 mg/kg). Se determinaron los cambios en la ingesta de alimentos para los períodos de 4 y 24 horas luego de la dosificación y los cambios en el peso corporal para el período de 24 horas posterior a la dosificación. También se midieron los cambios en el peso corporal y la ingesta de alimentos para los períodos de 48 horas y 72 horas luego de la dosificación para determinar la reversión de los cambios en los efectos del peso corporal y la ingesta de alimentos a niveles base (no se muestra).

Los resultados de ingesta de alimentos (IA, 0-4 h y 0-24 h) y peso corporal (PC, 0-24 h) de los estudios con 1,0 mg/kg subcutáneamente de los Ejemplos 43, 46 y 67 y los correspondientes testigos con vehículo realizados en paralelo se muestran en la Tabla 2 a continuación, expresados como promedios ± EEM (n=8-10).

**Tabla 2**

| Experimento | Tratamiento | Dosis (mg/kg, s.c.) | n | IA 0-4h (g) | IA 0-24h (g) | Cambio PC 0-24h (g) |
|---|---|---|---|---|---|---|
| 1 | Vehículo | | 10 | 10,53 ± 0,78 | 27,75 ± 1,00 | 1,49 ± 0,18 |
| 1 | Ej de Ref 2 | 1,0 | 10 | 4,41 ± 0,48 | 20,84 ± 1,01 | -0,38 ± 0,46 |
| 1 | Ej 43 | 1,0 | 10 | 6,85 ± 0,55 | 24,44 ± 0,85 | 0,45 ± 0,35 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2 | Vehículo | | 8 | 7,09 ± 0,39 | 27,46 ± 1,16 | 1,96 ± 0,55 |
| 2 | Ej de Ref 2 | 1,0 | 8 | 2,80 ± 0,27 | 21,81 ± 1,04 | 0,85 ± 0,45 |
| 2 | Ej 46 | 1,0 | 8 | 3,71 ± 0,68 | 20,56 ± 1,14 | -0,29 ± 0,55 |
| | | | | | | |
| 3 | Vehículo | | 8 | 7,76 ± 0,53 | 25,71 ± 0,25 | 2,25 ± 0,50 |
| 3 | Ej de Ref 2 | 1,0 | 8 | 3,17 ± 0,42 | 19,98 ± 0,60 | -0,27 ± 0,48 |
| 3 | Ej 67 | 1,0 | 8 | 4,20 ± 0,66 | 21,51 ± 1,27 | -0,05 ± 0,39 |

7.5 Inducción de erección peneana.

La capacidad de los péptidos de la presente invención de inducir la erección peneana (EP) en ratas macho se evaluó con péptidos seleccionados. Se mantuvieron ratas macho Sprague-Dawley que pesaban 250-300 g en un ciclo de luz/oscuridad de 12 horas con alimento y agua *ad libitum*. Todos los estudios de comportamiento se realizaron entre las 9 a.m. y las 4 p.m. Se administraron péptidos a grupos de 6-8 ratas con una variedad de dosis vía inyección subcutánea. Inmediatamente después del tratamiento las ratas se colocaron en jaulas de poliestireno individuales (27 cm de longitud, 16 cm de ancho y 25 cm de alto) para observar su comportamiento, típicamente mediante monitoreo remoto por video (sistema de grabación de video digital de alta velocidad EVS-DSX-16000DVD-H con cámaras CCD, Epic Systems Inc., St. Louis, MO, EE.UU.) con posterior puntuación fuera de línea ciega de los registros de video. Las ratas se observaron durante una hora y se registró el número de bostezos, acicalamientos y EP en intervalos de 10 minutos.

Los resultados de las EP de estudios con 1,0-3,0 mg/kg subcutáneamente de los Ejemplos 43, 46 y 67, junto con el Ej. de Ref. 2, se muestran en la Tabla 3 que figura a continuación, expresados como el número total de EP/rata, promedio ± EEM (n=7-11) y el número de ratas/grupo que mostraron al menos una erección durante el período del estudio (% individuos con respuesta al tratamiento). Se realizaron testigos con vehículo correspondientes (3,2% manitol/solución amortiguadora de Tris 50mM) en paralelo.

**Tabla 3**

| Tratamiento | Dosis (mg/kg, s.c.) | n | Número total de EP/rata 0-1h | % individuos con respuesta |
|---|---|---|---|---|
| Vehículo | | 11 | 1,0 ± 0,27 | 64 |
| Ref Ej 2 | 3,0 | 7 | 6,0 ± 0,44 | 100 |
| Ej 43 | 1,0 | 7 | 1,7 ± 0,36 | 29 |
| | 3,0 | 7 | 6.0 ± 0,76 | 100 |
| Ej 46 | 1,0 | 7 | 4,9 ± 1,1 | 100 |
| | 3,0 | 7 | 4,4 ± 1,1 | 86 |
| Ej 67 | 1,0 | 7 | 2,3 ± 0,42 | 86 |
| | 3,0 | 7 | 3,3 ± 1,0 | 100 |

8.0 Resultados del ensayo funcional de hMC4-R de alta y baja densidad

Los péptidos ejemplificados se evaluaron utilizando el ensayo funcional de hMC4-R de alta y baja densidad como se describió en la Sección 7.3 precedente y los resultados se muestran en la Tabla 4 a continuación. La Tabla 4 incluye tanto valores de un único punto como valores promedio.

**Tabla 4**

| **Compuesto** | **0,1 ng/mL doxiciclina** | | **10 ng/mL doxiciclina** | |
|---|---|---|---|---|
| | **$CE_{50}$ (nM)** | **Actividad intrínseca (%)** | **$CE_{50}$ (nM)** | **Actividad intrínseca (%)** |
| Ejemplo 1 | 0,34 | 91 | 0,045 | 96 |
| Ejemplo 2 | 0,56 | 36 | 0,095 | 99 |
| Ejemplo 3 | 0,07 | 28 | 0,16 | 100 |
| Ejemplo 4 | - | 11 | 0,245 | 100 |
| Ejemplo 5 | - | 5 | 0,38 | 92 |
| Ejemplo 6 | 37 | 29 | 2 | 100 |
| Ejemplo 7 | 0,3 | 48 | 0,135 | 100 |
| Ejemplo 8 | 48 | 71 | 0,55 | 87 |
| Ejemplo 9 | 0,09 | 91 | 0,035 | 89 |
| Ejemplo 10 | 0,45 | 77 | 0,17 | 94 |
| Ejemplo 11 | 0,065 | 83 | 0,06 | 90 |
| Ejemplo 12 | 34 | 64 | 0,5 | 97 |

| Compuesto | 0,1 ng/mL doxiciclina | | 10 ng/mL doxiciclina | |
|---|---|---|---|---|
| | $CE_{50}$ (nM) | Actividad intrínseca (%) | $CE_{50}$ (nM) | Actividad intrínseca (%) |
| Ejemplo 13 | 0,125 | 85 | 0,06 | 96 |
| Ejemplo 14 | 8 | 16 | 0,4 | 93 |
| Ejemplo 15 | 0,165 | 16 | 0,2 | 90 |
| Ejemplo 16 | 0,15 | 28 | 0,16 | 97 |
| Ejemplo 17 | 0,95 | 64 | 0,12 | 95 |
| Ejemplo 18 | 0,14 | 83 | 0,085 | 97 |
| Ejemplo 19 | 0,42 | 35 | 0,22 | 97 |
| Ejemplo 20 | - | 0,5 | 0,75 | 53 |
| Ejemplo 21 | - | 8 | 0,5 | 97 |
| Ejemplo 22 | 3 | 78 | 0,2 | 93 |
| Ejemplo 23 | 2 | 17 | 0,55 | 95 |
| Ejemplo 24 | 0,7 | 15 | 0,45 | 99 |
| Ejemplo 25 | 75 | 23 | 2 | 94 |
| Ejemplo 26 | 0,125 | 74 | 0,12 | 90 |
| Ejemplo 27 | 0,7 | 37 | 0,33 | 97 |
| Ejemplo 28 | 29 | 35 | 0,6 | 94 |
| Ejemplo 29 | 3 | 14 | 0,8 | 100 |
| Ejemplo 30 | - | 2 | 25 | 9 |
| Ejemplo 31 | 7 | 33 | 0,313 | 98 |
| Ejemplo 32 | 18 | 34 | 0,543 | 96 |
| Ejemplo 33 | 1 | 41 | 0,153 | 98 |
| Ejemplo 34 | 1 | 79 | 0,137 | 97 |
| Ejemplo 35 | - | 6 | 1 | 84 |
| Ejemplo 36 | - | 8 | 1 | 89 |
| Ejemplo 37 | - | 6 | 0,55 | 90 |
| Ejemplo 38 | 2 | 31 | 0,258 | 97 |
| Ejemplo 39 | - | 4 | 1 | 79 |
| Ejemplo 40 | - | 8 | 0,5 | 93 |
| Ejemplo 41 | - | 5 | 0,8 | 84 |

| Compuesto | 0,1 ng/mL doxiciclina | | 10 ng/mL doxiciclina | |
|---|---|---|---|---|
| | $CE_{50}$ (nM) | Actividad intrínseca (%) | $CE_{50}$ (nM) | Actividad intrínseca (%) |
| Ejemplo 42 | - | 9 | 0,5 | 84 |
| Ejemplo 43 | 1 | 43 | 0,177 | 100 |
| Ejemplo 44 | 11 | 22 | 0,617 | 99 |
| Ejemplo 45 | - | 12 | 0,45 | 87 |
| Ejemplo 46 | 0,666 | 40 | 0,173 | 97 |
| Ejemplo 47 | 0,31 | 36 | 0,373 | 100 |
| Ejemplo 48 | - | 6 | 4 | 93 |
| Ejemplo 49 | 2 | 74 | 0,235 | 93 |
| Ejemplo 50 | 0,21 | 94 | 0,085 | 94 |
| Ejemplo 51 | 0,64 | 22 | 0,4 | 95 |
| Ejemplo 52 | 0,325 | 31 | 0,2 | 99 |
| Ejemplo 53 | 0,13 | 86 | 0,13 | 90 |
| Ejemplo 54 | 0,075 | 56 | 0,075 | 92 |
| Ejemplo 55 | 10 | 28 | 0,8 | 98 |
| Ejemplo 56 | 5 | 41 | 0,3 | 98 |
| Ejemplo 57 | 0,25 | 89 | 0,095 | 100 |
| Ejemplo 58 | 5 | 67 | 0,25 | 100 |
| Ejemplo 59 | 0,6 | 90 | 0,1 | 98 |
| Ejemplo 60 | 0,45 | 62 | 0,14 | 95 |
| Ejemplo 61 | - | 6 | 0,95 | 89 |
| Ejemplo 62 | 16 | 23 | 0,47 | 84 |
| Ejemplo 63 | 0,37 | 30 | 0,157 | 93 |
| Ejemplo 64 | 1 | 57 | 0,08 | 90 |
| Ejemplo 65 | 1 | 58 | 0,085 | 93 |
| Ejemplo 66 | 5 | 32 | 0,265 | 88 |
| Ejemplo 67 | 1 | 38 | 0,14 | 99 |
| Ejemplo 68 | 0,85 | 55 | 0,075 | 91 |
| Ejemplo 69 | 0,25 | 76 | 0,095 | 92 |
| Ejemplo 70 | 0,4 | 64 | 0,1 | 91 |

| Compuesto | 0,1 ng/mL doxiciclina | | 10 ng/mL doxiciclina | |
|---|---|---|---|---|
| | $CE_{50}$ (nM) | Actividad intrínseca (%) | $CE_{50}$ (nM) | Actividad intrínseca (%) |
| Ejemplo 71 | 1 | 86 | 0,085 | 91 |
| Ejemplo 72 | 3 | 11 | 0,35 | 84 |
| Ejemplo 73 | 0,587 | 86 | 0,068 | 102 |
| Ejemplo 74 | 0,943 | 68 | 0,11 | 100 |
| Ejemplo 75 | 0,65 | 43 | 0,125 | 87 |
| Ejemplo 76 | 3 | 53 | 0,135 | 85 |
| Ejemplo 77 | 3 | 34 | 0,155 | 80 |
| Ejemplo 78 | 2 | 48 | 0,2 | 89 |
| Ejemplo 79 | 4 | 48 | 0,2 | 85 |
| Ejemplo 80 | 6 | 13 | 0,65 | 86 |
| Ejemplo 81 | 4 | 23 | 0,45 | 85 |
| Ejemplo 82 | 2 | 79 | 0,095 | 95 |
| Ejemplo 83 | 0,75 | 78 | 0,075 | 94 |
| Ejemplo 84 | 0,633 | 78 | 0,09 | 97 |
| Ejemplo 85 | 15 | 36 | 0,707 | 94 |
| Ejemplo 86 | 9 | 36 | 0,483 | 96 |
| Ejemplo 87 | 1 | 64 | 0,065 | 100 |
| Ejemplo 88 | 3 | 15 | 0,35 | 89 |
| Ejemplo 89 | | 6 | 17 | 87 |
| Ejemplo 90 | 4 | 31 | 0,283 | 96 |
| Ejemplo 91 | 1 | 18 | 0,265 | 96 |
| Ejemplo 92 | 0,1 | 81 | 0,04 | 89 |
| Ejemplo 93 | 0,3 | 44 | 0,17 | 97 |
| Ejemplo 94 | 0,24 | 32 | 0,09 | 92 |
| Ejemplo 95 | 1 | 42 | 0,125 | 100 |
| Ejemplo 96 | 2 | 24 | 0,235 | 100 |
| Ejemplo 97 | 0,8 | 49 | 0,1 | 100 |
| Ejemplo 98 | 0,45 | 47 | 0,14 | 100 |
| Ejemplo 99 | 0,7 | 32 | 0,14 | 94 |

| Compuesto | 0,1 ng/mL doxiciclina | | 10 ng/mL doxiciclina | |
|---|---|---|---|---|
| | $CE_{50}$ (nM) | Actividad intrínseca (%) | $CE_{50}$ (nM) | Actividad intrínseca (%) |
| Ejemplo 100 | 6 | 27 | 0,27 | 93 |
| Ejemplo 101 | 0,95 | 36 | 0,14 | 93 |
| Ejemplo 102 | 18 | 30 | 0,725 | 97 |
| Ejemplo 103 | 1 | 32 | 0,13 | 100 |
| Ejemplo 104 | 191 | 16 | 10 | 100 |
| Ejemplo 105 | 3 | 35 | 0,15 | 94 |
| Ejemplo 106 | | 3 | 113 | 77 |
| Ejemplo 107 | | 4 | | 64 |
| Ejemplo 108 | | 3 | 9 | 59 |
| Ejemplo 109 | | 2 | 269 | 69 |
| Ejemplo 110 | 0,6 | 84 | 0,06 | 105 |
| Ejemplo 111 | 0,575 | 81 | 0,053 | 104 |
| Ejemplo 112 | 0,39 | 83 | 0,07 | 101 |
| Ejemplo 113 | 0,72 | 80 | 0,065 | 100 |
| Ejemplo 114 | 1 | 73 | 0,185 | 117 |
| Ejemplo 115 | 0,8 | 54 | 0,17 | 108 |
| Ejemplo 116 | 0,68 | 77 | 0,095 | 104 |
| Ejemplo 117 | 1 | 50 | 0,18 | 112 |

Se cree que los péptidos de la invención que exhiben una actividad intrínseca igual o mayor que aproximadamente 0,1 (10%), tal como mayor que 0,2 (20%) o mayor que aproximadamente 0,3 (30%) o mayor que aproximadamente 0,4 (40%) o mayor que aproximadamente 0,5 (50%) o mayor que aproximadamente 0,6 (60%) %) o mayor que aproximadamente 0,7 (70%), o mayor que aproximadamente 0,8 (80%), o mayor que aproximadamente 0,9 (90%), o igual o mayor que aproximadamente 1,0 (100%), en el sistema de hMC4-R de alta densidad descrito anteriormente (es decir, células HEK293TRexMC4R tratadas con 10 ng/ml de doxiciclina), en base a la estimulación máxima de adenilil ciclasa alcanzable por el compuesto en el mismo sistema de hMC4-R de alta densidad en donde la estimulación máxima alcanzada por α-MSH o NDP-α-MSH

se designa como una actividad intrínseca de 1,0 (100%), proporcionan actividad agonista (completo o parcial) en el receptor de MC4.

La mayoría de los péptidos de los Ejemplos que se evaluaron en el sistema de hMC4-R de alta densidad descrito anteriormente (es decir, células HEK293TRexMC4R tratadas con 10 ng/ml de doxiciclina) proporcionaron valores de ensayo de $CE_{50}$ para la producción de cAMP menores que 0,05 μM, tales como menores que 0,01 μM y en particular menores que 0,001 μM.

Tal como se ve en la Tabla 4, los péptidos de la invención pueden carecer de actividad intrínseca en el sistema de hMC4-R de baja densidad y ser agonistas completos en el sistema de hMC4-R de alta densidad.

Tal como se ve, además, en la Tabla 4, los péptidos de la invención pueden ser agonistas parciales en el sistema de hMC4-R de baja densidad descrito anteriormente y ser agonistas completos en el sistema de hMC4-R de alta densidad descrito anteriormente.

Tal como se ve, además, en la Tabla 4, los péptidos de la invención pueden ser agonistas completos tanto en el sistema de hMC4-R de baja densidad como en el sistema de hMC4-R de alta densidad.

Sin estar sujeto a ninguna teoría, se cree que los péptidos que carecen de actividad intrínseca o que son agonistas parciales en el sistema de hMC4-R de baja densidad descrito anteriormente (es decir, péptidos que tienen actividad intrínseca de 0 a 70% en el sistema de hMC4-R de baja densidad) y son agonistas parciales o completos en el sistema de hMC4-R de alta densidad descrito anteriormente (es decir, péptidos que tienen actividad intrínseca igual o superior a 10%, o superior a 70%, en el sistema de hMC4-R de alta densidad) no proporcionarán ningún nivel o un nivel reducido de efectos sexuales que resulten de la activación del receptor de MC4, por ejemplo, erección peneana, en comparación con los péptidos que son agonistas completos tanto en el sistema de hMC4-R de baja densidad como de alta densidad. Como se explicó anteriormente, estos efectos sexuales se consideran efectos secundarios indeseados del tratamiento de enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo, la ingesta de alimentos y/o el equilibrio de energía y el peso corporal.

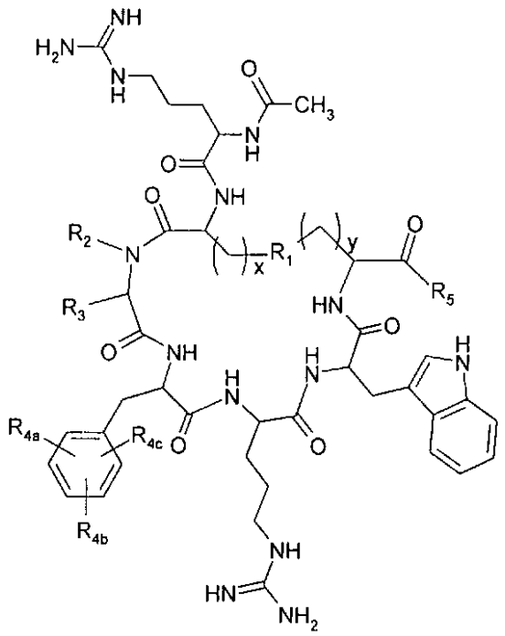
Se cree, por lo tanto, que los péptidos de acuerdo con la invención poseen afinidad, eficacia y potencia para con los receptores de MC4 que son útiles para el tratamiento de enfermedades, trastornos y/o afecciones sensibles a la activación del

receptor de MC4, en particular enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, la diabetes), relacionados con la ingesta de alimentos y/o el equilibrio de energía y relacionados con el peso corporal, incluida la obesidad, el sobrepeso y enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, tales como diabetes tipo 2 y síndrome metabólico.

Si bien la invención se ha descrito en detalle con referencia en particular a estas realizaciones preferidas, otras realizaciones pueden alcanzar los mismos resultados. Distintas variaciones y modificaciones de la presente invención serán evidentes para los expertos en la técnica y se pretende incluir todas dichas modificaciones y equivalentes.

REIVINDICACIONES

1. Un péptido cíclico de Fórmula (I):



(I)

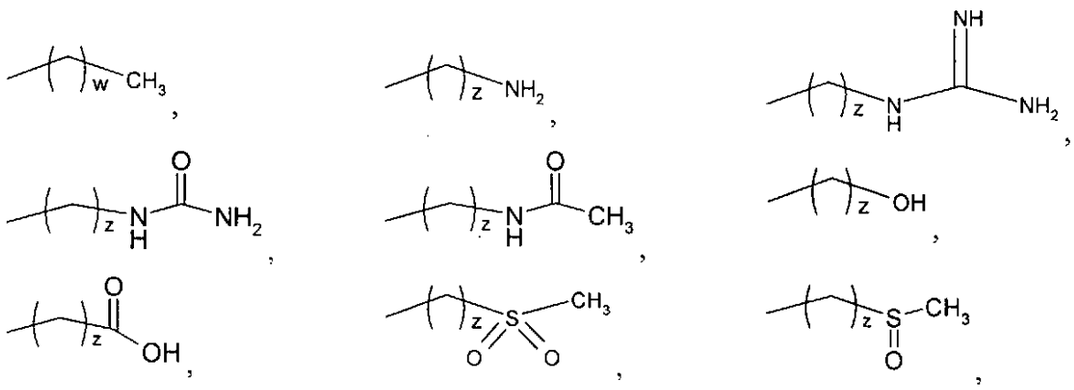
o una sal farmacéuticamente aceptable del mismo,

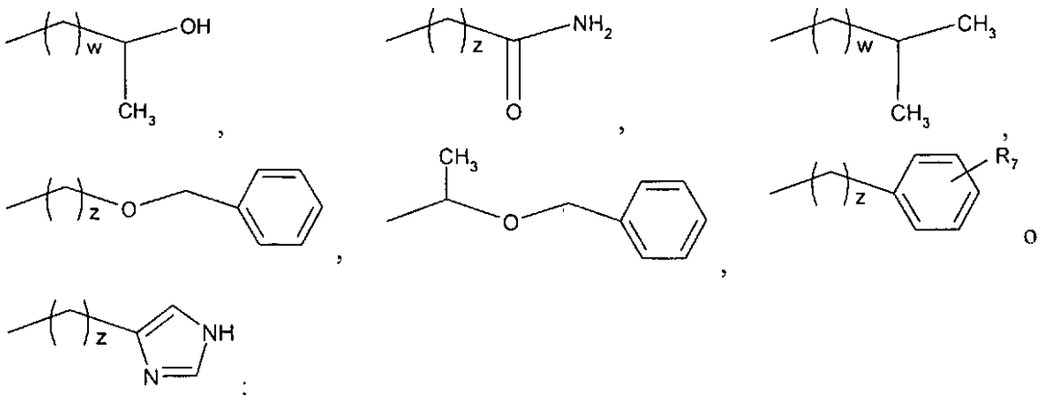
en donde:

$R_1$ es -NH-C(=O)- o -C(=O)-NH-;

$R_2$ es -H o $-CH_2-$ y, si $R_2$ es $-CH_2-$, forma con $R_3$ un anillo de pirrolidina, estando el anillo de pirrolidina opcionalmente sustituido por –OH;

$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de





$R_{4a}$, $R_{4b}$ y $R_{4c}$ se seleccionan cada uno independientemente de hidrógeno, halo, alquilo($C_1$-$C_{10}$)-halo, alquilo($C_1$-$C_{10}$)-dihalo, alquilo($C_1$-$C_{10}$)-trihalo, alquilo($C_1$-$C_{10}$), alcoxi($C_1$-$C_{10}$), alquil($C_1$-$C_{10}$)tio, arilo, ariloxi, nitro, nitrilo, sulfonamida, amino, amino monosustituido, amino disustituido, hidroxi, carboxi o alcoxi-carbonilo, con la condición de que al menos uno de $R_{4a}$, $R_{4b}$ y $R_{4c}$ no sea hidrógeno;

$R_5$ es -OH o -N($R_{6a}$)($R_{6b}$);

$R_{6a}$ y $R_{6b}$ son cada uno independientemente H o una cadena de alquilo $C_1$ a $C_4$ lineal, ramificada o cíclica;

$R_7$ es -H o -C(=O)-$NH_2$;

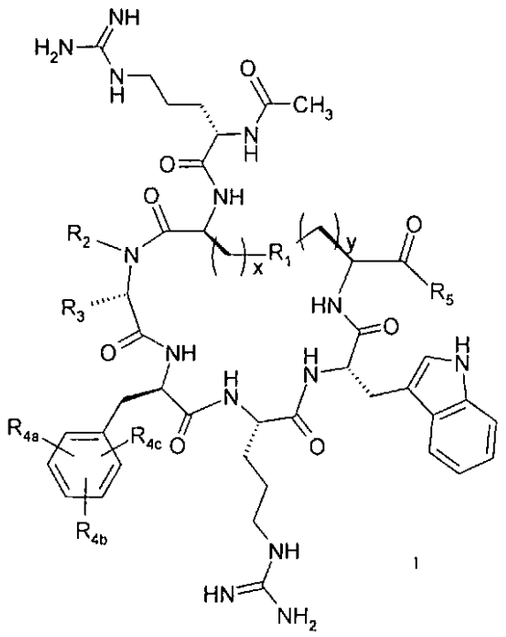
w es en cada instancia independientemente 0 a 5;

x es 1 a 5;

y es 1 a 5; y

z es en cada instancia independientemente 1 a 5.

2. El péptido cíclico de la reivindicación 1, que es de Fórmula (II):



(II)

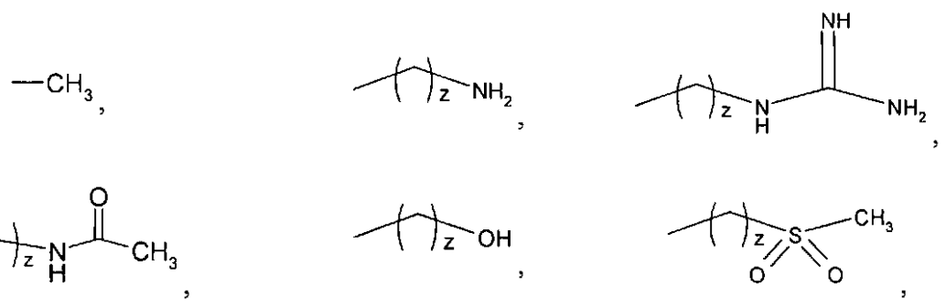
o una sal farmacéuticamente aceptable del mismo.

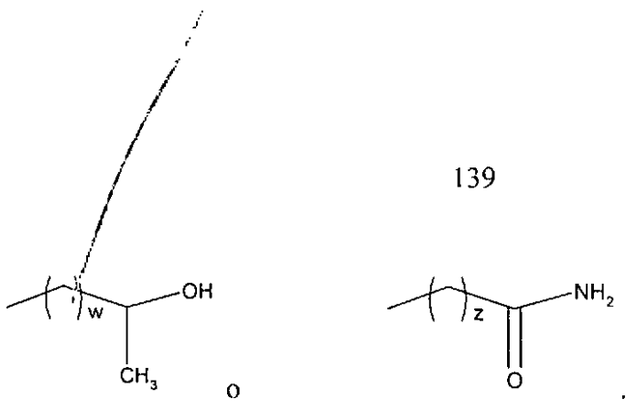
3. El péptido cíclico de la reivindicación 1 o la reivindicación 2, en donde $R_1$ es -C(=O)-NH-, x es 2 e y es 3.

4. El péptido cíclico de la reivindicación 1 o la reivindicación 2, en donde $R_1$ es -NH-C(=O)-, x es 3 e y es 2.

5. El péptido cíclico de cualquiera de las reivindicaciones 1-4, en donde $R_2$ es H o $-CH_2$-y, si $R_2$ es $-CH_2$-, forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH; y

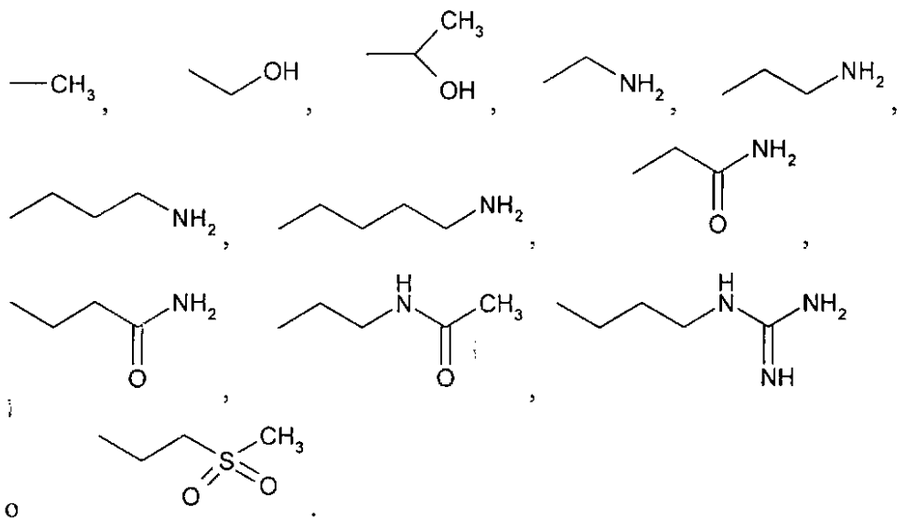
$R_3$ es $-(CH_2)_2$- si $R_2$ es $-CH_2$-, y de otro modo $R_3$ se selecciona de



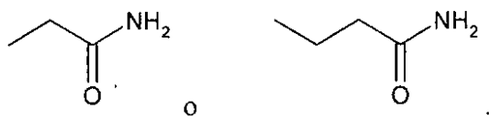


6. El péptido cíclico de cualquiera de las reivindicaciones 1-4, en donde $R_2$ es H o $-CH_2-$ y, si $R_2$ es $-CH_2-$, forma con $R_3$ un anillo de pirrolidina, sustituyéndose opcionalmente el anillo de pirrolidina por -OH; y

$R_3$ es $-(CH_2)_2-$ si $R_2$ es $-CH_2-$, y de otro modo $R_3$ se selecciona de

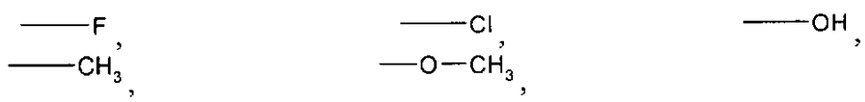


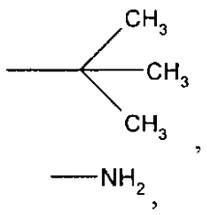
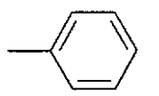
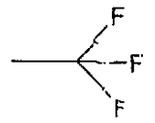
7. El péptido cíclico de cualquiera de las reivindicaciones 1-4, en donde $R_2$ es H, $R_3$ se selecciona de

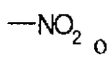
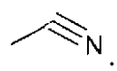


8. El péptido cíclico de cualquiera de las reivindicaciones 1-4, en donde $R_2$ es $-CH_2-$ y $R_3$ es $-(CH_2)_2-$, formando juntos $R_2$ y $R_3$ un anillo de pirrolidina insustituido.

9. El péptido cíclico de cualquiera de las reivindicaciones 1-8, en donde al menos uno de $R_{4a}$, $R_{4b}$ y $R_{4c}$ se selecciona independientemente de



10. El péptido cíclico de cualquiera de las reivindicaciones 1-8, en donde al menos uno de $R_{4a}$, $R_{4b}$ y $R_{4c}$ se selecciona independientemente de hidrógeno, halo, alquilo($C_1$-$C_4$)-halo, alquilo($C_1$-$C_4$)-dihalo, alquilo($C_1$-$C_4$)-trihalo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), nitro, nitrilo, amino o hidroxi, con la condición de que al menos uno de $R_{4a}$, $R_{4b}$ y $R_{4c}$ no sea hidrógeno.

11. El péptido cíclico de cualquiera de las reivindicaciones 1-8 en donde $R_{4a}$ está en la posición 4 y es -C≡N y $R_{4b}$ y $R_{4c}$ son cada uno H.

12. El péptido cíclico de cualquiera de las reivindicaciones 1-8 en donde $R_{4a}$ está en la posición 4 y es -F y $R_{4b}$ y $R_{4c}$ son cada uno H.

13. Un péptido cíclico seleccionado de:

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:48);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:51);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:74);

Ac-Arg-*ciclo*(Glu-Asn-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:90);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-CN)-Arg-Trp-Orn)-OH (SEQ ID NO:91);

Ac-Arg-*ciclo*(Glu-Gln-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:97);

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-CN)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:44);

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-$NH_2$ (SEQ ID NO:72);

Ac-Arg-*ciclo*(Glu-Pro-D-Phe(4-F)-Arg-Trp-Orn)-OH (SEQ ID NO:107); o una sal farmacéuticamente aceptable de cualquiera de los anteriores.

14. Una composición farmacéutica que comprende un péptido cíclico o una sal farmacéuticamente aceptable del mismo de cualquiera de las reivindicaciones 1-13 y un portador farmacéuticamente aceptable.

15. Un péptido de acuerdo con cualquiera de las reivindicaciones 1-13 para su utilización como medicamento.

16. Un péptido de acuerdo con cualquiera de las reivindicaciones 1-13 para su utilización en el tratamiento de enfermedades, trastornos y/o afecciones sensibles a la activación del receptor MC4.

17. Un péptido de acuerdo con cualquiera de las reivindicaciones 1-13 para su utilización en el tratamiento de diabetes; obesidad; sobrepeso; y/o enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, incluyendo resistencia a la insulina; tolerancia a la glucosa alterada; diabetes tipo 2; síndrome metabólico; dislipidemia; hiperlipidemia; hipertensión; trastornos cardíacos; trastornos cardiovasculares; esteatosis hepática no alcohólica; trastornos articulatorios; osteoartritis secundaria; reflujo gastroesofágico; apnea del sueño; ateroesclerosis; accidente cerebrovascular; enfermedades macro y micro vasculares; esteatosis; cálculos biliares; y trastornos de la vesícula biliar.

18. Un método para tratar una enfermedad, trastorno y/o afección sensible a la activación del receptor MC4 que comprende la administración de una cantidad terapéuticamente efectiva de un péptido de acuerdo con cualquiera de las reivindicaciones 1-13 a un paciente que lo necesita.

19. Un método para tratar diabetes, obesidad, sobrepeso y/o enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, incluyendo resistencia a la insulina; tolerancia a la glucosa alterada; diabetes tipo 2; síndrome metabólico; dislipidemia; hiperlipidemia; hipertensión; trastornos cardíacos; trastornos cardiovasculares; esteatosis hepática no alcohólica; trastornos articulatorios; osteoartritis secundaria; reflujo gastroesofágico; apnea del sueño; ateroesclerosis; accidente cerebrovascular; enfermedades macro y micro vasculares; esteatosis; cálculos biliares; y trastornos de la vesícula biliar que comprende la administración de una cantidad

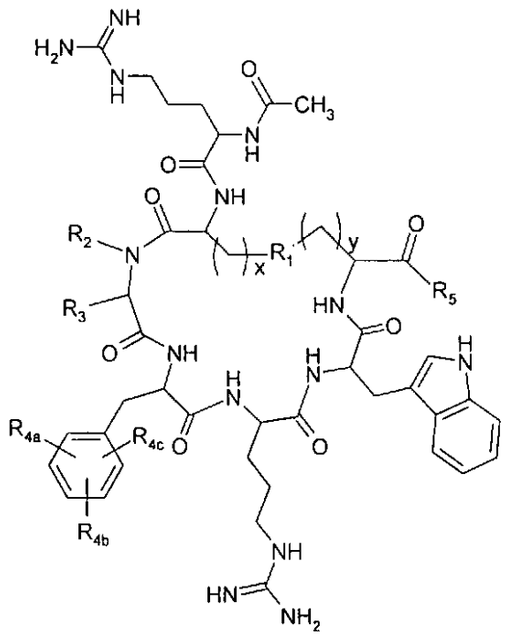
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terapéuticamente efectiva de un péptido de acuerdo con cualquiera de las reivindicaciones 1-13 a un paciente que lo necesita.

20. Un método para reducir la ingesta de alimentos, el peso corporal y/o el aumento del peso corporal que comprende la administración de una cantidad farmacológicamente efectiva de un péptido de acuerdo con cualquiera de las reivindicaciones 1-13 a un individuo que lo necesita.

Resumen

La invención se refiere a péptidos cíclicos específicos para receptores de melanocortina de Fórmula (I)



(I)

o una sal farmacéuticamente aceptable de los mismos, donde $R_1$, $R_2$, $R_3$, $R_{4a}$, $R_{4b}$, $R_{4c}$, $R_5$, x e y son como se definen en la memoria descriptiva. Estos compuestos son particularmente útiles en el tratamiento de enfermedades, trastornos y/o afecciones relacionados con la homeostasis de la energía y el metabolismo (por ejemplo, diabetes), relacionados con la ingesta de alimentos y/o relacionados con el equilibrio de energía y el peso corporal, incluidos la obesidad, el sobrepeso y enfermedades, trastornos y/o afecciones asociados con la obesidad y/o el sobrepeso, tales como la diabetes tipo 2 y el síndrome metabólico.

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Dodd, John H.

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From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA INTELLECTUAL PROPERTY
AstraZeneca AB
SE-151 85 Södertälje
SUÈDE

| | |
|---|---|
| Date of mailing *(day/month/year)*<br>14 October 2011 (14.10.2011) | |
| Applicant's or agent's file reference<br>103759-1P WO | IMPORTANT NOTIFICATION |
| International application No.<br>PCT/SE2010/050626 | International filing date *(day/month/year)*<br>07 June 2010 (07.06.2010) |

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| DODD, John H.<br>Palatin Technologies, INC<br>4-C Cedar Brook<br>Cedar Brook Corporate Center<br>Cranbury, New Jersey 08512<br>United States of America | US | US |
| | Telephone No. | |
| | Facsimile No. | |
| | E-mail address | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| DODD, John H.<br>c/o Palatin Technologies, INC<br>4-C Cedar Brook<br>Cedar Brook Corporate Center<br>Cranbury, New Jersey 08512<br>United States of America | US | US |
| | Telephone No. | |
| | Facsimile No. | |
| | E-mail address<br>☐ Notifications by e-mail authorized | |

3. Further observations, if necessary:
Please note : The new address is recorded for DODD, John, H, SHI, Yi-Qun and YANG, Wei.

4. A copy of this notification has been sent to:

☐ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

| | |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>Campin Helene |
| Facsimile No. +41 22 338 70 80 | e-mail pt03.pct@wipo.int<br>Telephone No. +41 22 338 74 03 |



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PATENT COOPERATION TREATY PCT/SE2010/050626

From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA INTELLECTUAL PROPERTY
AstraZeneca AB
S-151 85 Södertälje
SUÈDE

| | |
|---|---|
| Date of mailing *(day/month/year)*<br>15 November 2011 (15.11.2011) | |
| Applicant's or agent's file reference<br>103759-1P WO | IMPORTANT NOTIFICATION |
| International application No.<br>PCT/SE2010/050626 | International filing date *(day/month/year)*<br>07 June 2010 (07.06.2010) |

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| SHI, Yi-Qun<br>Palatin Technologies, INC<br>4-C Cedar Brook<br>Cedar Brook Corporate Center<br>Cranbury, New Jersey 08512<br>United States of America | US | US |
| | Telephone No. | |
| | Facsimile No. | |
| | E-mail address | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| SHI, Yi-Qun<br>c/o Palatin Technologies, INC<br>4-C Cedar Brook<br>Cedar Brook Corporate Center<br>Cranbury, NJ 08512<br>United States of America | US | US |
| | Telephone No. | |
| | Facsimile No. | |
| | E-mail address<br>☐ Notifications by e-mail authorized | |

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☐ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

| | |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br><br>Facsimile No. +41 22 338 70 80 | Authorized officer<br>Campin Helene<br>e-mail pt03.pct@wipo.int<br>Telephone No. +41 22 338 74 03 |

Form PCT/IB/306 (January 2009) 1/GWHVWYNSWY2FE0

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From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA INTELLECTUAL PROPERTY
AstraZeneca AB
S-151 85 Södertälje
SUÈDE

| | |
|---|---|
| Date of mailing *(day/month/year)*<br>02 November 2011 (02.11.2011) | |
| Applicant's or agent's file reference<br>103759-1P WO | IMPORTANT NOTIFICATION |
| International application No.<br>PCT/SE2010/050626 | International filing date *(day/month/year)*<br>07 June 2010 (07.06.2010) |

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| YANG, Wei<br>c/o Palatin Technologies, INC<br>4-C Cedar Brook<br>Cedar Brook Corporate Center<br>Cranbury, New Jersey 08512<br>United States of America | US | US |
| | Telephone No. | |
| | Facsimile No. | |
| | E-mail address | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| YANG, Wei<br>Palatin Technologies, INC<br>4-C Cedar Brook<br>Cedar Brook Corporate Center<br>Cranbury, NJ 08512<br>United States of America | US | US |
| | Telephone No. | |
| | Facsimile No. | |
| | E-mail address<br>☐ Notifications by e-mail authorized | |

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☐ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

| | |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>Zoltanski Andrzej |
| Facsimile No. +41 22 338 70 80 | e-mail pt03.pct@wipo.int<br>Telephone No. +41 22 338 74 03 |



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PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>103759-1P WO | FOR FURTHER ACTION | See item 4 below |
| International application No.<br>PCT/SE2010/050626 | International filing date *(day/month/year)*<br>07 June 2010 (07.06.2010) | Priority date *(day/month/year)*<br>08 June 2009 (08.06.2009) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>ASTRAZENECA AB | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(*a*).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☒ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☒ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>12 December 2011 (12.12.2011) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>Nora Lindner |
| Facsimile No. +41 22 338 82 70 | e-mail: pt03.pct@wipo.int |

Form PCT/IB/373 (January 2004)

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ASTRAZENECA INTELLECTUAL PROPERTY
AstraZeneca AB
SE-151 85 Södertälje

# PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 17-09-2010 |
| Applicant's or agent's file reference: 103759-1P WO | FOR FURTHER ACTION: See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/SE2010/050626 | 07-06-2010 | 08-06-2009 |

International Patent Classification (IPC) or both national classification and IPC
See Supplemental Box

Applicant
ASTRAZENECA AB et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will no be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/SE | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Patent- och registreringsverket<br>Box 5055<br>S-102 42 STOCKHOLM | 15-09-2010 | Carolina Gomez Lagerlöf |
| Facsimile No. + 46 8 666 02 86 | | Telephone No. + 46 8 782 25 00 |

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: cover sheet

## International Patent Classification (IPC)

***C07K 7/54*** (2006.01)
***A61K 38/12*** (2006.01)
***A61P 3/04*** (2006.01)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant data (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:



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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 18-20

because:

☒ the said international application, or the said claims Nos. 18-20 relate to the following subject matter which does not require an international search *(specify)*:

Claims 18-20 relate to a method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, see PCT rule 67.1.(iv). Nevertheless, an examination has been conducted for these claims. The examination has been made in respect of the technical content of the claims.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing: the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-17, 18-20* | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | 1-17, 18-20* | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | 1-17, 18-20* | YES |
| | Claims | | NO |

2. Citations and explanations

Claims marked with * relate to a method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, see PCT rule 67.1.(iv), see Box III.

Documents cited in the International Search Report:
A: US 7541430
B: WO 2005030797

The cited documents represent the general state of the art.

Documents A and B show similar compounds with the same use as the claimed compounds.

However, there is no indication in the art that would lead a person skilled in the art to the claimed compounds, in order to obtain new melancortin receptor-specific cyclic petides. Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1-20 is novel and is considered to involve an inventive step. The invention is industrially applicable.



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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. VI Certain documents cited**

1. Certain published documents (Rules 43*bis*.1 and 70.10)

| Application No. Patent No. | Publication date *(day/month/year)* | Filing date *(day/month/year)* | Priority date (valid claim) *(day/month/year)* |
|---|---|---|---|
| WO 2009/151383 | 17.12.2009 | 08.06.2009 | 09.06.2008 |

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

| Kind of non-written disclosure | Date of non-written disclosure *(day/month/year)* | Date of written disclosure referring to non-written disclosure *(day/month/year)* |
|---|---|---|

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 16 and 18 refer to diseases or disorders and/or conditions responsive to activation of the MC4 receptor.

The formulation "diseases or disorders and/or conditions responsive to activation of the MC4 receptor" , although indisputably referring to pharmacological effects, cannot in itself be regarded as a therapeutic application. There are an undefined number of diseases which might be related to this pharmacological effect. A practical application needs to be specified in the form of a defined, real treatment of a disease, in order to render the claims clear according to Article 6 PCT.

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ASTRAZENECA INTELLECTUAL PROPERTY
AstraZeneca AB
SE-151 85 Södertälje

# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 17-09-2010 |
| Applicant's or agent's file reference<br>103759-1P WO | **FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/SE2010/050626 | 07-06-2010 | 08-06-2009 |

International Patent Classification (IPC) or both national classification and IPC
See Supplemental Box

Applicant
ASTRAZENECA AB et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will no be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/SE | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Patent- och registreringsverket<br>Box 5055<br>S-102 42 STOCKHOLM | 15-09-2010 | Carolina Gomez Lagerlöf |
| Facsimile No. + 46 8 666 02 86 | | Telephone No. + 46 8 782 25 00 |

Form PCT/ISA/237 (cover sheet) (July 2009)

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International application No.
PCT/SE2010/050626

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: cover sheet

## International Patent Classification (IPC)

***C07K 7/54*** (2006.01)
***A61K 38/12*** (2006.01)
***A61P 3/04*** (2006.01)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:



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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. II Priority**

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant data (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 18-20

because:

☒ the said international application, or the said claims Nos. 18-20 relate to the following subject matter which does not require an international search *(specify)*:

Claims 18-20 relate to a method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, see PCT rule 67.1.(iv). Nevertheless, an examination has been conducted for these claims. The examination has been made in respect of the technical content of the claims.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.



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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. V** **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-17, 18-20* | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | 1-17, 18-20* | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | 1-17, 18-20* | YES |
| | Claims | | NO |

2. Citations and explanations

Claims marked with * relate to a method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, see PCT rule 67.1.(iv), see Box III.

Documents cited in the International Search Report:
A: US 7541430
B: WO 2005030797

The cited documents represent the general state of the art.

Documents A and B show similar compounds with the same use as the claimed compounds.

However, there is no indication in the art that would lead a person skilled in the art to the claimed compounds, in order to obtain new melancortin receptor-specific cyclic petides. Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1-20 is novel and is considered to involve an inventive step. The invention is industrially applicable.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. VI Certain documents cited**

1. Certain published documents (Rules 43*bis*.1 and 70.10)

| Application No. Patent No. | Publication date *(day/month/year)* | Filing date *(day/month/year)* | Priority date (valid claim) *(day/month/year)* |
|---|---|---|---|
| WO 2009/151383 | 17.12.2009 | 08.06.2009 | 09.06.2008 |

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

| Kind of non-written disclosure | Date of non-written disclosure *(day/month/year)* | Date of written disclosure referring to non-written disclosure *(day/month/year)* |
|---|---|---|



199

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050626

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 16 and 18 refer to diseases or disorders and/or conditions responsive to activation of the MC4 receptor.

The formulation "diseases or disorders and/or conditions responsive to activation of the MC4 receptor" , although indisputably referring to pharmacological effects, cannot in itself be regarded as a therapeutic application. There are an undefined number of diseases which might be related to this pharmacological effect. A practical application needs to be specified in the form of a defined, real treatment of a disease, in order to render the claims clear according to Article 6 PCT.

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference<br>103759-1P WO | **FOR FURTHER ACTION** | see Form PCT/ISA/220<br>as well as, where applicable, item 5 below. |
|---|---|---|
| International application No.<br>PCT/SE2010/050626 | International filing date *(day/month/year)*<br>07-06-2010 | (Earliest) Priority Date *(day/month/year)*<br>08-06-2009 |
| Applicant<br>ASTRAZENECA AB et al | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II).

3. ☐ **Unity of invention is lacking** (See Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. --

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050626

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-20
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 18-20 relate to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims). The search has been directed to the technical content of the claims.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050626

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:A61K, A61P, C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P, X | WO 2009151383 A1 (PALATIN TECHNOLOGIES INC ET AL), 17 December 2009 (2009-12-17); claims<br>-- | 1-20 |
| A | WO 2005030797 A2 (NOVO NORDISK AS ET AL), 7 April 2005 (2005-04-07); claim 28<br>-- | 1-20 |
| A | US 7541430 B2 (SENSFUSS ULRICH ET AL), 18 October 2007 (2007-10-18); claim 23<br>--<br>---------- | 1-20 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17-09-2010 | 17-09-2010 |
| Name and mailing address of the ISA/SE<br>Patent- och registreringsverket<br>Box 5055<br>S-102 42 STOCKHOLM<br>Facsimile No. + 46 8 666 02 86 | Authorized officer<br>Carolina Gomez Lagerlöf<br>Telephone No. + 46 8 782 25 00 |

Form PCT/ISA/210 (second sheet) (July 2009)

**Continuation of:** second sheet

**International Patent Classification (IPC)**

***C07K 7/06*** (2006.01)
***A61K 38/08*** (2006.01)
***A61P 3/04*** (2006.01)

**Download your patent documents at www.prv.se**

The cited patent documents can be downloaded:

- From "Cited documents" found under our online services at www.prv.se (English version)
- From "Anförda dokument" found under "e-tjänster" at www.prv.se (Swedish version)

Use the application number as username. The password is **HDKCZJDUOA**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE2010/050626

| | | | | | | |
|---|---|---|---|---|---|---|
| WO | 2009151383 | A1 | 17/12/2009 | AR | 072072 | A1 04/08/2010 |
| | | | | US | 20090305960 | A1 10/12/2009 |
| WO | 2005030797 | A2 | 07/04/2005 | AU | 2004275928 | A1 07/04/2005 |
| | | | | BR | PI0414890 | A 12/12/2006 |
| | | | | CA | 2539596 | A1 07/04/2005 |
| | | | | CN | 101497654 | A 05/08/2009 |
| | | | | CN | 100482682 | C 29/04/2009 |
| | | | | CN | 1860128 | A 08/11/2006 |
| | | | | EP | 1670815 | A2 21/06/2006 |
| | | | | JP | 2007532471 | T 15/11/2007 |
| | | | | KR | 20060089874 | A 09/08/2006 |
| | | | | MX | PA06003474 | A 05/06/2006 |
| | | | | RU | 2381233 | C2 10/02/2010 |
| | | | | RU | 2006109187 | A 10/11/2007 |
| | | | | US | 20070027091 | A1 01/02/2007 |
| | | | | US | 7517854 | B2 14/04/2009 |
| US | 7541430 | B2 | 02/06/2009 | US | 20090088388 | A1 02/04/2009 |
| | | | | US | 20070244054 | A1 18/10/2007 |

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-177219- -00000-0000

Fecha: 2011-12-22 17:36:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTE!YII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 202

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☒ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☒ Indicación que se solicita una PCT
- ☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita 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 ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐